# Reinvestigation of terrein absolute configuration using chiroptical spectroscopy

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## Abstract

The absolute configuration of terrein isolated from *A. terreus* is reassigned as (+)-4*R*,5*S* using chiroptical spectroscopy.

## Introduction

Terrein (**1,** *trans*-4,5-dihydroxy-3-[(*E*)-1-propenyl]-2-cyclopenten-1-one) is a biologically active fungal metabolite first isolated in 1935 from *Aspergillus terreus*.[1] Ever since then, it has been reported from different genera including *Penicillium*,[2] *Phoma*,[3] *Pestalotiopsis*[4] and *Neosartorya*.[5] In spite of its structural simplicity, the determination of the absolute configuration of **1** has been a recurring subject in the literature. In 2014, Trabolsy et al.[6] reported the assignment of the absolute stereostructure of (+)-**1** as 4*S*,5*R* by using ECD and TDDFT calculations. However, the experimental and calculated spectra showed a mirror image relationship, which suggests the opposite configuration. Therefore, herein we present a careful investigation of the chiroptical properties of **1** in order to unambiguously determine its absolute stereochemistry.

## Results and Discussion

The ECD spectrum of **1** (Figure 1) eluting from the HPLC system (C-18 column, MeOH/$H_2O$ 3:7, isocratic elution, 0.8 mL/min, 280 nm) was measured in a Jasco CD2095 detector by trapping in a 1.0 cm quartz cell. The theoretical calculations of the chiroptical properties of **1** were carried out after a conformational search at the molecular mechanics level (MM+ force field). The three lowest-energy conformers with relative energy within 6 kcal/mol were further geometry optimized at the B3LYP/6-31G(d) level in gas phase. The comparison of experimental and calculated ECD spectra at the CAM-B3LYP/PCM($H_2O$)/TZVP level established the configuration of the isolated terrein as 4*S*,5*R*. Calculations of the OR of (4*S*,5*R*)-**1** resulted in negative values at 633, 589.3, 578, 546, 436, 365 and 355 nm, both in water and acetone. These findings indicate the configuration of the levorotatory enantiomer as 4*S*,5*R*.

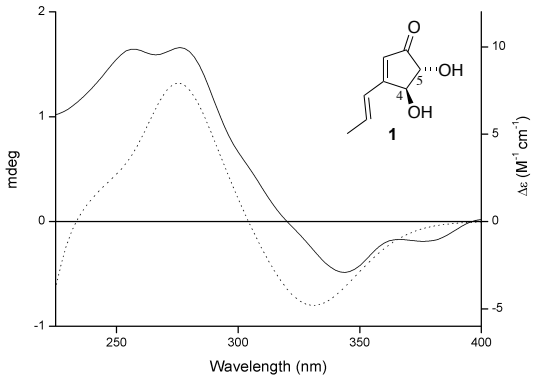


**Figure 1.** Comparison of experimental (solid line) and calculated [(dotted line), CAM-B3LYP/PCM($H_2O$)/TZVP] ECD spectra of (–)-4*S*,5*R*-**1**.

## Conclusions

The comparison of experimental and theoretical ECD and OR data for **1** reveals its absolute configuration to be (+)-4*R*,5*S* and not (+)-4*S*,5*R*, as previously reported. This work also reinforces the risks of relying upon a single chiroptical method for stereochemical characterization of natural products.

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FAPESP

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