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Micrandilactone A: A Novel Triterpene from *Schisandra micrantha*

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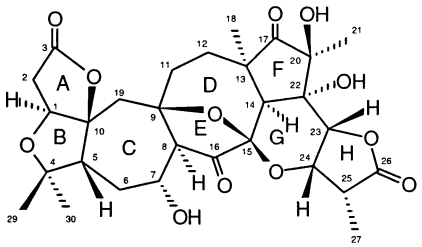
ABSTRACT



A novel nortriterpene, micrandilactone A, was isolated from the medicinal plant *Schisandra micrantha*. This is the first example of an unusual, natural, highly oxidized cycloartane skeleton with a biosynthetically modified eight-membered ring D isolated from the family Schisandraceae.

Plants belonging to the family Schisandraceae are known to be a rich source of lignans, especially dibenzocyclooctadiene lignans with various biological activities.[1,2] In recent years, triterpenoids showing anti-HIV activities[3,4] and inhibitory activities toward cholesterol biosynthesis[5−8] have also been isolated from this family.

Schisandra micrantha A. C. Smith, a plant indigenous to Yunnan Province of China, was traditionally used for the treatment of rheumatic lumbago and traumatic injury and related diseases.[9] It has been reported that the stems of *S. micrantha* contained a small amount of lignans.[10] In our search for new, potentially biologically active constituents from this family, we investigated the chemical constituent of the stems and leaves of *S. micrantha*. In present study, a novel nortriterpene, micrandilactone A (**1**), which presented an unprecedented highly oxidized, rearranged cycloartane skeleton, was isolated from this plant. This paper describes the structural elucidation of **1** by spectroscopic data in conjunction with single-crystal X-ray analysis.

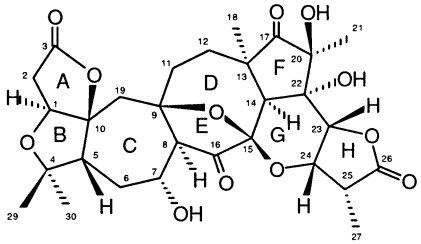


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Table 1. ^{1}H and ^{13}C NMR Assignments and HMBC Correlations of **1**[a]

no.	δ_H (mult, J, Hz)	δ_C	HMBC (^{1}H−^{13}C)	ROESY (^{1}H−^{1}H)
1	4.22 (d, 6.3)	81.4	3, 10, 19	2α, 2β, 19α, 19β, 30
2α	2.74 (d, 18.6)	35.0	1, 3, 10	1, 2β
2β	2.93 (dd, 6.3, 18.6)		3	1, 2α
3		175.2		
4		83.9		
5	2.47 (dd, 4.2, 13.4)	58.3	4, 10	7, 29
6α	2.09 (m)	36.4	7, 8	8, 19α, 30
6β	2.21 (overlap)		5, 7	7
7	4.51 (dd, 9.3, 10.1)	67.8	5, 16	5, 6β
8	2.99 (d, 10.1)	59.7	6, 7, 9, 15, 16, 19	6α, 12α
9		82.2		
10		95.6		
11β	1.79 (m)	42.3	13	8
11β	1.98 (m)		9, 19	
12α	1.67 (m)	32.6	13, 17	8, 12β
12β	1.98 (overlap)		14	12α
13		49.3		
14	3.31 (s)	54.1	13, 15, 16, 17, 18, 20, 22	18
15		99.7		
16		207.4		
17		220.7		
18	1.58 (s)	30.8	12, 13, 14, 17	14, 21
19α	2.52 (ABd, 15.8)	41.8	9	1, 11α, 19β, 30
19β	2.23 (ABd, 15.8)		9, 10, 11	1, 11β, 19α
20		80.2		
21	1.77 (s)	18.9	17, 20, 22	23
22		75.5		
23	4.99 (d, 1.5)	76.8	14, 20, 22, 24	21, 24, 25
24	5.42 (dd, 1.5, 2.0)	75.2	23, 26	23, 25, 20-OH
25	3.26 (m)	42.5	26	23, 24, 27
26		177.5		
27	1.17 (d, 7.1)	7.8	24, 25, 26	25
29	1.24 (s)	27.7	4, 5, 30	5
30	1.04 (s)	20.8	4, 5, 29	1, 6α, 19α
20-OH	5.90 (s)		17, 20, 21, 22	24
22-OH	7.56 (s)		20	14

[a] Data were recorded in C_5D_5N on Bruker AM-400 MHz (^{1}H, ^{13}C) and Bruker DRX-500 MHZ spectrometers (HMBC, ROESY); chemical shifts (δ) are given in parts per million.

Micrandilactone A (**1**) crystallized as colorless prisms and has the molecular formula of $C_{29}H_{36}O_{12}$ as deduced by its HREI MS (found 576.2178, calcd 576.2207), requiring 12 degrees of unsaturation. The IR spectrum showed absorptions at 3439 and 1776 cm^{-1}, revealing the presence of hydroxyl and γ-lactone groups.[11] The ^{1}H NMR (Table 1) spectrum exhibited signals due to four tertiary methyls and a secondary methyl. The ^{13}C NMR spectrum indicated that **1** contained two ester groups, two carbonyl groups, seven quaternary carbons (including six oxygenated ones), eight methines (including four oxygenated ones), five methylenes, and five methyls, which suggested a highly oxygenated triterpene skeleton. Since the NMR data of **1** were quite distinctive from those of the known triterpene skeleton, the possible structure of **1** was first established by a detailed analysis of two-dimensional NMR spectroscopic data. The still uncertain structural details were clarified by a single-crystal X-ray analysis.

Interpretation of HMBC data showed the following correlations (Table 1): Me-29 (δ 1.24, s) and Me-30 (δ 1.04, s) with C-4 and C-5; H-1 (δ 4.22), H_2-2 (δ 2.74/2.93), and H-5 (δ 2.47) with C-10; H-1 and H_2-2 with an ester group at C-3; H-8 (δ 2.99) with C-9 and C-19; and H_2-19 (δ 2.23/2.52) with C-9 and C-10. This, along with two proton spin systems deduced from COSY correlations, H-1−H-2 and H-5−H-8 (Supporting Information), led to the establishment of partial structure **1a** (Figure 1). A methyl singlet resonance at δ 1.58 corresponding to Me-18 showed HMBC cross-peaks with a quaternary carbon (C-13) and with C-12, C-14, and C-17, which required that C-12, C-14, and C-17 all be attached to the carbon (C-13) bearing the methyl group. This was confirmed by the observations of correlations between the methine at δ 3.31 (H-14, s) and C-13, C-17, and C-18. Another methyl singlet resonance at δ 1.77 (Me-21) also showing HMBC correlations with the other two oxygenated quaternary carbons (C-20 and C-22) and a ketone carbon (C-17) suggested that the quaternary carbon (C-20) bearing the methyl group (Me-21) was situated between C-17 and C-22. Furthermore, correlations of H-14 with C-20 and C-22 established the connection of C-14 with C-22. Additional COSY correlations (H_2-11−H_2-12) not only established the attachment of C-11−C-12 but also gave rise to partial structure **1b**. The third fragment, **1c**, was assigned by a continuous sequence from C-23 to C-26 and Me-27 deduced from COSY and HMBC spectra, as well as by the characteristic IR spectral γ-lactone group absorption (1776 cm^{-1}).[11] A hydroxyl group (δ 5.90) was assigned as 20-OH for its cross-peaks with C-17, C-20, C-22, and Me-21. In the same manner, another hydroxyl group (δ 7.56) was proven to be located at C-22 by its correlation to C-20. Moreover, HMBC correlations observed between H_2-19 and C-9 and C-11 and between H_2-11 (δ 1.79/1.98) and C-9 and C-19 allowed the combination of **1a** and **1b** to afford **1d**. Further, correlations of H-23 to C-14, C-20, and C-22 required direct connection of C-23 with C-22 and permitted fragments **1c** and **1d** to be joined to one another to get **1e**.

Up to now, the above NMR spectroscopic data analysis has elucidated the constitution of partial structure **1e**. However, no additional HMBC connectivities necessary for constructing the structure of **1** were observed among the three oxygenated methines (C-1, C-7, and C-24). In addition, because C-3, C-4, C-9, C-10, C-15, and C-16 were quaternary carbons, it was not possible to determine the correct connections among these carbons.

Since it was difficult to elucidate the complete structure of **1** only by NMR spectroscopic analysis, the crystals were

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(12) Crystal data: $C_{29}H_{36}O_{12}\cdot H_2O$, M = 576.60, orthorhombic system, space group $P2_12_12_1$, a = 10.9000(2), b = 15.5290(5), c = 16.7270(5) Å, V = 2831.31(13) Å^3, Z = 4, d = 1.395 g/cm^3. A crystal of dimensions 0.20 × 0.20 × 0.50 mm was used for measuremets 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 2782, of which 2780 were observed ($|F|^2 \geq 8\sigma|F|^2$). The crystal structure was solved by the direct method SHELX-86 (Sheldrick, G. M. University of Gottingen: Gottingen, Germany, 1985) and expanded using difference Fourier techniques, refined by the program and method NOMCSDP (Lu, Y.; Wu, B. M. *Chin. Chem. Lett.* **1992**, *3*, 637−640) and full-matrix least-squares calculations. Final indices: R_f = 0.058, R_w = 0.062 ($w = 1/\sigma|F|^2$).

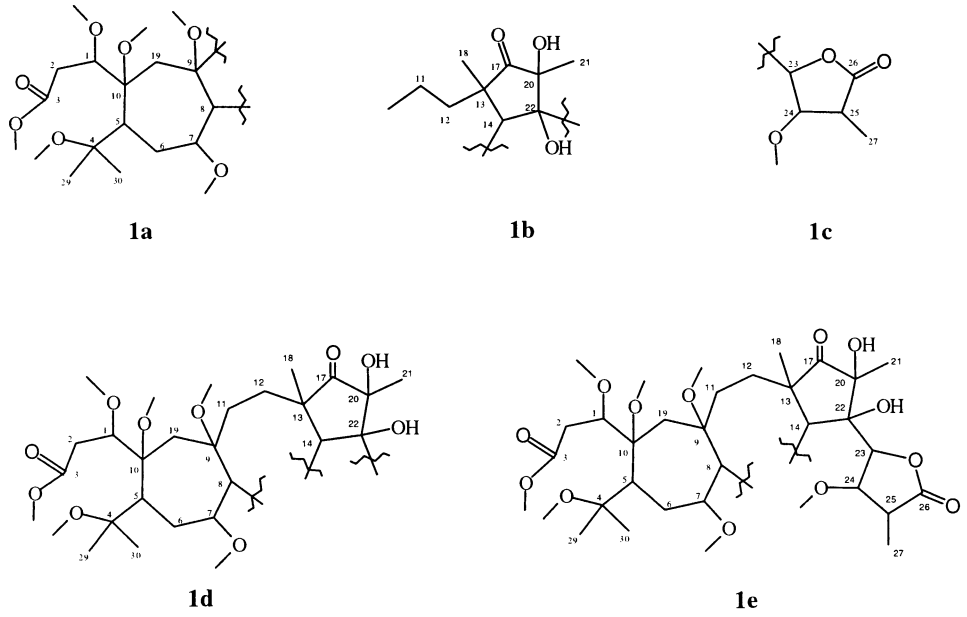

Figure 1. Structural fragments of **1**.

submitted to a single-crystal X-ray diffraction.[12] A view of the solid-state conformation was provided in Figure 2. It indicated that **1** had suffered an oxidative cleavage between C-3 and C-4, followed by lactonization, to give rise to a five-membered lactone ring A and a tetrahydrofuran ring B. C-9 connected to C-15 through an oxygen bridge with the hydroxyl group located at C-7. The signal due to the angular methyl attached to C-14 (Me-28) was obviously absent in the case of **1**, which suggested that Me-28 had suffered an oxidation to form a carboxylic group, followed by loss of CO_2. Thus, the basic skeleton of **1** was elucidated as 3,4: 9,10-*seco*-14-norcycloartane.

The relative stereochemistry of **1** was determined by a two-dimensional ROESY experiment and confirmed unequivocally by X-ray crystallographic data. Stereochemically, Me-29 was biogenetically β-oriented, while Me-30 and Me-21 were α-oriented. ROESY correlations for Me-30/H-1, Me-29/H-5, H-5/H-7, 20-OH/H-24, and H-24/H-23, H-25 indicated that H-1 was α-oriented, while H-5, H-7, H-23, H-24, and H-25 possessed the same β-orientations. Me-18 and H-14 showed mutual correlations but no cross-peaks with H-23, suggesting that H-14 and Me-18 were α-oriented. H-8 was suggested to be α-oriented considering the coupling constant (1H, d, $J_{7,8}$ = 10.1 Hz). The stereochemistry of the four quaternary carbons C-9, C-10, C-15, and C-22 was deduced as *R*, *S*, *R*, and *S*, respectively, by X-ray diffraction study.

The skeletal type displayed by compound **1** is noticeable for its unusual oxidative cleavages between C-16 and C-17 to form an altered carbon framework between rings D and F, which represents a new group of cycloartane. This is the first example of a unique natural norcycloartane skeleton with

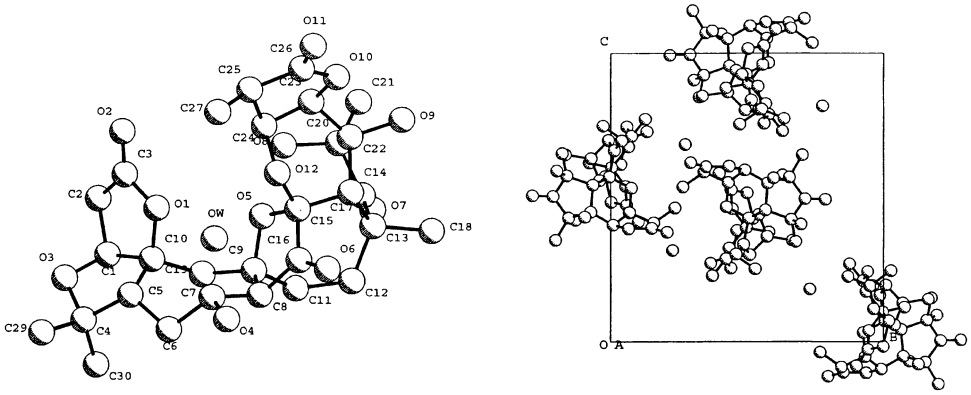

Figure 2. X-ray structure of **1** showing relative configuration.

a biosynthetically modified eight-membered ring D isolated from the family Schisandraceae.

Supporting Information Available: ^{1}H and ^{13}C NMR, $^{1}H-^{1}H$ COSY, HMQC, HMBC, and ROESY spectra and physical constants for micrandilactone A (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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