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Concise, Asymmetric, Stereocontrolled Total Synthesis of Stephacidins A, B and Notoamide B

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Abstract: Concise asymmetric total syntheses of the fungal metabolites (−)-stephacidin A, (+)-stephacidin B, and (+)-notoamide B are described. Key features of these total syntheses include (1) a facile synthesis of (*R*)-allyl proline methyl ester, (2) a revised route toward the pyranoindole ring system, (3) a novel cross-metathesis strategy for the introduction of important functional groups, and (4) an S_N2' cyclization to form the [2.2.2] bridged bicyclic ring system. Furthermore, our synthesis has taken advantage of microwave heating to shorten reaction times as well as increase yields for the preparation of vital intermediates.

Introduction

Fungi have proven to be a rich source of densely functionalized secondary metabolite alkaloids derived from proline, tryptophan, and isoprene. In 2002, Bristol-Myers Squibb reported the biologically active metabolites isolated from a fermentation broth of *Aspergillius ochraceus*.[1] The stephacidins A (**1**) and B (**2**) were identified as potent inhibitors of several human tumor cell lines with the complex alkaloid (−)-stephacidin B (**2**) exhibiting a high cytotoxic potency against testosterone-dependent prostate LNCaP lymphoma (Figure 1). An investigation into their mode of action determined that they inhibit cell growth via a novel mechanism possibly resulting in a new, as yet undetermined, target for treating cancer. In addition to the biological activity of **1** and **2**, their structures represent a new degree of complexity of prenylated indole alkaloids from fungi. Both are built around the [2.2.2] diazaoctane ring system common to the brevianamides, paraherquamides, marcfortines, asperparalines, and related alkaloids. The structural framework of (+)-stephacidin A was readily determined through NMR experiments. However, the skeletal connectivity of (−)-stephacidin B could not be elucidated using only NMR experiments. X-ray crystallography was required to reveal its unprecedented structure. Containing two [2.2.2]diazaoctane bridged bicycles, a nitrone, a *N*-hydroxyindole, and nine stereogenic centers, five of which are quaternary, prompted von Nussbaum[2] to comment that (−)-stephacidin B "*provides a new level of complexity within prenylated indole alkaloids from fungi.*"

The isolation of (−)-stephacidin B (**2**) also poses an interesting series of biosynthetic questions. The researchers at Bristol-Myers Squibb recognized that if the bonds between C20−C51 and C21−N55 of **2** are broken, two molecules of the related alkaloid, (+)-avrainvillamide (**3**), were in evidence, suggesting a simple dimerization-based biogenesis of **2** from **3**.[3] The unique dimeric nature of (−)-stephacidin B coupled with its potent biological activity has resulted in several groups initiating programs toward its total synthesis. The Baran group reported the first total synthesis of stephacidin A (**1**) using a novel oxidative enolate coupling to form the [2.2.2] bridged bicyclic ring system followed by an unusual cascade reaction for the formation of the natural product in 29 total steps from commercially available starting materials.[4a] Baran's initial report was followed shortly after by Herzon and Myers and co-workers first total synthesis of (+)-avrainvillamide (**3**) in 26 total steps from commercially available starting materials using a very clever radical-based strategy for the synthesis of the bridged bicyclic core.[5−7] Following a late stage installation of the chromene ring system and formation of the vinyl nitrone, they demonstrated that **3** spontaneously dimerizes to (−)-stephacidin B (**2**) in the presence of the weak base Et_3N in greater than 95% yield by ^1H NMR analysis. Alternatively, the Baran group completed a synthesis of avrainvillamide (**3**) from synthetic stephacidin A (**1**).[4b] Reduction of the indole 2,3-double-bond followed by oxidation of the intermediate dihydroindole with SeO_2 afforded **3** in 23% yield. Using the conditions reported by Myers, the Baran group dimerized **3** to stephacidin B (**2**) under basic conditions as well as under acidic conditions. Furthermore, the Baran group was able to establish the absolute stereochemistry of **1**−**3** through their synthetic efforts.[8]

Our laboratory has a rich history synthesizing and probing the biosynthesis of fungal metabolites containing a [2.2.2]

(1) (a) Qian-Cutrone, J.; Haung, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556−14557. (b) Qian-Cutrone, J.; Krampitz, K. D.; Shu, Y.-Z.; Chang, L. P. U.S. Patent 6,291,461, 2001.
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(3) Fenical, W.; Jensen, P.; Cheng, X. C. U.S. Patent 6,066,635, 2000; *Chem. Abstr.* **2000**, *132*, 346709.
(4) (a) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 606−609. (b) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3892−3895.
(5) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342−5344.
(6) For a preliminary account of Myers' work, see: Myers, A. G.; Herzon, S. B. *J. Am. Chem. Soc.* **2003**, *125*, 12080−12081.
(7) Myers, A. G.; Herzon, S. B.; Wulff, J. E.; Siegrist, R.; Svenda, J.; Zajac, M. A. WO Patent 2006102097, 2006.

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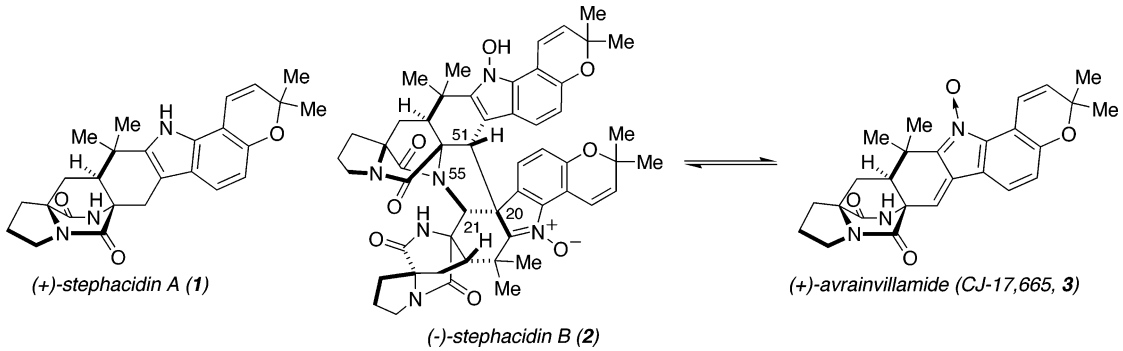
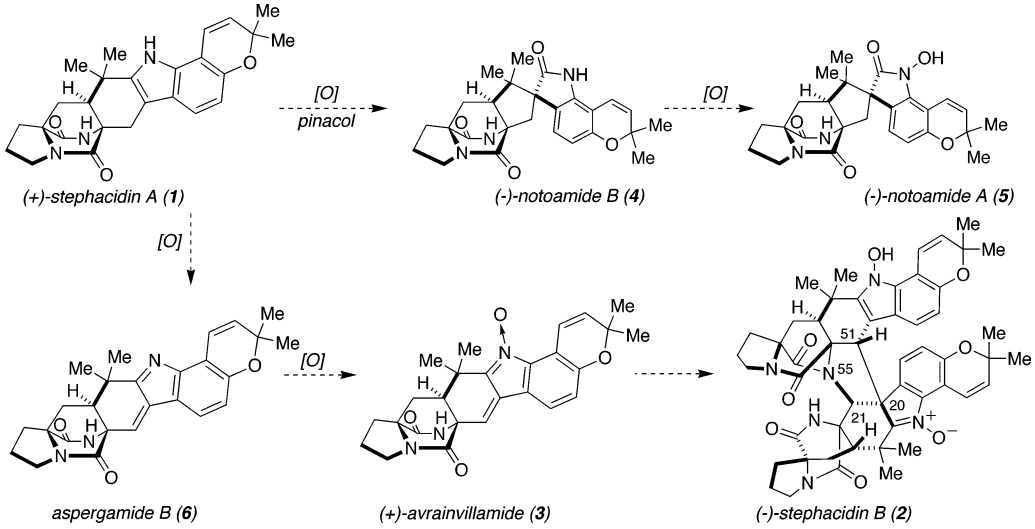


Figure 1. Stephacidin alkaloids and avrainvillamide.

Scheme 1. Proposed Biosynthesis of Related Alkaloids from (+)-Stephacidin A (**1**)



diazaoctane ring system.[9] In particular, we are astonished by the diverse series of natural products that appear to be biosynthetically derived from (+)-stephacidin A (**1**, Scheme 1). Oxidation of **1** via a pinacol rearrangement generates the *spiro*-oxindole ring system found in the recently isolated (−)-notoamide A (**4**) and (−)-notoamide B (**5**).[10,11] A different oxidation sequence can transform **1** into aspergamide B (**6**).[12] Oxidation of the vinyl imine of aspergamide B (**6**) yields the unusual vinyl nitrone moiety of (−)-avrainvillamide (**3**), which can dimerize to afford (+)-stephacidin B (**2**). To further explore these fascinating biosynthetic possibilities, we require access to isotopically labeled stephacidin A (**1**), which must be prepared through total synthesis. Recently, we were able to achieve a biomimetic total synthesis of *d*,*l*-stephacidin A (**1**) using a biogenetically inspired intramolecular Diels−Alder reaction for the preparation of the bridged [2.2.2] diazaoctane ring system.[11b,13] However, we also desired an enantioselective synthesis of **1**. To this end, the S_N2' approach for the formation of the bridged [2.2.2] diazaoctane ring system previously employed in the asymmetric total syntheses of brevianamide B[14] and paraherquamides A[15] and B[16] was envisioned. However, during our efforts toward stephacidin A, we have endeavored to employ several new chemical technologies in order to significantly condense our approach and render this technology for ongoing biosynthetic studies. Herein, we wish to detail our recent total synthesis of the antipodal series, (−)-stephacidin A (**1**) and subsequent syntheses of (−)-avrainvillamide (**3**), (+)-stephacidin B (**2**), and (+)-notoamide B (**4**).

Results and Discussion

In past syntheses employing the S_N2' cyclization strategy, (*R*)-allyl proline was prepared using the methodology developed by Seebach and co-workers.[17] Our syntheses commenced with the condensation of commercially available (*S*)-proline (**7**) with

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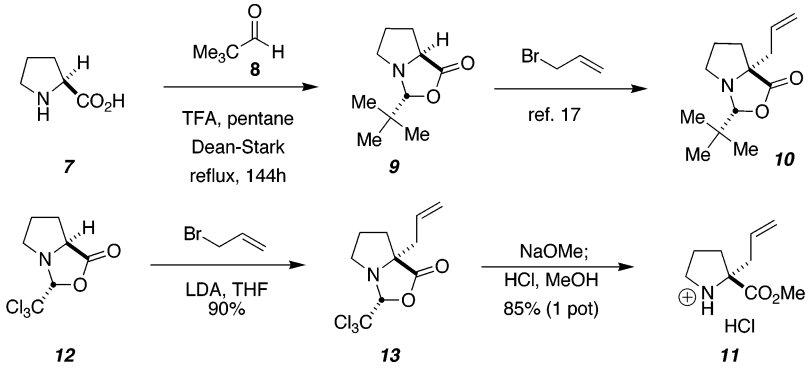
(15) Williams, R. M.; Cao, J.; Tsujishima, H. *J. Am. Chem. Soc.* **2003**, *125*, 12172−12178.

(16) (a) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323−9324. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557−579.

(17) (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (b) Beck, A. K.; Blank, S.; Job, K.; Seebach, D.; Sommerfield, T. *Org. Synth.* **1995**, *72*, 62.

Scheme 2. Gram-Scale Synthesis of (*R*)-Allyl Proline Methyl Ester (**11**)



pivaldehyde (**8**) in the presence of TFA under azeotropic conditions for ~7−10 days to afford **9** (Scheme 2).[17b] Following isolation of **9**, allylation can be achieved in a diastereoselective manner to afford **10** and subsequently the methyl ester **11** following removal of the auxiliary. However, the sensitive nature of **9** coupled with the cost of pivaldehyde (~$400/100 mL), which is required in 7-fold molar excess, has made the synthesis of **11** using the Seebach protocol less than desirable. Interestingly, Wang and Germanas have reported an alternative to **11** that can be prepared from the inexpensive starting materials of trichloroacetaldehyde and (*S*)-proline.[18] The trichloro oxazolinone **12** is an air- and moisture-stable, commercially available crystalline solid that can be stored at room temperature with no decomposition observed after several weeks. In a similar manner to the Seebach compound **9**, alkylation of the oxazolinone **12** with allyl bromide using LDA readily affords the allyl lactone **13** in high yield and as a single diastereoisomer. Cleavage of the chloral auxiliary from **13** to the amino ester salt **11** under the reported conditions of refluxing HCl/MeOH for 1 h only provided <10% of the desired product.[18] A search of the literature revealed that other groups that have employed this oxazolinone required greater than 24 h of reflux in HCl/MeOH to obtain modest yields of the desired product.[19] Interestingly, cleavage of the auxiliary to the *N*-formyl methyl ester using NaOMe is achieved in less than 30 min.[18] Recognizing that the slow step for the cleavage of the oxazolinone **13** under acidic conditions must be the formation of the methyl ester, we developed a one-pot process to rapidly cleave the auxiliary and in high yield. Exposure of the allyl lactone **13** to sodium in methanol followed by the addition of AcCl to the solution and heating to reflux readily removes the trichloroacetaldehyde auxiliary to produce the desired methyl ester hydrochloride salt **11** in 85% on a 20 g scale.[20]

The synthesis of the tryptophan derivative was achieved from the gramine derivative **19**, which we previously reported by an efficient six-step protocol.[21] Since our initial communication, we have been able to improve upon the overall yield of this key piece through several subtle modifications of the route. Commencing with commercially available 6-benzyloxyindole (**14**), the indole nitrogen was protected with a *t*-Boc group and the benzyl ether removed by hydrogenation to afford the intermediate phenol **15** (Scheme 3). Without isolation, alkylation of the phenol **15** using commercially available 3-chloro-3-methylbut-1-yne **16** (X = Cl) in the presence of $CuCl_2$ and DBU afforded the propargyl ether **17** in 58% yield over the three steps. Since our original communication, we have found that the yield of this alkylation can be improved using the methyl carbonate derivative[22] of **16** (X = OCO_2Me) to 92% yield over the three steps. Aromatic Claisen cyclization of **17** to introduce the pyran ring can be achieved via two sets of conditions. Under thermal heating of **17** in *o*-dichlorobenzene at 180 °C, the pyranoindole **18** can be prepared in 82% yield after ~2 h. Due to the difficulty of removing the solvent for the thermal conditions from the desired product, we have explored alternative conditions to synthesize **18**. To this end, we have taken advantage of microwave heating in order to facilitate the desired aromatic Claisen and *N*-Boc deprotection.[23] With the use of a microwave reactor, the propargyl ether **17** in MeCN was heated at 180 °C for 20 min to afford the desired product **18** in 95% yield. Use of microwave heating for this reaction not only greatly reduced the reaction time but also increased the yield. Furthermore, removal of the reaction solvent (MeCN) can easily be achieved at moderate reduced pressure and temperature.

With multiple grams of the pyranoindole **18** rapidly accessible, formation of the tryptophan derivative was explored. Conversion of **18** to the gramine **19** was conducted under standard conditions and in high yield. Coupling of the gramine **19** to the commercially available benzophenone imine of glycine **20** under standard Somei−Kametani conditions[24] of catalytic *n*-Bu_3P only afforded 65% yield of the desired protected tryptophan derivative **21** after 24 h of reflux. Once again, we found microwave technology to be superior to standard reflux conditions in that heating of the gramine **19** and **20** with *n*-Bu_3P in MeCN at 140 °C for 20 min cleanly afforded the coupled product **21**, which after removal of the benzophenone protecting group with 1 N HCl in THF afforded the amino ester **22** in 90% over the two steps. Chemoselective introduction of the Boc protecting group onto the primary amine of **22** followed by

(18) Wang, H.; Germanas, J. P. *Synlett* **1999**, 33−36.
(19) (a) Hoffman, T.; Lanig, H.; Waibel, R.; Gmeiner, P. *Agnew Chem., Int. Ed.* **2001**, *40*, 3361−3365. (b) Bittermann, H.; Einsiedel, J.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2004**, *47*, 5587−5590. (c) Bittermann, H.; Gmeiner, P. *J. Org. Chem.* **2006**, *71*, 97−102.
(20) Artman, G. D.; Williams, R. M. *Org. Synth.*, submitted for publication 2007.
(21) Grubbs, A. W.; Artman, G. D.; Williams, R. M. *Tetrahedron Lett.* **2005**, *46*, 9013−9016.
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(23) For reviews concerning microwave-assisted organic synthesis, see: (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578−1591. (c) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863−1866. (d) The thermal lability of the *N*-*t*-Boc protecting group has documented, see: Krakowiak, K. E.; Bradshaw, J. S. *Synth. Commun.* **1996**, *26*, 3999−4004.
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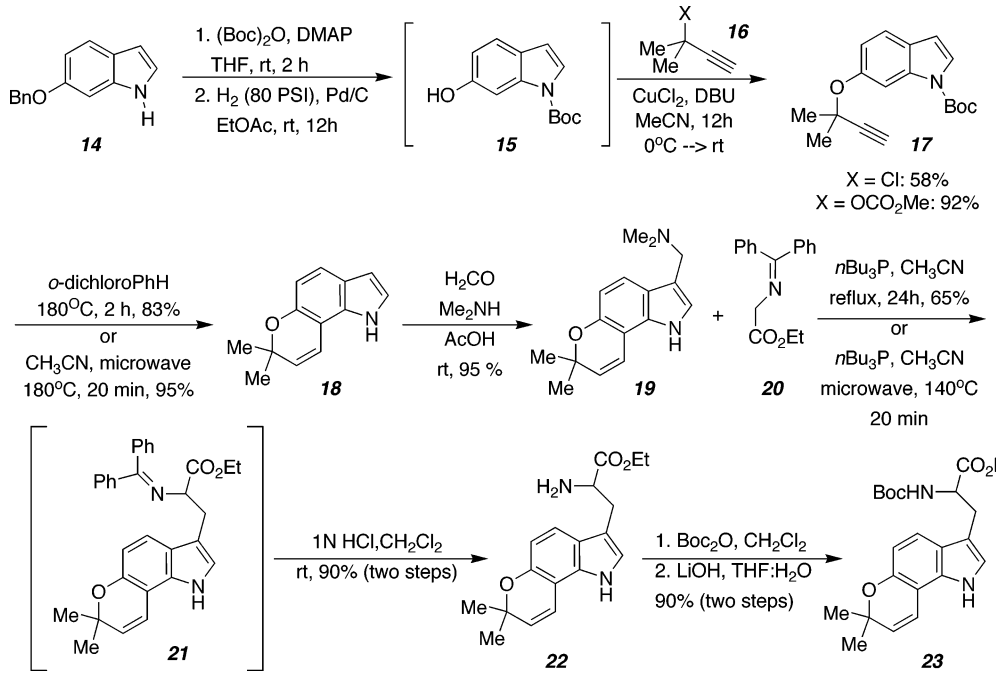
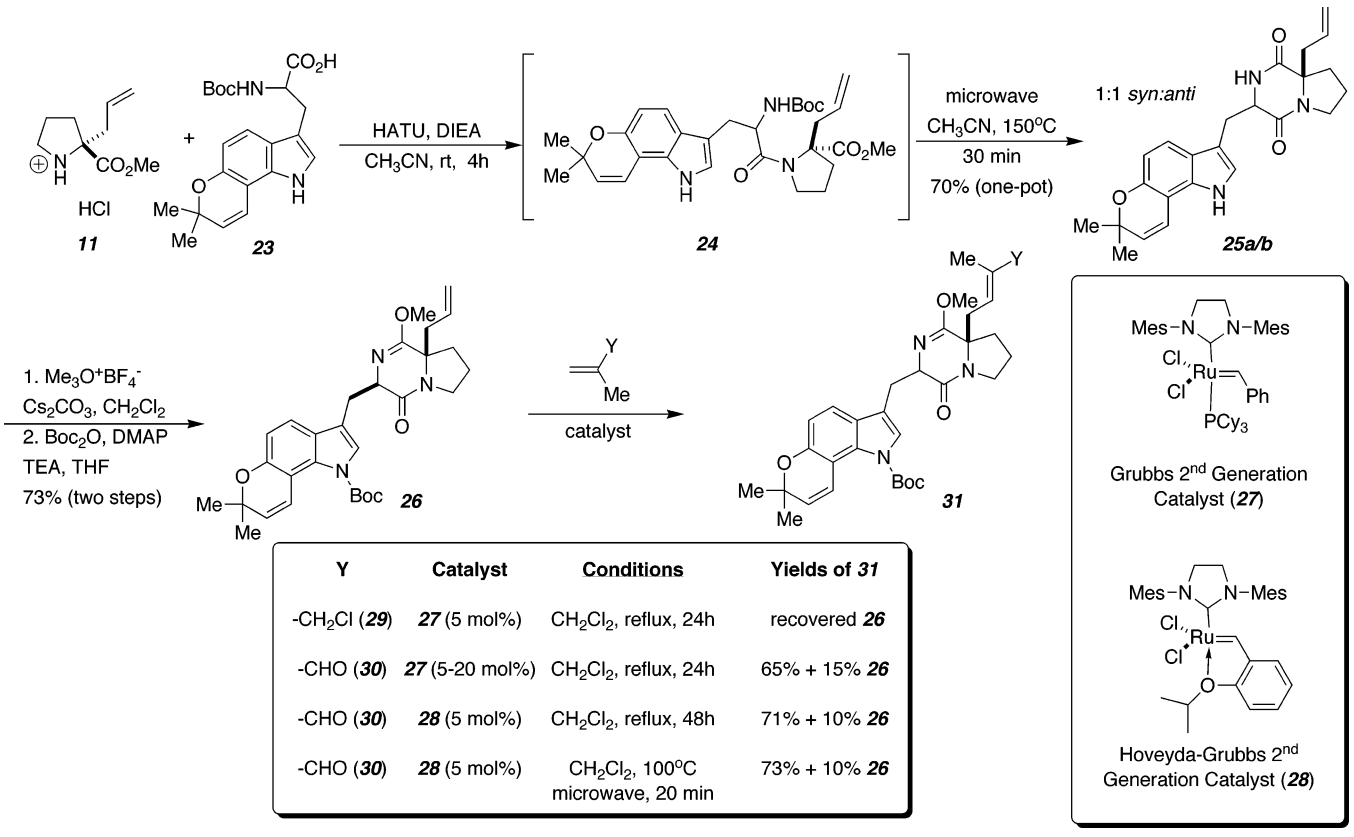
Scheme 3. Synthesis of the Pyranoindole Tryptophan Derivative **23**



Scheme 4. Formation of the Diketopiperazine and Cross-Metathesis Results

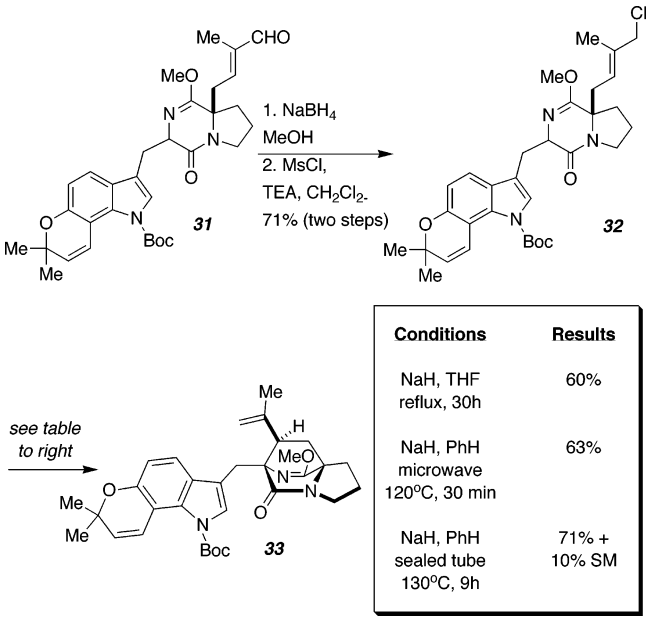


Y	Catalyst	Conditions	Yields of *31*
-CH_2Cl (***29***)	***27*** (5 mol%)	CH_2Cl_2, reflux, 24h	recovered ***26***
-CHO (***30***)	***27*** (5-20 mol%)	CH_2Cl_2, reflux, 24h	65% + 15% ***26***
-CHO (***30***)	***28*** (5 mol%)	CH_2Cl_2, reflux, 48h	71% + 10% ***26***
-CHO (***30***)	***28*** (5 mol%)	CH_2Cl_2, 100°C microwave, 20 min	73% + 10% ***26***

saponification using LiOH produced the *N*-Boc acid **23** in excellent yield over the two steps.

Coupling of the allyl proline **11** to the tryptophan acid **23** was accomplished using HATU in the presence of DIPEA in MeCN (Scheme 4). Previously, the Baran group reported a similar intermediate en route to stephacidin A, wherein ring closure to the diketopiperazine ring system can be facilitated under thermal conditions.[4a] Recognizing the thermal lability of the Boc protecting group employed, we found that heating of the crude reaction mixture for the coupling product **24** under microwave heating for 30 min at 150 °C produced the desired diketopiperazine **25a/b** as a 1:1 mixture of diastereomers that were separable by flash silica gel chromatography in 70% yield; both diastereomers were carried forward separately. Introduction of the lactim ether protecting group onto the amides **25a/b** using $Me_3O^+BF_4^-$ in the presence of Cs_2CO_3 followed by Boc

Scheme 5. Formation of the [2.2.2] Bridged Bicycle



protection of the indole nitrogen prepares our key substrate **26** for the desired olefin cross-metathesis reaction.[25,26] Attempts to directly convert the terminal olefin of **26** to the requisite allyl chloride **31** (Y = $-CH_2Cl$) using Grubbs' second-generation catalyst (**27**) or Hoveyda−Grubbs catalyst **28** and commercially available 3-choro-2-methyl-2-propene (**29**) failed to produce the desired product with most of the starting material **26** being recovered unchanged.[27] Alternatively, cross-metathesis of **26** with methacrolein (**30**) using catalytic amounts of **27** in refluxing CH_2Cl_2 for 24 h readily affords the aldehyde **31** (Y = CHO) in 65% yield with 15% recovered starting material. Unfortunately, additional quantities of the catalyst **27** had to be added during the reaction raising the catalyst loading from the initial 5 to 20 mol %. Switching to the Hoveyda derivative of the Grubbs second-generation catalyst (**28**), we were able to reduce the catalyst loading to 5 mol % and increased the yield for **31** (Y = CHO) to 70% with 10% recovered **26** after 48 h of reflux. Once again, we desired to reduce the time required for this reaction and turned to the microwave to facilitate the heating of this metathesis reaction.[28] In the event, heating of the olefin **26** with methacrolein (**30**) in the presence of 5 mol % of **28** in CH_2Cl_2 at 100 °C for 20 min generated the aldehyde **31** (Y = CHO) in 73% with 10% recovered starting material.

Reduction of the aldehyde **31** using $NaBH_4$ in MeOH afforded the relatively pure allylic alcohol, which was converted directly to the allyl chloride **32** (Scheme 5). However, attempts to perform this relatively simple transformation were often met with decomposition or low yield using a variety of standard conditions (MsCl, LiCl, collidine; NCS, Me_2S; Ph_3P, $Cl_3CCOCCl_3$). The requisite allyl chloride **32** was finally accessed by slow addition of MsCl/TEA to a 0 °C solution of the allylic alcohol in CH_2Cl_2 followed by slowly warming to room temperature and stirring for >12 h in 71% yield over the two steps. The addition of external chloride sources such as LiCl or Bu_4NCl to help increase the rate of reaction for the formation of **32** often led to lower yields and additional byproducts. Cyclization of the allyl chloride **32** under our standard S_N2' conditions for the formation of the [2.2.2] bridged bicycle were then explored. Exposure of **32** to 20 equiv of NaH in benzene followed by refluxing for 30 h afforded the desired bridged bicycle **33** in 60% yield and as a single diastereoisomer, which presumably arises through a tight ion-pair-driven closed-transition state.[9a] However, the length of the reaction time was less than desirable (~30 h).

Building off our success in previous steps employing microwave heating, we attempted our key cyclization under microwave-assisted conditions. Initial cyclizations of **32** in benzene at 120 °C for 30 min on a small scale (<75 mg) gave similar results to the thermal conditions. However, on slightly larger scales (>150 mg), microwave heating lead to the bursting of the glass microwave tube and loss of the valuable starting material and product. Recognizing that part of the so-called "microwave effect" may be the influence of pressure on the reaction, we made a second thermal attempt using a sealed tube. Heating of **32** with NaH in benzene at 130 °C for 9 h readily produced the desired product **33** in an improved 71% yield with 10% recovered starting allyl chloride **32**.

With formation of the [2.2.2] bridged bicycle completed, we were left with the task of forming the heptacyclic ring system as well as removing the lactim ether and Boc protecting groups. Closure to the heptacycle was achieved using a one-pot, two-step procedure previously developed by Trost and Fortunak[29] and employed in the paraherquamides A[15] and B[16] syntheses. Exposure of **33** to 5 equiv of $Pd(TFA)_2$ with 100 equiv of propylene oxide in acetonitrile at room temperature rapidly forms the alkyl palladium intermediate **34** (Scheme 6). The reaction mixture is diluted with EtOH, and the alkyl−Pd intermediate is reduced using $NaBH_4$ to afford **35** in 71% yield. After extensive investigation, we found that we were not able to cleave the lactim ether or the Boc protecting group to afford stephacidin A (**1**) under a wide range of acidic conditions often resulting in decomposition or multiple products.[30] As an alternative, we discovered that if the propylene oxide is not added to the palladium-mediated cyclization of **33** two products (**36**/**37**) can be cleanly formed as an inseparable mixture following quenching with acid. When 1 N HCl is employed, the allylic alcohol **36** and the heptacycle lacking the lactim ether (**37**) in a 1.6:1 ratio was obtained. The ratio between **36** and **37** can be perturbed by the acid strength employed during the workup of this reaction. By decreasing the concentration from 1 to 0.5 N HCl, the ratio moves in favor of **37** with a 0.7:1 ratio of **36:37**. Further dilution of the acid strength to 0.1 N HCl results in only the formation of the desired **37**. Heating of the crude product **37** in acetonitrile using the microwave reactor at 180 °C[23] for 15 min afforded (−)-stephacidin A (**1**) as an amorphous white powder, which displayed identical spectroscopic characteristics to the reported literature values. This last sequence has been performed several times with good

(25) For a general review on olefin cross-metathesis, see: Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.
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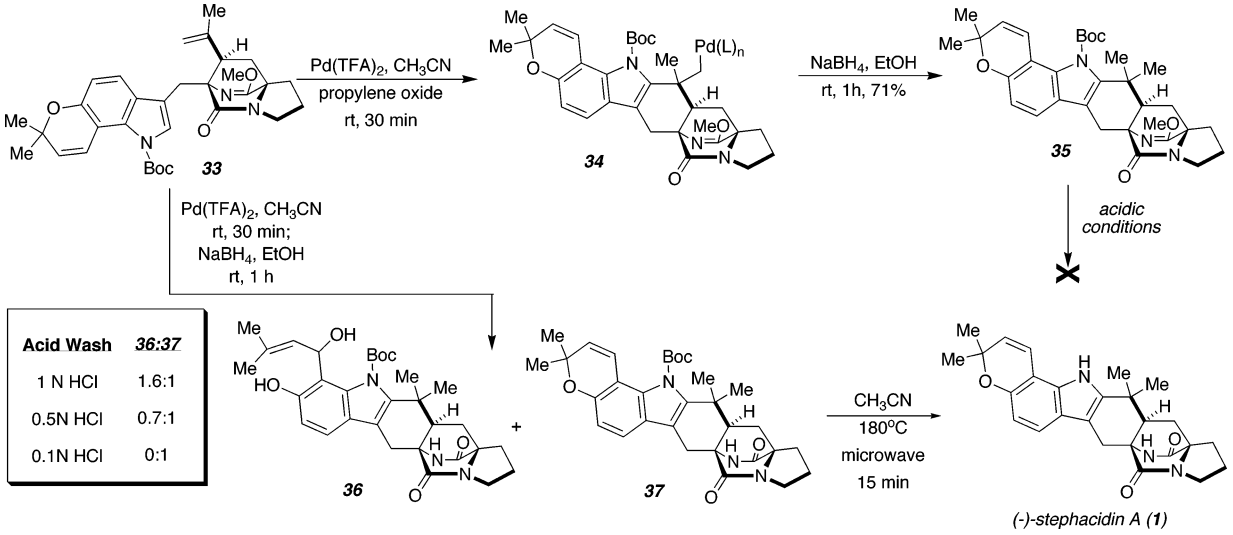
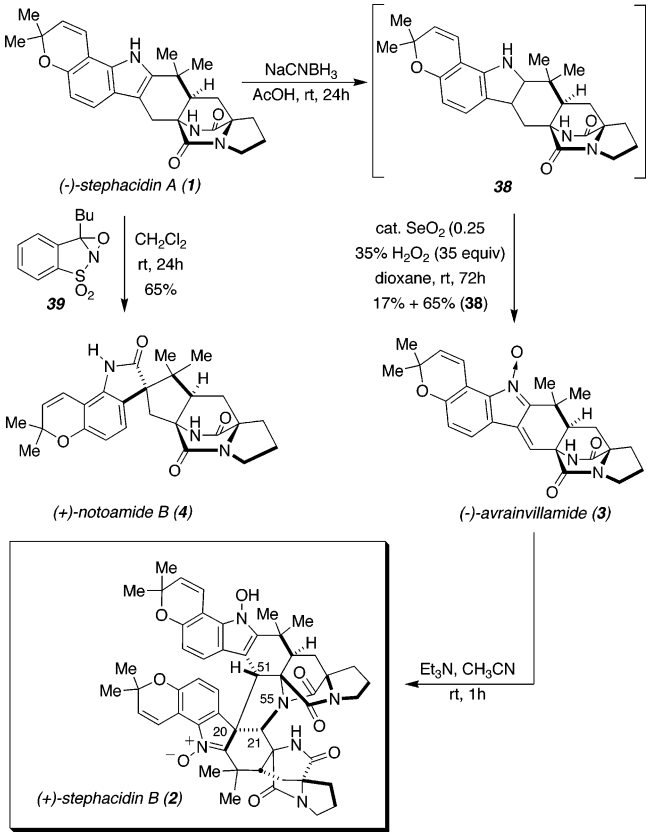
(29) Trost, B. M.; Fortunak, J. M. D. *Organometallics* **1982**, *1*, 7−13.
(30) Similar results were observed by the Baran group during their synthetic efforts towards stephacidin A. Please see their full account listed in ref 8 for exact conditions explored.

Scheme 6. Completion of the Total Synthesis of (−)-Stephacidin A (**1**)



Scheme 7. Conversion of Synthetic (−)-**1** to (−)-Avrainvillamide (**3**), (+)-Stephacidin B (**2**), and (+)-Notoamide B (**4**)



reproducibility yielding on the order of 7 mg of synthetic stephacidin A from 15 mg of **33**. This final protocol is a simple two-step procedure, where compound **37** does not need to be isolated and purified and the crude material obtained from **33** is subjected to a quick workup and redissolution for the final *N*-*t*-Boc removal.[23d]

Furthermore, we might note here as an aside, that we were quite surprised with the physical characteristics of (−)-stephacidin A. First, it has very poor UV activity on TLC and generally does not develop in numerous TLC stains such as $KMnO_4$, vanillin, etc., making the product unusually elusive to standard analytical detection. Second, stephacidin A is quite insoluble in a series of common organic solvents such as CH_2Cl_2, $CHCl_3$, THF, Et_2O, MeCN, benzene, etc. and is only sparingly soluble in DMSO. These two factors made it very difficult to determine if we had actually synthesized the natural product before NMR analysis after the final step.

The conclusion of the total synthesis of (−)-stephacidin A (**1**) has also allowed us to complete the synthesis of (−)-avrainvillamide (**3**), (+)-stephacidin B (**2**), and (+)-notoamide B (**4**) from a common intermediate. Following the previously reported Baran oxidation procedure, **1** was reduced to the 2,3-dihydroindole **38** using $NaCNBH_3$ in AcOH (Scheme 7).[8] Oxidation of the crude dihydroindole **38** using catalytic SeO_2 and excess 35% H_2O_2 for 3 days afforded (−)-avrainvillamide (**3**) in 17% yield in addition to 65% recovered starting material. Synthetic (−)-**3** was converted to (+)-stephacidin B (**2**) using the Myers' procedure[5] of excess Et_3N in CH_3CN, which showed 95% conversion to the desired alkaloid by ^1H NMR analysis and HRMS to the previously reported data as well as identity with an authentic, natural sample kindly provided by Bristol-Myers Squibb. Finally, synthetic (−)-**1** was transformed to (+)-notoamide B (**4**) using the procedure established by our group for the synthesis of *d*,*l*-**4** by exposure to oxaziridine **39** in 65% yield.[11b]

Conclusions

In conclusion, we have completed a very efficient, asymmetric total synthesis of the fungal metabolite (−)-stephacidin A (**1**), in a mere 17 total chemical transformations from commercially available starting materials and in 6% overall yield. This also constitutes a formal total synthesis of (+)-stephacidin B following Baran's reported conversion of **1** into **3** and then via Myers' landmark conversion of **3** into **2** in 19 steps (1% overall yield). Our synthetic (−)-stephacidin A was subjected to the Baran−Myers protocol yielding totally synthetic (−)-avrainvillamide (**3**) and totally synthetic (+)-stephacidin B (**2**, 19 steps; 1% overall yield). To place the economy of our synthesis in context, it is worthwhile comparing the data reported herein to the Myers' synthesis of stephacidin B, which was accomplished in 27 steps from commercially available materials in 0.5% overall yield and to that of the Baran laboratory, which reported stephacidin A in 29 steps (1% overall yield) and stephacidin B

in 31 total steps and 0.2% overall yield. During the course of our studies, we have been able to improve upon the synthesis of (*R*)-allyl proline using the commercially available oxazolidinone **12** as well as the synthesis of the previously reported gramine **19**. These technologies permit us to install either stable- or radioisotopes economically into the synthesis which is currently under study for ongoing biosynthetic investigations being conducted collaboratively with Professor David Sherman's laboratory. Furthermore, our synthesis has extensively taken advantage of microwave technology, which has reduced reaction times from hours to minutes as well as increased the yields of several key transformations. Finally, the synthesis of (−)-stephacidin A (**1**) has resulted in the first asymmetric total syntheses of (+)-notoamide B (**4**) utilizing an efficient one-step oxidative pinacol that we recently reported. This work constitutes the shortest asymmetric route to these four natural products currently reported in the literature. Current efforts are being directed to harnessing this technology to prepare numerous analogs of the stephacidins for biological evaluation and as probe molecules and provocative biosynthetic intermediates to further establish the fascinating web of biogenetic relationships within this family of alkaloids.[31,32]

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Note added in revision: (a) For a biomimetic synthesis of the related alkaloid *d,l*-marcfotine C, see: Greshock, T. J.; Grubbs, A. W.; Williams, R. M. *Tetrahedron* **2007**, DOI: 10.1016/j.tet.2007.03.016. (b) For a recent synthesis of *d,l*-marcfortine B, see: Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am. Chem. Soc.* **2007**, *129*, 3086−3087.

(32) Note added in proof: Myers, et al., recently reported that stephacidin B converts to avrainvillamide in cell culture with avrainvillamide being the biologically active species: Wulff, J. E.; Herzon, S. B.; Siegrist, R.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 4898−4899.