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Graphical Abstract

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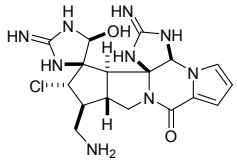
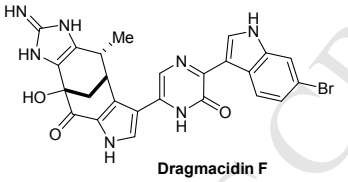


Palau'amine



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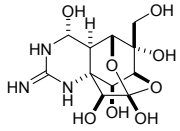
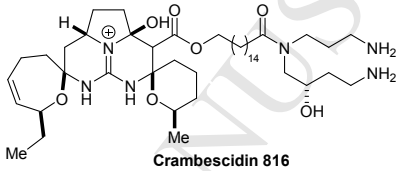


Tetrodoxin



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Syntheses of Cyclic Guanidine-Containing Natural Products

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ABSTRACT

Naturally occurring guanidine derivatives frequently display medicinally useful properties. Among them, the higher order pyrrole–imidazole alkaloids, the dragmacidins, the crambescidins/batzelladines, and the saxitoxins/tetradotoxins have stimulated the development of many new synthetic methods over the past decades. We provide here an overview of the syntheses of these cyclic guanidine-containing natural products.

1. Introduction

Guanidine plays an important role in medicinal chemistry, coordination chemistry, organocatalysis, and biochemistry.[1-4] The ability of this highly polar and basic functional group in establishing strong ionic/hydrogen bonding[5] and cation-π stacking[6,7] interactions with various functional groups has made it particularly useful in the design of small-molecule drugs, metal ligands, and organocatalysts. Additionally, many naturally occurring polycyclic guanidine derivatives possess useful and potent biological properties.[8-13] However, the mode of action of many naturally occurring guanidine derivatives is poorly understood because of the synthetic challenges associated with the preparation of their structural derivatives for in-depth biological studies.[14-17] Some examples are shown in Fig. 1.

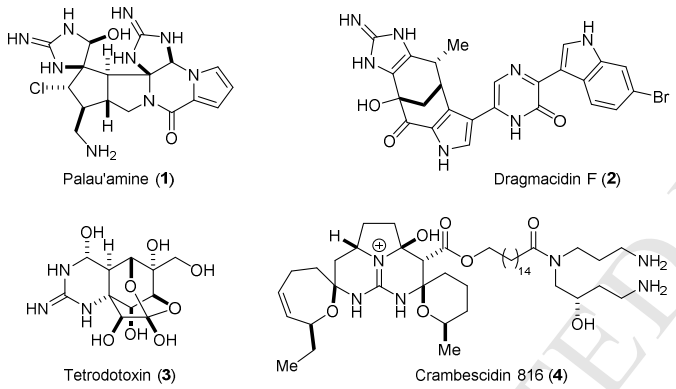


Figure 1. Structures of four representative polycyclic guanidine-containing natural products.

Alkaloids **1**–**4** each represents a class of natural products that are important to the field of total synthesis. Palau'amine (**1**) is a highly nitrogenated, noncrystalline, redox labile, and pH sensitive alkaloid.[18] Its unusual physical and chemical properties preclude the use of many traditional tools for its synthesis. Dragmacidin F (**2**) is another polycyclic alkaloid with exceptionally high nitrogen content.[19] Its drug-like skeleton encompasses four different heterocycles, including a cyclic guanidine-embedding aminoimidazole ring. This unique molecular architecture provides a valuable platform for the development of new chemical reactions. Tetrodotoxin (**3**) is a potent neurotoxin well known for its ability to block the sodium ion channels.[20] The compact and densely functionalized polycyclic skeleton of **3** makes its synthesis a daunting task. Crambescidin 816 (**4**) is a selective calcium ion channel inhibitor that is more potent than the FDA-approved hypertension drug nifedipine.[21] Its guanidine group is enclosed in a pentacyclic moiety. Several review articles exist highlighting the isolation, structural determination, biogenesis, biological functions, and total syntheses of these alkaloids.[22-46] We provide herein an overview of the total syntheses of these four classes of cyclic guanidine-containing natural products.

2. The higher order pyrrole–imidazole alkaloids

The pyrrole–imidazole alkaloids, also known as the oroidin family of alkaloids, are a large group of natural products isolated from a variety of marine sponges.[22,29,32,33] Many of these molecules possess anticancer, antimicrobial, antiviral, or immunosuppressive properties. Structurally, oroidin and its debrominated congeners (**5**) serve as the building blocks of this family of alkaloids in a way similar to isoprene in the world of terpenoids. Oxidation, cyclization, and oligomerization of **5** provide a diverse set of new molecules.[47-53] Among the monomeric family members, hymenialdisines (**6**),[54-61] cyclooroidin (**7**),[52,62-64] agelastatins (**8**),[53,65-82] and dibromophakellin/dibromophakellstatin (**9**)[48,83-90] have been the most popular synthetic targets (Fig. 2).[22,23,26,29,32]

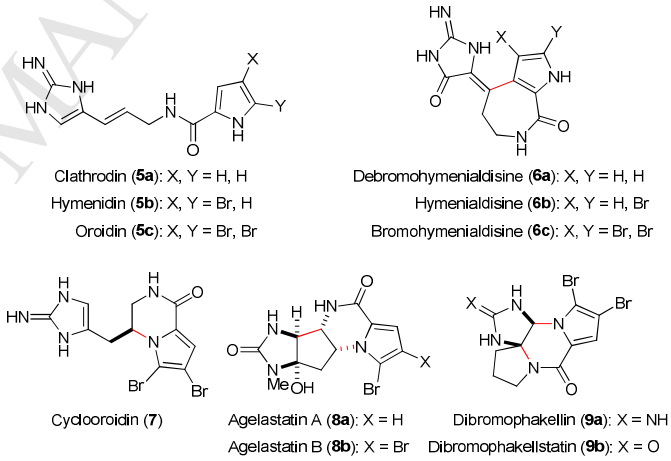


Figure 2. Structures of the basic units of the pyrrole–imidazole alkaloids and some monomeric members.

Several polycyclic pyrrole–imidazole alkaloids deriving from the dimerization of **5** have been found in nature (Fig. 3). With 15–30% nitrogen and 8–42% halogen by weight, these molecules are among the most synthetically challenging natural products. Since the discovery of the first oroidin dimer sceptrin (**10a**) in 1981, many research groups have devoted to studying the synthesis of these structurally unique alkaloids. Constitutionally, sceptrins (**10**)[91-97] are the [2+2] dimers; ageliferins/nagelamides (**11**)[92,98-100] are the [4+2] dimers; and palau'amines/konbu'acidins (**1**),[18,101-103] stylloguanidines/carteramines (**12**),[104-107] axinellamines (**13**),[108,109] massadines (**14**),[110-112] and donnazoles (**15**)[51] are the [3+2] dimers of **5**. Stylissadines (**16**),[113] the only tetrameric member known to date, are the dimers of massadine (**14a**) and 2-*epi*-massadine, which is yet to be identified as a natural product itself. The existence of nagelamides E–G (**11d**–**11f**), the C10-epimers of ageliferins (**11a**–**11c**), and the 2-*epi*-

massadine fragment in **16** indicate that the biogenic dimerization of **5** is not a concerted cycloaddition reaction. Instead, a single-electron oxidation is involved as indicated by Molinski and Romo's metabiosynthetic studies.[49,50]

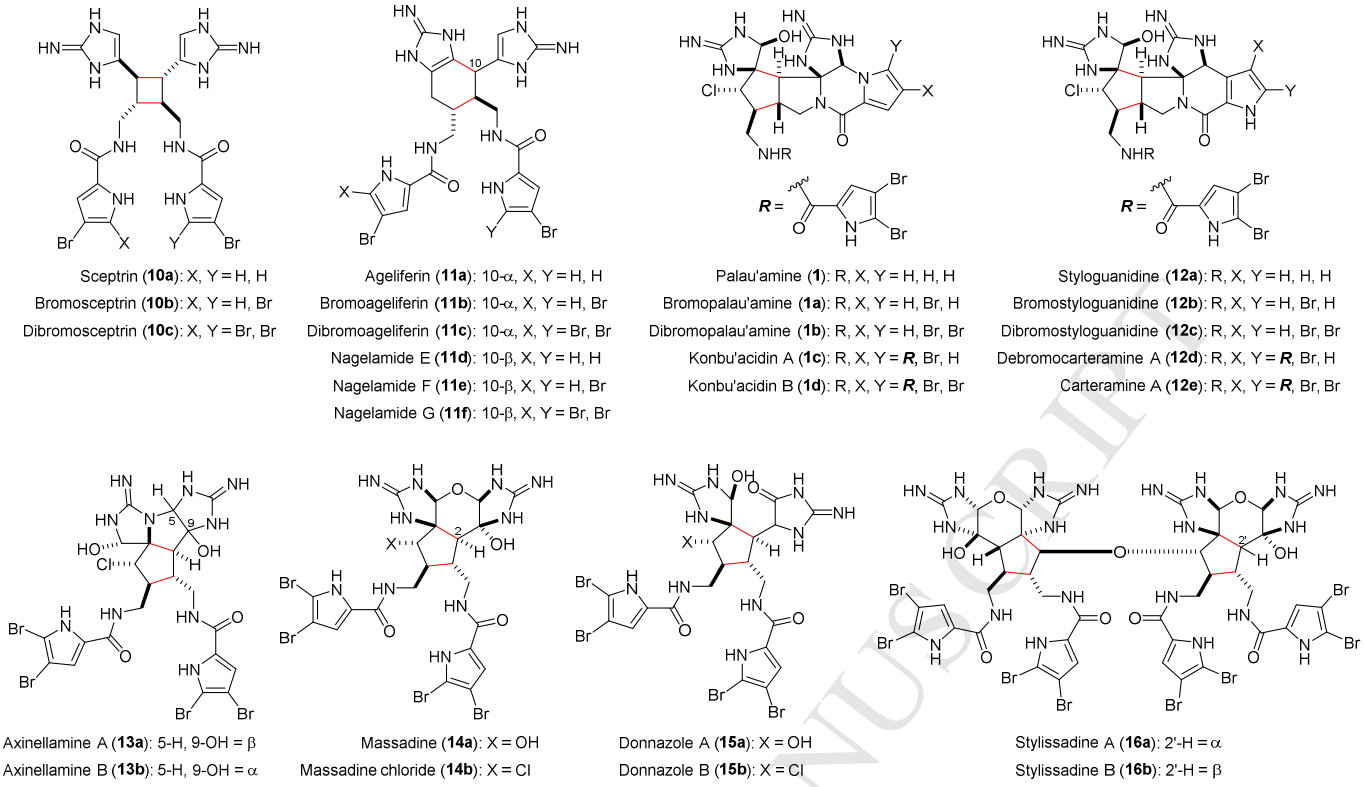


Figure 3. Structures of the dimeric and tetrameric pyrrole–imidazole alkaloids.

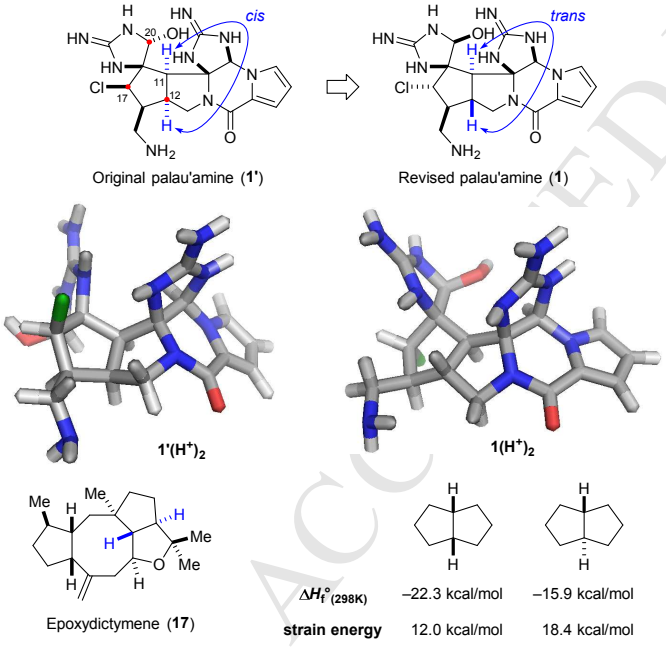


Figure 4. Structures of the originally proposed and revised palau'amine (**1'** and **1**) and epoxydictymene (**17**), the equilibrium geometry of **1'(H$^+$)$_2$** and **1(H$^+$)$_2$**, and the strain energies of *cis*- and *trans*-bicyclo[3.3.0]octane.

The structural determination of palau'amine (**1**) is quite an interesting story. Kinnel and Scheuer reported in 1993 the isolation of palau'amine, and proposed its structure to be **1'** with a *cis*-H11/H12 configuration (Fig. 4).[18] Although the H11/H12 coupling constant of palau'amine was unusually large for a *cis* configuration and the NOE/ROESY data could not be reconciled for the C20 aminal stereocenter with **1'**,[101] they considered that the *trans*-H11/H12 configured ring system would be too strained to exist. Styloguanidines (**12a**–**c**)[104] and konbu'acidins (**1c**,**d**)[102] are believed to have the same stereochemistry as palau'amine. It was not until 2007 that Köck, Quinn, and Matsunaga elucidated the correct structure of palau'amines, konbu'acidins, and styloguanidines.[103,105,106,114]. Surprisingly, palau'amine embeds a *trans*-fused 5,5-bicyclic ring system. Notably, although *trans*-bicyclo[3.3.0]octane is 6.4 kcal/mol more strained than its cis-isomer,[115] incorporation of a heteroatom (a nitrogen atom for palau'amine) into the ring system can help relieve the torsional strain.[116] We found that $\Delta\Delta G_{(gas)298K}$ (DFT, B3LYP/6-31G*) for the protonated "palau'amines" **1(H$^+$)$_2$** and **1'(H$^+$)$_2$** is only 3.7 kcal/mol although Köck reported that "*cis*-styloguanidine" is 6.5 kcal/mol more stable than **12a** (DFT, B3LYP/6-31G*).[25] Interestingly, **1** is not the only natural product bearing a *trans*-fused 5,5-bicyclic ring system. Epoxydictymene (**17**) isolated from the brown algae *Dictyota dichotoma* also possesses a heteroatom-containing *trans*-fused 5,5 ring system.[117] The structure of **17** was determined by X-ray analysis of its dihydroxylated derivative and confirmed by total synthesis by Schreiber[118,119] and Paquette[120] in 1994 and 1997, respectively.

2.1. Synthetic contributions from the Overman group

The Overman group reported the use of an azomethine imine cycloaddition reaction to establish the core structure of *cis*-"palau'amine" (**1'**) in 1997.[121-123] This approach allowed for an efficient synthesis of a highly functionalized *cis*-palau'amine analog **23** in 2007 (Fig. 5).[124] The NMR data of **23**, in particular, the H11/H12 coupling constant, are significantly different from those of the natural palau'amine, supporting the then proposed structural revision of palau'amine. The synthesis started with a

ring-closing metathesis of **17** to deliver dihydropyrrole **18**. Heating an ethanolic solution of **18** with thiosemicarbazide (**19**) initiated a tandem reaction sequence comprising a condensation of **18** and **19**, an intramolecular [3+2] cycloaddition reaction of the resulting **20**, and a cyclization of the cycloaddition product **21** to give **22**. The intramolecular cycloaddition of **20** was highly stereoselective, giving the 3-azabicyclo[3.3.0]octane molecular framework and the two nitrogen-containing quaternary centers with complete stereochemical control. Cleavage of the N–N linkage of **22** followed by installation of the second iminohydantoin group furnished **23**.

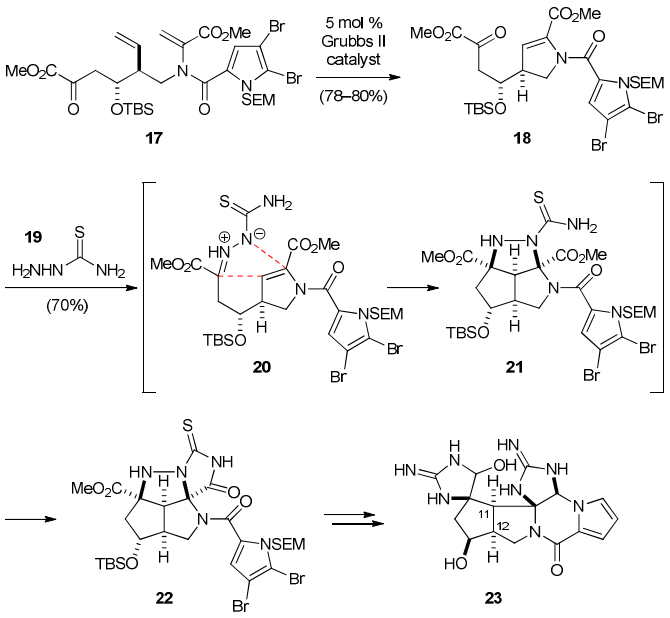


Figure 5. Overman's synthetic approach to "*cis*-palau'amine" (**1'**).

2.2. Synthetic contributions from the Carreira group

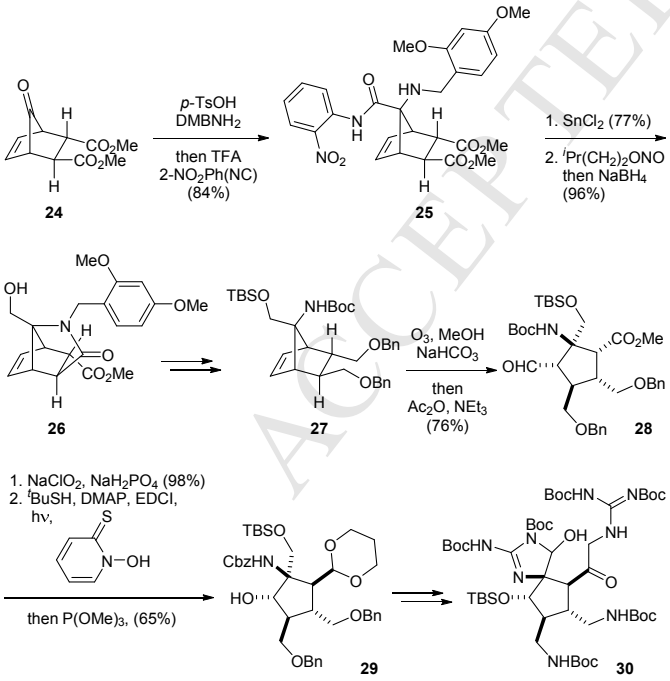


Figure 6. Carreira's synthetic approach to massadine (**14a**).

The first asymmetric synthesis of the core skeleton of the [3+2]-type pyrrole–imidazole dimers was reported by the Carreira group in 2000.[125,126] They also successfully constructed a fully functionalized massadine synthetic intermediate in 2011.[127,128] Specifically, they prepared ketone **24** from allyldimethylsilyl cyclopentadiene and dimethyl fumarate by a Diels–Alder reaction followed by Tamao oxidation (Fig. 6). Subjecting **24** to an Ugi four-component coupling reaction gave **25**. The amide group of **25** was then cleaved through reduction of the nitro group with tin(II) chloride and treatment of the resulting aniline with isoamyl nitrite to give a diazo intermediate that reacted with the amide group to yield an acylbenzotriazole. Subsequent reduction of the acylbenzotriazole group was accompanied with a lactam formation to yield **26**. After the *N*-protecting group switch and amide reduction, the olefin group of **27** was cleaved by ozonolysis to reveal the cyclopentyl core skeleton of massadine. Cleavage of the ozonide in the presence of methanol using the method developed by Schreiber[129] gave the terminally differentiated product **28**. Lindgren oxidation followed by Barton decarboxylation then yielded **29**. Finally, installation of the two guanidine groups provided the fully functionalized massadine core structure **30**.

2.3. Synthetic contributions from the Austin group

The Austin group used a [2+2+1] cycloaddition approach to construct the cyclopentyl core of palau'amine in 2000.[130,131] The intramolecular Pauson–Khand cyclization of enyne **31** gave **32** and **33** as a 4:1 mixture of diastereomers (Fig. 7). Subsequent reduction of the enone group and cleavage of the N–O linkage by single-electron reduction revealed the core skeleton of **1'**. Interestingly, without prior saturation of the enone group, reduction of **32** directly with samarium(II) iodide would lead to the cleavage of the enone γ-C–O bond instead of the N–O bond.

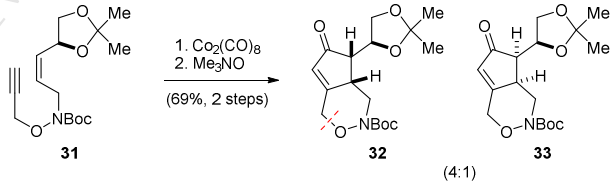


Figure 7. Austin's synthetic approach to "*cis*-palau'amine" (**1'**).

2.4. Synthetic contributions from the Romo group

The Romo group has made significant contributions to understanding of the special reactivity of the pyrrole–imidazole family of alkaloids.[132-136] They have also provided valuable insights into the biogenesis of both the monomeric[53] and the dimeric[132] pyrrole–imidazole alkaloids with biomimetic syntheses. Through collaboration with the Molinski group, they further provided evidence that the biogenic dimerization of **5** is promoted by single-electron oxidation.[49,50,137]

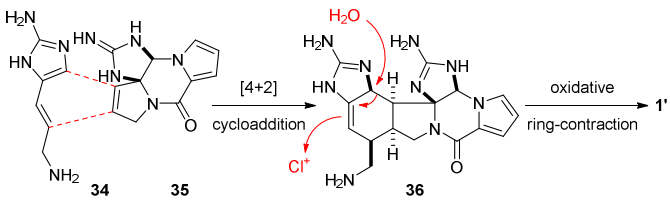


Figure 8. The Kinnel–Scheuer biosynthetic hypothesis.

It was generally believed that the [3+2]-type pyrrole–imidazole dimers were derived from the [4+2]-type dimers through an oxidative skeletal rearrangement. For example, the biosynthesis of "palau'amine" (**1'**) might involve a [4+2] cycloaddition reaction of 3-amino-1-(2-aminoimidazolyl)prop-1-ene (**34**) and 11,12-dehydrophakellin (**35**) (Fig. 8) as proposed by Kinnel and Scheuer in 1998.[101] A chloroperoxidase-mediated oxidative ring contraction of the resulting **36** would then yield **1'**. While attempts to thermally induce the homodimerization of oroidin (**5c**) failed to generate dibromoageliferin (**11c**),[52] the Romo group showed in 2001 that the ageliferin skeleton could be obtained from a Diels–Alder reaction of a vinylimidazolinone derivative and an electron-deficient dienophile.[132] They also demonstrated that the regioselectivity of this [4+2] cycloaddition reaction could be controlled by tuning the electronic properties of the imidazolinone group. For example, heating a solution of **37** bearing a tosylvinyl (Tsv) protecting group with enone **38** gave **39** exclusively (Fig. 9).[133] However, hydrogenation of the electron-deficient Tsv group of **38** to an electron-rich tosylethyl (Tse) group before reacting with **39** led to the formation of a 2.5:1 mixture of regioisomers.

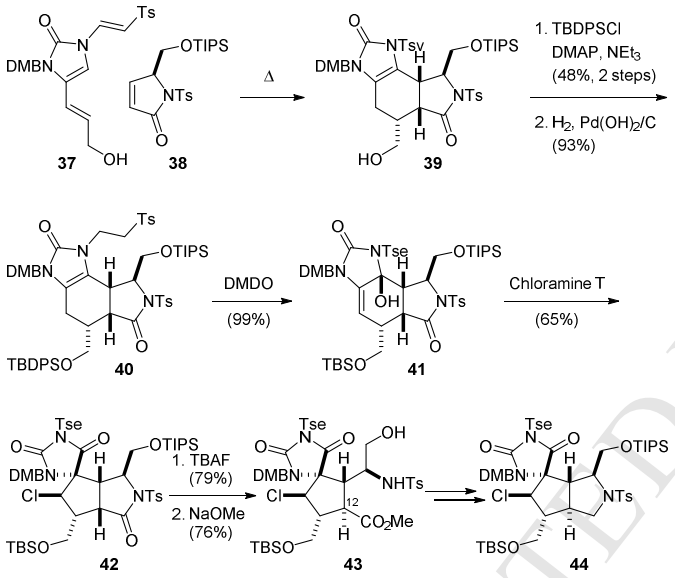


Figure 9. Romo's synthetic approach to palau'amine (**1**).

To induce the Scheuer oxidative skeletal rearrangement, the hydroxyl group of **39** was protected and the Tsv group was saturated to give the Tse-protected **40**. Oxidation of **40** with dimethyldioxirane (DMDO) provided allylic alcohol **41**. Subsequent treatment of **41** with chloramine T promoted the Scheuer-type ring contraction reaction to afford **42**. Notably, a fine control of the reaction conditions is crucial to the success of this rearrangement reaction. Oxidation of **40** with *meta*-chloroperoxybenzoic acid (mCPBA) would destroy the ageliferin skeleton. Oxidation of **41** with *N*-chlorosuccinimide (NCS), or replacing the electron-rich Tse group with the electron-deficient Tsv or Ts group would also lead to aromatization of the six-membered ageliferin core skeleton.

Since the relative stereochemistry of palau'amine was revised in 2007,[103,105,106,114] the Romo group has redirected their focus to establishing the *trans*-fused 5,5-bicyclic molecular framework of **1**.[136] Removal of the triisopropylsilyl (TIPS) protecting group of **42** followed by cleavage of the lactam group and C12-epimerization provided **43**. Subsequent protection of the hydroxyl group, reduction of the ester group, and cyclization under Mitsunobu conditions gave pyrrolidine **44**. The coupling constants and observed NOE signals of **44** are consistent with those reported for palau'amine (**1**), thus providing the first direct experimental support for the *trans*-H11/H12 configuration for palau'amine.

2.5. Synthetic contributions from the Lovely group

The Lovely group also reported the use of a Diels–Alder approach to construct the core skeleton of ageliferin in 2001.[138-140] They found that vinylimidazole could serve as either a diene or a dienophile in the Diels–Alder reactions. Heating a solution of **45** gave the Diels–Alder adduct **46** as the major product (Fig. 10). Interestingly, the inverse electron-demand Diels–Alder reaction product **47** was also obtained. Cleavage of the N–O linkage of **46** by single-electron reduction yielded **48**. Subsequent treatment of **48** with the Davis reagent or DMDO induced the Scheuer-type oxidative ring-contraction reaction to afford the palau'amine core **49**.

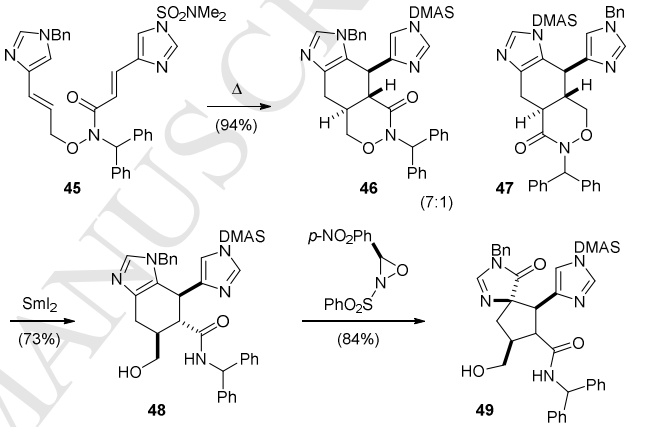


Figure 10. Lovely's synthetic approach to palau'amine (**1**).

2.6. Synthetic contributions from the Ohta group

The Ohta group has used the Diels–Alder approach to accomplish the biomimetic synthesis of 12,12'-dimethylageliferin in 2002.[141,142] Thermolysis of **50** promoted a homodimerization to give a 50:1 mixture of **51** and **52**, favoring the *exo*-Diels-Alder reaction product (*endo*/*exo* relative to the ester group) (Fig. 11). Computational studies confirmed that there is a favorable HOMO/LUMO interaction for the homodimerization of **50**. The ester groups of **51** were then reduced and the thiophenol groups were cleaved by nickel boride reduction to give **53** after protection of the hydroxyl groups. Lithiation of **53** followed by reaction with trisyl azide yielded **54**. The azido groups were reduced and protected as imines to provide **55**. Finally, installation of the pyrrole groups and deprotection furnished 12,12'-dimethylageliferin (**56**). This work is the first synthesis of a fully functionalized dimer pyrrole–imidazole alkaloid.

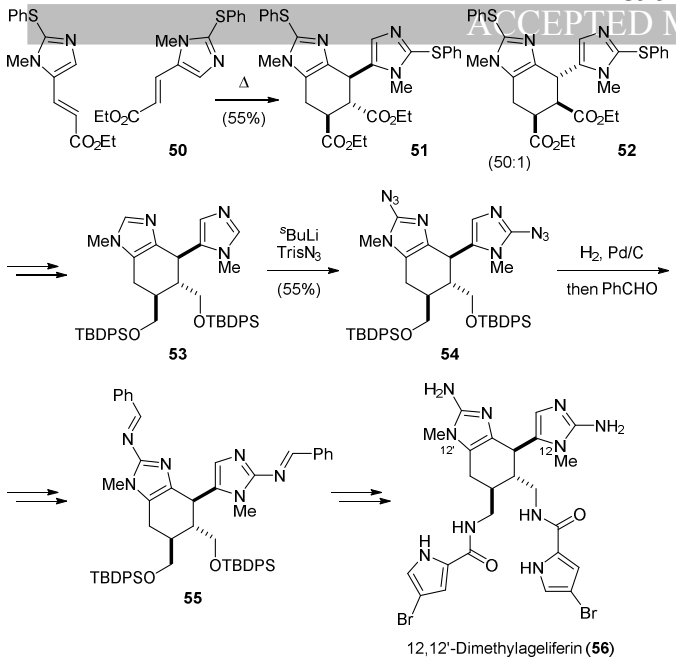


Figure 11. Ohta's synthesis of 12,12'-dimethylageliferin (**56**).

2.7. Synthetic contributions from the Baran group

The Baran group has completed the total syntheses of all cyclic pyrrole–imidazole dimers. They first achieved the synthesis of sceptrin (**10a**) and ageliferin (**11a**) in 2004.[143-147] They then accomplished the syntheses of axinellamines (**13**) and massadines (**14**) in 2008.[148-150] Subsequently, they completed the total synthesis of the legendary natural product palau'amine (**1**) in 2010.[151] In 2011, the Baran group further reported the asymmetric synthesis of **1**, **13**, and **14** using an enantioselective Diels–Alder reaction to set up the absolute stereochemistry of these alkaloids.[152] They also disclosed a practical approach that enables the gram-scale synthesis of **13** in 2011.[153]

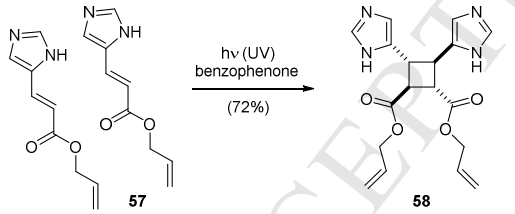


Figure 12. D'Auria's synthetic studies of sceptrin (**10a**).

Whereas the [2+2] photocycloaddition would be the most straightforward synthetic strategy for assembling sceptrin (**10a**), both the Faulkner group and the Baran group found that photolysis of hymenidin (**5b**) under various conditions failed to deliver the C_2 symmetric dimer **10a**.[91,143] To date, the only successful photo-dimerization of a vinylimidazole derivative was reported by the D'Auria group in 1998.[154] Photolysis of allyl urocanate (**57**) in the presence of the photosensitizer benzophenone gave the head-to-head dimer **58** (Fig. 12). Computational studies suggest that both the HOMO/LSOMO and the HSOMO/LUMO interactions play a role in this reaction. Intriguingly, low stereoselectivity was observed for the photo-dimerization of methyl and ethyl urocanates.

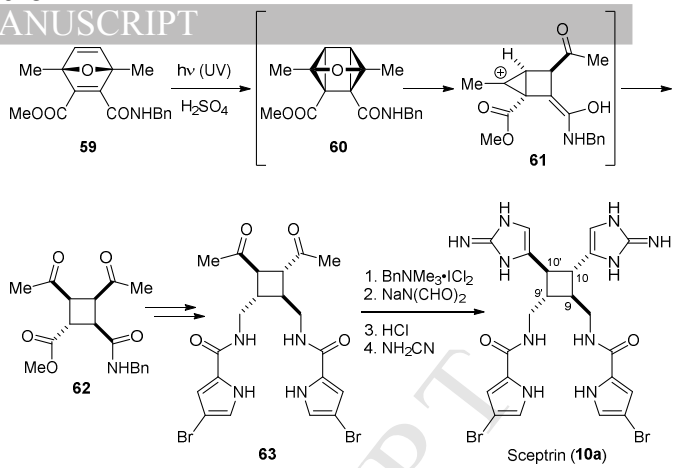


Figure 13. Baran's synthesis of sceptrin (**10a**).

Because of the difficulty associated with the photodimerization of **5b**, the Baran group used an alternative photocycloaddition approach to construct the cyclobutane ring of **10a**. Photolysis of **59** led to a facile [2+2] cycloaddition reaction to give **60** (Fig. 13). An acid-promoted 3-oxaquadricyclane rearrangement reaction[143] then occurred to give **62** via cation **61**. Subsequent installation of the pyrrole group afforded **63**. Chlorination of **63** followed by amination and hydrolysis of the formyl groups gave a bis-α-aminoketone. Subsequent reaction with cyanamide then provided sceptrin (**10a**). This approach allowed for a gram-scale synthesis of **10a** with an impressive 24% overall yield.

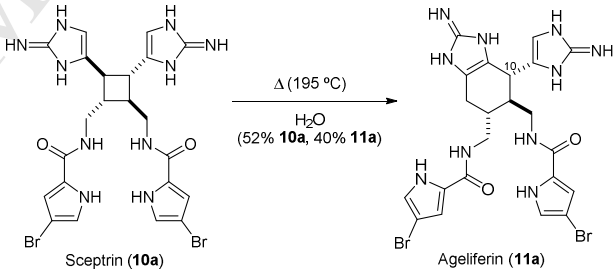


Figure 14. Baran's synthesis of ageliferin (**11a**).

Based on the observation that sceptrin (**10a**) and ageliferin (**11a**) were frequently isolated together in sponges, the Baran group proposed that **11a** is derived from **10a** through a [1,3]-sigmatropic rearrangement reaction.[155,156] Supportive of this hypothesis is the observation that thermolysis of **10a**•2HCl in water gave **11a**•2HCl, together with a small amount of nagelamide E (**11d**), the C10 diastereomer of **10a** (Fig. 14).[144] Computational studies by the Houk group suggest that this rearrangement reaction proceeds through a dicationic diradical intermediate.[146]

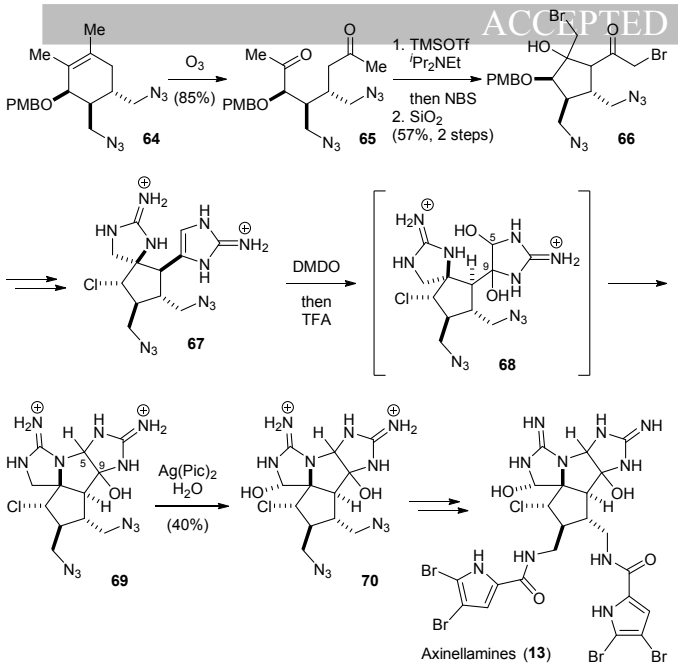


Figure 15. Baran's synthesis of axinellamines (**13**).

The Baran group has also accomplished the syntheses of all [3+2]-type pyrrole–imidazole dimers. They first completed the synthesis of axinellamines (**13**), using an intramolecular aldol reaction to establish its central cyclopentyl core skeleton.[148,149] Specifically, ozonolysis of **64** obtained from a Diels–Alder reaction provided diketone **65** (Fig. 15). Bromination of **65** followed by treatment of the resulting bis-α-bromoketone with dry silica gel induced an intramolecular aldol reaction to yield **66**. Subsequent installation of the two cyclic guanidine groups and the chlorine atom gave **67**. Oxidation of the aminoimidazole group of **67** with DMDO gave diol **68**, which cyclized in acid to afford **69**. Subsequent oxidation of **69** with silver(II) picolinate occurred selectively at the α-position of the cyclic guanidine group to provide **70**. Finally, installation of the pyrrole groups furnished **13**.

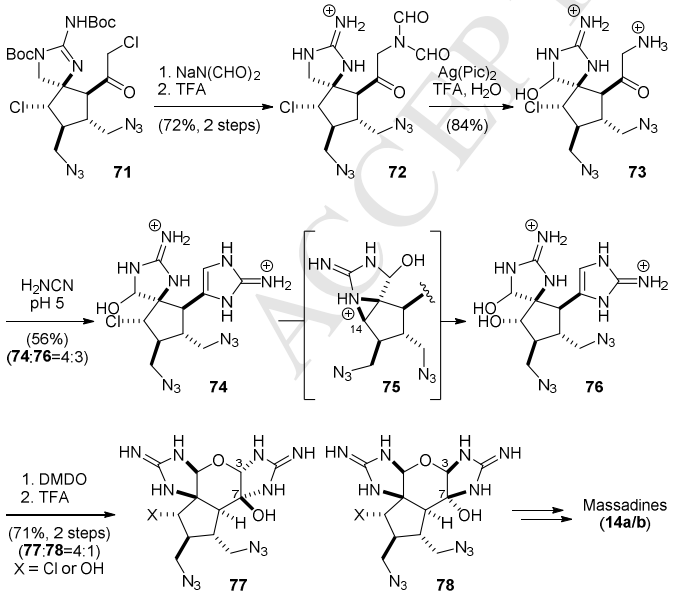


Figure 16. Baran's synthesis of massadines (**14**).

After completing the synthesis of axinellamines (**13**), the Baran group developed a modified route to enable the synthesis of massadines (**14**).[150] Reaction of α-chloroketone **71**, an advanced axinellamine synthetic intermediate, with diformylamide followed by removal of the guanidine protecting groups gave **72** (Fig. 16). Oxidation of **72** with silver(II) picolinate and hydrolysis of the formyl groups afforded α-aminoketone **73**. The aminoimidazole group was then introduced by reacting **73** with cyanamide to provide **74**. Partial hydrolysis of the chloride yielded **76**. Consistent with Romo's previous observation in the study of palau'amine synthesis,[135] this reaction proceeded through the intermediacy of aziridinium ion **75** leading to the retention of the C14 configuration. Oxidation of **74**/**76** with DMDO followed by an acid-promoted cyclization gave a mixture of **77** and **78**, favoring the undesired C3,C7-configurations. Finally, installation of the pyrrole groups completed the synthesis of massadines (**14**). It is believed that 3,7-*epi*-massadines are also natural products.

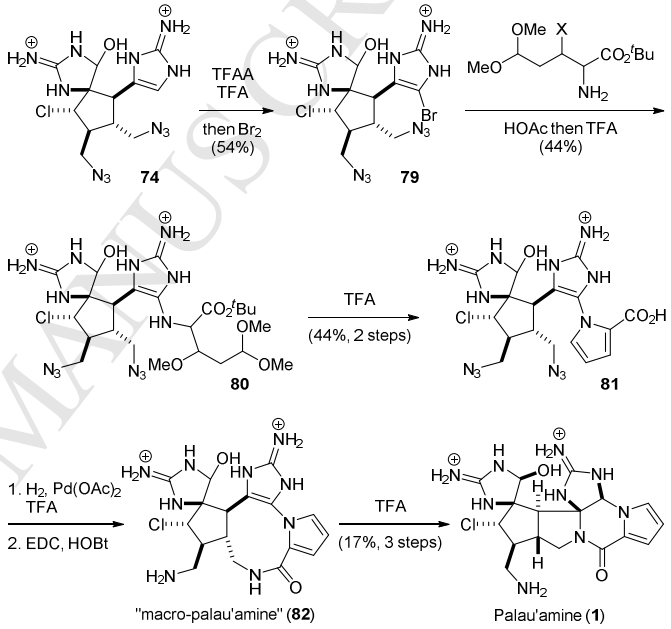


Figure 17. Baran's synthesis of palau'amine (**1**).

The Baran group accomplished the synthesis of legendary alkaloid palau'amine (**1**) in 2010, using an intriguing macrocyclization approach to construct its "phakellin" subunit.[151] The strategy of constructing highly strained natural products via macrocyclization was introduced by Kishi for the mitomycin synthesis in 1971.[157-160] To synthesize **1**, the aminoimidazole group of the massadine synthetic intermediate **74** was brominated to give **79** (Fig. 17). The pyrrole group was then installed through a more nucleophilic acylpyrrole surrogate to give **80**. Treatment of **80** with acid promoted the formation of pyrrole and the removal of the *tert*-butyl ester group to yield **81**. Reduction of the azido groups followed by an intramolecular amide coupling gave "macro-palau'amine" (**82**). Heating **82** in acid induced a smooth transannular cyclization and established the highly strained *trans*-fused 5,5 bicyclic ring system, furnishing the long-sought target palau'amine (**1**). In addition to minimizing the use of protecting groups, this elegant synthesis also exploits the concept of redox economy. The asymmetric syntheses of axinellamines (**13**), massadines (**14**), and palau'amine (**1**) were accomplished in 2011 by the development of a catalytic asymmetric Diels–Alder reaction to generate optically active **64**.[152]

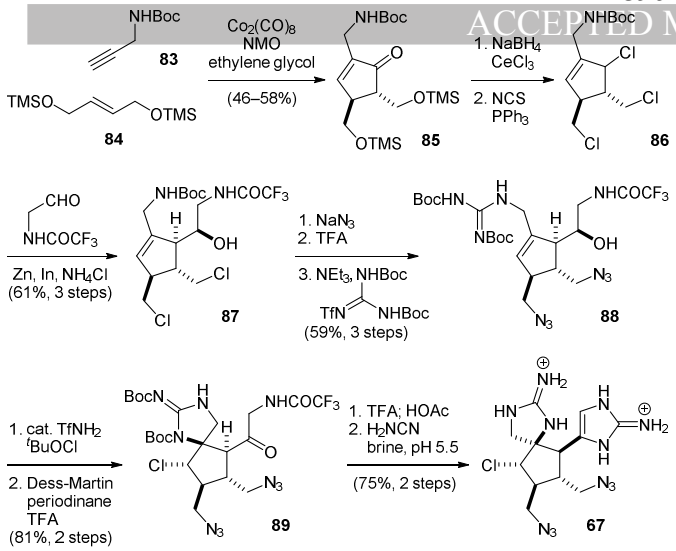


Figure 18. Baran's new synthesis of axinellamines (**13**).

In 2011, the Baran group reported a new synthetic route for achieving the gram-scale synthesis of axinellamines (**13**).[153] The central cyclopentane core was assembled by an intermolecular Pauson–Khand reaction of **83** and **84** (Fig. 18). Subsequent reduction of the resulting enone **85** followed by chlorination gave **86**. Next, an interesting In(0)/Zn(0)-promoted Barbier-type reaction was used to deliver the amino alcohol side-chain for constructing the aminoimidazole group. Introduction of the nitrogen functionalities to **87** then yielded **88**, which was subjected to a chloroamidation reaction in the presence of a catalytic amount of trifluoromethanesulfonamide ($TfNH_2$) to afford spiro-guanidine **89**. Finally, installation of the aminoimidazole group gave **67**, an advanced axinellamine synthetic intermediate in their previous approach. Only seven purifications were used for the entire synthesis and over 1 g of **13** was prepared in one run.

2.8. Synthetic contributions from the Birman group

The Birman group also accomplished the synthesis of sceptrin (**10a**) in 2004.[161] Both Baran and Birman recognized the symmetry of sceptrin and constructed its core skeleton using a [2+2] photocycloaddition reaction with a non-biogenic disconnection. Photolysis of **90** and **91** in the presence of benzophenone induced the [2+2] cycloaddition reaction to give **92** (Fig. 19). Methanolysis of the succinic anhydride group followed by the introduction of the nitrogen atoms for attaching the pyrrole groups provided **93**. Saponification of **94** was accompanied with C10-epimerization to give the desired all-*trans* configuration of **10a**. Subsequent Arndt–Eistert homologation followed by bromination afforded bis-α-bromoketone **94**. The aminoimidazole groups were then constructed by reacting **94** with Boc-guanidine to afford **95**. Finally, introduction of the bromopyrrole or dibromopyrrole groups concluded the syntheses of sceptrin (**10a**) and dibromosceptrin (**10c**).

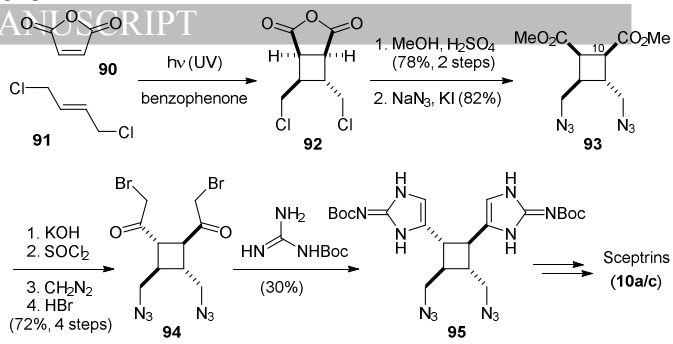


Figure 19. Birman's synthesis of sceptrin (**10a**).

2.9. Synthetic contributions from the Harran group

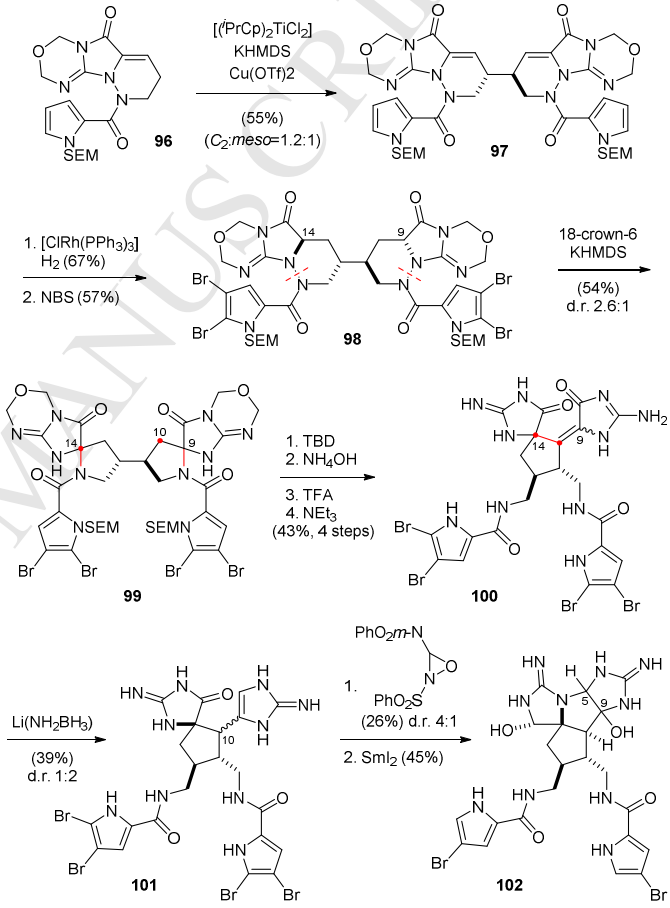


Figure 20. Harran's synthetic approach to axinellamine (**13**).

The Harran group reported a unique approach for the synthesis of palau'amine (**1**) in 2005.[162] A refined route allowing for the construction of the entire axinellamine skeleton was later published in 2012.[163] Using a retro-Scheuer-type rearrangement, they have also achieved the synthesis of ageliferin (**11a**).[164] To construct the axinellamine skeleton, they first oxidized the titanium enolate of **96** to initiate a homocoupling reaction (Fig. 20). Hydrogenation of the resulting C_2-symmetric **97** followed by bromination yielded **98**. Deprotonation of **98** at the C9 and C14 positions led to the cleavage of the N–N linkages. Cyclization of the resulting amide anions with the imines gave **99** as a mixture of diastereomers. Deprotonation of the two major ismoers with a strong amine base regenerated imines and induced the imine-enamine isomerization. Addition of the C10-enamine to the C14-

imine followed by hydrolysis of the oxadiazine group and removal of the protecting group of the pyrroles gave **100** as a mixture of C14- and *E*/*Z*-isomers. Reduction of the enone group using Myers' lithium amidotrihydroborate (LAB)[165] gave **101**. Interestingly, the natural C10-epimer was obtained as the minor product. Oxidation of the correct isomer **101** with the Davis reagent gave the axinellamine skeleton. Finally, reduction of the iminohydantoin group proceeded with debromination to provide 13-dechloro-6',6"-didebromo-axinellamines (**102**).

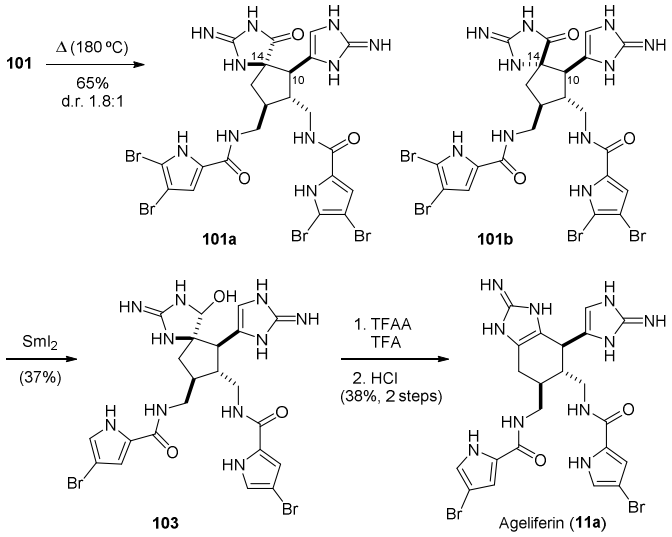


Figure 21. Harran's synthesis of ageliferin (**11a**).

The Harran group found that **101** readily equilibrated upon thermolysis to give a mixture of C10- and C14-diastereomers, with **101a** and **101b** being the major diastereomers (Fig. 21).[164] The cleavage of the C10–C14 linkage in this reaction is reminiscent of the sceptrin-ageliferin rearrangement reaction reported by Baran.[146] Reduction of the major product **101a** gave **103**, which underwent an acid-promoted ring-expansion reaction to yield ageliferin (**11a**).

2.10. Synthetic contributions from the Gleason group

The Gleason group reported an efficient synthesis of the skeleton of the originally proposed palau'amine (**1'**) in 2008.[166,167] They also used a Diels–Alder/oxidative cleavage strategy to establish the key cyclopentyl ring of **1**'. Although similar to the approach used by Carreira, the Gleason's approach allows for a more direct introduction of the requisite functionalities. They found that reaction of diene **104** and chloromethyleneoxazolone **105** gave a 1:1 ratio of **106** and **107** (Fig. 22). Diene **104** is rather stable toward 1,5-hydrogen shift and has a half-life time of 37 h at 23 °C. Subsequent Rubottom oxidation of **106**/**107** and methanolysis of the oxazolone group gave **108** and **109**. Oxidative cleavage of the α-hydroxy ketone group of **109** yielded **110** bearing the "*cis*-palau'amine" stereochemistry.

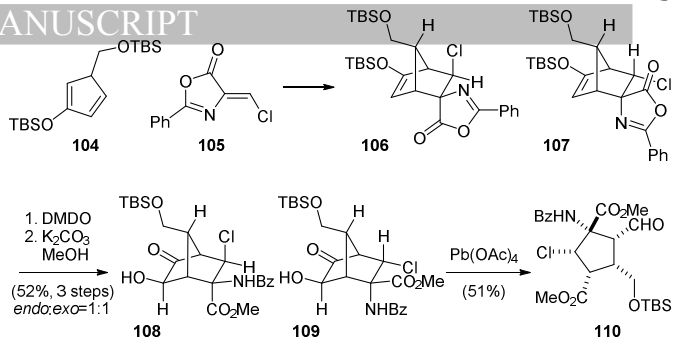


Figure 22. Gleason's synthetic approach to "*cis*-palau'amine" (**1'**).

2.11. Synthetic contributions from the Gin group

The Gin group also reported a creative and flexible approach for the syntheses of both the original and revised core structures of palau'amine (**1'**/**1**) in 2008.[168] Dihydroquinone **111** obtained from the Diels–Alder reaction of cyclopentadiene and benzoquinone was oxidized to afford epoxide **112** (Fig. 23). Treating **112** with sodium ethoxide induced a Favoskii-type rearrangement to give **113**. Alkylation of **113** then provided **114**, which underwent a spontaneous [3,3]-sigmatropic rearrangement to give an equilibrium mixture of **114** and **115** in a ratio of 2.6:1. The subsequent Meerwein–Verley–Pondorf reduction proceeded under Curtin–Hammett kinetic control through **115** to yield **116** after chlorination. Curtis rearrangement of **116** then provided **117**. Reaction of **117** with hydroxylamine followed by treatment of the resulting oxime with thionyl chloride promoted the Beckmann rearrangement to give **118**. The amide group was next protected and the olefin group was cleaved by ozonolysis. Reductive workup gave a diol that was treated with acid to induce the lactone formation. The alcohol group was protected in situ to give **119** bearing the correct relative stereochemistry of **1**. Elaboration of **114**/**115** through **114** could also be achieved by treating this mixture with benzeneselenol to protect the enone group of **114**. Further elaboration through a reaction sequence similar to that used for preparing **119** provided the "all-*cis*" diastereomer of **119** bearing the relative stereochemistry of **1'**.

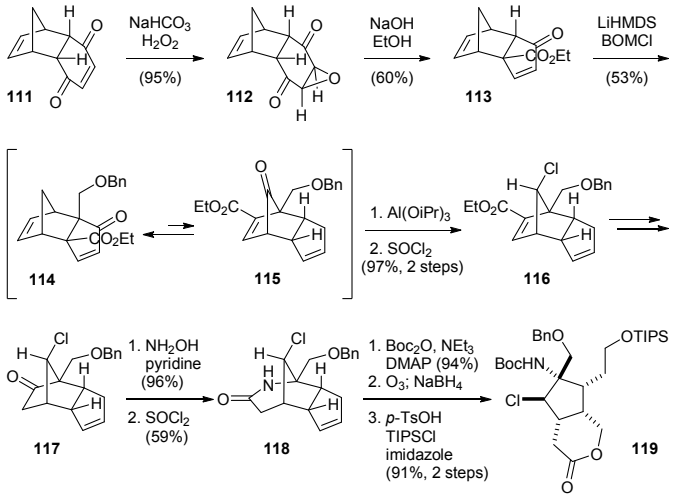


Figure 23. Gin's synthetic approach to palau'amine (**1**).

2.12. Synthetic contributions from the Namba–Nishigawa group

The Namba and Nishigawa groups disclosed an interesting cyclization approach for the construction the core skeleton of palau'amine in 2009.[169,170] In short, treating tosyl hydrazide **120** with a catalytic amount of Hg(II) triflate gave **121** (Fig. 24). Subsequent oxidation of the hydroxyl group to an enone followed by introduction of the two side-chains yielded **122**.

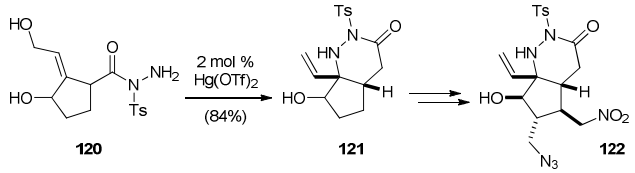


Figure 24. Namba and Nishigawa's synthetic approach to palau'amine (**1**).

2.13. Synthetic contributions from the Williams group

The Williams group reported the use of an asymmetric [3+2] dipolar cycloaddition approach to synthesize the core skeleton of palau'amine (**1**) in 2010.[171] Condensation of oxazinone **123** with formaldehyde gave azomethine ylide **124** that underwent an intramolecular [3+2] cycloaddition reaction to give **125** (Fig. 25). Reductive removal of the chiral auxiliary group and protection of the primary hydroxyl and secondary amino groups afforded **126**. Sequential oxidation of **126** then yielded enone **127**. Finally, Morita–Baylis–Hillman hydroxymethylation of **127** followed by lactam cleavage, Michael addition, and alcohol reduction provided the palau'amine core skeleton **128**.

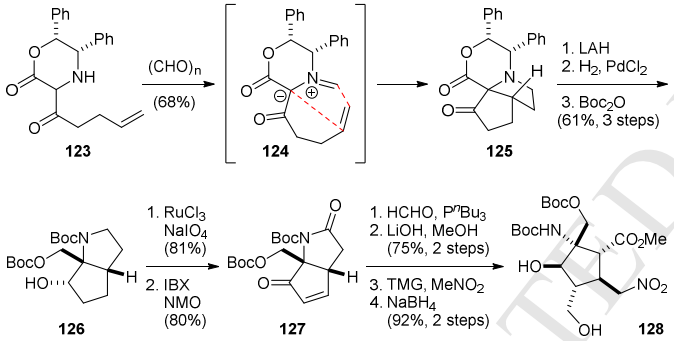


Figure 25. William's synthetic approach to palau'amine (**1**).

2.14. Synthetic contributions from the Feldman group

The Feldman group also used a Scheuer-type ring-contraction approach to synthesize the core skeleton of palau'amine (**1**) in 2010.[172,173] They first constructed the phakellin subunit using a Pummerer-type oxidation reaction. Oxidation of **129** with the Stang's reagent gave **130** (Fig. 26). Oxymercuration of **130** followed by oxidation provided **131** along with the regioisomers of the β-diketone. Finally, diazotransfer of this mixture of isomers and photolysis induced a Wolff rearrangement to give **132**.

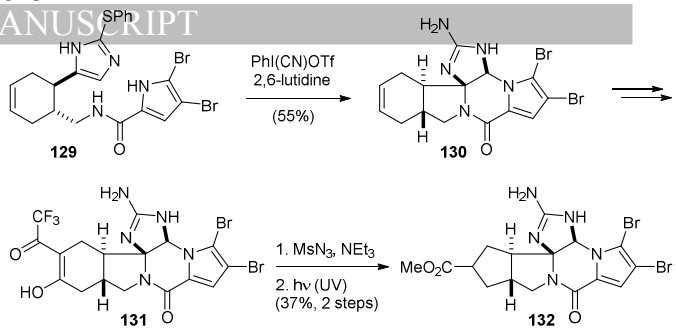


Figure 26. Feldman's synthetic approach to palau'amine (**1**).

2.15. Synthetic contributions from our group

Our lab is interested in studying the biomimetic syntheses of the pyrrole–imidazole family of alkaloids.[33,174-180] We have developed a palladium-catalyzed C–H functionalization reaction to enable an efficient synthesis of dibromophakellstatin in 2007.[175] We have also accomplished the asymmetric synthesis of ageliferins (**11**) in 2011, using a tandem radical cyclization approach as the key step to construct its cyclohexenyl core.[177,178] Recently, we have further achieved the asymmetric synthesis of sceptrin (**10a**) and massadine (**14a**), and corrected the absolute stereochemistries of sceptrins (**10**) and ageliferins (**11**).[179]

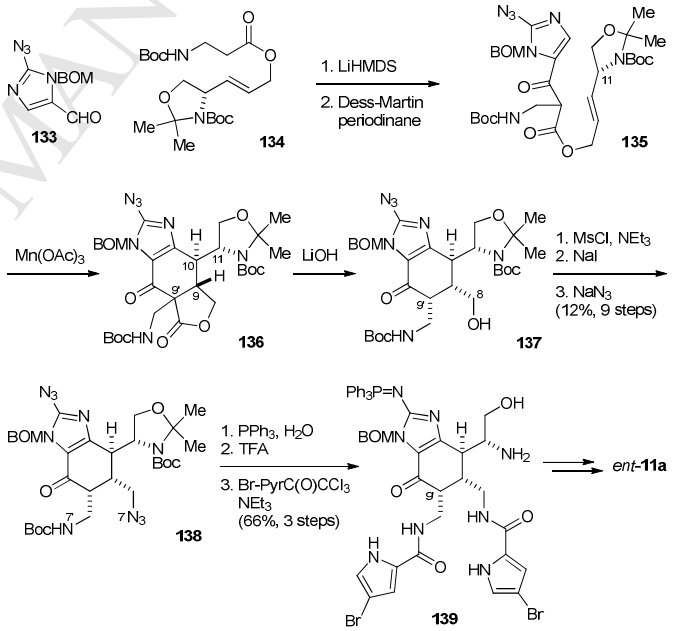


Figure 27. Our synthesis of ageliferin (**11a**).

We believed that the biogenic dimerization of **5** proceeds through a radical cyclization mechanism, and sought to provide support for the single-electron transfer (SET)[181-185] biosynthetic hypothesis put forth by Molinski and Romo.[49,50] Our biomimetic synthesis of ageliferins (**11**) involves the use of a SET-oxidation for setting up its cyclohexenyl core skeleton.[174,177,178] To improve the efficiency of the dimerization process, we tethered the two monomeric units with an ester linker. We also replaced one olefin with an enol, a highly electron-rich olefin, to enable the selective SET-oxidation. The synthesis started with an aldol reaction of **133** and **134** followed by an alcohol oxidation to provide β-ketoester **135** (Fig. 27). The oxidative radical cyclization of **135** proceeded smoothly to yield **136**. Subsequent decarboxylation

revealed the ageliferin core skeleton and gave **137**. Installation of the N7/N7' nitrogen atoms at the C8/C8' positions was challenging for steric reasons but could be achieved by sequential mesylation, iodination, and azidation to afford **138**. Installation of the bromopyrrole groups yielded **139**, and subsequent introduction of the second aminoimidazole group completed the synthesis of ageliferin (**11a**). The iminophosphorane of **139** served as a good protecting group of aminoimidazole. Because the N7 and N7' groups of **138** were differentially protected, pyrrole groups with different bromine patterns could be introduced selectively to give bromoageliferin (**11b**) and dibromoageliferin (**11c**).

Surprisingly, while we targeted ageliferin in its natural enantiomeric form, *ent*-ageliferin was obtained instead.[177] In our synthesis, L-serine was used as the source of chirality to establish the absolute stereochemistry of **11a**. Repeating the synthesis with D-serine gave *nat*-ageliferins.[178] MMFF calculations of the equilibrium geometry of **135** confirmed that the conformation of **135** was controlled by the $A^{1,3}$ strain created by the C11 stereocenter and oxidation of **135** should give **136**.[176] NMR analyses also suggested that **136** was the correct reaction product. However, this study could not provide direct evidence for the misassignment of the absolute stereochemistry of ageliferins because the C11 stereogenic center was transformed into a sp^2-hybridized carbon in ageliferins. Recently, we carried out the Scheuer-type oxidation on **138** and obtained three crystal structures confirming the oxidative cyclization product of **135** to be **136**.[179] Therefore, the originally assigned absolute stereochemistry of ageliferins (**11**) must be incorrect. Because the absolute stereochemistry of **11** was determined based on that of sceptrins (**10**),[145] the originally assigned absolute stereochemistry of **10** should also be reconsidered.

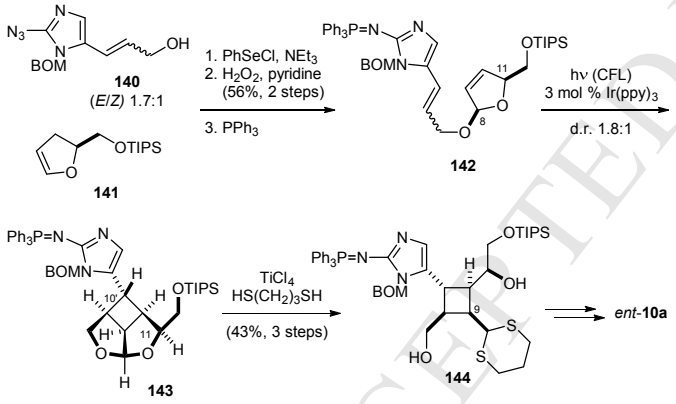


Figure 28. Our synthesis of sceptrin (**10a**).

To provide independent evidence for the misassignment of the original absolute stereochemistry of **10**, we developed a SET-mediated [2+2] cycloaddition approach for the asymmetric synthesis of **10a**.[179] L-Glutamic acid was used as the source of chirality for establishing the absolute stereochemistry of **141** (Fig. 28). Coupling of **140** and **141** via electrophilic selenation afforded **142** after oxidative elimination of the phenylselenyl group and reduction of the azido group. Irradiation of a solution of **142** in the presence of a photoredox catalyst[186-195] promoted a reversible SET reaction and induced the [2+2] cycloaddition[196-206] to give **143**. Transthioketalization of **143** revealed the cyclobutane core skeleton and gave **144**. Subsequent C9 epimerization and installation of the side-chain functional groups furnished **10a**. Consistent with our ageliferin synthesis, we obtained *ent*-sceptrin while targeting sceptrin in its originally assigned natural enantiomeric form.

The absolute stereochemistry of sceptrin (**10a**) was previously deduced from two X-ray crystallographic studies. A crystal structure of natural sceptrin was obtained by Faulkner and Clardy in 1981.[91] The Hamilton test favored *ent*-**10a** slightly (*R*-factors: 0.090 vs. 0.094) but not conclusively. Although Baran's synthetic study supported *ent*-**10a** to be the natural enantiomer, the synthetic intermediate used to co-crystallize with a chiral amine had only 75% ee.[145] Recently, the Baran group reexamined the absolute stereochemistry of natural sceptrin by anomalous X-ray scattering. With a Flack factor of –0.002(5) for **10a**, they confirmed that the original absolute stereochemistry of sceptrin was misassigned.[179]

For the synthesis of massadine (**14a**), we sought to follow the Scheuer hypothesis and verify whether the [3+2] dimers could be derived from the [4+2] dimers through an oxidative ring-contraction reaction.[179] We first reduced the carbonyl group of **145**, a protected 10'-oxo-dibromoageliferin obtained from our dibromoageliferin synthesis (Fig. 29).[177,178] The resulting **146** was oxidized in the presence of titanium(IV) isopropoxide to afford iminohydantoin **147**. The hydroxyl group of **146** was used to control the stereochemistry of the Scheuer-type oxidative ring-contraction reaction to give the desired spiro-configuration. Reduction of **147** then gave hemiaminal **148**. Subsequent removal of the protecting groups yielded "pre-massadine" (**149**). Oxidation of **149** with *N*-bromosuccinimide (NBS) in methanol gave a diastereomeric mixture of massadine-methanol adducts, which slowly converted into massadine (**14a**) and 3,7-*epi*-massadine[150] upon treatment with hydrochloric acid. Surprisingly, oxidation and deprotection of **145** gave *nat*-**14a** while deoxygenation and deprotection of **145** gave *ent*-**11c**. Consequently, massadine (**14a**) and dibromoageliferin (**11c**) must be antipodal and **14a** cannot be produced from oxidation of **11c** or its derivatives in nature. Although enantiomeric biosynthesis that produces both enantiomers of a natural product has been reported,[207] the biogenic dimerization of **5** giving antipodal pyrrole–imidazole dimers is the first example of enantiodivergent biosynthesis that produces opposite enantiomers of natural products as congeners.

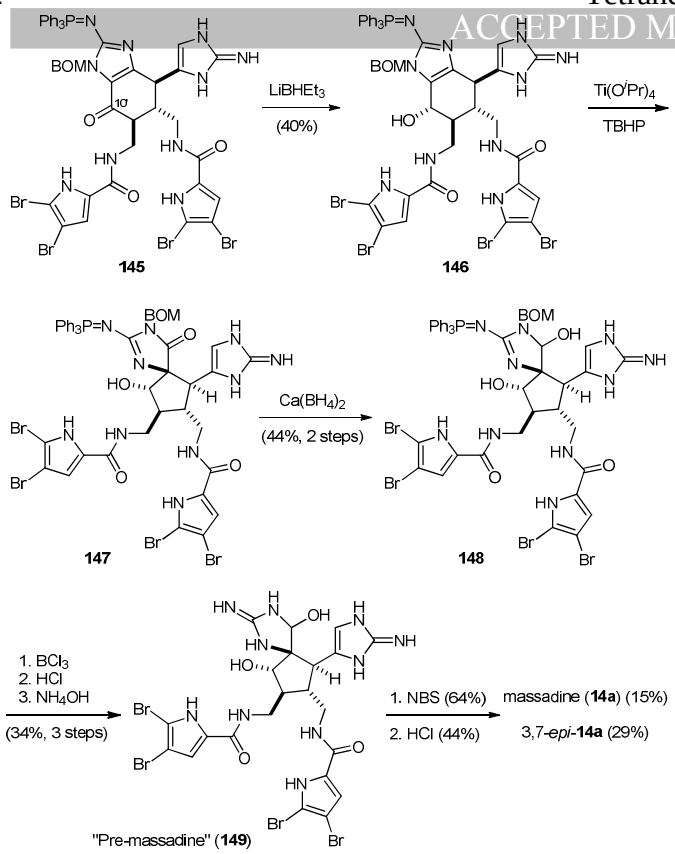


Figure 29. Our synthesis of massadine (**14a**).

3. The dragmacidin alkaloids

Dragmacidins (**2** and **150**–**152**) are a group of indole alkaloids that possess a central pyrazine/pyrazinone ring (Fig. 30).[19,208-212] Among them, dragmacidin D–F (**2**, **151**, and **152**) that contain an aminoimidazole or a cyclic guanidine unit in a highly complex molecular framework are particularly challenging synthetic targets. Biosynthetically, **2** and **152** are likely derived from **151**.[34] Notable biological activities of these marine sponge metabolites include selective inhibition of serine-threonine protein phosphatases 1 (PP1) over the 2A isoform (PP2A),[212] brain nitric oxide synthase (bNOS) over the inducible isoform (iNOS),[1] and HIV-1 over HSV virus.[19]

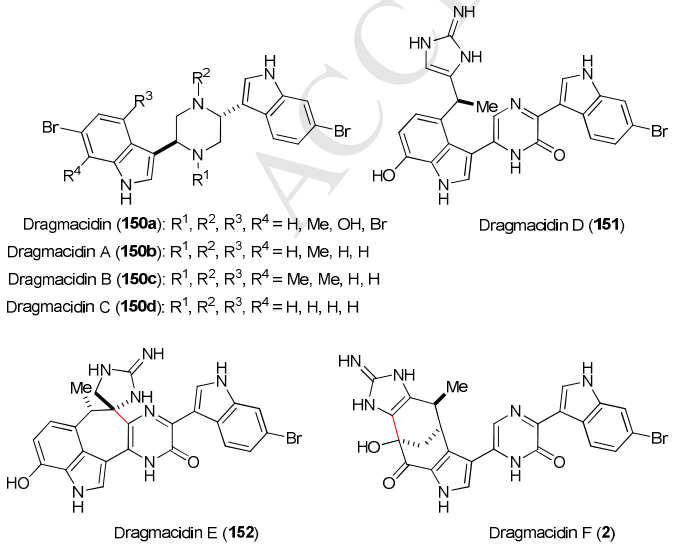


Figure 30. Structures of the dragmacidin alkaloids.

3.1. Synthetic contributions from the Stoltz group

The first synthesis of dragmacidin D (**151**) was completed by the Stoltz group in 2002, using a sequential Suzuki coupling approach.[213] A selective Suzuki coupling of bromoiodopyrazine **153** and boronic acid **154** gave heterobiaryl **155** (Fig. 31). Subsequent Suzuki coupling of dibromide **155** and pinacolborane **156** proceeded selectively to yield **157**. Removal of the alcohol protecting group, oxidation, and Henry reaction provided α-nitroketone **158**. Reduction of **158** followed by cleavage of the benzyl and methyl ethers afforded α-aminoketone **159**. Condensation of **159** with cyanamide concluded the synthesis of dragmacidin D (**151**). Impressively, this synthesis takes only 17 linear steps.

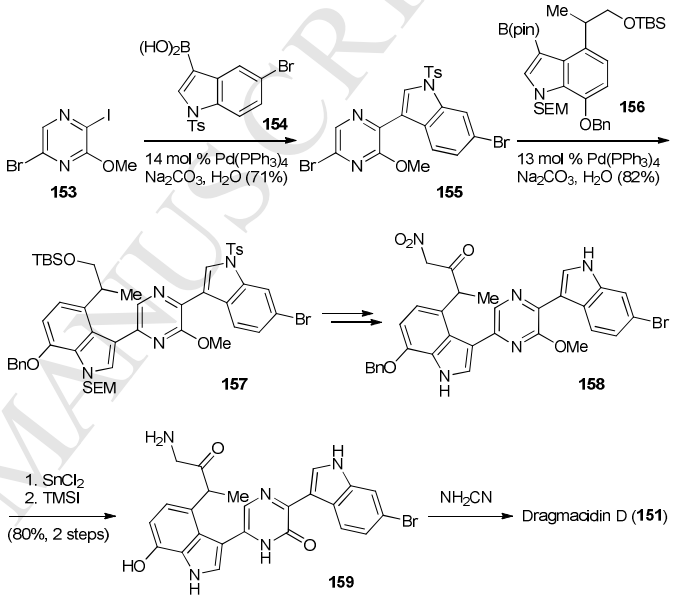


Figure 31. Stoltz's synthesis of dragmacidin D (**151**).

The Stoltz group also accomplished the asymmetric synthesis of dragmacidin F (**2**) and established its absolute stereochemistry in 2004.[214-216] Starting from (–)-quinic acid (**160**), lactonization and selective alcohol protection gave **161** (Fig. 32). Oxidation of **161** followed by Wittig olefination and palladium-catalyzed hydrogenation provided acid **162**. Subsequent installation of the pyrrole group afforded **163**, which was subjected to a palladium-catalyzed oxidative Heck carbocyclization to yield **164**. Hydrogenation of **164** followed by alcohol protection, and borylation gave **165**. Coupling of pinacolborane **165** with bromoindole **155** proceeded smoothly to give **166**. To install the aminoimidzole group, **166** was first converted into tosyloxime **167** and then treated with base to induce a Neber rearrangement. The resulting azirine **168** was hydrolyzed to give α-aminoketone **169**. Deprotection of **169** followed by condensation with cyanamide furnished *ent*-dragmacidin F (**2**). A slightly modified method has also been developed to provide *ent*-**162** from **160**, allowing for the asymmetric synthesis of **2**.[217]

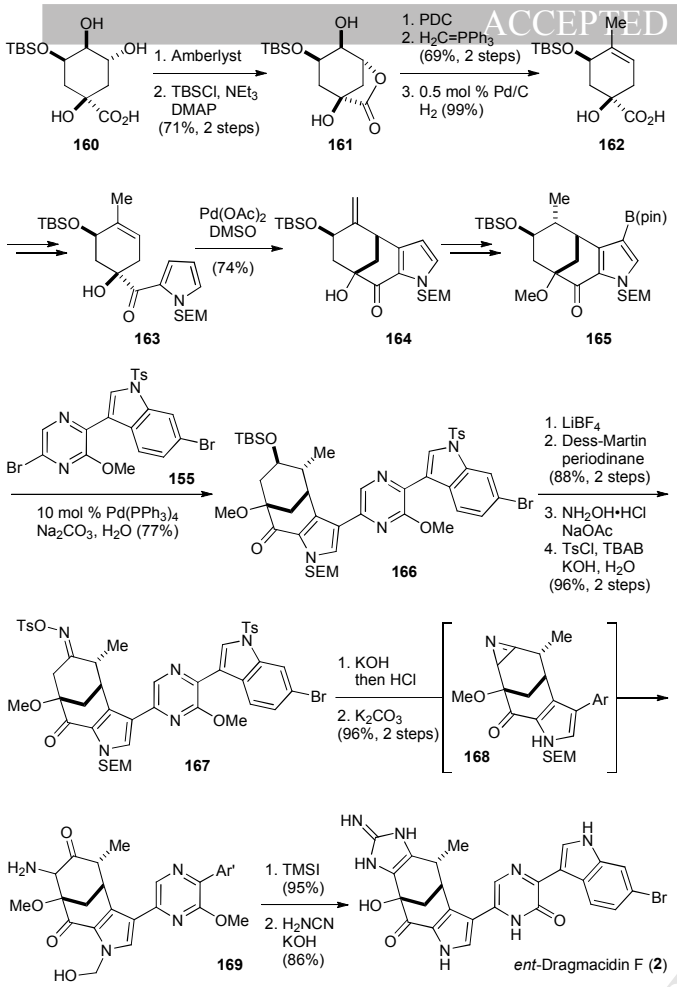


Figure 32. Stoltz's synthesis of dragmacidin F (**2**).

3.2. Synthetic contributions from the Yamaguchi–Itami group

The Yamaguchi–Itami group reported a highly efficient synthesis of dragmacidin D (**151**) in 2011.[218] They used a series of C–H functionalization reactions to assemble its molecular skeleton. First, coupling of 4-iodoindole **170** with thiophene **171**, a 2-butanone surrogate, through thiophene C–H functionalization gave **172** (Fig. 33). Next, removal of the silyloxy group, desulfation, debenzylation, and protection of the indole functional groups provided **173**. Subsequently, the pyrazinone group was introduced through another C–H functionalzation reaction. The C–H/C–H coupling of **173** and pyrazine *N*-oxide **174** afforded **175**, which was treated with trifluoroacetic anhydride to induce a rearrangement reaction to yield pyrazone **176**. An acid-promoted oxidative C–H/C–H coupling of **176** and **177** then afforded **178**. Finally, installation of the aminoimidazole group completed the synthesis of **151**.

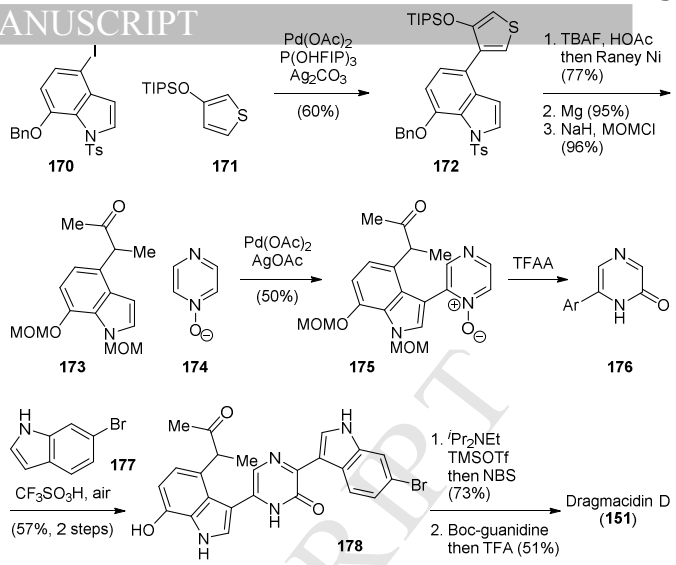


Figure 33. Yamaguchi and Itami's synthesis of dragmacidin D (**151**).

3.3. Synthetic contributions from the Feldman group

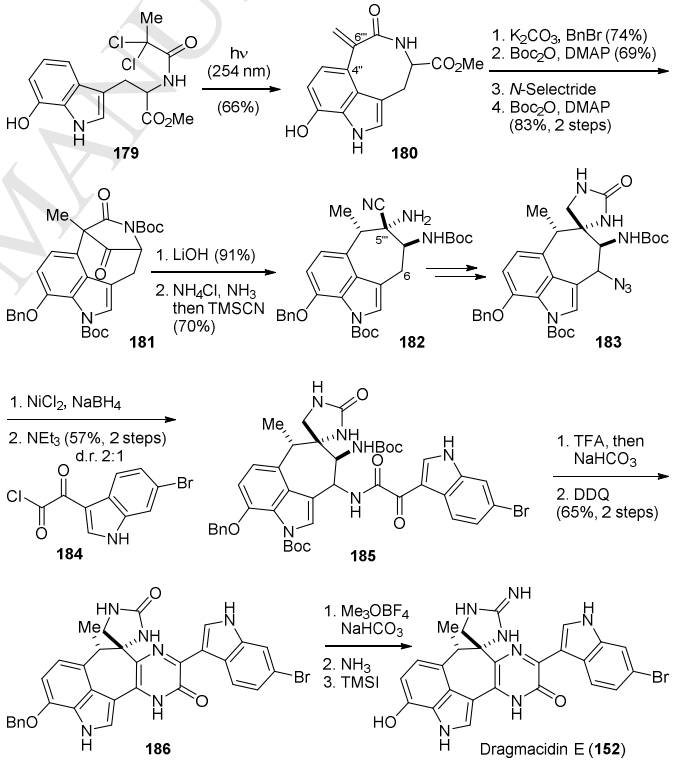


Figure 34. Feldman's synthesis of dragmacidin E (**152**).

The Feldman group completed the synthesis of dragmacidin E (**152**) in 2011, using a Witkop cyclization reaction to establish its C4"-C6‴ linkage.[219-222] Briefly, photolysis of the tryptophan derivative **179** afforded **180** (Fig. 34). Reduction of the enone group of **180** induced an intramolecular Dieckmann cyclization to provide **181**. Subsequent decarbonylative cleavage of the lactam linkage and C5‴-aminocyanation gave **182** as a 5:1 mixture of C5‴-diastereomers. The imidazolidinone group was then constructed and the C-6 position was functionalized through indolic oxidation to yield **183**. After reduction of the azido group and coupling with **184**, the resulting **185** was subjected to a

cyclodehydration reaction to generate the complete skeleton of **152**. The dihydropyrazinone group was then oxidized to give **186**. Finally, conversion of the urea group into a guanidine group and deprotection furnished **152**.

3.4. Synthetic contributions from the Oikawa group

The Oikawa group also disclosed an approach for constructing the dragmacidin D skeleton in 2008.[223,224] Similar to Feldman's strategy, a late-stage pyrazinone construction was planned. A Suzuki coupling of vinyl bromide **187** with thioimidazole group **188** was used to provide **189** (Fig. 35). After converting the amino ester group of **189** into a differentiated diamine, amine **190** was coupled with **184** to give **191**, an advanced synthetic intermediate of dragmacidin D (**151**).

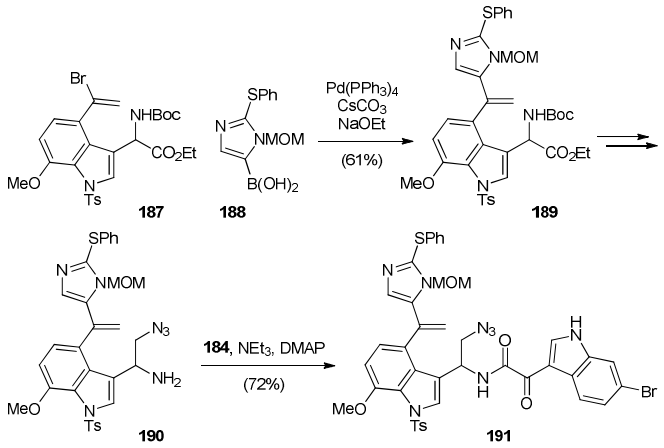


Figure 35. Oikawa's synthetic approach of dragmacidin D (**151**).

3.5. Synthetic contributions from the Jiang, Funk, and Jia groups

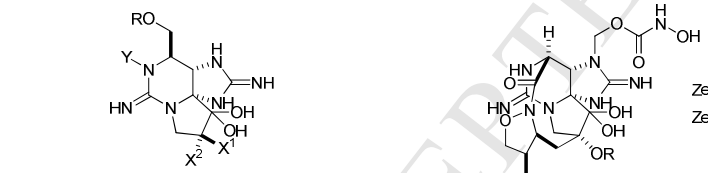
The Jiang, Funk, and Jia groups have each developed a unique synthetic approach to construct the pyrazinone core skeleton of dragmacidins.[225-228] The Jiang group reported the use of a sequential cross-coupling strategy for the synthesis of the core skeleton of dragmacidin D (**151**) in 2002.[225,226] The Funk group successfully constructed the molecular framework of dragmacidin E (**152**) in 2006,[227] using an electrocyclization reaction as the key step . The Jia group demonstrated the utility of the intramolecular Friedel–Crafts reaction in preparing the indole skeleton of dragmacidin E (**152**) in 2014.[228]

4. The saxitoxin/tetrodotoxin alkaloids

Saxitoxins/gonyautoxins (STXs/GTXs, **192**),[229-236] zetekitoxins (ZTXs, **193**),[237-239] tetrodotoxins (TTXs, **3**),[20,240-248] and chiriquitoxin (CHTX, **194**)[249,250] are highly toxic cyclic guanidine-containing alkaloids that block the voltage-gated ion channels (Fig. 36).[36-43] Among them, saxitoxin (STX, **192a**) and tetrodotoxin (TTX, **3**) are arguably the most infamous small-molecule toxins. STX (**192**) is responsible for the paralytic shellfish poisoning (PSP) and TTX (**3**) is the principle toxic component of puffer fish. Several different approaches have been developed for achieving the de novo synthesis of STXs/GTXs (**192**) and TTXs/CHTX (**3**/**194**). However, there is no report of the synthesis of ZTXs (**193**). The structure of ZTX C (**193b**) has also not been fully characterized. While the biosynthetic pathways of these exotic natural products are poorly understood, it is known that these neurotoxins are produced by symbiotic bacteria as they can be found in various animal species. For example, STX (**192a**) is also present in some puffer fish[251] and TTX (**3**) can be found in certain frogs and newts.[228,249,252,253]

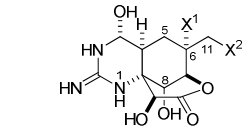
4.1. Synthetic contributions from the Kishi group

The first de novo synthesis of tetrodotoxin (**3**) was accomplished by the Kishi group in 1972.[254-257] In this seminal synthesis, a regioselective Diels–Alder reaction was first used to prepare **197** from butadiene (**195**) and quinone **196** after mesylation (Fig. 37). A Beckmann rearrangement was then used to introduce the nitrogen atom at the 8a-position. The subsequent dihydroquinone reduction proceeded with high regioselectivity to give **198** because of the steric effects of the axial acetamide group. Next, epoxidation of **198** in the presence of camphorsulfonic acid gave **199**, which was transformed into **200**

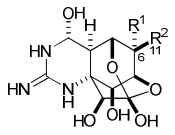


Saxitoxin (**192a**): X^1, X^2, Y, R = H, H, H, C(O)NH_2
Neosaxitoxin (**192b**): X^1, X^2, Y, R = H, H, OH, C(O)NH_2
Decarbamoylsaxitoxin (**192c**): X^1, X^2, Y, R = H, H, H, H
Gonyautoxin I (**192d**): X^1, X^2, Y, R = H, OSO_3H, OH, C(O)NH_2H
Gonyautoxin II (**192e**): X^1, X^2, Y, R = H, OSO_3H, H, C(O)NH_2H
Gonyautoxin III (**192f**): X^1, X^2, Y, R = OSO_3H, H, H, C(O)NH_2H
Gonyautoxin IV (**192g**): X^1, X^2, Y, R = OSO_3H, H, OH, C(O)NH_2H
Gonyautoxin V (**192h**): X^1, X^2, Y, R = H, H, H, C(O)$NHSO_3H$
Gonyautoxin VI (**192i**): X^1, X^2, Y, R = H, H, OH, C(O)$NHSO_3H$
Gonyautoxin VII (**192j**): X^1, X^2, Y, R = H, H, OH, H
Gonyautoxin VIII (**192k**): X^1, X^2, Y, R = OSO_3H, H, H, C(O)$NHSO_3H$

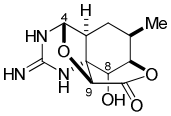
Zetekitoxin AB (**193a**): R = SO_3H
Zetekitoxin C (**193b**): R = H (?)



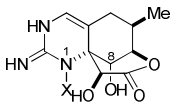
5-Deoxytetrodotoxin (**3g**): X^1, X^2 = OH, OH, 8-OH = β
5,11-Dideoxytetrodotoxin (**3h**): X^1, X^2 = OH, H, 8-OH = β
5,6,11-Trideoxytetrodotoxin (**3i**): X^1, X^2 = H, H, 8-OH = β
8-*epi*-5,6,11-Trideoxytetrodotoxin (**3j**): X^1, X^2 = OH, OH, 8-OH = α
1-Hydroxy-5,11-Dideoxytetrodotoxin (**3k**): X^1, X^2 = OH, OH, 8-OH = β
1-Hydroxyl-8-*epi*-5,6,11-Trideoxytetrodotoxin (**3l**): X^1, X^2 = OH, OH, 8-OH = α



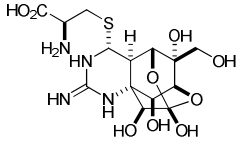
Tetrodotoxin (**3**): R^1, R^2 = OH, CH_2OH
6-Deoxytetrodotoxin (**3a**): R^1, R^2 = H, CH_2OH
11-Deoxytetrodotoxin (**3b**): R^1, R^2 = OH, CH_3
6,11-Dideoxytetrodotoxin (**3c**): R^1, R^2 = H, CH_3
6-*epi*-Tetrodotoxin (**3d**): R^1, R^2 = CH_2OH, H
11-*nor*-Tetrodotoxin-6(*S*)-ol (**3e**): R^1, R^2 = OH, H
6,11-Dideoxytetrodotoxin (**3f**): R^1, R^2 = H, CH_3



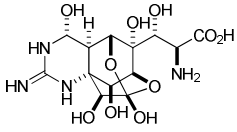
4,9-Anhdro-5,6,11-trideoxy-tetrodotoxin (**3m**): 8-OH = β
4,9-Anhdro-8-*epi*-5,6,11-trideoxy-tetrodotoxin (**3n**): 8-OH = α



4,4*a*-Anhydro-5,6,11-trideoxy-tetrodotoxin (**3o**): X = H, 8-OH = β
1-Hydroxy-4,4*a*-anhydro-8-*epi*-5,6,11-trideoxytetrodotoxin (**3p**): X = OH, 8-OH = α



4-*S*-Cysteinyltetrodotoxin (**3q**)



Chiriquitoxin (**194**)

Figure 36. Structures of saxitoxins/gonyautoxins (STX/GTX, **192**), zetekitoxins (ZTX, **193**), tetrodotoxins (**3**), and chiriquitoxin (**194**).

through a series of redox and protection operations. Baeyer–Villiger oxidation of **200** gave **201** exclusively. Treating the resulting lactone **201** with potassium acetate in acetic acid led to the cleavage of the lactone ring and the formation of the oxonium ion **202**. Trap of the oxonium ion with acetate and intramolecular attack of the epoxide of **202** by the carboxylate group yielded **203**. After installation of the guanidine group, selective removal of one of the acetyl protecting groups of **204** followed by oxidative cleavage of the dihydrofuran ring and global deprotection concluded the synthesis of **3**.

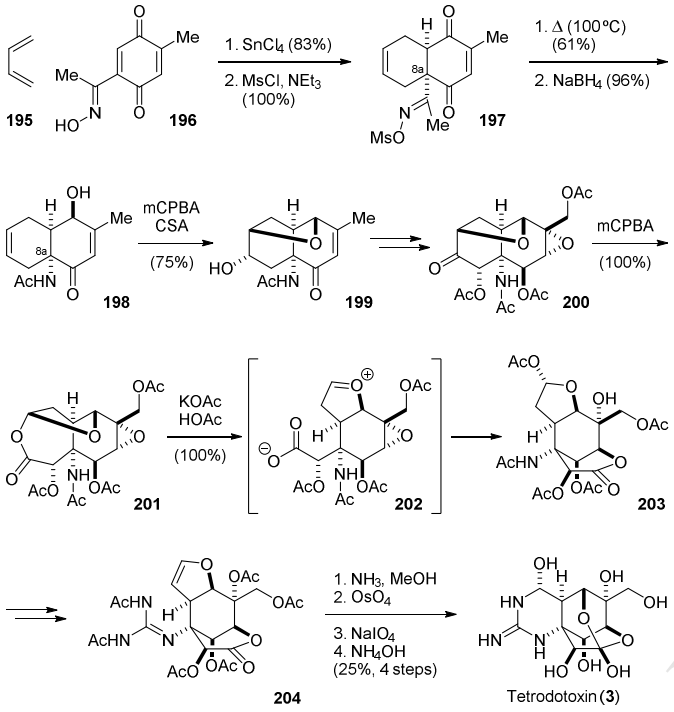


Figure 37. Kishi's synthesis of tetrodotoxin (**3**).

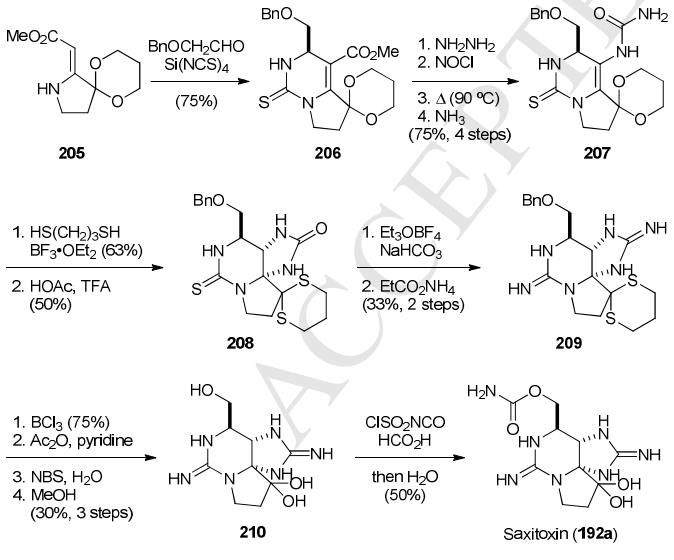


Figure 38. Kishi's synthesis of saxitoxin (**192a**).

The first synthesis of saxitoxin (**192a**) was accomplished also by the Kishi group in 1977.[258-262] This classic synthesis started with condensation of benzyloxyacetaldehyde, vinylogous carbamate **205**, and silicon tetraisothiocyanate to give **206** (Fig. 38). The ester group of **206** was then converted into a hydrazide, which was then treated with nitrosyl chloride to give an acyl azide. The subsequent Curtis-type rearrangement and trap of the resulting isocyanate with ammonia yielded **207**. After transthioketalization, an acid-promoted cyclization established the saxitoxin skeleton and provided **208**. The thiourea group of **208** was then converted into guanidine by treating with Meerwein salt followed by heating in melted ammonium propionate. Removal of the protecting groups of the resulting **209** afforded **210**. Finally, installation of the carbamate group completed the synthesis of saxitoxin (**192a**). The asymmetric synthesis of *ent*-**192c** was also accomplished in 1992 by condensing a 1,3-dithiane analog of **205** with (*R*)-glyceraldehyde to prepared *ent*-dithia-**206** after diol cleavage.[262]

4.2. Synthetic contributions from the Jacobi group

The Jacobi group reported the development of a practical synthesis of saxitoxin (**192a**) in 1984.[263-265] The first step of this elegant synthesis is the activation of imidazolinone **211** by the formation of acyl imidazolinone **212** (Fig. 39). The highly electrophilic compound **212** was then reacted with benzylhydrazine to give hydrazide **213**. Condensation of **213** with methyl glyoxylate hemiacetal provided azomethine imine **214**, which underwent a 1,3-dipolar cycloaddition reaction under kinetic control to afford pyrazolidine **215**. Subsequently, epimerization of the C6 stereocenter followed by reduction of the ester group yielded **216**. After hydrazide reduction, deprotection of the resulting hydrazide group, and introduction of the thiocarbamate group, the N–N linkage was cleaved to induce a cyclization reaction to provide thiourea **217**. Acetylation of the hydroxyl group followed by conversion of the urea and thiourea groups into cyclic guanidine groups afforded **218**, a late-stage intermediate of Kishi's synthesis. This route is remarkably efficient and requires no chromatographic purification. Impressively, more than 0.5 g of **217** was prepared in a single run by this route. This intramolecular azomethine imine cycloaddition strategy was later adapted by the Overman group to construct the core skeleton of *cis*-palau'amine (**1'**) (Fig. 5).

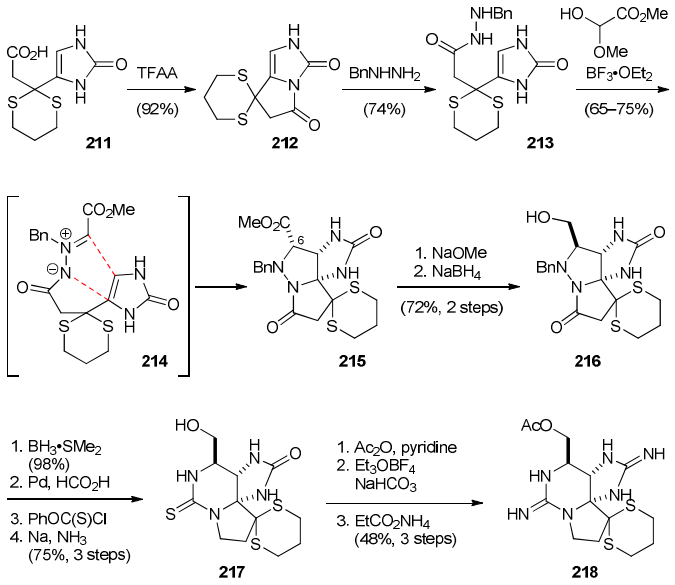


Figure 39. Jacobi's synthesis of saxitoxin (**192a**).

4.3. Synthetic contributions from the Isobe–Nishikawa group

The Isobe–Nishikawa group has devoted their efforts to studying the asymmetric synthesis of tetrodotoxin and saxitoxin alkaloids since 1987.[42,266-292] They first accomplished the synthesis of 5,11-dideoxytetrodotoxin in 1999.[275,277,286] They then achieved the syntheses of 8,11-dideoxytetrodotoxin[279,282] and 11-deoxytetrodotoxin (**3a**),[278] in 2002. Following these successes, they completed the synthesis of tetrodotoxin (**3**) in 2003,[281] reported an improved route in 2004,[283,284] and finished the synthesis of chiriquitoxin (**194**) in 2014.[287]

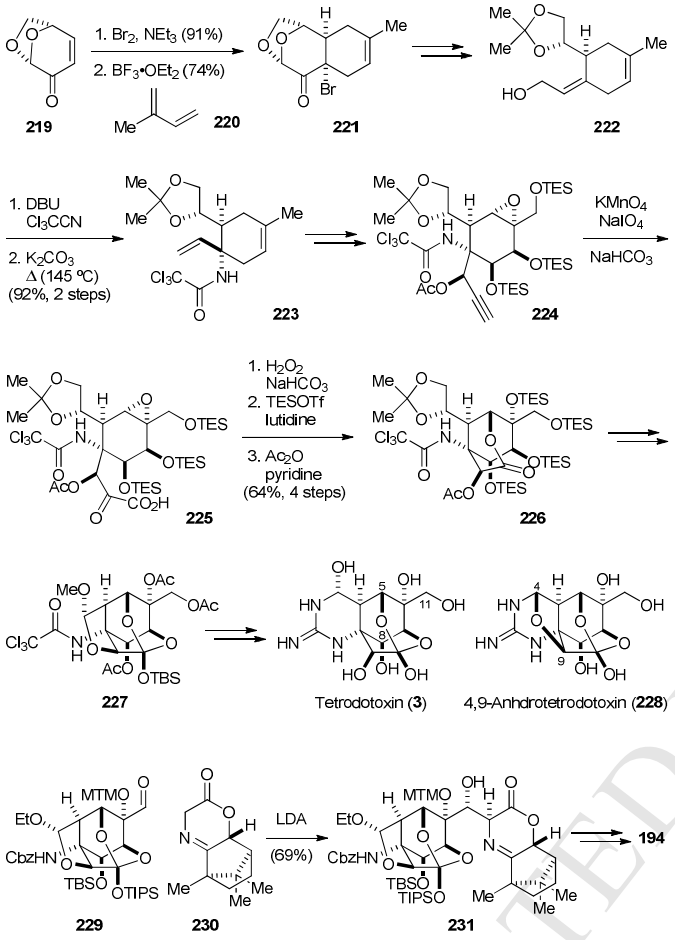


Figure 40. Isobe–Nishikawa's synthesis of tetrodotoxin (**3**) and chiriquitoxin (**194**).

Levoglucosenone (**219**) was used as the source of the chirality in all of these asymmetric syntheses (Fig. 40). The second-generation synthesis of **3** started with bromination of **219** followed by a regioselective Diels–Alder reaction with isoprene (**220**) to establish its central cyclohexane core.[283] The resulting bromide **221** was then functionalized to provide **222**, setting the stage for the introduction of the nitrogen-containing quaternary center by Overman rearrangement by thermolysis of the trichloroacetimidate of **222**. Subsequent oxidation, ozonolysis of the olefin, and alkynylation of the resulting aldehyde converted **223** to **224**. Oxidation of the acetylene group then yielded α-keto acid **225**. Next, epoxide opening and protection of the hydroxyl groups gave **226**. Finally, installation of the guanidine group via **227** provided tetrodotoxin (**3**) and 4,9-anhydrotetrodotoxin (**228**). Using a slightly revised route, the Isobe–Nishikawa group also successfully achieved the synthesis of chiriquitoxin (**194**).[287] The key step was the aldol reaction of **229** and the camphor-derived iminolactone **230** to give **231**. Subsequent deprotection and installation of the guanidine group yielded chiriquitoxin (**194**) and 4,9-anhydrochiriquitoxin.

The Nishikawa group also completed the synthesis of decarbamoyl α-saxitoxinol (**237**),[293] a nontoxic natural analogue of saxitoxin, in 2011.[290-292] Aziridine **232**, prepared from (*S*)-Garner's aldehyde, was transformed into mesylate **233** (Fig. 41). Treating **233** with pyridinium tribromide initiated a bromocyclization reaction to give **234**. The *gem*-dibromide group was then converted into enol acetate and reduced to yield alcohol **235**. Installation of the second guanidine group provided **236**, which was deprotected and cyclized to furnish **237**.

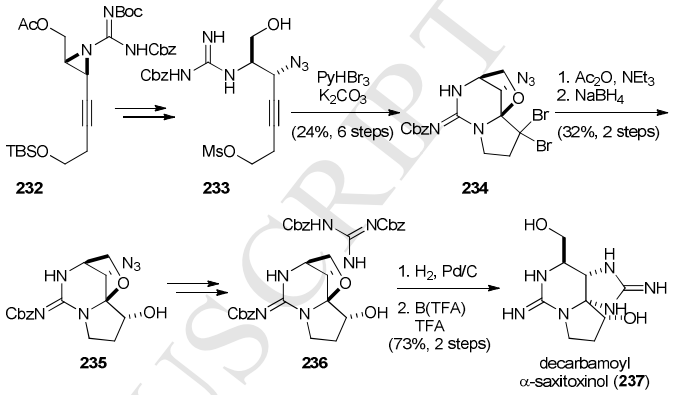


Figure 41. Nishikawa's synthesis decarbamoyl α-saxitoxinol (**237**).

4.4. Synthetic contributions from the Du Bois group

The Du Bois group has carried out a series of chemical and biological studies to provide better understanding of the reactivity and functions of the STXs/TTXs.[39,294-303] They first developed a series of new rhodium-catalyzed nitrene C–H insertion reactions[304,305] and used them to complete the synthesis of tetrodotoxin (**3**), saxitoxin (**182a**), and gonyautoxin 3 (**182e**) in 2003, 2006 and 2008, respectively.[294-297] They then designed several saxitoxin-based probe reagents to study the functions of sodium ion channels.[298-303]

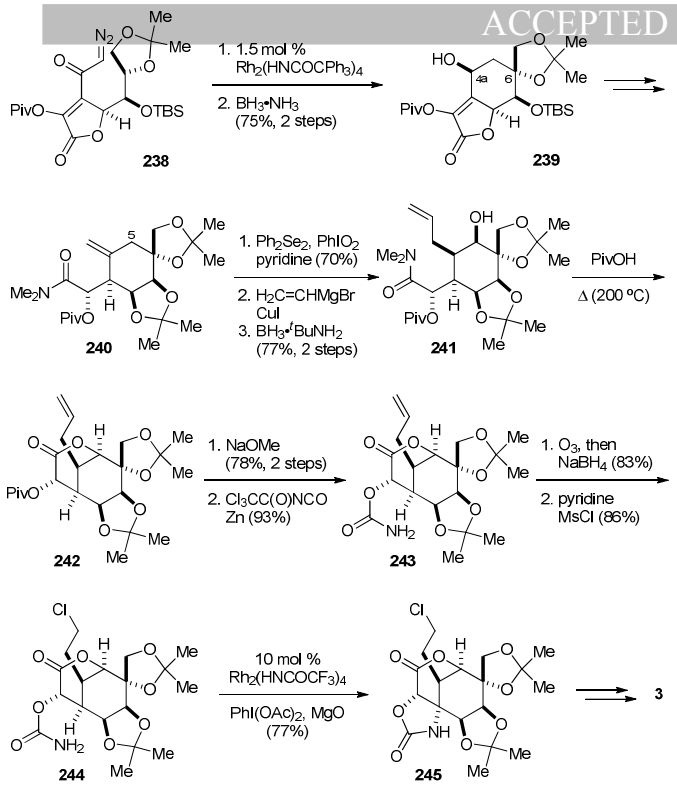


Figure 42. Du Bois' synthesis of tetrodotoxin (**3**).

For the synthesis of **3**, the DuBois group first used an intramolecular carbene C–H insertion reaction to construct the central cyclohexane ring and establish the C6 quaternary center.[294] The rhodium-catalyzed C–H carbene insertion[306,307] of **238** occurred exclusively at the congested tertiary ethereal position to give **239** after ketone reduction (Fig. 42). Subsequent enone reduction, diol protection, amidation, and C4a olefination yielded **240**. Allylic oxidation of **240** occurred selectively at the C5 position to give an enone. Conjugate addition of vinyl cuprate followed by ketone reduction then afforded **241**. Thermolysis of **241** induced the lactone formation and yielded **242**. Next, installation of the carbamate group provided **243**. The following olefin cleavage yielded **244**, which underwent an intramolecular nitrene C–H amination[304,305] at a highly hindered position to afford **245** selectively. Finally, installation of the guanidine group and deprotection completed the synthesis of **3**.

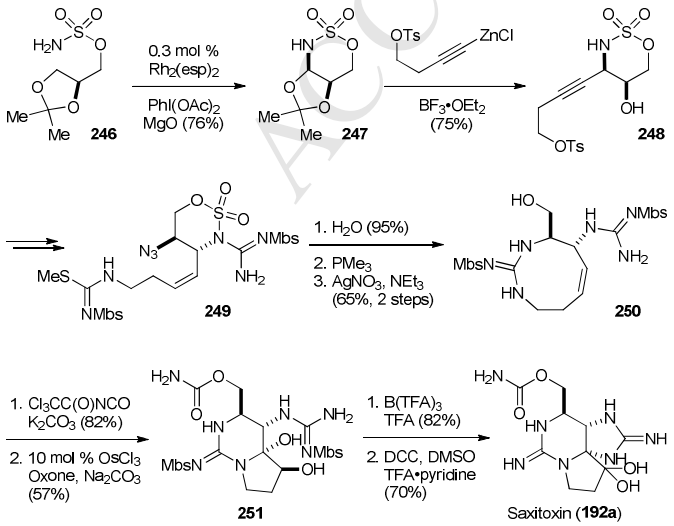


Figure 43. Du Bois' first-generation synthesis of saxitoxin (**192a**).

After accomplishing the asymmetric synthesis of tetrodotoxin (**3**), the Du Bois group turned their attention to the synthesis of saxitoxin (**192a**).[295] They first prepared sulfamate **246** from (*R*)-glycerol acetonide (Fig. 43). An intramolecular C–H amination of **246** was then used to establish the aminodiol triad. Alkynylation of the resulting *N*,*O*-acetal **247** gave **248**, which was transformed into guanidine **249**. Cleavage of the oxathiazinane ring, reduction of the azido group, and formation of the guanidine group by a silver-promoted cyclization reaction yielded **250**. Introduction of the carbamate group and ketohydroxylation[308] of the olefin afforded **251**. Interestingly, using osmium tetroxide as the catalyst for this (net) 4-electron oxidation reaction would result in a transannular cyclization through the alternative α-ketol tautomer to give a undesired bicyclic system. Finally, deprotection of **251** followed by alcohol oxidation furnished **192a**.

The Du Bois group also reported a highly efficient second-generation synthesis of **192a** in 2007.[296] This new synthesis started with functionalization of *N*-Boc-L-serine methyl ester (**252**) to give nitrone **253** via protection, reduction, and hydroxylamine condensation (Fig. 44). Alkynylation of **253** with **254** gave **255**, which was subjected to dimmide reduction and cleavage of the N–O linker to provide **256**. The second guanidine group was then introduced to yield **257**. Removal of the protecting groups and cyclization of the primary guanidine afforded **250**, an advanced synthetic intermediate in their first-generation synthesis (Fig. 43). Impressively, this route allowed for the asymmetric synthesis of saxitoxin (**192a**) to be achieved in 14 steps and 6.5% overall yield from the commercially available serine derivative **242**. Using this route, they have also prepared a series of STX derivatives for functional studies.[298-303]

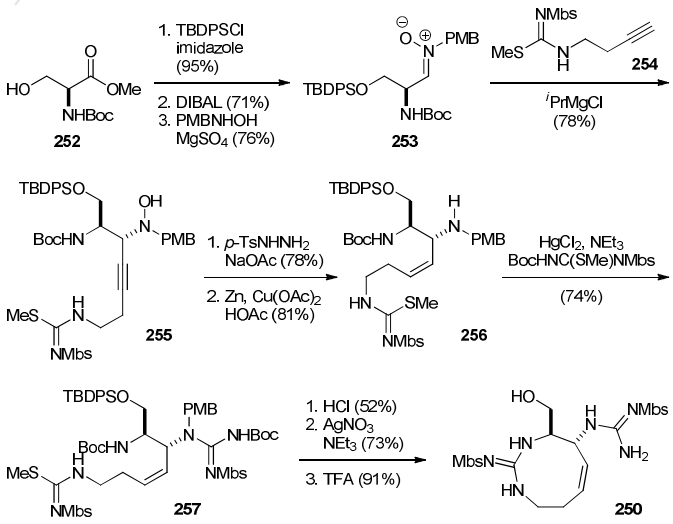


Figure 44. Du Bois' second-generation synthesis of saxitoxin (**192a**).

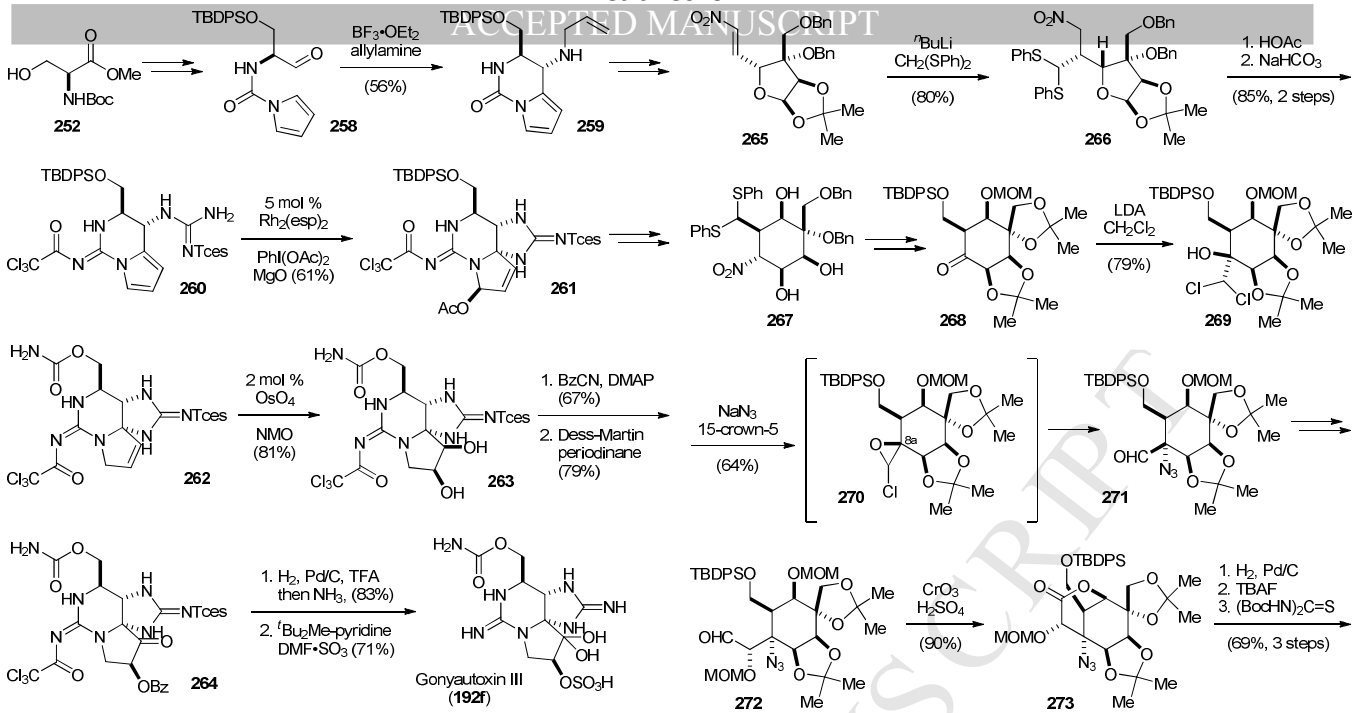


Figure 45. Du Bois' synthesis of gonyautoxin III (**192f**).

The Du Bois group further reported a new approach for the synthesis of gonyautoxin III (**192f**), a sulfate-derivative of saxitoxin (**192a**), in 2008.[297] Readily prepared from **252**, aldehyde **258** was condensed with allylamine to promote a cyclization reaction to give **259** (Fig. 45). Subsequently, introduction of the guanidine group afforded **260** and set the stage for the key C–H amination reaction. Generation of the rhodium-nitrenoid of **260** led to aziridination of the pyrrole group and the formation of **261** after aziridine opening. Deacetoxylation and installation of the carbamate group then yield **262**, which was dihydroxylated to afford **263**. Selective protection of the less hindered hydroxyl group of **263** followed by alcohol oxidation gave **264**. Finally, deprotection and sulfation furnished gonautoxin 3 (**192f**).

4.5. Synthetic contributions from the Sato group

The Sato group has also developed a unique chiron approach to synthesize tetrodotoxin (**3**).[309-313] They used *myo*-inositol as the carbon source of the central cyclohexane ring to achieve the racemic synthesis in 2005,[310] and D-glucose as the chiral building block to accomplish the asymmetric synthesis of **3** in 2008.[311]

Figure 46. Sato's synthesis of tetrodotoxin (**3**).

In their asymmetric synthesis, glucose was first functionalized to give nitroalkene **265** (Fig. 46).[311] Next, a conjugate addition of lithiated dithioacetal to **265** provided **266**. Removal of the acetonide protecting group followed by treatment with a base promoted a Henry reaction affording the *muco*-inositol derivative **267**. A Nef reaction was then used to convert the nitro group into a carbonyl group. The resulting ketone **268** was treated with lithiated methylene chloride to yield **269**. Subsequent azidation proceeded through α-chloroepoxide **270** to provide aldehyde **271** with an inversion of the C8a stereochemistry. Subsequent Strecker reaction followed by nitrile reduction and alcohol protection afforded **272**. The following Jones oxidation promoted the bridge formation and gave lactone **273**. Installation of the guanidine group then provided **274**. Finally, cyclization of the guanidine group afforded 4,9-anhydrotetrodotoxin (**228**), which slowly isomerized in acid to a 4:1 mixture of tetrodotoxin (**3**) and 4,9-anhydrotetrodotoxin **(228**).

4.6. Synthetic contributions from the Shinada–Ohfune group

The Shinada–Ohfune group reported an asymmetric synthesis of 5,6,11-trideoxytetrodotoxin (**3i**) in 2006.[314-316] Their synthesis started with preparing **275** from (–)-quinic acid (Fig. 47). The phenylalanine group of **275** was then used to activate the adjacent ketone group and direct the cyanide addition to set the nitrogen-containing C8a quaternary center. Treatment of **275** with trimethylsilyl triflate promoted an intramolecular imine condensation reaction. Cyanide then attacked from the less hindered face of the bicyclic system to give **276** following oxidation of the resulting amine to imine. After hydrolytic removal of the amino acid auxiliary group, the C7 hydroxyl group was installed and the acetoxyl ester and cyano groups were

reduced to provide **277**. Subsequently, **277** was subjected to another Strecker reaction and the guanidine group was introduced to give **278**. Oxidative cleavage of the olefin group occurred with concomitant hemiacetal formation to yield **279**. Treatment of **279** with acid induced the guanidine cyclization and lactone formation to afford **3i** as a 2:1 mixture of C4 diastereomers, together with 4,9-anhydro-5,6,11-trideoxytetrodotoxin (**3m**).

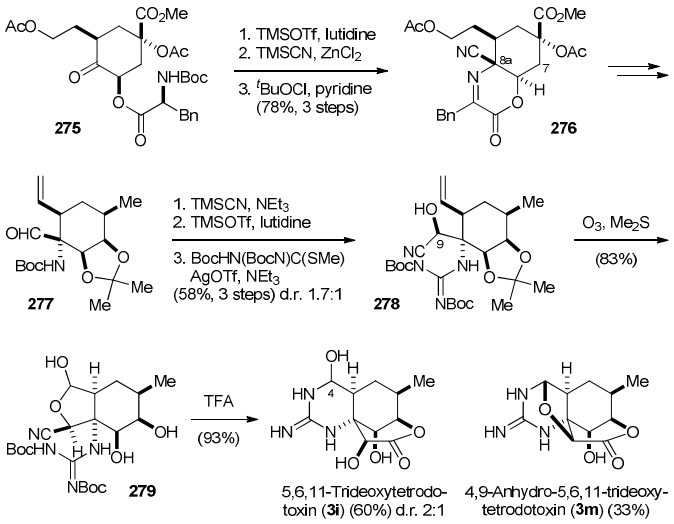


Figure 47. Shinada–Ohfune's synthesis of 5,6,11-trideoxytetrodotoxin (**3i**).

4.7. Synthetic contributions from the Nagasawa group

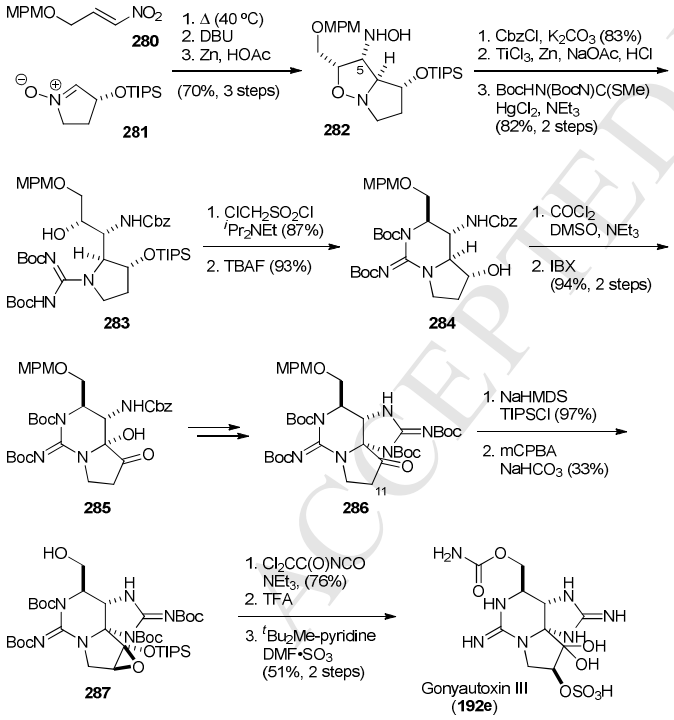


Figure 48. Nagasawa's synthesis of gonyautoxin III (**192f**).

The Nagasawa group has also reported a series of synthetic and biochemical studies of saxitoxins (**192**).[317-322] They used a 1,3-dipolar cycloaddition approach to complete the synthesis of decarbamoyloxysaxitoxin (**192c**), saxitoxin (**192a**) and gonyautoxin III (**192f**) in 2007, 2009 and 2010, respectively. The stereochemistry of the [3+2] cycloaddition reaction of nitroalkene **280** and nitrone **281** was controlled by the silyloxyl group of **281**, which was derived from D-malic acid (Fig. 48). Epimerization of the C5 stereocenter and reduction of the nitro group gave **282**. Protection of the hydroxylamine group, cleavage of the N–O bonds, and introduction of the guanidine group then provided pyrrolidine **283**. Subsequently, cyclization of **283** and removal of the silyl protecting group produced cyclic guanidine **284**. After sequential oxidation of **284** to give α-hydroxy ketone **285**, the second guanidine group was installed to yield **286**. The C11 hydroxyl group was next introduced by Rubbotom oxidation to afford **287**. Finally, carbamate formation, deprotection, and sulfation furnished gonyautoxin III (**192f**).

4.8. Synthetic contributions from the Looper group

The Looper group have developed a series of new methods for the synthesis of aminioimidazole and guanidine.[323-327] Using a novel metal-catalyzed sequential hydroamination approach,[323,325] they further achieved theasymmetric synthesis of saxitoxin (**192a**) in 2011.[328] The synthesis started with preparation of **288** following the method for the synthesis of **255** developed by Du Bois (Fig. 44).[296] Subsequently, reduction of the hydroxylamine followed by installation of the carbamate group provided **289** without cyclic carbamate formation (Fig. 49). The two guanidine groups were then introduced to yield **290**. Treating **290** with a catalytic amount of silver(I) acetate induced the first guanidine cyclization reaction. The 5-*exo* cyclization product **291** was subjected to a second guanidine cyclization reaction using silver(I) acetate and iodine to give **292**. Reaction of **292** with silver(I) acetate and acetic acid promoted a carbonate cyclization to provide **293**. This sequence of cyclization reactions could be carried out in one flask to deliver **293** directly from **290**. Deprotection and mesylation of the hydroxyl group followed by cleavage of the cyclic carbamate group afforded **294** bearing the complete skeleton of saxitoxin. Finally, alcohol oxidation and deprotection gave **192a** in only 14 steps from commercially available *N*-Boc-L-serine methyl ester (**242**).

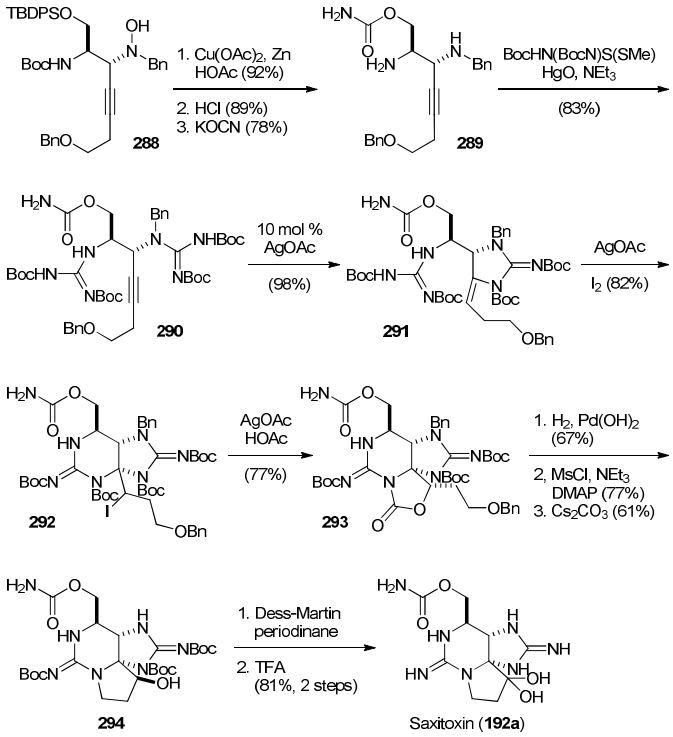


Figure 49. Looper's synthesis of saxitoxin (**192a**).

5. The crambescidin/batzelladine alkaloids

Ptilomycalin A (**4a**) is a structurally unique alkaloid discovered by Kusumi and Kashman from the Caribbean sponge *Ptilocaulis spiculifer* and the Red Sea sponge *Hemimycale* sp (Fig. 50).[329-331] The molecular topology of **4a** resembles a ship and its guanidine-containing pentacyclic core has been referred to as the "vessel" part and the spermidine-containing long aliphatic chain the "anchor" part.[330] Kusumi and Kashman's NMR studies suggested that **4a** can trap an anion between the "vessel" and "anchor" moieties and thus function as a phase-transfer molecule. Although ptilomycalin A (**4a**) contains one guanadium and two amino groups, **4a** is a "strikingly non-polar substance".[330] The "vessel" part of **4a** is structurally similar to the C_2-symmetric chiral anion-receptor **295** developed by Lehn and De Mendoza.[332] Murphy has carried out a series of crystallographic studies on **296** and **297**, the *meso*-symmetric analogs of the "vessel" part of **4a**, and found that **296** and **297** could effectively bind to a borate anion in different modes (Fig. 50).[333] Taking inspirations from **4a**, the Nagasawa group has developed a C_2-symmetric chiral phase-transfer catalyst (**298**) for the asymmetric alkylation of the Schiff base of *t*-butyl glycinate and benzophenone.[334]

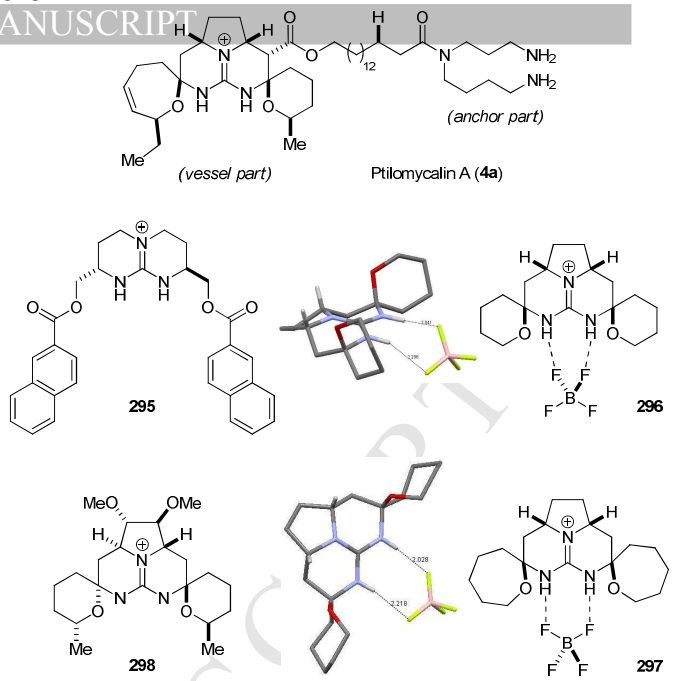


Figure 50. The structure of ptilomycalin A (**4a**) and its anion-recognition analogs.

The tricyclic part of the core of **4a** is structurally similar to ptilocaulin (**299**) (Fig. 51).[335,336] However, in contrast to **299**, **4a** has an endocyclic instead of an exocyclic guanidine group. The synthesis of **299** has been achieved by the Snider,[337-340] Roush,[341,342] Uyehara,[343,344] Hassner,[345,346] Asaoka,[347] Cossy,[348] Schmalz,[349] and Livinghouse groups.[350] A series of ptilomycalin congeners have also been discovered and named as crambescidins (**4**, **4b**–**g**, and **4m**,**n**),[21,351-356] crambidine (**300**),[21] celeromycalin (**4h**),[357] fromiamycalin (**4i**),[357] and neofolitispates (**4j**–**l**)[358] (Fig. 51). Crambescidins are named based on their molecular weights. For example, crambescidin 816 (**4**) has a molecular weight of 816 daltons. The batzelladines (**301**) and dehydrobatzelladine (**302**) contain the same central guanadium tricyclic core as **4** whereas a different "anchor" group.[359-365] The crambescins (**303**) have an even simpler monocyclic or bicyclic core.[356,366-369]

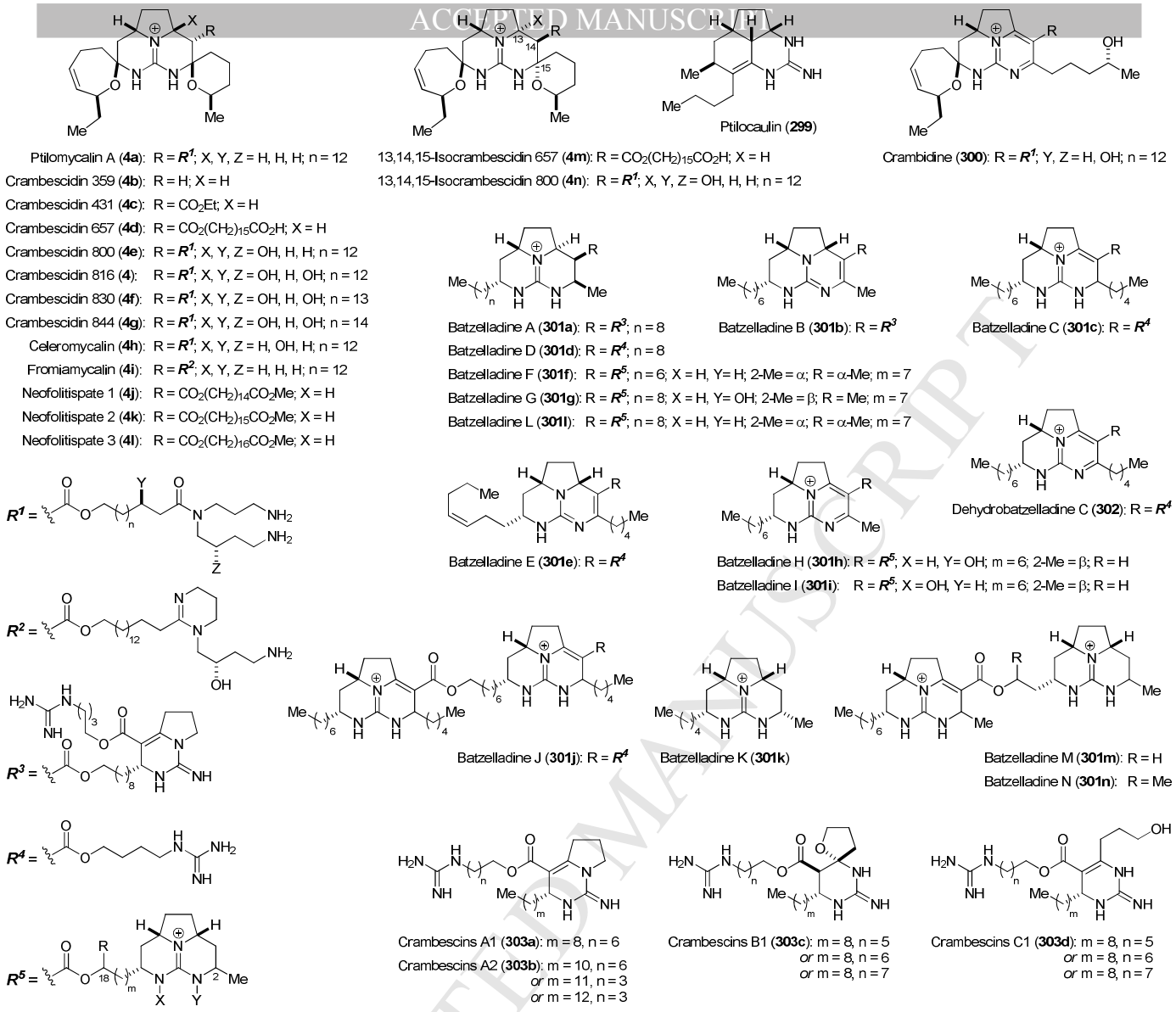


Figure 51. Structures of the crambescidin/batzelladine family of alkaloids.

The crambescidin/batzelladine family of alkaloids has shown various useful biological properties. Interestingly, crambescidin 816 (**4**) binds to the voltage-gated calcium ion channel selectively while crambescins (**303**) binds to the potassium ion channels preferentially.[370] The crambescidins (**4's**) and batzelladines (**301**) also show anticancer,[371,372] antiviral,[363,373,374] antifungal,[375] and antimalarial[376] activities. Based on the observation that the "vessel" part of **4** exists in a dynamic equilibrium between the spiroaminal and the imine forms under high pH, Overman proposed that **4** binds to their protein targets covalently through its imine form.[377]

5.1. Synthetic contributions from the Overman group

The Overman group has developed a tethered Biginelli reaction as a central strategy for the synthesis of the crambescidin/batzelladine alkaloids.[377-390] They first achieved the asymmetric synthesis of ptilomycalin A (**4a**) in 1995.[379] To construct the pentacyclic core of **4a**, amino alcohol **304** was reacted with potassium isocyanate to form a urea (Fig. 52). Its olefin group was then cleaved to promote a cyclization to give ureido aldehyde **305**. Biginelli condensation of **305** with β-ketoester **306** provided **307** with good diastereoselectivity (d.r. 7.5:1). After removal of the silyl protecting group, treatment of the resulting secondary alcohol with a catalytic amount of acid induced a spirocyclization to yield **308**. The primary hydroxyl group was then oxidized and the urea group was methylated to afford **309**. Reaction of aldehyde **309** with Grignard reagent **310** followed by alcohol oxidation gave ketone **311**. Desilylation followed by treatment with ammonia then established the central guanidinium functionality. The spiroaminal formation also occurred under the reaction conditions to provide **312**, the "vessel part" of ptilomycalin A (**4a**). Finally, introduction of the spermidine chain (the "anchor part") and epimerization of the C14 stereocenter concluded the synthesis of **4a**.

The Overman group later used a more streamlined route to synthesize a series of crambescidin alkaloids. They first accomplished the synthesis of 13,14,15-isocrambescidin 800 (**4n**) in 1999.[380] They then achieved the synthesis of crambescidin 657 (**4d**), neofolitispate 2 (**4k**), and carmbescidin 800 (**4e**) in 2000.[381] They subsequently completed the synthesis of crambescidin 359 (**4b**) and crambescidin 431 (**4c**) in 2005.[377] For the synthesis of **4n**, the carbon framework of the 7-membered cyclic spiroaminal

and the guanidine group were introduced at an early stage. They first constructed cyclic guanidine **313** using the same method as in their ptilomycalin A (**4a**) synthesis. Dihydroxylation of **313** followed by cleavage of the resulting diol gave pyrrolidine **314** (Fig. 53). Subsequent Biginelli condensation of **314** with **306** under Knoevenagel conditions provided exocyclic guanidine **315**. A good level of diastereoselectivity (7:1) was obtained when 2,2,2-trifluoroethanol was used as the solvent. The C13 stereochemistry of **315** is consistent with **4n** and opposite to that of **307**. Deprotection of **315** followed by an acid-promoted spirocyclization completed the skeleton of **4n**. Subsequent epimerization of the C14 stereocenter of **316** and introduction of the amide side-chain furnished **4n**.

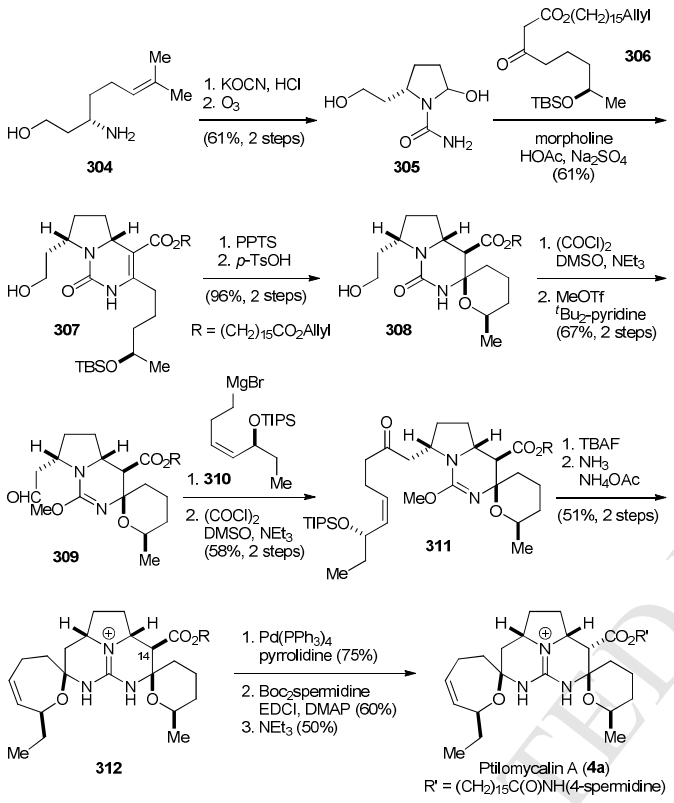


Figure 52. Overman's synthesis of ptilomycalin A (**4a**).

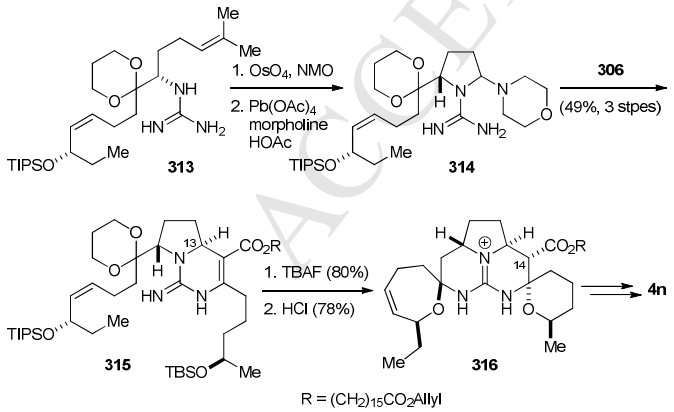


Figure 53. Overman's synthesis of 13,14,15-isocrambescidin 800 (**4n**).

The Overman group also completed the synthesis of crambidine (**300**) in 2005.[382] The synthesis of **300** started with desilylation of **315**, a synthetic intermediate of **4n**. Desilylation of **315** followed by treatment with a weak acid induced the spirocyclization of the seven-membered spiroaminal without the formation of the six-membered spiroaminal (Fig. 54). The resulting **317** was then oxidized to give a chromatographically separable mixture of **318** and **319**. Whereas the pentacyclic core **318** is the major isomer in deuterated chloroform, the tetracyclic core **319** exists predominantly in deuterated methanol, acetonitrile, and tetrahydrofuran. Consistently, acetylation of the primary alcohol of **319** is significantly slower in deuterated chloroform than in acetonitrile or pyridine. This mixture of **318** and **319** could also be obtained by oxidation of **315** followed by sequential desilylation. Subsequent installation of the hydroxyspermidine group furnished **300**.

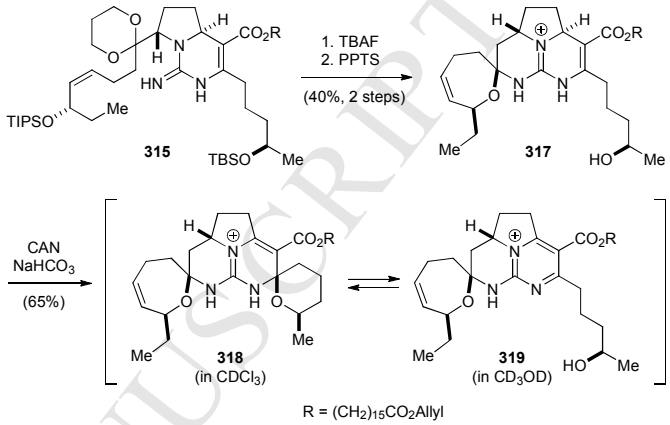


Figure 54. Overman's synthesis of crambidine (**300**).

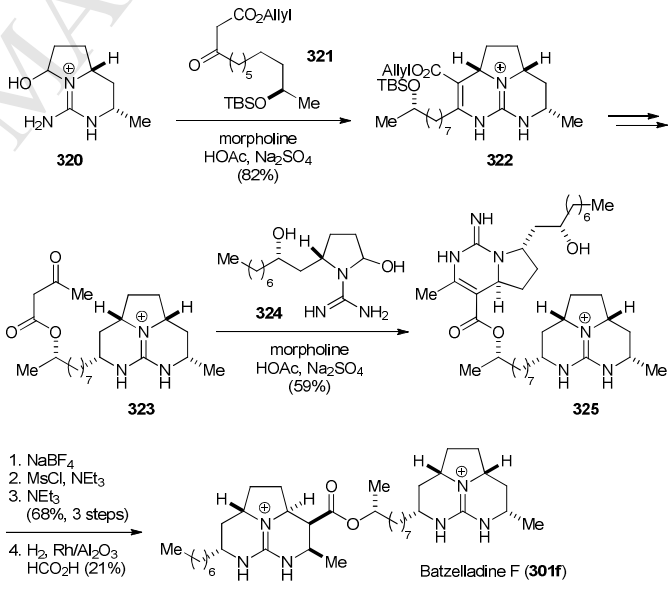


Figure 55. Overman's synthesis of batzelladine F (**301f**).

Additionally, the Overman group completed the asymmetric synthesis of batzelladine D (**301d**) in 1999.[384] They also revised the structure of batzelladine F (**301f**) and completed its asymmetric synthesis in 2001.[385,388,389] They further reported the synthesis of dehydrobatzelladine C (**302**) in 2004.[387] They found through synthetic studies that the originally proposed length of the alkyl chains and the relative stereochemistry of **301f** were both incorrect. The tethered Biginelli reaction was used again to construct both tricyclic cores of **301f**. Specifically, Biginelli condensation of guanidine **320** with **321** provided the tricyclic core **322** (Fig. 55). Decarboxylation of **322** followed by hydrogenation, and introduction of an acetoacetate group gave

323. Biginelli condensation of the highly functionalized **323** with guanidine **324** yielded **325**. Finally, cyclization and hydrogenation of **325** completed the synthesis of **301f**.

5.2. Synthetic contributions from the Snider group

The first biomimetic synthesis of the ptilomycalin A (**4a**) core was reported by the Snider group in 1994.[391,392] They assembled the polyketide framework of **4a** by a Knoevenagel condensation of **326** and **327** (Fig. 56). Reaction of the resulting double Michael acceptor **328** with *O*-methylisourea gave **329** as a 4:1 mixture of C10/C13 diastereomers. Subsequent treatment with ammonia provided the central tricyclic guanidinium core **330** as a 1:1 mixture of C10/C13 diastereomers. Removal of the silyl protecting groups under acidic conditions induced the formation of the seven-membered spiroaminal to yield **331**. The formation of the six-membered spiroaminal was achieved under basic conditions to give the ptilomycalin core skeleton **332**, which could be hydrolyzed back to **331**.

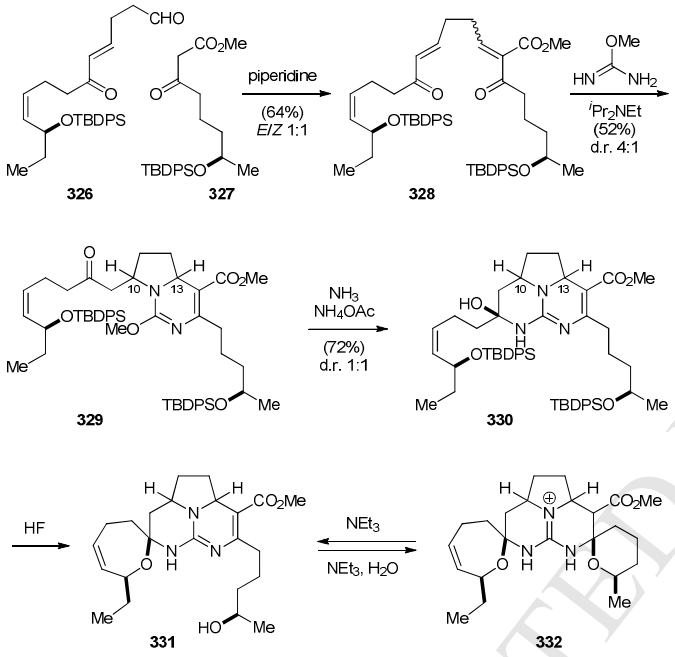


Figure 56. Snider's biomimetic synthesis of ptilomycalin A (**4a**) core.

The Snider group later used this flexible approach to achieve the first synthesis of a batzelladine alkaloid in 1998.[393-395] Impressively, batzelladine E (**301e**) was obtained in only nine steps. Their synthetic studies also indicated that the relative stereochemistries of the tricyclic core of batzelladines A, D and F (**301a**,**d**,**f**) were originally misassigned.[393,395]

5.3. Synthetic contributions from the Murphy group

The Murphy group also used a biomimetic double Michael addition/bis-spirocyclization approach to synthesize the pentacyclic core skeleton of ptilomycalin A (**4a**).[333,396-399] Unlike Snider who used *O*-methylisourea as the guanidine surrogate, Murphy used guanidine directly to construct the central core skeleton of **4a** by a double Michael addition reaction. The Murphy group also independently found that the originally proposed relative stereochemistry of the tricyclic core of batzelladine F (**301f**) was incorrect.[400-403] They completed the biomimetic synthesis of crambescidin 359 (**4b**) in 2003.[404,405] The synthesis of **4b** started with the Wittig reaction of **326** and **333** (Fig. 57). Condensation of the resulting bis-enone **334** with guanidine provided the tricyclic core of **4b**. Subsequently, one of the silyl protecting groups was selectively removed upon treatment with acid. This operation also induced the formation of the six-membered spiroaminal. Finally, desilylation of **335** followed by another spiro-cyclization under acidic conditions provided **4b**.

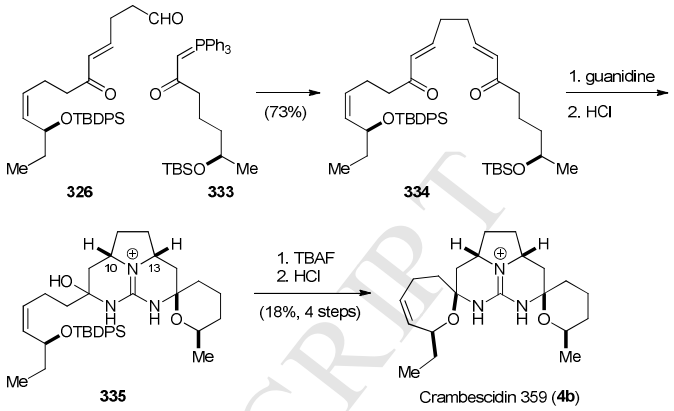


Figure 57. Murphy's biomimetic synthesis of crambescidin 359 (**4b**).

5.4. Synthetic contributions from the Rao group

Rao and co-workers reported a chiral synthon approach for the synthesis of the batzelladine core skeleton in 1995.[406] The commercially available azetidinone derivative **336** was used as the source of chirality (Fig. 58). Coupling of **336** with the 2-(1,3-dioxolan-2-yl)ethyl Grignard reagent followed by hydrolytic cleavage of the β-lactam ring gave **337**. The removal of the acetal protecting group and the oxidation of the resulting aldehyde were accomplished in one step by treating **337** with the Jones reagent. Subsequent Lawesson thionation gave **338**. The remaining polyketide framework was then introduced by Eschenmoser sulfide contraction to provide **339**. Next, reduction of the enone group of **339**, introduction of the C30 nitrogen atom by a Mitsunobu reaction, and manipulations of the protecting groups afforded **340**. The C32 nitrogen atom was introduced by another Mitsunobu reaction. Treatment of **341** with acid removed the amino protecting groups. The cyclic urea was then introduced to yield **342**. Finally, cyclic guanidine formation via the *O*-methylurea of **342** provided **343**, the originally proposed core structure of batzelladine A (**301a**).

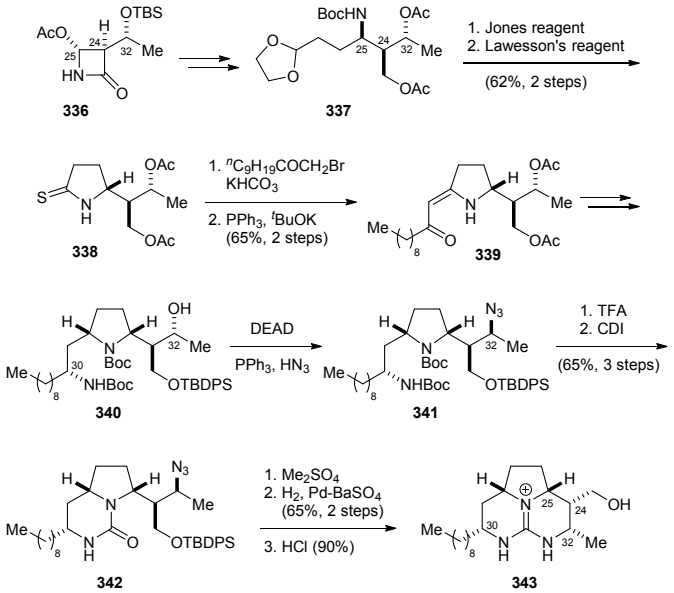


Figure 58. Rao's synthesis of the originally proposed tricyclic core of batzelladine A (**301a**).

5.5. Synthetic contributions from the Hiemstra group

The Hiemstra group reported a racemic approach for the synthesis of the tricyclic core skeleton of ptilomycalin A (**4a**) in 1996.[407-409] The overall strategy is similar to that developed by the Rao group.[406] Coupling of **344** and **345** gave **346** via an *N*-acyliminium ion (Fig. 59). The Eschenmoser condensation of the thiolactam of **346** and bromoacetophenone gave **347**. Subsequent sulfide contraction provided **348**. After adjustment of the oxidation state and protection of the amino group, the resulting **349** was converted to a mixture of mono- and bis-ketals. Finally, guanidination and bis-cyclization yielded **350**.

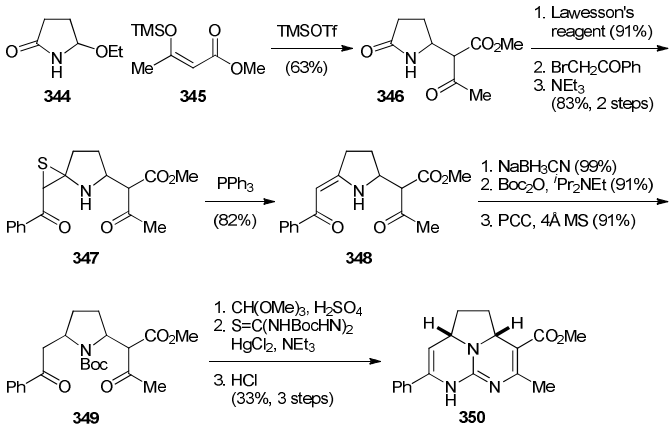


Figure 59. Hiemstra's synthesis of the tricyclic core of ptilomycalin A (**4a**).

5.6. Synthetic contributions from the Nagasawa group

The Nagasawa group reported a successive nitrone-olefin [3+2] cycloaddition approach for the synthesis of the core skeleton of ptilomycalin A in 2000.[410,411] They then applied the [3+2] cycloaddition approach to the syntheses of crambescidin 359 (**4b**)[412] and batzelladines A, D, and K (**301a**,**d**,**k**)[413-419] during 2002–2010. The anion-binding ability of this cage-like pentacyclic scaffold has also inspired them to design a C_2-symmetric phase-transfer catalyst for the asymmetric alkylation of glycinate Schiff bases.[334]

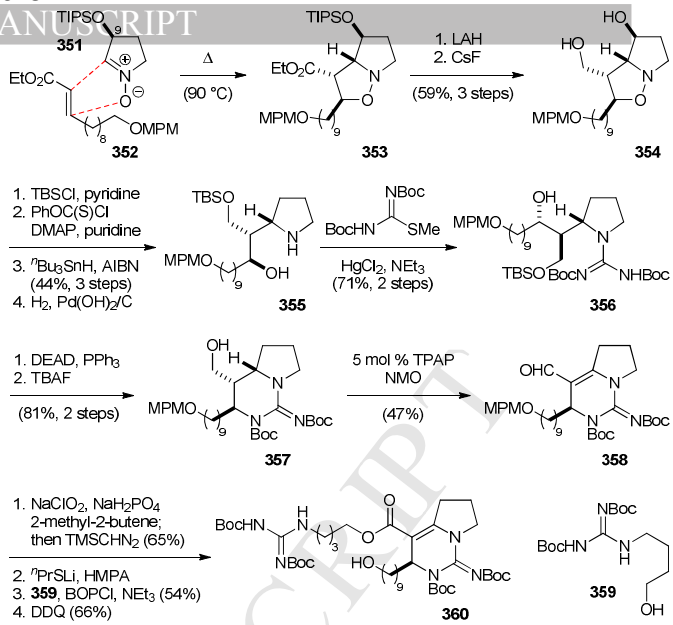


Figure 60. Nagasawa's synthesis of the bicyclic core of batzelladine A (**301a**).

The synthesis of the bicyclic core of batzelladine A (**301a**) started with reacting nitrone **351** with olefin **352** to give **353** (Fig. 60).[416] The bulky silyloxy group of **351** was used to control the stereochemistry of the nitrone–olefin [3+2] cycloaddition reaction. The ester group of **353** was then reduced and the silyl protecting group removed to yield **354**. Selective protection of the primary alcohol followed by deoxygenation of the secondary alcohol and cleavage of the N–O linkage gave **355**. Subsequently, installation of the guanidine group yielded **356**, which was cyclized to generate the bicyclic core **357**. The rhuthenium-catalyzed oxidation of **357** proceeded through an iminium intermediate to provide enal **358**. Lindgren oxidation of **358** gave the corresponding carboxylic acid, which was converted into a methyl ester to facilitate the purification process. After thiolate-mediated ester hydrolysis and amide coupling with **359**, the bicyclic guanidinium core **360** was obtained upon removal of the hydroxyl protecting group.

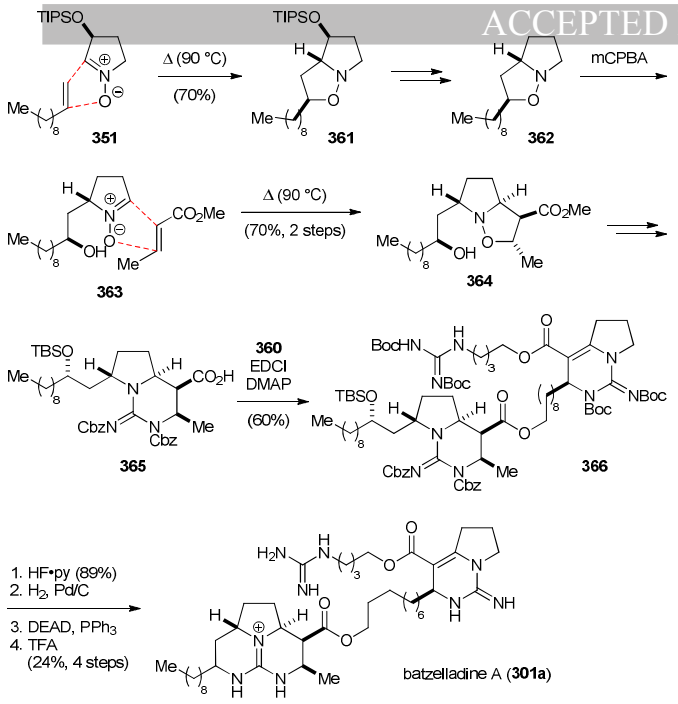


Figure 61. Nagasawa's synthesis of batzelladine A (**301a**).

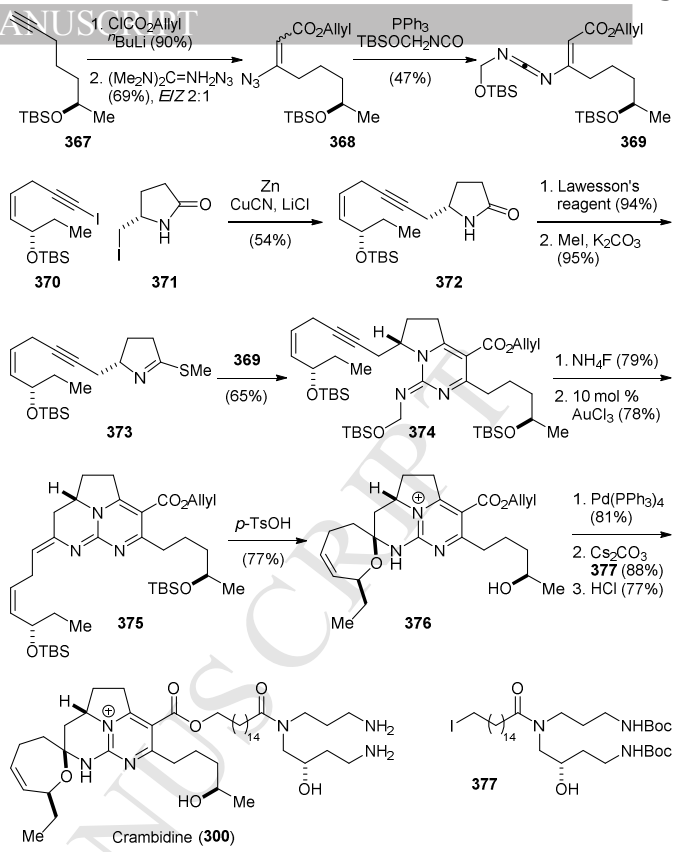


Figure 62. Gin's synthesis of crambidine (**300**).

The synthesis of the tricyclic guanidinium core of **301a** began with the nitrone–olefin [3+2] cycloaddition reaction of **351** and 1-undecene (Scheme 61).[416] Deoxygenation of the resulting **361** afforded **362**, which was oxidized to provide nitrone **363** with good regioselectivity. The [3+2] cycloaddition reaction of **363** and methyl crotonate yielded **364** selectively. After N–O cleavage, the guanidine group was introduced to afford **365**. Coupling of the two fragments **360** and **365** gave **366**. Deprotection and cyclic guanidine formation via a Mitsunobu reaction completed the synthesis of **301a**.

5.7. Synthetic contributions from the Gin group

The Gin group has made significant contributions to the field of the synthesis of crambescidin/batzelladine alkaloids. They first used the Eschenmoser sulfide contraction approach to synthesize the bicyclic core skeleton of batzelladine A (**301a**) and established its absolute stereochemistry in 2001.[420] They then developed an elegant diastereoselective [4+2] annulation strategy and completed the syntheses of batzelladine D (**301d**),[421] batzelladine A (**301a**),[422] and crambidine (**300**)[423] in 2005, 2006, and 2010, respectively.

The synthesis of crambidine (**300**) features a [4+2] annulation of a thioimidate with a vinyl carbodiimide, and a hydroamination of an alkyne with a 2-aminopyrimidine nucleophile.[423] To prepare the carbodiimide fragment, alkyne **367** was acylated and subjected to an azide conjugate addition to give β-azidoacrylate **368** as a mixture of *E*/*Z*-isomers (Fig. 62). After the Staudinger reduction and in situ condensation of the resulting enamine with siloxymethyl isocyanate, the two isomers converged to yield (*E*)-carbodiimide **369**. The preparation of the imine fragment started with coupling **370** and **371** to provide pyrrolidinone **372**. Lawesson thionation followed by *S*-methylation gave thioimidate **373**. Reaction of carbodiimide **369** and thioimidate **373** provided bicyclic pyrimidine **374**. The siloxymethyl protecting group was then removed and the resulting 2-aminopyrimidine was subjected to a gold(III)-catalyzed intramolecular alkyne hydroamination reaction to afford tricyclic pyrimidium core (*Z*)-**375** with good stereoselectivity. Treating **375** with acid induced the spiroaminal formation to yield **376**. Finally, deprotection of **376** and coupling with **377** completed the synthesis of **300**.

5.8. Synthetic contributions from the P.A. Evans group

The Evans group developed a unique radical cyclization strategy for the synthesis of the core skeleton of batzelladines in 2001,[424] and subsequently completed the synthesis of batzelladine D (**301d**) in 2007.[425] This convergent synthesis started with the treatment of **378** with octanyl cuprate followed by lithium trimethylsulfoxonium ylide to give *anti*-diol **379** (Fig. 63). Carbonate formation then yielded **380**, which was subjected to a rhodium-catalyzed allylic amination reaction to give **381** with excellent regio- and stereoselectivities. The dihydropyrimidinone nucleophile was prepared by a Bignelli condensation. Hydrosilylation of **381** followed by transesterification, and conversion of the hydroxyl group to an azido group using the

Mitsunobu method provided **382**. Whereas the platinum-catalyzed hydrosilylation of **381** could also deliver the desire product smoothly, poor regioselectivity or reactivity was observed with hydroboration and other hydrometallation reactions of **381**. Tamao–Fleming oxidation of **382** followed by conversion of the resulting alcohol into an iodide afforded **383**, setting the stage for the key radical cyclization reaction. Treatment of **383** with tributyltin hydride, triethylborane, and oxygen initiated a radical cyclization reaction to provide the bicyclic core **384**. In contrast, attempts to initiate the radical cyclization with AIBN led to competitive azide reduction. After removing the chiral sulfonyl group of **384**, the cyclic urea was methylated to afford **385**. Reduction of bis-azide **385** gave a diamine that cyclized under the reaction conditions to give the tricyclic core of batzelladines. Finally, installation of the acyclic guanidinium furnished **301d**. Remarkably, starting from the chiral bis-epoxide **378**, **301d** could be obtained in 14 steps and 10% overall yield.

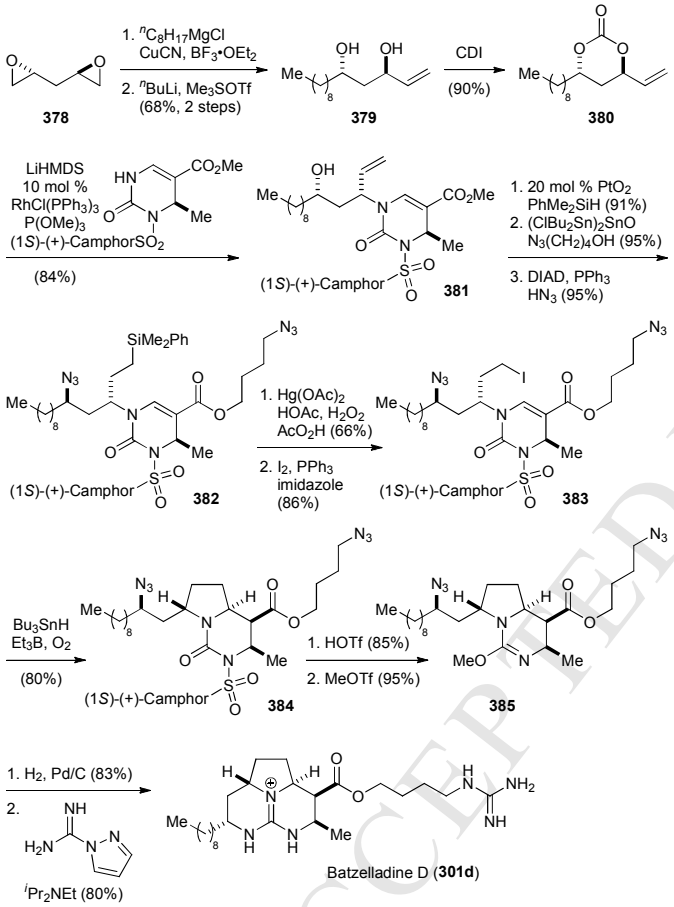


Figure 63. Evan's synthesis of batzelladine D (**301d**).

5.9. Synthetic contributions from the Elliott group

The Elliott group reported an asymmetric synthesis of the methyl ester of batzelladine C (**301c**) in 2009.[426-429] Similar to the Rao, Hiemstra, and Gin groups, they also used the Eschenmoser sulfide contraction reaction to derivatize the γ-lactam ring in preparing alkylidenepyrrolidine **387** from **386** (Fig. 64). They then constructed the bicyclic thiourea **388** by condensing **387** with hexanal and trimethylsilyl isothiocyante, a reaction previously developed by Kishi for the synthesis of saxitoxin (**192a**).[259] Subsequently, conversion of the thiourea group into a guanidine group provided **389**, which was transformed into **390** using the iodocyclization method developed by Gin for the synthesis of batzelladine D (**301d**).[421] Finally, dehalogenation of **390** afforded **391**, the methyl ester of **301c**.

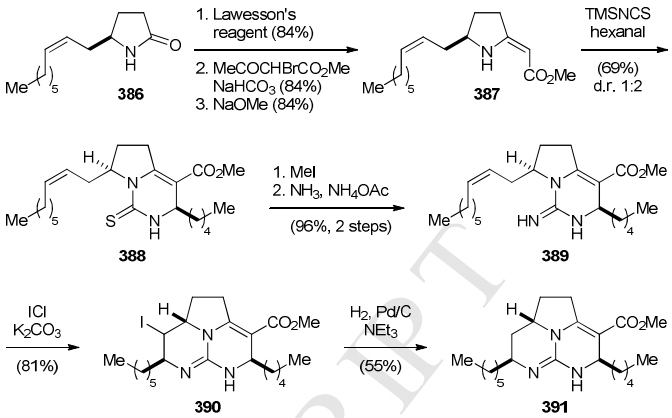


Figure 64. Elliott's synthesis of "batzelladine C methyl ester" (**391**).

5.10. Synthetic contributions from the Wolfe group

The Wolfe group has developed a series of palladium-catalyzed olefin carboamination reactions[430] and demonstrated their synthetic utility by applying the iterative carboamination reactions to the synthesis of merobatzelladine B (**398**) in 2012.[431] Briefly, reaction of **392** with bromovinyltrimethylsilane in the presence of a catalytic amount of palladium gave pyrrolidine **393** with complete stereochemical control (Fig. 65). Subsequent protodesilylation, deprotection of the pyrrolidine, and urea formation yielded **394**. The second carboamination reaction also proceeded well and the coupling of **394** with (*Z*)-1-bromobutene gave **395** with excellent stereoselectivity. Conversion of cyclic urea **395** into cyclic guanidine **396** followed by hydrogenation, Mitsunobu cyclization, and deprotection completed the synthesis of merobatzelladine B (**397**).

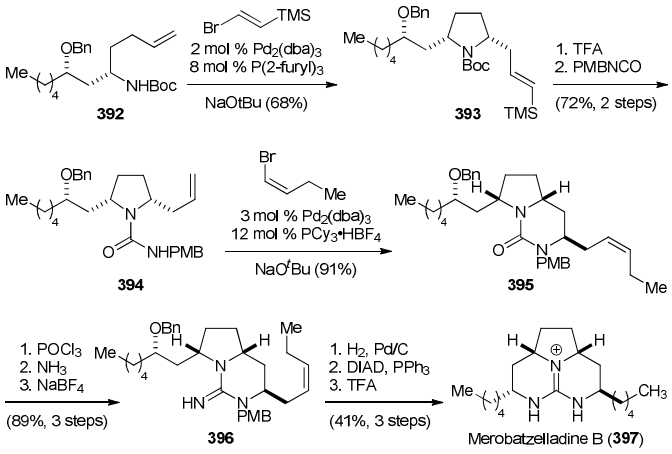


Figure 65. Wolfe's synthesis of merobatzelladine B (**397**).

6. Outlook

The biological properties associated with the guanidine-containing natural products have made them valuable tools for studying protein functions. In addition, their complex chemical structures have inspired the development of many synthetic methods. While the special chemical reactivity of many cyclic guanidine-containing alkaloids remains poorly understood,

significant progress has been made over the past decades. We anticipate that the utilities of this unique class of small molecules will continue to be unveiled through the chemical biological studies enabled by the newly developed chemical tools.

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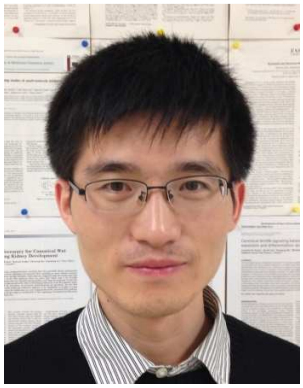

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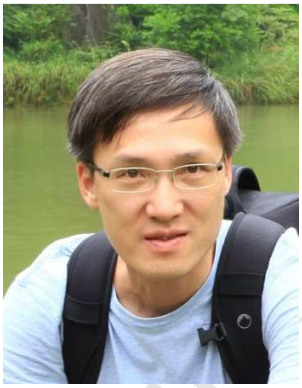

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