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Concise Enantioselective Synthesis of ent-Malbrancheamide B

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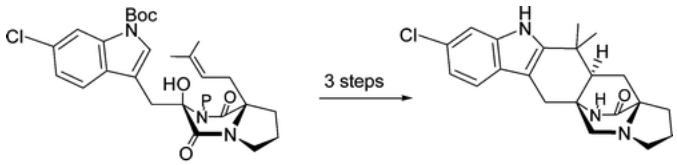
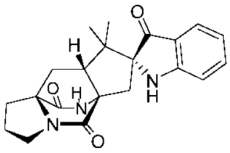
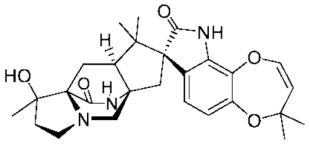


ent-malbrancheamide B

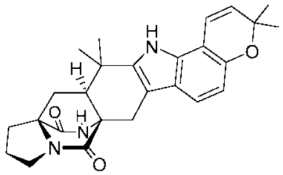
The bicyclo[2.2.2]diazaoctane core



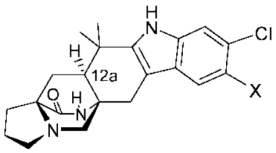
1 brevianamide B



2 paraherquamide A



3 stephacidin A



4 malbrancheamide X = Cl
5 malbrancheamide B X = H

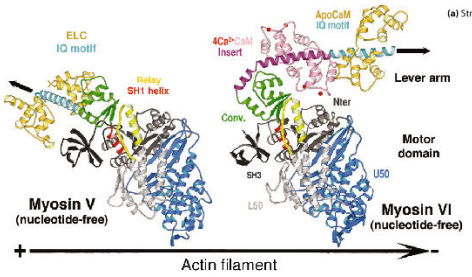
Malbrancheamide **4** is a calmodulin (CaM) inhibitor.

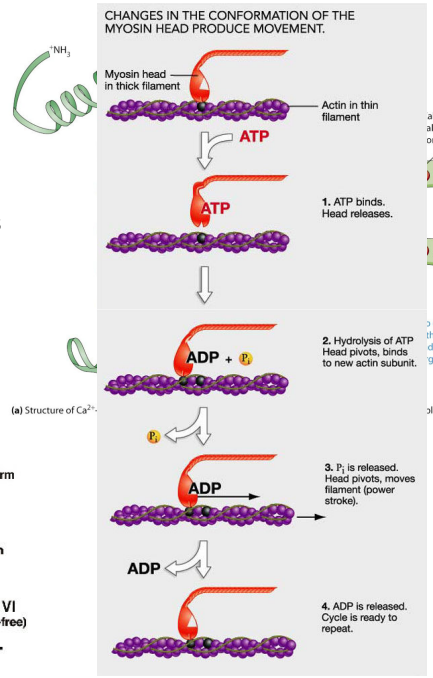
Miller, K. A.; Figueroa, M.; Valente, M. W. N.; Greshock, T. J.; Mata, R.; Williams, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6479-6481.

Calmodulin (CaM)

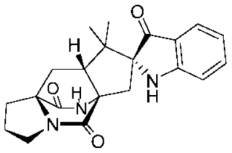
Calmodulin (CALcium MODULated proteIN) is a calcium-binding protein expressed in **all** eukaryotic cells.

In humans, CaM mediates processes such as inflammation, metabolism, apoptosis, muscle contraction, intracellular movement, short-term and long-term memory, nerve growth and the immune response.

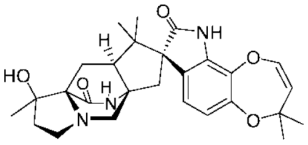




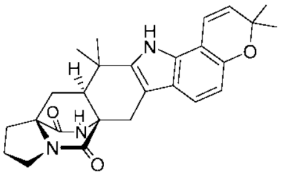
The bicyclo[2.2.2]diazaoctane core



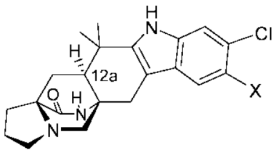
1 brevianamide B



2 paraherquamide A



3 stephacidin A



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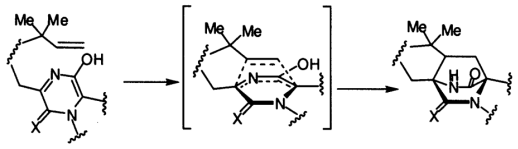
Proposed Biosynthesis

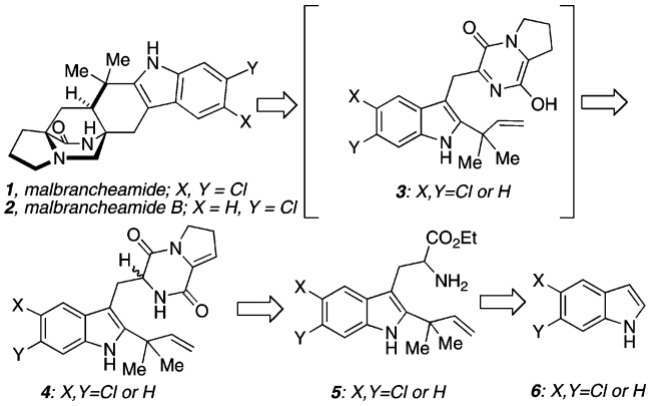


Cox, R. J.; Williams, R. M. *Acc. Chem. Res.* **2003**, *36*, 127-139.

The synthesis and biosynthesis of this compounds have been probed for many years by the Williams group.

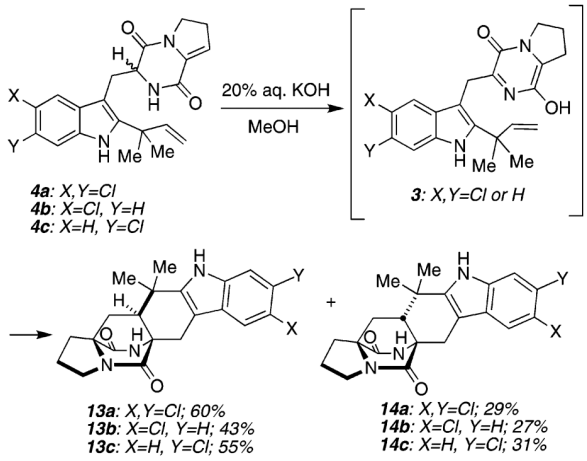
Several members of the family have been synthezised biomimetically using an intramolecular Diels-Alder strategy .

Synthesis of Malbrancheamides by Williams



Miller, K. A., Welch, T. R., Greshock, T. J., Ding, Y., Sherman, D. H., and Williams, R. M. *J. Org. Chem.* **2008**, *73*, 3116-3118.

Synthesis of Malbrancheamides by Williams



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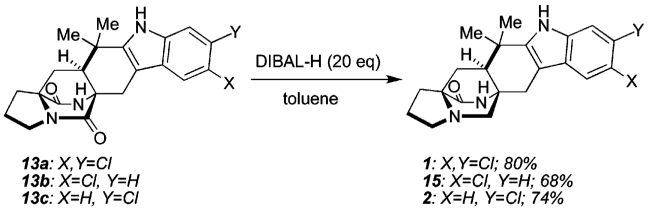

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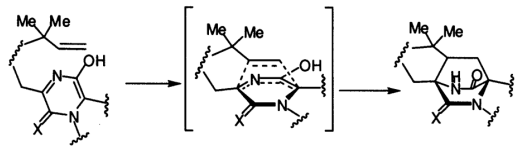
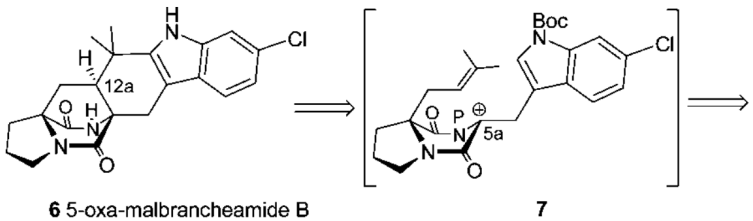
Proposed Biosynthesis



Cox, R. J.; Williams, R. M. *Acc. Chem. Res.* **2003**, *36*, 127-139.

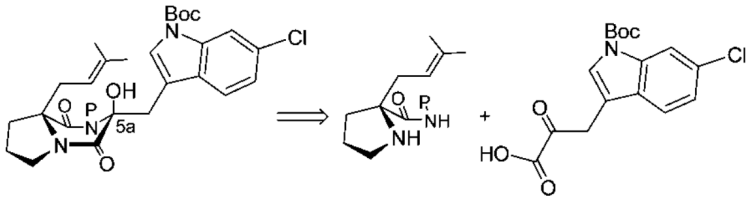
The problem:
There is no evidence for a "Diels-Alderase" involved in the process.

Retrosynthetic plan



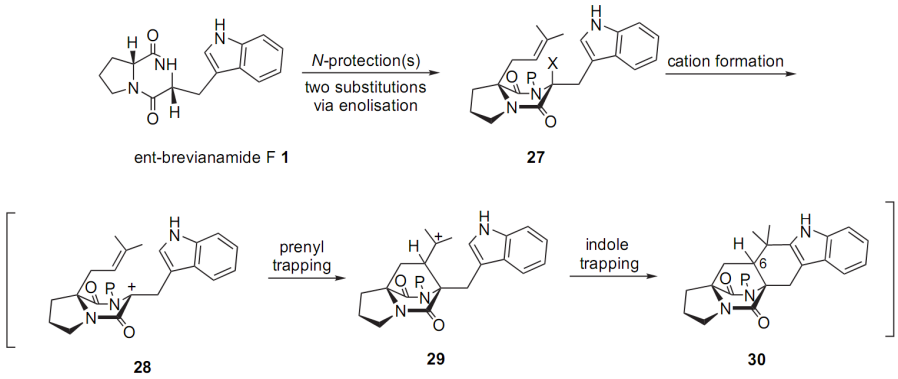
6 5-oxa-malbrancheamide B

7



8 **9** **10**

Will this work?

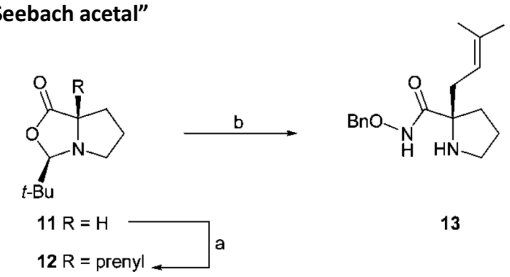


Scheme 6. Planned cationic cascade route to complex bridged DKPs.

Pichowicz, M., Simpkins, N. S., Blake, A. J., and Wilson, C. *Tetrahedron* **2008**, *64*, 3713

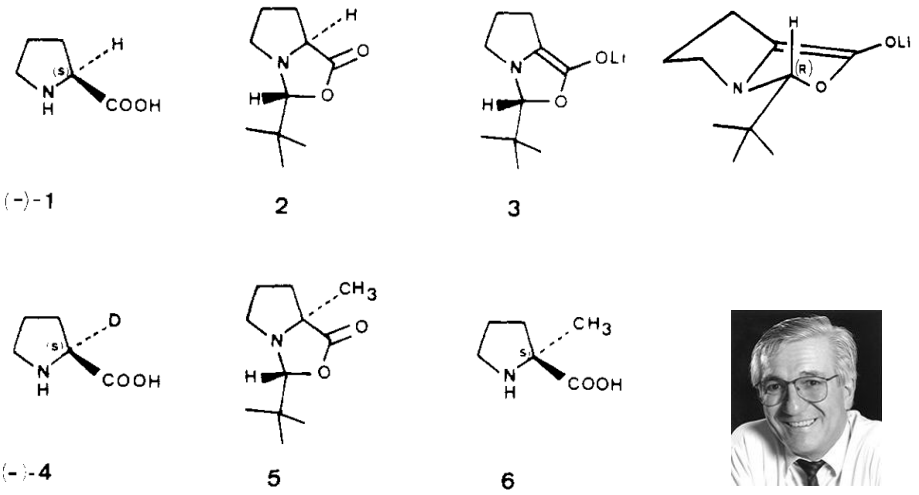
Synthesis of hydroxamic acid derivative 13a

"Seebach acetal"



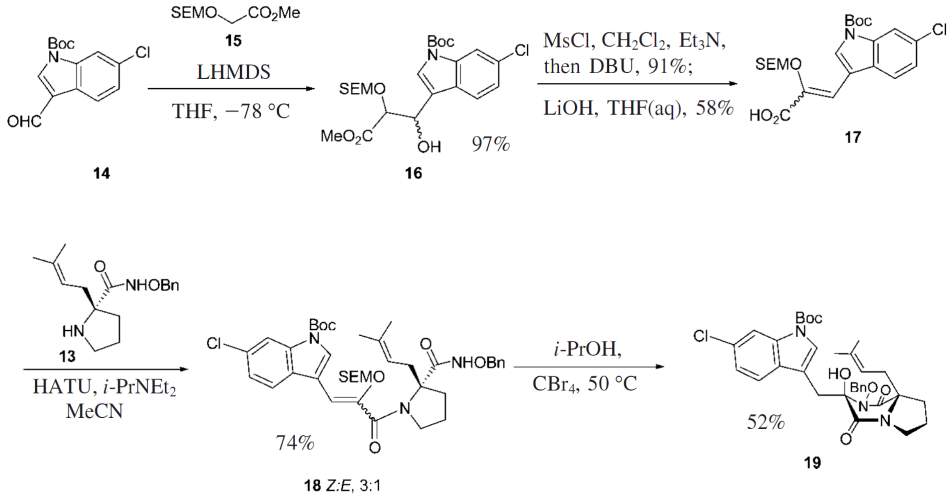
[a] Reagents and conditions: (a) LDA, THF, −78 °C, prenyl bromide, 76%; (b) $BnONH_2$, *n*-BuLi, THF, −78 °C, 75%.

Self reproduction of chirality



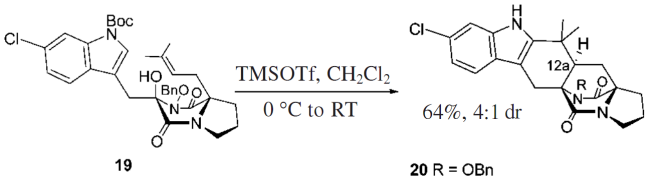
Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B., *J. Am. Chem. Soc.* **1983**, *105*, 5390-5398.

Amide formation and DKP synthesis



Chen, M.-Y., and Lee, A. S.-Y. *J. Org. Chem.* **2002**, *67*, 1384.

Completion of the synthesis



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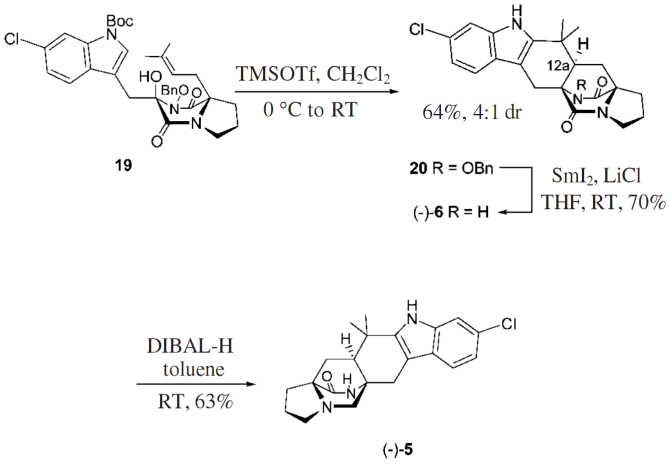

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