

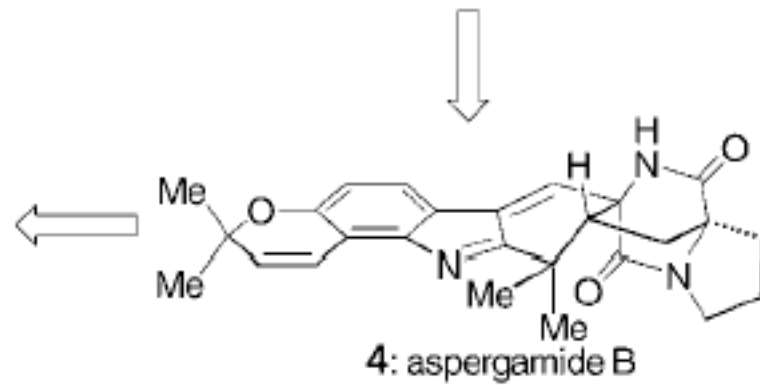
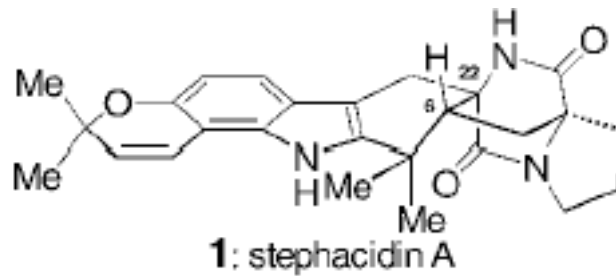
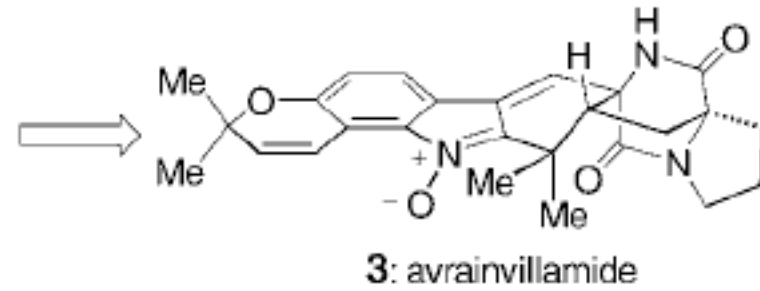
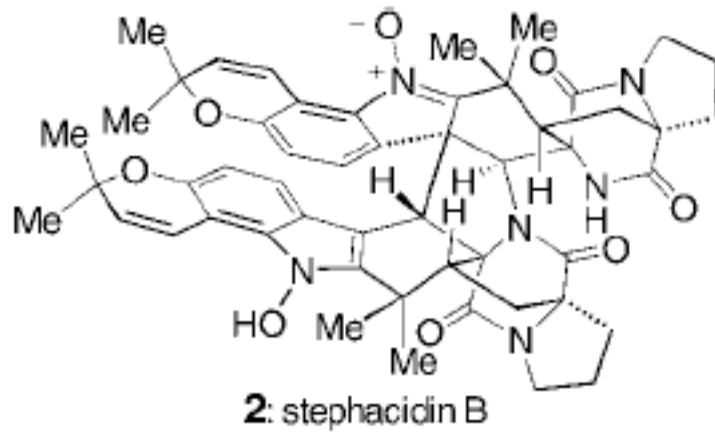
# Total Synthesis of Stephacidin A

Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D.  
*Angew. Chem. Int. Ed.* **2005**, *44*, 606-609.

Yiqian Lian

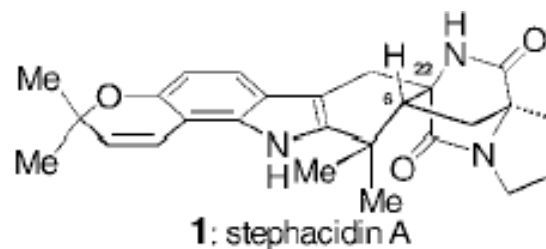
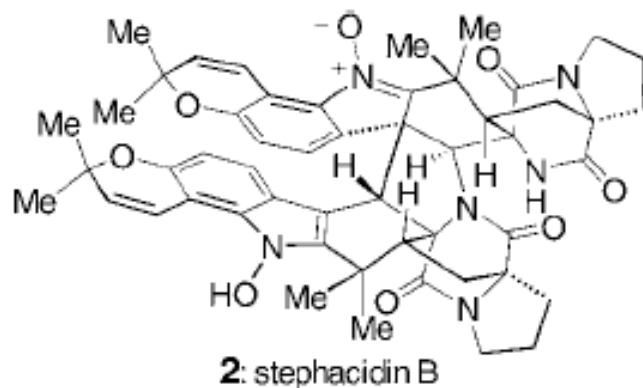
Jan-27-05

# Stephacidins



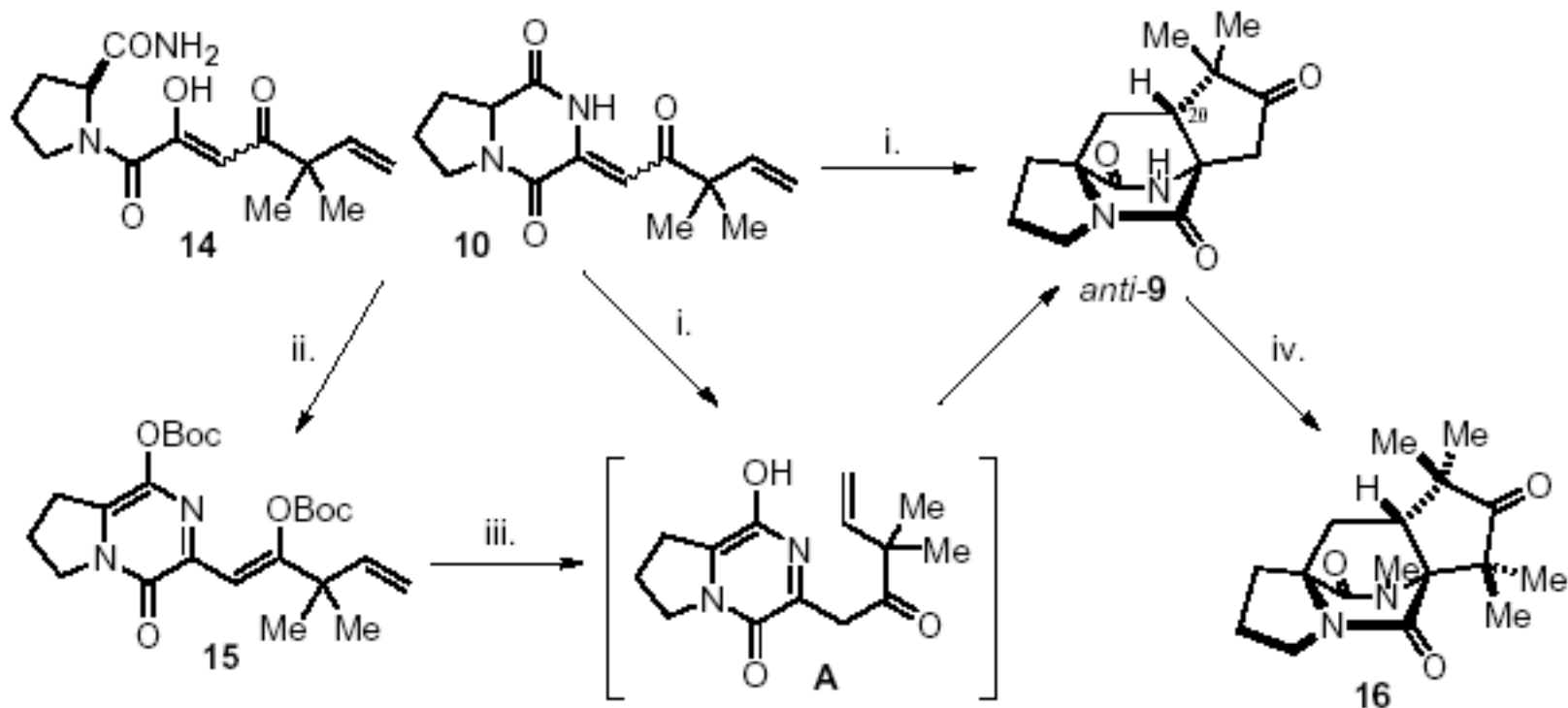
## Stephacidin A and B

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- Recently disclosed by scientists at BMS, signifying a new peak of structural complexity within the indole alkaloids family. (JACS, 2002, 124, 14556).
- Isolated from the fungus *Aspergillus ochraceus* WC76466, stephacidin B (**2**) represents one of the most structurally complex and novel alkaloids occurring in Nature, contains 15 rings, nine stereogenic centers, and the ubiquitous 6-oxyindole substructure.
- 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.

## Bicyclo[2.2.2]diazaoctane via DA Rxn from Diketopiperazine



(i) 4 M HCl/dioxane, 45%; (ii)  $\text{Boc}_2\text{O}$  (2.75 equiv), DMAP (1.1 equiv),  $\text{CH}_2\text{Cl}_2$ , 28%;

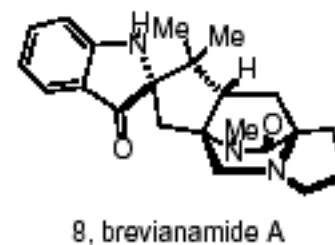
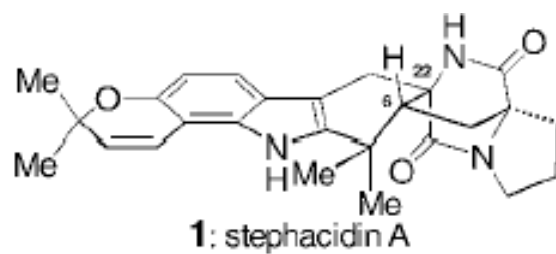
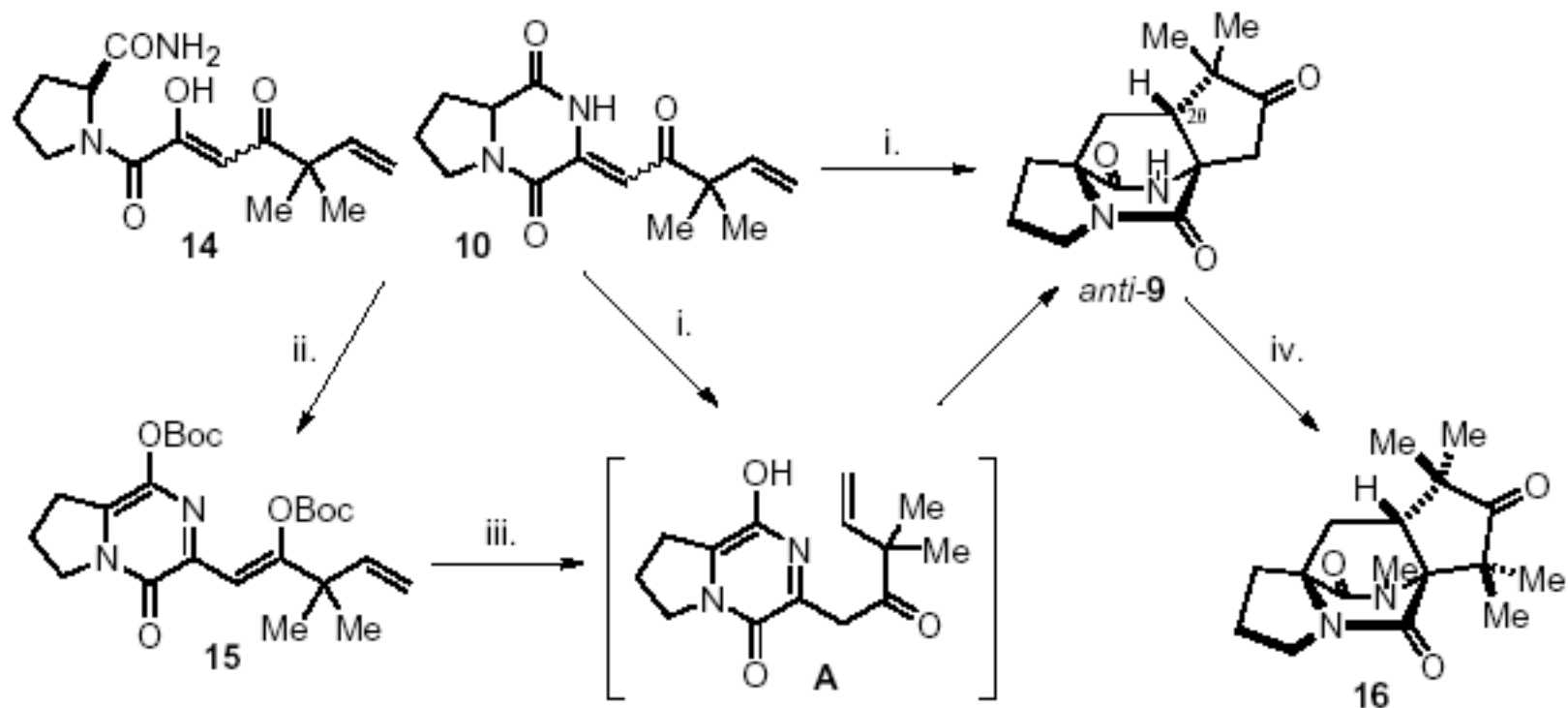
(iii)  $\text{AlCl}_3$  (5 equiv), EtOAc, reflux 5 days, 81%;

(iv) excess NaH, MeI, THF, reflux 1 h, 62%.

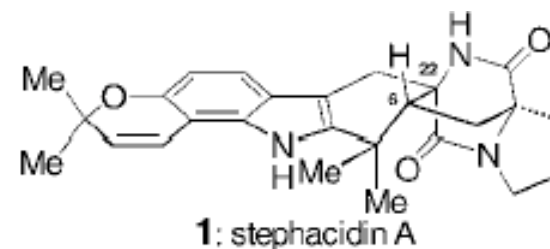
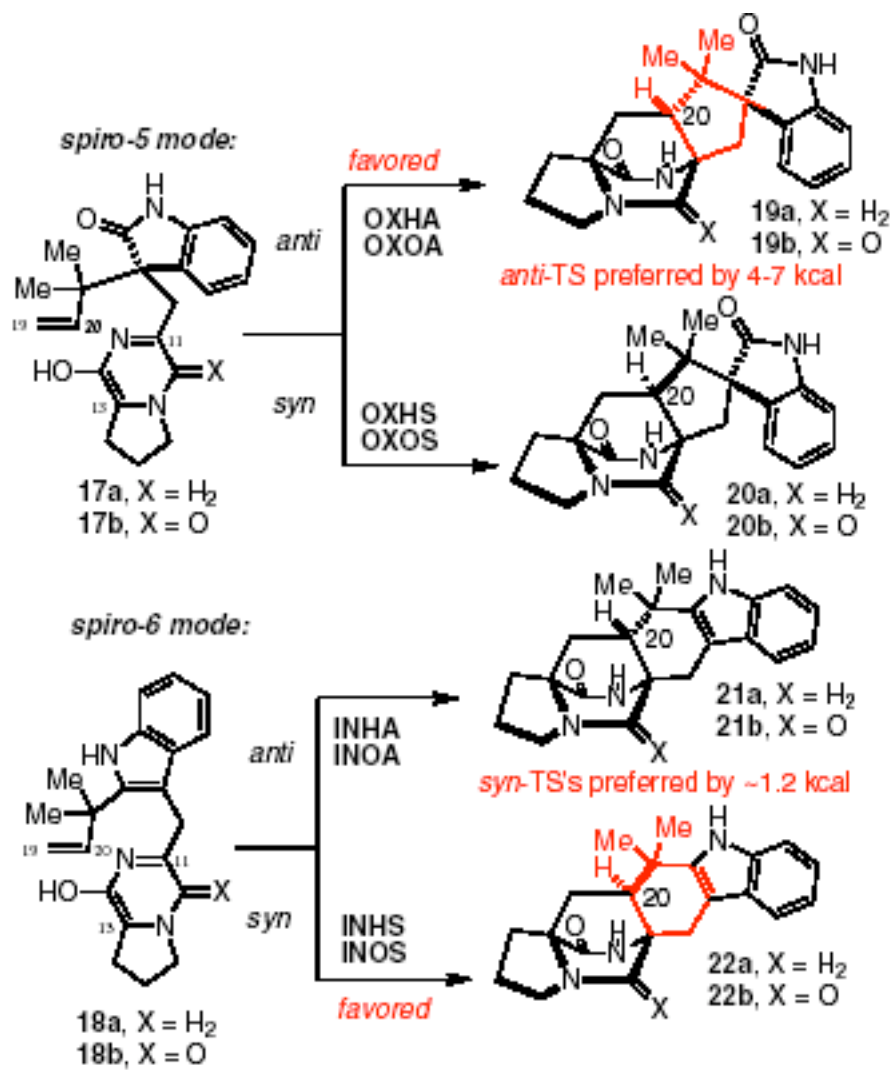
Williams, R. M. et al. TL, 2004, 45, 4489.

For a review on Biosynthetic DA: Ang. 2003, 3078.

## Bicyclo[2.2.2]diazaoctane via DA Rxn from Diketopiperazine



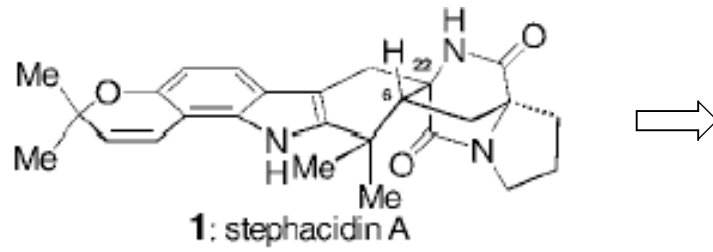
# Ab Initio Calculations



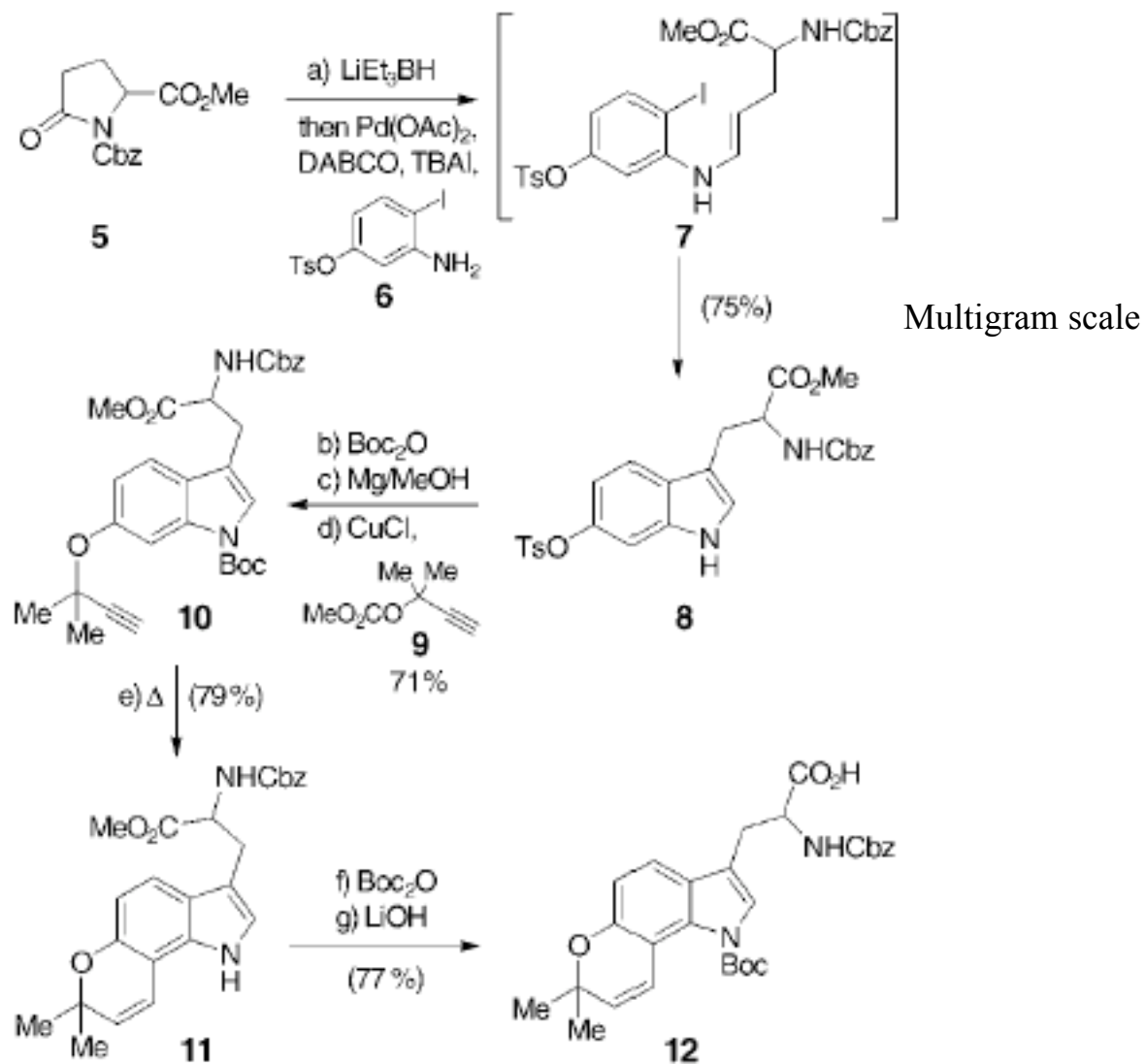
Williams, R. M. et al. TL, 2004, 45, 4489.

# Baran's Strategy

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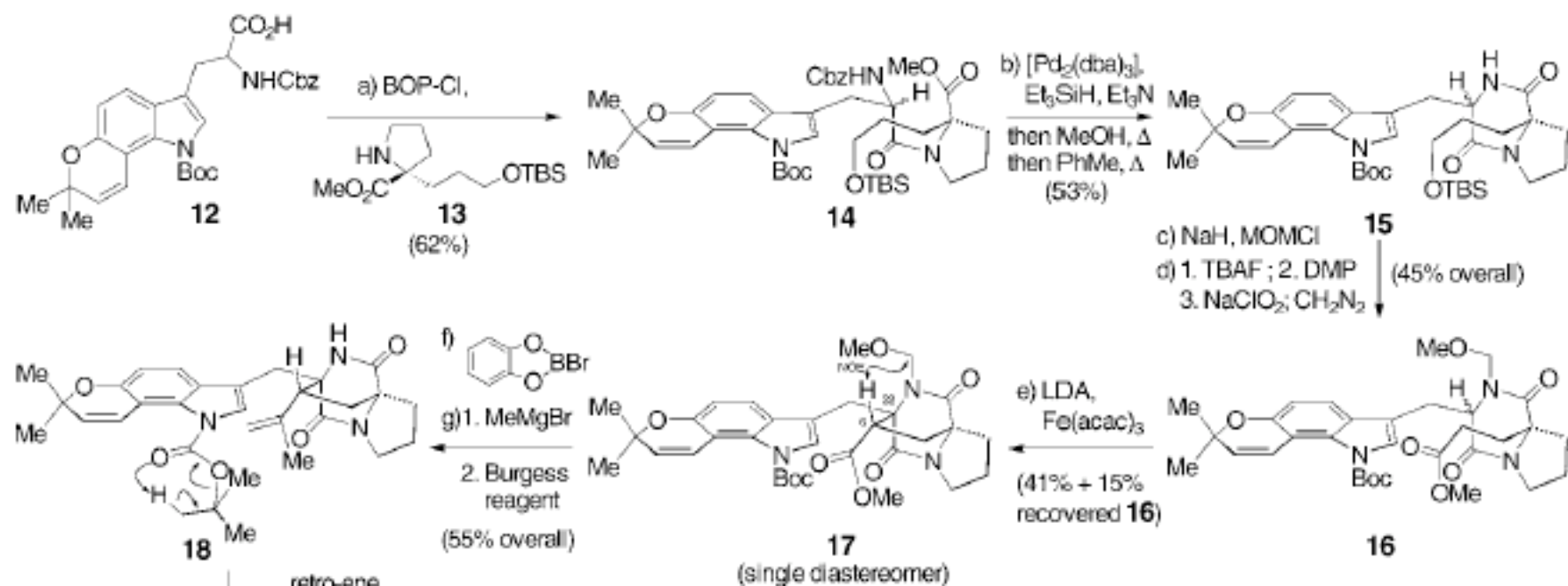


# Synthesis of Tryptophan Derivative 12 from Pyroglutamate



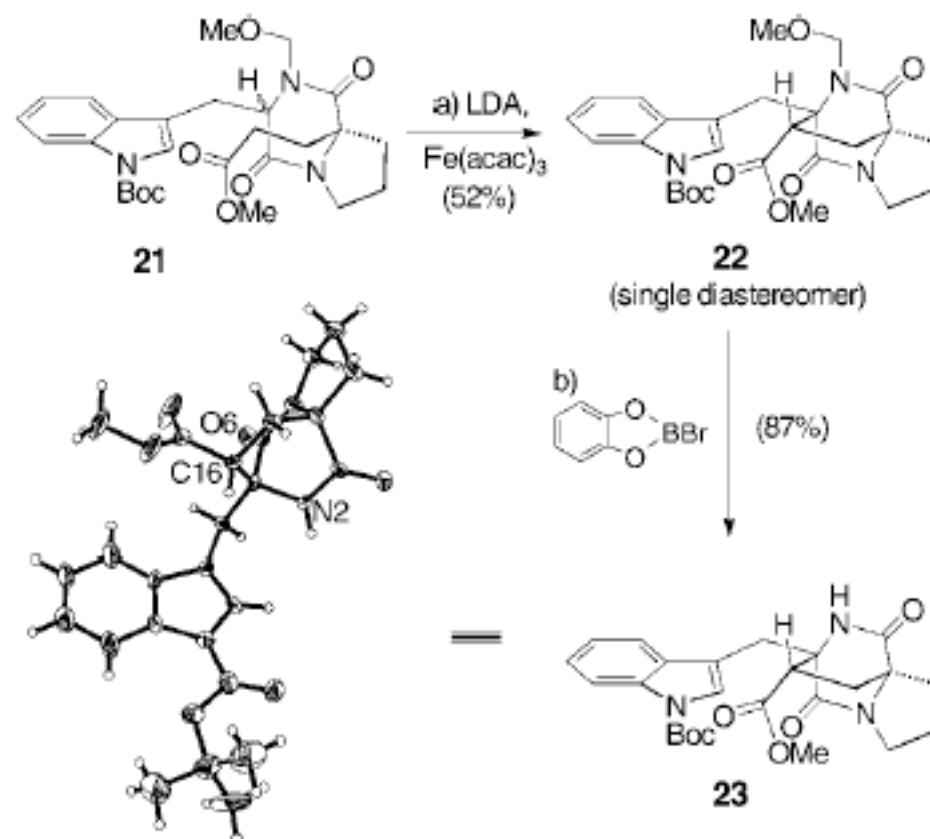


## The Journey Continues...



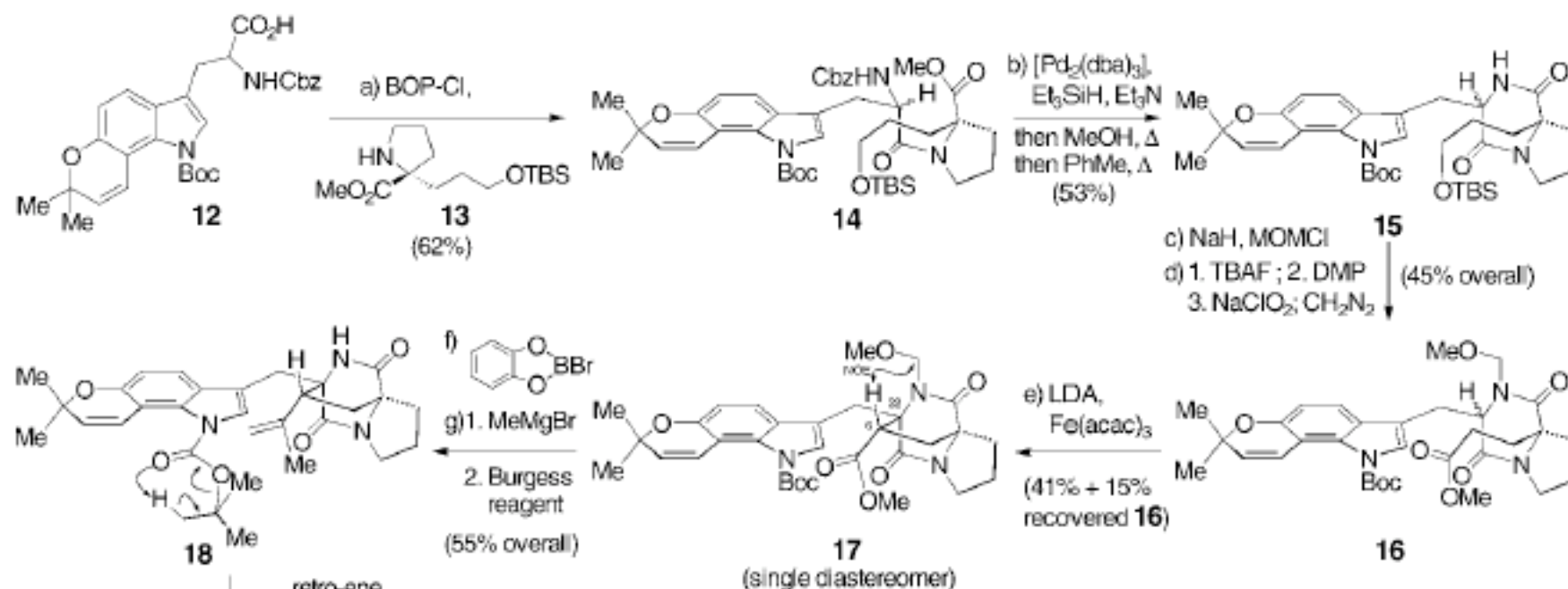
**Scheme 3.** Enantioselective total synthesis of stephacidin A (**1**). Reagents and conditions: a) **13** (1.5 equiv), BOPCl (1.1 equiv), *i*Pr<sub>2</sub>EtN (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0→25 °C, 10 h, 62%; b) [Pd<sub>2</sub>(dba)<sub>3</sub>] (0.2 equiv), Et<sub>3</sub>SiH (40 equiv), Et<sub>3</sub>N (2.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub>, 25 °C, 2 h; then 2-methyl-2-butene (20 equiv), NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O (3.0 equiv), NaClO<sub>2</sub> (2.8 equiv), THF, H<sub>2</sub>O, 20 min; then CH<sub>2</sub>N<sub>2</sub> in Et<sub>2</sub>O, MeOH, 5 min, 69% overall; e) LDA (2.2 equiv), THF, -78 °C, 5 min then [Fe(acac)<sub>3</sub>] (2.2 equiv), THF, -78→25 °C, 1 h, 41% **17** with 15% recovered **16**; f) *B*-bromocatecholborane (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 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-oxazolidinyl)phosphinic chloride; dba = *trans,trans*-dibenzylideneacetone; MOM = methoxymethyl; TBAF = tetra-*n*-butylammonium fluoride; DMP = Dess–Martin periodinane; LDA = lithium diisopropylamide; acac = acetylacetonate.

## Oxidative Coupling of the Model Ester



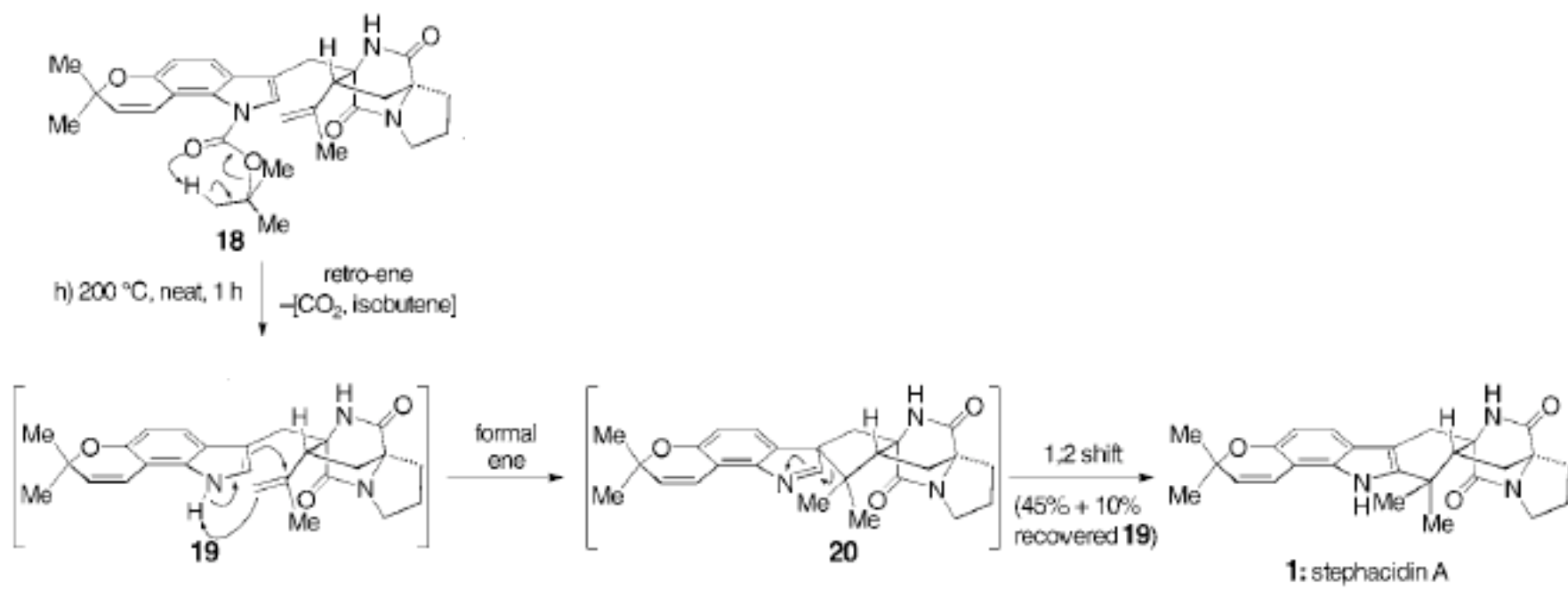
**Scheme 4.** Stereocontrolled intramolecular oxidative coupling of the model ester **21**. Reagents and conditions: a) LDA (2.5 equiv), THF,  $-78\text{ }^{\circ}\text{C}$ , 30 min then  $[\text{Fe}(\text{acac})_3]$  (2.5 equiv), THF,  $-78 \rightarrow 25\text{ }^{\circ}\text{C}$ , 1 h, 52% b) *B*-bromocatecholborane (2.0 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^{\circ}\text{C}$ , 1 h, 87%.

## The Journey Continues...



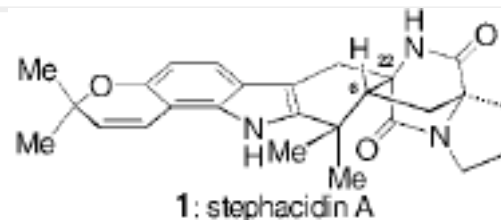
**Scheme 3.** Enantioselective total synthesis of stephacidin A (**1**). Reagents and conditions: a) **13** (1.5 equiv), BOPCl (1.1 equiv), *i*Pr<sub>2</sub>EtN (1.1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0→25 °C, 10 h, 62%; b) [Pd<sub>2</sub>(dba)<sub>3</sub>] (0.2 equiv), Et<sub>3</sub>SiH (40 equiv), Et<sub>3</sub>N (2.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub>, 25 °C, 2 h; then 2-methyl-2-butene (20 equiv), NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O (3.0 equiv), NaClO<sub>2</sub> (2.8 equiv), THF, H<sub>2</sub>O, 20 min; then CH<sub>2</sub>N<sub>2</sub> in Et<sub>2</sub>O, MeOH, 5 min, 69% overall; e) LDA (2.2 equiv), THF, -78 °C, 5 min then [Fe(acac)<sub>3</sub>] (2.2 equiv), THF, -78→25 °C, 1 h, 41% **17** with 15% recovered **16**; f) *B*-bromocatecholborane (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 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-oxazolidinyl)phosphinic chloride; dba = *trans,trans*-dibenzylideneacetone; MOM = methoxymethyl; TBAF = tetra-*n*-butylammonium fluoride; DMP = Dess–Martin periodinane; LDA = lithium diisopropylamide; acac = acetylacetonate.

## The Final Step

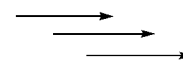


## Conclusions

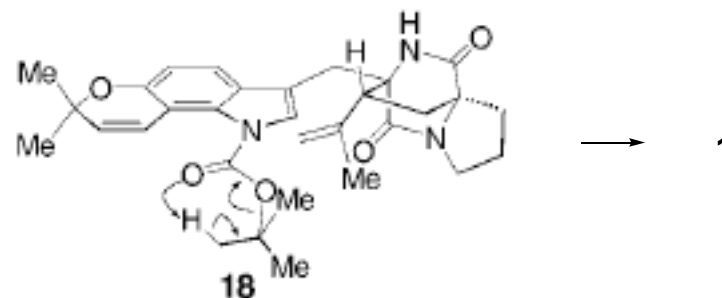
“ The first total synthesis of Stephacidin A was completed.



“ A general methodology for the rapid and practical synthesis of tryptophan derivative from pyroglutamate



“ A remarkable deprotection/annulation cascade which occurs simply with heat to forge the final ring (**18**→**1**),



◆ A simple, stereocontrolled assembly of two of the three stereocenters of **1** by a rare intramolecular oxidative coupling (**16** → **17** and **21** → **22**). This set of transformations proceeds cleanly and represents first such couplings of esters to amides.

