



Structure reassignment and absolute configuration of 9-*epi*-presilphiperfolan-1-ol

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ABSTRACT

Reevaluation of ¹³C NMR data in combination with X-ray diffraction and VCD studies led us to reassign the structure of (–)-*epi*-presilphiperfolan-1-ol (**1**), isolated from *Anemia tomentosa* var. *anthriscifolia*, to (–)-9-*epi*-presilphiperfolan-1-ol (**2**) and to establish its absolute configuration as 1S,4S,7R,8R,9S.

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Presilphiperfolanes are rare triquinane sesquiterpenes possessing the **2a,4,4,7-tetramethyldecahydro-1H-cyclopenta[cd]indene** ring system that have been found in the essential oil of some species of Asteraceae such as *Flourenzia heterolepis*¹ and *Echinops giganteus* var. *lelyi*² and in the Bryophyta *Conocephalum conicum*.³ Similar ring system molecules having the methyl groups at other positions can also be obtained by catalyzed rearrangements of modphenes⁴ and a new biogenic route for the formation of some of them has just been proposed.⁵

In a recent Letter we described the isolation and structural elucidation of (–)-*epi*-presilphiperfolan-1-ol (**1**)⁶ found as a constituent of the essential oil of *Anemia tomentosa* var. *anthriscifolia*, which displayed antimycobacterial activity.⁷ The proposed structure was based among other facts, on extensive 1D and 2D NMR studies as well as by making a comparison of the ¹³C NMR chemical shifts of **1** and presilphiperfolan-1-ol (**3**), isolated from *C. conicum*³, whose stereostructure was secured by single crystal X-ray diffraction.⁸ This ¹³C NMR spectral comparison revealed that fourteen of the fifteen carbon atom chemical shifts of **1** and **3** were almost identical, while the remaining carbon chemical shift, corresponding to the hydroxyl-bearing atom, was shifted 4.7 ppm to higher frequencies on going from **1** to **3**. A deeper evaluation of this situation leads to the conclusion that changing the stereochemistry at C-1 would modify the geometry of the ring junction and, therefore, several carbon atoms would have different chemical shifts on going from **1** to **3**. As a consequence of the above-mentioned rea-

soning we decided to revise our stereochemical assignments and to determine the absolute configuration of this sesquiterpene.

A single crystal of the natural product was mounted on a glass fiber and placed on a CAD4 X-ray diffractometer for data collection using a scintillation counter detector. A set of 25 machine-centered reflections were recentered affording a tetragonal system which is unusual⁹ for organic molecules and in particular for an optically active sesquiterpene. After collecting 2415 reflections, the crystal literally showed a hole, a damaged caused by the X-ray radiation due to the high volatility of this molecule showing mp 56–58 °C. Although the structure could be solved with this limited number of reflections in the P₄2₁2 system⁹, it was only refined to a modest discrepancy index *R* = 8.4%. Thus a second crystal was mounted in a capillary tube to avoid material lost, an experiment that allowed complete data collection of 4161 reflections which gave the satisfactory structural solution¹⁰ shown in Figure 1, with *R* = 5.2%. To confirm this determination a third crystal was mounted on a glass fiber, cooled to 173 K by means of a nitrogen stream, and collected on a diffractometer equipped with a charge-coupled detector (CCD). From the 18,728 obtained reflections, 3580 were considered as observed allowing structural solution and refinement to *R* = 5.4%. The smaller discrepancy index obtained with the scintillation counter detector instrument, as compared to that with the CCD instrument, is normal since the former detection method, although significantly slower, allows more precise individual data collection.

With the relative stereochemistry of the natural product secured, we turned our attention to the determination of its absolute configuration. The atom coordinates from the X-ray study of **2**

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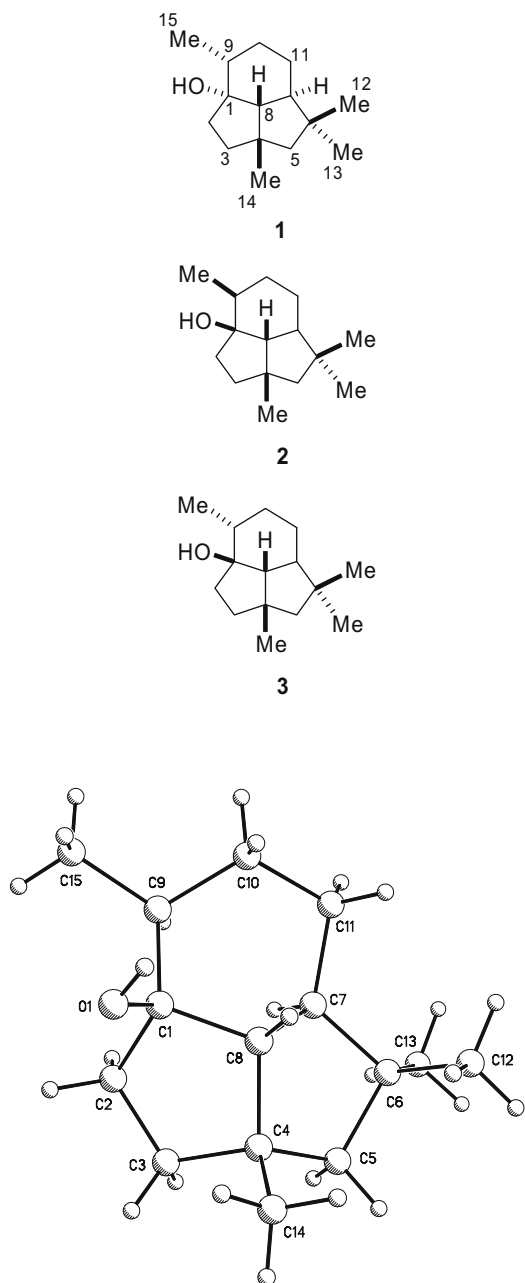


Figure 1. Crystal structure of (–)-9-*epi*-presilphiperfolan-1-ol (**2**).

were used as input data for a conformational distribution using a Monte Carlo guided search within the molecular mechanics force field (MMFF). The resulting nine low energy conformers appeared in the first 1.77 kcal/mol and account for the total conformational distribution (Table 1). Further energy minimization using DFT single point energy calculations at the B3LYP/6-31G(d) level of theory revealed that conformations **2b**, **2h**, and **2i** account for less than 2% of the total conformational distribution and were therefore ignored for further calculations. The remaining six conformers, representing 98% of the conformational distribution, were then optimized at the B3LYP/DGDZVP level of theory, their free energies were calculated at room temperature, and finally vibrational calculations to provide IR and VCD spectra were done at the same level of theory.

A conformational evaluation comparing the solid state structure with those calculated by DFT reveals that **2** in the gas phase has significant mobility, particularly for atoms C2, C3, C5, C6, C9, and

Table 1
Calculated relative energies (kcal/mol) and conformational population of **2**

Conf	ΔE_{MMFF}^a	% MMFF ^b	ΔE_{DFT}^c	% DFT ^d	ΔG_{OPT}^e	% OPT ^f
2a	0.00	26.72	1.19	4.85	0.36	14.75
2b	0.26	17.22	2.59	0.45	– ^g	–
2c	0.32	15.47	0.63	12.31	0.04	24.96
2d	0.34	15.00	0.54	14.50	0.62	9.66
2e	0.63	9.22	1.10	5.60	0.42	13.25
2f	0.88	6.00	0.21	24.93	0.62	9.66
2g	0.99	5.03	0.00	35.82	0.00	27.74
2h	1.13	4.00	2.30	0.74	– ^g	–
2i	1.77	1.34	2.25	0.80	– ^g	–

^a Relative to **2a** with $E_{\text{MMFF}} = 74.60$ kcal/mol.

^b From Spartan'04 according to $\Delta G = -RT \ln K$.

^c Relative to **2g** with $E_{6,31G(d)} = -415712.51$ kcal/mol.

^d From Spartan'04 energies according to $\Delta G = -RT \ln K$.

^e Relative to **2g** with $E_{\text{DGDZVP}} = -415538.17$ kcal/mol.

^f Calculated using GAUSSIAN'03 according to $\Delta G = -RT \ln K$.

^g Not calculated.

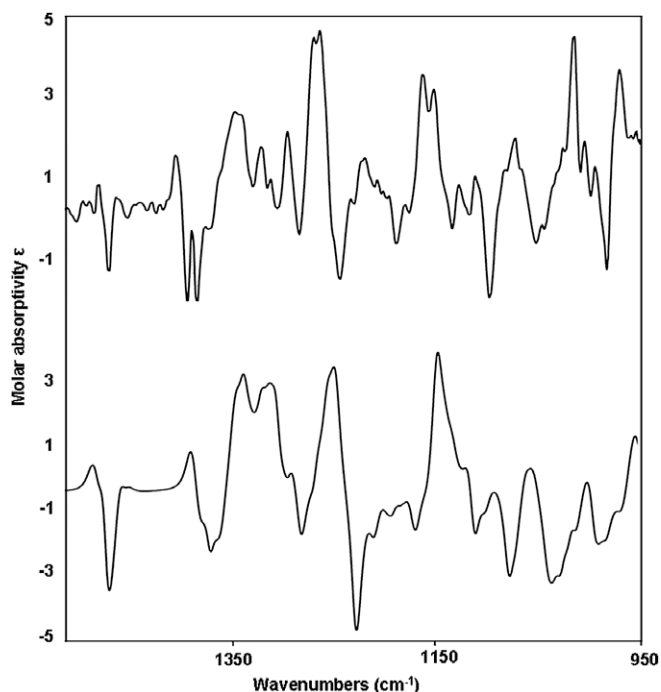


Figure 2. Experimental (top) and calculated (bottom) VCD spectra of **2**.

C10. Therefore no single DFT conformation closely resembles the solid state conformation.

A theoretical VCD spectrum, obtained by weighing the individual spectra of the 6 conformers, according to a Boltzmann distribution, is compared in Figure 2 to the experimental VCD spectrum¹¹ after application of an anharmonicity correction factor of 0.97 which was estimated from comparison of the corresponding theoretical and experimental IR¹¹ spectra. The VCD spectral comparison reveals that the correct enantiomer has been calculated.

In summary, a combined use of single crystal X-ray diffraction and VCD spectral analysis allows to conclude that the stereostructure of the studied natural product is (–)-(1*S*,4*S*,7*R*,8*R*,9*S*)-9-*epi*-presilphiperfolan-1-ol (**2**).

Acknowledgments

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10. The crystal was tetragonal, space group $P4_32_12$, with cell dimensions $a = b = 16.454(2)$ Å, $c = 20.69(3)$ Å, $V = 5601(9)$ Å³, $\rho_{\text{calc}} = 1.055$ g/cm³ for $Z = 8$, $Z' = 2$, $C_{15}H_{26}O$, $MW = 222.36$, and $F(000) = 1984$ e. The total reflections were 4161 (graphite-monochromated Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å), the unique reflections were 3512, and the observed reflections were 2497. The structure was solved by direct methods using SIR2004, the final discrepancy indices, refining 314 parameters, were $R_F = 5.2\%$, $R_w = 12.9\%$, and the highest residual peak in the final difference Fourier map showed an electron density of 0.158 e/Å³. The CCDC deposition number is 763672.
11. The IR and VCD spectra were measured using a BioTools ChiralIR FT spectrophotometer equipped with dual photoelastic modulation using 22.0 mg of **2** in 150 μ L of CCl_4 placed in a BaF_2 cell with 100 μ m pathlength acquiring data at a resolution of 4 cm⁻¹ during 4 h.