



Expedient synthesis of bisabolenol stink bug pheromones via stereodefined cyclohex-2-enones



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ABSTRACT

We recently synthesized all stereoisomers of 1,10-bisaboladien-3-ol and 10,11-epoxy-1-bisabolen-3-ol, including three stink bug pheromones, via a rhodium-catalyzed asymmetric addition of trimethylaluminum to diastereomeric mixtures of cyclohex-2-enones. However, yields of *trans* isomers were low, and scaling reactions using expensive catalysts were cumbersome. Now we describe a new synthesis of bisabolenol stink bug pheromones via (*S*)- and (*R*)-4-((*R*)-6-methylhept-5-en-2-yl)cyclohex-2-enones prepared by enantioselective Michael additions of methyl vinyl ketone to (*S*)- and (*R*)-citronellals and lithium hydroxide monohydrate-catalyzed stereoselective cyclizations of intermediate ketoaldehydes. Addition of methyllithium to these enones provided *cis*- and *trans*-1,10-bisaboladien-3-ols, which were separated by chromatography on silica and further converted to 10,11-epoxy-1-bisabolen-3-ols. Thus, we developed more convenient syntheses of pheromones of the rice stink bug, the harlequin bug, and brown marmorated stink bug.

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Introduction

There are at least four pentatomid stink bug species that use a bisabolenol entity in their male-secreted pheromone molecules. The rice stalk stink bug, *Tibraca limbativentris*, sex pheromone was identified as a mixture of two stereoisomers of zingiberenol, or 1,10-bisaboladien-3-ol,¹ without determining their absolute configuration.² The sex pheromone of rice stink bug, *Oebalus poecilus*, consists of a single isomer of zingiberenol identified as (3*R*,6*R*,7*S*)-1,10-bisaboladien-3-ol (**1**).^{3,4} Interestingly, ginger rhizomes also produce this compound along with (3*S*,6*R*,7*S*)-1,10-bisaboladien-3-ol (**2**), as minor components of their sesquiterpene content.⁵ The aggregation pheromone of the harlequin bug, *Murgantia histrionica*, was identified as 10,11-epoxy-1-bisabolen-3-ol^{6,7} and later revealed to be a 1.4:1 mixture of two stereoisomers, (3*S*,6*S*,7*R*,10*S*)-10,11-epoxy-1-bisabolen-3-ol (**3**) and (3*S*,6*S*,7*R*,10*R*)-10,11-epoxy-1-bisabolen-3-ol (**4**).⁸ Lastly, the brown marmorated stink bug, *Halyomorpha halys*, has been shown to share compound **3** as the main component of its aggregation pheromone, along with (3*R*,6*S*,7*R*,10*S*)-10,11-epoxy-1-bisabolen-

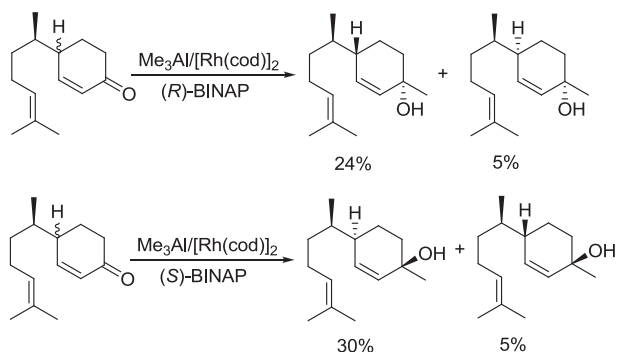
3-ol (**5**), produced by the male bug in a 3.5:1 ratio.⁹ The last two stink bug species are important agricultural pests for which the aggregation pheromones have successfully been used for detection and monitoring.^{10,11}

For syntheses of abovementioned bisabolenol stink bug pheromones, we earlier explored a rhodium-catalyzed asymmetric addition of trimethylaluminum to diastereomeric mixtures of cyclohex-2-enones.⁹ This conveniently provided two single stereoisomers from one reaction (Scheme 1) and thus allowed us to build a full library of stereoisomers of bisaboladienols and epoxybisabolenols.^{8,9}

However, the use of expensive catalysts and chiral reagents, and more importantly, low yields of *trans* isomers, hampered the practical application of this method. To overcome these shortcomings, we contemplated changing our strategy from the Rh-catalyzed enantioselective addition to a carbonyl group to introducing chirality in the precursor cyclohexenone molecule (i.e. ketones **6**, and **7**), then conducting a non-stereoselective addition of methyllithium and capitalizing on easy separation of *cis*- and *trans*-1,10-bisaboladien-3-ols. Fortunately, the stereodefined cyclohex-2-enone **7** has recently been reported in literature,¹² thus providing an assurance for successfully accomplishing the chosen strategy for the synthesis of bisabolenol stink bug pheromones.

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Scheme 1. Previous approach (Ref. 9) to bisabolol stink bug pheromones.

Results and discussion

The catalytic enantioselective Michael addition¹³ of (*S*)-citronellal to methyl vinyl ketone in the presence of (*R*)-diphenylprolinol methyl ether¹⁴ provided ketoaldehyde **8** in 65% yield and 95:5 dr (Scheme 2), with the diastereoselectivity in agreement with the originally reported addition of (*R*)-citronellal to methyl vinyl ketone catalyzed by (*S*)-diphenylprolinol methyl ether.¹² The latter reaction in our hands provided ketoaldehyde **9** in 69% yield and 96:4 dr.

The main challenge in the intramolecular aldol condensation of **8** and **9** to cyclohexenones **6** and **7**, respectively, was the requirement to conduct them without significant epimerization at the stereocenters adjacent to the aldehyde groups. Nicolaou et al. reported a base-catalyzed cyclization of **9** using KOH/*Bu*₄NOH that provided **7** in 85% yield and 12:1 (92:8) dr.¹² Somewhat reduced diastereoselectivity (83% *de*, or 89:11 dr) in the same base-catalyzed conversion of **9** to **7** was reported by others.¹⁵ Despite our

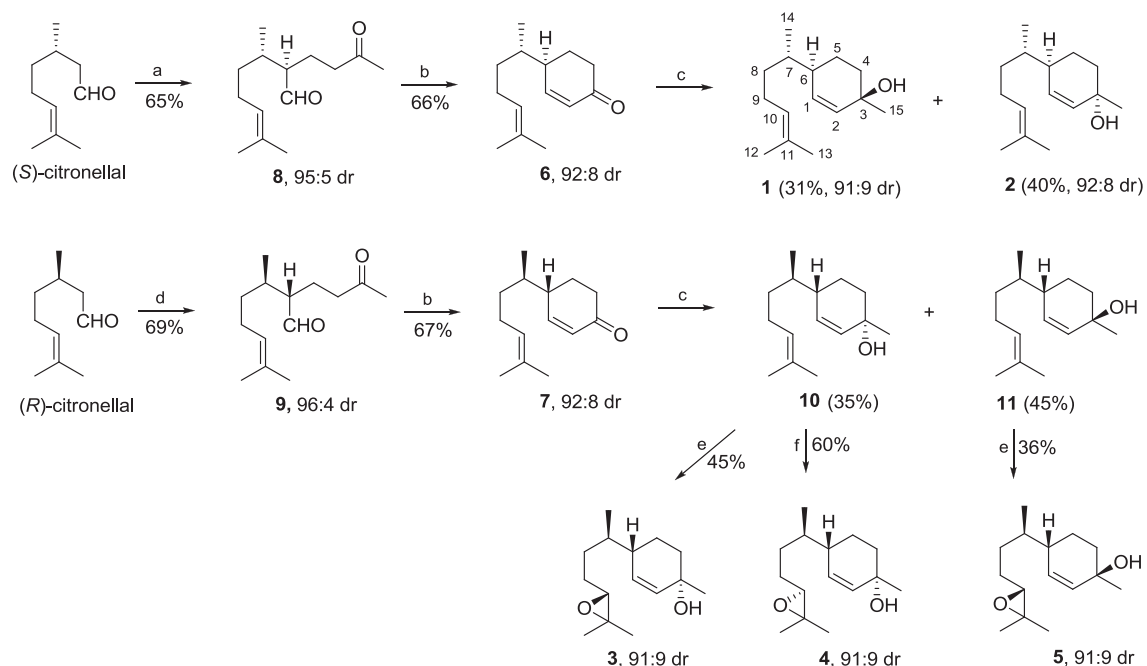
Table 1

Total numbers of harlequin bugs attracted to host plants in three-way choice test, Beltsville, Maryland, 18–24 August 2015.

Lure treatment	Total adults ^a	Total nymphs ^a
1.4:1 3/4 , 95:5 dr	120	37
1.4:1 3/4 , 91:9 dr	99	35
Blank	2	0

^a Within the same column, treatments followed by the same letter do not differ ($p < 0.05$) by exact binomial test.¹⁸

concerted efforts, we were unable to reproduce the described diastereoselectivity and isolated cyclohexenone **7** in 82:18 dr. We found that a reflux of the reaction mixture with KOH/*Bu*₄NOH under vigorous stirring for 8 h as recommended¹² lead to a significant amount of an intermediate compound visible by TLC (expectedly an aldol product), and the completion of condensation required a prolonged heating (18–20 h) resulting in 82:18 dr, presumably due to epimerization to (*R,R*)-diastereomer of **7**.¹⁶ In fact, other authors applying the same KOH/*Bu*₄NOH base system for the asymmetric synthesis of a structurally analogous cryptone also reported a loss of enantiopurity from 92–95% *ee* (in starting (*S*)-2-isopropyl-5-oxohexanal) to 56% *ee* in final (*S*)-cryptone.¹⁷ Intrigued by a significant mitigation of the loss of enantiopurity when KOH/*Bu*₄NOH was replaced by LiOH/*i*-PrOH (89% *ee*, or 94.5:5.5 *S/R*),¹⁷ we became interested in using this base system for cyclizations of ketoaldehydes **8** and **9**. Thus, stirring aldehydes **8** and **9** in an 10% isopropanol solution of lithium hydroxide hydrate at 25 °C for 5 h proceeded without significant epimerization and provided ketones **6** and **7** in 66% and 67% yields, respectively, and 92:8 dr (SM = Supplementary Material, p. 6–8). We also found that lithium hydroxide hydrate as a source of LiOH provided a more reproducible and better stereochemical output than anhydrous lithium hydroxide, and the cyclization is facilitated by an initial ultrasonication.



Reagents and conditions: a) $\text{CH}_3\text{C}(\text{O})\text{CH}=\text{CH}_2$ /*R*-Diphenylprolinol methyl ether, Ref.¹²; b) 10% LiOH·H₂O/*i*-PrOH, rt, c) MeLi/ether, -22 °C; d) $\text{CH}_3\text{C}(\text{O})\text{CH}=\text{CH}_2$ /*S*-Diphenylprolinol methyl ether; e) 1. AD-mix-β; 2. MsCl/Py, 3. KOH/MeOH; f) 1. AD-mix-α; 2. MsCl/Pyridine, 3. KOH/MeOH;

Scheme 2. Syntheses of rice stink bug (**1**), brown marmorated stink bug (**3+5**), and harlequin bug (**3+4**) pheromones through stereoisomeric cyclohexenones **6** and **7**.

A non-stereoselective addition of methyllithium to enone **6** provided (3*R*,6*R*,7*S*)-1,10-bisaboladien-3-ols (**1**) in 31% yield and 91:9 dr and (3*R*,6*S*,7*R*)-1,10-bisaboladien-3-ols (**2**) in 40% yield and 92:8 dr (SM, p. 9–12) easily separated by chromatography on silica. As mentioned in the Introduction, dienol **1** is a pheromone of the rice stink bug, *Oebalus poecilus*,^{3,4} and both dienols **1** and **2** were also found in ginger.⁵ Analogously to the reaction with **6**, a non-stereoselective addition of methyllithium to enone **7** provided (3*S*,6*S*,7*R*)-1,10-bisaboladien-3-ol (**10**) in 35% yield and (3*R*,6*S*,7*R*)-1,10-bisaboladien-3-ol (**11**) in 45% yield. Thus, both *H. halys* and *M. histrionica* pheromone precursors were synthesized from one reaction in comparable yields, whereas the previous synthesis required two Rh-catalyzed reactions (one with (*R*)-BINAP and the other one with (*S*)-BINAP) to make **10** and **11**.⁹ Most importantly, the yield of the sterically disfavored *trans* isomer **11** was improved from 5%⁹ to 45%. Enantioselective epoxidations of bisaboladienols **10** and **11** were conducted via earlier described asymmetric dihydroxylations, conversion of intermediate triols to secondary mesylates and further eliminations to epoxides **3–5**.⁹ The diastereomeric ratios of epoxides **3–5** were about 91:9 (SM, pp. 13–18), somewhat lower than 95:5 dr reported for these compounds in the previous communication.⁹ Hence, there was a need to compare the attractiveness of the newly synthesized and the original epoxybisabolanol pheromone samples.

A short field trapping experiment with harlequin bugs showed that numbers of both adult and nymphal bugs attracted to two pheromone treatments, 1.4:1 **3/4**, of 91:9 and 95:5 dr, were similar (Table 1).

Overall difference among the three treatments is significant by χ^2 goodness-of-fit test¹⁸ (for adults, $\chi^2 = 107.6$, $df = 2$, $p < 0.0001$; for nymphs, $\chi^2 = 36.1$, $df = 2$, $p < 0.0001$), but these differences were solely due to differences of both pheromone treatments compared to the blank. Thus, pheromones produced by the current method can successfully be used for monitoring stink bug populations.

In conclusion, a new method for the synthesis of bisabolanol stink bug pheromone via cyclohexenones **6** and **7** was developed providing an easy access to both *cis*- and *trans*-1,10-bisaboladien-3-ols. Because of the availability of both *L*- and *D*-prolines, starting

compounds to make (*S*)- and (*R*)-diphenylprolinol methyl ether catalysts, the method is expected to be applicable for syntheses of all stereoisomers of 10,11-epoxy-1-bisabolen-3-ols and 1,10-bisaboladien-3-ols.

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A. Supplementary data

Supplementary data (all experimental procedures and ¹H NMR spectra) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2017.04.050>.

References

1. For terpene nomenclature see: Connolly JD, Hill RA. *Dictionary of Terpenoids*, Vol. 1. London: Chapman and Hall; 1991, pp. 180–182.
2. Borges M, Birkett M, Aldrich JR, et al. *J Chem Ecol*. 2006;32:2749.
3. de Oliveira MWM, Borges M, Andrade CKZ, Laumann RA, Barrigossi JAF, Blassioli-Moraes MC. *J Agric Food Chem*. 2013;61:7777.
4. de Oliveira MWM, Borges M, Andrade CKZ, Laumann RA, Barrigossi JAF, Blassioli-Moraes MC. *J Agric Food Chem*. 2014;62:8542.
5. Khrimian A, Shirali S, Guzman F. *J Nat Prod*. 2015;78:3071.
6. Zahn DK, Moreira JA, Millar JG. *J Chem Ecol*. 2008;34:238.
7. Zahn DK, Moreira JA, Millar JG. *J Chem Ecol*. 2012;38:126.
8. Khrimian A, Shirali S, Vermillion KE, et al. *J Chem Ecol*. 2014;40:1260.
9. Khrimian A, Zhang A, Weber DC, et al. *J Nat Prod*. 2014;77:1708.
10. Leskey TC, Khrimian A, Weber DC, et al. *J Chem Ecol*. 2015;41:418.
11. Weber DC, Cabrera Walsh G, DiMeglio AS, Athanas MM, Leskey TC, Khrimian A. *J Chem Ecol*. 2014;40:1251.
12. Nicolaou KC, Wu TR, Sarlah D, Shaw DM, Rowcliffe E, Burton DR. *J Am Chem Soc*. 2008;130:11114.
13. Chi Y, Gellman SH. *Org Lett*. 2005;7:4253.
14. Enders D, Kipphardt H, Gerdes P, Brena-Valle LJ, Bhushan V. *Bull Soc Chim Belg*. 1988;97:691.
15. Yadav JS, Thirupathaiah B, Srihari P. *Tetrahedron*. 2010;66:2005.
16. Houjeiry TI, Poe SL, McQuade DT. *Org Lett*. 2012;14:4394.
17. Chen K, Ishihara Y, Galan MM, Baran PS. *Tetrahedron*. 2010;66:4738.
18. Lowry R. VassarStats: Website for Statistical Computation <http://vassarstats.net> 2017. Accessed 2 March.