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Lancifodilactone A, a novel bisnortriterpenoid from *Schisandra lancifolia*

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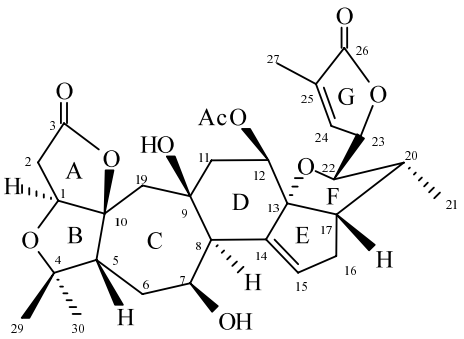
Abstract—A novel bisnortriterpenoid, lancifodilactone A, has been isolated from the leaves and stems of *Schisandra lancifolia*. Its structure and stereochemistry were determined primarily from 1D and 2D NMR spectroscopic data, and were confirmed by a single crystal X-ray analysis.

Much attention has been focused on the family *Schisandraceae* because lignans isolated from this family show various biological activities.[1,2] In recent years, several species have also been reported to contain triterpenoids.[2] Some triterpenoids were found to show anti-HIV activities.[3,4]

Schisandra lancifolia (Rehd. et Wils.) A. C. Smith was commonly used in Chinese traditional medicine to staunch, treat fractures and eliminating stasis to reduce swelling.[5] Its ethanol extracts were reported to contain lignans, 1.7% from the stems and 13.2% from the fruits.[6] Our present search for bioactive compounds from this plant resulted in the isolation of a novel bisnortriterpenoid, lancifodilactone A (**1**). The structure and stereochemistry of compound **1** were established primarily from 1D and 2D NMR spectroscopic data, and were confirmed by a single crystal X-ray analysis.

A 70% aqueous acetone extract of the stems and leaves (1970 g) of *S. lancifolia* was suspended in H_2O and partitioned successively with petroleum ether and EtOAc. The EtOAc layer (31 g) was absorbed on 50 g of silica gel and chromatographed on a prepacked (200 g) silica gel column, eluting stepwise with $CHCl_3$–Me_2CO (1:0–0:1). The $CHCl_3$–Me_2CO (9:1) eluate was subjected to column chromatography over MCI-gel CHP-20P (using MeOH–H_2O as eluent), RP-18 Si gel (using MeOH–H_2O as eluent) and silica gel (using $CHCl_3$–MeOH as eluent), followed by recrystallization from MeOH yielding compound **1** (31 mg).



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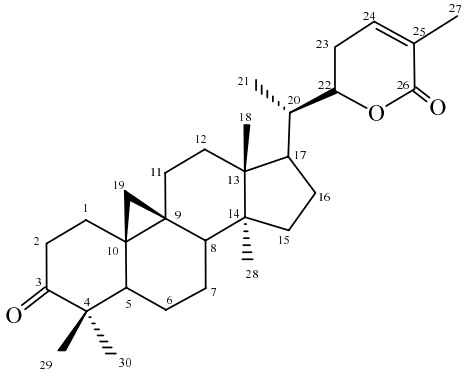

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Table 1. ^{1}H, ^{13}C NMR assignments and HMBC correlations of **1**[a,b]

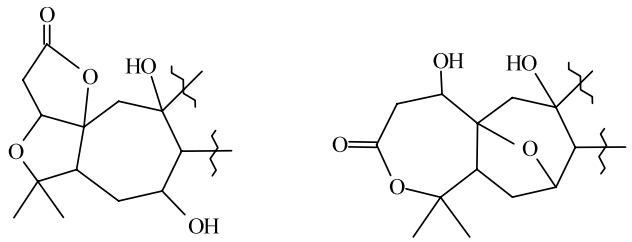
Position	δ_H	δ_C	HMBC (^{1}H–^{13}C)
1	4.17 (1H, d, J=4.6 Hz)	82.1 d	2, 3, 10, 19
2α	2.66 (1H, d, J=17.8 Hz)	36.0 t	1, 3, 10
2β	2.90 (1H, dd, J=4.6, 17.8 Hz)		3
3		175.1 s	
4		84.5 s	
5	3.23 (1H, dd, J=4.2, 13.6 Hz)	52.3 d	4, 6, 10, 29, 30
6α	1.52 (1H, t, J=13.6 Hz)	34.6 t	4, 5, 10
6β	2.05 (1H, overlap)		7
7	4.80 (1H, br s)	69.8 d	5, 6, 9, 14
8	2.62 (1H, br s)	50.8 d	9, 14, 15
9		76.0 s	
10		98.7 s	
11α	2.18 (1H, dd, J=2.2, 15.2 Hz)	41.4 t	9, 13
11β	2.26 (1H, dd, J=2.2, 15.2 Hz)		8, 19
12	5.29 (1H, br s)	73.5 d	9, 13, 14, -OAc-C=O
13		95.8 s	
14		140.7 s	
15	6.24 (1H, br s)	129.1 d	8, 13, 14, 16, 17
16	2.35 (2H, m)	31.7 t	14, 15, 17, 20
17	2.90 (1H, m)	45.6 d	12, 14, 15, 16, 20, 22
19α	2.08 (1H, ABd, J=15.3 Hz)	46.5 t	1, 8, 9, 10, 11
19β	2.02 (1H, ABd, J=15.3 Hz)		1, 8, 9, 10, 11
20	2.39 (1H, m)	37.7 d	16, 17, 21, 22
21	0.93 (3H, d, J=6.8 Hz)	12.4 q	17, 20, 22
22	3.66 (1H, dd, J=3.8, 10.0 Hz)	82.9 d	21
23	5.14 (1H, br s)	81.0 d	26
24	7.27 (1H, br s)	146.9 d	23, 25, 26, 27
25		130.6 s	
26		174.1 s	
27	1.83 (3H, s)	10.8 q	23, 24, 25, 26
29	1.22 (3H, s)	28.8 q	4, 5, 30,
30	1.04 (3H, s)	22.7 q	4, 5, 29
OAc	1.94 (3H, s)	21.3 q	
		170.4 s	

[a] Spectra were recorded in C_5D_5N on a Bruker AM-400 MHz spectrometer (^{1}H,^{13}C) and Bruker DRX-500 MHz spectrometer (HMBC), chemical shifts (δ) are in ppm and J in Hz.

[b] Me-18 and Me-28 are not present in lancifodilactone A (the numbering is based on kadsulatone **2**[8]).

Lancifodilactone A (**1**) was obtained as colorless needles. Its EI MS[7] showed a weak molecular ion peak at m/z 558 ($[M]^+$, 2%), and a base peak at m/z 498 ($[M-AcOH]^+$). HREI MS established the molecular formula as $C_{30}H_{38}O_{10}$ (found 558.2466, calcd 558.2465), indicating twelve degrees of unsaturation in the molecule. The ^{1}H NMR (Table 1) showed the presence of an acetyl methyl, a secondary methyl and three tertiary methyls. The ^{13}C NMR indicated that **1** possessed three ester groups, six quaternary carbons including two olefinic carbons and four oxygenated carbons, eleven methines including two olefinic carbons and five oxygenated carbons, five methylenes and five methyls, which suggested a highly oxygenated triterpene skeleton. As triterpenoids previously isolated from *Schisandraceae* were basically cycloartane-type (see the characteristic structure of kadsulactone **2**[8]), it was possible to recognize that the methyl groups at δ_H 0.93 (d, J=6.8 Hz), 1.83 (s), 1.22 (s) and 1.04 (s) correspond to Me-21, Me-27, Me-29 and Me-30 of a cycloartane skeleton.[9] A detailed HMBC (Table 1) and ^{1}H–^{1}H COSY analysis identified the presence of rings C, D and E. All the above data, along with the lack of a cyclopropyl group suggested that **1** possessed a 9,10-*seco*-cycloartane skeleton.

In the HMBC spectrum, both Me-29 and Me-30 showed correlations with C-4 (δ 84.5, s) and C-5 (δ 52.3, d). The signals of H-1 (δ 4.17), H_2-2 (δ 2.66/2.90), H-5 (δ 3.23), H_2-6 (δ 1.52/2.05) and H_2-19 (δ 2.02/2.08) showed cross peaks with C-10 (δ 98.7, s). Furthermore, H-1 and H_2-2 correlated with a lactone carbonyl group at C-3 (δ 175.1, s). These spectroscopic data suggested



I **II**

Figure 1. Two possible partial structures of rings A, B and C.

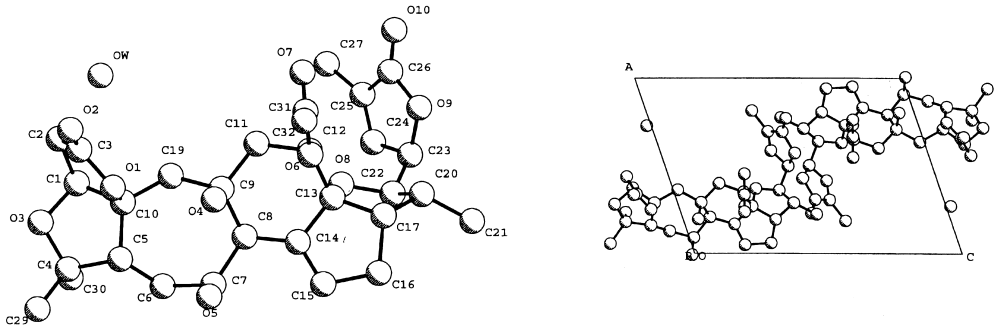


Figure 2. X-Ray structure of **1** showing the relative configuration.

that **1** had suffered an oxidative cleavage between C-3 and C-4 to give either **I** or **II** (Fig. 1). Although **1** possesses a 3,4:9,10-*seco*-cycloartane skeleton, the angular methyl signals attached to C-13 (Me-18) and C-14 (Me-28) were obviously absent in the case of **1**.

The above spectroscopic evidence indicated that **1** was a 13,14-bisnortriterpene. These assignments were confirmed by ^{1}H–^{1}H COSY and HMBC analysis. Cycloartane derivatives isolated from *Schisandraceae* usually possess a side chain with an $\Delta^{24,25}$ double-bond and a carboxyl group at C-27 or a six-membered α-methyl-α,β-unsaturated-δ-lactone.[3,4,8,9] However, the characteristic signals for the above-mentioned side chain were absent in the MS spectrum (m/z 111 $[M-C_6H_7O_2]^+$)[4] of **1**. The MS fragments at m/z 461 $[M-C_5H_5O_2]^+$, m/z 401 $[M-AcOH-C_5H_5O_2]^+$ and m/z 97 $[C_5H_5O_2]^+$, suggested the presence of a five-membered α-methyl-α,β-unsaturated-γ-lactone ring (ring G). HMBC also showed that H-23 (δ 5.14) correlated with a lactone carbonyl group (C-26, δ 174.1), which confirmed the presence of a five-membered lactone between C-23 and C-26. The acetoxy group was attached to C-12 because H-12 (δ 5.29, br s) showed a cross peak with the acetyl carboxyl carbon at δ 170.4 (s). The oxymethine signal at δ_H 4.80, attributable to H-7, showed cross signals with C-5, C-6 (δ 34.6, t) and C-9 (δ 76.0, s), respectively, indicating a hydroxyl group (δ 6.40, 1H, br s) at C-7. As required by its molecular formula, another oxygenated substituent should be a hydroxyl group at the C-9 position.

The relative stereochemistry of **1** was established by a 2D ROESY experiment. Stereochemically, Me-29 was biogenetically β, Me-30 and Me-21 were α. The cross peaks observed between Me-30 and H-1, Me-29 and H-5, H-12 and H-17, H-17 and H-20, indicated that H-1 had the α-orientation and H-5, OAc-12, H-17 and H-20 had β-orientations. H-7 and H-8 showed mutual correlations, but no cross peaks with H-5β, suggesting that H-7 and H-8 had α-orientations. The stereochemistry of H-22 corresponded to the α-orientation giving a cross peak with Me-21.

However, the NMR spectra, including the 2D NMR spectra, did not provide sufficient information to elucidate the pattern of connection of rings A, B and C. Furthermore, as C-10 and C-13 were fully substituted carbons, the σ-bond between C-22 and C-23 can rotate freely, the stereochemistry of C-10, C-13 and C-23 was also unclear. A single crystal X-ray diffraction analysis was thus used to solve this problem[10] (Fig. 2). It indicated that an oxidative cleavage between C-3 and C-4 had produced a five-membered lactone ring (ring A) and a tetrahydrofuran ring (ring B). The relative stereochemistry of C-10, C-13 and C-23 corresponded to the *S*, *R* and *R* configurations.

The natural product, lancifodilactone A is structurally unique among the triterpenoids previously found in *Schisandraceae* species.

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7. Lancifodilactone A (**1**): colorless needles. Mp: 178–179°C; $[\alpha]_D^{22.9}$: +33.20 (*c* 0.24, C_5H_5N); UV (MeOH) λ_{max} (log ε): 207 nm (3.94); IR (KBr) ν_{max}: 3520, 3440, 2970, 2926, 2862, 1758, 1651, 1635, 1442, 1375, 1227, 1112, 1045, 954, 857, 805 cm^{-1}; ^{1}H and ^{13}C NMR, data see Table 1; EI MS (70 eV) m/z $[M]^+$ 558 (2), 540 (3), 498 (100), 480 (12), 461 (9), 437 (11), 421 (20), 401 (12), 383 (18), 360 (10), 341 (25), 323 (25), 300 (11), 283 (23), 265 (8), 245 (8), 197 (10), 185 (16), 137 (44), 123 (13), 109 (12), 97 (16), 81 (9), 69 (12); HREI MS m/z $[M]^+$ 558.2466 (calcd for $C_{30}H_{38}O_{10}$, 558.2465).
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10. X-Ray crystallographic analysis. A colorless prism fragment of dimension 0.10×0.15×0.50 mm was used for data collection. Crystal data: $C_{30}H_{38}O_{10}\cdot H_2O$, $M=558.63$, monoclinic space group, $P2_1$, $a=10.624(1)$, $b=9.272(1)$, $c=15.262(1)$ Å, $\beta=109.23(1)°$, $V=1419.5(3)$ Å^3, $Z=2$, $d=1.354$ g cm^{-3}. Intensity data were recorded on a MAC DIP-2030K diffractometer with a graphite monochromator (ω–2θ scans, $2\theta_{max}=50.0°$), Mo Kα radiation. The total number of independent reflections measured was 2458, of which 2456 were observed ($|F|^2 \geq 8\sigma|F|^2$). The crystal structure was solved by direct methods using SHELX-86[11] and expanded using difference Fourier techniques, refined by the program and method NOMCSDP[12] and full-matrix least-squares calculations. Hydrogen atoms were fixed at calculated positions. The final indices were $R_f=0.079$, $R_w=0.074$ ($w=1/\sigma|F|^2$). Crystallographic data for the structure has been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 206588). Copies of this data can be obtained, free of charge, on application to the CCDC via www.ccdc.cam.ac.uk/conts/retrieving.html (or 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk).
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