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SYNTHESIS OF SPHINGOSINE-RELATED AZETIDINE ALKALOIDS, PENARESIDINS: CONSTRUCTION OF HIGHLY SUBSTITUTED AZETIDINE RINGS

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Abstract – Penaresidin A and B are sphingosine-related natural products that contain a 2,3,4-trisubstituted azetidine ring and a long alkyl side chain. Stereoselective construction of the trisubstituted azetidine ring is a crucial step in the synthesis of penaresidins, and all the currently reported syntheses have been accomplished by S_N2-type cyclization of a precursor having a 1-amino-2,3-diol structure with three continuous stereocenters. This cyclization is strongly influenced by the configurations of the vicinal amino alcohol moieties of the precursors. This review focuses on the S_N2-type cyclizations that are used to construct the trisubstituted azetidine ring in penaresidin synthesis.

Dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday.

CONTENTS

1. INTRODUCTION

Penaresidin A (**1**) and B (**2**) were first isolated as a mixture from the Okinawan marine sponge *Penares* sp. by the Kobayashi group in 1991 (Figure 1).[1] These compounds are regarded as sphingosine-related natural products and comprise a 2,3-*anti*-3,4-*syn*-trisubstituted azetidine ring core and a long alkyl side chain. The

absolute configurations of **1** and **2** were determined to be (2*S*,3*R*,4*S*,15*S*,16*S*) and (2*S*,3*R*,4*S*,15*S*), respectively, by synthetic studies[2,3] and NMR analysis[4] using the modified Mosher method. Penaresidins **1** and **2** exhibit potent actomyosin ATPase-activating activities,[1] and **2** shows modest cytotoxicity against murine lymphoma L1210 cells.[5] Several stereoisomers **3**–**7** and analogs **8**–**19** of **1** and **2** (Figure 2) have also been reported, and some of them have been evaluated using biological assays. The side chain analogs (16*S*)- and (16*R*)-penazetidine **8** and **9** have been demonstrated to exhibit protein kinase C inhibitory activities.[6] The straight side chain analogs **10**–**15** also provided interesting results,[5] with the 2,3-*anti*-3,4-*syn*- and 2,3-*anti*-3,4-*anti*-isomers **10** and **11** exhibiting higher cytotoxicity against human lung (A549) and colon (HT29) cancer cells than **2**. Analogs **10**, **13** (*ent*-**10**), and **14** (*ent*-**11**) exhibit antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*, *Micrococcus luteus*, and *Staphylococcus aureus*), and **11** exhibits antibacterial activity against both Gram-positive bacteria and the Gram-negative bacterium *Escherichia coli*.[5] Moreover, the *N*-acyl-*O*-glycosylated straight side chain analog of **10**, i.e., α-**18** (RCAI-18), has been reported to exhibit potent cytokine-inducing activity in mouse killer T cells.[7] Accordingly, the unique structural features and interesting biological activities of penaresidins, as well as their stereoisomers and analogs, have attracted considerable attention as synthetic targets.

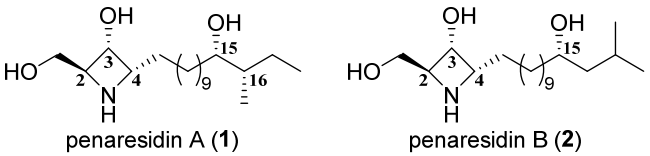


Figure 1. Structures of penaresidin A (**1**) and B (**2**)

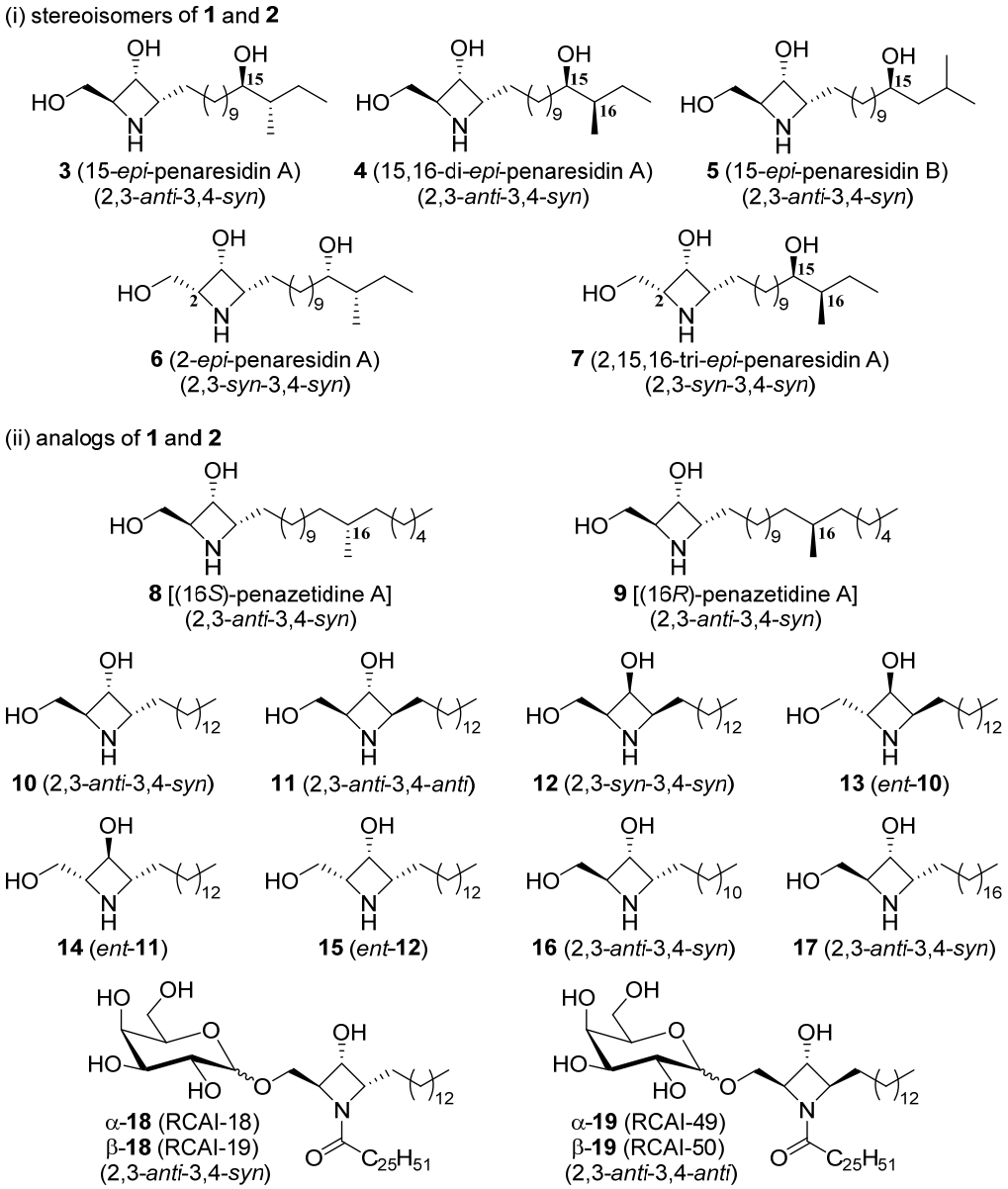
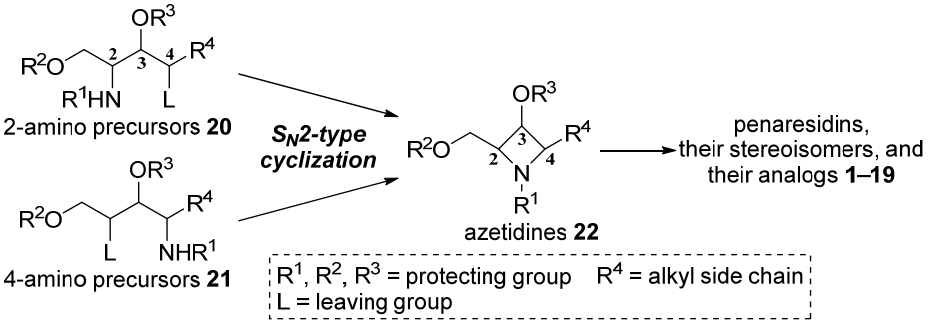


Figure 2. Structures of the currently reported penaresidin stereoisomers and analogs **3**–**19**

In the synthesis of these targets, a key issue is the construction of the trisubstituted azetidine structure because an azetidine is a highly strained four-membered heterocycle, which is rather difficult to form.[8] Among the various methods for azetidine synthesis developed to date, S_N2-type cyclization is the most common. Indeed, all of the reported syntheses of penaresidins, their stereoisomers, and their analogs have been accomplished using this methodology. These S_N2-type cyclizations are classified into two categories (Scheme 1): i) those proceeding from 2-amino precursors **20**, and ii) those proceeding from 4-amino precursors **21**. Both precursors should have three continuous stereocenters at the C-2, C-3, and C-4 positions. For the synthesis of natural penaresidins having 2,3-*anti*-3,4-*syn*-azetidine structures, stereoselective preparation of either 2,3-*anti*-3,4-*anti*-**20** or 2,3-*syn*-3,4-*syn*-**21** species is required. Precursors **20** are used more than **21** because penaresidins are biogenetically related to natural phytosphingosines. The cyclization

of **20** and **21** is dependent on their structural features, such as their configurations, protecting groups, and side chains. Thus, it is very important to understand the effects of such structural features on the cyclization. Herein, we present a review of the synthesis of penaresidins, their stereoisomers, and their analogs, mainly focusing on the construction of azetidine rings by SN2-type cyclizations. We also consider the stereoselective preparation of precursors for the cyclization.

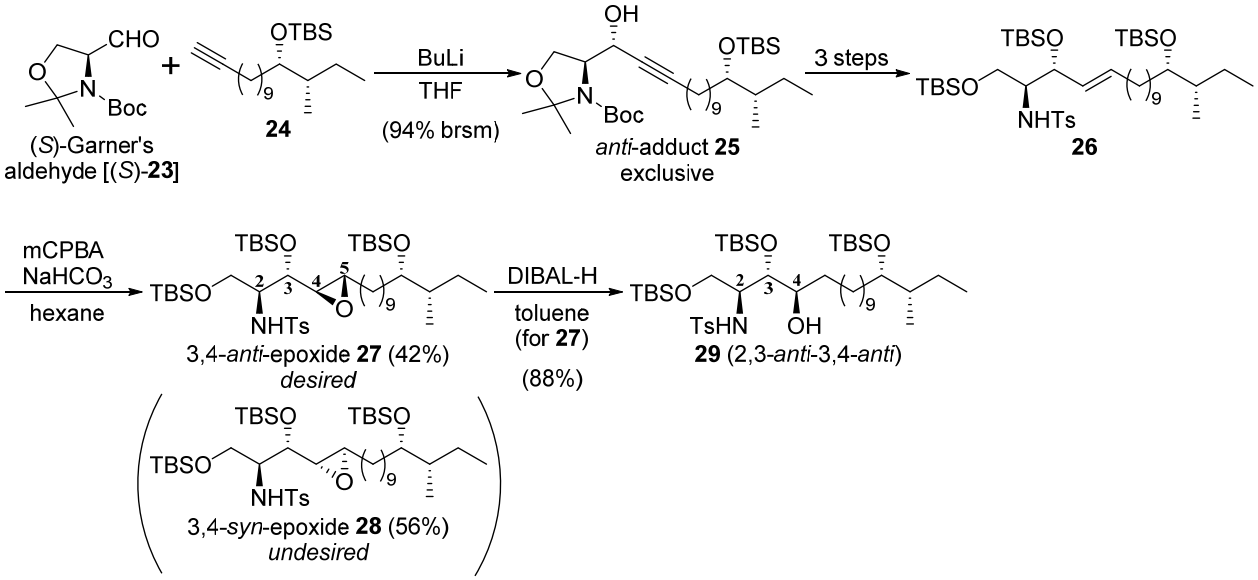


Scheme 1. SN2-type cyclizations in the synthesis of penaresidins, their stereoisomers, and their analogs

2. CONSTRUCTION OF AZETIDINE RINGS FROM 2-AMINO PRECURSORS

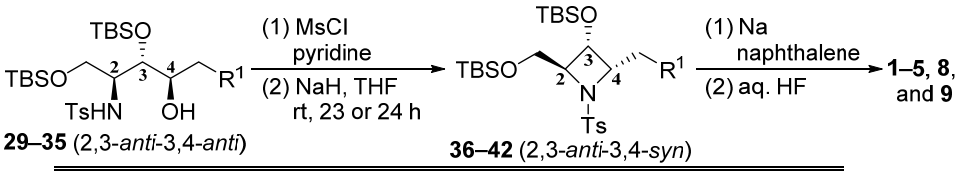
2.1 CONSTRUCTION AFTER INTRODUCTION OF THE SIDE CHAIN

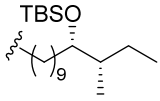
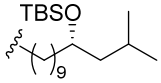
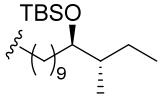
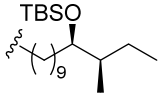
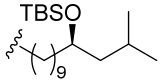
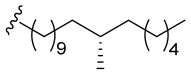
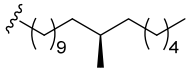
2-Amino precursors are often employed for the SN2-type cyclization. In most cases, these precursors bear a side chain moiety. The Mori group succeeded in the cyclization of several 2,3-*anti*-3,4-*anti*-precursors for the first syntheses of penaresidin A (**1**), B (**2**), as well as their stereoisomers **3**–**5** and analogs **8**, **9** in the mid-1990s.[2,3,9] The synthesis of the 2,3-*anti*-3,4-*anti*-precursor **29** proceeded from (*S*)-Garner's aldehyde [(*S*)-**23**] (Scheme 2). Based on Garner's procedure for the synthesis of sphingosines,[10] the reaction of (*S*)-**23** with the acetylide of alkyne **24** afforded the *anti*-adduct **25** diastereoselectively. Adduct **25** was then converted into *N*-Ts-*O*-*tert*-butyldimethylsilyl (TBS)-protected sphingosine derivative **26** in three steps. Epoxidation of **26** with *m*-chloroperbenzoic acid (mCPBA) gave the desired 3,4-*anti*-epoxide **27** in only 42% yield accompanied by the undesired 3,4-*syn*-epoxide **28** in 56% yield. After separation by column chromatography, reductive ring-opening of **27** with diisobutylaluminium hydride (DIBAL-H) proceeded regioselectively to afford the 2,3-*anti*-3,4-*anti*-precursor **29**. The other precursors **30**–**35** shown in Table 1 were synthesized in similar manner to **29**. Construction of azetidine rings from 2,3-*anti*-3,4-*anti*-precursors **29**–**35** was performed in two steps (Table 1). Thus, mesylation of **29**–**35** followed by SN2-type cyclization with NaH in THF at room temperature for 23 or 24 h successfully produced 2,3-*anti*-3,4-*syn*-azetidines **36**–**42** in high yields (72–88%) from **29** to **35**, respectively. Penaresidins **1**–**5**, **8**, and **9** were synthesized from **36** to **42** by removal of the protecting groups in two steps.



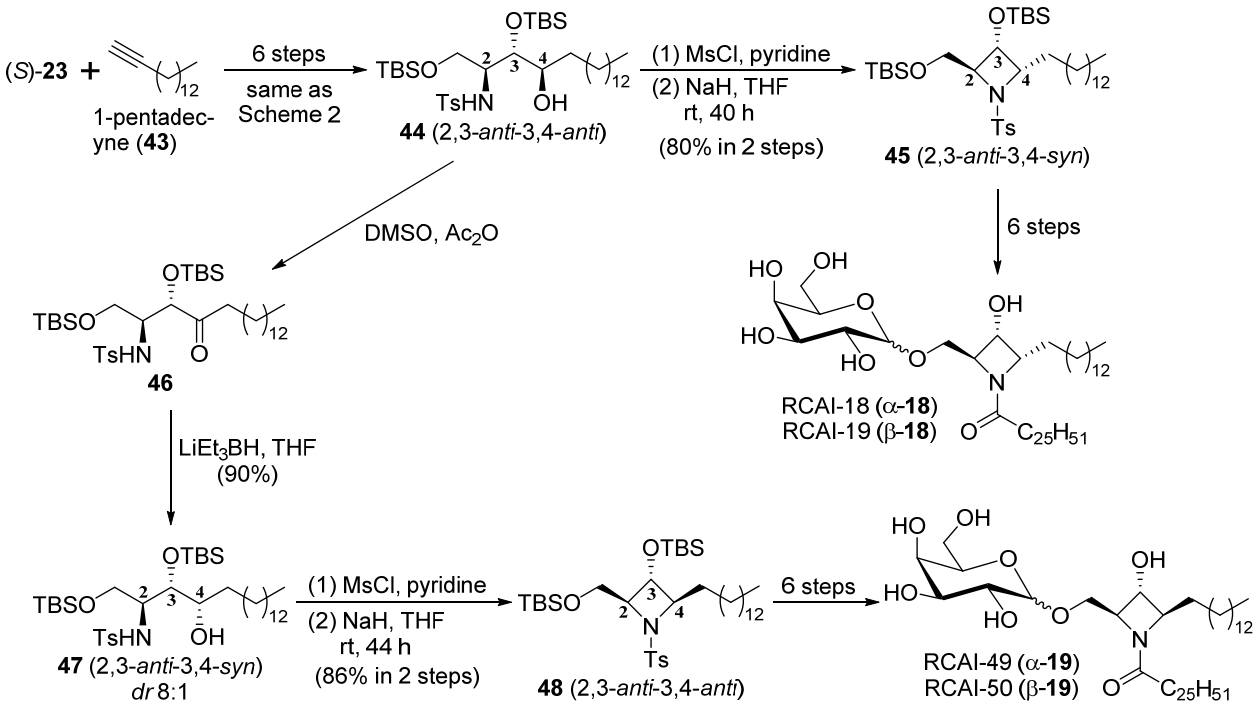
Scheme 2. Synthesis of 2-amino precursor **29**.[2,3] Boc = *tert*-butoxycarbonyl

Table 1. Mesylation and subsequent S_N2-type cyclization of **29**–**35** and synthesis of penaresidins **1**–**5**, **8**, and **9**[2,3,9]



entry	precursor	R^1	azetidine	yield (%)
1	**29**		**36**	81
2	**30**		**37**	75
3	**31**		**38**	88
4	**32**		**39**	78
5	**33**		**40**	72
6	**34**		**41**	76
7	**35**		**42**	79

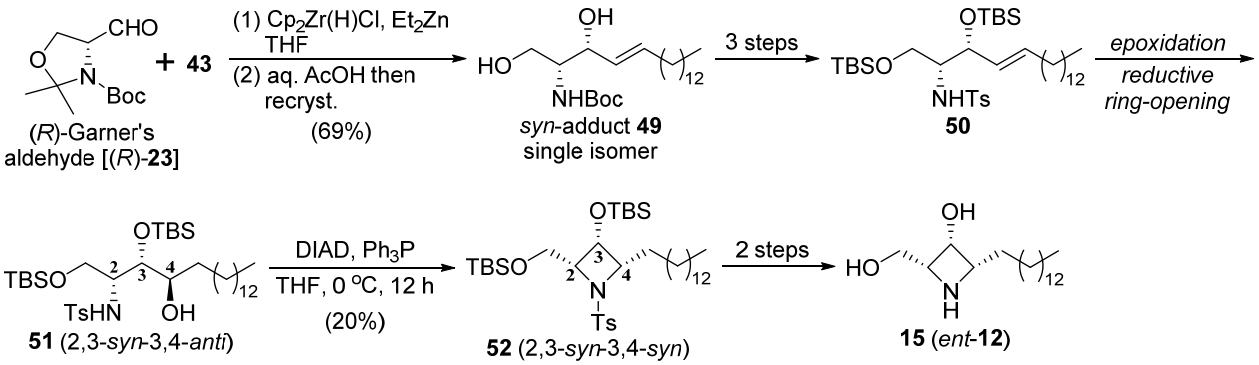
Mori and colleagues applied their method to the construction of 2,3-*anti*-3,4-*syn*-azetidine **45** and 2,3-*anti*-3,4-*anti*-azetidine **48** having straight alkyl side chains for the synthesis of *N*-acyl-*O*-glycosylated analogs **18** (RCAI-18 and 19) and **19** (RCAI-49 and 50) (Scheme 3).[7] To synthesize azetidine **45** with the same stereochemistries of the azetidine ring as **36**–**42**, the 2,3-*anti*-3,4-*anti*-precursor **44** was obtained from (*S*)-**23** and 1-pentadecyne (**43**) in a similar manner to that by which precursor **29** was obtained. S_N2-type cyclization of the mesylate of **44** was performed under similar reaction conditions to those used for **29**–**35** to afford 2,3-*anti*-3,4-*syn*-azetidine **45** in 80% yield from **44** after 40 h. Compound **45** was converted into α-**18** and β-**18** in six steps. The 2,3-*anti*-3,4-*syn*-precursor **47** for the synthesis of **48** was prepared from **44** through stereoinversion at the C-4 position. Thus, the oxidation of **44** under Albright-Goldman oxidation conditions[11] gave ketone **46**, which was reduced with $LiEt_3BH$ to afford **47** with high diastereoselectivity (*dr* 8:1). Cyclization of the mesylate of **47** under the same conditions as those used for **44** successfully generated the desired 2,3-*anti*-3,4-*anti*-azetidine **48** in 86% yield after 44 h. Azetidine **48** led to α- and β-**19** in the same manner.



Scheme 3. Synthesis of α-**18** (RCAI-18), β-**18** (RCAI-19), α-**19** (RCAI-49), and β-**19** (RCAI-50) using S_N2-type cyclization of the mesylates of 2,3-*anti*-3,4-*anti*- and 2,3-*anti*-3,4-*syn*-precursors **44** and **47**[7]

Kobayashi and colleagues reported the S_N2-type cyclization of 2,3-*syn*-3,4-*anti*-precursor **51** (Scheme 4) in addition to those of 2,3-*anti*-3,4-*anti*- and 2,3-*anti*-3,4-*syn*-isomers in the synthesis of the straight side chain analogs **10**–**12** and their enantiomers **13**–**15**.[5] Analogs **10**, **11**, **13**, and **14** were synthesized from (*S*)- or (*R*)-**23** and **43** using S_N2-type cyclization of the 2,3-*anti*-3,4-*anti*- and 2,3-*anti*-3,4-*syn*-isomers according

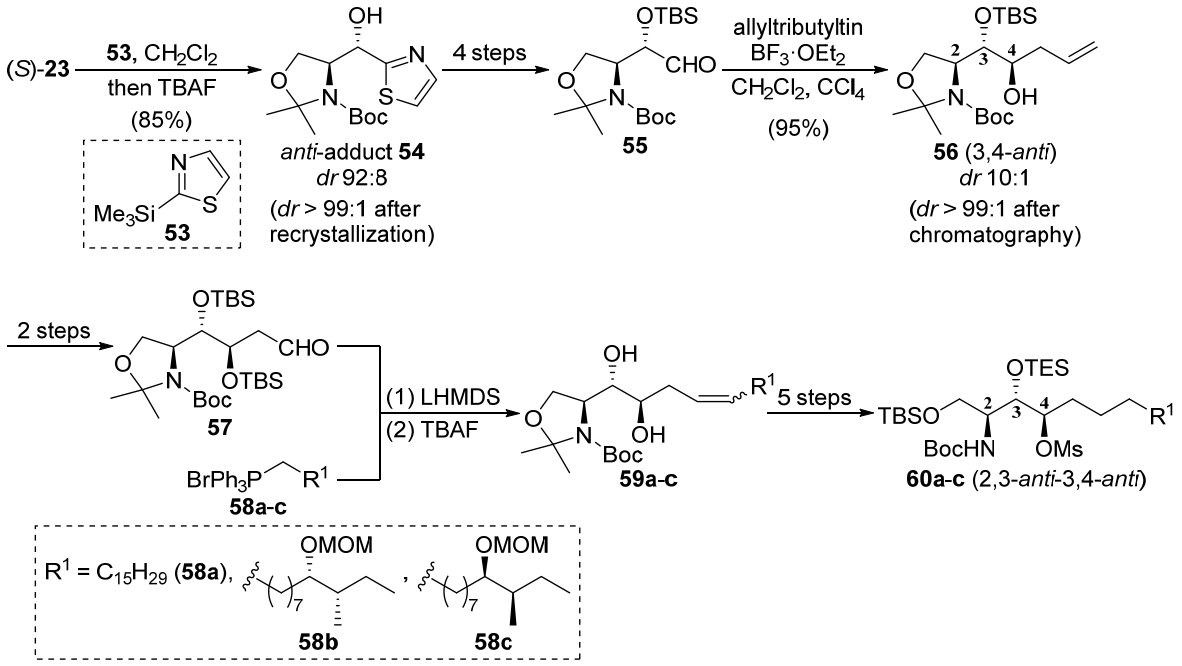
to Mori's procedure.[2,3,7,9] To synthesize **15**, the 2,3-*syn* relation of precursor **51** was established using zirconium chemistry. Thus, addition of 1-alkenyl nucleophiles derived by hydrozirconation of **43** with $Cp_2Zr(H)Cl$ and Et_2Zn to (*R*)-**23** and subsequent treatment with aqueous AcOH gave *syn*-adduct **49**[12] in diastereomerically pure form after recrystallization. Precursor **51** was obtained from **49** *via* alkene **50** by Mori's epoxidation-reduction sequence. When cyclization of **51** was performed under Mitsunobu reaction conditions using diisopropyl azodicarboxylate (DIAD) and Ph_3P in THF at 0 °C for 12 h, the desired 2,3-*syn*-3,4-*syn*-azetidine **52** was obtained, albeit in only 20% yield. Deprotection of **52** produced **15**. Synthesis of **12** was accomplished from (*S*)-**23** and **43** in the same manner as **15**.



Scheme 4. Synthesis of straight side chain analog **15** using S_N2-type cyclization of 2,3-*syn*-3,4-*anti*-precursor **51**[5]

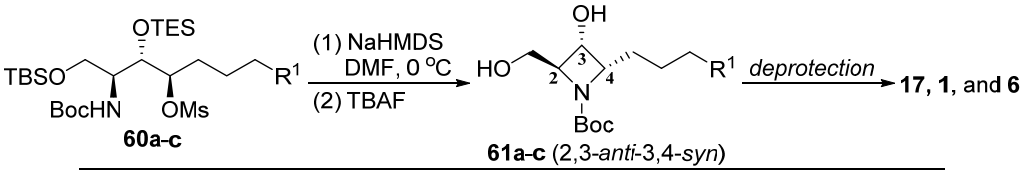
Knapp and coworkers employed a Boc group as an amino-protecting group in the 2,3-*anti*-3,4-*anti*-precursors **60a**–**c** for the synthesis of **1**, its stereoisomer **6** and analog **17**.[13] Precursors **60a**–**c** were prepared from the same starting material (*S*)-**23** as that used by Mori *et al.* by addition of 2-(trimethylsilyl)thiazole (**53**) as a formyl anion equivalent to (*S*)-**23** and Keck allylation of aldehyde **55** (Scheme 5). According to Dondonis' procedure,[14] the reaction of (*S*)-**23** with **53** followed by treatment with tetrabutylammonium fluoride (TBAF) selectively produced the *anti*-adduct **54** (*dr* 92:8), which was recrystallized to provide **54** in diastereomerically pure form. After conversion[15] of **54** into aldehyde **55**, Keck allylation[16] using allyltributyltin and $BF_3{\cdot}OEt_2$ generated 3,4-*anti*-homoallylic alcohol **56** with high diastereoselectivity (*dr* 10:1). Diastereomerically pure **56** was obtained by chromatographic separation. The pure diastereomer **56** was transformed into aldehyde **57** in two steps. Extension of the side chain of **57** by Wittig reaction using phosphonium bromide **58a** and lithium hexamethyldisilazide (LHMDS) followed by desilylation with TBAF gave alkene **59a**, which led to the 2,3-*anti*-3,4-*anti*-precursor **60a** in five steps. Synthesis of **60b** and **60c** was also achieved in the same manner as **60a** using **58b** and **58c** as phosphonium bromides, respectively. As shown in Table 2, S_N2-type cyclization of **60a**–**c** was performed with sodium hexamethyldisilazide (NaHMDS) in DMF at 0 °C to give the corresponding azetidines, the silyl groups of which were removed

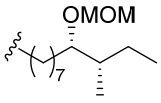
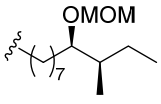
with TBAF to afford **61a**–**c** in high (81–84%) yields. The desired products **17**, **1**, and **6** were obtained by acidic deprotection of **61a**–**c**.



Scheme 5. Preparation of 2,3-*anti*-3,4-*anti*-precursors **60a**–**c**.[13] TES = triethylsilyl

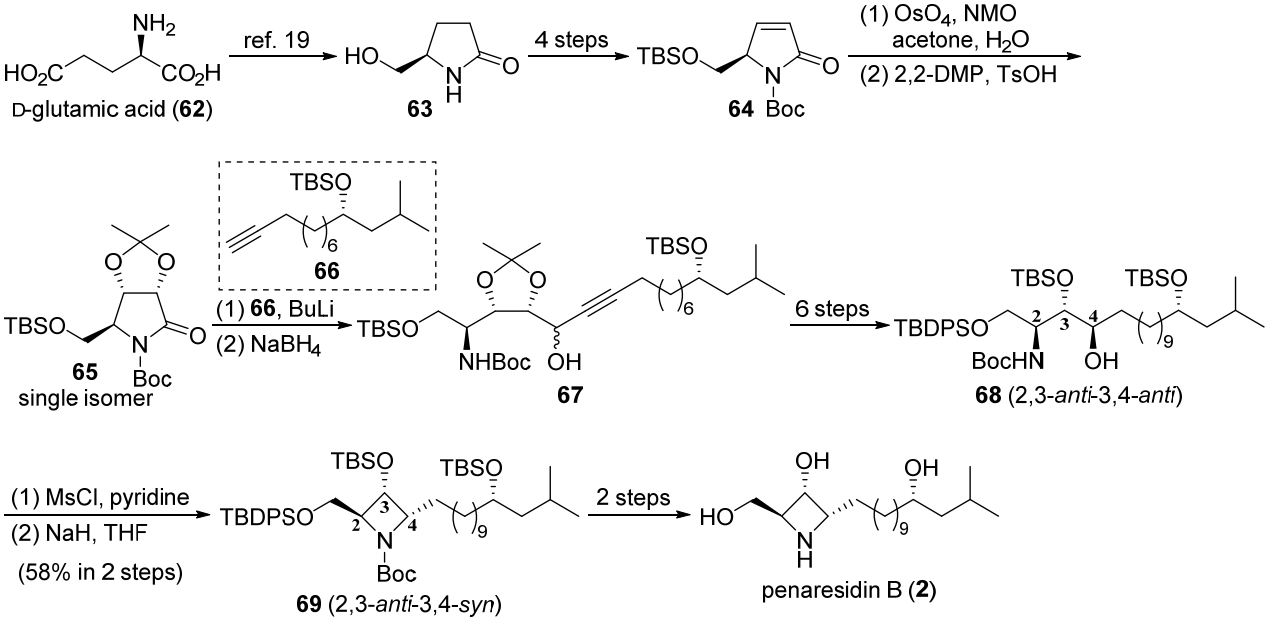
Table 2. S_N2-type cyclization of **60a**–**c** and synthesis of penaresidins **17**, **1**, and **6**[13]



entry	precursor	R^1	azetidine	yield (%)
1	**60a**	$C_{15}H_{29}$	**61a**	81
2	**60b**		**61b**	84
3	**60c**		**61c**	84

The *N*-Boc-2,3-*anti*-3,4-*anti*-precursor **68** was prepared from D-glutamic acid (**62**) through the formation of the bicyclic lactam **65**[17] for the synthesis of penaresidin B (**2**) by Yoda and coworkers (Scheme 6).[18] After preparation of hydroxylactam **63** from **62** according to literature methods,[19] **63** was converted into unsaturated lactam **64** in four steps. Stereoselective dihydroxylation of **64** with a catalytic amount of OsO_4

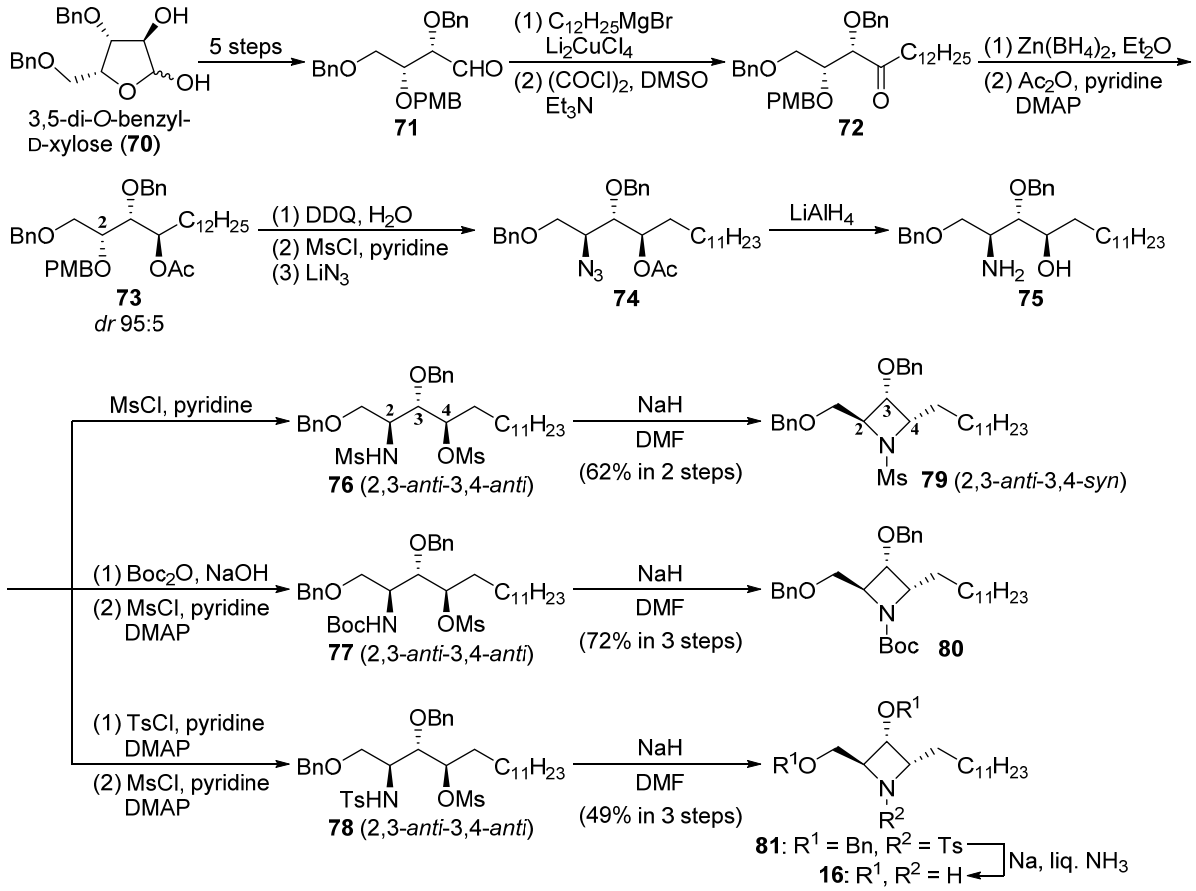
in the presence of *N*-methylmorpholine *N*-oxide (NMO) followed by protection of the resulting diol group with 2,2-dimethoxypropane (2,2-DMP) under acidic conditions provided bicyclic lactam **65** as a single isomer. After treatment of alkyne **66** with BuLi, reaction of the resulting acetylide with **65** and subsequent reduction with $NaBH_4$ generated secondary alcohol **67** as a mixture of diastereomers. The 2,3-*anti*-3,4-*anti*-precursor **68** was obtained in six steps from **67**. S_N2-type cyclization of the mesylate of **68** with NaH in THF resulted in a moderate (58%) yield of 2,3-*anti*-3,4-*syn*-azetidine **69** in two steps. The amino- and hydroxy-protecting groups of **69** were then removed to afford **2**.



Scheme 6. Synthesis of penaresidin B (**2**) using S_N2-type cyclization of the 2,3-*anti*-3,4-*anti*-precursor **68**[18]

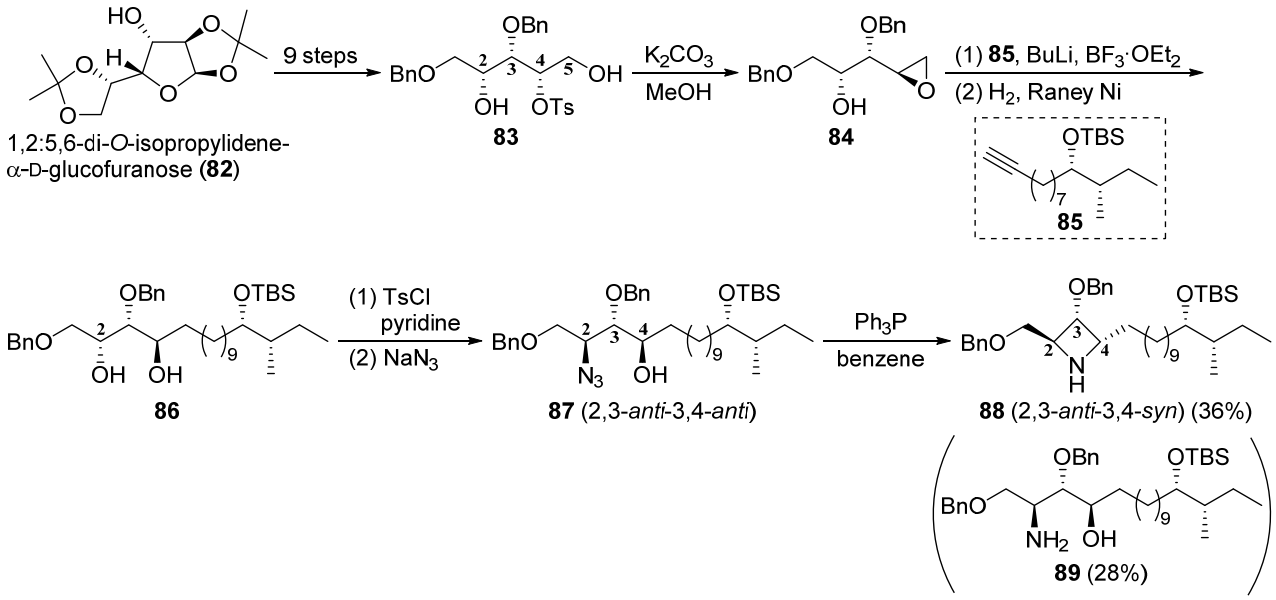
Kamikawa *et al.* used benzyl groups as hydroxy-protecting groups in the 2,3-*anti*-3,4-*anti*-precursors **76**–**78** having *N*-Ms, *N*-Boc, and *N*-Ts groups, respectively, for synthesizing the straight side chain analog **16** (Scheme 7).[20] Preparation of **76**–**78** was started from 3,5-di-*O*-benzyl-D-xylose (**70**) *via* amino alcohol **75**. After conversion of **70** into aldehyde **71** in five steps, nucleophilic addition of $C_{12}H_{25}MgBr$ to **71** in the presence of Li_2CuCl_4 produced the corresponding secondary alcohol as a mixture of diastereomers (*dr* 1:1). The mixture was then oxidized to ketone **72**, which was reduced with $Zn(BH_4)_2$ and then acetylated to give acetate **73** with high diastereoselectivity (*dr* 95:5). After removal of the *p*-methoxybenzyl (PMB) group of **73**, stereoinversion of the C-2 position was conducted using S_N2-type azidation to produce azide **74**. Reduction of **74** with $LiAlH_4$ gave **75**, which was converted into **76**–**78** in one or two steps. The *N*-Ms-precursor **76** was subjected to S_N2-type cyclization with NaH in DMF to provide 2,3-*anti*-3,4-*syn*-azetidine **79** in 62% yield in two steps. The *N*-Boc-precursor **77** was cyclized to give azetidine **80** in 72% yield in three steps. The cyclization of *N*-Ts-precursor **78** was also conducted, affording the corresponding azetidine

81 in lower (49%) yield than those of **76** and **77**. The synthesis of **16** was achieved by deprotection of **81** under Birch reduction conditions.



Scheme 7. Preparation and S_N2-type cyclization of 2,3-*anti*-3,4-*anti*-precursors **76**–**78** for the synthesis of analog **16**.[20] DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, DMAP = 4-(dimethylamino)pyridine

The *N*-unprotected 2,3-*anti*-3,4-*anti*-azidoalcohol **87** was employed as a precursor for the synthesis of penaresidin A derivative **88** by Ducrot *et al*. (Scheme 8).[21] Azidoalcohol **87** was prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**82**). The starting material **82** was converted into 4-tosyloxy-2,5-diol **83** in nine steps. The reaction of **83** with K_2CO_3 in MeOH proceeded with inversion of the C-4 configuration to afford epoxide **84**.[22] Addition of the lithium acetylide of **85** to **84** in the presence of $BF_3{\cdot}OEt_2$ followed by reduction of the alkyne moiety with Raney Ni under hydrogen afforded diol **86**. Tosylation of **86** proceeded regioselectively to afford the corresponding C-2 tosylate, which was subjected to S_N2-type azidation to form azidoalcohol **87** with inversion of the C-2 configuration. Reaction of **87** with Ph_3P in benzene proceeded through the formation of an iminophosphorane intermediate[23] to afford the desired penaresidin derivative **88** in 36% yield, even though a substantial amount (28% yield) of amino alcohol **89** was formed by hydrolysis of the iminophosphorane.

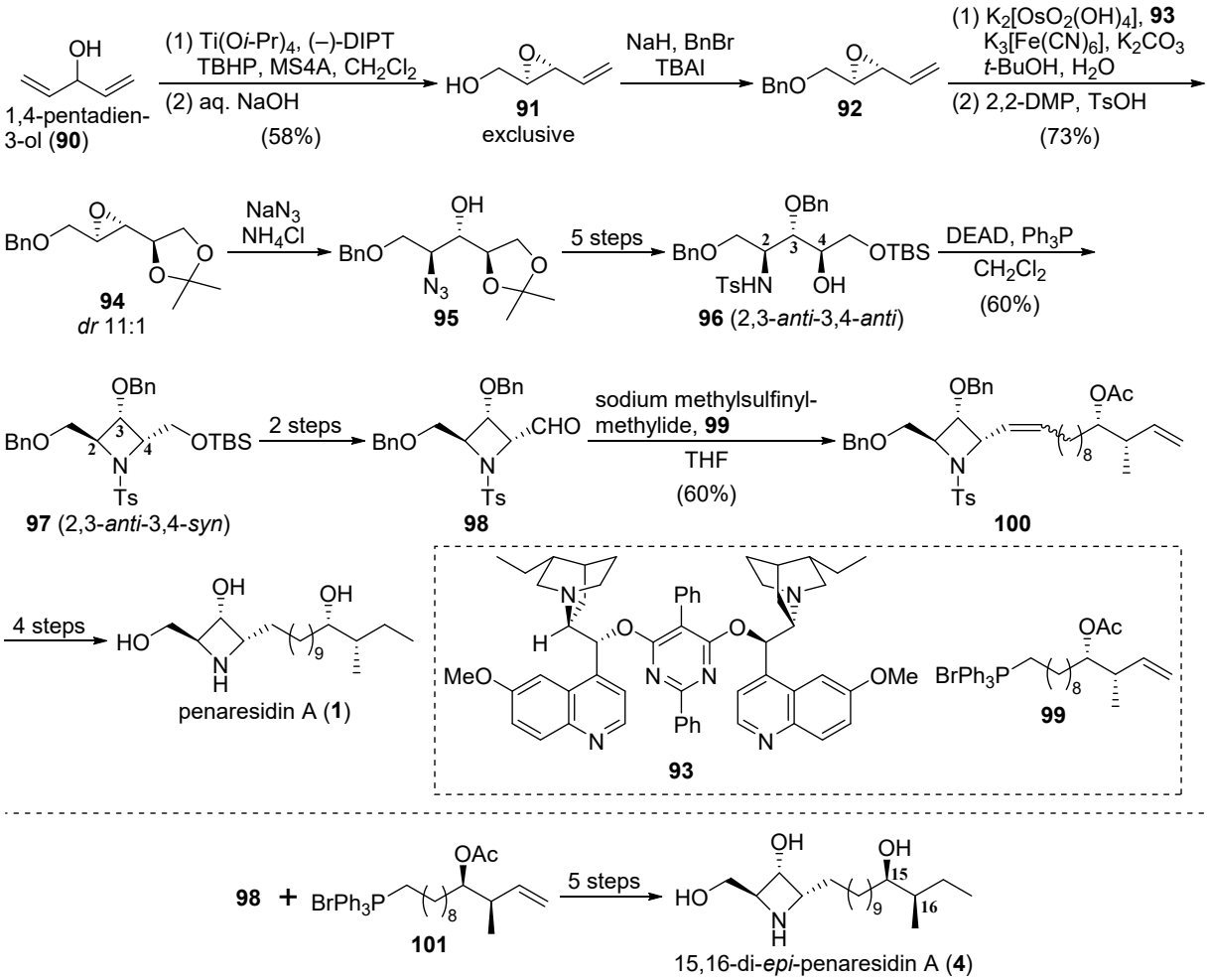


Scheme 8. Preparation and cyclization of 2,3-*anti*-3,4-*anti*-azidoalcohol **87** for synthesis of the penaresidin A derivative **88**[21]

2.2 CONSTRUCTION BEFORE INTRODUCTION OF THE SIDE CHAIN

In most cases in which 2-amino precursors are employed, the azetidine rings are constructed at a later stage after the introduction of the side chains. This may be because this late-stage construction can minimize the exposure of the reactive azetidine structure to the subsequent reactions required to obtain the target compounds. However, synthetic approaches in which the azetidine ring is constructed before introduction of the side chain moiety have been explored. Such approaches make it much easier to synthesize penaresidin analogs having different alkyl side chains. In these kinds of approaches, the azetidine fragments and the side chains are coupled at the later stage by olefination reactions, such as Wittig or Julia-Kocienski reactions. Lin and colleagues succeeded in the synthesis of **1** and **4** by construction of the azetidine ring before introduction of the side chain moiety by the Wittig reaction (Scheme 9).[24] In addition, they first performed the enantioselective synthesis of a 2,3-*anti*-3,4-*anti*-precursor. The *N*-Ts-*O*-Bn-precursor **96** was synthesized from 1,4-pentadien-3-ol (**90**). According to Jäger's procedure,[25] epoxide **91** was obtained exclusively from **90** by Sharpless asymmetric epoxidation. The primary hydroxy group of **91** was benzylated to give **92**. Sharpless asymmetric dihydroxylation[26] of **92** using **93** as a chiral ligand and subsequent protection of the resulting 1,2-diol moiety afforded **94** with high diastereoselectivity (*dr* 11:1). Ring-opening[27] of **94** with NaN_3 regioselectively provided azide **95**, which was transformed into precursor **96** in five steps. The cyclization of **96** under Mitsunobu reaction conditions using diethyl azodicarboxylate (DEAD) and Ph_3P in CH_2Cl_2 proceeded smoothly to form 2,3-*anti*-3,4-*syn*-azetidine **97** in 60% yield. Deprotection of **97** and subsequent oxidation yielded aldehyde **98**. The Wittig reaction of **98** with phosphonium bromide **99** and sodium methylsulfinylmethylide in THF successfully afforded a mixture of

(*Z*)- and (*E*)-isomers of the desired coupling product **100** in 60% yield, demonstrating that the azetidine structure can be stable under Wittig reaction conditions. Compound **100** was converted into **1** in four steps. Synthesis of **4** was also achieved in similar manner using **101** instead of **99**.



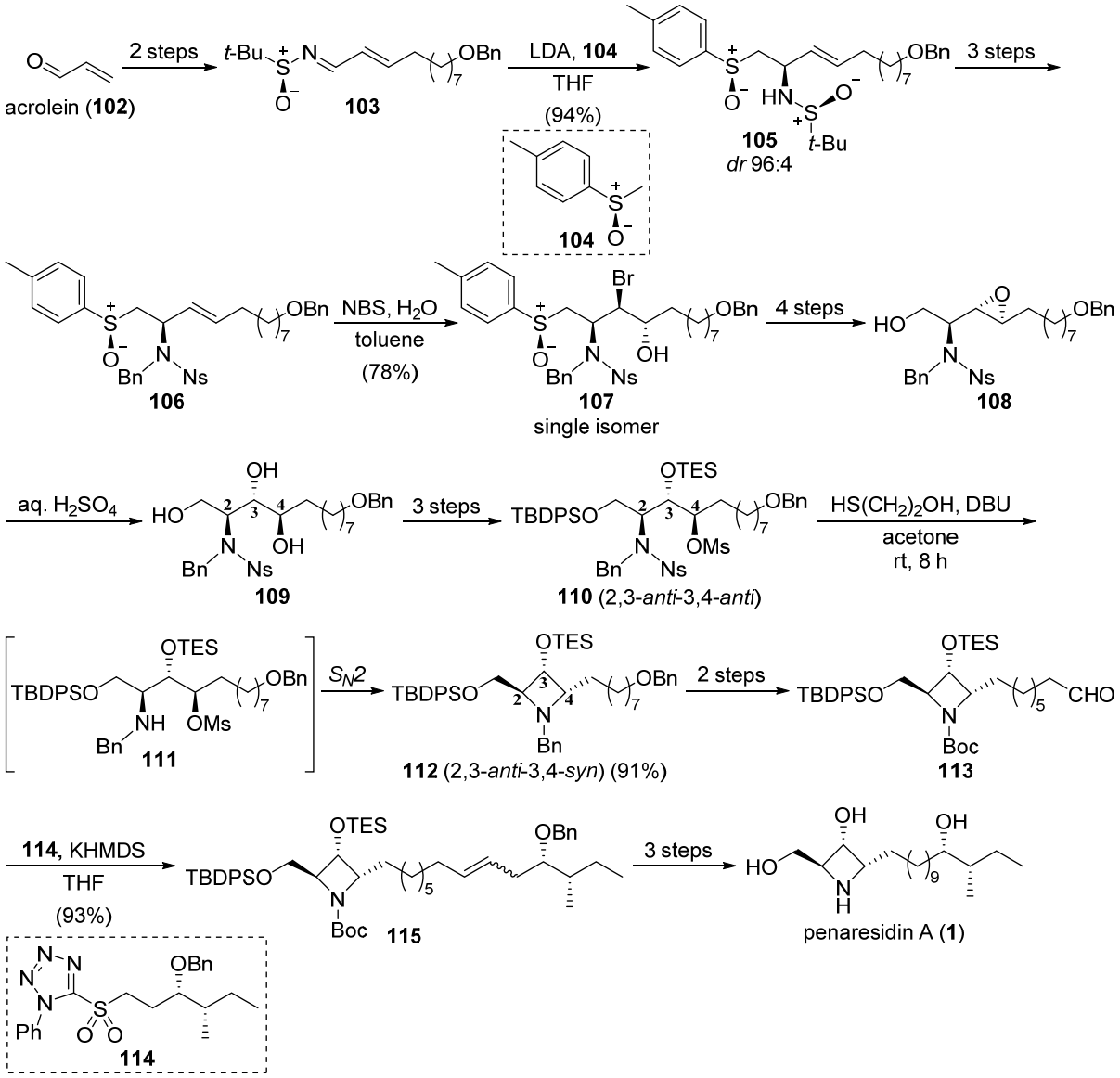
Scheme 9. Synthesis of penaresidin A (**1**) and its stereoisomer **4** using S_N2-type cyclization of the 2,3-*anti*-3,4-*anti*-precursor **96** and the late-stage introduction of a side chain by the Wittig reaction.[24] DIPT = diisopropyl tartrate, MS4A = molecular sieves 4 Å, TBAI = tetrabutylammonium iodide, TBHP = *tert*-butyl hydroperoxide

The Julia-Kocienski reaction was employed for the late-stage introduction of the side chain in the synthesis of penaresidin A (**1**) by Raghavan and Krishnaiah (Scheme 10).[28] They also used a benzyl group as an amino-protecting group in the 2,3-*anti*-3,4-*anti*-precursor **110**, which was enantioselectively synthesized from acrolein (**102**). The starting material **102** was transformed into the unsaturated sulfinylimine **103** in two steps. Stereoselective addition of the anion of chiral sulfoxide **104** to **103** in THF afforded the desired sulfinamide **105** with high diastereoselectivity (*dr* 96:4). Compound **105** was converted into *N*-Bn-*N*-2-nitrobenzenesulfonyl (Ns)-protected allylic amine **106** in three steps. When **106** was treated with NBS and H_2O, bromohydrin **107** was formed as a single isomer. Epoxy alcohol **108** was obtained from **107** in four

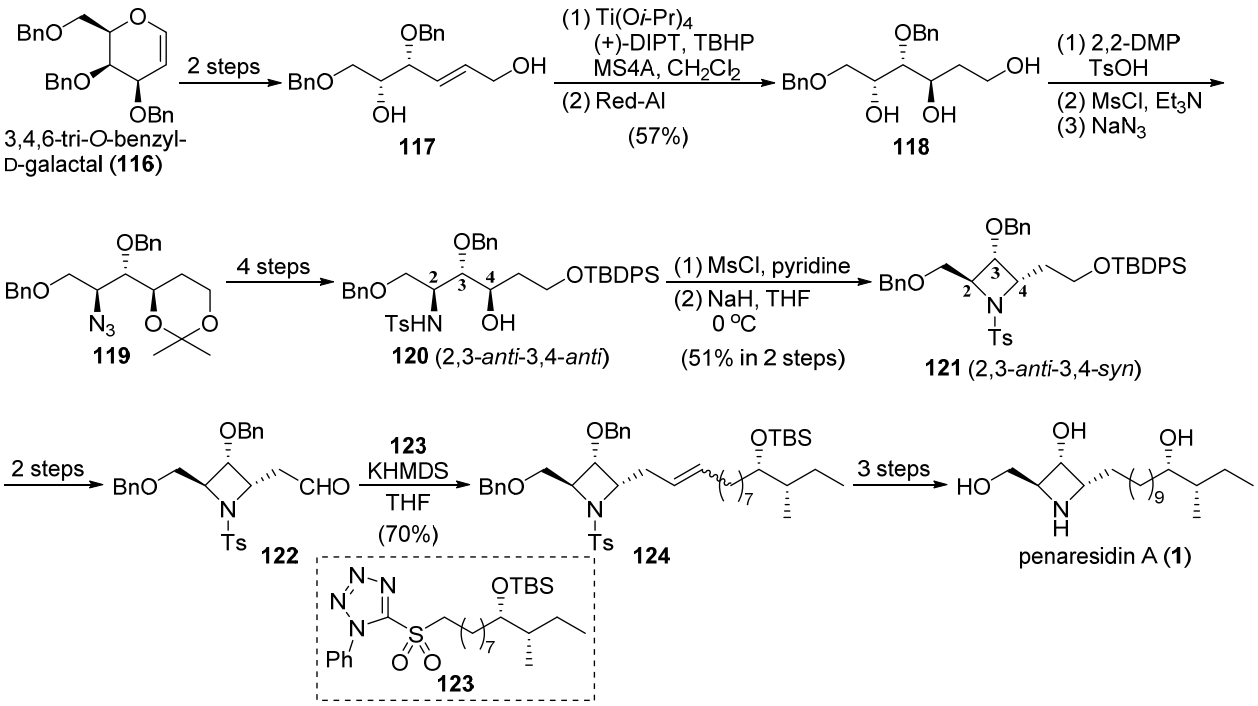
steps. Ring-opening of **108** with aq. H_2SO_4 regioselectively afforded 2,3-*anti*-3,4-*anti*-1,3,4-triol **109**, which was converted into 2,3-*anti*-3,4-*anti*-precursor **110** in three steps. Reaction of **110** with 2-mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetone at room temperature proceeded through removal of the Ns group and subsequent S_N2-type cyclization of the *N*-Bn intermediate **111** to give 2,3-*anti*-3,4-*syn*-azetidine **112** in 91% yield after 8 h. Aldehyde **113** was synthesized from **112** in two steps. The Julia-Kocienski reaction of **113** and 1-phenyl-1*H*-tetrazol-5-yl (PT)-sulfone **114** was performed with potassium hexamethyldisilazide (KHMDS) in THF, and the coupling product alkene **115** was obtained as a mixture of (*E*)- and (*Z*)-isomers in 93% yield. This result demonstrates the stability of azetidine rings under Julia-Kocienski reaction conditions. Hydrogenation and deprotection of **115** led to the formation of **1**.

Subba Reddy and coworkers also employed the Julia-Kocienski reaction for the late-stage introduction of the side chain in the synthesis of **1** (Scheme 11).[29] Preparation of *N*-Ts-*O*-Bn-2,3-*anti*-3,4-*anti*-precursor **120** for S_N2-type cyclization proceeded from 3,4,6-tri-*O*-benzyl-D-galactal (**116**). Allylic alcohol **117** was synthesized from **116** in two steps and then subjected to Sharpless asymmetric epoxidation[30] and subsequent ring-opening with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) to give triol **118** selectively. After protection of the 1,3-diol moiety of **118** as its acetal, the remaining hydroxy group was replaced with an azide group with inversion of the stereochemistry in two steps to yield azide **119**. Conversion of **119** into 2,3-*anti*-3,4-*anti*-precursor **120** was accomplished in four steps. The 2,3-*anti*-3,4-*syn*-azetidine **121** was obtained in moderate (51%) yield from **120** through cyclization of the mesylate of **120** with NaH in THF at 0 °C. After conversion of **121** into aldehyde **122** in two steps, coupling of **122** with PT-sulfone **123** with KHMDS successfully afforded alkene **124** in 70% yield. Reduction and deprotection of **124** produced **1**.

In the construction of azetidine rings from 2-amino precursors, the S_N2-type cyclization of 2,3-*anti*-3,4-*anti*-precursors produces 2,3-*anti*-3,4-*syn*-azetidines in moderate to excellent yields, allowing the synthesis of natural penaresidins. The 2,3-*anti*-3,4-*syn*-precursors are cyclized to 2,3-*anti*-3,4-*anti*-azetidines in high yields. In contrast, the cyclization of 2,3-*syn*-3,4-*anti*-precursors results in very low yields of the 2,3-*syn*-3,4-*syn*-azetidines. Recent studies have employed synthetic strategies in which the side chain was introduced after formation of the azetidine ring. Such strategies can be utilized to synthesize various side chain analogs.



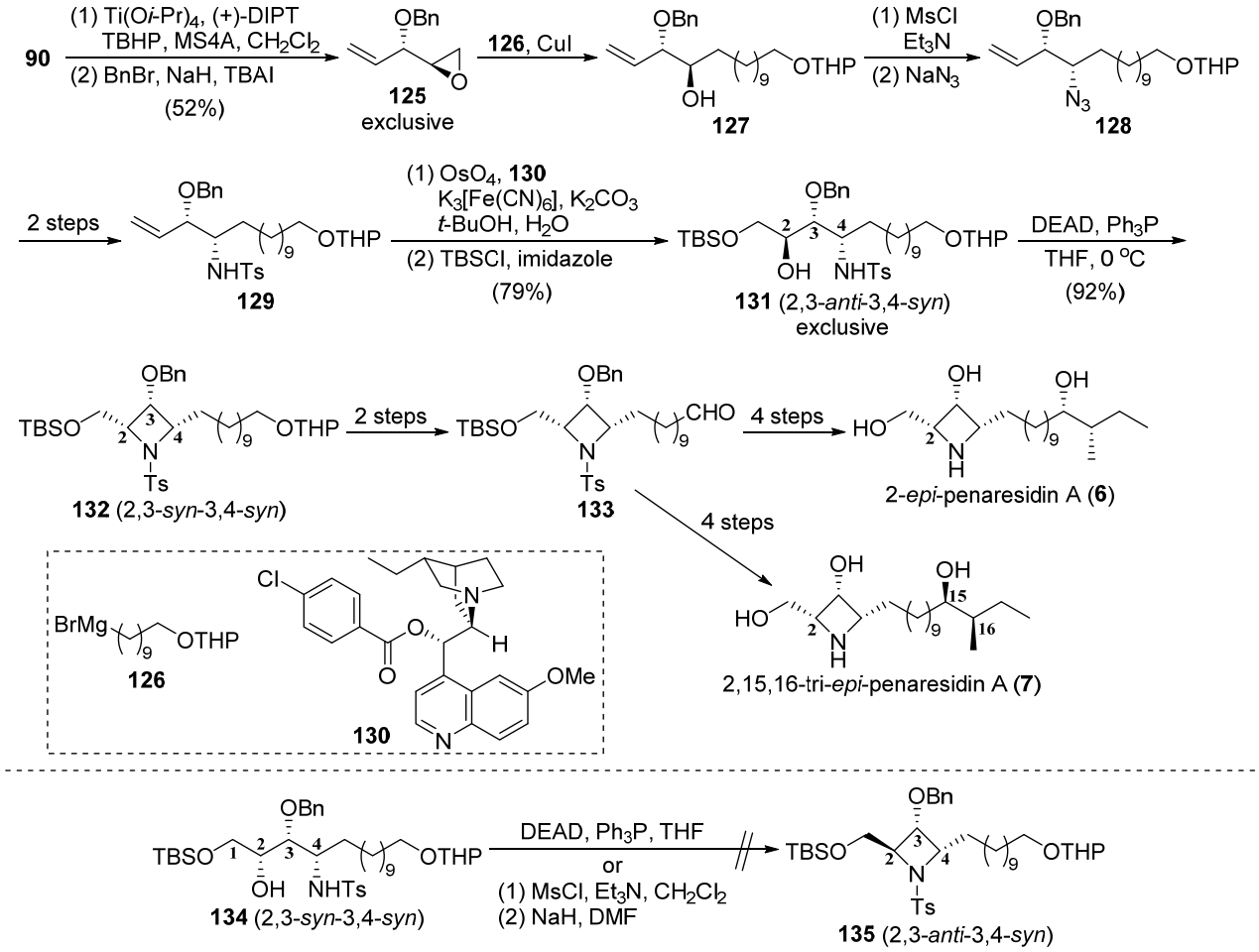
Scheme 10. Synthesis of penaresidin A (**1**) using S$_N$2-type cyclization of 2,3-*anti*-3,4-*anti*-precursor **110** and the late-stage introduction of a side chain by the Julia-Kocienski reaction.[28] LDA = lithium diisopropylamide, TBDPS = *tert*-butyldiphenylsilyl



Scheme 11. Synthesis of penaresidin A (**1**) using S_N2-type cyclization of 2,3-*anti*-3,4-*anti*-precursor **120** and the late-stage introduction of a side chain by the Julia-Kocienski reaction[29]

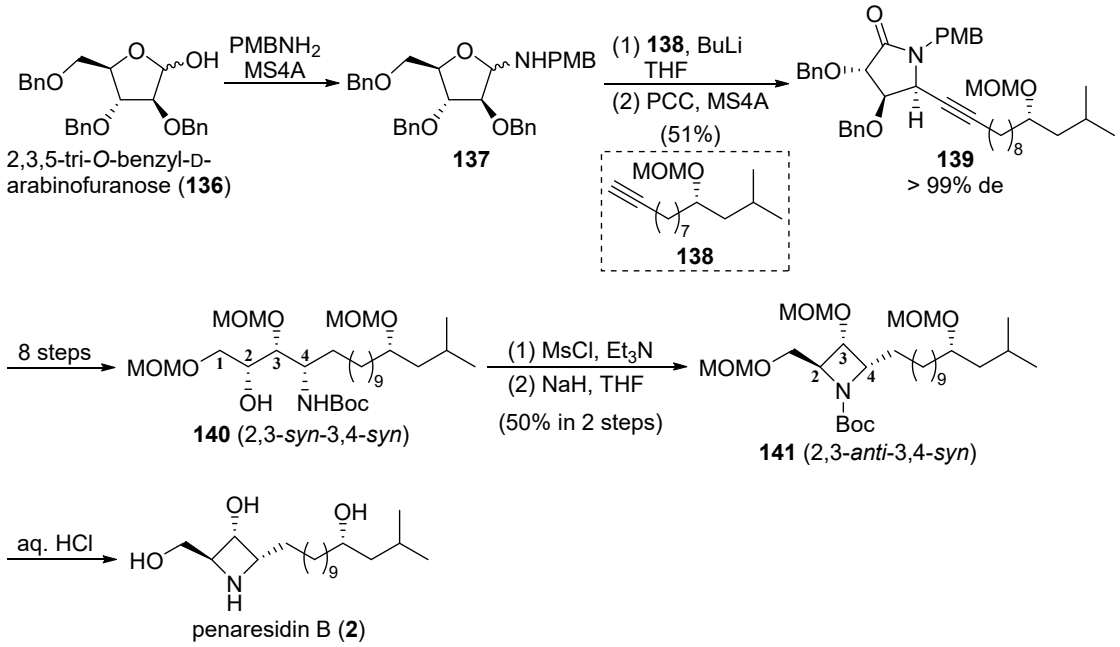
3. CONSTRUCTION OF AZETIDINE RINGS FROM 4-AMINO PRECURSORS

Several researchers including our group have synthesized penaresidins, their stereoisomers, and their analogs using construction of the azetidine ring from 4-amino precursors. Lin *et al.* reported that the S_N2-type cyclization is strongly influenced by the substitution pattern of the precursors in the synthesis of penaresidins **1**, **6**, and **7** (Scheme 12).[24,31] To synthesize **6** and **7**, *N*-Ts-1-*O*-TBS-3-*O*-Bn-2,3-*anti*-3,4-*syn*-4-amino precursor **131** was prepared from 1,4-pentadien-3-ol (**90**). According to the literature,[32] **90** was selectively converted into epoxide **125** by Sharpless asymmetric epoxidation. Reaction of **125** with Grignard reagent **126** and CuI afforded **127**, whose hydroxy group was displaced by an azide group with inversion of configuration to form **128**. After reduction of the azide group of **128** followed by protection, Sharpless asymmetric dihydroxylation of the resulting **129** using **130** exclusively produced the corresponding 1,2-diol, whose primary hydroxy group was selectively protected to generate precursor **131**. When cyclization of **131** was performed under Mitsunobu reaction conditions using DEAD and Ph_3P in THF at 0 °C, the desired 2,3-*syn*-3,4-*syn*-azetidine **132** was afforded in excellent (92%) yield, which is in stark contrast to the similar cyclization of 2,3-*syn*-3,4-*anti*-2-amino precursor **51** that gave 2,3-*syn*-3,4-*syn*-azetidine **52** in only 20% yield (Scheme 4).[5] Removal of the 2-tetrahydropyranyl (THP) group of **132** followed by oxidation afforded aldehyde **133**, which was converted into **6** and **7** in four steps. The S_N2-type cyclization of 2,3-*syn*-3,4-*syn*-4-amino precursor **134**, a 2-epimer of **131**, was explored for the synthesis of natural penaresidin **1**.[24] However, the desired 2,3-*anti*-3,4-*syn*-azetidine **135** was not obtained.

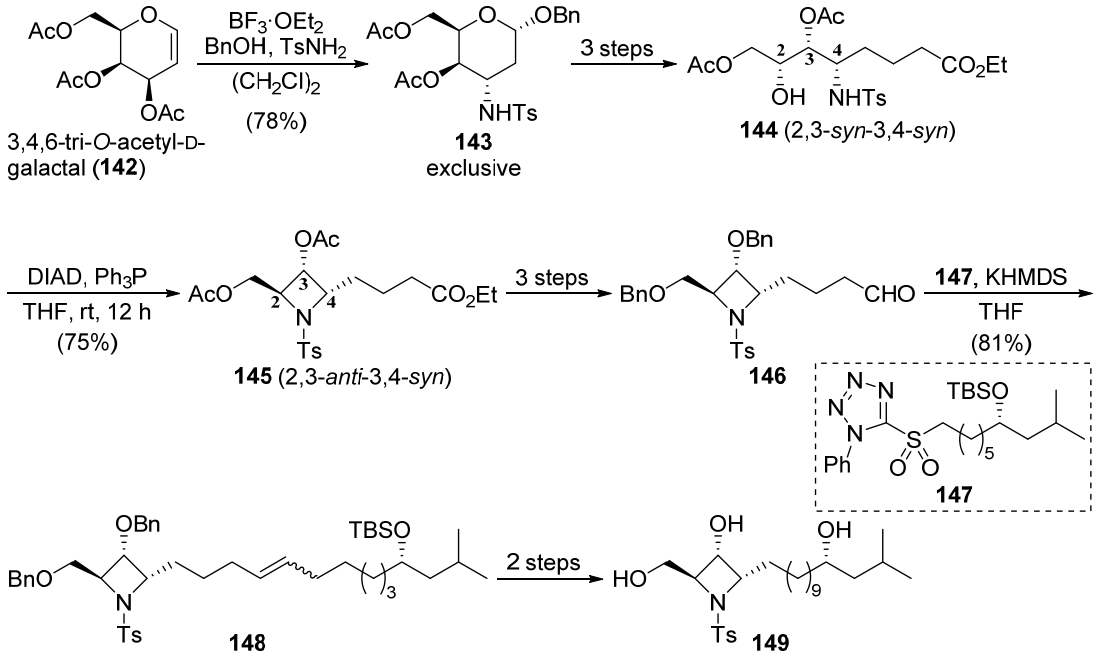


Scheme 12. Synthesis of penaresidins **6** and **7** using S$_N$2-type cyclization of 2,3-*anti*-3,4-*syn*-precursor **131** and the unsuccessful cyclization of 2,3-*syn*-3,4-*syn*-precursor **134**[24,31]

Yoda and colleagues succeeded in the cyclization of 2,3-*syn*-3,4-*syn*-4-amino precursor **140** having Boc and MOM groups as *N*- and *O*-protecting groups, respectively, in the synthesis of **2** from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**136**) (Scheme 13).[33] After conversion of **136** into furanosylamine **137** according to the literature,[34] stereoselective addition of the acetylide of **138** to **137** and subsequent oxidative degradation with pyridinium chlorochromate (PCC) produced lactam **139** with > 99% de. Compound **139** was transformed into precursor **140** in eight steps. The S$_N$2-type cyclization of the mesylate of **140** was performed with NaH in THF to afford the 2,3-*anti*-3,4-*syn*-azetidine **141** in moderate (50%) yield in two steps. Yoda suggested that the different result observed for the cyclization of **140** from that observed for **134** (Scheme 12)[24] is due to the steric bulkiness of the amino (*N*-Boc for **140**; *N*-Ts for **134**) and hydroxy (1,3-di-*O*-MOM for **140**; 1-*O*-TBS and 3-*O*-Bn for **134**) protecting groups. Natural penaresidin **2** was obtained from **141** by acidic treatment.



Scheme 13. Synthesis of penaresidin B (**2**) using S$_N$2-type cyclization of 2,3-*syn*-3,4-*syn*-precursor **140**[33]

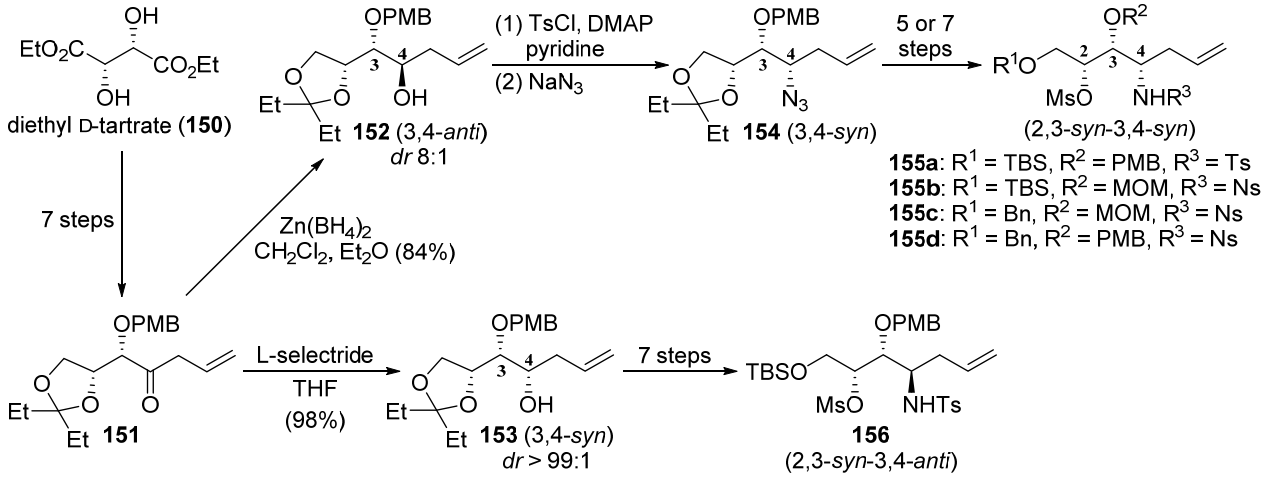


Scheme 14. Synthesis of *N*-Ts-penaresidin B **149** using S$_N$2-type cyclization of 2,3-*syn*-3,4-*syn*-precursor **144**[35]

Liu and colleagues reported a better result for the S$_N$2-type cyclization of the 2,3-*syn*-3,4-*syn*-4-amino precursor in the synthesis of *N*-Ts-penaresidin B **149** (Scheme 14).[35] They employed precursor **144** having a shorter alkyl side chain and *N*-Ts and *O*-Ac groups for the cyclization. The synthesis of **144** proceeded with regio- and stereoselective tandem hydroamination/glycosylation of 3,4,6-tri-*O*-acetyl-D-galactal (**142**), as developed by the authors.[36] Thus, reaction of **142** with benzyl alcohol and tosylamide in the presence of

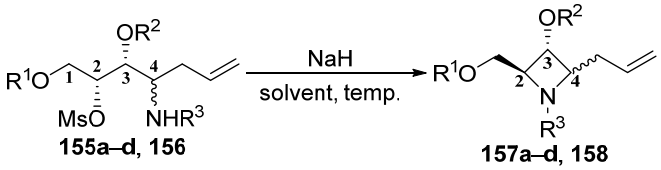
$BF_3 \cdot OEt_2$ proceeded to give amino sugar **143** exclusively. Conversion of **143** into the precursor **144** was accomplished in three steps. Cyclization of **144** was conducted under Mitsunobu reaction conditions using DIAD and Ph_3P in THF at room temperature for 12 h to furnish 2,3-*anti*-3,4-*syn*-azetidine **145** in high (75%) yield, although **144** has a bulky Ts group as an *N*-protecting group. Azetidine **145** was converted into *N*-Ts-penaresidin B **149** using the Julia-Kocienski reaction of aldehyde **146** with PT-sulfone **147** to form **148**.

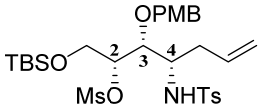
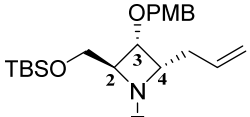
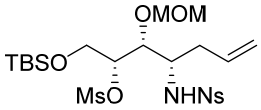
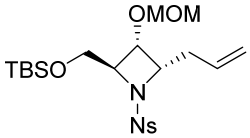
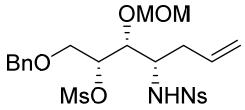
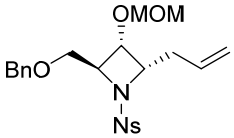
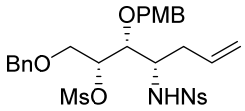
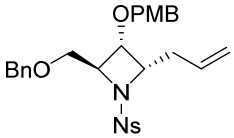
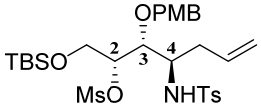
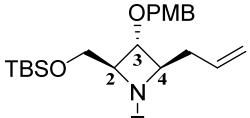
Recently, we explored the S_N2-type cyclization of 2,3-*syn*-3,4-*syn*-precursors **155a–d** and 2,3-*syn*-3,4-*anti*-precursor **156** to evaluate the effects of their hydroxy-protecting groups and configurations in the synthesis of **2** and **10**.[37] Precursors **155a–d** and **156** were synthesized from diethyl D-tartrate (**150**) using stereoselective reduction[38] of allylic ketone **151** with different reducing agents (Scheme 15). After conversion of **150** into **151** in seven steps, **151** was reduced with $Zn(BH_4)_2$ to afford 3,4-*anti*-homoallylic alcohol **152** with high diastereoselectivity (*dr* 8:1). Conversely, reduction of **151** with L-selectride provided 3,4-*syn*-homoallylic alcohol **153** as a single isomer. To synthesize **155a–d**, substitution of the hydroxy group of 3,4-*anti*-alcohol **152** with an azide group with inversion of the stereochemistry furnished azide **154**, which was transformed into **155a–d** in five or seven steps. Precursor **156** was synthesized from 3,4-*syn*-alcohol **153** in the same manner. The S_N2-type cyclization of **155a–d** and **156** with NaH is shown in Table 3. We found that the 1-OH protecting group has a considerable effect on the cyclization of 2,3-*syn*-3,4-*syn*-precursors and that the Bn group is the most suitable protecting group. Furthermore, the 3-OH group is not important for the cyclization. The best result was obtained using the 1-*O*-Bn-3-*O*-PMB-precursor **155d** at 80 °C in DMF, whereby 2,3-*anti*-3,4-*syn*-azetidine **157d** was obtained in 92% after 0.75 h (entry 5). In contrast to the 2,3-*syn*-3,4-*syn*-precursor **155a** (entry 1), 2,3-*syn*-3,4-*anti*-precursor **156** was cyclized smoothly with NaH in THF at room temperature to afford 2,3-*anti*-3,4-*anti*-azetidine **158** in high (82%) yield after 19 h (entry 6). The late-stage introduction of the alkyl side chain was accomplished by olefin cross-metathesis (Scheme 16). Thus, after removal of the PMB group of **157d**, the resulting **157e** was treated with alkenes **159a** and **159b** in the presence of Grubbs 2nd catalyst to give high yields of coupling products **160a** and **160b**, which were converted into **10** and **2** in four steps.

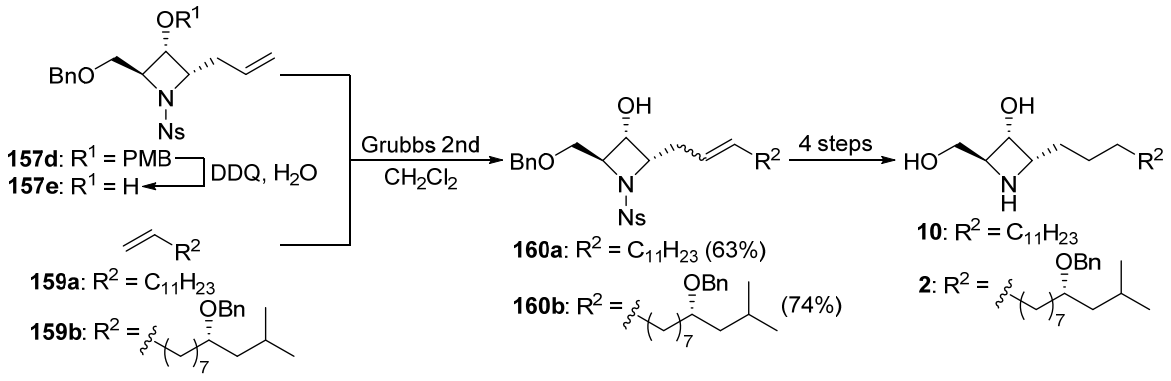


Scheme 15. Preparation of 2,3-*syn*-3,4-*syn*-precursors **155a–d** and 2,3-*syn*-3,4-*anti*-precursor **156**[37]

Table 3. S_N2-type cyclization of **155a–d** and **156**[37]



entry	precursor	solvent	temp (°C)	time (h)	azetidine	yield (%)
1	 **155a** (2,3-*syn*-3,4-*syn*)	THF	reflux	24	 **157a** (2,3-*anti*-3,4-*syn*)	11
2	 **155b**	THF	reflux	24	 **157b**	20
3		DMF	120	1		50
4	 **155c**	DMF	120	24	 **157c**	72
5	 **155d**	DMF	80	0.75	 **157d**	92
6	 **156** (2,3-*syn*-3,4-*anti*)	THF	rt	19	 **158** (2,3-*anti*-3,4-*anti*)	82



Scheme 16. Synthesis of penaresidin B (**2**) and the straight side chain analog **10**[37]

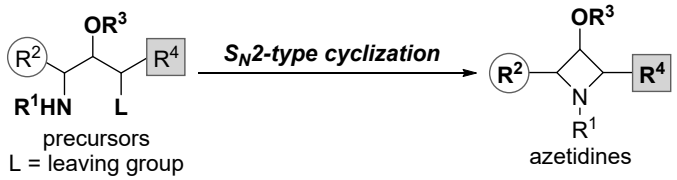
In the construction of azetidine rings from 4-amino precursors to synthesize penaresidins, the cyclization of 2,3-*syn*-3,4-*syn*-precursors is rather difficult. In this cyclization, the choice of the 1-hydroxy-protecting group and alkyl side chain is important. In contrast, 2,3-*syn*-3,4-*anti*- and 2,3-*anti*-3,4-*syn*-precursors are smoothly cyclized to 2,3-*anti*-3,4-*anti*- and 2,3-*syn*-3,4-*syn*-azetidines, respectively, in high to excellent yields. Similarly to the synthesis of penaresidins, their stereoisomers, and their analogs using the S_N2-type cyclization of 2-amino precursors, recent syntheses using the cyclization of 4-amino precursors have employed the late-stage introduction of the side chains.

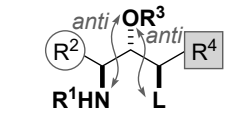
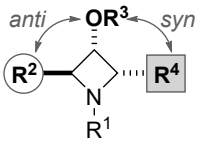
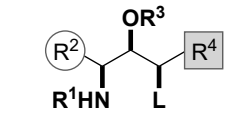
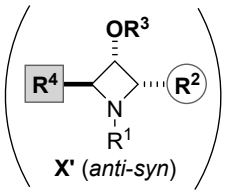
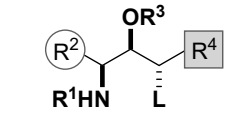
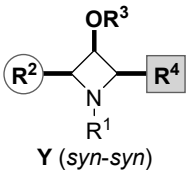
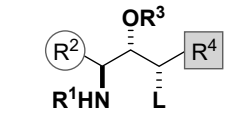
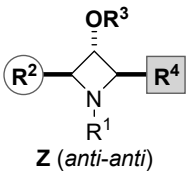
4. CONCLUSIONS

Penaresidins have attracted attention as synthetic targets because they have interesting structures, including 2,3,4-trisubstituted azetidine cores and alkyl side chains, in addition to their potent biological activities. Owing to the structural relation between penaresidins and phytosphingosines, most syntheses of penaresidins are achieved using construction of the azetidine ring by the S_N2-type cyclization of 2-amino precursors (phytosphingosine derivatives). In addition, their regioisomeric 4-amino precursors have also been used. By comparison of the cyclizations reported for penaresidin synthesis, we identified interesting features of the cyclization, as shown in Table 4. Because the precursors possess different substituents, amino (N), hydroxy (O), and leaving (L) groups, on three continuous stereocenters, they can be classified into four categories by their relative stereochemistries, i.e., i) **A** (*N*,*O-anti-O*,*L-anti*), ii) **B** (*N*,*O-syn-O*,*L-syn*), iii) **C** (*N*,*O-syn-O*,*L-anti*), and iv) **D** (*N*,*O-anti-O*,*L-syn*). Conversely, azetidines having two alkyl and one hydroxy group on the stereocenters can be classified into three categories, i.e., i) **X** and **X'** (*anti-syn*), ii) **Y** (*syn-syn*), and iii) **Z** (*anti-anti*). Precursors **A** and **B** give azetidines **X** and **X'**. Their *N*,*O-syn-O*,*L-anti*- and *N*,*O-anti-O*,*L-syn*-isomers **C** and **D** provide **Y** and **Z**, respectively. The cyclization is strongly dependent on the configurations of the N and O groups (vicinal amino alcohol moieties) in the precursors. Thus, the cyclization of *N*,*O-anti*-precursors **A** and **D** successfully produces azetidines **X** and **Z**,

respectively. A silyl protecting group would be preferred as the hydroxy-protecting group for the cyclization of **A** (see Chapter 2). The cyclization of *N*,*O*-*syn*-isomers **B** and **C** is rather problematic and often provides very low yields of **X'** and **Y**. The cyclization of **B** is strongly affected by the steric bulkiness of oxymethyl group (CH_2OPG, R^4, PG = protecting group). A benzyloxymethyl group as R^4 is beneficial for obtaining azetidine **X'** in higher yields (see Chapter 3, Table 3). Shorter alkyl groups as R^2 are also preferred for the cyclization of **B** (see Chapter 3, Schemes 13 and 14, Table 3). In the case of the cyclization of **C**, both alkyl and oxymethyl groups as substituents R^2 and R^4, respectively, are required for a higher yield of azetidine **Y** (see Chapter 2, Scheme 4, and Chapter 3, Scheme 12). In all cases, choice of the amino-protecting group is not important for the cyclization. We hope that this review would be useful for synthesizing highly substituted azetidine derivatives.

Table 4. Summary of S_N2-type cyclizations for the synthesis of penaresidins, their stereoisomers, and their analogs



entry	precursor	azetidine	yield	notes	ref
1	 **A** (*N*,*O*-*anti*-*O*,*L*-*anti*) R^2 = CH_2OPG, R^4 = alkyl	 **X** (*anti*-*syn*)	moderate to excellent	PG (in R^2) and R^3: silyl group would be preferred	2, 3, 5, 7, 9, 13, 18, 20, 21, 24, 28, 29
2	 **B** (*N*,*O*-*syn*-*O*,*L*-*syn*) R^2 = alkyl, R^4 = CH_2OPG	 **X'** (*anti*-*syn*)	very low to excellent	R^2: shorter alkyl group is preferred and/or R^4: CH_2OBn group is preferred	24, 33, 35, 37
3	 **C** (*N*,*O*-*syn*-*O*,*L*-*anti*)	 **Y** (*syn*-*syn*)	low or excellent	both R^2: alkyl and R^4: CH_2OPG groups are required	5, 31
4	 **D** (*N*,*O*-*anti*-*O*,*L*-*syn*)	 **Z** (*anti*-*anti*)	high		7, 37

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