Synthetic conversion of bryostatin 2 to bryostatin 1 and related bryopyrans[1]

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Received August 22, 1990

GEORGE R. PETTIT, DIPANJAN SENGUPTA, CHERRY L. HERALD, NANCY A. SHARKEY, and PETER M. BLUMBERG. Can. J. Chem. **69**, 856 (1991).

Bryostatin 2 (**1***a*) has been converted to bryostatin 1 (**1***e*) and bryostatin 12 (**1***i*) by a selective protection and deprotection involving the C-26 hydroxyl group. The new bryostatins **1***g*, **1***k*, and **1***m* were also prepared starting from bryostatin 2. The C-7 substituents of natural bryostatins 4 and 5 were revised from isovalerate → pivalate employing comparative ^{1}H and ^{13}C NMR studies of the semi-synthetic bryostatins **1***k* and **1***m* and the natural products.

Key words: bryostatin 2 → 1, selective conversion, bryostatins 4 and 5, pivalates.

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On a transformé la bryostatine 2 (**1***a*) en bryostatine 1 (**1***e*) et en bryostatine 12 (**1***i*) grâce à une protection et une déprotection sélective impliquant le groupement hydroxyle en C-26. On a aussi préparé les bryostatines **1***g*, **1***k* et **1***m* à partir de la bryostatine 2. En se basant sur des études comparatives de RMN du ^{1}H et du ^{13}C, effectuées sur les bryostatines semi-synthétiques **1***k* et **1***m* et sur les produits naturels, on propose une révision de la nature de substituants en position C-7 des bryostatines 4 et 5 d'isovalérate à pivalate.

Mots clés : bryostatine, conversion sélective, bryostatines 4 et 5, pivalates.

[Traduit par la rédaction]

The marine Bryozoan *Bugula neritina* has been found to contain a series of biologically and chemically exciting constituents now known as the bryostatins (2*a*–*g*). Other interesting biosynthetic products of the Phylum Bryozoa such as the β-lactam bearing chartellines have recently been isolated from *Chartella papyracea* (3). Bryostatin 1 (**1***e*) has been found to profoundly affect protein kinase C at picomolar concentrations (4*a*). Uniquely among protein kinase C modulators, whereas bryostatin 1 activates protein kinase C in vitro, it antagonizes phorbol ester responses in many biological systems (4*b*) and is deficient in tumor promoting activity (4*c*,*d*). Bryostatin 1 has powerful immunopotentiating activities (4*e*,*f*). The ability of bryostatin 1 to initiate cytotoxic T lymphocyte development (4*f*), and to induce production of interleukin-2 (4*f*,*g*) and growth of normal bone marrow cells (4*h*), combined with its strong *anti*tumor (4*i*) promoter and antineoplastic effects resulted in its selection for clinical development by the U.S. National Cancer Institute. To increase significantly the availability of bryostatin 1 (**1***e*) it became very important to convert bryostatin 2 (**1***a*), which was also obtained from *Bugula neritina* in nearly equal amounts, to bryostatin 1 in an efficient and selective way. Realization of this objective was accomplished as follows.

The bryostatin hydroxyl groups at C-3, C-9, and C-19 were earlier found (2*b*) to resist acetylation (under mild conditions), presumably due to intramolecular hydrogen bonding, while the C-7 and C-26 hydroxyl groups were readily acetylated (2*b*,*g*). Thus, synthetic conversion was undertaken by methods utilizing selective protection of the C-26 hydroxyl group. The steric environment of the two hydroxyl groups (viz. C-7 and C-26) suggested that a bulky silyl ether[3] would offer an attractive possibility.

Application of *tert*-butyldimethylsilyl chloride (6) was found very effective for selective protection of the bryostatin 2 C-26 hydroxyl group. Bryostatin 2 (**1***a*) was allowed to react (7) at room temperature with excess *tert*-butyldimethylsilyl (TBDMS) chloride in the presence of 4-(*N*,*N*-dimethyl)aminopyridine (and triethylamine in dimethylformamide) to produce 26-*tert*-butyldimethylsilyl ether **1***b* and bryostatin 2 7,26-di-*tert*-butyldimethylsilyl ether **1***c*. The disilyl ether was reconverted to bryostatin 2 employing 48% hydrofluoric acid – acetonitrile (1:20) (8). The yield of monosilyl ether **1***b* was 71% on the basis of total recovered bryostatin 2. Treatment of the C-26 silyl ether with acetic anhydride – pyridine (room temperature) gave acetate **1***d*. The C-26 hydroxyl was regenerated using 48% hydrofluoric acid – acetonitrile (1:20 at 0–5°C). The product was isolated in 80% overall yield (from **1***a*) by silica gel column chromatography and found to be identical with natural bryostatin 1 (**1***e*).

The high resolution SP-SIMS spectrum of bryostatin **1***e* displayed *m*/*z* 911 $(M + Li)^+$ and 927 $(M + Na)^+$ corresponding to the molecular formula $C_{47}H_{68}O_{17}$. The ^{1}H NMR spectrum revealed an acetate chemical shift at δ 2.04, the C-7 proton signal at δ 5.14 (dd, J = 12, 4.9 Hz), and the three-proton doublet of the C-27 methyl at δ 1.23 (J = 6.5 Hz). The significant downfield shift of the C-7 proton from δ 3.95 (**1***a*, **1***b*) to δ 5.14 (**1***e*) further confirmed acetylation at the C-7 hydroxyl group.

Selective protection of the C-26 hydroxyl group in bryostatin 2 allowed us to selectively introduce other groups at C-7.

[1]Part 192 of Antineoplastic Agents. For part 191 see ref. 1.

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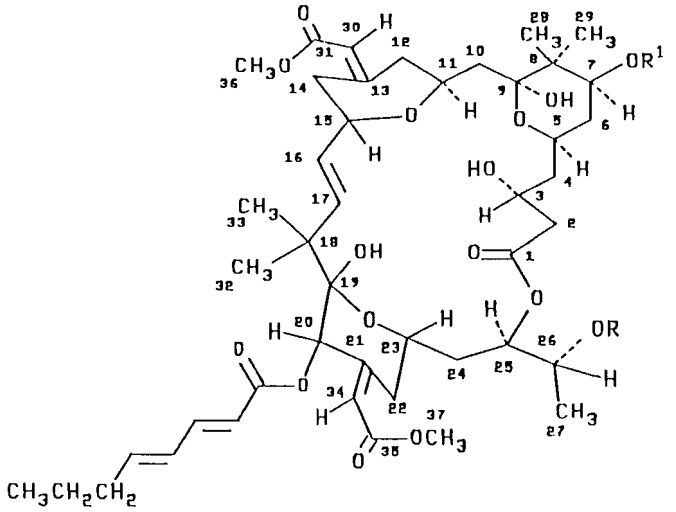
[3]For review see Use of organosilicon reagents as protective groups in organic synthesis, ref. 5.

Printed in Canada / Imprimé au Canada



1, *a* R = R^1 = H, bryostatin 2
b R = TBDMS, R^1 = H
c R = R^1 = TBDMS
d R = TBDMS, R^1 = -$COCH_3$
e R = H, R^1 = -$COCH_3$, bryostatin 1
f R = TBDMS, R^1 = -$COCH_2CH_3$
g R = H, R^1 = -$COCH_2CH_3$
h R = TBDMS, R^1 = -$COCH_2CH_2CH_3$
i R = H, R^1 = -$COCH_2CH_2CH_3$, bryostatin 12
j R = TBDMS, R^1 = -$COCH_2CH(CH_3)_2$
k R = H, R^1 = -$COCH_2CH(CH_3)_2$
l R = TBDMS, R^1 = -$COC(CH_3)_3$
m R = H, R^1 = -$COC(CH_3)_3$

Treatment of 26-*tert*-butyldimethylsilyl ether **1***b* with butyric anhydride and pyridine, followed by deprotection, led to bryostatin 2 7-butyrate (**1***i*) identical to bryostatin 12 (**1***i*). Bryostatin 2 7-propionate (**1***g*) was obtained in an analogous manner.

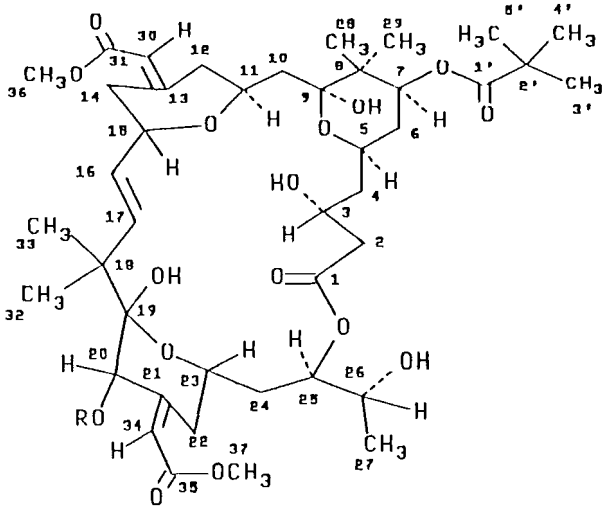
Conversion of bryostatin 2 to bryostatin 2 7-isovalerate (**1***k*) and bryostatin 2 7-pivalate (**1***m*) provided convincing support for the revision[4] of C-7 substituents in bryostatins 4 (**2***a*) (2*d*) and **5** (**2***b*) (2*e*). Esterification of bryostatin 2 26-OTBDMS (**1***b*) with isovaleric acid in the presence of dicyclohexylcarbodiimide and 4-pyrrolidinopyridine (10) in methylene chloride provided ester **1***j*. The TBDMS protecting group was removed to afford the new bryostatin **1***k*. Treatment of bryostatin 2 26-OTBDMS (**1***b*) with pivalic anhydride and 4-(*N*,*N*-dimethyl)aminopyridine (50–55°C) (for a review, see ref. 11) in methylene chloride provided bryostatin 2 26-OTBDMS-7-pivalate (**1***l*). Removal of the protecting group afforded bryostatin 2 7-pivalate (**1***m*) in 42% overall yield from **1***b*. The ^{1}H NMR spectrum of bryostatin **1***m* showed a strong singlet for the pivalate unit at δ 1.17 (Table 1) and a multiplet for the C-7 proton at δ 5.08 (dd, J = 11.8, 4.8 Hz), whereas bryostatin **1***k* showed a doublet at δ 0.93 (J = 6.3 Hz, Table 1) for the isovalerate unit.

The isovalerate → pivalate revision was further supported by the ^{13}C NMR spectra of natural bryostatins 4 and 5 (Table 2).

[4]In 1988, during another reisolation of bryostatins 4 and 5, recharacterization employing high-field NMR techniques suggested possible presence of a pivalate ester at C-7. The realization of this minor modification at C-7 was made possible by newer NMR techniques and these structural changes have already been entered in a contribution by Pettit *et al.* (9).

Comparison of the ^{1}H and ^{13}C NMR spectra of natural bryostatins 4 and 5 with those of the semi-synthetic bryostatins **1***m* and **1***k* confirmed the C-7 pivalate substitution. The strong singlet at δ 1.17 in the ^{1}H NMR spectrum of semi-synthetic bryostatin **1***m* (Table 1) was nearly identical to the singlet at δ 1.16 and δ 1.19 of natural bryostatins 4 and 5, respectively. Moreover, the bryostatin **1***m* gave rise to ^{13}C chemical shifts at δ 177.99 (C-1′), 39.01 (C-2′), and 27.14 (C-3′, -4′, and -5′, Table 2), in close agreement with the ^{13}C NMR shifts displayed by the C-7 substituents of natural bryostatins 4 and 5. The proton spectrum of bryostatin **1***k* showed a doublet due to two methyl groups at δ 0.93 (J = 6.3 Hz) (Table 1) and the ^{13}C NMR spectrum gave evidence of C-1′ at δ 172.81, C-2′ at δ 43.75, C-3′ at δ 24.93, and C-4′ and -5′ at δ 22.35 (Table 2), thereby substantiating that bryostatins 4 (**2***a*) and 5 (**2***b*) contain the unusual pivalate ester group at C-7 (2*d*,*e*, 9).

In initial biochemical characterization, the binding affinities of bryostatins **1***g*, **1***k*, and **1***m* for protein kinase C were determined by competition of [^{3}H]bryostatin 4 binding as described previously for bryostatins 1–10 (4*i*). The assay conditions involve reconstitution of protein kinase C in Triton X-100/phosphatidylserine. Although these conditions give



2, *a* R = -$COCH_2CH_2CH_3$, bryostatin 4
1″ 2″ 3″ 4″

b R = -$COCH_3$, bryostatin 5
1″ 2″

significantly lower affinity than found for the enzyme reconstituted under the more physiological conditions of phospholipid alone, they permit quantification under equilibrium conditions. The K_i values for bryostatins **1***g*, **1***k*, and **1***m* were 1.7 ± 0.5, 0.74 ± 0.23, and 0.73 ± 0.17 nM (mean ± range, n = 2 experiments) respectively. Similar values were thus observed for the isovalerate and pivalate esters, with slightly less activity for the propionate ester **1***g* and the acetate ester (bryostatin 1, K_i = 1.4 ± 0.2 nM, 4*i*).

The strategy for selective reaction at the C-7 hydroxyl group of bryostatin 2 with protection and deprotection of the more reactive C-26 hydroxyl now opens a useful pathway to a variety of new bryostatins (12). In time, that will allow further study of the structure/activity relationships among this fascinating group of marine animal antineoplastic constituents.

TABLE 1. Bryostatin ^{1}H NMR (400 MHz) chemical shift assignments in deuteriochloroform solution[a]

	Bryostatin **1***g*			Bryostatin **1***k*			Bryostatin **1***m*		
H	δ	Multiplicity	$J_{H,H}$ (Hz)	δ	Multiplicity	$J_{H,H}$ (Hz)	δ	Multiplicity	$J_{H,H}$ (Hz)
2	2.45	m		2.45	m		2.45	m	
3	4.16	m		4.17	m		4.17	m	
4	2.01, 1.56	m		2.06, 1.58	m		2.05, 1.58	m	
5	4.22	d	12	4.22	d	12	4.21	d	11.4
6	1.45, 1.75	m		1.44, 1.71	m		1.43, 1.71	m	
7	5.14	dd	11.8, 4.8	5.14	dd	11.8, 4.7	5.08	dd	11.8, 4.8
10	2.06, 2.15	m		2.07, 2.17	m		2.07, 2.14	m	
11	3.79	m		3.78	m		3.78	m	
12	2.06, 3.64	m		2.07, 3.63	m		2.06, 3.63	m	
14	1.86, 3.62	m		1.93, 3.63	m		1.89, 3.63	m	
15	4.04	dt	8.5, 2	4.03	m		4.04	m	
16	5.30	dd	15.8, 8.5	5.30	dd	15.7, 8.4	5.30	dd	15.7, 8.4
17	5.79	d	15.8	5.78	d	15.7	5.77	d	15.7
20	5.16	s		5.18	s		5.19	s	
22	2.08	m		2.09	m		2.09	m	
	1.66	d	15.1	1.67	d	15.2	1.64	d	15.1
23	4.01	m		4.01	m		4.00	m	
24	1.92, 2.06	m		1.91, 2.07	m		1.92, 2.07	m	
25	5.14	m		5.15	m		5.17	m	
26	3.79	m		3.80	m		3.80	m	
27	1.23	d	6.6	1.22	d	6.4	1.22	d	7.0
28[b]	0.93	s		0.92	s		0.93	s	
29[b]	0.99	s		0.99	s		0.99	s	
30	5.67	s		5.66	s		5.67	s	
32[c]	1.14	s		1.14	s		1.13	s	
33[c]	1.08	s		0.99	s		0.99	s	
34	6.00	d	1.5	5.99	d	1.5	5.99	d	1.5
36	3.69	s		3.69	s		3.68	s	
37	3.65	s		3.65	s		3.64	s	
2′	2.31	q	6.8	2.16	m		1.17	s	
3′	1.12	t	7.6	~1.9–2.0	m				
4′, 5′				0.93	d	6.3	1.17	s	
2″	5.80	d	15.4	5.80	d	15.2	5.80	d	15.2
3″	7.25	m		7.26	m		7.25	m	
4″	6.16	dd	8.5, 2.4	6.16	dd	8.5, 2.6	6.15	dd	8.2, 2.4
5″	6.16	dd	4.9, 1.5	6.16	dd	4.8, 1.5	6.16	dd	4.9, 1.5
6″	2.15	m		2.15	m		2.14	m	
7″	1.45	m		1.45	m		1.45	m	
8″	0.91	t	7.2	0.91	t	7.4	0.90	t	7.4

[a]Residual $CHCl_3$ as internal reference (7.25 ppm).
[b]Chemical shift values are interchangeable.
[c]Chemical shift values are interchangeable.

Experimental section

General procedures

Solvent solutions from reaction mixtures washed with water were dried over anhydrous sodium sulfate. All chromatographic solvents were redistilled. Silica gel (E. Merck, Darmstadt, 70–230 mesh) was employed for column chromatography and silica gel GHLF uniplates (Analtech, Inc., Newark, DE) were used for thin-layer chromatography (TLC). The TLC plates were viewed with UV light and developed with anisaldehyde – sulfuric acid spray reagent followed by heating. The NMR spectra were measured using a Bruker AM-400 instrument with deuteriochloroform employed as solvent. All high and low resolution fast atom bombardment (FAB) mass spectra (13) were recorded using a Kratos MS-50 mass spectrometer (Mid West Center for Mass Spectrometry, University of Nebraska, Lincoln, NE).

*Bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1***b*). General procedure*

The following procedure for silyation, acylation, and desilyation was repeated in analogous fashion for each bryostatin interconversion. A solution of bryostatin 2 (**1***a*, 50 mg), 4-(*N*,*N*-dimethyl)aminopyridine (15 mg), *tert*-butyldimethylsilyl chloride (40 mg), and triethylamine (20 μL) in dimethylformamide (2 mL) was stirred at room temperature (under argon) for 22 h. The reaction mixture was diluted with ice water, stirred for 10 min, and extracted with methylene chloride. The organic phase was washed with saturated aqueous sodium bicarbonate, followed by water, dried, and solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (1:1 hexane – ethyl acetate) to afford silyl ether **1***b* (21.8 mg), bryostatin 2 7,26-di-*tert*-butyldimethylsilyl ether **1***c* (21.4 mg), and bryostatin 2 (5.5 mg). The silyl protecting groups in **1***c* were removed with 48% hydrofluoric acid – acetonitrile (1:20, 10 mL). The reaction mixture was stirred at 0–5°C (1.5 h), diluted with water, and extracted with methylene chloride. The chlorocarbon phase was washed with saturated aqueous sodium bicarbonate followed by water, and dried. The residue (from solvent removal at reduced pressure) was separated by silica gel column chromatography (1:1 hexane – ethyl acetate) to afford 17.2 mg of bryostatin 2. On the basis of total recovered bryostatin 2, the yield of monosilyl ether **1***b* was 71%. The 400 MHz ^{1}H NMR spectrum of silyl ether **1***b* displayed significant

TABLE 2. Bryostatin ^{13}C NMR chemical shift assignments in deuteriochloroform solution

C	Bryostatin 4 (**2***a*)	Bryostatin 5 (**2***b*)	Bryostatin **1***k*	Bryostatin **1***m*
1	172.21	172.31	172.15	172.11
2	42.14	42.14	42.35	42.37
3	65.45	65.50	65.79	65.79
4	39.94	39.89	39.98	39.86
5	68.46	68.46	68.46	68.46
6	33.19	33.17	33.35	33.16
7	72.68	72.60	72.43	72.23
8	41.20	41.19	40.93	41.17
9	101.72	101.75	101.79	101.76
10	44.13	44.11	44.09	44.08
11	64.70	64.69	64.68	64.68
12	31.21	31.17	31.27	31.28
13	157.25	157.09	156.42	156.41
14	36.47	36.40	36.32	36.31
15	78.88	78.92	79.12	79.12
16	129.67	129.67	129.39	129.38
17	138.96	138.91	139.26	139.27
18	44.73	44.75	44.89	44.89
19	98.83	98.71	98.99	98.99
20	74.25	74.39	74.03	74.03
21	151.84	151.68	151.96	151.97
22	41.86	41.86	41.97	41.94
23	71.44	71.43	71.46	71.45
24	35.81	35.79	35.84	35.83
25	73.56	73.61	73.65	73.61
26	70.01	70.02	70.13	70.10
27	19.60	19.66	19.79	19.78
28	19.76	19.81	19.79	19.78
29	20.99	21.00	21.07	21.01
30	113.96	114.05	114.45	114.46
31	166.70	166.72	166.68	166.68
32	16.91	16.92	16.88	16.89
33	24.57	24.58	24.57	24.57
34	119.58	119.67	119.56	119.57
35	166.97	166.96	167.00	167.01
36, 37	51.03	51.02, 51.10	51.04	51.05
1′	178.33	178.27	172.81	177.99
2′	39.01	39.01	43.75	39.01
3′	27.07	27.09	24.93	27.14
4′, 5′	27.07	27.09	22.35	27.14
1″	171.98	169.32	165.58	165.58
2″	36.47	21.43	118.60	118.59
3″	18.16		146.35	146.33
4″	13.57		128.36	128.37
5″			145.49	145.50
6″			35.04	35.05
7″			21.85	21.02
8″			13.67	13.68

chemical shifts at δ 0.07 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.08 (d, 3H, J = 5.6 Hz), 3.65 (s, 3H), 3.68 (s, 3H), 3.73 (m, 1H), and 3.95 (m, 1H).

*Conversion of bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1**b) to bryostatin 1 (**1**e)*

A solution of bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1***b*, 1.6 mg) in acetic anhydride (100 μL) and pyridine (150 μL) was stirred for 18 h (room temperature), diluted with methanol, and stirred for an additional 30 min. Solvent was removed (reduced pressure) and the residue was chromatographed on a column of silica gel (1:1 hexane – ethyl acetate) to afford 1.2 mg (72%) of acetate **1***d*. The product (**1***d*) was subjected to desilylation by treating with 48% hydrofluoric acid – acetonitrile (1:20, 100 μL). The reaction mixture was stirred at 0–5°C (1.5 h), diluted with water, and extracted with methylene chloride. The organic phase was washed with saturated aqueous sodium bicarbonate, water, and dried. After solvent removal (reduced pressure) the residue was purified by silica gel column chromatography (1:1 hexane – ethyl acetate) to afford bryostatin 1 (**1***e*, 0.8 g, 80%), identical with the natural product (by comparison with TLC, analytical HPLC, SP-SIMS (13), and ^1H NMR).

*Conversion of bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1**b) to bryostatin 2 7-propionate (**1**g)*

Bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1***b*, 2 mg) was treated with propionic anhydride (100 μL) – pyridine (130 μL) and stirred for 18 h at room temperature. The product was purified as described directly above to afford **1***f* (2.0 mg, 95%). Desilylation and purification as described above afforded bryostatin **1***g* (1.5 mg, 88%): for ^1H NMR data see Table 1.

*Conversion of bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1**b) to bryostatin 12 (**1**i)*

Bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1***b*, 2.7 mg) was esterified (20 h) with butyric anhydride (100 μL) in pyridine (120 μL) employing the same procedure as utilized above to provide ester **1***h* (1.9 mg, 73%). Desilylation (150 μL of the 1:20 48% hydrofluoric acid – acetonitrile) as described above gave bryostatin 12 (**1***i*, 0.8 mg, 47%), identical to the natural product (by comparison with TLC, SP-SIMS (13), and ^{1}H NMR spectra.

*Conversion of bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1**b) to bryostatin 2 7-isovalerate (**1**k)*

A solution of isovaleric acid (5 μL), *N,N*-dicyclohexylcarbodiimide (10 mg), bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1***b*, 4.6 mg), and 4-pyrrolidinopyridine (1.3 mg) in methylene chloride (150 μL) was stirred at room temperature for 5 h (under argon). The *N,N*-dicyclohexylurea was removed by filtration, and the filtrate was concentrated (reduced pressure). The residue was separated by column chromatography on silica gel (1:1 hexane – ethyl acetate) to afford isovalerate **1***j* (4.5 mg, 90%). Removal of the silyl group as summarized above (cf., **1***e*, 150 μL of the 1:20 reagent) afforded bryostatin 2 7-isovalerate (**1***k*, 2.2 mg, 55%); FAB-MS (DTT/DTE as matrix), *m/z*: 969 $[M + Na]^+$ for $C_{50}H_{72}O_{16}Na$ (20% of base peak), and 911 $[M + H - 2H_2O]^+$ as base peak; for the ^{1}H and ^{13}C NMR data refer to Tables 1 and 2.

*Conversion of bryostatin 2 26-*tert*-butyldimethylsilyl ether (**1**b) to bryostatin 2 7-pivalate (**1**m)*

To a solution of bryostatin 2 26-*tert*-butyldimethylsilyl ether (6.9 mg) in methylene chloride (150 μL) were added 4-(*N,N*-dimethyl)aminopyridine (45 mg) and pivalic anhydride (40 mg). The reaction mixture was stirred at 52–55°C for 4 h (under argon) followed by addition of methanol at room temperature. The residue obtained following solvent removal was separated by column chromatography on silica gel (1:1 hexane – ethyl acetate) to afford pivalate **1***l* (5.7 mg, 76%). Desilylation was performed as described earlier to afford bryostatin **1***m* (2.8 mg, 56%): FAB-MS (3-NBA LiI as matrix), *m/z*: 969 $[M + Na]^+$ for $C_{50}H_{72}O_{16}Na$ (10% of base peak), 953 $[M + Li]^+$ for $C_{50}H_{72}O_{16}Li$ as base peak; for the ^{1}H and ^{13}C NMR data consult Tables 1 and 2.

Acknowledgments

Very necessary financial assistance was provided by Eleanor W. Libby, the Waddell Foundation (Donald Ware), the Fannie E. Rippel Foundation, The Robert B. Dalton Endowment Fund, the Arizona Disease Control Research Commission, the National Cooperative Drug Discovery Group Grant AI 25696-02-03, NIAID, the Outstanding Investigator Grant CA 44344-01A1 awarded by the Division of Cancer Treatment, National Cancer Institute, DHHS, and by the U.S. Army Medical Research and Development Command under Grant No. DAMD-17-89-Z-9021. For other assistance we are pleased to thank Drs. D. L. Doubek and D. E. Schaufelberger, the National Science Foundation Regional Instrumentation Facility in Nebraska (Grant CHE 8620177), and NSF NMR equipment grant (CHE-8409644).

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