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ISOLATION AND STRUCTURE OF MORTONOL A, A POSSIBLE BIOGENETIC SESQUITERPENE PRECURSOR OF MORTONINS A, C AND D*

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Key Word Index—*Mortonia greggii*; Celastraceae; agarofurane sesquiterpene; mortonol A.

Abstract—The structure of mortonol A isolated from *Mortonia greggii* was established as a benzoate diester of 1α,4β,9β-trihydroxy-dihydroagarofurane-6-one. Its structure and stereochemistry were determined by chemical and spectroscopic means.

INTRODUCTION

Plants of the Celastraceae have been the subject of a continued and growing interest, due to the range of biological activities shown by many members of this family [1]. Some of them have been used in folk medicine [2] (*Euonymus europaea*) or as stimulants [3, 4] as in the case of *Catha edulis*, from ancient times.

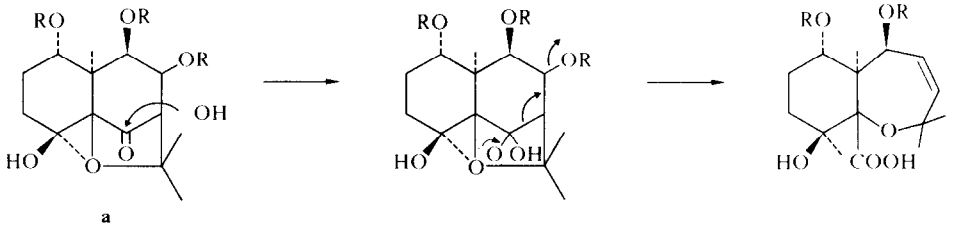
In the last 10 years several sesquiterpenes have been isolated from members of the Celastraceae and their structures determined. They have been found to contain a polyhydroxylated dihydroagarofurane nucleus, in which the hydroxyl groups are esterified by acetic, benzoic, furoic, nicotinic or substituted nicotinic acids [1].

From *Mortonia greggii* we were able to isolate several sesquiterpene derivatives which were called mortonins. The structures **1**–**3** proposed for the mortonins [5–7] can be biogenetically derived from a common precursor with a polyhydroxylated dihydroagarofurane skeleton, such as **a**, in which the B-ring has suffered an oxidative cleavage to give the tetrahydro oxepine nucleus, found in all the mortonins (Scheme 1).

In this work we describe the isolation and structural determination of mortonol A (**4**), a new sesquiterpene diester ketone, which could be considered a biogenetic precursor of the mortonins.

RESULTS AND DISCUSSION

Chromatography of the chloroform extract of leaves and stems of *Mortonia greggii* led to the isolation of a new crystalline product which was called mortonol A (**4**), mp 208–209°. It analysed for $C_{29}H_{32}O_7$ (M^+ at m/z 492), $[\alpha]_D^{25}$ +24.6° ($CHCl_3$). The IR spectrum showed a sharp absorption at 3500 cm^{-1} due to a tertiary hydroxyl group; two carbonyl bands at 1750 and 1705 cm^{-1} were attributed to ketone and ester functions. Aromatic absorption characteristic of a benzoate ester group was present at 1605 and 1590 cm^{-1}. Mortonol A contains two benzoate groups, as shown by the consecutive loss of two m/z 122 units in the mass spectrum, and the absorption between δ 7.2 and 7.95 (10 H) in the ^1H NMR spectrum. The ^1H NMR spectrum also showed four quarternary methyl signals at 1.3–1.73 (Table 1). A signal observed at 2.5 (1 H), which disappeared after addition of D_2O, was assigned to the tertiary hydroxyl group. The data presented account for six of the seven oxygen atoms present in mortonol A. The seventh oxygen atom must be of ethereal nature, which led us to propose a dihydroagarofurane skeleton, as shown in structure **4**. The ^{13}C NMR spectrum is in agreement with this structure. The ^{13}C signal assignments (Table 2) were made taking into consideration the multiplicities



Scheme 1.

*Contribution No. 577. Taken in part from the thesis to be submitted by M. Mora to the Universidad Veracruzana.

Table 1. ^{1}H NMR chemical shifts of mortonol A and its derivatives

Compound	H_1	H_3	H_6	H_9	$C_{11}(Me)_2$	C_{10}-Me	C_4-Me	OH
Mortonol A (**4**)	5.75 *dd* (10, 5)			5.15 *dd* (6, 2)	1.40 *s* 1.55 *s*	1.30 *s*	1.73 *s*	2.50 (1 H)
5	5.94 *dd* (10, 5)			5.17 *dd* (6, 2)	1.13 *s* 1.50 *s*	1.12 *s*	*5.17 *br s* *5.51 *br s*	
6	5.8 *dd* (10, 6)	5.72 *m*		5.22 *dd* (6, 2)	1.3 *s* 1.5 *s*	1.18 *s*	1.80 *br s*	
7a	5.61 *dd* (10, 5)		4.45 *d* (5)	5.10 *dd* (5, 0)	1.52 *s* 1.60 *s*	1.51 *s*	1.64 *s*	3.3 (1 H) 5.1 (1 H)
7b	5.5 *dd* (10, 5)		5.20 *d* (8)	5.05 *t* (4)	1.45 *s* 1.50 *s*	1.35 *s*	1.65 *s*	2.65 (1 H)

*The spectra were recorded in $CDCl_3$, using TMS as int. reference. The coupling constants in Hz are in parentheses. All the compounds showed aromatic proton absorption at δ 7.25–8.2 (10 H).

Table 2. ^{13}C NMR chemical shifts of mortonins and mortonol A

	Mortonin		
C^n	A	C	Mortonol A
1	72.2 *d*	72.1 *d*	72.6 *d*
2	25.8 *t*	24.3 *t*	23.9 *t*
3	37.5 *t*	35.2 *t*	38.5 *t*
4	71.6 *s*	76.6 *s*	70.6 *s*
5	84.9 *s*	86.6 *s*	86.1 *s*
6	172.2 *s*	170.9 *s*	212.0 *s*
7	143.1 *d*	134.4 *d*	55.2 *d*
8	121.7 *d*	132.6 *d*	33.5 *t*
9	85.8 *d*	74.1 *d*	72.3 *d*
10	49.8 *s*	46.4 *s*	56.0 *s*
11	81.6 *s*	81.2 *s*	78.1 *s*
12	26.8 *q**	23.2 *q**	21.2 *q**
13	20.4 *q**	24.4 *q**	23.5 *q**
14	22.8 *q*	13.8 *q*	17.1 *q*
15	32.8 *q*	33.2 *q*	29.6
ψCO	165.0 *s*	165.9 *s*	165.3 *s*
		167.2 *s*	165.4 *s*

*These assignments are interchangeable.

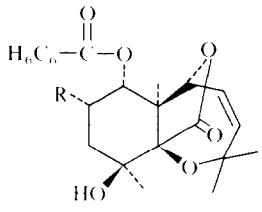
obtained by the method of gated decoupling. The chemical shifts found for the carbons of mortonol A are compared with those of mortonins A and C [8] (Table 2).

Since the ^{1}H NMR spectrum of mortonol A showed two doublets of doublets at δ 5.75 and 5.1, the benzoate groups must be attached to secondary carbon atoms. Similarity of the signals observed at 5.75 (J = 10 and 5 Hz) with the signal shown by the C-1 proton in the mortonins A, C and D [7] led us to place one of the ester groups at C-1 with an equatorial configuration, as found in all the sesquiterpenes with an agarofurane skeleton isolated from Celastraceae plants [9]. The second benzoate ester must be axially attached at C-9, since it is responsible for the doublet of doublets observed at 5.1 with coupling constants of 6 and 2 Hz, due to equatorial–axial and equatorial–equatorial interactions with the C-8 methylene group.

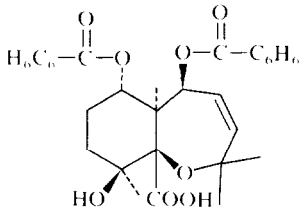
The tertiary hydroxyl group was shown to be attached to a carbon atom bearing one of the quaternary methyl groups. Dehydration of mortonol A gave two anhydro derivatives **5** and **6**, which were separated by TLC. The anhydro derivative **5** showed, in the IR spectrum, the absence of the hydroxyl absorption and the presence of bands at 1650 and 925 cm^{-1}, characteristic of an exocyclic methylene group; all the other bands were unchanged. The ^{1}H NMR spectrum of **5** showed only three quaternary methyl signals. The exocyclic methylene was responsible for two broad singlets at δ 5.06 (superimposed on the C-9 proton) and 5.52 (1 H each). The second anhydro derivative, **6**, showed three quaternary methyl signals in the ^{1}H NMR spectrum and a broad singlet at 1.8 (3 H) ascribed to a vinylic methyl group. The vinylic proton appeared at 5.72, superimposed on the C-1 signal.

The carbonyl band, observed in the IR spectrum of mortonol A at 1750 cm^{-1}, was attributed to a strained cyclopentanone function. The presence of a carbonyl absorption at 212 ppm in the ^{13}C NMR spectrum of mortonol A, is in agreement with this assignment [10]. Therefore the ketone must be placed at C-6. In order to confirm this assumption, mortonol A was submitted to sodium borohydride reduction. Under normal conditions (sodium borohydride in methanol at room temperature) it was recovered unchanged. Treatment of mortonol A with sodium borohydride in isopropanol under reflux, gave two products which were separated by preparative TLC. The 1750 cm^{-1} band was absent in the IR spectrum of the less polar product **7a**. In the ^{1}H NMR spectrum a new doublet appeared at δ 4.45 (J = 5 Hz, 1 H), which was assigned to the proton attached to the carbon atom bearing the new hydroxyl group at C-8. The coupling constant (5 Hz) found for this proton, is in agreement with a hydride attack from the α phase of the molecule, giving rise to an equatorial hydroxyl group. The new hydroxyl group is responsible for a signal observed at 5.1 (exchangeable with D_2O). The strong displacement to lower field shown by this proton, can be explained by a strong hydrogen bond formed between the equatorial C-6 hydroxyl and the equatorial C-4 hydroxyl (Dreiding models). The ^{1}H NMR signal of the C-4 hydroxyl is also displaced down field and is observed at 3.3.

The second more polar product obtained, **7b**, was shown to be the C-8 epimer of **7a**. The C-6 proton of **7b** was observed in the ^{1}H NMR spectrum at δ 5.20 (J = 8 Hz), which is in agreement with the equatorial



1a R = H
1b R = OAc



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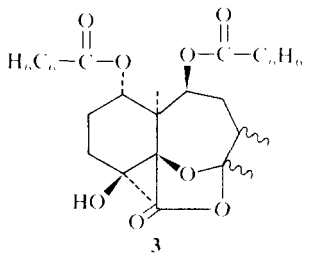

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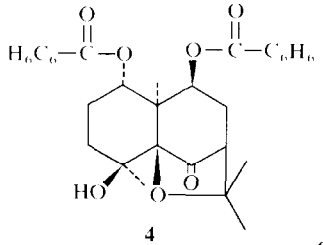

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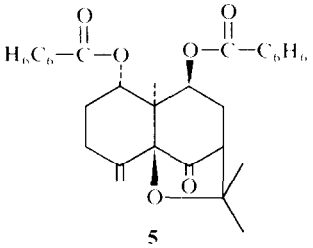

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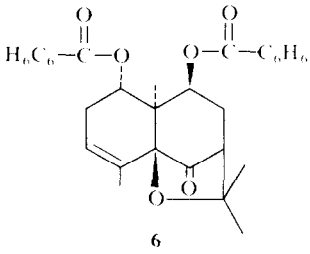

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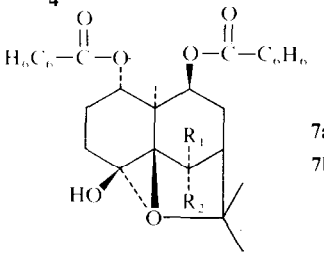

7a R_1 = OH; R_2 = H
7b R_1 = H; R_2 = OH

configuration assigned to it. One of the C-8 protons was displaced to lower field and appeared as a doublet of doublet of doublet (16, 7, 4) at 2.75 due to a diaxial interaction with the hydroxyl group at C-6.

The structure **4** proposed for mortonol A is in agreement with all the data described.

EXPERIMENTAL

Mps are uncorr. IR spectra were recorded in $CHCl_3$, and UV in 95% EtOH, unless otherwise stated. ^1H NMR and ^{13}C NMR spectra were recorded in a HA 100, FT 80 Varian Instruments and performed in $CDCl_3$ using TMS as int. standard. Analyses were determined by Dr. Pasher, Bonn, W. Germany.

Isolation of mortonol A (**4**). The dried leaves and stems of *Mortonia greggii* (Gray) collected near Matehuala (4 kg), were extrd as previously described [5]. The $CHCl_3$ extract was chromatographed on Si gel. The fraction eluted with EtOAc–hexane (1:4) yielded mortonin A (**1a**) (10 g). The mother liquors were rechromatographed on Si gel. Elution with Me_2CO–$CHCl_3$ (5:95) gave mortonol A (775 mg). The analytical sample showed mp 208–209° (Me_2CO–isopropyl ether). UV λ_{max} nm: 230 (ε 25 000); $[\alpha]_D^{25}$ +24.6° ($CHCl_3$). IR ν_{max} cm^{-1}: 3500, 1750, 1705, 1600, 1590. (Found: C, 70.53; H, 6.60; O, 22.5. $C_{29}H_{32}O_7$ requires: C, 70.71, H, 6.65; O, 22.74%), MS *m/z*: 492 $[M]^+$, 370, 248.

Sodium borohydride reduction of mortonol A. Mortonol A (200 mg), in *i*-PrOH (10 ml), was heated under reflux with $NaBH_4$ (20 mg) for 2 hr. The solvent was removed under vacuum. The mixture of products obtained (**6** and **7**) was separated by prep. TLC ($CHCl_3$–Me_2CO, 95:5). The less polar product **7a** (76 mg) showed mp 198–199° (Me_2CO–hexane). UV λ_{max} nm: 230 (ε 10 000); IR ν_{max} cm^{-1}: 3400, 1710, 1600, 1590. (Found: C, 70.39; H, 7.00; O, 22.43: $C_{29}H_{34}O_7$ requires: C, 70.42; H, 7.14; O, 23.08%). Product **7b** showed mp 270–272° (Me_2CO–isopropyl ether), UV λ_{max} nm: 230 (ε 12 500); IR ν_{max} cm^{-1}: 3630, 1710, 1600, 1590; MS *m/z*: 494 $[M]^+$: 372, 250.

Dehydration of mortonol A. Mortonol A (100 mg) in dry pyridine (5 ml), was treated with $SOCl_2$ (0.3 ml) for 1 hr at 5°. After the usual work-up, the crude product was separated by prep. TLC (EtOAc–hexane, 5:95). The less polar product **5** (30 mg) showed mp 178–180°; UV λ_{max} nm: 230 (ε 23 600); IR ν_{max} cm^{-1}: 1760, 1710, 1640, 1600, 1590, 925. MS *m/z*: 474, $[M]^+$, 352, 230. The second product, **6**, showed mp 211–213° (Me_2CO–isopropyl ether); UV λ_{max} nm: 230 (ε 24 300); IR ν_{max} cm^{-1}: 1760, 1720, 1600, 1590; MS *m/z* 474, $[M]^+$, 446, 352, 230.

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