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Psymberin, A Potent Sponge-Derived Cytotoxin from *Psammocinia* Distantly Related to the Pederin Family

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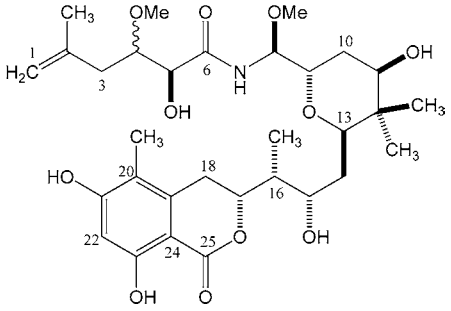
ABSTRACT

psymberin (**1**)



Bioassay-guided fractionation of the sponge *Psammocinia* sp. afforded psymberin (1) possessing 5*S*,8*S*,9*S*,11*R*,13*R*,15*S*,16*R*,17*R* stereochemistry. Psymberin exhibits structural similarities to the pederin family metabolites. The potent cytotoxicty and unique structural features of 1 make it a promising lead for therapeutic development.

Until now, our efforts to isolate and elucidate the structure of an extremely potent cytotoxin from an undescribed and inconspicuous sponge, *Psammocinia* sp. (Dictyoceratida, Irciniidae), were unsuccessful. For over a decade, we have repeatedly observed that *Psammocinia* extracts collected from the waters of Papua New Guinea exhibited significant solid-tumor cytotoxicity. In the course of these studies, a moderately cytotoxic halogenated hexapeptide, cyclocinamide A,[1] and actin inhibitor, swinholide A,[2] were isolated, but their biological activities did not account for the potency of the crude sponge extracts. Furanosesterpenes such as variabilin and polybrominated phenol ethers have also been identified from *Psammocinia*, but these compounds lack significant cytotoxicity.[2] A new approach to this project was adopted with the goal of obtaining the minor constituent possessing the potent cytotoxicity. The revised plan involved a focused bioassay-guided effort utilizing all of the previously prepared fractions from our extract library. Described here are the results of this unusual approach that led to the isolation and study of psymberin (**1**) (Figure 1), an extremely potent cytotoxin.

Approximately 600 *Psammocinia* fractions prepared between 1990 and 2001 were combined. The methanol-soluble material was subjected to bioassay-guided fractionation against a human colon cancer cell line (HCT-116), yielding **1**[3] (9.16×10^{-5}% wet weight of sponge), which exhibited a perplexing array of positive FABMS (NBA matrix) ions including those at *m*/*z* 632 $[M + Na]^+$, 610 $[M + H]^+$, 578 $[M - MeOH + H]^+$ (base peak), and 560 $[M - H_2O -$

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(1) (a) Isolation: Clark, W. D.; Corbett, T.; Valeriote, F.; Crews, P. *J. Am. Chem. Soc.* **1997**, *119*, 9285−9286. (b) Synthesis of a diastereomer: Grieco, P. A.; Reilly, M. *Tetrahedron Lett.* **1998**, *39*, 8925−8928.

(2) (a) Swinholide A was identified by comparison to data in Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963−2966. (b) Variabilin was identified by comparison to data in Faulkner, D. J. *Tetrahedron Lett.* **1973**, *39*, 3821−3822. (c) Polybrominated phenol ethers were identified by comparison to data in Bowden, B. F.; Towerzey, L.; Junk, P. C. *Aust. J. Chem.* **2000**, *53*, 299−301. Salva, J.; Faulkner, D. J. *J. Nat. Prod.* **1990**, *53*, 757−760.

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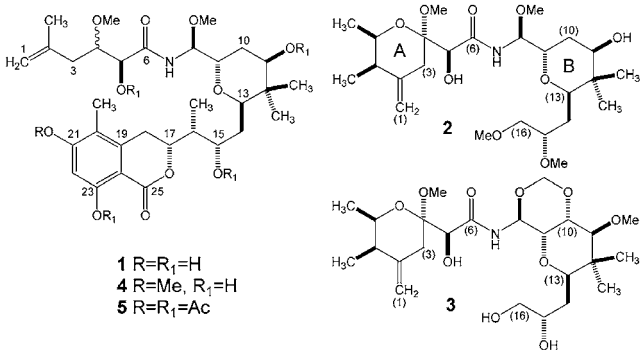


Figure 1. Structures of psymberin (**1**), its methylester (**4**) and acetyl (**5**) derivatives, pederin (**2**), and mycalamide A (**3**) (atom positions analogous to **1** are shown in parentheses).

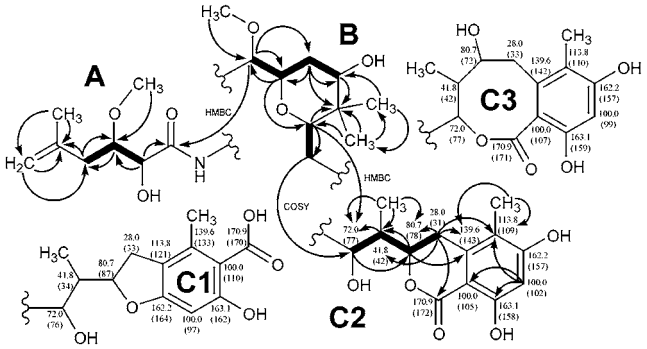


Figure 2. Psymberin (**1**) partial structures with significant $^{2-3}J_{H,C}$ HMBC and COSY correlations represented as arrows and bold bonds, respectively. Numbers for **C1**−**C3** are experimental and calculated (in parentheses) ^{13}C NMR shifts.

MeOH + H]$^+$. The molecular ion was confidently assigned on the basis of ESI-MS/MS analysis of the *m*/*z* 610 ion that fragmented to give *m*/*z* 578 and 560 and a negative ESIMS ion that was observed at *m*/*z* 608 [M − H]$^-$.

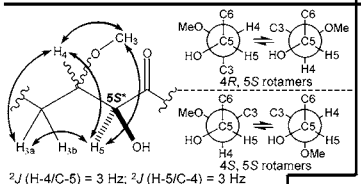
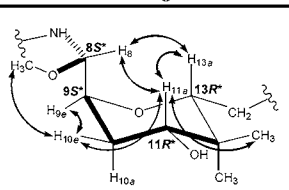
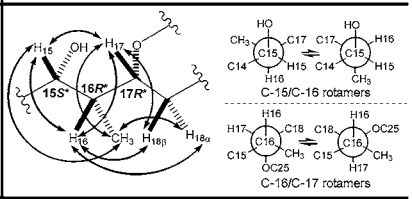
The molecular formula for psymberin (**1**) of $C_{31}H_{47}NO_{11}$ was consistent with the ^{13}C NMR DEPT estimate of $C_{31}H_{41}$ (7 CH_3, 5 CH_2, 10 CH, and 9 C) with six additional protons attached to heteroatoms. The obvious functionalities included 2 carbonyl groups, 2 aryl oxygen sites, and 10 sp^3 carbon centers with attached oxygens. Comparison of this oxygen count with the MS-derived molecular formula meant that there were at least three ether groups, two of which were OCH_3's. Dereplication based on the ^{1}H and ^{13}C NMR data revealed **1** shared several structural features with the pederin family of terrestrial and marine metabolites, as shown in Figure 1 and further discussed below. The geminal protons (δ_H 4.69 and 4.71) of a low field methylene (δ_C 111.5) were chosen as the starting point for the structure elucidation of substructure **A**. The $^{2-3}J_{H,C}$ HMBC correlations linked this vinylic methylene to other adjacent carbons, and additional connectivities were established by COSY data between mutually coupled vicinal protons. A $^2J_{H,C}$ HMBC correlation between H-5 and an amide carbonyl (δ_C 174.6) established the C-5 to C-6 linkage, while a $^3J_{H,C}$ HMBC correlation from δ_H 3.18 to C-4 (δ_C 81.2) permitted the assignment of the attached methoxy. Next, substructure **B** was established and confirmed by 2D NMR experiments. The HMBC correlations shown in Figure 2, especially that from H-8 to C-6 allowed joining substructures **A** and **B**. Thus, psymberin (**1**) possessed the oxane ring B present in **2** and **3**, but unlike all previously reported pederin biomolecules it lacked the signature ring A.

The most challenging aspect of the structure elucidation pertained to defining substructure **C**, comprising $C_{13}H_{15}O_5$. The resonance for H-16 (δ_H 1.87, ddd) served as the anchor point for defining the chain C-15 to C-18 via the COSY correlations shown in Figure 2. Unexpectedly, unraveling the interrelationships of the remaining atoms ($C_8H_6O_4$) that were a part of a pentasubstituted aromatic ring proved to be challenging. These hydrogens appeared in the ^{1}H NMR spectrum as a methyl singlet (δ_H 2.08, CH_3-16), two exchangeable protons (δ_H 8.58 s and 11.20 s in dioxane-d_8), and a low field aryl ring singlet (δ_H 6.22, H-21). Initially the remaining nonaromatic ring carbon (δ_C 170.9) was assumed to be a carboxylic acid based on the smooth conversion of **1** to a methylated product **4** (ESIMS *m*/*z* 592 [M − MeOH + H]$^+$ (base peak) and 646 [M + Na]$^+$).[4] The ^{1}H NMR spectrum of **4** in dioxane-d_8 revealed the persistence of the most downfield exchangeable singlet whose extreme low-field shift was ultimately rationalized as due to intramolecular hydrogen bonding of the phenol proton to a carbonyl. The carbon chemical shifts and significant $^{2-3}J_{H,C}$ HMBC correlations from the aryl proton and CH_3 were initially concluded to be consistent with partial structure **C1**. Alternatively, structure **C2**, not initially considered by us but embedded in the structure proposed for irciniastatin A,[5] was also consistent with these data. Another substructural variant, **C3**, was also in general agreement with the preceding data.

(3) Psymberin (**1**): clear glasslike solid; $[\alpha]^{27}_D = +29$ (*c* 0.02, MeOH); CD (EtOH) 280 ($\Delta\epsilon$ 14), 310 ($\Delta\epsilon$ −6) nm; IR (film) ν_{max} 3378, 2935, 1653, 1617, 1508, 1450, 1377, 1252, 1173, 1108, 1064, 970, 898 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 6.22 (H-22, s, 1H), 5.36 (H-8, d, J = 8.0 Hz, 1H), 4.71 (1-H_E, s, 1H), 4.69 (1-H_Z, s, 1H), 4.46 (H-17, ddd, J = 3.0, 6.0, 12.0 Hz, 1H), 4.33 (H-5, d, J = 2.5 Hz, 1H), 3.91 (H-9, ddd, J = 3.0, 6.0, 8.0 Hz, 1H), 3.91 (H-15, m, 1H), 3.65 (H-4, ddd, J = 2.5, 3.5, 9.5 Hz, 1H), 3.57 (H-11, dd, J = 4.5, 11.0 z, 1H), 3.47 (H-13, dd, J = 1.0, 11.0 Hz, 1H), 3.33 (8-OCH_3, s, 3H), 3.18 (4-OCH_3, s, 3H), 3.11 (H-18$_\beta$, dd, J = 3.0, 17.0 Hz, 1H), 2.83 (H-18$_\alpha$, dd, J = 12.0, 17.0 Hz, 1H), 2.32 (3-H_b, dd, J = 9.5, 14.5 Hz, 1H), 2.08 (20-CH_3, s, 3H), 2.06 (H-3$_a$, dd, J = 3.5, 14.5 Hz, 1H), 1.98 (H-10$_e$, ddd, J = 2.5, 4.5, 13.5 Hz, 1H), 1.87 (H-16, ddq, J = 2.0, 6.0, 6.0, 1H), 1.75 (H-10$_a$, ddd, J = 6.0, 11.0, 13.5 Hz, 1H), 1.75 (H-14, m, 2H), 1.69 (1-CH_3, s, 3H), 1.07 (16-CH_3, d, J = 6.5 Hz, 3H), 0.95 (12-CH_{3e}, s, 3H), 0.87 (12-CH_{3a}, s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.6 (C-6, s), 170.9 (C-25, s), 163.1 (C-23, s), 162.2 (C-21, s), 142.4 (C-2, s), 139.6 (C-19, s), 113.8 (C-20, s), 111.5 (1-CH_2, t), 99.98 (C-22, d), 99.92 (C-24, s), 81.2 (C-4, d), 80.7 (C-17, d), 80.5 (C-13, d), 78.4 (C-8, d), 72.6 (C-9, d), 72.0 (C-15, d), 71.9 (C-5, d), 70.6 (C-11, d), 56.2 (4-OCH_3, q), 55.0 (8-OCH_3, q), 41.8 (C-16, d), 38.3 (C-12, s), 37.2 (C-3, t), 32.9 (C-14, t), 29.0 (C-10, t), 28.0 (C-18, t), 22.2 (12-CH_{3e}, q), 21.4 (2-CH_3, s), 12.6 (12-CH_{3a}, q), 9.3 (20-CH_3, q), 7.7 (16-CH_3, q).

(4) Methylation of **1** was performed as described in Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475−1478. Although we originally favored **C1** as a possible substructure, we are grateful to an anonymous reviewer who noted the potential of phenols to undergo *O*-methylation (Toyohiko, A.; Terasawa, S.; Sudo, K.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 3759−3760.).

Table 1. Relative Stereochemistry of Subunits 1−3 Showing Selected NOE Enhancements (arrows) and $^3J_{H,H}$ Spin Coupling Constants Used for the Configuration Analysis of Psymberin (**1**) with Comparative Data for Pederin (**2**)

	subunit 1 configuration of C-4 to C-5		subunit 2 configuration of C-8 to C-13								subunit 3 configuration of C-15 to C-17				
															
position	4	5	8	9	10_e	10_a	11	12	13	14	15	16	17	18_α	18_β
^{1}H-NMR data for psymberin (**1**)[a]	3.65, ddd, *J*=2.5, 3.5, 9.5	4.33, d, *J*=2.5	5.36, d, *J*=8.0	3.91, ddd, *J*=3.0, 6.0, 8.0	1.98, ddd, *J*=2.5, 4.5, 13.5	1.75, ddd, *J*=6.0, 11.0 13.5	3.57, dd, *J*=4.5, 11.0	0.95, s (12-CH_{3e}); 0.87, s (12-CH_{3a})	3.47, dd, *J*=1.0,10.0	1.75, m[b]	3.91, m	1.87, ddq, *J*=2.0, 6.0, 6.0	4.46, ddd, *J*=3.0, 6.0, 12.0	2.83, dd, *J*=12.0, 17.0	3.11, dd, *J*=3.0, 17.0
^{1}H-NMR data for pederin (**2**)[c]	NA[d]	4.31, dd, *J*=2.2, 2.2	5.39, dd, *J*=8.0, 9.7[e]	3.81, ddd, *J*=2.5, 6.3, 8.0	2.05, ddd, *J*=2.5, 4.6, 13.4	1.76, ddd, *J*=6.2, 10.9, 13.4	3.65, dd, *J*=4.6, 10.9	0.95, s (12-CH_{3e}); 0.88, s (12-CH_{3a})	3.25, dd, *J*=2.0, 10.2	1.73, ddd; 1.61, ddd[f]	3.3-3.5, m	NA	NA	NA	NA
absolute configuration of pederin (**2**)	NA	*S*	*S*	*S*	NA	NA	*R*	NA	*R*	NA	*S*	NA	NA	NA	NA

[a] Data recorded in CD_3OD. [b] Isochronouse diastereotopic C-14 protons. [c] In $CDCl_3$, reported by Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223−227. See Figure 1 for numbering. [d] Not applicable [e] Splitting (dd) due to coupling with amide protons and H-9. [f] Analogous C-14 protons in mycalamide A (**3**) appear as an overlapping multiplet in $CDCl_3$ (refer to reference in footnote c).

Distinguishing among substructures **C1**−**C3** involved an evaluation of the experimental versus calculated ^{13}C shifts. Overall, **C2** provided the best agreement with the calculated values (Figure 2). Alternatively there was substantive divergence for many experimental shifts of substructure **C1** both in the vicinity of the carboxylic acid (δ_C 100.0, 113.8, 139.6) and beyond (δ_C 41.8, 80.7). The agreement between experimental and calculated data for substructure **C3** was good except at two carbons in the lactone ring (at δ_C 72.0, 80.7). The IR data of **1** revealed characteristic C═O stretching bands for an amide (1653 cm^{-1}) and α,β-unsaturated lactone (1617 cm^{-1}) that were unchanged in **4**, and the broad band at 3378 cm^{-1} was characteristic of a hydrogen-bonded phenol and not a carboxylic acid, thereby eliminating **C1**. Acetylation of **1** (1:1 acetic anhydride/pyridine) yielded penta-acetate **5** supporting the presence of five hydroxyl moieties. The slight shift in the H-17 resonance of **1** (δ_H 4.46) versus that of **5** (δ_H 4.42) provided the final evidence to rule out substructure **C3**.

With the planar structure identified, attention shifted toward defining the relative stereochemistry of **1**. Efforts to crystallize **1** and its acetylated and benzyl ester products proved unsuccessful. Instead, NMR-based methods including NOE enhancements in addition to $^3J_{H,H}$ and $^{2-3}J_{C,H}$ coupling constants (HSQMBC) were utilized for the configuration analysis of **1** as outlined in Table 1. A small $^3J_{H,H}$ (J = 2.5 Hz) H-4/H-5 *gauche* coupling combined with intermediate $^2J_{C,H}$ (J = 3 Hz) couplings between H-5/C-4 and H-4/C-5 indicated the presence of two C-4/C-5 rotamers[6] in subunit 1. Difference NOE data supported this conclusion with three key enhancements from H-5 to H-4, 4-OCH_3, and H-3_a. As a result of rotational freedom, these data cannot distinguish between 4*R**,5*S** and 4*S**,5*S** configurations. Similarly, two C-4/C-5 rotamers were previously reported for **3**.[7]

In view of the intervening amide functionality, the relative stereochemistry of subunit 2 was examined separately. A chair conformation was deduced for the oxane ring on the basis of diagnostic vicinal spin−spin couplings and was supported by NOE enhancements (H-10_e/H-11_a, H-11_a/12-CH_{3e}, and H-11_a/H-13_a). Additional NOE enhancements between H-8/H-11_a, H-8/H-13_a, and 8-OCH_3/H-10_e were corroborated by *gauche* H-8/C-10 (J = 3 Hz) and H-8/C-9 (J = 6 Hz) couplings, confirming the 8*S**,9*S**,11*R**,13*R** configuration in compound **1**.[8]

In subunit 3, H-17 showed *gauche* (J = 3.0 Hz) and *anti* (J = 12.0 Hz) couplings with H-18_α and H-18_β, respectively. In turn, H-17 exhibited an intermediate coupling (J = 6.0 Hz) with H-16 that combined with the observed NOEs suggested the two C-16/C-17 rotamers shown in Table 1. Likewise, the *gauche* coupling of H-15/H-16 (J = 2.0 Hz) was accompanied by NOE enhancements that supported two C-15/C-16 rotamers. Combined, these data justify a relative stereochemistry of 15*S**,16*R**,17*R** in **1**.

Attempts to define the absolute stereochemistry of **1** through the preparation of chiral derivatives were thwarted by the formation of multiple degradation products. Instead the well-defined Cotton effect at the $n \rightarrow \pi^*$ (ca. 270 nm)

(5) Shortly after the completion of this work we learned that iciniastatin A, possessing properties identical to those of psymberin (**1**) had been disclosed: Pettit, G. R.; Xu, J.-P.; Chapuis, J.-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149−1152. The name has been retained because of its prior incorporation in the research at collaborating institutions.

(6) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866−876.

(7) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223−227.

(8) A different 7*R** (same as position C-8 in psymberin, **1**) configuration was proposed for irciniastatin A (see ref 5).

transition for a chiral dihydroisocoumarin moiety was employed.[9] The positive Cotton effect at 280 nm clearly justified assignment of a 17-*R* configuration.

Compound **1** shares certain features with the sponge- and beetle-derived pederin family of metabolites (Table 1).[10] The structures of several pederin biomolecules, such as **2** and **3**, have been confirmed by synthesis and X-ray crystallography.[11] These data served as a benchmark to further examine the absolute stereochemistry of **1**. The important considerations included: (1) a probable shared biogenetic origin among **1**−**3**, (2) analogous NMR data (Table 1), (3) comparable cytotoxicity,[12] and (4) similar [α] value.[13] Therefore, we propose the stereochemistry of **1** as 5*S*,8*S*,9*S*,-11*R*,13*R*,15*S*,16*R*,17*R*.

Thirty-four pederin-like molecules have been described to date (Table S1) from across the globe (Figure S7), and **1** stands apart from these in light of its unique structural features. The mixed PKS/NRPS gene cluster described from an unculturable *Paederus* beetle bacterial symbiont sheds light on the biosynthesis of **2**.[14] Thus, **1** is probably biosynthesized by a similar route as **2**; however, it is the first analogue lacking the A-ring oxane and is also devoid of the 1,3-dioxane ring common among sponge-derived analogues such as **3**. The biosynthetic findings for **2** suggest production of **1** by a sponge microsymbiont and are the basis for its proposed name, psymberin.[15]

Psymberin (**1**) was initially detected via a disk diffusion assay in which it exhibited phenomenal activity against a human colon cancer cell line (HCT-116) (600 zone units, 900 pg/disk).[16] Interestingly, the potencies of the methylester (**4**) and penta-acetate (**5**) derivatives of **1** were significantly abated, exhibiting 17- and 1044-fold reductions in activity, respectively. Compound **1** was further evaluated in vitro against an extended panel of 60 human cancer cell lines. The results of this analysis are very intriguing in light of the selective activity exhibited by psymberin against numerous tumor types (Table 2). For example, several melanoma, breast, and colon cancer cell lines demonstrated considerable sensitivity ($LC_{50} < 2.5 \times 10^{-9}$ M) to psymberin, and all six of the leukemia cell lines proved comparably insensitive ($LC_{50} > 2.5 \times 10^{-5}$ M). These data, supporting a $>10^4$ fold activity differential for **1**, are exceptional in view of the equipotent toxicity observed for other pederin analogues.[17]

Table 2. Differential Sensitivities (LC_{50}) of Various Cell Lines to Psymberin (**1**) as Identified in the NCI Developmental Therapeutics in Vitro Screening Program

cell line	LC_{50} (M)	cell line	LC_{50} (M)
leukemia		melanoma	
CCRF-CEM	$>2.5 \times 10^{-5}$	LOX IMVI	$>2.5 \times 10^{-5}$
HL-60(TB)	$>2.5 \times 10^{-5}$	MALME−3M	$<2.5 \times 10^{-9}$
K-562	$>2.5 \times 10^{-5}$	SK-MEL-2	$>2.5 \times 10^{-5}$
MOLT-4	$>2.5 \times 10^{-5}$	SK-MEL-5	$<2.5 \times 10^{-9}$
RPMI-8226	$>2.5 \times 10^{-5}$	SK-MEL-28	1.41×10^{-5}
SR	$>2.5 \times 10^{-5}$	UACC-257	$>2.5 \times 10^{-5}$
		UACC-62	$<2.5 \times 10^{-9}$
breast cancer		colon cancer	
MCF7	$>2.5 \times 10^{-5}$	HCC-2998	3.76×10^{-7}
HS 578T	$>2.5 \times 10^{-5}$	HCT-116	$<2.5 \times 10^{-9}$
MDA-MB-435	$<2.5 \times 10^{-9}$	HT29	$>2.5 \times 10^{-5}$
NCI/ADR−RES	1.9×10^{-5}	SW-620	$>2.5 \times 10^{-5}$
T-47D	1.36×10^{-5}		

The discovery of **1** sheds further light on the structure−activity relationships within the pederin family. Our data indicate the A ring is not essential for activity, while the *N*-acyl aminal moiety is crucial for cytotoxicity.[5] Moreover, the dihydroisocoumarin moiety and/or vinylic methyl termini in **1** may be essential for the differential cytoxicity profile of psymberin. Further tests are underway to determine the in vivo antitumor activity of **1**.

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Supporting Information Available: NMR spectra, isolation scheme and modeling data for **1**; tables and figures summarizing the structures, distribution, and sources of pederin metabolites. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049503Q

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(10) (a) Narquizian, R.; Kocienski, P. J. In *The Role of Natural Products in Drug Discovery*; Mulzer, J., Bohlmann, R., Eds.; Ernst Schering Research Foundation Workshop 32; Springer: New York, 2000; pp 25−56. (b) See also Table S1.

(11) (a) Furusaki, A.; Watanabé, T.; Matsumoto, T.; Yanagiya, M. *Tetrahedron Lett.* **1968**, *60*, 6301−6304. (b) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357−2384. (c) See also ref 10.

(12) SAR studies have revealed that a 5*S*,8*S* absolute configuration is required for the potent cytotoxicity observed for analogous pederin-like compounds (see Figure 1 for numbering and ref 10).

(13) (a) All reported members of the pederin family possess optical rotations ranging between [α] = +22 (onnamide F: Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *J. Nat. Prod.* **2001**, *64*, 640−642) and [α] = +172 (theopederin C: Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1992**, *57*, 3828−3832). (b) See Table S1 for the optical rotations for all pederin metabolites.

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(15) The name psymberin is derived from ***Ps****ammocinia* + s***ymb****iont* + ped***erin*** in view of its relationship to the pederin family.

(16) Bioassay procedures are described in Valeriote, F.; Grieshaber, C. K.; Media, J.; Pietraszkewicz, H.; Hoffmann, J.; Pan, M.; McLaughlin, S. *J. Exp. Ther. Oncol.* **2002**, *2*, 228−236.

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