Cembrane and Pseudopterane Diterpenes from the Soft Coral *Gersemia rubiformis*[1]

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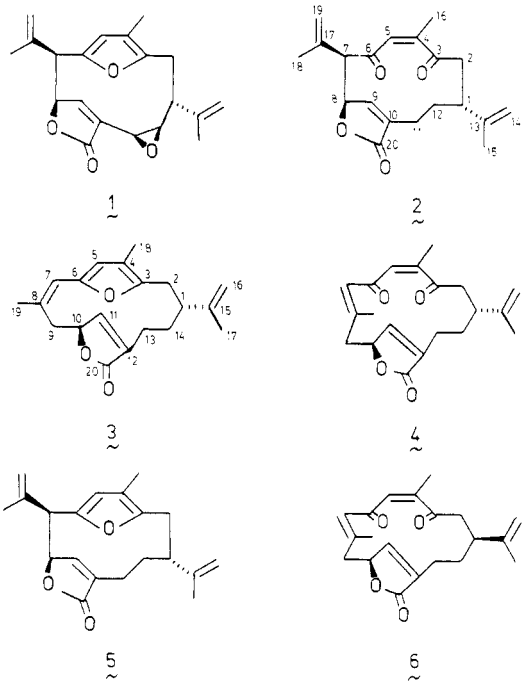
Three new diterpenes, gersemolide (2), rubifolide (3), and epilophodione (4), have been isolated from the soft coral *Gersemia rubiformis*. The structure of gersemolide (2) was solved via X-ray diffraction analysis and the structures of rubifolide (3) and epilophodione (4) were inferred from spectral data. Gersemolide (2) has a pseudopterane skeleton, while rubifolide (3) and epilophodione (4) are cembranes.

Gorgonians and soft corals, two groups of coelenterates that belong to the orders Gorgonacea and Alcyonacea respectively, are very abundant in tropical reef environments.[2] Indo Pacific reefs tend to be dominanted almost exclusively by soft corals, while western Atlantic reefs are populated primarily by gorgonians. The abundance and ease of collection of these invertebrates has facilitated an extensive investigation of their secondary metabolism.[2-4] Sesquiterpenoids and diterpenoids, having a wide variety of both well-known and rare carbon skeletons, are the most common soft coral and gorgonian metabolites. Cembrane diterpenoids account for the majority of compounds reported thus far from both orders of Alcyonaria. The pseudopterane diterpenoids, recently discovered by Fenical's group,[5,6] represent a family of Alcyonarian metabolites that have a previously unknown carbon skeleton. To date, the pseudopteranes have been taxonomically restricted to the Gorgonacea. In their report of pseudopterolide (1), Fenical et al. suggested that the pseudopterane carbon skeleton, which superficially looks like a simple dimerization of two geranyl residues, might instead arise from a ring contraction of a cembranoid precursor.

The cold temperate waters off the coastline of British Columbia, in contrast to tropical waters, harbour only one species of intertidal or subtidal soft coral.[7] Our routine bioactivity screening program[8] revealed that extracts of this soft coral, *Gersemia rubiformis*, exhibited potent in vitro antimicrobial activity. Prompted by this observation, we have investigated the secondary metabolites of *G. rubiformis* and we now report the structures of three new diterpenoids: gersemolide (2), rubifolide (3), and epilophodione (4).

G. rubiformis was collected by hand using SCUBA (~5 to ~15 m) around the Gordon Islands off the northern tip of Vancouver Island, British Columbia. Freshly collected specimens were immediately immersed in methanol. The methanol extract was fractionated by sequential application of flash, LH20, preparative thin layer (TLC), and high performance (HPLC) chromatographies.



Gersemolide (2), obtained as colorless needles, was shown by mass spectrometry to have a molecular formula of $C_{20}H_{24}O_4$. Resonances at 208.3, 197.6, and 173.7 ppm in the ^{13}C NMR of **2** could be assigned to the carbonyls of two ketones and one ester, respectively, thereby accounting for all four oxygen atoms. Eight olefinic carbon resonances in the ^{13}C NMR (Table II) indicated four carbon–carbon double bonds. Subtracting the seven sites of unsaturation required by the carbonyl and olefinic functionalities, from the total of nine sites required by the molecular formula, indicated that gersemolide (2) was bicyclic.

A one-proton resonance at 7.12 ppm in the ^1H NMR and ^{13}C NMR resonances at 173.6 (C), 150.0 (CH), 134.2 (C), and 79.0 (CH) ppm could be assigned to an α,γ-disubstituted α,β-unsaturated γ-lactone by analogy with the reported spectral data for pseudopterolide (1)[5] and kallolides A to C[6] which all contain such a fragment. The lactone accounts for one of the required rings in gersemolide (2). Two isopropenyl groups were identified from ^{13}C NMR resonances at 116.0 (CH_2) and 112.2 (CH_2) ppm and ^1H NMR resonances at 1.64 (s, 3 H), 1.73 (s, 3 H), 4.77 (brs, 2 H), 5.20 (s, 1 H), and 5.38 (s, 1 H) ppm, suggesting that gersemolide (2) contained a pseudopterane carbon skeleton

(1) This manuscript is dedicated to Professor George Büchi on the occasion of his 65th birthday.
(2) Tursch, B.; Braekman, J. C.; Daloze, D.; Kaisin, M. In *Marine Natural Products, Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. II, Chapter 4.
(3) Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421.
(4) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551.
(5) Bandurraga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463.
(6) Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
(7) Austin, W. C. *An Annotated Checklist of Marine Invertebrates in the Cold Temperate Northeast Pacific*; Khoyatan Marine Laboratory: Cowichin Bay, B.C., 1985.
(8) See for example: Fahy, E.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 57.

0022-3263/87/1952-0332$01.50/0

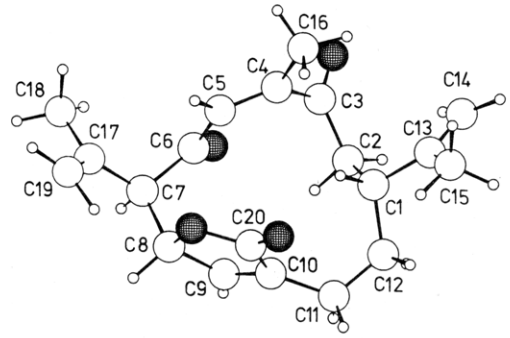


Figure 1. Computer-generated perspective drawing of gersemolide (**2**).

with the 12-membered carbocyclic ring accounting for the remaining site of unsaturation. The complete structure of gersemolide (**2**) was secured via single-crystal X-ray diffraction analysis.

A computer-generated perspective drawing of the final X-ray model of gersemolide (**2**) is presented in Figure 1. It should be noted that the X-ray experiment did not define the absolute configuration, so the enantiomer shown is arbitrary. While the structure shown in Figure 1 is completely compatible with the spectral data, there are some troubling aspects in the molecular geometry. The C10–C11–C12–C1 region of the X-ray model is unacceptable. The C11–C12 distance is 1.417 (9) Å, much too short for a sp^3–sp^3 bond, and the C10–C11–C12–C1 torsional angle is −8°, an essentially eclipsed conformation. This type of situation is not unprecedented and is usually explained by assuming a disordered structure. There are presumably at least two low energy conformations which occur in the crystal, and the resulting X-ray structure is their superposition. Careful inspection of various electron density syntheses did not reveal discrete peaks for the disordered mates but did reveal that the electron densities of C10 and C11 were rather broad. Since the X-ray analysis did not resolve the problem, we used molecular mechanics (MM2[9]) to find the suspected minima. Two local minima on the MM2 surface were found by varying the C10–C11–C12–C1 torsional angle. The first has a torsional angle of −37° and the second, +43°. The region around 0° represented a broad maximum. The calculated heats of formation for the minima differed by only 0.5 kcal/mol. The X-ray geometry was, as expected, the superposition of the two minima. Drawings and coordinates for the MM2 minima are given in the supplementary material.

Rubifolide (**3**), obtained as a crystalline solid, was shown by mass spectrometry to have a molecular formula of $C_{20}H_{24}O_3$. A number of fragments could be readily identified from the ^1H and ^{13}C NMR spectra of rubifolide. Carbon resonances at 78.7 (CH), 152.1 (CH), 132.8 (C), and 174.5 (C) ppm and a proton resonance at 6.86 (s, 1 H) ppm could be assigned to an α,γ-disubstituted, α,β-unsaturated γ-lactone identical with the corresponding substructure of gersemolide (**2**). A 2,5-dialkyl-3-methylfuran was indicated by carbon resonances at 9.5 (CH_3), 149.4 (C), 117.1 (C), 113.8 (CH), and 149.9 (C) ppm which were almost identical in chemical shift with the resonances assigned to the corresponding fragment in kallolide B (**5**)[6] (Table II). ^1H NMR resonances at 1.92 (brs, 3 H) and 5.99 (brs, 1 H) ppm were assigned to the furan methyl substituent and β proton, respectively. An isopropenyl residue (^{13}C NMR: 145.4 (C), 115.6 (CH_2), 17.2 (CH_3); ^1H NMR: 4.88 (brs, 1 H), 4.90 (brs, 1 H), 1.74 (brs, 3 H)) and a trisubstituted olefin bearing a methyl group (^{13}C NMR: 117.4 (CH), 127.0 (C), 22.3 (CH_3); ^1H NMR: 6.07 (s, 1 H), 1.98 (s, 3 H)) were also readily apparent. One aliphatic methine and four aliphatic methylene carbons (^{13}C NMR: 43.2 (CH), 31.2 (CH_2), 39.5 (CH_2), 30.5 (CH_2), 20.0 (CH_2)) accounted for the rest of the atoms in rubifolide.

The cembranoid structure **3** effectively accommodates all the identified structural fragments of rubifolide. A series of NOE and spin–spin decoupling experiments were used to verify that **3** represented the correct structure. Irradiation of the methyl resonance at 1.98 ppm (C19) in the ^1H NMR of rubifolide induced positive NOE's into an olefinic proton at 6.07 (H7) and a methylene proton at 2.68 (H9a) and induced a weak negative NOE into a methylene proton at 3.22 ppm (H9b). The lactone methine proton at 4.95 ppm (H10) showed vicinal coupling to the methylene protons H9a and H9b (2.68 and 3.22 ppm) and to the olefinic proton H11 (6.86 ppm), and it showed homoallylic coupling to the methylene proton H13a (2.08 ppm). Decoupling experiments clearly demonstrated the connectivity in the seven-spin system found on C13 to C2, and they allowed the assignment of resonances at 2.55 ppm (m, 2 H) to H2a and H2b. Finally, irradiation of the furan methyl resonance at 1.92 ppm induced NOE's into an olefinic proton at 5.99 (H5) and into the methylene protons at 2.55 (H2a and H2b). This set of experiments demonstrated the expected connectivities starting at C7 and progressing around the ring to C6.

The observed NOE between the C19 methyl protons and the C7 olefinic proton requires the *Z* configuration for the C7–C8 olefinic bond in **3**. We have assumed that the relative configurations of the chiral centers at C1 and C10 in rubifolide (**3**) are the same as the relative configurations of the corresponding centers in gersemolide (**2**).

Epilophodione (**4**), obtained as colorless needles, was shown by mass spectrometry to have a molecular formula of $C_{20}H_{24}O_4$. The ^1H and ^{13}C NMR data (Tables I and II) observed for epilophodione showed a striking resemblance to the data reported by Bandurraga et al. for lophodione (**6**),[10] suggesting that the two metabolites have the same constitution and differ only in some stereochemical sense.

Irradiation of the C18 methyl protons (1.91 ppm) in **4** induced an NOE into the H5 olefinic proton (6.40 ppm) indicating that the C4–C5 olefinic bond in epilophodione (**4**) has the *Z* configuration in common with the corresponding bond in lophodione (**6**). No NOE could be demonstrated between the C19 methyl protons and the H7 olefinic proton in epilophodione (**4**), a result that is consistent with the C7–C8 olefinic bond having the *E* configuration found in lophodione (**6**).[10] Since the olefin geometries in epilophodione (**4**) are identical with those in lophodione (**6**), the sterochemical difference in the two structures must involve the relative configurations at the

(9) QCPE Program No. 395 as modified by Serana Software was used for the MM2 calculations.

(10) Bandurraga, M. M.; McKittrick, B.; Fenical, W.; Arnold, E.; Clardy, J. *Tetrahedron* **1982**, *38*, 305.

(11) All crystallographic calculations were done on a PRIME 9950 computer operated by the Cornell University Computing Facility. Principal programs employed were REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN80 and RANTAN80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson synthesis) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1980; BLS78A, an aniostropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a locally modified crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hiratsu and G. Van Duyne, Cornell University, 1985.

Table I. ^{1}H NMR Assignments for Gersemolide, Rubifolide, Epilophodione, and Lophodione[10] (Spectra Were Run in $CDCl_3$ and Chemical Shifts Are in ppm from Me_4Si)

C no.	gersemolide (2)	rubifolide (3)	epilophodione (4)	lophodione (6)[10]
1	2.26 (m, 1 H)[a]	2.36 (td, J = 13, 4 Hz, 1 H)	2.13–2.47 (m)	
2	2.30 (dd, J = 15, 10 Hz, 1 H)	2.55 (m, 2 H)	2.51 (m, 2 H)	2.64 (br d, J = 14 Hz, 1 H)
	2.53 (dd, J = 15, 5 Hz, 1 H)			2.40 (m, 1 H)
5	6.33 (br s, 1 H)	5.99 (br s, 1 H)	6.40 (br s, 1 H)	6.42 (br s, 1 H)
6				
7	3.29 (br s, 1 H)	6.07 (br s, 1 H)	6.15 (br s, 1 H)	6.12 (br s, 1 H)
8	5.46 (br s, 1 H)			
9	7.12 (br s, 1 H)	2.68 (dd, J = 11, 4 Hz, 1 H)	2.66 (dd, J = 13, 5 Hz, 1 H)	3.04 (dd, J = 13, 4.6 Hz, 1 H)
		3.22 (t, J = 11 Hz, 1 H)	2.83 (dd, J = 13, 5 Hz, 1 H)	2.61 (br d, J = 13 Hz, 1 H)
10		4.95 (dm, J = 11 Hz, 1 H)	5.27 (m, 1 H)	5.31 (m, 1 H)
11	2.01 (m, 1 H)[a]	6.86 (br s, 1 H)	7.18 (br s, 1 H)	6.97 (br s, 1 H)
	2.42 (m, 1 H)[a]			
12	1.28 (m, 2 H)			
13		2.08 (dm, J = 14 Hz, 1 H)	1.83 (m, 1 H)	
		2.43 (td, J = 14, 3 Hz, 1 H)	2.13–2.47	
14	5.20 (br s, 1 H)[b]	1.18 (tq, J = 14, 3 Hz, 1H)	1.37 (tm, J = 13 Hz, 1 H)	
	5.38 (br s, 1 H)[b]	1.64 (m, 1 H)	1.63 (m, 1 H)	
15	1.64 (br s, 3 H)[c]			
16	1.83 (br s, 3 H)[c]	4.88 (br s, 1 H)	4.88 (br s, 2 H)	4.97 (br s, 1 H)
		4.90 (m, 1 H)		4.72 (br s, 1 H)
17		1.74 (br s, 3 H)	1.59 (br s, 3 H)	1.60 (br s, 3 H)
18	1.73 (br s, 3 H)[c]	1.92 (br s, 3 H)	1.91 (br s, 3 H)	1.84 (br s, 3 H)
19	4.77 (m, 2 H)[b]	1.98 (br s, 3 H)	2.19 (br s, 3 H)	2.19 (br s, 3 H)

[a–c] Signals within a column may be reversed.

Table II. ^{13}C NMR Assignments for Gersemolide, Rubifolide, Epilophodione, Kallolide B,[6] and Lophodione[10] (Spectra Were Run in $CDCl_3$ and Chemical Shifts Are in ppm from Me_4Si)

C no.	gersemolide (2)[a]	rubifolide (3)[b]	epilophodione (4)[a]	kallolide B (5)	lophodione (6)
1	41.2 (CH)	43.3 (CH)	41.8 (CH)	42.1	41.3
2	44.9 (CH_2)	31.2 (CH_2)	45.5 (CH_2)	30.1	45.7
3	208.3 (C)[c]	149.4 (C)	205.5 (C)	149.6	205.4
4	156.2 (C)	117.1 (C)	143.9 (C)[c]	114.4	144.8
5	123.8 (CH)	113.8 (CH)	133.5 (CH)	112.4	133.4
6	197.6 (C)[c]	149.9 (C)	192.1 (C)	150.0	190.7
7	62.4 (CH)	117.4 (CH)	127.1 (CH)	48.8	125.9
8	79.0 (CH)	127.0 (C)	151.8 (C)	81.2	156.3
9	150.0 (CH)	39.5 (CH_2)	43.6 (CH_2)	147.1	43.5
10	146.4 (C)	78.7 (CH)	78.4 (CH)	136.8	80.1
11	22.0 (CH_2)	152.1 (CH)	148.1 (CH)	23.1	148.4
12	31.4 (CH_2)	132.8 (C)	136.2 (C)	34.5	134.1
13	134.2 (C)[d]	20.0 (CH_2)	21.0 (CH_2)	148.2	25.7
14	112.3 (CH_2)[e]	30.5 (CH_2)	33.5 (CH_2)	110.7	30.3
15	19.8 (CH_3)[f]	145.4 (C)	145.4 (C)[c]	19.5	145.5
16	21.9 (CH_3)[f]	112.9 (CH_2)	115.6 (CH_2)	9.7	115.9
17	138.1 (C)[d]	19.2 (CH_3)	17.2 (CH_3)	142.7	17.0
18	23.1 (CH_3)[f]	9.5 CH_3)	21.1 (CH_3)[d]	114.5	21.5
19	116.1 (CH_2)[e]	25.7 (CH_3)	22.3 (CH_3)[d]	21.8	22.6
20	173.7 (C)	174.5 (C)	173.6 (C)	175.6	173.1

[a] Hydrogen attachments were determined by using DEPT and/or ADEPT. [b] Assignments based on chemical shift and 2D-HETCOR. Hydrogen attachments were determined by using fully coupled spectrum. [c–f] Signals within a column may be reversed.

two chiral centers. The reported relative configurations for the C1 and C10 chiral centers in lophodione are R^*,S^*. If the two chiral centers in epilophodione (4) have the same configurations as the corresponding chiral centers in gersemolide (2), their relative configurations must be R^*,R^*, making 4 epimeric with 6. The absolute configuration of lophodione (6) was not reported, and we have not determined the absolute configuration of epilophodione (4), so it is not possible to say which of the two chiral centers has the opposite configuration in the two metabolites.

The isolation of diterpenes 2 to 4[12] from *Gersemia rubiformis* is of interest for a number of reasons. First, gersemolide (2), extracted from a soft coral, is the first example of a pseudopterane diterpene isolated from any source other than a gorgonian. Secondly, *G. rubiformis* represents the first organism to contain both pseudopterane and cembrane diterpenes, a fact which lends additional credence to Fenical's suggestion[5] that the pseudopterane skeleton might arise from a ring contraction of a cembrane. Epilophodione (4) and gersemolide (2) are in principle directly related by such a contraction, although it is likely that the contraction would take place before complete functionalization of the hydrocarbon skeleton. Finally, the discovery of metabolites in a cold water soft coral that are virtually identical with those previously reported from tropical soft corals and gorgonians suggests that although not many species of Gorgonacea and Alcyonacea grow in cold temperate waters, the species that do might reasonably be expected to have chemistry similar to their tropical relatives.

(12) None of the diterpenoids reported in this manuscript show appreciable antimicrobial activity. Efforts are underway to isolate the active constituent(s) of the crude extracts.

Experimental Section

^{1}H NMR spectra were recorded on Bruker WP-80, Varian XL-300, and Bruker WH-400 spectrometers. ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. Me_4Si was used an an internal standard. Low-resolution mass spectra were re-

corded on an AEI MS902 spectrometer and high resolution mass spectra on an AEI MS50 spectrometer. IR spectra were recorded on a Perkin-Elmer 1710 fourier transform spectrometer. UV–vis spectra were recorded on a Bausch and Lomb Spectronic-2000 instrument. Optical rotation measurements were recorded on a Perkin-Elmer 141 polarimeter.

Merck silica gel (230–400 mesh) was used for flash and preparative thin layer chromatography and a Whatman Magnum-9 Partisil-10 column was used for preparative HPLC. Sephadex LH-20 was used for molecular exclusion chromatography.

Specimens of *G. rubiformis* were collected by hand using SCUBA in several exposed rocky channels (–5 to –15 m) located within the Gordon Group of Islands, British Columbia. Freshly collected animals were immediately immersed in methanol and allowed to extract at room temperature for 2–3 days before decanting the methanol to give a skin extract. The animals were next homogenized in a Waring blender with fresh solvent and extracted at room temperature for a further 2 days followed by vacuum filtration through Celite to give a whole body extract. The skin and whole body extracts were separately concentrated to 1000 mL (approximately $^1/_3$ of the original volumes), and in both cases the yellow brown solutions were sequentially extracted with hexanes (4 × 250 mL), methylene chloride (2 × 250 mL), and ethyl acetate (2 × 250 mL). Recombination of the hexane, methylene chloride, and ethyl acetate soluble materials from each of the extractions gave an oily yellow brown skin extract (12.0 g) and an oily dark red whole body extract (14.2 g).

The two oils were fractionated by flash chromatography (50-mm diameter columns, 20-cm silica gel, step gradient of 5% ethyl acetate/hexanes to 10% methanol/acetate, run repetitively with 4-g samples) to yield fractions containing fats, steroids, carotenoids, and crude samples of rubifolide (**3**) and epilophodione (**4**) from both skin and whole body extracts. Fractions containing **3** and **4** from both separations were combined (total yields: **3**, 2.39 g, and **4**, 1.19 g). Crude gersemolide (**2**) (87.3 mg) was obtained only from the skin extract column.

Gersemolide (2). Further purification of crude **2** by preparative TLC (5% methanol/methylene chloride), LH20 column chromatography (80% methanol/chloroform), and reverse phase HPLC (60% methanol/water) yielded pure gersemolide (**2**) (4.5 mg, 3×10^{-6} dry wt) as clear crystalline needles: R_f 0.71 (5% MeOH/CH_2Cl_2); ^{1}H NMR (Table I); ^{13}C NMR (table II); HRMS, observed m/z 328.1686, $C_{20}H_{24}O_4$ requires 328.1675; MS, m/z (rel intensity) 328 (31), 283 (21), 268 (13), 246 (33), 232 (10), 229 (14), 213 (11), 201 (16), 189 (23), 178 (62), 164 (42), 159 (32), 151 (85), 135 (52), 121 (43), 119 (43), 105 (79), 91 (100), 82 (86), 68 (64), 53 (62).

Single-Crystal X-ray Diffraction Analysis of Gersemolide (2). Suitable single crystals were grown by slow evaporation at 0 °C from 1:1 diethyl ether/methanol. Preliminary X-ray photographs displayed orthorhombic symmetry, and accurate lattice constants of a = 6.2098 (14), b = 13.9068 (33), and c = 20.7523 (68) Å were determined from a least-squares fit of 15 moderate 2θ values. The systematic extinctions, crystal density, and optical activity uniquely indicated space group $P2_12_12_1$ with 1 molecule of composition $C_{20}H_{24}O_4$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer using graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å) and variable speed, 1° ω scans. Of the 1433 unique reflections measured in this fashion, 1115 (78%) were judged observed ($F_o > 3\sigma(F_o)$) and used in subsequent calculations.[11] A phasing model was found with the MULTAN series of programs, and the starting structure was extended by weighted Fourier refinements. Most hydrogens were located in this fashion; most notably the hydrogens attached to C11 and C12 were included at calculated positions. Block-diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.0642 for the observed reflections. Additional crystallographic details are available and are described in the paragraph entitled Supplementary Material Available at the end of this paper.

Rubifolide (3). Impurities (fats etc.) in samples of **3** were partially removed via preparative TLC (2% methanol/methylene chloride) and LH20 column chromatography (70% methanol/chloroform). The resulting enriched sample of **3** (350 mg) was further purified by a combination of normal phase HPLC (3:3:1 diethyl ether/hexanes/methylene chloride) and reverse phase HPLC (7:2:1 methanol/water/chloroform) to yield pure rubifolide (**3**) (220 mg, 1.5×10^{-4} % dry wt) as a white crystalline solid (from 1:1 methylene chloride/methanol): mp 159–160 °C; $[\alpha]^{25}_D$ +31.7° (c 0.39, CH_2Cl_2); R_f 0.80 (5% MeOH/CH_2Cl_2); UV (MeOH) λ_{max} 279 nm (ϵ 16 433); IR (CH_2Cl_2) 3076, 2998, 2931, 2867, 1753, 1644, 1606, 1447, 1199, 1069, 902, and 863 cm^{-1}; ^{1}H NMR (Table I); ^{13}C NMR (Table II); HRMS, observed m/z 312.1275, $C_{20}H_{24}O_3$ requires 312.1276; MS, m/z (rel intensity) 312 (41), 216 (12), 201 (11), 173 (6), 148 (100), 133 (44), 120 (22), 105 (34), 91 (19), 79 (13), 77 (15), 69 (7), 68 (11), 67 (11), 65 (9), 55 (5), 53 (12).

Epilophodione (4). Crude **4** was further purified by preparative TLC (5% methanol/methylene chloride), LH20 column chromatography (80% methanol/chloroform), and chromatotron chromatography (step gradient consisting of two solvent systems 50% methylene chloride/hexanes followed by 1:1:1 diethyl ether/hexanes/methylene chloride). The resulting enriched sample (85 mg) was purified via reverse phase HPLC (60% methanol/water) to yield pure epilophodione (**4**) (25 mg, 1.6×10^{-5} % dry wt) as clear crystalline needles (from 1:1 methylene chloride/methanol): mp 153–155 °C; $[\alpha]^{25}_D$ +136.2° (c 0.42, CH_2Cl_2); R_f 0.67 (5% MeOH/CH_2Cl_2); UV (MeOH) λ_{max} 264 (ϵ 10 893), 211 nm (14 133); IR (CH_2Cl_2) 2940, 1756, 1683, 1645, 1619, 1607, 1443, 1201, 1065, 948, and 900 cm^{-1}; ^{1}H NMR (Table I); ^{13}C NMR (Table II); HRMS, observed m/z 328.1680, $C_{20}H_{24}O_4$ requires 328.1675; MS, m/z (rel intensity) 328 (9), 310 (3), 295 (1), 285 (2), 267 (3), 323 (7), 219 (9), 201 (6), 178 (50), 151 (100), 135 (55), 133 (32), 107 (31), 105 (31), 95 (31), 91 (40), 82 (95), 79 (45), 77 (36), 67 (48), 53 (39).

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, interatomic angles, torsional angles, and drawings and coordinates for the local minima on the MM2 surface for gersemolide (**2**) (15 pages). Ordering information is given on any current masthead page.