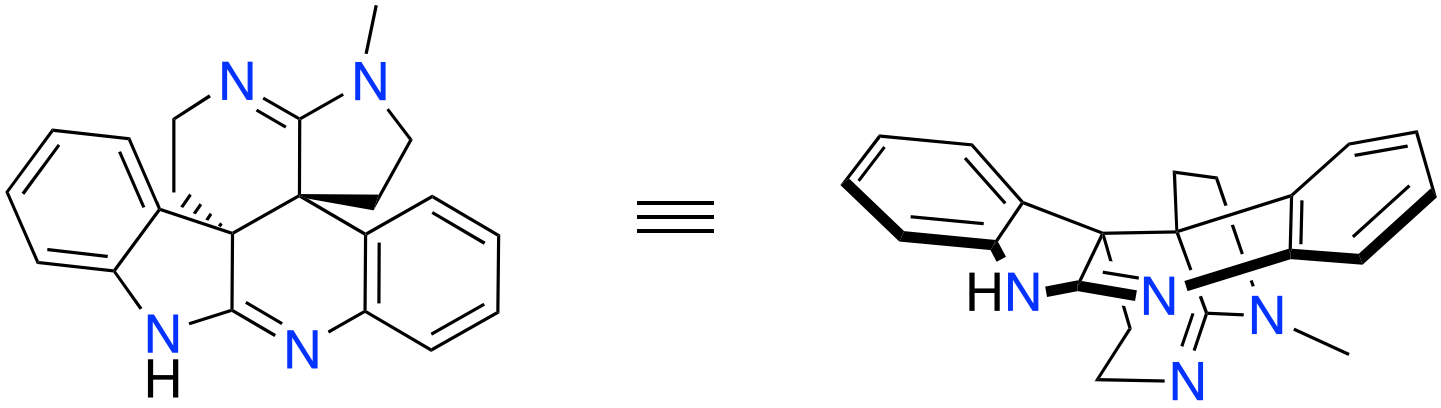
Dearomatizing Conjugate Addition to Quinolinyl Amidines for the Synthesis of Dehaloperophoramidine through Tandem Arylation and Allylation

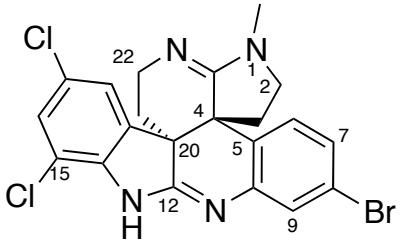
Takayuki Ishida, Hideo Ikota, Kei Kurahashi, ChihiroTsukano and Yoshiji Takemoto. *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.20135581



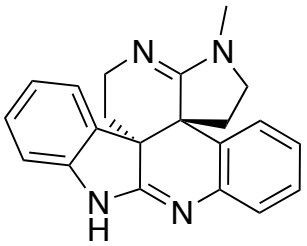
Stephanie McCabe
Wipf Group Current Literature
21st September 2013

Isolation and Activity

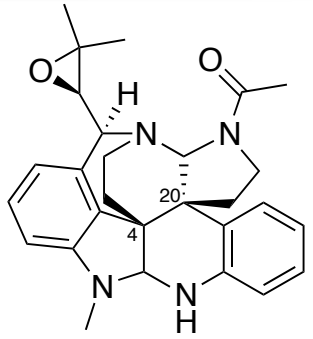
Perophora namei



perophoramidine



dehaloperophoramidine



communesin A

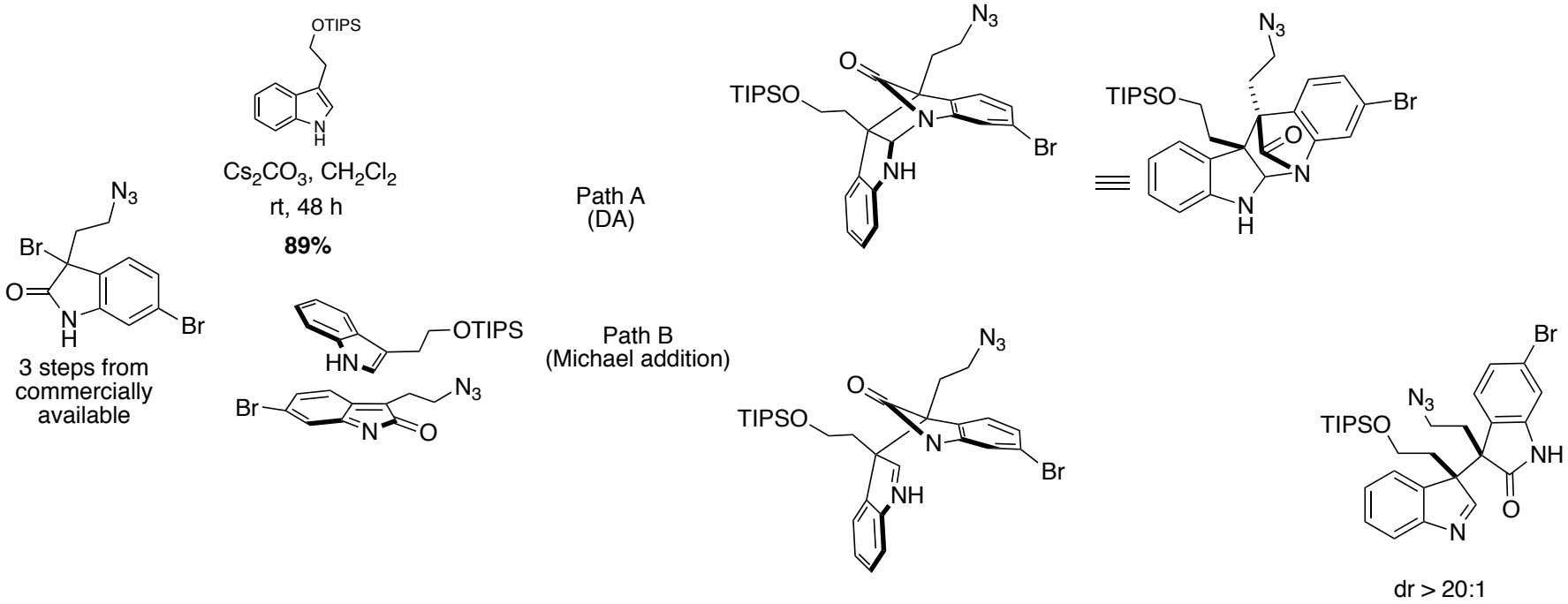
- Perophoramidine was isolated in 2002 by Ireland *et al* from the Philippine ascidian *Perophora namei* . Dehalogenation afforded dehaloperophoramidine. Structurally related to the communesins.
- Exhibits cytotoxicity toward HCT-116 colon carcinoma cells and is able to induce apoptosis via poly(adenosine-5'-diphosphateribose)polymerase (PARP) cleavage
- The structure was determined by spectroscopic methods
- Relative stereochemistry of the C4-C20 vicinal quaternary stereocentres was assigned a *trans*-relationship based on ROESY correlations. Computer modeling showed the *trans*-isomer to be favoured by 44 kcal/mol
- Absolute stereochemistry determined by Qin *et al* 2010

Verbitski, S. M., Mayne, C. L., Davis, R. A., Concepcion, G. P., Ireland, C. M., *J. Org. Chem,* **2002**, *67*, 7124

Wu, H., Xue, J., Xu, Y., Qin, Y., *JACS*, **2010**, *132*, 14052-12054

Previous Syntheses

Fuchs and Funk 2004 – (±)-Perophoramidine



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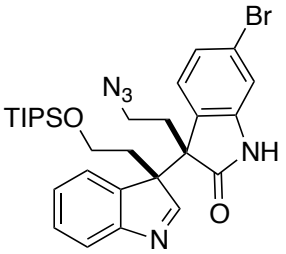
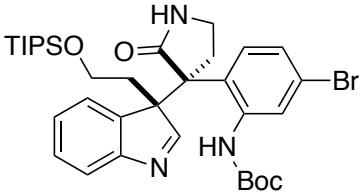
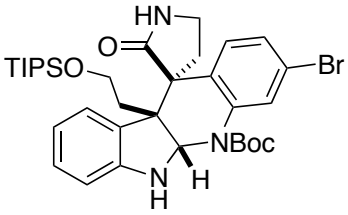


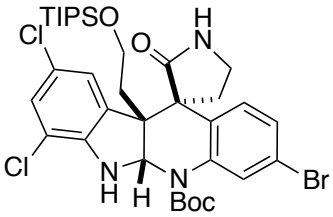
1) NaH, Boc_2O
THF, rt, 1 h, **92%**

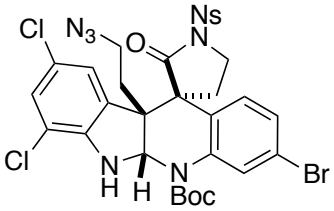
2) PPh_3, THF, H_2O
50 °C, 5 h, **89%**





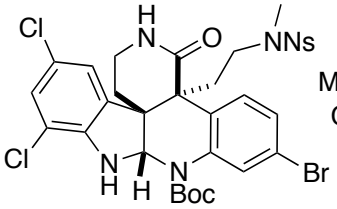
1) NCS, AcOH
rt, 24 h, **86%**





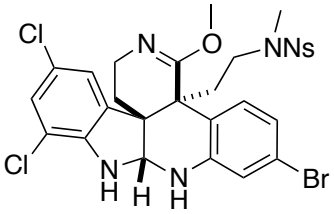
1) PMe_3, THF
rt, 2 h, 86%

2) Cs_2CO_3, MeI,
MeCN, rt, 6 h, 92%



Me_3OBF_4, DIPEA
CH_2Cl_2, rt, 48 h

68%



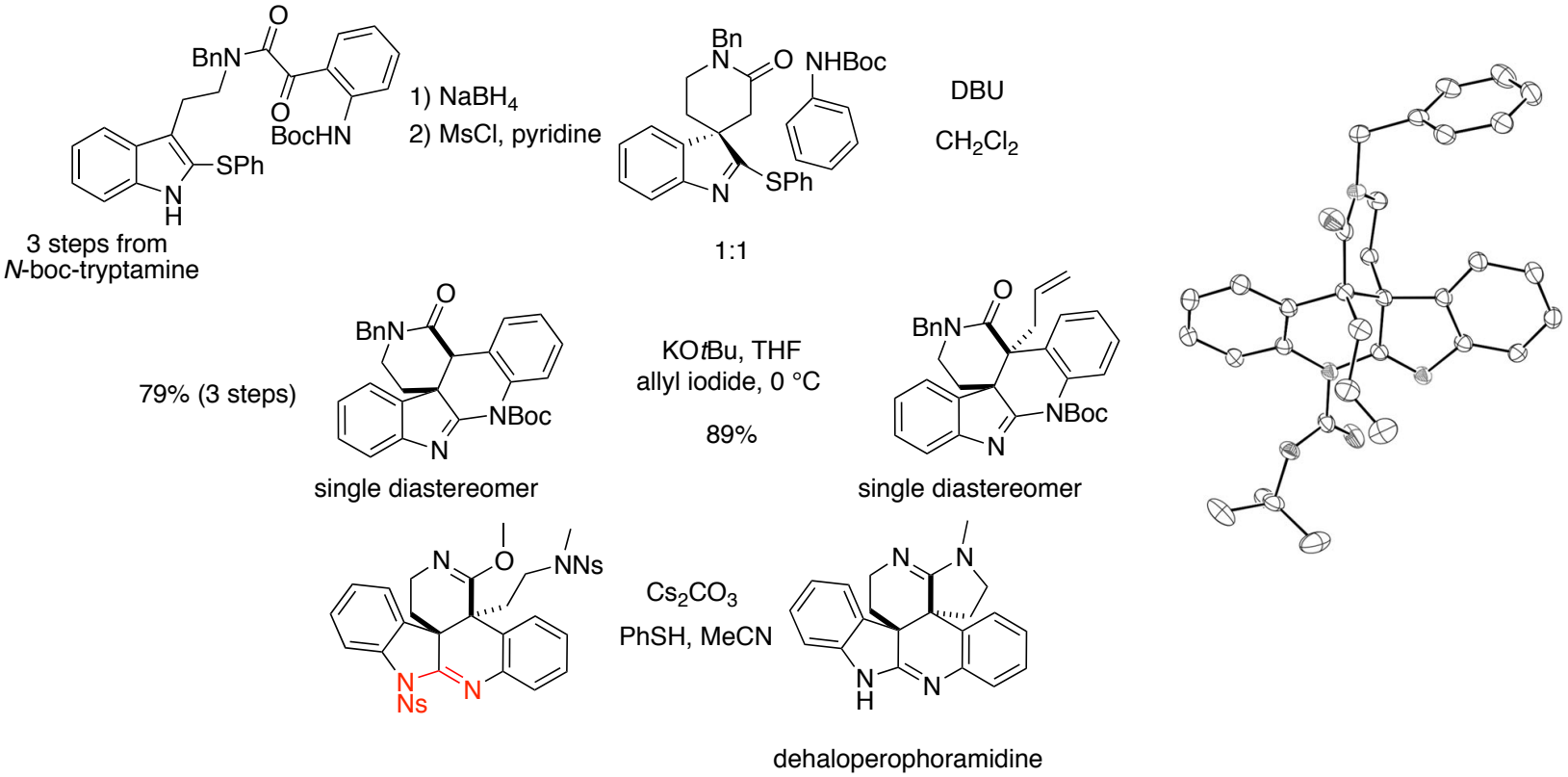
1) Cs_2CO_3, PhSH,
DMF, 45 °C, 24 h,
70%

2) MnO_2, CH_2Cl_2,
rt, 0.5 h, 65%

(±)-perophoramidine

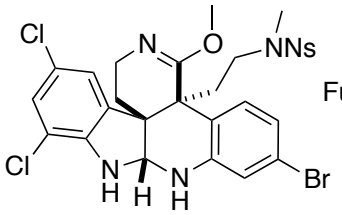
Previous Syntheses

Rainer, 2006 – (±)-Dehaloperophoramidine

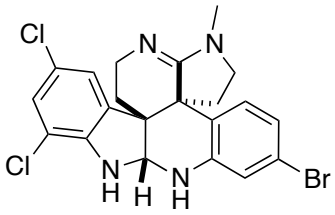


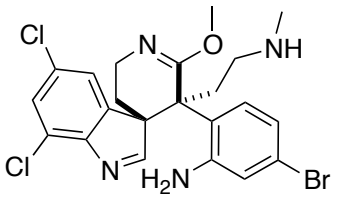
Previous Syntheses

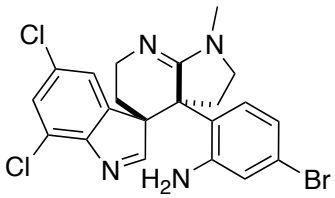
Rainer, 2006 – (±)-Dehaloperophoramidine

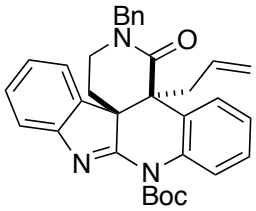


Fuchs and Funk

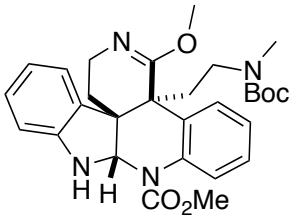








9 steps

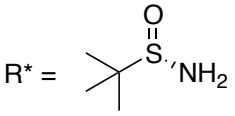


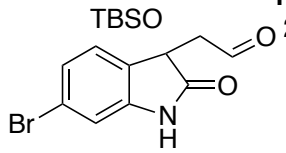
1) TFA, CH_2Cl_2, 95%
2) KOH, MeOH
   H_2O, 71%
3) MnO_2, CH_2Cl_2, 64%

dehalo-perophoramidine

Previous Syntheses

Qin 2010 – (+)-Perophoramidine

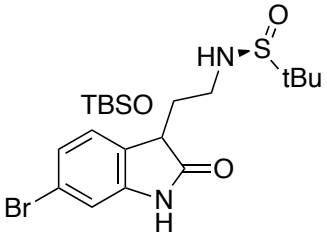




3 steps from isatin

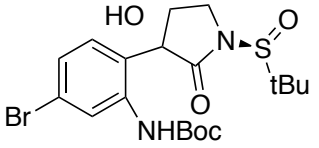
1. R*NH_2, $KHSO_4$, PhMe,
2. $NaBH_4$, MeOH, 0 °C,
81-85% (over 2 steps)

yield expressed as a range due to parallel synthesis of diene precursors

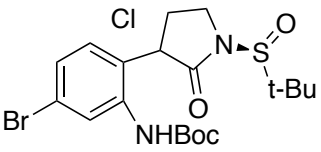


1. Boc_2O, NaOH, CH_2Cl_2,
87-93%

2.TBAF, THF, rt, **89-90**%



$SOCl_2$, pyridine,
CH_2Cl_2, 0 °C



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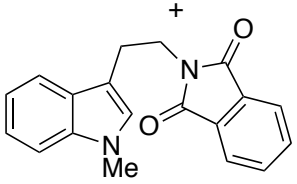
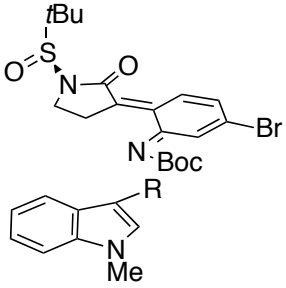
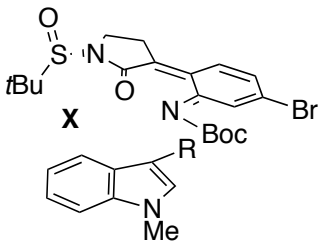


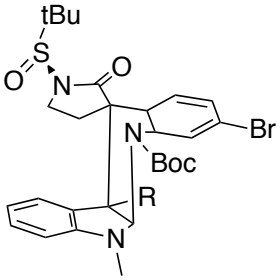


exo-transition state

or



$AgClO_4$, PhMe, -78 °C
88%



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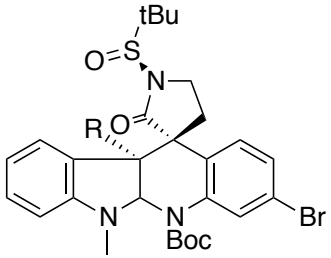

dr **11**: 1

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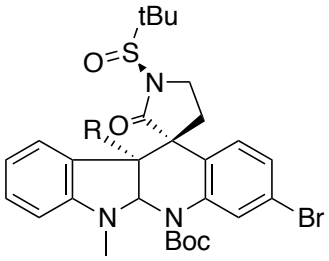
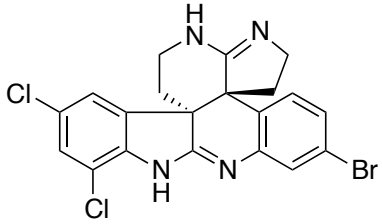
Previous Syntheses

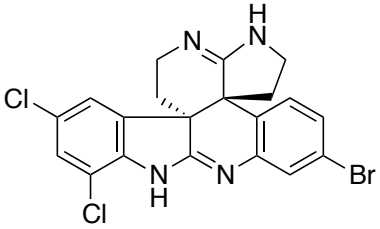
Qin 2010 – (+)-Perophoramidine



steps



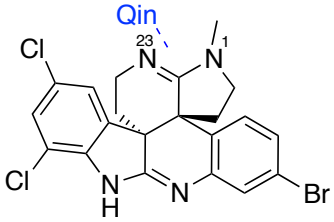
PPTs, $CHCl_3$,
reflux, **quant.**



MeOTf, NaHMDS,
THF, -78 °C, **73%**

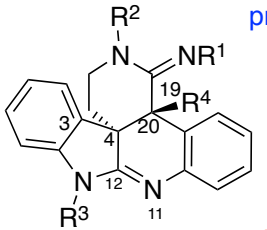
(+)-perophoramidine

Retrosynthesis/ Strategy

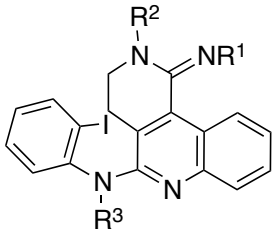


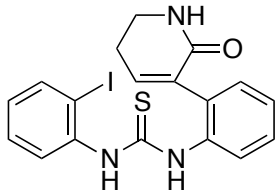
Perophoramidine

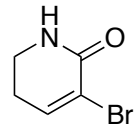
previous work



this work







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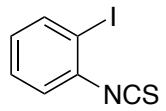
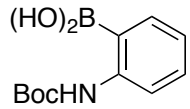
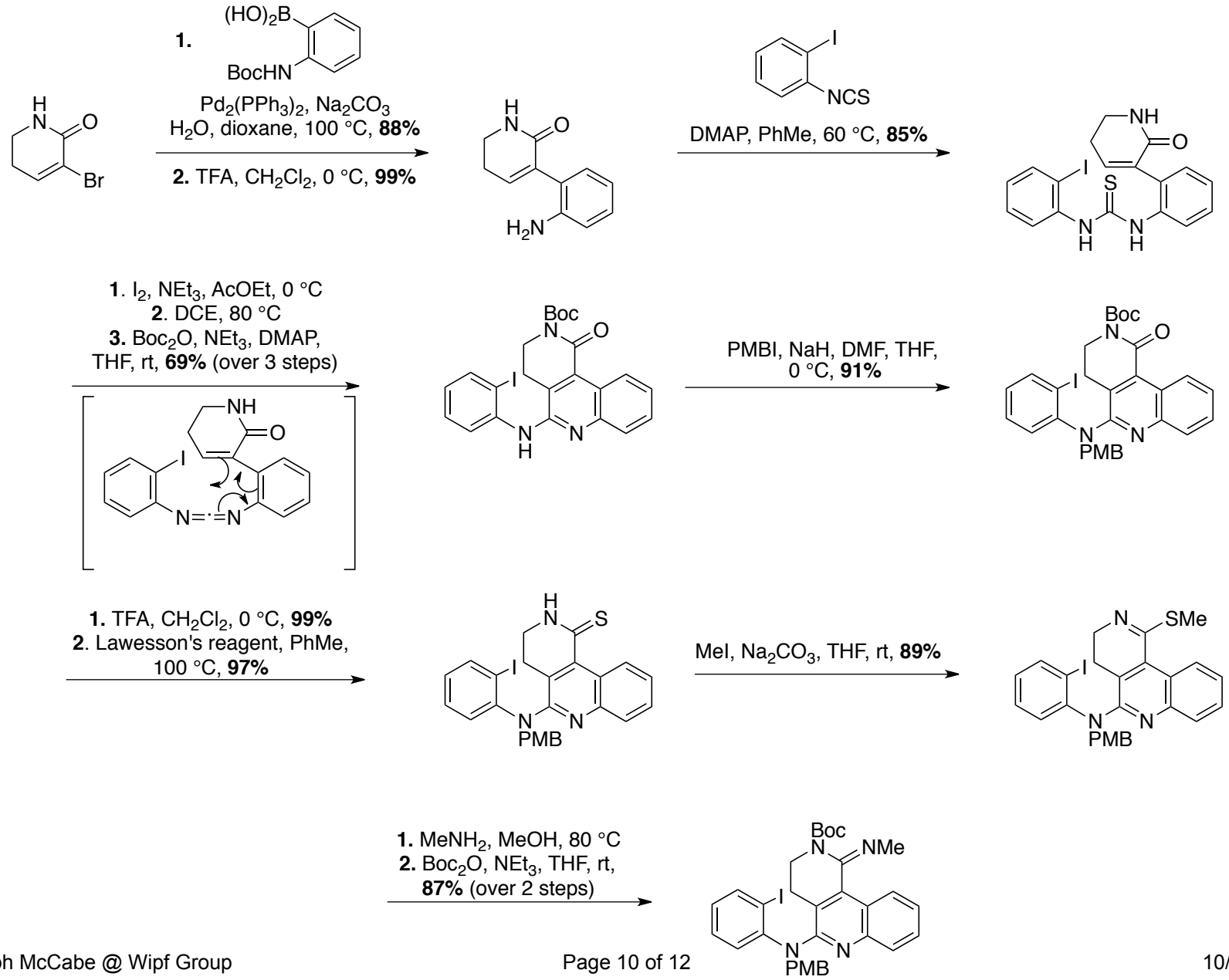


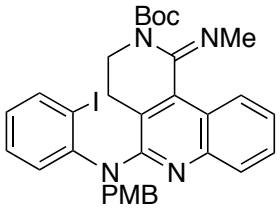


- Different disconnection strategy which features simultaneous assembly of the vicinal stereocentres in a single operation with amidine nitrogens in place
- Compared to predecessors does not involve oxidation of an aminal intermediate to install the lower amidine unit

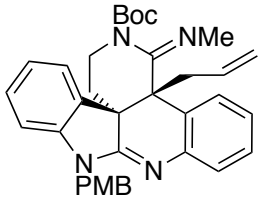
Synthesis of Key Dearomatization/ Alkylation Precursor

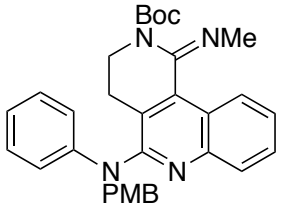


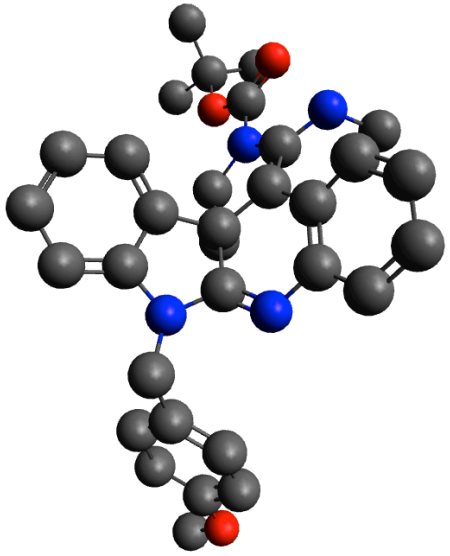
Key Step and Completion of the Synthesis

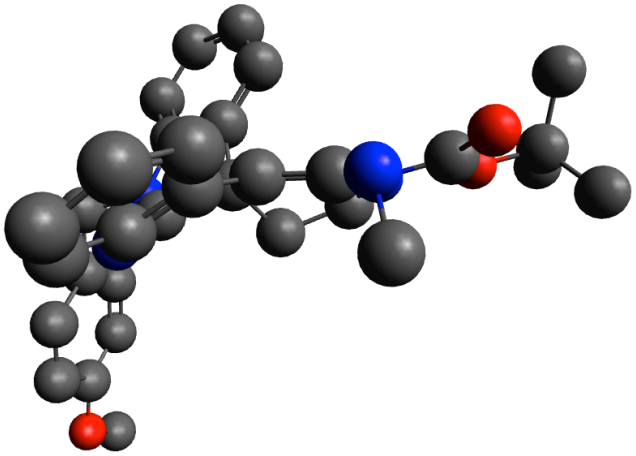


1. *n*BuLi, THF, -78 °C
2. allyl iodide, -78 °C – 0 °C, **67%**



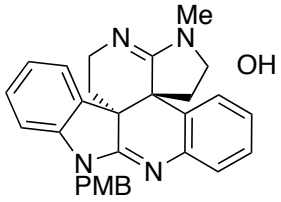






1. OsO_4, NMO, acetone, rt

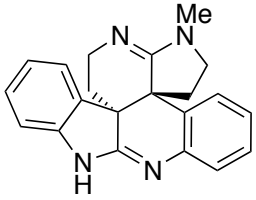
2. $NaIO_4$, $NaHCO_3$, THF, H_2O, rt, **75%** (over 2 steps



(3:2)

1. $NaCNBH_3$, AcOH, MeOH, 0 – 60 °C, **76%**

2. H_3PO_4, anisole, 120 °C, **71%**



Evans, M. A., Sacher, J. R., Weinreb, S. M., *Tetrahedron*, 65, *33*, 6712-6719
Sabahi, A., Novikov, A., Rainier, J. D., *ACIE*, **2006**, *45*, 4317-4320
Lopez Ortiz, F., Iglesias, M., Fernandez, I, Andujar Sanchez, C. M., Ruiz Gomez, G., *Chem. Rev.*, **2007,** *107,* 1580–1691
Lui, L., Wang, Z., Zhao, F., Xi, Z., *JOC*, **2007**, *72*, 3484

Summary and Conclusionss

- 17 steps, 9.5 % overall yield (compared to Rainer 18 steps, 7.5 % yield)
- Did not pass through an aminal intermediate
- First example of a nucleophilic dearomatization of a 10 π –electron aromatic system that enables the construction of two vicinal quaternary stereocentres.