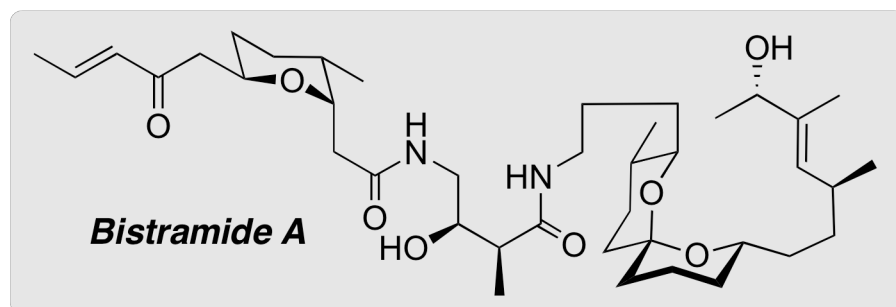


Total Synthesis & Structure Elucidation of Bistramide

P. Wipf - Chem 2320 - Journal Club

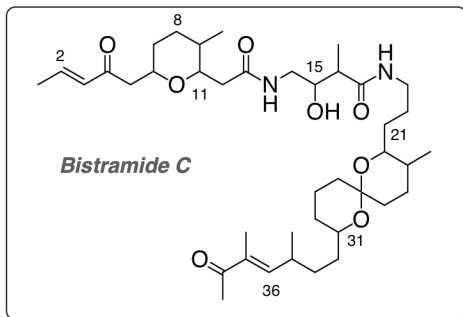
Lowe, Jason T.; Wrona, Iwona E.; Panek, James S. **Total Synthesis of Bistramide A**. Organic Letters ACS ASAP.



1. Introduction
2. Structure Elucidation
3. Panek Group Synthesis
4. Conclusions

This topic was selected to highlight allylic silane chemistry and to introduce modern multi-step natural product target synthesis.

Total Synthesis of (+)-Bistramide C



from *Lissoclinum bistratum* Sluiter,
a marine ascidian from New Caledonia

Gouiffes, D.; Moreau, S.; Helbecque, N.; Bernier, J. L.; Henichart, J. P.; Barbin, Y.; Laurent, D.; Verbist, J. F. *Tetrahedron* **1988**, *44*, 451.

cf. Bistratenes A&B,
from *Lissoclinum bistratum*,
a marine ascidian from Heron Island

Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.

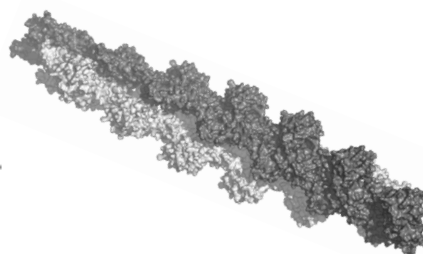
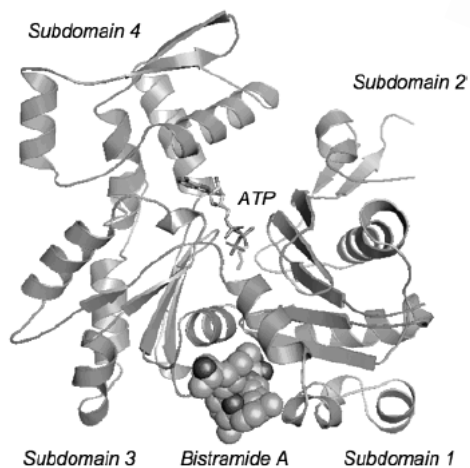
- IC₅₀ of 0.03-0.32 µg/mL for P388/dox, B16, HT29 and NSCLC-N6 cell lines
- G1 phase arrest
- G2/M arrest in HL60 cells

- 10 stereocenters - 1024 possible stereoisomers!
- 3 rings
- unique γ-amino β-hydroxy acid core segment

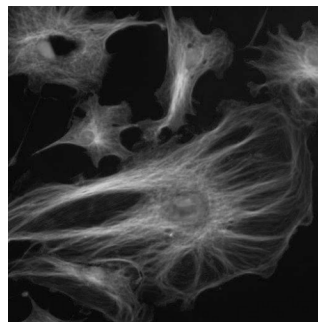
Synthetic work:

- Wipf, P.; Uto, Y.; Yoshimura, S. *Chem. Eur. J.* **2002**, *8*, 1670.
- Statsuk, A. V.; Liu, D.; Kozmin, S. A. *JACS* **2004**, *126*, 9546.
- Wipf, P.; Hopkins, T. D. *Chem. Commun.* **2005**, 3421.
- Crimmins, M. T.; Debaillie, A. C. *JACS* **2006**, *128*, 4936.

Bistramide binds to Actin



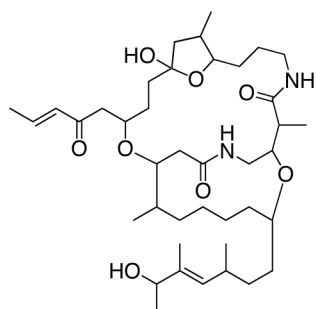
The eukaryotic cytoskeleton. Actin filaments are shown in red, microtubules in green, and the nuclei are in blue.



Rizvi, S. A.; Tereshko, V.; Kossiakoff, A. A.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 3882-3883.

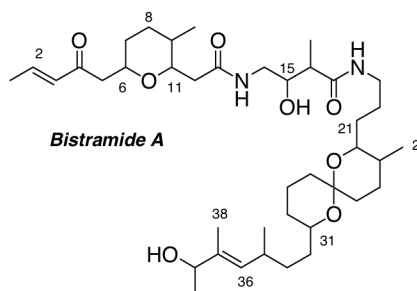
Bistramides - A Structural Puzzle

Originally Proposed Structure



Gouiffes, D. *Tetrahedron* **1988**, 44, 451

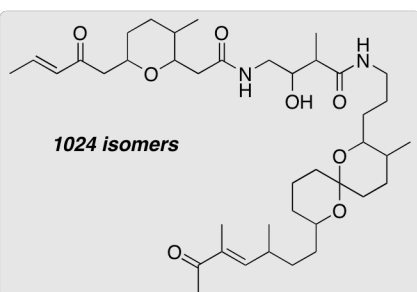
Revised Structure



Ireland, C. M. *J. Am. Chem. Soc.* **1992**, 114, 1110

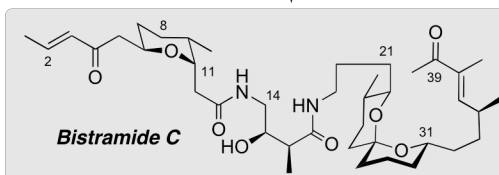
⇒ 2048 configurational isomers!

Systematic Assignment of the Configuration of Flexible Natural Products by Spectroscopic & Computational Methods



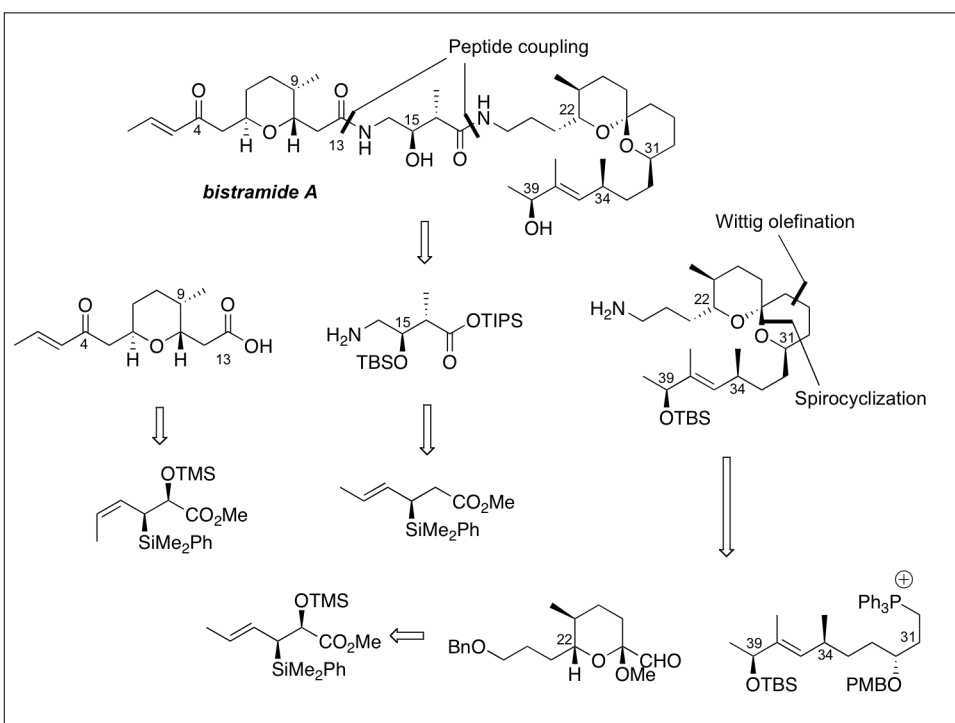
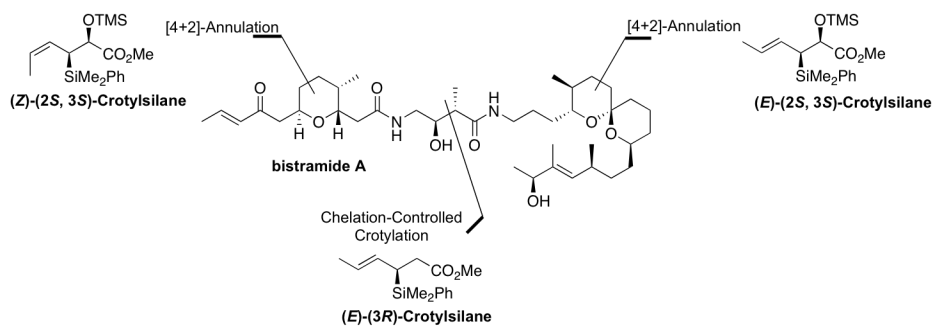
NMR → 16 isomers → $[\alpha]_D$ → 3 isomers

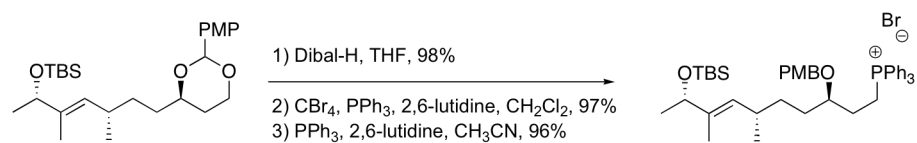
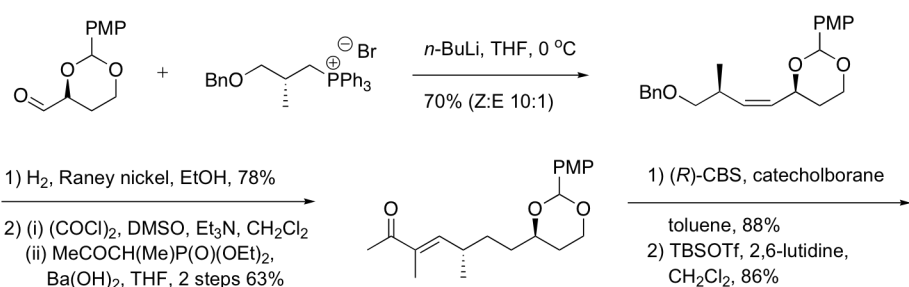
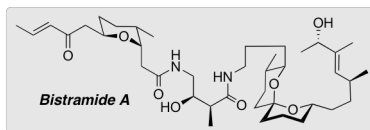
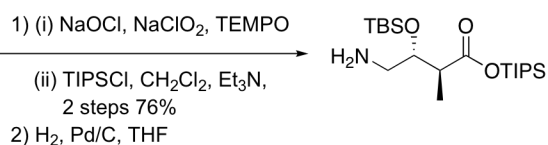
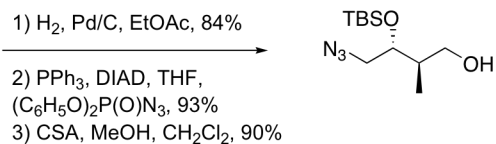
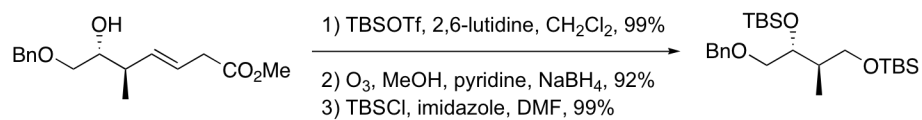
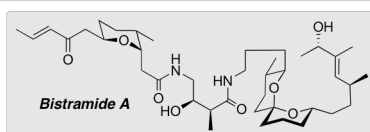
CD

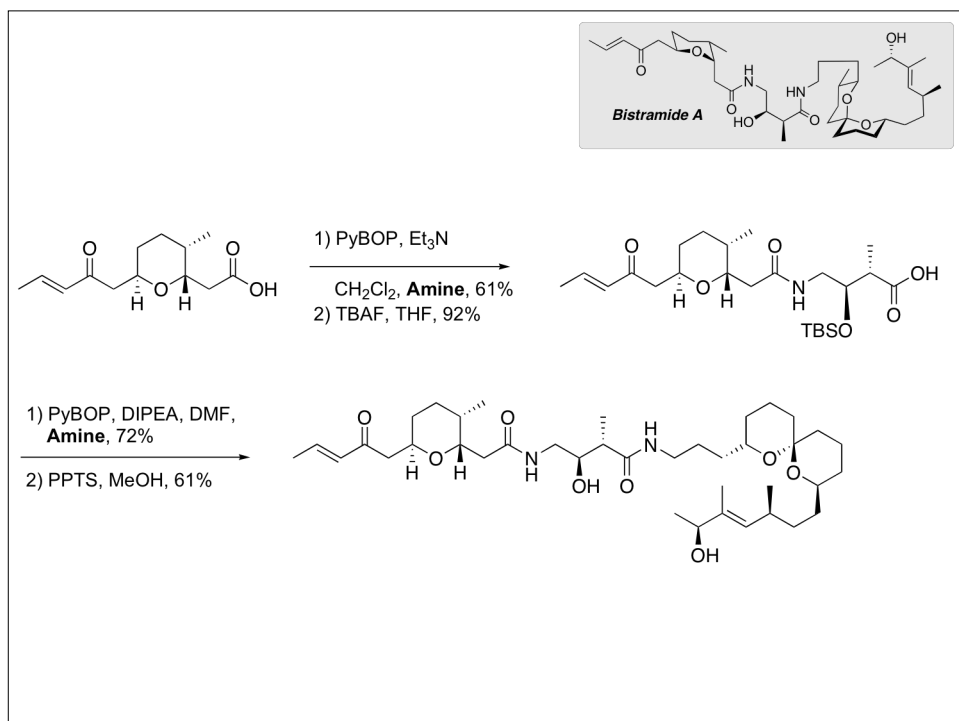
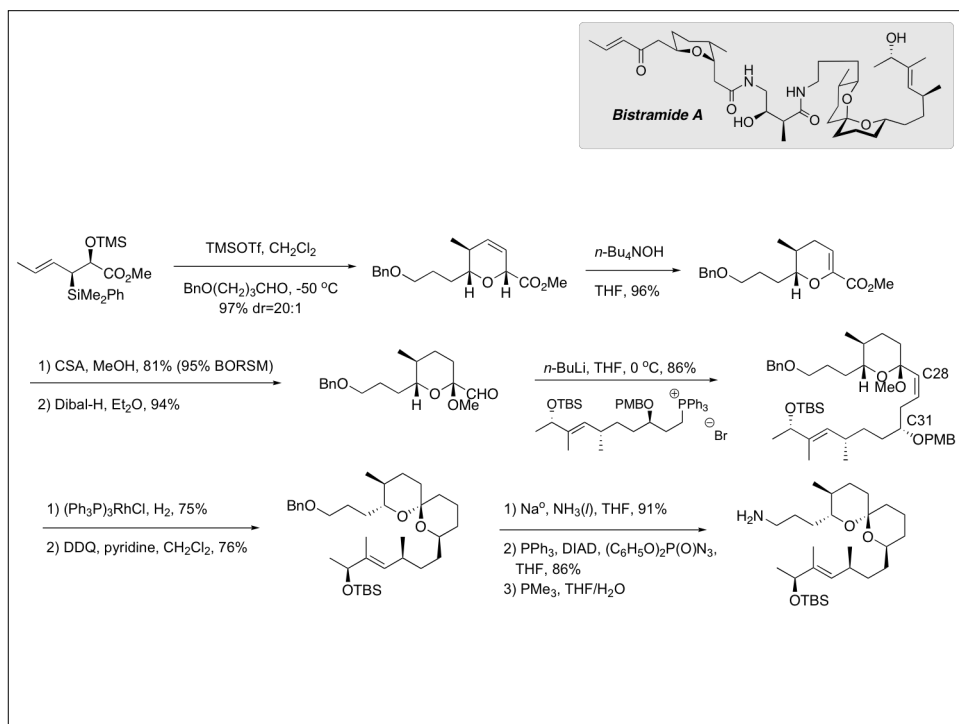


Zuber, G.; Goldsmith, M.-R.; Hopkins, T. D.; Beratan, D. N.; Wipf, P., "Systematic Assignment of the Configuration of Flexible Natural Products by Spectroscopic and Computational Methods: The Bistramide C Analysis." *Org. Lett.* **2005**, 7, 5269-5272.

Lowe, Jason T.; Wrona, Iwona E.; Panek, James S. **Total Synthesis of Bistramide A.** Organic Letters ACS ASAP.







Conclusions:

- Synthesis is convergent (3 fragments)
- Novelty lies in the preparation of the fragments
- 3 Organosilanes are used to construct 8 of 11 stereogenic carbons
- Segment selection and condensation strategy isprecedented