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The absolute configuration of the palmarumycins C_9, C_{10}, and C_{12} by quantum-mechanical calculations of CD spectra

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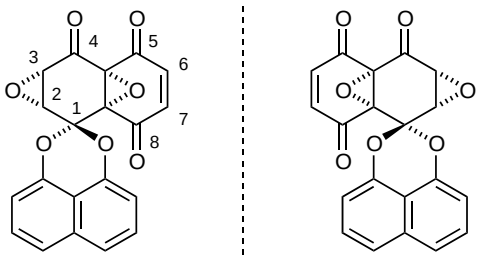
Abstract—The absolute configurations of the palmarumycins C_9 **1a**, C_{10} **2**, and C_{12} **3** were assigned by comparison of the quantum-mechanically calculated with the experimental CD spectra as (2*R*,3*S*,4a*S*,8a*R*), (2*R*,3*R*,4*S*,4a*S*,8a*R*), and (2*R*,3*R*,4*R*), respectively.

The palmarumycins are part of the spirobisnaphthalene group of secondary metabolites isolated from the fungus *Coniothyrium palmarum*,[1] another *Coniothyrium* species[2] and several other fungi (review[3]). Generally, a spironaphthodioxin subunit is connected to a decalin unit as shown in the structure of palmarumycin C_9 **1a** (Fig. 1). Several of the spirobisnaphthalene secondary metabolites show interesting biological activities such as anticancer activity[4,5] as discussed in detail at the 1994 AACR (American Association for Cancer Research) meeting.[6] Palmarumycins C_9 **1a**, C_{10} **2** and C_{12} **3** (Fig. 1) also show antifungal and antibacterial activity.[2]



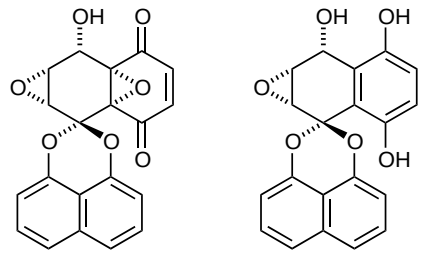


Figure 1. Enantiomers of palmarumycin C_9 **1a** and **1b**, and structures of palmarumycins C_{10} **2** and C_{12} **3**.

The absolute configuration of the diepoxins, spirobisnaphthalenes related to the palmarumycins, was determined using the exciton coupling CD method.[7] In a different approach we employed quantum-chemical calculations of the CD spectra and comparison with their experimental CD spectra to elucidate the absolute configuration of palmarumycins C_2 and CP_3,[8] as well as that of CP_{4a} and CP_5.[9] Herein, we describe the use of this method to assign the absolute configuration of palmarumycins C_9 **1a**, C_{10} **2**, and C_{12} **3**.

The relative configuration of the palmarumycins C_9 **1a**, C_{10} **2**, and C_{12} **3**, in particular the *cis* orientation of the two epoxide rings and/or the hydroxyl groups, was deduced from the NMR spectra,[2] in agreement with identical results for the related diepoxins.[10] The procedure is exemplified for palmarumycin C_9 **1**, which can either exist as the (2*R*,3*S*,4a*S*,8a*R*) enantiomer **1a** or the (2*S*,3*R*,4a*R*,8a*S*) enantiomer **1b** as shown in Fig. 1.

Conformational analysis, using the Spartan SGI Version 5.1.3 package,[11] showed that the upper part of the molecule with the two epoxide rings is very rigid. In contrast, the bottom naphthyl moiety can oscillate around the dioxin ring plane. The heat of formation ΔH_f in dependence on the torsional angle ϑ is shown in Fig. 2a.

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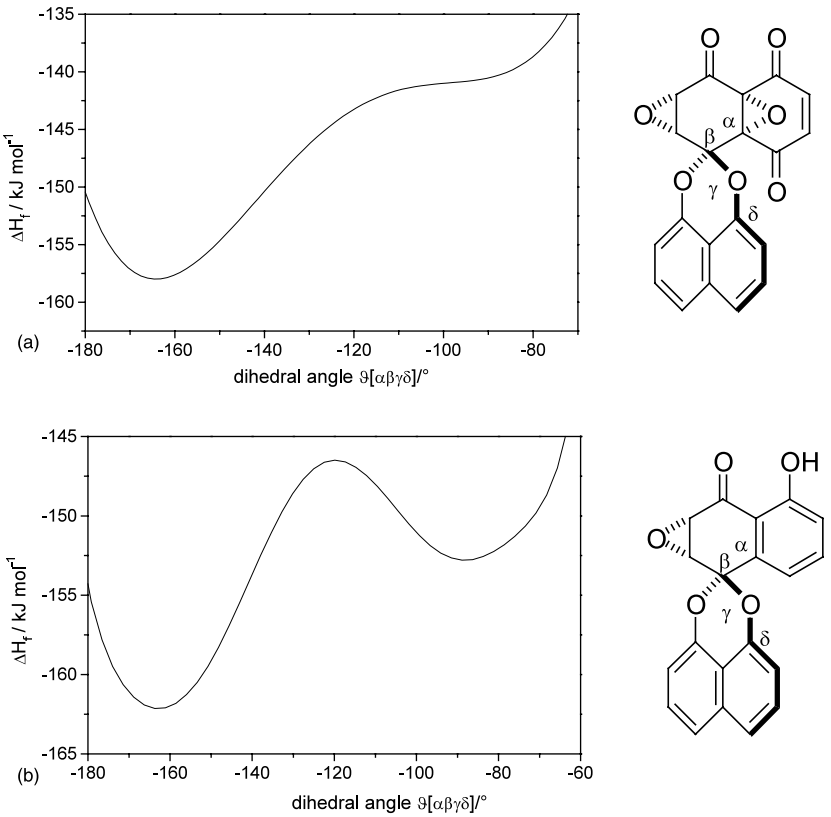

Figure 2. (a) Conformational energy minimum of palmarumycin C_9 **1** in relation to the torsional angle ϑ. Only one energy minimum can be detected. This is in contrast to calculations with palmarumycin C_2 with two distinct minima.[8] The carbonyl group present at C(8) in palmarumycin C_9 probably restricts the movement of the naphthalene ring due to steric hindrance. (b) Conformational energy minimum of palmarumycin C_2 **5** in relation to the torsional angle ϑ.

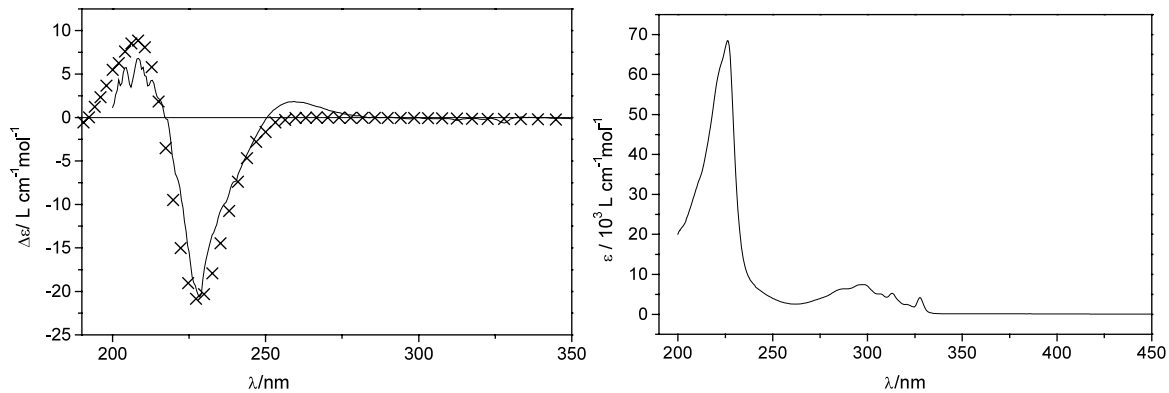

Figure 3. Experimental CD spectrum for palmarumycin C_9 (line) and the calculated one (cross) for the (2*R*,3*S*,4a*S*,8a*R*) enantiomer **1a**. Right-hand diagram: UV spectrum.

Accordingly, for the calculation of the CD spectrum of palmarumycin C_9 **1**, only one major conformation had to be considered in view of the fact that the saddle point seen in Fig. 1a is more than 10 kJ/mol higher in energy. In Fig. 3, the CD spectra (experimental and calculated[8,9,12,13]) for palmarumycin C_9 **1a** one for the (2*R*,3*S*,4a*S*,8a*R*) enantiomer are shown. The right-hand diagram is the UV spectrum

The CD spectrum shows a weak positive Cotton effect at 256 nm and a strong negative effect at ca. 227 nm, originating from a ^1B_b transition of the naphthalene ring. The calculated and the experimental spectra show good agreement and the (2*R*,3*S*,4a*S*,8a*R*) configuration **1a** (Fig. 1) can be assigned to palmarumycin C_9. Similar results were obtained for palmarumycin C_{10} (Fig. 4, see structure **2** in Fig. 1), identical with 5-oxo-cladospironebisepoxide[14] or diepoxin ϕ, independently confirming the absolute configuration established by Schlingmann et al. for diepoxin ϕ employing the exciton coupling CD method.[7]

The situation was somewhat more complicated with palmarumycin C_{12} **3**. In addition to the oscillation of

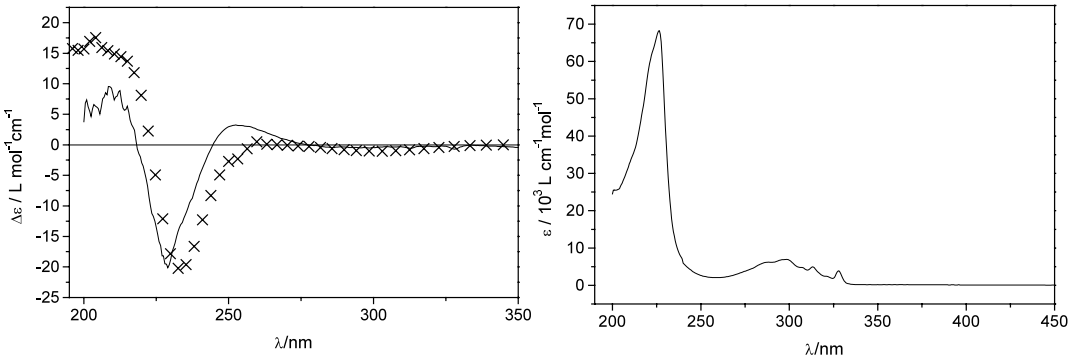

Figure 4. Experimental CD spectrum for palmarumycin C_{10} (line) and the calculated one (cross) for the (2*R*,3*R*,4*S*,4a*S*,8a*R*) enantiomer **2**. Right-hand diagram: UV spectrum.

the naphthalene ring, the cyclohexane ring is more flexible than in **2** and the hydroxyl groups show free rotation. The calculation showed that four major conformers have to be considered. In two of these conformers, the cyclohexane adopts a pseudo boat conformation, whereas the six-membered rings in the other two conformers are nearly planar as shown in Fig. 5.

The Boltzmann-weighted CD spectrum for the (2*R*,3*R*,4*R*) enantiomer was calculated[13] and compared with the experimental CD spectrum as shown in Fig. 6.

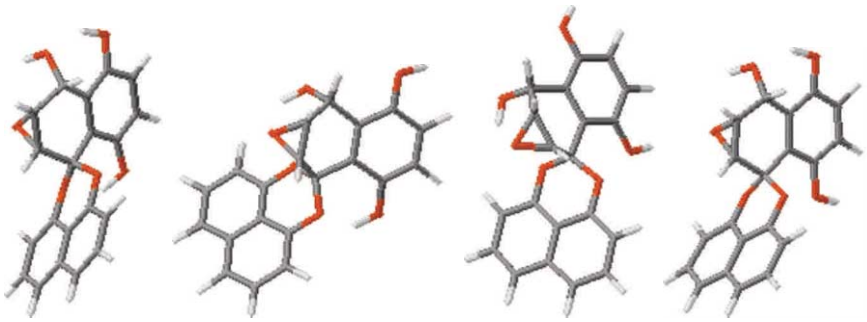

Figure 5. The four relevant conformations of palmarumycin C_{12} **3**.

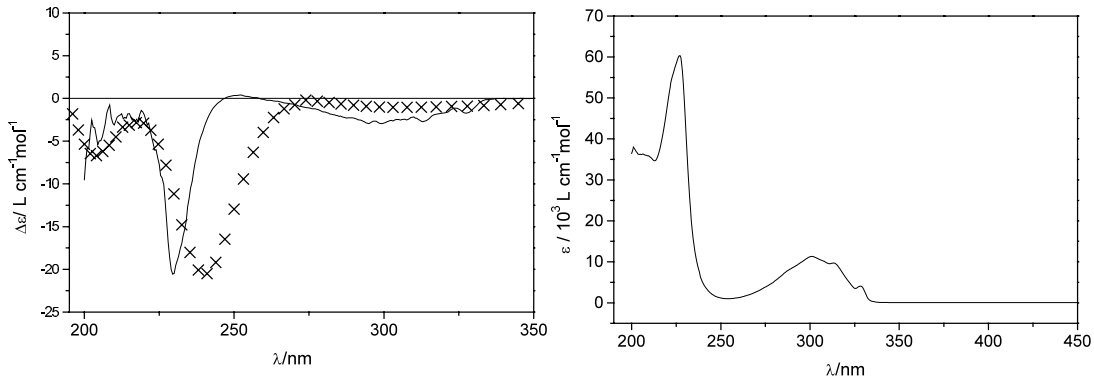

Figure 6. Experimental CD spectrum for palmarumycin C_{12} (line) and the calculated one (cross) for the (2*R*,3*R*,4*R*) enantiomer **3**. Right-hand diagram: UV spectrum

Table 1. CD maxima of palmarumycins C_9, C_{10}, and C_{12} **1**–**3**[12]

Palmarumycin C_9 **1a**		Palmarumycin C_{10} **2**		Palmarumycin C_{12} **3**	
λ/nm	$\Delta\varepsilon$/L mol^{-1}cm^{-1}	λ/nm	$\Delta\varepsilon$/L mol^{-1}cm^{-1}	λ/nm	$\Delta\varepsilon$/L mol^{-1}cm^{-1}
228.5	−20.62	229	−20.15	229.5	−20.57
259	1.82	252	3.24	249.5	0.31
		293	−0.53	299.5	−2.93
		373	−0.75		

Again, the CD spectrum shows a strong negative Cotton effect at 230 nm, originating from the ^1B_b transition of the naphthalene ring, and a weak Cotton effect at ca. 300 nm. In the calculated spectrum, a red shift of 11 nm can be detected. However, the general identity of the shape of the curves leaves no doubt that the (2*R*,3*R*,4*R*)-configuration must be assigned to palmarumycin C_{12} **3**. The CD-maxima of the experimental spectra are listed in Table 1.

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