Recent Progress of the Synthetic Studies of Biologically Active Marine Cyclic Peptides and Depsipeptides

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1. Introduction

Cyclic peptides including cyclic depsipeptides are still a growing research area even in the 21st century.[1] They are mainly produced by marine organisms and terrestrial microorganisms. Marine organisms are a well-known rich source of biologically active cyclic peptides having unique structures. They contain unusual amino acids and building blocks. Most of them will offer a new frontier in both synthetic organic chemistry and biological activities. In particular, unique unusual structures will offer the challenge of exploitation of novel synthetic methods, reactions, reagents, catalysts, etc. Thanks to the progress of isolation procedures such as HPLC and methods for structure determination such as NMR and mass spectral means, numbers of natural products of marine origin having both unique structures and intriguing biological activities are increasing.[2] However, generally speaking, it is rather difficult to isolate a larger amount of marine natural products because of minute constituents in organisms, difficulty of collection of organisms, and resistance of laboratory culturing. Thus, the limits of the quantity preclude the precise structure determination as well as clarification of detailed biological activities. In fact, the proposed structures of many cyclic peptides have been revised by synthetic works. Thus, the total synthesis is still playing a final means for the structure determination of marine natural products just like several decades ago. Furthermore, the efficient large-scale production of marine natural products by synthesis will offer an opportunity to investigate their biological activities in detail. One of the characteristic features of cyclic peptides will be their conformational rigidity and stability in vivo, in contrast to their linear counterparts. In addition, unusual amino acid and non-amino acid moieties of marine cyclic peptides will offer the lead structures of new biologically useful compounds.

This review focuses on examples of broad interest in the recent progress of the synthetic studies of marine cyclic peptides and depsipeptides having unique structures and intriguing biological activities. There are some reviews on the synthesis of cyclic peptides which generally describe the progress until the end of the 20th century.[3] This review is not intended to be comprehensive, but the more recent results will be presented. Some microorganisms of

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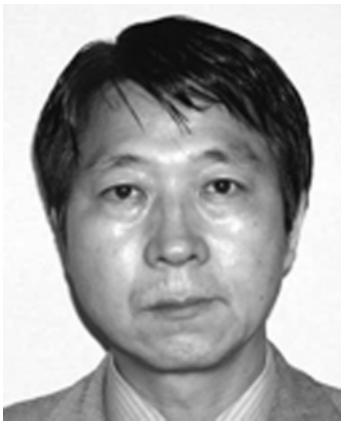


Yasumasa Hamada was born in 1949. He received his B.S. degree from Toyama University (Japan) in 1973 and M.S. degree from the University of Tokyo (Japan) in 1975. During his Ph.D. studies at the University of Tokyo he was appointed Assistant Professor, collaborating with Professor Takayuki Shioiri at Nagoya City University in 1977. After obtaining his Ph.D. degree from the University of Tokyo in 1982, he worked for Professor E. J. Corey (1990 Nobel Laureate) at Harvard University as a postdoctoral fellow in 1985. He was promoted to Associate Professor at Nagoya City University in 1988. Then he joined the staff as Professor in the Faculty of Pharmaceutical Sciences at Chiba University in 1995. His research interests are peptide chemistry, total synthesis of natural products, asymmetric synthesis, and organometallic chemistry.

Takayuki Shioiri was born in 1935 and received his B.S. degree in 1959 and M.S. degree in 1961 from the University of Tokyo. During his Ph.D. studies he was appointed Assistant Professor at the University of Tokyo in 1962. After obtaining his Ph.D. degree in 1967, he worked for Professor D. H. R. Barton (1969 Nobel Laureate) at the Imperial College from 1968 to 1970. He returned to his alma mater and was promoted to Associate Professor in 1977. In the same year he was appointed Professor of Nagoya City University. He retired in 2001 and became an Emeritus Professor. Since 2002 he has been a Professor at Meijo University. He was a recipient of the 1993 Pharmaceutical Society of Japan Award and 1999 Japanese Peptide Society Award. He has been a regional executive editor of *Tetrahedron* since 1990 and President of the Japanese Society for Process Chemistry since 2001. His research interests are exploitation of new methods and reagents in organic synthesis and their utilization in the synthesis of biologically interesting natural products.

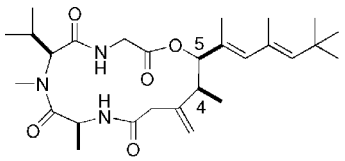
freshwater origin also produce interesting cyclic peptides,[3a] but most of them are out of the scope of this review. Diazonamides isolated from ascidian also belong to a kind of cyclic peptides, but it is also out of the scope because its peptide part is so small in the whole structure and the recent progress is too enormous to review.[4]

2. Cyclic Peptides from Cyanobacteria

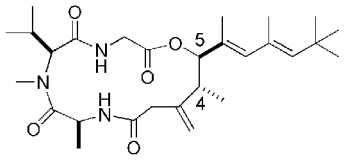
Cyanobacteria (blue-green algae) of aquatic origin are known to produce a number of interesting biologically active cyclic peptides,[5] which are sometimes called cyanopeptides.[5c] They are now known as a rich source of the lead compounds for pharmaceuticals and biologically useful compounds. In particular, recent findings that the biologically active metabolites of various marine organisms are actually produced by cyanobacteria as symbionts or feeding materials have prompted studies on the metabolites of cyanobacteria.

2.1. Antillatoxin

Antillatoxin is a cyclic lipodepsipeptide isolated in low yield by Gerwick and co-workers[6] from the marine cyanobacterium *Lyngbya majuscula* collected in Curaçao. It shows a strong ichthyotoxicity and neurotoxicity which is derived by activation of the mammalian voltage-gated sodium channel at a pharmacological site.[7] The unique structure **1a** involving many methyl and one *tert*-butyl functions was determined by extensive NMR spectral studies, and the absolute configurations of the *N*-methylvaline and alanine parts were deduced to be (*S*) by comparison of chiral-phase TLC results of their acid hydrolysis products. The stereochemistry at the C4 and C5 positions was assigned to be (4*S*,5*R*) by combination of NMR spectra (NOESY and *J* value), CD spectroscopy, and molecular modeling (the lowest energy conformation). As described later, the (4*S*,5*R*) configurations of **1a** was revised to the (4*R*,5*R*) ones as **1b** by synthetic works (Figure 1).[8]



(4*S*,5*R*)-Antillatoxin (**1a**)
(proposed)



(4*R*,5*R*)-Antillatoxin (**1b**)
(revised)

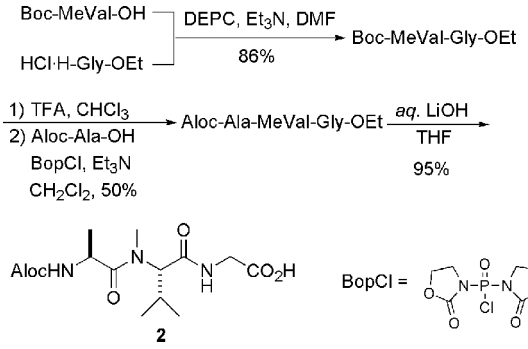
Figure 1.

2.1.1. Total Synthesis of (4S,5R)-Antillatoxin Having the Proposed Structure

The first total synthesis of antillatoxin having the proposed structure **1a** was achieved by Yokokawa and Shioiri.[8a] They constructed the whole molecule by coupling of the tripeptide unit with the conjugated diene unit. The lactamization instead of lactonization was employed to construct the macrocyclic depsipeptide because of the higher nucleophilicity of the amino group compared to the hydroxyl one.[9]

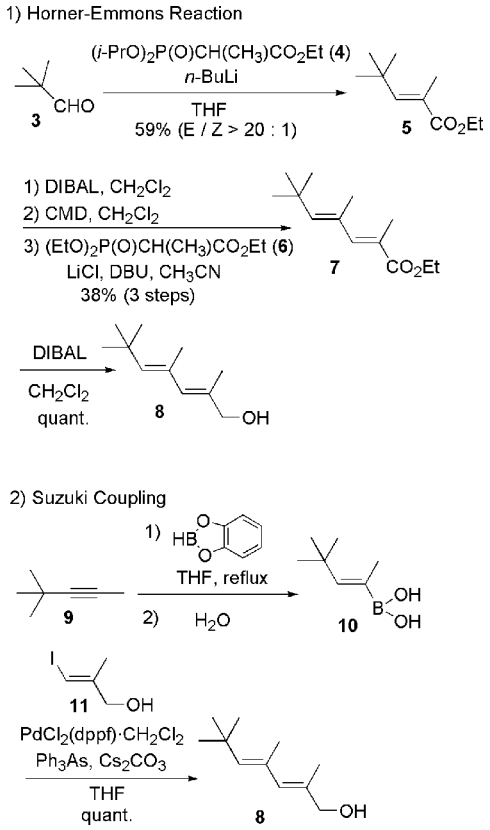
Preparation of the tripeptide unit **2** was rather straightforward utilizing diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$)[10] and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BopCl)[11] as the coupling reagents, as shown in Scheme 1.

Scheme 1



Synthesis of the conjugated diene unit was carried out in two ways. The first route employed Horner−Emmons reaction twice to construct the diene, as shown in Scheme 2. The Horner−Emmons reaction

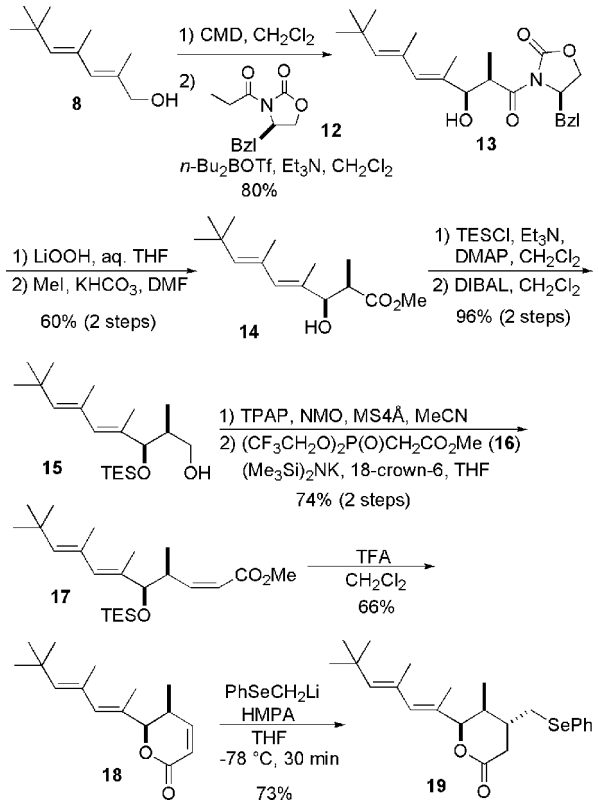
Scheme 2



of pivalaldehyde (**3**) with the phosphonate **4** mainly afforded the *E*-isomer **5**, which was sequentially treated with diisobutylaluminum hydride (DIBAL, *i*-Bu_2AlH), chemical manganese dioxide (CMD),[12] and the phosphonate **6**, giving the conjugated diene **7**. Reduction of **7** with DIBAL afforded the required alcohol **8**. The improved route to the diene **8** employed Suzuki−Miyaura coupling[13] (Scheme 2). The pentyne **9** underwent the hydroboration with catecholborane followed by hydrolysis to give the boronic acid **10**. The Suzuki−Miyaura coupling of **10** with the iodide **11** afforded the dienyl alcohol **8**.

The Evans syn-selective asymmetric aldol reaction[14] was employed to construct the C4 and C5 chirality in antillatoxin (**1a**), shown in Scheme 3. Oxidation of the dienyl alcohol **8** with CMD followed

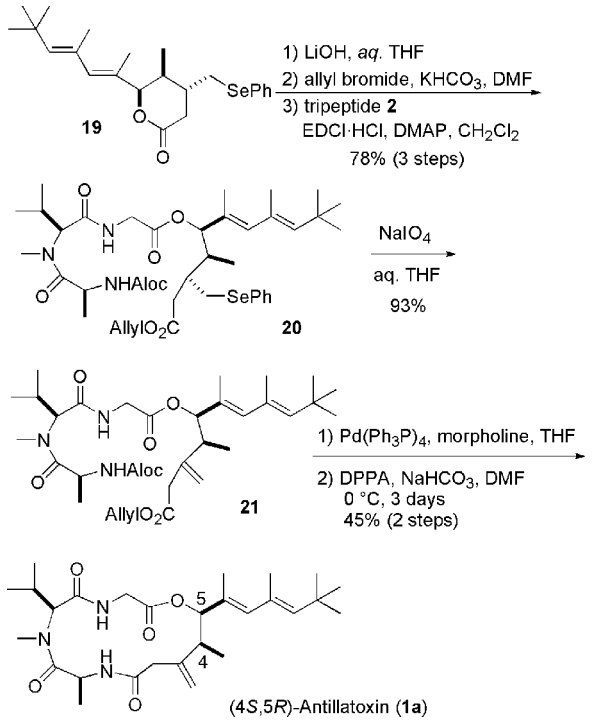
Scheme 3



by the Evans aldol reaction with the boron enolate from the carboximide **12** afforded the aldol adduct **13**. After removal of the chiral auxiliary, methyl esterification afforded the ester **14**. Protection of the secondary alcohol with triethylsilyl (TES, Et_3Si) chloride and then treatment with DIBAL afforded the alcohol **15**, which was oxidized with tetrapropylammonium perruthenate (TPAP, Pr_4NRuO_4).[15] The resulting aldehyde underwent the Still−Horner *cis*-selective olefination[16] with the phosphonate **16** to give the (*Z*)-ester **17**. Acidic treatment of **17** afforded the α,β-unsaturated lactone **18**, which was converted to the selenolactone **19** using phenylselenomethyllithium.[17] The stereochemistry of **19** was confirmed by NOE experiments.

Ring opening of the selenolactone **19** by saponification, allyl esterification, followed by coupling with the tripeptide **2** using 1-[3-(dimethylaminopropyl)]-3-ethylcarbodiimide hydrochloride (EDCI·HCl, $Me_2N(CH_2)_3-N{=}C{=}N-Et\cdot HCl$) afforded the linear ester **20**, from which the phenylselenyl group was oxidatively removed with sodium periodate. The resulting *exo*-methylene compound **21** underwent deprotection of both *N*- and *C*-terminals at the same time, and final macrocyclization was achieved with diphenyl phosphorazidate (DPPA, $(PhO)_2P(O)N_3$)[10,18] in the presence of sodium hydrogen carbonate to produce (4*S*,5*R*)-antillatoxin (**1a**) (Scheme 4). However, the NMR spectrum of the synthetic antillatoxin (**1a**) was revealed to be different from those of natural antillatoxin. In addition, the optical rotation of the synthetic antillatoxin (**1a**) ($[\alpha]_D = -55$ (*c* 0.24, MeOH)) was different from that of the natural one ($[\alpha]_D = -140$ (*c* 0.13, MeOH)). This discrepancy clearly indicated that structure **1a** did not show the stereostructure of natural antillatoxin.

Scheme 4



In this synthetic work[8] choice of the substrates and sites for macrolactamization was very important because the other substrates **22**−**25** shown in Figure 2 could not afford the cyclized products by attempted macrocyclization.

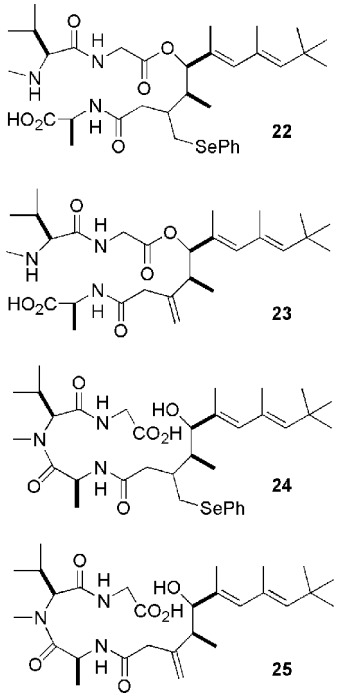
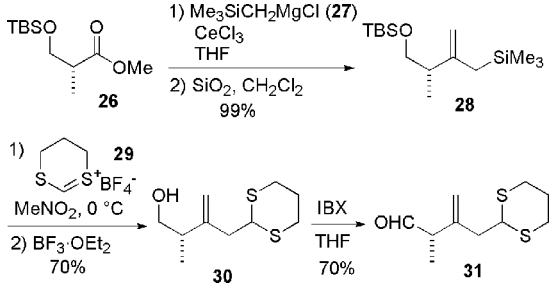


Figure 2.

A little bit later White and co-workers[19] also achieved the total synthesis of (4*S*,5*R*)-antillatoxin and reached the same conclusion.

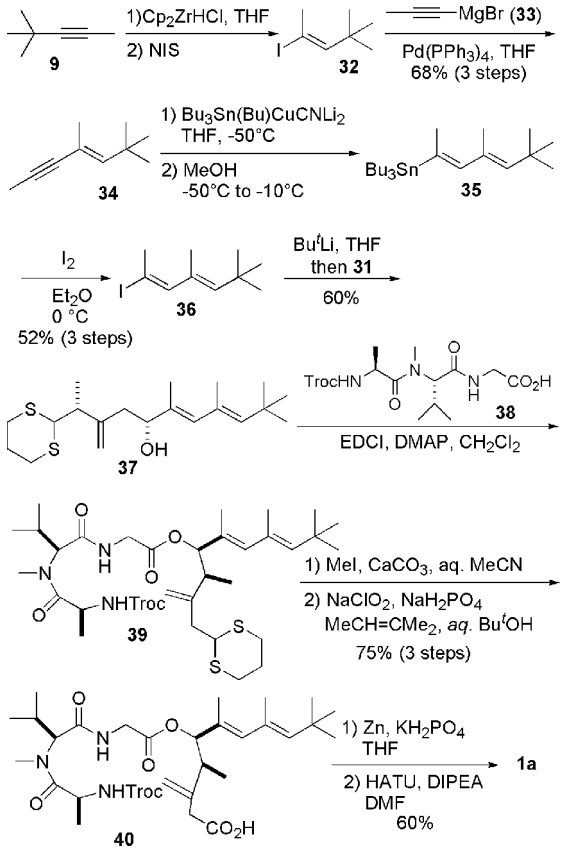
The ester **26** was first converted to the allysilane **28** by addition of an excess amount of Grignard reagent **27** in the presence of cerium chloride, followed by the Peterson elimination with silica gel. Reaction of **28** with the dithienium salt **29** and then treatment with boron trifluoride etherate afforded the alcohol **30**, which was converted to the aldehyde **31** with *o*-iodoxybenzoic acid (IBX), as shown in Scheme 5.

Scheme 5



In a parallel procedure the alkyne **9** underwent hydrozirconation and then iodination with *N*-iodosuccinimide (NIS) to produce the iodide **32**, from which the eneyne **34** was obtained by coupling with the Grignard reagent **33**, shown in Scheme 6. Conversion of the eneyne **34** to the dienylstannane **35** followed by iodination afforded the diene iodide **36**. After the halogen−lithium exchange reaction with *tert*-butyllithium, addition to the aldehyde **31** afforded the syn-adduct **37** as a major product. The ratio of syn and anti isomers was 8:1, which is easily explained by the Felkin−Anh model. Coupling of **37** with the tripeptide **38** using EDCI afforded the linear peptide **39**, from which the dithiane part was con-

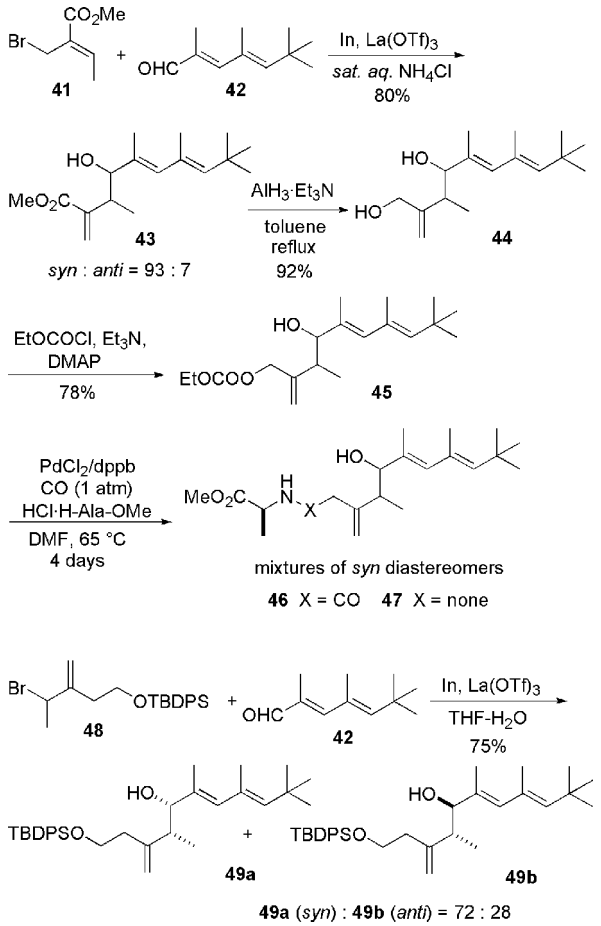
Scheme 6



verted to the carboxylic acid **40** via the corresponding aldehyde. Removal of the trichloroethoxycarbonyl (Troc) group followed by macrolactamization with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)−diisopropylethylamine (DIPEA)[20] afforded (4*S*,5*R*)-antillatoxin (**1a**), which was also not identical to natural antillatoxin. Thus, the White group also concluded that the proposed structure of natural antillatoxin should be revised.

Loh and co-workers also reported their synthetic studies of antillatoxin.[21] They developed indium-mediated allylation reactions of carbonyl compounds with allylic bromides. As shown in Scheme 7, the

Scheme 7



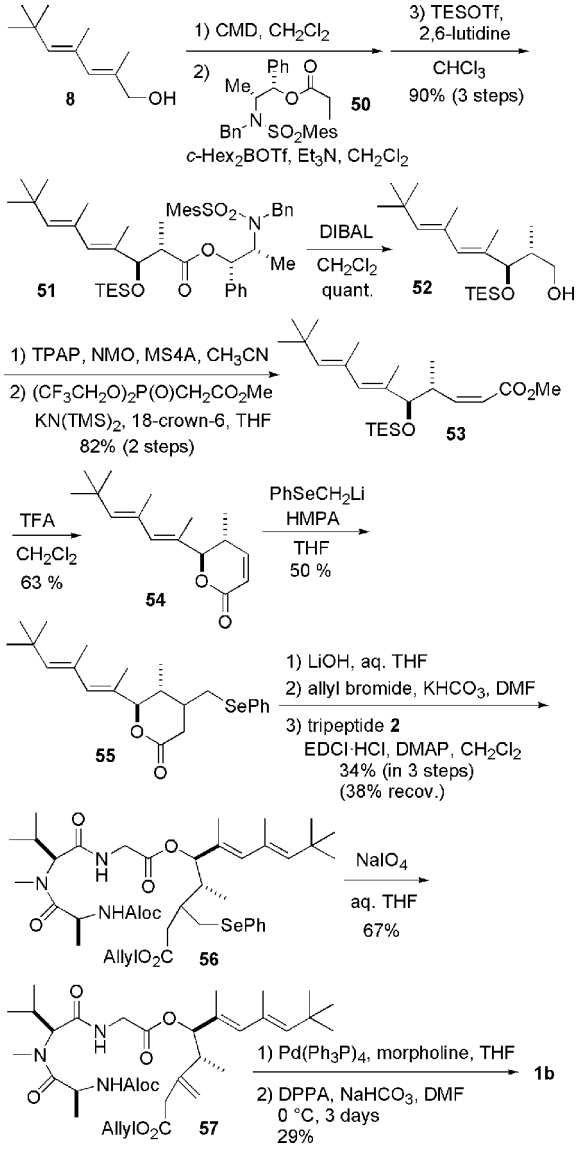
indium-mediated allylation of **42**, prepared from pivalaldehyde (**3**) using aldol reactions twice, with the allylic bromide **41** smoothly proceeded in saturated ammonium chloride catalyzed by lanthanide triflate to give the adduct **43** as a mixture of syn and anti isomers (93:7). Reduction of the ester **43** afforded the alcohol **44**, which was converted to the carbonate **45**. Although the carbonate **45** was first reported to be transformed into the β,γ-unsaturated amide **46** by an insertion reaction of carbon monoxide followed by the coupling reaction with alanine methyl ester, the real product later proved to be the non-carbonylated one **47**.[21c]

Furthermore, the indium-mediated allylation reaction of the aldehyde **42** with the bromide **48** proceeded under analogous conditions to give a mixture of the homoallylic alcohols **49** in which the syn isomer **49a** was the major one (syn:anti = 72:28).[21d]

2.1.2. Total Synthesis of (4R,5R)-Antillatoxin (Natural Form) Having the Revised Structure

When unavailability of natural products precludes further structural studies by spectral and other methods, synthetic studies of the compounds having analogous structures will be the best choice for structure determination. This was the case for antillatoxin also. Thus, (4*R*,5*R*)-antillatoxin (**1b**) was selected as the next synthetic target,[8b−d] which was proposed as the second possible configuration by the Gerwick group.[6] Since the relationship between the C4 and C5 positions is anti, the anti-selective aldol reaction developed by Abiko and Masamune[22] was employed to construct the required stereochemistry, as shown in Scheme 8. The aldehyde obtained from

Scheme 8



the dienyl alcohol **8** by its CMD oxidation was subjected to the anti-aldol reaction with the (*E*)-enolate generated from the propionate ester **50** of mesitylenesulfonyl ($MesSO_2$) norephedrine derivative

using dicyclohexylboron triflate and triethylamine. After protection of the secondary alcohol with TESOTf, the resulting anti-aldol adduct **51** was converted to the primary alcohol **52** with DIBAL. The alcohol **52** was transformed into (4*R*,5*R*)-antillatoxin (**1b**) in the same way as developed in the synthesis of (4*S*,5*R*)-antillatoxin (**1a**), as summarized in Scheme 8. The synthetic (4*R*,5*R*)-antillatoxin (**1b**) was identical to the natural antillatoxin by comparison of the spectral details and optical rotation. Thus, the structure of natural antillatoxin was revised to be **1b** by total synthesis.[8b−d]

In addition, (4*R*,5*S*)- and (4*S*,5*S*)-antillatoxins were analogously synthesized using the antipodal syn- or anti-selective aldol reactions as key steps.

2.1.3. Biological Activities of Antillatoxins

The natural antillatoxin has been shown to produce neuronal death, which is prevented by co-application of an NMDA receptor antagonist.[7d] In addition, antillatoxin was revealed to be a novel activator of voltage-gated sodium channels (VGSC).[7c]

Using four synthesized stereoisomers, (4*R*,5*R*)-, (4*S*,5*R*), (4*S*,5*S*)-, and (4*R*,5*S*)-antillatoxins, detailed biological evaluation was carried out in different biological assay systems: ichthyotoxicity to gold fish, microphysiometry using cerebeller granule cells (CGCs), lactose dehydrogenase (LDH) efflux from CGCs, monitoring of intracellular Ca^{2+} concentrations in CGCs, and cytotoxicity to Neuro 2a cells.[7c] The natural antillatoxin, the (4*R*,5*R*)-isomer, was revealed to be greater than 25-fold more potent than any of the other stereoisomers.

2.2. Somamide A

2.2.1. Total Synthesis

Somamide A was isolated by Gerwick and coworkers[23] from assemblages of the marine cyanobacteria *Lyngbya majuscula* and *Schizothrix* sp. from the Fijian Island. Its structure was determined to be the 19-membered macrocyclic depsipeptide **58** having a 3-amino-6-hydroxy-2-piperidone (Ahp) unit, a (*Z*)-2-amino-2-butenoic acid (Abu) unit, and a sulfoxide function, as shown in Figure 3. The Ahp unit has been recently characterized as a constituent in more than 60 19-membered cyclic depsipeptides derived from cyanobacteria.[5] They generally exhibit an interesting and significant inhibiting action against peptide proteases. The Ahp moiety may be biosynthetically derived from glutamate and probably plays an important role for protease inhibition because it may participate in converting the cyclic depsipeptides into a bioactive conformation due to the conformationally restricted structure and hydrogen bonding with the free hydroxyl group.

The first total synthesis of a cyclic depsipeptide possessing the Ahp unit was accomplished by Yokokawa, Inaizumi, and Shioiri[24] for micropeptin T-20 (**59**). This Ahp-depsipeptide was isolated from the cyanobacterium *Microcyctis aeruginosa* of freshwater origin.[25] Its total synthesis revealed that the proposed structure **59** should be reexamined.

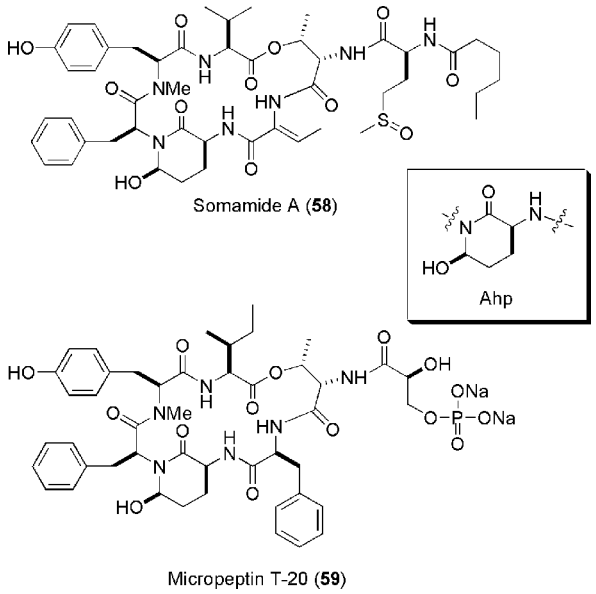
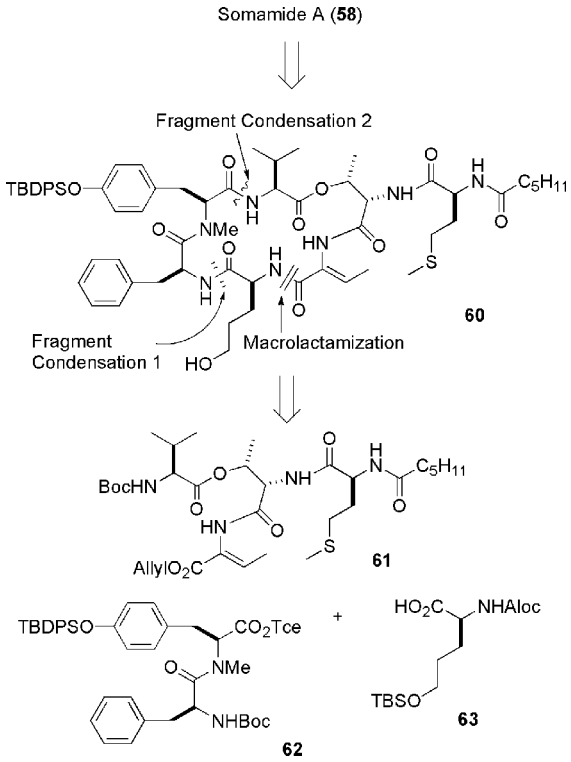


Figure 3.

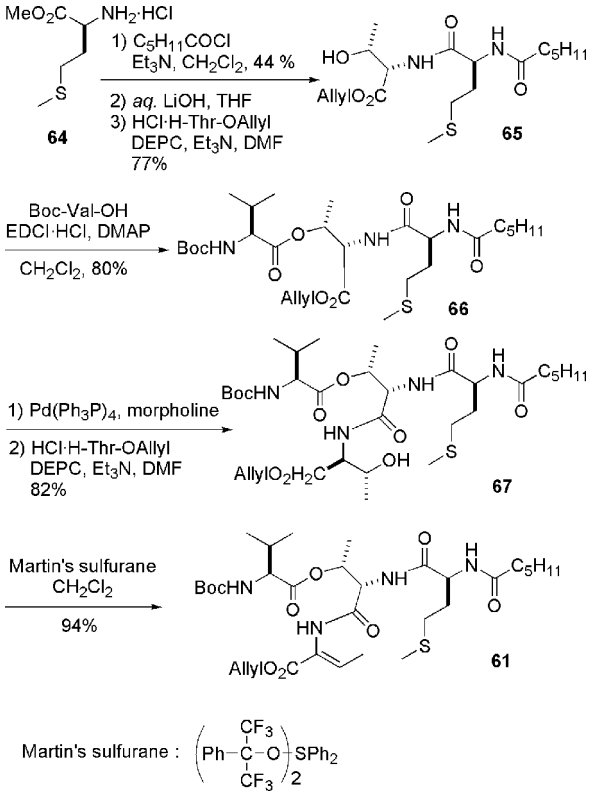
The total synthesis of somamide A (**58**) by Yokokawa and Shioiri[26] is the second example of the total synthesis of the Ahp-depsipeptides. The retrosynthetic plan is shown in Scheme 9, in which the cyclic precursor **60** was disconnected into three fragments **61**−**63**. The precursor of the Ahp unit in **60** was the 2-amino-5-hydroxypentanoic acid unit, which was cyclized to the Ahp moiety at the last stage of the synthesis.

Scheme 9



As for the synthesis of the Abu-containing depsipeptide fragment **61**, Martin's sulfurane (diphenyl bis(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl)sulfurane)[27] was employed to dehydrate the corresponding threonine derivative **67**, which was straightforwardly prepared from HCl·H−Met−OMe (**64**) via the alcohol

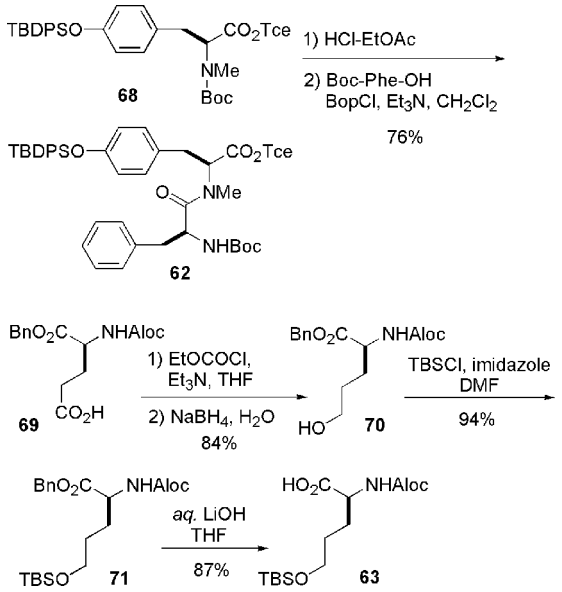
Scheme 10



65 and the depsipeptide **66**, shown in Scheme 10. Dehydration of **67** with Martin's sulfurane afforded the (*Z*)-Abu derivative **61** in excellent yield. Application of Martin's sulfurane to the stereospecific dehydration of the amino acid derivatives was further developed by Yokokawa and Shioiri,[28] which will be described later in section 2.2.2.

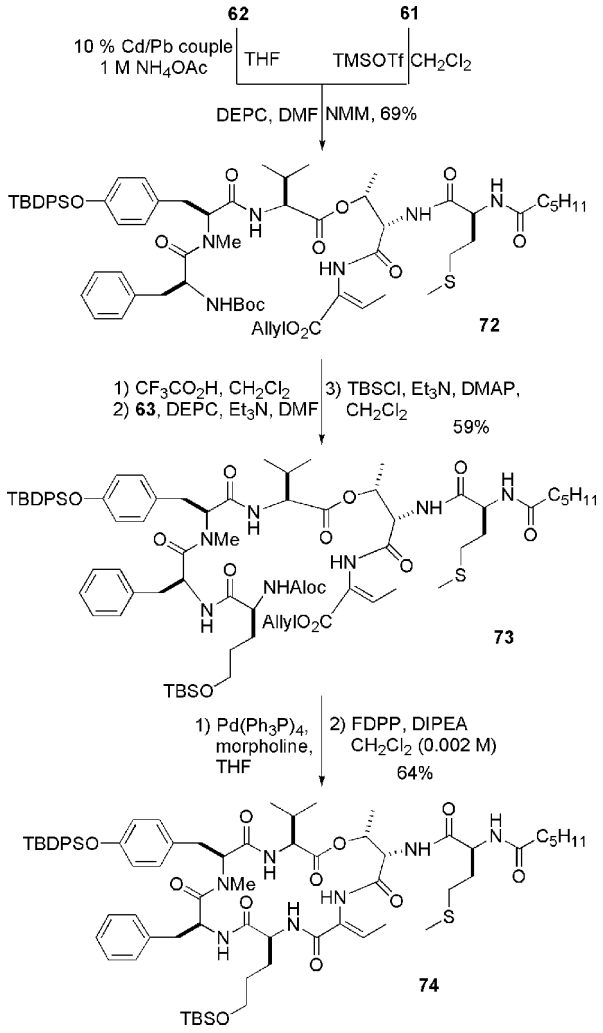
The dipeptide **62** was prepared from Boc-*N*-MeTyr-(TBDPS)-OTce (**68**) by acidic deprotection and then coupling with Boc-Phe-OH utilizing BopCl,[11] and the 2-amino-5-hydroxypentanoic acid derivative **63** was smoothly prepared from Aloc-Glu-OBzl (**69**) via **70** and **71**, as shown in Scheme 11.

Scheme 11



Respective deprotection of **61** and **62** followed by coupling with DEPC afforded the depsipeptide **72**, which, after acidic deprotection, was condensed with **63** and treated with TBSCl to give the linear peptide **73** having the full carbon skeleton of somamide A (**58**), as shown in Scheme 12. Simultaneous depro-

Scheme 12



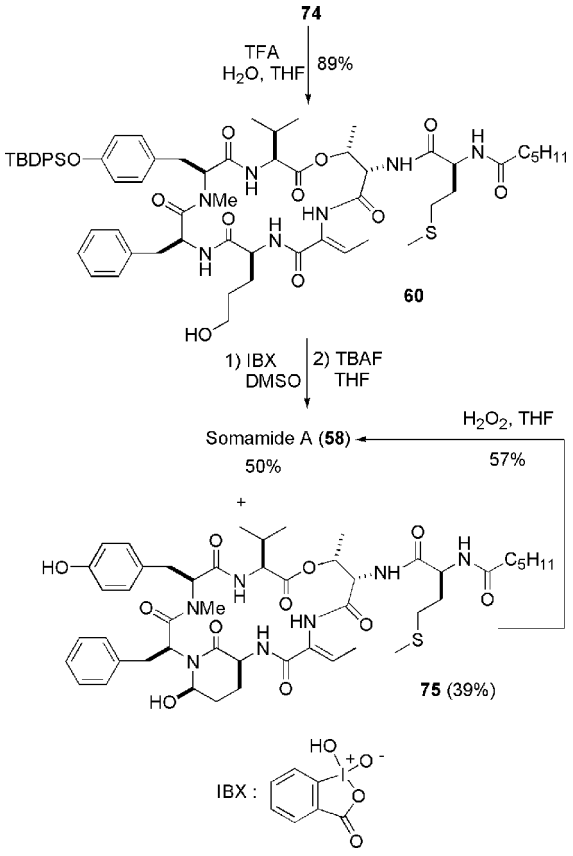
tection of both *N*- and *C*-terminal protective groups followed by macrolactamization with pentafluorophenyl diphenylphosphinate (FDPP, $Ph_2P(O)OC_6F_5$)[29] afforded the cyclic depsipeptide **74**.

Construction of the Ahp unit in **58** was achieved by the method established in the total synthesis of micropeptin T-20.[24] Thus, after removal of the TBS function, oxidation of the resulting alcohol **60** with IBX and then treatment with tetrabutylammonium fluoride (TBAF, $Bu_4N^+F^-$) afforded somamide A (**58**) as a major product and the sulfide **75** as a minor one, shown in Scheme 13. The latter was transformed into **58** on standing in air or with hydrogen peroxide, which would suggest that the sulfide **75** is a true natural product and somamide A is an artifact.

2.2.2. Stereospecific Dehydration of β-Hydroxy-α-amino Acids Using Martin's Sulfurane

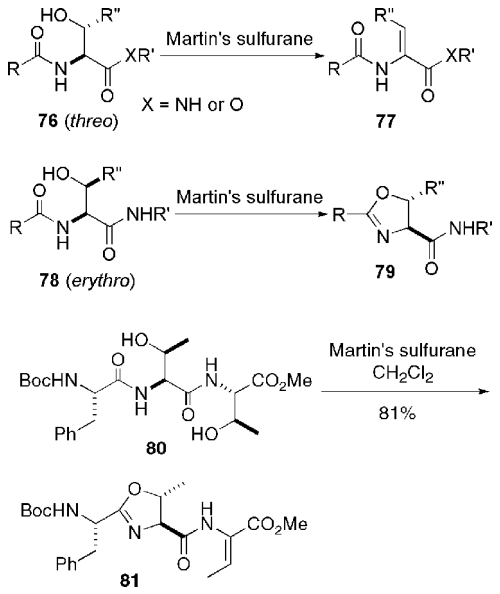
As described in section 2.2.1, Martin's sulfurane proved to be very effective for construction of (*Z*)-Abu.

Scheme 13



Further investigations[28] revealed that *threo*-*N*-acyl-*β*-hydroxy-α-amino acid derivatives **76** afford (*Z*)-α,*β*-dehydroamino acids **77** using Martin's sulfurane, while *erythro*-*N*-acyl-*β*-hydroxy-α-amino acid amides **78** are converted to 4,5-*trans*-oxazolines **79** under analogous reaction conditions, as shown in Scheme 14. One noteworthy stereospecific feature of the

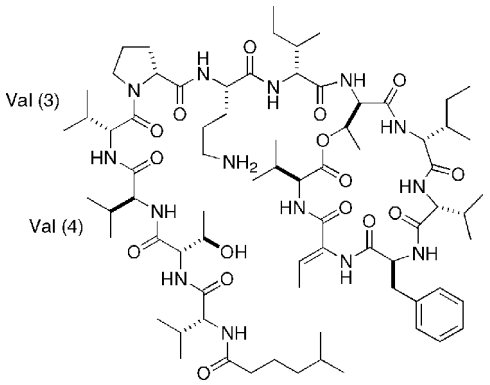
Scheme 14



method is demonstrated in the dehydration of the tripeptide **80** having both *threo* and *erythro* configurations to the oxazoline-Abu product **81**.

2.3. Kahalalide F

Kahalalides are a family of peptides bearing a variety of cyclic or acyclic skeletons isolated from the sacoglossan mollusc *Elysia rufescens* and the green alga *Bryopsis* sp.[30] Among these peptides kahalalide F is the largest 19-membered cyclic depsipeptide, which is known to exhibit very interesting antitumor activity[31] and is in phase II clinical trials for treatment of lung and prostate cancers and melanoma. The first assigned primary structure is consisted of mostly common amino acids except (*Z*)-Abu and 5-methylhexanoic acid. Further investigation of the absolute stereochemistry of kahalalide F led to two structures with different stereochemistry in Val (3) and Val (4) parts proposed independently by Scheuer et al.[32] and Rinehardt et al.[33] As described later, the discrepancy was unambiguously solved by the synthetic work of Giralt, Albericio, and co-workers.[34] Although kahalalide B, having only common amino acids and 5-methylhexanoic acid, was also synthesized by the same workers,[35] the following discussion will be limited to kahalalide F (**82**) due to the subject of this review (Figure 4).



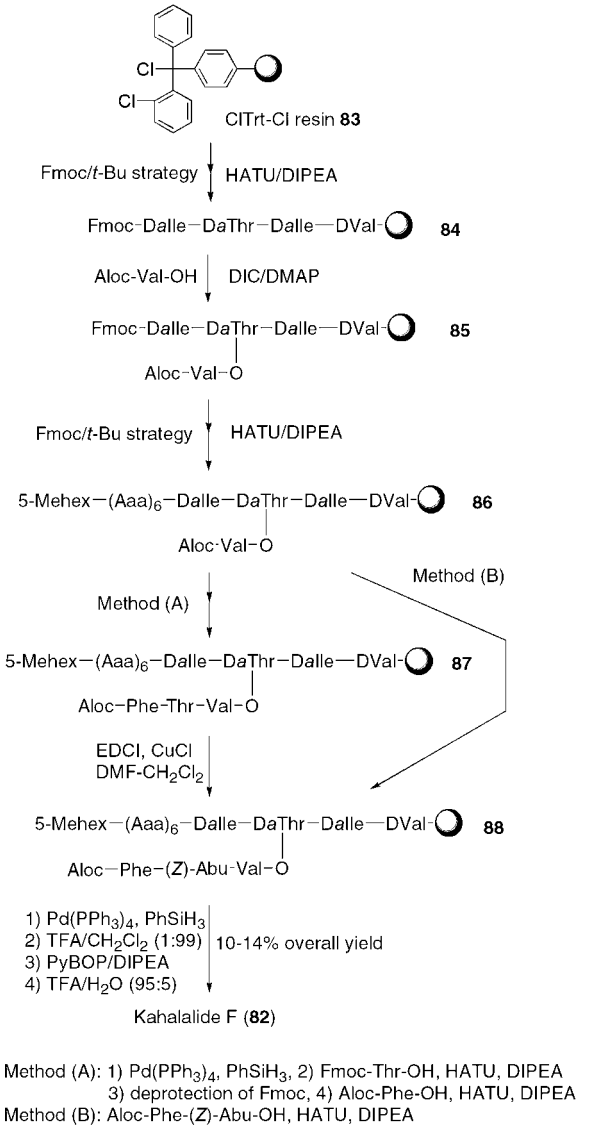
Kahalalide F (**82**)

Figure 4.

Giralt, Albericio, and co-workers synthesized the two proposed structures because of the uncertainty regarding the stereochemistry at Val (3) and Val (4) and accomplished the synthesis and structural determination of kahalalide F. From the simplicity of the structure, their synthesis includes solid-phase synthesis of the linear precursors and subsequent macrocyclization of the off-resin peptides at the D-Val/Phe site. Construction of (*Z*)-Abu was carried out by stereoselective dehydration of the threonine precursor at a late stage of the synthesis (Scheme 15).

The tetrapeptide resin **84** was synthesized from the Fmoc-D-Val-resin, prepared from the commercially available chlorotrityl chloride resin (**83**), by a sequential attachment of D-alloisoleucine, D-allothreonine, and D-alloisoleucine derivatives using Fmoc/*t*-Bu strategy and HATU/DIPEA as the coupling reagent. Ester linkage between **84** and Aloc-Val-OH was formed using diisopropylcarbodiimide (DIC) in the presence of DMAP. For chain elongation to the decapeptide **86** from **85**, six amino acids were sequentially attached and capped with 5-methylhex-

Scheme 15

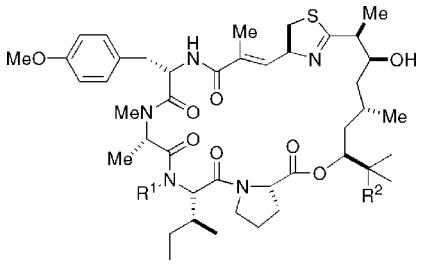


Method (A): 1) $Pd(PPh_3)_4$, $PhSiH_3$, 2) Fmoc-Thr-OH, HATU, DIPEA
3) deprotection of Fmoc, 4) Aloc-Phe-OH, HATU, DIPEA
Method (B): Aloc-Phe-(*Z*)-Abu-OH, HATU, DIPEA

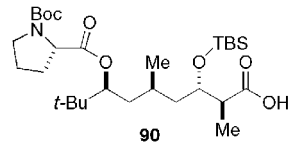
anoic acid at the *N*-terminal. Construction of (*Z*)-Abu was carried out by two different methods: (1) after side-chain elongation from **86** to the tridecapeptide **87**, stereoselective formation of the (*Z*)-Abu residue on the resin[36] (method A) by Fukase's method[37] using EDCI and cuprous chloride and (2) direct introduction of the dipeptide, Aloc-Phe-(*Z*)-Abu-OH, to **86** with HATU/DIPEA (method B). The Aloc group in **88** was deprotected with $Pd(PPh_3)_4$ and phenylsilane,[38] and cleavage from the resin with TFA/CH_2Cl_2 (1:99) afforded the linear depsipeptide, which was subjected to macrocyclization using 1*H*-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP)-DIPEA[39] to furnish, after removal of side-chain protection with TFA/H_2O (95:5), kahalalide F (**82**) in 10−14% yields. The synthetic kahalalide F and the diastereomer were compared by coeluting on HPLC with an authentic sample of kahalalide F, and the stereochemistry at the Val (3) and Val (4) residues was unambiguously determined as *R* and *S*, respectively. Interestingly, the biological activity of the diastereoisomer with (*S*)-Val (3) and (*R*)-Val (4) was 10 times less active than that of natural kahalalide F with (*R*)-Val (3) and (*S*)-Val (4).

2.4. Apratoxin A

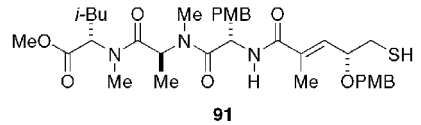
Apratoxins A−C, isolated from cyanobacterial *Lyngbya* sp. collected at Guam[40a] and Palau[40b] in 2001, are highly functionalized cyclic depsipeptides that are known to exhibit potent cytotoxicity against KB cell and LoVo cancer cell (IC_{50} = 0.52 and 0.36 nM). The pharmacological profiles of the unique peptides are unknown, and their elucidation is limited by their scarcity from marine origin. The structural feature of apratoxins shown in Figure 5 includes a hybrid structure from polypeptide and polyketide, which contains the 4-vinylthiazoline fused with novel 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid.



Apratoxin A (**89**) $R^1 = CH_3$, $R^2 = CH_3$
Apratoxin B $R^1 = H$, $R^2 = CH_3$
Apratoxin C $R^1 = CH_3$, $R^2 = H$



90



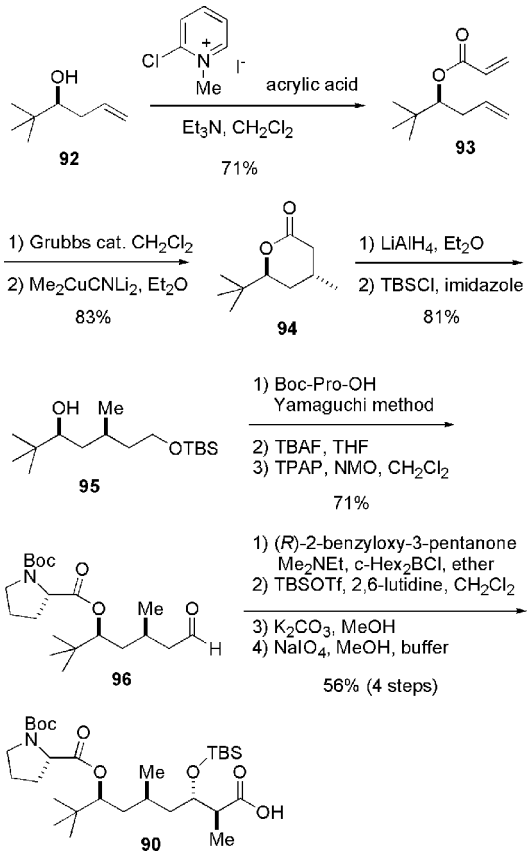
91

Figure 5.

The first total synthesis of apratoxin A (**89**) was accomplished by Chen and Forsyth.[41] Their synthetic feature includes final macrocyclization at the Ile/Pro site, coupling of two segments, the ester **90** and the triamide **91**, by thiol ester formation as the latent thiazoline, and thiazoline formation by a one-pot Staudinger reduction−intramolecular aza-Wittig (S-aW) process[42] developed by them. It has been reported that the thiazoline part of **89** is susceptible to acid conditions and undergoes dehydration to give the less active apratoxin analogue, (*E*)-34,35-dehydroapratoxin A.[40b] It was therefore necessary to introduce a 4-vinylthiazoline moiety at a late stage of the synthesis.

Synthesis of the ester fragment **90**, 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid derivative with L-proline, was achieved in 12 steps, as shown in Scheme 16. The known alcohol **92,** readily available by Brown's asymmetric allylation,[43] was acylated with acrylic acid and *N*-methyl-2-chloropyridinium iodide,[44] and the resulting ester **93** was cyclized by ring-closing metathesis (RCM)[45] using the Grubbs catalyst. Introduction of the C37 methyl group to the α,β-unsaturated lactone was performed by conjugate

Scheme 16

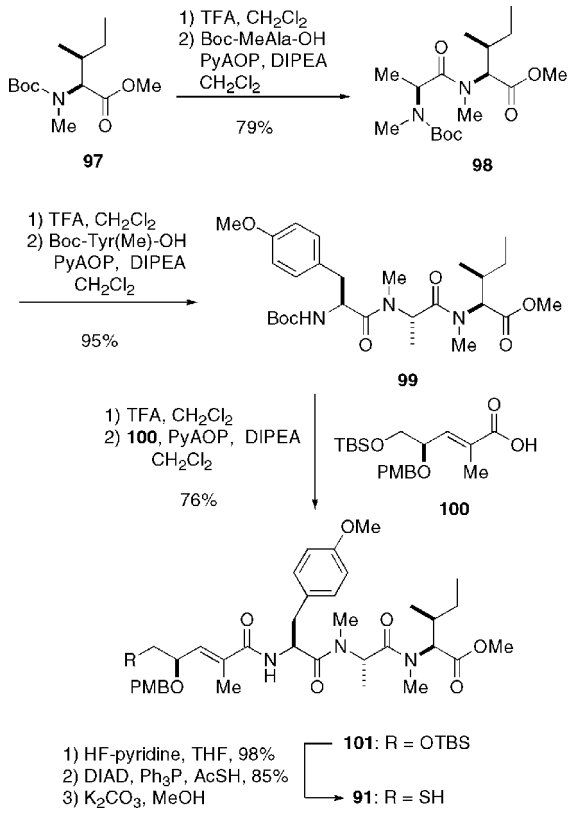


addition with a higher order methyl cuprate.[46] Reductive cleavage of the lactone **94** with $LiAlH_4$ and TBS protection of the primary alcohol provided the secondary alcohol **95**, which was subjected to esterification with Boc-Pro-OH by the Yamaguchi method,[47] subsequent deprotection of the TBS group, and TPAP oxidation of the primary alcohol to afford the aldehyde **96**. The anti-aldol part in **90** was constructed by Paterson's anti-selective aldol condensation[48] from **96**. The resulting aldol with the skeleton of the segment **90** was protected with TBSOTf, and Paterson's chiral auxiliary was cleaved in two steps to furnish the ester **90**.

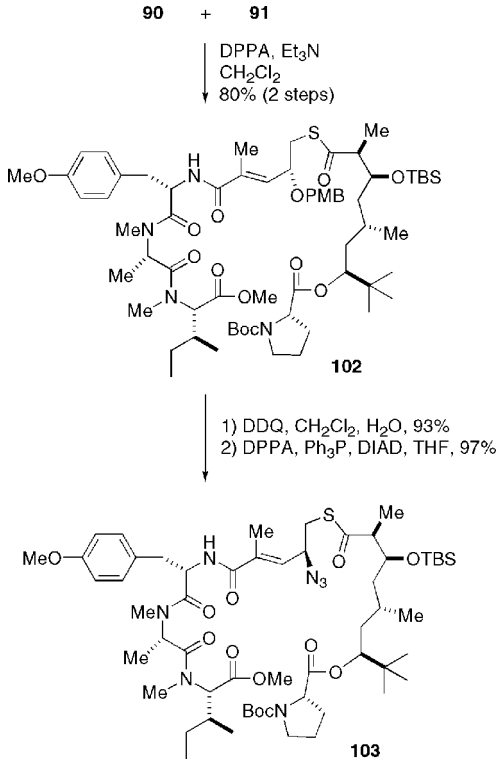
The triamide segment **91** was prepared from Boc-MeIle-OMe by a sequential coupling of Boc-MeAla-OH, Boc-Tyr(Me)-OH, and the α,β-unsaturated carboxylic acid **100** using (7-azabenzotriazole-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyAOP)/DIPEA[49] and subsequent exchange of the protected primary hydroxyl group in **101** to the thiol one using the Mitsunobu method[50] in three steps. The thiol-containing α,β-unsaturated acid residue in **91** served as a precursor to the vinylogous cysteine residue at a later stage (Scheme 17).

The thiol ester **102** was efficiently formed from the two segments **90** and **91** using DPPA and triethylamine according to the method developed by Yokoyama, Shioiri, and Yamada.[51] For introduction of the nitrogen function, the PMB ether in **102** was deprotected with DDQ and subsequent one-step azidation[52] of the allylic alcohol was effective by employing DPPA again together with triphenylphosphine and diisopropyl azadicarboxylate (DIAD) to afford the azide **103** in 90% yield, Scheme 18.

Scheme 17



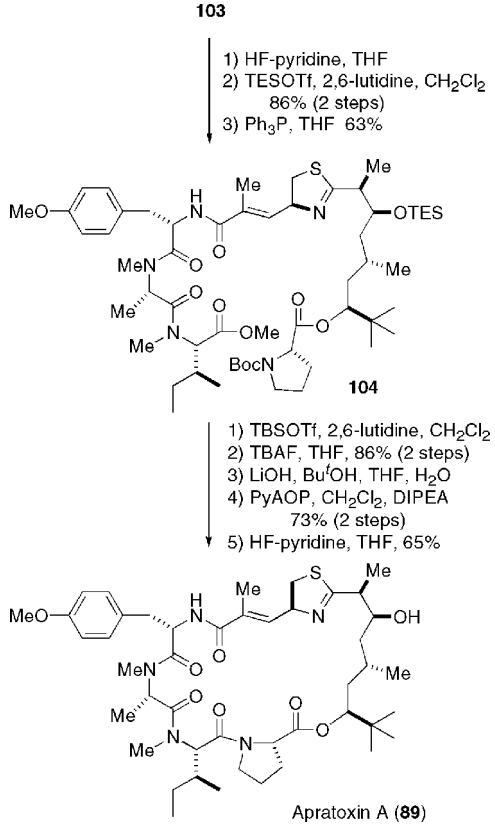
Scheme 18



The labile thiazoline was efficiently constructed using the S-aW process developed[42] using triphenylphosphine after exchange of the TBS protection to the TES one for the solution of final difficult deprotection. The Boc group of **104** with acid-labile 2-hydroxyethyl-4-vinylthiazoline moiety was carefully deprotected in two steps by conversion to the

TBS urethane using TBSOTf and its cleavage with TBAF according to the Ohfune's procedure.[53] After saponification with lithium hydroxide, macrocyclization of the free peptide with PyAOP/DIPEA smoothly proceeded at room temperature for 2 h to give, after careful TES deprotection with HF−acetonitrile, apratoxin A (**89**) in 47% yield (three steps). Synthetic apratoxin A was identical in all respects with spectroscopic data provided for the natural substance, Scheme 19.

Scheme 19



The oxazoline-containing analogue of apratoxin A was synthesized by Ma and co-workers.[54] In the synthesis, preparation of the polyketide fragment was accomplished by a very similar approach to that described above (Forsyth's method). Very recently the polyketide fragment was synthesized by Xu and coworkers.[55]

2.5. Lyngbyabellins A and B

As described in sections 2.1, 2.2, and 2.4, *Lyngbya majuscula* is a rich source of biologically active secondary metabolites, and lyngbyabellins A and B were also isolated from this cyanobacterium.[56] These cyclic depsipeptides exhibit attractive cytotoxic properties against the human cancer cell lines. Their structures **105** and **106** are closely related each other, and lyngbyabellin A (**105**) has two thiazole rings, while one of the thiazole rings is replaced by a thiazoline ring in lyngbyabellin B (**106**), shown in Figure 6. These show a resemblance to the structure of dolabellin (**107**), a metabolite isolated from the sea hare *Dolabella auricularia*.[57] This striking structural relationship will support a cyanobacterial origin for dolabellin.

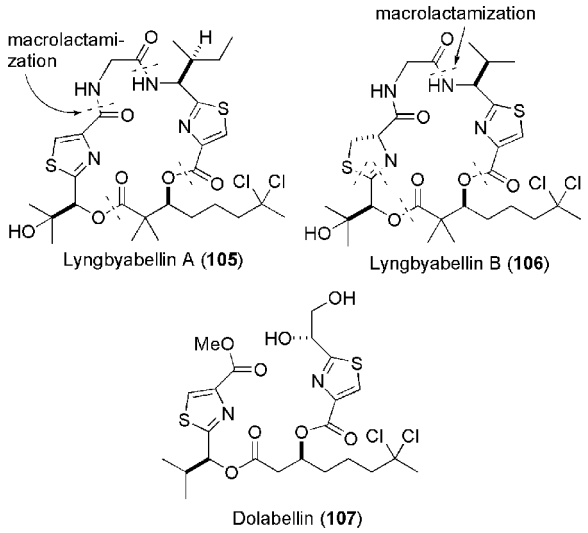
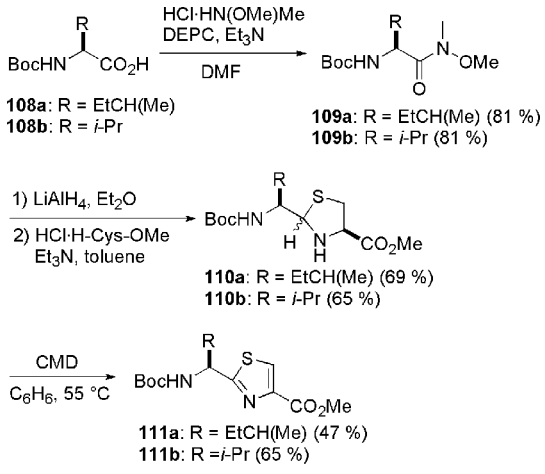


Figure 6.

Lynbyabellins A and B were synthesized by Yokokawa, Shioiri, and co-workers.[58] In their strategy the molecules were disconnected at the peptide and ester bonds, and macrolactamization was accomplished by activation of the carboxyl group at the *C*-terminal peptide where no epimerization occurred. Construction of the thiazoline ring of **106** was postponed to the final stage of the synthesis because of its facile racemization.

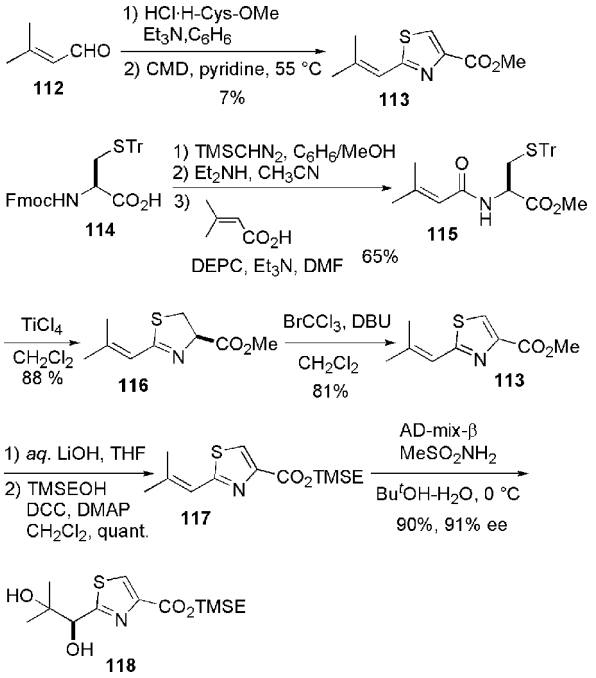
The required thiazole amino acids **111** were prepared using the method established by Hamada and Shioiri[59] from the corresponding amino acids **108** through (1) transformation into the Weinreb amides **109**, (2) reduction with $LiAlH_4$, (3) condensation with cysteine methyl ester, and (4) dehydrogenation with CMD, as shown in Scheme 20.

Scheme 20



The α,β-dihydroxy thiazole **118** was prepared from the thiazole **113**, which was obtained by condensation of the aldehyde **112** with cysteine methyl ester followed by the CMD oxidation. Although the thiazole **113** was prepared in only two steps, the yield was miserable because of the instability of the intermediate thiazolidine, shown in Scheme 21. Alternatively, preparation of the thiazole **113** was accomplished from Fmoc-*S*-trityl cysteine (**114**) through (1) methyl esterification using trimethylsilyldiazomethane (TM-

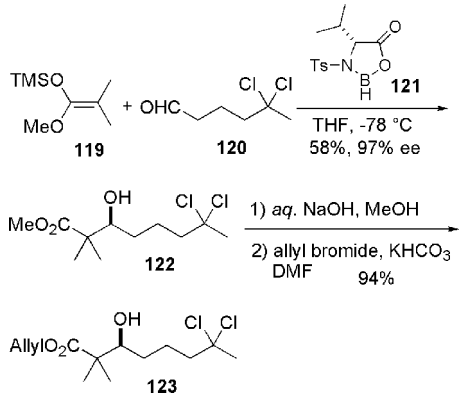
Scheme 21



$SCHN_2$, Me_3SiCHN_2),[60] (2) deprotection of the Fmoc (9-Fluorenylmethoxycarbonyl) group, and (3) coupling with 3-methylcrotonic acid. The resulting cysteine amide **115** underwent titanium(IV)-mediated tandem deprotection−dehydrocyclization[61] to give the thiazoline **116**, which was dehydrogenated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/$BrCCl_3$[62] to produce the thiazole **113**. After replacement of the methyl ester of **113** with the 2-trimethylsilylethyl (TMSE) one, the Sharpless asymmetric dihydroxylation[63] using AD-mix-β afforded the α,β-dihydroxy thiazole **118** with 91% enantiomeric excess (ee).

The dichlorinated β-hydroxy acid fragment **123** was constructed with excellent stereoselectivity (97% ee) by enantioselective aldol reaction of the ketene acetal **119** with the aldehyde **120** using the chiral oxazaborolidine **121** developed by Kiyooka,[64] followed by replacement of the ester group of **122**, shown in Scheme 22.

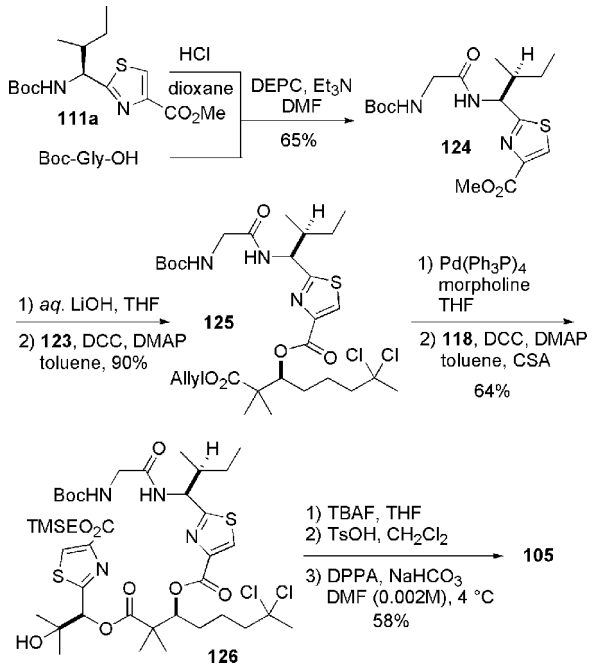
Scheme 22



2.5.1. Total Synthesis of Lyngbyabellin A

The total synthesis of lyngbyabellin A (**105**) was started by dicyclohexylcarbodiimide (DCC)-mediated coupling of the dichloro ester **123** with the dipeptide

Scheme 23



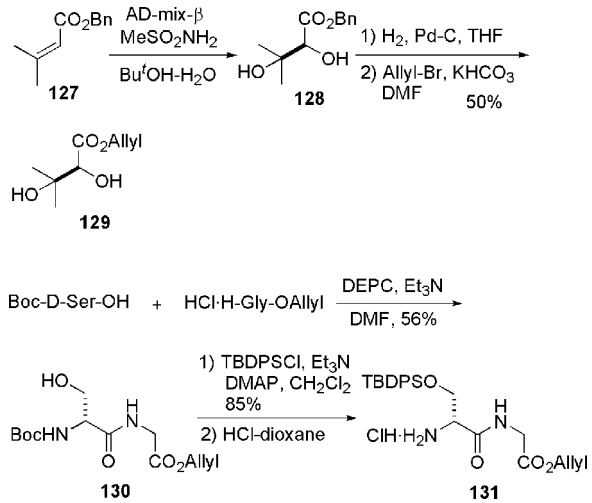
124, prepared from the thiazole **111a** and Boc-Gly-OH, shown in Scheme 23. After deprotection of the allyl group from the ester **125**, coupling with the diol **118** using DCC afforded the linear precursor **126**. After deprotection, the macrolactamization was achieved under high dilution conditions using DPPA in the presence of sodium hydrogen carbonate to give lyngbyabellin A (**105**).

2.5.2. Total Synthesis of Lyngbyabellin B

Instead of the thiazole ring in lyngbyabellin A (**105**), lyngbyabellin B (**106**) has a thiazoline ring which will readily undergo racemization during synthesis and handling. Hence, construction of the thiazoline ring was postponed to the later stage of synthesis and Wipf's oxazoline−thiazoline interconversion protocol[65] was employed.

The remaining two building blocks for the preparation of lyngbyabellin B (**106**) were the diol **129** and the dipeptide **131**, which were, respectively, prepared

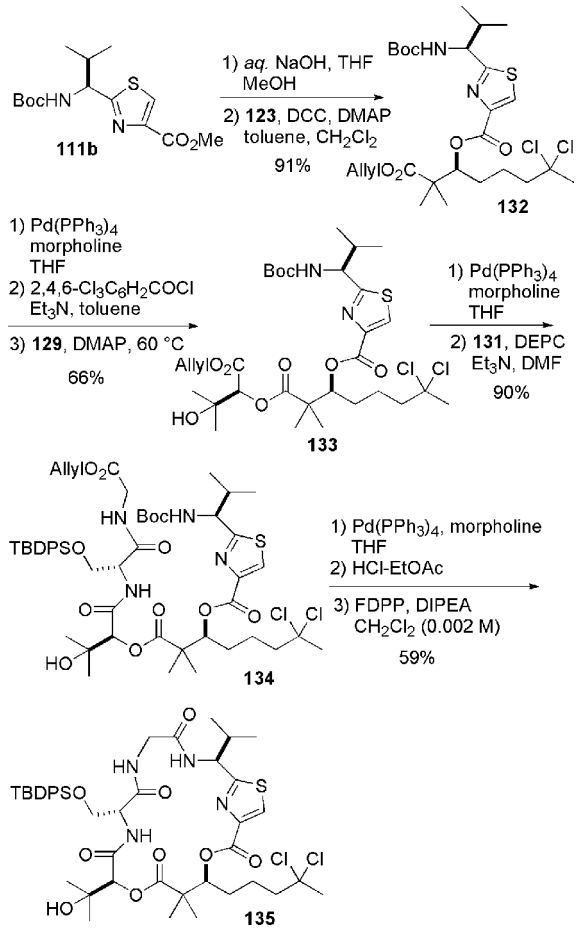
Scheme 24



using the Sharpless asymmetric dihydroxylation and the DEPC coupling, as shown in Scheme 24.

The thiazole **111b** was hydrolyzed and condensed with the dichlorohydroxy ester **123** using DCC to give the ester **132**. After removal of the allyl group from **132**, the resulting carboxylic acid sluggishly underwent coupling with the dihydroxy ester **129**, and it was necessary to activate the carboxyl group with 2,4,6-trichlorobenzoyl chloride[47] before coupling. The coupling product **133** was connected with the dipeptide **131** using the DEPC method after deprotection to give the linear peptide **134**. Removal of the protective groups at both *N*- and *C*- terminals and then macrolactamization with FDPP afforded the macrocycle **135** (Scheme 25).

Scheme 25

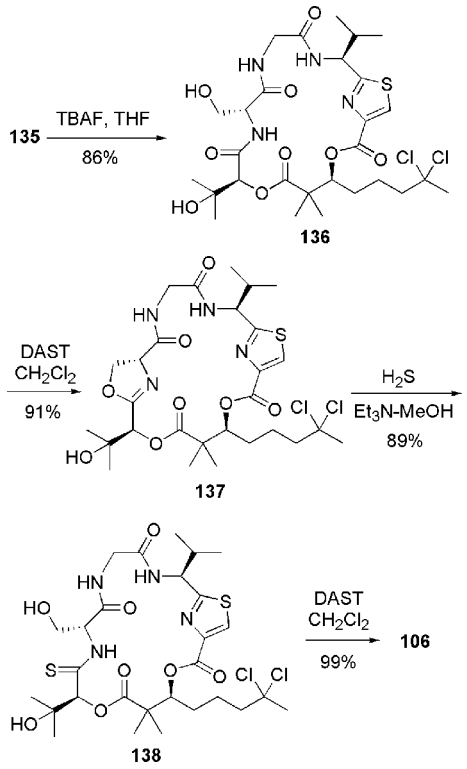


Final formation of the thiazoline ring was accomplished by Wipf's oxazoline−thiazoline interconversion protocol,[65] as shown in Scheme 26. Thus, treatment of **135** with TBAF and then (diethylamino)sulfur trifluoride (DAST, $(Et_2N)S^+F_3^-$) afforded the oxazoline **137**. After thiolysis of the oxazoline **137**, the resulting thioamide **138** was treated with DAST to give lyngbyabellin B (**106**) in excellent yield.

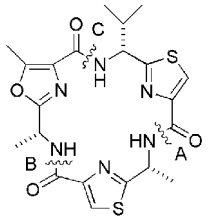
2.6. Dendroamide A

As already shown there are many marine cyclic peptides having oxazole, oxazoline, thiazole, and thiazoline amino acids as their constituents.[3e] Dendroamide A (**139**) is also a modified cyclic peptide having the oxazole and thiazole rings and was

Scheme 26



isolated from the terrestrial cyanobacterium *Stigonema dendroideum* fremy on the basis of its ability to reverse drug resistance in tumor cells that overexpress either of the transport proteins, P-glycoprotein or MRP 1.[66] Because of this multidrug resistance reversing activity, dendroamide A may serve as the starting point for the synthesis of a variety of analogues for structure−biological activity analyses (Figure 7).



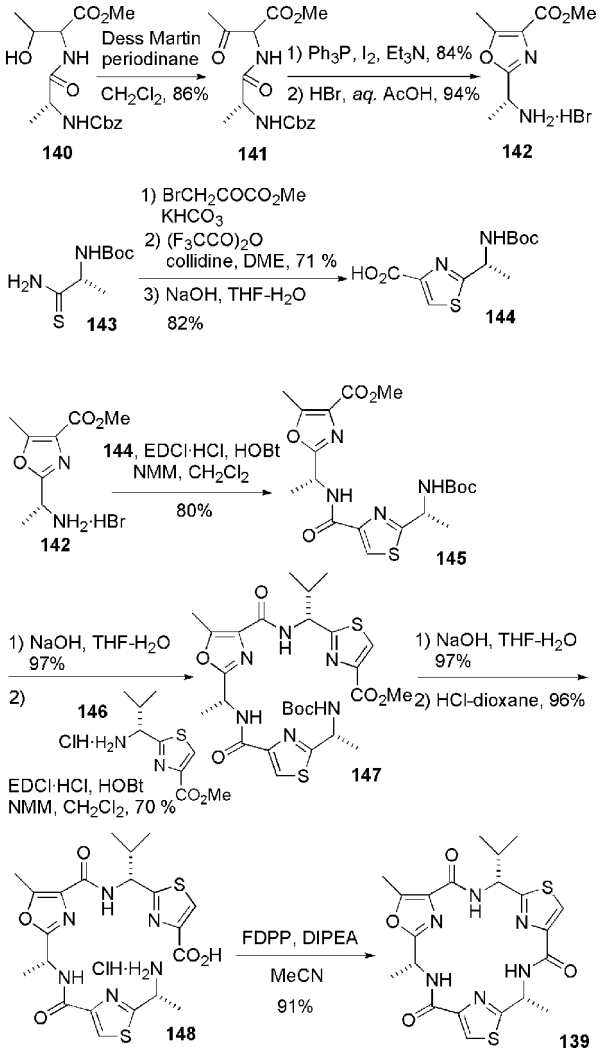
Dendroamide A (**139**)

Figure 7.

The first synthesis of dendroamide A (**139**) was achieved by Bertram and Pattenden.[67] Further total syntheses were reported by the groups of Smith,[68] Kelly,[69] and Shin.[70]

Bertram and Pattenden[67] first used a linear approach for the total synthesis of **139**. The required oxazole amino acid **142** was prepared from Z-D-Ala-DL-Thr-OMe (**140**) by oxidation with Dess−Martin periodinane,[71] cyclization with triphenylphosphine−iodine in the presence of triethylamine,[72] and then deprotection of the Z group, as shown in Scheme 27. The thiazole derivative **144** was prepared through a modified Hantzsch method[73] by condensation of ethyl bromopyruvate with the thioamide **143** of alanine. Utilizing these oxazole and thiazole derivatives, sequential couplings of **142** and **144**, **145** and **146**

Scheme 27

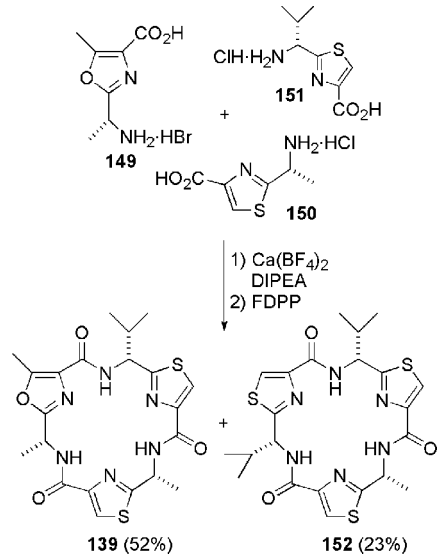


with EDCI-*N*-hydroxybenzotriazole (HOBt) in the presence of *N*-methylmorpholine (NMM) afforded the linear precursor **147**. Deprotection followed by macrolactamization with FDPP/DIPEA afforded dendroamide A (**139**) in 91% yield.

Next, Bertram and Pattenden applied an interesting method of metal-templated assemblies developed by them to the one-pot synthesis of **139**.[67] A 1:1:1 mixture of the heterocyclic amino acids **149**, **150**, and **151**, respectively, derived from **142**, **144**, and **146**, underwent the metal-templating reactions by treatment with various metal tetrafluoroborate salts in the presence of DIPEA and then FDPP, giving a mixture of dendroamide A (**139**) and its analogues such as **152**. When no metal salts were used the yield was 75% and the percentage composition of cyclic products was 23:29 for **139** and **152**. Although use of $AgBF_4$ afforded **152** only, $Ca(BF_4)_2$ was found to act as a better template in the assembly of trimeric cyclic peptides to raise the proportion of **139** to 52% with only 23% of analogue **152** (Scheme 28).

As already pointed out earlier, one of the most important strategies for the preparation of macrocyclic peptides is selection of the most suitable point for the cyclization of linear precursors. Prior to the synthesis of dendroamide A Xia and Smith first determined the lowest energy conformation of each

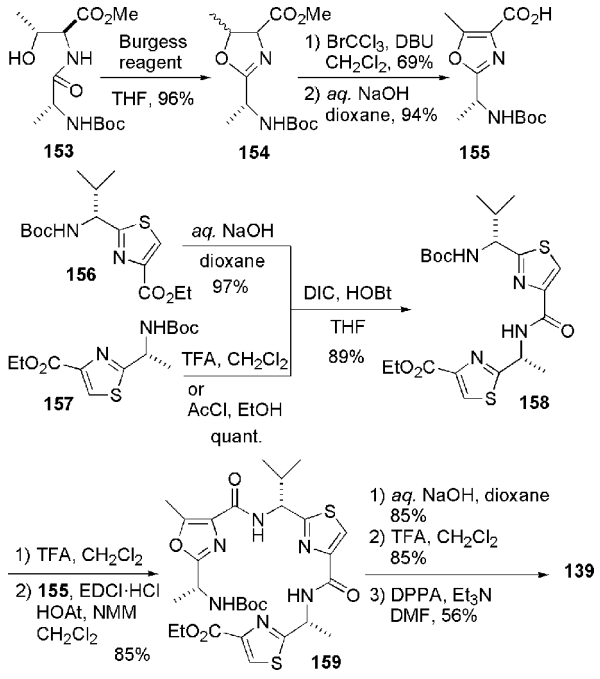
Scheme 28



of the three possible acyl−azide linear precursors (see the disconnection A−C in Figure 7) using both MM2 and MOPAC modeling.[68] Disconnection B was selected as the most suitable point because the distance between the *N*-terminal nitrogen and the *C*-terminal carbon was revealed to be the closest by calculation.

Preparation of the required oxazole amino acid **155** was carried out from the dipeptide, Boc-D-Ala-L-Thr-OMe (**153**), by dehydration with Burgess reagent ($Et_3N^+SO_2N^-CO_2Me$)[74] and then oxidation of the epimeric oxazoline mixture **154** with bromotrichloromethane and DBU,[62] as shown in Scheme 29. The

Scheme 29



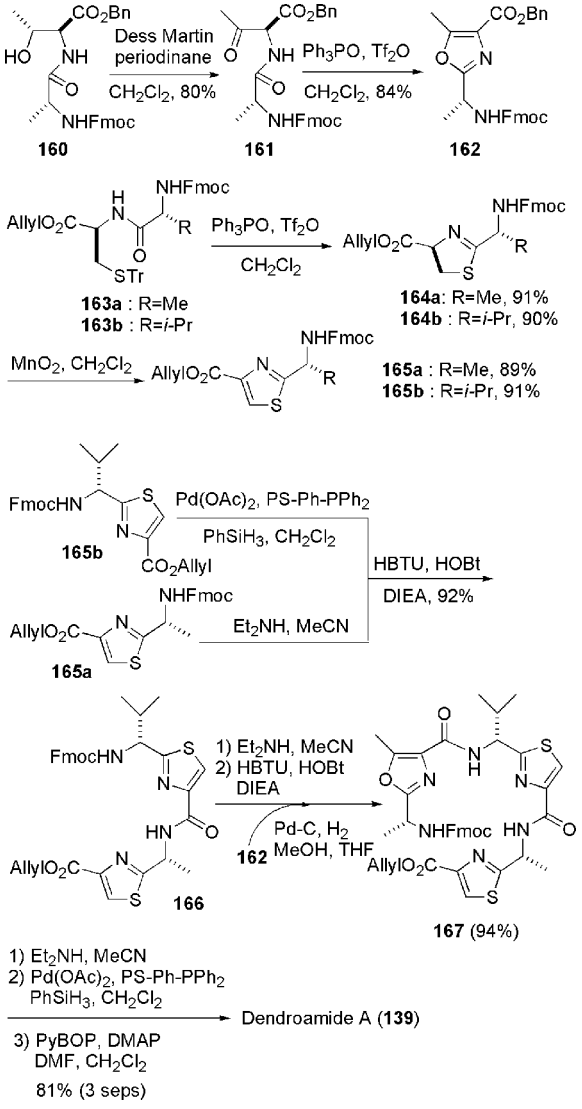
chiral thiazole amino acids **156** and **157** were prepared using a modified Hantzsch reaction[73] just like Scheme 27 (from **143** to **144**). Construction of the full carbon skeleton of **139** started from deprotection of the thiazoles **156** and **157**. The dipeptide **158** obtained using DIC and HOBt was deprotected and

coupled with the oxazole carboxylic acid **155** to give the linear precursor **159**. Deprotection at the *C*- and *N*-terminals followed by macrocyclization with DPPA afforded dendromide A (**139**) in 56% yield together with its conformational isomer in 18% yield.

Highlights of the synthesis of dendroamide A (**139**) by You and Kelly[69] will be application of bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate[75] to the preparation of the oxazole structure from a α-ketodipeptide and the thiazolines from fully protected cysteine-containing dipeptides.

Synthesis of the oxazole amino acid **162** is outlined in Scheme 30. The α-ketodipeptide **161** prepared by

Scheme 30



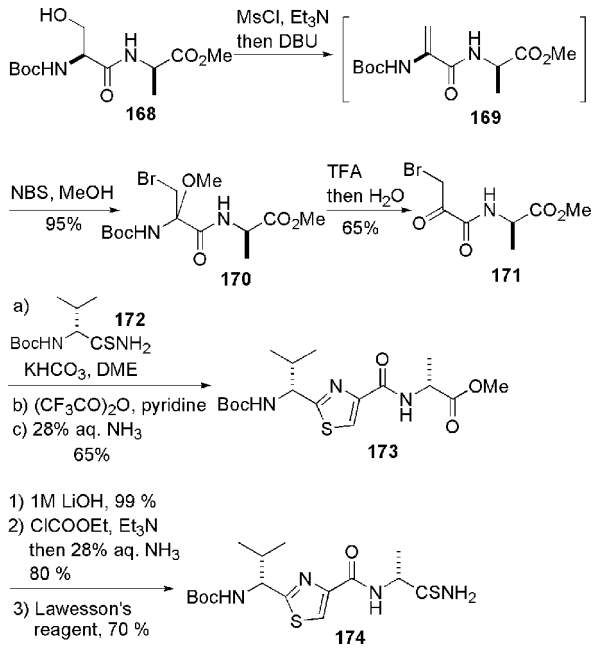
the Dess−Martin oxidation of **160** smoothly afforded the oxazole **162** by treatment with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate generated from triphenylphosphine oxide and triflic anhydride. The triphenylphosphine−iodine reagent might be used in this case[67] like the oxobisphosphonium salt but requires use of a base, increasing the risk of racemization.[72]

Synthesis of the thiazole amino acids **165a** and **165b**, respectively, started from **163a** and **163b**, which were easily transformed into the thiazolines **164a** and **164b**, respectively, utilizing bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate. Oxidation of **164a** and **164b** with active manganese dioxide afforded the required thiazoles **165a** and **165b**, respectively.

Synthesis of the linear precursor **167** proceeded from three heterocyclic amino acids **162**, **165a**, and **165b**. Removal of the Fmoc group of **165a** was carried out with diethylamine, while deprotection of the allyl group of **165b** was accomplished utilizing a palladium catalyst, generated from palladium acetate and polystyrene-supported triphenylphosphine (PS-Ph-PPh$_2$) in the presence of phenylsilane.[76] Coupling with *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU)/HOBt/DIPEA, deprotection from the product **166** with diethylamine, and then coupling with the carboxylic acid derived from oxazole **162** yielded the linear precursor **167**. After deprotection, final cyclization with PyBOP/DMAP was achieved by slowly adding the deprotected linear peptide to a solution of PyBOP/DMAP in CH_2Cl_2/DMF (2/1) with a syringe pump over 8 h to give dendroamide A (**139**) in good yield. These reaction conditions are analogous to high-dilution conditions essential for macrocyclization.

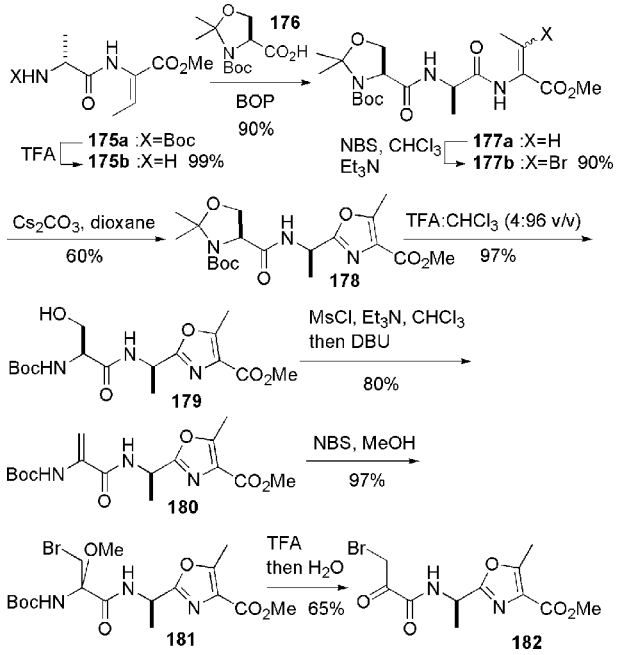
The key step for the preparation of dendroamide A (**139**) by Yonezawa, Tani, and Shin is formation of the oxazole and thiazole rings from dehydropeptides.[70] The starting dehydrodipeptide **169**, prepared from Boc-L-Ser-D-Ala-OMe (**168**), was converted to the bromide **170** with *N*-bromosuccinimide (NBS), and then treatment with TFA afforded the bromo pyruvate derivative **171**. The Hantzsch condensation of **171** with the thioamide **172** produced the thiazole peptide **173**, which was converted to the corresponding thioamide **174** according to the usual procedure, shown in Scheme 31.

Scheme 31



Preparation of the required oxazole fragment **182** was started by deprotection of the Boc group of **175a** and then coupling with the serine derivative **176**

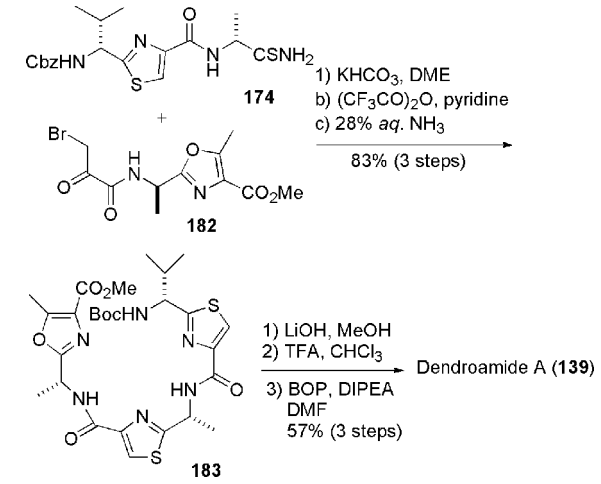
Scheme 32



using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), as shown in Scheme 32. The oxazole ring was formed by treatment of **177a** with NBS and then cesium carbonate. Removal of the isopropylidene group from the resulting oxazole peptide **178** followed by dehydration afforded the dehydropeptide **180**, which was treated with NBS in methanol and then TFA to give the bromide **182** via **181**.

Condensation of the thioamide **174** with the bromide **182** using potassium hydrogen carbonate afforded the *N*,*O*-diprotected linear precursor **183**, which after deprotection was cyclized with BOP and DIPEA to give dendroamide A (**139**) in 57% yield (Scheme 33).

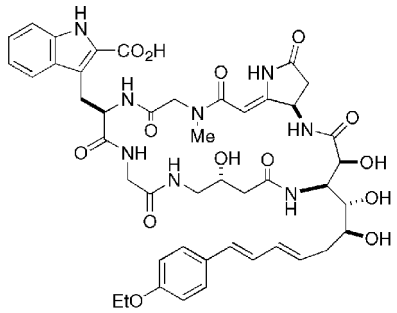
Scheme 33



3. Cyclic Peptides from Sponges

3.1. Microsclerodermin E

Microsclerodermins A−I, isolated from both *Theonella* sp. and *Microscleroderma* sp., are a growing family of 23-membered cyclic peptides that are known to exhibit antifungal activity as well as cytotoxicity.[77] The significant features common to all members of these molecules include six amino acid residues, four of which ((3*R*)-4-amino-3-hydroxybutyric acid (GABOB), a modified tryptophan, an unusual 3-aminopyrrolidone-4-acetic acid (PyrAA), and aromatic 3-amino-2,4,5-trihydroxy acids (AETD, AMMTD, etc.)) are uncommon components. There are slight variations on the tryptophan, the 3-aminopyrrolidinone-4-acetic acid (PyrAA), and aromatic 3-amino-2,4,5-trihydroxy acids. To date, synthetic studies on microsclerodermin A have been reported by Sasaki, Hamada, and Shioiri,[78] and recently, the first total synthesis of microsclerodermin E (**184**) was achieved by Zhu and Ma.[79] In this section the discussion will be limited to Ma's synthesis because the works of Hamada and Shioiri were complied in their review[3a] (Figure 8).



Microsclerodermin E (**184**)

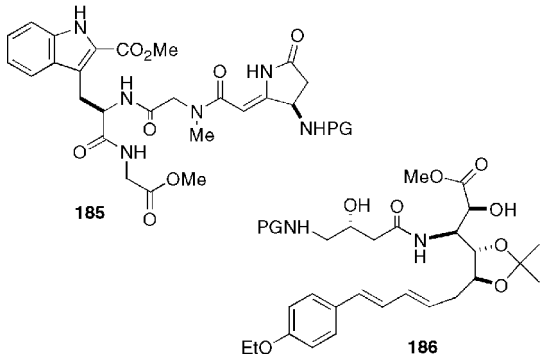
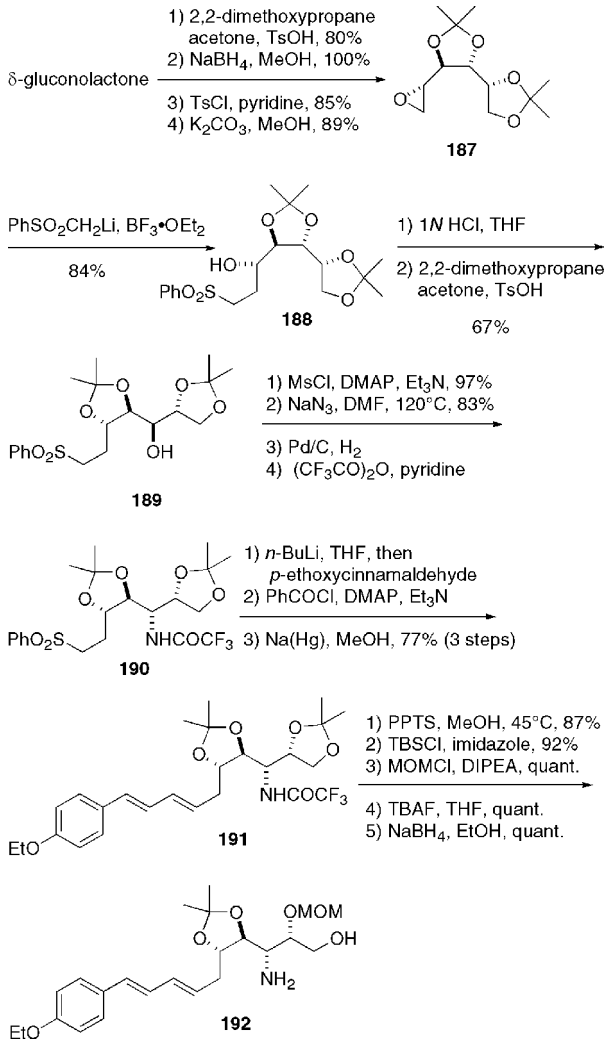


Figure 8.

Microsclerodermine E (**184**) has Trp(CO_2H), dehydroPyrAA, and 3-amino-10-(*p*-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid (AETD) as unusual components. Synthesis of microsclerodermin E was accomplished by [4 + 2] segment strategy including the segment coupling of the tetrapeptide **185** and the dipeptide **186** at AETD/dehydroPyrAA site and macrocyclization at Gly/GABOB site.

AETD was constructed from commercially available *δ*-gluconolactone with four asymmetric centers using Julia coupling as a key step, shown in Scheme 34. *δ*-Gluconolactone was first converted to the epoxide **187** by a sequence of reactions including protection with 2,2-dimethoxypropane and *p*-toluenesulfonic acid (TsOH), reduction of the ester, activation of the primary alcohol with TsCl, and treatment with potassium carbonate. The resulting

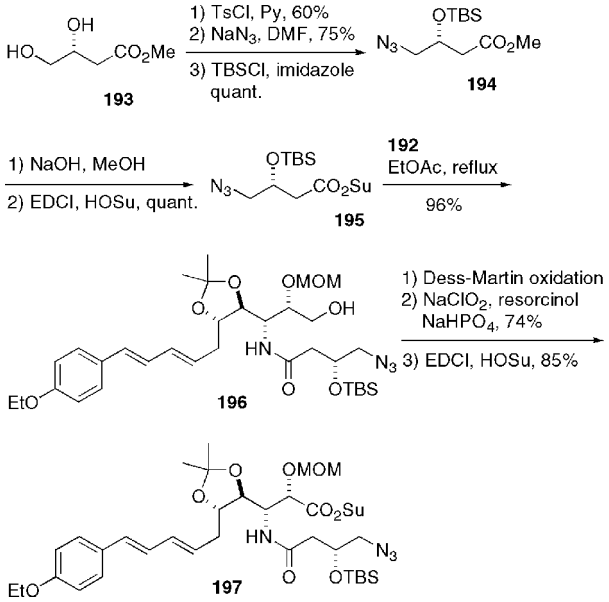
Scheme 34



epoxide **187** underwent an epoxide-opening reaction with the lithium anion generated from methyl phenyl sulfone in the presence of boron trifluoride etherate[80] to produce the sulfone **188**. For introduction of the nitrogen function, the 4,5-6,7-bisacetonide **188** was subjected to deprotection with hydrochloric acid followed by regioselective reprotection with 2,2-dimethoxypropane and TsOH to yield the isomeric 3,4-6,7-bisacetonide **189** in 67% yield. Transformation of the hydroxyl group to the amino one was achieved in four steps by mesylation of **189**, azidation of the mesylate with sodium azide, hydrogenation of the azide to the amine, and *N*-protection with trifluoroacetic anhydride to produce the trifluoroacetamide **190**. The chain extension was carried out by a three-step Julia coupling with the anion generated from **190** with *p*-ethoxycinnamaldehyde. Benzoylation of the resulting alcohol followed by treatment with sodium amalgam in methanol provided the aromatic diene **191** with the skeleton of AETD together with the corresponding (*Z*)-isomer in a 5:1 ratio. The diene **191** was transformed to the AETD derivative **192** by a sequence of selective deprotection and selective protection followed by reductive deprotection[81] of the *N*-trifluoroacetyl group.

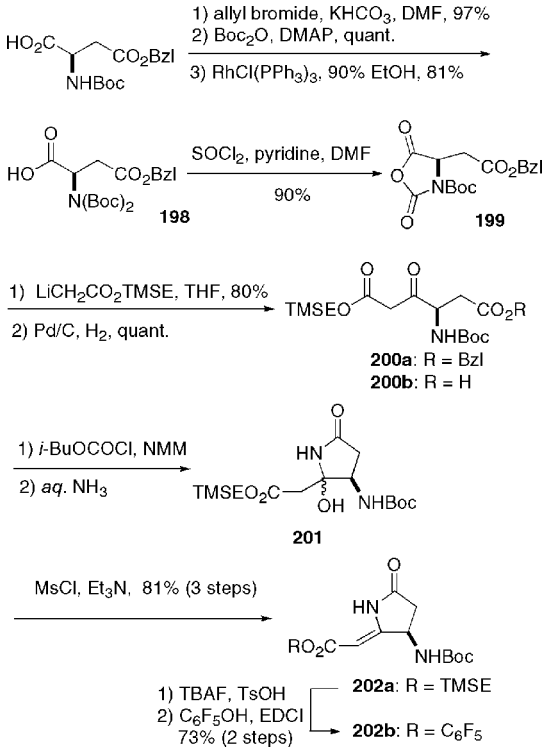
Synthesis of the dipeptide **197** commenced with preparation of the GABOB derivative **195** from the known diol **193** in five steps. The diol **193** underwent selective tosylation of the primary hydroxyl group and subsequent azidation using sodium azide in DMF to produce the GABOB skeleton, which was converted to the active ester **195** by TBS protection of the secondary alcohol followed by replacement of the methyl ester with the OSu ester. Coupling of **195** with the AETD derivative **192** was conducted under refluxing conditions to provide the dipeptide **196**, which was converted to the dipeptide active ester **197** for the next segment coupling by Dess−Martin oxidation of the primary hydroxyl group, sodium chlorite oxidation to the carboxylic acid, and subsequent active ester formation using EDCI/HOSu (Scheme 35).

Scheme 35



The dehydroPyrAA **202** was prepared from aspartic acid, as shown in Scheme 36. Boc-Asp(OBzl)-OH was converted to the diBoc derivative **198** by allyl ester formation, *N*-*tert*-butoxycarbonylation with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of DMAP, and subsequent deprotection of the allyl ester using Wilkinson's catalyst. Treatment of **198** with thionyl chloride and pyridine in DMF provided the *N*-Boc-*N*-carbonic anhydride **199**, which reacted with the lithium enolate generated from trimethylsilylethyl acetate to afford the enantiomerically pure β-ketoester **200a** without any racemization. In the case of employing known methods using the imidazolide and the pentafluorophenyl active ester, considerable racemization was observed. A different strategy using the *N*-carbonic anhydride[82] was therefore required for construction of the aspartic acid β-ketoester. For construction of the pyrrolidinone ring, **200a** was hydrogenolyzed, and the resulting carboxylic acid **200b** was converted to the carboxamide by treatment with ammonia via the mixed anhydride, which directly cyclized to the hydroxypyrrolidinone **201**. Mesylation of **201** was spontaneously accompanied by dehydration to form the dehydropyrrolidinone amino acid (dehydroPyrAA) **202a**. In the course of conversion to the active ester **202b** **202a** was found to be

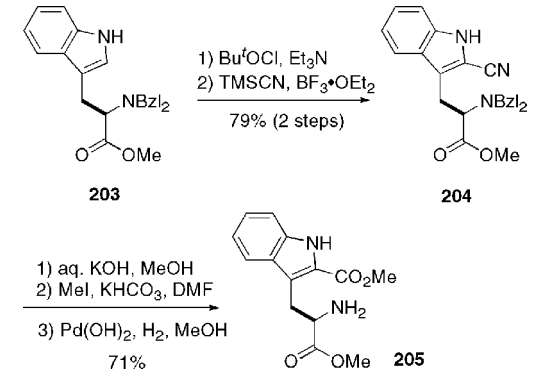
Scheme 36



susceptible to basic conditions due to the unfavorable racemization. Deprotection of the TMSE ester with TBAF caused considerable racemization. The additive TsOH together with TBAF was a better choice and minimized racemization to a 4:1 *R*/*S* ratio.

For preparation of the tryptophan derivative, introduction of the cyano group at the C2 position was performed according to Danishefsky's procedure[83] from *N*,*N*-dibenzyltryptophan methyl ester (**203**), shown in Scheme 37. Chlorination of **203** with *tert*-

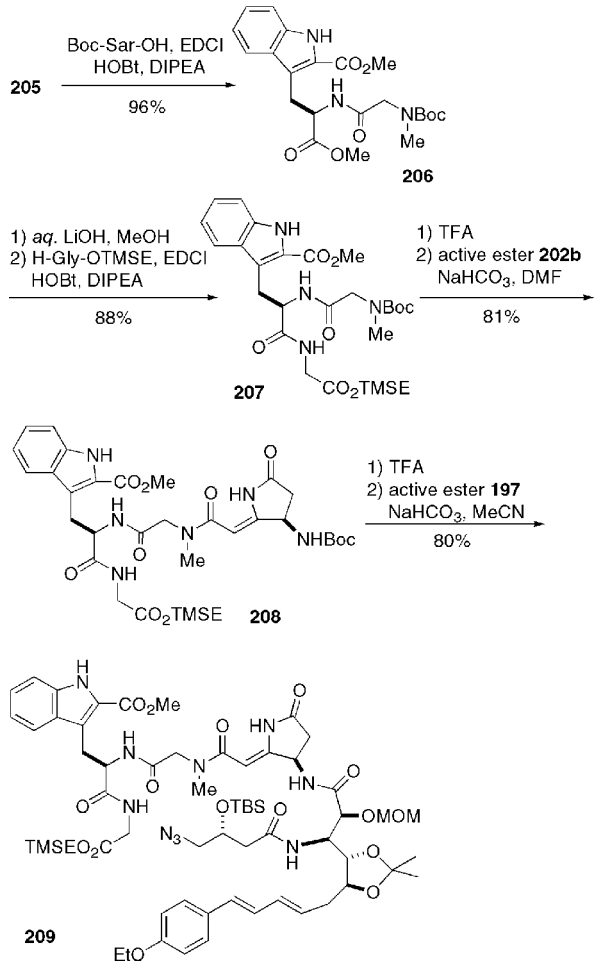
Scheme 37



butyl hypochlorite and subsequent cyanation with trimethylsilyl cyanide in the presence of boron trifluoride etherate gave the 2-cyanotryptophan **204**. Hydrolysis of the cyano group in **204**, esterification of the resulting carboxylic acid, and subsequent hydrogenolysis of the *N*,*N*-dibenzyl group with Pearlman catalyst afforded the Trp(CO_2Me) derivative **205**.

Trp(CO_2Me) **205** was coupled with Boc-Sar-OH, and the resulting dipeptide was saponified and condensed with H-Gly-OTMSE using EDCI/HOBt, as shown in Scheme 38. The tripeptide **207**, after

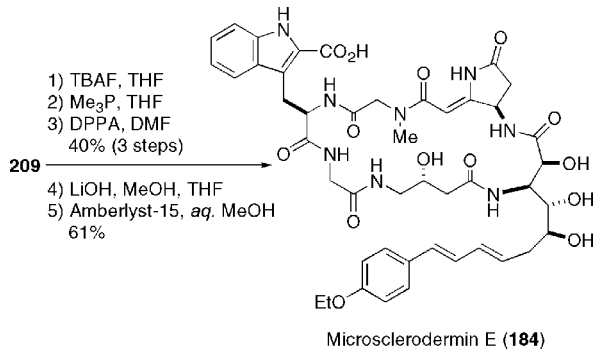
Scheme 38



treatment with TFA, was then elongated by coupling with the dehydroPyrAA-activated ester **202b** to yield the tetrapeptide **208**, which after deprotection was again condensed with the dipeptide segment active ester **197** to give the linear precursor **209** for microsclerodermin E.

For final assembly to microsclerodermin E the ester function in **209** was deprotected with TBAF and the azide was reduced to the amine with trimethylphosphine[84] to provide the free-linear precursor, which was subjected to macrocyclization with DPPA for 14 days to furnish microsclerodermin E methyl ester in 40% yield together with 9% yield of the separable diastereomer at the dehydroPyrAA residue, as summarized in Scheme 39. Saponification at the Trp(CO_2Me) part and then mild removal of the MOM group

Scheme 39

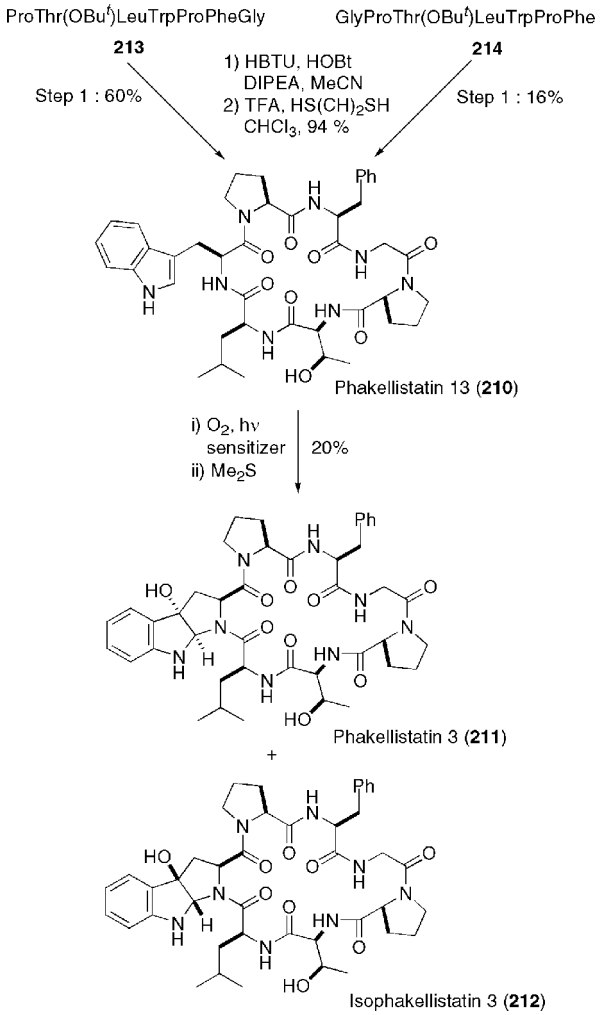


from the acid-labile protected microsclerodermin with Amberlyst-15 resin[85] gave microsclerodermin E (**184**), which was identical in all respects with spectroscopic data provided for the natural substance. In the reduction of the azide function it is notable that standard reagents, Ph_3P, n-Bu_3P, and $SnCl_2$, are ineffective for this case and the only sterically less hindered reagent, Me_3P, gives the desired product. In addition, use of EDCI/1-hydroxy-7-azabenzotriazole (HOAt) in the macrocyclization was ineffective and the shorter reaction time in the macrocyclization using even DPPA resulted in a much lower yield.

3.2. Phakellistatins

Phakellistatin 3 (**211**) and isophakellistatin 3 (**212**) were isolated from the Western Indian ocean sponge *Phakellia carteri*.[86] Phakellistatin 3 was shown to inhibit P388 leukemia cell growth ($ED_{50} = 0.4$ μM), while the diastereoisomer, isophakellistatin 3, was inactive. Both of these cyclic peptides contain the 3*a*-hydroxypyrrolidino[2,3-*b*]indoline (Hpi) moiety, which will be biosynthetically derived from the tryptophan moiety by oxidation. In fact, phakellistatin 13 (**210**) containing the Trp residue was isolated from the sponge *Phakellia fusca* Thiele, collected at Yongxing Island in China.[87] Phakellistatin 13 was also cytotoxic against the human hepatoma BEL-7404 cell line with an $ED_{50} < 10^{-2}$ μg/mL. As shown in Scheme 40

Scheme 40



its structure **210** is identical to those of **211** and **212** except for the Trp residue.

The unique peptides **211** and **212** having the Hpi residue were synthesized from **210** by Greenman, Hach, and Van Vranken[88] just like the biosynthetic pathway. The linear precursor heptapeptides **213** and **214** were synthesized on chlorotrityl resin from Fmoc-protected amino acids using HBTU and cleaved from resin with TFA-1,2-ethanedithiol. Macrocyclization of **213** was carried out using HBTU/HOBt/DIPEA to give the cyclic lactam in 60% yield, from which phakellistatin 13 (**210**) was obtained by acidic treatment. In contrast, the efficiency for macrocyclization of the hexapeptide **214** proved to be poor (16%). This synthesis establishes the undetermined absolute configuration of the Trp moiety in **210** to be L.

Utilizing the synthesized phakellistatin 13 (**210**), photooxidation with rose bengal as a sensitizer[89] afforded a 1:1 mixture of phakellistatin 3 (**211**) and isophakellistatin 3 (**212**) in a combined yield of 20%. Multiple rounds of HPLC purification produced phakellistatin 3 (**211**) with over 95% purity, but isophakellistatin 3 (**212**) was obtained in 85% purity along with 15% phakellistatin 3 (**211**). Although the efficiency of the oxidation should be much improved, this work demonstrates for the first time that a tryptophan residue can be directly converted to the corresponding 3*a*-hydroxypyrrolo[2,3-*b*]indoline in a full-length peptide. Further, spectroscopic and molecular modeling studies revealed a similar backbone conformation for all three cyclic peptides despite their markedly different biological activity against tumor cell lines.

Before the above synthetic work phakellistatins 1, 2, 5, 10, and 11, shown in Figure 9, isolated from the

Phakellistatin 1 : cyclo(Pro-Tyr-Pro-Ile-Pro-Ile-Phe)
Phakellistatin 2 : cyclo(Pro-Tyr-Pro-Phe-Pro-Ile-Ile)
Phakellistatin 5 : cyclo(Pro-Phe-Asn-Ala-Met-Ala-Ile)
Phakellistatin 10 : cyclo(Pro-Ile-Pro-Trp-Val-Pro-Leu-Thr)
Phakellistatin 11 : cyclo(Pro-Phe-Pro-Phe-Ile-Phe-Pro-Gln)

Figure 9.

marine sponges of genus *Phakellia,* were synthesized in a similar manner.[90] Although these phakellistatins were reported to show a moderate cytotoxicity, the synthetic specimens were found to be chemically but not biologically (cancer cell lines) identical to the natural products. The reason for this discrepancy might be a conformational difference, especially around the proline residue, or more likely the presence of a trace amount of a highly active antineoplastic agent that noncovalently binds to the natural cyclic peptides. The results clearly indicated the importance of the total syntheses for confirmation of the biological activity of the natural products.

3.3. Cyclotheonamides E_2 and E_3

In 1990 Fusetani and co-workers reported isolation of cyclotheonamides A and B[91a] from a sponge of the genus *Theonella,* and then they isolated closely related congeners C−E[91b] in 1998. The basic structural motif of the cyclotheonamides consists of a 19-

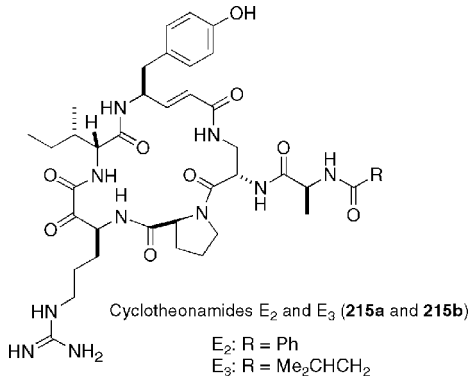


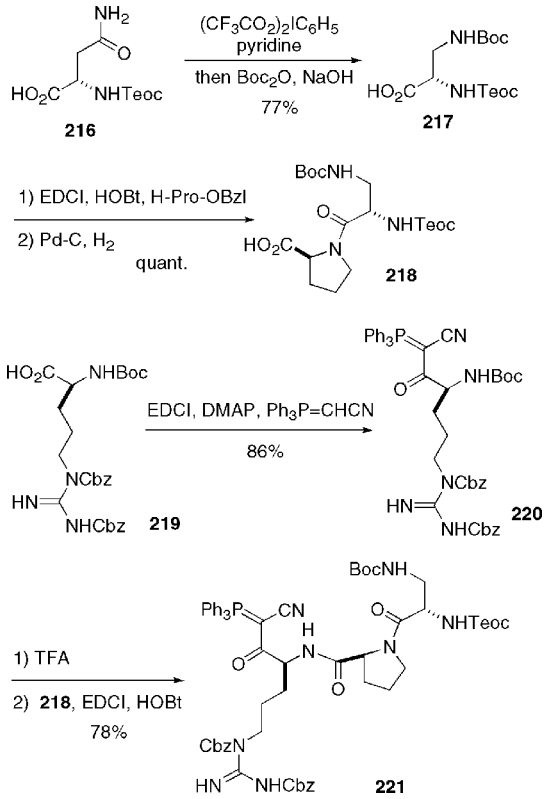
Figure 10.

membered cyclic peptide constructed from five amino acid residues, two of which (vinylogous tyrosine and α-ketoarginine) are common, unique components in the family. These unique cyclic peptides attracted considerable attention immediately for interesting inhibitory activity to serine proteases. Syntheses of cyclotheonamides A and B have been accomplished by several groups[92] and compiled as a review.[3e] The following discussion will be limited to the most recent work,[93] the synthesis of cyclotheonamides E_2 and E_3 (**215a** and **215b**), which differ from counterparts A and B in the presence of D-alloisoleucine residue in place of D-phenylalanine and the side-chain containing benzolylalanine and isovalerylalanine residues (Figure 10).

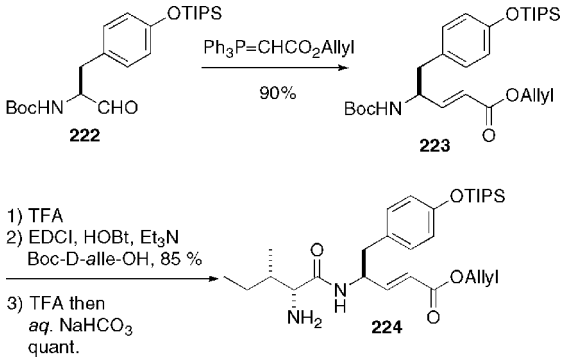
Wasserman and Zhang achieved the synthesis of cyclotheonamides E_2 (**215a**) and E_3 (**215b**)[93] by a [3 + 2] segment coupling strategy, which contains efficient construction of the arginine α-ketoacid using the cyano ylide activation method[94] developed by themselves. The tripeptide **221** was prepared by reverse stepwise elongation from the *N*-terminal diaminopropanoic acid **217**, which was synthesized according to the Izumiya's method[95] from $Me_3Si(CH_2)_2OCO$ (Teoc)-asparagine (**216**), as shown in Scheme 41. After formation of the dipeptide with H-Pro-OBzl using EDCI/HOBt and subsequent removal of the benzyl ester, the resulting dipeptide **218** was coupled with the acyl cyano ylide **220**, which was prepared from Boc-Arg(diCbz)-OH (**219**) by *C*-acylation of cyanomethylidenephosphorane using EDCI/DMAP, to yield the tripeptide **221**.

On the other hand, Boc-Tyr(TIPS)-al (**222**) was olefinated with a Wittig reagent to give the vinylogous tyrosine (**223**), shown in Scheme 42. After Boc deprotection, coupling with Boc-D-*a*lle-OH using EDCI/HOBt followed by acidic deprotection afforded **224**.

Scheme 41

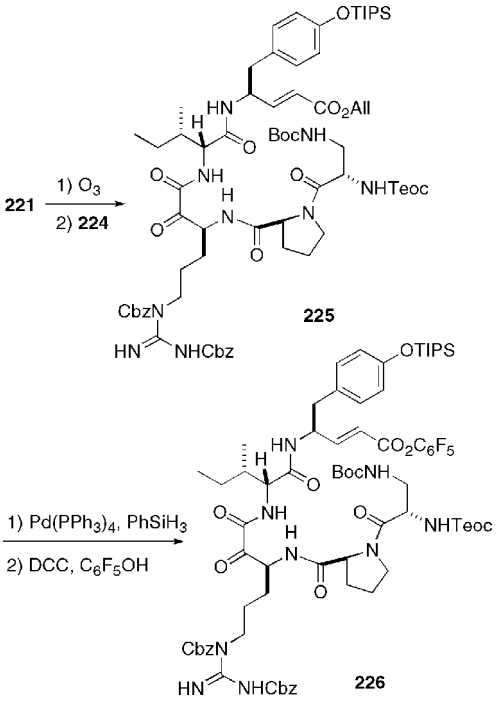


Scheme 42



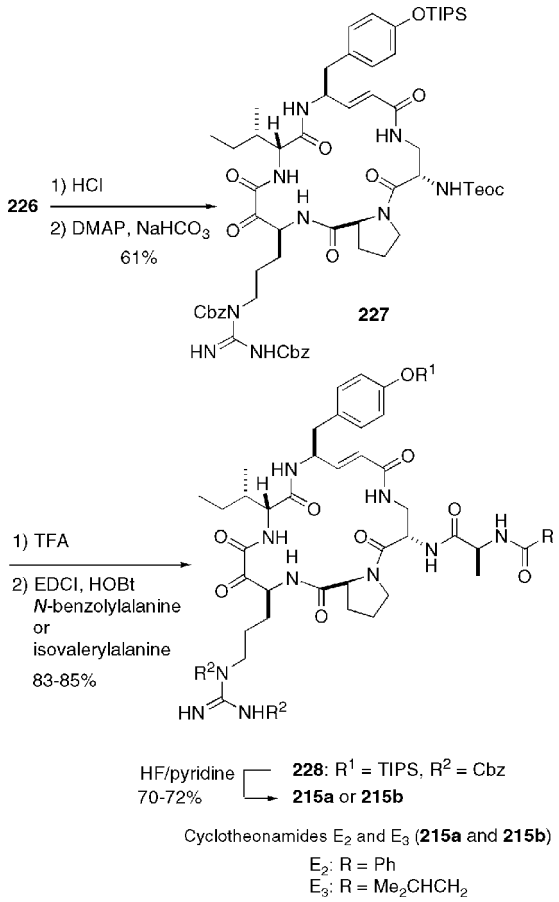
The tripeptide **221** was exposed to ozone for activation of the cyano ylide, and the resulting acyl cyanide was directly coupled with the dipeptide **224** to provide in good yield the linear precursor **225**, shown in Scheme 43. The allyl function of **225** was replaced with the pentafluorophenyl ester.

Scheme 43



The linear precursor **226** thus obtained was selectively deprotected with hydrogen chloride to afford the free pentapeptide, which was subjected to cyclization in the presence of DMAP and sodium hydrogen carbonate to produce the cyclic peptide **227** in 61% yield. After cleavage of the Teoc group, coupling with *N*-benzolylalanine and *N*-isovalerylalanine using EDCI/HOBt followed by TIPS and Cbz deprotection afforded cyclotheonamides E_2 (**215a**) and E_3 (**215b**), respectively (Scheme 44).

Scheme 44



3.4. Papuamides A and B

Papuamides A (**229**) and B are a new family of novel cyclic depsipeptides isolated from the marine sponge genus *Theonella* collected at Papua New Guinea by Boyd et al.[96] Papuamides are known to strongly inhibit the infection of human T-lymphoblastanoid cells by HIV-1_{RF} and also exhibit potent cytotoxicity against a number of human cancer cell lines. These cyclic heptadepsipeptides have a unique structure containing (4*Z*,6*E*)-2,3-dihydroxy-2,6,8-trimethyldecadienoic acid (Dhtda) and unusual amino acid residues, such as (3*S*,4*R*)-3,4-dimethylglutamine (3,4-DiMeGln), (2*R*,3*R*)-3-hydroxyleucine (3-OHLeu), and β-methoxytyrosine (β-OMeTyr), as shown in Figure 11. The stereochemistry of papuamides remains to be determined because of the uncertainty regarding the stereochemistry in the β-OMeTyr and the Dhtda parts. Interestingly, two unusual amino acids, β-OMeTyr and 3,4-DiMeGln, are known as common components of the cyclic depsipeptide cal-

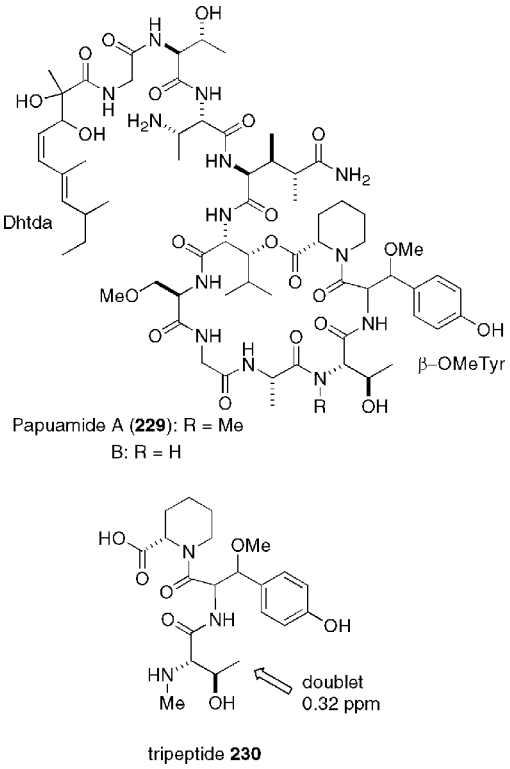
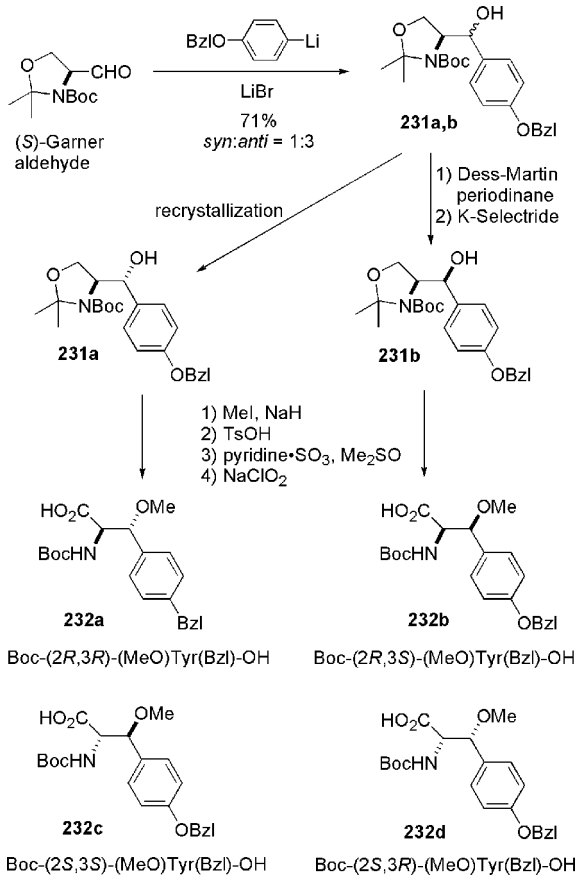


Figure 11.

lipeltin A,[97] which shows anti-HIV and antifungal activities. Although total synthesis of the papuamides has been not accomplished yet, the unique structure as well as interesting biological activities of these compounds made considerable efforts directed toward total synthesis of papuamides.[98] The discussion in this section will be limited to synthetic efforts of Hamada and co-workers.[99]

To accomplish total synthesis as well as structural determination of papuamides, determination of two stereo-undefined components, MeOTyr and Dhtda, is necessary. Boyd and co-workers reported the interesting experiment in which the hydrolysate, H-MeThr-MeOTyr-Hpr-OH (**230**) (Hpr: pipecolic acid), derived from solvolysis of papuamide A with triethylamine in methanol shows the anomalous high-field shift (0.32 ppm, doublet) at the methyl proton of the MeThr residue in the NMR spectrum (Figure 11).[96] The experiment encouraged Hamada and co-workers to synthesize the four tripeptides with different stereochemistry in the MeOTyr residue.[99] The required four diastereomers of the methoxytyrosine were prepared from (*S*)- and (*R*)-Garner aldehydes[100] by a concise route, as shown in Scheme 45.[98d] Addition of the benzyloxyphenyllithium to the (*S*)-Garner aldehyde in the presence of lithium bromide gave the protected hydroxyamino alcohol **231** in moderate yield with a 1:3 ratio of syn and anti. The anti-rich crude product was directly crystallized to provide pure (2*S*,3*R*)-**231a**, whose stereochemistry was deduced by the Felkin−Ahn model and clearly determined by the NOE experiment. On the other hand, (2*S*,3*S*)-**231b** was produced by racemization-free oxidation of a mixture of **231a** and **231b** with Dess−Martin periodinane and subsequent syn-selective reduction with K-selectride. The latter was sluggish and proved problematic for easy racemization, even

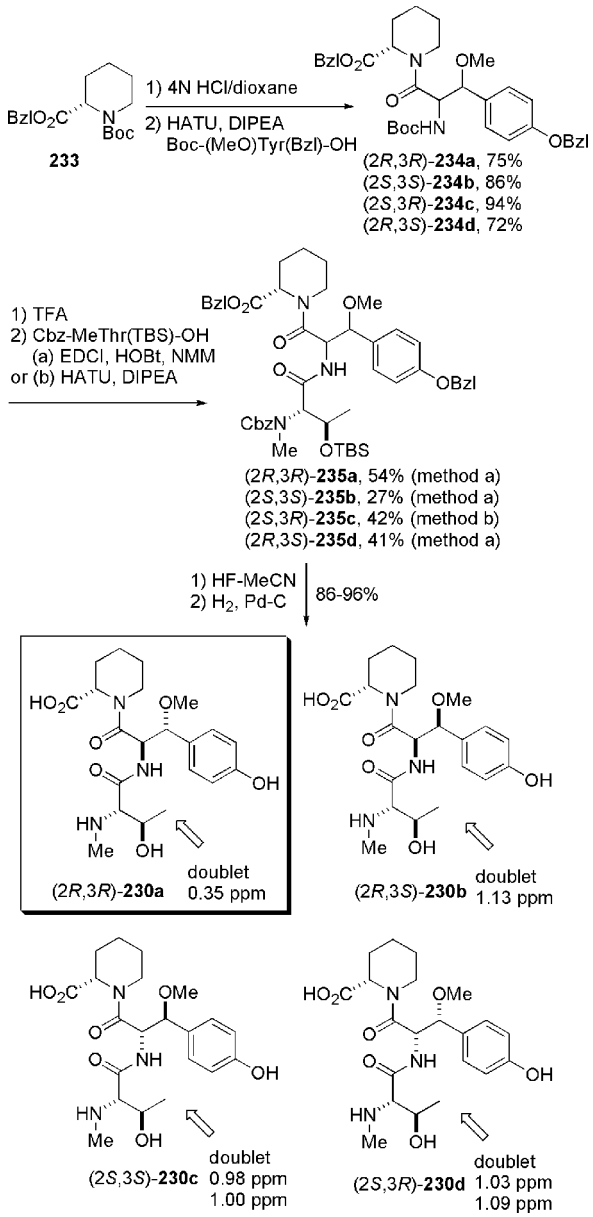
Scheme 45



at −78 °C. One recrystallization of the crude product, however, gave enantiomerically pure (2*S*,3*S*)-**231b**. Conversion of (2*S*,3*R*)-**231a** to Boc-(2*S*,3*R*)-MeOTyr-(Bzl)-OH (**232a**) was performed by standard manipulation containing *O*-methylation with sodium hydride and iodomethane, selective removal of the acetonide with TsOH, Parikh−Doering oxidation to the aldehyde, and final reoxidation to the carboxylic acid **232a** with sodium chlorite. The diastereomer (2*S*,3*S*)-**231b** was transformed to Boc-(2*S*,3*S*)-MeOTyr(Bzl)-OH (**232b**) in a similar fashion. The remaining diastereomers, **232c** and **232d**, were synthesized from the (*R*)-Garner aldehyde with similar stereoselectivities.

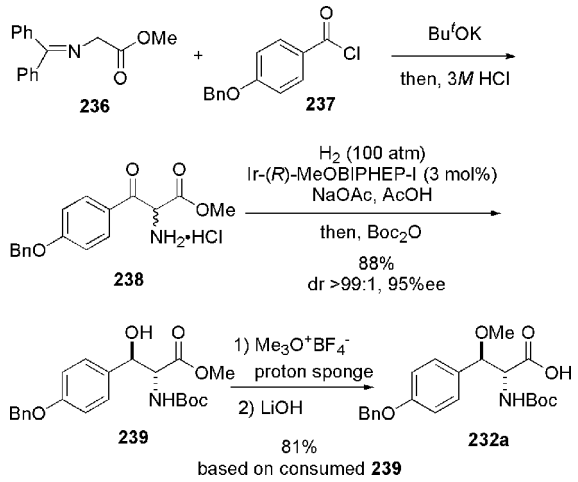
The four tripeptides **230a**−**d** required for structural determination of MeOTyr were prepared from Boc-(*S*)-Hpr-OBzl by stepwise coupling with Boc-MeOTyr(Bzl)-OH and Cbz-MeThr(TBS)-OH using the HATU/DIPEA and EDCI/HOBt methods, shown in Scheme 46. Sequential deprotection of the TBS group with HF−acetonitrile and the Cbz group by hydrogenolysis furnished the free tripeptides **230a**−**d**. Comparisons of the ^{1}H NMR spectrum of the hydrolysate from natural papuamide A with those of the synthetic four tripeptides **230a**−**d** were consistent with that of the (2*R*,3*R*)-isomer **230a**. The chemical shifts of the other three diastereomers at the methyl proton of the MeThr residue differed largely from the 0.32 ppm of the naturally derived one. Accordingly, the stereochemistry of the MeOTyr residue in the papuamide A was unambiguously established as 2*R*,3*R*.[99]

Scheme 46



For efficiently stereoselective production of (2*R*,3*R*)-MeOTyr, new Ir-catalyzed asymmetric hydrogenation accompanied by dynamic kinetic resolution was developed.[101] Readily available 2-amino-3-keto ester hydrochloride **238**, prepared from glycine methyl ester benzophenoneimine (**236**) by acylation with *p*-benzyloxybenzoyl chloride (**237**) in the presence of KO*t*-Bu followed by acid hydrolysis, was hydrogenated with the Ir catalyst, prepared from [IrClcod]$_2$ and (*R*)-MeOBIPHEP, under 100 atm of hydrogen. After Boc protection, the (2*R*,3*R*)-3-hydroxytyrosine derivative **239** was obtained in a >99:1 diastereomeric ratio with 95% ee, as shown in Scheme 47. The reaction is noteworthy because this demonstrates the first example of Ir-catalyzed anti-selective hydrogenation of 2-amino-3-keto ester hydrochlorides with high diastereo- and enantioselectivity through dynamic kinetic resolution. *O*-Methylation of **239** with trimethyl oxonium tetrafluoroborate and proton sponge followed by saponification of the methyl ester provided the Boc-(2*R*,3*R*)-MeOTyr(Bzl)-OH **232a**.

Scheme 47

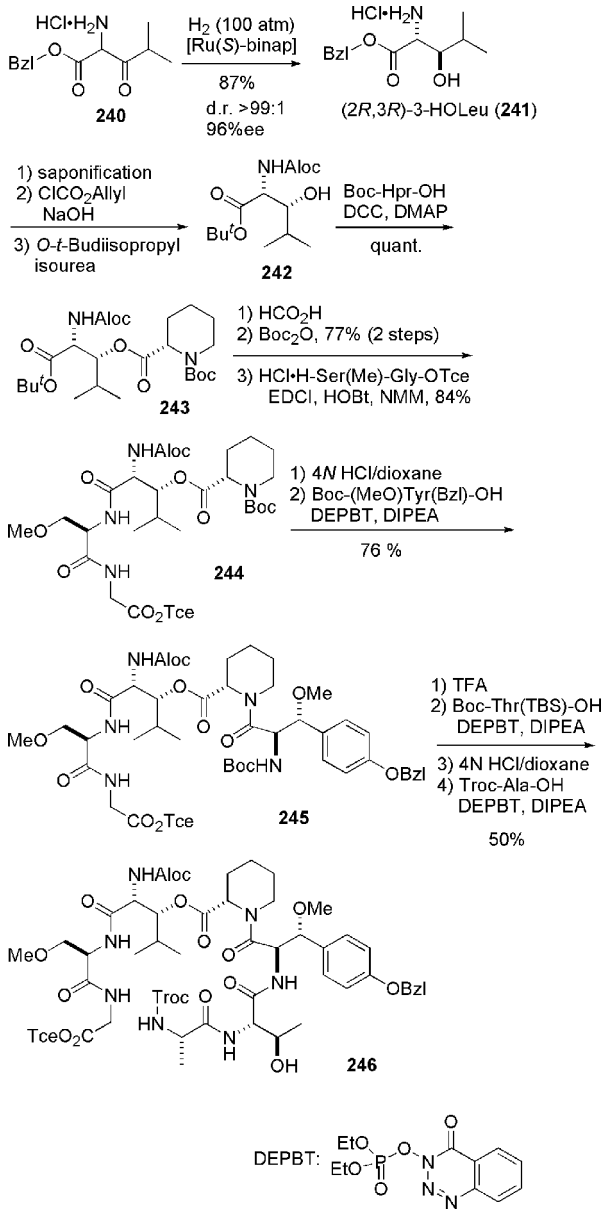


With the stereo-defined methoxytryrosine available, the cyclic depsipeptide skeleton in papuamide B was constructed from (2*R*,3*R*)-3-hydroxyleucine benzyl ester **241**,[97] which was stereoselectively and efficiently synthesized by asymmetric hydrogenation of the 2-amino-3-keto ester hydrochloride **240** through dynamic kinetic resolution using Ru−(*S*)-BINAP catalyst developed by Hamada and co-workers,[102,103] as shown in Scheme 48. The depsipeptide **244** was synthesized by [2 + 2] segment coupling of the ester fragment **243**, prepared from the hydroxyleucine **242** and Boc-(*S*)-Hpr-OH with DCC/DMAP followed by cleavage of the *t*-Bu ester, with H−Ser(Me)-Gly-OTce. After deprotection of the Boc group, coupling of the resulting tetrapeptide with Boc-(2*R*,3*R*)-MeOTyr-(Bzl)-OH proved to be a new difficult sequence to couple. Standard reagents, HATU/DIPEA, Bop-Cl/DIPEA,[11] and Brop/DIPEA,[104] for assembling hindered sequence gave no coupling product, whereas FDPP/DIPEA[29] and BMTB/DIPEA[105] gave only 6% and 20%, respectively, of the pentapeptide **245**. Among the several reagents examined, DEPBT/DIPEA (Goodman reagent)[106] was most effective for the difficult sequence to provide **245** in 76% yield. The following segment coupling of **245** with Troc-Ala-Thr-OH again proved to be problematic for the difficult coupling. HATU/DIPEA and even BMTB/DIPEA afforded no desired product. DEPBT/DIPEA again was most superior to the standard coupling procedures, yielding the hexapeptide **246** in 72% yield. However, careful examination of the product showed partial racemization at the Thr residue. Finally, pure **246** was obtained by stepwise couplings of Boc-Thr(TBS)-OH and Troc-Ala-OH using DEPBT/DIPEA in 50% yield and four steps.

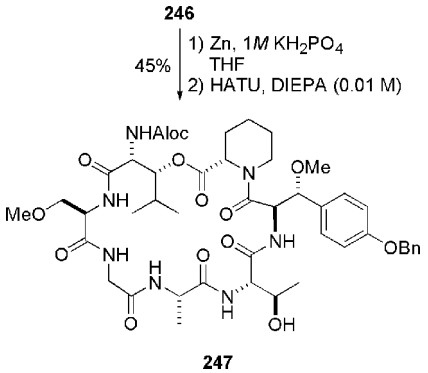
After deprotection of the Troc and Tce groups with zinc dust and phosphate buffer, macrocyclization at 0.01 M using HATU/DIPEA proceeded in good yield to afford the cyclic depsipeptide **247**, whose ^{1}H NMR spectrum showed good agreement with that of the cyclic core in natural papuamide B (Scheme 49).[99]

(3*S*,4*R*)-3,4-Dimethyl-(*S*)-glutamine, a common component of cyclic depsipeptides, papuamide A[96] and callipeltin A,[97] was stereoselectively prepared from (*S*)-pyroglutamic acid, as shown in Scheme 50. The bicyclic lactam **248**[107] prepared from (*S*)-pyroglutamic

Scheme 48

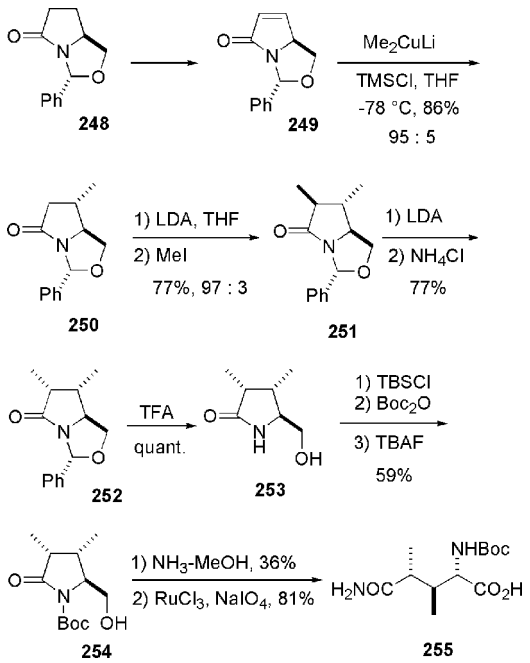


Scheme 49



acid according to Thottathil's procedure[108] was converted to the unsaturated lactam **249**. Treatment of **249** with lithium dimethylcuprate (Me_2CuLi) in the presence of chlorotrimethylsilane[109] preferentially provided the 6-methylated product **250** in a 19:1 ratio. Methylation of **250** at the C7 position through enolate formation with LDA followed by alkylation

Scheme 50

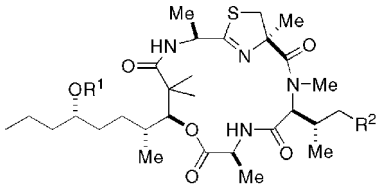


with iodomethane afforded the *trans*-dimethyl lactam **251** with a 97:3 diastereomeric ratio. Conversion of the *trans*-product to the desired *cis*-dimethyl lactam **252** was achieved by deprotonation with LDA followed by stereoselective protonation. The benzylidene group was cleaved by exposure to excess trifluoroacetic acid, and the hydroxy and amine functions of the lactam were, respectively, protected with TBS and Boc groups. Ring opening of the lactam **253** into the carboxamide was carried out by ammonolysis with 2.4% ammonia−methanol to give the desired product, which was directly oxidized with $RuCl_3$−$NaIO_4$ to give *N*-Boc-3,4-dimethylglutamine **255** without epimerization. The stereostructure of natural dimethylglutamine was unambiguously confirmed to be 2*S*,3*S*,4*R* by comparisons of the CD and NMR spectra of the synthetic 3,4-dimethylpyroglutamic acid prepared from the lactam **253** with the hydrolysate of callipeltin A.

3.5. Halipeptins A and B

Halipeptins A (**256a**) and B (**256b**)[110a] are novel 16-membered cyclic depsipeptides isolated from the marine sponge *Haliclona* sp. collected in waters off the Vanuatu Islands by Gomez-Paloma and coworkers in 2001. Halipeptin A is known to show strong antiinflammatory activity in vivo, causing 60% reduction of edema in mice at a dose of 0.3 mg/kg. In 2002 Gomez-Paloma et al. reported isolation of halipeptin C (**256c**), closely related to **256a** and **256b,** from the same sponge, reexamined the original assignments with a novel oxazetidine ring for halipeptins, and corrected the oxazetidine amino acid to the thiazoline amino acid in halipeptins A and B as shown in Figure 12.[110b] Snider reported confirmation of the above revision based on synthesis of the oxazetidine amino acid.[111]

Halipeptins consist of L-alanine and three unique components, the thiazoline-amino acid (alaThz), *N*-



Halipeptin A (**256a**): R^1 = Me, R^2 = CH_2OH
Halipeptin B (**256b**): R^1 = H, R^2 = CH_2OH
Halipeptin C (**256c**): R^1 = H, R^2 = H

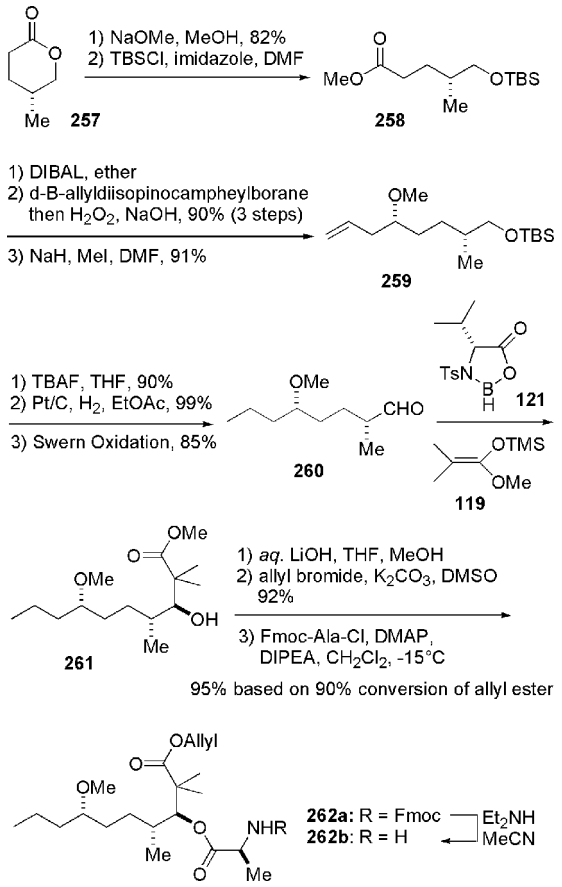
Figure 12.

methyl hydroxyisoleucine (*N*-MeOHIle) (or *N*-MeVal for **256c**), and 3-hydroxy-2,2,4-trimethyl-7-methoxy (or hydroxy for **256b** and **256c**) decanoic acid (HTMMD or HTMHD). The structures of HTMMD and HTMHD were determined by extensive NMR studies, and the only relative stereochemistry at C3 and C4 was elucidated to be *threo* ((3*S*,4*R*) or (3*R*,4*S*)) except C7, which was confirmed to be *S* by Mosher's method using HTMHD. In addition to their potent biological activities, their intriguing structures prompted several groups to initiate efforts directed toward the total synthesis. De Riccardis[112] and Hamada[113] reported synthesis of the *N*MeOHIle derivative using a diastereoselective silyl-assisted [3,3]-sigmatropic rearrangement and diastereoselective methylation of the bicyclic lactam derived from pyroglutamic acid, respectively. HTMMD was synthesized by De Riccardis.[114] Total synthesis of this unique cyclic depsipeptide, halipeptin A (**256a**), was accomplished by Ma and co-workers, leading to structural confirmation of the revised halipeptins.[115] Ma and co-workers employed [2 + 2] coupling of the ester and amide segments including final macrocyclization at the HTMMD/alaThz site for construction of this molecule.

HTMMD with (3*S*,4*R*,7*S*)-stereochemistry was prepared from (*R*)-4-methyl-5-valerolactone **257**, an oxidative degradation product of diosgenin,[116] in nine steps as shown in Scheme 51.[115] Ring cleavage of **257** with sodium methoxide in methanol and TBS protection of the resulting primary alcohol gave the ester **258**. For construction of the stereochemistry at C7 secondary alcohol, **258** was reduced with DIBAL, the aldehyde was alkylated by Brown's asymmetric allylation using D-*B*-allyldiisopinocampheylborane,[117] and the resulting alcohol was *O*-methylated. Desilylation of **259** with TBAF, hydrogenation of the terminal alkene, and Swern oxidation provided the aldehyde **260**. Asymmetric aldol condensation of **260** with the ketene acetal **119** using chiral oxazaborolidine **121**[64] was employed for construction of the C3 and C4 stereochemistry to produce the HTMMD skeleton **261** as a single isomer. After exchange of the ester function to the allyl ester, the alcohol was coupled with Fmoc-Ala-Cl in the presence of DMAP and DIPEA at −15 °C to afford the ester segment **262a** in excellent yield. The amount of DMAP and the low temperature were critical for success of the racemization-free esterification in this case. Deprotection of the Fmoc group gave the ester segment **262b**.

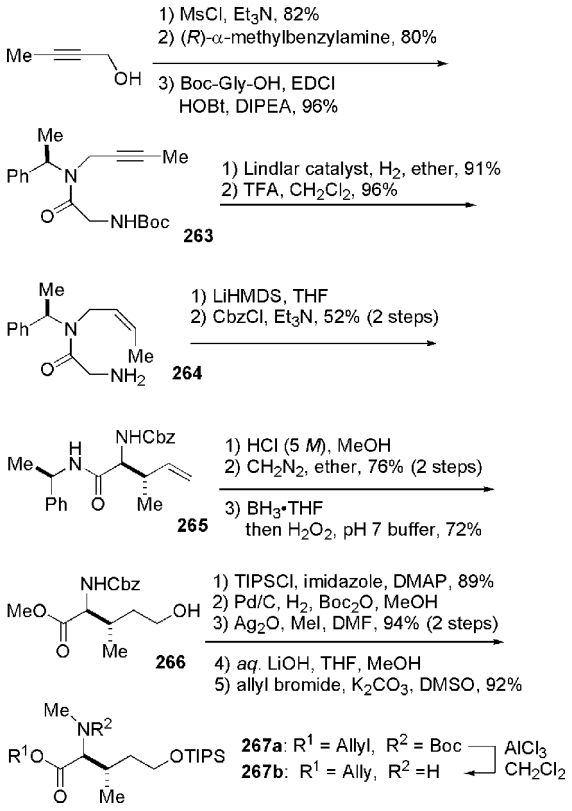
N-Methylhydroxyisoleucine was prepared in 13 steps from 2-butyn-1-ol using a slightly modified

Scheme 51



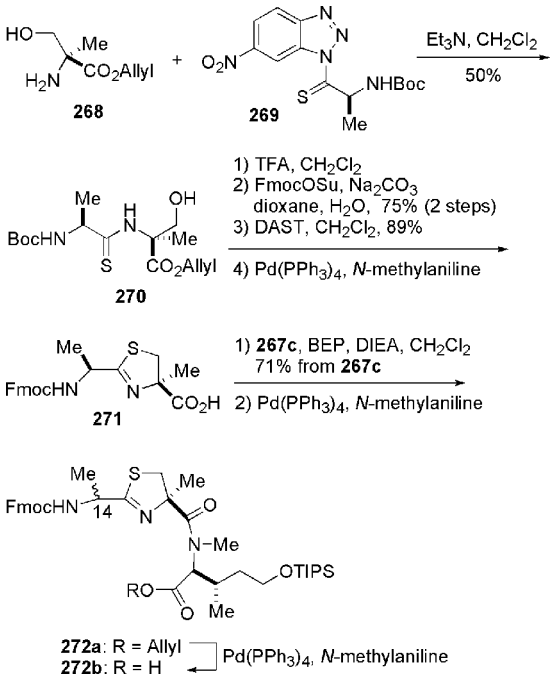
Tsunoda's diastereoselective aza-Claisen rearrangement[118] as the key step, shown in Scheme 52. Mesylation of 2-butyn-1-ol, *N*-alkylation with (*R*)-α-methylbenzylamine, followed by *N*-acylation with Boc-Gly-OH using EDCI/HOBt afforded the alkyne **263**, which was converted to the substrate **264** for the aza-Claisen rearrangement through hydrogenation to the *cis*-olefin using Lindlar catalyst and then *N*-deprotection. Exposure of the resulting amide **264** to an excess amount of lithium hexamethyldisilazide (LiHMDS) generated the (*Z*)-enolate dianion, which spontaneously rearranged to the 4,5-dehyrdoisoleucine **265** in a 3:1 diastereomeric ratio to provide pure **265** after recrystallization in 52% yield. After hydrolytic cleavage of the chiral auxiliary from **265**, methylation with diazomethane followed by hydroboration of the double bond gave the hydroxyisoleucine **266**. Conversion to the *N*-MeOHIle building block **267b** was performed by protection of **266** with the TIPS group, exchange of the Cbz group to the Boc one, *N*-methylation with iodomethane and silver oxide, saponification with lithium hydroxide, allyl ester formation, and Boc deprotection with aluminum chloride.

Scheme 52

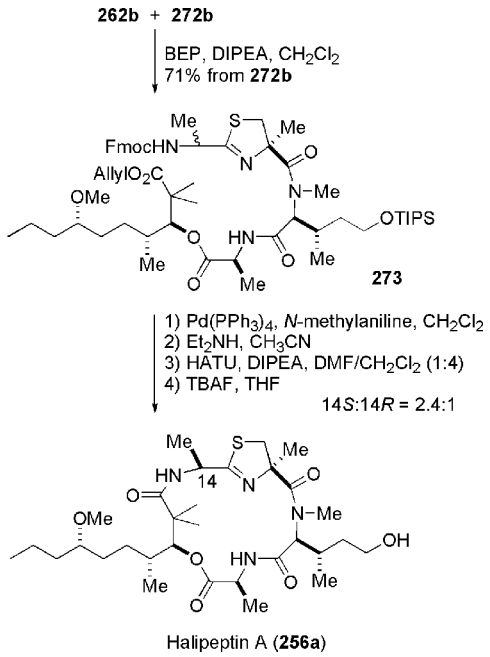


The thiazoline amino acid was prepared according to Rapoport's method.[119] Coupling of α-methylserine allyl ester (**268**) and the nitrobenzothiotriazolide **269** gave the thiopeptide **270**, which was converted to the thiazoline **271** by a sequence of deprotection with TFA and reprotection with FmocOSu, cyclization to the thiazoline with DAST,[120] and cleavage of the allyl group with $Pd(PPh_3)_4$ and *N*-methylaniline. The thiazoline **271** was then coupled with the *N*-MeOHIle **267c** using 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP)/DIPEA.[121] The Cα-chirality of the thiazoline part was sensitive to the coupling conditions and found to epimerize to an inseparable 3:1 diastereomeric mixture of the dipeptide **272a**. The problem was solved by chromatographic separation of the final product. The resulting dipeptide **272a** was then deprotected with $Pd(PPh_3)_4$ and *N*-methylaniline to afford the amide segment **272b** (Scheme 53).

Scheme 53



Scheme 54



Coupling of the ester segment **262b** with **272b** with BEP/DIPEA furnished the linear protected peptide **273**, as shown in Scheme 54. After sequential deprotection at the *C*- and *N*-terminals by palladium chemistry and base-mediated reaction, respectively, macrocyclization with HATU/DIPEA was sluggish but afforded the cyclic depsipeptide, which was deprotected with TBAF to furnish halipeptin A (**256a**) in 27% yield after chromatographic purification. The Cα-chirality of the thiazoline moiety again proved to be sensitive to TBAF treatment by changing from a 3:1 to 5:1 ratio, and the epimer at thiazoline was obtained in 5% yield. The synthetic halipeptin A was firmly confirmed by comparisons to the spectral data of natural halipeptin A. The total synthesis of halipeptin A by the Ma group unambiguously established the uncertain stereochemistry in the halipeptins.

4. Cyclic Peptides from Red Alga

4.1. Ceratospongamides

cis,cis- and *trans,trans*-Ceratospongamides (**274** and **275**), conformationally isomeric at the two proline amide bonds, were isolated by Gerwick and coworkers[122] from the Indonesian red alga *Ceratodictyon spongiosum* containing the symbiotic sponge *Sigmadocia symbiotica*. *trans,trans*-Ceratospongamide (**275**) exhibits potent inhibition of $sPLA_2$ expression in a cell-based model for antiinflammation (ED_{50} 32 nM), whereas the *cis,cis*-isomer is inactive. *cis,cis*-Ceratospongamide (**274**) was claimed[122] to be converted to the *trans,trans*-isomer **275** by heating at 175 °C in DMSO according to HPLC (Figure 13).

The first total synthesis of *cis,cis*-ceratospongamide (**274**) was achieved by Yokokawa, Sameshima, and Shioiri in two ways utilizing a [5 + 2] convergent strategy.[123a−c] Their further investigations of the thermal behavior of the *cis,cis*-isomer **274** revealed that the proposed structure of the *trans,trans*-isomer

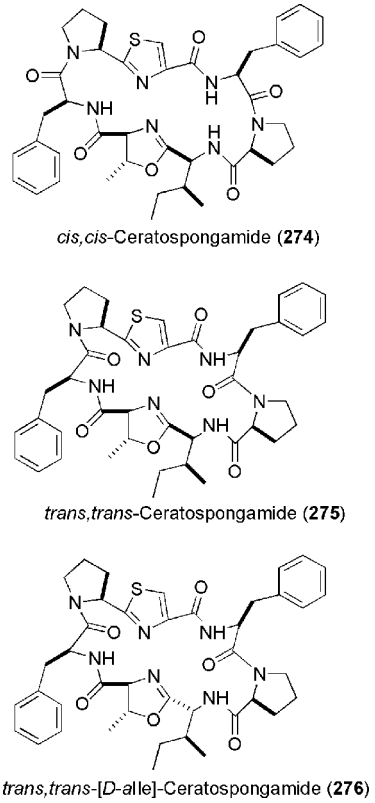


Figure 13.

275 should be revised to be the *trans,trans*-[D-*allo*-Ile]-isomer **276**.[123c,d]

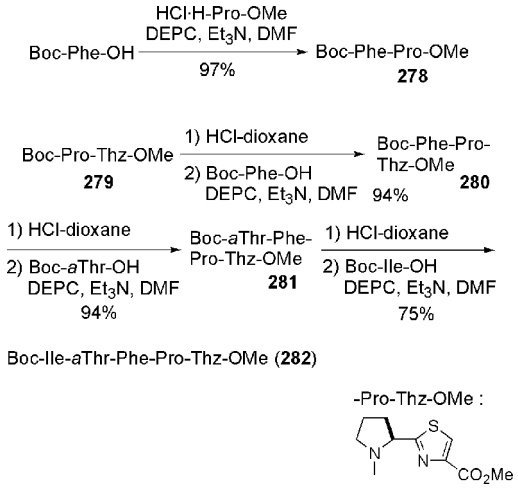
In their strategy the oxazoline ring in **274** was to be constructed at the final stage because of its sensitivity to acidic and basic conditions. Activation of the carboxyl group in the macrolactamization was carried out at either thiazole or L-proline to avoid possible racemization.

First, the dipeptide **278** was prepared from Boc-Phe-OH and H-Pro-OMe. The required proline thiazole methyl ester (**279**, Boc-Pro-Thz-OMe) was prepared from Boc-Pro-OH and H−Cys-OMe by the method just described in the synthesis of lyngbyabellins (see Scheme 20). The pentapeptide derivative **282** was prepared from **279** by sequential coupling of each Boc-amino acid using DEPC-Et_3N for coupling and hydrogen chloride in dioxane for deprotection of the Boc group via **280** and **281**, shown in Scheme 55.

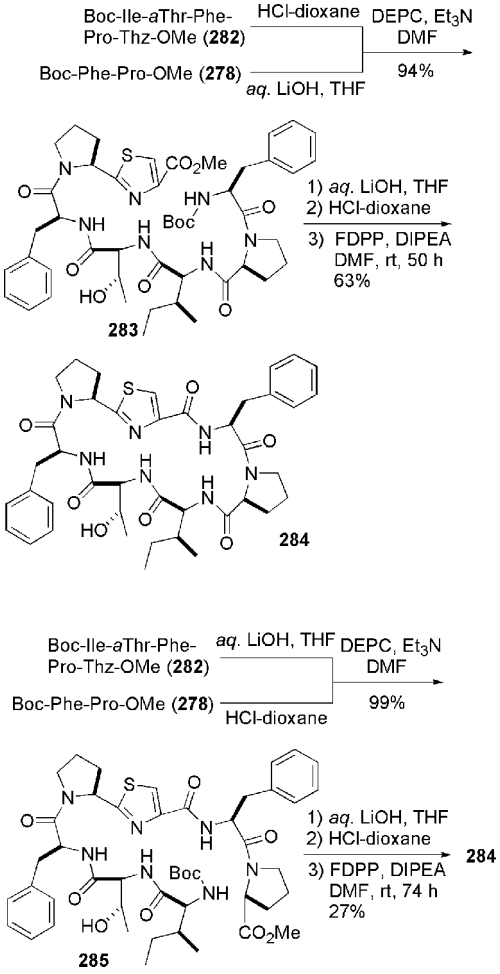
After deprotection of the *N*-terminal Boc group of **282** and the *C*-terminal methyl ester of **278**, coupling with DEPC afforded the linear precursor **283**, as shown in Scheme 56. Analogously, deprotection of the Boc group in **278** and the methyl ester in **282** followed by DEPC coupling afforded another linear precursor **285**. Then comparison of the macrolactamization step at the two sites (Thz/Phe vs Pro/Ile) was carried out after deprotection of **283** and **285**. Cyclization at the Thz/Phe site more smoothly proceeded to give the macrocycle **284**, and FDPP afforded **284** in 63% yield, while the cyclization with FDPP at the Pro/Ile site sluggishly proceeded to give **284** in 27% yield. FDPP proved to be superior to DPPA and HATU in both cases.

Final dehydrative cyclization of the *allo*-threonine residue to the oxazoline was performed using [bis(2-

Scheme 55



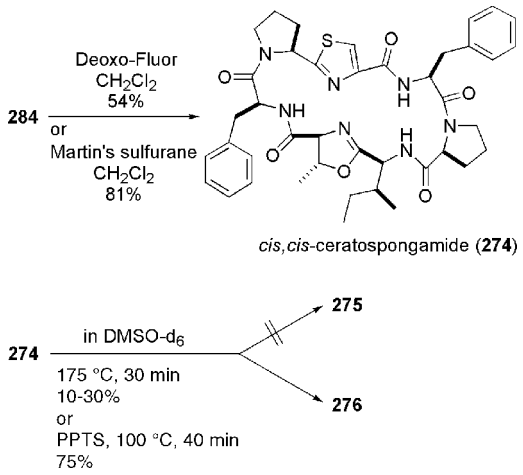
Scheme 56



methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor) to give *cis,cis*-ceratospongamide (**274**) in 54% yield, as shown in Scheme 57.[123] Later, use of Martin's sulfurane[28] proved to be much better (81% yield) for formation of the oxazoline. X-ray analysis of **274** further confirmed its structure.[123c,124]

Attempted thermal isomerization of the *cis,cis*-isomer **274** to the *trans,trans*-isomer **275** was carried out according to Gerwick's conditions (175 °C for 30 min in DMSO-d_6),[122] producing a compound different from **275**. This thermal isomerization much more

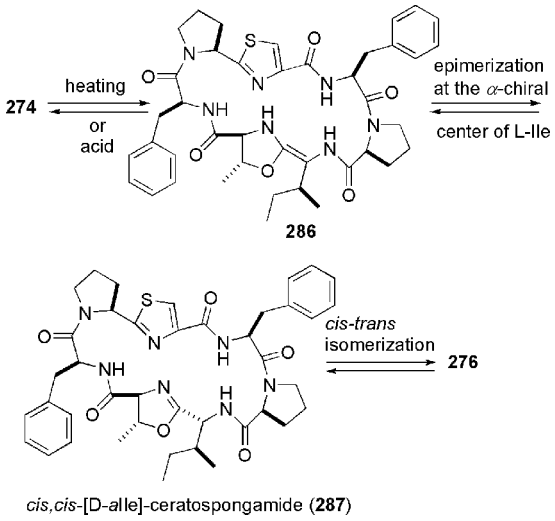
Scheme 57



smoothly proceeded in the presence of PPTS, shown in Scheme 57. The product clearly proved to be *trans,trans*-[D-*a*Ile]-isomer **276** by its synthesis using Boc-D-*a*Ile-OH, analogous to the synthesis of **274**, and identical to natural *trans,trans*-ceratospongamide.

The thermodynamic isomerization of **274** occurred by C_α epimerization of the Ile residue to provide the intermediate *cis,cis*-[D-*allo*-Ile]-isomer **287** via **286**. The epimer **287** was immediately isomerized at the two Phe-Pro peptide bonds to produce the *trans,trans*-[D-*allo*-Ile]-isomer **276**, as shown in Scheme 58.

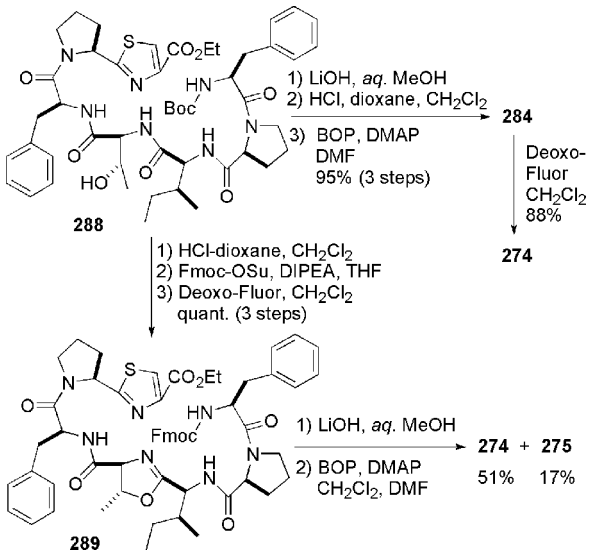
Scheme 58



Conformational studies using NMR spectra and molecular mechanics/dynamics calculations support this mechanism.[123c]

Conflicting results about *trans,trans*-ceratospongamide have been reported by Deng and Taunton,[125] who adopted the same [5 + 2] convergent strategy as Yokokawa et al.[123] The linear precursor **288** was deprotected and cyclized with BOP in the presence of DMAP to give the macrolactam **284** in excellent yield, shown in Scheme 59. The oxazoline formation was efficiently carried out with Deoxo-Fluor to give *cis,cis*-ceratospongamide (**274**). Then, to prepare *trans,trans*-ceratospongamide (**275**), the Boc group of the linear precursor **288** was replaced with the Fmoc group, and the oxazoline formation was accomplished

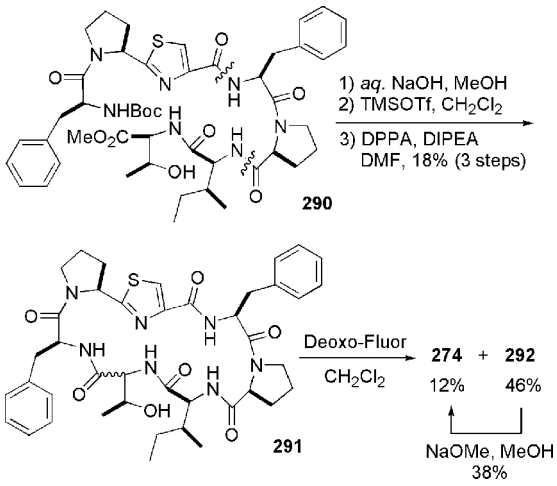
Scheme 59



before macrolactamization to give the Fmoc-oxazoline precursor **289**. Simultaneous deprotection of both *N*- and *C*-terminals with LiOH followed by macrocyclization with BOP-DMAP in CH_2Cl_2−DMF afforded a 1:3 ratio of *trans,trans*- and *cis,cis*-ceratospongamides. Furthermore, thermal isomerization of **274** in DMSO at 175 °C[122] afforded a 5:1 mixture favoring the *trans,trans*-isomer **275**. *trans,trans*-Ceratospongamide obtained here was identical to the natural one and claimed[125] to have the structure **275**. However, it should be corrected as *trans,trans*-[D-*allo*-Ile]-ceratospongamide (**276**) according to the experiments by Yokokawa, Shioiri, and co-workers.[123,126]

Kutsumura, Sata, and Nishiyama[127] also succeeded in the synthesis of *cis,cis*-ceratospongamide (**274**), as shown in Scheme 60. The linear heptapeptide **290**

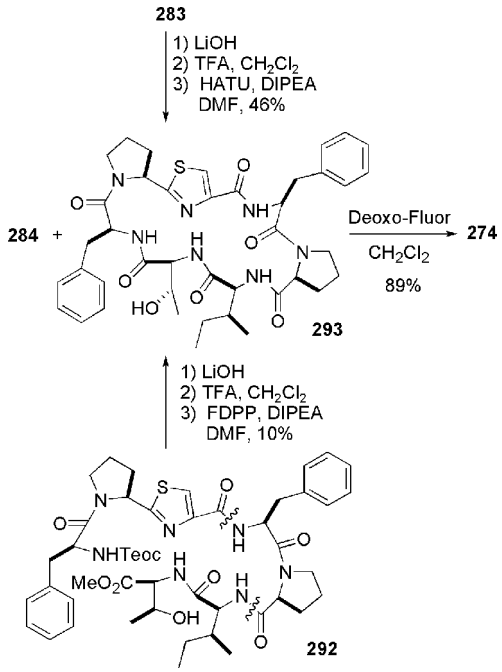
Scheme 60



was prepared by a stepwise connection of (Phe-Pro)-thiazole residue, Phe-Pro-OMe, and Ile-*a*Thr-OMe utilizing BOP−Et_3N as a coupling reagent. After deprotection at the *C*- and *N*-terminals, macrolactamization with DPPA−DIPEA afforded the cyclized peptide as a mixture of two diastereomers. Deoxo-Fluor provided *cis,cis*-ceratospongamide (**274**) in 12% yield together with the *cis*-oxazoline isomer **292**, isomeric at the oxazoline part, in 46% yield, the latter of which could be converted to **274** with NaOMe.

Synthesis of *cis,cis*-ceratospongamide (**274**) was also achieved by Chen, Deng, and Ye,[128] who adopted [4 + 3] fragment condensation, macrolactamization, and subsequent cyclodehydration, shown in Scheme 61. Both the linear peptides **283** and **292** were

Scheme 61



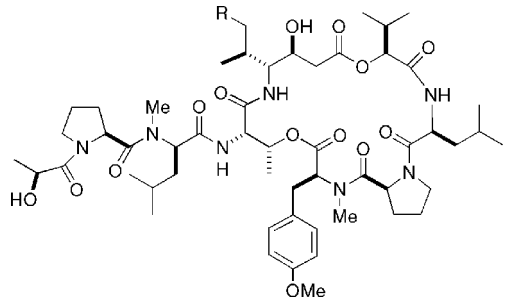
prepared from Phe-Pro-thiazole and Phe-Pro-Ile-*a*Thr derivatives. Interestingly, macrolactamization of **283** with HATU proceeded much more smoothly than that of **292**, and both produced a mixture of two conformational isomers, *cis,cis*-isomer **284** and *cis,trans*-isomer **293**, in a ratio of 1:1.3 in both cases. Finally, the oxazoline ring closure of the mixture afforded *cis,cis*-ceratospongamide (**274**) only, which suggested that conformer **293** would equilibrate to the corresponding isomer **284** prior to formation of the oxazoline ring.

5. Cyclic Peptides from Ascidians

5.1. Tamandarins A and B

Tamandarins A (**294a**) and B (**294b**) were isolated by Fenical and co-workers from the unidentified species of didemnid ascidian and determined to be cyclic depsipeptides closely related to didemnins, as shown in Figure 14.[129] Although tamandarins A and B contain isostatine and norstatine, respectively, similar to the didemnins, the hydroxyisovalerylpropionic acid (HIP) residue in the didemnins is replaced by more simple hydroxyisovaleric acid. Interestingly, the antitumor activities of tamandarins A and B are superior to those of didemnins, and their ED_{50} values are 1.2−2.0 ng/mL.

Joullié and co-workers[130] achieved synthesis of tamandarins A and B using the methods developed for total synthesis of didemnins.[3e,131] They employed a [4 + 2] segment coupling strategy. Although allo-

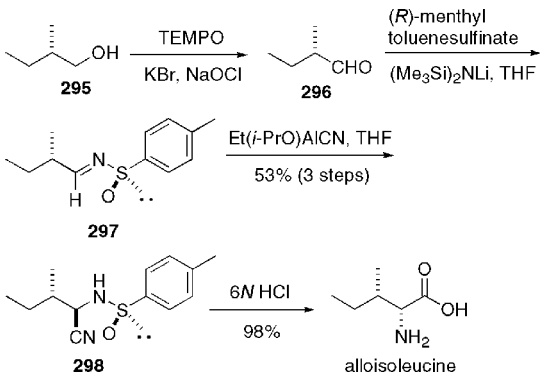


Tamandarin A (**294a**): R = H
Tamandarin B (**294b**): R = Me

Figure 14.

isoleucine, a starting material for synthesis of the isostatine, is commercially available, Joullié et al. reported a practical route from (*S*)-2-methyl-1-butanol (**295**) in four steps,[132] which includes novel imine formation and diastereoselective Strecker synthesis, as shown in Scheme 62. The alcohol **295** was

Scheme 62

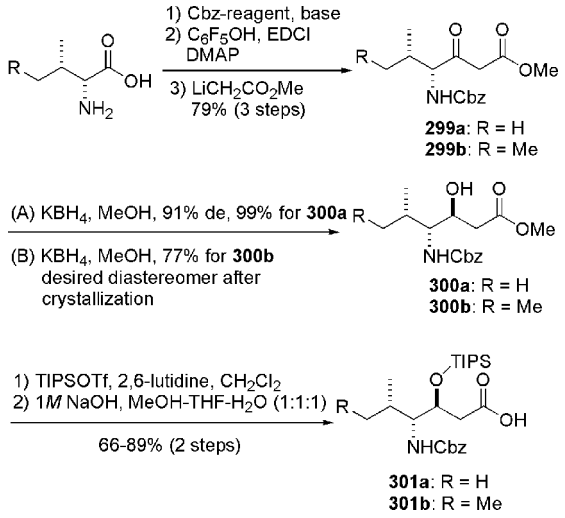


oxidized with 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and sodium chlorite,[133] and the resulting aldehyde **296** was condensed with the sulfinamide anion generated in situ from (*R*)-(+)-menthyl *p*-toluenesulfinate and $(Me_3Si)_2NLi$. Diastereoselective Strecker synthesis of the sulfinylimine **297** was achieved using Et(*i*-PrO)AlCN to provide the α-amino nitrile **298** in 90% de. After purification, the stereochemistry of **298** was established by X-ray crystallography. Acid hydrolysis of **298** afforded the alloisoleucine in 52% overall yield.

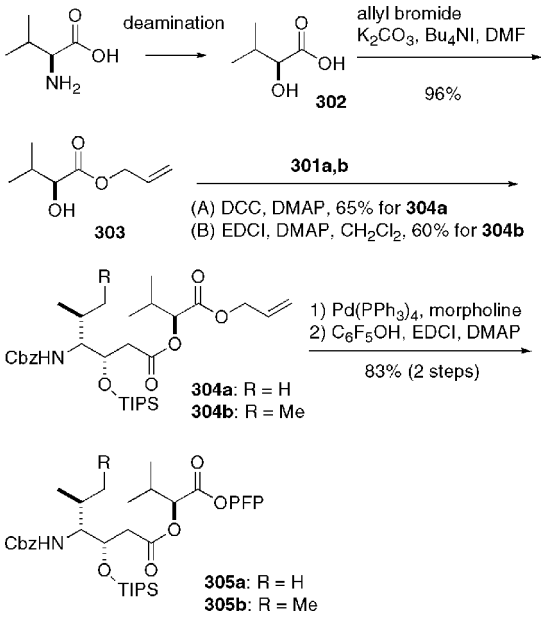
Synthesis of the statins, summarized in Scheme 63, was carried out in six steps from alloisoleucine and valine in which *N*-Cbz-protection, conversion to the activated pentafluorophenyl ester using the carbodiimide method, Claisen condensation with the lithium enolate of methyl acetate, and diastereoselective reduction of the *β*-keto esters **299** with potassium borohydride in methanol gave after diastereomeric purification by crystallization the desired isomers **300** in the pure state. TIPS protection followed by saponification afforded the statine building blocks **301**.

(*S*)-2-Hydroxyisovaleric acid (**302**) was synthesized by the standard method, deamination of L-valine with retention of stereochemistry, and converted to the allyl ester **303**. The dipeptide segments **305** were prepared by condensation of **303** with the statines

Scheme 63

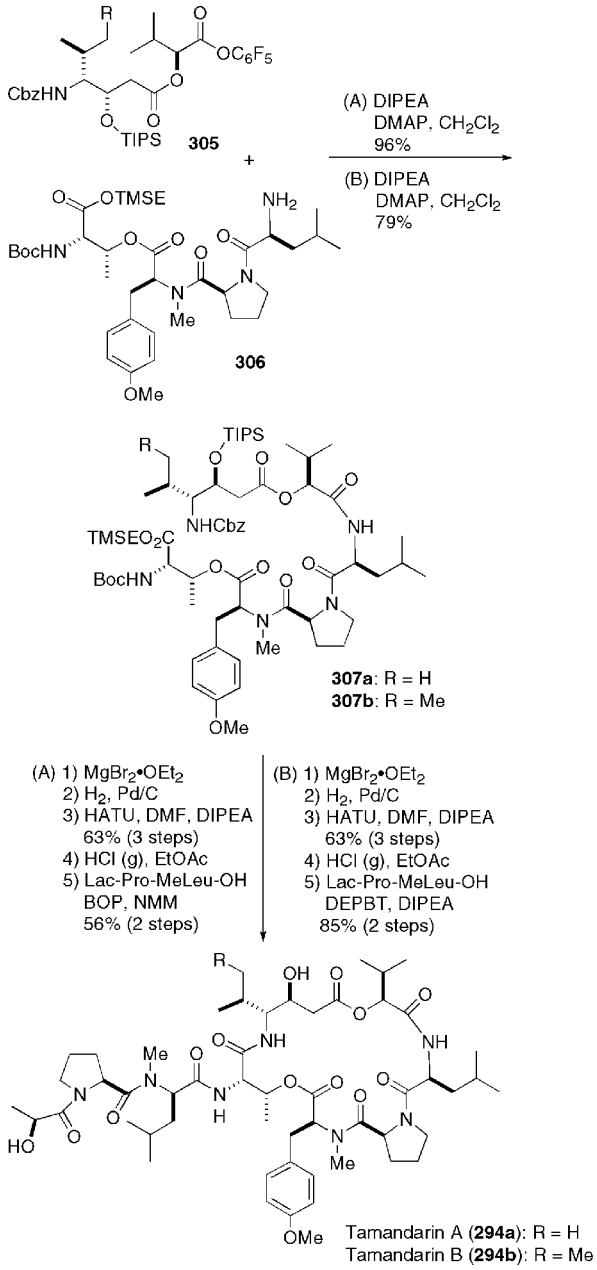


Scheme 64



The resulting esters **305** were directly coupled with the tetrapeptide TMSE ester **306** used previously for synthesis of the didemnins, shown in Scheme 65. The linear precursors **307** thus obtained were macrocyclized in three steps using deprotection of the TMSE group with magnesium bromide, hydrogenolysis of the Cbz group, and cyclization with the HATU/DIPEA method to afford the cyclic depsipeptides in 63% yield for the precursor of **294a** and in 23% yield for the precursor of **294b**. After simultaneous deprotection of Boc and TIPS groups with hydrogen chloride−ethyl acetate, introduction of the side chain was accomplished using BOP for **294a** and DEPBT for **294b** to furnish tamandarins A (**294a**) and B (**294b**), respectively, which were identical to the natural products.

Scheme 65



5.2. Mollamide

Mollamide (**308**) is a member of a more rare family of cyclic peptides having a reverse-prenyl unit associated as a serine ether residue together with a thiazoline ring. This cyclic peptide was isolated from the ascidian *Didemnum molle*[134] and displays moderate cytotoxicity against a range of cell lines with IC_{50} values of 1 μg/mL against P388 (murine leukaemia) and 2.5 μg/mL against A549 (human lung carcinoma), HT29 (human colon carcinoma), and CV1 (monkey kidney fibroblast) cells (Figure 15).

Total synthesis of mollamide (**308**) was accomplished by McKeever and Pattenden,[135] who began with construction of the pentapeptide **313** from proline methyl ester in seven steps (Scheme 66). DCC−HOBT was used for coupling and acetyl chloride−methanol for the Boc deprotection. The dipeptide **309** was converted to the tripeptide **310**, which reacted with the thioacylating reagent **311**[119] to give

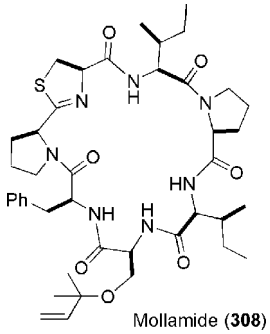
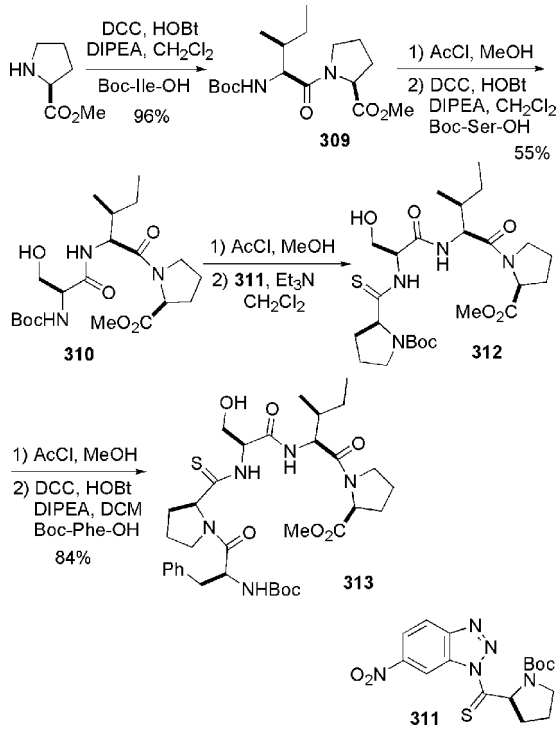


Figure 15.

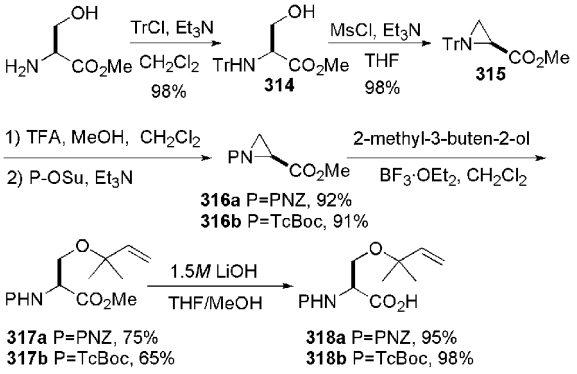
the tetrapeptide **312**. After removal of the Boc function, addition of Boc-Phe-OH afforded the pentapeptide **313**.

Scheme 66



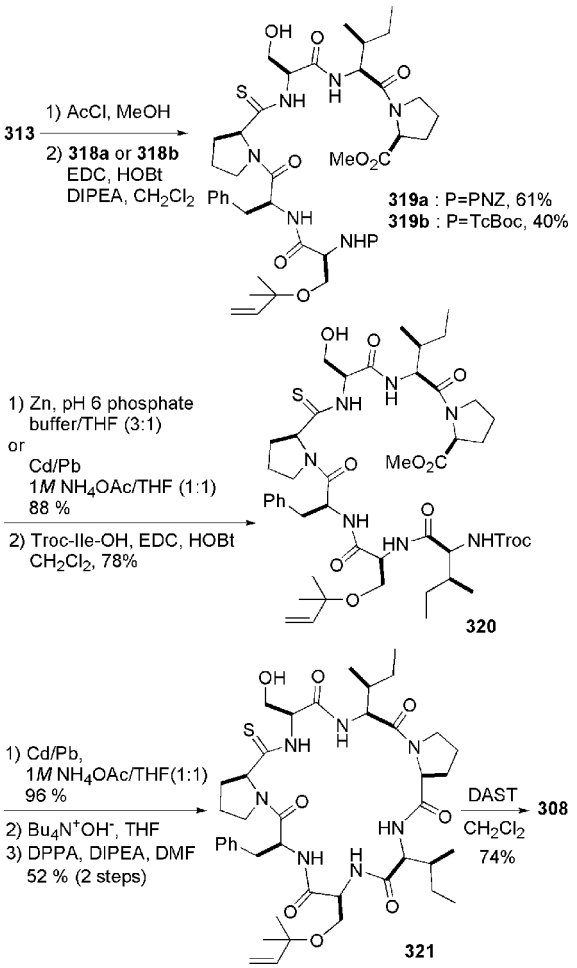
The required reverse prenylated amino acids **318** were synthesized using the Lewis-acid-assisted ring opening of activated aziridines with alcohols according to the method developed by Okawa and coworkers.[136] The chiral aziridine **315** was first prepared from H-Ser-OMe in two steps, as shown in Scheme 67. Replacement of the trityl (Tr) group with more electron-withdrawing groups was necessary to facilitate the aziridine ring opening. After investigations of a number of alternatives, the 4-nitrobenzyloxycarbonyl (PNZ) and the 2,2,2-trichloro-*tert*-butyloxycarbonyl (TcBoc) carbamate groups were selected. Replacement of the trityl group with the PNZ and TcBoc groups afforded the aziridines **316a** and **316b**, which underwent ring opening with 2-methyl-3-buten-2-ol in the presence of boron trifluoride etherate to give the *O*-prenylated amino acids **317a** and **317b**, respectively. Saponification of these compounds produced the required carboxylic acids **318a** and **318b**.

Scheme 67



After deprotection of the Boc group from **313**, coupling with **318a** and **318b** in the presence of EDCI−HOBT proceeded to give **319a** and **319b**, respectively. Although the PNZ group in **319a** was smoothly removed, subsequent purification proved to be problematic. In contrast, removal of the TcBoc group from **319b** according to Ciufolini's protocol[137] was clean and efficient to give the free amine, which was coupled with Troc-Ile-OH to give the heptapeptide **320**. Removal of the Troc group,[137] saponification of the methyl ester group, and then macrolactamization using DPPA afforded the macrocycle **321**. Finally, cyclodehydration of the β-hydroxy thioamide unit to the corresponding thiazoline was accomplished using DAST to give mollamide **308**. Formation of the sterically problematic thiazoline ring was carried out at the last stage of the synthesis in this work too (Scheme 68).

Scheme 68



5.3. Trunkamide A

Ascidians of the genus *Lissoclinum* have proven to be a rich source of novel cyclic peptides.[3e] Most of them have interesting cytotoxic properties.

Trunkamide A also belongs to the Lissoclinum peptides and was isolated from the colonial ascidian *Lissoclinum* sp. collected at the Great Barrier Reef, Australia, by Bowden, Ireland, and co-workers in 1996.[138] It is reported to have promising antitumor activity and is under preclinical trials. The structure of trunkamide A was initially assigned as **322a**, but extensive synthetic works by Wipf and Uto[139] clearly showed that the real structure of trunkamide A is **322b**, epimeric at C45, as shown in Figure 16.

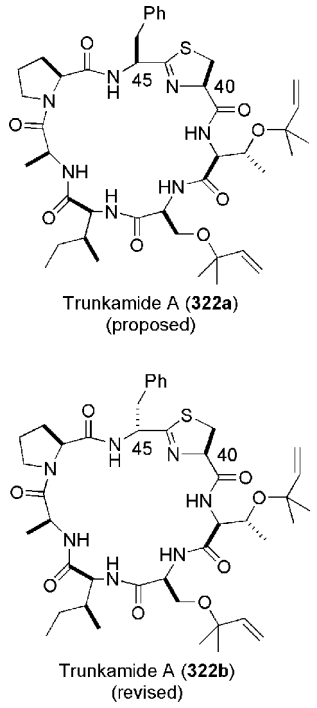


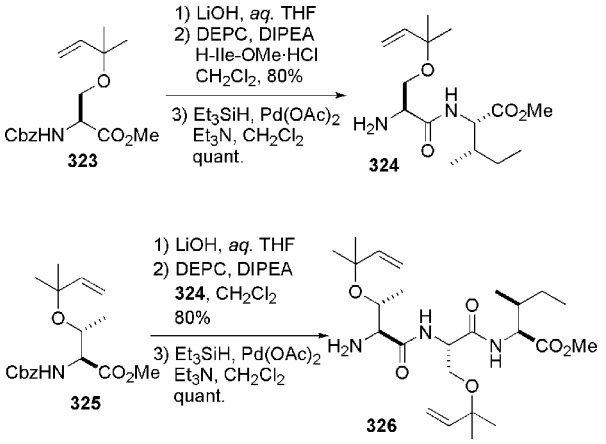
Figure 16.

Trunkamide A is a reverse-prenylated member of cyclic peptides having a thiazoline ring, similar to mollamide (**308**).

Total synthesis of natural trunkamide A (**322b**) was achieved by Wipf and Uto,[139b] McKeever and Pattenden,[140] and Giralt[141] and co-workers. The Wipf and Pattenden groups employed the BF_3-assisted aziridine ring opening for construction of the reverse-prenylated (rPr) serine and threonine side chains as in the mollamide case (see Scheme 67).[132,134]

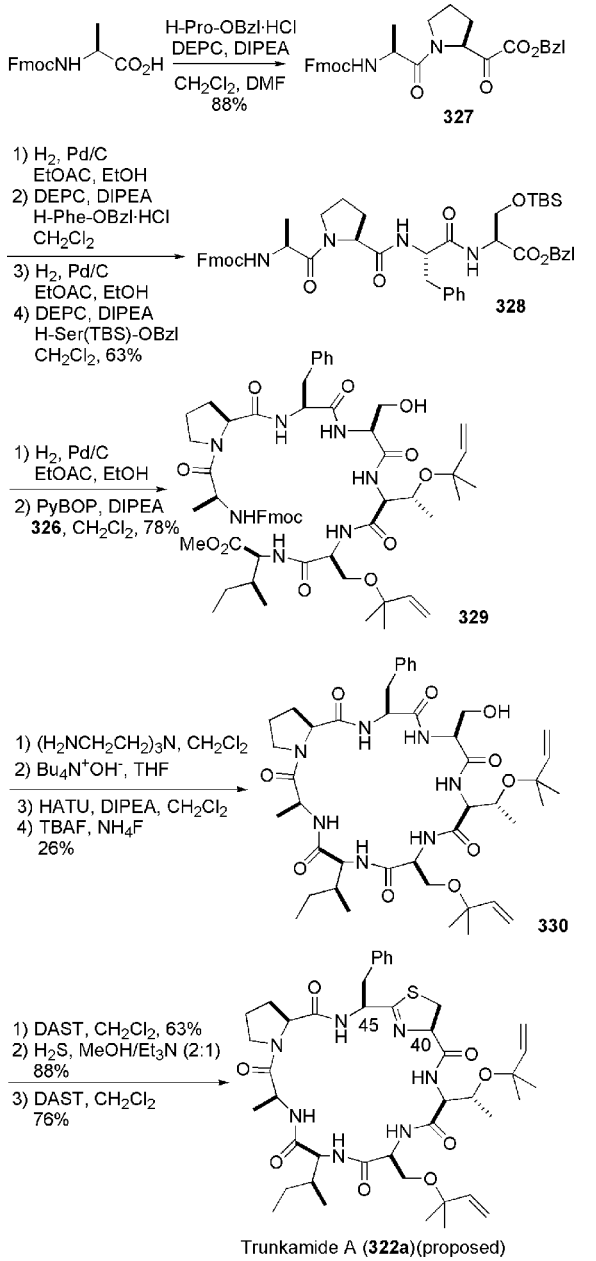
Wipf and Uto[139] started their synthesis of trunkamide A having the proposed structure **322a** from the reverse-prenylated serine derivative (**323**), which was hydrolyzed and coupled with the isoleucine derivative using DEPC to yield the dipeptide **324**, as shown in Scheme 69. After chemoselective removal of the Cbz group with $Et_3SiH-Pd(OAc)_2$,[142] the amine **324** underwent the DEPC coupling with the carboxylic acid derived from the reverse-prenylated threonine **325**

Scheme 69



and then chemoselective deprotection to give the amine **326**.

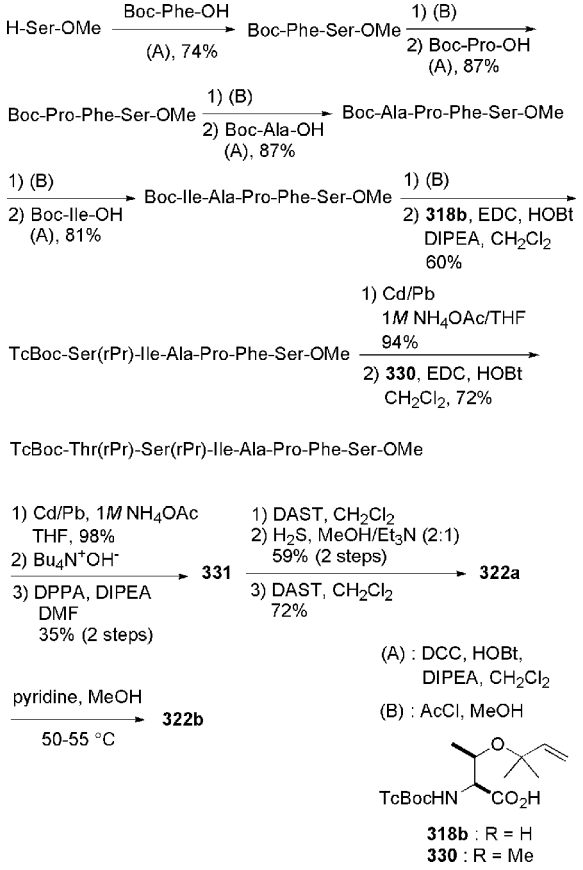
Scheme 70



Assembly of the tetrapeptide **328** employed the iterative DEPC-mediated couplings of Fmoc-alanine with proline, phenylalanine, and *O*-TBS-serine derivatives, as shown in Scheme 70. Catalytic removal of the benzyl function from **328** followed by fragment coupling with the tripeptide **326** using PyBOP afforded the linear heptapeptide **329**. After deprotection at the *N*-and *C*-terminals, the 21-membered ring closure with HATU and then desilylation produced the macrolactam **330**. Wipf's oxazoline−thiazoline interconversion protocol[65] (see also section 2.5.2) was employed to convert **330** to trunkamide A with the proposed structure **322a**, which was not identical to the natural one. Thus, Wipf and Uto further synthesized the (40*R*,45*R*)-, (40*S*,45*S*)-, and (40*S*,45*R*)-stereoisomers and determined the structure of natural trunkamide A to be **322b**.

Synthesis of trunkamide A by Mckeever and Pattenden[140] started by the coupling of L-serine methyl ester with Boc-Phe-OH, as shown in Scheme 71. They

Scheme 71

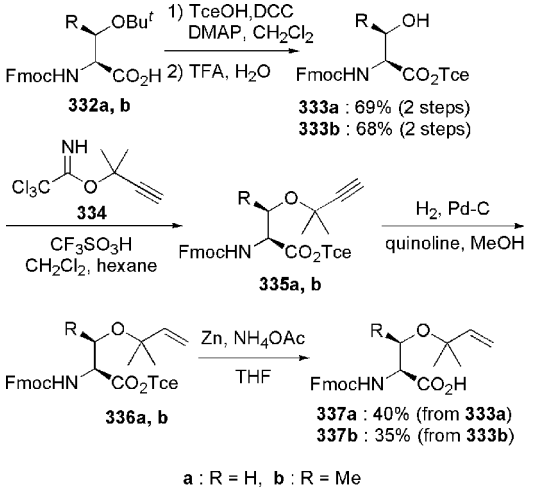


used the TcBoc derivatives of the reverse-prenylated serine and threonine, **318b** and **330**, as in their synthesis of mollamide (**308**, see section 5.2).[135] Wipf's method[65] was again adopted for formation of the thiazoline ring. The thioamide derivative of the phenylalanine was initially used, but the macrolactamization did not proceed at all in this particular case. Synthesis of trunkamide A having the revised structure **322b** was finished by the interesting stereoselective C45 epimerization of trunkamide A having the proposed structure **322a**. It was done using methanolic pyridine at 50 °C for 9 days

without any detectible formation of other diastereoisomers.

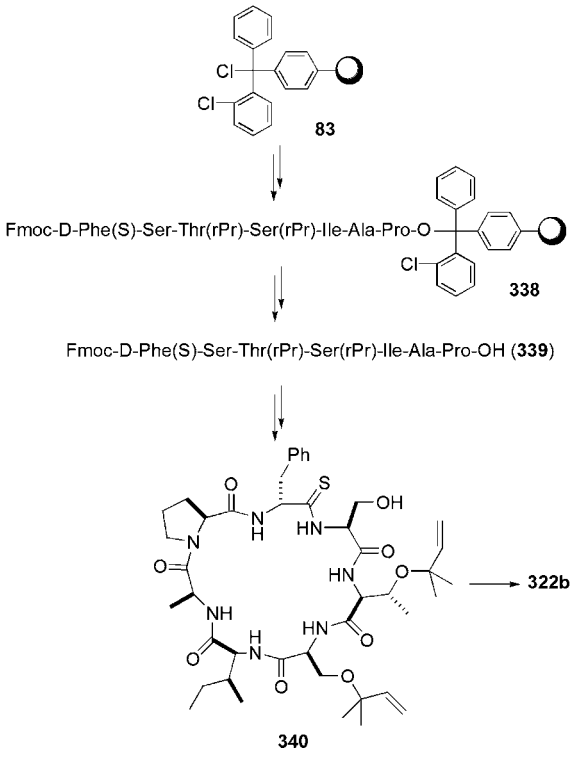
Albericio, Giralt, and co-workers[141] prepared the reverse-prenylated serine and threonine **337** by reaction of Fmoc-Ser-OTce and Fmoc-Thr-OTce (**333**), respectively, with 1,1-dimethylpropynyl trichloroacetimidate (**334**),[143] partial reduction, followed by removal of the trichloroethyl function in an overall yield of 28% for serine and 24% for threonine, as shown in Scheme 72.

Scheme 72



The linear precursor **339** was synthesized on the chlorotrityl resin **83** using the Fmoc strategy and DIC as the coupling reagent, shown in Scheme 73. After

Scheme 73



cleavage from the resin with hexafluoro-2-propanol-CH_2Cl_2 (1:4), the macrocyclization of the linear peptide **339** was accomplished with PyAOP/DIPEA[144] to give the macrocycle **340**. Final construction of the thiazoline ring was performed with DAST to give trunkamide (**322b**) in an overall yield of 5%. Other methods such as Burgess or Mitsunobu reactions were not effective at all in this case. This strategy will be quite useful for the rapid preparation of other peptides containing the same motif.

6. Cyclic Peptides from Sea Hare

6.1. Aurilide

Aurilide has been isolated from the Japanese sea hare *Dollabella auricularia* by Suenaga, Kigoshi, Yamada, and co-workers.[145a,c] This depsipeptide exhibits potent cytotoxicity against Hela S_3 cells with an IC_{50} of 0.011 μg/mL. Aurilide (**341**) is a 26-membered cyclic depsipeptide having a unique dihydroxy fatty acid part in addition to the peptide part (Figure 17).

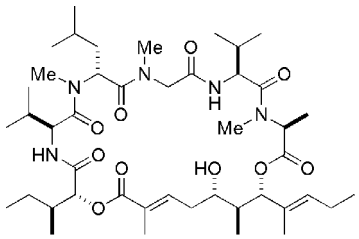
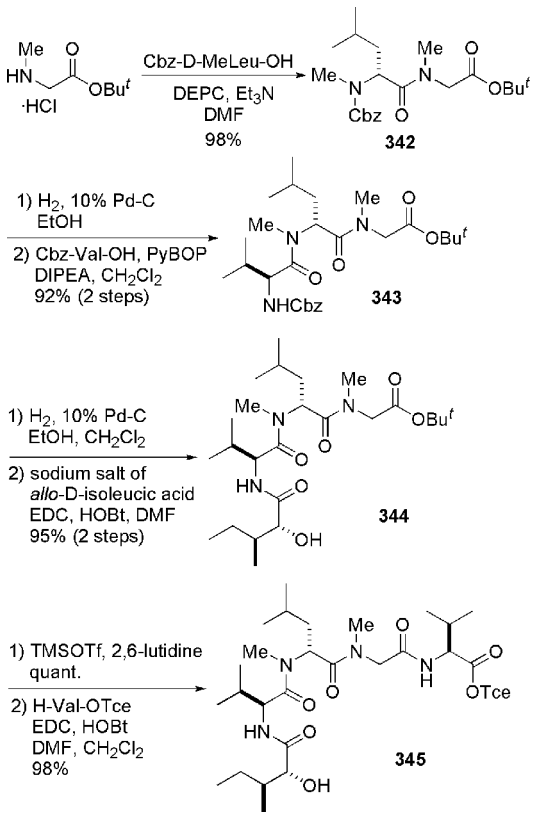


Figure 17.

Yamada's synthesis of aurilide (**341**)[145b,c] started from *N*-MeGly-OBu^t, which was coupled with Cbz-*N*-Me-D-Leu-OH using DEPC, as shown in Scheme 74. Catalytic removal of the Cbz group followed by

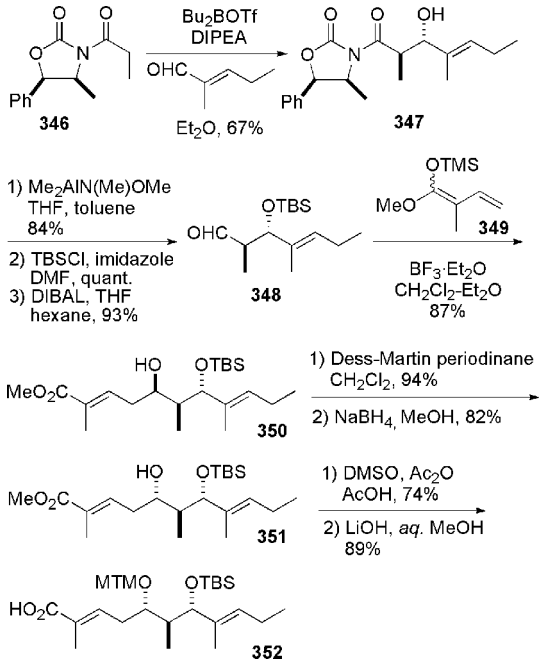
Scheme 74



coupling with Cbz-Val-OH using PyBOP afforded the tripeptide **343**, which was analogously condensed with *allo*-D-isoleucic acid using EDCI/HOBT. Deprotection of the *tert*-butyl group of the tetrapeptide **344** gave the carboxylic acid, which was condensed with Val-OTce to provide the pentapeptide **345**.

Synthesis of the protected dihydroxy acid **352** began with an anti-selective aldol reaction[146] between the imide **346** and *trans*-2-methyl-2-pentenal to give the hydroxyimide **347** (67%) accompanied with the syn-isomer (14%). Transamidation of **347** with the aluminum salt of *N*,*O*-dimethylhydroxylamine, silylation, and then reduction with DIBAL afforded the aldehyde **348**, as shown in Scheme 75. The vinylo-

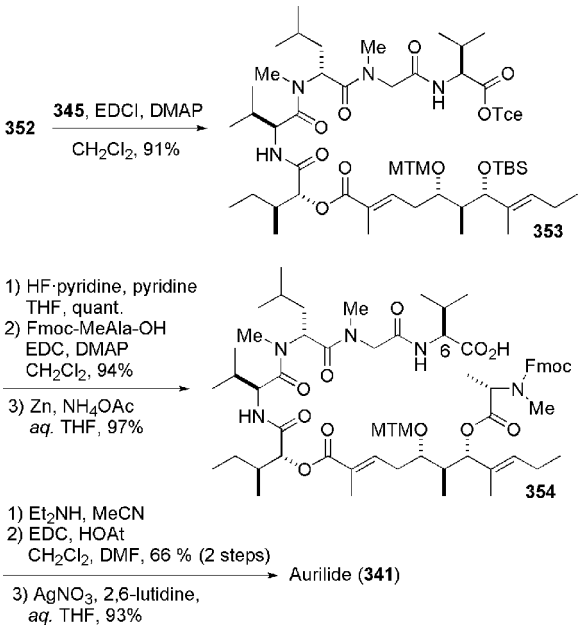
Scheme 75



gous Mukaiyama aldol reaction[147] of **348** with the silyl ketene acetal **349** afforded the methyl ester **350** as a single diastereomer. Inversion of the C35 hydroxy group in **350** was carried out by Dess−Martin oxidation and then reduction with $NaBH_4$ to give the alcohol **351** with good stereoselectivity (α:β = 20:1). After conversion of **351** to the (methylthio)methyl (MTM) ether with DMSO−Ac_2O−AcOH,[148] alkaline hydrolysis produced the protected dihydroxy acid **352**.

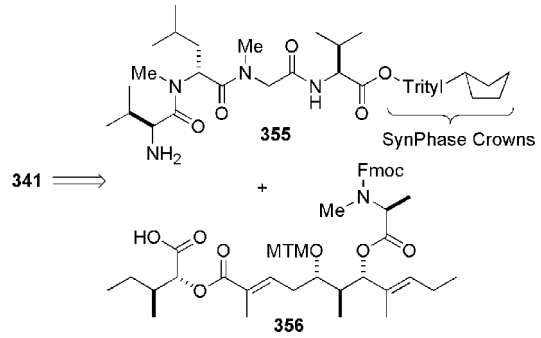
Coupling of the dihydroxy acid **352** with the pentapeptide **345** was accomplished with EDCI to give the ester **353**, as shown in Scheme 76. Removal of the TBS group and addition of *N*-Fmoc-*N*-MeAla-OH gave the ester, from which the 2,2,2-trichloroethyl group was removed to give the carboxylic acid **354**. Deprotection of the Fmoc group followed by macrolactamization with EDCI−HOAt afforded the required lactam (66%) together with the *epi*-lactam (24%). Apparently epimerization occurred at the C6-valine part. In this particular case EDCI−HOAt was superior to PyBOP, DPPA, and EDCI−HOBt for macrolactamization. Removal of the MTM group with $AgNO_3$ afforded aurilide (**341**) in an overall yield of 12%.[145b,c]

Scheme 76



A second synthesis of aurilide (**341**) was reported by Takahashi, Doi, and co-workers, who achieved a solid-phase library synthesis of **341** and related analogues.[149] Their strategy is summarized in Scheme 77. The tetrapeptide fragment **355** was assembled on

Scheme 77



trityl linear-functionalized SynPhase Crowns using an Fmoc strategy. Preparation of the dihydroxy carboxylic acid **356** was carried out according to the procedure developed by Yamada and co-workers[145] with slight modification. The carboxylic acid **356** was coupled with the solid-supported **355** using DIC/HOBt. After deprotection and cleavage of the linear precursor, macrolactamization with EDCI/HOAt under high dilution conditions followed by removal of the MTM group provided aurilide (**341**) in 11% overall yield. Utilizing a similar protocol using the TranSort technique, a combinatorial library of aurilide derivatives was synthesized.

7. Cyclic Peptides from Bacteria

7.1. Cyclomarins

As is well known, soil bacteria of terrestrial origin produce a number of antibiotics having intriguing structures. In recent years soil bacteria of marine origin have also attracted considerable attention as

a source of biologically active compounds. Cyclomarins A−C is a group of such cyclic peptides which were isolated from the marine bacterium *Streptomyces* sp. by Fenical and co-workers.[150] The structure of cyclomarin A (**357a**) has been determined by X-ray crystallographic analysis of its diacetate derivative. As shown in Figure 18, cyclomarins A−C (**357a**−**c**)

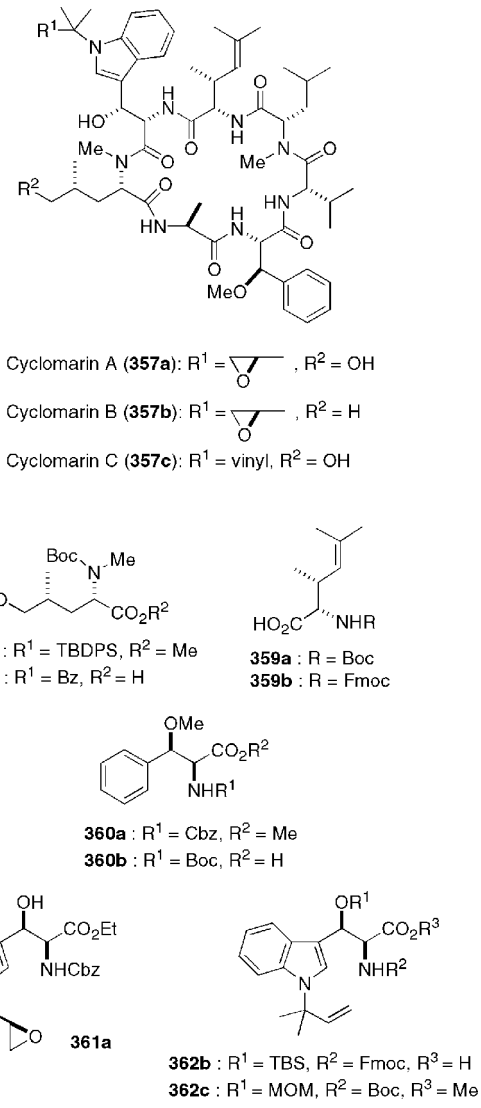
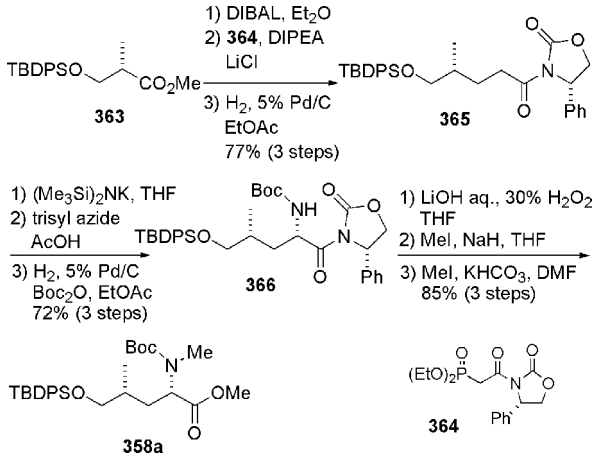


Figure 18.

are 21-membered cyclic heptapeptides that are slightly different from each other and contain four structurally interesting and hitherto unknown unusual amino acids. The major constituent, cyclomarin A, displays significant antiinflammatory properties in both in vitro and in vivo assays as well as antitumor activity and is now under preclinical trials.[151] The synthetic approach to cyclomarins was first reported by Sugiyama, Shioiri, and Yokokawa[152] and then Yao and co-workers.[153] The latter group succeeded in the total synthesis of cyclomarin C.[153b,c]

The first task was synthesis of the unusual amino acid components **358**−**362**, shown in Figure 18. Synthesis of the *N*-methylhydroxyleucine derivatives **358** was carried out by using Evans' asymmetric azide-transfer reaction[154] with trisyl azide (2,4,6-triisopropylbenzenesulfonyl azide).[152b,153b] Sugiyama, Shioiri, and Yokokawa[152b] utilized the methyl ester **363** as the starting material, which successively underwent reduction with DIBAL, condensation with the chiral phosphonate **364** under Masamune−Roush conditions,[155] followed by catalytic hydrogenation to give the *N*-acyl oxazolidinone **365**, shown in Scheme 78. Deprotonation and then azidation with trisyl

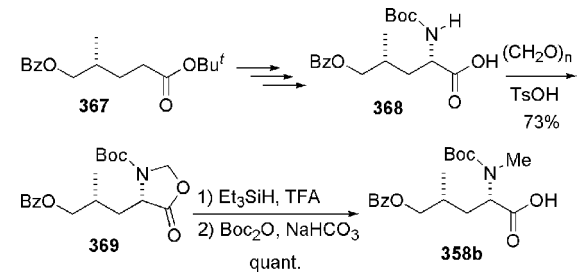
Scheme 78



azide[154] afforded the azide as a single isomer, which was hydrogenated over Pd/C in the presence of Boc_2O to furnish the *N*-Boc imide **366**. Removal of the chiral auxiliary, *N*-methylation, and methyl esterification provided the *N*-methylhydroxyleucine derivative **358a** in excellent yield.

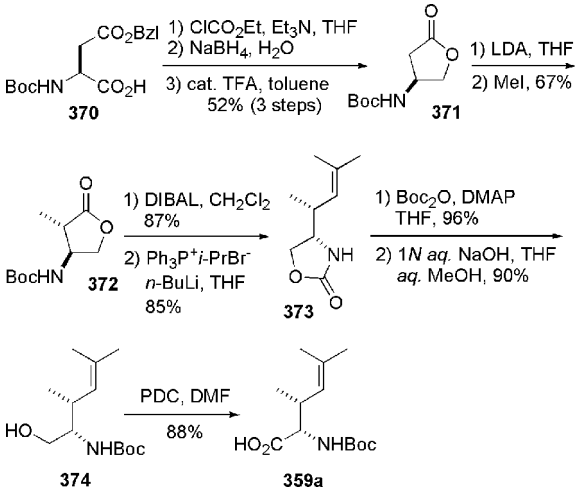
Yao and co-workers[153b] also employed the same Evans' azidation methodology[154] as above to synthesize the amino acid derivative **368** from the benzoyl ester **367**. The acid **368** was converted to the required benzoyl derivative **358b** via the oxazolidinone **369** by a ketalization−reduction sequence for the *N*-methylation, as shown in Scheme 79.

Scheme 79



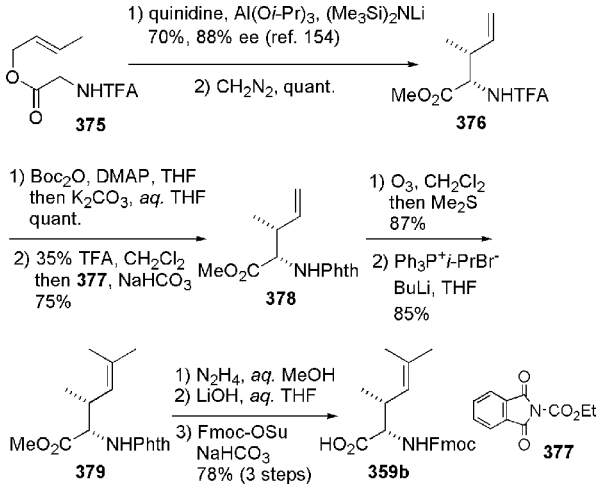
The second unusual amino acid component **359** was synthesized in three ways.[152b,153b,156] First, Boc-Asp-(OBzl)-OH (**370**) was converted to the lactone **371** by reduction of the corresponding mixed anhydride and then acid-catalyzed lactonization,[152a] as shown in Scheme 80. α-Methylation afforded a diastereoisomeric mixture in a ratio of 10:1, which was readily separated on a silica gel column to produce **372**. After DIBAL reduction of the lactone to the lactol, Wittig homologation afforded the oxazolidinone **373**. Reinstallation of the Boc group followed by alkaline hydrolysis gave the alcohol **374**, which was smoothly oxidized to yield the amino acid **359a**.

Scheme 80



Another synthesis[153b] utilized an enantioselective [3.3]-Claisen rearrangement of the ester **375** according to the known procedure,[157] as shown in Scheme 81. The *N*-trifluoroacetyl (TFA) amino acid methyl

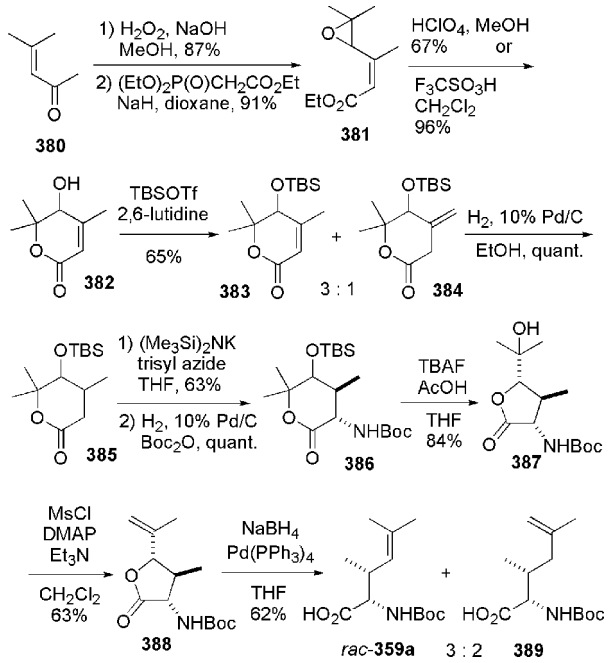
Scheme 81



ester **376** thus obtained was converted to the *N*-phthaloyl (Phth) derivative **378** via the Boc derivative. Ozonolysis followed by Wittig olefination afforded the isopropylidene derivative **379**, which was converted to the *N*-Fmoc derivative **359b**.

Traver and Joullié[156] also reported racemic synthesis of the amino acid **359a** utilizing mesityl oxide (**380**) as the starting material, which was converted to the dihydropyrane **382** via the ester **381** in three steps, as shown in Scheme 82. Silylation of **382** resulted in formation of a mixture of the desired TBS ether **383** and its exo isomer **384** in a ratio of 3:1. Catalytic hydrogenation of the mixture afforded the δ-lactone **385**, which underwent azidation with trisyl azide and then catalytic hydrogenation in the presence of Boc_2O to give the Boc derivative **386**. Treatment of the Boc-δ-lactone **386** with TBAF buffered with acetic acid produced the γ-lactone **387** through rearrangement. The alcohol function of **387** was eliminated with MsCl−DMAP−Et_3N to furnish the lactone **388**, which afforded a mixture of the desired amino acid *rac*-**359a** and its double-bond isomer **389**

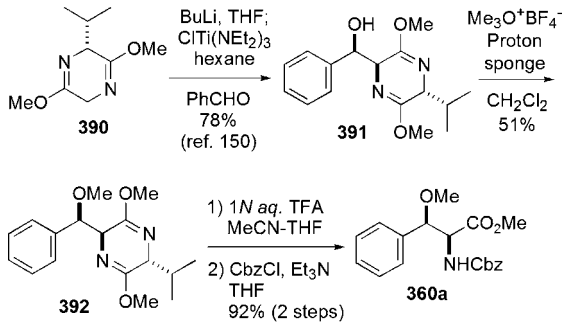
Scheme 82



in a ratio of 3:2 through reduction with $NaBH_4$−Pd-$(PPh_3)_4$.

Preparation of *syn*-β-methoxyphenylalanines **360** was accomplished in two ways: use of (1) the aldol reaction with Schöllkopf's chiral glycine enolate[152b] and (2) the radical-based bromination of a phenylalanine derivative.[153b] In the first case benzaldehyde reacted with the titanium enolate derived from the bislactim ether **390**[158a] to give the known aldol product **391**[158b] as a single diastereomer, as shown in Scheme 83. *O*-Methylation with $Me3O^+BF_4^-$[159] in the presence of proton sponge afforded the methyl ether **392**, which, after removal of chiral auxiliary, was converted to the Cbz derivative **360a**.

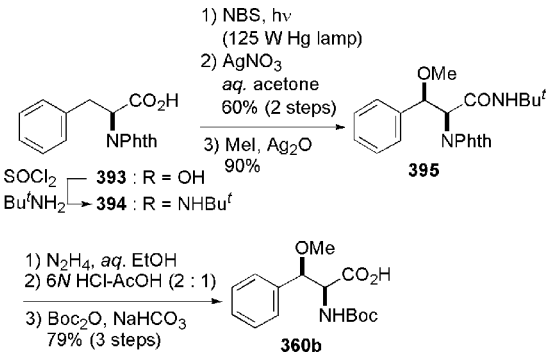
Scheme 83



Alternatively, the *syn*-methyl ether **395** was prepared by radical bromination[160] at the benzyl position of the phenylalanine *tert*-butylamide **394**, substitution with hydroxide, and then methylation, as shown in Scheme 84. Removal of the phthaloyl group followed by acid-catalyzed amide hydrolysis and *N*-Boc protection afforded the *N*-Boc derivative **360b**.

The key part for the synthesis of the remaining unusual amino acid, the *N*-reverse-prenylated tryptophan derivative **361** or **362**, will be how to introduce the hydroxyl function at the benzylic position of the tryptophan residue. This was done by either

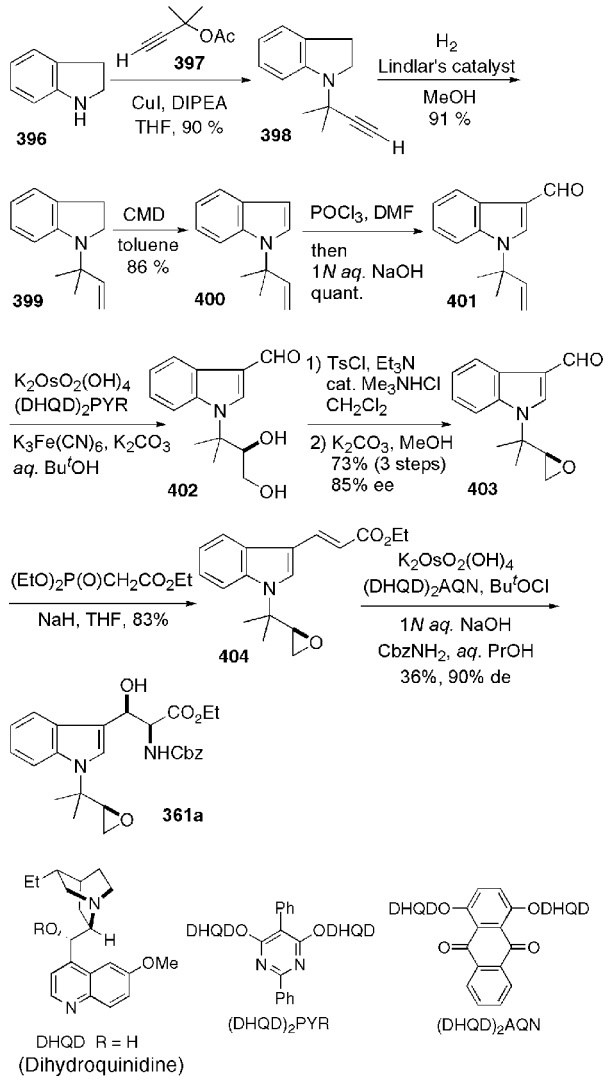
Scheme 84



using Sharpless asymmetric aminohydroxylation[152b,153b] or DDQ oxidation followed by stereoselective reduction.[153a]

The starting material employed by Yokokawa and co-workers[152b] was indoline (**396**), which was smoothly converted to the *N*-reverse-prenylated indole[152a,c] by *N*-propargylation,[161] partial hydrogenation, and then dehydrogenation with CMD,[12] as shown in Scheme 85. The Vilsmeier formylation of **400** quantitatively

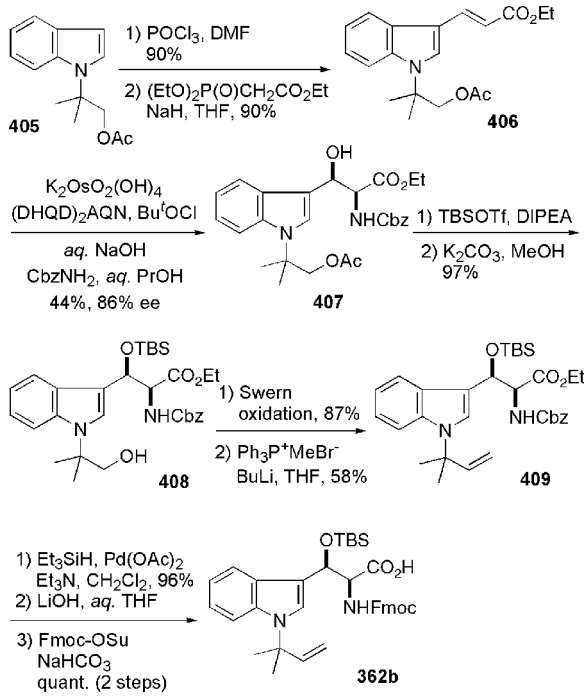
Scheme 85



afforded the 3-formylindole **401**. The Sharpless asymmetric dihydroxylation of the terminal olefin using (DHQD)$_2$PYR as a chiral ligand[63,152a,c] gave the diol **402**, which was converted to the epoxide **403** via tosylation[162] and then alkaline treatment. The Horner−Emmons reaction with triethyl phosphonoacetate afforded the α,β-unsaturated ester **404**. The pivotal Sharpless asymmetric aminohydroxyration[63b] was accomplished using (DHQD)$_2$AQN as a chiral ligand to produce the desired epoxide **361a**, a building block of cyclomarin A (**357a**).

An analogous strategy was adopted by Yao and co-workers[153b] for synthesis of the *N*-reverse-prenylated tryptophan **362b**, a precursor for synthesis of cyclomarin C. (**357c**).[153b,c] The *N*-reverse-prenylated indole **405** was converted to the α,β-unsaturated ester **406** by the Vilsmeier and Horner−Emmons reactions, as shown in Scheme 86. Sharpless asymmetric amino-

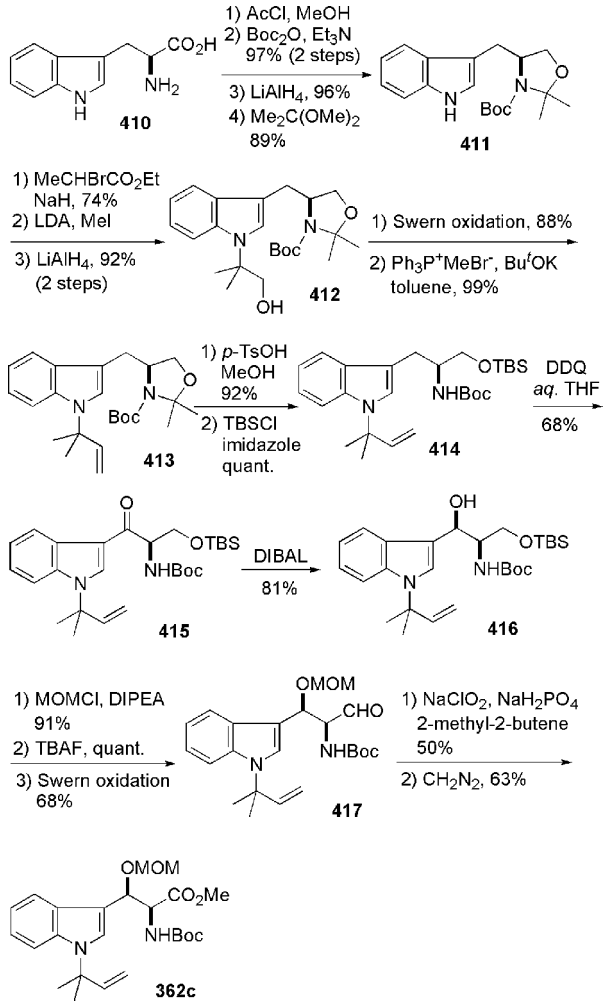
Scheme 86



hydroxylation of the ester **406** using (DHQD)$_2$AQN afforded the hydroxytryptophan derivative **407**, which was treated with TBSOTf and then K_2CO_3 to produce the alcohol **408**. Swern oxidation followed by Wittig methylenation yielded the alkene **409**. Replacement of the Cbz group with the Fmoc group was carried out by selective *N*-Cbz removal through a Pd-mediated reaction,[139a,142] ethyl ester hydrolysis, and *N*-Fmoc protection to produce the *N*-reverse-prenylated tryptophan **362b**.

Before the above synthesis[153b] Yao and co-workers prepared the analogous tryptophan derivative **362c** from tryptophan utilizing DDQ oxidation followed by stereoselective reduction as key steps.[153a] The method is methodologically interesting but requires a longer step, as shown in Scheme 87. Tryptophan (**410**) was first converted to the oxazolidine derivative **411** in four steps. The required reverse-prenyl group was attached at the indole-nitrogen by indirect introduction of the hydroxylalkyl substituent, Swern oxidation, followed by Wittig methylenation to give the *N*-reverse-prenylated derivative **413** via **412**. Acidic

Scheme 87

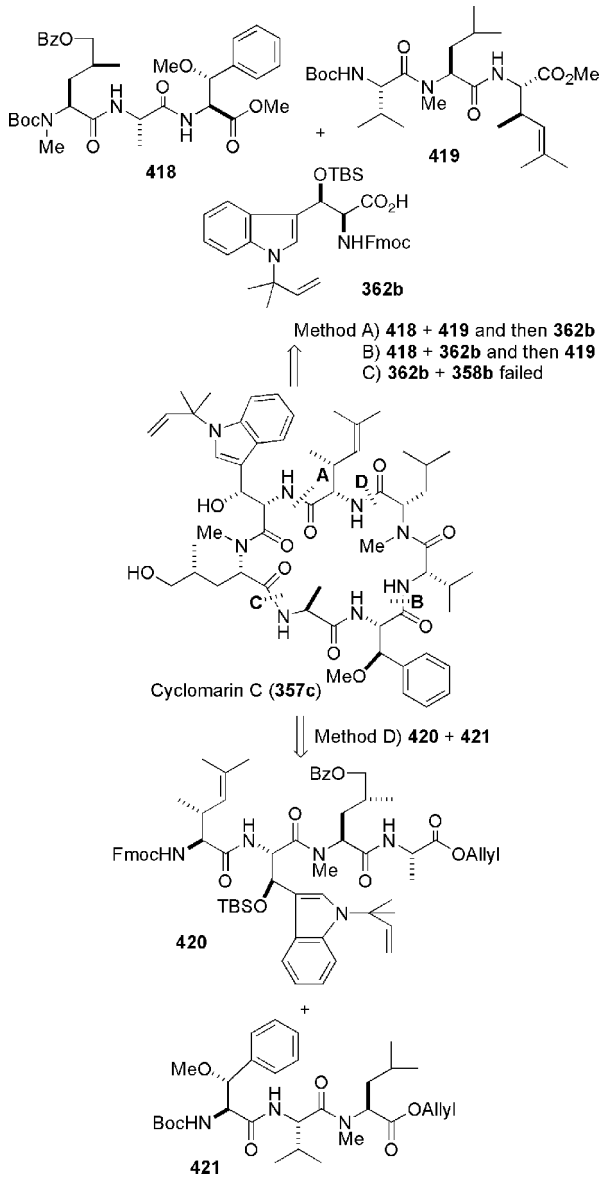


ring opening of the oxazolidine ring, silylation, and then DDQ oxidation[160] afforded the ketone **415**, which was reduced with DIBAL to give the alcohol **416** with high stereoselectivity (>19:1). After protection of the hydroxyl group and then removal of the TBS group, oxidation followed by esterification finally furnished the *N*-reverse-prenylated tryptophan derivative **362c**.

With all of the required building blocks in hand, Yao and co-workers succeeded in the total synthesis of cyclomarin C (**353c**).[153b,c] They examined several combinations of the [4 + 3] coupling strategies, Methods A−D in Scheme 88.

After respective deprotection, the tripeptides **418** and **419** were coupled using EDCI−HOBt, followed by attachment of the tryptophan derivative **362b**, for method A in Scheme 88.[153b] Final cyclization of the linear precursor with BOP/DIPEA sluggishly proceeded to give the macrocycle in only 2−4% yield. The tryptophan residue situated at the N-terminal was suggested to be labile. Thus, the tryptophan residue was designed to occupy the middle part of the molecule in method B. However, all efforts toward macrocyclization of the linear precursor again failed. Similar to method A, the last step resulted in a complex mixture, indicating that the β-methoxyphenylalanine residue is not a suitable *C*-terminus for the cyclization precursor. The third method C encountered problems in the coupling of the deprotected

Scheme 88



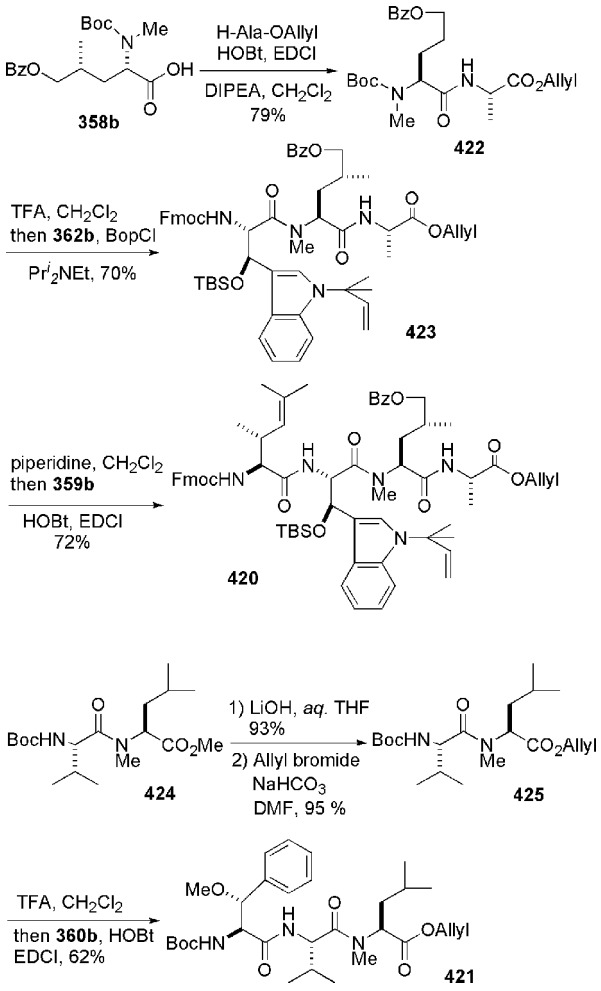
forms of **362b** and **358b** during the early stage of total synthesis.

Finally, method D was adopted that led to the total synthesis of cyclomarin C (**357c**). The dipeptide allyl ester **422** was prepared from **358b** with alanine allyl ester, as shown in Scheme 89. After acidic deprotection, coupling with the tryptophan residue **362b** using BopCl/DIPEA to give the tripeptide **423**, to which the Fmoc derivative **359b** was attached after deprotection, produced tetrapeptide **420**.

On the other hand, replacement of the methyl ester function in **424** with the allyl ester one afforded the allyl ester **425**, which, after acidic treatment, reacted with the phenylalanine derivative **360b** to give the tripeptide **421** (Scheme 89).

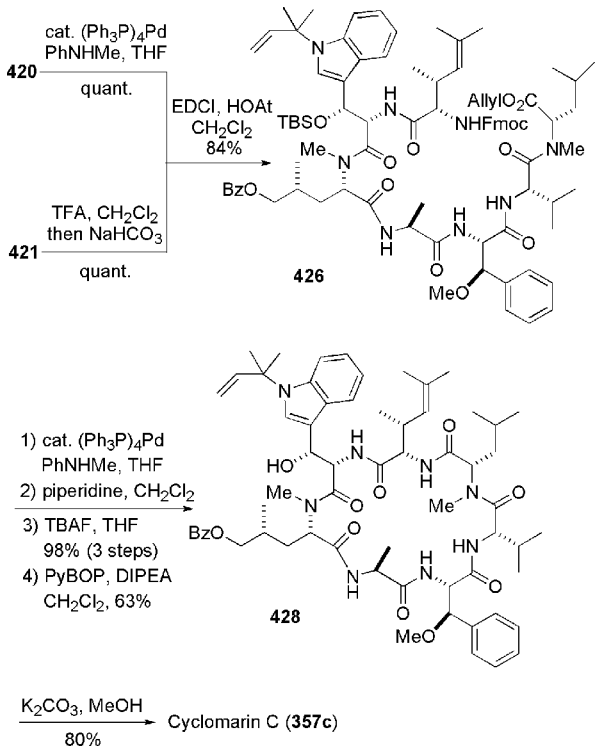
After respective deprotection of **420** and **421**, the coupling using EDCI/HOAT afforded the linear precursor **426**, as shown in Scheme 90. Successive removal of the allyl, Fmoc, and TBS groups, followed by macrolactamization with PyBOP/DIPEA, afforded the cyclic lactam **428** in 63% yield. Alkaline treatment of **428** produced cyclomarin C (**357c**). Removal

Scheme 89



of the TBS function proved to be essential before macrocyclization.

Scheme 90



8. Conclusion

Complete racemization (or epimerization)-free peptide synthesis during the fragment coupling, i.e., coupling of acylated amino acids or peptides with amino acids or peptides, might be a never-ending problem as long as activation of the *C*-terminal carboxyl group is necessary prior to coupling with amine components. The situation is quite similar to the complete stereoselective formation of glycosyl bonds (α/β) in saccharide synthesis. However, the present status of the linear peptide synthesis has reached a high degree of perfection mainly due to development of excellent urethane-type protective groups, the Boc, Cbz, or Fmoc groups, as well as development of the solid-phase technology pioneered by Merrifield. In contrast, macrocyclization of linear peptides will sometimes still pose problems such as low yield, epimerization, selection of a suitable cyclization point, necessity of high dilution conditions, etc. Future computational chemistry progress might suggest a suitable cyclization point in consideration of synthetic strategies. Further, many cyclic peptides and depsipeptides of marine origin contain unusual (non-proteinogenic) amino acids and aliphatic portions as building blocks, efficient construction of which is another important problem to solve before total synthesis. Thus, new methods, reagents, and catalysts are always needed for facile and convenient larger scale synthesis of peptides.

Further investigations on the constituents of marine organisms will provide new cyclic peptides and depsipeptides having exciting structures and biological activities. Total synthesis of these peptides will be a new and attractive challenging problem. In addition, since proposed structures have been quite often revised by synthetic works as described in the Introduction, total synthesis will play an important role for structure determination. A recent review by Nicolaou and Snyder fully describes the role of chemical synthesis in modern structure elucidation of natural products.[164]

Definitely, cyclic peptides of marine origin will play an important role to provide lead compounds and/or lead structures for searching new medicines and some other biologically useful compounds.

By the way, why do marine organisms produce such interesting cyclic peptides and what are their roles for themselves?

9. Acknowledgments

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10. Abbreviations

Aloc	CH_2=$CHCH_2OCO$
BEP	2-bromo-1-ethylpyridinium tetrafluoroborate
BMTB	2-bromo-3-methyl-4-methyl thiazolium bromide
Boc	Bu^tOCO
BOP	benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate

BopCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bppb	1,4-bis(diphenylphosphino)butane
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
Burgess reagent	$Et_3N^+SO_2N^-CO_2Me$
Bzl	benzyl
Cbz	$PhCH_2OCO$
CMD	chemical manganese dioxide
CSA	10-camphorsulfonic acid
DAST	$(Et_2N)S^+F_3^-$
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	c-C_6H_{11}−N=C=N−C−C_6H_{11}
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Deoxo-Fluor	$(MeOCH_2CH_2)_2NSF_3$
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DEPC	$(EtO)_2P(O)CN$
Dess−Martin	1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxal-3-(1*H*)-one periodinane
DIAD	*i*-PrO_2C−N=N−CO_2-*i*-Pr
DIBAL	*i*-Bu_2AlH
DIC	*i*-Pr−N=C=N-*i*-Pr
DIPEA	*i*-Pr_2NEt
DMAP	4-(dimethylamino)pyridine
DPPA	$(PhO)_2P(O)N_3$
dppf	1,1′-bis(diphenylphosphino)ferrocene
EDCI	$Me_2N(CH_2)_3N$=C=N−Et
FDPP	$Ph_2P(O)OC_6F_5$
Fmoc	9-fluorenylmethyloxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HBTU	*O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphortriamide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HOSu	*N*-hydroxysuccinimide
Hpr	pipecolic acid
IBX	*o*-iodoxybenzoic acid
Lawesson's reagent	2,4-bis(4-methoxyphenyl-1,3-dithia-2,4-diphosphetane-2,4- disulfide
Martin's sulfurane	diphenyl bis(1,1,1,3,3,3)-hexafluoro-2-phenyl-2-propyl)-sulfurane
Mes	mesitylene
MOM	$MeOCH_2$
Ms	$MeSO_2$
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
MTM	(methylthio)methyl
NMO	*N*-methylmorpholine *N*-oxide
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PyAOP	(7-azabenzotriazol-1-yloxy)tripyrrolinophosphonium hexafluorophosphate
PyBOP	(1*H*-benzotriazol-1-yloxy)tripyrrolinophosphonium hexafluorophosphate
TBAF	Bu_4NF
TBDPS	Bu^tPh_2Si
TBS	Bu^tMe_2Si
Tce	Cl_3CCH_2
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Teoc	$Me_3Si(CH_2)_2OCO$
TES	Et_3Si
Tf	CF_3SO_2
TFA	CF_3CO_2H
TIPS	*i*-Pr_3Si
TMS	Me_3Si
TMSE	$Me_3SiCH_2CH_2$
TPAP	Pr_4NRuO_4
Tr	trityl
Troc	Cl_3CCH_2OCO

11. References

(1) Abbreviations used for amino acids and the designations of peptides follow the rules of the IUPAC−IUB Commission on Biochemical Nomenclature in *J. Biol. Chem.* **1985**, *260*, 14. Amino acid symbols denote the L-configuration unless stated otherwise. For other abbreviations, see section 10.

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