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Application of multicomponent reactions in the total synthesis of natural peptides

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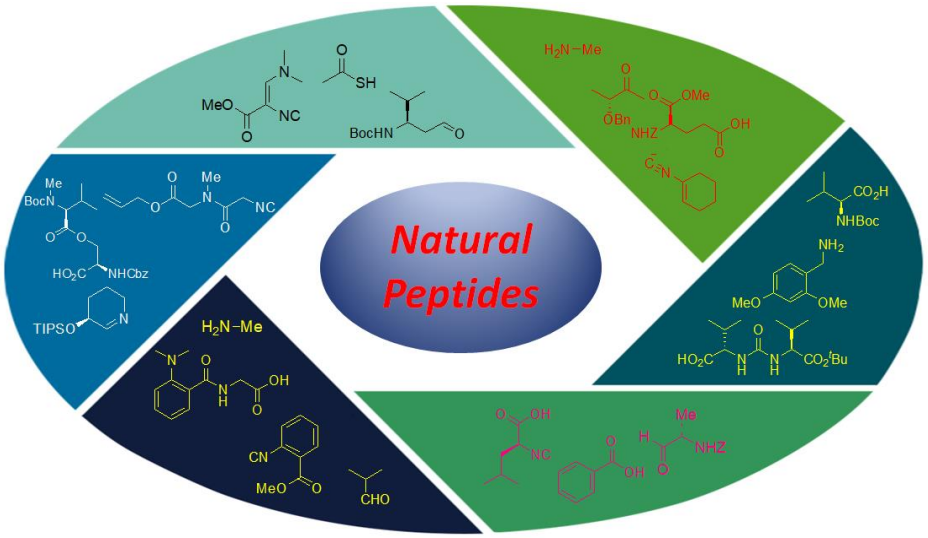
Abstract

Multicomponent reactions (MCRs) have been widely applied for the synthesis of biologically active molecules with high complexity and diversity. Nowadays, total synthesis of natural peptides, due to their multifarious application areas, has attracted much attention of organic chemists. MCRs are a powerful and efficient method for the production of natural peptides in a limited number of steps. This review presents an overview on application of multicomponent reactions as a key step in the synthesis of natural peptides.



Keywords: Natural peptides, natural products, multicomponent reactions, biological activity

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1. Introduction

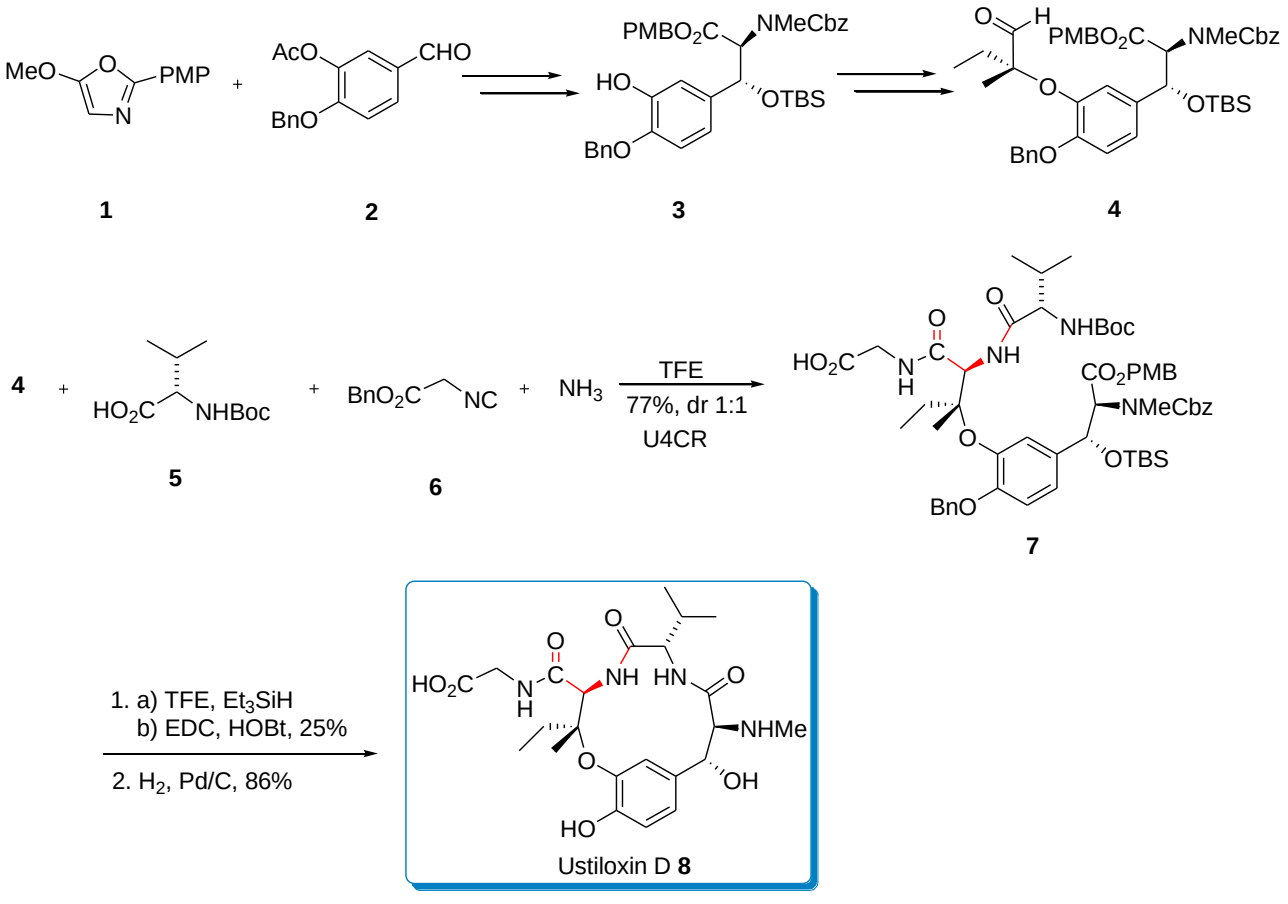
Short chains of amino acid monomers which are linked together by peptide bonds (–CONH–), form the proteins and peptides.[1,2] Since the 1920s and particularly since the commercial introduction of insulin and thyroid hormones, many peptides have been employed as drugs.[3, 4] Although peptides often have lower bioavailability and metabolic stability than antibodies and proteins, they also have beneficial properties such as being less immunogenic, of greater stability, of lower manufacturing costs and better penetration into organs and tissues.[5] Peptides as highly attractive molecular structures have played key roles in biological research and therapeutic applications and they possess a wide range of physiological and cellular functions. [6-8] Advances in this regard are due to discovery of solid-supported synthesis[9, 10] and the development of reagents and methods for direct amide formation.[7] Nevertheless, novel methods for the rapid production of these biopolymers are constantly being explored. Numerous strategies have been developed in order to facilitate the synthesis of complex natural products. One avenue in emulating nature's efficiency would consist of merging compatible single bond forming processes to allow multiple bond forming events to occur between several substrates, a concept generally termed multicomponent reactions (MCRs). The development of multi-component reactions has created an emerging concept in this context. MCRs are described, regardless of their mechanistic nature, as a "one-pot" transformations that involve the reaction of at least three components to generate a single product. The significant features of these reactions included speed, atom economy, diversity, step efficiency, and environmental friendliness. MCRs have a high potential for the synthesis of diversity-oriented combinatorial libraries to accomplish the preparation of highly complex natural products and biological targets[7, 8, 11-13]In this paper, and in continuation of our studies on multi-component reactions, [11-20] we present an overview on the total synthesis of natural peptides via multicomponent reactions.

2. Application of Multicomponent Reactions in the Total Synthesis of Natural Peptides

2.1. Syntheses based on the Ugi reaction

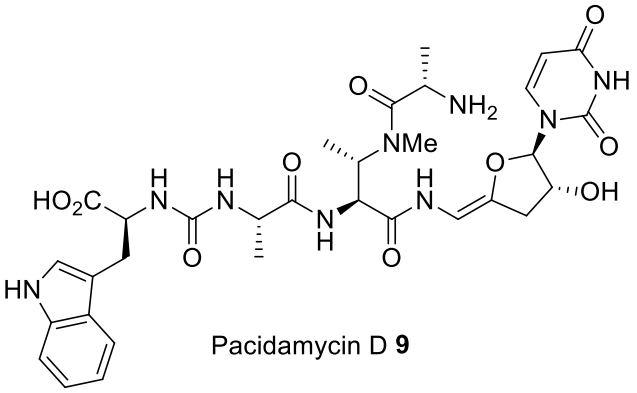
The Ugi reaction, discovered by Ivar Karl Ugi in 1959, is a highly efficient method in which a primary amine, an aldehyde, an isocyanide, and a carboxylic acid, react in a one pot procedure to furnish an *N*-substituted α-amino acid amide backbone.[21]

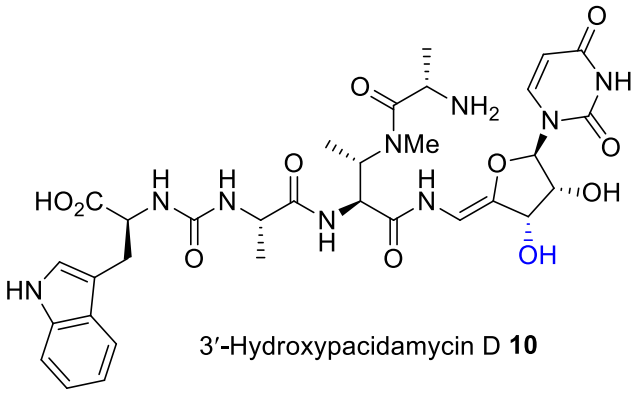
As an example in the area of peptide chemistry, the Ugi reaction was used as main step for the synthesis of ustiloxin D (**8**): Joullié and co-workers reported in 2002 the first synthesis of this 13-membered cyclic antimitotic peptidefrom readily available D-serine and an aryl fluoride as the starting materials. The total synthesis of compound **8** was also performed in 2015 by Hutton *et al.* in several steps respectively *via a)* aldol reaction, b) Tsuji-Trost asymmetric allylic alkylation (AAA) reaction, c) Ugi reaction with ammonia and d) macrocyclization as the key steps (Scheme 1).[22] This antimitotic agent was originally isolated in 1992 by Iwasaki and co-workers from the water extract of false smut balls found on the panicles of rice plants, a plant disease caused by the fungus *Ustilaginoidea virens*.[23] Biological screening of ustiloxin D (**8**) exhibited potent inhibition for microtubule assembly by interfering with tubulin polymerization at low micromolar concentrations.[24, 25] The synthetic route started with the β-OH DOPA derivative **3** which was in turn obtained in several steps from the reaction of oxazole **1** with benzaldehyde **2** through the aldol-type reaction.[26] Then, compound **3** was converted in several steps into the corresponding aldehyde **4** which was subjected to Ugi reaction with benzyl isocyanoacetate **5**, *N*-Boc-valine **6**, and NH_3 to furnish a 1:1 mixture of inseparable epimers of tripeptide-DOPA adduct **7** in high yield. Finally, deprotection and macrolactamization of compound **7** followed by hydrogenolysis of the benzylic protecting groups of the corresponding macrocycle furnished the desired natural product **8**. During macrocyclization of mixture of epimers **7** deprotected with EDC, only the expected (α*S*)-isomer undergoes macrolactamization, whereas the (α*R*)-isomer undergoes oligomerization, providing a way to separate the epimeric products in this step.



Scheme 1. Synthesis of the antimitotic peptide ustiloxin D **8.**

Also based on the Ugi reaction, the total syntheses of pacidamycin D (**9**) and its 3′-hydroxyl analogue **10** were reported *via* a copper-catalyzed C–N cross-coupling (Scheme 2).[27] The pacidamycins belong to the class of naturally occurring nucleosidyl-peptide antibiotics which were originally isolated from the fermentation broth of *Streptomyces coeleorubidus* AB 1183F-64.[28] These products inhibited phospho-MurNAc-pentapeptidetransferase (MraY) and showed highly specific activity with *Pseudomonas aeruginosa*.

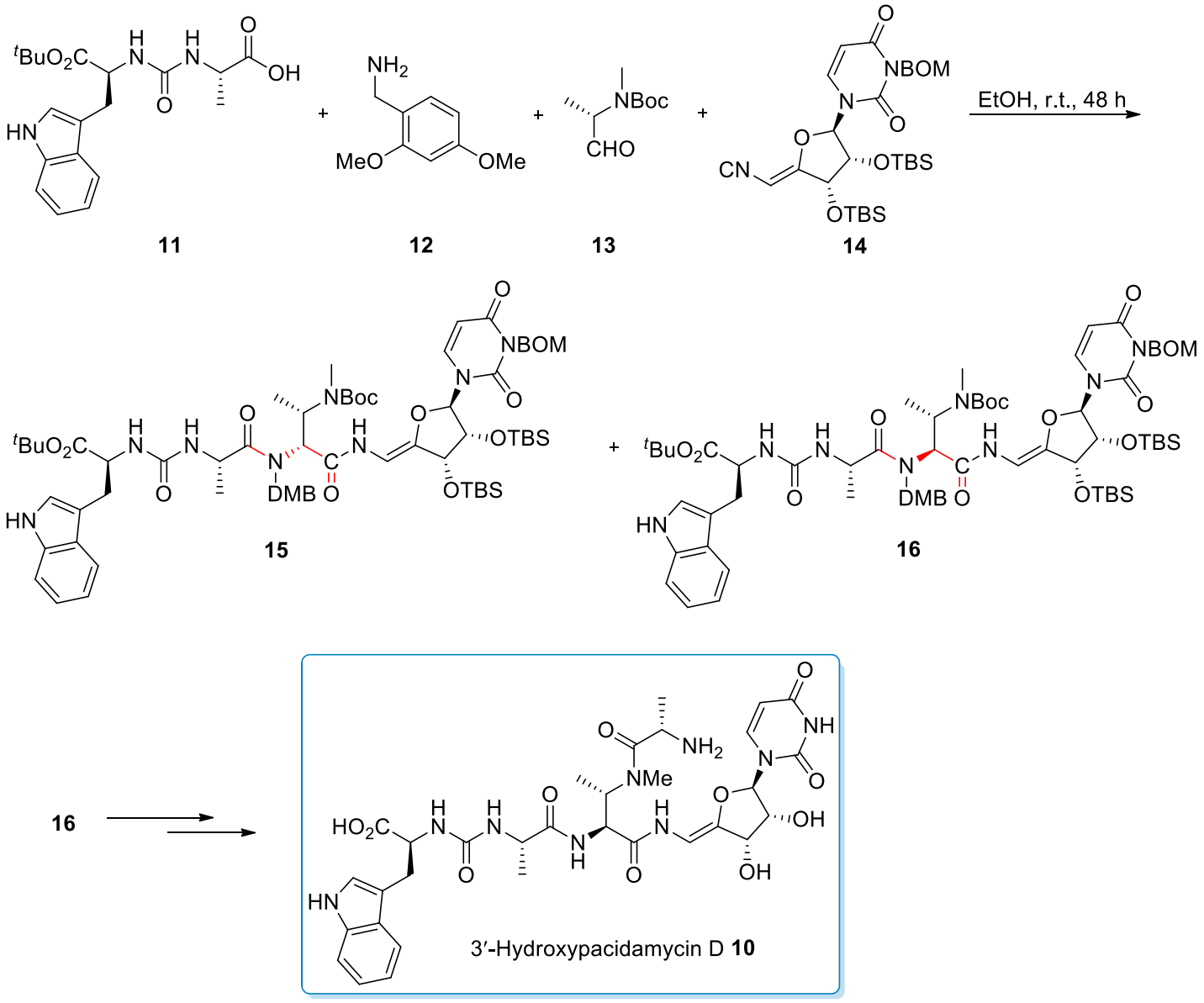




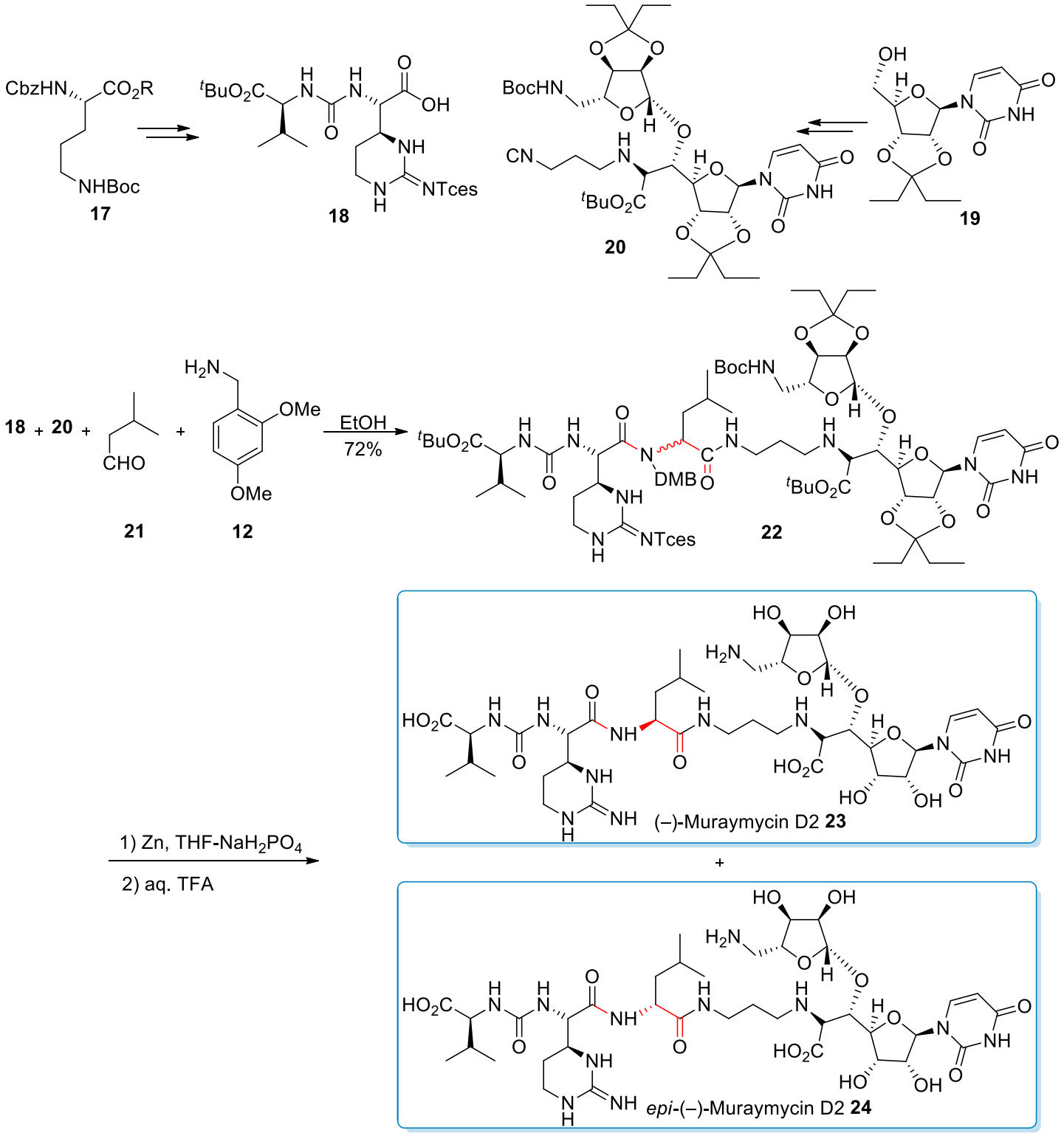
Scheme 2. The structures of pacidamycin D **9** and its 3'-hydroxyl analogue **10.**

In another study, based on the Ugi reaction, an efficient and convergent pathway for the second-generation total synthesis of 3'-hydroxypacidamycin D **10** was reported by Ichikawa's group (Scheme 3).[29] Biological evaluation showed that the presence of OH group at the 3'-position in product **10** does not have any impact on either MraY inhibition or whole-cell antibacterial activity. The synthesis of antibiotic **10** was achieved through key intermediate **16**. The Ugi reaction of the urea dipeptide **11**, 2,4-dimethoxybenzylamine **12**, the 2-*N*-methylaminopropionaldehyde derivative **13** and the unsaturated isonitrile derivative of uridine **14** provided the diastereomers **15** in 30% yield and **16** in 33% yield. The desired isomer **16**, after separation, was converted into compound **10** in several steps.

The Ugi reaction has been also applied by Ichikawa *et al.* in 2010 for the total synthesis of (–)-muraymycin D2 and its epimer (Scheme 4).[30] Muraymycins (MRY) belong to the class of naturally occurring 6′-*N*-alkyl-5′-α-*O*-aminoribosyl-*C*-glycyluridine antibiotics which possess a unique core structure. McDonald *et al.* first isolated them from the culture broth of *Streptomyces sp* in 2002.[31] These natural products showed *in vitro* antimicrobial activity against Gram-positive bacteria such as *Staphylococcus aureus*. They also displayed strong activity against *E. coli* translocase Initially, the commercially available δ-*N*-Boc-R-*N*-Cbz-L-ornithine **17** was converted into the carboxylic acid **18** in several steps. The isonitrile **20**, which was obtained in several steps from 2′,3′-*O*-isopropylideneuridine **19**,[32] reacted with the carboxylic acid **18**, isovaleraldehyde **12**, and 2,4-dimethoxybenzylamine **21** through an Ugi reaction to afford the product **22** in 54% yield as a mixture of diastereomers (1:1). Subsequent deprotection of the diastereomeric mixture **22** in the presence of Zn and NaH_2PO_4, followed by treatment with TFA (80%) provided the antibacterial nucleoside natural product, (–)-MRY D2 **23** along with its epimer **24**.



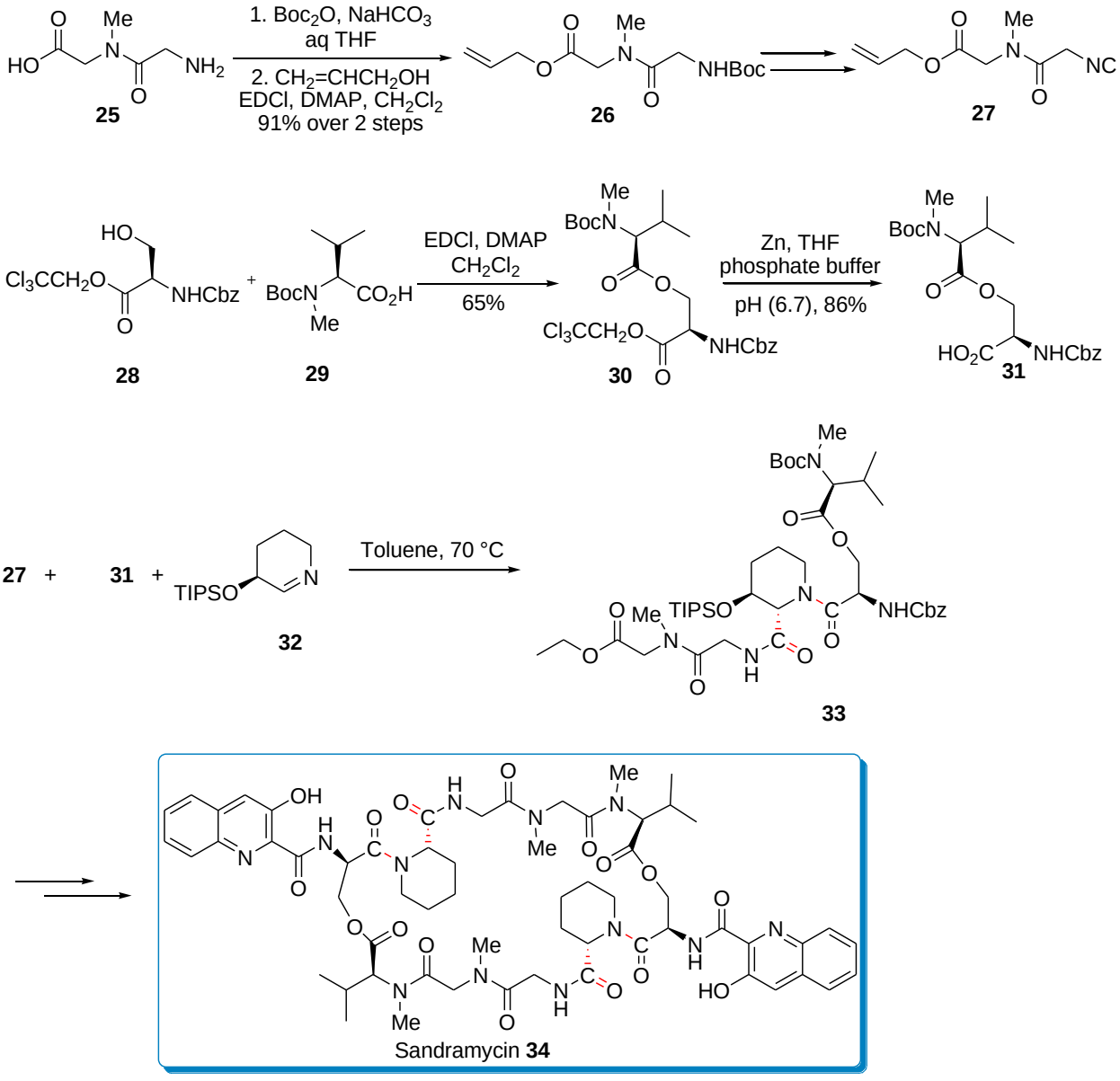
Scheme 3. Application of the Ugi reaction in the synthesis of 3′-hydroxypacidamycin D (**10**).



Scheme 4. Total synthesis of (–)-muraymycin D2 **23** and its epimer **24.**

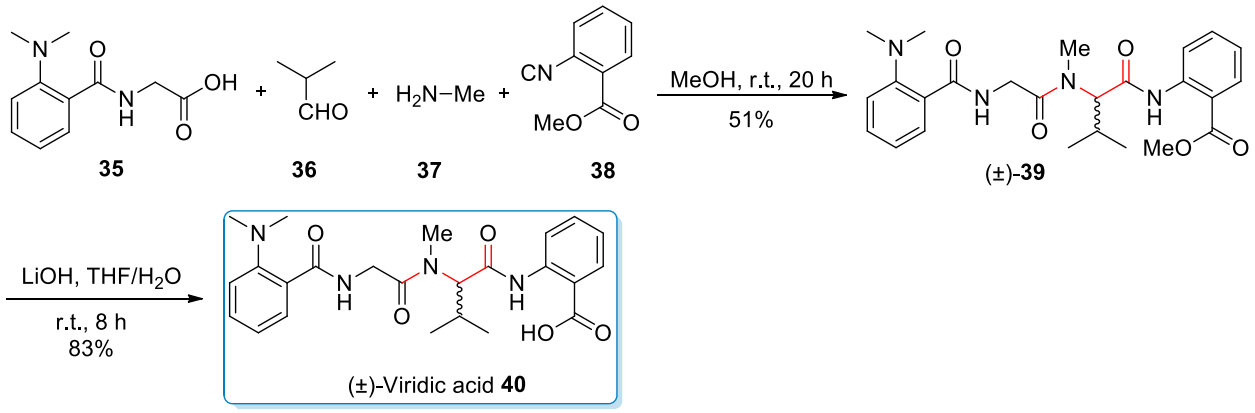
The Ugi reaction was also used for the synthesis of sandramycin (**34**), a peptide natural product. In 2013, Ichikawa and co-workers synthesized the natural product **34** *via* Staudinger reaction, aza-Wittig reaction, diastereoselective Ugi three-component reaction (U3CR), racemization-free [5 + 5] coupling and macrolactamization (Scheme 5).[33] In 1989, Matson and Bush reported the isolation of from the culture broth of *Norcardioides sp.* (ATCC 39419).[34] This unusual peptide possesses moderate activity against Gram-positive

organisms which was shown by *in vitro* activity assay. In particular, the *in vivo* evaluation of compound **34** revealed a good activity against leukemia P388 in mice. Boger and Chen in 1993 performed the first total synthesis of the natural product **34**.[35] The vital precursor for U3CR reaction, the isonitrile **27** was prepared in several steps from the conversation of compound **26**, which was in turn obtained in 91% yield from compound **25**. The synthesis of another precursor, the component-acylated serine **31**, was commenced with *D*-Ser derivative **28**[36, 37] and *N*-Boc-*N*-Me-*L*-Val **29**[38] as the starting materials. Compound **28** was reacted with compound **29** in the presence of EDCI and DMAP in CH_2Cl_2 to give compound **30** in 65% yield. Then, the 2,2,2-trichloroethyl group was removed to provide **31** in 86% yield. The pentadepsipeptide **33** was prepared in 68% yield (*S*/*R* = 85/15) by applying a diastereoselective U3CR upon treatment of isonitrile **27** with the carboxylic acid **31** and cyclic imine **32** in toluene at 70 °C. In order to control the stereoselectivity at the new stereogenic center, the triisopropylsilyl group was introduced at the α-position to the imine **32**. After several steps, the Ugi product **33** was converted into the desired antitumor antibiotic sandramycin (**34**) while remeving the stereogenic center that permitted the stereochemical control of the U3CR in a radical deoxygnation.



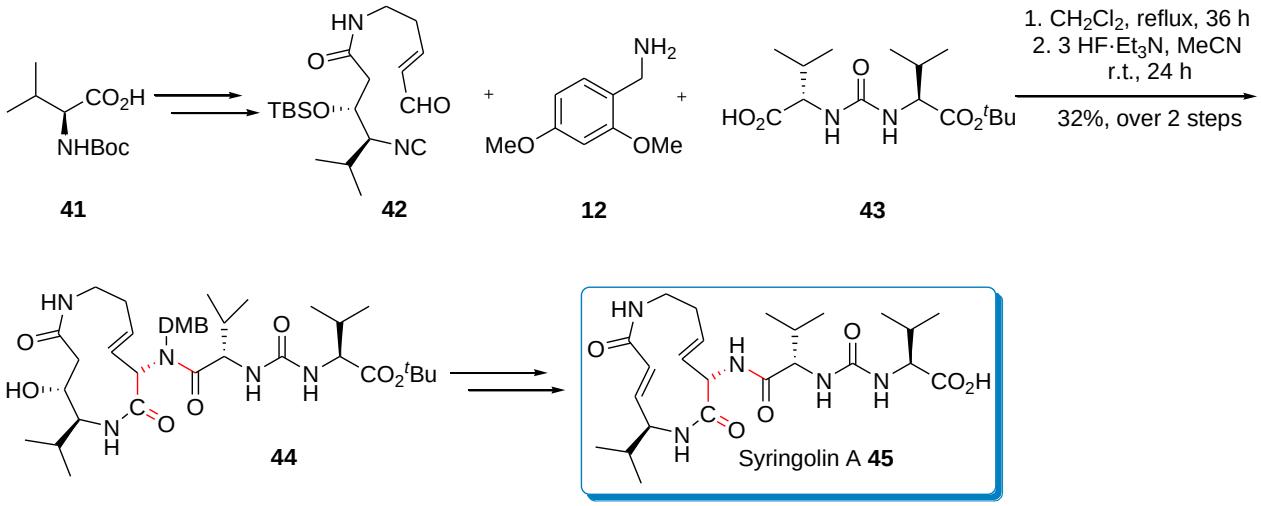
Scheme 5. Application of a multicomponent reaction in the synthesis of sandramycin (**34**).

In another study, Wessjohann and co-workers reported the total synthesis of antibacterial drug viridic acid (**40**) through the Ugi reaction (Scheme 6).[39] This tetrapeptide mycotoxin was isolated from *Penicillium viridicatum* Westling (CSIR strain No. 354).[40] The condensation reaction of the dipeptidic carboxylate **35**, isobutyraldehyde **36**, methylamine **37**, and anthranilic isonitrile **38** under Ugi conditions yielded intermediate (±)-**39** which was converted into the desired racemic viridic acid (±)-**40** *via* saponification with LiOH at room temperature.



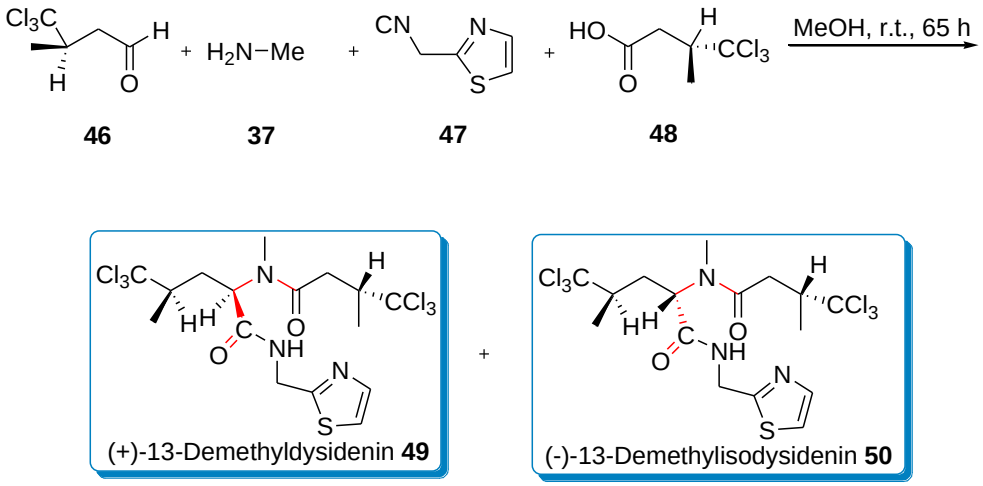
Scheme 6. Synthesis of the tetrapeptide mycotoxin, viridic acid **40.**

In a separate study, Ichikawa's group presented a convergent pathway for the total synthesis of 12-membered dipeptide macrolactam **45** by a rare intramolecular three-component Ugi reaction (Scheme 7).[41] Syringolin A (**45**), has been obtained from the strains of plant pathogen *Pseudomonas syringae*[42] and showed inhibitory activities for the p53 mutant NB cell line LAN-1 and the p53 wild-type NB cell line SK-N-SH.[43] In addition, it irreversibly and selectively inhibited the 20S proteasome through treating the S3 subsite of the b5 subunit.[44, 45] The total synthesis of **45** was reported in 2009 by Huber and co-workers.[46] Firstly, Boc-L-valine **41** was transformed into the isocyanoaldehyde **42** as a precursor for the intra-U3CR in several steps. Ugi reaction of **42** with 2,4-dimethoxybenzylamine **12** and the urea dipeptide carboxylic acid **43** followed by the removal of the *t*-butyldimethylsilyl (TBS) group to furnish the intermediate **44** in 32% over two steps. The natural product **45** was obtained from intermediate **44** in several steps.



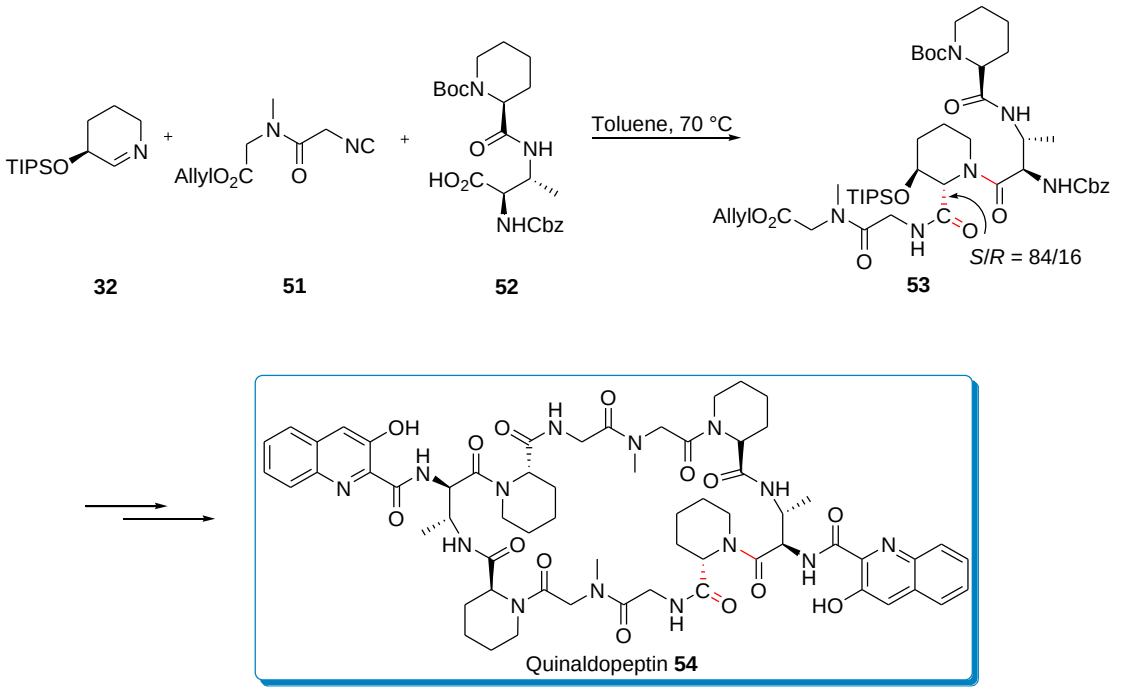
Scheme 7. Application of Ugi reaction in the synthesis of syringolin A **45.**

The Ugi reaction was also used as a key step for the synthesis of (+)-13-demethyldysidenin (**49**) and (–)-13-demethylisodysidenin (**50)**. In 1985, Williard and Laszlo performed the total synthesis of optically pure diastereomers **49** and **50** through the Ugi reaction (Scheme 8).[47] Two novel polychlorinated metabolites, demethyldysidenin (**49**) and demethylisodysidenin (**50**), were extracted from the marine sponge *Dysidea herbacea.*[48] The one pot condensation reaction of aldehyde **46** with methylamine **37**, the isonitrile **47** and acid **48** gave the desired (+)-13-demethyldysidenin (**49**) in 17% yield and (–)-13-demethyldysidenin (**50**) in 13% yield.



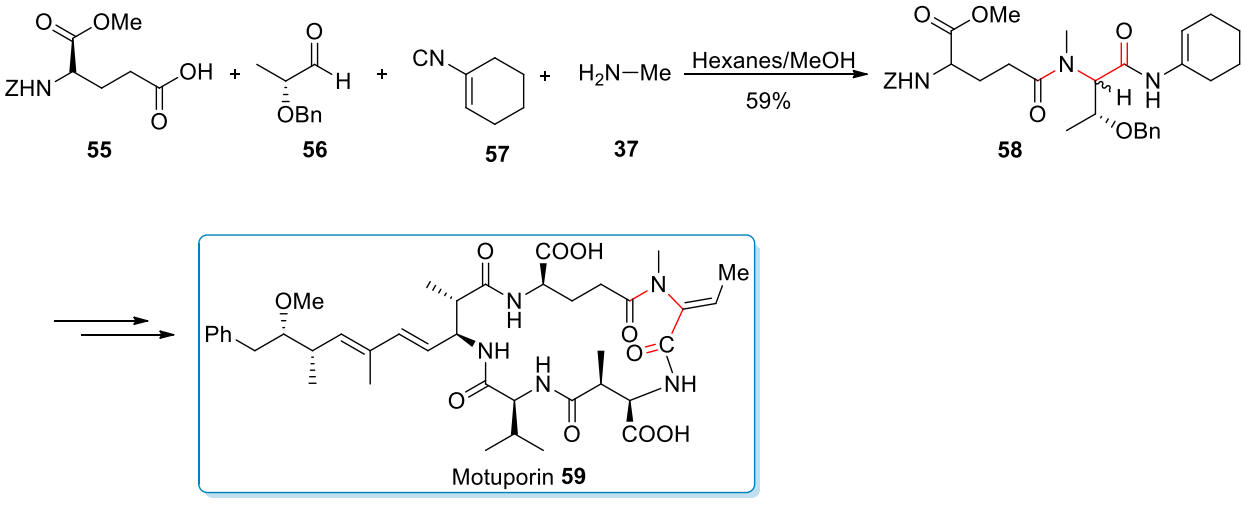
Scheme 8. Application of Ugi reaction in the total synthesis of (±)-13-demethyldysidenin **49** and its epimer **50.**

Also, Quinaldopeptin **54** was prepared using the Ugi reaction as the key step. This natural peptide was synthesized for the first first time by solid-phase peptide synthesis in 2013 by Ichikawa and co-workers.[49] In 2014, the same group reported a second-generation synthesis of this natural product through the Staudinger reaction, an aza-Wittig reaction, a diastereoselective U3CR, a [5 + 5] peptide coupling and a macrolactamization as the key steps (Scheme 9).[50] In 1990, Toda *et al.* isolated a unique antibiotic, quinaldopeptin (**54**), from a culture of *Streptoverticillium album* strain Q132-6[51] which is highly active against Gram-positive bacteria. It also showed *in vitro*-activity against anaerobes and strong cytotoxic activities against B16 (marine melanoma) and Moser (human colorectal carcinoma) cells. The synthesis started with the Ugi reaction of the imine **32**, the isonitrile **51** and the carboxylic acid **52** to furnish the expected pentapeptide **53** with a 84:16 diastereomeric ratio at the newly formed stereogenic center of the L-pipecolic acid residue. Then, after separation, the major diastereomer **53** was converted into quinaldopeptin (**54**) in several steps.

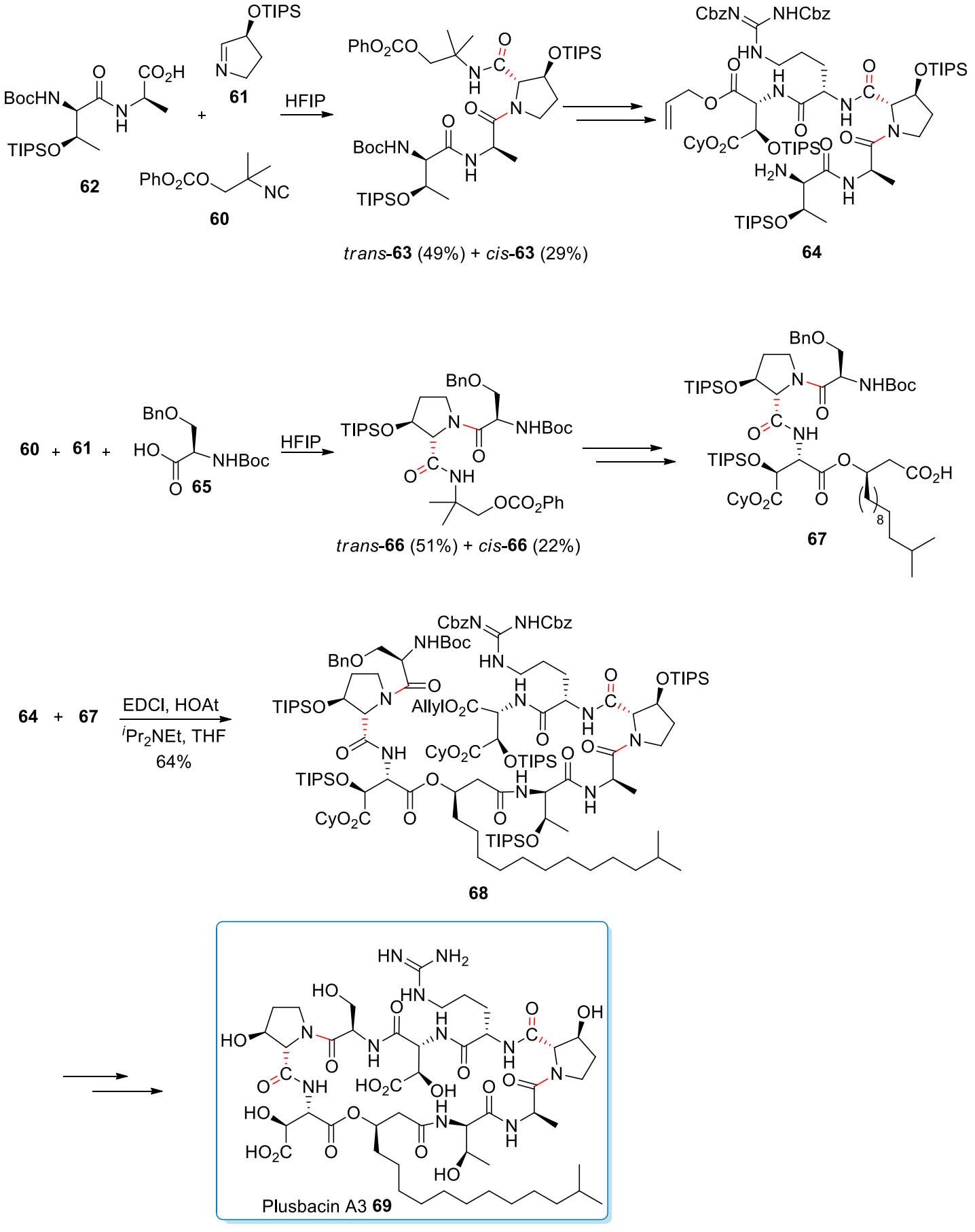


Scheme 9. Application of the Ugi reaction in the total synthesis of quinaldopeptin (**54**).

Schreiber and Valentekovich reported the enantiospecific total synthesis of motuporin.[52] The second total synthesis of motuporin in 1999 by Armstrong and co-workers included an Ugi reaction and Matteson's dihalomethyllithium insertion methodology (Scheme 10).[53] The unusual bioactive metabolite, motuporin (**59**), has been isolated from the marine sponge *Theonella swinhoei.*[54] This natural product showed *in vitro* cytotoxicity against various cancer cell lines including murine leukemia as well as human ovarian, colon, human lung, breast, and brain cancer cell lines. Initially, the carboxylbenzyloxy (*Z*) protected glutamate ester **55** was reacted with aldehyde **56**, cyclohexenyl isocyanide **57** and methylamine **37** under Ugi reaction conditions in the mixture of hexane and methanol to provide cyclohexenamide dipeptide **58** as a mixture of separable diastereomers in 59% yield. Then, the Ugi product **58** was transformed into motuporin (**59**) in several steps.

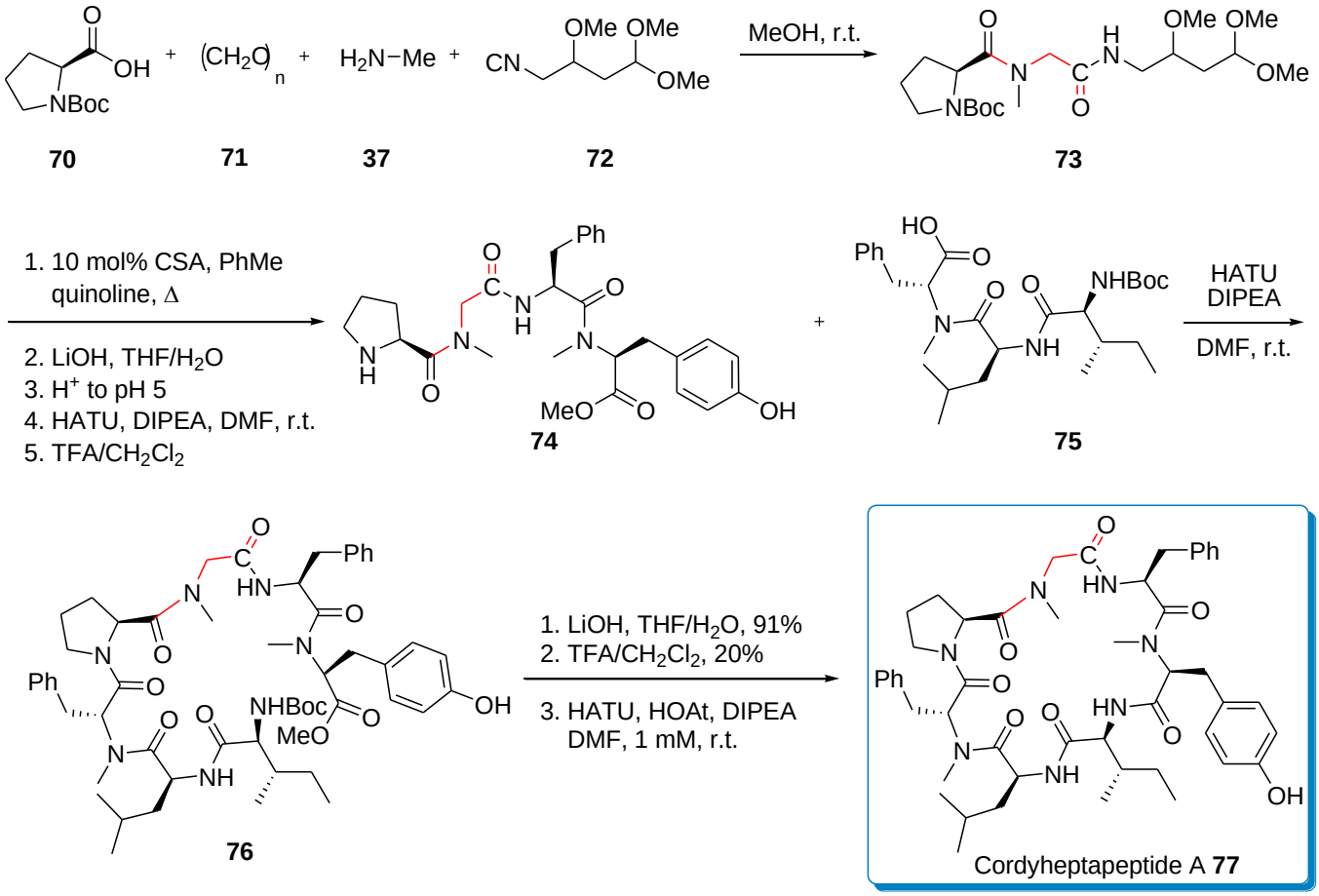


Scheme 10. Application of Ugi reaction in the synthesis of motuporin **59.**



Scheme 11. Application of the Joullié–Ugi three-component reaction (JU-3CR) in the synthesis of plusbacin A3 (**69**).

Recently, the total synthesis of plusbacin A_3 **69** was achieved *via* a solvent-dependent diastereodivergent Joullié−Ugi three-component reaction (JU-3CR) (Scheme 11).[55] At first, VanNieuwenhze and his research team in 2007 performed the total synthesis of **69** through a conventional peptide coupling starting from *trans*-Pro-(3-OH).[56] Yoshida and co-workers had isolated plusbacin A_3 in 1992 from the culture broth of *Pseudomonas sp.* PB-6250.[57] This natural product displayed strongly antibacterial activities *in vitro* and *in vivo* against varied Gram-positive bacteria such as the strains of methicillin-resistant *Staphylococcus aureus*. The cyclic lipodepsipeptide antibiotic **69** was synthesized in several steps from the linear peptide **68** which was in turn obtained in 64% yield by condensation of amine **64** with carboxylic acid **67** in the presence of EDCl, HOAt and *i*-Pr_2NEt. Compound **64** was prepared by reaction of isocyanide **60**, imine **61** and acid **62** in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent under the JU-3CR conditions to produce the expected *trans*-**63** (49% yield) as a major product and the *cis* isomer **63** (29% yield) (*trans*/*cis* = 62/38). After several steps, the major *trans* isomer **63** was converted into the product **64**. On the other hand, Boc-*D*-Ser(OBn)-OH **65** was reacted with isocyanide **60** and imine **61** under the same conditions to give the desired *trans*-isomer **66** (51%) as along with the *cis* isomer-**66** (37%). The product **67** was synthesized in several steps from the *trans* isomer *trans*-**66**.



70 **71** **37** **72** **73** **74** **75** **76**

Scheme 12. Application of the Ugi reaction in the total synthesis of cordyheptapeptide A (**77**)

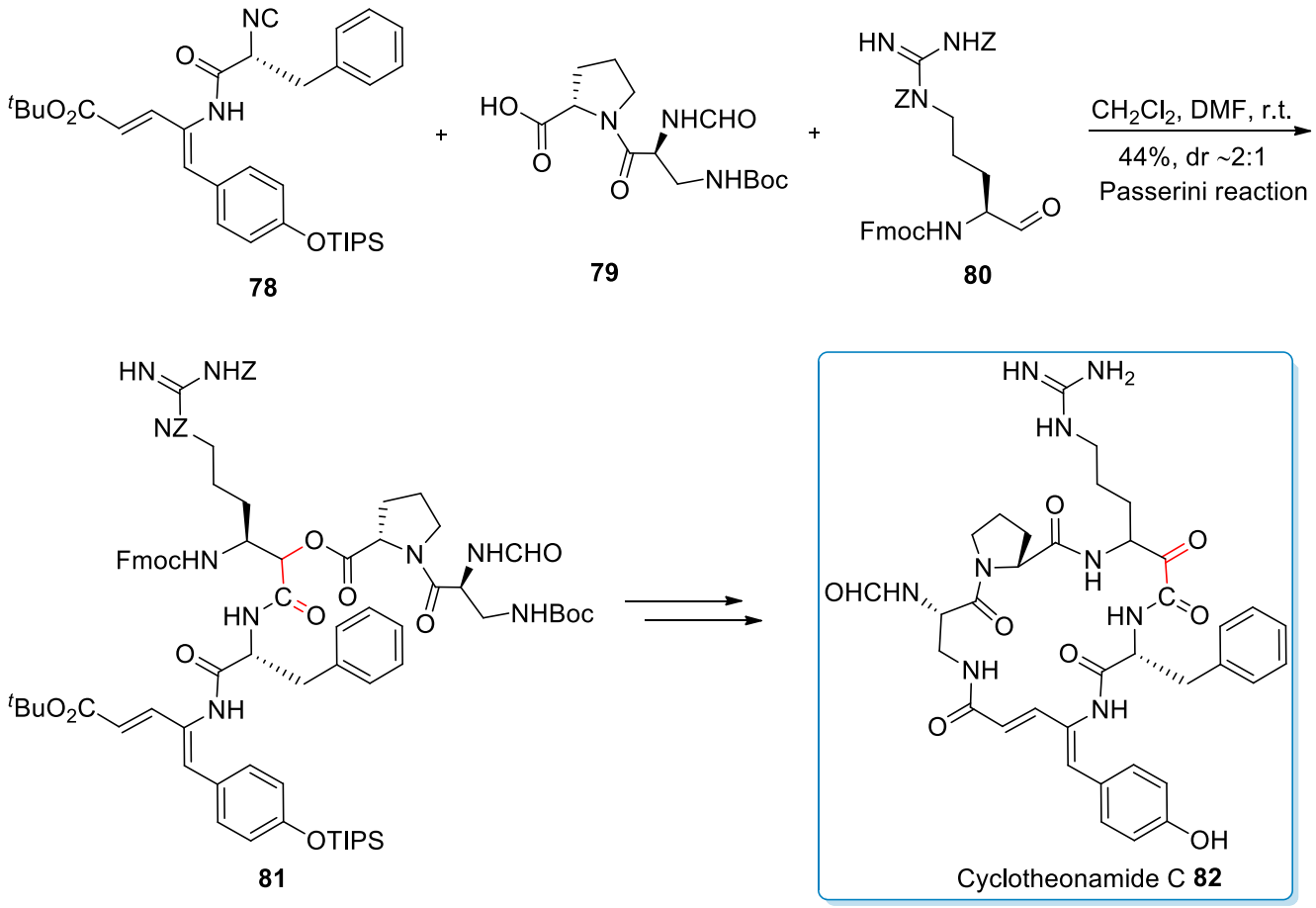
Recently, Rivera and Wessjohann presented the first total synthesis of cordyheptapeptide A **77** based on the Ugi reaction, peptide-coupling and macrocyclic-ring-closing (MRC) reaction with an overall yield of 30% (Scheme 12).[58] Cordyheptapeptide A (**77**) is a secondary metabolite which was isolated from the insect pathogenic fungus *Cordyceps sp.* BCC 1788.[59] This natural product exhibited strong cytotoxic activity against a wide range of cancer cell lines such as oral human epidermoid carcinoma, breast carcinoma, and human small

cell lung cancer. The synthesis of target product **77** began with the reaction of L-Boc-Pro-OH **70** with paraformaldehyde (**71**), methylamine **37** and isonitrile 4-isocyanopermethylbutane-1,1,3-triol (IPB) **72** to prepare the intermediate **73** in 80% yield which was transformed to the compound **74** in five steps. The reaction between **74** and **75** in the presence of HATU and DIPEA in DMF at room temperature resulted in the formation of **76**. Finally, the desired cordyheptapeptide A (**77**) was successfully obtained in three steps from **76**.

2.2. Synthesis based on the Passerini reaction

The Passerini reaction is the first isocyanide-based MCR which was disclosed by Mario Passerini in 1921. It involves the condensation reaction between a aldehyde, an isocyanide, and carboxylic acid to form the α-acyloxy amide.[60, 61]

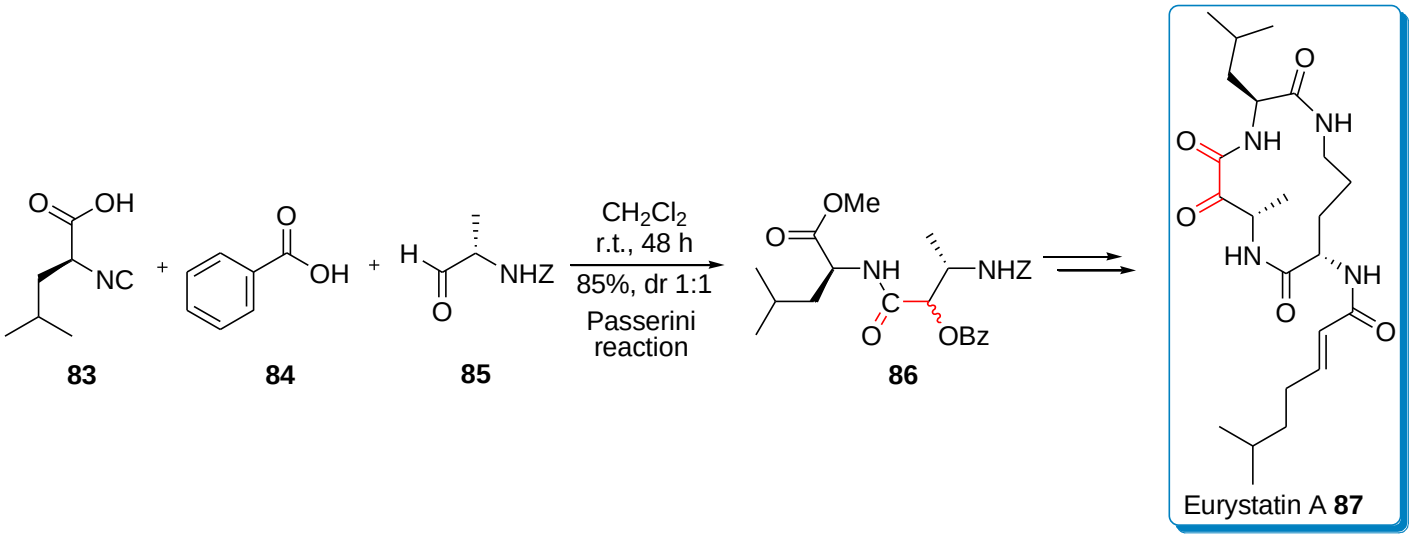
In 2009, Aitken *et al.* presented a short and convergent pathway for the formal total synthesis of cyclotheonamide C (**82**) *via* a three-component Passerini reaction-amine deprotection-*O*,*N*-acyl migration (PADAM) strategy (Scheme 13).[62] The dipeptide isonitrile **78** was condensed with the protecteddipeptide acid **79** and Fmoc-amino aldehyde **80** under Passerini reaction conditions in a mixture of CH_2Cl_2 and DMF to provide a 44% yield of pentadepsipeptide **81** with a ~2:1 diastereomeric ratio (estimated by 1H NMR spectral analysis). In several steps, **81** was converted into the natural product **82**.



Scheme 13. The formal total synthesis of cyclotheonamide C (**82**) *via* a three-component Passerini reaction.

In 1994, the first total synthesis of a new 13-membered macrocycle, eurystatin A (**87**) was accomplished utilizing the Passerini reaction by Schmidt and Weinbrenner (Scheme 14).[63] This natural product had been

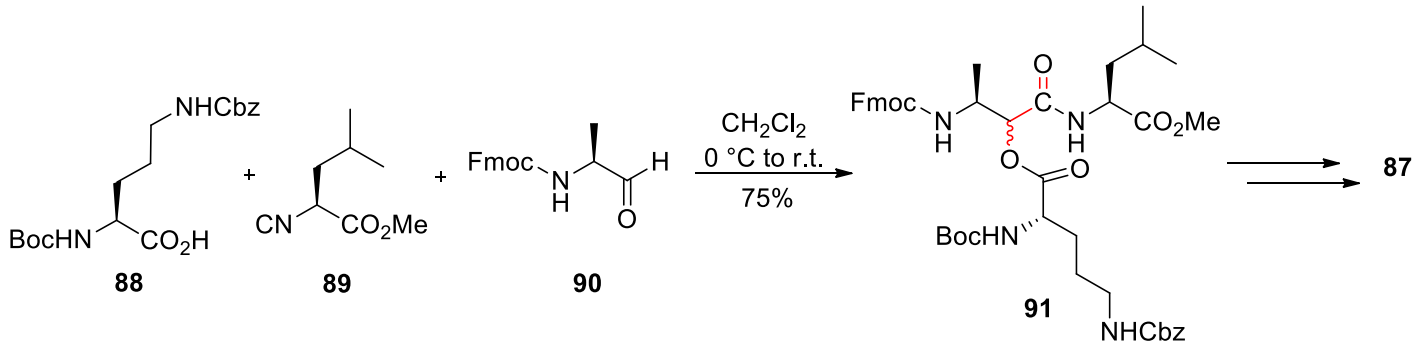
isolated from the *Streptomyces eurythermus* R353-21 by Toda and co-workers.[64] It showed potent inhibitory activity against the serine protease prolyl endopeptidase (PEP). The target product **87** was accessed through dipeptolide **86** (prepared in a multistep sequence) and the one step Passerini reaction with methyl (*S*)-2-isocyano-4-methylpentanoate **83**, benzoic acid **84** and *N*-protected (*S*)-*Z*-alaninal **85** provided a 1:1 mixture of the diastereoisomers **86** in yield of 85%.



83 **84** **85** **86**

Scheme 14. Application of a Passerini reaction in the total synthesis of eurystatin A (**87**).

The same product **87** was also synthesized through a one pot Passerini reaction by Semple *et al*. (Scheme 15).[65] The total synthesis was achieved from intermediate **91** which was produced in a Passerini reaction from suitably protected ornithine **88**, leucine-derived isonitrile **89** and Fmoc-L-alaninal **90** in 75% yield.



88 **89** **90** **91**

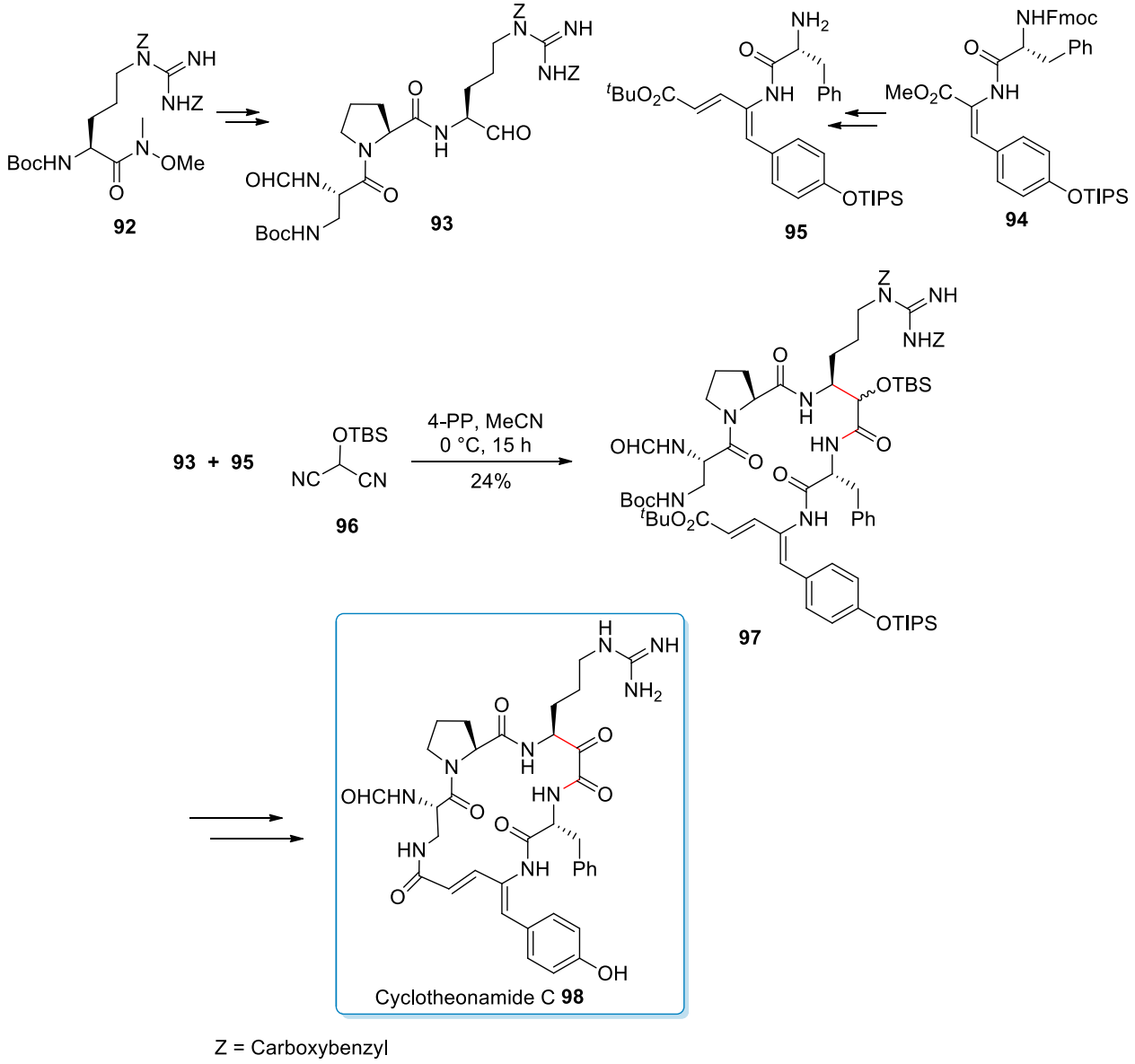
Scheme 15. The total synthesis of eurystatin A (**87**) by Semple *et al*.

2.3. Miscellaneous reactions

There are several studies on the multicomponent reactions for the synthesis of natural peptides which are not included in any of the previous sections. This section explores this category of reactions.

In 2008 and for the first time, Aitken and co-workers successfully accomplished the total synthesis of natural product **98** using unconventional multicomponent reaction as key step (Scheme 16).[66] Fusetani *et al.* reported the isolation of a potent thrombin and trypsin inhibitor, cyclotheonamide C (**98**) from *Theonella swinhoei* in 1995.[67] The sequence began with the preparation of intermediate **97**. The precursor tripeptide

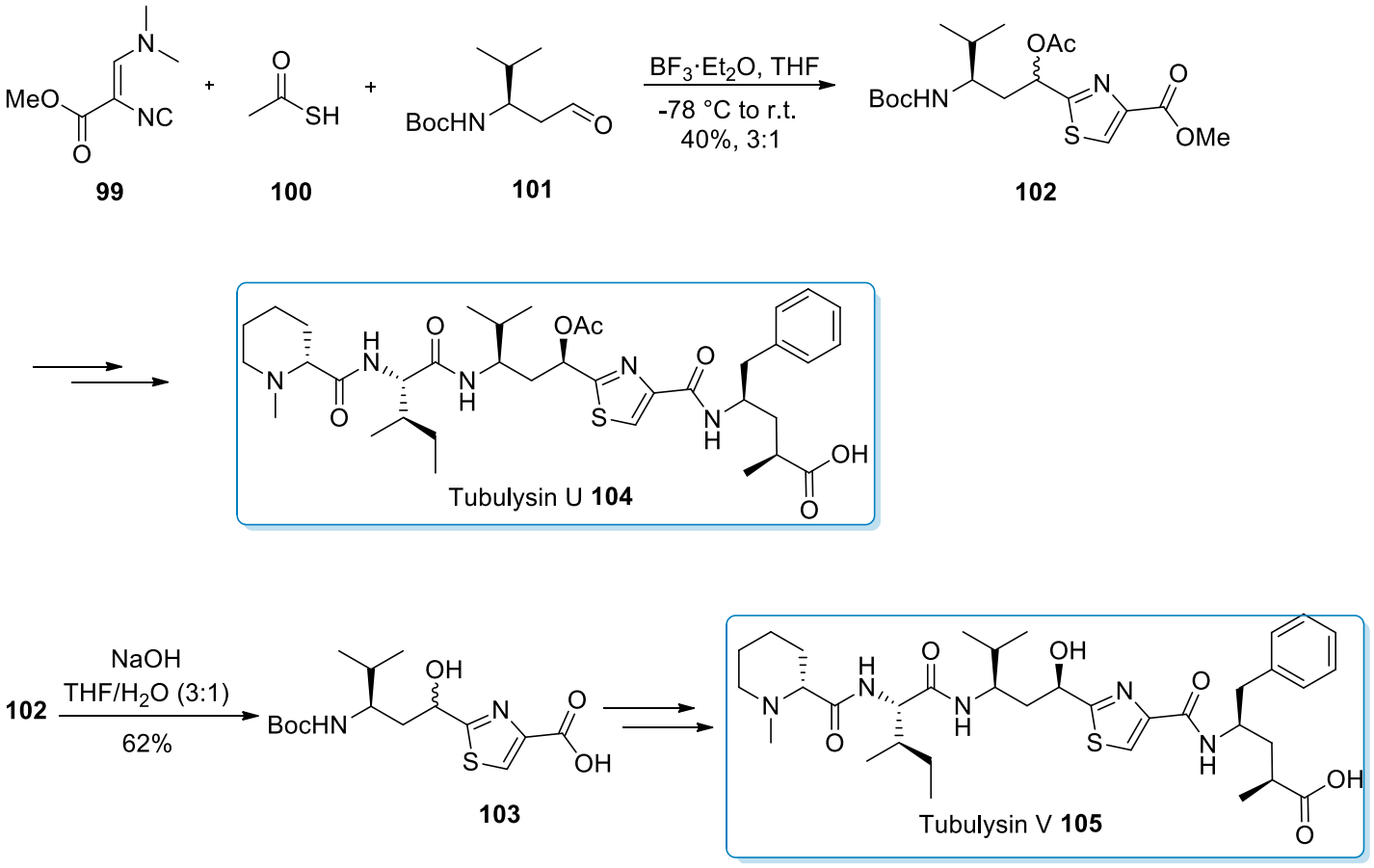
aldehyde **93** was synthesized from readily available Weinreb amide **92** in several steps. The conversion of the protected dehydrotyrosine dipeptide **94** furnished amine **95** in several steps. The one pot multicomponent condensation reaction of tripeptide aldehyde **93** with amine **95** and α-(*t*-butyldimethylsilyloxy)malononitrile **96**, using 4-pyrrolidinopyridine as a base, obtained the expected linear pentapeptide **97** in 24% yield which was converted into the cyclotheonamide C (**98**) over several steps.



Scheme 16. Application of multicomponent reaction in the synthesis of cyclotheonamide C (**98**).

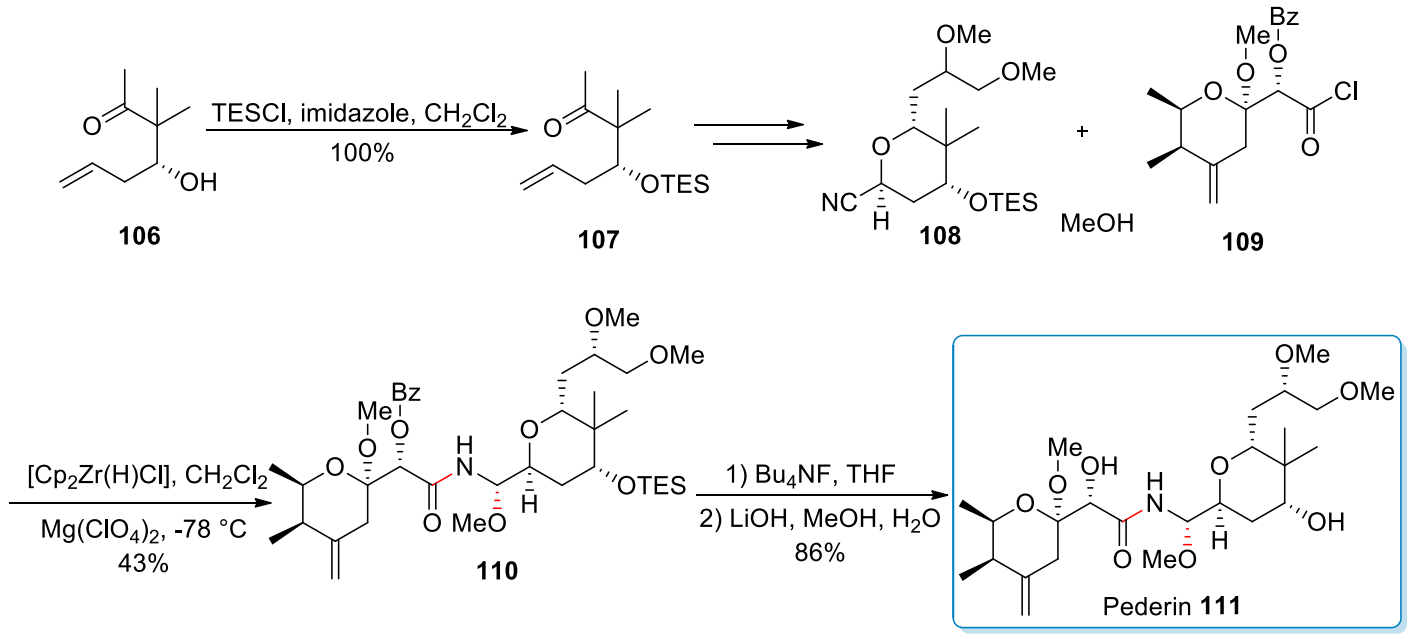
In 2006, Dömling *et al.* presented a multicomponent reaction-based short convergent pathway for the stereoselective total synthesis of tubulysin U (**104**) and tubulysin V (**105**) (Scheme 17).[68] Tubulysins are members of an interesting family of tetrapeptide secondary metabolites which were first isolated from the culture broth of the myxobacteria *Archangium gephyra* and *Angiococcus disciformis* by Höfle and co-workers in 2000. These natural products are highly active against mammalian cell lines.[69] The multicomponent reaction of the commercially available Schöllkopf isocyanide **99** with thioacetic acid **100** and Boc-protected L-homovaline aldehyde **101** in the presence of $BF_3{\cdot}Et_2O$ in THF provided the Boc-protected methyl ester **102** in

40% yield with a 3:1 diastereomeric ratio. Over several steps, intermediate **102** was converted into the desired natural product tubulysin U (**104**). In another pathway, tubulysin V (**105**) was prepared in a multistep sequence starting with the hydrolysis of acetate **102** to alcohol **103** in the presence of NaOH.



Scheme 17. Total synthesis of tubulysin U (**104**) and tubulysin V (**105**).

In 2010, Floreancig and co-workers accomplished the total synthesis of pederin using the multicomponent reaction (Scheme 18).[70] Pederin (**111**), a potent insect toxin, was isolated for the first time from the beetle *Paederus fuscipes* Curt.[71] The nitrile **108** was obtained in several steps from TES-ether **107**, which was synthesized by silylation of keto alcohol **106**[72] using chlorotriethylsilane and imidazole. Nitrile **108** was reacted with acid chloride **109** and MeOH in the presence of the Schwartz reagent to afford the *N*-acyl aminal **110** in 43% yield as a single stereoisomer. Finally, removal of protecting groups in **110** gave the desired natural product **111** in 86% yield.



Scheme 18. Synthesis of pederin (**111**), a potent insect toxin.

3. Conclusions

While natural peptides have been produced by various strategies, multicomponent reactions have shown a great potential among them. Multicomponent reactions reduce the number of reaction steps and increase atom economy. The present review highlights some of these approaches to demonstrate the general feasibility of the concept.

List of abbreviations

Boc	*t*-Butyloxycarbonyl
BOM	Benzyloxymethyl acetal
Cbz	Carbobenzoxy
DMAP	4-Dimethylaminopyridine
DMB	2,4-Dimethoxybenzylamine
DMF	Dimethylformamide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
Fmoc	9-Fluorenylmethoxycarbonyl
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
PMB	*p*-Methoxybenzyl
4-PP	4-Pyrrolidinopyridine
TBS	*t*-Butyldimethylsilyl

Tces	Trichloroethoxysulfonyl
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl

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