

Literature Report

**Total synthesis of malagashanine:
a chloroquine potentiating indole alkaloid
with unusual stereochemistry**

Reporter: Hong-Qiang Shen

Checker: Cong Liu

Date: 2016/11/01

Blakey, S. B. *et al. Chem. Sci.* **2016**, 7, DOI:10.1039/c6sc03578g

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- ◆ **Blakey's Method for Synthesis of Malagashanine**
- ◆ **Tang's Method for Synthesis of 11-Demethoxymyrtoidine**
- ◆ **Summary**

CV of Simon B. Blakey



Position: Associate Professor
in Emory University

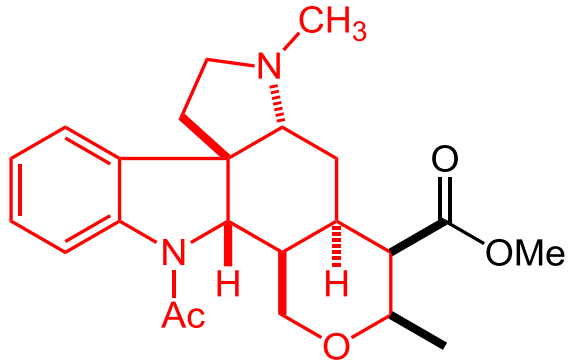
Education:

1997 B. Sc., University of Auckland (NZ)

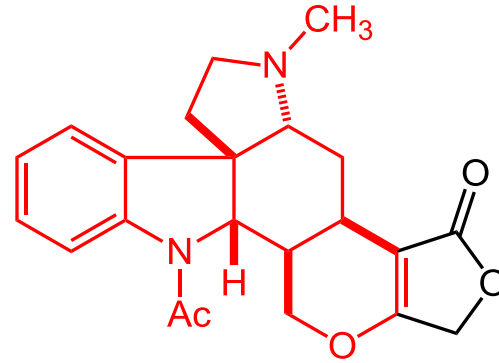
2002 Ph. D., Chemistry, University of Cambridge (UK)

2005 Postdoctoral fellow, California Institute of Technology

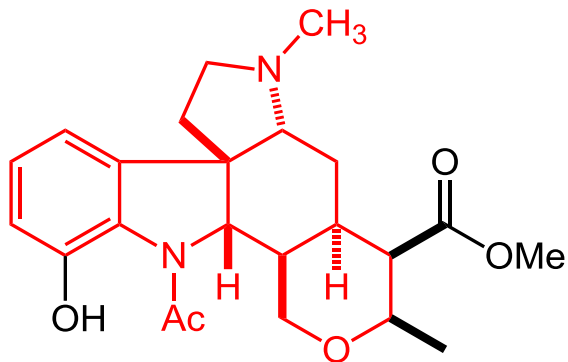
Malagasy Alkaloids



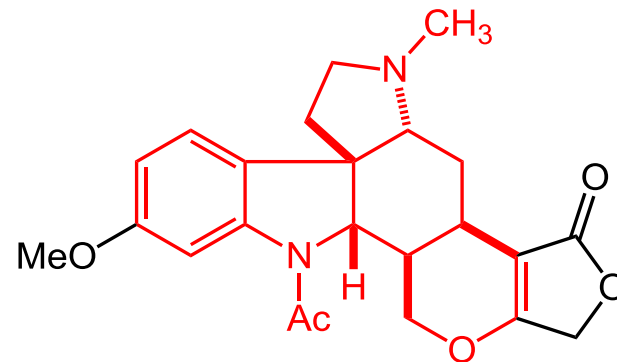
Malagashanine



11-Demethoxymyrtoidine

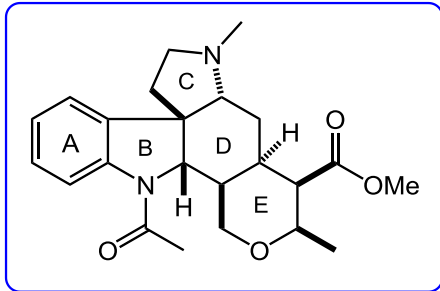


12-Hydroxymalagashanine



Myrtoidine

Malagashanine



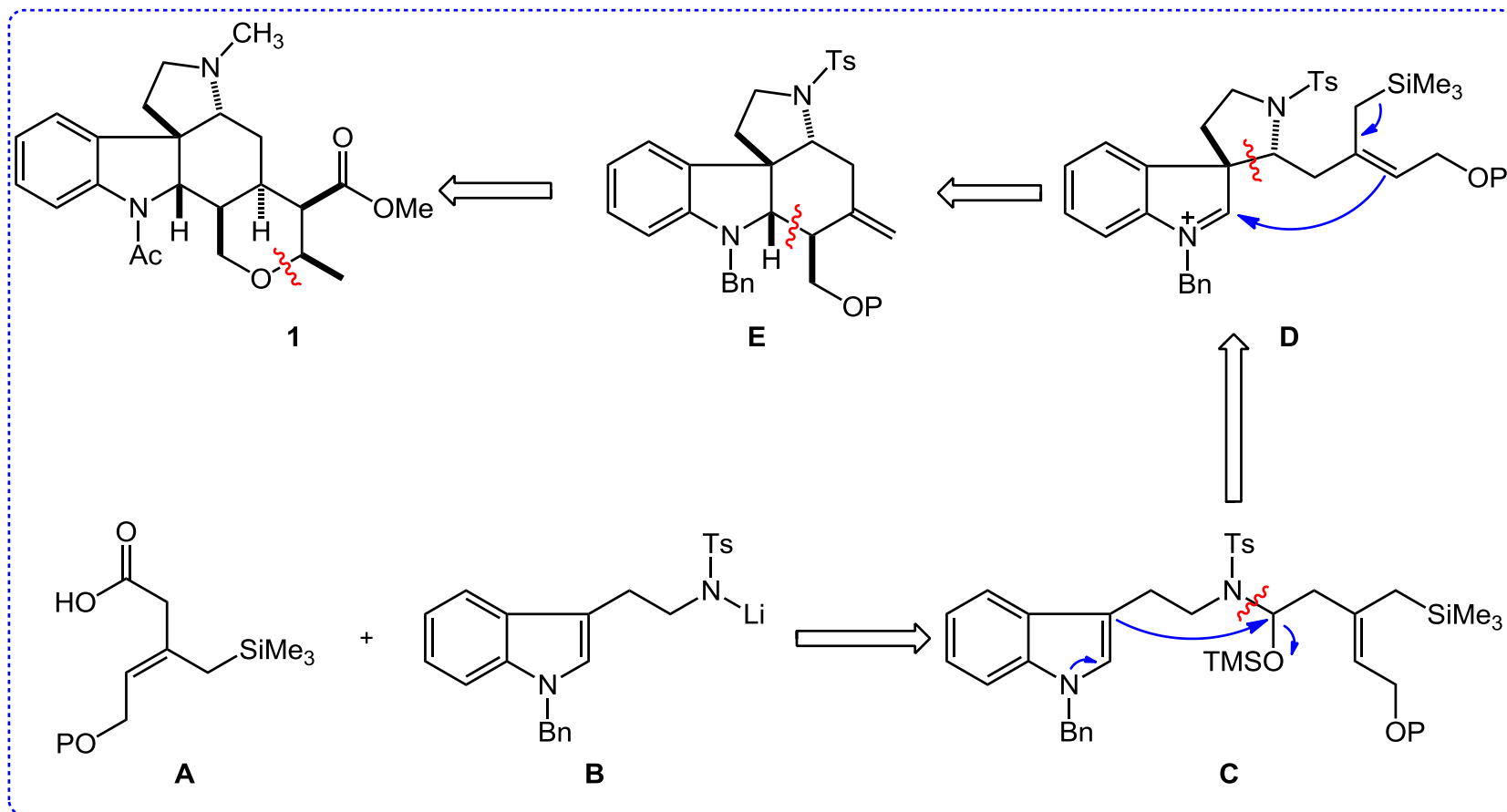
Malagashanine



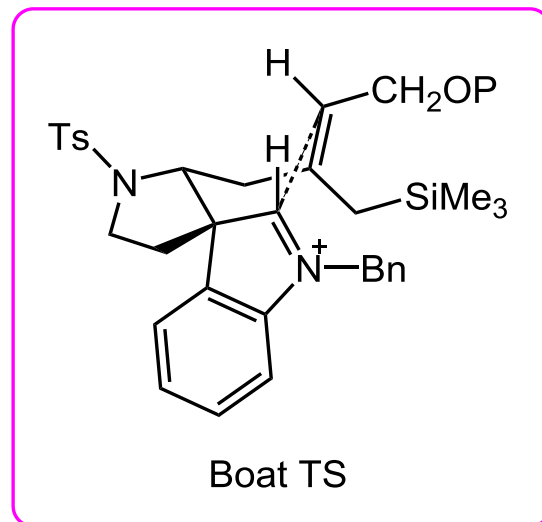
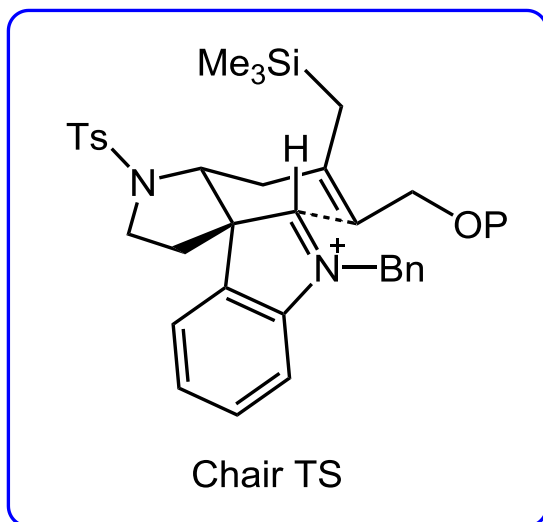
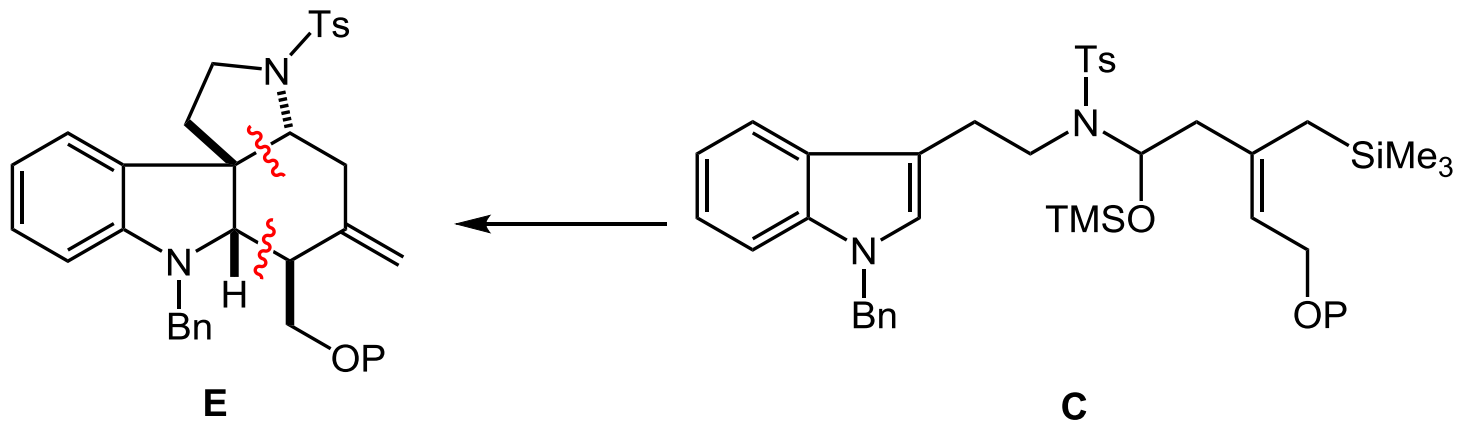
Strychnos myrtoides
马钱子

- Isolated from *Strychnos myrtoides* in the early 1990s
- Promising anti-malaria activity
- Seven stereocenters, complex fused rings in pentacyclic framework

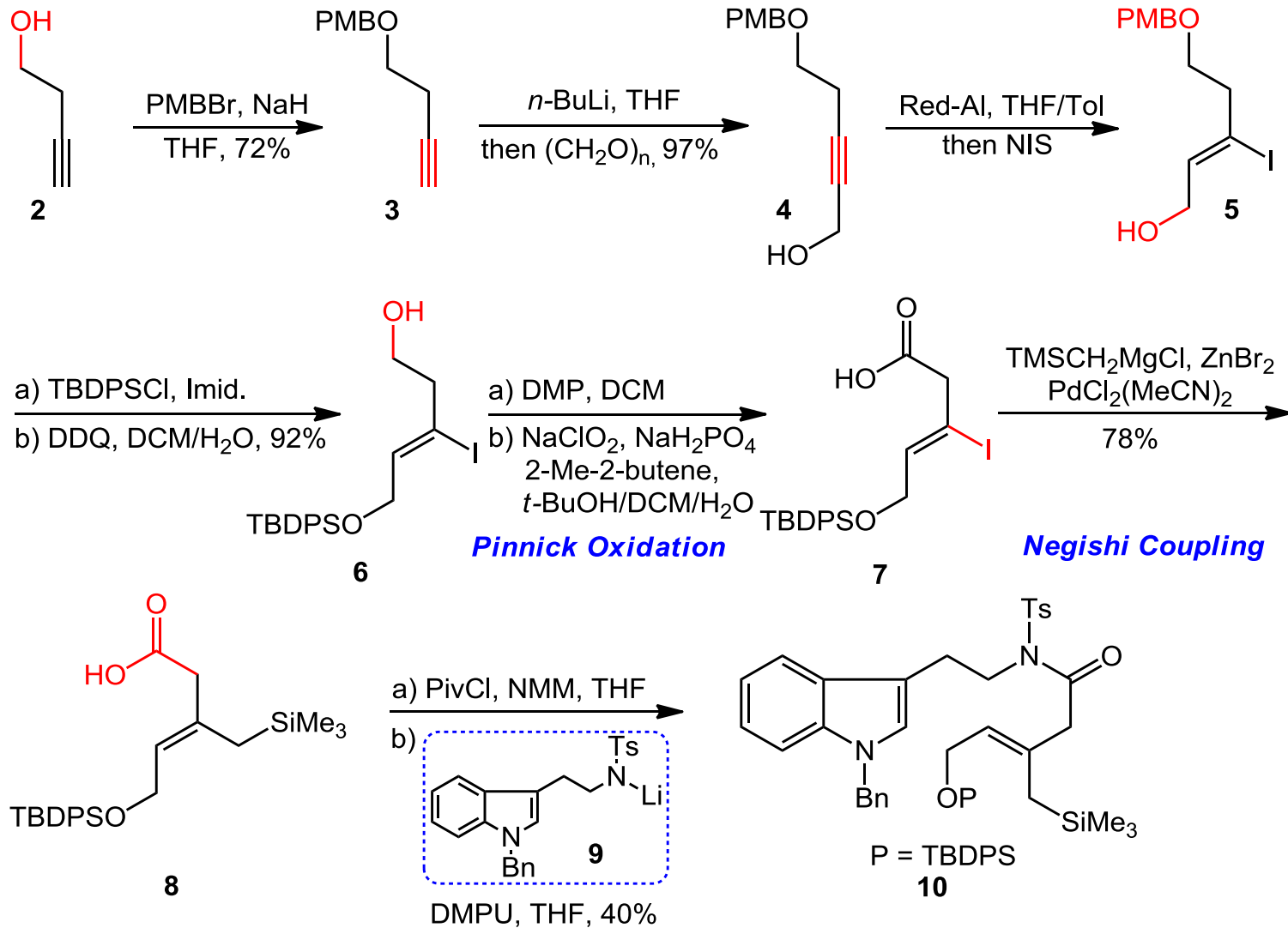
Proposed Retrosynthesis



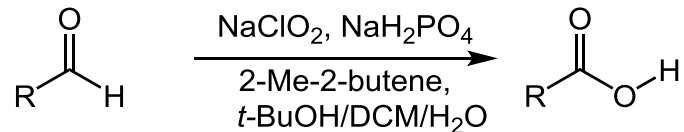
Cascade Annulation



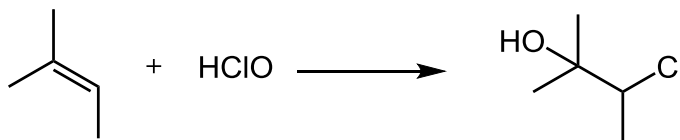
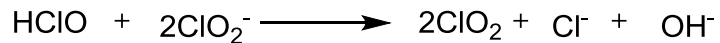
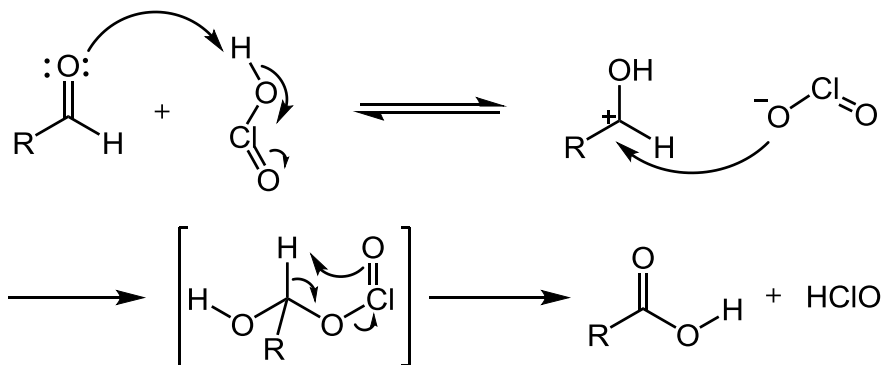
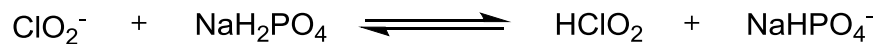
Blakey's Method



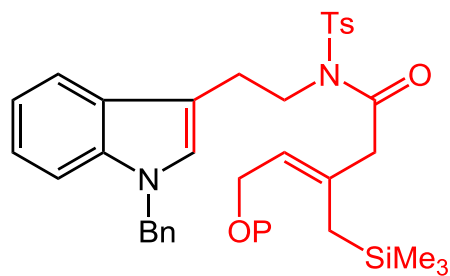
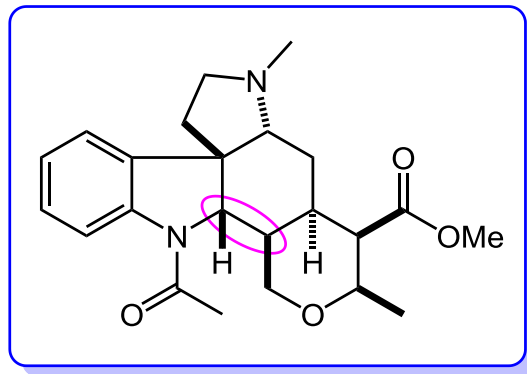
Pinnick Oxidation



Pinnick Oxidation



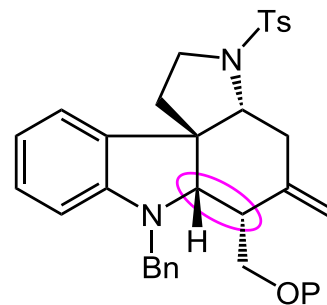
Blakey's Method



P = TBDPS

10

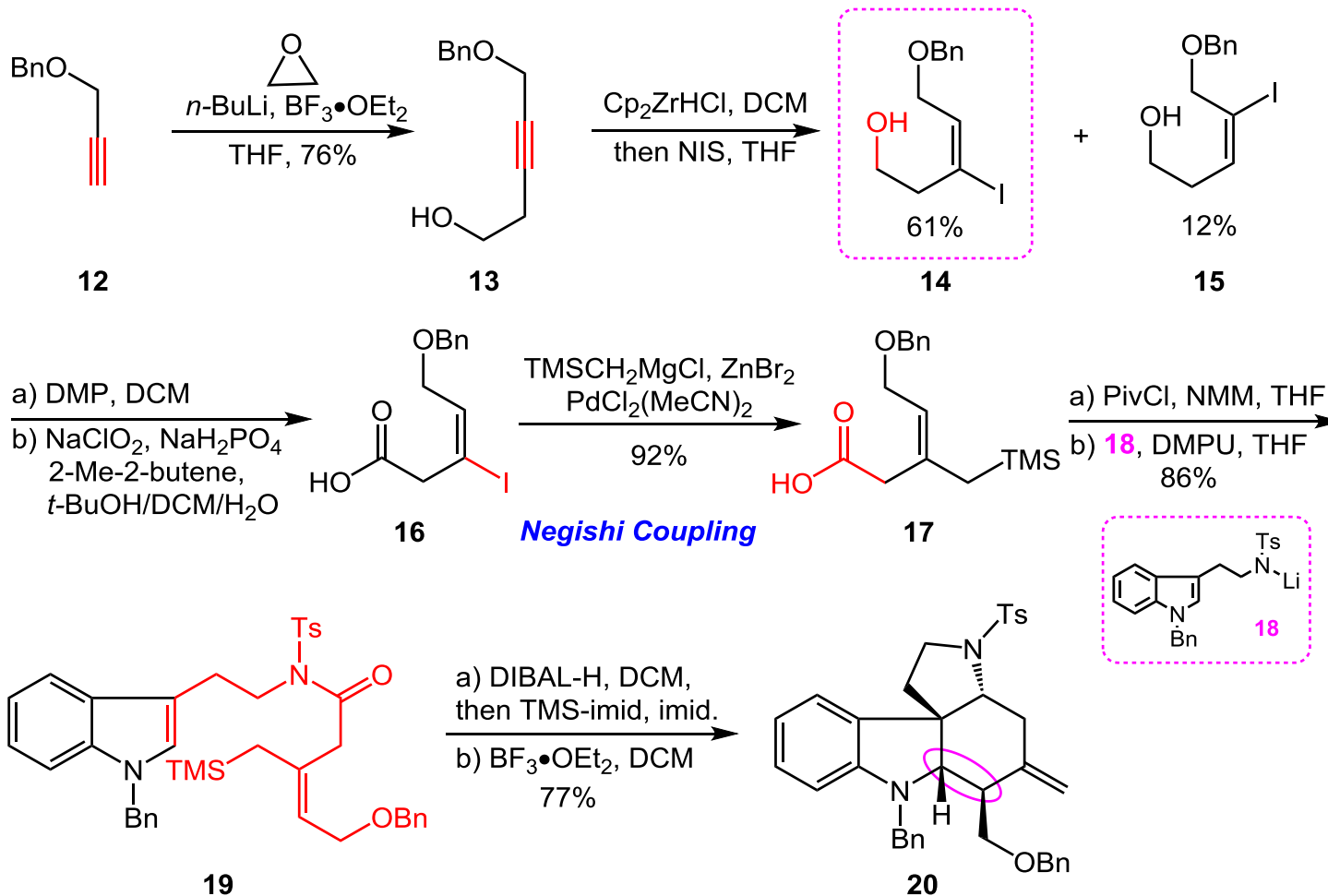
a) DIBAL-H, DCM,
then TMS-imid, imid.
b) BF₃•OEt₂, DCM
70%



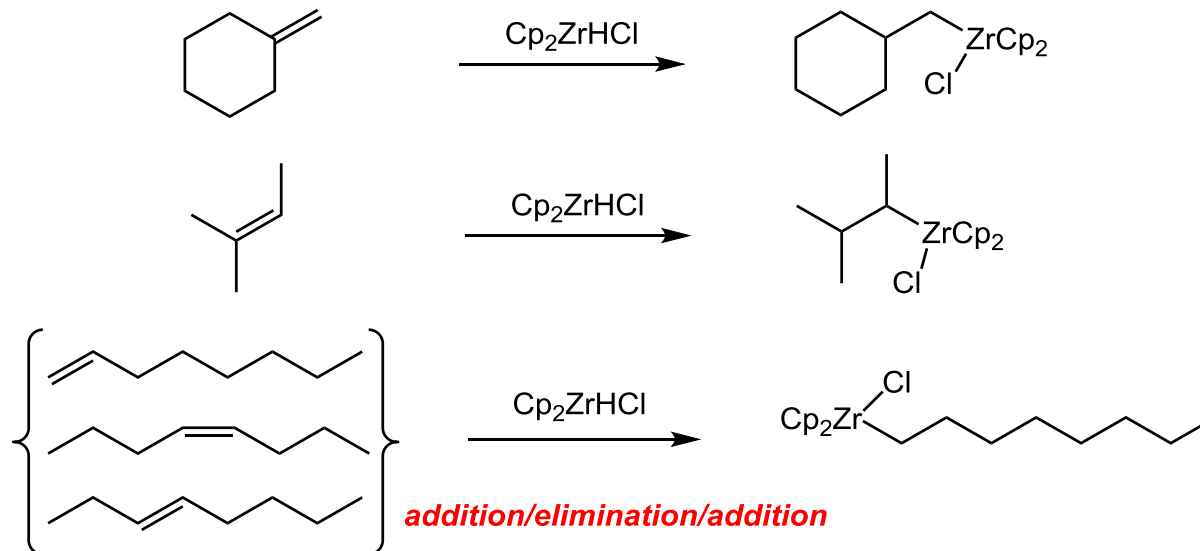
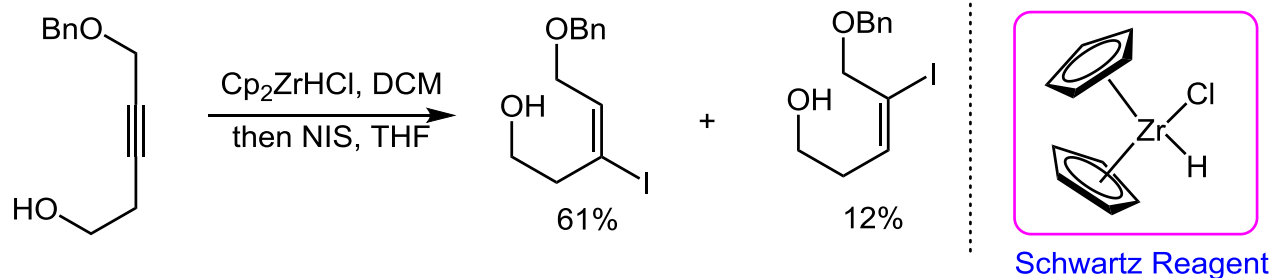
P = TBDPS

11

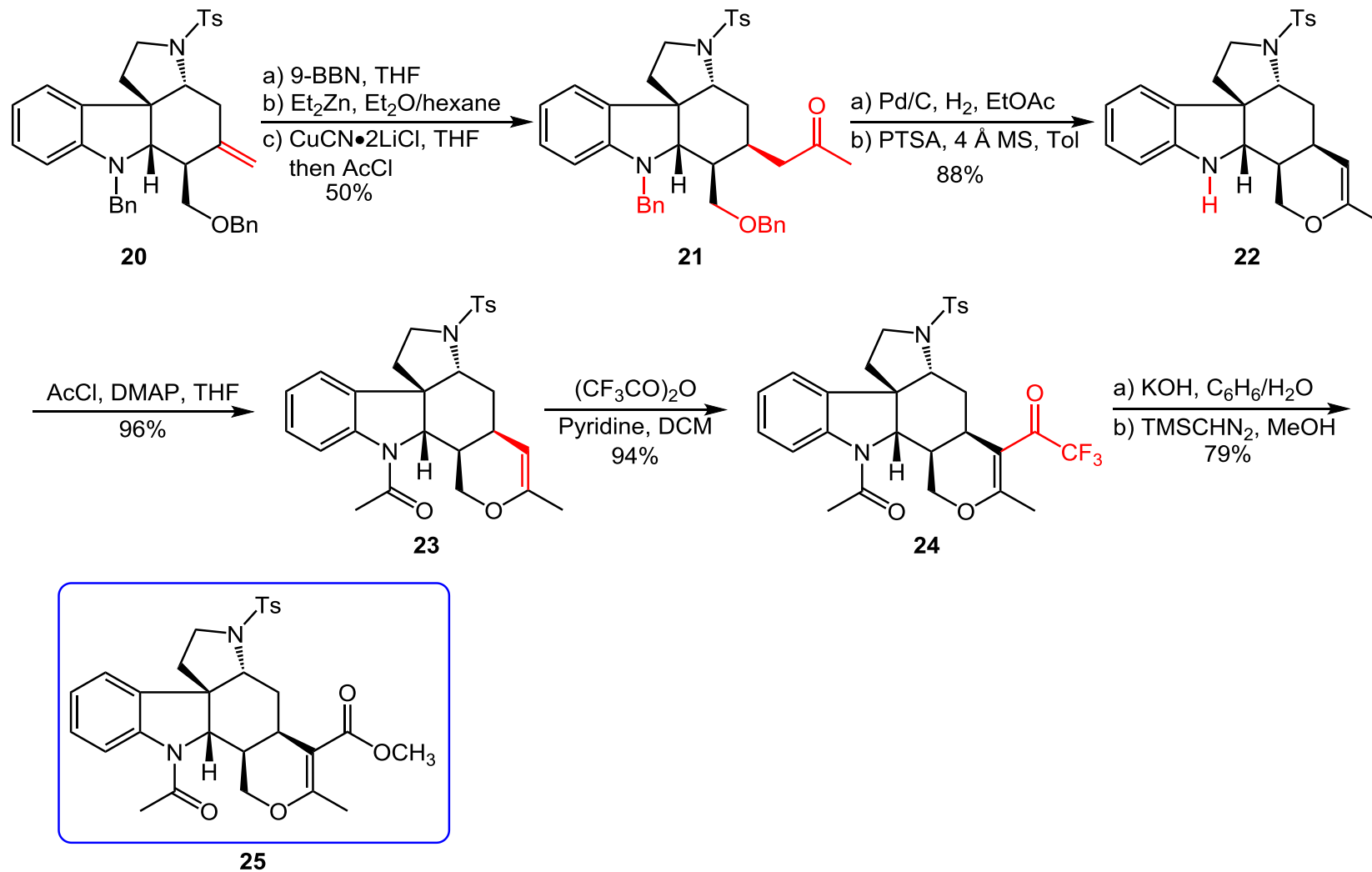
Blakey's Method



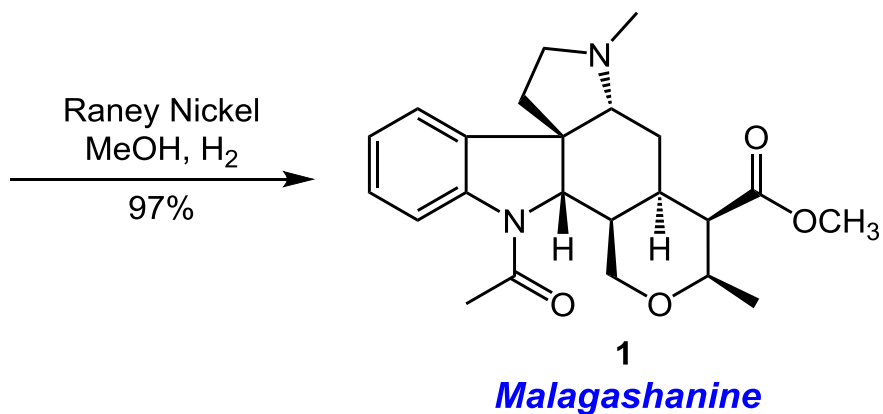
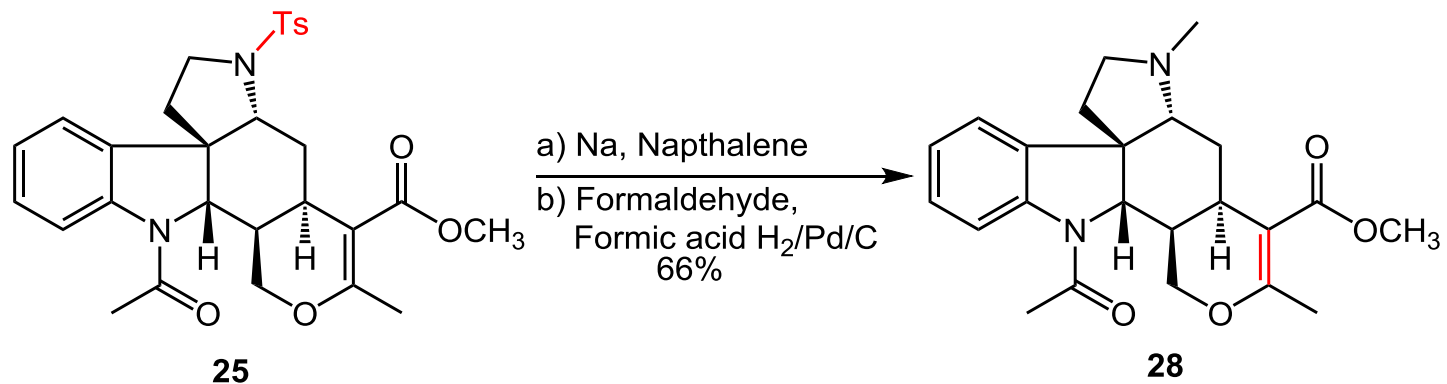
Schwartz Reagent



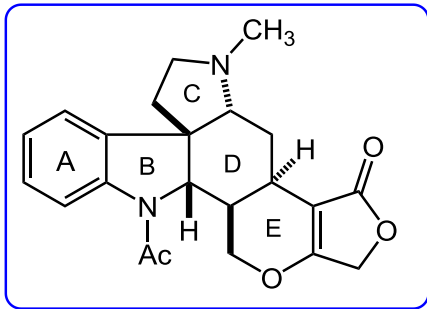
Synthesis of Key Intermediate 25



Synthesis of Malagashanine



11-Demethoxymyrtoidine



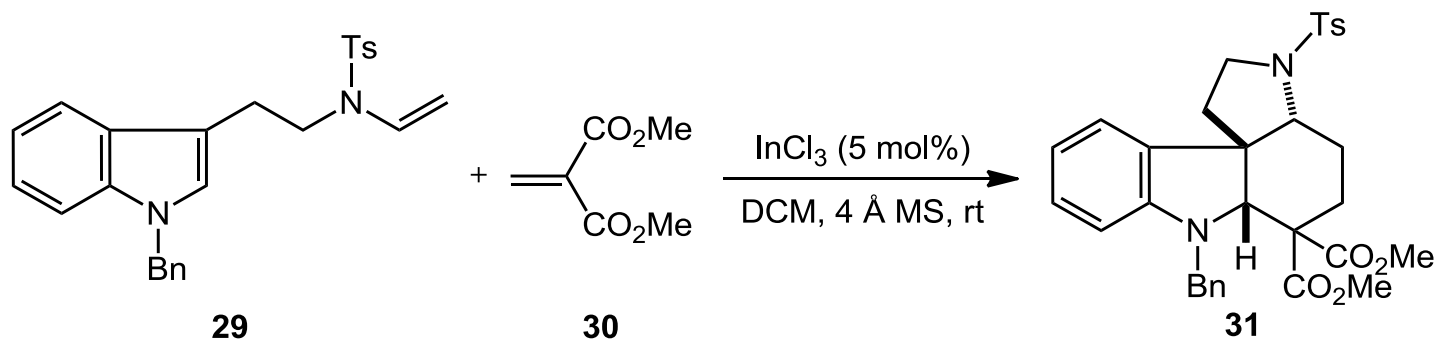
**11-Demethoxy-
myrtoidine**



Strychnos myrtoides
马钱子

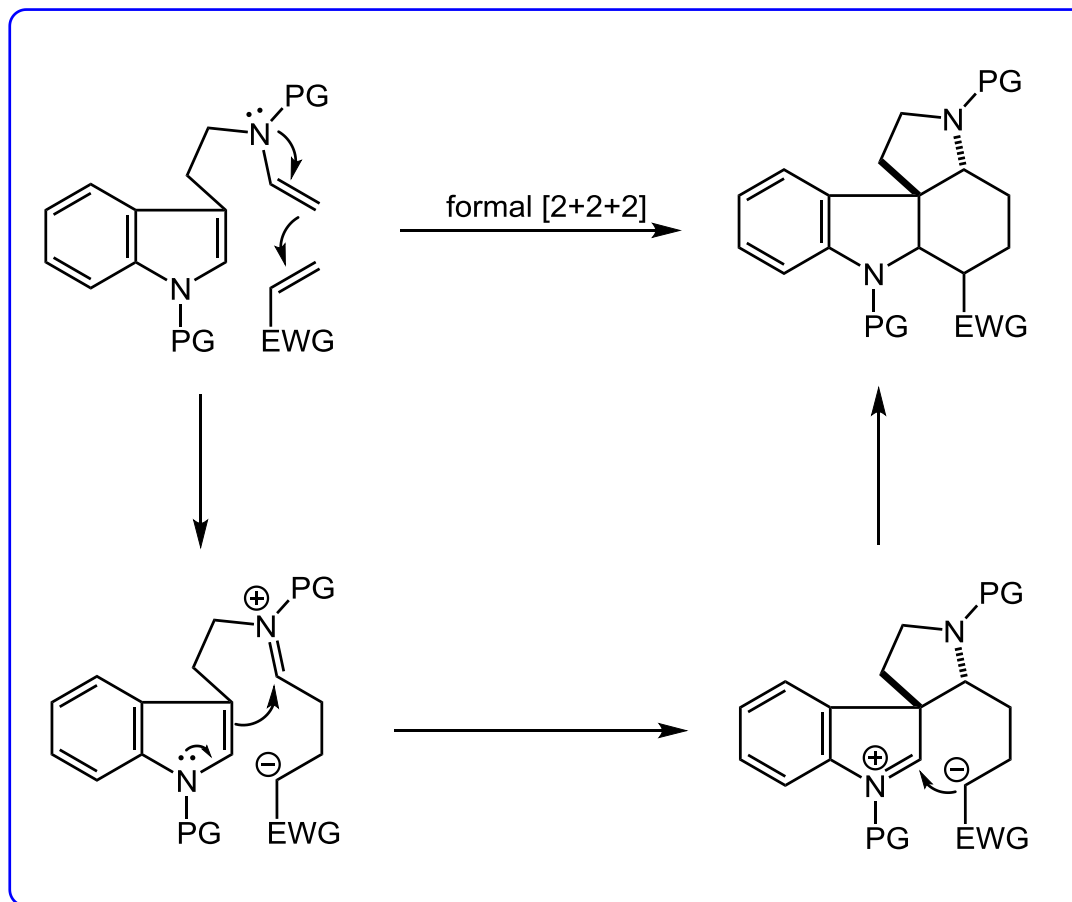
- Isolated from *Strychnos mostueoides* in 1999
- Promising anti-malaria activity
- Five stereocenters, complex fused rings in hexacyclic framework

Formal [2+2+2] Strategy



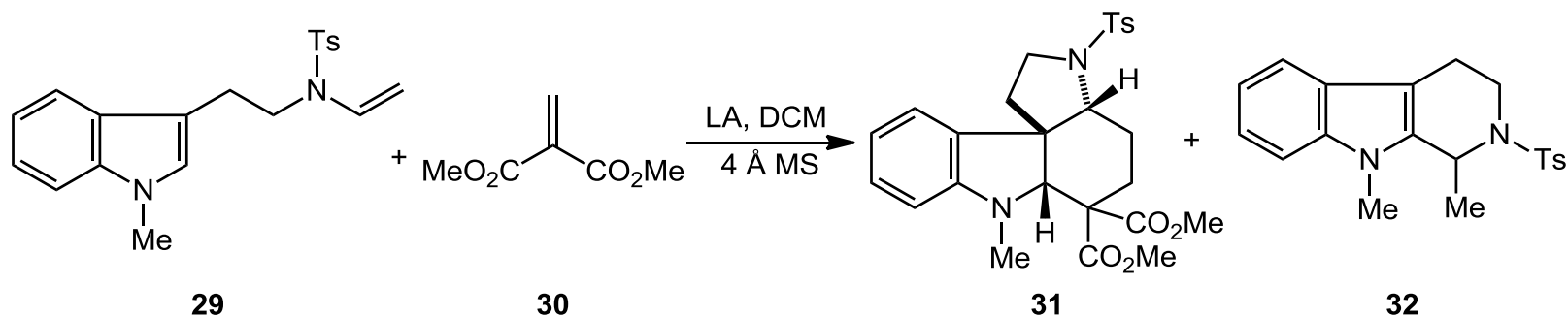
Tang, Y. *et al.* *Angew. Chem. Int. Ed.* **2016**, *55*, 9224.

Formal [2+2+2] Strategy



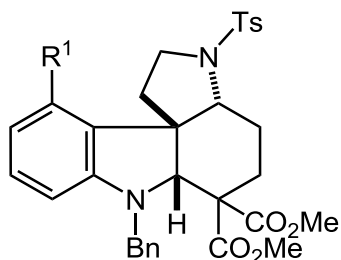
Tang, Y. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 9224.

Reaction Optimization

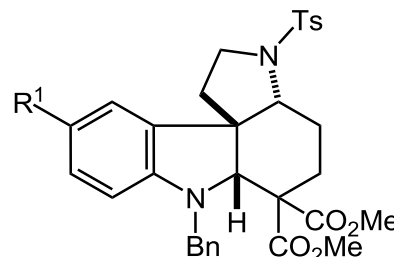


Entry	LA	<i>t</i>	31 (yield %)	32 (yield %)	d.r.
1	CuBr ₂	1 h	0	97	--
2	Cu(SbF ₆) ₂	23 h	0	72	--
3	FeCl ₃	40 min	73	trace	> 95:5
4	All ₃	25 min	0	> 99	--
5	InF ₃	17 h	trace	0	nd
6	InCl ₃	6 h	91	0	95:5
7	InBr ₃	20 min	85	0	> 95:5
8	InI ₃	15 min	85	0	> 95:5

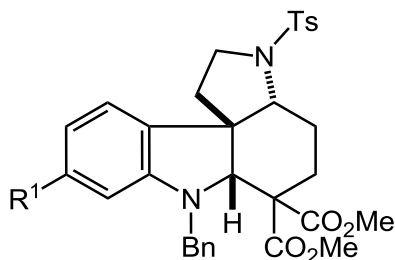
Reaction Scope



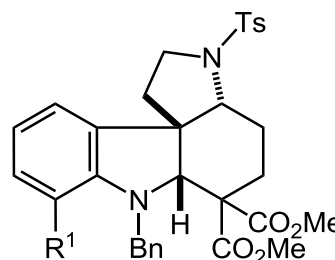
R¹ = H, 95:5 d.r., 90% yield
R¹ = F, 91:9 d.r., 65% yield
R¹ = Cl, 90:10 d.r., 90% yield
R¹ = Br, 89:11 d.r., 92% yield



R¹ = CH₃, > 95:5 d.r., 88% yield
R¹ = OCH₃, > 95:5 d.r., 88% yield
R¹ = F, 91:9 d.r., 65% yield
R¹ = Cl, 90:10 d.r., 90% yield
R¹ = Br, 89:11 d.r., 92% yield

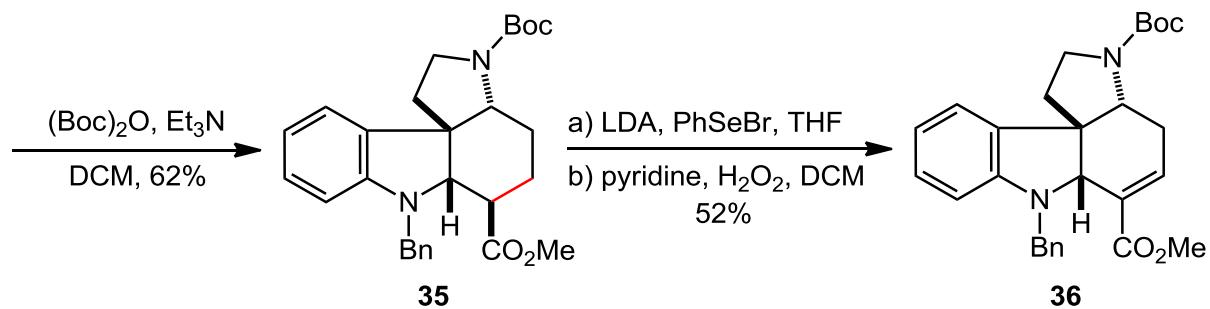
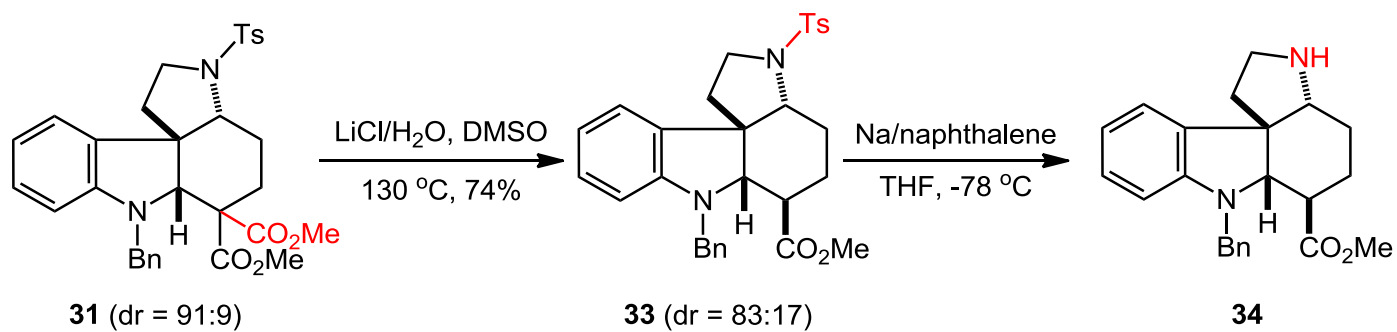
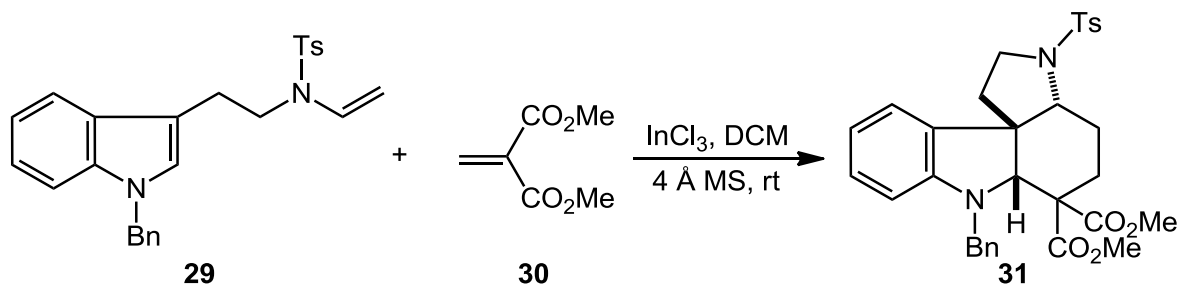


R¹ = Cl, 86:14 d.r., 86% yield
R¹ = Br, 87:13 d.r., 93% yield

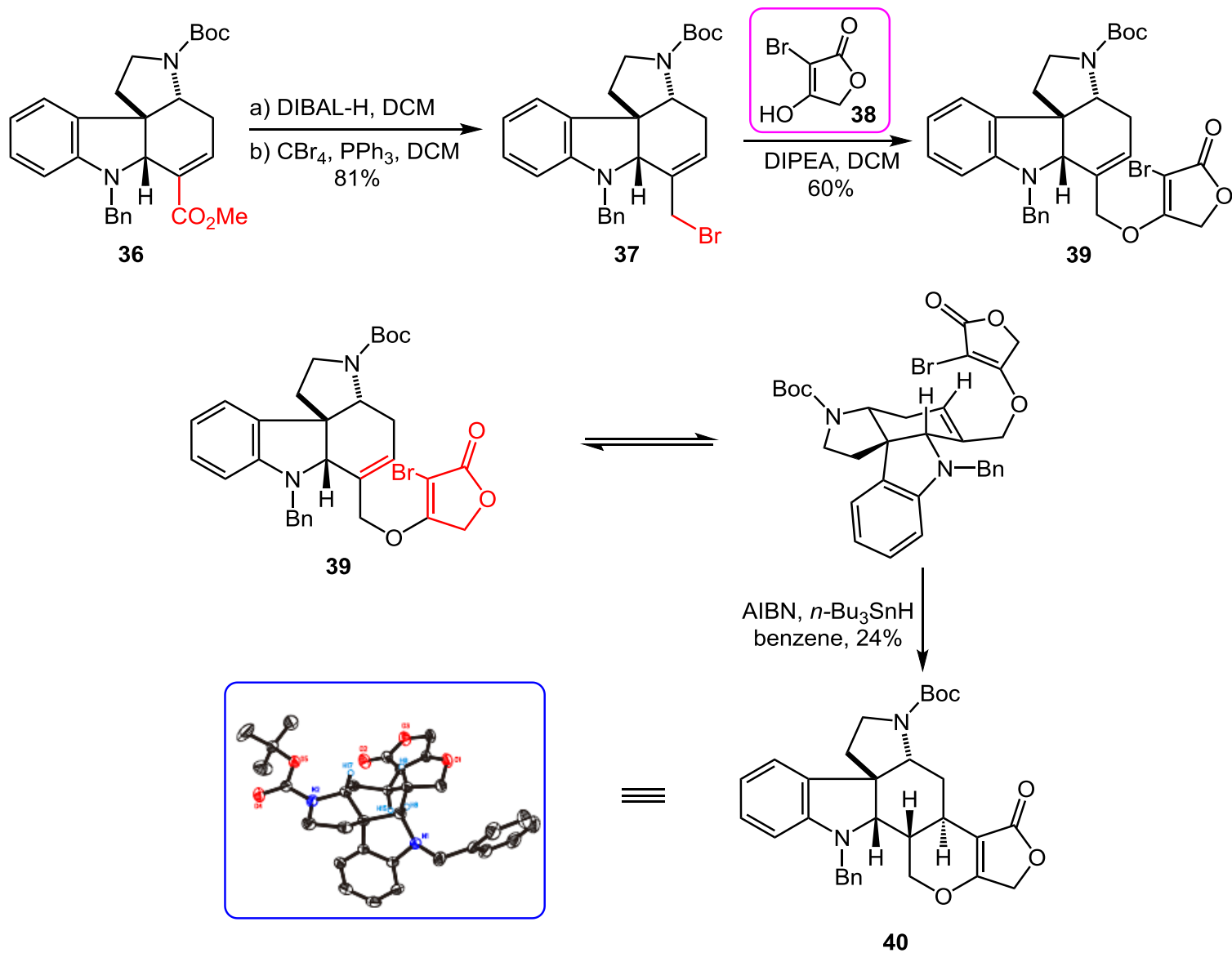


R¹ = CH₃, 95:5 d.r., 89% yield
R¹ = Et, 95:5 d.r., 85% yield
R¹ = OBn, 92:8 d.r., 87% yield
R¹ = Cl, 75:25 d.r., 91% yield
R¹ = Br, 75:25 d.r., 93% yield

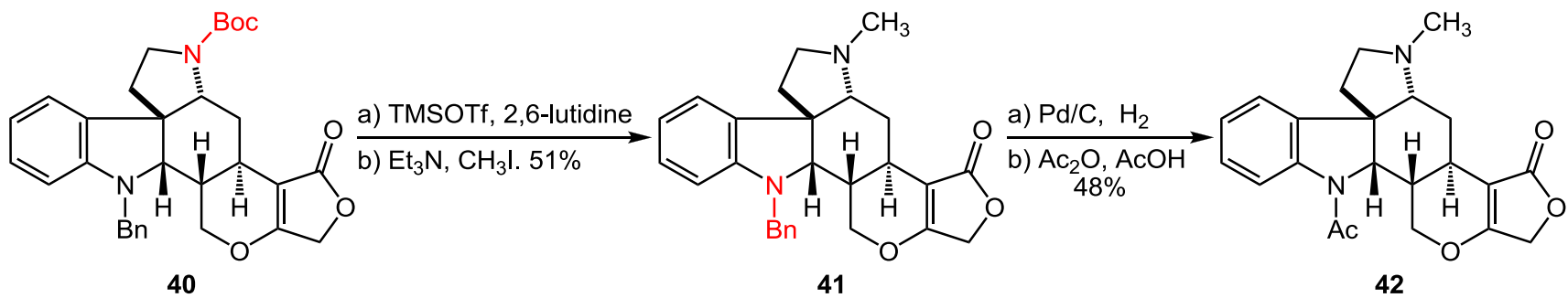
Tang's Method



Tang's Method

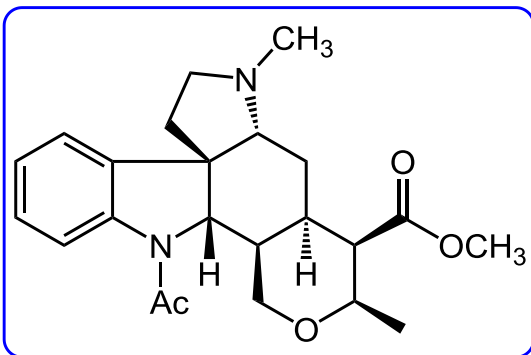


Tang's Method



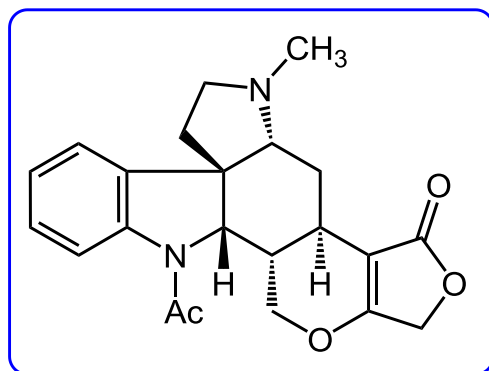
11-Demethoxy-16-epi-myrtoidine

Summary



- 21 steps, 2.6% overall yield
- Cascade annulation
- Hydrozirconation

Blakey, S. B. *et al. Chem. Sci.* **2016**, 7, ASAP.



- 14 steps, 1.3% overall yield
- Formal [2+2+2] strategy
- Radical cyclization

Tang, Y. *et al. Angew. Chem. Int. Ed.* **2016**, 55, 9224.

The First Paragraph

Malagashanine is a structurally unusual alkaloid that was isolated from the stem bark of the Madagascan shrub *Strychnos myrtoides* in the early 1990s. It was isolated during an ethnobotanical study investigating local approaches to malaria treatment, and was found to potentiate chloroquine against otherwise resistant *Plasmodium falciparum*. To date, the mechanism of action for this observed activity has not been established, although it was noted that malagashanine impacts chloroquine accumulation in the food vacuole of the malaria parasite.

The First Paragraph

Although initially incorrectly assigned, the structure of malagashanine was unambiguously determined by X-ray crystallography. The pentacyclic alkaloid contains seven consecutive stereocenters, and most strikingly, a *trans*-ring fusion between the C and D rings. To the best of our knowledge, this represents the first report of a *trans*-ring fusion in a Strychnos alkaloid and as a result, this core structure had not been the focus of any synthetic studies.

The Last Paragraph

In summary, we report a stereoselective synthesis of the chloroquine potentiating natural product malagashanine. A novel cascade annulation protocol efficiently constructs the C and D rings and installs four of the five consecutive D-ring stereocenters, including the critical *trans*-CD ring fusion. This represents the first total synthesis of a member of the Malagasy alkaloid family of natural products and provides a foundation for an exploration of the interesting biological activity presented by these compounds.