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Phaeochromycins I–K, Three Methylene-Bridged Dimeric Polyketides from *Streptomyces* sp. 166#

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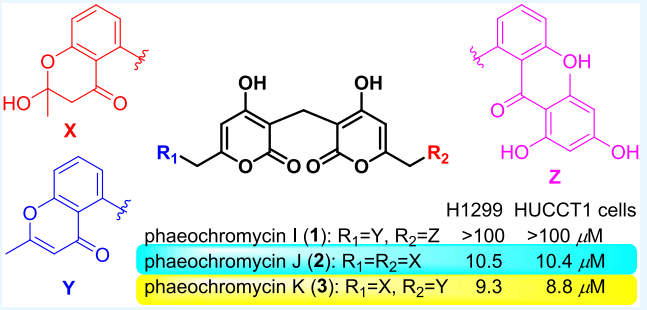
ABSTRACT: Three new dimeric polyketides, i.e., phaeochromycins I–K (**1**–**3**, respectively) and a known polyketide phaeochromycin F (**4**), were isolated from the culture broth of a saline Qinghai–Tibet Plateau permafrost soil-derived *Streptomyces* sp. 166#. The structures were determined by analyzing one-dimensional and two-dimensional NMR as well as HRESIMS data. Compounds **2** and **3** exhibited a selective antiproliferative activity against H1299 and HUCCT1 cell lines, exhibiting IC_{50} values ranging from 8.83 to 10.52 μM.



1. INTRODUCTION

Polyketides are recognized as a rich source of pharmaceutical and agrochemical lead compounds.[1] New and bioactive polyketide analogues are continuously isolated and identified, such as doxorubicin,[2] rapamycin,[3] lovastatin,[4] flavonoids,[5] pafuranones A and B,[6] and cladodionen.[7] The genus *Streptomyces* was determined to be one of the best producers of polyketides owing to its well-studied biosynthesis pathway.[8]

Phaeochromycins are type II polyketide derivatives, mainly produced by *Streptomyces* sp. However, only eight compounds named as phaeochromycins, namely phaeochromycins A–E[9] and F–H,[10] have been reported. Among these compounds, phaeochromycins A and C are weak inhibitors of MAPKAP kinase-2, and phaeochromycin H exhibits a modest inhibitory rate (46.0%) against the HeLa cell line at a concentration of 10 μg/mL. Our previous study reported four type II polyketide analogues from *Streptomyces* sp. 166#.[11] Further isolation led to the identification of three new phaeochromycins: I–K (**1**–**3**, respectively) and the previously reported phaeochromycin F (**4**) (Figure 1),[10] from the fermentation broth of the *Streptomyces* sp. 166#. Herein, we report the isolation, structure elucidation, cytotoxic activity, and plausible biosynthetic pathway of the new phaeochromycins I–K (**1**–**3**, respectively).

2. RESULTS AND DISCUSSION

Phaeochromycin I (**1**) was obtained as a colorless powder. Its molecular formula was determined as $C_{37}H_{28}O_{12}$ based on the HRESIMS peak observed at m/z 665.1660 $[M + H]^+$ (calcd. 665.1654), indicating 24 degrees of unsaturation. The ^1H and ^{13}C NMR and HSQC spectra suggested the presence of four carbonyls, seventeen nonprotonated olefinic carbons, eleven olefinic methines, three sp^3 methylenes, and two methyl groups (Table 1). The ^{13}C NMR data search in the MICRONMR database (www.nmrdata.com) revealed that compound **1** contains a SEK34b moiety[12] and a SEK43 moiety,[13] which could be verified by the key $^1H–^1H$ COSY and HMBC correlations (Figure 2). Furthermore, ^{13}C NMR comparison revealed that two nonprotonated carbons ($\delta_{C\text{-}2}$ 99.8 and $\delta_{C\text{-}2'}$ 100.1) substituted the corresponding olefinic methines of SEK34b ($\delta_{C/H}$ 88.0/5.14)[12] and SEK43 ($\delta_{C/H}$ 88.6/5.14).[13] Moreover, the obvious shifts for C-1, C-3, C-4, and C-5 in SEK34b and SEK43, as well as an additional methylene ($-CH_2-$) signal ($\delta_{C/H}$ 18.3/3.18), were observed. These data indicated that SEK34b and SEK43 combined by a $-CH_2-$ linker at the two 2-positions to form compound **1**, which was confirmed by the key HMBC correlations of the methylene protons ($\delta_{H\text{-}15}$ 3.18) to C-1/1′ (δ_C 165.7, 165.7) and C-2/2′ (δ_C 99.8, 100.1) (Figure 2). Consequently, phaeochromycin I (**1**) could be identified as 5-((3-((6-(2-(2,4-dihydroxy-6-methylbenzoyl)-3-hydroxybenzyl)-4-hydroxy-2-oxo-2*H*-pyran-3-yl)methyl)-4-hydroxy-2-oxo-2*H*-pyran-6-yl)methyl)-2-methyl-4*H*-chromen-4-one.

The molecular formula of compound **2** was established as $C_{33}H_{28}O_{12}$ based on the HRESIMS peak observed at m/z 617.1654 $[M + H]^+$ (calcd. 617.1654), indicating an index of hydrogen deficiency (IHD) of 20. However, the ^1H and ^{13}C NMR spectra showed only half the number of expected signals along with an additional methylene signal ($\delta_{C/H}$ 18.2/3.21), implying that compound **2** was a symmetrical dimer. Similar to

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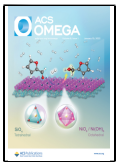

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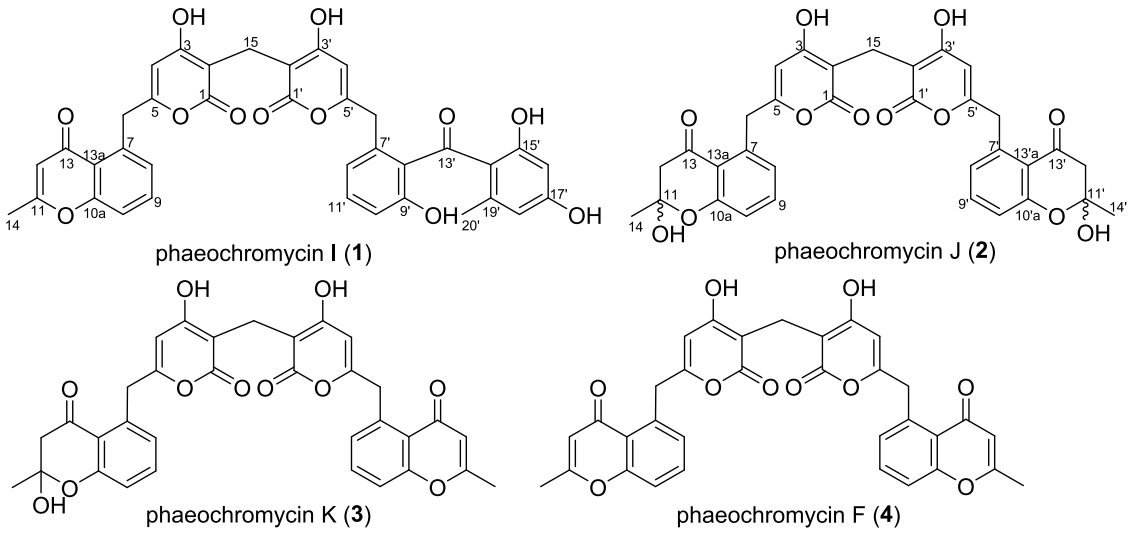

Figure 1. Structures of compounds **1**−**4**.

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR Data of Compounds 1−3

	1 (in DMSO-d_6)		**2** (in DMSO-d_6)		**3** (in CD_3OD)	
no.	δ_c, type	δ_H (J in Hz)	δ_c, type	δ_H (J in Hz)	δ_c, type	δ_H (J in Hz)
1	165.7, C		178.5, C		169.8, C	
2	99.8, C		99.8, C		102.4, C	
3	165.5, C		165.6, C		162.7, C	
4	103.8[a], CH	5.29, s	111.2, CH	6.14[a], s	105.0, CH	5.60, s
5	161.2, C		160.9, C		164.6, C	
6	37.5, CH_2	4.36, s	37.1, CH_2	4.02, d (15.8)	38.7, CH_2	4.19, brs
				4.15, d (15.8)		
7	136.8, C		137.1, C		137.7, C	
8	128.3, CH	7.23, d (7.4)	124.2, CH	6.83, d (7.4)	126.0, CH	6.89, d (7.3)
9	133.3, CH	7.69, t (7.9)	134.9, CH	7.47, t (7.8)	136.3, CH	7.46, t (7.9)
10	117.8, CH	7.52, d (8.5)	117.7, CH	6.92, d (8.2)	119.5, CH	6.95, d (8.2)
10a	157.5, C		159.7, C		161.6, C	
11	165.4, C		100.8, C		101.8, C	
12	111.2, C	6.14, s	49.7, CH_2	2.62, d (15.9)	63.9, CH_2	2.66, s
				3.05, d (15.9)		2.95, s
13	178.5, C		193.2, C		195.2, C	
13a	120.9, C		118.5, C		119.8, C	
14	19.6, CH_3	2.34, s	27.6, CH_3	1.58, s	20.1, CH_3	1.65, s
15	18.3, CH_2	3.18, s	18.2, CH_2	3.21, s	18.6, CH_2	3.42, s
1′	165.7, C		178.5, C		169.8, C	
2′	100.1, C		99.8, C		102.4, C	
3′	165.4, C		165.6, C		163.0, C	
4′	105.2[a], CH	5.51, s	111.2, CH	6.14[a], s	105.0, CH	5.65, s
5′	159.3, C		160.9, C		164.4, C	
6′	36.0, CH_2	3.42, brs	37.1, CH_2	4.02, d (15.8)	38.7, CH_2	4.45, s
				4.15, d (15.8)		
7′	133.5, C		137.1, C		137.3, C	
8′	130.8, C		124.2, CH	6.83, d (7.4)	130.0, CH	7.29, d (7.3)
9′	153.7, C		134.9, CH	7.47, t (7.8)	134.7, CH	7.69, brs
10′	114.3, CH	6.76, d (8.2)	117.7, CH	6.92, d (8.2)	119.3, CH	7.51, d (8.1)
10′a			159.7, C		159.4, C	
11′	130.0, CH	7.18, t (7.9)	100.8, C		168.0, C	
12′	120.4, CH	6.68, d (7.7)	49.7, CH_2	2.62, d (15.9)	111.9, CH	6.13, s
				3.05, d (15.9)		
13′	200.2, C		193.2, C		181.4, C	
13′a			118.5, C		122.0, C	
14′	115.5, C		27.6, CH_3	1.58, s	28.0, CH_3	2.38, s
15′	165.4, C					
16′	100.8, CH	6.14, s				
17′	163.4, C					
18′	111.8, CH	6.11, s				
19′	143.2, C					
20′	21.7, CH_3	1.83, s				
11/11′-OH				6.99, s		
15′-OH		12.82, s				

[a]Confirmed by HSQC and HMBC spectra.

compound **1**, the ^{1}H and ^{13}C NMR data of compound **2** were almost the same as those for SEK34,[12] apart from the substitution of a nonprotonated olefinic carbon ($\delta_{C\text{-}2}$ 99.8) for sp^2-methine ($\delta_{C/H}$ 88.2/5.18)[12] and the noticeable changes of chemical shifts for C-1, C-3, C-4, and C-5 (Table 1). Furthermore, the key HMBC correlations of the methylene proton ($\delta_{H\text{-}15}$ 3.21) to C-2/2′ (δ_C 99.8) and C-3/3′ (δ_C 165.6) were observed (Figure 2), suggesting that the two SEK34 units

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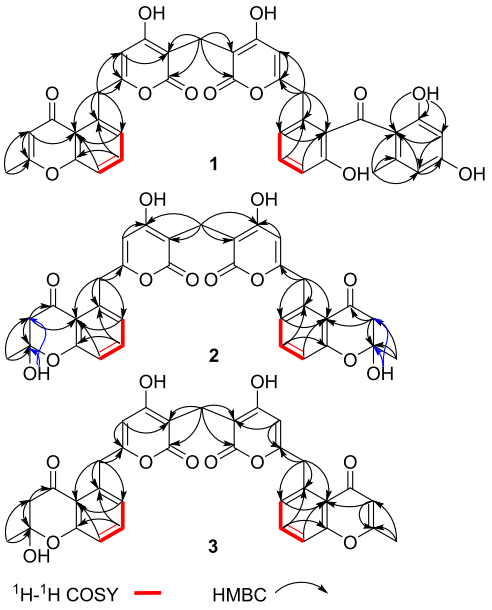

Figure 2. Key COSY and HMBC correlations of compounds **1**−**3**.

were connected at C-2 and C-2′ by a methylene (−CH_2−) linkage to form compound **2**. Thus, phaeochromycin J (**2**) could be elucidated as 5,5′-((methylenebis(4-hydroxy-2-oxo-2*H*-pyran-3,6-diyl))bis(methylene))bis(2-hydroxy-2-methylchroman-4-one).

The molecular formula of phaeochromycin K (**3**) was determined as $C_{33}H_{26}O_{11}$ based on the HRESIMS peak observed at *m*/*z* 599.1544 $[M + H]^+$ (calcd. 599.1548), indicating an IHD of 21. The comparison of ^{1}H and ^{13}C NMR data (Table 1) and two-dimensional NMR patterns (Figure 2) of compound **3** with compounds **1** and **2** revealed that compound **3** contains SEK34 and SEK34b fragments. The presence of the methylene (CH_2-15) between C-2 and C-2′ was confirmed via the key HMBC correlations of the methylene proton ($\delta_{H\text{-}15}$ 3.42) to C-1/1′ (δ_C 169.8) and C-2/2′ (δ_C 102.4) (Figure 2). Thus, phaeochromycin K (**3**) could be determined as 5-((4-hydroxy-3-((4-hydroxy-6-((2-hydroxy-2-methyl-4-oxochroman-5-yl)methyl)-2-oxo-2*H*-pyran-3-yl)methyl)-2-oxo-2*H*-pyran-6-yl)methyl)-2-methyl-4*H*-chromen-4-one.

Compound **2** comprised three stereoisomers (*R*,*S*; *S*,*R*; *R*,*R* or *S*,*S*) and was a symmetric homodimer with two chiral centers. However, compound **3** was an unsymmetric heterodimer **1** with one chiral center. Both compounds **2** and **3** did not show optical rotation. Therefore, compounds **2** and **3** were subjected to chiral separation using an NB chiral column. Each isomer (**2a**/**2b**/**2c** and **3a**/**3b**) was purified by collecting the corresponding peak and was then subjected to a purity check independently at the same conditions (Figure 3). The results indicate that compounds **2** and **3** were inseparable stereoisomers, and compound **2** could slowly dehydrate to form compound **3**. Meanwhile, the three stereoisomers **2a**, **2b**, and **2c** of **2** could spontaneously be converted to each other (Figure 3A), and so could the two stereoisomers **3a** and **3b** of **3** (Figure 3B). SEK34 and SEK43 were reported as the products of the polyketide synthase pathway.[12−14] The methylene linkages in heterodimer **1** and homodimer **2** were caused by formaldehyde and were presumed to form via the Michael addition between SEK43 and SEK34b or two SEK34, respectively.[15,16] High-performance liquid chromatography (HPLC) analysis (Figure 3) confirmed that compound **2** was subjected to intramolecular dehydration to generate compounds **3** and **4** spontaneously via the loss of one and two H_2O molecules (Scheme 1). Thus, the physico, spectral, and

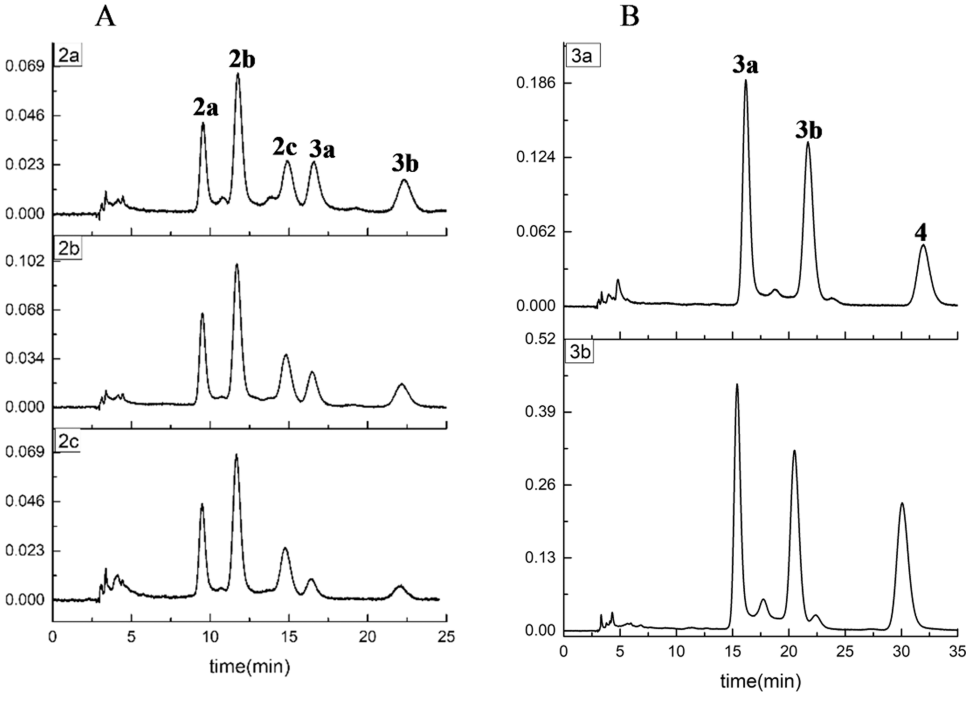

Figure 3. Chiral analysis of compounds **2** and **3** using an NB chiral column eluted with *n*-C_6H_{14}−EtOH (65/35 for **2** and 60/40 for **3**, v/v) at 1 mL/min. (A) Three isomers of compound **2** (**2a**/**2b**/**2c**) could be converted into each other spontaneously, and all of them can slowly dehydrate to form **3**. (B) Two isomers of **3** (**3a**/**3b**) could be converted into each other spontaneously, and both can slowly dehydrate to form **4**.

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Scheme 1. Plausible Biosynthetic Pathway of 1−4

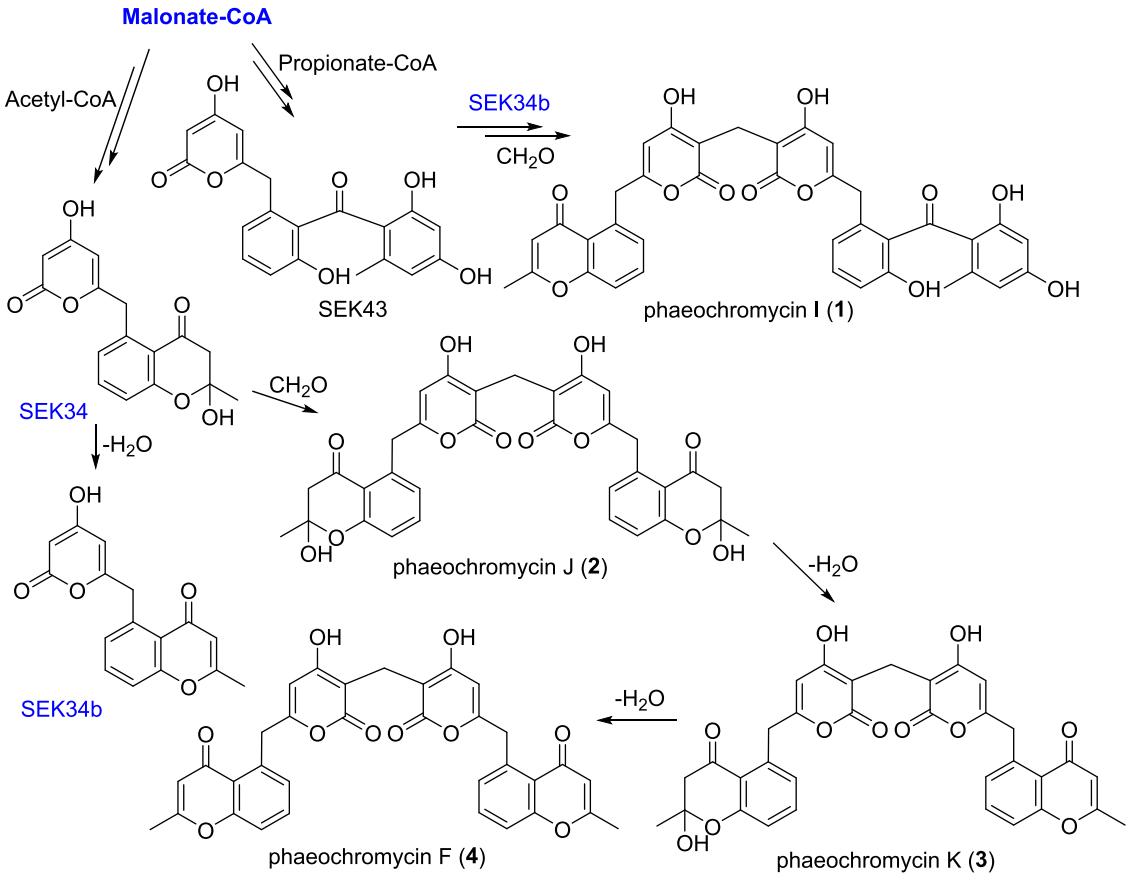

Table 2. Cytotoxic Activities of Compounds 1−4

	IC_{50} (μM)							
compounds	A549	N87	H1299	HUCCT1	143B	B16F10	SPC-A1	HCT-116
1	>100	>100	>100	>100	>100	>100	>100	>100
2	>100	>100	10.52	10.41	>100	>100	>100	>100
3	>100	>100	9.33	8.83	>100	>100	>100	>100
4[a]	>100							>100
DOX	0.109	0.047	0.504	0.048	0.101	0.016	0.181	0.104

[a]IC_{50} values for **4** and DOX against MCF-7 cells were >100 and 0.45 μM, respectively.

cytotoxic data of compounds **2** and **3** were acquired as soon as possible after they were purified.

The cytotoxic activities of new dimers **1**−**3** were evaluated against the tumor cells A549, N87, H1299, HUCCT1, 143B, B16F10, SPC-A1, and HCT-116 via the CTG assay.[17,18] The cytotoxic activity of the known dimer **4** was evaluated against MCF-7, A549, and HCT-116 tumor cell lines via the MTT assay[17] using doxorubicin (DOX) as the positive control. Only compounds **2** and **3** showed cell proliferation inhibition against H1299 (human lung adenocarcinoma) and HUCCT1 (human bile duct cancer) cell lines with the IC_{50} values of 10.52 and 10.41 μM for **2** and 9.33 and 8.83 μM for **3**, respectively (Table 2 and Figure S1). No inhibitory activity was observed for other compounds and tumor cell lines (IC_{50} > 100 μM).

3. CONCLUSIONS

In addition to the reported phaeochromycin F (**4**), we identified three new polyketide dimers within a methylene linkage, phaeochromycins I−K (**1**−**3**, respectively). According to the literature, phaeochromycin F (**4**) was the sole phaeochromycin possessing the SEK34b dimer joined by a methylene linkage.[10] Phaeochromycins J (**2**) and K (**3**) with one or two hemiacetal groups exhibited selective antiproliferative activities against H1299 and HUCT1 cell lines, indicating that SEK34b with a hemiacetal group at C-11 was the pharmacophore or bioactive function unit against these two tumor cells.

4. EXPERIMENTAL SECTION

4.1. General Experimental Procedures. Ultraviolet (UV) data were obtained using a Waters 2487 dual λ absorbance detector. Infrared (IR) spectra were measured on a Nicolet Nexus 470 spectrophotometer using KBr disks. NMR spectra were recorded using a Varian System 500. The corresponding residual solvent signals ($\delta_{H/C}$ 2.50/39.5 for DMSO-d_6, 7.26/77.2 for $CDCl_3$, or 3.31/49.2 for CD_3OD) were used to reference the chemical shifts in NMR spectra. Furthermore, HRESIMS spectra were measured using a Q-

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TOF Ultima Global GAA076 LC mass spectrometer, and LRESIMS spectra were obtained using a Waters SQ Detector 2 mass spectrometer. Semipreparative HPLC was performed using a phenyl column (YMC-pack Ph, 10 mm × 250 mm) or a π-NAP column (COSMOSIL, 10 mm × 250 mm). TLC was performed on plates precoated with silica gel GF254 (10−40 μm). Column chromatography (CC) was performed over silica gel (200−300 mesh, Qingdao Marine Chemical Factory) and Sephadex LH-20 (Amersham Biosciences). Finally, vacuum liquid chromatography (VLC) was performed using silica gel H (Qingdao Marine Chemical Factory).

4.2. Fermentation and Extraction. The fermentation and extraction of *Streptomyces* sp. 166# were described in detail in our previous report.[11]

4.3. Purification. The ethyl acetate (EtOAc) extract (5.0 g) of the fermentation broth was separated into 12 fractions (Fr.1−Fr.12) via VLC using a silica gel column. The column was eluted with a step gradient of petroleum ether (PE)−CH_2Cl_2 (1:0, 1:1, and 0:1, v/v) and then of CH_2Cl_2−MeOH (100:1, 80:1, 70:1, 60:1, 40:1, 20:1, 15:1, 10:1, and 1:1, v/v). Fr.10 (407 mg) was separated into 13 subfractions (Fr.10.1−Fr.10.13) via CC using Sephadex LH-20. The column was eluted with MeOH−CH_2Cl_2 (1:1, v/v). Fr.10.13 (20 mg) was further purified via HPLC using the semipreparative π-NAP column. This column was eluted with 30% MeCN−H_2O containing 0.05% trifluoroacetic acid (TFA) at a flow rate of 4 mL/min to obtain compounds **1** (2.8 mg; t_R = 12.1 min) and **2** (3.2 mg; t_R = 15.2 min). Similarly, Fr.11 (151 mg) was separated into eight subfractions (Fr.11.1−Fr.11.8) via CC using Sephadex LH-20. The column was eluted with MeOH−CH_2Cl_2 (1:1, v/v). Fr.11.6 (18 mg) was purified via HPLC using a phenyl column. This column was eluted with 30% MeCN−H_2O (with 0.05% TFA) at a flow rate of 4 mL/min to obtain compound **3** (6.6 mg; t_R = 14.4 min). Using the same CC and elution with 45% MeCN−H_2O (with 0.05% TFA) at 4 mL/min, compound **4** (2.0 mg; t_R = 12.3 min) was obtained from Fr.11.8 (7 mg).

*4.3.1. Phaeochromycin I (**1**).* Colorless powder; UV (MeOH) λ_{max} (log ε): 221 (4.68), 300 (4.37) nm; IR (KBr) ν_{max}: 3424, 2927, 1685, 1644,1620, 1508, 1437, 1388, 1210, 1140, 1030, 841, 803, 724 cm^{-1}; ^1H and ^{13}C NMR data are presented in Table 1; HRESIMS *m/z* 665.1660 $[M + H]^+$ (calcd. for $C_{37}H_{29}O_{12}$, 665.1654).

*4.3.2. Phaeochromycin J (**2**).* Colorless powder; $[\alpha]_D^{25}$ 0 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 215 (4.68), 252 (4.20), 280 (4.09), 309 (4.11) nm; IR (KBr) ν_{max}: 3394, 2927, 1683, 1603,1577, 1473, 1439, 1385, 1320, 1209, 1140, 1028, 880, 841, 802, 724 cm^{-1}; ^1H and ^{13}C NMR data are presented in Table 1; HRESIMS *m/z* 617.1654 $[M + H]^+$ (calcd. for $C_{33}H_{29}O_{12}$, 617.1654).

*4.3.3. Phaeochromycin K (**3**).* Colorless powder; $[\alpha]_D^{25}$ 0 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 215 (4.14), 248 (3.77), 303 (3.77) nm; IR (KBr) ν_{max}: 3368, 2261, 2131, 1684, 1541, 1507, 1456, 1385, 1209, 1141, 1051, 1026, 1004, 829, 801, 768, 721 cm^{-1}; ^1H and ^{13}C NMR data are presented in Table 1; HRESIMS *m/z* 599.1544 $[M + H]^+$ (calcd. for $C_{33}H_{27}O_{11}$, 599.1548).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07038.

NMR and HRESIMS spectra for compounds **1**−**3**, physico and spectral data for compound **4**, and a description of the bioassay protocol used (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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