12-epi-Heteronemin: New Sesterterpene From The Marine Sponge Hyrtios erecta

M.L. Bourguet-Kondracki*, M.T. Martin*, C. Debitus** and M. Guyot*.

*Laboratoire de Chimie, associé au CNRS, Muséum National d'Histoire Naturelle, 63 rue Buffon, 75231-PARIS Cedex 05 (France).

**Laboratoire de Pharmacologie, ORSTOM, B.P. A5, Noumea, New Caledonia.

Abstract: 12-epi-heteronemin, a novel tetracarbocyclic sesterterpene was isolated from the marine sponge *Hyrtios* erecta and its structure has been established through spectral studies.

Sponges of the order of Dictyoceratida are known as a source of sesterterpenes, an otherwise rare group of terpenoids. Tetracyclic sesterterpenes of the scalarane type have been frequently reported from sponges of the genus *Hyrtios*. A study on the methanolic extract of the sponge *Hyrtios erecta*, collected in New Caledonia in 1988, has now led to the isolation of a new member of this class of sesterterpenes: 12-epi-heteronemin 1 and to the previously described heteronemin 2¹ and 12-epi-heteronemin acetate 3².

The methanol extract (4.7 g) of lyophilized Hyrtios erecta (500 g), was fractionated by silicagel chromatography using a gradient of MeOH in CH_2Cl_2 . The fraction eluted with 5% MeOH/ CH_2Cl_2 (1.3 g) was a crystallized mixture of two major compounds, further separated on silica gel (hex/AE 8:2), Sephadex LH-20 (CHCl3/MeOH 4:6) column chromatography and preparative tlc (CH_2Cl_2 /Acetone 95:5), thus affording two crystallized pure compounds. The minor one (0.1% animal dry weight), heteronemin 2, was easily identified by its accordance with the spectral data given in the literature³, m.p: 182°C, $[\alpha]_D$ = - 37 (c 0.009, Chf).

We shall here discuss the structure elucidation of the major (0.5% animal dry weight) and less polar compound 1, m.p: 175° C, $[\alpha]_{D}$ = - 35 (c 0.01, Chf).

The spectral data in the ¹H NMR spectrum of 1 were almost identical with those of heteronemin 2, with the exception of the proton H-12, which appeared at δ 3.84 ppm as a typical broad triplet (J= 2.7 Hz) for an equatorial proton, whereas the ¹H NMR of heteronemin 2 indicated the presence of an axial proton at δ 3.44 ppm (J= 3.9, 11.3 Hz). This was confirmed by comparison of the ¹³C NMR data, by the shielded signal at δ 71.52 ppm (δ 80.51 ppm for 2) and the deshielded signal at δ 56.86 ppm (δ 64.18 ppm for 2), respectively

attributed to the C-12 and C-18 carbons (Table 1). Thus, compound 1 was identified as 12-epi-heteronem	in.
U.V., I.R. and MS data, supported this structural assignment ⁴ .	

1 39.91 2 18.17a 3 42.03 4 33.21b 5 56.51 5 56.51 6 18.56a 7 41.82 8 37.41 9 58.75 10 38.06 11 27.20 12 80.51 13 42.70 14 54.67 15 27.99 16 69.33 15 5.34 17 114.41 18 64.17 19 101.63 6.74 d.J=1.3 10.35.24 13.31b 15.38 16.31 17 13.34 18 64.17 19 101.63 19 101.63 10 6.74 d.J=1.3 10 135.34 10 10.35 10 30.35 10 10.35 10 10.35 10 30.06 11 27.20 12 80.51 13 42.70 14 54.67 15 27.99 16 69.33 15 27.99 17 114.41 18 64.17 19 101.63 10 35.34 10 36.86 10 36.87 10 36.86 1		heterone	emin 2	12-epi-heteronemin 1	
2 18.17 ^a 3 42.03 41.96 1.04 ax and 1.34 eq 3 42.03 41.96 33.24 ^b 5 56.51 56.51 56.30 6 18.56 ^a 18.52 ^a 1.36 m 7 41.82 41.76 0.98 ax and 1.72 eq 8 37.41 38.05 9 58.75 50.92 1.38 ax 10 38.06 36.85 11 27.20 21.38 ax 12 80.51 3.44 J=3.8, 11.3 71.52 3.84 brt J=2.7, 2.7 13 42.70 41.60 49.90 1.37 ax 15 27.99 28.29 1.34 ax and 2.04 eq 16 69.33 5.34 69.15 5.34 dddd J=10.1, 6.2, 2.1, 11.31 17 114.41 115.38 18 64.17 2.40 56.86 3.02 d J= 1.3 20 135.34 6.14 t J=2 134.48 6.11 t J= 2 21 33.23 ^b 0.87 33.19 ^b 0.80 eq 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax OAc 21.24 2.07 20.99 2.06	п°	13C	¹ H	13C	¹ H
3 42.03 4 33.21b 5 56.51 6 18.56a 7 41.82 8 37.41 9 58.75 10 38.06 11 27.20 12 80.51 13 42.70 14 54.67 15 27.99 16 69.33 15 27.99 16 69.33 15 27.99 16 69.33 15 27.99 17 114.41 18 64.17 19 101.63 17 114.41 18 64.17 19 101.63 17 114.41 18 64.17 19 101.63 10.34 10.35 10.35 10.35 10.35 10.35 10.36 10.35 10.36 10.35 10.37 ax 10.37 ax 10.37 ax 10.37 ax 10.38 ax 10.37 ax 10.37 ax 10.37 ax 115.38 115 27.99 128.29 1.34 ax and 2.04 eq 15 56.86 3.02 d J= 1.3 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.36 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.31 10.35 10.36 10.36 10.31 10.3	1	39.91		39.61	1.61 m
3 42.03 4 33.21b 5 56.51 6 18.56a 7 41.82 8 37.41 9 58.75 10 38.06 11 27.20 12 80.51 13 42.70 14 54.67 15 27.99 16 69.33 15 27.99 16 69.33 15 27.99 16 69.33 15 27.99 17 114.41 18 64.17 19 101.63 17 114.41 18 64.17 19 101.63 17 114.41 18 64.17 19 101.63 10.34 10.35 10.35 10.35 10.35 10.35 10.36 10.35 10.36 10.35 10.37 ax 10.37 ax 10.37 ax 10.37 ax 10.38 ax 10.37 ax 10.37 ax 10.37 ax 115.38 115 27.99 128.29 1.34 ax and 2.04 eq 15 56.86 3.02 d J= 1.3 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.35 10.36 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.37 10.35 10.36 10.31 10.35 10.36 10.36 10.31 10.3	2	18.17 ^a		18.14ª	1.58 m
5 56.51 6 18.56a 7 41.82 8 37.41 9 58.75 10 38.06 11 27.20 12 80.51 3.44 J=3.8, 11.3 71.52 3.84 brt J=2.7, 2.7 41.60 44.60 49.90 1.37 ax 28.29 1.34 ax and 2.04 eq 16 69.33 5.34 17 114.41 18 64.17 2.40 19 101.63 6.74 d J=1.3 20 135.34 6.14 t J=2 21 33.23b 0.87 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 24 17.31 0.81 25 8.75 0.81 0Ac 21.24 2.07 0Ac 21.03 2.07 20.99 2.06	3	42.03		41.96	1.04 ax and 1.34 eq
5 56.51 6 18.56a 7 41.82 8 37.41 9 58.75 10 38.06 11 27.20 12 80.51 3.44 J=3.8, 11.3 71.52 3.84 brt J=2.7, 2.7 41.60 44.60 49.90 1.37 ax 28.29 1.34 ax and 2.04 eq 16 69.33 5.34 17 114.41 18 64.17 2.40 19 101.63 6.74 d J=1.3 20 135.34 6.14 t J=2 21 33.23b 0.87 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 24 17.31 0.81 25 8.75 0.81 0Ac 21.24 2.07 0Ac 21.03 2.07 20.99 2.06	4	33.21 ^b		33.24b	•
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	5			56.30	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	6				1.36 m
9 58.75 10 38.06 11 27.20 12 80.51 3.44 J=3.8, 11.3 13 42.70 14 54.67 15 27.99 16 69.33 5.34 17 114.41 18 64.17 2.40 19 101.63 6.74 d J=1.3 19 101.63 6.74 d J=1.3 20 135.34 6.14 t J=2 21 33.23b 0.87 22 21.34 0.77 23 16.31 0.79 24 17.31 0.81 25 8.75 0Ac 21.24 2.07 0Ac 21.03 2.07 24.75 1.64 m 1.1.64 m 1.1.54 1.64 m 1.1.52 1.34 ax and 2.04 eq 49.90 1.37 ax 28.29 1.34 ax and 2.04 eq 5.86 3.02 d J= 1.3 100.35 6.27 d J= 1.3 100.81 10.81 ax		41.82		41.76	0.98 ax and 1.72 eq
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	8	37.41		38.05	•
11 27.20 24.75 1.64 m 12 80.51 3.44 J =3.8, 11.3 71.52 3.84 brt J =2.7, 2.7 13 42.70 41.60 14 54.67 49.90 1.37 ax 15 27.99 28.29 1.34 ax and 2.04 eq 16 69.33 5.34 69.15 5.34 dddd J =10.1, 6.2, 2.1, 1 17 114.41 115.38 18 64.17 2.40 56.86 3.02 d J = 1.3 19 101.63 6.74 d J =1.3 100.35 6.27 d J = 1.3 20 135.34 6.14 t J =2 134.48 6.11 t J =2 21 33.23b 0.87 33.19b 0.80 eq 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax 25 8.75 0.81 14.61 0.81 ax 20 21.24 2.07 21.36 2.05	9	58.75		50.92	1.38 ax
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10	38.06			
13	11	27.20		24.75	1.64 m
14 54.67 49.90 1.37 ax 15 27.99 28.29 1.34 ax and 2.04 eq 16 69.33 5.34 69.15 5.34 dddd J=10.1, 6.2, 2.1, 11 17 114.41 115.38 18 64.17 2.40 56.86 3.02 d J= 1.3 19 101.63 6.74 d J=1.3 100.35 6.27 d J= 1.3 20 135.34 6.14 t J=2 134.48 6.11 t J= 2 21 33.23b 0.87 33.19b 0.80 eq 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax 0Ac 21.24 2.07 21.36 2.05 0Ac 21.03 2.07 20.99 2.06			3.44 <i>J</i> =3.8, 11.3		3.84 brt <i>J</i> =2.7, 2.7
15 27.99 16 69.33 5.34 17 114.41 18 64.17 2.40 19 101.63 6.74 d J=1.3 20 135.34 6.14 t J=2 21 33.23b 0.87 22 21.34 0.77 23 16.31 0.79 24 17.31 0.81 25 8.75 0.81 0.82 0.82 0.83 0.84 0.84 0.84 0.85 0.86 0.86 0.87 0.80 0.80 0.80 0.80 0.80 0.80 0.80					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					
18 64.17 2.40 56.86 3.02 d J= 1.3 19 101.63 6.74 d J= 1.3 20 135.34 6.14 t J=2 134.48 6.11 t J= 2 21 33.23b 0.87 33.19b 0.80 eq 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax 0Ac 21.24 2.07 21.36 2.05 0Ac 21.03 2.07 20.99 2.06			5.34		5.34 dddd <i>J</i> =10.1, 6.2, 2.1, 1.2
19 101.63 6.74 d J=1.3 100.35 6.27 d J= 1.3 20 135.34 6.14 t J=2 134.48 6.11 t J= 2 21 33.23b 0.87 33.19b 0.80 eq 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax 20 0.80 eq 21.24 2.07 21.36 2.05 0.80 eq 21.36 2.05 0.80 eq 20.99 2.06					
20 133.34 6.14 t J=2 134.48 6.11 t J= 2 21 33.23b 0.87 33.19b 0.80 eq 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax OAc 21.24 2.07 21.36 2.05 OAc 21.03 2.07 20.99 2.06					
21 33.23b 0.87 33.19b 0.80 eq 22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax OAc 21.24 2.07 21.36 2.05 OAc 21.03 2.07 20.99 2.06					
22 21.34 0.77 21.26 0.76 ax 23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax OAc 21.24 2.07 21.36 2.05 OAc 21.03 2.07 20.99 2.06					
23 16.31 0.79 16.24 0.78 ax 24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax OAc 21.24 2.07 21.36 2.05 OAc 21.03 2.07 20.99 2.06					
24 17.31 0.81 16.81 0.81 ax 25 8.75 0.81 14.61 0.81 ax OAc 21.24 2.07 21.36 2.05 OAc 21.03 2.07 20.99 2.06					
25 8.75 0.81 14.61 0.81 ax OAc 21.24 2.07 21.36 2.05 OAc 21.03 2.07 20.99 2.06					
OAc 21.24 2.07 21.36 2.05 OAc 21.03 2.07 20.99 2.06					
OAc 21.03 2.07 20.99 2.06					
			2.07		2.00
CO 171.30 171.81 169.96					

Assignments were determined by ¹H-¹H COSY, ¹H-¹³C correlations via HMQC and HMBC NMR experiments, J values are expressed in Hz, a-b: Assignments may be reversed.

Hyrtios erecta from Australian Barrier Reef and Red Sea localities have already yielded a variety of sesterterpenes of which heteronemin is the dominant metabolite. Thus, it is surprising that in the New Caledonia sample, 12-epi-heteronemin 1 is the major compound (0.5%) and has not been isolated to-date. Marine sponges can biosynthesize several isomers of tetracarbocyclic sesterterpenes such as scalaradial 4, 12-epi-scalaradial 5 and 12-18-diepi-scalaradial, which were isolated from Spongia nitens⁵ and Cacospongia mollior⁶, all of which are PLA2 inhibitors⁷. Similarly, 12-epi-heteronemin acetate and 12-epi-scalaradial 5 have been reported from Hyrtios erecta². Hence, 12-epi-heteronemin can be considered as the missing piece of this series. Further studies on the chemical behaviour and on the biological activities of 1 and derivatives are in progress.

References

- Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. Tetrahedron Lett., 1976,30, 2631-2634.
- Crews, P.; Besansca, P. J. Nat. Prod., 1986, 49, 1041-1052.
- Kashman, Y.; and Rudi, A. Tetrahedron, 1977, 33, 2997-2998. 3.
- UV (MeOH) 210 (e, 13859), IR (film) 3545 (alcohol), 1732, 1748 and 1237 (acetate) cm⁻¹; MS: m/e 470 (17%), 428 (30%), 4. 386 (17%), 368 (100%), 350 (30%), 191 (47%).
- Cimino, G.; De Stefano, S.; Di Luccia, A. Experientia, 1979, 35, 1277-1278. Cimino, G.; De Stefano, S.; Minale, L. Experientia, 1973, 29, 934-935.
- Potts, B.C.M.; Faulkner, D.J. J. Nat. Prod., 1992, 55, 1701-1717.