Total Synthesis of the Neotropical Poison-Frog Alkaloid (-)-205B

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Organic Letters **2005**, ASAP.

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Current Literature
June 25, 2005

Dendrobates Pumilio
(Strawberry Poison Dart Frog)

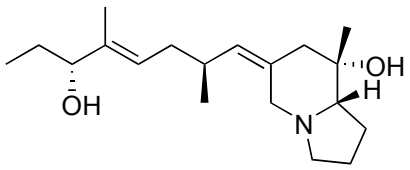
Outline

- Natural Products from *Dendrobates Pumilio*
- Multi-Component Linchpin Methodology
- *The Current Literature*
  - 3-Component Linchpin Strategy
  - Total Synthesis
- Summary and Future Work

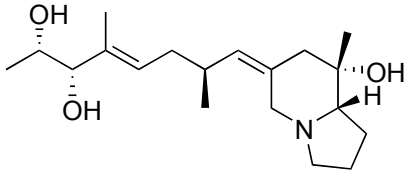
Poison-Frog Alkaloids

Daly, J.W. et al. *Tetrahedron* **1987**, *43*, 643.

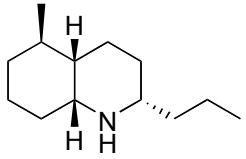
- Leading provider of compounds from poison-frogs' skins
  - Daly laboratory at the NIH
- Code system implemented in 1978
  - Designated by molecular weight with letters to identify isomers
- 500+ compounds isolated - "dendrobatid alkaloids"
  - Steroidal batrachotoxins
  - Histrionicotoxins
  - Gephyrotoxins
  - Pumiliotoxins
- Pumiliotoxins A-C originate from a Panamaniam poison frog, *Dendrobates pumilio*



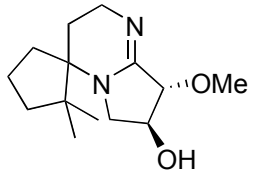
Pumiliotoxin A (307A')



Pumiliotoxin B (323A)



Pumiliotoxin C (195A)



Amidine 252

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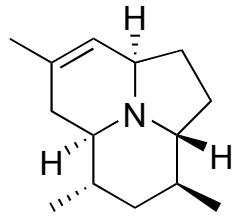
1 Out of the 500+

Alkaloid (-)-205B



(-)-205B

- Provisionally reported in 1987 (diastereomer)
- Assigned in 1998 (Daly et al.) by extensive FTIR, NMR, and HRMS studies in conjunction with molecular modeling
- First synthesis of (+)-antipode by Toyooka et al.[1]

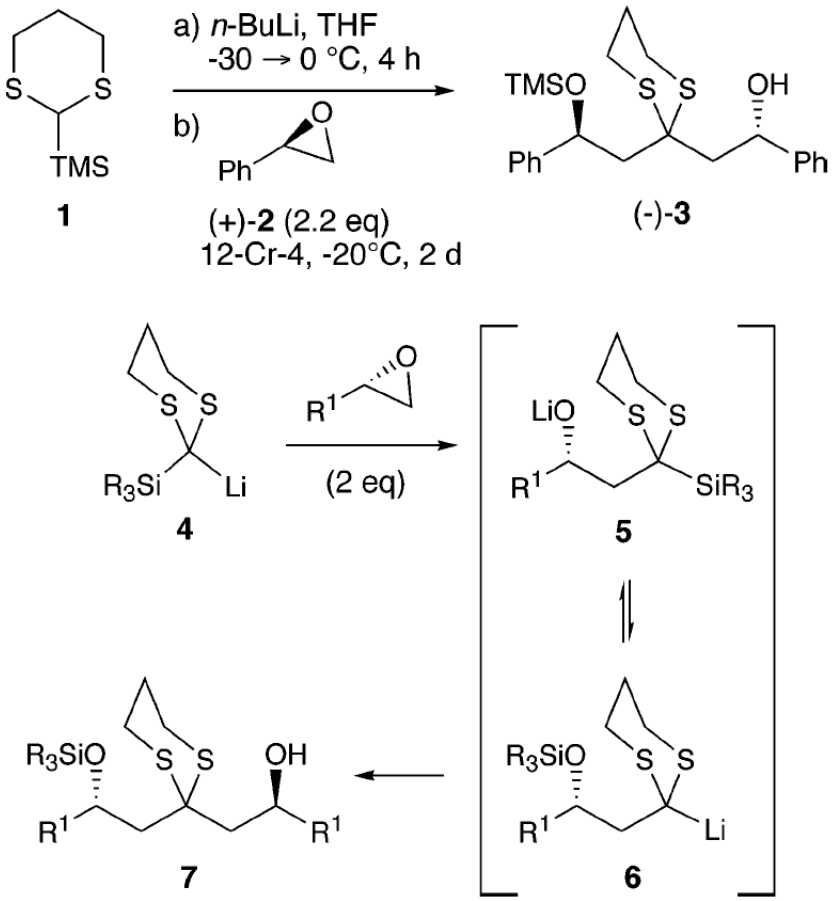
(+)-205B

- (+)-Antipode selectively blocked the α7 nicotinic receptor[2]
- Naturally occurring (-)-enantiomer
  - No previous reported synthesis or biological activity

[1]Toyooka, N. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 3808.
[2]Tsuneki, H. et al. *Mol. Pharmacol.* **2004**, *66*, 1061.

3-Component Linchpin Background

- Tietze (1994) - Tandem bisalkylation of TMS-dithiane[1]
- Presumed 1,4-Brook rearrangement
- 48 h reaction times
- Single electrophile only
- Limited synthetic utility

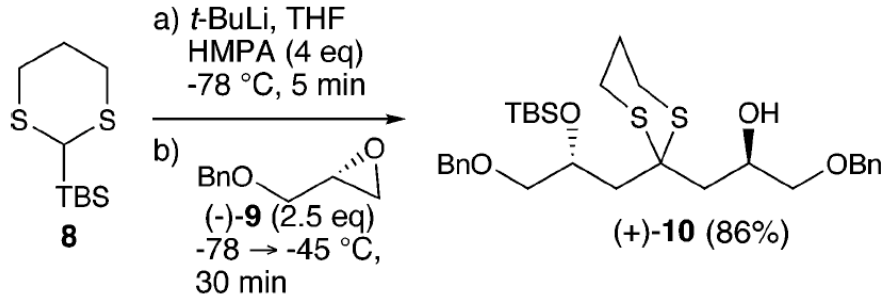


[1]Tietze, L. et al. *Synlett* **1994**, 511.

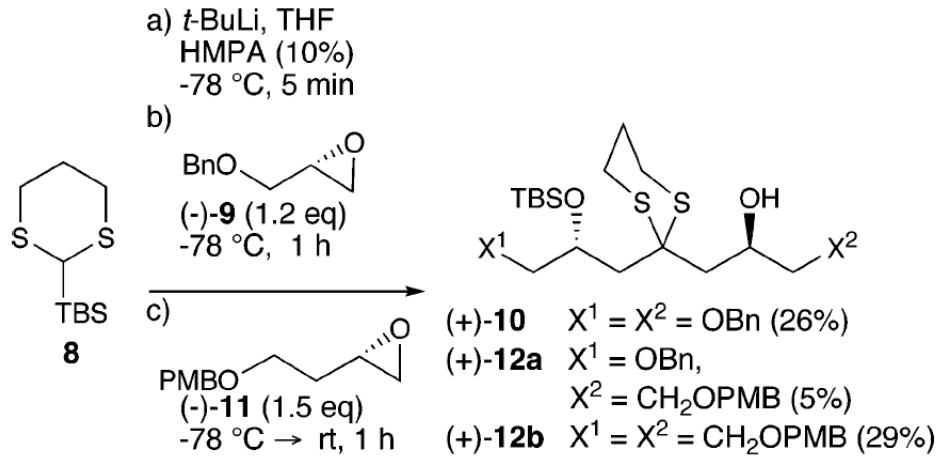
3-Component Linchpin Methodology

Smith, A. et al. *J. Am. Chem. Soc.* **2003**, *125*, 14435.

- Initial contributions from Smith's group:



- Sequential addition of 2 electrophiles failed:



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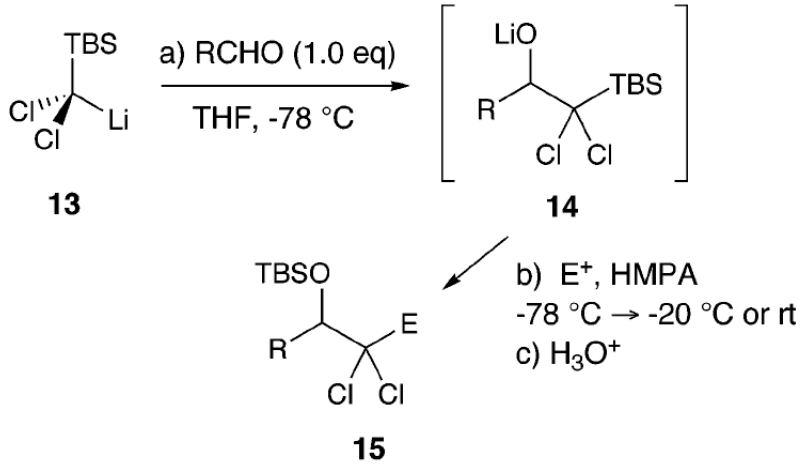
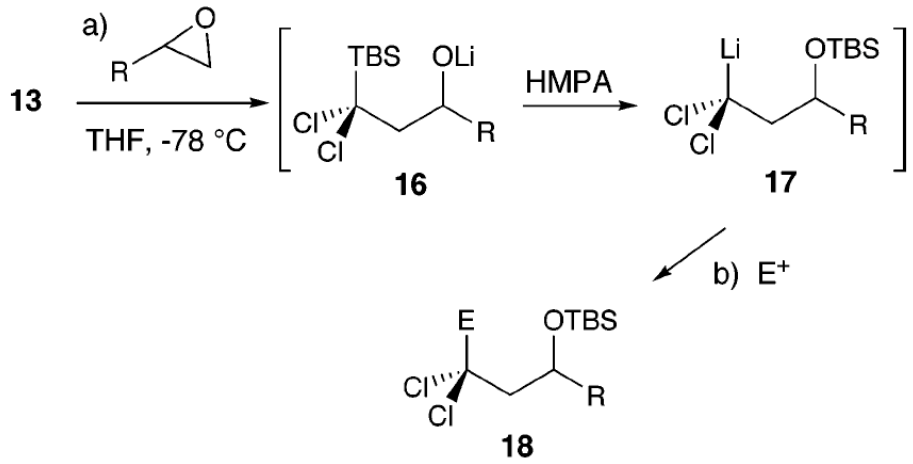
A Solvent Effect

Utimoto, K. et al. *Tetrahedron* **1996**, *52*, 503.

- HMPA induces Brook rearrangement





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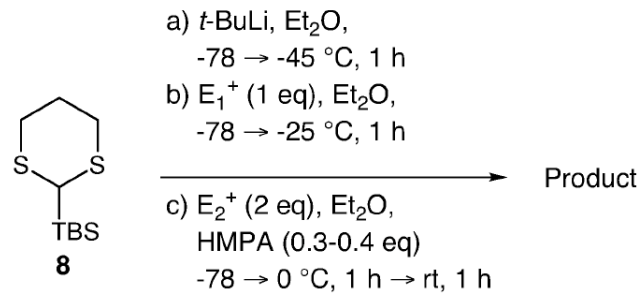
Smith's Methodology Revised

Smith, A. et al. *J. Am. Chem. Soc.* **1997**, *119*, 6925.

✧ Successful 3-component coupling strategy:



Entry	E_1^+	E_2^+	Product	Yield (%)
1	BnO, O — (-)-**9**	O, OTBS — (-)-**24**	TBSO, S, S, OH, BnO, OTBS — (+)-**25**	56
4	BnO, O — (-)-**9**	O, Cl — (-)-**30**	TBSO, S, S, BnO, O — (+)-**31**	60[a]

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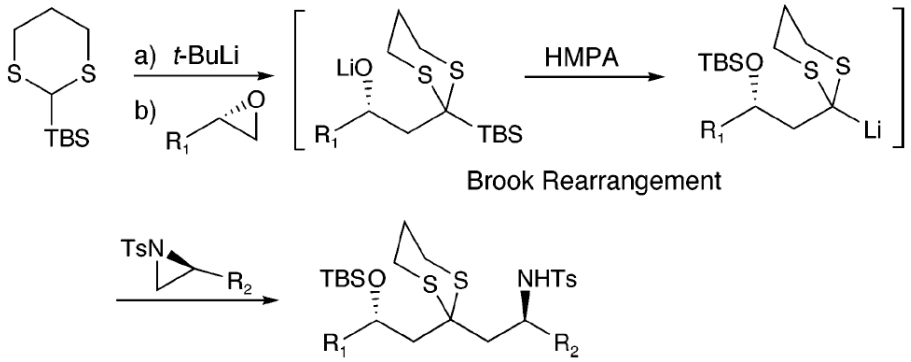
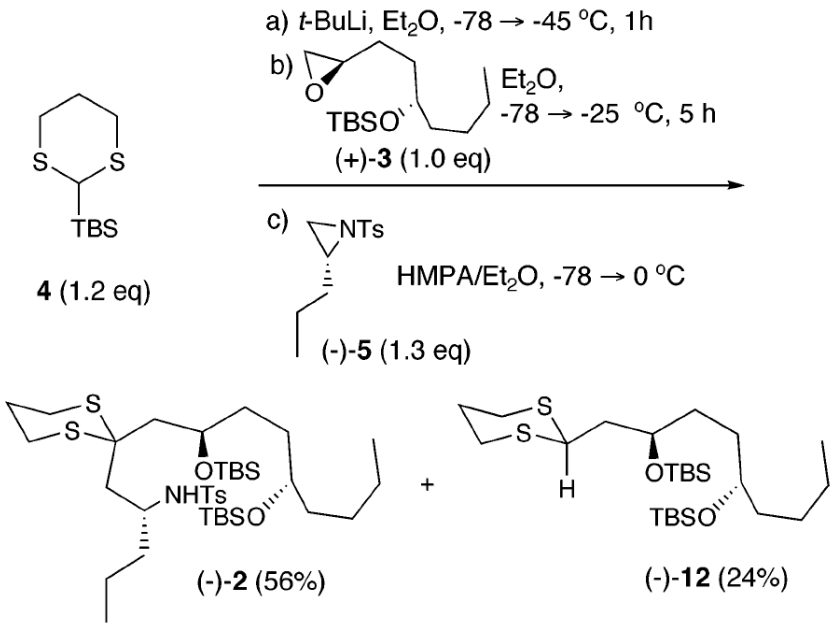
Scope: Aziridines?

Smith, A. et al. *Org. Lett.* **2004**, *6*, 1493.





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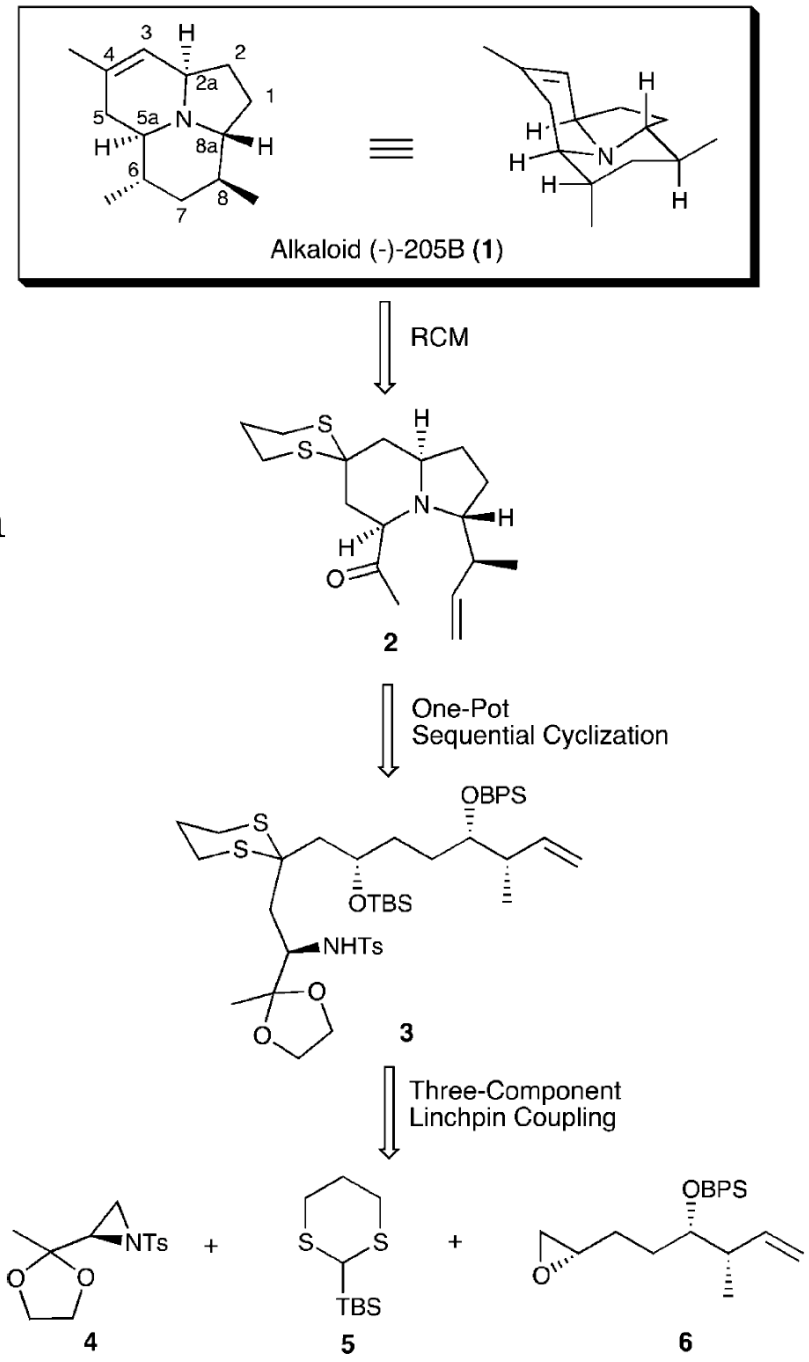
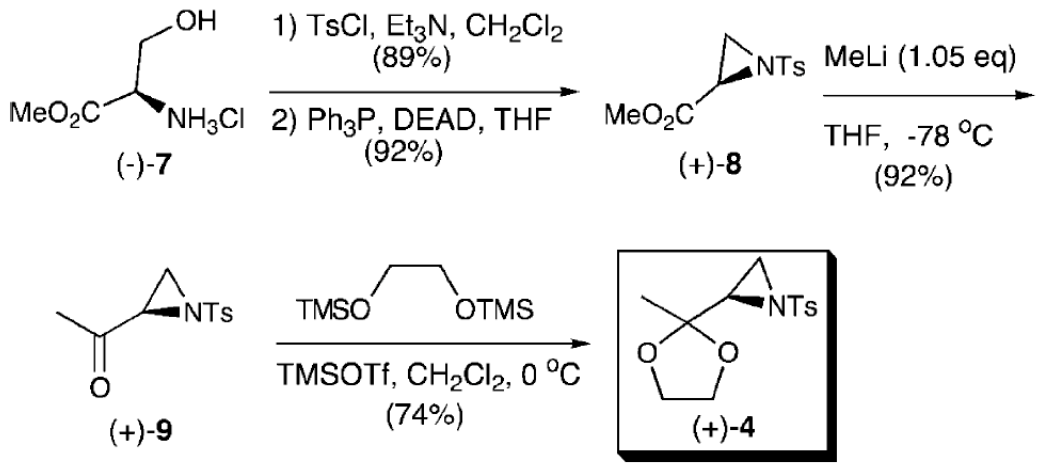
Current Literature

- Retrosynthesis
  - Linchpin coupling
  - One-pot bicycle formation



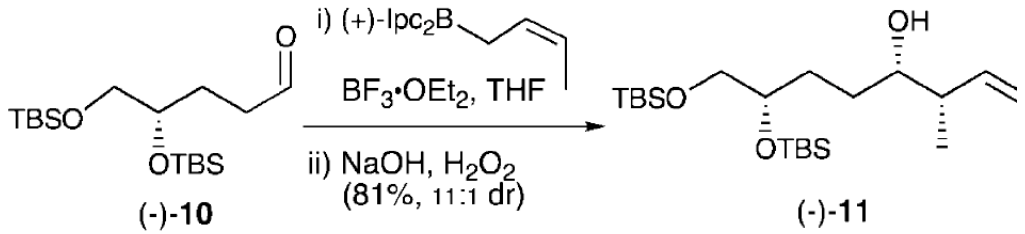
Component Synthesis

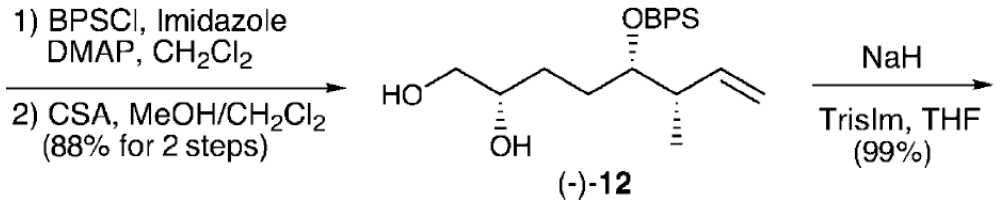
- Route to the aziridine coupling partner

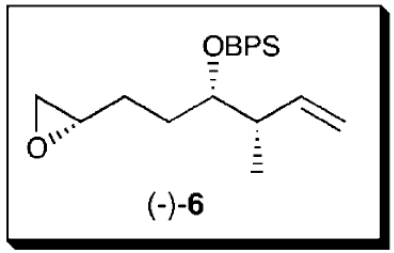


Component Synthesis

- Accessing the first electrophile
  - One-pot Fraser-Reid epoxide protocol







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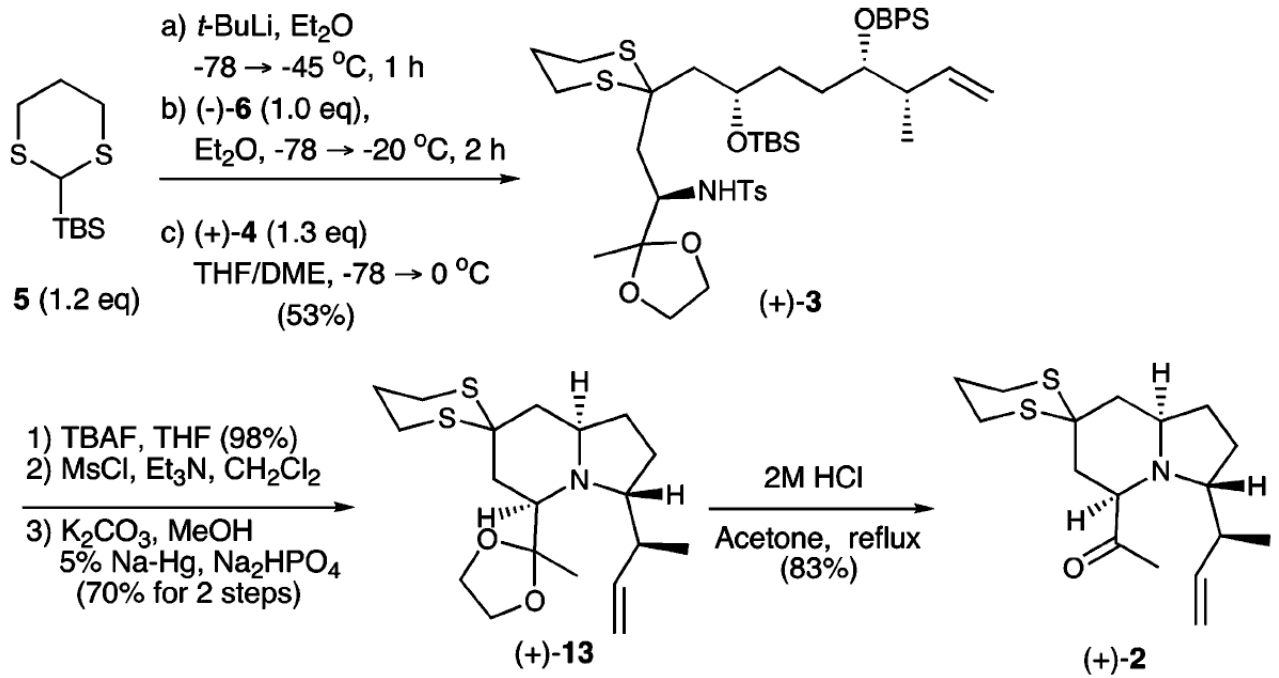
Key Steps - Coupling & Cyclization

- Note use of DME, not HMPA to trigger Brook rearrangement



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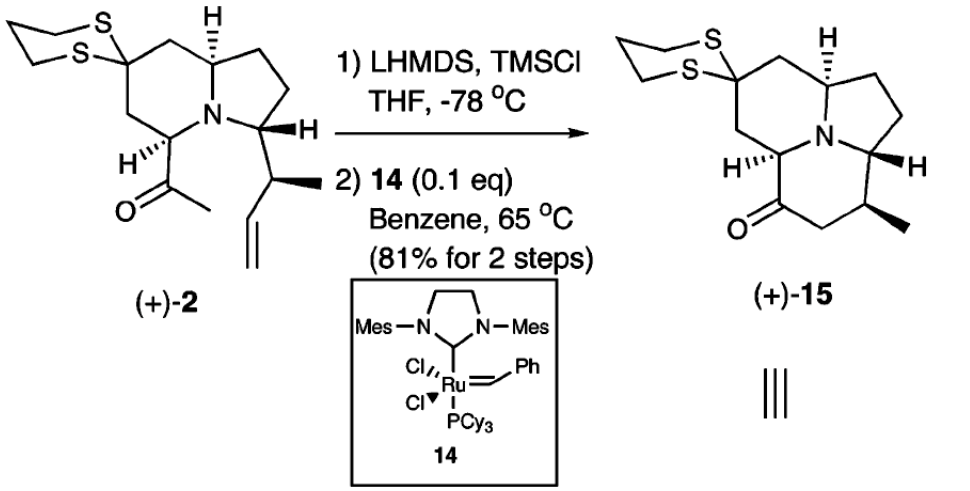
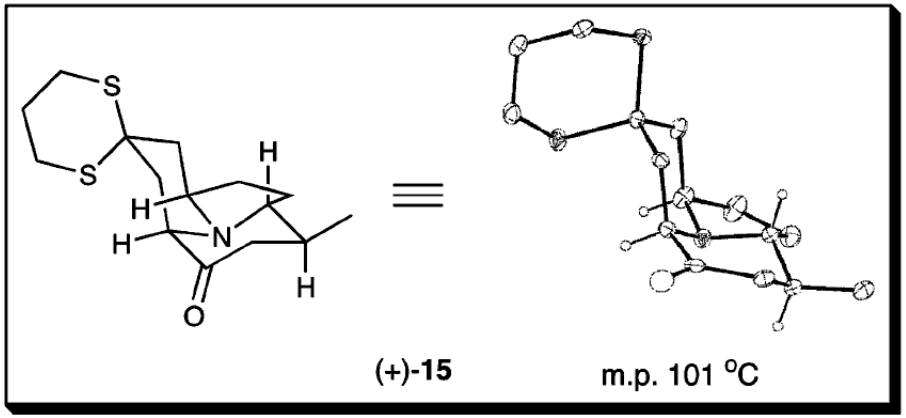
Tricycle Formation





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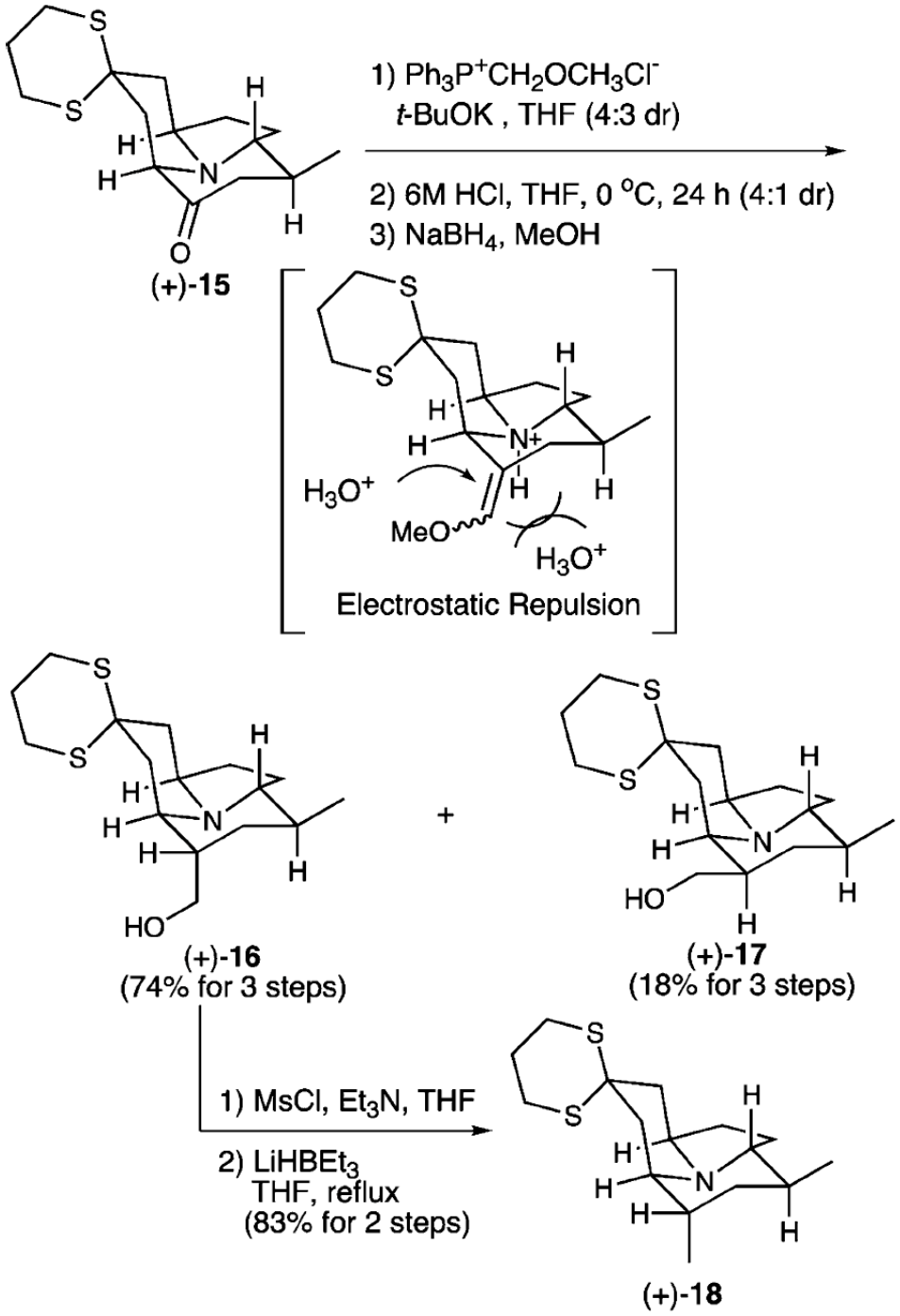
Final Stages



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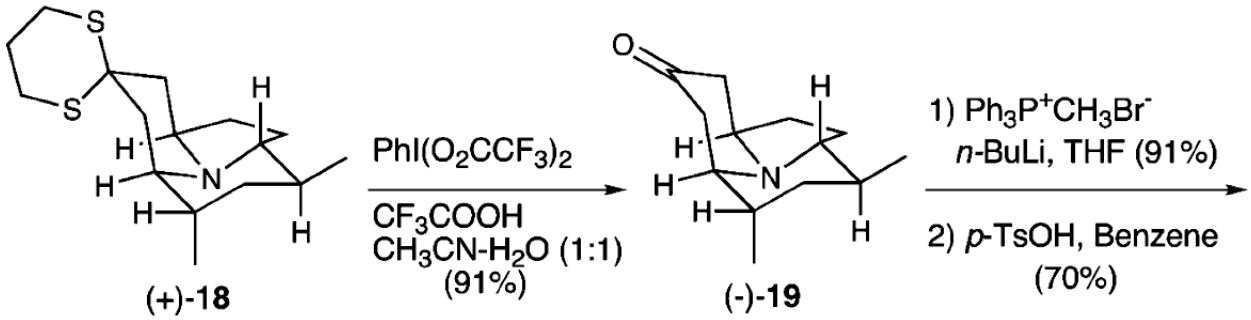
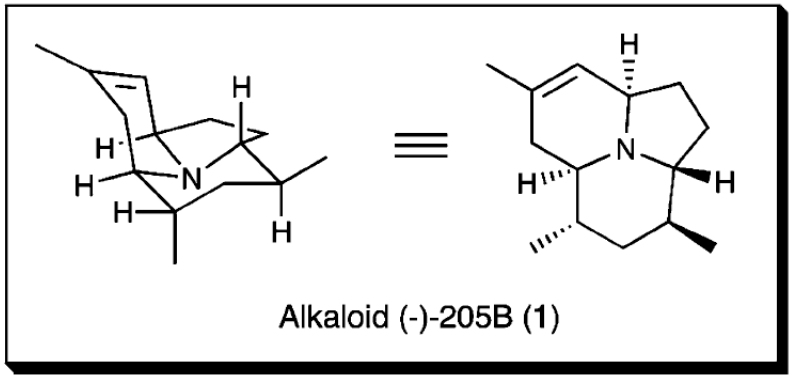
Stork Protocol and Toyooka's Endgame

- Smith's synthesis:
  - Longest Linear - 19 steps
  - Overall Yield - 5.6%





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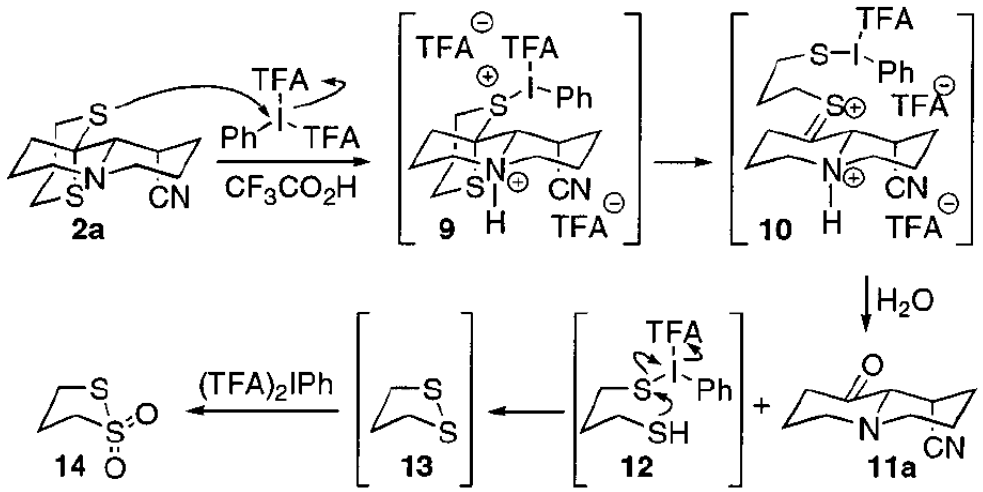
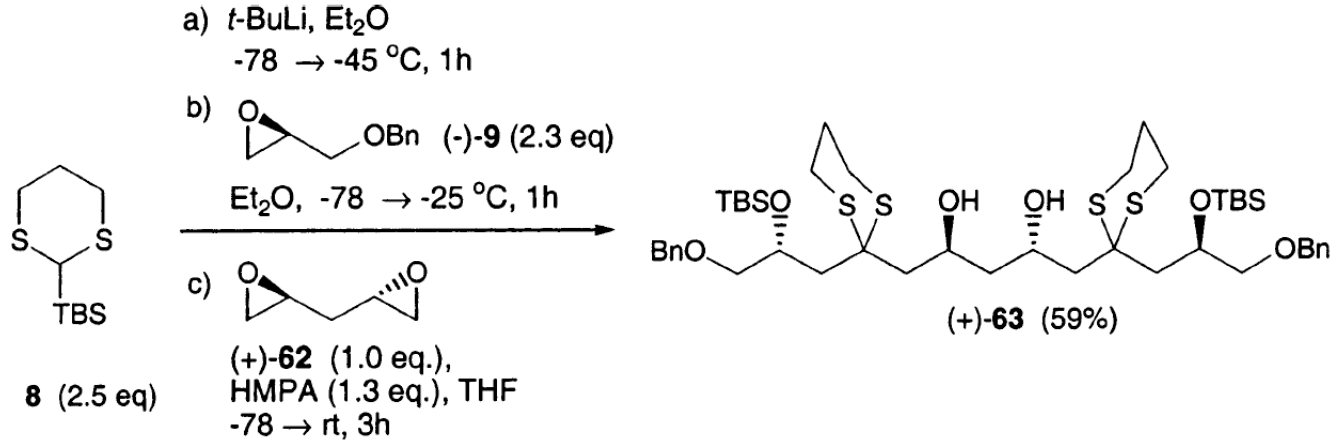
Stork Protocol for Dithiane Removal

Fleming, F. et al. *J. Org. Chem.* **2001**, *66*, 6502.



Summary & Future Research

- ✧ First total synthesis of (-)-205B
- ✧ Extended multi-component coupling methodology to aziridines
- ✧ Concise construction of tricyclic 8b-azaacenaphthylene system
- ✧ Perform biological testing on (-)-205B
- ✧ Prepare congeners using methodology (SAR studies)
- ✧ Higher order multi-component coupling:



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