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Britanlins A–D, four novel sesquiterpenoids from *Inula britannica*

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ABSTRACT

A phytochemical investigation on the flowers of *Inula britannica* has led to the isolation of four novel sesquiterpenoids, britanlins A–D. Britanlins A–C feature the rare presilphiperfolane-type frameworks, which play an important role in biogenesis of triquinane sesquiterpenoids. Britanlin D possessed a rearranged pseudoguaiane skeleton, which was first isolated from nature. The structures of britanlins A to D were elucidated on the basis of extensive spectroscopic methods. The structures of britanlins A and D were further confirmed by single crystal X-ray diffraction.

1. Introduction

Biogenesis played an important role in natural product research. Not only does it make the existence of chemical constituents in nature more reasonable, but also provides strategies for reference to the synthesis of natural products. The discovery of triquinane sesquiterpenoids made natural product chemists proud of the structural diversity of sesquiterpenoids, which also raised interesting questions concerning the biogenetic origins and relationships of these natural products. A hypothesis on the biogenesis of the triquinane sesquiterpenoids has been proposed by Bohlmann.[1] The key to confirm this hypothesis is to confirm the existence of intermediate presilphiperfolan-8-yl ion. In 1981, the discovery of presilphiperfolanol from nature, corresponding to hydration of the key branchpoint intermediate presilphiperfolan-8-yl ion, made Bohlmann's hypothesis more reasonable.

Presilphiperfolane-type sesquiterpenoids feature a rare 5/5/6 tricyclic system and limited compounds with this type were found from nature up to now. For years, due to the intriguing molecular structures and as a branchpoint marker in the triquinane sesquiterpenoid biogenesis, this carbon skeleton has captured the interest of nature product chemists. Papers on the synthesis and biogenesis of this carbon skeleton continuously appeared.[2–6] In 2009, a research on the biogenesis of this framework was listed as highlighted by *Natural Product Reports*.[7]

In this Letter, we reported britanlins A–C isolated from *Inula britannica*, with closely similar structural pattern to that of presilphiperfolanol. This discovery provided new examples to support Bohlmann's biogenesis for triquinane sesquiterpenoids and may stimulate again the interest of natural product chemists on the research of this kind of skeleton. Additionally, we also obtained a rearranged pseudoguaiane sesquiterpenoid, britanlin D with a novel carbon skeleton, to our best knowledge, which was first reported here and this kind of rearranged skeleton was isolated from nature for the first time.

An EtOH extract of the dried flowers of *I. britannica* was partitioned in turn with petroleum ether (60–90 °C), ethyl acetate, and *n*-butanol against water. After repeated column chromatography over silica gel, the petroleum ether and ethyl acetate partition afforded britanlins A, C, and D, respectively. Britanlin B, isolated as an artifact, was yielded from britanlin A in a $CDCl_3$ solution.

2. Results and discussion

Compound **1**, mp 96–97 °C, $[\alpha]_D^{20}$ −7.3 (*c* 0.1, MeOH), was isolated as colorless crystals in a $CHCl_3$–MeOH (3:1, v:v) solution. Detailed analysis of its 1D NMR data, combined with the ESIMS ion peak at *m*/*z* 221.1 $[M-H_2O+H]^+$, indicated the molecular formula of $C_{15}H_{26}O_2$ in accordance with the positive HRESIMS pseudomolecular ion peak at 221.1905 ($[M-H_2O+H]^+$) and 261.1822 ($[M+Na]^+$), corresponding to three degrees of unsaturation. The IR absorption at 3378 cm^{-1} suggested the presence of one or more hydroxyl groups. ^1H, ^{13}C and DEPT (Table 1) spectra showed fifteen carbon resonances ascribed to three methyls, six methylenes (including oxygenated methylene), three methines, and three quaternary carbons (of which one was oxygenated). The NMR feature analysis implied a rare carbon skeleton. Detailed analysis of the

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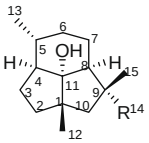
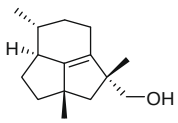


1 R=CH_2OH
3 R=COOH



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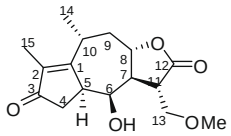

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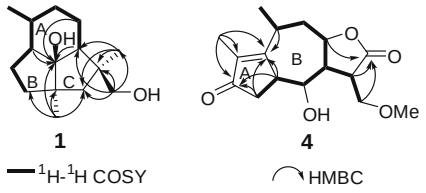
Compound **2**, $[\alpha]_D^{20}$ −5.1 (*c* 0.1, MeOH), was yielded during the NMR experiment of **1** in a $CDCl_3$ solution. Its molecular formula was established as $C_{15}H_{24}O$ from the HRESIMS ($[M+H]^+$, obsd 221.1904, calcd 221.1900). Based on the above-observation, we supposed compound **2** was yielded by compound **1** losing a H_2O moiety. This hypothesis was supported by its NMR data. Compared to that of **1**, the ^{13}C spectrum of compound **2** showed two double bond quaternary carbon resonances at δ_C 126.0 and δ_C 161.5 instead of the quaternary carbon at δ_C 94.7 and one methine signal. The findings, in combination with the HMBC interaction from the resonance at δ_C 126.0 to H_3-15 (δ_H 1.20, s) as well as the signal shift of C-7 from δ_C 27.6 to δ_C 39.3 unambiguously indicated the double bond formed between C-11 and C-8. So, the structure of britanlin B was elucidated as **2**.

Table 1
^1H and ^{13}C NMR data (400 MHz and 100 MHz, resp.) of compounds **1**–**3**

No.	**1**[a]		**2**[b]		**3**[b]	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1		57.0 s		49.3 s		56.5 s
2	1.96 m	34.2 t	2.01 (overlap)	33.0 t	1.98 m	33.0 t
	1.05 m		1.18 (overlap)		1.23 m	
3	2.27 m	33.9 t	1.61 (overlap)	35.0 t	2.43 (overlap)	33.3 t
	1.85 m		1.41 (overlap)		1.50 (overlap)	
4	1.33 td (9.2, 4.0)	49.2 d	1.79 (overlap)	43.3 d	1.38 m	47.6 d
5	1.42 m	37.9 d	1.51 m	35.8 d	1.41 m	36.9 d
6	1.64 m	35.3 t	1.23 (overlap)	31.9 t	1.66 m	33.7 t
	0.99 m		1.06 (overlap)		1.09 m	
7	1.61 m	27.6 t	1.61 td (11.2, 4.1)	39.3 t	1.68 (overlap)	26.3 t
	1.50 m		1.14 (overlap)		1.50 (overlap)	
8	1.75 dd (12.8, 7.6)	47.5 d		126.0 s	2.19 dd (12.4, 7.6)	47.5 d
9		53.7 s		58.4 s		58.2 s
10	2.11 d (12.0)	43.8 t	1.98 d (12.0)	47.9 t	2.43 d (12.4)	46.4 t
	0.94 d (12.0)		1.51 d (12.0)		1.33 (overlap)	
11		94.7 s		161.5 s		98.0 s
12	1.07 s	28.6 q	1.09 s	29.1 q	1.31 s	28.0 q
13	0.86 d (6.4)	22.0 q	0.95 d (6.4)	20.06 q	0.90 d (6.0)	21.2 q
14	3.36 d (10.0)	72.5 t	3.39 d (10.0)	70.8 t		183.2 s
			3.23 d (10.0)			
15	1.12 s	22.9 q	1.20 s	20.9 q	1.43 s	21.6 q

[a] Measured in acetone-D_6.
[b] Measured in $CDCl_3$.

^1H–1H COSY and HSQC spectra demonstrated the spin system as shown in Figure 1. The gross structure of **1** was established by further HMBC analysis as follows. One quaternary carbon (C-11, δ_C 94.7) showed J^2 correlation to H-8/4 and J^3 correlation to H_2-7, which indicated the existence of ring A (shown in Fig. 1). The occurrence of ring B was deduced from the HMBC interactions between H_3-12 and C-1/2/11 (shown in Fig. 1). HMBCs between H_3-15 and C-8/9/10 as well as from H_3-12 to C-10 unambiguously established ring C (shown in Fig. 1). Meanwhile, the above information demonstrated the linkage positions of Me-12 and Me-15 should be at C-1 and C-9, respectively. In addition, the oxymethylene moiety was attached to C-9 based on the HMBC interactions between H_2-14 and C-8/9/10/15. The other hydroxyl was attached to C-11 from the quaternary carbon resonance feature (δ_C 94.7, C-11). So, the planar structure of **1** was determined as shown in Figure 1 and confirmed by single-crystal X-ray diffraction analysis (Fig. 2A), which also determined the relative stereochemistry of **1**. Thus, the final structure of **1** was determined and named britanlin A.



1 **4**
^1H-^1H COSY HMBC

Figure 1. Key HMBC (H→C) and ^1H–^1H COSY correlations of **1** and **4**.

Compound **3**, $[\alpha]_D^{20}$ −10.1 (*c* 0.1, MeOH), gave a quasi-molecular ion peak at *m*/*z* 235.1 $[M-H_2O+H]^+$ in its positive ESIMS and was assigned a molecular formula of $C_{15}H_{24}O_3$, which was further confirmed by the HRESIMS ion peak at *m*/*z* 235.1698 $[M-H_2O+H]^+$ (calcd 235.1693). The IR spectrum exhibits absorption bonds at 3414 (OH) and 1718 cm^{-1} (C=O). The ^1H and ^{13}C NMR spectral data demonstrated general features similar to those of **1** (Table 1) except for the missing of oxymethylene signals (δ_H 3.36; δ_C 72.5) and the existence of a carboxyl carbon resonance (δ_C 183.2), which implied the C-14 location of a carboxyl group instead of a hydroxyl group. This hypothesis was supported by the correlations from NMR peak at δ_C 183.2 (C-14) to H-8/10 and H_3-15 in the HMBC spectrum. From biogenetic considerations, the relative configurations at C-1/4/5/8/9/11 of compound **3** showed the same as those of **1**, which were further confirmed by the NOESY experiment. Hence, the determined structure of britanlin C was figured out as **3**.

Compound **4**, mp 160–162 °C, $[\alpha]_D^{20}$ −16.2 (*c* 0.1, MeOH), was isolated as colorless crystals in a MeOH–$CHCl_3$ (1:1, v:v) solution. The positive HRESIMS exhibited a protonated molecular ion peak $[M+H]^+$ at 295.1544 (calcd 295.1540), corresponding to a molecular formula of $C_{16}H_{22}O_5$, requiring six degrees of unsaturation. ^1H and ^{13}C NMR and DEPT (Table 2) spectra showed sixteen carbon

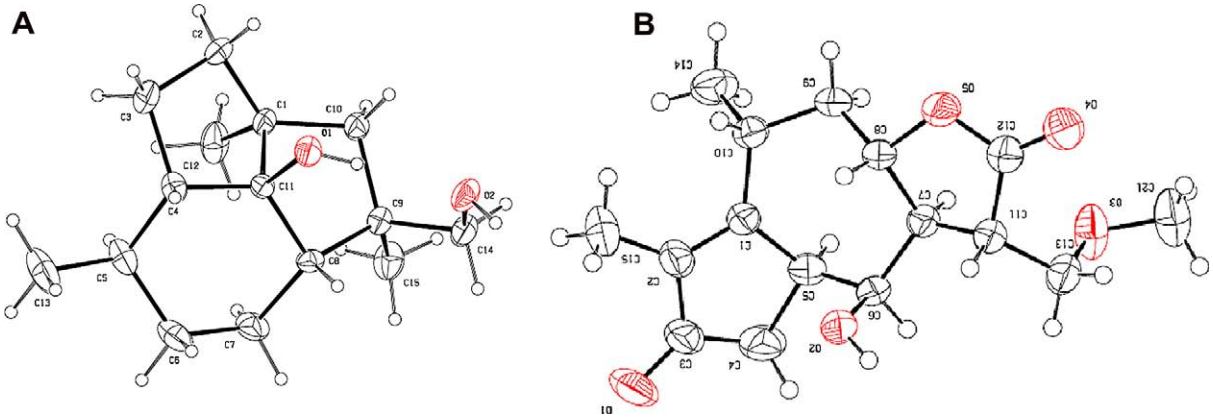


Figure 2. X-ray crystal structures of **1** (**A**) and **4** (**B**).

Table 2
^{1}H and ^{13}C NMR data (400 MHz and 100 MHz, resp.) of compounds **4**[a]

No.	δ_H (J in Hz)	δ_C
1		173.4 s
2		140.7 s
3		208.8 s
4	2.54 d (6.8)	41.7 t
	2.32 d (18.0)	
5	3.16 (overlap)	44.8 d
6	4.13 (overlap)	67.7 d
7	2.41 td (11.2, 2.0)	54.5 d
8	4.13 (overlap)	75.8 d
9	2.53 t (5.6)	38.9 t
	1.74 (overlap)	
10	3.16 (overlap)	32.0 d
11	2.99 dt (12.4, 4.0)	43.8 d
12		175.8 s
13	3.70 m	68.7 t
14	1.41 d (6.8)	21.0 q
15	1.70 s	8.4 q
OCH_3	3.36 s	59.3 q

[a] Measured in $CDCl_3$.

resonances due to three methyls (including one oxymethyl), three methylenes (of which one was oxygenated), six methines (including two oxygenated methines), and four quaternary carbons (including two olefinic carbons and two carbonyls). Detailed analysis of 1D and 2D spectra indicated the spin system as shown in Figure 1. The presence of an α,β-unsaturated carbonyl moiety was suggested by the following spectroscopic data: UV (MeOH) 240 nm; IR (KBr) 1678 and 1624 cm^{-1}; ^{13}C δ_C 173.4 (s), δ_C 140.7 (s) and 208.8 (s). Additionally, a methyl was linked to C-2 (δ_C 140.7) from the diagnostic methyl signal (δ_H 1.70, s; δ_C 8.4, s) and the HMBCs from the methyl signal at δ_H 1.70 (C-15) to the double bond resonances at δ_C 173.4, δ_C 140.7 (C-1 and C-2) and to the carbonyl at δ_C 208.8 (C-3). Further analysis was as follows. In HMBC spectrum, C-3 (δ_C 208.8) showed J^2 correlation to H_2-4 and J^3 correlation to H-5; C-1 (δ_C 173.4) showed J^2 correlation to H-5 and J^3 correlation to H_2-4. The above-mentioned observations indicated the existence of ring A. Ring B was established by the HMBCs between C-1 and H-10/H_3-14. Thus, 4 out of 6 unsaturations were pointed out, considering the IR absorption at 1781 cm^{-1}, a lactone ring was proposed. This view was confirmed by HMBCs from the carbonyl carbon at δ_C 175.8 (C-12) to H-8/H-11/H_2-13. Moreover, the oxymethyl and the hydroxyl group were attached to C-13 and C-6, respectively, based on the NMR data. Thus, the structure of britanlin D was finally determined and further confirmed by single-crystal X-ray diffraction (Fig. 2B), which also established its relative stereochemistry. Britanlin D represented a rare rearranged pseudoguaiane skeleton, which was first discovered from nature. From biogenetic view, this kind of carbon skeleton was biosynthetically formed from the pseudoguaiane skeleton by 1, 3-rearrangement of C-15 from C-5 to C-2.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.129.

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