REVIEW

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# Natural guanidine derivatives

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The literature on guanidine-bearing natural products is reviewed, with emphasis on occurrence, isolation, structure determination, biosynthesis, synthesis and biological activities, with 365 references. The literature survey includes macrocycles and peptides from bacteria and cyanobacteria, as well as alkaloids and peptides isolated from marine and terrestrial invertebrates and higher plants.



## 1 Introduction

This review is an update of previous reviews dealing with guanidine-bearing natural products.[1–4] The topics covered in the present review include the isolation, structure determination, biosynthesis, synthesis and biological activities of natural guanidines that have appeared in the literature between 2002 and 2004.

Reviews on guanidine chemistry that have appeared in the literature include "Modified guanidines as chiral auxiliaries",[5] "The terminology of guanidine formation"[6] and "Solid-phase synthesis of guanidinium derivatives from thiourea and isothiourea functionalities".[7] A non-specific review on "Peptides with anticancer use or potential"[8] included many examples of guanidine-bearing peptide derivatives. An array of new synthetic guanidines display potent, selective and specific biological activities.[9–71] As a consequence, methods for the synthesis of guanidine derivatives continue to be developed. These include the synthesis of [5-$^{13}$C]-L-arginine from L-aspartic acid,[72] the reaction of several thiourea-based guanidinylating reagents in the presence of a polymer-supported Mukaiyama catalyst,[73] the synthesis of arginine-containing peptides using a side-chain anchoring reagent,[74] the preparation of *N*-aryl-*N*′-carboalkoxy guanidines from alcohols under Mitsunobu conditions,[75] an unexpected 1,3-diaza-Claisen rearrangement reaction between azanorbornenes with *N*-substituted-*N*′-tosylthioureas and EDCl that afforded bicyclic substituted guanidines,[76] a method for the selective reaction between secondary amines and protected thioureas,[77] the use of a new, cellulose-supported guanidinylating reagent,[78] the synthesis of *N*-tosylguanidines,[79] the synthesis of guanidines using *ortho*-bromo-carboxybenzyl chloride and

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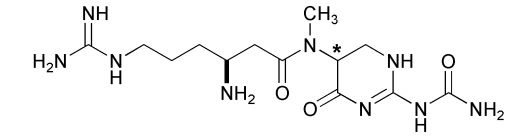
*ortho*-chloro-carboxybenzyl chloride as protecting groups,[80] the use of hetero Diels–Alder reactions of nitrosoamidines,[81] the synthesis of phosphoryl guanidines,[82] the use of a microwave-assisted reaction between diamines and cyanogen bromide,[83] the use of the recently introduced (benzotriazol-1-yl)carboximidamides in the preparation of acylguanidines and guanylureas[84] and the synthesis of cyclic arylguanidines *via* palladium acetate and dpppentane mediated cycloaddition between 2-vinylpyrrolidines and carbodiimides.[85] Synthetic guanidines continue to be of interest as peptide mimetics,[86–95] as nucleotide mimetics,[96–104] as catalysts,[105–116] as chemosensors,[117–121] as polymeric materials for various applications,[122–127] as receptor-acting, binding and chelating agents,[128–143] as cross-membranes translocating agents,[144,145] in supramolecular chemistry,[146–148] and as fuel stabilizers.[149]

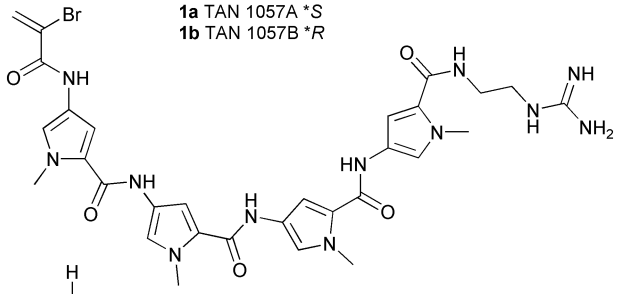
## 2 Natural guanidines from terrestrial microorganisms

An array of new derivatives of TAN 1057 A/B (**1a** and **1b**) antibiotics have been synthesized, using a combination of liquid and solid phase library synthesis, aimed at improving the antibiotic activity and human tolerance for these compounds.[150–154] The first enantioselective synthesis of TAN 1057A was achieved in 9% overall yield[155] using an approach similar to one that was previously reported for the synthesis of a racemic TAN 1057 A/B mixture[156] (summarized in a previous review[4]) but including a few more steps in order to avoid amino acid racemization.

Although not a natural product, brostallicin (**2**) was disclosed in 2001 as a potent minor groove DNA-binding agent derivative of distamycin (**3**),[157] an amidine-bearing natural product isolated from *Streptomyces distallicus* in 1962.[158] Brostallicin has recently entered Phase II clinical trials.[159–166]



**1a** TAN 1057A *S
**1b** TAN 1057B *R



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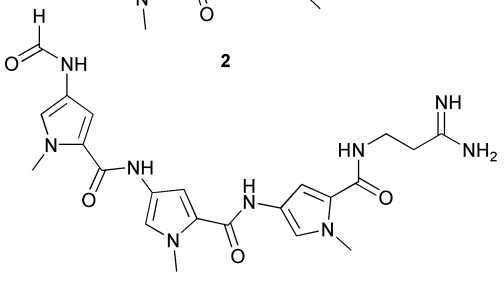
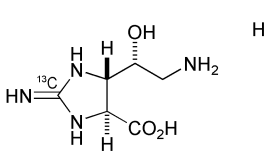


**3**

Both [guanidino-$^{13}$C]streptolidine (**4**) and [guanidino-$^{13}$C]capreomycidine (**5**) have been synthesized in order to clarify the last biosynthetic steps of streptothricin F (**6**),[167] which was originally isolated from *Streptomyces lavendulae*.[168] The synthesis of [guanidino-$^{13}$C]streptolidine (**4**) was achieved according to the first synthesis of this compound,[169] treating the furanone **7** with $^{13}$C labelled cyanogen bromide in an alkaline media.



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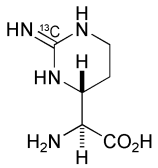

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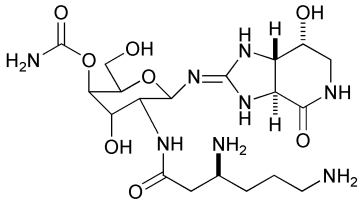


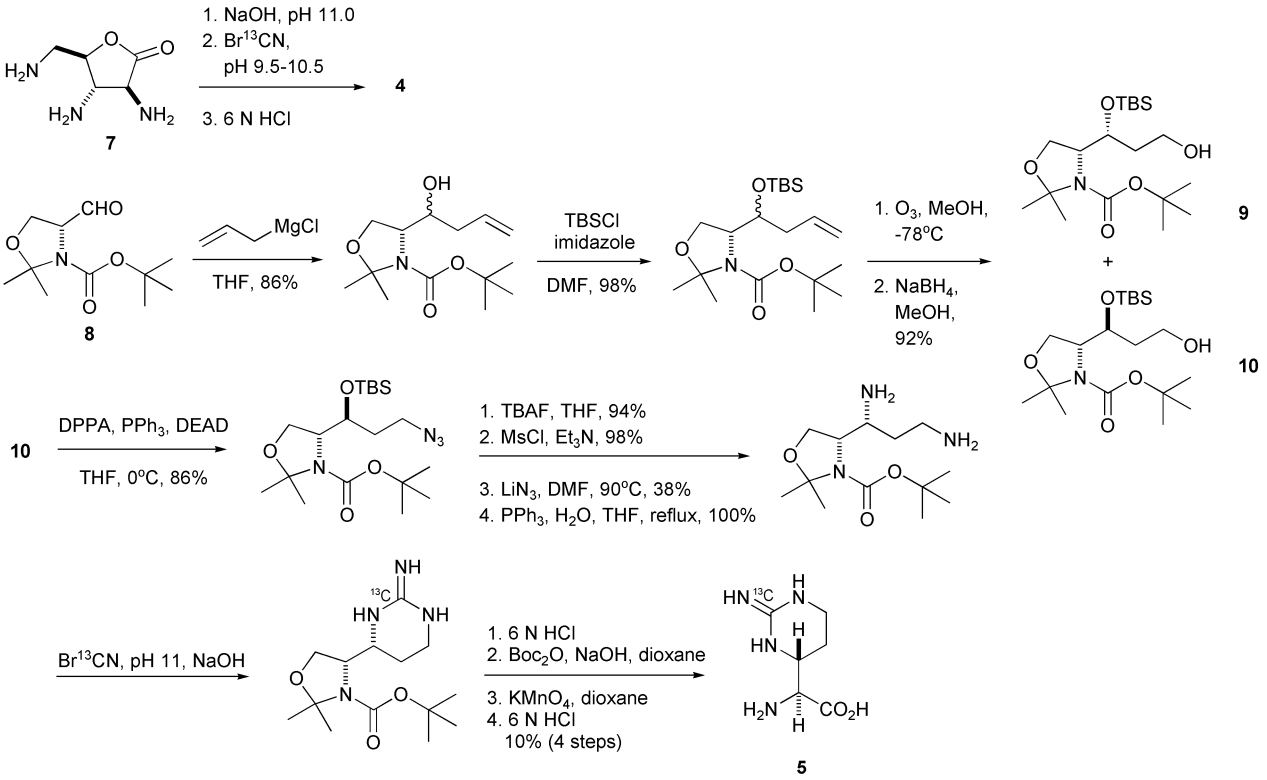
**6**

(2*S*,3*R*)-[Guanidino-$^{13}$C]-capreomycidine (**5**) was synthesized from the oxazolidine aldehyde **8** through a multi step procedure (Scheme 1). The absolute configuration of the deprotected diols **9** and **10** was established by the Mosher method. The alternate Mitsunobu and mesylate–$LiN_3$ procedures improved yields for the synthesis of the diazide that generated a diamine after reduction, which was subsequently transformed into **5**. However, no incorporation of (2*S*,3*R*)-[guanidino-$^{13}$C]-capreomycidine (**5**) into streptothricin F (**6**) was observed. The authors suggested that this may be due to the fact that compound **5** is not able to cross cell membranes, or even does not constitute a precursor to the more elaborated guanidine alkaloid **6**.[167]

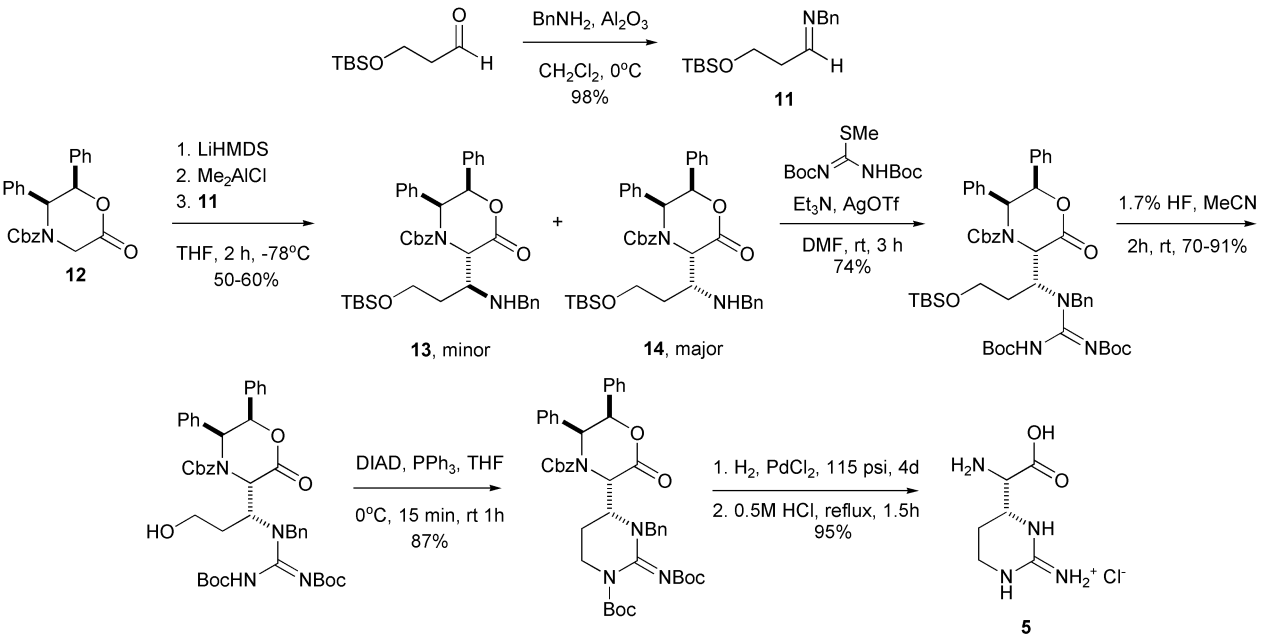
Unlabelled (2*S*,3*R*)-capreomycidine (**5**) and capreomycin IB (**21**)[170] have both been synthesized[171] from the chiral glycinate derivative **12** (Schemes 2–4). Compound **12** was condensed with 3-*tert*-butyldimethylsiloxy benzylimine **11** to give a 3.3 : 1 mixture of diastereomers **13** (minor) and **14** (major). Guanidylation of **14** was accomplished using silver triflate rather than mercury(II) chloride as a catalyst. The final cyclic guanidine amino acid **5** was obtained after a Mitsunobu reaction with the fully protected guanidine group, followed by deprotection, in 33% overall yield.

In the synthesis of capreomycin IB (**21**, Schemes 3 and 4), the amino acid derivative *R*-α-formylglycine diethyl acetal (**15**) was obtained from the glycinate **12** using titanium enolate conditions. The diaminopropanoic acid β-lysine residue **16** was prepared from protected diaminopropanoic acid and bis(*tert*-butoxycarbonyl)-β-lysine *N*-hydroxysuccinyl ester. The subsequent tripeptide **17** was obtained in standard conditions. After deprotection, **17** was reacted with asparagine–alanine dipeptide also in standard conditions, to yield an asparagine containing pentapeptide as a precursor of the second diaminopropionic acid group of capreomycin IB *via* a Hofmann rearrangement. The product **19** was condensed with α-amino protected capreomycidine to give the opened capreomycin IB peptide **20**, which was deprotected and cyclized in low yield due to multiple purification (SiOH) steps. After cleavage of the dimethylketal, the corresponding aldehyde was directly reacted with urea (excess) to give capreomycin IB in 27 total steps and 2% overall yield, a synthesis that significantly improved upon the first capreomycin IB (**21**) synthesis (45 steps, 0.008% overall yield).[171]

The complete biosynthetic gene cluster of viomycin (**22**)[172] has recently been established,[173] and enabled the authors to postulate that the biosynthetic formation of (2*S*,3*R*)-capreomycidine (**5**) is derived from an NRPS-independent two-enzyme (VioC and VioD) pathway.[174] These studies demonstrated that VioC is an $Fe^{2+}$ and α-ketoglutarase-dependent oxygenase, responsible for the production of (3*S*)-hydroxy-(2*S*)-arginine from the corresponding α-amino acid in the presence of $O_2$,[175] and that VioD catalyzed the transformation of (3*S*)-hydroxy-(2*S*)-arginine into (2*S*,3*S*)-capreomycidine.[176,177]



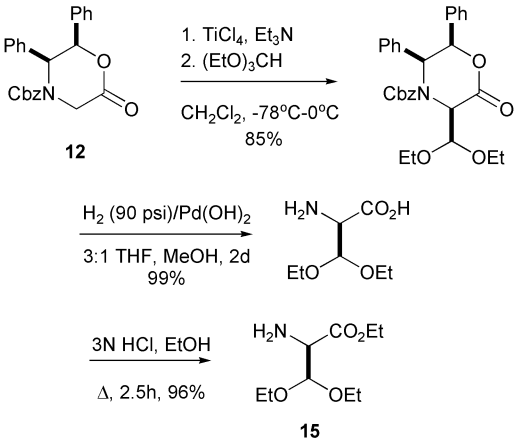

**Scheme 1**




**Scheme 2**

Tripropeptins A–E, Z (**23–28**) are lipophilic cyclodepsipeptides which have been isolated from a strain of *Lysobacter*.[178–180] The absolute configuration of amino acid residues was determined by Marfey's analysis, including the absolute stereochemistry of threo-β-L-hydroxyaspartic acid and threo-β-D-hydroxyaspartic acid. The absolute configuration of L-*trans*-3-hydroxyproline was established by $^1$H NMR and circular dichroism analysis. The absolute configuration of the (3*R*)-hydroxy-13-methyltetradecanoic acid moiety of tripropeptin C (**25**) was determined by an optical rotation measurement. The antibiotic activities of **23–28** were measured against various strains of pathogenic bacteria and fungi. Tripropeptin D (**26**) was the most active against seven strains of methycillin-resistant *Staphylococcus aureus* and four strains of vancomycin-resistant *Enterococcus faecalis*. Tripropeptin C was the second most active antibiotic, showing antagonistic activity to chloramphenicol by inhibiting the synthesis of the microbial cell envelope but not of the intracellular organelles and cytoplasm.[180]

Closely related antibiotics are the plusbacins $A_1$–$A_4$ (**29–32**) and $B_1$–$B_4$ (**33–36**) which have been isolated from *Pseudomonas* sp.,[181,182] and empedopeptin (**37**) isolated from *Empedobacter haloabium* sp.[183,184] Plusbacin $A_3$ (**31**) showed strong antibacterial activity against methicillin-resistant *S. aureus* and VanA-type vancomycin-resistant enterococci, as well as against other Gram-positive bacteria, with MICs (minimum inhibitory concentrations) ranging from 0.39 to 3.13 μg mL$^{-1}$. Plusbacin

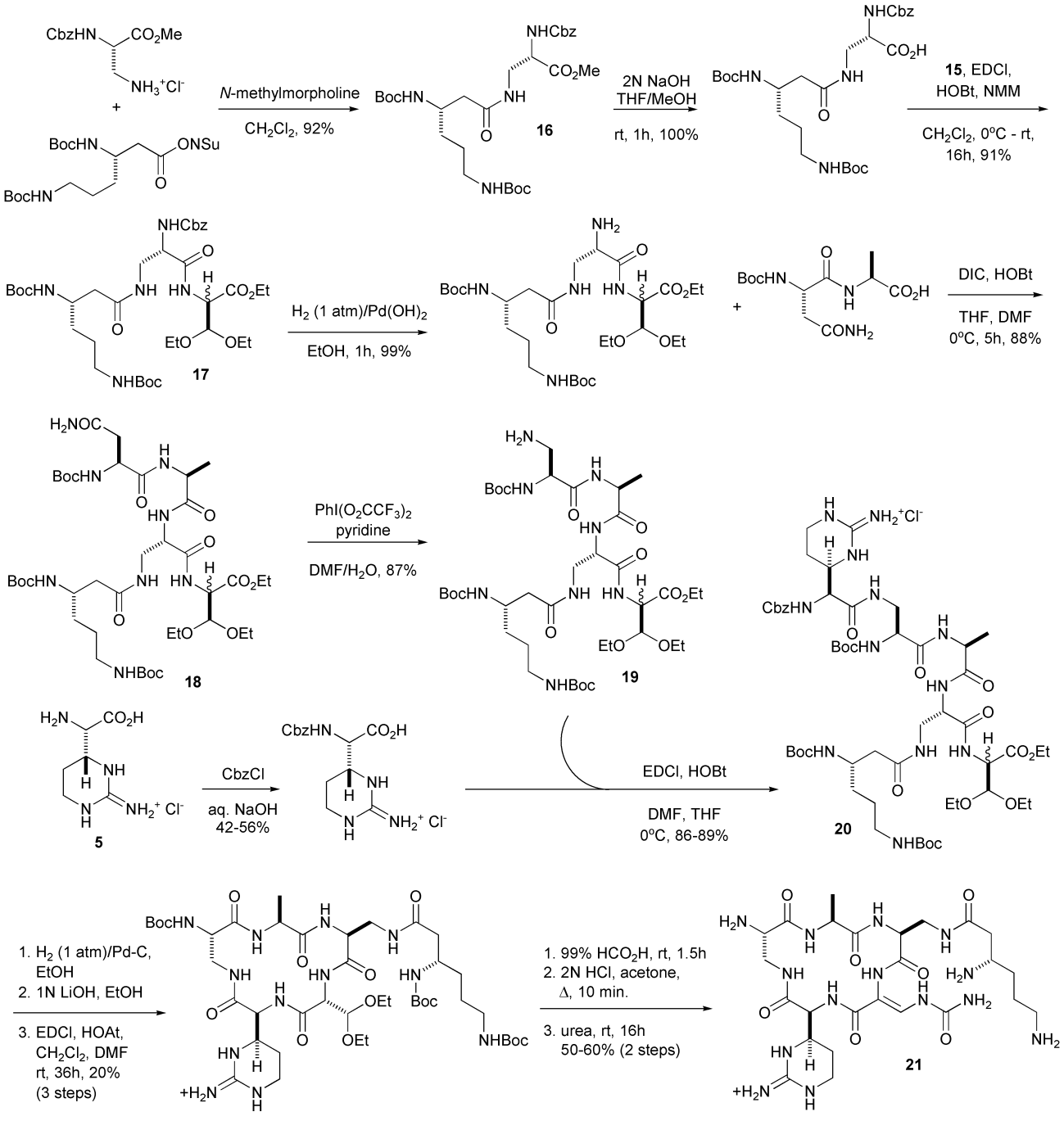



**Scheme 3**

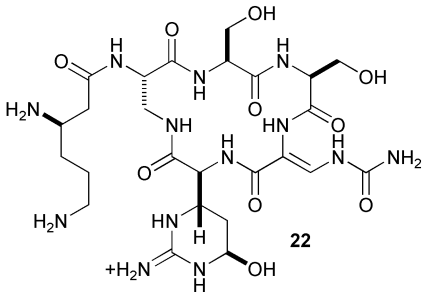
$A_3$ inhibited the incorporation of *N*-acetylglucosamine into peptidoglycan of *S. aureus* whole cells, as well as the formation of lipid intermediates and the formation of nascent peptidoglycan, indicating that the antibacterial activity of plusbacin $A_3$ is due to blocking of transglycosylation of cell wall peptidoglycan synthesis and its foregoing steps, *via* a mechanism differing from that of vancomycin.[185]

New lydicamycin derivatives, named TPU-0037-A to -D (**38**–**41**), have been isolated from *Streptomyces platensis*.[186] Compounds **38**–**41** inhibited the growth of Gram-positive bacteria only, TPU-0037 C (**40**) being the most active.

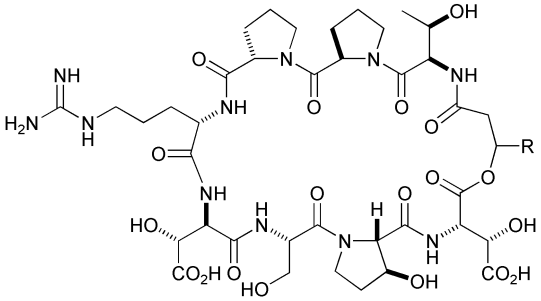
Asterobactin (**42**) was isolated as a new siderophore from *Nocardia asteroides*, and presented two nitrogen-oxidized amino acids, $N^5$-hydroxy-$N^5$-formylornithine and $N^5$-hydroxyarginine-$N^1$-hydroxyamide.[187] Seminal to structure determination was the analysis of the fragmentation patterns of **42** by ESI-CID-MS and ESI-CID-MS$^n$, confirming the positions of the oxidized nitrogens. The siderophore role of asterobactin was suggested by the formation of a brown colored complex with $Fe^{3+}$ in MeOH,




**Scheme 4**



**22**

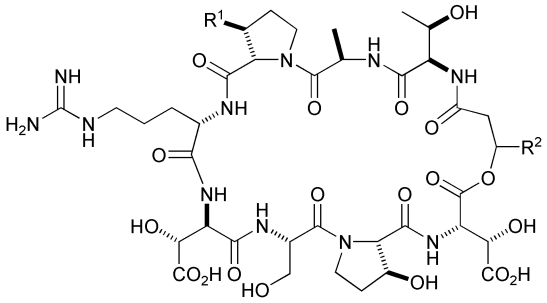


**23**: R = $(CH_2)_7CH(CH_3)CH_3$
**24**: R = $(CH_2)_8CH(CH_3)CH_3$
**25**: R = $(CH_2)_9CH(CH_3)CH_3$
**26**: R = $(CH_2)_{10}CH(CH_3)CH_3$
**27**: R = $(CH_2)_{11}CH(CH_3)CH_3$
**28**: R = $(CH_2)_5CH(CH_3)CH_3$

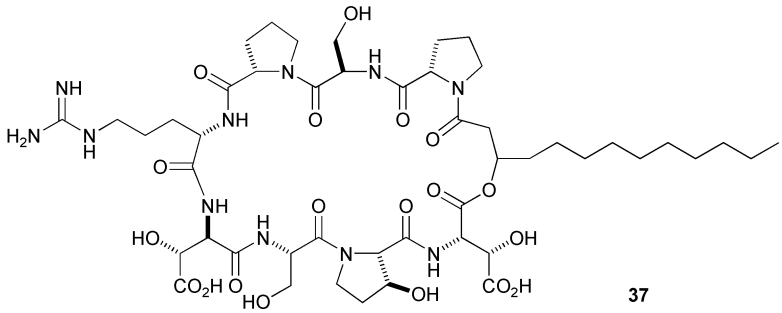
and by the decrease of cytotoxic activity against five cancer cell lines also in the presence of $Fe^{3+}$.

A whole collection of unusual, modified peptide derivatives named muraymycins A1–A5 (**43–47**), B1–B7 (**48–54**), C1–C4 (**55–58**) and D1–D3 (**59–61**), have been isolated from a *Streptomyces* strain.[188] Muraymycins A5 (**47**) and C4 (**58**) appeared to be artifacts of isolation. All compounds were identified by analysis of spectroscopic data, including Fourier transform ion-cyclotron-resonance MS analysis which enabled the detection of double and triply charged molecular ions.[189] The hexahydro-2-imino-4-pyrimidylglycyl moiety in muraymycins corresponds to L-epicapreomycidine found in chymostatins[190,191] and elastatinal.[192,193] Muraymycin A1 (**43**) was the most bioactive member of this class, and displayed antibiotic activity against *Staphylococcal*, *Enterococcal* and Gram-negative bacterial strains, as well as potent antibiotic activity against *Escherichia coli* imp mutant (MIC $<0.03$ μg $mL^{-1}$) and in *S. aureus* infected mice ($ED_{50}$ 1.1 mg $kg^{-1}$). Muraymycin derivatives bearing a primary guanidine or hydroxyguanidine groups were the most active members. Muraymycins inhibited the transfer and attachment of *E. coli p*-MurNAc-pentapeptide to the lipid transfer. Moreover, some of the muraymycins inhibited *E. coli* lipid II formation and peptidoglycan synthesis at 0.027 μg $mL^{-1}$. Several muraymycin derivatives have been synthesized and their inhibition of peptidoglycan biosynthesis has been evaluated.[194]

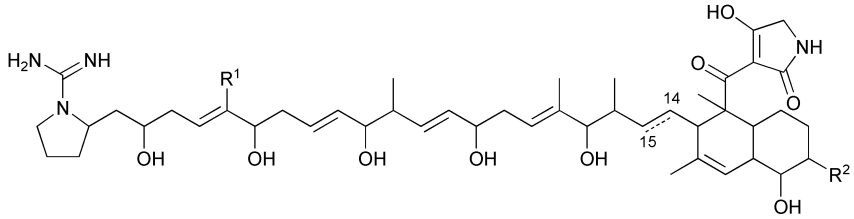
During a survey for new antibiotics, five new glycopeptides have been isolated from *Streptomyces hygroscopicus* LL-AC98.[195] Mannopeptimycins α–ε (**62–66**) presented a new guanidine-containing amino acid, α-amino-β-[4′-(2′-iminoimidazolidinyl)]-β-hydroxypropionic acid, which conferred basicity to the peptide moiety.[195] The structures of all glycopeptides were established by analysis of spectroscopic data, as well as by chemical degradation of the sugar moiety of mannopeptimycin β (**63**) and spectroscopic analysis of the corresponding cyclic peptide aglycone. The absolute stereochemistries of common amino acids were established by Marfey's analysis. The stereochemistry of the α-amino-β-[4′-(2′-iminoimidazolidinyl)]-β-hydroxypropionic acid residue was established by a recently reported *J*-configuration analysis method.[196] Mannopeptimycin ε (**66**) was the most active against seven different strains of methycillin-susceptible and methicillin resistant *S. aureus*, *S. hemolyticus*, *E. faecalis*, vancomycin-susceptible and



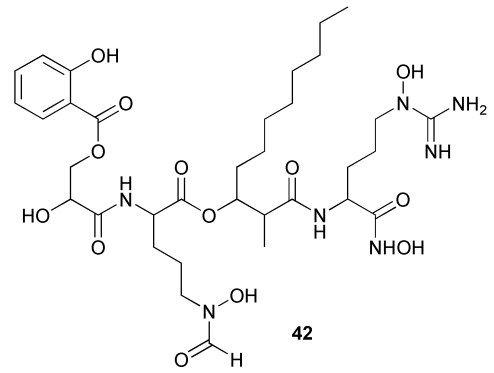
**29**: $R^1$= OH, $R^2$ = $(CH_2)_{10}CH_3$
**30**: $R^1$= OH, R = $(CH_2)_9CH(CH_3)CH_3$
**31**: $R^1$= OH, R = $(CH_2)_{10}CH(CH_3)CH_3$
**32**: $R^1$= OH, R = $(CH_2)_{12}CH_3$
**33**: $R^1$= H, R = $(CH_2)_{10}CH_3$
**34**: $R^1$= H, R = $(CH_2)_9CH(CH_3)CH_3$
**35**: $R^1$= H, R = $(CH_2)_{10}CH(CH_3)CH_3$
**36**: $R^1$= H, R = $(CH_2)_{12}CH_3$



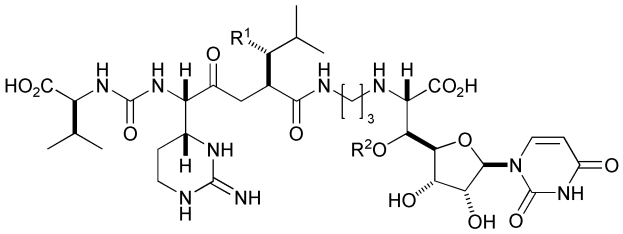
**37**

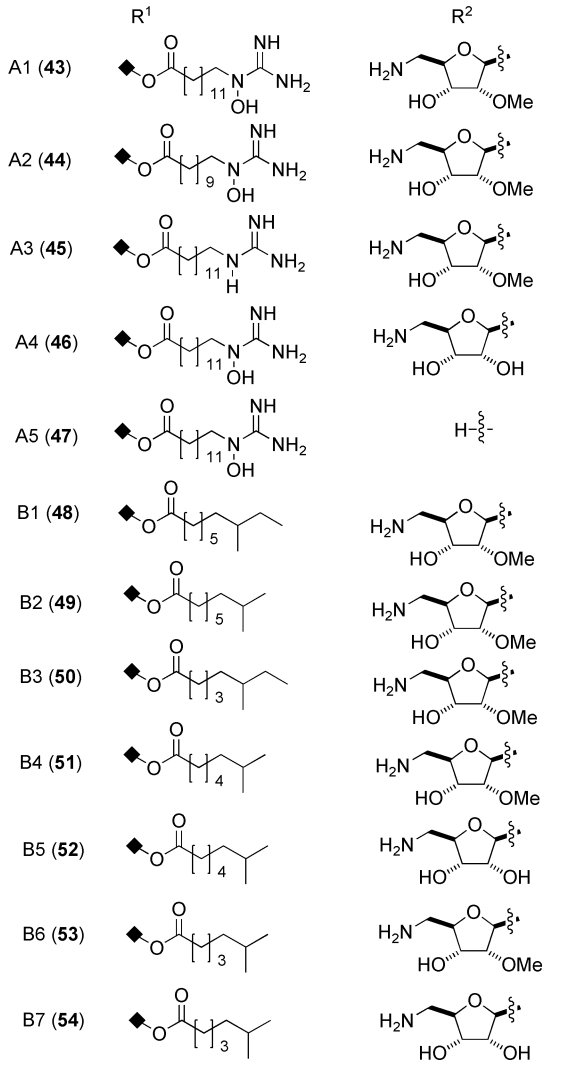


**38**: $R^1$ = H, $R^2$ = OH
**39**: $R^1$ = Me, $R^2$ = H
**40**: $R^1$ = $R^2$ = H $\Delta^{14,15}$
**41**: $R^1$ = Me, $R^2$ = H

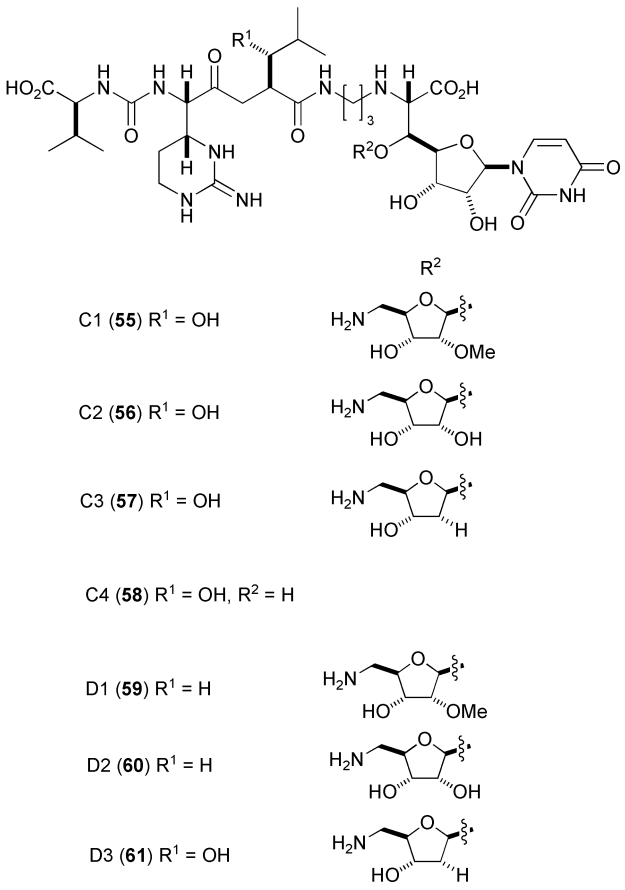


**42**






vancomycin resistant *E. faecium*, *E. coli*, *Bacillus subtilis* and *Micrococcus luteus*, indicating the importance of the presence and of the position of the isovaleryl group in the terminal mannose residue for biological activity.[195] Several derivatives of mannopeptimycins have been synthesized in order to explore and enhance their antibiotic activity.[197–199]

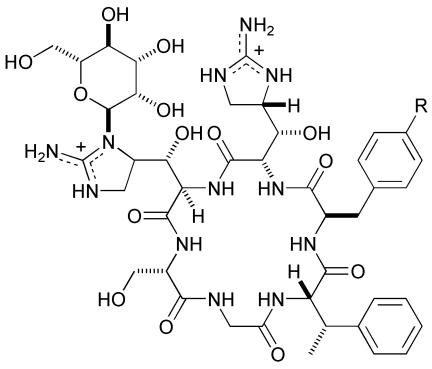


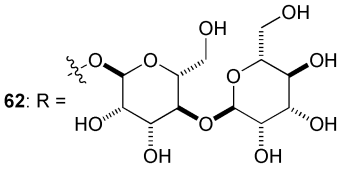

## 3 Natural guanidines from marine and freshwater microorganisms

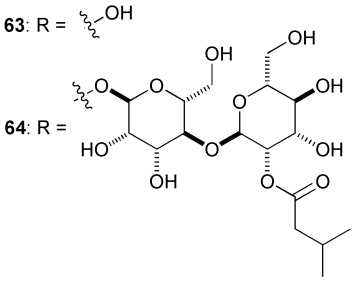
A review on the "Distribution and Origin of Tetrodotoxin" discussed the etiological sources of tetrodotoxin (TTX) and several of its derivatives.[200] Another review on "The Chemistry of Puffer Fish Toxin" discussed the natural occurrence of TTX and its derivatives as well as spectroscopic and chemical methods for the identification of these guanidine alkaloids, including tables with $^{1}H$ and $^{13}C$ NMR data.[201] A very interesting and thoughtful review discussed the origin of tetrodotoxin and its derivatives, considering different possible explanations for the wide distribution of these toxins in animals belonging to phylogenetically unrelated taxa, in terms of a bacterial origin and/or evolutionary convergence.[202] A recent example that gives further support to a bacterial origin for tetrodotoxin was the isolation of TTX from a bacterium taxonomically related to *Pseudoalteromonas haloplanktis tetraodonis*, deadly to the sea urchin *Meoma ventricosa*.[203] The rare 11-oxotetrodotoxin derivative (**67**) has been found in the tissues of the Brazilian frog *Brachycephalus ephippium*[204] and in the North-American newt *Notophthalmus viridescens*.[205]

A major achievement during the 2002–2004 period was the completion of asymmetric total syntheses of tetrodotoxin (**68**) as well as of 11-deoxytetrodotoxin (**69**)[206] and 8,11-dideoxytetrodotoxin (**70**),[207–209] unnatural derivatives of tetrodotoxin. The two asymmetric syntheses of tetrodotoxin (**68**),[210–212] were achieved practically forty years after the report of its structure determination,[213–220] and almost one hundred years after the first reports on tetrodotoxin isolation.[221] Interestingly, in 1913, Tahara obtained a patent for the application of TTX "in the treatment of leprosy and other diseases",[222] in spite of its potent toxicity.

The total asymmetric synthesis of TTX developed by Isobe (Schemes 5 and 6)[210,211] started by the interconversion of the diol **71** to the unstable enol ether **72**, which was directly converted to the dihydroxyacetone **73** as the major product of a 7 : 1

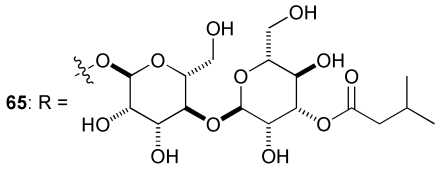


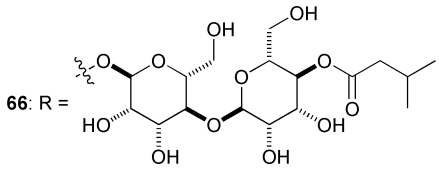


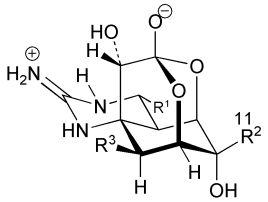









**67** $R^1$=OH, $R^2$ = $CH(OH)_2$, $R^3$ = OH
**68** $R^1$=OH, $R^2$ = $CH_2OH$, $R^3$ = OH
**69** $R^1$=OH, $R^2$ = $CH_3$, $R^3$ = OH
**70** $R^1$=OH, $R^2$ = $CH_3$, $R^3$ = H

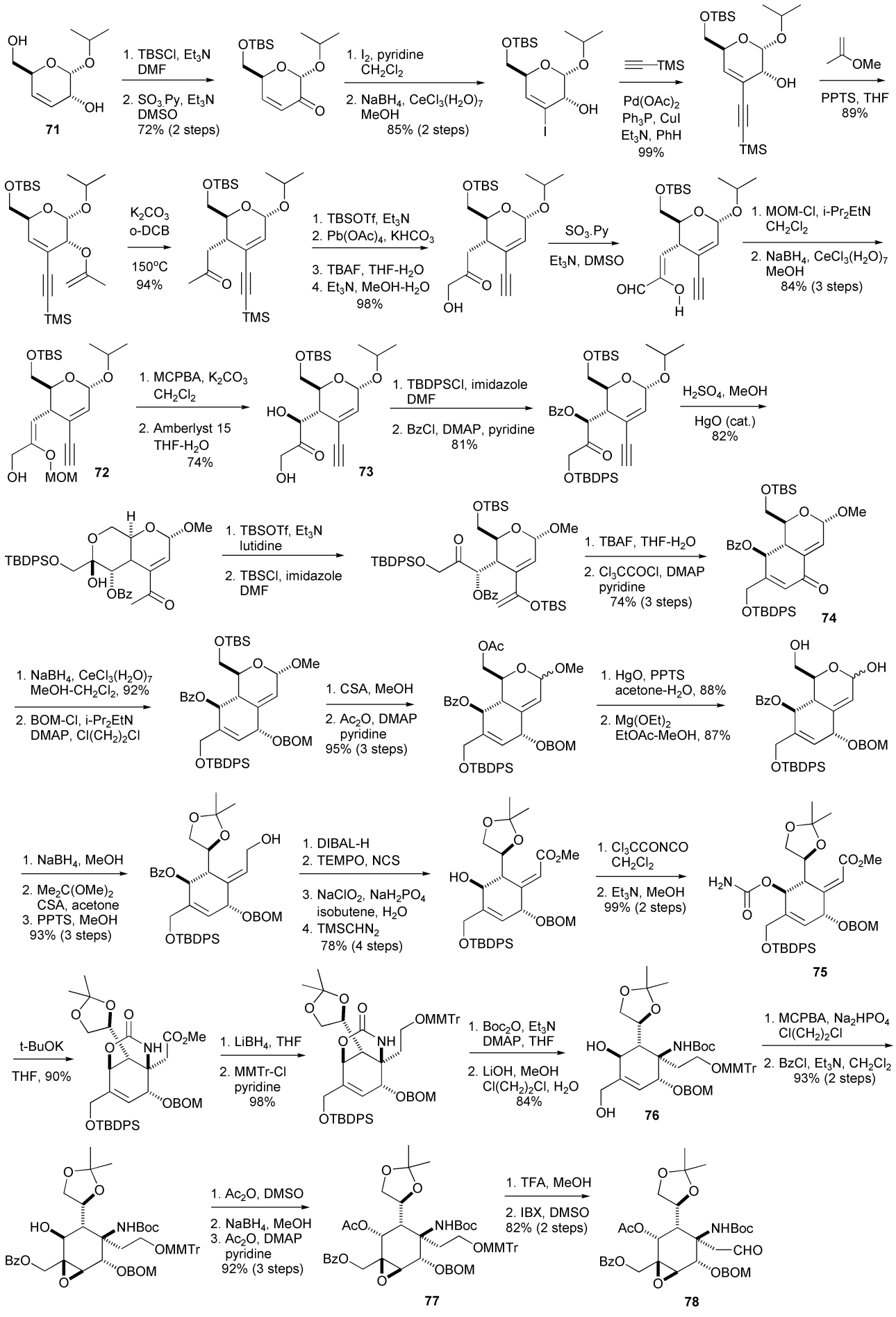
mixture of diastereomers. Further stepwise interconversions yielded the enone **74**, with a confirmed stereochemistry at the benzoyl protected oxymethine carbon. Further stepwise interconversions gave the carbamate **75** which was subjected to a conjugate addition. The product **76** obtained after ester reduction, carbamate cleavage and *tert*-butyldiphenylsilyl alkaline hydrolysis had the required nitrogen functionality for the introduction of the guanidine group. Epoxidation and benzoate protection of **76** were followed by inversion of configuration of the secondary alcohol functionality *via* Albright–Goldman oxidation ($Ac_2O$ and DMSO), reduction and acetylation to give **77**. After generation of the aldehyde **78**, the cyclic vinyl ether **79** was obtained by heating **78** in an alkaline medium *via* the respective enolate with the required conformation to give the *Z* stereoisomer under stereoelectronic control. After oxidation to the corresponding α-ketolactone, reduction and formation of the hemilactal functionality, followed by protecting group exchange, the guanidine group was introduced to give **80**. Cyclization of the guanidine group followed by guanidine deprotection, formation of methyl aminal and peracetylation furnished the direct precursor of 4-methoxytetrodotoxin (**81**) and 4,9-anhydro-4-epitetrodotoxin (**82**), obtained after cleavage of all, but the methoxy, protecting groups. Finally, treatment of **81** with deuterated trifluoroacetic acid in deuterium oxide yielded tetrodotoxin (**68**) in 65% yield as well as **82** (15%). Treatment of **82** under the same conditions also gave **68** in 63% yield after purification. The overall yield was 0.3%, in 65 reaction steps from **71**.[210] This synthesis was later improved.[211]

The elegant Du Bois' synthesis of (−)-tetrodotoxin (−)-(**68**) (Scheme 7)[212] started from the amide **83** previously synthesized from D-isoascorbic acid in four steps. The lactone **84** was obtained in two steps with more than 90% stereoselectivity. After conversion to the diazoketone **85**, the cyclohexanone **86** was stereospecifically obtained under Rh-catalyzed carbene insertion conditions. Reduction of cyclohexanone yielded the corresponding (*S*)-alcohol as a single stereoisomer, which was subsequently transformed into the dimethylamide **87**. After allylic oxidation and 1,4-addition of allyl cuprate, the intermediate **88** obtained had the full tetrodotoxin carbon skeleton with the required stereochemistry. After amide lactonization, replacement of the pivaloyl group by a carbamate, ozonolysis, reduction and chlorination through the mesylate, followed by carbamate cyclization *via* a stereospecific nitrene insertion yielded the suitable oxazolidinone **89**. Subsequent stepwise interconversions, which included dehydrohalogenation, *N*-protection and carbamoyl removal, followed by synthesis of the protected guanidine, double bond ozonolysis and protecting group removal, provided (−)-tetrodotoxin (−)-(**68**) in 28 reaction steps from **83** and in 1.3% overall yield.

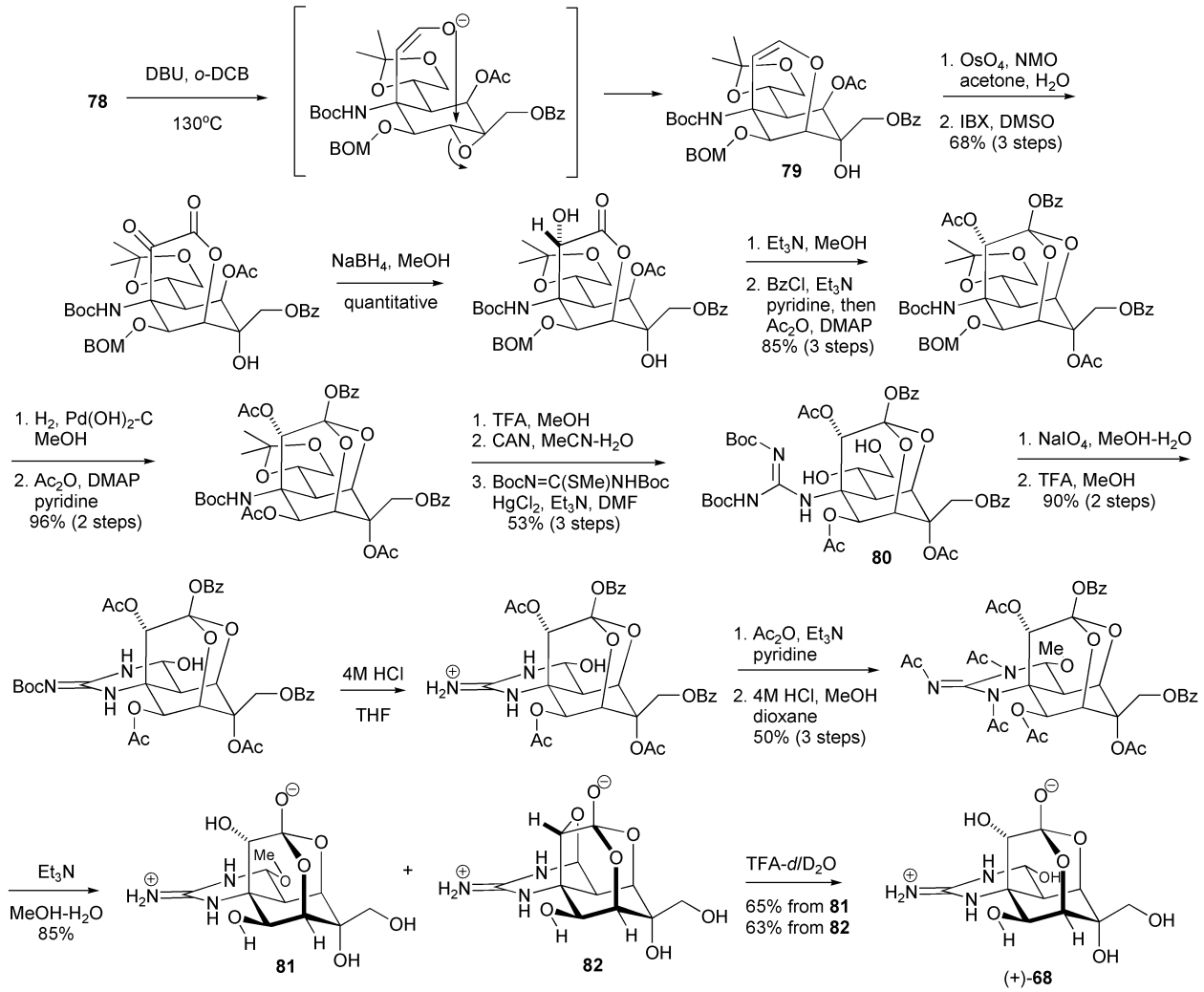
Three new saxitoxin analogues, GC1–GC3 (**90–92**), have been isolated from the dinoflagellate *Gymnodinium catenatum*.[223] A sulfotransferase enzyme specific to N-21 of saxitoxin (**93**) and of gonyautoxins 2 (**94**) and 3 (**95**) has been isolated from *G. catenatum*.[224] The enzyme does not promote the sulfation of saxitoxin analogues such as neosaxitoxin and gonyautoxins 1–4, and required only 3′-phosphoadenosine 5′-phosphonosulfate as a sulfate source.

Reviews on cyanobacterial peptides having arginine or modified arginine residues, as well as other guanidine-bearing secondary metabolites, include "Serine proteases inhibiting cyanopeptides",[225] "New structural insights into the inhibition of serine proteases by cyclic peptides from bacteria",[226] and the excellent "Production of secondary metabolites by freshwater cyanobacteria".[227] The genes encoding the biosynthesis of different cyanobacteria peptides have been sequenced and characterized,[223–237] including genes encoding the degradation of toxic peptides.[237,238] Additionally, phylogenetic analysis of microcystin- and nodularin-producing cyanobacteria indicated coevolution of housekeeping genes and microcystin synthetase genes and strongly suggested that gene transfer was not involved in the biosynthesis of modified peptides by cyanobacteria. It is also postulated that genes encoding nodularin synthetase are recently derived from those encoding microcystin synthetase.[239]

The chemical diversity of *Microcystis*[240] and of *Planktothrix*[241] cyanobacteria has been accessed by single-colony MALDI-TOF mass spectrometry analysis, indicating many new cyanobacterial strains, most of them producers of modified peptide toxins, including compounds not yet identified. Since the majority of cyanobacterial strains produce a variety of modified peptides, it seems that simultaneous biosynthesis of different toxins enhances the adaptive fitness of cyanobacteria, even considering that the exact ecological role of such compounds has not yet been established.




**Scheme 5**




**Scheme 6**

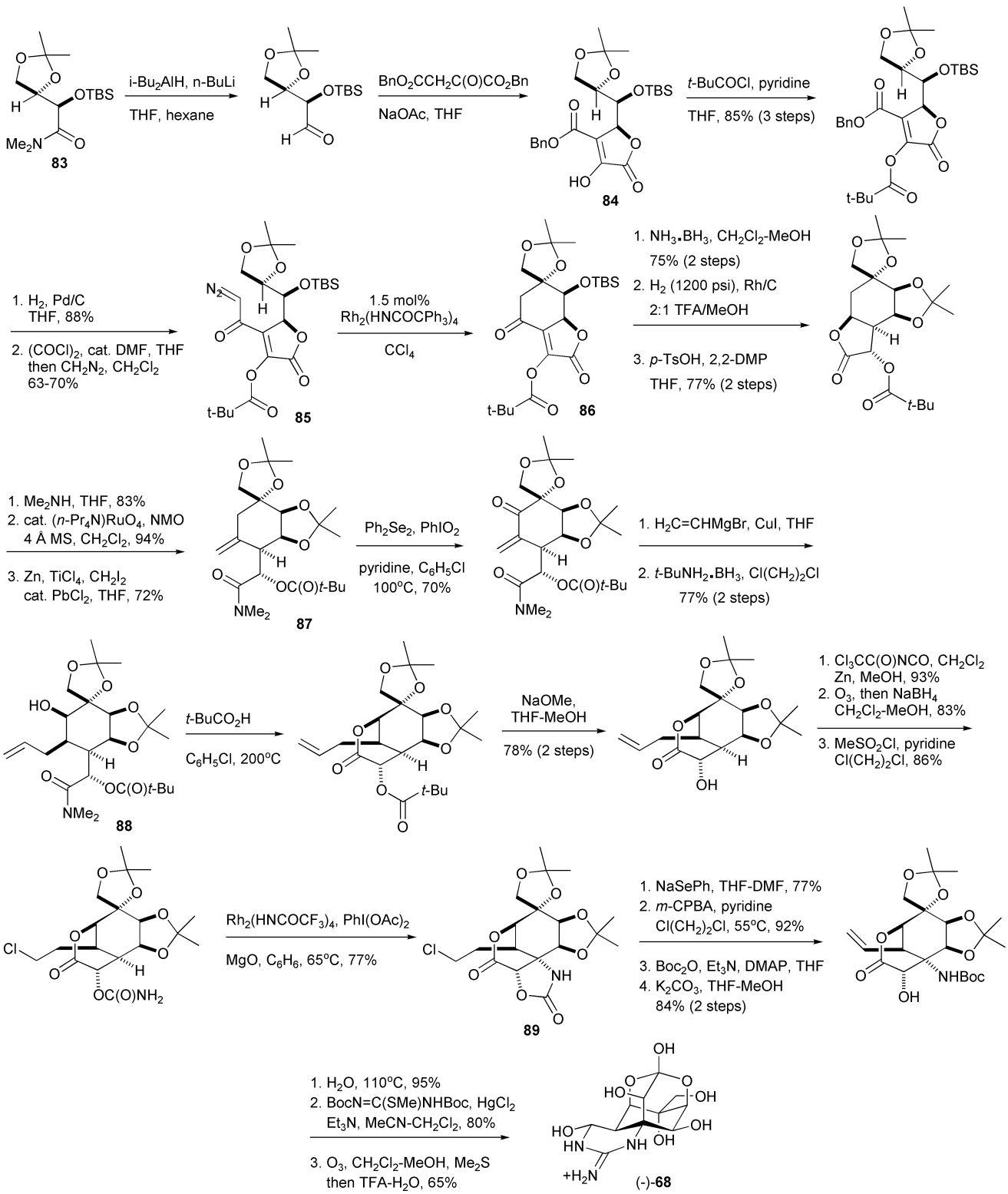
Aeruginoguanidines 98-A (**96**), 98-B (**97**) and 98-C (**98**) constitute a completely new class of cyanobacterial toxins isolated from *Microcystis aeruginosa* (NIES-98).[242] The absolute configuration of the $N^{\alpha}$-methyl-$N^{\omega}$-prenyl-arginine moiety of **96** was established by NMR analysis after hydrolysis of the hydrogenated natural product and derivatization with (*R*)- and (*S*)-phenylglycine methyl ester, while the absolute configuration of the (1-(4-hydroxy-3-hydroxymethyl)-phenyl-1-hydroxy-2-propylamine moiety of **96** was established by NMR analysis of the corresponding Boc-phenylglycine derivative. The absolute configurations of both **97** and **98** were established by comparison of spectroscopic data with **96**. Aeruginoguanidines 98–A to 98–C displayed moderate cytotoxic activity against P388 leukemia cells ($IC_{50}$ of 26, 27 and 50 μg $mL^{-1}$, respectively).

Two new micropeptins have been isolated from *Microcystis aeruginosa* strains IL-217 and IL-231.[243] The stereochemistry of the 3-amino-6-hydroxy-2-piperidone residue of both **99** and **100** was established by HPLC analysis of L-glutamic acid obtained after Jones oxidation, hydrolysis and derivatization. Micropeptins EI922 and EI964 inhibited trypsin, but not chymotrypsin, with $IC_{50}$ of 3.8 and 4.2 μg $mL^{-1}$, respectively.

Seco[D-$Asp^3$]microcystin-RR (**101**) and [D-$Asp^3$, D-$Glu(OMe)^6$]microcystin-RR (**102**) have been isolated from *Planktothrix rubescens* collected in Lake Bled, Slovenia.[244] The structures of both compounds were established by extensive analysis of spectroscopic data, including MALDI-TOF, Marfey's amino acid analysis and HPLC analysis of the (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda) moiety by comparison with an authentic sample. Compound **101** inhibited recombinant protein phosphatase 1 with an $IC_{50}$ of 0.8 μM.

Microcin SF608 (**103**) from *M. aeruginosa*[245] was synthesized from the methyl ester of *N*-Boc-L-(2*S*,3a*S*,6*R*,7a*S*)-6-hydroxyoctahydroindole-2-carboxylic acid (**104**) [*N*-Boc-L-Choi(OMe)] (Scheme 8),[246] obtained from *O*-methyl-L-tyrosine in six steps, by sequential coupling reactions, firstly with protected phenylalanine, then with diprotected (*S*)-hydroxyphenyl-lactic acid (**105**), and finally with protected agmatine. The diprotected form of (*S*)-hydroxyphenyl-lactic acid was obtained from *O*-benzyl-L-tyrosine, and its absolute configuration was confirmed after conversion into the deprotected form and NMR analysis of the corresponding methoxyphenylacetic acid (MPA) derivative. It is worth noting that the synthesis of the dipeptide **106** yielded both free alcohol and the corresponding trifluoroacetate, which did not interfere in the following reaction steps. The authors observed that the synthetic intermediates of microcin SF608 synthesis presented two rotamers around the Choi-phenylalanine amide bond in $CDCl_3$ and in DMSO-$d_6$. Additionally, the authors also verified chemical shift variations of both H-2 and H-7a within the Choi residue, depending on its absolute configuration.

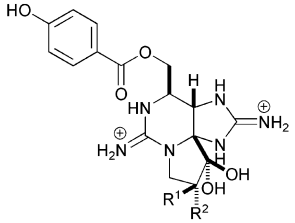
The oscillarin structure **108**[247] was revised to **107** after completion of its total synthesis (Scheme 9),[248] starting from C-4 alkylation of dimethyl *N*-Boc-L-glutamate and subsequent transformation into the hemiaminal acetate **109** before cyclization with tin tetrabromide. The 6-bromo-octahydroindole derivative **110** was converted to the methyl ester of the *N*-Boc protected (2*S*,3a*S*,6*R*-hydroxy,7a*S*)-octahydroindole-2-carboxylic acid (L-Choi) unit before condensation with D-phenyllactyl-D-phenylalanine dipeptide. The structure and stereochemistry of the product were confirmed by X-ray diffraction analysis. The final synthesis steps included ester cleavage,



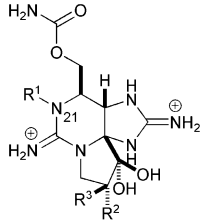

**Scheme 7**

condensation with a suitable Boc-diprotected aminoguanidine previously synthesized by the same authors,[249] and protecting group removal, to give **107**, whose structure and biological activities matched with those reported for the natural product.[247] The authors also synthesized the compound corresponding to the original structure proposed for oscillarin **108**, in order the confirm the structure revision.

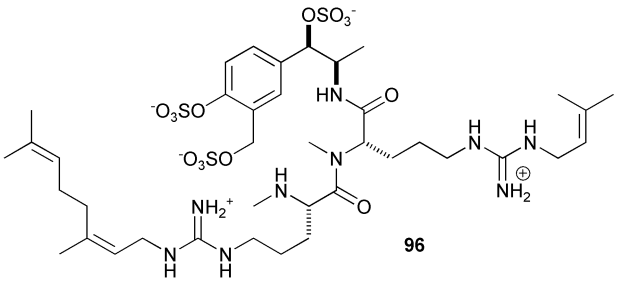
The gene encoding the amidinotransferase implied in the biosynthesis of cylindrospermopsin (**111**) has been sequenced and characterized.[250] The total syntheses of both cylindrospermopsin (**111**)[251] and 7-epicyclindrospermopsin (**112**)[252] continue



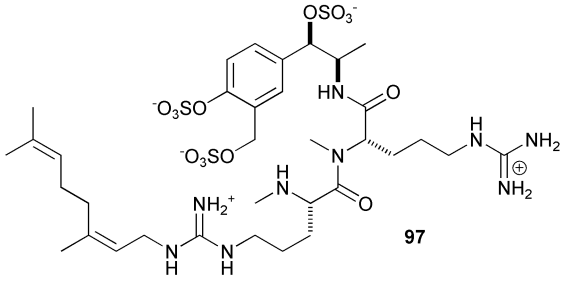
**90** $R^1$ = H, $R^2$ = $OSO_3^-$
**91** $R^1$ = $OSO_3^-$, $R^2$ = H
**92** $R^1$ = $R^2$ = H



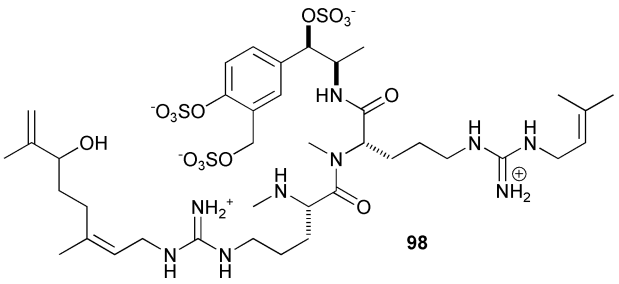
**93** $R^1$ = $R^2$ = $R^3$ = H
**94** $R^1$ = $R^2$ = H, $R^3$ = $OSO_3^-$
**95** $R^1$ = $R^3$ = H, $R^2$ = $OSO_3^-$



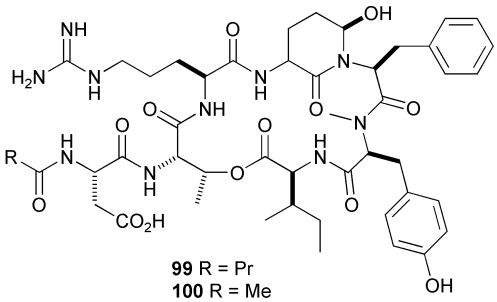
**96**



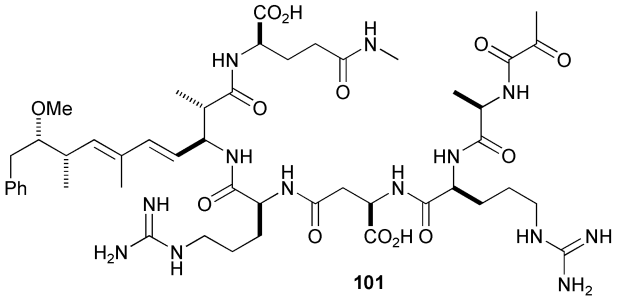
**97**



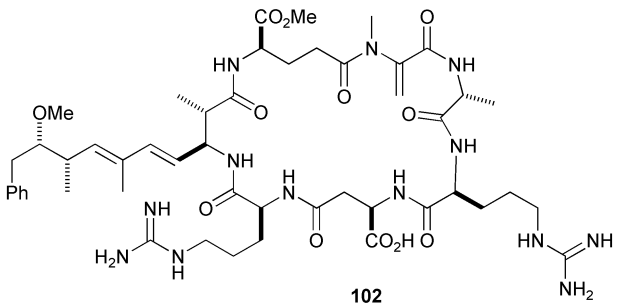
**98**



**99** R = Pr
**100** R = Me



**101**



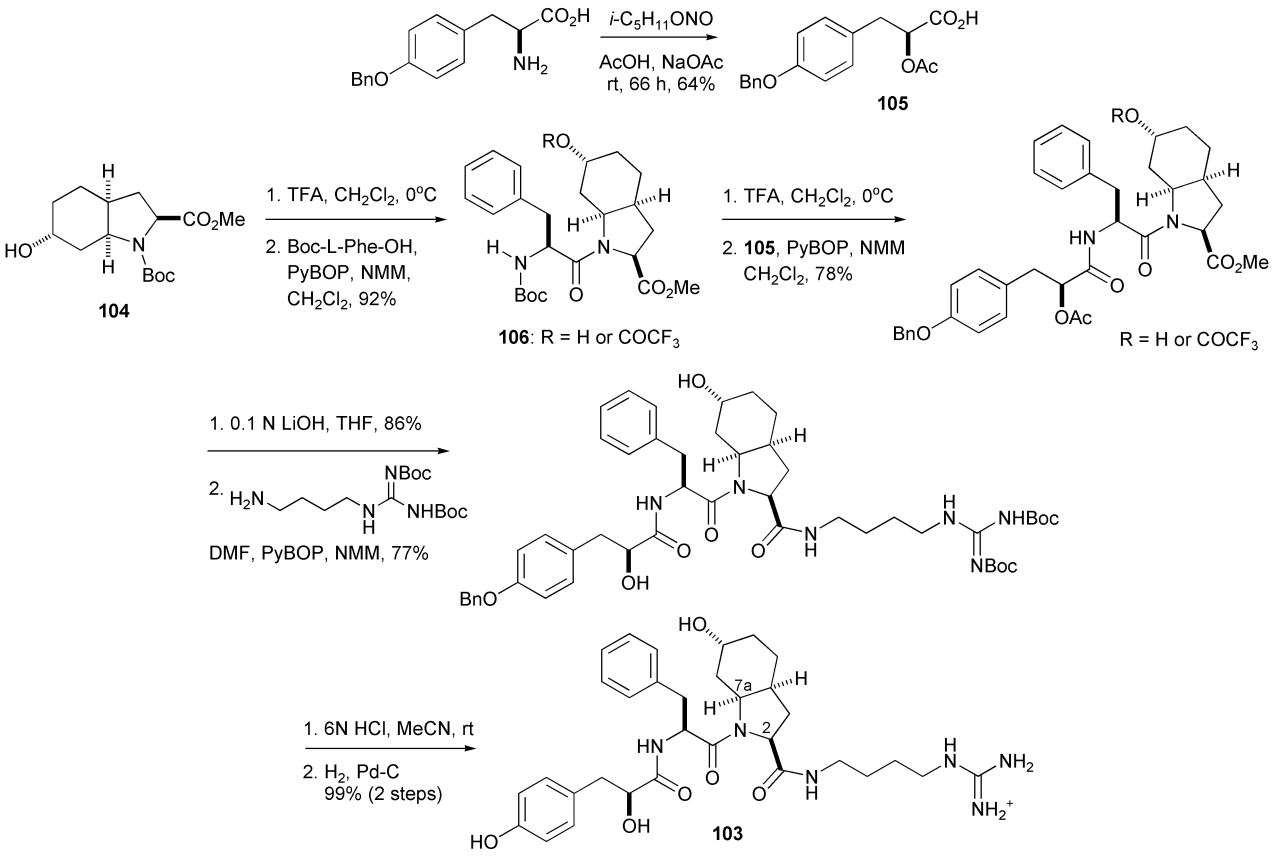
**102**

to be of interest. While Snider reviewed his own synthetic approach,[253] three other groups achieved the synthesis of either **111** or **112**.

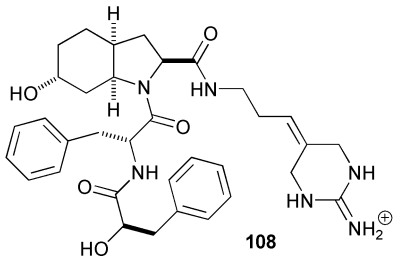
Weinreb's group developed a total synthesis of cylindrospermopsin **112** starting from 4-methoxypyridine (Scheme 10).[254,255] After *N*-protection, formation of the piperidin-4-one **113** was achieved by a series of alkylation reactions with good stereoselectivity. The following reaction sequence included ketone reduction, alcohol protection and subsequent silane oxidation to give the bicyclic carbamate **114**. After hydroboration of the double bond and Swern oxidation, the corresponding aldehyde was condensed with an α,β-unsaturated ester phosphonate **115** to give the (*E*,*E*)-diene ester **116**. A subsequent four step reaction sequence yielded the intermediate **117**. A second carbamate introduction was followed by an intramolecular hetero Diels–Alder reaction which led to the tricyclic intermediate **118** as a single stereoisomer. After *p*-methoxybenzyl protecting group removal, the dihydrothiazine group was cleaved in order to give the suitable protected allylic alcohol **119**. A subsequent five step reaction sequence yielded an α,β-unsaturated methyl ester which was converted into the hydroxylamine **120** and subsequently into the *N*-hydroxydihydrouracyl **121**. After nitrogen protection and acetonide hydrolysis, the configuration of the secondary alcohol was inverted, followed by benzyl protecting group removal and selective azide introduction. Acetylation of the diol before activation of the urea carbonyl by a triflate methyl ester was necessary to improve the substrate solubility in $CH_2Cl_2$. The cyclic guanidine was formed after azide reduction. Removal of protecting groups yielded C-12 desulfated cylindrospermopsin, which was converted to the natural product in 70% yield and 25% of the disulfated derivative was obtained.

White and Hansen's convergent synthesis of 7-epicylindrospermopsin (Schemes 11–13)[256] started with the synthesis of the hydroxylamine **122** from *p*-bromobenzyloxyacetaldehyde *via* asymmetric crotylation, and of pyrimidine aldehyde **124** from the (*R*)-methionine derivative **123** *via* a stepwise reaction sequence to obtain the suitable aldehyde under Ley's oxidation [tetra-*n*-propylammonium perruthenate(VII)/4-methylmorpholine *N*-oxide]. Condensation between **122** and **124** gave a *Z*-nitrone, which was subjected to an intramolecular 1,3-dipolar cycloaddition, reduction and Boc-protecting group removal to give the piperidine **125** with five of six 7-epicylindrospermopsin stereocenters. Synthesis of the urea derivative **126** was followed by inversion of the configuration of the secondary alcohol *via* oxidation and reduction, and removal of the *p*-bromobenzoyl protecting group to yield a crystalline diol urea **127**, whose stereochemistry was confirmed by X-ray diffraction analysis. The subsequent synthetic steps included the introduction of the remaining nitrogen *via* the azide **128**, activation of the urea group before the formation of the guanidine, removal of protecting groups and sulfation to give (−)-7-epicylindrospermopsin.

Looper and Williams' concise synthesis of 7-epicylindrospermopsin (Scheme 14)[257] involved the preparation of tricyclic isoxazolidine **130** from the oxazinone **129** *via* a 1,3-dipolar cycloaddition. Reduction of the lactone was followed by preparation of the urea functionality by reductive amination, N–O cleavage and carbonation. The subsequent steps were aimed at preparing the substrate for condensation with a suitably protected pyrimidine, and included conversion of the primary alcohol to a nitroethyl group *via* oxidation and Henry nitroaldol condensation, while the secondary alcohol group was protected and the urea activated for further transformation into the guanidine. Intermediate **131** was condensed to a modified protected pyrimidine and simultaneously reduced at the nitro group to form the tricyclic guanidine moiety. A second nitroaldol condensation appeared to be reversible, and the reaction provided two major stereoisomers which could only be separated after pyrimidine deprotection. Natural 7-epicylindrospermopsin (**112**) was obtained in a 2 : 1 ratio along with the bis-sulfate derivative after treatment of the major stereoisomer with a sulfur trioxide–pyrimidine complex.




**Scheme 8**




## 4 Natural guanidines from marine invertebrates

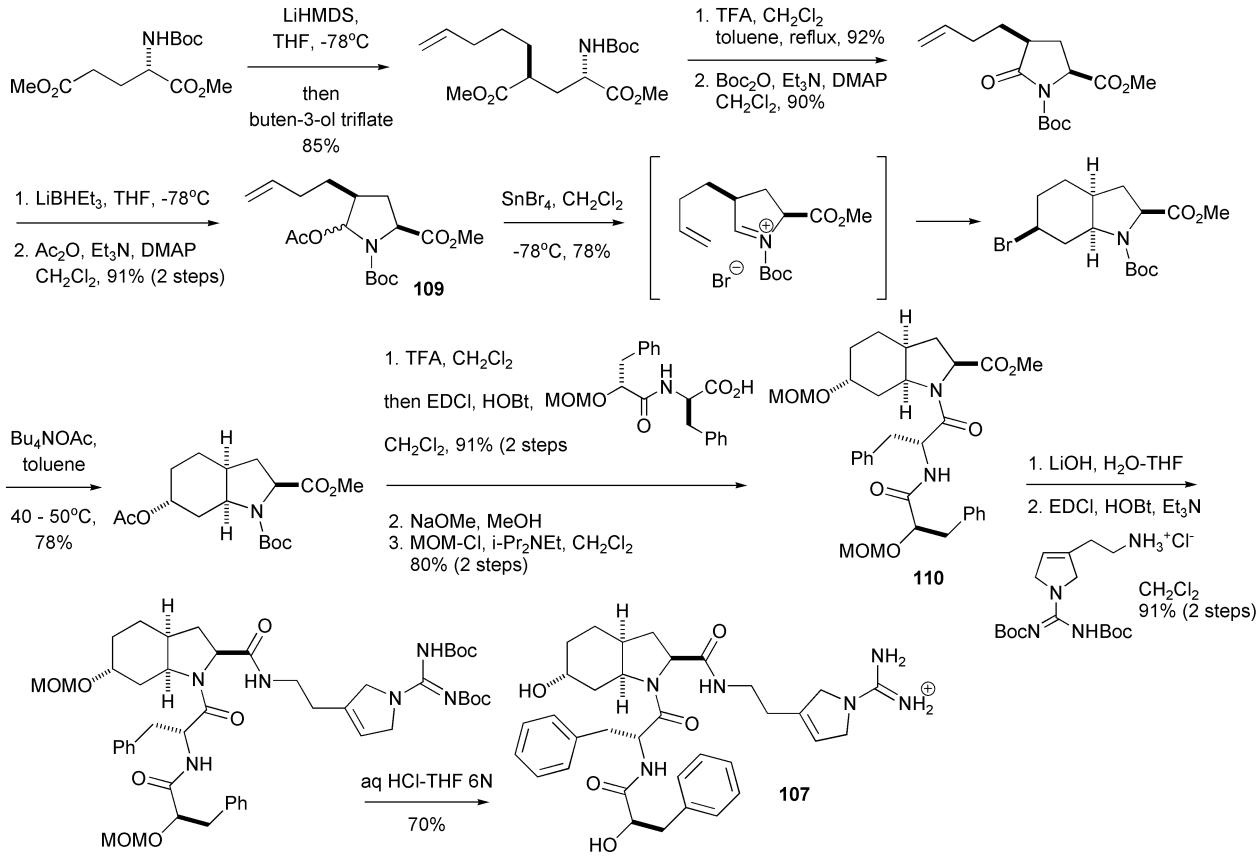
### 4.1 Marine sponges

Reviews on guanidine natural products isolated from marine sponges include overviews of the synthesis of polycyclic guanidine alkaloids, such as "Polycyclic guanidines—from nature's shaped cations to abiotic anion hosts",[258] "Synthesis of marine guanidine alkaloids and their application as chemical/biological tools",[259] "Synthesis of the pyrrole–imidazole alkaloids"[260] and "The tethered Biginelli condensation in natural product synthesis".[261]

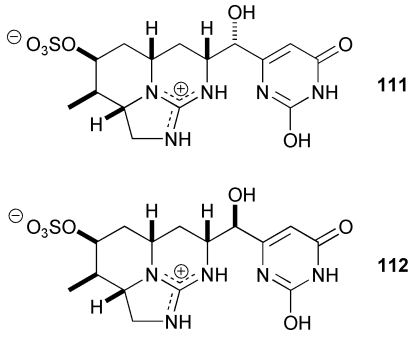
Marine sponges belonging to the genera *Leucetta* and *Clathrina* (class Calcarea) have yielded a variety of alkaloids containing imidazole and modified-imidazole units, which are frequently reduced to a guanidine unit. With the aim of investigating the occurrence of imidazole-bearing bioactive secondary metabolites, a survey on *Leucetta* sponges has been carried by Crews' group, resulting in the isolation of several new members of this structural class, including calcaridine A (**132**), (−)-spirocalcaridine A (**133**) and (−)-spirocalcaridine C (**134**) from an unidentified species of *Leucetta* sponge.[262] Establishing the structure of compound **133** was particularly challenging due to the number of sequential quaternary carbons. Compound **134** does not appear to be an artifact of isolation, since **133** did not react with MeOH even for long periods of time or if warmed to 40 °C. (−)-Spiroleucettadine (**135**) is another example of a guanidine alkaloid isolated from the same sponge.[263] The absolute configuration of (−)-spiroleucettadine was established by ORD-CD analysis and molecular modeling. Compound **135** displayed moderate antibiotic activity against *S. epidermitis* and *E. coli* (MIC of 200 μg $mL^{-1}$) and good activity against *Enterococcus durans* (MIC of <6.25 μg $mL^{-1}$). Leucettamine (**136**) is a further alkaloid belonging to this class isolated from *Leucetta* sp., which displayed only moderate antibacterial activity against *E. coli*, *S. aureus*, *B. subtilis* and *C. albicans*.[264]

Modified diketopiperazines are also frequently isolated from marine sponges. An early example is barettin, which was isolated from the sponge *Geodia baretti* several years ago,[265] with the incorrect structure **137** originally assigned, but was recently revised to **138** by analysis of spectroscopic data.[266] Subsequent fractionation of the *G. barretti* polar extract led to the isolation of barettin (**138**) as an 87 : 13 mixture of the *E* and *Z* isomers, and of dihydrobarettin (**139**) as inhibitors of the settlement of the barnacle *Balanus improvisus* cyprid larve, with $EC_{50}$ of 0.9 and 7.9 μM, respectively.[267] Under injury, the sponge *G. barretti* releases both **138** and **139** in seawater, suggesting that both diketopiperazine derivatives are antifoulant chemical defenses.

Several new guanidine-containing bromopyrrole alkaloids have been isolated from marine sponges. These include monobromoisophakellin (**140**) from *Agelas* sp., which displayed antifeedant activity toward the fish *Thalassoma bifasciatum*, and whose absolute configuration was assigned by CD analysis,[268] as well as (−)-7-*N*-methyldibromophakellin (**141**) and (−)-7-*N*-methylmonobromophakellin (**142**) isolated from *Agelas* sp.,[269] both of which presented the same absolute configuration, assigned by comparison of optical rotation values with literature data. Compound **141** was moderately active as a human lypoxygenase inhibitor. Massadine (**143**) was isolated




**Scheme 9**

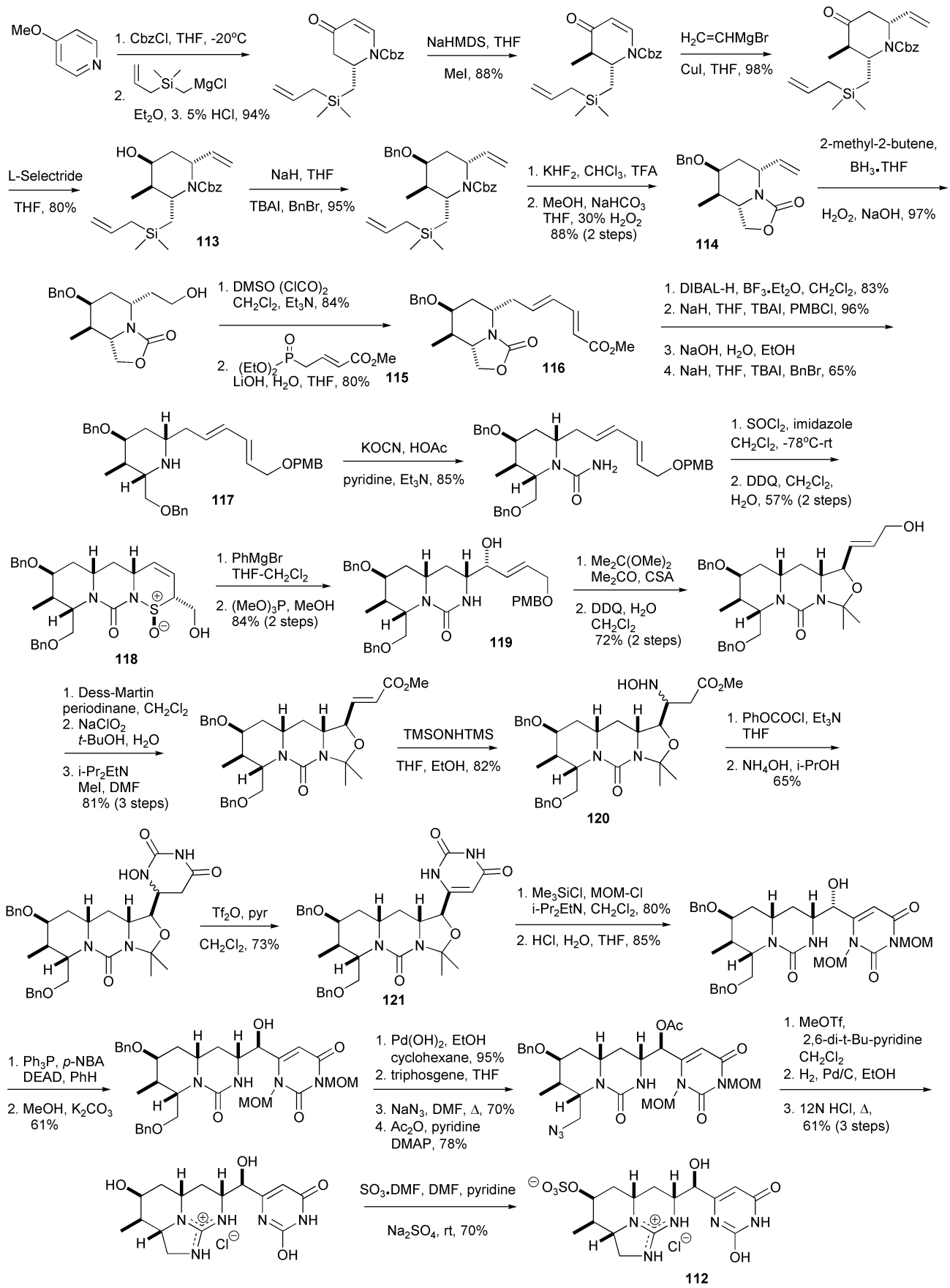



as a new geranylgeranyltransferase type I inhibitor from the sponge *Stylissa* aff. *massa*.[270] Massadine inhibited GGTAse from *Candida albicans* with an $IC_{50}$ of 3.9 μM and the growth of *Cryptococcus neoformans* with a MIC of 32 μM.

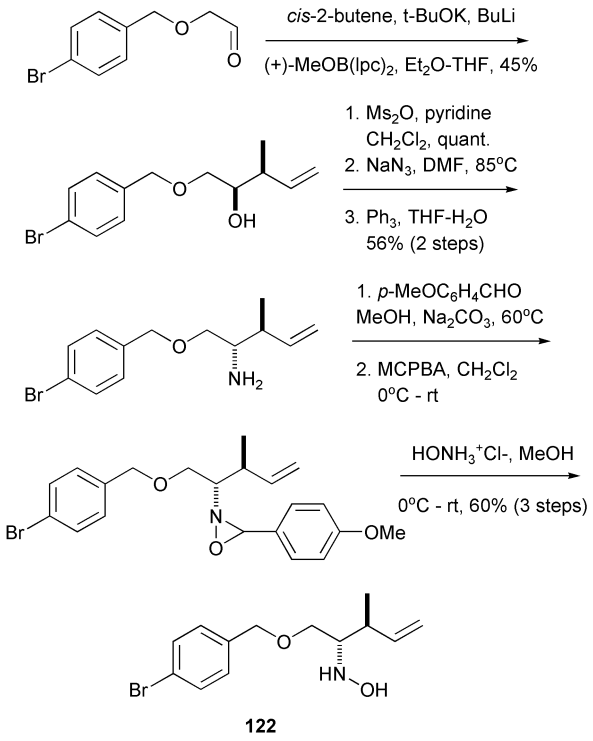
Ageladine A (**144**) has been isolated from *Agelas nakamurai*, and inhibited gelatinase A (MMP-2), a protein implied in tumor metathesis and angiogenesis.[271] The structure of ageladine A is proposed to be biogenetically derived from proline and histidine. Ageladine A displayed 33% inhibition of bovine aortic endothelial cell migration at 5 μg $mL^{-1}$ and inhibited the vascular formation of mouse ES cells at 10 μg $mL^{-1}$. A new series of bromopyrrole alkaloids bearing two 2-aminoimidazole units has been isolated from a sponge of the genus *Agelas*, among them nagelamide 8 (**145**) with an imidazolidine-2,4-diimine moiety and modest antimicrobial activity against *Micrococcus luteus*, *B. subtilis* and *E. coli*.[272]

An interesting study on the chiroptical properties of guanidine-bearing bromopyrrole alkaloids using circular dichroism and Mosher esters NMR analysis demonstrated that a Cotton effect observed at 254 nm is related to the absolute configuration at the 2-amino-hexahydro-1*H*-imidazo[4,5-*b*]pyrazin-5(6*H*)-one ring junction, while a Cotton effect observed at 280 nm is influenced by the relative stereochemistry of tricyclic and tetracyclic alkaloids.[273] Hymenialdisine bromopyrrole alkaloids, such as debromohymenialdisine (**146**), 10*E*-hymenialdisine (**147**), 10*Z*-hymenialdisine (**148**) and a related synthetic derivative (**149**), have displayed selective enzyme inhibitory activity in different mechanism-based assays. Compound **146** specifically inhibited the $G_2$ checkpoint of MCF-7 breast cancer cells with an $IC_{50}$ of 8 μg $mL^{-1}$ and moderate cytotoxicity (25 μg $mL^{-1}$). It also inhibited protein kinases Chk1 ($IC_{50}$ = 3 μM) and Chk2 ($IC_{50}$ = 3.5 μM). 10*Z*-Hymenialdisine (**148**) displayed inhibition of the $G_2$ checkpoint of MCF-7 cells at 6 μM.[274] Both isomeric **147** and **148** displayed inhibitory activity of the Raf/MEK-1/MAPK cascade, which is implied in cellular signaling processes, with $IC_{50}$ of 3 and 6 nM, respectively, *via* a phosphorylating pathway.[275] Previously, 10*Z*-hymenialdisine (**148**) had displayed potent inhibition of several cyclin-dependent kinases, glycogen synthase kinase-3β and casein kinase 1, in particular CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclin E, CDK5/p25, GSK3-β and CK1 and the nanomolar level.[276] In this particular study, a crystal structure of the CDK2–10*Z*-hymenialdisine complex was obtained and the mechanism of enzyme inhibition established at the atomic level. Furthermore, 10*Z*-hymenialdisine also presented CDK5/p35 and GSK-3β inhibition *in vivo*, demonstrating good potential for its development as a drug lead for the treatment of neurodegenerative diseases.[276] A new hymenialdisine derivative **149** was synthesized and presented potent inhibitory activity of Chk2 ($IC_{50}$ of 8 nM),[277] of interleukin-2 ($IC_{50}$ of 3.5 mM) and of tumor necrosis factor α production ($IC_{50}$ of 8.2 mM).[278]

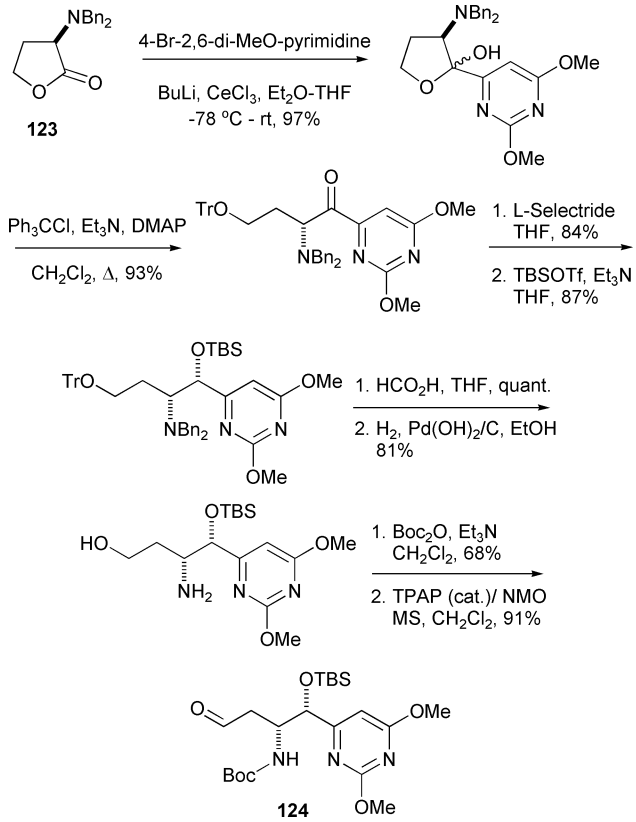
Investigation on the biosynthesis of bromopyrrole alkaloids included a liquid chromatography–mass spectrometry survey with crude extracts obtained from three Australian specimens of the *Agelas* sponge species. The results revealed that dimerized and non-dimerized bromopyrrole alkaloids are the main constituents in the crude extracts, some of them with unknown structures. The investigation suggested the presence of an active [2 + 2] cycloaddition dimerizing enzyme of yet unknown structure.[279] The *in vitro* production of stevensine (**150**) within



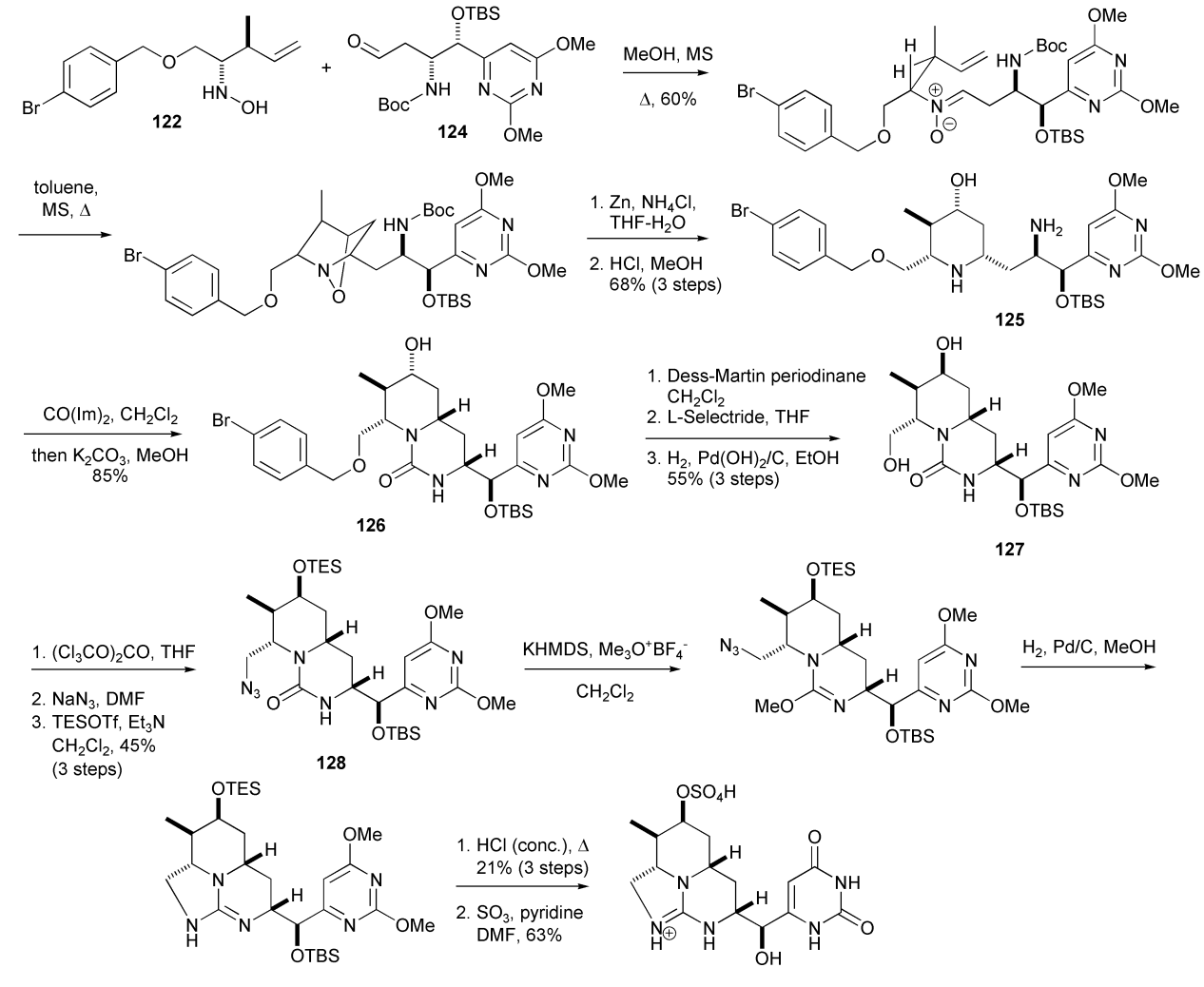

**Scheme 10**



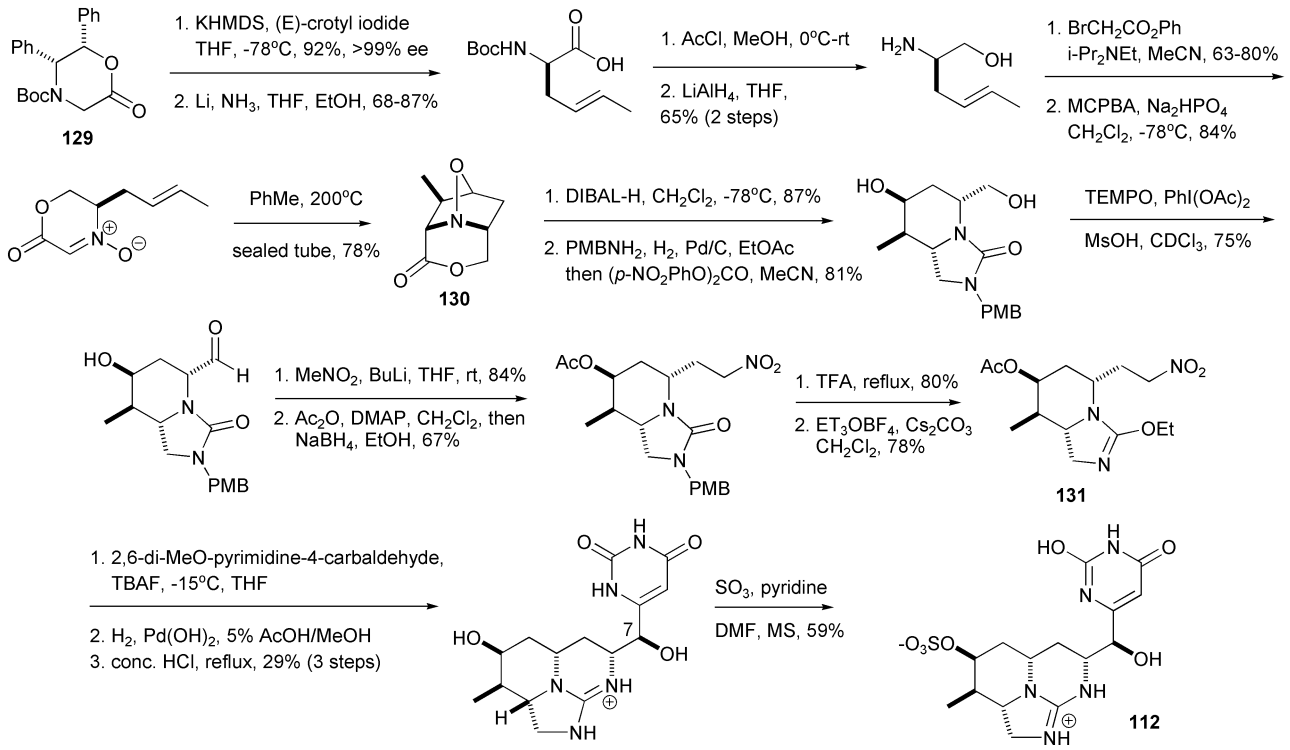

Scheme 11



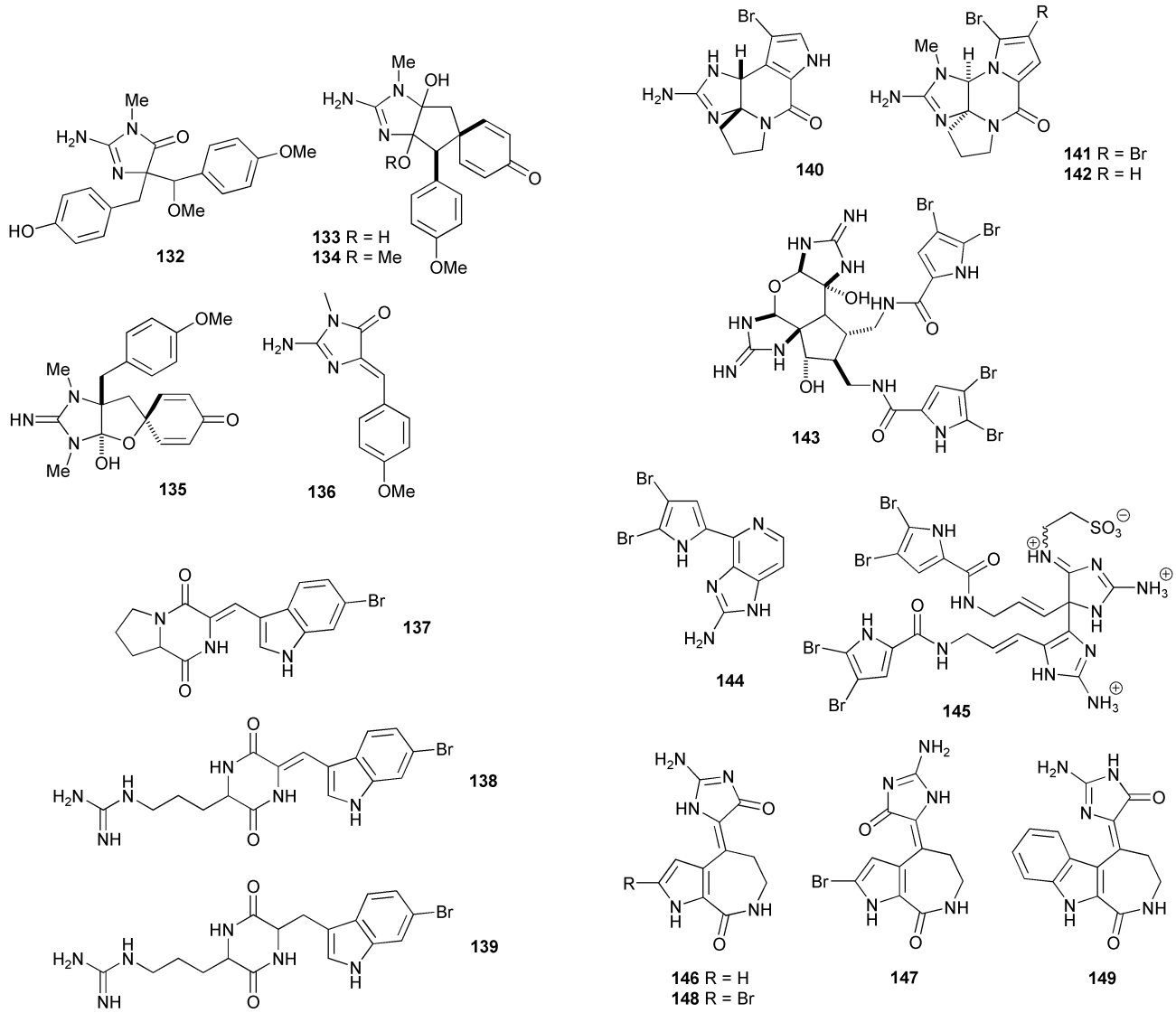

Scheme 12



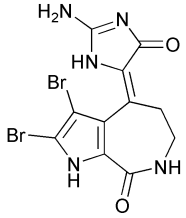

Scheme 13




**Scheme 14**

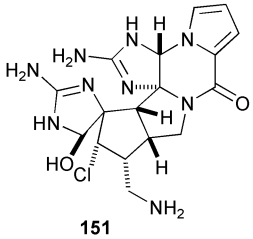


cells of the sponge *Axinella corrugata* was also investigated,[280] and demonstrated that explants with a 3 fold increase of natural cell concentration enhanced the production of **150** by 157%.

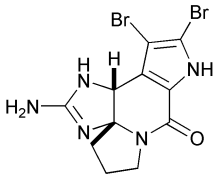


**150**

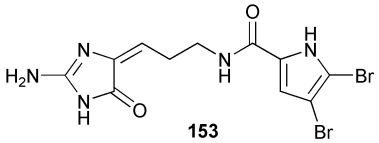
A different synthetic approach[281] to the complex polycyclic bromopyrrole alkaloids palau'amine (**151**)[282] and related styloguanidines,[283] as well as interesting biomimetic syntheses of dibromoisophakellin (**152**)[284] and discapamide A (**153**),[285] have been developed.



**151**

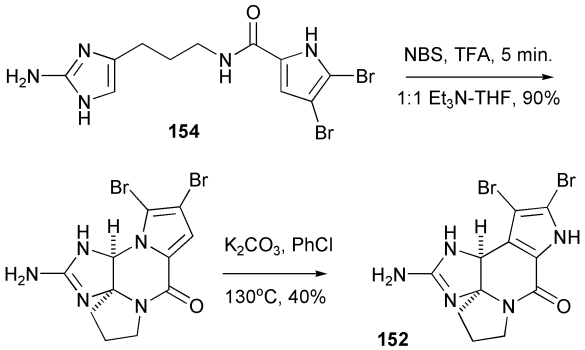


**152**



**153**

Dibromoisophakellin's (**152**) new synthesis[284] involved simply the acid-catalyzed cyclization of dihydrooroidin (**154**), previously synthesized by the authors,[286] followed by thermal rearrangement (Scheme 15). The synthesis of discapamide A (Scheme 16)[285] involved an initial condensation of pyrrole-2-carboxylic acid and L-proline, followed by diketopiperazine formation under alkaline conditions and subsequent guanidine formation through diketopiperazine opening. The mixture of monoprotected guanidines **155a** and **155b** was transformed into discapamide A *via* bromination, Boc-protecting group removal and dehydration.



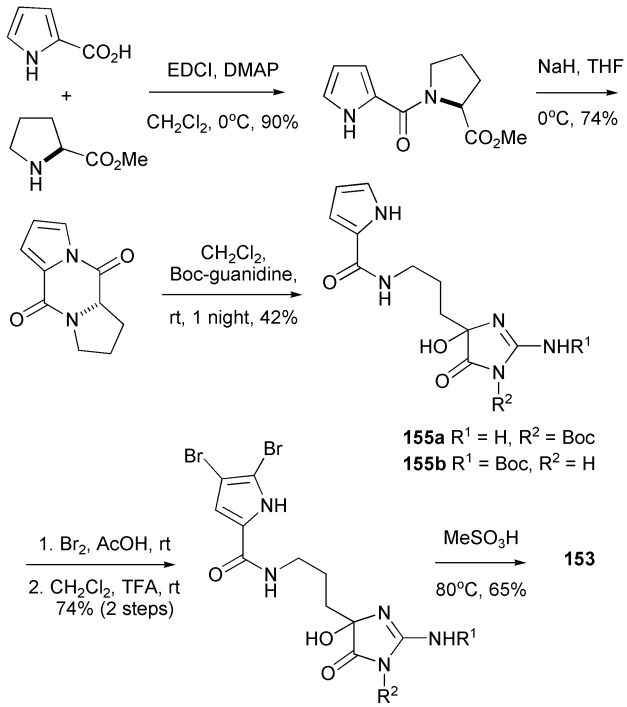

**154**

**152**

**Scheme 15**

A series of 17 new phloeodictynes **156–172** has been isolated from the sponge *Oceanapia fistulosa* from New Caledonia, and identified by LC-ESI-MS analysis.[287] Alkaloid-enriched fractions displayed antimalarial activity against the chloroquinone resistant *Plasmodium falciparum* FCB1 strain between 0.1–10 μg $mL^{-1}$ and cytotoxic activity against the human lung carcinoma cell line A-549 with an $IC_{50}$ between 0.62 and 6.36 μM.

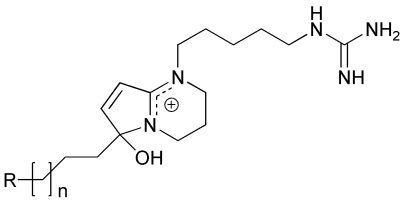
Dysinosins are a series of amino acid derived guanidine alkaloids which have been isolated from sponges of the family Dysideidae. The first member of this class, dysinosin A (**173**), was isolated from an unidentified sponge collected at North



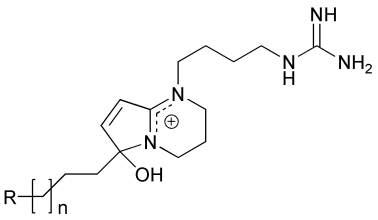

**155a** $R^1$ = H, $R^2$ = Boc
**155b** $R^1$ = Boc, $R^2$ = H

**153**

**Scheme 16**

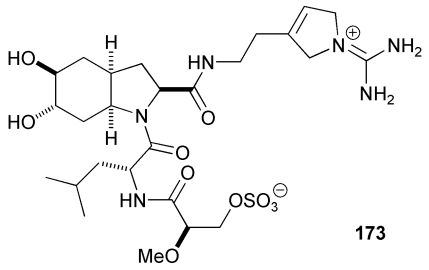


**156** phloeodictyne 5,4i n = 4, R = -$CH_2CH{=}CH_2$
**157** phloeodictyne 5,5i n = 5, R = i-Pr
**158** phloeodictyne 5,6i n = 6, R = i-Pr
**159** phloeodictyne 5,7i n = 7, R = i-Pr
**160** phloeodictyne 5,8a n = 8, R = -$CH_2CH{=}CH_2$
**161** phloeodictyne 5,9a n = 9, R = -$CH_2CH{=}CH_2$
**162** phloeodictyne 5,9i n = 9, R = i-Pr
**163** phloeodictyne 5,10a n = 10, R = -$CH_2CH{=}CH_2$
**164** phloeodictyne 5,10i n = 10, R = i-Pr



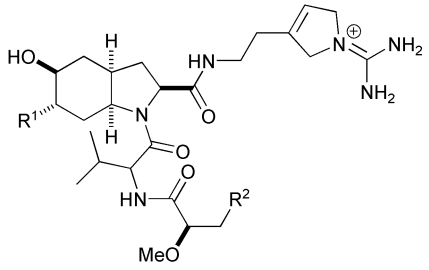
**165** phloeodictyne 4,5i n = 5, R = i-Pr
**166** phloeodictyne 4,6a n = 6, R =-$CH_2CH{=}CH_2$
**167** phloeodictyne 4,6i n = 6, R = i-Pr
**168** phloeodictyne 4,7i n = 7, R = i-Pr
**169** phloeodictyne 4,8a n = 8, R = -$CH_2CH{=}CH_2$
**170** phloeodictyne 4,10a n = 10, R = -$CH_2CH{=}CH_2$
**171** phloeodictyne 4,10i n = 10, R = i-Pr
**172** phloeodictyne 4,11a n = 11, R = -$CH_2CH{=}CH_2$

Queensland, Australia, and was identified with a full absolute stereochemistry assignment. The dysinosin A–thrombin-hirugen complex was solved by X-ray diffraction analysis. The complex showed an enzyme conformation change in order to accommodate dysinosin A, which is binded *via* hydrogen bonds to the enzyme through guanidine, D-leucine amide, methoxy and sulfate groups. Dysinosin A inhibited factor VIIa with a $K_i$ of 108 nM and thrombin with a $K_i$ of 452 nM.[288]



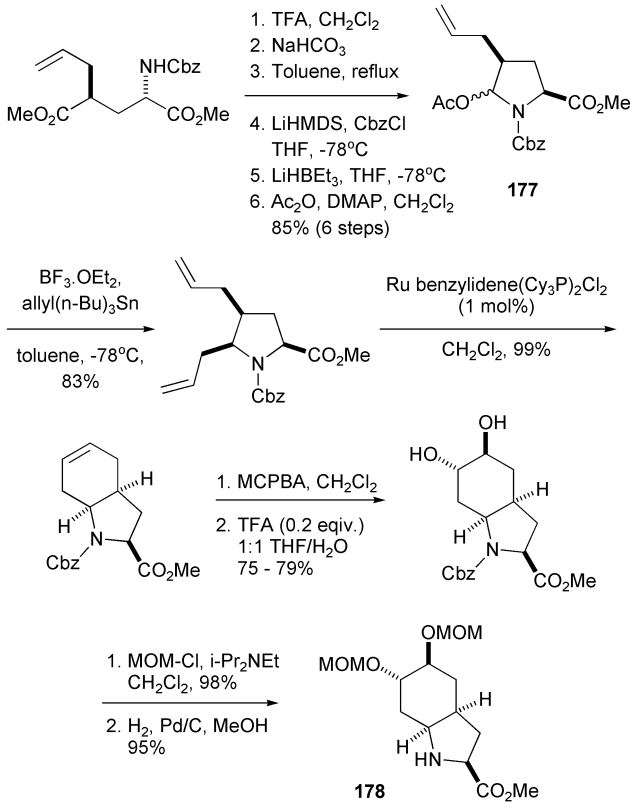
**173**

Additional dysinosins B–D (**174–176**) were isolated from the sponge *Lamellodysia chlorea*, also from Australia.[289] Dysinosin B (**174**) displayed the highest inhibition of factor VIIa ($K_i$ of 0.090 μM) compared with the other dysinosins. Desulfated dysinosin D (**176**) is the less potent inhibitor of both factor VIIa and thrombin, indicating the importance of the sulfate group for biological activity.[289]

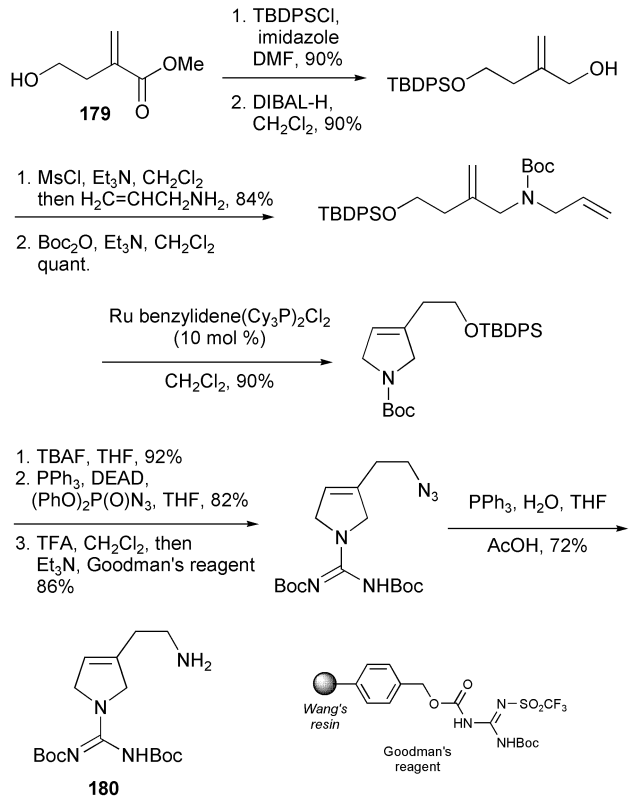


**174** $R^1$ = α-glucose, $R^2$ = $OSO_3^-$
**175** $R^1$ = OH, $R^2$ = $OSO_3^-$
**176** $R^1$ = $R^2$ = OH

The highly convergent synthesis of dysinosin A (Schemes 17–19) was reported simultaneously with its isolation,[290] starting with a six reaction step sequence from *N*-Cbz protected (2*S*,4*S*)-2-allyl-4-aminopentanedioic dimethyl ester in order to obtain the functionalized pyrrolidine **177**, which was subsequently allylated and submitted to olefin metathesis, double bond epoxidation, acid-catalyzed epoxide opening, vicinal diol protection and nitrogen deprotection to give the suitable stereoisomer




**Scheme 17**



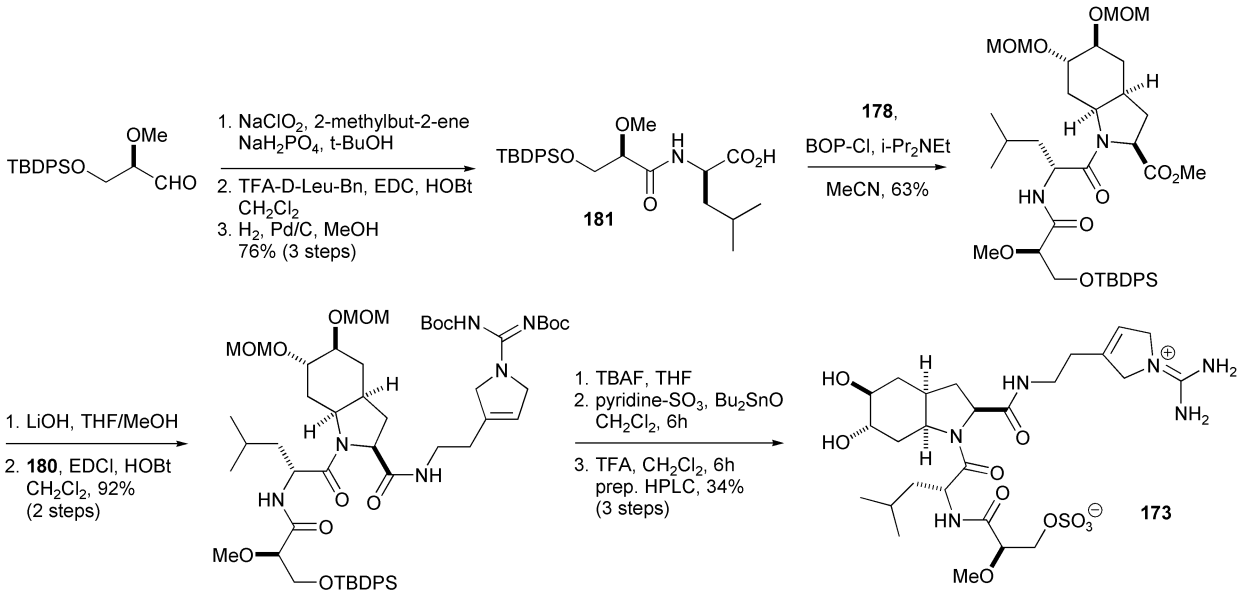

**Scheme 18**

of 5,6-dihydroxyoctahydroindole-2-carboxylic acid methyl ester **178**. The guanidine moiety **180** was obtained from 4-hydroxy-2-methylenebutanoic acid methyl ester **179** by a series of stepwise interconversions, also including an olefin metathesis and a first example of solid-phase guanidylation in natural product synthesis. The last steps of dysinosin A synthesis included the preparation of protected (*R*)-3-hydroxy-2-methoxypropanal from D-mannitol, and its subsequent conversion to the dipeptide **181**, before coupling with **178** and the product obtained was coupled with the protected guanidine **180**. Removal of protecting groups provided dysinosin A **173**.[290,291]

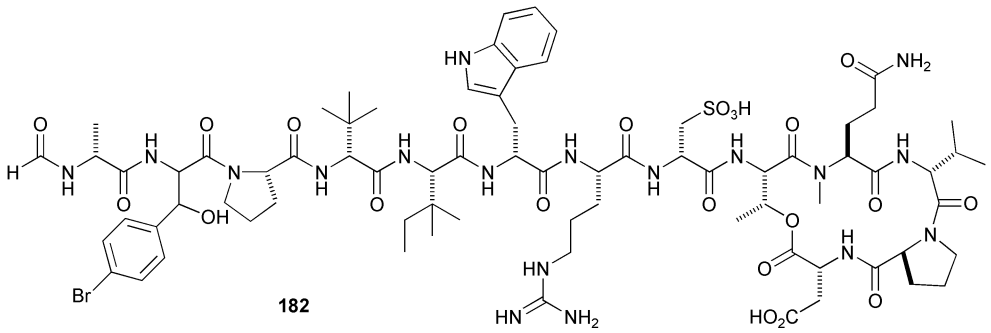
Several new peptide metabolites presenting an arginine or modified arginine residue have been isolated from marine sponges. Microspinosamide (**182**) has been isolated from the sponge *Sidonops microspinosa* as a new inhibitor of the human immunodeficiency virus (HIV-1) cytopathic effect in CEM-SS target cells, with an $EC_{50}$ of 0.2 μg $mL^{-1}$.[292] The absolute stereochemistry of **182** was established by analysis of spectroscopic data, including LC-MS analysis of the amino acids after derivatization with Marfey's reagent and with 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate. An unusual feature in the structure of microspinosamide is the presence of the new amino acid, β-hydroxy-*p*-bromophenylalanine.

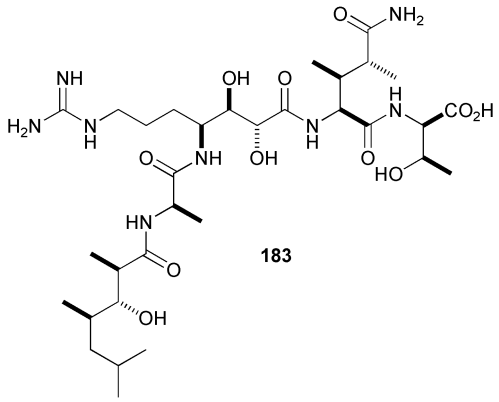
Two new callipeltins, callipeltin D (**183**) and E (**184**), have been isolated from a sponge of the genus *Latrunculia*.[293] The new callipeltin peptides did not show inotropic activity or inhibition of the cardiac Na/Ca exchanger.

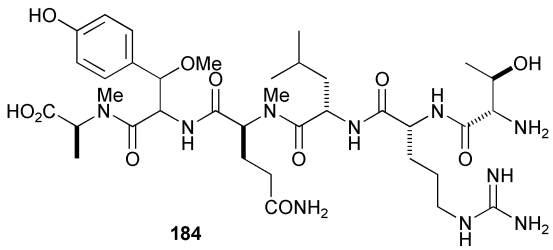
Neamphamide A (**185**) has been isolated from the sponge *Neamphius huxleyi*, also as an inhibitor of the HIV-1 cytopathic effect in CEM-SS target cells, with an $EC_{50}$ of 28 nM.[294] The absolute stereostructure of **185** was defined by spectroscopic analysis, Marfey's analysis and chemical degradations. Cyclonellin (**186**), a new cyclopeptide, was isolated from the sponge *Axinella carteri*, a rich source of modified peptides.[295] Cyclonellin was inactive as a cytotoxic agent against COLO-205 (colon) and OVCAR-3 (ovarian) cancer cell lines. Cyclotheonamides E4 (**187**) and E5 (**188**) have been isolated from a sponge of the genus *Ircinia* as new tryptase inhibitors, with inhibitory activities in the nM range.[296]




**Scheme 19**



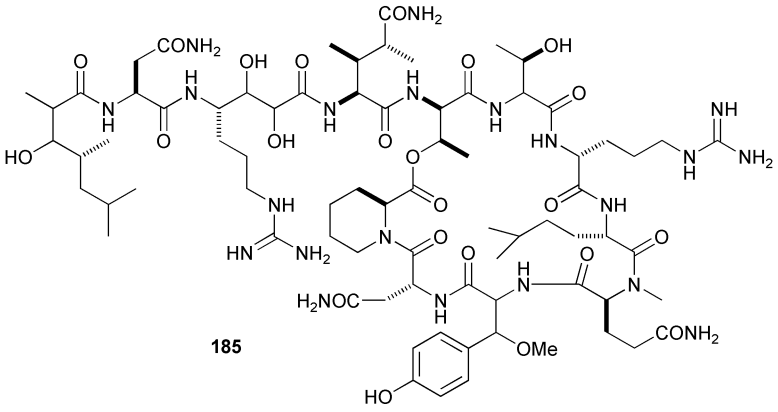



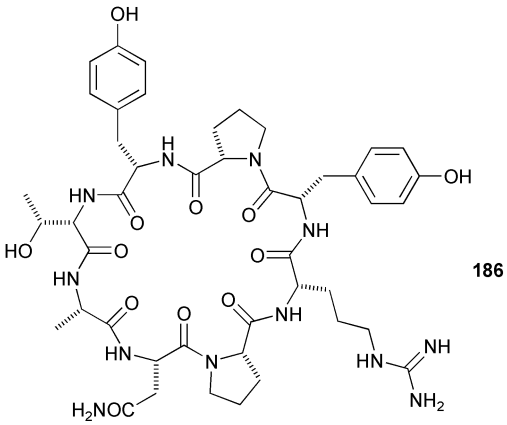

Cyclotheonamides E2 (**189**) and E3 (**190**)[297] have been synthesized by a new "cyano ylide methodology" (Scheme 20).[298,299] Initially, prolyl-β-aminoglycyl (**191**) and the arginyl cyano ylide (**192**) were separately prepared. Synthesis of **191** included a Curtius-degradation from trimethylsilylethyl carbamate (Teoc) protected asparagine. Coupling of **191** and **192** yielded the cyano ylide tripeptide **193** which was coupled with **194**, itself prepared by a stepwise reaction sequence from L-Boc-tyrosine, also including a Wittig reaction. The pentapeptide obtained had the allyl protecting group exchanged with a pentafluorophenoxy protecting group with the use of $Pd^0$ in order to regenerate the acid and subsequent fluorophenol ester formation. After macrocyclization, the whole cyclotheonamide skeleton **195** was obtained in good yield, generating both cyclotheonamides E2 (**189**) and E3 (**190**) after the introduction of a suitably protected amino acid in each case, followed by removal of protecting groups.

Caissarine A (**196**) is a new member of the bromotyrosine derivatives, frequently isolated from marine sponges of the order Verongida. Compound **196** has been isolated from *Aplysina caissara* from Brazil.[300] The *Mycobacterium tuberculosis* and *M. smegmatis* mycothiol-S-conjugate inhibitor **197** (unnamed) presented the strongest inhibitory activity when compared with 20 other inhibitors obtained during a screening with extracts from marine sponges and terrestrial fungi, as well as with synthetic derivatives.[301,302] Compound **197**, previously isolated from a sponge of the genus *Oceanapia*,[303] presented an $IC_{50}$ of 3 and 2 μM against each mycobacteria, respectively. Subsequently, two syntheses have been reported for **197** (Schemes 21 and 22).[304,305] The first one (Scheme 21) provided **197** through an unstable oxazole in 38% overall yield from 3,5-dibromotyrosine.[304] The second synthesis started from 4-hydroxyphenylpyruvic acid, with slight variations of the preceding synthesis, providing synthetic **197** in 24% overall yield.[305] The same authors improved this synthesis by changing the oxime protecting group to a tetrahydropyranosyl and by changing the reaction sequence.[305]

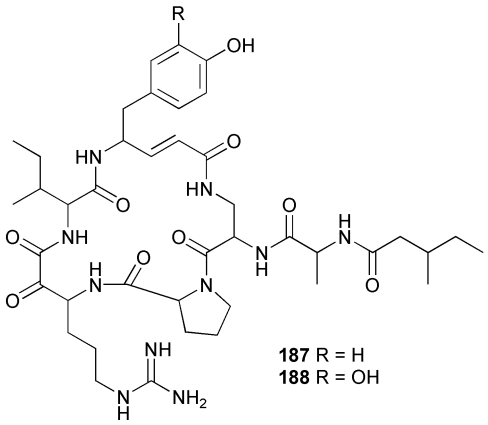
Poecilosclerida sponges belonging to the genera *Crambe*, *Ptilocaulis* and *Batzella* are an impressive source of guanidine alkaloids. New members of this class include crambescidin 826



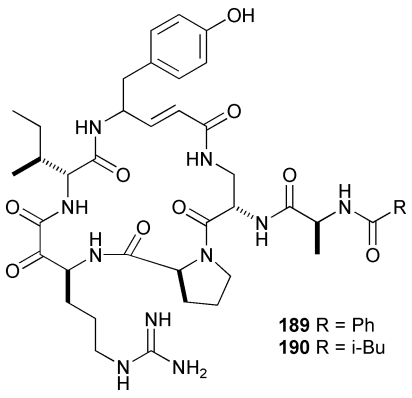
185



186



187 R = H
188 R = OH



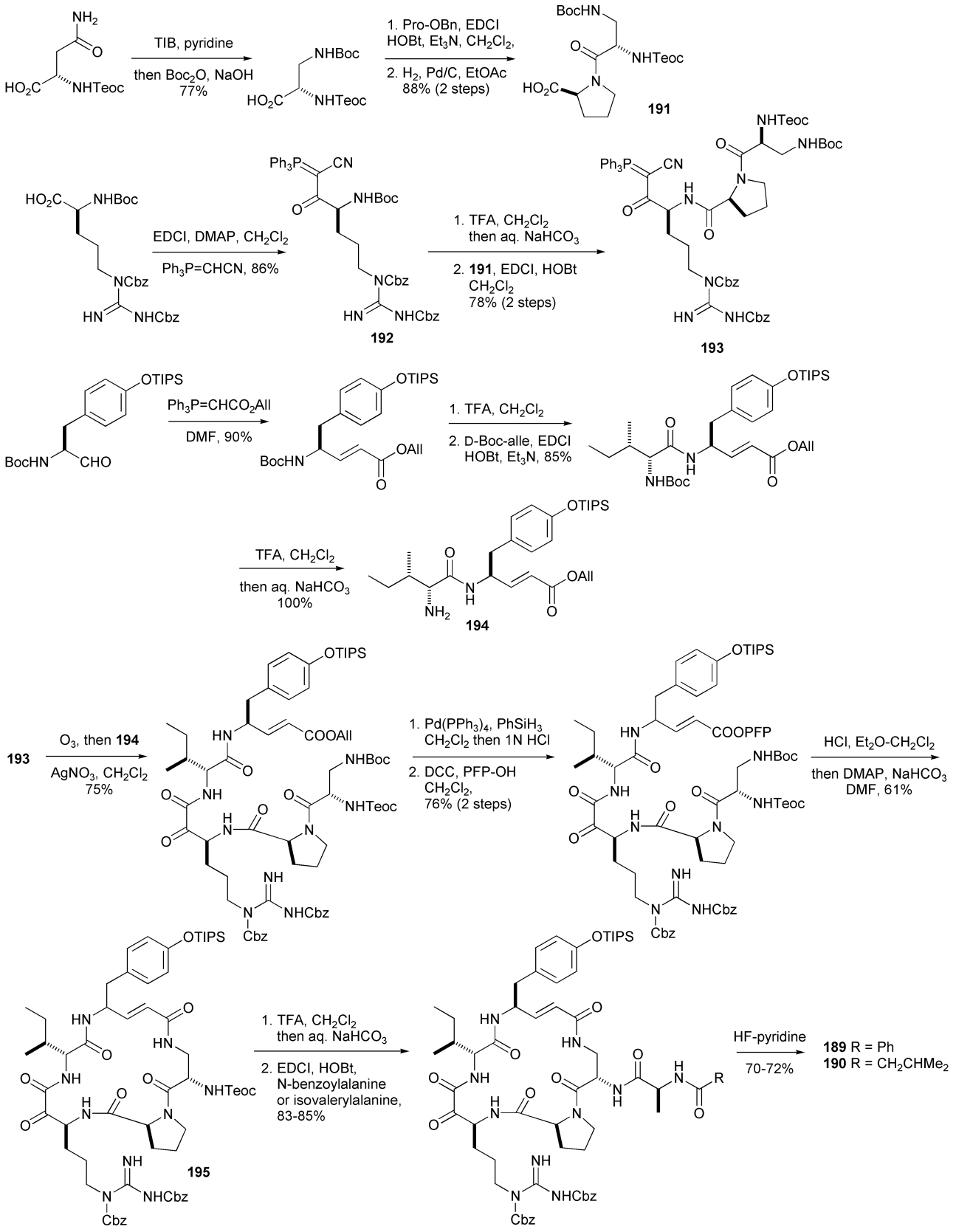
189 R = Ph
190 R = i-Bu

(**198**) and dehydrocrambine A (**199**), both of which have been isolated from a sponge of the genus *Monanchora*.[306] A notable feature of dehydrocrambine A (**199**) is an optical rotation of $[\alpha]_D^{20}$ −12.1° (*c* 0.09, MeOH), since it does not present a chiral carbon.

Crambescin 826 inhibited HIV-1 envelope-mediated fusion with an $IC_{50}$ between 1 and 3 μM, while for dehydrocrambine A the value of $IC_{50}$ lies at 35 μM. A related alkaloid, Sch575948 (**200**), has been isolated from the sponge *Ptilocaulis spiculifer*, and displayed antibacterial activity against a super sensitive strain of *S. aureus* (RN4220), with inhibition zones of 13, 15 and 18 mm at 25, 50 and 100 μg per disc concentrations, respectively.[307] An interesting new member of this class is monanchorin (**201**), isolated from *Monanchora ungiculata* collected in the Maldive Islands.[308] The structure of monanchorin was assigned by spectroscopic analysis, including $^{1}H$–$^{15}N$ HMBC, which enabled the authors to distinguish **201** from the isomeric structure **202**. The authors also isolated crambescidin 431 acid **203**. Both **201** and **203** displayed moderate cytotoxic activity against IC2 murine mast cancer cells.

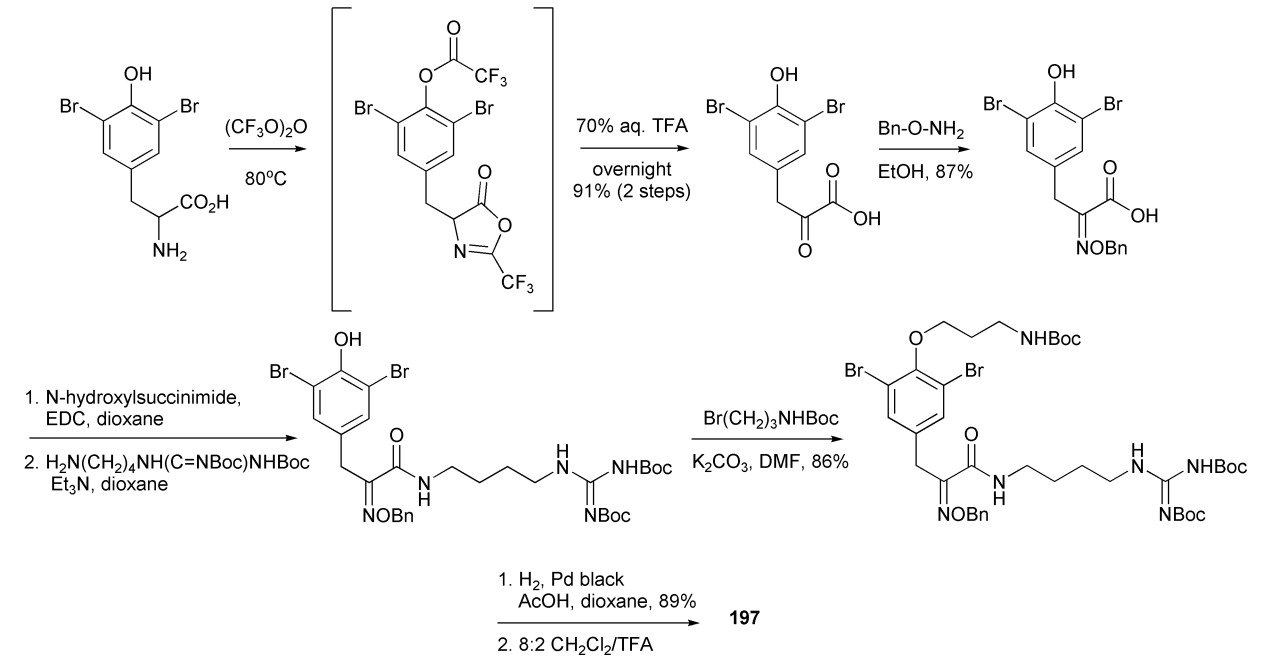
Three new ptilocaulin analogues, 1,8a;8b,3a-didehydro-8β-hydroxyptilocaulin (**204**), 1,8a;8b,3a-didehydro-8α-hydroxyptilocaulin (**205**) and mirabilin B (**206**), have been isolated from the sponge *Monanchora unguifera*, and identified by analysis of spectroscopic data and X-ray diffraction analysis in the case of **204** and **205**, isolated as a 1 : 1 mixture.[309] Mirabilin B (**206**) displayed antifungal activity against *Cryptococcus neoformans* ($IC_{50}$ 7.0 μg $mL^{-1}$) and antiprotozoal activity against *Leishmania donovani* ($IC_{50}$ 17 μg $mL^{-1}$). The mixture of **204** and **205** displayed antimalarial activity against *Plasmodium falciparum* ($IC_{50}$ 3.8 μg $mL^{-1}$). All compounds did not present significant cytotoxic activity against various cancer cell lines, against HIV-1 or *Mycobacterium tuberculosis*.[309]

Due to their complex polycyclic skeleton and potent biological activities, syntheses of different analogues of ptilomycalin A (**207**),[310] and related crambescidins,[311] as well as of different batzelladines (*e.g.* batzelladine A, **208**),[312–315] have been developed. Additionally, two syntheses of crambescidin 359 (**209**), isolated from *Monanchora* sp.,[316] have been reported.[317,318] The first one (Schemes 23 and 24) included two 1,3-dipolar cycloadditions,[317] the first of such reactions between (*S*)-4,5-dihydro-3*H*-pyrrol-3-ol *N*-oxide and TBS-protected (*R*)-hept-6-en-2-ol, and the second between the cleaved isoxazolidine **211** and the previously prepared diene **210**, to afford the intermediate **212**, with the complete carbon skeleton of crambescidin 359. Compound **212** was also subjected to isoxazolidine cleavage, reduction of the resulting unsaturated *N*-oxide, and *N*-oxide reduction after chromatography, to yield the corresponding substituted pyrrolidine **213** in 42% yield after a 4 step reaction sequence. Intermediate **213** was subsequently guanylated, diol oxidized, subjected to acid-catalyzed cyclization and counter-ion exchange, to give (3*S*,8*R*,10*S*,13*R*,15*R*,19*R*)-crambescidin 359 (**209**), identical to the natural product, and thus establishing its absolute stereochemistry.[317] A second synthesis reported for crambescidin 359 (Scheme 25)[318] involved a one step polycyclization with the guanidine free base of intermediate **216**, itself prepared by a Witting reaction of **214** and **215b**. Compound **215b** was obtained *via* an alternative route, in better yield and also with better *E*/*Z* selectivity than the analogue **215a**. The final steps of crambescidin 359 synthesis involved similar counter-ion exchange, to give the natural (−)-stereoisomer **209**.

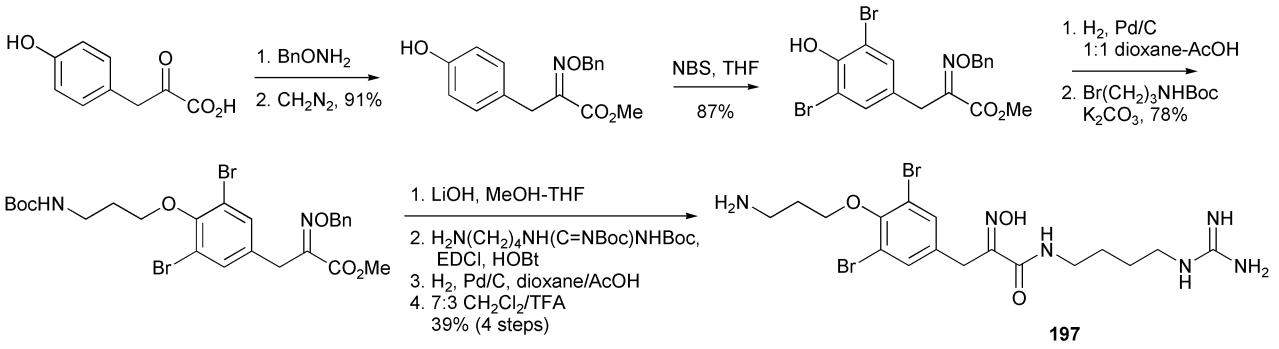



**Scheme 20**

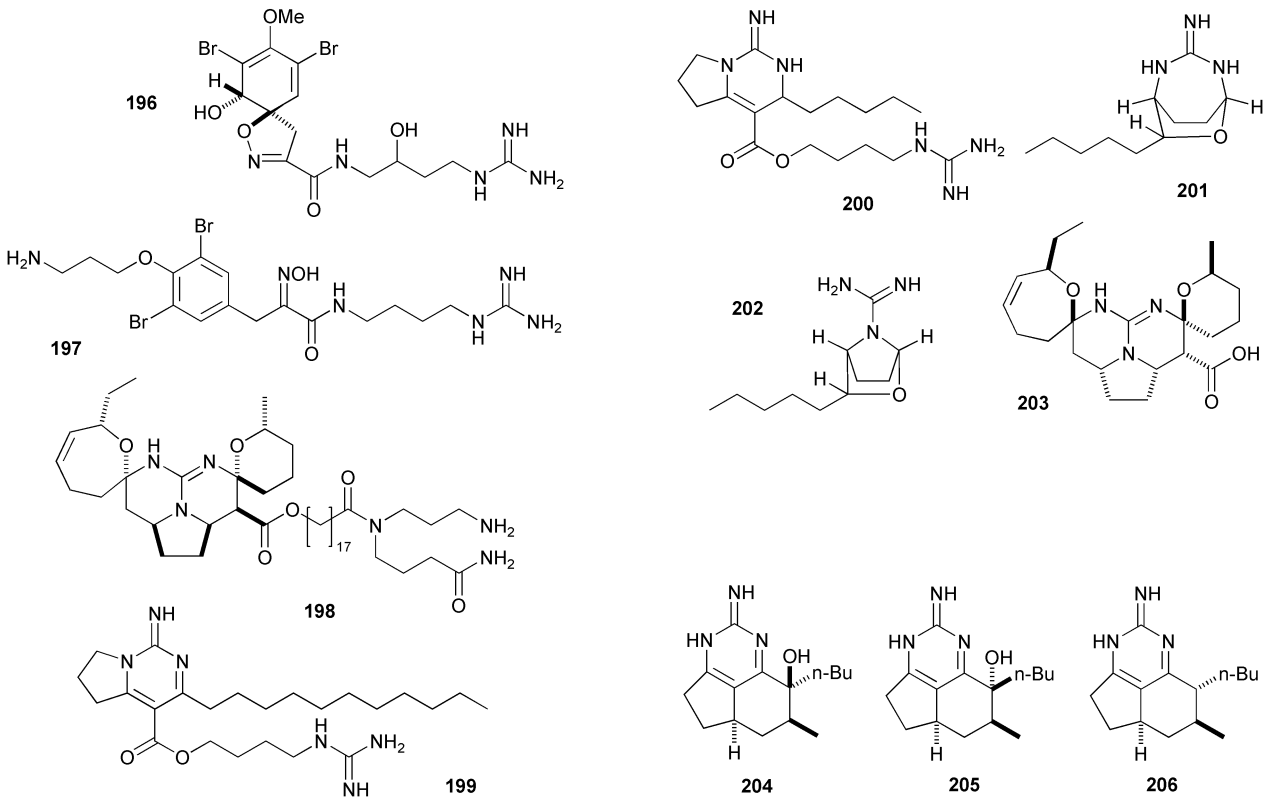
Nagasawa's total synthesis[319] of batzelladine D (**217**)[320] was developed in essentially the same approach as the first synthesis of crambescidin 359 outlined above in Schemes 23 and 24, using two 1,3-dipolar cycloaddition reactions to construct the left side of the central core carbon skeleton, followed by esterification with di-*N*-Boc protected-4-guanidinobutanol and subsequent formation of the tricyclic guanidine. The same group reported the synthesis of batzelladine A (**218**)[320] (Schemes 26–28),[321] in which the left side bicyclic guanidine was constructed first, then condensed with di-*N*-Boc protected-4-guanidinobutanol. After synthesis of the right side bicyclic di-Cbz-protected guanidine, the resulting intermediate was condensed with the right side moiety before the final formation of the tricyclic core of batzelladine A.

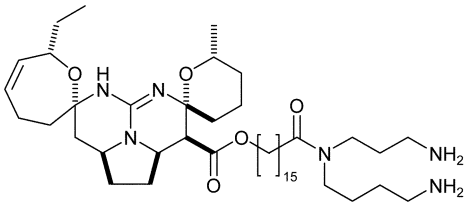



**Scheme 21**




**Scheme 22**





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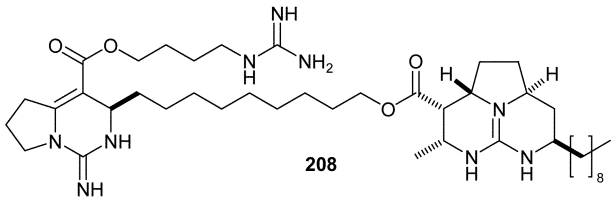

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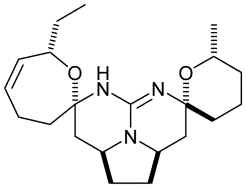

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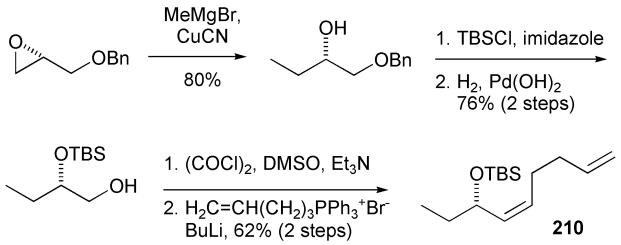
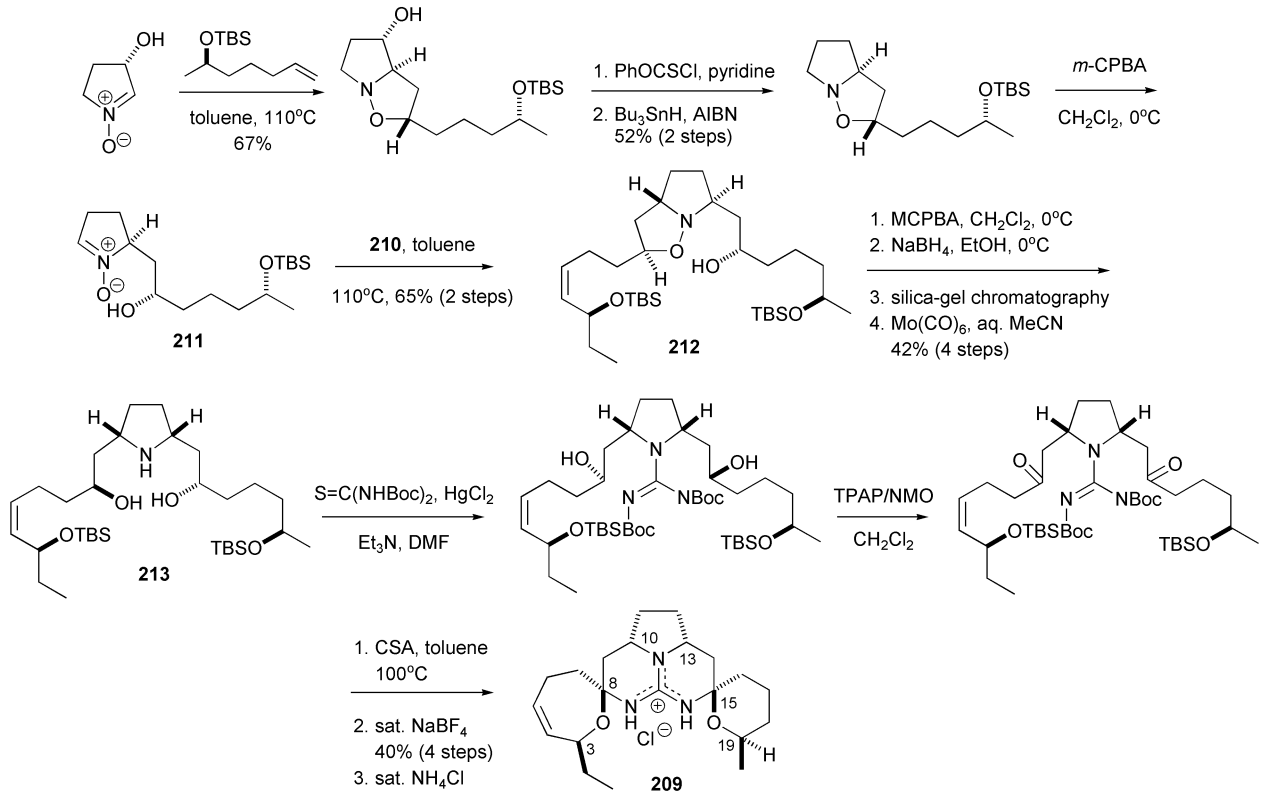


Scheme 23

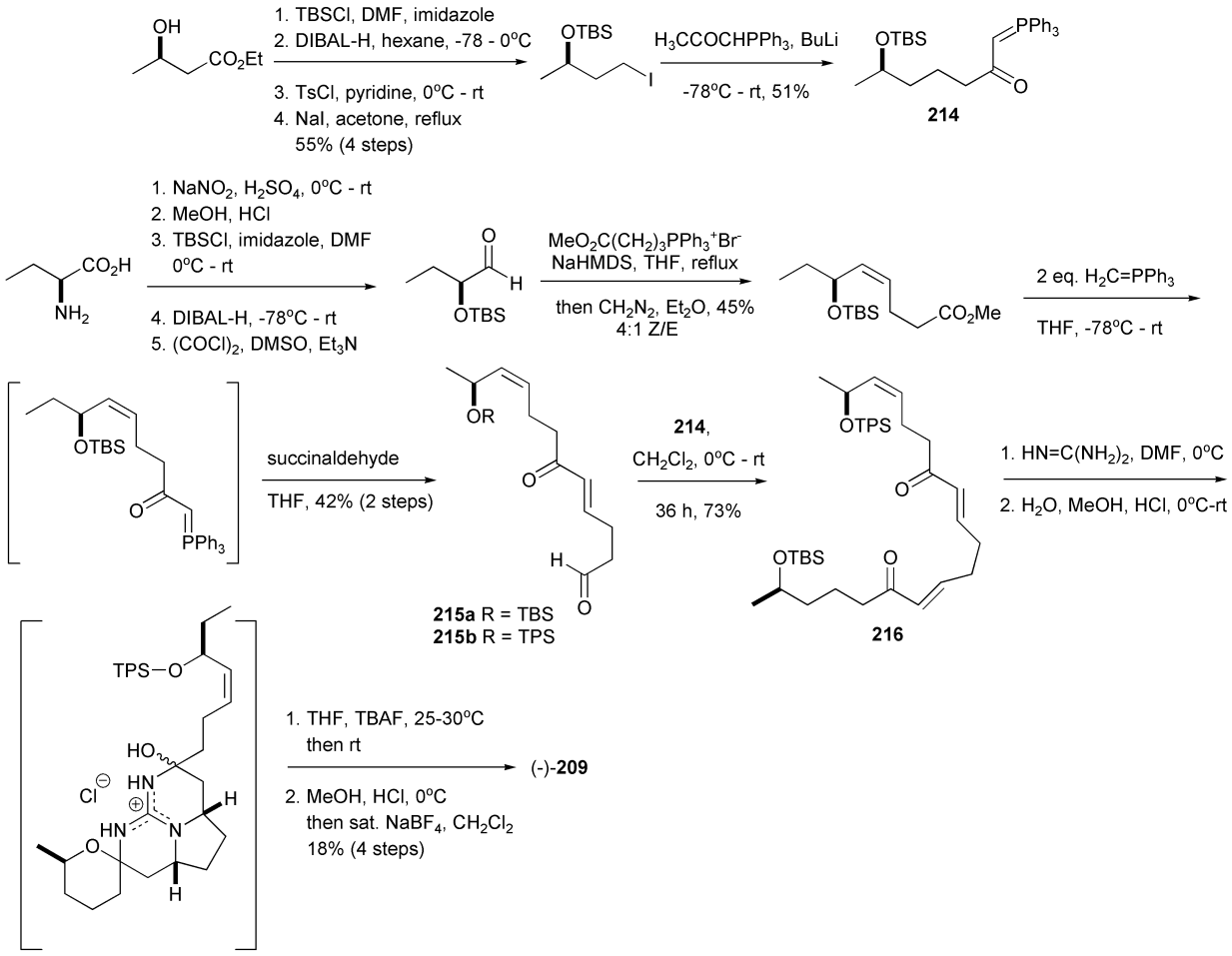
Overman's tethered Biginelli synthetic strategy[261] was used for the synthesis of unnatural (−)-dehydrobatzelladine C (**219**).[322] Overman's group also synthesized a plethora of batzelladine and crambescidin analogues, in order to investigate their inhibition of HIV-1.[323,324] Firstly, the authors investigated the inhibition of HIV-1 Env-mediated cell-cell fusion by batzelladine analogues.[323] The most active derivatives were compounds presenting two tricyclic guanidine cores, such as **220** and **221**. Additionally, manual docking molecular modeling indicated a possible mechanism of action for the most active analogues. Furthermore, the inhibition of HIV-1 Nef protein, which contributes for HIV-1 propagation and viral loads, was investigated with related guanidine derivatives.[324] Structurally somewhat unrelated **222**, **223** and **224** were the most active as Nef-p53, Nef-actin and Nef-p56$^{lck}$ inhibitors, but unfortunately they were too cytotoxic to be evaluated *in vivo*.

A gene cluster that is probably responsible for the biosynthesis of onnamide A (**225**), originally isolated from the marine sponge *Theonella swinhoei*,[325] has been isolated and compared to the *Paederus fuscipes* beetle *Pseudomonas* symbiont gene cluster responsible for the biosynthesis of pederin (**226**).[326] It was suggested that the gene cluster isolated from *T. swinhoei* includes not only polyketide synthases, but also a 3-hydroxy-3-methylglutaryl-CoA synthase (HMGS), oxygenases, methyl transferases and a non-ribosomal peptide synthase (NRPS), along with genes with unidentified functions. Therefore, it seems likely that onnamide A from *Theonella swinhoei* is biosynthesized by a symbiotic microorganism not yet identified. This investigation constituted the first isolation of biosynthetic genes of a symbiotic microorganism from a marine invertebrate.[326]

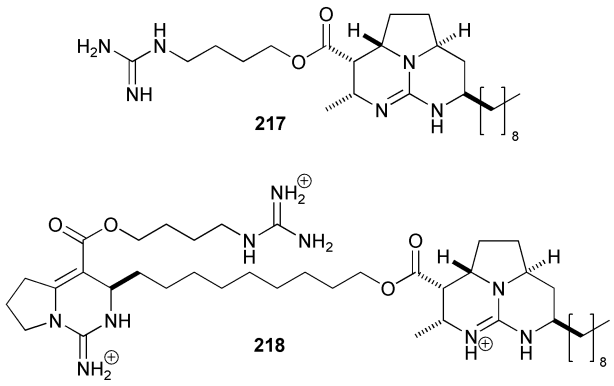
Both 7,8-dihydrotubastrine (**227**) and 4-deoxy-7,8-dihydrotubastrine (**228**) have been isolated from the sponge *Petrosia cf. contignata* and were not active against *S. aureus* and *B. subtilis*.[327] A new synthesis of the guanidine sesquiterpene siphonodictidine (**229**) was disclosed (Scheme 29).[328]



Scheme 24




**Scheme 25**




### 4.2 Other marine invertebrates

Bioluminescence in crustaceans belonging to the genus *Cypridina* is due to a luciferin–luciferase reaction in the presence of oxygen. *Cypridina* luciferin (**230**) is the substrate of the bioluminescent reaction. Deuterium-labelled precursor incorporation into *Cypridina* (*Vargula*) *hilgendorfii*, followed by LC-/ESI-TOF-MS analysis, showed that *Cypridina* luciferin is biosynthesized from L-tryptophan, L-arginine and L-isoleucin.[329,330]

The stony coral *Tubastrea* sp. is the source of three new bis-indole alkaloids bearing 2-imino-1,3-dimethylimidazolidin-4-one moieties, tubastrindoles A–C (**231–233**).[331]

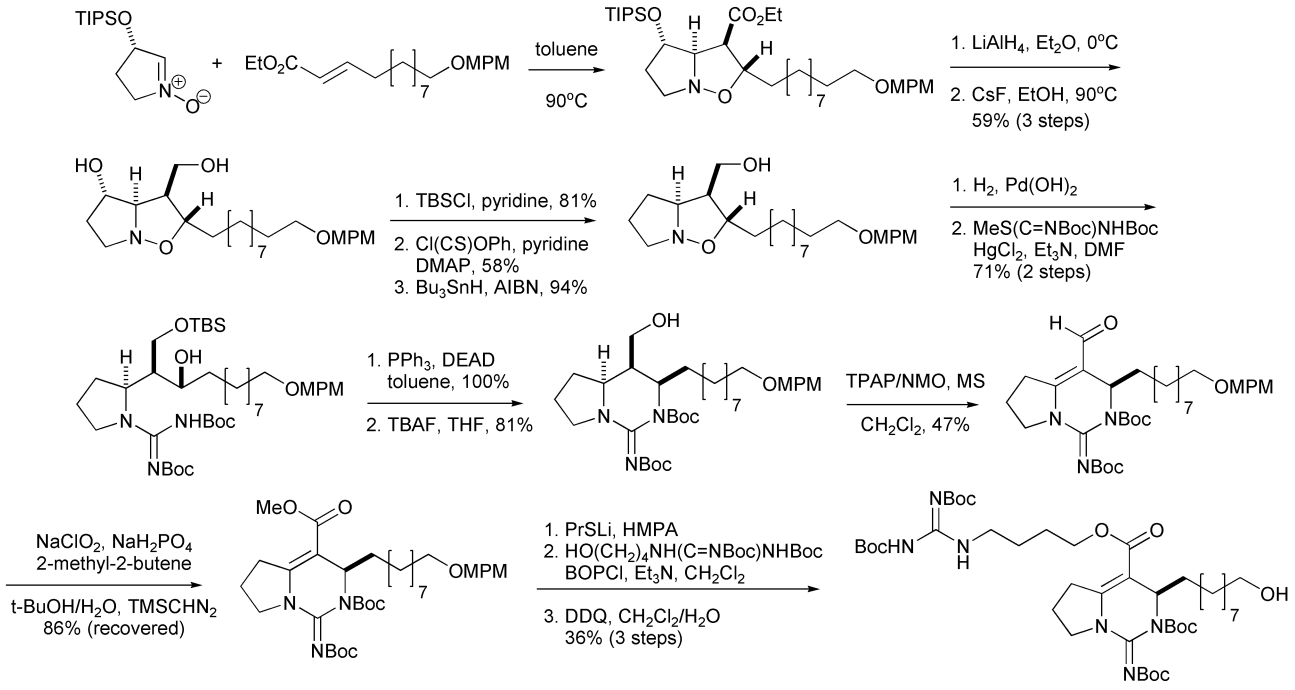
A new pentapeptide with a modified guanidine-containing amino acid has been isolated from the hydroid (Phylum Coelenterata, Class Hydrozoa) *Gymangium regae*.[332] The absolute configuration of gymnangiamide (**234**) was established by analysis of spectroscopic data as well as by hydrolysis and amino acid derivatizations and analysis with either Marfey's reagent or 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate. The absolute stereochemistry of α-guanidino serine, *O*-desmethyldolaproine, *N*-desmethyldolaisoleucine and phenylserine was established by a series of well devised chemical derivatizations, followed by either $C_{18}$ reversed-phase or D-penicillamine chiral HPLC analyses. Gymnangiamide displayed cytotoxic activity in the range between 0.46 to >11 μg $mL^{-1}$ against a panel of 10 tumor cell lines, including colon, leukemia, lung, melanoma, ovarian and central nervous system cells, suggesting a mechanism involving tubulin inhibition, such as that observed for dolastatin 10, a very potent cytotoxic peptide which is structurally somewhat related to gymnangiamide (**234**). The lower cytotoxic potency of **234** was suggestively assigned to the occurrence of ionizable guanidinium and carboxylic acid groups, as well to the presence of desmethylated dolaisoleucine and dolaproine amino acid residues.[332]

Two new polyheteroaromatic alkaloids bearing an ethylguanidine side chain, distomadines A (**235**) and B (**236**), have been isolated from the ascidian *Pseudodistoma aureum*.[333] Distomadine A was essentially inactive in antifungal, antiviral, anti-inflammatory and antimycobacterial bioassays.

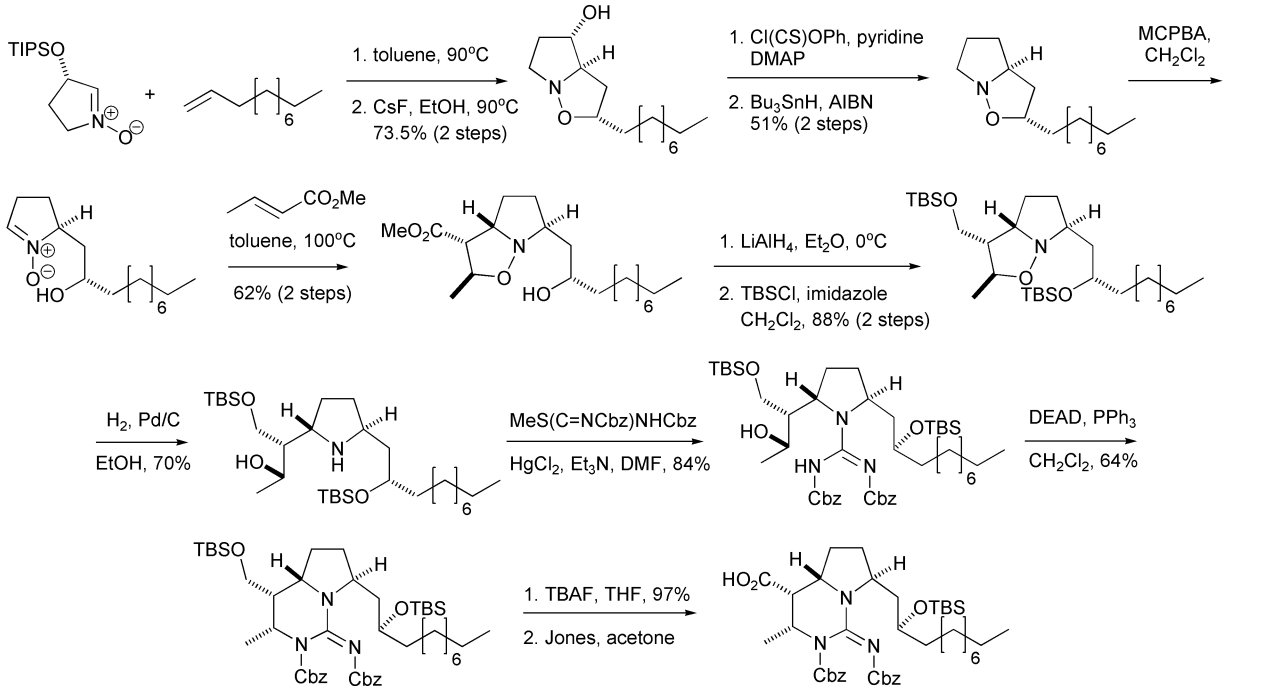
Several amino acid derivatives have been isolated from the ascidian *Atriolum robustum*, among them a new guanidine derivative **237** (unnamed), which was identified by analysis of spectroscopic data and GC-MS analysis of the lysine moiety obtained after hydrolysis and reaction with pentafluorophenylpropionic anhydride.[334]

## 5 Natural guanidines from higher plants

A detailed review on the chemistry and pharmacology of coumaroylagmatine and cinnamoylagmatine derivatives isolated from *Verbesina carcasana* has been published.[335] A regrettable




**Scheme 26**

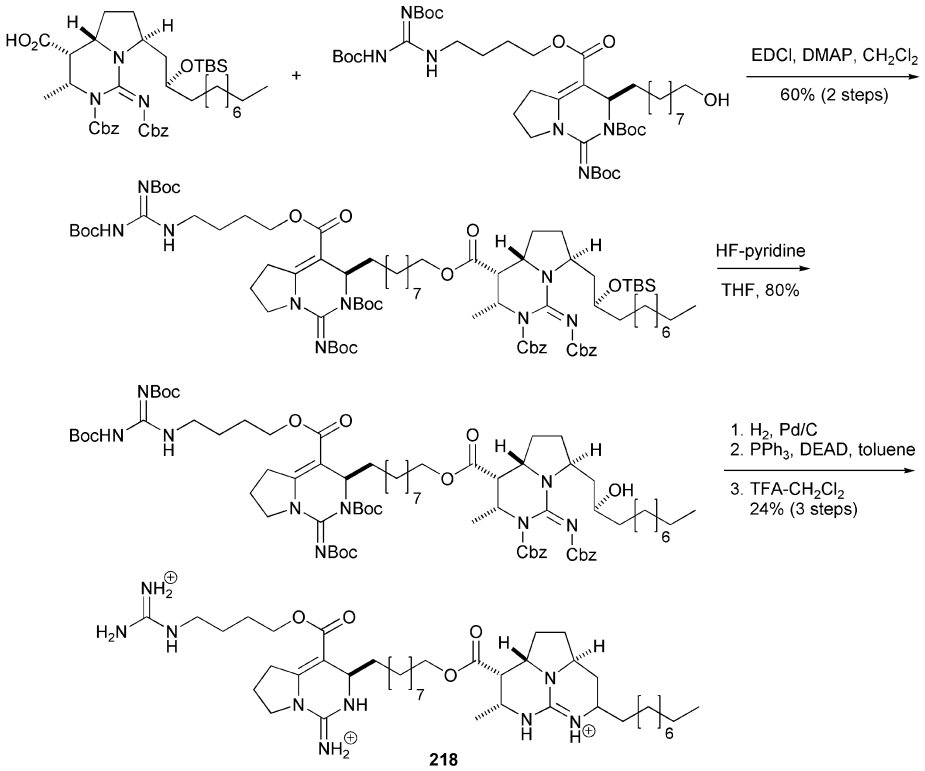



**Scheme 27**

omission in previous reviews was the isolation and structure determination of moroidin (**238**) from the tropical stinging tree *Laportea moroides* (Urticaceae).[336] Cutaneous contact with *L. moroides* stinging hairs promotes intense pain, piloerection, arteriolar dilatation and local sweating. The structure determination of moroidin was an early example of the application of high resolution two dimensional NMR methods, including $^{1}H$–$^{1}H$ COSY and NOESY, as well as EI and FABMS, along with enzymatic and chemical degradations. Later, molecular modeling computational methods, using the COSMIC forcefield, were also used in combination with a detailed NMR analysis in order to fully establish the stereochemistry of moroidin.[337] Recently, it has been observed that moroidin promotes the inhibition of tubulin polymerization, with an $IC_{50}$ of 3.0 μM, more potently than colchicine ($IC_{50}$ of 10 μM).[338] A first approach toward the total synthesis of moroidin has been reported.[339]

New members of the moroidin peptides are celogentins D–H, J (**239–244**), which have been isolated from *Celosia argentea*.[340] Celogentins D–H were evaluated as inhibitors of tubulin polymerization, along with moroidin (**238**) and celogentins A–C (**245–247**). Celogentin C (**247**) displayed the highest inhibitory potency, with an $IC_{50}$ of 0.8 μM.

Another omission in the previous reviews was the synthesis of (±)-alchornéine (**248**) and (±)-isoalchornéine (**249**), alkaloids isolated several years ago from the aphrodisiac *Alchornea floribunda* and *A. hirtella*,[341,342] respectively. The synthesis of both **248** (Scheme 30) and **249** (Scheme 31)[343] started with the alkylation of disodium cyanamide with a 1 : 1 mixture of

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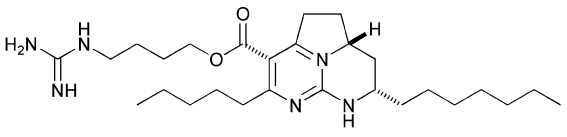
**Scheme 28**



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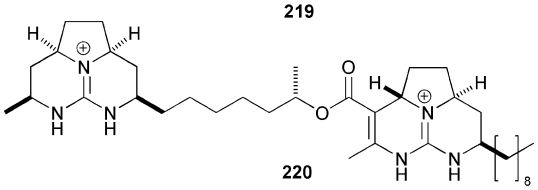

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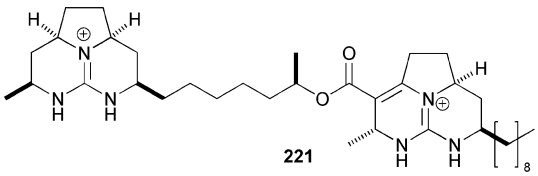

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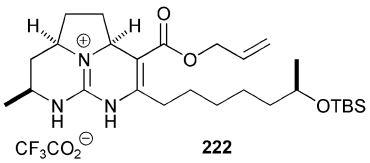

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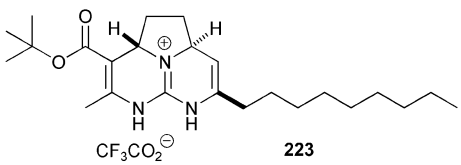

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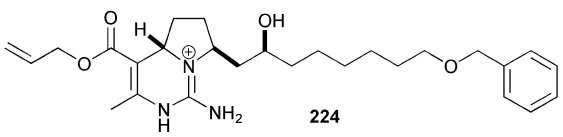

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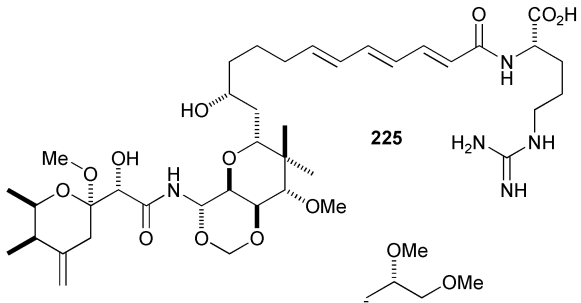

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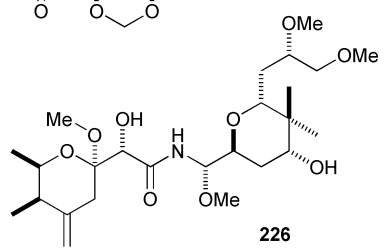

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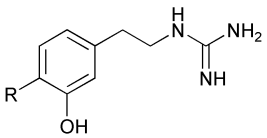
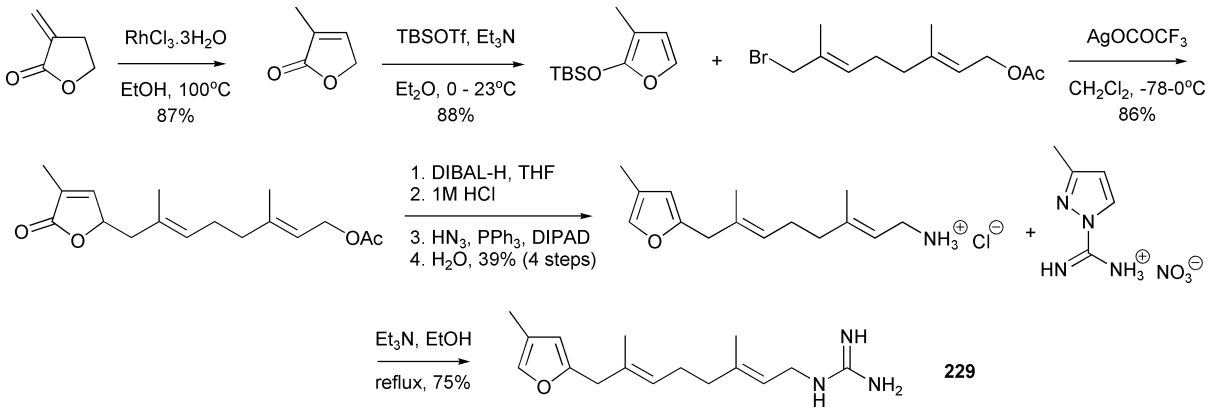


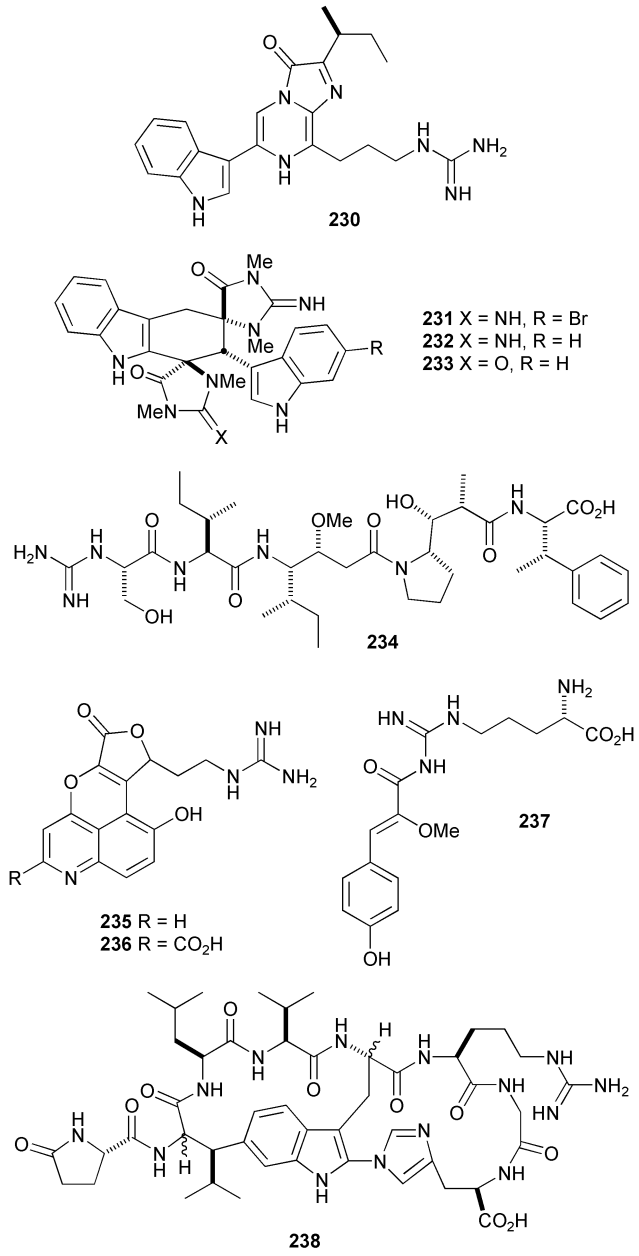
**227** R = OH
**228** R = H

1-bromo-3-methyl-2-butene and (*E*)-1-(benzoyloxy)-4-bromo-2-methyl-2-butene, to give a separable mixture of alkylated cyanamides **250** and **251**. Alchornéine (**248**) was prepared from **250** *via* palladium coupling and palladium assisted olefin amination, while isoalchornéine was cyclized from **251**, giving a 1 : 1 separable mixture of natural **249** and unnatural **252** stereoisomers.

While various new approaches toward the synthesis of both martinelline (**253**) and martinellic acid (**254**) have been reported in the literature,[344–358] two new total syntheses of martinelline, one of which also yielded martinellic acid, alkaloids isolated from *Martinella iquitosensis*,[359] have been developed. Ma's synthesis (Scheme 32)[360] used an acid-catalyzed Diels–Alder cycloaddition as the first reaction step to yield the central tricyclic core of




**Scheme 29**




martinelline **256**, with the desired stereochemistry, along with a minor stereoisomer **257** at C-2 (martinelline numbering) in a 2 : 1 ratio. A further series of stepwise reactions gave the bicyclic protected bis-guanidine **258**. Coupling of intermediate **258** with bis-Boc-protected [(*E*)-4-hydroxy-3-methylbut-2-enyl]guanidine **255** prepared from 1-hydroxypropan-2-one gave, after removal of Boc protecting groups, racemic martinelline (±)-**253** in 8% overall yield.

Batey's martinelline and martinellic acid syntheses used basically the same approach (Scheme 33),[361] also starting with an acid-catalyzed hetero Diels–Alder cycloaddition between 4-aminobenzoic acid methyl ester and *N*-Cbz protected 2,3-didehydropyrrolidine in order to obtain the tricyclic *exo*-stereoisomer **260**, which was separated from the *endo*-product **259**. A subsequent series of interconversions yielded racemic martinellic acid **254** in 14% overall yield. Martinelline was prepared by coupling the direct synthetic precursor of martinellic acid with di-Boc protected [(*E*)-5-hydroxy-3-methylpent-2-enyl]guanidine in the presence of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl) and triethylamine, followed by treatment with trifluoroacetic acid in methylene chloride.

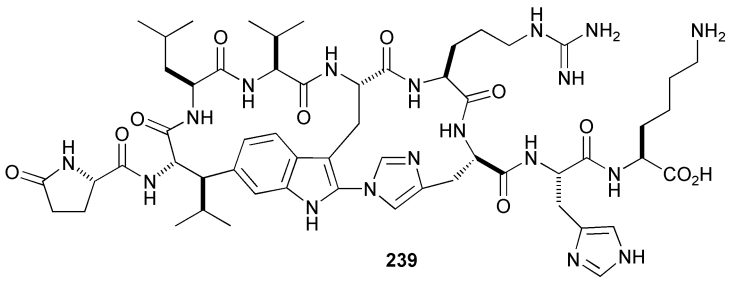
## 6 Natural guanidines from terrestrial invertebrates

An excellent review on the subject of "Pharmacology and biochemistry of spider venoms" included arginine-containing polyamine toxins isolated from arachnids.[362]

A notable new saxitoxin derivative, zetekitoxin AB (**261**), was isolated from the Panamian golden frog *Atelopus zeteki*,[363] after more than 30 years of its first mention in the literature.[364,365] According to the authors,[363] establishing the structure identity of zetekitoxin was difficult because *A. zeteki* was considered an endangered species, and therefore no additional biological material was available for collection and extraction. Structure determination was carried with 300 μg of **261** isolated in 1986, in a 3 : 1 mixture with its de-sulfated derivative. Structure determination included not only extensive NMR analysis, but also a detailed mass spectrometry study, with ESI-MS and CID MS/MS analyses. Zetekitoxin displayed very potent blockage of sodium channels, with an $IC_{50}$ for human heart, rat brain and rat skeletal muscle of 280 ± 3 pM, 6.1 ± 0.4 pM and 65 ± 10 pM, respectively, showing the same selectivity as saxitoxin but with an enhanced potency. This is the first report of a saxitoxin derivative from an amphibian.

## 7 Abbreviations

AIBN = azobisisobutyronitrile; BOM-Cl = benzyloxymethyl chloride; BOP-Cl = bis(2-oxo-3-oxazolidinyl)phospinic chloride; CAN = ceric ammonium nitrate; $CO(Im)_2$ = dimidazolecarbonyl; CSA = camphorsulfonic acid; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC = dicyclohexylcarbodiimide; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD = diethylazodicarboxylate; DIAD = diisopropylazodicarboxylate; DIBAL-H = diisobutylaluminium hydride; DIC = diisopropylcarbodiimide; DIPAD = diisopropylazodicarboxylate; 2,2-DMP = 2,2-dimethoxypropane; DPPA = diphenylphosphorylazide; EDCl = 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride; HMPA = hexamethyl



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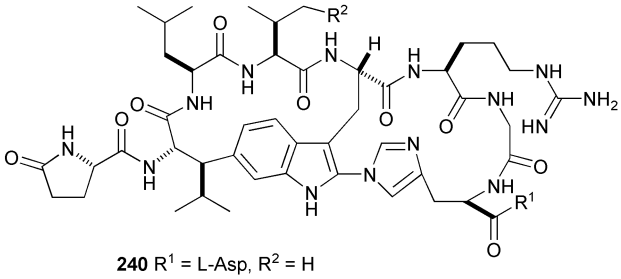
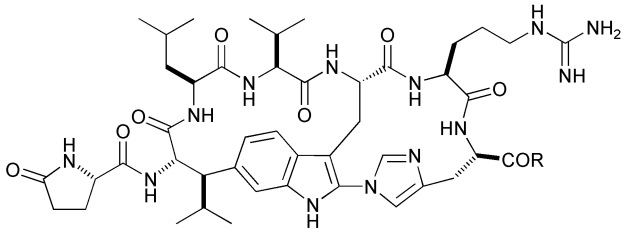
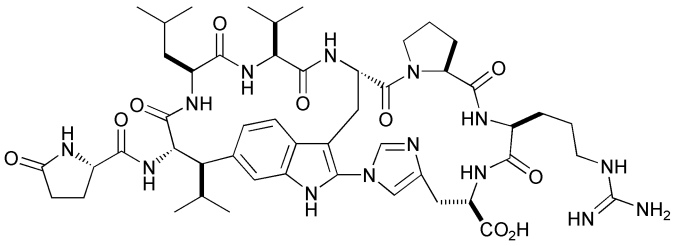


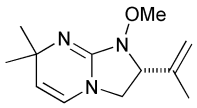
**240** $R^1$ = L-Asp, $R^2$ = H
**241** $R^1$ = L-Arg, $R^2$ = H
**242** $R^1$ = OH, $R^2$ = Me
**243** $R^1$ = L-Asp, $R^2$ = Me
**244** $R^1$ = L-Arg, $R^2$ = Me



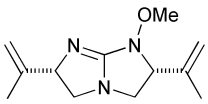
**245** R=H
**246** R= L-His



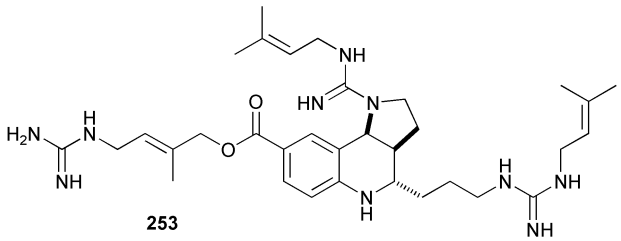
**247**



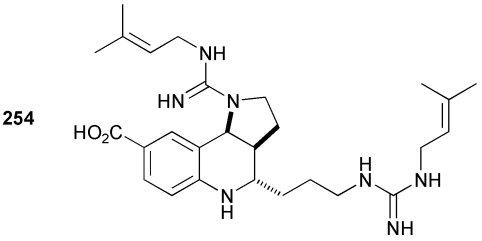
**248**



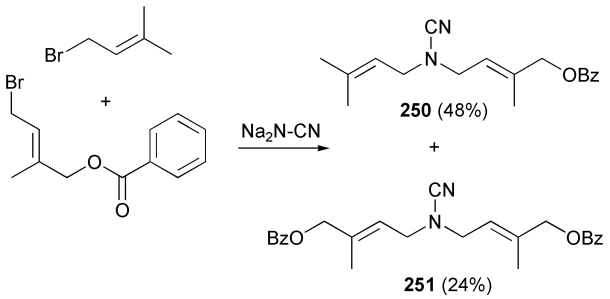
**249**



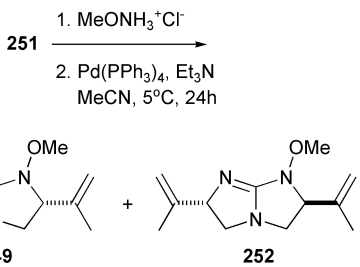
**253**



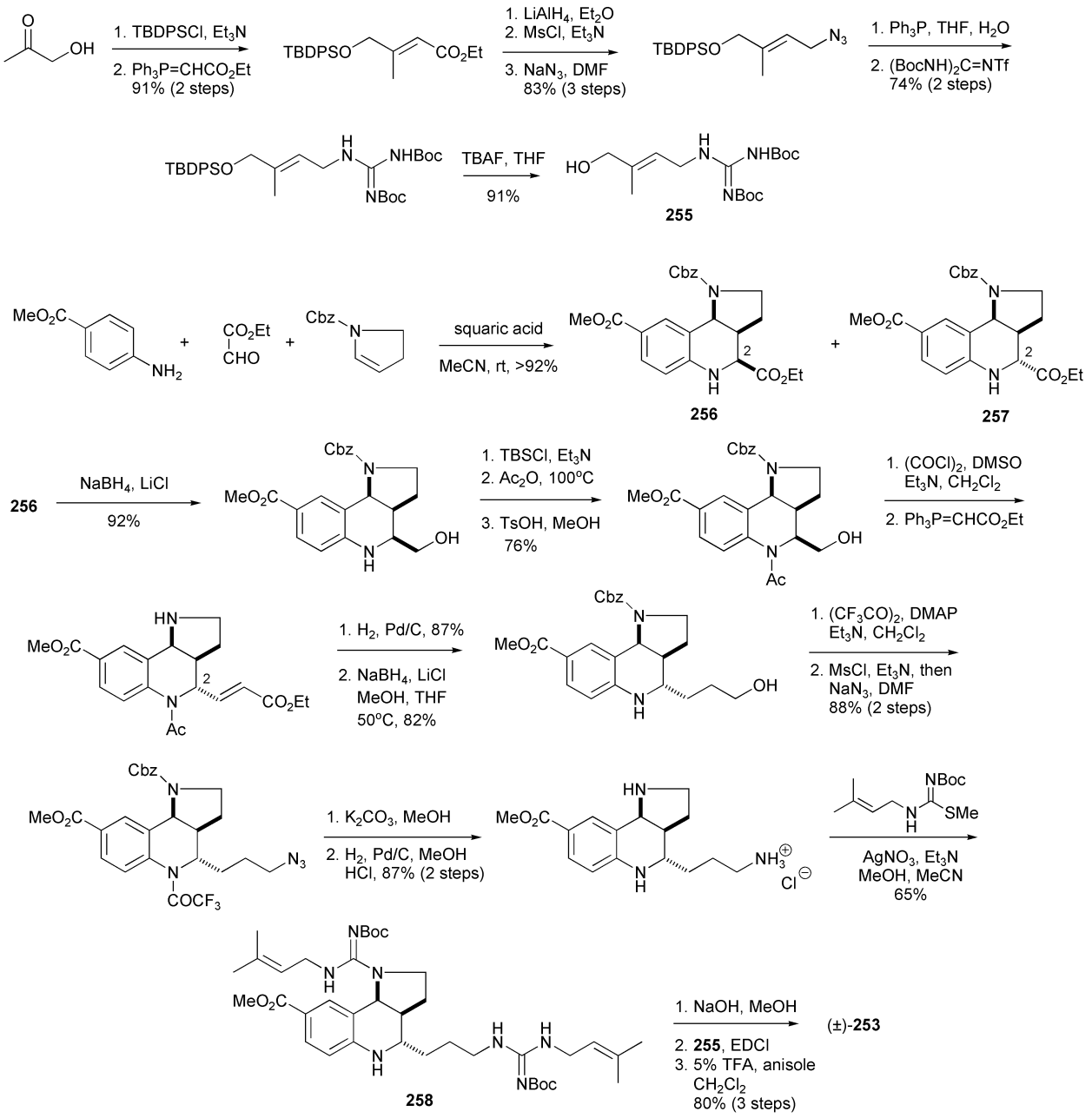
**254**



**Scheme 30**

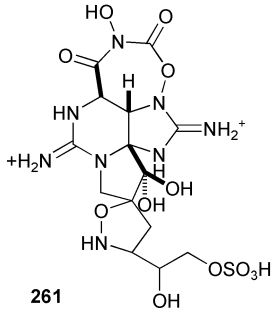


**Scheme 31**

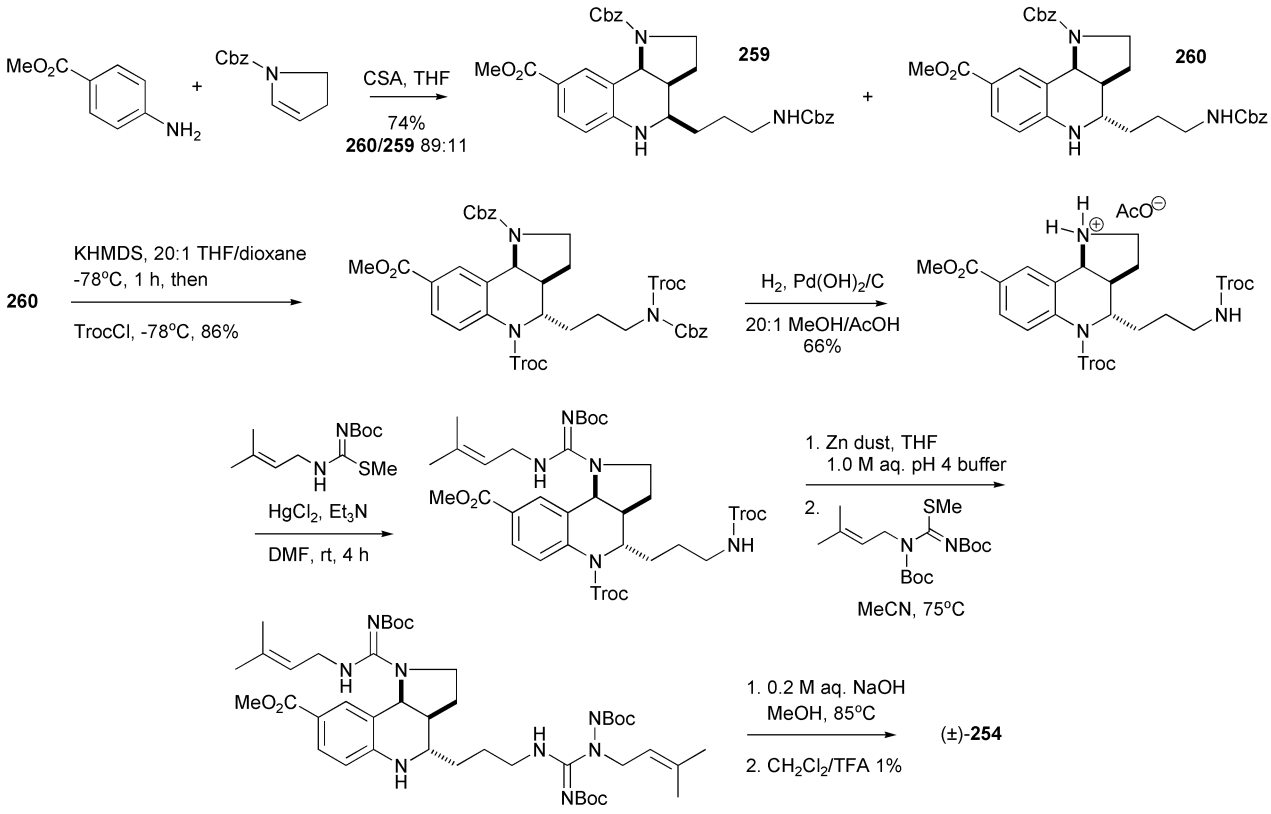



**Scheme 32**

phosphoramide; HOBt = hydroxybenzotriazole; IBX = *o*-iodoxybenzoic acid; i-$C_5H_{11}ONO$ = isoamyl nitrite; LiHMDS = lithium hexamethyldisilazide; KHMDS = potassium hexamethyldisilazide; (+)-MeOB(Ipc)$_2$ = (+)-diisopinocampheylmethoxyborane; MMTr-Cl = *p*-methoxyphenyldiphenylmethyl chloride; MOM-Cl = methoxymethyl chloride; MPM = 4-methoxyphenylmethyl; MS = molecular sieves; NaHMDS = sodium hexamethyldisilazide; NBS = *N*-bromosuccinimide; NCS = *N*-chlorosuccinimide; NMM = *N*-methylmorpholine; NMO = *N*-methylmorpholine *N*-oxide; *o*-DCB = *ortho*-dichlorobenzene; PFP-OH = pentafluorophenol; PMBCl = *p*-methoxybenzyl chloride; PMBNH$_2$ = *para*-methoxybenzylamine; *p*-NBA = *p*-nitrobenzoic acid; PPTS = pyridinium *para*-toluenesulfonate; PyBOP = benzotriazol-1-yl-*N*-oxytris(pyrrolidino)phosphonium hexafluorophosphate; Su = succinimide; TBAF = tetrabutylammonium fluoride; TBAI = tetrabutylammonium iodide; TBDPSCl = *tert*-butyldiphenylsilyl chloride; TBSCl = *tert*-butyldimethylsilyl chloride; TBSOTf = *tert*-butyldimethylsilyl triflate; Teoc = trimethylsilylethyl carbamate ($Me_3SiCH_2CH_2O(CO)N$); TESOTf = triethylsilyl triflate; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical; TIB = bis(trifluoroacetyl) iodobenzene; TIPS = triisopropylsilyl; TMSCHN$_2$ = (trimethylsilyl)diazomethane; TMSONHTMS = N,O-bis-trimethylsilylhydroxylamine; Tr = trityl (triphenylmethyl); TPAP/NMO = tetra-*n*-propylammonium perruthenate(VII)/4-methylmorpholine *N*-oxide; TrocCl = 2,2,2-trichloroethoxychloroformate chloride.



**261**




**Scheme 33**

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