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A Short Biomimetic Synthesis of the Meroterpenoids Guajadial and Psidial A

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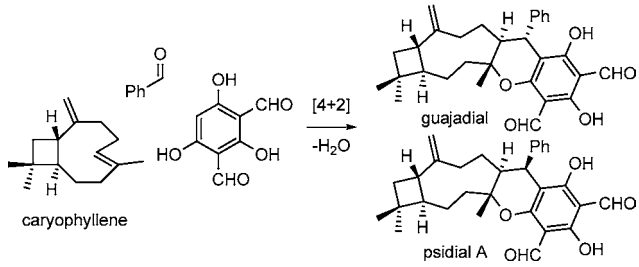
ABSTRACT



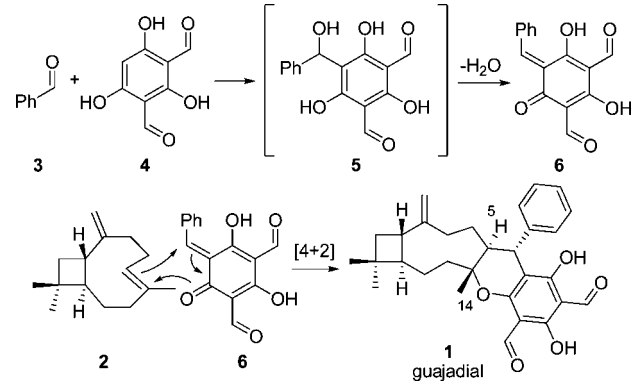
The biosynthesis of the meroterpenoid guajadial was previously hypothesized to occur via a hetero-Diels−Alder reaction between caryophyllene and an *o*-quinone methide. This hypothesis has been verified via the biomimetic synthesis of guajadial and psidial A in an aqueous three-component coupling reaction, between caryophyllene, benzaldehyde, and diformylphloroglucinol.

Psidium guajava (guava) has long been used in African and Asian folk medicine to treat conditions such as diabetes and hypertension. Pharmacological screening has shown that extracts from the bark, fruit, and leaves possess varied biological activities.[1] Guajadial (**1**) is a novel meroterpenoid that was recently isolated from the leaves of *Psidium guajava* (guava) (Scheme 1).[1]

Liu et al. have suggested that guajadial (**1**) is formed biosynthetically via a hetero-Diels−Alder reaction between caryophyllene **2** and an *o*-quinone methide.[1] Interestingly, in their proposal isocaryophyllene (*cis*-caryophyllene) not caryophyllene **2** was presented in the biosynthetic scheme, despite the *anti* relationship between H-5 and C-14 (Scheme 1).[1]

We envisaged that the relative stereochemistry of guajadial (**1**) may be partly controlled by the conformation of caryophyllene **2** during the hetero-Diels−Alder reaction.[2] However, other influential factors like hydrophobic interaction or π-stacking in the active site of the enzyme cannot be

Scheme 1. Our Proposed Biomimetic Approach to Guajadial (**1**)



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(1) (a) Yang, X.-L.; Hsieh, K.-L.; Liu, J.-K. *Org. Lett.* **2007**, *9*, 5135, and references cited therein. (b) *o*-quinone methide **6** (Scheme 1) is an analogue of the biological *o*-quinone methide proposed by J.-K. Liu. (c) For reviews on biosynthetic Diels−Alder reactions see: (d) Laschat, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 289. (e) Ichihara, A.; Oikawa, H. *Curr. Org. Chem.* **1998**, *2*, 365. (f) Stocking, E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078. (g) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321.

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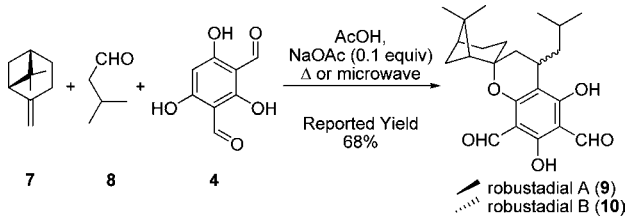
disregarded. Retrosynthetically, the requisite *o*-quinone methide **6** can be derived from a simple Knoevenagel condensation[3] between diformylphloroglucinol **4** and benzaldehyde **3**, via intermediate **5**. Therefore a domino three-component one-pot reaction between diformylphloroglucinol **4**, benzaldehyde **3**, and caryophyllene **2** would constitute a simple biomimetic synthesis of guajadial (**1**) (Scheme 1).

A search in the literature revealed that such a strategy had been applied in the synthesis of the robustadials A and B (**9** and **10**) by Bharate and Singh (Scheme 2).[4] A three-component coupling of diformylphloroglucinol **4**, isovaleraldehyde **8**, and β-pinene **7** was achieved under both thermal and microwave irradiation conditions.[4] The high efficiency of their synthesis was very encouraging, as intermolecular Diels−Alder reactions between *o*-quinone methides and nonelectron-rich double bonds are known to be difficult to achieve, due to the facile dimerization of the *o*-quinone methides.[5]

Scheme 2. Bharate and Singh's Biomimetic Synthesis of Robustadial A and B (**9** and **10**)[4]



However, the situation with the biomimetic approach to guajadial (**1**) is further complicated by three issues. First, benzaldehyde **3** is less reactive toward nucleophilic attack than isovaleraldehyde **8**. Second, there are two double bonds in caryophyllene **2**, each of which is potentially capable of reacting with *o*-quinone methide **6**. It is known, however, that the endocyclic double bond in caryophyllene **2** is the more reactive alkene, due to the intrinsic strain of the nine-membered ring.[2] Third, in the case of the robustadials (**9** and **10**), the *o*-quinone methide approached β-pinene **7** in an *anti* fashion with respect to the *gem*-dimethyl groups (Scheme 2).[4] However, caryophyllene **2** has a certain degree of conformational mobility and it was not certain how this flexibility would affect the facial bias in the in vitro hetero-Diels−Alder reaction. It is known from ^{13}C NMR studies and molecular mechanics calculations that caryophyllene **2** has four possible conformations ($\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, $\beta\beta$), which vary according to the relative disposition of the exocyclic methylene and olefinic methyl groups (Figure 1).[2] We believe the proposed biogenetic hetero-Diels−Alder reaction (Scheme 1) must involve the $\beta\alpha$ conformer (the most stable conformer) of caryophyllene **2**, with our proposed transition states shown below (Figure 2).

The preparation of diformylphloroglucinol **4** was previously reported by Bharate and Singh from phloroglucinol dihydrate **11**, using 3 equiv of $POCl_3$ and DMF.[4] However, in our hands, attempts to reproduce this double formylation

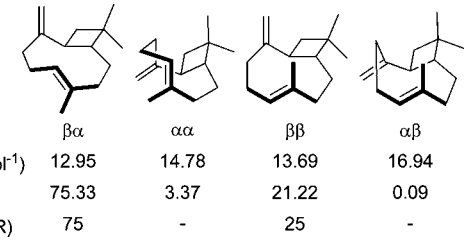


Figure 1. Conformations of caryophyllene **2** with the predicted and ^{13}C NMR determined relative populations.[2]

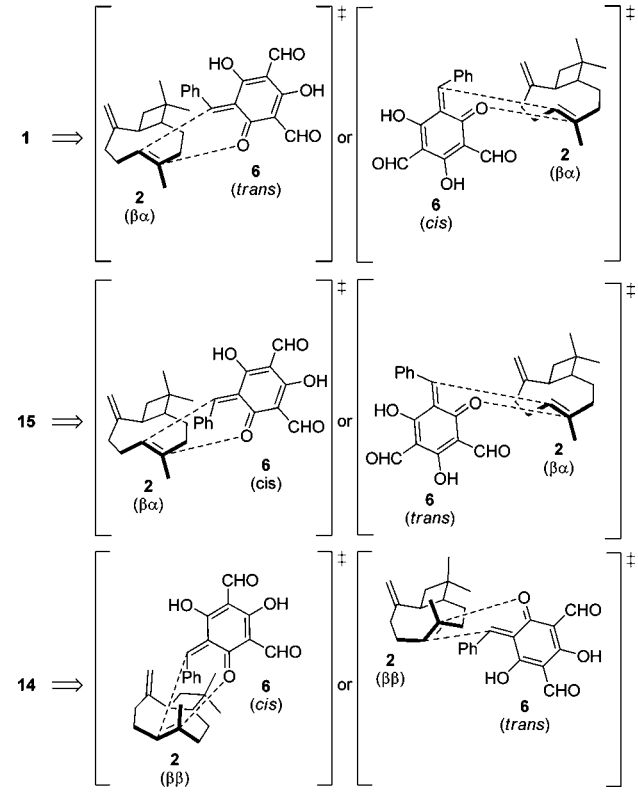


Figure 2. Plausible transition states leading to guajadial (**1**) psidial A (**15**) and compound **14**.

failed. Instead it was observed that after workup formylphloroglucinol **12** was formed in good yield (Scheme 3). Attempts to achieve the formylation of **12** were unsuccessful, resulting in complete decomposition (Scheme 3). A search of the literature revealed that Hintermann et al. had also reported the diformylation of phloroglucinol.[6] Crucially, however, they conducted the reaction upon anhydrous

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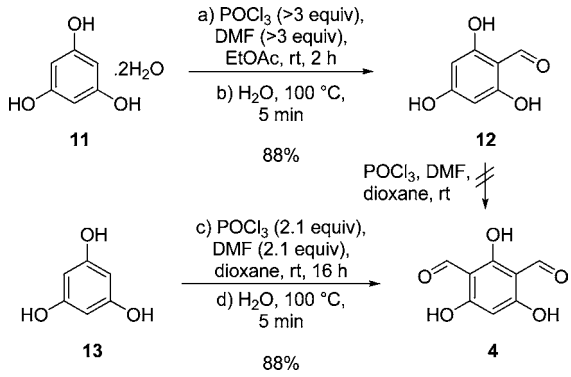
(3) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2596.
(4) Bharate, S. B.; Singh, I. P. *Tetrahedron Lett.* **2006**, *47*, 7021. It should be noted that attempts to reproduce the synthesis of the robustadials only gave a 9% yield of the desired products.
(5) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.
(6) Dittmer, C.; Rabbe, G.; Hintermann, L. *Eur. J. Org. Chem.* **2007**, 5886.

Scheme 3. Synthesis of Diformylphloroglucinol **4** and Formylphloroglucinol **12**



phloroglucinol **13**.[6] Indeed when the diformylation was attempted upon anhydrous phloroglucinol **13** a good yield of diformylphloroglucinol **4** was achieved (Scheme 3).

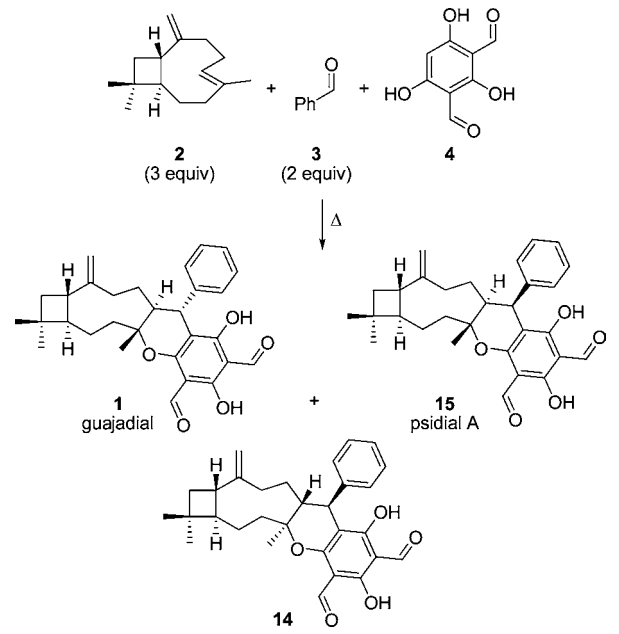
Initial attempts to synthesize guajadial (**1**) were made by using the conditions of Bharate and Singh.[4] This gave very little guajadial (**1**), along with two other compounds which were later shown to be a diastereomer of guajadial (**14**) and psidial A (**15**), an epimer of guajadial that is a protein tyrosine phosphatase inhibitor,[7] in a total ca. 3% yield (Table 1, entry 1). We believe psidial A (**15**) is formed via a hetero-Diels−Alder reaction involving the $\beta\alpha$ conformer of caryophyllene **2**, while diastereomer **14** is formed from the $\beta\beta$ conformer (Figure 2). The ratio of guajadial (**1**) and psidial A (**15**) to compound **14** is in good agreement with the reported $\beta\alpha-\beta\beta$ conformation populations (Figure 1).[2]

Heating the same mixture for 24 h improved the yield to 14% (Table 1, entry 2), and extending the heating period to 7 days gave a 19% yield (Table 1, entry 3). It should be noted that the ratio of psidial A (**15**) to guajadial (**1**) increased upon extending the reaction time, indicating that epimerization does occur under these reaction conditions. Attempts to conduct the biomimetic synthesis under microwave conditions gave a complex mixture in which compounds **1**, **14**, and **15** were only barely observable on the ^{1}H NMR baseline (Table 1, entry 4). In addition, this microwave experiment was found to have variable reproducibility. The three-component reaction was next examined in organic solvents, with neither toluene nor acetonitrile proving to be effective solvents for this reaction (Table 1, entries 5 and 6).

Water has been used with great success to promote otherwise sluggish Diels−Alder reactions;[8,9] additionally all the reactants are either hydrophobic or only sparingly soluble in water, and therefore not predicted to be heavily hydrated.

Heating the three-component mixture in water for 15 h generated a promising 14% yield (Table 1, entry 7). Further

Table 1. Condition Screen for the Biomimetic Synthesis of Guajadial (**1**)



entry	conditions	t [°C]	time [h]	yield[a] [%]
1	AcOH + NaOAc (0.1 equiv)	80	2	3
2	AcOH + NaOAc (0.1 equiv)	80	24	14[b]
3	AcOH + NaOAc (0.1 equiv)	80	168	19[c]
4	AcOH + NaOAc (0.1 equiv), microwave, 300W[d]	200	0.25	N.D.[e]
5	toluene	110	15	
6	acetonitrile	82	15	
7	H_2O	100	15	14
8	sat. $NaCl_{(aq)}$	100	15	16
9	H_2O + proline (0.2 equiv)	100	15	14
10	5% w/w $PTS_{(aq)}$	100	15	21
11	5% w/w $PTS_{(aq)}$ (slow addition)	100	15	25
12	excess **2** (10 equiv)	100	15	21

[a] NMR yields with pyridine as internal standard; ratio of **1**:**15**:**14** of ca. 60:20:20. [b] 56:24:20. [c] 50:30:20. [d] Reaction was conducted in a CEM Discover microwave reactor. [e] Not determined.

improvements were envisaged for the initial Knoevenagel condensation: addition of organocatalysts[10] and use of a saturated brine solution as the reaction medium, due to its dehydrating nature.[11] However, neither alteration gave a significant improvement to the observed yield (Table 1, entries 8 and 9). One reason for the low efficiency of the aqueous reactions may be the unequal dispersal of the reactants in water. Surfactants have been used to decrease

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(11) He, H.; Pei, B.-J.; Chou, H.-H.; Tian, T.; Chan, W.-H.; Lee, A. W. M. *Org. Lett.* **2008**, *10*, 2421.

the heterogeneity of aqueous reaction mixtures,[12] indeed performing this reaction in an aqueous 5% w/w PEG-600/α-Tocopherol-based diester of Sebacic acid (PTS) solution resulted in a 21% yield (Table 1, entry 10).[13] Eventually the optimal conditions were found to be slow addition of diformylphloroglucinol **4** to a mixture of benzaldehyde **3** and caryophyllene **2** in an aqueous 5% w/w PTS solution under reflux, resulting in a 25% yield (Table 1, entry 11). Interestingly when using neat caryophyllene **2** as both reactant and solvent, the products were obtained in a 21% yield (Table 1, entry 12). The reaction conditions screened all gave a ratio of 80:20 for guajadial (**1**) and psidial A (**15**) to diastereomer **14**, which is in good agreement with the relative populations of the $\beta\alpha$ and $\beta\beta$ conformers of caryophyllene **2**.

A preparative synthesis of guajadial (**1**) was carried out. Subsequent column chromatography was followed by HPLC purification of the cleanest fractions, resulting in an unoptimized 6% isolated yield of guajadial (**1**) as a white powder. Crystals of guajadial (**1**) and psidial A (**15**) suitable for X-ray diffraction studies (Figure 3)[14] were formed by cooling saturated acetonitrile solutions from ambient temperature to −25 °C.

Despite extensive HPLC purification and recrystallization, it was observed that a small quantity of psidial A (**15**) was always present in synthetic guajadial (**1**). Professor Liu kindly provided us with an authentic sample of natural guajadial (**1**) for direct comparison with our synthetic material. However, their authentic sample was now also a mixture of

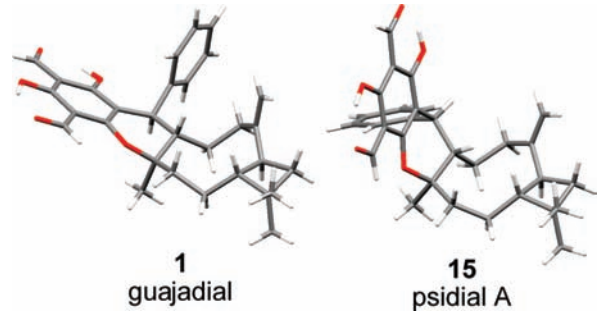

Figure 3. Molecular structure of guajadial (**1**) and psidial A (**15**) from single crystal diffraction data.[14]

guajadial (**1**) and psidial A (**15**) (see the Supporting Information). Liu et al. reported an $[\alpha]^{26}_{D}$ of −23.1 (*c* 0.5, acetone) for natural guajadial (**1**).[1] We obtained an $[\alpha]^{26}_{D}$ of +1.6 (*c* 0.5, acetone) for synthetic guajadial (**1**). However, synthetic psidial A (**15**) has a large $[\alpha]^{26}_{D}$ of +88.8 (*c* 0.5, acetone), and so the small quantity of **15** present in our synthetic sample would obviously have a large effect upon the recorded optical rotation.

In conclusion, a short biomimetic synthesis of guajadial (**1**) and psidial A (**15**) has been achieved, providing experimental support for the proposed biosynthesis.[1] It was found that the stereochemical outcome of the hetero-Diels−Alder reaction is largely controlled by the local conformation and intrinsic chirality of caryophyllene **2** (Figure 2).[2] In addition the absolute configurations of guajadial (**1**) and psidial A (**15**) were established. A biomimetic hetero-Diels−Alder reaction, involving an *o*-quinone methide, has been successfully conducted in water as a green and universal biological solvent, without the use of acid or base catalysis. We believe water has the potential to become a very useful solvent for other *o*-quinone methide reactions.

Acknowledgment. We thank Givaudan SA, Genève (Dr. Philip Kraft) for the generous supply of caryophyllene. We also thank Professor Ji-Kai Liu (Kunming Institute of Botany) for providing us with an authentic sample of guajadial, and Prof. Gouverneur's group (Chemistry Research Laboratory, University of Oxford) for the use of their HPLC equipment.

Supporting Information Available: Synthetic procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Single crystal X-ray diffraction data were colleced on a sample mounted using the oil drop technique at 150 K with an Oxford Cryosystems Cryostream open flow N_2 cooling device: Cosier?.; Glazer?. *J. Appl. Crystallogr.* **1986**, *19*, 105. Data were collected using a Nonius Kappa-CCD area detector diffractometer, with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Cell parameters and intensity data were processed using the DENZO-SMN package and reflection intensities were corrected for absorption effects by the multiscan method, based on multiple scans of identical and Laue equivalent reflections. [Otwinowski; Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode*, *Methods Enzymology*; Academic Press: New York , 1997; p 276]. The structures were solved by direct methods [Altomare, A.; Cascarano, G.; Givcovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435]. and refined by full-matrix least squares on F2, using the CRYSTALS suite. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487. The Flack *x* parameter [Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876] was determined for both compounds and the Bijovet pairs analyzed to give the Hooft *y* parameters. Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Crystallogr.* **2008**, *41*, 96. Thompson, A. L.; Watkin, D. J. *Tetrahedron: Asymmetry* **2009**, *20*, 712. Full refinement details including *x*, *y*, and derived probabilities are given in the CIF. Crystallographic data (excluding structure factors) for the structures of **1** and **15** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 767572 and 767573). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.