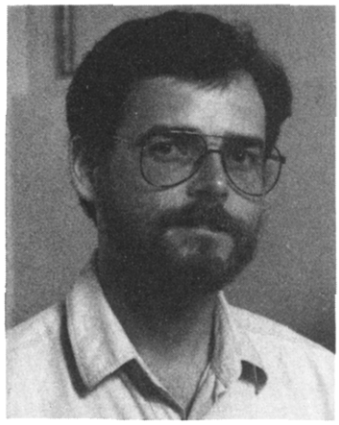
Synthetic Studies of Biologically Active Marine Cyclopeptides

Peter Wipf

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received April 25, 1995 (Revised Manuscript Received June 16, 1995)

Contents



Peter Wipf grew up near Lenzburg in Switzerland and studied chemistry at the University of Zürich. He received his Ph.D. in 1987, under the direction of Heinz Heimgartner. After postdoctoral studies with Robert E. Ireland at the University of Virgina, he joined the Chemistry Department at the University of Pittsburgh as an Assistant Professor in 1990. His research interests include the total synthesis of natural products, the application of organometallic reagents in organic synthesis, and bioorganic chemistry. He is an NSF Presidential Faculty Fellow, an A. P. Sloan Foundation Fellow, an Eli Lilly Grantee, and a recipient of the Ruzicka and American Cyanamid Faculty Awards.

I. Introduction

Marine organisms are the source of a great variety of biologically active secondary metabolites. Many of these are heterocyclic and contain considerably modified amino acid building blocks. This review focuses on marine cyclopeptides and cyclodepsipeptides of >10-membered ring sizes. Several aspects of the diverse structure and the properties of this loosely defined class of compounds render them particularly interesting to synthetic and medicinal chemistry alike. Whereas many natural products show promise for therapeutic potential in *in vitro* biological screening, small cyclopeptides are generally among the more promising lead structures. The absence of ionized C- and N-termini results in a more facile crossing of membrane barriers, greater resistance to *in vivo* enzymatic degradation, and improved bioavailability. Cyclization considerably reduces the conformational flexibility of the peptide backbone and facilitates the determination and the rational manipulation of the biologically significant three-dimensional structures of active compounds.

Synthetic organic chemistry plays a central role in marine chemistry in general and in developing the therapeutic potential of bioactive marine cyclopeptides and cyclodepsipeptides in specific. Often only small quantities of marine natural products can be isolated from an exploration site, and many of the marine species have been resistant to laboratory culturing. Since symbiotic relationships are common among marine life forms, there are even considerable ambiguities about the actual biological source of certain samples. Therefore, the evaluation of the biological potential of promising bioactive compounds frequently has to await the development of a suitable synthetic route. In addition, the small sample quantities and the unusual structural features of marine natural products make structure elucidation extremely challenging even with modern spectroscopic tools and leave doubts especially on stereochemical assignments. It is possible that more than 50% of all structures of marine natural products that were originally assigned have to be corrected upon reinspection, usually after synthetic work highlights ambiguities. Therefore, the preparation of sufficient quantities of material for further studies and the proof of structure, two of the traditional major missions of total synthesis, are central contributions of synthetic chemistry to marine biotechnology.

The presence of unusual amino acid and heterocyclic building blocks and challenges in macrocyclization has stimulated the interest of synthetic chemists in marine cyclopeptides and cyclodepsipeptides. Very often, new synthetic methodology and strategy have to be developed to achieve the target structure, and frequently a total synthesis has been followed by fruitful analyses of conformational properties and biological modes of action. It is therefore of general value to compare the different synthetic approaches toward marine cyclopeptides. Rather than being comprehensive, this review focuses on examples of broad interest and the most recent work in this area.[1] Since biological activity and conformation are closely correlated and secondary structure effects are often a major consideration in devising cyclization strategies, the available solid-state and solution structural information is included in the discussion.

0009-2665/95/0795-2115$15.50/0

II. Cyclopeptides from Ascidians

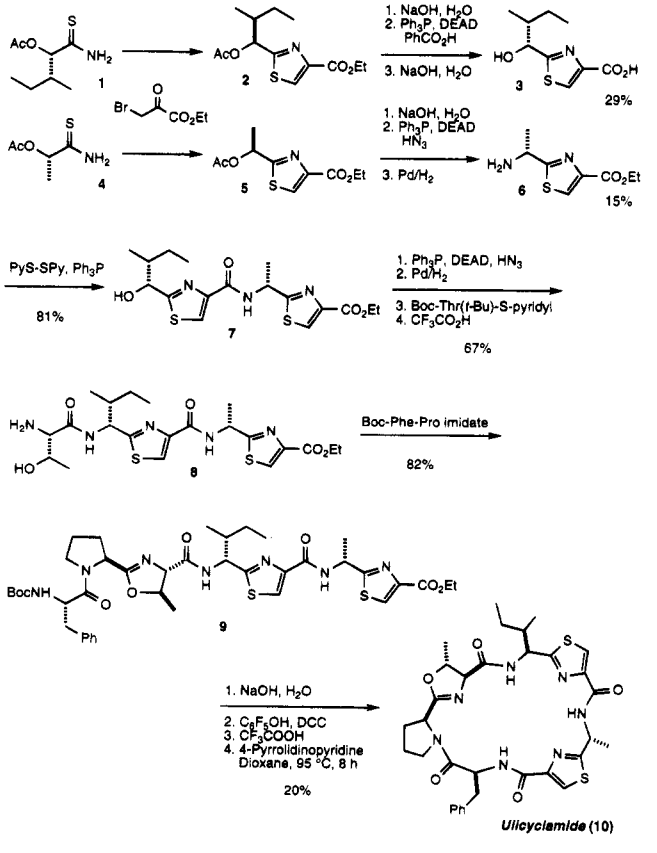
Nitrogenous secondary metabolites from ascidians have been reviewed recently.[2] A broad range of bioactivities such as cytotoxicity; tumor promotion; and anticancer, antiviral, and antiinflammatory activities have been reported for extracts from ascidians and other tunicates. Most of the synthetic work in this area has focused on *Lissoclinum* peptides and didemnins.

A. *Lissoclinum* Peptides

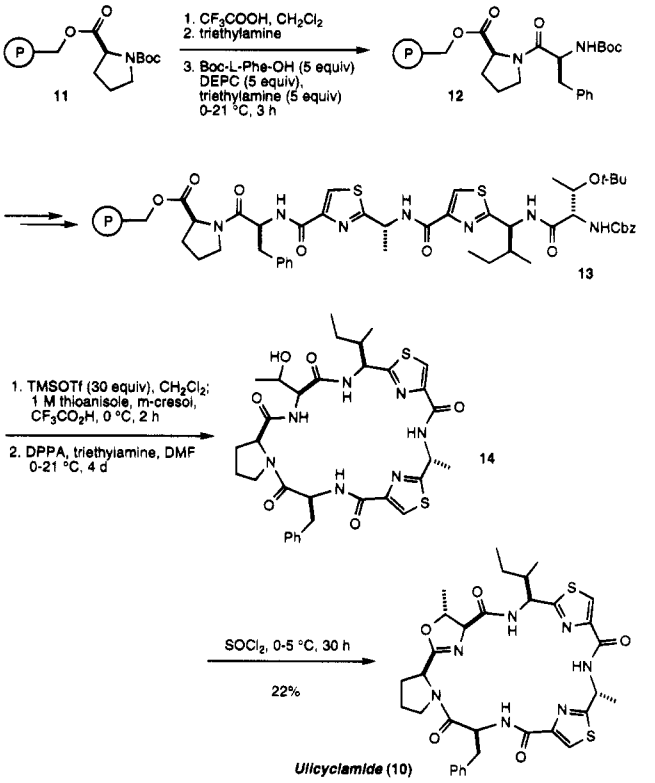
In *Lissoclinum* cyclopeptides, small heterocycles (oxazolines, oxazoles, thiazolines, and thiazoles) alternate within standard amino acid segments (the heterocycle coming between the terminal carbonyl of the acid function and the α-carbon; in this paper, this linkage will be indicated by the amino acid name hyphenated to the heterocycle name). The majority of marine metabolites show moderate to strong cytotoxic activities, with ulithiacyclamide and lissoclinamide 7 being the most potent (IC_{50} values of <50 ng/mL in SV40-transformed fibroblasts cell lines (MRC5CV1)). Patellamide D was recently reported to reverse multidrug resistance in a human leukemia cell line.[3]

The first synthesis of a *Lissoclinum* peptide, ulicyclamide (**10**), was reported by Schmidt and Gleich in 1985.[4,5] This 21-membered macrocycle was isolated from *Lissoclinum patella* and its structure was elucidated by Scheuer and Ireland.[6,7] Thiazoles **2** and **5** were prepared by Hantzsch condensation of thioamides **1** and **4** with ethyl bromopyruvate (Scheme 1). Mitsunobu inversions at the stereocenters provided acid **3** and amine **6** that were combined in a

Scheme 1



Scheme 2

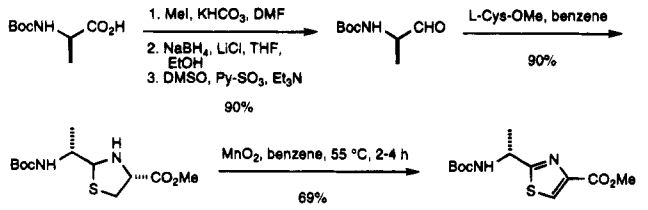


redox condensation to give amide **7**. The use of optically active α-acyloxy thioamides such as **1** and **4** was necessary since racemic thiazole derivatives are obtained in the classical Hantzsch synthesis with optically active α-acylamino thioamides.[8] Transformation of the hydroxyl group of **7** into an amino group was achieved by a third Mitsunobu reaction, and reduction and N-acylation with protected L-threonine followed by cleavage of the two protective groups gave amino alcohol **8**. Condensation with Boc-phenylalanylproline imidic ester provided oxazoline heptapeptide **9**. Hydrolysis of the thiazole ester, conversion to the activated pentafluorophenyl ester, acidic cleavage of the Boc group, and cyclization as a 0.2 mM solution in hot dioxane in the presence of 4 equiv of 4-pyrrolidinopyridine gave ulicyclamide (**10**) in 20% yield.

Interestingly, Sugiura, Hamada, and Shioiri successfully applied a solid-phase strategy toward an alternative synthesis of ulicyclamide.[9] A Boc-L-proline-polystyrene resin was sequentially coupled to excess Boc-L-phenylalanine, Boc-D-alanine-thiazole, Boc-L-isoleucine-thiazole, and *O-tert*-butyl-Cbz-L-*allo*-threonine in the presence of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) and triethylamine in DMF (Scheme 2).

Introduction of the thiazole amino acids required longer reaction times (0−21 °C, 12 h), and an extensive washing procedure was applied to the resin between each coupling step. Removal of the peptide from the solid support and deprotection was achieved with 2 M trimethylsilyl triflate and trifluoroacetic acid in the presence of cation quenchers. After chromatography on a Dowex 50W×4 column, the crude peptide was treated with DPPA to give the macrocycle **14**. Conversion of the *allo*-threonine residue to the desired *trans*-oxazoline with thionyl chloride completed the total synthesis of ulicyclamide

Scheme 3



in a highly respectable 22% overall yield from the starting resin.

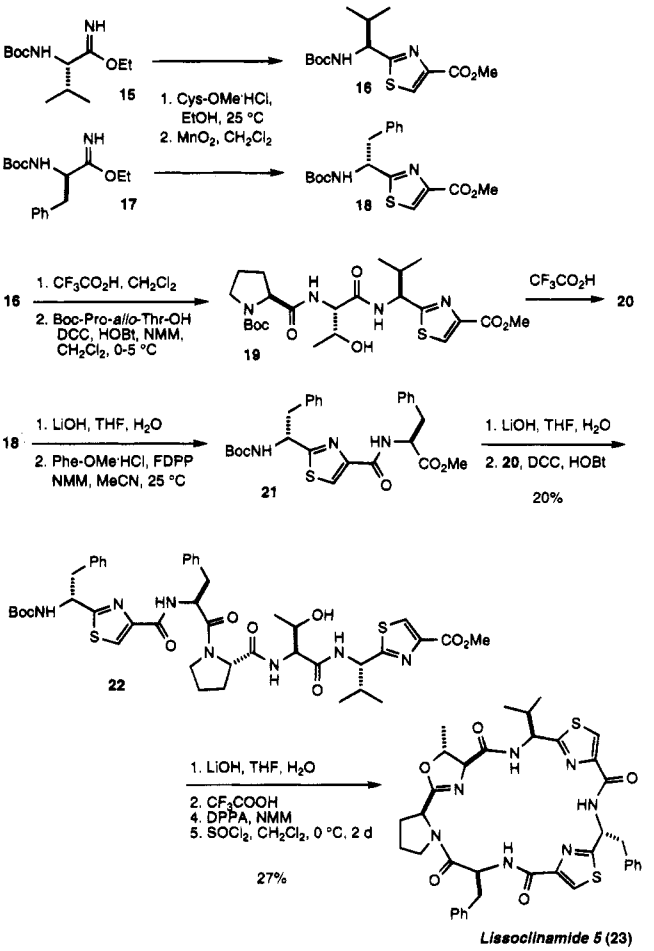
Optically pure thiazole amino acids for this synthesis were prepared by oxidation of thiazolidines with chemical manganese dioxide manufactured industrially for batteries (Scheme 3).[10] This provided results superior to standard activated manganese dioxide.

More recently, Boden and Pattenden[11] reported the total synthesis of lissoclinamide 5, another *L. patella* metabolite isolated by Hawkins and Watters[12] as well as Schmitz and van der Helm[28] and co-workers. Watters et al. have also discussed structure–activity relationships of the cytotoxic lissoclinamides.[13] Stereochemical assignments of thiazoline- and thiazole-containing cyclopeptides, however, are particularly challenging, since the standard hydrolytic degradation protocols lead to considerable racemization of these residues. Indeed, the structure of lissoclinamide 5 had to be reassigned to **23** as a consequence of the synthetic work by Boden and Pattenden. The synthesis of the natural product is outlined in Scheme 4.

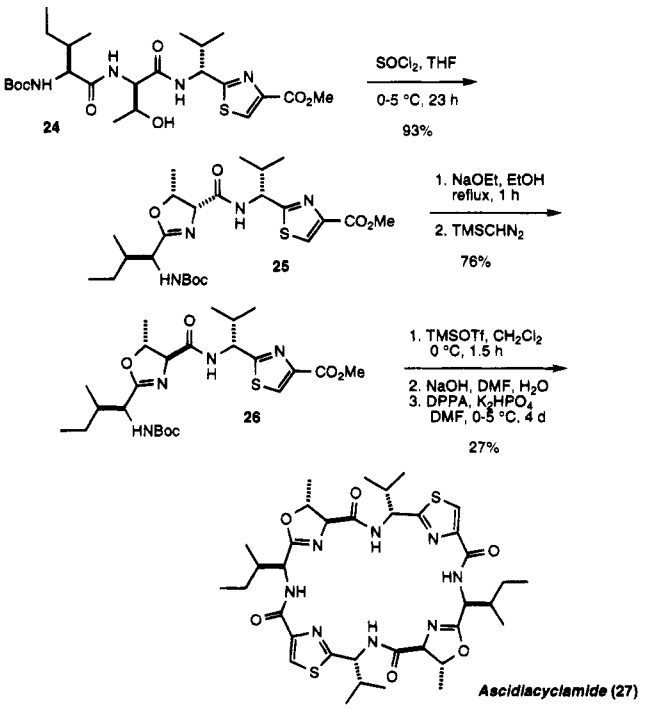
Synthesis of thiazole segments **16** and **18** was accomplished by condensation of cysteine esters and N-protected imidates derived from chiral amino acids.[14] Deprotection of the N-terminus of **16** and coupling with Boc-L-prolyl-L-*allo*-threonine acid in the presence of DCC, 1-hydroxybenzotriazole (HOBt), and *N*-methylmorpholine (NMM) gave tetrapeptide **19** that was further converted to its trifluoroacetate salt **20**. After saponification of **18**, coupling with phenylalanine methyl ester and pentafluorophenyl diphenylphosphinate (FDPP), followed by saponification of tripeptide **21** and segment coupling with DCC/HOBt produced heptapeptide **22** in 20% overall yield. Sequential deprotection of C- and N-termini, macrolactamization with diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$), and oxazoline formation by treatment with thionyl chloride gave synthetic material **23** that was identical to natural lissoclinamide 5, whereas the synthetic macrocycle obtained by pursuit of the originally proposed[13,28] stereochemistry was spectroscopically clearly different. In terms of sequence and stereochemistry, there is a close resemblance between lissoclinamide 5 and ulicyclamide.

The first synthesis of a 24-membered *Lissoclinum* peptide, ascidiacyclamide (**27**), was reported by Hamada, Kato, and Shioiri in 1985.[15] Tetrapeptide **24**, prepared by segment coupling of Boc-L-isoleucyl-D-threonine and D-valine-thiazole methyl ester, was cyclized to the oxazoline **25** by exposure to thionyl chloride in THF (Scheme 5). Epimerization of the *cis*-oxazoline to the *trans*-oxazoline proceeded with sodium ethoxide in refluxing ethanol, and, due to partial hydrolysis of the C-terminal methyl ester function, reesterification with (trimethysilyl)diazomethane was necessary to give methyl ester **26** in good yield. Surprisingly, the relatively harsh epimerization conditions did not appear to lead to partial racemization at the sensitive[16] chiral center derived from L-isoleucine. After chemoselective removal of the N-terminal Boc group with trimethylsilyl triflate

Scheme 4



Scheme 5



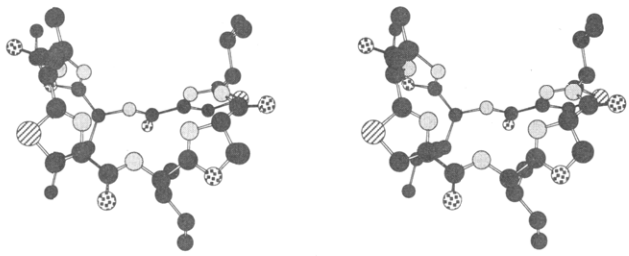


Figure 1. Stereoprojection of X-ray structure of ascidiacyclamide.

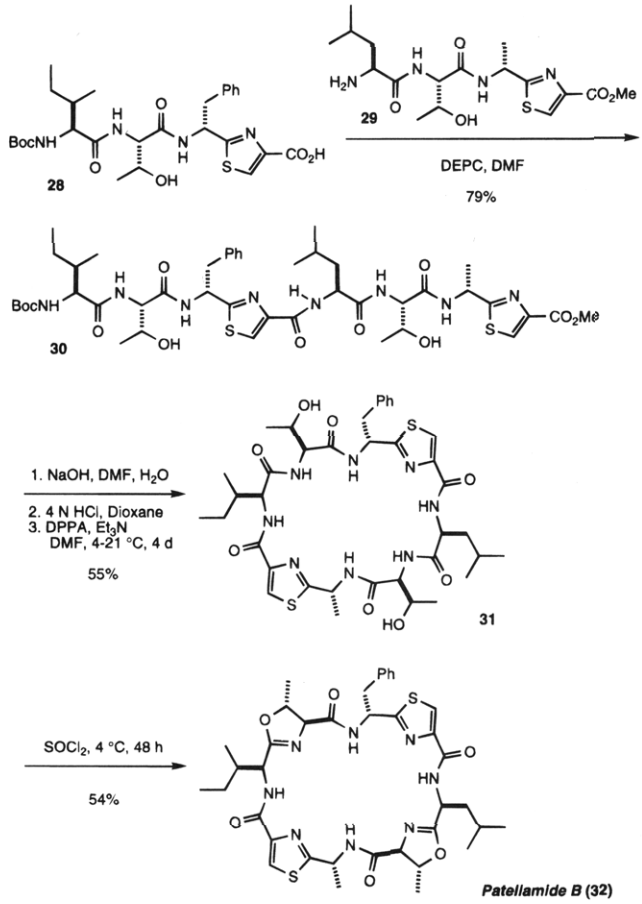
and saponification in aqueous DMF at 0 °C, the resulting sodium salt was dried over molecular sieves. Subsequent cyclodimerization in 5 mM solution in DMF in the presence of DPPA provided ascidiacyclamide in 27% yield. This synthesis also established the absolute configuration of this cytotoxic cyclopeptide which had been isolated from an unspecified Australian ascidian by a research group from the Suntory institute in 1983.[17]

A rectangular, saddle-shaped conformation was detected by X-ray analysis for the C_2-symmetric ascidiacyclamide[18] (Figure 1). There are no intramolecular hydrogen bonds present, but all N−H bonds and nitrogen lone pairs are directed toward the center of the macrocycle. This conformation appears essentially unchanged in solution.[19]

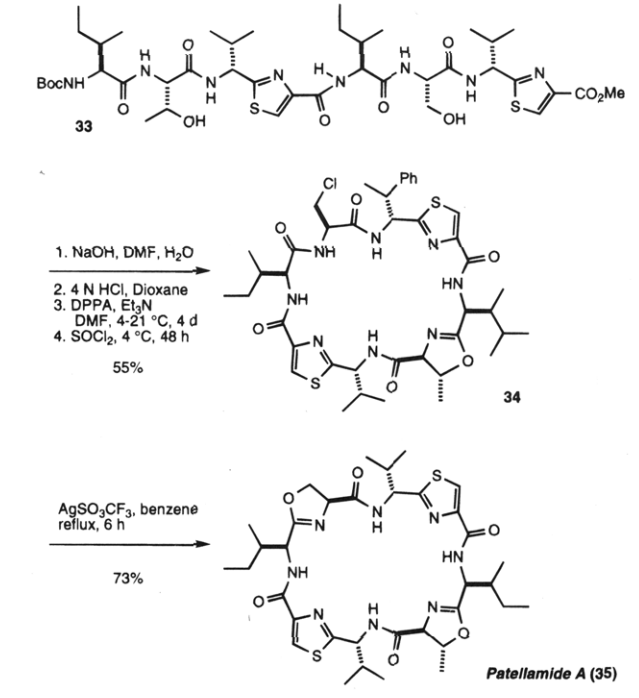
Further work by Hamada, Shibata, and Shioiri on the total syntheses of patellamides B and C led to a reassignment of the structures originally proposed by Ireland and co-workers[20] for these cytotoxic *Lissoclinum patella* metabolites.[21] The proposed directly linked thiazole-oxazoline units were corrected to a closely ascidiacyclamide-related backbone structure (Scheme 6). Since the patellamides are devoid of C_2-symmetry, however, the previously applied efficient cyclodimerization strategy had to be replaced by a less direct synthetic approach.[22] Segment coupling of thiazoles **28** and **29** with DEPC gave Boc-L-isoleucyl-L-*allo*-threonyl-D-phenylalanine-thiazole-L-leucyl-L-*allo*-threonyl-D-alanine-thiazole methyl ester **30** in 79% yield (Scheme 6). Saponification of **30** with 1 N NaOH in DMF followed by removal of the Boc group with 4 N HCl in dioxane afforded the octapeptide hydrochloride which was subjected to cyclization with excess DPPA and triethylamine in a 1 mM solution of DMF at 4 °C for 3 days and at room temperature for 1 day to afford the cyclopeptide **31** in 55% yield. Treatment of **31** with excess thionyl chloride at 4 °C for 2 days afforded patellamide B (**32**) identical to the natural material.

A similar strategy by Hamada, Shibata, and Shioiri culminated in the synthesis of patellamide A (**35**, Scheme 7).[23] Cyclization of the L-isoleucyl-L-*allo*-threonyl-D-valine-thiazole-L-isoleucyl-L-seryl-D-valine-thiazole octapeptide **33** with DPPA proceeded in good yield as expected. However, simple chlorination of the serine side chain was observed upon treatment of the cyclopeptide with thionyl chloride. Formation of β-chloroalanine is commonly found with serine residues in the thionyl chloride protocol, and subsequent cyclization to give oxazolines can be effected by exposure to silver(I) salts, albeit sometimes with serious epimerization at chiral centers exocyclic to the oxazoline ring.[24,25]

Scheme 6

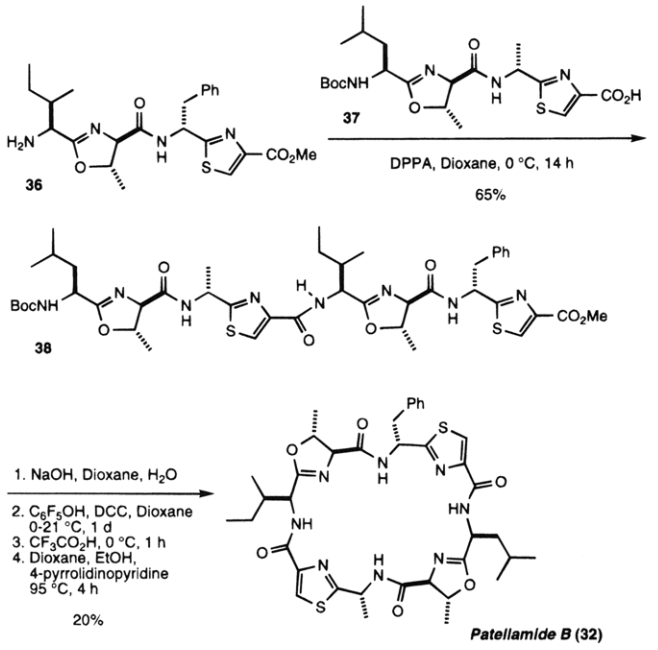


Scheme 7



A second synthesis of patellamide B, but with oxazoline formation preceding macrocyclization, was reported by Schmidt and Griesser.[26] In agreement with Shioiri's group, these authors also noticed the spectroscopic differences between synthetic material corresponding to the original structure assignment and the actual natural product. The total synthesis of patellamide B confirmed the corrected structure

Scheme 8



(Scheme 8). *trans*-Oxazolines **36** and **37** were prepared by condensation of L-threonine amino alcohols with amino acid imidates. Peptide coupling in the presence of DPPA provided octapeptide **38** in 65% yield.

Saponification, conversion to the C-terminal pentafluorophenyl ester, cleavage of the Boc group, and macrolactamization under high dilution conditions gave patellamide B in 20% yield.

Comparison of the Shioiri and Schmidt protocols for patellamide B synthesis reveals that independent of the different retrosynthetic disconnections and the presence or absence of oxazoline heterocycles in the backbone of the seco-octapeptide, a high-yielding macrocyclization can be achieved. In contrast, cyclization of peptides with predominant regular α-amino acid building blocks often requires considerable experimentation toward the best linear precursor.[27] The thiazole rings appear to restrict the conformational flexibility and facilitate ring closure. This is supported by Shioiri's high-yielding introduction of two oxazoline subunits into the cyclooctapeptide sequence, a reaction that would have been likely to fail if the secondary structure of the precursor was significantly different from the product after heterocycle formation. Nonetheless, comparison of the X-ray structures of patellamide D and ascidiacyclamide shows that structurally very similar macrocycles can have quite different preferred conformations[28] (Figure 2). Shaped like a twisted "figure eight", the solid-state conformation of patellamide D (**39**) is stabilized by four transannular hydrogen bonds. The isoleucine/oxazoline pairs form nearly ideal type II β-turns that account for two of the four intramolecular hydrogen bonds.

It has been suggested[29] that the deviation from a C_2-symmetrical structure in these cyclooctapeptides is responsible for shifting the molecular shape from the saddle-shaped ascidiacyclamide conformation to the folded patellamide D type. Indeed, the almost C_2-symmetric patellamide A still takes on a saddle-shaped rectangular form by X-ray crystal analysis.[30]

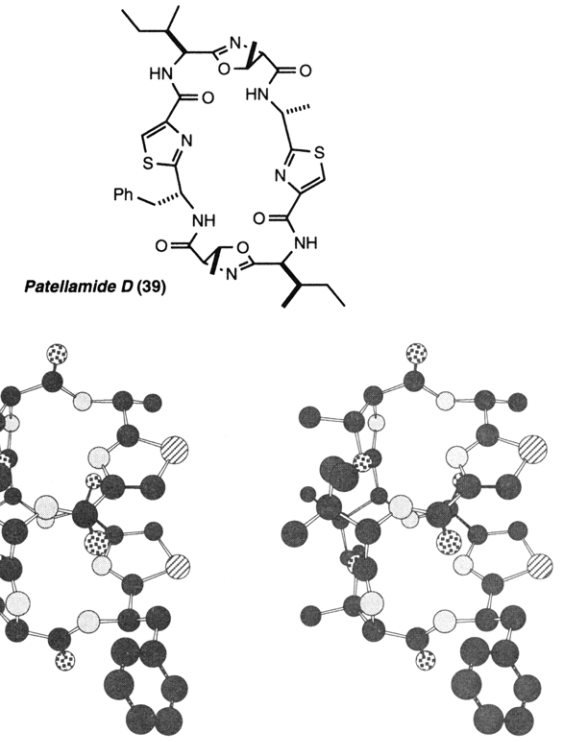
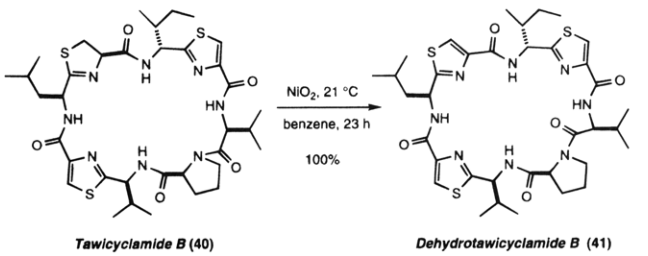


Figure 2. Stereoview of the X-ray of patellamide D (**39**).

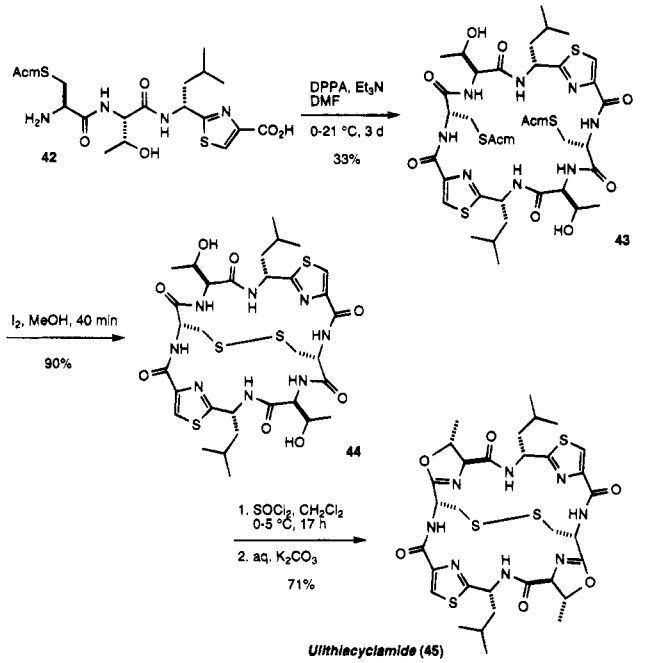
The recently isolated tawicyclamides nicely demonstrate that a conformational transition between patellamide D and ascidiacyclamide structures is indeed possible.[31] The 24-membered tawicyclamide B (**40**) has a twisted solid-state conformation similar to patellamide D. Oxidation to dehydrotawicyclamide B (**41**) induces a *cis*-valine−proline amide bond to isomerize to *trans*, and the conformation shifts to a saddle shape reminiscent of ascidiacyclamide.[31] The tawicyclamides as well as their dehydro analogs exhibit only weak cytotoxicity.



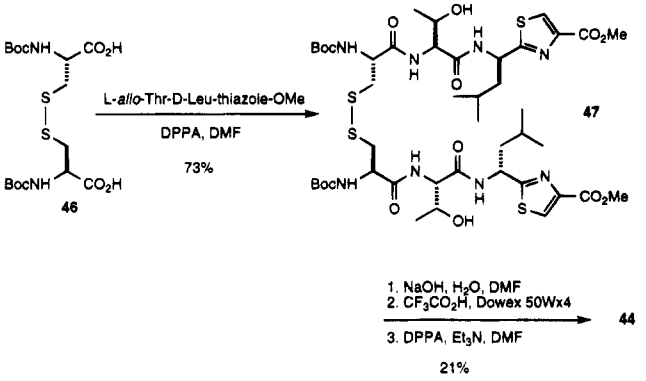
Ulithiacyclamide (**45**) was first isolated from the ascidian *Lissoclinum patella* and its structure was elucidated by Ireland and Scheuer.[6,7,20] It is one of the most potent *Lissoclinum* peptides (*in vitro* IC_{50} = 40 ng/mL against L1210 leukemia cells). The compound was shown to be a potentiator of cytotoxicity of the anticancer drug bleomycin and to inhibit predominantly protein biosynthesis.[32] The presence of a disulfide bridge accross the C_2-symmetric macrocycle adds an interesting structural variation to this *Lissoclinum* peptide.

The first total synthesis of ulithiacyclamide was achieved by Kato, Hamada, and Shioiri in a strategy closely related to their ascidiacyclamide synthesis (Scheme 9).[33] Cyclodimerization of *S*-(acetamidomethyl)-Boc-L-cysteine-L-*allo*-threonine-D-leucine-thiazole **42** (Acm = acetamidomethyl) with DPPA as a 5 mM solution in DMF provided the 24-membered

Scheme 9



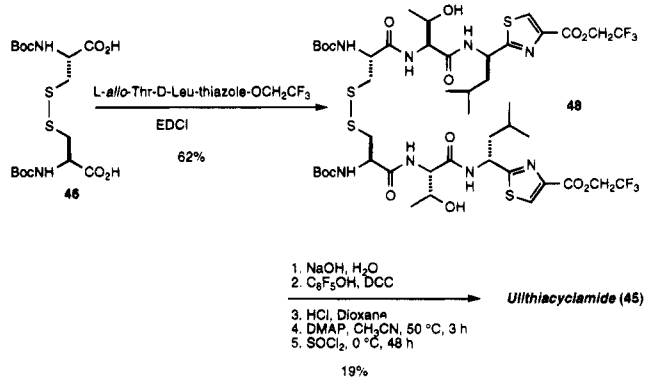
Scheme 10



macrocycle **43** in 33% yield. Removal of the Acm protective groups and disulfide formation was accomplished by exposure of **43** to 5 equiv of iodine in methanol. Alternatively, this compound was also obtained in 15% overall yield by chain extension of cystine **46** and double cyclization (Scheme 10). Treatment of **44** with a large excess of thionyl chloride in methylene chloride provided ulithiacyclamide (**45**) in 71% yield.

Boc-cystine was also chosen as starting material in Schmidt and Weller's synthesis of ulithiacyclamide (Scheme 11).[34] Coupling with 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide (EDCI) led to dimer **48** in 62% yield. Saponification of the trifluoroethyl esters, followed by conversion to the activated pentafluorophenyl esters, acidolytic cleavage of Boc, tandem cyclization in warm acetonitrile, and oxazoline formation with thionyl chloride provided ulithiacyclamide in 19% yield from **48**. It is interesting to compare Shioiri's and Schmidt's macrocyclization protocols for **45**. Macrocyclization with DPPA is straightforward in adding the coupling agent directly to the amino acid salt, but the reaction requires low temperatures, proceeds slowly, and results only in 21% of product. Cyclization via the pentafluorophenyl esters requires an additional step, e.g. active ester formation with DCC, but the reaction is considerably

Scheme 11



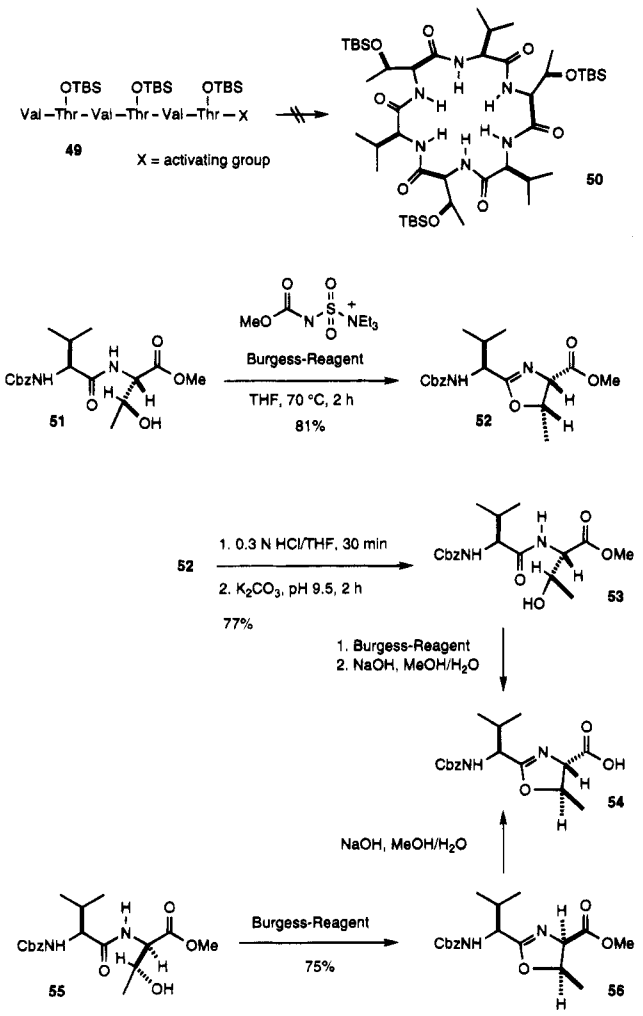
faster since elevated temperatures (50−100 °C) can be employed. For ulithiacyclamide, an overall higher yield (39% for the deprotection−activation−cyclization sequence) was achieved by the latter route. It is quite likely that the pentafluorophenyl ester protocol is especially superior for macrocyclization of peptides when the linear precursor is conformationally biased against cyclization, since higher temperatures can be used. With sensitive or easily epimerizable substrates, however, the milder conditions of the DPPA protocol are more attractive.[35] In the case of ulithiacyclamide, this was a minor concern, since activation or the terminal thiazole carboxylates circumvented the problem of epimerization of C-terminal amino acid residues.[36]

As expected by its C_2-symmetry and the constraints imposed by the disulfide bridge, ulithiacyclamide appears to assume an ascidiacyclamide-like saddle-shaped conformation in solution based on NMR spectroscopy.[37] The presence of the oxazoline rings and the disulfide bond was proposed to be responsible for the high cytotoxic activity of ulithiacyclamide.[38]

The first synthesis of an 18-membered *Lissoclinum* peptide, westiellamide (**60**), was reported by Wipf and Miller in 1992.[39] This C_3-symmetric cytotoxic macrocycle was first isolated from the ascidian *Lissoclinum bistratum* by Watters and co-workers, who named the compound cycloxazoline.[40] Interestingly, the terrestrial blue-green alga *Westiellopsis prolifica* yielded an identical compound, characterized independently as westiellamide.[41] This is evidence for the possible involvement of prokaryotic symbionts (e.g. *Prochloron* sp.) in the biosynthesis of certain *Lissoclinum* peptides. There is strong structural resemblance between westiellamide and the bistratamides, another group of cyclohexapeptides isolated from *L. bistratum*.[42] The moderately cytotoxic westiellamide was recently shown to interfere with cytokinesis.[43]

Whereas the initial approach toward westiellamide/cycloxazoline, the preparation of (Val-Thr)$_3$ (**50**) followed by oxazoline formation, failed due to an unfavorable extended conformation of the precursor peptide **49**,[44] the cyclotrimerization of dipeptide oxazoline **54** provided the natural product with high efficiency (Schemes 12 and 13).[39,45] Treatment of the readily available Cbz-L-valyl-L-threonine (**51**) with Burgess reagent in THF provided oxazoline **52** without epimerization at the valine α-carbon.[46] Subsequent hydrolysis of **52** with dilute acid gave an *O*-acyl amine, which was *in situ* rearranged to the *N*-acyl alcohol to give the *allo*-threonine dipeptide **53**. This

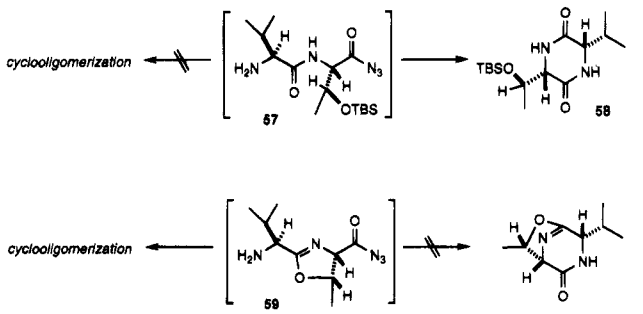
Scheme 12



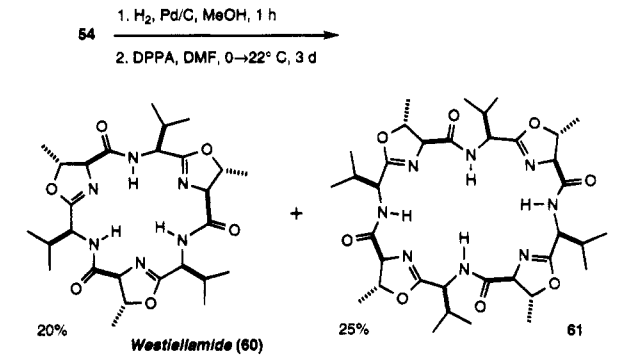
protocol allows a straightforward preparation of multigram quantities of rare threonine isomers from proteinogenic threonine within an intact peptide chain and a minimum of synthetic manipulations.[47] Subsequent cyclization of Cbz-L-valyl-L-*allo*-threonine **53** and saponification led to the desired *trans*-oxazoline acid **54**. In an even more direct approach, this acid was prepared in two steps and high yields from Cbz-L-valyl-D-threonine **55** upon oxazoline formation (which inverted the stereochemistry at the threonine β-carbon) and room temperature ester hydrolysis with 2 equiv of sodium hydroxide, which also quantitatively led to inversion of stereochemistry at the former threonine α-carbon (Scheme 12).[45]

Preparation of cyclic hexapeptides by cyclotrimerization of dipeptide sequences is usually not feasible, since diketopiperazines **58** are formed much more rapidly.[48] For oxazoline **59**, however, diketopiperazine formation is inaccessible due to the rigid *trans*-orientation of the modified amide linkage fused into the five-membered ring.

Indeed, after removal of the Cbz protective group by hydrogenolysis, activation of the C-terminal carboxylate with DPPA in a 40 mM solution of DMF led in good overall yields to macrocyclic peptides (Scheme 13).[39] Westiellamide (**60**) and the 24-membered cyclotetramer **61** were isolated in overall yields of 20% and 25%, respectively. The distribution of these ring isomers reflects the conformational properties of the linear dipeptide oxazolines, which favor β-turn



Scheme 13



structures and considerably facilitate ring closure. Therefore, high dilution conditions are generally not required in the cyclization of short peptide segments containing these heterocycles.

There has been considerable speculation linking marine natural products in general and *Lissoclinum* peptides in specific to metal ion chelation and transport functions.[49] Systematic metal ion binding studies to synthetic westiellamide revealed a unique selectivity and affinity of the natural product to silver(I) ions.[50] X-ray analysis of the complex formed with a K_a of 2.8×10^{13} in MeOH/H_2O revealed a novel sandwich structure: A cluster of four silver cations contained within two neutral macrocyclic ligands. A further interesting aspect of this structure is the complete reorganization of the cyclopeptides upon silver binding. Both in solution and in the solid state, uncomplexed westiellamide assumes a flattened ascidiacyclamide-like conformation with the carbonyl groups pointing outward and all the nitrogen atoms oriented toward the center of the ring.[40] Upon metal chelation, the 18-membered macrocycles turn inside out and the carbonyl groups point inward toward the center silver atom in the C_3-symmetric planar Ag_4 cluster (Figure 3). Quite possibly, this considerable conformational reorganization upon binding contributes to the high level of reversibility of metal binding that was observed.

Additional evidence for metal complexation properties of *Lissoclinum* peptides comes from recent studies of copper(II) binding to the cyclooctapeptides patellamide D and ascidiacyclamide.[51]

Another synthesis of an 18-membered *Lissoclinum* peptide, bistratamide C (**67**),[52] was recently reported by Aguilar and Meyers.[53] Cyclodehydration of dipeptide **62** with Burgess reagent gave oxazoline **63** in 78% yield (Scheme 14). Oxidation with manganese dioxide in benzene followed by acidolytic cleavage of the Boc group gave the hydrochloride of **64**, which was sequentially coupled via the mixed anhydride to Boc-L-valine-thiazole and Boc-L-alanine-thiazole to

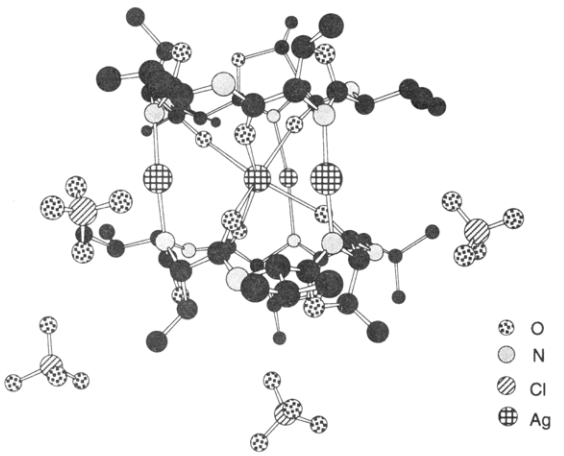
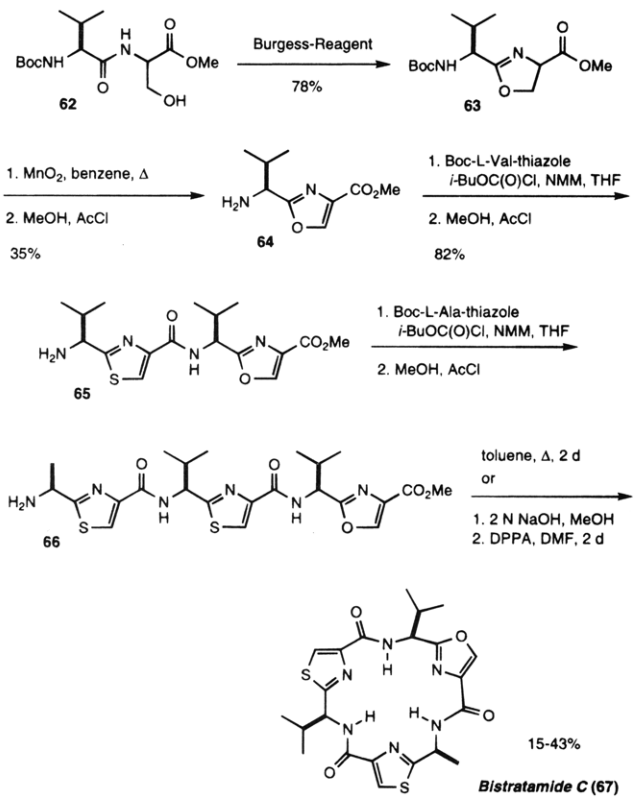


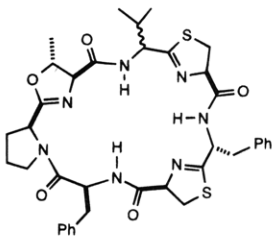
Figure 3. X-ray of $[(westiellamide)_2Ag_4](ClO_4)_4$ complex.

Scheme 14



give the hydrochloride of **66**. The necessary thiazoles were prepared enantiomerically pure by a modified Hantzsch reaction from the amino acid thioamides.[8c] Macrocyclization of **66** was performed in refluxing toluene for 2 days, which led to variable yields, or, after saponification, with DPPA in DMF at room temperature in 17% overall yield from tetrapeptide **65**.

In spite of the significant advances made in the synthesis of *Lissoclinum* peptides, the potentially greatest synthetic challenges in this group of marine cyclopeptides have not been met yet. Lissoclinamide 7,[13] for example, contains two thiazoline residues that are extremely easily epimerized[16,54] during synthetic and analytical manipulations. New methodology and synthetic strategy will have to be developed to access this and related thiazoline-containing *Lissoclinum* metabolites.



Lissoclinamide 7

B. Didemnins

In 1981, Rinehart and co-workers isolated a new class of cyclodepsipeptides from a marine tunicate *Tridemnum solidum* that showed potent antiviral, antitumor, and immunosuppressive activities.[55] In addition to didemnins A, B, and C (Figure 4), several other didemnins and nordidemnins have been identified to date.[56] Because of their exceptionally attractive biological profile, didemnins have been the focus of considerable attention. Didemnin B was indeed the first marine natural product to enter clinical trials.[56]

Total syntheses of didemnins were reported by Rinehart,[57] Schmidt,[58] Shioiri,[59] Jouin,[60] and Joullié[61] and co-workers, and the original structural assignment was corrected by synthesis.[62] The mechanism of action of the didemnins still remains to be elucidated, but advances toward the identification of specific cellular binding factors have been made.[63,64] An X-ray structure determination of didemnin B established the conformation of the 23-membered depsipeptide as a twisted "figure eight" with an attached type II β-turn with proline and *N*-methyl-D-leucine at the $i + 1$ and $i + 2$ positions, respectively. The tyrosine side chain and the β-turn subunit conspicuously extend out of the core of the molecule, but several additional groups are placed in an orientation potentially favorable for receptor interactions. Indeed, the extremely broad biological profile of the didemnins suggests that different sites are probably interacting with different receptors.

Recent reviews provide a comprehensive survey of synthetic and biological studies of didemnins.[1a,e] Therefore, the following discussion will be limited to two major syntheses, the preparation of didemnin B by Shioiri and co-workers in 1989[59] and a recent optimized protocol for the preparation of didemnin B analog **68**[65] by Joullié et al. that can be used for the synthesis of gram quantities of the target.

In Shioiri's synthesis,[59] a [3 + 3] segment condensation strategy was applied toward the didemnin macrocycle. For the preparation of the (hydroxyisovaleryl)propionyl-containing segment **72**, (*S*)-2-silyloxyisovaleric acid **69** was condensed with Meldrum's acid in the presence of diethyl phosphorocyanidate (DEPC), and alcohol **70** was immediately refluxed with benzyl alcohol in benzene to give, after C-methylation, the β-keto ester **71** (Scheme 15). The epimerizable methyl group in **71** equilibrates to the thermodynamically preferred orientation in the natural product. The control of the hydrogenolysis of the benzyl ester was rather delicate, since decarboxylation occurred readily, but immediate coupling of the crude reaction mixture with L-leucyl-L-proline methyl ester and O-desilylation gave segment **72** in 71% yield.

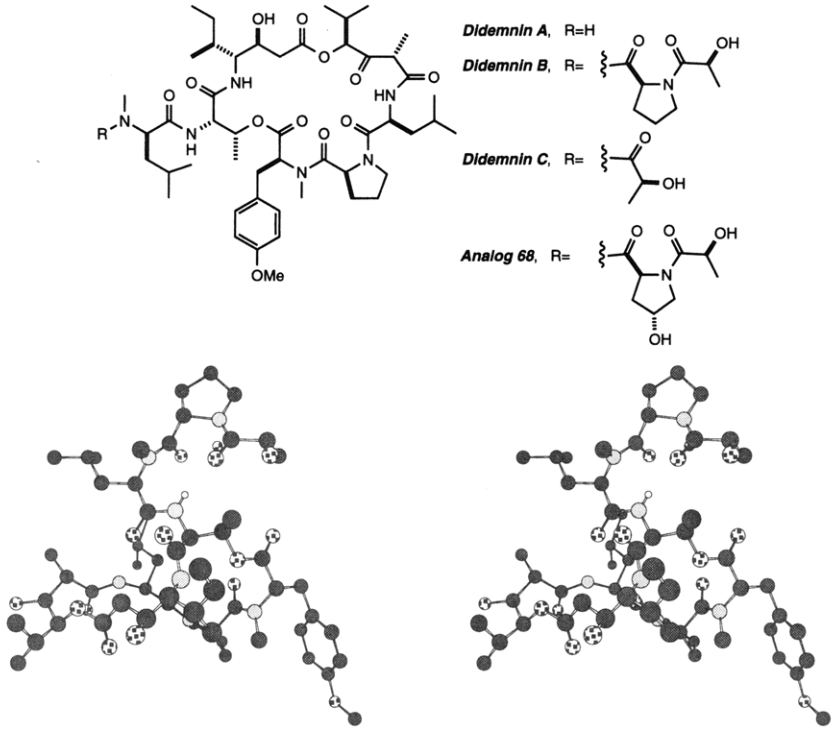
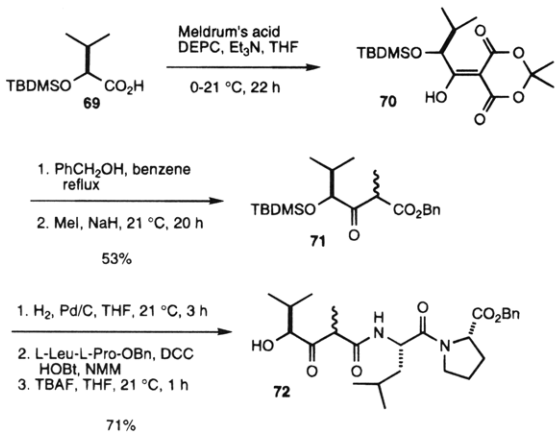
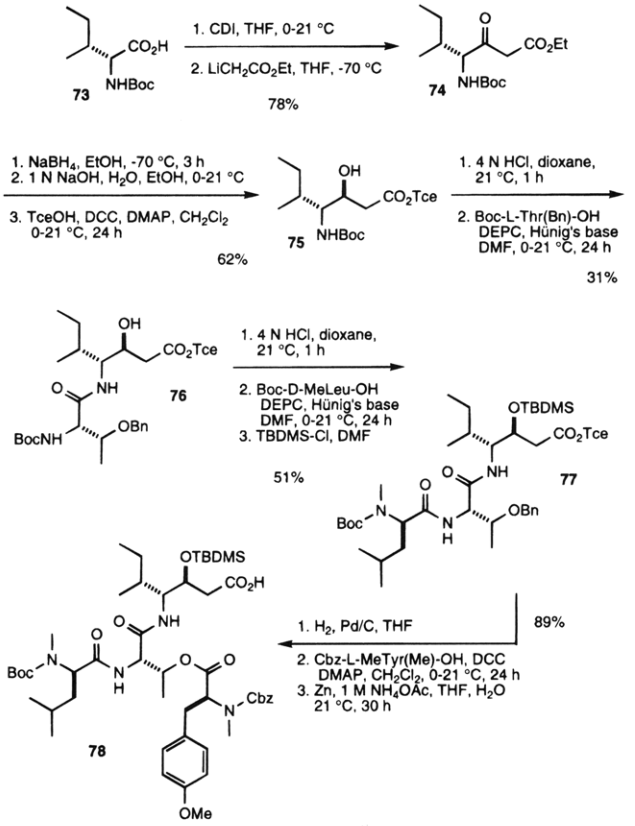


Figure 4. Stereoviews of X-ray structure of didemnin B.

Scheme 15



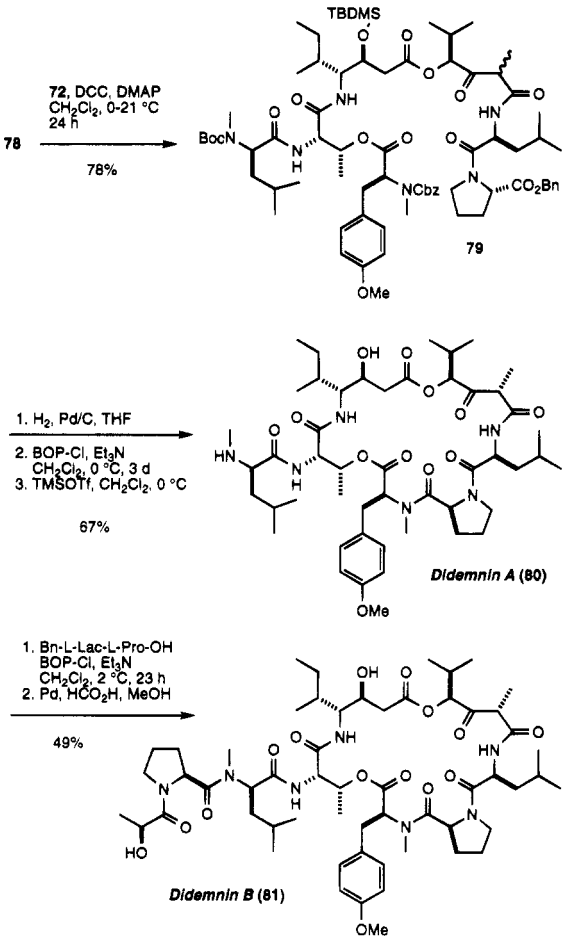
Scheme 16



The second segment contained an unusual isostatine unit that was obtained according to the method of Joullié by the addition of ethyl lithioacetate to the imidazolide prepared *in situ* from Boc-D-*allo*-isoleucine **73** and carbonyldiimidazole (CDI, Scheme 16). Subsequent ketone reduction with $NaBH_4$ proceeded with high stereoselectivity (>10:1). Exchange of the ethyl ester to the corresponding trichloroethyl (Tce) ester gave (3*S*,4*R*,5*S*)-isostatine **75** in 62% yield from **74**. Condensation with O-benzyl protected Boc-L-threonine and *N*-methyl Boc-D-leucine in the presence of diethyl phosphorocyanidate (DEPC), followed by silylation of the hydroxyl function gave tripeptide **77**. After deprotection of the threonine hydroxyl, the ester linkage with *N*,*O*-dimethyl Cbz-L-tyrosine was formed with DCC in the presence of DMAP, and the resulting depsipeptide was converted to segment **78** by treatment with zinc powder. The necessary *N*-methylamino acids were prepared by N-methylation with sodium hydride/methyl iodide according to Benoiton's protocol.[66]

Segment condensation between **72** and **78** was performed with the DCC/DMAP protocol in 78% yield (Scheme 17). After simultaneous removal of both the Cbz and the benzyl ester protective groups, macrolactamization to the secondary amine succeeded in high yield with the coupling agent bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl). After deprotection with trimethylsilyl triflate, the intermediate **80** (didemnin A) was N-acylated with *O*-benzyl (*S*)-lactate-L-proline by use of BOP-Cl. Catalytic hydrogen transfer reaction provided didemnin B (**81**) in 49% yield. This synthesis is noteworthy for its

Scheme 17

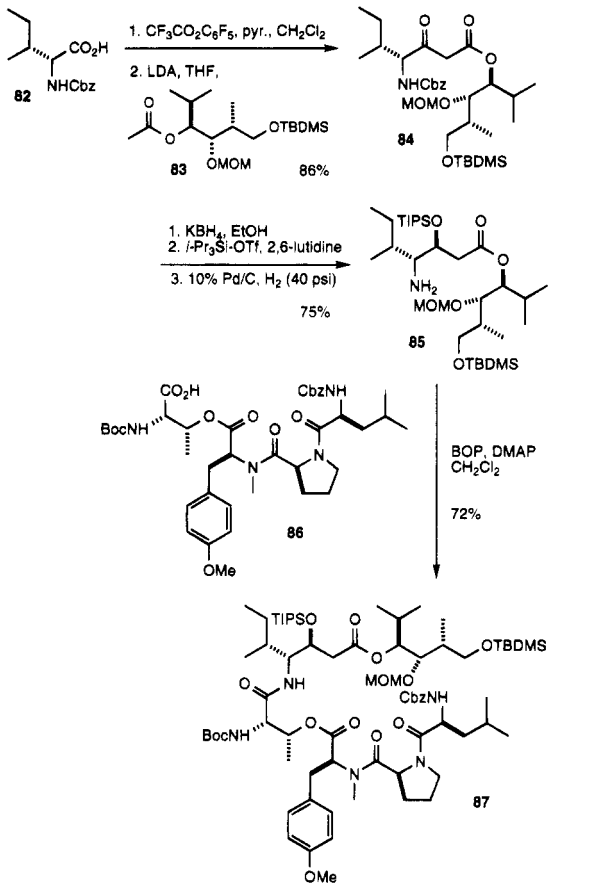


convergence and efficiency in peptide and depsipeptide couplings.

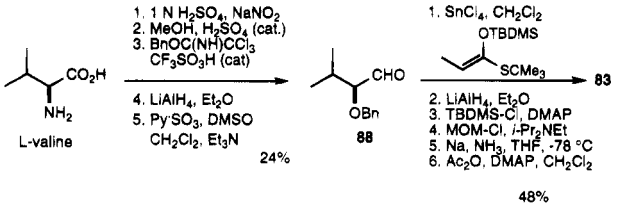
On the basis of their earlier total synthesis of didemnins,[61] Joullié and co-workers have recently reported an improved route toward new didemnin B analogs suitable for biological SAR studies.[65] The activity of didemnins depends critically on the peptides attached to the macrocyclic core, with β-turns showing the most potent effects. Introduction of a hydroxyproline residue as in analog **68**, for example, provides a specific molecular probe for functionalization at potential binding sites. The synthesis of this analog is discussed below.

Joullié's synthetic strategy employs a [2 + 4] segment condensation. Activation of Cbz-D-*allo*-isoleucine **82**, prepared by N-protection of the commercially available amino acid, with pentafluorophenyl trifluoroacetate was superior to the use of CDI, and condensation with the lithium enolate of the HIP (α-(α-hydroxyisovaleryl)propionyl) unit **83** provided the β-keto ester **84** in 86% yield (Scheme 18). Compound **83** was prepared by a chelation-controlled aldol condensation according to Gennari's protocol (Scheme 19).[61] Diastereoselective borohydride reduction (12.6:1), chromatographic separation, and hydrogenation led to segment **85** which originally had been coupled to tetrapeptide **86** using isopropenyl chloroformate activation at −15 °C.[61] An improved coupling yield was now[65] achieved with (1*H*-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) in the presence of a catalytic amount of DMAP.

Scheme 18



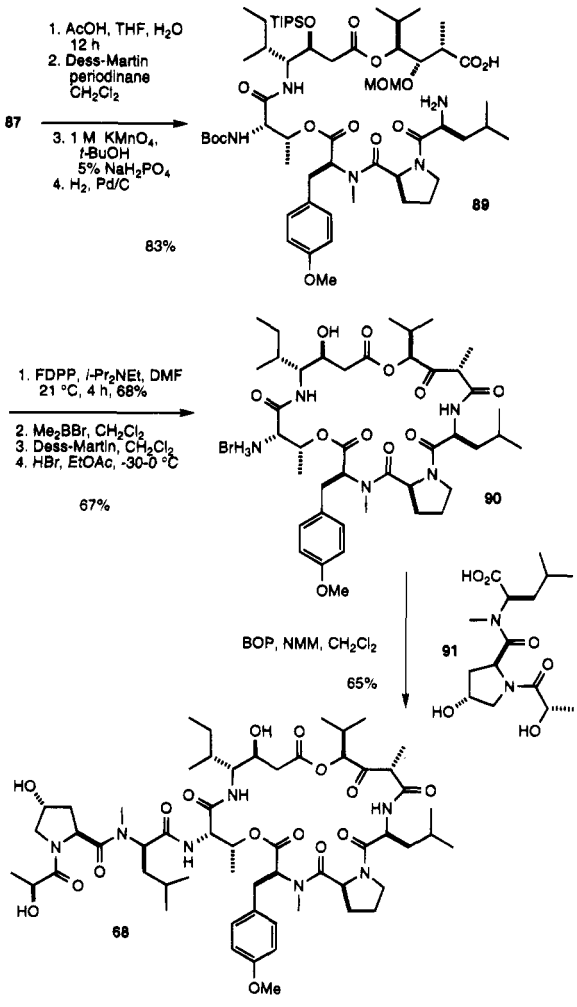
Scheme 19



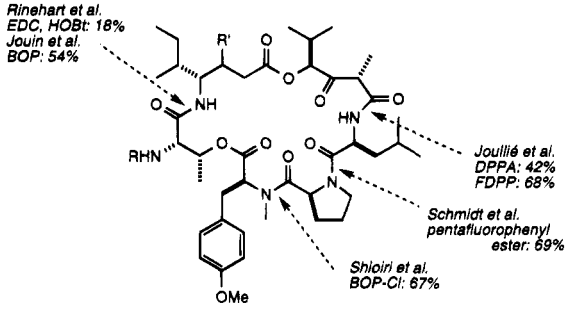
Selective removal of the TBDMS ether with acetic acid, oxidation with the Dess–Martin periodinane,[67] followed by further oxidation to the acid according to Masamune's procedure and hydrogenolysis of the Cbz group gave the hexapeptide **89** in 83% yield (Scheme 20). Macrocyclization with DPPA gave yields up to 42% but required 3 days at 0 °C. Activation of **89** with pentafluorophenyl diphenylphosphinate, however, yielded 68% of macrocycle after 4 h at room temperature. Removal of the MOM protective group with dimethylboron bromide, oxidation of the resulting secondary alcohol to the ketone, and treatment with HBr afforded the macrocycle salt **90**. Final acylation with hydroxyproline segment **91** (hydroxyproline is readily available from collagen) provided the desired didemnin **68**, which was slightly less active than didemnin B. According to the authors,[65] these procedures can easily be scaled up to provide gram quantities of didemnins.

A comparison of the different macrocyclization protocols that have been employed for didemnin synthesis reveals that all amide bonds have successfully been formed in ring closures with a variety of

Scheme 20



reagents, whereas the more difficult macrocyclization via depsipeptide bond formation has been avoided.

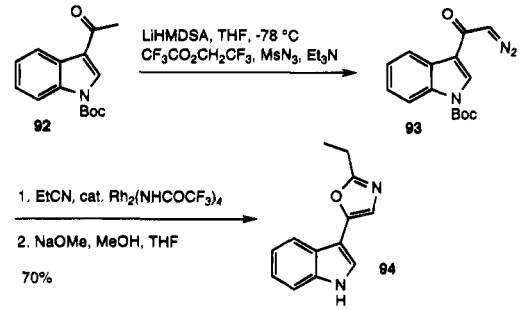


C. Diazonamides

The diazonamides were isolated in 1991 by Fenical, Clardy, and co-workers from the marine ascidian *Diazona chinensis*.[68] These unusual halogenated cyclopeptides demonstrated potent *in vitro* activity against human colon carcinoma and murine melanoma cancer cell lines, with IC_{50} values of less than 15 ng/mL. The X-ray analysis of the *p*-bromobenzoate of diazonamide B revealed an extremely rigid polycyclic core structure (Figure 5).

Considerable efforts are currently being directed toward the total synthesis of diazonamides. Moody and co-workers have recently reported results of a model study toward diazonamide A.[69] Their approach used rhodium(II)-catalyzed reactions of diazocarbonyl compounds for the construction of the oxazoles as well as the indole and benzofuran units. The preparation of the oxazolylindole system is outlined in Scheme 21.

Scheme 21

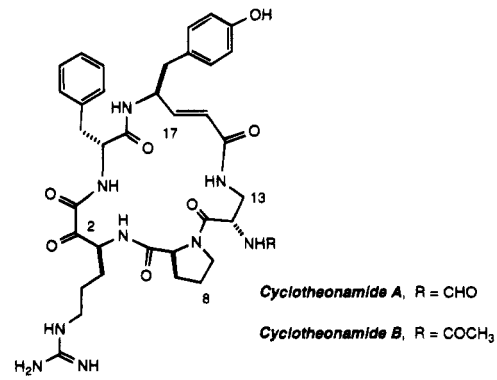


3-acetylindole gave the diazocarbonyl compound **93** which was decomposed with catalytic rhodium(II) trifluoroacetamide in propionitrile at room temperature. Deprotection with sodium methoxide gave oxazolylindole **94** in 70% yield from **92**.

III. Cyclopeptides from Sponges

A. Cyclotheonamides

The 19-membered cyclotheonamide A and B were reported in 1990 by Fusetani and co-workers and immediately attracted considerable interest due to their strong inhibitory activity toward thrombin and other serine proteases.[70] Synthetic low-molecular



weight thrombin inhibitors are actively being developed in the pharmaceutical industry.[71] Cyclotheonamide A inhibits dose dependently the aggregation of human platelets with an IC_{50} of 1.5 μM, and its K_i toward trypsin was determined as 0.2 nM.[72] Novel structural features of cyclotheonamides include the vinylogous tyrosine and the α-keto arginine residues.

The first synthesis of cyclotheonamide B was reported by Schreiber and Hagihara in 1992 and led to a correction of the stereochemistry of the natural product at C(3) and C(18) to the (*S*) configuration.[73] Further total syntheses of cyclotheonamides were reported by Maryanoff,[74] Wipf,[75] and Shioiri[76] and co-workers.[77]

Hagihara and Schreiber used a linear approach for the total synthesis of cyclotheonamide B (Schemes 22–24). Their macrocyclization strategy connected the proline carboxyl with the amino function of the α-keto arginine residue. Homologation of arginine aldehyde **96**, obtained by reduction of the Weinreb amide of N_η-Mtr protected L-arginine (Mtr = 2,5,6-

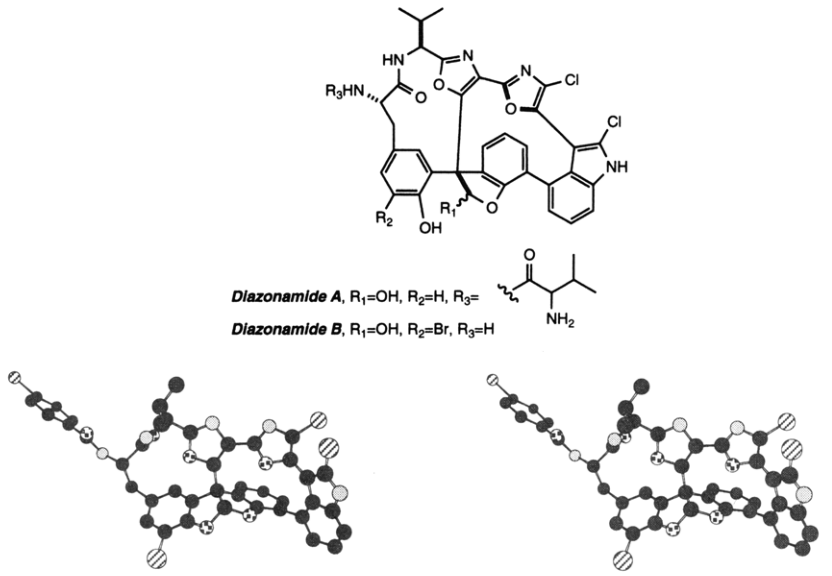
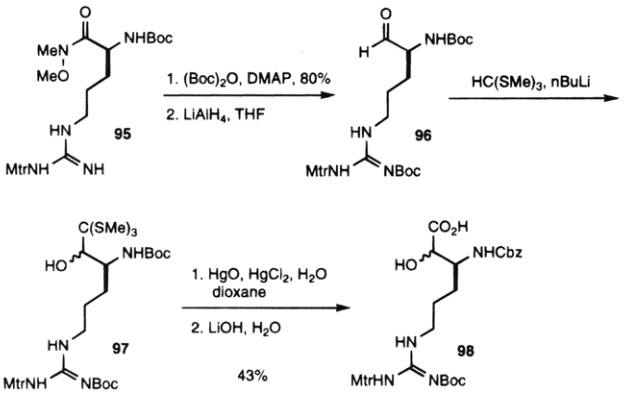
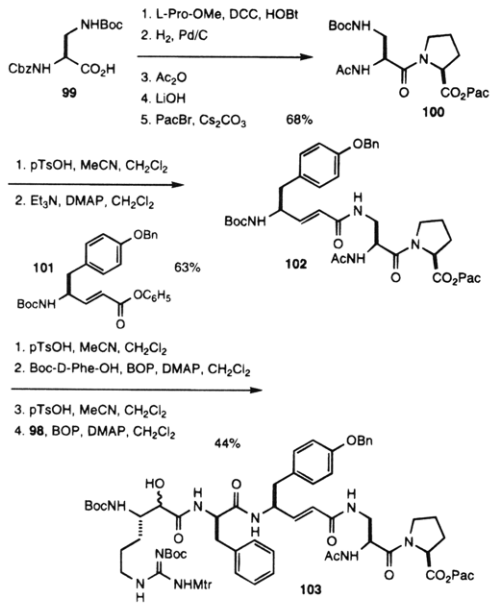


Figure 5. Stereoview of X-ray structure of diazonamide B derivative.

Scheme 22



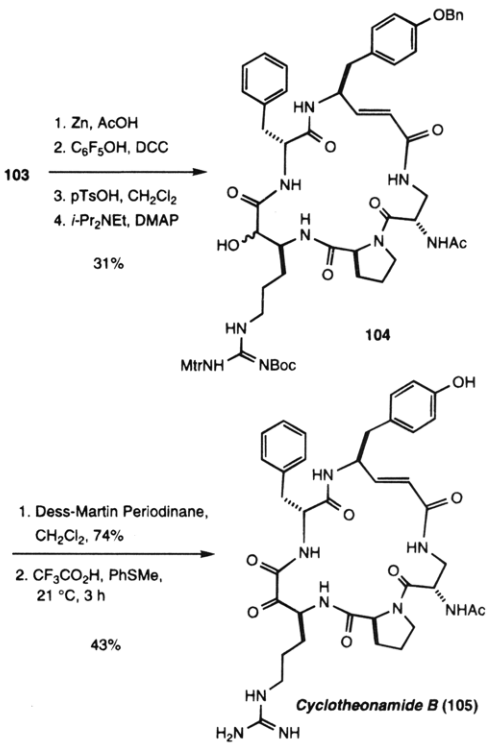
Scheme 23



trimethyl-4-methoxybenzenesulfonyl), by Seebach's procedure gave α-hydroxy acid **98** in 34% yield from hydroxamate **95** (Scheme 22).

The bisprotected diaminopropanoic acid residue **99** was prepared via Izumiya's procedure[78] and condensed to L-proline methyl ester in the presence of DCC and HOBt (Scheme 23). Hydrogenolysis of the

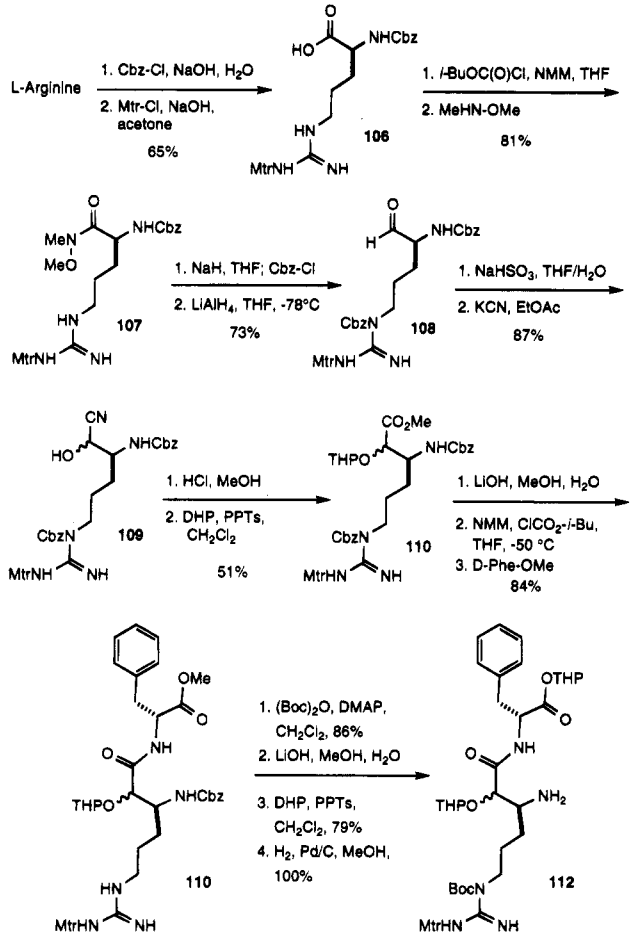
Scheme 24



Cbz group, N-acetylation, saponification, and conversion of the carboxylate to the Pac ester (Pac = phenacyl) yielded dipeptide **100**. In a linear repetitive sequence, the N-terminus was deprotected with pTsOH in acetonitrile and amide couplings were performed with the active ester of the vinylogous tyrosine **101** as well as Boc-D-phenylalanine and **98** in the presence of BOP reagent. Cyclization precursor **103** was thus obtained in 28% yield from dipeptide **100**.

Macrolactamization was achieved in four steps from pentapeptide **103** (Scheme 24). Removal of the phenacyl group with zinc in acetic acid, pentafluorophenyl ester formation, selective removal of the amino terminal Boc group with TsOH in methylene chloride, and exposure of the resulting ammonium salt to Hünig's base and DMAP gave macrocycle **104** in 31% yield. Interestingly, the secondary hydroxyl

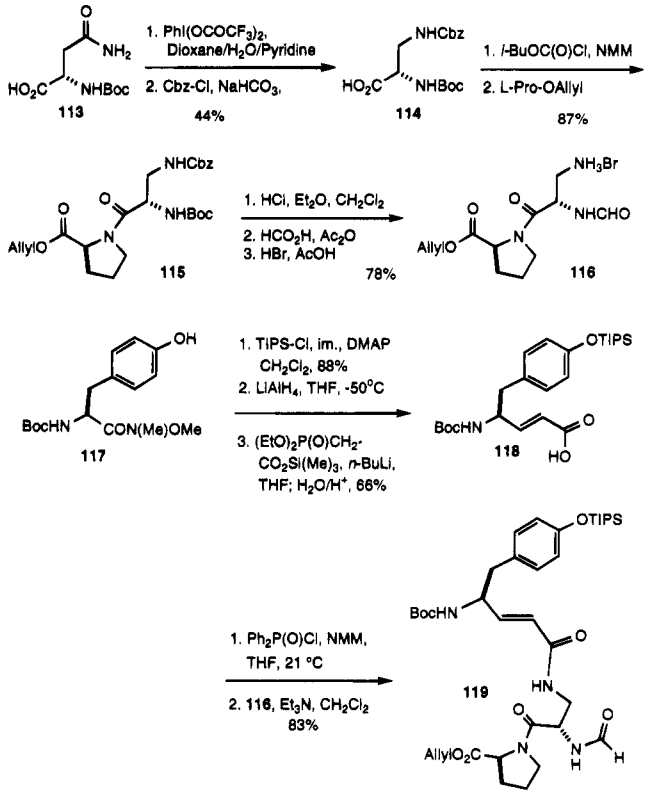
Scheme 25



function did not interfere with any of these synthetic manipulations and was subsequently oxidized with Dess–Martin reagent[67] in methylene chloride to the α-keto amide. Simultaneous removal of the phenolic benzyl ether and the remaining Boc and Mtr functions gave synthetic cyclotheonamide B that was spectroscopically identical to the natural product. This total synthesis of the marine cyclopeptide and earlier syntheses of C(3)- and C(18)-epimers unambiguously established stereochemistry and sequence of the cyclotheonamides. In a related study, Schreiber and co-workers also investigated the general conformational properties of one of the unusual residues found in cyclotheonamides, the vinylogous amino acid.[79]

Wipf and Kim synthesized cyclotheonamide A by macrolactamization at the vinylogous tyrosyl-D-phenylalanine site.[75] The seco-pentapeptide was obtained by a highly convergent [3 + 2] segment condensation strategy (Schemes 25–27). For the preparation of the α-keto arginine, bisprotected L-arginine derivative **106** was converted to the aldehyde **108** via reduction of the Weinreb amide **107** with lithium aluminum hydride. Bisprotection of guanidine function was necessary to avoid intramolecular attack at the aldehyde carbonyl group.[75a] The bisulfite derivative of **108** was converted to the cyanohydrin **109**, and acidic methanolysis of the nitrile followed by O-protection with dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulfonate (PPTs) gave the fully protected α-hydroxy-β-amino acid **110** in 17% overall yield from L-arginine. Coupling with D-phenylalanine via the mixed

Scheme 26

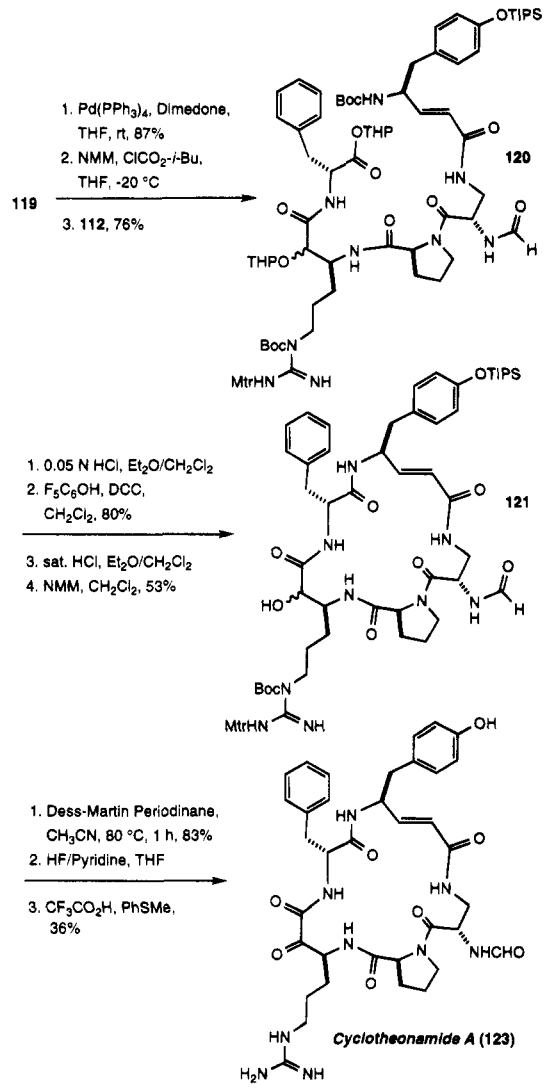


anhydride with isobutyl chloroformate was followed by a change of the N_ϵ-protective group to the more base-resistant Boc and the conversion of the C-terminus to the very acid-labile THP ester. These operations were necessary to ensure chemoselectivity in the subsequent macrolactamization and oxidation steps with dipeptide segment **112**.

The nonproteinogenic amino acid **114** was prepared by modified Hoffman oxidation and N-protection of L-asparagine **113** (Scheme 26).[78] Coupling of **114** with L-proline allyl ester, acidolysis of Boc, N-formylation, and deprotection of the primary amine with 48% HBr in acetic acid gave hydrobromide **116** in 30% yield from asparagine **113**. This dipeptide was acylated with the vinylogous tyrosine building block **118**, which was obtained from the N-protected Weinreb amide of L-tyrosine **117** via O-silylation, reduction to the aldehyde, and Wittig condensation with $(EtO)_2P(O)CH_2CO_2TMS$. Activation of the α,β-unsaturated acid **118** with diphenylphosphinic chloride provided the highest yield of tripeptide segment **119**.

Palladium(0)-catalyzed deallylation of the C-terminus of **119** and segment condensation with **112** via the mixed anhydride gave the highly functionalized pentapeptide **120** in 76% yield (Scheme 27). Mild hydrolysis cleaved the THP ester in **120** preferentially over the THP ether. Conversion of the carboxylate into the pentafluorophenyl ester was followed by cleavage of both the N-terminal Boc group and the THP ether with saturated HCl in ether/dichloromethane. The N_ϵ-Boc group on the guanidine residue, however, was found to be stable to these conditions. Macrocyclization in CH_2Cl_2 in the presence of NMM at room temperature for 12 h provided the cyclopeptide **121** in 42% yield. A series of attempts to oxidize the α-hydroxy function in **121** under standard conditions failed or resulted in low

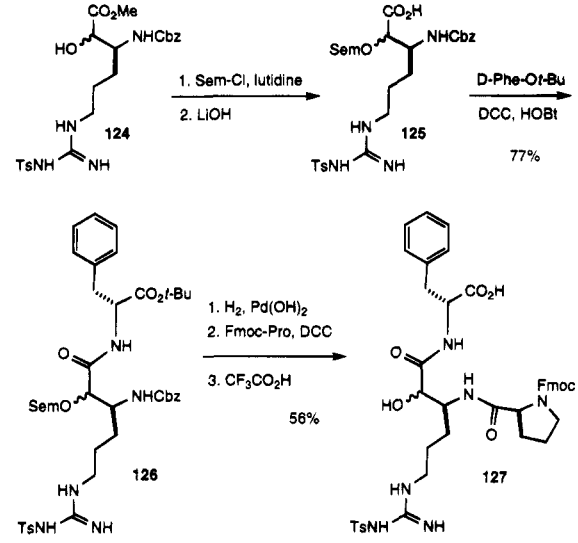
Scheme 27



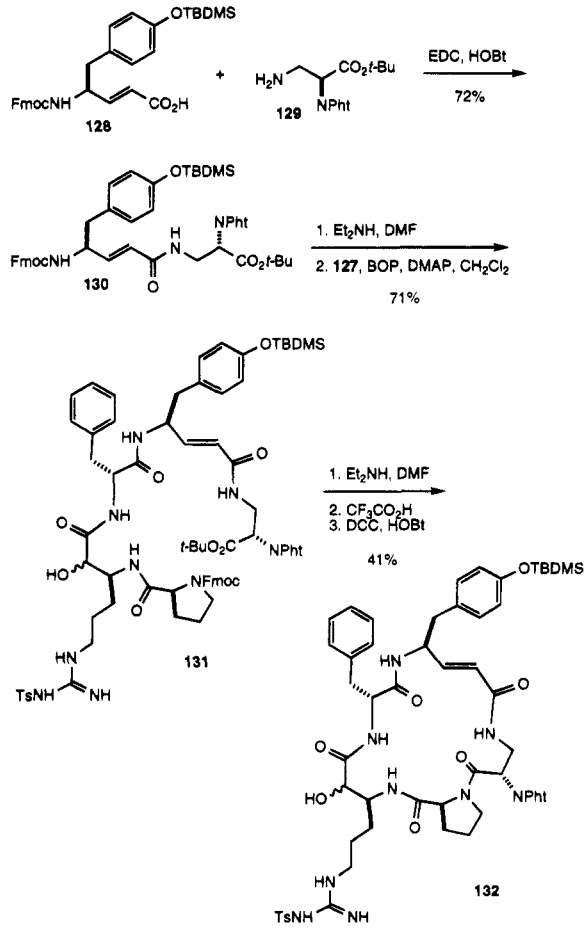
yields of the desired α-keto amide. Possibly, this hydroxyl group is buried within the macrocycle and is sterically not easily accessible to oxidizing agents. High-temperature oxidation with the Dess–Martin periodinane in acetonitrile, however, proceeded smoothly, and, after removal of the remaining protective groups, cyclotheonamide A (**123**) was isolated in 36% yield from **121**. The protective group strategy and the high-temperature oxidation that circumvented a possible detrimental conformational bias of the cyclopeptide are among the most noteworthy features of this synthesis.

Maryanoff and co-workers applied a convergent [3 + 2] fragment condensation route with a macrolactamization between the proline and diaminopropanoic acid residues for the synthesis of both cyclotheonamide A and B.[74] Due to the unexpectedly high base and acid lability of silyl ethers at the secondary alcohol, several protective group strategies were explored for the preparation of the α-keto arginine building block **124** (Scheme 28). Unprotected derivatives suffered from facile intramolecular displacement of benzyl alcohol from the N-terminal Cbz group and oxazolidinone formation. Ultimately, α-hydroxy ester **124**, obtained from L-arginine via the corresponding cyanohydrin, was protected as the Sem ether, saponified, and coupled with D-phenylalanine ester to give dipeptide **126**. Tripeptide segment **127**

Scheme 28



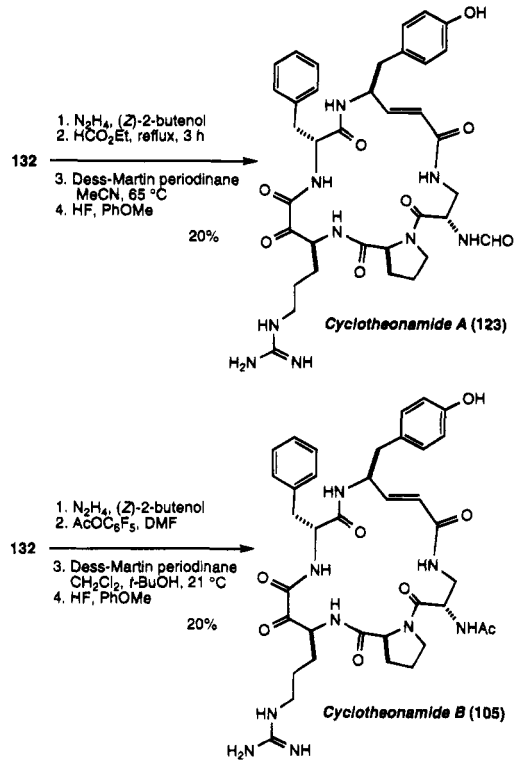
Scheme 29



was obtained in 56% yield by subsequent hydrogenolysis, DCC-mediated coupling with Fmoc-proline, and cleavage of the *tert*-butyl ester with trifluoroacetic acid.

Coupling of the L-tyrosine-derived vinylogous amino acid **128** and L-diaminopropanoic acid **129**, prepared by Mokotoff's procedure,[80] with EDC in the presence of HOBt gave the dipeptide segment **130** in 72% yield (Scheme 29). Deprotection with diethylamine and segment coupling with **127** in a 0.1 M solution in the presence of BOP reagent gave the linear pentapeptide **131** without any δ-lactone formation with the secondary hydroxyl group of **127**. In the subsequent

Scheme 30

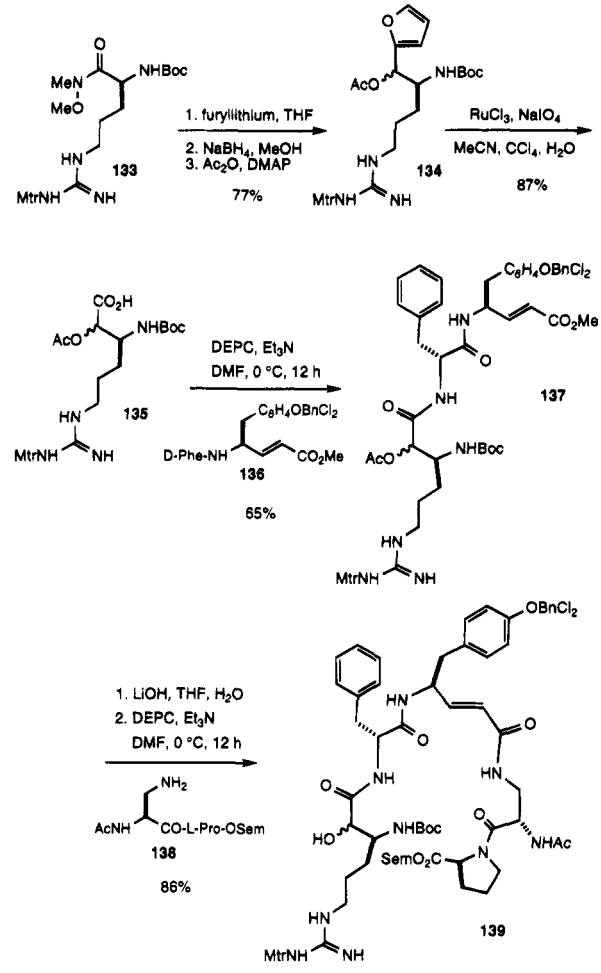


macrolactamization, however, some 15-membered lactone side product (ca. 10%) was detected. Among peptide coupling reagent such as BOP-Cl, BOP, EDC/HOBt, DPPA, and BBC,[81] DCC/HOBt was found to provide the highest yield (41%) of the 19-membered macrocycle **132** under high-dilution conditions (1 mM in CH_2Cl_2). During the acidic cleavage of the *tert*-butyl ester, some loss of the phenolic TBDMS group was noticed especially upon scale-up.

Hydrazinolysis of the phthalimide **132** was performed in the presence of high-boiling olefin scavengers to avoid concomitant reduction of the carbon–carbon double bond by traces of diimide (Scheme 30). The resulting amine was successfully converted to cyclotheonamide A and B by formylation in refluxing ethyl formate and acetylation with pentafluorophenyl acetate, respectively, followed by Dess–Martin oxidation and deprotection with anhydrous HF at 0 °C in the presence of anisole. As noted previously, the Dess–Martin oxidation of the cyclotheonamide A intermediate required hot acetonitrile to go to completion, whereas for the corresponding cyclotheonamide B precursor room temperature in methylene chloride/*tert*-butyl alcohol was sufficient.

The straightforward access to both cyclotheonamides from a late synthetic intermediate is one of the most attractive features of this joint effort by the R. W. Johnson and Scripps groups. This strategy also offered the possibility for extensive structure–activity studies at the diaminopropanoic acid residue. The structures of the complex of cyclotheonamide A with thrombin[74] and trypsin[82] were elucidated by X-ray crystallography that established the formation of a covalent complex via a tetrahedral hemiketal of the ketoarginine moiety of the cyclopeptide and serine-195 at the active site of the serine proteases. On the basis of these analyses, it could also be expected that the substitution of the formyl group in cyclotheonamide A with larger hydrophobic residues would provide greater affinity as well as selectivity toward thrombin. However, preliminary studies by Maryanoff et al. appear not to support this hypothesis.[74]

Scheme 31

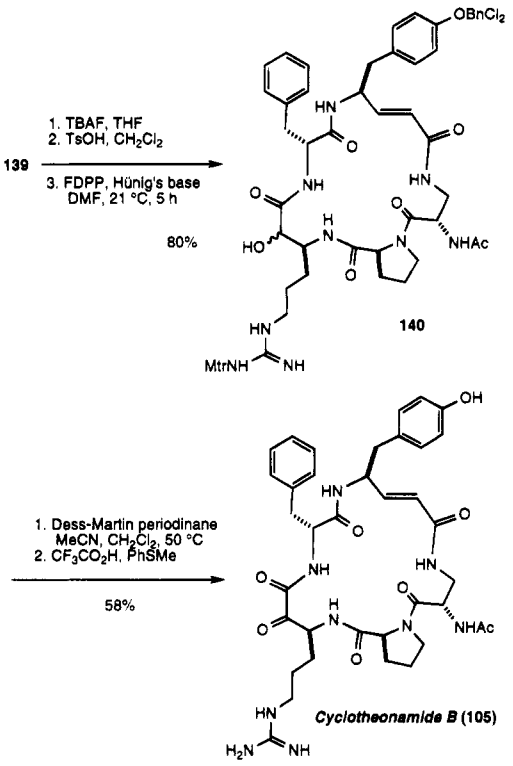


A fourth synthesis of cyclotheonamide was reported by Shioiri and co-workers.[83] A convergent [3 + 2] segment condensation strategy was chosen, and macrolactamization was performed between the α-ketoarginylproline residues. Addition of furyllithium to Weinreb amide **133**, followed by reduction of the ketone, acylation of the resulting alcohol, and ruthenium-catalyzed oxidation of the heterocycle gave α-hydroxy acid **135** in 67% overall yield (Scheme 31). DEPC-mediated condensation with dipeptide **136** resulted in the left-side segment **137**, which was further extended with dipeptide **138** to give the pentapeptide **139** in high yield without apparent problems caused by the unprotected secondary hydroxyl function and monoprotected guanidine.

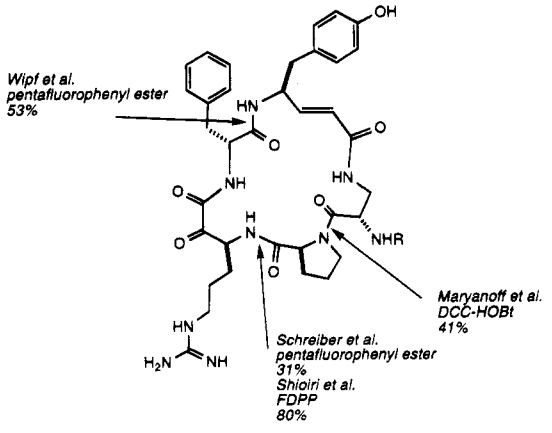
After deprotection of C- and N-termini in **139**, an efficient macrolactamization in the presence of FDPP provided the cyclopentapeptide **140** in 80% yield (Scheme 32). Oxidation with Dess–Martin reagent in warm acetonitrile, followed by simultaneous removal of both the 2,6-dichlorobenzyl and the Mtr protective groups with trifluoroacetic acid resulted in 58% of cyclotheonamide B. The overall yield of this very efficient approach is close to 10%, calculated for the longest linear sequence.

Comparison of the different strategies employed in the four total syntheses of cyclotheonamides reveals

Scheme 32



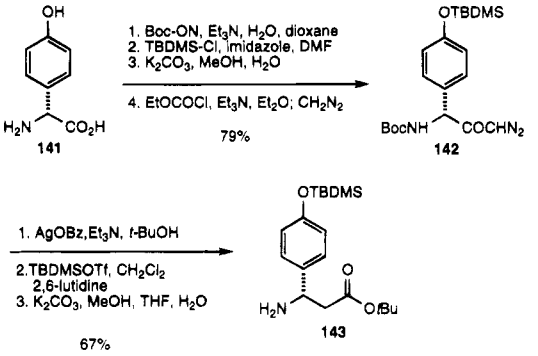
the importance of protective group strategies and macrocyclization conditions. Within small variations, similar methods were used for the preparation of the unnatural amino acid building blocks, but protective group tactics, segment condensations and ring formations were varied considerably. Therefore, the cyclotheonamides represent an excellent case study for modern cyclopeptide synthesis and general protective group compatibility. The results of macrocyclizations are summarized below. The prevalence of pentafluorophenyl ester based activation methodology is remarkable.



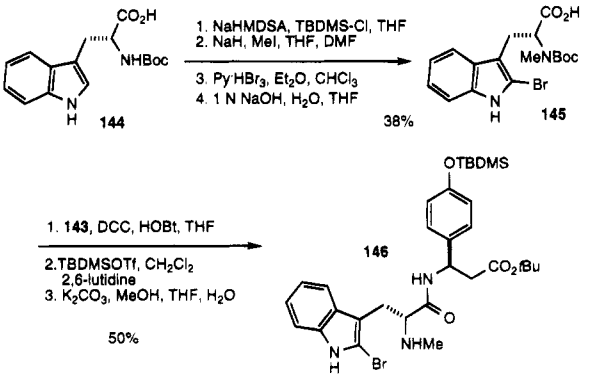
B. Jaspamide and Geodiamolides

The cyclodepsipeptide jaspamide (jasplakinolide) was discovered independently by Faulkner[84] as well as Crews[85] and co-workers in extracts of *Jaspis* sp. The related geodiamolides are secondary metabolites of the marine sponge *Geodia* sp.[86-88] Structurally, jaspamide and geodiamolides are related to the recently isolated[89] and synthesized[90] doliculide. The X-ray structure of jaspamide acetate[84] displayed in Figure 6 reveals the absence of intramolecular hydrogen bonds, and a face–face stacking or molecular tweezers conformation of the aromatic rings was proposed for the solution conformation.[91]

Scheme 33



Scheme 34



Jaspamide has potent cytotoxic, antifungal, ichthytotoxic, and insecticidal properties that make it an attractive target for pharmacological and SAR studies. It contains two rare amino acids, (*R*)-β-tyrosine and D-δ-bromotryptophan (= 2-bromoabrine) in conjunction with a polyketide chain. Not surprisingly, a series of total syntheses of jaspamide and geodiamolide by Grieco,[92,93] White,[94] Momose,[95] Konopelski,[96] Rama Rao,[97] Shioiri,[98] and Kocienski[99] and co-workers have been reported.[100] In the spirit of a case study, the following discussion will be limited to the first and the most recent syntheses of jaspamide.

In their total synthesis of jaspamide published in 1988,[92] Grieco, Hon, and Perez-Medrano constructed the 18-membered depsipeptide via a convergent segment condensation strategy followed by macrolactonization. The (*R*)-β-tyrosine residue was prepared from L-4-hydroxyphenylglycine **141** (Scheme 33). N-Protection with 2-[[(*tert*-butoxycarbonyl)oxy]-imino]-2-phenylacetonitrile (Boc-ON), O-silylation, and conversion to a mixed anhydride followed by treatment with diazomethane gave diazo ketone **142** in 79% yield. Wolff rearrangement in the presence of silver(I) and *tert*-butyl alcohol and selective cleavage of the Boc protective group in the presence of the *tert*-butyl ester with TBDMS-OTf provided amine **143** after hydrolysis of the intermediate *N*-[(*tert*-butyldimethylsilyl)oxy]carbonyl group.

For the preparation of the bromoabrine residue, Boc-D-tryptophan was N-silylated with TBDMS-Cl in the presence of sodium hexamethyldisilazide (NaHMDSA, Scheme 34). Simultaneous N- and O-methylation, bromination/desilylation of the indole nucleus,

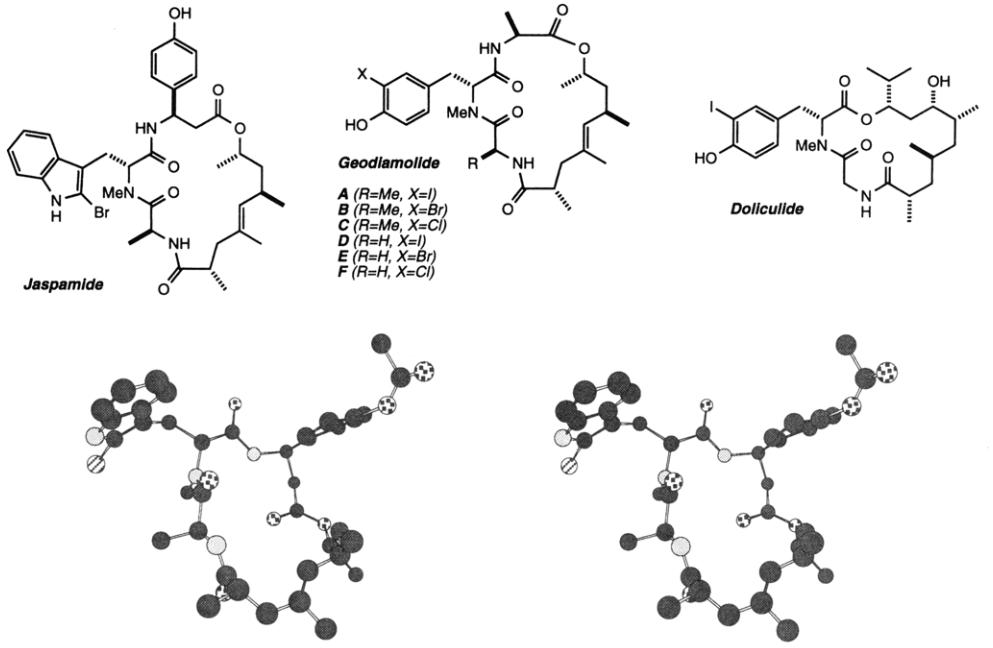
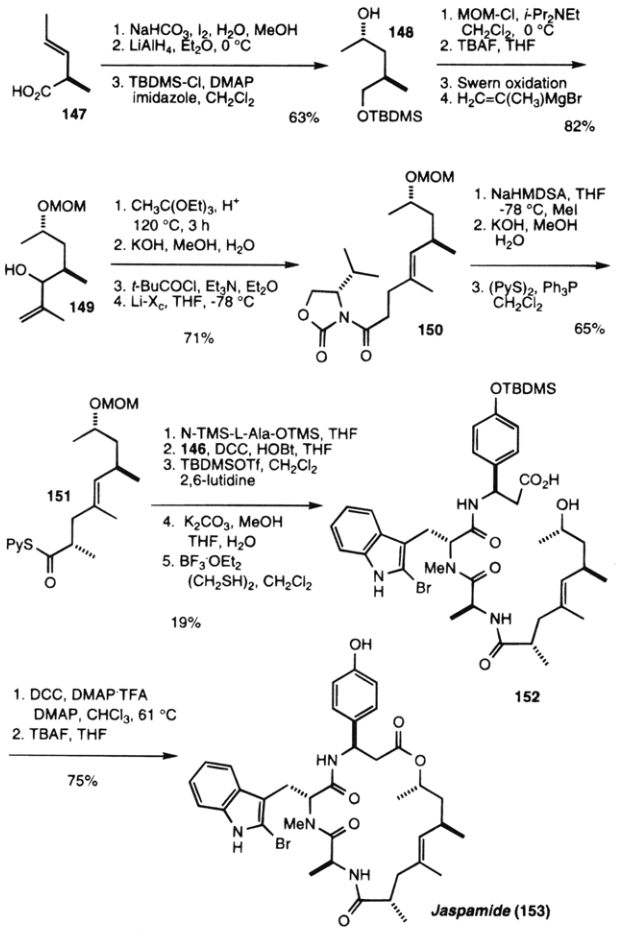


Figure 6. Stereoview of X-ray structure of jaspamide acetate.

Scheme 35



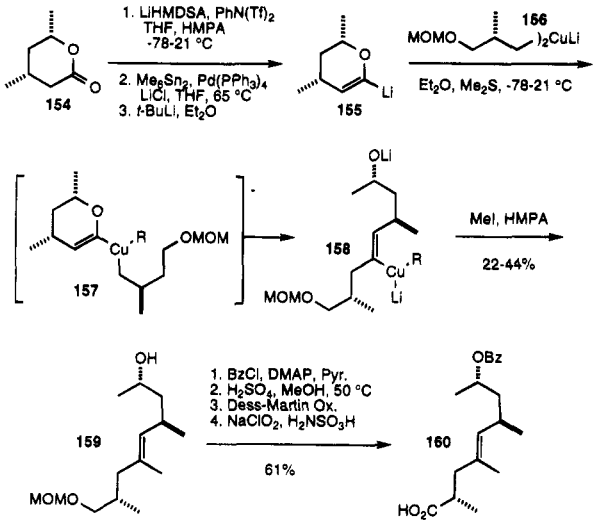
and saponification gave acid **145** in 38% yield. DCC/HOBt-mediated coupling with β-tyrosine **143** proceeded in 91% yield. Another selective cleavage of the Boc group with silyl triflate led to secondary amine **146**.

For the preparation of the polyketide segment, acid **147**[101] was iodolactonized and reduced, and the resulting diol was selectively protected at the primary position (Scheme 35). Conversion of the secondary hydroxyl into a MOM-ether, desilylation, oxidation, and Grignard addition to the aldehyde provided allylic alcohol **149** in 82% yield. Johnson orthoester Claisen rearrangement of **149**, saponification, and condensation of the mixed anhydride of the resulting acid with the lithium salt of (*S*)-4-isopropyl-2-oxazolidinone[102] (Li-X_c) set the stage for a diastereoselective methylation of the sodium enolate of imide **100**. The chiral auxiliary was removed, and the resulting acid was converted to the pyridinethiol ester **151** according to Mukaiyama's[103] procedure. Coupling with bis-silylated L-alanine in THF for 15 h, and segment condensation with dipeptide **146** in the presence of DCC and HOBt gave a protected seco-jaspamide derivative that was sequentially deprotected with silyl triflate/potassium carbonate and boron trifluoride etherate/ethanedithiol. Macrolactonization using Keck's conditions[104] proceeded readily in 79% yield, and desilylation gave synthetic jaspamide **153** identical to the natural compound. The overall yield calculated for the longest linear sequence of this synthesis was 3%.

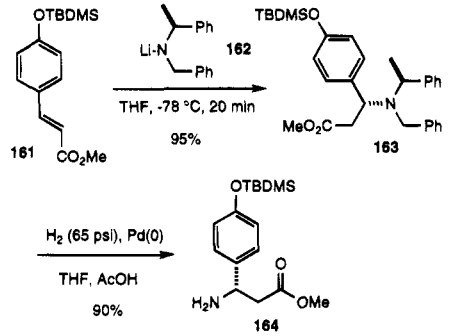
In the recent total synthesis of jaspamide by Kocienski and co-workers,[99] the polyketide segment was prepared by a novel 1,2-metalate rearrangement (Scheme 36). The metalated dihydropyran **155**, prepared from lactone **154** via enoltriflate and vinyl stannane, was added to 2 equiv of cuprate **156**, obtained from the corresponding alkyllithium reagent. The resulting ate complex **157**, presumably a higher order cuprate intermediate, underwent a 1,2-metalate rearrangement with inversion of configuration to give cuprate **158** which was further methylated to the trisubstituted alkene **159**. This highly efficient process provided alkene **159** in 22–44% overall yield from lactone **154**.

The (*R*)-β-tyrosine segment of jaspamide was prepared by an interesting concise pathway from methyl *p*-hydroxycinnamate (**161**, Scheme 37). Asymmetric conjugate addition of lithium amide **162** in THF gave amino ester **163** in 95% yield and >95% diastereo-

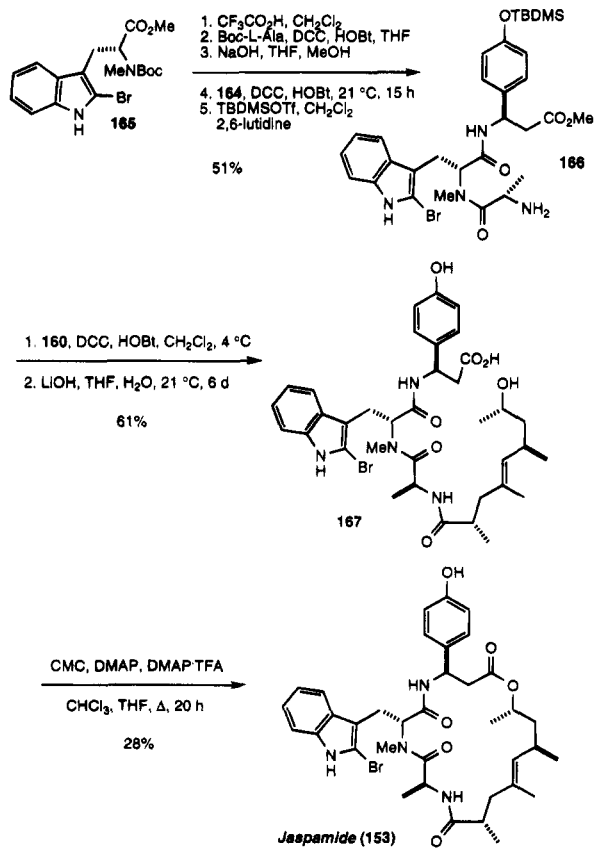
Scheme 36



Scheme 37



Scheme 38



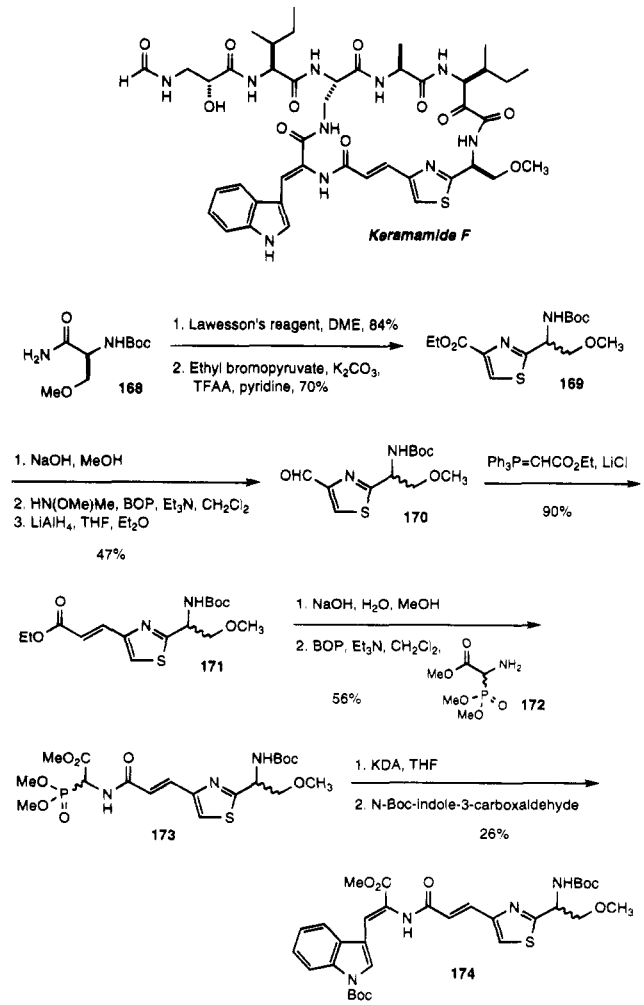
selectivity. Palladium-catalyzed hydrogenolysis provided amine **164** in 82% overall yield.

Bromoabrine **165**, prepared according to Grieco's protocol,[92] was N-deprotected in TFA and coupled with Boc-L-alanine in the presence of DCC and HOBt (Scheme 38). After saponification of the methyl ester, further condensation with β-tyrosine **164** led to tripeptide segment **166**. In the presence of TBDMS-OTf, selective deprotection of the Boc group could be achieved without concomitant loss of the phenolic silyl ether. Segment condensation of **166** and **160** was slow, but proceeded in 78% yield to give, after ester cleavage, secojaspamide (**167**). Unfortunately, lithium hydroxide also removed the β-tyrosine O-TBDMS group, and the subsequent macrolactonization with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (CMC) under Keck's conditions[104] accordingly suffered from low yield (the corresponding methyl ether provided 83% of *O*-methyljaspamide under identical conditions, however, this group could not be removed). Nonetheless, this approach excels by the highly efficient formation of polyketide and β-tyrosine building blocks. The overall yield calculated from the longest linear sequence amounts to 5% (18% before the last step).

C. Keramamides

Orbiculamide A[105] and keramamides B, C, D,[106] and E[107] are oxazole-containing weakly cytotoxic cyclopeptides isolated from the sponge *Theonella* sp.

Scheme 39



They contain unusual building blocks such as vinylogous and α-keto homologs of amino acids. Keramamides F, G, H, and J have a similar structure but contain a thiazole ring in place of the oxazole.[108,107] Synthetic studies toward keramamide F have recently been disclosed by Sowinski and Toogood.[109] The synthesis of the southern segment **174** is shown in Scheme 39. Carbonyl thiation of amide **168** with Lawesson's reagent followed by thiazole formation under the conditions described by Holzapfel or Meyers et al.[8] led only to a 4:1 mixture of enantiomers of **169**. Conversion of the ester to the aldehyde followed by Wittig condensation in the presence of LiCl provided the enoate **171** in a 20:1 ratio of *E*/*Z*-isomers. Saponification and coupling to trimethyl phosphonoglycine (**172**) in the presence of BOP reagent gave phosphonate **173** which underwent a Horner–Wadsworth–Emmons reaction with indolecarboxaldehyde to give **174** in 4% overall yield from **168** (*E*-**174**/*Z*-**174** = 4:1).

IV. Conclusion

Some of the most exciting natural products discovered in recent years, cyclosporin A, FK-506, cyclotheonamides, didemnins, dolastatins, microcystins, etc. are strongly modified amino acid derived metabolites. Cyclopeptides offer attractive opportunities for the study of ligand–receptor or substrate–enzyme interactions due to their conformational preorganization, increased lipophilicity, and improved resistance to metabolic degradation. The laboratory synthesis of complex cyclopeptides and cyclodepsipeptides has made major advances in recent years. Highly functionalized nonproteinogenic amino and hydroxy acid building blocks are now readily accessible from either natural precursors or by asymmetric methodology. A range of orthogonal protective group schemes for all common functional groups has been explored and has successively endured the test of total synthesis. Macrocyclization yields, while still depending on the judicious choice of linear precursors, have greatly improved due to the availability of a new generation of powerful yet selective coupling agents. It can be expected that these advances in synthetic strategy and tactics will stimulate further investigations of the biological and medicinal potential of structurally complex marine natural products.

Acknowledgments. Research in the author's laboratory has been generously supported by the National Science Foundation and the National Institutes of Health.

V. References

(1) (1) For related reviews, see: (a) Albizati, K. F.; Martin, V. A.; Agharahimi, M. R.; Stolze, D. A. In *Bioorganic Marine Chemistry*; Scheuer, P. J., Ed.; Springer: Berlin, 1991; Vol. 6, pp 1–68. (b) Ireland, C. M.; Molinski, T. F.; Roll, D. M.; Zabriskie, T. M.; McKee, T. C.; Swersey, J. C.; Foster, M. P. In *Bioorganic Marine Chemistry*; Scheuer, P. J., Ed.; Springer: Berlin, 1989; Vol. 3, pp 1–46. (c) Shioiri, T.; Hamada, Y. In *Studies in Natural Products Chemistry. Stereoselective Synthesis*; Rahman, A.-u., Ed.; Elsevier: Amsterdam, 1989; Vol. 4 (Part C), pp 83–110. (d) Schmidt, U. *Pure Appl. Chem.* **1986**, *58*, 295. (e) Li, W.-R.; Joullie, M. M. In Stereoselective Synthesis (Part F). *Studies in Natural Products Chemistry*; Rahman, A.-u., Ed.; Elsevier: Amsterdam, 1992; Vol. 10, pp 241–302. (f) Pettit, G. R. *Pure Appl. Chem.* **1994**, *66*, 2271. (g) Pharmaceutical and Bioactive Natural Products. *Marine Biotechnology*; Attaway, D. H., Zaborsky, O. R., Eds.; Plenum Press, New York, 1993; Vol. 1. (h) Marine Natural Products Chemistry. *Chem. Rev.* **1993**, *93* (5), 1671–1944. (I) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355.
(2) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771.
(3) Williams, A. B.; Jacobs, R. S. *Cancer Lett.* **1993**, *71*, 97.
(4) Schmidt, U.; Gleich, P. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 569.
(5) For synthetic studies of the structurally related dolastatin 3, see: (a) Schmidt, U.; Utz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 725. (b) Hamada, Y.; Kohda, K.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5303. (c) Pettit, G. R.; Holzapfel, C. W. *J. Org. Chem.* **1986**, *51*, 4580. (d) Pettit, G. R.; Kamano, Y.; Holzapfel, W.; van Zyl, W. J.; Tuinman, A. A.; Herald, C. L.; Baczynskyj, L.; Schmidt, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 7581. (e) Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Bahr, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 236.
(6) Ireland, C. M.; Scheuer, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 5688.
(7) Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 4445.
(8) For recent reinvestigations of this problem, see: (a) Bredenkamp, M. W.; Holzapfel, C. W.; Van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235. (b) Bredenkamp, M. W.; Holzapfel, C. W.; Synman, R. M.; Van Zyl, W. J. *Synth. Commun.* **1992**, *22*, 3029. (c) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473. (d) Boden, C. D. J.; Pattenden, G.; Ye, G. *Synlett* **1995**, 417.
(9) Sugiura, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1987**, *28*, 2251.
(10) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252.
(11) Boden, C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 8271.
(12) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Brenk, A. L. v. d.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1349.
(13) Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; Brenk, A. L. v. d.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634.
(14) See also: North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267.
(15) Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223.
(16) Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302.
(17) Hamamoto, Y.; Endo, M.; Kanagawa, M.; Nakanishi, T.; Mizukawa, K. *J. Chem. Soc., Chem. Commun.* **1983**, 323.
(18) Ishida, T.; Inoue, M.; Hamada, Y.; Kato, S.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, 370.
(19) Ishida, T.; Tanaka, M.; Nabae, M.; Inoue, M.; Kato, S.; Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1988**, *53*, 107.
(20) (a) Ireland, C. M.; Durso, A. R.; Newman, R. A.; Hacker, M. P. *J. Org. Chem.* **1982**, *47*, 1807. (b) Biskupiak, J. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 2302.
(21) Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 5155.
(22) Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 5159.
(23) Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 6501.
(24) Smith, A. B.; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859.
(25) Salvatore, B. A.; Smith, A. B., III. *Tetrahedron Lett.* **1994**, *35*, 1329.
(26) Schmidt, U.; Griesser, H. *Tetrahedron Lett.* **1986**, *27*, 163.
(27) See, for example: Cavelier-Frontin, F.; Pepe, G.; Verducci, J.; Siri, D.; Jacquier, R. *J. Am. Chem. Soc.* **1992**, *114*, 8885.
(28) Schmitz, F. J.; Ksebati, M. B.; Chang, J. S.; Wang, J. L.; Hossain, M. B.; Helm, D. v. d. *J. Org. Chem.* **1989**, *54*, 3463.
(29) Ishida, T.; In, Y.; Doi, M.; Inoue, M.; Hamada, Y.; Shioiri, T. *Biopolymers* **1992**, *32*, 131.
(30) (a) In, Y.; Doi, M.; Inoue, M.; Ishida, T.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1993**, *41*, 1686. (b) In, Y.; Doi, M.; Inoue, M.; Ishida, T.; Hamada, Y.; Shioiri, T. *Acta Crystallogr.* **1994**, *C50*, 432.
(31) McDonald, L. A.; Foster, M. P.; Phillips, D. R.; Ireland, C. M.; Lee, A. Y.; Clardy, J. C. *J. Org. Chem.* **1992**, *57*, 4616.
(32) (a) Kohda, K.; Ohta, Y.; Yokoyama, Y.; Kawazoe, Y.; Kato, T.; Suzumura, Y.; Hamada, Y.; Shioiri, T. *Biochem. Pharmacol.* **1989**, *38*, 4497. (b) Kohda, K.; Ohta, Y.; Kawazoe, Y.; Kato, T.; Suzumura, Y.; Hamada, Y.; Shioiri, T. *Biochem. Pharmacol.* **1989**, *38*, 4500.
(33) Kato, S.; Hamda, Y.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 2653.
(34) Schmidt, U.; Weller, D. *Tetrahedron Lett.* **1986**, *27*, 3495.
(35) For a survey of methods used in macrocyclizations, see: Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1991**, *161*, 109.
(36) For a comparison of a series of peptide coupling agents in macrocyclization of linear peptides, see: Ehrlich, A.; Rothemund, S.; Brudel, M.; Beyermann, M.; Carpino, L. A.; Bienert, M. *Tetrahedron Lett.* **1993**, *34*, 4781.
(37) Ishida, T.; Oishi, H.; Inoue, M.; Kamigauchi, M.; Sugiura, M.; Takao, N.; Kato, S.; Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1989**, *54*, 5337.
(38) Shioiri, T.; Hamada, Y.; Kato, S.; Shibata, M.; Kondo, Y.; Nakagawa, H.; Kohda, K. *Biochem. Pharmacol.* **1987**, *36*, 4181.

(39) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975.
(40) Hambley, T. W.; Hawkins, C. J.; Lavin, M. F.; Brenk, A. v. d.; Watters, D. J. *Tetrahedron* **1992**, *48*, 341.
(41) Prinsep, M. R.; Moore, R. E.; Levine, I. A.; Patterson, G. M. L. *J. Nat. Prod.* **1992**, *55*, 140.
(42) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.
(43) Watters, D. J.; Beamish, H. J.; Marshall, K. A.; Gardiner, R. A.; Seymour, G. J.; Lavin, M. F. *Cancer Chemother. Pharmacol.* **1994**, *33*, 399.
(44) Peptides with all L-amino acids and devoid of glycine or proline residues are notoriously difficult to cyclize. This is especially true for sequences with β-branched residues such as valine, isoleucine, and threonine. For related results, see: Kessler, H.; Kutscher, B. *Liebigs Ann. Chem.* **1986**, 869 and references cited therein.
(45) Wipf, P.; Miller, C. P.; Venkatraman, S.; Grant, C. Unpublished results.
(46) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907.
(47) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575.
(48) (a) Rothe, M.; Kreiss, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 113. (b) Wipf, P.; Li, W.; Sekhar, V. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 745.
(49) Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1.
(50) Wipf, P.; Venkatraman, S.; Miller, C. P.; Geib, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1516.
(51) (a) Vandenbrenk, A. L.; Byriel, K. A.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Hawkins, C. J.; Jones, A.; Kennard, C.; Moubaraki, B.; Murray, K. S. *Inorg. Chem.* **1994**, *33*, 3549. (b) Vandenbrenk, A. L.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R.; Hawkins, C. J.; Jones, A. *Inorg. Chem.* **1994**, *33*, 2280.
(52) Foster, M. P.; Concepcion, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671.
(53) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2477. This compound was erroneously named bistatramide by these authors.
(54) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397.
(55) Rinehart, K. L.; Gloer, J. B.; Cook, J. C.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857.
(56) Sakai, R.; Stroh, J. G.; Sullins, D. W.; Rinehart, K. L. *J. Am. Chem. Soc.* **1995**, *117*, 3734 and references cited therein.
(57) Rinehart, K. L.; Kishore, V.; Nagarajan, S.; Lake, R. J.; Gloer, J. B.; Bozich, F. A.; Li, K. M.; Malecka, R. E.; Todsen, W. L.; Munro, M. H. G.; Sullins, D. W.; Sakai, R. *J. Am. Chem. Soc.* **1987**, *109*, 6846.
(58) Schmidt, U.; Kroner, M.; Griesser, H. *Tetrahedron Lett.* **1988**, *29*, 3057, 4407.
(59) Hamada, Y.; Kondo, Y.; Shibata, M.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 669.
(60) (a) Jouin, P.; Poncet, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *J. Org. Chem.* **1989**, *54*, 617. (b) Jouin, P.; Poncet, J.; Dufour, M.-N.; Aumelas, A.; Pantaloni, A. *J. Med. Chem.* **1991**, *34*, 486.
(61) Li, W.-R.; Ewing, W.-R.; Ewing, W. R.; Harris, B. D.; Joullié, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659.
(62) (a) Ewing, W. R.; Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Tetrahedron* **1986**, *42*, 2421. (b) Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Tetrahedron Lett.* **1987**, *28*, 2837. (c) Harris, B. D.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 3489.
(63) Shen, G. K.; Zukoski, C. F.; Montgomery, D. W. *Int. J. Immunopharmacol.* **1992**, *14*, 63.
(64) Crews, C. M.; Collins, J. L.; Lane, W. S.; Snapper, M. L.; Schreiber, S. L. *J. Biol. Chem.* **1994**, *269*, 15411.
(65) Mayer, S. C.; Ramanjulu, J.; Vera, M. D.; Pfizenmayer, A. J.; Joullié, M. M. *J. Org. Chem.* **1994**, *59*, 5192. A total of five analogs were prepared in this paper.
(66) Cheung, S. T.; Benoiton, N. *Can. J. Chem.* **1977**, *55*, 906.
(67) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(68) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.
(69) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, *66*, 2107.
(70) Fusetani, N.; Matsunaga, S.; Matsumoto, H.; Takebayashi, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7053.
(71) Tapparelli, C.; Metternich, R.; Ehrhardt, C.; Cook, N. S. *TIPS* **1993**, *14*, 366.
(72) Lewis, S. D.; Ng, A. S.; Baldwin, J. J.; Fusetani, N.; Naylor, A. M.; Shafer, J. A. *Thromb. Res.* **1993**, *70*, 173.
(73) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570.
(74) (a) Maryanoff, B. E.; Qiu, X. Y.; Padmanabhan, K. P.; Tulinsky, A.; Almond, H. R.; Andradegordon, P.; Greco, M. N.; Kauffman, J. A.; Nicolaou, K. C.; Liu, A. J.; Brungs, P. H.; Fusetani, N. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8048. (b) Maryanoff, B. E.; Greco, M. N.; Zhang, H. C.; Andradegordon, P.; Kauffman, J. A.; Nicolaou, K. C.; Liu, A. J.; Brungs, P. H. *J. Am. Chem. Soc.* **1995**, *117*, 1225.
(75) (a) Wipf, P.; Kim, H. Y. *Tetrahedron Lett.* **1992**, *33*, 4275. (b) Wipf, P.; Kim, H. Y. *J. Org. Chem.* **1993**, *58*, 5592.
(76) Deng, J. G.; Hamada, Y.; Shioiri, T.; Matsunaga, S.; Fusetani, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1729.
(77) For other synthetic work, see also: Roth, P.; Metternich, R. *Tetrahedron Lett.* **1992**, *33*, 3993.
(78) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266.
(79) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J. C.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.
(80) Mokotoff, M.; Logue, L. W. *J. Med. Chem.* **1981**, *24*, 554.
(81) BBC = Benzotriazolyloxybis(pyrrolidino)carbonium hexafluorophosphate: Chen, S.; Xu, J. *Tetrahedron Lett.* **1992**, *33*, 647.
(82) Lee, A. Y.; Hagihara, M.; Karmacharya, R.; Albers, M. W.; Schreiber, S. L.; Clardy, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 12619.
(83) Deng, J. G.; Hamada, Y.; Shioiri, T.; Matsunaga, S.; Fusetani, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1729.
(84) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123.
(85) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2979.
(86) Braekman, J. C.; Daloze, D.; Moussiaux, B. *J. Nat. Prod.* **1987**, *50*, 994.
(87) (a) Chan, W. R.; Tinto, W. F.; Manchand, P. S.; Todaro, L. J. *J. Org. Chem.* **1987**, *52*, 3091. (b) Dilip de Silva, E.; Andersen, R. J.; Allen, T. M. *Tetrahedron Lett.* **1990**, *31*, 489.
(88) Talpir, R.; Benayahu, Y.; Kashman, Y.; Pannell, L.; Schleyer, M. *Tetrahedron Lett.* **1994**, *35*, 4453.
(89) Ishiwata, H.; Nemoto, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4710.
(90) (a) Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4712. (b) Ishiwata, H.; Sone, H.; Kigoshi, H.; Yamada, K. *Tetrahedron* **1994**, *50*, 12853.
(91) Inman, W.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 2822.
(92) Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630.
(93) Grieco, P. A.; Perez-Medrano, A. *Tetrahedron Lett.* **1988**, *29*, 4225.
(94) White, J. D.; Amedio, J. C. *J. Org. Chem.* **1989**, *54*, 736.
(95) (a) Hirai, Y.; Yokota, K.; Sakai, H.; Yamazaki, T.; Momose, T. *Heterocycles* **1989**, *29*, 1865. (b) Hirai, Y.; Yokota, K.; Yamazaki, T.; Momose, T. *Heterocycles* **1990**, *30*, 1101. (c) Hirai, Y.; Yokota, K.; Momose, T. *Heterocycles* **1994**, *39*, 603.
(96) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196.
(97) Rama Rao, A. V.; Gurjar, M. K.; Nallaganchu, B. R.; Bhandari, A. *Tetrahedron Lett.* **1993**, *34*, 7085.
(98) Imaeda, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 591.
(99) Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocienski, P.; Pimm, A.; Bell, R. *Synthesis* **1995**, *2*, 199.
(100) For syntheses of segments of these cyclodepsipeptides, see: (a) Schmidt, U.; Siegel, W.; Mundinger, K. *Tetrahedron Lett.* **1989**, *29*, 1269. (b) Kato, S.; Sugiura, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 6465. (c) Chiarello, J.; Joullié, M. M. *Synth. Commun.* **1988**, *18*, 2211. (d) Chiarello, J.; Joullié, M. M. *Synth. Commun.* **1989**, *19*, 3379. (e) Kang, S.-K.; Lee, D.-H. *Synlett* **1991**, 175. (f) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355.
(101) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, 335.
(102) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(103) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1901.
(104) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.
(105) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Am. Chem. Soc.* **1991**, *113*, 7811.
(106) Kobayashi, J.; Itagaki, F.; Shigemori, H.; Ishibashi, M.; Takahashi, K.; Ogura, M.; Nagasawa, S.; Nakamura, T.; Hirota, H.; Ohta, T.; Nozoe, S. *J. Am. Chem. Soc.* **1991**, *113*, 7812.
(107) Kobayashi, J.; Itagaki, F.; Shigemori, H.; Takao, T.; Shimonishi, Y. *Tetrahedron* **1995**, *51*, 2525.
(108) Itagaki, F.; Shigemori, H.; Ishibashi, M.; Nakamura, T.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 5540.
(109) Sowinski, J. A.; Toogood, P. L. *Tetrahedron Lett.* **1995**, *36*, 67.

CR941126F