Synthesis and Biological Activity of Penaresidins A and B, Penazetidine A, and Related Analogs

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Abstract. Since the first reports of their isolation, the penaresidins A and B together with penazetidine A and related analogs have attracted interest from the synthetic community for their unique structural features, specifically the highly functionalized azetidine core. This review provides a comprehensive overview of the biological activity of the penaresidins, penazetidine, and their analogs together with reported synthetic strategies developed since their isolation.

Key words total synthesis, azetidine, penaresidin, sphingolipid, marine sponge

1. Introduction

In 1991, Kobayashi and coworkers reported the isolation of two new alkaloids, penaresidin A (**1**) and B (**2**), from the methanol extract of the marine sponge *Penares sp.* collected in Unten Bay, Okinawa, Japan (Figure 1).[1] Structural elucidation was accomplished upon conversion to the corresponding tetraacetates, which revealed an unusual 2,3,4-trisubstituted azetidine core in the (2*S*, 3*R*, 4*S*) absolute configuration. Penaresidins A (**1**) and B (**2**) are considered members of the sphingolipid class of natural products. The sphingolipids are ubiquitous membrane constituents that are lipid mediators involved in signal transduction and cancer development. Sphingosine (**4**) is one of the most common sphingolipid natural products, which usually refer to compounds incorporating a (2*S*, 3*R*, 4*E*)-2-aminooctadec-4-ene-1,3-diol backbone. The penaresidins A (**1**) and B (**2**) formally represent sphingosin-analogs resulting upon hydroamination of the pendant primary amine to the 1,2-disubstituted alkene to form the characteristic azetidine core. Only three years later, in 1994, Crews and coworkers reported the isolation of penazetidine A (**3**) from the indo-pacific sponge, *Penares sollasi*. Similarly to penaresidin A (**1**) and B (**2**), penazetidine A is characterized by a (2*S*, 3*R*, 4*S*)-trisubstituted azetidine core while the configuration of the C-12 stereocenter remains undefined.

The highly functionalized azetidine core of the penaresidins A (**1**), B (**2**), and penazetidine A (**3**) combined with the potential

for important and desirable biological activities have spurred significant interest in this class of sphingolipids. Today, 3 total syntheses of penaresidin A (**1**) and 6 total syntheses of penaresidin B (**2**) have been reported. The synthesis of penazetidine A (**3**) has been completed once. Importantly, the invested interest in their biology has led to the syntheses of numerous analogs differing in the absolute configuration of the azetidine core and the structure of the pendant aliphatic chain. Notably, the majority of currently reported synthetic strategies towards the penaresidins relies on a nucleophilic substitution approach to build up the azetidine core. This review will provide a detailed overview of the penaresidin analogs synthesized as well as the reported biological activity of penaresidin A (**1**), B (**2**), penazetidine A (**3**), and their related analogs. The individual synthetic strategies will subsequently be discussed first from a general perspective, followed by a detailed description of the individual approaches to highlight the current state of the field.

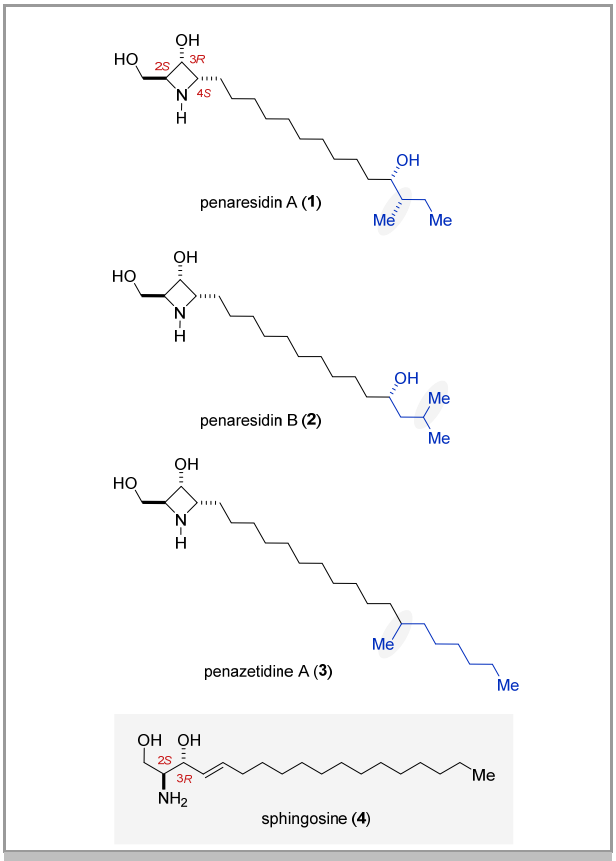
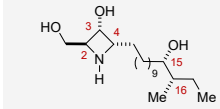


Figure 1. The naturally occurring azetidine-containing sphingolipids: penaresidin A (**1**), penaresidin B (**2**), and penazetidine A (**3**).

2. Biological Activity of Penaresidins A and B, Penazetidine A, and Related Analogs

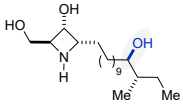
Upon the isolation of penaresidin A (**1**), Kobayashi and coworkers initiated biological evaluations, which showed potent activity as an ATPase-activator.[1] Notably, the tetraacetate derivatives synthesized for initial structural elucidation did not show activation of actomyosin ATPase. Recent studies have suggested penaresidin A (**1**) to function as a potential new biomarker to indicate monoresistance, multi-drug resistance and polyresistance of Mycobacterium tuberculosis (Figure 2).[2] It was suggested that together with other compounds identified as potential biomarkers, penaresidin A (**1**) could facilitate assessment of drug resistance in tuberculosis and significantly enhance the current diagnostic specificity. Related efforts focused on the discovery of new biomarkers for cancer. Specifically, the onset of cancer is accompanied by host systemic responses that are reflected in plasma proteins and metabolites, which hold great potential as early indicators for the development of cancer. Penaresidin A (**1**) was identified as a promising biomarker for cervical cancer, which is one of the main causes of death for women in developing countries.[3] To determine the relative stereochemistry of the natural product penaresidin A (**1**), Mori and coworkers synthesized its 15,16-anti (**5**) and 15,16-syn (**6**) isomers. In 1998 Lin and coworkers synthesised epimers **7** and **8** due to issues with cyclizing the azetidine core of all other isomers.[4] Similarly to penaresidin A (**1**), penaresidin B (**2**) was shown to be an ATPase-activator and a potential biomarker for serum metabolism in patients with cervical cancer. Additionally, penaresidin B (**2**) displayed cytotoxicity against murine lymphoma L1210 cells.[5] *Epi*-penaresidin B (**9**) was synthesized to aid in absolute structural determination of Penaresidin B (**2**).[6] Penazetidine A (**3**) was identified as a potent protein kinase C (PKC) inhibitor with an IC_{50} = 1 μM. Notably, penazetidine A (**3**) proved inactive against protein tyrosine kinase (PTK), which led Crews and coworkers to suggest that it may bind to the lipid-binding regulatory site of PKC instead of the ATP binding site.[7] The PKC family of enzymes is known to mediate signal transduction across membranes. Additionally, these enzymes impact the regulation of cell proliferation and gene expression. Inhibitors of PKC enzymes are thus considered important target structures for new cancer therapeutics. Penazetidine A (**3**) also proved to have in vitro cytotoxicity against human and murine cell lines, including A549, HT-29, B16/F10, and P388. *Epi*-penazetidine A (**10**) was synthesized to investigate potential bioactivity.[8] In efforts to investigate the structure-activity relationships of stereoisomers of penaresidin B, Kobayashi and coworkers synthesized and evaluated six stereoisomers (**11-16**).[5] Importantly, their results suggest that the configuration of the 2,3,4-trisubstituted azetidine core significantly impacts the exhibited cytotoxicity and antibacterial activity. Specifically, stereoisomers **11-16** were evaluated relying on the murine lymphoma L1210 (lymphoma) cell line, in addition to the human solid tumor cell lines KB (carcinoma), A549 (lung), and HT29 (colon). The (2*S*, 3*R*, 4*S*) (**11**) and (2*S*, 3*R*, 4*R*) (**12**) stereoisomers showed potent cytotoxicity against A549 and HT29 cells. Investigation of their antimicrobial activities against bacteria and fungi revealed antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*, *Micrococcus luteus*,



penaresidin A (**1**)

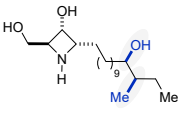
(2*S*,3*R*,4*S*)

actomyosin ATPase-activating activity[1]
potential biomarker to indicate mono-resistance, multi-drug resistance and polyresistance in Mycobacterium tuberculosis[2]
potential bionarker of serum metabolism in patients with cervical cancer[3]



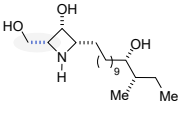
15-*epi*-penaresidin A (**5**)

(2*S*,3*R*,4*S*)



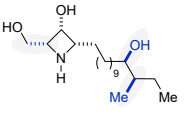
15,16-di-*epi*-penaresidin A (**6**)

(2*S*,3*R*,4*S*)



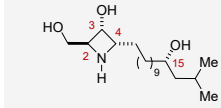
2-*epi*-penaresidin A (**7**)

(2*R*,3*R*,4*S*)



2,15,16-tri-*epi*-penaresidin A (**8**)

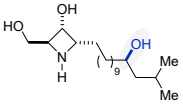
(2*R*,3*R*,4*S*)



penaresidin B (**2**)

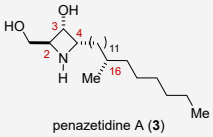
(2*S*,3*R*,4*S*)

actomyosin ATPase-activating activity
cytotoxicity against lymphoma L1210 cells
potential bionarker of serum metabolism in patients with cervical cancer[5]
L1210: IC_{50} = 2.9 μg/mL
KB: IC_{50} = >10 μg/mL
A549: IC_{50} = >2 μg/mL
HT529: IC_{50} = >2 μg/mL



15-*epi*-penaresidin B (**9**)

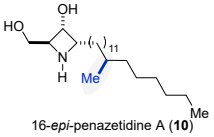
(2*S*,3*R*,4*S*)



penazetidine A (**3**)

(2*S*,3*R*,4*S*)

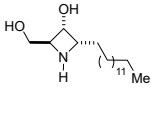
protein kinase inhibitor
in vitro cytotoxicity against human and murine cell lines[7]:
A549: IC_{50} = 0.099 μg/mL
HT-29: IC_{50} = 0.13 μg/mL
B16/F10: IC_{50} = 0.079 μg/mL
P388: IC_{50} = 0.22 μg/mL



16-*epi*-penazetidine A (**10**)

(2*S*,3*R*,4*S*)

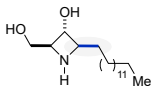
protein kinase inhibitor[7]



11

(2*S*,3*R*,4*S*)

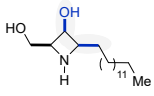
cytotoxicity against human lung (A549) and colon (HT29) cancer cells
L1210: IC_{50} = 4.5 μg/mL
KB: IC_{50} = 3.4 μg/mL
A549: IC_{50} = 0.34 μg/mL
HT529: IC_{50} = 0.56 μg/mL
antibacterial activity against Gram-positive bacteria (Bacillus subtilis, Micrococcus luteus, Staphylococcus aureus)[5]



12

(2*S*,3*R*,4*R*)

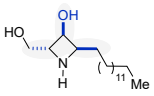
cytotoxicity against human lung (A549) and colon (HT29) cancer cells
L1210: IC_{50} = 1.6 μg/mL
KB: IC_{50} = 3.2 μg/mL
A549: IC_{50} = 0.22 μg/mL
HT529: IC_{50} = 0.17 μg/mL
antibacterial activity against Gram-positive bacteria and the Gram-negative bacterium Escherichia coli.[5]



13

(2*S*,3*S*,4*R*)

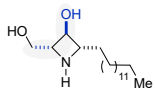
L1210: IC_{50} = >10 μg/mL
KB: IC_{50} = >10 μg/mL
A549: IC_{50} = 1.38 μg/mL
HT529: IC_{50} = 1.65 μg/mL[5]



14

(2*R*,3*S*,4*R*)

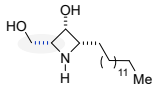
L1210: IC_{50} = 4.5 μg/mL
KB: IC_{50} = 6 μg/mL
A549: IC_{50} = >2 μg/mL
HT529: IC_{50} = 1.23 μg/mL
antibacterial activity against Gram-positive bacteria (Bacillus subtilis, Micrococcus luteus, Staphylococcus aureus)[5]



15

(2*R*,3*S*,4*S*)

L1210: IC_{50} = 4.5 μg/mL
KB: IC_{50} = >10 μg/mL
A549: IC_{50} = 1.97 μg/mL
HT529: IC_{50} = 0.79 μg/mL
antibacterial activity against Gram-positive bacteria (Bacillus subtilis, Micrococcus luteus, Staphylococcus aureus)[5]

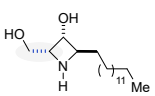


16

(2*R*,3*R*,4*S*)

L1210: IC_{50} = 7.5 μg/mL
KB: IC_{50} = >10 μg/mL
A549: IC_{50} = >2 μg/mL
HT529: IC_{50} = >2 μg/mL[5]

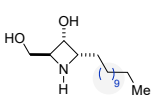
BLM: IC_{50} = 8.65 μmol/L
MCF-7: IC_{50} = 4.26 μmol/L
HCT-116: IC_{50} = 28.16 μmol/L
HeLa: IC_{50} = 8.66 μmol/L
Jurkat: IC_{50} = 7.37 μmol/L[10]



17

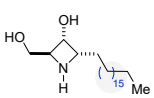
(2*R*,3*R*,4*R*)

BLM: IC_{50} = 8.45 μmol/L
MCF-7: IC_{50} = 9.05 μmol/L
HCT-116: IC_{50} = 5.74 μmol/L
HeLa: IC_{50} = 6.53 μmol/L
Jurkat: IC_{50} = 2.53 μmol/L[9]



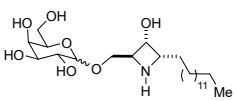
18

(2*S*,3*R*,4*S*)



19

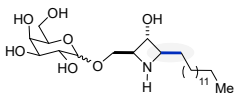
(2*S*,3*R*,4*S*)



α-**20a**
β-**20b**

(2*S*,3*R*,4*S*)

α-**20a**
cytokine-inducing activity in mouse killer T-cells[9]



α-**21a**
β-**21b**

(2*S*,3*R*,4*R*)

Figure 2. Bioactivity for penaresidins A and B, penazetidine A, and related analogs.[9]

Staphylococcus aureus) for all except the (2*S*, 3*S*, 4*R*) (**13**)- and (2*R*, 3*R*, 4*S*) (**16**)- stereoisomer. Notably, only the (2*S*, 3*R*, 4*R*) (**11**) showed antibacterial activity against Gram-negative bacterium (*Escherichia coli*). Notably, none of these stereoisomers showed antifungal activity. The (2*R*, 3*R*, 4*R*) (**17**)-stereoisomer, synthesized by Bodnár and coworkers (alongside with (2*R*, 3*R*, 4*S*) (**16**)), were screened for cytotoxicity against five human cell lines: BLM (melanoma), MCF-7 (adenocarcinoma), HCT-116 (carcinoma), HeLa (adenocarcinoma), and Jurkat (leukemia). (2*R*, 3*R*, 4*S*) (**16**) and (2*R*, 3*R*, 4*R*) (**17**) were significantly more active on leukemia cells than cisplatin. [10] Kamikawa and coworkers synthesized **18** to study its novel isomerization through acetylation. Mori and coworkers synthesized four distinct penaresidin analogs **20a** and **b** as well as **21a** and **b** bearing a glucose substituent in the 2-position. These compounds were designed as analogs of an α-*D*-galactosyl ceramide KRN7000 as potential inducers of cytokine production by mouse NKT cells. Upon biological evaluation of these structures, 19a was shown to induce the production of IFN-γ, IL-4, and IL-13 and proved to possess high cytokine inducing activity.

3. Retrosynthetic Analysis

The synthesis of penaresidin and various side chain analogs has been targeted by several groups since the original isolation of Penaresidins A and B in 1991.[1] Several unique strategies have been employed, each seeking to improve upon the last via higher overall yields, shorter step counts, or access to previously unobtained stereoisomers. The central motif which all routes revolve around, however, is the 2-amino-1,3,4-triol scaffold (**29**) that builds the stereochemical foundation for the azetidine core of the molecule (with the exception of Yoda's 2002 work which uses the 4-amino-1,2,3-triol); nonetheless a 2,4 relationship between an amine and a leaving group is present (Fig. 3). This four-heteroatom relationship not only introduces the alcohol groups and their corresponding stereocenters present on the final Penaresidin structure but sets the stage for a key azetidine ring formation. Introduction of these heteroatoms from an early stage could be resultant of prudently chosen starting materials, which are classified based on their number of heteroatoms as shown in Figure 3. This figure contains an analysis of common starting materials among all 17 syntheses of penaresidin and its related analogs included in this review, grouping them by their number of relevant included heteroatoms. While the identity of an oxygen may change to nitrogen over the course of the synthesis, the position of each heteroatom is retained and leveraged towards the desired molecule.

Starting materials with all 4 required heteroatoms for a fully functionalized azetidine ring were sugar-derived, rising from a protected, commercially available carbohydrate. Six groups employed this sugar strategy of early heteroatom incorporation, three of which published more recently (within the last ten years). Garner's aldehyde (**25**) was another common starting place, used in five syntheses and carrying forward 3 heteroatoms to the final product. Alternatively, Yoda's 1997 synthesis used a lactam derived from *D*-glutamic acid (**24**) to similarly start with 3 incorporated heteroatoms.[11] The only example of a 2-heteroatom containing starting material was demonstrated by DuBois in 2020, using a vinyl-1,3-dioxolane (**26**).[12] Three groups used an alcohol or alcohol derivative, with oxygen as the single incorporated heteroatom, as a starting material. These were often transformed into a chiral epoxide, a common intermediate present in more than half of all syntheses.

Importantly, the unifying step for all of these reported syntheses relies on a cyclization event via nucleophilic substitution where an unprotected amine takes advantage of an activated C-O bond (or C-Br in the case of DuBois) and displaces an oxygen atom to form a new C-N bond. In most cases, the oxygen atom in the 4-position of **29** is protected with a sulfonate group or activated under Mitsunobu-type conditions preceding nucleophilic substitution facilitated by the nitrogen atom in the 2-position. This cyclization is often the penultimate step in the synthesis, which would be followed by deprotection to afford the desired final product, to avoid concerns of azetidine ring preservation under harsher conditions throughout the synthesis. The required 2-amino-1,3,4-triol scaffold (**29**) for the cyclization is handled in one of two ways across the considered syntheses. In the first scenario, it is assembled in a traditional manner across the synthesis, where the long pendant chain of the molecule is introduced at an early stage through an epoxide opening/nucleophilic introduction of an alkyne or olefination. This strategy was popular in older syntheses of penaresidins, before and up to the early 2000's. Alternatively, a convergent approach was developed that requires the independent synthesis of the azetidine core to be subsequently joined with a long-chain olefin fragment and deprotection to access the final product. First achieved by Raghavan in 2009, this set a standard that most syntheses followed going forward.[13] The decision to couple two fragments means fewer total stereocenters to focus on at once and coincided with shorter steps counts.

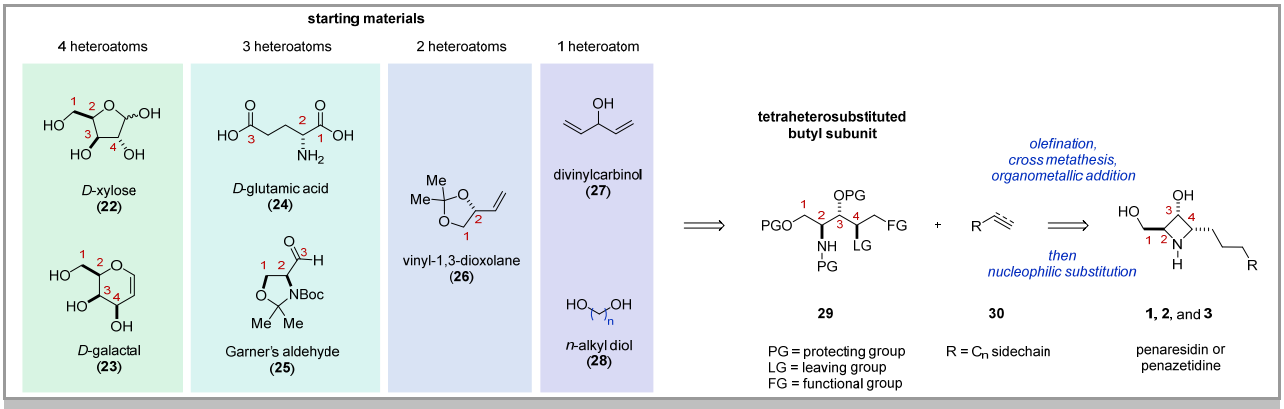


Figure 3. Retrosynthetic analysis organized by heteroatom configuration in common starting materials.

4. Penaresidin A Analog (Kamikawa, 1995)

In 1995 Kamikawa and co-workers disclosed the synthesis of a straight-chain penaresidin A analog **18** (Figure 4).[14] Although developed *in absentia* of a known biosynthetic route, the authors proposed that the azetidine product could be accessed via an intramolecular S_N2 cyclization of phytosphingosine **31**. This intermediate was traced back via methylation and Grignard addition to aldehyde **33** which can be derived from commercially available *D-xylose* **22**.

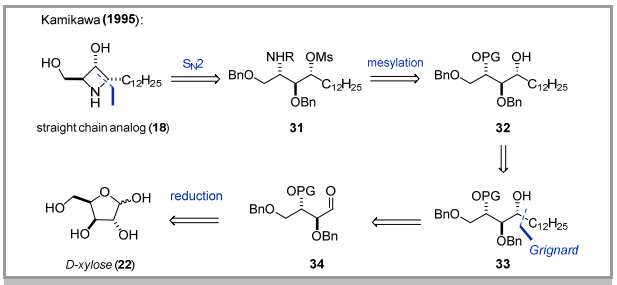


Figure 4. Kamikawa's 1995 retrosynthesis of straight chain analog **18**.

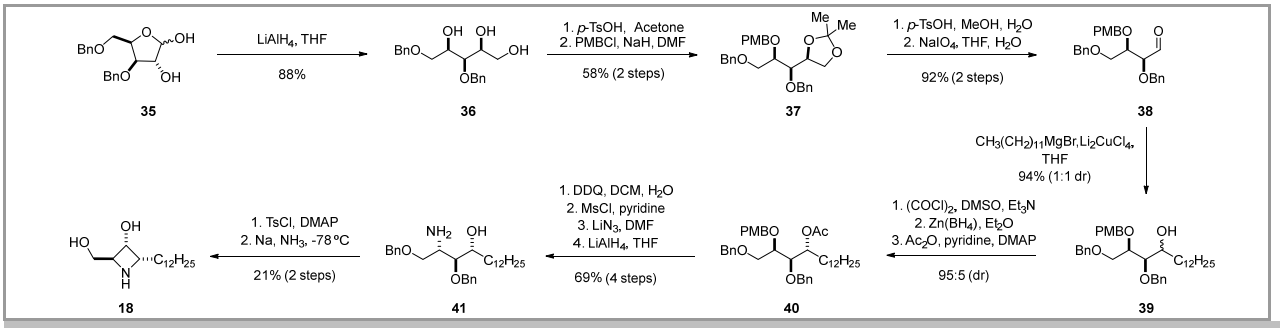


Figure 5. Kamikawa's forward synthesis of **18** starting from Benzylated D-Xylose derivative **35**.

In the forward synthetic direction the dibenzyl *D-Xylose* derivative was subjected to Lithium Aluminum Hydride reduction to afford the acyclic triol **36** (Figure 5). Subsequent selective acetylation and PMB protection gave the protected intermediate **37** which was then hydrolyzed and exposed to sodium periodate to furnish aldehyde **38**. Upon addition of a dilithium tetracuperate, the aldehyde was converted to alcohol **39** in a 1:1 diastereomeric ratio. The mixture of diastereomers was then resolved via Swern oxidation and a Zinc borohydride mediated selective reduction. The reduced product was subsequently acylated to give **40** in 95:5 diastereomeric purity. Selective DDQ reduction of the PMB group allowed for a mesylation and azidation sequence that upon a Lithium Aluminum Hydride rection yielded amino alcohol **41** in 69% over four steps. Tosylation of the alcohol and deprotonation of the free amine **41** provided access to the azetidine core, which underwent a global deprotection to afford the straight-chain penaresidin A analog **18** in 6.4% overall yield over 15 steps.[14]

5. 15-*epi*-Penaresidin A (Mori, 1995)

Prompted by Kamikawa's synthesis of the straight chain analog, Kenji Mori's group sought to synthesize a set of enantiopure isomers of penaresidin A in order to confirm the natural products' absolute configuration. [15]

The group postulated that the configuration of the azetidine would be 2*S*, 3*R*, and 4*S* given its possible biosynthetic relationship to the phytosphingosines. The cyclic product was envisioned to arise from the cyclization of 2-amino,1,3,4-triol **42** (Figure 6). It was then noticed that mesylate **42** could be accessed from the directed epoxidation of alkene **44** and epoxide-opening of **43**. **44** was realized to be a product of a nucleophilic coupling (followed by reduction and production) between Garner's Aldehyde (**25**) and protected alkyne **48** (arising from epoxide **46**). The configuration of **46** could be attributed to that of commercially available *L*-isoleucine or (*Z*)-2-penten-1-ol .

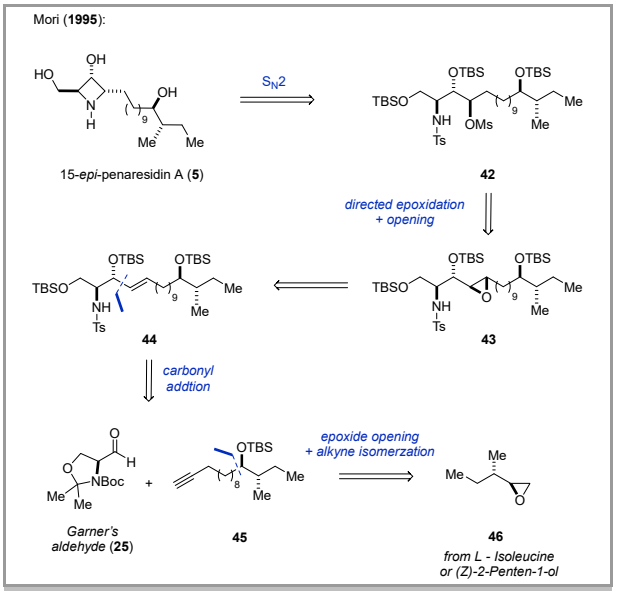


Figure 6. Mori's 1995 retrosynthetic strategy for 15-*epi*-penaresidin A (**5**).

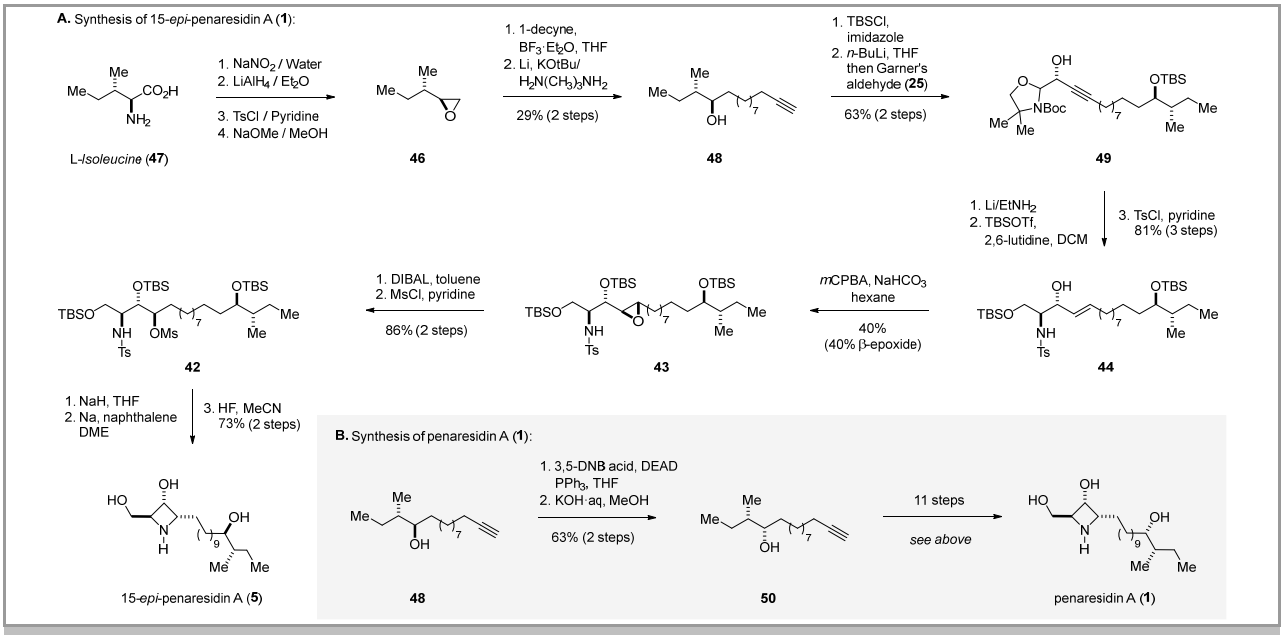


Figure 7. Mori's 1995 forward synthesis of 15-*epi*-penaresidin A (**5**).

The forward synthesis began with the deamination, reduction, tosylation, and epoxidation of *L*-isoleucine (**47**) to form enantiopure epoxide **46** (Figure 7). Upon treatment with 1-decyne and $BF_3{\cdot}Et_2O$ as Lewis Acid, the epoxide was opened and then subjected to the acetylene zipper reaction to afford terminal alkyne **48.** The free alcohol of alkyne **48** was then TBS protected. The protected alkyne was subsequently subjected to a directed nucleophilic coupling with Garner's aldehyde to result in a diasteroselective mixture of alcohol **49**. Exposure to lithium and ethylamine both reduced the alkyne to the corresponding alkene and deprotected the oxazolidine to afford both a free alcohol and amine which were subsequently protected to result in alkene **44**. With the alkene in hand, α-hydroxy-directed epoxidation was the subject of much optimization. Ultimately, it was conceded that *m*CPBA was best, giving rise to the desired β-epoxide **43** in 40% yield. DIBAL reduction of the epoxide and mesylation of the resultant alcohol gave cyclization precursor **42** which was then cyclized in the presence of NaH, subjected to deprotection with sodium naphthalide and HF to give the C15 epimer **5**, ending the sequence in 176 steps with a 3.7% overall yield. The group having been interested in the synthesis of both C15 isomers realized that Mitsunobu inversion of **48** could furnish alcohol **50** which when converted through the same route arrived at penaresidin A **1**, over 19 steps in 2.3% yield.

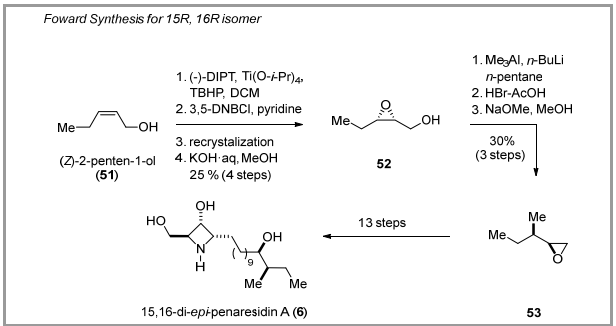


Figure 8. Mori's 1995 synthesis of the 15,16 epimer of penaresidin A (**6**).

In a final effort to elucidate the configuration of the natural product, the C15, C16-isomer of **1** was synthesized (Figure 8). This synthesis began with (*Z*)-2-penten-1-ol (**51**) which underwent Sharpless Asymmetric Epoxidation, esterification with 3,5- dinitro benzoyl chloride, recrystallization, and hydrolysis to give enantiopure epoxide **52**. With **52** in hand a methylation, dehydration and epoxidation sequence was conducted to result in epoxide **53**, which was used in the previously pioneered route to arrive at 15,16-di-*epi*-penaresidin A **6** in 20 steps with a 0.31% overall yield.

It is worth noting that upon publication the absolute configuration of the natural product was not known so the group asserted that the natural product was either **6** or **1**, although despite all efforts they were unfortunately unable to determine which one. [15]

6. 16-*epi*-Penaresidin A (Mori, 1996)

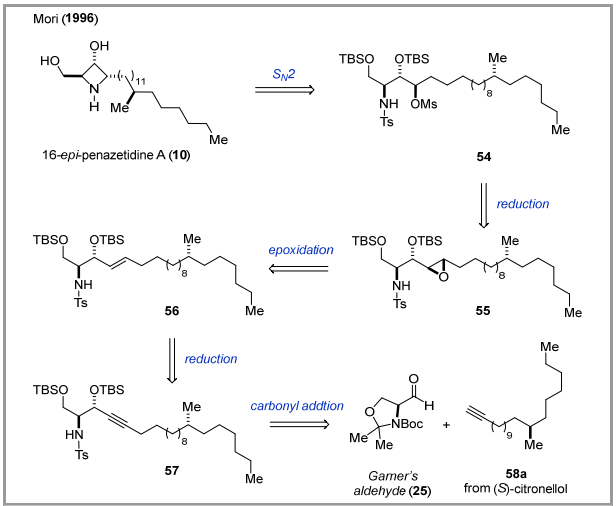


Figure 9. Mori's 1996 retrosynthetic strategy for 16-epi-penazetidine A (**10**) starting from **25** and **58a.**

In 1996, the laboratory of Kenji Mori undertook the synthesis of both enantiomers of penazetine A in part to determine the absolute configuration of the natural product.[8] However, despite successfully synthesizing both isomers, the configuration of the natural product remained elusive.

From a retrosynthetic standpoint, the alkaloid was first traced back to the phytosphingosine **54,** which is accessible upon a reduction, selective epoxidation, and reduction sequence arriving, at alkyne **57** (Figure 9). Alkyne **57** was recognized to be accessible from the addition of **58a** (derived from (*S*)-citronellol) to Garners aldehyde **25**. It was recognized that this strategy could provide parallel access to both 16-C epimers of penazetidine A given that the 16-C stereocenter is dictated by the chirality of the commercial starting material.

The forward synthesis began with (*S*)-citronellol (**59a**), which upon tosylation and cuperate addition gave alkene **60** in 91% yield (Figure 10). The resultant alkene was then epoxidized and cleaved with sodium periodate to reveal aldehyde **62**. The aldehyde was then coupled to 1-lithium nonynide to give a diastereomeric mixture of alcohol **63**, which then underwent an acetylene zipper reaction to afford terminal alkyne **64**. The diastereomeric mixture was resolved via tosylation and reduction with super hydride to form alkyne **58a**. With this acyclic fragment in hand, a nucleophilic addition to Garners aldehyde (**25**) resulted in the incorporation of three of the requisite heteroatoms for the construction of the azetidine core. Exposure of alkyne **57** to lithium and ethylamine allowed for a dual reduction and global deprotection. The deprotected alcohol was then TBS protected and the free amine was subsequently tosylated. Alkene **56** was the subject of intense optimization efforts. Ultimately, *m*CPBA was identified as the reagent resulting in superior selectivity of 1:1.2 for the desired diastereomer. With epoxide **67** in hand, the authors were able to introduce the final element of the 2-amino-1,3,4 triol motif via diisobutylaluminium hydride reduction and mesylation arriving at mesylate **54**. Upon treatment with sodium hydride, **64** underwent an intramolecular S_N2 cyclization to give the azetidine core which when deprotected with sodium naphthalenide and HF was found to give the C16 epimer of the natural product, **10**, in 19 steps overall with a total yield of 5.1%. Similarly, the natural product was synthesized using an analogous sequence wherein the enantiomer of citronellol **57b** was used as the starting material to arrive at alkyne **58b** which was subsequently added to Garner's aldehyde to give **65**. This intermediate was then carried through the previously developed synthetic sequence to yield penazetidine A (**3**) in 19 steps in 5.1% yield as well.[8]

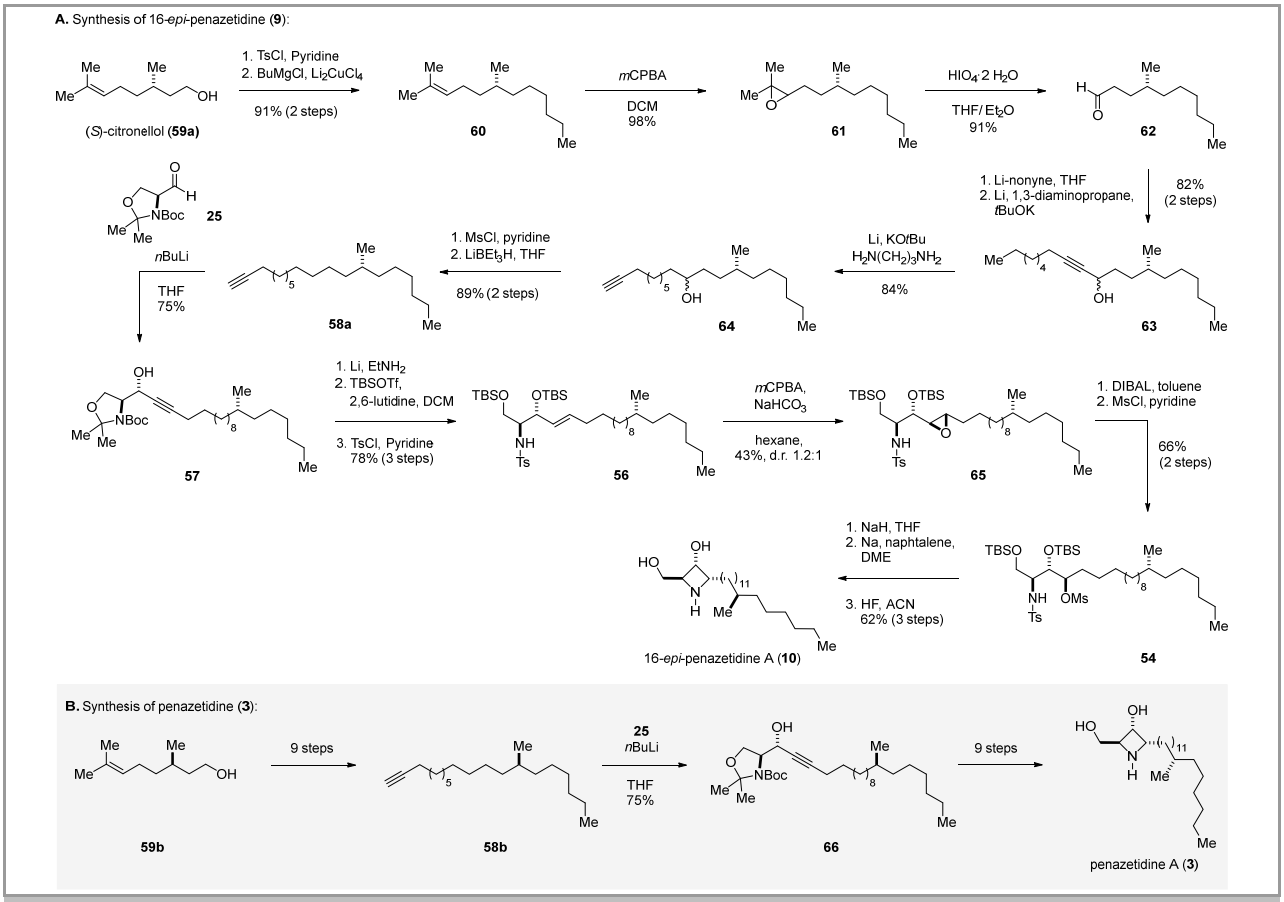


Figure 10. Mori's 1996 forward synthesis of both the 16-epi (**10**) and classical isomer (**3**) of penazetidine A.

7. Penaresidin B (Yoda, 1997)

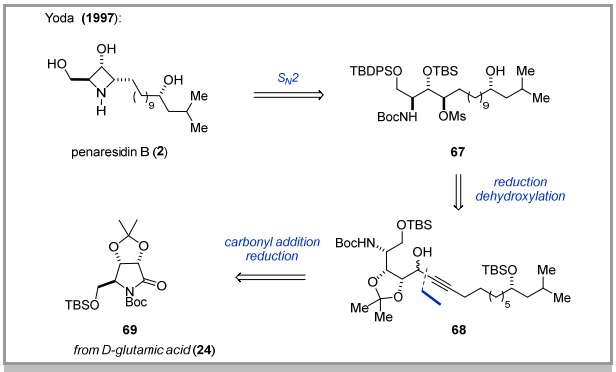


Figure 11. Yoda's retrosynthetic strategy for penaresidin B (**2**) starting from *D-glutamic acid derivative* **24.**

Yoda's 1997 synthesis of penaresidin B was completed in the wake of the stereochemical assignment of the natural product, allowing the group to target a single enantiomer.[11] Like the previous synthesis, the first disconnection was made to parse apart the azetidine core to a 2-amino-1,3,4-triol, **67** (Figure 11). This intermediate was envisioned to arrive from alkyne **68** via a reduction and deoxygenation. Ketal **68** was postulated to result upon nucleophilic coupling of lactam **69** with an alkyne fragment that had been previously synthesized by Mori from *D*-Leucine. Finally, lactam **69** is accessible relying on *D*-glutamic acid as a chiral pool reagent.

The forward synthesis of the core fragment began with the conversion of *D*-glutamic acid, **24**, to the di-acid chloride, which underwent spontaneous lactamization (Figure 12). The appended acid chloride was then reduced with $NaBH_4$ to give the free alcohol **70**. Protection of the lactam with TBSCl and Boc anhydride resulted in the protected lactam **71**. Selenoxide elimination was then performed followed by dihydroxylation and ketal formation to yield pyrrolidine partner **69**.

Synthesis of the penaresidin B side chain relied on *D*-leucine **72a** which upon aziridination, displacement, THP protection, and reduction resulted in the free alcohol **73**. Conversion of 73 to the chiral epoxide 74a relied on a tosylation, THP-ether deprotection, and final base-mediated cyclization sequence. The addition of 1-decyne (**62**) in the presence of *n*-butyl lithium, followed by an acetylene zipper reaction and TBS protection of the free alcohol, afforded the enantiopure alkyne **75**.

Both chiral fragments were subsequently coupled through a nucleophilic addition to the pyrrolidine followed by a reduction to give a diastereomeric mixture of alcohol **68**. Thioimidazolide formation and radical deoxygenation of the diastereomeric mixture of alkyne **68** formed acetal **76** as a single diastereomer. A global deprotection and reprotection were then performed, wherein the ketal was liberated revealing a set of secondary alcohols, one of which was protected as a TBS ether, and the primary alcohol was reprotected as a TBDPS ether to form the free secondary alcohol **77**. With this fully functionalized intermediate in hand, the free alcohol was mesylated and treated with sodium hydride to induce azetidine formation in 58% yield over the two-step sequence. The cyclized product was then deprotected to give rise to the natural product, penaresidin B (**2**), in 20 steps (longest linear sequence) and 1.9% total yield.[11]

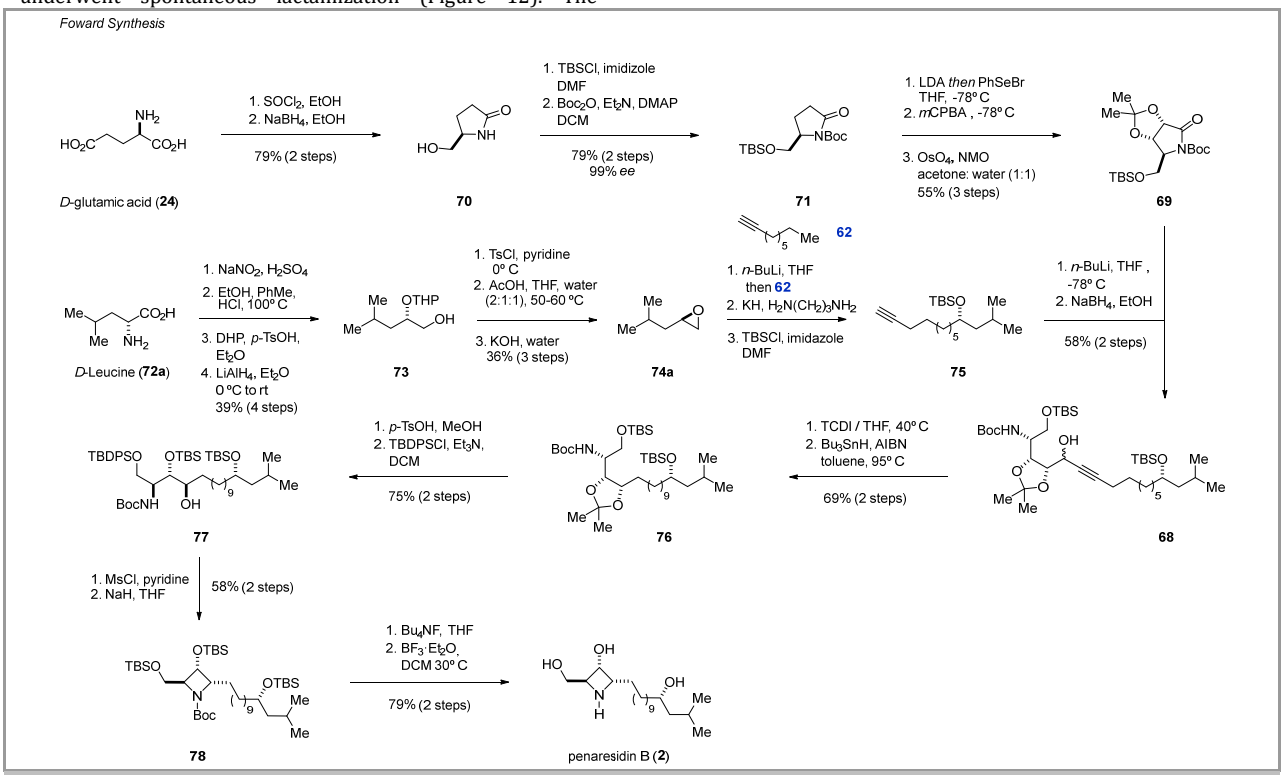


Figure 12. Yoda's forward synthesis for penaresidin B (**2**).

8. 15-*epi*-Penaresidin B and Penaresidin B (Mori, 1997)

Mori's 1997 synthesis of penaresidin B was presented along side a reprint of his 1995 synthesis.[6] The two syntheses share a retrosynthetic analysis for the construction of the 2-amino-1,3,4-triol motif and differ only in the construction of the side chain. The retrosynthesis relied on the initial opening of the azetidine to reveal the requisite 2-amino-1,3,4-triol, **79**, which was further taken back to a 1,2-directed epoxidation and subsequent epoxide opening (Figure 13). Epoxide **80** was further derived back to alkene **81**, which was predicted to be the product of a nucleophilic carbonyl addition and reduction. The alkyne partner **82a,** was envisioned to be elaborated from *L*-leucine, while the aldehyde fragment would stem from Garner's aldehyde (**25**).

The groups foyer into the synthesis of *epi*-penaresidin B, **8**, relied on *L*-leucine (**72b**) (Figure 41). Upon initial amine oxidation and acid reduction, the primary alcohol was tosylated and subjected to basic conditions to facilitate the formation of epoxide **74b**. Epoxide opening was achieved with 1-decyne and *n*-butyllithium, followed by an acetylene zipper reaction to give the terminal alkyne **82a**.[16] The resultant free alcohol was TBS protected prior to treatment with *n*-butyl lithium to facilitate diastereoselective acetylide addition to Garners aldehyde (**25**). Tandem alkyne reduction and oxazolidine deprotection provided alkene **81**. α-Hydroxy directed epoxidation with *m*CPBA gave 40% yield of the desired β-epoxide, which despite intense efforts could not be increased. The desired isomer was taken forward and regioselective epoxide opening followed by mesylation gave rise to mesylate **79**. The 2-amino-1,3,4,-triol was then cyclized upon exposure to sodium hydride and deprotected to give the 15-C epimer of penaresidin B in 17 steps with a 3.8% overall yield. After the analysis of NMR spectra wherein it was discerned that the product did not have the same configuration as the isolated natural product, the synthesis was revised starting from alkyne **82a**. Upon Mitsunobu inversion of the secondary alcohol in **82a** and hydrolysis of the 3,5-dinitrobenzoate, the epimerized alcohol **82b** was obtained and could be carried through the aforementioned sequence to give rise to the natural product, penaresidin B (**2**), in 19 steps overall with a total yield of 2.4%. [6]

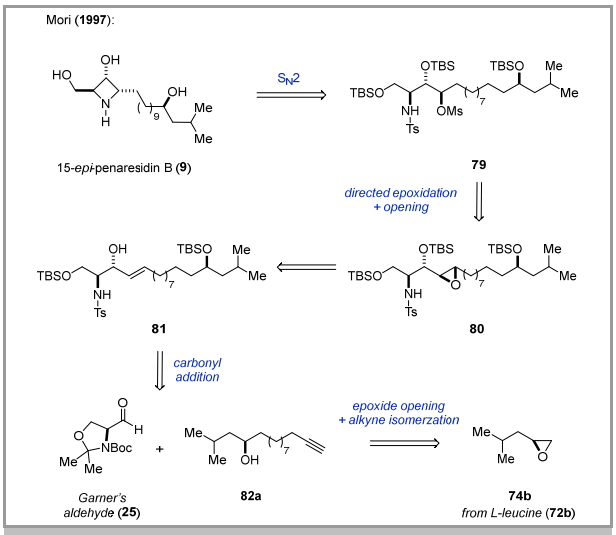


Figure 13. Mori's 1997 retrosynthetic analysis of 15-*epi*-penaresidin B (**9**) starting from *L-leucine* (**72b**).

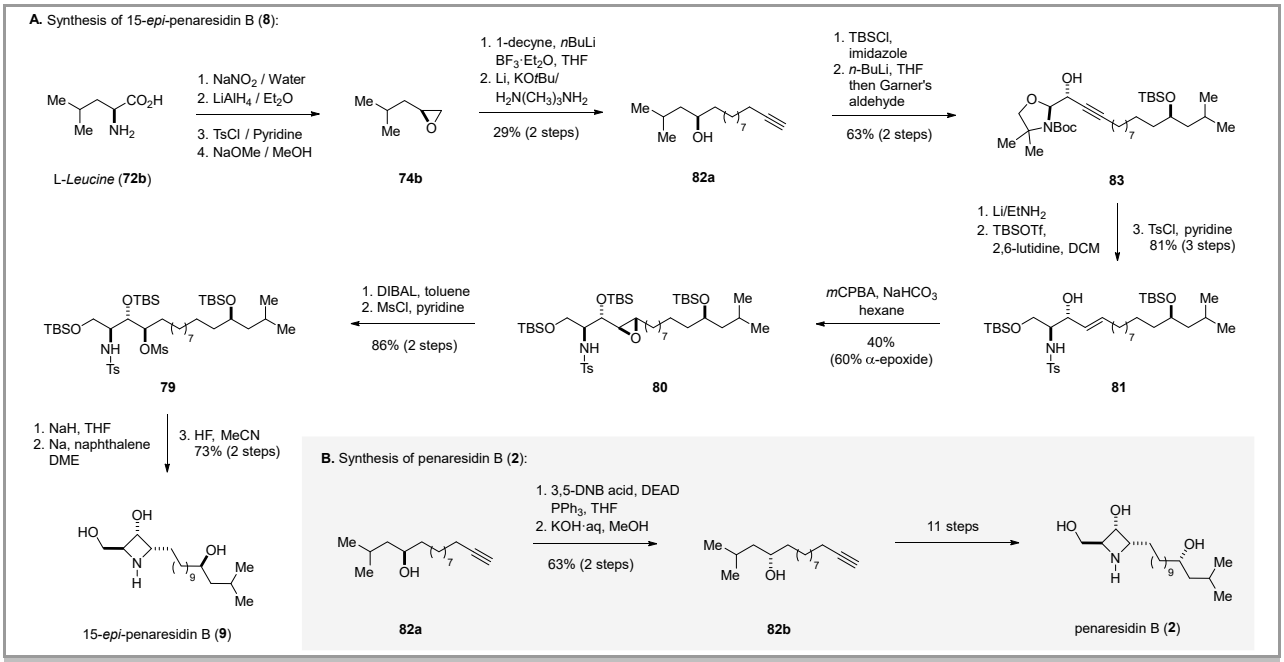


Figure 14. Mori's 1997 forward synthesis of both 15-*epi*-penaresidin B (**9**) and classical penaresidin B (**2**).

9. Penaresidin A and 16-*nor*-Penazetidine A (Knapp, 1997)

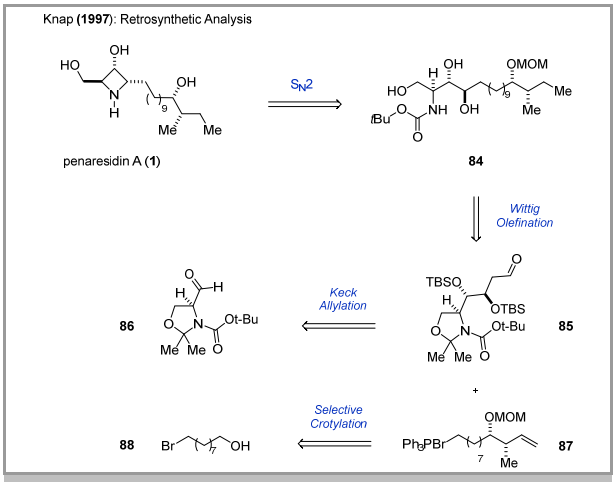


Figure 15. Knapp's retrosynthetic strategy for penaresidin A (**1**).

In 1997 the Knapp group published the stereoselective synthesis of penaresidin A, **1**, 16-*nor*-penazetidine A (**19**), and an analog lacking an elongated sidechain which they coined "mini-penazetidine". [17]

The group's retrosynthetic strategy began with the deconstruction of the azetidine core, revealing the carbamate-protected 2-amino-1,3,4-triol **84** (Figure 15). This highly functionalized molecule was postulated to be derived from a Wittig olefination of aldehyde **85**, derived from Garner's aldehyde (**25**), and the bromophosphonium salt **87**, derived from bromoalcohol **88**, followed by hydrogenolysis and hydrogenation.

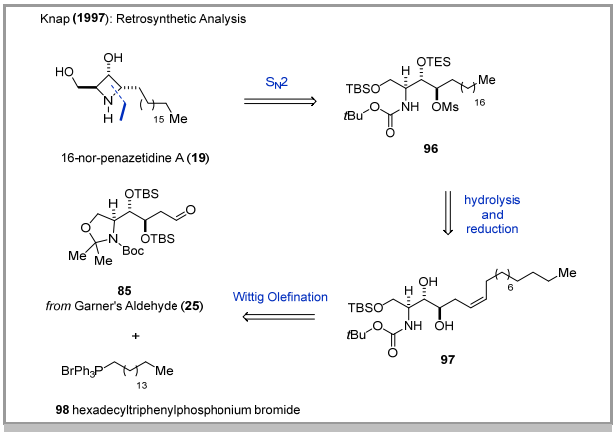


Figure 16. Knapp's retrosynthetic strategy for 16-nor-penazetidine A (**19**).

16-*nor*-penazetidine A **12** was similarly traced back to a straight chain analog of 2-amino-1,3,4-triol **96**. Triol **96** could be obtained upon hydrolysis and reduction from alkene **97**, which was envisioned to arise upon Wittig olefination of hexadecyltriphenylphosphonium bromide, **98**, and the Garner's aldehyde derivative **85** (Figure 16).

The Knapp synthesis of penaresidin A (**1**) was composed of two fragments each of which were brough together through olefination (Figure 17). For the aldehyde coupling partner the synthesis began with the stereospecific nucleophilic coupling of the boc protected Garner's aldehyde **86** with the silyl thiazole, **88**, to give **89**. Subsequent two step thiazole reduction liberated aldehyde **90**. The aldehyde then underwent selective keck allylation in 10:1 d.r. Following column chromatography the desired diastereomer was carried forward. The new alcohol was TBS protected and the alkene cleaved via ozonolysis to give aldehyde **85.**

For the triphenylphosphnoim coupling fragment the synthesis began with 9-bromonanol, which underwent swern oxidation and stereospecific crotylation with either (*S*,*S*) or (*R*, *R*)- Roush Z-crotylbornonate. The enantiopure alcohol was then converted to a mom ether and reaction with triphenylphosphine furnished the Wittig reagent **87**. With both aldehyde **85** and phosphonium bromide **87** in hand, the Wittig olefination was accomplished in the presence of LiHMDS. Silyl deprotection gave free alcohol **93**. Both hydrolysis of the oxazolidine and reduction of the *Z*-alkene were accomplished next using acetic acid, and Pd/C respectively. With the reduced product **84** in hand, selective protection of the primary alcohol relying on TBSCl, selective mesylation of the less hindered secondary alcohol, and final TES protection of the remaining alcohol was accomplished. With the functionalized 2-amino-1,3,4-triol, **94**, in hand, the compound was exposed to NaHMDS which resulted in azetidine formation. The appended silyl groups were then deprotected and the Boc group hydrolyzed to give the acetic acid adduct of penaresidin A (**1**) in 19 steps (longest linear sequence) with a 17% overall yield.[17]

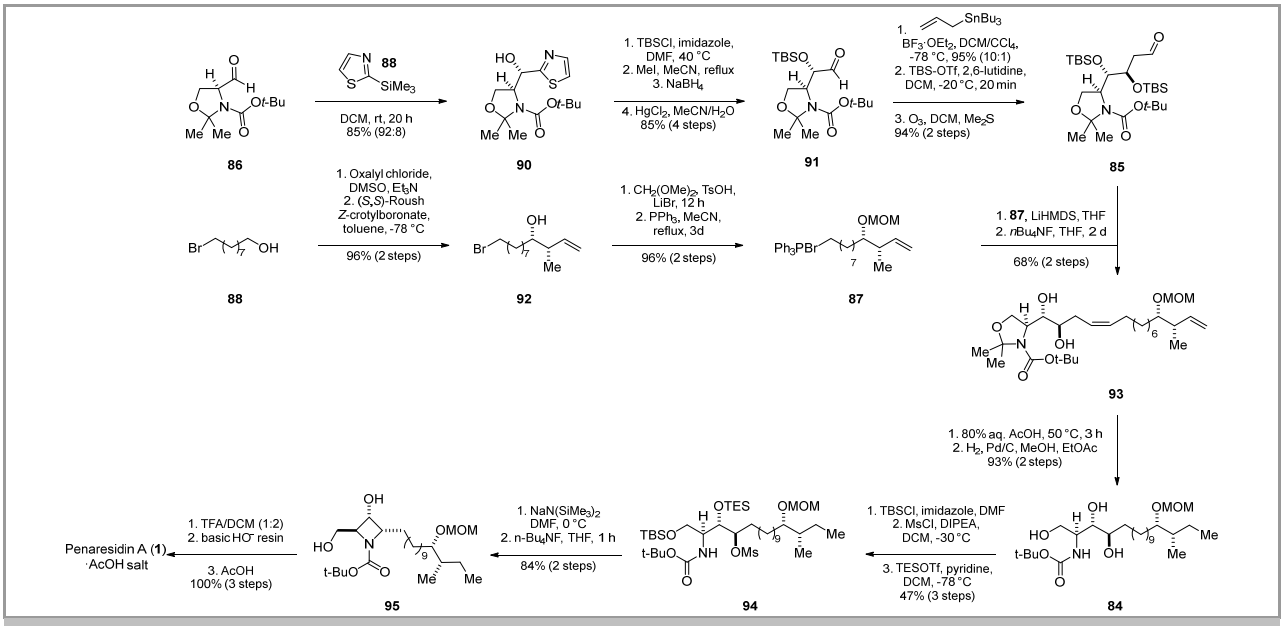


Figure 17. Knapp's forward synthesis of Penaresidin A (**1**).

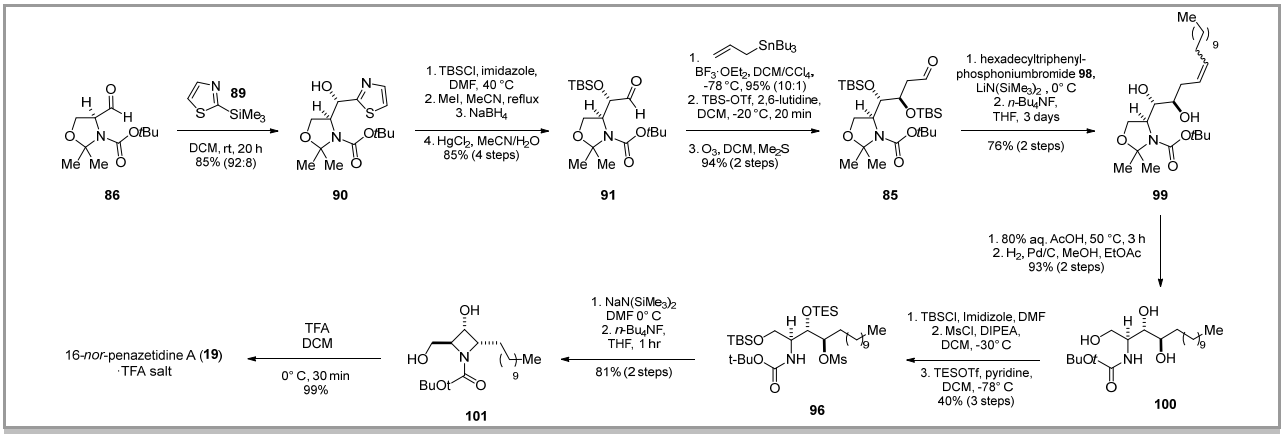


Figure 18. Knapp's forward synthesis of 16-nor-penazetidine A (**19**).

The synthesis of 16-*nor*-penazetidine A was accomplished in an analogous manner to the synthesis of penaresidin A relying on hexadecyltriphenylphosphoniumbromide **98** in the Wittig reaction, which initially resulted in a mixture of isomeric alkenes (Figure 18). Subsequent reduction of the alkene gave rise to alcohol **100** as a crucial intermediate to complete the synthesis of **19** in 18 steps (longest linear sequence) with a total yield of 15.3%.

The synthesis of the penazetidine analog termed "mini-penazetidine" by the authors relied on terminal alkene **102** which represents an intermediate in Knapp's previous two syntheses (Figure 19). This alkene was reduced and the oxazolidine hydrolyzed to give the 2-amino,1,3,4-triol **103**. TBS protection of the primary alcohol, mesylation of the secondary alcohol, and TES protection of the remaining secondary alcohol gave rise to mesylate **104**. The cyclization precursor **104** was the treated with NaHMDS and *n*-Bu_4NF to give the analog **105** in 12 steps with a 21% overall yield.[17]

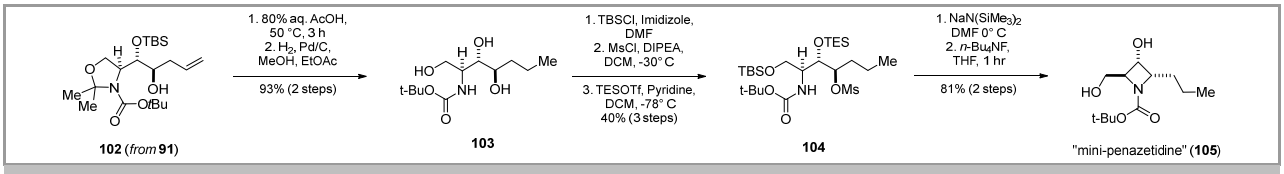


Figure 19. Knapp's synthesis of "mini-penazetidine" (**105**).

10. Substituted Penaresidin Core (Beauhaire and Ducrot, 1998)

Beauhaire and Ducrot recognized the common feature consisting of a terminal tetraheterosubstituted butyl subunit amongst penaresidin alkaloids which prompted their design of a unifying strategy to access this versatile intermediate.[18] They envisioned that an epoxide-containing precursor (**109**) to the azetidine core with a well-defined configuration could be diversified by a late-stage side chain addition via an organometallic alkylation and functional group conversion to introduce nitrogen. This would allow direct access to a broad range of sphingolipids following a standard ring closure via unimolecular nucleophilic substitution. The coworkers identified commercially available diacetone alpha-(*D*)-glucose (**111**) as the most appropriate starting material according to the desired stereogenic configuration of the azetidine core (Figure 20). Notably, a similar strategy was previously reported by Kamikawa in 1995 to introduce the pendant sidechain via carbonyl addition, but this arguably presents a significant challenge in retaining diastereomeric control.[15]

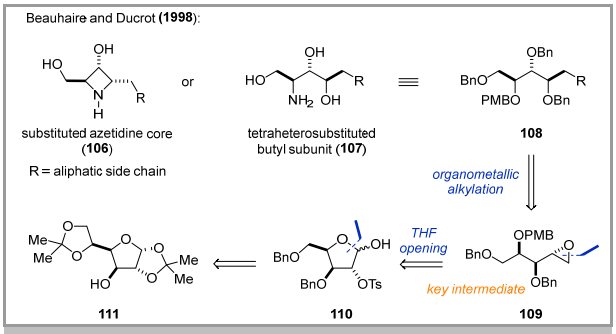


Figure 20. Beauhaire and Ducrot's 1998 Retrosynthetic analysis of azetidine **106** proceeding through key epoxide intermediate **109.**

The C3 hydroxyl group on **111** was first benzylated to afford a crude mixture containing **112** which was pushed forward without purification (Figure 21).[18] The mixture was treated with H_2SO_4 to regioselectively afford the crude 5,6-deprotected diol, which underwent a Malaprade oxidation to afford the C5 aldehyde **113**. Aldehyde **113** was subsequently reduced to its corresponding primary hydroxyl **114** relying on $NaBH_4$. Benzyl protection of this hydroxyl to **115** and Amberlyst 15 acid hydrolysis of the 1,2-ketal and column chromatography afforded a C1 anomeric mixture of alcohol **116** in 88% yield over six steps. A tosyl protection of the secondary hydroxyl afforded C1 anomers of **117** in 75% yield, which was then hydrolyzed using TFA and water to afford anomeric hemiketal **110** in 75% yield. A standard hemiketal reduction with $NaBH_4$ facilitates ring opening of the THF moiety to provide the enantiopure tetraheterosubstituted unit **118** in 97% yield. Upon treatment with K_2CO_3, an intramolecular substitution yields the desired epoxide unit **109** in 85% yield. Based on already-known procedures, this target epoxide could be converted to tetrahydroxy compounds in sphingolipids or penaresidin analogs with good overall yields.

Although not extensively discussed in this report, the authors identify lithium salts of 1-alkynes as effective side chain surrogates when introduced in the presence of boron trifluoride etherate as a Lewis acid. Overall, this strategy features a 41% overall yield from diacetone alpha-(D)-glucose (**111**) to tetraheterosubstituted butyl epoxide subunit (**109**) readily prepared for side chain diversification. [18]

11. Substituted Penaresidin Core (Ducrot, 1999)

One year after Ducrot's synthesis of the azetidine precursor epoxide **109** (Figure 21), a complete synthesis of the protected penaresidin A analog **139** including a truncated side chain was reported.[19] Notably, Ducrot's approach eliminates the final protection/deprotection sequences often included in prior synthetic strategies of these polyhydroxylated azetidinic alkaloids. The authors envisioned two routes to minimize the use of protecting groups that both involve organometallic addition of the sidechain fragment to an epoxide: specifically, introducing a leaving group at position 2 before the epoxide opening, or alternatively carrying out the epoxide opening without prior protection of the hydroxyl at position 2. Ultimately, they chose the latter route (Figure 22).

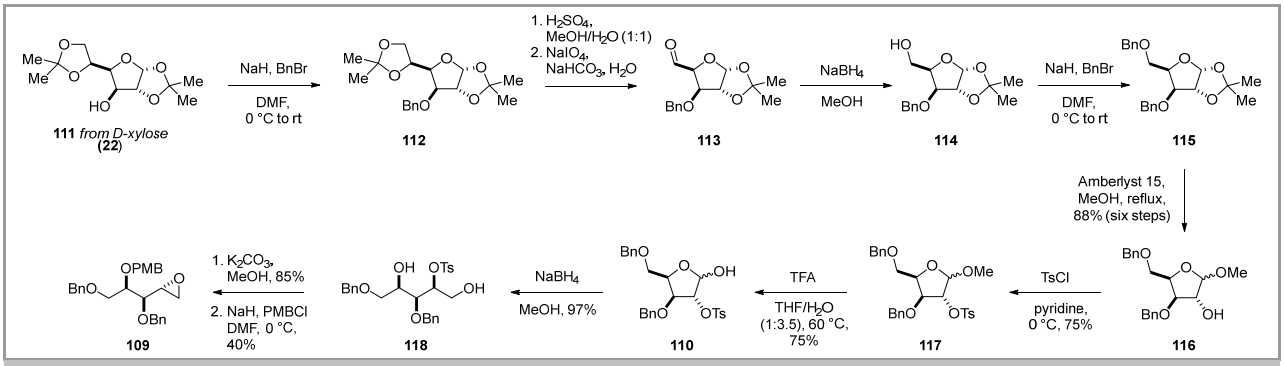


Figure 21. Beauhaire and Ducrot's 1998 forward synthesis of key epoxide **109.**

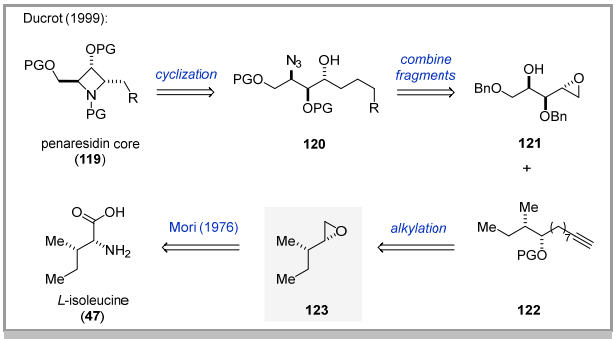


Figure 22. Ducrot's 1999 retrosynthetic strategy for penaresidin core **119**.

The side chain fragment was built up following a protocol reported by K. Mori which relies on *L*-isoleucine **47** to access the key epoxide-containing intermediate **123** in 8 steps and 29% overall yield (Figure 23).[20] From intermediate **123**, condensation with lithium alkylidine **131** in the presence of boron trifluoride etherate resulted in homopropargylic alcohol **132** in 39% yield of the intended regiosiomer (Figure 24). A silyl ether protection of the free hydroxyl on **132**, and subsequent alkyne hydrogenation in the presence of palladium gave **133** in 81% yield over two steps. Then, **133** was converted to the bromide **134** over a three-step reduction/substitution sequence in 60% overall yield. The authors mention that an Appel reaction may also be used to introduce the bromide, however, it led to unconquerable challenges with the separation. A further substitution with lithium acetylide resulted in alkyne **135.**

Alkyne **135** was subsequently lithiated and then reacted with epoxide **121** that was prepared according to their 1998 route[18] (Figure 20) to return the desired homopropargylic alcohol **136** in 27% yield (Figure 24). The triple bond was then hydrogenated in the presence of Raney nickel to give **137** in 80% yield, which then underwent a regioselective tosylation at the C2 hydroxyl and subsequent nucleophilic substitution with sodium azide to afford key intermediate **138** in 41% yield over the two steps. While the completion of the synthesis from intermediate **138** has been reported before,[14] the authors chose to construct the azetidine from the azide in a single step according to a method first demonstrated by J. Blum that utilizes the reactivity of an intermediate in the Staudinger reduction of azides to form aziridines.[21] Adapted to their system, the addition of PPh_3 to **138** facilitated formation of the azetidine with free NH in 36% yield, followed by an acyl protection to produce the fully protected penaresidin A derivative **139** in 36% yield.[19]

To demonstrate the generality of this method to access azetidines, and to examine the effects of the length of the side chain compatible with their cyclization step, regioisomeric monotosylates **141a** and **141b** were prepared starting with **121** by a $LiAlH_4$ reduction and subsequent tosylation (Figure 25). Upon introduction of the azide to form **142a** and **142b**, respectively, cyclization to the racemic azetidine mixture of **143** upon treatment with PPh_3 occurred in quantitative yield.

Overall, it was demonstrated by Ducrot that the synthesis of azetidines from 2,4-unprotected diol intermediates **136** is possible without the need for protection steps. Additionally, they conclude that the formation of the azetidine is more efficient when the steric hinderance of the side chain is reduced, which underscores the importance of considering steric effects when designing future azetidine-containing compounds.[19]

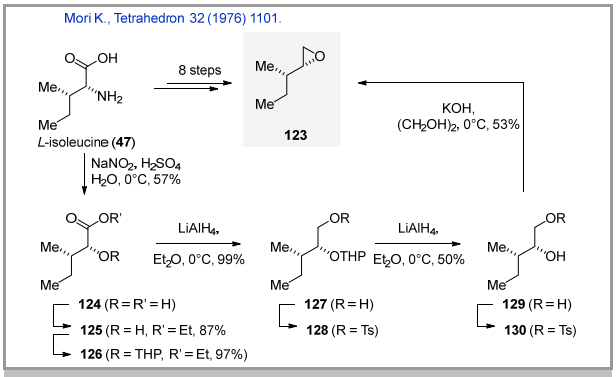


Figure 23. Mori's 1976 forward synthesis of key epoxide **123** from *L*-isoleucine (**47**).

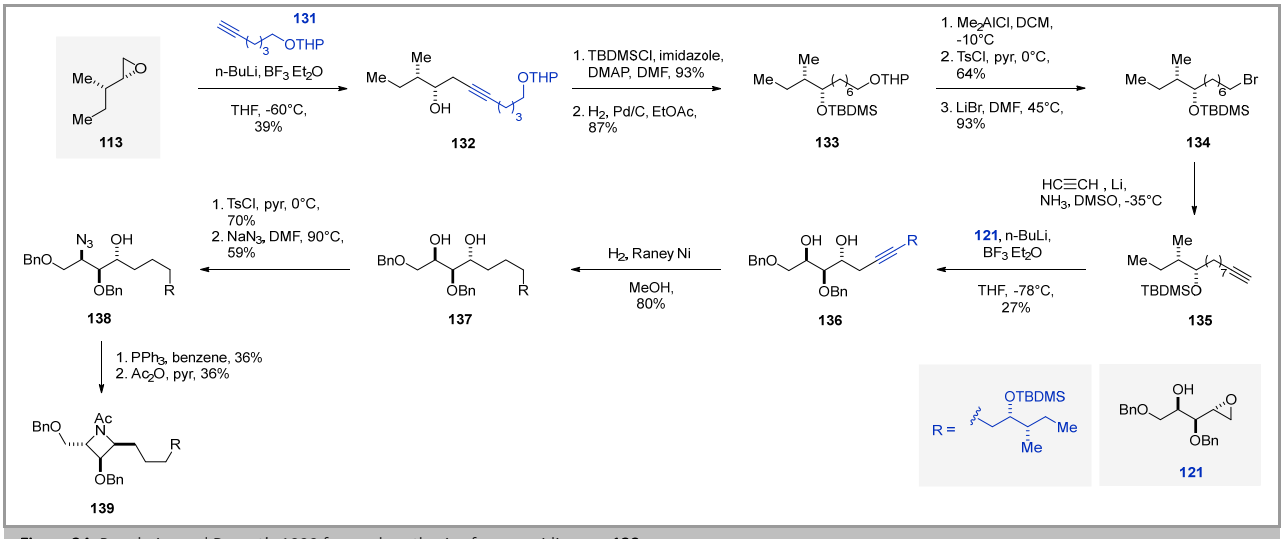


Figure 24. Beauhaire and Ducrot's 1999 forward synthesis of penaresidin core **139.**

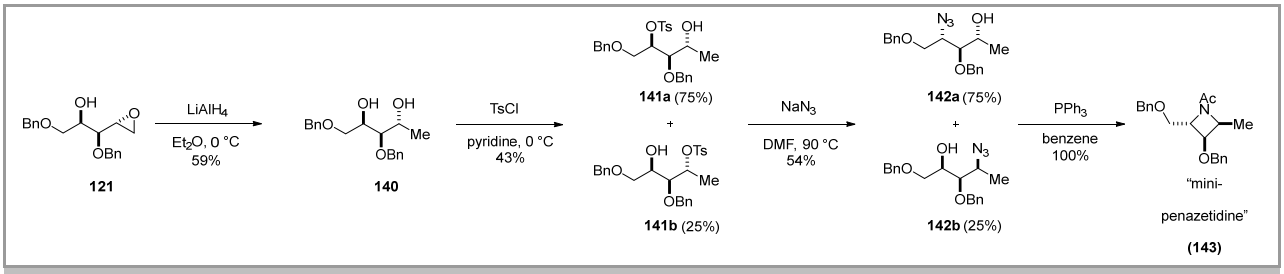


Figure 25. Beauhaire and Ducrot's synthesis of "mini -penaresidin" (**143**) from epoxide **12**

12. Penaresidin A (Lin, 1999)

Lin and Liu designed their synthetic strategy of penaresidin A (**1**) based on their own previous efforts to access the azetidine moiety from divinylcarbinol (**27**).[22] Their 1999 synthesis is a redesigned strategy from their 1998 route which featured only stereoisomers of penaresidin A (**7** and **8**) due to challenges cyclizing their respective azetidine precursor with the desired configuration.[4] The current synthesis achieved access to both penaresidin A (**1**) and isomer 15,16-di-*epi*-penaresidin A (**6**) via a convergent route that prepared enantiopure azetidine precursor **148** from **27** which, upon cyclization, was conjoined with the respective side chain fragment via a Wittig olefination to give the desired connectivity (Figure 26).[22]

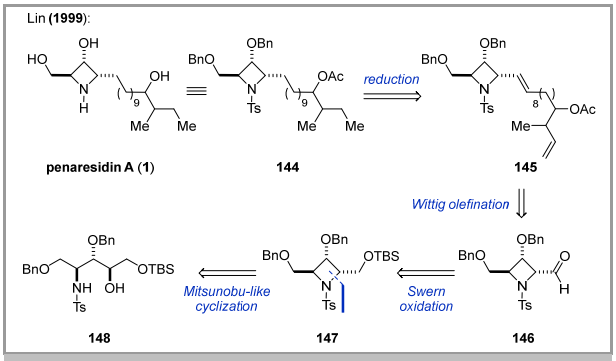


Figure 26. Lin's 1999 retrosynthetic strategy for penaresidin A (**1**).

Lin's forward synthesis of their azetidine intermediate began with a two-step sequence reported by B. Koppenhoefer by which an initial asymmetric Sharpless epoxidation of divinylcarbinol (**27**) at either terminus followed by a subsequent epoxide transposition upon intramolecular nucleophilic substitution resulted in internal epoxide (**149**) in 58% over two steps (Figure 27).[23] The resulting hydroxyl group was protected as benzyl ether (**150**) in 87% yield and then underwent Sharpless asymmetric dihydroxylation and subsequent protection to give the protected diol **151** in 11:1 diastereomeric ratio and 73% over two steps.[22] Treatment with NaN_3 at reflux regioselectively cleaved the epoxide to yield azide **152** in 87%. This was followed by a three-step sequence in which, first, its free hydroxyl was protected as benzyl ether followed by subsequent $LiAlH_4$ reduction of the azide to the free primary amine. Lastly, amino protection was carried out by treatment with TsCl and Et_3N to afford **153** in 80% overall yield. At this point, the acetonide was cleaved with 2N HCl in methanol (1:1) at 40ºC, and the primary alcohol was protected with TBSCl to give **148** in 87% yield over two steps. Next, the key cyclization to form the azetidine moiety **147** was carried out under Mitsunobu conditions in 60% yield. Finally, a TBAF deprotection and subsequent Swern oxidation of the resulting primary hydroxyl gave aldehyde **146** in 95% overall yield.

The pendant sidechain was prepared from the treatment of decanediol **154** with HBr to give bromo-alcohol **155** in 80% yield (Figure 28). A subsequent Swern oxidation afforded an aldehyde intermediate to undergo crotylation with Z-(*S,S*)-crotylboronate via 6-membered transition state **TS1** to afford alkene **156** in 88% overall yield. Notably, treatment with Z-(*R,R*)-crotylboronate instead, with no other adjustments to the synthesis, would ultimately achieve 15,16-di-*epi*-penaresidin A (**6**). To continue the synthesis towards penaresidin A (**1**), an acyl protection of alkene **156** afforded **157** in 96% yield, which was subsequently converted to Wittig salt **158** upon addition of PPh_3 in 95% yield. The key Wittig olefination was then carried out by the addition of aldehyde **146** to achieve the desired connectivity, thereby converging the synthetic routes of the requisite fragments. This key step was initially explored using NaHMDS as the base, for which a diminished yield of 20% was observed. Upon switching the base to NaDMSO, a higher olefination yield of 60% as a mixture of E/Z- isomers **159** was observed. A failed H_2, Pd/C hydrogenation attempt of **159** inspired a diimide reduction of the alkene to **160** which was successful in 92% yield of the crude product which was pushed forward without purification. A smooth completion of deacylation was achieved with $LiAlH_4$ in 85% yield, and subsequent benzyl deprotections with H_2, Pd/C and tosylamine deprotection with sodium naphthalenide afforded penaresidin A (**1**). In total, Lin's reported convergent synthesis of penaresidin A (**1**) totals 19 steps and 6.1% overall yield from commercially available divinylcarbinol (**27**) and decanediol (**154**).[22]

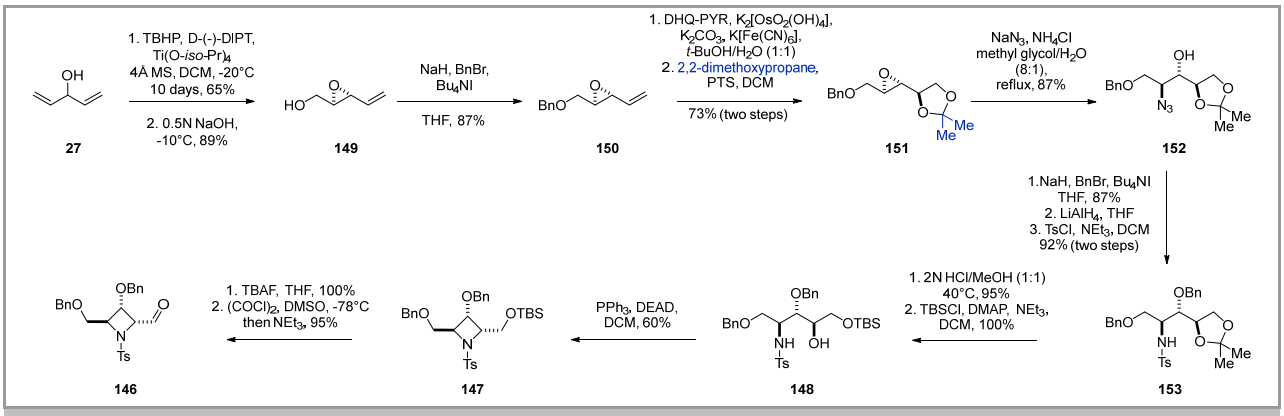


Figure 27. Lin's forward synthesis of the azetidine core (**146**) en route to penaresidin A (**1**).

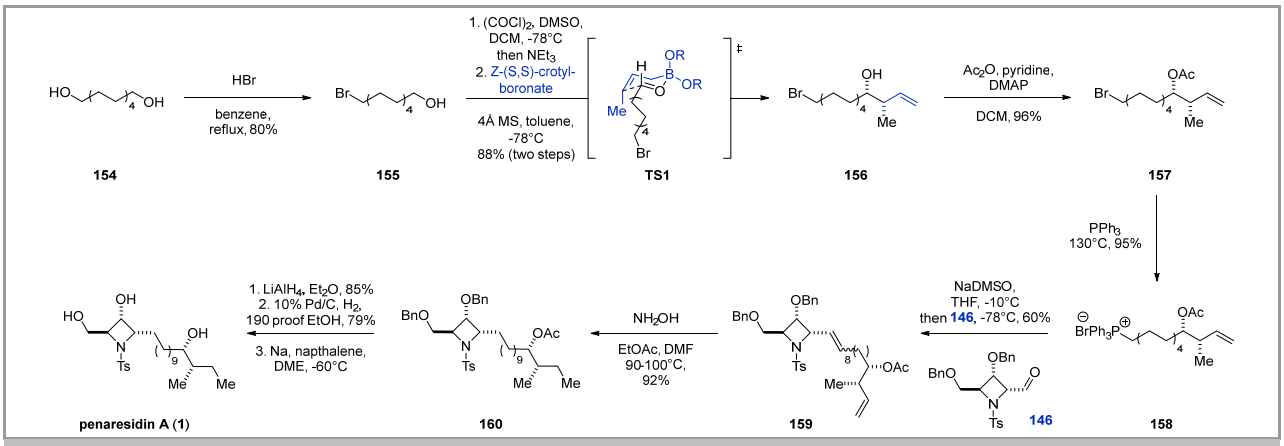


Figure 28. Lin's sidechain build-up and azetidine fragment (**146**) combination to complete the synthesis of penaresidin A (**1**).

13. Penaresidin B (Yoda, 2003)

In 2003, Yoda and coworkers reported an asymmetric synthesis of penaresidin B (**2**) from *D*-arabinose derivative **164**.[24] They envisioned this sugar to be an appropriate precursor to the key homochiral lactam intermediate **162** which can be reductively cleaved and recyclized to afford the target natural product. Their synthesis relies on a route developed in 1993 by Nicotra *et al.* for the synthesis of azasugars following an oxidative degradation pathway (Figure 29).[25]

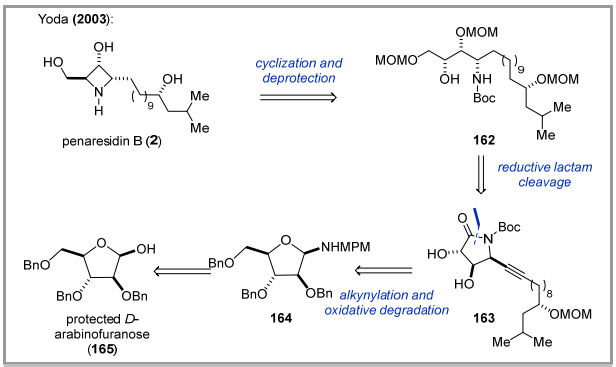


Figure 29. Yoda's 2003 retrosynthetic strategy of penaresidin B (**2**).

As was demonstrated by Nicotra, Yoda's synthesis commences with a functional group exchange of the C1 hydroxyl on *D*-arabinose derivative **164** using $MPMNH_2$ to afford **165** in quantitative yield (Figure 30).[24] At this point, treatment with acetylide **166** derived from *D*-leucine via the acetylene zipper reaction generates an acyclic aminoalcohol intermediate, which upon subsequent oxidative degradation with PCC affords **167** in 51% overall yield and >99% diastereomeric ratio. Following the exchange of the *p*-methoxybenzyl (MPM) protecting group for *N-tert*-butoxycarbonyl (N-Boc), a palladium (black) hydrogenation afforded dihydroxylactam **168** in 95% yield. Two regioselective protections were carried out in sequence with **74** and quantitative yields, respectively, to afford protected lactam intermediate **169** with the desired configuration to reach penaresidin B asymmetrically.

A reduction of **169** with $NaBH_4$ affords the acyclic tetrahetereosubstituted butyl subunit with free primary alcohol and deprotected C2 secondary alcohol which was subsequently regioselectively protected as methoxymethyl ether (MOM) to afford **161** in quantitative yield over two steps. The free secondary alcohol was tosylated and then cyclized with NaH via a unimolecular nucleophilic substitution pathway to afford protected penaresidin B **170** in 50% yield over two steps, which was quantitatively deprotected under acidic conditions to yield enantiopure penaresidin B (**2**). The overall 13 step sequence affords penaresidin B (**2**) asymmetrically in an impressive 12% overall yield from commercially available *D*-arabinose derivative **164**.[24]

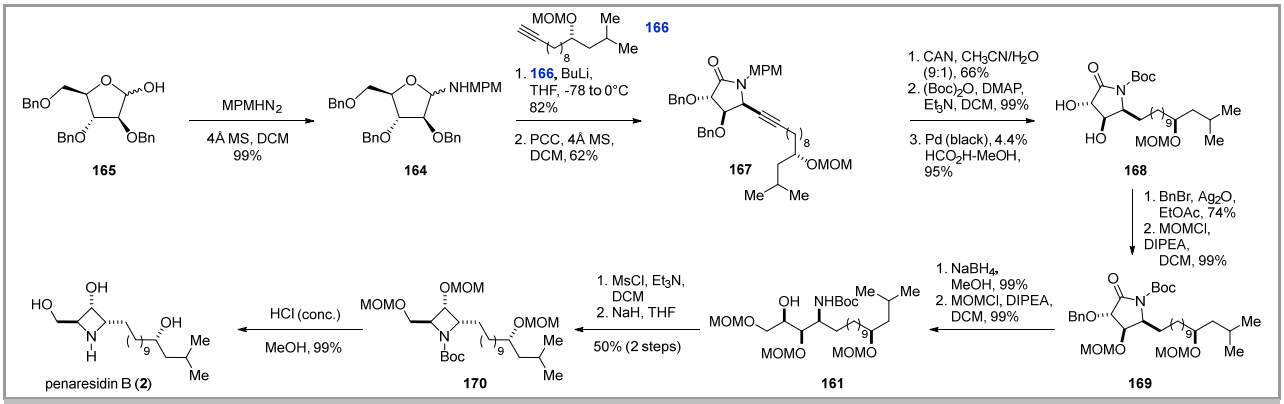


Figure 30. Yoda's 2003 forward synthesis of penaresidin B (**2**) from protected *D*-arabinofuranose (**165**).

14. Penaresidin Structure-Activity Relationship (Kobayashi, 2007)

Kobayashi and coworkers took interest in the structure-activity relationship of stereoisomers for the azetidine ring of penaresidin and penazetidine compounds.[5] In 2007, their group reported a unifying synthetic strategy of six stereoisomers of a penaresidin derivative incorporating a C_{14} alkyl sidechain (**14**, **15**, and **16**, plus enantiomers, Figure 2), and evaluated the biological activities demonstrated by each. They hypothesized that the configuration of the pre-cyclized substrate **171** could be controlled via homochiral epoxide intermediate **172**, which can be obtained by a proper diastereomer separation technique. Upon employing Garner's general method of sphingosine synthesis,[26] **175** can be generated by the respective Garner's aldehyde **25** and alkyne **176** fragments (Figure 31). These disconnections were applied to the synthesis of all three isomers, however (2*R*, 3*R*, 4*S*) isomer **16** required slight modifications to the route to properly set the C3 stereocenter. [5]

Their forward synthesis of the (2*R*, 3*S*, 4*R*) isomer **14** and the (2*R*, 3*S*, 4*S*) isomer **15** follow the same route that relies on the addition of alkylinide generated from **176** to Garner's aldehyde **25**, which is known to proceed stereoselectively to **177** with >95% diastereomeric ratio and 73% respective yield (Figure 32). The triple bond was then reduced with Li and ethylamine with an accompanying deprotection of the oxazolidine to afford a free β-amino alcohol intermediate with *E*-alkene that was subsequently protected as a TBS ether in 27% yield over two steps, followed by an amine tosylation to afford protected sphingosine **175** in quantitative yield. Epoxidation with *m*CPBA yields a diastereomeric mixture of products which were separated to obtain **174** and **172** in 21% and 25% yields, respectively. Reduction of intermediate **174** with DIBAL gave the key precyclized substrate **178** with free secondary hydroxyl in 87% yield which was tosylated and subsequently cyclized relying on NaH as base in 60% overall yield. A final treatment with sodium napthalenide followed by HF deprotects the N-*tosyl* and OTBS groups, respectively, to afford (2*R*, 3*S*, 4*R*) isomer **14** in 70% yield over two steps. Similarly, epoxide containing intermediate **172** followed the same protocol to obtain (2*R*, 3*S*, 4*S*) isomer **15**.

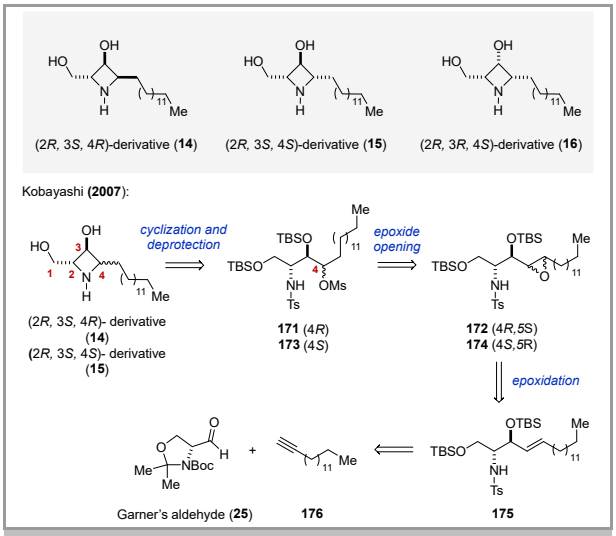


Figure 31. Kobayashi's 2007 retrosynthetic analysis of stereoisomers of straight-chain penaresidin analog **14** and **15**.

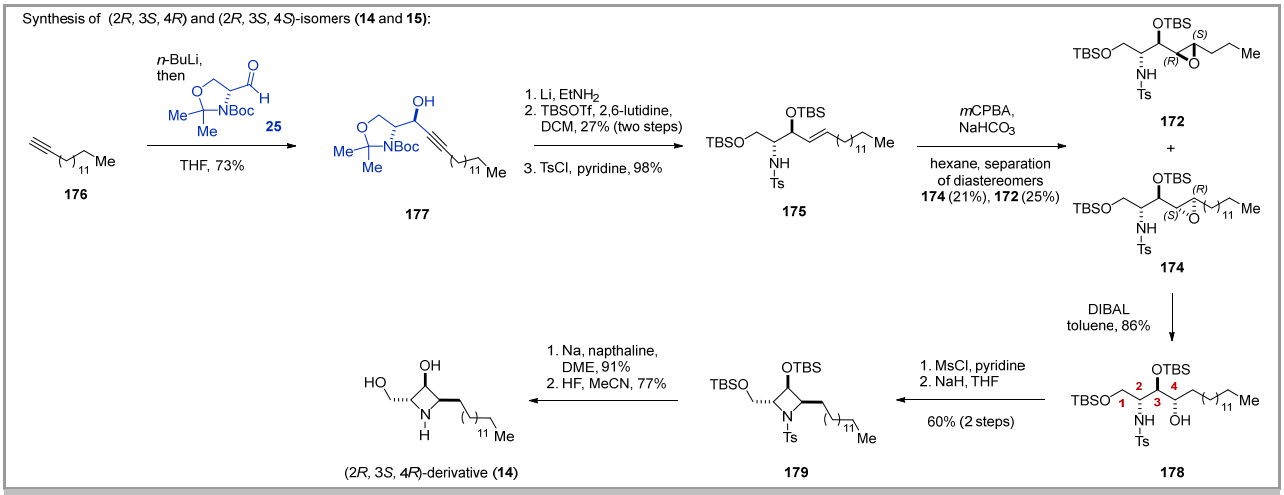


Figure 32. Kobayashi's 2007 forward synthesis of straight-chain penaresidin analog **14**.

As for accessing the (2*R*, 3*R*, 4*S*) isomer **16**, an early adjustment to the synthesis was necessary to generate the C3 epimer of **175** (Figure 33). Again, in the presence of Garner's aldehyde, a hydrozirconation of alkyne **176** was employed to yield sphingosine **180** as a single isomer in 69% overall yield. Removal of Boc and subsequent TBS protection of the free hydroxyls afforded alkene **181** in 73% yield over three steps, which underwent epoxidation with *m*CPBA to yield a mixture of diastereomers in quantitative yield. Treatment of the mixture with DIBAL was found to reduce one diastereomer while decomposing the other, which accessed enantiopure pre-cyclized alcohol **182** in 16% yield. A ring closure under Mitsunobu conditions gives protected azetidine **183** in 20%, which was deprotected in the same way as the previous isomers to reach (2*R*, 3*R*, 4*S*) isomer **16** in 89% over the final two steps.

Employing the two synthetic strategies described above, the respective enantiomers of **14, 15** and **16** (**18**, **12**, and **11,** respectively) were synthesized as well. The authors continue their report to evaluate the cytotoxicity of all six synthetic isomers using human solid tumor cell lines, KB (carcinoma), 4549 (lung) and HT29 (colon) in addition to murine lymphoma L1210, the results of which are summarized in Figure 2. Isomers **18** and **12** demonstrated potent cytotoxicity against A549 and HT29 cells. Isomers **14**, **15**, **18**, and **12** showed antibacterial activity against Gram-positive-bacteria (*Bacillus subtilis, Micrococcus luteus,* and *Staphylococcus aureus*) and **12** demonstrated antibacterial activity against Gram-negative-bacteria. They conclude from this study that the stereochemistry of the azetidine ring in penaresidin derivatives significantly impacts its biological activity.[5]

15. Penaresidin A (Raghavan, 2009)

In 2009, Raghavan and Krishnaiah reported a modular asymmetric synthesis of penaresidin A (**1**), following incorporation of a Julia-Kocienski olefination to couple the independently synthesized azetidine **184** and side chain **186** fragments (Figure 34).[13] It was hypothesized that azetidine **186** would come about from the cyclization of **185**, which can be traced back to the unsaturated sulfoxide **189**. They were attracted to intermediate **189** on account of Garcia-Ruano and co-workers' addition of sulfinyl carbanions to sulfinylimines,[27] which ultimately represented a key asymmetric transformation in Raghavan's forward synthetic route. The side chain fragment **186** was thought to be attainable from nucleophilic addition to epoxy alcohol **187**, which could be traced back to alcohol **188** through a sulfone addition and a subsequent desaturation protocol.[13]

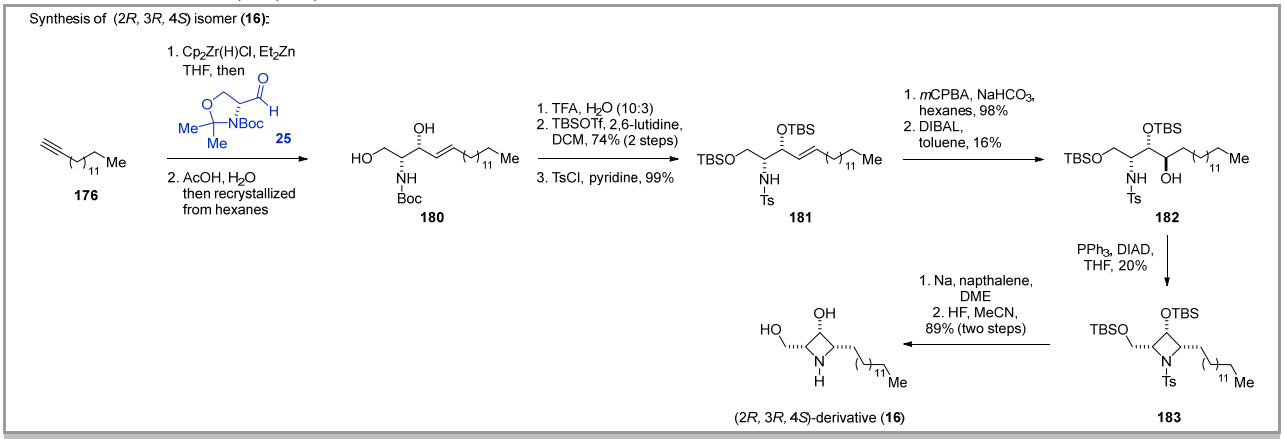


Figure 33. Kobayashi's 2007 forward synthesis of straight-chain penaresidin analog **16**.

The synthesis of key intermediate **189** begins with a single protection followed by a Swern oxidation of nonane diol **190** to yield aldehyde **191** in 77% overall (Figure 35). A subsequent Wittig olefination afforded trans-ester **192** in 92% yield, which was chemoselectively reduced to the primary alcohol and subsequently reoxidized to α,β-unsaturated aldehyde **193**. Reacting **193** with chiral sulfinamide (***S*)-194** in the presence of titanium methoxide afforded sulfinimine **195** in 91% yield. Raghavan's report demonstrates an alternative, two step protocol to prepare **195** via a cross methathesis, but the forward route illustrated here allows for a more modular diversification of stereocenters. At this point, the alpha amino stereocenter was set by the stereoselective addition of sulfinyl carbanion from (***R*)-196**, based on precedent from Garcia-Ruano and co-workers, to afford key intermediate **197** in 94% yield via the proposed transition state **TS2**. *N*-sulfinyl deprotection was accomplished via treatment with HCl to generate an amine hydrochloride which was reacted with *o*-nitrobenzenesulfonyl (*o*-Ns) in 70% yield over two steps, and the resulting free *NH* was benzyl protected to afford fully *N*-protected intermediate **198** in 95% yield.

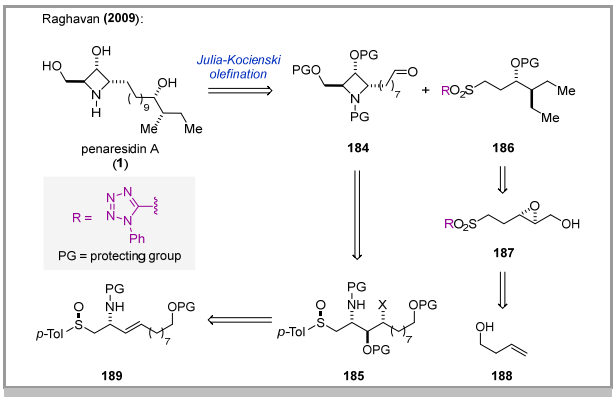


Figure 34. Raghavan's 2009 retrosynthetic analysis for penaresidin A (**1**).

To proceed with the synthesis of the azetidine core, hydrobromination of alkene **198** with NBS and water afforded a regio- and enantio-pure bromohydrin intermediate which upon treatment with K_2CO_3 generates epoxide **199** in 74% overall yield. A Pummerer reaction followed by hydrolysis and subsequent reduction all in one pot afforded β-amino alcohol **200** in 78% yield over three steps. Intermolecular epoxide opening under acidic conditions proceeded regioselectively at the least hindered carbon to afford triol **201** in 89% yield. The primary hydroxyl group was selectively protected as a TBS ether, followed by a regioselective mesylation at the C4 hydroxyl, and a final protection of the free C3 hydroxyl as a TES ether in 95, 90 and 94% yields, respectively, to reach **202**. The nosyl group was removed by treatment with *2*-mercaptoethanol and DBU as base which self-cyclized to the fully protected azetidine core **203**. Upon hydrogenolysis of the *O*-benzyl group to the primary free alcohol with $Pd(OH)_2/C$ in the presence of di-*tert*-butyl decarbonate, an final IBX oxidation yielded key intermediate aldehyde **204**.

To build up the side chain fragment, Raghavan began with homoallylic alcohol **188** which was protected as PMB ether and subject to cross metathesis with *cis*-2-buten-1,4-diol and Hoveyda-Grubbs catalyst[28] to afford allylic alcohol **205** in 85% yield (Figure 36). A Sharpless asymmetric epoxidation afforded **206** in 85%, which underwent regioselective epoxide opening with ethylmagnesium bromide promoted by catalytic CuI to yield diol **207** as a 9:1 mixture of 1,3- to 1,2-diols. The primary hydroxyl was tosylated in 90% yield and then subsequently reduced with $LiAlH_4$ to facilitate removal of OTs in 90% yield, and then protected at the secondary hydroxyl as benzyl ether **208** in 80% yield. Deprotection of the PMB ether with DDQ gave **209** in 94% yield, which was then converted to the sulfide under Mitsunobu conditions. A final epoxidation with *m*CPBA generated sulfone **212**, which is an analog of their intended key intermediate **186**.

With both key fragments of penaresidin A in hand, Raghavan and coworkers moved forward with the completion of their synthesis by treatment with KHMDS as a base to facilitate their key Julia-Kocienski olefination step, affording the fully protected penaresidin A **213** in 93% (Figure 36). Finally, a series of deprotections by hydrogenolysis with $Pd(OH)_2/C$, TBAF, and acidic cleavage of the carbamate afforded their penaresidin A (**1**) as an amine salt. In summary, this report demonstrated the synthesis of penaresdin A with incorporation of stereoselective addition of a sulfinyl carbanion, tandem *o*-Ns deprotection and azetidine cyclization, and Julia-Kocienski olefination as key steps. In total, their route accesses penaresidin A (**1**) in 20 steps and 10.5% overall yield.[13]

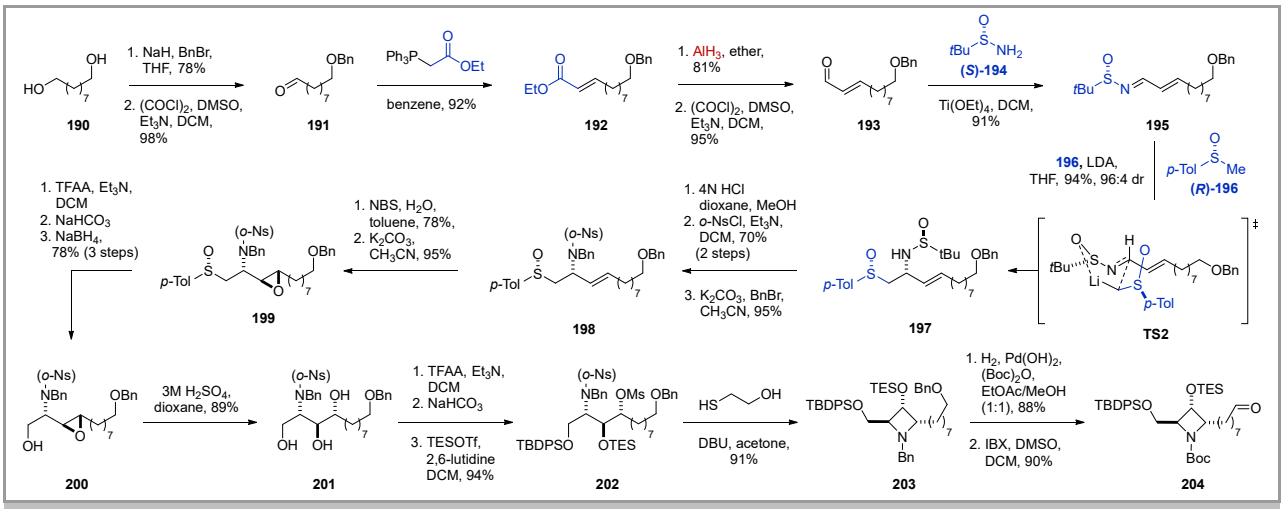


Figure 35. Raghavan's forward synthesis of the azetidine core (**204**) en route to penaresidin A (**1**).

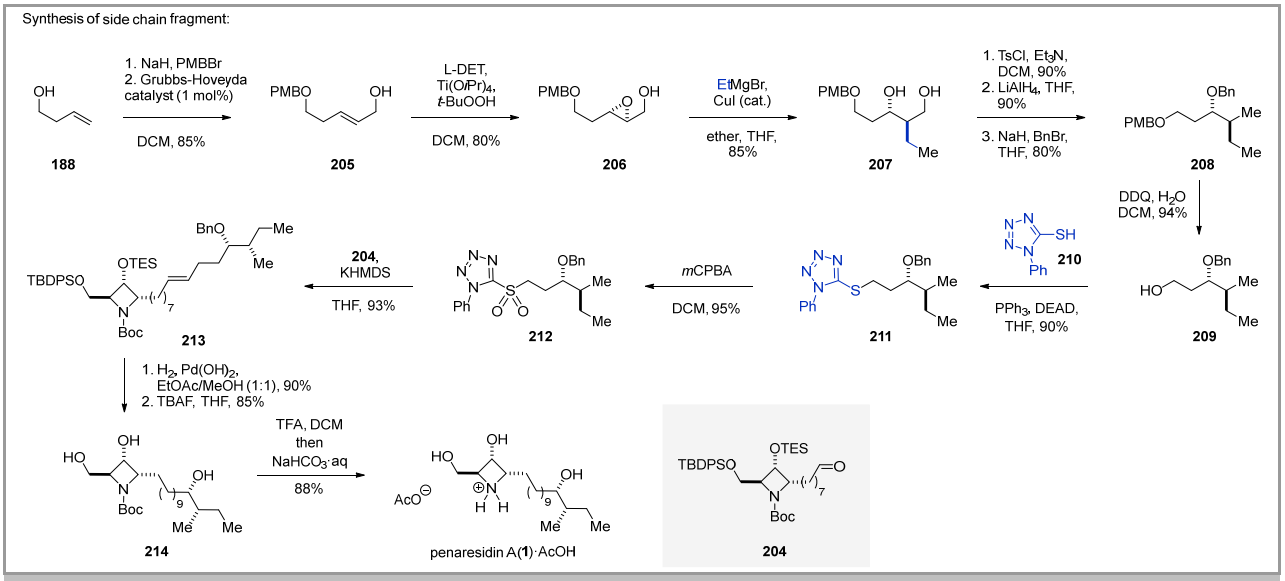


Figure 36. Raghavan's sidechain build-up and azetidine fragment (**204**) combination to complete the synthesis of penaresidin A (**1**).

16. Penaresidin A (Reddy, 2013)

Reddy and coworkers reported a strategy towards Penaresidin A (**1**) in 2013, utilizing a convergent approach and combining two fragments, azetidine **215** and sulfone **219**, in a key Julia-Kocienski olefination step (Figure 37).[29] The azetidine core fragment was accessed from commercially available 3,4,6-tri-O-benzyl-*D*-galactal **218**, which underwent ring-opening via a mercuration-demercuration sequence to form alcohol **217**. A selective amination was applied to allyl alcohol **217** to result in amino alcohol **216**, which preceded azetidine **215** by ring closure. Simple nonanediol (**190**) was used to prepare fragment **220** through an asymmetric Sharpless epoxidation, which upon a Mitsunobu reaction gave rise to tetrazoyl sulfone **219**.

Reddy began their efforts towards penaresidin A (**1**) with treatment of benzylated *D*-galactal with $HgSO_4$ and aq. H_2SO_4 in dioxane at room temperature to exclusively obtain hydroxy-trans-enal (Figure 38). Subsequent Luche reduction resulted in allyl alcohol **217** in 65% yield across two steps. Asymmetric Sharpless epoxidation of **217** followed by ring opening via Red-Al gave rise to triol **221** in 57% yield over two steps. Protection of the triol with 2,2-DMP and cat. *p*-TSA gave acetal **222** in 85% yield. The unprotected secondary alcohol in **222** was protected with mesyl chloride and substituted with sodium azide in refluxing DMF to reach azide **223** in 75% yield across two steps. LAH reduction of the azide was followed by treatment with triethylamine and tosyl chloride to give tosylated amine **224** in 90% over two steps. Deprotection with *p*-TSA in methanol led to selective protection of the primary alcohol with *tert*-butyldiphenylsilyl chloride, affording **216** in 73% across two steps. The free secondary alcohol was mesylated with methanesulfonyl chloride in pyridine before cyclization with NaH to give azetidine **225** in 51% yield over two steps. Desilylation using TBAF followed by oxidation with IBX in DMSO resulted in the formation of key azetidine aldehyde fragment **215** in 56% yield over two steps.

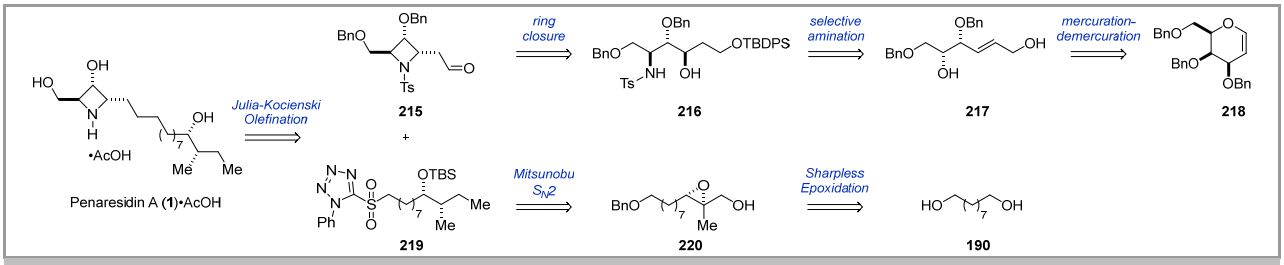


Figure 37. Reddy's 2013 retrosynthetic strategy for penaresidin A (**1**).

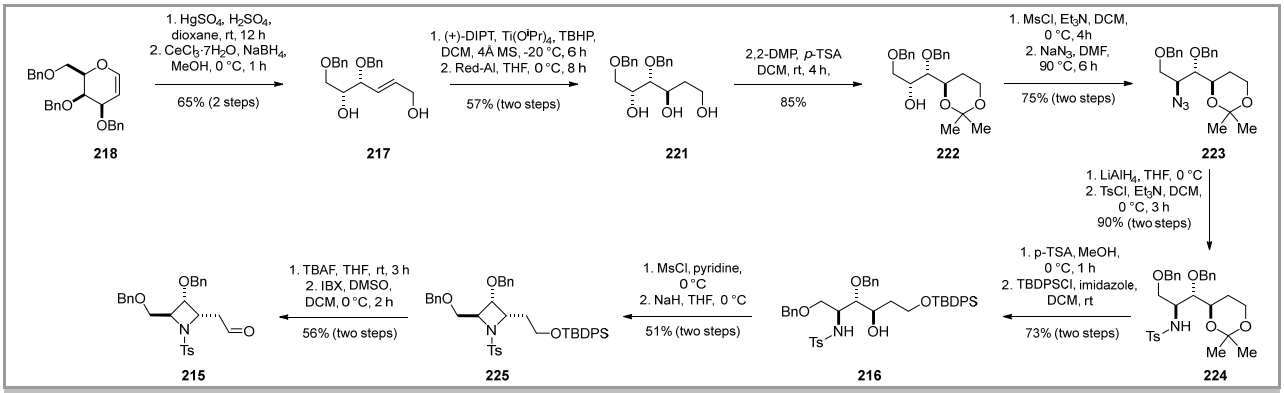


Figure 38. Reddy's forward synthesis to azetidine core (**215**).

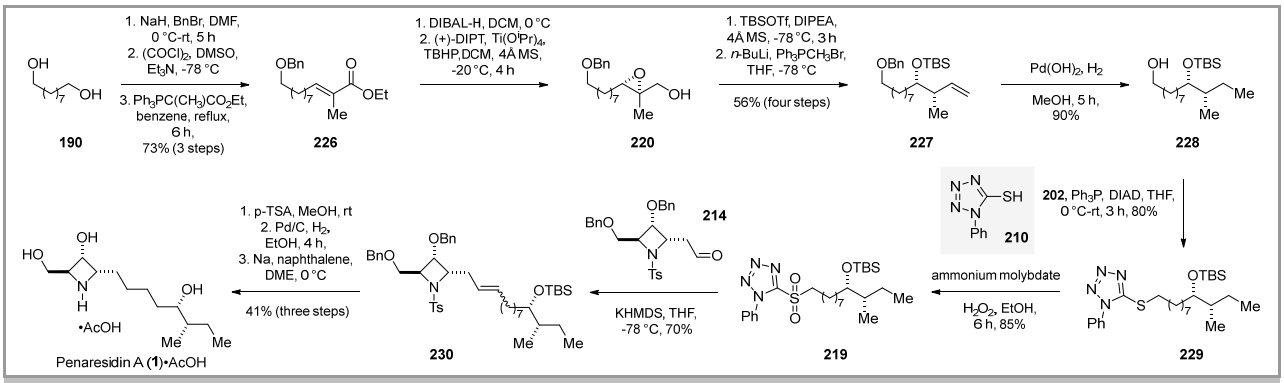


Figure 39. Reddy 's side chain synthesis and combination with azetidine core (**215**) towards penaresidin A (**1**).

The second key fragment was constructed from 1,9-nonanediol **190** (Figure 39). The diol was mono-protected using NaH and benzyl bromide in DMF and subsequently subjected to oxidation under Swern conditions. A Wittig reaction then selectively provided (*E*)-α,β-unsaturated ester **226** in 73% yield across three steps. Reduction with DIBAL-H in DCM and ensuing Sharpless asymmetric epoxidation gave epoxy alcohol **220**, which was protected with TBSOTf and DIPEA in DCM. A second Wittig reaction afforded terminal olefin **227** in 56% yield across four steps. Reduction with $Pd(OH)_2/C$ provided free alcohol **228** in 90% yield, which was subsequently treated with 1-phenyl-1*H*-tetrazole-5-thiol and TPP/DIAD to give thioether **229** in 80% yield, followed by treatment with molybdenum salt and H_2O_2 to afford sulfone **219** in 85% yield. Sulfone **219** was used in a Julia-Kocienski olefination with fragment **215** relying on KHMDS as base to give olefin **230** in 70% yield. Global deprotection of **230** involved desilylation with *p*-TSA in methanol, debenzylation with Pd/C under hydrogen atmosphere, and detosylation with Na/naphthalene and subsequent salt formation with acetic acid to give the salt of Penaresidin A (**1**) in 41% yield across three steps. The overall synthesis was conducted across 19 steps in 2.1% overall yield from commercially available D-galactal and nonanediol.[29]

17. Penaresidin B (Liu, 2015)

In 2015 Liu and coworkers sought to address the challenge that is a short and straightforward route to enantiomerically pure Penaresidin molecules, which include long-chain azetidines with contiguous stereocenters.[30] They applied a novel strategy involving a regio- and stereoselective tandem hydroamination/glycosylation as the key step to access 3-amino-2,3-dideoxysugar intermediate **233** from commercially available 3,4,6-tri-*O*-acetyl-D-galactal (**234**) (Figure 40). Diacetate **233** could be subjected to ring opening and Wittig olefination, which could then undergo an intramolecular Mitsunobu reaction to form azetidine **231**. The azetidine core **231** could be joined with **235** in a Julia-Kocienski olefination, used to access the target molecule. Fragment **235** was derived

from a Witting reaction between aldehyde **237** and stable ylide **236**.

Liu was able to construct the azetidine core in only 8 synthetic steps, beginning with tandem hydroamination/glycosylation of 3,4,6-tri-*O*-acetyl-D-galactal (**234**) with benzyl alcohol and *p*-toluenesulfonamide in DCE with $BF_3{\cdot}OEt_2$ to form **233** stereoselectively in 78% yield (Figure 41). Subsequent deprotection of the benzyl ether using $Pd(OH)_2/C$ under hydrogen atmosphere resulted in an aldehyde which was then subjected to a Wittig olefination and then reduction with Pd/C under a hydrogen atmosphere to give ester **238** in 43% yield across three steps. Treatment of the ester with PPh_3 and DIAD facilitated the intramolecular Mitsunobu reaction needed to achieve azetidine **239**, in 75% yield. A protecting group swap involved deacetylation under basic conditions and benzylations of both free alcohols with BnBr and NaH with cat. TBAI, followed by a chemoselective reduction with DIBAL-H afforded azetidine aldehyde **231** in 96% yield over three steps.[30]

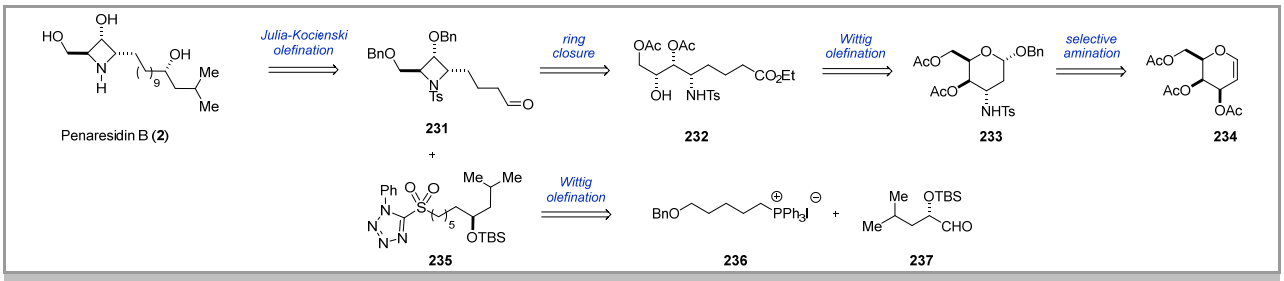


Figure 40. Liu 's 2015 retrosynthetic strategy for penaresidin B (**2**).

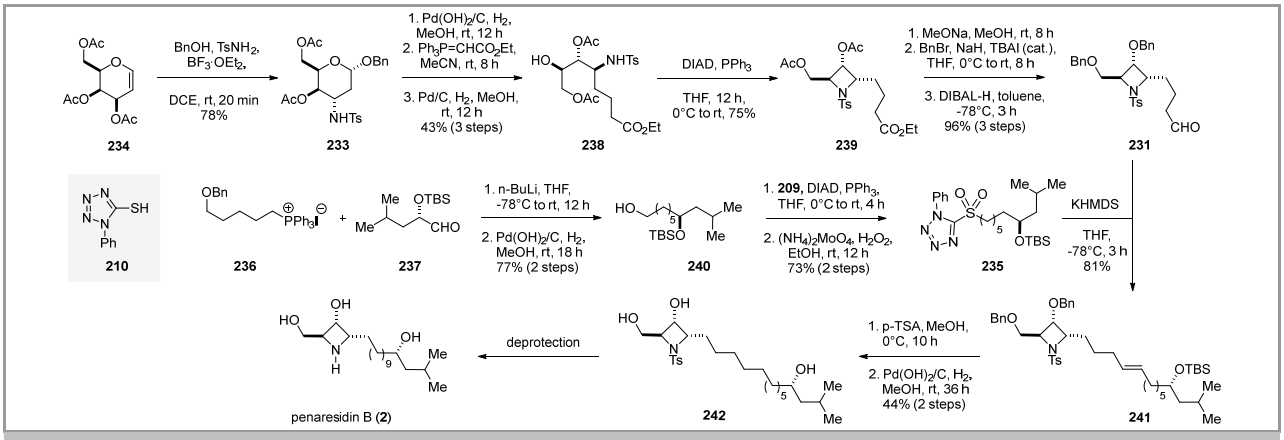


Figure 41. Liu 's forward synthesis toward penaresidin B (**1**).

18. Penresidin B (Yakura, 2018)

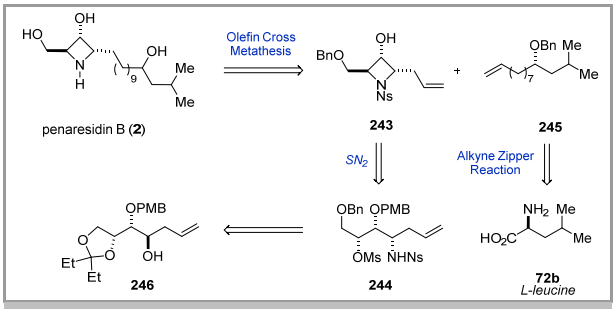


Figure 42. Yakura's 2018 retrosynthetic strategy for penaresidin B (**2**).

Yakura and coworkers took a more investigative approach to their 2018 synthesis of Penaresidin B (**2**), screening a range of conditions for the S_N2 type cyclization of amino-alkyl precursors for formation of the azetidine core.[31] They also differed in their strategy by applying olefin cross-metathesis to couple azetidine **243** and olefin fragment **245**, requiring less preparation of coupling partners than previously reported convergent methods such as Wittig and Julia-Kocienski olefinations (Figure 42). The azetidine fragment could be formed using **244** under optimized S_N2 cyclization conditions, which could be derived from acetal **246**, an intermediate used by Yakura in previous syntheses of pachastrissamines. The olefin fragment **245** could be reached from *L*-leucine (**72b**) via an alkyne zipper reaction.

Yakura leveraged their group's existing work to use **246** as a starting material, generated from commercially available diethyl *D*-tartrate. The free alcohol of **246** was tosylated and then treated with NaN_3 in DMF to afford **247** in 71% yield over two steps (Figure 43). The azide **247** was subsequently exposed to PPh_3 in THF-H_2O to reach the corresponding free amine in 87% yield. This then underwent a series of protecting group manipulations; first NsCl with Et_3N to protect the amine in 89% yield, then H_2SO_4 to deprotect the acetal in 81% yield yielding **248**, then BnBr, Bu_2SnO, and cat. TBAI to selectively protect the terminal alcohol in 89% yield, and finally treatment with MsCl and Et_3N in DCM to give protected olefin **244** in 96% yield. This set the stage for the optimized SN2 type cyclization of **244**, using NaH in DMF at 80 ℃ to afford an azetidine in 92% yield in under an hour. A subsequent reaction with DDQ selectively deprotected the benzyl ether to give fragment **243** in 75% yield.

L-leucine (**72b**) was subjected to Schurig's conditions of first HCl and $NaNO_2$ and then $LiAlH_2$ to stereoselectively afford epoxide **74b**. **74b** was then treated with a 1-octyne-derived lithium acetylide in the presence of $BF_3{\cdot}OEt_2$ to give the internal alkyne in 96% yield. An alkyne zipper reaction was then carried out with neat 1,3-diaminopropane and KH to isomerize to the terminal alkyne **249** in 85% yield. Lindlar's catalyst was used in the presence of quinoline to facilitate a partial hydrogenation affording the corresponding terminal alkene in 96% yield, which was subsequently protected with BnBr, NaH, and TBAI to give **245** in 80% yield. This fragment was then coupled with azetidine **243** using Grubbs 2nd generation catalyst in refluxing DCM to give mixed-olefin **250** in 74% yield. A protecting group swap on the amine was done with first PhSH and Cs_2CO_3 and then Boc-anhydride and Et_3N to give **251** in 79% yield across two steps. Treatment with Pd/C under a hydrogen atmosphere in ethanol then gave the straight chain azetidine in 99% yield. Finally, treatment with concentrated HCl afforded Penaresidin B (**2**) in 92% yield completing Yakura's total synthesis in overall 0.16% yield from 17 linear steps.[31]

19. Penaresidin B (DuBois, 2020)

In 2020 DuBois and coworkers showcased the utility of their intermolecular sp^3 C-H amination method in their strategy to reach Penaresidin B (**2**).[32] They had hypothesized that a complex azetidine core could be accessed by selective amination followed by intramolecular cyclization of **252** (Figure 44). Similar to the work of Yakura in 2018, the shortest reported synthesis of Penaresidin B at the time, DuBois also proposed using olefin cross-metathesis to join alkene fragments **253** and **26** to reach epoxide **252**. With (*R*)-2,2-dimethyl-4-vinyl-1,3-dioxolane (**26**) being commercially available, olefin **253** could be obtained from enantiopure oxirane **74b**.

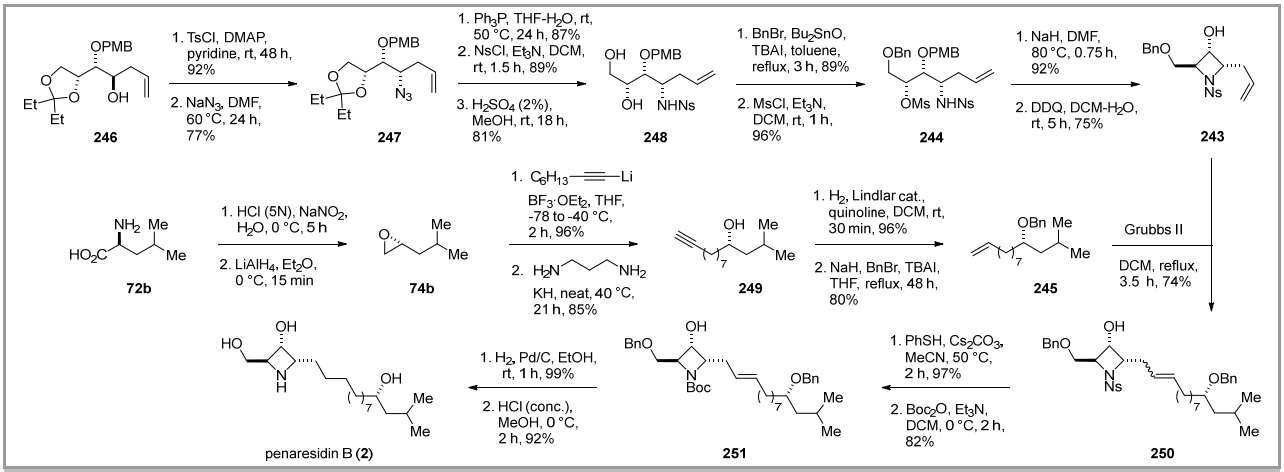


Figure 43. Yakura's forward synthesis to penaresidin B (**2**).

DuBois' first step was a selective organocuprate addition into enantiopure epoxide **74b** (hailing from an asymmetric epoxidation of terminal olefin **254**) to afford the alcohol utilized in the subsequent EDC coupling to provide *p*-nitrobenzoyl ester **255** in 69% yield over two steps (Figure 45). This was intended to limit reactivity of other C-H bonds for the key amination step, deactivating the carbinol and proximal tertiary sites. Grubb's cross-metathesis was then applied to protected **255** and commercially available (*R*)-2,2-dimethyl-4-vinyl-1,3-dioxolane (**26**), followed by epoxidation to give oxirane **256** as a ~7:1 mixture of diastereomers in 63% yield across two steps. The next step would involve sp^3 C-H amination of the dioxolane to give an intermediate *N*,*O*-acetal, however challenges in isolation necessitated the development of a one-pot procedure for sequential amination and reduction. With 1 mol% $[Rh_2(esp)_2]$ and $PhOSO_2NH_2$ followed by $NaBH_3CN$ in AcOH, the desired transformation was achieved resulting in amino alcohol **257** in 32% over two steps as a ~5:1 mixture favoring the desired stereoisomer. From here epoxide **257** was opened using $CeBr_3$ at the internal position to furnish a bromohydrin, which was treated with potassium carbonate to facilitate SN2-type cyclization to form azetidine **258** in 58% yield over two steps. Global deprotection involved $Ni(dppp)Cl_2$ and MeMgBr to remove the nitrobenzoate, then HCl to remove the sulfamate reaching Penaresidin B (**2**) in 86% yield. This concluded DuBois' enantioselective synthesis in overall 6.8% yield across only 9 steps, a substantial decrease in step count from past efforts.[32]

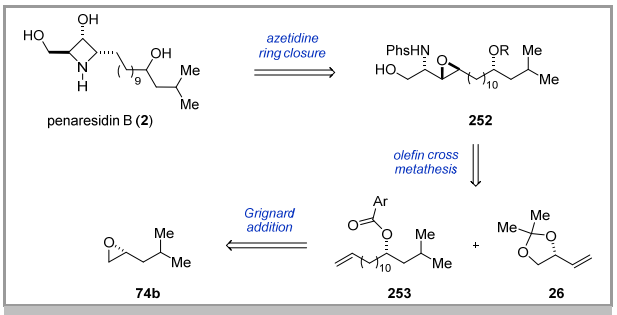


Figure 44. DuBois' 2020 retrosynthetic strategy for penaresidin B (**2**).

20. Penaresidin Analogs (Bodnár, 2021)

Due to the promising bioactivity of penaresidins, synthetic analogs have been made and investigated for their biological activities.[10] Kobayashi has synthesized six novel stereoisomeric analogs of penaresidin B (**2**) and showed that they possessed comparable or better activities in anticancer and antimicrobial screens than the original molecule.[5] Bodnár and coworkers expanded on this in 2021 with the synthesis of two more novel stereoisomers of Penaresidin B with simple non-functionalized side chains, **16** and **17**.[10] Bodnár proposed that both target molecules could be reached using the same strategy (Figure 46); access to the desired alkaloid could be achieved through a ring-closing substitution in **259**/**261**, which followed olefin cross-metathesis to couple tetradec-1-ene and alkene fragment **260**/**262** together. Fragments **260** and **262** could arise from an Overman rearrangement of **263**, introducing a nitrogen atom and key stereocenter. Olefin **264** could be derived from a known *D*-ribofuranose scaffold.

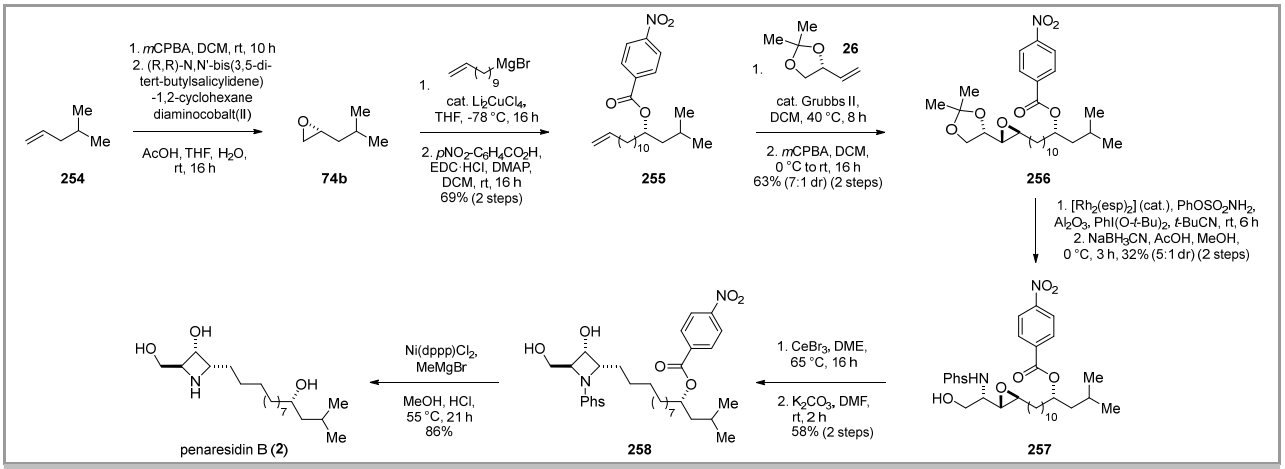


Figure 45. DuBois' forward synthesis for penaresidin B (**2**).

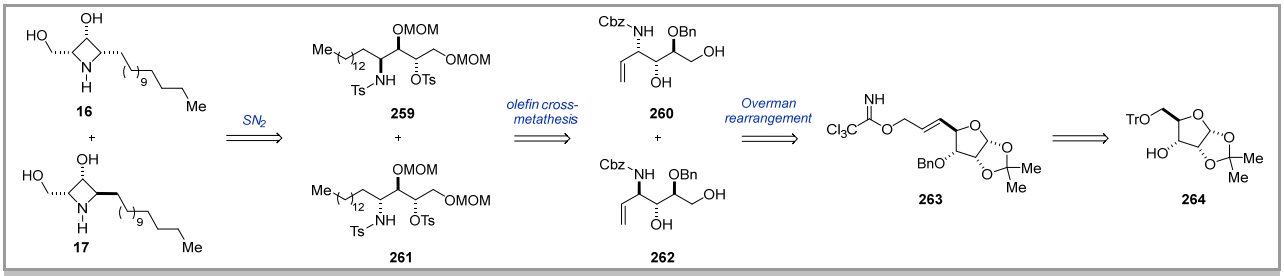


Figure 46. Bodnár's 2021 retrosynthetic strategy for penaresidin analogs **16** and **17**.

Bodnár started preparation of ribofuranose **264** with benzylation of the free alcohol (Figure 47). Detritylation using CSA in MeOH followed. Next a IBX oxidation/Horner-Wadsworth Emmons olefination was delivered in a one-pot fashion to furnish exclusively the (*E*)-α,β-unsaturated ester **265** in 85% yield across four steps. **265** was then reduced with DIBAL-H to give the corresponding alcohol in 96% yield. Subsequent treatment with Cl_3CCN and DBU led to imidate **263** in quantitative yield. Overman rearrangement of **263** was mediated by microwave irradiation in the presence of potassium carbonate at the optimized temperature of 210 ℃ to provide a mixture (51:49) of acetamide epimers **266** and **267** in 95% yield. The two intermediates were then separated and each subjected to the same synthetic strategy proposed by Bodnár.

A protecting group swap was achieved across by treating **266** and **267** with DIBAL-H in DCM then CbzCl in the presence of $NaHCO_3$ to afford protected furanoses **268** (94% yield across two steps) and **269** (95% yield across two steps) respectively. Acetonide deprotection was carried out under acidic conditions ($AcOH/H_2O$ and HCl for **268**, TFA/H_2O for **269**) before oxidation cleavage of the carbohydrates with $NaIO_4$ and subsequent reduction with $NaBH_4$ to reach aminotriols **260** (82% yield over three steps) and **262** (60% yield over three steps). Selective protection of the terminal alcohol using MOMCl and Hünig's base gave the corresponding ethers. Tetradec-1-ene was then coupled to each intermediate in the presence of Grubbs 2nd generation catalyst exclusively yielding the (*E*)-olefins, which was then followed by reduction of the alkene by catalytic hydrogenation and protection of the internal secondary alcohol using TsCl and Et_3N to furnish fully protected intermediates **259** (58% yield across four steps) and **261** (52% yield across four steps). DBU was chosen as the base to facilitate cyclization, forming the core azetidines. Global deprotection followed, first using sodium naphthalenide in THF to remove the tosyl group, and then refluxing in HCl to give the penaresidin-based alkaloids **16** (50% yield across three steps) and **17** (47% yield across three steps). This leads to an overall yield of 9.3% for **16** and 5.8% for **17**.[10]

21. Conclusion

The natural products penaresidin A (**1**) and B (**2**), and penazetidine A (**3**) have fascinated and challenged synthetic chemists since the first reports of their isolation by Kobayashi and Crews in 1991 and 1994, respectively. The highly functionalized azetidine core common to the penaresidins A (**1**), B (**2**), and penazetidine A (**3**) in connection with desirable

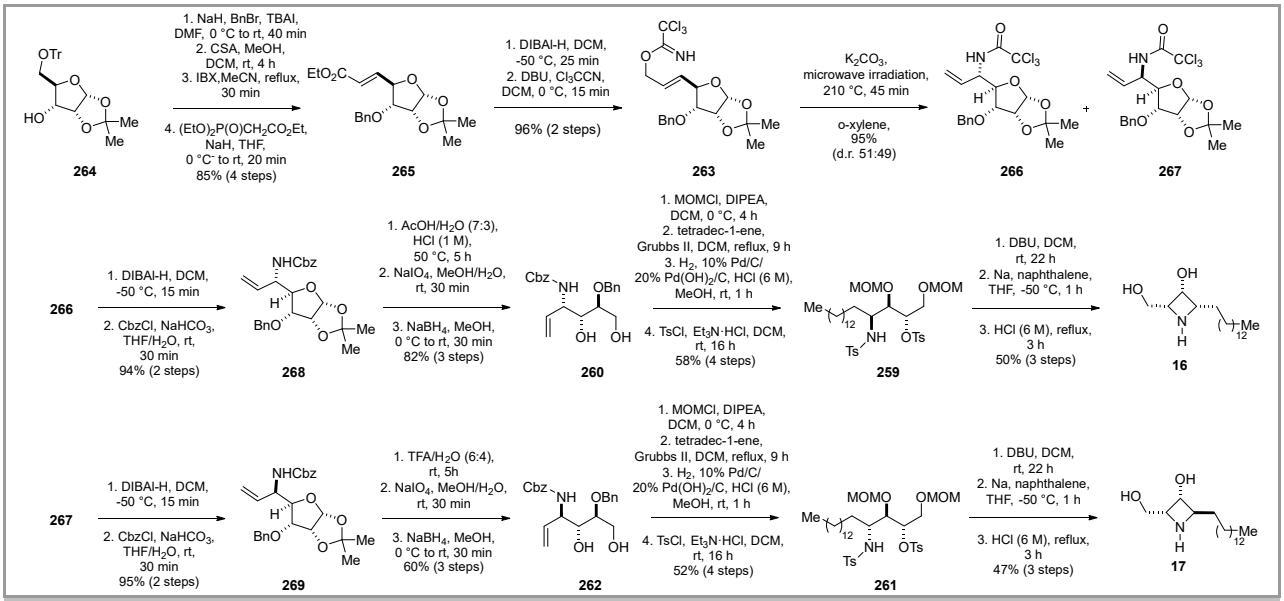


Figure 47. Bodnár's forward synthesis for penaresidin straight chain analogs **16** and **17**.

biological activities associated with these sphingolipids have led to significant synthetic interest with a first report towards a penaresidin analog published as early as 1995 by Kamikawa and coworkers. Since then, numerous synthetic penaresidin and penazetidin analogs varying in the absolute configuration of the penaresidin core and pendant aliphatic sidechain have been synthesized and evaluated upon their biological activity. In addition to significant efforts concerning analog synthesis, 3 total syntheses of penaresidin A (**1**) and 6 total syntheses of penaresidin B (**2**) have since been reported. Furthermore, one successful total synthesis of penazetidine A (**3**) has been achieved. It is important to note that all of these approaches rely on a nucleophilic substitution strategy to access the core azetidine scaffold.

Conflict of Interest

The authors declare no conflict of interest.

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