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Three Sesquiterpenes from the Roots and Stems of *Aristolochia Heterophylla* Hemsl with Novel Skeletons

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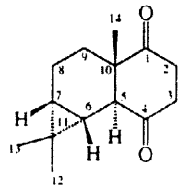
Abstract: Three novel skeleton sesquiterpenes, namely, madolin-F (**1**), -G (**2a**), and -H (**3**), were isolated and characterised from the fresh roots and stems of *Aristolochia heterophylla*. Madolin-F belongs to a novel skeleton, normaaliane type. Madolin-G and -H were constructed from three- and eleven-membered rings and named madolin type.

Aristolochia heterophylla (*A. shimadai*) is a perennial shrub.[1] It has been used as an alternative of the well known traditional Chinese medicine " Madouling " and is used as an expectorant, antitussive, analgesic, antiasthmatic and also for the treatment of snakebite and lung inflammation.[2] Several aristolochic acids and aristolactams were isolated from this plant.[3-7] We are interested in the constituents of this plant due to the pharmacological action of related species of the genus *Aristolochia*.

The methanol extract of *A. heterophylla* was partitioned between H_2O and $CHCl_3$, n-BuOH, successively. Then, the $CHCl_3$ layer was subjected to chromatography through a silica gel column to afford three sesquiterpenes madolin-F(**1**), -G(**2a**) and-H(**3**) with novel skeletons.



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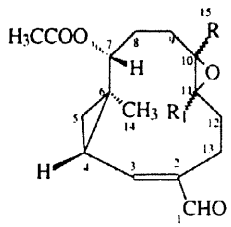
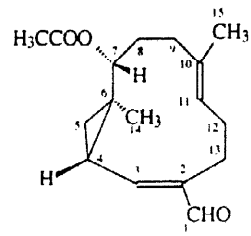


2a R= β-CH_3 R_1= α-H
2b R= CH_3 R_1= H



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Madolin-F (**1**) was obtained as optically active colorless needles. Its molecular formula was determined as $C_{14}H_{20}O_2$ by HREIMS. The presence of two carbonyl carbons at δ 208.4 and 212.9 and the absence of sp^2 and sp carbon in the ^{13}C-NMR spectrum indicated **1** to be a tricyclic compound. The ^{1}H- and ^{13}C-NMR spectra of **1** contained signals for three tertiary methyls, four methylenes, three methines and four quaternary carbons. The

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gross structure of **1** was proved by extensive 2DNMR experiments involving the analyses of its COSY, HMQC, HMBC and NOESY spectra. The stereochemistry of **1** was confirmed by X-ray analysis (Fig.1). Hence structure **1** was established for madolin-F, which was a novel skeleton, normaaliane type.

Table 1: ^{1}H-NMR and ^{13}C-NMR spectral data of compounds **1-3** in $CDCl_3$

compound	1		2		3	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	212.9		193.1	9.26 s	194.0	9.32 s
2	35.9	2.62 td (10.4, 7.2)	143.1		143.5	
		2.74 dd (10.4, 4.3)				
3	36.0	2.79 m	154.5	6.09 d (11.6)	156.7	6.06 d (11.6)
4	208.4		24.0	1.86 ddd (11.6, 9.7, 5.0)	27.9	2.25~2.05
5	48.9	2.35 d (4.9),	24.2	0.75 t (5.0)	25.6	0.79 t (5.2)
				1.24 dd (9.7, 5.0)		1.27, m
6	16.2	1.38 dd (8.8, 4.9)	28.0		28.9	
7	18.5	0.68 t (8.8)	83.2	4.03 d (10.0)	83.4	4.13 dd (9.6, 1.2)
8	14.6	1.65 dd (14.0, 7.2)	27.7	1.54 dd (13.5, 8.9)	29.5	1.57 m
		1.80 ddd (14.0, 8.8, 7.2)		2.05 td (13.5, 10.0)		2.25~2.05
9	30.2	1.17 dd (8.7, 7.2)	37.5	1.22 t (13.5)	38.6	2.25~2.05
		1.75 t (8.7)		2.14 dd (13.5, 8.9)		
10	46.0		61.4		135.2	
11	17.2		68.1	2.77 dd (11.2, 2.6)	127.2	5.29 m
12	15.1	0.89 s	28.8	1.08 ddd (13.4, 11.2, 1.7)	27.4	2.25~2.05
				2.26 ddd (13.4, 6.8, 2.6)		
13	28.7	1.06 s	18.9	2.20 br.d (12.8)	22.9	2.25~2.05
				2.82 dd (12.8, 6.8)		2.80 dd (11.6, 5.7)
14	17.5	0.96 s	14.6	1.31 s	14.9	1.26, s
15			16.2	1.03 s	15.1	1.48 s
16			170.4		170.4	
17			21.3	2.01 s	21.3	2.07 s

Madolin-G (**2a**) was isolated as a colorless oil and was determined to have the molecular formula $C_{17}H_{24}O_4$. The presence of an α,β-unsaturated aldehyde was inferred by IR absorption band at 1678 cm^{-1}, UV spectrum at 253 nm, together with ^{13}C-NMR signals at δ 193.1(s), 154.5(d) and 143.1(s). One acetyl group was observed from IR band at 1726cm^{-1} and NMR signals at δ_H 2.01(3H, s) and δ_C170.4(s) and 21.3(q). One epoxy group was shown by signals at δ 68.1(d) and 61.4(s) in the ^{13}C-NMR spectrum as well as one proton at δ 2.77(1H, dd, J=11.2, 2.6Hz) in the ^{1}H-NMR spectrum. The COSY and HMQC spectra established three structural fragments : -CH_2-CH-CH=C-CHO (A), -O-CH-CH_2-CH_2- (B) and -CH_2-CH_2-CH-C- (C). The skeleton of **2a** was constructed from the HMBC experiment (Fig.2). The ^{2}J and ^{3}J correlations of the quaternary carbon signal at δ 61.4 (C-10) with the protons at δ 2.26 (H-12), 2.14 (H-9) 1.54 (H-8) and 1.03 (H-15) established the connection of fragment B, C and one methyl group at C-10. Other important correlations in the HMBC spectrum of **2a** observed at δ 28.0 (C-6) with δ 1.54 (H-8) and 1.31(H-14); δ 93.2 (C-7), 24.0 (C-4) with δ 1.31 (H-14) suggested that the linkage between fragments A and B were at C-6. In addition, the connection between fragments A and C were determined from the long-range correlations between δ 2.82 (H-13) with δ 154.5 (C-3) and 143.1 (C-2) . Therefore, the plane structure of **2a** was established from the above spectral data. The relative stereochemistry of madolin-G was determined by NOESY experiment (Fig.3). Based on the above analysis, the structure **2a** was assigned for madolin-G, which was also a novel skeleton and named

madolin type.

Madolin-H (**3**) was isolated as an oil. The HRMS showed a $[M]^+$ at m/z 276.1726 corresponding to the molecular formular $C_{17}H_{24}O_3$. The spectral data were similar to those of **2a**. The ^1H and ^{13}C NMR spectra of **3** differ from those of **2a** only a double bond signal at δ 5.29 (1H, m, H-11); δ 127.2 (d, C-11) and 135.2 (s, C-10) instead of an epoxy group in **2a**. Therefore, the structure of madolin-H was suggested as **3**, which was supported by the COSY, HMQC, HMBC (Fig.2) and NOESY (Fig. 3) experiments. Furthermore, epoxidation of **3** with *m*-CPBA at 0 °C yielded **2a** and **2b** (6:1). **2a** was identified as madolin-G by comparison of their spectroscopic data.

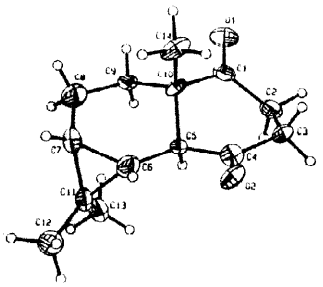

Fig. 1 Structure and Solid-State conformation of madolin-F(**1**); small circles represent hydrogen.

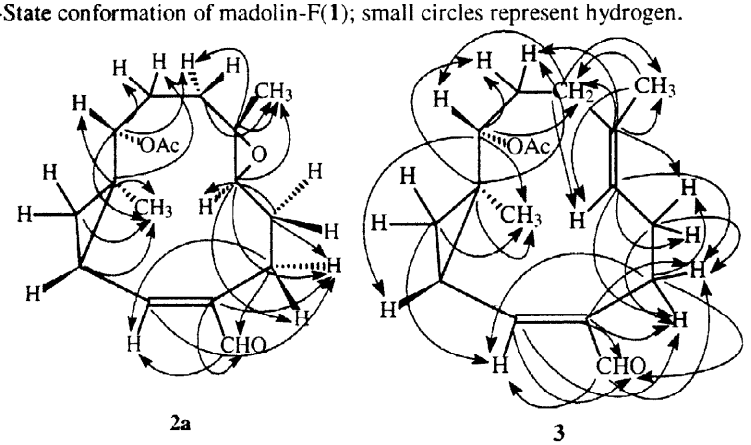

Fig. 2 HMBC experiments for madolin-G(**2a**) and madolin-H(**3**)

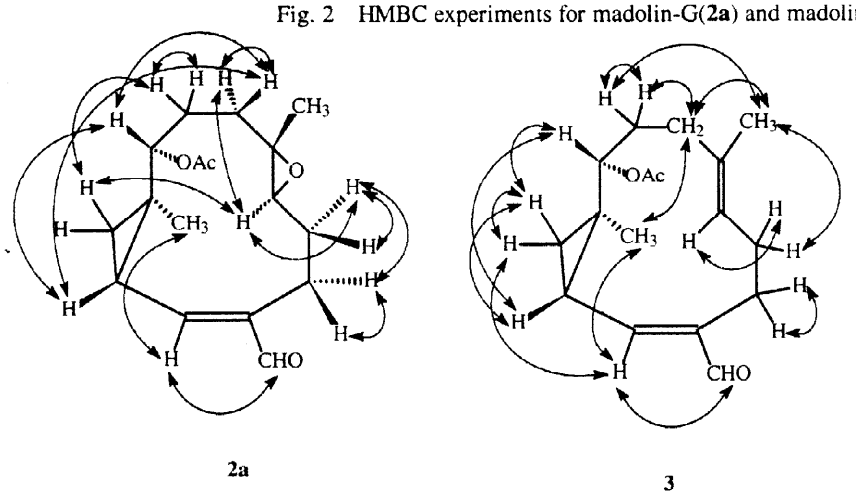

Fig. 3 NOESY experiments for madolin-G(**2a**) and madolin-H(**3**)

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8. **Madolin-F** (**1**): mp. 128-129℃; $[\alpha]_D$ +164.02° (C 0.0378, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 2950, 2862, 1708, 1515; HREIMS: Anal. Calcd. $C_{14}H_{20}O_2$(m/z, M^+ 220.1463), Found 220.1467; EI-MS m/z(rel. int.): 220(M^+, 100), 205(52), 192(57), 177(52), 163(34), 149(36), 121(46), 93(51), 91(30); Crystal data: monoclinic, space group $P2_12_12_1$ a=12.400(3), b=5.905(4), c=16.994(7) Å, U=1242.8(10) $Å^3$, Z=4, Dc=1.177mg m^{-3}, μ(MoK$_\alpha$ radiation, λ=0.7093 Å) crystal dimensions: 0.25×0.22×0.16mm. Intensity data (+h, +k, +l, $2\theta_{max}$=45.0°) were recorded on a Nonius diffractometer. The crystal structure was solved by a direct method. Full-Matrix Least-Squares refinement of atomic parameters (anisotropic C, O; isotopic H) converged at R=0.02 (R_W=0.056) over 531 reflections with $I > 2.5\sigma(I)$.
9. **Madolin-G** (**2a**): $[\alpha]_D$ -121.12° (C 0.0046, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 2926, 2855, 1726, 1678, 1641, 1516, 1454, 1369, 1245, 1020; HREIMS: Anal. Calcd. $C_{17}H_{24}O_4$(m/z, M^+ 292.1674), Found 292.1674; EI-MS m/z(rel. int.): 292(M^+,7), .263(4), 250(26), 232(43), 203(49), 175(58), 147(47), 119(47), 93(67), 91(64), 43(100).
10. **Madolin-H** (**3**): $[\alpha]_D$ -77.51° (C 0.1561, $CHCl_3$); UV λ_{max}^{MeOH} (log ε)nm: 250(3.81); IR ν_{max}^{KBr} cm^{-1}: 2931, 2858, 1735, 1678, 1452, 1371, 1242; HREIMS: Anal. Calcd. $C_{17}H_{24}O_3$(m/z, M^+ 276.1725), Found 276.1726; EI-MS m/z(rel. int.): 276(M^+, 13), 232(10), 216(21), 201(14), 187(48), 173(17), 159(24), 148(40), 131(39), 119(64), 105(73), 93(100), 79(93), 67(77), 55(92).