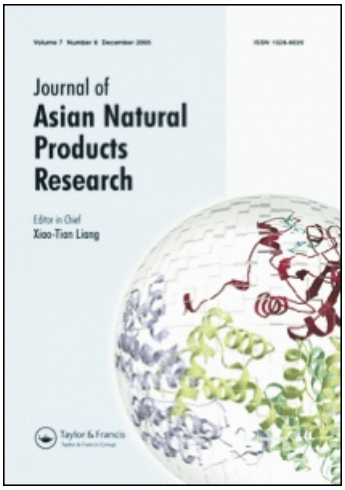

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REARRANGED ABIETANE DITERPENOIDS FROM *CLERODENDRUM MANDARINORUM*

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Five new abietane derivatives which have a commonly rearranged abietane skeleton contained a 17(15 → 16),18(4 → 3)-diabeo-abietane framework, mandarones D–H, were isolated from the stem of *Clerodendrum mandarinorum* Diels (Verbenaceae). The structures were characterized as (16S)-12,16-epoxy-11-hydroxy-17(15 → 16), 18(4 → 3)-diabeo-abieta-3,5,8,11,13-pentaene-7-one (mandarone D, **1**), 12,16-epoxy-11,14-dihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-7-one (mandarone E, **2**), 12,16-epoxy-6,11,14-trihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-7-one (mandarone F, **3**), 12,16-epoxy-11,14-dihydroxy-6-methoxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-2,7-dione (mandarone G, **4**) and 12,16-epoxy-11,14-dihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-1,7-dione (mandarone H, **5**) respectively, mainly based on the spectral analysis and by comparison with those of closely related compounds.

Keywords: *Clerodendrum mandarinorum*; Verbenaceae; Rearranged abietane; Mandarone D; Mandarone E; Mandarone F; Mandarone G; Mandarone H

INTRODUCTION

Clerodendrum mandarinorum Diels is an original plant of one of the traditional Chinese medicines, "Hai Tang". The crude drug has a good reputation in the treatment of infantile paralysis and apoplexy. In a previous

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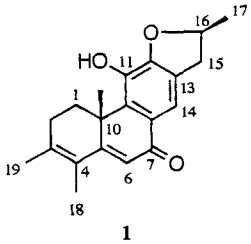
paper we have reported the isolation and characterization of rearranged abietane derivatives, mandarones A–C, from *C. mandarinorum* Diels (Verbenaceae) [1]. Further study of the same plant material allowed the isolation of five new rearranged abietane derivatives (**1**–**5**). In this paper the structural elucidation of **1**–**5** is described.



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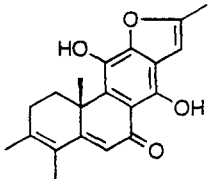

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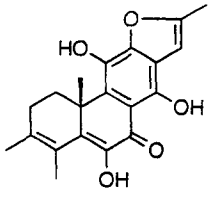

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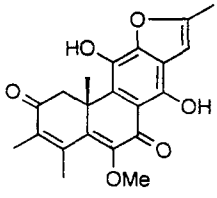

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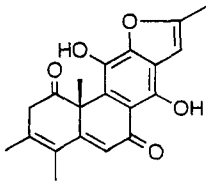

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RESULTS AND DISCUSSION

Repeated column chromatography of a chloroform extract of the stem of *C. mandarinorum* on silica gel resulted in the isolation of compounds **1**–**5**.

Compound **1**, mandarone D, obtained as orange needles, showed a molecular ion [M^+] at *m/z* 314.1884 in the high-resolution mass spectrometry corresponding to the molecular fromula $C_{20}H_{26}O_3$. The NMR spectral data (Tables I and II) were almost identical with those of uncinatone [2], and the presence of a partial structure of 12,16-epoxy-17(15 → 16),18(4 → 3)-diabeo-abieta-7-one was supported. The difference was that uncinatone has two hydroxyl groups at C-11 and C-14, but mandarone D had a hydroxyl group at C-11, because the highly deshielded resonance due to the phenoxyl proton at δ 13.73 in uncinatone disappeared and the phenoxyl proton only was observed at δ 4.82 as well as the HMBC spectrum of mandarone D showed correlations between C-7 (δ 190.4) with H-14 (δ 7.84) and H-6 (δ 6.20). The singlet signal at δ 7.84 assigned to H-14 also suggested that no

TABLE I ^{1}H NMR spectral data of compounds **1–5** (400 MHz, $CDCl_3$, TMS as internal standard)

H	**1**	**2**	**3**	**4**	**5**
1α	1.57 (m)	1.61 (m)	1.58 (m)	2.50 (d)	
1β	3.22 (dd)	3.30 (dd)	3.28 (dd)	4.25 (d)	
2α	2.20 (dd)	2.25 (dd)	2.21 (dd)		2.71 (d)
2β	2.50 (m)	2.54 (m)	2.51 (m)		2.76 (d)
6	6.20 (s)	6.28 (s)			6.27 (s)
14	7.84 (s)				
15α	3.40 (dd)				
15β	2.87 (dd)	6.51 (q)	6.55 (s)	6.58 (s)	6.39 (s)
16α	5.10 (m)				
Me-17	1.51 (d)	2.24 (d)	2.46 (br s)	2.47 (s)	2.43 (s)
Me-18	1.91 (s)[a]	1.92 (s)[b]	1.91 (s)[c]	2.03 (s)	1.98 (s)
Me-19	1.87 (s)[a]	1.88 (s)[b]	1.89 (s)[c]	2.25 (s)	2.14 (s)
Me-20	1.49 (s)	1.53 (s)	1.53 (s)	1.64 (s)	1.66 (s)
OH-6			13.79 (br s)[d]		
OH-11	4.82 (s)[d]	6.60 (s)[d]	4.74 (s)[d]	5.51 (s)	13.72 (s)[d]
OH-14		13.89 (br s)[d]	13.79 (s)[d]	113.74 (s)[d]	10.11 (s)[d]
OMe-6				3.98 (s)	
J (Hz)					
1α,1β	13.8	13.2	13.3	13.7	
2α,2β	14.3	14.6	13.9		14.2
15α,15β	15.6				
15α,16α	9.0				
15β,16α	7.6				
15,17	1.1	1.1			
16α,17	7.0				

[a,b,c] Assignment may be reversed. [d] Exchangeable with D_2O.

TABLE II ^{13}C NMR spectral data of compounds **1–5** (100 MHz $CDCl_3$, TMS as internal standard)

C	**1**	**2**	**3**	**4**	**5**
1	29.5	30.2	30.1	45.4	194.0
2	30.3	30.6	30.8	196.5	34.8
3	141.2	141.2	141.0	132.4	141.5
4	125.6	125.6	125.5	146.3	117.2
5	165.6	165.9	166.0	162.1	167.2
6	117.6	118.8	154.2	123.2	111.9
7	190.4	186.8	190.5	190.2	191.6
8	108.7	107.2	107.4	108.6	109.6
9	132.6	129.5	129.8	135.6	125.6
10	40.7	40.1	39.8	42.4	58.4
11	132.5	142.1	143.8	148.9	141.8
12	155.6	151.7	151.6	150.5	150.1
13	111.3	130.2	131.4	117.3	131.2
14	134.5	154.8	155.1	155.5	154.9
15	33.9	101.8	111.6	100.9	118.8
16	81.9	148.6	148.5	149.8	148.7
17	22.4	22.9	22.7	20.2	22.7
18	16.7	15.6	15.2	15.7	15.1
19	14.9	14.4	14.2	13.7	14.7
20	21.9	20.7	20.8	20.7	20.8

hydroxyl was substituted at C-14. Therefore the hydroxyl group should be substituted at C-11. The CD spectrum [254 nm (+CE), 312 nm (−CE), 335 nm (+CE)] showed that mandarone D possessed a normal abietane S-configuration at C-10 such as uncinatone [2]. Comparison of the δ_H of furan ring of compound **I** with those of teuvincenone A [3] were easily assigned (Table I) to Hα-15, Hβ-15 and H-16 indicated that the signals at δ 3.40 ($J = 15.6$, 9.0 Hz), δ 2.87 ($J = 15.6$, 7.6 Hz) and δ 5.10 ($J = 9.0$, 7.6 Hz). The stereochemistry of a β-methyl furan part was inferred by the literature [3] and biogenesis that may be rational. The structure of mandarone D was then characterized as (16S)-12,16-epoxy-11-hydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13-pentaene-7-one.

Compound **2**, mandarone E, obtained also as orange needles, showed [M^+] at m/z 324.1360 in HREIMS corresponding to the molecular formula $C_{20}H_{20}O_4$. Its UV and NMR spectral data (Tables I and II) were almost in agreement with those of **1**. One difference was consistent with the presence of a 2-methyl-benzo [b] furan moiety in mandarone E [δ 2.24 (3H, d, $J_{17,15} = 1.1$ Hz, Me-17), 6.51 (1H, q, $J_{15,17} = 1.1$ Hz, H-15); δ_C 101.8 (C-15), 148.6 (C-16) f and 22.9 (C-17)] instead of an α-methyldihydrofuran which was condensed with an aromatic ring in **1** [δ 1.51 (3H, d, $J_{17,16\alpha} = 7.0$ Hz, Me-17), 5.10 (1H, m, $J_{16\alpha,15\alpha} = 9.0$ Hz, $J_{16\alpha,15\beta} = 7.6$ Hz, H-16), 3.40 (1H, dd, $J_{15\alpha,15\beta} = 15.6$ Hz, H-15α), 2.87(1H, dd, $J_{15\alpha,15\beta} = 15.6$ Hz, $J_{16\alpha,15\beta} = 9.0$ Hz, H-15β)]. These NMR spectral data indicated that mandarone E must be a 15,16-dehydro derivative of **1**. Another difference from **1** was the presence of a hydroxyl at C-14, which was supported by the appearance of the hydroxyl signal at δ 13.89 and disappearance of aromatic proton signal at δ 7.84 in **1**. The CD spectrum [251 nm (+CE), 302 (−CE), 334 (+CE)] showed that **2** also possessed a normal abietane S-configuration at C-10. Thus the structure of mandarone E was determined to be 12,16-epoxy-11,14-dihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-7-one.

Compound **3**, mandarone F, obtained as orange rectangles, showed [M^+] at m/z 340.1312 in HREIMS corresponding to the molecular formula $C_{20}H_{20}O_5$. The ^{1}H NMR spectrum was almost the same as those of **2**. Mandarone **F** had another hydroxyl group at C-6 compared with **2**, which was supported by appearance of the hydroxyl signal at δ 7.12 and disappearance of an olefinic proton at δ 6.28 assigned to H-6 in **2**. The CD spectrum [252 (+CE), 288 (−CE), 321 (+CE)] showed that **3** also possessed a normal abietane S-configuration at C-10. Therefore the structure of mandarone F was characterized as 12,16-epoxy-6,11,14-trihydroxy-17 (15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-7-one.

Compound **4**, mandarone G, obtained as brown column crystals, showed [M^+] at *m/z* 368.1258 in HREIMS corresponding to the molecular formula $C_{21}H_{20}O_6$. The ^{1}H NMR spectrum revealed the existence of a partial structure of 12,16-epoxy-11,14-dihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-8,11,13-trienc-7-one and was fundamentally the same as those of **3**. However, there were still some differences from **3**. Mandarone G possessed two ketone groups (δ_C 196.5, 190.2) and one methylene group [δ 2.50 (1H, d, J = 13.7 Hz) and 4.25 (1H, d, J = 13.7 Hz)] in the structure. One of the ketones could be substituted as C-1 or C-2. Owing to the strong down-field shift of the methylene group, the proton signal at δ 4.25 must be due to the methylene group substituted at C-1 and the HMBC spectrum showed that the C-5 (δ 162.1) had correlation with H-1α (δ 2.50, 1H, d) and H-1β (δ 4.25, 1H, d). Therefore another ketone group must be at C-2. The partial structure of 12,16-epoxy-11,14-dihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-8,11,13-triene-2,7-dione thus deduced is corresponding to that of teuvincenone F [4], and the NMR spectral data of mandarone G was very similar to those of teuvincenone F. The ^{1}H NMR spectrum showed the presence of a methoxyl group at δ 3.98. Considering the absence of an olefinic proton and the presence of two hydroxyl groups at C-11 and C-14, the methoxyl group was rationally substituted at C-6. The absolute configuration was ascertained by CD spectral data in comparison with those of (16R)-plectrionon A [5,6]. The Cotton effect at 257 (−CE), 282 (+CE) and 345 nm (+CE) showed that mandarone G possessed the same S-configuration at C-10 as (16R)-plectrionon A. Therefore the structure of mandarone G was concluded to be 12,16-epoxy-11,14-dihydroxy-6-methoxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-2,7-dione.

Compound **5**, mandarone H, obtained as yellowish needles, showed [M^+] at *m/z* 338.1152 in HREIMS corresponding to the molecular formula $C_{20}H_{18}O_5$. Mandarone H had two ketone groups in the structure like **4**, but the position was different from that of **4**. In the ^{1}H NMR spectrum, the methylene proton signals were observed at δ 2.71 (1H, d, J = 14.2 Hz) and 2.76 (1H, d, J = 14.2 Hz) in mandarone H, however, the corresponding signals were at δ 2.50 and 4.25 in **4**. The HMBC spectrum showed that one of ketones (δ_C 194.0) had long-range correlations with a methyl δ 1.66 (3H, s, Me-20), a methylene proton δ 2.71 (H-2α) and 2.76 (H-2β). The methine proton (δ 6.27) had long-range correlations with another ketone (δ 191.6, C-7) and C-5 (δ 167.2), the remaining methine proton δ 6.39 (1H, s, H-15) had correlations with C-13 (δ 131.2) and C-16 (δ 148.7). Further long-range coupling between a methyl group δ 2.43 (3H, s, Me-17) and C-16 (δ 148.7) was also observed. These results supported the ketone groups to be located

at C-1 and C-7. The stereochemistry at C-10 was determined by CD spectrum. The negative Cotton effect at 295 and 306 nm showed that the methyl group at C-10 was β-oriented and that the ketone groups were substituted at C-1 and C-7 of an abietane diterpene [7]. Thus the structrue of mandarone H was drawn as 12,16-epoxy-11,14-dihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-1,7-dione.

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were determined on a X_4 apparatus and are uncorrected. UV spectra were taken on Shimadzu UV-265 spectrometer. IR spectra were taken on Impact-410 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruder AM-400 Spectrometer. Mass spectra were measured on Finnigan MAT SSQ 710 spectrometer.

Plant Material

Stems of *C. mandarinorum* Diels cultivated in Lushan Plant Garden of Jiangxi, China were used in the present study.

Extraction and Isolation

The naturally dried and pulverized stems of *C. mandarinorum* (5 kg) were extracted with hot EtOH three times. The solvent was removed in vacuum to yield crude extract (180 g). A certain volume of H_2O was added to the crude extract and the mixture was agitated thoroughly to form a suspension, which was extracted with $CHCl_3$. After evaporation, the $CHCl_3$ extract (80 g) was subjected to column chromatography on silica gel eluting with $CHCl_3$ to give **1** (16 mg), and eluting with an EtOAc–petroleum ether gradient to give **2** (10 mg), **3** (13 mg), **4** (11 mg) and **5** (8 mg).

Compound **1** [mandarone D, (16S)-12,16-epoxy-11-hydroxy-17(15 → 16), 18(4 → 3)-diabeo-abieta-3,5,8,11,13-pentaene-7-one]. m.p. 216-217°C ($CHCl_3$), yellowish needles. $[\alpha]_D$ +51.2 ($CHCl_3$, c, 0.0158), CD: 227(0), 254(+4.74), 289(0), 312(−1.82), 328(0), 335(+3.39) nm, IR ν_{max}^{KBr}: 3320(OH), 1640, 1620, 1600, 1580, 1480, 1360, 1060 cm^{-1}, UV λ_{max}^{MeOH}: 258, 314, 373 nm. ^1H NMR and ^{13}C NMR spectral data are listed in Tables I and II. HREIMS *m/z*: 314.1884 for $C_{20}H_{26}O_3$ (calcd. 314.1883).

Compound **2** [mandarone E, 12,16-epoxy-11,14-dihydroxy-17(15 → 6), 18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-7-one]. m.p. 223–224°C ($CHCl_3$), orange needles, $[\alpha]_D$ +75.5 ($CHCl_3$, c, 0.0171), CD: 213 (−6.76), 228(0), 251(+4.75), 268(0), 274(−0.61), 280(0), 302(−2.32), 312(0), 334 (+3.22) nm, IR ν_{max}^{KBr}: 3400(OH), 1600 (ketone), 1610, 1575, 1480, 1320, 1010 cm^{-1}, UV λ_{max}^{MeOH}: 258, 314, 373 nm. ^1H and ^{13}C NMR spectral data are shown in Tables I and II. HREIMS *m/z*: 324.1360 for $C_{20}H_{20}O_4$ (calcd. 324.1362).

Compound **3** [mandarone F, 12,16-epoxy-6,11,14-trihydroxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-7-one]. m.p. 221–222°C ($CHCl_3$), orange rectangles $[\alpha]_D$ +83.2 ($CHCl_3$, c, 0.0183), CD: 211(−4.41), 231(0), 252(+4.09), 272(0), 288(−2.10), 301(0), 321(+4.48) nm, IR ν_{max}^{KBr}: 3200(OH), 1640 (ketone), 1600, 1580, 1470, 1340, 1000 cm^{-1}. ^1H and ^{13}C NMR spectral data are listed in Tables I and II, respectively. HREIMS *m/z*: 340.1312 for $C_{20}H_{20}O_5$ (calcd. 340.1311).

Compound **4** [mandarone G, 12,16-epoxy-11,14-dihydroxy-6-methoxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-2,7-dione]. m.p. 331°C ($CHCl_3$), brown column crystals, $[\alpha]_D$ +45.1 ($CHCl_3$, c, 0.0171), CD: 210(+0.49), 228(+7.68), 242(0), 257(−5.74), 275(0), 282(+1.81), 307(+0.81), 345(+3.36) nm, IR ν_{max}^{KBr}: 3400 (OH), 1660 (ketone), 1640, 1620, 1600, 1570, 1460, 1290, 1030 cm^{-1}. ^1H and ^{13}C NMR spectral data are listed in Tables I and II, respectively. HREIMS *m/z*: 368.1258 for $C_{21}H_{20}O_6$ (calcd. 368.1260).

Compound **5** [mandarone H, 12,16-epoxy-11,14-dihydroxy-6-methoxy-17(15 → 16),18(4 → 3)-diabeo-abieta-3,5,8,11,13,15-hexaene-1,7-dione]. m.p. 218-220°C ($CHCl_3$), yellowish needles. CD: 272(0), 295(−12.3), 306 (−8.24), 331(0), 348(+4.17) nm, IR λ_{max}^{KBr}: 3300 (OH), 1640 (ketone), 1610, 1575,1480, 1320, 1010 cm^{-1}, UV λ_{max}^{MeOH}: 237, 282 nm. ^1H and ^{13}C NMR spectral data are listed in Tables I and II, respectively. HREIMS *m/z*: 338.1152 for $C_{20}H_{18}O_5$ (calcd. 338.1154).

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