

New Spectinabilin and Hexadienamide Derivatives from *Streptomyces* sp. S012

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(Received December 24, 2019; Revised February 19, 2020; Accepted March 05, 2020)

Abstract: A new spectinabilin derivative (**1**) and a new hexadienamide derivative (**3**), together with (-)-spectinabilin (**2**) and sarmentosamide (**4**), were isolated from *Streptomyces* sp. S012. Their structures were elucidated on the basis of spectroscopic analysis, including ¹H, ¹³C NMR, ¹H-¹H COSY, HSQC, HMBC, NOESY and HRESIMS. Their antibacterial activity was also evaluated in this study.

Keywords: Spectinabilin; hexadienamide; *Streptomyces* sp. S012; spectral data. © 2020 ACG Publications. All rights reserved.

1. Introduction

Streptomyces sp. S012 was isolated from the rhizosphere soil of Nanjing Zhongshan Botanical Garden. Previously, a series of streptovaricins with diverse bioactivities were isolated from this strain [1, 2]. Herein, a new spectinabilin derivative (**1**) and a new hexadienamide (**3**) together with (-)-spectinabilin (**2**) and sarmentosamide (**4**) are reported including their isolation, structural elucidation and antimicrobial activities. Compounds **1** and **2** are unusual nitroaryl-substituted polyene polyketides, while **3** and **4** are rare hexadienamide derivatives [3, 4]. Prior to this study, only a few spectinabilin and hexadienamide analogues have been reported, such as spectinabilin [2, 5], aureothin [6, 7], SNF4435 C and D [8-10], arabilin [11], sarmentosamide [3], erythrococcamides A-E [12] and *N*-isobutyl-6-(2-thienyl)-2*E*,4*E*-hexadienamide [13].

2. Materials and Methods

2.1. General Experimental Procedure

Optical rotation was measured on a Perkin-Elmer 341 polarimeter (Anton Paar GmbH, Graz, Austria). UV spectra were recorded on a UV-1800 UV spectrophotometer (Shimadzu, Kyoto, Japan).

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NMR spectra were recorded on a Bruker DRX-600 MHz and DRX-400 MHz NMR spectrometer (Bruker Daltonics Inc., Billerica, Massachusetts) with tetramethylsilane (TMS) as an internal standard. HRESIMS was measured on an LTQ-Orbitrap XL. *Sephadex* LH-20 was obtained from the GE Amersham Biosciences (Piscataway, New Jersey). Reversed-phase C-18 (RP-18) silica gel for column chromatography (CC) was obtained from Merck (Darmstadt, Germany). HPLC separations were mainly performed on Waters 1525 Binary HPLC Pump equipped with Waters 996 Photodiode Array Detector using Agilent Eclipse XDB-C18 column (5 μm , 9.4 * 250 mm). Silica gel GF₂₅₄ for thin-layer chromatography (TLC) was purchased from Qingdao Marine Chemical Ltd (Qingdao, China).

2.2. Fermentation and Isolation

The *Streptomyces* sp. S012 strain was cultured for 12 d on ISP3 agar plates (40 L) at 28 °C. At the end of fermentation, the agar cultures were diced and extracted three times with EtOAc-MeOH (4:1, v/v) at room temperature. The organic solvents were evaporated and the extract was partitioned between ddH₂O and EtOAc (1:1, v/v). The EtOAc extract was further partitioned between 95% aqueous MeOH and petroleum ether (PE) to afford MeOH extract (9.0 g). The MeOH extract was subjected to CC over *Sephadex* LH-20 eluted with MeOH to obtain *Fr.1* and *Fr.2* (8.0 g). *Fr.2* was further fractionated by MPLC (145 g RP-18 silica gel; 30%, 50%, 70% MeOH and 100% MeOH, 1 L each, respectively) to afford *Fr.2a-2d*. *Fr.2a* was chromatographed over *Sephadex* LH-20 (120 g; MeOH) to afford *Fr. 2a1-2a4*. *Fr.2a4* was subjected to reversed-phase HPLC (Waters 1525 instrument; Agilent Eclipse XDB-C18 column ID: 5 μm , 9.4 * 250 mm) eluted with 20% CH₃CN (4 mL/min, UV 254 nm) to obtain **4** (*t_R* 13.0 min, 8.0 mg).

Fr.2c was fractionated by CC over *Sephadex* LH-20 and MPLC over RP-18 silica gel to afford *Fr.2c1-Fr.2c7*. *Fr.2c2* was further purified by HPLC (Waters 1525 instrument; column ID: 9.4 * 250 mm, 5 μm) eluted with 55% and 70% CH₃CN (4.0 mL/min, UV 254 nm) to obtain **3** (*t_R* 22 min, 7.2 mg) and **1** (*t_R* 10.6 min, 5.2 mg, UV 254 nm), respectively. By the similar procedure, **2** (*t_R* 19.5 min, 5.4 mg, UV 254 nm) was purified from *Fr.2d* by HPLC eluted with 60% CH₃CN.

Compound **1**: Pale yellow oil; $[\alpha]_D^{25}$ -239.50 (*c* 0.1, MeOH); ¹H and ¹³C NMR data see Table 1 and Table S1. UV/Vis (log ϵ): λ_{max} 212 (4.10), 267 (3.92), 296 (3.61) nm; HRESIMS (*m/z*): 955.4301 [2M + H]⁺ (Calcd. for C₅₆H₆₃N₂O₁₂⁺, 955.4376).

(-)-Spectinabilin (**2**): Pale yellow oil; $[\alpha]_D^{25}$ -40 (*c* 0.1, CHCl₃); ¹H and ¹³C NMR data see Table 1 and Table S2. UV/Vis (log ϵ): λ_{max} 258 (3.36) nm; HRESIMS (*m/z*): 478.2168 [M + H]⁺ (Calcd. for C₂₈H₃₂NO₆⁺, 478.2222).

Compound **3**: Pale yellow oil; $[\alpha]_D^{25}$ -66.7 (*c* 0.1, MeOH); ¹H and ¹³C NMR data see Table 2 and Table S3. UV/Vis (log ϵ): λ_{max} 216 (3.44), 259 (3.50), 296 (2.91) nm; HRESIMS (*m/z*): 238.0702 [M + H]⁺ (Calcd. for C₁₃H₂₀NO₃⁺, 238.1438).

Sarmentosamide (**4**): Pale yellow oil; $[\alpha]_D^{25}$ -174.5 (*c* 0.2, MeOH); ¹H and ¹³C NMR data see Table 2 and Table S4. UV/Vis (log ϵ): λ_{max} 211 (4.36), 224 (4.39), 264 (3.93) nm; ESIMS (*m/z*): 223.4 [M + H]⁺ and 245.5 [M + Na]⁺.

2.3. Biological Assays

The antimicrobial activities of compounds **1-4** were tested with the paper disc diffusion assay against four plant pathogenic fungi (*Magnaporthe oryzae*, *Phomopsis asparagi*, *Colletotrichum truncatum*, *Colletotrichum gloeosporioides*), three Gram-positive bacteria (*Mycobacterium smegmatis* mc² 155, *Bacillus subtilis* PCI219 and *Staphylococcus aureus* ATCC 25923), and three Gram-negative bacteria (*Proteus bacillus vulgaris* CICC 160013, *Escherichia coli* CICC 10003 and *Salmonella enterica* serovar Typhimurium UK-1 χ 8956). Amphotericin B and ampicillin were used as positive controls for fungi and bacteria, respectively. The diameters of the inhibition zones were measured to describe the activity after 24 h of incubation at 37 °C.

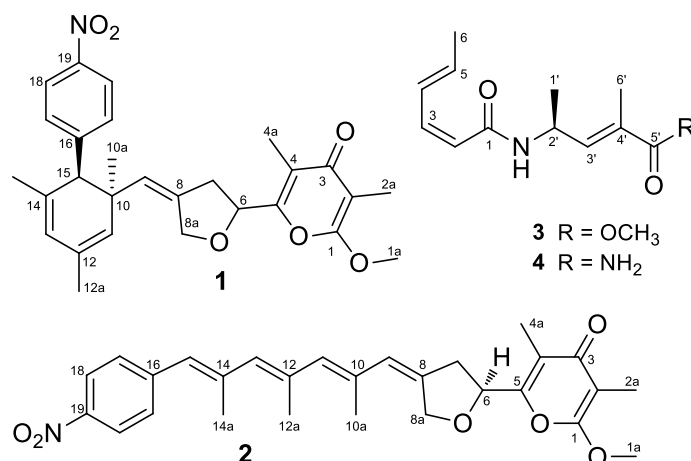


Figure 1. The chemical structures for compounds **1–4**

3. Results and Discussion

3.1. Structure Elucidation

Compounds **1** and **2** were obtained as pale yellow oil. The molecular formulas of both **1** and **2** were determined to be C₂₈H₃₁NO₆ with 14 degrees of unsaturation on the basis of high-resolution ESIMS (m/z 955.4301 [2M + H]⁺ and 478.2168 [M + H]⁺, respectively). The ¹H, ¹³C and HSQC NMR data of both **1** and **2** (Table 1, Tables S1 and S2) revealed 28 carbon signals for five methyls, a methoxyl group, two methylenes, nine methines and eleven quaternary carbons (including a carbonyl group). The NMR data of **2** were almost identical to those of spectinabilin (Table S5) [5, 11, 14]. Further analyzing the ¹H-¹H COSY and HMBC correlations (Table S2) confirmed the structure of **2** to be Spectinabilin (Figure S17). Spectinabilin was initially discovered by Rinehart group in 1976 [5] with [α]_D +60 (*c* 5.0, CHCl₃) and later by Imoto group in 2010 [11] with [α]_D²⁶ +60.6 (*c* 5.0, CHCl₃), while our current work reported the isolation of spectinabilin with similar spectroscopic data, but different optical rotation at [α]_D²⁵ -40 (*c* 0.1, CHCl₃), suggesting **2** to be (-)-spectinabilin.

The HMBC and ¹H-¹H COSY correlations proved that compound **1** also has a 2-methoxy-3,5-dimethyl- γ -pyrone moiety (C(1) to C(5)), a 1,3-disubstituted furan ring (C(6)-C(8a)) and a *p*-nitrophenyl group (C(16) to C(21)), similar to that of spectinabilin (Figure 1). The presence of a 1,3,5-trimethylcyclohexa-2,4-diene moiety (C(10)-C(15)) was determined on basis of the HMBC correlations from H-C(10a) to C(10), C(11) and C(15), from H-C(12a) to C(11), C(12) and C(13), and from H-C(14a) to C(13), C(14) and C(15). Finally, the linkage of the above four fragments were confirmed by the key HMBC correlations from H-C(6) and H-C(7) to C(5), H-C(9) to C(7), C(8a), C(10) and C(11), and from H-C(15) to C(10), C(16), C(17) and C(21), respectively (Figure 2). Thus, the planar structure of **1** was elucidated to be 2-methoxy-3,5-dimethyl-6-(4-(2,4,6-trimethyl-4'-nitro-1,2-dihydro-[1,1'-biphenyl]-2-yl)methylene)tetrahydrofuran-2-yl)-4*H*-pyran-4-one. The relative stereo-configurations of C-10 and C-15 were determined on the basis of the NOE correlation between H-C(10a) and H-C(15) (Figure 2).

Biosynthetic studies have revealed that these nitroaryl-substituted polyene metabolites are assembled from nitrobenzoate, malonate, and methylmalonate by modular polyketide synthases followed by tailoring reactions [5, 7, 15, 16]. Compound **1**, as a biogenesis analogue, should have the same biosynthetic origin. The formation of the carbon-carbon bond between C(10) and C(15) may arise from the mechanism of carbon cation rearrangement similar to the cyclization catalyzed by terpene synthases (Figure 3).

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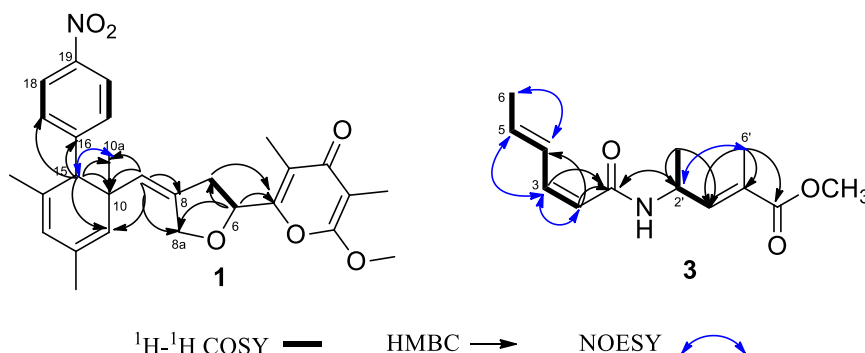


Figure 2. The key ^1H - ^1H COSY, NOESY and HMBC correlations for compounds **1** and **3**

Table 1. ^1H (600 MHz) and ^{13}C (150 MHz) NMR data of **1** (CD_3OD) and **2** ($\text{C}_5\text{D}_5\text{N}$)

No.	1		2	
	δ_{H} (mult., J in Hz)	δ_{C}	δ_{H} (mult., J in Hz)	δ_{C}
1	/	164.5 (C)	/	162.1 (C)
1a	3.94 (s)	56.5 (CH_3)	3.85 (s)	55.3 (CH_3)
2	/	100.6 (C)	/	99.3 (C)
2a	1.75 (s)	7.0 (CH_3)	2.01 (s)	7.3 (CH_3)
3	/	182.8 (C)	/	180.0 (C)
4	/	121.0 (C)	/	120.3 (C)
4a	1.81 (s)	9.3 (CH_3)	2.18 (s)	9.5 (CH_3)
5	/	157.0 (C)	/	155.8 (C)
6	4.41 (t, $J = 7.3$ Hz)	74.4 (CH)	5.28 (dd, $J = 6.1, 7.3$ Hz)	73.5 (CH)
7a	2.49 (dd, $J = 6.6, 15.0$ Hz)	38.2 (CH_2)	3.01 (dd, $J = 6.1, 14.7$ Hz)	38.2 (CH_2)
7b	2.71 (dd, $J = 7.9, 15.0$ Hz)		3.09 (dd, $J = 7.4, 14.7$ Hz)	
8	/	138.1 (C)	/	139.7 (C)
8a	3.54 (d, $J = 13.1$ Hz)	69.5 (CH_2)	5.04 (m)	70.8 (CH)
	4.36 (d, $J = 13.1$ Hz)		4.87 (d, $J = 14.0$ Hz)	
9	5.31 (s)	129.8 (CH)	6.22 (s)	126.9 (CH)
10	/	45.2 (C)	/	134.9 (C)
10a	1.24 (s)	29.0 (CH_3)	2.10 (s)	18.4 (CH_3)
11	5.25 (s)	126.8 (CH)	6.06 (s)	136.0 (CH)
12	/	131.9 (C)	/	135.5 (C)
12a	1.82 (s)	21.6 (CH_3)	2.08 (s)	17.8 (CH_3)
13	5.87 (s)	124.7 (CH)	6.19 (s)	135.5 (CH)
14	/	137.1 (C)	/	139.9 (C)
14a	1.66 (s)	22.8 (CH_3)	2.10 (s)	19.7 (CH_3)
15	3.19 (s)	57.4 (CH)	6.62 (s)	128.6 (CH)
16	/	149.5 (C)	/	145.0 (C)
17	7.39 (d, $J = 8.5$ Hz)	131.9 (CH)	7.51 (d, $J = 8.8$ Hz)	129.9 (CH)
18	8.07 (d, $J = 8.5$ Hz)	123.5 (CH)	8.27 (d, $J = 8.8$ Hz)	123.7 (CH)
19	/	148.4 (C)	/	146.7 (C)
20	8.07 (d, $J = 8.5$ Hz)	123.5 (CH)	8.27 (d, $J = 8.8$ Hz)	123.7 (CH)
21	7.39 (d, $J = 8.5$ Hz)	131.9 (CH)	7.51 (d, $J = 8.8$ Hz)	129.9 (CH)

The molecular formula of **3** was determined to be $\text{C}_{13}\text{H}_{19}\text{NO}_3$ on the basis of the HRESIMS quasi molecular ion peak at m/z 238.0702 $[\text{M} + \text{H}]^+$ (Calcd. for $\text{C}_{13}\text{H}_{20}\text{NO}_3^+$, 238.1438). The ^1H , ^{13}C NMR and HMBC data of **3** revealed 13 signals for four methyls (one oxygenated), five olefinic methines, an aliphatic methine and three quaternary sp^2 carbons (Table 2). Two fragments including a pentadiene moiety from C(2) to C(6) and a three carbon moiety of C(1')-C(2')-C(3') were confirmed by the ^1H - ^1H COSY correlations. The HMBC correlations from H-C(2) and H-C(3) to C(1) indicated a 2,4-hexadienoyl moiety. The planar structure was confirmed by the key HMBC correlations (Figure 2 and

Table S3). The geometries of the C(2)/C(3) and C(4)/C(5) double bonds were determined to be *2Z* and *4E* on the basis of the *cis* ^1H - ^1H coupling constants of $J_{2,3} = 11.2$ Hz and the *trans* ^1H - ^1H coupling constant of $J_{4,5} = 15.0$ Hz, respectively, which was supported by the NOE correlations between H-C(2) and H-C(3), H-C(3) and H-C(5), and H-C(4) and H-C(6). Additionally, the NOE between H-C(2') and H-C(6') determined an *E*-configuration of the C(3')/C(4') double bond. Thus, compound **3** was elucidated to be methyl-4-((*2Z,4E*)-hexa-2,4-dienamido)-2-methylpent-2-enoate.

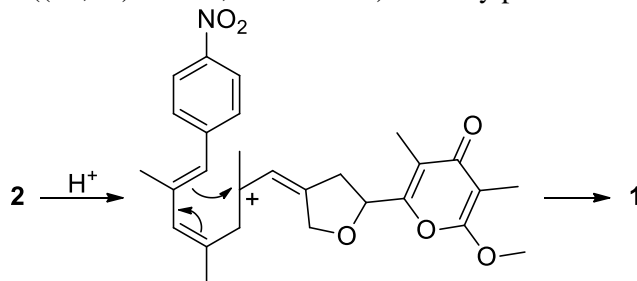


Figure 3. The proposed formation of **1**

The 1D NMR and HMQC data of **4** indicated the presence of three methyls, five olefinic methines, an aliphatic methine and three quaternary sp^2 carbons (Table 2), which were identical with those of sarmentosamide (Table S6) [3]. Detailed analysis of the ^1H - ^1H COSY and HMBC spectra data of **4** (Table S4) confirmed the structure of **4** as *N*-(4'-carbamoyl-3'*E*-penten-2'-yl)hexa-2*Z,4E*-dienamide, which was supported by the ESIMS quasi molecular ion peak at m/z 223.4 [$\text{M} + \text{H}$] $^+$.

Table 2. ^1H (400 MHz) and ^{13}C (100 MHz) NMR data of **3** ($\text{C}_5\text{D}_5\text{N}$) and **4** (CD_3OD)

No.	3		4	
	δ_{H} (mult., J in Hz)	δ_{C}	δ_{H} (mult., J in Hz)	δ_{C}
1	/	166.6 (C)	/	168.3 (C)
2	5.96 (d, $J = 11.2$ Hz)	120.1 (CH)	5.58 (d, $J = 11.4$ Hz)	119.3 (CH)
3	6.49 (dd, $J = 11.2, 12.8$ Hz)	141.7 (CH)	6.43 (t, $J = 11.4$ Hz)	142.7 (CH)
4	8.18 (dd, $J = 12.8, 15.0$ Hz)	130.2 (CH)	7.43 (dt, $J = 11.4, 14.8$ Hz)	129.9 (CH)
5	5.91 (dq, $J = 6.7, 15.2$ Hz)	137.8 (CH)	6.05 (dd, $J = 6.8, 14.8$ Hz)	139.1 (CH)
6	1.68 (d, $J = 6.7$ Hz)	18.8 (CH_3)	1.84 (dd, $J = 1.0, 6.8$ Hz)	18.8 (CH_3)
1'	1.31 (d, $J = 6.8$ Hz)	20.7 (CH_3)	1.26 (d, $J = 6.8$ Hz)	20.7 (CH_3)
2'	5.22 (m)	44.1 (CH)	4.81 (dq, $J = 6.8, 8.6$ Hz)	44.4 (CH)
3'	6.91 (d, $J = 9.1$ Hz)	144.4 (CH)	6.25 (dd, $J = 1.3, 8.6$ Hz)	139.2 (CH)
4'	/	128.5 (C)	/	132.4 (C)
5'	/	169.1 (C)	/	174.3 (C)
5'a	3.65 (s)	52.1 (CH_3)		
6'	2.10 (s)	13.3 (CH_3)	1.93 (d, $J = 1.2$ Hz)	13.3 (CH_3)

Diverse activities of spectinabilin derivatives have been reported such as immunosuppressant activity [8, 9], androgen antagonist activity [11], cytotoxic [17], nematocidal activity [14, 18] and antifungal activity [2]. In this study, compounds **1–4** showed no apparent inhibitory activities against all tested bacterial and fungal strains in agar diffusion assay at 50 $\mu\text{g}/\text{disc}$, while amphotericin B and ampicillin as positive controls clearly showed inhibitory zones against all the tested microorganisms.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81673317, 81530091, 81602979), the Open Funding Project of State Key Laboratory of Microbial Metabolite Funding (MMLKF17-09), and the Program for Changjiang Scholars and Innovative Research Team in University (IRT_17R68).

Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/records-of-natural-products>

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