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Macrophyllidimers A and B, two novel sesquiterpene dimers from the bark of *Inula macrophylla*

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Abstract

Macrophyllidimers A and B, two novel sesquiterpene dimers in whose structures the two sesquiterpene units are connected by a C–C bond directly, have been isolated from the bark of *Inula macrophylla*. Their structures were determined on the basis of spectral evidence. The structure of macrophyllidimer B was finally confirmed by X-ray analysis. The possible biosynthetic pathways of macrophyllidimers A and B are also discussed.

Keywords: Inula macrophylla; Compositae; macrophyllidimers A and B; sesquiterpene dimer; NMR data; X-ray analysis.

The characteristic components of the *Inula* (Compositae) genus are sesquiterpenes (especially eudesmanolide and guaianolide)[1–6] and monoterpenes (thymol derivatives).[7,8] So far, the chemical constituents of *Inula macrophylla* have not been studied. As a part of our continuing study on Uzbekistan plants, in this comunication we wish to report two novel sesquiterpene dimers, named macrophyllidimers A (**1**) and B (**2**), which were isolated from the bark of *I. macrophylla*. Their structures were determined on the basis of spectral evidence, especially by HREIMS and 2D NMR. In the structures of both macrophyllidimers A and B, the two sesquiterpene units are not connected by an ether or an ester group as in general natural dimers, but by a C–C bond directly. The structure of macrophyllidimer B was finally confirmed by X-ray analysis. The possible biosynthetic pathways of macrophyllidimers A and B are also discussed.

The MeOH extract of the powdered air-dried bark (1.6 kg) of *I. macrophylla* was partitioned between H_2O and $CHCl_3$. The $CHCl_3$-soluble fraction was chromatographed over a silica gel column (eluted with *n*-hexane:EtOAc, from 10:1 to 1:1) and further purified by HPLC (*n*-hexane:EtOAc, 7:2) and GPC (general permeation chromatography), to give macrophyllidimers A (**1**) (21 mg) and B (**2**) (23 mg) (Fig. 1).

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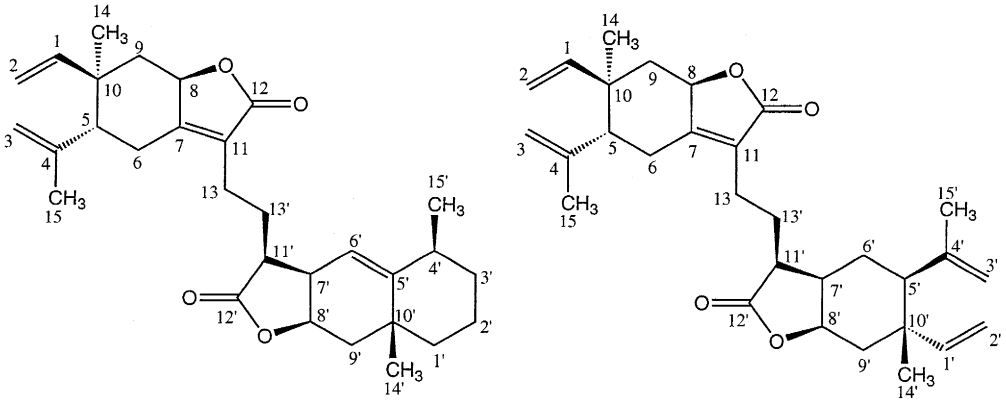
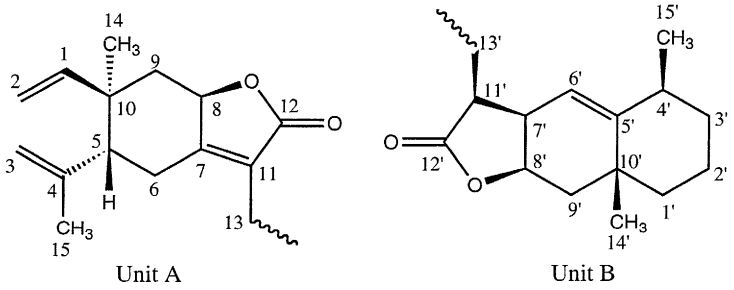


1 **2**

Fig. 1. The structures of compounds **1** and **2**

Macrophyllidimer A (**1**) was obtained as a colorless oil, $[\alpha]_D^{25}$ −87.1 ($CHCl_3$, *c* 0.42). Its HREIMS showed an intensive molecular ion peak at *m/z* 464.2923, which indicated a molecular formula of $C_{30}H_{40}O_4$ (calcd 464.2927). The ^{1}H NMR spectral data (Table 1) of compound **1** displayed the presence of six olefinic protons at δ_H 5.73 (1H, dd, *J*=17.5, 10.8 Hz, H-1), 5.02 (1H, d, *J*=17.5 Hz, H-2) and 4.97 (1H, d, *J*=10.8 Hz, H-2), 4.99 and 4.71 (each 1H, br s, H-3), and 5.28 (1H, d, *J*=2.7 Hz, H-6′), two oxygenated methines at δ_H 4.85 (1H, dd, *J*=12.0, 6.1 Hz, H-8) and 4.70 (1H, m, H-8′), and four methyls at δ_H 1.17 (3H, s, H-14), 1.76 (3H, s, H-15), 1.23 (3H, s, H-14′) and 1.12 (3H, d, *J*=7.5 Hz, H-15′), as well as other signals belonging to other methylenes and methines. The ^{13}C NMR and DEPT spectral data (Table 1) exhibited 30 carbon signals consisting of eight quaternary carbons, eight methines, ten methylenes and four methyls. The characteristic signals of δ_H 5.73 (1H, dd, *J*=17.5, 10.8 Hz, H-1), 5.02 (1H, d, *J*=17.5 Hz, H-2) and 4.97 (1H, d, *J*=10.8 Hz, H-2), 4.99 and 4.71 (each 1H, br s, H-3), and δ_C 146.5 (d, C-1), 112.0 (t, C-2), 114.2 (t, C-3) and 144.6 (s, C-4), suggested the presence of an elemanolide sesquiterpene unit (unit A, Fig. 2) in compound **1**.



Unit A Unit B

Fig. 2. The partial structures of macrophyllidimer A (**1**)

The ^{1}H–^{1}H COSY spectrum of **1** showed the correlations from H-1 to H-2a and H-2b, H-3a to H-3b, H-8 to H-9, and H-5 to H-6. Combined with the observed HMBC correlations from H-8 to C-11, C-12, C-6, C-7, C-9 and C-10, H-13 to C-11, C-12 and C-7, H-15 to C-3, C-4 and C-5, H-14 to C-1, C-5, C-9 and C-10, and H-6 to C-4, C-5, C-7, C-8 and C-10, the structure of the partial structure of unit A was determined.

The remaining signals, except for those of the unit A, are consistent with an eudesmanolide sesquiterpene (unit B, Fig. 2), and its structure was also determined on the basis of the correlations of ^{1}H–^{1}H COSY, HSQC and HMBC.

The connected positions of the above determined two units were established according to the following key correlations: In the ^{1}H–^{1}H COSY spectrum, H-13′ correlated to H-13; in the HMBC spectrum (Fig.

Table 1
The NMR spectral data of compounds **1** and **2**

	1		**2**	
No	δ_H	δ_C	δ_H	δ_C
1	5.73, dd (17.5, 10.8)	146.5 d	5.73, dd (17.5, 10.8)	146.4 d
2	5.02, d (17.5); 4.97, d (10.8)	112.0 t	5.02, d (17.5); 4.97, d (10.8)	112.0 t
3	4.99, br s; 4.71, br s	114.2 t	4.99, br s; 4.73, br s	114.2 t
4		144.6 s		144.6 s
5	2.05, dd (13.2, 4.1)	53.4 d	2.06, dd (13.1, 4.2)	53.3 d
6	2.74, dd (14.2, 4.1), 2.54, dd (14.2, 13.2)	28.7 t	2.72, dd (14.4, 4.0); 2.58, m	28.5 t
7		163.9 s		164.1 s
8	4.85, dd (12.0, 6.1)	78.0 d	4.85, dd (12.2, 6.2)	78.0 d
9	2.22, dd (12.3, 6.1); 1.32, dd (12.3, 12.0)	45.9 t	2.22, dd (12.4, 6.1); 1.33, dd (12.4, 12.0)	45.9 t
10		40.8 s		40.8 s
11		123.4 s		123.3 s
12		174.4 s		174.5 s
13	2.49, br t (7.5)	20.9 t	2.43, br t (7.5)	20.9 t
14	1.17, s	17.2 q	1.17, s	17.1 q
15	1.76, s	24.7 q	1.76, s	24.8 q
1′	1.61, m; 1.09, m	42.4 t	5.73, dd (17.5, 10.8)	148.8 d
2′	1.40-1.44, m	17.0 t	4.96, d (10.8); 4.94, d (17.5)	111.3 t
3′	2.51, m	38.7 t	4.87, br s; 4.61, br s	113.1 t
4′	1.58, m	33.2 d		146.5 s
5′		151.2 s	1.97, dd (12.6, 2.6)	49.7 d
6′	5.28, d (2.7)	115.0 d	1.53, m; 1.47, m	24.4 t
7′	3.15-3.19, m	37.9 d	2.55, m	39.0 d
8′	4.70, m	77.4 d	4.47, m	77.7 d
9′	2.10, dd (14.7, 3.1); 1.53, m	42.9 t	2.02, m; 1.68, m	39.9 t
10′		33.0 s		38.9 s
11′	2.72, m	44.9 d	2.65, m	46.4 d
12′		178.2 s		178.5 s
13′	1.85, m	25.2 t	1.85, m; 1.78, m	24.0 t
14′	1.23, s	28.5 q	1.05, s	18.0 q
15′	1.12, d (7.5)	23.1 q	1.72, s	24.7 q

400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and DEPT. Figures in parentheses are coupling constants in Hz.

3), H-13′ correlated to C-11 and C-13, and H-13 correlated to C-11′ and C-13′. Thus, the units A and B were connected from C-13 to C-13′ by a C–C bond directly.

In the NOESY spectrum of **1**, H-8 correlated to H-14 and H-6α (δ_H 2.54, dd, *J*=14.2, 13.2 Hz), H-5 correlated to H-6β (δ_H 2.74, dd, *J*=14.2, 4.1 Hz) and H-9β (δ_H 2.22, dd, *J*=12.3, 6.1 Hz), H-13 correlated to H-6β and H-13′, H-7′ correlated to H-8′, H-6′, H-11′ and H-9′α (δ_H 1.53, m), and H-14′ correlated to H-15′ and H-9′β (δ_H 2.10, dd, *J*=14.7, 3.1 Hz). The relative configuration of **1** was determined as shown according to these NOESY correlations as well as the study of the coupling constants and the molecular model. Compound **1** was named macrophyllidimer A.

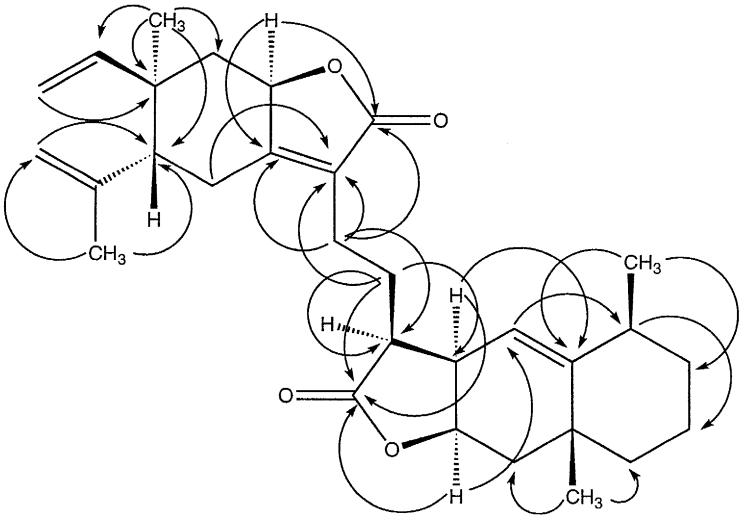


Fig. 3. Selected HMBC correlations of compound **1** H→C

Macrophyllidimer B (**2**) was obtained as colorless needles, $[\alpha]_D^{25}$ −18.7 ($CHCl_3$, *c* 0.60). Its HREIMS (*m/z* 464.2961) gave a molecular formula of $C_{30}H_{40}O_4$ (calcd 464.2927), the same as that of **1**. The NMR spectral data (Table 1) of compound **2** revealed it was also a sesquiterpene dimer, and the partial structure of unit A was the same as that of **1**. However, in compound **2**, analysis of its NMR data and the correlations of 2D NMR (^{1}H–^{1}H COSY, NOESY, HSQC and HMBC) to know the other partial structure (unit B) was still an elemanolide sesquiterpene which was very similar to unit A. The same ^{1}H–^{1}H COSY and HMBC key correlations as those of **1** were observed for compound **2**, and the structure was determined as shown. The relative configuration of **2** was determined on the basis of the observed correlations of H-8 to H-14 and H-6α (δ_H 2.58, m), H-5 to H-6β (δ_H 2.72, dd, *J*=14.4, 4.0 Hz) and H-9β (δ_H 2.22, dd, *J*=12.4, 6.1 Hz), H-13 to H-6β and H-13′, H-7′ to H-8′, H-6′, H-11′ and H-9′α (δ_H 1.68, m), and H-1′ to H-5′ in its NOESY spectrum. Compound **2** was named macrophyllidimer B, and its structure was finally confirmed by X-ray analysis (Fig. 4).[9]

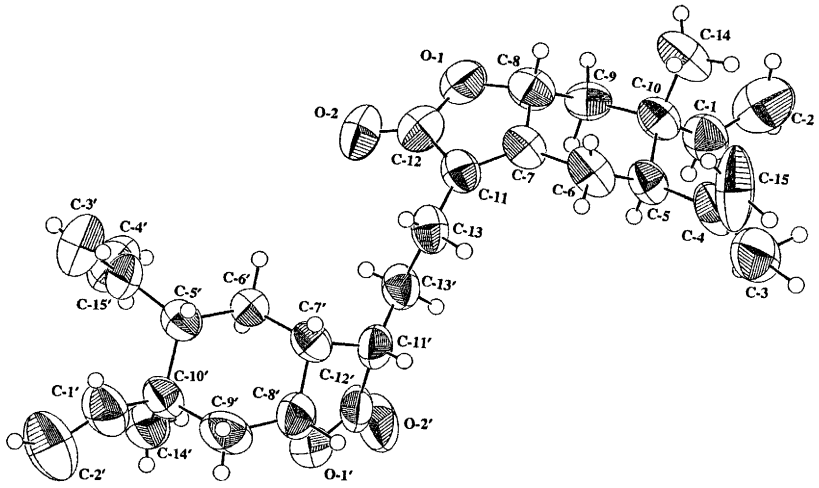


Fig. 4. ORTEP drawing of **2**

We postulate a possible biosynthetic pathway of macrophyllidimer A from the related sesquiterpene units A and B as follows (Fig. 5): Macrophyllidimer B should be derived in the same way as for macrophyllidimer A.

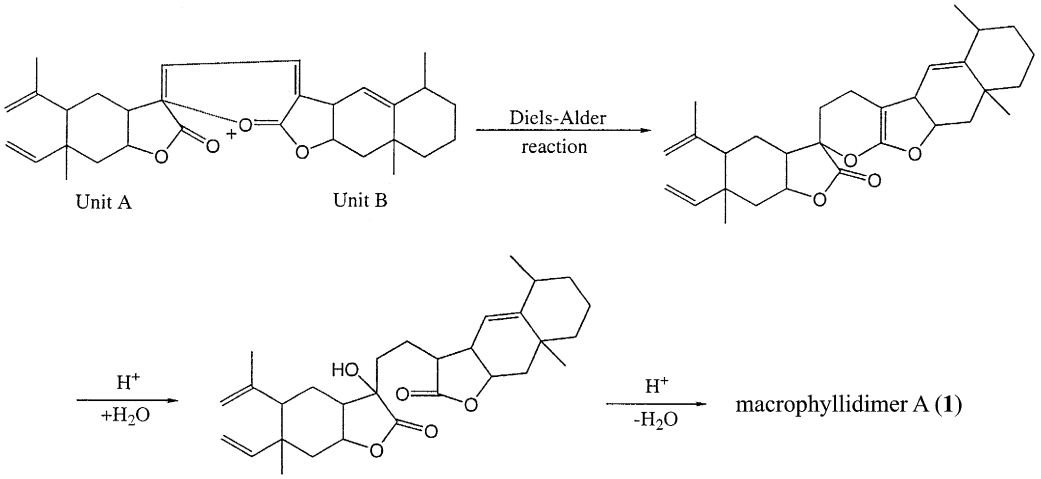


Fig. 5. The possible biosynthetic pathway of macrophyllidimer A (**1**)

References

1. Abu Zarga, M. H.; Hamed, E. M.; Sabri, S. S.; Voelter, W.; Zeller, K.-P. *J. Nat. Prod*. **1998**, *61*, 798–800.
2. Tan, R. X.; Tang, H. Q.; Hu, J.; Shuai B. *Phytochemistry* **1998**, *49*, 157–161.
3. Oksuz, S.; Topcu, G.; Krawiec, M.; Watson, W. *Phytochemistry* **1997**, *46*, 1131–1134.
4. Topcu, G.; Oksuz, S.; Shieh, H.-L.; Gordell, G. A.; Pezzuto, J. M.; Bozok-Johansson, C. *Phytochemistry* **1993**, *33*, 407–410.
5. Oksuz, S.; Topcu, G. *Phytochemistry* **1992**, *31*, 195–197.
6. Goyal, R.; Chhabra, B. R.; Kalsi, P. S. *Phytochemistry* **1990**, *29*, 2341–2343.
7. Marco, J. A.; Sanz-Cervera, J. F.; Manglano, E. *Phytochemistry* **1993**, *33*, 875–878.
8. Bokadia, M. M.; MacLeod, A. J.; Mehta, S. C.; Mehta, B. K.; Patel, H. *Phytochemistry* **1986**, *25*, 2887–2888.
9. X-Ray crystallographic analysis data of macrophyllidimer B (**2**): Monoclinic crystal was obtained from a solvent system of *n*-hexane:EtOAc (5:1). Crystal size=0.50 Å×0.40 Å×0.05 mm, cell parameters: *a*=12.170000 (0) Å, *b*=7.984000 (0) Å, *c*=14.460000 (0) Å, *V*=1373.800049 Å^3, space group $P2_12_12_1$ (*Z*=2). Data collection was performed on a DIP Image plate, and the structure was solved by direct method (maXus SIR92) and the final *R* and *Rw* values were 0.070 and 0.094 for 1636 observed reflections.