

# New Cytotoxic Cembranes

## from the Sea Pen *Gyrophyllum sibogae*

Fernando Reyes, \*<sup>†</sup> Ana Ardá,<sup>‡</sup> Rocío Martín,<sup>†</sup> Rogelio Fernández,<sup>†</sup> Ana Rueda,<sup>†</sup>  
David Montalvo,<sup>†</sup> Cristina Gómez,<sup>†</sup> Carlos Jiménez,<sup>‡</sup> Jaime Rodríguez<sup>‡</sup> and José M<sup>a</sup>  
Sánchez-Puelles<sup>†</sup>

*Drug Discovery Department, PharmaMar S.A., Pol. Ind. La Mina Norte. Avda. de los Reyes 1. 28770 (Colmenar Viejo) Madrid, Spain, and Departamento de Química Fundamental, Facultade de Ciencias, Universidade de A Coruña, 15071 A Coruña, Spain.*

### SUPPORTING INFORMATION

**Table 2.** Key <sup>1</sup>H NMR signals (CDCl<sub>3</sub>, 200 MHz) of the (*S*)- and (*R*)- MPA ester derivatives of compound **1**.

Position	$\delta_{\text{H}}$ <i>S</i> -MPA ( <b>1b</b> )	$\delta_{\text{H}}$ <i>R</i> -MPA ( <b>1c</b> )	$\Delta\delta^{\text{SR}}$ ( <b>1b-1c</b> )
2	6.899	6.803	+0.096
3	6.198	6.193	+0.005
15	2.978	2.977	+0.001
16	1.110	1.111	+0.001
17	1.223	1.223	0
20	0.784	0.783	+0.001



**Table 3.** Key  $^1\text{H}$  NMR signals ( $\text{CDCl}_3$ , 500 MHz) of the (*S*)-MPA ester derivative **1b** at different temperatures.

Position	$\delta_{\text{H}}$ (298 K)	$\delta_{\text{H}}$ (263 K)	$\delta_{\text{H}}$ (223 K)	$\Delta\delta$ ( $\delta_{298}-\delta_{223}$ )
2	6.793	6.750	6.699	+ 0.094
3	6.186	6.167	6.154	+ 0.032
8	2.571	2.573	2.592	- 0.021
11	0.739	0.587	0.480	+ 0.259
15	2.968	2.945	2.931	+ 0.037
16	1.101	1.081	1.062	+ 0.039
17	1.213	1.200	1.181	+ 0.032
20	0.775	0.761	0.756	+ 0.019

## X-RAY of 7,8-dihydroflabellatene A (1)

Table 1: Final coordinates for 1

Num	Label	SFAC	Coordinates			Uij					
1	C1	1	1.263	-0.121	0.437	0.0386	0.0435	0.0379	0.0000	0.0025	0.0035
2	C2	1	1.136	-0.072	0.432	0.0413	0.0489	0.0375	-0.0021	0.0029	0.0061
3	C3	1	1.068	-0.027	0.368	0.0556	0.0664	0.0338	-0.0035	-0.0002	0.0171
4	C4	1	0.941	0.021	0.366	0.0578	0.0603	0.0390	-0.0115	-0.0122	0.0189
5	C5	1	0.851	0.031	0.433	0.0360	0.0501	0.0540	-0.0093	-0.0075	0.0059
6	C6	1	0.893	0.136	0.481	0.0426	0.0497	0.0405	-0.0057	0.0010	0.0005
7	C7	1	0.810	0.140	0.552	0.0388	0.0590	0.0453	-0.0062	0.0041	-0.0034
8	C8	1	0.870	0.227	0.607	0.0450	0.0464	0.0429	-0.0048	0.0079	-0.0001
9	C9	1	1.022	0.202	0.623	0.0461	0.0439	0.0386	-0.0086	0.0065	-0.0066
10	C10	1	1.061	0.086	0.660	0.0550	0.0546	0.0415	-0.0011	0.0100	-0.0002
11	C11	1	1.217	0.063	0.663	0.0577	0.0555	0.0411	-0.0046	-0.0092	0.0033
12	C12	1	1.284	0.016	0.593	0.0391	0.0460	0.0397	0.0037	-0.0040	0.0012
13	C13	1	1.246	-0.116	0.580	0.0396	0.0462	0.0369	0.0083	0.0019	-0.0004
14	C14	1	1.309	-0.164	0.509	0.0387	0.0375	0.0469	0.0050	0.0013	0.0018
15	C15	1	1.356	-0.144	0.372	0.0451	0.0615	0.0426	0.0007	0.0053	0.0120
16	C16	1	1.505	-0.101	0.383	0.0519	0.0721	0.0703	0.0026	0.0196	0.0035
17	C17	1	1.349	-0.274	0.349	0.0711	0.0894	0.0752	-0.0353	0.0077	0.0079
18	C18	1	0.881	0.072	0.298	0.0948	0.1245	0.0474	-0.0091	-0.0183	0.0575
19	C19	1	0.783	0.226	0.677	0.0507	0.0799	0.0472	-0.0130	0.0112	0.0025
20	C20	1	1.442	0.032	0.595	0.0427	0.0647	0.0767	0.0010	-0.0046	-0.0062
21	H001	2	1.145	-0.124	0.578	0.0491	0.0000	0.0000	0.0000	0.0000	0.0000
22	H01a	2	0.948	0.067	0.260	0.1334	0.0000	0.0000	0.0000	0.0000	0.0000
23	H01b	2	0.856	0.154	0.306	0.1334	0.0000	0.0000	0.0000	0.0000	0.0000
24	H01c	2	0.799	0.028	0.285	0.1334	0.0000	0.0000	0.0000	0.0000	0.0000
25	H002	2	1.267	-0.166	0.676	0.0869	0.0000	0.0000	0.0000	0.0000	0.0000
26	H003	2	1.247	0.062	0.553	0.0499	0.0000	0.0000	0.0000	0.0000	0.0000
27	H004	2	1.463	0.115	0.600	0.0921	0.0000	0.0000	0.0000	0.0000	0.0000
28	H005	2	1.480	-0.012	0.635	0.0921	0.0000	0.0000	0.0000	0.0000	0.0000
29	H006	2	1.481	0.003	0.550	0.0921	0.0000	0.0000	0.0000	0.0000	0.0000
30	H007	2	1.263	0.136	0.677	0.0617	0.0000	0.0000	0.0000	0.0000	0.0000
31	H008	2	1.234	0.005	0.702	0.0617	0.0000	0.0000	0.0000	0.0000	0.0000
32	H009	2	1.024	0.087	0.709	0.0604	0.0000	0.0000	0.0000	0.0000	0.0000
33	H010	2	1.017	0.021	0.634	0.0604	0.0000	0.0000	0.0000	0.0000	0.0000
34	H011	2	0.863	0.308	0.587	0.0537	0.0000	0.0000	0.0000	0.0000	0.0000
35	H012	2	0.688	0.251	0.667	0.0711	0.0000	0.0000	0.0000	0.0000	0.0000
36	H013	2	0.779	0.145	0.697	0.0711	0.0000	0.0000	0.0000	0.0000	0.0000
37	H014	2	0.798	0.303	0.765	0.1216	0.0000	0.0000	0.0000	0.0000	0.0000
38	H015	2	0.715	0.164	0.540	0.0572	0.0000	0.0000	0.0000	0.0000	0.0000
39	H016	2	0.807	0.061	0.573	0.0572	0.0000	0.0000	0.0000	0.0000	0.0000
40	H017	2	0.991	0.130	0.493	0.0531	0.0000	0.0000	0.0000	0.0000	0.0000
41	H018	2	0.879	0.209	0.455	0.0531	0.0000	0.0000	0.0000	0.0000	0.0000

42	H019	2	0.859	-0.043	0.461	0.0561	0.0000	0.0000	0.0000	0.0000	0.0000
43	H020	2	0.755	0.040	0.419	0.0561	0.0000	0.0000	0.0000	0.0000	0.0000
44	H024	2	1.116	-0.032	0.324	0.0623	0.0000	0.0000	0.0000	0.0000	0.0000
45	H025	2	1.085	-0.066	0.475	0.0511	0.0000	0.0000	0.0000	0.0000	0.0000
46	H026	2	1.318	-0.097	0.332	0.0597	0.0000	0.0000	0.0000	0.0000	0.0000
47	H027	2	1.505	-0.017	0.392	0.0971	0.0000	0.0000	0.0000	0.0000	0.0000
48	H028	2	1.546	-0.143	0.423	0.0971	0.0000	0.0000	0.0000	0.0000	0.0000
49	H029	2	1.558	-0.117	0.340	0.0971	0.0000	0.0000	0.0000	0.0000	0.0000
50	H030	2	1.389	-0.323	0.386	0.1178	0.0000	0.0000	0.0000	0.0000	0.0000
51	H031	2	1.253	-0.296	0.342	0.1178	0.0000	0.0000	0.0000	0.0000	0.0000
52	H032	2	1.399	-0.284	0.304	0.1178	0.0000	0.0000	0.0000	0.0000	0.0000
53	O001	3	1.402	-0.238	0.515	0.0628	0.0567	0.0577	0.0083	-0.0003	0.0228
54	O002	3	1.298	-0.189	0.637	0.0725	0.0628	0.0386	0.0176	0.0036	0.0044
55	O003	3	1.110	0.272	0.604	0.0504	0.0538	0.0946	0.0073	0.0034	-0.0139
56	O004	3	0.844	0.303	0.727	0.0790	0.1088	0.0553	-0.0314	0.0121	-0.0031

Table 2. Bond distances (Angstroms) for **1**

Atom	A	B	Dist	ADC(A)	ADC(B)
	C1	C2	1.343	55501	55501
	C1	C14	1.483	55501	55501
	C1	C15	1.519	55501	55501
	C2	H025	0.930	55501	55501
	C2	C1	1.343	55501	55501
	C2	C3	1.441	55501	55501
	C3	H024	0.930	55501	55501
	C3	C4	1.337	55501	55501
	C3	C2	1.441	55501	55501
	C4	C3	1.337	55501	55501
	C4	C18	1.492	55501	55501
	C4	C5	1.506	55501	55501
	C5	H019	0.970	55501	55501
	C5	H020	0.970	55501	55501
	C5	C4	1.506	55501	55501
	C5	C6	1.529	55501	55501
	C6	H017	0.970	55501	55501
	C6	H018	0.970	55501	55501
	C6	C7	1.522	55501	55501
	C6	C5	1.529	55501	55501
	C7	H015	0.970	55501	55501
	C7	H016	0.970	55501	55501
	C7	C6	1.522	55501	55501
	C7	C8	1.529	55501	55501
	C8	H011	0.980	55501	55501
	C8	C9	1.519	55501	55501
	C8	C7	1.529	55501	55501

C8	C19	1.529	55501	55501
C9	O003	1.203	55501	55501
C9	C10	1.511	55501	55501
C9	C8	1.519	55501	55501
C10	H009	0.970	55501	55501
C10	H010	0.970	55501	55501
C10	C9	1.511	55501	55501
C10	C11	1.521	55501	55501
C11	H007	0.970	55501	55501
C11	H008	0.970	55501	55501
C11	C10	1.521	55501	55501
C11	C12	1.532	55501	55501
C12	H003	0.980	55501	55501
C12	C11	1.532	55501	55501
C12	C20	1.535	55501	55501
C12	C13	1.540	55501	55501
C13	H001	0.980	55501	55501
C13	O002	1.422	55501	55501
C13	C14	1.535	55501	55501
C13	C12	1.540	55501	55501
C14	O001	1.219	55501	55501
C14	C1	1.483	55501	55501
C14	C13	1.535	55501	55501
C15	H026	0.980	55501	55501
C15	C1	1.519	55501	55501
C15	C16	1.522	55501	55501
C15	C17	1.522	55501	55501
C16	H027	0.960	55501	55501
C16	H028	0.960	55501	55501
C16	H029	0.960	55501	55501
C16	C15	1.522	55501	55501
C17	H030	0.960	55501	55501
C17	H031	0.960	55501	55501
C17	H032	0.960	55501	55501
C17	C15	1.522	55501	55501
C18	H01a	0.960	55501	55501
C18	H01b	0.960	55501	55501
C18	H01c	0.960	55501	55501
C18	C4	1.492	55501	55501
C19	H012	0.970	55501	55501
C19	H013	0.970	55501	55501
C19	O004	1.402	55501	55501
C19	C8	1.529	55501	55501
C20	H004	0.960	55501	55501
C20	H005	0.960	55501	55501
C20	H006	0.960	55501	55501
C20	C12	1.535	55501	55501

H001	C13	0.980	55501	55501
H01a	C18	0.960	55501	55501
H01b	C18	0.960	55501	55501
H01c	C18	0.960	55501	55501
H002	O002	0.820	55501	55501
H003	C12	0.980	55501	55501
H004	C20	0.960	55501	55501
H005	C20	0.960	55501	55501
H006	C20	0.960	55501	55501
H007	C11	0.970	55501	55501
H008	C11	0.970	55501	55501
H009	C10	0.970	55501	55501
H010	C10	0.970	55501	55501
H011	C8	0.980	55501	55501
H012	C19	0.970	55501	55501
H013	C19	0.970	55501	55501
H014	O004	0.820	55501	55501
H015	C7	0.970	55501	55501
H016	C7	0.970	55501	55501
H017	C6	0.970	55501	55501
H018	C6	0.970	55501	55501
H019	C5	0.970	55501	55501
H020	C5	0.970	55501	55501
H024	C3	0.930	55501	55501
H025	C2	0.930	55501	55501
H026	C15	0.980	55501	55501
H027	C16	0.960	55501	55501
H028	C16	0.960	55501	55501
H029	C16	0.960	55501	55501
H030	C17	0.960	55501	55501
H031	C17	0.960	55501	55501
H032	C17	0.960	55501	55501
O001	C14	1.219	55501	55501
O002	H002	0.820	55501	55501
O002	C13	1.422	55501	55501
O003	C9	1.203	55501	55501
O004	H014	0.820	55501	55501
O004	C19	1.402	55501	55501

Table 3. Bond angles (degrees) for **1**

Atom	A	B	C	Angle	ADC(A)	ADC(B)	ADC(C)
	C2	C1	C14	118.57	55501	55501	55501
	C2	C1	C15	123.22	55501	55501	55501
	C14	C1	C15	118.01	55501	55501	55501

H025	C2	C1	116.00	55501	55501	55501
H025	C2	C3	116.01	55501	55501	55501
C1	C2	C3	128.00	55501	55501	55501
H024	C3	C4	117.74	55501	55501	55501
H024	C3	C2	117.73	55501	55501	55501
C4	C3	C2	124.53	55501	55501	55501
C3	C4	C18	121.34	55501	55501	55501
C3	C4	C5	122.67	55501	55501	55501
C18	C4	C5	115.96	55501	55501	55501
H019	C5	H020	107.90	55501	55501	55501
H019	C5	C4	109.19	55501	55501	55501
H019	C5	C6	109.19	55501	55501	55501
H020	C5	C4	109.20	55501	55501	55501
H020	C5	C6	109.20	55501	55501	55501
C4	C5	C6	112.06	55501	55501	55501
H017	C6	H018	107.88	55501	55501	55501
H017	C6	C7	109.16	55501	55501	55501
H017	C6	C5	109.18	55501	55501	55501
H018	C6	C7	109.16	55501	55501	55501
H018	C6	C5	109.16	55501	55501	55501
C7	C6	C5	112.20	55501	55501	55501
H015	C7	H016	107.73	55501	55501	55501
H015	C7	C6	108.92	55501	55501	55501
H015	C7	C8	108.92	55501	55501	55501
H016	C7	C6	108.92	55501	55501	55501
H016	C7	C8	108.92	55501	55501	55501
C6	C7	C8	113.28	55501	55501	55501
H011	C8	C9	107.65	55501	55501	55501
H011	C8	C7	107.66	55501	55501	55501
H011	C8	C19	107.65	55501	55501	55501
C9	C8	C7	111.67	55501	55501	55501
C9	C8	C19	111.66	55501	55501	55501
C7	C8	C19	110.35	55501	55501	55501
O003	C9	C10	120.54	55501	55501	55501
O003	C9	C8	120.42	55501	55501	55501
C10	C9	C8	119.01	55501	55501	55501
H009	C10	H010	107.57	55501	55501	55501
H009	C10	C9	108.59	55501	55501	55501
H009	C10	C11	108.60	55501	55501	55501
H010	C10	C9	108.58	55501	55501	55501
H010	C10	C11	108.59	55501	55501	55501
C9	C10	C11	114.69	55501	55501	55501
H007	C11	H008	107.41	55501	55501	55501
H007	C11	C10	108.34	55501	55501	55501
H007	C11	C12	108.34	55501	55501	55501
H008	C11	C10	108.34	55501	55501	55501
H008	C11	C12	108.34	55501	55501	55501



C10	C11	C12	115.77	55501	55501	55501
H003	C12	C11	107.87	55501	55501	55501
H003	C12	C20	107.87	55501	55501	55501
H003	C12	C13	107.87	55501	55501	55501
C11	C12	C20	111.02	55501	55501	55501
C11	C12	C13	111.46	55501	55501	55501
C20	C12	C13	110.59	55501	55501	55501
H001	C13	O002	109.13	55501	55501	55501
H001	C13	C14	109.14	55501	55501	55501
H001	C13	C12	109.14	55501	55501	55501
O002	C13	C14	106.45	55501	55501	55501
O002	C13	C12	110.65	55501	55501	55501
C14	C13	C12	112.25	55501	55501	55501
O001	C14	C1	121.66	55501	55501	55501
O001	C14	C13	116.85	55501	55501	55501
C1	C14	C13	121.48	55501	55501	55501
H026	C15	C1	106.51	55501	55501	55501
H026	C15	C16	106.52	55501	55501	55501
H026	C15	C17	106.52	55501	55501	55501
C1	C15	C16	113.74	55501	55501	55501
C1	C15	C17	110.79	55501	55501	55501
C16	C15	C17	112.23	55501	55501	55501
H027	C16	H028	109.48	55501	55501	55501
H027	C16	H029	109.48	55501	55501	55501
H027	C16	C15	109.47	55501	55501	55501
H028	C16	H029	109.47	55501	55501	55501
H028	C16	C15	109.47	55501	55501	55501
H029	C16	C15	109.47	55501	55501	55501
H030	C17	H031	109.48	55501	55501	55501
H030	C17	H032	109.47	55501	55501	55501
H030	C17	C15	109.47	55501	55501	55501
H031	C17	H032	109.46	55501	55501	55501
H031	C17	C15	109.47	55501	55501	55501
H032	C17	C15	109.47	55501	55501	55501
H01a	C18	H01b	109.47	55501	55501	55501
H01a	C18	H01c	109.47	55501	55501	55501
H01a	C18	C4	109.47	55501	55501	55501
H01b	C18	H01c	109.46	55501	55501	55501
H01b	C18	C4	109.47	55501	55501	55501
H01c	C18	C4	109.48	55501	55501	55501
H012	C19	H013	108.38	55501	55501	55501
H012	C19	O004	110.04	55501	55501	55501
H012	C19	C8	110.04	55501	55501	55501
H013	C19	O004	110.03	55501	55501	55501
H013	C19	C8	110.03	55501	55501	55501
O004	C19	C8	108.32	55501	55501	55501
H004	C20	H005	109.47	55501	55501	55501

H004	C20	H006	109.47	55501	55501	55501
H004	C20	C12	109.48	55501	55501	55501
H005	C20	H006	109.48	55501	55501	55501
H005	C20	C12	109.47	55501	55501	55501
H006	C20	C12	109.47	55501	55501	55501
H002	Q002	C13	109.47	55501	55501	55501
H014	O004	C19	109.48	55501	55501	55501