Published By Guangdong Pharmaceutical University, Guangzhou

Journal of Holistic Integrative Pharmacy

2022, 3(3):201-207

EXPERIMENTAL RESEARCH

Three bisabolane sesquiterpenoids and a phenolic derivative from the fungus *Stereum hirsutum*

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[Abstract] **Objective** To explore the secondary metabolites of the higher fungus *Stereum hirsutum*. **Methods** The structures of these compounds were elucidated by extensive spectroscopic analyses and NMR calculations. **Results** Three new bisabolane sesquiterpenoids, sterene acids A−C (**1**−**3**), and one new phenolic derivative, sterephenol A (**4**), were isolated from the higher fungus *S. hirsutum*. **Conclusion** Compound **1** is the first example of bisabolane sesquiterpenoid bearing an allene group. It is also the first time to discover bisabolane sesquiterpenoids from the fungus *S. hirsutum*.

[Key words] *Stereum hirsutum*; Sesquiterpenoids; Phenolic derivative

1 Introduction

Natural products, having diverse and complex structures and significant biological activities, have been a valuable source of drug development. Sesquiterpenoids, one of the largest classes of natural products, have increasingly attracted attention from the communities of chemistry and pharmacologists not only due to their highly diversified chemical structures but also extensive bioactivities[1-4]. Structurally, bisabolane sesquiterpenoids, which are derived from farnesyl diphosphate (FPP), are a family of naturally occurring sesquiterpenoids that featured a hexatomic ring core incorporating with eight continuous carbons, which cause high structural variability along the alkyl side chain to form abundant functionalities[5-6]. To date, more than 360 naturally occurring bisabolanes have been reported, which exhibit a wide spectrum of bioactivities, such as antimicrobial[7], anticonvulsant[8], anti-entomopathogen[9], anti-inflammatory[10], neuroprotective[11], enzyme inhibitory[12], and cytotoxic properties[1].

The mushroom *Stereum hirsutum*, which is widely distributed and lives on dead wood of limbs and trunks of both hardwoods and conifers, are rich in novel bioactive secondary metabolites, including triquinane sesquiterpenoids[13], hirsutane-type sesquiterpenoids[14-15], acetylenic sesquiterpenoids[16], phenol derivatives[17], isoprenylated depsides[18], benzoate derivatives[19]. In our early research on secondary metabolites of *S. hirsutum*, we reported eight new vibralactone dimers, bisvibralactones A−H, three new vibralactone monomers, hirsutumins A−C[20], and three new acetylenic aromatic

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compounds[21]. In our further search for new and bioactive metabolites from *S. hirsutum*, three new bisabolane sesquiterpenoids (**1**–**3**) and one new phenolic derivative (**4**) were isolated from the ethyl acetate extract (Fig. 1). In this paper, we describe the isolation and structural elucidation of **1**–**4**.

2 Materials and methods

2.1 General experimental procedures

Semipreparative Dionex HPLC was using an Ultimate 3000 DAD detector with a reversed-phase (RP) C_{18} column (5 μm, 10 × 250 mm, Welch Materials, Inc.). (Thermo Fisher, Scientific, Germany). 1D and 2D NMR spectra were collected on Bruker AV-400 NMR spectrometer with TMS as the internal standard (Bruker, Karlsruhe, Germany). HRESIMS data were recorded on a Bruker micrOTOF II spectrometer. Chemical shifts are expressed in ppm with reference to the CD_3OD (δ_H 3.31/δ_C 49.0) and $CDCl_3$ (δ_H 7.26/δ_C 77.16) signals. Column chromatography was carried out on silica gel (200-300 mesh, Qingdao Marine Chemical Inc., P. R. China). ODS (50 μm, Merck, Germany), and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden). Thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} and RP-C_{18} F_{254} plates (Yantai Chemical Industry Research Institute). Fractions were monitored by TLC, and spots were visualized by spraying heated silica gel plates with 10% H_2SO_4 in EtOH.

2.2 Fungal material

S. hirsutum was purchased from China General Microbiological Culture Collection Center (CGMCC) with the number of 5.1499.

2.3 Cultivation, extraction and isolation

The fungal culture was incubated on potato dextrose agar (PDA) at 28 °C for 6 days. Agar plugs were cut into small pieces (approximately 0.5 × 0.5 × 0.5 cm^3) and then inoculated into 50 Erlenmeyer flasks (1 L) that were previously sterilized by autoclaving; each flask contained 250 g of rice and 250 mL of distilled water. All flasks were incubated at 28 °C for 30 days. After harvesting, the rice medium was extracted with ethanol to yield a crude ethanol extract, then suspended in water and extracted by ethyl acetate.

The ethyl acetate fraction (250.0 g) was separated by column chromatography on silica gel eluted with petroleum ether:ethylacetate (20∶1, 10∶1, 5∶1, 2∶1, 1∶1, and 0∶1), to furnish five fractions (Fr. 1–Fr. 5). Fr. 3 (15.5 g) was further separated on the ODS column (MeOH–H_2O, 20%, 40%, 60%, 80%, 100%) to yield six fractions (Fr. 3.1–Fr. 3.6). Fr. 3.3 was further purified on a silica gel column eluted with CH_2Cl_2∶MeOH (200∶1–0∶1) and repeated semi-preparative HPLC separations (MeCN∶H_2O, 47∶53) to yield compound **1** (1.4 mg). Fr. 3.4 was subjected to CC on Sephadex LH-20 (CH_2Cl_2∶MeOH, 1∶1) to produce five subfractions

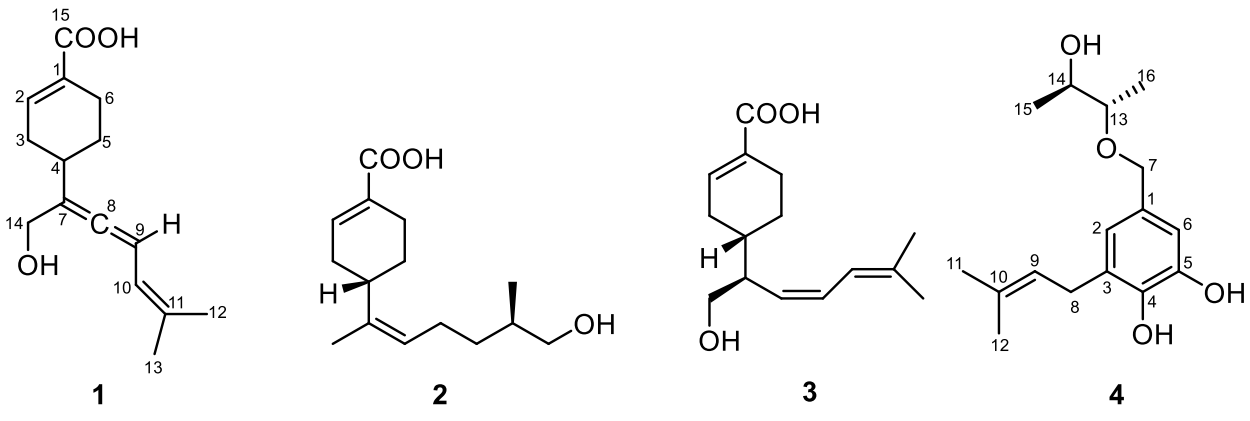

Fig. 1 Structures of 1–4.

(Fr. 3.4.1–3.4.5). Fr. 3.4.3 was further purified by semi-preparative HPLC (MeOH∶H_2O, 70∶30) to yield compound **2** (2.9 mg). Fr. 3.5 was subjected to CC on Sephadex LH-20 (MeOH) to yield two subfractions (Fr. 3.5.1 and Fr. 3.5.2). Fr. 3.5.2 was separated on a silica gel column eluted with ether-ethylacetate (20∶1–0∶1) and was further purified by preparative HPLC (MeOH∶H_2O, 50∶50) to yield compounds **3** (2.2 mg) and **4** (8.2 mg).

2.4 NMR calculation

In general, conformational analyses were carried out via random searching in the Sybyl-X 2.0 using the MMFF94S force field with an energy cutoff of 5.0 kcal/mol. The results showed fourteen lowest energy conformers. Subsequently, the conformers were re-optimized at the B3LYP-D3(BJ)/6-31G* level by the Gaussian 09 program. All conformers used for property calculations in this work were characterized to be stable point on potential energy surface (PES) with no imaginary frequencies. NMR shielding constants were computed using the GIAO method at the mPW1PW91/6-311+G** level. Gibbs free energies for conformers were determined by using thermal correction at B3LYP-D3(BJ)/6-31G* level and electronic energies evaluated at the wB97M-V/def2-TZVP level using ORCA Boltzmann weights were computed using relative gibbers free energies. The unscaled chemical shifts (δ_u) were computed using TMS as a reference standard according to $\delta_u = \sigma_0 - \sigma_x$, where σ_x is the Boltzmann averaged shielding tensor and σ_0 is the shielding tensor of the TMS computed at the same level of theory employed for σ_x. The scaled chemical shifts (δ_s) were calculated as $\delta_s = (\delta_u - b) / m$, where m and b are the slope and intercept, respectively, deduced from a linear regression calculation on a plot of δ_u against δ_{exp}. The DP4+ calculations were run by the Excel spreadsheet available for free at sarotti-nmr.weebly.com.

3 Results and discussion

Compound **1** was obtained as a white powder with the molecular formula of $C_{15}H_{20}O_3$, as determined on the basis of the positive ion peak at *m/z* 271.1307 $[M+Na]^+$ (calcd. for $C_{15}H_{20}O_3Na$, 271.131 0) in the HREISMS spectrum, corresponding to six degrees of unsaturation. The ^1H NMR spectrum (Table 1) showed the presence of two methyl groups (δ_H 1.76 brs; 1.73 brs), one oxygenated methylene [δ_H 4.14 (dd, J = 12.4, 2.2 Hz); 4.09 (dd, J = 12.4, 2.0 Hz)], and three olefinic protons [δ_H 6.68 s; 6.14 (dd, J = 10.8, 2.0 Hz); 5.59 (dt, J = 10.8, 1.3 Hz)]. The ^{13}C NMR data (Table 1) of **1**, together with DEPT showed the presence of 15 carbons, including two methyls (δ_C 18.1 and 26.1), four methylenes of which one was oxygenated at δ_C 63.1, four methines with three olefinic groups (δ_C 94.6, 121.2, and 135.4), and five nonprotonated carbons (including four olefinic groups at δ_C 110.6, 133.4, 134.8, and 204.7, and one carboxyl at δ_C 173.5). The resonances for C-7 (δ_C 110.6), C-8 (δ_C 204.7), and C-9 (δ_C 94.6) are indicative of an allenyl moiety. The above data indicated that 1 might belong to bisabolane sesquiterpenoid derivatives. The ^1H and ^{13}C NMR data of **1** were similar to those of the known compound hamanasic acid A[22], which was isolated from *Rosa rugose* leaves in 1991, except that three sp^3 hybrid carbons of C-7, C-8, and C-9 in hamanasic acid A was substituted by an allenyl moiety, and the methyl group of C-14 was oxygenated in **1**. This assignment was supported by the HMBC correlations (Fig. 2) from H-10 to C-8, H-9 to C-7 and C-8, and H_2-14 to C-4, C-7, and C-8. Collectively, the planar structure of sterene acid A (**1**) was determined.

Compound **2** gave a molecular formula of $C_{15}H_{24}O_3$, with 4 degrees of unsaturation, as determined by HRESIMS analysis with a protonated molecular ion peak $[M+Na]^+$ at *m/z* 275.162 0 (calcd. for $C_{15}H_{24}O_3Na^+$, 275.162 3). The ^1H and ^{13}C NMR data (Table 1) were similar to these of bisabolanoic acid A, previously isolated from the mangrove derived endophytic fungus *Colletotrichum* sp. SCSIO KcB3-2[12], except for the presence of a

Table 1 ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data for compounds 1–4 (δ in ppm, J in Hz)

No.	1[a]		2[a]		3[b]		4[a]	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		133.4		133.6		132.3		130.6
2	6.68 s	135.4	6.71 s	135.8	6.66 brs	134.9	6.56 d (1.9)	121.4
3	2.35 m	25.4	2.20 overlapped 2.06 overlapped	30.8	2.26 m 1.98 m	30.4		129.4
4	2.31 m	34.0	2.71 m	35.9	1.60 m	34.3		143.7
5	2.01 m 1.42 m	28.7	1.68 m 1.60 overlapped	28.2	1.87 m 1.22 m	25.5		145.9
6	2.42 m 2.09 m	32.4	2.42 m 2.26 overlapped	26.0	2.33 m 2.14 m	24.7	6.66 d (1.9)	113.8
7		110.6		139.1	2.64 m	44.8	4.42 d (11.3) 4.35 d (11.3)	72.3
8		204.7	5.19 t (7.0)	127.0	5.10 t (10.7)	127.7	3.28 m	29.1
9	6.14 dd (10.8, 2.0)	94.6	2.07 overlapped	25.7	6.46 t (11.3)	129.2	5.30 ddt (8.7, 6.0, 1.4)	124.1
10	5.59 dt (10.8, 1.3)	121.2	1.47 m 1.13 m	34.9	6.04 d (11.5)	120.2		132.7
11		134.8	1.58 overlapped	36.4		137.4	1.72 s	25.9
12	1.76 br s	26.1	3.41 dd (10.6, 5.9) 3.34 dd (10.6, 6.5)	68.3	1.78 s	26.5	1.71 s	17.8
13	1.73 br s	18.1	0.91 d (6.7)	17.0	1.75 s	18.3	3.35 m	79.7
14	4.14 dd (12.4, 2.2) 4.09 dd (12.4, 2.0)	63.1	1.64 s	19.2	3.72 dd (10.3, 4.8) 3.47 overlapped	64.2	3.68 qd (6.4, 4.9)	71.1
15		173.5		173.6		170.8	1.14 d (6.4)	19.1
16							1.13 d (6.4)	15.2

[a]Recorded in CD_3OD. [b]Recorded in $CDCl_3$.

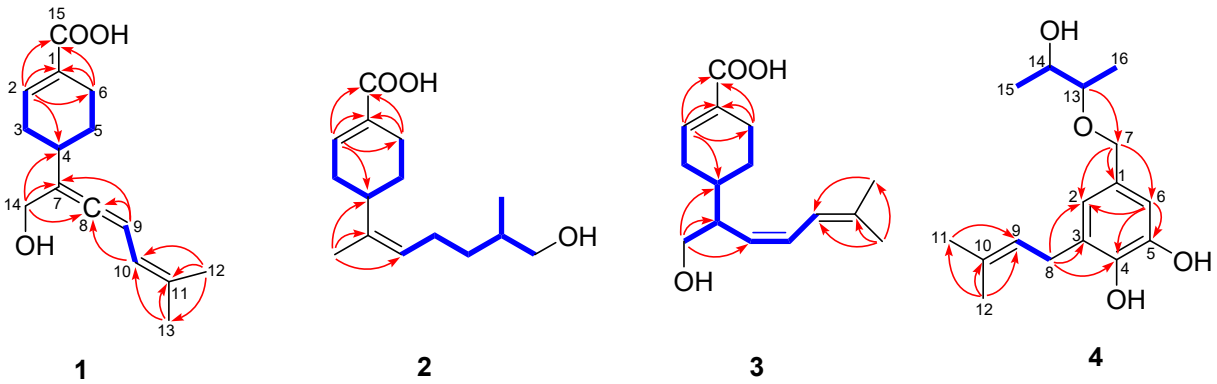

Fig. 2 Key ^{1}H–^{1}H COSY and HMBC correlations of 1–4.

double bond, an oxygenated methylene, and a methine. The HMBC correlations from Me-14 to C-4, C-7, and C-8 confirmed the location of the double bond $\Delta^{7,8}$. In addition, the ^{1}H–^{1}H COSY correlations of H-8/H_2-9/H_2-10/H-11(Me-13)/H_2-12 established the side chain of **2**. The geometry of the double bond $\Delta^{7,8}$ was deduced to be 7*E* on the basis of the NOESY correlations of H-8/Me-14 and H-4/H_2-9. In order to confirm the relative configuration of **2**, the calculations for ^{13}C NMR chemical shifts and the

DP4+ analysis were performed (Fig. 3). The isomer (4*S**,11*R**)-**2** showed the highest DP4+ probabilities (96.13%) and was named as sterene acid B.

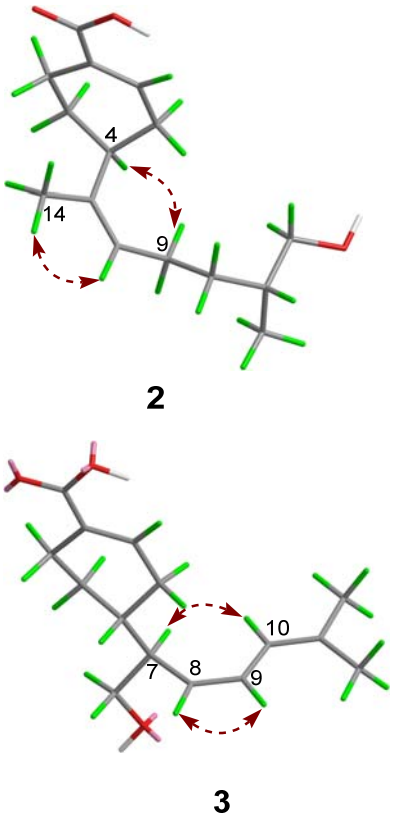

Fig. 3 Key NOESY correlations of 2 and 3.

Compound **3** was obtained as a colorless oil. The molecular formula of **3** was established to be $C_{15}H_{22}O_3$ from its HREIMS data, which was 2 mass units less than **2**, with five degrees of unsaturation. The ^{1}H and ^{13}C NMR data (Table 1) of **3** were similar to these of **2**, except that an extra double bond was present in **3**. The ^{1}H–^{1}H COSY correlation of H_2-14/H-7/H-8/H-9/H-10, and the HMBC correlations from Me-12 and Me-13 to C-10 and C-11 revealed the presence of double bonds $\Delta^{8,9}$ and $\Delta^{10,11}$. Therefore, the planar structure of **3** was assigned as shown. The geometry for the $\Delta^{8,9}$ double bond was assigned as *Z* on the basis of the coupling constant between the H-8 and H-9 ($^3J_{\text{H-8, H-9}}$ = 11.3 Hz) and the strong NOESY correlations of H-8/H-9 and H-7/H-10. The configuration of the two stereogenic centers (C-4 and C-7) in **3** were analyzed using a quantum mechanics-based chemical shift calculations and DP4+ analysis method. Between the two possible diastereomers (4*S**/7*S** and 4*S**/7*R**), the DP4+ calculation proposed the 4*S** and 7*S** diastereomers with 100% possibility and was named as sterene acid C (**3**).

Sterephenol A (**4**) was purified as a colorless oil. Its molecular formula was determined as $C_{16}H_{24}O_4$ by HRESIMS (*m/z* 303.158 1 $[M + Na]^+$, calcd. for $C_{16}H_{24}O_4Na^+$, 303.157 2), requiring five degrees of unsaturation. The ^{1}H NMR data (Table 1) alongside HSQC spectrum displayed notable signals ascribable to four methyl groups [δ_H 1.72, s; 1.71, s: 1.14 (d, *J* = 6.4 Hz); and 1.13 (d, *J* = 6.4 Hz)], one oxygenated methylene [δ_H 4.42 (d, *J* = 11.3 Hz); 4.35 (d, *J* = 11.3 Hz)], three methines including one olefinic proton [δ_H 5.30 (ddt, *J* = 8.7, 6.0, 1.4 Hz)] and two oxygenated ones [δ_H 3.68 (qd, *J* = 6.4, 4.9 Hz); 3.35 (m)], and an 1,3,4,5-tetrasubstitutedphenyl [δ_H 6.66 (d, *J* = 1.9 Hz) and 6.56 (d, *J* = 1.9 Hz)]. The ^{13}C NMR data (Table 1) of compound **4**, in conjunction with DEPT and HSQC spectra, displayed the presence of 16 carbon resonances attributable to four methyls (δ_C 17.8, 19.1, 15.2, and 25.9), two methylenes with one oxygenated (δ_C 72.3), five methines including three olefinic/aromatic (δ_C 113.8, 121.4, and 124.1) and two oxygenated (δ_C 79.7 and 71.1), and five sp^2 nonprotonated carbons. Comprehensive analyses of the NMR spectroscopic data suggested that **4** was a phenol derivative and similar to 1-[2',3'-dihydroxy-5'-(hydroxymethyl) phenyl]-3-methyl-but-2-ene[23], except that an additional 2,3-butanediol group were observed. The ^{1}H–^{1}H COSY correlations of Me-15/H-14/H-13/Me-16 together with the HMBC correlations from H-13 to C-7 confirmed the planar structure of **4**. Natural products with a 2,3-butanediol group are widely discovered, the eight stereoisomers of naturally occurring talaropyrazines B and C were synthesized by our group to determine the relative configuration of the 2,3-butanediol group[24]. By comparing the split of 2,3-butanediol ^{1}H NMR spectrum of the four configurations, the relative configuration of

4 was speculated as 13*S**,14*R**. Compounds **1**–**4** were evaluated for cytotoxic activities in five human cancer cell lines (HL-60, A-549, SMMC-7721, MCF-7, and SW-480), unfortunately, none of them exhibited significant activities.

4 Conclusion

In summary, the investigation of the fungus *S. hirsutum* led to the isolation of three undescribed bisabolane sesquiterpenoids, sterene acids A−C (**1**−**3**), and one new phenolic derivative, sterephenol A (**4**). Notably, Compound **1** represents the first example of bisabolane sesquiterpenoid featuring an allene group, and bisabolane sesquiterpenoids were discovered for the first time from *S. hirsutum*. The isolation of three bisabolane sesquiterpenoids enriches the structural diversity of sesquiterpenoids and the metabolites from the higher fungus *S. hirsutum*.

5 Conflicts of interest

These authors have no conflict of interest to declare.

6 Acknowledgments

This work was supported by the Program for Changjiang Scholars of Ministry of Education of the People's Republic of China (T2016088); the National Natural Science Foundation for Distinguished Young Scholars (81725021); the National Natural Science Foundation for Excellent Young Scholars (81922065); the National Science and Technology Project of China (2018ZX09201001-001-003); Innovative Research Groups of the National Natural Science Foundation of China (81721005); the National Natural Science Foundation of China (82173706 and 82104028); the Fundamental Research Funds for the Central Universities (2020kfyXJJS083, 2021yjsCXCY094); the Science and Technology Major Project of Hubei Province (2021ACA012); the Research and Development Program of Hubei Province (2020BCA058), the Academic Frontier Youth Team of HUST (2017QYTD19); the Integrated Innovative Team for Major Human Diseases Program of Tongji Medical College (HUST).

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