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Malfilamentoside A 的构型确定与新呋喃糖苷类化合物 Malfilamentoside D

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摘要 基于高效液相色谱-二级阵列检测器(HPLC-DAD)追踪方法, 从高原土壤来源真菌 *Auxarthron umbrinum* SCSIO 40432 发酵产物中分离获得 8 个化合物, 包括 malfilamentoside A (**1**)、新的芳香呋喃酮糖苷类化合物 malfilamentoside D (**2**)及 6 个已知化合物(**3**～**8**). 通过 1D、2D NMR 确定了化合物的平面结构, 首次通过 X 射线单晶衍射确定了 malfilamentoside A (**1**)的绝对构型, 比较化合物 **1** 和 **2** 的电子圆二色谱(ECD)谱确定了 malfilamentoside D (**2**)的立体构型. 化合物 **1** 对黄嘌呤氧化酶有弱的抑制活性.

关键词 *Auxarthron umbrinum* SCSIO 40432; 芳香呋喃酮糖苷类化合物; Malfilamentoside; 构型确定

Configurational Assignment of Malfilamentoside A and a New Furanone Glycoside Malfilamentoside D

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Abstract High performance liquid chromatography-diode array detection (HPLC-DAD)-based chemical analysis of the extract fraction library of the plateau soil-derived fungus *Auxarthron umbrinum* SCSIO 40432 led to the identification of eight compounds, including a known aromatic furanone glycoside malfilamentoside A (**1**) whose stereochemistry remained unsolved, and a new malfilamentoside D (**2**), together with six known compounds (**3**～**8**). The planar structures of malfilamentaosides A (**1**) and D (**2**) were elucidated by HRESIMS, 1D and 2D NMR spectroscopic analysis. The absolute configuration of malfilamentoside A (**1**) was unambiguously resolved for the first time by a single crystal X-ray diffraction analysis and the stereochemistry of malfilamentoside D (**2**) was determined by comparing electronic circular dichroism (ECD) spectra of **1** and **2**. Malfilamentoside A (**1**) exhibited inhibitory activity to xanthine oxidase at the concentration of 20 μmol/L.

Keywords *Auxarthron umbrinum* SCSIO 40432; aromatic furanone glycoside; malfilamentoside; configurational assignment

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1 Introduction

Malfilamentosides belong to the family of aromatic furanone glycosides, and contain a 3-benzyl-2-phenyl-4*H*-furanone (ralfuranones) skeleton with an *O*-linked aminosugar at the 4-position. Ralfuranones skeleton was derived from the condensation of *p*-hydroxyphenylpyruvic acid (phenylpyruvate, PPA), which was generated by the oxidation of *L*-phenylalanine.[1-2] Different linkage of the two phenylpyruvate building blocks and unique biosynthetic pathway by combining non-enzymatic and enzymatic reactions endow ralfuranones with structural diversity.[2-5] To date, three malfilamentosides A～C were reported from *Malbarnchea filamentosa*[6] or *Auxarthron* sp.[7] The stereochemistry of malfilamentoside B was recently resolved by theoretical electronic circular dichroism (ECD) analysis,[7] while the absolute configuration of malfilamentoside A is still unassigned.[6]

Microorganisms inhabiting in unique environments usually offer opportunities for discovering novel natural products[8] or novel agents.[9-10] Encouraged by these findings, our group has been exploring special environments derived-microorganisms as sources of antibiotics with novel structure.[11-12] Recently, we reported isolation of phomalichenone I, which bears an unusual benzofuranone scaffolds from *Parengyodontium album* SCSIO 40430,[13] and ocauxarthrol A, a new tetrahydroanthraquinone containing a carbonate group which is rare among natural products, from *Auxarthron umbrinum* SCSIO 40432.[14] Reanalysis of HPLC-DAD data sets of the strain SCSIO 40432 revealed several distinct signals that indicated the presence of compounds different from those of previously reported. Subsequently, extensive chromatographic separation of the butanone extracts of *Auxarthron umbrinum* SCSIO 40432 led to the discovery of malfilamentoside A (**1**), malfilamentoside D (**2**) (Figure 1), together with six known compounds (Figure 1), 2,4-dihydroxybenzoic acid (**3**),[15] 2,3-dihydroxybenzoic acid (**4**),[15] auxarconjugatins A (**5**),[16] 6-acetyl-4-methoxy-3-methyl-a-pyrone (**6**),[17] cyclo(*L*-leucyl-*L*-prolyl) (**7**),[18] and anthranilic acid-derived peptides (**8**).[19] Their structures were elucidated using spectroscopic data and X-ray diffraction analyses. Herein, the isolation, structural elucidation and bioactivities of these compounds were reported.

2 Results and discussion

Compound **1** was obtained as white crystals. The molecular formula of **1** was established by HRMS (ESI-TOF) calcd for $C_{26}H_{29}NO_8$ $[M+H]^+$ 484.1966, found 484.1973. Based on extensive analysis of the 1D and 2D NMR data (Table 1, Figure 2), the planar structure of **1** was determined to be identical to malfilamentoside A, whose stereochemistry was only partially assigned.[6] The relative configuration of the sugar residue was assigned by NOESY correlations and coupling constants. The large vicinal coupling constant of $J_{H\text{-}2',\,H\text{-}3'}$ (10.1 Hz), and $J_{H\text{-}3',\,H\text{-}4'}$ (9.1 Hz) indicated H-2', H-3', and H-4' in an axial orientation, which was confirmed by NOESY correlations of H-2'/H-4'. The axial position of H-5' was suggested by NOESY correlation of H-3'/H-5', and the equatorial position of the H-1' was deduced by small constant of $J_{H\text{-}1',\,H\text{-}2'}$ (3.7 Hz) (Figure 2). It is difficult to assign the relative configuration of C-4 due to the absence correlations. Finally, the crystallization of **1** from MeOH/H_2O (V∶V=9∶1) was achieved in white prisms, giving a single crystal x-ray structure with a Flack parameter value of −0.03(8) (Cu Kα radiation, CCDC2093378), to confirm the planar structure of **1** and to unambiguously assign the absolute configuration of **1** as 4*R* and *α*-*D*-glucosamine.

Compound **2** was obtained as white powders. The molecular formula of **2** was established by HRMS (ESI-TOF) calcd for $C_{25}H_{27}NO_8$ $[M+H]^+$ 470.1809, found 470.1810. The ^1H NMR data of **2** (Table 1) showed a methyl singlet (δ_H 1.88, H-12), a methylene (δ_H 4.02, d, J=15.6; 3.96, d, J=15.6, H-11), an oxymethine singlet (δ_H 5.87, H-4), a group of aliphatic proton signals from sugar residue (δ_H 3.34, 3.54, 3.57～3.61, 3.72, 4.90), a group of aromatic signals (δ_H 7.19, 7.26, 7.32, 7.45～7.49), four exchangeable protons (δ_H 4.54, t, J=8.4, H-6'; δ_H 4.94, br s, H-3'; δ_H 5.01, br d, J=3.1, H-4'; δ_H 8.00, d, J=7.4, NH). The ^{13}C NMR data of **2** (Table 1) displayed twenty-five carbons

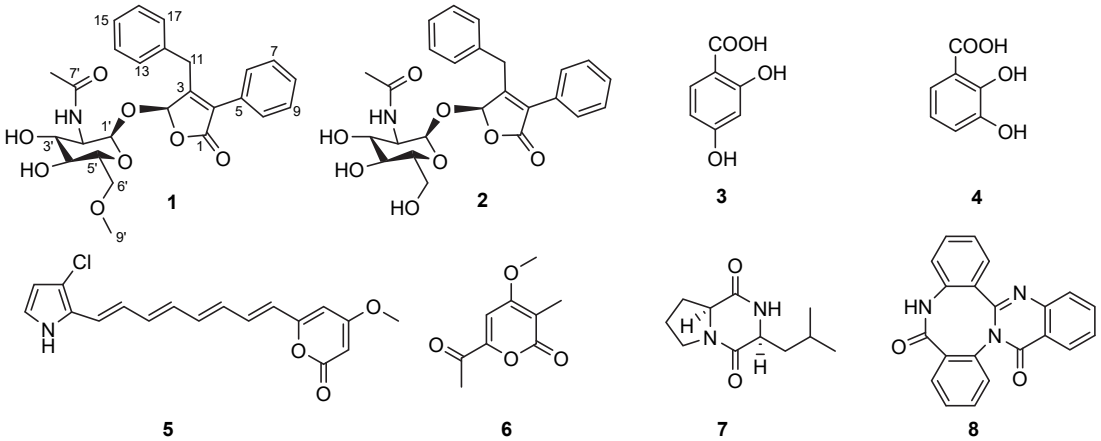


Figure 1 Sructures of compounds **1**～**8**

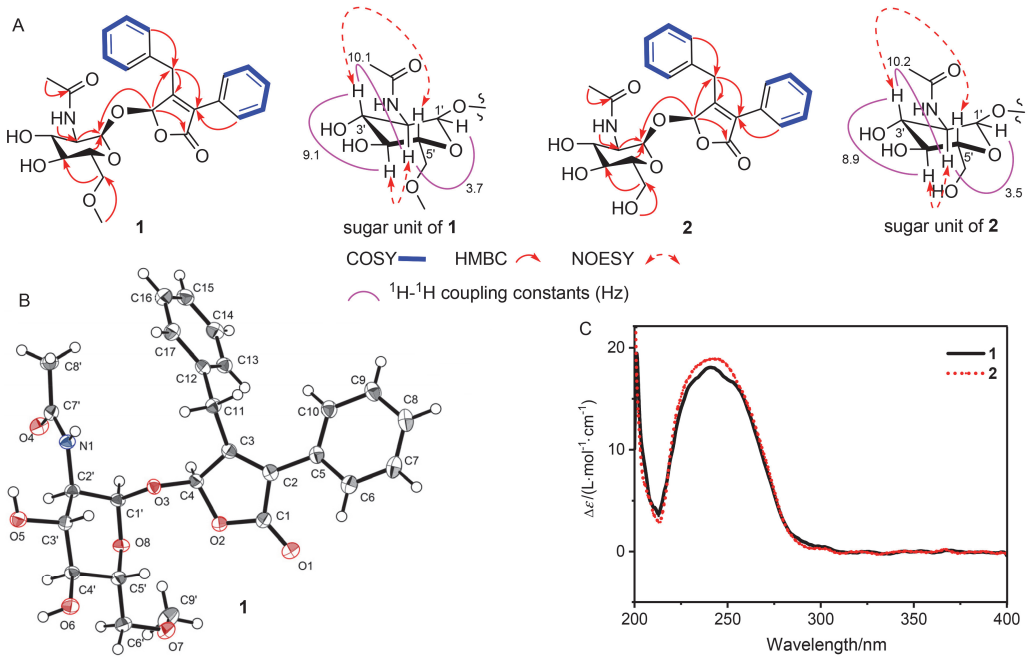


Figure 2 (A) Key COSY and HMBC correlations of compounds **1** and **2**, ^{1}H-^{1}H coupling constants (Hz) and key NOESY correlations of the sugar unit in **1** and **2**; (B) X-ray crystal structures of **1** (the ellipsoids of non-hydrogen atoms are shown at 50% probability levels); (C) Comparison of experimental ECD spectra of **1** and **2**

Table 1 ^{1}H NMR (700 MHz) and ^{13}C NMR (175 MHz) data of compounds **1**～**2**

No.	**1**		**2**	
	δ_H (J in Hz)	δ_C, type	δ_H (J in Hz)	δ_C, type
1		170.3, C		170.3, C
2		136.6, C		136.6, C
3		158.3, C		158.4, C
4	5.89, s	101.2, CH	5.87, s	101.1, CH
5		127.4, C		127.4, C
6/10	7.18, d (7.2)	129.1, CH	7.18, d (7.3)	129.1, CH
7/9	7.30, dd (4.6, 10.2)	129.1, CH	7.30, t (7.4)	129.1, CH
8	7.24, t (7.4)	129.3, CH	7.24, t (7.3)	129.1, CH
11	4.01, d (15.6) 3.95, d (15.6)	32.1, CH_2	4.02, d (15.6) 3.96, d (15.6)	32.2, CH_2
12		141.4, C		141.4, C
13/17	7.47, overlapping	129.3, CH	7.47, overlapping	129.3, CH
14/16	7.47, overlapping	129.3, CH	7.47, overlapping	129.3, CH
15	7.47, overlapping	129.5, CH	7.47, overlapping	129.6, CH
1'	4.90, d (3.7)	99.4, CH	4.90, d (3.5)	99.3, CH
2'	3.71, ddd (10.1, 7.8, 3.8)	54.0, CH	3.72, ddd (10.2, 8.0, 3.5)	54.1, CH
3'	3.24, ddd (10.1, 9.1, 6.9)	70.9, CH	3.33, overlapping	70.5, CH
4'	3.49～3.52, m	70.4, CH	3.52, dd (10.1, 3.5)	70.4, CH
5'	3.49～3.52, m	72.7, CH	3.57～3.58, m	74.2, CH
6'	3.49～3.5, m 3.56, dd (5.0, 11.0)	71.7, CH_2	3.58～3.61, m 3.32～3.34, m	60.4, CH_2
7'		170.0, C		170.0, C
8'	1.87, s	23.0, CH_3	1.88, s	23.1, CH_3
9'	3.28, s	58.8, CH_3		
3'-OH	4.93, s		4.94, s	
4'-OH	5.20, d (6.3)		5.09, d (5.6)	
6'-OH			4.54, t (8.4)	
NH	7.89, d (8.0)		7.98, d (7.9)	

Data were recorded on a Bruker Avance 700 NMR spectrometer in DMSO-d_6 with TMS as an internal standard. The signals were assigned with the aid of ^{1}H-^{1}H COSY, HSQC, and HMBC data.

signals for two *mono*-substituted benzene rings, a group of aliphatic carbon signals from sugar residue (δ_H 54.1, 60.4, 70.4, 70.5, 74.2, 99.3), a methyl, one methylene, one methine, one sp^2 quaternary carbon, an ester carbonyl (δ_C 170.3, C-1) and an amide carbonyl carbon (δ_C 170.0, C-7'). The ^{1}H NMR and ^{13}C NMR data of **2** were higher similar to those of **1**. Given observed ^{1}H-^{1}H COSY correlations of 6'-OH/CH_2-6' in **2**, compound **2** was deduced to be different from **1** by the absence of the methoxy group at C-6 (Figure 2). This deduction was supported by heteronuclear multiple bond correlation (HMBC) from 6'-OH to C-6'/C-5' and H-6' to C-4'. The relative configuration of the sugar residue was assigned by NOESY correlations and coupling constants. The large vicinal coupling constant of $J_{H\text{-}2',H\text{-}3'}$ (10.2), and $J_{H\text{-}3',H\text{-}4'}$ (10.1) indicated H-2', H-3', and H-4' in an axial orientation, which was confirmed by NOESY correlations of H-2'/H-4'. The axial position of H-5' was suggested by NOESY correlation of H-3'/H-5', and the equatorial position of the H-1' was deduced by small constant of $J_{H\text{-}1',H\text{-}2'}$ (3.5) (Figure 2). On the consideration of **2** (designated malfilamentoside D) as a biosynthetic precursor of **1**, the absolute configuration of **2** was assigned as 4*R* and *α*-*D*-glucosamine. This assignment was also supported by comparison of the experimental ECD spectra of **2** with that of **1** (Figure 2).

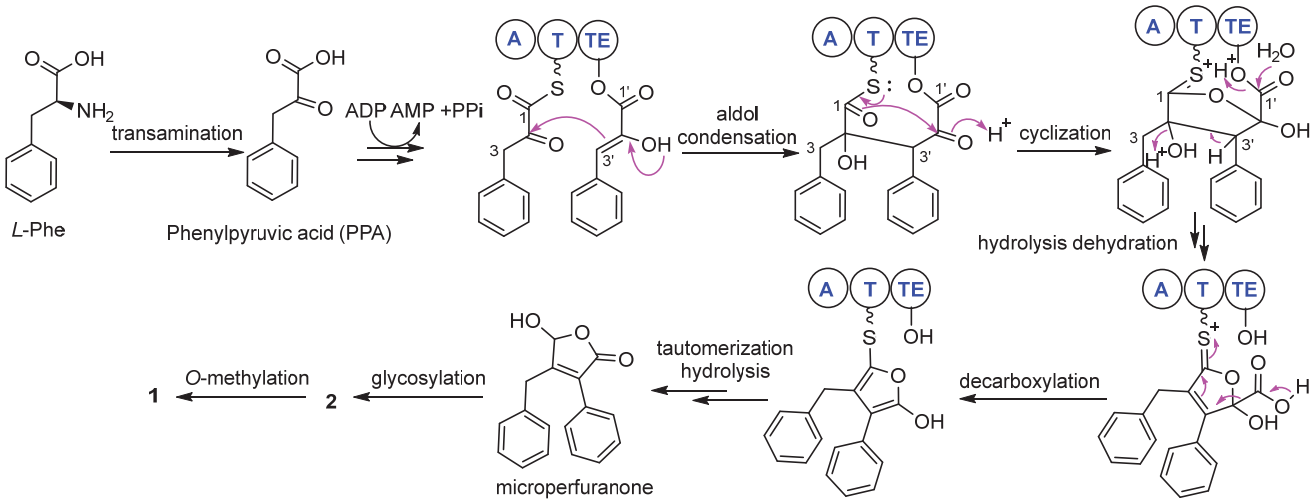
Compounds **1**～**2** belong to aromatic furanone glycosides. A plausible biosynthetic scheme was proposed for the production of **1**～**2** (Scheme 1). Furanones skeleton was derived from two phenylpyruvic acids, which generated by *L*-phenylalanine (Phe). Two of phenylpyruvic acids were selected and activated by the adenylation domain (A) of nonribosomal peptide synthesis (NRPS) module, and transferred onto the thiolation domain (T) and the putative thioesterase (TE) domain. Then, the phenylpyruvic acids were supposed to undergo aldol condensation, sulfur-assisted cyclization, hydrolysis, dehydration, decarboxylation, tautomerization, hydrolysis to produce the key biosynthetic intermediate microperfuranone.[1] Glycosylation of microperfuranone gave **2**, and subsequent *O*-methylation of **2** gave **1** (Scheme 1).

Compounds **3**～**8** were characterized to be 2,4-dihydroxybenzoic acid (**3**),[15] 2,3-dihydroxybenzoic acid (**4**),[15] auxarconjugatins A (**5**),[16] 6-acetyl-4-methoxy-3-methyl-*α*-pyrone (**6**),[17] cyclo(*L*-leucyl-*L*-prolyl) (**7**),[18] and anthranilic acid-derived peptides (**8**)[19] by comparison of the HRESIMS and NMR data with those reported in literatures.

Compounds **1**～**2**, **5**, **7**～**8** were assayed for their antibacterial activities and enzyme inhibition effects on tyrosinase, acetylcholinesterase *α*-glucosidase, xanthine oxidase, and porcine pancreatic elastase. All compounds showed no inhibitory activity towards test bacterial strains. Malfilamentoside A (**1**) and cyclo(*L*-leucyl-*L*-prolyl) (**7**) exhibited moderate inhibitory activity against xanthine oxidase at the concentration of 20 μmol/L, indicating that **1** and **7** are potentially useful in treating gout, a metabolic syndrome that is caused by a disturbance of the uric-acid metabolism, by inhibiting the oxidation of xanthine to uric acid.[20] Compounds **2**, **5** and **8** have no inhibition effects on the test enzymes.

3 Conclusions

In conclusion, two aromatic furanone glycosides, malfilamentoside A (**1**) and malfilamentoside D (**2**), together with six known compounds (**3**～**8**) were isolated from the plateau soil-derived fungal strain *Auxarthron umbrinum* SCSIO 40432. The structures including absolute configurations of malfilamentoside A (**1**) and malfilamentoside D (**2**) were determined by spectroscopic, X-ray diffraction analyses, and the comparison of ECD spectra. Although ralfuranones have structural diversity, to date, only three *γ*-butenolide glycosides, namely malfilamentosides A～C were discovered from fungi. In addition, we showed that malfilamentoside A (**1**) exhibited moderate inhibitory activity against xanthine oxidase.



Scheme 1 Proposed biosynthesis of compounds **1**～**2**

4 Experimental section

4.1 General experimental procedures

Optical rotations were measured on a 341 polarimeter (Perkin Elmer, Inc.). UV spectra were recorded on UV-2600 spectrophotometer (Shimadzu). Melting points were recorded on a SGWX-5 micro-melting point apparatus (Shanghai). IR spectra were recorded on Affinity-1 FT-IR spectrometer (Shimadzu). ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra were recorded on a Bruker AV-700 MHz NMR spectrometer (Bruker Biospin) with tetramethylsilane (TMS) as the internal standard. Mass spectrometric data were obtained on a quadrupole-time-of-flight mass spectrometry (Bruker Maxis 4G UHR-TOFMS spectrometer) for HRESIMS. Materials for column chromatography (CC) were silica gel (100～200 mesh; 300～400 mesh; Jiangyou Silica gel development, Inc.), Sephadex LH-20 (40～70 μm; Amersham Pharmacia Biotech AB), and YMC*GEL ODS-A (12 nm S-50 μm; YMC Company Ltd.). Medium pressure liquid chromatography (MPLC) was performed on a CHEETAH flash system (Bonna-Agela technologies Inc.). Semi-preparative HPLC was performed on a Hitachi HPLC station (Hitachi-L2130) with Diode Array Detector (Hitachi L-2455) using a Phenomenex ODS column (250 mm×10.0 mm, 5 μm; Phenomenex, USA). Preparative thin layer chromatography (PTLC) was conducted with precoated glass plates (silica gel 60 F254, 0.5 mm).

4.2 Fermentation, extraction and isolation

The isolation of strain *Auxarthron umbrinum* SCSIO 40432 has been previously described.[14] The fungal strain *A. umbrinum* SCSIO 40432 was grown and maintained on the potato dextrose agar (PDA) medium at 28 ℃ for 5 d, then inoculated into 50 mL of seed medium (potato-dextrose broth 24 g/L, natural sea salt 2%, pH 7.0～7.3) in a 250 mL Erlenmeyer flask. The cultivation was carried out on a rotary shaker (200 r/min) at 28 ℃ for 5 d. Production medium (potato-dextrose broth 24 g/L, natural sea salt 2%, pH 7.0～7.3, 300 mL/L) was prepared by adding 10% of the seed medium, and cultured on a rotary shaker (200 r/min) at 28 ℃ for 8 d, after which the supernatants and mycelia were extracted with butanone and acetone, respectively. The organic extracts were concentrated under vacuum to yield an oily extract (24.5 g). The extract was subjected to 100～200 mesh silica gel column chromatography, eluting with a gradient of petroleum ether/EtOAc (*V*/*V*=100/0 to 0/100) to afford thirteen fractions (A～M). Fr.J was separated by Sephadex LH-20 column chromatography and eluted with $CHCl_3$/MeOH (*V*∶*V*=1∶1) to give four subfractions (Fr.J-L1～Fr.J-L4). Fr.J-L2 was isolated by preparative HPLC and obtained four subfractions (Fr.J-LP1～Fr.J-LP4). Fr.J-LP3 and Fr.J-LP4 were purified by semipreparative HPLC to yield compound **1** (50.2 mg) and **2** (16 mg), respectively. Fr.G and Fr.H were separated by Sephadex LH-20 column chromatography and eluted with $CHCl_3$/MeOH (*V*∶*V*=1∶1), respectively to give four subfractions (Fr.G-L1～Fr.G-L4, Fr.H-L1～Fr.H-L4). Fr.H-L2-4 were mixed and subjected to C18 reversed-phase column eluted with a linear gradient of H_2O/CH_3CN (0～100%, 20 mL•min^{-1}, 200 min) to obtain eight subfractions (Fr.H-LO1～Fr.H-LO8). FrH-LO1 was purified by Sephadex LH-20 eluted with $CHCl_3$/MeOH (*V*∶*V*=3∶7), PTLC and semipreparative HPLC to yield compounds **3** (9.3 mg) and **4** (4.7 mg). Compound **5** (13.8 mg) was isolated from Fr.G-L2 by semipreparative HPLC. Compounds **6** (3.1 mg) and **7** (16.1 mg) were purified from FrH-LO2 by pHPLC, Sephadex LH-20, or semipreparative HPLC [*V*(H_2O)∶*V*(CH_3CN)=75∶25, flow rate 2.5 mL•min^{-1}]. Fr.H-LO3 was subjected to Sephadex LH-20 eluted with $CHCl_3$/MeOH (*V*∶*V*=3∶7) then further purified by PTLC [*V*(petroleum ether)∶*V*(ethyl acetate)=30∶70] and semipreparative HPLC [*V*(H_2O)∶*V*(CH_3CN)=85∶15, flow rate 2.5 mL•min^{-1}] to give compound **8** (11.3 mg).

Malfilamentoside A (**1**): White crystal, m.p. 184～187 ℃ (Ref.[6] 188 ℃); $[\alpha]_D^{25}$ +162 (*c* 0.1, MeOH); UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 257 (3.80), 207 (4.23) nm; ECD (*c* 2.4×10^{-4} mol/L, MeOH) λ_{max} ($\Delta\varepsilon$): 8.58 (241) nm; ^{1}H NMR (700 MHz, DMSO-d_6) and ^{13}C NMR (175 MHz, DMSO-d_6) data see Tables 1; IR (film) ν_{max}: 3308, 2928, 1771, 1645, 1539, 1317, 1126, 1099, 1049 cm^{-1}; HRESIMS calcd for $C_{26}H_{30}NO_8$ $[M+H]^+$ 484.1966, found 484.1973.

Malfilamentoside D (**2**): White amorphous powder, $[\alpha]_D^{25}$ +158.6 (*c* 0.1, MeOH); UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 257 (3.86), 208 (4.27) nm; ECD (*c* 2.4×10^{-4} mol/L, MeOH) λ_{max} ($\Delta\varepsilon$): 9.23 (242) nm; ^{1}H NMR (700 MHz, DMSO-d_6) and ^{13}C NMR (175 MHz, DMSO-d_6) data see Tables 1; IR (film) ν_{max}: 3365, 3294, 1775, 1647, 1533 1315, 1103, 1043, 985 cm^{-1}; HRESIMS calcd for $C_{25}H_{28}NO_8$ $[M+H]^+$ 470.1809, found 470.1810.

4.3 Biological assays

4.3.1 Xanthine oxidase inhibitory activity

Xanthine oxidase inhibiting reaction assay contained 17.2 μL of 0.01 U/mL xanthine oxidase (Sigma-Aldrich (Shanghai) Trading CO., Ltd.) and samples of **1**～**2**, **5**, **7**～**8** at different concentration were carried out in PBS buffer (100 mmol/L, pH 7.5) with a total volume of 100 μL. After mixing, 34.3 μL of 0.15 mmol/L xanthine solution (Sigma-Aldrich (Shanghai) Trading CO., Ltd.) was added, and the enzyme activity was determined at 295 nm for 10 min at 25 ℃. Spectrophotometric determination was made in an Ultrospec 2100 sepctrometer (Enspire, PerkinElmer, Singapore). The inhibition rate of each sample was calculated according to following formula: inhibition rate (%)=[(A_{blank}−$A_{compound}$)/A_{blank}]×100%.

4.3.2 Antibacterial assay

The antibacterial assay was performed using the filter paper disk method against ten indicator strains: *Staphylococcus aureus* ATCC 29213, methicillin-resistant *Staphylococcus aureus*, *Micrococcus luteus* SCSIO ML01, *Bacillus subtilis* 1064, *Klebsiella pneumoniae* ATCC 13883,

Vibrio alginolyticus 13214, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *Acinetobacter baumannii* ATCC 19606. Vancomycin and Trimethoprim were used as the positive controls, and dimethyl sulfoxide (DMSO) was used as the negative control.

Supporting Information NMR and MS data for compounds **1**～**8**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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