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Tennessenoid A, an Unprecedented Steroid–Sorbicillinoid Adduct From the Marine-Derived Endophyte of *Aspergillus* sp. Strain 1022LEF

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Marine natural products, characterized by fascinating drug-like functionalities and promising biological activities, are important base materials for innovative drugs and agrochemicals. Chemical investigations of the marine-algal-derived endophytic fungus *Aspergillus* sp. 1022LEF residing in the inner tissue of marine red alga yielded a novel polyketide-terpene hybrid metabolite, namely tennessenoid A (**1**), as well as six known biosynthetic congeners including two steroids, ergosta-4,6,8(14),22-tetraen-3-one (**2**) and (22*E*,24*R*)-3α-ureido-ergosta-4,6,8(14),22-tetraene (**3**), and four sorbicillinoid-based compounds, saturnispol G (**4**), trichodimerol (**5**), and dihydrotrichodimer ethers A and B (**6** and **7**). Their structures were unambiguously determined based on extensive 1D/2D NMR and HRESIMS spectroscopic analyses. Tennessenoid A (**1**) was characterized as an unprecedented steroid–sorbicillinoid adduct *via* a C–C bond, which was rarely-observed in natural products. All of the isolated compounds were evaluated for their antifungal activities against eight plant pathogenetic fungi. **1**, in particular, demonstrated broad-spectrum activities against *Sclerotium rolfsii* Sacc., *Fusarium oxysporum* (Schl.) F.sp *cucumerinum* Owen, *Coniella diplodiella* Petrak et Sydow, *Physalospora piricola* Nose., *Fusarium graminearum* schw., *Alternaria mali* rob., *Colletotrichum orbiculare* Arx., and *Alternaria porri* (E11iott) Cifed., with the inhibition zone diameters ranging from 2 to 7 mm.

Keywords: steroids, sorbicillinoids, marine fungus, *Aspergillus*, antifungal activity

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INTRODUCTION

Natural products, which possessed attractive structures and potent bioactivities, traditionally contributed significantly in the development of new innovative drugs and agrochemicals (Butler, 2005). Since the first broad-spectrum antibiotic agent penicillin has been discovered as early as 1928, the "Golden Age of Antibiotics" was sparked in the last century (Knight et al., 2003; Zhang et al., 2020). From then on, the tendency in searching for new natural-product-based drugs is uptapped. It is estimated that over half (> 60%) of approved therapeutic agents are derived from natural products or their derivatives covering the period 1981 to 2019 (Newman and Cragg, 2020). Among them, microbial natural products, also known as secondary metabolites or specialised metabolites, have played nonnegligible and irreplaceable role (Knight et al., 2003). More than 20,000 microbial natural

products, which offered incomparable chemical diversity with structural complexity and biological potency, have been described (Li et al., 2018a). Nowadays, along with the rapid development of new technologies such as functional genomics, the burgeoning microbial natural products-based drug discoveries for pharmaceutical and agrochemical applications are in a revolutionary period. Meanwhile, in spite of outstanding developments in microbial natural products over the last few years, there is still an insistent necessity for searching for more interesting microbial natural products, especially those from extreme and unexplored environments.

Marine microorganisms are one of the most notable and prolific sources of bioactive natural products (Carroll et al., 2021). Although a large amount of natural products have been discovered from marine microorganisms (Rateb and Ebel, 2011; Zhang et al., 2020), it is a matter of fact that, the trend towards finding new natural products is approaching saturation due to the redundancy of the isolation and characterization of both microorganisms and biosynthetic pathways. Consequently, the discovery of new compounds from unexplored environments has proven to be an alternative strategy for the sake of pursuing for microbial novelty (Soldatou and Baker, 2017). Marine-derived endophytic fungi residing in marine alga and mangroves are extraordinary adapted and metabolically active under extreme environmental conditions, which promote them to produce abundant novel secondary metabolites (El-Bondkly et al., 2021).

As part of our ongoing research on bioactive secondary metabolites from marine-derived endophytic fungi (Zhao et al., 2018; Yuan et al., 2020; Zhao et al., 2020), the fungal strain *Aspergillus* sp. 1022LEF isolated from the inner tissue of the marine red alga *Grateloupia turuturu* was selected for a detailed chemical investigation. A scaled-up fermentation and subsequent chromatographic purification yielded a novel polyketide-terpene hybrid metabolite tennessenoid A (**1**) and six known biosynthetic congeners including two steroids (**2** and **3**) and four sorbicillinoid-based compounds (**4**–**7**) (**Figure 1**). The newly-discovered tennessenoid A (**1**) was characterized as an unprecedented steroid–sorbicillinoid adduct *via* a C–C bond, which was rarely-observed in natural products. Furthermore, compound **1** demonstrated broad-spectrum antifungal activity against eight plant pathogenetic fungi [*Sclerotium rolfsii* Sacc., *Fusarium oxysporum* (Schl.) F.sp *cucumerinum* Owen, *Coniella diplodiella* Petrak et Sydow, *Physalospora piricola* Nose., *Fusarium graminearum* schw., *Alternaria mali* rob., *Colletotrichum orbiculare* Arx., and *Alternaria porri* (E11iott) Cifed.], which highlighted its potential as an antifungal agrochemical in agriculture. Herein we report the isolation, structural elucidation, and antifungal activities of the isolated compounds.

MATERIALS AND METHODS

General Experimental Procedures

Optical rotations data were measured by a Jasco P-1020 digital polarimeter (Jasco, Tokyo, Japan) with MeOH as solvent. UV spectra were obtained on a Shimadzu UV-2700 spectrophotometer (Shimadzu, Kyoto, Japan). NMR spectra were recorded on an Agilent DD2 NMR spectrometer (Agilent Technologies, Santa Clara, CA, United States) operating at 500 MHz for the ^{1}H channel and 125 MHz for the ^{13}C channel. HRESIMS data were acquired on a Waters ACQUITY UPLC I-Class-Vion IMS Q-TOF mass spectrometer (Waters Corp., Massachusetts, U.S.A.). Column chromatography was carried out with silica gel (200–300 mesh, Haiyang Chemical Factory, Qingdao, China), Lobar LiChroprep RP-18 (40–60 μm, Merck, Darmstadt, Germany), and Sephadex LH-20 (Merck). All solvents used for extraction and purification were of analytical grade for column chromatography, or of HPLC grade for HPLC analysis. Precoated silica gel plates were used for thin-layer chromatography (TLC) with detection at 254 nm, while preparative TLC was performed with precoated TLC plates (GF_{254}, Haiyang Chemical Factory).

Fungal Material

Following standard procedures (Li et al., 2018b), the endophytic fungal strain 1022LEF was isolated from the inner tissue of the marine red alga *Grateloupia turuturu*, which was collected from

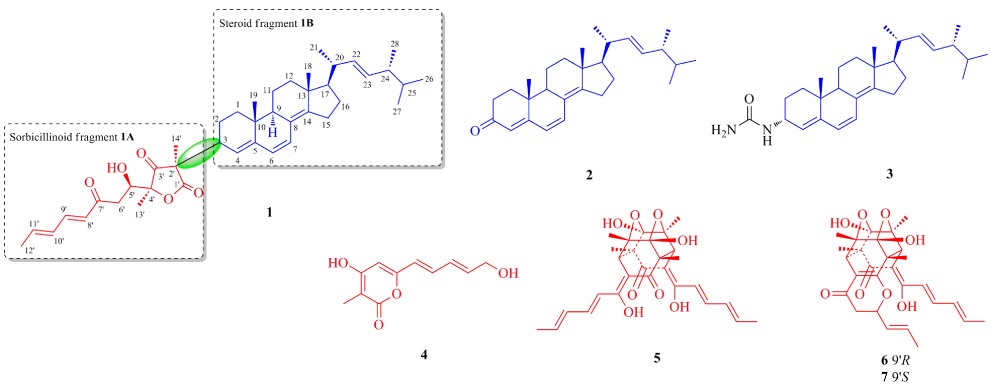

FIGURE 1 | Chemical structures of compounds **1**–**7**.

Qingdao, China. It was preliminary identified as *Aspergillus* sp. by comparing the sequence of the ITS region of the rDNA. The ITS sequence of the isolated fungus was 99% identical to that of *Aspergillus* sp. (GenBank accession: MK605984.1). The GenBank number of MH785494 was assigned to this fungal strain. This fungus was deposited in Tobacco Research Institute of Chinese Academy of Agricultural Sciences with a deposition number of 1022LEF.

Fermentation, Extraction, and Purification

The fungus *Aspergillus* sp. 1022LEF was statically cultured at 28°C in 150 × 1 L Erlenmeyer flasks, each containing 300 mL of potato dextrose broth medium (Solarbio Life Sciences CO., LTD., Beijing, China). Following fermentation for 50 days, the cultures were collected and filtered to separate the broth and mycelia. The broth and the crushed mycelia were extracted with EtOAc. Then, the separate EtOAc extracts were combined and evaporated to give 18.6 g of residue. Detailed separation process was as follows: (i) The resulting residue was subjected to silica gel vacuum liquid chromatography with a stepwise PE/EtOAc (30:1→1:1, v/v) and CH_2Cl_2/MeOH (20:1→1:1, v/v) mixture systems to afford four major fractions A–D. (ii) Fraction A eluting with PE/EtOAc 2:1 was purified by silica gel column chromatography (CC) (CH_2Cl_2/MeOH, 30:1→10:1, v/v) to yield the new compound **1** (5.8 mg). (iii) Compounds **2** (6.2 mg) and **3** (4.6 mg) were obtained from fraction B eluting with PE/EtOAc 1:1 by preparative TLC (plate: 20 × 20 cm; developing solvents: CH_2Cl_2/MeOH 30:1). (iv) Fraction C eluting with CH_2Cl_2/MeOH 20:1 was refractionated by reversed-phase C18 CC with a mixture of MeOH/H_2O system (1:9→10:0, v/v) to give five subfractions (Fraction C-1–C-5). Fraction C-1 was subjected to Sephadex LH-20 (MeOH) to yield **5** (8.9 mg). Fraction C-3 was further purified by silica gel CC (CH_2Cl_2/MeOH, 30:1→10:1, v/v), and followed by Sephadex LH-20 (MeOH) to give **6** (10.2 mg) and **7** (9.0 mg). Finally, compound **4** (11.6 mg) was separated from fraction C-4 *via* preparative TLC (plate: 20 × 20 cm; developing solvents: CH_2Cl_2/MeOH 20:1).

Tennessenoid A (**1**): amorphous powder; $[\alpha]_D^{20}$ +15.6 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 201 (3.29), 268 (3.05), 290 (4.19), 305 (3.10) nm; ^1H and ^{13}C NMR data (measured in $CDCl_3$), see **Table 1**; HRESIMS *m/z* 665.4183 $[M + Na]^+$ (calcd for $C_{42}H_{58}O_5Na$, 665.4182).

Antifungal Assay

Antifungal activity of compounds **1**–**8** was evaluated by modified agar diffusion test method (Ahmed et al., 2011). The test compounds were dissolved in acetone at a concentration of 1 mg/mL, and then were made up to a final concentration of 20 μg/mL. The solution was transferred to a sterile filter disk (each 50 μL), which was placed on the agar growth medium for the test pathogenetic fungi. Fungal diseases commonly found in agriculture, *Sclerotium rolfsii* Sacc., *Fusarium oxysporum* (Schl.) F.sp *cucumerinum* Owen, *Coniella diplodiella* Petrak et Sydow, *Physalospora piricola* Nose., *Fusarium graminearum* schw., *Alternaria mali* rob., *Colletotrichum orbiculare* Arx., and *Alternaria porri* (E11iott) Cifed., were chosen as the test pathogenetic fungi. The radius of the zone of inhibition was measured in millimeters starting at the middle of the filter. Prochloraz was used as the positive control.

RESULTS AND DISCUSSION

Structural Elucidation of the Isolated Compounds

Tennessenoid A (**1**) was isolated as an amorphous powder. The molecular formula of **1** was determined to be $C_{42}H_{58}O_5$ by observation of the $[M + Na]^+$ ion peak in the HRESIMS

TABLE 1 | ^1H NMR (500 MHz, δ in ppm) and ^{13}C NMR Data (125 MHz, δ in ppm) for **1** (measured in $CDCl_3$).

No.	δ_H (*J* in Hz)	δ_C, type	No.	δ_H (*J* in Hz)	δ_C, type
1	1.75, m; 1.31, m	34.4, CH_2	22	5.19, d (15.1, 7.8)	135.3, CH
2	1.77, m; 1.73, m	20.8, CH_2	23	5.24, d (15.1, 6.8)	132.2, CH
3	2.69, m	43.8, CH	24	1.87, m	42.9, CH
4	5.31, br s	119.9, CH	25	1.47, m	33.1, CH
5		146.8, C	26	0.82, d (5.9)	19.7, CH_3
6	5.84, d (9.6)	125.9, CH	27	0.84, d (5.9)	20.0, CH_3
7	6.13, d (9.6)	125.6, CH	28	0.92, d (5.8)	17.6, CH_3
8		124.7, C	1′		176.2, C
9	1.93, m	45.3, CH	2′		52.7, C
10		35.6, C	3′		214.6, C
11	1.60, m; 1.56, m	19.3, CH_2	4′		89.6, C
12	2.01, m; 1.25, m	36.4, CH_2	5′	4.35, br d (10.4)	72.5, CH
13		43.6, C	6′	3.02, dd (17.5, 10.4); 2.79, d (17.5)	40.3, CH_2
14		149.7, C	7′		199.2, C
15	2.39, m; 2.29, m	25.0, CH_2	8′	6.05, d (15.7)	127.2, CH
16	1.77, m; 1.44, m	27.9, CH_2	9′	7.18, dd (15.7, 10.1)	144.7, CH
17	1.20, m	55.9, CH	10′	6.20, dd (15.6, 10.1)	130.0, CH
18	0.92, s	19.2, CH_3	11′	6.27, dq (15.6, 6.4)	142.2, CH
19	0.81, s	18.6, CH_3	12′	1.89, d (6.4)	18.9, CH_3
20	2.11, m	39.4, CH	13′	1.48, s	18.4, CH_3
21	1.04, d (6.6)	21.2, CH_3	14′	1.41, s	16.5, CH_3

spectrum at *m/z* 665.4183 (calcd for $C_{42}H_{58}O_5Na$, 665.4182). The ^{13}C NMR spectrum of **1** (**Table 1**) revealed 42 carbon resonances, which were classified into two ketone carbonyls at δ_C 214.6 (C-3′) and 199.2 (C-7′), one ester carbonyl at δ_C 176.2 (C-1′), seven quaternary carbons including three sp^2 and one oxygenated at δ_C 89.6 (C-4′), 16 methines including nine olefinic at δ_C 127.2 (C-8′), 144.7 (C-9′), 130.0 (C-10′), 142.2 (C-11′), 119.9 (C-4), 125.9 (C-6), 125.6 (C-7), 135.3 (C-22), and 132.2 (C-23) and one oxygenated at δ_C 72.5 (C-5′), seven methylenes, and nine methyl groups with the aid of DEPT spectra. The ^1H NMR data of **1** (**Table 1**) displayed signals for nine methyl groups [including five doublets at δ_H 1.89 (d, J = 6.4 Hz), 1.04 (d, J = 6.6 Hz), 0.92 (d, J = 5.8 Hz), 0.84 (d, J = 5.9 Hz), 0.82 (d, J = 5.9 Hz), and four singlets at δ_H 1.48, 1.41, 0.92, and 0.81], nine olefinic protons (from δ_H 5.19 to 7.18), and a series of indistinguishable aliphatic multiplets. Further analysis of the 1D and 2D NMR data allowed for the establishment of fragments **1A** and **1B** for compound **1** (**Figure 2**).

Interpretation of the 2D NMR data (^1H–^1H COSY and HMBC cross-peaks) of fragment **1A**, two spin-coupling systems, H-8′/H-9′/H-10′/H-11′/H_3-12′ and H-5′/H_2-6′, were readily established. The connectivities of these spin systems, the ketone/ester carbonyls, and the methyls were achieved by analysis of the key HMBC correlations (**Figure 2**). The HMBC correlations from H_3-14′ to C-1′/C-3′ and from H_3-13′ to C-3′/C-4′generated a furan lactone moiety and it was linked to C-5′ by HMBCs from H-5′ to C-3′ and H_3-13′ to C-5′. Fragment **1A** was deduced to be a vertinolide derivative, a sorbicillinoid-type polyketide isolated from the endophytic fungus *Clonostachys rosea* B5-2 (Supratman et al., 2021).

Fragment **1B** was deduced as a steroid moiety by analysis of characteristic signals in 1D and 2D NMR spectrum. A combination of ^1H–^1H COSY and HMBC correlations (**Figure 2**) enabled us to identify the (22*E*)-ergosta-4,6,8 (14),22-tetraene nucleus, which was similar to compounds **2** and **3**. Moreover, the connection between fragments **1A** and **1B** *via* the C–C bond was established by the diagnostic HMBC correlations from H_3-14′ to C-3 and from H-3 to C-1′ (**Figure 2**). Accordingly, the planar structure of **1** was determined.

The relative stereochemistry of **1** was established by interpretation of NOESY spectrum. As for fragment **1A**, the mutual NOE correlations of H-5′/H_3-13′/H_3-14′ indicated a cofacial relationship among H-5′, H_3-13′, and H_3-14′ (**Figure 3**). In fragment **1B**, NOE correlations between H_3-19

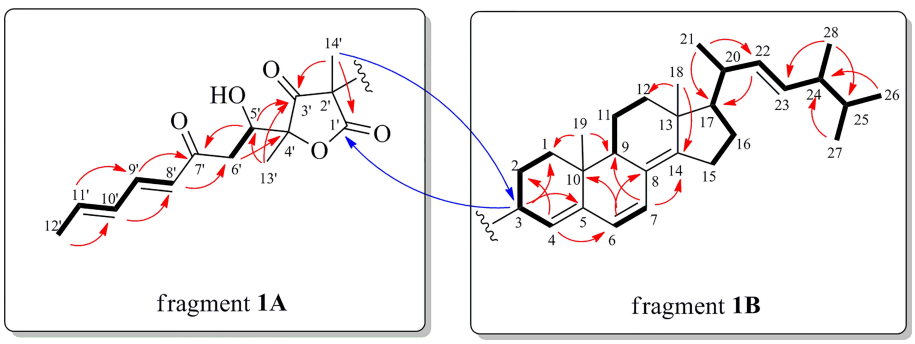

FIGURE 2 | Key ^1H-^1H COSY (bold lines) and HMBC (red and blue arrows for intra- and inter-fragments **1A** and **1B**, respectively) correlations of **1**.

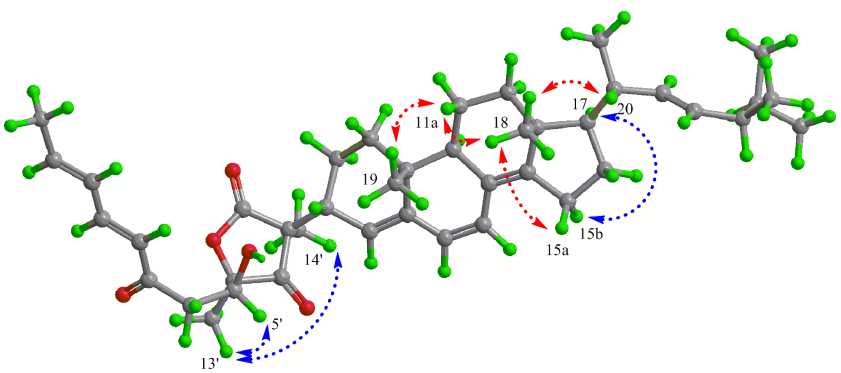

FIGURE 3 | NOESY correlations of **1**.

and H-11a, between H-11a/H_3-18, and between H_3-18 and H-15a/H-20 suggested that these groups were located at the same side of the 6/6/6/5 tetracyclic nucleus, while on the contrary, NOE correlation between H-17 and H-15b indicated they oriented towards opposite side (**Figure 3**). This deduction was also in consistance with the reported ergosteroids **2** and **3**. The β-orientations of H-20 and H-24 were deduced by biosynthesis considerations based on those in **2** and **3**. Furthermore, the coupling constants between H-8′ and H-9′ (J = 15.7 Hz) and between H-10′ and H-11′ (J = 15.7 Hz) illustrated that the double bonds at C-8' and C-10' were in the *E* configurations. However, since fragments **1A** and **1B** can be rotated freely, the high flexibility made the relative configurations of **1A** and **1B** unsolved, as well as the absolute configurations. Many attempts to cultivate single crystals which were suitable for X-ray diffraction analysis in mixed solvent systems (MeOH/H_2O, CH_2Cl_2/H_2O, acetone/H_2O, etc.) were tried. However, they all failed unfortunately.

In addition, six known biosynthetic congeners including two steroids, ergosta-4,6,8(14),22-tetraen-3-one (**2**) (Fujimoto et al., 2004) and (22*E*,24*R*)-3α-ureido-ergosta-4,6,8(14),22-tetraene (**3**) (Yoshikawa et al., 2001), and four sorbicillinoid-based compounds, saturnispol G (**4**) (Meng et al., 2018), trichodimerol (**5**) (Zhai et al., 2016), and dihydrotrichodimer ethers A and B (**6** and **7**) (Zhai et al., 2016) were isolated and identified by comparison of the spectroscopic data with those reported in the literatures. Compound **1** was characterized as an unprecedented steroid–sorbicillinoid adduct, while compounds **5**–**7** were previously reported bisorbicillinoids. The putative biosynthesis of **1** can be traced back to vertinolide and ergosteroid (**Figure 4**). The aldolization of **2** and vertinolide generated the unique C–C bond, which was rarely-observed in natural ergosteroids, while dimerization of vertinolide formed dimers **5**–**7**.

Antifungal Activity

The isolated compounds **1**–**8** were evaluated to determine their antifungal activity against eight pathogenetic fungi. As a result, the new compound **1**, in particular, exhibited modest but broad-spectrum activities against S. rolfsii, F. oxysporum, C. diplodiella, P. piricola, F. graminearum, A. mali, C. orbiculare, and A. porri, with the radius of the inhibition zone of 7, 5, 5, 5, 3, 3, 2, and 2 *mm*, respectively (**Figure 5**), while the radius of the inhibition zone of the positive control prochloraz were ranging from 7 to 12 mm. Sorbicillinoids are a family of hexaketide secondary metabolites with a characteristic sorbyl side chain residue. Previous studies reported sorbicillinoids possessed high antimicrobial activity and can be used as a biological control agent (Zhai et al., 2016). Moreover, sorbicillinoids are also found to potently inhibit fungal pathogens both in vitro and in vivo. Bisvertinolone, a bisorbicillinoid produced by Trichoderma

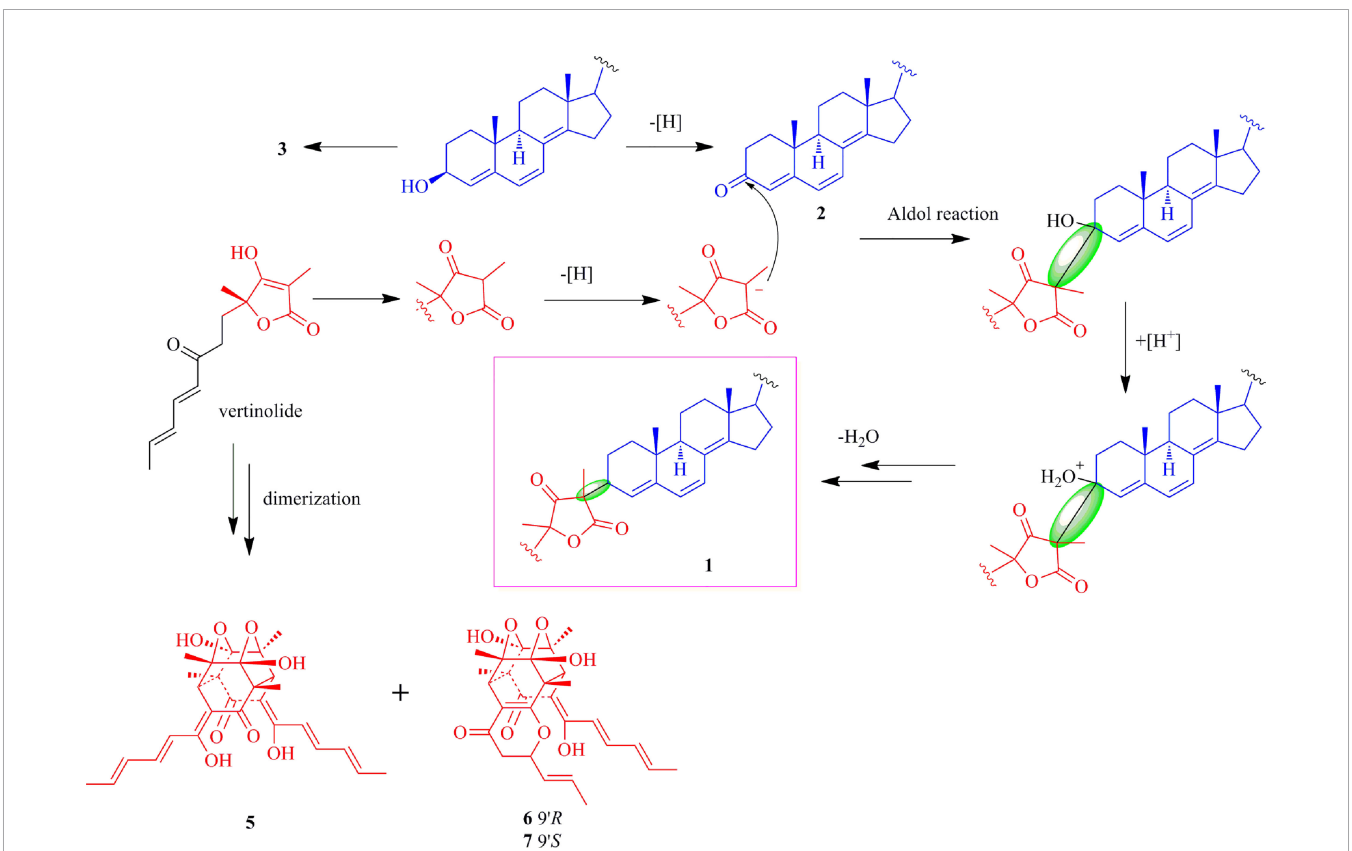

FIGURE 4 | Proposed biosynthetic pathway of **1** and related compounds.

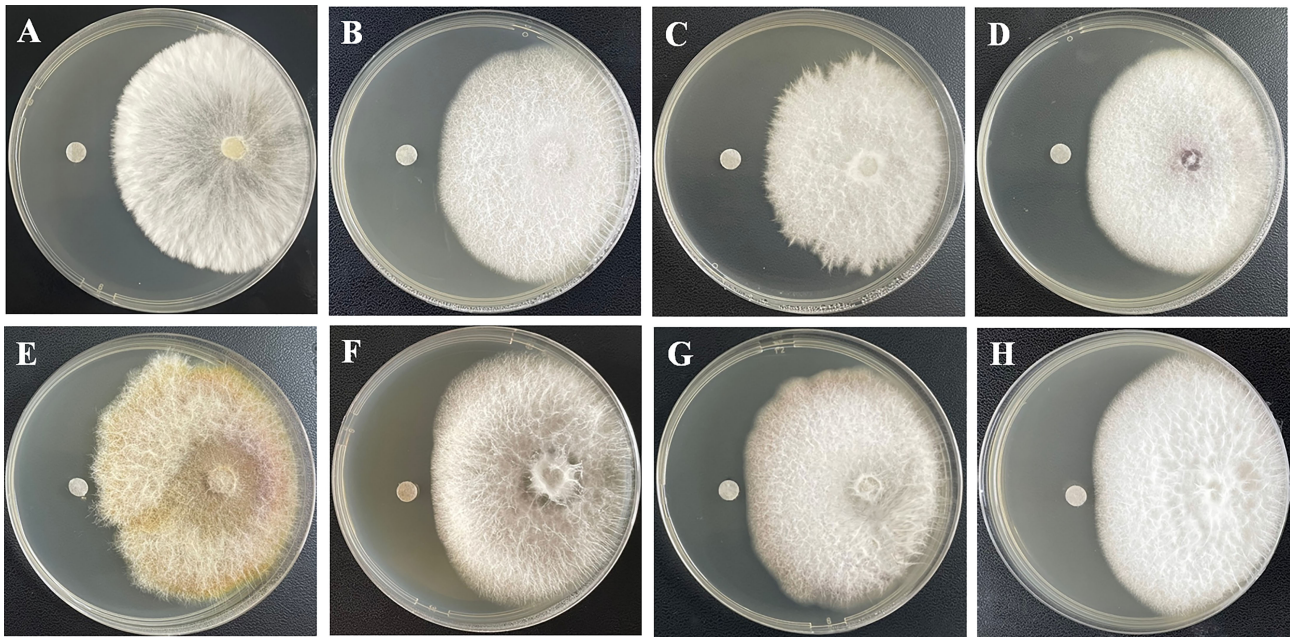

FIGURE 5 | Antifungal activities of **1** against eight plant pathogenetic fungi–*S. rolfsii* **(A)**, *F. oxysporum* **(B)**, *C. diplodiella* **(C)**, *P. piricola* **(D)**, *F. graminearum* **(E)**, *A. mali* **(F)**, *C. orbiculare* **(G)**, and *A. porri* **(H)**.

longibrachiatum SFC100166, not only showed considerable activity against phytopathogenic fungi Cladosporium coccodes, Colletotrichum coccodes, Cylindrocarpon destructans, Magnaporthe oyrzae, and Phytopathora infestans, with MIC values ranging from 6.3 to 100 μg/mL, but also reduced the development of tomato late blight disease strongly (Ngo et al., 2021). Further studies such as in vivo assay and mode of action of antifungal activities may reveal the potential of the newly-isolated steroid–sorbicillinoid adduct **1** as an antifungal agrochemical in agriculture.

CONCLUSIONS

In conclusion, a novel polyketide-terpene hybrid metabolite, tennessenoid A (**1**), as well as six known biosynthetic congeners, ergosta-4,6,8(14),22-tetraen-3-one (**2**), (22*E*,24*R*)-3α-ureido-ergosta-4,6,8(14),22-tetraene (**3**), saturnispol G (**4**), trichodimerol (**5**), and dihydrotrichodimer ethers A and B (**6** and **7**) were isolated from the marine-derived endophyte of *Aspergillus* sp. 1022LEF. Their structures were determined by detailed analysis of NMR data and HRESIMS. The steroids **2**–**3** and the sorbicillinoids **4**–**7** were common fungal secondary metabolites, whereas the new compound **1** represented the first example of steroid–sorbicillinoid adduct *via* a C–C bond. Moreover, this unprecedented compound exhibited broad-spectrum antifungal activities against several plant pathogenetic fungi. This study indicated that the marine-derived microbes were considered to be valuable resources for the development of new agrochemicals.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Experiment implementation, D-LZ and H-SW. Writing—original draft preparation, D-LZ and L-WG. Writing—review and editing, PZ. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmars.2022.923128/full#supplementary-material

REFERENCES

Ahmed, I., Hussain, H., Schulz, B., Draeger, S., Padula, D., Pescitelli, G., et al. (2011). Three New Antimicrobial Metabolites From the Endophytic Fungus Phomopsis Sp. *Eur. J. Org. Chem.* 2011, 2867–2873. doi: 10.1002/ejoc.201100158

Butler, M. S. (2005). Natural Products to Drugs: Natural Product Derived Compounds in Clinical Trials. *Nat. Prod. Rep.* 22, 162–195. doi: 10.1039/b402985m

Carroll, A. R., Copp, B. R., Davis, R. A., Keyzers, R. A., and Prinsep, M. R. (2021). Marine Natural Products. *Nat. Prod. Rep.* 38, 362–413. doi: 10.1039/D0NP00089B

El-Bondkly, E. A. M., El-Bondkly, A. A. M., and El-Bondkly, A. A. M. (2021). Marine Endophytic Fungal Metabolites: A Whole New World of Pharmaceutical Therapy Exploration. *Heliyon* 7, e06362. doi: 10.1016/j.heliyon.2021.e06362

Fujimoto, H., Nakamura, E., Okuyama, E., and Ishibashi, M. (2004). Six Immunosuppressive Features From an Ascomycete, *Zopfiella Longicaudata*, Found in a Screening Study Monitored by Immunomodulatory Activity. *Chem. Pharm. Bull.* 52, 1005–1008. doi: 10.1248/cpb.52.1005

Knight, V., Sanglier, J. J., DiTullio, D., Braccili, S., Bonner, P., Waters, J., et al. (2003). Diversifying Microbial Natural Products for Drug Discovery. *Appl. Microbiol. Biotechnol.* 62, 446–458. doi: 10.1007/s00253-003-1381-9

Li, Z. X., Wang, X. F., Ren, G. W., Yuan, X. L., Deng, N., Ji, G. X., et al. (2018b). Prenylated Diphenyl Ethers From the Marine Algal-Derived Endophytic Fungus *Aspergillus Tennesseensis*. *Molecules* 23, 2368. doi: 10.3390/molecules23092368

Li, Z., Zhu, D., and Shen, Y. (2018a). Discovery of Novel Bioactive Natural Products Driven by Genome Mining. *Drug Discov. Ther.* 12, 318–328. doi: 10.5582/ddt.2018.01066

Meng, J., Cheng, W., Heydari, H., Wang, B., Zhu, K., Konuklugil, B., et al. (2018). Sorbicillinoid-Based Metabolites From a Sponge-Derived Fungus *Trichoderma Saturnisporum*. *Mar. Drugs* 16, 226. doi: 10.3390/md16070226

Newman, D. J., and Cragg, G. M. (2020). Natural Products as Sources of New Drugs Over the Nearly Four Decades From 01/1981 to 09/2019. *J. Nat. Prod.* 83, 770–803. doi: 10.1021/acs.jnatprod.9b01285

Ngo, M. T., Nguyen, M. V., Han, J. W., Park, M. S., Kim, H., and Choi, G. J. (2021). *In Vitro* and *In Vivo* Antifungal Activity of Sorbicillinoids Produced by *Trichoderma Longibrachiatum*. *J. Fungi* 7, 428. doi: 10.3390/jof7060428

Rateb, M. E. M., and Ebel, R. (2011). Secondary Metabolites of Fungi From Marine Habitats. *Nat. Prod. Rep.* 28, 290. doi: 10.1039/c0np00061b

Soldatou, S., and Baker, B. J. (2017). Cold-Water Marine Natural Products 2006 to 2016. *Nat. Prod. Rep.* 34, 585–626. doi: 10.1039/C6NP00127K

Supratman, U., Suzuki, T., Nakamura, T., Yokoyama, Y., Harneti, D., Maharani, R., et al. (2021). New Metabolites Produced by Endophyte *Clonostachys Rosea* B5-2. *Nat. Prod. Res.* 35, 1525–1531. doi: 10.1080/14786419.2019.1656629

Yoshikawa, K., Ikuta, M., Arihara, S., Matsumura, E., and Katayama, S. (2001). Two New Steroidal Derivatives From the Fruit Body of *Chlorophyllum Molybdites*. *Chem. Pharm. Bull.* 49, 1030–1032. doi: 10.1248/cpb.49.1030

Yuan, X. L., Wang, X. F., Xu, K., Li, W., Chen, D., and Zhang, P. (2020). Characterization of a New Insecticidal Anthraquinone Derivative From an Endophyte of *Acremonium Vitellinum* Against *Helicoverpa Armigera*. *J. Agric. Food Chem.* 68, 11480–11487. doi: 10.1021/acs.jafc.0c05680

Zhai, M. M., Qi, F. M., Li, J., Jiang, C. X., Hou, Y., Shi, Y. P., et al. (2016). Isolation of Secondary Metabolites From the Soil-Derived Fungus *Clonostachys Rosea* YRS-06, a Biological Control Agent, and Evaluation of Antibacterial Activity. *J. Agric. Food Chem.* 64, 2298–2306. doi: 10.1021/acs.jafc.6b00556

Zhang, P., Wei, Q., Yuan, X., and Xu, K. (2020). Newly Reported Alkaloids Produced by Marine-Derived *Penicillium* Species (Covering 2014–2018). *Bioorg. Chem.* 99, 103840. doi: 10.1016/j.bioorg.2020.103840

Zhao, D. L., Han, X. B., Wang, M., Zeng, Y. T., Li, Y. Q., Ma, G. Y., et al. (2020). Herbicidal and Antifungal Xanthone Derivatives From the Alga-Derived Fungus *Aspergillus Versicolor* D5. *J. Agric. Food Chem.* 68, 11207–11214. doi: 10.1021/acs.jafc.0c04265

Zhao, D. L., Yuan, X. L., Du, Y. M., Zhang, Z. F., and Zhang, P. (2018). Benzophenone Derivatives From an Algal-Endophytic Isolate of *Penicillium Chrysogenum* and Their Cytotoxicity. *Molecules* 23, 3378. doi: 10.3390/molecules23123378

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