Natural Products Synthesis

Short, Enantioselective Total Synthesis of Stephacidin A**

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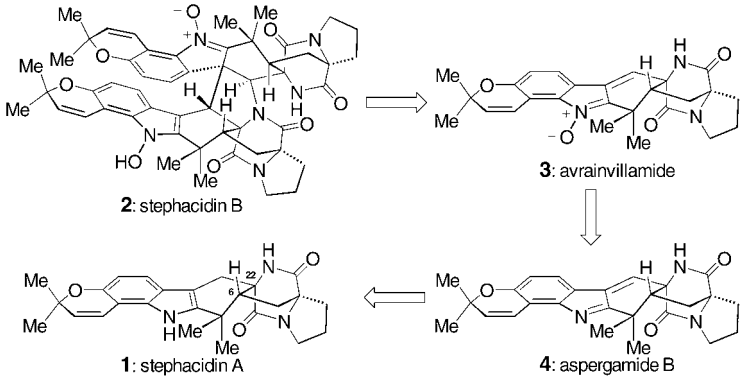
Prenylated indole alkaloids have been a vibrant source of inspiration for synthetic chemists for over half a century.[1] Representative members of this natural product family include the spirotryprostatins,[2] brevianamides,[3] austamides,[4] and okaramines.[5] Stephacidin A and B (**1** and **2**, respectively in Scheme 1), recently disclosed by scientists at Bristol-Myers Squibb, signify a new peak of structural complexity within this family.[6,7] Isolated from the fungus *Aspergillus ochraceus* WC76466, stephacidin B (**2**) "represents one of the most structurally complex and novel alkaloids occurring in Nature"[6] and contains 15 rings, nine stereogenic centers, and the ubiquitous 6-oxyindole substructure. Furthermore, compounds **1** and **2** exhibit potent in vitro cytotoxic activity against a variety of human tumor cell lines. The bioactivity of the stephacidins is not mediated by p53, mdr, bcl2, tubulin, or topoisomerase II, which suggests a novel mechanism of action.[6] Taken together, these facts provided a strong impetus for the design of a concise total synthesis that employs **1** en route to **2** (Scheme 1) and that proceeds through the intermediacy of avrainvillamide[7] (**3**) and aspergamide B (**4**).[8]

The heptacyclic alkaloid stephacidin A (**1**) poses a number of challenges for synthesis. Pioneering work from the Williams laboratory[9] has verified the proposals of Birch[3] and Sammes[10] that the bicyclo[2.2.2]diazaoctane core of these alkaloids are likely formed by a Diels–Alder reaction in Nature. However, this elegant biomimetic approach would be difficult to employ in an enantioselective laboratory synthesis of **1**, especially as a proposed intermediate in the cascade sequence is achiral.[11] Furthermore, there is a clear gap in indole synthesis methodology, as published methods[12,13] for the preparation of the 6-hydroxytryptophan core require multistep, tedious procedures. Herein we report a concise, enantioselective total synthesis of stephacidin A (**1**) that establishes its relative configuration and addresses its inherent chemical challenges in a unique way.



Scheme 1. Stephacidins and their proposed[6,7] biogenetic relationships.

The challenge of a practical and rapid synthesis of the 6-hydroxytryptophan core of **1** was met by modifying a palladium-catalyzed indole synthesis developed at Merck (Scheme 2).[14] Thus, after extensive optimization, readily available pyroglutamate **5** was chemoselectively reduced with Super Hydride[15] and the crude lactol was immediately converted into tryptophan **8** in 75% overall yield through the intermediacy of enamine **7**. This enamine could be isolated, characterized, and converted into **8**. The high yield of this simple process is not diminished even on a multigram scale. Tetrabutylammonium iodide (3.0 equiv) was vital as the yield ranged from 10–35% in its absence. The benzopyran subunit was then installed and subsequently modified for coupling to the proline subunit through the sequence shown in Scheme 2. Protection with Boc_2O was followed by removal of the tosylate group.[16] Propargylation of the resulting phenol under standard Cu-catalyzed conditions with **9** [17] furnished **10** in 75% yield over two steps. Allenyl Claisen rearrangement[18] followed by reprotection of the indole NH group and subsequent hydrolysis led to the formation of acid **12**.

Racemic tryptophan derivative **12** was then coupled with the enantiomerically pure proline derivative **13**[19] to afford an

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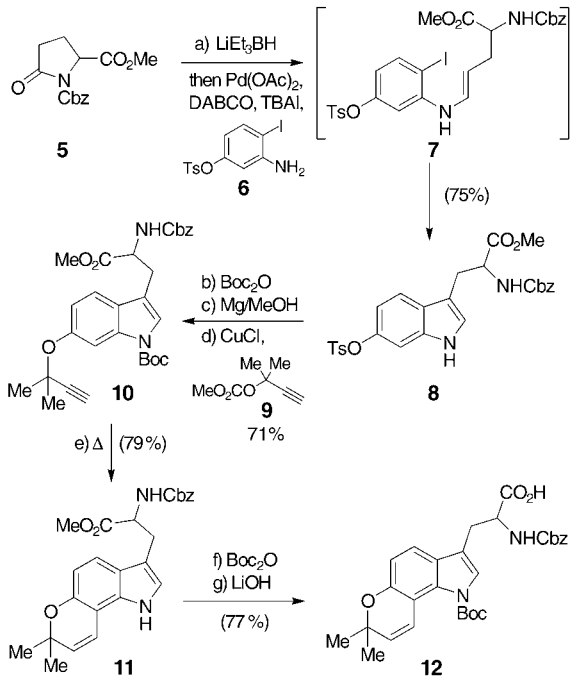
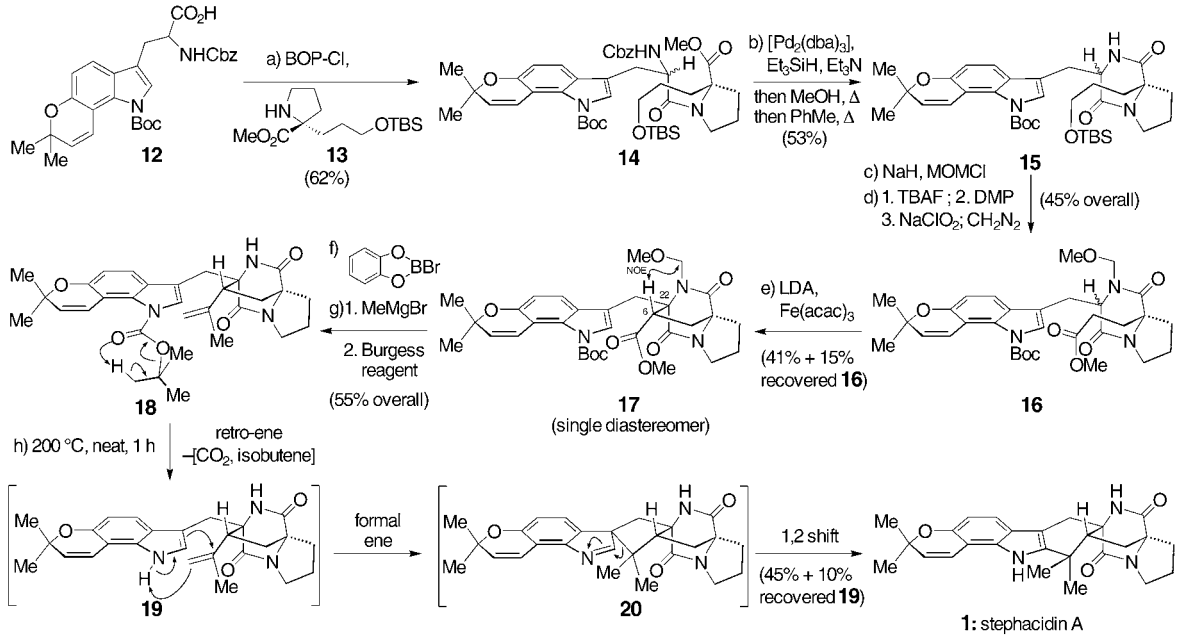


Scheme 2. Synthesis of the benzopyran-tryptophan subunit **12**. Reagents and conditions: a) 1. $LiEt_3BH$ (1.1 equiv), THF, −78 °C, 10 min; 2. $Pd(OAc)_2$ (0.05 equiv), DABCO (3.0 equiv), **6** (1.1 equiv), TBAI (3.0 equiv), DMF, 105 °C, 4 h, 75% overall; b) Boc_2O (1.0 equiv), DMAP (0.01 equiv), CH_2Cl_2/CH_3CN (1:1), 25 °C, 30 min, 95%; c) Mg (10.0 equiv), MeOH, 0→25 °C, 2.5 h; d) **9** (3.0 equiv), $CuCl_2$ (0.001 equiv), DBU (3.0 equiv), CH_3CN, 0 °C, 24 h, 75% over two steps; e) AcOH, 120 °C, 80 min, 79%; f) Boc_2O (1.0 equiv), DMAP (0.01 equiv), CH_2Cl_2/CH_3CN (1:1), 25 °C, 30 min, 77%; g) LiOH (15.0 equiv), THF/H_2O (1:1), 0 °C, 3 h, 100%. DABCO = 1,4-diazabicyclo[2.2.2]octane; TBAI = tetra-*n*-butylammonium iodide; DMF = *N*,*N*-dimethylformamide; Boc = *tert*-butoxycarbonyl; DMAP = 4-dimethylaminopyridine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

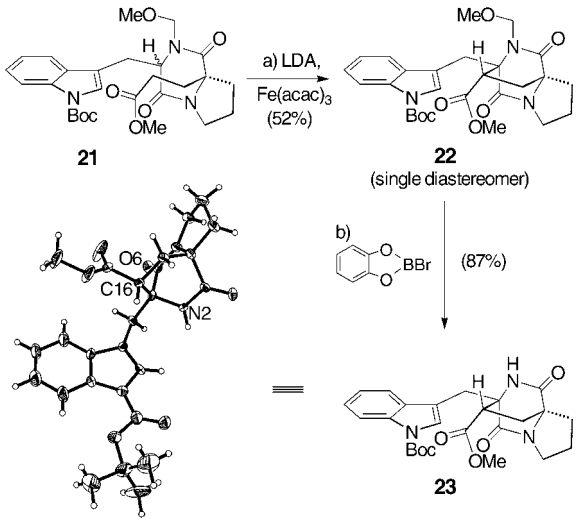
inconsequential mixture of diastereomeric amides **14** in 62% yield (Scheme 3). The Cbz group was chemoselectively excised and the diketopiperazine was formed in a single operation[20] without harm to the benzopyran or to either the *N*-Boc or silyl ether functionalities to provide diketopiperazine **15** in 53% yield. Protection of the diketopiperazine NH function followed by TBAF-mediated removal of the TBS group and sequential oxidation to the corresponding ester **16** set the stage for a remarkable C–C bond-forming event.

Although the metal-mediated oxidative coupling of enolates has immense potential for synthesis, it has been employed only sporadically since the seminal reports from the groups of Mislow and Saegusa.[21,22] Our objective was to effect the conversion of **16** into **17** by forming the key C6–C22 bond (stephacidin A numbering,[6] see Scheme 3, **17**) with complete stereocontrol through an oxidative coupling. Mechanistically, it is believed that such reactions proceed via radical species, despite a lack of evidence to rule out metal-bound intermediates. Recent findings in our laboratory[23]



Scheme 3. Enantioselective total synthesis of stephacidin A (**1**). Reagents and conditions: a) **13** (1.5 equiv), BOPCl (1.1 equiv), iPr_2EtN (1.1 equiv), CH_2Cl_2, 0→25 °C, 10 h, 62%; b) $[Pd_2(dba)_3]$ (0.2 equiv), Et_3SiH (40 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 25 °C, 4 h; then MeOH, reflux, 30 min; then toluene, reflux, 2 h, 53% overall; c) NaH (1.2 equiv), MOMCl (1.1 equiv), DMF, 0 °C, 1 h, 65%; d) TBAF (3.0 equiv), THF, 25 °C, 1 h; then DMP (1.5 equiv), CH_2Cl_2, 25 °C, 2 h; then 2-methyl-2-butene (20 equiv), $NaH_2PO_4{\cdot}H_2O$ (3.0 equiv), $NaClO_2$ (2.8 equiv), THF, H_2O, 20 min; then CH_2N_2 in Et_2O, MeOH, 5 min, 69% overall; e) LDA (2.2 equiv), THF, −78 °C, 5 min then $[Fe(acac)_3]$ (2.2 equiv), THF, −78→25 °C, 1 h, 41% **17** with 15% recovered **16**; f) *B*-bromocatecholborane (1.5 equiv), CH_2Cl_2, 0 °C, 1.5 h, 63%; g) MeMgBr (6.0 equiv), toluene, 25 °C, 1 h, then Burgess reagent (2.0 equiv), benzene, 50 °C, 30 min, 88% overall; h) 200 °C, 1 h, 45% **1** with 10% recovered **19**. BOP = bis(2-oxo-3-oxazlidinyl)phosphinic chloride; dba = *trans*,*trans*-dibenzylideneacetone; MOM = methoxymethyl; TBAF = tetra-*n*-butylammonium fluoride; DMP = Dess–Martin periodinane; LDA = lithium diisopropylamide; acac = acetylacetonate.

suggest that some of the metallic oxidants employed (Fe^{III}- and Cu^{II}-based) may play a more intimate role in these reactions. We imagined that the reaction of **16** would proceed with the desired stereochemical outcome to furnish **17** through a metal-chelated transition state. To probe this possibility, the model ester **21** (Scheme 4) was synthesized



Scheme 4. Stereocontrolled intramolecular oxidative coupling of the model ester **21**. Reagents and conditions: a) LDA (2.5 equiv), THF, −78 °C, 30 min then [Fe(acac)$_3$] (2.5 equiv), THF, −78 → 25 °C, 1 h, 52 % b) *B*-bromocatecholborane (2.0 equiv), CH_2Cl_2, 0 °C, 1 h, 87 %.

and subjected to modified oxidative coupling conditions, which furnished the desired cyclized product **22** in 52 % yield. The stereochemistry was secured upon removal of the MOM group in 87 % yield with *B*-bromocatecholborane[24] and X-ray crystallographic analysis of the resulting crystalline pentacycle **23**[25] (colorless needles, m.p. 125–128 °C (EtOAc), see Scheme 4 for ORTEP illustration). Notably, this reaction fails when using silver salts, iodine, and ferricinium hexafluorophosphate (an oxidant known to give radicals from enolates).[26] Participation of the MOM group in this reaction was ruled out as a PMB group could be used interchangeably with the same stereochemical outcome and yield.

With the encouraging reconnaissance gained in the model study, addition of LDA (2.2 equiv) to a solution of substrate **16** in THF at −78 °C followed by [Fe(acac)$_3$] after 5 minutes of enolization and warming to room temperature led to **17** in 41 % yield as a single diastereomer (along with 15 % recovery of **16**, Scheme 3). The extremely brief enolization time (5 min) was essential for the success of this reaction. With the exception of the benzopyran resonances, the NMR spectral properties of **17** were nearly identical to the model compound **22** (Scheme 3); the stereochemistry of the newly formed C6–C22 bond of **17** was further verified by the observed NOE (see **17** in Scheme 3 and Supporting Information).

To complete the synthesis of **1**, only one ring remained to be stitched onto **17**. The challenge of installing this ring led to the discovery of a new method for indole annulation. Thus, following removal of the MOM group in 63 % yield with *B*-bromocatecholborane, reaction with MeMgBr cleanly furnished a tertiary alcohol, which was directly dehydrated with Burgess reagent[27] to afford olefin **18** in 88 % overall yield. Although a variety of acidic conditions are known to effect ring closure in closely related systems,[28] our efforts to convert **18** or its hydrated precursor into **1** were all thwarted by the acid-labile nature of the substrate. Remarkably, when **18** was simply heated at 200 °C, in the absence of solvent, for 1 h, **1** was obtained in 45 % yield. We believe that thermolytic removal of the Boc group (through a retro-ene reaction) of **18** occurs first to afford **19** followed by a formal ene reaction leading to a fleeting spirocyclic intermediate **20** reminiscent of the venerable Pictet–Spengler reaction. A 1,2-shift then terminates the cascade and furnishes **1** (Scheme 3). The exact nature of the latter transformation has not been fully elucidated. However, this thermal reaction appears to be general for these types of systems and will be detailed in the full account. Synthetic **1** has identical spectral properties (both in [D$_6$]DMSO and $CDCl_3/CD_3OD$ 4:1) to that reported by Cutrone et al., thus establishing the relative configuration as shown in Scheme 1. The absolute configuration could not be secured as the optical rotation of natural **1** was not recorded and little or no material remains.[29] Incidentally, **23** could be converted into epibrevianamide by following a similar pathway, further confirming our assignment of the relative configuration.[30]

In summary, the first total synthesis of **1** from the commodity chemicals pyroglutamate and L-proline was completed in 15 operations. Efforts are now underway to access the highly oxidized congeners of stephacidin A (Scheme 1). The journey to stephacidin A was accompanied by some interesting discoveries and inventions, including: 1) a general methodology for the rapid and practical synthesis of tryptophan derivatives from pyroglutamate, 2) a remarkable deprotection/annulation cascade which occurs simply with heat to forge the final ring (**18**→**1**), and 3) simple, stereocontrolled assembly of two of the three stereocenters of **1** by a rare intramolecular oxidative coupling (**16**→**17** and **21**→**22**). The latter set of transformations proceeds cleanly and represents the first such couplings of esters to amides. The counterintuitive strategy employed in this total synthesis points to an attractive direction for further study in the general areas of oxidative C–C bond formation and synthetic design.[31]

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[31] Detailed experimental procedures, copies of spectral data and full characterization are contained in the Supporting Information.

