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Stucturally Diverse Sesquiterpenes Produced by a Chinese Tibet Fungus *Stereum hirsutum* and Their Cytotoxic and Immunosuppressant Activities

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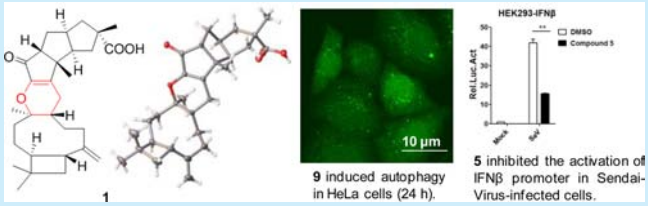
Supporting Information

ABSTRACT: Two new heterodimeric sesquiterpenes, sterhirsutins C (**1**) and D (**2**), along with eight new sesquiterpenoid derivatives, sterhirsutins E−-L (**3**−**10**), were isolated from the culture of *Stereum hirsutum*. The absolute configuration of **1** was assigned by a single-crystal X-ray diffraction experiment. Compounds **1** and **2** possessed an unprecedented chemical skeleton with a 5/5/5/6/9/4 fused ring system. Compound **10** is the first sesquiterpene coupled with a xanthine moiety. Compounds **1**−**10** showed cytotoxicity against K562 and HCT116 cell lines. Compound **9** induced autophagy in HeLa cells. Compound **5** inhibited the activation of IFNβ promoter in Sendai virus infected cells.



Innate immunity is critical for host defense against invading microorganisms. There are three major classes of pathogen recognition receptors (PRRs) in host cells, Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors.[1] RLRs are a family of DExD/H box RNA helicases, including RIG-I (retinoic acid-inducible gene I), MDA5 (melanoma differentiation associated factor 5), and LGP2 (laboratory of genetics and physiology 2).[2] RLRs serve as cytoplasmic sensors for viral RNA recognition. RLR signaling is essential to the control of virus infection and the immune response. Dysregulation of RLR signaling leads to the development of autoimmune diseases.[2] Inhibitors of RLR signaling, such as BX795, have been considered potential therapeutic agents for autoimmune diseases.[3]

Hirsutane-type sesquiterpenes with various structures and interesting bioactivities have been isolated from fungi, including hirsutanol A with an apoptosis-inducing effect on human colon cancer cells from *Chondrostereum* sp.,[4] sequiterpenes with nitric oxide inhibitory activity from *Stereum hirsutum*,[5] coriolin derivatives with antitumor and antibacterial activities from *Xeromphalina* sp.,[6] and diketocoriolin B with stimulatory activity on antibody formation in T cell-deficient spleen cells from *Coriolus consors*.[7] In our early research on secondary metabolites from a Chinese Tibet fungus *S. hirsutum*, we reported two novel heterodimeric sesquiterpenes, sterhirsutins A (**11**) and B (**12**), two new sesquiterpenes, hirsutic acids D (**14**) and E (**15**), and one known sesquiterpene (**13**) from its solid culture (Figure S1, Supporting Information).[8] Sterhirsutins A and B possessing an unusual chemical skeleton of cyclopenta[5,6]pentaleno[2,1-*b*]cycloundeca[*e*]pyran are postulated to be synthesized via a hetero-Diels−Alder cycloaddition of a hirsutane-type sesquiterpene and α-humulene. Their novel skeleton and unique biosynthetic pathway attracted our attention to conduct further chemical investigation on this fungus. As a result, 10 new hirsutane-type sesquiterpene derivatives (**1**−**10**) were isolated from the ethyl acetate extract (Figure 1). In this paper, we describe the isolation, structural elucidation, cytotoxicity, autophagy-inducing effect, and the inhibitory effect on RLR signaling pathways for **1**−**10**.

Sterhirsutin C (**1**) was isolated as a needle crystal. Its molecular formula was determined to be $C_{30}H_{42}O_4$ (10 degrees of unsaturation) on the basis of HRTOFMS data at *m*/*z* 467.3159 $[M + H]^+$. Analysis of its ^1H, ^{13}C, and HSQC NMR data revealed the presence of five methyl groups [δ_H 0.81, 0.86, 0.92, 1.20, 1.60; δ_C 22.8, 19.4, 30.1, 21.2, and 28.3], nine methylenes, six methines, four quaternary carbons with one oxygenated (δ_C 81.9), four olefinic carbons, two of which being the carbons of a terminal double bond [δ_C 110.4 (=CH_2), 155.5, 149.0, 150.6], and two carbonyl carbons (δ_C 181.4 and 203.0) (Table S1, Supporting Information). Analysis of its $^1H-^1H$ COSY and HMBC spectra revealed the presence of a hirsutane-type sesquiterpene unit (A), as found in sterhirsutins A (**11**),[8] and a β-caryophyllene unit (B) (Figure S2, Supporting Information). Finally, the linkage of the structural unit A with B by the formation of a 2*H*-pyran ring was confirmed by the HMBC correlations from H_2-15 to C-16, C-17, and C-26, the

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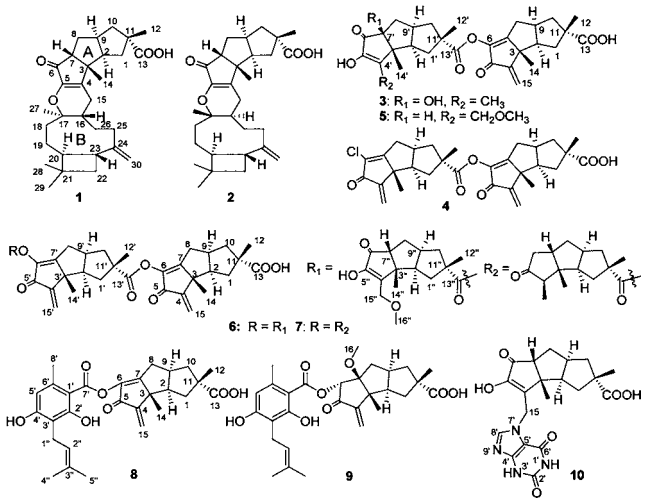

Figure 1. Structures of **1**−**10**.

oxygen-bearing characteristic of C-5 (δ_C 149.0) and C-17 (δ_C 81.9), and the requirement of unsaturation degree of **1**.

The relative configuration of **1** was determined on the basis of the ROESY experiments (Figure 2). NOE correlations from

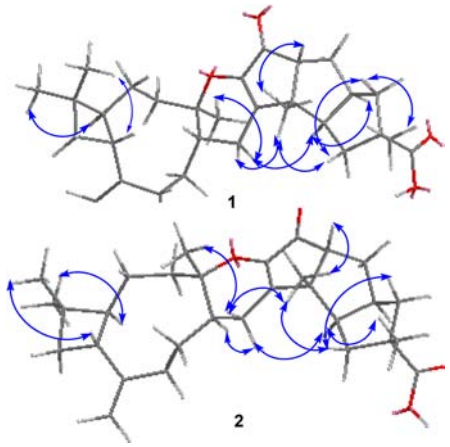

Figure 2. Key NOE correlations of **1** and **2**.

H-10β (δ_H 1.45) to H-1β (δ_H 1.63) and H_3-12 (δ_H 1.60), from H_3-14 (δ_H 1.20) to H-1β, H-7 (δ_H 2.48), and H-15β (δ_H 2.43, dd, J = 19.0, 5.4 Hz), and from H-16 (δ_H 2.13) to H-15β placed these protons on the same face of the rings. In addition, NOE correlations from H-2 (δ_H 2.75) to H-9 (δ_H 2.39), H-10α (δ_H 2.87), and H-15α (δ_H 1.71, dd, J = 19.0, 10.3 Hz) and from H-15α to H_3-27 (δ_H 0.86) placed H-2, H-9, and H_3-27 on the other side of the rings. Moreover, NOE correlations from H-20 to H_3-28 and from H-23 to H_3-29 indicated a *trans*-relationship between H-20 and H-23. Finally, the structure of **1** was confirmed by single-crystal X-ray crystallographic analysis (Figure S3, Supporting Information). The absolute configuration of **1** was determined to be 2*R*,3*S*,7*R*,9*S*,11*S*,16*S*,17*R*,-20*S*,23*R* on the basis of the Flack parameter [−0.1 (2)] obtained by Cu Kα radiation.

Sterhirsutin D (**2**) was assigned the same molecular formula of $C_{30}H_{42}O_4$ as that of **1** by HRTOFMS data at m/z 467.3153 $[M + H]^+$ and NMR data (Table S1, Supporting Information). The ^{1}H and ^{13}C NMR spectra of **2** showed much resemblance with those of **1**. Further interpretation of its ^{1}H, ^{13}C, and 2D NMR data indicated that **1** and **2** possessed the same planar structure. Therefore, compounds **1** and **2** are deduced as a pair of stereoisomers. The relative configuration of **2** was determined on the basis of the 1D NOE experiments (Figure 2). NOE correlations from H-10β (δ_H 1.35) to H-1β (δ_H 1.54) and H_3-12 (δ_H 1.54), from H_3-14 (δ_H 1.20) to H-1β, H-7 (δ_H 2.51), and H-15β (δ_H 1.87, dd, J = 19.1, 10.8 Hz), and from H_3-27 (δ_H 1.04) to H-15β placed H-7, H_3-12, H_3-14, and H_3-27 on the same side of the rings. NOE correlations from H-2 (δ_H 2.69) to H-1α (δ_H 2.52), H-9 (δ_H 2.22), and H-15α (δ_H 2.27, dd, J = 19.1, 5.6 Hz) and from H-16 (δ_H 2.19) to H-15α placed H-2, H-9, and H-16 on the other side of the rings. NOE correlations of H-20 with H_3-28 and H-23 with H_3-29 also showed a *trans*-relationship between H-20 and H-23. The absolute configuration for C-2, C-3, C-7, C-9, C-11, C-16, and C-17 in **2** was assigned as 2*R*,3*S*,7*R*,9*S*,11*S*,16*R*,17*S* by comparing the CD spectral data between **2** and **12**. The CD data of **2** (a negative Cotton effect at about 270 nm; a positive Cotton effect at about 303 nm) were almost the same as that of **12** whose absolute configuration has been determined by X-ray crystallographic analysis in combination with ECD calculation.[8] Considering the same biosynthetic origin of **1** and **2**, the absolute configuration of C-20 and C-23 was tentatively assigned as 20*S* and 23*R*. Compounds **1** and **2** were confirmed as natural products by an LC−MS analysis. The results showed a detectable amount of **1** and **2** in the crude extract of this fungus (Figure S36, Supporting Information).

Sterhirsutin E (**3**) gave a pseudomolecular ion peak at m/z 525.2485 $[M + H]^+$ in its HRTOFMS spectrum, indicating a molecular formula of $C_{30}H_{36}O_8$ (13 degrees of unsaturation). Analysis of its ^{1}H, ^{13}C, and HSQC NMR data (Table S2, Supporting Information) revealed the presence of five methyl groups [δ_H 1.12, 1.29, 1.39, 1.50, 1.92; δ_C 17.6, 23.8, 24.8, 26.9, and 10.2], six methylenes, four methines, five sp^3 quaternary carbons with one oxygenated (δ_C 86.3), two pairs of tetrasubstituted olefinic carbons, one pair of exocyclic olefinic carbons, two carboxylic carbons (δ_C 181.2 and 176.6), and two ketone carbons (δ_C 190.7 and 204.2). The ^{1}H−^{1}H COSY and HMBC spectra analysis confirmed the presence of two isolated hirsutane-type sesquiterpene moieties which, respectively, corresponded to **13** and the deacetylated product of **15** (Figure S1, Supporting Information).[8] Finally, an enol ester bond was assigned between C-6 and C-13′ to satisfy the requirement of the molecular weight, which was also supported by the downfield shift of C-6 (δ_C 142.4) and upfield shift of C-13′ (δ_C 176.6), as observed in 3-hydroxyambrosin damsinate,[9] arrivacin B,[10] and **15** with a similar structural feature. NOE correlations (Figure S4, Supporting Information) of H-1β (1′β) with H_3-12 (12′) and H_3-14 (14′) and H-2 (2′) with H-9 (9′) and H-1α (1′α) confirmed the relative configuration in **3** as described.

The molecular formula of **4** was determined to be $C_{30}H_{33}ClO_6$ (14 degrees of unsaturation) by HRTOFMS. The presence of chlorine atom was confirmed by the typical isotopic pattern observed in the HRTOFMS spectrum [m/z 527.2041 (37) $[M(^{37}Cl) + H]^+$, 525.2052 (100) $[M(^{35}Cl) + H]^+$. The ^{1}H and ^{13}C NMR data of **4** showed similarity with those of **3**, indicating a similar dimeric structural feature. Detailed analysis of its ^{1}H−^{1}H COSY, HMBC, and NOESY data confirmed two hirsutane-type sesquiterpene moieties closely related to the deacetylated product of **15** and cholorsterenone.[11] The substitution of a chlorine atom at C-6′ was supported by the chemical shift of C-6′ (δ_C 126.7) and

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C-7′ (δ_C 180.3), as observed in chlorosterenone. Finally, an enol ester bond was deduced between C-6 and C-13′ as described in **3**.

The molecular formula of sterhirsutin G (**5**) was determined to be $C_{31}H_{38}O_8$ on the basis of HRTOFMS data at *m/z* 539.2639 $[M + H]^+$, which in combination with ^1H and ^{13}C NMR data analysis indicated the characteristic of the dimeric hirsutane sesquiterpene of **5**. Two substructure moieties corresponding to **14** and the deacetylated product of **15** were elucidated by the detailed interpretation of the ^1H, ^{13}C, HSQC, HMBC, and NOESY NMR spectra of **5** and connected by an enol ester bond that was supported by the chemical shift variation of C-6 and C-13′.

The molecular formula of sterhirsutins H (**6**) and I (**7**) were assigned as $C_{46}H_{54}O_{11}$ (20 degrees of unsaturation) and $C_{45}H_{54}O_9$ (19 degrees of unsaturation) by HRTOFMS analysis, respectively. The trimeric hirsutane-type sesquiterpenoid feature of **6** and **7** was deduced on the basis of ^1H and ^{13}C NMR data (Table S4, Supporting Information), as well as the requirement of molecular weight. Two structural units closely related to the deacetylated product of **15** were determined in **6** and **7** by ^1H, ^{13}C, $^1H-^1H$ COSY, and HMBC spectral elucidation. The structural difference between **6** and **7** was the third moiety. The third unit in **6** was determined to be a hirsutic acid D (**14**) derivative by interpretation of its 2D NMR spectra and comparison with the NMR data of **14**. In compound **7**, the $^1H-^1H$ COSY correlations of H_2-6″-H-7″-H_2-8″-H-9″-H-2″ (H_2-10″), H_2-1″-H-2″, and H-4″-H_3-15″, as well as the HMBC correlations from H_3-12″ (δ_H 1.46) to C-1″, C-10″, C-11″, and C-13″, from H_3-14″ (δ_H 0.83) to C-2″, C-3″, C-4″, and C-7″, and from H_3-15″ (δ_H 0.95, d, J = 7.0 Hz) to C-3″, C-4″, and C-5″ confirmed the hirsutane-type structure for the third unit. The sequence of these three moieties and their connected positions in **6** and **7** were established by comparing their ^{13}C NMR data with those of **14** and **15**.[8]

Sterhirsutin J (**8**) was obtained as a yellow oil. Its molecular formula was established as $C_{28}H_{32}O_7$ by HRTOFMS data at *m/z* 503.2044 $[M + Na]^+$. Analysis of its ^1H and ^{13}C NMR spectra (Table S4, Supporting Information) together with the NMR data comparison between **8** and **15** revealed the presence of a deacetylated product of **15**. The $^1H-^1H$ COSY correlations between H_2-1″ (δ_H 3.37, d, J = 7.0) and H-2″ (δ_H 5.23, t, J = 7.0), the HMBC correlations from H_3-4″ (δ_H 1.79, s) and H_3-5″ (δ_H 1.72, s) to C-2″ and C-3″, from H-2″ to C-3′, C-1″, C-3″, C-4″, and C-5″, from H_2-1″ to C-2′, C-3′, C-4′, C-2″, and C-3″, from H-5′ (δ_H 6.24, s) to C-1′, C-3′, C-4′, C-6′, and C-8′, and from H_3-8′ (δ_H 2.50, s) to C-1′, C-5′, and C-6′ as well as the NMR data comparison between **8** and methyl 2,4-dihydroxy-6-methyl-3-(3-methylbut-2-en-1-yl)benzoate[12] confirmed the presence of an isoprenylated phenol moiety. The ester bond between C-6 and C-7′ was assigned on the basis of NMR data comparison between **8** and **15** and the requirement of the molecular weight. The relative configuration in the hirsutane-type skeleton was determined by the NOE correlations from H-10β (δ_H 1.36) to H-1β (δ_H 1.65) and H_3-12 (δ_H 1.43), from H_3-14 (δ_H 1.31) to H-1β, and from H-2 (δ_H 2.60) to H-9 (δ_H 2.85) and H-10α (δ_H 2.56) as depicted in Figure S4, Supporting Information.

The molecular formula of sterhirsutin K (**9**) was determined to be $C_{29}H_{36}O_8$ on the basis of the HRTOFMS data at *m/z* 535.2305 $[M + Na]^+$ and NMR data. The ^1H and ^{13}C NMR data of **9** showed much similarity with those of **8**, except for the presence of an oxygenated quaternary carbon (δ_C 91.3), one oxygenated methine (δ_H 6.09, s; δ_C 82.2), and one methoxyl group (δ_H 3.30, s; δ_C 52.8) and the loss of two tetrasubstituted olefinic carbons. HMBC correlations from H_3-14 to C-2, C-3, C-4, and C-7 and from the oxygenated methine proton H-6 to C-3, C-4, C-5, C-7, C-8, and C-7′ confirmed the substitution of the 2,4-dihydroxy-6-methyl-3-(3-methylbut-2-en-1-yl)benzoic acid moiety at C-6 and a methoxyl group at C-7, respectively. In the ROESY experiment, NOE correlations (Figure S4, Supporting Information) from H-1β (δ_H 1.85) to H_3-12, and H_3-14, from H-6 to H_3-14, and H_3-16, and from H_3-16 to H-8β (δ_H 1.67) placed these protons on the same face of the rings. NOE correlations from H-2 to H-1α (δ_H 2.28) and H-9 and from H-9 to H-8α (δ_H 2.06) located those protons on the opposite side. Considering the same biosynthetic origin of **8**, **9**, **13**, and **15**, the absolute configuration was strongly inferred to be 2*R*,3*S*,9*S*,11*S* in **8** and 2*R*,3*R*,6*R*,7*S*,9*R*,11*S* in **9**, respectively.

Sterhirsutin L (**10**) was obtained as yellow oil. It has a molecular formula of $C_{20}H_{22}N_4O_6$ on the basis of HRTOFMS at *m/z* 415.1617 $[M + H]^+$. The ^1H and ^{13}C NMR spectra of **10** recorded in DMSO-d_6 (Table S5, Supporting Information) showed resonances attributed to a hirsutane-type sesquiterpene moiety closely related to **13**, including two methyls (δ_H 1.16, s; 1.26, s), four methylenes, three methines, two quaternary carbons, a pair of tetra-substituted olefinic carbons (δ_C 144.0 and 150.0), a carboxylic group (δ_C 179.6), and one ketone moiety (δ_C 205.1). The remaining signals of one proton-bearing olefinic carbon (δ_H 7.81, s; δ_C 143.1), two carboxylic groups (δ_C 151.6 and 156.0), two tetrasubstituted olefinic carbons (δ_C 107.3 and 149.2), two broad active hydrogen signals at δ_H 10.84 and 11.54, and the fragment ion peak at *m/z* 153.0407 (calcd for $C_5H_5N_4O_2$, 153.0407) in its HRTOFMS spectrum suggested the presence of a xanthine moiety in **10**. The connection of the sesquiterpene moiety with xanthine unit was confirmed by the HMBC correlations from H_2-15 (δ_H 5.11, d, J = 16.6 Hz; 5.15, d, J = 16.6 Hz) to C-5′ and C-8′. The relative configuration in **10** was determined to be the same as that of **14** by the NOESY experiment. The similar CD spectrum observed between **10** and **14** revealed the absolute configuration of **10** as 2*R*,3*S*,7*R*,9*S*,11*S*.

In the cytotoxicity assay against K562 and HCT116 cancer cells (Table S6, Supporting Information), compounds **3**−**5** and **7** showed moderate antiproliferative activity with IC_{50} values in the range of 6−20 μM.

Natural products with autophagy-inducing activity have potential to be new drug candidates for the treatment of neurodegenerative disorders and cancer. The autophagy-inducing effect can be evaluated via quantification the number of GFP-LC3 dots in cells. Taking advantage of this method, compounds **1**−**15** were screened using GFP-LC3 stable HeLa cells. As a result, **9** was found to possess strong autophagy-inducing activity at a concentration of 50 μM (Figure 3A). All other compounds did not present any autophagy-inducing activity at this dose. Compound **9** exhibited autophagy inducing effect on HeLa cells in a dose- and time-dependent manner

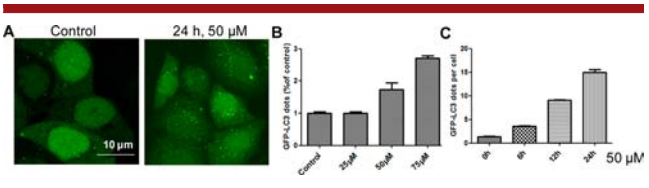

Figure 3. Compound **9** induced autophagy in HeLa cells.

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(Figure 3B,C). The growth of HeLa cells was not influenced by compound **9** within the range of 25−75 μM. Further confirmation of the autophagy-inducing activity of **9** and deep investigation on the action mechanism is undergoing. In comparison with **9**, compounds **8** and **15** showed strong cytotoxicity instead of autophagy-inducing effect on GFP-LC3 stable HeLa cells at the dose of 50 μM (inhibition rate = 100%). The double bond between C-6 and C-7 in **8** and **15** increases cytotoxicity, but significantly decreases the autophagy-inducing activity.

The effect of **1**−**15** on Sendai virus- (SeV-)induced type I interferon signaling was assayed by a cell-based luciferase reporter system. As shown in Figure 4A, compound **5**

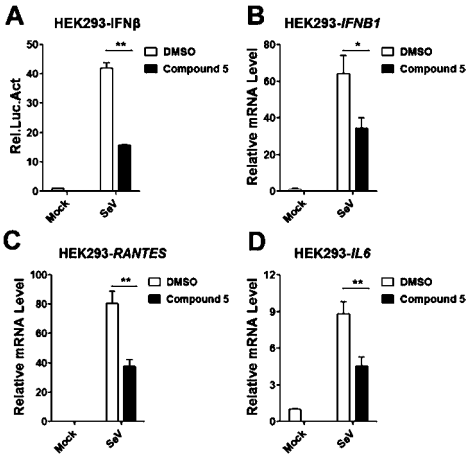

Figure 4. Compound **5** inhibited SeV induced type I interferon signaling in SeV-infected HEK293 cells (* $p < 0.05$; ** $p < 0.01$).

sufficiently inhibited the activation of IFNβ promoter at a dose of 10 μM in HEK293 cells, whereas other compounds exhibited no apparent inhibitory activity on the IFNβ promoter activation under the same experimental conditions (data not shown). We then examined whether **5** affected mRNA levels of *IFNB1*, *RANTES*, and *IL6* induced by SeV infection. As expected, compound **5** dramatically reduced the SeV-induced mRNA level of *IFNB1*, *RANTES*, and *IL6* (Figure 4B−D). In support of these observations, compound **5** also suppressed the IFNβ promoter activity induced by overexpression of RIG-I(N), MAVS, TBK1, P65 and IRF3-5D, key components of the RLR pathway in HEK293 cells (Figure S5, Supporting Information). Compound **5** also negatively regulated SeV induced type I interferon signaling in HeLa cells (Figure S6, Supporting Information). In comparison with **5**, compound **3** showed no inhibitory activity on the IFNβ promoter activation, which indicated the significance of the ether bond between C-15′ and C-16′ for immunosuppressant bioactivity. Collectively, our findings support a notion that **5** possesses an ability to inhibit the RLRs-mediated antiviral signaling in cells, and has potential to be leading compound in the treatment of autoimmune diseases.

In conclusion, we identified 10 new sesquiterpenes with diverse structures from the culture of *S. hirsutum*, including two novel heterodimeric sesquiterpenes with a 5/5/5/6/9/4 fused ring system (**1** and **2**), three dimeric and two trimeric hirsutane-type sesquiterpenes (**3**−**7**), and one new xanthine coupling hirsutane-type sesquiterpene (**10**).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, bioassay method, characterization data, ^{1}H and ^{13}C NMR spectra of **1**−**10**, and CD spectra for **1**−**5**, **8**, and **10**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01356.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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