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Xylariterpenoids A–D, four new sesquiterpenoids from the Xylariaceae fungus

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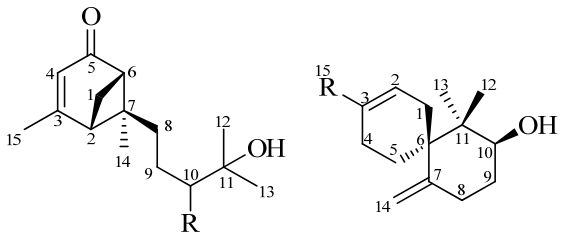
Four new sesquiterpenoids, sesquiterpenoids A–D (**1**–**4**), were isolated from the solid cultures of the Xylariaceae fungus (No. 63-19-7-3). Their structures were determined through NMR analyses, CD calculation, *in situ* dimolybdenum CD method, the modified Mosher's method, and X-ray data analysis. The cytotoxicities of all compounds against HL-60, SMMC-7721, A-549, MCF-7 and SW480 human cancer cell lines were assayed.

Introduction

The Xylariaceae is one of the largest families of ascomycetes (over 60 genera and far more than 1000 species). Moreover, excess of 500 metabolites have been reported from Xylariaceae fungi.[1] Previous chemical investigations reveal that this family produces a variety of secondary metabolites including dihydroisocoumarins, punctaporonins, cytochalasins, butyrolactones and succinic acid derivatives.[2] During our ongoing search for bioactive secondary metabolites from endolichenic fungi,[3] the chemical investigation of the Xylariaceae fungus (No. 63-19-7-3) was carried out, which led to the isolation of four new sesquiterpenoids (**1**–**4**). The planar structures of **1**–**4** were established primarily by NMR experiments. The absolute configurations of **1** and **2** were determined by CD and *in situ* dimolybdenum CD methods, while the absolute configurations of **3** and **4** were deduced *via* the modified Mosher's method and X-ray data analysis, respectively. Detail of the isolation, structural and absolute configurations elucidation, and cytotoxicity of all the compounds are reported herein.



1 R= (R)-OH
2 R= (S)-OH
3 R= COOH
4 R= CH_2OH

Fig. 1 Chemical structures of **1**–**4**

Materials and methods

The fermented material of the Xylariaceae fungus (No. 63-19-7-3) was extracted with EtOAc, and the organic solvent was evaporated under vacuum to afford the dry crude extract (28.1g). Then the crude extract was dissolved in 90% (v/v) aqueous MeOH (500 mL) and partitioned against the same volume cyclohexane to afford cyclohexane fraction (C, 15.3 g) and aqueous MeOH fraction (W, 12.5 g). The aqueous MeOH fraction was successively subjected to column chromatography over ODS, Sephadex LH-20 and reversed-phase HPLC (RPHPLC) to obtain compounds **1**–**4**. Then, the cytotoxicity assay of compounds **1**–**4** was performed. The detailed experimental procedures are available in the ESI.†

Results

Structural elucidation

Xylariterpenoid A (**1**) was obtained as a oil with a molecular formula of $C_{15}H_{24}O_3$ (four degrees of unsaturation), which was determined by HRESIMS at *m/z* 275.1615 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_3Na$, 275.1623). The UV spectrum (252 nm) indicated the presence of an α, β-unsaturated carbonyl moiety. The IR spectrum showed bands corresponding to hydroxyl (3424 cm^{-1}) and α, β-unsaturated carbonyl (1663 cm^{-1}) group. The ^1H NMR spectrum (Table 1) exhibited four methyls, three sp^3 methylenes, three sp^3 methines and one olefinic proton. The ^{13}C NMR and DEPT spectra of **1** (Table 1) displayed 15 carbon signals consisting of four methyls, three methylenes, three sp^3 methines, two sp^3 quaternary carbons, two olefinic carbons, and one carbonyl carbon. The proton resonances were assigned to relevant carbon atoms through the HSQC experiment. Analysis of the ^1H, ^1H-COSY spectrum led to the identification of two isolated ^1H spin-systems corresponding to the C-2–C-1–C-6 and C-8–C-9–C-10 subunits (Fig. 2). In addition, the HMBC correlations from H_3-15 to C-2/C-3/C-4, from H-4 to C-

2/C-6, from Ha-1 to C-5, from H_3-14 to C-2/C-6/C-7/C-8, from H_3-12 to C-10/C-11/C-13, from H_3-13 to C-10/C-11/C-12, and from Ha-8 to C-2/C-6/C-7 deduced the planar structure of **1** with a bicyclo[3.1.1]heptane skeleton, which was shown in Fig. 2. Furthermore, the observed $^4J_{H\text{-}2\text{–}H\text{-}6}$ (5.8 Hz) was consistent with the bridgehead-bridgehead coupling constant of the bicyclo[3.1.1]heptanes,[4] which confirmed the above deduction.

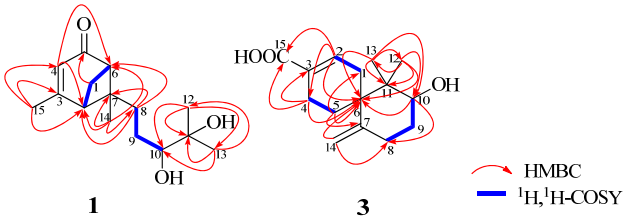


Fig. 2 Key HMBC and ^{1}H, ^{1}H-COSY of compounds **1** and **3**.

The partial relative configuration of **1** was established by the NOESY. The NOESY correlations between Hb-1 and Ha-8/Hb-8 indicated the relative configurations of C-2, C-6 and C-7 in **1** were 2S*, 6S*, and 7S*, respectively. The absolute configurations of C-2, C-6 and C-7 were determined by comparison of the experimental and the simulated circular dichroism (CD) spectra. Since the conformations of the flexible side chain in **1** had an insignificant effect on the CD spectrum, the simplified structures (**2R, 6R**)-**5** and (**2S, 6S**)-**5** were used for CD calculations (Fig. 3). The preliminary conformational analyses for a pair of enantiomers ((**2R, 6R**)-**5** and (**2S, 6S**)-**5**) were performed with Conflex version 7.0 *via* the MMFF94S force field. The corresponding minimum geometries were further fully optimized by DFT at the B3P86/6-31G(d) level as implemented in the Gaussian 09 program package. The obtained stable conformers were submitted to CD calculation by TDDFT [B3P86/6-311++G (2d, p)] method.[5–8] The result showed that the experimental CD spectrum of **1** and the calculated CD spectrum of (**2S, 6S**)-**5** have similar negative Cotton effects (CEs) in the region of 320-350 nm (Fig. 3), which suggested that the absolute configurations of C-2, C-6 and C-7 in **1** were 2S, 6S, and 7S, respectively. In addition, the absolute configuration of the C-10 of **1** was determined by the *in situ* dimolybdenum CD method, which was developed by Snatzke and Frelek.[9,10] The negative Cotton effect (~ 310 nm), observed in the induced CD spectrum, permitted the assignment of 10R configuration according to the empirical rule proposed by Snatzke (Fig. 4). On the basis of the above deduction, the absolute configuration of **1** was assigned as 2S, 6S, 7S, 10R. Thus, the structure of **1** was established as (1S,5S,6S)-6-((R)-3,4-dihydroxy-4-methylpentyl)-4,6-dimethylbicyclo[3.1.1]hept-3-en-2-one, named as xylariterpenoid A.

Xylariterpenoid B (**2**) was isolated as a oil with the same molecular formula as **1**. Except for the chemical shifts of protons around C-10 (Ha-8, Hb-8, Hb-9, H-10, and H_3-12, H_3-13, H_3-14), the ^{1}H and ^{13}C NMR data (Table 1) of **2** were similar to those of **1**, which disclosed that both the skeleton and the functional groups presented in **2** were same as those of **1**, and suggested that **2** was a epimer of **1** different at C-10. The ^{1}H, ^{1}H-COSY and HMBC correlations (the details are available in the ESI†) observed fully supported that **2** had the same planar structure as that of **1**. The NOESY correlation between Hb-1 and Ha-8 indicated that the relative configurations of C-2, C-6 and C-7 were also the same as **1**, which confirmed that **2** was a epimer of **1** different at C-10. In the CD spectrum, **2** showed the same Cotton effects as **1** (Fig. 5), indicating that the absolute configurations of C-2, C-6 and C-7 were S. However, the positive Cotton effect at around 310 nm, observed in the *in situ* dimolybdenum CD spectrum, permitted the assignment of 10S configuration for **2** (Fig. 4). On the basis of the above data, the absolute configuration of **2** was assigned as 2S, 6S, 7S, 10S. Thus, the structure of **2** was determined as (1S,5S,6S)-6-((S)-3,4-dihydroxy-4-methylpentyl)-4,6-dimethylbicyclo[3.1.1]hept-3-en-2-one, named as xylariterpenoid B.

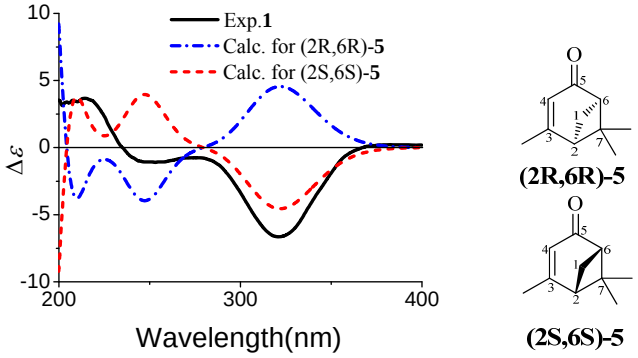


Fig. 3 Experimental CD spectrum of **1** in MeOH and calculated CD spectrum of a pair of enantiomers of the corresponding simplified structures [(**2R,6R**)-**5** and (**2S,6S**)-**5**].

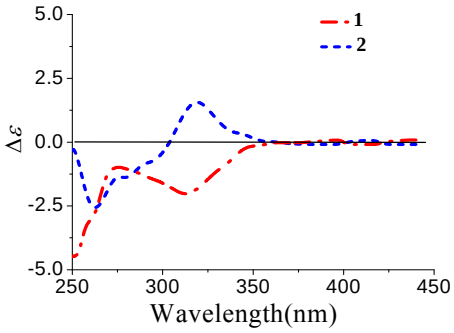


Fig. 4 CD spectra of **1** (red) and **2** (blue) in DMSO containing $Mo_2(OAc)_4$ with the inherent CD spectrum subtracted.

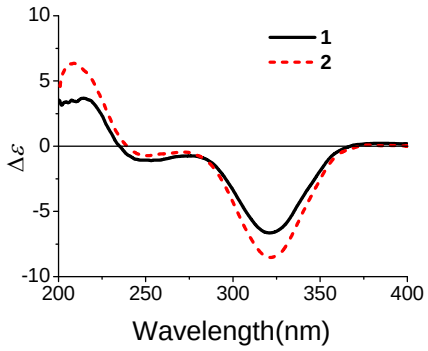


Fig. 5. CD spectra of **1** and **2** in MeOH.

Xylariterpenoid C (**3**) was assigned as $C_{15}H_{22}O_3$ (five degrees of unsaturation) on the basis of its HRESIMS at *m/z* 273.1465 [M + Na]$^+$ (calcd for $C_{15}H_{22}O_3Na$, 273.1467). The IR spectrum showed bands corresponding to hydroxyl (3439 cm^{-1}). The ^{1}H NMR spectrum (Table 1) exhibited two methyls, five sp^3 methylenes, one oxygenated sp^3 methine and three olefinic protons. The ^{13}C NMR and DEPT spectra of **3** (Table 1) displayed 15 carbon signals consisting of two methyls, five sp^3 methylenes, one oxygenated sp^3 methine, two sp^3 quaternary carbons, four olefinic carbons, and one carbonyl carbon. The proton resonances were assigned to relevant carbon atoms through the HSQC experiment. Interpretation of the ^{1}H, ^{1}H-COSY spectrum of **3** identified three isolated proton spin systems, which were C-1–C-2, C-4–C-5, and C-8–C-9–C-10 (Fig. 2). Combined with the analysis of ^{1}H, ^{1}H-COSY spectrum, the HMBC correlations from H_3-13 to C-6/C-10/C-11/C-12, from H_3-12 to C-6/C-10/C-11/C-13, from H_2-14 to C-6/C-8, from H-2 to C-4/C-6/C-15, from Hb-4 to C-3/C-6/C-15, from Hb-5 to C-1 and from Ha-5 to C-6/C-7 completed the planar structure of **3** (Fig.1).

The relative configuration of **3** was established by the NOESY data analysis. The orientation of H-10 was the same as those of H_2-5 and H_3-13, which was determined by the NOESY correlations between H-10 and H_3-13/Hb-5. Thus, the relative configuration of **3** was designated as 6R*, 10S*. The absolute configuration of **3** was determined by the modified Mosher method.[11] The $\Delta\delta$ values of the (*S*)- and (*R*)-MTPA esters (**3a** and **3b**) indicated the S configuration for C-10 (Fig. 6). On the basis of the above deduction, the absolute configuration 6R, 10S was proposed for **3**. Therefore, the structure of **3** was elucidated as (6R,8S)-8-hydroxy-7,7-dimethyl-11-methylenespiro[5.5]undec-2-ene-3-carboxylic acid, named as xylariterpenoid C.

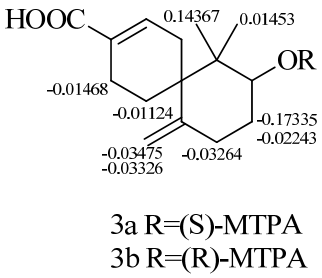


Fig. 6. $\Delta\delta$ ($\delta_S - \delta_R$) values (in ppm) obtained for (*S*)- and (*R*)-MTPA esters (**3a** and **3b**).

Xylariterpenoid D (**4**) was isolated as a crystal. Its HRESIMS analysis gave a quasi-molecular ion peak at *m/z* 259.1667 [M + Na]$^+$(calcd for $C_{15}H_{24}O_2Na$, 259.1674), 14 mass units less than **3**. The 1D NMR data of **4** revealed its structural features were similar to those of **3**, except that the resonance for C-15 [δ_C 171.7 (C-15)] was replaced by an oxygenated methylene group [$\delta_{C/H}$ 67.2 (C-15)/3.92 (br s, H_2-15)]. At the same time, the ^{1}H, ^{1}H-COSY and HMBC correlations (the details are available in the ESI†) observed fully supported the locations of functional groups. Thus, the planar structure of **4** was established as shown in Fig.1.

The relative configuration of **4** was established on the basis of the NOESY data. The NOESY correlation between H-10 and Hb-5 indicated that **4** had the same relative configuration with **3**. In the meanwhile, the relative configuration of **4** was confirmed by single-crystal X-ray crystallographic analysis (Fig. 7). Furthermore, the values of the Flack parameter (-0.1(3)) and the Hooft y parameter 0.04(16) allowed the assignment of the absolute configuration of **4** as 6R, 10S. Therefore, the structure of **4** was determined as (2S,6R)-9-(hydroxymethyl)-1,1-dimethyl-5-methylenespiro[5.5]undec-8-en-2-ol, named as xylariterpenoid D.

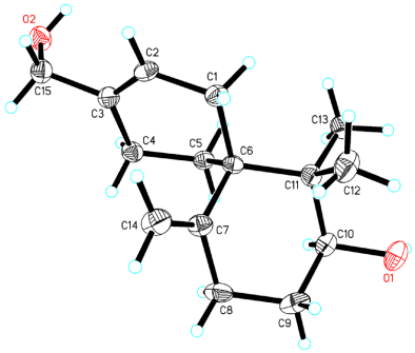


Fig. 7. X-ray crystal structure of **4**.

Biological activities

All compounds were tested for the cytotoxicities against HL-60, A-549, MCF-7, SMMC-7721, and SW-480 human cancer cell lines using MTT method. However, compounds **1**–**4** exhibited no significant cytotoxicity, with $IC_{50} > 40$ μM.

Discussion and conclusion

Sesquiterpenes incorporating the bergamotane skeleton have been reported from fungi (such as *Ampulliferina* sp.,[12] *Ampulliferina*-like sp. No 27,[13,14] *Aspergillus fumigatus*,[15,16] *Massarina tunicate*,[17] *Penicillum expansum*,[18] and *Podospora decipiens*[19]) and plants (such as *Tanacetum vulgare*,[20] and *Lepidolaena clavigera*[21,22]). Compounds **1** and **2** are the first examples of the bergamotane-type sesquiterpenes with carbonyl at C-5 position. In addition, the previously reported chamigrane-type sesquiterpenes are halogenated analogues, which were isolated from red algae.[22] Compounds **3** and **4** are new members of the non-halogenated chamigrane-type sesquiterpenes. Although all new compounds exhibited no significant cytotoxicity, further studies still need to elucidate their promising bioactivity.

Acknowledgements

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Table1 ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR Spectroscopic Data for xylariterpenoid A–D (**1**–**4**) in $CDCl_3$ (δ in ppm, J in Hz).

	1		**2**		**3**		**4**	
No.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	2.07, d (9.1), a 2.80, dt (9.1, 5.3), b	40.8	2.08, d (9.5), a 2.80, dt (9.5, 5.5), b	40.8	2.17, m, a 2.31, m, b	30.2	2.05, m, a 2.15, m, b	28.9
2	2.45, br t (5.8)	48.6	2.47, br t (5.7)	48.4	7.09, m	141.5	5.63, br s	122.0
3		170.6		170.6		128.8		136.3
4	5.73, q (1.0)	121.5	5.74, q (1.4)	121.5	1.80, m, a 2.31, m, b	21.4	1.67, m, a 1.96, m, b	23.1
5		204.4		204.2	1.48, m, a 1.95, m, b	25.2	1.50, m, a 1.87, m, b	25.4
6	2.71, br t (5.8)	55.5	2.71, br t (5.7)	55.8		45.4		45.7
7		57.1		57.1		146.4		146.8
8	1.73, td (12.8, 4.0), a 2.31, td (12.8, 4.0), b	35.6	1.90, td (12.4, 4.5), a 2.17, td (12.4, 4.5), b	35.7	2.17, m, a 2.31, m, b	30.0	2.17, m, a 2.33, m, b	30.1
9	1.34, m, a 1.48, m, b	26.5	1.34, m, a 1.50, m, b	26.5	1.47, m, a 1.86, m, b	31.9	1.45, m, a 1.82, m, b	32.0
10	3.33, dd (10.3, 1.6)	78.8	3.36, dd (10.4, 1.8)	78.8	3.88, dd (11.9, 4.6)	73.3	3.87, dd (11.9, 4.7)	73.5
11		73.2		73.3		41.9		42.0
12	1.16, s	23.3	1.17, s	23.2	0.76, s	15.1	0.73, s	15.0
13	1.21, s	26.5	1.23, s	26.7	1.02, s	20.4	1.01, s	20.4
14	0.96, s	19.0	0.98, s	19.0	4.44, br s, a 4.92, br s, b	112.0	4.55, br s, a 4.92, br s, b	111.9
15	2.00, d (1.0)	23.6	2.01, d (1.4)	23.6		171.7	3.92, br s	67.2

Notes and references

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‡ Crystal data of xylariterpenoid D (**4**): Data were collected using a Sapphire CCD with a graphite monochromated Cu Kα radiation, λ = 1.54184 Å at 173.00 (10) K. Crystal data: $C_{15}H_{24}O_2$, M = 236.34, orthorhombic, space group $P212121$; unit cell dimensions were determined to be a = 6.5259(3) Å, b = 13.1402(5)Å, c = 15.6863(7) Å, α = 90.00 °, β = 90.00 °, γ = 90.00 °, V =1345.13(10) Å^3, Z = 4, Dx = 1.167 g/cm^3, F (000) = 520, μ (Cu K_α) = 0.586 mm^{-1}. 10952 reflections were collected until θ_{max} = 62.93°, in which independent unique 1950 reflections were observed [$F^2 > 4\sigma$ (F^2)]. The final refinement gave R = 0.0363, R_W = 0.0909, S = 1.079, Flack = -0.1(3), and Hooft y = 0.04(16). Crystal data of **4** was deposited in the Cambridge Crystallographic Data Centre (CCDC 1023174).

†Electronic Supplementary Information (ESI) available: the general experimental procedure, fungus material, extraction and isolation, spectroscopic data of **1**–**4**, quantum chemical CD calculation of **5**, single-crystal X-ray data of **4**, the *in situ* dimolybdenum CD method, preparation of (*S*)- and (*R*)-MTPA esters of **3** (**3a** and **3b**), cytotoxicity assay, and 1D and 2D NMR spectra of compounds **1**–**4**. See DOI: 10.1039/b000000x/

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Graphic abstract