

Literature Report 9

Total Synthesis of (-)-Welwitindolinone B

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Checker: Lei Shi

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Rawal, V. H. *et al*
Angew. Chem. Int. Ed. **2017**, *56*, 9962.

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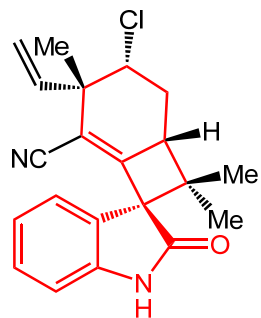
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2 Total Synthesis of (-)-Welwitindolinone B by Garg

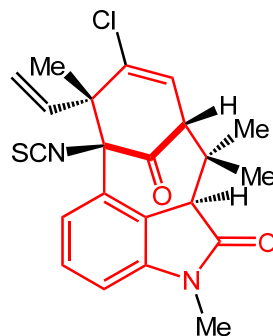
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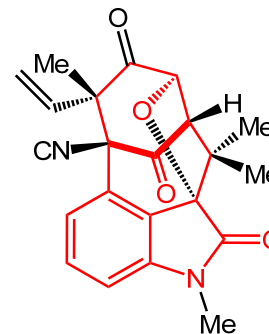
Introduction



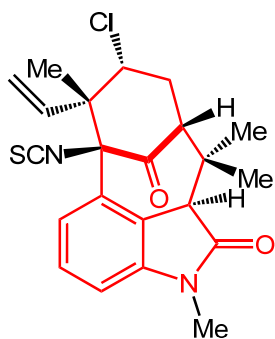
**Welwitindolinone
A isonitrile (1)**



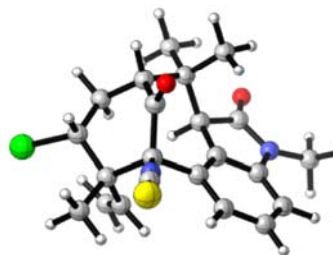
**N-Methylwelwitindolinone
C isothiocyanate (3)**



**N-Methylwelwitindolinone
D isonitrile (4)**

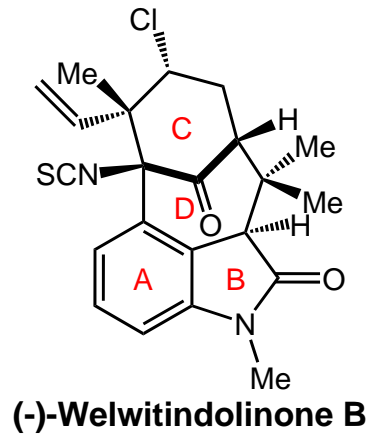


**N-Methylwelwitindolinone
B isothiocyanate (2)**



Moore, R. E. *et al J. Nat. Prod.* **1999**, 62, 569.
Garg, N. K. *et al J. Am. Chem. Soc.* **2014**, 136, 14710.

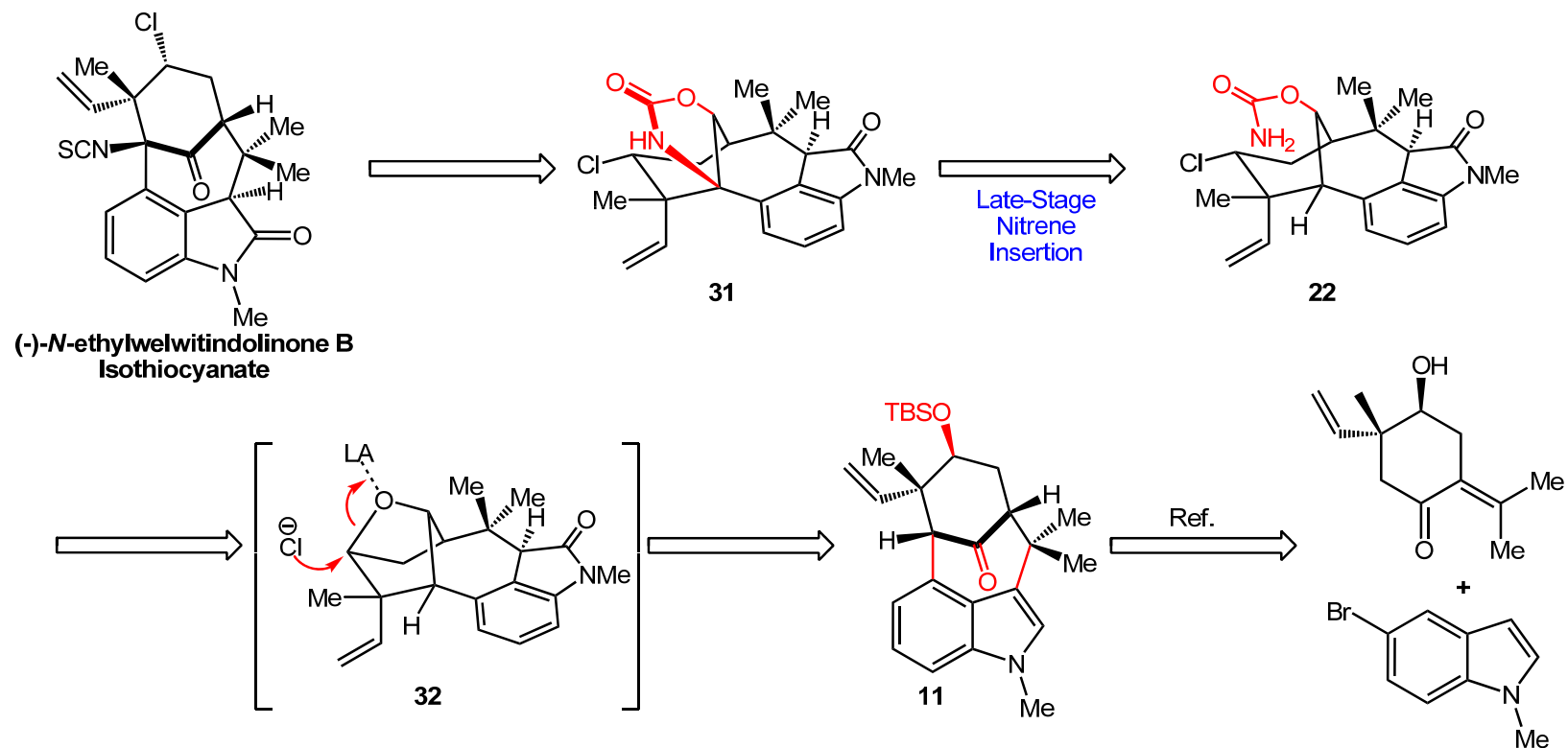
Introduction



Blue-green algae

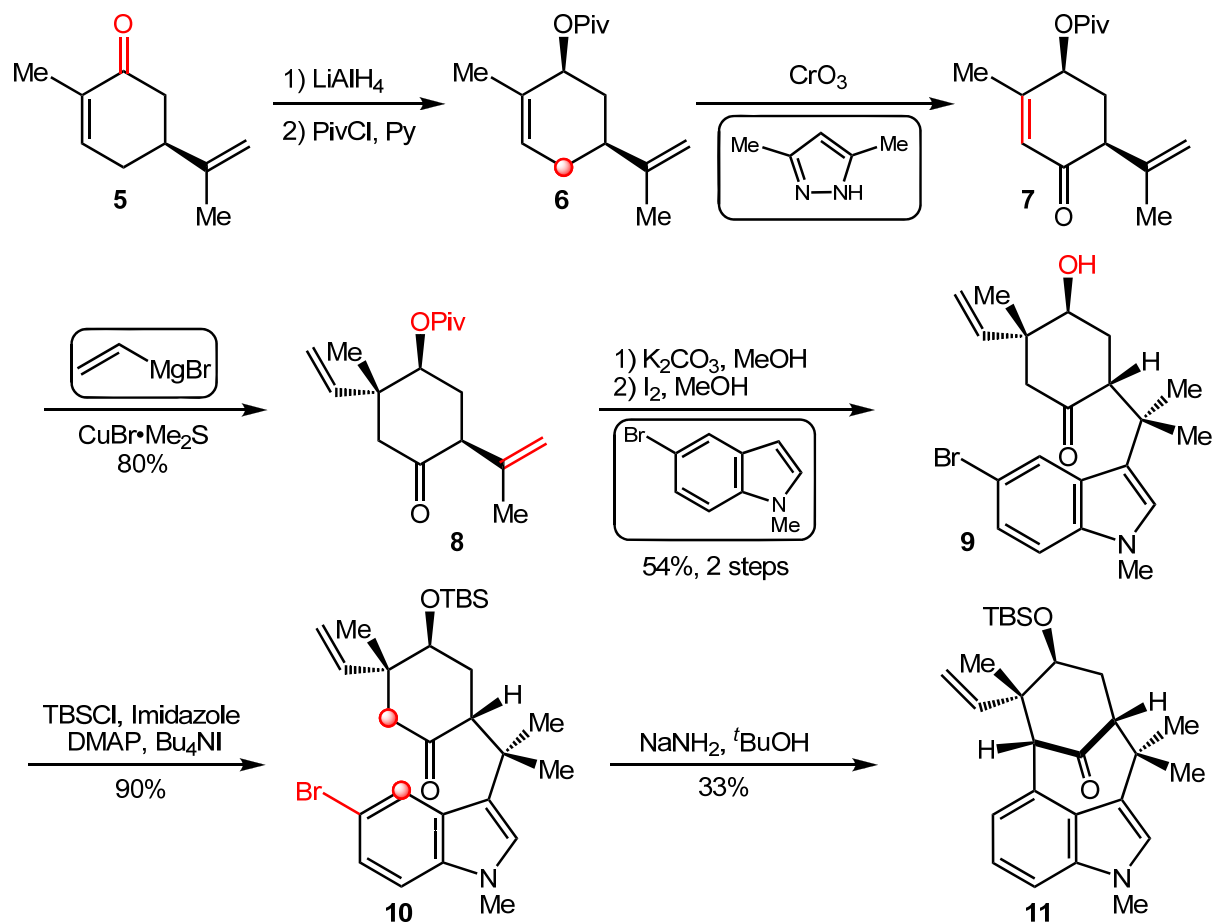
-
- ◆ It was isolated from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata* by Moore group in 1994.
 - ◆ It features a bicyclo[4.3.1]decane framework obtained by conjoining a diversely functionalized cyclohexanone fragment to the C3 and C4 positions of an oxindole.

Retrosynthetic Analysis



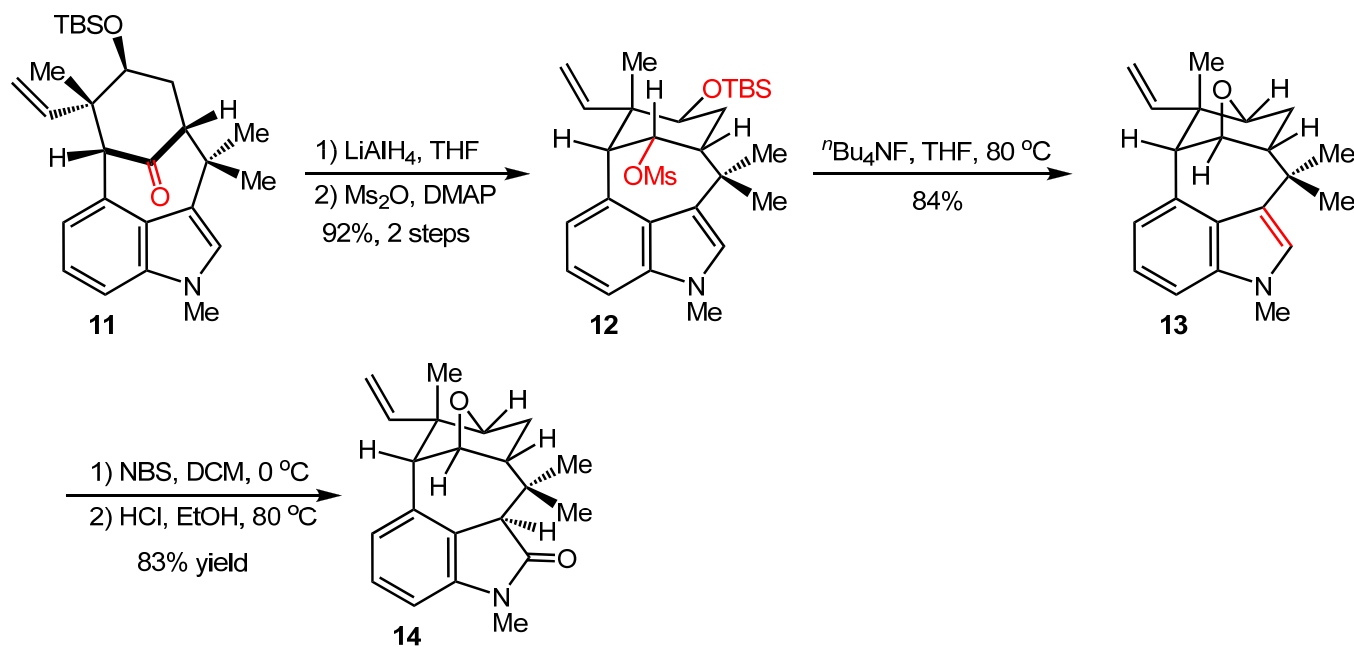
Garg, N. K. *et al* *J. Am. Chem. Soc.* **2014**, *136*, 14710.

Synthesis of Key Intermediate

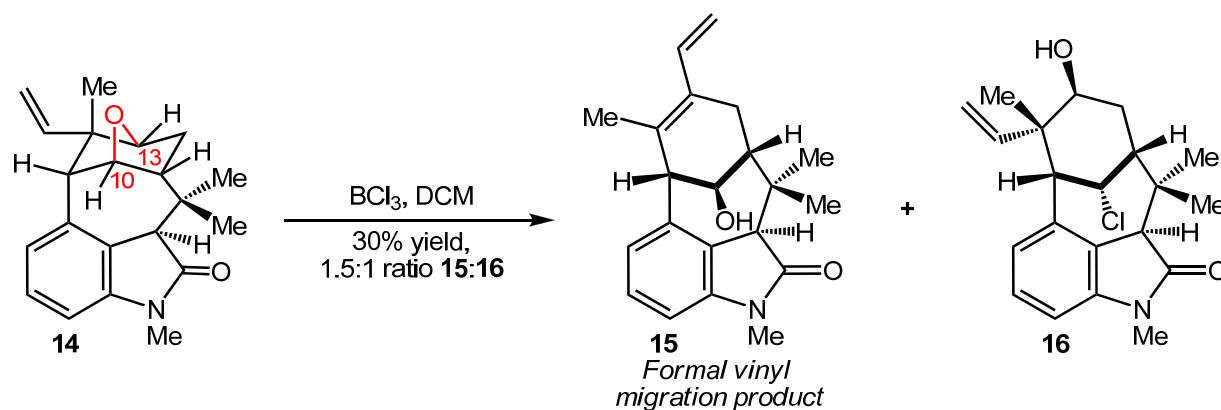
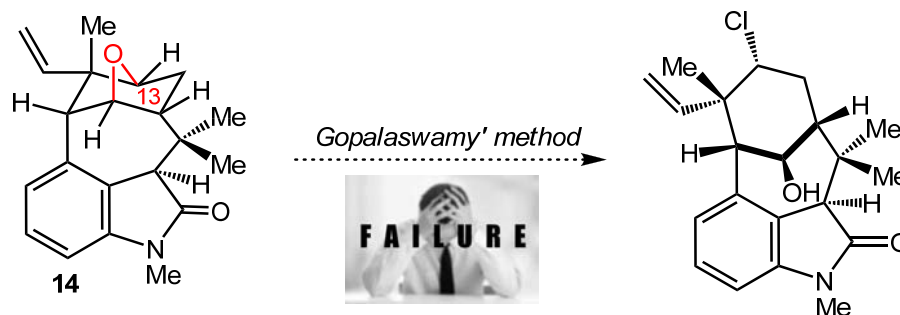


Natsume, M. *et al* *Chem. Pharm. Bull.* **1994**, *42*, 1393.
Garg, N. K. *et al* *J. Am. Chem. Soc.* **2011**, *133*, 15797.

Total Synthesis of (-)-Welwitindolinone B by Garg



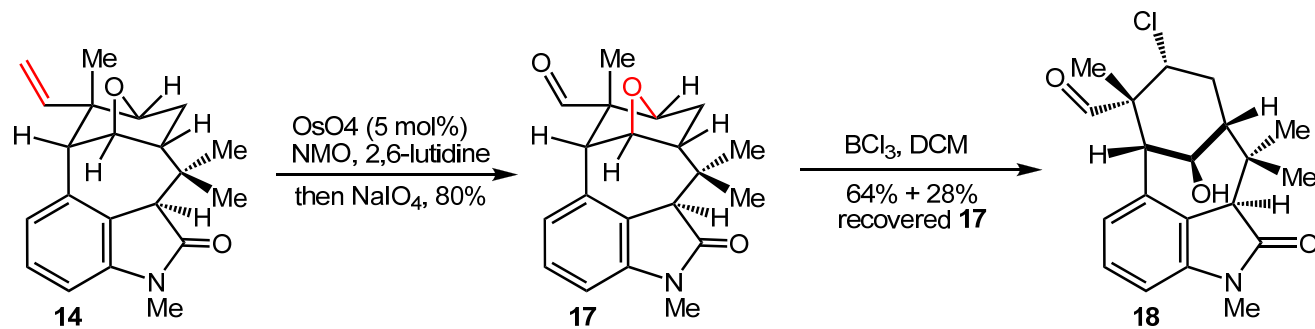
Attempts to Achieve the Chlorinative Ring Opening



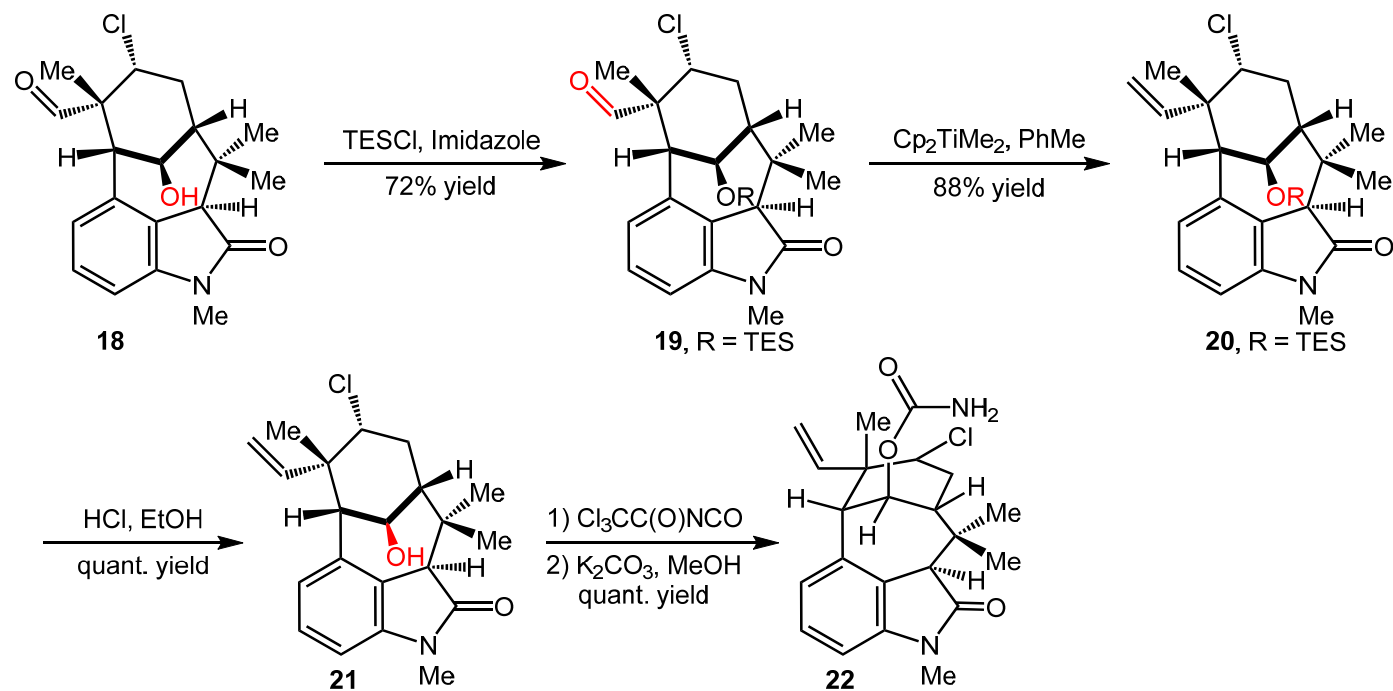
Attempts to achieve the chlorinative ring opening of indolooxabicyclo resulted in undesired byproducts.

Gopalswamy, R. *et al* *J. Am. Chem. Soc.* **1995**, *117*, 10595.

Attempts to Achieve the Chlorinative Ring Opening

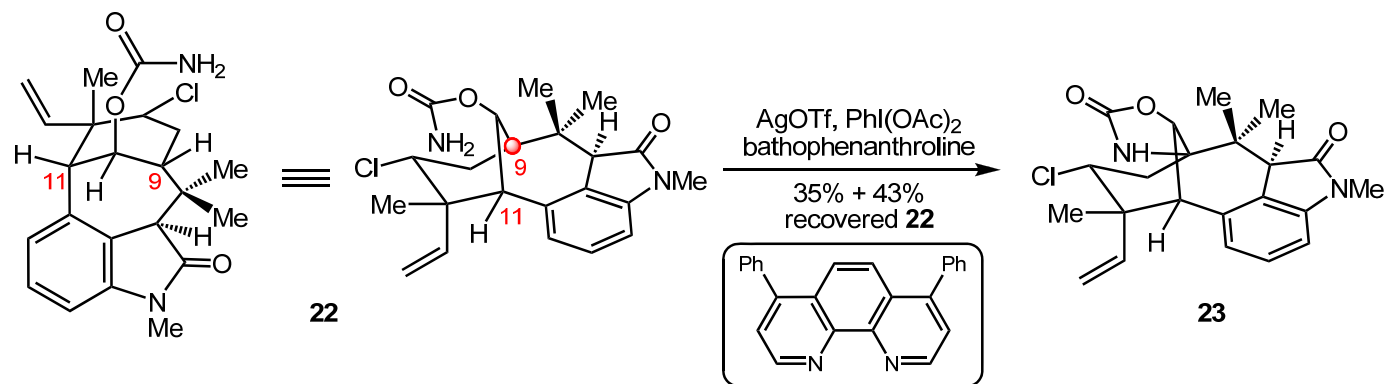


Total Synthesis of (-)-Welwitindolinone B by Garg



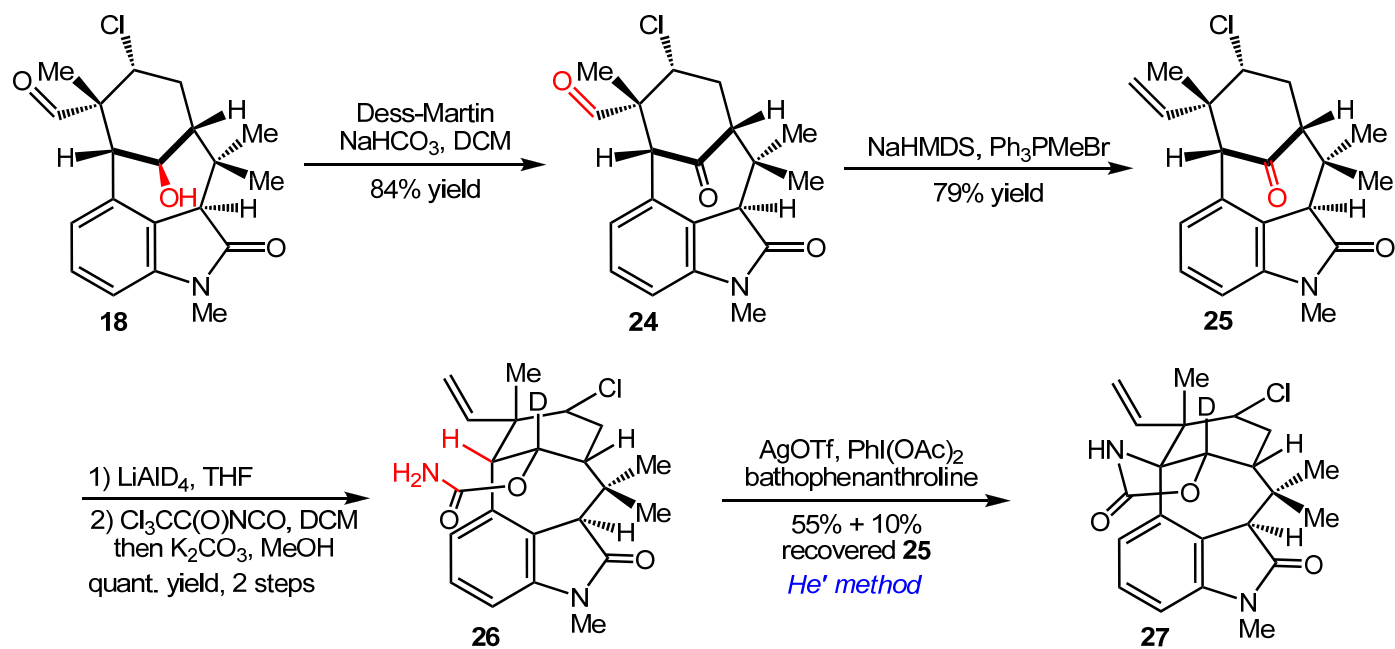
Attempted Nitrene Insertion

Ag-Promoted Nitrene Insertion Reaction

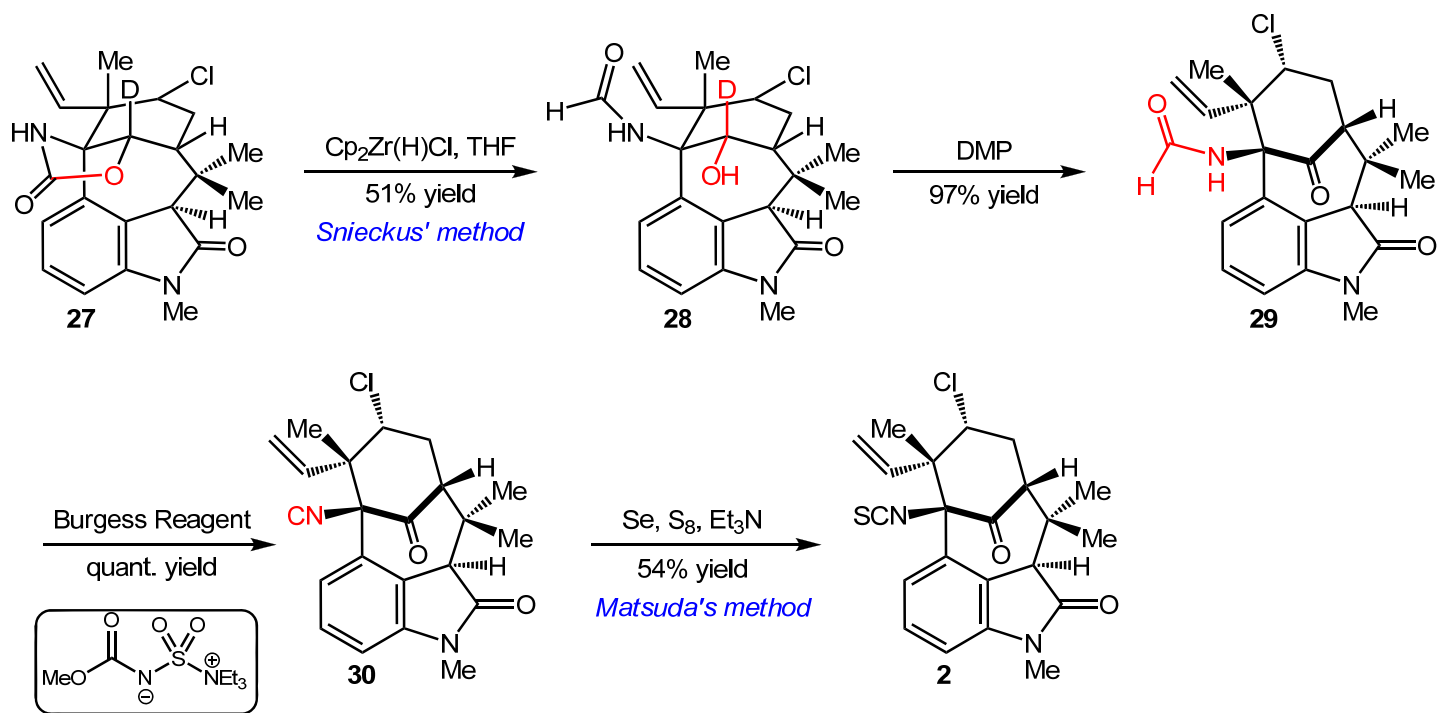


He, C. *et al* *Angew. Chem. Int. Ed.* **2004**, 43, 4210.

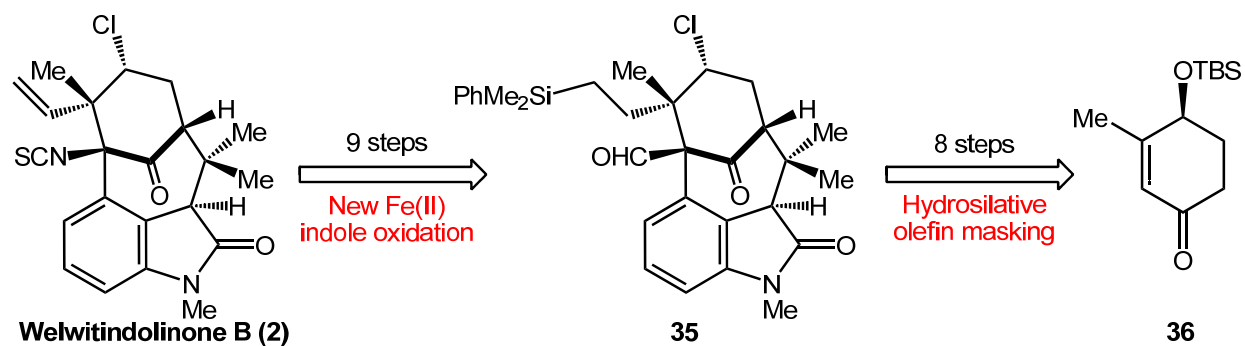
Total Synthesis of (-)-Welwitindolinone B by Garg



Total Synthesis of (-)-Welwitindolinone B by Garg



Total Synthesis of (-)-Welwitindolinone B by Rawal



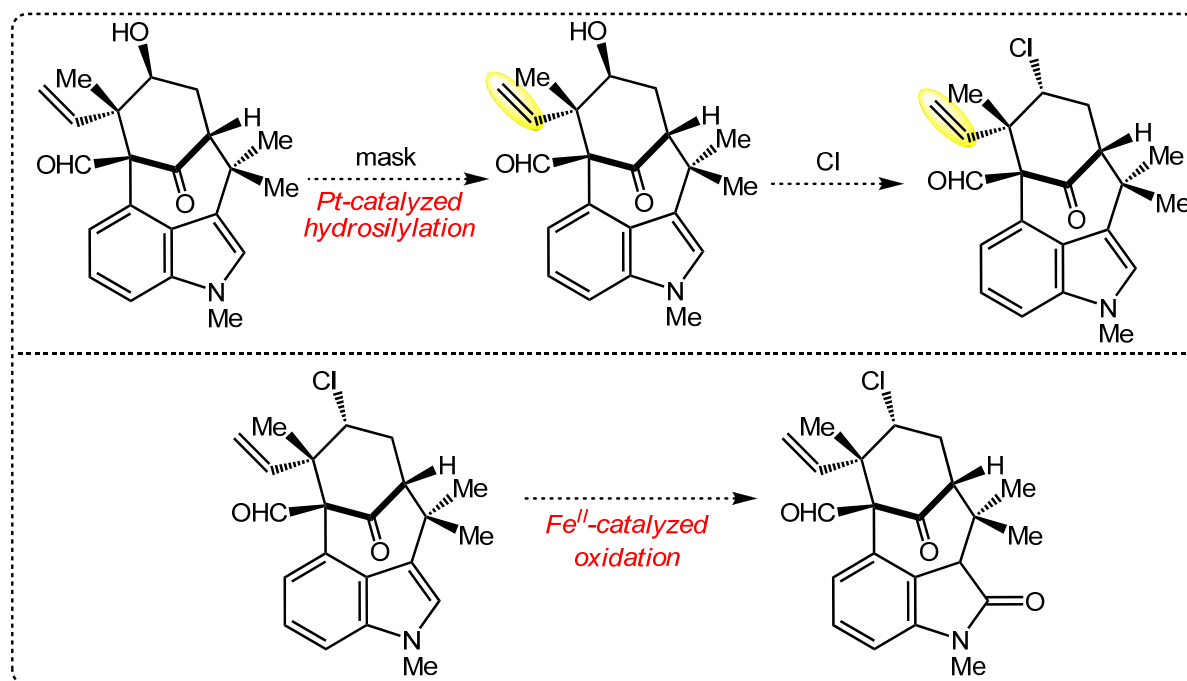
Rawal, V. H. *et al* *Angew. Chem. Int. Ed.* **2017**, *56*, 9922.

Challenges and Planned Strategy

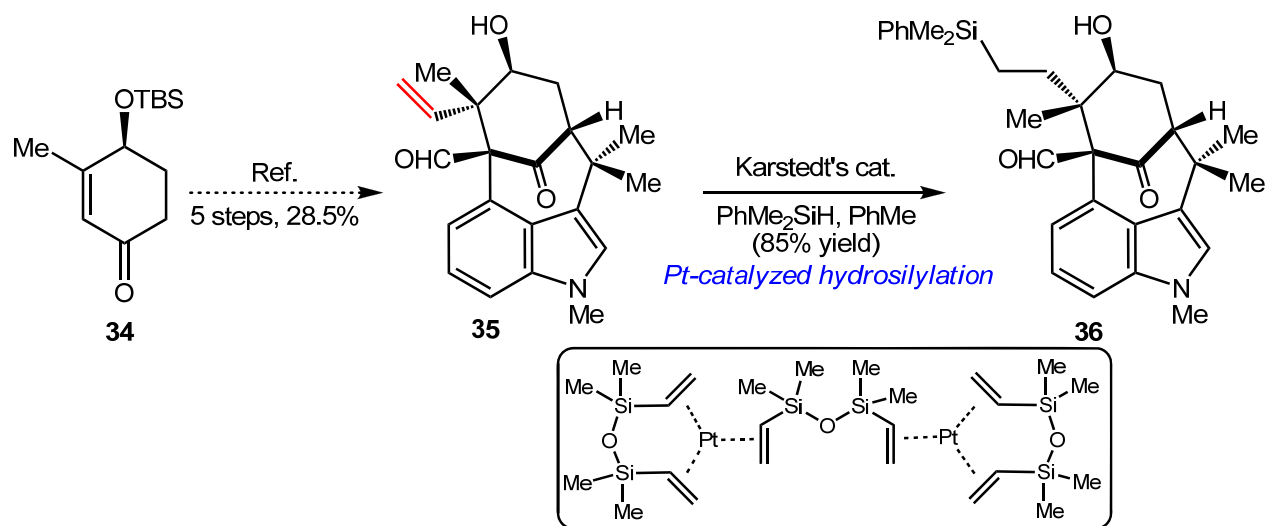
Challenges:

- ◆ Stereoselective installation of the sterically congested C13 alkyl chloride
- ◆ Control of the wayward reactivity of the indole unit

Planned Strategy:



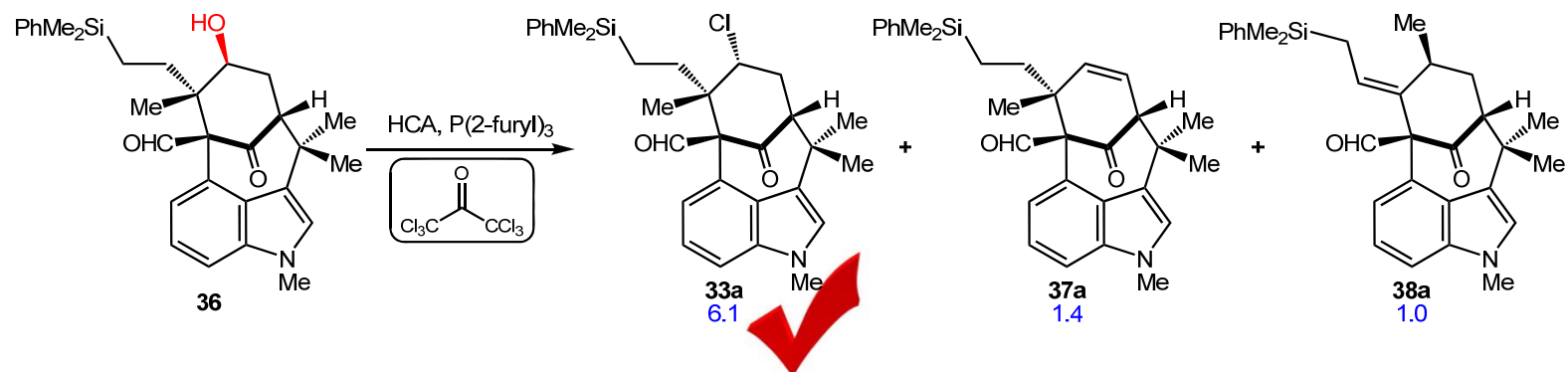
Total Synthesis of (-)-Welwitindolinone B by Rawal



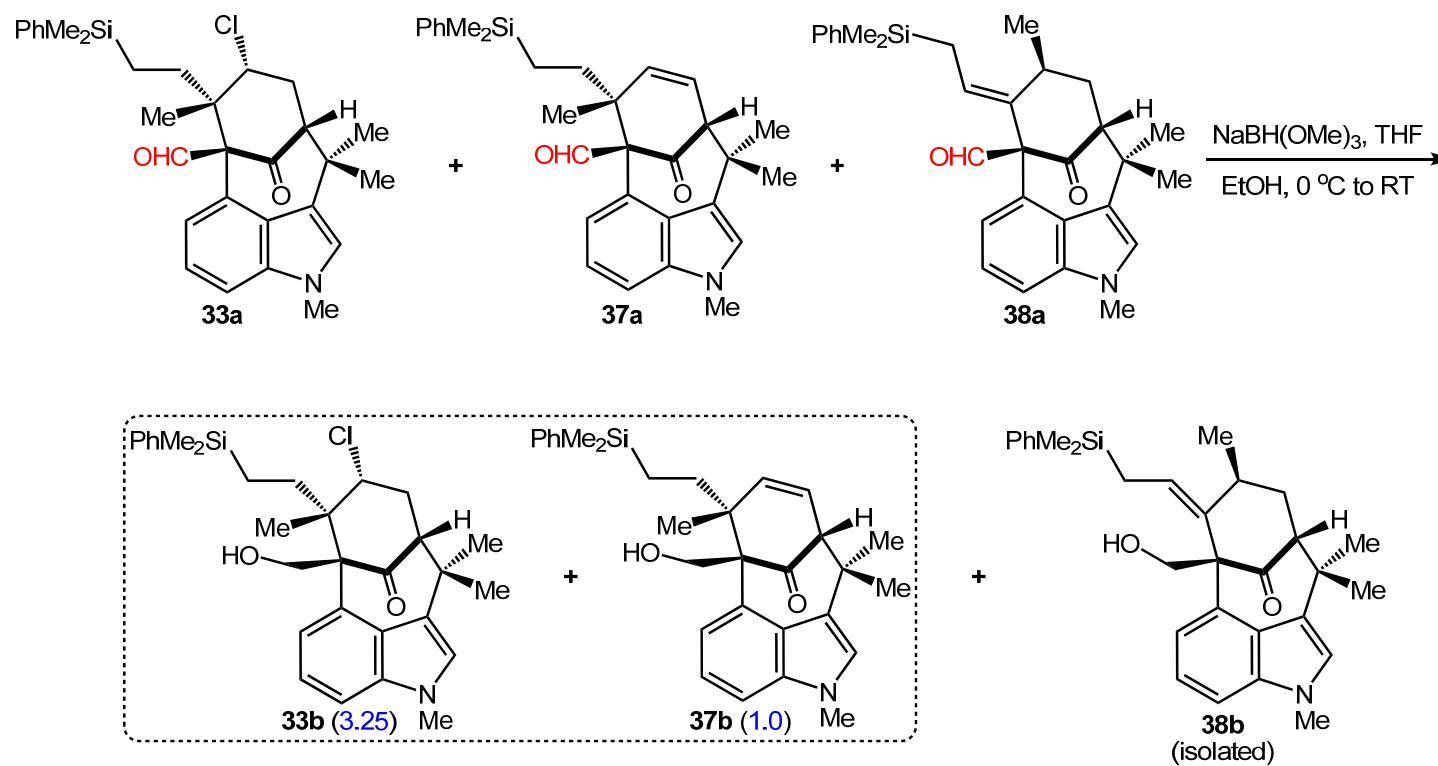
Rawal, V. H. *et al* *J. Am. Chem. Soc.* **2011**, *133*, 5798.
Rawal, V. H. *et al* *Angew. Chem. Int. Ed.* **2017**, *56*, 9922.

Total Synthesis of (-)-Welwitindolinone B by Rawal

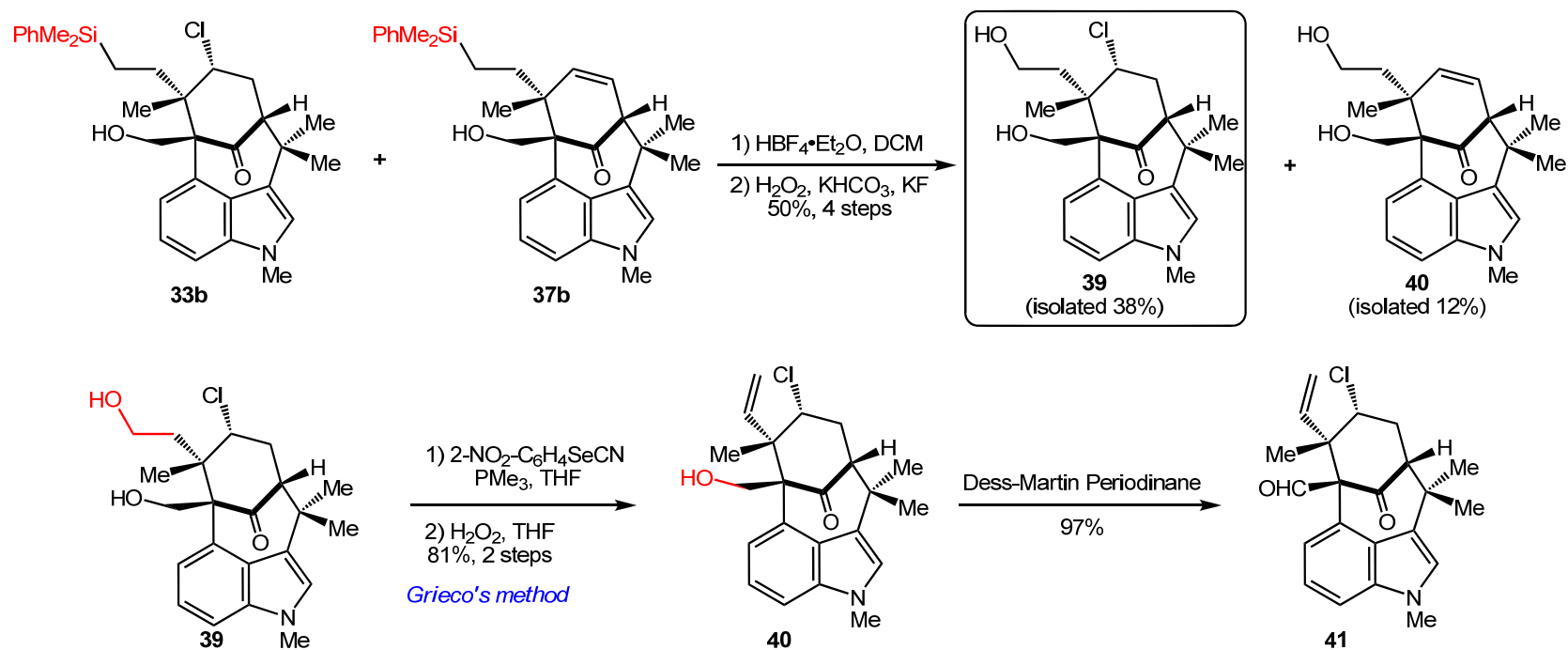
Stereoselective Installation of Chloride



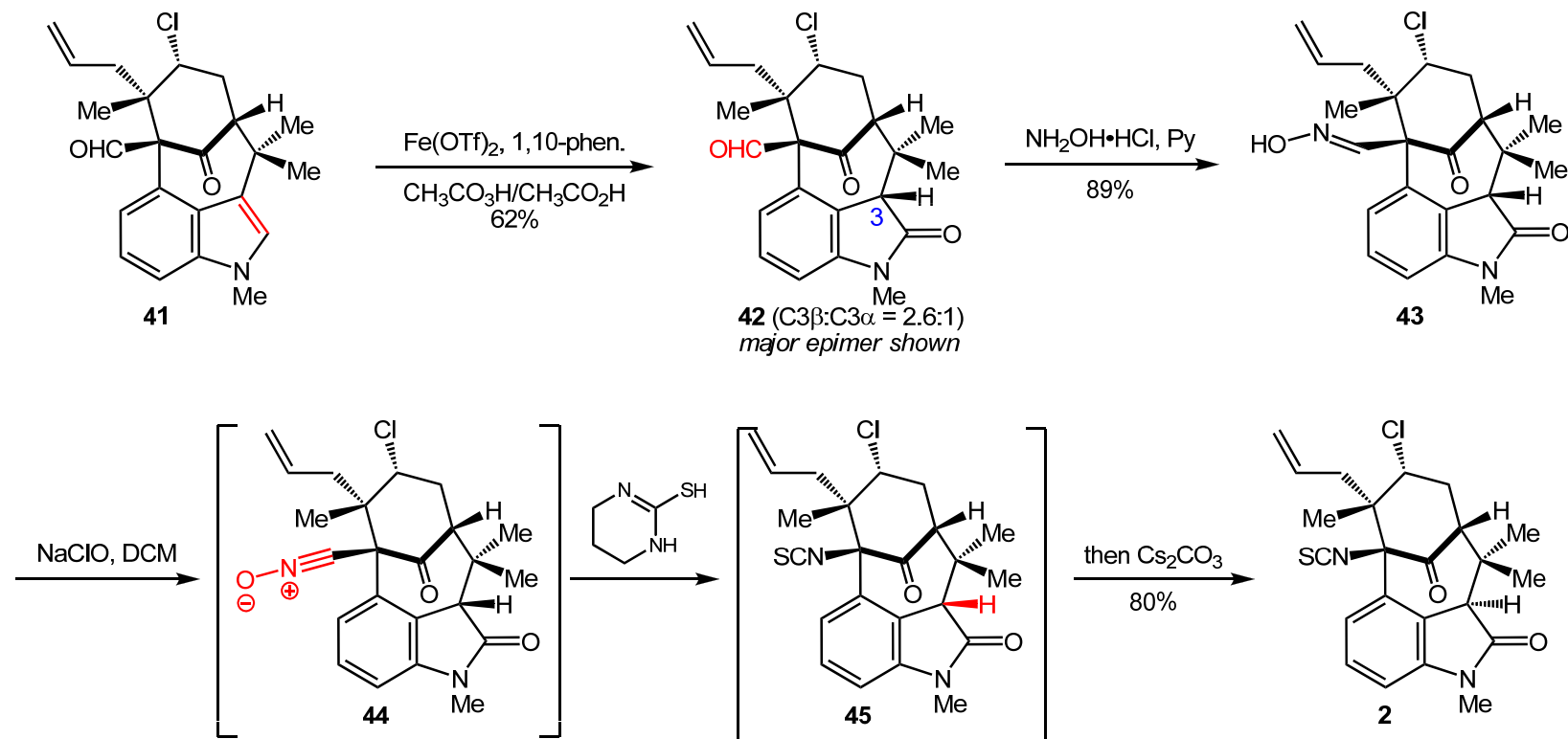
Total Synthesis of (-)-Welwitindolinone B by Rawal



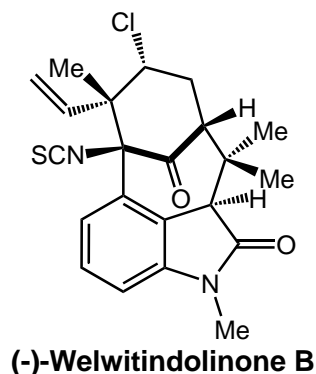
Total Synthesis of (-)-Welwitindolinone B by Rawal



Total Synthesis of (-)-Welwitindolinone B by Rawal



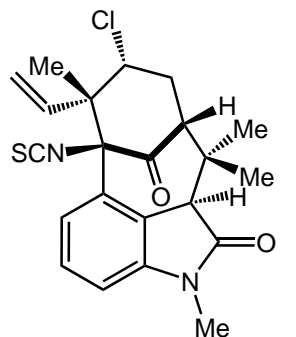
Summary



- ◆ The **first asymmetric** total synthesis of (-)-*N*-methylwelwitindolinone B isothiocyanate.
- ◆ The total synthesis of (-)-*N*-methylwelwitindolinone B isothiocyanate was achieved **in 15 steps** with **3.2% overall yield**.
- ◆ It features the use of a regio- and diastereoselective chlorinative oxabicyclic ring-opening reaction to introduce the challenging alkyl chloride.

Garg, N. K. *et al J. Am. Chem. Soc.* **2014**, 136, 14710.

Summary



- ◆ The total synthesis of was achieved **in 15 steps** with **3.5% overall yield**.
- ◆ Critical challenges include the stereoselective installation of the sterically congested C13 alkyl chloride and control of the wayward reactivity of the indole unit to standard oxidants.

Rawal, V. H. *et al Angew. Chem. Int. Ed.* **2017**, *56*, 9922.

The First Paragraph

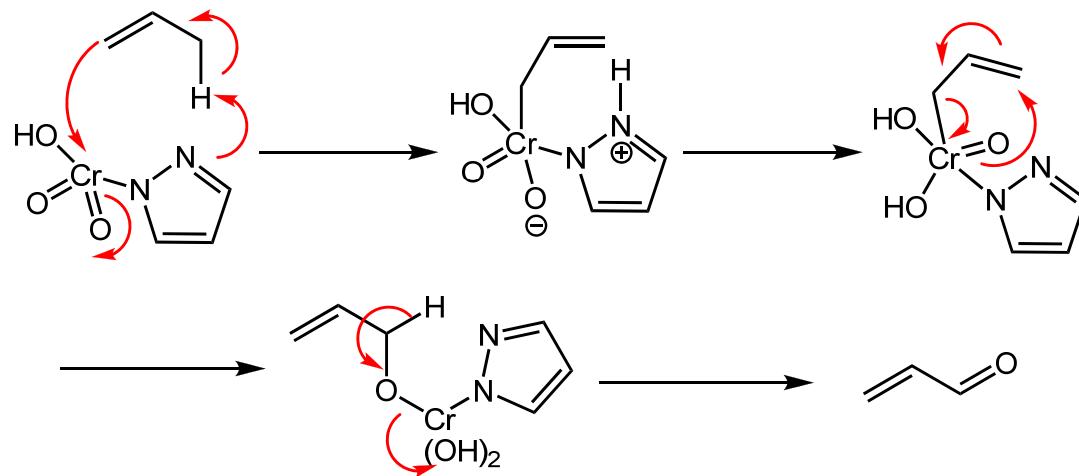
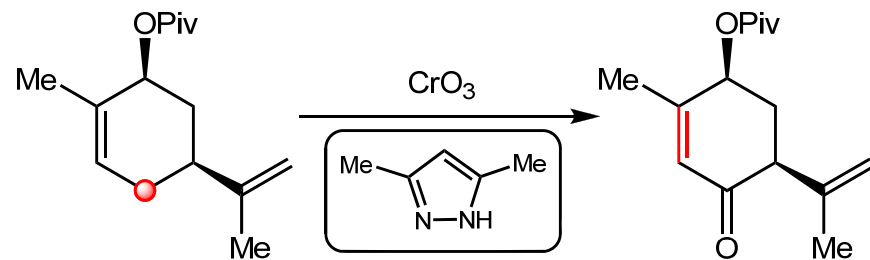
The welwitindolinone alkaloids, with their alluringly intricate structures, challenging oxidation patterns, promising biological activities, and intriguing biogenetic pathways, have been the subject of intense chemical research since their discovery by Moore and co-workers over twenty years ago (Figure 1). Isolated from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricata*, as well as the terrestrial cyanophytes *Fischerella muscicola* and *Fischerella major*, nearly all welwitindolinones feature a bicyclo[4.3.1]decane framework obtained by conjoining a diversely functionalized cyclohexanone fragment to the C3 and C4 positions of an oxindole.

The First Paragraph

The compact, densely substituted architecture of the welwitindolinones together with the unique biological activities displayed by some members have commanded the interest of numerous synthetic chemists, and preliminary and successful campaigns have been reported to many members. We present here an effective solution to the singular synthetic challenge posed by (-)-*N*-methylwelwitindolinone B isothiocyanate (**1b**), the only member of this class possessing a chloride attached to an sp³-hybridized carbon.

The Last Paragraph

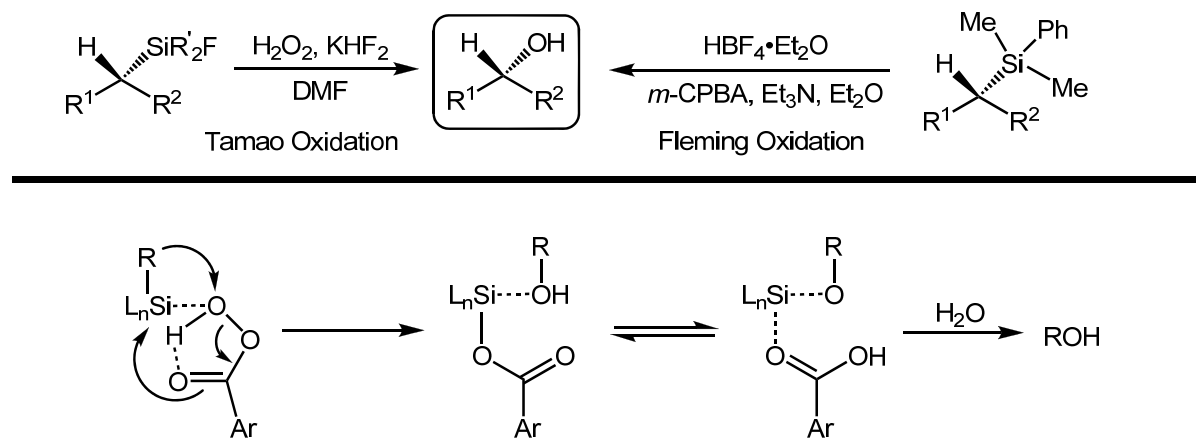
In summary, we have delineated an asymmetric total synthesis of (-)-*N*-methylwelwitindolinone B isothiocyanate (**1b**) in >11% overall yield from **7**, through a unified strategy that provides access to all members of the bridged welwitindolinones from this common intermediate. In the route, unforeseen complications engendered by the C20, C21 vinyl group were overcome through hydrosilative masking of the double bond, which then allowed stereocontrolled introduction of the challenging neopentyl, homoallylic chloride in **1b**. Significantly, this work motivated the discovery of an Fe^{II}-catalyzed oxidation of sterically demanding 3-substituted indoles to the corresponding oxindoles, a transformation that until now had belonged to the realm of cytochrome P-450 oxygenases.



Havens, J. L. *et al* *J. Org. Chem.* **1978**, *43*, 2057.

Fleming–Tamao Oxidation

The Fleming–Tamao oxidation, or Tamao–Kumada–Fleming oxidation, converts a carbon–silicon bond to a carbon–oxygen bond with a peroxy acid or hydrogen peroxide.



Wagner–Meerwein Rearrangement

Wagner–Meerwein rearrangement is a class of **carbocation 1,2-rearrangement reactions** in which a hydrogen, alkyl or aryl group migrates from one carbon to a neighboring carbon.

