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Review

The Cyclization of Peptides and Depsipeptides

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Abstract: Constricting the peptide backbone into a more defined conformational form through cyclization is an activity evolved in nature and in synthetic work, the latter straddling only the most recent decades. The resulting conformational constraints increase the probability of an optimum response with bio-receptors. The purpose of this review is to highlight developments that have proved to be reasonably efficient in the macrocyclization of linear precursors into cyclic peptides and depsipeptides. Copyright © 2003 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: macrocyclization of peptides; peptide cyclization; homodetic cyclic peptides; heterodetic cyclic peptides; cyclopeptides; cyclodepsipeptides; cyclic depsipeptides; macrolactamization; macrolactonization; head to tail cyclization; side-chain to side-chain cyclization.

INTRODUCTION

Cyclic peptides and depsipeptides [heterodetic peptides which include ester (depside) bonds as part of their backbone] have been characterized in many natural environments, and show a wide spectrum of biological activity. They are therefore sought after as promising lead compounds for drug discovery. The reduction in conformational freedom brought about by cyclization often results in higher receptor-binding affinities. Frequently in these cyclic compounds, extra conformational restrictions are also built in, such as the use of D- and *N*-alkylated-amino acids, α,β-dehydro amino acids or α,α-disubstituted amino acid residues. Probably the most general of nature's conformational restrictors is the disulfide bond formed by the oxidation of the thiol side chains of appropriately sited cysteine residues. The synthesis of disulfide bonds has been explored right from the early days of peptide synthesis and lies a little outside the scope of this review, except to note that the variety of strategies for the formation of -S-S- bonds have been recently reviewed [1,2].

This review will therefore concentrate on strategies for cyclization of peptides which have found favour over the past decade (up to 2002), although the rationale behind some of the developments will be alluded to from a database of over 30 years of specialist reviews in this area [3]. Recent years have seen a significant increase in structural diversity as exemplified by compounds derived from marine sources [4–8], fungi [9–11], microorganisms [12–14] and higher plants [15–17].

In the early days of cyclic peptide synthesis, the impetus for the work came from the need for structural proof of natural compounds, and the preparation of more active analogues. Whilst this is still a major and necessary incentive, a great deal of thrust is also currently generated in recognizing cyclic analogues as convenient stepping stones on the journey from a biologically active lead peptide to peptidomimetics and hence to active pharmacophores. Typical aspects of this journey have been summarized recently in the work of Murray Goodman *et al.* [18]. Although

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BIOGRAPHY

John Davies

Since returning from Post-doctoral work in the USA (at MIT), John Davies has carried out all his research work on the chiral analysis of peptides, and on the synthesis of cyclic peptides and depsipeptides, at his alma mater, the University of Wales Swansea. He has contributed frequent Chapters on 'unusual features of peptides' to the Royal Society of Chemistry's Specialist Report books on 'Amino Acids, Peptides and Proteins', and currently is a Senior Reporter (i.e Editor) of this series. He was Secretary of the European Peptide Society for six years in the 1990s.

the pharmaceutical industry has not been overenthusiastic in its development of peptides as drugs [19–21], there are islands of success quoted for cyclic peptides, e.g. octreotide (Novartis), integrilin a cyclic peptide heptapeptide Gp IIb/IIIa inhibitor (Cor Pharmaceuticals) and the naturally occurring cyclosporin A in immunosuppression. The cost of synthesizing cyclic peptides is often prohibitive, as the sophisticated reagents required are not cheap commodities. However, optimized yields of cyclization, the use of cheaper reagents and advantageous chromatographic separations have been raised [22] as criteria capable of pushing the balance in favour of the synthesis of cyclosporin A, as compared with its isolation from microbiological preparations.

Cyclic peptides and analogues have generated a great deal of interest of late, and reviews on the subject matter dealt with here have recently appeared [23–27]. Inevitably the topics reviewed here will overlap with material in these authoritative texts, but the hope is that a fresh and separate assessment will enrich and generate further interest in the field. The approach taken in this review will initially be to discuss the general consensus for carrying out a particular cyclization, followed by a review of some of the more specific problems with different families of structures. Acronyms galore percolate through the literature in this field. Usage here will follow good practice [28], but augmented with specific definitions as well.

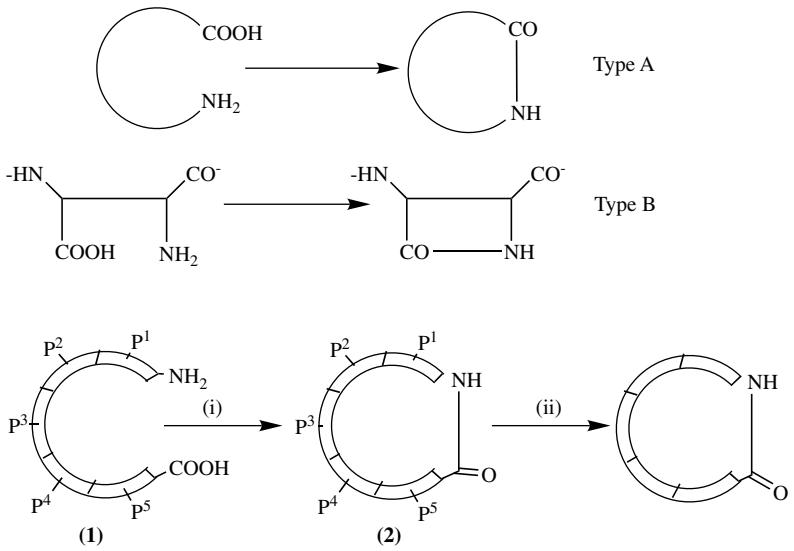
CYCLIZATION OF HOMODETIC PEPTIDES (ALL-AMIDE LINKED)

In the Solution Phase

While many combinations exist, head to tail cyclization (type A) and side-chain to side-chain cyclization (type B) are the most common examples, and very similar conditions can be used to attain the macrocyclization step in these examples. But both types depend greatly on the availability of orthogonally protected linear precursors being available. It is outside the scope of this review to put on record the great strides made in peptide synthesis in general, but the macrocyclization step, which is after all the yield-determining step, relies heavily on years of careful development of peptide coupling reagents. A recent 406-reference update [29] discusses the 'state of the art' of peptide coupling in general.

Where grammes of cyclic peptide is a requirement it is more than probable that cyclization of protected linear peptides in the solution phase would still be the best choice. Intramolecular cyclizations as summarized in Scheme 1 are favoured by high dilution (10^{-3}–10^{-4} M), and as cyclizations tend to be inherently slow reactions, the activated carboxyl should not undergo unimolecular or solvent-induced decomposition. Inherent in the activation of a carboxyl group without the advantage of a urethane-designed protection of the terminal residue's amino group, is racemization at the *C*-terminus. Judicious choice of Gly or Pro residues at the *C*-terminus activation point overcomes this problem, and if this choice is not possible, the racemization potential of the chosen coupling agent needs to be checked. Sterically hindered amino acids and *N*-methylated amino acids have been known to give problems at the cyclization stage, and depending on the size of the macrocycle, the presence of a D-residue in the linear sequence is often mandatory, as will be seen in later examples.

The early trends [3,30] in the choice of coupling methods for stage (i) of Scheme 1 were focused on *p*-nitrophenyl esters, the azide method (no racemization), 2,4,5-trichlorophenyl and pentafluorophenyl esters and the mixed anhydride method. But the more direct method of activation using *N*,*N*′-dicyclohexylcarbodiimide (DCC) with catalysts such as HOBt **(3)** [31], HONSu [32] and the more successful reagent HOAt **(4)** [33] have made a significant impact on macrocyclization. The precipitated urea from this method is not always easy to remove from the cyclic peptide formed, and in some cases



(i) Range of coupling agents (ii) Side-chain deprotection

Scheme 1

the *N*,*N*′-diisopropylcarbodiimide (DIC) [34] whose urea is more soluble is advantageous. Even better in the presence of a completely derivatized **(2)** in Scheme 1, is the use of a water soluble carbodiimide EDC [1-ethyl-3-(3′-dimethylaminopropyl) carbodiimide hydrochloride] [35], whose urea can be washed out by aqueous extraction [36].

A worthy successor to the conventional azide coupling has been the use of DPPA **(5)** [37], and PyBrop **(6)** [38]. So together with these newer coupling agents and those listed in Table 1, anyone contemplating a macrocyclization step at present has a wide choice of reagents. Yet, even now, the number of variables associated with the cyclization step still makes it a 'test it and see' approach, although percolating through the most recent reports is the deduction that HOAt — based couplings have advantages of yield and low racemization when compared with the others. In making choices, however, it would be best to steer away from the tetramethyluronium derivatives as there is evidence [36,39] that the tetramethylguanidinium group is involved in end-capping the amino group involved in macrocyclization.

Table 1 Recent Popular Coupling Agents

Phosphonium derivatives of (3) and (4)	So-called* 'Uronium' derivatives of (3) and (4)
BOP 1-benzotriazole-tris-dimethyl aminophosphonium hexafluorophosphate	HBTU O-(benzotriazol-1-yl)-1,1,3,3 tetramethyl uronium hexafluorophosphate
PyBOP 1-benzotriazolyloxy-tris-pyrrolidino phosphonium hexafluorophosphate	TBTU O-(benzotriazol-1-yl)-1,1,3,3 tetramethyl uronium tetrafluoroborate
PyAOP 7-azabenzotriazol-1-yloxy tris pyrrolidino phosphonium hexafluorophosphate	HATU O-(7-azabenzotriazol-1-yl)-1,1,3,3 tetramethyl uronium hexafluorophosphate
AOP 7-azabenzotriazol-1-yloxy-tris-dimethyl aminophosphonium hexafluorophosphate	HAPyU O-(7-azabenzotriazol-1-yl)-1,1,3,3 tetramethylene uronium hexafluorophosphate
	HAPipU O-(7-azabenzotriazol-1-yl)-1,1,3,3 pentamethylene uronium hexafluorophosphate

* On the difficulty of referring to these compounds as they were thought to be (i.e. uronium salts) as opposed to what they are (isomeric *N*-oxides) see *J. Peptide Sci.* 2003; **9**: 1–8.

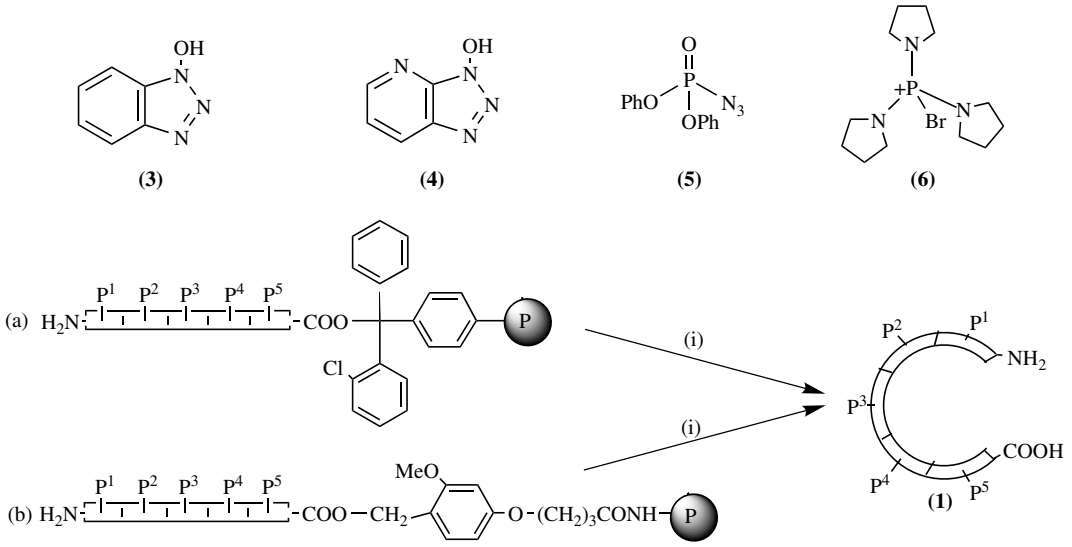
It is not a trivial matter to reach structure **(1)** in Scheme 1, i.e. having the terminal groups free to couple while side-chain protection is intact. However, in recent years the task has been made relatively easier using solid phase assembly using acid labile linkers, which allow detachment from the polymer without sacrificing side-chain protection. Two of the best examples here are summarized in Scheme 2, (a) using the 2-chlorotrityl resin [40] and (b) the 4-hydroxymethyl-3-methoxyphenoxybutyric acid linker [41].

On-Resin Cyclizations

In the 1990s the significant move into on-resin macrocyclization occurred, and one of the earliest developments involved the use [42,43] of the Kaiser oxime resin [44] as summarized in Scheme 3 the final cyclization step removes the cyclic product from the resin. Instead of an oxime-based linker, similar cyclizations can be carried out [45] by oxidative cyclative cleavage of an aryl hydrazide linker. Proof was also obtained in this work that no epimerization took place at the *C*-terminal residue. Alternative linkers used in this approach include thioesters [46], 'safety-catch' linkers based on sulfonamide [47], or the most recent catechol example [48] summarized in Scheme 4. A totally on-resin approach has been developed by linking the side chain of a trifunctional amino acid to the resin, and through use of three levels of orthogonal protection, a protocol such as the one depicted in Scheme 5 [49,50] has proved successful. Many aspects of this on-resin approach have been reviewed authoritatively by Spatola and Romanovskis [25]. The choice of side chains, which have been explored for initial attachment to the resin, has been expanded to include Glu, Asn, Gln, Lys, Orn and Dab. A comparison of these various approaches has been made [51], together with the development of new orthogonal strategies, involving *p*-nitrobenzyl protection of the α-carboxyl which enabled use to be made of the side chains of Ser and Tyr. On-resin cyclization still requires careful choice of coupling agent to minimize racemization levels at the linked residue (Asp in Scheme 5). Pentafluorophenyl esters and a lowering of the base concentration have been advantageous in this context [51]. One of the more recent developments in this field [52] is illustrated in Scheme 6, where the linker is attached to a backbone amide group. Epimerization at the Phe residue is a problem, but could be reduced to 12% using BOP/DIEA in DMF.

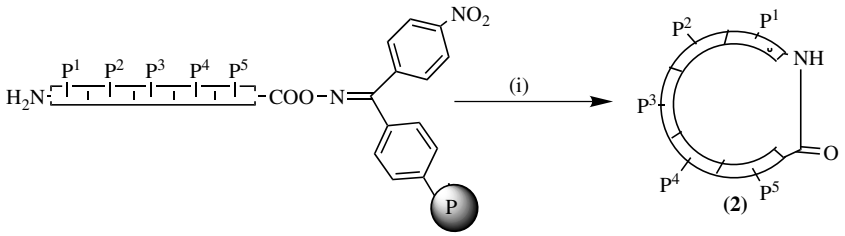
Amide-Bond Formation via Side-Chain Cyclization (Lactam Bridges)

The easiest way to achieve a side chain–side chain lactamization (introduced as a type B cyclization earlier in the review) is to arrange for suitably protected Lys and Glu residues to be assembled into a linear precursor. After specific deprotection of



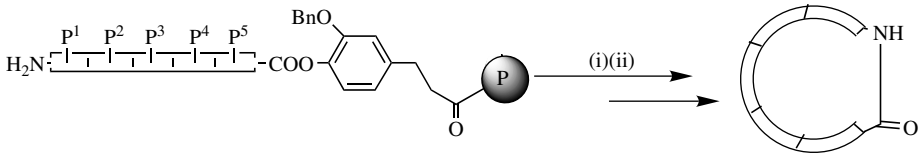
Reagent: (i) mild acid
Use of labile linkers on-resin

Scheme 2



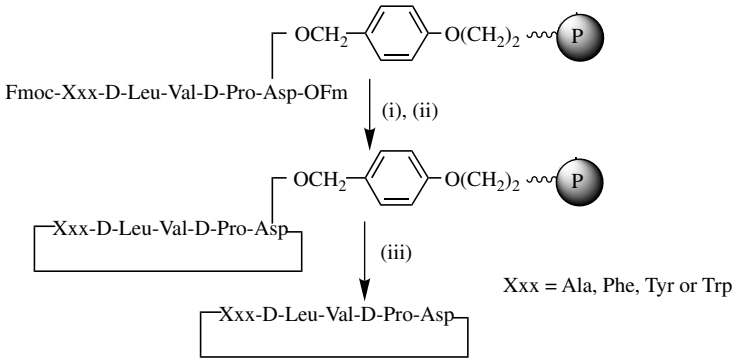
Reagents: (i) HOAc / Et_3N

Scheme 3



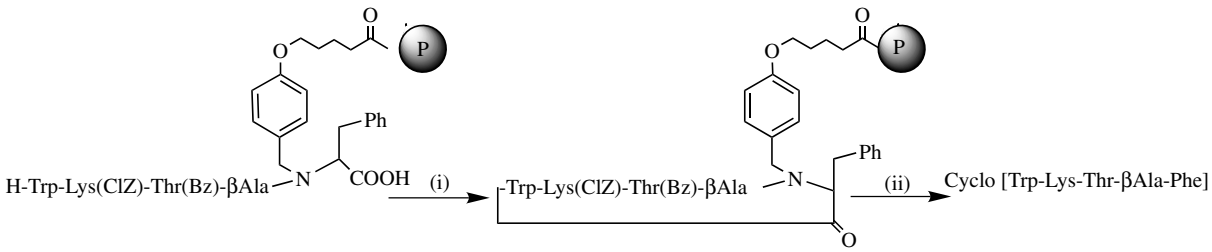
Reagents: (i) HF /cresol (ii) 2% DIEA in DMF or 20% piperidine in DMF

Scheme 4



Reagents: (i) 20% piperidine (ii) BOP or HOAt (iii) HF

Scheme 5



Reagents: (i) 3 eq activating agent, base -10° C 3 h (ii) HF or strong acid and scavenger 1 h

Scheme 6

the Lys and Glu side chains, conventional strategies can then be used to form the amide bond between the side chains. Model studies [54] on utilizing an on-resin (4-methylbenzhydryl resin) cyclization of Fmoc-Lys-Phe-D-Ala-Pro-Glu-Gly (Peptide 1) and its analogue (Peptide 2) with the positions of Lys and Glu reversed, provided the results shown in Table 2. DIC over extended times proved to be the best conditions, with peptide 1 being lactamized easier than peptide 2.

Table 2 Comparison of Side-chain Lactamisation Conditions

	Peptide 1			Peptide 2		
	Linear	Cyclic	Oligomeric	Linear	Cyclic	Oligomeric
(A) BOP/DIEA	0	42	56	4	24	67
(B) BOP/HOBt/DIEA	2	51	46	16	30	54
(C) HBTU/HOBt/DIEA	0	35	56	13	32	54
(D) DIC/HOBt	33	61	6	87	7	5

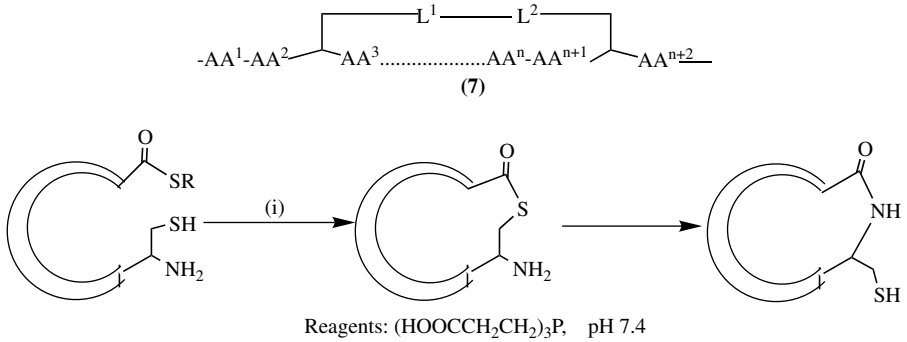
The impetus created by the demands for cyclic peptide libraries has spawned new approaches to side-chain lactamization. An allyl/allyloxycarbonyl strategy [55] for lactam bridge formation has been tested on a small library with seven amino acid residues. The Guibe method [$(PPh_3)_4$/$PhSiH_3$/DCM] proved efficient in removing the allyl/allyloxycarbonyl groups under neutral conditions. Some of the disadvantages of these lactamizations, e.g. the need for Lys and Glu to be specifically sited in the main chain, can be overcome by the approach based on the work of Gilon *et al.* in which two backbone nitrogens can be connected via bridges as in **(7)** [56]. Suitable *N*-derivatized building blocks have to be prepared for prior insertion.

Cyclization via an Orthogonal Coupling Strategy

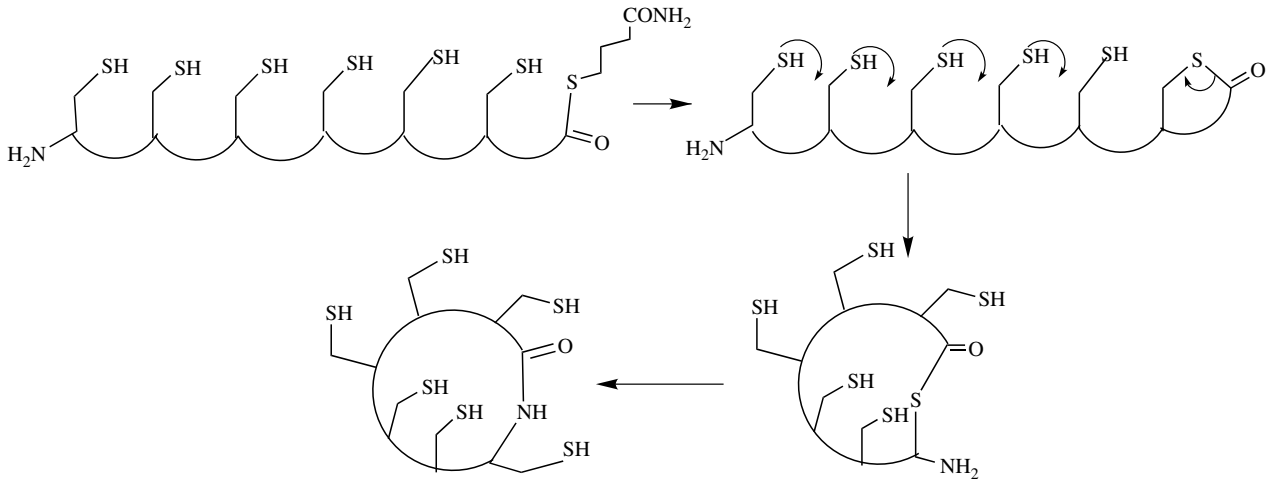
Based on an original idea by Stephen Kent and co-workers, Tam and Lu [57] have exploited the reactivity of a thiolactone intermediate to generate a very subtle method for making homodetic cyclic peptides without the need for protected peptide precursors. The essence of the methodology is summarized in Scheme 7. The disulfide rich cyclopeptide, cyclopsychotride, was synthesized using this method, which depends on ring contraction brought about by attack of the thiolactone intermediate by the amino group. No evidence of racemization was detected.

A thioester at the *C*-terminus, an *N*-terminus Cys, and at least one internal free thiol group is the fundamental requirement for the 'thia-zip' version for the synthesis of large cyclopeptides. The synthesis of cyclopsychotride as depicted in Scheme 8 [58] is representative of the strategy, which is initiated by an internal thiolactone, and followed by successive thiol-thiolactone exchanges until it reaches the final irreversible S to *N*-acyl isomerization. Both examples rely on the availability of Cys residues in the peptide. Attempts to overcome this necessity have included coordination of the *N*-terminal end of a peptide with *C*-terminal thioesters using Ag^+ ion coordination [59] and Kent *et al.*'s [60] formation of a transient thiolactone link which includes an auxiliary group which is removed, leaving a Gly residue as summarized in Scheme 9.

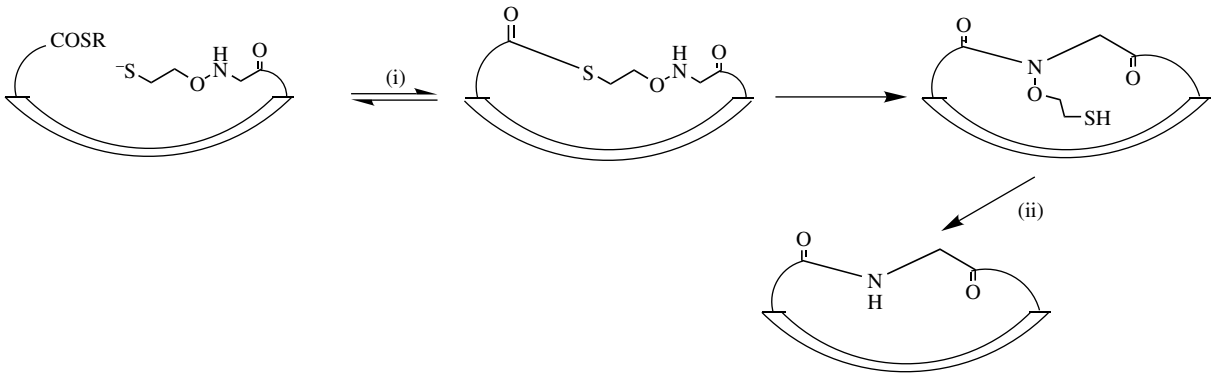
A very interesting challenge to the conventional and orthogonal coupling strategy was set by the attempted synthesis [61] of all-L cyclo (Ala-Phe-Leu-Pro-Ala) from its linear precursor. Using conventional conditions, e.g. BOP, the cyclic dimer and trimer were the only products, while the thioester approaches highlighted already also failed. However, a newly developed photolabile auxiliary did



Scheme 7



Scheme 8



Reagents: (i) H_2O / pH 7.5 (ii) Zn reduction

Scheme 9

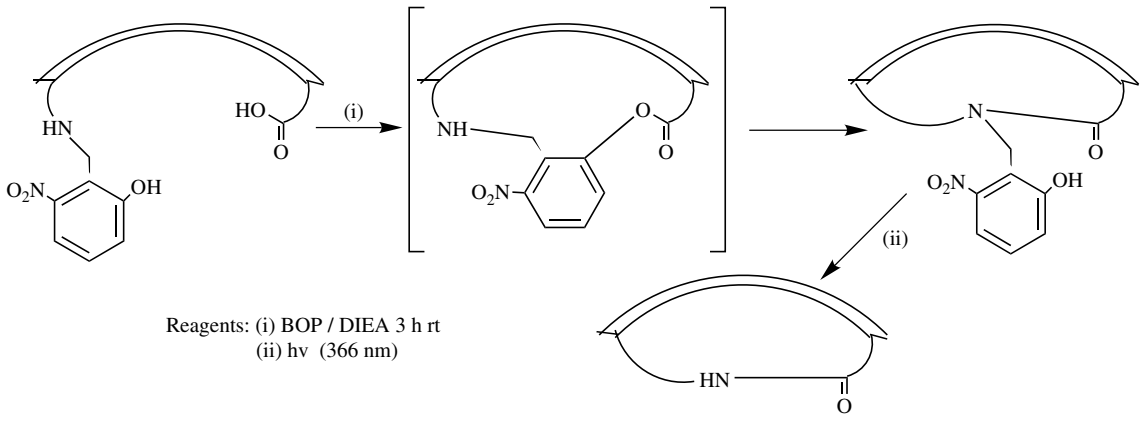
produce the required cyclic pentapeptide in 45% yield using the stages summarized in Scheme 10. Just a little racemization at the Ala residue was observed.

Enzyme Catalysed Cyclization

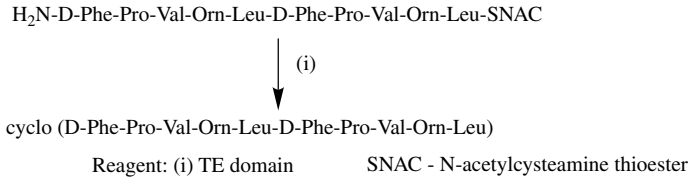
A short review [62] of what has been achieved and what the future might be, gives a good background to the 'state of the art'. The recent isolation [63,64] of the thioesterase domain of tyrocidine synthetase, (which in nature catalyses the assembly of cyclodecapeptide antibiotic tyrocidine A) showed that the isolated domain could also catalyse cyclization of a synthetic thioester precursor to form gramicidin S as in Scheme 11.

A mutant of subtilisin BPN'(subtiligase) has been shown [65] to catalyse cyclization of peptide glycolate phenylalanylamide esters of chain lengths between 12 and 31 amino acids. Shorter peptides do not cyclize, but for the larger peptides yields of 30%–85% proved possible. The antibody ligase 16G3 has been shown to catalyse the cyclization of D-Trp-Gly-Pal-Pro-Gly-Phe-*p*-nitrophenyl ester [66] to give cyclo (D-Trp-Gly-Pal-Pro-Gly-Phe) in >90% yield with a rate enhancement of 22-fold.

A mechanism reminiscent of the orthogonal strategy discussed in the previous section underlies the use of the intein (internal protein) strategy Scheme 12 [67,68], for catalysis of cyclization of long peptide sequences, e.g. for the making of thioredoxin (135 amino acids), as well as shorter sequences of 9,10 and 14 residues. Serine can replace cysteine at the *N*-terminus as confirmed by the synthesis of the cyclic tyrosinase inhibitor pseudostellarin F, cyclo (Ser-Gly-Gly-Tyr-Leu-Pro-Pro).



Scheme 10



Scheme 11

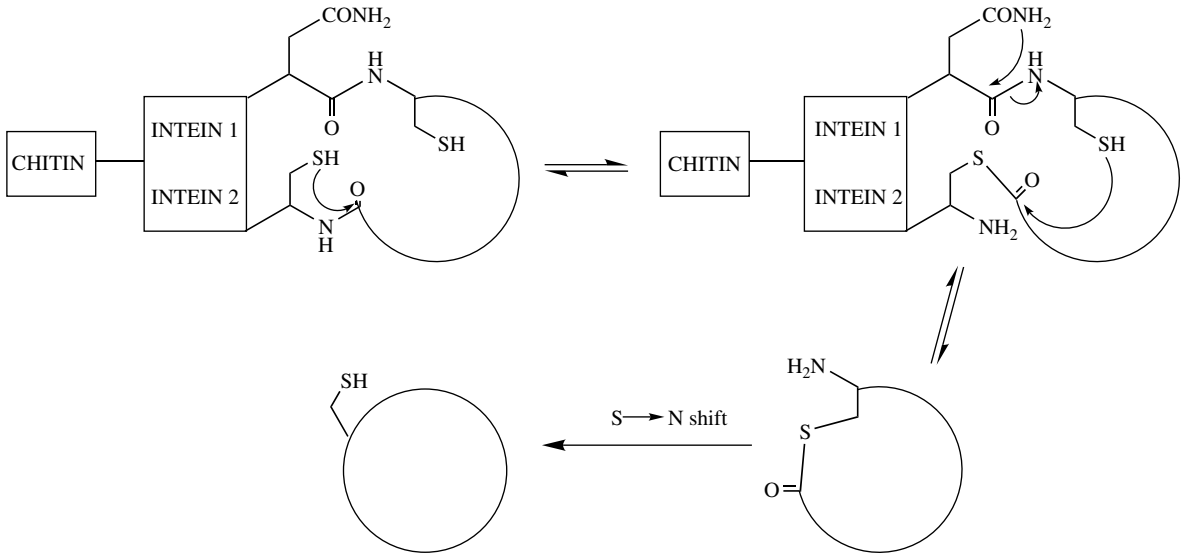
Cyclizations Specific to the Size of Peptide

Cyclodipeptides (dioxo- or diketo-piperazines). Although these structures are totally unrepresentative of cyclic peptides (they have *cisoid* amide bonds, and a flagpole boat conformation), interest in these structures have experienced a resurgence due to their role as scaffolds for generating combinatorial libraries. In peptide synthetic circles [69,70] dioxopiperazines are usually unwelcome, since any free dipeptide ester autocyclizes to these cyclic compounds. The tendency to cyclize, however, can be minimized by judicious selection of protecting groups [71]. Cyclization to dioxopiperazines has been used [72] for the cleavage of peptides off resins. The stages and energetics of cyclization has been studied in detail [73], and is a multi-step process, a *trans-cis* isomerization of the linear precursor, followed by an amino group attack on the *C*-terminal carbonyl group. These aspects, and a great deal more about diketopiperazines have been the subject of a detailed 217-reference review [74], and a *Tetrahedron* report [75] covering synthesis.

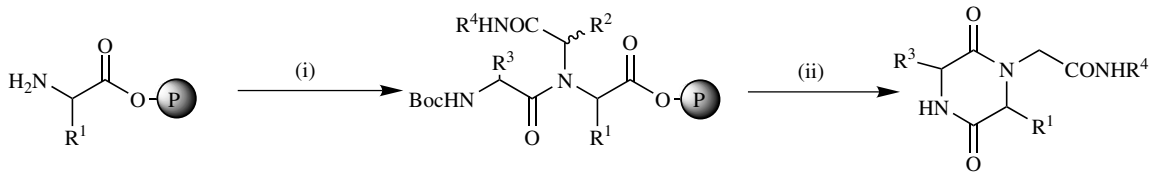
For combinatorial synthesis there has been a resurgence of interest in the Ugi reactions exemplified in Scheme 13 [76,77]. A new resin-bound isonitrile has also been designed [78] for the Ugi 4CC reaction and has been shown to work according to Scheme 14.

In the synthesis [79] of building blocks based on cyclo (Aax-Bbx) consisting of Glu or Asp (Aax) and Lys, Orn or Dab (Bbx), the authors have returned to conventional cyclization of linear dipeptide esters. However, cyclization was not so straightforward as anticipated, requiring long reaction times to reduce the amount of racemization detected when higher temperatures and shorter times had been used.

Cyclotripeptides. All-L cyclotripeptides with all α-amino acids are almost impossible to construct as the corresponding cyclodimers, the cyclohexapeptides, are the main products. However, it is feasible to synthesize trimers containing *N*-alkylated amino acids, such as cyclo $(\text{L-Pro})_3$, or cyclo $(\text{MeGly})_3$ [80], which allow the cyclotripeptides to adopt all-*cis* conformations. Syntheses were achieved on polymer-bound *p*-sulfophenyl esters. Increasing the propensity of *cis*-amide bonds has enabled the synthesis of **(8)** to be successful (85% yield) from linear precursors using PyBOP [81], while stretching the ring size to include β-amino acids allows cyclo $(\beta^3 \text{— HGlu})_3$ **(9)** to be synthesized [82]. Useful analogues such as cyclo $[\beta^3\text{-HSer(OBn)}]_3$ and cyclo $[\beta^3\text{-HMet}]_3$ have also been synthesized [83] from linear pentafluorophenyl ester precursors, but trifluoroethanol had to be used as solvent due to the inherent insolubility of the β-peptides.

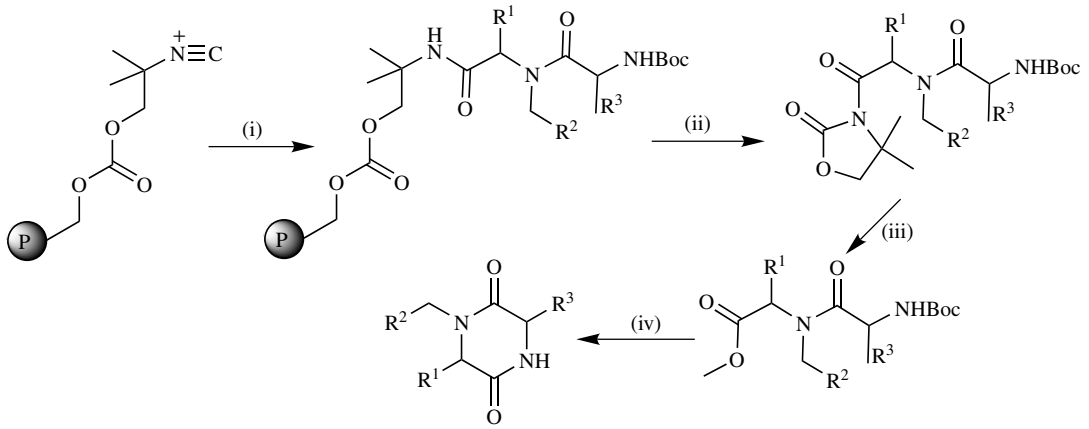


Scheme 12



Reagents: (i) R^2CHO, $BocNHCH(R^3)COOH$, R^4-NC, MeOH; (ii) TFA, toluene / EtOH

Scheme 13



Reagents: (i) $R^2CH_2NH_2$, R^1CHO, Boc-D,L-amino acids, DCM 3 days. (ii) $KOBu^t$ / THF room temp. (iii) NaOMe / MeOH / THF 48 h. (iv) TFA, hexafluoroisopropanol, Silicycle TMA carbonate, and Silicycle isocyanate-3 / THF.

Scheme 14

Cyclotetrapeptides. The unfavourable strain in a 12-membered ring containing four *trans* amide bonds is disadvantageous to the synthesis of all-L cyclotetrapeptides. Incorporation of Pro, *N*-alkylated amino acids or D-amino acids facilitate cyclization. Cyclotetrapeptides contain a β-amino acid have the advantage of a 13-membered ring thus making them easier to synthesize as exemplified by the synthesis of cyclo (Phe-(*R*)Pro-Asu-βHPhe) using BOP in DMF for cyclization [84]. The strain in

a cyclotetrapeptide ring is even manifested in *C*-terminal residues undergoing enantiomerization to the D-form before cyclization as shown in the formation of cyclo (Pro-Val-Pro-D-Tyr) when an all-L linear precursor was cyclized [85]. In a detailed study [86] of the cyclization of all-L, Leu-Pro-Leu-Pro, successful cyclization to cyclo (Leu-Pro-Leu-Pro) was obtained under special high dilution conditions using BOP (ratio of cyclomonomer to cyclodimer 1 : 1.1). Attempts at transient *N*-alkylation of the secondary amide bonds to increase the chance of having a cyclizable conformation failed in this example.

Using DPPA for activation of a series of diastereoisomeric tetraprolines [87], cyclo (D-Pro-D-Pro-L-Pro-L-Pro) could only be obtained from a DLLD-Pro_4 precursor. Prediction of the sequence best able to cyclize has been attempted using the GenMol programme [88], which identified H-Ala-Aib-Phe-D-Pro-OPh as the best linear precursor for making cyclo (Aib-Phe-D-Pro-Ala). In a real comparison test [89] for the synthesis of cyclo (Arg-Gly-Asp-Phg) on a Kaiser oxime resin, the linear precursor, Arg(Tos)-Gly-Asp(c-Hex)-Phg giving 75% cyclic monomer, 20% cyclic dimer, proved to be the best sequence.

Cyclopentapeptides. The discovery that cyclopentapeptides, carrying the Arg-Gly-Asp- motif, offer ideal conformations for interactions with integrin receptors (e.g. $\alpha_v\beta_3$) has initiated detailed studies [90] on their synthesis. Cyclo (Arg-Gly-Asp-D-Phe-Val) and cyclo (Arg-Gly-Asp-D-Phe-Lys) are amongst the most potent and selective inhibitors of $\alpha_v\beta_3$ integrin and are continually being modified to attain greater integrin selectivity [91]. Many cyclization protocols have been attempted in these studies and the most successful macrocyclizations used DPPA with a solid base. However, an improved synthesis [92] of cyclo (Arg-Gly-Asp-D-Phe-Lys) has been reported, utilising 1-propanephosphonic acid cyclic anhydride for cyclization at *C*-terminal Gly, which gave a 79% yield (*cf* 44% with DPPA). The 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pbf) gave improved release of the Arg protecting group when compared with the original use of Mtr. In another study of Arg-Gly-Asp cyclopentapeptide analogues [93] EDCI/DMAP gave satisfactory results at the macrocyclization step.

Seventeen linear precursors of two cyclopentapeptides, cyclo (Gly-Ala-Tyr-Leu-Ala), cyclo (Gly-Pro-Tyr-Leu-Ala) and of the heptamer cyclo (Gly-Tyr-Gly-Gly-Pro-Phe-Pro), isolated from a Chinese medicinal herb [94] have been chosen for a model study of structural influences and coupling reagents on their cyclization. DEPBT **(10)** turned out to be the best cyclization agent, (53% yield) followed by DPPA (52% yield). Coupling agents BOP, HBTU and TBTU also led to cyclization in a short time, but there were more by-products and racemization recorded for these reagents. From the results on structural influences, it is concluded that: (i) precursors that have one small terminus and the other large, give satisfactory yields; (ii) Pro could be chosen at either terminus and (iii) any turn-inducing properties in solution are beneficial.

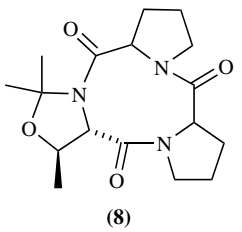
Six cyclic pentapeptides, as potential LHRH antagonists, have been used [95] to study influences on cyclization. The best results achieved for each cyclic peptide, out of 72 cyclizations, are summarized in Table 3 where the cyclic peptides (I–VI) correspond to cyclo [Trp(Boc)-Phg-Arg(Tos)-Aph(Boc)-D-Ala], cyclo [Trp(Boc)-Phg-Arg(Tos)-D-Aph(Boc)-D-Ala], cyclo [D-Nal-Phg-Arg(Tos)-Aph(Boc)-D-Ala], cyclo [D-Nal-Phg-Arg(Tos)-D-Aph(Boc)-D-Ala], cyclo [D-Pal-Phg-Arg(Tos)-Aph(Boc)-D-Ala] and cyclo [Cit-Arg(Tos)-Aph(Boc)-D-Ala-Trp(Boc)], respectively. Again having a small D-Ala or Phg residue as *C*-terminal was advantageous, while at the *N*-terminal residues configuration was a governing factor. Cyclic pentapeptides containing only one D-residue were easier to synthesize than those containing two or three adjacent D-residues. The linear precursor with the sequence L-L-L-D-D was easier to cyclize than that of D-L-L-D-D.

The natural endothelin antagonist BQ 123 cyclo (D-Trp-D-Asp-Pro-D-Val-Leu) has also been the subject of a number of syntheses, amongst them a 100 g scale solution phase synthesis [96], which only required purification at the last step. A *C*-terminal benzyl ester and side-chain protection of D-Asp as the methyl ester were key to this efficient synthesis. The thioester link on to a polymer as given in Scheme 15 also proved efficient [97].

Cyclohexapeptides. With six amino acid residues in the ring, and the potential of a stabilized two β-turn structure, it might be thought that cyclization of an all-L precursor should be 'plain sailing'. However, this is not borne out by experience. For the synthesis [98] of cyclo (Leu-Tyr-Leu-Glu-Ser-Leu) using the Leu^6-Leu^1 bond for macrocyclization with the azide method, varying each residue for a D-residue in turn, the yield did not vary much from the 55% average. However, an all-L equivalent

Table 3 Structural Influences on Cyclization

Cyclic pentapeptide	Linear precursor	Reagent	Yield % (isolated HPLC)
I	H-Trp(Boc)-Phg-Arg(Tos)-Aph(Boc)-D-Ala-OH	EDCI/DMAP	32
II	H-Trp(Boc)-Phg-Arg(Tos)-D-Aph(Boc)-D-Ala-OH	DEPBT	22
III	H-D-Nal-Phg-Arg(Tos)-Aph(Boc)-D-Ala-OH	HBTU/DMAP	12
IV	H-Arg(Tos)-D-Aph(Boc)-D-Ala-D-Nal-Phg-OH	HBTU/DMAP	19
V	H-D-Pal-Phg-Arg(Tos)-Aph(Boc)-D-Ala-OH	EDCI/DMAP	11
VI	H-Trp(Boc)-Cit-Arg(Tos)-Aph(Boc)-D-Ala-OH	EDCI/DMAP	30



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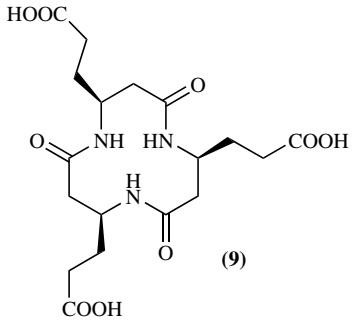

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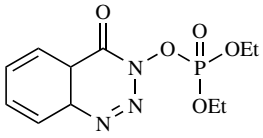

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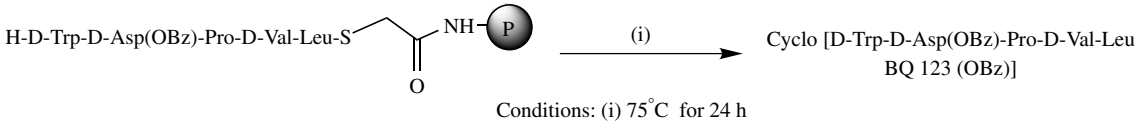


Conditions: (i) 75°C for 24 h

Scheme 15

only gave a 1% yield. So both for synthesis, and to stabilize β-turns, a favourable structure should contain at least one Gly, Pro or D-residue. Further proof of the advantages of a D-residue was obtained in the cyclization [99] of a thymopentin analogue. Using BOP and other HOBt reagents on H-Val-Arg-Lys(Ac)-Ala-Val-Tyr-OH did achieve up to 25% cyclization but extensive racemization of the Tyr residue took place. However, HAPyU afforded the all-L form without racemization in 55% yield. Gly residues of course function as D-equivalents and provide for an efficient cyclization as shown in the PyBOP catalysed cyclization of H-Leu-Met-Gln-Trp-Phe-Gly-OH [100].

Segetalin A, cyclo (Gly-Val-Pro-Val-Trp-Ala) from *Vaccaria segetalis* seeds has been synthesized [101] by macrocyclization between *C*-terminal Ala and Gly. Ring closure using the pentafluorophenyl ester gave no results, but DPPA with a linear precursor at 10^{-4}M gave a 45% yield (PyBrop registered a

10% yield). Linear precursors of segetalin A and analogues were assembled on a Sasrin resin. Both linear tri- and hexa-peptide active esters have been used [102] for the synthesis of cyclo (Pro-Leu-Aib)$_2$ with the sterically hindered Aib residue contributing to a lowering of the yield to 18%.

Cyclo hepta-, octa- and nona-peptides. Having these numbers of residues in the ring system allows more flexibility, and the efficiency of macrocyclization is much less residue-dependent. The need to get *N*-terminal amino groups to attack the activated *C*-terminal group still remains paramount. The major thrust for synthesis under this category is for the structural proof of nature's molecules which are too numerous to list comprehensively, but a flavour of the richness of the source can be gleaned from Table 4.

Seven linear heptapeptides have been synthesized [94] to measure the extent of DEPBT **(10)** catalysed cyclization to cyclo (Gly-Tyr-Gly-Gly-Pro-Phe-Pro). Results showed that the H-Gly-Tyr-Gly-Gly-Pro-Phe-Pro-OH gave the highest yield at the cyclization stage (57% after 3 h; 88% after 24 h). Deductions regarding the efficiency of cyclization, included the surprise that small residues at both termini give low yields, in a similar way to having large residues at both. The best compromise appears to be one small and one large terminal residue, although the pre-cyclization conformation of the linear peptide precursor matters as well. A solid phase strategy [117] starting from Fmoc-Asp-α-OAllyl attached to a PAL resin via its β-COOH has been used to synthesize *R*- and *S*-Asn forms of phakellistatin-5, cyclo (Phe-Asn-Ala-Met-Ala-Ile-Pro). After assembly of the heptamers and removal of the allyl group, cyclization was carried out on-resin by PyAOP. The *R*-analogue was obtained in 28% yield, the *S*-analogue (which corresponds to the natural form) in 15% yield. In the synthesis of phakellistatin-2 cyclo (Tyr-Pro-Phe-Pro-Ile-Ile-Pro^7), cyclization at the Pro^7 position proceeded in 50%–65% yield using TBTU, BOP-Cl, PyBroP or HOAt, with TBTU giving the consistently highest yield [118]. Pseudostellarin D, cyclo (Gly-Gly-Tyr-Pro-Leu-Ile-Leu) has been synthesized in the solution phase [119] via *p*-nitrophenyl ester which took 10 days to achieve success. In contrast, for the synthesis of stylostatin, cyclo (Ile-Pro-Phe-Asn-EtGly-Leu-Ala), a resin linker attached to the α-nitrogen of a *C*-terminal residue (Ala in this case), was used to assemble the linear precursor, which was then cyclized on-resin [120].

The BOP reagent was found to be best in the macrocyclization step to give axinastatin 4, cyclo (Pro-Leu-Thr-Pro-Leu-Trp-Val) [121], while chevalierin C, cyclo (Tyr-Thr-Ile-Phe-Asp-Ile-Phe-Gly-Ala) was cyclized using HBTU under high dilution [122]. Cyclic octapeptides, cyclo (D-Phe-Asp-D-Phe-Asn-D-Phe-Asp-D-Phe-Asn) and cyclo (D-MeAla-Asp-D-MeAla-Asn-D-MeAla-Asp-D-MeAla-Asn) have been prepared [123] on-resin with the *C*-terminal Asp residue, protected as an allyl ester, attached via its side-chain to the resin. HOAt/HATU — catalysed cyclization secured a result in the D-Phe analogue but the *N*-methylated analogue cyclized best with DIC/HOAt.

Table 4 Representative Naturally-Occuring Cyclopeptides

Name	Size of cyclopeptide	Reference
Viroisin and phalloidin	Hepta	9
Hymenamides	Hepta	103
Phakellistatins	Hepta	104
Axinastatins	Hepta	105
Stylostatins	Hepta	106
Segetalins	Hepta	107
Yunnanins	Hepta	108
Pseudostellarins	Hepta/Octa	109
Hymenistatins	Octa	110
Stelladelins	Octa	111
Stellarins	Octa	112
Aciculitins	Octa	113
Cyclolinopeptides	Nona	114
Cycloleonuripeptides	Nona	115
Dichotomins	Nona	116

Cyclodecapeptides. The dominant structure representing this category for more than 40 years is gramicidin S **(11)**, with its two β-turn/β-sheet structure and Gram-positive activity. Synthetic methodologies have almost all, at one time or another, been weaned or tried out on gramicidin S from *Bacillus brevis*. Amongst the most recent synthetic activity has been the use of the Kaiser oxime on-resin method [124] to make [D-pyrenylalanine$^{4,4'}$]-gramicidin S. Biosynthetically, gramicidin S is produced via the dimerization of activated pentapeptide esters and in a study to mimic this process using *N*-hydroxysuccinimide esters [125], it was only the 'natural' sequence H-D-Phe-Pro-Val-Orn-Leu-ONSu that gave the cyclic pentapeptide monomer and cyclodimer (gramicidin S) in 15% and 38% yield, respectively. This confirms the existence of sequence

features that promote cyclization, seen also in the results [126] summarized in Table 5 of a series of pentapeptides cyclized with EDCI/HOBt.

The cyclodecapeptide β-sheet conformation typified by **(11)**, has also been adopted for a new generation of regioselectively addressable functionalized templates (RAFT) for use in *de novo* design as exemplified [127] in the synthesis of cyclo [Phe(p-NO_2)-D-Pro-Gly-Phe(p-NO_2)-Ala-Phe(p-NO_2)-D-Pro-Gly-Phe(p-NO_2)-Ala].

In contrast to the poisonous principles, *Amanita* mushrooms also contain the antitoxic principle antamanide, cyclo (Val^1-Pro-Pro-Ala-Phe-Phe^6-Pro-Pro-Phe-Phe), first synthesized in 1969 [128] from a linear decapeptide. More recently an analogue, cyclo [Pro-Phe-Phe-Ala-Glu(OBu^t)]$_2$ with the postulated active sequence Pro-Pro-Phe-Phe has been synthesized [129], and shown to have similar biological activity to cyclolinopeptide A. Rudinger's version of the azide coupling method brought success in the macrocyclization stage leading to Tyr^6-antanamide [130]. Gly^6- and Gly^9- antanamide have also been synthesized [131].

By linking the side chain of Fmoc-Tyr-OMe to benzyl type resin using the Mitsunobu reaction two cyclic analogues, cyclo (βAla-Tyr-Pro-Ser-Lys-βAla-Arg-Gln-Arg-Tyr) and cyclo (Ahx-Tyr-Pro-Ser-Lys-Ahx-Arg-Gln-Arg-Tyr), each containing the *N*- and *C*-terminal tetrapeptide segments of neuropeptide Y have been synthesized [132]. On-resin cyclization was carried out using DIC/HOBt or HOBt/TBTU. A similar strategy but this time using an Asp-side chain linked to polystyrene RAM resin has been used [133] for the synthesis of the loloatins, cyclo (Val-Orn-Leu-D-Tyr-Pro-X-D-Phe-Asn-Asp-Y), A, X = Phe, Y = Tyr; B, X = Phe, Y = Trp; C, X = Trp, Y = Trp.

Table 5 Cyclodimerization Yields (%) to Gramicidin S derivatives

Linear precursor	Semi Gramicidin S	Gramicidin S
H-Val-Orn(Z)-Leu-D-Phe-Pro-OH	10	90
H-Orn(Z)-Leu-D-Phe-Pro-Val-OH	56	44
H-Leu-D-Phe-Pro-Val-Orn(Z)-OH	97	3
H-D-Phe-Pro-Val-Orn(Z)-Leu-OH	65	35
H-Pro-Val-Orn(Z)-Leu-D-Phe-OH	58	42

Yields of 31–37% were achieved at the on-resin cyclization stage using HATU/HOAt.

Other higher cyclic peptides. With well over 20 000 publications purported to have been written on cyclosporin A, this immunosuppressing cycloundecapeptide **(12)** can certainly be considered the main attraction in this sub-section. With so many *N*-methylated amide bonds, creating steric hindrance problems, the synthesis is very demanding but was achieved first in the solution phase by the groups of Wenger and Rich. The further significant breakthrough came with Rich *et al.*'s solid phase synthesis of the MeLeu^1 — cyclosporin A in 1995 [134]. Availability of HOAt and HATU, and utilizing double couplings in many places proved to be critical to the success. Key macrocyclization at the Ala-D-Ala bond was carried out using propylphosphonic anhydride/DMAP. A detailed study [135] of the possible coupling strategies to use in the making of cyclosporin analogues has reported that couplings at 10/11, 9/10, 6/5 and 11/1 were difficult to achieve. It was concluded that the best strategy was to start at MeVal^{11} and assemble the linear peptide to reach MeBmt^1 and then cyclize with BOP. The difficulties in synthesizing the molecule has made structure–activity studies a daunting task, but with serendipity in some case (e.g. [136] where Sar^3 could be stereochemically modified via Li enolates and electrophiles) modifications have been possible.

Apart from the large number of *N*-methylated amino acids in cyclosporin A, synthesis of MeBmt with its three chiral centres has also been a challenge. So efforts recently have been directed at a congener, cyclosporin O, cyclo (MeLeu-Nva-Sar-MeLeu-Val-MeLeu-Ala-D-Ala-MeLeu-MeLeu-MeVal), which differs from cyclosporin A in having MeLeu^1-Nva^2 instead of MeBmt^1–Abu^2, but retains much of its immunosuppressive activity. Using both solution and solid phase strategies cyclosporin O has been synthesized [137] using BEMT **(10)** and BEP (2-bromo-1-ethylpyridinium tetrafluoroborate)/HOAt for constructing hindered amide bonds, and BDMP [5-(1H-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2H pyrrolium hexachloroantimonate] for coupling coded amino acids. Cyclization (80% yield) was carried out between Ala and D-Ala using HAPyU/DIEA. In a more recent synthesis [138], triphosgene proved to be a highly efficient reagent for coupling *N*-methyl amino acids, with cyclization expedited in a crude yield of 75% using EDCI/HOAt/DIEA for 16 h. In both these

publications racemization had been controlled to a minimum.

Small libraries of conformationally defined β-hairpin protein epitope mimetics based on loop III of human platelet-derived growth factor B have been created on templates [139] such as cyclo (Pro-Lys-Ile-Glu-Ile-Val-Arg-Lys-Lys-Pro-Ile-Ile-Phe-Lys-D-Pro). Two approaches were used, either Fmoc chemistry starting at *C*-terminal Arg followed by cyclization using HOAt/HATU in solution, or macrocyclization on-resin with the same reagents starting from Fmoc-Lys-OAllyl coupled to chlorotrityl resin. Cyclization in solution gave a cleaner product.

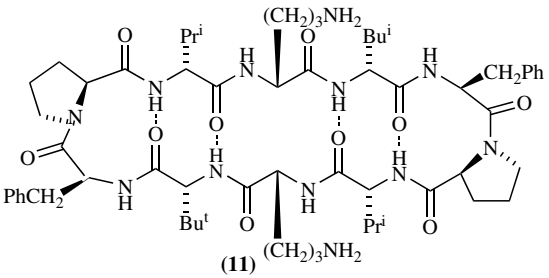
With the large sized cyclic peptides, advantages are gained in zipping up the termini using techniques that require no side chain protection of the amino acid residues. Although the methodology developed leaves a heterodetic unit in the final cyclic structure, this probably does not significantly influence the overall final activity. Two examples are summarized in schemes 16 [140] and 17 [141], and a similar theme [142] incorporating a reactive hydroxylamine aldehyde pair in the peptide precursor.

CYCLIZATION OF HETERODETIC PEPTIDES

This category is used to review work on cyclic peptides which contain features other than peptide bonds in their macrocyclic backbone. Almost all the synthetic work carried out on these molecules has been geared towards synthetic confirmation of the diverse structures found in nature.

Cyclodepsipeptides

These cyclopeptides contain ester (depside) bonds as part of the backbone, and also include esters formed between the side chains of Ser and Thr and the main backbone carboxyls (macrocyclic lactones). Nature is a rich source of the most fascinating cyclodepsipeptides, although the significance of incorporating the depside bond is not clear, but



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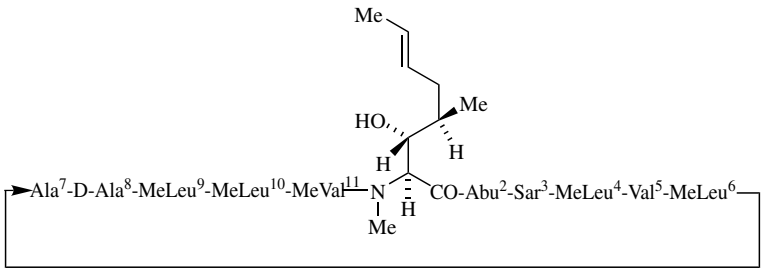

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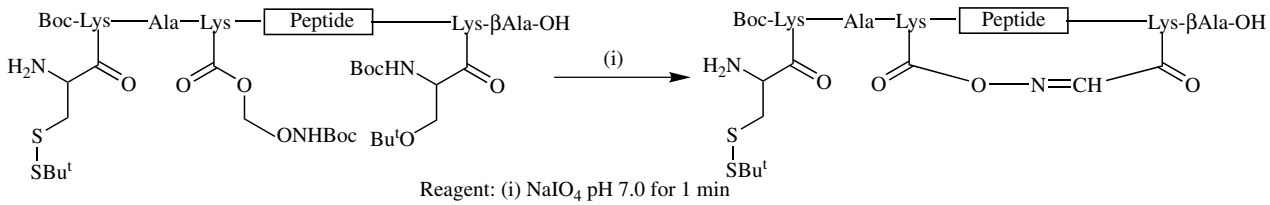
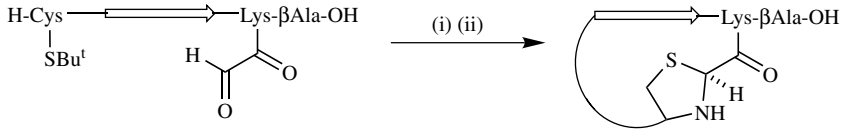


Scheme 16



Reagents: (i) $NaIO_4$ pH 6.8
(ii) tris (carboxyethyl)phosphine pH 4.2

Scheme 17

appears to be essential for biological activity, since all-amide analogues are often inactive. The depside bond is recognized as being more difficult to incorporate into the backbone than amides, so it tends to be pre-formed in the linear precursor prior to cyclization at an amide bond to form the cyclic depsipeptides.

The best known structures in this category belong to the ion-selective antibiotics, valinomycin, cyclo (Val-D-Hyiv-D-Val-L-Lac)$_3$, where Hyiv = α-hydroxyisovaleric acid and Lac = lactic acid, and the closely related enniatin family, enniatin A, cyclo(D-Hyiv-MeIle)$_3$; B, cyclo (D-Hyiv-MeVal)$_3$; C, cyclo (D-Hyiv-MeLeu)$_3$; D, cyclo (D-Hyiv-MeLeu-D-Hyiv-MeVal-D-Hyiv-MeVal); E, cyclo (D-Hyiv-MeIle-D-Hyiv-MeLeu-D-Hyiv-MeVal); F, cyclo (D-Hyiv-MeLeu-MeIle-D-Hyiv-MeIle). The early thrust in the synthesis of these molecules came from the Shemyakin group in Russia [143], and the need to improve the performance of valinomycin derivatives in selective ion electrode applications has up-dated the procedures [144]. Macrocyclization of linear depside precursors in this case was carried out at 90 °C with a *C*-terminal Hyiv carboxyl group activated as a pentafluorophenyl ester. The difficult task of assembling amide and depside bonds on-resin has been overcome [36,145] using a Wang type resin, with hydroxy acids protected, e.g. as tetrahydropyranyl derivatives and coupled using DIC/DMAP. The linear precursor of a valinomycin analogue cyclo (L-Val-D-Man-D-Val-L-Lac)$_3$ was entirely synthesized on resin, and then cyclized in solution using either acid chloride (14% yield) or HATU (24% yield) activation at a Lac residue.

The natural cyclodepsipeptides have offered demanding synthetic challenges to a number of research groups, so what follows is a progress summary of the area over recent years. Key to the total synthesis [146] of tamandarins A **(13)** and B **(14)** was a macrocyclization at point (a) using HATU (63% yield). The related didemnin family have been intensively studied for over a decade since didemnin B **(16)** has undergone clinical trials for antitumour activity. Didemnin A **(15)** has also become a prime target for synthesis as other family members are congeners based only on differences in the side chain. Many syntheses were reported in the 1980s which have been noted in a recent publication [147] of a new synthesis of didemnin A and dehydrodidemnin B. In this strategy the Pro^4-Me$_2$Tyr^5 bond was selected for the macrocyclization step (using HATU/HOAt in 28% yield), and the depside bond was incorporated using DIPCDI/DMAP in the presence of DMAP.CF_3COOH in refluxing chloroform.

The multidrug resistance reverser, hapalosin **(17)** has recently been the focus of synthetic attention. The most recent account [148] moves the basic structure into a combinatorial scaffold with amide bonds replacing the depside bonds. TBTU proved an efficient (33–64% yield) macrocyclization reagent using amide bonds as the key step. In earlier syntheses [149–151], the general trend has been to pre-form the depside links in linear precursors, then cyclizing at the tertiary amide bond. Reagents used include, DPPA/Pr^{i}NEt$_2$ (23% yield), 2,4,6-trichlorobenzoyl chloride/DMAP/Pr^{i}NEt$_2$/toluene/room temp. and BOP-Cl/DIPEA/toluene/85 °C (58% yield).

The destruxins are a family of cyclodepsipeptides represented by structures **(18),** isolated from *Metarrhizium anisopliae* and *Oospora destruktor* (Hyphomycetes). The depside link seems essential to activity as the all-amide analogues are inactive [152]. An efficient synthesis [153,154] of destruxin B utilizes a (3 + 3) fragment coupling with macrocyclization via an azide at the MeAla-βAla bond to inhibit diketopiperazine formation and racemization. The linear precursor of destruxin A has been synthesized on-resin [155], and cyclized using a number of reagents with PyBOP being the most impressive. The synthesis [156] of the novel immunosuppressant sanglifehrin A **(19)** represents a masterpiece in natural product synthesis, the macrocyclic

ring this time was 'zipped up' at position (a) using $Pd_2(dba)_3{\cdot}CHCl_3/AsPh_3/Pr^i_2NEt/DMF/36$ h (62% yield) (Stille coupling conditions). Structures summarized under **(20)** are just representative of more than 20 members of the cryptophycin family isolated from blue-green algae, which have become interesting because of their tumour selective cytotoxicity. Since the middle 1990s a number of synthetic protocols have appeared and have been referred to in the most recent report [157]. Generally the accepted protocol usually ends up with a macrolactamization step, as exemplified in the cyclization at (b) using the pseudo azide coupling afforded by $DPPA/NaHCO_3/DMF/0\,^{\circ}C$ [157].

The theme expounded in this section that macrolactonization is more difficult than macrolactamization has been further supported by the failure to synthesize stevastelin B **(21)** via the former strategy [158]. However, macrolactamization does not have a monopoly, as a few notable examples of macrolactonization have been reported. Thus jasplakinolide **(22)** was cyclized at point (a) using DCC/DMAP.TFA (79% yield) [159] and using DCC only [160] in 36% yield. It is implied that DMAP.TFA in the former example raises the effective concentration of protons thus catalysing macrolactonization. These conditions were also able to catalyse the macrolactonization to form geodiamolide A and B at point (b) in **(23)** [161,162].

It is rather unusual to find that by just heating a linear amide precursor with HCl/toluene, an efficient cyclization takes place [163] which is summarized in Scheme 18. No doubt the steric restrictions associated with the α,α-dialkyl substituted residues, assembled via the azirine methodology influences the ease of macrolactonization.

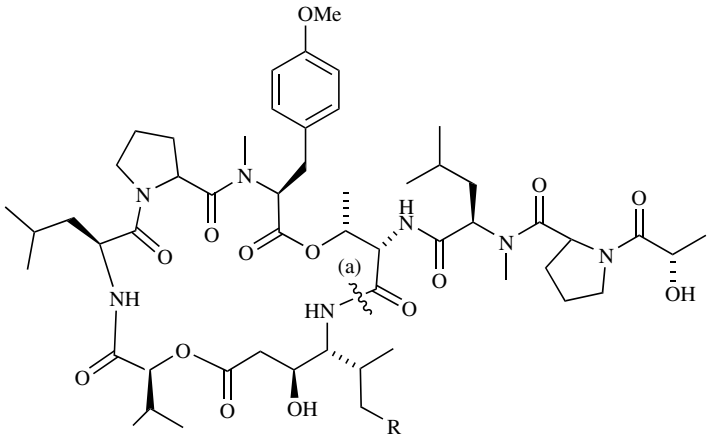
The great wealth of structures produced by Nature precludes a more comprehensive coverage of all syntheses carried out over the past decade in this one sub-section. Equally as representative as the above syntheses would be the strategies used in making luzopeptins [164], HUN-7293 [165], kahalalide B and F [166,167], dolastatin 11 [168], AM toxin II [169] and doliculide [170]. In many of these examples the non-peptidic parts are as, or even more, demanding than the cyclodepsipeptide skeleton itself.

Cyclic Peptides Containing Thiazole/Oxazole Rings

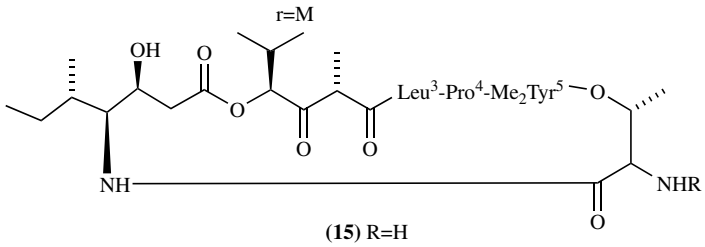
This has been very much the growth area of the last decade driven by the wealth of biologically active structures found in the marine environment. Nature seems to have evolved the thiazole and oxazole rings as a means of imposing conformational restrictions on cyclic peptides [171]. The heterocyclic rings emanate from a condensation between side chain cysteine thiols or Thr/Ser hydroxy groups and neighbouring amide bonds as depicted in Scheme 19, resulting in a highly constrained pseudo-boat or saddle-shaped macrocycle. Most of what has been realized in synthesis prior to 1995 has been authoritatively reviewed by Wipf [172], and augmented subsequently by Shioiri [173]. Synthesis is fully justified in this field as a significant number of the original structures have had to be re-assigned on the basis of synthetic results.

Trunkamide **(24)** which is in preclinical trials has been synthesized by both solid phase [174] and solution phase [175,176] methodologies. In the former approach the linear precursor was assembled on a chlorotrityl resin, with Pro initially linked to the resin, with the final two residues being D-PheΨ[CSNH]Ser, added as the precursor of the thiazoline ring. Macrocyclization was carried out with PyAOP/DIEA. The thiazoline ring was generated post-cyclization using diethylamino sulfur trifluoride (DAST). The first synthesis [175] of **(24)** utilizing D-Phe was carried out in solution using the authors' assisted aziridine ring opening technique for the novel reverse-prenylated Ser/Thr side chains. The thiazoline ring precursor in the synthesis was an oxazoline ring formed by DAST dehydration of a Ser which had been macrocyclized using HATU. Thiolysis of the oxazoline, and a second cyclodehydration with DAST gave **(24)** with still some re-orientation of absolute configurations necessary. Another solution synthesis [176], initially attempted via cyclization of an acyclic thioamide precursor failed, but on using a normal amide-Ser bond in the linear precursor DPPA (35% yield) provided a successful cyclization with the thiazoline ring being introduced by treatment with DAST followed by H_2S.

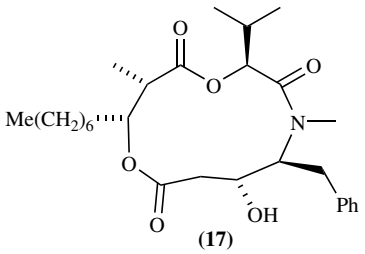
Two research groups have published syntheses of nostocyclamide **(25)**. Pre-formed heterocyclic amino acids were successfully coupled [177] to form a linear precursor which was cyclized directly at point (a) in **(25),** by activation using a pentafluorophenyl ester (74% yield). The second synthesis [178] showed that oxazole and thiazole amino acids undergo cyclization in the presence of FDPP to form nostocyclamide with yields governed by the amount and type of metal ions present in the reaction



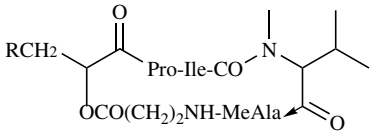
(**13**) R=Me
(**14**) R=H



(**15**) R=H
(**16**) R=Pro-Lac

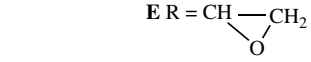


(**17**)

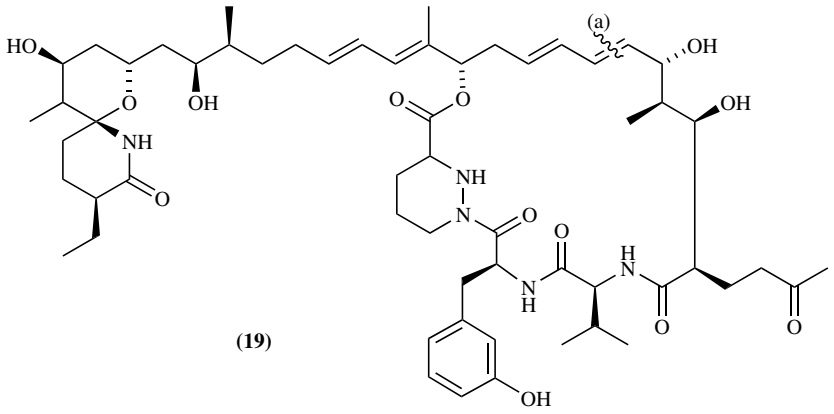


A R = CH═CH_2; **B** R =$CHMe_2$;

C R = $CH(Me)CH_2OH$; **D** R = CH(Me)COOH;

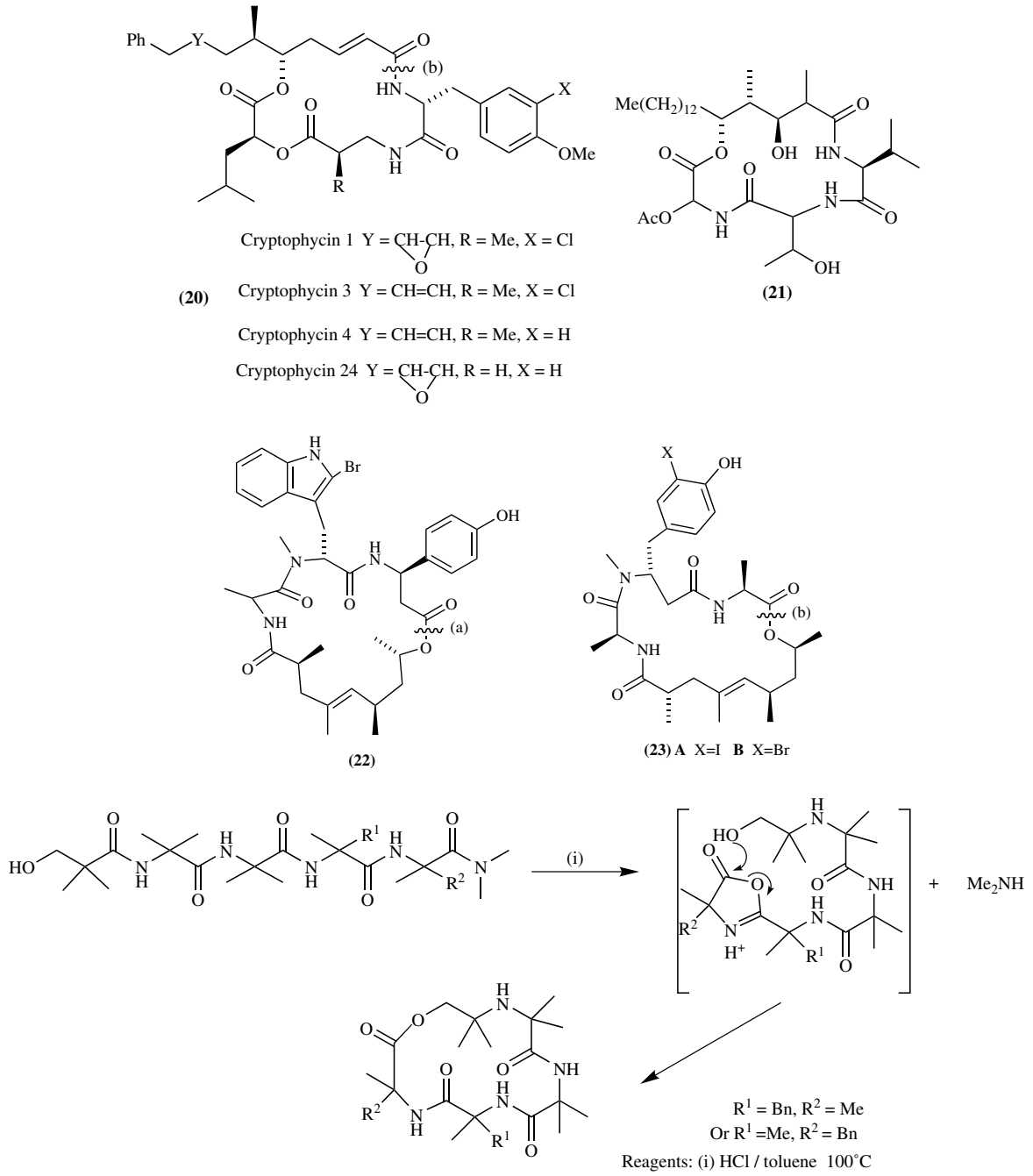
E R = 

(**18**)



(**19**)

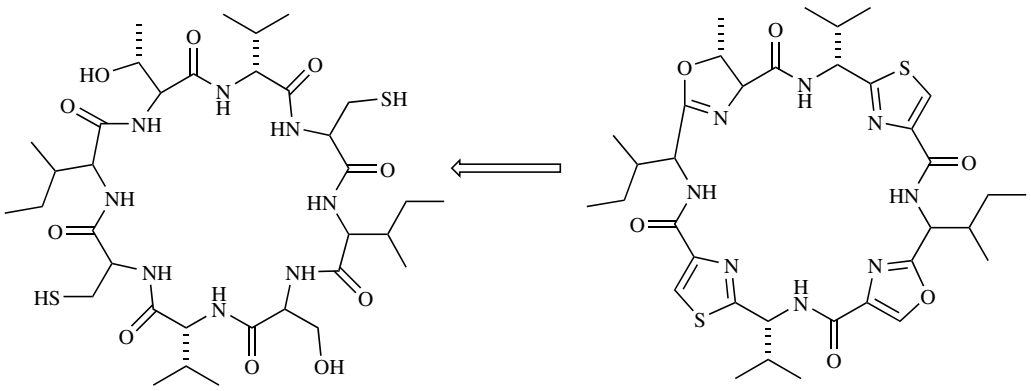
Scheme 18



Scheme 18 (*Continued*).

mixture. A related natural product dendroamide A **(26),** which reverses multiple drug resistance, has also been synthesized [179] from a linear precursor with the heterocyclic amino acids already built in. Modelling studies had predicted that cyclization at position (b) using DPPA would be optimal, and this proved a reasonable choice since 56% of dendroamide A was obtained.

Ceratospongamide **(27)** in its *cis, cis* form at the acyl-prolyl bonds, has been synthesized [180] using a (5 + 2) convergent strategy to form a linear precursor which allowed cyclization by activation of the triazole carboxyl group. Macrocyclization with DPPA gave a 31% yield while FDPP gave 63%, with cyclization to form the oxazoline kept to the last step using bis (2-methoxyethyl)amino sulfur trifluoride.



Scheme 19

Macrocyclization [181] with amide formation at position (a) in **(28)** using DPPA (58% yield) was also used for the cytotoxic metabolite lyngbyabellin A **(28)**. In this case the thiazole unit had been built prior to cyclization.

Griseoviridin **(29),** a member of the streptogramin family of antibiotics, currently licensed in the USA against bacteria resistant to vancomycin, has been synthesized [182] for the first time after two decades of endeavour by many groups. The oxazole carboxamide link was chosen for macrolactamization using EDCI/HOBt. Two strategies [183] for cyclization using pentafluorophenyl esters of linear precursors, at either point (a) or (b) in **(30)** have successfully given the antibiotic promothiocin A **(30)**. A modified Bohlmann-Rahtz pyridine synthesis provided the oxazolyl-thiazolyl-pyridine centrepiece, while dirhodium (II)–catalysed carbenoid N-H insertion were used to make oxazole building blocks. The thiazoles were produced via the Hantzsch reaction.

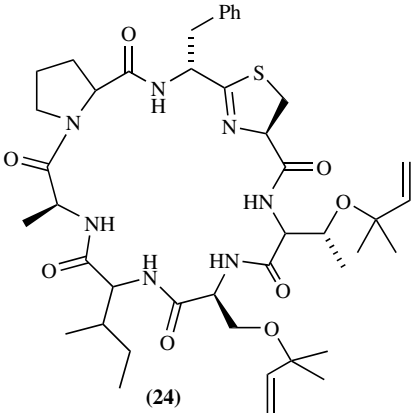
Having established the theme for synthesis, using the above examples, space only allows mention that the syntheses have also been recently published for cyclodidemnamide [184], lissoclinamides 4 and 5 [185], micrococcin P and P_1 [186,187], dolastatin I [188], mollamide [189], keranamide J [190], bistratamide D [191], 14,15 anhydropristinamycin II_B (a virginiamycin) [192], lissoclinamide 7 [193] and raocyclamide [194]. Each one represents demanding exercises in the art of contemporary synthesis.

However, before leaving this sub-group, it has to be noted that one of the most demanding synthetic challenges has been achieved by the synthesis of the anti-cancer agent diazonamide A **(31)**. Amongst keen competition from many research groups world-wide, the synthesis [195,196] of the presumed structure **(31)** was accomplished in 16 steps. But even after this noble effort, differences in physical data and biological activity between natural and synthetic samples had to be explained by re-assignment of the structure to **(32)**. A new synthesis [197] has now confirmed the authenticity of structure **(32)** as representative of diazonamide A. While many macrocyclization were needed to achieve such a feat, the macrolactamization step occurred mid-way in the synthesis at point (a) using HATU/collidine (36% yield).

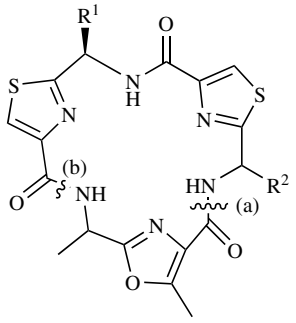
Macrocyclizations using Functions other than the Main Peptide Backbone

As shown for diazonamide A above, macrolactamization or macrolactonization, often become only a small player in the overall synthetic strategy. In heterodetic cyclic peptides key macrocyclizations often utilize chemical methods away from the mainstream peptide protocol. As the area is vast and becoming increasingly important, only the main achievements can be reviewed here as typical examples.

For a number of years antibiotics and antitumour compounds whose heterodetic character involve coupled aromatic rings, either of the biphenyl or diaryl ether type, have proved a significant synthetic challenge. From 1998 onwards, the main representative members, vancomycin **(33)** and teicoplanin **(34)** have succumbed to total synthesis. Three research groups have separately reported successful syntheses of vancomycin, the details of which are beyond the scope of this review. However, their key macrocyclization steps illustrate important themes. In the Evans *et al.* [198,199] approach to vancomycin aglycone synthesis, the A-B diphenyl link was accomplished using vanadyl trifluoride oxidative cyclization, while the diphenyl

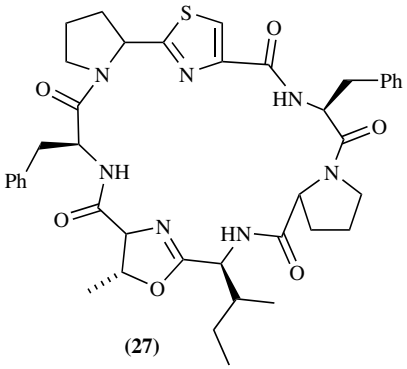


(24)

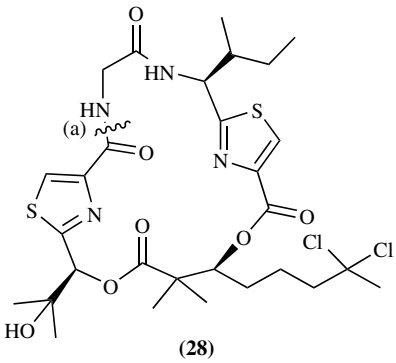


(25) $R^1 = CHMe_2$, $R^2 = H$

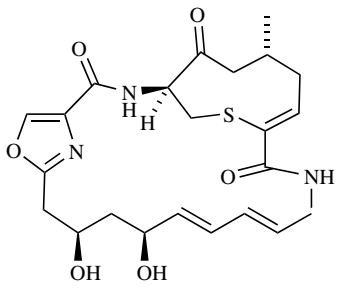
(26) $R^1 = Me$, $R^2 = CHMe_2$



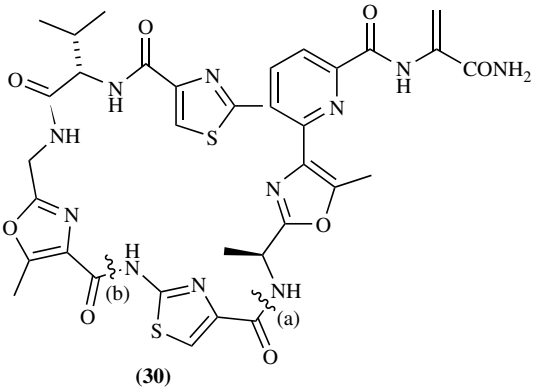
(27)



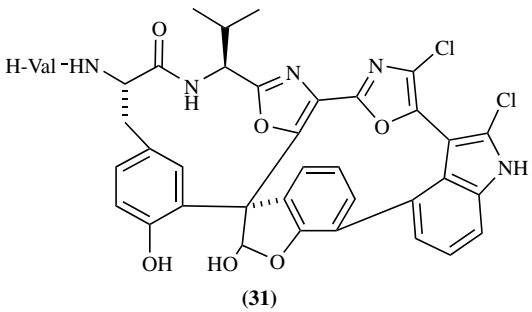
(28)



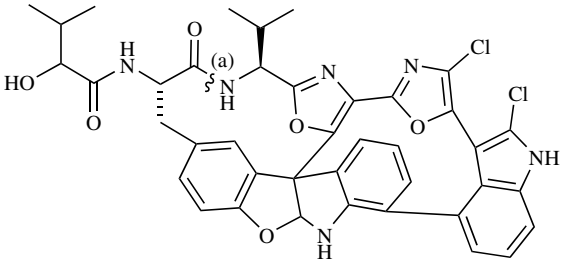
(29)



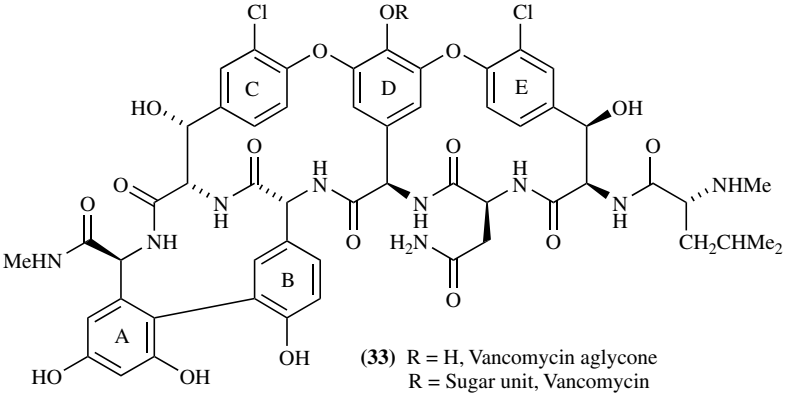
(30)



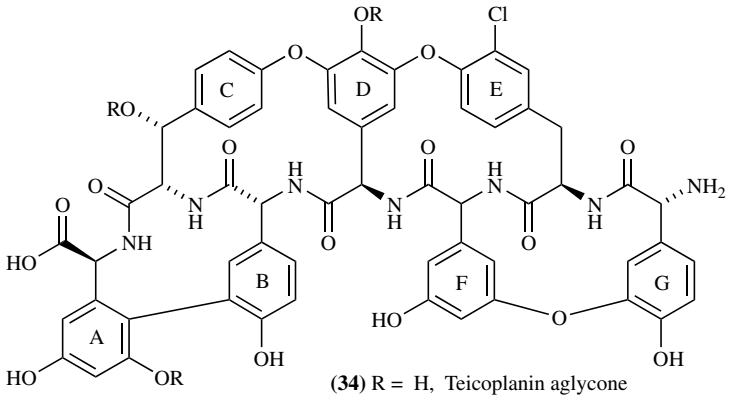
(31)



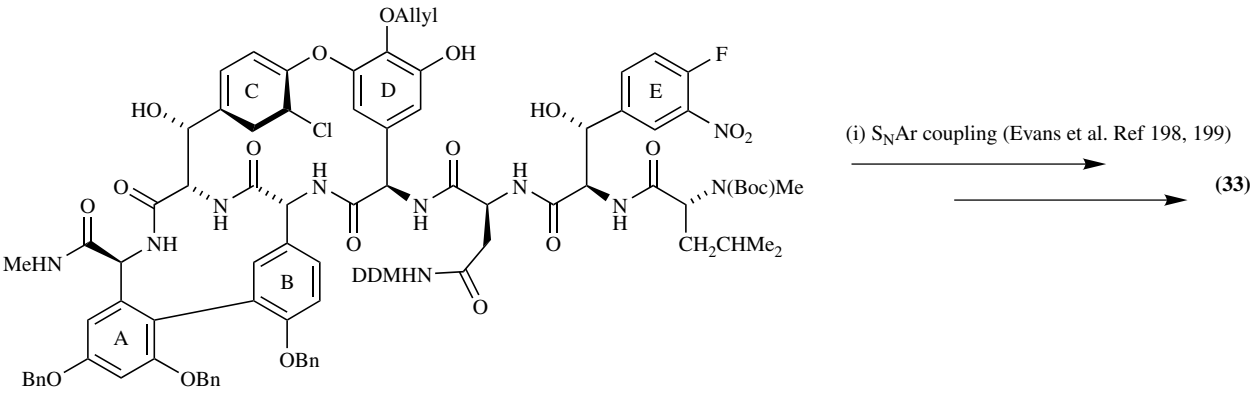
(32)



(33) R = H, Vancomycin aglycone
R = Sugar unit, Vancomycin



(34) R = H, Teicoplanin aglycone
R = Sugar units, Teicoplanin

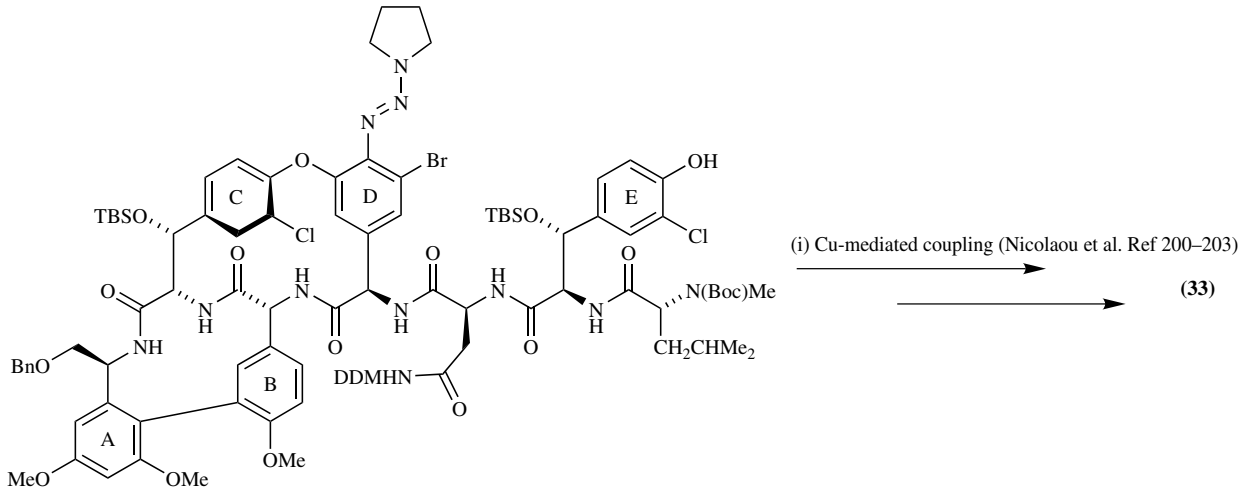


Scheme 20

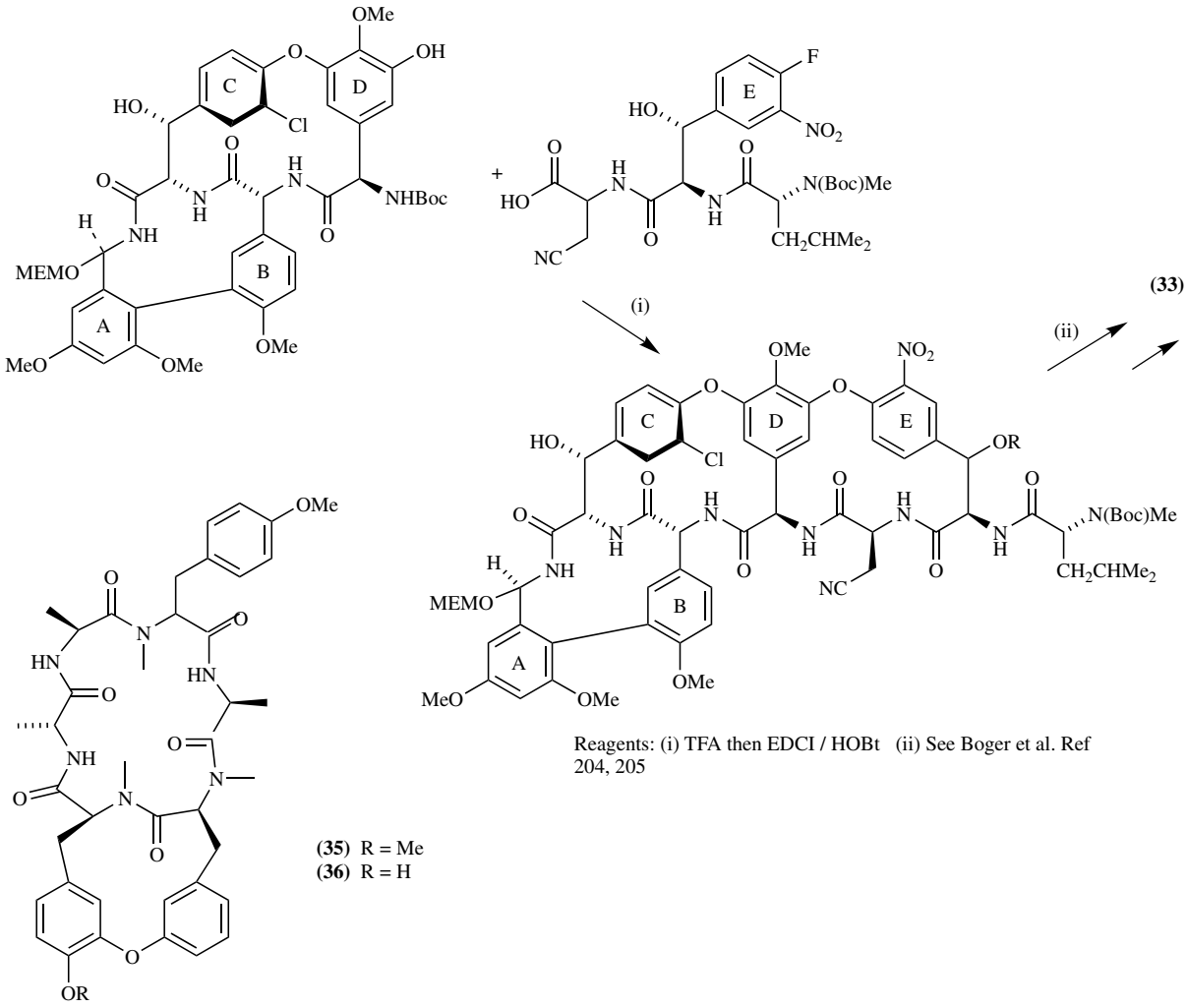
ethers were constructed by S_NAr fluoride displacement reactions of nitro-substituted aryl rings (Scheme 20). Nicolaou *et al.*'s approach [200–203] saw the A-B system effected by the Suzuki conditions $[Pd(Ph_3P)_4]/Na_2CO_3$ for coupling an iodoaryl compound to a boronic acid aryl group, while diphenyl ethers were produced via their in-house triazene-based technology (Scheme 21).

Boger *et al.* [204,205] used as key to their strategy the defined order of CD, AB and DE ring closures which permitted selective thermal atropisomerism of the newly formed ring system (Scheme 22). The teicoplanin aglycone **(34)** has also been synthesised [206,207]. Macrocyclization at the *N*-terminus brought about the closure of the extra F-G 14-membered ring.

Another of nature's contributions under this category is the potent anti-tumour cyclohexapeptide RA VII **(35)** and its congener deoxybouvardin **(36)**. The extra diphenyl ether link in the structure

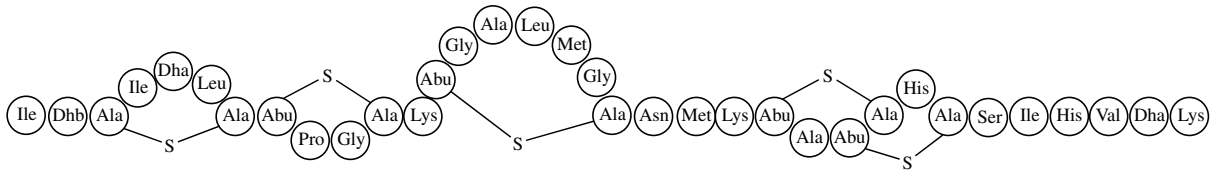


Scheme 21

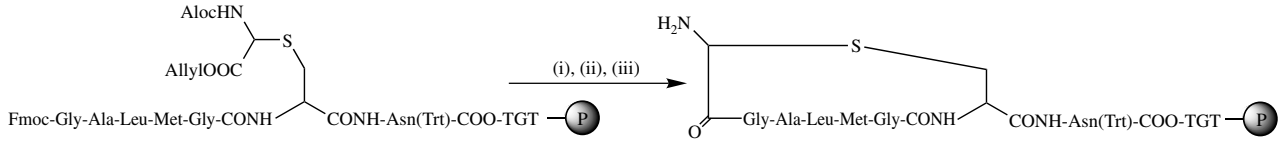


Reagents: (i) TFA then EDCI / HOBt (ii) See Boger et al. Ref 204, 205

Scheme 22

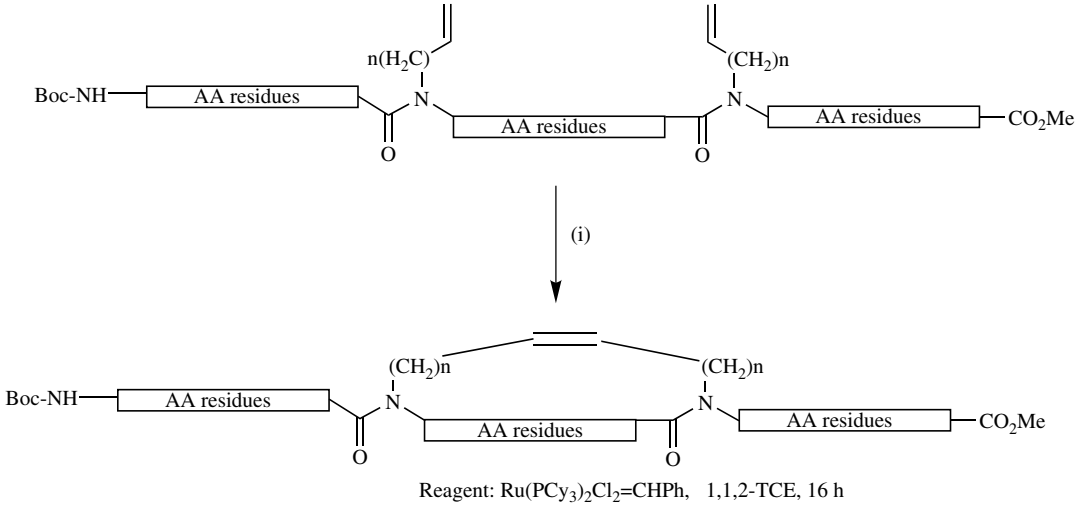


(37)



Reagents: (i) $Pd(PPh_3)_4$, AcOH / NMM
(ii) 20% piperidine
(iii) PyAOP, HOAt, DIEA

Scheme 23



Reagent: $Ru(PCy_3)_2Cl_2$=CHPh, 1,1,2-TCE, 16 h

Scheme 24

proved difficult to synthesize, but has now been accomplished by two groups [208,209], using either the Ullmann reaction or a thallium trinitrate mediation reaction.

Side-chain modification where sulfur bridges are built in via *meso* lanthionine or *threo* β-methyllanthionine are widely distributed in nature, belonging to a series now known as lantibiotics [210,211]. Probably the best known member is nisin **(37)** from *Streptococcus lactis*, widely used as a food preservative against *Clostridium botulinum*. The only reported total synthesis in the solution phase is by Shiba *et al.* [212], with the cyclized sulfur bridges being formed by extrusion of sulfur from cystine, followed by fragment condensation. In progressing to solid phase techniques, lanthionine bridges have been made compatible with peptide cyclization on an oxime resin [213,214], and using a biomimetic approach of assembling linear peptides containing cysteine and dehydroalanine residues, and forming the sulfur bridges by intramolecular 1,4-addition of the cysteine SH to the dehydroalanine [215,216]. In the more recent solid phase approach [217], an analogue of the ring C of nisin has been introduced via a pre-formed sulfur bridge as part of a triply orthogonal protecting group strategy summarized in Scheme 23.

The thrust of combinatorial library construction has moved macrocyclization steps into the wider echelons of contemporary organic chemistry and a popular recent development is to construct the cyclic constraints via ring closing olefine metathesis [218,219] as shown in Scheme 24.

In summary, it is hoped that the cyclization examples discussed in this review, reflect the perception that nature's often seemingly complex ways of adding constraints to peptides, can now be mimicked in the laboratory utilizing a vast range of organic chemical armoury. The knowledge gained by these demanding synthetic challenges will hopefully benefit the move to create mimetics and designer molecules which can surpass nature's activity and be of service in the development of more efficient pharmaceuticals.

REFERENCES

1. Eichler J, Houghten RA. Synthesis of cyclic disulfide peptides: comparison of oxidation methods. *Protein Pept. Lett.* 1997; **4**: 157–164.
2. Hargittai B, Barany G. Disulfide bond formation in peptides. *Methods Enzymol.* 1997; **289**: 198–221.
3. Chapters in *'Amino Acids, Peptides and Proteins'*, Specialist Periodical Reports, Royal Society of Chemistry, Volumes 1–34 (1969–2003) eds. Young GT (Vol 1–4), Sheppard RC (5–13). Jones JH (14–23), Davies JS (24–32), Davies JS and Barrett GC (33–34).
4. Fusetani N, Matsunaga S. Bioactive sponge peptides. *Chem. Rev.* 1993; **93**: 1793–1806.
5. Michael JP, Pattenden G. Marine metabolites and metal ion chelation. *Angew. Chemie. Int. Ed.* 1993; **32**: 1–23.
6. Wipf P. Synthetic studies of biologically active marine cyclopeptides. *Chem. Rev.* 1995; **95**: 2115–2134.
7. Faulkner DJ. Highlights of marine natural products chemistry (1972–1999). *Nat. Pro. Rep.* 2000; **17**: 1–6.
8. Burja AM, Banaigs B, Abou-Mansour E, Burgess JG, Wright PC. Marine cyanobacteria — a prolific source of natural products. *Tetrahedron* 2001; **57**: 9347–9377.
9. Wieland Th. *Peptides of poisonous Amanita Mushrooms*. Springer Series in Molecular Biology. Springer-Verlag 1986.
10. Wenger RM. Synthesis of cyclosporine and analogues — structural requirements for immunosuppressive activity. *Angew. Chem. Int. Ed.* 1985; **24**: 77–85.
11. Loiseau N, Cavalier F, Noel JP, Gomis JM. High yield synthesis of tentoxin, a cyclic tetrapeptide. *J. Pept. Sci.* 2002; **8**: 335–346.
12. Yamada K, Unno M, Kobayashi K, Oku H, Yamamura H, Araki S, Matsumoto H, Katakai R, Kawai M. Stereochemistry of protected ornithine side chains of Gramicidin S derivatives. *J. Am. Chem. Soc.* 2002; **124**: 12 684–12 688.
13. Harris CM, Harris TM. Structure of vancomycin — evidence for an asparagine residue in the peptide. *J. Am. Chem. Soc.* 1982; **104**: 4293–4295.
14. Guder A, Wiedemann I, Sahl HG. Post-translationally modified bacteriocins — the lantibiotics. *Biopolymers* 2000; **55**: 62–73.
15. Kobayashi K, Suzuki H, Shimbo K, Takeya K, Morita H, Celogentins A–C. new antimitotic bicyclic peptides from the seeds of *Celosia argentea*. *J. Org. Chem.* 2001; **66**: 6626–6633.
16. Mu Q, Teng RW, Li CM, Wang DZ, Wu Y, Sun HD, Hu CQ. Leicyclocin A and B, two cyclopeptides from *Goniothalmus leiocarpus*. *Chin. Chem. Lett.* 2001; **12**: 607–610.
17. Matsumoto T, Shishido A, Morita H, Itokawa H, Takeya K. Cyclolinopeptides F-I, cyclic peptides from Linseed. *Phytochemistry* 2001; **57**: 251–260.
18. Goodman M, Zapf C, Rew Y. New reagents, reactions and peptidomimetics for drug design *Biopolymers* 2001; **60**: 229–245.
19. Loffet A. Peptides as drugs: Is there a market? *J. Pept. Sci.* 2002; **8**: 1–7.
20. Cappelletti S, Annoni P, DiGregorio G, Storace O, Pinori M. Peptides for the pharmaceutical market: Chemical synthesis and downstream processing on an industrial scale. *Chim. Oggi/Chem. Today* 2002; **20**: 47–50.
21. Verlander M. Large scale manufacturing methods for peptides — A status report. *Chim. Oggi/Chem. Today* 2002; **20**: 62–66.
22. Mizhiritskii M, Shpernat Y. Trends in peptide chemistry 3. Natural cyclic peptides: Is the chemical synthesis commercially feasible? *Chim. Oggi/Chem. Today* 2002; **20**: 43–45.
23. Lambert JN, Mitchell JP, Roberts KD. The synthesis of cyclic peptides. *J. Chem. Soc. Perkin I.* 2001; 471–484.
24. Humphrey JM, Chamberlin AR. Chemical synthesis of natural product peptides: Coupling methods for the incorporation of non-coded amino acids into peptides. *Chem. Rev.* 1997; **97**: 2243–2266.
25. Spatola A, Romanovskis P. Head to tail cyclic peptides and cyclic libraries. In *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry and Material Science*, Greenberg A, Breneman C, Liebman JF (eds). Wiley: Chichester, 2000; 519–564.
26. Horton DA, Bourne GT, Smythe ML. Exploring privileged structures: the combinatorial synthesis of cyclic peptides. *J. Computer-Aided Mol. Design* 2002; **16**: 415–430.
27. *Fmoc Solid Phase Peptide Synthesis*: *A Practical Approach*, Chan WC, White PD (eds). Oxford University Press: Oxford, 2000; 366.
28. Jones JH. A revised guide to abbreviations in peptide science and a plea for conformity. *J. Pept. Sci.* 2003; **9**: 1–8.

29. Albericio F, Chinchilla R, Dodsworth DJ, Najera C. New trends in peptide coupling reagents. *Org. Prep. Proc. Int.* 2001; **33**: 203–303.
30. *The Peptides: Analysis, Synthesis, Biology*. Vol. 1. Gross E, Meienhoffer J (eds). Academic Press: Oxford, 1979; 433.
31. Koenig W, Geiger R. Eine neue methode zur synthese von peptiden. Aktivierung der carboxylgruppe mit dicyclohexylcarbodiimide unter zuzatz von 1-Hydroxybenztriazole. *Chem. Ber.* 1970; **103**: 788–798.
32. Rich DH, Singh J. The carbodiimide method. In *The Peptides: Analysis, Synthesis, Biology*, Gross E, Meienhoffer J (eds). Academic Press: New York, 1979; 1: 241–262.
33. Carpino LA. 1-Hydroxy-7-azabenzotriazole: an efficient peptide coupling additive. *J. Am. Chem. Soc.* 1993; **115**: 4397–4398.
34. Benoiton NL, Chen FMF. Not the alkoxycarbonylamino acid O-acylisourea. *J. Chem. Soc. Chem Commun.* 1981; 543–545.
35. Nozaki S. Effect of the amounts of additives on peptide coupling mediated by a water-soluble carbodiimide in alcohol. *J. Pept. Res.* 1999; **54**: 162–167.
36. Davies JS, Howe J, Jayatilake J, Riley T. Synthesis and applications of cyclopeptides and depsipeptides. *Lett. Pept. Sci.* 1997; **4**: 441–445.
37. Shioiri T, Ninomiya K, Yamada S. Diphenylphosphoryl azide: A new convenient reagent for a modified Curtius reaction and for peptide synthesis. *J. Am. Chem. Soc.* 1972; **94**: 6203–6205.
38. Coste J, Dufour M-N, Pantolini A, Castro B. A new reagent for coupling *N*-methylated amino acids. *Tetrahedron Lett.* 1990; **31**: 669–672.
39. Delforge D, Dieu M, Delaive E, Art M, Gillon B, Deuveese B, Raes M, van Beeumen J, Remacle J. Solid phase synthesis of tailed cyclic peptides: the use of α-allyl-protected aspartic acid leads to an aspartimide and tetramethylguanidinium formation. *Lett. Pept. Sci.* 1996; **3**: 89–97.
40. Wermuth J, Goodman SL, Jonczyk A, Kessler H. Stereoisomerism and biological activity of the selective and superactive $\alpha_v\beta_3$ integrin inhibitor cyclo (RGDfV). *J. Am. Chem. Soc.* 1997; **119**: 1328–1335.
41. Lim D, Burgess K. Spirocyclic peptidomimetics featuring 2,3- methano amino acids. *J. Am. Chem Soc.* 1997; **119**: 9632–9640.
42. Nishino N, Xu M, Mihara H, Fujimoto T, Ohba M, Ueno Y, Kumagai H. Facile synthesis of cyclic peptides containing α-aminosuberic acid with oxime resin. *J. Chem. Soc. Chem. Comm.* 1992; 180–181.
43. Mihara H, Hayashida J, Hasegawa H, Ogawa HI, Fujimoto T, Nishino N. A pair of pyrene groups as conformational probes for antiparallel β- sheet structure formed in cyclic peptides. *J. Chem. Soc. Perkin Trans I.* 1997; 517–522.
44. DeGrado WF, Kaiser ET. Solid phase synthesis of protected peptides on a polymer-bound oxime. *J. Org. Chem.* 1982; **47**: 3258–3261.
45. Rosenbaum C, Waldmann H. Solid phase synthesis of cyclic peptides by oxidative cyclative cleavage of an aryl hydrazide linker — Synthesis of stylostatin 1. *Tetrahedron Lett.* 2001; **42**: 5677–5680.
46. Richter LS, Tom JYK, Brunier JP. Peptide cyclisation on solid support: A fast and efficient route to small cyclopeptides. *Tetrahedron Lett.* 1995; **35**: 5547–5550.
47. Yang L, Morriello G. Solid phase synthesis of head to tail cyclic peptides using a sulfonamide safety catch linker: the cleavage by cyclisation approach. *Tetrahedron Lett.* 1999; **40**: 8197–8200.
48. Bourne GT, Golding SW, McGeary RP, Meutermans WDF, Jones A, Marshall GR, Alewood PF, Smythe ML. Development and application of a novel safety catch linker for Boc-based assembly of libraries of cyclic peptides. *J. Org. Chem.* 2001; **66**: 7706–7713.
49. Alsina J, Rabonal F, Albericio F, Barany G. Solid phase synthesis of head to tail cyclic peptides via lysine side-chain. *Tetrahedron Lett.* 1994; **35**: 9633–9636.
50. Spatola AF, Dorlak K, Romanovskis P. An approach to cyclic peptide libraries: reducing epimerisation in medium-sized rings during solid phase synthesis. *Tetrahedron Lett.* 1996; **37**: 591–594.
51. Romanovskis P, Spatola AF. Preparation of head to tail cyclic peptides via side chain attachment. *J. Pept. Res.* 1998; **52**: 356–374.
52. Bourne GT, Golding SW, Meutermans WDF, Smythe ML. Synthesis of a cyclic peptide library based on the somatostatin sequence using backbone amide linker approach. *Lett. Pept. Sci.* 2001; **7**: 311–316.
53. Alsina J, Jensen KJ, Albericio F, Barany G. Solid phase synthesis with tris (alkoxy) benzyl backbone amide cleavage. *Chem-Eur. J.* 1999; **5**: 2787–2795.
54. Cavallaro V, Thompson P, Hearn M. Solid phase synthesis of cyclic peptides; model studies involving i — (i+4) side chain-side chain cyclisation. *J. Pept. Sci.* 1998; **4**: 335–343.
55. Grieco P, Gitu PM, Hruby VJ. Preparation of side-chain to side-chain cyclic peptides by allyl and alloc strategy: potential for library synthesis. *J. Pept. Sci.* 2001; **57**: 250–256.
56. Gellerman G, Elgavi A, Salitra Y, Kramer M. Facile synthesis of orthogonally protected amino acid building blocks for combinatorial N-backbone cyclic peptide chemistry. *J. Pept. Res.* 2001; **57**: 277–291.
57. Tam JP, Lu YA. Synthesis of large cyclic cystine-knot peptide by orthogonal coupling strategy using unprotected peptide precursor. *Tetrahedron Lett.* 1997; **38**: 5599–5602.
58. Tam JP, Lu YA, Yu Q. Thia-Zip reaction for synthesis of large cyclic peptides: mechanisms and applications. *J. Am Chem. Soc.* 1999; **121**: 4316–4324.

59. Zhang L, Tam JP. Lactone and lactam library synthesis by silver ion assisted orthogonal cyclisation of unprotected peptides. *J. Am Chem. Soc.* 1999; **121**: 3311–3320.
60. Shao Y, Lu W, Kent SBH. A novel method to synthesise cyclic peptides. *Tetrahedron Lett.* 1998; **39**: 3911–3914.
61. Meutermans WDF, Golding SW, Bourne GT, Miranda LP, Dooley MJ, Alewood PF, Smythe ML. Synthesis of difficult cyclic peptides by inclusion of a novel photolabile auxiliary in a ring contraction strategy. *J. Am Chem. Soc.* 1999; **121**: 9790–9796.
62. Bordusa F. Enzymes for peptide cyclisation. *ChemBiochem* 2001; **2**: 405–409.
63. Trauger JW, Kohli RM, Mootz HD, Marahiel MA, Walsh CT. Peptide cyclisation catalysed by thioesterase domain of tyrocidine synthetase. *Nature* 2000; **407**: 215–218.
64. Kohli RM, Walsh CT. Enzymology of acyl chain macrocyclisation in natural product biosynthesis. *Chem. Comm. (Cambridge)* 2003; 297–307.
65. Jackson DY, Burnier JP, Wells JA. Enzymatic cyclisation of linear peptide esters using subtiligase. *J. Am. Chem. Soc.* 1995; **117**: 819–820.
66. Smithrud DB, Benkovic PA, Benkovic SJ, Roberts V, Liu J, Neagu I, Iwama S, Phillips BW, Smith III AB, Hirschmann R. Cyclic peptide formation catalysed by an antibody ligase. *Proc. Natl Acad. Sci. USA* 2000; **97**: 1953–1958.
67. Scott CP, Abel-Santos E, Wall M, Wahnon DC, Benkovic SJ. Production of cyclic peptides and proteins *in vivo*. *Proc. Natl Acad. Sci. USA* 1999; **96**: 13 638–13 643.
68. Camarero JA, Cotton GJ, Adeva A, Muir TW. Chemical ligation of unprotected peptides directly from a solid support. *J. Pept. Res.* 1998; **51**: 303–316.
69. Fischer PM, Solbakken M, Undheim K. Diketopiperazine cyclisation of Glu-Asp dipeptide esters and Asp racemisation during segment condensation. *Tetrahedron* 1994; **50**: 2277–2288.
70. Carpenter KA, Weltrowska G, Wilkes BC, Schmidt R, Schiller PW. Spontaneous diketopiperazine formation via end to end cyclisation of non-activated linear tripeptide. An unusual chemical reaction. *J. Am. Chem. Soc.* 1994; **116**: 8450–8458.
71. Alsina J, Giralt E, Albericio F. Use of N-tritylamino acids and PyAOP for the suppression of diketopiperazine formation in Fmoc/Bu^t solid phase peptide synthesis using alkoxybenzyl ester anchoring linkages. *Tetrahedron Lett.* 1996; **37**: 4195–4198.
72. Bray AM, Maeji NJ, Valerio RM, Campbell RA, Geysen HM. Direct cleavage of peptides from a solid support into aqueous buffer. Application in simultaneous multiple peptide synthesis. *J. Org. Chem.* 1991; **56**: 6659–6666.
73. Capasso S, Vergara A, Mazzarella L. Mechanism of 2,5-dioxopiperazine formation. *J. Am. Chem. Soc.* 1998; **120**: 1990–1995.
74. Fischer PM. Diketopiperazines in peptide and combinatorial chemistry. *J. Pept. Sci.* 2003; **9**: 9–35.
75. Dinsmore CJ, Bashore DC. Recent advances in the synthesis of diketopiperazines. *Tetrahedron* 2002; **58**: 3297–3312.
76. Szardenings AK, Burkoth TS, Lu HH, Tien DW, Campbell DA. A simple procedure for the solid phase synthesis of diketopiperazines and diketomorpholine derivatives. *Tetrahedron* 1997; **53**: 6573–6593.
77. Szardenings AK, Antoneko V, Campbell DA, DeFrancisco N, Ida S, Shi L, Sharkov N, Tien D, Wang Y, Navre M. Identification of highly selective inhibitors of collagenase-1 from combinatorial libraries of diketopiperazines. *J. Med. Chem.* 1999; **42**: 1348–1357.
78. Kennedy AL, Fryer AM, Josey JA. A new resin-bound universal isonitrile for the Ugi CC reaction: Preparation and application to the synthesis of 2,5-diketopiperazines. *Org. Lett.* 2002; **4**: 1167–1170.
79. Rodionov IL, Rodinova LN, Baidakova LK, Romashko AM, Balashova TA, Ivanov VT. Cyclic dipeptides as building blocks for combination libraries Pt. 2. Synthesis of bifunctional diketopiperazines. *Tetrahedron* 2002; **58**: 8515–8523.
80. Rothe M, Lohmüller M, Fischer W, Taiber W, Breuksch U. *Multiple Cyclo-Oligomerisations on Polymeric Supports in Solid Phase Synthesis*, Epton R (ed.). SPCC(UK) Ltd: Birmingham, 1990; 551–558.
81. Ruckle T, DeLavallez P, Keller M, Dumy P, Mutter M. Pseudo prolines in cyclic peptides. Conformational stabilisation of cyclo [Pro-Thr(Ψ(Me,Me)Pro)-Pro]. *Tetrahedron* 1999; **55**: 11 281–11 288.
82. Gademann K, Seebach D. Preparation and NMR structure of the cyclo β-tripeptide cyclo[β-HGlu]$_3$ in aqueous solution. *Helv. Chim. Acta* 1999; **82**: 957–962.
83. Gademann K, Seebach D. Synthesis of cyclo β-tripeptides and their biological *in vitro* evaluation. *Helv. Chim. Acta* 2001; **84**: 2924–2937.
84. Glenn MP, Kelso MJ, Tyndall JDA, Fairlie DP. Conformationally homogeneous cyclic tetrapeptides: Useful new 3D-scaffolds. *J. Am. Chem. Soc.* 2003; **125**: 640–641.
85. Schmidt U, Langner J. Cyclotetrapeptides and cyclopentapeptides: Occurrence and synthesis. *J. Pept. Res.* 1997; **49**: 67–73.
86. El-Haddadi M, Cavalier F, Vives E, Azmani A, Verducci J, Martinez J. All-L Leu-Pro-Leu-Pro: a challenging cyclisation. *J. Pept. Sci.* 2000; **6**: 560–570.
87. Maestle W, Link U, Thewalt U, Weber T, Rothe M. Conformation and formation tendency of the cyclotetrapeptide cyclo(D-Pro-D-Pro-L-Pro-L-Pro): Experimental results and molecular modelling studies. *Biopolymers* 1991; **31**: 735–744.
88. Cavalier-Frontin F, Pèpe G, Verducci J, Siri D, Jacquier R. Prediction of the best linear precursor in the synthesis of cyclotetrapeptides by molecular mechanics calculations. *J. Am. Chem. Soc.* 1992; **114**: 8885–8890.

89. Nishino N, Xu M, Mihara H, Fujimoto T, Ueno Y, Kumagai H. Sequence-dependence in SPPS cyclisation-cleavage for cyclo (Arg-Gly-Asp-Phg). *Tetrahedron Lett.* 1992; **33**: 1479–1482.
90. Haubner R, Finsinger D, Kessler H. Stereoisomeric peptide libraries and peptidomimetics for designing selective inhibitors of the $\alpha_v\beta_3$ integrin for new cancer therapy. *Angew. Chem. Int. Ed.* 1997; **36**: 1375–1389.
91. Goodman SL, Hölzemann G, Sulyok GAG, Kessler H. Nanomolar small molecule inhibitors for $\alpha_v\beta_6$, $\alpha_v\beta_5$ and $\alpha_v\beta_3$ integrins. *J. Med. Chem.* 2002; **45**: 1045–1051.
92. Dai X, Su Zh, Liu JO. An improved synthesis of a selective $\alpha_v\beta_3$ — integrin antagonist cyclo (RGDfK). *Tetrahedron Lett.* 2000; **41**: 6295–6298.
93. Davies JS, Enjalbal C, Nguyen C, Al-Jamri L, Naumer C. The synthesis and properties of Gla- and Phe-containing analogues of cyclic RGD pentapeptides. *J. Chem. Soc. Perkin I* 2000; 2907.
94. Tang YC, Xie HB, Tian GL, Ye YH. Synthesis of cyclopentapeptides and cycloheptapeptides by DEPBT and the influence of some factors on cyclisation. *J. Pept. Res.* 2002; **60**: 95–103.
95. Gao XM, Ye YH, Bernd M, Kutscher B. Studies on the synthesis of cyclic pentapeptides as LHRH antagonists and the factors that influence cyclisation yield. *J. Pept. Sci.* 2002; **8**: 418–430.
96. Fukami T, Nagase T, Mase T, Naya A, Fujita K, Niiyama K, Ishikawa K. Practical synthesis of a cyclic pentapeptide in solution: Large scale preparation of a representative ET_A — selective antagonist BQ-123Na. *Bioorg. Med. Chem. Lett.* 1994; **4**: 1613–1618.
97. Vlattus I, Dellureficio J, Dunn R, Sytwu II, Stanton J. The use of thioesters in solid phase organic synthesis. *Tetrahedron Lett.* 1997; **38**: 7321–7324.
98. Kessler H, Haase B. Cyclic hexapeptides derived from the human thymopoietin III. *Int. J. Pept. Protein Res.* 1992; **39**: 36–40.
99. Ehrlich A, Rothemund S, Brudel M, Beyermann M, Carpino LA, Bienert M. Synthesis of cyclic peptides via efficient coupling reagents. *Tetrahedron Lett.* 1993; **34**: 4781–4784.
100. Sowemimo V, Scanlon D, Jones P, Craik DJ. Synthesis of cyclic pentapeptides and hexapeptides — a general synthetic strategy on DAS resin. *J. Protein Chem.* 1994; **13**: 339–346.
101. Sonnet P, Petit L, Marty D, Guillon J, Rochette J, Brion JD. First synthesis of segetalin A and analogous cyclohexapeptides. *Tetrahedron Lett.* 2001; **42**: 1681–1683.
102. Wang J, Osada S, Kodama H, Kondo M. Conformational studies of cyclo (Pro-Leu-Aib)$_2$ by ^{1}NMR and CD. *Bull. Chem. Soc. Jpn* 2000; **73**: 1221–1226.
103. Kobayashi J, Nakamura T, Tsuda M. Hymenamide F, a new cyclic heptapeptide from marine sponge *Hymeniacidin* sp. *Tetrahedron* 1996; **52**: 6355–6360.
104. Pettit GR, Tan R, Herald DL, Williams MD, Cerry RL. Isolation and structure of phakelistatin-3 and isophakellistatin-3. *J. Org. Chem.* 1994; **59**: 1593–1595.
105. Mechnich O, Hessler G, Kessler H, Bernd M, Kutscher B. Cyclic heptapeptides axinastatins 2, 3 and 4. Conformational analysis and biological potential. *Helv. Chim. Acta* 1997; **80**: 1338–1354.
106. Pettit GR, Srirangam JK, Herald DL, Ericksen KL, Doubek DL, Schmidt JM, Tackett LP, Bakuo GJ. Isolation and structure of stylostatin 1 from Papua New Guinea marine sponge *Stylotella aurantum*. *J. Org. Chem.* 1992; **57**: 7217–7220.
107. Horishi M, Yun YS, Takeya K, Itokawa H, Shirota O. A cyclic heptapeptide from *Vaccaria segetalis*. *Phytochemistry* 1996; **42**: 439–441.
108. Morita H, Kayashita T, Takeya K, Itokawa H, Shiro M. Conformation of cyclic heptapeptides. Solid and solution state conformation of yunnanin A. *Tetrahedron* 1997; **53**: 1607–1616.
109. Morita H, Kayashita T, Takeya K, Itokawa H, Shiro M. Crystal and solution structure of cycloheptapeptide pseudostellarin D. *Tetrahedron* 1995; **51**: 12 539–12 548.
110. Konat RK, Mierke DF, Kessler H, Bernd M, Kutscher B, Voegeli R. Synthesis and solvent effects on the conformation of hymenstatin 1. *Helv. Chim. Acta* 1993; **76**: 1649–1666.
111. Zhao YR, Zhou J, Wang XK, Wu HM, Huang XL, Zou C. Three cyclopeptides from *Stellaria delavayi*. *Phytochemistry* 1997; **46**: 709–714.
112. Zhao YR, Wang XK, Zhao TF, Zhou J, Huang XL, Wu HM. Two new cyclopeptides from *Stellaria yunnanensis*. *Chin. J. Chem.* 1995; **13**: 267–272.
113. Bewley CA, He H, Williams DH, Faulkner DJ. Aciculitins A-C: Cytotoxic and antifungal cyclic peptides from the sponge *Aciculites orientalis*. *J. Am. Chem. Soc.* 1996; **118**: 4314–4321.
114. Morita H, Shishido A, Matsumoto T, Takeya K, Itokawa H, Hirano T, Oka K. A new immunosuppressive cyclic nonapeptide, cyclolinopeptide B from *Linum usitatissimum*. *Biorg. Med. Chem. Lett.* 1997; **7**: 1269–1272.
115. Morita H, Gonda A, Takeya K, Itokawa H. Cycloleonuripeptides A, B, and C, three new Pro-rich cyclic nonapeptides from *Leonurus heterophyllus*. *Bioorg. Med. Chem. Lett.* 1996; **6**: 767–770.
116. Morita H, Takeya K, Itokawa H. Cyclic octapeptides from *Stellaria dichotoma var. Lanceolata*. *Phytochemistry* 1997; **45**: 841–845.
117. Pettit GR, Toki BE, Xu JP, Brune DC. Synthesis of the marine sponge cycloheptapeptide phakellistatin 5. *J. Nat. Prod.* 2000; **63**: 22–28.
118. Pettit GR, Rhodes MR, Tan R. Synthesis of the Indian Ocean marine sponge cycloheptapeptide phakellistatin 2. *J. Nat. Prod.* 1999; **62**: 409–414.

119. Himaja M, Kumar KH, Ramana MV, Belagali SL. Synthesis and biological evaluation of pseudostellarin D. *Eur. J. Med. Chem.* 1999; **34**: 525–529.
120. Bourne GT, Meutermans WDF, Alewood PF, McGeary PF, Scanlon M, Watson AA, Smythe ML. A backbone linker for Boc-based peptide synthesis and on-resin cyclisation: Synthesis of stylostatin 1. *J. Org. Chem.* 1999; **64**: 3095–3101.
121. Bates RB, Caldera S, Ruane MD. Synthesis and stereochemistry of axinastatin 4. *J. Nat. Prod.* 1998; **61**: 405–405.
122. Baraguey C, Auvin-Guette C, Blond A, Cavalier F, Lezenven F, Pousset JL, Bodo B. Isolation, structure and synthesis of chevalierins A, B and C. Cyclic peptides from the latex of *Jatropha chevalieri*. *J. Chem. Soc. Trans 1* 1998; 3033–3039.
123. Polaskava ME, Ede NJ, Lambert JN. Synthesis of nanotube-forming cyclic octapeptides via a Fmoc-strategy. *Aust. J. Chem.* 1998; **51**: 535–540.
124. Mihara N, Hayashida J, Hasegawa H, Ogawa HI, Fujimoto T, Nishino N. A pair of pyrene groups as a conformational probe for antiparallel β-sheet structure formed in cyclic peptides. *J. Chem Soc. Trans 2* 1997; 517–522.
125. Tamaki M, Akabori S, Muramatsu I. Direct formation of the antibiotic gramicidin S from pentapeptide active esters having no protection on the Orn side-chain. *J. Am. Chem. Soc.* 1993; **115**: 10 492–10 496.
126. Tamaki M, Akabori S, Muramatsu I. CD spectra and cyclisation of linear pentapeptides as gramicidin S precursors with Orn(Z). *Bull Chem. Soc. Jpn* 1993; **66**: 3113–3115.
127. Peluso S, Ruckle T, Lehmann C, Mutter M, Peggion C, Crisma M. Crystal structure of a synthetic cyclodecapeptide for TASP design. *ChemBiochem.* 2001; **2**: 432–437.
128. Wieland Th, Faesel J, Kanz W. Synthesen des antanamid. *Annalen* 1969; **722**: 197–209.
129. Zanotti G, Rossi F, Saviano M, Tancredi T, Saviano G, Maione A, Filizola M, DiBlasio B, Pedone C. A potent cyclolinopeptide analogue — solid state and solution conformation of cyclo[Pro-Phe-Phe-Ala-Glu-(OBu^t)]. *J. Am. Chem. Soc.* 1995; **117**: 8651–8658.
130. Ruzza P, Calderan A, Biondi B, Carrora M, Tancredi T, Borin G. Ion-binding and pharmacological properties of Tyr^6 and Tyr^9 antamanide analogues. *J. Pept. Res.* 1999; **53**: 442–452.
131. Amodeo P, Saviano G, Borin G, Calderan A, Ruzza P, Tancredi T. Solution conformation of sodium-complexed Gly^6 and Gly^9 antamanide analogues. *J. Pept. Res.* 1998; **51**: 180–187.
132. Cabrele C, Langer M, Beck-Sickinger AG. Amino acid side-chain attachment approach and its application to the synthesis of Tyr-containing cyclic peptides. *J. Org. Chem.* 1999; **64**: 4353–4361.
133. Scherkenbeck J, Chen HR, Haynes RK. Solid phase synthesis of loloatins A-C. *Eur. J. Org. Chem.* 2002; 2350–2355.
134. Angell YM, Thomas TL, Flentke GR, Rich DH. Solid phase synthesis of cyclosporine peptides. *J. Am. Chem. Soc.* 1995; **117**: 7279–7280.
135. Ko SY, Wenger RM. Solid phase synthesis of cyclosporine analogues. *Helv. Chim. Acta* 1997; **80**: 695–705.
136. Seebach D, Beck AK, Bossler HG, Geber C, Ko SY, Murtiashaw CW, Naef R, Shoda S, Thaler A, Krieger M, Wenger RM. Modification of cyclosporine A. Generation of an enolate at the Sar residue and reactions with electrophiles. *Helv. Chim. Acta* 1993; **76**: 1564–1590.
137. Li P, Xu JC. Total synthesis of cyclosporin O both in solution and solid phase, using coupling reagents BEMT, BDMP and BEP. *J. Org. Chem.* 2000; **65**: 2951–2958.
138. Thern B, Rudolph J, Jung G. Triphosgene as highly efficient reagent for the solid phase coupling of N-alkylated amino acids — total synthesis of cyclosporin O. *Tetrahedron Lett.* 2002; **43**: 5013–5016.
139. Jiang L, Moehle K, Dhanapal B, Obrecht D, Robinson JA. Combinatorial biomimetic chemistry: parallel synthesis of a small library of β-hairpin mimetics based on loop III from human platelet-derived growth factor B. *Helv. Chim. Acta* 2000; **83**: 3097–3112.
140. Pallin TD, Tam JP. Assembly of cyclic peptide dendrimers from unprotected linear building blocks in aqueous solution. *J. Chem. Soc. Chem. Comm.* 1996; 1345–1346.
141. Botti P, Pallin TD, Tam JP. Cyclic peptides from linear unprotected peptide precursors through thiazolidine formation. *J. Am. Chem. Soc.* 1996; **118**: 10 018–10 024.
142. Wahl F, Mutter M. Analogues of oxytocin with an oxime bridge using chemoselectively addressable building blocks. *Tetrahedron Lett.* 1996; **37**: 6861–6864.
143. Ovchinnikov YA, Ivanov VT. In *Proteins*, 3rd edn, Neurath H, Hill RL (eds). Academic Press: New York, 1982; 3: 307.
144. Dawson JR, Dory YL, Mellor JM, McAleer JF. Synthesis of novel potassium selective valinomycins. *Tetrahedron* 1996; **52**: 1361–1378.
145. Kuisle O, Quinoá E, Riguero R. A general methodology for automated solid phase synthesis of depsides and depsipeptides. Preparation of a valinomycin analogue. *J. Org. Chem.* 1999; **64**: 8063–8075.
146. Liang B, Richard DJ, Portonovo P, Joullie MM. Total synthesis and biological investigations of tamandarins A and B and analogue. *J. Am. Chem. Soc.* 2001; **123**: 4469–4474.
147. Jou G, González I, Albericio F, Lloyd-Williams P, Giralt E. Total synthesis of dehydrodidemnin B. Use of uronium and phosphonium salt coupling reagents

in peptide synthesis in solution. *J. Org. Chem.* 1997; **62**: 354–366 and syntheses refs. cited therein.
148. Hermann C, Giammasi C, Geyer A, Maier ME. Synthesis of hapalosin analogues by solid phase assembly of acyclic precursors. *Tetrahedron* 2001; **57**: 8999–9010.
149. Hermann C, Pais GCG, Geyer A, Künhert SM, Maier ME. Total synthesis of hapalosin and two ring-expanded analogues. *Tetrahedron* 2000; **56**: 8461–8471.
150. O'Connell CE, Salvato KA, Meng Zh, Littlefield BA, Schwartz CE. *Bioorg. Med. Chem. Lett.* 1999; **9**: 1541–1546.
151. Dinh TQ, Smith CD, Armstrong RW. Analogues incorporating trans 4-hydroxyproline that reverse multidrug resistance better than hapalosin. *J. Org Chem.* 1997; **62**: 790–791.
152. Cavalier F, Jacquier R, Mercadier J-L, Verducci J. Destruxin analogues: depsipeptidic bond replacement by amide bond. *Tetrahedron* 1996; **52**: 6173–6186.
153. Ward DE, Lazny R, Pedras MSC. Synthesis of host-selective phytoxin destruxin B avoiding diketopiperazine formation from an N-methyl amino acid dipeptide by use of Boc-hydrazide derivative. *Tetrahedron Lett.* 1997; **38**: 339–342.
154. Ward DE, Gai YZ, Lazny R, Pedras MSC. Probing host-selective phytotoxicity: synthesis of destruxin B and several natural analogues. *J. Org. Chem.* 2001; **66**: 7832–7840.
155. Ast T, Barron E, Kinne L, Schmidt M, Geremeroth L, Simmons K, Wenschuh H. Synthesis and biological evaluation of destruxin A and related analogues. *J. Pept. Res.* 2001; **58**: 1–11.
156. Nicolaou KC, Murphy F, Barluenga S, Ohshima T, Wei H, Xu J, Gray DLF, Baudoin O. Total synthesis of the novel immunosuppressant sanglifehrin A. *J. Am. Chem. Soc.* 2000; **122**: 3830–3838.
157. White JD, Hong J, Robarge LA. Total synthesis of cryptophycins-1,-3,-4 and -24 (arenastatin A) and -29, cytotoxic depsipeptides from cyanobacteria of the nostocacae. *J. Org. Chem.* 1999; **64**: 6206–6216 and refs. cited therein.
158. Chakraborty TK, Ghosh S, Dutta S. Studies directed towards the synthesis of stevastelins — a macrolactonisation approach to stevastelin B. *Tetrahedron Lett.* 2001; **42**: 5085–5088.
159. Grieco PA, Hon YS, Perez-Medrano A. A convergent enantiospecific total synthesis of the novel cyclodepsipeptide (+) jasplakinolide (jaspamide). *J. Am. Chem. Soc.* 1988; **110**: 1630–1631.
160. Chu KS, Negrete GR, Konopelski JP. Asymmetric total synthesis of (+) jasplakinolide. *J. Org. Chem.* 1991; **56**: 5196–5202.
161. White JD, Amedio JC. Total synthesis of geodiamolide A — a novel cyclodepsipeptide of marine origin. *J. Org Chem.* 1989; **54**: 736–738.
162. Ishiwata H, Sone H, Kigoshi H, Yamada K. Total synthesis of doliculide, a potent cytotoxic cyclodepsipeptide from the Japanese sea hare *Dolabella auricularia*. *J. Org. Chem.* 1994; **59**: 4712–4713.
163. Koch KN, Linden A, Heimgartner H. Synthesis of conformationally restricted cyclic pentadepsipeptides via direct amide cyclisations. *Tetrahedron* 2001; **57**: 2311–2326.
164. Valognes D, Belmont P, Xi N, Ciufolini MA. Total synthesis of luzopeptin C. *Tetrahedron Lett.* 2001; **42**: 1907–1909.
165. Boger DL, Chen Y, Foster CA. Synthesis and evaluation of hapalosin and analogs as MDR-reversing agents. *Bioorg. Med. Chem. Lett.* 2000; **10**: 1741–1744.
166. Lopez-Macia A, Jimenez JC, Royo M, Giralt E, Albericio F, Kahalalide B. Synthesis of a natural cyclodepsipeptide. *Tetrahedron Lett.* 2000; **41**: 9765–9769.
167. Lopez-Macia A, Jimenez JC, Royo M, Giralt E, Albericio F. Synthesis and structure determination of kahalalide F. *J. Am. Chem. Soc.* 2001; **123**: 11 398–11 401.
168. Bates RB, Brusoe KG, Burns JJ, Caldera S, Sryiani C, Cui W, Gangwar S, Gramme MR, McClure KJ, Rouen GP, Schadow H, Stessman CC, Taylor ST, Vu VH, Yarick GV, Zang J, Pettit GR, Bontems R. Dolastatins 26. Synthesis and stereochemistry of dolastatin 11. *J. Am. Chem. Soc.* 1997; **119**: 2111–2113.
169. Miyashita M, Nakamori T, Murai T, Miyagawa H, Akamatsu M, Ueno T. Facile synthesis of AM-toxins and analogues as cyclic depsipeptides by the solid phase method. *Biosci. Biotech. Biochem.* 1998; **62**: 1799–1801.
170. Ghosh AK, Liu CF. Total synthesis of antitumour depsipeptide (–)- doliculide. *Org. Lett.* 2001; **3**: 635–638.
171. Abbenante G, Fairlie DP, Gahan LR, Hanson GR, Pierens GK, van den Brank AL. Conformational control by thiazole and oxazoline rings in cyclic octapeptides of marine origin. Novel macrocyclic chair and boat conformation. *J. Am Chem. Soc.* 1996; **118**: 10 384–10 388.
172. Wipf P. Synthetic studies of biologically active marine cyclopeptides. *Chem. Rev.* 1995; **95**: 2115–2134.
173. Shioiri T, Hamada Y. Efficient syntheses of biologically active peptides of aquatic origin involving unusual amino acids. *Synlett* 2001; 184–201.
174. Caba JM, Rodriguez IM, Manzanares I, Giralt E, Albericio F. Solid phase total synthesis of trunkamide A. *J. Org. Chem.* 2001; **66**: 7568–7574.
175. Wipf P, Uto Y. Total synthesis and revision of stereochemistry of the marine metabolite trunkamide A. *J. Org. Chem.* 2000; **65**: 1037–1049.
176. McKeever B, Pattenden G. Total synthesis of the prenylated cyclopeptide trunkamide A, a cytotoxic metabolite from *Lissoclinum* sp. *Tetrahedron Lett.* 2001; **42**: 2573–2577.

177. Moody CJ, Bagley MC. Total synthesis of (+)- nostacyclamide. *J. Chem. Soc. Perkin Trans 1* 1998; 601–607.
178. Bertram A, Pattenden G. Synthesis and metal-templated assembly of oxazole and thiazole-based amino acids. Total synthesis of nostacyclamide and related cyclic peptides. *Synlett* 2001; 1873–1874.
179. Xia Z, Smith CD. Total synthesis of dendroamide A, a novel cyclic peptide that reverses multiple drug resistance. *J. Org. Chem.* 2001; **66**: 3459–3466.
180. Yokokawa F, Sameshima H, Shioiri T. Total synthesis of *cis,cis*-ceratospongamide, a bioactive thiazole-containing cyclic peptide from marine origin. *Synlett* 2001; 986–988.
181. Yokokawa F, Sameshima H, Shioiri T. Total synthesis of lyngbyabellin A, a potent cytotoxic metabolite from the cyanobacterium *Lyngbya majuscula*. *Tetrahedron Lett.* 2001; **42**: 4171–4174.
182. Dvorak CA, Schmitz WD, Poon DJ, Pryde DC, Lawson JP, Amos RA, Meyers AI. The synthesis of streptogramin antibiotics (–)- griseoviridin and its C-8 epimer. *Angew. Chem. Int. Ed.* 2000; **39**: 1664–1664.
183. Bagley MC, Bashford KE, Hesketh CL, Moody CJ. Total synthesis of the thiopeptide promothiocin A. *J. Am. Chem. Soc.* 2000; **122**: 3301–3313.
184. Boden CDJ, Norley M, Pattenden G. Total synthesis and assignment of configuration of the thiazole-based cyclopeptide cyclodidemnamide isolated from sea squirt *Didemnin molle*. *J. Chem Soc. Perkin Trans. 1* 2000; 883–888.
185. Boden CDJ, Pattenden G. Total synthesis and re-assignment of configuration of the cyclopeptides lissoclinamides 4 and 5 from *Lissoclinum patella*. *J. Chem. Soc. Perkin Trans I* 2000; 875–882.
186. Okumura K, Nakamura Y, Shin C-g. Total synthesis of macrocyclic antibiotic, micrococcin P. *Bull. Chem. Soc. Jpn* 1999; **72**: 1561–1569.
187 Okumura K, Suzuki T, Nakamura Y, Shin C-g. Total synthesis of macrocyclic antibiotic micrococcin P_1. *Bull. Chem. Soc. Jpn* 1999; **72**: 2483–2490.
188. Yamada S, Kigoshi H. Synthesis of dolastatin 1, a cytotoxic cyclic hexapeptide from the sea hare *Dolabella auricularia*. *Tetrahedron* 1999; **55**: 12 301–12 308.
189. McKeever B, Pattenden G. Total synthesis of mollamide, a reverse prenyl substituted cytotoxic cyclic peptide from *Didemnum molle*. *Tetrahedron Lett.* 1999; **40**: 9317–9320.
190. Toogood PL, Sowinski JA. Total synthesis of keranamide. *Chem Commun.* 1999; 981–982.
191. Downing SV, Aguilar E, Meyers AI. Total synthesis of bistratamide D. *J. Org. Chem.* 1999; **64**: 826–831.
192. Entwistle DA, Jordan SI, Montgomery J, Pattenden G. Total synthesis of oxazole-based virginiamycin antibiotics 14,15 anhydro pristinamycin IIB. *Synthesis* 1998; 603–612.
193. Wipf P, Fritch PC. Total synthesis and assignment of configuration of lissoclinamide 7. *J. Am. Chem. Soc.* 1996; **118**: 12 358–12 367.
194. Freeman DJ, Pattenden G. Total synthesis and assignment of stereochemistry of raocyclamide, cyclopeptide from cyanobacterium *Oscillatoria rao*. *Tetrahedron Lett.* 1998; **39**: 3251–3254.
195. Li J, Jeong S, Esser L, Harran PG. Synthesis of nominal diazonamides Pt 1. Convergent preparation of the structure proposed for (–)-diazonamide A. *Angew. Chem. Int. Ed.* 2001; **40**: 4765–4770.
196. Li J, Burgett ANG, Esser L, Amezcua C, Harran PG. Total synthesis of nominal diazonamides Part 2. On the true structure and origin of natural isolates. *Angew. Chem. Int. Ed.* 2001; **40**: 4770–4773.
197. Nicolaou KC, Bella M, Chen DYK, Huang XH, Ling TT, Snyder SA. Total synthesis of diazonamide A. *Angew. Chem. Int. Ed.* 2002; **41**: 3495–3499.
198. Evans DA, Wood MR, Trotter BW, Richardson TI, Barrow JC, Katz JL. Total synthesis of vancomycin and eremomycin aglycones. *Angew. Chem Int. Ed.* 1998; **37**: 2700–2704.
199. Evans DA, Dinsmore CJ, Watson PS, Wood MR, Richardson TI, Trotter BW, Katz JL. Non-conventional stereochemical issues in the design of the synthesis of vancomycin antibiotics: Challenges imposed by axial and non-planar chiral elements in the heptapeptide aglycones. *Angew. Chem. Int. Ed.* 1998; **37**: 2704–2708.
200. Nicolaou KC, Boddy CNC, Li H, Ramanjuli JM, Chu X-J, Brase S, Rubsam F. Total synthesis of vancomycin Pt I: Design and development of methodology. *Chem-Eur. J.* 1999; **5**: 2584–2601.
201. Nicolaou KC, Boddy CNC, Li H, Koumbis AE, Hughes R, Natarajan S, Jain NF, Ramanjuli JM, Brase S, Solomon ME. Total synthesis of vancomycin Pt 2: Retrosynthetic analysis, synthesis of amino acid building blocks and strategy evaluations. *Chem-Eur. J.* 1999; **5**: 2602–2621.
202. Nicolaou KC, Koumbis AE, Takayanagi M, Li H, Bando T, Hughes R, Natarajan S, Jain NF. Total synthesis of vancomycin Pt 3. Synthesis of aglycone. *Chem-Eur. J.* 1999; **5**: 2622–2647.
203. Nicolaou KC, Mitchell HJ, Bando T, Koumbis AE, Hughes R, Natarajan S, Jain NF, Winssinger N. Total synthesis of vancomycin Pt 4. Attachment of the sugar moieties and completion of synthesis. *Chem-Eur. J.* 1999; **5**: 2648–2667.
204. Boger DL, Miyazaki S, Kim SH, Wu JH, Loiseleur O, Castle SL. Total synthesis of vancomycin aglycone. *J. Am. Chem. Soc.* 1999; **121**: 10 004–10 011.
205. Boger DL, Miyazaki S, Kim SH, Wu JH, Loiseleur O, Castle SL. Diastereoselective total synthesis of the vancomycin aglycone with ordered atropisomer equilibrations. *J. Am. Chem. Soc.* 1999; **121**: 3226–3227.
206. Boger DL, Kim SH, Miyazaki S, Strittmatter H, Weng J-H, Mori Y, Rogel O, Castle SL, McAtee JJ.

Total synthesis of the teicoplanin aglycone. *J. Am. Chem. Soc.* 2000; **122**: 7416–7417.
207. Boger DL. Vancomycin, teicoplanin and ramoplanin: synthetic and mechanistic studies. *Med. Res. Rev.* 2001; **21**: 356–381.
208. Boger DL, Zhou J, Borzilleri RM, Nukii S, Castle SL. Synthesis of (9*R*, 12*S*)- and (9*S*, 12*S*)-cycloisodityrosine and their N-methyl derivatives. *J. Org. Chem.* 1997; **62**: 2054–2069.
209. Inoue T, Inaba T, Umezawa I, Yuasa M, Itokawa H, Ogura K, Komatsu K, Hara H, Hoshino O. Regioselective synthesis of 14-membered biaryl ethers. Total synthesis of RA VII and deoxybouvardin. *Chem. Pharm. Bull.* 1995; **43**: 1325–1335.
210. Jack RW, Bierbaum G, Sahl H-G. *Lantibiotics and Related Peptides*. Springer: Berlin Heidelberg, New York, 1998.
211. Kaiser D, Jack RW, Jung G. Lantibiotics and microcins: novel post-translational modifications of polypeptides. *Pure Appl. Chem.* 1998; **70**: 97–104.
212. Fukase K, Kitazawa M, Sano A, Shimbo K, Horimoto S, Fujita H, Kubo A, Wakamiya T, Shiba T. Synthetic study on peptide antibiotic nisin 5. Total synthesis of nisin. *Bull. Chem. Soc. Jpn* 1992; **65**: 2227–2240.
213. Ösapay G, Prokai L, Kim H-S, Medzihradsky KF, Coy DH, Liapakis G, Reisine T, Melacini G, Zhu Q, Wang SH-H, Mattern RH, Goodman M. Lanthionine-somatostatin analogues: Synthesis, characterisation, biological activity and enzymatic stability studies. *J. Med Chem.* 1997; **40**: 2241–2251.
214. Melacini G, Zhu Q, Ösapay G, Goodman M. A refined model for the somatostatin pharmacophore: Conformational analysis of lanthionine-sandostatin analogues. *J. Med. Chem.* 1997; **40**: 2252–2258.
215. Mayer JP, Zhang J, Groeger S, Liu CG, Jarosinski MA. Lanthionine macrocyclisation by *in situ* activation of serine *J. Pept. Res.* 1998; **51**: 432–436.
216. Burrage S, Raynham T, Williams G, Essex JW, Allen C, Cardno M, Swali V, Bradley M. Biomimetic synthesis of lantibiotics. *Chem-Eur. J.* 2000; **6**: 1455–1466.
217. Mustapa MFM, Harris R, Mould J, Chubb NAL, Schultz D, Driscoll PC, Tabor AB. Synthesis of cyclic peptides containing norlanthionine bridges via a triply-orthogonal protecting group strategy. *Tetrahedron Lett.* 2002; **43**: 8363–8366.
218. Reichwein JF, Wels B, Kruijtzer JAW, Versluis C, Liskamp RMJ. Rolling loop scan: An approach featuring ring-closing metathesis for generating libraries of peptides with molecular shapes mimicking bioactive conformations or local folding of peptides and proteins. *Angew. Chem. Int. Ed.* 1999; **38**: 3684–3687, and ref. cited therein.
219. Hebach C. Kazmaier. Via Ugi reactions to conformationally fixed cyclic peptides. *Chem. Commun.* 2003; 596–597.

