Cyclonerane sesquiterpenes and an isocoumarin derivative from the marine-alga-endophytic fungus *Trichoderma citrinoviride* A-WH-20-3

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**ABSTRACT**

Two new cyclonerane sesquiterpenes, (10E)-isocyclonerotriol (1) and (10Z)-isocyclonerotriol (2), and one new isocoumarin derivative, trichophenol A (3), were isolated from *Trichoderma citrinoviride* A-WH-20-3, an endophyte from the marine red alga *Laurencia okamurai*. Their structures and relative configurations were assigned by spectroscopic techniques, highlighted by using Sarotti’s DP4+ sheet to confirm the cyclopentane ring. The absolute configuration of 1 was established by comparison of experimental and calculated specific rotation data. Compounds 1 and 2 represent the first occurrence of ring-isomerized cycloneranes. Compound 3 is the first 3-phenylisocoumarin derivative from *Trichoderma* and features inhibition of several marine-derived bacteria and phytoplankton species.

1. Introduction

*Trichoderma* metabolites comprise structurally diverse terpenes, steroids, polyketides, alkaloids, and peptides [1], and new members have continuously been characterized recently [2–6]. Cyclonerane sesquiterpenes with a monocyclic carbon framework have been isolated and identified from a broad spectrum of *Trichoderma* species, such as *T. asperellum* [5], *T. harzianum* [6], *T. citrinoviride* [7], *T. polysporum* [8], and *T. viride* [9]. They have also been discovered from some species of the fungal genera *Ascotricha* [10], *Aspergillus* [11], *Botrytis* [12], *Epichloë* [13–15], *Fusarium* (Gibberella) [16–18], *Myrothecium* [19], *Paecilomyces* [20], and *Trichothecium* [21]. It is interesting that the five-membered ring of all the isolates features the same relative configuration. Although trichoderriol A and B from *T. atroviride* and lignoren from *T. lignorum* have been reported to possess different configurations [22,23], their structures should be revised to (10E)-cyclonerotriol [17], epicycloneradiol oxide [8], and cycloneradiol [24], respectively, in view of their identical spectroscopic data. In our ongoing search for new and bioactive secondary metabolites from marine-derived *Trichoderma* species [2–7], an endophytic strain (A-WH-20-3) of *T. citrinoviride* isolated from the marine red alga *Laurencia okamurai* was investigated, which led to the isolation and identification of two new cyclonerane sesquiterpenes (1 and 2) with an isomeric five-membered ring and one new phenolic derivative (3) with a methylated 3-phenylisocoumarin skeleton as well as the known (10E)-cyclonerotriol [17]. Herein, the isolation, structure elucidation, and bioactivity of the new compounds (Fig. 1) are described.

2. Experimental

2.1. General

Optical rotations and UV spectra were measured on a Chirascan CD spectrophotometer. IR spectra were acquired on a Bruker Avance III 500 NMR spectrometer (500 and 125 MHz for \(^1\)H and \(^13\)C, respectively) using tetramethylsilane (TMS) as an internal standard. Low and high resolution EI mass spectra were obtained on an Agilent G6230 TOF mass spectrometer. Low and high resolution ESI mass spectra were determined on an Agilent G6230 TOF mass spectrometer. HPLC separation was operated on an Agilent HPLC system (1260 infinity quaternary pump, 1260 infinity diode-array detector) using an Eclipse SB-C18 (5 µm, 9.4 × 250 mm) column. Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Haiyang Chemical Co.), RP-18 (AAG12S50, YMC Co., Ltd.), and Sephadex LH-20 (GE Healthcare). Thin-layer chromatography (TLC) was carried out with precoated silica gel plates (GF-254, Qingdao Haiyang Chemical Co.). Quantum chemical calculations were run with Gaussian 09 software.

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2.2. Fungal material and fermentation

*Trichoderma citrinoviride* A-WH-20-3 was isolated from the inner tissue of the surface-sterilized red alga *Laurencia okamurai* collected from the coast of Weihai, China, in August 2016. The species was identified by morphology and by analysis of the ITS regions of its rDNA, whose sequence data have been deposited in GenBank with the accession number MN088387. Its fermentation was carried out statically at room temperature for 30 days in 200 × 1 L Erlenmeyer flasks, each containing 50 g of rice, 0.55 g of peptone, 0.55 g yeast extract powder, 0.033 g calcium bromide, 0.33 g monosodium glutamate, and 55 mL of natural seawater from the coast of Yantai, China.

2.3. Extraction and isolation

The mycelia were separated from the culture broth by filtration, and then they were dried in the shade and exhaustively extracted with CH₂Cl₂ and MeOH (1:1, v/v). After removing organic solvents by evaporation under vacuum, the residue was partitioned between EtOAc and H₂O to give an EtOAc-soluble extract (80 g). The partitioned organic layer was passed through LH-20 (MeOH) and preparative TLC (CH₂Cl₂/MeOH, 10:1) as well as Sephadex LH-20 CC (MeOH) to obtain five fractions (Frs. 1–5). Fr. 1 was further purified by Sephadex LH-20 (MeOH) and preparative TLC (CH₂Cl₂/MeOH, 3:2) to yield 6a (15.2 mg). Fr. 2 was further purified by Sephadex LH-20 (MeOH) and preparative TLC (CH₂Cl₂/MeOH, 10:1) as well as semi-preparative HPLC (acetone/MeOH, 3:7 to 2:3) to yield 1 (2.0 mg) and 4 (15.2 mg), and Fr. 4 was further purified by Sephadex LH-20 (MeOH) and preparative TLC (CH₂Cl₂/MeOH, 10:1) as well as semi-preparative HPLC (acetone/MeOH, 2:3 to 3:2) to produce 2 (2.0 mg).

2.4. Spectral data of new compounds

(10E)-Isocyclonerotriol (1): Colorless oil; [α]D20 20 = 64 (c 0.070, MeOH); IR (KBr) vmax 3386, 2963, 2926, 2873, 2855, 1618, 1459, 1379, 1117, 1034, 914 cm⁻¹; 1H and 13C NMR data, Table 1; ESI+MS m/z 279 [M + Na]+; HRESI+MS m/z 279.1932 [M + Na]+ (caled for C15H28O3Na, 279.1936).

(10Z)-Isocyclonerotriol (2): Colorless oil; [α]D20 20 = 64 (c 0.070, MeOH); IR (KBr) vmax 3385, 2965, 2923, 2873, 1630, 1459, 1383, 1115, 1038, 1002, 915 cm⁻¹; 1H and 13C NMR data, Table 1; ESI+MS m/z 279 [M + Na]+; HRESI+MS m/z 279.1930 [M + Na]+ (caled for C15H28O3Na, 279.1936).

Trichophenol A (3): White powder; UV (MeOH) λmax (log ε) 200 (4.60), 237 (4.55), 246 (4.58), 338 (4.02) nm; IR (KBr) vmax 279 [M + Na]+; HRESI+MS m/z 279.1932 [M + Na]+ (caled for C15H28O3Na, 279.0364).

2.5. Bioassay

Following the previous procedures [3,25], compounds 1–3 were assayed for the antimicrobial activity against the marine phytoplankton *Chattonella marina*, *Heterosigma akashiwo*, *Karlodinium veneficum*, and *Prorocentrum donghaiense* and the antibacterial activity against the marine-derived pathogenic bacteria *Vibrio parahaemolyticus*, *V. splendidus*, *V. anguillarum*, and *V. harveyi*.

Table 1

| Pos | δ_C (ppm) | δ_H (J in Hz) |
|-----|-----------|---------------|
| 1   | 166.2, C  | 6.60, s       |
| 3   | 151.4, C  | 6.65, d (2.1) |
| 4   | 189.8, C  | 6.45, d (2.1) |
| 5   | 103.0, CH | 6.15, C       |
| 6   | 251.7, CH | 6.17, C       |
| 7   | 198.3, C  | 6.35, d (2.1) |
| 8   | 111.5, C  | 6.17, C       |
| 9   | 157.2, C  | 6.24, d (2.2) |
| 10  | 100.2, CH | 6.17, C       |
| 11  | 159.1, C  | 6.18, d (2.2) |
| 12  | 191.1, C  | 6.18, d (2.2) |
| 13  | 19.8, CH  | 2.12, s       |
| 14  | 11.07, s  | 6.03, s       |

Table 2

| Pos | 1H (500 MHz) and 13C NMR (125 MHz) for 3 (in CD3OD) |
|-----|--------------------------------------------------|
| 1   | 166.2, C  | 6.60, s       |
| 3   | 151.4, C  | 6.65, d (2.1) |
| 4   | 189.8, C  | 6.45, d (2.1) |
| 5   | 103.0, CH | 6.15, C       |
| 6   | 251.7, CH | 6.17, C       |
| 7   | 198.3, C  | 6.35, d (2.1) |
| 8   | 111.5, C  | 6.17, C       |
| 9   | 157.2, C  | 6.24, d (2.2) |
| 10  | 100.2, CH | 6.17, C       |
| 11  | 159.1, C  | 6.18, d (2.2) |
| 12  | 191.1, C  | 6.18, d (2.2) |
| 13  | 19.8, CH  | 2.12, s       |
| 14  | 11.07, s  | 6.03, s       |
3. Results and discussion

Compound 1 was purified as a colorless oil. Its molecular formula was established to be C_{15}H_{28}O_{3} by interpretation of HRESI+ MS data, requiring two degrees of unsaturation. The IR spectrum exhibited a broad absorption band at 3386 cm\(^{-1}\), indicating the presence of hydroxy groups. In combination with HSQC data, the \(^1H\) NMR spectrum (Table 1) showed notable signals including one methyl doublet, three methyl singlets, one singlet ascribable to an oxymethylene, and one broad triplet attributable to an olefinic proton. Aided by DEPT experiments, 15 resonances in the \(^{13}C\) NMR spectrum (Table 1) were classified as four methyls, five methylenes, three methines, and three non-protonated carbons. HMBC correlations from H-2 to C-2, C-3, and C-6 and from H-13 to C-2, C-3, and C-4 and COSY correlations of H-1/H-2/H-6/H-5/H-4 confirmed the connectivity around ring A, which then extended to C-10 as seen from the HMBC correlations from H-2 to C-6, C-7, and C-8 and COSY correlations of H-2 with H-1 and H-5. These ambiguous data failed to and from H-13 to C-2, C-3, and C-4 and COSY correlations of H-3 to C-6, C-7, and C-8 and COSY correlations of H-3 with H-2 and H-10 (Fig. 1). Additionally, the connectivity of the side chain was confirmed by the HMBC correlations from H-12 to C-10, C-11, and C-15 and from H-13 to C-10, C-11, and C-12. In view of the deshielded NMR signals of C-3, C-7, and C-12, they were deduced to be hydroxylated. Thus, the planar structure of 1 was assigned to be the same as that of (10E)-cyclonerotriol [17], and the \(R\) configuration of the double bond at C-10 was supported by the NOE correlations between H-10 and H-12 and between H-9 and H-15.

In view of the biogenetic considerations and chemical shift deviations for ring A and its affiliated groups, compound 1 was speculated to be a ring A-isomerized derivative of (10E)-cyclonerotriol with the absolute configuration being 2S, 3R, 6R, and 7R. It is notoriously hard to ascertain the relative configuration of a five-membered ring. As for 1, H-2 was indicated to be opposite to H-6 by their small coupling constant \((J = 4.2\) Hz) [26], whereas H-2 showed obvious correlations with H-3 and H-5 in the NOESY spectrum. Additionally, H-13 exhibited NOE correlations with both H-2 and H-2'. These ambiguous data failed to establish the relative configuration of ring A, which prompted us to try quantum chemical calculations via Gaussian 09 software [27]. The energy-minimized conformers of 2S*, 3S*, 6R*, and 7R* (1), 2R*, 3R*, 6R*, and 7R* (1*), and 3S*, 3R*, 6S*, and 7R* (1**) isomers of (10E)-cyclonerotriol optimized at the B3LYP/6-31G(d) level in MeOH were subjected to the \(^{13}C\) NMR calculations using the gauge-independent atomic orbital (GIAO) method at the B3LYP/6-31 + G(d,p) level in MeOH. Both experimental and calculated shifts were input into Sarottis' DP4+ sheet [28], and the calculated data displayed 99.98%, 0.01%, and 0.01% DP4+ probabilities for 1, 1*, and 1**, respectively. Thus, the relative configuration of the isolate was proposed to be 2S*, 3S*, 6R*, and 7R*.

In order to ascertain the absolute configuration of compound 1, its specific optical rotation was determined \((-66)\). On the other hand, the specific optical rotation for the 2S, 3S, 6R, and 7R configuration was calculated to be \(-114\) at the B3LYP/aug-cc-pVDZ level in MeOH [29]. The agreement of experimental and calculated values and sign suggested the absolute configuration of 1, trivially named (10E)-cyclonerotriol, to be 2S, 3S, 6R, and 7R.

Compound 2 was obtained as a colorless oil. HRESI+ MS analysis gave the molecular formula C_{15}H_{29}O_{3}, the same as for 1. The IR absorption at 3385 cm\(^{-1}\) suggested the presence of hydroxy groups. A detailed comparison of the \(^1H\) and \(^{13}C\) NMR spectra (Table 1) revealed that 2 differed from 1 mainly at the side chain terminus. HMBC and COSY correlations (Fig. 1) indicated the same planar structure of 2 as that of 1. However, the double bond at C-10 was deduced to feature a Z configuration based on the NOE correlations between H-10 and H-15 and between H-9 and H-12. The relative and absolute configurations around ring A were proposed to be the same as those of 1 on the basis of their identical NMR and specific rotation data.

Compound 3 was isolated as a white powder. The molecular formula C_{15}H_{29}O_{3} was determined by HREIMS, implying eleven degrees of unsaturation. Its IR spectrum showed a broad absorption band at 3420 cm\(^{-1}\), corresponding to one or more hydroxy groups. The \(^1H\) NMR spectrum (Table 2) displayed one methyl singlet, four methylenes and one nonprotonated carbons by DEPT and HSQC data. The NMR data partially resembled those for thunberginol B [30], which indicated the presence of a 6,8-dihydroxyisocoumarin moiety. It was further supported by the HMBC correlations (Fig. 1) from H-4 to C-4a, C-5, and C-8a, from H-5 to C-7 and C-8a, from H-7 to C-5 and C-8a, and from OH-8 to C-7, C-8, and C-8a. A comparison of the remaining NMR data with those for 4-methoxy-6-(2',4'-dihydroxy-6'-methylphenyl)-pyran-2-one revealed the presence of a 2',4'-dihydroxy-6'-methylphenyl moiety [31], which was verified by the HMBC correlations from H-3' to C-1' and C-5', from H-5' to C-1' and C-3', and from H-7' to C-1', C-5', and C-6'. The linkage of these two units was established by the HMBC correlation from H-4 to C-1'. The above information evidenced the structure of 3, trivially named trichophenol A.

Compounds 1–3 were assayed for inhibition of four marine phytoplankton species (Chattonella marina, Heterosigma akashiwo, Karlodinium venenificum, and Prorocentrum donghaiense) that can cause red tides [25]. The results (Table 3) showed that 1 was more active against C. marina, H. akashiwo, and P. donghaiense. Compared to 1 and 2, (10E)- and (10Z)-cyclonerotriol were previously reported to possess high inhibition of P. donghaiense (IC_{50} 1.1 and 3.4 μg/mL, respectively) [32], which suggested that the isomerization of ring A greatly affected their activities. As analogs of 3, thunberginols A and B exhibited inhibition of oral bacteria [30]. During an antibacterial assay against the marine-derived bacteria Vibrub parahaemolyticus, V. anguillarum, V. harveyi, V. splendidus, and P. citrea, 3 displayed inhibition of the five bacteria tested (Table 3), and the MIC against V. citrea was determined to be 16 μg/mL.

### Table 3

| Compound | MIC (μg/mL) | Inhibitory zone diameter (mm) at 50 μg/disk |
|----------|------------|------------------------------------------|
| C. marina | H. akashiwo | K. venenificum | P. donghaiense | V. anguillarum | V. harveyi | V. parahaemolyticus | V. splendidus | P. citrea |
| 1 | – | 17 | 8.1 | 51 | 0 | 7.0 | 6.5 | 6.5 | 0 |
| 2 | – | 70 | 22 | 54 | 7.0 | 6.5 | 6.5 | 6.5 | 0 |
| 3 | 4.4 | 9.1 | 20 | 5.9 | 8.0 | 7.0 | 7.0 | 7.5 | 21 |
| KClO₃ | 0.40 | 1.1 | 1.4 | 1.1 | 22 | 28 | 25 | 25 | 26 |
| Chloramphenicol | | | | | | | | |

4. Conclusion

Chemical survey on the marine-alga-endophytic fungus Trichoderma citrinoviride A-WH-20-3 has resulted in the discovery of two new cyclonerane sesquiterpenes (1 and 2) and one new isocoumarin derivative (3). Of those, 1 and 2 are the first ring-isomerized cyclonerane derivatives, and 3 features a 3-phenylisocoumarin unit that has never
occurred in Trichoderma metabolites. These new isolates diversify the molecular structures of sesquiterpenes and polyketides from Trichoderma, and they possess inhibitory effects on some marine-derived bacteria and phytoplankton species.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fitote.2020.104469.

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