Aspterrics A and B, New Sesquiterpenes from Deep Sea-derived Fungus Aspergillus terreus YPGA10

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Abstract: Two new sesquiterpenes, namely aspterric A (1) and aspterric B (2), together with aspterric acid (3), were isolated from the deep-sea-derived fungus Aspergillus terreus YPGA10. The structures of aspterrics A and B were determined by NMR and HRESIMS data. Biogenetically, aspterrics A and B were assumed to be the intermediates to derive aspterric acid.

Keywords: Aspergillus terreus; deep-sea-derived fungus; sesquiterpenoids; aspterrics A and B. © 2019 ACG Publications. All rights reserved.

1. Introduction

The fungus Aspergillus terreus, widely distributes in natural environment, has proved to be a potential fungus for producing molecules with significant bioactivity or complex structures. Previous studies of this fungus have led to the identification of meroterpenoids [1, 2], sesterterpenoids [3], butenolides [4-6], alkaloids [7], and cyclic peptides [8]. Some possess unique carbon skeletons and some exhibit remarkable bioactivities such as enzyme inhibition, antitumor activity, and antiviral activity. As part of our ongoing efforts to discover bioactive molecules from marine-derived fungi [9-11], chemical examination of a deep-sea sediment-derived Aspergillus terreus YPGA10 led to the isolation of a carotane-type sesquiterpene aspterric acid (3) and two new biogenetically related sesquiterpenes (1 and 2). Herein, the isolation and structural identification were described.

Figure 1. Structures of compounds 1–3 from Aspergillus terreus YPGA10

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2. Materials and Methods

2.1. Microorganism Material

Fungus Aspergillus terreus (YPGA10) was isolated from the deep-sea sediment collected in the Yap Trench at a depth of 4159 m. The strain was identified as Aspergillus terreus based on microscopic examination and by internal transcribed spacer (ITS) sequencing. The ITS sequence has been deposited in GenBank (http://www.ncbi.nlm.nih.gov) with accession number MG835907. The strain YPGA10 (MCCC 3A01013) was deposited at the Marine Culture Collection of China.

2.2. Fermentation and Isolation

The fermentation was conducted in 40 Fernbach flasks (500 mL), each containing 70 g of rice. Distilled H₂O (90 mL) was added and the contents were autoclaved at 15 psi for 30 min. After cooling to room temperature (r.t.), each flask was inoculated with 3.0 mL of the spore inoculum and incubated at r.t. for 40 days. The fermented material was extracted with EtOAc (4000 mL) for three times. After evaporation under vacuum, the EtOAc extract was purified by HPLC eluted with CH₃CN/H₂O (65:35, 2 mL/min) to obtain seven fractions (F7a–F7g). F7f was purified by HPLC eluted with CH₃CN/H₂O (57:43, 2 mL/min) to obtain 1 (7.1 mg, tₗ 35.5 min) and 2 (2.8 mg, tₗ 39.5 min). F6 was subjected to Sephadex LH-20 CC using MeOH to give four fractions (F6a–F6d). F6a was separated on the YMC column with a mobile phase of CH₃CN/H₂O (53:47, 2 mL/min) to afford 3 (15 mg, tₗ 25.5 min).

Aspterric A (1): Colorless oil; [α]D⁰₂⁰ 0 (c 0.05, MeOH); ¹H NMR (methanol-d₄, 400 MHz) δH 2.45 (2H, s, H₂-2), 1.57 (2H, m, H₂-4), 2.09 (2H, m, H₂-5), 5.14 (1H, t, J = 7.1 Hz, H-6), 2.03 (2H, m, H₂-8), 2.16 (2H, m, H₂-9), 5.46 (1H, t, J = 7.1 Hz, H-10), 1.28 (3H, s, H₃-12), 1.63 (3H, s, H₃-13), 4.44 (2H, s, H₂-14), 1.65 (3H, s, H₃-15), 2.04 (3H, s, COCH₃). ¹³C NMR (methanol-d₄, 100 MHz) δC 175.9 (C-1), 46.5 (C-2), 72.1 (C-3), 42.7 (C-4), 23.5 (C-5), 125.9 (C-6), 135.6 (C-7), 40.1 (C-8), 27.1 (C-9), 130.3 (C-10), 131.4 (C-11), 27.2 (C-12), 16.0 (C-13), 71.3 (C-14), 14.0 (C-15), 172.9 (COCH₃), 20.8 (COCH₃). HRESIMS m/z 311.1853 [M – H]⁺ (calcd for C₁₇H₂₇O₆S, 311.1864).

Aspterric B (2): Colorless oil; ¹H NMR (methanol-d₄, 400 MHz) δH 4.06 (2H, dd, J = 6.8, 0.8 Hz, H₂-1), 5.36 (1H, br t, J = 6.8 Hz, H-2), 2.10 (2H, m, H₂-4), 2.10 (2H, m, H₂-5), 5.15 (1H, t, J = 7.0 Hz, H-6), 2.02 (2H, m, H₂-8), 2.14 (2H, m, H₂-9), 5.39 (1H, t, J = 7.0 Hz, H-10), 1.75 (3H, s, H₃-12), 1.63 (3H, s, H₃-13), 3.91 (2H, s, H₂-14), 1.65 (3H, s, H₃-15). ¹³C NMR (methanol-d₄, 100 MHz) δC 59.2 (C-1), 125.7 (C-2), 139.6 (C-3), 32.9 (C-4), 27.6 (C-5), 125.2 (C-6), 136.3 (C-7), 40.5 (C-8), 27.3 (C-9), 126.5 (C-10), 135.9 (C-11), 23.7 (C-12), 16.1 (C-13), 68.9 (C-14), 13.7 (C-15). HRESIMS m/z [M + Na]⁺ 261.1826 (calcd for C₁₅H₂₈O₇Na⁺, 261.1825).

Aspterric acid (3): Colorless oil; ¹³C NMR (methanol-d₄, 100 MHz) δC 35.2 (C-1), 84.8 (C-2), 76.4 (C-3), 33.1 (C-4), 36.7 (C-5), 56.7 (C-6), 54.2 (C-7), 24.8 (C-8), 35.0 (C-9), 136.7 (C-10), 125.1 (C-11), 177.7 (C-12), 79.4 (C-13), 21.0 (C-14), 23.4 (C-15).

3. Results and Discussion

The molecular formula of compound 1 was determined to be C₁₇H₂₈O₇ by the HRESIMS data, requiring four degrees of unsaturation. The ¹H NMR and HSQC spectra displayed signals for four methyl singlets [δH 1.28 (3H, s, H₂-12), 1.65 (3H, s, H₂-13), 1.67 (3H, s, H₂-14)], two olefinic protons [δH 5.14 (1H, t, J = 7.1 Hz, H-6), 5.46 (1H, t, J = 7.1 Hz, H-10)], and six methylenes [δH 2.45 (2H, s, H₂-2), 1.57 (2H, m, H₂-4), 2.09 (2H, m, H₂-5), 2.03 (2H, m, H₂-8), 2.16 (2H, m, H₂-9), 4.44 (2H, s, H₂-14)]. The ¹³C NMR spectrum exhibited a total of 17 carbon resonances, including four olefinic carbons [δC 125.9, 135.6, 130.3, 131.4] for two double bonds, a
carbonyl carbon [\(\delta_C 172.9\) (COCH\(_3\))] for an acetyl carbonyl carbon, and a carboxylic acid group [\(\delta_C 175.9\) (C-1)]. The two carbonyl carbons and two double bonds accounted for all four degrees of unsaturation, indicating 1 to be acyclic. The structure was further established to be a new farnesol derivative by 2D NMR data (Figure 2). The HMBC correlations from H-12 (\(\delta_H 1.28\)) to C-2 (\(\delta_C 46.5\)), C-3 (\(\delta_C 72.1\)), C-4 (\(\delta_C 42.7\)) and H-2 (\(\delta_H 2.45\)) to the carboxylic acid carbon (\(\delta_C 175.9\)) established a 3-hydroxy-3-methylbutanoic acid moiety (unit A). The COSY relationship from H-2 (\(\delta_H 2.09\)) to H-6 (\(\delta_H 5.14\)) and HMBC correlations from H-13 (\(\delta_H 1.63\)) to C-6 (\(\delta_C 125.9\)), C-7 (\(\delta_C 135.6\)), and C-8 (\(\delta_C 40.1\)) established an isopentenyl unit (unit B). Additional HMBC correlations from H-2-14 (\(\delta_H 4.44\)) to C-10 (\(\delta_C 130.3\)), C-11 (\(\delta_C 131.4\)), C-15 (\(\delta_C 14.0\)) and the COSY relationship between H-2-9 (\(\delta_H 2.16\)) and H-10 (\(\delta_H 5.46\)) established another isopentenyl unit (Unit C). The above three units were connected by the COSY correlations from H-2-8 to H-2-9 and from H-2-4 to H-2-5. The remaining acetyl group was located at C-14 (\(\delta_C 71.3\)) to C-14 (\(\delta_C 71.3\)) and H-14 (\(\delta_H 5.14\)) to the acetyl carbonyl carbon (\(\delta_C 172.9\)). The strong NOESY correlations of H-3-13/H-2-5, H-2-8/H-6, H-15/H-2-9, and H-2-14/H-10 indicated that both \(\Delta^6\) and \(\Delta^{10}\) had an E configuration. The specific rotation of 1 ([\(\alpha\])\(^D_{20} 0\)) indicated that 1 was racemic. Compound 1 was given the trivial name aspterric A.

**Figure 2.** H-1^H COSY (---), HMBC (→), and NOE (←) correlations of 1 and 2.

Compound 2 had the molecular formula C\(_{15}\)H\(_{26}\)O\(_2\) based on the HRESIMS and NMR data, indicating three degrees of unsaturation. The \(^1\)H NMR and HSQC spectra displayed the signals for three three olefinic protons [\(\delta_H 5.36\) (1H, t, \(J = 6.8\) Hz, H-2), 5.15 (1H, t, \(J = 7.0\) Hz, H-6), 5.39 (1H, t, \(J = 7.0\) Hz, H-10)], three olefinic methyls [\(\delta_H 1.63\) (3H, s, H-13), 1.65 (3H, s, H-15), 1.75 (3H, s, H-12)], and six methylenes [\(\delta_H 4.06\) (2H, dd, \(J = 6.8, 0.8\) Hz, H-2-1), 2.10 (2H, m, H-2-4), 2.10 (2H, m, H-2-5), 2.02 (2H, m, H-2-8), 2.14 (2H, m, H-2-9), 3.91 (2H, s, H-12-14)]. The \(^1\)C NMR spectrum, in combination with HSQC spectrum, resolved 15 carbon resonances attributable to three double bonds, three methyls, and six methylenes. The aforementioned data were similar to those of 1, indicating a farnesol derivative [12]. The structure was further established by detailed 2D NMR analyses (Figure 2). The HMBC and COSY correlations established the same units B and C as those of 1, while unit A was determined to be an isopentenyl alcohol moiety by the HMBC correlations from the additional olefinic proton H-2 (\(\delta_H 5.36\)) to C-3 (\(\delta_C 139.6\)), C-4 (\(\delta_C 32.9\)), and C-12 (\(\delta_C 23.7\)) and between its COSY relationship with the extra oxygenated methylene protons H-2-1 (\(\delta_H 4.08\)). The three moieties were connected by the HMBC correlation from H-6 (\(\delta_H 5.15\)) to C-4 (\(\delta_C 32.9\)) and COSY relationship from H-2-8 (\(\delta_H 2.02\)) to H-9 (\(\delta_H 2.14\)). The strong NOESY correlations of H-3-13 (\(\delta_H 1.63\))/H-2-5 (\(\delta_H 2.10\)), H-2-8/H-6, H-15 (\(\delta_H 1.65\))/H-2-9 (\(\delta_H 2.14\)), H-14 (\(\delta_H 3.91\))/H-10 (\(\delta_H 5.39\)), H-1 (\(\delta_H 4.08\))/H-2-4 (\(\delta_H 2.10\)), H-2 (\(\delta_H 5.36\))/H-12 (\(\delta_H 1.75\)) indicated that both \(\Delta^6\) and \(\Delta^{10}\) had an E configuration, while \(\Delta^7\) had a Z configuration. Compound 2 was named aspterric B.

Compound 3 was identified to be aspterric acid by careful comparison with NMR data and specific rotation reported in the literature [13].
4. Conclusion

Three sesquiterpenoids including two new farnesol derivatives were isolated from the deep-sea-derived fungus *Aspergillus terreus* YPGA10. The structures of aspterrics A and B were established by detailed analyses of the NMR data and HRESIMS data. Biogenetically, aspterrics A and B were assumed to be the intermediates to derive aspterric acid.

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Supporting Information

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