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A Novel Bioactive Sesterterpene Based on an Unprecedented Tricyclic Skeleton from the Caribbean Sponge *Cacospongia* cf. *linteiformis*

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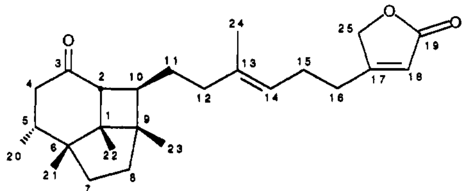
A novel sesterterpene, lintenone (1), with an unprecedented tricyclic skeleton was isolated from the caribbean sponge *Cacospongia* cf. *linteiformis*. The structure of lintenone was assigned on the basis of extensive spectral studies, including ^1H–^1H (COSY and HOHAHA) and ^1H–^{13}C (XHCORR and COLOC) 2D NMR experiments. Compound 1 was found to possess high ichthyotoxicity and antifeedant properties. It is also moderately toxic against brine shrimp.

Sesterterpenes are metabolites largely widespread in the Keratosa sponges belonging to the Dyctioceratida suborder, where they are present in the families Spongidae and Thorectidae.[2] Within the latter family they were found in two Cacospongia species (*Cacospongia scalaris* and *Cacospongia mollior*) which contain essentially sesterterpenes with the scalarane skeleton.[3] In the course of our continuing studies for bioactive constituents of marine organisms, we have been investigating a further Cacospongia species, *Cacospongia* cf. *linteiformis*, collected along the coast of Grand Bahama Island (Bahamas) in the summer of 1990. The examination of the EtOAc extract of this organism revealed the presence in large amounts of a novel bioactive sesterterpene, lintenone (1), based on an unprecedented tricyclic skeleton.



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C. linteiformis (Larmarck) (family Irciniidae, Gray, 1867) is a poorly known species, redescribed by Topsent[4] (1933) on Lamarck's material conserved in the Paris Museum and not found anymore. Our specimens from Grand Bahama Island are massive, rather tough and scarcely elastic, with a conulose, black or dark grey surface and beige choanoderm. Sponge spicules are included in the primary fibers (about 120–150-μm thick) but not in the secondary ones which are remarkably thinner (40–100 μm). The sponge is very easy to tear, due to the fragility of its spongin fibers, which is typical of the genus. Since the type species *Spongia linteiformis* Lamarck is known only from the skeletal frame, and the present one is actually the second record of the species, our specimens are referred to as *C. linteiformis* with the dubitative notation cf. (i.e., to be compared with) waiting for the collection of further samples. Nothing is known about the ecology of this sponge which is the only known *Cacospongia* species from the Caribbean Sea.

Table I. ^{13}C and ^1H NMR Assignments[a] for Lintenone (1) in $CDCl_3$ Solution

carbon	DEPT	^{13}C	^1H
1	C	50.71	
2	CH	56.68	2.05 d
3	C	214.76	
4	CH_2	43.78	2.21 further coupled AB system
5	CH	35.73	1.89 m
6	C	45.57	
7	CH_2	30.42	1.38 m, 1.92 m
8	CH_2	38.76	1.48 m
9	C	47.33	
10	CH	42.42	1.79 m
11	CH_2	30.89	1.40, 1.55 further coupled AB systems
12	CH_2	37.16	1.80 m, 1.97 m
13	C	137.38	
14	CH	121.90	5.05 bt
15	CH_2	25.58	2.26 bq
16	CH_2	28.68	2.42 bt
17	C	174.08	
18	CH	115.40	5.82 bs
19	C	170.21	
20	CH_3	17.57	0.93 d
21	CH_3	23.41	0.87 s
22	CH_3	19.38	0.95 s
23	CH_3	16.94	1.00 s
24	CH_3	16.13	1.56 s
25	CH_2	73.10	4.72 bs

[a] *J* (Hz): 7a–7b = 15; 5–20 = 7; 4_{ax}–4_{eq} = 16; 4_{ax}–5 = 12; 4_{eq}–5 = 6; 2–10 = 8; 11a–11b = 16; 14–15 = 7.5; 15–16 = 7.5.

Freshly collected animals were stored frozen and subsequently exhaustively extracted with MeOH/toluene (3:1). Medium-pressure liquid chromatography on a silica gel column of the EtOAc-soluble material followed by successive silica HPLC separation of the nonpolar fractions gave pure lintenone (1) as an oily product (0.0025% of dry weight after extraction).

High-resolution mass spectrometric analysis gave the molecular composition of 1 as $C_{25}H_{36}O_3$, confirmed by ^{13}C-NMR spectra which in the region of the unsaturated carbons contained the signal for two carbonyls and two C–C double bonds (see Tables I and II), thus indicating the tetracyclic nature of the molecule. The chemical shifts ($CDCl_3$) of the two carbonyl functions and the corre-

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Table II. ^{13}C and ^{1}H NMR Assignments[a] for Lintenone (1) in C_6D_6 Solution

carbon	DEPT	^{13}C	^{1}H
1	C	50.65	
2	CH	56.70	2.01 d
3	C	212.35	
4	CH_2	43.87	2.17 further coupled AB system
5	CH	35.54	1.62 m
6	C	45.65	
7	CH_2	30.48	1.83 m, 1.19 m
8	CH_2	39.13	1.39 m
9	C	47.22	
10	CH	42.66	1.86 m
11	CH_2	31.24	1.47, 1.60 further coupled AB systems
12	CH_2	37.27	2.03 m, 2.16 m
13	C	136.80	
14	CH	122.97	5.08 bt
15	CH_2	25.58	1.90 bq
16	CH_2	28.31	1.80 bq
17	C	173.31	
18	CH	115.52	5.54 bs
19	C	169.53	
20	CH_3	17.64	0.75 d
21	CH_3	23.24	0.67 s
22	CH_3	19.21	0.80 s
23	CH_3	17.10	0.95 s
24	CH_3	16.02	1.52 s
25	CH_2	72.46	4.02 bs

[a] J (Hz): 7a–7b = 15; 5–20 = 7; 4_{ax}–4_{eq} = 16; 4_{ax}–5 = 11.5; 4_{eq}–5 = 5; 2–10 = 7.7; 11a–11b = 15; 14–15 = 7.5; 15–16 = 7.5.

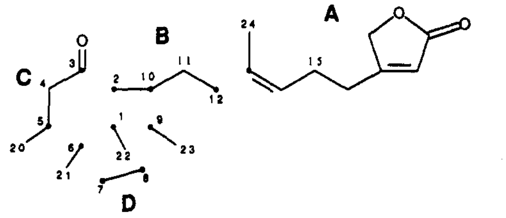

Figure 1. Segments of lintenone (1).

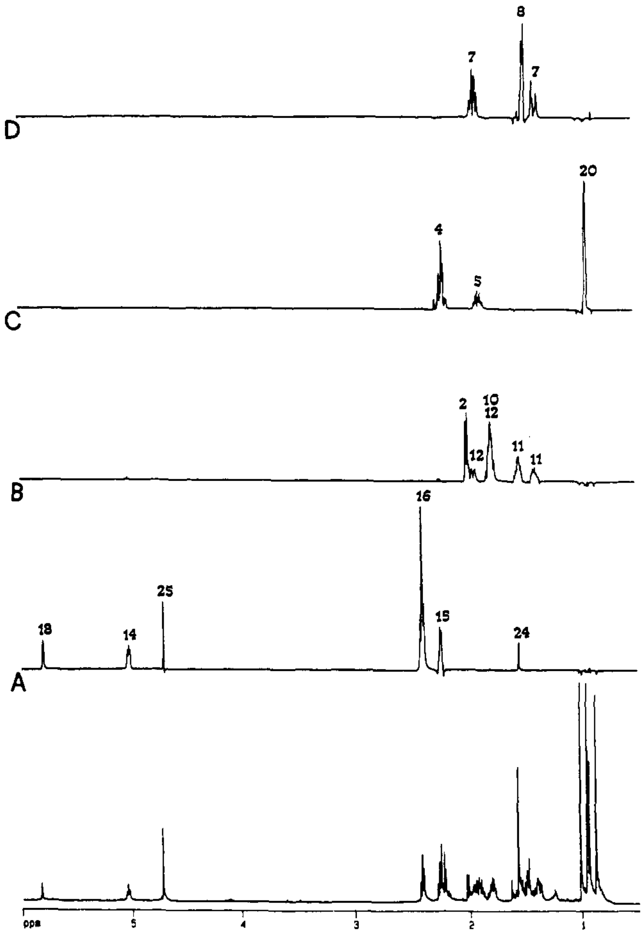

Figure 2. Subspectra derived from the 2D HOHAHA of lintenone (1) in $CDCl_3$.

sponding bands in the IR spectrum suggested the two carbonyls to be a ketone (δ 214.76; ν_{max} 1714 cm^{-1}) and a β-substituted α, β-unsaturated γ-lactone[5,6] (δ 170.21; ν_{max} 1783 and 1749 cm^{-1}), which accounted for all the oxygen atoms in the molecular formula. The presence of the latter functionality was also evident from ^{1}H NMR spectrum in $CDCl_3$ solution which displayed a broad singlet at δ 5.82 (H-18), long-range coupled with the oxymethylene signal resonating at δ 4.72 (H_2-25). The extension of this part structure up to C-24 was straightforward, based on one-dimensional spin decoupling and homonuclear 2D-correlation experiments. On the other hand, in these experiments no long-range interactions involving H_2-12 protons were observed, thus preventing the connection of the above segment to the rest of the molecule.

Decisive information on the structure of 1 was obtained through a series of 1D- and 2D-NMR experiments performed in $CDCl_3$ and/or C_6D_6 (see Tables I and II) on a Bruker AMX-500 spectrometer equipped with a X32 computer using a UXNMR software package. The DEPT pulse sequences were used to assign the number of the attached protons to each carbon resonance, which were then associated with directly attached proton signals using the 2D short-range ^{13}C-^{1}H correlation experimental procedure. By use of HOHAHA and COSY-45 techniques, interproton coupling chains were established which enabled segments of the molecule to be built up (Figure 1). The 2D-HOHAHA experiments (Figure 2) clearly showed correlation signals for the aforecited segment A; it also revealed the presence of three further spin systems: C-12, C-11, C-10, and C-2 (segment B), C-4, C-5, and C-20 (segment C), and C-7 and C-8 (segment D).

The COSY experiment confirmed these data and indicated also the proton sequence within each part structure. In particular the segment B was evident from couplings which linked the methylenes H_2-12 and H_2-11. The latter signal was shown to be coupled to the methine at C-10 which in turn was adjacent to H-2. The third significant fragment was established from interproton couplings of the methine proton at C-5 with both the C-20 methyl and C-4 methylene protons. Finally, the mutually coupled methylene protons 7 and 8 individuated the segment D.

At this point, to delinate the gross structure of 1 it was necessary to assemble the above fragments along with the three methyl groups linked to quaternary carbons and the three fully substituted sp^3 carbons whose presence was evidenced by ^{1}H [$CDCl_3$: δ 0.87 (s, C-21), 0.95 (s, C-22), 1.00 (s, C-23)] and/or ^{13}C [$CDCl_3$: δ 23.41 (q, C-21), 19.38 (q, C-22), 16.94 (q, C-23), 45.57 (s, C-6), 50.71 (s, C-1), 47.33 (s, C-9)] NMR spectra. This was accomplished by a long-range (two and three bonds) ^{13}C–^{1}H shift correlation experiment (COLOC) whose results are reported in Table III. Particularly, the following correlations were found to be decisive for assigning structure 1 (devoid of stereochemistry) to lintenone.

The methylene carbon C-12 was coupled to methyl protons of H_3-24 allowing partial structure A to be connected to segment B.

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Table III. Long-Range Carbon–Proton Correlations (COLOC) of Lintenone (1)

carbon	protons	carbon	protons
1	8, 21, 22, 23	14	24
2	22	15	16
3	2, 4	16	15, 25
4	20	17	16, 25
5	20, 21	18	25
6	21, 22	19	18
7	21	20	4
8	23	21	7
9	8, 22, 23	22	2
10	23	23	
11		24	
12	24	25	16, 18
13	24		

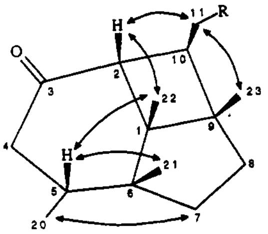

Figure 3. Most diagnostic NOE observed for lintenone (1) in C_6D_6.

The carbonyl carbon at C-3 was coupled to protons H_2-4 and H-2, and thus the connection B and C through C-3 was established.

The positioning of the three isolated methyl groups on three adjacent quaternary carbon atoms was deduced from the presence in the contour plot of intense cross-peaks correlating C-9 with H_3-22 and H_3-23, C-1 with H_3-21, H_3-22, and H_3-23, and C-6 with H_3-21 and H_3-22. These contiguous quaternary carbon atoms could be logically accommodated to join substructure A–B–C and segment D (see structure 1) as follows. The connection 8–9 was evident from the observed correlations of both C-9 and C-1 with H_2-8. On the other hand the linkage between C-6 and C-7 with consequent formation of a pentacarbocyclic ring was inferred from long-range couplings of C-21 with H_2-7 and C-7 with H_3-21. C-6 must be linked to C-5 since a correlation between C-5 and H_3-21 was observed.

Finally, long-range coupling between C-2 and H_3-22 and between C-22 and H-2 established the connection C-1–C-2, whereas the linkage C-9–C-10 was deduced from the correlation C-10–H-23, thus allowing the completion of the gross structure of lintenone.

Lintenone possesses six asymmetric centers requiring stereochemical assignment. Inspection of molecular models showed that the fusion of the cyclohexane, cyclopentane, and cyclobutane rings to constitute the unique tricarbocyclic skeleton of 1 imposes precise sterical features, leaving no alternative to the relative configuration of the chiral center at C-1, C-2, C-6, and C-9 as depicted in formula 1. Thus, the consequent cis-junction of the three cycles leads to a very peculiar, hollow stereostructure with the three methyl groups and H-2 positioned on the convex surface of the molecule. This spatial arrangement was fully substantiated by NOE difference experiments (Figure 3), which were performed in C_6D_6 since a better proton dispersion in the region of the methyl resonances was observed in this solvent. These experiments also allowed us to assign the relative stereochemistry of the remaining two chiral centers C-5 and C-10. In particular, intense NOE effects observed for H-5 with H_3-21 and H_3-22 pointed to the cis relationship among these protons. This was substantiated by the enhancement of the H_2-7 signals by irradiation at H_3-20 frequency. As for the stereochemistry at C-10, it came from irradiation of the H_3-23 signal which showed this methyl to be in the NOE proximity with H_2-11 (Figure 3).

All the above data established the relative stereochemistry of lintenone; the absolute configuration of the chiral centers of the cyclohexanone ring and therefore of the whole molecule were suggested by its CD spectrum, when compared with those of 6-oxo-(5β)-steroids,[7] which, like 1, possess an α,β-cis-fused cyclohexanone structure. These model compounds are characterized by an intense negative ellipticity associated with the ketone chromophore: a comparable value was observed in the CD spectrum of lintenone ($\theta = -9574$, EtOH), which, therefore, must have the absolute chyralities shown in structure 1.

Finally, the *E*-configuration of the C-13 double bond was inferred by both chemical shifts[8] of C-24 (see Table I and II) and confirmed by the NOE enhancement of H_2-15 on irradiation at H_3-24 frequences.

Lintenone is composed of a tricarbocyclic skeleton of unprecedented nature, which contains fused cyclohexane, cyclopentane and cyclobutane rings. It could derive from geranylfarnesyl pyrophosphate through a biogenetic pathway involving a single methyl migration.

Lintenone (1) was found to be very toxic to the mosquito fish *Gambusia affinis*[9] at 10 ppm. Antifeedant assays conducted with the fish *Carassius auratus*[10] showed for 1 high feeding deterrence at a concentration of 30 μg per cm^2 of food pellets. Finally, lintenone was also found to possess moderate toxicity (LD_{50} = 109 ppm) in the brine shrimp (*Artemia salina*) assay.[11]

Experimental Section

General Methods. Optical rotation was measured on a Perkin-Elmer 243-B polarimeter in $CHCl_3$ solution at 20–22 °C. The CD spectrum was obtained on a JASCO J710 spectropolarimeter in EtOH solution. FT-IR spectrum (KBr) was determined on a Bruker IFS-48 spectrometer. High-resolution mass spectra (HREIMS) were obtained by electron impact at 70 eV on a Kratos MS-50 mass spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker AMX-500 spectrometer both in $CDCl_3$ and C_6D_6. Proton and carbon chemical shifts were referenced to the residual solvent signals. ^{13}C–^{1}H shift correlation 2D NMR spectra via ^1J (HXCORR) and $^{2,3}J$ (COLOC) were recorded using interpulse delays optimized for a $^1J_{CH}$ = 125 Hz and $^{2,3}J_{CH}$ = 7 and 9 Hz. The 2D HOHAHA experiment was performed in the phase-sensitive mode (TPPI) using a MLEV-17 sequence of mixing.[12] Medium-pressure liquid cromatography (MPLC) was performed on a Buchi 861 apparatus using a SiO_2 (230–400 mesh) column. High-performance liquid chromatography (HPLC) was performed on a Varian 5000 apparatus equipped with a RI-3 refractive index detector using a Hibar Si-60 LiChrospher 10-μm column.

Collection and Extraction. Specimens of *C.* cf. *linteiformis* were collected by scuba in the Caribbean Sea near Grand Bahama Island during an expedition in July 1990. They were frozen when still alive at −18 °C and then dispatched to the laboratory. A voucher specimen is deposited at the Istituto di Zoologia University of Genova, Italy. The sponge (103 g, dry weight after extraction) wax next repeatedly extracted with MeOH/toluene

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(3:1) (500 mL × 5) at room temperature, and the combined extracts were evaporated in vacuo to give an aqueous phase, which was extracted with EtOAc. Evaporation of the combined EtOAc extracts afforded 23 g of a crude organic extract, which was separated by MPLC on a SiO_2 column using sequential mixtures of petroleum ether and EtOAc as eluants.

Isolation of Lintenone. Fractions eluted with petroleum ether/EtOAc (4:6) afforded a mixture of 980 mg containing lintenone. Its purification was achieved by HPLC using a Hibar LiChrospher Si60 (7-μm) column with a mobile phase of *n*-hexane/EtOAc (7:3).

Lintenone: yield 253 mg; $[\alpha]^{25}_D = -75.5°$ (*c* 0.004, $CHCl_3$); $[\theta]_{300} = -9574$ (EtOH); IR = 1783, 1749, 1714 cm^{-1} (KBr); ^1H and ^{13}C NMR spectra see Tables I and II; HREIMS (70 eV) obsd *m/z* 384.2666, $C_{25}H_{36}O_3$, calcd *m/z* 384.2666.

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Supplementary Material Available: 1D and 2D NMR spectra and a CD spectrum of lintenone (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Solution Structure and Conformational Equilibria of a Symmetrical Calix[6]arene. Complete Sequential and Cyclostereospecific Assignment of the Low-Temperature NMR Spectra of a Cycloasymmetric Molecule

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A calix[6]arene containing *tert*-butyl and chlorine substituents in alternate rings, with a 3-fold sequential symmetry, could be frozen in a completely asymmetrical conformation at 183 K in CD_2Cl_2. The ^1H-NMR spectrum could be completely assigned by low-temperature ROESY, DQF-COSY, HMQC, and HMBC experiments using a sample in which the phenolic protons had been partially exchanged by deuterons to reduce both spin diffusion and conformational exchange processes. The three-dimensional structure obtained using restrained molecular dynamics is a winged cone made asymmetric by the clockwise or anticlockwise sense of a cyclic array of hydrogen bonds. Three different types of exchange processes, leading to a statistically symmetric conformation at room temperature, could be identified in the NOESY and ROESY experiments. Hexa-*tert*-butylcalix[6]arene, with a potential 6-fold symmetry, seems to have a very similar conformation at low temperature with a C_2 axis as the only symmetry element.

Introduction

One of the major goals of supramolecular chemistry is the design of receptors for cationic, anionic, or neutral organic substrates. A large number of macrocyclic and cleftlike structures have been designed for this purpose.[1] Calix[4]arenes, the cyclic tetramers of phenols linked by methylene groups between the ortho positions, have attracted particular attention for this issue because they can adopt conformations (cone, partial cone) that contain a cavity.[2] However, due to their small size, inclusion complexes are not easily formed in solution,[3] and calix[4]arenes are now better viewed as molecular platforms on which functional groups can be oriented in space to define cavities or clefts.[4]

The cavities of calix[6]arenes, the cyclic hexamers of phenols, are larger, and therefore they show better prospects for the formation of inclusion complexes or channels. These substances are much more flexible, and they can adopt a number of conformations. Proper functionalization in the upper or lower rim can be envisaged as a mean of controlling the conformation and, therefore, modulating the properties of calix[6]arenes. For example, lower rim hexa-O-substituted derivatives of hexa-*tert*-butylcalix[6]arene (1)[5] have been reported for the development of ionophores selective for uranyl,[6] alkali and metal,[7] and

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