The Pederin Family: A Synthetic Overview

by

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Abstract: A comprehensive synthetic review of the pederin family of cytotoxins, including pederin, the mycalamides, and psymberin, is presented. A number of approaches to the synthesis of these molecules is covered, including pederic acid, the tetrahydropyranyl ring of pederin, the trioxadecalin ring of the mycalamides, and psymberin fragments. Coupling strategies for these compounds are also summarized. An overview of biological activity at various positions of mycalamide A, as well as some analogs, is given.

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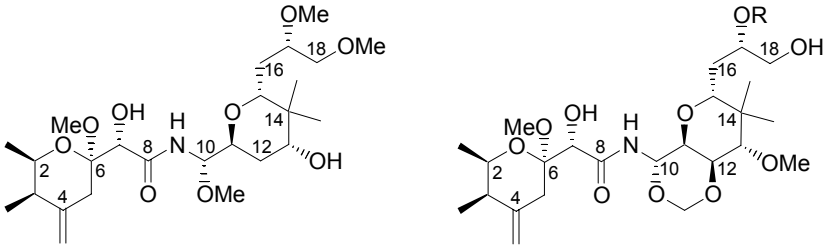
1. Introduction

Psymberin (**Ps**ammoncinia, s**ymb**iont, ped**erin**), a potent cytotoxin, was recently isolated from the *Psammoncinia* sponge off the coast of Papua New Guinea.[1] This compound showed a strong structural resemblance to several other cytotoxins that had been previously isolated, including pederin,[2] the mycalamides,[3] the onnamides A-F,[4] and theopederins A-L.[5] The general structures of pederin and mycalamides A and B are shown in Figure 1.

Figure 1 Pederin and Mycalamides A and B



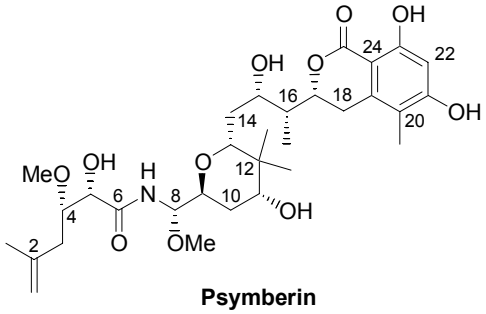
Pederin

Mycalamide A: R = H
Mycalamide B: R = Me

Note that these cytotoxic compounds contain the same left portion, known as pederic acid.

The structure of psymberin is shown in Figure 2.

Figure 2 Psymberin



Psymberin

The most notable common feature of the compounds in this family is the presence of the N-acyl aminal portion bridging the left and right fragments. The molecules above have been numbered

to highlight the similarity of the structures: C4 to C14 of pederin and mycalamide correspond to C2 to C16 of psymberin.

The scope of this paper will be limited to pederin, the mycalamides, and psymberin. All of these cytotoxins show both anticancer and immunosuppressant activity in nanomolar concentrations and have potential medical applications.[6]

2. Isolation

Pederin was first isolated in 1949 from *Paederus fuscipes*, a Japanese beetle known for its severely irritating bite.[2a] This compound was later characterized and identified as pederin.[2b]

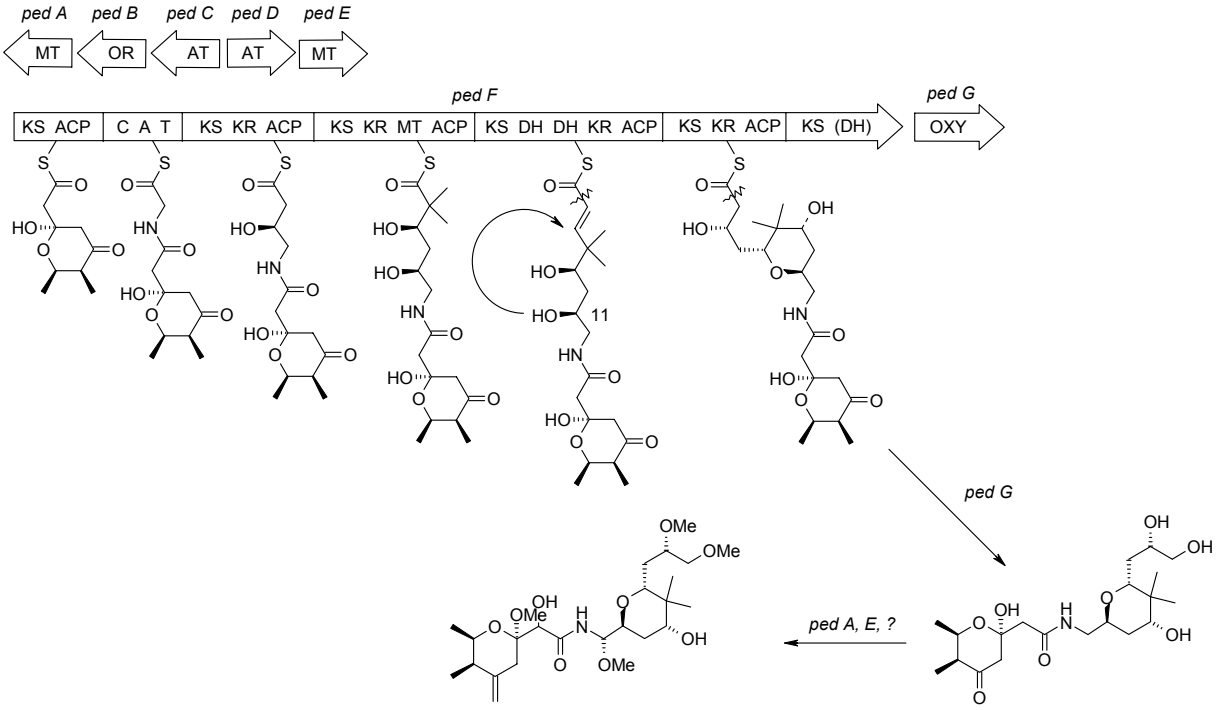
The mycalamides were isolated from the *Mycale* sponge off the coast of New Zealand in the Otago harbor in 1988.[3a] Using gel permeation and various chromatographic techniques, Munro and others successfully extracted the active metabolite and identified it as mycalamide A. Several years later, mycalamide B was also identified as part of another collection of this sponge.[3b] More recently, mycalamides C and D were isolated by the same group of researchers in 2000.[3c]

Psymberin was also isolated from a marine sponge, *Psammoncinia*, from the Papua New Guinea waters.[1,7] Although the extracts of this sponge were known to show anti-tumor activity, psymberin, the compound responsible for this activity, was not identified until 2001.

3. Biosynthesis

Early work by Cardani et. al. suggested that pederin is derived from polyketide biosynthesis.[8] Recent studies involving gene cloning of the symbiont bacterium established the structure of the series of genes that form pederin.[9] The proposed biosynthetic pathway is shown in Figure 3.

Figure 3 Pederin Biosynthetic Pathway



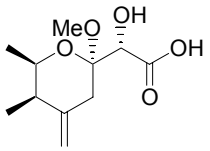
The ped F gene is a polyketide synthase (PKS) gene, as predicted in the earlier work by Cardani. The current theory is that these cytotoxins are produced by symbiotic bacteria in both the *Paederus* beetle and the various sponges.[9b]

Unfortunately, the bacteria responsible for pederin production have not yet been successfully cultured, and these compounds are isolated in very small quantities from each source. For this reason, a need for a viable synthesis is desirable. A summary of synthetic approaches are presented in detail in the paragraphs that follow.

4. Synthesis: Pederic Acid

The structure of pederic acid, a subunit common to pederin and mycalamides A and B, is shown in Figure 4.

Figure 4 Pederic Acid

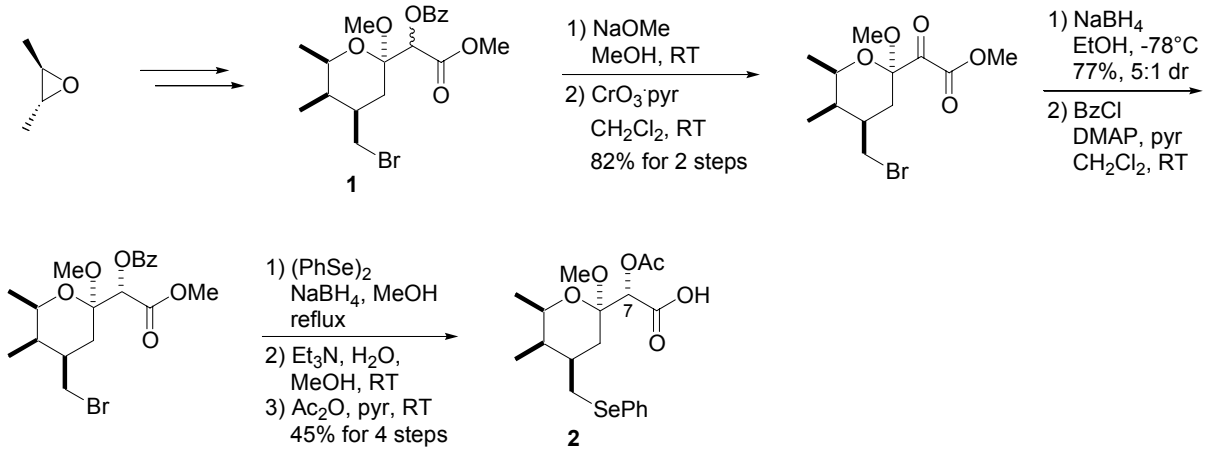


Many synthetic approaches to this molecule have been published by various research groups.

To organize the large number of syntheses of pederic acid and its derivatives, the schemes have been arranged based on the nature of the starting materials. The work with chiral starting materials is presented first, leading up to the most efficient synthesis. Then the schemes involving chiral reagents are presented.

Matsumoto's group used trans-butene oxide in their synthesis of pederin (Figure 5).[10] The synthesis of the bromomethyl benzoate **1** was originally published in 1978 in a Ph.D. thesis. The completion of the synthesis proceeded through a series of standard transformations to form the phenylselenide product **2**.

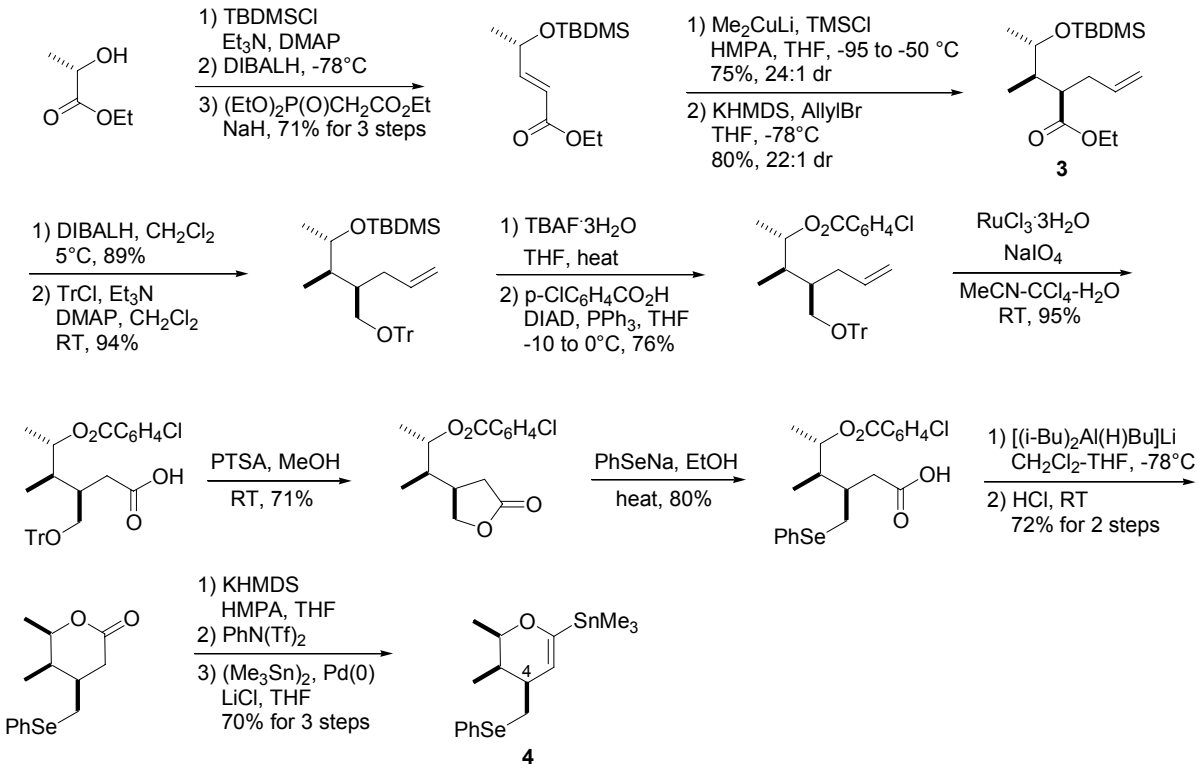
Figure 5 Matsumoto's Pederic Acid Precursor Synthesis



The stereoselectivity of the synthesis was good, yielding the 7-(S) alcohol in a 5:1 diastereomeric ratio, but the scheme was very lengthy.

Extensive work has also been done by Kocienski to construct pederin.[11] The group's most recent synthesis of the pederic acid precursor **4** is shown below (Figure 6).[12]

Figure 6 Kocienski's Pederic Acid Analog Synthesis



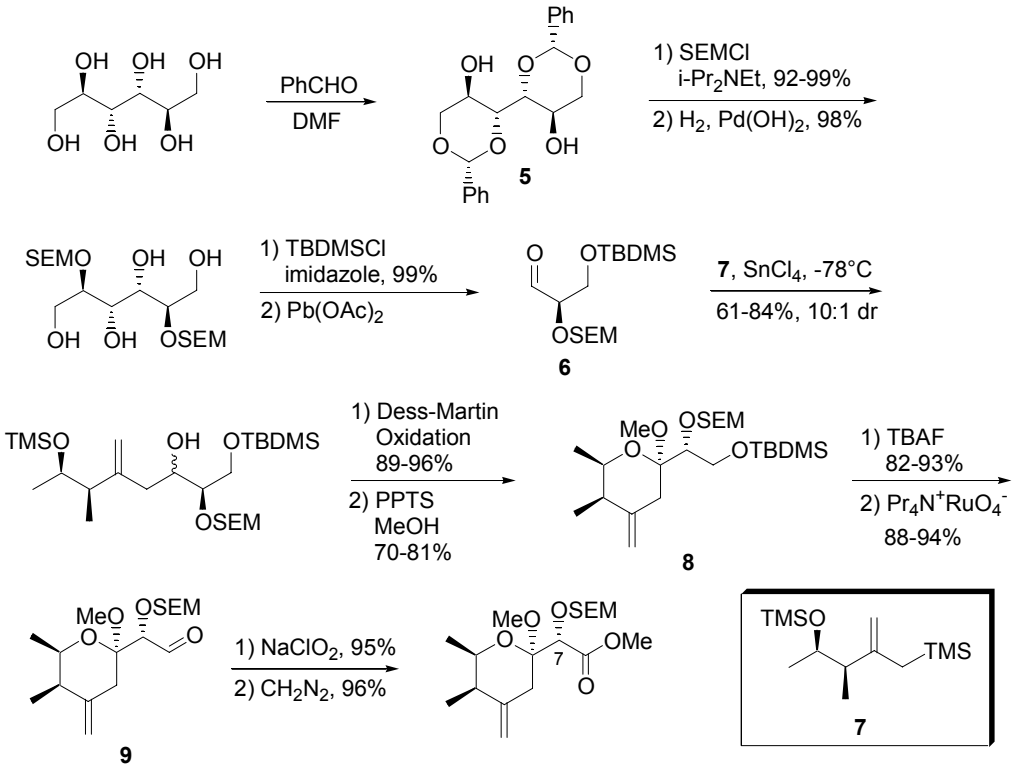
The final product was later lithiated for addition to the trioxadecalin ring, an approach pioneered by this group.[13] Formation of the double bond from the phenylselenylmethyl substituent at the 4-position (pederin numbering) was completed after coupling with the right half, as described later.

An advantage of this work was the very high diastereoselectivity of the cuprate 1,4-addition and allylation reactions that formed **3**. However, the synthesis was still rather long, requiring seventeen steps.

Recently, Hoffmann and others made a protected pederic acid from D-mannitol (Figure 7).[14] The first product, 1,3:4,6-di-*o*-benzylidene-D-mannitol **5**, was first synthesized by Baggett and Stribblehill a few years prior to this publication.[15] Notable features included an acid-catalyzed cyclization to form the tetrahydropyranyl ring of **8** and a Ley oxidation of the C8 primary alcohol to the aldehyde **9**. Although the tin chloride-mediated reaction of **6** provided the

R isomer in a 10:1 diastereomeric ratio, this stereocenter was eliminated by the oxidation in the next step.

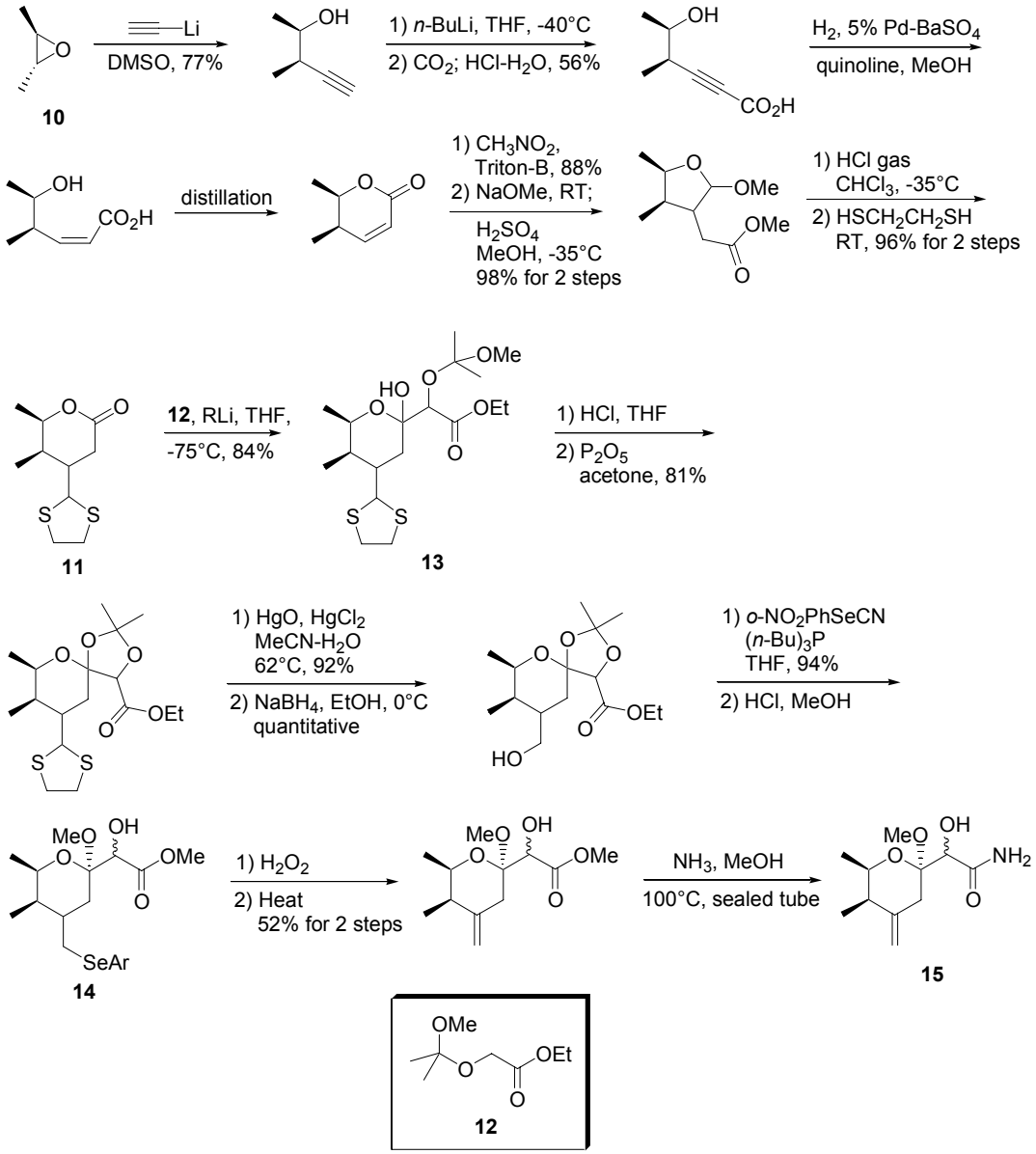
Figure 7 Hoffmann's Pederic Acid Analog Synthesis



D-mannitol provided the proper stereochemistry at C7, avoiding the hassles encountered by several other approaches. The synthesis involved twelve steps, which was significantly shorter than Kocienski's scheme.

Meinwald also used trans-butene oxide **10** to make a racemic mixture of pederamide **15**, the amide equivalent of pederic acid. The thioacetal-protected lactone **11** in Figure 8 was made using a series of cyclization reactions.[16]

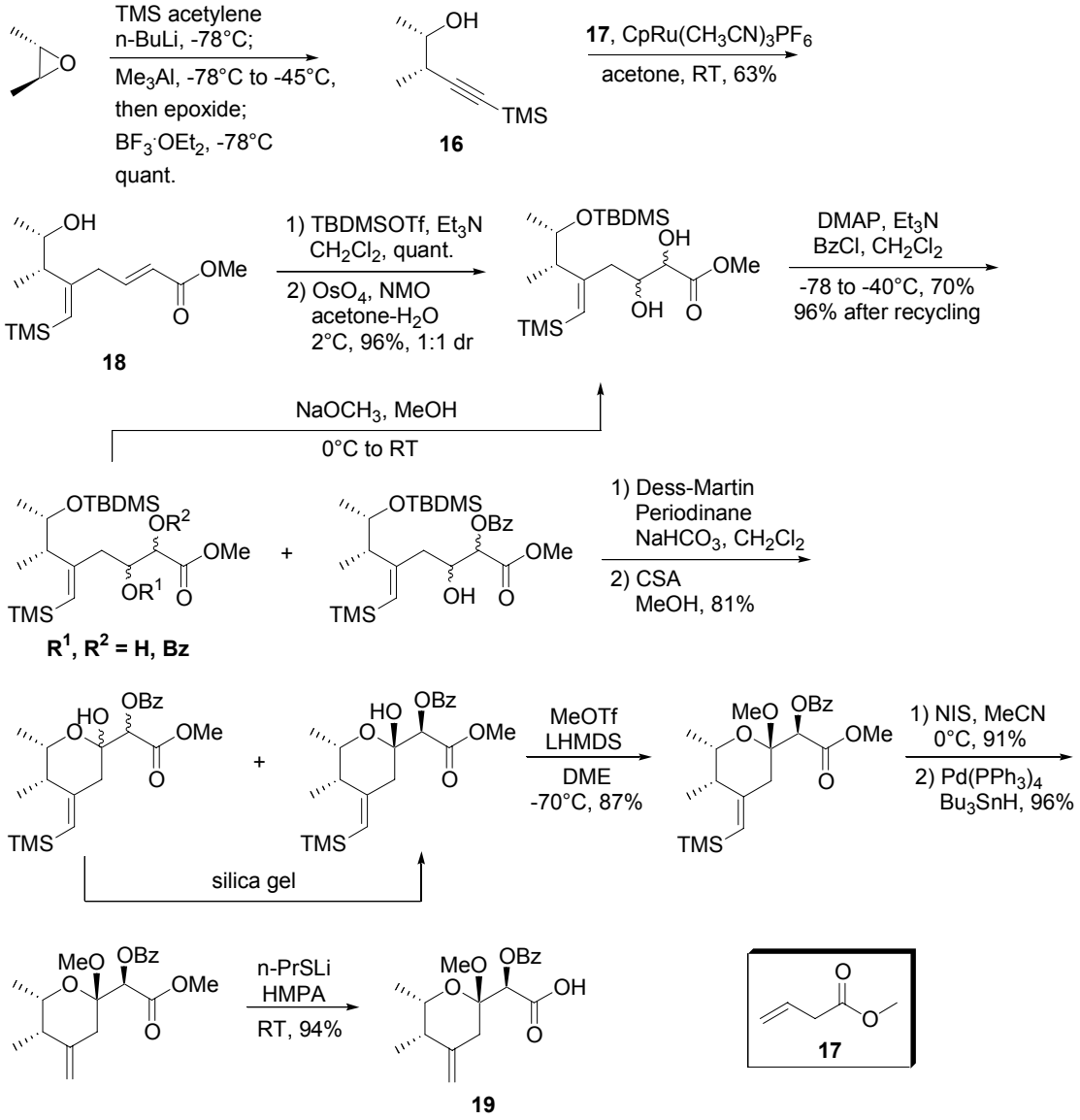
Figure 8 Meinwald's Pederamide Synthesis



The chain was then attached via addition to the lactone carbonyl to form **13**. Oxidation of the arylselenide **14** to create the exocyclic double bond formed methyl pederate, which was easily converted into pederamide. This synthesis was rather extensive with sixteen steps, and the stereoselectivity was poor.

The same starting material was used by Trost's group to construct an enantiomer of pederic acid **19** as part of a formal synthesis of (-)-mycalamide A,[17] as shown in Figure 9.

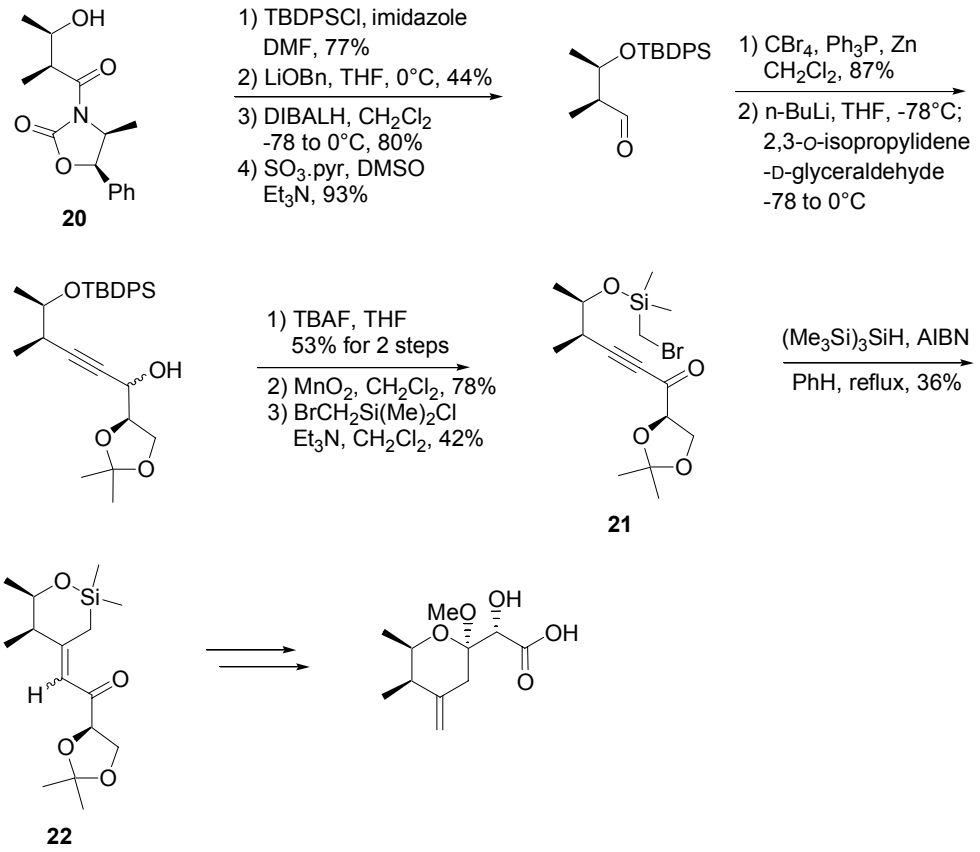
Figure 9 Trost's Pederic Acid Synthesis



A key feature of this synthesis was the ruthenium catalyzed coupling of alkyne **16** and alkene **17**, which allowed attachment of the chain at an early stage. The synthesis was done in eleven steps, but there was no selectivity for the dihydroxylation of **18**.

In their first published paper on this topic, Toyota et. al. used a silylmethyl radical cyclization of **21** to form a heterocyclic ring starting from a chiral Evans aldol derivative **20** as shown in Figure 10.[18]

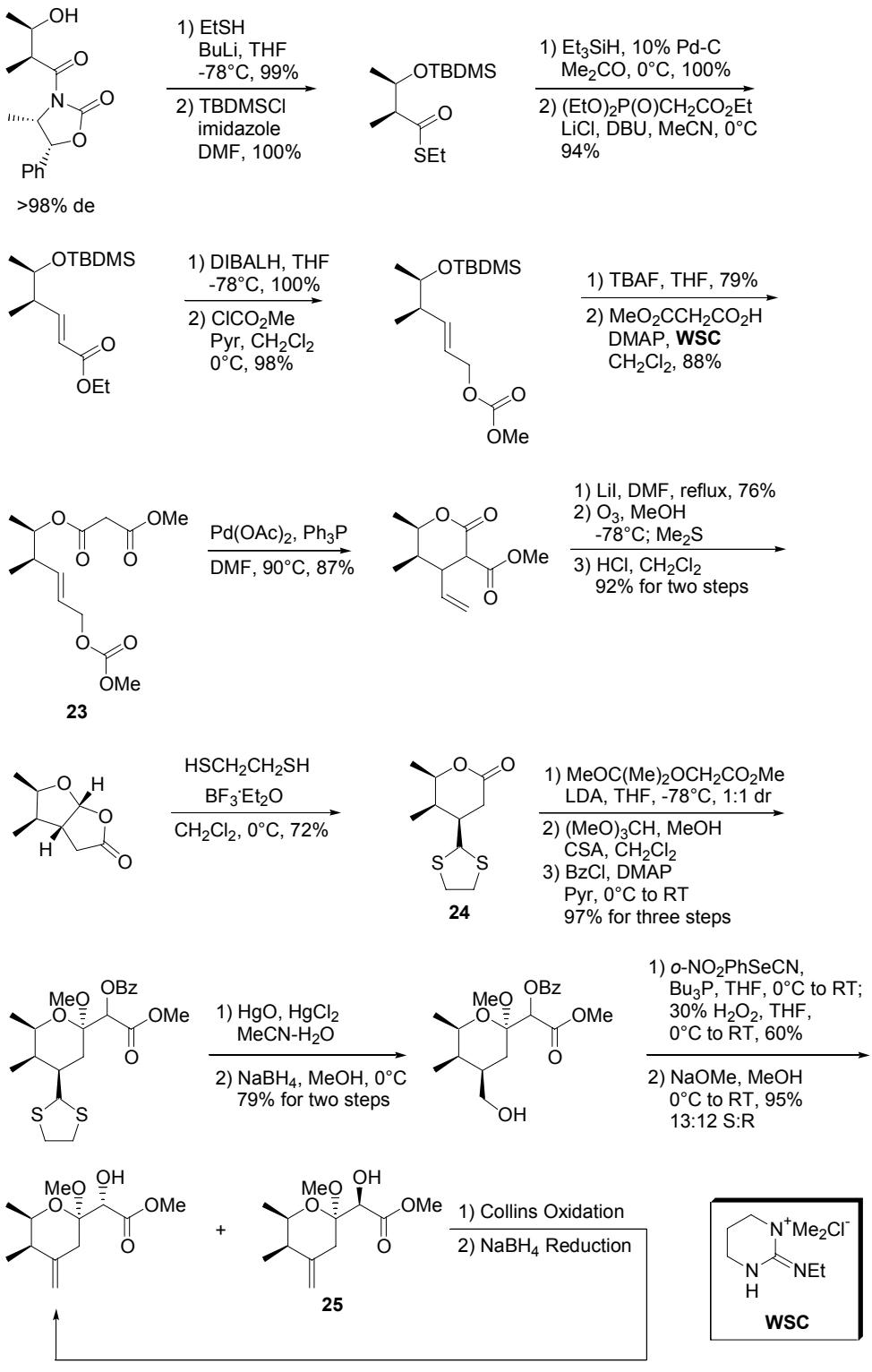
Figure 10 Toyota's Partial Pederic Acid Synthesis



This approach is very interesting, but the final steps for the conversion of the cyclization product **22** to pederic acid were not provided.

Several years later, the same group implemented a palladium catalyzed reaction to form the THP ring via an intramolecular cyclization.[19] Once the allyl ether **23** was obtained, the stage was set to employ the palladium-catalyzed cyclization. The synthesis is summarized in Figure 11.

Figure 11 Toyota's Methyl Pederate Synthesis



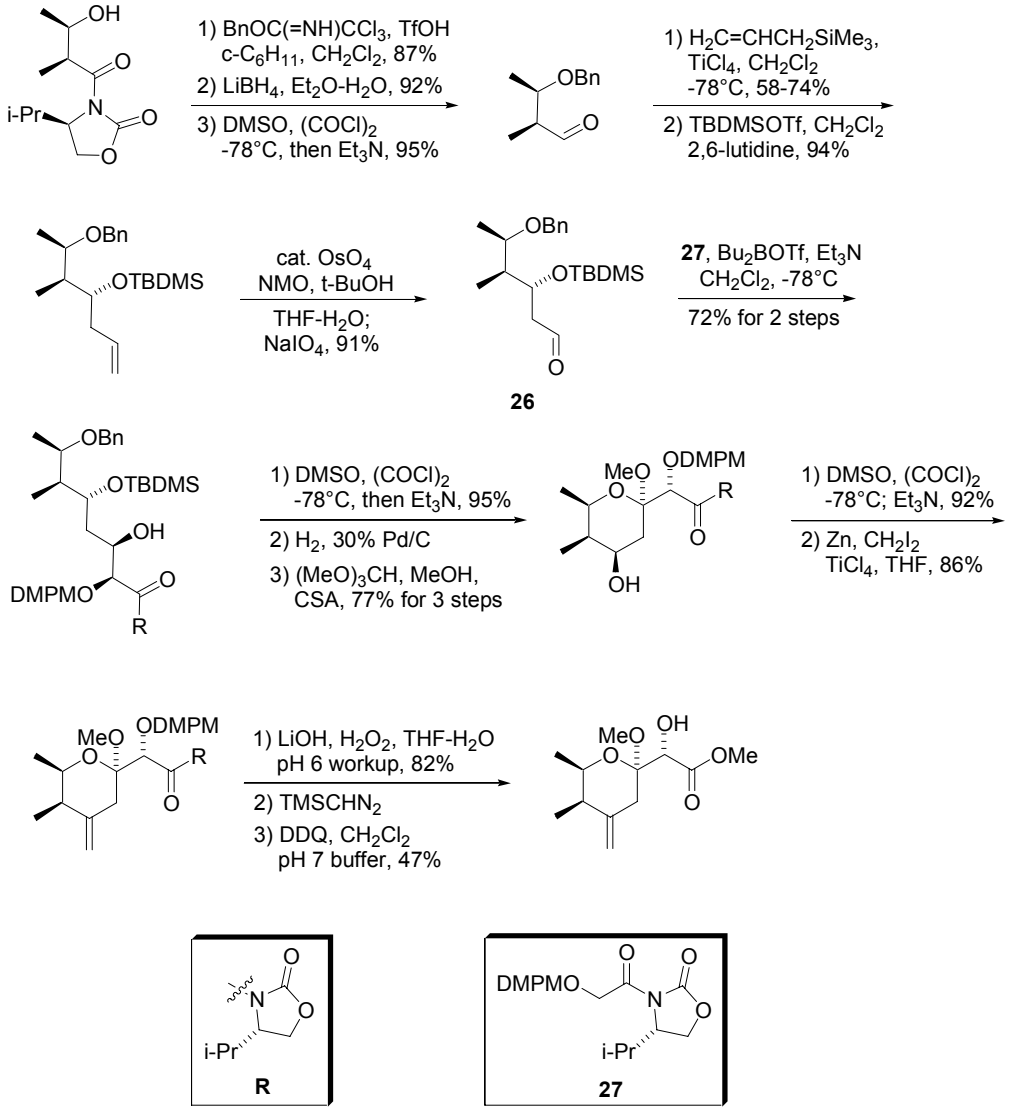
The authors discovered that the selectivity of the lactone formation depended on both the palladium catalyst used as well as the solvent. Notably, the 7-(R) epimer of the final product **25**

was converted to the desired isomer by Collins oxidation and sodium borohydride reduction in a 5:1 diastereomeric ratio, as described in their earlier work.[20]

This scheme introduced new palladium chemistry as part of the synthesis, but it had several disadvantages. The diastereomeric ratio of the Claisen condensation of **24** was 1:1, showing no selectivity. Also, the synthesis was quite lengthy, requiring twenty steps initially, and two more for the C7 epimerization.

The Roush group completed several pederic acid syntheses.[21] Their most successful contribution involved a diastereoselective aldol reaction of **26** to introduce the C7-(S) stereochemistry using a chiral acyloxazolidinone **27** (Figure 12).[22] The enol borane formed in this reaction provided the *syn*-aldol in high yield (79% for the aldol reaction).

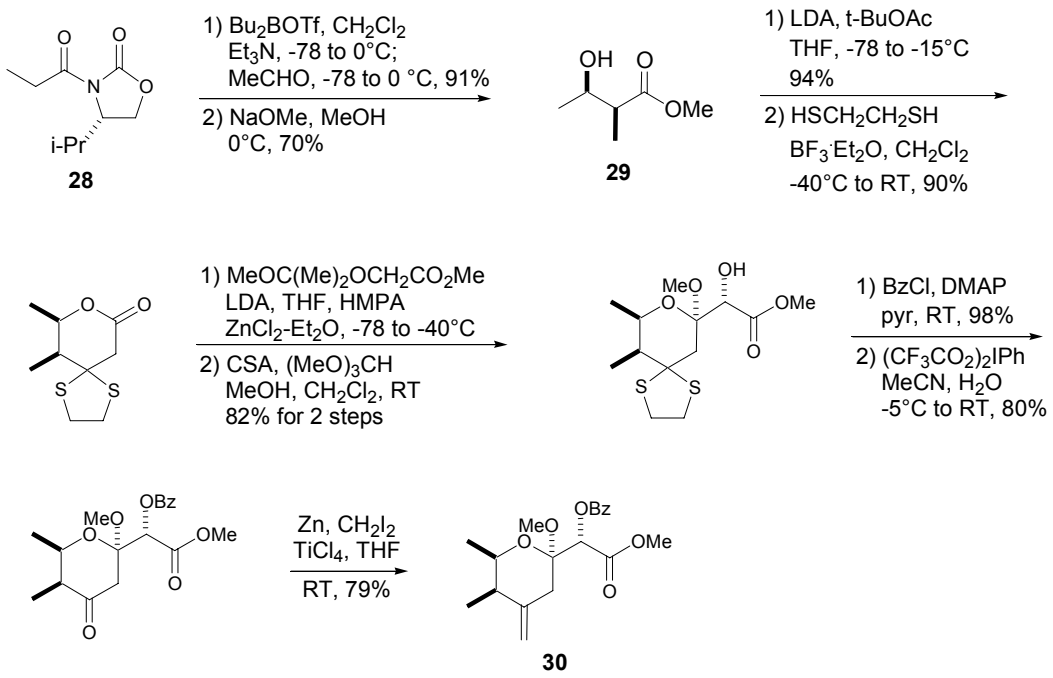
Figure 12 Roush's Methyl Pederate Synthesis



This work required fifteen steps (five fewer than Toyota) and provided good stereoselectivity. However, a shorter sequence was desirable.

A considerable amount of work has been done by the Nakata group. After first synthesizing (+)-benzoylselenopederic acid, described in an earlier paper,[23] this group developed a very efficient synthesis of protected methyl pederate **30** from the L-valine derived propionimide **28**.[24] The synthesis is summarized in Figure 13.[25]

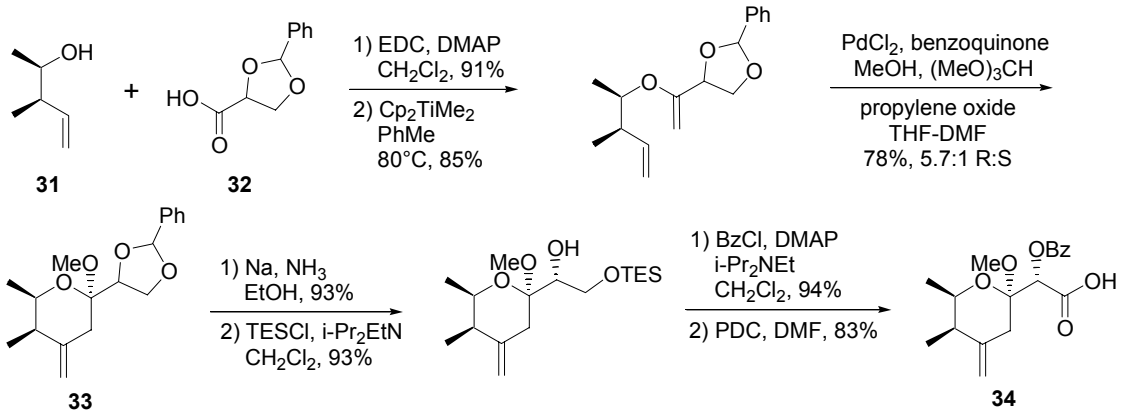
Figure 13 Nakata's Methyl Pederate Synthesis



Stereoselectively controlled steps included the Evans aldol reaction of **28**, which proceeded with very high stereoselectivity, and the intramolecular Claisen condensation of **29**, which gave a single isomer. Overall, the synthesis proceeded through only nine steps and gave a 26% overall yield.

Recently, Rawal *et.al.* completed a synthesis of a pederic acid derivative using the chiral homoallylic alcohol **31** (Figure 14).[26] The group utilized a Heck reaction for the cyclization of the tetrahydropyranyl ring to form **33**.

Figure 14 Rawal's Pederic Acid Synthesis

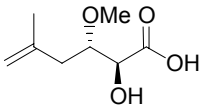


The synthesis improved on Nakata's work, entailing only seven steps from the protected glyceric acid **32** and provided the final product **34** in 35% overall yield.

5. Synthesis: Psymberic Acid

Psymberic acid is analogous to pederic acid, as it refers to the left carboxylic acid segment of psymberin (Figure 15).

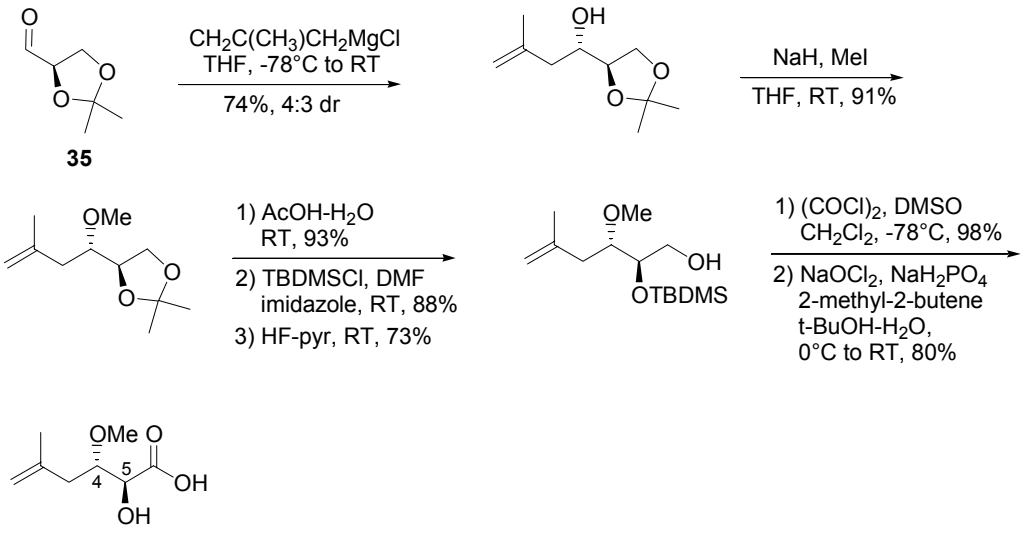
Figure 15 Psymberic Acid



The synthesis of this molecule typically requires seven to eight steps, as discussed below.

Only three syntheses of this molecule have been published to date. The first was done by Kiren and Williams using a protected dihydroxy aldehyde **35** as the starting material (Figure 16).[27]

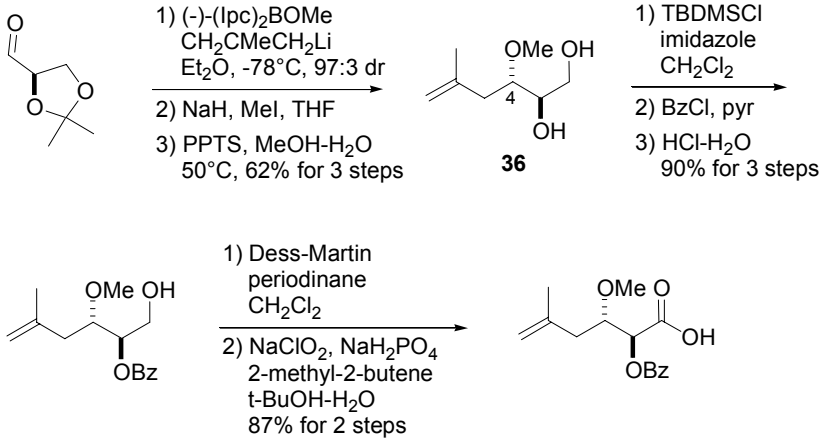
Figure 16 Kiren and Williams' Psymberic Acid Synthesis



Prior to this work, assignment of the C4 and C5 stereochemistry shown in Figure 16 was based on homology with other molecules in the pederin family. These researchers proposed that the amide side chain configuration was the *anti*-isomer based on NMR data of the product. This synthesis was a good first approach to psymberic acid; however, the stereoselectivity at C4 was poor (4:3 S:R)

De Brabander et. al. reported a similar synthesis of psymberic acid using the same starting material as Kiren and Williams (Figure 17).[28]

Figure 17 De Brabander's Psymberic Acid Synthesis

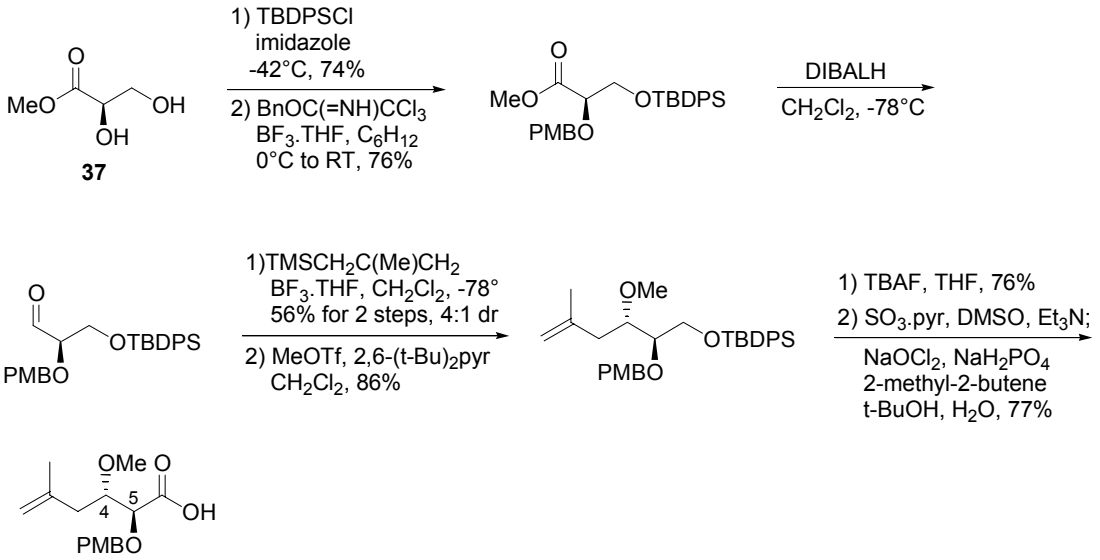


Additionally, the paper proposed a complete synthesis of psymberin utilizing a chiral methallylating agent, the remainder of which will be presented later. This work also established that psymberin and irciniastatin A, isolated by Pettit and others,[7] are identical compounds.

Although the synthesis required an additional step, the 97:3 diastereomeric ratio was very high at C4 of **36**. The yield was also improved to 48.5% from the 31.5% reported by Kiren and Williams.

Recently, Floreancig et. al. published experiments that further elaborated on the Kiren and Williams amide side chain findings. Their synthesis of psymberic acid using the D-serine derivative **37** is shown in Figure 18.[29]

Figure 18 Floreancig's Psymberic Acid Synthesis



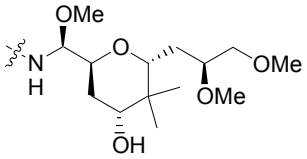
To establish the stereochemistry, four variants of this molecule were synthesized with varying stereochemistry at the 4 and 5 positions. The products were exposed to acid degradation and compared to the degradation product of the natural compound. The configuration was determined to be 4-(S), 5-(S).

The yield was 16% for this sequence, the stereoselectivity was 4:1 at C4, and the synthesis required only seven steps.

6. Synthesis: THP Ring

Synthesis of the tetrahydropyranyl ring of pederin, commonly referred to as the right half of the molecule, also presents a challenge for researchers. The structure is shown in Figure 19.

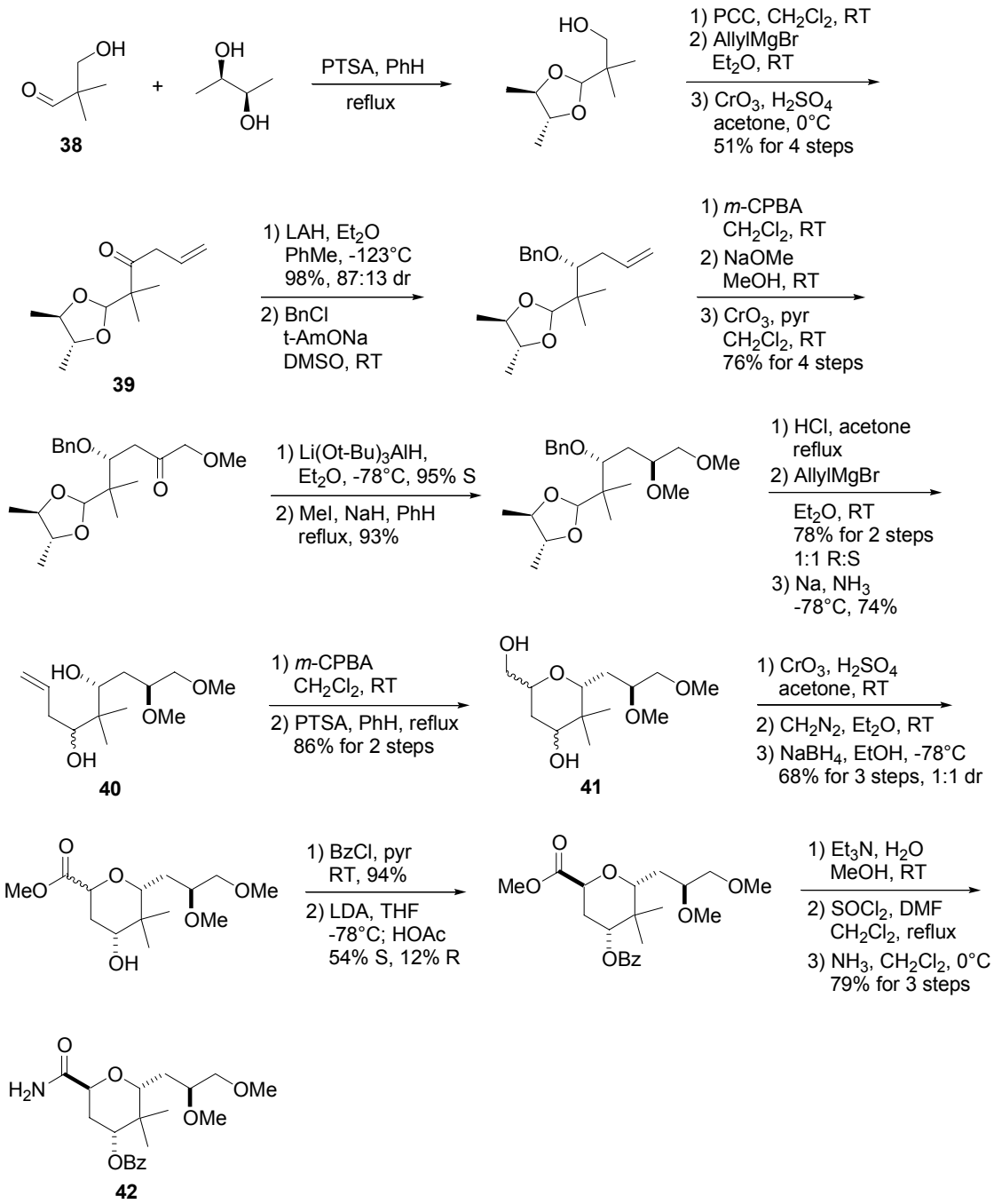
Figure 19 THP Ring



Strategies for constructing this portion of the molecule date back almost three decades, and many researchers have developed unique syntheses, as demonstrated below.

Matsumoto published some early work establishing a total synthesis of (+)-pedamide using the hydroxy aldehyde **38**.[30] The ring of diol **41** was formed through an acid catalyzed cyclization, followed by construction of the amide functionality of **42** (Figure 20).

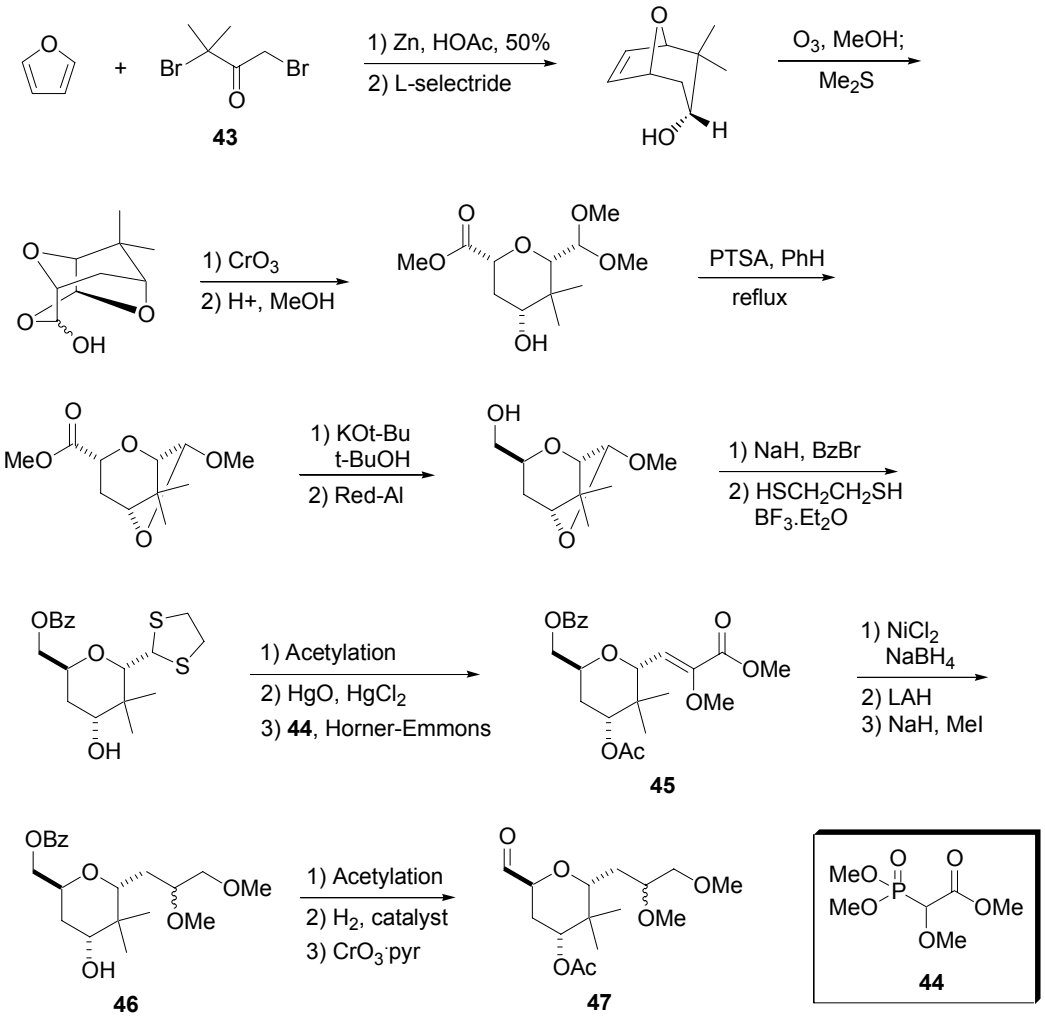
Figure 20 Matsumoto's THP Ring Synthesis



A key step in this scheme was the asymmetric reduction of the ketone **39** to form the alcohol with high stereoselectivity. On the downside, the synthesis was very lengthy, and stereoselectivity was low for the allylation intermediate **40**.

Meinwald began his synthesis of the THP ring using cyclopentanone and the dibromoketone **43** (Figure 21).[31] A Horner-Emmons reaction was used to attach the side chain of **45**, and a series of oxidations and reductions were used to form the final aldehyde **47**.

Figure 21 Meinwald's THP Ring Synthesis

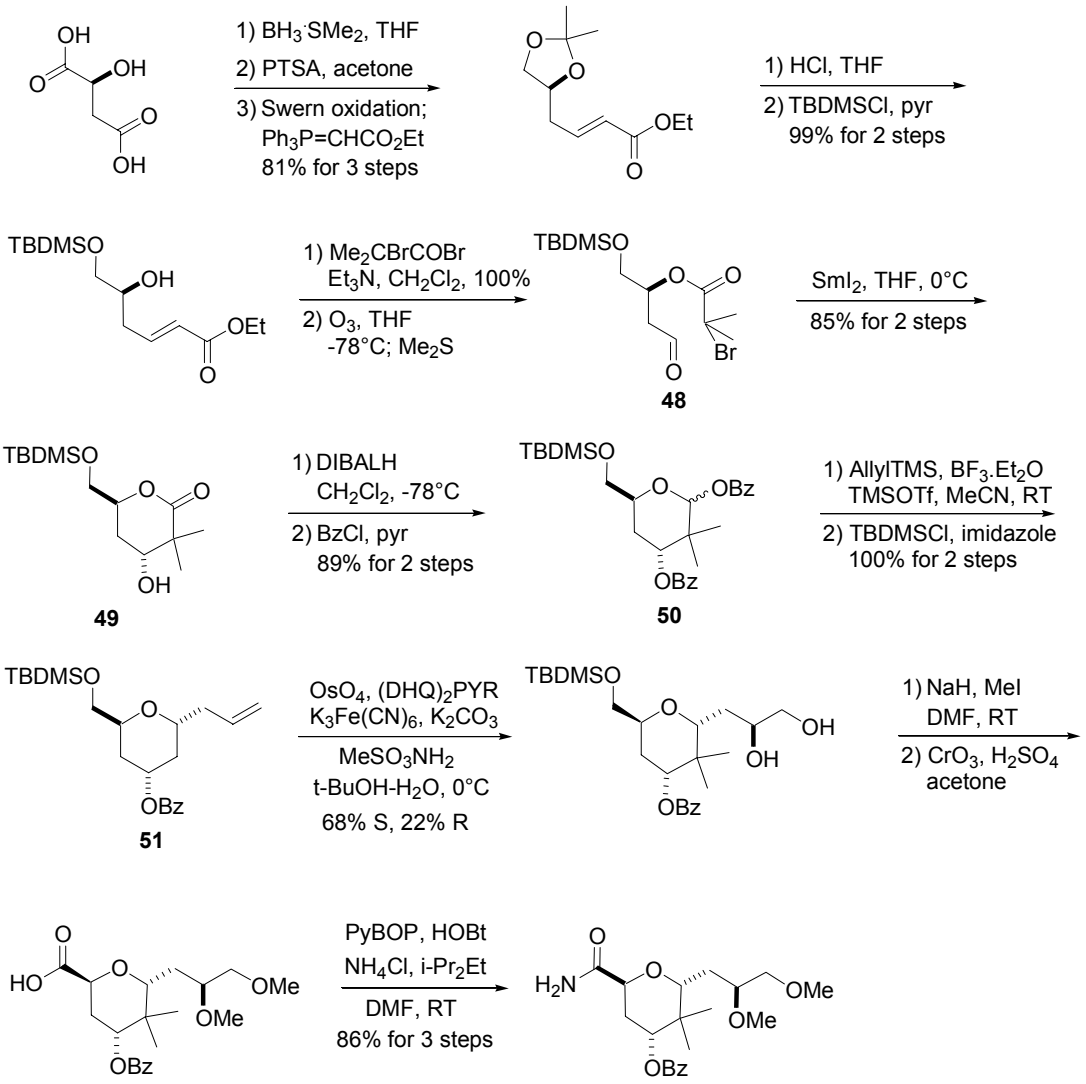


The final aldehyde was a non-dehydrated version of pederenal, an acid hydrolysis product of pederin.

Meinwald's work provided a unique tricyclic approach to forming the right side of pederin. However, this synthesis was also lengthy, and the diastereomeric ratio after formation of the C17 methoxy group of **46** was low.

Following an earlier attempt,[32] Nakata's group synthesized (+)-benzoylpedamide using a SmI_2-mediated Reformatsky reaction on **48**, as shown in Figure 22.[33]

Figure 22 Nakata's THP Ring Synthesis

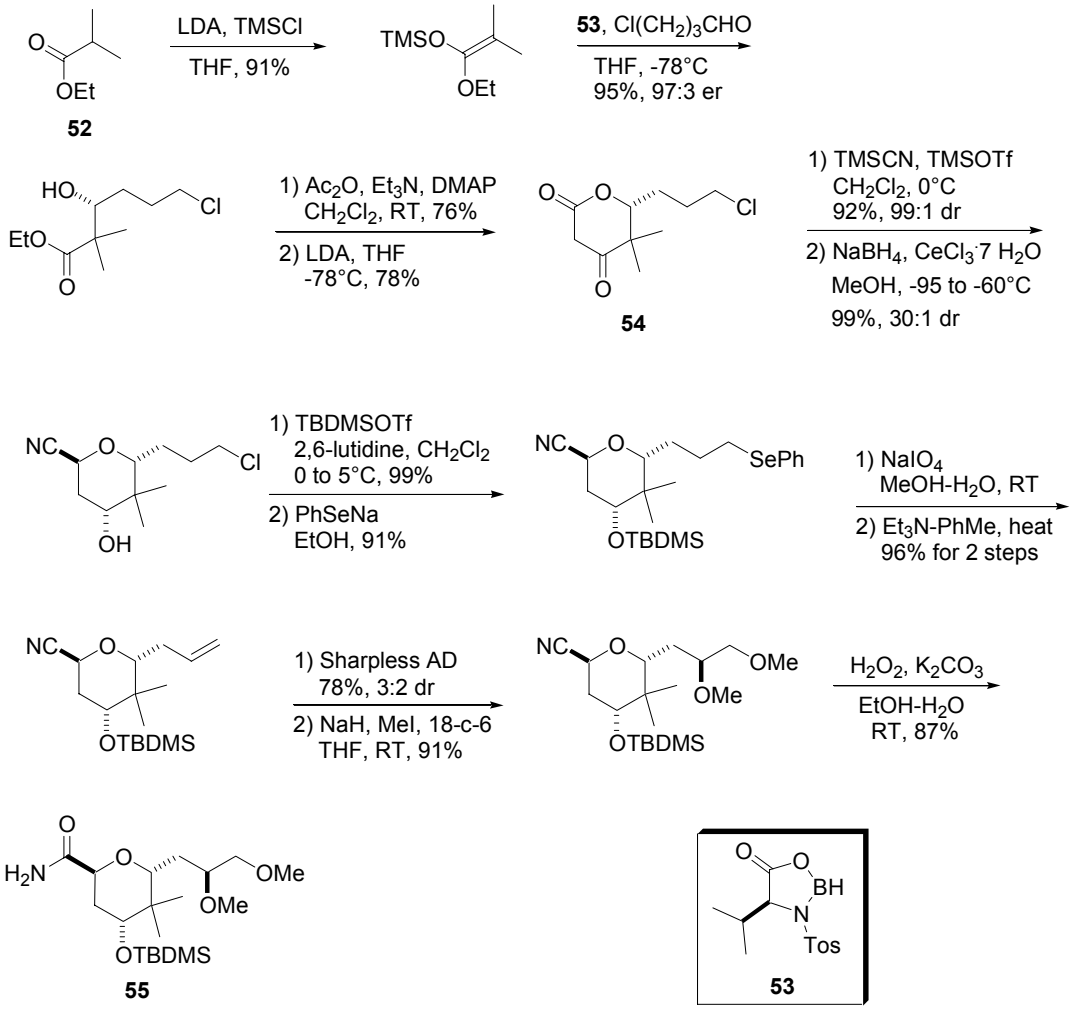


Reduction of the lactone **49** followed by selective allylation of **50** allowed efficient attachment of the side chain. This synthesis was shorter than the previous two schemes, completed in sixteen steps with a 35% overall yield, but the diastereomeric ratio of the dihydroxylation of **51** was low.

Kocienski's contributions date back more than two decades.[34] In his latest publication,[12] ethyl isobutyrate **52** was used as the achiral starting material. The intermediate **54** was quite

versatile, as it can be used to make both the THP ring of pederin as well as the trioxadecalin ring of the mycalamides. The final steps of the synthesis created the amide **55** for coupling (Figure 23).

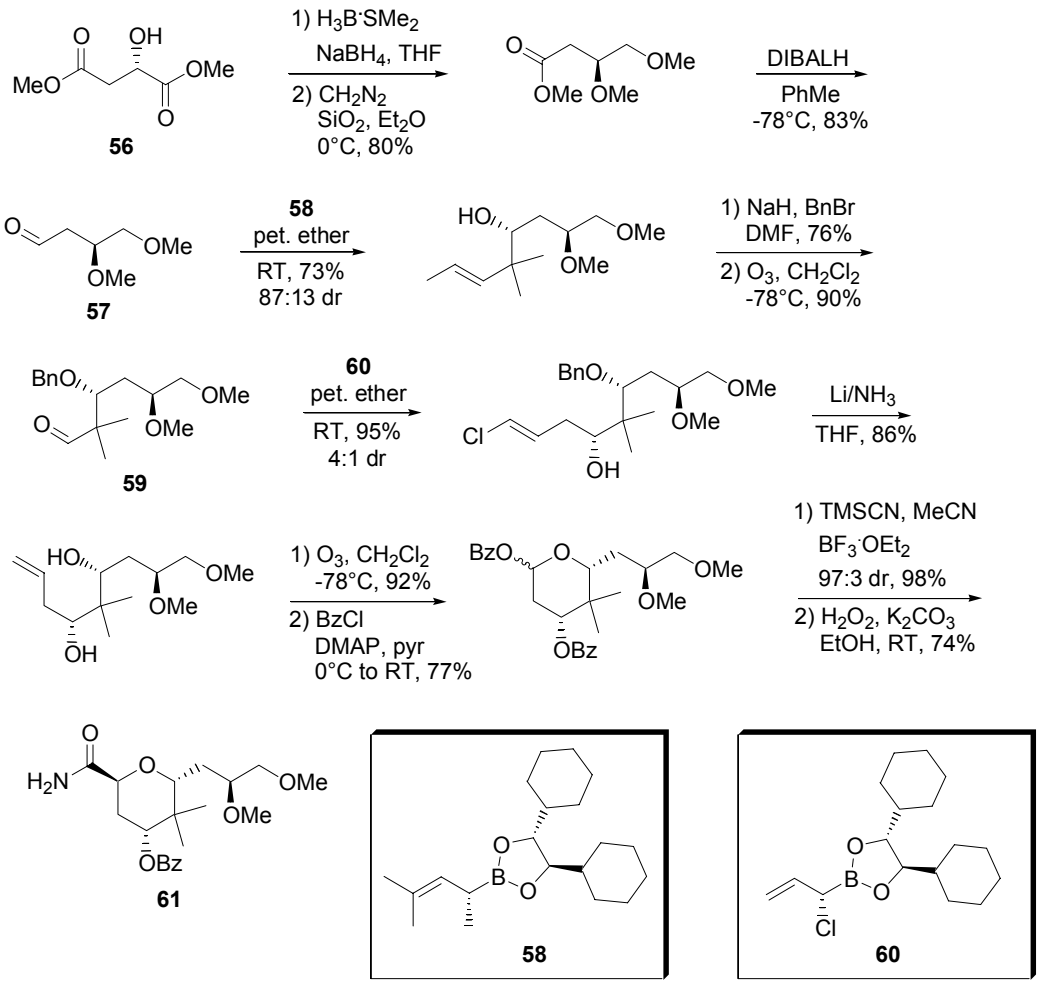
Figure 23 Kocienski's THP Ring Synthesis



This work provided very high diastereoselectivity for cyanation and reduction of **54**, but the synthesis still consisted of seventeen steps.

Hoffmann reported a shorter synthesis of benzoylpedamide from diester **56**, derived from malic acid.[35] Chiral allylboronate compounds **58** and **60** were used to control diastereoselectivity of the chain extensions (Figure 24).

Figure 24 Hoffmann's THP Ring Synthesis

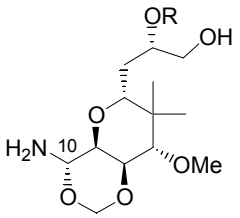


A major advantage of this work was that the use of malic acid provided the proper C17 stereochemistry at the outset. Also, high stereoselectivity was obtained for the allylboration reactions: 87% for the reaction of **58** and 80% for the reaction of **60**. This newer scheme produced benzoyl pedamide **61** in twelve steps, the fewest steps of the syntheses presented here. A negative point was that the diastereomeric ratios were not as high as Kocienski's.

7. Synthesis: Amido Trioxadecalin Ring System

The amido trioxadecalin ring system of the mycalamides is analogous to the THP ring of pederin with an additional ring (Figure 25).

Figure 25 Amido Trioxadecalin Ring System

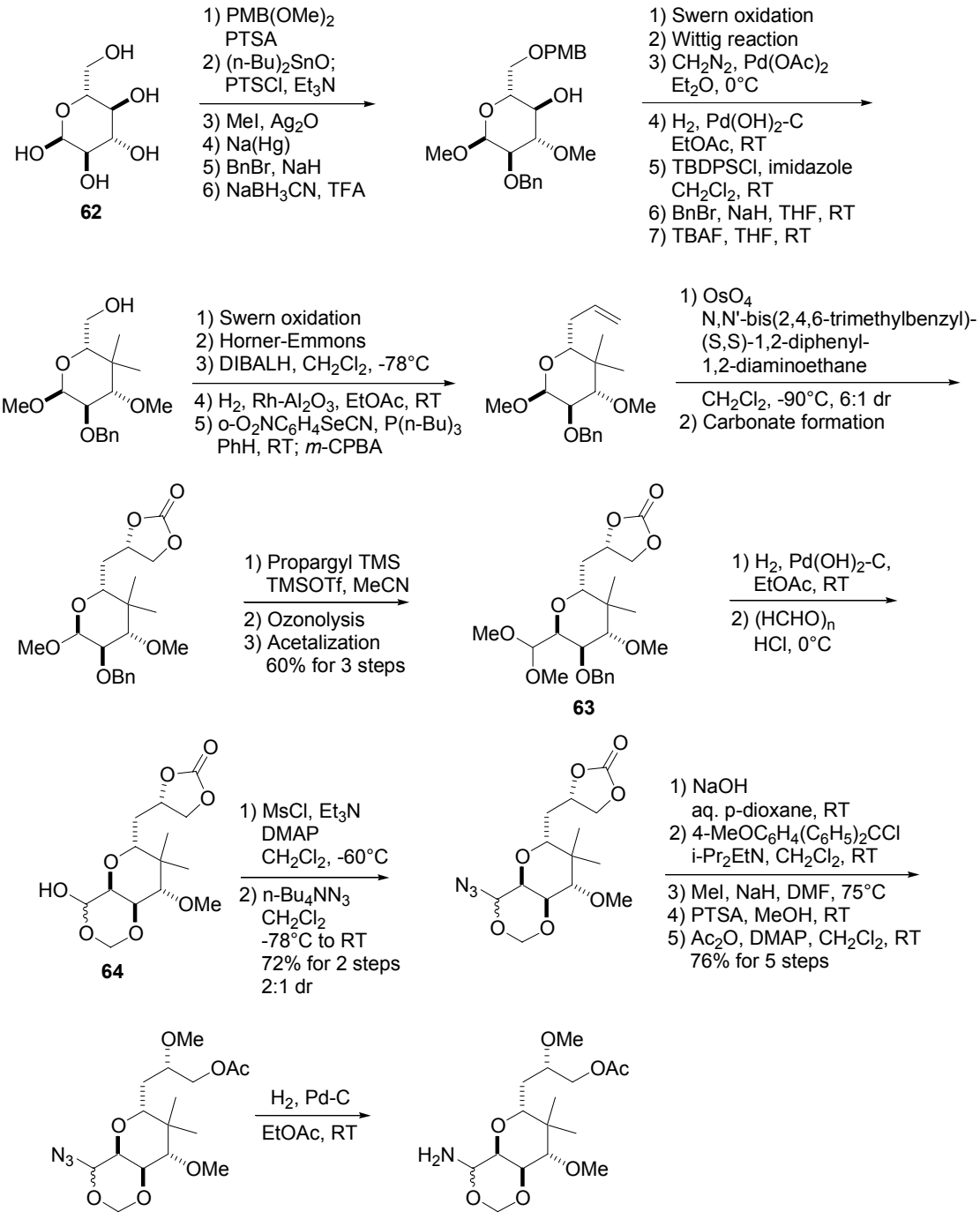


Mycalamide A: R = H
Mycalamide B: R = Me

Note that the C10 aminal methoxy of pederin is now part of the second ring of mycalamide. A number of researchers have published papers pertaining to this compound. As with the pederic acid syntheses, the work below is organized from earlier work up to the most efficient synthesis.

The Kishi group published a synthesis of the right half of pederin that started with **62** and the second ring was constructed through acetalization of deprotected **63** (Figure 26).[36]

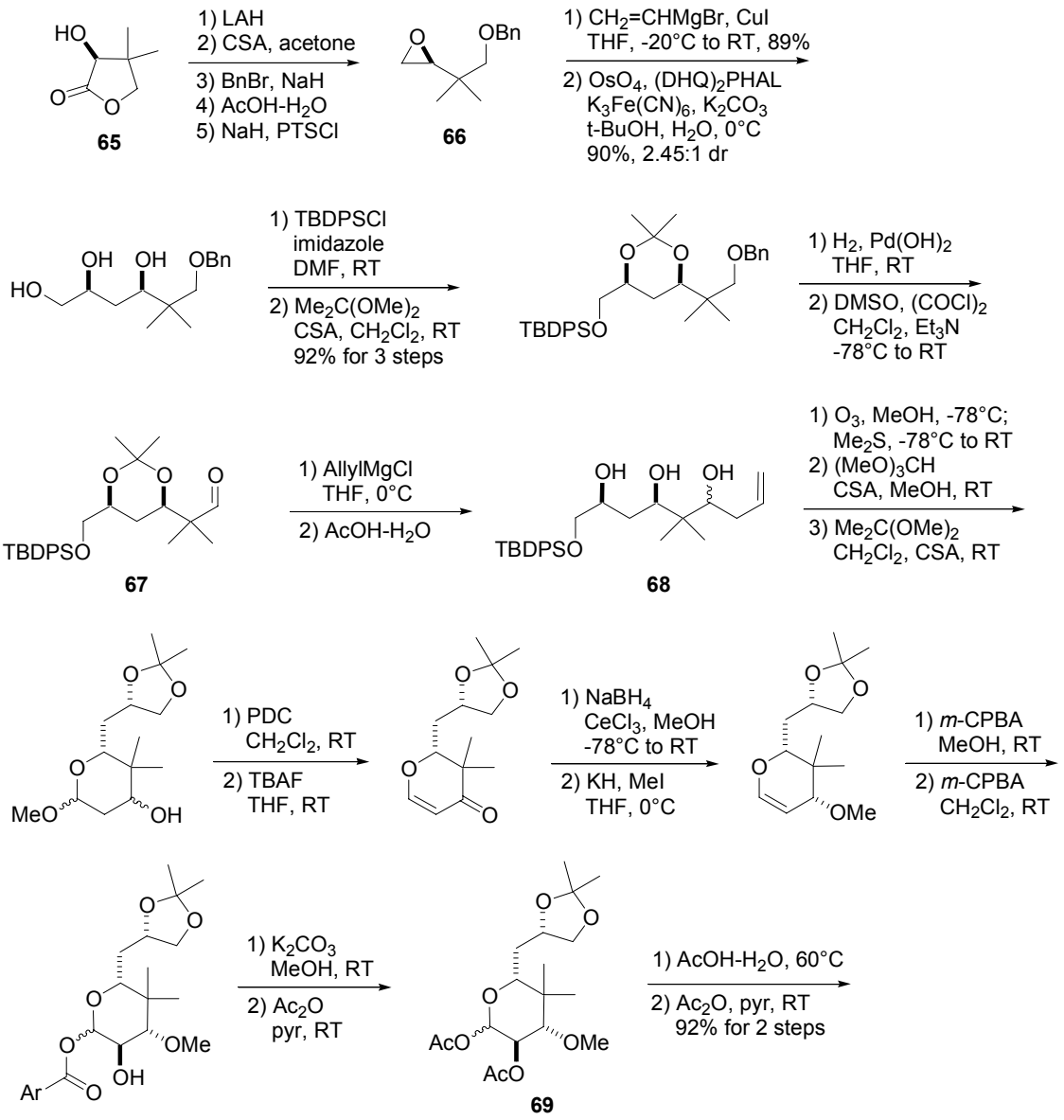
Figure 26 Kishi's Amido Trioxadecalin Ring Synthesis

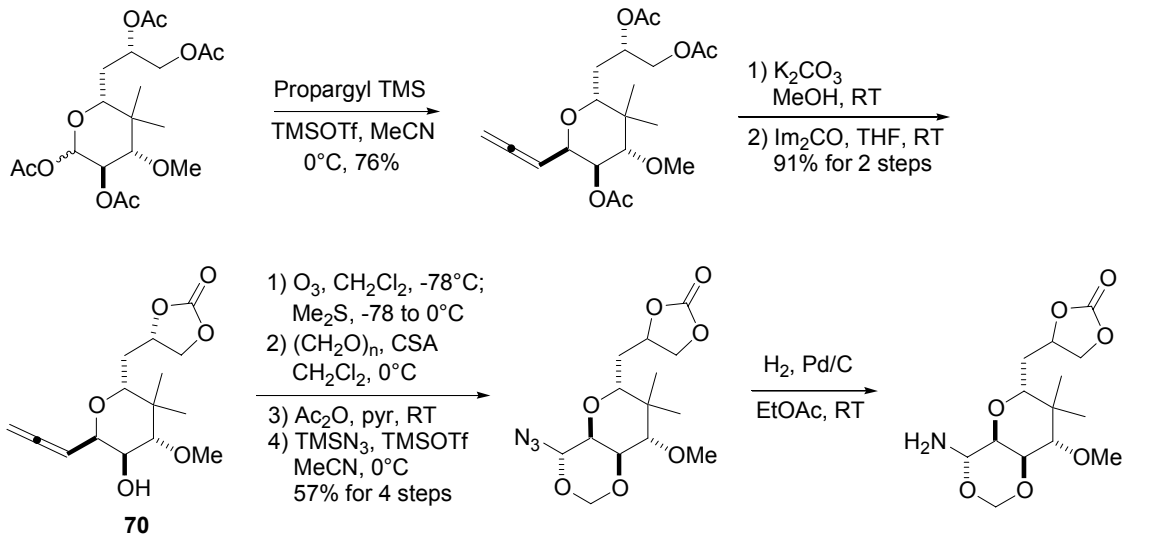


This group pioneered the synthesis of the trioxadecalin ring; however, the synthesis was very long with thirty-three steps, and the diastereoselectivity during formation of the second ring of **64** was low.

Nakata and his group have done several syntheses of the right half of mycalamide A.[37] In 1996, a synthesis involving a chiral starting material was published.[38] The synthesis began with the transformation of (S)-pantolactone **65** into the epoxide **66**, which was then converted to the triol **68** as shown (no diastereomeric ratio was provided for the allylation reaction of aldehyde **67**). The triol was then cyclized and converted to the diacetal-methoxy compound **69**. The trioxadecalin ring was constructed from the allene **70** and converted to the amine as shown in Figure 27.

Figure 27 Nakata's Amido Trioxadecalin Ring Synthesis



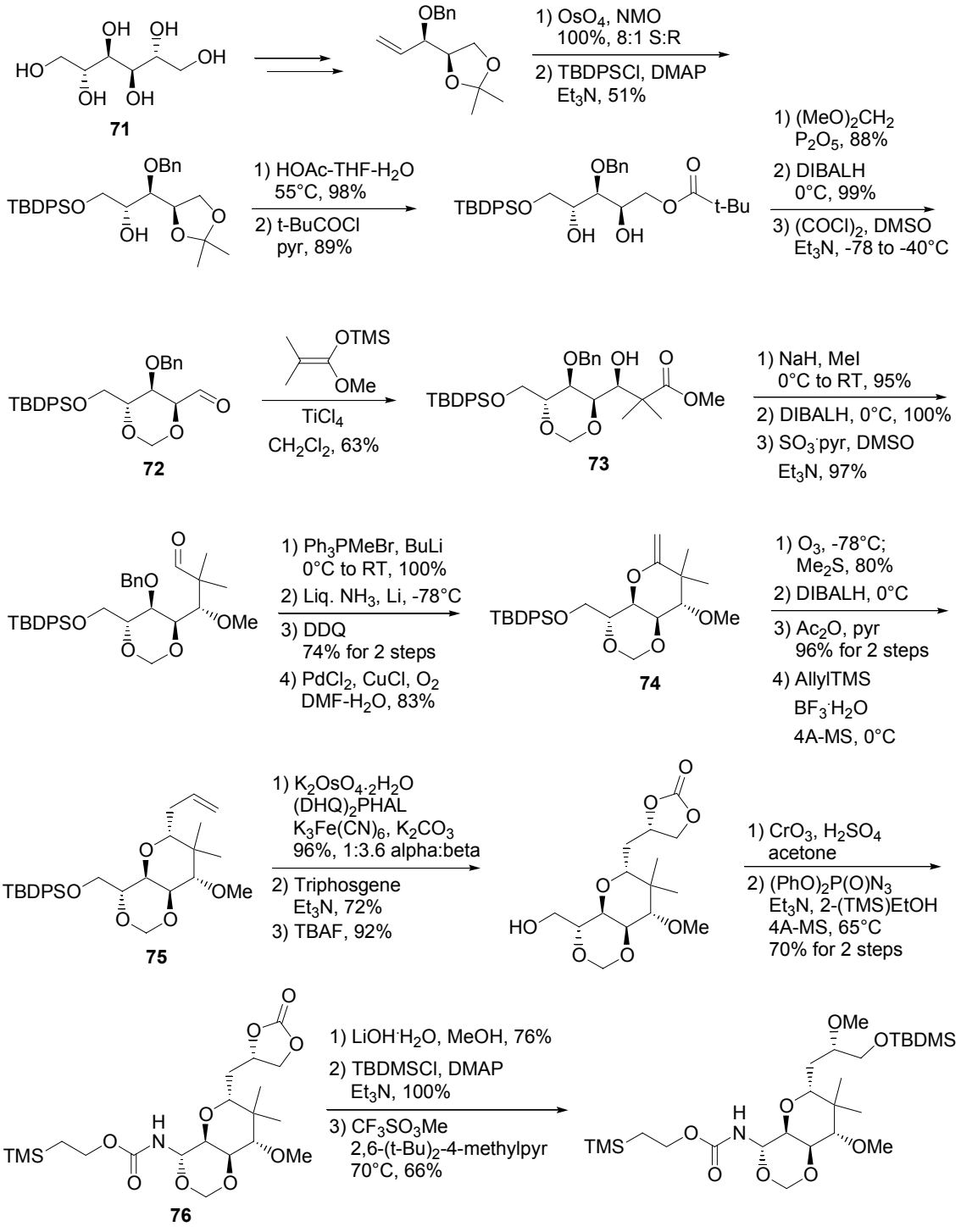


70

This scheme was proposed as a more useful way to produce the molecule on a larger scale compared to their previous syntheses. However, the reaction scheme was also very lengthy, and the stereoselectivity was not very good for the Sharpless dihydroxylation.

Toyota's group created the trioxadecalin ring from the sugar D-mannitol **71** (Figure 28).[39] The primary step in this sequence is the $TiCl_4$ catalyzed aldol condensation of **72** to form the hydroxyester **73**. The second ring of **74** was formed using a stereoselective oxypalladation, which provided the cis-trioxadecalin in high yield (83% for this step). To complete the N-acyl aminal functionality, the carbamate **76** was constructed as illustrated in the figure.

Figure 28 Toyota's Amido Trioxadecalin Ring Synthesis

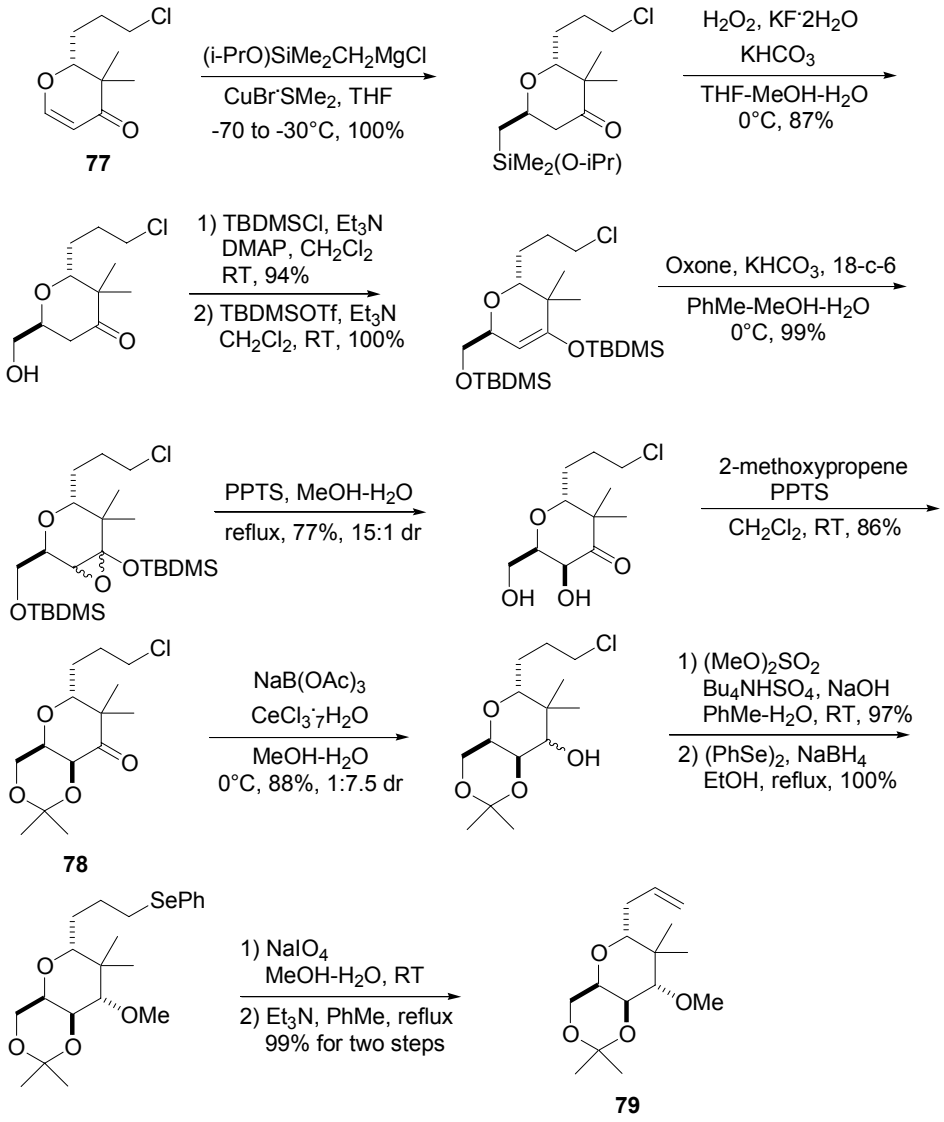


The reaction sequence was shorter than the previous two by Kishi and Nakata, requiring twenty-seven steps from the starting alkene, and utilized the innovative oxypalladation step. However, the selectivity of the side chain dihydroxylation of **75** was low.

More recently, they have proposed an isoxazoline intermediate for 12-*epi*-mycalamide A, but a complete synthesis was not presented. [40]

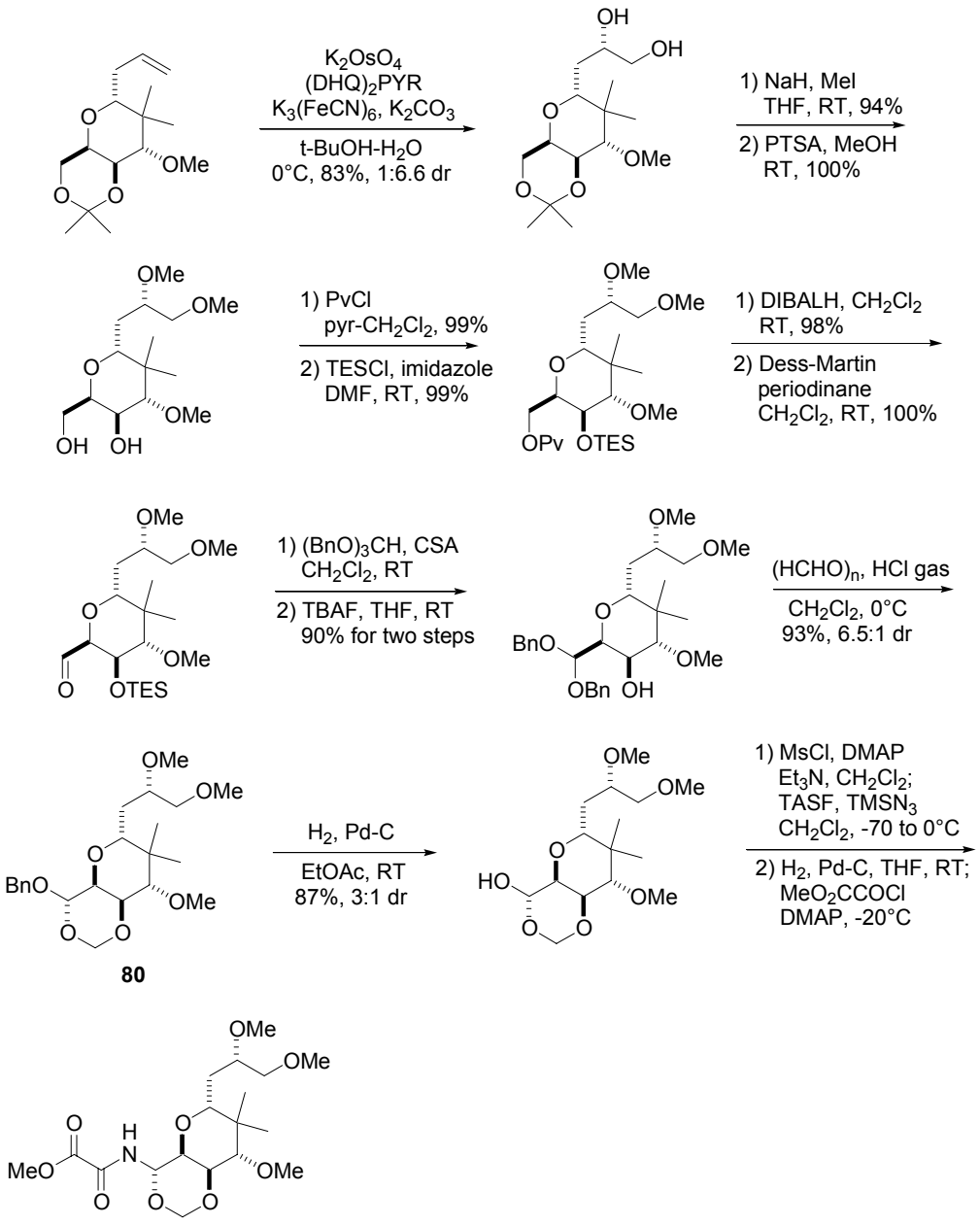
In the late 1990s, Kocienski published several papers concerning mycalamide B.[41] Their most recent synthesis began with the dihydropyranone **77**.[42] The first seven steps yielded the isopropylidene acetal **78** in 53% overall yield, which was then transformed into the terminal alkene **79** (Figure 29).

Figure 29 Kocienski's Amido Trioxadecalin Ring Synthesis – Part I



To complete the synthesis, the side chain was constructed, followed by formation of the trioxadecalin ring system of **80** by reaction with formalin.

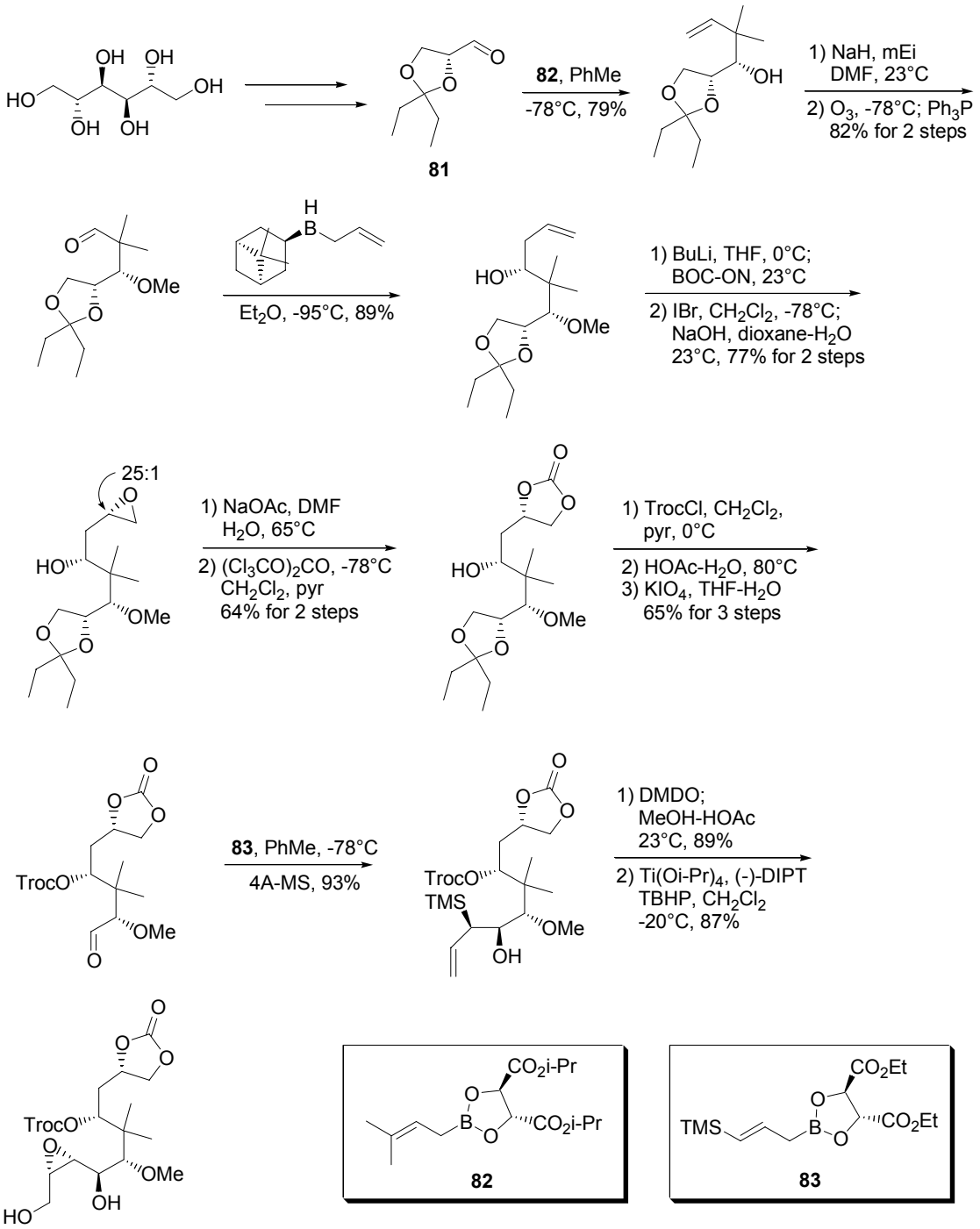
Figure 30 Kocienski's Amido Trioxadecalin Ring Synthesis – Part II



A major advantage of this synthesis is how efficiently the dioxane ring was constructed (93% yield). Also, the functionality of the side chain can be varied to produce artificial analogs of the mycalamides. Although the yields are quite good, a shorter synthesis is desirable.

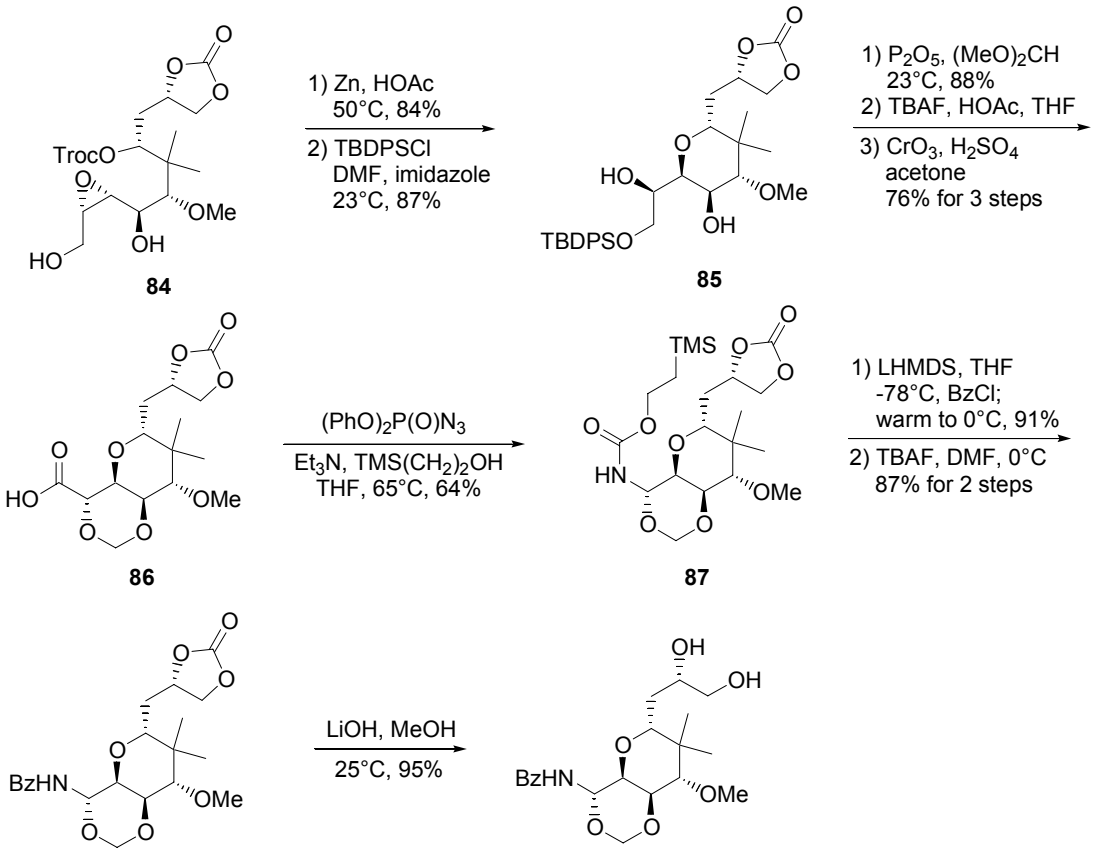
Marron and Roush developed a highly diastereoselective method for making the right half of mycalamide using the D-mannitol derived starting material **81**.[43]

Figure 31 Marron and Roush's Amido Trioxadecalin Ring Synthesis – Part I



Reaction of **84** with zinc in acetic acid resulted in formation of one of the rings, and reaction of **85** with phosphorous pentoxide and methylal produced the trioxadecalin ring system of **86**. Curtius rearrangement of the carboxylic acid **86** formed the carbamate **87** with (S)-stereochemistry at C10 as the only isomer.

Figure 32 Marron and Roush's Amido Trioxadecalin Ring Synthesis – Part II

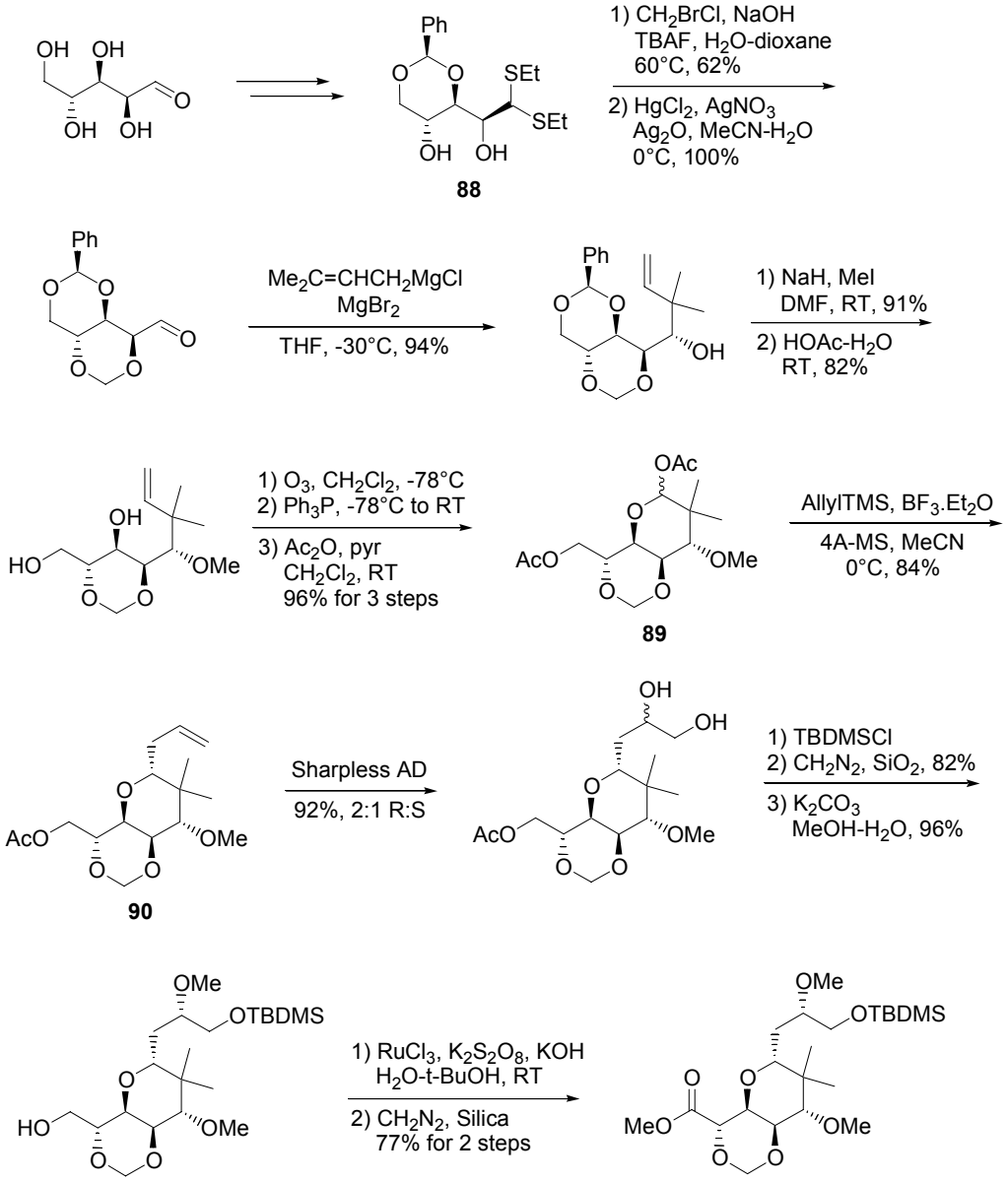


The most important part of this work was that it demonstrated stereocontrol at the N-acyl aminal carbon. In addition, use of the boronate reagents **82** and **83** provided very good control of the stereochemistry. This synthesis was again quite lengthy, consisting of twenty-three steps from the D-glyceraldehyde 3-pentylidene ketal starting material **81**.

Hoffmann made the trioxadecalin ring system of mycalamide B using sugars as the chiral starting material. The group's first approach involved L-xylose.[44] Their most recent synthesis

began with an acetal-protected D-arabinose **88**, which contained three properly configured stereogenic centers (Figure 33).[45]

Figure 33 Hoffmann's Amido Trioxadecalin Ring Synthesis

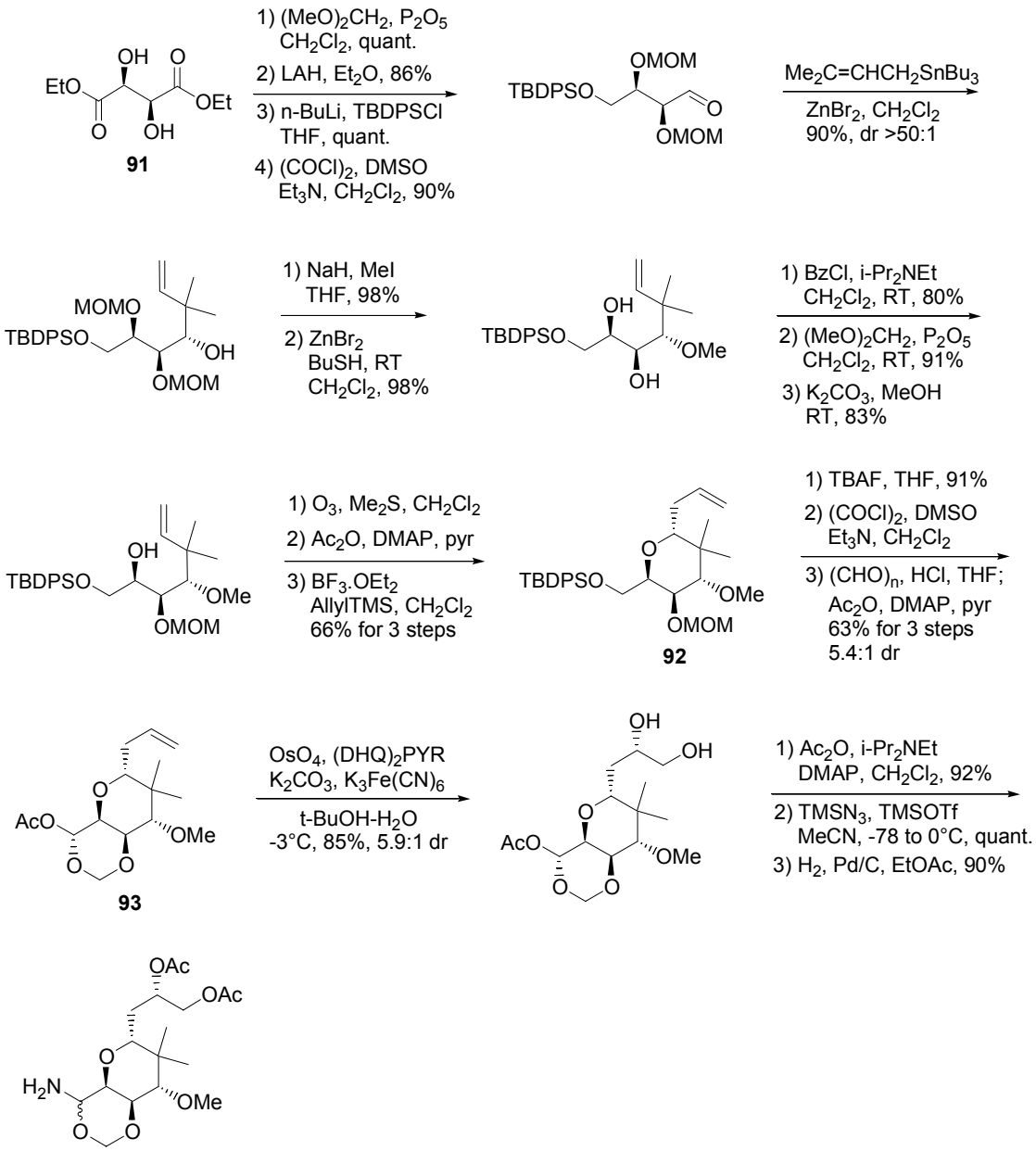


The high stereoselectivity of the allylation of **89** was possible because the trioxadecalin ring system prefers the cis-conformation due to gauche effects, as described in the reference. At the

time this paper was published, this approach was the shortest synthesis of the trioxadecalin ring system, requiring only fifteen steps from the thioacetal. The dihydroxylation of **90** did not give very high diastereoselectivity.

Rawal's total synthesis of mycalamide A reported a scheme using diethyl D-tartrate **91** as the starting material.[26] The first ring was formed through a Lewis acid catalyzed cyclization to form **92**, and the second by formylating the deprotected hydroxyl groups. Sharpless dihydroxylation of **93** was used to functionalize the side chain.

Figure 34 Rawal's Amido Trioxadecalin Ring Synthesis

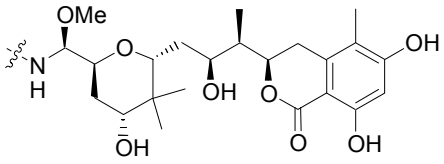


Overall, the synthesis required twenty-one steps with a 10.5% overall yield, and efficient stereoselective reactions were used.

8. Synthesis: Psymberin – Right Fragment

The structure of the right half of psymberin is shown in Figure 35.

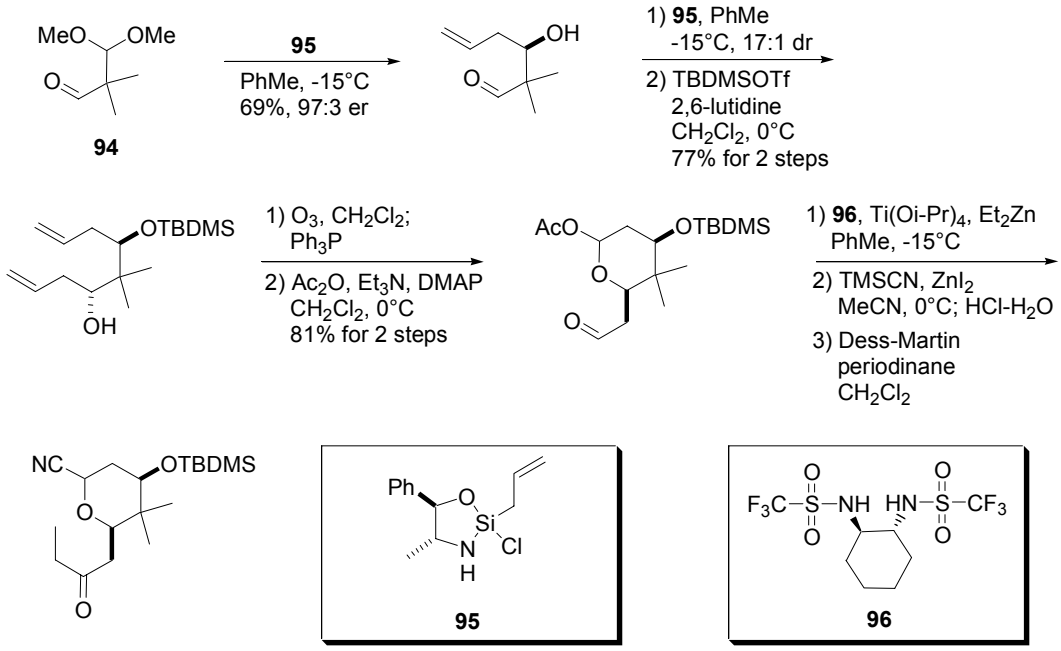
Figure 35 Psymberin - Right Fragment



The two published syntheses of this fragment are described below.

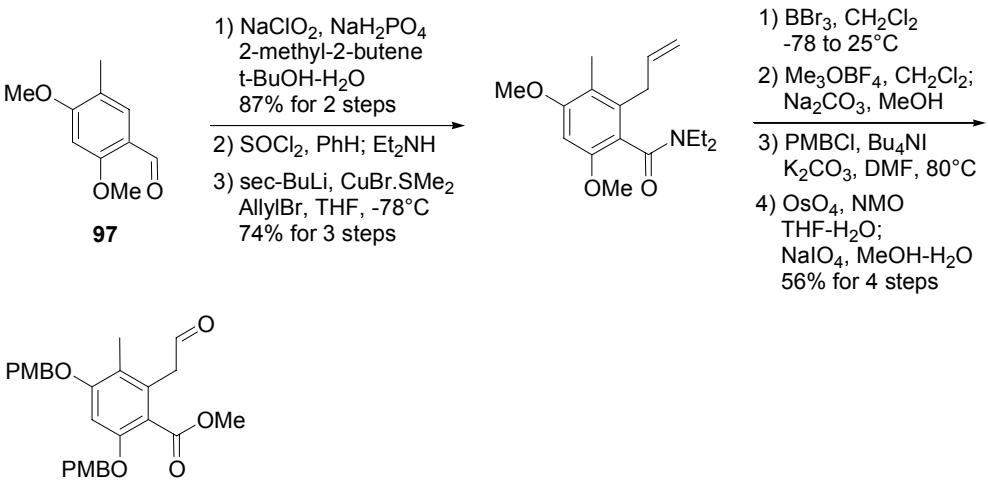
The right side of psymberin was prepared by De Brabander by first making the fragment in two parts.[28] The first molecule was constructed from aldehyde **94** starting with Leighton's allylsilane **95** in two consecutive steps (Figure 36).

Figure 36 De Brabander's Psymberin - Right Fragment Synthesis – Part I



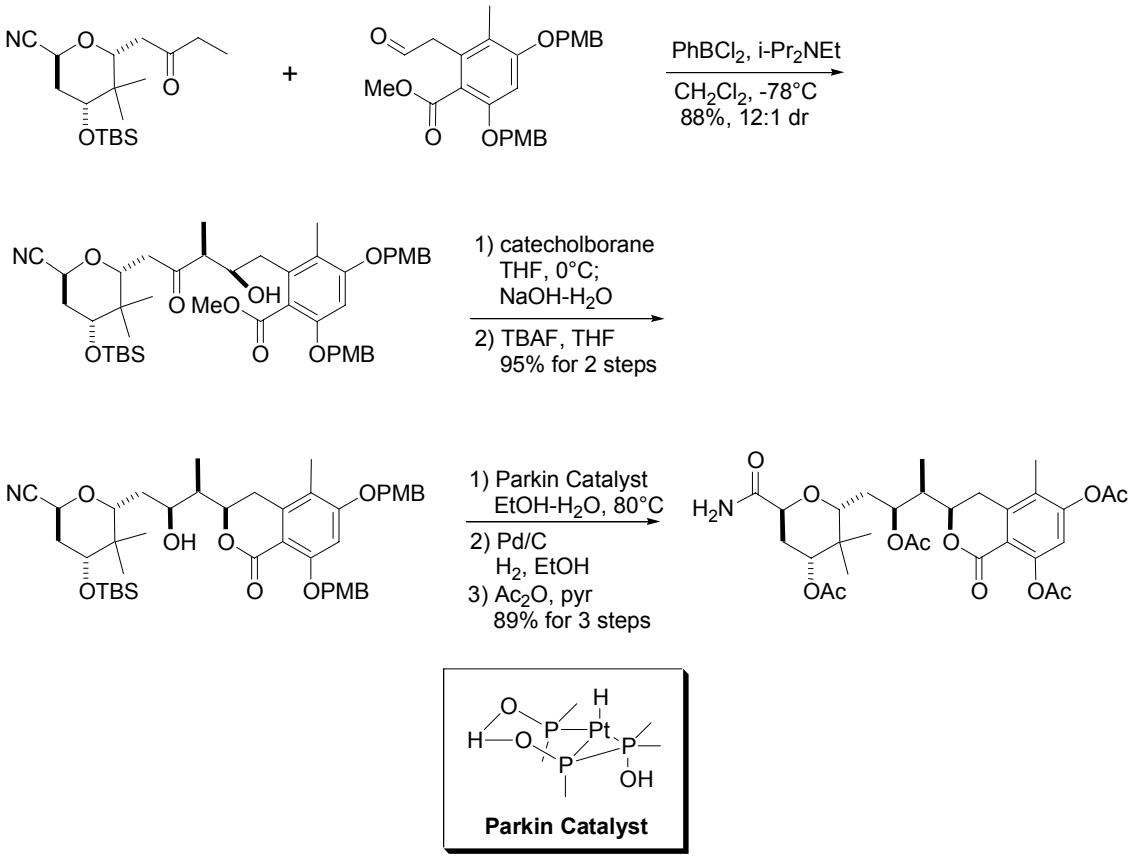
Next, the terminal portion of psymberin was made from the dimethoxy-substituted benzaldehyde **97** (Figure 37).

Figure 37 De Brabander's Psymberin - Right Fragment Synthesis – Part II



The fragments were connected using a coupling method shown in Figure 38 to form the right fragment of psymberin.

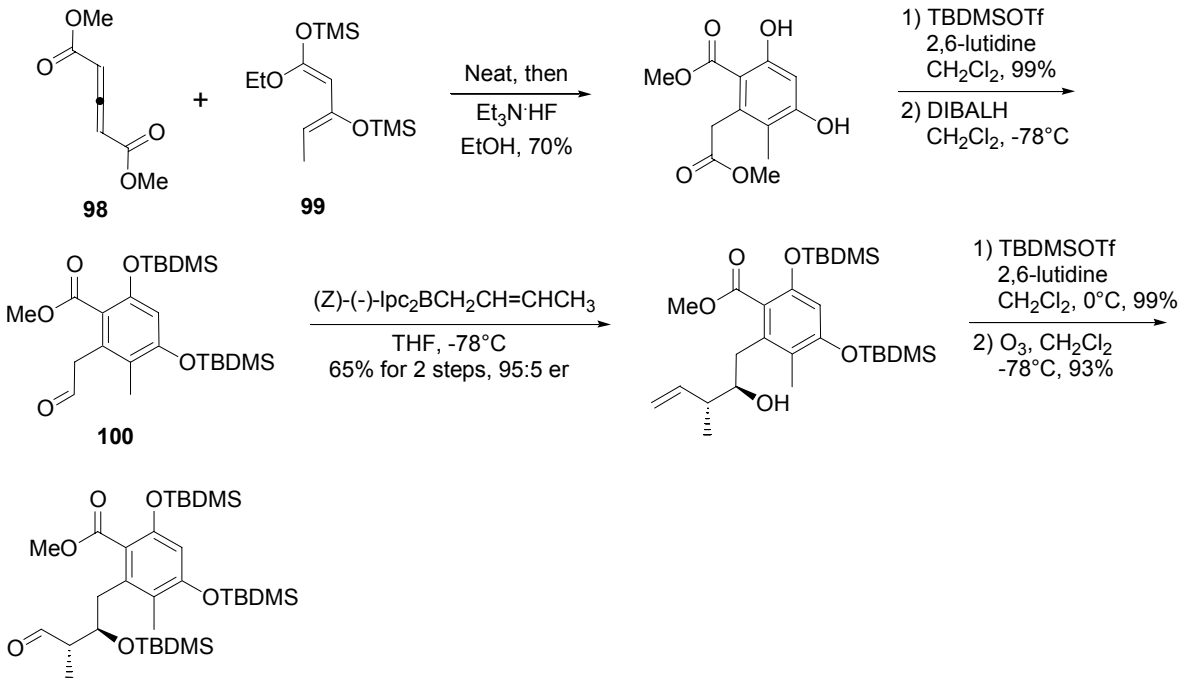
Figure 38 De Brabander's Psymberin - Right Fragment Synthesis – Part III



De Brabander's scheme proceeded with very good stereoselectivity in 17 steps.

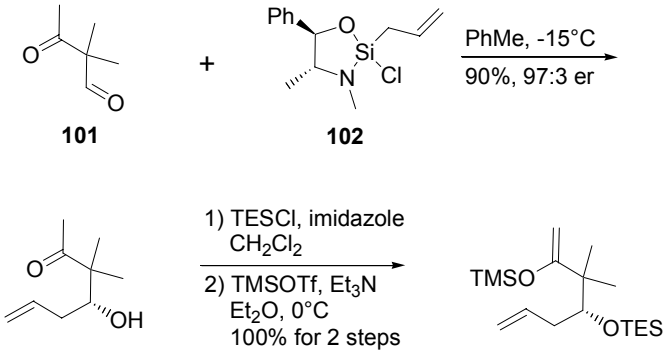
In the same year, Floreancig *et. al.* published a synthesis of the N7 to C25 fragment of psymberin.[46] The construction of the aryl ring included a cycloaddition with allene dicarboxylate **98** and a silylketene acetal **99**. The C16-C17 stereocenters were established through a Brown crotylation reaction of **100**, as shown in Figure 39.

Figure 39 Floreancig's Psymberin - Right Fragment Synthesis – Part I



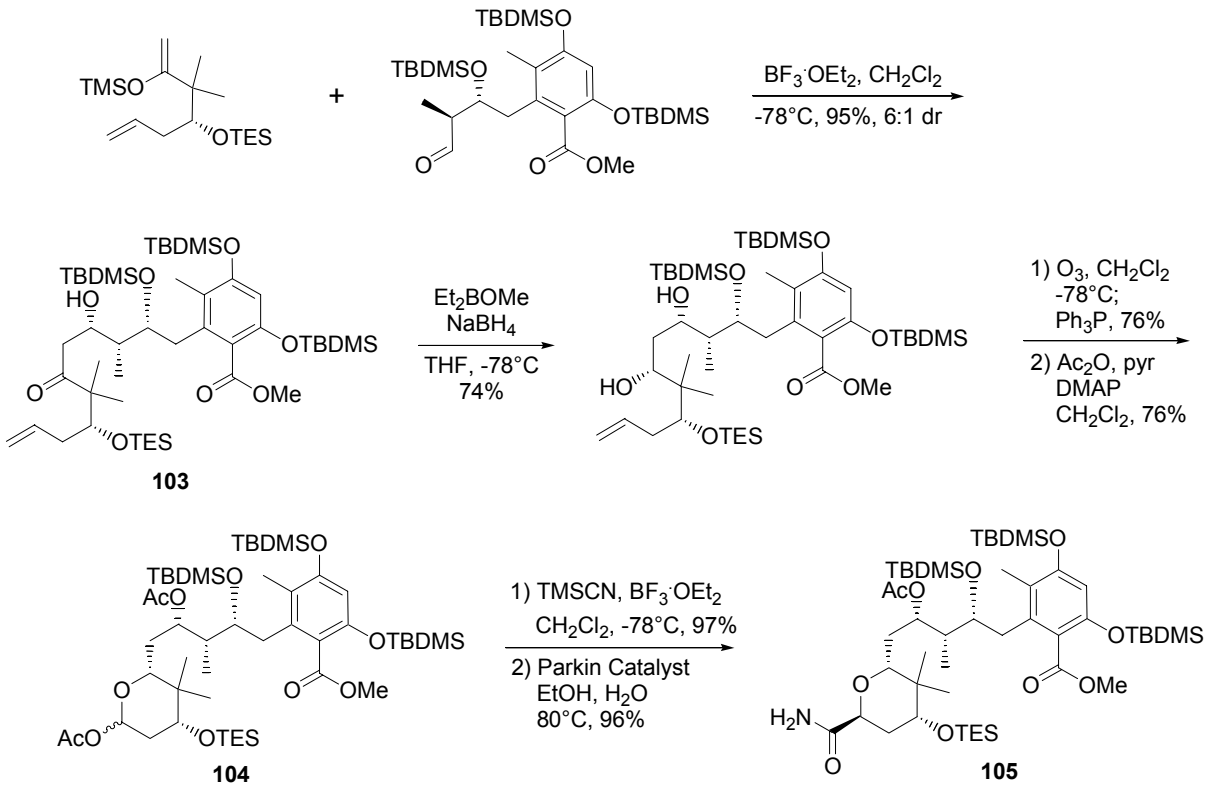
Allylation of **101** with Leighton's allylsilane **102** was the key step in forming the fragment in Figure 40.

Figure 40 Floreancig's Psymberin - Right Fragment Synthesis – Part II



These fragments were coupled using a Mukaiyama aldol reaction to form **103**. Following cyanation of **104**, the intermediate was converted to the amide **105** using the Parkin catalyst (Figure 41).

Figure 41 Floreancig's Psymberin - Right Fragment Synthesis – Part III



Although the 6:1 diastereoselectivity of the Mukaiyama reaction was lower than De Brabander's 12:1, this approach to the right half was shorter than the previous one, requiring only fifteen total steps. Also, the 15% overall yield was higher than the 8.9% reported by De Brabander.

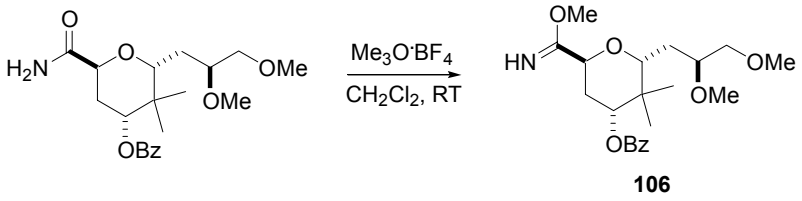
9. Synthesis: Fragment Coupling/Synthesis Completion

One of the most important steps in the synthesis of pederin compounds is the coupling of the various fragments. Several strategies have been proposed and are summarized in this section.

Pederin

After divulging a unique coupling method in previous papers,[47] Matsumoto completed the first total synthesis of pederin using a methyl imidate.[10] The amide was first converted to the N-(1-methoxyalkyl)amide **106** using trimethyloxonium tetrafluoroborate (Figure 42).

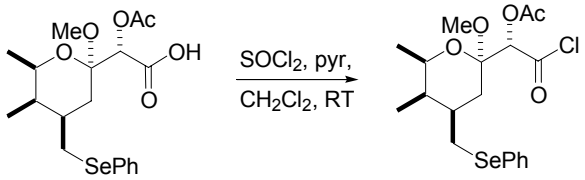
Figure 42 Matsumoto's Pederin Coupling – Part I



106

Also, the pederic acid fragment was converted to the acid chloride **107** using thionyl chloride (Figure 43).

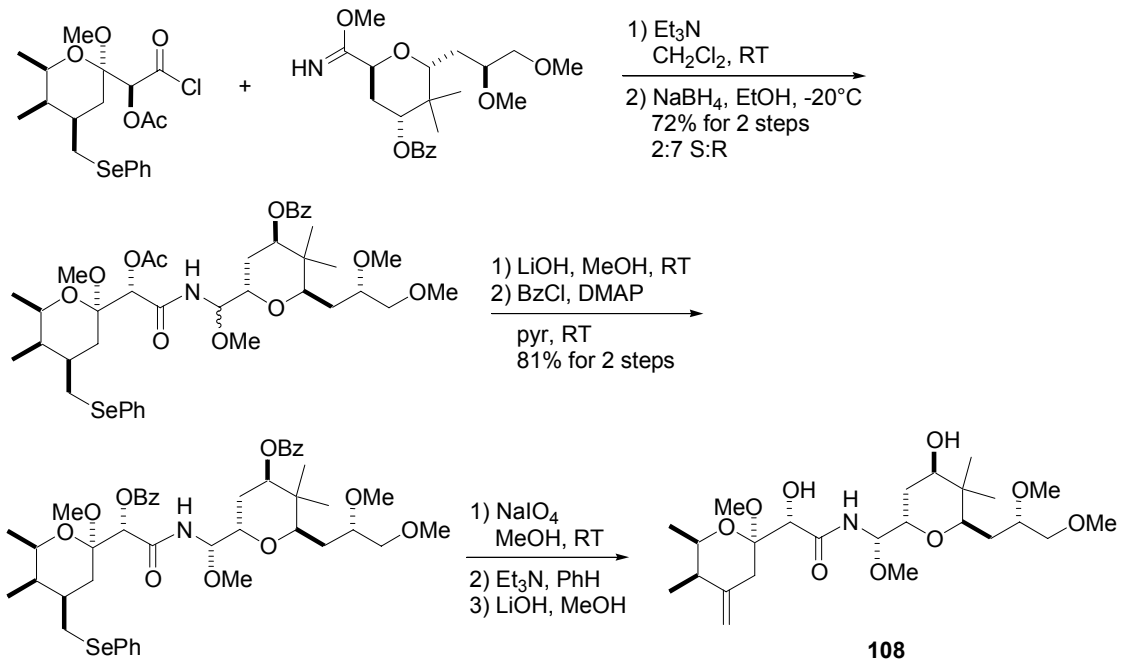
Figure 43 Matsumoto's Pederin Coupling – Part II



107

The two intermediates were then coupled using the method shown in Figure 44.

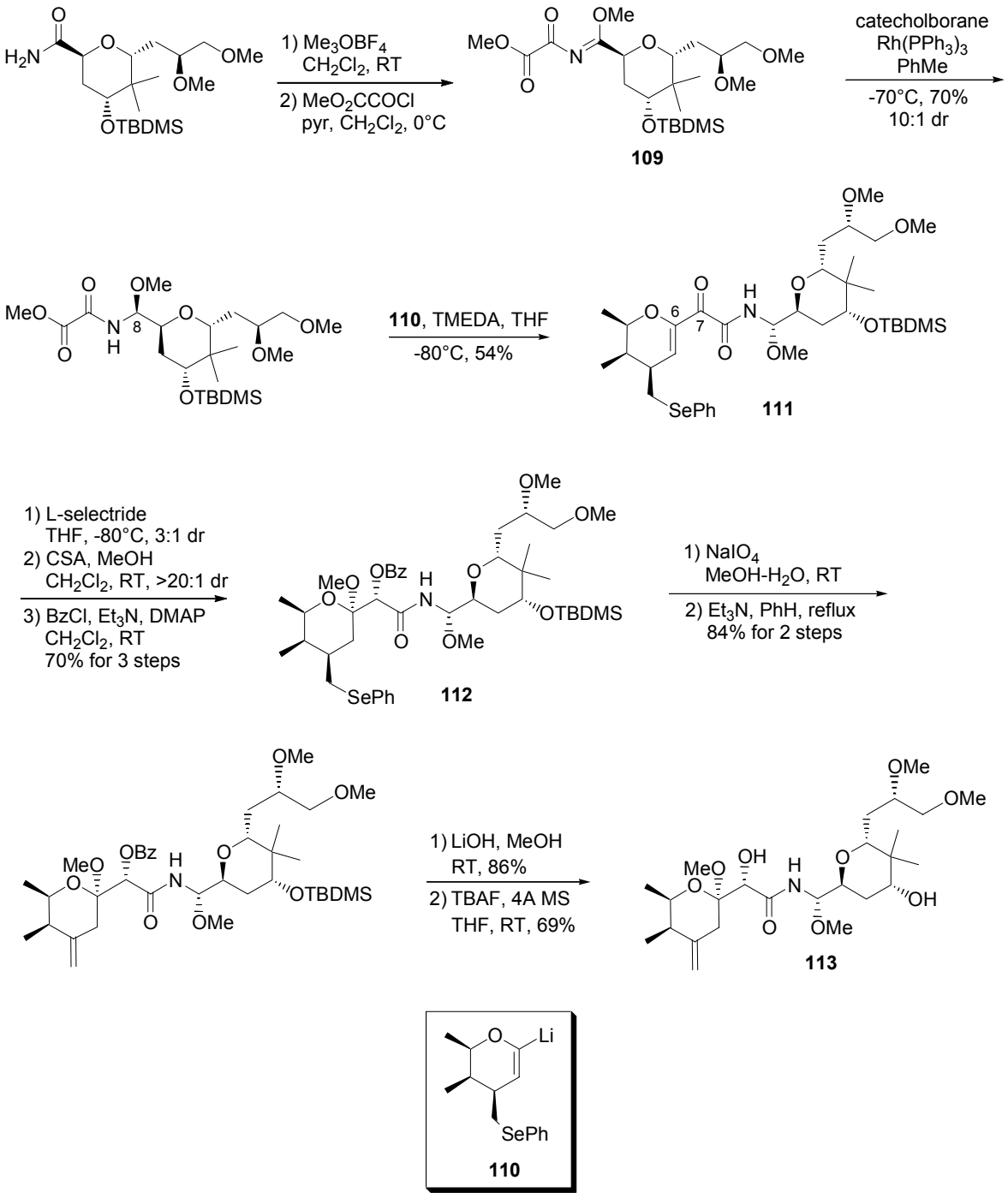
Figure 44 Matsumoto's Pederin Coupling – Part III



This coupling was a pioneering step in pederin synthesis; however, the desired product **108** was present in a 2:7 ratio with the *epi*-analog. The ratio was improved using kinetically controlled alkoxy exchange reactions to increase the proportion of the preferred product, as described in the paper.

Employing a similar method, Kocienski coupled the two fragments of pederin via the N-acylimidate **109** derived from the amide shown in Figure 45.[11d] Subsequent coupling with the metallated dihydropyran **110** and formation of the 4-methylene group through removal of the phenylselenium group of **112** yielded the final pederin product **113.** This coupling method was also used by Kocienski for mycalamide coupling.

Figure 45 Kocienski's Pederin Coupling

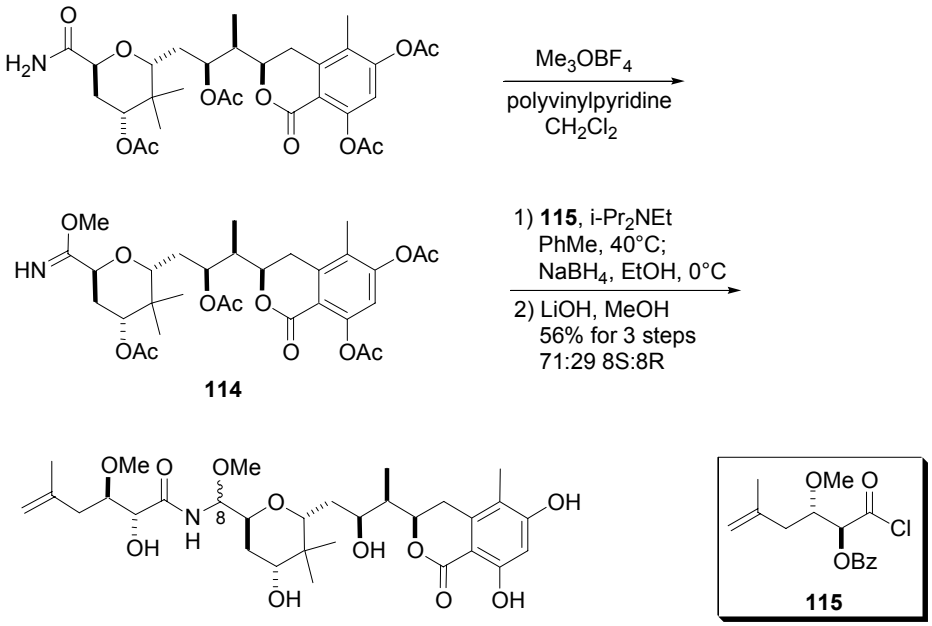


A key step here is the rhodium catalyzed hydroboration of the imidate **109**, which stereoselectively forms the desired C10 configuration with a much higher 10:1 diastereomeric ratio. Diastereoselectivity of the addition of methanol at C6 of **111** was very high as well (>20:1). The reduction of the C7 carbonyl of **111** was not as successful, yielding the desired product in only a 3:1 ratio.

Psymberin

De Brabander's group presented a coupling strategy for psymberin using the three fragments that were constructed previously.[28] The acid chloride **115** was prepared from protected psymberic acid using oxalyl chloride. Their approach is shown in Figure 46.

Figure 46 De Brabander's Psymberin Coupling

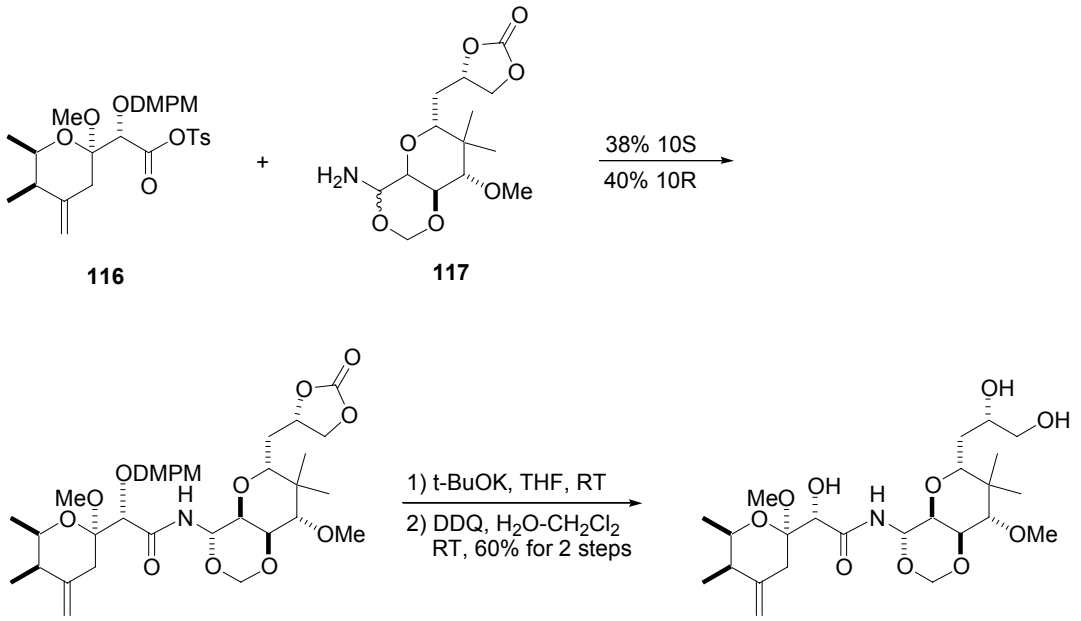


The final product of this synthesis was used to establish that psymberin and irciniastatin are identical compounds. A higher diastereoselectivity of the coupling reaction of **114** and **115** would be an improvement on this work.

Mycalamides

Kishi coupled a tosyl pederic acid derivative **116** with the amino trioxadecalin ring system **117** to make a mixture of diastereomers, which were converted to the desired epimer using a basic equilibrium as shown in Figure 47.[36]

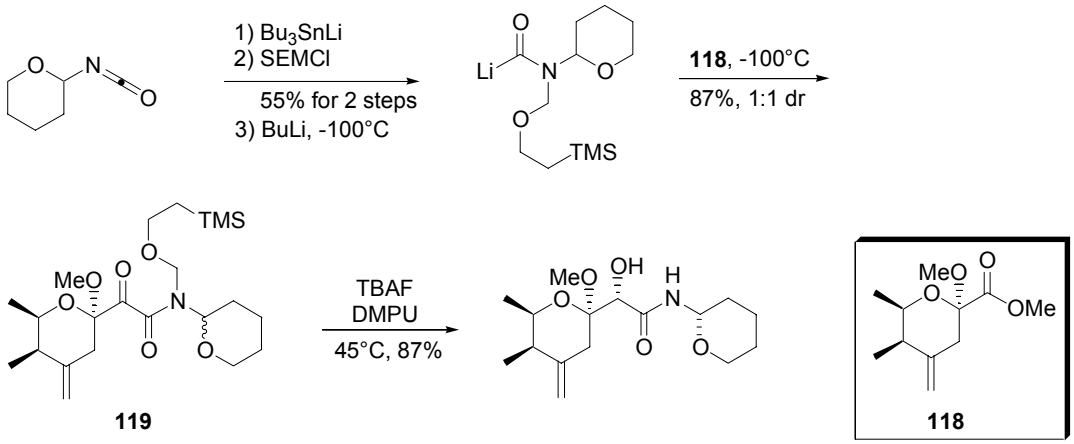
Figure 47 Kishi's Mycalamide Coupling



A milestone of this work was the establishment of the absolute configuration of mycalamides A and B using enantioselective synthesis (mycalamide B was synthesized using different protection of the side chain hydroxyls, as described in the paper). The 78% yield for this coupling was very good, and the approach was simple. However, there was very little diastereoselectivity for the reaction.

Hoffmann proposed a novel approach to coupling using an isocyanate analog of the trioxadecalin portion of the molecule as a model (Figure 48).[48] Unexpectedly, deprotection of the SEM group of **119** also reduced the C7 carbonyl to the hydroxyl group. The authors speculate that this reduction may be caused by a methoxylate anion generated during the deprotection.

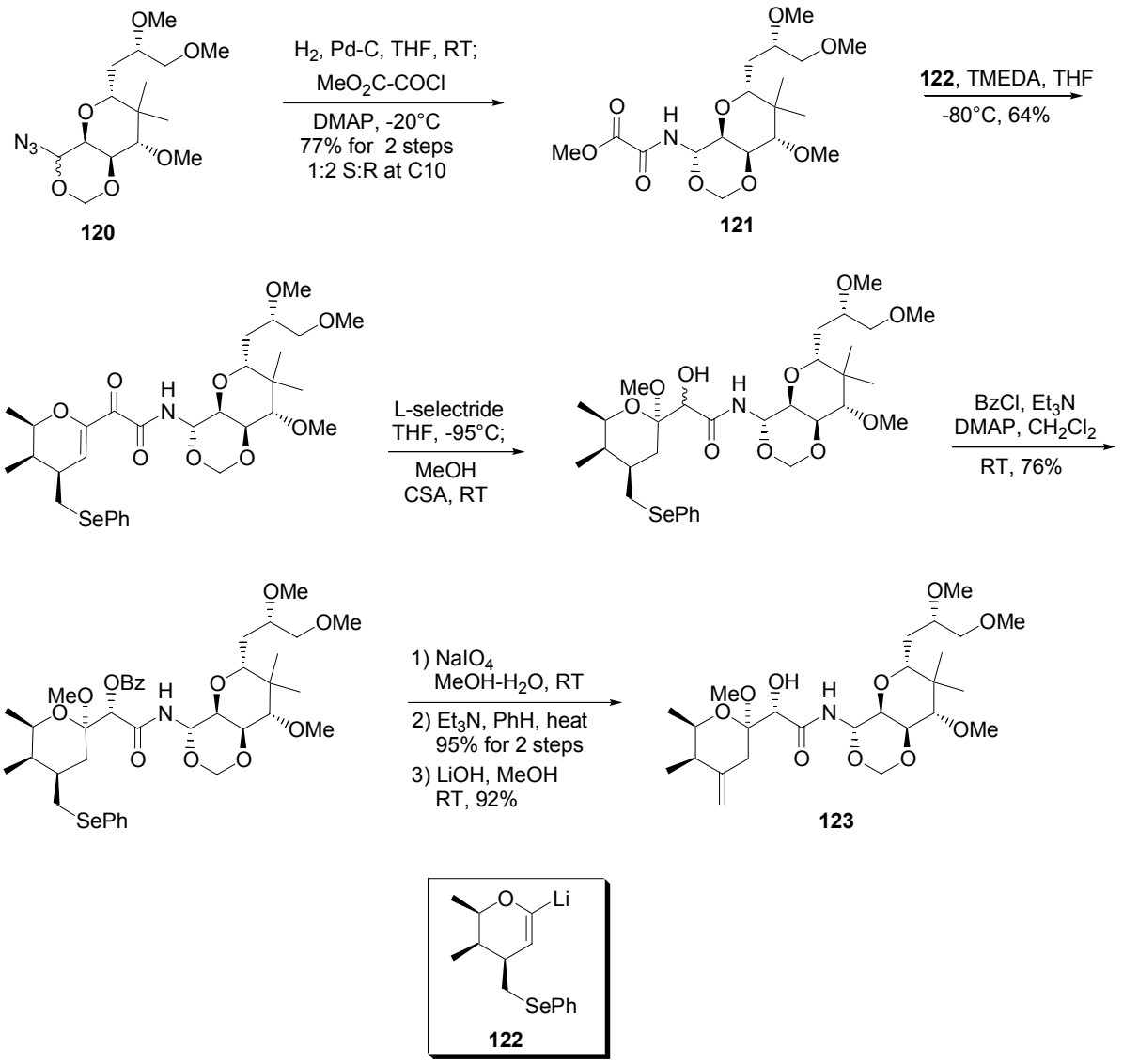
Figure 48 Hoffmann's Mycalamide Coupling



Although the 87% yield for this method is quite high, the 1:1 diastereoselectivity is poor.

As mentioned earlier, Kocienski used the metallated dihydropyran approach from his pederin synthesis to form 18-*o*-methyl mycalamide B.[40a] The azido trioxadecalin ring system **120** was converted to the N-acyl aminal **121** before coupling (Figure 49).

Figure 49 Kocienski's Mycalamide Coupling

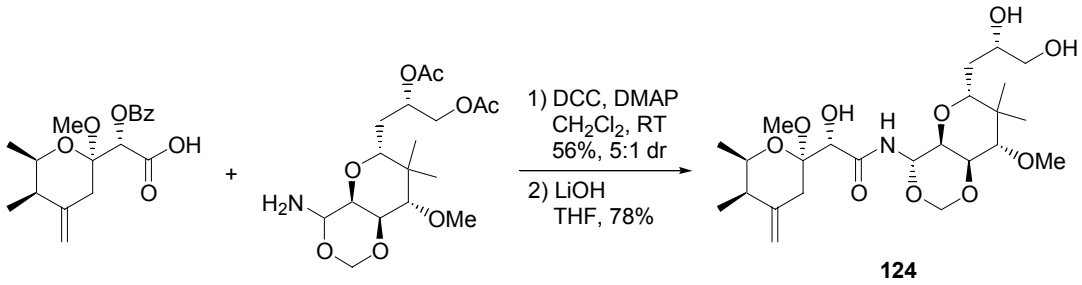


This C18 methylated analog **123** showed similar anti-tumor activity to the naturally occurring mycalamides A and B against various carcinoma cell lines.

Kocienski's work provided a unique approach to mycalamide coupling, and the yield is reasonably good. Due to the poor stereoselectivity of several steps in this reaction scheme, though, the four stereoisomers present following reduction of the C7 ketone required separation.

To couple the mycalamide fragments, Rawal used a classic DCC coupling method with DMAP as a catalyst (Figure 50).[26] The desired 10-(S) configuration of **124** was obtained in a 5:1 ratio.

Figure 50 Rawal's Mycalamide Coupling



This approach to mycalamide coupling is very appealing due to its simplicity and good stereoselectivity.

10. Analogs

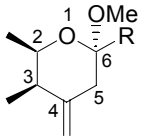
As can be seen from the examples above, synthesis of pederin and the mycalamides involves lengthy and challenging strategies. In an attempt to determine what regions of these molecules are responsible for pederin bioactivity, many synthetic analogs have been made by either treating the original compounds with various reagents or synthesizing them from simple starting materials. These experiments have provided some insight toward designing artificial analogs with the same anti-tumor and immunosuppressive properties as the pederin cytotoxins.

Munro et. al. systematically transformed the mycalamides into non-natural analogs using various reagents.[49] Among the treatments were acylation, alkylation, silylation, hydrolysis, oxidation, and reduction. These compounds were then tested for *in vitro* cytotoxicity against P388 leukemia cells, and relevant results are discussed below.

Additionally, analogs were synthesized by several researchers. These experiments also provided some insight into structure-activity relationships of the pederin family. For clarity, the results of this research will be discussed by position along the molecule.

The O1-C6 pederic acid portion of the molecule will be considered first (Figure 51).

Figure 51 O1-C6 Fragment of Pederin



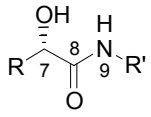
No variations of the C1 and C2 positions have been studied to date. As for the C3 position, Nakata et. al. concluded that the methyl substituent is not important in analogs of mycalamide;[50] however, a recent study by this group suggests that the C3 position may in fact be significant for biological effectiveness against HeLa cells.[51] When a C3-C4 double bond was introduced, the compound was 100 times less efficacious. The C4 exo-methylene group therefore shows some significance.

When reduced to the 4β-methyl analog, the cytotoxicity of mycalamide A more than doubled (no change was observed for mycalamide B). However, the α isomers were 4-8 times less active than the natural compounds.[49c]

No data have been collected for C5 variations, likely due to the lack of substitution at that position. Notably, conversion of the C6 acetal to a hydroxyl results in a 20-40 fold loss in effectiveness.

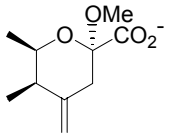
The C7-N9 amide portion connecting the left and right fragments was studied by several groups (Figure 52).

Figure 52 C7-N9 Fragment of Pederin

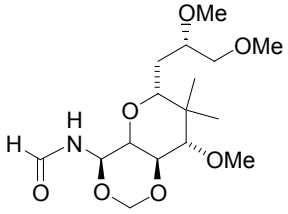


A consistent finding was that this α-hydroxy amido group is critical for cytotoxicity, as shown by the 1000 fold reduction in activity when the 7-hydroxy group and the amide nitrogen were methylated. The efficacy was reduced 100 fold when the 7-hydroxyl alone was methylated. Also, when the molecule was cleaved between C7 and C8, and each half of the molecule was tested separately, cytotoxicity was orders of magnitude less than the parent molecule (800 ng/mL for the left half **125**, 110 ng/mL for the right half **126**), suggesting that both segments shown in Figure 53 are involved in the bioactivity.

Figure 53 Pederin Fragments for Bioactivity Study



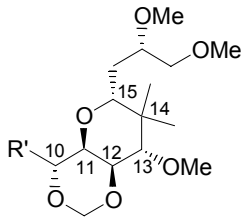
125



126

The C10-C15 portion of the trioxadecalin ring system, shown in Figure 54, also shows some notable findings.

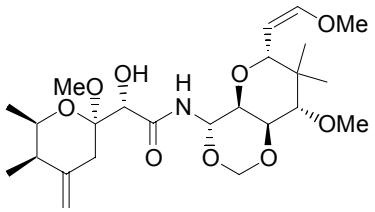
Figure 54 Trioxadecalin Ring System



The C10 acetal is important, as conversion to the hydroxy significantly reduced the IC_{50} value. The (S) configuration at C10 is also important for cytotoxicity, as the R epimer of mycalamide B showed a pronounced reduction in activity.

Modification of the side chain revealed some interesting data. Ruthenium catalyzed oxidation of mycalamide B introduced a C16-C17 double bond and simultaneous elimination of C18 yielded normycalamide B (Figure 55).

Figure 55 Normycalamide B



This product was a much less effective cytotoxin than mycalamide B.[49c] This 100 fold reduction in activity implies that the side chain may play a role in this molecule's bioactivity. However, the lower activity may be the result of the instability of this molecule.

A methoxy group at C17 is much better than a hydroxy substituent, as demonstrated by comparison of the natural mycalamides A and B. Oxidation of the side chain yielded various side products, including a terminal C17 aldehyde and terminal C17 alcohol. Both were more active than mycalamide A. Methylation of the 18-hydroxy improves the toxicity of mycalamide B to the same level as pederin.

Overall, the amide functionality appears to play the most important role in the biological activity of these compounds. These studies show promise for the design of a pederin analog that will ideally be as biologically active, yet be produced through a shorter, more efficient synthesis.

11. Conclusion

Since its discovery, pederin and its relatives have been the subject of a significant amount of research. Their unique cytotoxic properties have spurred a great deal of synthetic research of pederin, the mycalamides, and more recently psymberin.

Ultimately, cloning of the symbiont itself would be the most efficient method of producing these cytotoxins. Continued work may one day make this option a reality, but for now syntheses like those presented above are the most viable approach.

A great deal has been learned about the structure-property relationships through modification of the mycalamides and synthesis of analogs. Continued research of these molecules and their analogs may potentially lead to advancement in the treatment of cancer.

APPENDIX A

Chemical Acronyms

Am	amyl
BOC-ON	2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile
Bn	benzyl
Bz	benzoyl
m-CPBA	meta-chloroperbenzoic acid
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$(DHQ)_2PYR$	1,4-bis(dihydroquinidyl)benzo[g]phthalazine
DIAD	diisopropylazodicarboxylate
DIBALH	diisobutyl aluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMPM	3,4-dimethoxyphenylmethyl
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
Ipc	isopinocamphenyl
KHMDS	potassium hexamethyldisilazane
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
MPM	*p*-methoxyphenylmethyl
MS	molecular sieve
Ms	methanesulfonyl
NIS	N-iodosuccinimide
NMO	N-methylmorpholine-N-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PPTS	pyridinium p-toluenesulfonate

PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate
SEM	2-(trimethylsilyl)ethoxymethyl
TASF	tris-(diethylamino)sulfonium difluorotrimethyl silicate
TBAF	tetrabutylammonium fluoride
TBDMS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
TBHP	t-butylhydroperoxide
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilyl
Tr	trityl, triphenylmethyl
Troc	2,2,2-trichloroethoxycarbonyl
WSC	[1-(3-(dimethylamino)propyl)]-3-ethylcarbodiimide hydrochloride

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