Identification and Synthesis of Leptotriene, a Unique Sesquiterpene Hydrocarbon from Males of the Leaffooted Bugs *Leptoglossus zonatus* and *L. occidentalis*

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ABSTRACT The leaffooted bugs *Leptoglossus zonatus* and *L. occidentalis* (Hemiptera: Coreidae) cause substantial damage in nut crops in North America, and pine seed orchards in North America and Europe, respectively. Sexually-mature males of both species produce a number of aldehydes, esters, and sesquiterpenes which are hypothesized to constitute an aggregation pheromone attractive to both sexes. Amongst the volatiles produced by males of both species, we identified a unique sesquiterpene hydrocarbon, given the common name "leptotriene" (**5**), which elicited strong responses from antennae of both sexes in electroantennogram assays. Here, we report its structure, and its synthesis from (-)-(*E*)-β-caryophyllene (**1**).

The leaffooted bug, *Leptoglossus zonatus* (Dallas 1852) (Heteroptera: Coreidae), is widely distributed throughout the Americas, from the southern United States to Brazil.[1] It is polyphagous, and over its broad range it can be an important pest of a variety of crops, including maize, sorghum, citrus, and nut crops. Over the past two decades, it has become a major pest in California's multibillion dollar almond and pistachio industries, in part because large populations can rapidly migrate into crops, causing substantial damage before appropriate controls can be applied.[2] A congeneric species, *Leptoglossus occidentalis* Heidemann, whose native range encompasses western North America, was introduced into Europe in the 1990s, and it has since spread rapidly throughout the continent.[3] This species is a specialist on conifer cones.[4] In both its native and invasive ranges, it can be a major pest in conifer seed orchards,[5] and in Europe is of particular concern to growers of edible pine nuts, *Pinus pinea* L.[6,7] For both of these species, the development of better methods to monitor and control bugs would be of major benefit to growers and forest managers. Whereas recent research has produced optimized trap designs,[2] the development of effective attractants to use as lures in these traps has remained elusive.

Adult leaffooted bugs (LFB) often form sizeable aggregations,[8] and it is likely that pheromonal attractants aid in their formation.[9] It has been known for some time that adult male LFB produce sex-specific secretions from ventral abdominal glands, comprised of small aromatic molecules such as benzyl alcohol and vanillin, but in bioassays, these were not attractive to bugs of either sex.[10-13] There have also been reports that sexually mature *Leptoglossus* males produce sex-specific blends of volatiles, composed of simple aldehydes such as decanal, monoterpenes such as (*Z*)- -ocimene and (*Z*,*Z*)-*allo*-ocimene, and sesquiterpenes such as *cis*- and/or *trans*-bergamotenes, (*E*)- -caryophyllene, and (*E*)- -farnesene.[14] In laboratory bioassays with *L. zonatus*, an extract of these volatiles was attractive to females but not males, suggesting that the

blend might constitute a male-produced sex pheromone.[14] However, the authors did not bioassay any individual compounds or subsets of compounds, nor were any field trials carried out, so the components of the blend that are both necessary and sufficient to achieve attraction remain unknown. There is also preliminary evidence for a male-produced pheromone in *L. occidentalis.* In field trials, caged live males or mixed-sex adults, but not females, attracted adult bugs of both sexes,[9] and Benelli and coworkers observed male-specific sternal gland pores which were proposed to be the site of pheromone production.[15]

To follow up on these preliminary results, we collected and analyzed the volatiles produced by *L. zonatus* and *L. occidentalis*. As expected from the reports described above, we found that sexually mature males of both species produced sex-specific blends of aldehydes, esters, and terpenoids. We also found that males of both species produced a previously unreported sesquiterpene (**5**), which elicited strong electroantennogram responses from antennae of bugs of both species (Figure 1, Figure S14). We report here the identification and synthesis of this novel sesquiterpene.

Results and Discussion

In GC-MS analyses of volatiles produced by *L. zonatus* or *L. occidentalis,* the EI mass spectrum of the unknown compound (Figure 2) showed a possible molecular ion at *m/z* 202, suggesting a sesquiterpene hydrocarbon or alcohol (M^+- H_2O). The GC retention indices of 1468 and 1697 on non-polar and polar GC columns, respectively, indicated it to be an unsaturated hydrocarbon with no polar functional groups, and this was confirmed by the finding that the unknown compound could be partially purified by liquid chromatography on silica gel, eluting

with hexane. The likely molecular ion at *m/z* 202 in the EI mass spectrum corresponded to a possible molecular formula of $C_{15}H_{22}$, with five double bond equivalents. Reduction with hydrogen and 5% Pd on carbon produced a mixture of four isomers with essentially the same mass spectrum and molecular ion at *m/z* 208 (Figures S2-S5), indicating that the compound had three reducible double bonds, and, by default, two rings. The fact that four isomers were produced suggested that there were two pendant substituents with unsaturations at the ring connection, i.e., that reduction of each double bond could occur from the - or -face of the ring(s), resulting in the mixture of stereoisomers derived from reduction. The mass spectra of the reduced products were notable for having several even mass ions from mass losses via rearrangements rather than simple cleavages, including the base peak at *m/z* 124 (M^+-84), and ions at *m/z* 152 (M^+-56, loss of C_4H_8), and *m/z* 180 (M^+-28, loss of ethylene).

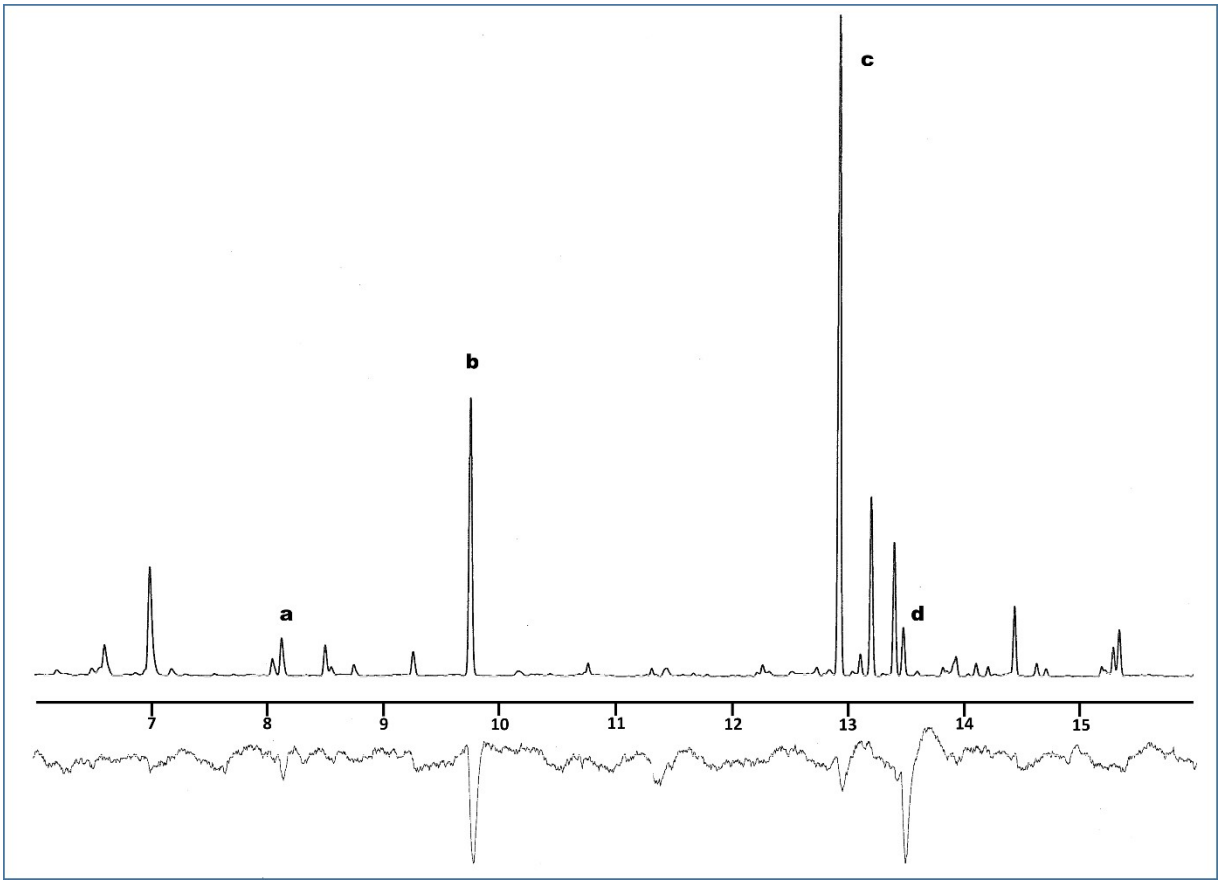


Figure 1. Coupled gas chromatography-electroantennogram detection (GC-EAD) analysis of an extract of volatiles from a male *Leptoglossus zonatus*, tested with an antenna from a female. Top trace = GC detector response, inverted bottom trace = antennal response. Peak identities for peaks which elicited antennal responses: **a**, nonanal; **b**, decanal; **c**, *cis*- -bergamotene; **d**, unknown.

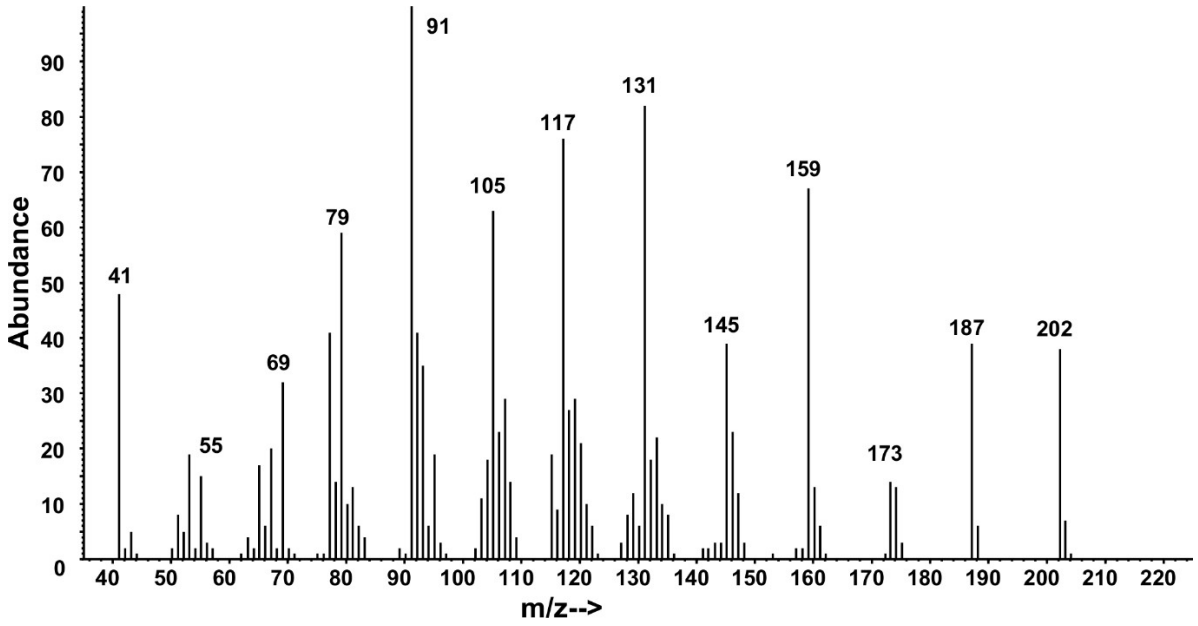
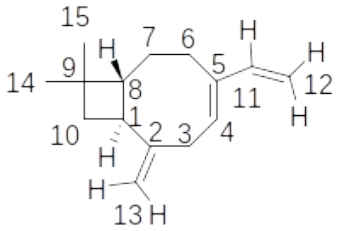


Figure 2. Electron impact ionization mass spectrum of the unknown compound with molecular ion at *m/z* 202.

The unknown compound was purified further by preparative gas chromatography, providing sufficient material for a standard ^{1}H NMR spectrum, simple decoupling experiments, and partial COSY and NOESY spectra (Figures S6-S8). The ^{1}H NMR spectrum in CD_2Cl_2 (Figure S6, Table 1) showed signals for a conjugated diene, consisting of a pendant vinyl group with chemical shifts 6.29 [1H, dd, J = 17.5, 10.8 Hz], 5.16 [1H, d, J = 17.5 Hz], and 4.95 ppm [1H, d, J = 10.8 Hz] attached to an sp^2 carbon with no attached protons, in turn connected to the fourth sp^2 carbon

of the diene with one attached proton (5.55 ppm, overlapped dd, J ~ 8 Hz). From the multiplicity, the latter proton had to be coupled to a diastereotopic methylene, one proton of which was clear (2.81 ppm, J = 13.0, 8.8 Hz). The second proton was not obvious because it exhibited as a featureless hump at 3.11 ppm, but was tentatively identified by a weak COSY correlation, and by a strong NOESY signal between the two protons. The chemical shifts of these two protons suggested that they were bisallylic, flanked on the other side by an exomethylene group (4.76 and 4.51 ppm, both broadened singlets). This accounted for the three double bonds. The remainder of the spectrum was more difficult to interpret because of overlap of signals and contamination from impurities, but some clarification was obtained from a combination of COSY and decoupling experiments. In particular, due to the limited amount of sample, some of the expected COSY signals were weak or absent, whereas the quantity of sample was adequate for simple decoupling. Thus, irradiation of the multiplet at 2.50 ppm, which integrated to two overlapped protons, resulted in the simplification of the single-proton allylic multiplet at 2.32 ppm, but did not collapse it to a doublet, suggesting that the 2.32 proton was further coupled to a methylene rather than a methine. This, coupled with their chemical shifts, suggested that one of the protons contributing to the 2.50 ppm multiplet and the 2.32 ppm proton constituted a geminal allylic methylene adjacent to another methylene. Selective decoupling of the proton at 2.32 ppm showed that in addition to being coupled to the 2.50 ppm proton, it was coupled to two diastereotopic methylene protons at 1.67 and 1.38 ppm. By default, the second allylic proton at 2.50 ppm had to be on the carbon adjacent to the exomethylene group.

Table 1. NMR Data for Insect-Produced and Synthesized Leptotriene (5), in CD_2Cl_2 and Benzene-d_6 (Figures S6, S9, S21, S22)



Natural leptotriene			Synthetic leptotriene	
Carbon number	CD_2Cl_2 δ_H (J in Hz)	Benzene-d_6 δ_H (J in Hz)	CD_2Cl_2 δ_c, type	CD_2Cl_2 δ_H (J in Hz)
1	2.50, m	2.45, m	40.60, CH	2.52, m
2			154.02, C	
3a 3b	3.11, m 2.81, br dd (13, 8.8)	3.03, m 2.73, dd (12.6, 7.2)	36.51, CH_2	3.12, m 2.82, dd (13, 7.4)
4	5.55, overlapped dd (~8, 8)	5.50, (~8, 8)	130.83, CH	5.56, dd (~8, 8)
5			141.08, C	
6a 6b	2.50, m 2.32, m	2.36, ddd (13.4, 8.7, 3.2) 2.17, m	24.11, CH_2	2.51, m 2.33, m
7a 7b	1.67, m 1.38, m	1.7? 1.29, m	28.29, CH_2	1.69, m 1.39, m
8	~1.75	1.7?	51.99, CH	1.76, m
9			33.44, C	
10	?? ??	?? ??	38.56, CH_2	1.78, m 1.66, m
11	6.29, dd (17.5, 10.8)	6.29, dd (17.5, 10.7)	140.41, CH	6.30, dd (17.5, 10.8)
12a 12b	5.16, d (17.5) 4.95, d (10.8)	5.14, d (17.5) 4.94, (d, 10.7)	111.13, CH_2	5.17, d (17.2) 4.96, d (10.8)
13a 13b	4.76, br s 4.51, br s	4.83, br s 4.64, br s	108.08, CH_2	4.77, br s 4.52, br s
14	0.964, s	0.90, s	30.61, CH_3	0.97, s
15	0.957, s	0.85, s	23.60, CH_3	0.98, s

Overall, the data so far accounted for 11 of the 15 carbons and 13 of the 22 protons, and the fragment shown in Figure 3A. Two additional carbons and six protons were accounted for by two methyl singlets at 0.964 and 0.957 ppm, which were likely to be geminal because there was no other satisfactory way to complete a structure with two rings and two methyl singlets from the remaining carbons and protons. Thus, a carbon with two geminal methyls accounted for three of the four remaining carbons, leaving one carbon and three protons (two between 1.75 and 1.65 ppm and one indeterminate) still to assign, and two rings to be closed. Furthermore, the remaining carbon had to be a methylene or methine. Superficially, this allowed nine possible skeletons (Figure 3B), but most could be eliminated based on the available data. Thus, spiro structures **I** and **II** were eliminated, because they would require one of the remaining unassigned protons to be allylic, which seemed unlikely based on their chemical shifts. Spiro structures **III** and **IV** could also be eliminated because neither of them had a sufficient number of allylic protons. Bicyclo[6.1.1] structure **V** and bicyclo[7.1.0] structures **VI** and **VII** seemed improbable because their reduction products could not easily accommodate the loss of a C_4H_8 fragment in their EI mass spectra. Structure **VII** would also require an additional allylic proton. Of the remaining bicyclo[6.2.0] structures **VIII** and **IX**, examination of the NOESY spectrum taken in CD_2Cl_2 provided support for structure **VIII**. In particular, a NOESY correlation between the exomethylene proton at 4.51 ppm and the multiplet at ~ 1.68 ppm and lack of a NOESY correlation between this proton and those of either of the geminal methyl groups favored this structure rather than **IX**. Furthermore, the right-hand portion of structure **VIII** bore distinct similarities to (*E*)- -caryophyllene (**1**), with the same relationships between the exomethylene group adjacent to the four-membered ring, and the geminal dimethyl group being furthest away

from the exomethylene. Thus, the unknown compound was tentatively identified as structure **VIII**, with the relative and absolute configurations not determined.

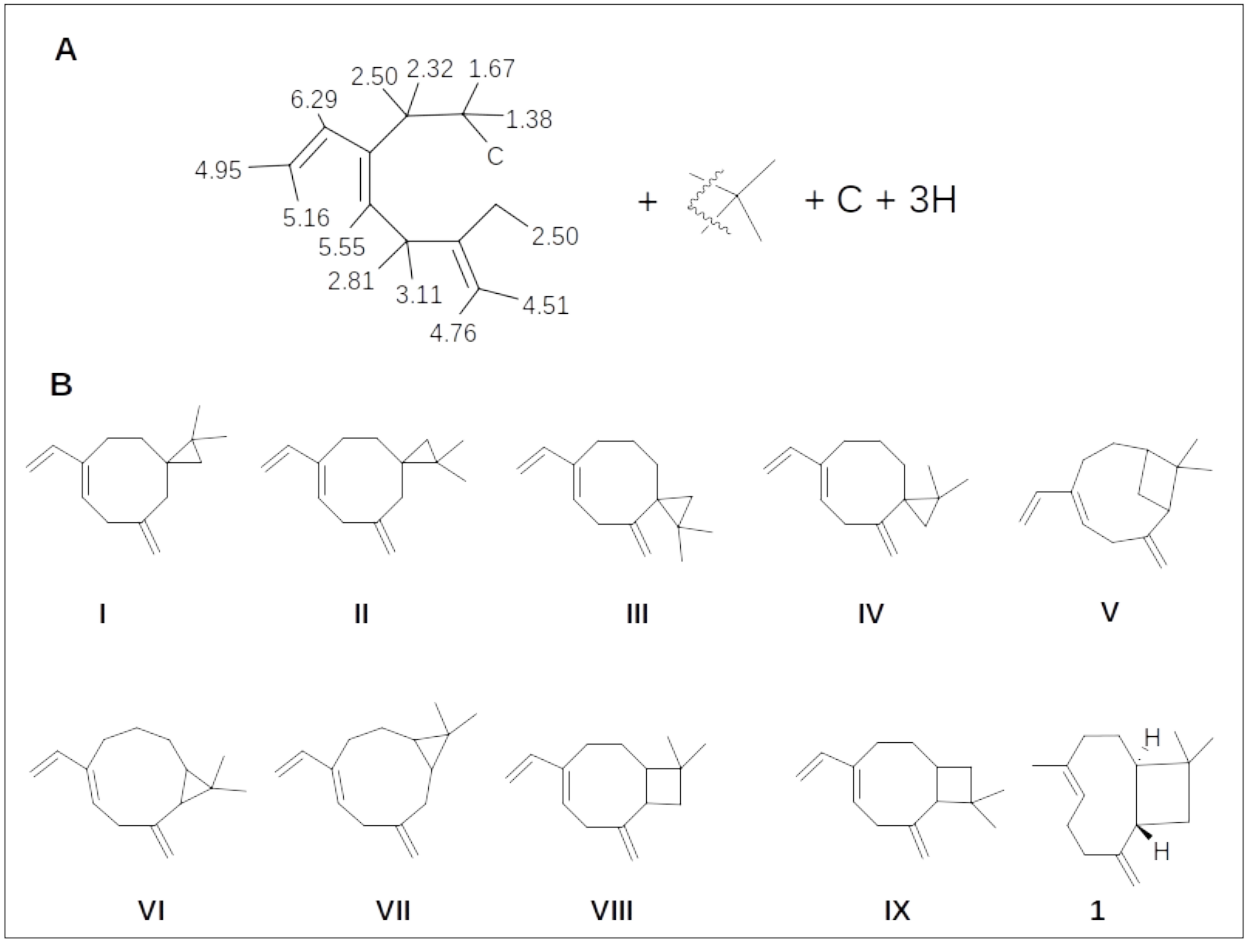


Figure 3. A) Spin systems from the proton NMR of the unknown compound; B) Possible structures **I-IX** for the unknown compound, and structure of (*E*)- -caryophyllene (**1**).

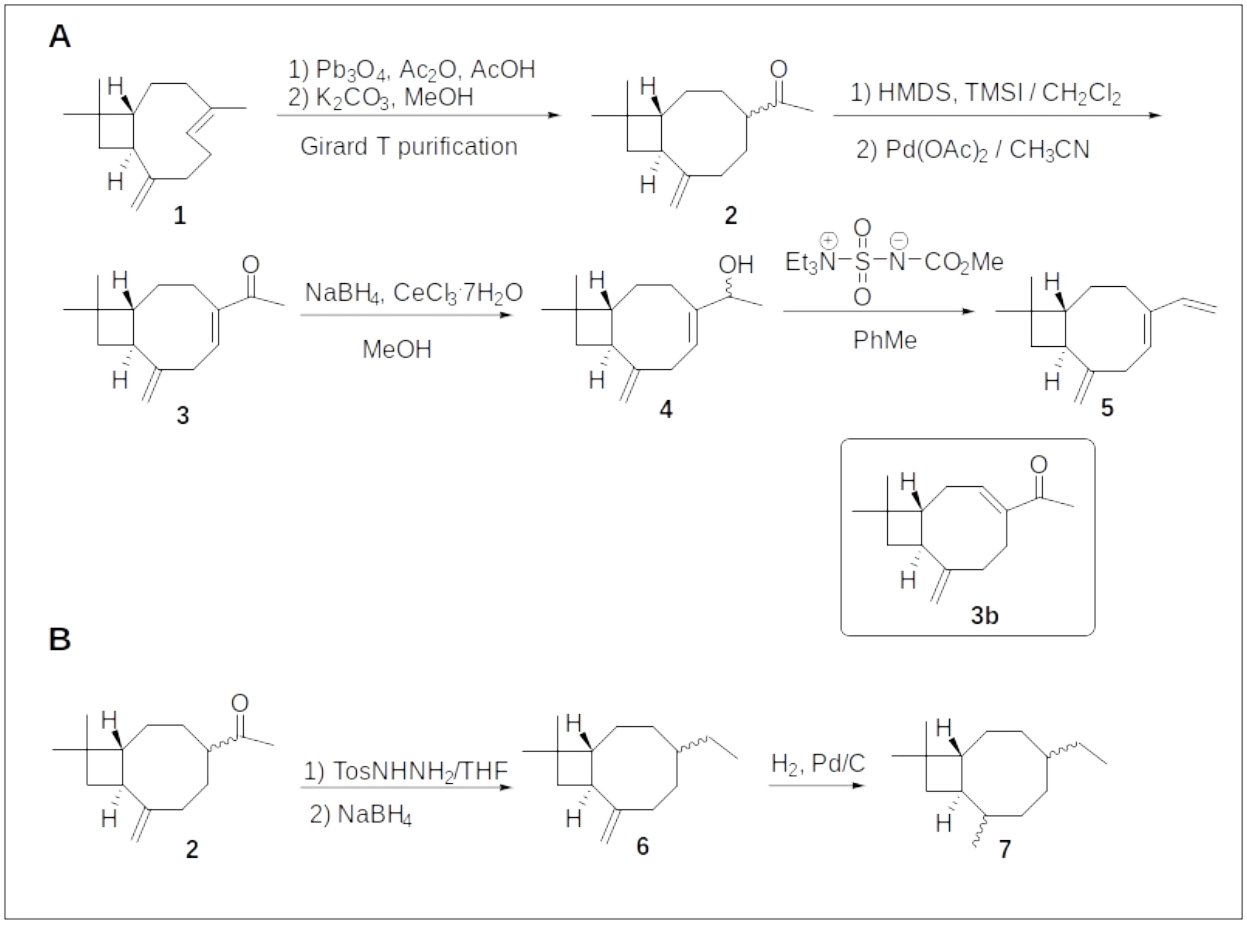
In an effort to elucidate the ^{1}H NMR spectrum further, a second sample was partially purified by liquid chromatography, and run in deuterobenzene, resulting in better resolution of some of the multiplets (Figure S9, Table 1). In this solvent, one of the bisallylic protons appeared as a dd at 2.73 ppm (J = 12.6, 7.2 Hz), although the second bisallylic proton still showed as a featureless hump at 3.03 ppm. Furthermore, one of the two protons of the allylic methylene at 2.36 ppm

was now revealed as a ddd, with a large geminal coupling of 13.4 Hz, and two additional couplings of 8.7 and 3.2 Hz respectively, confirming the connection of the allylic methylene to an adjacent methylene group. COSY indicated that the other geminal allylic methylene proton corresponded to an amorphous multiplet at 2.17 ppm, whereas the protons on the adjacent methylene were in indecipherable multiplets at ~1.7 and 1.29 ppm. Because of the presence of contaminants and overlap of signals, identification and assignment of several protons was still unclear.

In considering a synthesis of **VIII**, comparison of its proposed structure to that of (*E*)-β-caryophyllene (**1)** showed significant structural similarities as described above, including the cyclobutane ring with a geminal dimethyl and the placement of the exomethylene, and possibly the relative configuration of the two stereogenic centers. Thus, we reasoned that oxidation of the trisubstituted double bond of **1** followed by rearrangement of the resulting epoxide and ring contraction with extrusion of one carbon from the ring to serve as the precursor to the vinyl group (a possible semipinacol-type rearrangement), might provide a short route to one stereoisomer of the proposed structure. Such an oxidation-ring contraction sequence had been described previously, via lead tetraacetate oxidation of **1**.[16,17] The reported oxidation produced a complex mixture of products, two of which were the diastereomeric ketones **2** (Scheme 1A), with a combined yield of ~20%. We further reasoned that this low yield in the first step would be compensated for by the facts that the starting materials were cheap, the number of additional steps required to convert the ketones **2** to leptotriene should be minimal, and the ketones **2** could be readily recovered in multigram scale from the complex reaction mixture by selectively derivatizing the ketones with (carboxymethyl)trimethylammonium chloride hydrazide (Girard's

T reagent) to create water-soluble hydrazones, from which the remaining hydrophobic contaminants could be easily separated by solvent extraction. Furthermore, the ketones **2** could easily be reduced to the fully-saturated derivative **7** (Scheme 1B) of the proposed structure **VIII** which would essentially confirm the structure and possibly also the absolute configuration.

Scheme 1. A) Synthesis of Leptotriene (5) from (-)-(*E*)- -Caryophyllene (1); B) Conversion of Ketones 2 to Saturated Hydrocarbons 7



Thus, heating (-)-(*E*)-*β*-caryophyllene (**1**) with Pb_3O_4 or lead tetraacetate in a mixture of acetic acid and acetic anhydride at 60 °C gave, after hydrolysis, 14 products including ketones **2** as a 1:1 mixture of diastereomers and 12 non-ketonic compounds (Scheme 1A).[16,17] The desired

ketones **2** were converted to water-soluble hydrazones with Girard's T reagent,[18,19] and the remaining unreacted compounds were readily removed by extraction of the mixture with hexane. The derivatives were then hydrolyzed with H_2SO_4, providing the ketones **2** in ~85% purity by GC**.** Further purification by flash chromatography on silica gel gave pure ketones **2** as a 1:1 mixture of diastereomers.

Reaction of ketones **2** with *p*-toluenesulfonyl hydrazide in THF and subsequent reduction with sodium borohydride[20] gave monounsaturated compounds **6** which were hydrogenated over 10% palladium on charcoal to give the saturated hydrocarbons **7** (Scheme 1B). GC analysis of **7** showed the same four peaks as those obtained on hydrogenation of the natural unknown compound in similar relative amounts (Figure S1) and with the same mass spectra (Figures S2-S5).

The key transformation of ketones **2** to enone **3** was achieved after considerable experimentation (See Supporting Information). Ultimately, the desired, thermodynamically more stable enol ether of **2** was formed with high selectivity by treatment of **2** with trimethylsilyl iodide (TMSI) and hexamethyldisilazane (HMDS) in CH_2Cl_2 at room temperature.[21-23] Saegusa oxidation[24,25] of the enol then produced the desired enone **3**. With the key intermediate enone **3** in hand, Luche reduction with $NaBH_4$ and $CeCl_3$[26] gave allylic alcohol **4** as a pair of diastereomers, which was of no consequence because the alcohol stereocenter was eliminated in the next step. Alcohol **4** underwent dehydration with Burgess' reagent[27,28] to provide the desired product **5**. The GC retention times and spectra of **5** matched those of the insect-produced compound, proving the structure and its relative configuration unambiguously. The absolute configuration was determined by analysis of **5**, and the four products from its Pd-catalyzed hydrogenation, on a

chiral stationary phase GC column. The retention times of the insect-produced **5**, and synthetic **5** derived from (-)-(*E*)- -caryophyllene (**1**), and their four reduction products, all matched exactly (*L. zonatus*, Figures S10A-B, *L. occidentalis*, Figures S11-12), providing strong evidence that the absolute configuration of the insect-produced compound corresponded to that in **1**. Thus, the proposed *Leptoglossus* pheromone component was fully identified as (1*S*,8*R*,*E*)-9,9-dimethyl-2-methylene-5-vinylbicyclo[6.2.0]dec-4-ene, and given the name "leptotriene" (**5**).

In coupled GC-electroantennogram assays, the synthetic leptotriene elicited electroantennographic responses from antennae of males and females of both *L. zonatus* and *L. occidentalis*, of similar magnitudes to those elicited by the insect-produced compound (Figures S13-14), further verifying the identification. Furthermore, leptotriene alone has been shown to attract males and females of both species in preliminary field trials in California and Spain respectively. Thus this compound is likely a component of the male-produced aggregation-sex pheromones for both species. However, leptotriene is only one component of the blends of aldehydes, esters, and terpenoids produced by the bugs (10 others from male *L. zonatus* and five others from *L. occidentalis*; see Supporting Information Table S1 for details). Thus, the subsets of compounds which are both necessary and sufficient to attract congeners, are the subject of ongoing bioassays, which will be fully reported in due course.

The [6.2.0] leptotriene skeleton with its pendant vinyl group is unprecedented in natural products, and it is not obvious how it might be biosynthesized. The biosynthetic pathway likely shares some steps with that of (*E*)- -caryophyllene (**1**) given their structural similarities. However, proposals for the steps leading to the pendant vinyl group, e.g. by cyclization of a

farnesyl diphosphate analogue with head-to-head linkage or rearrangement of a β-caryophyllene precursor, are speculative at best.

EXPERIMENTAL SECTION

Insect Rearing and Collection of Headspace Volatiles. A colony of *Leptoglossus zonatus* was started from adults collected from infested pistachio and pomegranate orchards near Fresno, California. Cohorts of bugs were reared in screen cages in an environmentally-controlled chamber (temp 21 ± 2 °C, ~50% relative humidity (RH), l6L:8D). Bugs were fed pesticide-free green beans, zucchini squash, and raw almonds, as well as juniper sprigs collected from the University of California, Riverside, Botanical Gardens. As nymphs reached the 5th instar, cohorts were separated into small groups and reared separately in 500 mL canning jars with green beans and almonds. Within 2 days of these nymphs molting to adults, they were sexed, and individual bugs were reared in canning jars until 16 days after their final molt, after which they were considered sexually mature and used for collection of headspace odors.

A colony of *L. occidentalis* was reared in the Forest Pest and Disease Laboratory of the University of Valladolid (Palencia, Spain), from adults collected by forestry agents in Castile and Leon region (Spain) in fall and in a *P. pinea* clone bank ("El Molinillo", Tordesillas, Valladolid, Spain) in summer. Bugs were reared and kept under standard laboratory conditions (21 ± 2 °C; 40% RH) and natural daylight in rectangular breeding boxes (47.5 × 47.5 × 93 cm, 160 micron mesh) (Entomopraxis, Barcelona, Spain). *Ad libitum* shelled *P. pinea* kernels were provided as food, while young potted *Pinus halepensis* Mill. (2–3 years old) were provided as sources of water and ovipositional substrate. Eggs and nymphs were kept in small groups until their final

molt, when they were sexed and kept in separate boxes. Sexually mature males were used for collection of headspace odors.

Collections of *L. zonatus* volatiles were carried out by placing groups of 5-10 sexually mature adult male or female bugs in modified 500 mL wide-mouth screwcap canning jars, with 2-3 green beans for nutrition and water. The lids of the jars were replaced with Teflon discs fitted with Swagelok bulkhead unions (Swagelok Co.), for connection of inlet and outlet tubes. Charcoal-filtered air was pulled through the jars at 500 mL/min, and odors were trapped on activated charcoal collectors made from ~ 10-cm-long glass tubes (0.5 cm ID) with a 1-cm-long bed of activated charcoal (50–200 mesh; Fisher Scientific) held in place by glass wool plugs. A collector was attached to the outlet of each aeration chamber via one of the two bulkhead unions. Collectors were changed every 72-96 h, with the trapped volatiles being recovered by elution of the collectors with 0.5 mL of hexane. Between October 2018 and May 2019, a total of 76 aerations was carried out.

Collections of *L. occidentalis* volatiles were carried out in Spain by placing groups of 1 – 21 sexually mature male or female adults in a 2000 mL wide neck flange flask with a lid with 5 sockets hermetically bonded by a retaining clip (SciLabware Ltd.), with a wet paper towel as water source. Air was pulled by vacuum at 5 L/min through an activated charcoal scrubber (18 cm long x 4 cm ID, 1-4 mm granular activated charcoal), then through the flask, with volatiles being trapped on a collector made from a Pasteur pipette (4 mm i.d.) containing purified Porapak Q (50-80 mesh, 200 mg; SigmaAldrich Co.) held between glass wool plugs. Volatiles were collected for 24-48 h, then collectors were wrapped in aluminum foil and sent to the UK for analysis. A total of 318 collections was made between 2013-2021.

Analyses of Headspace Volatiles. Extracts of volatiles from *L. zonatus* were analyzed by coupled gas chromatography–mass spectrometry (GC–MS) in splitless mode, using an Agilent 7820A GC interfaced to a 5977E mass selective detector. The GC was equipped with a DB-5 column (30 m × 0.25 mm id. × 0.25 μm film; Agilent Technologies), with helium carrier gas and a temperature program of 40 °C/1 min, increased 10 °C/min to 280 °C, and held for 10 min; the injector and transfer line temperatures were set to 280 °C. Extracts were assessed for presence of the unidentified male compound. Extracts were also analyzed on a Cyclodex B chiral stationary phase GC column (30 m x 0.25 mm i.d., J&W Scientific), with an oven program of 50 °C/1 min, then increased 3 °C/min to 220 °C.

Collected volatiles from *L. occidentalis* on Porapak filters were eluted with CH_2Cl_2 (1 mL; Pesticide Residue Grade) and analyzed by GC-MS using a Varian 3700 GC interfaced to a Saturn 2200 ion-trap MS (Varian, now Agilent Technologies). Columns (30 m x 0.25 mm i.d., 0.25 μm film thickness) were coated with polar DBWax (Supelco) or non-polar VF5 (Varian/Agilent). The carrier gas was helium (1 mL/min), injection splitless (220 °C) and the oven temperature was held at 40 °C for 2 min then programmed at 10 °C/min to 250 °C and held for 5 min.

Collections of volatiles from *L. occidentalis* were also analyzed by enantioselective GC-FID using an Agilent 6890 GC with a Chirasil-Dex CB column (25 m x 0.32 mm i.d.; Chrompack, now Agilent Technologies), with helium carrier gas (2.4 mL/min) and splitless injection (200 °C). The oven temperature was held at 50 °C for 2 min and then programmed at 5 °C/min to 200 °C.

Coupled gas chromatography-electroantennogram detection analyses (GC-EAD) for *L. zonatus* were carried out on an HP 5890 Series II GC (Agilent) fitted with a flame ionization detector (FID) and a DB-5MS column (30 m + 10m DuraGuard x 0.25mm i.d. x 0.25 μm film thickness; Agilent). The column head pressure was held at 200kPa, and injections onto the column were in splitless mode (250 °C). The oven was held at 50 °C for 1 min and then programmed at 10 °C/min to 280 °C, then held for 10 min. The effluent of the column was split to the FID (280 °C) and a heated transfer line (280 °C) with a glass X-cross, with helium being added at the fourth arm at 3 mL/min as makeup gas in order to maintain the flowrate to both detectors. Effluent passing through the transfer line was directed into a humidified air stream flowing at 650 mL/min in a glass tube (15 mm ID), which then passed over the *L. zonatus* antennal preparation.

Electroantennogram preparations for *L. zonatus* were made by filling two glass capillary electrodes with saline solution (7.5 g NaCl, 0.21 g $CaCl_2$, 0.35 g KCl, and 0.20 g $NaHCO_3$ in 1 L Milli-Q purified H_2O). Each electrode contained a 0.2 mm diam gold wire for connection to a custom-built amplifier. Antennae were prepared by removing the terminal three segments and the distal tip with a razor. The antenna was then placed between the two glass electrodes. Signals from both the FID and the amplifier were recorded using Peak-Simple software (SRI International).

GC-EAD analyses for *L. occidentalis* were carried out on a HP6890 GC (Agilent) fitted with a flame ionization detector (FID) and fused silica capillary columns (30 m x 0.32 mm i.d. x 0.25 μm film thickness) coated with DBWax and DB5 (Supelco). Injections onto the DBWax column were in splitless mode (220 °C), with helium carrier gas (2.4 mL/min), and the oven temperature was held at 50 °C for 2 min and then programmed at 20 °C/min to 250 °C and held for 3 min. The effluents of the two columns were combined with a glass press-fit Y connector (Agilent)

connected to a second Y connector with deactivated fused silica tubing (10 cm x 0.32 mm i.d.). One arm of this connector was connected with deactivated fused silica tubing (50 cm x 0.32 mm i.d.) to the FID (250 °C) and the other to an equal length of deactivated silica tubing passing through a heated transfer line (250 °C; Syntech) into a glass tube (4 mm i.d.) through which air passed (500 mL/min) over the EAG preparation. Both the FID and EAG signals were collected and analyzed with EZChrom software (Elite v3.0; Agilent Technologies).

EAD preparations for *L. occidentalis* were made with glass microelectrodes filled with saline (0.1M KCl with 1% polyvinylpyrrolidone) attached to silver wire electrodes held by integrated electrode holders in micromanipulators, and signals were amplified with an INR-2 amplifier (Syntech). The head of a bug was excised, and the indifferent electrode inserted into the back of the head. The distal tip of one antenna was inserted into the recording electrode and EAG responses were amplified x10.

Purification of Leptotriene. A composite sample of the 50 *L. zonatus* extracts that contained the highest amounts of the unknown was concentrated almost to dryness under a stream of nitrogen to remove most of the CH_2Cl_2. Hexane was added (0.5 mL) and the extract was concentrated down again to ~100 µL, then loaded onto a column of 500 mg of silica gel that had been oven-dried at 120 °C for 2 h, cooled in a sealed container, and wetted with hexane immediately before use. The column was eluted with 10 x 0.25 mL pentane, 5 x 0.5 mL pentane, and finally with 2 mL of diethyl ether. Leptotriene eluted in fractions 5-10, with fractions 7, 8, and 9 being 60-90% pure. Fractions 8 and 9 were combined and concentrated to <10 µL, and subjected to preparative gas chromatography, on a DB-5 Megabore column (25 m x 0.53 mm ID,

5 μ film, J&W Scientific). The sample was injected splitless over ~ 15 sec, with an injector temperature of 200 ºC. The GC oven was programmed from 50-100 ºC at 20 ºC/min, then at 4 ºC/min to 250 ºC. The column effluent was split between a 0.1 mm ID uncoated fused silica column going to the FID detector of the GC, and a 0.53 mm ID column going to the collection port, which was maintained at 250 ºC. The column effluent was collected in dry-ice cooled glass capillaries. The collected compound was rinsed from the capillary with CD_2Cl_2, transferred to a 1 mm OD NMR tube, and NMR spectra obtained on an Avance 500 spectrometer, taking ^1H, COSY, and NOESY spectra. A second sample purified by the same procedure some months later was run on an Avance III 700 instrument in a 3 mm OD tube.

General Synthetic Experimental Procedures. Optical rotation measurements were made with an Autopol IV digital polarimeter and a T32 microsample cell (2.5 mm i.d. × 50 mm length; 250 μL volume; Rudolph Research Analytical) at 25 ºC, with the light source set at 589 nm. IR spectra were obtained on a Thermo-Nicolet 6700 FTIR spectrometer with neat liquid or solid samples. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance NEO 400 (400 and 100.5 MHz respectively) spectrometer, as $CDCl_3$ solutions (compounds **2**, **3**, and **4**) or CD_2Cl_2 solution (compound **5**). ^1H NMR chemical shifts are expressed in ppm relative to residual $CHCl_3$ (7.26 ppm) or CH_2Cl_2 (5.32 ppm). ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (77.16 ppm) or CD_2Cl_2 (53.84 ppm). Mass spectra were obtained on an Agilent 6890 GC fitted with a DB-17 column (30 m × 0.25 mm i.d.), interfaced to an Agilent 5973 mass selective detector, run in electron impact ionization mode at 70 eV. Accurate mass measurements were run by Dr. Felix Grun, Mass Spectrometry Facility, Department of Chemistry, University of California, Irvine,

using a Waters (Micromass) GCT GC-MS with chemical ionization (ammonia), in positive ion mode.

Flash chromatography was carried out with 230-400 mesh silica gel. Unless otherwise stated, reactions were carried out in oven-dried glassware under argon atmosphere. Solutions of crude products were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure by rotary evaporation. Solvents (Optima grade, Fisher Scientific) were used as purchased, with the exception of tetrahydrofuran, which was distilled from sodium-benzophenone ketyl.

1-((1*R*,8*S*)-10,10-Dimethyl-7-methylenebicyclo[6.2.0]decan-4-yl)ethanone (2). Trilead tetraoxide (137.12 g, 200 mmol) was added in portions to a mixture of (-)-*trans*-*β*-caryophyllene (TCI America, Product Number C0796, Purity > 90.0% (GC), 40.87 g, 200 mmol), acetic acid (366 mL) and acetic anhydride (127 mL), keeping the temperature below 60 °C. The reaction mixture was then stirred at 60 °C for 1 h, during which time the red slurry became a clear light yellow solution. After cooling to room temperature (rt), the solution was poured into H_2O and extracted with hexanes. The organic layer was stirred with saturated Na_2CO_3 solution for 30 min, then washed with H_2O and brine, and dried. After concentration, the residue was dissolved in MeOH (500 mL) and K_2CO_3 (69.11 g, 500 mmol) was added. The mixture was stirred overnight, poured into H_2O, and extracted with hexanes. The organic layer was washed with H_2O and brine, dried, and concentrated, and the residue was heated with Girard's T reagent ((carboxymethyl)trimethylammonium chloride hydrazide, 24.0 g) in a mixture of EtOH (384 mL) and acetic acid (38.4 mL) at 60 °C for 1 h. The cooled solution was neutralized with 1M NaOH (670 mL). After most of the EtOH was removed by rotary evaporation, the aqueous residue was extracted with hexanes to remove the unreacted non-ketone material. Sufficient 6 M

H_2SO_4 was added to bring the remaining aqueous solution to pH 1, and the mixture was stirred at rt for 30 min to hydrolyze the Girard's T hydrazone and regenerate ketones **2**. The reaction mixture was extracted with hexanes, and the organic layer was washed with saturated $NaHCO_3$, H_2O, and brine, dried, and concentrated. The ketones **2** were obtained ca. 85% pure by GC, as a 1:1 mixture of diastereomers, which was further purified by flash chromatography (hexanes/EtOAc = 95/5) to give **2** as a colorless liquid (4.86 g, 11%). IR (neat) ν_{max} 3076, 2949, 2928, 2859, 1709, 1635, 1462, 1365, 1352, 1163, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.83 (s, 2H), 4.78 (m, 1H), 4.58 (t, *J* = 2.2 Hz, 1H), 2.67 (m, 1H), 2.50 (m, 1H), 2.21-2.44 (m, 5H), 2.14 (m, 1H), 2.12 (s, 6H = 3H + 3H), 1.92-2.02 (m, 2H), 1.73-1.85 (m, 4H), 1.21-1.69 (m, 12H), 1.02 (s, 3H), 1.00 (s, 6H = 3H + 3H), 0.98 (s, 3H). The ^1H NMR spectrum was in agreement with that previously reported;[16] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.96 (2C), 154.36, 151.72, 109.81, 109.29, 54.36, 53.15, 51.09, 48.29, 42.49, 40.99, 40.85, 36.51, 35.89, 33.78, 33.61 (2C), 31.08, 30.20, 30.17, 29.51, 28.63, 28.13, 28.00, 27.43, 25.42, 22.71, 22.28, 21.85; EIMS (*m/z*, rel. intensity) earlier eluting peak: 41 (48), 43 (92), 55 (23), 71 (100), 79 (71), 91 (45), 93 (64), 95 (59), 107 (41), 121 (94), 135 (25), 149 (27), 162 (21), 177 (54), 187 (21), 205 (19), 220 (M^+, 5); later eluting peak: 41 (43), 43 (87), 55 (22), 71 (100), 79 (73), 91 (45), 93 (62), 95 (59), 107 (40), 121 (84), 135 (23), 149 (21), 164 (26), 177 (48), 187 (17), 205 (15), 220 (M^+, 10); HRMS *m/z* 221.1911 [M+H+] (calcd for $C_{15}H_{25}O$, 221.1905).

1-((1*R*,8*S*,*E*)-10,10-Dimethyl-7-methylenebicyclo[6.2.0]dec-4-en-4-yl)ethanone (3). Hexamethyldisilazane (HMDS, 12.5 mL, 60 mmol) was added to a solution of ketones **2** (4.41 g. 20 mmol) in CH_2Cl_2 (50 mL), followed by trimethylsilyl iodide (6.8 mL, 50 mmol). The reaction mixture was stirred at rt for 1.5 h, diluted with hexanes, and poured into saturated aq. $NaHCO_3$

solution. The organic layer was washed with H_2O and brine, and dried. The crude silyl enol ether was dissolved in CH_3CN (100 mL) and added to $Pd(OAc)_2$ (6.74 g, 30 mmol) and stirred overnight. The reaction mixture was diluted with ether and filtered through celite. The crude product was purified by flash chromatography (hexanes/EtOAc = 25/1) to give enone **3** as a white waxy solid (1.75 g, 40%). $[\alpha]_D^{25}$ +49.4 (*c* 2.67, CH_2Cl_2); IR (neat) ν_{max} 3073, 2951, 2920, 2888, 2858, 1655, 1629, 1448, 1376, 1348, 1271, 1221,1026, 973, 935, 885 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70 (dd, *J* = 9.6, 7.2 Hz, 1H), 4.86 (m, 1H), 4.59 (m, 1H), 3.25 (t, *J* = 10.6 Hz, 1H), 2.92 (dd, *J* = 12.4, 7.2 Hz, 1H), 2.71 (m, 1H), 2.45 (m, 1H), 2.30 (s, 3H), 2.20 (m, 1H), 1.62-181 (m, 4H), 1.30 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.38, 151.37, 143.82, 141.07, 109.58, 51.50, 40.09, 38.32, 36.80, 33.15, 30.38, 28.55, 25.65, 23.31, 23.18; EIMS (*m/z*, rel. intensity): 41 (45), 43 (100), 53 (16), 69 (67), 77 (28), 79 (32), 91 (73), 105 (41), 107 (40), 119 (78), 135 (37), 147 (43), 151 (41), 161 (15), 175 (80), 185 (7), 203 (27), 218 (M^+, 46); HRMS *m/z* 218.1678 [M+] (calcd for $C_{15}H_{22}O$, 218.1671).

1-((1*R*,8*S*,*E*)-10,10-Dimethyl-7-methylenebicyclo[6.2.0]dec-4-en-4-yl)ethanol (4). Enone **3** (1.75 g, 8.0 mmol) and $CeCl_3 \cdot 7H_2O$ (2.98 g, 8.0 mmol) were dissolved in MeOH (32 mL). Sodium borohydride (0.30 g, 8.0 mmol) was added and the mixture was stirred at rt for 30 min, then poured into dilute HCl and extracted with ether. The organic layer was washed with H_2O and brine, dried, and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc = 9/1) to give allylic alcohol **4** as a colorless liquid (1.69 g, 96%, as a mixture of diastereomers, which did not separate on either DB-5 or DB-17 GC columns). However, the ratio was immaterial as the stereogenic center was eliminated in subsequent steps. IR (neat) ν_{max} 3329, 3073, 2949, 2929, 2860, 1635, 1451, 1366, 1286, 1060, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 400

MHz) δ 5.51 (t, *J* = 8.4 Hz, 1H), 4.76 (m, 1H), 4.48 (m, 1H), 4.24 (q, *J* = 6.4 Hz, 1H), 3.06 (m, 1H), 2.68 (m, 1H), 2.57 (m, 1H), 2.20-2.27 (m, 2H), 1.74-1.84 (m, 2H), 1.62-1.72 (m, 2H), 1.50 (br s, 1H), 1.42 (m, 1H), 1.29 (d, *J* = 6.4 Hz), 1.28 (d, *J* = 6.4 Hz), total 3H, 0.973 (s), 0.970 (s), 0.966 (s), 0.962 (s), total 6H; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.72 (minor), 153.47 (major), 145.30 (minor), 144.92 (major), 123.19 (minor), 122.87 (major), 107.65 (overlap), 72.98 (minor), 72.86 (major), 51.51 (minor), 51.24 (major), 40.14 (major), 39.90 (minor), 38.68 (minor), 38.40 (major), 35.36 (major), 35.16 (minor), 33.13 (overlap), 30.38 (overlap), 29.59 (minor), 29.40 (major), 25.10 (minor), 25.04 (major), 23.36 (major), 23.29 (minor), 22.29 (major), 22.20 (minor); EIMS (*m/z*, rel. intensity): 41 (58), 43 (63), 55 (28), 69 (65), 77 (40), 79 (69), 81 (47), 91 (100), 93 (64), 105 (82), 106 (55), 107 (54), 117 (41), 119 (50), 121 (46), 131 (61), 133 (39), 135 (36), 145 (24), 147 (21), 149 (28), 153 (27), 159 (47), 177 (38), 187 (28), 202 (12), 220 (M^+, 13); HRMS *m/z* 220.1821 [M+] (calcd for $C_{15}H_{24}O$, 220.1827).

(1*S*,8*R*,*E*)-9,9-Dimethyl-2-methylene-5-vinylbicyclo[6.2.0]dec-4-ene (5). Allylic alcohol **4** (1.97 g, 8.94 mmol) in toluene (18 mL) was added dropwise to a solution of Burgess' reagent (2.34 g, 9.83 mmol) in toluene (18 mL). The reaction mixture was stirred at rt for 30 min, then at 50 °C for 30 min. After cooling to rt, the reaction mixture was poured into brine and extracted with hexanes. The combined organic layer was washed with H_2O and brine, dried, and concentrated. The crude product was purified by flash chromatography (hexanes), followed by Kugelrohr distillation (0.25 torr, 80 °C) to give triene **5** as a colorless liquid (0.43 g, 24%). $[\alpha]_D^{25}$ +50.2 (*c* 2.67, CH_2Cl_2); IR (neat) ν_{max} 3086, 2950, 2932, 2862, 1630, 1467, 1367, 1285, 989, 882, 855 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 6.30 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.56 (t, *J* = 8.4 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 4.77 (m, 1H), 4.52 (m, 1H), 3.12

(m, 1H), 2.82 (dd, *J* =13.0, 7.4 Hz, 1H), 2.48-2.56 (m, 2H), 2.33 (m, 1H), 1.64-1.81 (m, 4H), 1.39 (m, 1H), 0.98 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 154.02, 141.08, 140.41, 130.83, 111.13, 108.08, 51.99, 40.60, 38.56, 36.51, 33.44, 30.61, 28.29, 24.11, 23.60; EIMS (*m/z*, rel. intensity): 41 (45), 53 (18), 69 (30), 79 (58), 91 (100), 105 (64), 117 (78), 131 (85), 145 (42), 159 (71), 173 (15), 187 (41), 202 (M^+, 43); HRMS *m/z* 202.1720 [M+] (calcd for $C_{15}H_{22}$, 202.1721).

(1*S*,8*R*)-5-Ethyl-9,9-dimethyl-2-methylenebicyclo[6.2.0]decane (6). A solution of ketones **2** (0.220 g; 1 mmol) and *p*-toluenesulfonyl hydrazine (0.279 g; 1.5 mmol) in anhydrous THF (5 mL) was heated with stirring at reflux for 2 h until ketones **2** could not be detected by GC analysis. The mixture was cooled and sodium borohydride (0.190 g; 5 mmol) was added. Once the effervescence had subsided, the mixture was heated at reflux for a further 2 h. The reaction mixture was cooled, diluted with petroleum spirit (bp 40-60 ºC; 20 mL) and extracted three times with brine, and the combined brine extracts were re-extracted with petroleum spirit (10 mL). The combined petroleum spirit extracts were dried over anhydrous magnesium sulfate and purified by flash chromatography on silica gel (12 g) in hexane followed by Kugelrohr distillation (0.04 torr, 60 ºC) to give **6** (0.10 g, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.76 (br s, 1H), 4.74 (br s, 1H), 4.73 (t, *J* = <1 Hz, 1H), 4.51 (t, *J* = 2.5 Hz, 1H), 2.71 (q, *J* = 10 Hz, 1H), 2.43 (m, 1H), 2.20 (m, 2H), 2.07 (m, 1H), 1.94 (dd, *J* = 10, 8.5 Hz, 1H), 1.76 (m, 2H), 1.55 (m, 6H), 1.47 (m, 4H), 1.22 (m, 12H), 1.01 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.87 (t, *J* = 7 Hz, 3H), 0.86 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.06, 153.36, 108.09, 107.75, 54.24, 51.17, 42.39, 40.82, 40.80, 40.38, 36.43, 35.87, 35.74, 35.19, 33.61, 33.50 (2H), 31.80 (2H), 31.73, 30.92, 30.18, 30.06, 29.03, 27.40, 25.64, 22.68, 21.81, 12,13, 11.80; EIMS (*m/z*, rel. intensity): 41 (60),

51 (13), 53 (13), 55 (26), 65 (17), 67 (65), 68 (10), 69 (23), 77 (41), 79 (81), 80 (13), 81 (58), 82 (16), 91 (43), 93 (78), 94 (21), 95 (71), 105 (12), 107 (58), 108 (21), 109 (41), 121 (100), 122 (29), 123 (21), 135 (40), 136 (15), 149 (12), 150 (12), 163 (18), 177 (23), 191 (23), 206 (M^+, 2).

(1*R*,8*R*)-5-Ethyl-2,9,9-trimethylbicyclo[6.2.0]decane (7). Monoene **6** (0.050 g; 0.25 mmol) was dissolved in hexane (5 mL) with 10% palladium on charcoal (10 mg) and stirred under a positive pressure of hydrogen for 3 h. The suspension was filtered through Celite, chromatographed on silica gel (10 g) in hexane and Kugelrohr distilled (0.04 torr, 60 ºC) to give **7** (0.030 g; 60%). The mass spectra of the four reduction products are shown in Figures S2-S5, and the ^{1}H and ^{13}C NMR spectra, respectively, of the mixture in Figures S26-27.

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: Supporting information includes experimental details of attempted transformation of ketones **2** into enone **3**, a list of compounds identified from extracts from male *Leptoglossus zonatus* and *L. occidentalis*, GC-MS trace of the four products from hydrogenation and their mass spectra, NMR spectra of insect-produced and synthetic leptotriene and all synthetic intermediates, GC traces of natural and synthetic leptotriene, and their reduction products, on a chiral stationary phase column, and coupled gas chromatography-electroantennogram traces of an extract of volatiles from *Leptoglossus zonatus*, and synthesized leptotriene, and NMR spectra of isolated and synthesized compounds.

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