# Total Synthesis of (-)-*N*-Methylwelwitindolinone B Isothiocyanate via a Chlorinative Oxabicycle Ring-Opening Strategy

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*J. Am. Chem. Soc.*, 2014, 136 (42), pp 14710–14713
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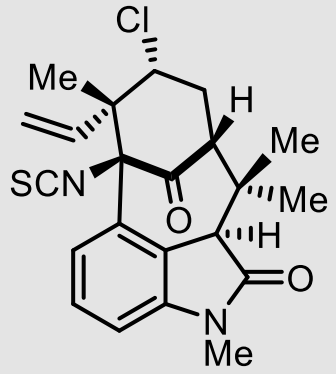
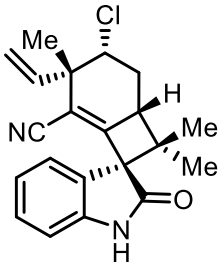


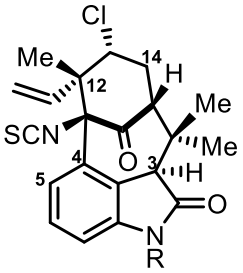

Tanja Krainz
Wipf Group Current Literature
8th November, 2014

# Family of Welwitindolinones

**Welwitindolinones**

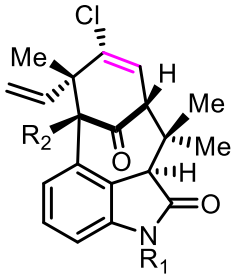


Welwitindolinone A isonitrile



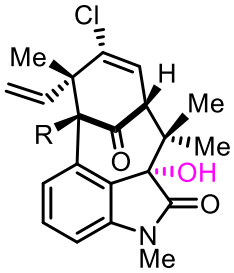
Welwitindolinone B isothiocyanate

R=H
R=Me



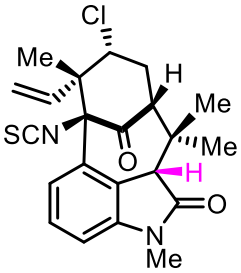
Welwitindolinone C isothiocyanate

R1=H, R2=NCS
R1=Me, R2=NCS
R1=Me, R2=NC

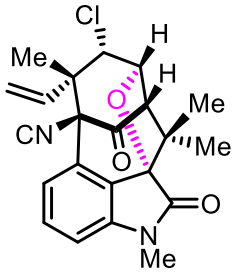


*C3*-Hydroxy-*N*-Mehtyl Welwitindolinone B isothiocyanate

R= NCS
R= NC

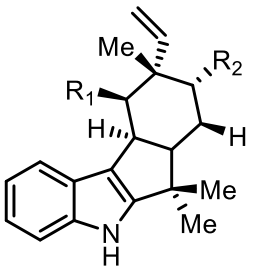


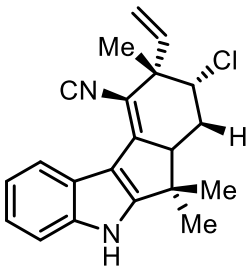
3-*epi*-Welwitindolinone B isothiocyanate



*N*-Methyl-welwitindolinone D isonitrile

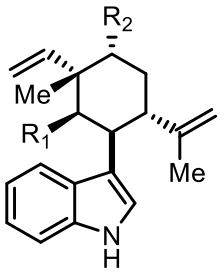
**Fischerindoles**





R1=NC, R2=Cl
R1=NC, R2=H
R1=NCS, R2=H

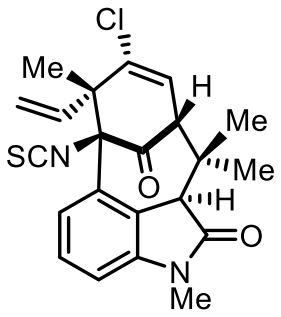
**Hapalindoles**



R1=NC, R2=Cl
R1=NC, R2=H
R1=NCS, R2=Cl
R1=NCS, R2=H

*JACS*, **1994**, 116, 9935; *J. Nat. Prod*. **1999**, 62, 569

# Welwitindolinones: Isolation and Biological activity




*N*-Methylwelwitindolinone C isothiocyanate

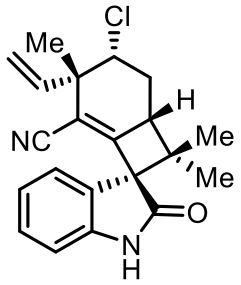
**Isolation:**
1994 and 1999 by Moore and co-workers from blue-green algae *Hapalosiphon welwitschii* and Westiella intricata

**Biological activity:**
- Insecticidal
- Antimycotic

- *N*-Methylwelwitindolinone C isothiocyanate has the ability to reverse P-glycoprotein-mediated multiple drug resistance (MDR) to a variety of anti-cancer drugs in human cancer cell lines.
- Lead therapeutic in drug resistant tumors

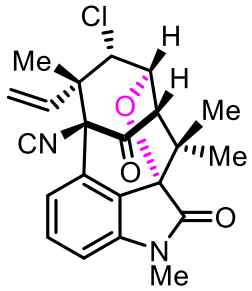
*Mol. Pharmacol*. **1995**, 47, 241; *Mol. Pharmacol*. **1996**, 49, 288

# Completed Total Syntheses of Welwitindolinones



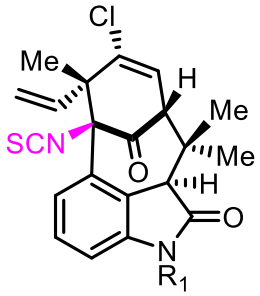

Welwitindolinone A isonitrile

Baran (JACS, 2005, 127, 15394-15396)
Wood (JACS, 2006, 128, 1448-1449)

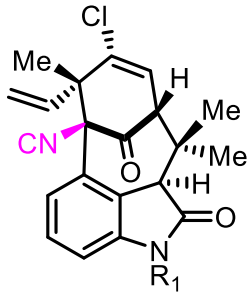



N-Methylwelwitindolinone D isonitrile

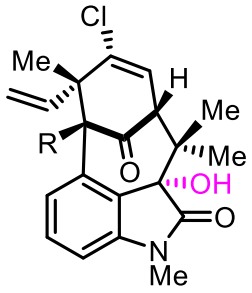
Rawal (JACS, 2013, 133, 5789-5801)
Garg (ACIE, 2013, 12422-12425)




Garg (JACS, 2011, 133, 15797-15799)



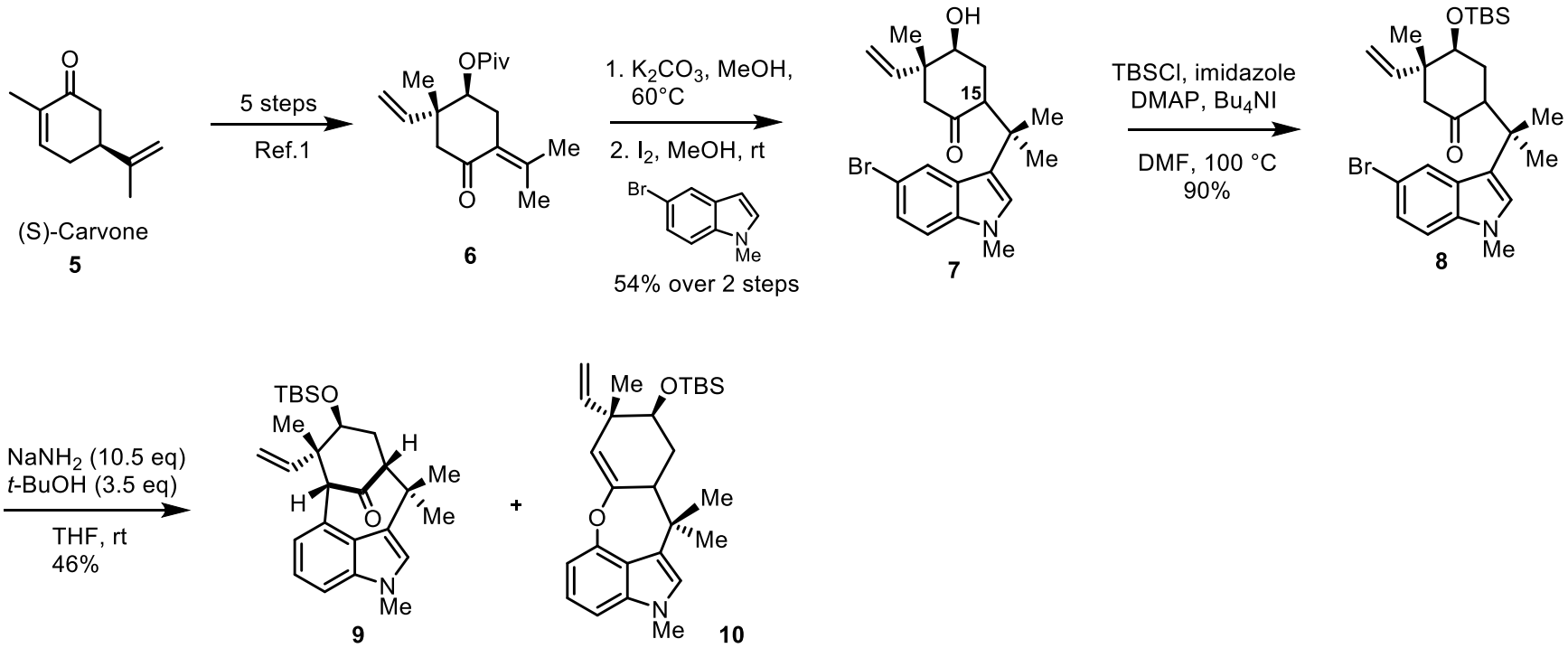

Garg (JACS, 2012, 134, 1396-1399)




R= NCS
R= NC

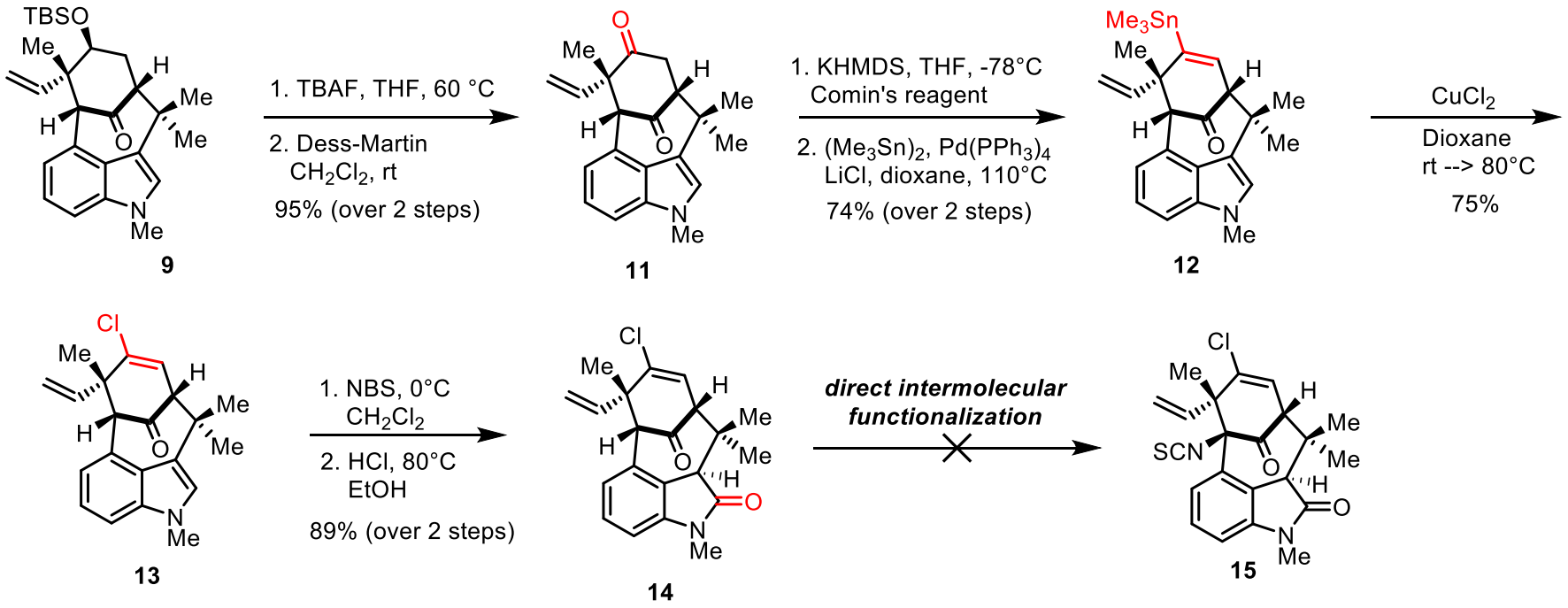
Garg (JACS, 2012, 134, 1396-1399)

# Previous Work: Garg's Total Syntheses of (-)-*N*-Methylwelwitindolinone C Isothiocyanate



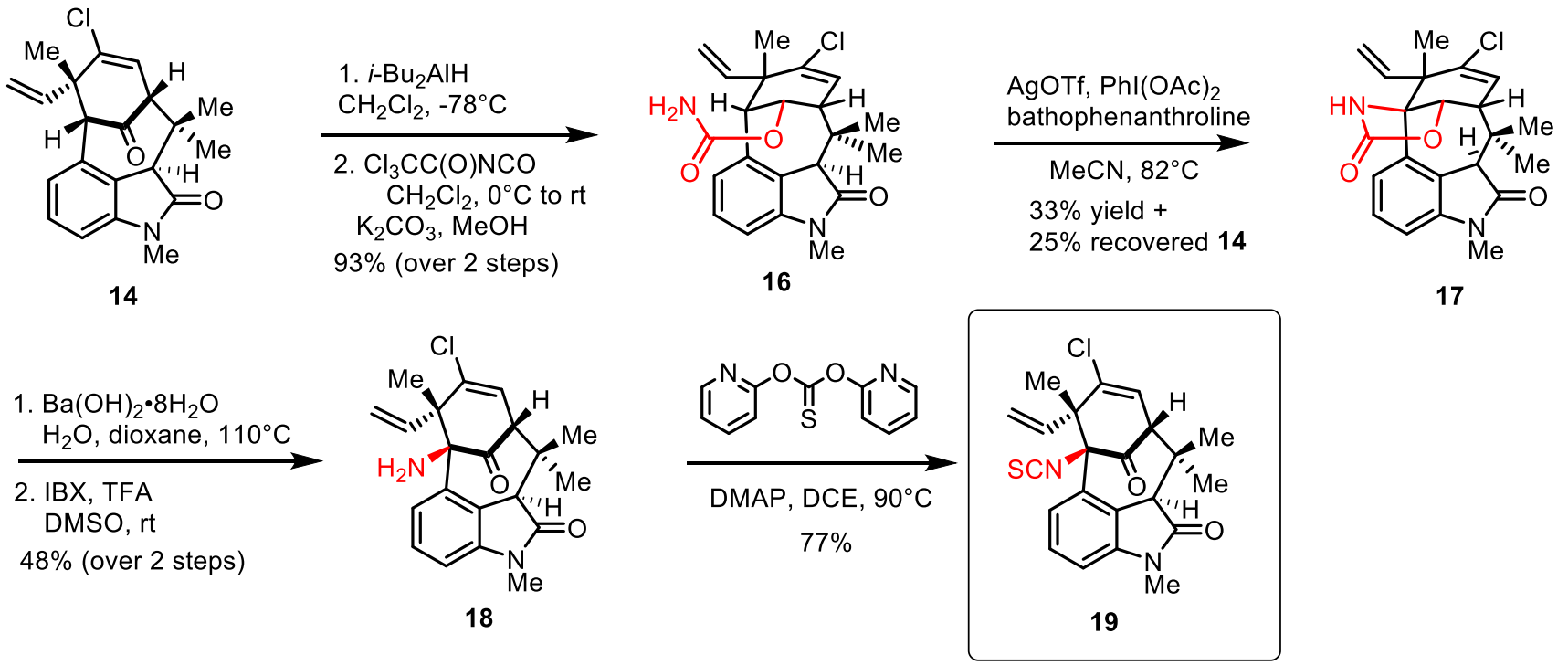

Ref 1: Chem. Pharm. Bull., 1994, 42, 1393-1398

# Introducing vinyl chloride and oxindole moieties



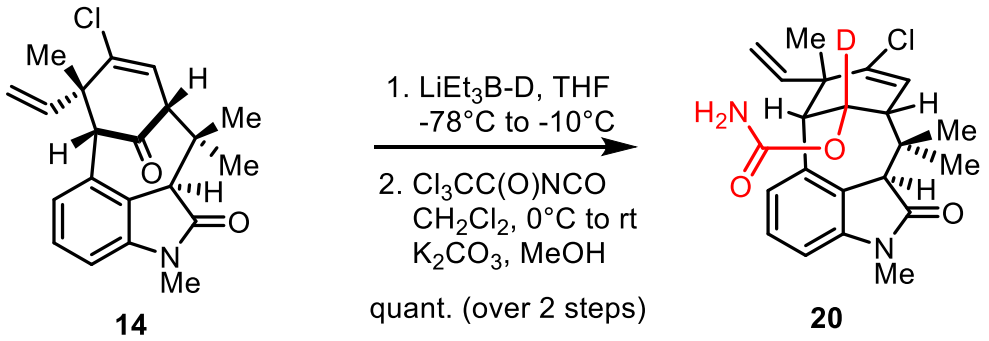

Intermolecular functionalization methods including bridgehead enolate chemistry, Nitrene insertion reactions, and radical halogenations were unsuccessful.

# Intramolecular Nitrene C-H insertion

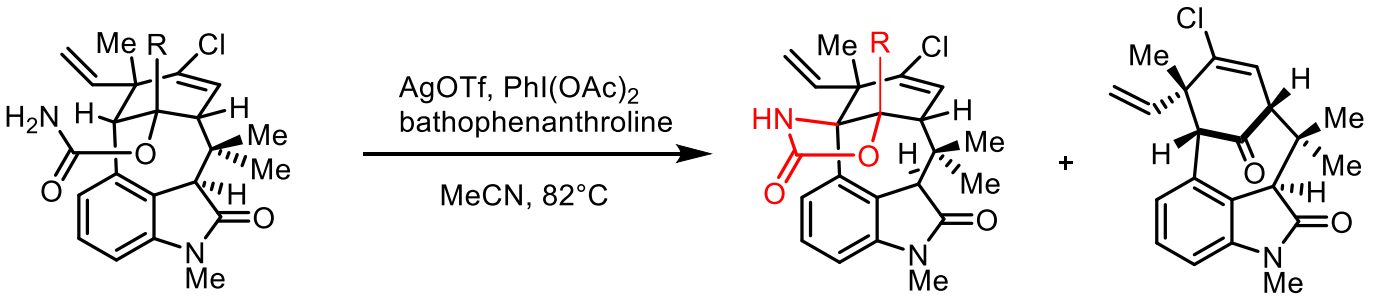



**(-)-N-Methylwelwitindolinone C Isothiocyanate**

# Strategic Manipulation of a kinetic isotope effect




**14** **20**

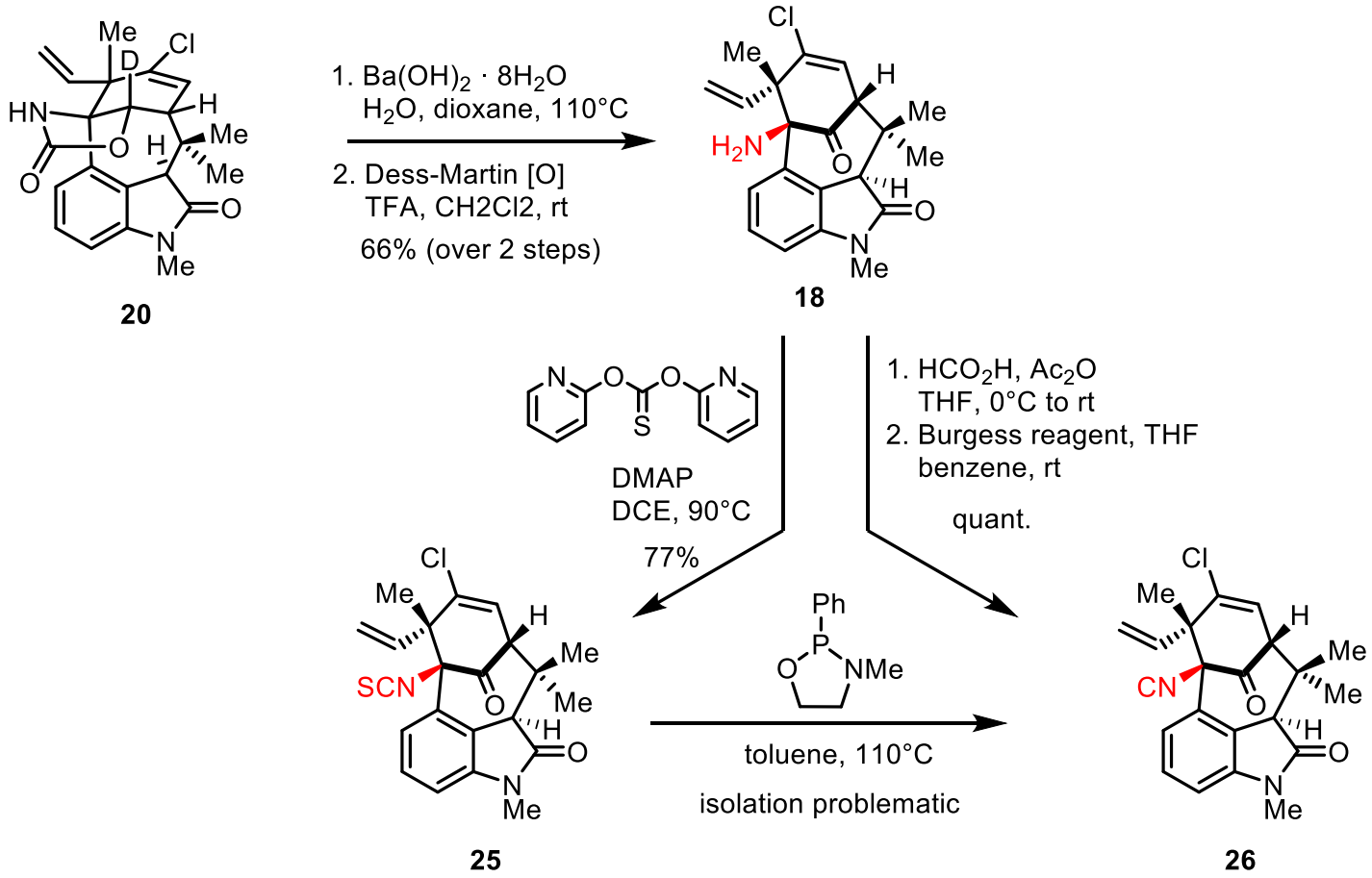



**21a, R=H**
**21b, R=D**

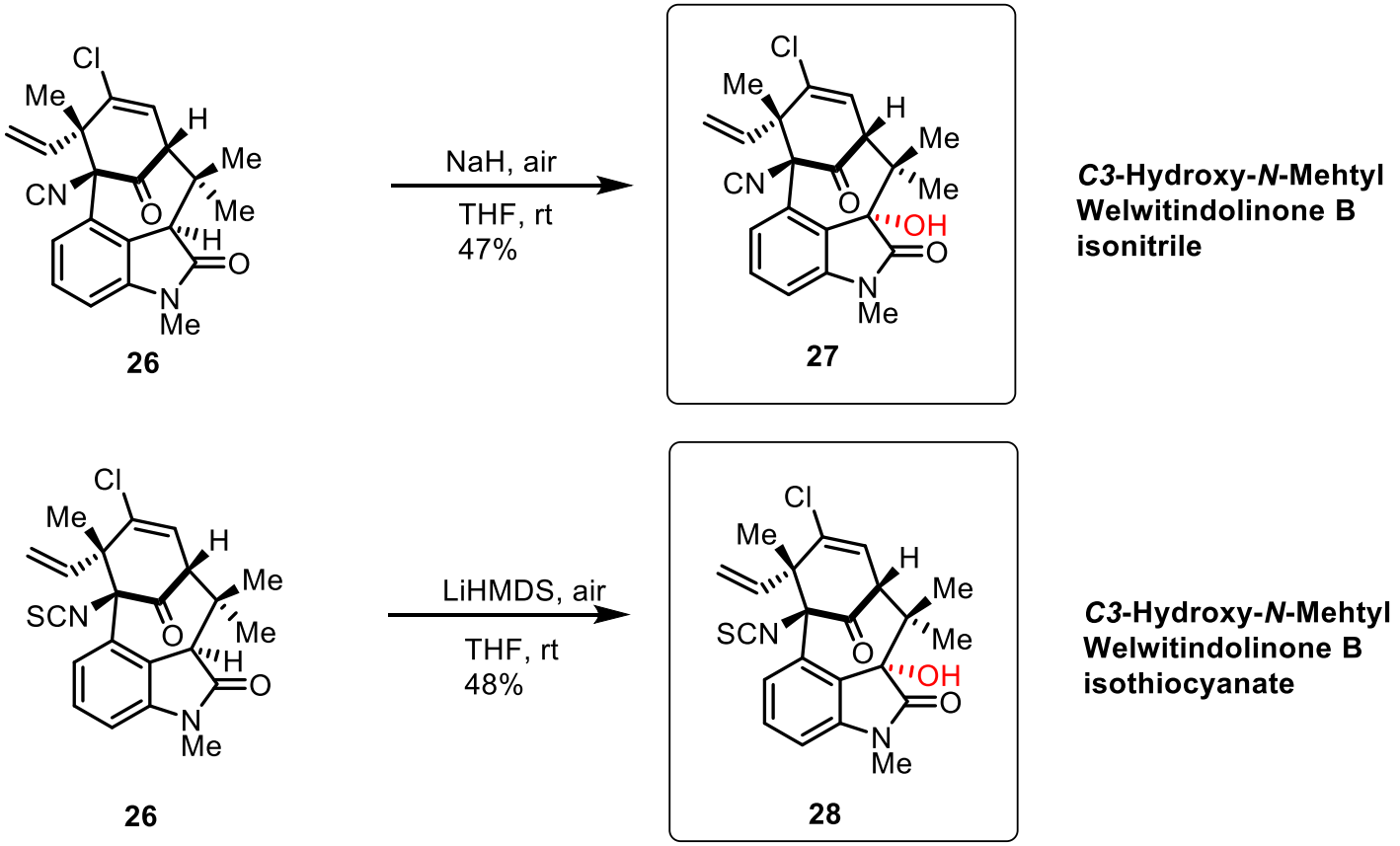
**22a, R=H, 33%**
**22b, R=D, 60%**

**23a, 25%**
**23b, 8%**

# Total Synthesis of N-Methylwelwitindolinone C Isonitrile

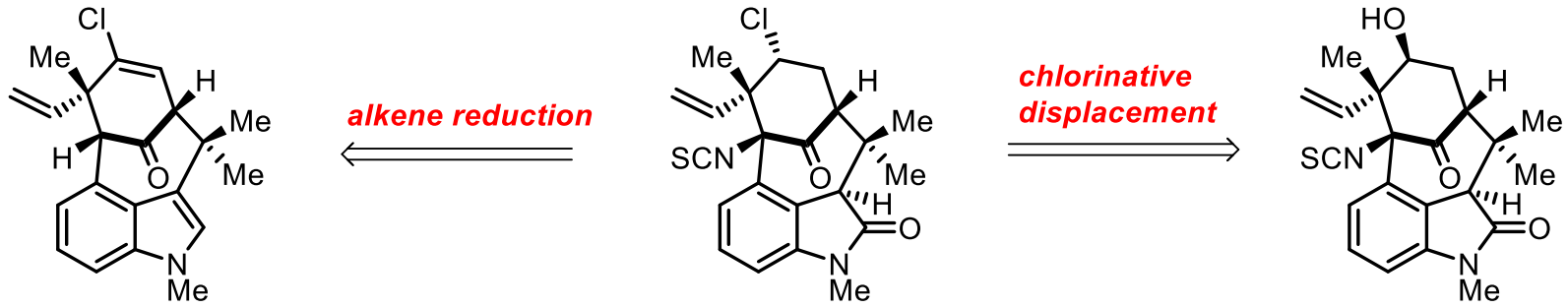


# Synthesis of oxidized Welwitindolinones




- Both oxidations occurred selectively to furnish single diastereomers

# This work: Total Synthesis of (-)-N-Methylwelwitindolinone B Isothiocyanate



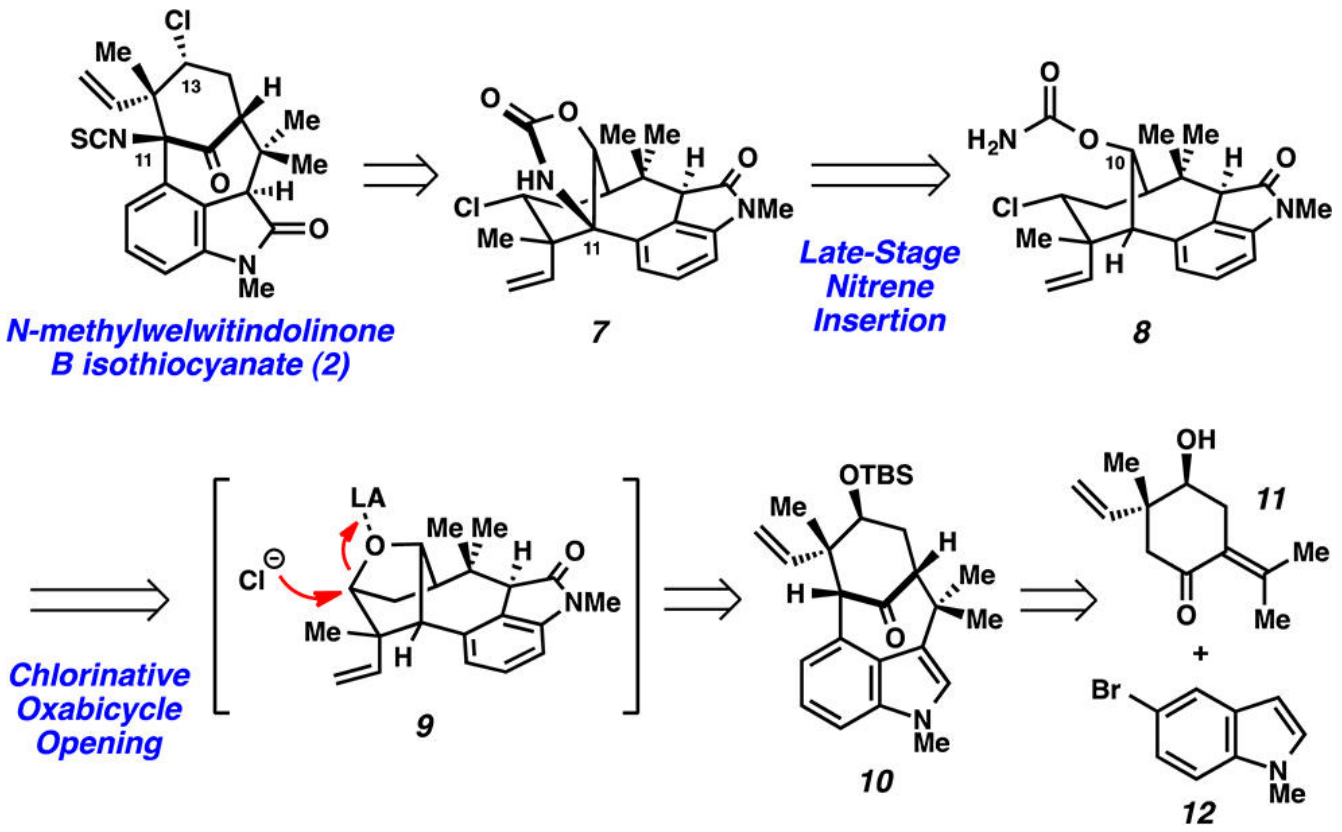

***N-Methylwelwitindolinone B isothiocyanate***

**Problems:**

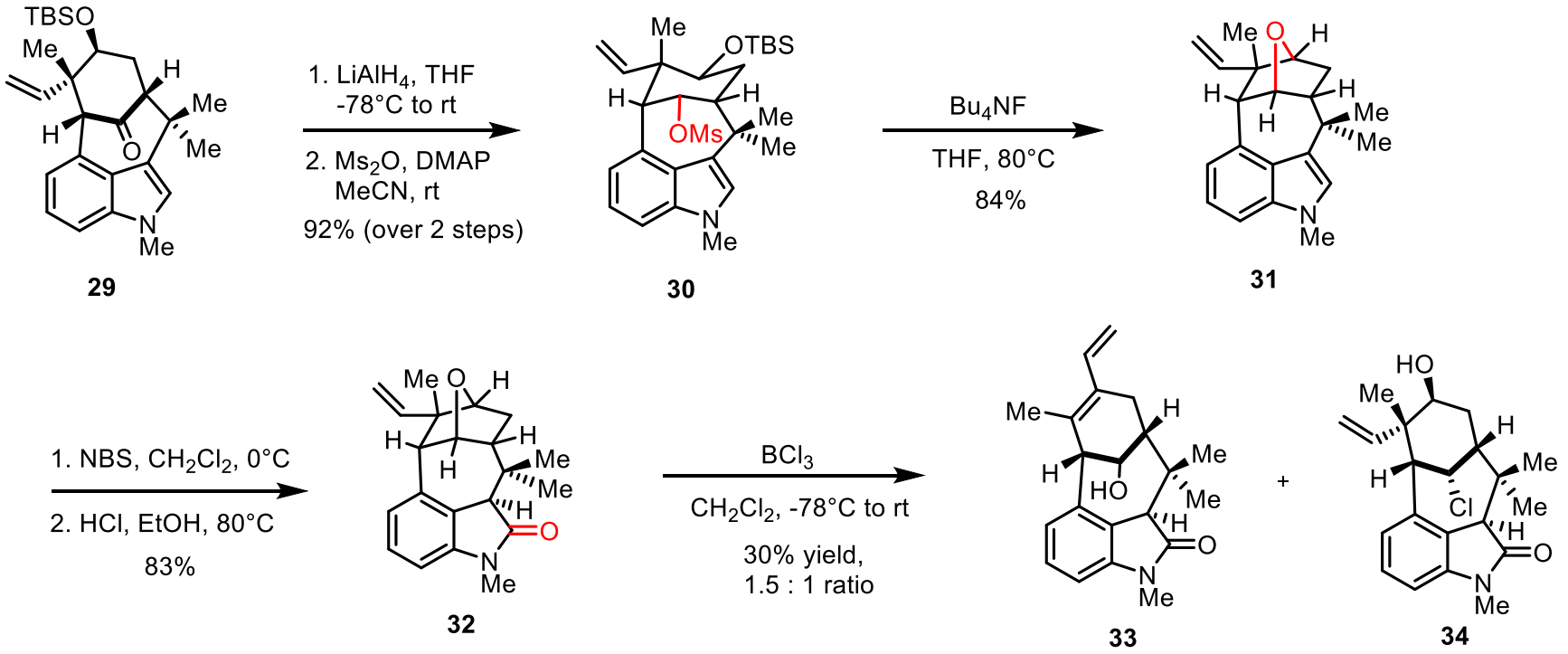
- Facile reduction of the terminal olefin
- Formal migration of the vinyl group to C13 upon activation of the alcohol

# This work: Total Synthesis of (-)-N-Methylwelwitindolinone B Isothiocyanate

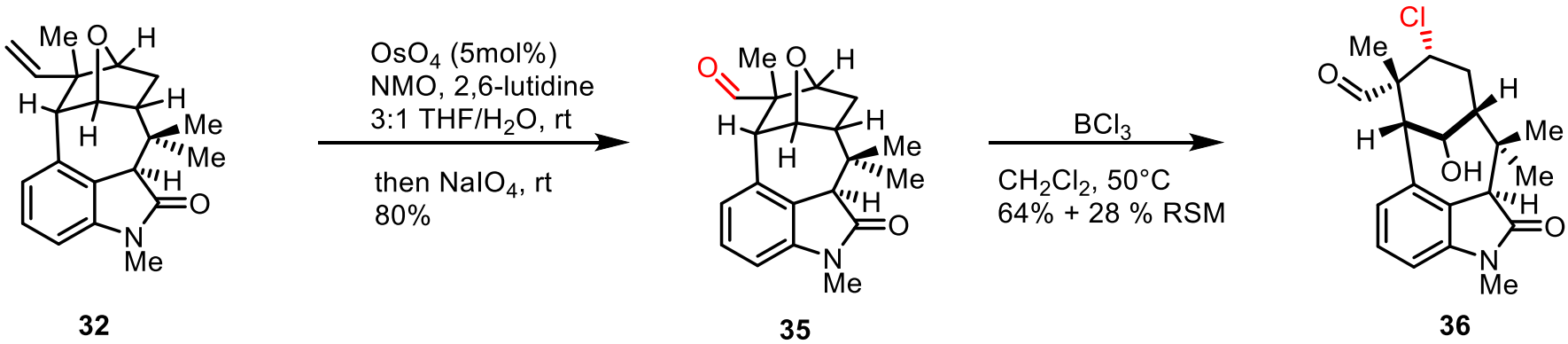
## Retrosynthetic Analysis



# Synthetic Studies to Oxabicycle 32 and Chlorinative Oxabicycle Opening Studies

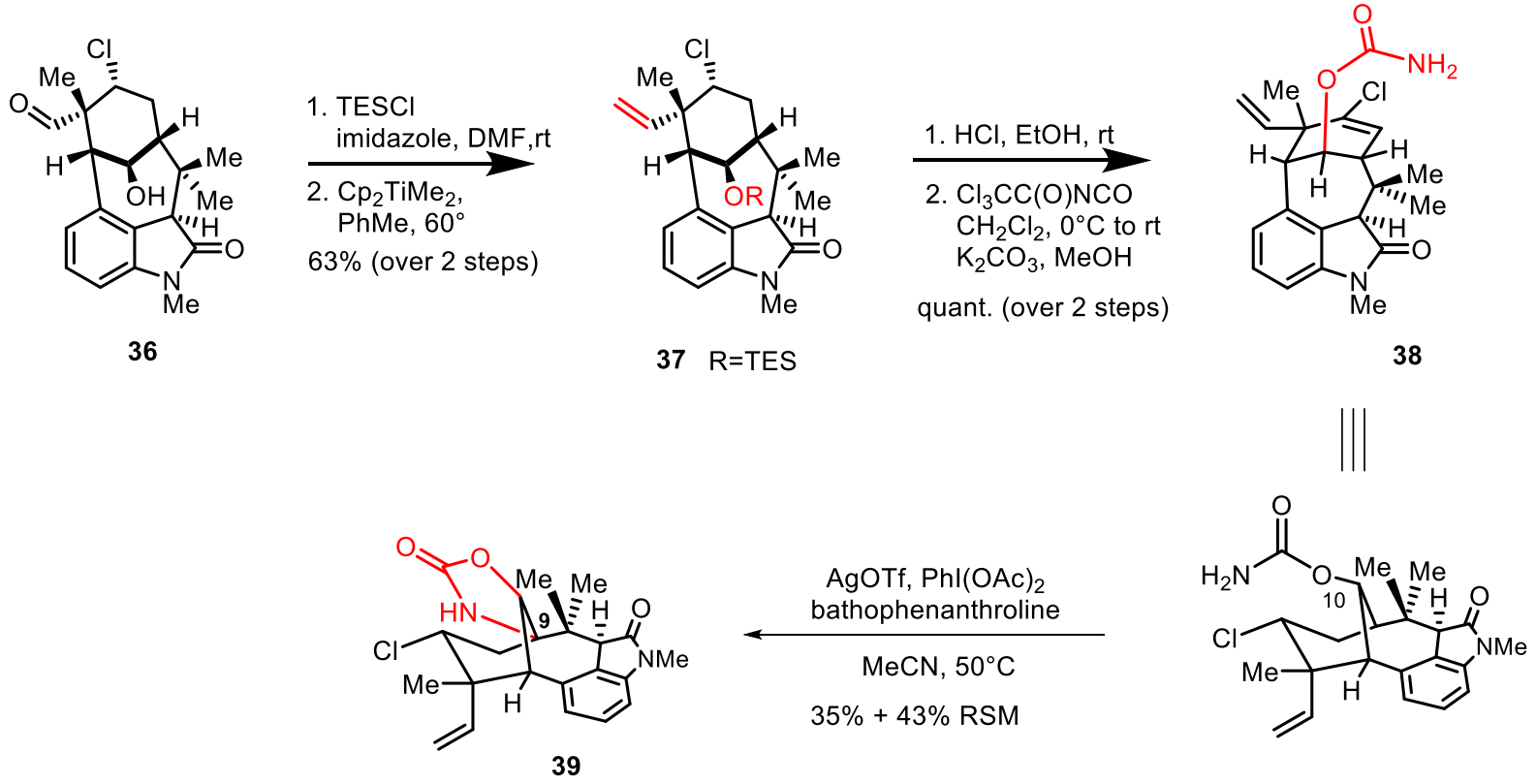


# Chlorinative Oxabicycle Opening Studies



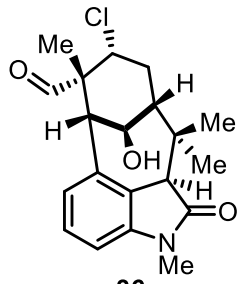

Single diasteroisomer

# Nitrene Insertion Studies with C10 epimer



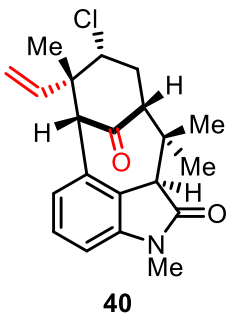

**36** **37** R=TES **38** **39**

# Garg's End Game Strategy



**36**

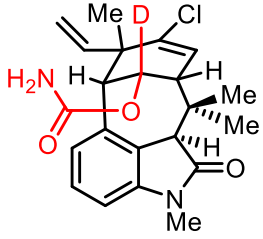
1. Dess-Martin, $NaHCO_3$
   $CH_2Cl_2$, rt
2. $NaHMDS$, $Ph_3PMeBr$
   THF, rt



**40**

1. $LiAlD_4$, THF
   -78°C to 0°C
2. $Cl_3CC(O)NCO$
   $CH_2Cl_2$, 0°C to rt
   $K_2CO_3$, MeOH

quant (over 2 steps)

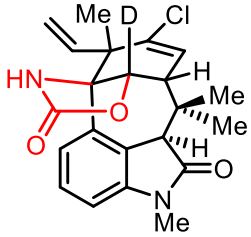


**41**

$AgOTf$, $PhI(OAc)_2$
bathophenanthroline

MeCN, 50°C

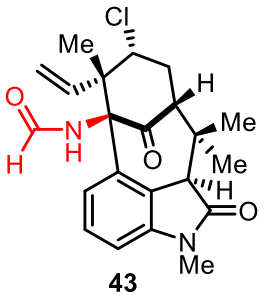
55% yield + 10% RSM



**42**

1. Schwartz's reagent
   THF, rt
2. Dess Martin
   $NaHCO_3$, $CH_2Cl_2$, rt

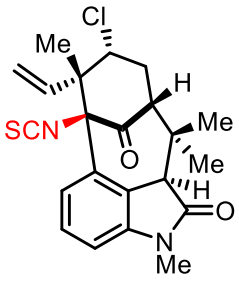
49% (over 2 steps)



**43**

1. Burgess reagent
   PhH, THF, rt
2. Se, $S_8$, $NEt_3$, THF
   65°C

54% (over 2 steps)



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

# Conclusion

- ✓ First total synthesis of (-)-*N*-Methylwelwitindolinone B Isothiocyanate
- ✓ 15 steps from previously synthesised bicyclic precursor
- ✓ With this synthesis completed, all welwitindolinones containing the bicyclic [4.3.1]decane core are now accessible by synthetic chemistry