Structure of Bryostatin 4. An Important Antineoplastic Constituent of Geographically Diverse *Bugula neritina* (Bryozoa)[1]

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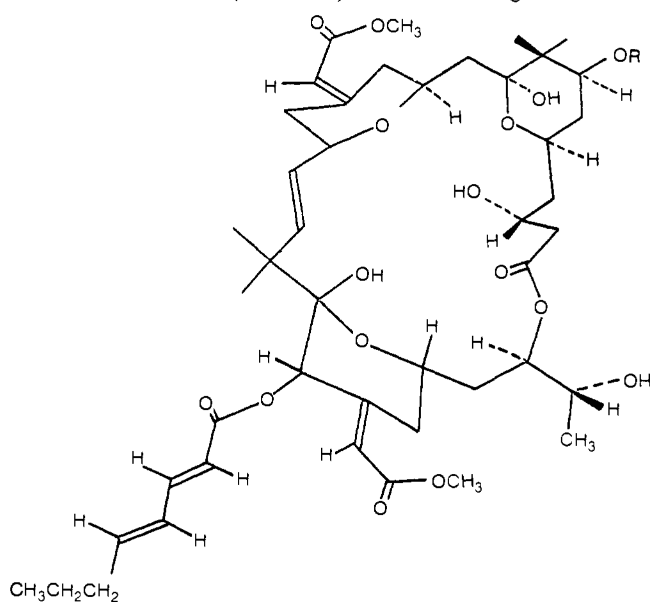
Abstract: A new antineoplastic macrocyclic lactone designated bryostatin 4 has been isolated from specimens of the marine bryozoan *Bugula neritina* (Linnaeus) collected in the Gulfs of California, Mexico, and Sagami (Japan). The discovery of bryostatin 4 in geographically distant collections of *Bugula neritina* suggests that such unique cell growth inhibitors may be true biosynthetic products of the animal. The structure (3) of bryostatin 4 was assigned employing high-resolution (400 MHz) ^{1}H NMR and ^{13}C NMR as well as solution phase secondary ion mass spectrometry techniques combined with results of hydrolysis experiments. Bryostatin 4 exhibited substantial cell growth inhibitory (PS cell line ED_{50}, 10^{-3}–10^{-4} μg/mL) and antineoplastic (PS, 62% increase in life extension at 46 μg/kg) properties.

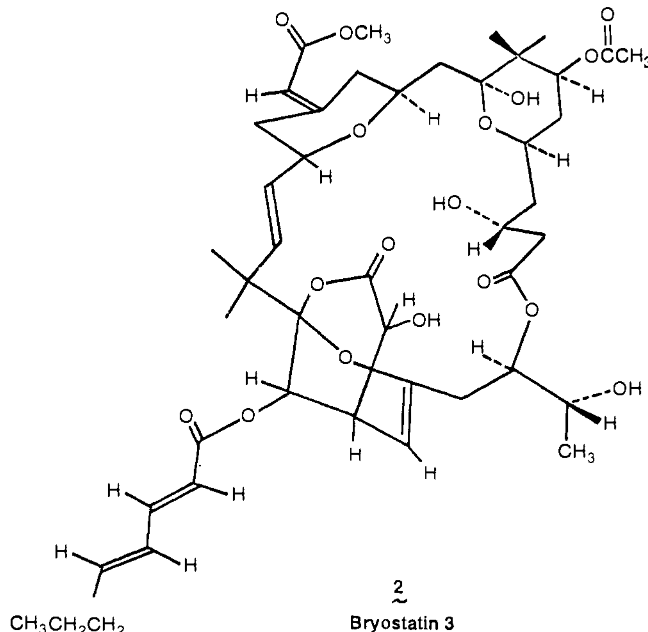
In 1968 we initiated a study of antineoplastic biosynthetic products contained in the marine bryozoan *Bugula neritina* (Linnaeus).[2] And this investigation recently led to the isolation and structural elucidation of bryostatins 1–3 (**1a**, **1b**, **2**) from eastern Pacific Ocean (California) collections of *Bugula neritina*.[3]



1a, R = CO-CH$_3$
Bryostatin 1

b, R = H
Bryostatin 2

These unique 20-membered cyclic lactones were found to substantially inhibit growth of the U.S. National Cancer Institute's (NCI) murine P388 lymphocytic leukemia (PS system). Subsequently bryostatin 1 (NSC 339555) was found by the NCI to afford 31–68% life extension at 5–40 μg/kg against the M531 murine ovary sarcoma (ip tumor implant with ip treatment).



2
Bryostatin 3

Meanwhile collections of *Bugula neritina* from the Gulf of Mexico (USA), Gulf of California (Mexico), and Gulf of Sagami (Japan) have been under study. We are now pleased to report that *Bugula neritina* from these geographically diverse marine areas contains a new and very potent cell growth inhibitory substance designated bryostatin 4 (**3**, NSC 362621) that differs markedly in respect to side-chain esterification from the California Series (**1a**, **1b**, **2**). Furthermore, the discovery of bryostatin 4 (**3**) with pronounced cell growth (PS cell line ED_{50}, 10^{-3}–10^{-4} μg/mL) and antineoplastic (PS, 62% increase in life extension at 46 μg/kg) properties eliminates the (*E*,*E*)-octa-2,4-dienoic ester at C-20 of bryostatins 1–3 as essential for such important biological properties. The isolation and structural elucidation of bryostatin 4 were conducted as summarized in the sequel.

The methylene chloride fraction of the methylene chloride–methanol–water extraction of *Bugula neritina* (50 kg wet weight, Gulf of Mexico) was partitioned between 9:1 methanol–water and hexane. Next, the methanol–water phase was diluted to 4:1 methanol–water and extracted with methylene chloride. Overall separations were guided by bioassay (PS system), and a variety

(1) (a) Dedicated to Professor Carl Djerassi on the occasion of his 60th birthday. (b) The 96th contribution in the series Antineoplastic Agents, and for part 95 see: Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc. Chem. Commun.*, in press. (c) Department of Chemistry, The Jikei University School of Medicine, Kokuryo, Chofu-shi, Tokyo, 182, Japan.

(2) Pettit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature (London)* **1970**, *227*, 962–963.

(3) (a) Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846–6848. (b) Pettit, G. R.; Herald, C. L.; Kamano, Y.; Gust, D.; Aoyagi, R. *J. Nat. Prod.* **1983**, *46*, 528–531. (c) Pettit, G. R.; Herald, C. L.; Kamano, Y. *J. Org. Chem.* **1983**, *48*, 5354–5356.

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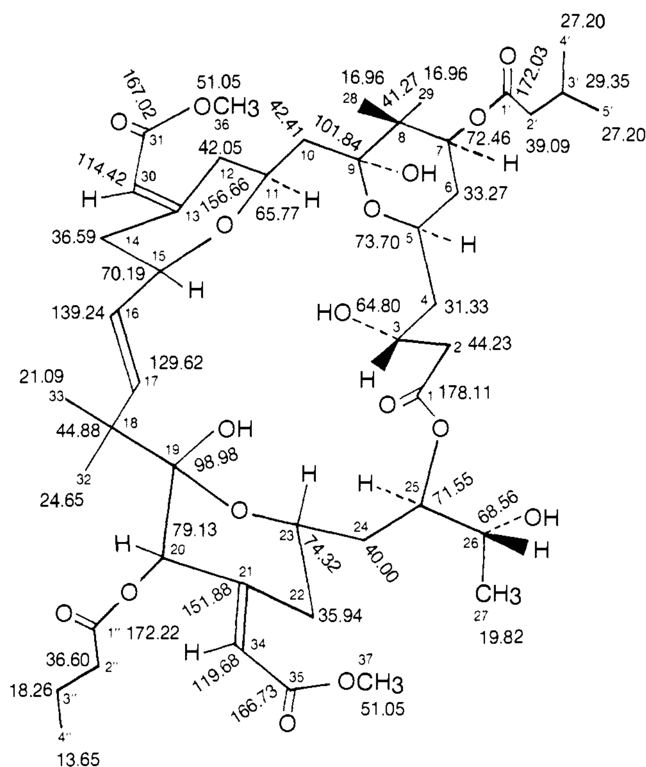
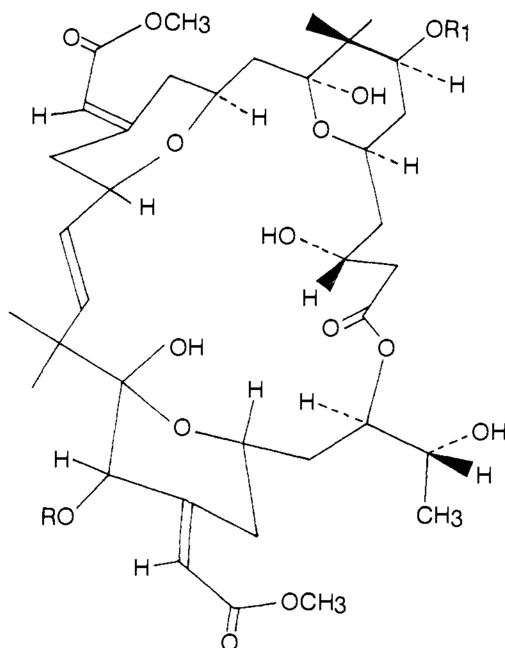


3
Bryostatin 4 (with ^{13}C-NMR)



4 a, R = COCH2CH2CH3, R1 = H
b, R = H, R1 = COCH2CH(CH3)2

of isolation procedures were investigated. The following techniques proved to be most effective. The methylene chloride fraction was subjected to a series of gel permeation (Sephadex LH-20, 2:3 and 2:1 methylene chloride–methanol), silica gel (hexane–acetone, hexane–ethyl acetate), and reversed phase (C-18, methanol–water) HPL chromatographic procedures. Bryostatin 4 (**3**) was obtained (44.5 mg, (8.9×10^{-5})% yield) from methylene chloride–methanol as an amorphous powder.

Detailed interpretation of the 400-MHz ^{1}H NMR spectrum (Table I) of bryostatin 4 uncovered a series of signals that very closely corresponded to the high-resolution proton assignments for the bryopyran ring system of bryostatins 1[3a] and 2.[3b] In addition, the side-chain protons of the esters at C-7 and C-20 characteristic of bryostatins 1–3 were absent. The ^{13}C NMR (see structure **3**) signals at δ 172.03 and δ 172.22 suggested the presence of new ester substitution at C-7 and C-20. Such a possibility was further strengthened by the C-7 carbon resonance at δ 72.46 and the C–20 carbon resonance at δ 79.13. Similarly, in the ^{1}H NMR spectrum of bryostatin 4, the C-7 proton appeared at δ 5.10 (m) and the C-20 proton at δ 5.167 as a sharp singlet. Both signals were very characteristic of the bryostatin 1 molecular geometry.

Because of substantial difficulties in recognizing the molecular ion in mass spectra of bryostatins, by a variety of methods, we were led to develop a new series of techniques based on solution phase secondary ion mass spectrometry.[4] These new procedures utilizing an alkali metal iodide, silver tetrafluoroborate or thallium tetrafluoroborate in sulfolane provided, with a great variety of substances including the bryostatins, the facile and routine detection of molecular ions. Application of these new mass spectral methods to further determining the structure of bryostatin 4 proved decisive. With sodium iodide in sulfolane, bryostatin 4 exhibited m/z 917 $[M + Na]^+$ as parent peak with other ions at 899 $[M + Na - 18]^+$, 829 $[M + Na - 88]^+$, and 815 $[M + Na - 102]^+$. Analogously, with silver tetrafluoroborate was found m/z 1001 and 1003 $[M + Ag^{107}$ and $M + Ag^{109}]^+$ as parent peaks accompanied by 983 and 985 $[M + Ag - 18]^+$, 913 and 915 $[M + Ag - 88]^+$, and 899 and 901 $[M + Ag - 102]^+$. The loss of 88 mass units suggested elimination of a butyrate ester and water while the loss of 102 indicated elimination of a valerate group and water. Confirmation for these assumptions was obtained by assignment of the remaining ^{1}H and ^{13}C NMR signals. By this means the butyrate group was found to be *normal* and the valerate ester to be *iso*.

A study of the selective acid-catalyzed hydrolysis of bryostatin 1 (**1a**) to bryostatin 2 (**1b**) with hydrochloric acid provided a basis for assigning positions to the butyrate and isovalerate esters. The relative steric compression of C-20 compared to C-7 seemed to favor hydrolysis at the less hindered position (C-7), and bryostatin 1 was found convertible to bryostatin 2 in reasonable yield.[3b] Selective hydrolysis of bryostatin 4 (1 mg) with hydrochloric acid (1% in aqueous methanol, 24 h at room temperature) yielded (0.72 mg) bryostatin **4a** with a molecular ion complex at m/z 833 $[M + Na]^+$ corresponding to the C-7 desisovalerate and as minor product (0.100 mg) bryostatin **4b** with m/z 847 $[M + Na]^+$ for the C-20 desbutyrate. From these results the butyrate ester was assigned to C-20 and the isovalerate ester to C-7.

Assignment of structure **3** to bryostatin 4 clearly eliminates the (*E,E*)-octa-2,4-dienoate ester unit of bryostatins 1–3 as a prerequisite for antineoplastic activity. Evidence now on hand suggests that the bryopyran ring system and substitutents common to bryostatins 1–4 constitute the unique requirements for anticancer activity while the ester substituents at C-7 and C-20 influence the degree of cytotoxicity (cf. 1 vs. 4) and antineoplastic effects.

Discovery of bryostatin 4 (**3**) as a prominent antineoplastic constituent of *Bugula neritina* found in such diverse geographical areas as the Gulfs of Mexico (U.S.) and Sagami (Japan) suggests that this fascinating macrocyclic lactone system is more likely a biosynthetic product of the animal rather than a dietary source. But a definitive conclusion regarding this biochemical question will require a careful chemical examination of the microorganisms ingested by *Bugula neritina* and/or (^{14}C)acetate biosynthetic feeding experiments.

Experimental Section

Sephadex LH-20 (25-100 μ) employed for gel permeation and partition chromatography was obtained from Pharmacia Fine Chemicals, AB, Uppsala, Sweden. Column chromatographic separations with silica gel were performed with the 70–230 mesh size supplied by E. Merck (Darmstadt). The Partisil-10 M-9-ODS-2 (C-18 reversed phase) column (9.4-mm ID $\times$ 500 mm) used for HPLC was obtained from Whatman, Inc., Clifton, NJ. An Altex HPLC with System Controller Model 420

(4) Pettit, G. R.; Holzapfel, C. W.; Cragg, G. M.; Herald, C. L.; Williams, P. *J. Nat. Prod.* **1983**, *46*, 917–922.

Table I. Bryostatin ^{1}H NMR (400 MHz) Chemical Shift Assignments Relative to Tetramethylsilane in Deuteriochloroform Solution

structure 4 assign no.	bryostatin 4 δ	bryostatin 4 multiplicity (J, Hz)	bryostatin 1 δ	bryostatin 1 multiplicity (J, Hz)
2	2.45	m	2.45	m
3	4.16	m	4.19	m
4	1.61, 2.04	m, m	1.55, 1.95	m, m
5	4.22	m	4.1	m
6	1.40, 1.72	m, m	1.4, 1.5	m, m
7	5.10	m	5.15	m
10	1.65, 2.15	m, m	2.1–2.2	m
11	3.87	m	3.95	m
12	2.18	m	2.1–2.2	m
14	1.85, 2.05	m, m	1.9–2.0	m, m
15	4.08	m	4.08	m
16	5.250	dd (8.4, 15.7)	5.300	dd (8.3, 15.9)
17	5.738	d (15.7)	5.758	d (15.9)
20	5.167	s	5.162	m
22	1.85, 2.00	m, m	~1.90	m
23	3.98	m	~3.65	m
24	1.78, 1.90	m, m	1.95	m
25	5.07	m	5.19	m
26	3.77	m	3.73	m
27	1.211	d (6.3)	1.226	d (6.3)
28[a]	1.138	s	1.132	s
29[a]	0.996	s	0.982	s
30	5.660	s	5.657	s
32[a]	0.985	s	0.982	s
33[a]	0.920	s	0.919	s
34	5.961	s	5.983	s
36	3.686	s		
37	3.658	s		
2′	2.25	m	2.051	s
3′	1.88–1.99	m		
4′	1.16	d (14.5)		
5′				
2″	2.25	m	5.796	d (15.3)
3″	1.60	m	7.261	m
4″	0.901	t (7.2)	6.157	m
5″			6.157	m
6″			~2.15	m
7″			1.42	m
8″			0.904	t (7.3)

[a] Assignments for these four positions may be interchanged.

and Model 110A pumps was used for final separations. All solvents used for chromatographic techniques were redistilled, and Gilson UV monitor Model HM and Gilson microfractionators (FC-80) were used for fractionation.

Preparative layer silica gel and reversed phase thin-layer chromatographic (TLC) plates (KC18) were obtained from Whatman, Inc., and silica gel GF uniplates for TLC were supplied by Analtech, Inc., Newark, DE. The TLC plate results were interpreted by UV light and/or developed by anisaldehyde–acetic acid–sulfuric acid spray by heating at approximately 150 °C for 5–10 min.

Melting points are uncorrected and were determined by using a Kofler-type melting point apparatus. The ultraviolet spectra were obtained by using a Hewlett-Packard 8450A UV/VIS spectrophotometer equipped with an HP 7225A plotter. Optical rotations were observed with a Perkin-Elmer 241 variable wavelength polarimeter. Infrared spectral data were determined by using a Nicolet FTIR Model MX-1 instrument. All mass spectra were recorded by D. Adams with a MAT 312 spectrometer, and our new solution phase secondary ion mass spectral (SP-SIMS)[4] methods were employed for these determinations. Nuclear magnetic resonance experiments were conducted with Varian XL-100, Bruker WH-90, and Bruker WH-400 instruments. In each case, deuteriochloroform was employed as solvent and tetramethylsilane as internal standard.

Animal Taxonomy. Taxonomic studies of *Bugula neritina* (Linnaeus) were nicely provided by the Smithsonian Institution, Washington, DC.

Animal Habitats. A. Gulf of Mexico. In June 1968, 0.5 kg of *Bugula neritina* (Linnaeus), Bryozoa phylum, was collected in the Eastern Gulf of Mexico (Alligator Harbor, Franklin County, FL). The animal was preserved in 2-propanol, and this extract showed PS T/C 190 at 800 mg/kg. A recollection (Alligator Harbor) in April 1970 provided 6.2 kg of initial 2-propanol extract, and this material was subjected to an extended series of isolation studies, at various times, over the next decade.

A 50-kg (wet weight) re-collection from the same site in July 1982 afforded an initial methylene chloride extract (see Animal Extraction) that was toxic at 6.25 mg/kg and showed PS T/C 129 at 3.12 mg/kg. Bryostatin 4 was eventually isolated from this re-collection.

B. Gulf of California. A 1-kg collection was obtained at Bahia de Navachiste, Sinaloa, Mexico, in March 1976. The preserving solution extract (2-propanol) showed PS T/C 200 at 100 mg/kg. Unfortunately, re-collection was unsuccessful in 1978 due to an intervening hurricane that destroyed the original collecting site. Meanwhile we had located (1973) *B. neritina* at Bahia Kino, Sonora, Mexico, and re-collections were commenced there in 1978. A January 1982 collection amounting to 12.5 kg (wet weight) was used for the isolation studies reported here and the initial methylene chloride extract showed PS T/C 170 at 25 mg/kg.

C. Gulf of Sagami. A 5-kg (wet weight) amount of *B. neritina* was collected in the Gulf of Sagami near the Misaki Marine Biological Station (Tokyo area) in May and July of 1982. The preserving solution (2-propanol) extract showed PS T/C 135 at 17.5 mg/kg, and the derived methylene chloride fraction displayed T/C 206 at 20 mg/kg.

Animal Extraction. A typical separation scheme[5] found most effective for all (A → C) collections of *B. neritina* now follows with detail illustrated for the 1982 Gulf of Mexico recollection.

The 2-propanol solution used to preserve 50 kg (wet weight) of the animal was concentrated to dryness. The residue was partitioned between methylene chloride (12 L, 5 ×) and water (12 L). Each phase was separated and solvent removed. The aqueous fraction weighed 733 g and was inactive (PS ED_{50}, >100). Animal residue was further extracted with 1:1 methylene chloride–methanol[6] (120 L) for 28 days in 15-gal stainless-steel vessels. A second extraction (170 L) was performed in an analogous manner for 14 days. After addition of enough water to cause phase separation, the methylene chloride fractions from the first (212 g, PS ED_{50}, 0.64 μg/mL) and second (65 g, PS ED_{50}, 1.4 μg/mL) extractions were separated and the solvent was removed. The residue was combined with the methylene chloride fraction (195 g, PS ED_{50}, 1.5 μg/mL) from the 2-propanol extract and partitioned between hexane (4 L, 6 ×) and methanol–water (9:1, 4 L). The hexane phase was separated and the methanol–water adjusted to a concentration of 3:2 and extracted with methylene chloride (4 L, 5 ×). The hexane (299 g, PS ED_{50}, 45 μg/mL), methylene chloride (37.6 g, PS ED_{50}, 0.058 μg/mL), and methanol–water (24 g, PS ED_{50}, >100 μg/mL) fractions were concentrated (reduced pressure) to dryness.

Isolation of Bryostatin 4. The PS cell line active methylene chloride fraction (37.4 g) was chromatographed (dry column method) on silica gel (3.8 × 95 cm column) with a solvent gradient from methylene chloride to increasing (0.5 to 20%) concentrations of methanol. Progress of the chromatogram was followed by TLC with methylene chloride–methanol–water (90:10:0.8). The fraction (2.7 g) eluted by 98:2 to 97:3 methylene chloride–methanol contained the antineoplastic activity (PS ED_{50}, <10^{-4}, T/C 157 at 0.8 mg/kg) and was rechromatographed on a column of silica gel using a similar solvent gradient to give a 1.61-g active fraction (PS ED_{50}, 2.2 × 10^{-4}, T/C 181 at 0.58 mg/kg). The chromatographic procedure was again repeated with the active 1.61 g to yield a fraction (0.55 g) greatly enriched in bryostatin 4 (**3**). An orange pigment accompanied the antineoplastic components, and it was removed by a combination of steric exclusion and partition chromatography on Sephadex LH-20 (3 × 120 cm column) employing 2:3 methylene chloride–methanol.

The resulting active fraction was rechromatographed on Sephadex LH-20 with 2:1 methylene chloride–methanol as eluent. By this means the major antineoplastic fraction (0.38 g, PS ED_{50}, 1.6 × 10^{-3}) separated from methylene chloride–methanol as a colorless amorphous powder. By use of two TLC systems (7:3 *n*-hexane–acetone and 2:3 *n*-hexane–ethyl acetate) this fraction proved to be a mixture of very closely related components. Resolution of the mixture in respect to bryostatin 4 was achieved by using dry column (2 × 60 cm column) silica gel chromatographic methods with *n*-hexane–acetone (5:1 → 1:1) and *n*-hexane–ethyl acetate (2:1 → 1:2) solvent systems. Six fractions were selected and each was further purified employing HPLC using a Partisil-10 M9 ODS-2 column (C-18 reversed phase) with a 1:1 → 9:1 methanol–water solvent gradient (flow rate of 2 mL/min). Bryostatin 4 (**3**, 44.5 mg, 8.9 × 10^{-5}%

(5) (a) Pettit, G. R.; Ode, R. H. "Biosynthetic Products for Cancer Chemotherapy"; Plenum Publishing Corp.: New York, 1979; Vol. 3, 59. (b) Pettit, G. R.; Fujii, Y.; Hasler, J. A.; Schmidt, J. M.; Michel, C. *J. Nat. Prod.* **1982**, *45*, 263–269.

(6) Developed by one of us (G.R.P.) with Drs. D. L. Doubek and D. L. Herald.

yield) was isolated from the first fraction. By the same sequence, the Gulf of California *B. neritina* (12.5 kg) afforded 12.3 mg (9.8×10^{-5}% yield) and the Gulf of Sagami collection (5 kg) provided 1.0 mg (2×10^{-5}% yield) of bryostatin 4.

When necessary, bryostatin 4 was brought to analytical purity by repeating the HPLC sequence. A pure specimen ($C_{46}H_{70}O_{17}$, mol wt 894) was obtained as a colorless amorphous powder (PS ED_{50}, 6.7×10^{-4}, T/C 162 at 46 μg/kg) melting at 198-200 °C: MS (SP-SIMS)[4], with lithium iodide in sulfolane, *m/z* 901 $[M + Li]^+$, 883 $[M + Li - 18]^+$, and 799 $[M + Li - 102]^+$, with sodium iodide in sulfolane, *m/z* 917 $[M + Na]^+$, 899 $[M + Na - 18]^+$, 829 $[M + Na - 88]^+$, and 815 $[M + Na - 102]^+$, and with silver tetrafluoroborate in sulfolane, *m/z* 1001 and 1003 $[M + Ag^{107}$ and $Ag^{109}]^+$, 983 and 985 $[M + Ag - 18]^+$, 913 and 915 $[M + Ag - 88]^+$, and 899 and 901 $[M + Ag - 102]^+$; $[\alpha]^{27}_D$ +93.6° (*c* 0.032, CH_3OH); UV (CH_3OH) λ_{max} 228 (ϵ 36 500); IR (KBr) 3470, 2980-2945, 1740, 1725, 1660-1645, 1440, 1390, 1370, 1290, 1240, 1170, 1100, 1080, 1050, and 1000 cm^{-1}. The 400-MHz ^1H NMR data have been displayed in Table I in comparison with bryostatin 1, and the ^{13}C NMR assignments accompany structure **3**. Because of the unequivocal spectral evidence and exceptional value of bryostatin 4, elemental analyses were not performed.

Acid-Catalyzed Hydrolysis of Bryostatin 4. A specimen of bryostatin 4 (**3**, 1.0 mg) in 0.5 mL of 1% hydrochloric acid in methanol was hydrolyzed for 24 h at room temperature. The mixture (0.9 mg) obtained by extraction with methylene chloride, washing with water, and drying was separated by HPLC reversed phase (C-18) column chromatography with methanol-water (from 1:1 to 9:1) to furnish C-7 des-ester **4a** (0.72 mg) and C-20 des-ester **4b** (0.100 mg). The C-7 des-ester **4a** ($C_{41}H_{62}O_{16}$) was obtained as an amorphous powder from aqueous methanol: MS (SP-SIMS)[4] using sodium iodide in sulfolane, *m/z* 833 $[M + Na]^+$, 815 $[M + Na - 18]^+$, and 727 $[M + Na - 88]^+$; IR (KBr) 3475, 3420, 2975-2950, 1740, 1720, 1640, 1615, 1440, 1380, 1290, 1240, 1165, 1095, 1080, 1050, and 870 cm^{-1}. Analogously the C-20 des-ester **4b** ($C_{42}H_{64}O_{16}$) was obtained as an amorphous solid from aqueous methanol: MS (SP-SIMS) with sodium iodide in sulfolane, *m/z* 847 $[M + Na]^+$, 829 $[M + Na - 18]^+$, and 727 $[M + Na - 102]^+$.

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Registry No. 3, 91523-82-9; **4a**, 91523-83-0; **4b**, 91549-41-6.

MNDO Calculations for Compounds Containing Tin[1]

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Abstract: The MNDO parametric SCF-MO treatment has been parametrized for tin. Calculations are reported for a number of compounds of tin. The results are comparable with those for the third-period elements.

The MNDO semiempirical SCF-MO method[3,4] is now established[5] as a practical procedure for studying chemical behavior, giving results comparable[6] with those from quite good ab initio models (e.g., 4-31G) while requiring only one-thousandth as much computer time. Parameters are currently available for hydrogen,[4] for the second-period elements beryllium,[7] boron,[8] carbon,[4] nitrogen,[4] oxygen,[4] and fluorine,[9] for the third-period elements aluminum,[10] silicon,[11] phosphorus,[11] sulfur,[12] and chlorine,[13] and for bromine[14] and iodine.[15] Since MNDO currently uses an s,p basis set without d AOs, calculations are confined to compounds involving only normal group valencies. Schleyer et al.[16] have also reported extensive MNDO calculations for compounds containing lithium, but the parameters for lithium have not yet been published.

Table I. MNDO Parameters for Tin

optimized parameters	value	derived parameters	value
U_{ss}	−40.851802[a]	E_{heat}	72.2[b]
U_{pp}	−28.560249[a]	E_{el}	−92.3241020[a]
ζ_s	2.080380[c]	D_1	1.5697766[d]
ζ_p	1.937106[c]	D_2	1.3262292[d]
β_s	−3.235147[a]	AM	0.3601617[d]
β_p	−4.290416[a]	AD	0.3219998[d]
A_{1p}	1.800814[e]	AQ	0.3713827[d]
G_{ss}	9.800000[a]		
G_{pp}	7.300000[a]		
G_{sp}	8.300000[a]		
G_{p2}	6.500000[a]		
H_{sp}	1.300000[a]		

[a] In eV. [b] In kcal/mol at 298 K (heat of atomization). [c] Atomic units (Bohrs). [d] In atomic units. [e] In Å^{-1}.

(1) Part 68 of the series Ground States of Molecules. For Part 67 see: Dewar, M. J. S.; Healy, E. F.; Stewart, J. J. P. *J. Comput. Chem.* **1984**, *4*, 358.
(2) On sabbatical leave from St. Michael's College, Winooski, VT 05404.
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(5) For example, a CA search lists 148 citations of MNDO in the period since January 1982, to be compared with 1073 for ab initio.
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