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## Literature Report 2014-01-07

Huang, W.-X. checker: Chen, Z.-P.

# Enantiospecific Total Synthesis of *N*-Methylwelwitindolinone D Isonitrile

Garg, N. K. *et al.*  
*Angew. Chem. Int. Ed.* **2013**, 52, 12422.

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## 1. Introduction of the Corresponding Author



**Neil K. Garg**

**B.S., New York University (2000, Marc Walters)**

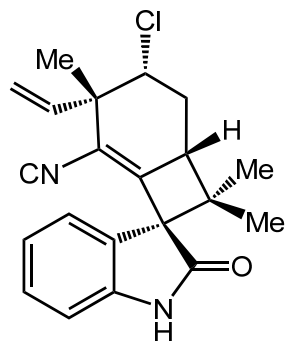
**Ph.D., California Institute of Technology (2005, Brian Stoltz)**

**NIH postdoctoral scholar (2005-2007, Larry Overman)**

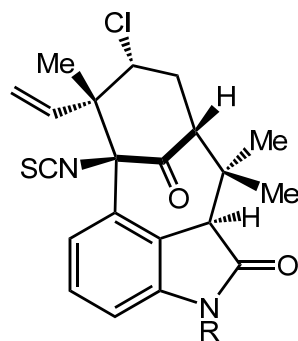
**Joined the faculty at UCLA (2007)**

**Research: total synthesis of natural products, transition-metal catalyzed cross-coupling**

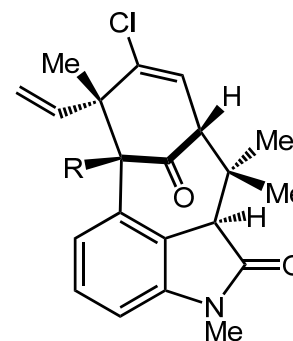
## 2. Introduction of Representative Welwitindolinones



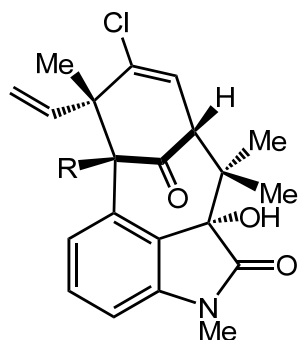
Welwitindolinone A  
isonitrile



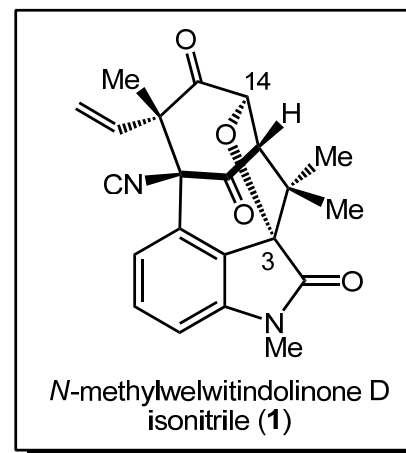
Welwitindolinone B  
isothiocyanate  
R = H, or Me



N-methylwelwitindolinone C  
R = -NCS, or -NC



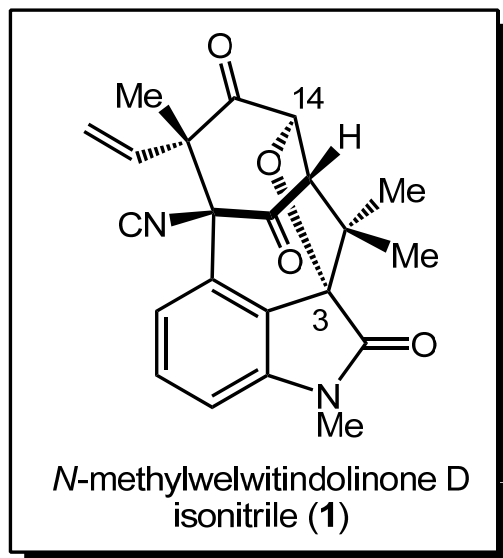
3-Hydroxy-  
N-methylwelwitindolinone C  
R = -NCS, or -NC



N-methylwelwitindolinone D  
isonitrile (1)

1. D was isolated from *Fischerella muscicola* and *Fischerella major*;
2. Biological activities: antifungal effects, microtubule depolymerization.

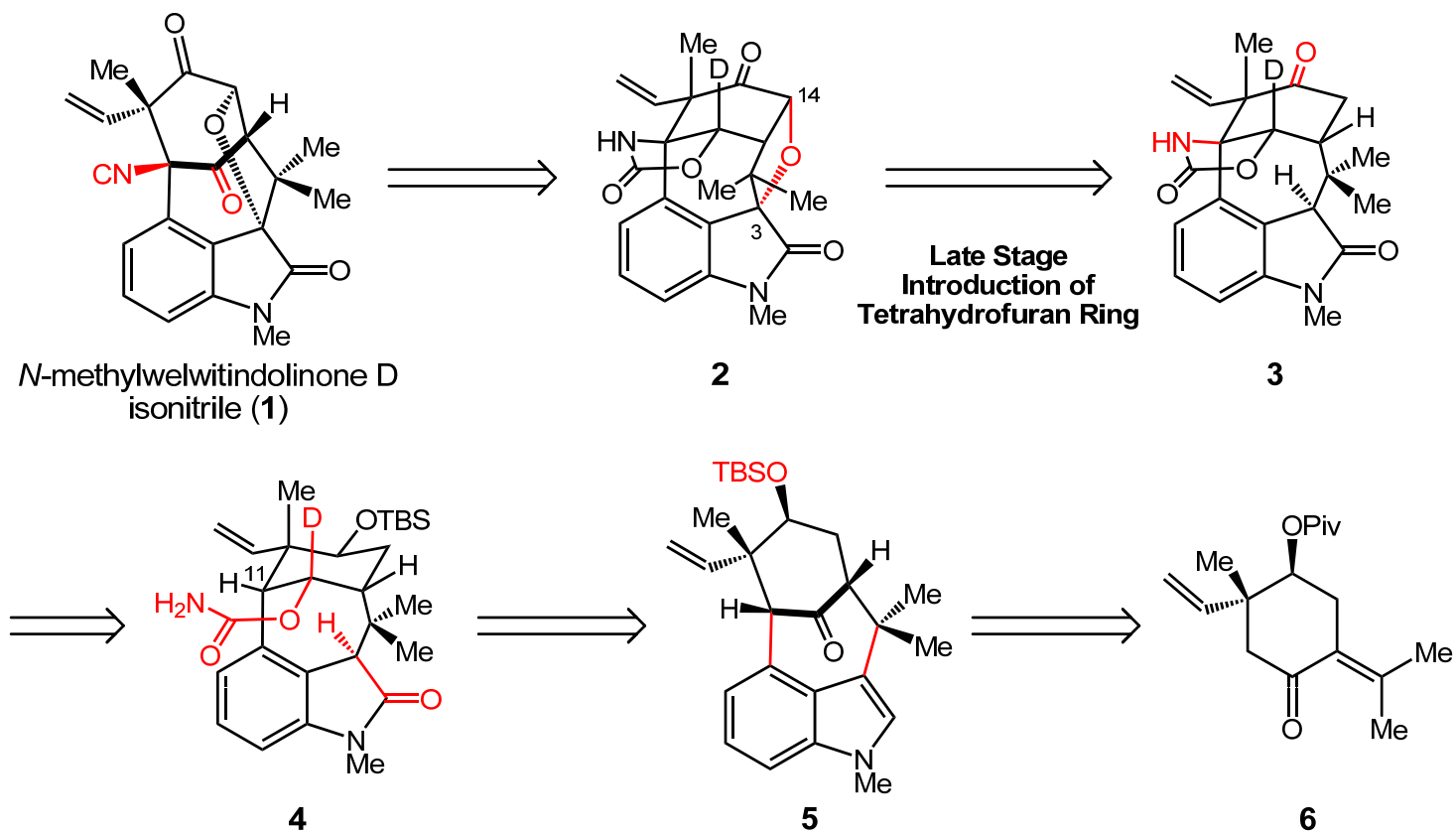
**Figure 2. Structural Analysis of Welwitindolinone D Isonitrile**



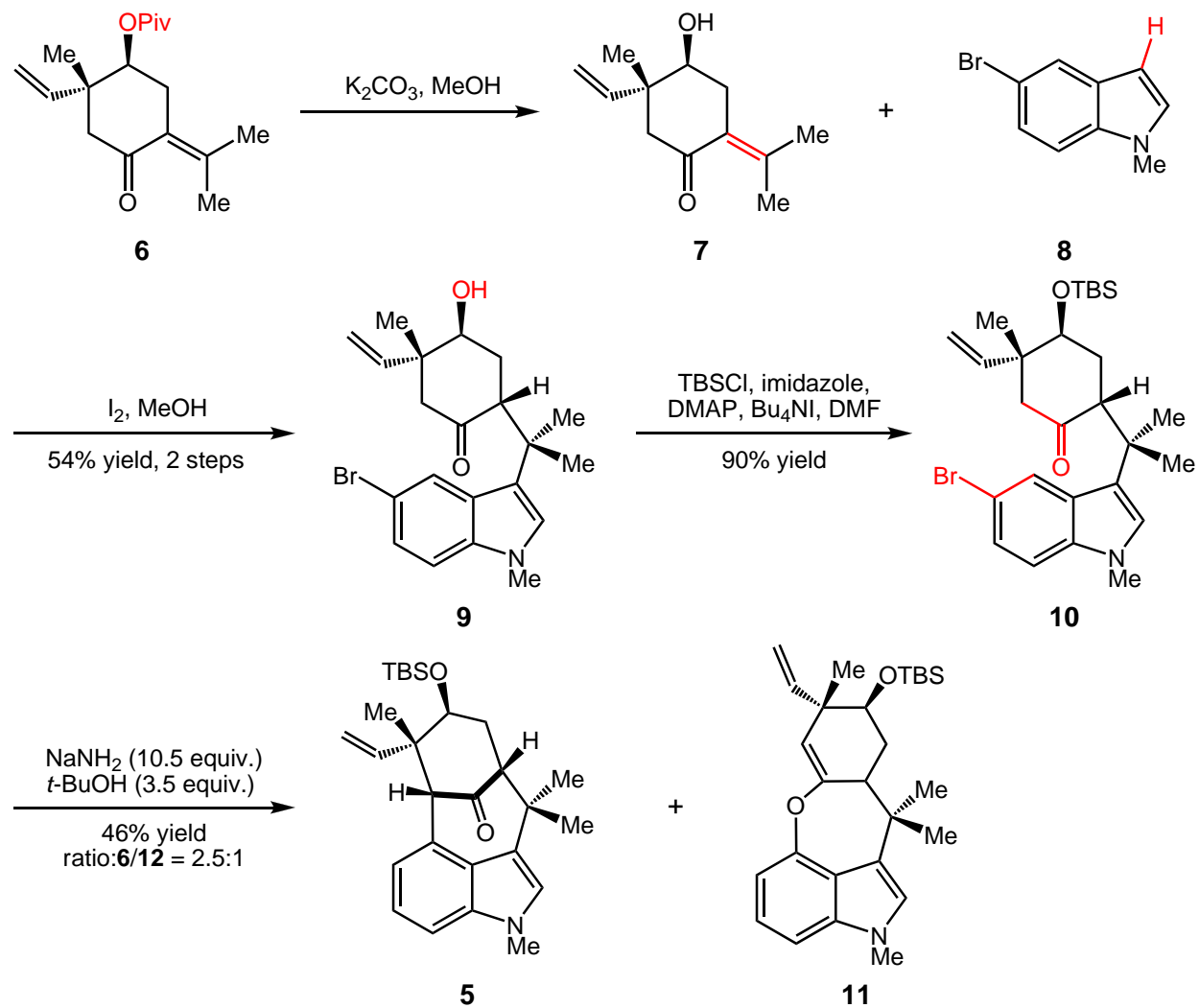
1. Oxindole-fused bicyclo[4.3.1] framework;
2. Five stereocenters, two quaternary carbons;
3. A heavily substituted cyclohexyl ring;
4. An ether linkage between C3 and C14.

### 3. Total Synthesis of Welwitindolinone D by Garg Group

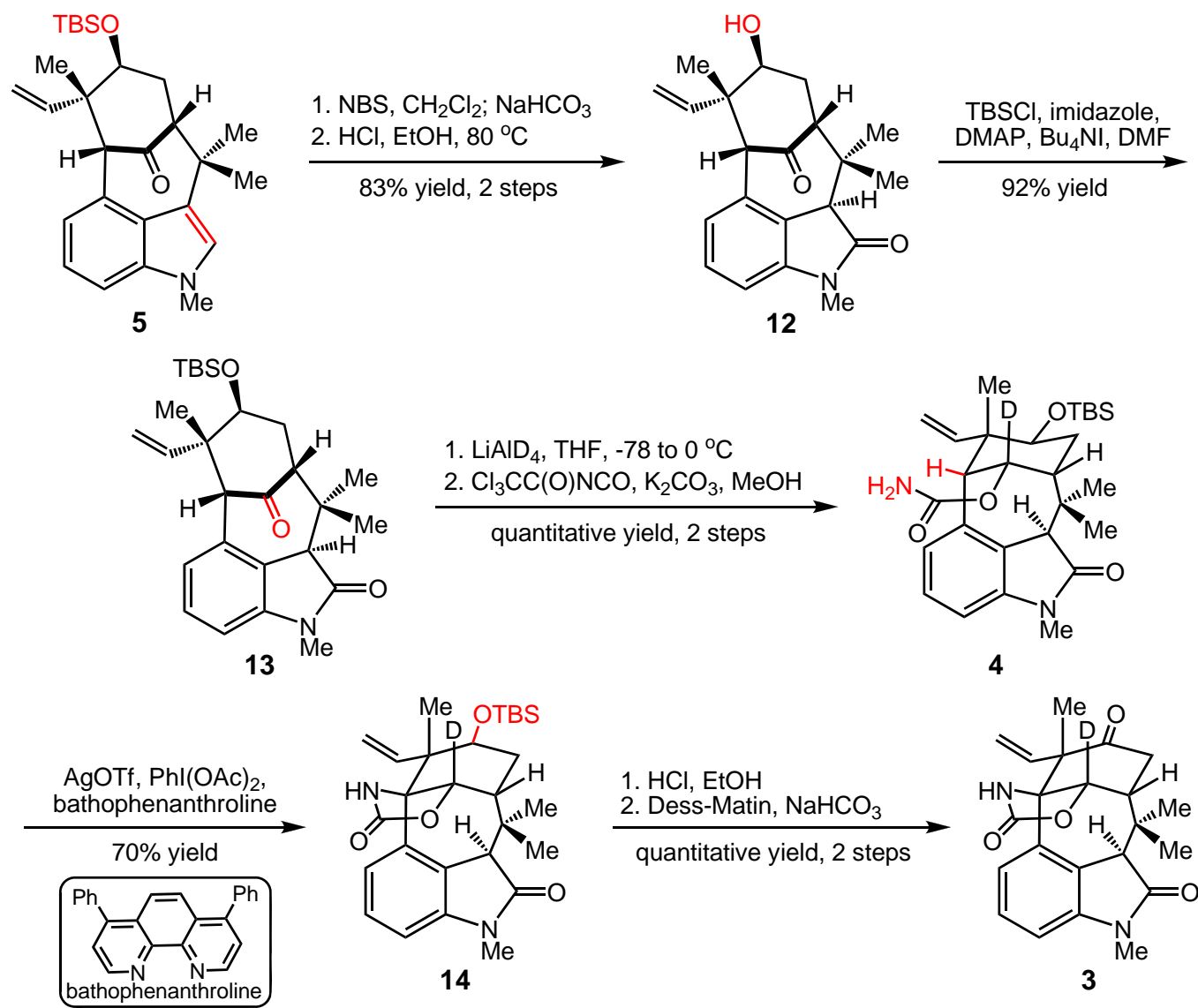
#### Scheme 1. Retrosynthetic Analysis of 1



## Scheme 2. Total Synthesis of 1

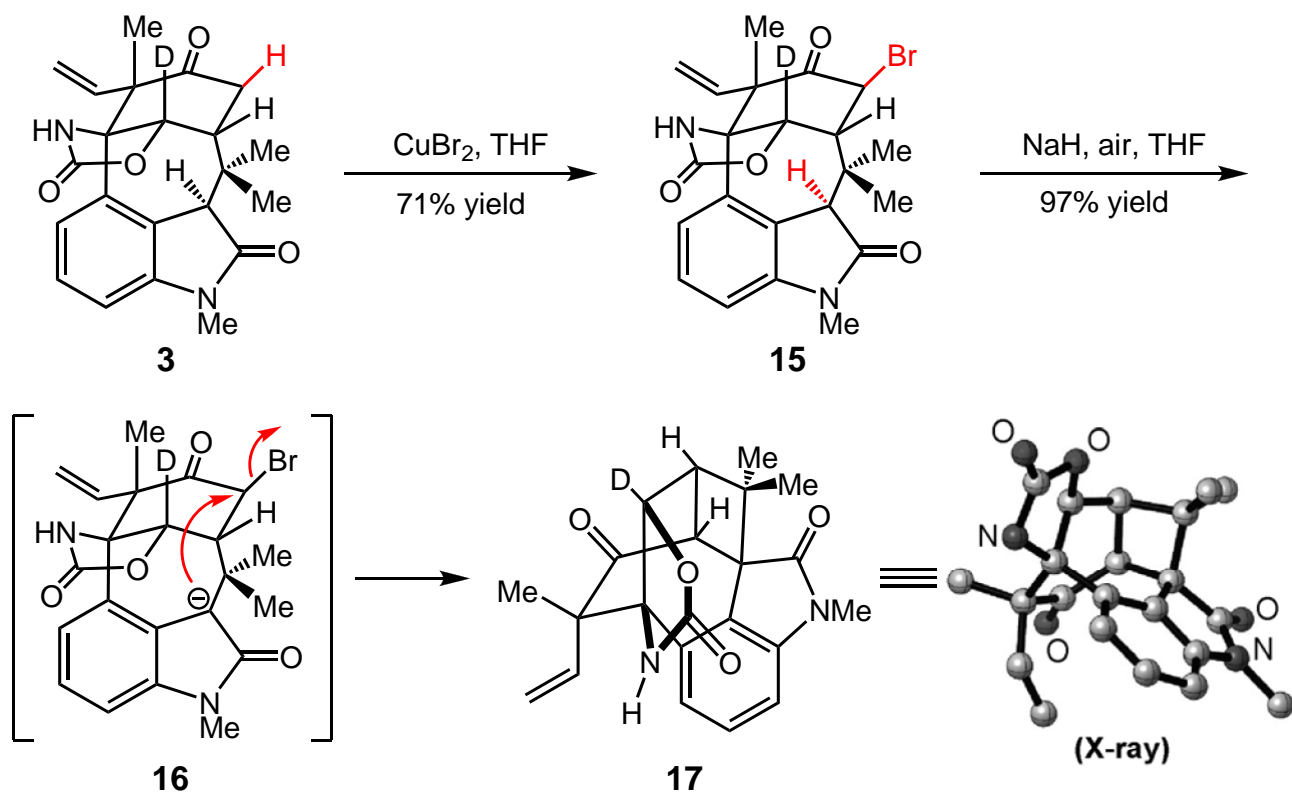


### Scheme 3. Elaboration of 5 to Keto Oxindole 3

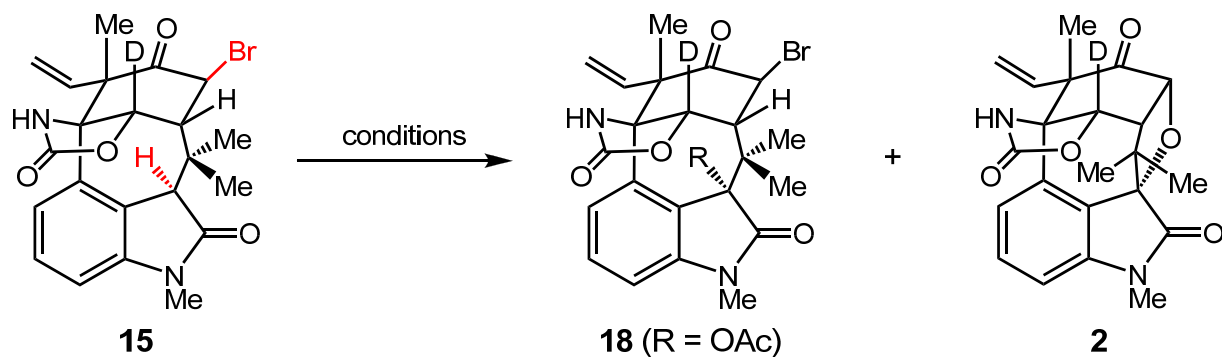




## Scheme 4. Unexpected Formation of Cyclobutane 17

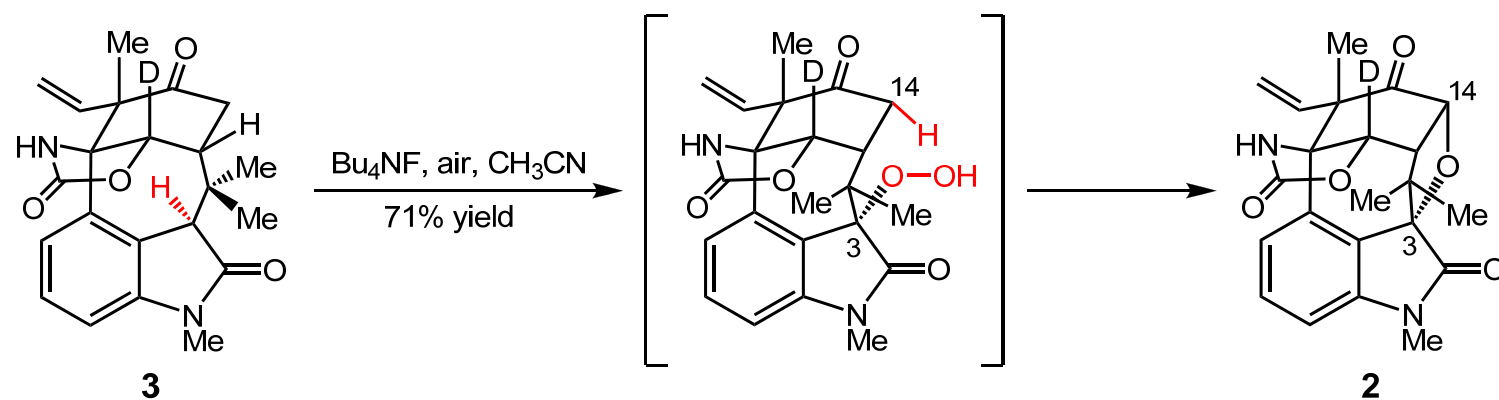


**Table 1: Conversion of 15 to Acetate 18 and Cyclized Product 2**

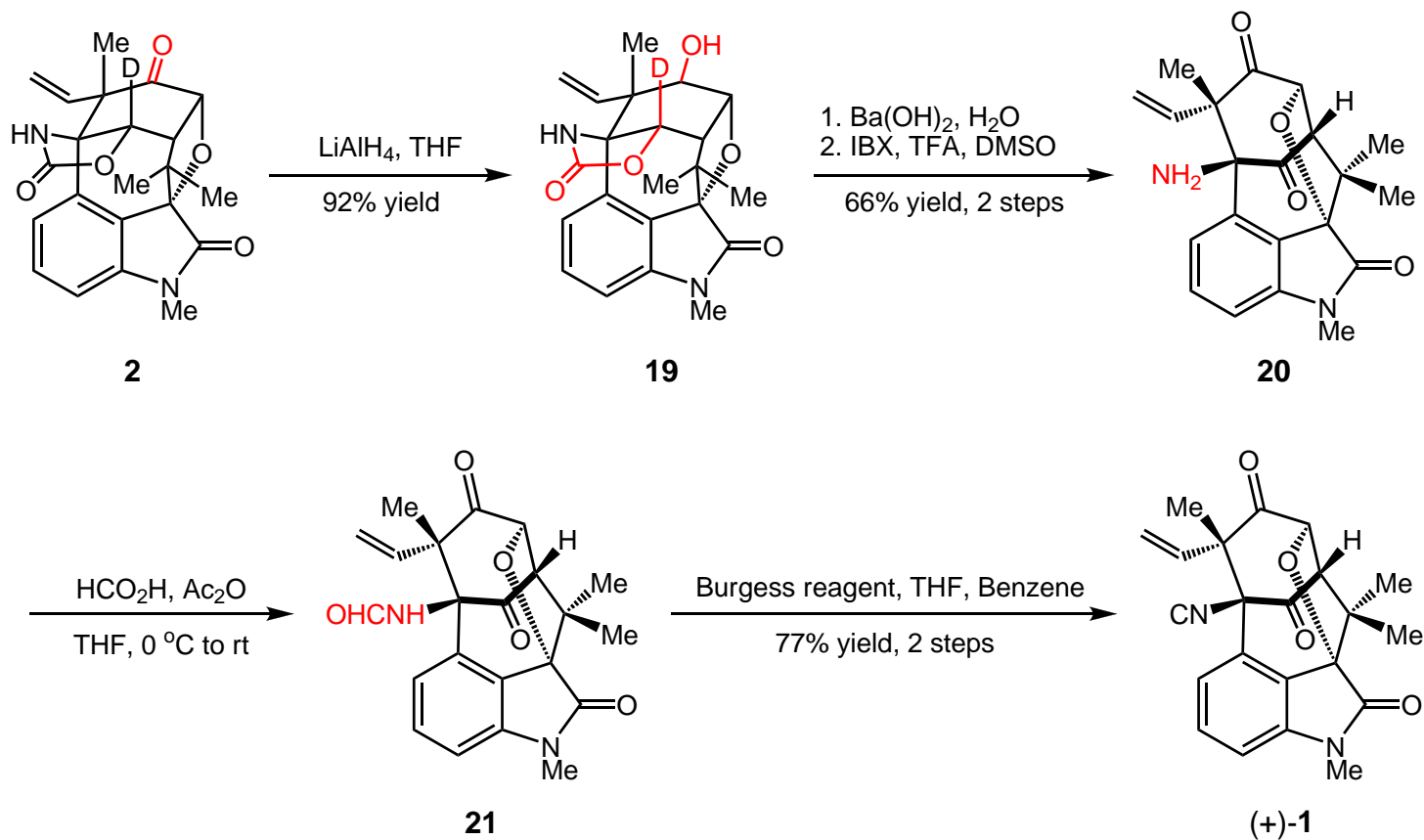


Entry	Conditions	Conversion to products	
		<b>18</b> (%)	<b>2</b> (%)
1	Mn(OAc) <sub>3</sub> (4.0 eq.), AcOH, 80 °C	74	0
2	Mn(OAc) <sub>3</sub> (4.0 eq.), AcOH, 150 °C	2	53
3	Mn(OAc) <sub>3</sub> (4.0 eq.), AcOH, 150 °C; K <sub>2</sub> CO <sub>3</sub> , MeOH, H <sub>2</sub> O, 70 °C	0	56

## Scheme 5. Double C–H Functionalization of Substrate 3 to Install the Tetrahydrofuran Ring

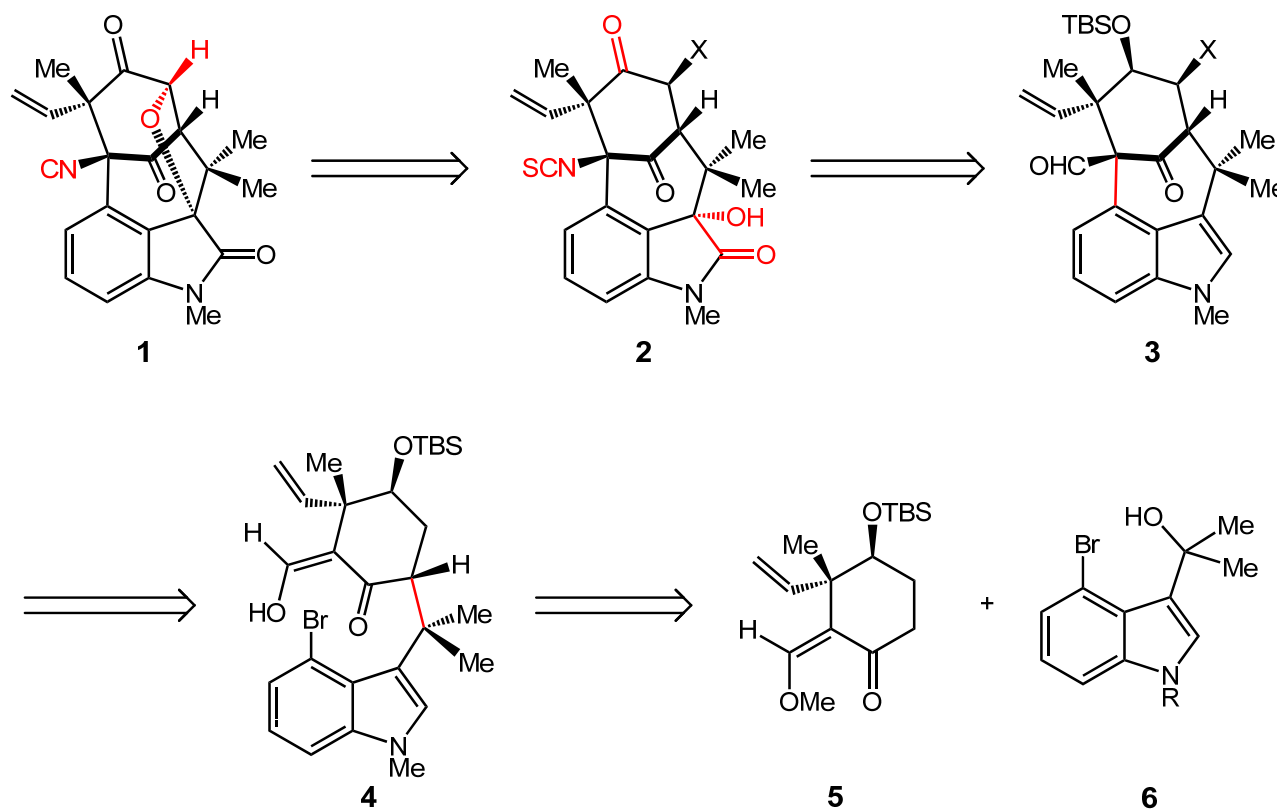


## Scheme 6. Completion of (+)-1



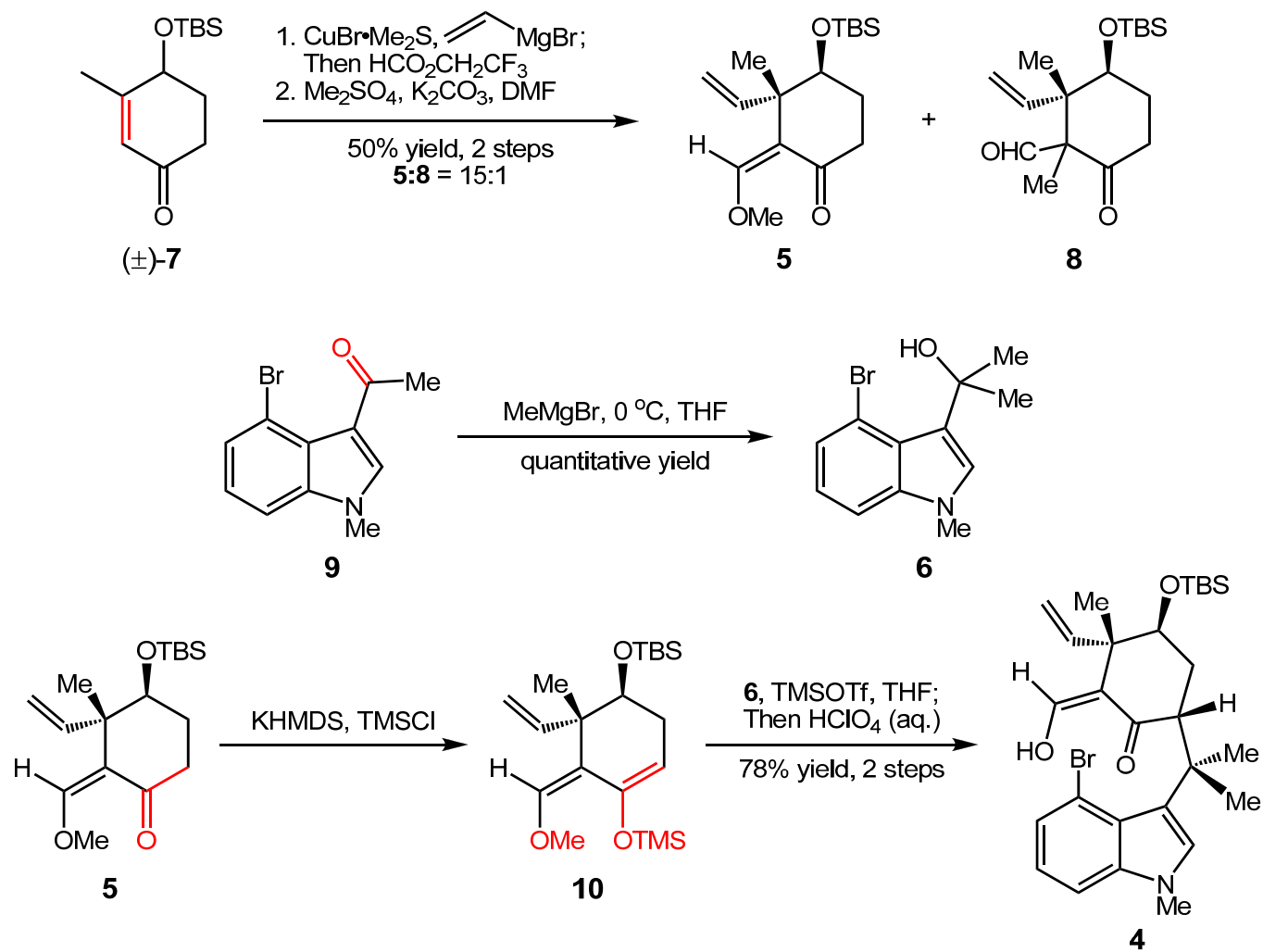
## 4. Total Synthesis of Welwitindolinone D by Rawal Group

### Scheme 1. Retrosynthetic Analysis of 1

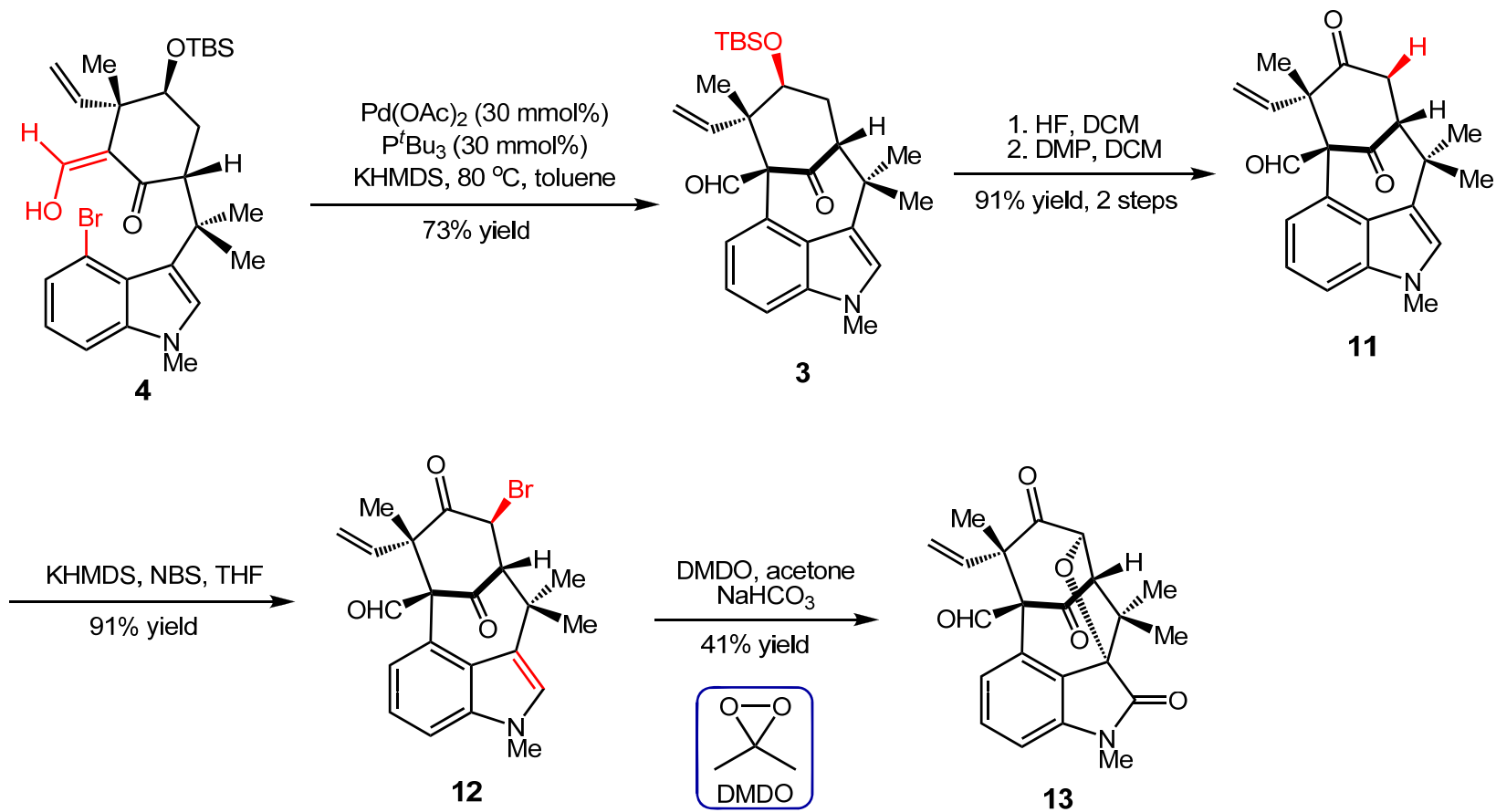


Rawal, V. H. *et al. J. Am. Chem. Soc.* **2011**, *133*, 5798.

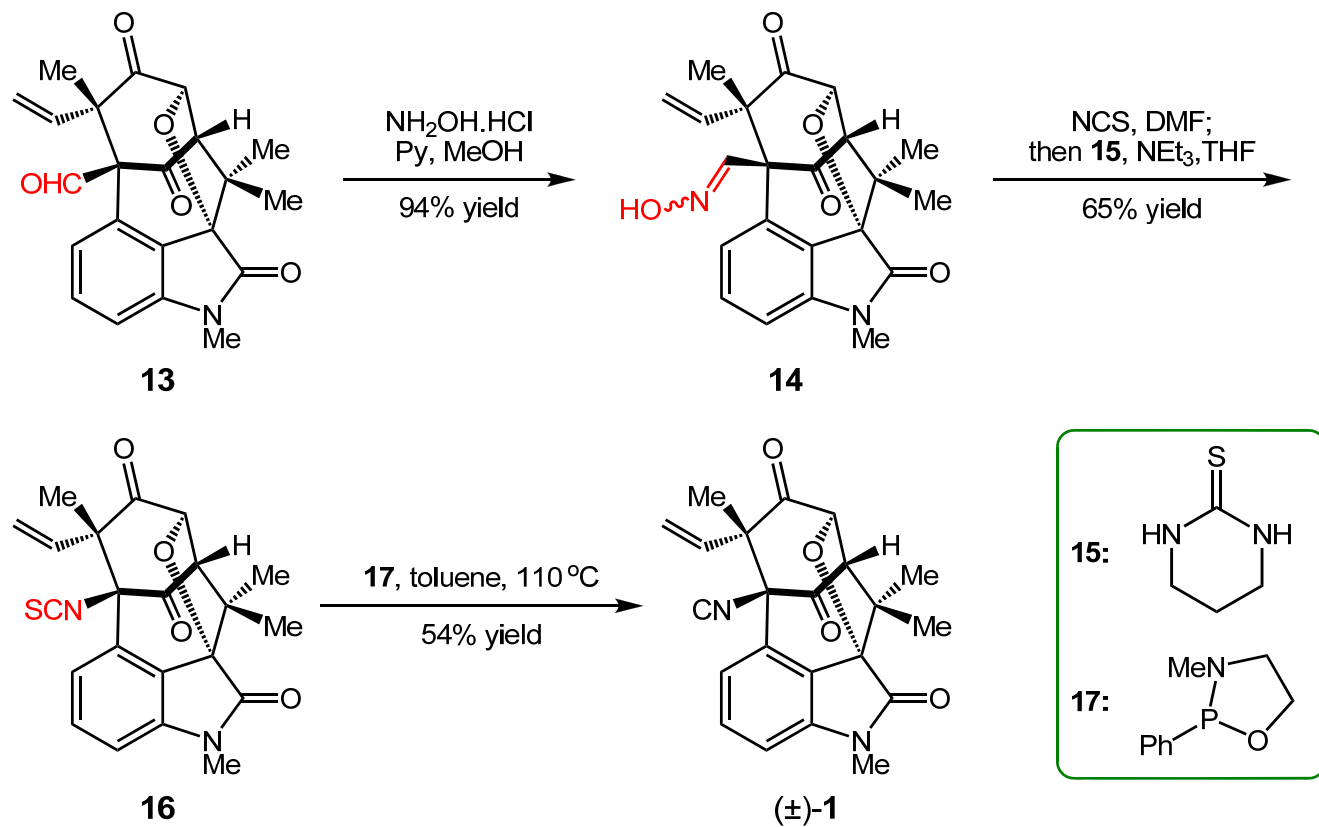
## Scheme 2. Synthesis of Cyclization Precursor 4



### Scheme 3. Synthesis of Pentacycle 13

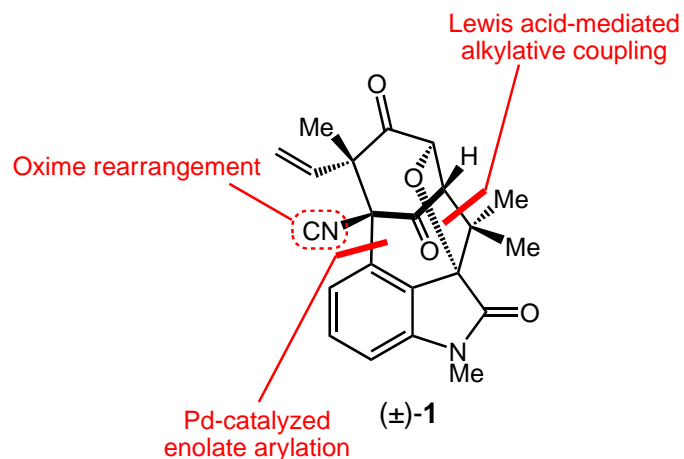


## Scheme 4. Synthesis of *N*-Methylwelwitindolinone D Isonitrile (1)



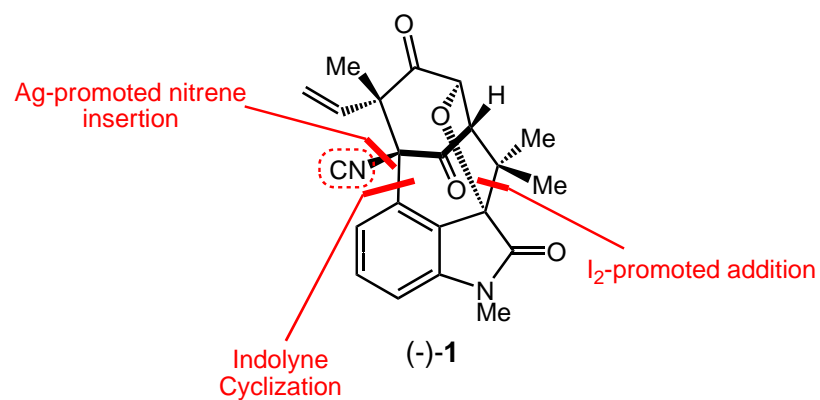


## 5. Summary



### Rawal group in 2011:

1. first total synthesis;
2. 14 steps, 4.8% overall yield.



### Garg group in 2013:

1. enantiospecific total synthesis;
2. 17 steps, 2.8% overall yield.

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The welwitindolinone family of natural products has attracted tremendous attention from the synthetic community over the past two decades. Interest in these compounds stems from their promising biological profiles, in addition to their compact, yet daunting structures. Synthetic efforts toward the welwitindolinones have led to at least ten methods for building the bicyclo[4.3.1] core that is common to most of these natural products. However, the sheer difficulty associated with late-stage manipulations has plagued most synthetic routes and only a few completed syntheses have been reported in recent years.

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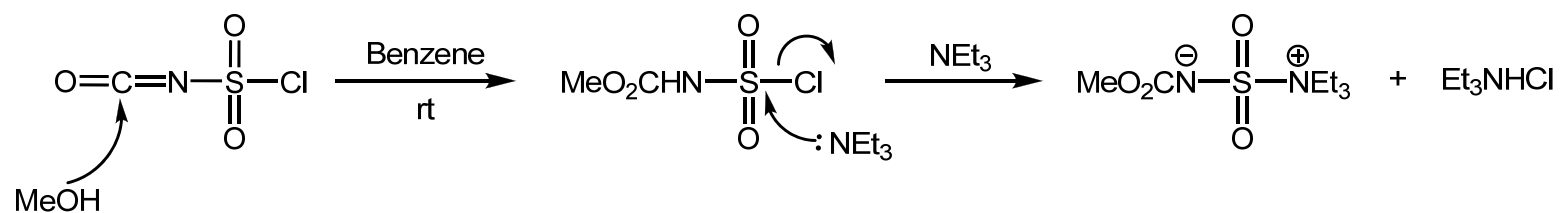
In summary, we have completed the enantiospecific total synthesis of N-methylwelwitindolinone D isonitrile. Several unexpected hurdles, including the formation of the unusual cyclobutane-containing compound **17** were overcome en route to the natural product. Our total synthesis features a double C-H functionalization of keto oxindole **3** to introduce the tetrahydrofuran ring of **1** and is achieved in 17 steps from readily available carvone derivative **6**.

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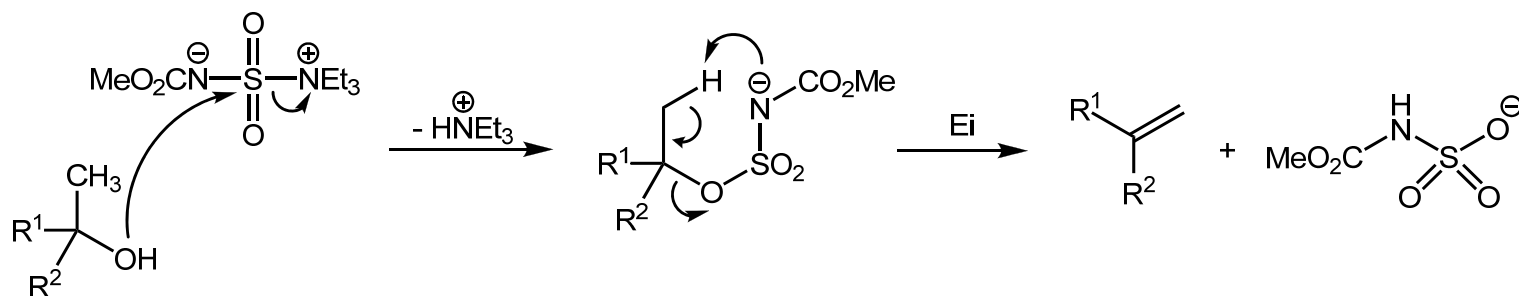
谢谢大家， 请多批评指正！

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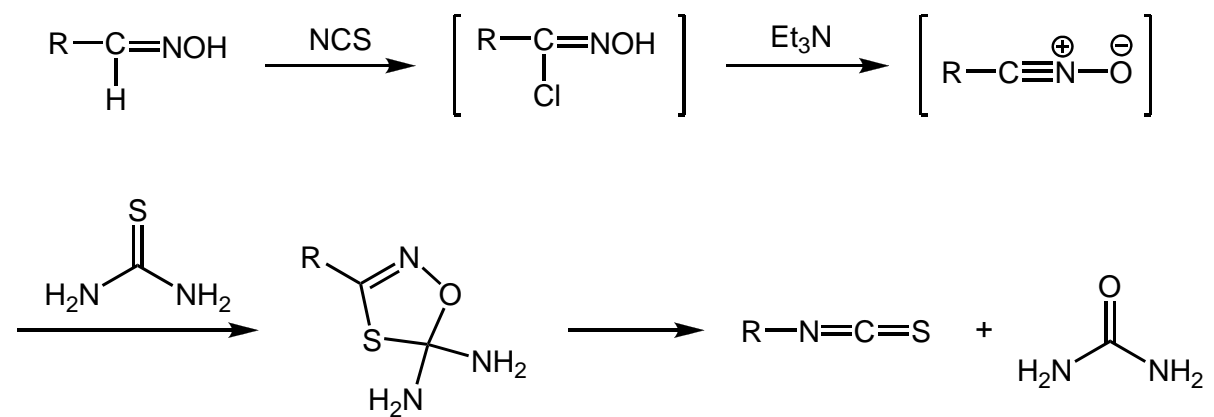
**Burgess Reagent** 由氯磺酰异氰酸酯与甲醇和三乙胺在苯中反应制取:



**Burgess Reagent** 脱水机理:

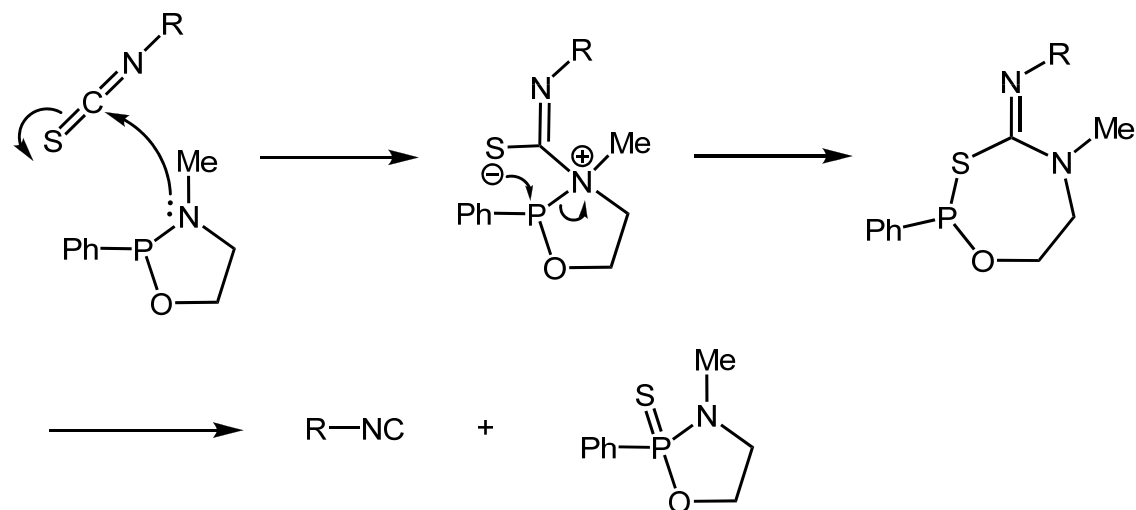


## Mechanism of Iximes to Isothiocyanates



Kim, J. N. *et al. Tetrahedron Lett.* **1997**, 38, 1597.

## Mechanism for Desulfurization of the Isothiocyanate



Mukaiyama, T. *et al. Bull. Chem. Soc. Jpn.* **1965**, *38*, 858.