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Mycalamides, Pederin and Psymberin as Natural Carbohydrates and Potential Antitumor Agents: Past and Future Perspectives

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Abstract: The mycalamide class of potent antiviral and antitumor natural compounds originally isolated from marine sponges in 1988 is a new interdisciplinary approach to molecular recognition. We review new synthetic approaches to this new family of natural products with remarkable biological activity. Some biological evaluation data are compiled and compared to other structurally similar molecular targets.

Keywords: Mycalamides, pederin, psymberin, cytotoxicity, immunosuppression.

INTRODUCTION

In the mid-1980s, extracts from sponges of the genus *Mycale* from waters off the Indian sub-continent yielded bioactive constituents whose structures proved to be the unusual ring system of mycalamides A and B [1-7]. Originally isolated from New Zealand marine sponges Mycales [1], mycalamides A and B showed close structural similarity to the insect toxin pederin and exhibited potent comparable cytotoxicity and antitumor activity.

This unusual similarity to the only other structurally related natural product pederin [8] and later discovered onnamide A, an antiviral extract from a Japanese sponge [9], suggest their similar/identical biosynthetic pathways (Scheme **1**).

Pederin is an extremely active vesicant isolated from the blister beetle *Paederus fuscipes*. Approximately 100 kg (25 million insects) were required to isolate sufficient material for structure elucidation. Pederin is characterized as highly toxic to eukaryotic cells, despite being a very weak antibacterial agent. Pederin's high level of toxicity appears to be strongly related to its inhibition of protein biosynthesis and cell division. Additionally, this particular effect on protein synthesis suggests that pederin's analogs converted the morphology by preferentially inhibiting the biosynthesis of the p21 protein.

Detailed studies of the pharmacological, toxicological and clinical potential of all these structurally related compounds have been hampered by their availability, only in extremely limited quantities from natural sources. Therefore, alternative and practical synthetic approaches are highly in demand for this fascinating molecular target of this mycalamide family. Particularly important are future development of new leads and their extremely important aspects of biological activity as well as medicinal chemistry.

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SYNTHETIC METHODOLOGIES

All selected synthetic approaches to these special class derivatives are highly elaborative and include multi-step strategies with a very low overall yield. Stereoselectivity, at each step, is critical to the overall successful synthetic strategy. Therefore, the development of synthetic methodologies on improved and highly efficient approaches is expected in the near future.

The following approaches from different laboratories were developed and contributed to the synthetic chemistry of mycalamides, pederin and psymberin families. All of them are the result of genuine mastery of synthetic strategies using modern techniques and reagents.

The first synthetic approaches to pederin family was described in early 1985 by Nakata and co-workers [10-11] exploring the utilization of the convenient chiral building block, (+)-benzoylselenopederic acid, which was synthesized stereoselectively by using new reducing agent $Zn(BH_4)_2$. Two key steps in Nakata's approach were: (a) use of a metallated dihydropyran to construct the very fragile aminal bridge; (b) use of a rhodium-catalysed reductive hydroboration of an acyl imine to construct an N-acyl aminal.

KISHI'S APPROACH TO MYCALAMIDE A & B

His strategy utilizes α-D-glucopyranoside as the starting material for the synthesis of the right-half segment of mycalamide. A seven-step sequence toward this important intermediate was published in early 1990. [12, 13] Modification of the previously published methodology for the synthesis of the right half (ring A) of mycalamide constitutes the general synthetic strategy. The coupling strategy required the activation of pederic acid (left-hand segment) with *p*-toluenesulfonyl chloride/DMAP/CH_2Cl_2 at room temperature following treatment with the amines conveniently produced by hydrogenation of azides and is depicted in (Scheme **2**).

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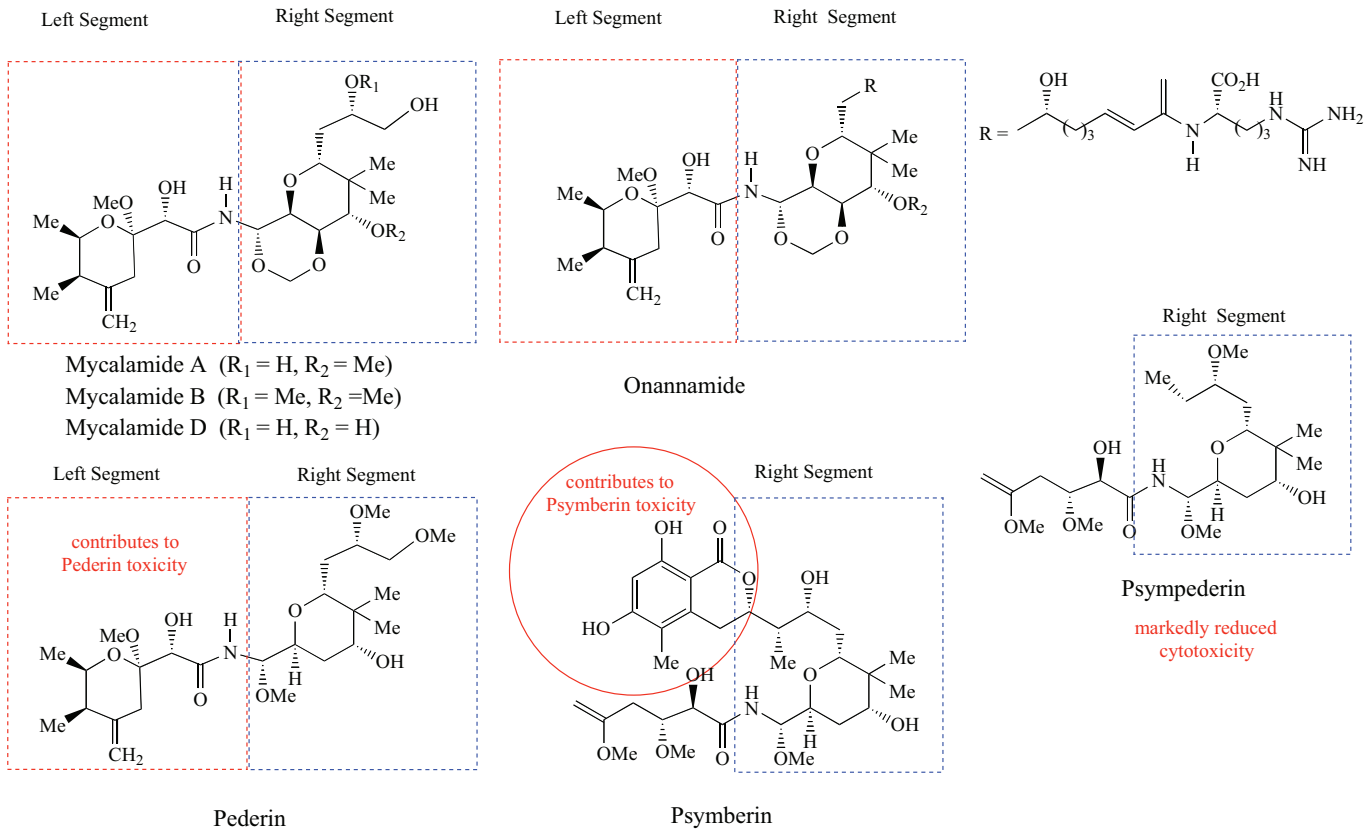
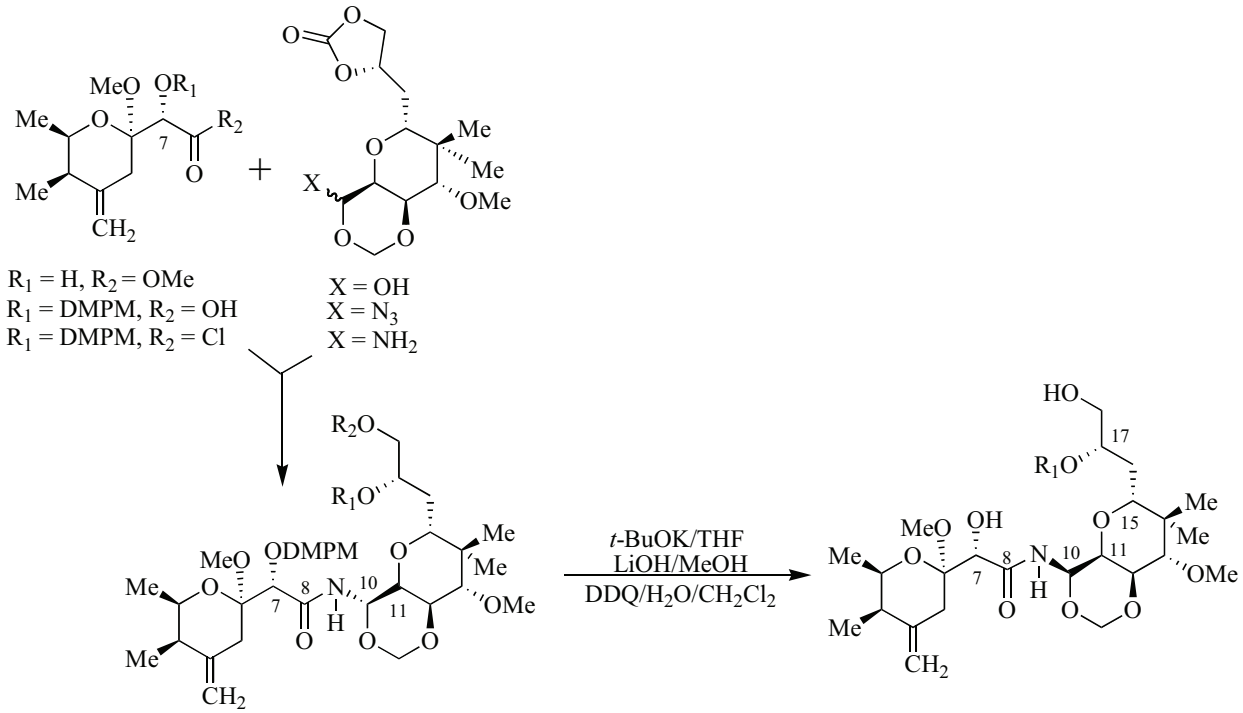


Scheme (1). Mycalamides, onannamide and structuraly related pederin, psymberin and psymberin hybrid.



Scheme (2). Kishi's approach to mycalamide **A** & **B**.

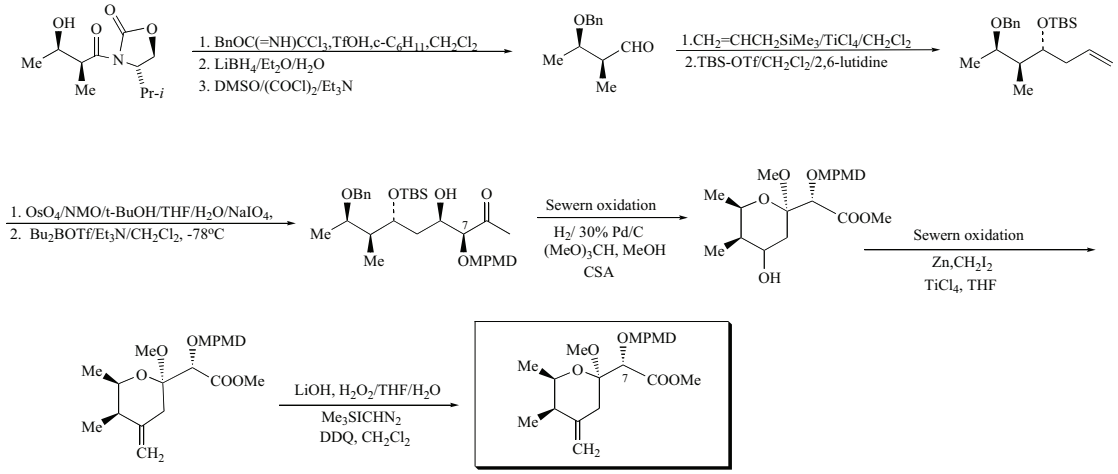
ROUSH'S APPROACH TO 7-*O*-(3, 4-DIMETHOXY-BENZOYL PEDERIC ACID

These early synthetic studies were designed to utilize one of the best chiral precursors (methyl 7-benzoylpederate) for efficiently controlling the reaction of stereoselectivity and efficiency of the coupling strategy for construction of amide bridge [14-17].

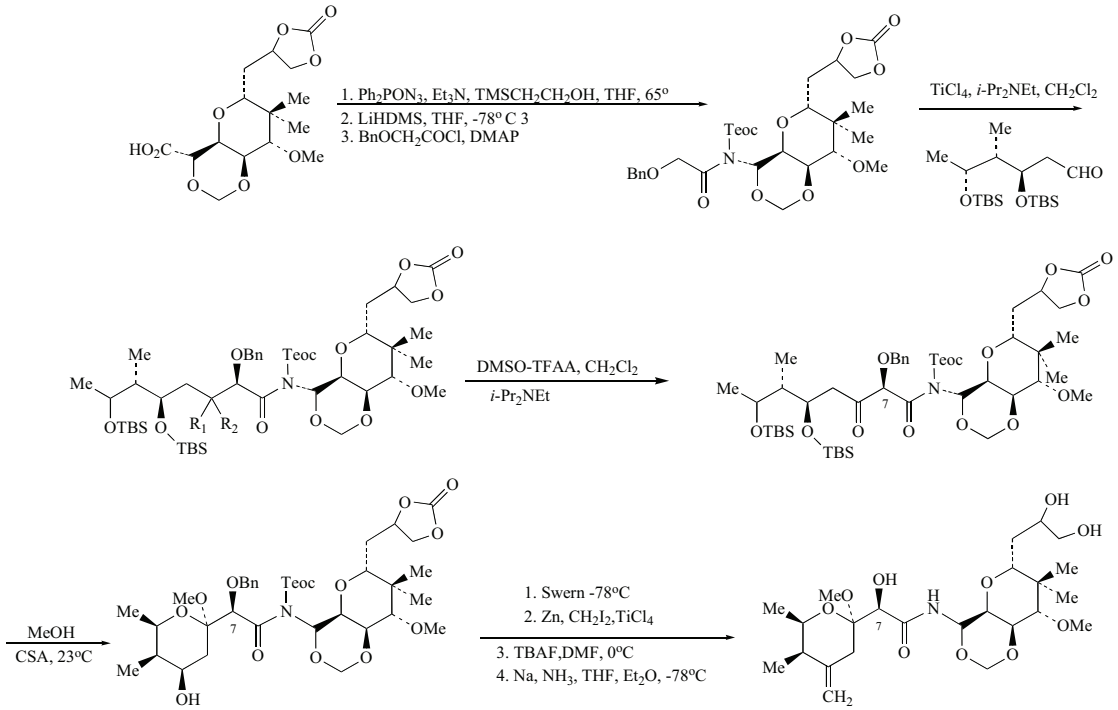
The alternative strategy to synthesize methyl pederate proceeds by way of 7-*O*-(3,4-dimethoxybenzyl) pederic acid an intermediate template in earlier Kishi's approach to mycalamides A and B as well as onnamide A. [12-13] This highly diastereoselective synthesis is outlined in (Scheme **3**). The key step for introduction of the exo methylene moiety is based on the Takai-Nozaki protocol (CH_2I_2, $TiCl_4$, Zn, THF) and is illustrated in (Scheme **3**).

ROUSH'S APPROACH TO 7-*EPI*-MYCALAMIDE A & B

Roush's clever strategy [14-18] for the synthesis of pederic acid derivatives was further explored in the synthesis of 7-*epi*-mycalamide with the key step of the aldol reaction (mismatched) of imide and aldehyde which provided a ca. 5:4 mixture of two isomeric aldols, with incorrect C-7 stereochemistry. This particular elaboration of the isomeric mixture to mycalamide A required epimerization of C-7 at the stage of beta-keto imide. Alternatively, Swern oxidation of the isomeric mixture of aldols, under reaction conditions that minimize C-7 epimerization lead to 7-*epi*-mycalamide A selectively (Scheme **4**).



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



Scheme (4). Roush's approach to Mycalamide and 7-*epi*-Mycalamide A.

NAKATA'S APPROACH TO (+)-METHYL 7-BENZOYLPEDERATE

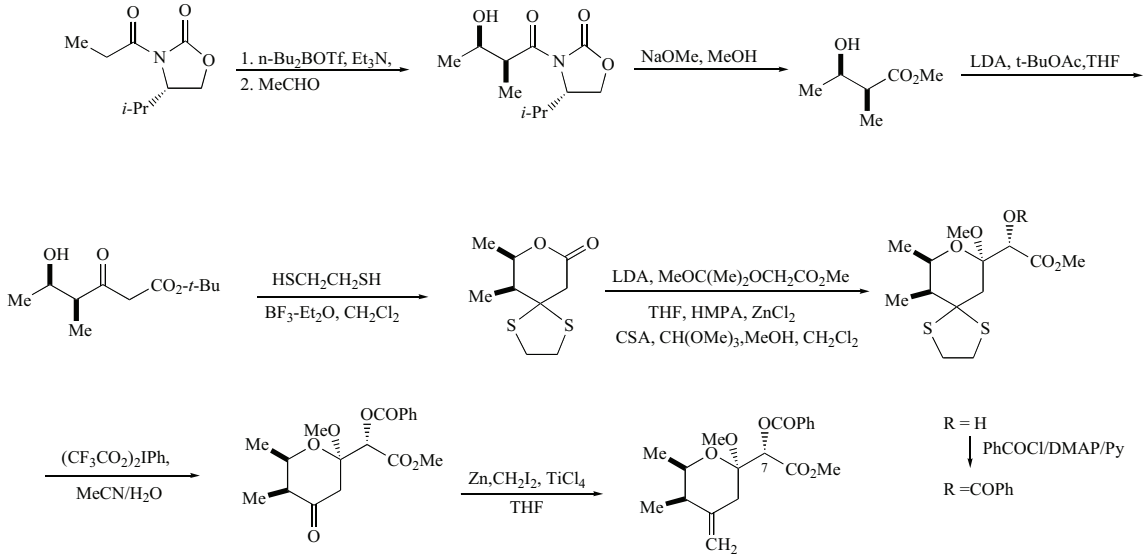
This highly efficient strategy utilizes the common Nakata's [19] precursor previously employed in similar types of approaches leading to the construction of the basic skeleton of the system. The coupling methodology however still employs the original technique leading to the isomeric mixture of target products, which are difficult to separate (Scheme **5**).

TOYOTA'S/IHARA'S APPROACH TO MYCALAMIDES

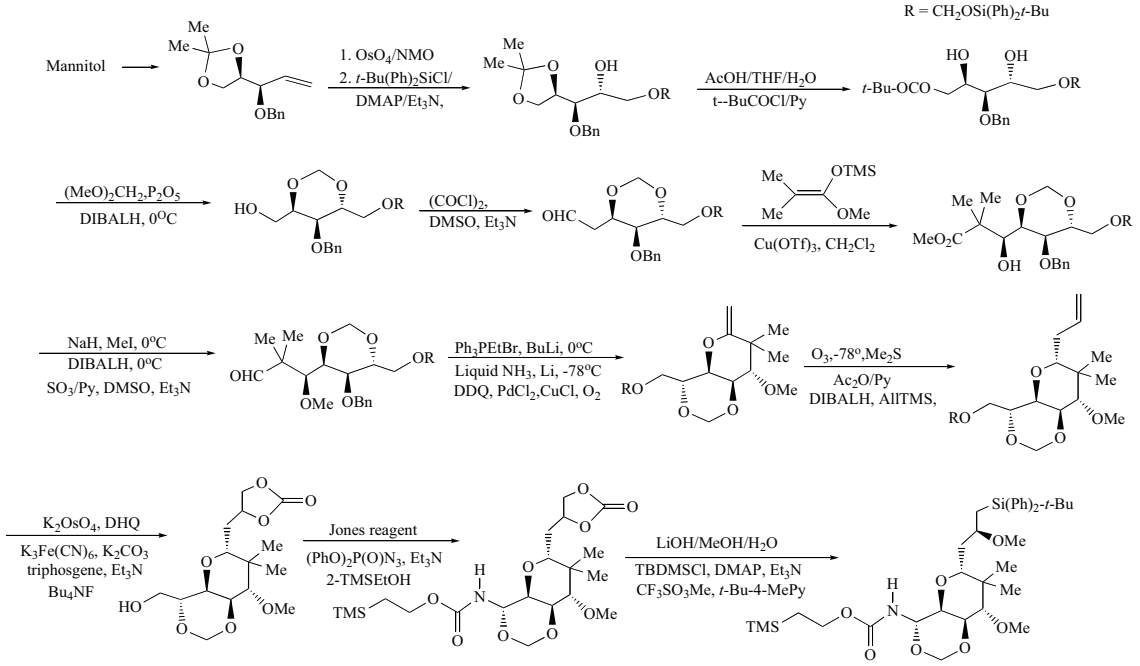
Toyota's stereoselective approach to the stereoselective synthesis of the right-half segment of the mycalamides employs Lewis acid catalyzed intermolecular aldol reaction and oxypalladation as the key steps and begins with D-mannitol as convenient chiral precursor [20-23]. This multistep strategy conveniently produce properly protected right-half segment of the mycalamide skeleton suitable for further functionalization and coupling with left-hand segment as depicted in (Scheme **6**).

KAGAWA AND TOYOTA'S SYNTHESIS OF (+) - MYCALAMIDE A

Kagawa's approach involves the synthesis of α, β-unsaturated ester from D-mannitol as described earlier [20]. Upon synthesis of intermediate directly from the ester, the left and right segments are coupled by transmethalation of the intermediate. The regioselective nucleophilic addition of the resulting vinyl anion to the ester group of template conveniently produces the final precursor in 50% yield.



Scheme (5). Nakata's Synthesis of (+) -Methyl 7-benzoylpederate.



Scheme (6). Toyota's/Ihara's synthesis of right-half segment of mycalamides.

Functional group manipulations of the above precursor as shown in (Scheme **7**) provide (+)-mycalamide A [24].

TROST'S/PROBST'S FORMAL SYNTHESIS OF (-) - MYCALAMIDE A

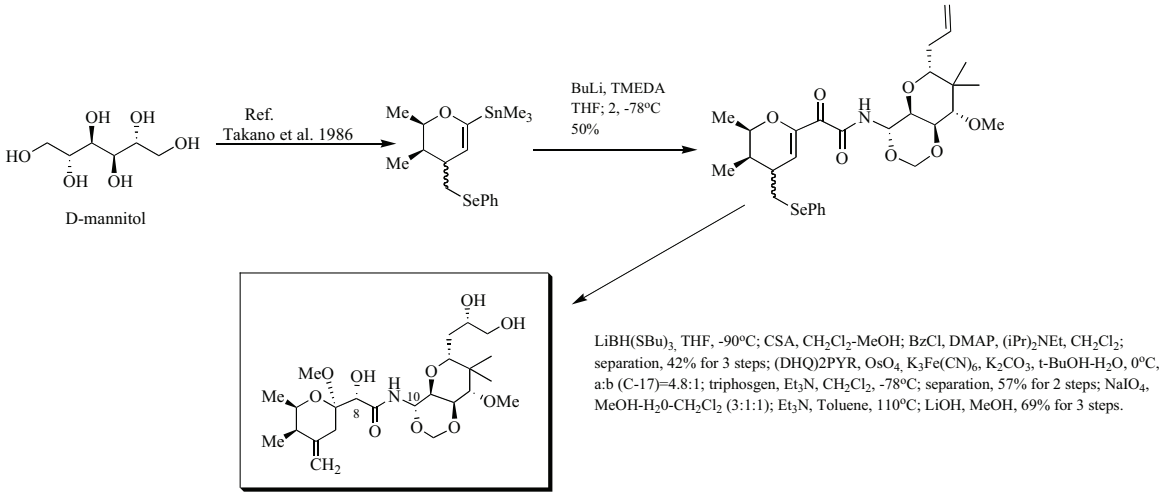
Trost's approach specifically addressed the important issue of synthesis of (-)-7-benzoylpederic acid (half-left fragment) from (2*S*,3*S*)-2, 3-epoxybutane and the synthesis of right-half segment from (*R*)-pantolactone [25] (Scheme **8**).

The right-half segment of terminal azide suitable for the coupling with left-right segment was synthesized *via* multiple steps sequence as depicted in (Scheme **9**).

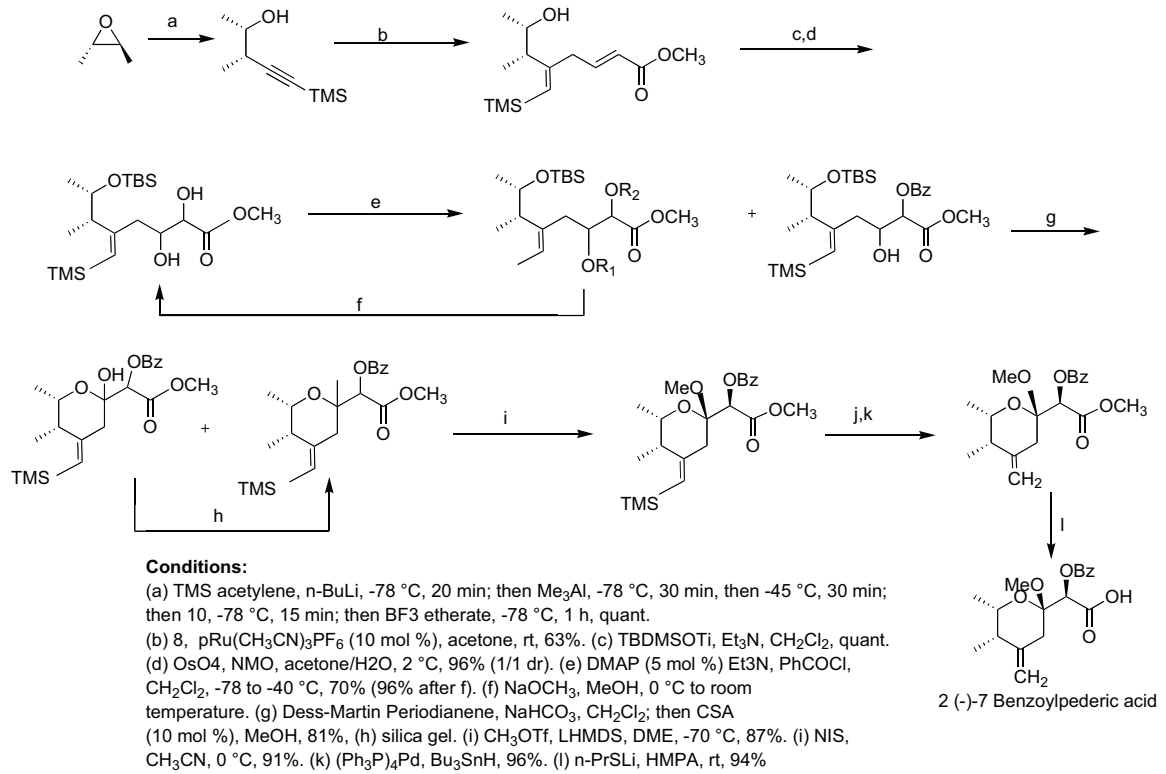
RAWAL'S SYNTHETIC APPROACH

In their total synthesis of mycalamide A, Rawal and coworkers [26] used the convergent coupling of pederic acid piece (structure A, as shown in the Scheme **10**) with mycalamide unit (structure B).

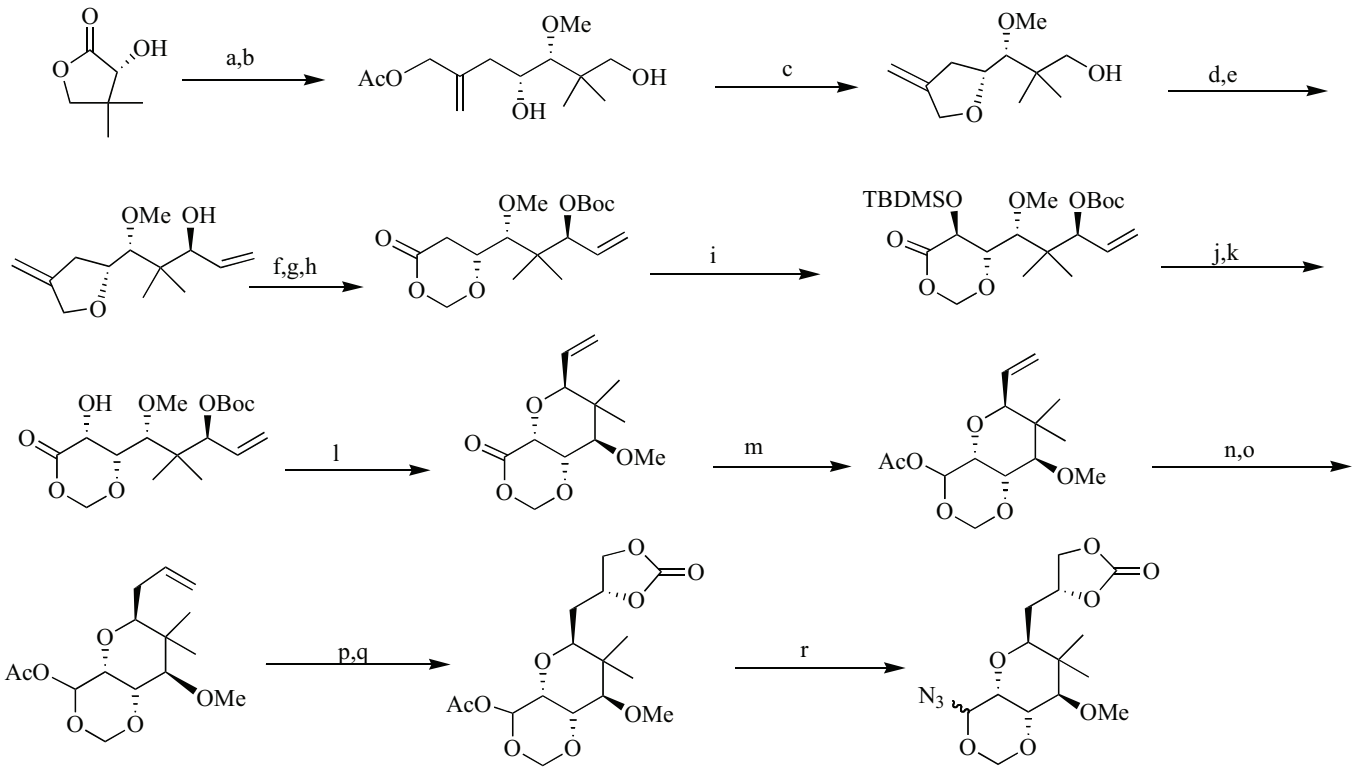
The synthesis of the left half, (+)-7-benzoylpederic acid as shown in (Scheme **11**) was a one-step Pd (II)-catalyzed tandem Wacker/Heck cyclization reaction to prepare the tetrahydropyran ring system. The right-half segment unit (structure B) was synthesized from diethyl D-tartarate in 21 steps.



Scheme (7). Kagawa & Toyota Approach to mycalamide A.



Scheme (8). Trost's formal Synthesis of Mycalamide A.

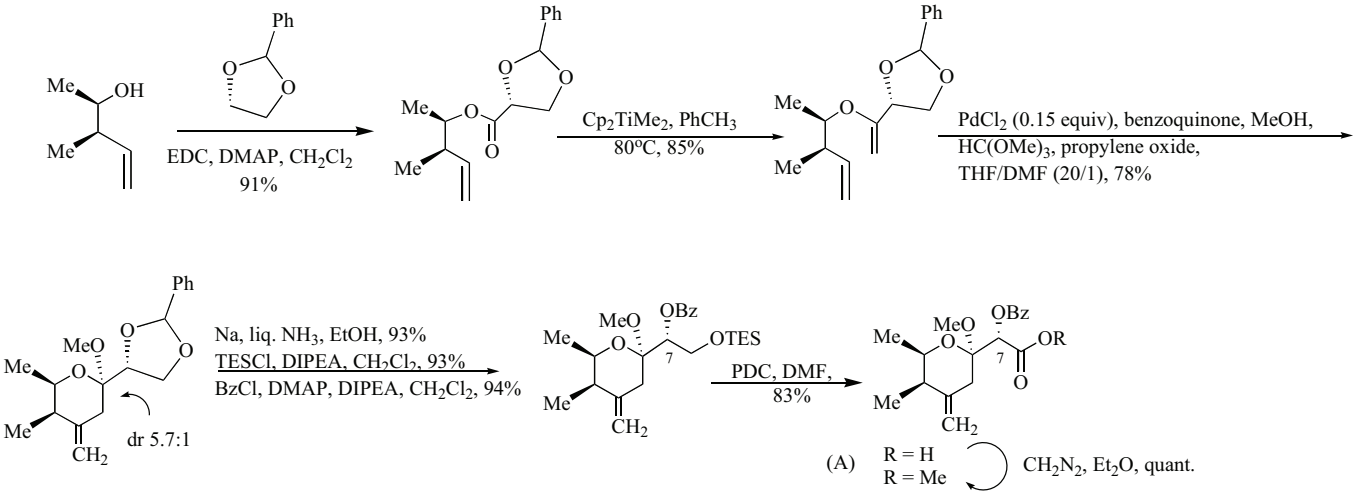


Conditions:

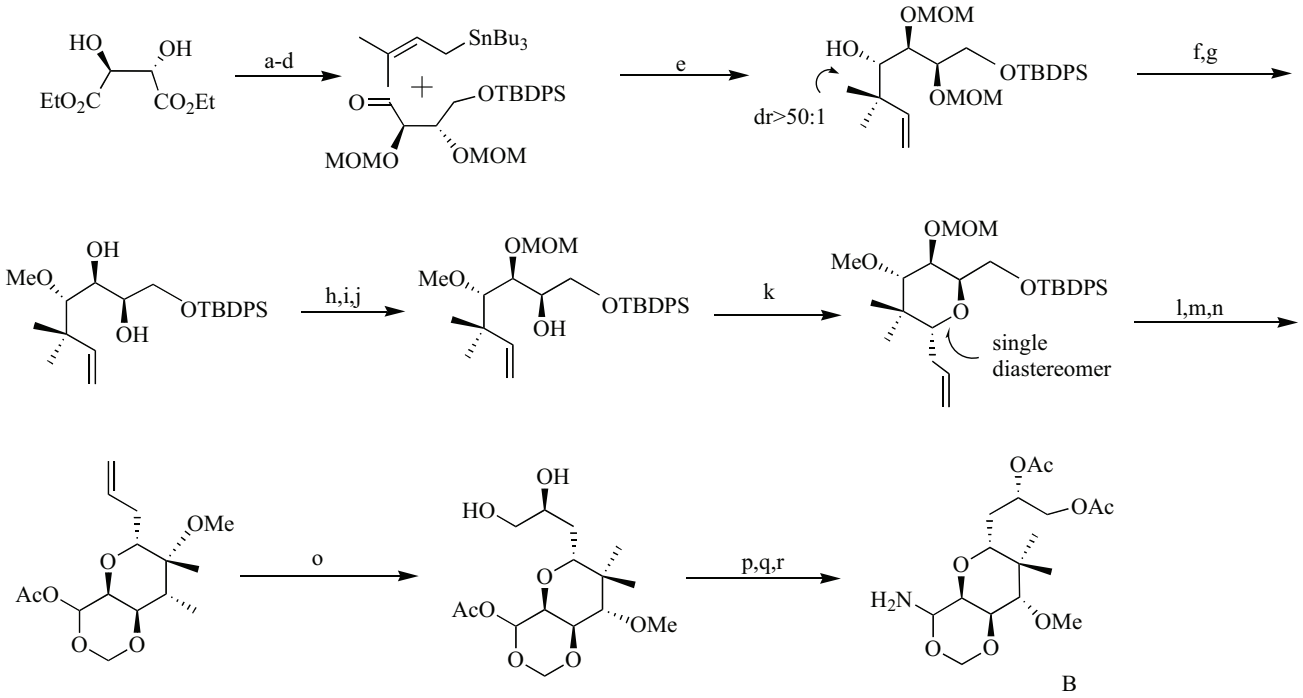
(a) Ag_2O, MeI, CH_3CN, 58 °C, 86%, 98% ee, (b) (i) DIBAL-H, CH_2Cl_2, -78 °C; then 2-(chloromethyl)allyl acetate, In powder, sat. aq NH_4Cl, 62% (5/1 dr). (c) $PdCl_2$(dppf), BEt_3, Et_3N, THF, reflux, 99%. (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °D, 90% (96% BRSM) (e) vinyl magnesium bromide, $MgBr_2$ diethyl ether complex, CH_2Cl_2, -78 °C to rt, 96%. (f) n-BuLi, $(Boc)_2O$, THF, 87% (95% BRSM). (g) $(DHQD)_2$-PHAL, $K_3Fe(CN)_3$, K_2CO_3, $MeSO_2NH_2$, t-BuOH/H_2O; then NalO4, THF/H_2O, 91%. (h) m-CPBA, 30% Li_2CO_3, CH_2Cl_2, rt, 98%. (i) TBDMSOTf,TEA, CH_2Cl_2, -78 °C, 30 min; then DMDO, acetone, CH_2Cl_2, molecular sieves, -5 °C, 68%. (j) TBAT, benzoic acid, THF, 50 °C, 83%. (k) Tf_2O,pyridine, 0 °C; then $NaNO_2$, DMF, rt, 75%. (I)$Pd_2(dba)_3$ CHCl3, dppf, DCE,70 °C, 58%. (m) DIBAL-H, -78 °C; then pyridine, DMAP, Ac_2O, -78°C to rt, 100% (1.6/1 dr). (n) 9-BBN, Wilkinson's catalyst; then PCC, DCM,45 °C. (o) Ph_3PdCH_2, toluene, -40 to -20 °C, 47% over two steps. (p)(DHQD)2PYR, OsO_4, K_2CO_3, $K_3Fe(CN)_6$, t-BuOH/H_2O, for R-AcO 74%,4.3/1 dr; for â-AcO quant., 9/1 dr. (q) Triphosgen, pyridine, DCM, -78°C, R-AcO 73%, â-AcO 84%.

(r) TMSOTf, $TMSN_3$, CH_3CN, 0 °C, 68% (1.6/1 dr).

Scheme (9). Trost's Synthesis of right-half segement.



Scheme (10). Rawal's Synthesis of left-half segment (+)-methyl-7-benzoylpederate.



Conditions:

(a) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2 (quant). (b) LAH, Et_2O (86%). (c) n-BuLi, TBDPSCl, THF (quant).
(d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (90%). (e) $Me_2CCHCH_2SnBu_3$, $ZnBr_2$, CH_2Cl_2 (90%). (f) NaH, MeI, THF, 98%.
(g) $ZnBr_2$ (2.5 equiv), n-BuSH (3.0 equiv), room temp (rt), 8 min, CH_2Cl_2, 98%. (h) BzCl, DIPEA, CH_2Cl_2, rt, 11 h, 80%.
(i)$CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, rt, 3 h, 91%. (j) K_2CO_3, MeOH, rt, 3 h, 83%.
(k) O_3, Me_2S, CH_2Cl_2; Ac_2O, DMAP, pyr; BF_3OEt_2, CH_2CHCH_2TMS, CH_2Cl_2, 66%. (l) TBAF, THF, 91%.
(m) $(COCl)_2$, DMSO, NEt_3, CH_2Cl2, (n) CHO)n, concd HCL, THF; Ac_2O,DMAP, pyr, 63%, dr 5.4:1.
(o) OsO_4, $(DHQ)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, t-BuOH/H_2O, -3ºC (alpha-AcO 83%, dr 5.0:1; Beta-OAc 85%, dr 5.9:1).
(p) Ac_2O, DIPEA, DMAP, CH_2Cl_2, 92%. (q) $TMSN_3$, TMSOTf, CH_3CN, -78 to 0ºC (quant.) (r) H_2, Pd/C, EtOAc, 90%

Scheme (11). Rawal's Synthesis of right-half segment.

The coupling of half-left fragment with half-right fragment was accomplished *via* DCC/DMAP catalyzed reaction in 56% yield of mycalamide A. Alternative coupling reaction catalyzed by benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate/ diisopropylethylamine (PyAOP/DIPEA) resulted with 61% yield of *C* (10)-*epi*-mycalamide A (Scheme **12**).

FLOREANCIG'S SYNTHESIS OF THE RIGHT HALF OF PEDERIN

Kocienski's approach [27-28] to the right segment template was originally described in 1987. It is still one of the best synthetic strategies for the efficient synthesis of the important precursor of the whole family of mycalamides. The brand new concept published recently by Floreancig and co-workers [29-30] explore the Paterson's pinene-derived boron enolate aldol strategy. This particular approach proceeds with high degree of stereocontrol of aldol reaction, which is critical step for achieving the correct stereochemistry at C-15. The synthetic sequence is illustrated in (Scheme **13**).

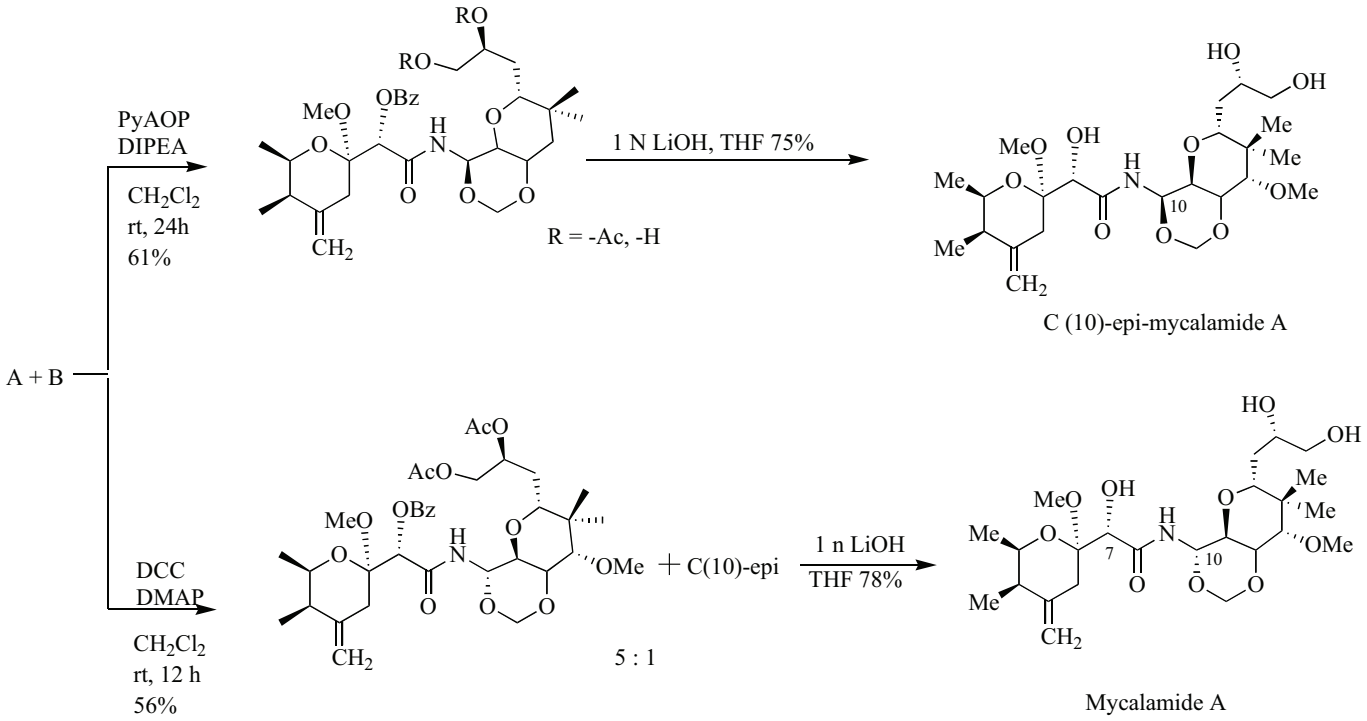
RAWAL'S TOTAL SYNTHESIS OF PEDERIN

The total synthesis of pederin was first reported by Tsuzuki and co-workers [31]. Many literature reports [32-41] describe total synthesis of pederin.

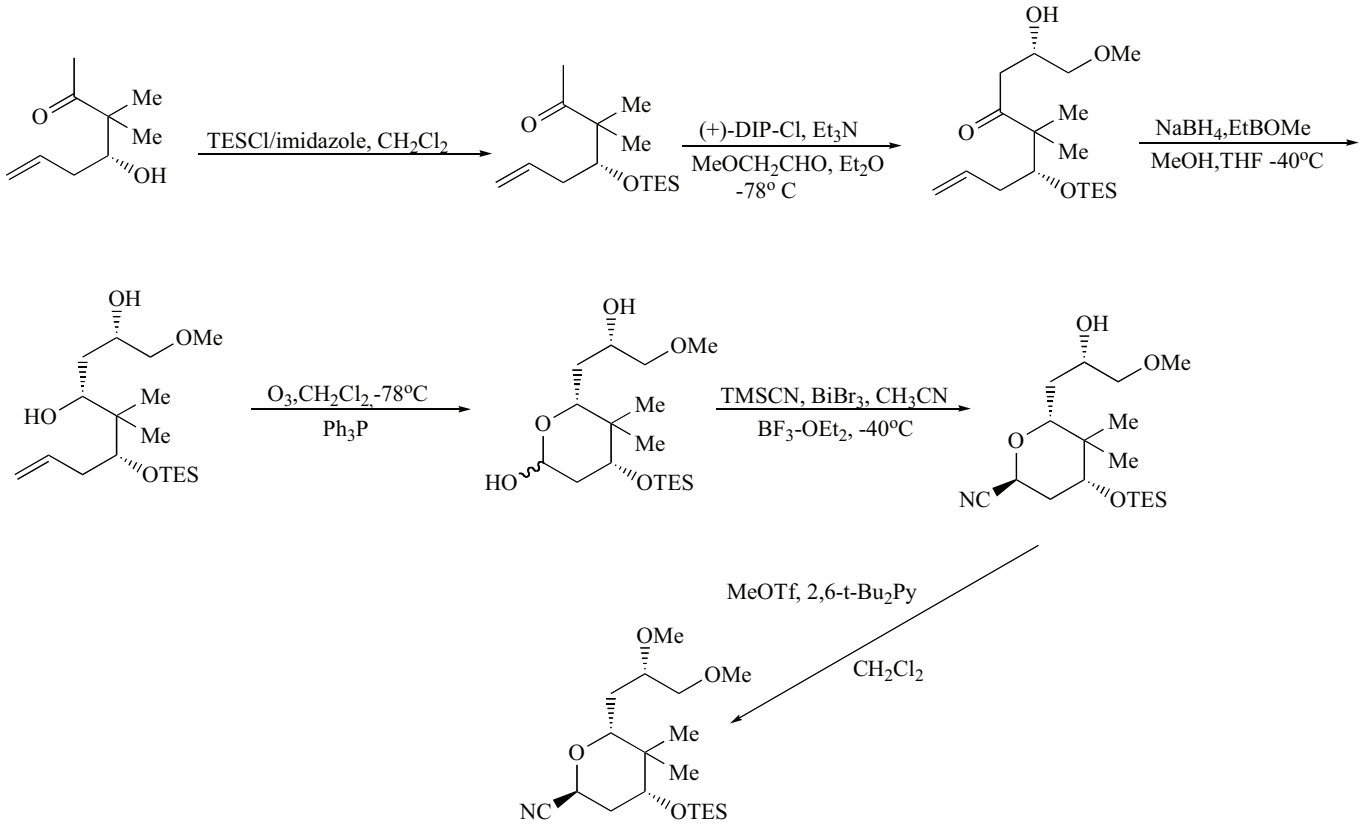
Rawal's total synthesis of pederin [32] by direct coupling of both precursors of ring A (left-half segment) and ring B (right-half segment) using pederic acid chloride (A) with lithium anion of carbamate (B) in toluene/pyridine solution was highly effective. The final complete deprotection steps of the above strategy required to use *tert*-butyl ammonium fluoride (TBAF) in tetrahydrofuran solution followed by a hydrolytic quench with lithium hydroxide in methanol and resulted in the formation of target pederin in 88% yield. Several other strategies of the syntheses of pederic acid esters as specific templates for coupling approaches have also been reported [42-46] (Scheme **14**).

DE BRABANDER'S SYNTHESIS OF PSYMBERIN ANALOGUES

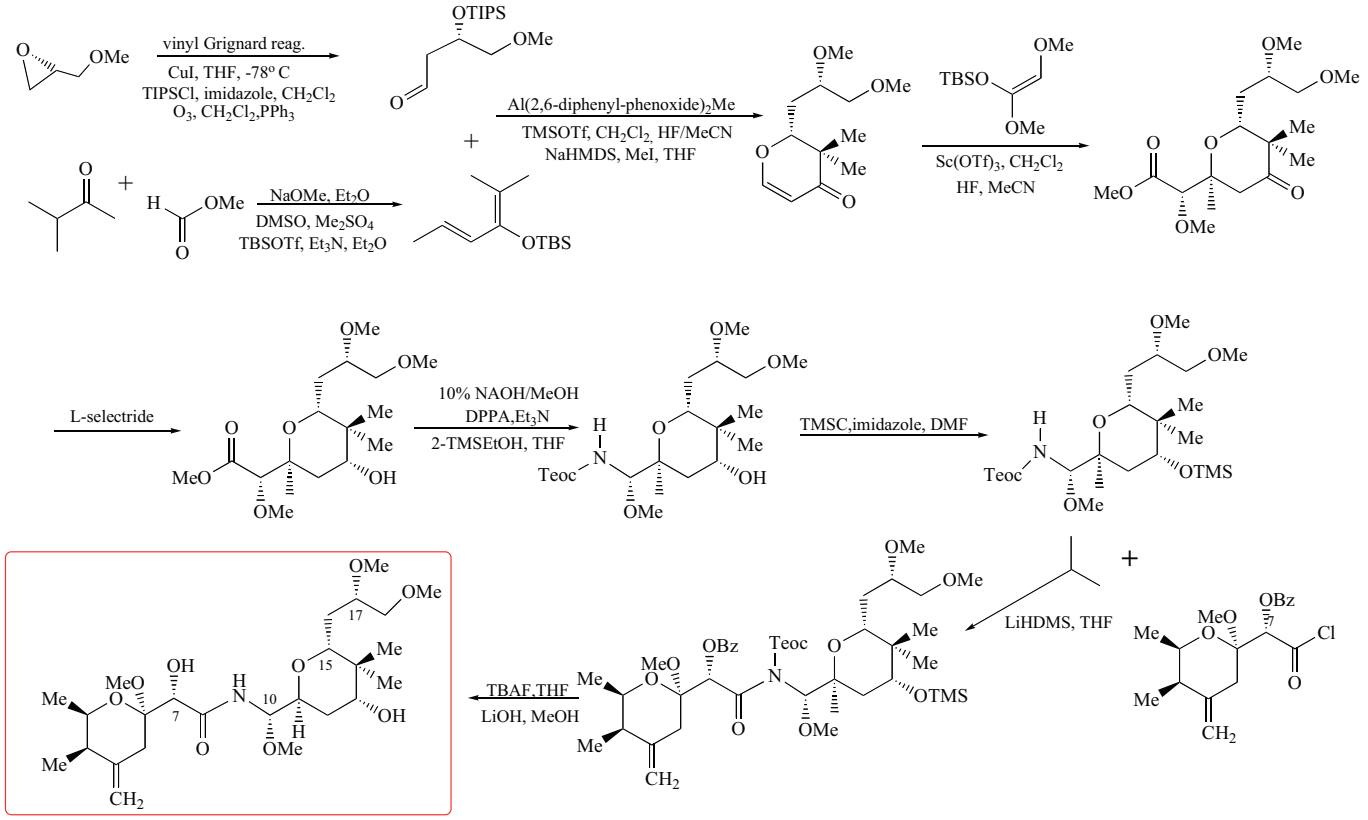
Psymberin was first isolated by Crews and co-workers [48]. Coincidently, psymberin was later determined to be identical with irciniastatin A, independently isolated by Pettit and co-workers. [49] The synthesis of *syn* and *anti* diastereomers of amide side chain was reported in 2005 by Williams [50] and confirmed by X-ray crystallographic analysis that the natural product has *anti* configuration and not the corresponding *syn* configuration of the isomer as established earlier. Crews and coworkers [51] 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



Scheme (12). Rawal's coupling approach to mycalamide A.



Scheme (13). Floreancig's Synthesis of right-half segment of pederin.



Scheme (14). Rawal's synthesis of pederin.

enhancements. Psymberin was further evaluated *in vitro* against an extended panel of over 60 human cancer cell lines [51].

The latest synthesis of Psymberin epimers was reported by De Brabander and co workers [52-53]. The sequence for the synthesis of psymberin-pederin hybrid (the final structure in the scheme) is depicted in (Scheme **15**) and started with C_2-symmetrical diol which was conveniently acetylated *via* acid-catalyzed into cyclic orthoformate. Hydrolysis of monoacetate, following reduction with triphenylphosphine produced lactol in 95 % yields. Lactol intermediate was functionalized through multiple steps to amide which on the final step was converted into psymberin-pederin hybrid.

Many new synthetic approaches to psymberin and new functionalized analogs were reported recently [54-60].

BIOLOGICAL ACTIVITY

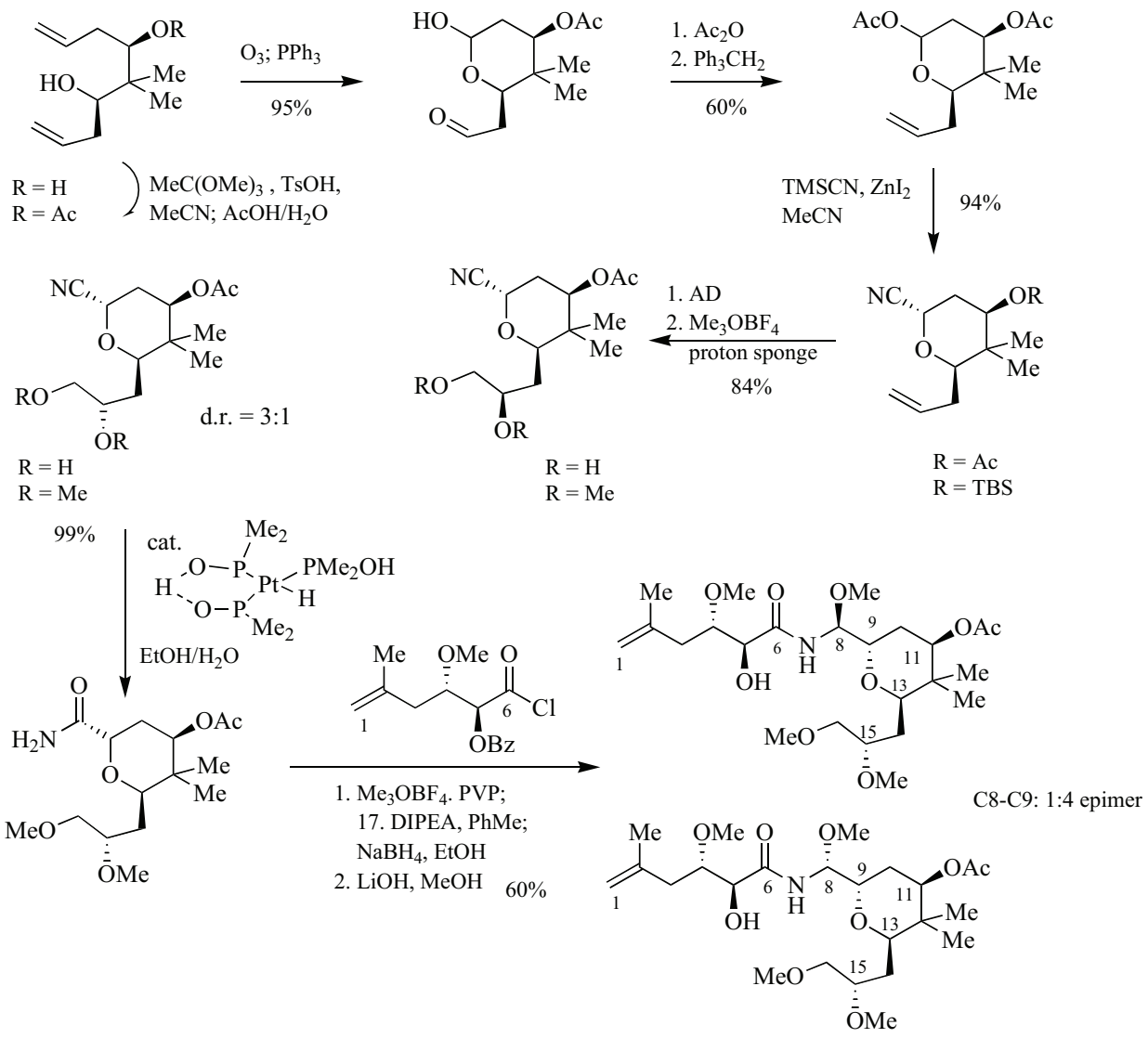
The supply of the mycalamides from marine sources is extremely limited, and thus, synthetic approaches to compounds of this class are required for continuing biological evaluations, and for potential future therapeutic applications.

All the mycalamides show promising *in vivo* antiviral activity. [1] These structurally challenging natural products also show interesting *anti-tumor* properties, [61] and potent inhibitors of both protein and DNA biosynthesis at nanomolar concentrations. Recently, they have also been shown to be powerful immunosuppressive agents with comparable *in vitro* efficacy to the clinical agent, cyclosporin A, and to the promising new drugs - and exciting biochemical tools – such as rapamycin. This ranks the mycalamides amongst the most potent immunosuppressive agents yet discovered. [62-66]

Moreover, the Mycalamides possess an alternate mechanism of action to these agents. This is of interest potentially for studying the immunobiology of T cells, providing novel agents that can regulate T-cell activation. The powerful immunosuppressive activity of these agents and their novel mechanism of action makes them extremely exciting, both as potential biochemical tools (FK506 and rapamycin, for example, have already been used to provide some major discoveries in cell biology) and as potential therapeutic agents for post-transplant surgery therapy and for treatment of a variety of autoimmune conditions.

Mycalamide-A and -B and onnamide, were isolated from Mycale sp. and Theonella sp. sponges collected in New Zealand waters. Each exhibited potent *in vitro* toxicity and *in vivo* efficacy against murine and human tumor cells. Concentrations of each that inhibited replication of cultured murine lymphoma P388 cells by 50% were 5 nM or less.

Mycalamide-A and -B were also potent inhibitors of HL-60, HT-29, and A549 human tumor cell replication (50% inhibitory concentration less than 5 nM), while values for onnamide were greater (50% inhibitory concentrations between 25 and 200 nM).



Scheme (15). De Brabander's synthesis of psymberin.

Mycalamide-A (10 micrograms/kg) and -B (2.5 micrograms/kg) were moderately active against P388 leukemia (increase in life span, approximately 50%), while onnamide was inactive (40 micrograms/kg; increase in life span, 15%). Mycalamide-A also exhibits high activity to transform *ras*-mutated NRK cells to normal morphology at the range of 10ng/ml concentration through selective inhibition of P21 [51].

Mycalamide-A was 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. Mycalamide A has also been shown to block $CD4^+$ T-cell activation [62], inhibit eukaryotic protein synthesis by binding to the E site usually occupied by tRNA [63] and also induce apoptosis more potently in 32 D myeloid cells that have Ras or Bcr/abl alterations [66].

Mechanism of action studies clearly indicates that the three agents inhibited protein synthesis. For example, after 1-h exposures to 20 nM mycalamide-A and -B, the rates of [3H] leucine incorporation into acid- precipitable material of cultured P388 cells were inhibited 54 and 99%, while the effects on incorporation of [3H] uridine and [3H] thymidine were less. The relative effects of 20 to 2000 nM mycalamide-A on protein, RNA, and DNA synthesis were consistent with those observed during exposure of P388 cells to 1 microM emetine, a known inhibitor of protein synthesis. Also, the three agents inhibited translation of RNA into protein in a cell-free lysate of rabbit reticulocytes. Interestingly, as mycalamide-A disrupted DNA metabolism, the agent apparently did not intercalate into DNA, and a mixture of four deoxynucleosides (250 microM each) did not decrease the antiproliferative effects of the agent. Collectively, these data clearly indicate that this class of compounds represents novel antitumor agents, which should be further evaluated to define their high potential.

Some cytotoxicity data of mycalamides with comparison to psymberin and its new analogs are compiled in Table **1**.

Psymberin – exhibits very potent antiproliferative activity against 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 [51]. The data pertinent to differential sensitivities of various cell lines to psymberin is summarized in Table **2**.

Crews and co-workers [51] also reported that Psymberin exhibits phenomenal activity against a human colon cancer cell line HCT-116 with IC_{50} at range 2.5 x 10^{-9} M. It is interesting to note that according to the authors [51] the ring A is not essential for activity, but in contrast *N*-acylaminal functionality is absolutely crucial for cytotoxicity.

Table 1. Cytotoxicity of Psymberin, Mycalamide A and Analogues against various Human Tumor Cell Lines

	IC $_{50}$ (nM)		
Compound	**KM 12 (Colon tumor)**	**PC3 (Prostate tumor)**	**T98G (Glioblastoma)**
Psymberin	0.45 ± 0.01	0.98 ± 0.12	1.37 ± 0.06
Mycalamide A	0.95 ± 0.02	2.5 ± 0.2	2.87 ± 0.07
8-*epi*-psymberin	37.1 ± 5.5	200.2 ± 27.6	85.8 ± 48.4
4-*epi*-psymberin	126.08 ± 8.6	346.5 ± 102.8	186.7 ± 51.3
Psympederin	710.9 ± 35.8	821.8 ± 89.1	> 1000
c-8-*epi*-psympederin	> 1000	255.5 ± 11.4	> 1000

Table 2. Differential Sensitivities (LC_{50}) of Various Cell Lines to Psymberin 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 x 10^{-5}	LOX IMVI	>2.5 x 10^{-5}
HL-60 (TB)	>2.5 x 10^{-5}	MALME-3M	<2.5 x 10^{-9}
K-562	>2.5 x 10^{-5}	SK-MEL-2	>2.5 x 10^{-5}
MOLT-4	>2.5 x 10^{-5}	SK-MEL-28	<2.5 x 10^{-9}
RPMI-8226	>2.5 x 10^{-5}	SK-MEL-28	1.41 x 10^{-5}
SR	>2.5 x 10^{-5}	UACC-257	>2.5 x 10^{-5}
		UACC-62	<2.5 x 10^{-9}
Breast Cancer		**Colon Cancer**	
MCF7	>2.5 x 10^{-5}	HCC-2998	3.76 x 10^{-7}
HS578T	>2.5 x 10^{-5}	HCT-116	<2.5 x 10^{-9}
MDA-MB-435	<2.5 x 10^{-9}	HT29	>2.5 x 10^{-5}
NCI/ADR-RES	1.9 x 10^{-5}	SW-620	<2.5 x 10^{-5}
T-47D	1.36 x 10^{-5}		

CONCLUSIONS AND FUTURE PROSPECTS

This literature review reports on all synthetic approaches to mycalamides and similar classes of highly functionalized natural carbohydrates such as pederin and psymberin. Recent developments in synthetic approaches to mycalamides have already provided tremendous advantages and provide potential for future development of this fascinating class of biologically active compounds. In the search for an understanding of molecular recognition, particularly in combining interdisciplinary chemistry/biology studies, it is critical to clearly identify similar molecular targets with similar or identical pharmacological responses. This class of natural products is by no means an exception to this particular requirement and clearly supports

the design of new analogs with powerful immunosuppresive activity.

These multiple functionalized natural templates are highly valuable synthons for further chemical transformations, into various classes of other amino derivatives and in particular for the synthesis of valuable carbohydrate mimetics, such as disaccharides, thio-disaccharides, amino antibiotics, and glycoconjugates.

Glycopeptides, on the other hand, combine the distinct structural features of both peptide core and functionalized carbohydrates and expand the repertoire of active epitopes beyond those based on carbohydrate or peptide alone. Though chemically and structurally challenging, synthetic glycopeptides (directly from azides or amines) with an inherent structural definition and specificity have a lot to offer as new glyco- or carbohydrate mimetics as specifically designated prototypes of new therapeutics.

In the areas of carbohydrate peptides, great strides have been made within the past few years. Whether it is in synthetic, analytic, or biological activity, the very simple chemistry of these molecules continues to open doors to important new fields of carbohydrate research. Furthermore, we believe that these challenging new hot topics constitutes a high degree of topical interest and that for this crucially important molecules, the chemical future is likely to be even more exciting than the past.

Mycalamides, pederin and psymberin not only provide an exciting synthetic target containing a high density of functionality, but also multiple stereogenic centers that will spawn substantial interest for many years to come.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

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Received: December 01, 2011 Revised: December 21, 2011 Accepted: December 23, 2011