Dimeric pyrrole-imidazole alkaloids: Synthetic approaches and biosynthetic hypotheses

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Abstract

The pyrrole-imidazole alkaloids are a group of structurally unique and biologically interesting marine sponge metabolites. Among them, the cyclic dimers have caught synthetic chemists' attention particularly. Numerous synthetic strategies have been developed and various biosynthetic hypotheses have been proposed for these fascinating natural products. We discuss herein the synthetic approaches and the biosynthetic insights obtained from these studies.

Natural products have been a rich resource for discovering new drugs over the past decades.[1] Studying their total synthesis and biosynthesis often leads to the discovery of new chemical reactivities and recognition of structural issues that may be difficult to identify by other means.[2,3] The unique chemical properties of dimeric pyrrole-imidazole alkaloids have attracted numerous research groups to study their total synthesis. Several excellent review articles discussing the chemistry of pyrroleimidazole alkaloids have been published.[4] This review focuses on the chemistry of cyclic pyrrole-imidazole dimers. In particular, we present an overview our synthetic work[5–10] and the biosynthetic insights obtained from these studies.

Introduction

The pyrrole-imidazole alkaloids are a group of densely functionalized, highly nitrogenated natural products widely distributed within a few genera of marine sponges (Phylum Porifera) (Fig. 1). While their biological activities have not been fully investigated, many family members possess anticancer, antimicrobial, antiviral, or immunosuppressive activities. To date, about 100 pyrrole-imidazole alkaloids have been discovered. Although their biosynthesis[11,12] is poorly understood, it is generally agreed that these sponge metabolites are derived from clathrodin (**1a**), hymenidin (**1b**), and oroidin (**1c**) through oxidation, cyclization, and dimerization reactions. This family of natural products possesses a diverse set of molecular skeletons, and is often referred to as the oroidin family of alkaloids because **1c** is highly abundant in the producing sponges (up to 4.2% dry weight).[13]

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Many pyrrole-imidazole alkaloids contain a polycyclic skeleton, making them attractive platforms for developing new synthetic methods and strategies. For example, there are several reports of the synthesis of cyclooroidin (2),[14] agelastatins (3),[15] and dibromophakellin/dibromophakellstatin (4).[16] The most synthetically challenging family members are the cyclic dimers. Structurally, the sceptrins (5) are [2+2] dimers of 1; the massadines (6), axinellamines (7), and palau'amine (8) are [3+2] dimers, and the ageliferins (9) are [4+2] dimers. Numerous synthetic approaches have been reported[17–28] and the syntheses of 5–9 have been achieved.[8–10,29–35] In particular, the seminal syntheses of 5–9 by the Baran group involve many revolutionary developments at both the strategic and methodological levels.[29–33] Currently, there is no report of the synthesis of the stylissadines (10), which are the only known tetrameric family members.

Biosynthetic hypotheses

Many biosynthetic hypotheses have been proposed for the pyrrole-imidazole alkaloids.[11] However, much remains to be learned about how sponges assemble these natural products. For example, while it is generally agreed that the biogenic cyclization, oxidation, and dimerization of 1 are catalyzed by enzymes, the corresponding cyclases and oxidases have not been identified although it has been demonstrated that proline and lysine are the amino acid precursors for 1.[11h,i]

The isolation of the first dimeric pyrrole-imidazole alkaloid sceptrin (5a) was reported by the Faulkner and Clardy groups in 1981.[36] They suggested the biosynthesis of 5a would not involve a [2+2] photocycloaddition reaction with 1b because the producing sponges live 20–30 m below the ocean's surface. Sunlight is insufficient at these depths for photocycloaddition reactions. In addition, a direct photoreaction would give rise to racemic 5a while the natural product was found optically active. Furthermore, all attempts to synthetically induce the photodimerization of 1b in either solid-state or solution phase failed to deliver 5a (Fig. 2A).[29a,36] The inaccessibility of 5a from 1b via photolysis has been confirmed by the Baran group recently.[29a] Interestingly, D'Auria and Racioppi have showed that photolysis of urocanic esters (11) in the presence of benzophenone (photosensitizer) gave the desired cyclobutane skeleton of 5a (Fig. 2B).[37] Only the head-to-head dimers 12 and 13 were obtained. This regioselectivity was explained by the frontier molecular orbital theory with either a HOMO/LSOMO (primary) or a HSOMO/LUMO (secondary) interaction. The observed stereoselectivities could also be explained by steric effects.

The Rinehart group and the Kobayashi group reported the isolation of the second type of dimeric pyrrole-imidazole alkaloids ageliferins (9) in 1989 and 1990, respectively.[38,39] While Kobayashi considered that ageliferins (9) could be derived from 1b/c through a Diels–Alder reaction followed by olefin isomerization, Rinehart disagreed because natural 9 are optically active. Instead, Rinehart proposed that the dimerization of 1b would be an acid-promoted, stepwise process with the C9-C9' linkage formed first (Fig. 2C).[38b] Subsequent C10-C10' cyclization would then yield sceptrin (5a), while C15-C10' cyclization would provide ageliferin (9a). However, Lindel found that thermolysis of 1c•HCOOH did not give any dimerization products (Fig. 2D), but instead observed *rac*-2.[14c]

To explain the mismatched electronic properties toward homodimerization, an alternative mechanism involving single-electron transfer (SET) has recently been reported. The Molinski and Romo groups found that cell-free enzyme extracts collected from pyrrole-imidazole alkaloid-producing sponges could promote the dimerization of **1c** to give benzosceptrin C (**5d**) (Fig. 3).[12] They suggested that the biosynthesis of **5c** and **5d** would involve oxidoreductase-catalyzed SET reactions. Specifically, a single-electron oxidation of **1c** would give a highly reactive radical cation **1c•+**. A radical addition of **1c•+** to another molecule of **1c** would then give **15** after loss of a proton. Subsequent cyclization of **15** would yield **16**. A single-electron reduction of **16** followed by protonation would then provide **5c**. This reversible SET mechanism nicely fits the redox-neutral dimerization of **1c** for the biosynthesis of **5c**. Similarly, **5d** would be formed from **15** through a net three-electron oxidation. Molinski and Romo also suggested that this SET biosynthetic hypothesis could be extended to other pyrrole-imidazole alkaloids, including both the monomeric and dimeric members. They further argued that the high-energy radical species renders the corresponding cyclization reactions kinetically favorable over the two-electron mechanisms.

We agree to the biosynthetic hypothesis put forth by Molinski and Romo, and believe that sponges use reversible SET reactions to generate **5–9** through divergent biosyntheses (Fig. 4). We envision that the biosynthesis of dibromosceptrin (**5c**) would involve a SET of **1c** to give **1c•+**, which would undergo a [2+2] cycloaddition (stepwise or concerted) with another molecule of **1c** to provide **5c•+** (*path a*), or a [4+2] cycloaddition to provide **9c•+** (*path b*). A subsequent back-SET and aromatization would then yield **5c** and **9c**.

We further propose that a redox-neutral, reversible SET process was also involved in the formation of the core skeleton of the [3+2] dimers. Unlike the biosyntheses of sceptrins (**5**) and ageliferins (**9**) that involve a homodimerization of **1**, we believe that the [3+2] dimers involve a heterodimerization of dispacamide A (**17**) and oroidin (**1**) (Fig. 4). A SET-oxidation of **17** would give **17•+**, which would then undergo a [3+2] cycloaddition with **1c** to give "pre-massadine" radical cation (**18•+**) (*path c*). Subsequent SET-reduction of **18•+**, protonation, and trapping with water or chloride would provide "premassadine" (**18**-OH) or "pre-massadine chloride" (**18**-Cl). Oxidation of "pre-massadine chloride" (**18**-Cl) would give rise to "pre-axinellamine" (**14**), a common biosynthetic intermediate proposed by Köck and Baran for all [3+2] pyrroleimidazole dimers (Fig. 2E).[31,40] Cyclization of **14** would afford massadine chloride (**6b**), axenellamines (**7**), and konbu'acidins (**8b,c**). While massadine (**6a**) and massadine chloride (**6b**) could be produced independently, Köck and Baran showed that **6a** could be converted to **6b** completely by incubating **6a** in water at 60 °C for 4 h.[40] The retention of stereochemistry could be explained by an aziridinium intermediate that was previously proposed by Romo.[19d]

Because enzymes that promote [3+2] cycloaddition reactions remain elusive, it is generally believed that the [3+2] pyrrole-imidazole dimers are produced from skeletal rearrangement of the [4+2] dimers. This biosynthetic hypothesis was first put forth by Kinnel and Scheuer in 1998.[41] They proposed that the biosynthesis of "palau'amine" (**22**) would involve a [4+2] cycloaddition of 3-amino-1-(2-aminoimidazolyl)prop-1-ene (AAPE, **19**) and 11,12-dehydrophakellin (**20**). A chloroperoxidase-mediated oxidative ring contraction of the

Diels–Alder adduct **21** would then yield "palau'amine" (**22**). Interestingly, they noted that this biosynthetic pathway was a "better alternative" suggested by a reviewer.

Recently, the structure of palau'amine has been revised from **22** to **8a**. The new *trans* C-11/C-12 configuration could not be easily explained by the original "Kinnel–Scheuer hypothesis". We thus proposed a modified scheme that involves the intermediate **23** to reconcile the C-11/C-12 stereochemical issue.[7] Specifically, a [4+2] cycloaddition reaction of **19** and clathrodin (**1a**) would give rise to **23** and set the *trans* C-11/C-12 stereochemistry. An oxidative bicyclization and a chlorinative ring contraction would then afford **8a**.

Total Syntheses

Synthesis of sceptrin

The isolation of sceptrin (**5a**), a [2+2] pyrrole-imidazole dimer, was first reported by the Faulkner and Clardy groups in 1981.[36] Its total synthesis has been accomplished by the Baran and Birman groups in 2004.[29,34] As noted by Baran, "unexpected reactivity, intermediate fragility, and forbidding elements of complexity" render **5a** a significant synthetic problem. Baran used a 3-oxaquadricyclane rearrangement as the key step to generate the core skeleton of **5a**.[29] The Baran group also achieved the asymmetric synthesis of **5a** with an enzymatic desymmetrization approach to generate **24**.[30b] Photolysis of **24** promoted a [2+2] cycloaddition to form the cyclobutane framework of **5a**. Treating the resulting cycloadduct **25** directly with acid initiated the oxaquadricyclane rearrangement reaction to give **26**. This practical approach allowed for a gram-scale synthesis of **5a** with an impressive 24% overall yield. The Birman group used an intermolecular [2+2] photocycloaddition of **27** and **28** to construct the sceptrin precursor **29**. Both the Baran and Birman's approaches involved a cycloaddition reaction to construct the C9-C10 and C9'-C10' bonds in a "non-biogenetic" fashion.

Synthesis of ageliferin

The isolation and characterization of ageliferins (**9a**) were first reported by the Rinehart group and the Kobayashi group in 1989 and 1990, respectively.[38,39,42] While attempts to synthesize ageliferins by inducing the dimerization of **1** via a thermal Diels–Alder reaction have not been successful,[14c] the Romo group and the Lovely group successfully used the Diels–Alder reaction to construct the core skeleton of **9a**.[19,20] The Ohta group also used this Diels–Alder approach to accomplish the synthesis of 12,12'-dimethylageliferin in 2002.[21]

The first synthesis of **9a** was achieved by the Baran group in 2004 using a completely orthogonal synthetic approach.[30] Because ageliferin (**9a**) was always co-isolated with sceptrin (**5a**), they proposed that **9a** was a formal [1,3]-sigmatropic rearrangement product of **5a**. Supportive to this hypothesis, they found that microwave-thermolysis of the acid salts of **5a** gave **9a** stereospecifically (Fig. 7).[30] Incubating *nat*-**5a** in water at 200 °C for 2 min yielded *nat*-**9a**, while thermolysis of *ent*-**5a** gave *ent*-**9a**.[30b] A small amount of nagelamide E, the C-10 isomeric natural product of ageliferin (**9a**) was also obtained. Computational studies by the Houk group indicated that this rearrangement reaction proceeded through

dicationic diradical **30**.[30c] The Harran group also reported synthesis of **9a** using an acid-promoted ring-expansion reaction.[35]

Synthesis of axinellamine, massadine and palau'amine

The [3+2] class of pyrrole-imidazole alkaloid dimers are among the most complicated marine alkaloids. Palau'amine (**8a**), the first known member was isolated by the Kinnel and Scheuer groups in 1993.[41] The pyrrole-isomeric congener styloguanidine and the bis-pyrrole congener konbu'acidins (**8b,c**) were isolated by the Kato group and the Kobayashi group in 1995 and 1997, respectively.[43] Unlike other [3+2]-type pyrrole imidazole alkaloid dimers (**6–9**), they were originally proposed to bear an all-*cis* stereochemistry on the central all-carbon 5-memebered ring (**22**) because a *trans*-fused 5,5-bicyclic system would be significantly strained. However, the Köck, Quinn, and Matsunaga groups independently reported structural revisions of Palau'amine to **8a** in 2007.[44] The stereochemistry of the central 5-membered ring in **8a** is now consistent with that of **6–9**.

The second type of [3+2] dimers identified are the axinellamines (**7**), first reported by the Quinn group in 1999.[45] Instead of bearing a phakellin substructure, it possesses a C–N linkage between the two cyclic guanidine units. The isolation of massadine (**6a**), the third type of the [3+2] dimers, was first reported by the Fusetani group in 2003.[46] It contains an ether linkage between the two cyclic guanidine units, and is currently the only [3+2] dimer that does not bear a chlorine atom. The Köck group further discovered that dimers of massadine also exist in nature. They reported the isolation of the first tetrameric pyrrole-imidazole alkaloid stylissadine in 2006,[47] and proposed that **6a** was derived from massadine chloride (**6b**) via hydrolysis. Together with the Baran group, they have successfully discovered **6b** and demonstrated that slow hydrolysis of **6b** gave **6a**.[40] Finally, donnazoles, discovered by Muñoz and the Al-Mourabit group in 2012, are the fourth type of [3+2] dimers.[48] They closely resemble "pre-axinellamine" (**14**) and bear a hydantoin group without further cyclization.

The fascinating structures of **6–9** have inspired many research groups to develop new strategies and methodologies for total synthesis. The first approach was reported by the Overman group.[17] They developed a novel azomethine imine cycloaddition reaction to construct the core structure of [3+2] dimers (Fig. 8). Tandem condensation-cycloaddition of **33** and **34** afforded the tetracyclic thiohydantoin **35**. Cleavage of the N–N bond followed by installation of the second iminohydantoin group furnished the original proposed Palau'amine skeleton **36**. The Carreira group subsequently reported a Diels–Alder cycloaddition/oxidative cleavage approach to construct the core structure of axinellamine (**6**).[18] Ozonolysis of **37**, in which the norbonene skeleton was constructed from an intermolecular Diels–Alder reaction, gave **38**. The chlorine atom was then introduced through a Barton decarboxylation reaction followed by *in situ* trapping of a chlorine atom to afford the highly functionalized cyclopentane skeleton **39**. The Romo group first demonstrated the use of the Diels–Alder/Kinnel–Scheuer oxidative ring-contraction approach to synthesize the core structure of Palau'amine (**8a**).[19] The intermolecular Diels–Alder reaction of vinylimidazolinone **40** and the reactive dienophile **41** proceeded smoothly to give cyclohexene **42**. Oxidation of the imidazolinone group of **42** installed the requisite olefin for

the Kinnel–Scheuer rearrangement. Subsequent oxidative chlorination of **43** induced the pinacol-type rearrangement to afford **44**. The Lovely group also independently developed a similar biomimetic approach to construct the core skeleton of [3+2] pyrrole-imidazole dimers.[20] The Harran group has reported an oxidative enolate coupling/skeletal rearrangement approach to synthesize "axinellamines deficient in halogen".[23] Additional synthetic approaches have been reported by the Austin,[22] Gin,[24] Gleason,[25] Williams,[26] Feldman,[27] and Nagasawa[28] groups.

The syntheses of [3+2] pyrrole-imidazole dimers have been accomplished by the Baran group with two different approaches (Fig. 9).[31–33] In their first approach, an intramolecular aldol reaction was used to construct the core skeleton and a novel silver(II)-mediated oxidation to adjust the oxidation state of the spirocyclic guanidine. They first established the core skeleton of **45** by a Diels–Alder reaction. Ozonolysis of **45** then gave **46**, which was brominated and treated with dry silica gel to induce the intramolecular aldol reaction to yield **47**. Installation of the two cyclic guanidines and the chlorine atom provided **48**, setting the stage for the key oxidation reactions. Treating **48** with dimethyldioxirane (DMDO) afforded **49** with the complete axinellamine skeleton. Subsequent oxidation with silver(II) picolinate provided **50** with the desired axinellamine oxidation state. Using this approach, they successfully completed the first synthesis of axinellamines (**7**)[31] and massadine (**6**)[32] in 2008. They then developed a macrocyclization approach to construct the highly strained "phakellin" subunit of Palau'amine (**8a**). The synthesis of the legendary natural product Palau'amine (**8a**) was therefore achieved for the first time in 2010.[33] The Baran group further developed an asymmetric approach in 2011 and accomplished the enantioselective synthesis of **6**–**8a**.[33b] In the same year, they also reported a new, practical approach that allowed for the gram-scale synthesis of axinellamines (**7**).[31c] Some notable discoveries include the intriguing role of ethylene glycol in the Pauson–Khand cycloaddition reaction of **51** and **52** to give **53**, the unprecedented combination of In(0) and Zn(0) for promoting a facile Barbier-type reaction of **54** to give **55**, and the beneficial effects of trifluoromethanesulfonimidic acid (TfNH$_2$) in the chloroamidation of **56** to give **57**. These reports demonstrated once again that total synthesis is a fertile ground for studying chemical reactivities and developing new methodologies.

Our synthetic strategy

We are interested in developing a biomimetic approach for the synthesis of ageliferins (**9a**–**c**) (Fig. 10). Our work started with the design of an oxidative radical cyclization reaction that mimics the dimerization of **1**.[5] We envisioned that the reaction efficiency could be improved significantly by tethering the two dimerization units and replacing the olefin group with an enol. We used **58$^{\bullet+}$** that could be readily generated from a single electron oxidation of the corresponding β-ketoester to mimic **1c$^{\bullet+}$/1c**. After losing a proton, radical **59** would undergo a 5-*exo* cyclization followed by a 6-*endo* cyclization to afford the ageliferin core skeleton **60**, or a 5-*exo* cyclization followed by another 5-*exo* cyclization to afford the massadine core skeleton **61**. The pathway selectivity could be controlled by the electronic properties of the substituent group X. When X=H, the 5-*exo*/6-*endo* ageliferin-cyclization was preferred, giving **60** selectively. When X=Cl or CN, the 5-*exo*/5-*exo* massadinecyclization was preferred, giving **61** selectively. For example, oxidation of **62a**

gave **63** as the only product, while oxidation of **62b** gave **64** exclusively. Our computational studies suggested that both **63** and **64** were kinetic products.[9]

Based on our calculations, the 6-*endo* cyclization product of **59** is 11.4 kcal/mol more stable than the 5-*exo* cyclization product when X=H and R,R'=Me, consistent with the reported ESR studies on the captodative stabilization of radicals. The radical stabilization enthalpy of an amino group was estimated to be 3.9 kcal/mol and that of a carbonyl group to be 6.0 kcal/mol.[49] Together, these two groups were estimated to provide 20.7 kcal/mol stabilization. The 10.8 kcal/mol captodative stabilization provided by the amino and carbonyl groups was the thermodynamic driving force for the 6-*endo* cyclization pathway when X=H. The captodative stabilization also greatly contributed to stabilization of the transition states that led to **60** and **61** as judged by their atomic spin densities. Consequently, we predicted that a captodative stabilization could to introduce to the 5-*exo* cyclization pathway when X=Cl or CN, resulting in a switch of the pathway selectivity. Computational studies indicated that the introduction of a chloro or a cyano group would lower the activation barrier of the 5-*exo* cyclization pathway without affecting the 6-*endo* cyclization pathway (Fig. 10). For **60**, the 6-*endo* cyclization pathway was favored by 4.1 kcal/mol when X=H. However, for **61**, the 5-*exo* cyclization pathways was favored by 3.7 and 6.2 kcal/mol when X=Cl and CN, respectively. The 6-*endo* cyclization was also predicted to undergo a barrierless elimination of the chlorine atom.

Based on these results, we hypothesized that sponges utilize a divergent biosynthetic approach to produce **6–9**. The biosyntheses of sceprins (**6**) and ageliferins (**9**) would involve a homodimerization of **1**, while that of pre-massadine (**18**) would include a hetereodimerization of **1** and dispacamide A (**17**) (Fig. 4). A SET-oxidation of **17** would give **17**$^{•+}$. The hydroxyl group of **17**$^{•+}$ would provide additional stabilization for **18**$^{•+}$ and the corresponding transition state to direct the reaction toward [3+2] cyclization.

Using this radical cyclization approach, we have successfully completed the synthesis of ageliferins (**9a–c**) (Fig. 11).[8,9] We started our synthesis with (*S*)-Garner's aldehyde (**65**) that could be easily prepared from L-serine. Horner–Wadsworth–Emmons homologation of **65** followed by ester reduction and coupling with Boc-β-alanine gave **66**. Incorporation of the azidoimidazole group through an aldol reaction with **67** provided allylic β-ketoester **68** after alcohol oxidation. Treating **68** with Mn(OAc)$_3$ induced the key oxidative radical cyclization to deliver the ageliferin core skeleton **69** as a mixture of C-9' diastereomers. The allylic stereocenter (C-11) of **68** controlled the selective installation of the C-9 and C-10 stereocenters by minimizing the A^{1,3} strain.[50] The two diastereomers of **69** converged upon decarboxylation to give **70**. Subsequent installation of the bromopyrrole and aminoimidazole groups yielded ageliferin. The CD spectra of our synthetic sample indicated that we obtained *ent*-ageliferin while expecting to get *nat*-ageliferin. Consistently, repeating the synthesis using (*R*)-Garner's aldehyde as the source of chirality gave *nat*-ageliferins. Our approach also allows for the differential installation of the pyrrole groups bearing different bromine patterns. In addition to ageliferin (**9a**), bromoageliferin (**9b**) and dibromoageliferin (**9c**) have also been synthesized using this flexible approach.

Conclusions

Natural products have proved to be useful in providing new chemical entities to target both known and unknown biological domains. Their "privileged skeletons" have also provided precious platforms to study chemical principles. Because natural products often modulate signal transduction pathways and affect cell cycles, studying their chemistry and biology often leads to the development of new therapeutic agents. However, the primary function of many natural products remains unknown, rendering them uninteresting targets from biological perspectives. We believe that natural product evolution is driven by selection for functions and the biosynthetic machineries are purpose-built. In particular, complex natural products produced by lower marine organisms that heavily rely on chemicals for defence and symbiosis would be a rich resource for drug development. The successful identification of the primary functions of natural products and exploration of their therapeutic potentials heavily rely on chemists' ability to synthesize and modify these natural products. We anticipate that natural product synthesis will continue to play a central role in chemical research and stimulate the development of new chemical tools, offer insights into biosynthesis, and facilitate drug discovery.

Acknowledgments

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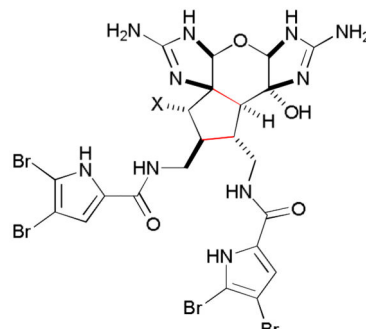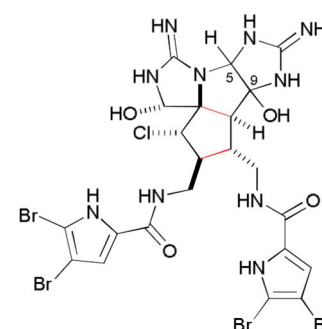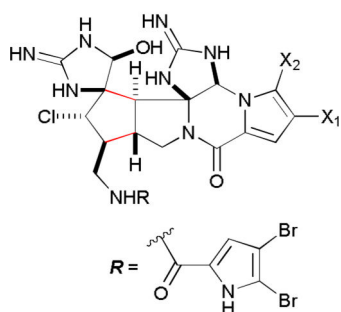
Fig. 1.
Structures of the representative pyrrole-imidazole alkaloids.
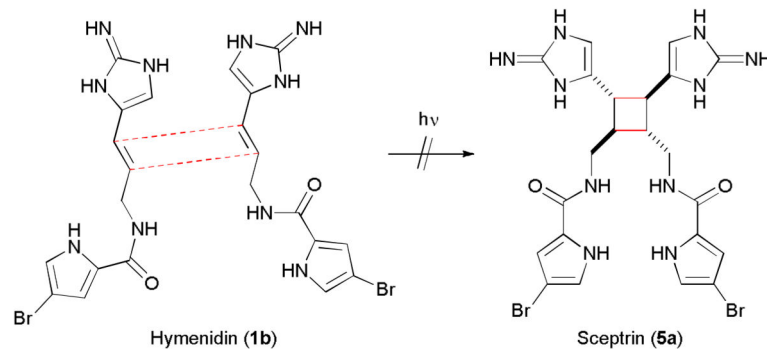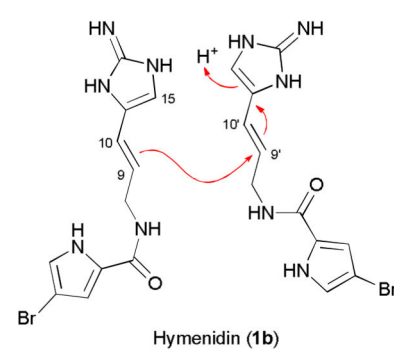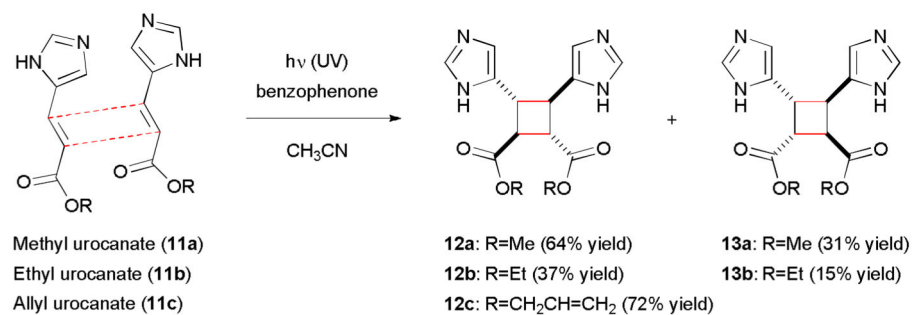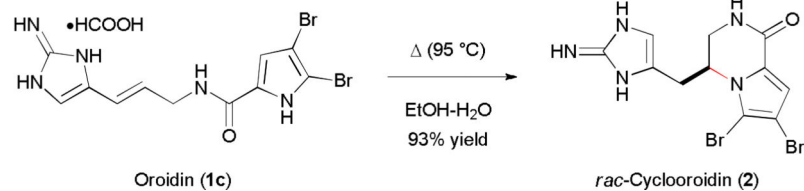
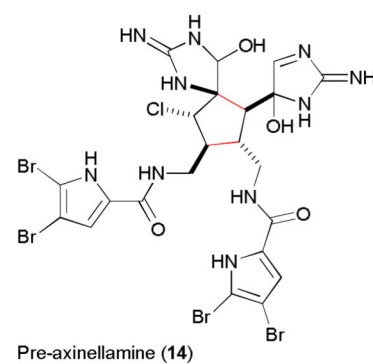**Fig. 2.**
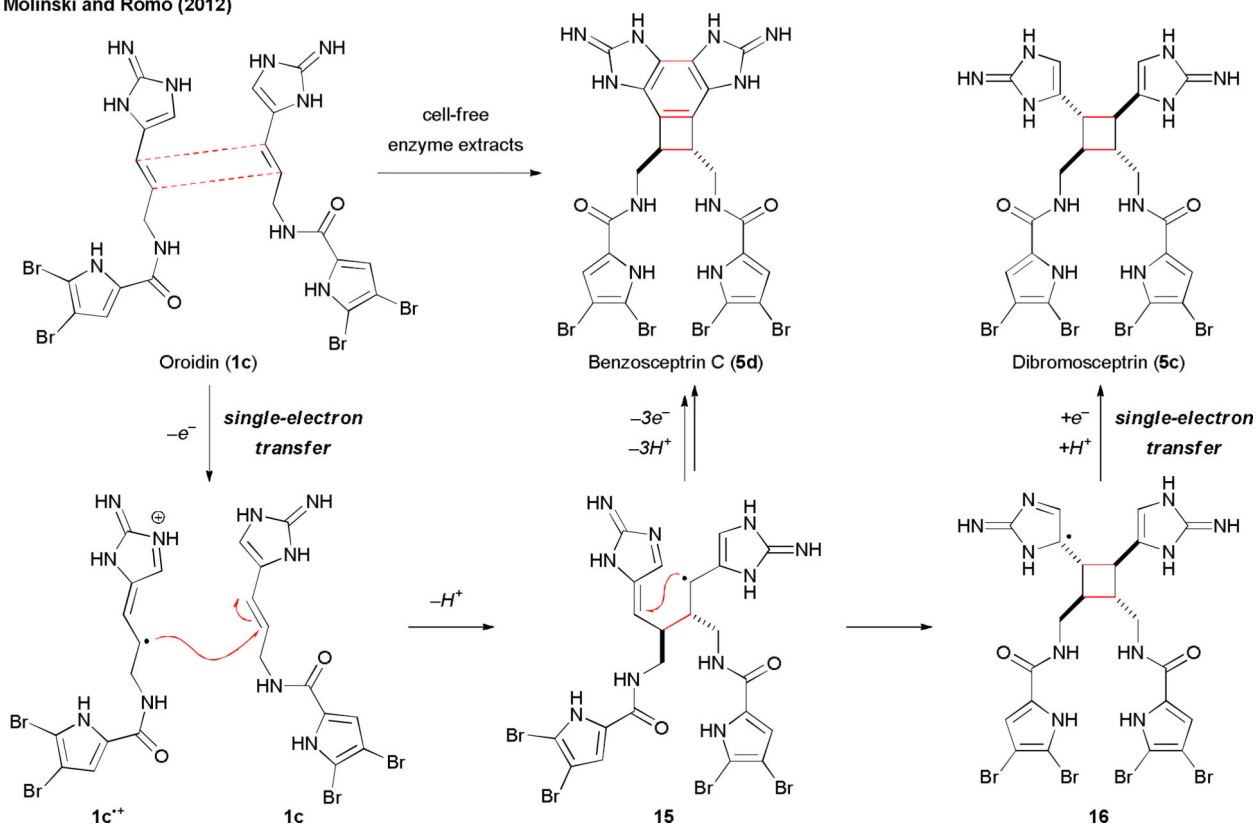Probing the biosynthetic hypotheses of the dimerization of the pyrrole-imidazole alkaloid by biomimetic synthesis.

Fig. 3.
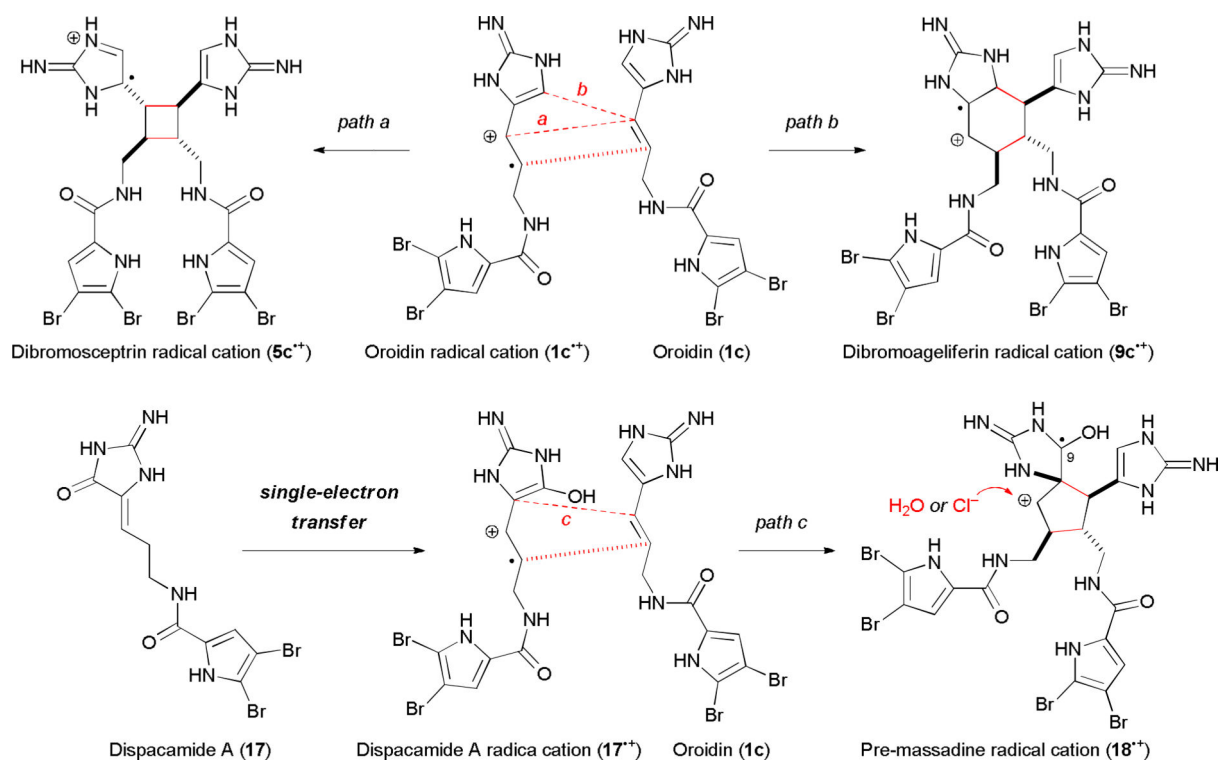The SET-mediated dimerization biosynthetic hypothesis.

Fig. 4.
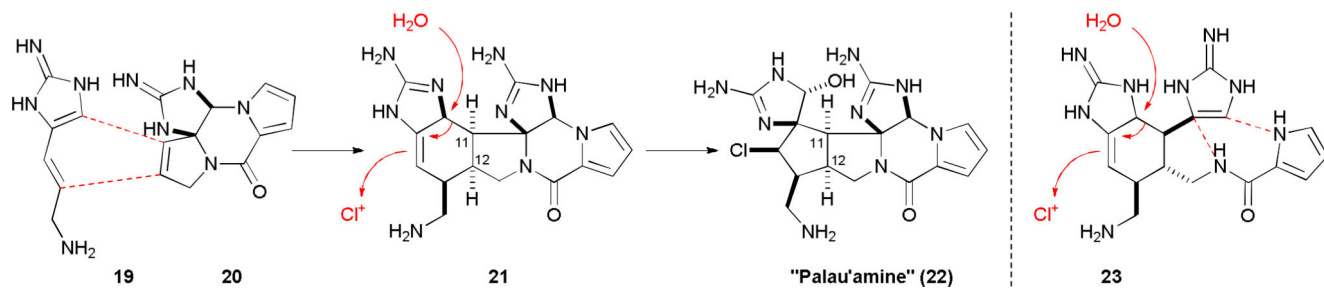The divergent SET-mediated dimerization biosynthetic hypothesis.
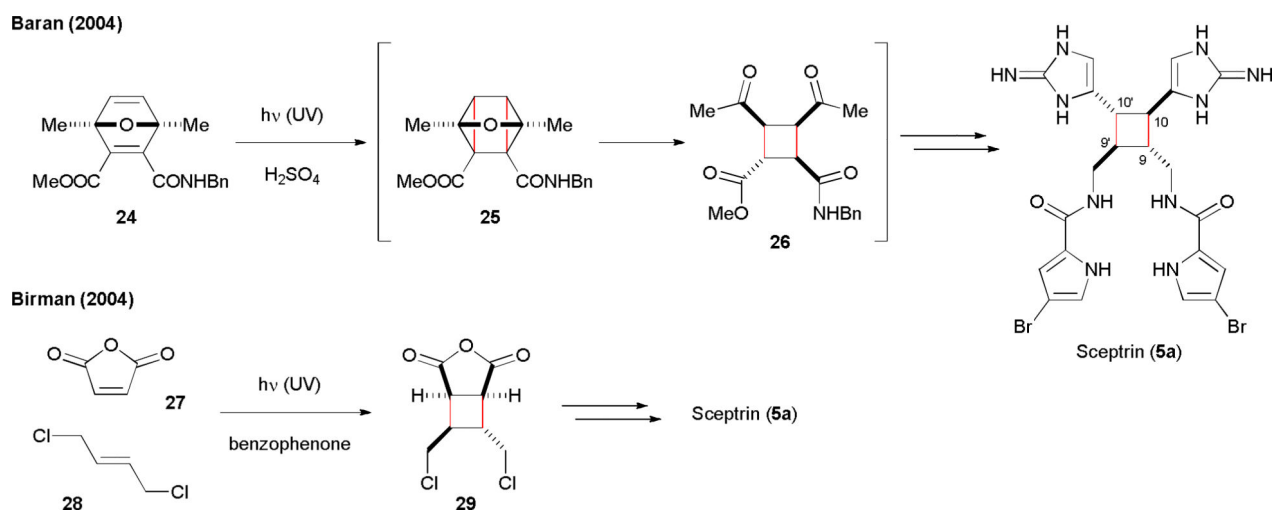
Fig. 5.
The Kinnel–Scheuer biosynthetic hypothesis.

Fig. 6.
The total syntheses of sceptrins (**5**) reported by the Baran and Birman's groups.
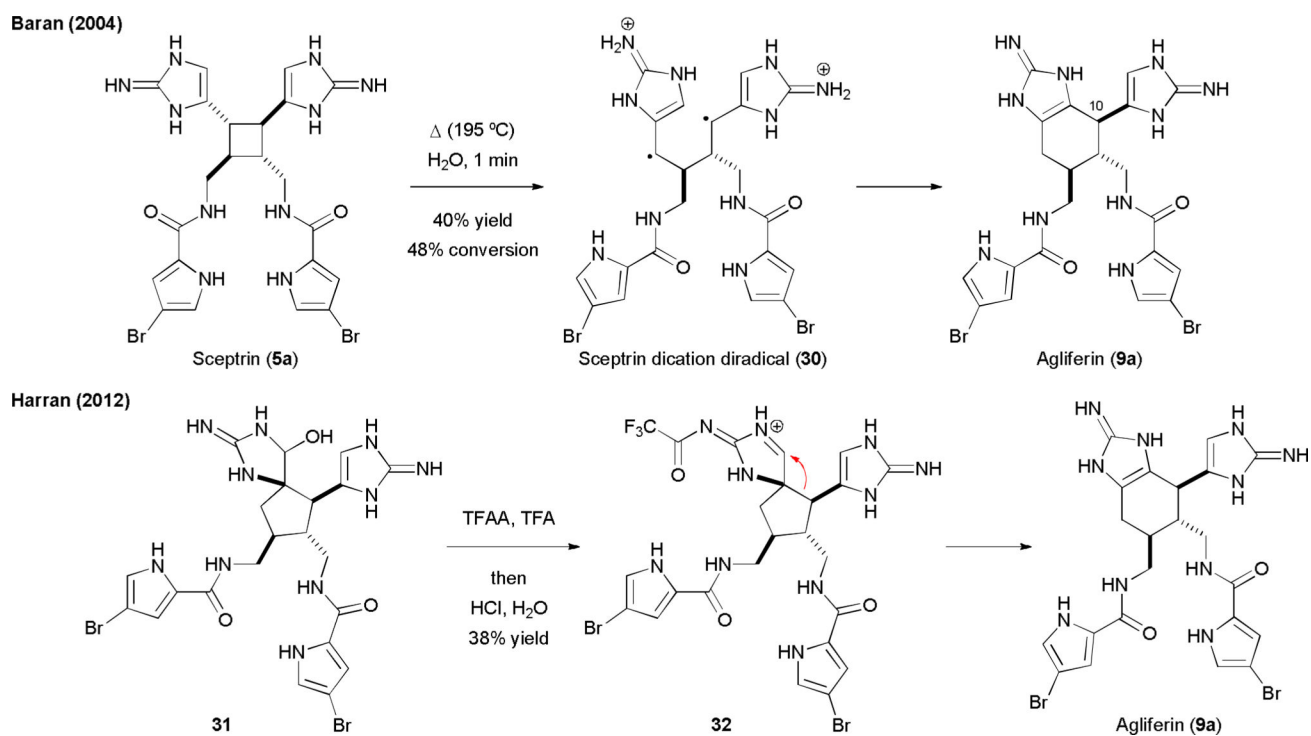
Fig. 7.
The total syntheses of ageliferins (**9**) reported by the Baran and Harran's groups.
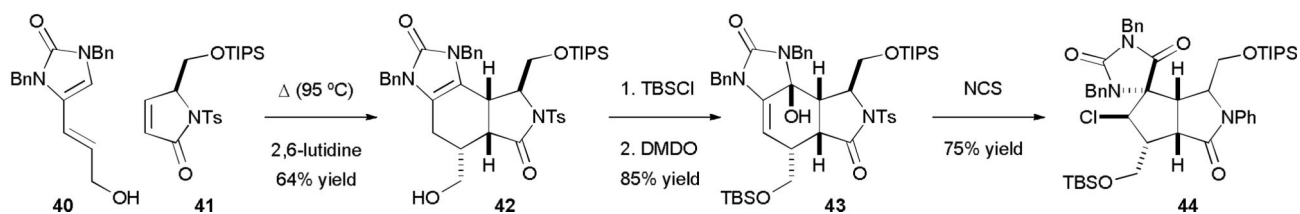
Overman (1997)
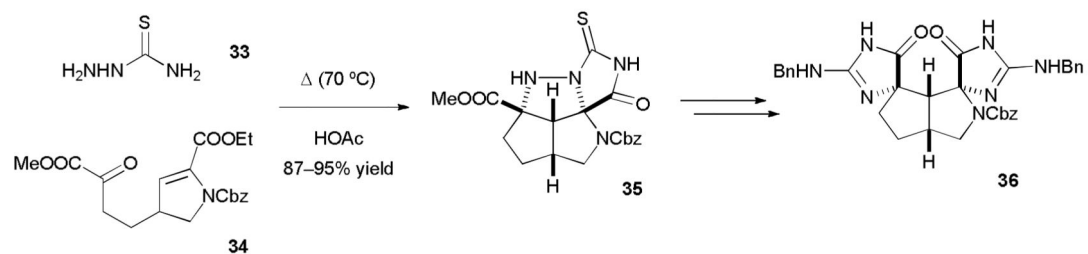
Carreira (2000)
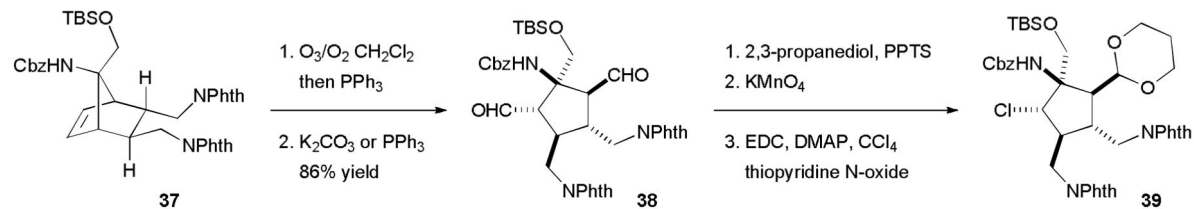
Romo (2001)

Fig. 8.

The synthetic approaches of massadines (**6**)/axinellamines (**7**)/Palau'amine (**8a**) reported by the Overman, Carreira, and Romo groups.
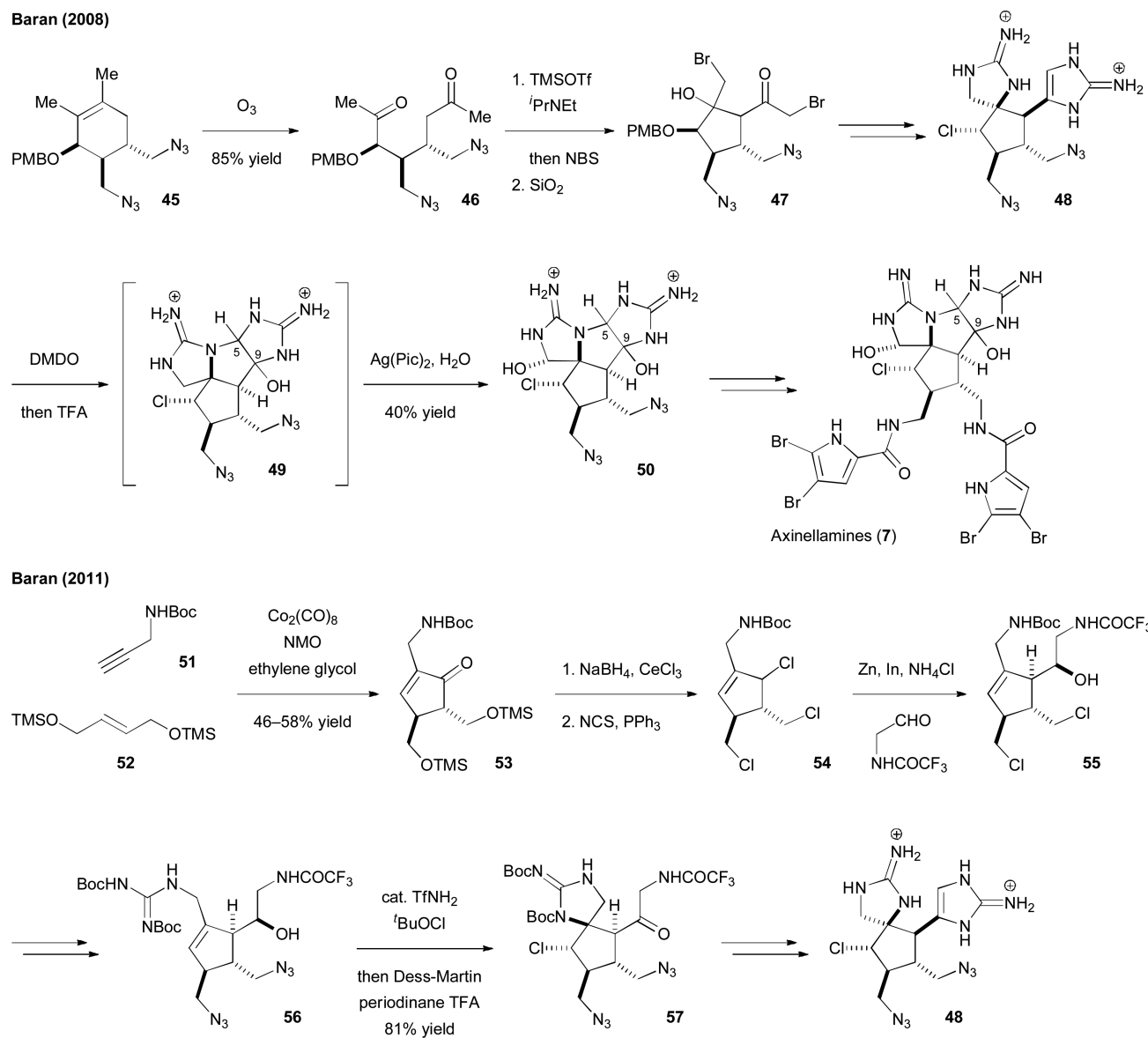
Baran (2008)

Baran (2011)

Fig. 9.
The total syntheses of massadines (**6**)/axinellamines (**7**)/Palau'amine (**8a**) reported by the Baran group.
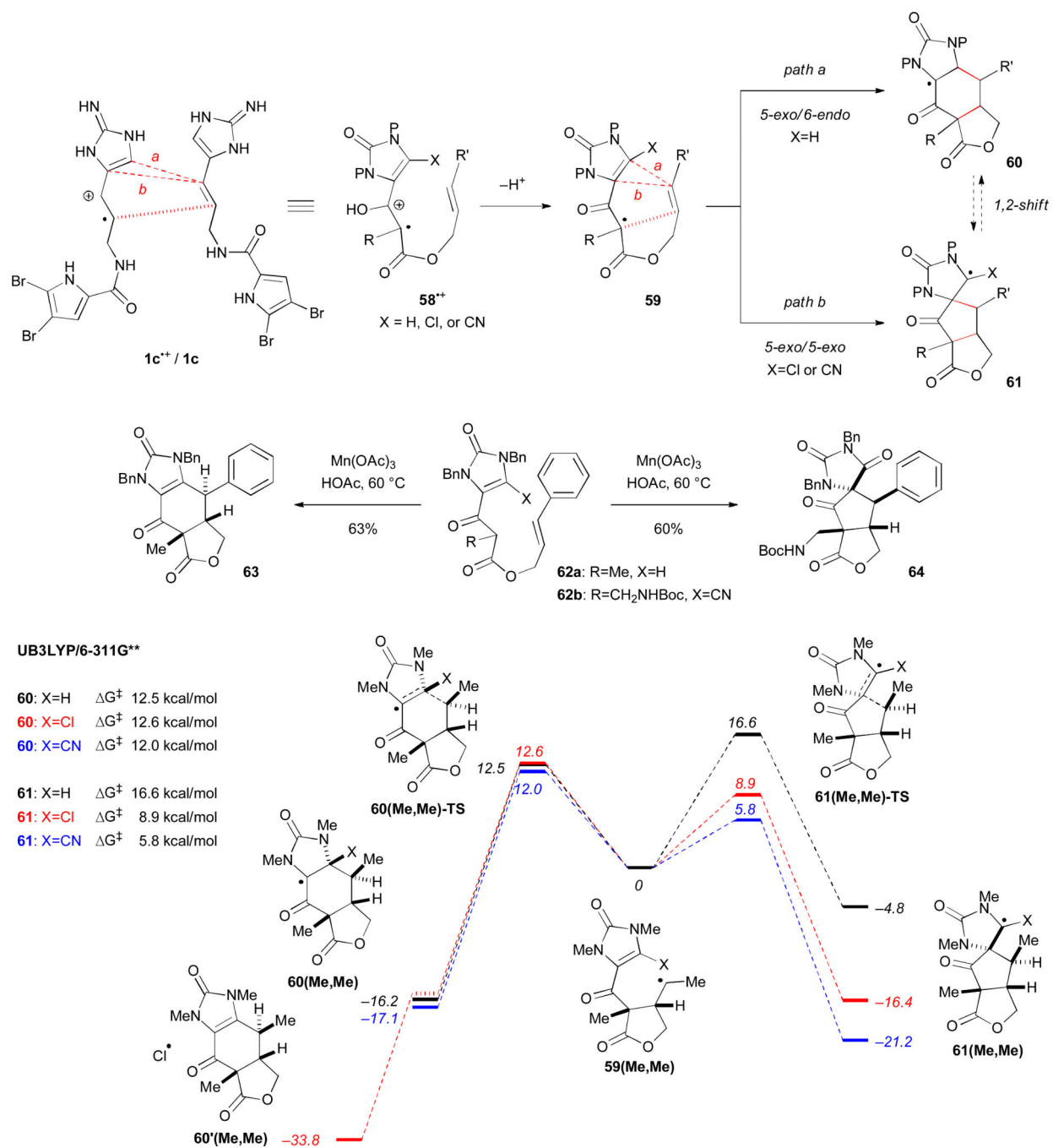
Fig. 10.
Our divergent biomimetic synthetic strategy and the energy diagram of the reaction pathways.
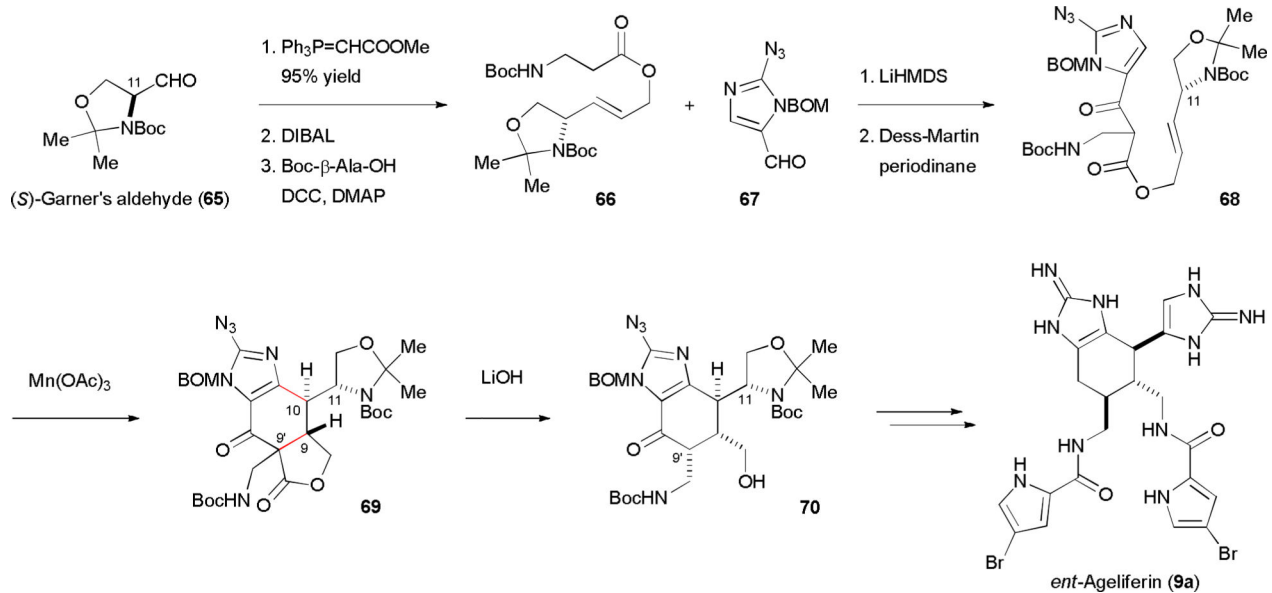
Fig. 11.
Our synthesis of ageliferin (**9a**).