



Stereochemical correction and total structure of roridin J



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ABSTRACT

The (2′Z)-configuration of roridin J (**1**) was revised to the (2′E) form by conducting NOE experiments. Although the configurations with respect to the stereogenic carbons on the macrocyclic ring of **1** had remained unknown, a combination of NMR analysis and molecular modeling calculations revealed the (2′E,5′R,6′S,7′E,9′Z,13′S) form. In addition, the modeling calculations successfully reproduced the ¹H and ¹³C NMR chemical shifts as well as the ECD spectrum. An X-ray crystallographic analysis verified all the relative configurations.

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1. Introduction

Trichothecenes carrying macrocyclic rings, such as roridins,^{1,2} verrucarins, baccharins,^{3,4} and muconomyins,⁵ have been isolated from fungal sources, such as the *Myrothecium* and *Fusarium* species. In addition to unique structures, these exhibit potent antifungal,^{6,7} lethal,⁸ and/or cytotoxic^{9–11} properties. Accordingly, this family has attracted attention of the organic chemists and biological scientists.^{1,12,13} Although a comprehensive biological investigation requires well-established three-dimensional structures, the configurations of the macrocyclic moiety in some roridin congeners, e.g., roridin J (**1**) were not determined (Fig. 1). While exploring the fungal secondary metabolites, we had an opportunity to isolate **1** from *Calcarisporium arbuscular*, which led us to fully determine its stereostructure using a combination of spectral analysis and molecular modeling calculations. We succeeded in not only revising the configuration of the C2′/C3′ double bond but also establishing all configurations of asymmetric centers on the macrocycles. The proposed configuration was confirmed by an X-ray crystallographic diffraction analysis.

2. Results and discussion

Roridin J (**1**) was isolated from the culture broth of *C. arbuscula*. The ¹³C NMR spectral data of our sample were coincident with those reported by Jarvis in 1980 (max |Δδ¹³C|: 0.1 ppm, both in CDCl₃).¹⁴ Although Jarvis reported a potent NOE between H₃-12′ and H-2′ to conclude the (2′Z) form for the original structure of roridin J (**1′**), irradiation of H-2′ resulted a remarkable signal enhancement at H-4′ (13%) in our experiment, while that at H₃-12′ was not obvious (1.3%), as shown in Fig. 2. This result allowed us to revise that into the (2′E) configuration shown as **1**. The chemical shift for C12′ (13.26 ppm) supported our revision by taking account of the steric compression effect due to the C1′ carbonyl group.¹⁵ Methyl carbons on the trisubstituted Z-double bonds usually resonate at 22–27 ppm, while those of corresponding E-isomers appear at around 5–10 ppm lower frequency. This was further verified through chemical shift calculations, as described later.

Although several trichothecenes carrying macrocyclic rings have been reported, there is a poor consistency in the configurations of the stereogenic centers on the macrocycles; e.g., four diastereomers at C6′ and C13′ are known as roridin E and its analogs [only episororidin E (**2**) is shown in Fig. 1].¹⁶ As the configurations C4′, C5′, C6′, and C13′ of **1** were unknown, isolation of **1** allowed us to experimentally deduce them.

Prior to these investigations, the relative and absolute

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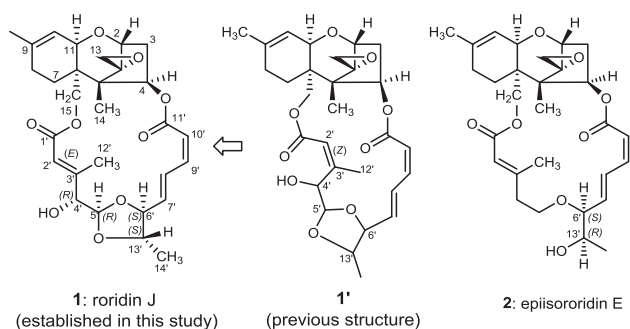


Fig. 1. Structures of roridin J (**1**), its original structure (**1'**), and epiisororidin E (**2**).

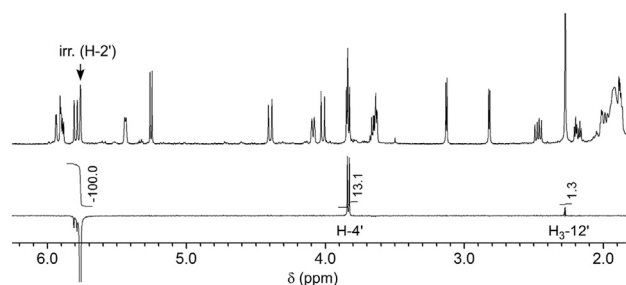
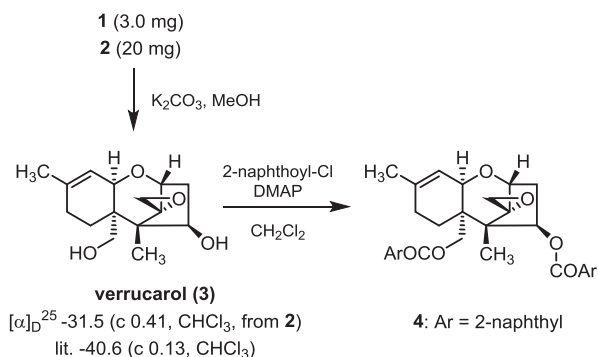


Fig. 2. Medium-frequency region of the difference NOE spectrum of **1** obtained by irradiating H-2'.

configurations of the C1–C16 trichothecene moiety were experimentally confirmed. The NOESY spectrum afforded the correlations at $H\alpha$ -3/H-4, $H\alpha$ -3/H-11, H-4/H-11, H-4/H-14, H-4/H-15, and $H\beta$ -7/H-13, indicating that the relative stereochemistry of trichothecene part is identical to those of other roridins.^{11,17,18} The absolute configuration of this moiety was established by a chemical correlation with verrucarol (**3**)^{19,20} being obtained by a basic methanolysis of **1** as shown in Scheme 1. Crude sample **3** thus prepared (1.5 mg) provided an ¹H NMR spectrum that showed accordance with the data in the literature;¹⁹ however, it was both qualitatively and quantitatively insufficient for measuring the specific rotation. It was found that the following derivatization into bis-O-2-naphthoate **4** resulted in giving distinct Cotton effects at 242 ($\Delta\epsilon$ +6.8) and 229 nm ($\Delta\epsilon$ –20.2) in the ECD spectrum after purification with preparative silica gel TLC. Fortunately, the producer fungus *C. arbuscula* afforded a considerable amount of **2**, a congener carrying the same trichothecene unit.¹⁶ Basic methanolysis of **2** under the same abovementioned conditions afforded authentic **3** (4.5 mg), which allowed us to obtain a reliable specific rotation



Scheme 1. Chiral assignment of the trichothecene part.

($[\alpha]_D^{25}$ –31.5 (c 0.41, CHCl₃)). The following 2-naphthoylation afforded **4c** which gave identical ECD spectrum to that of the sample prepared from **1**. Ishihara and Tadano synthesized verrucarol in an optically active form to report its specific rotation ($[\alpha]_D^{25}$ –40.6 (c 0.13, CHCl₃)).^{19,20} A combination of these results established the absolute configuration for the trichothecene moiety in **1**, despite the indirect manner.

The vicinal spin couplings $^3J_{H-7'/H-8'}$ (15.0 Hz) and $^3J_{H-9'/H-10'}$ (11.1 Hz) confirm the same (7'*E*,9'*Z*) form as Jarvis's assignment. The NOESY spectrum affords a correlation between H-7' and H-9', suggesting a *transoid* conformation for the C7'–C10' diene moiety as shown in Fig. 3. In addition, NOESY correlations are found at H-4'/H-13' and H-5'/H-6', establishing a *rel*-(5'*R*,6'*S*,13'*S*) configuration of the 1,3-dioxolane ring moiety on the macrocycle.

The remaining structural unknowns were the absolute configurations of C4' and C5', which were investigated with the stable conformation, theoretical ¹H and ¹³C chemical shifts, and ECD spectrum based on DFT ω B97X-D/6-31G* (structural optimization and chemical shift calculations) and B3LYP/def2-TZVP// ω B97X-D/6-31G* (ECD spectral calculations) by using a protocol similar to that used in previous studies.^{21,22} Since the macrocyclic part of **1** has high conformational flexibility, the conformational distribution was estimated based on the free energy (*G*) by adding the entropic factor (*S*) and the temperature term (298 K) to the steric energy (*H*). The δ_C and δ_H root-mean-square (RMS) values of each isomer were obtained from the residuals between the experimental and theoretical chemical shifts. As we have established the *rel*-(5'*R*,6'*S*,13'*S*) configuration and the (2'*E*,7'*E*,9'*Z*) geometry via NMR analysis, the (4'*R*) and (4'*S*) epimers of both (2'*E*,5'*R*,6'*S*,7'*E*,9'*Z*,13'*S*) and (2'*E*,5'*S*,6'*R*,7'*E*,9'*Z*,13'*R*) forms (in total, four isomeric models) were subjected to the calculations. The models are expressed using three letters, e.g., **ERR**, and these three letters refer to the configurations at the 2',3' double bond, the 4', and 5' asymmetric carbons.

The calculations naturally revealed the stable conformers as shown in Fig. 4. First, we analyzed the transannular NOEs based on their stable conformers suggested by these calculations. Roridin J (**1**) shows transannular NOEs at H₃-14/H-2', H₃-14/H-8', H-2'/H-8', and H-4'/H-13'. The most stable conformer of model **ERR** explains all these NOEs. Since C4'-epimeric model **ESR** adopts the similar conformation on the basis of these calculations, this isomer would also satisfy most of the above NOEs; however, the distance between H-4' and H-13' (3.6 Å) is slightly large to expect a distinct NOE between those (note that the distance between the vicinal *trans*-axial protons on a chair formed cyclohexane is around 3.1 Å). The calculations also revealed that the C1'–C4'-conjugated planes in the stable conformers of models **ERS** and **ESS** are flipped around from that in model **ERR**, which increased the distance between H₃-14 and H-2' (**ERS**: 4.2 Å and **ESS**: 4.0 Å). Thus, the NOE between these protons cannot be expected in those models. The

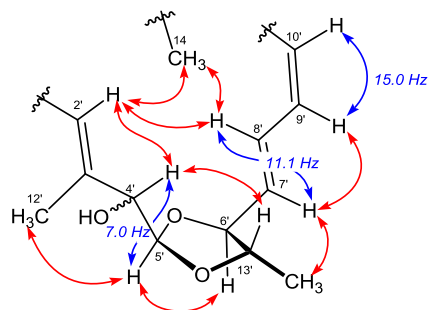


Fig. 3. Relative configuration of the macrocyclic moiety and the characteristic NOEs as well as the ¹H coupling constants.

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