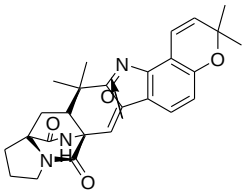
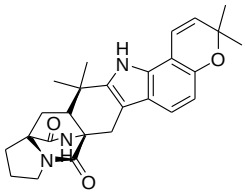
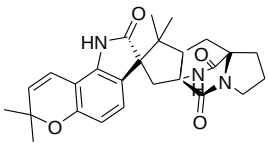
Concise, Asymmetric, Stereocontrolled Total Synthesis of Stephacidins A, B and Notoamide B



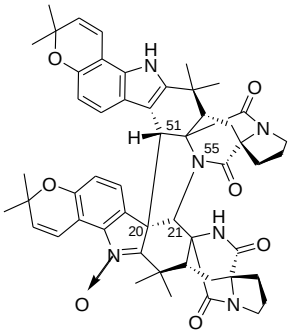
(+)-avrainvillamine



(-)-stephacidin A



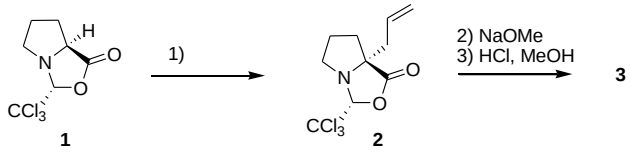
(+)-notoamide B



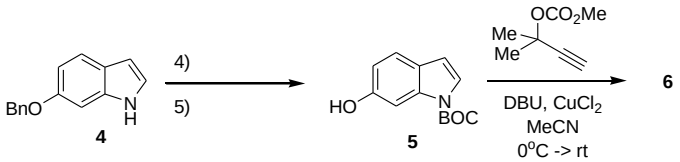
(-)-stephacidin B

In 2002, Bristol-Myers Squibb reported the biologically active metabolites isolated from a fermentation broth of *Aspergillius ochraceus*. The stephacidins A and B were identified as potent inhibitors of several human tumor cell lines with the complex alkaloid (-)-stephacidin B exhibiting a high cytotoxic potency against testosterone-dependent prostate LNCaP lymphoma. (+)-Avrainvillamide were in evidence, suggesting a simple dimerization-based biogenesis of (-)-stephacidin B if the bonds between C20-C51 and C21-N55 of 2 are broken. The Baran group reported the first total synthesis of stephacidin A 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 in 2005.

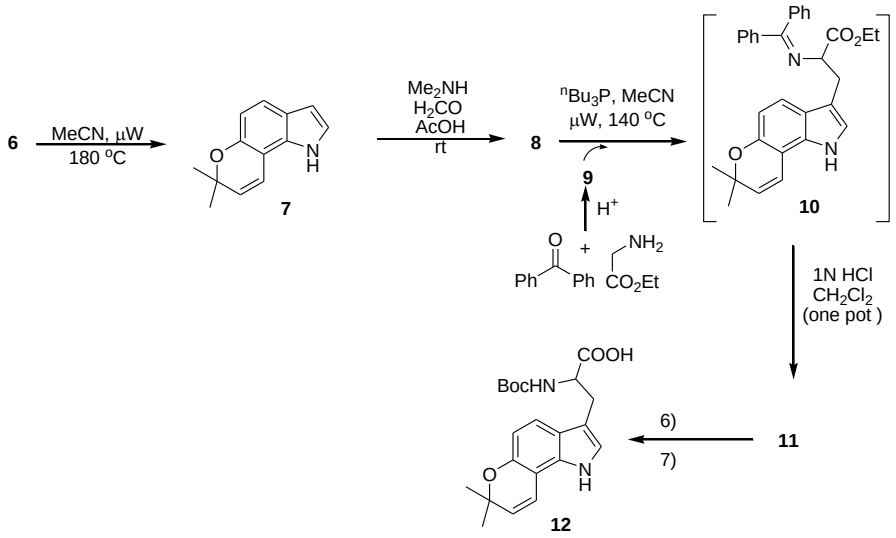
Fragment I & II:



1. Preparation of product **3** is a gram-scale process, please finish this process: What is the precursor/transformation might you use for the preparation of starting material **1**; and what kind of reagent/condition could be employed for the transformation of **1** to give **2**?



2. Please suggest the reagents for step 4 and 5.
3. Propose the structure of product **6**.



4. Please suggest the reaction mechanism for formation of product **7** and what is the name of this reaction called?
5. With **7** in hand, it is treated with Me_2NH and formaldehyde under acidic condition to furnish **8**. What is this conversion named? And what is the structure of **8**?
6. To form the intermediate 10, compound **8** was treated with **9** accelerated by microwave. What is **9**? And propose the reaction mechanism for the formation of intermediate **10**. [Hint: elimination followed by nucleophilic addition]
7. Intermediate **10** was subsequently treated with 1N HCl to give **11**, please finish the final steps from **11** to **12**.

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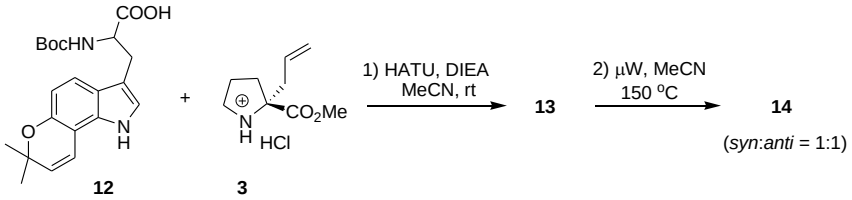
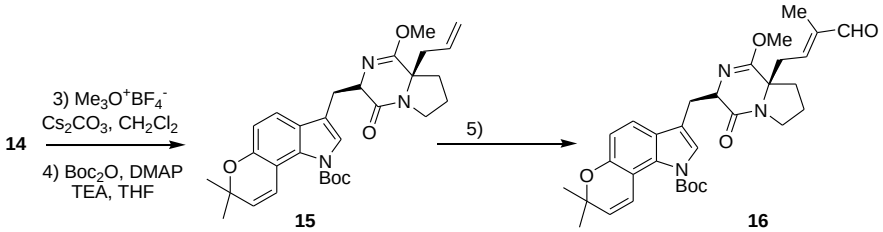
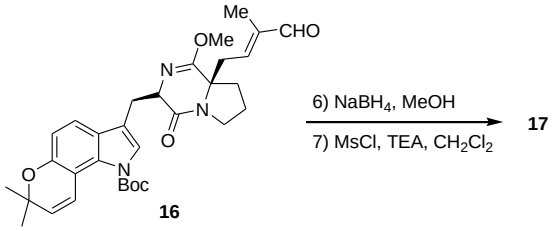
Combination of fragment I and II (3 & 12)



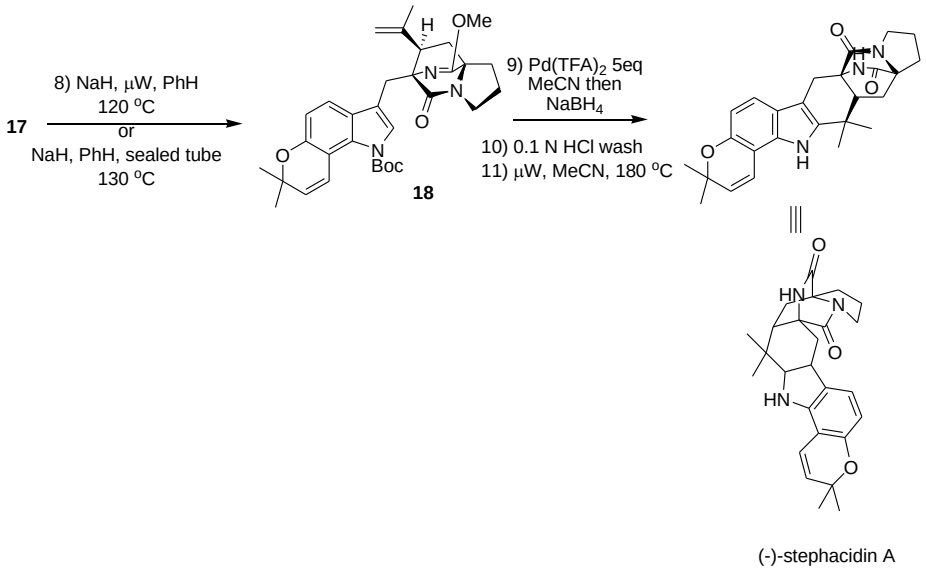
8. By combination fragment **12** and **3**, HATU and DIEA was employed to form compound **13**. What does HATU stand for and please draw the mechanism and product for this transformation.
9. Compound **13** was then subjected to microwave reaction condition at 150 ^{o} in MeCN to give compound **14**. What is the structure of **14** ? (Hint: μW assists cyclization reaction).



10. Protecting of **14** with lactim ether and Boc protection group in **15**, compound **14** was treated with $Me_3O^+BF_4^-$, please suggest reasonable mechanism for this reaction.
11. Please suggest reagents, catalysts or conditions to furnish aldehyde 16.

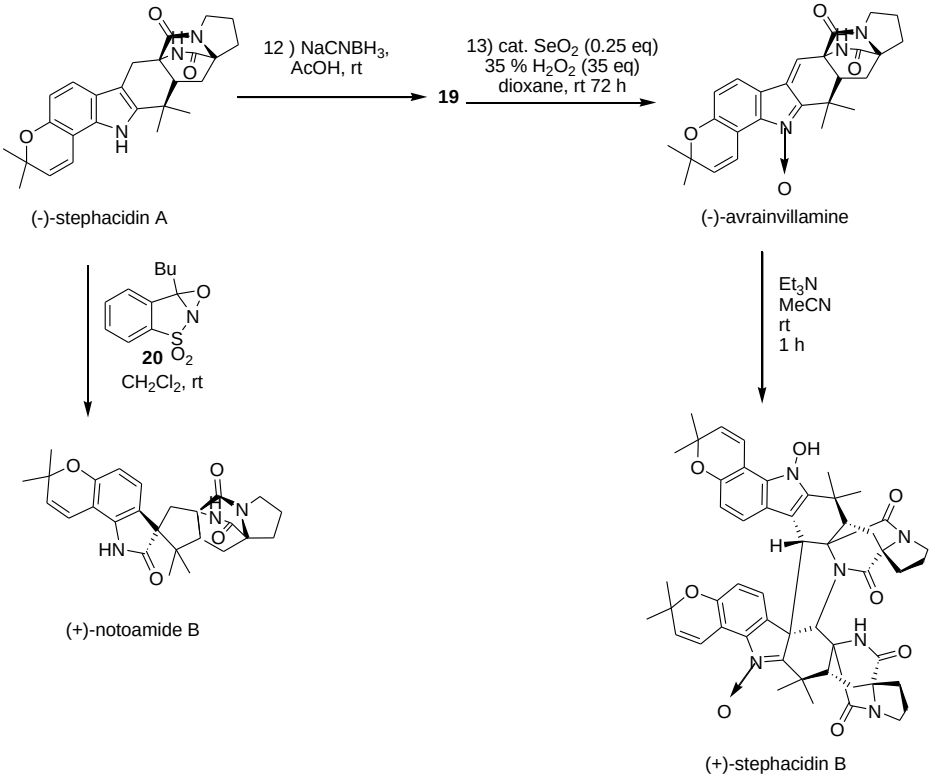


12. By treating aldehyde 16 with $NaBH_4$ followed by treating with MsCl, **17** was formed. What is the structure of compound **17**?



(-)-stephacidin A

13. [2,2,2]-Bicyclic system on **18** was established by treating **17** with NaH under microwave condition. What is the reaction mechanism?
14. To finish one of the natural product (-)-stephacidin A, compound **18** was treated with 5 eq of $Pd(TFA)_2$ in MeCN to give a palladium intermediate. What's the structure of the pd-intermediate you will expect to? Please specify the regioselectivity. After reduced the pd-intermediate by $NaBH_4$, followed by acidic wash (0.1 N HCl) and then heating at 180 °C, (-)-stephacidin A was formed as an amorphous white powder.



(-)-stephacidin A

(-)-avrainvillamine

(+)-notoamide B

(+)-stephacidin B

15. (+)-Notoamide B was synthesised by treating (-)-stephacidin A with oxaziridine **20** in CH_2Cl_2 at rt. Please draw the reaction mechanism for this reaction.
16. On the other hand, reduction of (-)-stephacidin A with $NaCNBH_3$ under AcOH condition gave compound **19** followed by oxidation under cat. SeO_2/H_2O_2 system to afford a precursor (-)-avrainvillamide. What is the intermediate **19** and please suggest the mechanism of cat. SeO_2/H_2O_2 oxidation.
17. Please suggest a reasonable electron flow for the final dimerisation process to affoed (+)-stephacidin B.