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Synthesis of novel cyclopeptides containing heterocyclic skeletons†

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Cyclopeptides can be considered as naturally biologically active compounds. Over the last several decades, many attempts have been made to synthesize complex naturally occurring cyclopeptides, and great progress has been achieved to advance the field of total synthesis. Moreover, cyclopeptides containing heterocyclic skeletons have been recently developed into powerful reactions and approaches. This review aims to highlight recent advances in the synthesis of cyclopeptides containing heterocyclic skeletons such as triazole, oxazole, thiazole, and tetrazole.

1. Introduction

Previous reviews of this subject discussed the natural existence of cyclopeptides but failed to provide important knowledge about the synthesis of cyclopeptides containing heterocyclic skeletons. Due to the rapid development of this field, we believe it is worthwhile to update this subject. Selected examples from recent reports will be discussed, with emphasis on approaches that are very interesting and will open new portals for science to exploit these recent methods for the synthesis of these cyclopeptides.

A key step in chemistry and biology is molecular recognition. Many cellular processes are controlled by the binding of

hormones and peptides to receptors. Due to their therapeutic abilities, peptides have received growing interest in recent years. To date, more than 60 peptide drugs have been released to the market for the benefit of patients, and hundreds of novel therapeutic peptides are in preclinical and clinical development. The reason behind this success is the potent and specific, yet safe, mode of action of peptides.¹ Despite their high potential, peptides have limitations, such as short half-life, rapid metabolism, and poor oral bioavailability. However, different types of modifications can be employed to improve the pharmacokinetic properties of peptides. For several key reasons, cyclization of linear peptides is often used as an attractive modification. First, it is anticipated that by obtaining fixed geometries, cyclic peptides can bind more efficiently to their respective receptors. It is additionally hoped that these conformationally constrained cyclic peptides will be selective to explicit receptor subtypes, resulting in higher receptor binding affinities compared with their linear analogues. Moreover, cyclic peptides are often chosen over their linear analogues due to their enhanced enzymatic stability and provide enhanced membrane permeability, which result in improved

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† Dedicated to Prof. Lutz Tietze on the occasion of his 75th birthday.



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Fatemeh Tahoori was born in Iran in 1983; she received her PhD at K. N. Toosi University of Technology in 2013 under the supervision of Prof. Saeed Balalaie, where her work focused on the synthesis of cyclopeptides containing triazole moieties. Currently, she is working as an assistant professor at Razi Vaccine and Serum Research Institute.



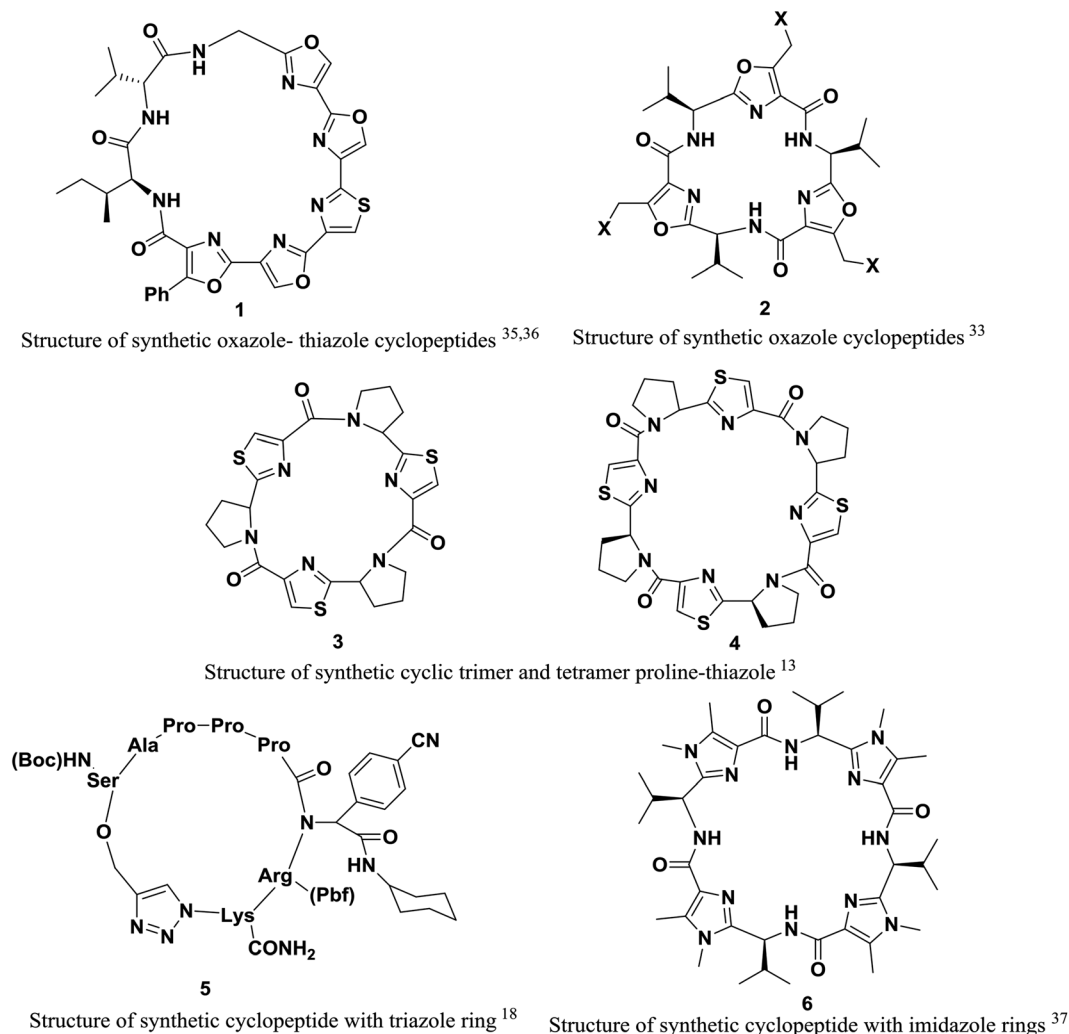


Fig. 1 Structures of some synthetic cyclopeptides.

bioavailability of the cyclopeptides; they also possess entropic advantages in molecular recognition.² Therefore, they are



Saeed Balalaie was born in Iran in 1965; he received his BSc degree from the University of Tehran in 1989, his MSc from Shahid Beheshti University, Iran, in 1991, and his PhD degree from Sharif University of Technology, Iran, in 1996. He started his career as an assistant professor at K. N. Toosi University of Technology in Iran, Tehran, Iran, in 1997; he was promoted to associate professor in 2003 and full professor in 2007 at

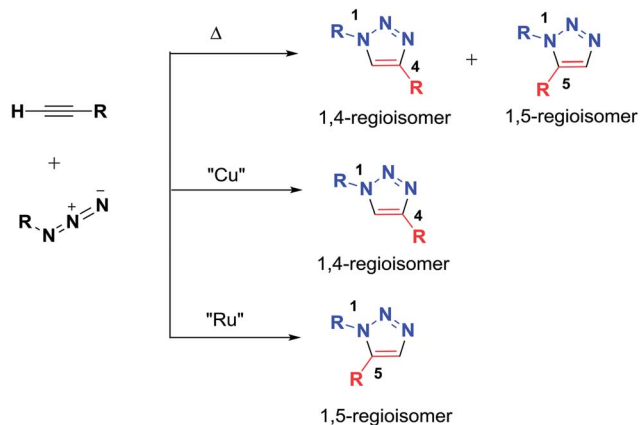
the aforementioned university. He received an Alexander von Humboldt research fellowship in 2001 and worked with Professor Rolf Gleiter at the University of Heidelberg, Germany. His research interests focus on the synthesis of organic compounds through designing novel domino reactions as well as the synthesis of peptides and cyclopeptides.

sought as promising lead compounds for drug discovery and the development of new peptide analogues; simulated peptides, which can provide biological targets of relevant receptors and adjust their properties, are the most important areas of medicine, chemistry, and biology.³⁻⁹ Due to the unique, promising properties and biological significance of cyclopeptides in addition to their additional level of synthetic complexity, naturally occurring cyclic peptides have been attracting the attention of synthetic chemists. In the past decades, different cyclopeptides containing heterocyclic motifs have been developed. This review aims to highlight novel, recently developed peptide cyclizations with heterocyclic skeleton approaches.³

Over 100 cyclopeptides have been isolated and characterized from plants, marine organisms,^{10,11} fungi¹² and microorganisms. Due to the widespread occurrence of these compounds, they represent an important class of natural products. These peptides have certain advantages over chemical drugs, such as relatively simple structures, fewer side effects, and good absorption.

Cyclic peptides have established many successes, *e.g.* octreotide (Novartis); integrilin, a cyclic peptide heptapeptide Gp IIb/IIIa inhibitor (Cor Pharmaceuticals); and the naturally





Scheme 1 Synthesis of 1,4- and 1,5-disubstituted 1,2,3-triazoles by heat, CuAAC, and RuAAC.

occurring cyclosporine A for immunosuppression. However, the cost of cyclic peptide synthesis is high because the required reagents are expensive. Meanwhile, many attempts have been made to optimize cyclization yields; the use of inexpensive reagents and chromatographic separation has pushed the balance toward the synthesis of cyclosporine A compared to its isolation from its natural source.¹³

The synthesis of cyclic peptides that simulate natural compounds is of great interest to chemists. Various approaches and methods to form rings of peptide sequences have been suggested and provided. One of these methods is head-to-tail loop forming for shorter sequences, performed on resins. The type of reagents used for each sequence depends on various parameters, such as the size of the ring.^{13,14}

Other methods of ring formation require the use of different chemical reactions, such as the creation of lactam bridges;¹⁵ disulfide bridges, which are most commonly used for sequences with two cysteine amino acids;^{16,17} click chemistry;^{18,19} metathesis;^{20,21} and the Ugi,^{22,23} Hantzsch,^{24,25} Horner–Wadsworth–Emmons (HWE),²⁶ Mannich²⁷ and Heck²⁸ reactions.

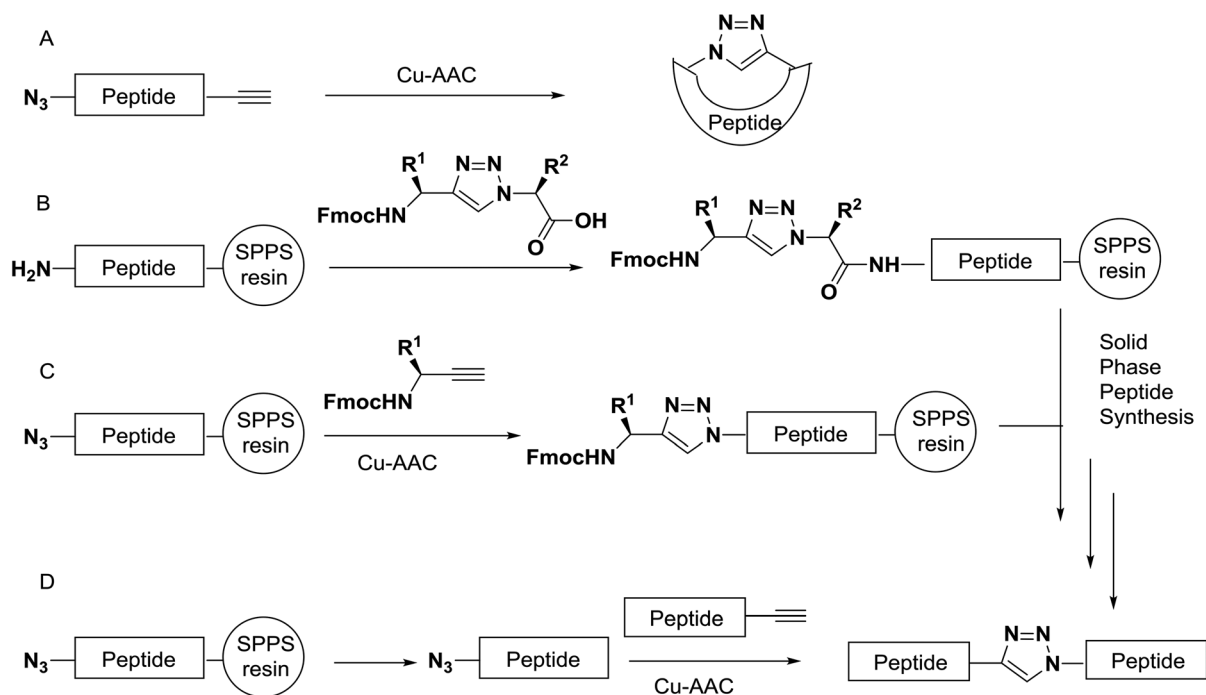
Also, new methods have been used in the past decade to cyclize linear peptides through the use of enzymes²⁹ and microwaves.^{8,30}

However, in this review, we decided to investigate the insertion of heterocycle rings in cyclopeptides. Heterocycles, which are an extensively published subject, include triazole,¹⁸ imidazole,^{31–33,37} oxazole^{25,33–35} and thiazole rings.^{13,24,25,34,36} These rings endow peptide structures with rigidity, and the interactions of these structures with receptors can be studied more readily and accurately (Fig. 1).

2. Cyclopeptides with triazole moieties

In the last decade, the synthesis of 1,2,3-triazole units has been of great interest. 1,2,3-Triazoles represent a class of heterocycles with extended properties for employment in peptide sciences because they are considered to be amide bond isosteres while being stable to enzymatic degradation. Due to these characteristics, 1,2,3-triazoles are promising candidates for the development of novel peptidomimetics with possibly improved biological activities. Only a few examples of triazole-based peptidomimetics can be found in the literature.³⁸

The first to study and investigate 1,2,3-triazoles was Huisgen in 1960; he described the Huisgen 1,3-dipolar cycloaddition from the reaction of an alkyne and an azide to afford 1,4- and

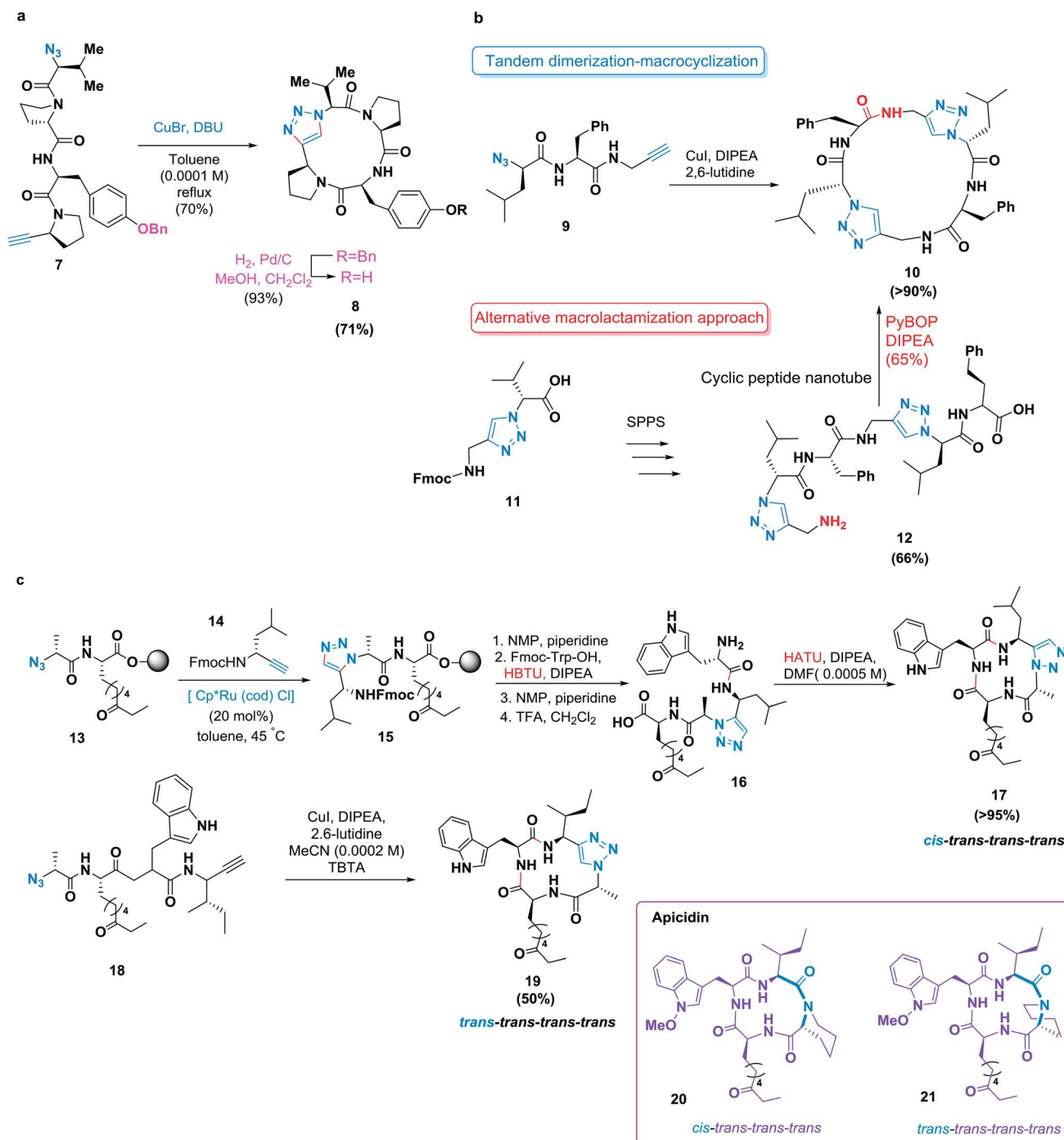


Scheme 2 Schematic examples of the synthesis of triazole peptides.



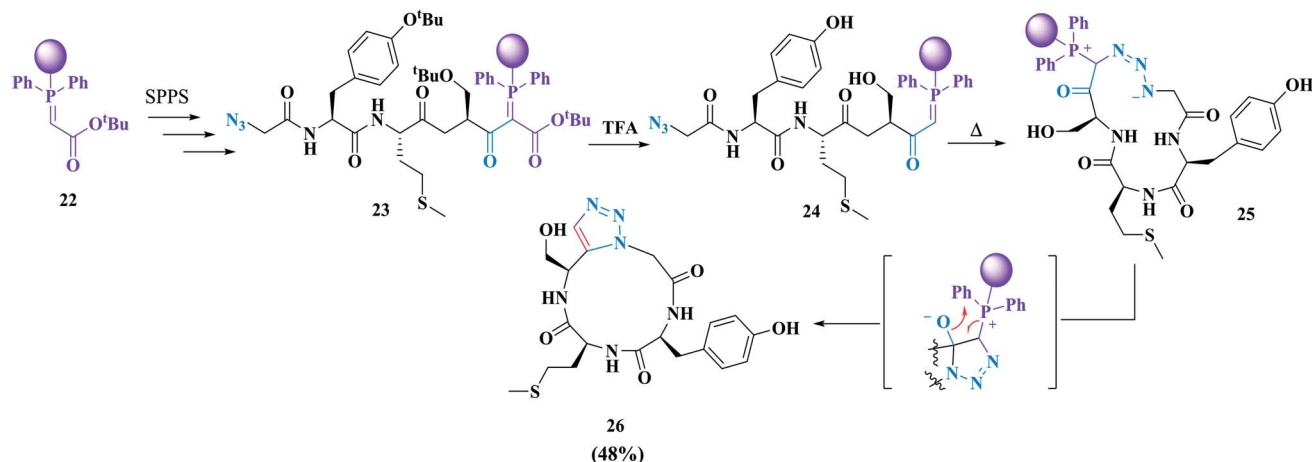
1,5-disubstituted triazole regioisomers. Several methodologies using transition metals have been investigated to control the regioselectivity and to improve the reaction conditions for the formation of 1,2,3-triazoles. Basically, Sharpless and Meldal developed the copper-catalyzed azide-alkyne cycloaddition

reaction (CuAAC), which afforded regioselective formation of the 1,4-regioisomer; meanwhile, ruthenium-catalyzed cycloaddition afforded the 1,5-regioisomer (Scheme 1). To date, many examples of the application of the click chemistry reaction in chemical biology and medicinal chemistry have been reported.

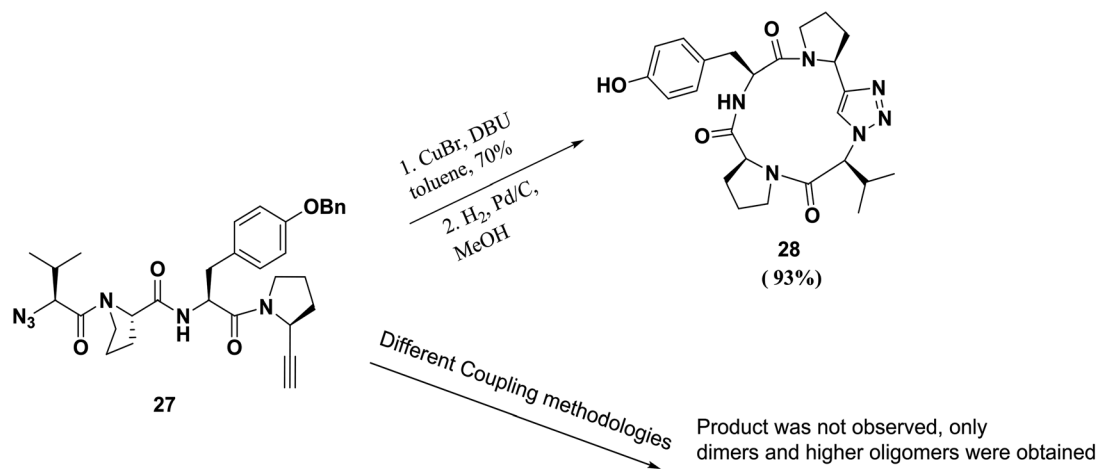


Scheme 3 Azide-alkyne cycloadditions in the synthesis of peptide macrocycles. (a) A click-mediated macrocyclization of Tyr-Pro-Val-Pro. (b) Synthesis of a cyclic peptide nanotube through either a high-yielding tandem dimerization-macrocyclization approach by two tandem click reactions of an azido-dipeptide alkyne (top) or through a less efficient conventional macrolactamization approach (bottom). (c) The synthesis of triazole-modified analogues of the cyclic tetrapeptide apicidin. Top: ruthenium-catalyzed formation of a 1,5-disubstituted 1,2,3-triazole on a solid phase is followed by macrolactamization to yield an analogue resembling the biologically active conformation of apicidin. Bottom: a $\text{Cu}(\text{i})$ -catalyzed intramolecular azide-alkyne cycloaddition to yield an analogue of apicidin resembling its predominant conformation in solution.





Scheme 4 Synthesis of a cyclic tetrapeptide analogue containing a 1,5-disubstituted 1,2,3-triazole through intramolecular cyclative cleavage of a solid-support-bound azidopeptidylphosphorane. HATU, 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; NMP, *N*-methyl-2-pyrrolidone; TBTA, tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl] amine.



Scheme 5 Application of click chemistry to the macrocyclization of peptidomimetics and the synthesis of cyclopeptides containing triazole skeletons.

Thus, 'click' has been successfully applied to the macrocyclization of peptides.^{2,39,40}

Azido- and alkyne building blocks can be built into the backbones of peptides by classical methods of solid-phase or solution peptide chemistry.^{41,42} The triazole moiety can be incorporated by different approaches. For example, the synthesis of small cyclic triazolo-peptides is usually attained by solution-phase synthesis of the precursor followed by cyclisation employing Cu-AAC (Scheme 2A). For the synthesis of longer triazole peptides, the triazole can be incorporated during peptide elongation by coupling of a triazole-containing dipeptide mimic by classical solid phase peptide synthesis (SPPS) methods (Scheme 2B).⁴³ Alternatively, the heterocycle can be installed on a solid support by Cu-AAC of an alkyne precursor with an immobilized azide (Scheme 2C).⁴⁴ Finally, peptide fragments functionalized with azides and alkynes can be bonded by Cu-AAC in solution, a strategy that has been

successfully used as a ligation method for the assembly of larger proteins by Cu-AAC⁴⁵ (Scheme 2D).

Various experimental reaction conditions have been established for Cu-AAC in solution and on solid supports. Cu-AAC is a metal-catalyzed, stepwise reaction that requires the presence of an active copper(i) species, an azide, an alkyne, and a proton acceptor.⁴⁶ The reaction is very robust, provided that all the aforementioned reactants are maintained in solution and that the copper(i) is not oxidized or disproportionated. In particular, the copper(i) source should be chosen in accordance with the solvent system employed. In general, copper(i) halides or [Cu(CH₃CN)PF₆] are the preferred Cu(i) sources to perform Cu-AAC in organic solvents such as THF, DMSO, and toluene. Employment of these salts often requires an equivalent of an amine base, such as triethylamine, diisopropylethylamine, or piperidine.^{46,47} For Cu-AAC conjugations in aqueous media, *in situ* generation of the Cu(i) catalyst from Cu(II) salts in the



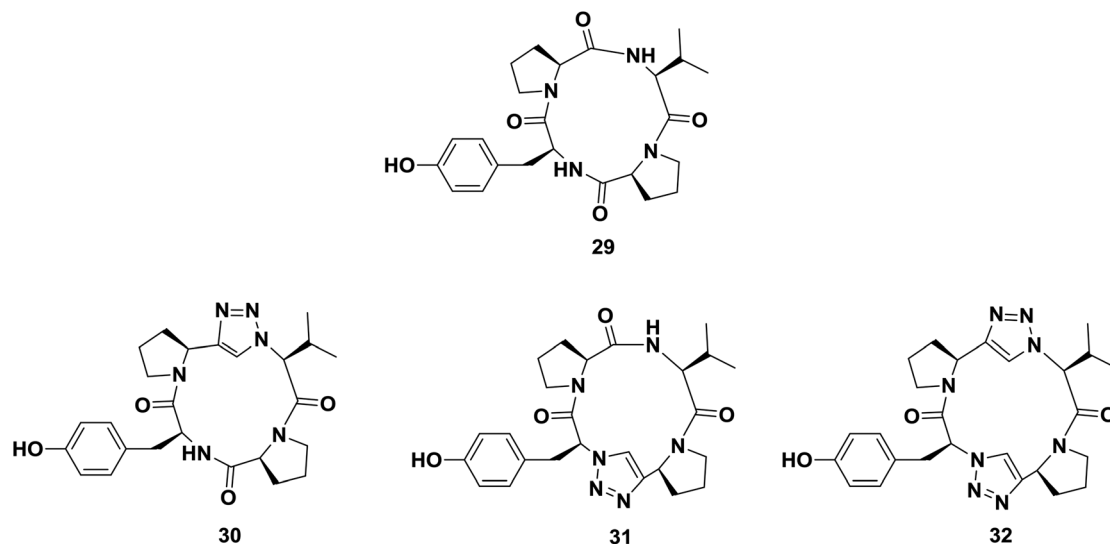


Fig. 2 Examples of cyclopeptides and their triazolo-analogues synthesized by Bock.

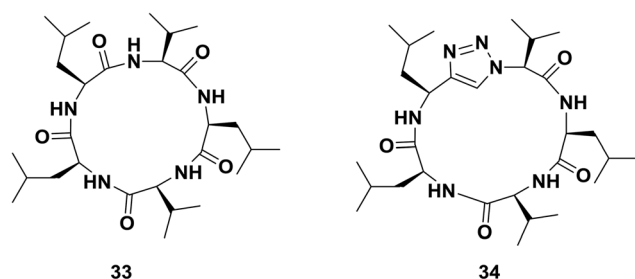


Fig. 3 Examples of a cyclopeptide and its triazolo-analogue synthesized by Davis and co-workers.

presence of a reducing agent, *e.g.* sodium ascorbate, has become the method of choice. Water-soluble sources of copper(i) have found frequent application because Cu(II) salts are often less expensive and available in higher purity than copper halides. The combination of CuSO₄ and sodium ascorbate is particularly suited for Cu-AACs in polar solvents, such as water, alcohols, acetonitrile, DMF, or mixtures thereof. If the substrates of Cu-AAC possess potential coordination or chelation sites for copper species (*e.g.* carboxylates, phosphates, thiols, imidazoles, or amines) it is recommended to add

a stabilizing ligand to prevent segregation of the copper catalyst.⁴⁸ In addition, the presence of such ligands often accelerates the reaction and prevents oxidation of the Cu(I) catalyst.^{49,50} A large number of stabilizing ligands for Cu(I) have been reported, of which polytriazole-based systems are the most frequently employed. Among these readily accessible and structurally diverse ligands,^{51,52} tris-(benzyltriazolylmethyl)amine (TBTA) is commercially available and, thus, most commonly used. Although some general procedures and reaction conditions can be defined for performing Cu-AAC with peptidyl substrates, it should be noted that individual optimizations may be required in certain cases in order to achieve optimal results.⁴⁵

Due to hydrogen bonding and dipole interactions, triazole products can function as more than passive linkers and can readily interact with biological targets.^{53,54} The cycloaddition of an N-terminal azide and a C-terminal alkyne allows the synthesis of triazole-containing cyclopeptide analogues⁵⁵ (Scheme 3a). Basically, the tyrosinase inhibitory activity of these isosteres was retained.⁵⁶ Lokey and co-workers described the utility of this reaction as a macrocyclization tool.⁵⁷ They achieved the cyclization of leucine-rich tetra-, penta-, hexa- and heptapeptides on solid supports. However, the formation of dimeric and trimeric by-products has been noted in many

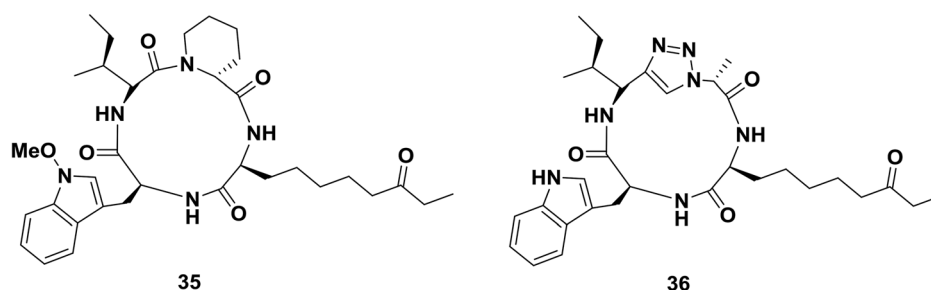


Fig. 4 Examples of a cyclopeptide and a triazole-containing peptide synthesized by Horne and co-workers.



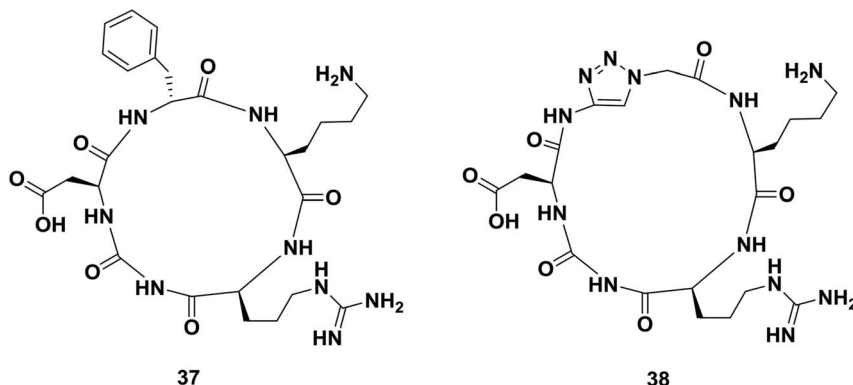


Fig. 5 Examples of a cyclopeptide and a triazole-containing peptide synthesized by Liu and co-workers.

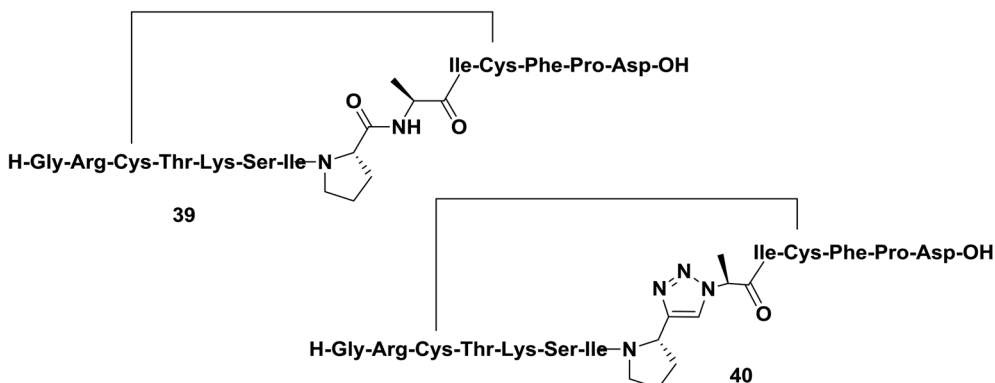
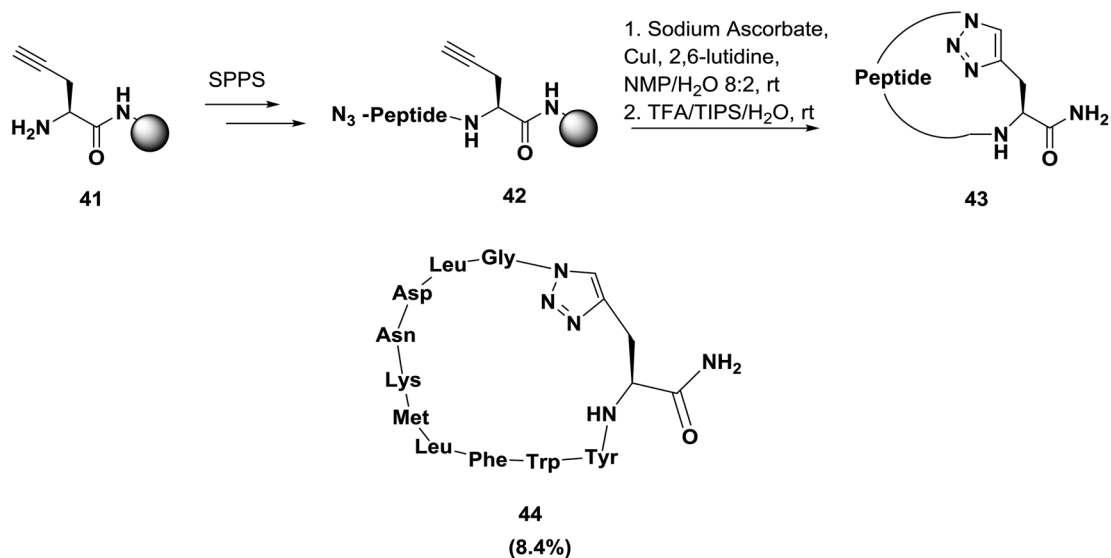


Fig. 6 Examples of a cyclopeptide and a triazole-containing peptide synthesized by Tischler and co-workers.

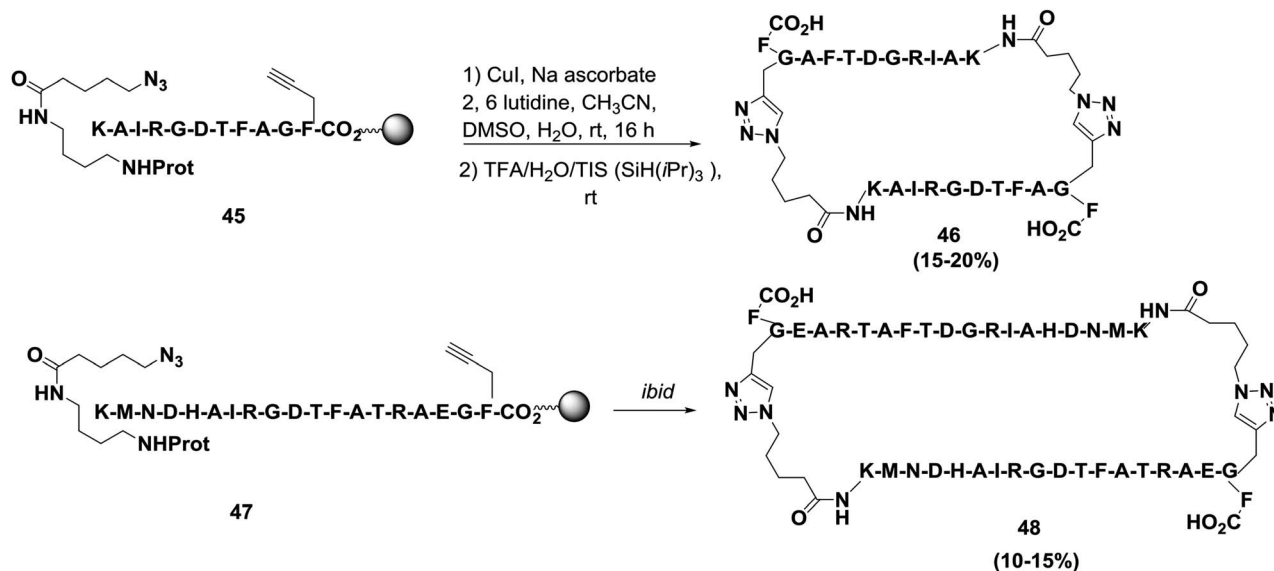
copper-catalyzed azide-alkyne cycloadditions.²⁶ A tandem dimerization-macrocyclization approach enabled by several tandem click reactions was demonstrated by Ghadiri and co-workers;⁵⁸ they synthesized C₂-symmetric cyclic peptide

scaffolds that self-assembled into peptide nanotubes.⁵⁹ This approach was more successful than a conventional macro-lactamization of a linear precursor already containing both triazole units (Scheme 3b).



Scheme 6 Application of click chemistry to the macrocyclization of peptidomimetics.





Scheme 7 Preparation of cyclodimeric peptides using click chemistry.

Meanwhile, 1,5-disubstituted 1,2,3-triazoles are also known as surrogates for *trans*-amide bonds. In another approach, Ghadiri and co-workers proved that the incorporation of one or two of these moieties into cyclic tetrapeptides resulted in a stronger binding affinity for the somatostatin (SST) receptor.^{60a} In addition, Ghadiri and co-workers successfully fused these heterocycles as *cis*-amide isosteres of a naturally occurring cyclic tetrapeptide. This approach was accomplished through initial ruthenium(II)-catalyzed formation of the 1,5-disubstituted 1,2,3-triazole moiety in the linear peptide on the resin surface, followed by a conventional macrolactamization of the pseudotetrapeptide.^{60b} The synthesized analogue, incorporating a 1,5-disubstituted 1,2,3-triazole, displayed similar biological activity to that of the naturally occurring apicidin.

Rademann and co-workers successfully reported the first cyclization of azido-alkynyl peptides to produce 1,5-disubstituted triazole-containing macrocycles. They developed an on-solid-support peptide synthesis strategy. In their approach, cyclization and cleavage from the solid support were carried out in the same chemical reaction.⁶¹ Using this strategy, simple purification of the synthesized cyclic peptide can be achieved because the open-chain by-product oligomers remain attached to the solid support. This approach includes a dipolar cycloaddition of polymer-bound azidopeptidylphosphoranes which is metal-free and does not require amino acid alkynes (Scheme 4).⁶²

One of the major applications of click chemistry is the preparation of small cyclic peptide analogues that are too strained for closure *via* lactamization. The synthesis of cyclo-[(L)-Pro-(L)-Tyr-(L)-Pro-(L)-Val], a potent tyrosine inhibitor, is difficult to achieve using traditional methods due to its unfavorable transition states. In order to perform this cyclization, Bock and co-workers designed and synthesized its triazole analogue.⁵⁵ The desired cyclic peptide was isolated in 70% yield after CuI-catalyzed cycloaddition, as shown in Scheme 5. All the resulting triazole-peptides 30–32 were as active as the parent cyclopeptide 29 with regard to the inhibition of tyrosinase^{51,52}

(Fig. 2). This approach allows this strategy to be used as a general method for preparing conformational constrained cyclic peptidomimetics in solution phase.⁶³

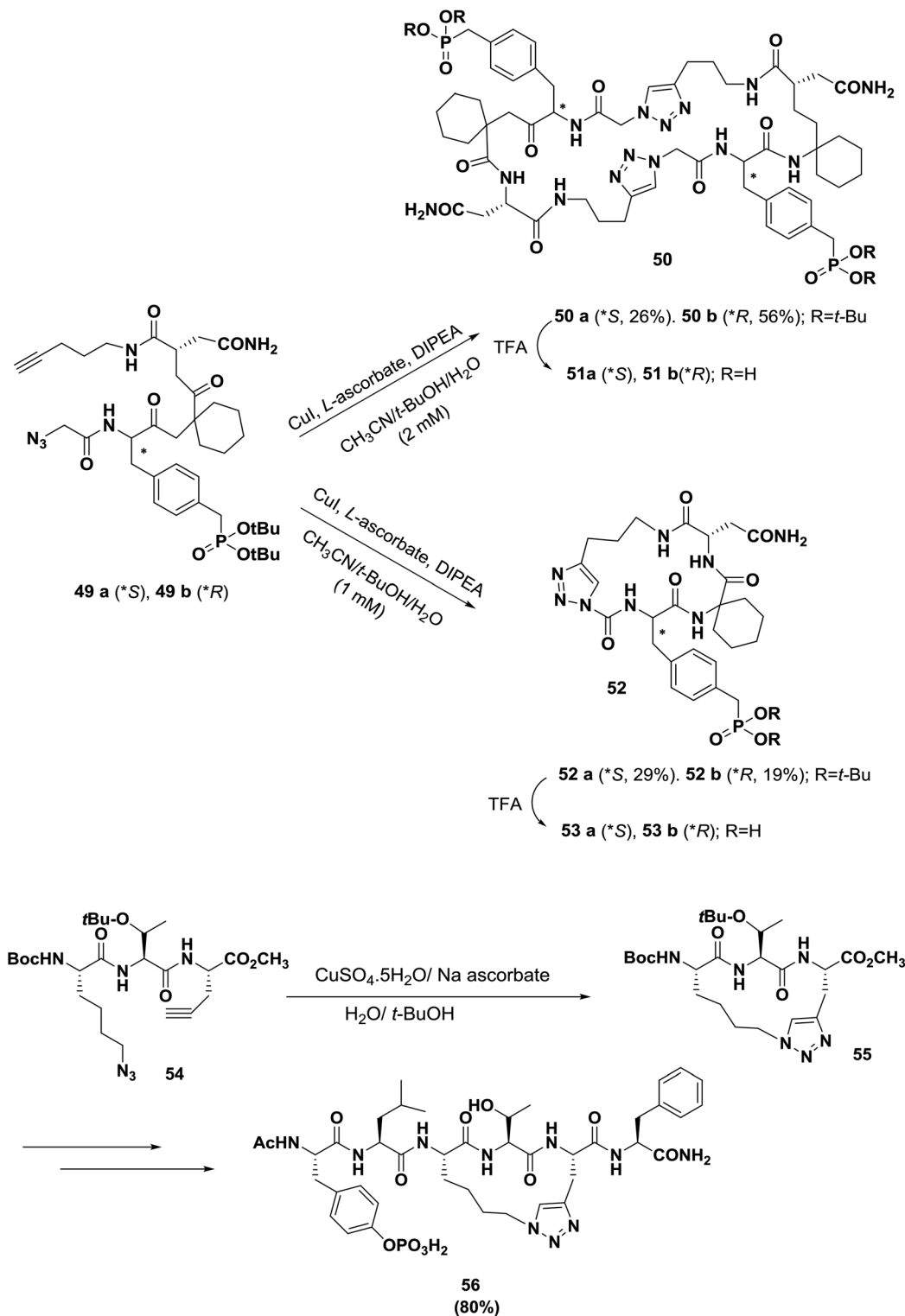
On the other hand, Davis and co-workers also reported triazole-peptide 34, an analogue of sansalvamide A 33, an inhibitor of heat shock protein 90 with cytotoxic effects against several cancer cell lines.⁶⁴ In their work, they studied the utility of different moieties as amide bond surrogates (1,2,3-triazole, oxazole, thiazole, or pseudoproline) in the same position. Evaluation of the compounds *in vitro* revealed that only triazole and thiazole heterocycles could be incorporated into the peptide without decreasing its cytotoxicity. In the case of triazole derivative 34, the potency of the reference compound 33 was preserved in terms of the inhibition of cell proliferation³⁸ (Fig. 3).

Horne and co-workers replaced an isoleucyl-pipecolyl residue with an isoleucyl-1,2,3-triazole-alanyl dipeptide mimic of apicidin 35, an inhibitor which binds with nanomolar affinity to several subtypes of histone deacetylases (HDACs; Fig. 4).^{60b} Interestingly, the modification changed the subtype-specificity of the original compound. Compared to apicidin 35, triazole-peptide 36 showed an 8-fold decreased inhibitory effect against HDAC-subtype 1, while its effect against HDCA-subtype 3 was retained.

Cyclic peptides containing the amino acid sequence Arg-Gly-Asp (cRGD) bind to $\alpha v \beta_3$ integrins, which are involved in tumor angiogenesis and metastasis. Thus, several cRGD-based compounds have been developed to target tumor cells specifically. In 2008, Liu and co-workers reported the synthesis of a mimic of cyclopeptide 37 in which the *D*-phenylalanyl residue was replaced by a glycyl-1,2,3-triazole-glycyl dipeptide mimic (Fig. 5).⁶⁵ *In vitro* studies performed with both compounds showed that triazole-peptide 38 had an affinity towards its receptor comparable to that of the parent compound 37.³⁸

Sunflower trypsin inhibitor 1 (SFTI-1) is a potent cyclic protease inhibitor with a turn conformation that is critical for its activity. Tischler and co-workers replaced a *trans*-amide bond located between the prolyl and the alanyl residue of SFTI-1 analog



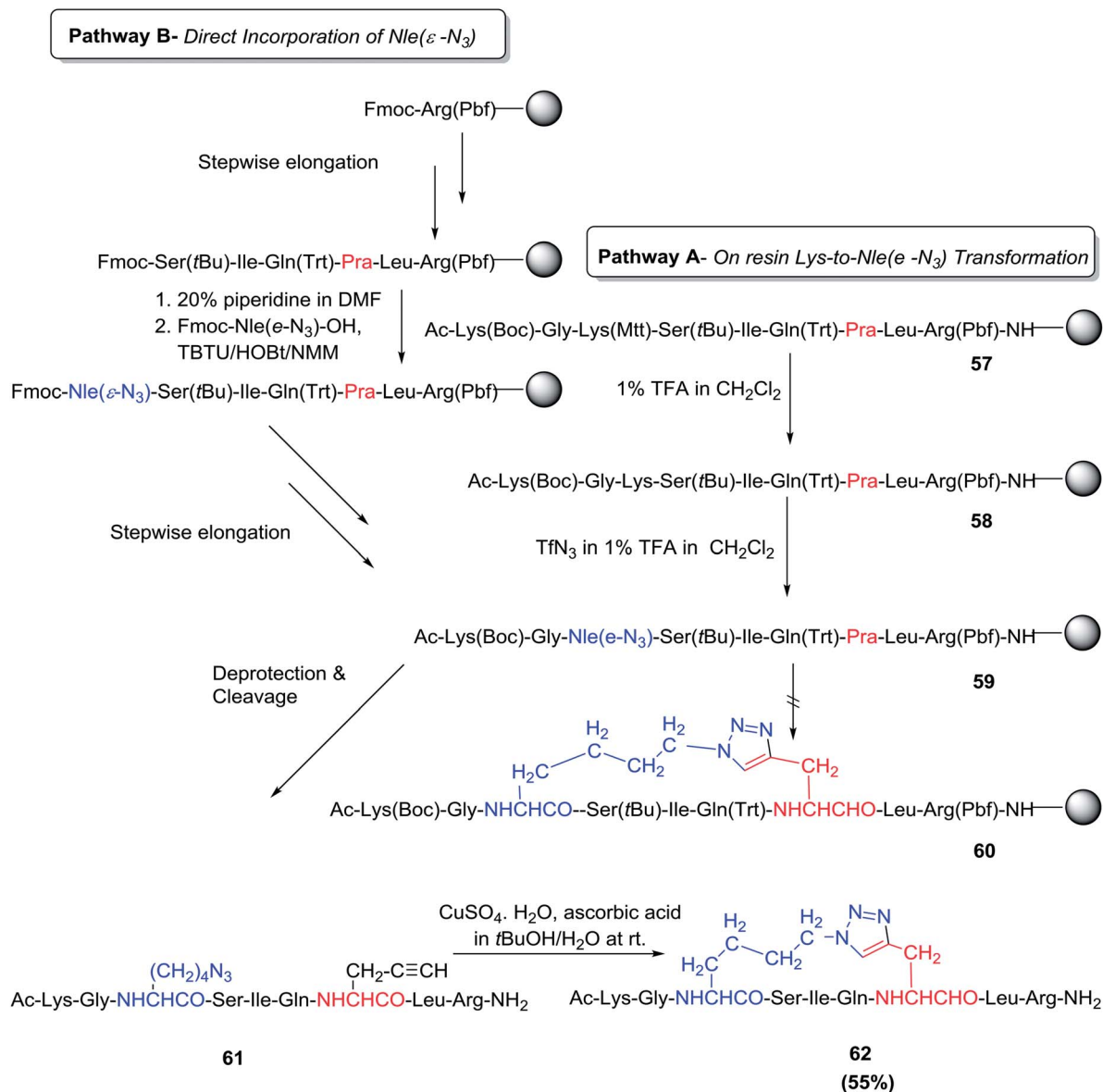


Scheme 8 Application of click chemistry to construct triazole bridges in peptides.

39 with a prolyl-1,2,3-triazole-alanyl dipeptoid (Fig. 6).⁴⁴ In their work, the authors reported the use of both 1,4- and 1,5-disubstituted 1,2,3-triazoles as amide-bond surrogates. As expected, only compound 40 derivatized with a 1,4-disubstituted triazole adopted a conformation close to that of the parent cyclopeptide and exhibited nanomolar affinity against bovine trypsin.

Later, Inguibert and co-workers were able to establish a convenient method for the creation of a library of triazole peptidomimetics on a solid phase, as shown in Scheme 6.⁶⁶ After the synthesis of the peptide, cyclization of the peptidyl-resin was performed by exposure to 0.5 equivalents of copper(i) iodide in the presence of sodium ascorbate and 2,6-lutidine in NMP/





Scheme 9 Strategies employed in the solid-phase synthesis of N^{α} Ac-[Xaa¹³(δ^1), Yaa¹⁷(δ^2)] hPTHrP (11–19)NH₂-[(δ^1 (CH₂)₄-1,4-[1,2,3]triazolyl-CH₂ δ^2)]^a. The δ sign indicates the positions of the side-chain-to-side-chain cyclization.^a Pathway A: stepwise assembly of the fully protected resin-bound peptide in which the ϵ -NH₂ groups of the two lysine residues are differently protected to allow selective deprotection and subsequent diazo-transfer reaction in the on-resin transformation of Lys¹³ into Nle (ϵ -N₃). Pathway B: stepwise on-resin assembly of the fully protected peptide **59** incorporating Fmoc-Nle (ϵ -N₃)-OH as a building block. Cleavage and deprotection of **59** obtained by either pathway generated the linear precursor **61**, which was then cyclized by CuI-catalyzed azide-alkyne 1,3-dipolar cycloaddition to yield the cyclic (1,2,3) triazolyl-containing peptide **62**.

CH₂Cl₂. Then, the peptide was cleaved from the resin surface using TFA to afford the final cyclic triazole bridged peptidomimetic in good yield and high purity. Using this methodology, Inguibert's group was able to successfully assemble and screen 18 conformationally constrained peptidomimetics; they discovered some promising lead compounds, such as compound **44**, which exhibits potent bioactivity in inhibiting VEGFR 1.³⁸

Finn and co-workers successfully synthesized two cyclodimerized peptides, 22-residue cyclic peptide **46** and 38-residue cyclic peptide **48**, as shown in Scheme 7.⁶⁷ The cyclizations were performed by exposing each resin to 0.5 equivalents of CuI for 16 h at room temperature. The approximate yield of

cyclodimerization was 60%. Meanwhile, this cyclization required a certain density on the solid support, and the dimeric pathway was favored even when the two chains were difficult to bring together. Based on their experimental observations, Finn and co-workers suggested that the reaction proceeds *via* two alkynes bound to a dicopper intermediate. The reason behind the formation of macrocyclodimers over the corresponding monomeric forms is that *exo*-like intermediates are favored over *endo*-like due to the geometric constraints of forming 1,4-disubstituted triazoles.^{67–69}

In another example of the development of tyrosine kinase-dependent signal transduction inhibitors, Burke's group



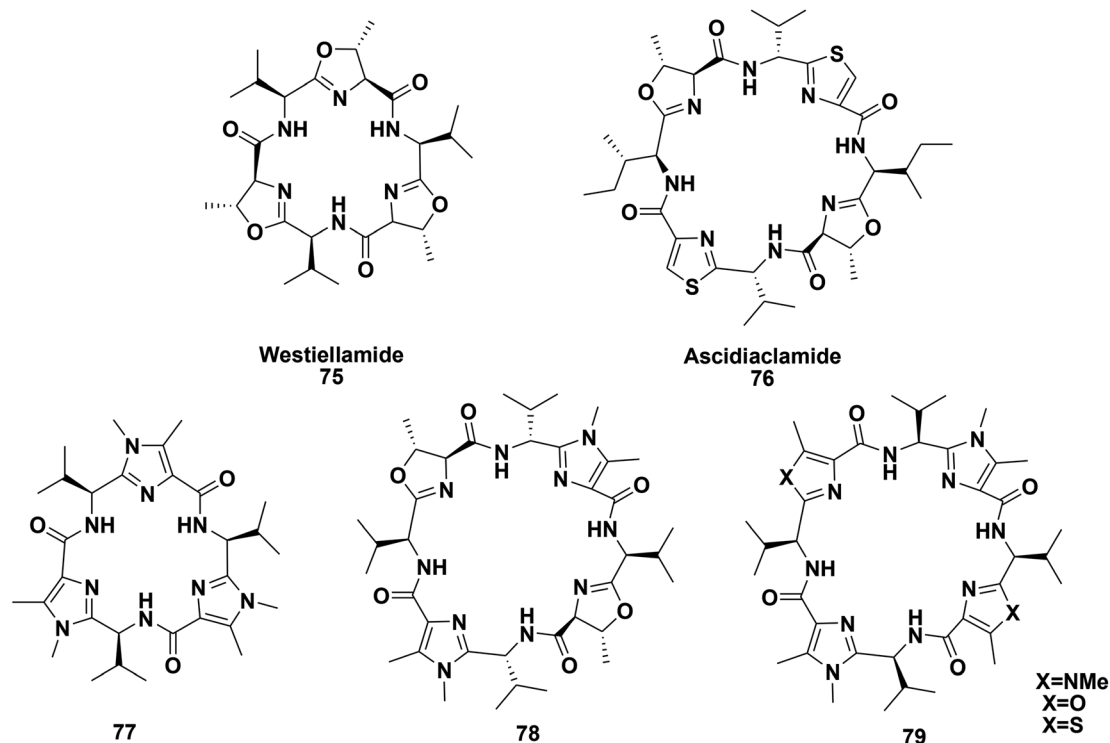
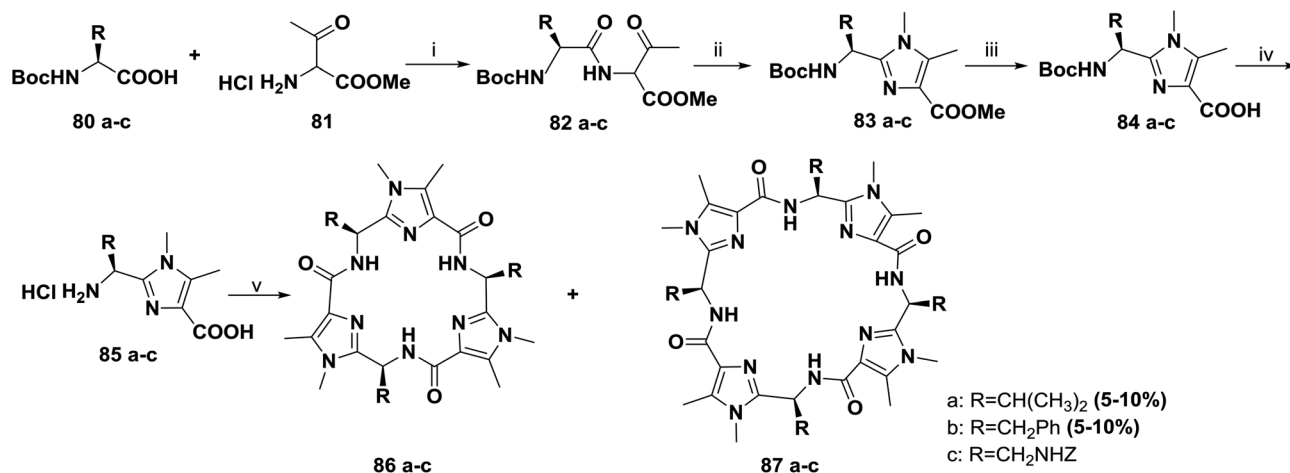


Fig. 7 *Lissoclinum* cyclopeptides and their imidazole analogues.

8.^{63,71} Compound 54 was converted to the key intermediate 55 in 80% yield in the presence of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ /sodium ascorbate. Macrocyclic compound 56 binding to STAT3 is a promising initial lead compound for further optimization for the design and development of potent small-molecule inhibitors of STAT3 as a new class of anticancer drugs.

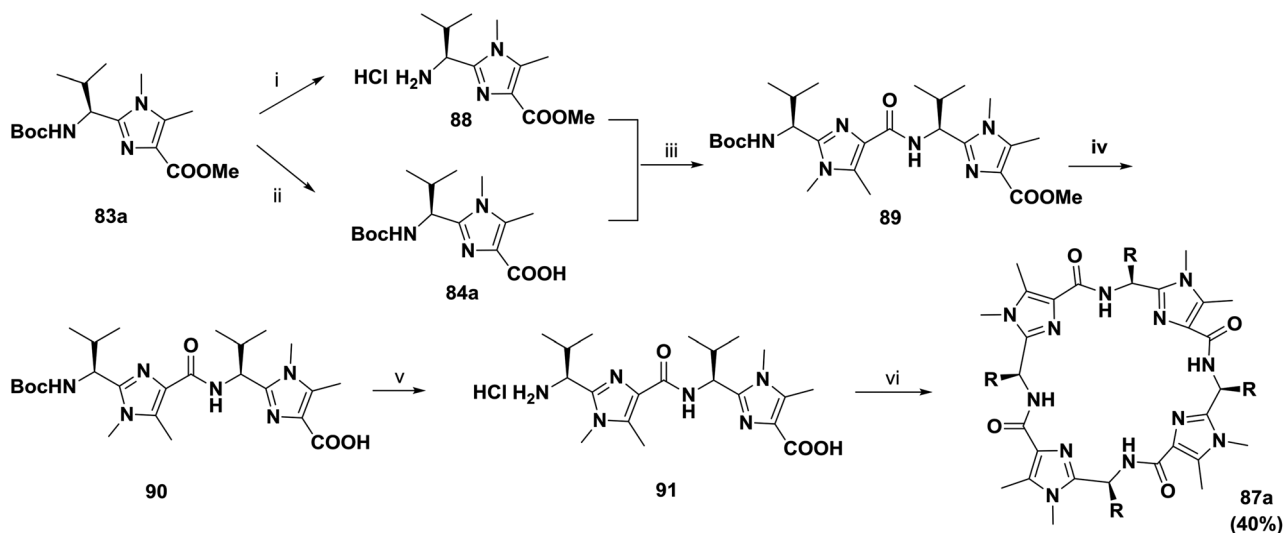
Chorev and co-workers developed 1,2,3- triazole-containing cyclic peptides through solid-phase peptide side-chain-to-side-chain synthesis by assembling the azido and alkynyl side-chains within the peptide and cyclizing the resin-bound peptide through CuI-catalyzed azide-alkyne 1,3-dipolar

cycloaddition.⁷² Two different approaches were used to insert the L-2-amino-6-azidohexanoic acid residue [$\text{Nle}(\epsilon\text{-N}_3)$] into the resin-bound peptide. In pathway A, the Nle ($\epsilon\text{-N}_3$) residue was produced *via* a diazo-transfer reaction on the selectively deprotected ϵ -amino moiety of the fully protected resin-bound peptide; meanwhile, in pathway B, Fmoc-Nle ($\epsilon\text{-N}_3$)-OH was incorporated as part of the standard stepwise on-resin peptide assembly strategy (Scheme 9). The assembly of the resin-bound peptides 58 and 59 by either DEPBT/DIEA or TBTU/HOBt/NMM-mediated coupling was accomplished in a straightforward manner by both pathways A and B.



Scheme 12 Synthesis of cyclopeptides 86a–c and 87a–c containing imidazole moieties. Reagents and conditions: (i) isobutyl chloroformate, NMM, THF, -20°C , 85%; (ii) MeNH_2 , AcOH, xylenes, reflux, 70%; (iii) 2 M NaOH, MeOH/dioxane, rt, 95%; (iv) HCl/AcOEt, rt, quant.; (v) DPPA, iPr_2NEt , CH_3CN , rt, 25% to 35% for 86a–c, 5% to 10% for 87a, 87b.

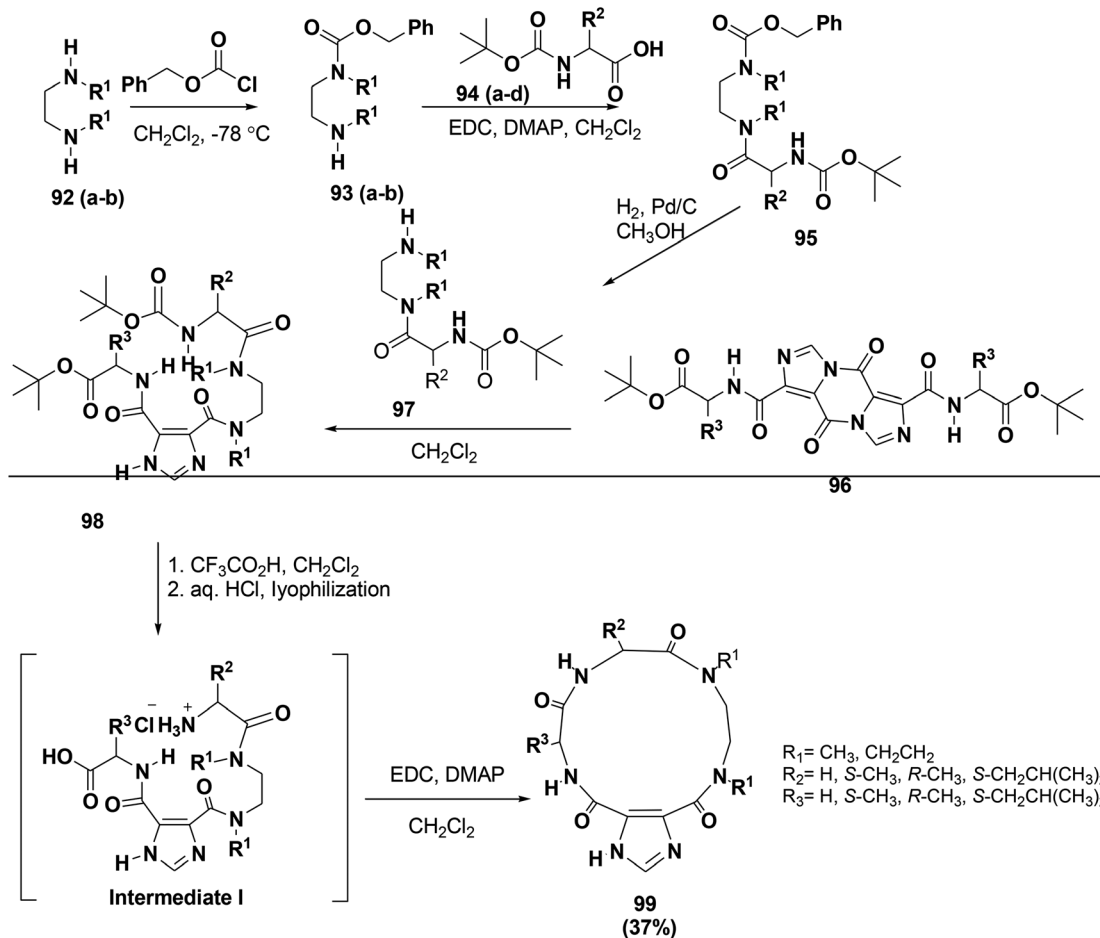




Scheme 13 Synthesis of cyclopeptide **87a** containing imidazole moieties. Reagents and conditions: (i) HCl/AcOEt, rt, quant.; (ii) 2 M NaOH, MeOH/dioxane, rt, 95%; (iii) DPPA, $i\text{Pr}_2\text{NEt}$, CH_3CN , rt, 70%; (iv) 2 M NaOH, MeOH/dioxane, rt, 95%; (v) HCl/AcOEt, rt, quant.; (vi) FDPP, $i\text{Pr}_2\text{NEt}$, CH_3CN , rt, 40%.

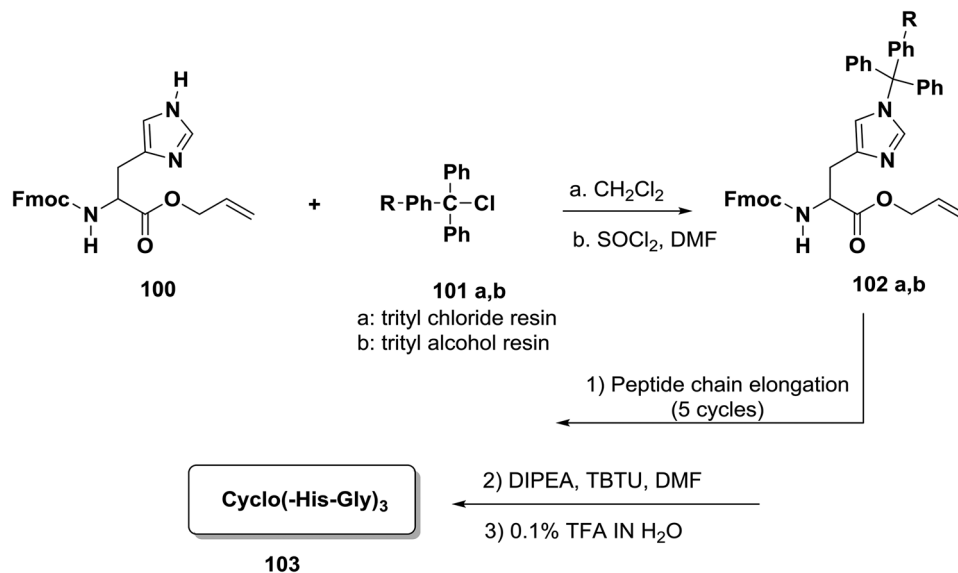
Deprotection of all side-chain protecting groups and simultaneous cleavage from the resin surface yielded the crude linear peptide **61**. Complete conversion of the linear peptide **61** to the

desired cyclic 1,2,3-triazolyl-containing peptide **62** was achieved after ON incubation at r.t. in $t\text{-BuOH}/\text{H}_2\text{O}$ (1 : 2 v/v) in the presence of a 4.4-fold molar excess of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and

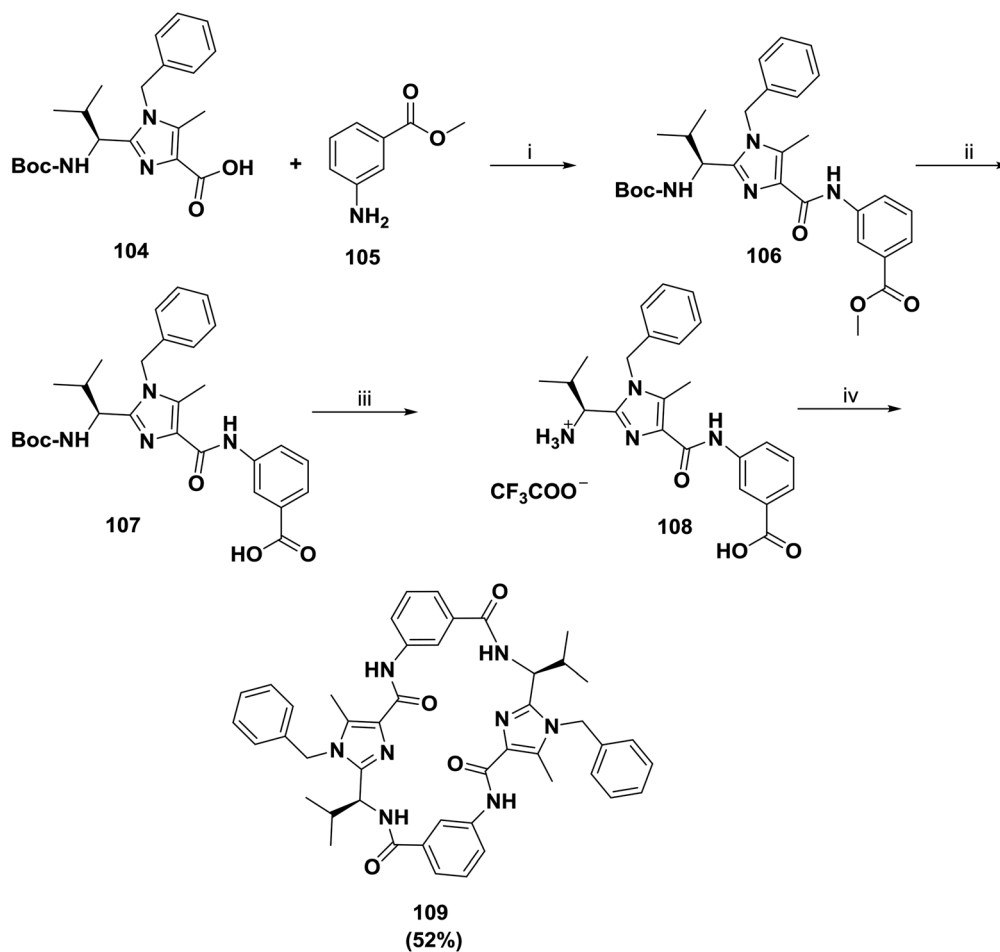


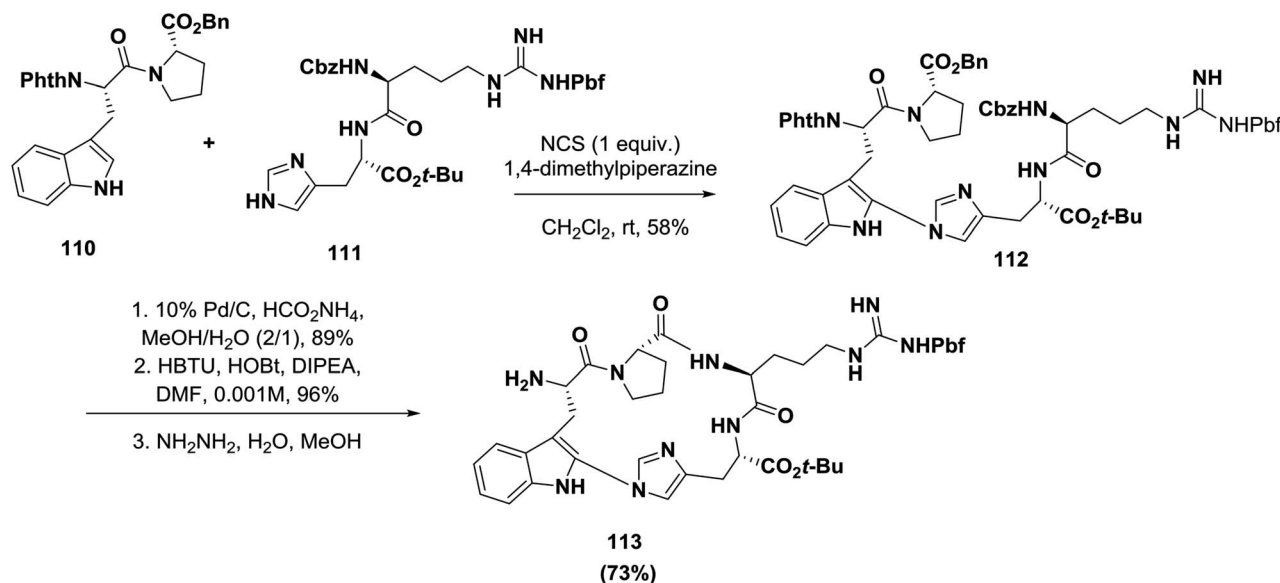
Scheme 14 Synthetic strategy for the macrocycle synthesis.





Scheme 15 Cyclization of histidine-containing peptides.

Scheme 16 Synthesis of receptor 109. Reagents and conditions: (i) FDPP, *i*Pr₂NEt, CH₃CN, r.t., 41%; (ii) 2N NaOH, MeOH/dioxane, 0 °C → rt, quant.; (iii) TFA, CH₂Cl₂, 0 °C → rt, quant.; (iv) FDPP, *i*Pr₂NEt, CH₃CN, rt, 52%.



Scheme 17 Synthesis of indole-imidazole linkage cyclic peptidomimetics by an oxidative coupling reaction.

ascorbic acid.⁷² It is worth noting that all attempts to carry out on-resin intra-chain CuI-catalyzed side-chain-to-side-chain azide-alkyne 1,3-dipolar cycloaddition with different reported approaches failed.

A cyclopeptide-containing triazole moiety was reported by Balalaie and co-workers as a selective anti-lung cancer compound (A549, PC3, and C26 cells). To access this cyclopeptide, a heptapeptide was synthesized and was later used in a sequential Ugi/Huisgen 1,3-dipolar cyclization reaction.¹⁸ The detailed synthesis is shown in Schemes 10 and 11. This study clearly shows the importance of the triazole skeleton in the biological activities of the peptides. It may be possible to overcome the difficulties involved in synthesizing complex peptides by employing this elegant chemistry.

In addition to the above applications, click chemistry has been demonstrated to be a powerful tool in biomedical research, ranging from combinatorial chemistry and target-template *in situ* chemistry for lead discovery to providing an alternative approach for facile cyclization when regular approaches do not work. Moreover, this methodology will provide an effective strategy for the design and synthesis of peptide-based drugs with high bioavailability, metabolic stability, functional specificity, and potent activity.

3. Cyclopeptides with imidazole moieties

Imidazoles are well-known heterocyclic compounds that have important features in a variety of medicinal agents. Based on various literature studies, imidazole derivatives show different pharmacological activities, such as antibacterial, anticancer, analgesic, anti-inflammatory, cardiovascular, antineoplastic, anti-fungal, enzyme inhibition, anti-anthelmintic, anti-filarial,

anti-viral, anti-HIV and anti-ulcer activities. Moreover, imidazole derivatives are structural isosteres of naturally occurring nucleotides, which permits them to interact simply with biopolymers of living systems; this accounts for their varied biological activities and functions. In addition to their pharmacological actions, they can also be used as dyestuff catalysts and polymerizing agents.⁷³

The imidazole moiety, which is present in the side chain of histidine, performs major roles in the biological functions of many peptides and proteins. Imidazoles, for example, are well known as ligands in many metalloenzymes (*e.g.* metalloproteases);^{74–76} also, due to their basicity, they have been proven to be main structural elements in the basic active sites of enzymes.^{77,78} However, cyclopeptides containing imidazoles have not yet been isolated from nature because the occurrence of the diamino-propanoic acid (Dap), which is an analogue of serine, is rare in natural sources.^{79,80}

Haberhauer and co-workers described the synthesis of peptides 77–79 (Fig. 7) with imidazole units in their backbones; they resemble the naturally occurring marine cyclopeptides westiellamide 75 and ascidiacyclamide 76. In addition, they also investigated the structural modifications caused by the introduction of these imidazole moieties.⁸¹

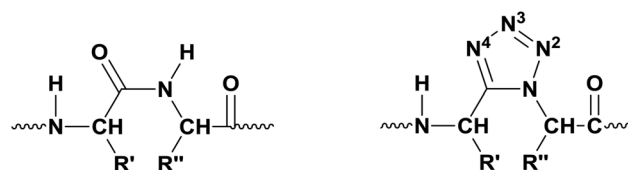
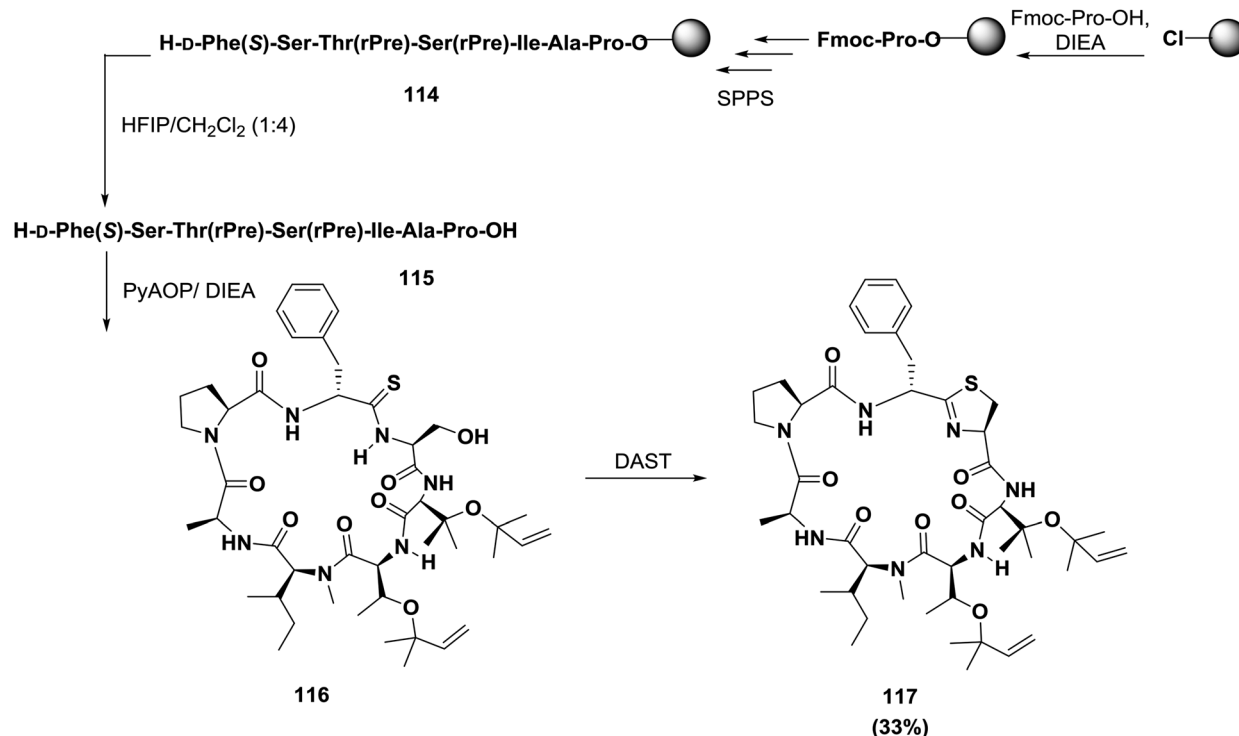


Fig. 8 Left: dipeptide with a *cis* amide bond. Right: Dipeptide with a *cis* amide bond replaced by the tetrazole surrogate ($\Psi[\text{CN}_4]$). In this study, $\text{R}' = \text{benzyl}$ and $\text{R}'' = \text{methyl}$.

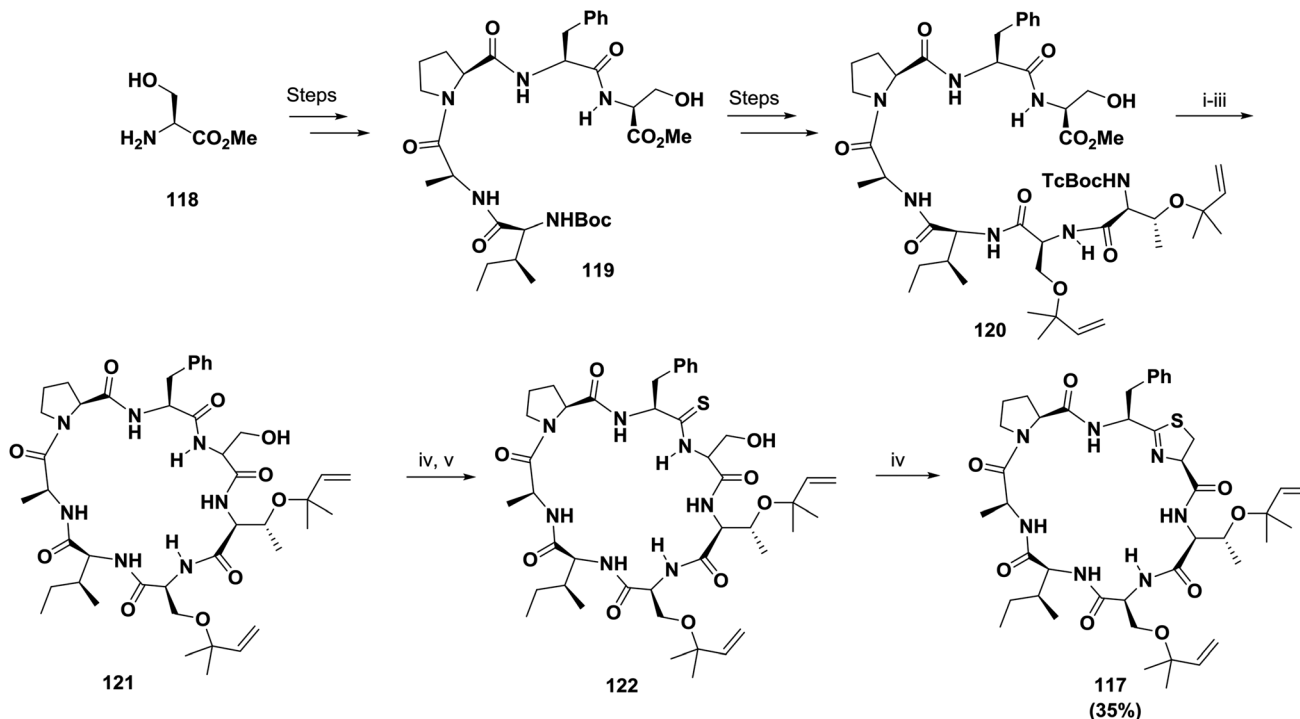




Scheme 18 A synthetic strategy for Trunkamide A.

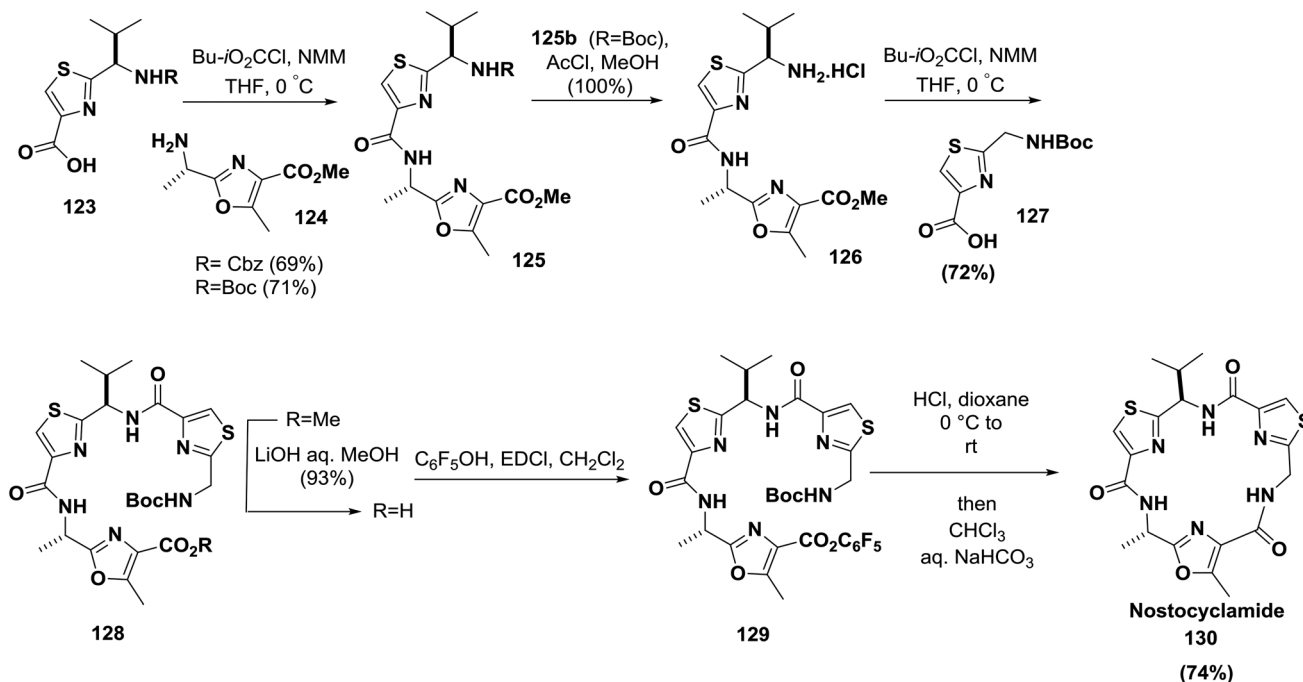
In continuation of their work, Haberhauer and co-workers also reported the synthesis of the cyclic peptides **86a–c** and **87a–c** based on the dipeptidyl imidazoles **83a–c** (Scheme 12).

Several approaches for one-pot macrocyclization of imidazoles **85a–c** were tested. The most efficient route was to react the monomers (**85a–c**) with diphenyl phosphorazidate (DPPA) in



Scheme 19 Synthesis of the cyclopeptide Trunkamide A. Reagents: (i) Cd : Pb, 1 M NH_4OAc : THF (1 : 1), 98%; (ii) TBAH, THF, 0 °C; (iii) DPPA, DIPEA, DMF, 35% (two steps); (iv) DAST, CH_2Cl_2 ; (v) H_2S , Et_3N , MeOH.



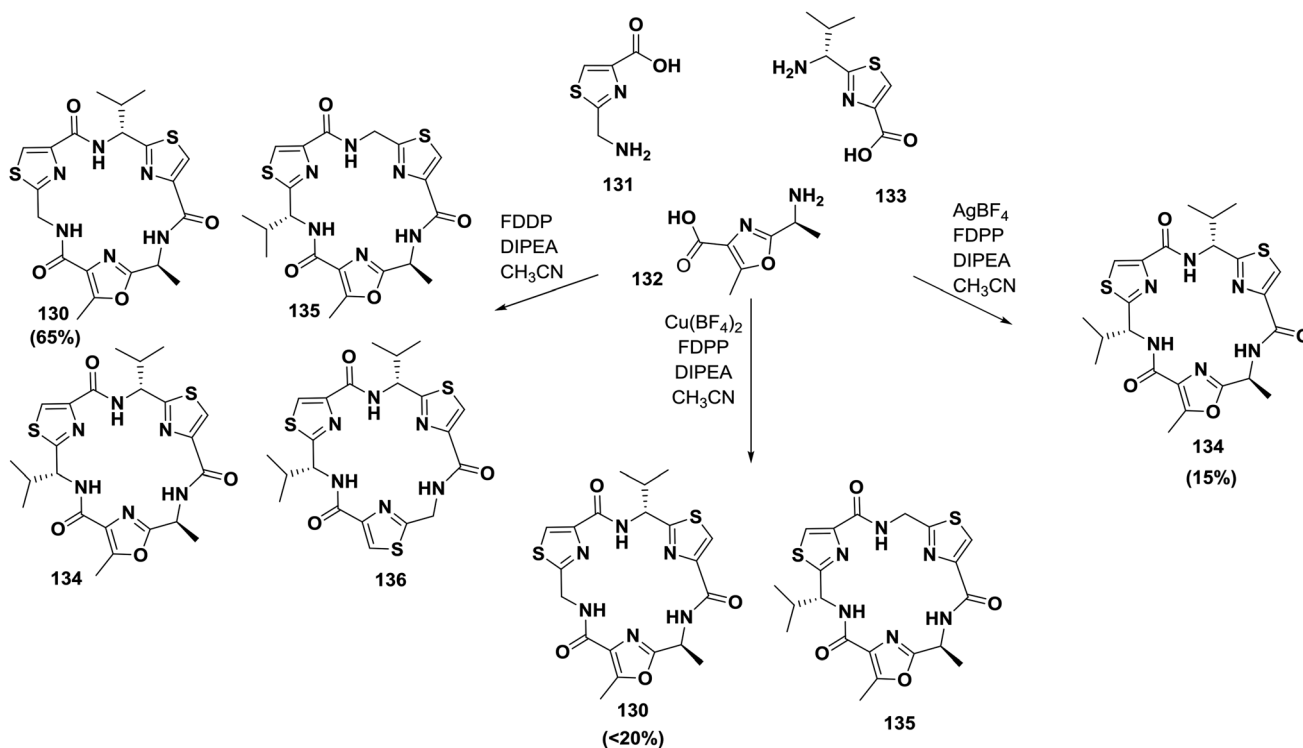


Scheme 20 Synthesis of nostocyclamide.

the presence of an excess of Hünig's base in acetonitrile under highly diluted conditions (0.05 M) at room temperature. This method provided two products; the trimers **86a–c** were obtained in relatively good yields (25% to 35%), and the tetrameric compounds **87a** and **87b** were obtained in lower yields (5% to

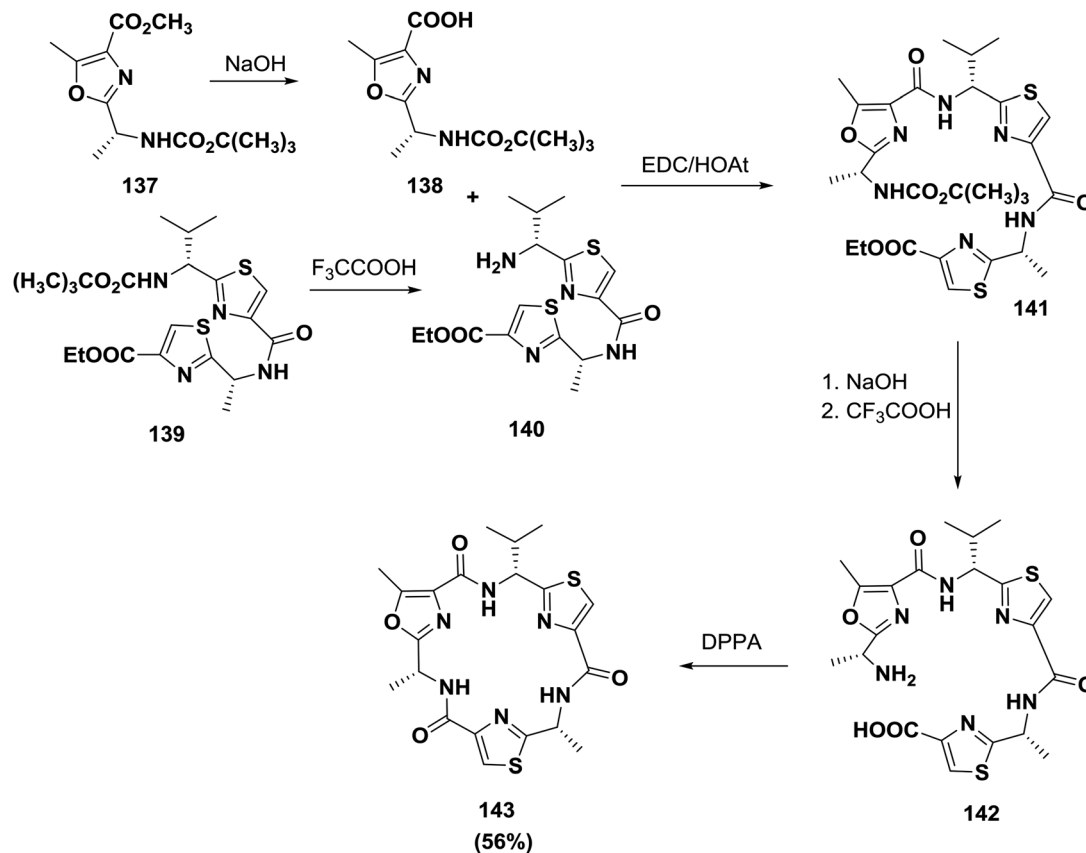
10%), whereas the yield of tetramer **87c** was very low and it could not be isolated.⁸¹

To improve the yield and the purity of the abovementioned reaction, Haberhauer and co-workers also developed an alternative synthetic route.^{82,83} The macrodimerization of the linear dimer **91**



Scheme 21 Synthesis of nostocyclamide and related cyclic peptides by metal-templated assembly.





Scheme 22 Synthesis of dendroamide A.

was carried out by pentafluorophenyl diphenylphosphinate (FDPP) activation and the addition of Hünig's base in acetonitrile; this afforded the tetramer **87a** in 40% yield (Scheme 13).

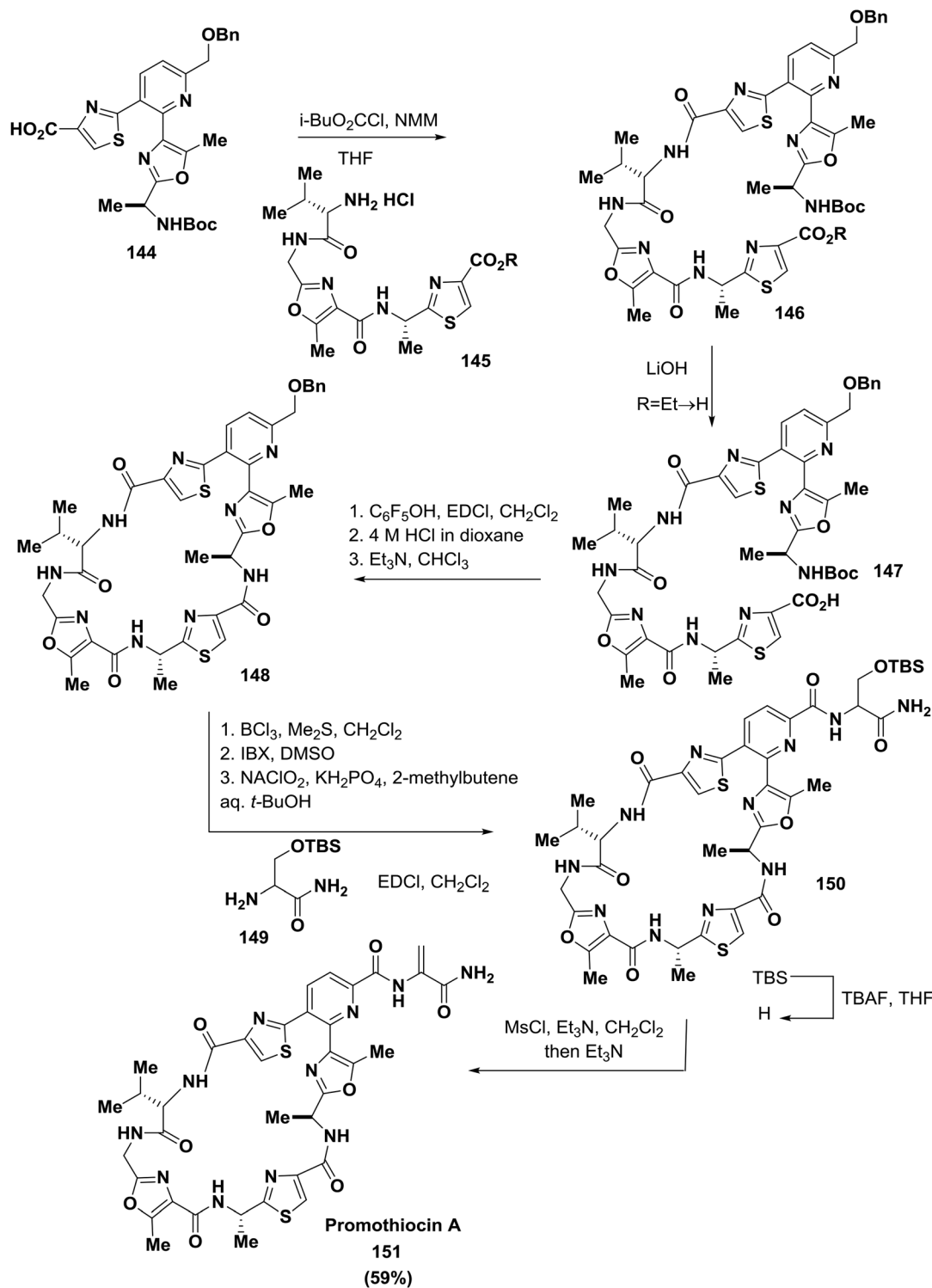
Due to their synthetic challenges, macrocycles are not highly present in screening libraries.^{84,85} Meanwhile, many reports investigated the importance of the imidazole-4,5-dicarboxylic acid scaffold in drug discovery.^{86–89} To extend the library of peptide-macrocycles that contain imidazole-4,5-dicarboxylic acid, Baures and co-workers designed and synthesized a unique novel compound class inspired by macrocyclic natural products. The synthesized compounds are 14-membered macrocycles with differences in their stereochemistry and amino acid side chains. The synthesis started with commercially available *N,N'*-dialkylalkanediamines, **92**, as shown in Scheme 14. To afford compound **93**, compound **92** was treated with benzyloxycarbonyl chloride using an excess of the diamine. However, this method did not work well for **92** and resulted in significant amounts of deprotected diamine. However, a different synthetic approach was used by employing *N*-Boc protection first followed by benzyloxycarbonyl chloride protection to afford the orthogonally protected diamine. Finally, macrocyclic ring closure to form **99** was attained by dissolving intermediate **I** in CH_2Cl_2 and adding EDC with DMAP⁹⁰ (Scheme 14).

Papini and co-workers reported an efficient approach for the preparation of head-to-tail cyclic peptides on a solid phase which has wide application and is based on the principle of

anchoring the peptide to the resin through a side chain.^{91,92} The reaction of Fmoc/*t*Bu/allyl provided a highly flexible three-dimensional orthogonal compound that allowed the building of more complex peptides, such as cyclic peptides which have side chains that contain post-translational modifications or are conjugated to sugars and oligonucleotides.^{93,94} One approach to the synthesis of head-to-tail cyclic peptides was incorporating the imidazole ring within histidine residues into a trityl-resin.⁹⁵ This approach was used to provide an efficient solid-phase Fmoc/*t*Bu/allyl strategy.⁹⁶ In order to establish this approach, Papini and co-workers synthesized a new building block, Fmoc-His-OAl **100**. The trityl-chloride-resin **101a** was treated with **100** under stirring. Around 0.4 to 0.6 mmol g^{-1} of the amino acid was chosen in order to obtain a final level of substitution. Firstly, deprotection at the N-terminal of the linear hexapeptide present on the resin surface was performed, followed by suspension in a solution of DIPEA and TBTU in DMF to allow the formation of the cyclopeptide. After cleavage from the resin with TFA- H_2O (95 : 5) and purification by HPLC, cyclo (-His-Gly)₃ **103** was obtained⁹⁷ (Scheme 15).

In another approach, Haberhauer and co-workers reported the synthesis of a larger receptor, **109**, as shown in Scheme 16.⁹⁸ Imidazole carboxylic acid **104** was coupled using FDPP in CH_3CN to commercially available methyl 3-aminobenzoate **105** to afford building block **106**. To acquire good yields of the products (41% for **106**), the coupling required long reaction





Scheme 23 Synthesis of the cyclopeptide promothiocin A.

times (1 week at room temperature) due to the low nucleophilicity of aniline. Saponification allowed the deprotection of the carboxyl residue and afforded the acid **107**. Later, the removal of the Boc group provided the free amino acid **108**, which underwent cyclodimerization with FDPP to afford receptor **109** in a good yield of 52%.

Castle's group recently synthesized the indole-imidazole linkage through an oxidative coupling reaction during the synthesis of the antimitotic bicyclic peptide celogentin C, as shown in Scheme 17. The desired product **112** containing the required indole-imidazole linkage was obtained in 58% yield when the dipeptides **110** and **111** were subjected to NCS and 1,4-



dimethylpiperazine in CH_2Cl_2 at room temperature. The resulting product was afterward cyclized to afford the peptidomimetic **113**.⁹⁹

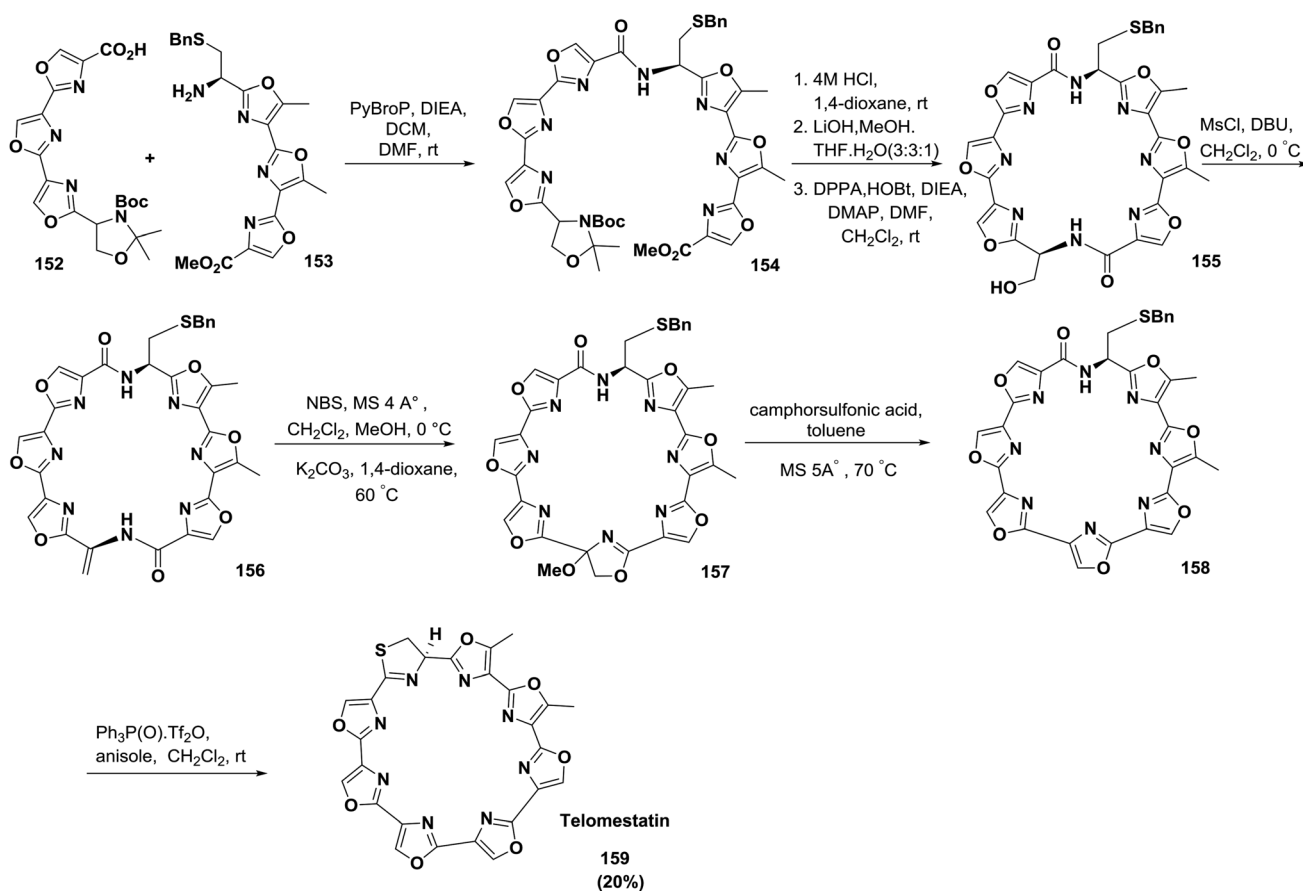
4. Cyclopeptides with tetrazole moieties

The synthesis and study of tetrazole compounds did not receive much early attention due to the late emergence of azoles in general. However, since the 1950s, tetrazoles have been widely applied in agriculture, pharmacology, medicine, biochemistry, explosives and other aspects; thus, tetrazole research has developed rapidly.^{100,101} The tetrazolyl functional group is considered to be a carboxylic acid isostere in drugs because its $\text{p}K_{\text{a}}$ is similar. In addition, it has almost the same required planar delocalized system space, and among the heterocyclic compounds, it provides the most nitrogen content.¹⁰² Due to their extended biological applications and unique structures, tetrazole and its derivatives have thus attracted the interest of scientists.^{103–106}

Kaczmarek and co-workers reported the synthesis of analogues of cyclolinopeptide A (CLA) in linear and cyclic forms. However, in their approach, two dipeptide segments ($\text{Val}^5\text{-Pro}^6$ and $\text{Pro}^6\text{-Pro}^7$) were replaced with tetrazole using the solid phase peptide synthesis (SPPS) technique and cyclized using TBTU (*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium

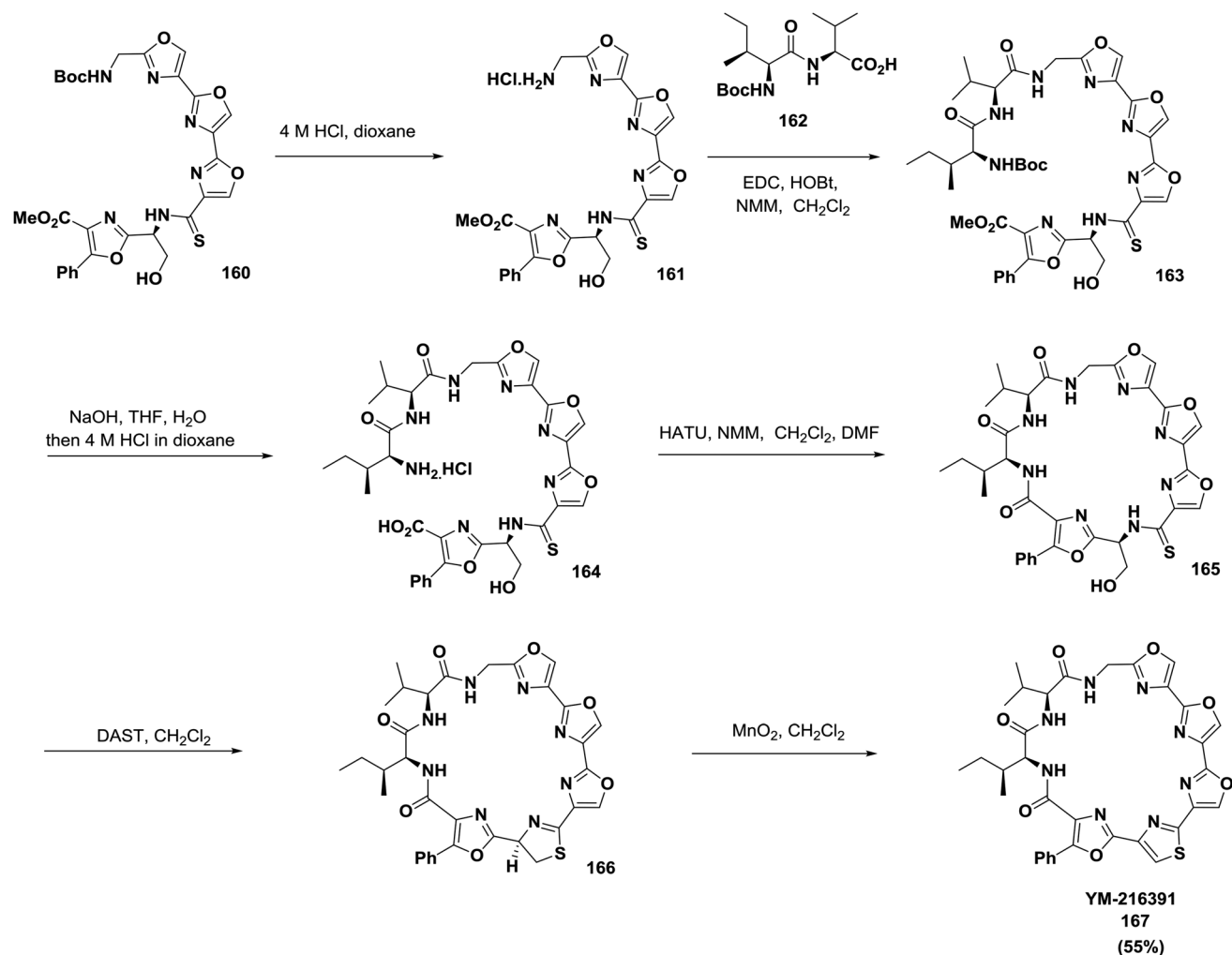
tetrafluoroborate) as the coupling reagent. NMR and computational techniques were used to examine the conformational properties of the cyclic peptide containing the tetrazole moiety $\text{c}(\text{Leu}^1\text{-Ile}^2\text{-Ile}^3\text{-Leu}^4\text{-Val}^5\text{-Pro}^6\text{-}\Psi[\text{CN}_4]\text{-Ala}^7\text{-Phe}^8\text{-Phe}^9)$.¹⁰⁷ The overall solution structure of this cyclic peptide resembled that observed for CLA in the solid state. The synthesized cyclic tetrazole CLA analogue confirmed that the 1,5-disubstituted tetrazole ring functions as an effective, well-tolerated *cis*-amide bond mimic in solution.

On the other hand, somatostatin¹⁰⁸ is a cyclic tetradecapeptide hormone ($\text{H-Ala}^1\text{-Gly}^2\text{-Cys}^3\text{-Lys}^4\text{-Asn}^5\text{-Phe}^6\text{-Phe}^7\text{-Trp}^8\text{-Lys}^9\text{-Thr}^{10}\text{-Phe}^{11}\text{-Thr}^{12}\text{-Ser}^{13}\text{-Cys}^{14}\text{-OH}$) whose role is to inhibit the release of a variety of other hormones, including gastrin, glucagon, insulin, and somatotropin (growth hormone).¹⁰⁹ Moreover, analogues of somatostatin present promise in the treatment of hypersecretory disorders,¹¹⁰ as antineoplastic agents,¹¹¹ and as tumor imaging reagents.¹¹² Marshall and co-workers designed the synthesis of new analogues of somatostatin; in their approach, a 1,5-disubstituted tetrazole that is a *cis*-amide surrogate or mimic is incorporated into a cyclic hexapeptide analog of somatostatin in order to constrain the *cis*-amide bond by replacing the $\text{Xxx}^{11}\text{-Xxx}^6$ amide (Fig. 8). Both chemical and enzymatic methods were employed to accomplish the final cyclization. The product, $\text{cyclo}(\text{Ala}^6\text{-Tyr}^7\text{-D-Trp}^8\text{-Lys}^9\text{-Val}^9\text{-Phe}^{10}\text{-}\Psi[\text{CN}_4])$, was found to have 83% of the activity of somatostatin.¹¹³



Scheme 24 Synthesis of the cyclopeptide telomestatin.





Scheme 25 Synthesis of the cyclopeptide YM-216391.

5. Cyclopeptides with oxazole/thiazole moieties

Oxazoles can be categorized as biologically active heterocyclic backbones that are found in extensive natural products and pharmaceuticals and are used as synthetic intermediates for further transformations. Oxazoles are synthesized in nature from serine and threonine. Oxazole derivatives have drawn considerable attention in medicinal research because they have extensive biological activities, such as hypoglycemic, anti-inflammatory, and antibacterial activities.^{114–116}

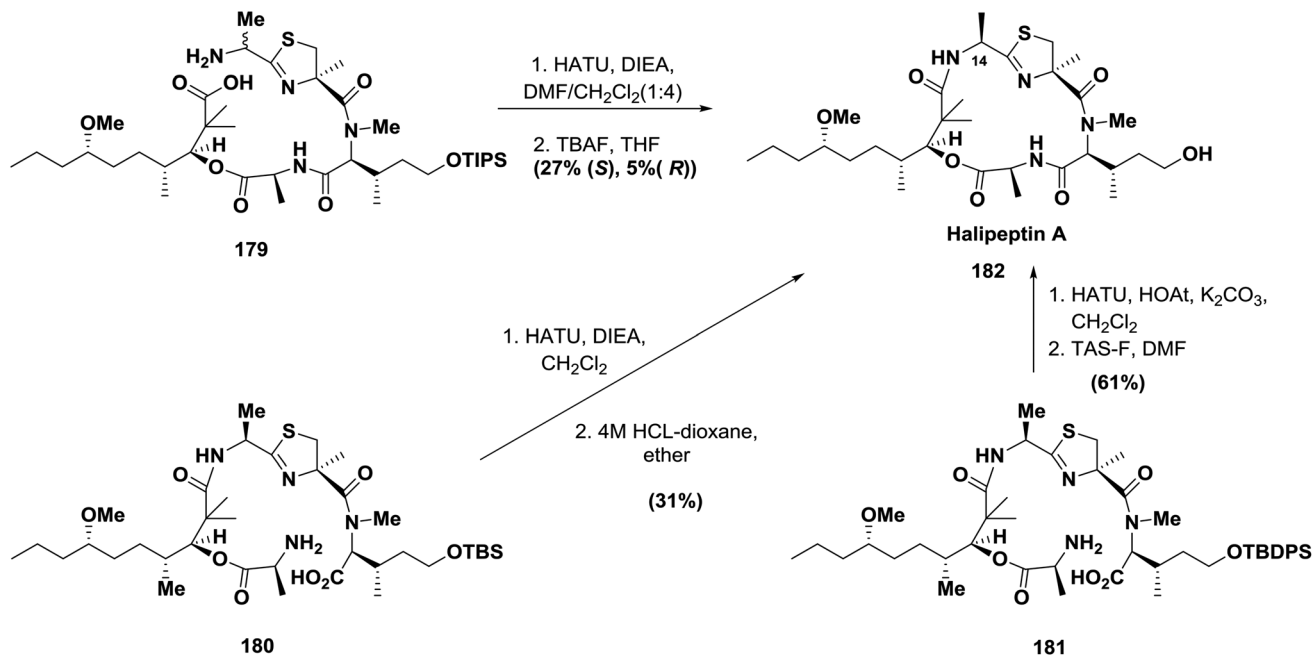
Meanwhile, thiazoles are essential scaffolds that exist in many natural sources, such as vitamin B1, thiamine, and other synthetic medicinally important compounds. The application of thiazoles in many drugs, such as penicillin, antimicrobials (sulfazole), antiretrovirals (ritonavir), antifungals (abafungin), and their antihistaminic and antithyroid activities demonstrate the importance of these heterocycles. In addition, thiazole derivatives have applications as anticancer drugs (tiazofurin), anthelmintics, vulcanizing accelerators (mercaptobenzothiazole) and photographic sensitizers.¹¹⁷

Since oxazoles and thiazoles were naturally discovered in the backbones of cyclopeptides, confirming that their presence can impose conformational restrictions on cyclic peptides, many studies have been performed on these heterocycles.^{118,119}

Condensation between side chain cysteine thiols or threonine/serine hydroxy groups and neighboring amide bonds affords heterocyclic rings, as illustrated in Scheme 18, resulting in highly constrained pseudo-boat or saddle-shaped macrocycles. Wipf reviewed most of the syntheses investigated before 1995³³, and subsequent research was reviewed by Shioiri.¹²⁰ Albericio and co-workers used both solid phase and solution phase approaches to synthesize trunkamide A 117¹²¹ (Scheme 18). In their approach, the linear peptide was constructed on a chlorotrityl resin; proline was the first amino acid linked to the resin, and the final two residues were D-Phe-[CSNH]Ser, which is the precursor of the thiazoline ring. Macrocyclization was carried out with PyAOP/DIEA. Post-cyclization using diethylamino sulfur trifluoride (DAST) afforded the thiazoline ring. Thiolytic cleavage of the oxazoline and the second cyclodehydration with DAST afforded 117.¹²¹

On the other hand, McKeever and Pattenden initially failed to synthesize the cyclopeptide trunkamide A 117 in solution *via*





Scheme 28 Different approaches for the synthesis of halipeptin A.

Later, Pattenden and co-workers reported another approach for the synthesis of nostocyclamide; they showed that amino acids containing oxazole and thiazole can undergo cyclization in the presence of FDPP to form nostocyclamide with yields controlled by the amount and type of the metal ions present in the reaction mixture¹²⁴ (Scheme 21).

Smith and co-workers synthesized a related natural product, dendroamide A **143**. The synthesis was performed using amino acids containing heterocycles. Cyclization of the linear peptide was performed using DPPA and afforded dendroamide A **143** (56% yield)¹²⁵ (Scheme 22).

Moody and co-workers, using a modified Bohlmann-Rahtz pyridine synthesis, described the total synthesis of the thiopeptide antibiotic promothiocin A **151** to establish the oxazolylthiazole-pyridine heterocycle of the antibiotic. The oxazole building blocks were obtained by a dirhodium(II)-catalyzed chemoselective carbenoid N-H insertion reaction followed by cyclodehydration and a Hantzsch reaction to afford the thiazoles. Two different macrocyclization strategies were successfully employed, and in the last steps of the synthesis, the dehydroalanine side chain of the natural product was introduced¹²⁶ (Scheme 23).

Pattenden and co-workers also reported a convergent, complete synthetic approach of the directly linked tris-oxazole units in telomestatin **159** and YM-216391 **167**¹²⁷ (Schemes 24 and 25).

The synthesis of the marine-derived anti-cancer agent diazonamide A **168** is considered to be one of the most demanding synthetic challenges.^{13,128-131} Nicolaou and co-workers have established a new path to obtain diazonamide A. The approach described a SmI₂-induced heteropinacol coupling cascade to assemble the 12-membered heterocyclic core of the target and

an exceptional oxidation of an indoline to an oxindole using Pd(OH)₂/C **168**¹³¹ (Scheme 26).

In 2002, Palauan isolated the cyclic depsipeptide ulonga-mide A from collections of the marine cyanobacterium *Lyngbya* sp.; it possessed activity against some cancer types. Guzman and co-workers achieved the final macrocyclization of compound **177** using the coupling reagent BOP in 60% yield, as shown in Scheme 27.^{63,132,133}

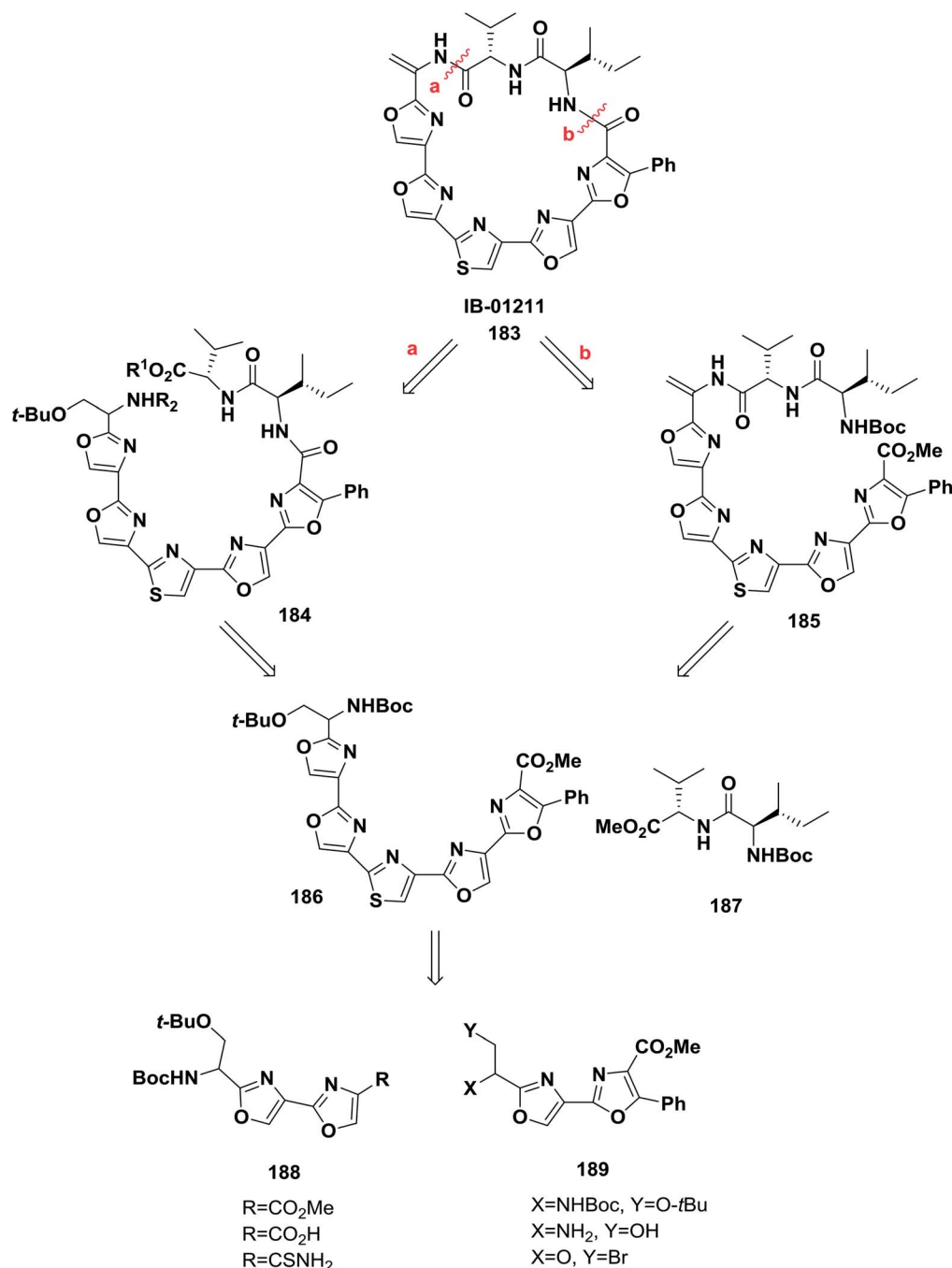
In 2001, the cyclic depsipeptides halipeptin A and B were isolated from the marine sponge *Haliclona* sp. and appeared to have promising anti-inflammatory activities *in vivo*.¹³⁴ Formation of the novel oxazetidine ring failed using the original approach, which was later revised to include thiazoline amino acid.¹³⁵ The use of HOAt-derived uronium type reagents, such as HATU, proved to be efficient. For example, during the synthesis of halipeptin A, three approaches were used in different groups, including Ma's cyclization at the decanoic acid (HTMMD)/thiazoline-amino acid (alaThz) site (**179**); this macrocyclization was achieved in 27% yield using the highly efficient coupling reagent HATU¹³⁶ (Scheme 28).

On the other hand, Nicolou's cyclization was performed between *N*-methylhydroxyisoleucine (*N*-MeOHile) and *L*-alanine (Ala) (**180**) in 31% yield using the highly efficient coupling reagent HATU¹³⁷ (Scheme 28).

Shortly after, Hamada and co-workers also succeeded in the synthesis of halipeptin A. Macrocyclization was achieved by using the coupling reagent HATU at the *N*-MeOHile/Ala site (**181**), which provided halipeptin A **182** in 61% yield with 29% yield of the epimer, which was produced from racemization at the *N*-MeOHile residue during the cyclization.¹³⁸ (Scheme 28).

Hernandez and co-workers reported the synthesis of some analogs of the natural product IB-01211 **183** fromazole-based





Scheme 29 Retro-synthetic analysis of IB-01211.

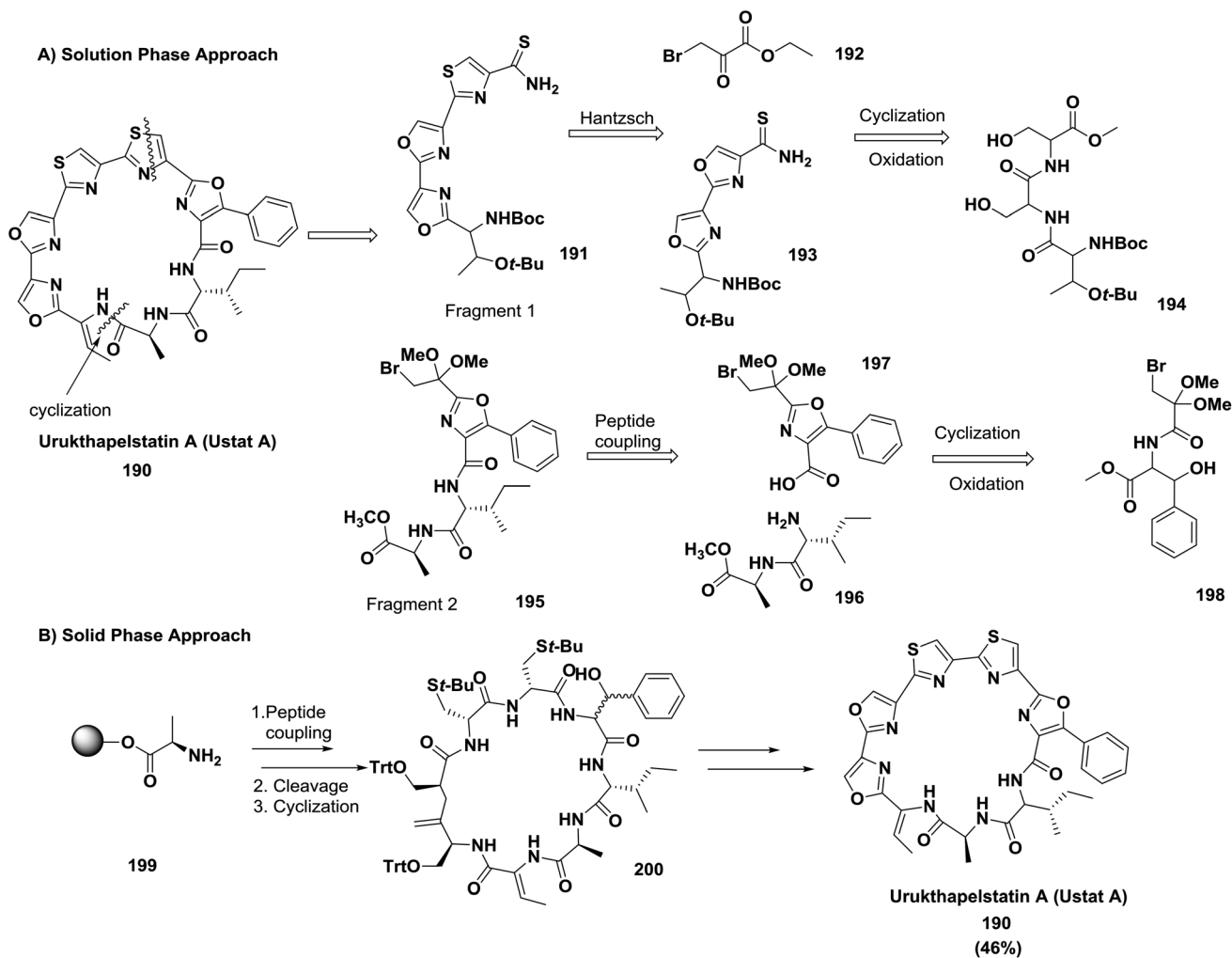
compounds *via* a biomimetic pathway based on cyclization-oxidation of serine-containing peptides combined with the Hantzsch synthesis. Macrocyclization of the linear peptides **188** and **189** was performed to afford IB-01211 (ref. 139) (Scheme 29).

McAlpine and co-workers compared the solution phase route to the solid phase route for the synthesis of the cytotoxic natural product urukthapelstatin A (Ustat A) and ascertained that the solid phase method is superior. They reported the synthesis through two approaches: (A) the solution phase approach,

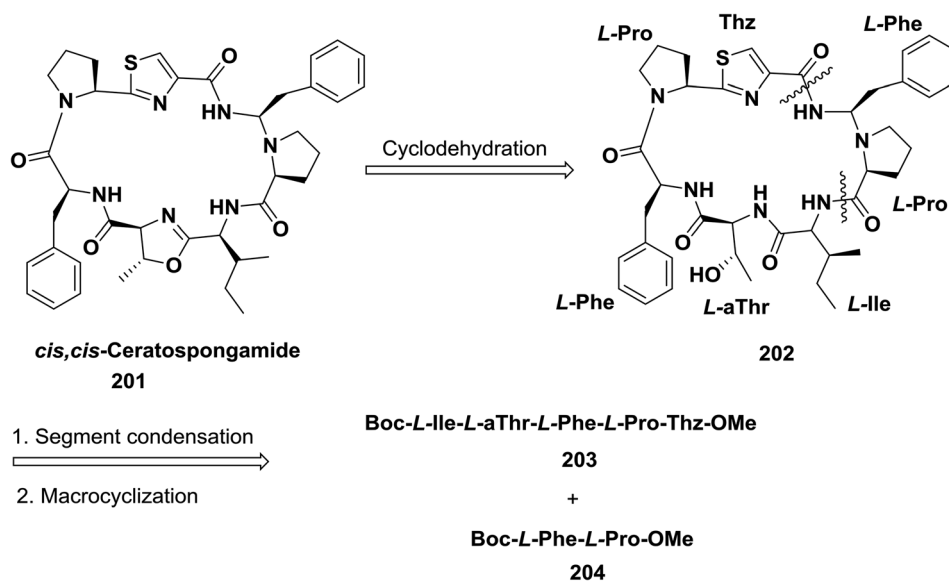
which was difficult and involved cyclization of a ridged heterocyclic precursor; (B) the solid phase approach, which allowed the rapid and facile generation of a flexible linear peptide. Meanwhile, cyclization of the linear peptide was facile, and subsequent generation of three oxazoles located within the structure of Ustat A **190** was obtained in a relatively straightforward manner¹⁴⁰ (Scheme 30).

Yokokawa and Shioiri and co-workers synthesized *cis,cis*-ceratospongamide **201** using a (5 + 2) convergent strategy to form a linear peptide which allowed cyclization *via* activation of



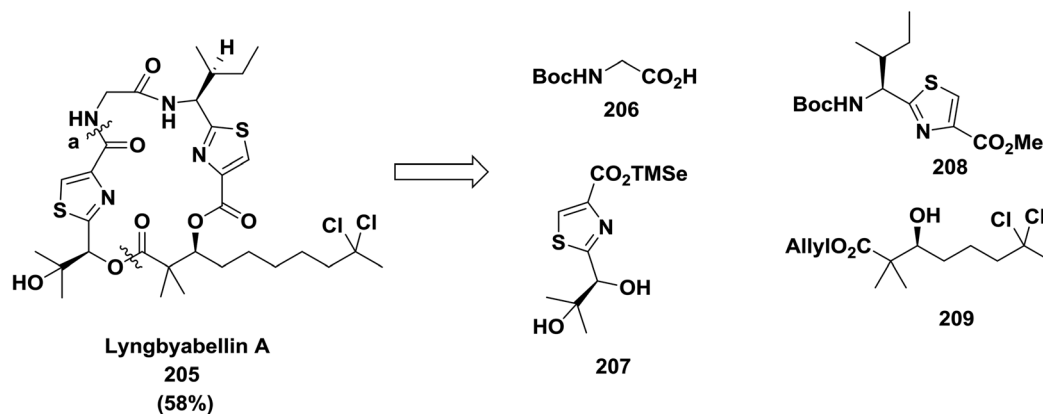


Scheme 30 Two synthetic approaches: (A) solution phase retrosynthesis of Ustat A and (B) solid phase synthesis of Ustat A.

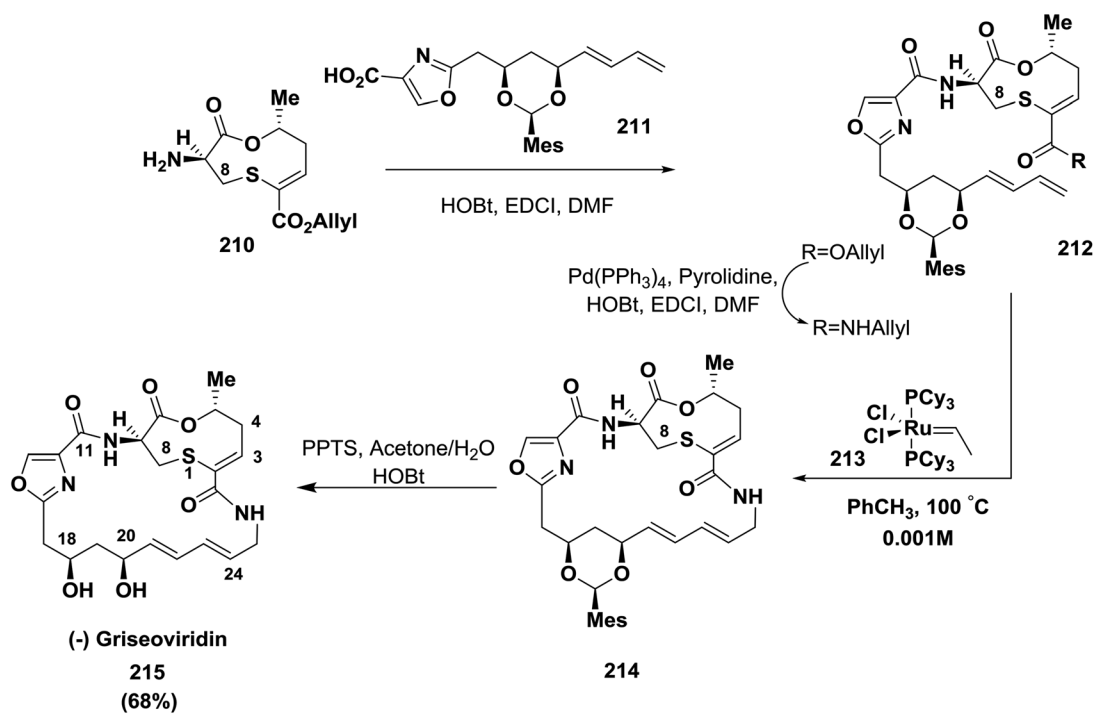


Scheme 31 Retrosynthetic analysis of ceratospongamide.

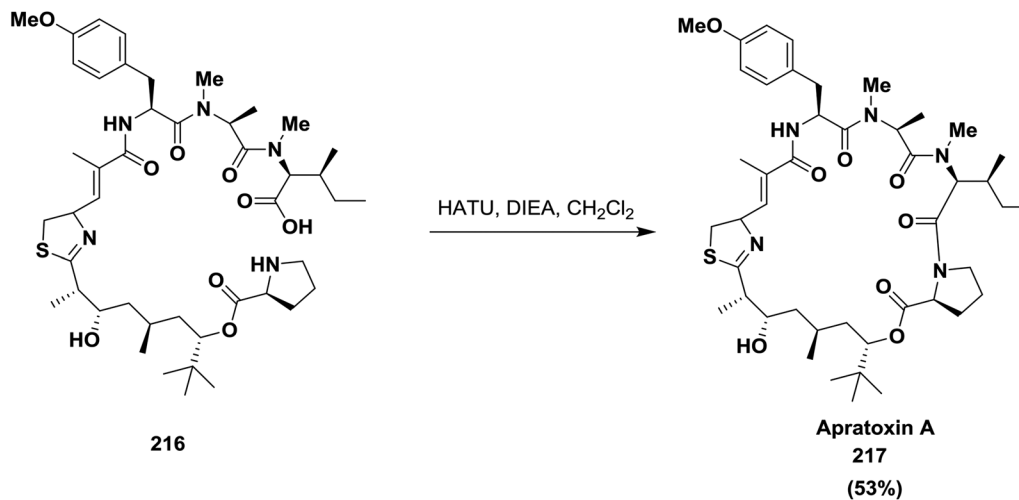




Scheme 32 Retrosynthetic analysis of lyngbyabellin A.

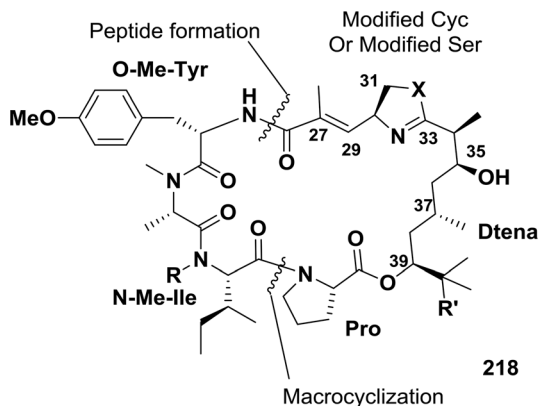


Scheme 33 Synthesis of griseoviridin.



Scheme 34 Cyclization of apratoxin A.





- 218 a:** X=S, R=R'=Me, Apratoxin A
218 b: X=S, R=H, R'=Me, Apratoxin B
218 c: X=S, R=Me, R'=H, Apratoxin C
218 d: X=O, R=R'=Me, Oxazoline analogue of Apratoxin A

Fig. 9 Structures of apratoxins A–C and an oxazoline analogue of apratoxin A.

the thiazole carboxyl group. The macrocyclization was examined with different coupling reagents, and FDPP enabled a yield of 63%. Finally, to obtain the oxazoline in the target compound, cyclodehydration was performed with bis(2-methoxyethyl) aminosulfur trifluoride (deoxo-fluor)¹⁴¹ (Scheme 31).

Yokokawa and co-workers also reported macrocyclization with amide formation at position (a) in cytotoxic metabolite

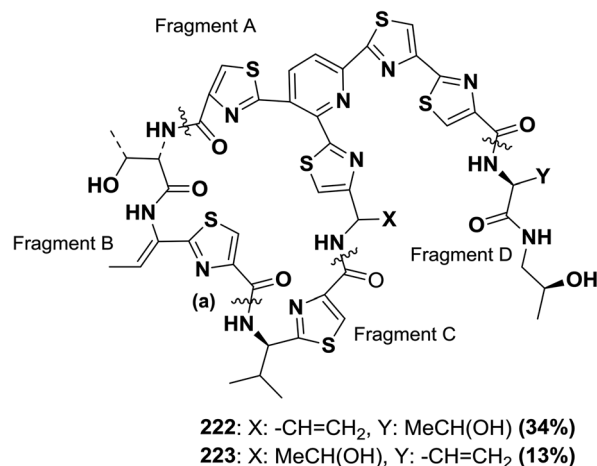
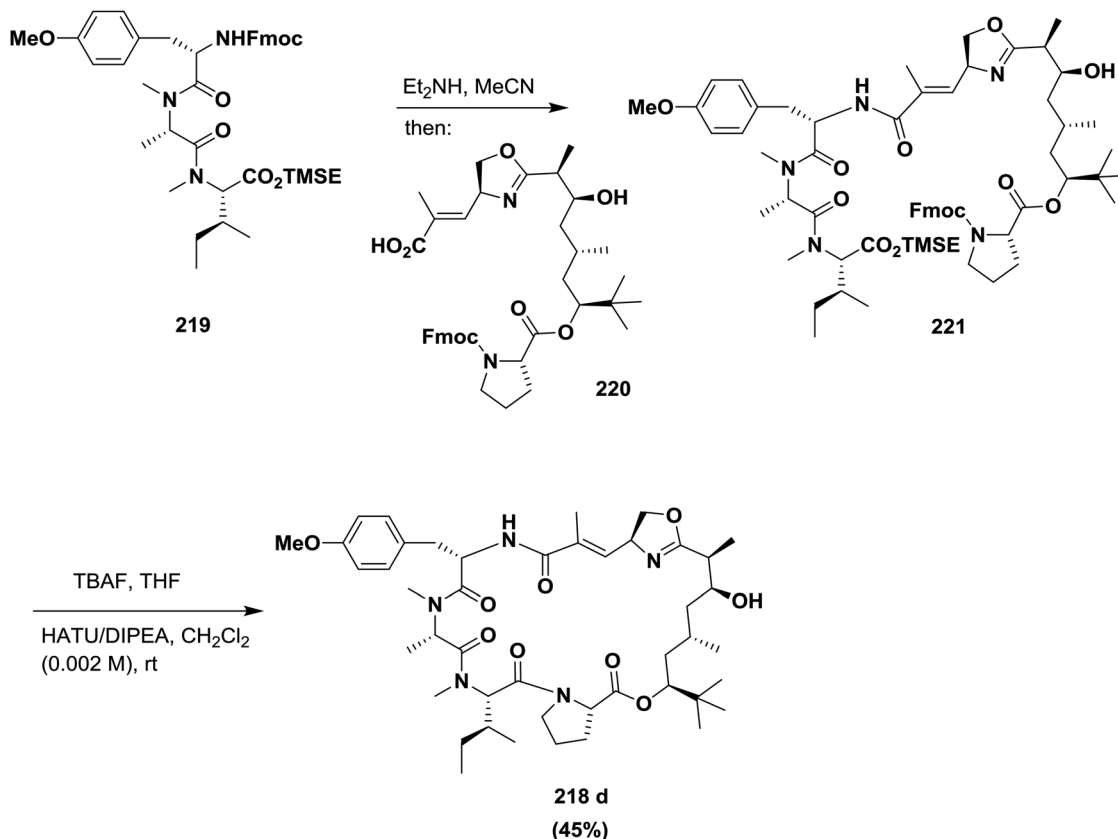


Fig. 10 Structure of micrococccin P (222) and its analogue.

lyngbyabellin A 205 using DPPA (58% yield). In this approach, the thiazole unit was built before cyclization¹⁴² (Scheme 32).

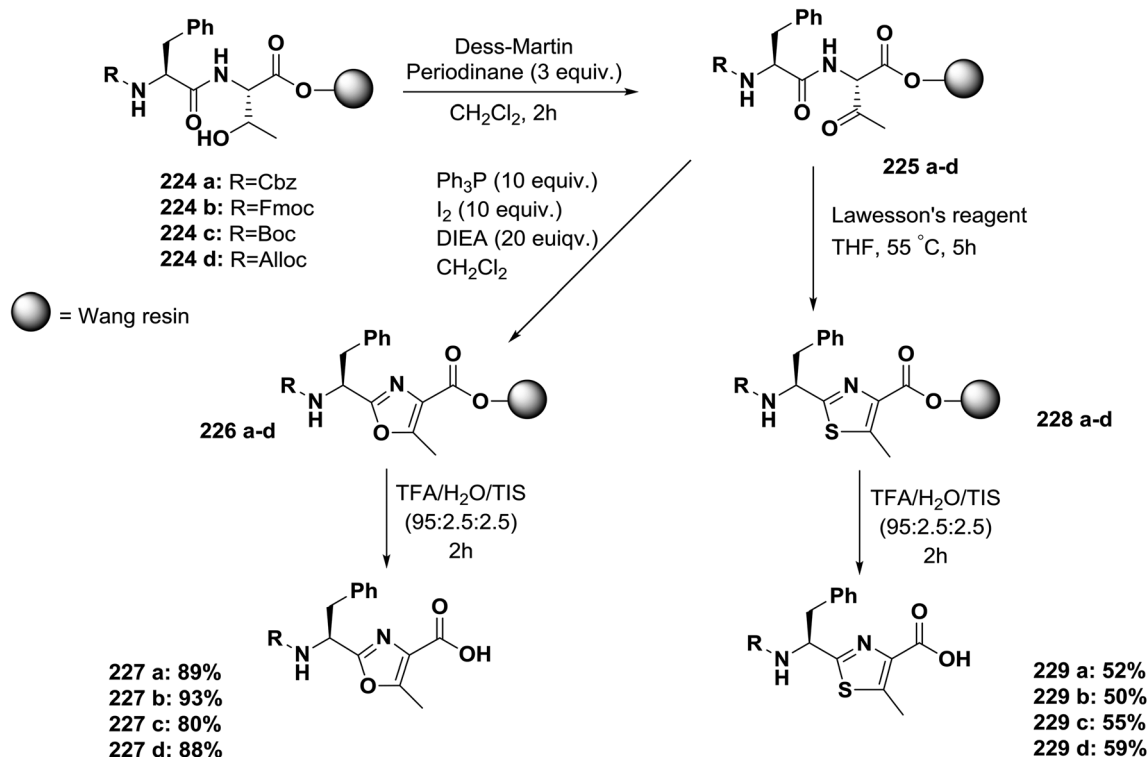
Meyers and co-workers reported the synthesis of griseoviridin 215, a member of the streptogramin family of antibiotics, in 68% yield. The oxazole carboxamide link was selected for macrolactamization using EDCI/HOBt; this was reported for the first time after many endeavors^{63,143} (Scheme 33).

Takahashi and co-workers described the synthesis of naturally occurring cyclic depsipeptide apratoxin A 217, which is isolated

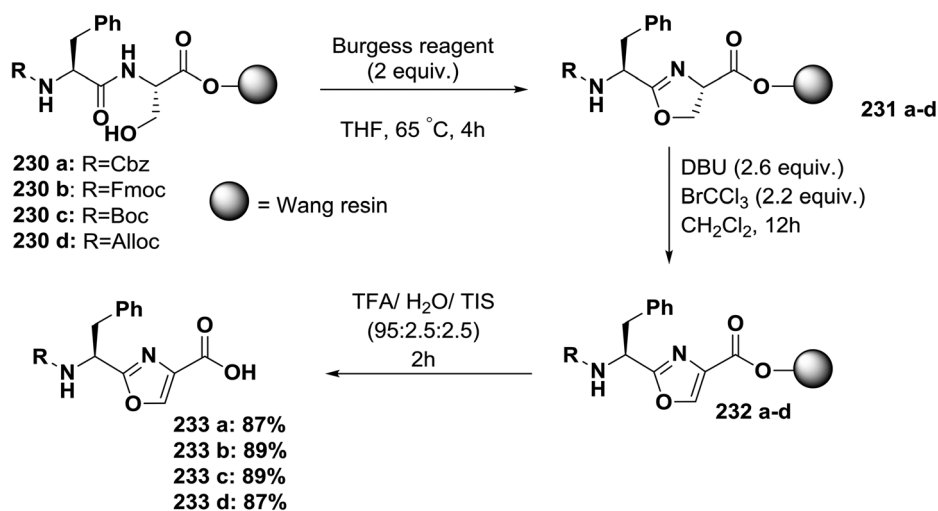


Scheme 35 Synthesis of an oxazoline analogue of apratoxin A.





Scheme 36 Solid-phase synthesis of oxazole- and thiazole-based peptides from threonine-containing dipeptides.



Scheme 37 Solid-phase synthesis of 1,3-oxazole-based peptides from serine-containing dipeptides.

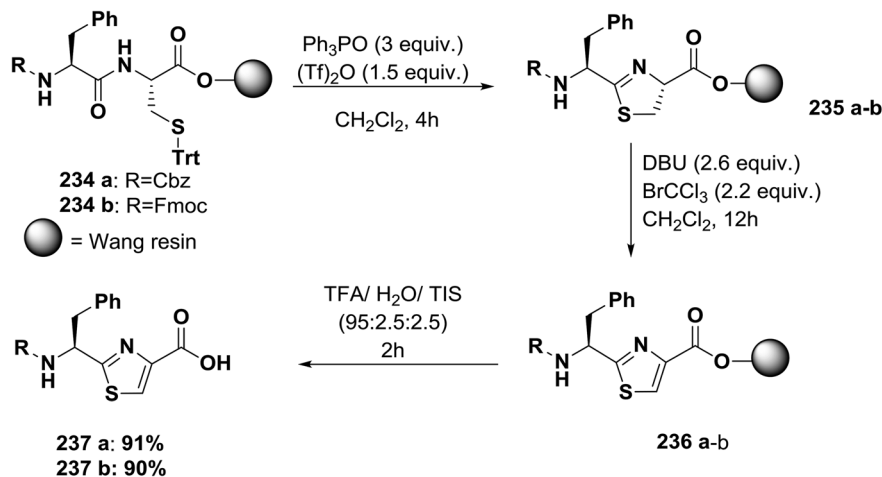
from *Lyngbya majuscula* and has potent cytotoxic activity, by adopting HATU as a coupling reagent to accomplish the macrolactamization of the linear precursor **216**. HATU was able to activate the carboxylic group of the linear precursor **216**, which resulted in selective formation of the amide bond^{63,144} (Scheme 34).

Ma and co-workers described an efficient approach for the synthesis of an oxazoline analogue of apratoxin A **218** (Fig. 9). A highly diastereoselective assembly of the Dtena moiety and consecutive installation of the oxazoline ring bearing an α,β -unsaturated ester side chain were performed. In addition, the

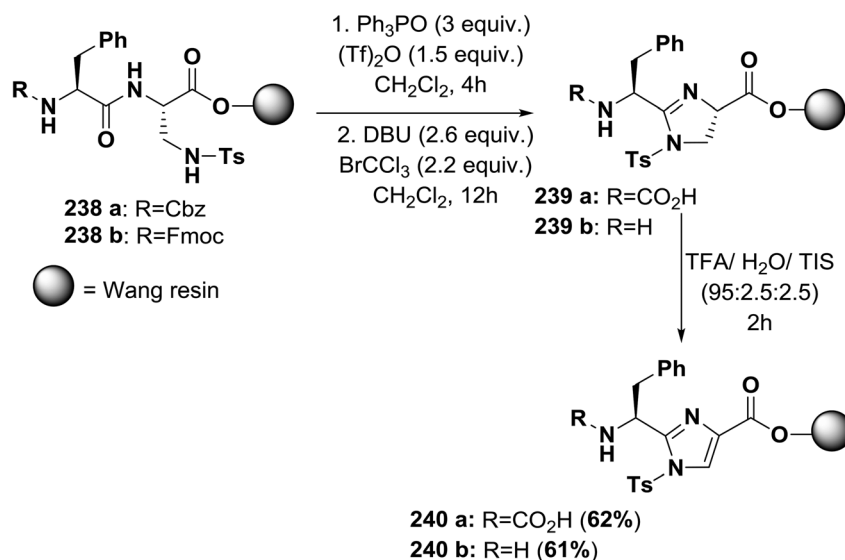
success of macrocyclization at the *N*-Me-Ile-Pro site further indicates that this site is a suitable macrolactamization site to synthesize apratoxins and their analogues¹⁴⁵ (Scheme 35).

Shin and co-workers synthesized micrococcin P **222** from protected fragments A–D, as shown in Fig. 10. The final macrocyclization using BOP occurred at position (a), affording total accordance between the physical and spectral properties of the synthetic and natural products. The same strategy has been applied to micrococcin P **223** with similar success^{146,147} (Fig. 10).

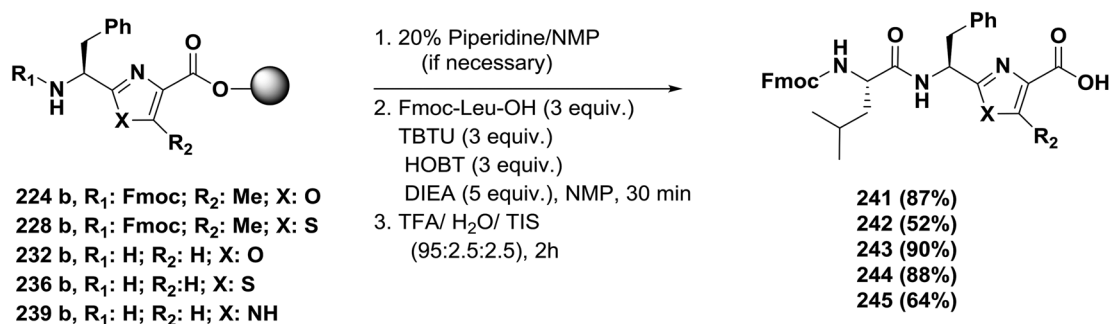




Scheme 38 Solid-phase synthesis of thiazole-based peptides.



Scheme 39 Solid-phase synthesis of imidazole-based peptides.



Scheme 40 Solid-phase synthesis of azole-containing tripeptides.

6. Solid phase approach for the synthesis of azoles

Usually, azole-based amino acids are prepared in solution in advance and later used as building blocks in solution and solid-

phase synthesis. There are some reported approaches for the synthesis of oxazoles, thiazoles, or imidazoles in solution, such as (1) a modified Hantzsch's procedure; (2) a condensation reaction between N-protected imino ethers and serine esters, cysteine esters, or 2,3-diaminopropionic acid esters; and (3)



cyclodehydration of β -hydroxyamides or β -hydroxythioamides. The freshly synthesized 1,3-azolines are readily converted into 1,3-azoles by oxidation. Unfortunately, many of these methods have drawbacks, such as long synthetic sequences, harsh reaction conditions, or extensive purification procedures that lead to low yields.¹⁴⁸

Kessler and co-workers reported a solid-phase approach for the synthesis of oxazole, thiazole, and imidazole-based peptides. The reported procedures are compatible with Fmoc-solid phase peptide synthesis. This reported method opens the way for the synthesis of natural product libraries of peptidomimetics containing 1,3-azoles¹⁴⁸ (Schemes 36–40).

7. Conclusion

In conclusion, cyclopeptides have attracted the attention of synthetic chemists not only because of their unique, promising properties and biological significance but also because of the high synthetic complexity of these endeavors. In future, we will witness many approaches involving various sophisticated synthetic methods. Moreover, naturally occurring cyclopeptides containing heterocyclic skeletons in various sources, such as plant cyclopeptides, marine cyclopeptides, and fungi, have confirmed the importance of these skeletons in the extensive biological activities of these cyclopeptides.

There are many resources of biologically active structures isolated from marine organisms, plants, and fungi that consist of cyclic peptides embedded in heterocyclic skeletons. In many examples, the existence of thiazole and oxazole rings establishes conformational restrictions in the corresponding cyclopeptides. Consequently, the incorporation of heterocycles into the backbones of cyclopeptides is eliciting growing interest, especially for medicinal chemistry prospects.

Moreover, studies have demonstrated that the incorporation of heterocyclic skeletons into cyclopeptides has a good influence on the conformations of the cyclopeptides. In addition, it allows the formation of noncovalent interactions that are important in molecular recognition, which is a key process in chemistry and biology. These interactions are illustrated in four groups: (1) hydrogen bonds, (2) cation- π interactions, (3) ion-pair interactions and (4) London dispersion forces. Variation of the azole units within the heterocycle skeleton enables scientists to design receptors that are either selective or have affinities for specific anions, allowing stronger interactions between the cyclopeptide and its target.

In summary, it is hoped that this review has successfully highlighted different approaches for peptide cyclizations containing heterocyclic skeletons. The examples discussed in this review reflect the complexity of nature's methods of adding constraints to peptides and illustrate the persisting challenges in their syntheses, such as control of stereochemistry, incompatibility of chemical functionalities, and difficulties with solid-phase approaches; these constraints can currently be mimicked utilizing a vast range of organic chemical techniques in the laboratory, but further research is still required to establish more widely applicable synthetic methodologies. These demanding synthetic challenges will afford necessary

knowledge that will help to create mimics and design molecules which will definitely be useful in the development of more effective pharmaceuticals.

Conflicts of interest

There are no conflicts to declare.

Abbreviations

CuAAC	Copper-catalyzed azide-alkyne cycloaddition
RuAAC	Ruthenium-catalyzed azide-alkyne cycloaddition
THF	Tetrahydrofuran
DMS	Dimethyl sulfide
SPPS	Solid phase peptide synthesis
Tyr: Y	Tyrosine
Pro: P	Proline
Val: V	Valine
Arg: R	Arginine
Gly: G	Glycine
Asp: D	Aspartic acid
Phe: F	Phenylalanine
Cys: C	Cysteine
Thr: T	Threonine
Ser: S	Serine
Lys: K	Lysine
Ile: I	Isoleucine
Glu: E	Glutamic acid
Met: M	Methionine
Asn: N	Asparagine
Leu: L	Leucine
Trp: W	Tryptophan
NMP	<i>N</i> -Methyl-2-pyrrolidone
TBTA	Tris[(1-benzyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amine
HATU	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxide hexafluorophosphate
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl ether
HDAC	Histone deacetylases
Dap	Diaminopropanoic acid
Nle	Norleucine
DEPBT	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3 <i>H</i>)-one
DIEA:	<i>N,N</i> -Diisopropylethylamine or Hünig's base
DIPEA	
NMM	<i>N</i> -Methylmorpholine
TBTU	2-(1 <i>H</i> -Benzotriazole-1-yl)-1,1,3,3-tetramethylammonium tetrafluoroborate
FDPP	Pentafluorophenyl diphenylphosphinate
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
HPLC	High performance liquid chromatography
NCS	<i>N</i> -Chlorosuccinimide
PyAOP	(7-Azabenzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate
DAST	Diethylaminosulfur trifluoride



DPPA	Diphenylphosphoryl azide
IBX	2-Iodoxybenzoic acid
DBU	1,8-Diazabicyclo [5.4.0] undec-7-ene
NBS	<i>N</i> -Bromosuccinimide
Bop	(Benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate
Thz	Thiazole
aThr	Alloc-L-threonine
Dtena	3,7-Dihydroxy-2,5,8,8- tetramethylnonanoic acid
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
PPTS	Pyridinium <i>p</i> -toluenesulfonate
TIS	Triisopropylsilane

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