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Pipestelides A–C: Cyclodepsipeptides from the Pacific Marine Sponge *Pipestela candelabra*

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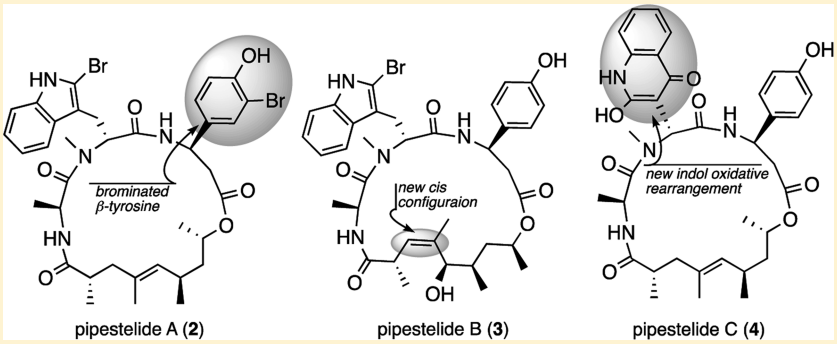
Supporting Information



ABSTRACT: Pipestelides A–C (**2**–**4**) are three new NRPS–PKS hybrid macrolides containing uncommon moieties, isolated from the Pacific marine sponge *Pipestela candelabra*. Their structures were elucidated on the basis of spectroscopic data. These cyclodepsipeptides appear to be biosynthetically related to jaspamide (aka jasplakinolide) (**1**) by chemical modification of the building blocks of the polyketide or peptide chains. Pipestelides A–C (**2**–**4**) contain a bromotyrosine [3-amino-3-(bromo-4-hydroxyphenyl)propanoic acid] unit, a polypropionate with a *Z* double bond, and a 2-hydroxyquinolinone, respectively. Revised chemical shift assignments are provided for the co-isolated known jasplakinolide C_a (**5**). In addition, compounds **2** and **3** exhibited cytotoxic activities in the micromolar range.

The NRPS–PKS cyclodepsipeptide jaspamide (aka jasplakinolide)[1] (**1**) and its derivatives have attracted the attention of several research groups for their isolation and structure elucidation, synthesis, and biological activities. Many of these compounds have been isolated from taxonomically distant groups of marine sponges such as *Jaspis splendens* (order Astrophorida; family Ancorinidae)[2] and *Auletta* cf. *constricta* (order Halichondrida; family Axinellidae).[3] Structurally related cyclodepsipeptides are also produced by sponges belonging to other genera and orders such as the geodiamolides from *Geodia* sp. (order Astrophorida; family Geodidae)[4] and *Cymbastela* sp. (order Halichondrida, family Axinellidae)[5] or the seragamides from *Suberites japonicus* (order Hadromerida; family Suberitidae).[6] These 19-membered macrolides share the same 11-carbon unit polypropionate 8-hydroxy-2,4,6-trimethyl-4-nonenoic acid, but they differ in the composition of the tripeptide portion. It should be noted that similar 18-membered cyclodepsipeptides named chondramides were found in the terrestrial myxobacterium *Chondromyces crocatus*.[7] Beyond the remarkable anticancer properties of jaspamide/jasplakinolide and derivatives,[3b,8] several analogues play an important role in stabilizing actin microfilaments.[3b,9]

Our investigation of the underexplored[10] Indo-Pacific marine sponge *Pipestela candelabra* (order Halichondrida; family Axinellidae) led to the discovery of three new unusual derivatives of jaspamide (**1**). These are pipestelide A (**2**), containing an *ortho*-brominated *β*-tyrosine residue, pipestelide B (**3**), with the first natural *Z*-configuration of the double bond in the polypropionate region, and pipestelide C (**4**), with an unprecedented hydroxyquinolinone. In this paper, we report their isolation, structure elucidation, and biological evaluation.

The freeze-dried *P. candelabra* sponge was extracted with MeOH, and the extract was partitioned between *n*-BuOH and H_2O. A preliminary LC-MS analysis of the butanolic extract revealed an interesting metabolite profile. The major compound, which exhibited an intense doublet pattern of pseudomolecular ions (ESI, $[M + H]^+$) at *m*/*z* 709.3/711.3, was assigned by NMR comparison with literature data as the cyclodepsipeptide jaspamide (**1**).[2a,b] The butanolic extract was then subjected to a Sephadex LH-20 column chromatography using MeOH as eluent. Further fractionation by C-18 reversed chromatography led to **1** together with other minor fractions

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Chart 1

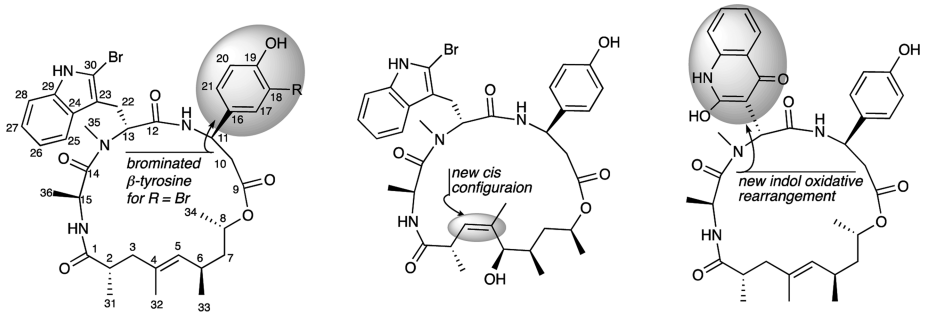

Table 1. NMR Data[a,b] for Compounds 3 and 4 in CD_3OD

	pipestelide A (2)		pipestelide B (3)		pipestelide C (4)		
C	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	HMBC[c]
1	178.0		177.7		177.6		
2	40.5	2.67, m	40.9	3.23, qd (10.1, 6.7)	38.4	2.83, m	
3	42.7	2.20, dd (15.3, 11.6)	128.5	5.29, d (10.1)	41.1	(3a) 2.48, dd (16.9, 11.6)	
		1.94, bd (15.3)				(3b) 1.87, m	
4	134.0		140.5		134.0		
5	130.7	4.87, d (9.7)	75.3	4.15, d (7.6)	128.4	4.78, d (9.3)	3, 33
6	30.6	2.32, m	35.0	1.76, m	30.3	2.27, m	
7	44.2	(7a) 1.54, m	40.1	(7a) 1.44, ddd (14.2, 7.1, 2.1)[d]	44.4	0.90, m	
		(7b) 1.23, m		(7b) 1.15, m			
8	71.8	4.70, m	71.4	4.88, m	71.4	4.69, m	
9	172.5		172.2		173.6		
10	41.9	(10a) 2.72, dd (15.4, 4.1)	42.0	(10a) 2.85, dd (17.0, 11.4)	41.9	(10a) 2.86, dd (13.8, 4.6)	9, 11, 16
		(10b) 2.65, dd (15.4, 8.4)		(10b) 2.65, dd (17.0, 3.0)		(10b) 2.68, dd (13.8, 4.2)	9, 11, 16
11	50.4	5.21, dd (8.4, 4.1)	50.9	5.16, dd (11.4, 3.0)	50.5	5.18, dd (4.6, 4.2)	9, 17
12	171.1		171.1		173.7		
13	57.0	5.65, dd (9.3, 7.0)	57.0	5.65, t (8.2)	58.0	6.46, s	12, 22, 23, 30
14	175.0		175.2		174.2		
15	47.1	4.69, m	46.9	4.40, q (6.9)	48.3	5.13, m	14, 31
16	132.6[b]		131.5		131.8		
17	131.2	7.29, d (2.1)	128.2	6.98, m	128.7	7.10, m	11, 19, 21
18	112.2[b]		117.8	6.66, d (8.6)	117.0	6.67, m	16, 20
19	157.4[b]		161.1		158.4		
20	120.1	6.72, d (8.4)	117.8	6.66, d (8.6)	117.0	6.67, m	16, 18
21	127.5	6.88, dd (8.4, 2.1)	128.2	6.98, m	128.7	7.10, m	11, 17, 19
22	25.2	3.20, m	24.6	3.19, d (8.2)	101.9		
23	110.2		110.6		176.4		
24	128.7		128.9		123.0		
25	119.2	7.53, bd (8.0)	119.3	7.52, bd (7.9)	126.2	8.04, dd (8.0, 1.4)	23, 27, 29
26	120.6	6.99, ddd (8.0, 7.1, 0.9)	120.6	7.00, m	121.9	7.07, ddd (8.0, 8.1, 1.1)	24, 28
27	123.0	7.07, ddd (8.1, 7.1, 0.9)	122.9	7.07, ddd (8.1, 7.9, 1.0)	131.2	7.37, ddd (8.1, 8.1, 1.4)	25, 29
28	111.8	7.24, bd (8.1)	111.7	7.24, bd (8.1)	116.3	7.18, bd (8.1)	24, 26
29	138.1		138.1		140.1		
30	110.6		110.5		167.4		
31	19.8	1.07, d (6.9)	20.0	1.16, d (6.7)	21.5	1.21, d (7.1)	1, 2, 3
32	18.5	1.59, s	19.3	1.68, d (1.3)	18.6	1.62, s	3, 4, 5
33	22.2	0.86, d (6.6)	16.1	0.97, d (6.7)	22.8	0.80, d (6.4)	5, 6, 7
34	20.1	1.08, d (6.2)	19.8	1.15, d (6.2)	19.2	1.03, d (6.1)	8, 7
35	31.8	3.09, s	32.2	3.07, s	32.3	3.20, s	13, 14
36	18.1	0.71, d (6.8)	17.1	0.64, d (6.9)	18.6	1.37, d (6.7)	14, 15

[a] ^1H chemical shifts were recorded at 600 MHz, and ^{13}C chemical shifs at 150 MHz. [b] ^{13}C NMR chemical shifts were confirmed or determined indirectly from HMBC NMR data. [c] HMBC correlations are from protons stated to the indicated carbon. [d] Coupling constants are $^3J_{H7a\text{-}7b}$ = 14.2, $^3J_{H7a\text{-}8}$ = 7.1, $^3J_{H7a\text{-}6}$ = 2.1.

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containing several analogues with similar UV spectra to that for **1**. The minor compounds were separated by SFC chromatography to yield 15 pure compounds including **2**–**4**. The known compounds were characterized by comparison with their spectroscopic data available in the literature. These were jaspamide B,[11] jasplakinolide C_a,[3b] jasplakinolide C_b,[3b] jaspamide D,[8a] jaspamide E,[8a] jaspamide K,[8b] jaspamide L,[8b] jasplakinolide R_1,[8d,12] jasplakinolide S,[3b] and epi-jasplakinolide S.[3b] Revised chemical shift assignments are provided for the known jasplakinolide C_a. The structures of the minor metabolites **2**–**4** were elucidated by spectroscopic methods together with their comparison with the known analogues in the series.

The ESI mass spectrum of **2** showed pseudomolecular ion peaks at *m*/*z* 787.3, 789.3, and 791.3 $[M + H]^+$ in the ratio 1:2:1, indicating the presence of two bromine atoms. The molecular formula of **2** was determined by HRMS as $C_{36}H_{44}{}^{79}Br_2N_4O_6$. ^{1}H NMR data in CD_3OD indicated that the structure of **2** was very similar to **1**. The molecular formula of this dibrominated compound indicated an isomeric structure of jaspamide R.[8d] The main structural difference was localized on the *β*-tyrosine residue. The coupling constants between H-21 (δ_H 6.88, dd, J_H = 8.4 and 2.1 Hz) and the two protons H-20 (δ_H 6.72, d, J_H = 8.4 Hz) and H-17 (δ_H 7.29, d, J_H = 2.1 Hz) suggested a 1,2,4 aromatic substitution pattern. In addition to the hydroxy, the aromatic ring of the *β*-tyrosine residue bears a bromine atom at position C-18 (δ_C 112.2) (Table 1). This proposal is consistent with the *meta*-coupling constant value of 2.1 Hz observed between H-21 and H-17. Important evidence for the regiosubstitution of the aromatic ring came from the NOESY correlations between H-11 (δ_H 5.26) and the *ortho* protons H-17 (δ_H 7.29) and H-21 (δ_H 6.28). The relative configurations of the tripeptide and the polypropionate units were deduced from the similarity of the ^{1}H and ^{13}C NMR chemical shifts observed for **2** and the parent compound **1** (Supporting Information). This proposed configuration was also based on the biosynthetic analogy to **1**.[2] The co-isolated jaspamide (**1**) displayed a similar specific rotation ($[\alpha]^{25}_D$ +36.9 (*c* 1.0, MeOH) to the literature value ($[\alpha]^{25}_D$ +35 (*c* 3.62, MeOH)).[2b] Compound **2** was named pipestelide A, a new jaspamide macrolide.

Pipestelide B (**3**) had a molecular formula of $C_{36}H_{45}{}^{79}BrN_4O_7$ as determined by HRMS. A preliminary dereplication by LC/MS indicated that the molecular formula was the same as for jasplakinolide K (**3**),[8b] but the NMR analysis indicated an isomeric structure. A comparison of ^{1}H NMR spectra of **3** (Table 1) and **1** revealed that while the regions corresponding to the peptide unit were very similar, notable differences indicated structural modifications to the polypropionate chain of **3**. From COSY correlations (Figure 1), we deduced the presence of an allylic alcohol with the hydroxy at C-5. The assignment of the entire polypropionate part was supported by the HMBC correlations between Me-31 (δ_H 1.16, d, J_H = 6.7 Hz) (Table 1) and the carbons C-1 to C-3 (δ_C 177.7, 40.9, and 128.5, respectively), on one hand, and between Me-32 (δ_H 1.68, d, J_H = 1.3 Hz) and the carbons C-3 to C-5 (δ_C 128.5, 140.5, and 75.3 ppm, respectively) on the other hand (Figure 1 and Table 1).

Important evidence to determine the configuration of the polypropionate part including the *Z*-configuration of the 3,4-double bond came from NOESY and ROESY correlations between H-3 (δ_H 5.29) and the methyl groups Me-31/Me-32; H-5 (δ_H 4.15) and the protons H-2 (δ_H 3.23)/H-6 (δ_H 1.76)/

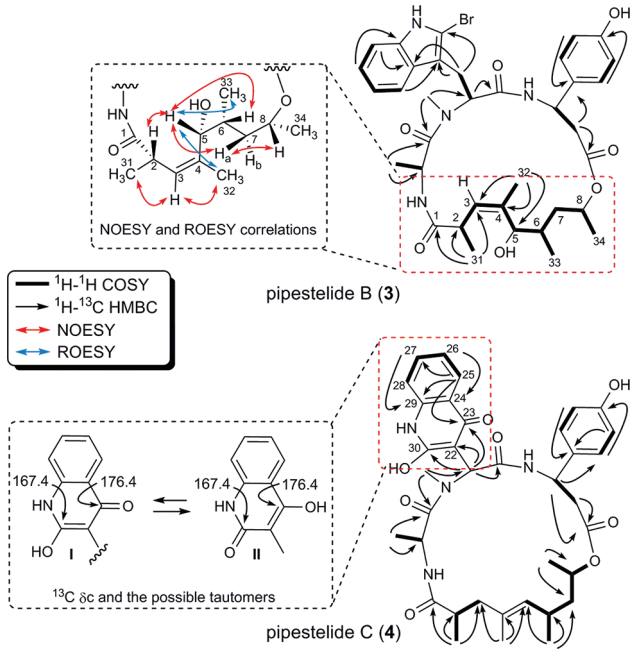

Figure 1. Key COSY, HMBC, NOESY, and ROESY correlations for **3** and **4**.

H-7a (δ_H 1.44); and H-7a and H-8 (δ_H 4.88). These NOESY/ROESY correlations suggest a general orientation of the polyketide backbone where H-2, H-5, H-6, H-7a, and H-8 show a network of NOE correlations (Figure 1), and this conformation is likely the consequence of the steric hindrance of methyl groups Me-31, Me-33, and Me-34. Further analysis of the coupling constants between the vicinal protons H-5 and H6 ($J_{(H5-H6)}$ = 7.6 Hz) and the observed NOESY correlations indicating their spatial orientation were coherent with the relative configurations of both the polypropionate chain and the tripeptide unit as shown in **3**. A ROESY experiment confirmed the same configuration/conformation with the additional correlations of H-5 with H-32, H-6, and H-33. It should be noted that the absolute configuration of the asymmetric centers 2*S*, 6*R*, 8*S*, 11*R*, 13*R*, and 15*S* within this family of compounds has proven to be invariant and identical to **1**.[2] Compound **3** was named pipestelide B.

The ESIMS spectrum of compound **4** displayed a pseudomolecular ion peak at *m*/*z* 661.3 $[M + H]^+$. The molecular formula of **4** was determined to be $C_{36}H_{44}N_4O_8$ by HRESIMS. Due to the very small amount of the isolated compound (100 *μ*g), the NMR analysis and the structure elucidation of **4** required intensive use of the advanced 600 MHz 1.7 mm microprobe. The ^{1}H NMR spectrum displayed only a few differences from jaspamide (**1**) and suggested that **4** was modified at the indolic ring. Analysis of the HMBC spectrum (Table 1) revealed the important correlations H-13 (δ_H 6.46, s) with the carbons C-12 (δ_C 173.7), C-22 (δ_C 101.9), C-23 (δ_C 176.4), and C-30 (δ_C 167.4), on one hand, and H-25 (δ_H 8.04, dd, J_H = 8.0 and 1.4 Hz) to C-23 (δ_C 176.4) and C-29 (δ_C 140.1) on the other hand (Figure 1 and Table 1). The aromatic protons H-25 to H-28 were assigned by a COSY NMR experiment.

At this stage, the 2D NMR correlations left room for two possible tautomers, I and II: 2-hydroxy-4-quinolone (tautomer I) and 4-hydroxy-2-quinolone (tautomer II) (Figure 1). We initially favored the assignment with the carbonyl at position C-

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23 with respect to its chemical shifts at 176.4 ppm, the enol form having the C-30 at 167.4 ppm. Similar structure ranking of chemical shifts was observed for a related structure.[13] However, it should be noted that the enolic sodium salt form displays a comparable value to that of the pipestelide C (**4**).[14] Thus, the two tautomeric forms must still be considered. The comparison of the ^{1}H NMR spectrum of **4** with the data of **1** and detailed study of the 2D NMR spectra suggested a unique modification of the indole section into a hydroxyquinolinone ring system (Supporting Information). The supposed preservation of the absolute configuration of the co-isolated parent compound jaspamide (**1**) suggests the same configuration for **4**. Compound **4** was named pipestelide **C**.

Jasplakinolide C$_a$[3b] was one of the known compounds that we have isolated from this sponge. According to our ^{13}C NMR data, the carbon chemical shift assignments have been revised.[15] The corrected ^{13}C NMR (CD_3OD) chemical shifts are C-6 (δ_C 33.0), C-7 (δ_C 42.1), and C-36 (δ_C 16.2), instead of C-6 (δ_C 30.8), C-7 (δ_C 35.7), and C-36 (δ_C 12.9), in ref 2b.

Compounds **2** and **3** were subjected to cytotoxicity assay against the KB cell line[16] together with the co-isolated known compounds from the same sponge (Table 2). Most of the

Table 2. Cytotoxicity Assay Results for the Isolated Compounds against the KB Cell Line

	concentration (μM)		
compound	10 μM[a]	1 μM[a]	IC$_{50}$ (μM)[b]
jasplakinolide Ca (**5**)	80 ± 2	0 ± 8	nd[c]
jaspamide (**1**)	100 ± 1	99 ± 1	0.013/0.013
jaspamide B	99 ± 1	99 ± 1	0.036/0.029
jasplakinolide Cb	100 ± 1	75 ± 7	nd
jaspamide D	100 ± 1	100 ± 1	0.0044/0.0050
jaspamide E	100 ± 1	100 ± 1	0.126/0.121
jaspamide K	100 ± 1	100 ± 1	3.35/3.43
jaspamide L	99 ± 1	100 ± 1	0.214/0.247
jasplakinolide Z$_1$	30 ± 2	nd	nd
pipestelide A (**2**)	100 ± 1	100 ± 1	0.11/0.10
pipestelide B (**3**)	100 ± 1	0 ± 15	nd

[a]Cell proliferation was measured with Celltiter 96 Aqueous One solution reagent (Promega), and results are expressed as the percentage of inhibition of cellular proliferation of KB cells treated for 72 h with compounds compared to cells treated with DMSO only (mean ± SE of triplicate). [b]For IC$_{50}$ values results are expressed as individual values in experiments performed in duplicate. IC$_{50}$ values were determined only for those compounds exhibiting 100% inhibition at both preliminary concentrations. [c]nd = not determined.

macrolides showed significant but variable cytotoxicity ranging from nano- to micromolar values. Pipestelide B (**3**) had only very modest activity, whereas pipestelide A (**2**) was more active, with an IC$_{50}$ value of 0.1 μM, but remained weaker than the known jaspamide (**1**)[3b] and jaspamide B,[11] which displayed potent cytotoxicity in the low nanomolar range.

EXPERIMENTAL SECTION

General Experimental Procedures. The optical rotations were determined on a Jasco P-1010 polarimeter, and UV data were recorded on a Varian Cary 100 spectrometer. All NMR spectra were recorded on a Bruker DRX 600 MHz in CD_3OD with a 5 mm or 1.7 mm TXI (HCN) probe. The chemical shifts are reported in ppm relative to CD_3OD (δ_H 3.31 and δ_C 49.15). HRMS data were obtained with a hybrid linear trap/orbitrap mass spectrometer (LTQ-orbitrap, ThermoFisher) in electrospray ionization mode by direct infusion of the purified compounds. Preparative HPLC was performed on an AutoPrep system (Waters 600 controller and Waters 600 pump with a Waters 996 photodiode array detector) and used a Waters Atlantis T3 5 μm column (19 × 150 mm). UV (220 nm) was used for peak detection. SFC purifications were performed on a Thar Waters SFC Invistigator II with a Waters 2998 photodiode array detector and used a Viridis SFC 2-ethylpyridine 5 μm column, 4.6 × 250 mm.

Animal Material. The sponge was collected in the Solomon Islands in July 2004, off Guadalcanal at 9°25.376′ S and 159°55.946′ E, between 10 and 27 m deep. It was identified as *Pipestela candelabra* by John Hooper of Queensland Museum, South Brisbane, Australia. A voucher specimen is deposited in the Queensland museum under the accession number G324821.

Extraction and Isolation. The freeze-dried sample of sponge (712 g) was homogenized and extracted under pressure (100 bar) three times with MeOH (1.5 L and 2 × 0.75 L) using a Dionex apparatus to give 70 g of extract. This methanolic extract was partitioned between H_2O and butanol to provide 8 g of *n*-butanol-soluble extract. The resulting butanolic extract was filtered on Sephadex LH-20 (Sigma) with MeOH as an eluent yielding 20 fractions (F1 to F20). Fractions F6, F7, and F8 were purified on a C-18 (Sepra C18; 50 μm, Phenomenex) column eluting with successive mixtures of H_2O–MeOH (1:0, 4:1, 1:1, 1:4, and 0:1) and finally with CH_2Cl_2–MeOH (1:1). The fraction eluting with H_2O–MeOH (1:4) was subjected to RP HPLC (Atlantis T3, 5 μm, 19 × 150 mm) using a gradient (H_2O + 0.1% HCOOH/CH_3CN + 0.1% HCOOH, 65:35 to 15:85 in 30 min), resulting in seven fractions (A–G). Fraction A (2.7 mg) was purified by SFC (isocratic 17% of MeOH as cosolvent, 150 bar, 40 °C) to afford **2** (0.4 mg, t_R = 8 min). Fraction G (3.0 mg) was purified by SFC (isocratic 17% of MeOH as cosolvent, 150 bar, 25 °C) to afford **3** (0.4 mg, t_R = 11 min). Fraction E (4.0 mg) was purified by SFC (isocratic 16% of CH_3OH as cosolvent, 150 bar, 20 °C) to afford **4** (0.1 mg, t_R = 7 min).

The known isolated compounds were jaspamide B (0.8 mg), jasplakinolide C$_a$ (0.8 mg), jasplakinolide C$_b$ (0.8 mg), jaspamide D (0.4 mg), jaspamide E (0.3 mg), jaspamide K (0.5 mg), jaspamide L (0.3 mg), jasplakinolide R$_1$ (0.4 mg), jasplakinolide S (0.5 mg), and epi-jasplakinolide S (0.5 mg).

*(+)-Pipestelide A (**2**):* white, amorphous solid (0.3 mg); $[\alpha]^{25}_D$ +13 (*c* 0.06, MeOH); UV (MeOH) λ_{max} (log ε) 201 (2.70), 219 (2.44), 282 (1.81) nm; ^{1}H and ^{13}C NMR (Table 1); HRESITOMS [M + NH_4]$^+$ *m*/*z* 804.2006 (calcd for $C_{36}H_{44}{}^{79}Br_2N_4O_6$, 804.1971).

*(−)-Pipestelide B (**3**):* white, amorphous solid (0.4 mg); $[\alpha]^{25}_D$ −62 (*c* 0.06, MeOH); UV (MeOH) λ_{max} (log ε) 201 (2.57), 222 (2.45), 281 (1.75) nm; ^{1}H and ^{13}C NMR (Table 1); HRESITOMS [M + H]$^+$ *m*/*z* 725.2529 (calcd for $C_{36}H_{45}{}^{79}BrN_4O_7$, 725.2550).

*Pipestelide C (**4**):* white, amorphous solid (100 μg); UV (MeOH) λ_{max} (log ε) 201 (4.61), 221 (4.54), 299 (3.85) nm; CD (MeOH) λ ($\Delta\varepsilon$) 200 (+24.8), 235 (−6.9), 287 (−2.19) nm; ^{1}H and ^{13}C NMR (see Table 1); HRESITOMS [M + H]$^+$ *m*/*z* 661.3229 (calcd for $C_{36}H_{44}N_4O_8$, 661.3237).

Cell Culture and Cell Proliferation Assay. The human cell line KB originated from the NCI and was grown in D-MEM medium supplemented with 10% fetal calf serum, in the presence of penicillin, streptomycin, and fungizone in a 75 cm^2 flask under 5% CO_2. A total of 600 cells were plated in 96-well tissue culture plates in 200 μL of medium and treated 24 h later with 2 μL of stock solution of compounds dissolved in DMSO using a Biomek 3000 (Beckman-Coulter). Controls received the same volume of DMSO (1% final volume). After 72 h exposure, cell titer 96Aqueous One solution (Promega, Madison, WI, USA) was added and incubated for 3 h at 37 °C: the absorbance was monitored at 490 nm, and results were expressed as the inhibition of cell proliferation calculated as the ratio [(1 − (OD_{490} treated/OD_{490} control)) × 100] in triplicate experiments. For IC$_{50}$ determination [50% inhibition of cell proliferation], cells were incubated for 72 h following the same protocol with compound concentrations ranging from 5 nM to 100 μM in separate duplicate experiments.

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of compounds **1**−**4** are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Trivial names of the known molecules were intentionally given with respect to the first submitted paper corresponding to their isolation.

(2) (a) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123−3124. (b) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797−2800. (c) Murray, L. M.; Johnson, A.; Diaz, M. C.; Crews, P. *J. Org. Chem.* **1997**, *62*, 5638−5641.

(3) (a) Crews, P.; Farias, J. J.; Emrich, R.; Keifer, P. A. *J. Org. Chem.* **1994**, *59*, 2932−2934. (b) Robinson, S. J.; Morinaka, B. I.; Amagata, T.; Tenney, K.; Bray, W. M.; Gassner, N. C.; Lokey, R. S.; Crews, P. *J. Med. Chem.* **2010**, *53*, 1651−1661.

(4) (a) Chan, W. R.; Tinto, W. F.; Manchand, P. S.; Todaro, L. J. *J. Org. Chem.* **1987**, *52*, 3091−3093. (b) Tinto, W. F.; Lough, A. J.; McLean, S.; Reynolds, W. F.; Yu, M.; Chan, W. R. *Tetrahedron* **1998**, *54*, 4451−4458. (c) Coleman, J. E.; Van Soest, R.; Andersen, R. J. *J. Nat. Prod.* **1999**, *62*, 1137−1141.

(5) (a) de Silva, E. D.; Andersen, R. J.; Allen, T. M. *Tetrahedron Lett.* **1990**, *31*, 489−492. (b) Talpir, R.; Benayahu, Y.; Kashman, Y.; Pannell, L.; Schleyer, M. *Tetrahedron Lett.* **1994**, *35*, 4453−4456. (c) Coleman, J. E.; de Silva, E. D.; Kong, F.; Andersen, R. J.; Allen, T. M. *Tetrahedron* **1995**, *51*, 10653−10662.

(6) Tanaka, C.; Tanaka, J.; Bolland, R. F.; Marriott, G.; Higa, T. *Tetrahedron* **2006**, *62*, 3536−3542.

(7) Jansen, R.; Kunze, B.; Rieichenbach, H.; Höfle, G. *Liebigs Ann.* **1996**, 285−290.

(8) (a) Gala, F.; Zampella, A.; De Marino, S.; Zollo, F.; Smith, C. D.; Copper, J. E.; D'Auria, M. V. *Tetrahedron* **2007**, *63*, 5212−5219. (b) Gala, F.; D'Auria, M. V.; De Marino, S.; Sepe, V.; Zollo, F.; Smith, C. D.; Copper, J. E.; Zampella, A. *Tetrahedron* **2008**, *64*, 7127−7130. (c) Gala, F.; D'Auria, M. V.; De Marino, S.; Sepe, V.; Zollo, F.; Smith, C. D.; Keller, S. N.; Zampella, A. *Tetrahedron* **2009**, *65*, 51−56. (d) Ebada, S.; Wray, V.; de Voogd, N.; Deng, Z.; Lin, W.; Proksch, P. *Mar. Drugs* **2009**, *7*, 435−444.

(9) (a) Ghosh, A. K.; Dawson, Z. L.; Moon, D. K.; Bai, R.; Hamel, E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5104−5107. (b) Tannert, R.; Milroy, L.-G.; Ellinger, B.; Hu, T. S.; Arndt, H.-D.; Waldmann, H. *J. Am. Chem. Soc.* **2010**, *132*, 3063−3077.

(10) (a) McCloud, T, G. *Molecules* **2010**, *15*, 4526−4563. (b) Bugni, T. S.; Harper, M. K.; McCulloch, M. W. B.; Reppart, J.; Ireland, C. M. *Molecules* **2008**, *13*, 1372−1383.

(11) Zampella, A.; Giannini, C.; Debitus, C.; Roussakis, C.; D'Auria, M. V. *J. Nat. Prod.* **1999**, *62*, 332−334.

(12) Watts, K. R.; Morinaka, B. I.; Amagata, T.; Robinson, S. J.; Tenney, K.; Bray, W. M.; Gassner, N. C.; Lokey, R. S.; Media, J.; Valeriote, F. A.; Crews, P. *J. Nat. Prod.* **2011**, *74*, 341−351.

(13) Sultanbekova, I. A.; Kamaioni, E.; Pellichiari, R. *Bashk. Khim. Zh.* **2007**, *14*, 67−68.

(14) sSee ^{13}C NMR chemical shifts for 2,4-quinolinediol monosodium salt SDBS: ^{13}C NMR SDBS No. 13681CDS-12-088 22.53 MHz, C9H6NNaO2; SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology, 11.28.2011).

(15) See ref 2b by Crews and co-workers. We thank Prof. Crews for his kind exchange regarding the NMR spectra and the revision of the chemical shifts of jasplakinolide C_a.

(16) Zampella, A.; Sepe, V.; Bellotta, F.; Luciano, P.; d'Auria, M. V.; Cresteil, T.; Debitus, C.; Petek, S.; Poupat, C.; Ahond, A. *Org. Biomol. Chem.* **2009**, *7*, 4037−4044.