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Crotomacrine, a new clerodane diterpene from the fruits of *Croton macrostachyus*

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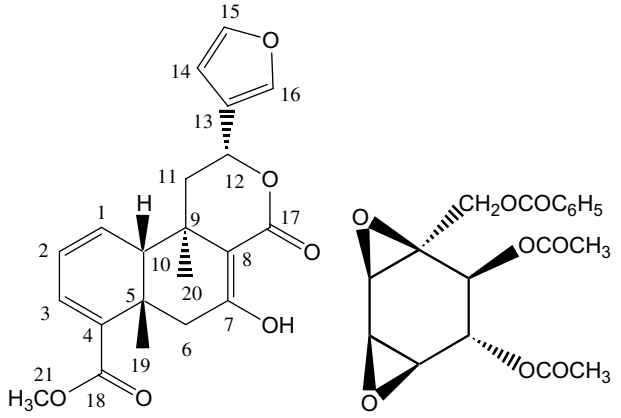
Abstract—A new clerodane diterpene, crotomacrine **1**, together with the known crotepoxide were isolated from the fruits of *Croton macrostachyus*. Their structures were elucidated on the basis of spectral evidence.

1. Introduction

Croton macrostachyus Hochst. (Euphorbiaceae) is a tall tree widely distributed in mountainous forests and savannah of the tropical regions.[1] It has been reported that the genus *Croton* contains alkaloids,[2] flavonoids,[3] and diterpenes.[4,5] We have investigated the fruits of *C. macrostachyus* and report herein the isolation and structural elucidation of crotomacrine **1**, a new clerodane diterpene, along with the known crotepoxide **2**.[6]



1

2

Keywords: *Croton macrostachyus*; Euphorbiaceae; Crotoacrine; Clerodane diterpenoid.
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2. Isolation and characterization of 1

The air-dried and ground fruits of *C. macrostachyus* (2.2 kg) were successively extracted with hexane and MeOH. The hexane-soluble fraction (75 g) was chromatographed on silica gel and eluted with hexane–EtOAc mixtures. Purification of fractions obtained with 10% hexane–EtOAc fractions afforded crotomacrine **1** (235 mg). Crotepoxide **2** (50 mg) was isolated from 30% hexane–EtOAc fractions after gel permeation on Sephadex LH-20.

Compound **1** was obtained as white needles in hexane–EtOAc, mp 203–205 °C, $[\alpha]_D$ −1.3 (*c* 0.085, CH_2Cl_2). The molecular formula $C_{21}H_{22}O_6$, was deduced from its ^{13}C NMR spectral and CIMS (*m*/*z* 371 $[M+H]^+$) data. UV absorptions λ_{max} 362 and 316 nm were characteristic of highly conjugated carbonyl systems.[7] The band at ν_{max} 874 cm^{-1} on the IR spectrum was indicative of a furan moiety.[8] The ^1H NMR spectrum (Table 1) showed typical downfield signals of a β-substituted furan ring[8] at δ 6.45 [1H, d, $J_{14.15}$ = 1.5 Hz (H-14)], 7.43 [1H, d, $J_{15.14}$ = 1.5 Hz (H-15)], and 7.50 [1H, br s (H-16)], three olefinic protons at δ 6.15 [dd, $J_{2.1,2.10}$ = 9.5, 2.1 Hz (H-2)], 6.27 [ddd, $J_{1.2,1.3,1.10}$ = 9.3, 5.4, 3.2 Hz (H-1)], 6.95 [d, $J_{3.1}$ = 5.4 Hz (H-3)], and a chelated hydroxy group at δ 12.78, similar to that of 7-hydroxy-17-oxo-7,8-dehydro-8,17-dihydroconycephaloide.[9] The chemical shift of H-12 (δ 5.68) required an oxygen function at C-12, which, according to the typical couplings of H-11, could be present as a lactone ring.[9] From the ^{13}C NMR spectral data (Table 1), two conjugated

Table 1. NMR spectral data of compound **1** ($CDCl_3$, δ in ppm)

Position	δ_C, mult.	δ_H, mult. (J in Hz)	HMBC (^1H–^{13}C)
1	125.4, d	6.27, ddd (9.3, 5.4, 3.2)	
2	132.8, d	6.15, dd (9.3, 2.1)	C-5, C-10, C-3
3	132.6, d	6.95, d (5.4)	C-2, C-18
4	137.1, s		
5	34.1, s		
6α	40.8, t	3.21, d (18.7)	C-19, C-10, C-7, C-8
6β		2.54, d (18.7)	
7	171.9, s		
8	100.5, s		
9	37.2, s		
10	50.2, d	2.46, dd (3.2, 2.1)	
11α	43.8, t	1.69, t (12.8)	
11β		2.34, dd (12.8, 4.0)	C-8, C-20, C-12
12	71.9, d	5.68, dd (12.8, 4.0)	C-13, C-16
13	125.3, s		
14	108.9, d	6.45, d (1.5)	C-15, C-16
15	144.1, d	7.43, d (1.5)	
16	140.1, d	7.50, br s	
17	170.9, s		
18	167.3, s		
19	21.9, q	1.27, s	C-5, C-4, C-10
20	19.3, q	1.45, s	C-9, C-8, C-10
21	52.0, q	3.78, s	C-18
OH		12.78, s	C-8, C-6, C-7

NMR spectra were acquired on a BRÜKER DPX-400 spectrometer in $CDCl_3$, 400 MHz for ^1H and 100 MHz for ^{13}C.

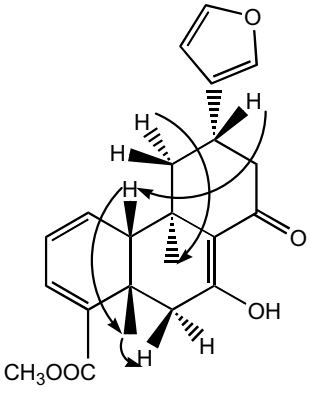

Figure 1. Selected NOESY correlations for **1**.

carbonyl functions of an ester (δ 167.3, s) and a lactone (δ 170.9, s) were deduced. Furthermore, signals of a methoxyl group (δ 52.0, q), and an enolic function (δ 171.9, s) were also observed.

The carbon skeleton of **1** was established by analysis of the ^2D NMR experiments [HMQC, COSY and HMBC (Table 1)]. From the ^1H–^1H COSY spectrum, it was possible to distinguish the proton sequences H-10/H-1, H-1/H-2, H-2/H-3, and H-11/H-12. In the HMBC spectrum pertinent correlations of H-19 to C-5, C-4, C-10 and of H-20 to C-9, C-8, and C-10 indicated that Me-19 and Me-20 were attached to C-5 and C-9, respectively. Further HMBC connectivities of H-12 to C-13 and C-16 placed the furan ring at C-12. That the ester function was at C-4 was deduced from the correlation of H-3 to C-18.

The relative stereochemistry of **1** was determined by the NOESY experiments (Fig. 1), which revealed pertinent correlations between H-12 and H-10; Me-19, H-6β and H-10; Me-20 and H-11α. On the basis of all the NMR data, we were able to complete the structure elucidation of **1**, which is a new clerodane diterpene derivative, trivially named crotomacrine.

The spectral data of crotepoxide were all in agreement with those previously published.[6]

Acknowledgements

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