NATURAL PRODUCTS

Discovery of the Aggregation Pheromone of the Brown Marmorated Stink Bug (*Halyomorpha halys*) through the Creation of Stereoisomeric Libraries of 1-Bisabolen-3-ols

Ashot Khrimian,^{*,†} Aijun Zhang,[†] Donald C. Weber,[†] Hsiao-Yung Ho,[‡] Jeffrey R. Aldrich,^{†,§} Karl E. Vermillion,[⊥] Maxime A. Siegler,^{||} Shyam Shirali,[†] Filadelfo Guzman,[†] and Tracy C. Leskey[∇]

[†]U.S. Department of Agriculture, Agricultural Research Service, Beltsville Area, IIBBL, Maryland 20705, United States

[‡]The Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan 115

[⊥]U.S. Department of Agriculture, Agricultural Research Service, NCAUR, Peoria, Illinois 61604, United States

^{II}Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, United States

^VU.S. Department of Agriculture, Agricultural Research Service, AFRL, Kearneysville, West Virginia 25430, United States

Supporting Information

ABSTRACT: We describe a novel and straightforward route to all stereoisomers of 1,10-bisaboladien-3-ol and 10,11-epoxy-1-bisabolen-3-ol via the rhodium-catalyzed asymmetric addition of trimethylaluminum to diastereomeric mixtures of cyclohex-2-enones 1 and 2. The detailed stereoisomeric structures of many natural sesquiterpenes with the bisabolane skeleton were previously unknown because of the absence of stereoselective syntheses of individual stereoisomers. Several of the bisabolenols are pheromones of economically important pentatomid bug species. Single-crystal X-ray crystallography of underivatized triol 13 provided unequivocal proof of the relative and absolute configurations. Two of the epoxides, (3S,6S,7R,10S)-10,11-epoxy-1-bisabolen-3-ol (3) and



(3R,6S,7R,10S)-10,11-epoxy-1-bisabolen-3-ol (4), were identified as the main components of a male-produced aggregation pheromone of the brown marmorated stink bug, *Halyomorpha halys*, using GC analyses on enantioselective columns. Both compounds attracted female, male, and nymphal *H. halys* in field trials. Moreover, mixtures of stereoisomers containing epoxides 3 and 4 were also attractive to *H. halys*, signifying that the presence of additional stereoisomers did not hinder attraction of *H. halys* and relatively inexpensive mixtures can be used in monitoring, as well as control strategies. *H. halys* is a polyphagous invasive species in the U.S. and Europe that causes severe injury to fruit, vegetables, and field crops and is also a serious nuisance pest.

• he bisabolane skeleton is a recurring structural motif in the semiochemistry of stink bugs (Hemiptera: Pentatomidae). Bisabolene epoxides comprise male-specific pheromones of Nezara viridula^{1,2} and Chinavia (=Acrosternum) spp.^{3,4} The related zingiberene, β -sesquiphellandrene, and α -curcumene constitute part of the *Thyanta pallidovirens* pheromone,⁵ and β sesquiphellandrene was identified as a pheromone component of Piezodorus hybneri.⁶ More recently, two stereoisomeric 1,10bisaboladien-3-ols⁷ were identified as part of the male-produced pheromone of the rice stalk stink bug, *Tibraca limbativentris*,⁸ and 10,11-epoxy-1-bisabolen-3-ol (called "murgantiol") has been reported as an aggregation pheromone of the harlequin bug, *Murgantia histrionica*.^{9,10} As with murgantiol, the relative and absolute configurations of the 1,10-bisaboladien-3-ols from T. limbativentris have not been determined. Reliable assignment of relative configurations across the cyclohexene ring of the murgantiol structure was problematic, and ¹H and ¹³C NMR recordings of murgantiol failed to provide a conclusive answer.

Several related compounds were isolated from the oil of ginger, *Zingiber officinale*, among them a 1,10-bisaboladien-3-ol, called "zingiberenol".¹¹ The latter was assigned a *trans*-configuration based on similarities of its IR spectrum with that of *trans*-p-menth-2-en-1-ol,¹² but the structure was presented as the *cis*-isomer¹¹ and the absolute configuration has not been disclosed. A sex pheromone of the rice stink bug, *Oebalus poecilus*, has recently been also identified as zingiberenol and, more specifically, (1R,4R,1'S)-(1',5'-dimethylhex-4'-enyl)-1-methyl-cyclohex-2-en-1-ol.¹³ The absolute configuration has been assigned based on the correlation to natural zingiberene and similarities of ¹³C NMR spectra of a synthetic mixture containing the pheromone and (R,R)-quercivorol. However, the pheromone of *O. poecilus* has not been synthesized in pure form and

Received: May 6, 2014



Scheme 1. Syntheses of Bisaboladienol Stereoisomers 5–12 by the Reaction of ~1:1 Diastereomeric Mixtures of (6S,7R)-1 and (6R,7R)-1 (Left) and (6S,7S)-2 and (6R,7S)-2 (Right) with Trimethylaluminum (2 equiv) in the Presence of $[Rh(cod)Cl]_2$ (0.05 equiv) and (R)- or (S)-BINAP (0.12 equiv)



characterized, nor has any single stereoisomer of 1,10bisaboladien-3-ol and/or 10,11-epoxy-1-bisabolen-3-ol been synthesized elsewhere to assist identifications.

The brown marmorated stink bug, *Halyomorpha halys* (Stäl), is an invasive pest from Asia, now well established in the mid-Atlantic region and spread to most of the continental U.S. as well as parts of Canada and central Europe. *H. halys* is a polyphagous pest of many crops including tree fruits, vegetables, field crops, and ornamentals, with significant economic damage recorded in the U.S.^{14,15} A monitoring tool to assess the presence, abundance, and seasonal activity of *H. halys* was urgently sought to determine the need for and timing of management actions. In this study, we describe all eight stereoisomers of 10,11-epoxy-1-bisaboladien-3-ol that provided guidance for the identification of a male-produced aggregation pheromone of *H. halys*.¹⁶

RESULTS AND DISCUSSION

Syntheses of Individual Stereoisomers of 1,10-Bisaboladien-3-ol. We used a rhodium-catalyzed asymmetric 1,2addition of organoaluminum compounds to enones¹⁷ to synthesize bisaboladienol intermediates. This catalytic reaction was highly enantioselective (>96% ee), with unsubstituted cyclohex-2-enone providing (R)-1-methyl-2-cyclohexen-1-ol with (S)-BINAP and (S)-1-methyl-2-cyclohexen-1-ol with (R)-BINAP chiral ligands complexed to the rhodium.¹⁷ We did not find any example of such a reaction with a cyclohex-2-enone substituted at position 4; yet one might anticipate that the diastereotopic face selectivity of this reaction would be dependent on the size and spatial orientation of substituents. Because individual stereoisomers of ketones 1 and 2 were difficult to synthesize,¹⁸ we studied Rh-catalyzed additions of trimethylaluminum with mixtures of these diastereomeric ketones.¹⁹

Thus, the reaction of a $\sim 1:1$ mixture of (6S,7R)-1 and (6R,7R)-1 with trimethylaluminum in the presence of chloro-(1,5-cyclooctadiene)rhodium(I) dimer and (R)-BINAP yielded two easily separable compounds (Scheme 1, left). The major product had a higher retention factor (R_f) by TLC analysis on silica gel eluted with hexane/EtOAc, but a lower retention time by GC analysis on an HP-5 column as compared to the minor product. Including the stereocenter at C-3, 1,10-bisaboladien-3ols can exist in two relative configurations: cis, if the hydroxy group at C-3 and the alkyl group at C-6 are on the same side, and trans, if these groups are on the opposite sides of a plane formed by C-6, C-1, C-2, and C-3. On the basis of the chromatographic parameters, X-ray crystallography, ¹H and ¹³C NMR data, and dehydration to stereochemically defined 1,3,10-bisabolatrienes (see further in the text), the major compound was identified as *cis* and assigned structure 5; the minor product was found to have trans relative configuration and assigned structure 6. The stereochemical course of the trimethylaluminum addition in



Scheme 2. Syntheses of Triols and Epoxy Alcohols Including H. halys Pheromone Components 3 and 4^a

^{*a*}a, AD-mix- α ; b, AD-mix- β ; c, (1) MsCl/Py, (2) KOH/MeOH. Diastereomeric purities were determined by GC analysis on Hydrodex- β -6TBDM* or Chiraldex G-TA[#] columns. Top right: Displacement ellipsoid plot (50% probability level) of triol **13** at 110(2) K.

the presence of (*R*)-BINAP is shown in Scheme 1 (left). Of the two diastereomers, (6S,7R)-1 is the favored isomer because the substituent at position 6 is oriented above the plane formed by C-6, C-1, C-2, and C-3 (*si*-face) and does not cause steric hindrance to the delivery of the methyl group from the *re*-face as postulated in the original report.¹⁷ Thus, the reaction was highly diastereoselective and provided (3*S*,6*S*,7*R*)-stereoisomer **5**. In the case of (6*R*,7*R*)-1, the *re*-face is shielded by the side chain and the *si*-face is intrinsically restricted.

As a result, the Rh-catalyzed addition of trimethylaluminum was disfavored and accompanied by side reactions, including polymerization. Nevertheless, the *re*-face approach was still prevalent over the *si*-face, leading to (3S,6R,7R)-stereoisomer 6, albeit in low yield. Both 5 and 6 were isolated in greater than 95% chemical purities. Because of difficulties in separation of stereoisomers having the same relative (cis/trans) configuration and the ease of separation of *cis* stereoisomers from *trans*, alcohol 5 was cross-contaminated with *cis*-stereoisomer 7, arising from (6R,7R)-1, and alcohol 6 contained some of *trans*-isomer 8 originating from (6S,7R)-1. Diastereomeric ratios of 96:4 for 5/7 and 86:14 for 6/8 were found by integration of H-14 signals in the ¹H NMR spectra available in the Supporting Information.

As expected from the results above, the reaction of a ~1:1 diastereomeric mixture of ketones 1 with trimethylaluminum in the presence of chloro(1,5-cyclooctadiene)rhodium(I) dimer and (S)-BINAP provided stereoisomers 7 and 8 as major products (Scheme 1, left). In accordance with an *si*-face approach postulated in the presence of (S)-BINAP,¹⁷ (6R,7R)-1 was highly favored in this reaction and provided (3R,6R,7R)-alcohol 7. Due to steric constraints, the addition of trimethylaluminum to (6S,7R)-1 was low-yielding and nondiastereoslective (*si*-face/*re*-face, 62:38). In this milieu, *cis*-alcohol 7 was cross-contaminated with *cis*-alcohol 5 and *trans*-alcohol 8 with *trans*-alcohol 6 with

diastereomeric ratios of 91:9 and 89:11, respectively. NMR signals from minor stereoisomers **5** and **6** were easily discernible because they were major products when (R)-BINAP was used.

The four remaining stereoisomers of 1,10-bisaboladien-3-ol were synthesized from a diastereomeric mixture of ketones 2 with (7S)-configuration (Scheme 1, right). The stereochemistries of the addition of trimethylaluminum to the carbonyl group in the presence of chloro(1,5-cyclooctadiene)rhodium(I) dimer and (S)- and (R)-BINAP were essentially governed by the same rules as described for the (7R)-ketones. With (R)-BINAP enabling an re-face approach, (6S,7S)-2 was a preferred diastereomer, leading to the (3S,6S,7S) stereoisomer 9 in 93:7 dr, and the sterically disfavored (6R,7S)-2 provided primarily byproducts but, nonetheless, yielded the (3S,6R,7S)-stereoisomer 10 in 96:4 dr. With (S)-BINAP enabling an si-face approach, (6R,7S)-2 did not sterically hinder the approaching nucleophile and provided the (3R,6R,7S)-isomer 11 in 96:4 dr as the main product, while (6S,7S)-2 led (as a disfavored diastereomer) to the (3R,6S,7S)-stereoisomer 12 in 93:7 dr.

Surprisingly, alcohol 5, a precursor to the main component of the *H. halys* pheromone (3S,6S,7R,10S)-10,11-epoxy-1-bisabolen-3-ol (3), was obtained in 96:4 dr. The efficient production of 5 was due to two factors: first, the highly diastereotopically selective addition of trimethylaluminum to (6S,7R)-1 and, second, because (6R,7R)-1 present in the mixture with (6S,7R)-1 primarily underwent side reactions rather than producing sufficient *cis*-stereoisomer 7 to significantly contaminate isomer 5. Thus, low yields from disfavored reactions allowed ready production of *cis*-stereoisomers of 1,10bisaboladien-3-ols. Conversely, *trans*-stereoisomers were isolated from disfavored reactions because only trace amounts of *trans*isomers were produced from favored reactions. As a result, a pair of diastereomerically enriched stereoisomers (one *cis* and another *trans*) could be synthesized from a single reaction of a diastereomeric mixture of 1 or 2 with trimethylaluminum in rhodium-catalyzed asymmetric 1,2-addition conditions.

Assignment of Relative (cis/trans) Configurations of 1,10-Bisaboladien-3-ols. Assignments of the relative configurations of 1,10-bisaboladien-3-ols are largely absent from the literature. We observed that, regardless of the absolute configuration at C-7, all eight stereoisomers of 1,10-bisaboladien-3-ols could be divided into two groups. Four major stereoisomers from our syntheses, 5, 7, 9, and 11 (Scheme 1), had identical retention factors by TLC analyses (SiO₂; hexane/ EtOAc) that were higher than those of four minor stereoisomers, 6, 8, 10, and 12. GC retention times of the major stereoisomers on an HP-5 column were almost indistinguishable from each other but were shorter than those for the minor stereoisomers, which also eluted as a tight group. Thus, reliably proving a relative configuration for at least one stereoisomer would suffice for assigning relative configurations of all eight stereoisomers of 1,10-bisaboladien-3-ols.

We found that the Sharpless asymmetric dihydroxylation²⁰ of stereoisomer **8** with AD-mix α proceeded smoothly and provided crystalline triol **13** (Scheme 2). After crystallization of **13** using a liquid–liquid diffusion technique, we obtained single crystals suitable for X-ray structure determination using Cu K α radiation and unequivocally proved its absolute configuration. The displacement ellipsoid plot of crystalline **13** presented in Scheme 2 clearly shows a (3*R*,6*S*,7*R*,10*S*)-absolute configuration, underlining that the hydroxy group at C-3 and alkyl group at C-6 are *trans*. This provided direct evidence that the lower TLC $R_{f/}$ longer GC retention time stereoisomers of 1,10-bisaboladien-3ol had the *trans* relative configuration and that this rule must apply to the other minor stereoisomers **6**, **10**, and **12**. Conversely, higher $R_{f/}$ shorter retention time stereoisomers **5**, **7**, **9**, and **11** must have the *cis*-configuration.

In fact, monoterpene analogues of 1,10-bisaboladien-3-ols display the same chromatographic behavior. For instance, individual stereoisomers and mixtures of *cis-p*-menth-2-en-1-ols eluted faster (hence had higher retention factors) during chromatography on SiO₂ using hexane/EtOAc than the corresponding *trans*-isomers.²¹

Comparison of ¹³C NMR spectra of menth-2-en-1-ols and 1,10-bisaboladien-3-ols supported assignments of the relative (and absolute) configurations. Resonances from C-1 and C-2 of stereoisomer 5 occurred at 133.9 and 133.6 ppm, respectively, and the signals from the olefinic carbons of cis-(S,S)-menthenol and cis-(R,R)-menthenol were remarkably similar: 133.5 and 133.8 ppm²² and 133.0 and 133.4 ppm,²³ respectively. In contrast to 5, resonances of C-1 and C-2 in bisaboladienol 6 appeared at 130.5 and 135.1 ppm, analogous to signals of olefinic carbons in trans-(S,R)-menthenol at 131.5 (131.2) and 134.8 (134.5) ppm.^{22,23} Other stereoisomeric 1,10-bisaboladien-3-ols complied with the observed differences in chemical shifts of C-1 and C-2, with *trans*-isomers displaying greater $\Delta \delta$ (3.1–4.6 ppm) than cis-isomers (0.3-1.2 ppm) regardless of the absolute configuration at C-7. In addition, resonances of C-3 and C-15 in trans- and cis-1,10-bisaboladien-3-ols and 10,11-epoxybisabolen-3-ols closely corresponded to those of menth-2-en-1-ols of known configurations.^{22,23}

Absolute Configurations of 1,10-Bisaboladien-3-ols. The absolute configurations of stereoisomers 5-12 were established on the basis of knowledge of their relative configurations and chemical correlations. We used dehydration reactions with phosphorus oxychloride²⁴ to correlate bisabola-

dienol stereoisomers with natural β -sesquiphellandrene and zingiberene and their stereoisomers with established absolute configurations. The reaction of a ~1:1 mixture of **6** and **8** with POCl₃ provided the expected 1,3(15),10-bisabolatriene **14** (= β -sesquiphellandrene) and 1,3,10-bisabolatriene **15** (= zingiberene) (both as mixtures of two diastereomers), plus an unknown sesquiterpene hydrocarbon, in a 43:52:5 ratio (Scheme S1, left, Figure 1, panel b). Major dehydration products **14** and **15** were



Figure 1. Gas chromatograms of bisabolatrienes on Hydrodex- β -6TBDM at 110 °C; H₂ 2.0 mL/min: (a) (6R,7R)-1,3(15),10bisabolatriene (16) from alcohol 7 after removal of zingiberene and other products; (b) from 6 + 8; (c) from alcohol 5.

identified by GC-MS with authentic samples of zingiberene²⁵ and β -sesquiphellandrene,⁵ respectively. Diastereomeric 1,3(15),10-bisabolatrienes and 1,3,10-bisabolatrienes were not separated on an HP-5MS column, but 1,3(15),10-bisabolatrienes were almost baseline-separated on a Hydrodex- β -6TBDM column (Figure 1, panel b). Because 1,3(15),10-bisabolatrienes derived from 6 + 8 had the (7R)-configuration and the natural (-)- β -sesquiphellandrene has the (6R,7S)-configuration,²⁶ the latter could not be used for the identification of the compounds associated with these GC peaks. Hence, we synthesized an individual 1,3(15),10-bisabolatriene with the (7R)-configuration as follows. Stereoisomer 7 was dehydrated with POCl₃ analogously to 6 + 8, and the mixture of hydrocarbons (Scheme S1, left) was subjected to reaction with 4-phenyl-1,2,4-triazoline-3,5-dione, whereupon 1,3,10-bisabolatriene acted as a dienophile to form Diels-Alder adduct 17 (Scheme S1, left).²⁵ Compound 16 (Figure 1, panel a), which did not undergo a Diels-Alder reaction,²⁵ was isolated by chromatography in 97% chemical purity. ¹H and ¹³C NMR spectra of **16** were in good agreement

with those of (6S,7S)-1,3(15),10-bisabolatriene,²⁶ but because 16 was dextrorotatory, this compound was assigned the (6R,7R)configuration, which was then also assigned to 7, from which 16 originated. Finally, because alcohol 7 belonged to the pool of higher R_t /shorter retention time *cis*-1,10-bisaboladien-3-ols, it was assigned the (3R, 6R, 7R) absolute configuration. With the absolute configuration of compound 16 established, we assigned the faster-eluting 1,3(15),10-bisabolatriene the (6R,7R)-configuration and the slower-eluting diastereomer the (6S,7R)configuration (Figure 1, panel b). Determinations of the absolute configurations of the three other 1,10-bisaboladien-3-ols with the (7R)-configuration were carried out using the developed GC method. Thus, reaction of alcohol 5 with POCl₃ (Scheme S1, left) produced a mixture of sesquiterpene hydrocarbons, the GC-FID trace of which is presented in Figure 1, panel c. 1,3(15),10-Bisabolatriene present in that mixture matched the slowereluting compound and, hence, has the (6S,7R)-configuration. Because alcohol 5 has the *cis* relative configuration (higher R_f / shorter retention time), its absolute configuration is (3S, 6S, 7R). Dehydrations of the two *trans* (lower R_f /longer retention time) alcohols 6 and 8 produced expected mixtures of hydrocarbons (Scheme S1, left). Because 6 produced primarily (6R,7R)-1,3(15),10-bisabolatriene (Figure S1, a) and 8 (6S,7R)-1,3-(15),10-bisabolatriene (Figure S1, c), they were assigned (3S,6R,7R)- and (3R,6S,7R)-configurations, respectively.

The dehydration of a ~1:1 mixture of **9** and **11** with (7*S*)configurations provided the expected hydrocarbon mixtures (Scheme S1, right). Interestingly, in this case diastereomeric 1,3,10-bisabolatrienes (= zingiberenes), but not 1,3(15),10bisabolatrienes, were separated on a Hydrodex- β -6TBDM column (Figure S2, panel a).

This simplified our task of assigning their absolute configurations because natural (-)-zingiberene is (6R,7S)-1,3,10-bisabolatriene,^{24,27} and this compound matched (Figure S2, panel b) the slower-eluting of the two stereoisomeric 1,3,10bisabolatrienes. Hence, the faster-eluting compound in Figure S2, panel a, was identified as (6S,7S)-1,3,10-bisabolatriene, or 6epi-zingiberene. Dehydration of alcohol 11 provided zingiberene (Figure S2, panel c), and because 11 is a *cis*-alcohol, its absolute configuration must be (3R,6R,7S). Conversely, alcohol 12 formed 6-epi-zingiberene upon dehydration (Figure S3, panel b), and because it has a *trans* relative configuration, its absolute configuration has to be (3R,6S,7S). Dehydrations of *cis*-alcohol 9 led to 6-epi-zingiberene, and trans alcohol 10 to zingiberene (Scheme S1, right). Hence, these compounds were assigned (3S,6S,7S)- and (3S,6R,7S)-configurations, respectively. The presence of minor diastereomers in the 1,3(15),10-bisabolatriene and 1,3,10-bisabolatriene dehydration products, as determined from GC analyses on a Hydrodex- β -6TBDM column, was ascribed to isomeric 1,10-bisaboladien-3-ols formed along with the main stereoisomers during the Rh-catalyzed addition of trimethylaluminum to ketones 1 and 2.

Syntheses of Stereoisomers of 10,11-Epoxy-1-bisabolen-3-ols. For enantioselective epoxidation of the 10,11 carbon–carbon double bond of 1,10-bisaboladien-3-ols we used a sequence of a Sharpless asymmetric dihydroxylation and stereoselective cyclization of intermediate diols through intermediate mesylates.^{28,29} Dihydroxylations of 1,10-bisaboladien-3-ols (5, 7, 8, and 11) occurred regioselectively at the trisubstituted double bonds and provided triols **18–23** (Scheme 2). The absolute configuration of triol **13**, determined by singlecrystal X-ray crystallography, confirmed that C-10 has the Sconfiguration (Scheme 2), as expected from Sharpless asymmetric dihydroxylation with AD-mix α .²⁰ Thus, we assigned the other triols originating from AD-mix α dihydroxylations (18, **20**) (10*S*)-configurations, and triols obtained from AD-mix β dihydroxylations (19, 21, 22, and 23) (10R)-configurations. Triols were regioselectively converted to the corresponding mesylates of the secondary hydroxy groups, and the mesylates were cyclized to epoxides (Scheme 2) by treatment with KOH in MeOH.^{28,29} Because this intramolecular cyclization proceeded with inversion of configuration, 2^{28-30} carbon atoms at position 10 in the epoxybisabolenols 24 and 25 were assigned the Rconfiguration, and those in compounds 3, 4, 26, and 27 the Sconfigurations. Thus, the Sharpless asymmetric dihydroxylation of 1,10-bisaboladien-3-ols followed by the epoxide ring closure of the intermediate triols offered a simple two-step route to make individual stereoisomers of 10,11-epoxy-1-bisabolen-3-ols with predictable stereochemistry. Herein, we describe the preparation of the six stereoisomers of 10,11-epoxy-1-bisabolen-3-ol that were essential for H. halys pheromone identification; details for the remaining stereoisomers will be reported elsewhere.

Identification of Male-Specific Aggregation Pheromone Components from *Halyomorpha halys*. We collected airborne extracts from separate groups of male and female *H*. *halys*. GC-MS analyses of these aerations showed that *H*. *halys* males produced several compounds not present in the extract of volatiles from females (Figure 2). Electron impact ionization



Figure 2. GC-MS total ion chromatograms of *Halyomorpha halys* male and female aerations on a DB-SMS column, 40(1) to $300 \degree$ C at $10 \degree$ C/min; He 1.0 mL/min. Two male-specific compounds (A and B) are indicated.

mass spectra of two main male-specific compounds, A and B, were quite similar (Figure 3) and resembled the mass spectra of sesquiterpenoids, with the ion at m/z 93 suggesting a methylcyclohexadiene fragment and the peak at m/z 220 possibly being a molecular ion. Chemical ionization mass spectra of these two compounds with ammonia as a reagent gas



Figure 3. GC-MS total ion chromatogram of aeration extract from virgin *H. halys* males on an HP-5MS, He 1.0 mL/min, 50(5) to 270 °C at 10 °C/min. Mass spectra of main male-specific compounds A and B are presented.

contained an ion at m/z 256 (238 +NH₄), suggesting that the molecular weight of both A and B is 238 amu, corresponding to a molecular formula of $C_{15}H_{26}O_2$, and the ion at m/z 220 is formed apparently by the loss of 18 amu (H_2O) under EIMS conditions. Interestingly, we found a striking similarity between the mass spectra of compounds A and B and that of the recently reported aggregation pheromone of the harlequin bug, Murgantia histrionica.^{9,10} Thus, using the authentic samples described above, we identified the faster-eluting compound A as a cis-10,11epoxy-1-bisabolen-3-ol and the slower-eluting compound B as a trans-10,11-epoxy-1-bisabolen-3-ol. In order to determine the absolute configurations of compounds A and B, we compared GC retention times of the compounds in the extract of volatiles from males with those of mixtures and individual stereoisomers of 10,11-epoxy-1-bisabolen-3-ol on enantioselective columns. We resolved all four *cis*-10,11-epoxy-1-bisabolen-3-ols with (7R)configuration on a Chiraldex G-TA column and identified individual compounds by co-injections with authentic samples

(Figure 4). We found that (3*S*,6*S*,7*R*,10*S*)-stereoisomer 3 matched compound A in the *H. halys* male airborne collection.



Figure 4. Segments of GC-MS total ion chromatograms on a Chiraldex G-TA column, He 1.0 mL/min, 50(3) to 140 °C at 10 °C/min. (a) Coinjection of *H. halys* male aeration and four *cis*-(7R)-10,11-epoxy-1bisabolen-3-ols; (b) *cis*-(7R)-10,11-epoxy-1-bisabolen-3-ols, **25**, **26**, **24**, and **3**; (c) *H. halys* male aeration.

Hydrodex- β -6TBDM was the column of choice for separation of all four *cis*-10,11-epoxy-1-bisabolen-3-ols with the (7S)-configurations (Figure S4), with the second peak, identified as stereoisomer 27, being close but not accurately matching compound A in the H. halys male extract. Compounds A and 27 were in fact clearly separated on the Chiraldex G-TA column (Figure S5). Thus, out of eight *cis*-10,11-epoxy-1-bisabolen-3-ols, only (3S,6S,7R,10S)-10,11-epoxy-1-bisabolen-3-ol (3) matched the main male-specific compound A present in the H. halvs male aeration. Next, we found that four trans-10,11-epoxy-1bisabolen-3-ols with the (7R)-configuration baseline separated on Hydrodex- β -6TBDM (Figure 5), and the third component of that mixture matched compound B in the H. halys male airborne extract. This stereoisomer was identified as (3R,6S,7R,10S)-10,11-epoxy-1-bisabolen-3-ol (4). Finally, no trans-10,11-epoxy-1-bisabolen-3-ols with the (7S)-configuration matched compound B (Figure S6).³¹ Thus, in a pursuit of behaviorally active compounds that could constitute an aggregation pheromone of BMSB we focused on the field bioassay of stereoisomers 3 and 4.

Field Bioassay. Comparison of lures containing each of the synthetic pheromone components **3** and **4** separately and together in the natural ratio of 3.5:1 demonstrated that the treatments differed for both adult and nymphal captures (Table 1; ANOVAs for treatment effects [using arcsin-square-root-transformed block proportions of totals for the trapping period]: $F_{(3,16)} = 59.6$; p < 0.0001 for adults; $F_{(3,16)} = 15.1$; p < 0.0001 for nymphs). Means comparison (Tukey's HSD test)³² indicated that for adult captures the major component **3** was more attractive than the minor component **4**, which in turn was more attractive than the blank lure, but the mixture at the natural 3.5:1 ratio was more attractive than either **3** or **4** alone. For nymphal captures, lures containing the major component **3** caught



Figure 5. Segments of GC-MS total ion chromatograms on a Hydrodex- β -6TBDM column, He 2.0 mL/min, 140 °C isothermal: (a) *Halyomorpha halys* male aeration; (b) co-injection of *H. halys* male aeration and *trans*-(7*R*)-10,11-epoxy-1-bisabolen-3-ols; (c) (3*R*,6*S*,7*R*,10*S*)-stereoisomer 4; (d) *trans*-(7*R*)-10,11-epoxy-1-bisabolen-3-ols.

 Table 1. Captures of *H. halys* in Pyramid Traps Baited with

 Pheromone Components

lure treatment	adults per trap ^a		nymphs per trap ^a	
4 mg 3 + 1.1 mg 4	34.6	a ^b	54.0	a ^b
4 mg 3	22.6	b	32.4	a
4 mg 4	8.2	с	20.4	b
blank	0.8	d	4.4	b

^{*a*}Total per trap for 6 wk, June 21 through July 30, 2013, Beltsville, Maryland, with traps adjacent to woody borders of agricultural fields, 5 randomized blocks collected and rerandomized $2\times$ per wk and with lures replaced every 2 wk. ^{*b*}Within each life stage (column), total trap captures followed by a common letter do not differ by Tukey's HSD test, p < 0.05. See text for ANOVA. Means shown are original untransformed capture totals per trap.

significantly more than lures not containing the major component.

Furthermore, field tests of a 3:1 mixture of cis- and trans-10,11epoxy-1-bisabolen-3-ols with the (7R)-configuration (mixedisomer lure), which was prepared from (R)-citronellal without stereoselective reactions as a mixture of eight isomers,⁹ showed that this mixture was 9.6 times more attractive to adults than the blank lure (15.4 adults per trap versus 1.6 for unbaited; ANOVA for treatment effect (using arcsin-square-root-transformed block proportions of totals for the trapping period): $F_{(1,8)} = 70.1$; p <0.0001 for adults). No nymphs were captured during this trial because of the early season time frame of the experiment. In subsequent studies that will be summarized elsewhere, nymphs were readily captured with the mixed-isomer lure. Thus, field bioassays demonstrated that both pheromone components were important for optimal attraction, but the presence of additional stereoisomers apparently does not hinder attraction of H. halys. Therefore, relatively inexpensive mixtures of the stereoisomers can be developed for trapping the brown marmorated stink bug. Finally, the recently discovered synergy of the H. halys aggregation pheromone with methyl (E,E,Z)-2,4,6-decatrienoate³³ identifies a season-long attractive tool for detection, monitoring, and potential control of this polyphagous invasive pest of North America and Europe.

CONCLUSION

We isolated and identified the aggregation pheromone of the brown marmorated stink bug, *H. halys.* Rhodium/BINAPcatalyzed addition of trimethylaluminum to diastereomeric mixtures cyclohex-2-enones 1 and 2 afforded two stereoisomers from one reaction and thus provided an access to all eight stereoisomers of 1,10-bisaboladien-3-ol and six of stereoisomers of 10,11-epoxy-1-bisabolen-3-ol, previously unreported. In addition to enabling the complete stereochemical identification of the *H. halys* main pheromone components, the creation of these stereoisomeric libraries will be useful in identifying the relative and absolute configurations of other natural products, including the pheromones of at least two other pentatomid bugs, *Murgantia histrionica* and *Tibraca limbativentris*.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were measured on a Thomas-Hoover capillary melting point apparatus. Optical rotations were obtained using a PerkinElmer 241 polarimeter with a 1.0 mL cell. NMR spectra of all compounds but 16 were collected on a Bruker Avance 500 spectrometer running Topspin 1.4 pl8 using a 5 mm BBO probe. Spectra were recorded in CD₂Cl₂ at 500 MHz for ¹H and 125 MHz for ¹³C NMR. Chemical shifts are reported as parts per million from tetramethylsilane based on the lock solvent. COSY, ¹³C-DEPT 135, HMBC, and HSQC spectra were also recorded to assign protons and carbons in the synthetic molecules. The ¹H NMR spectrum of 16 was obtained at 600 MHz and the ¹³C spectrum at 151 MHz on a Bruker AVIII-600 MHz spectrometer. Chemical shifts are referenced to the residual CDCl₃ solvent signal; coupling constants are reported in Hz. Electron impact 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 either a 30 m \times 0.25 mm i.d. \times 0.25 μ m film HP-5MS column or one of the chiral-phase columns described below. The HP-5MS column temperature was maintained at 50 °C for 5 min and then raised to 270 °C at 10 °C/min. Helium was used as a carrier gas at 1 mL/min. GC-HRMS analyses were performed by time-of-flight in EI or ESI modes on a Waters GCT Premier instrument equipped with a DB5-MS column. Routine GC analyses were performed on a Shimadzu 17A (Shimadzu Scientific Instruments, Inc.) GC equipped with a flame ionization detector, an AOC-20s autosampler, and an AOC-20i autoinjector and with an HP-5 capillary column (30 m \times 0.25 mm \times 0.25 μ m 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 (i) a 25 m \times 0.25 mm i.d. Hydrodex β -6TBDM capillary column (Macherey-Nagel GmbH & Co. KG) and (ii) a $30 \text{ m} \times 0.25 \text{ mm}$ \times 0.12 μ m film Astec Chiraldex G-TA column (Sigma-Aldrich/ Supelco). 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).

All reagents and solvents were purchased from Aldrich Chemical Co., unless otherwise specified. (*S*)-(–)-Citronellal (97% ee) was purchased from Sigma-Aldrich, and (*R*)-(+)-citronellal (98% ee) was purchased from Takasago International. Diastereomeric cyclohexenones **1** and **2** were synthesized following Hagiwara et al.¹⁹

Synthesis of Stereoisomers of 1,10-Bisaboladien-3-ol: General Procedure. Chloro(1,5-cyclooctadiene)rhodium(I) dimer ([Rh- $(cod)Cl]_2$, 0.05 equiv) and (R)-(-)- or (S)-(+)-2,2'-bis-(diphenylphosphino)-1,1'-binaphthalene ((R)- or (S)-BINAP, 0.12 equiv) were placed under N₂ in a round-bottom three-neck flask. Dry tetrahydrofuran (30 mL) was added to the mixture, and the resulting solution was stirred at room temperature (rt) for 0.5 h and then cooled

to 0 °C. A solution of ketone 1 or 2 (1 equiv) in dry THF (5 mL) was added to the mixture followed by trimethylaluminum (2 equiv, 2.0 M in heptane) maintaining the temperature at 0 to -5 °C. After stirring for 4 h at 0 °C, the mixture was left in a refrigerator at 0-2 °C for 20 h, then was poured into NH₄Cl solution, acidified with 10% HCl to pH 3-4, and extracted with hexane/ether, 5:1. Combined organic extracts were washed with water and brine and dried with Na2SO4. After evaporation of the solvent, the residue was flash chromatographed on SiO₂ with hexane/EtOAc, 6:1 to 3:1, to provide two main fractions. The less polar fractions were further purified on SiO2 with CH2Cl2/EtOAc, 40:1, to provide cis-1,10-bisaboladien-3-ols 5, 7, 9, and 11 of >95% chemical purity. GC retention times were ~18.030 min (HP-5MS) and R_f 0.45 (SiO₂, hexane/EtOAc, 3:1). The more polar fractions were further purified on SiO₂ with CH₂Cl₂/EtOAc, 30:1, to provide >95% pure trans-1,10-bisaboladien-3-ols 6, 8, 10, and 12. GC retention times were ~18.240 min; R_f 0.32 (hexane/EtOAc, 3:1). The isolated 1,10bisaboladien-3-ols are characterized in Tables S1, S2, and S3.

Dehydrations of 1,10-Bisaboladien-3-ols. (a) A solution of a ~1:1 mixture of 6 and 8 (70 mg, 0.32 mmol) in dry pyridine (3 mL) was cooled to 0 °C and treated with POCl₃ (58 μ L, 0.58 mmol). The mixture was warmed to rt, stirred for 18 h, poured into ice—water (5 mL), and extracted with hexane (4 × 5 mL). The combined hexane extracts were washed with 1 M HCl and brine and dried with Na₂SO₄. After evaporation of the solvent, the residue was chromatographed with hexane to provide a mixture of hydrocarbons (55 mg) consisting of 5% unknown sesquiterpene, 43% 1,3(15),10-bisabolatriene 14, and 52% 1,3(10-bisabolatriene 15).

(b) Alcohol 7 (222 mg, 1 mmol) was treated with POCl₃ (193 μ L, 1.93 mmol) in dry pyridine (3 mL) at 0 °C; then the mixture was stirred 2 h at rt. After the workup as described above, the products were extracted with CH₂Cl₂ and purified by chromatography with hexane to provide a mixture of hydrocarbons (53 mg) consisting of 56% 1,3,10bisabolatriene, 31% 1,3(15),10-bisabolatriene, and 13% of an unidentified sesquiterpene. This mixture was added to a solution of 4phenyl-1,2,4-triazoline-3,5-dione (31 mg) in dry THF (2.5 mL). After 0.5 h, the mixture was concentrated with a gentle stream of N_2 and chromatographed with pentane/methyl acetate (99:1). (6R,7R)-(-)-1,3(15),10-Bisabolatriene (16, 9 mg) of 97% chemical purity by GC-MS was isolated in the first fraction (Scheme S1, left, and Figure 1): $[\alpha]^{20}_{D}$ -54.2 (c 0.58, CHCl₃). The specific rotation of (6S,7S)-(+)-1,3(15),10-bisabolatriene was reported as +39.6 (c 0.43, CHCl₃).²⁶ GC-MS m/z (% relative intensity, ion) 204 (30, M⁺), 161 (40), 133 (40), 120 (36), 119 (15), 109 (25), 105 (21), 93 (64), 92 (36), 91 (55), 79 (21), 77 (38), 69 (100), 55 (22), 41 (47); ¹H NMR (600 MHz, $CDCl_{3}, \delta$ 0.87 (d, J = 6.5 Hz, 3H), 1.14–1.22 (m, 1H), 1.36–1.46 (m, 2H), 1.47-1.53 (m, 1H), 1.59 (s, 3H), 1.68 (br s, 3H), 1.69-1.75 (m, 1H), 1.89-1.95 (m, 1H), 1.99-2.05 (m, 1H), 2.16-2.23 (m, 1H), 2.25-2.32 (m, 1 H), 2.42 (dt, J = 12.0, 6.0 Hz, 1H), 4.72 (br s, 1H), 4.74 (br s, 1H), 5.09 (br t, J = 7.0 Hz, 1H), 5.70 (br d, J = 11.0 Hz, 1H), 6.15 (dm, J = 11.0 Hz, 1H); ¹³C NMR (CDCl₃, 150 MHz, δ) 16.46, 17.68, 25.73, 26.06, 26.26, 30.50, 33.90, 36.51, 41.02, 109.94, 124.80, 129.79, 131.29, 134.02, 143.80. Mass spectrometry and NMR data are in good agreement with those reported for (65,7S)-(+)-1,3(15),10-bisabolatriene.²⁶ A Diels-Alder adduct of zingiberene with 4-phenyl-1,2,4triazoline-3,5-dione 17 (42 mg, Scheme S1) was also isolated in the second fraction.

(c) In separate experiments, alcohols **5**, **6**, **8**, **9** + **11**, **9**, **10**, **11**, and **12** (4 mg each) in pyridine (50 μ L) were treated with POCl₃ (4 μ L), and the resulting hydrocarbon mixtures were separated as described in experiment (a). The mixtures were analyzed by GC-MS on HP-5MS and by GC-FID on Hydrodex- β -6TBDM columns.

Enantioselective Dihydroxylations of 1,10-Bisaboladien-3ols to 1-Bisabolen-3,10,11-triols. Solutions of alcohols (1 mmol) in *tert*-butyl alcohol (4.7 mL) were added to a mixture of AD-mix- α or ADmix- β (1.38 g), depending on the stereoisomer being synthesized (Figure 2), and methanesulfonamide (91 mg) in water (4.7 mL) at 0 °C. Mixtures were stirred at 0–2 °C for 24 h and treated with sodium sulfite (1.47 g), and the temperature was allowed to rise to 20–25 °C within 0.5 h. The mixtures were extracted with CH₂Cl₂ (4 × 30 mL), and the combined organic extracts were washed with 2 N KOH and brine and dried with Na_2SO_4 . After evaporation of the solvent, residues were chromatographed on SiO_2 with ethyl acetate to yield triols characterized in Table S4. ¹H and ¹³C NMR spectra of triols are presented in Tables S5 and S6, respectively.

X-ray Structure Determination of Triol 13. After recrystallizing 13 (mp 125 °C) from tert-butyl methyl ether, a sample for X-ray structure determination was prepared as follows. A solution of 2 mg of 13 in 120 μ L of CH₂Cl₂ was placed in an NMR tube; then 110 μ L of hexane was added, allowing needle-like crystals to gradually precipitate. All reflection intensities were measured at 110(2) K using a SuperNova diffractometer (equipped with an Atlas detector) with $Cu K\alpha$ radiation (mirror optics, $\lambda = 1.5418$ Å) under the program CrysAlisPro (version 1.171.36.24, Agilent Technologies, 2012). This program was used for unit cell determination and data reduction. The structure was solved with the program SHELXS-97 and was refined on F^2 with SHELXL-97.³⁴ Analytical numeric absorption corrections based on a multifaceted crystal model were applied using CrysAlisPro. The temperature of the data collection was controlled using the system Cryojet (Oxford Instruments). The H atoms (unless otherwise specified) were placed at calculated positions using the instructions AFIX 13, AFIX 23, AFIX 43, or AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 times U_{eq} of the attached C atoms. The H atoms attached to O1, O2, and O3 were found from difference Fourier maps, and the O-H distances were restrained to be 0.84(3) Å using the DFIX instructions. The structure is ordered. The absolute configuration 3R,6S,7R,10S was established by anomalous dispersion effects in diffraction measurements on the crystal (Scheme 2). The Flack³⁵ and Hooft³⁶ parameters refine to 0.05(13) and 0.03(4), respectively. Compound 13: fw = 256.37, colorless plate, $0.43 \times 0.38 \times 0.07 \text{ mm}^3$, monoclinic, P2₁ (no. 4), a =9.58434(13) Å, b = 6.33143(8) Å, c = 12.29045(17) Å, $\beta =$ 92.0157(12)°, V = 745.355(17) Å³, Z = 2, $D_x = 1.142$ g cm⁻³, $\mu =$ 0.611 mm⁻¹, abs corr range 0.824-0.963. A total of 8786 reflections were measured up to a resolution of $(\sin \theta / \lambda)_{max} = 0.62 \text{ Å}^{-1}$, of which 2921 were unique ($R_{int} = 0.0163$) and 2848 were observed [$I > 2\sigma(I)$]. A total of 180 parameters were refined using four restraints. R_1/wR_2 [I > $2\sigma(I)$]: 0.0253/0.0647. R_1/wR_2 [all reflns]: 0.0261/0.0655. S = 1.062. Residual electron density was found between -0.13 and 0.20 e Å^{-3.37}

Syntheses of Stereisomeric 10,11-Epoxy-1-bisabolen-3-ols. Methanesulfonyl chloride (77 μ L, 1.14 mmol) was added to a stirred solution of a triol (1.0 mmol) in dry pyridine (1.5 mL) at 0-5 °C; then the mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was poured into ice-water (4 mL) and extracted with CH₂Cl₂ $(3 \times 10 \text{ mL})$. Combined organic extracts were washed with ice–water, dried with Na₂SO₄, and concentrated to yield a crude mesylate. This was taken into MeOH (5 mL), cooled to 0 °C, and treated with a solution of KOH (112 mg, 2 mmol) in MeOH (1.3 mL), which resulted in an instantaneous precipitation of inorganic salts. The reaction mixture was warmed to rt, stirred for 0.5 h, and concentrated to remove most of MeOH. The residue was treated with an NH₄Cl solution to pH 7-8 and extracted with ether $(3 \times 10 \text{ mL})$. Combined organic extracts were washed with ice-water and brine, dried with Na₂SO₄, and concentrated. Flash chromatography (hexane/EtOAc, 3:2) yielded epoxybisabolenols 3, 4, and 24–27 (Table S4). 1 H and 13 C NMR spectra of epoxybisabolenols are presented in Tables S5 and S6, respectively.

Insect Rearing. The brown marmorated stink bug colony in Taiwan was established in 2000 from adults collected in Nangang. The *H. halys* colony at Beltsville was established in 2007 from adults collected in Allentown, PA, USA, supplemented annually with ~20 adult bugs field-collected in the vicinity of Beltsville, MD, USA. Rearing was accomplished in ventilated plastic cylinders (21 cm \times 21 cm o.d.) on a diet of organic green beans and shelled sunflower and buckwheat seeds (2:1, w/w), glued onto squares of brown wrapping paper with wallpaper paste, and distilled water supplied in two cotton-stopped 7 cm \times 2 cm o.d. shell vials held together with a rubber band. Eggs were collected weekly and hatched in plastic Petri dishes with a water vial, and after molting to second-instars, the nymphs were transferred to the larger rearing cages as described above for the remaining four instars. Adult males and females were separated 1 or 2 days after emergence and subsequently maintained in different containers. Insects were

maintained in Thermo Forma chambers (Thermo Fisher Scientific) at 25 $^\circ$ C and 72% relative humidity, under a 16L:8D photoperiod.

Semiochemical Collection and Isolation. Initially, aeration experiments were conducted using groups of 20-30 virgin adults as was successfully employed previously for other stink bugs. Under these conditions no sex-specific volatiles were detected. Eventually, evidence in the literature indicated pheromone production of some stink bugs is inhibited when males are grouped in large numbers.^{9,38} Therefore, successful aerations were originally conducted in Taiwan with one female and three males, both 14 days old, for 2 days (Figure 2). Thereafter, at the Beltsville Research Center volatiles were collected (as described below) with one to three laboratory-reared virgin H. halys adults (at least 1 week old) and with one to three wild adults (Figure 3). Subsequently, the male-specific volatiles were collected from different numbers per container of virgin males only. The males were placed separately into two 1 L, four-necked glass containers. Humidified air was drawn into the container through 6-14 mesh activated charcoal (Fisher Scientific) and out of the container through two traps (15 cm \times 1.5 cm o.d.) containing Super Q (200 mg each; Alltech Associates, Inc.) by vacuum ($\sim 1 \text{ L/min}$).³⁹ Insects were fed with organic green beans (replaced weekly) and water on cotton balls and aerated continuously for 20 to 90 days at rt and a 16L:8D photoperiod. The adsorbent traps were changed every day (some of them in 3 days for the weekend), and the adsorbents were eluted with CH2Cl2 (0.5 mL/sample). The solutions were stored at -30 °C before analyses.

Bioassay Methods. Pyramid traps described previously were used for both field trials.⁴⁰ Hercon Vaportape II (Hercon Environmental) was added as a killing agent to prevent escape from traps and was replaced at four-week intervals. H. halys adults and nymphs were removed from traps, and the lure placement within each block was rerandomized twice weekly, recording the numbers and sexes of adults. Rubber septa used to evaluate pheromone treatments were replaced at two-week intervals. Single isomers 3 and 4, and a combined lure in the natural ratio, as well as an unbaited trap (Table 1) were compared from June 21 to July 30, 2013, in Beltsville, MD, USA, with traps adjacent to woody borders of agricultural fields, in five randomized blocks. A mixed-isomer lure at 10.7 mg was compared with unbaited traps deployed in five randomized blocks ~5 m from the border of apple and pear orchards at the Appalachian Fruit Research Station, Kearneysville, WV, USA, from March 20 to April 17, 2012. ANOVA was used to evaluate overall effects for the single-isomer test as well as the mixed-isomer test, using arcsinsquare-root-transformed block proportions of totals for the trapping period. Adjacent means were compared using Tukey's HSD test.³² The effect of sex was dropped from all models because it was not a significant factor.

ASSOCIATED CONTENT

S Supporting Information

Dehydration products from compounds 5-12 and selected gas chromatograms thereof, entire CIF file for triol 13, as well as Tables S1–S6 and ¹H and ¹³C NMR spectra of all new compounds are available free of charge via the Internet at http:// pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone: 301-504-6138. E-mail: ashot.khrimian@ars.usda.gov.

Present Address

[§]Department of Entomology, University of California, Davis, CA 95616, United States.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank G. Cabrera Walsh, A. DiMeglio, and M. Athanas for pheromone trap field collection and enumeration of all Maryland samples. Support for this study was from USDA, National

REFERENCES

(1) Aldrich, J. R.; Oliver, J. E.; Lusby, W. R.; Kochansky, J. P.; Lockwood, J. A. J. Exp. Zool. **1987**, 244, 171–175.

(2) Baker, R.; Borges, M.; Cooke, N. G.; Herbert, R. H. J. Chem. Soc., Chem. Commun. 1987, 414–416.

(3) McBrien, H. L.; Millar, J. G.; Gottlieb, L.; Chen, X.; Rice, R. E. J. Chem. Ecol. 2001, 27, 1821–1839.

(4) Aldrich, J. R.; Lusby, W. R.; Marron, B. E.; Nicolaou, K. C.;

Hoffmann, M. P.; Wilson, L. T. Naturwissenschaften **1989**, 76, 173–175. (5) McBrien, H. L.; Millar, J. G.; Rice, R. E.; McElfresh, J. S.; Cullen, E.;

Zalom, F. G. J. Chem. Ecol. 2002, 28, 1797–1817. (6) Leal, W. S.; Kuwahara, S.; Shi, X. A.; Higuchi, H.; Marino, C. E. B.;

Ono, M.; Meinwald, J. J. Chem. Ecol. 1998, 24, 1817–1829. (7) For terpene nomenclature see: Connolly, J. D.; Hill, R. A.

Dictionary of Terpenoids; Chapman and Hall: London, 1991; Vol. 1, pp 180–182.

(8) Borges, M.; Birkett, M.; Aldrich, J. R.; Oliver, J. E.; Chiba, M.; Murata, Y.; Laumann, R. A.; Barrigossi, J. A.; Pickett, J. A.; Moraes, M. C. B. *J. Chem. Ecol.* **2006**, *32*, 2749–2764.

(9) Zahn, D. K.; Moreira, J. A.; Millar, J. G. J. Chem. Ecol. 2008, 34, 238–251.

(10) Zahn, D. K.; Moreira, J. A.; Millar, J. G. J. Chem. Ecol. 2012, 38, 126.

(11) Terhune, S. J.; Hogg, J. W.; Bromstein, A. C.; Lawrence, B. M. Can. J. Chem. 1974, 53, 3287–3293.

(12) Mitzner, B. M.; Mancini, V. J.; Lemberg, S.; Theimer, E. T. Appl. Spectrosc. **1968**, 22, 34–53.

(13) de Oliveira, M. W. M.; Borges, M.; Andrade, C. K. Z.; Laumann, R. A.; Barrigossi, J. A. F.; Blassioli-Moraes, M. C. *J. Agric. Food. Chem.* **2013**, *61*, 7777–7785. [The pheromone is incorrectly named (1S,4R,1'S)-(1',5'-dimethylhex-4'-enyl)-1-methylcyclohex-2-en-1-ol in the title. The correct name is (1R,4R,1'S)-(1',5'-dimethylhex-4'-enyl)-1-methylcyclohex-2-en-1-ol.]

(14) Leskey, T. C.; Hamilton, G. C.; Nielsen, A. L.; Polk, D. F.; Rodriguez-Saona, C.; Bergh, J. C.; Herbert, D. A.; Kuhar, T. P.; Pfeiffer, D.; Dively, G.; Hooks, C. R. R.; Raupp, M. J.; Shrewsbury, P. M.; Krawczyk, G.; Shearer, P. W.; Whalen, J.; Koplinka-Loehr, C.; Myers, E.; Inkley, D.; Hoelmer, K. A.; Lee, D.-Y.; Wright, S. E. *Outlooks Pest Manag.* **2012**, *23*, 218.

(15) Leskey, T. C.; Short, B. D.; Butler, B. B.; Wright, S. E. *Psyche* **2012**, Article ID 535062.

(16) U.S. and International Patents have been filed. See: Khrimian, A.; Zhang, A.; Aldrich, J. R.; Leskey, T. C., Weber, D. C. Compositions and Methods to Attract the Brown Marmorated Stink Bug *Halyomorpha halys.* Int. Pat. Appl. PCT/US2012/069721, Dec 14, 2012.

(17) Siewert, J.; Sandmann, R.; von Zezschwitz, P. Angew. Chem., Int. Ed. 2007, 46, 7122–7124.

(18) Yadav, J. S.; Thirupathaiah, B.; Srihary, P. *Tetrahedron* **2010**, *66*, 2005–2009.

(19) Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. J. Chem. Soc., Perkin Trans. 1 2002, 895–900.

(20) 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*, 2768–2771.

(21) Mori, K. Tetrahedron: Asymmetry **2006**, 17, 2133–2142.

(22) Blair, M.; Tuck, K. L. Tetrahedron: Asymmetry 2009, 20, 2149–2153.

(23) Kashiwagi, T.; Nakashima, T.; Tebayashi, S.-I.; Kim, C.-S. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 2544–2546.

(24) Bhonsle, J. B.; Deshpande, V. H.; Ravindranathan, T. Indian J. Chem. **1994**, 33B, 313–316.

(25) Millar, J. G. J. Nat. Prod. 1998, 61, 1025-1026.

(26) Kreiser, W.; Körner, F. Helv. Chim. Acta 1999, 82, 1427-1433.

(27) Soffer, M. D.; Burk, L. A. Tetrahedron Lett. 1985, 26, 3543-3546.

(28) Frater, G.; Müller, U. Helv. Chim. Acta 1989, 72, 653-658.

(29) Moore, C. J.; Possner, S.; Hayes, P.; Paddon-Jones, G. C.; Kitching, W. J. Org. Chem. **1999**, 64, 9742–9744.

(30) Khrimian, A.; Fay, H. A. C.; Guzman, F.; Chauhan, K.; Moore C.; Aldrich, J. R. *Psyche* **2012**, Article ID 536149.

(31) Individual stereoisomers of *trans* 10,11-epoxy-1-bisabolen-3-ol with (7S)-configurations and a mixture thereof will be described in our subsequent paper.

(32) SAS Institute. StatView 2nd ed.; SAS Institute: Cary, NC, 1998.

(33) Weber, D. C.; Leskey, T. C.; Cabrera Walsh, G.; Khrimian, A. J. Econ. Entomol. 2014, 107, 1061–1068.

(34) Sheldrick, G. M. Acta Crystallogr. 2008, A64, 112-122.

(35) Flack, H. D. Acta Crystallogr. 1983, A39, 876-881.

(36) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. J. Appl. Crystallogr. 2008, 41, 96–103.

(37) Crystallographic data for triol **13** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. (Deposition number CCDC 959242). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(38) Ho, H.-Y.; Hsu, Y.-C.; Chuang, Y.-C.; Chow, Y.-S. J. Chem. Ecol. 2005, 31, 29–37.

(39) Zhang, A.; Oliver, J. E.; Aldrich, J. R.; Wang, B.; Mastro, V. C. Z. *Naturforsch., C: Biosci.* **2002**, *57*, 553–558.

(40) Leskey, T. C.; Wright, S. E.; Short, B. D.; Khrimian, A. J. Entomol. Sci. 2012, 47, 76–85.