Literature Presentation

Total Synthesis of (+)-Perophoramidine & Determination of the Absolute Configuration

Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J.Am.Chem.Soc.* 2010, *132,* 14052-14054

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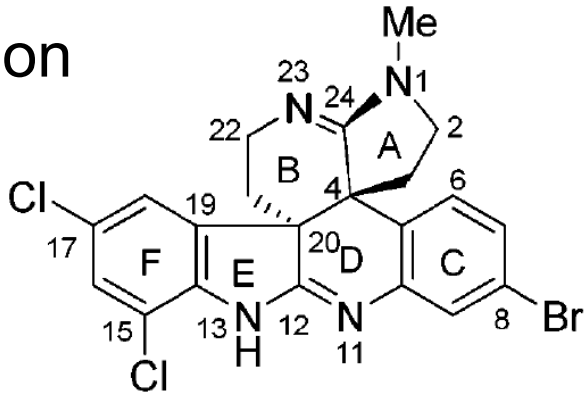
Introduction



- Perophoramidine was first isolated from colonial ascidian ***Perophora namei*** by Chris M. Ireland et. in 2002.

- Perophoramidine is the first reported metabolite from the genus ***Perophora***

- It exhibits cytotoxicity toward the HCT116 colon carcinoma cell line and induces apoptosis via PARP (poly ADP ribose polymerase) cleavage within 24h.

Previous work on the synthesis of Perophoramidine:

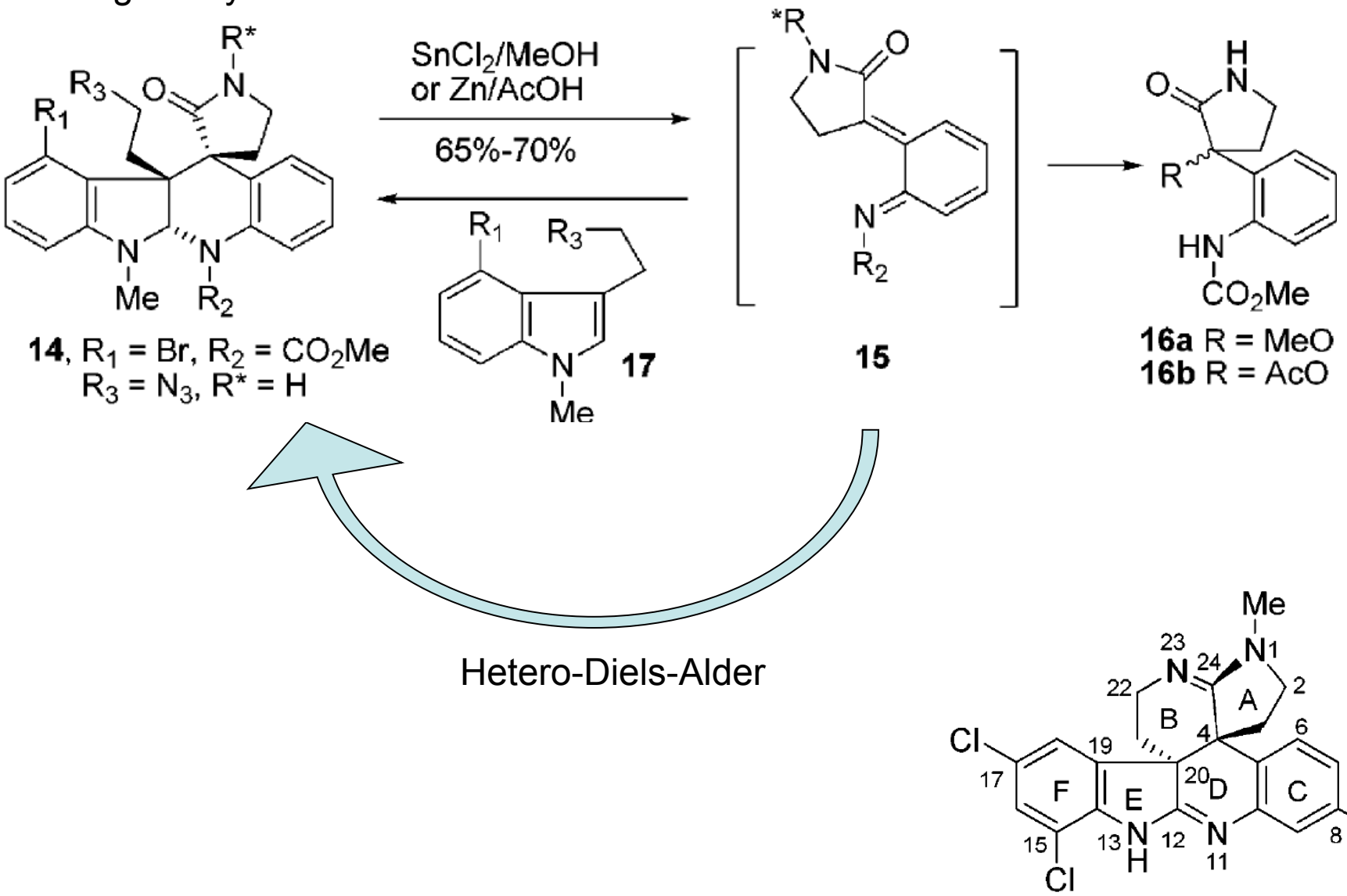
Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126,* 5068
-- First completed synthesis (racemic)

A. Sabahi, A. Novikov, J. D. Rainier, ***Angew. Chem***. 2006, *118*, 4423 – 4426; ***Angew. Chem. Int. Ed***. 2006, *45*, 4317 – 4320.
-- Dehaloperophoramidine (racemic)

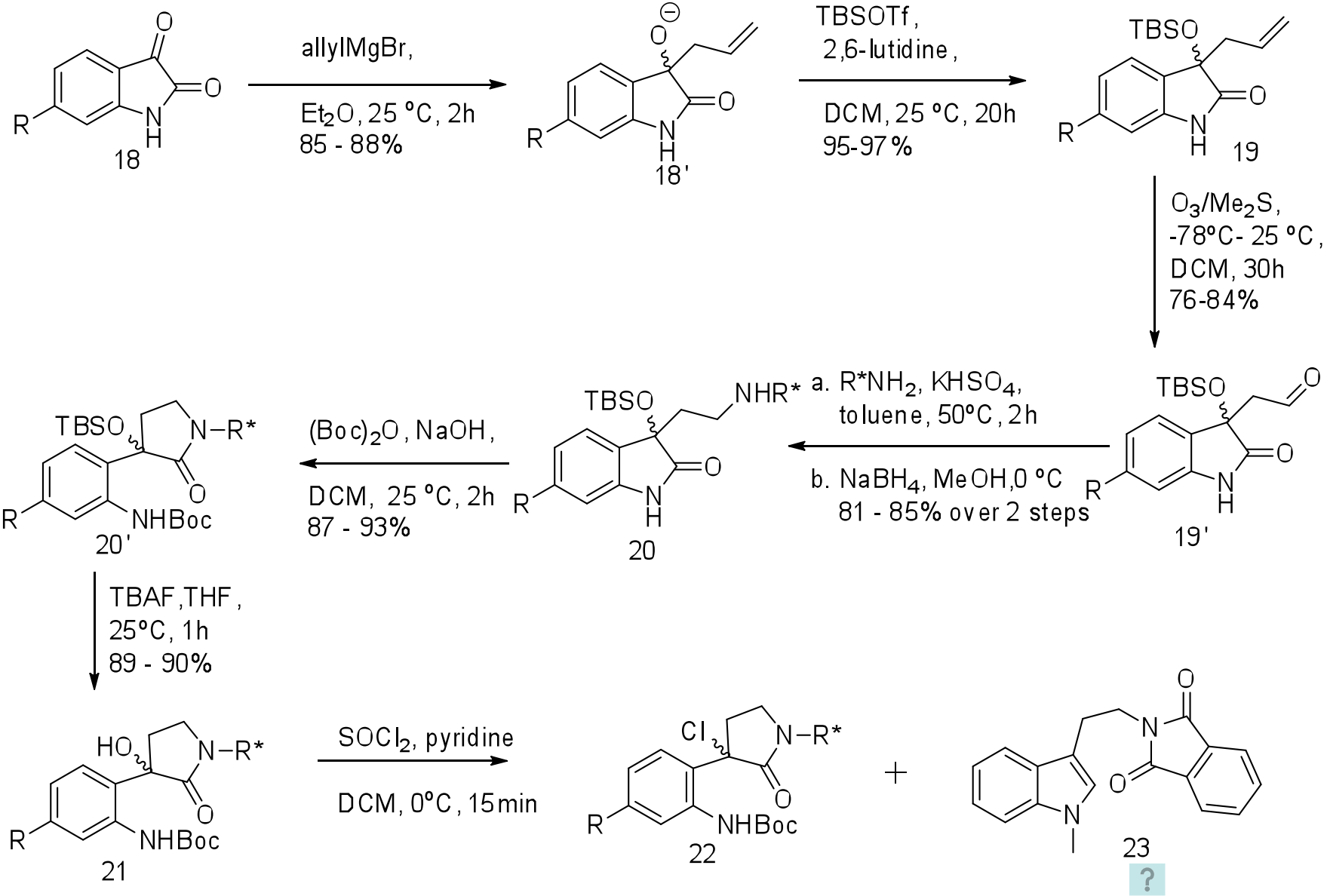
J. Yang, H. Song, X. Xiao, J. Wang, Y. Qin, ***Org. Lett***. 2006, *8*, 2187 – 2190.
-- Substructure was synthesized (racemic)

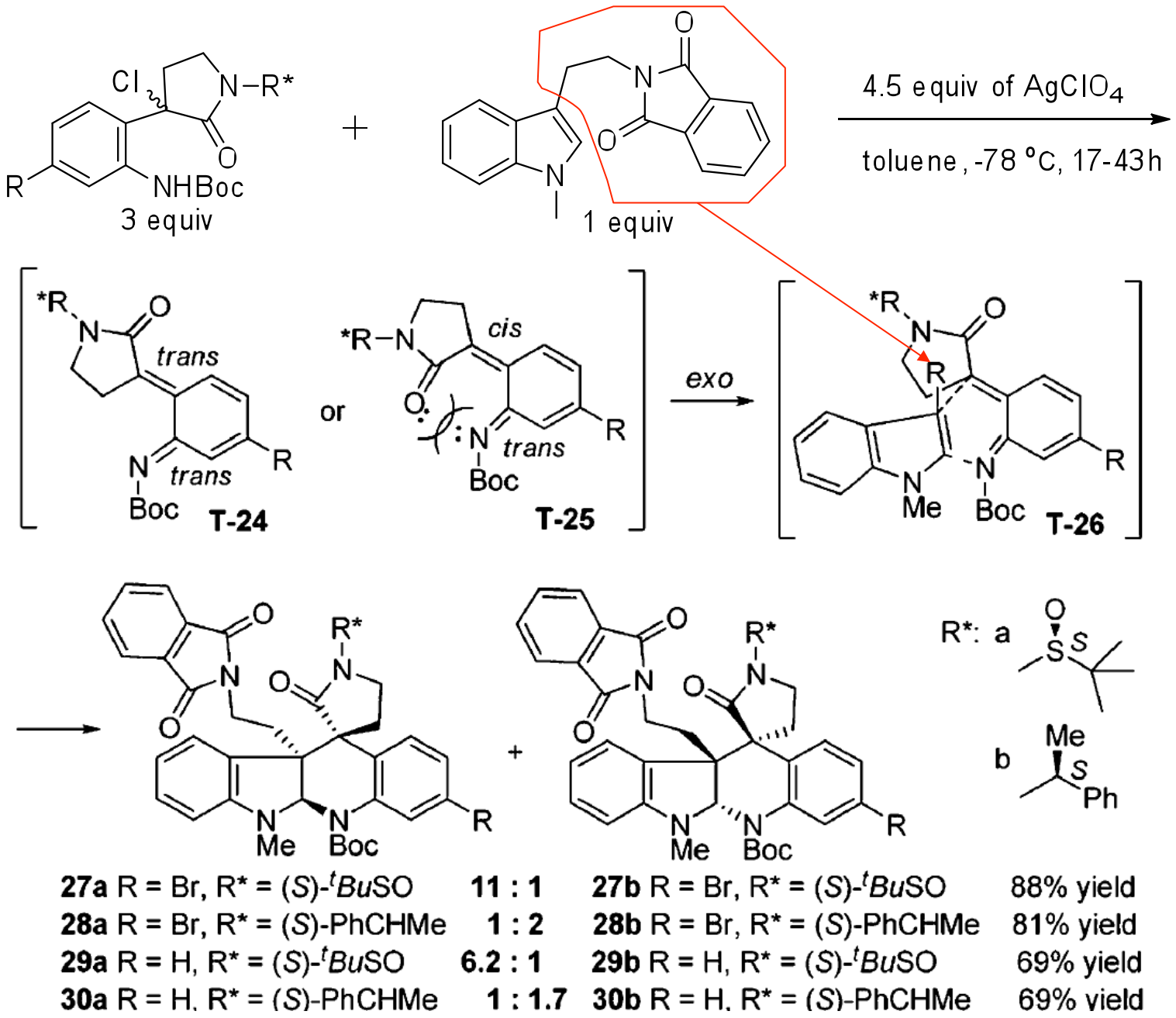
How did they develop this synthesis route?

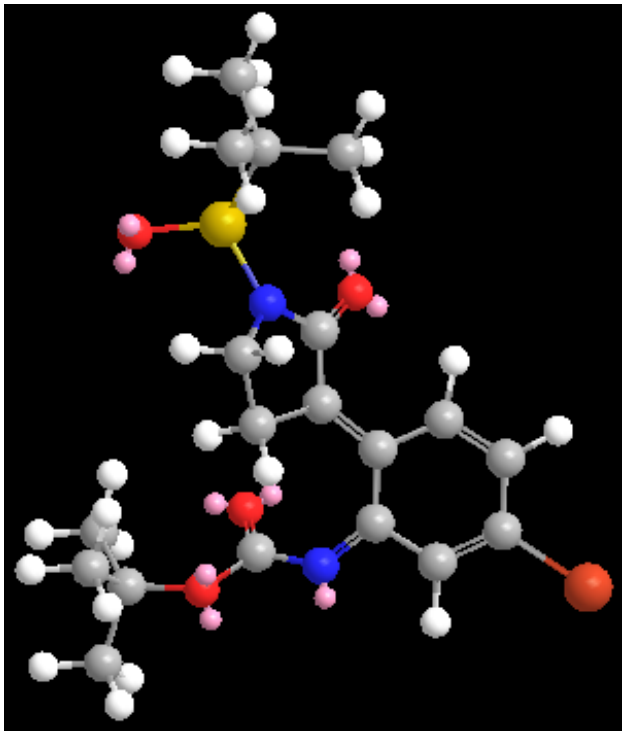
During the synthesis of communesin:

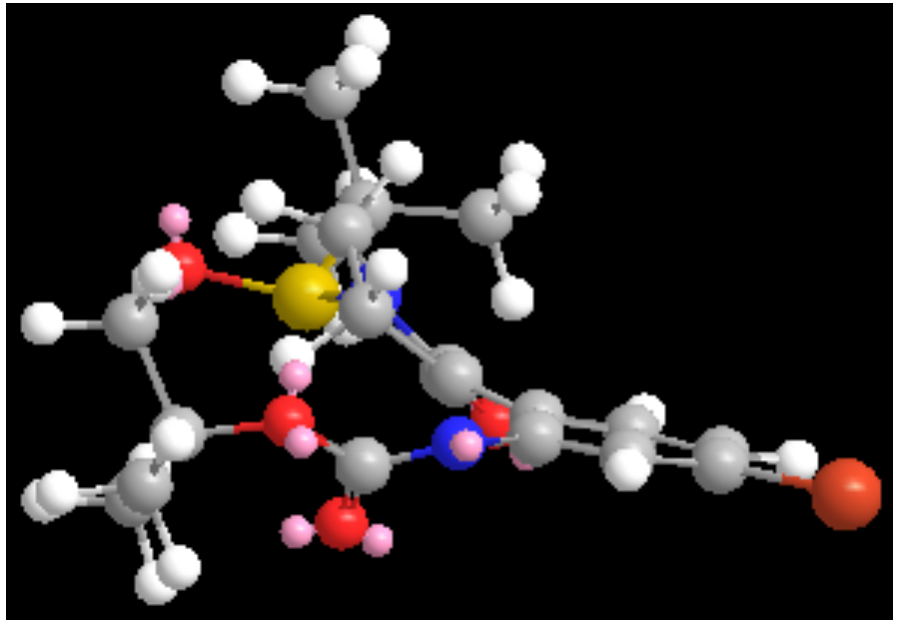


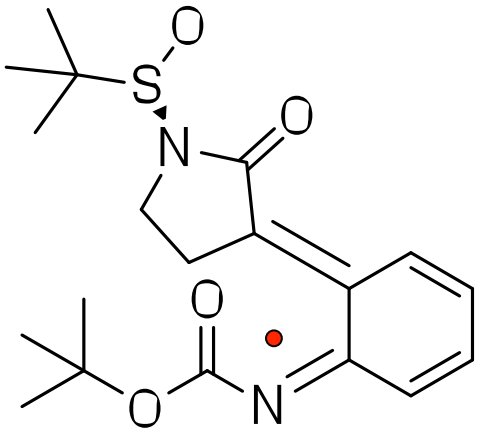
Synthesis starts:

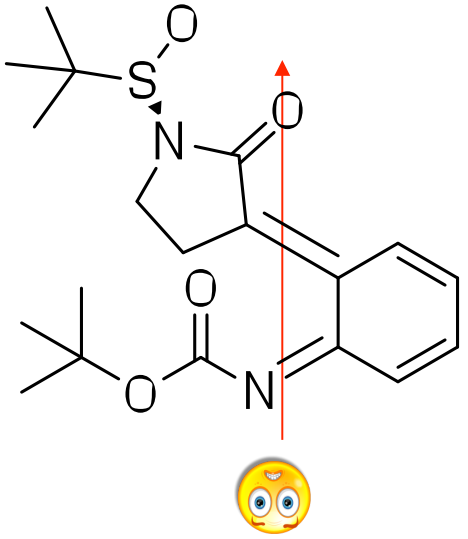


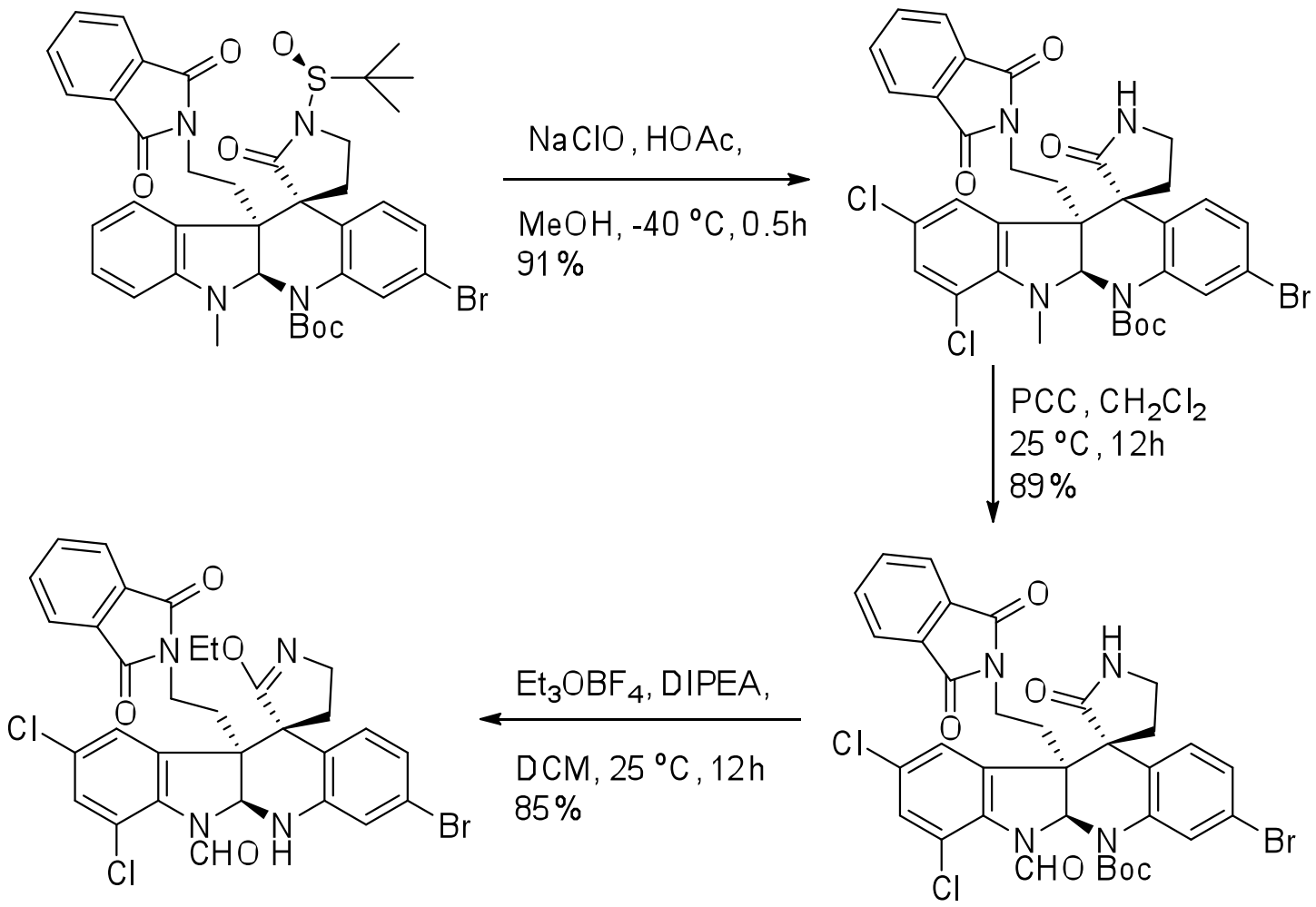

4.5 equiv of AgClO4
toluene, -78 °C, 17-43h
3 equiv
1 equiv
trans
cis
or
exo
T-24
T-25
T-26
R*: a
b
27a R = Br, R* = (S)-tBuSO 11 : 1
28a R = Br, R* = (S)-PhCHMe 1 : 2
29a R = H, R* = (S)-tBuSO 6.2 : 1
30a R = H, R* = (S)-PhCHMe 1 : 1.7
27b R = Br, R* = (S)-tBuSO 88% yield
28b R = Br, R* = (S)-PhCHMe 81% yield
29b R = H, R* = (S)-tBuSO 69% yield
30b R = H, R* = (S)-PhCHMe 69% yield

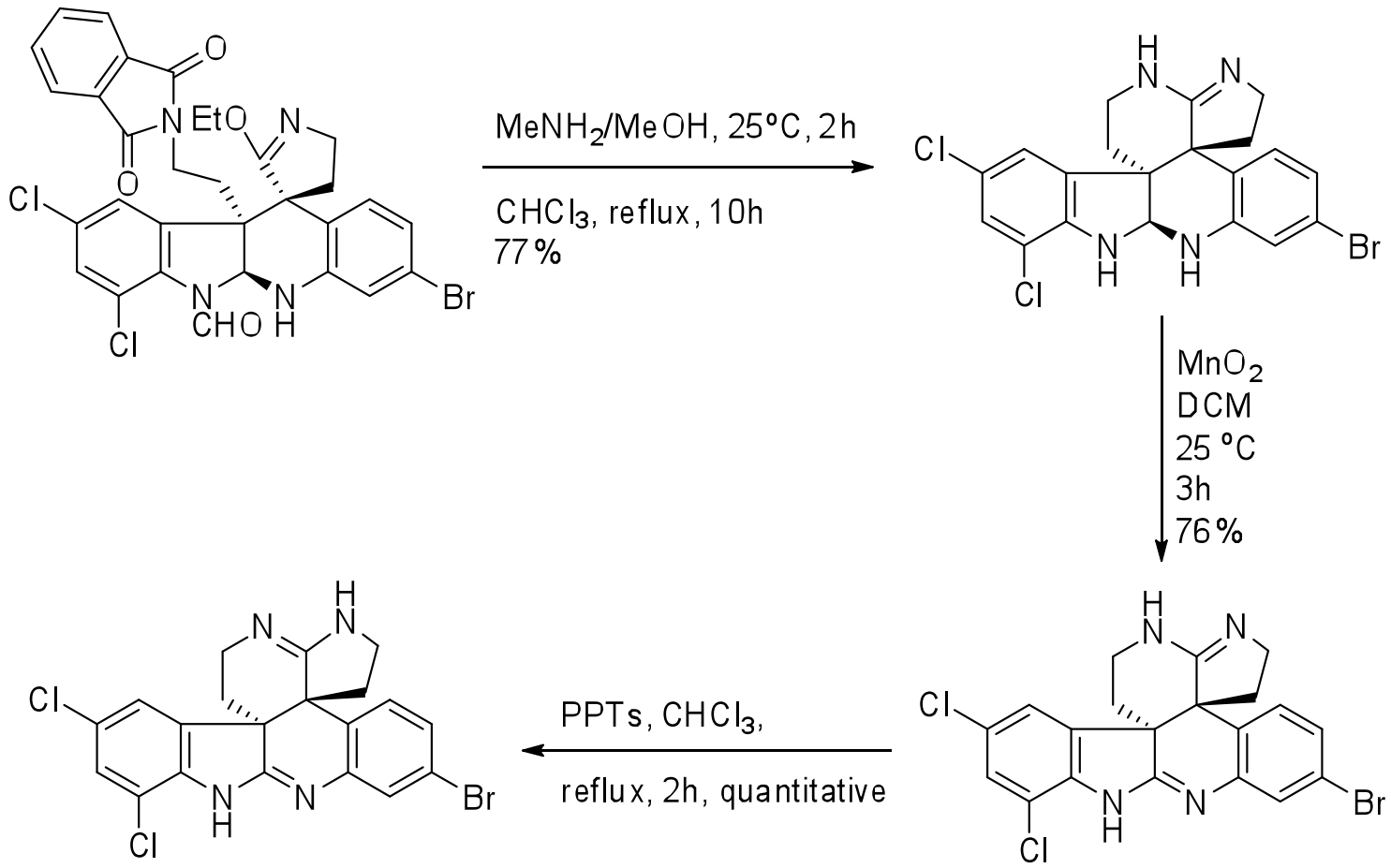


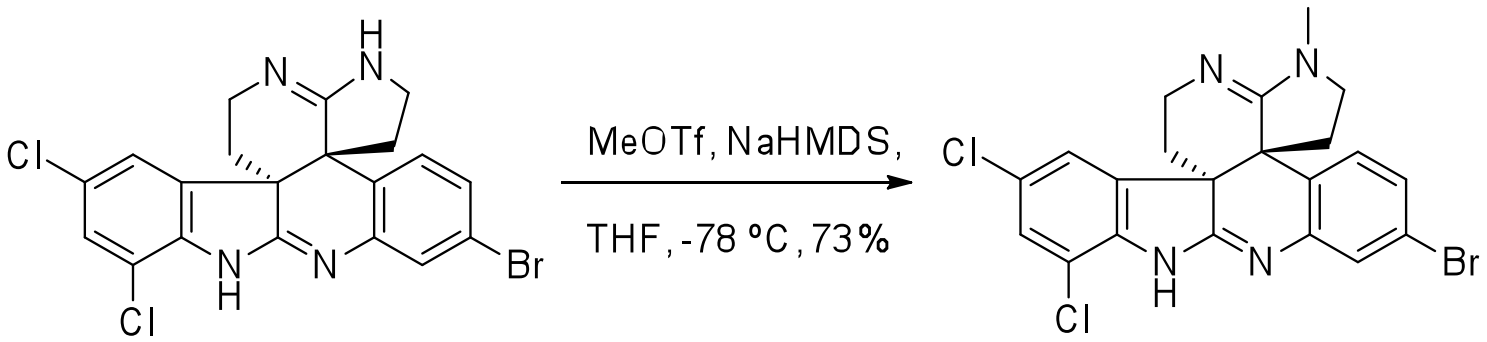



O
S
N
O
O
O
O
N

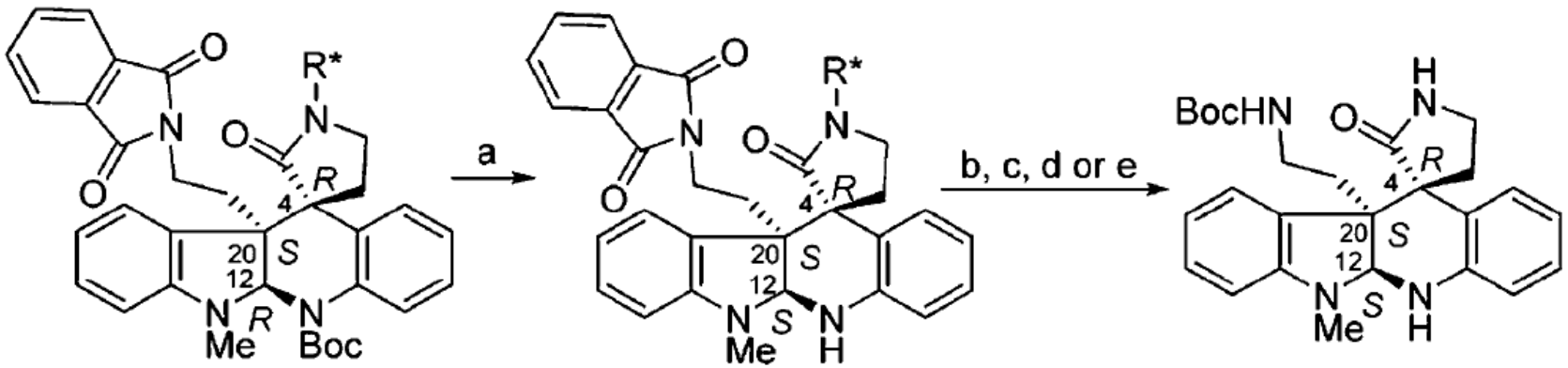

O
S
N
O
O
O
O
N


NaClO, HOAc,
MeOH, -40 °C, 0.5h
91%
PCC, CH2Cl2
25 °C, 12h
89%
Et3OBF4, DIPEA,
DCM, 25 °C, 12h
85%


MeNH2/MeOH, 25°C, 2h
CHCl3, reflux, 10h
77%
MnO2
DCM
25 °C
3h
76%
PPTs, CHCl3,
reflux, 2h, quantitative



Determination of the absolute stereochemistry:



29a R* = (*S*)-^{t}BuSO
30a R* = (*S*)-PhCHMe

31 R* = (*S*)-^{t}BuSO
32 R* = (*S*)-PhCHMe

33

a. TMSOTf, 2,6-lutidine, DCM, 0 °C, 2h, 82 - 85%
b. $MeNH_2$/MeOH, 25 °C, 12h
c. $(Boc)_2O$, Na_2CO_3, DCM, 25 °C, 2h, 78% - 80%(b+c)
d. Li/NH_3, THF, -78 °C, 30min, 83%
e. NaOH, DCM, 25 °C, 12h, 81%

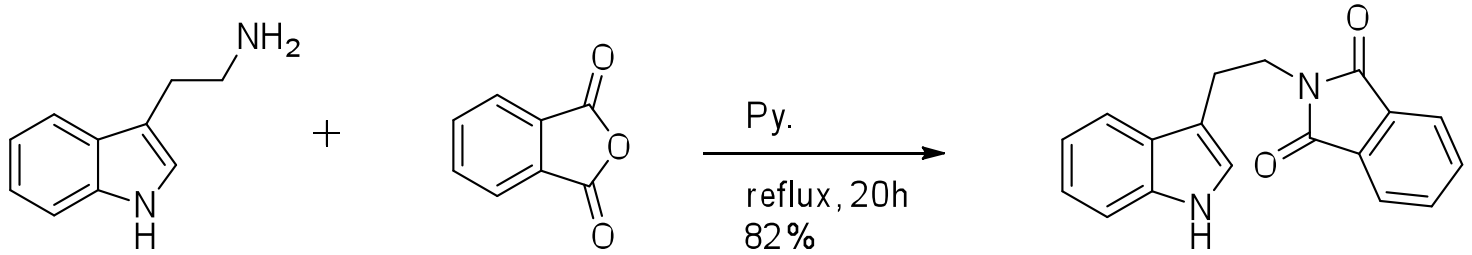
Summary:

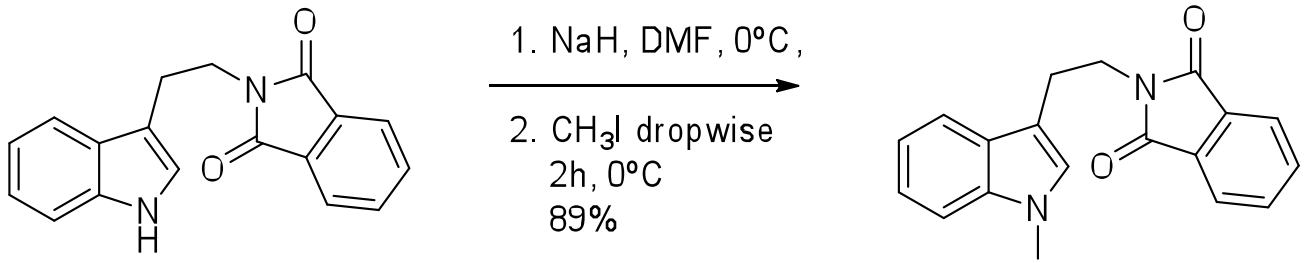
The first asymmetric total synthesis of (+)-perophoramidine has been achieved in 17 steps with ~11% overall yield.

Key step: chiral-auxiliary-induced hetero-Diels-Alder reaction to generate the core structure.

Absolute stereochemistry was determined by X-ray analysis and comparison of the rotation of synthetic (+)-perophoramidine with that of the natural product.

Thanks!


NH2
O
O
O
N
H
Py.
reflux, 20h
82%
O
N
O
N
H


O
N
O
N
H
1. NaH, DMF, 0°C,
2. CH3I dropwise
2h, 0°C
89%
O
N
O
N