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FOUR NEW PENICITRINOLS AND TWO NEW PENICILLENOLS FROM THE MARINE-DERIVED FUNGUS *PENICILLIUM CITRINUM*

Li Chen,[a,*] Tong Zhou,[a] Yang-Yang Zhao,[a] Mei-Wei Gong,[a] Qi-Wen Xia,[a] Min-Gang Ying,[b] Qiu-Hong Zheng,[b] Qin-Ying Liu,[b] and Qi-Qing Zhang[a,c,*]

[a]Institute of Biomedical and Pharmaceutical Technology, Fuzhou University, Fuzhou, 350002, P. R. China. [b]Fujian Provincial Key Laboratory of Tumor Biotherapy, Fujian Provincial Tumor Hospital, Fuzhou, 350014, P. R. China. [c]Institute of Biomedical Engineering, Chinese Academy of Medical Science, Peking Union Medical College, Tianjin, 300192, P. R. China. E-Mail: ibptcl@fzu.edu.cn; zhangqiq@126.com

Abstract – Six new compounds, penicitrinols L–O (**1**–**4**), penicillenols D_1 (**9**) and D_2 (**10**), together with six known compounds were isolated from the marine--derived fungus *Penicillium citrinum*. Their structures were elucidated on the basis of comprehensive spectral analysis and chemical methods. All the new compounds were evaluated for their cytotoxic effects on the A-549, HL-60 and SW-620 cell lines by the MTT method. Penicitrinols L (**1**) and M (**2**) showed weak cytotoxicities against SW-620 cell line, while penicillenols D_1 (**9**) and D_2 (**10**) showed weak cytotoxicities against A-549 and HL-60 cell lines, respectively.

Penicillium citrinum is a rich source of various anticancer compounds.[1] Our previous chemical investigation of *P. citrinum* resulted in the isolation of seven new citrinin derivatives, penicitrinols C–I,[1a,1f] two new tumonoic acids (K and L),[1g] and a new benzene derivative,[1g] which showed different degrees of cytotoxicities against the P388, HL-60 and A-375 cell lines. Our continuing search for bioactive compounds from this organism has further resulted in the isolation of another four new citrinin derivatives, namely, penicitrinols L–O (**1**–**4**), along with two new tetramic acid analogues, namely, penicillenols D_1 and D_2 (**9**, **10**). Additional, six known compounds, including penicitrinol J (**5**),[2] citrinin (**6**),[2] dihydrocitrinone (**7**),[1g] 2, 4-dihydroxy-3, 5, 6-trimethylbenzaldehyde (**8**),[3] penicillenol B_1 (**11**),[4] and penicillenol B_2 (**12**),[4] were purified together. In this paper, we report the isolation, structural elucidation and bioactivities of these metabolites.

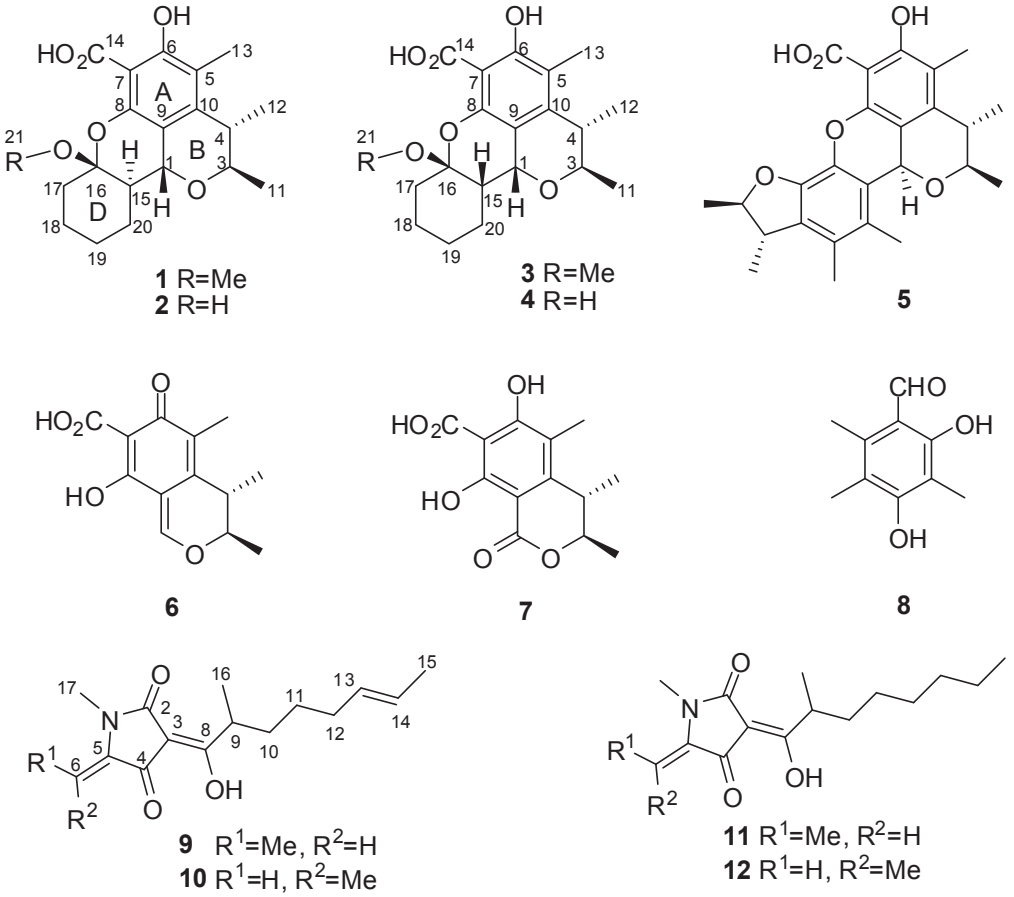

Figure 1. Structures of compounds **1**–**12**

Compound **1**, which is trivially named as penicitrinol L, was obtained as white powder and was analyzed have the molecular formula $C_{20}H_{26}O_6$ through negative high-resolution electrospray ionization mass spectroscopy (HRESIMS) (*m/z*: 361.1671 $[M - H]^-$, Calcd. for $C_{20}H_{25}O_6$: 361.1657). Its NMR data 1 and 2), combined with DEPT and HMQC spectrum analyses, revealed twenty carbon signals, including four methyls, four methylenes, four methines, and eight quaternary carbons. The planar structure of **1** was revealed through COSY and HMBC spectrum analyses (Figure 2). The COSY correlations of H-15 with H-1 and H-20, H-18 with H-17 and H-19, as well as H-19 with H-20 demonstrated the connections from H-1 to H-20 via H-15 and from H-17 to H-20 via H-18 and H-19. The COSY correlations of H-3 with H-11 and H-4 with H-12 demonstrated the connections from H-3 to H-11 and from H-4 to H-12. The HMBC correlations of OH-6 with C-5, C-6 and C-7, H-13 with C-5, C-6 and C-10, H-4 with C-5, C-9 and C-10, and H-1 with C-8 and C-9 confirmed the existence of ring A. The HMBC correlations of H-1 with C-9, H-3 with C-1, C-10 and C-12, H-4 with C-5, C-9 and C-10, H-11 with C-4, and H-12 with C-10 linked rings B to A. The HMBC correlations from H-15, H-17, H-20 and H-21 to C-16 connected C-15, C-17 and OCH_3-21 to C-16, which formed ring D. Considering the HMBC correlations from H-1 to C-8

and C-9, the COSY correlations of H-1 with H-15, as well as the low-field chemical shifts of C-8 (δ_C 147.0) and C-16 (δ_C 105.2), the three rings were finally connected via an oxygen atom between C-8 and C-16 and a carbon chain between C-1 and C-15. Furthermore, in view of the molecular formula of $C_{20}H_{26}O_6$, an extra carboxyl group and the absence of H-7 compared with the known analogues, penicitrinols C–I, it was the only choice that the carboxyl group was fixed to C-7. The relative configurations of **1** were revealed through the NOE experiment. Enhancement of the signals of H-1 and H-4, H-11 and H-21, as well as H-12 and H-15 occurred on irradiation of the signals of H-11, H-1 and H-3, respectively, indicating that H-1, H-4, H-11 and H-21 were on the same side, whereas H-3, H-12 and H-15 were on the opposite side. Therefore, the structure of **1** was elucidated as shown (Figure 1).

Table 1. ^{1}H -NMR spectroscopic data (500 MHz, $CDCl_3$) for compounds **1**–**4**

NO.	**1**	**2**	**3**	**4**
	δ_H (*J* in Hz)	δ_H (*J* in Hz)	δ_H (*J* in Hz)	δ_H (*J* in Hz)
1	4.52 (1H, d, 11.2)	4.53 (1H, d, 11.4)	5.09 (1H, d, 5.0)	5.12 (1H, d, 4.8)
3	4.12 (1H, q, 6.8)	4.13 (1H, q, 6.8)	4.12 (1H, q, 6.8)	4.13 (1H, q, 6.8)
4	2.70 (1H, q, 7.0)	2.71 (1H, q, 7.0)	2.71 (1H, q, 7.0)	2.71 (1H, q, 7.0)
11	1.35 (3H, d, 6.8)	1.36 (3H, d, 6.8)	1.36 (3H, d, 6.8)	1.36 (3H, d, 6.8)
12	1.21 (3H, d, 7.0)	1.21 (3H, d, 7.0)	1.18 (3H, d, 7.0)	1.20 (3H, d, 7.0)
13	2.12 (3H, s)	2.11 (3H, s)	2.12 (3H, s)	2.11 (3H, s)
15	1.92 (1H, m)	1.90 (1H, m)	2.14 (1H, m)	2.22 (1H, m)
17	2.44 (1H, m)	2.20 (1H, m)	2.45 (1H, m)	2.25 (1H, m)
	1.62 (1H, m)	1.92 (1H, m)	1.56 (1H, m)	1.85 (1H, m)
18	1.83 (1H, m)	1.83 (1H, m)	1.82 (1H, m)	1.80 (1H, m)
	1.38 (1H, m)	1.38 (1H, m)	1.36 (1H, m)	1.41 (1H, m)
19	1.77 (1H, m)	1.66 (1H, m)	1.73 (1H, m)	1.75 (1H, m)
	1.45 (1H, m)	1.45 (1H, m)	1.28 (1H, m)	1.29 (1H, m)
20	2.15 (1H, m)	2.18 (1H, m)	1.94 (1H, m)	1.92 (1H, m)
	1.90 (1H, m)	1.89 (1H, m)	0.95 (1H, m)	0.92 (1H, m)
21	3.33 (3H, s)		3.39 (3H, s)	
6-OH	12.17 (1H, brs)	12.13 (1H, brs)	12.21 (1H, brs)	12.23 (1H, brs)
CO_2H	11.54 (1H, brs)	11.53 (1H, brs)	11.54 (1H, brs)	11.51 (1H, brs)

Compound **2**, which is trivially named as penicitrinol M, was obtained as white powder and was analyzed to have the molecular formula $C_{19}H_{24}O_6$ through negative HRESIMS (*m/z*: 347.1510 $[M - H]^-$, Calcd. for $C_{19}H_{23}O_6$, 347.1500). Its NMR data (Tables 1 and 2), combined with DEPT and HMQC spectrum analyses, revealed nineteen carbon signals, including three methyls, four methylenes, four methines, and eight quaternary carbons. The 1D-NMR data of **2** indicated that its structure was similar to that of **1**, except for the disappearance of a methoxyl group (δ_H 3.33 s, δ_C 48.9 s). Considering the similar COSY and HMBC correlations of **2** and **1** (Figure 2), as well as 14 amu differences between their molecular

weights, it was revealed that the planar structure of **2** was 16-demethylation derivative of **1**. The relative configurations of **2** were revealed through the NOE experiment and chemical method. Enhancement of the signals of H-1 and H-4 as well as H-12 and H-15 occurred on irradiation of the signals of H-11 and H-3, respectively, indicating that H-1, H-4 and H-11 were on the same side, whereas H-3, H-12 and H-15 were on the opposite side. Moreover, after dissolving and heating compound **2** in methanol for 96 hours, compound **1** gradually appeared while HPLC analysis accompanied, which suggested **2** and **1** owned the same relative configuration of C-16. Therefore, the structure of **2** was elucidated as shown (Figure 1).

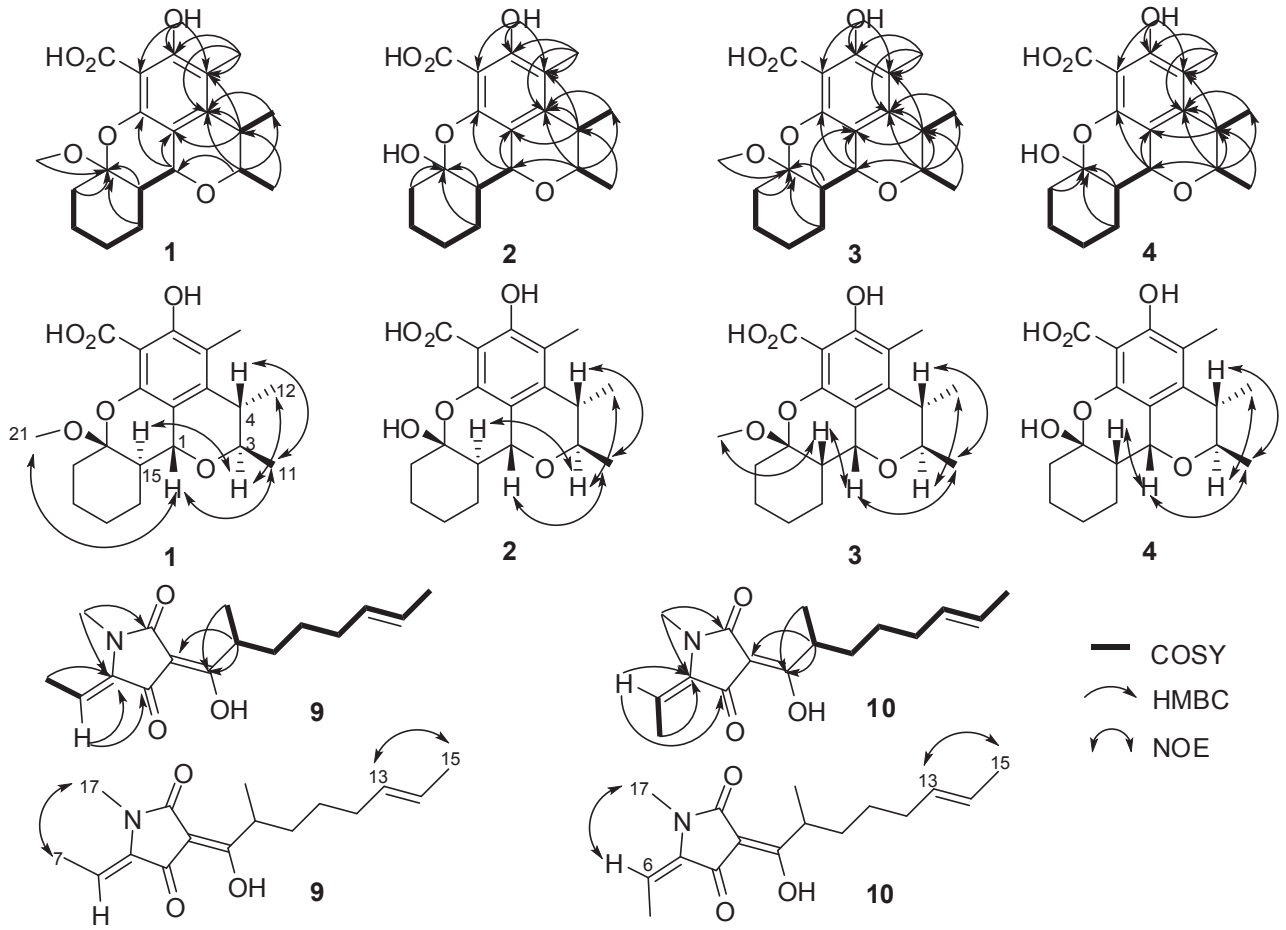

Figure 2. Key COSY, HMBC and NOE correlations of compounds **1**–**4**, **9** and **10**

Compound **3**, which is trivially named as penicitrinol N, had the same molecular formula as **1** ($C_{20}H_{26}O_6$) as revealed by HRESIMS data (*m/z*: 361.1649 $[M - H]^-$, Calcd. for $C_{20}H_{25}O_6$, 361.1657). The NMR (^{1}H-NMR, ^{13}C-NMR, COSY, HMQC, and HMBC) data revealed that both **3** and **1** possessed the same planar structure. However, the NOE correlations of H-15 with H-1 and H-21 in **3** suggested **3** and **1** were stereoisomers that differed in the configuration of C-15 (Figure 2).

Compound **4**, which is trivially named as penicitrinol O, had the same molecular formula as **2** ($C_{19}H_{24}O_6$) as revealed by HRESIMS data (*m/z*: 347.1505 $[M - H]^-$, Calcd. for $C_{19}H_{23}O_6$, 347.1500). The similar 1D and 2D-NMR data revealed that both **4** and **2** also possessed the same planar structure (Figure 2). In view of the nearly same NOE correlations in **4** and **3**, as well as the similar transformation result from **4** to **3** as from **2** to **1** in methanol, the structure of **4** was finally determined to be 16-demethylation derivative of **3** as shown in Figure 1.

Table 2. ^{13}C -NMR spectroscopic data (125 MHz, $CDCl_3$) for compounds **1**–**4**

NO.	**1**		**2**		**3**		**4**	
1	61.4	CH	61.7	CH	61.0	CH	61.0	CH
3	74.4	CH	74.4	CH	74.3	CH	74.3	CH
4	35.5	CH	35.5	CH	35.4	CH	35.4	CH
5	118.4	qC	118.3	qC	118.5	qC	118.4	qC
6	160.8	qC	160.9	qC	160.8	qC	160.8	qC
7	98.3	qC	98.2	qC	98.2	qC	98.0	qC
8	147.0	qC	147.2	qC	146.8	qC	147.1	qC
9	110.7	qC	110.4	qC	108.1	qC	107.7	qC
10	144.9	qC	144.9	qC	145.3	qC	145.3	qC
11	19.0	Me	18.8	Me	18.6	Me	18.5	Me
12	22.4	Me	22.3	Me	22.0	Me	21.9	Me
13	10.4	Me	10.3	Me	10.1	Me	10.1	Me
14	171.3	qC	171.6	qC	171.3	qC	171.6	qC
15	44.6	CH	44.0	CH	41.3	CH	41.1	CH
16	105.2	qC	102.9	qC	105.4	qC	102.9	qC
17	31.9	CH_2	38.8	CH_2	33.2	CH_2	39.3	CH_2
18	24.8	CH_2	24.8	CH_2	22.7	CH_2	23.1	CH_2
19	22.5	CH_2	23.1	CH_2	23.7	CH_2	23.7	CH_2
20	24.7	CH_2	24.8	CH_2	22.3	CH_2	22.2	CH_2
21	48.9	Me			49.2	Me		

Compound **9**, which is trivially named as penicillenol D_1, was obtained as yellow oil and was analyzed to have the molecular formula $C_{16}H_{23}NO_3$ through positive HRESIMS (*m/z*: 278.1740 $[M + H]^+$, Calcd. for $C_{16}H_{24}NO_3$, 278.1751). The IR spectrum suggested the presence of OH group(s) (3399 cm^{-1}) and conjugated carbonyl group(s) (1716, 1654, 1618 cm^{-1}). Its NMR data (Table 3), combined with DEPT and HMQC spectrum analyses, revealed sixteen carbon signals, including four methyls, three methylenes, four methines, and five quaternary carbons. The 1D-NMR data of **9** indicated that its structure was similar to that of **11**, except for the four obviously downfield shifts of C-12, C-13, C-14 and C-15. In addition, the similar COSY, HMBC and NOE correlations of **9** and **11** as well as 2 amu differences between their

molecular weights, suggested **9** was the 13,14-dehydro derivative of **11** (Figure 1). The *E* configuration was assigned to the C-13 and C-14 double bond by the NOE correlations between H-13 and H-15 and comparison of the chemical shifts of C-12 (δ_C 32.7) and C-15 (δ_C 18.0) with the reported calculated values (δ_C (*E*) 33.0, (*Z*) 27.0 for C-12; δ_C (*E*) 17.0, (*Z*) 11.0 for C-15).[4,5] Considering the 9*S* absolute configuration of penicillenol C_1 confirmed by total synthesis,[6] the derivatization from penicillenol D_1 to penicillenol C_1 was attempted. Unfortunately, the reaction failed and the sample was exhausted. Thus, the stereochemistry of C-9 of **9** remains undetermined at this time.

Table 3. ^{1}H and ^{13}C-NMR spectroscopic data for compounds **9** and **10** ($CDCl_3$)*

NO.	Penicillenol D_1 (Exo A)		Penicillenol D_2 (Exo A)	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2		172.9 qC[a]		171.0 qC[e]
3		100.1 qC[b]		101.5 qC[f]
4		180.3 qC[c]		183.0 qC[g]
5		136.7 qC		134.4 qC
6	5.88 (1H, q, 8.0)	107.6 CH	5.39 (1H, q, 7.8)	112.1 CH
7	2.03 (3H, d, 8.0)	11.6 Me	2.23 (3H, d, 7.8)	11.9 Me
8		191.1 qC[d]		190.7 qC[h]
9	3.70 (1H, m)	35.8 CH	3.71 (1H, m)	35.7 CH
10	1.69 (1H, m)	33.4 CH_2	1.71 (1H, m)	33.3 CH_2
	1.46 (1H, m)		1.47 (1H, m)	
11	1.36 (2H, m)	27.3 CH_2	1.35 (2H, m)	27.3 CH_2
12	1.96 (2H, m)	32.7 CH_2	1.96 (2H, m)	32.6 CH_2
13	5.38 (1H, m)	131.0 CH	5.36 (1H, m)	131.1 CH
14	5.40 (1H, m)	125.3 CH	5.40 (1H, m)	125.2 CH
15	1.63 (3H, d, 4.9)	18.0 Me	1.62 (3H, d, 4.8)	18.0 Me
16	1.17 (3H, d, 6.9)	17.4 Me	1.18 (3H, d, 6.9)	17.2 Me
17	3.39 (3H, s)	28.0 Me	3.05 (3H, s)	24.9 Me

*Spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C using TMS as internal standard: chemical shifts in Exo B (a: 166.9, b: 102.1, c: 185.1, d: 197.4, e: 164.2, f: 103.9, g: 187.5, h: 196.6).

Compound **10**, which is trivially named as penicillenol D_2, was obtained as yellow oil and was analyzed to have the same molecular formula $C_{16}H_{23}NO_3$ (*m/z*: 278.1741 $[M + H]^+$, Calcd. for $C_{16}H_{24}NO_3$, 278.1751) as **9**. The IR and NMR (^{1}H-NMR, ^{13}C-NMR, COSY, HMQC, and HMBC) data of **10** revealed that its structure was similar to that of **12**, except for the four obviously downfield shifts of C-12, C-13, C-14 and C-15. Furthermore, considering 2 amu differences between the molecular weights of **10** and **12**, and similar chemical shifts from C-9 to C-15 in ^{1}H and ^{13}C-NMR data of **9** and **10**, **10** was finally

elucidated to be the 13,14-dehydro derivative of **12** (Figure 1). The *E* configuration of the C-13 and C-14 double bond was determined by the same method as **9**. In order to determine the stereochemistry of C-9, similar reaction as **9** was attempted. However, the derivatization was also unsuccessful and absolute configuration of C-9 of **10** remains unknown.

The citrinin derivatives, penicitrinols L–O (**1**–**4**) likely have the same biogenetic origin from intermediate (**7**) via the polyketide pathway.[7] For a detailed explanation of the interrelationship of these metabolites, a plausible biosynthetic pathway was proposed in Figure 3, which was very similar to the reported biosynthesis of penicitrinols C–E.[1f]

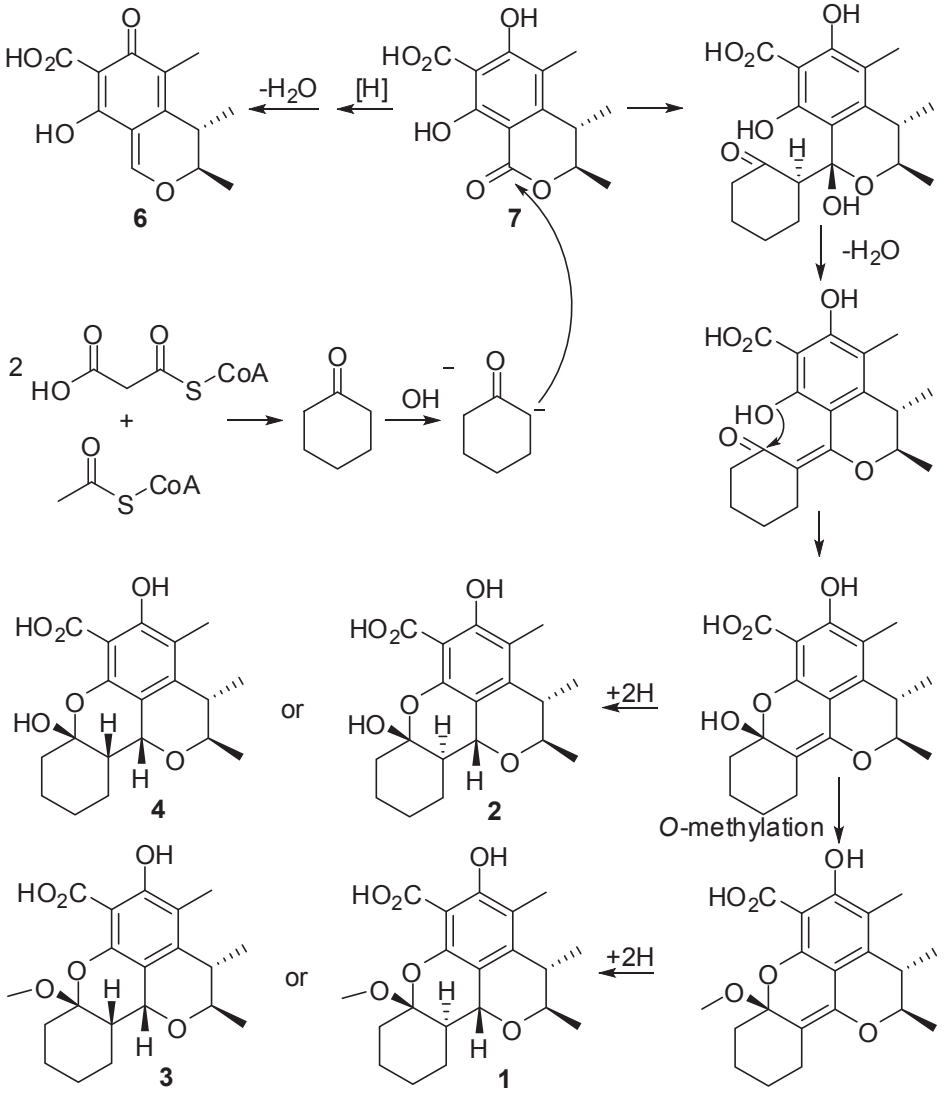

Figure 3. Plausible biosynthetic pathway of compounds **1**–**4**

All the new compounds were evaluated for their cytotoxic effects on the A-549, HL-60 and SW-620 cell lines by the MTT method. Penicitrinols L (**1**) and M (**2**) showed weak cytotoxicities against SW-620 cell line, while penicillenols D_1 (**9**) and D_2 (**10**) showed weak cytotoxicities against A-549 and HL-60 cell

lines, respectively. By contrast, penicitrinols N (**3**) and O (**4**) were inactive against these three cell lines (Table 4).

Table 4. Cytotoxicity of compounds **1**–**4**, **9** and **10** in three cancer cell lines

	cytotoxicity (IC_{50}, μg/mL)		
compounds	A-549 cell	HL-60 cell	SW-620 cell
1	>100	>100	25.6
2	>100	>100	20.9
3	>100	>100	>100
4	>100	>100	>100
9	17.2	18.5	>100
10	12.1	14.5	>100

EXPERIMENTAL

General Experimental Procedures. Optical rotations were obtained from a Shenguang SGW-1 digital polarimeter. UV spectra were recorded on a Shimadzu UV-2450 spectrophotometer. IR spectra were recorded on a Nicolet Avatar 670 spectrophotometer. ^{1}H-NMR, ^{13}C-NMR, DEPT spectra and 2D-NMR were recorded on a BRUKER BIOSPIN AVANCE III spectrometer using TMS as the internal standard. ESI-MS were obtained by an AGILENT 1200/Q-TOF 6510 LC mass spectrometer. Semipreparative HPLC was performed using an ODS column (ODS-A, 10×250 mm, 5 μm) at 5 mL/min.

Fungal Material. The fungus *P. citrinum* was isolated from marine sediments collected from Langqi Island, Fujian, China. It was identified according to its morphological characteristics and ITS by Beijing Sunbiotech Co. Ltd, and preserved in our laboratory at −80 ˚C. The producing strain was prepared on Martin medium and stored at 4 ˚C.

Fermentation and Extraction. The fungus was cultured under static conditions at 28 ˚C for 30 days in 1000-mL conical flasks containing the liquid medium (400 mL/flask), composed of glucose (10 g/L), maltose (20 g/L), mannitol (20 g/L), monosodium glutamate (10 g/L), KH_2PO_4 (0.5 g/L), $MgSO_4 \cdot 7H_2O$ (0.3 g/L), yeast extract (3 g/L), and seawater. The fermented whole broth (60 L) was filtered through cheese cloth to separate supernatant from mycelia. The former was extracted two times with EtOAc to give an EtOAc solution that was concentrated under reduced pressure to give a crude extract (32.0 g).

Purification. The broth extract (32.0 g) was separated into 11 fractions on a Si gel column using a step gradient elution of petroleum ether, CH_2Cl_2, and MeOH. Fraction 3 (1.8 g) eluted with CH_2Cl_2 was further purified on a Si gel column using a step gradient elution. Subfraction 3-1 (350 mg) was purified by semipreparative HPLC (70% MeCN containing 0.1% TFA) to yield compounds **1** (7.2 mg), **2** (2.8 mg),

3 (6.5 mg) and **4** (3.9 mg). Subfraction 3-2 (210 mg) was purified by semipreparative HPLC (60% MeCN containing 0.1% TFA) to yield compound **8** (29.8 mg). Subfraction 3-3 (420 mg) was purified by semipreparative HPLC (70% MeCN containing 0.1% TFA) to yield compound **5** (13.6 mg). Fraction 7 (4.2 g) eluted with CH_2Cl_2/MeOH (100:1) was further purified on a Si gel column using a step gradient elution. Subfraction 7-1 (330 mg) was purified by semipreparative HPLC (65% MeOH containing 0.1% TFA) to yield compound **7** (27.1 mg). Subfraction 7-3 (1.5 g) was purified by a reversed-phase column (MeOH/H_2O, 3:2) and semipreparative HPLC (80% MeOH containing 0.1% TFA), yielding compounds **11** (111.7 mg) and **12** (125.8 mg). Subfraction 7-5 (710 mg) was purified by a reversed-phase column (MeOH/H_2O, 3:2) and semipreparative HPLC (80% MeOH containing 0.1% TFA), yielding compounds **9** (2.3 mg) and **10** (2.8 mg). Subfraction 7-7 (450 mg) was purified by semipreparative HPLC (85% MeOH containing 0.1% TFA) to yield compound **6** (21.3 mg).

Penicitrinol L (**1**): white powder ($CHCl_3$); $[\alpha]^{20}_D$ +42.3 (*c* 0.10, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 254 (2.23), 322 (1.78) nm; IR (KBr) ν_{max} 3407, 3223, 2933, 2864, 1683, 1617, 1585, 1417, 1278, 1106 cm^{-1}; ^1H- and ^{13}C-NMR data (see Tables 1 and 2); HRESIMS *m/z* 361.1671 $[M - H]^-$ (calcd. for $C_{20}H_{25}O_6$, 361.1657).

Penicitrinol M (**2**): white powder ($CHCl_3$); $[\alpha]^{20}_D$ +5.0 (*c* 0.10, $CHCl_3$); UV(MeOH) λ_{max} (log ε) 256 (2.15), 328 (1.76) nm; IR (KBr) ν_{max} 3405, 3211, 2928, 2865, 1690, 1622, 1579, 1431, 1280, 1114 cm^{-1}; ^1H- and ^{13}C-NMR data (see Tables 1 and 2); HRESIMS *m/z*: 347.1510 $[M - H]^-$ (calcd. for $C_{19}H_{23}O_6$, 347.1500).

Penicitrinol N (**3**): white powder ($CHCl_3$); $[\alpha]^{20}_D$ +24.8 (*c* 0.12, $CHCl_3$); UV(MeOH) λ_{max} (log ε) 255 (2.21), 324 (1.83) nm; IR (KBr) ν_{max} 3395, 3217, 2929, 2860, 1695, 1621, 1582, 1430, 1285, 1113 cm^{-1}; ^1H- and ^{13}C-NMR data (see Tables 1 and 2); HRESIMS *m/z*: 361.1649 $[M - H]^-$ (calcd. for $C_{20}H_{25}O_6$, 361.1657).

Penicitrinol O (**4**): white powder ($CHCl_3$); $[\alpha]^{20}_D$ +15.5 (*c* 0.10, $CHCl_3$); UV(MeOH) λ_{max} (log ε) 257 (2.08), 330 (1.74) nm; IR (KBr) ν_{max} 3401, 3217, 2932, 2862, 1689, 1616, 1581, 1430, 1280, 1115 cm^{-1}; ^1H- and ^{13}C-NMR data (see Tables 1 and 2); HRESIMS *m/z*: 347.1505 $[M - H]^-$ (calcd. for $C_{19}H_{23}O_6$, 347.1500).

Penicillenol D_1 (**9**): yellow oil (MeOH); $[\alpha]^{20}_D$ –51.0 (*c* 0.10, MeOH); UV(MeOH) λ_{max} (log ε) 264 (3.75) nm; IR (KBr) ν_{max} 3399, 2962, 2933, 2856, 1716, 1654, 1618, 1458, 1372, 1340, 1262, 1115, 1050 cm^{-1}; ^1H- and ^{13}C-NMR data (see Table 3); HRESIMS *m/z*: 278.1740 $[M + H]^+$ (calcd. for $C_{16}H_{24}NO_3$, 278.1751).

Penicillenol D_2 (**10**): yellow oil (MeOH); $[\alpha]^{20}_D$ –20.5 (*c* 0.10, MeOH); UV(MeOH) λ_{max} (log ε) 264 (3.83) nm; IR (KBr) ν_{max} 3391, 2954, 2921, 2852, 1712, 1672, 1618, 1458, 1376, 1344, 1279, 1164, 1050 cm^{-1};

^{1}H- and ^{13}C-NMR data (see Table 3); HRESIMS *m/z*: 278.1741 $[M + H]^+$ (calcd. for $C_{16}H_{24}NO_3$, 278.1751).

Biological Assays. The cytotoxic activity for the A-549, HL-60 and SW-620 cell lines was evaluated by the MTT method.[4]

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