Cedronolactone E, a Novel C_{19} Quassinoid from *Simaba cedron*

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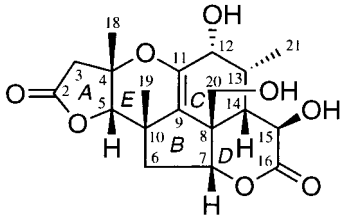
A novel pentacyclic C_{19} quassinoid, cedronolactone E (**1**), was isolated from the wood of *Simaba cedron*. Its structure was elucidated by interpretation of spectroscopic data.

Simaba cedron Planch. (Simaroubaceae) is a medicinal plant distributed in tropical America and is used for the treatment of stomachache and fever. Several cytotoxic quassinoids, including cedronolactones A−D, have been isolated from this plant in our previous work.[1] In the present note, we report a novel C_{19} quassinoid, designated as cedronolactone E (**1**), having an unusual pentacyclic skeleton from the same plant source.



cedronolactone E (**1**)

A methanolic extract from the wood of *S. cedron* was partitioned between $CHCl_3$ and H_2O, and then the aqueous layer was extracted with *n*-BuOH.[1] The *n*-BuOH-soluble material was applied to Diaion HP-20 column chromatography (H_2O−MeOH). The fraction eluted with 20% MeOH was separated from crystals of glaucarubol[2,3] that formed when the eluate was left on standing, and the filtrate was further subjected to reversed-phase medium-pressure liquid chromatography (MPLC) and then HPLC to give cedronolactone E (**1**).

Cedronolactone E (**1**), obtained as crystalline powder, mp 118−121 °C, was assigned the molecular formula $C_{19}H_{24}O_8$ as established by HREIMS, which is the same as that of cedronolactone C (**2**)[1] (Scheme 1), also isolated from the same plant. The IR spectral data suggested the presence of a γ-lactone (1776 cm^{-1}) and a δ-lactone (1747 cm^{-1}). The ^1H NMR spectrum revealed the presence of two singlet methyls (δ 1.26 and 1.59), one doublet methyl (δ 1.67, J = 7.3 Hz), and two AB-quartet methylene groups (δ 2.90 and 3.12, J = 17.6 Hz; δ 3.81 and 4.06, J = 11.4 Hz).

The HMBC spectra of **1** and **2** were very similar, which suggested that **1** possesses the same carbon framework as that of **2**. The ^{13}C NMR and DEPT spectra of **1** revealed that the C-3 (δ 44.9) and C-4 (δ 80.6) carbons were aliphatic methylene and oxygenated quaternary carbons, respectively (Table 1). These spectra also suggested that an olefinic bond occurred between C-9 (δ 116.1) and C-11 (δ 149.9) and that C-11 was connected to an oxygen atom. The position of this olefinic bond was supported by the observation of HMBC correlations between H-12 and C-9 and C-11. Accordingly, the structure of **1** was determined as an isomeric form of **2**, having an ether linkage between C-4 and C-11.

Scheme 1. Proposed Biogenetic Pathway from Cedronolactone C (**2**) to Cedronolactone E (**1**)

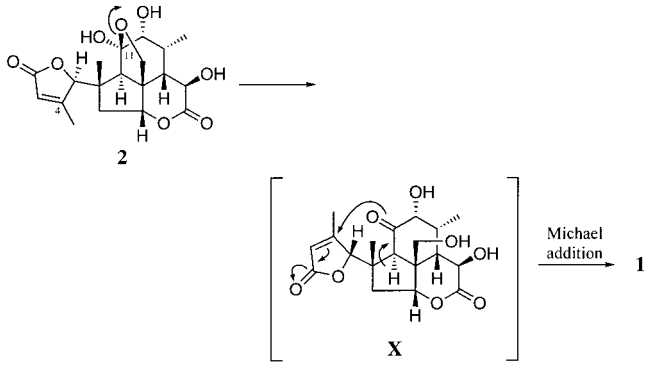


Table 1. ^1H and ^{13}C NMR Chemical Shifts and HMBC Correlations of Cedronolactone E (**1**) in C_5D_5N[a]

position	δ_C	δ_H	HMBC correlations
2	173.7		
3	44.9	α 3.12 (d, 17.6)	C-2, C-4, C-5
		β 2.90 (d, 17.6)	C-18
4	80.6		
5	87.7	4.53 (s)	C-4, C-9, C-18, C-19
6	45.4	α 2.51 (dd, 14.4, 4.4)	C-5, C-7, C-10, C-19
		β 2.30 (dd, 14.4, 7.2)	C-8, C-9, C-10, C-19
7	83.9	5.50 (dd, 7.2, 4.4)	C-6, C-9, C-10, C-16, C-20
8	52.5		
9	116.1		
10	40.7		
11	149.9		
12	67.0	4.29 (d, 4.2)	C-9, C-11, C-13, C-14
13	34.5	2.66 (m)	
14	41.5	3.09 (dd, 11.2, 2.6)	C-8, C-9, C-12, C-13, C-15, C-16, C-20
15	68.1	5.30 (d, 11.2)	C-13, C-14
16	174.8		
18	24.0	1.59 (s)	C-3, C-4, C-5
19	25.3	1.26 (s)	C-5, C-6, C-9, C-10
20	64.7	a 4.06 (d, 11.4)	C-7, C-8, C-14
		b 3.81 (d, 11.4)	C-7, C-14
21	17.4	1.67 (d, 7.3)	C-12, C-13, C-14

[a] Chemical shifts are reported in ppm relative to residual C_5D_4HN resonance at 7.21 ppm for ^1H NMR and C_5D_5N resonance at 135.5 ppm for ^{13}C NMR; multiplicity and J values in Hz are given in parentheses.

The stereochemistry of **1** was determined from the NOESY spectrum (Figure 1). Correlations between H-5 and Me-18, H-5 and Me-19, and Me-18 and Me-19 suggested

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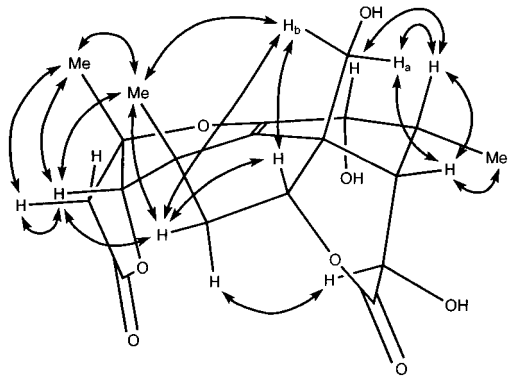

Figure 1. Selected NOESY correlations for cedronolactone E (**1**).

that these proton and methyl groups are all in β-configurations and the A/E ring junction is *cis* oriented. Correlations between Me-19 and H-20$_b$, H-7 and H-20$_b$, and H-14 and H-20$_a$ suggested that the C-20 hydroxymethyl group is in a β-configuration, and the B/D and C/D ring junctions are both *cis*. Correlations between H-12 and H-13, H-13 and H-20$_a$, and H-6$_\alpha$ and H-15 suggested that the hydroxyl groups at C-12 and C-15 are in α- and β-configurations, respectively, and Me-13 is in an α-configuration. From these observations, the structure of cedronolactone E was determined as shown.

Cedronolactone E (**1**) possesses a unique pentacyclic structure. The structural similarity between cedronolactone C (**2**), possessing a shinjulactone B-type skeleton,[1,4−8] and cedronolactone E (**1**) may suggest a biogenetic relation between these. A proposed biogenetic correlation of **1** and **2** is shown in Scheme 1. The cleavage of the hemiketal at C-11 produces the cyclic ketone intermediate **X**, which via Michael addition of the ketone oxygen atom to C-4 from the *si* face produces **1**.

Cedronolactone E (**1**) showed a weak cytotoxic activity against P-388 murine leukemia cells with an IC_{50} value of 51 μg/mL.

Experimental Section

General Experimental Procedures. Melting points are uncorrected. UV spectra were taken on a Hitachi 557 spectrophotometer. IR spectra were run on a Perkin-Elmer 1710 spectrophotometer. ^{1}H, ^{13}C, and 2D (COSY, NOESY, HMBC, and HMQC) NMR spectra were measured on a Bruker DPX-400 spectrometer. Mass spectra were obtained with a VG AutoSpec E spectrometer. Preparative MPLC was performed on a Kusano C.I.G. system equipped with a Kusano KU 331 UV detector. HPLC was performed on a Shimadzu LC-6AD system equipped with a SPD-10A UV detector and a reversed-phase column, Wakosil-II 5C18HG Prep (5 μm, 20 × 250 mm) (Wako Pure Chemical Industries, Ltd., Tokyo, Japan).

Plant Material. The wood of *Simaba cedron* Planch. was purchased in São Paulo, Brazil, in August 1991. The botanical identification was made by Dr. S. de M. Alves. A voucher specimen has been deposited in the herbarium of Tokyo University of Pharmacy and Life Science (91BRA012).

Extraction and Isolation. The wood of *S. cedron* (2.0 kg) was extracted with MeOH (3 × 4 L). The solvent was removed, and the residue (120 g) was partitioned between $CHCl_3$ and H_2O. The aqueous layer was treated with *n*-BuOH. After the removal of the solvent, the *n*-BuOH-soluble fraction (41 g) was applied to Diaion HP-20 (500 g) column chromatography using a H_2O−MeOH (1:0−0:1) gradient solvent system to give seven fractions (A−G). Fraction C (20% MeOH, 6.26 g) was separated by MPLC (Si gel) using $CHCl_3$−MeOH (9:1) to give six fractions. The second fraction was filtered to remove crystals of glaucarubol (259 mg), and the filtrate (726 mg) was further separated by MPLC (Si gel) using $CHCl_3$−acetone−MeOH (8:1:1) to afford seven fractions. The third fraction (78.8 mg) was purified by MPLC (ODS Si gel) using H_2O−MeOH (17:3) and then HPLC (ODS Si gel) using the same solvent system to give cedronolactone E (**1**, 10.0 mg, 5.0 × 10^{-4}% yield).

Cedronolactone E (1): colorless crystalline powder, mp 118−121 °C; $[\alpha]_D$ +20.8° (*c* 0.13, pyridine); UV (MeOH) λ_{max} (log ϵ) 209 (3.83) nm; IR (KBr) ν_{max} 3431, 1776, 1747, 1262, 1103, 1029 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 380 (M^+, 4), 243 (44), 105 (100); HREIMS *m*/*z* 380.1481 (calcd for $C_{19}H_{24}O_8$, 380.1471).

References and Notes

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