

Chapter 32

Pederin, Psymberin and the Structurally Related Mycalamides: Synthetic Aspects and Biological Activities

Zbigniew J. Witzcak, Ajay Bommarreddy and Adam L. VanWert

Abstract Pederin, psymberin, and mycalamides are related members of a relatively new family of potent natural antiviral and antitumor compounds originally isolated from marine sponges in 1988. This natural family of chemicals is of great interest to medicinal chemists and biologists, stemming from its extremely low abundance in source organisms and strikingly potent biological activity. They have clearly emerged as promising new synthetic targets, and are the focus of quite an interdisciplinary approach to molecular characterization. In this chapter we review diverse synthetic approaches to this family of natural products that has been demonstrating remarkable biological activity. We discuss relevant history, biological origins with the latest information on source organisms and their hosts, in-depth synthetic approaches, and biological data supporting their potential as therapeutic compounds.

Keywords Mycalamides · Psymberin · Psympederin · Irciniastatin A · Pederin · Onnamide · Marine · Natural products · Anticancer activity · Antineoplastic · Marine sponge · *Paederus fuscipes* · Polyketides · PC3 · Hela · T98G · KM12

32.1 Introduction

In 1988, an extract from the sponge genus *Mycale* in New Zealand's Otago Harbour yielded a small quantity of brown oil (307 mg from 200 g of sponge) whose bioactive components exhibited the unusual ring system which is now known as the mycalamides [1–7]. Structurally, mycalamides A and B are remarkably similar to the insect toxin pederin, and exhibit potent and comparable cytotoxicity and antitumor activity.

Despite their production in highly distinct species, the commonalities between these mycalamides, pederin [8], and the subsequently discovered onnamide A, an antiviral compound from a Japanese sponge [9], indicate that they likely have related modes of biosynthesis. Pederin is found in some beetles, e.g., *Paederus fuscipes*,

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and structurally is considered a polyketide that bears vesicant and potent antitumor properties. Although pederin has weak antibacterial properties, it is severely toxic to eukaryotic cells. This property likely stems from its ability to block protein synthesis and cell division. There is significant evidence indicating that pederin is synthesized by a bacterial symbiont of host beetles, perhaps a close relative to *P. aeruginosa* [10]. This finding raises the possibility of culturing bacteria to generate a large quantity of pederin for therapeutic use or chemical modification to enhance pharmacodynamics/pharmacokinetics. Currently, however, isolating a practical quantity of pederin from biological sources remains challenging. Approximately 220 lb, or 25 million insects, were needed to extract enough pederin for structural analysis (Scheme 32.1).

Comprehensive characterization of the pharmacodynamic, toxicological, and therapeutic potential of all these congeners has been limited by their paucity. Therefore, alternative and practical synthetic approaches should prove to be highly useful for this remarkably potent set of compounds. Developing new and efficient synthetic strategies should facilitate the production of new lead modifications. Ideally, such derivatives of the natural compounds will have more suitable pharmacodynamic and pharmacokinetic properties, and most importantly, tissue targeting may become a realistic goal.

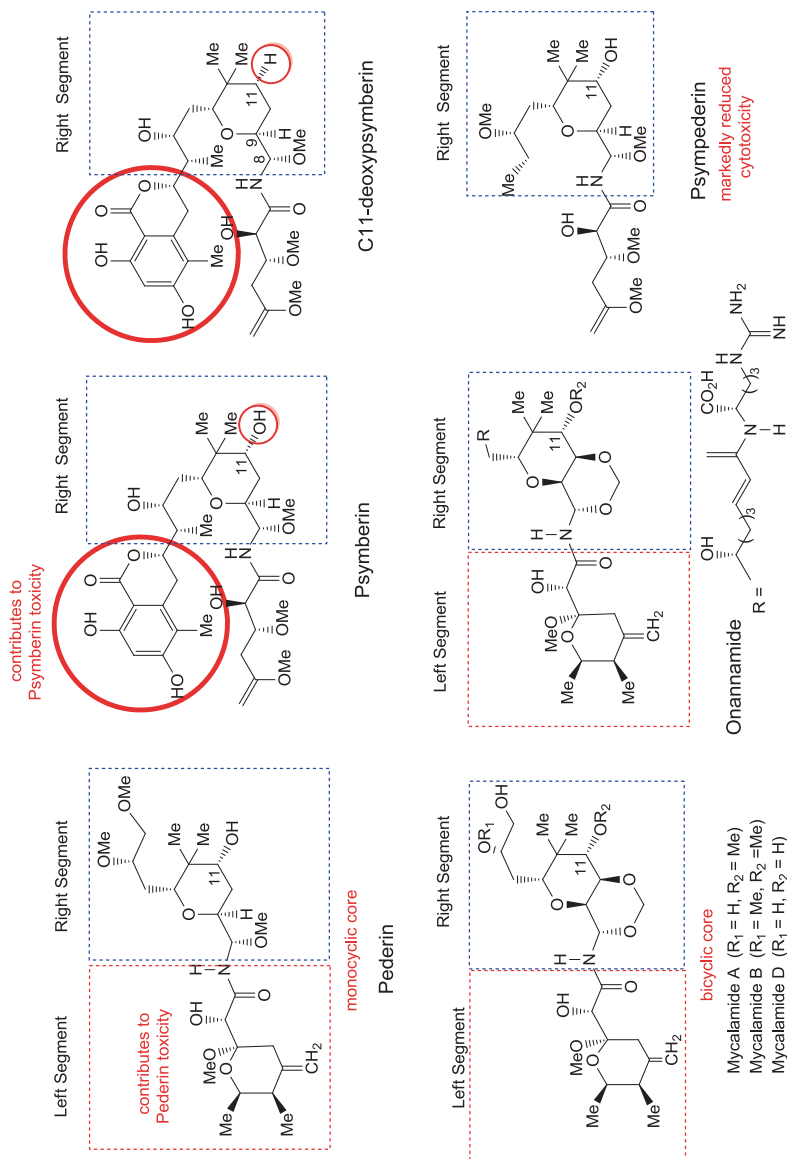
32.2 Synthetic Methodologies

An account of the major synthetic strategies for producing compounds from the mycalamide, pederin, and psymberin families is presented in separate sections below. All presented methods reflect a clear mastery of modern synthesis techniques and reagents by the investigators.

32.3 Synthetic Methodologies for Mycalamides

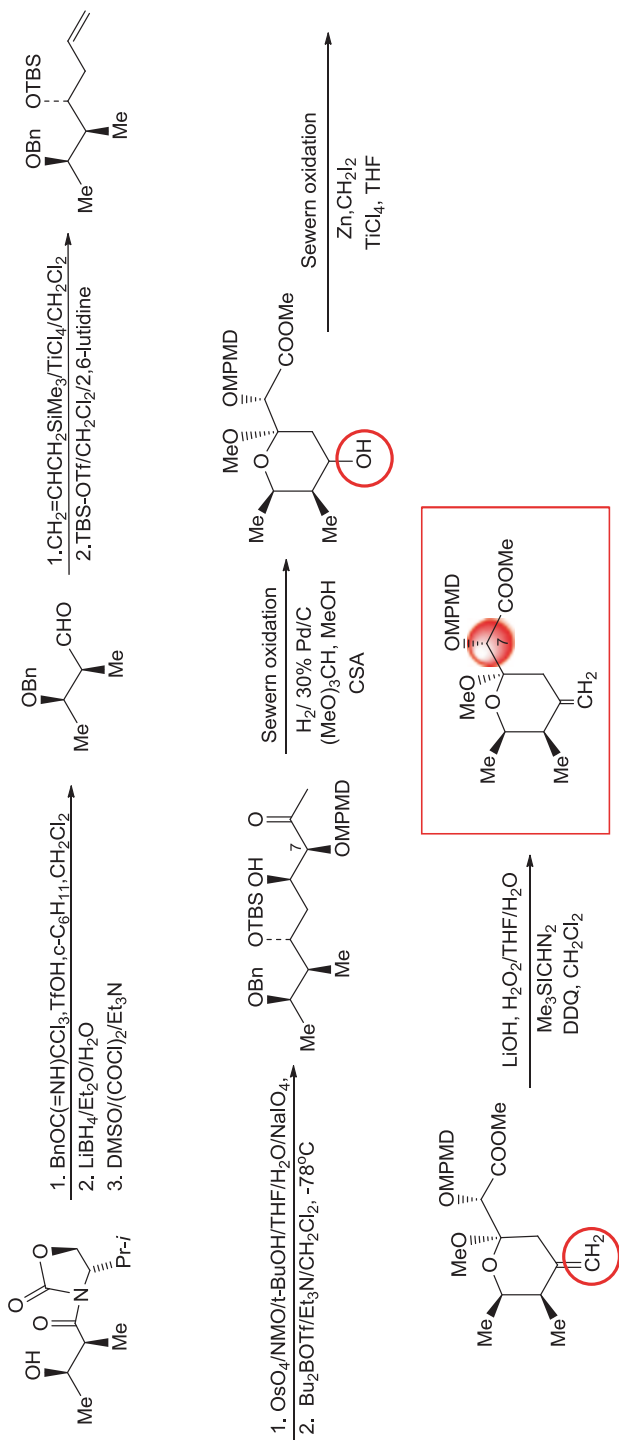
Several synthetic strategies for producing mycalamides have been published. All proposed methods to date have been complex strategies with low yields. Adding to the complexity of these strategies is the requirement for stereospecificity at several steps. Thus, development of more efficient synthetic strategies is critical for realizing the full potential of this class of compounds.

A synthetic approach to produce the right half of mycalamides was demonstrated using Kishi's method. This technique utilizes α -D-glucopyranoside as the starting material. In the early 1990s a multi-step sequence for developing this significant portion of the mycalamide structure was published [11, 12]. The basic synthetic strategy involves an alteration of the previously published methodology [13, 14]. The conjugation method to produce total mycalamide required the activation of pederate, the left portion of the molecule, with *p*-toluenesulfonyl chloride/DMAP/dichloromethane at room temperature followed by treatment with the amines produced by hydrogenation of azides. In Roush's method, an excellent chiral precursor, methyl



Scheme 32.1 Pederin, psymberin, and psympederin and structurally related mycalamides, onnamide

7-benzoylpederate, is used to effectively control the stereoselectivity of the coupling strategy for generation of the amide bridge [15–18]. An alternative approach to synthesize methyl pederic acid involves 7-*O*-(3,4-dimethoxybenzyl) pederate, an intermediate in Kishi's synthesis of mycalamides A and B and onnamide A [11, 12]. Scheme 32.2 depicts this significantly diastereoselective synthesis. Incorporation of the *exo* methylene moiety involves use of the very important Takai-Nozaki protocol (CH_2I_2 , TiCl_4 , Zn, THF).



Scheme 32.2 Roush's synthesis of 7-O-(3,4-dimethoxybenzyl)

A strategy for producing pederic acid derivatives was employed in the synthesis of 7-*epi*-mycalamide [15–19]. One key step in the method is the mismatched aldol reaction of the imide and aldehyde. This step yielded a ca. 5:4 mixture of two isomeric aldols, with incorrect C-7 stereochemistry. Enrichment of the isomeric mixture to mycalamide A required epimerization of C-7 at the beta-keto imide step. A divergent and effective approach involves Swern style oxidation of the isomeric mixture of aldols. This approach proceeds under reaction conditions that minimize C-7 epimerization, selectively yielding 7-*epi*-mycalamide.

A strategy for producing (+)-methyl 7-benzoylpederate, a mycalamide intermediate, has been reported by Trotter et al. in the Nakata group [20]. This effective strategy employs the well-known Nakata's [20] precursor, that has been utilized in similar methods, resulting in generation of the basic framework of the system. One limitation of the approach is that the conjugation strategy employs the original technique that yields an isomeric mixture of target products. These products are challenging to purify.

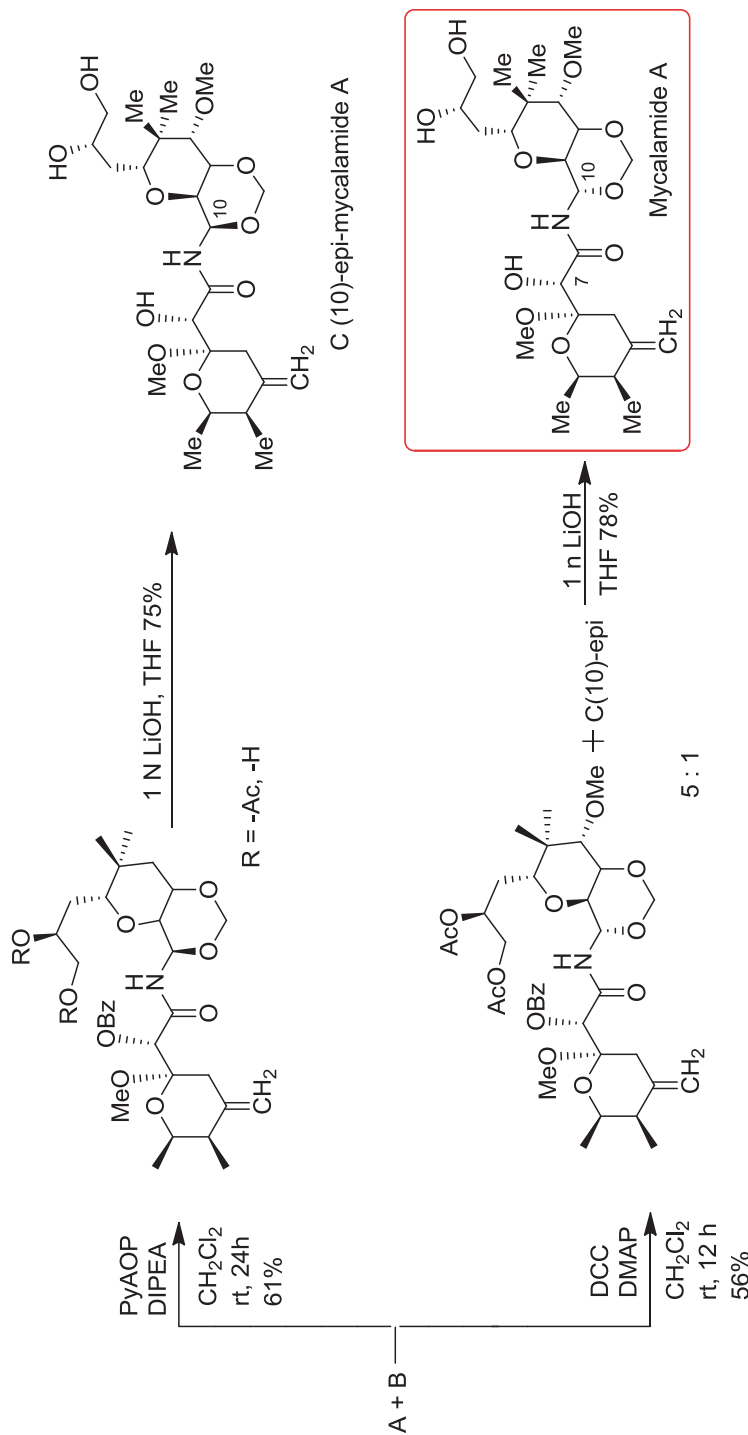
Stereoselectivity is a focus of Toyota's/Ihara's method for mycalamide synthesis. In this procedure D-mannitol is a useful chiral precursor for eventual production of the right half of the mycalamide structure. In this strategy, a Lewis-acid-catalyzed intermolecular aldol reaction and oxypalladation are critical steps [21–24]. This approach yields an effectively protected right half of the mycalamide structure that is primed for functionalization and conjugation with the remaining half of the structure.

For the total synthesis of (+)-mycalamide A, Kagawa and Toyota produce an α , β -unsaturated ester from D-mannitol as described above [21]. The ester is then used to synthesize an intermediate, and the left and right portions are joined by trans-methylation of the intermediate. Subsequently, conjugating the resultant vinyl anion to the ester group regioselectively via nucleophilic addition effectively produces the final precursor in 50% yield. Modifications of the functional group of this precursor can produce (+)-mycalamide A [25].

Trost and Probst demonstrated an approach for the synthesis of (–)-mycalamide A. In this method they synthesized (–)-7-benzoylpederate (left-half of mycalamide) from (2*S*,3*S*)-2, 3-epoxybutane and the right-half of mycalamide from (R)-pantolactone [26]. A multi-step sequence was used to form a terminal azide on the right half that was suitable for conjugation with the left half, yielding the total mycalamide.

Sohn and Rawal's approach to mycalamide A synthesis employed a convergent coupling of pederic acid (Structure A, Scheme 32.3) with mycalamine (structure B) [27].

In this approach the left portion, (+)-7-benzoylpederic acid, was produced through 7 steps with ~35% overall yield. A major step in this method is the palladium (II)-catalyzed tandem Wacker/Heck cyclization reaction to form a tetrahydropyran ring (Scheme 32.3) prior to coupling to the right half of mycalamide. The right half, mycalamine (structure B), was synthesized from diethyl D-tartrate in 21 steps with 10.5% yield. Joining of the two halves stereoselectively was accomplished *via* (1) DCC/DMAP catalysis with 56% yield of mycalamide A, or (2) reaction with



Scheme 32.3 Rawal's coupling approach to mycalamide A

benzotriazol-1-yl-oxytrypyrrolidinophosphonium-hexafluoro-phosphate/ Diisopropyl-ethyl-amine (PyAOP/DIPEA) to produce *C* (10)-*epi*-mycalamide A (61 % yield).

32.4 Synthetic Methodologies for Pederin

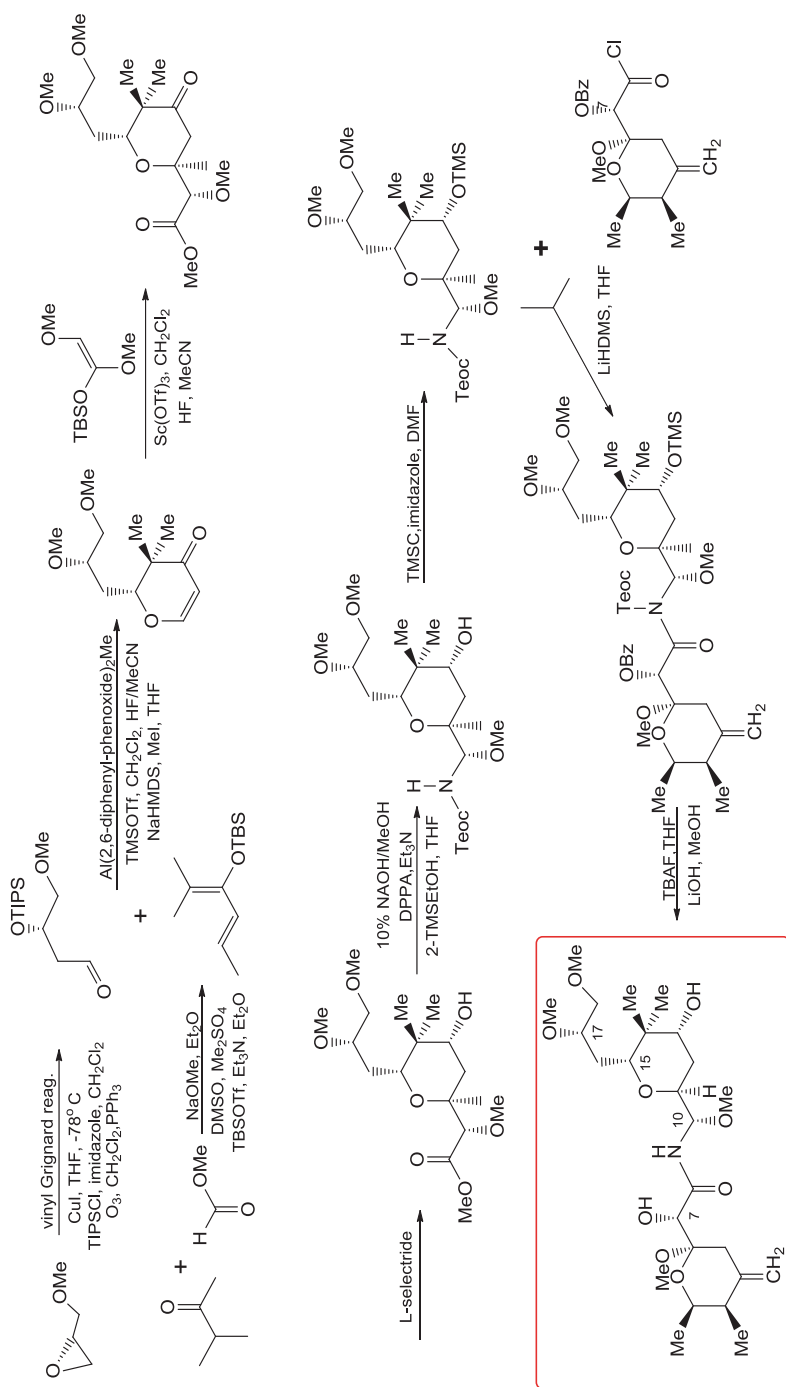
From earlier years to more recent times many literature reports [13, 14, 28–44] describe total synthesis of pederin, precursors, or related structures. The total synthesis of pederamide, a hydrolysis product of pederin, was first reported by Tsuzuki and co-workers in 1976 [41]. Subsequently, Nakata et al. reported the first synthetic method for production of total pederin in 1985 [13, 14]. In this method they stereoselectively produced (+)-benzoyselenopederic acid via the novel reducing agent, $\text{Zn}(\text{BH}_4)_2$. Two major steps in their procedure were (1) construction of an aмина linker using a metallated dihydropyran; and (2) production of an N-acyl aмина via a rhodium-catalyzed reductive hydroboration of an acyl aмина.

Kocienski's strategy [45] for the right portion template, originally described in 1987 [28], is one of the most useful synthetic methods for efficient production of an important precursor of the whole family of mycalamides. A relatively new approach, published by Floreancig et al. [42, 43] employs the Paterson's pinene-derived boron enolatealdol strategy. This effective strategy proceeds with a highly stereoselectivealdol reaction. This reaction is a pivotal step for ensuring appropriate orientation of bonds at C-15.

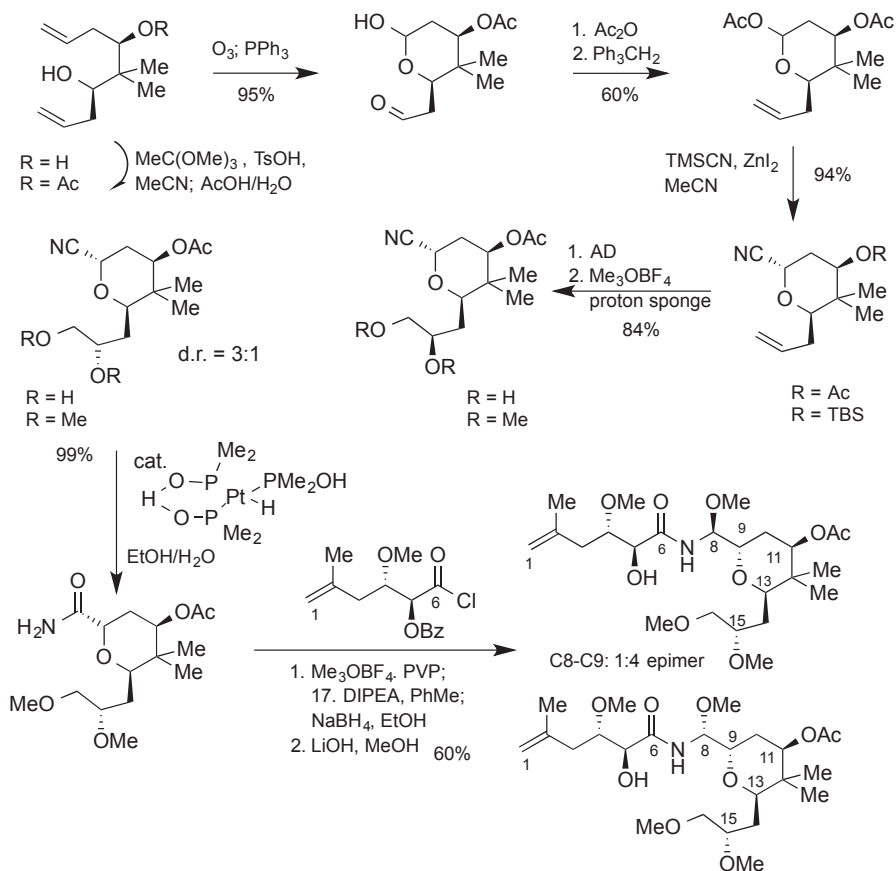
In 2007, another approach for the total synthesis of pederin was reported by Jewett and Rawal [30]. The group achieved direct coupling of the left and right halves using pederic acid chloride with the lithium anion of carbamate in a toluene/pyridine solution. This approach was highly effective. The deprotection steps to complete the approach required the use of *t*-butyl ammonium fluoride (TBAF) in a tetrahydrofuran solution followed by a hydrolytic quench with lithium hydroxide in methanol. This strategy resulted in formation of total pederin with a marked 88 % yield (Scheme 32.4). Various other diverse methods for the production of pederic acid esters, which serve as specific templates for coupling approaches, have also been published [37–40].

32.5 Synthetic Methodologies for Psymberin

Psymberin was first isolated by Crews et al. in 2004 from the Marine Sponge *Psammocinia* using a "bioassay-guided fractionation" method [46]. Irciniastatin A, isolated by Pettit et al. in the same year from the marine sponge *Ircinia ramose*, was found to be identical to psymberin [47]. The amide side chain of psymberin was a focus of Williams et al. in a 2005 report [48]. Their group employed X-ray crystallography and synthetic model compounds for comparison with natural psymberin.



Scheme 32.4 Rawal's synthesis of pederin

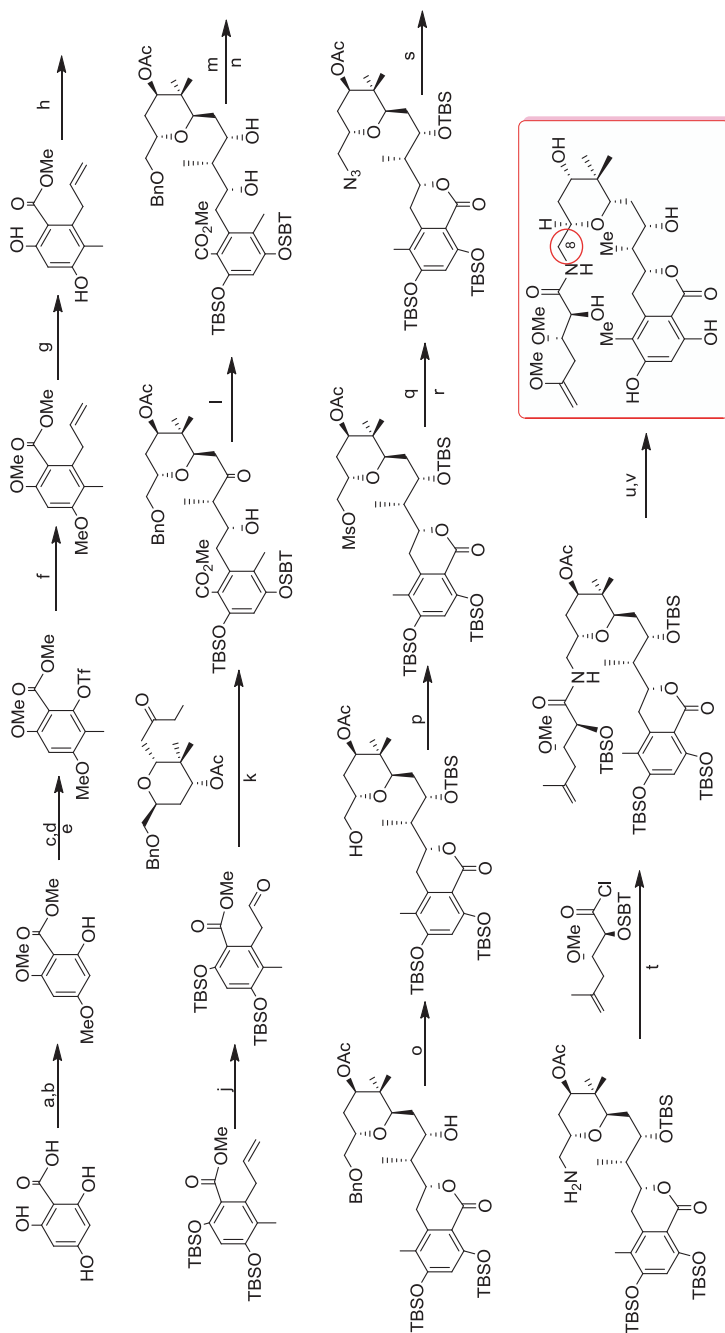


Scheme 32.5 De Brabander's synthesis of psymberin

They determined that the *anti* configuration of the side chain is the natural form [48]. Crews and coworkers [46] also reported assignment of absolute stereochemistry of Psymberin as 5*S*, 8*S*, 9*S*, 11*R*, 13*R*, 15*S*, 16*R*, 17*R* and with multiple NOE enhancements. Psymberin was assessed for *in vitro* activity against an impressive 60 human cancer cell lines [46].

Generation of psymberin stereoisomers was reported by De Brabander et al. [49]. In the following year the group reported on the synthesis of a novel compound sharing characteristics with psymberin and pederin [50]. They referred to the new compound as “psympederin”. This hybrid is depicted in Scheme 32.5, and starts with a C_2 -symmetrical diol that is conveniently acetylated by acid catalysis into cyclic orthoformate [50]. Hydrolysis of the monoacetate, followed by reduction with triphenylphosphine, resulted in production of a lactol with a yield of 95%. Subsequently, the lactol intermediate was functionalized with multiple steps to the amide. In the final step of the pathway, the amide was converted into “psympederin” (Scheme 32.5).

Several diverse methodologies for the synthesis of psymberin and functionalized congeners have been reported in the past 10 years [51–60]. Konopelski et al. and



Scheme 32.6 Pietruszka's synthesis of 8-desmethoxy psymberin

Shao and Huang et al. [51, 57], in addition to Pietruszka and co-workers [58–60], have designed methods for synthesizing new analogues of psymberin, including putative intermediates in the natural biosynthetic pathway. Pietruszka's synthetic approach to 8-desmethoxy psymberin is depicted in Scheme 32.6.

32.6 Biological Activity

32.6.1 Activity of Mycalamides

Evaluation of the biological and potential therapeutic activity of this class of compounds has been difficult, stemming from their very low concentration in host organisms. Mycalamide-A exhibited promising *in vivo* anti-viral activity against the A59 coronavirus in mice [2]. Furthermore, mycalamides A and B and onnamide showed *anti-cancer* properties *in vitro* and *in vivo* in mice and human tumor cells at concentrations ranging from 5 to 200 nM and 2.5 to 10 $\mu\text{g}/\text{kg}$ [61]. All three compounds were shown to inhibit protein synthesis, some at low nanomolar concentrations [61, 62]. Mycalamides A and B exhibited the ability to convert transformed rat kidney epithelial cells (NRK) back to their normal morphology, possibly through selective inhibition of protein synthesis [63]. More recently, Dyshlovoy et al. showed that mycalamide A was able to block epidermal growth factor-induced cancerous transformation of a murine epidermal cell line (JB6 Cl41 P(+)), and induce apoptosis at subnanomolar concentrations, possibly through inhibition of NF- κB and AP-1 nuclear transcription factors [64]. Richter et al. showed that synthetic congeners of mycalamide-B, i.e., 18-O-methyl mycalamide-B and 10-epi-18-O-methyl mycalamide-B, exhibited anti-proliferative effects against carcinomas [65]. Specific cell lines that demonstrate susceptibility to mycalamide A, mycalamide B, or onnamide include murine lymphoma P388 cells, HL-60, HT-29, and A549 human tumor cells, and leukemia cells [61–63, 65]. Mycalamide-A is also active against B16 melanoma, Lewis lung carcinoma, M5076 ovarian sarcoma, colon26 carcinoma, and the human MX-1, CX-1, and Burkitt's lymphoma tumor xenografts [61].

In addition to its antitumor properties, mycalamide-A has demonstrated powerful immunosuppressive action, with a potency at inhibiting CD4^+ T cells of approximately 1000 times that of cyclosporin A on a molar basis [66]. This places mycalamides amongst the most powerful immunosuppressive compounds discovered to date. Mycalamide A has also been shown to induce apoptosis with a preference for 32 D myeloid cells that have Ras or Bcr/abl alterations [67].

The mycalamides appear to have a unique mechanism of action, which is of great interest for studying the immunobiology of T cells and potentially for developing agents that can modulate T-cell function. The strong immunosuppressive ability of these compounds and their unique mechanism of cytotoxicity makes them promising, both as potential biochemical tools (e.g., FK506 and rapamycin have already led to several advances in cell biology), and as potential therapeutic agents for preventing graft-vs.-host and host-vs.-graft disease in post-transplant surgery patients. In addition, these agents have potential in alleviating patients with autoimmune disorders. It is also of potential utility that mycalamide A does not appear to be a substrate for the major drug efflux pump, P-glycoprotein (MDR1/ABCB1). Therefore, P-gp is not expected to be a limiting factor in its cytotoxicity [68].

Table 32.1 Differential sensitivities (LC_{50}) of various cell lines to Psymberin as identified in the NCI developmental therapeutics in Vitro screening program [59]

Cell line	LC_{50} (M)	Cell line	LC_{50} (M)
<i>Breast cancer</i>		<i>Colon cancer</i>	
MCF7	$>2.5 \times 10^{-5}$	HCC-2998	3.76×10^{-7}
HS578T	$>2.5 \times 10^{-5}$	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}		
<i>Melanoma</i>		<i>Leukemia</i>	
LOX IMVI	$>2.5 \times 10^{-5}$	CCRF-CEM	$>2.5 \times 10^{-5}$
MALME-3M	$<2.5 \times 10^{-9}$	HL-60 (TB)	$>2.5 \times 10^{-5}$
SK-MEL-2	$>2.5 \times 10^{-5}$	K-562	$>2.5 \times 10^{-5}$
SK-MEL-28	$<2.5 \times 10^{-9}$	MOLT-4	$>2.5 \times 10^{-5}$
SK-MEL-28	1.41×10^{-5}	RPMI-8226	$>2.5 \times 10^{-5}$
UACC-257	$>2.5 \times 10^{-5}$	SR	$>2.5 \times 10^{-5}$
UACC-62	$<2.5 \times 10^{-9}$		

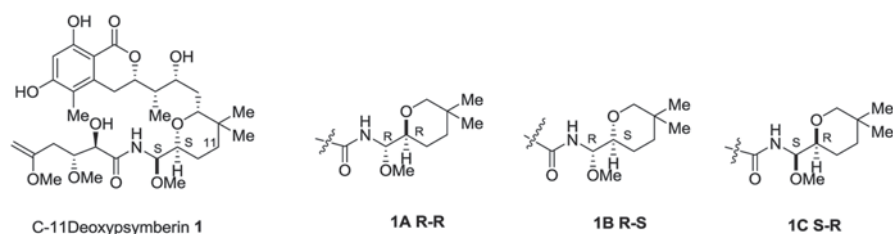
32.6.2 Activity of Psymberin

Psymberin also known as Irciniastatin A is a naturally occurring cytotoxic agent which was independently isolated by Pettit et al. [47] from marine sponge *Psammocina* species and Crews et al. [46] from *Ircinia ramosa* species in 2004. It has been recently documented that psymberin is rather produced by the symbiotic bacteria associated with the marine sponges and not by marine sponges themselves [10]. Psymberin structural features closely resemble that of other pederin family members including mycalamide A. In general, psymberin lacks the commonly present acetal-containing pederate side chain, but is identified with a dihydroisocoumarin unit that is not widely found with other members of pederin family. The activity of psymberin on various human cancer cell lines is listed in Table 32.1. Out of the 60 cell lines tested, psymberin displayed a differential cytotoxicity profile and was more potent against colon cancer, melanoma and breast cancer cell lines. Several research groups have attempted to synthesize this fascinating marine drug owing to its complex structure, limited natural abundance and biological properties [59]. Huang et al. reported several analogues of psymberin which were constructed by modifying the tetrahydropyran ring core of psymberin. All the analogues (**1**, **1A**, **1B**, **1C**) were biologically tested using major human cancer cell lines to identify their IC_{50} values (Table 32.3). Compound **1** (C11-Deoxypsymberrin) was found to be most potent of all the analogues and its potency was 3 to 10 fold more compared to psymberin or its epimer [57]. Modifications of **1** further revealed high potency against the HOP62 human lung cancer cell line [57] (Fig. 32.1).

De Brabander et al. [69] synthesized psymberin and its analogues whose biological activity against major human cancer cell lines is listed in Table 32.2 [70]. Psymberin and its two epimers 8-epipsymberrin and 4-epipsymberrin exhibited

Table 32.2 Mycalamide A, Psymberin and its analogues cytotoxicity against different human cancer cell lines [69–71]

IC ₅₀ (nM)					
Structure	PC-3	SK-MEL-5	Hela	T98G	KM 12
Mycalamide A	2.5±0.2	–	–	2.87±0.07	0.95±0.02
Psymberin	0.98±0.12	2.29±0.13	0.64±0.14	1.37±0.06	0.45±0.01
4- <i>epi</i> -psymberin	346.5±102.8	762.8±70	618.6±267	186.7±51.3	126.08±8.6
8- <i>epi</i> -psymberin	200.2±27.6	352.0±2.1	>1000	85.8±48.4	37.1±5.5
Psympederin	821.8±89.1	>1000	>1000	>1000	710.9±35.8
c-8- <i>epi</i> -psympederin	255.5±11.4	>1000	>1000	>1000	>1000

**Fig. 32.1** Structural variations at the tetrahydropyran core of C11-Deoxypsymben and its Epimers**Table 32.3** Activity of Psymberin, C-11 Deoxypsymben 1 and its Epimers, 1A, 1B, 1C [53]

IC ₅₀ (nM)							
Tissue type (human)	Cell line	Psymberin	1	1A R/R	1B R/S	1C S/R	<i>epi</i> -Psy
Normal	NHDF	0.84	0.066	n. d.	n. d.	3.8	n.d.
Kidney	ACHN	0.76	0.265	n. d.	n. d.	8.7	6800
Prostate	DU145	0.30	0.149	n. d.	n. d.	5.9	3800
Prostate	PC3	0.19	0.073	n. d.	n. d.	2.9	3100
Lung	H226	0.18	0.034	n. d.	n. d.	1.6	2400
Lung	HOP62	0.42	0.055	177	46	3.0	4600
Breast	MB231	0.27	0.142	n.d.	n.d.	5.3	4200
Gastric	MKN45	0.28	0.076	n.d.	n.d.	3.9	5200
Colon	SW620	0.82	0.160	n.d.	n.d.	6.1	4800

meaningful IC₅₀ values whose values were relatively lower when compared to the two hybrids that were synthesized with a dimethoxy unit instead of dihydroisocoumarin unit. The structural variations of psymberin and its epimers when compared with the two hybrids indicate that retention of dihydroisocoumarin unit is essential for the biological activity of psymberin [70]. Furthermore, it was revealed that

structural alterations of psymberin could result in decreased cellular uptake of these compounds in HeLa cells compared to psymberin [70]. After incubation of HeLa cells with 100 nM of psymberin and its epimers, the intra-cellular concentration of psymberinepimers (4-epi & 8-epi) was about 20-fold less than psymberin and the intra-cellular concentration of psympederin was below the limit of detection [70]. The same study [70] employing forward genetic screen in *C. elegans* identified that ribosome was the primary target for psymberin and also demonstrated that in contrast to other pederins, psymberin does not exhibit blistering activity due to the absence of acetal group. Most recently, Pietruszka group synthesized 8-desmethoxy psymberin, a putative biosynthetic precursor of psymberin in 25 steps whose biological activity is yet to be determined [58].

Psymberin exhibits very potent antiproliferative activity against a wide selection of human tumor cell lines including KM12, PC3, SK-MEL-5, and T98G with IC_{50} at range 0.45–2.29 nM [46]. The data pertinent to differential sensitivities of various cell lines to psymberin is summarized in Table 32.2. Crews and co-workers [46] also reported that psymberin exhibits phenomenal activity against a human colon cancer cell line HCT-116 with IC_{50} at range 2.5×10^{-9} M. It is interesting to note that according to the authors [46] ring A is not essential for activity, but in contrast *N*-acylaminal functionality is absolutely crucial for cytotoxicity.

32.7 Summary and Conclusions

The mycalamides and their congeners, which were initially isolated from various natural sources, have garnered significant attention from the scientific community in recent years. Owing to their limited supply from the natural sources, several research groups have focused on their biosynthesis and biological evaluation. The various schemes presented in this chapter highlight the selected synthetic approaches employed for preparing structurally unique motifs and their analogs. In addition, recent advancements in the synthetic approaches to these compounds have improved their total synthesis. These compounds and their derivatives have been evaluated for their biological activities and are proven to be very effective in extremely low concentrations. Potent cytotoxicity was observed when various cancer cell lines were treated with mycalamides, psymberin, and their analogs in the lower nanomolar range. Similarly, mycalamides have also demonstrated antiviral properties and T-cell-modulating potential. Hence, advances with this class of natural products exemplify the power of an interdisciplinary approach to drug discovery. The design of newly functionalized analogs, with potent anticancer, antiviral, and immunosuppressive activity, can now be realized.

While much remains to be revealed about the biological properties of psymberin, pederin, mycalamides, and analogs, it is reasonable to conclude that the novel synthetic approaches discussed here and in recent reviews [71, 72] will evolve to yield more potent and more highly-targeted compounds in the near future.

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