

Micrandilactone A: A Novel Triterpene from *Schisandra micrantha*

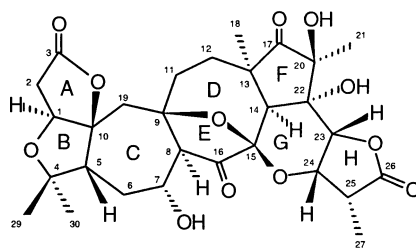
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ABSTRACT

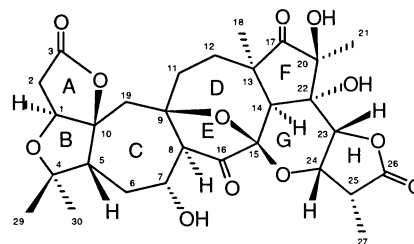


A novel nortriterpene, micrandilactone A, was isolated from the medicinal plant *Schisandra micrantha*. This is the first example of an unusual, natural, highly oxidized cycloartane skeleton with a biosynthetically modified eight-membered ring D isolated from the family Schisandraceae.

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

no.	δ_{H} (mult, J , Hz)	δ_{C}	HMBC (^1H – ^{13}C)	ROESY (^1H – ^1H)
1	4.22 (d, 6.3)	81.4	3, 10, 19	2 α , 2 β , 19 α , 19 β , 30
2 α	2.74 (d, 18.6)	35.0	1, 3, 10	1, 2 β
2 β	2.93 (dd, 6.3, 18.6)		3	1, 2 α
3		175.2		
4		83.9		
5	2.47 (dd, 4.2, 13.4)	58.3	4, 10	7, 29
6 α	2.09 (m)	36.4	7, 8	8, 19 α , 30
6 β	2.21 (overlap)		5, 7	7
7	4.51 (dd, 9.3, 10.1)	67.8	5, 16	5, 6 β
8	2.99 (d, 10.1)	59.7	6, 7, 9, 15, 16, 19	6 α , 12 α
9		82.2		
10		95.6		
11 β	1.79 (m)	42.3	13	8
11 β	1.98 (m)		9, 19	
12 α	1.67 (m)	32.6	13, 17	8, 12 β
12 β	1.98 (overlap)		14	12 α
13		49.3		
14	3.31 (s)	54.1	13, 15, 16, 17, 18, 20, 22	
15		99.7		
16		207.4		
17		220.7		
18	1.58 (s)	30.8	12, 13, 14, 17	14, 21
19 α	2.52 (ABd, 15.8)	41.8	9	1, 11 α , 19 β , 30
19 β	2.23 (ABd, 15.8)		9, 10, 11	1, 11 β , 19 α
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, 6 α , 19 α
20-OH	5.90 (s)		17, 20, 21, 22	24
22-OH	7.56 (s)		20	14

^a Data were recorded in $\text{C}_5\text{D}_5\text{N}$ on Bruker AM-400 MHz (^1H , ^{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 $\text{C}_{29}\text{H}_{36}\text{O}_{12}$ 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 ^1H 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.

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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), H₂-2 (δ 2.74/2.93), and H-5 (δ 2.47) with C-10; H-1 and H₂-2 with an ester group at C-3; H-8 (δ 2.99) with C-9 and C-19; and H₂-19 (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 (H₂-11–H₂-12) 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 H₂-19 and C-9 and C-11 and between H₂-11 (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

(12) Crystal data: $\text{C}_{29}\text{H}_{36}\text{O}_{12} \cdot \text{H}_2\text{O}$, $M = 576.60$, orthorhombic system, space group $P2_12_12_1$, $a = 10.9000(2)$, $b = 15.5290(5)$, $c = 16.7270(5)$ Å, $V = 2831.31(13)$ Å³, $Z = 4$, $d = 1.395$ g/cm³. A crystal of dimensions $0.20 \times 0.20 \times 0.50$ mm was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator (ω - 2θ scans, $2\theta_{\text{max}} = 50.0^\circ$), Mo K α 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: $R_f = 0.058$, $R_w = 0.062$ ($w = 1/\sigma|F|^2$).

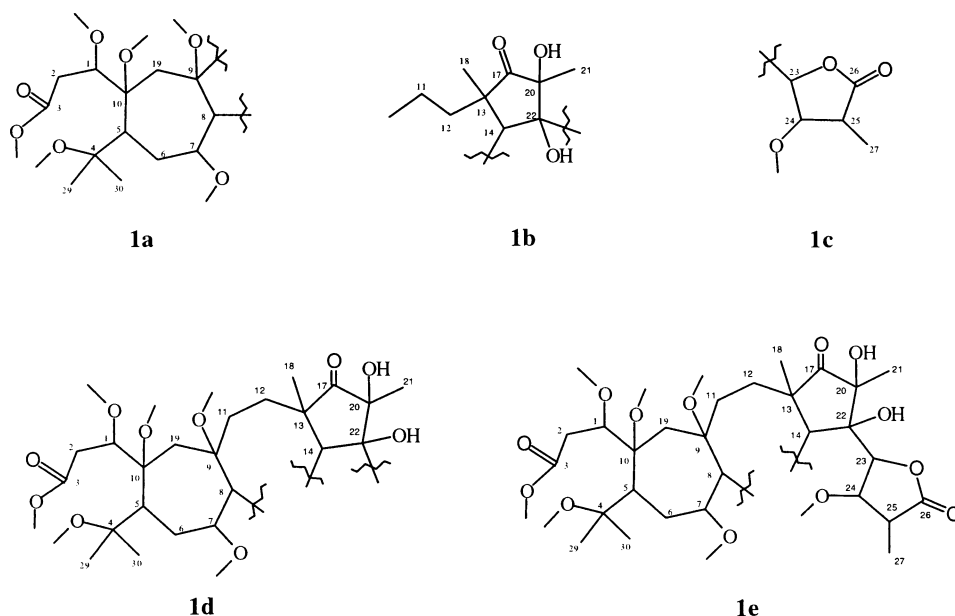


Figure 1. Structural fragments of **1**.

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 CO₂. 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

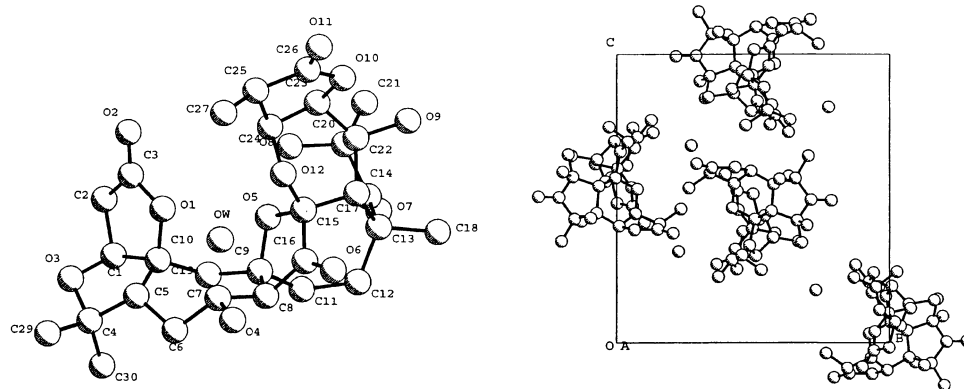


Figure 2. X-ray structure of **1** showing relative configuration.

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

Supporting Information Available: ^1H and ^{13}C NMR, ^1H – ^1H 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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