New Meroterpenoids from the Ascidian *Aplidium conicum*

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The ascidian *Aplidium conicum* from Tarifa Island contains the four new meroterpenoids conidione (**1**), conicol (**2**), 2-[(1′*E*)-3′-methoxy-3′,7′-dimethylocta-1′,6′-dienyl]benzene-1,4-diol (**3**), and conitriol (**4**) together with five related known compounds (**5**−**9**). It is proposed that the nonaromatic compound conidione (**1**) was derived by cyclization of an intermediate conitriol quinone **11**. The structures of the new compounds were elucidated by interpretation of spectral data.

Ascidians of the genus *Aplidium* are renown for the vast array of structurally diverse components that they present.[1] These compounds can be grouped in nitrogenous and non-nitrogenous metabolites. This latter group is dominated by the presence of meroterpenoids with structures of prenyl hydroquinone or prenyl quinone derivatives either linear or cyclic, with the longithorones as the most prominent example.[2−4]

In our project directed to examine the biomedical potential of marine invertebrates and, in particular, ascidians from the southern coast of Spain we obtained specimens of the ascidian *Aplidium conicum* Olivi (Polyclinidae) collected off Tarifa Island (Cádiz, Spain). In a previous communication, *A. conicum* had been reported to contain a normonoterpene sulfate.[5] Our specimens contained four new meroterpenoids (**1**−**4**)[6] together with five related known compounds (**5**−**9**).

Colonies of *A. conicum* were collected by hand using scuba near Tarifa Island and immediately frozen. The frozen tissue was extracted with methanol, and after evaporation of the solvent, the aqueous residue was extracted with Et_2O. In cytotoxicity assays performed on P-388 mouse lymphoma, A-549 human lung carcinoma, and HT-29 human colon carcinoma cell lines the organic extract of *A. conicum* showed a moderate but selective activity against the P-388 tumor cell line ($IC_{50} = 5\ \mu g/mL$). Column chromatography of the extract followed by HPLC separation of bioactive fractions ($IC_{50} = 1\ \mu g/mL$ against P-388 cell line) afforded in order of increasing polarity conidione (**1**, 0.002% dry wt), a tetrahydrocannabinol derivative (**5**, 0.005% dry wt), conicol (**2**, 0.003% dry wt), cordiachromene A (**6**, 0.016% dry wt), geranylhydroquinone (**7**, 0.065% dry wt), 2-[(1′*E*)-3′-methoxy-3′,7′-dimethylocta-1′,6′-dienyl]benzene-1,4-diol (**3**, 0.001% dry wt), conitriol (**4**, 0.002% dry wt), 2-(3′-hydroxy-3′,7′-dimethylocta-6′-enyl)benzene-1,4-diol (**8**, 0.003% dry wt), and 2-[(2′*E*)-7′-hydroxy-3′,7′-dimethylocta-2′-enyl]benzene-1,4-diol (**9**, 0.004% dry wt). Compounds **5**,[7] **6**,[8,9] **7**,[10] **8**,[11] and **9**[12] were identified by comparison of spectral data with those reported in the literature.[13]

Conidione (**1**) was obtained as an orange oil of molecular formula $C_{16}H_{20}O_3$ as indicated by HRMS. The ^{13}C NMR (Table 1) contained two α,β-unsaturated ketone carbonyl signals at δ 197.9 (s) and 196.6 (s) and four signals at δ 116.2 (d), 139.0 (s), 141.1 (d), and 140.7 (d), attributable to a trisubstituted and a disubstituted double bond, respectively. Two carbonyls and two double bonds accounted for four unsaturations, and since the remaining carbon signals were assigned to sp^3 carbons, conidione (**1**) must be tricyclic.

The ^1H NMR signals (Table 2) of the disubstituted double bond at δ 6.71 (1H, d, $J = 10.3$ Hz) and 6.87 (1H, d, $J = 10.3$ Hz) were correlated in the HMBC experiment with the carbonyl signals at δ 197.9 and 196.6, respectively. This latter signal was also correlated with the signals of an isolated methylene group at δ 2.88 (1H, d, $J = 16.7$ Hz) and 2.81 (1H, d, $J = 16.7$ Hz), defining the presence of a 2,2-disubstituted cyclohexenedione ring in the molecule. Since the molecular formula of conidione (**1**) contains only

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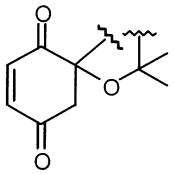

Figure 1. Subunit A of the structure of conidione (**1**).

Table 1. ^{13}C NMR Data for Compounds **1**−**4**

C no.	**1**[a] δ_C, mult	**2**[a] δ_C, mult	**3**[b] δ_C, mult	**4**[a] δ_C, mult
1	197.9 s	147.3 s	147.3 s	148.6 s
2	86.9 s	125.9 s	135.9 s	130.8[f] s
3	50.4 t	112.0 d	113.2[d] d	118.7 d
4	196.6 s	148.6 s	150.3 s	148.8 s
5	141.1 d	114.2 d	115.2[d] d	114.2 d
6	140.7 d	117.7 d	116.8[d] d	118.4 d
1′	41.8 d	34.3 d	125.2[e] d	34.3 d
2′	116.2 d	121.7 d	124.5[e] d	125.4 d
3′	139.0 s	135.2 s	77.6 s	133.7[f] s
4′	29.2 t	30.8 t	40.6 t	31.5 t
5′	21.9 t	24.6 t	23.0 t	20.7 t
6′	46.0 d	44.6 d	nd[c,e]	49.1 d
7′	84.7 s	77.5 s	131.1 s	75.3 s
8′	24.2 q	28.0 q	25.8 q	32.5 q
9′	23.7 q	23.5 q	22.1 q	23.3 q
10′	29.0 q	20.7 q	17.7 q	22.9 q
OMe			49.9 q	

[a] Assignments aided by HMQC experiment. Spectrum recorded at 100 MHz in $CDCl_3$. [b] Spectrum recorded at 100 MHz in C_6D_6. [c] nd: not detected, presumably obscured by C_6D_6 signal. [d−f] Values with the same superscript may be interchanged.

three oxygen atoms, the two signals of the ^{13}C NMR spectrum at δ 86.9 (s) and 84.7 (s) must be assigned to two quaternary carbons bearing the same oxygen. Furthermore, the correlations observed in the HMBC spectrum between the methylene proton signals mentioned above and the signal at δ 86.9 and between two methyl signals at δ 1.25 (3H, s) and 1.23 (3H, s) and the signal at δ 84.7 allowed defining the presence of the subunit A in the structure of **1** (Figure 1).

A careful analysis of the COSY correlations, starting from the proton signal of the trisubstituted double bond at δ 5.11 (1H, m), indicated that the seven carbons remaining were due to the presence of a 3,4-disubstituted-1-methylcyclohexene ring. The connections of this ring to the subunit A were confirmed on the basis of the correlations observed in the HMBC and HMQC spectra and defined the plain structure of conidione (**1**).

The relative stereochemistry of C-2, C-1′, and C-6′ was established as follows. The mutual NOE enhancements observed upon irradiation of the H-6′ signal at δ 1.95 and of the H-1′ signal at δ 3.48 require a *cis* orientation of these protons. Furthermore, the chemical shift for H-1′ implies a strong deshielding effect which requires both H-1′ and the 1-carbonyl group to be oriented on the same face of the tetrahydrofuran ring.

Conicol (**2**) was obtained as an oil of molecular formula $C_{16}H_{20}O_2$. The ^{1}H NMR signals at δ 6.80 (1H, br d, J = 2.8 Hz), 6.66 (1H, d, J = 8.7 Hz), and 6.59 (1H, br dd, J = 8.7, 3.0 Hz) indicated the presence of a 1,2,4-trisubstituted aromatic ring, which gave rise in the ^{13}C NMR spectrum to three doublets at δ 117.7, 114.2, and 112.0 and to three singlets at δ 148.6, 147.3, and 125.9. These chemical shifts fit for a *para* oxygen-disubstituted aromatic ring.

The analysis of the ^{1}H NMR spectrum with the aid of the correlations observed in the COSY spectrum indicated the presence in compound **2** of a 3,4-disubstituted-1-methylcyclohexene ring as that present in conidione (**1**). In general, the MS, ^{1}H NMR, and ^{13}C NMR data of compound **2** were essentially similar to those reported for the known compound **5**[7] except for the H-1′ and H-2′ signals. In particular, the H-1′ signal at δ 3.15 (1H, br d, J = 11.4 Hz) in conicol (**2**) was diagnostic of a *trans*-diaxial relationship between H-1′ and H-6′. It was therefore concluded that conicol (**2**) was the C-1′ epimer of the tetrahydrocannabinol derivative **5**.

Compound **3** was isolated as an orange oil. The ^{1}H and ^{13}C NMR spectra of **3** showed signals attributable to a trisubstituted aromatic ring, a *trans*-disubstituted and a trisubstituted double bond, and a methoxyl group. Since the compound showed signs of decomposition, the structural elucidation was performed on its acetate **10** obtained by treatment with acetic anhydride in pyridine of a fraction containing compound **3**.

The molecular formula of the acetate **10**, $C_{21}H_{28}O_5$, was obtained from the HRMS. Its ^{1}H NMR spectrum contained two signals at δ 2.33 (3H, s) and 2.30 (3H, s), which together with the analysis of the aromatic protons region indicated the presence of a 2-substituted hydroquinone nucleus in the natural compound which upon acetylation gave rise to diacetate **10**. Following the COSY correlations the independent spin systems −CH=CH− and −CH_2−CH_2−CH=$C(CH_3)_2$ were identified and located on a C_{10} isoprenoid side chain linked to the aromatic ring. The ^{1}H NMR signals at δ 3.18 (3H, s) and 1.24 (3H, s) were assigned to a methoxyl and a methyl group, respectively,

Table 2. ^{1}H NMR Data for Compounds **1**−**4**[a]

C no.	**1**[b] δ_H, mult, J (Hz)	**2**[b] δ_H, mult, J (Hz)	**3**[c] δ_H, mult, J (Hz)	**4**[b] δ_H, mult, J (Hz)
3	2.88 d (16.7) 2.81 d (16.7)	6.80 br d (2.8)	6.75 d (3.0)	6.64 d (3.1)
5	6.71 d (10.3)	6.59 br dd (8.7,3.0)	6.45 dd (8.5,3.0)	6.59 dd (8.5,3.1)
6	6.87 d (10.3)	6.66 d (8.7)	6.14 d (8.5)	6.76 d (8.5)
1′	3.48 m	3.15 br d (11.4)	6.97 d (16.5)	3.91 br dd (4.9,4.9)
2′	5.11 m	5.84 br s	6.20 d (16.5)	5.36 br d (5.6)
4′	2.00 m	2.10 m	1.73 m	2.16 m
5′	1.74 dddd (13.4,4.7,4.7,2.3) 1.43 dddd (13.4,13.4,11.4,6.2)	1.87 dddd (12.5,5.2,2.8,2.3) 1.39 m	2.19 m	1.65 dddd (12.9,12.9,10.1,7.4) 1.43 br d (12.4)
6′	1.95 ddd (13.4,7.2,4.7)	1.56 ddd (12.3,11.4,2.2)	5.19 br t (7.0)	2.02 ddd (12.8,4.8,2.1)
8′	1.25 s	1.41 s	1.65 br s	1.32 s
9′	1.69 d (0.8)	1.73 d (0.9)	1.24 s	1.75 br s
10′	1.23 s	1.15 s	1.54 br s	0.61 s
OH		4.45 br s	4.28 br s 4.16 br s	4.51 br s
OMe			3.08 s	

[a] Assignments aided by COSY experiments. [b] Spectrum recorded at 400 MHz in $CDCl_3$. [c] Spectrum recorded at 400 MHz in C_6D_6.

located at C-3′ of the side chain since this carbon must be fully substituted to make independent the spin systems mentioned above. Structure **10** was proposed for the acetate, and therefore the natural component was identified as the prenyl hydroquinone **3**, which is the 3′-*O*-methyl derivative of an antioxidant prenyl hydroquinone isolated from the tunicate *Amaroucium multiplicatum*.[11]

Compound **4** had the molecular formula $C_{16}H_{22}O_3$, which implies six degrees of unsaturation. The presence of a substituted hydroquinone nucleus, like that of compound **3**, was confirmed by the IR absorption at 3334 cm^{-1}, the UV absorption at 295 nm, and the ^1H NMR signal analysis, which, in addition, showed the presence of a 3,4-disubstituted-1-methylcyclohexene ring, like that present in compounds **1** and **2**. Since these two rings account for the six unsaturations of the molecular formula, the remaining ^1H NMR signals at δ 1.32 (3H, s) and 0.61 (3H, s) together with the ^{13}C NMR singlet at δ 75.3 were assigned to a 1-hydroxyisopropyl unit which must be attached to C-6′ of the cyclohexene ring upon observation of the ROESY cross-peak between the methyl signal at δ 1.32 and the H-6′ signal at δ 2.02 (1H, ddd, J = 12.8, 4.8, 2.1 Hz). Furthermore, the correlations exhibited in the ROESY spectrum and, in particular, that observed between H-1′ and H-6′ required a *cis* orientation of the substituents about the cyclohexene ring, thus defining the relative stereochemistry of conitriol (**4**).

In general, the new meroterpenoids isolated from *Aplidium conicum* were unstable, and this fact prevented pharmacological assays from being carried out, even though in a previous communication we had reported the cytotoxic activity of the known compounds **7** and **9**.[12] This instability might be responsible for the low values of specific optical rotations observed for compounds **1**, **2**, and **4**, although the possibility that they were isolated as racemic mixtures cannot be ruled out. In fact, the formation of compounds **1**, **2**, and **4** from hydroquinone **3** can be easily rationalized through a sequence of acid-catalyzed cyclizations. With the data available it is not possible to ascertain whether the new compounds **1**, **2**, and **4** are generated by cyclizations in the organism either enzymatically or not but prior to its extraction, or if they are generated by acid-catalyzed cyclizations of hydroquinone **3**. However, decomposition of compound **3** observed during the spectroscopic handling of the sample led to the well-known chromene **6**, and none of the new compounds were detected as transformation products of **3**. Furthermore, conidione (**1**) might be derived by a 5-*exo*-*trig* cyclization of the corresponding conitriol quinone (**11**). The alternative 6-*endo*-*trig* cyclization, permitted under Baldwin's rules,[14] would give rise to the more stable aromatic compound **12**, which was not found among the metabolites of *A. conicum*.

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Mattson Genesis Series FT-IR spectrophotometer, and UV spectra were recorded on a Philips PU 8710 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR were recorded on a Varian Unity 400 apparatus. Low-resolution mass spectra were measured on a Finnigan Voyager GC 8000^{top} spectrometer. High-resolution mass spectra were obtained on a VG Autospec spectrometer. In high-performance liquid chromatography (HPLC) separations, Li-Chrosorb Si-60 was used in normal-phase mode and Li-Chrosorb RP-18 in reversed-phase mode using a differential refractometer. All solvents were distilled from glass prior to use.

Animal Material. Specimens of *A. conicum* were collected by hand using scuba in Tarifa Island (Spain) and immediately frozen. A voucher specimen is deposited with the Marine and Environmental Sciences Faculty Invertebrate Collection (#Q80).

Extraction and Isolation Procedures. The frozen tissue was chopped into small pieces and extracted with methanol. Evaporation of the solvent led to an aqueous residue that was extracted with Et_2O. The ether-soluble material (2.5 g) was chromatographed on a SiO_2 column using solvents of increasing polarity from hexane to Et_2O and finally MeOH. Fractions of the general chromatography eluted with hexane/Et_2O (4:1) were further chromatographed on a SiO_2 column eluting with mixtures of hexane/EtOAc (from 95:5 to 4:1). Subsequent HPLC separations of the fraction eluted with hexane/EtOAc (9:1) using either normal- (hexane/EtOAc, 9:1) or reversed-phase (MeOH/H_2O, 4:1) yielded conidione (**1**, 2.8 mg, 0.002% yield), conicol (**2**, 4.0 mg, 0.003% yield), tetrahydrocannabinol derivative **5** (6.8 mg, 0.005% yield), and cordiachromene A (**6**, 22.6 mg, 0.016% yield). The fraction of the general chromatography eluted with hexane/Et_2O (7:3) was further chromatographed on a SiO_2 column using mixtures of hexane/Et_2O of increasing polarity (from 9:1 to Et_2O) to yield geranylhydroquinone (**7**, 93.5 mg, 0.065% yield). A portion (14 mg) of the fractions of the general chromatography eluted with hexane/Et_2O (1:1) was subjected to normal-phase HPLC separation using hexane/EtOAc (4:1) as eluant to yield 2-[(1′*E*)-3′-methoxy-3′,7′-dimethylocta-1′,6′-dienyl]benzene-1,4-diol (**3**, 1.9 mg, 0.001% yield), while another portion was acetylated as detailed below. Fractions of the general chromatography eluted with hexane/Et_2O (2:3) were further chromatographed using normal-phase HPLC eluting with hexane/EtOAc (7:3) to yield conitriol (**4**, 2.6 mg, 0.002% yield). Finally, the more polar fractions of the general chromatography were subjected to normal-phase HPLC separation using $CHCl_3$/MeOH (98:2) as eluant to yield 2-(3′-hydroxy-3′,7′-dimethyloct-6′-enyl)benzene-1,4-diol (**8**, 4.9 mg, 0.003% yield) and 2-[(2′*E*)-7′-hydroxy-3′,7′-dimethyloct-2′-enyl]benzene-1,4-diol (**9**, 5.3 mg, 0.004% yield).

Acetylation of the Fraction Containing Compound 3. A portion of 19 mg of the fraction of the general chromatography eluted with hexane/Et_2O (1:1) was treated with 0.5 mL of dry pyridine and 0.4 mL of acetic anhydride at room temperature for 3 h. The reaction mixture was taken to dryness and chromatographed using normal-phase HPLC eluting with hexane/EtOAc (85:15) to yield 3.0 mg of the acetate 1,2-diacetoxy-2-[(1′*E*)-3′-methoxy-3′,7′-dimethylocta-1′,6′-dienyl]benzene (**10**): oil; $[\alpha]^{27}_D$ +7.8° (*c* 0.19, $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 282 (2782), 248 (17584), 209 (28880) nm; IR (dry film) ν_{max} 1764, 1485, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23 (1H, d, J = 2.7 Hz, H-3), 7.05 (1H, d, J = 8.8 Hz, H-6), 6.98 (1H, dd, J = 8.8, 2.6 Hz, H-5), 6.46 (1H, d, J = 16.4 Hz, H-1′), 6.09 (1H, d, J = 16.4 Hz, H-2′), 5.09 (1H, tqq, J = 7.0, 1.3, 1.3 Hz, H-6′), 3.18 (3H, s, $-OCH_3$), 2.33 (3H, s, $-COCH_3$), 2.30 (3H, s, $-COCH_3$), 1.99 (2H, m, H-5′), 1.67 (3H, br s, H-8′), 1.61 (2H, m, H-4′), 1.59 (3H, br s, H-10′), 1.31 (3H, s, H-9′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4 (s, $-COCH_3$), 169.2 (s, $-COCH_3$), 148.3 (s, C-4), 145.3 (s, C-1), 138.2 (d, C-2′), 131.7 (s, C-7′ or C-2), 131.1 (s, C-7′ or C-2), 124.2 (d, C-6′), 123.4 (d, C-6), 122.4 (d, C-1′), 121.3 (d, C-5), 119.5 (d, C-3), 50.2 (q, $-OCH_3$), 39.8 (t, C-4′), 25.7 (q, C-8′), 22.3 (t, C-5′), 22.3 (q, C-9′), 21.8 (q, $-COCH_3$), 21.1 (q, $-COCH_3$), 17.7 (q, C-10′); EIMS *m*/*z* 360 $[M]^+$ (0.1), 277 (9), 235 (15), 203 (80), 161 (100); HRCIMS *m*/*z* 360.1913 (calcd for $C_{21}H_{28}O_5$, 360.1937).

Conidione (1): orange oil; $[\alpha]^{27}_D$ +0.5° (*c* 0.20, $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 293 (8961), 222 (11844), 206 (12338) nm; IR (dry film) ν_{max} 1695 cm^{-1}; ^1H NMR, see Table 2; ^{13}C NMR, see Table 1; EIMS *m*/*z* 260 $[M]^+$ (2.6), 245 (4), 164 (96), 121 (100); HRCIMS *m*/*z* 261.1498 (calcd for $C_{16}H_{21}O_3$, 261.1491).

Conicol (2): colorless oil; $[\alpha]^{27}_D$ +1.0° (*c* 0.40, $CHCl_3$); ^1H NMR, see Table 2; ^{13}C NMR, see Table 1; EIMS *m*/*z* 244 $[M]^+$ (37), 229 (22), 201 (42), 161 (100).

2-[(1′*E*)-3′-Methoxy-3′,7′-dimethylocta-1′,6′-dienyl]benzene-1,4-diol (3): orange oil; $[\alpha]^{27}_D$ +13.2° (*c* 0.20, $CHCl_3$); ^1H NMR, see Table 2; ^{13}C NMR, see Table 1; EIMS *m*/*z* 244 (40), 229 (13), 161 (100).

Conitriol (4): colorless oil; $[\alpha]^{27}_D$ +1.0° (*c* 0.26, $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 295 (4406), 212 (11589) nm; IR (dry film) ν_{max} 3334, 1453, 1202, 1140 cm^{-1}; ^1H NMR, see Table 2; ^{13}C NMR,

see Table 1; EIMS *m*/*z* 262 $[M]^+$ (5.2), 244 (32), 229 (22), 201 (49), 161 (100); HRCIMS *m*/*z* 262.1576 (calcd for $C_{16}H_{22}O_3$, 262.1569).

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(13) The absolute configurations of the known compounds have not been reported in the literature. The specific optical rotations encountered for compounds **5** $\{[\alpha]^{27}_D$ +1.2° (*c* 0.60, $CHCl_3)\}$ and **8** $\{[\alpha]^{27}_D$ +11.8° (*c* 0.33, $CHCl_3)\}$ significantly differed from the values reported in ref 7 ($[\alpha]^{25}_D$ +58.0°) for compound **5** and in ref 11, in which compound **8** is described as optically inactive.
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