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Minor Diterpenoids from Cascarilla (*Croton eluteria* Bennet) and Evaluation of the Cascarilla Extract and Cascarillin Effects on Gastric Acid Secretion

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Three new diterpenoids belonging to the clerodane (**2**−**3**) and halimane (**4**) structural types have been isolated from the bark of *Croton eluteria* Bennet, commonly known as cascarilla. Their structures have been fully characterized by spectroscopic means. Cascarilla extract and its major component, cascarillin, were found to significantly increase histamine-induced gastric acid secretion in the mouse stomach. These preliminary results provide the first rationale for the use of cascarilla in bitter preparations aimed at improving digestion.

KEYWORDS: Cascarilla; *Croton eluteria*; diterpenes; halimane; clerodanes; gastric secretion, digestive liqueurs

INTRODUCTION

The bitter bark of the South American tree *Croton eluteria* Bennett (Euphorbiaceae), commonly known as cascarilla, has been widely used in traditional folk medicine as a replacement for Cinchona and Cascara, and to treat various diseases (*1*). Today, its major use is in the realm of aromatization, where its fragrance and bitter taste make it a popular ingredient of liqueurs (*2*).

Cascarilla has been under chemical scrutiny since the beginning of natural products chemistry. Thus, cascarillin (**1**, **Figure 1**), its major constituent, was first isolated in 1845 (*1*) and stands out as the first diterpenoid obtained in pure form from a plant source. The structural elucidation of cascarillin was painfully slow and was only achieved in 1966, through X-ray analysis of its 7-deacetyl-3 iodoacetate derivative (*3*). In the following years, interest in cascarilla faded but was rekindled by the recent characterization of the new analogues, cascarillone and cascarillin A (*4*, *5*).

As part of an investigation on aromatic bitter plants, we have undertaken a systematic study of cascarilla, reporting the characterization of eluterins A−J, 10 new clerodanes chemically related to cascarillin. Eluterins differ from the parent compound in the functionalization of ring A and/or the ethylidene linker connecting ring B and the furan moiety (*6*). In addition, we also demonstrated that cascarillin is a mixture of interconverting γ-lactols and not a γ-hydroxyaldehyde, as previously reported (*6*).

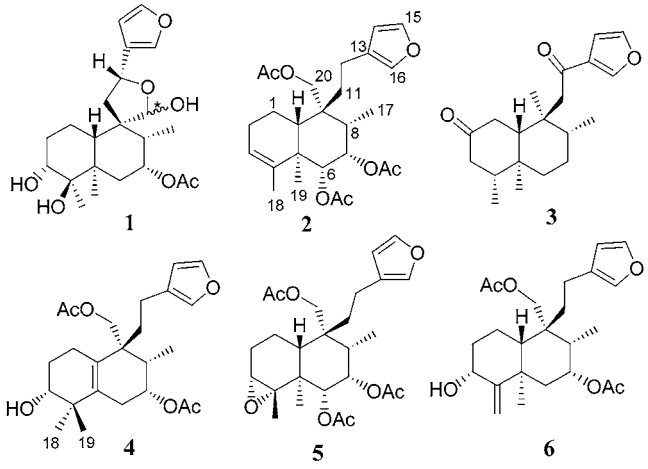

Figure 1. Chemical structures of cascarillin (**1**), of the novel diterpenes (**2**–**4**), and of eluterin F (**5**).

While interesting biological activities including insect antifeedant (*7*), anticancer (*8*), gastroprotective (*9*), and antiinflammatory (*10*), have been attributed to some clerodane diterpenes, no pharmacological investigation has ever been performed on the constituents of *C. eluteria*. Given the popularity of cascarilla as a constituent of bitter liqueurs aimed at improving digestion, we focused on the effect of cascarilla and its major constituents

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on both basal and histamine-stimulated gastric acid secretion. The pharmacological data are here reported. During the isolation of the major constituents of the drug in amounts sufficient to perform the biological tests, we have also characterized three new diterpenoids, whose structure elucidation is reported. Two of them, named eluterin K (**2**, **Figure 1**) and cascarilladione (**3**, **Figure 1**) belong to the furano-clerodane class, while the third compound (pseudoeleuterin B, **4**, **Figure 1**) is an unusual furano-halimane diterpene.

MATERIALS AND METHODS

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer 192 polarimeter eq. uipped with a sodium lamp (589 nm) and 10-cm microcell. IR (KBr) spectra were obtained on a Perkin-Elmer IFS-48 spectrophotometer. UV spectra (CH_3CN) were measured on a Beckman DU70 spectrophotometer. Mass spectra were recorded in the electrospray (ES) and electron impact (EI, low and high resolution, 70 eV, direct inlet) ionization mode on a LCQ Finnigan spectrometer and a Prospec Fisons mass spectrometer, respectively. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Bruker AMX-500 spectrometer. Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H 7.26, δ_C 77.0; C_6D_6: δ_H 7.18, δ_C 128.0). The multiplicities of ^{13}C resonances were determined by DEPT experiments. One-bond heteronuclear ^{1}H-^{13}C connectivities were determined with 2D HMQC and 2D HSQC experiments. Two and three bond heteronuclear ^{1}H-^{13}C connectivities were determined with 2D gradient-HMBC (g-HMBC) experiments, optimized for $^{2-3}J_{CH}$ of 7 Hz. Nuclear Overhauser effect (NOE) measurements were performed by 2D ROESY experiments. MPLC was performed on a Büchi 861 apparatus using columns packed with silica gel (230−400 mesh) or with Sephadex LH-20. HPLC in isocratic mode was performed on a Beckmann apparatus equipped with a refractive index detector. LUNA (Phenomenex) SI60 columns (4 × 250 mm) and (10 × 250 mm) were used.

Plant Material. Cascarilla, *Croton eluteria* Bennet, was purchased from Minardi, Bagnacavallo (RA). A voucher specimen is held at DISCAFF.

Extraction and Isolation. Powdered bark of *Croton eluteria* (cascarilla, 500 g) was exhaustively extracted by percolation with acetone at rt (4 × 2 L). Evaporation of the pooled extracts left a brown gum (50 g). Part of this (38 g) was fractionated by column chromatography (silica gel) with a petroleum ether−EtOAc gradient (from 9:1 to 1:9) to give four main fractions (A−D). Fraction A (petroleum ether−EtOAc 9:1, 3.5 g) was crystallized from petroleum ether to afford lupeol (0.25 g, 0.05% of the powder), while fraction D (petroleum ether−EtOAc, 4:6) afforded cascarillin (1.55 g, 0.31%) after crystallization with ether−acetone 1:1. Fractions B (3.1 g) and C (2.9 g) (petroleum ether−EtOAc, 7:3 and 5:5, respectively) were combined and then chromatographed on Sephadex LH-20 ($MeOH-CH_2Cl_2$,1:1), which afforded six sub-fractions: A1 (99 mg), A2 (870 mg), A3 (450 mg), B1 (760 mg), B2 (420 mg), and B3 (290 mg). HPLC purification of fraction A1 (eluent *n*-hexanes−EtOAc, 9:1) afforded eluterin K (**2**, 2.0 mg) and cascarilladione (**3**, 1.2 mg), while HPLC purification of fraction A2 (*n*-hexanes−EtOAc, 65:35) afforded pseudoeluterin B (**4**, 2.4 mg).

Eluterin K (2). White powder. $[\alpha]_D^{25}$ −21.0 (c = 0.01, $CHCl_3$). IR (KBr): ν_{max} 1724, 1722, 1235, 885 cm^{-1}. EIMS *m*/*z*: 460 $[M]^+$, 400 $[M - AcOH]^+$. HREIMS *m*/*z*: found, 460.2473; calcd for $C_{26}H_{36}O_7$, 460.2461. ^{1}H and ^{13}C NMR data are reported in Table 1.

Cascarilladione (3). White powder. $[\alpha]_D^{25}$ −8.0 (c = 0.01, $CHCl_3$). IR (KBr): ν_{max} 1698, 1658, 1511, 1160, 875 cm^{-1}. UV (CH_3CN): λ_{max} 215 (log ϵ 3.5), 248 (log ϵ 3.5), 287 (log ϵ 0.9). EIMS *m*/*z*: 316 $[M]^+$, 206 [base peak, attributable to M − side chain at C-9]. HR-EIMS *m*/*z*: found, 316.2045; calculated for $C_{20}H_{28}O_3$, 316.2038. ^{1}H and ^{13}C NMR data (in C_6D_6) are reported in Table 2.

Pseudoeluterin B (4). Amorphous solid. $[\alpha]^{25}_D$ −23.0 (c = 0.2, $CHCl_3$); IR (KBr): ν_{max} 3560, 1729, 1719, 1235, 888 cm^{-1}; EIMS *m*/*z*: 418 $[M]^+$, 358 $[M - AcOH]^+$. HREIMS *m*/*z*: found, 418.2363; calculated for $C_{24}H_{34}O_6$, 418.2355. ^{1}H and ^{13}C NMR data (in $CDCl_3$) are reported in Table 1. ^{1}H NMR (C_6D_6): δ 7.19 (s, H-15), 7.13 (s, H-16), 6.26 (s, H-14), 5.37 (m, H-7), 4.23 (d, J = 11.0 Hz, H-20a), 4.15 (d, J = 11.0 Hz, H-20b), 3.21 (dd, J = 6.0, 2.9 Hz, H-3), 2.64 (dt, J = 12.5, 3.7 Hz, H-12a), 2.36 (dt, J = 12.5, 5.1 Hz, H-12b), 2.28 (m, H-8), 2.17 (overlapped, H-6a), 2.15 (overlapped, H-6b), 1.97 (dt, J = 12.5, 5.1 Hz, H-11a), 1.94 (m, H-1a), 1.80 (dt, J = 12.5, 3.7 Hz,

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR Data of Eluterin K (**2**) and Pseudoeluterin B (**4**)[a]

pos.	δ_H, mult., J in Hz	δ_C, mult.	δ_H, mult., J in Hz	δ_C, mult.
1a	1.76[b]	17.5, t	2.10[b]	21.3, t
b	1.84[b]		2.05[b]	
2a	2.06[b]	28.3, t	1.81[b]	25.3, t
b	1.97[b]		1.76[b]	
3	5.22, bs	124.2, d	3.52, dd, 6.6, 2.2	74.1, d
4		144.1, s		38.5, s
5		43.4, s		132.3, s
6a	4.78, d, 4.4	77.4, t	2.29[b]	27.5, t
b			2.15[b]	
7	5.38, dd, 4.4, 3.7	75.7, d	5.22, m	70.3, d
8	2.02[b]	43.1, d	2.28[b]	34.5, d
9		38.7, s		44.3, s
10	1.69, dd, 8.2, 2.0	47.6, d		127.8, s
11a	1.96[b]	34.5, t	1.98, dt, 13.2, 4.4	37.5, t
b	1.83[b]		1.72[b]	
12a	2.27, t, 8.8	20.6, t	2.55, dt, 13.2, 4.4	19.0, t
b	2.27, t, 8.8		2.37, dt, 13.2, 4.4	
13		126.3, s		124.1, s
14	6.28, s	112.8, d	6.29, s	109.5, d
15	7.37, s	144.5, d	7.34, s	142.0, d
16	7.24, s	140.2, d	7.24, s	138.0, d
17	0.98, d, 7.3	14.2, q	0.89, d, 7.3	9.5, q
18	1.57, bs	19.8, q	1.03, s	27.0, q
19	1.33, s	18.8, q	1.05, s	21.5, q
20a	4.50, d, 11.8	69.1, t	4.22, d, 11.0	68.3, t
b	4.42, d, 11.8		4.12, d, 11.0	
6-Ac	2.12, s	172.1, s		
		20.0, q		
7-Ac	2.05, s	172.6, s	2.07, s	170.2, s
		20.5, q		20.5, q
20-Ac	2.00, s	171.9, s	2.06, s	170.4, s
		21.1, q		20.5, q

[a] Data in $CDCl_3$. [b] Overlapped with other signals.

Table 2. ^{1}H and ^{13}C NMR Data of Cascarilladione (**3**)[a]

pos.	δ_H, mult., J in Hz	δ_C, mult.
1a	2.39, bd, 14.0	39.6, t
b	1.99, dd, 14.0, 13.6	
2		207.8, s
3a	2.04, bd, 15,4	46.1, t
b	1.79, dd, 15.4, 14.5	
4	1.09, m	44.5, d
5		36.2, s
6a	1.38, bd, 14.0	37.8, t
b	0.83, m	
7a	1.18[b]	27.3, t
b	1.17[b]	
8	2.09[b]	37.3, d
9		41.2, s
10	2.11[b]	48.5, d
11a	2.30, d, 16.2	46.1, t
b	2.22, d, 16.2	
12		193.4, s
13		129.5, s
14	6.62, s	108.8, d
15	6.79, s	144.0, d
16	7.40, s	146.9, d
17	0.75, d, 6.6	16.5, q
18	0.45, d, 6.6	14.6, q
19	0.56, s	12.3, q
20	0.52, s	16.7, q

[a] Data in C_6D_6. [b] Overlapped with other signals.

H-11b), 1.74 (s, OAc), 1.72 (m, H-1b), 1.63 (s, OAc), 1.48 (overlapped, H-2a), 1.46 (overlapped, H-2b), 0.94 (s, H_3-18), 0.90 (d, $J = 6.6$ Hz, H_3-17), 0.82 (s, H_3-19).

Pharmacological Tests. Gastric acid secretion was measured in the isolated, lumen-perfused, stomach preparation of the mouse as previously described (*11*). Briefly, male ICR mice (Harlan Nossan; Correzzana, Italy) were killed by cervical dislocation, the abdomen opened and the esophagus ligated close to the stomach. The stomach was removed and two polythene cannulae (2 mm internal diameter) were inserted and tied in, one into the pylorus via the duodenal bulb and the other into a small incision made in the fundus through which the stomach contents were first gently washed out. The stomachs were transferred into a 40 mL organ bath containing buffered serosal solution (mM: NaCl, 118; KCl, 4.8; $MgSO_4$, 1.2; KH_2PO_4, 1.14; Na_2HPO_4, 15.9; $CaCl_2$, 0.65; glucose, 31.6) maintained at 37 °C and gassed with 95% O_2 and 5% CO_2. The preparations were continuously perfused from the fundic through the pyloric cannulas (1 mL min^{-1}) with warmed, unbuffered, mucosal solution (mM: NaCl, 135; KCl, 4.8; $MgSO_4$, 1.2; $CaCl_2$, 1.3; glucose, 31.6) gassed with 100% O_2. This solution was passed over a pH-electrode system set at 12 cm above the preparation to distend the stomach wall. Four preparations were used simultaneously and showed stable responses after a 60 min period. Any preparation not showing stable response was rejected (<5%). Histamine (volume not exceeding 1 mL) was added to the serosal solution to obtain a single cumulative agonist concentration-effect (E/A) curve (and usually required 20−40 min to reach each plateau). Changes in pH (Δ pH) following each experimental intervention were recorded. All tested substances were added to the serosal solution in the baths 15 min before starting E/A curves. Histamine · 2HCl (Sigma, Milan, Italy) was dissolved in distilled water to give a 1 M stock that was back neutralized to pH 7.4 with NaOH. All tested substances were dissolved in ethyl acetate. None of the vehicle concentrations and volumes used had an effect on basal acid output.

Pharmacological Data Analysis. Results are expressed as means ± s.e. mean. Nonlinear regression analysis for all concentration response curves were performed (Graph Pad Instat program). Data were analyzed by ANOVA followed by Bonferroni modified *t*-test. Values of $p < 0.05$ were considered significant.

RESULTS AND DISCUSSION

A commercial sample of cascarilla was exhaustively extracted by percolation with acetone at room temperature affording a brown gum, which was next fractionated by silica gel into four main fractions (A−D). Crystallization of fraction A afforded the triterpene lupeol, while fraction D, triturated with ether/acetone, gave cascarillin (**1**). Fractions B and C were complex mixtures of diterpenoids and were combined and subjected to column chromatography on Sephadex LH-20 in MeOH/CH_2Cl_2, followed by HPLC on silica gel to yield, in addition to the already reported eluterins A−J, three novel diterpenoids belonging to the furano-clerodane (eluterin K, **2**, and cascarilladione, **3**) and furano-halimane (pseudoeluterin B, **4**) structural classes.

Eluterin K (**2**) was closely related to the already reported eluterin F (**5**, **Figure 1**) (*6*), the only difference being the replacement of the 3,4-epoxide by a double bond, as indicated by the following data. The molecular formula $C_{26}H_{36}O_7$ of eluterin K (**2**), deduced by HR-EIMS, showed the absence of an oxygen atom compared to eluterin F. The epoxide broad singlet at δ 2.90 in the ^{1}H NMR spectrum of **5** was replaced by an olefin resonance at δ 5.22 in the spectrum of **2** (Table 1) and an accompanying downfield shift of the neighboring protons (H-2a, $\Delta\delta + 0.29$; H_3-18, $\Delta\delta + 0.41$). The COSY spectrum of eluterin K (**2**) showed the presence of three spin systems, the first extending from H-10 to H-3, the second spanning multiplets from H-6 to H_3-17, and including two oxymethine functions (at C-6 and C-7, respectively), with the last comprising only H_2-11 and H_2-12. With the exception of the first fragment, the

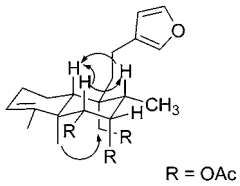

Figure 2. Key ROESY correlations of eluterin K.

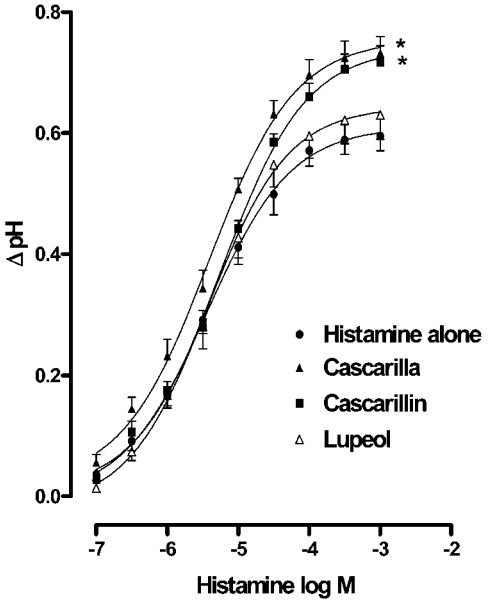

Figure 3. Acid gastric secretion in isolated mouse stomach stimulated with histamine alone and in the presence of cascarilla extract, cascarillin or lupeol (10^{-4} M). Each point represents ± sem of 6–8 animals for each experimental group. *$p < 0.05$.

pattern of resonances and coupling constants of the proton signals closely paralleled values reported for eluterin F. The ^{13}C NMR resonances of C-3 (δ 64.4) and C-4 (δ 66.0) in eluterin F were replaced in **2** by two signals in the sp^2 region at δ 124.2, associated with the signal at δ 5.22 through the HSQC spectrum and δ 144.1 (unprotonated carbon). The remaining ^{13}C NMR resonances of **2** (Table 1) appeared almost identical to those assigned to eluterin F. Some key g-HMBC cross-peaks, particularly those of H_2-2 with C-3 and C-4, of H-3 with C-4 and C-18, of H-6 with C-4 and C-19, and of H_3-18 with both C-3 and C-4, unambiguously corroborated the proposed structure. The pattern of ROESY correlations of **2** (**Figure 2**) showed 1,3-diaxial relationships for H_3-19/H_2-20, H-10/H-8, and H-10/H-6, while the coupling constants $J_{H-6/H-7} = 4.4$ Hz and $J_{H-7/H-8} = 3.7$ Hz required an equatorial orientation for H-7, thus setting the same configuration of the six stereogenic centers around ring B for eluterin K (**2**) and eluterin F.

The molecular formula of cascarilladione (**3**), determined to be $C_{20}H_{28}O_3$ by HR-EIMS, showed a lower degree of oxygenation compared to eleuterins. A detailed investigation of the ^{1}H NMR spectrum of **3** recorded in $CDCl_3$ was hampered by the severe overlapping of resonances in the high-field region, but a better signal dispersion was observed in C_6D_6 (Table 2). In this solvent, the presence of four methyl signals (δ 0.75, d; δ 0.56, s; δ 0.52, s; δ 0.45, d) and three broad singlets in the low-field region (δ 6.62, 6.79, and 7.40) suggested a furano-clerodane structure for **3**. The remaining signals in the ^{1}H NMR spectrum could be sorted into four distinct spin systems with the aid of the correlation peaks of the COSY spectrum. In particular, the first spin system (*a*) comprised H-10 and H_2-1, the second one (*b*) spanned H_2-3 to H_3-18, the third one (*c*)

H_2-6 to H_3-17, and the last one (*d*) was the AB system of two diastereotopic methylene protons (δ 2.30 and 2.22, $J = 16.2$ Hz). DEPT experiments assigned the ^{13}C NMR resonances of **3** in C_6D6, (Table 2) to four methyls, five methylenes, six methines, and five nonprotonated carbon atoms, two of them being ketone carbonyls (δ 207.8 and 193.4). The chemical shift of one of ketone carbonyl (δ 193.4) suggested conjugation, as confirmed by IR absorptions bands at ν_{max} 1698 and 1658 cm^{-1}, respectively.

An HSQC experiment associated all the proton resonances with those of the relevant carbon atoms, while analysis of the g-HMBC cross-peaks combined the above spin system into the planar structure **3** for cascarilladione. Thus, correlations of H-1a, H-10, H-3a, and H-4 with the carbonyl carbon at δ 207.8 located the first ketone group at C-2 and joined fragments *a* and *b*, while g-HMBC cross-peaks of H_3-19 with C-4, C-5, C-6, and C-10 extended the connection to fragment *c*. Finally, the correlations of H_2-11 with C-8, C-9, C-10, C-20 (δ 16.7, HSQC associated with the methyl singlet at δ 0.52) and the unprotonated carbon atoms at δ 193.4 and 129.5 unambiguously located the second ketone group at C-12, identifying the unprotonated C-9 as the pivotal link between the first and the third spin system. The relative configuration of **3** was deduced by ROESY cross-peaks of H-10 with H-4 and H-8, and of H_3-19 with H_3-20. Cascarilladione (**3**) is the 12-oxo derivative of cascarillone, a compound whose structure was first reported in 1976 (*5*) and then revised in 1989 (*12*).

The molecular formula $C_{24}H_{34}O_6$ was assigned to **4** on the basis of HR-EIMS. The ^1H NMR spectrum of **4** in $CDCl_3$, (Table 1) showed three broad singlets at δ 7.34, 7.24, and 6.29, indicating the presence of a β-substituted furan ring, four signals in the midfield region (δ 5.22, m; δ 4.22 and 4.12, mutually coupled doublets; δ 3.52, dd), five methyl signals (two acetate singlets (δ 2.06 and 2.07), two singlets and a doublet in the high-field region), and a series of signals between δ 2.55 and 1.70. Analysis of the ^1H-^1H COSY spectrum of **4** arranged all the proton multiplets into three different spin systems (H_2-1 to the oxymethine H-3; H_2-6 to H_3-17, including the oxymethine at C-7; H_2-11 to H_2-12), while an HSQC experiment associated all the proton resonances with those of the directly linked carbon atoms. The g-HMBC correlations of H_2-1 with two unprotonated sp^2 carbons at δ 127.8 (C-10) and 132.3 (C-5), combined to the correlations H-3 (δ 3.52)/C-5, H_2-6/C-5, H-7/C-5, H_2-6/C-4, H_2-1/C-9, and H-8/C-10 unambiguously indicated the presence of a Δ^5(*10*) Decalin core. In addition, the cross-peaks of both H_3-18 and H_3-19 with the same unprotonated carbon atom at δ 38.5 (C-4), and furthermore, the cross-peaks H_3-18/C-19 and H_3-19/C-18 indicated that C-4 is *gem*-dimethyl substituted. Finally, the correlations H_2-11/C-9, H_2-11/C-10, H_2-20/C-9, and H_2-20/C-10 completed the analysis of the diterpenoid core of **4**. The two acetate groups were located at C-7 and C-20 on the basis of the g-HMBC cross-peaks of H-7 and the acetate singlet at δ 2.07 with the ester carbonyl at δ 170.2 and of H_2-20 and the acetate singlet at δ 2.06 with the ester carbonyl at δ 170.4.

A straightforward analysis of vicinal and spatial couplings was prevented in $CDCl_3$ by overlapping of key signals such as the ones of the methylene at C-1 and the *gem*-dimethyls at C-4, but a better signal dispersion was achieved in C_6D_6. After assignment of all the proton signals by a COSY spectrum, interpretation of 2D ROESY cross-peaks disclosed the relative configuration of **4**. The correlations H_3-17/H_2-20 and H_2-11/H-7 defined the relative geometry around ring B, while the correlations of the methyl singlet at δ 0.82 (H_3-19) with both H-3 and H-7 completely defined the relative configuration of **4**.

Compound **4** belongs to the rare halimane structural class and is the first compound of this type isolated from cascarilla, though a previous example from the large genus *Croton* (*13*) was known. The close structural similarity, both in the substitution pattern and in the stereochemistry, between the halimane **4** and the previously reported clerodane eluterin B (**6**, **Figure 1**) (*6*) suggests a biogenetic relationship between these compounds we have thus named **4** pseudoeluterin B.

Neither an acetone extract of cascarilla nor its two major components, cascarillin and lupeol (10^{-4} M) affected the basal pH (4.58 ± 0.06; ΔpH: 0.01 ± 0.005) of the lumen-perfusion outflow from mouse stomach preparation. However, the cascarilla extract produced a leftward displacement of the histamine curve ($10^{-7}-10^{-3}$ M) and increased significantly ($p < 0.05$) the histamine-induced gastric acid secretion ($p < 0.05$; **Figure 3**) in this preparation. Cascarillin had the same effect as the extract, although less pronounced, while lupeol was unable to potentiate the histamine-stimulated gastric acid secretion. Several mechanistic possibilities for this activity are possible, including: (i) a direct effect on histamine receptors, (ii) a stimulation of histamine release, or (iii) a sensitization of the histamine receptors. Furthermore, other regulating factors or the H^+/K^+ ATPase cannot be excluded as the target. While further experiments are necessary to evaluate the mechanism(s) involved in the activity of cascarilla and its components on gastric secretion, it is nevertheless important to point out that a direct effect has been demonstrated for the first time, backing up the use of this bitter drug in preparations aimed at improving digestion.

In conclusion, *Croton eluteria*, while being validated as a prolific producer of new diterpenes differing in their carbon framework as well as in their functional group pattern, has also been identified as source of compounds capable of potentiating the histamine-stimulated gastric acid secretion, rationalizing the use of cascarilla in bitter preparations aimed at improving digestion. It is interesting to point out that these products are typically consumed after a meal, that is, under conditions of histamine stimulation by the ingested food, and when a potentiation of gastric acid secretion can be beneficial.

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Mass and NMR spectra were recorded at the "Centro Interdipartimentale di Analisi Strumentale" of the University of Naples "Federico II".

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