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(1*R*,2*S*,6*R*)-2-Hydroxymethyl-2,6-dimethyl-3-oxabicyclo[4.2.0]octane, a New Volatile Released by Males of the Papaya Borer *Pseudopiazurus obesus* (Col.: Curculionidae)

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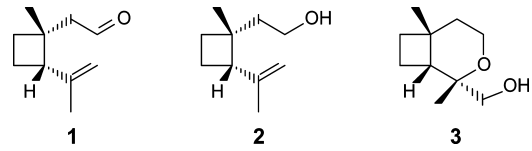
ABSTRACT



Sex-specific volatiles produced by males of the papaya beetle *Pseudopiazurus obesus* are (1*R*,2*S*)-grandisal (1), (1*R*,2*S*)-grandisol (2), and the new (1*R*,2*S*,6*R*)-2-hydroxymethyl-2,6-dimethyl-3-oxabicyclo[4.2.0]octane (3) termed papayanol.

Larvae of the papaya borer, *Pseudopiazurus obesus* (Boheman 1838) (Coleoptera: Curculionidae), cause irreversible damage to papaya stalks, and high infestations may even kill a plant. The species is found throughout Northeast Brazil and can only be controlled by conventional insecticides.[1] To develop an environmentally friendly pest management system, attempts were made to identify relevant semiochemicals from both the host plant and the insect.[2] As a result, (1*R*,2*S*)-(+)-grandisal (**1**) and (1*R*,2*S*)-(+)-grandisol (**2**) (Figure 1) at a ratio of 5.5:1 were detected as important components of a male-produced pheromone; however, a minor volatile, ca. 10% of grandisal, remained unknown.[2] Here we describe the structure elucidation

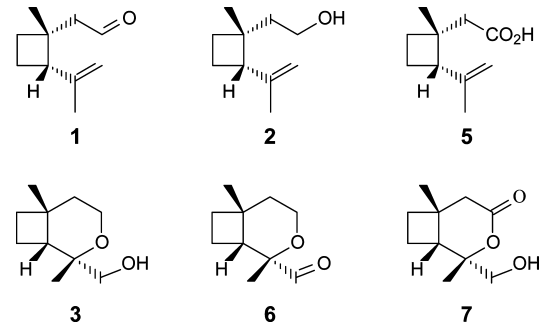


Figure 1. Grandisal (**1**) and related structures.

of this new natural product and its synthesis, as well as the assignment of its absolute configuration.

Since available amounts of material were too small for NMR investigations, the structure of the target compound

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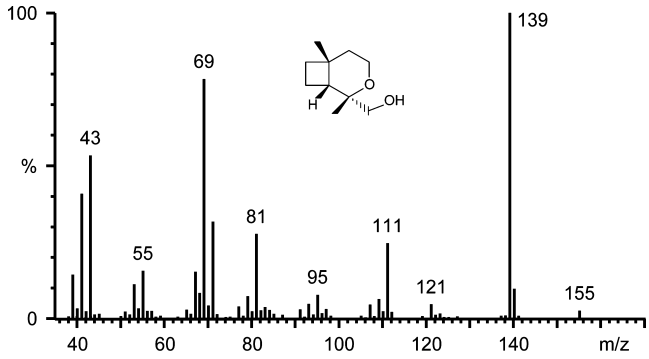

Figure 2. 70 eV mass spectrum of papayanol (**3**).

had to be assigned based on mass spectrometric data and microreactions. The mass spectrum (Figure 2) showed a base peak at *m*/*z* 139 and a general fragmentation pattern resembling that of a terpene. The highest visible signal at *m*/*z* 155 indicated a possible molecular mass of M = 170: the signal at *m*/*z* 139 would then represent (M^+-hydroxymethyl) or (M^+-methoxy), while the one at *m*/*z* 155 would be formed upon loss of a methyl group from the molecular ion.

The presence of a hydroxymethyl group was supported by the fact that the product could be trifluoroacetylated.[3] Furthermore, microhydrogenation or reaction with lithium aluminum tetrahydride[3] left the molecule unchanged, which excluded the presence of a C−C double bond or a carbonyl group. The high intensity of *m*/*z* 139 indicated the formation of an oxonium ion,[4,5] which suggested the presence of a second oxygen in the molecule. Therefore, a dioxygenated monoterpene with a molecular formula of M = $C_{10}H_{18}O_2$ was the most logical, and because of the two degrees of unsaturation, the compound was postulated to be bicyclic. Taking into account that the two earlier identified components of the pheromone bouquet were grandisal and grandisol,[2] it was reasonable to believe the target compound to be structurally related to the same terpene skeleton. Consequently, a reasonable candidate seemed to be 2-hydroxymethyl-2,6-dimethyl-3-oxabicyclo[4.2.0]octane, which would be formed after epoxidation of the 1-methylethenyl group of grandisol followed by opening of the epoxide intermediate upon intramolecular attack of the hydroxyl group. Epoxides are well-known biogenetic intermediates in the formation of pheromones, and the process outlined here strongly resembles that postulated for the formation of pityol from sulcatol.[6]

In a kind of biomimetic approach, racemic grandisol was reacted with *m*-chloroperbenzoic acid (Figure 3). The expected epoxide could not be isolated, as the target compound had already been spontaneously formed from the intermediate under the employed reaction conditions.

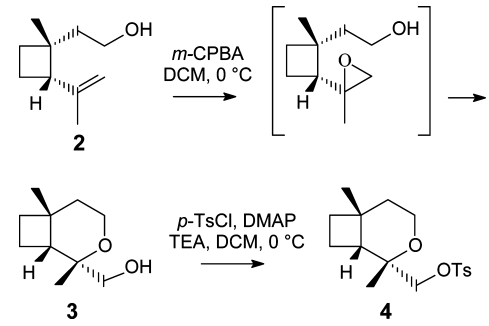

Figure 3. Synthesis of papayanol (**3**) and its tosylate (**4**).

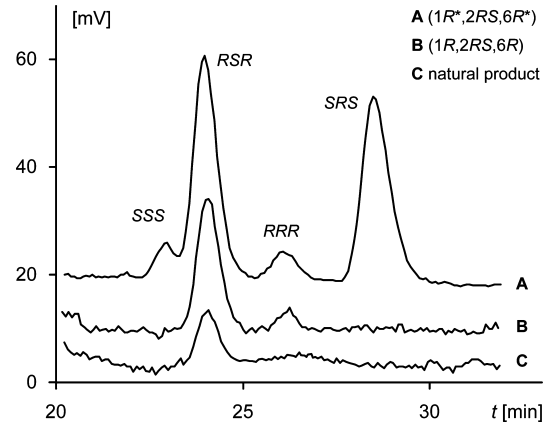

Figure 4. Enantioselective separation of papayanol (**3**).

The reaction yielded two (racemic) diastereomers, which were well separated by gas chromatography on a conventional column. The mixture was strongly biased by the later eluting racemate, and the natural extract showed the same relations: a very minor peak and a highly dominating one. Both natural products showed the same mass spectra and the same retention times (coinjection) as the synthetic compounds.

Upon enantioselective gas chromatography, using a modified β-cyclodextrin as the stationary phase,[7] the two pairs of synthetic enantiomers, obtained from racemic grandisol, were well separated. Using (1*R*,2*S*)-(+)-grandisol as the starting material[8] revealed the earlier eluting main compound and its later eluting minor stereoisomer to show (1*R*,6*R*)-configuration. Under the same conditions, the major pair of enantiomers was baseline separated, showing an α-value $tr_{(1S,6S)}$:$tr_{(1R,6R)}$ = 1.19. Comparison of the retention times of synthetic and natural products (coinjection) revealed the latter to show (1*R*,6*R*)-configuration (Figure 4).

Finally, the absolute configuration at C2 of the bicyclus was assigned according to results of NMR experiments using

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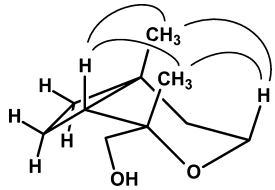

Figure 5. NOESY correlation in papayanol (**3**).

the synthesized compound. Due to the chemical shift of the methyl groups at C2 and C6, no NOESY-cross-peak could be observed for a direct coupling. The correlation pair of H-10/H-1 and H-11/H-1 indicated that the methyl groups in the main compound are positioned on the same side of the molecule, which was further supported by the presence of cross-peaks between the protons H-10/*ax*H-4 and H-11/*ax*H-4 (Figure 5).

Structure assignments were further confirmed by X-ray crystal structure determinations of 2,6-dimethyl-2-(*p*-toluylsulfonyloxy)methyl-3-oxabicyclo[4.2.0]octane (**4**) (Figure 6).

As a result, the third male-produced volatile released by the papaya borer *Pseudopiazurus obesus* could be identified to be the new (1*R*,2*S*,6*R*)-2-hydroxymethyl-2,6-dimethyl-3-oxabicyclo[4.2.0]octane (**3**), to which we have assigned the trivial name papayanol. In nature, papayanol is accompanied by small amounts of its (1*R*,2*R*,6*R*)-diastereomer (see above). While grandisol (**2**), grandisal (**1**), and grandisoic acid (**5**) are relatively widespread among curculionid and scolytid beetles,[9] this is the first time that a grandisol derivative has

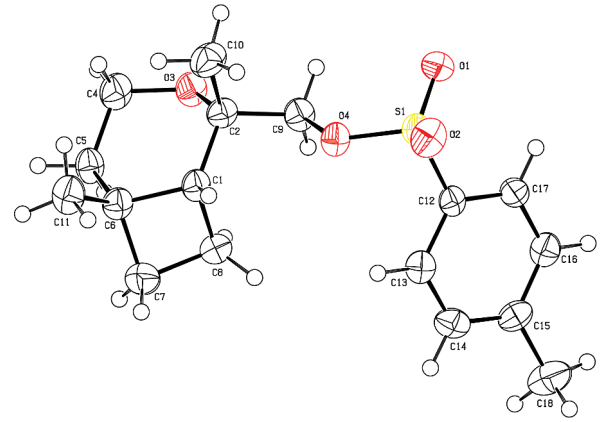

Figure 6. Ortep projection of the tosylate (**4**).

been identified showing a more complex (bio)genesis. Given the present results, one could expect the corresponding "papayanal" (**6**) or the lactone (**7**) (see Figure 1) derived from grandisoic acid to be found in nature. Investigations concerning the biological activity of the *Pseudopiazurus* compounds will be published elsewhere.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H, ^{13}C NMR, and 2D spectra for **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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