### Title

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### Journal

Nature Chemistry, 10(1)

### ISSN

1755-4330



### Authors

Mukai, Ken

de Sant'Ana, Danilo Pereira

Hirooka, Yasuo

et al.



### Publication Date

2018

### DOI

10.1038/nchem.2862

Peer reviewed

# Bio-inspired chemical synthesis of monomeric and dimeric stephacidin A congeners

*Ken Mukai,† Danilo Pereira de Sant'Ana,† Yasuo Hirooka, Eduardo V. Mercado-Marin, David E. Stephens, Kevin G. M. Kou, Sven C. Richter, Naomi Kelley, and Richmond Sarpong**

Department of Chemistry, University of California, Berkeley, California 94720, United States

† These authors contributed equally

## Abstract

Stephacidin A and its congeners are a collection of secondary metabolites that possess intriguing structural motifs. They stem from unusual biosynthetic sequences that lead to the incorporation of a prenyl or reverse-prenyl group into a bicyclo[2.2.2]diazaoctane framework, a chromene unit, or the vestige thereof (e.g., a chromanone). To complement biosynthetic studies (such as isotopic labeling) which normally play a significant role in unveiling the biogenesis of natural products, here we demonstrate that chemical synthesis can also provide important insight into biosynthesis. We have identified a short total synthesis of congeners in the reverse-prenylated indole alkaloid family related to stephacidin A by taking advantage of a direct indole C6-halogenation of the related but simpler keto-premalbrancheamide that proceeds via the corresponding halo-indolenine. This novel strategic approach has now made possible the syntheses of several natural products including malbrancheamides B, and C, notoamides F, I, and R, aspergamide B, and waikialoid A, which is a heterodimer of avrainvillamide and aspergamide B. Our approach to the preparation of these prenylated and reverse-prenylated indole alkaloids is bio-inspired, and may also inform the as yet undetermined biogenesis of several congeners.

## Introduction

Secondary metabolites of terrestrial and marine origin (natural products) have served as the basis for many pharmaceuticals.[1] Given the ease in collecting terrestrial flora and fauna relative to their marine counterparts,[2] research on terrestially-derived natural products has historically outpaced that of marine-derived metabolites. However, over the last few decades,[3,4] there has been an exponential increase in the number of natural products isolated from all sources, especially the marine environment, given the significant advances in collection, sequencing, and analysis that have been made during this period.

This increase in the number and diversity of secondary metabolites has also revealed diverse structural novelty, likely stemming from unusual biosynthetic sequences. In general, decoding the mechanisms for the biogenesis of secondary metabolites is the purview of synthetic biologists, who have utilized synthetic chemistry to support their studies.[5] However, synthetic chemistry may also lead the way to unveiling biosynthetic connections that have been under-appreciated or gone unsubstantiated. Thus, biosynthesis and chemical synthesis studies are of mutual benefit. Specifically, strategies for chemical synthesis may be inspired by biosynthetic understanding or, in turn, provide insight into the biosynthesis of secondary metabolites. Here, we report an example of this fruitful intersection through chemical syntheses of several indole-derived secondary metabolites related to stephacidin A (**1**, Figure 1).

Among the growing array of known marine indole-derived alkaloids is an intriguing subset of compounds isolated from *Penicillium aspergillus* that are enantiomeric with a series of terrestial fungal-derived natural products.[6] These secondary metabolites are broadly referred to as "prenylated" or "reverse-prenylated" indole alkaloids since many contain a prenylated or reverse-prenylated indole or the vestige of this structural motif.[7] Reverse-prenylated indole alkaloids display a diverse range of biological activity. For example, stephacidin A (**1**) is cytotoxic toward various tumor cell lines (e.g., LNCaP cells; $IC_{50}$ =1.0 μM),[8,9] whereas sclerotiamide (**2**) activates caseinolytic protease P and could provide a starting point for the development of new antibiotics.[10] In a related vein, waikialoid A (**7**) is among the most potent natural product inhibitors of fungal biofilms and may present a novel approach to combating refractory infections.[11] Perhaps the best known among the reverse-prenylated indole alkaloids from a bioactivity standpoint is paraherquamide A (**3**), a derivative of which, derquantel or Startect® (lacking the C2 carbonyl group), is used in veterinary medicine to rid sheep of worms.[12] Numerous reverse-prenylated indole alkaloid congeners also display anthelmintic activity.[6]

The dizzying array of functional groups on the core framework of these compounds has spurred intense efforts to understand their biosynthesis. Over the last four decades, a clearer picture as to the biogenesis of the reverse-prenylated indole alkaloids has begun to emerge,[6] led principally by the efforts of Birch,[13] Sammes,[14] Williams,[15] Sherman,[15] Tsukamoto,[15] and Kobayashi.[16] For example, the bicyclo[2.2.2]diazaoctane framework of these secondary metabolites is believed to arise through an intramolecular cycloaddition involving a precursor such as **10** (Figure 2a). It has also been demonstrated that stephacidin B (**8**) arises from avrainvillamide (**5**) through dimerization, as illustrated in Figure 2b. This particularly fascinating biosynthetic homodimerization raises the question as to whether a similar process involving the heterodimerization of aspergamide B (**4**; isolation reported by Fuchser and Zeeck in 1995)[17] and avrainvillamide (**5**) could account for the formation of waikialoid A (**7**) and associated congeners.

We set out to answer this question using chemical synthesis, which required the preparation of various stephacidin A congeners to probe the biogenesis of waikialoid A (**7**) and other related compounds. To accomplish such a goal, efficient syntheses of the dimerization partners (i.e., **4** and **5**) needed to be achieved. We envisioned a unified approach from a common precursor as the best strategy to prepare these natural

product ‘addends’. Inspired by the emerging biosynthetic picture,[18,19,20] stephacidin A (**1**), a lower oxidation level congener of the reverse-prenylated indole alkaloid family, could serve as a precursor to **2**, **4**, **5**, and **6**. In turn, heterodimerization of **4** and **5**, homodimerization of **5**, or formal heterodimerization of **5** and **6** would yield **7**, **8**, or **9**, respectively.

Key to the success of a chemical synthesis approach that would deliver all these secondary metabolites is a high yielding and robust route to **1**. Considering the fact that several laboratories,[21,22,23,24] including our own,[25] have previously reported total syntheses of **1**, we were optimistic that the quantities of **1** required to support our studies could be obtained through chemical synthesis. However, close examination of the existing syntheses of **1** reveals that no synthesis has demonstrated the ability to provide more than 2–10 mg in a single pass. As such, we conclude that the existing approaches are inadequate in providing the amounts of **1** (>200 mg) that would be required for this study.

Generally, past approaches to **1** have relied on the early installation of the chromene unit or of a group (e.g., a phenolic hydroxyl at C6 of the indole moiety) that could be employed in constructing the chromene unit. As an alternative, we envisioned that late-stage chromene formation would simplify the task of preparing **1** down to the synthesis of keto-premalbrancheamide (**11**, Figure 3a).[26] A position-selective halogenation at C6 of **11** would then set the stage for not only the preparation of **1** but also of malbrancheamides C[27] and B[28] (**16** and **17**, respectively; Figure 3b). Gratifyingly, **11** can be accessed in a six-step sequence from D-proline and indole pyruvic acid following the succinct route developed by Simpkins and coworkers.[29] We have utilized and further optimized this sequence to provide **11** in 17% overall yield, and have prepared >2 g in a single pass (See supplementary section 2).

Our perusal of the literature revealed that despite the substantial progress that has been made in site-selective indole C6 functionalization, a directing group is often required on the indole nitrogen in order to introduce, for example, a boron[30] or carbon substituent[31,32,33] at C6. Biocatalysis has also been utilized to achieve C6 halogenation.[34] Unfortunately, these methods are either restrictive (require a directing group) or are quite specialized (biocatalysis) making them non-ideal for our purposes. On the other hand, the existing (albeit under-appreciated) precedent for position-selective, metal-free, *and direct* C6 bromination of 2,3-disubstituted indole derivatives (i.e., without the need for *N*-functionalization),[35,36] seemed perfectly suited for functionalization at C6 of keto-premalbrancheamide.

When **11** was treated with *N*-bromosuccinimide (NBS) (Figure 3b), rapid conversion to a brominated compound was observed by liquid chromatography mass spectrometry (LCMS) and NMR analysis. This intermediate was assigned as haloindolenine **14**.[36] Heating the reaction mixture to 70 °C provided the C6 brominated compound (**15**). This simple, one-step sequence directly affords the C6 halogenated derivative without the need to first functionalize the indole nitrogen to introduce a directing group or evolve an enzyme for this purpose. The mechanism by which this translocation of the halogen occurs is the subject of ongoing studies in our laboratory. Chemoselective reduction of the tertiary amide carbonyl group of **15** yields malbrancheamide C (**16**), which provided spectral data fully consistent with those of the naturally isolated material.[27] This outcome also provided unambiguous evidence for the C6 selective indole bromination.

Curiously, we were unable to accomplish the analogous C6 chlorination of **11** via the chloroindolenine. However, we envisioned the chlorine group being readily installed via the pincacolboronic ester to ultimately afford malbrancheamide B (**17**). While various methods for the conversion of aryl iodides and bromides to the corresponding pinacolboronic esters are known,[37] we found that the photoirradiation methods of Larionov[38] and of Li[39] were the most effective in our case. The boronic ester was carried on to

**17** as illustrated in Figure 3b. The spectral data for **16** and **17** prepared in our laboratory were fully consistent with that reported previously (See supplementary Tables 16 and 17 for **17**).

Despite the utility of the C6-selective bromination strategy in delivering malbrancheamides B and C, the photo-borylation step from bromide **16** proved insuperably low-yielding. This motivated us to investigate the analogous iodination, which was anticipated to provide an aryl iodide better suited for borylation. Unlike in the bromination sequence, migration of the C3 iodine atom of an iodoindolenine (analogous to **14**) to C6 was slow to occur and led to a complex mixture of unidentifiable compounds. To accelerate this process and improve the selectivity, exogenous additives were investigated. Varying position-selectivity for translocation of the iodine atom to the benzenoid portion of the indole moiety was observed depending on the additive. For example, use of acetic acid (AcOH),[35,36] provided only a complex mixture that included small amounts of the C5 and C6 halogenated isomers. On the other hand, use of trifluoroacetic acid (TFA) resulted in a cleaner halogenation reaction. However, only moderate selectivity between C5 and C6 iodination was observed. Gratifyingly, adding $BF_3$•$OEt_2$ (1.2 equiv) gave, after optimization, the C6-iodinated material as the major product in a 1:9:1 ratio of iodinated C5:C6:SM on gram scale.

The inherent challenges associated with photochemical irradiation on large scale in a batch reactor[40] inspired us to develop a flow apparatus akin to the efforts of Li et al.[39] that has allowed us to achieve higher throughput for the borylation reaction (See supplementary section 2). For example, for the purposes of preparing **1**, we desired a hydroxyl at C6 (see **19**, Figure 4a). This was readily achieved from iodide **18** by photo-mediated borylation (conducted in flow) followed by oxidation of the resulting boronic ester to provide phenol **19** in 55% yield over the two steps. While it is possible to combine the borylation and oxidation steps by direct addition of $H_2O_2$ to the reaction mixture following UV irradiation, the potential formation of explosive triacetone triperoxide caused us to resort to the two-pot process. Stephacidin A was easily obtained from **19** by installation of the chromene unit following the precedent of Williams.[41] Thus, the synthesis of **1** can now be accomplished in 4.7% yield over 11 total steps from D-proline. Each reaction can also be conducted on reasonable scale leading to a total of 300 mg of **1** prepared to date.

Stephacidin A (**1**) has proven to be a versatile intermediate for the synthesis of several more highly oxidized reverse-prenylated indole alkaloid congeners. First, following the precedent of Baran,[20] avrainvillamide (**5**) was prepared through sequential reduction of stephacidin A (to 'dihydrostephacidin A') followed by oxidation to install the α,β-unsaturated nitrone unit of **5**. This oxidation sequence is low yielding (as noted by Baran and Williams)[20,22,23] and only provides, at best, **5** in 27% yield over the 2 steps with a 50% recovery of dihydrostephacidin A. An alternative preparation of **5** would involve oxygenation of the α,β-unsaturated imine group of **4**. In this way, both **4** and **5** could be accessed in short order. As such, the preparation of **4** became a focus of our studies.

Previously, we had observed the formation of notoamide I (**21**, Figure 4b) upon treatment of **1** with manganese dioxide ($MnO_2$, 120 equiv) in wet ethyl acetate.[25] Presumably, **21** results from initial oxidation of **1** to aspergamide B (**4**) followed by conjugate addition of water to the α,β-unsaturated imine and oxidation of the resulting 'indolic' hydroxyl. The use of strictly anhydrous ethyl acetate as the solvent avoids the conjugate addition of water to afford **4** in 83% yield from **1**.

While the mass spectral data for synthetic **4** is consistent with that obtained by Fuchser and Zeeck for the natural isolate reported as aspergamide B (**4**),[17] the $^1H$ and $^{13}C$ NMR data obtained for our synthetic material differed substantially from that of the natural isolate. This prompted us to investigate the difference computationally. Utilizing density functional theory (DFT), the computed $^{13}C$ NMR spectrum[42] for **4** is in better agreement with the spectrum for the material synthesized in our laboratory. Specifically, the corrected

mean absolute deviation (CMAD) for the $^{13}C$ NMR resonances are 1.7 ppm for our synthetic **4** compared to 3.6 ppm with respect to the spectrum of the natural isolate ascribed as **4**. Interestingly, the $^{13}C$ NMR spectra of the natural isolate and avrainvillamide (**5**), subsequently isolated in 2000 by Fenical and coworkers,[43,44] are nearly identical (mean absolute deviation of 0.1 ppm). Thus, based on the spectroscopic data, we believe that the natural isolate reported by Fuchser and Zeeck in 1995[17] to be avrainvillamide (**5**) (See details in supplementary section 3 and 5).

While an unimpeachable conclusion cannot be drawn about the reported isolation of **4**, our collected evidence from chemical synthesis suggests that **4** may be a starting point for other reverse-prenylated indole alkaloid congeners. For example, notoamides F (**22**)[45,46] and R (**23**)[46,47] are likely produced from **4** through the conjugate addition of methanol or water, respectively. Indeed, we have demonstrated the feasibility and facility of these additions in the laboratory using TFA/MeOH, and TFA/$H_2O$ solutions, respectively (Figure 4b). The conditions that lead to these products (often employed as purification eluents) suggest that these natural products may be isolation artifacts that result from **4**.[46] Subsequent oxidation or oxygenation of **23** may then lead to **21** or **2**, respectively. Support for this latter assertion comes from a recent report by Li on the oxidative conversion of **23** to **2**.[48]

With **4** and **5** in hand, we could now test the possible heterodimerization of these compounds to give waikialoid A (**7**, Figure 5). However, several challenges were anticipated. First, it was unclear whether homodimerization of either **4**, or of **5**, would out-compete their heterodimerization to **7**. Second, should the heterodimerization of **4** and **5** proceed, either compound could serve as the initial aza-Michael acceptor (see Figure 2b for a depiction of an aza-Michael process), only one of which leads to **7**. While there is precedent for the homodimerization of **5** to stephacidin B (**8**) – Figure 2b,[19] homodimerization of **4** is without precedent. We have found that treatment of **4** with triethylamine in acetonitrile yields the corresponding homodimer (**24**), which was unambiguously characterized by X-ray crystallographic analysis. Unlike **8**, which is known to revert to **5**, we have not found conditions that convert **24** back to **4**.

However, because the homodimerization of **5** is reversible and homodimerization of **4** is kinetically fast, we expected that the heterodimerization of **4** and **5** would likely proceed if we maintained a reasonable concentration of **4** in large excess. This expectation assumes that the heterodimerization of **4** and **5** would be irreversible. In the event, mixing a 2:1 ratio of **4** and **5** in acetonitrile with triethylamine affords a 4:1 ratio of **24** to **7** (20% isolated yield of **7**), whereas mixing an 8:1 ratio of **4** and **5** affords an 11:1 ratio of **24** to **7** (29% isolated yield of **7** and 95% yield of **24**).

In sum, the shortest synthesis of stephacidin A (**1**) reported to date has been achieved, which has facilitated the first synthesis of the purported secondary metabolite aspergamide B (**4**). While the report of the isolation of **4** is not fully certain, this likely fleeting secondary metabolite now serves as an important synthetic intermediate to many alkaloids in the reverse-prenylated indole alkaloid family. Specifically, access to **4** has led to syntheses of notoamides F (**22**), R (**23**), and I (**21**), as well as waikialoid A (**7**) and a formal synthesis of sclerotiamide (**2**). A key position-selective C6 halogenation of keto-premalbrancheamide (**11**) was critical to installing the chromene moiety present in stephacidin A and related congeners. This C6-selective halogenation has also yielded short syntheses of the natural products malbrancheamides C (**16**) and B (**17**).

Several questions as to the biogenesis of several of the stephacidin A congeners described here have been prompted by this chemical synthesis study. Not least of which is how waikialoid A (**7**) and related dimeric congeners (e.g., **9**, Figure 1) arise in nature. If heterodimerization of **4** and **5** accounts for the formation of **7**, then it would be our expectation that the homodimer of aspergamide B (**24**) would also form rapidly. Because **24** was not co-isolated with **7** from the producing organism, it may be the case that **7** arises through

a different biosynthetic pathway or that **24** is converted in a facile manner to other congeners (e.g., **7**) in the producing organism. This latter hypothesis is provocative as it may imply the oxidation of the imine group of **24** to the nitrone found in stephacidin B (**8**), a transformation without biosynthetic precedent.[49] This scenario also begs the question as to how avrainvillamide (**5**) arises in nature. Finally, the recent isolation from *A. tennesseensis* of versicoamides F–H (e.g., **25** and **26**),[50] which are the formal kojic acid conjugates of **4** and **5**, strongly suggests that capture of **4** or **5** through a formal [4+2] cycloaddition (as may be the case for **7**) may be more widespread in the biogenesis of related congeners. Should a heterodimerization of **4** and kojic acid account for the biosynthesis of **25**, one would have again expected the co-isolation of **24** from *Aspergillus tennesseensis*. Therefore, **24** may yet be isolated from a natural source.

## Conclusion

Our chemical synthesis of a number of secondary metabolites in the reverse-prenylated indole alkaloid family has culminated in the synthesis of the heterodimer waikialoid A. These syntheses may inform the possible biogenesis of several congeners structurally related to stephacidin A. For example, our studies provide insight into a possible site-selective halogenation that affords the malbrancheamides from the precursor keto-premalbrancheamide. While bromination to afford malbrancheamide C may occur without the assistance of an enzyme, it may be that the analogous chlorination requires an enzyme. Efforts to better understand the biosynthesis of these molecules through a combination of chemical synthesis and biosynthetic engineering studies are underway.

## Acknowledgments

This work is supported by a grant from the USA National Institutes of Health (NIGMS RO1 086374). We are grateful for a JSPS Postdoctoral Fellowship to K.M., a Science without Borders Postdoctoral Fellowship to D.S.P (Brazil; CSF/CNPq 200205/2014-5), the USA NSF GRFP, the ACS DOC and Hellman Graduate Awards Program (UC Berkeley) for awards to E.V.M-M, the NSERC (Canada) for a Postdoctoral Fellowship to K.G.M.K. We are grateful to Professors David H. Sherman (University of Michigan) and Robert M. Williams (Colorado State University), as well as Prof. Dean Tantillo (University of California–Davis) for helpful discussions regarding the prenylated and reverse-prenylated indole alkaloids, and the NMR CMAD computational analysis, respectively. We thank Prof. Robert Cichewicz (University of Oklahoma) for an authentic sample of waikialoid A as well as for an initial secondary metabolite screen on the producing *Penicillium aspergillus* sp. Prof. Axel Zeeck (Georg-August-Universität Göttingen) is graciously acknowledged for his tireless efforts to locate and obtain analytical data for the material reported by his laboratory in 1995 to be aspergamide B. X-ray crystallography instrumentation are supported by NIH Shared Instrumentation Grant S10-RR027172. The AV-600, AV-500, DRX-500, AVQ-400, and AVB-400 NMR spectrometers are partially supported by NIH Grants SRR023679A and 1S10RR016634-01 and NSF Grants CHE-9633007 and CHE-0130862. The 900 MHz NMR instrument is funded by NIH Grant GM68933. The Molecular Graphics and Computation Facility is funded by the NIH (S10OD123532). We thank Kyle Owens (UC Berkeley), Dr. Kathleen Durkin (UC Berkeley) and Dr. Yinka Olatunji-Ojo (UC Berkeley) for assistance with DFT computations and Dr. Antonio G. DiPasquale for X-ray crystallographic analysis.

## Author Contributions

R.S., K.M., and D.S.P. designed the research with assistance from Y.H., and E.M.M. All synthetic chemistry was performed by K.M., D.S.P, Y.H., E.M.M., D.E.S., S.C.R., and N.K. Computational studies

were conducted by D.E.S., K.G.M.K, and K.M. R.S. wrote the manuscript with contributions from all authors; all authors were actively engaged in the editing of the manuscript and gave their approval of the final version. K.M. and D.S.P. contributed equally to this work.

## Additional information

Supplementary information including characterization data for new chemical compounds are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. The .cif file has been deposited to the Cambridge Crystallographic Data Centre (CCDC 1544164).

## List of the figure captions

**Figure 1 | Selected reverse-prenylated indole alkaloid congeners**

Monomeric compounds **1–6** consist of a prenyl or reverse-prenyl group, a bicyclo[2.2.2]diazaoctane framework, and a chromene unit. Homo- and heterodimeric compounds **7–9** arise from the non-symmetric association of monomeric units (bonds giving rise to the non-symmetetric dimers highlighted in red).

**Figure 2 | Hypotheses for the biogenesis of stephacidin A congeners.**

(a) Prevailing biogenetic hypotheses for the biosynthesis of stephacidin A and 6-*epi*-stephacidin A.

(b) Proposed biosynthesis of stephacidin B from 2 equivalents of avrainvillamide.

**Figure 3 | Synthetic strategy for stephacidin A and the application of C-6 halogenation.**

(a) Retrosynthetic analysis of (+)-stephacidin A from keto-premalbrancheamide (**11**) and the

Simpkins route to **11**. (b) Syntheses of malbrancheamide C (**16**) and malbrancheamide B (**17**) from **11**.

**Figure 4 | Syntheses of stephacidin A and congeners.**

(a) Synthesis of (+)-stephacidin A from C6-iodide 18.

(b) Syntheses of stephacidin congeners notoamide I, aspergamide B, notoamide F, notoamide R and sclerotiamide from **1**.

**Figure 5 | Conjugation possibilities for aspergamide B and avrainvillamide.**

Homocoupling of aspergamide B (**4**) and avrainvillamide (**5**) afforded aspergamide B dimer (**24**) and stephacidin B (**8**), respectively, while the heterodimerization of aspergamide B (**4**) and avrainvillamide (**5**) produced waikialoid A (**7**). We hypothesize that the newly isolated versicoamide G (**25**) and versicoamide H (**26**) would similarly arise from the dimerization of aspergamide B or avrainvillamide with formal kojic acid. The stereochemistry of aspergamide B dimer (**24**) is supported by X-ray analysis.

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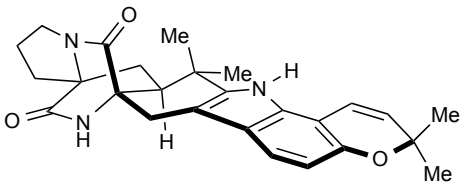
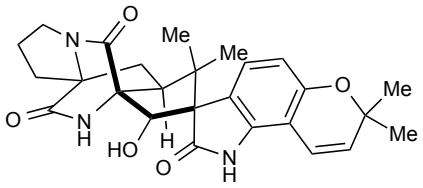
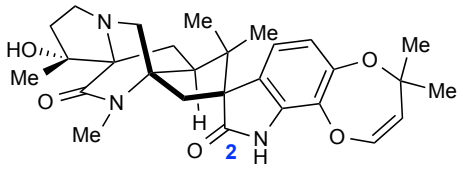


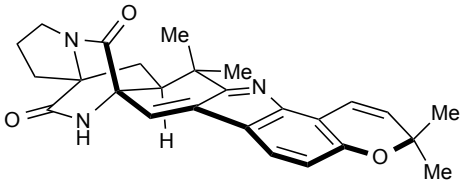
(+)-Stephacidin A (**1**)



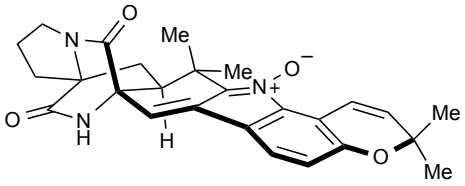
Sclerotiamide (**2**)



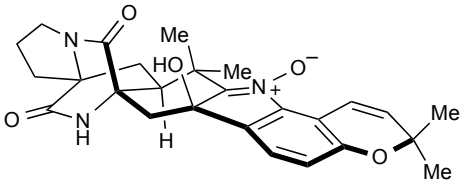
Paraherquamide A (**3**)



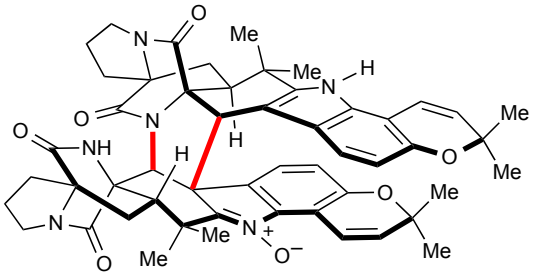
Aspergamide B (**4**)



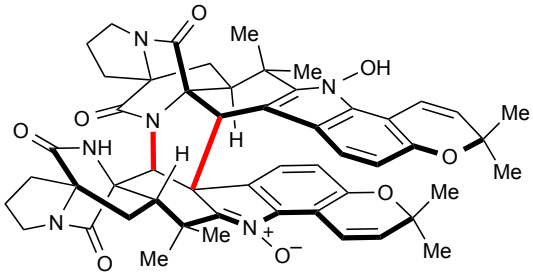
Avrainvillamide (**5**)



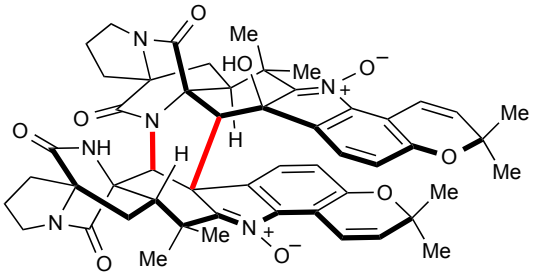
Aspergamide A (**6**)



Waikialoid A (**7**)



Stephacidin B (**8**)



Waikialoid B (**9**)

**Figure 1 | Selected reverse-prenylated indole alkaloid congeners.**
Monomeric compounds **1**–**6** consist of a prenyl or reverse-prenyl group, a bicyclo[2.2.2]diazaoctane framework, and a chromene unit. Homo- and heterodimeric compounds **7–9** arise from the non-symmetric association of monomeric units (bonds giving rise to the non-symmetetric dimers highlighted in red).

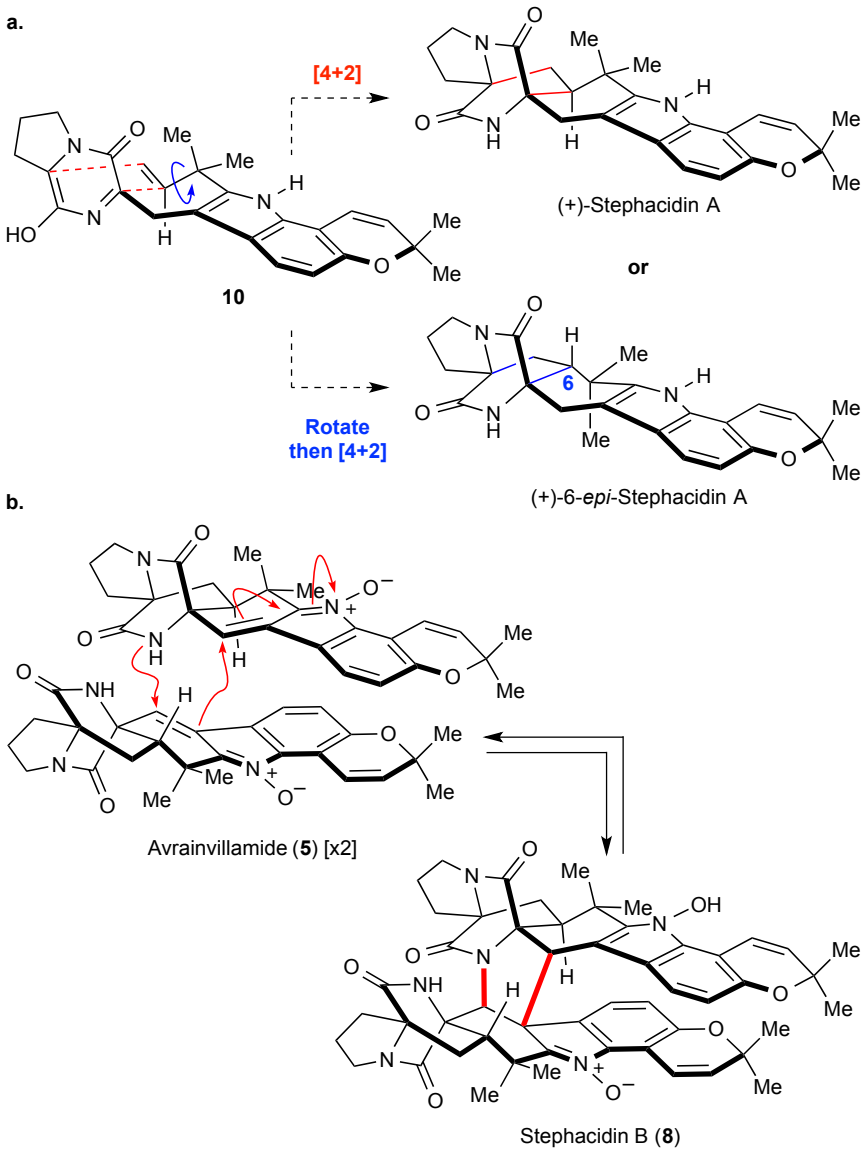



**Figure 2 | Hypotheses for the biogenesis of stephacidin A congeners.**
(a) Prevailing biogenetic hypotheses for the biosynthesis of stephacidin A and 6-*epi*-stephacidin A
(b) Proposed biosynthesis of stephacidin B from 2 equivalents of avrainvillamide

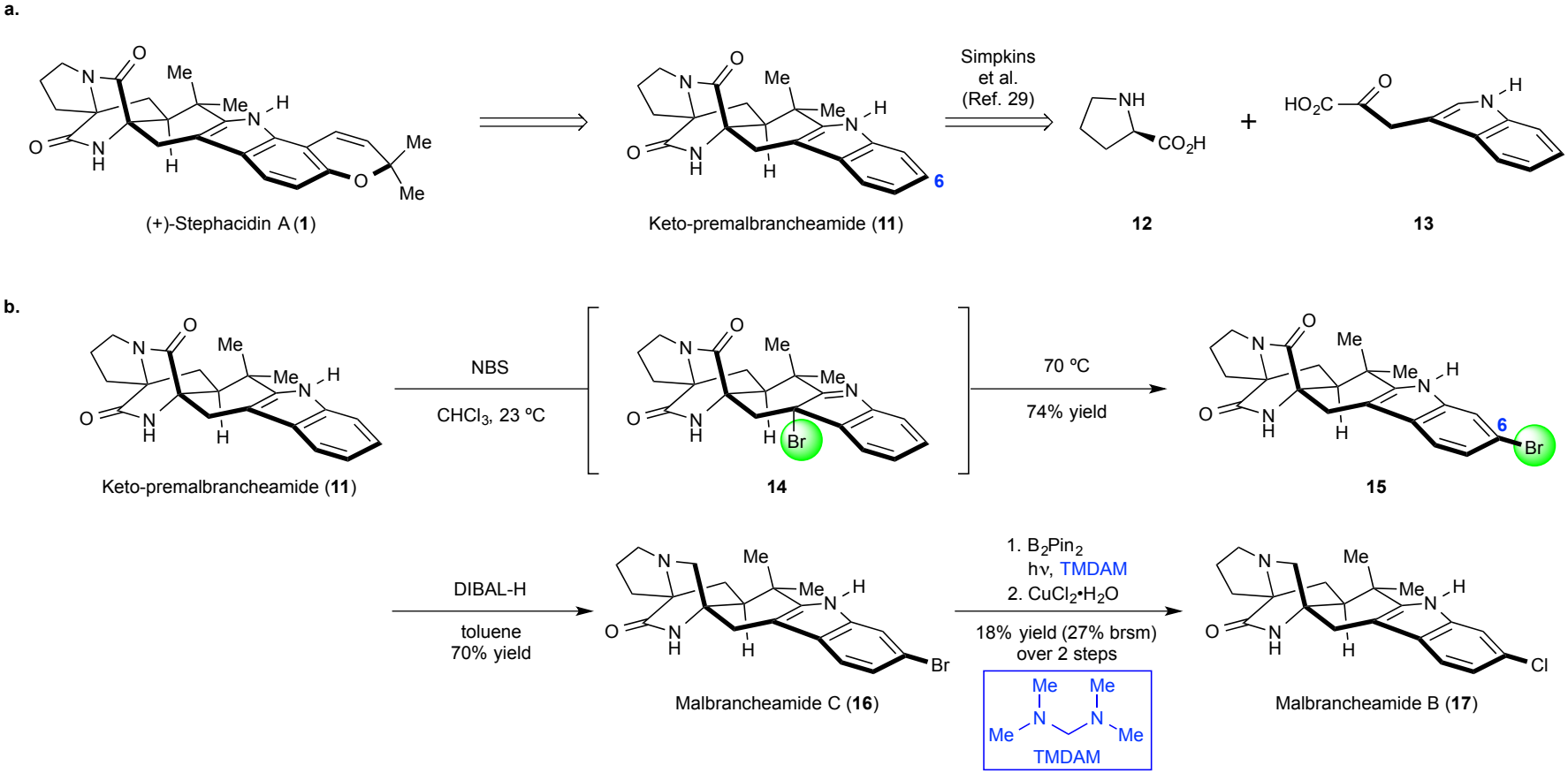
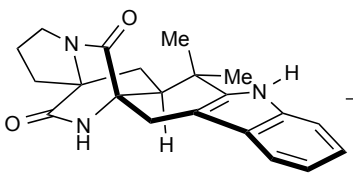



**Figure 3 | Synthetic strategy for stephacidin A and the application of C-6 halogenation.**
(a) Retrosynthetic analysis of (+)-stephacidin A from keto-premalbrancheamide (**11**) and the Simpkins route to **11**. (b) Syntheses of malbrancheamide C (**16**) and malbrancheamide B (**17**) from **11**.

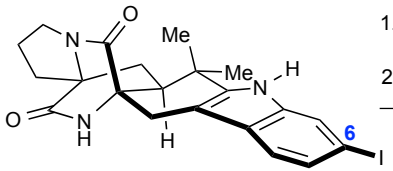
**a.**



Keto-premalbrancheamide (**11**)

NIS, $CHCl_3$, 23 °C;
$BF_3$•$OEt_2$

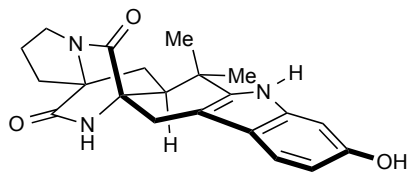
82% + 18% (**11**,C5-isomer)



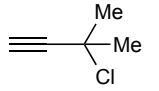
**18** (+**11**, C5-isomer)

1. $B_2Pin_2$, TMEDA, MeCN/$H_2O$, $Me_2CO$, hν (flow 40 min)
2. $H_2O_2$, MeCN, pH 8.7 buffer

55% yield (2 steps)

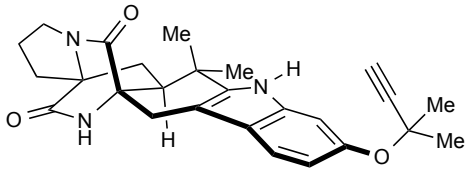


**19**



$CuCl_2$, DBU, MeCN

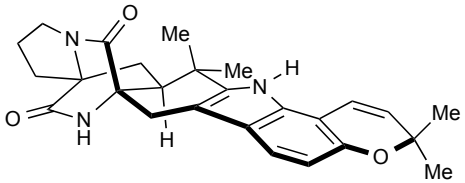
69% yield



**20**

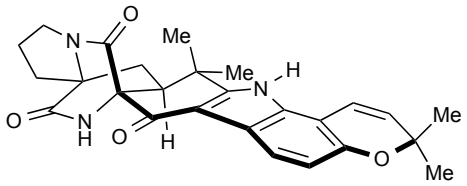
170 °C
1,2-dichlorobenzene

89% yield



(+)-Stephacidin A (**1**)

**b.**



Notoamide I (**21**)

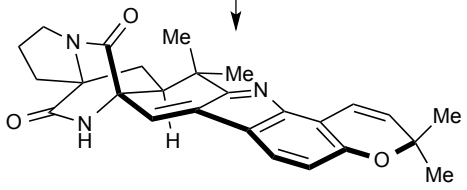
$MnO_2$ (120 equiv)
Wet EtOAc, 23 °C

32% yield
(Ref. 25)

(+)-Stephacidin A (**1**)

$MnO_2$ (30 equiv)
Dry EtOAc, 23 °C

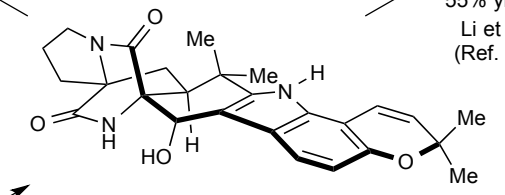
83% yield



Aspergamide B (**4**)

TPAP, 4Å MS

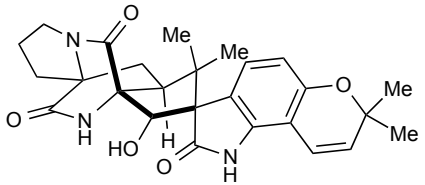
78% yield



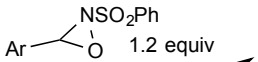
Notoamide R (**23**)

TFA
$H_2O$/THF

87% yield



Sclerotiamide (**2**)

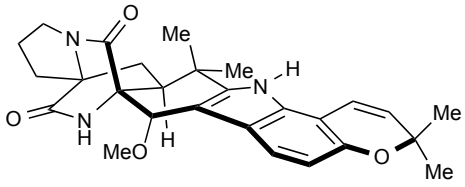


1.2 equiv
(Ar = p-$NO_2$Ph)

55% yield
Li et al.
(Ref. 48)

TFA
MeOH/THF

76% yield



Notoamide F (**22**)

**Figure 4 | Syntheses of stephacidin A and congeners.**
(a) Synthesis of (+)-stephacidin A from C6-iodide **18**.
(b) Syntheses of stephacidin congeners notoamide I, aspergamide B, notoamide F, notoamide R and sclerotiamide from **1**

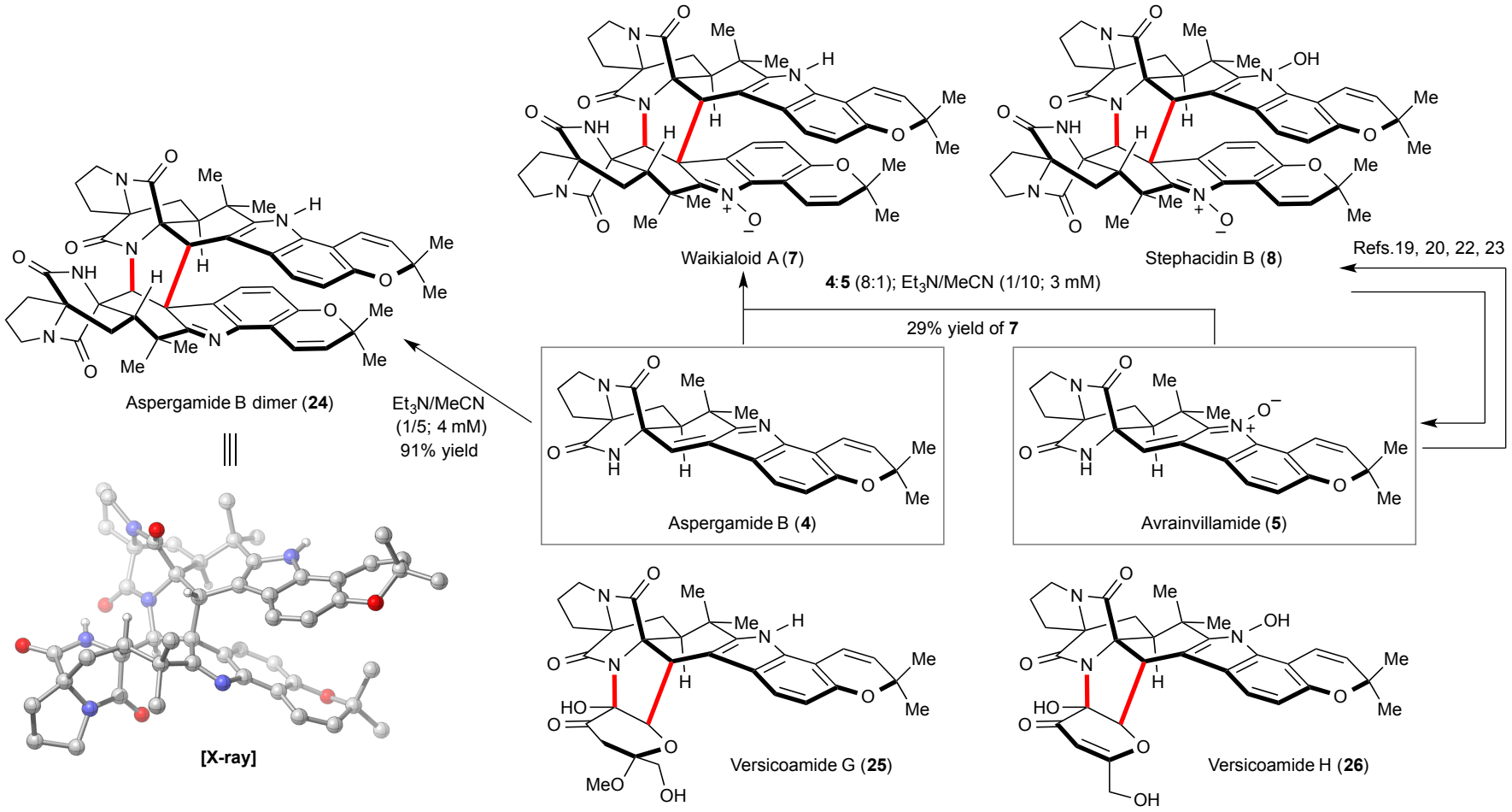



**Figure 5 | Conjugation possibilities for aspergamide B and avrainvillamide.**
Homocoupling of aspergamide B (**4**) and avrainvillamide (**5**) afforded aspergamide B dimer (**24**) and stephacidin B (**8**), respectively, while the heterodimerization of aspergamide B (**4**) and avrainvillamide (**5**) produced waikialoid A (**7**). We hypothesize that the newly isolated versicoamide G (**25**) and versicoamide H (**26**) would similarly arise from the dimerization of aspergamide B or avrainvillamide with formal kojic acid. The stereochemistry of aspergamide B dimer (**24**) is supported by X-ray analysis.