Dehydroconicasterol and Aurantoic Acid, a Chlorinated Polyene Derivative, from the Indonesian Sponge *Theonella swinhoei*

Rihab F. Angawi,[†,‡] Barbara Calcinai,[§] Carlo Cerrano,[⊥] Henny Adeleida Dien,[∥] Ernesto Fattorusso,[†] Fernando Scala,[†] and Orazio Taglialatela-Scafati*[,†]

Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli "Federico II", Via D. Montesano 49, 80131 Napoli, Italy, Dipartimento di Scienze del Mare, Università Politecnica delle Marche, Via Brecce Bianche, 60131 Ancona, Italy, Dipartimento per lo Studio del Territorio e delle sue Risorse, Università di Genova, Corso Europa 26, 16132, Genova, Italy, and Faculty of Fishery and Marine Science, Sam Ratulangi University, Manado, Indonesia

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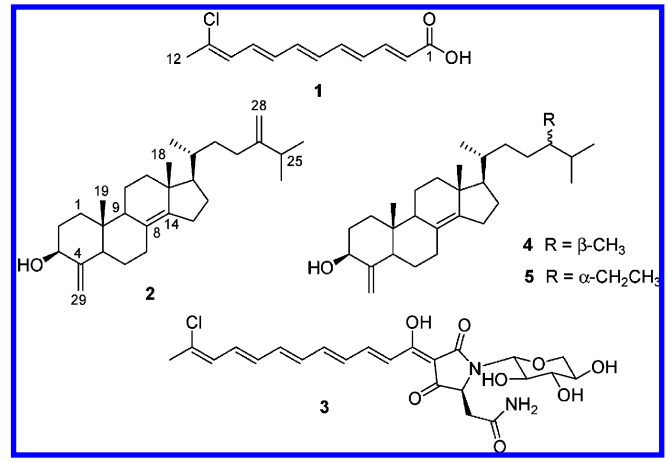
The chlorinated polyene aurantoic acid (**1**) and the 4-methylene sterol dehydroconicasterol (**2**) were isolated from the Indonesian sponge *Theonella swinhoei*, and their structures were elucidated by interpretation of spectroscopic data. Aurantoic acid is a unique member in the class of naturally occurring conjugated polyene derivatives, while dehydroconicasterol is the likely biogenetic precursor of the major *Theonella* 4-methylene sterols.

Marine sponges belonging to the genus *Theonella* (Lithistida, Theonellidae) are remarkably prolific sources of structurally intriguing and diverse secondary metabolites, which have been calculated to represent more than nine biosynthetic classes.[1] These include non-ribosomal peptides with promising biological activities (the antifungal theonellamides,[2] the cytotoxic polytheonamides,[3] and the antiviral papuamides[4]), complex polyketides such as swinholide A,[5] and tetramic acid glycosides such as the aurantosides.[6] There is continuing speculation that symbiotic microorganisms could be the true producers of many of these compounds. This hypothesis has been convincingly supported in the cases of swinholide A and the onnamides: the former has been isolated from two field collections of marine cyanobacteria,[7] while the involvement of symbiotic microorganisms in the production of the latter has been demonstrated through the isolation of the biosynthetic gene cluster from the complex metagenome of the sponge.[8]

In the context of our continuing project aimed at the screening of Indonesian marine invertebrates for new secondary metabolites,[9] we recently had the opportunity to examine a specimen of *Theonella swinhoei* collected in North Sulawesi, Indonesia. From the less polar fractions of the organic extract we obtained two previously undescribed secondary metabolites, a chlorinated polyene that we named aurantoic acid (**1**) and a 4-methylene sterol, named dehydroconicasterol (**2**), together with the known molecules aurantoside G (**3**), conicasterol (**4**), and theonellasterol (**5**). The present paper describes the isolation and the structure elucidation of these compounds.

A specimen of the sponge *T. swinhoei* was collected by hand in the area of the Bunaken Marine Park of Manado and kept frozen until sequentially extracted with MeOH and CH_2Cl_2 by soaking the sliced sponge tissues (560 g wet wt). The extracts were concentrated, combined, and then partitioned between EtOAc and H_2O. The EtOAc-soluble fraction was chromatographed on a silica gel column, using a gradient solvent system of *n*-hexane/EtOAc/MeOH. Fractions eluted with *n*-hexane/EtOAc (3:7) were combined and further purified by reversed-phase HPLC to obtain a new chlorinated polyene as a yellow, amorphous solid, which we named aurantoic acid (**1**).



The electrospray mass spectrum of **1** showed pairs of ions at *m/z* 225/227 $[M + H]^+$ and at *m/z* 247/249 $[M + Na]^+$, both in approximately a 3:1 ratio, indicating the presence of a chlorine atom. The high-resolution ESIMS data, in agreement with ^1H and ^{13}C NMR data, pointed to the molecular formula $C_{12}H_{13}ClO_2$, indicating six unsaturation degrees. The UV−visible spectrum (MeOH) showed absorptions characteristic of a polyene system (λ_{max} 346 and 363 cm^{-1}).[6] The ^1H NMR spectrum of **1** (500 MHz, $CDCl_3$) showed the signals of a vinylic methyl (δ 2.19, bs) and multiplets in the downfield region (δ 5.8−7.4). Four of these resonances appeared as well-resolved and isolated signals (δ 7.31, 6.54, 6.26, and 5.86), while two clusters centered around δ 6.62 (two overlapping signals) and 6.40 (three overlapping signals) were deconvoluted with the aid of 2D NMR experiments. Careful analysis of the COSY and TOCSY spectra allowed us to build up a single spin system going from H-2 to H-10, while the HSQC experiment guaranteed the association of the resonances of all these sp^2 methines with those of the relevant carbon atoms. In addition to the resonance of the methyl at δ_C 25.3, the ^{13}C NMR spectrum of **1** showed also the signals of two sp^2 quaternary carbons at δ_C 132.6 and 169.1, respectively. The latter resonance could be assigned to a carboxylic acid group, located at C-1 on the basis of its HMBC cross-peaks with both H-2 and H-3. Analogously, the resonance at δ_C 132.6 should necessarily be assigned to the chlorine-linking carbon atom, which was placed at C-11 on the basis of its HMBC cross-peaks with Me-12, H-10, and H-9. The *E* geometry of the four disubstituted double bonds was easily inferred from the coupling constant values ($J_{H\text{-}2/H\text{-}3}$, $J_{H\text{-}4/H\text{-}5}$, $J_{H\text{-}6/H\text{-}7}$, $J_{H\text{-}8/H\text{-}9}$), ranging

* To whom correspondence should be addressed. Tel: + 39 081678509. Fax: + 39 081678552. E-mail: scatagli@unina.it.
† Università di Napoli "Federico II".
‡ Present address: Department of Chemistry, King Abdulaziz University, Jedda, Saudi Arabia.
§ Università Politecnica delle Marche.
⊥ Università di Genova.
∥ Sam Ratulangi University, Manado.

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Table 1. ^{13}C (125 MHz) and ^{1}H (500 MHz) NMR Data for Dehydroconicasterol (**2**) in $CDCl_3$

position	δ_C, mult.	δ_H (*J* in Hz)	position	δ_C, mult.	δ_H (*J* in Hz)
1a	36.7, CH_2	1.76[a]	16a	24.6, CH_2	1.58[a]
1b		1.32[a]	16b		1.37[a]
2a	33.1, CH_2	2.01, ddt (12.8, 7.3, 4.0)	17	57.0, CH	1.16[a]
2b	31.8, CH_2	1.37[a]	18	18.2, CH_3	0.83, s
3	73.4, CH	4.04, dd (11.0, 4.0)	19	13.7, CH_3	0.58, s
4	153.1, qC		20	34.3, CH	1.50[a]
5	49.4, CH	1.82[a]	21	19.1, CH_3	0.96, d (7.3)
6a	27.0, CH_2	1.85[a]	22a	34.4, CH_2	1.59[a]
6b		1.40[a]	22b		1.24[a]
7	25.8, CH_2	2.25, m	23a	25.8, CH_2	2.09[a]
8	125.7, qC		23b	30.9, CH_2	1.90, dt (12.4, 3.0)
9	49.1, CH	1.79[a]	24	156.8, qC	
10	40.1, qC		25	33.9, CH	2.22, hep (7.3)
11a	20.4, CH_2	1.64[a]	26	22.0, CH_3	1.03, d (7.3)
11b		1.57[a]	27	22.0, CH_3	1.01, d (7.3)
12a	37.5, CH_2	1.94[a]	28a	105.8, CH_2	4.71, bs
12b		1.13[a]	28b		4.65, bs
13	42.8, qC		29a	102.8, CH_2	5.07, bs
14	142.9, qC		29b		4.63, bs
15a	29.4, CH_2	2.47, ddd (14.5, 4.0, 2.0)			
15b		1.74[a]			

[a] Overlapped with other signals.

from 14.9 to 15.4 Hz. The *Z* geometry of the Δ^{10} double bond was deduced from the NOE correlation of H-10 with CH_3-12.

The extensively conjugated system of aurantoic acid (**1**), consisting of a sequence of five double bonds and one carboxylic acid, make this compound a particularly labile molecule. Indeed, we observed that both the storage in moderately acidic solvents, such as chloroform, and the exposure to light triggered the slow formation of a mixture of products. Although the structures of these molecules have not been characterized in detail, available data suggest the occurrence of extensive *trans/cis* isomerizations. Indeed, the ESI mass spectrum of the mixture showed unchanged molecular ions at *m/z* 225/227 $[M + H]^+$ and 247/249 $[M + Na]^+$, while its ^1H NMR spectrum exhibited a series of new resonances in the vinylic region, overlapping those of the original molecule.

Aurantoic acid (**1**) can be viewed as a unique member in the class of naturally occurring conjugated polyene derivatives. Interestingly, the nonchlorinated analogue of aurantoic acid (2,4,6,8,10-dodecapentenoic acid) has never been found in nature, while the isomeric 3,5,7,9,11-dodecapentenoic acid was obtained from the insect *Llaveia axin*.[10] A chlorinated polyene moiety, clearly reminiscent of aurantoic acid, is evident in the structures of the aurantosides, particularly of aurantosides G (**3**) and H.[6] These tetramic acid glycosides have been proposed to derive from a condensation reaction between an amino acid (L-aspartic acid) and a polyene acid, followed by *N*-glycosylation.[6] Thus, it is interesting to notice that the carbon chain of aurantoic acid (C_{12}) lacks one acetate unit compared to the postulated polyene precursor of aurantosides G and H (C_{14}) and two acetate units compared to the corresponding precursor of aurantosides A−E (C_{16}).[11]

Interestingly, we isolated aurantoside G (**3**) as a reddish solid from the polar fractions (Si fractions eluted with EtOAc/MeOH, 9:1) of the organic extract of *T. swinhoei* and assigned its structure on the basis of the comparison with literature data.[6] Our isolation of aurantoside G is in perfect agreement with the Crews proposal for the classification of *T. swinhoei* phenotypes.[1] Indeed, sponges belonging to phenotype III, characterized by red-orange ectosomes and endosomes (as our specimen), should contain good amounts of aurantosides, while non-ribosomal peptides and complex polyketides should be very scarce or absent.

We then turned our attention to the sterol composition of *T. swinhoei*. Fractions of the Si column eluted with *n*-hexane/EtOAc (7:3) were combined and subjected to further HPLC purification. This procedure allowed us to obtain pure samples of the 4-methylene sterols conicasterol (**4**)[12] and theonellasterol (**5**),[12] which represent the major components of the sterol fraction of several *Theonella* species. Careful inspection of the ^1H NMR spectra of tailing fractions resulting from the above purification led us to suspect the presence of an additional sterol showing a different pattern of sp^2 methylene proton signals (see Figure S1, Supporting Information), which was later supported by GC-MS. Thus, the peracetylated crude sterol fraction, obtained upon reaction with an excess of Ac_2O in dry pyridine, was subjected to GC-MS analysis under standard conditions for peracetylated sterols. The GC separation evidenced the presence of three peaks, which on the basis of the corresponding mass spectra were assigned to conicasterol acetate, theonellasterol acetate, and a third molecule whose molecular ion (*m/z* 452) was two mass units lower than that of conicasterol acetate (*m/z* 454). Unfortunately, all our attempts to completely separate the crude fraction, through repeated HPLC on normal and reversed stationary phases, also employing different solvent mixtures, proved to be unfruitful. At this stage, we reasoned that the efficiency of this separation could be significantly improved through the use of argentation silica gel chromatography.[13] Because Ag^+ ions and alkenes form a strong complex by two-electron/three-center bonding, the retention times of molecules differing in the number of double bonds, as the yet unidentified sterol and conicasterol likely were, should be sufficiently different. Thus, the sterol crude fraction was chromatographed through a Ag^+-impregnated silica gel column, eluting with *n*-hexane/EtOAc mixtures of increasing polarities. As expected, the new sterol **2** eluted after conicasterol and theonellasterol.

Dehydroconicasterol (**2**) was obtained as an optically active, colorless, amorphous solid. The molecular formula $C_{29}H_{46}O$, requiring seven degrees of unsaturation, was established through NMR data (Table 1) and HREIMS. The ^{13}C NMR spectrum of **2** (Table 1, $CDCl_3$), interpreted with the help of the HSQC experiment, showed the presence of 29 carbon atoms, including one oxygen-bearing methine carbon (δ_C 73.4) and six sp^2 carbons, four of which were unprotonated (δ_C 125.7, 142.9, 153.1, 156.8), while the remaining two carbons were identified as sp^2 methylenes (δ_C 105.8, δ_H 4.71 and 4.65; δ_C 102.8, δ_H 5.07 and 4.63). The ^1H NMR spectrum of **2** (Table 1, $CDCl_3$), in addition to the four broad singlets assigned to the sp^2 methylene protons, showed two methyl singlets (δ_H 0.83 and 0.58), three methyl doublets (δ_H 0.96, 1.01, and 1.03), a series of multiplets between δ_H 1.00 and 2.50, and a carbinol methine resonance at δ_H 4.04.

The COSY experiment allowed the building of the five spin systems indicated in bold in Figure 1, while a series of HMBC correlations (Figure 1) allowed the connection of these fragments and the assembly of the dehydroconicasterol (**2**) structure. Particu-

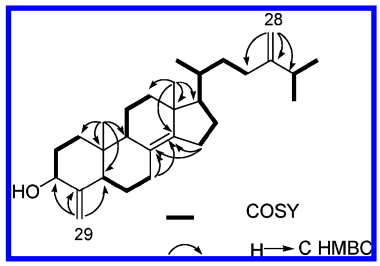

Figure 1. COSY and key HMBC correlations detected for dehydroconicasterol (**2**).

larly informative were the cross-peaks exhibited by the two methyl singlets Me-18 and Me-19; moreover, the correlations of H_2-29 with C-3, C-4, and C-5 indicated the attachment of an sp^2 methylene at C-4, while the other sp^2 methylene was attached at C-24 on the basis of the correlations of H_2-28 with C-23, C-24, and C-25. Finally, the tetrasubstituted double bond was placed at $\Delta^{8(14)}$ on the basis of the HMBC cross-peaks of both H_2-7 and H_2-15 with C-8 (δ_C 125.7) and C-14 (δ_C 142.9). These data indicated that **2** was a C_{29} sterol differing from conicasterol by the presence of an additional double bond between C-24 and C-28. Comparison of the ^{1}H and ^{13}C NMR data of **2** (Table 1) with those of conicasterol (**4**)[12] provided further support to this assignment and also indicated that the two compounds share the same configuration at the common stereogenic carbons.

Steroids bearing a 4-methylene group are relatively rare metabolites; to date, only five papers have been published on 4-methylene steroids from marine organisms.[14] This unusual group has been proposed to biogenetically arise from a shunt in the oxidative demethylation of the 4α-methyl series, through the dehydration of the primary alcohol formed in the first oxidation of the methyl group.[12] The isolation of dehydroconicasterol (**2**) adds an interesting piece to this hypothesis; indeed this compound is the likely biogenetic precursor of both conicasterol (**4**) and theonellasterol (**5**), which could derive from **2** through reduction or transmethylation with *S*-adenosylmethionine, respectively.[15]

In conclusion, the chemical analysis of an Indonesian specimen of the widely studied sponge *T. swinhoei*[16] yielded two new compounds, aurantoic acid (**1**) and dehydroconicasterol (**2**), both having a likely biogenetic relationship with well-known *Theonella* metabolites (aurantosides and conicasterol/theonellasterol, respectively). Compounds **1**−**5** were tested for in vitro cytotoxic activity against three cell lines (C6, glioma; HeLa, epithelial carcinoma; H9c2, cardiac myoblast), and they exhibited no significant inhibition of the cell growth ($IC_{50} > 70$ μM).

Experimental Section

General Experimental Procedures. Optical rotations ($CHCl_3$) were measured at 589 nm on a Perkin-Elmer 192 polarimeter. UV spectra (MeOH) were recorded on a Beckman spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were measured on Varian INOVA spectrometers. Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H 7.26, δ_C 77.0). Homonuclear ^{1}H connectivities were determined by the COSY experiment; one-bond heteronuclear ^{1}H−^{13}C connectivities by the HSQC experiment; two- and three-bond ^{1}H−^{13}C connectivities by gradient-HMBC experiments optimized for a $^{2,3}J$ of 8 Hz. ESIMS spectra were performed on a LCQ Finnigan MAT mass spectrometer. GC-MS analysis was performed on a Focus GC-Polaris Q (Thermo) with EI (70 eV) ionization. A 5% diphenyl 30 m × 0.25 mm × 0.25 μm column (Trace TR-5, Thermo) was used, with He as carrier gas. TLC plates: silica gel 60 F_{254} (Merck). Medium-pressure liquid chromatography was performed on a Büchi apparatus using a silica gel (230−400 mesh) column. In the argentation silica gel chromatography, the silica gel stationary phase was impregnated with a solution of $AgNO_3$ in EtOH/H_2O; then the liquid was evaporated and the silica dried in the oven at 100 °C overnight. HPLC was achieved on a Knauer apparatus equipped with a refractive index detector and analytical LUNA (Phenomenex) SI60 (250 × 4 mm) columns.

Animal Material, Extraction, and Isolation. A specimen of *Theonella swinhoei* (order Lithistida, family Theonellidae) was collected in January 2008 along the coast of the Bunaken Island in the Bunaken Marine Park (North Sulawesi, Indonesia). The species is very common in this area, from 20 to 50 m depth, on substrata subjected to strong currents. In vivo, the sponge is red-orange, but specimens living in shadow habitats are pale pink to white. It is frequently exploited as food by fishes and turtles. A voucher sample has been deposited at the Dipartimento di Chimica delle Sostanze Naturali, Università di Napoli Federico II (Man08-02). After homogenization, the organism (wet wt 560.2 g) was exhaustively extracted, in sequence, with MeOH and CH_2Cl_2. The combined extracts were partitioned between H_2O and EtOAc, and the obtained organic extract (2.6 g) was subjected to medium-pressure liquid chromatography over a silica column (230−400 mesh) eluting with a solvent gradient of increasing polarity of *n*-hexane/EtOAc/MeOH. Fractions eluted with EtOAc/MeOH (9:1) were combined and further purified by reversed-phase HPLC (eluent MeOH/H_2O, 65:35) to obtain aurantoside G (**3**, 12.4 mg). Fractions eluted with *n*-hexane/EtOAc (3:7) were combined and further purified by reversed-phase HPLC (eluent MeOH/H_2O, 85:15) to obtain aurantoic acid (**1**, 2.5 mg). Fractions eluted with *n*-hexane/EtOAc (7:3) were combined and subjected to normal-phase HPLC (*n*-hexane/EtOAc, 75:25) to obtain conicasterol (**4**, 75.2 mg) and theonellasterol (**5**, 63.4 mg). The crude sterol fraction was also peracetylated with an excess of Ac_2O in dry pyridine and subjected to GC-MS analysis with the following gradient: initial 200 °C (3.5 min), increment of 10 °C/min to reach 330 °C, inlet 270 °C, transfer line 280 °C, ion source 250 °C, blink window 3.5 min. Theonellasterol acetate (min 13.18, *m/z* 468), conicasterol acetate (min 12.49, *m/z* 454), and dehydroconicasterol acetate (min 12.42, *m/z* 452) were detected. The crude sterol fraction was also chromatographed through a Ag^+-impregnated silica gel column, eluting with *n*-hexane/EtOAc mixtures from 95:5 to 55:45. Fractions eluted with *n*-hexane/EtOAc (65:35) afforded dehydroconicasterol (**2**, 4.8 mg).

Aurantoic Acid (1): yellow, amorphous solid; UV (MeOH) λ_{max} (log ε) 346 (4.30), 363 (4.26), ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.31 (1H, dd, J = 15.4, 11.5 Hz, H-3), 6.69 (1H, dd, J = 14.9, 11.2 Hz, H-5), 6.60 (1H, dd, J = 15.3, 10.6 Hz, H-9), 6.54 (1H, dd, J = 15.0, 11.3 Hz, H-7), 6.43 (1H, dd, J = 14.9, 11.0 Hz, H-4), 6.41 (1H, dd, J = 15.3, 11.3 Hz, H-8), 6.39 (1H, dd, J = 15.0, 11.2 Hz, H-6), 6.26 (1H, d, J = 10.6 Hz, H-10), 5.86 (1H, d, J = 15.4 Hz, H-2), 2.19 (3H, bs, H-12); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 169.1 (C, C-1), 145.0 (CH, C-3), 140.7 (CH, C-5), 139.0 (CH, C-6), 137.0 (CH, C-7), 132.7 (CH, C-8), 132.6 (C, C-11), 130.1 (CH, C-4), 130.0 (CH, C-9), 125.4 (CH, C-10), 120.6 (CH, C-2), 25.3 (CH_3, C-12); (+) ESIMS *m/z* 225 and 227 (3:1) $[M + H]^+$, *m/z* 247 and 249 (3:1) $[M + Na]^+$; HR-ESIMS *m/z* 247.0505 (calcd for $C_{12}H_{13}{}^{35}ClO_2Na$ 247.0502).

Dehydroconicasterol (2): colorless, amorphous solid; $[\alpha]_D$ +82 (*c* 0.2, $CHCl_3$); UV−vis (MeOH) λ_{max} (log ε) 237 (3.16); ^{1}H NMR ($CDCl_3$, 500 MHz) see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) see Table 1; (+) EIMS *m/z* 410 $[M]^+$; HR-EIMS *m/z* 410.3553 (calcd for $C_{29}H_{46}O$ 410.3549).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1** and **2** (500 MHz, $CDCl_3$), 2D NMR COSY and HMBC of compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) On October 19, 2009, the database SciFinder showed 68 entries reporting chemical studies with the isolation of new molecules from *Theonella swinhoei*.

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