

## Structural characterization of unusually stable polycyclic ozonides



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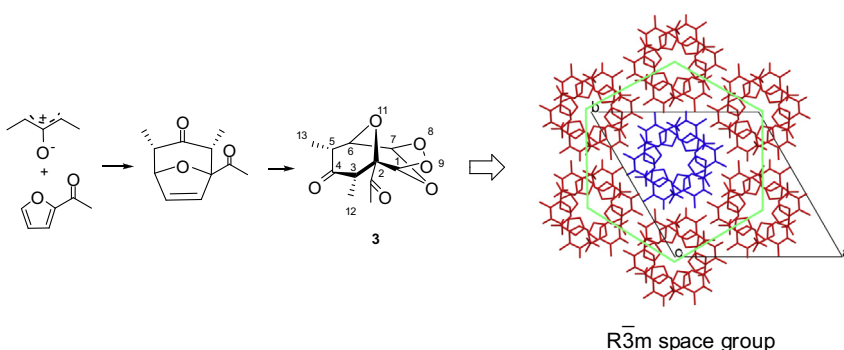
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### HIGHLIGHTS

- Compound **3** crystallizes in the unusual space group  $R\bar{3}m$ .
- Most ozonides crystallize in the monoclinic system with  $P2_1/c$  space group as racemic crystal.
- Compound **3** space group represents only  $\sim 0.04\%$  of small-molecule crystal structures.
- X-ray crystallographic studies of stable polycyclic ozonides were carried out.

### GRAPHICAL ABSTRACT



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### ABSTRACT

The single crystal structure of seven tri- and tetracyclic ozonides derived from 8-oxabicyclo[3.2.1]oct-6-en-3-one have been characterized by X-ray diffraction method. Five ozonides (**4**, **5**, **6**, **7** and **8**) crystallize in the monoclinic crystal system with  $P2_1/c$  space group. Compound **3** crystallize in the unusual centrosymmetric space group  $R\bar{3}m$ , which represents  $\sim 0.04\%$  of the total number of structures know. The supramolecular structure of **3** forms infinite channels in a hexagram fashion, resulting in a honeycomb-like structure. Semi-empirical (PM6) and density functional theory methods (DFT) with the B3LYP functional and the 6-31G(d) basis set were used to optimize the geometries and compute structural parameters (bond lengths, angles and dihedral angles) that could be compared to the refined crystal structure. The theoretical results show good agreements with the experimental structure.

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### Introduction

Chemical crop protection plays a vital role in ensuring sufficient food supply to a growing world population, since the expansion of cultivated areas is not enough to allow a harvest increase at the

required rate [1,2]. To improve the world agriculture performance it is necessary to ensure an intensive control of pests, diseases, and specially selected weeds, always taking into account environmental issues. In the face of ever more stringent demands, the discovery of new agrochemicals has become an important research area since it contributes to reduce the losses in the production and storage of crops, reducing the costs of agricultural products [3–5].

Natural products can be used as models to inspire the synthesis of new bioactive molecules. In this context, artemisinin (**1**, Fig. 1), a

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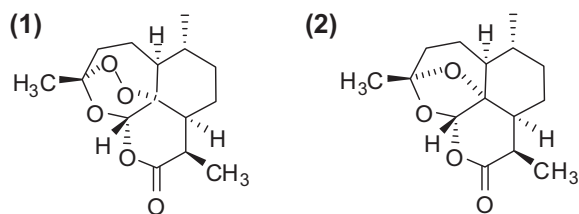


Fig. 1. Structures of artemisinin (1) and deoxyartemisinin (2).

secondary metabolite isolated from the shoots of sweet wormwood (*Artemisia annua* L.), and its semi synthetic analogs have a powerful inhibitory effect on plant growth [6–9]. Artemisinin and selected derivatives are also known for their antimalarial activity against multidrug-resistant forms of the parasite *Plasmodium falciparum*. In fact such compounds are widely used as antimalarial drugs as part of the Artemisinin Combination Therapy (ACT) protocols recommended by WHO [10].

The phytotoxic and antimalarial activities of these compounds are dependent upon the presence of the peroxide moiety, since deoxyartemisinin (2, Fig. 1) is inactive.

Following our ongoing research to develop new compounds with herbicidal and/or plant growth regulating activity [11–14], we have described the synthesis and biological activities of some stable ozonides [15,16]. This research was based on a seminal discovery by our group that several ozonides derived from oxabicyclic compounds are stable and endowed with activity against *P. falciparum* [17,18]. Several of such ozonides showed an appreciable stability that allowed their purification and characterization, although that class of compounds has been described as very unstable and explosive [19,20].

Considering that there are few reports in the literature on X-ray studies of ozonides due to their general instability [21,22], and also taking into account the importance of molecular structure in the biological activities, in this work the crystal structures of a series of stable tri- and tetracyclic ozonides were investigated. The

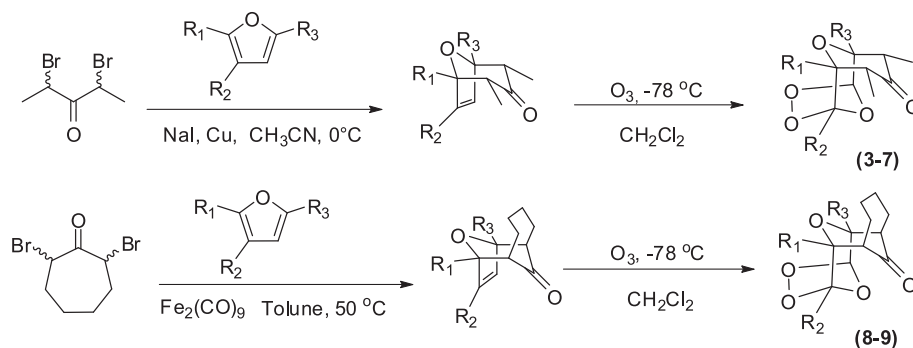
structural experimental results were analyzed and compared with computational studies in order to complete the compounds characterization.

## Experimental

The ozonides (3–9) were prepared following the procedure previously described. All experimental detail and spectroscopic data are in accordance to the literature [15,16].

### Single crystal X-ray diffraction studies

Crystals of compounds 3–9 (Scheme 1) were obtained by warming each compound in hexane, followed by addition of some drops of dichloromethane until the solid was completely dissolved and the resulting solutions were left static at room temperature. White well-shaped single crystals suitably for X-ray analyses were formed after 24 h. They were separated, washed with cold hexane, and dried. Single crystals of 3–9 were selected for the X-ray experiments. All measurements were made at room temperature (293 K) on an Enraf-Nonius Kappa-CCD diffractometer with graphite monochromated Mo K $\alpha$ . The final unit cell parameters were based on all reflections. Data collection was made using the COLLECT software [23]; integration and scaling of the reflections were performed with the HKL Denzo–Scalepack software system [24]. The structures were solved and the models refined using the SHELXL-2013 software [25]. Non-hydrogen atoms of all structures were clearly solved and full-matrix least-squares refinements of these atoms in  $F^2$ , with anisotropic thermal parameters, were carried out. Hydrogen atoms were positioned stereochemically and were refined with fixed individual displacement parameters [Uiso(H) = 1.5Ueq(C) for methyl groups or 1.2Ueq(C) methyne and methylene groups], using the SHELXL riding model with C–H bond lengths of 0.96, 1.00 and 0.99 Å for methyl, methyne and methylene groups, respectively. The hydroxyl H atom in 6 was located by difference Fourier synthesis and was refined with free coordinates and Uiso(H) = 1.5Ueq(O). WINGX software [26] was



Compound	Yield (%)	Substituents		
		R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
3	98	COCH <sub>3</sub>	H	H
4	100	CH <sub>2</sub> CH <sub>3</sub>	H	H
5	50	CH <sub>3</sub>	(CO)OCH <sub>3</sub>	H
6	75	CH <sub>3</sub>	CH <sub>2</sub> OH	H
7	100	CH <sub>3</sub>	CH <sub>2</sub> OCH <sub>3</sub>	H
8	42	CH <sub>2</sub> CH <sub>3</sub>	H	H
9	55	CH <sub>3</sub>	H	CH <sub>3</sub>

Scheme 1. Structures of ozonides 3–9. The yields correspond to the ozonolysis step ([15,16]).

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