

# Total Synthesis of (–)-*N*-Methylwelwitindolinone C Isothiocyanate Based on a Pd-Catalyzed Tandem Enolate Coupling Strategy

Keita Komine, Yusuke Nomura, Jun Ishihara, and Susumi Hatakeyama\*

Nagasaki University, Japan

*Org. Lett.* **2015**, *17*, 3918–3921.

## Structural Features of the Target

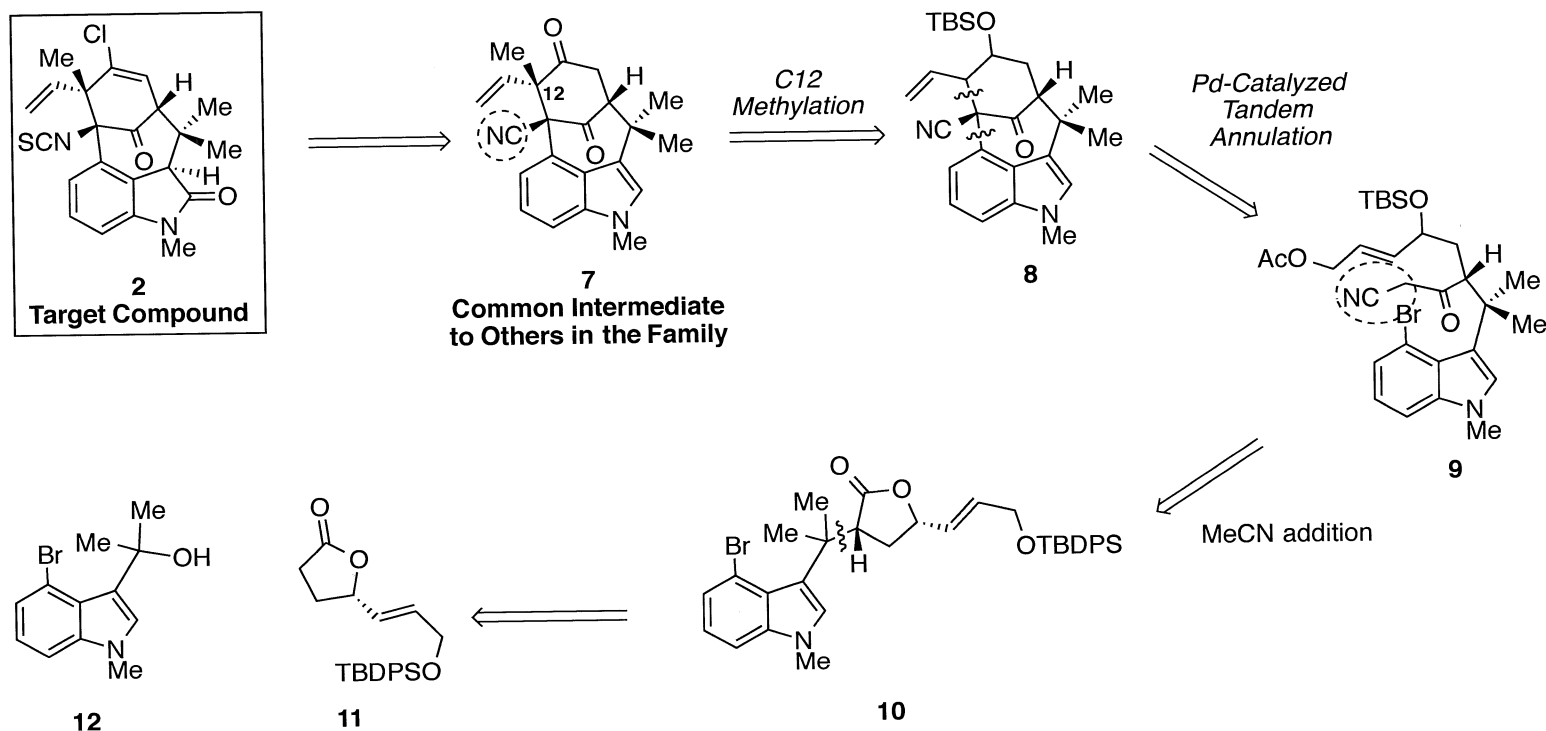
- Multi-fused ring system
- Pendant alkene
- Isothiocyanate  
(can be replaced by other functionality in series)

## Previous Syntheses Include:

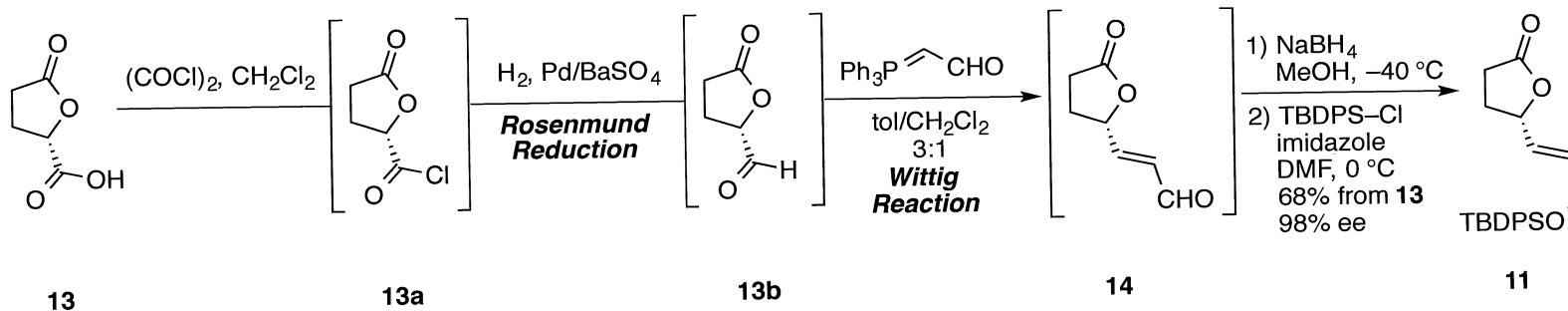
Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 1392–1395.

Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 1396–1399.

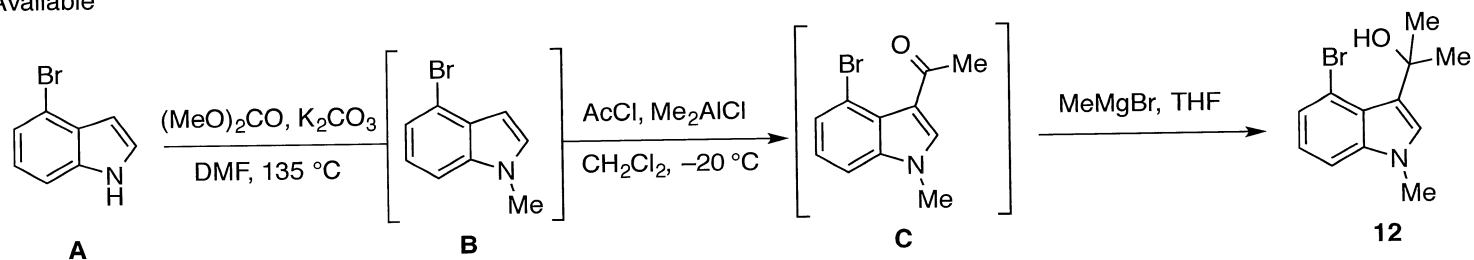
## Retrosynthesis



**Forward Synthesis**

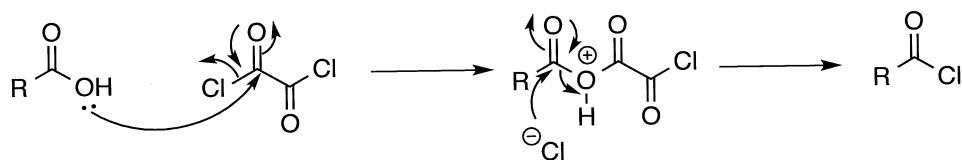


Commercially Available

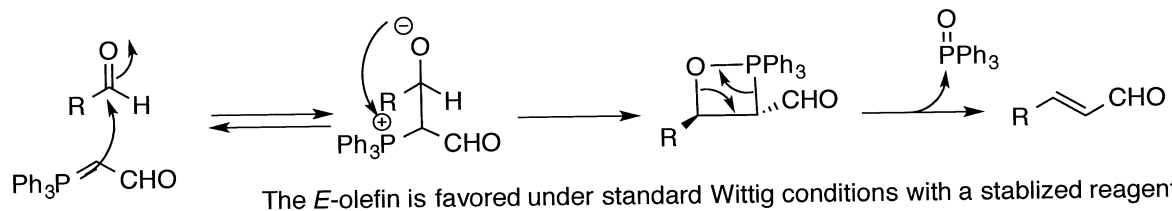


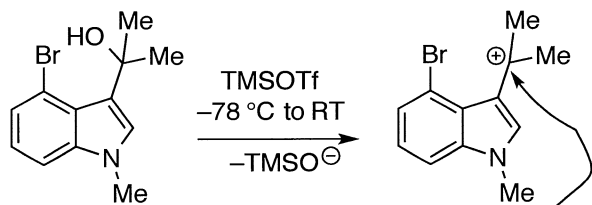
Route to 12: Martin, S. F. *Org. Lett.* 2010, 12, 2492–2495.

*Acid chloride formation: 13a*

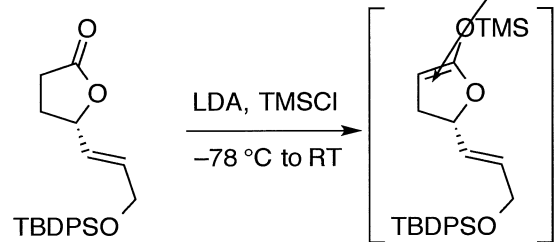


*Wittig Reaction: 14*

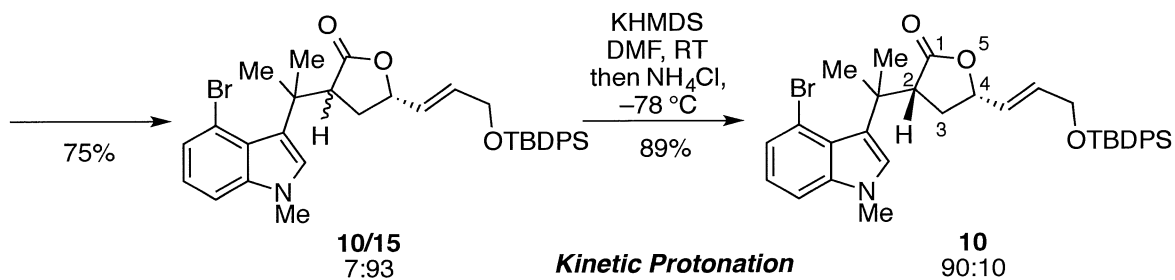




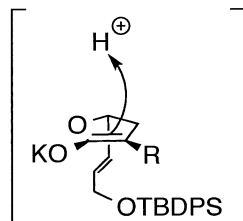
12



11



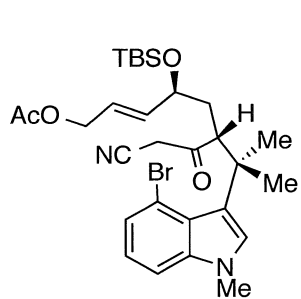
*Kinetic Protonation*



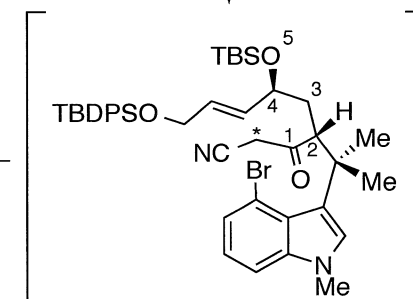
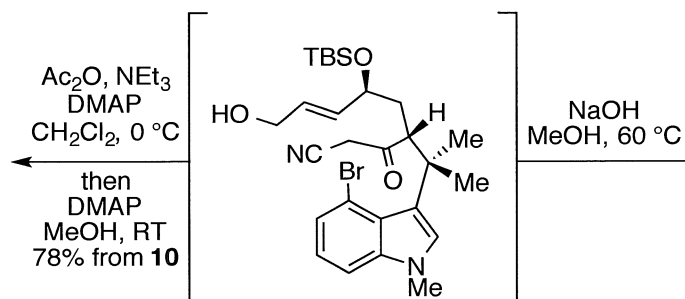
O-[Si] blocks bottom-face approach

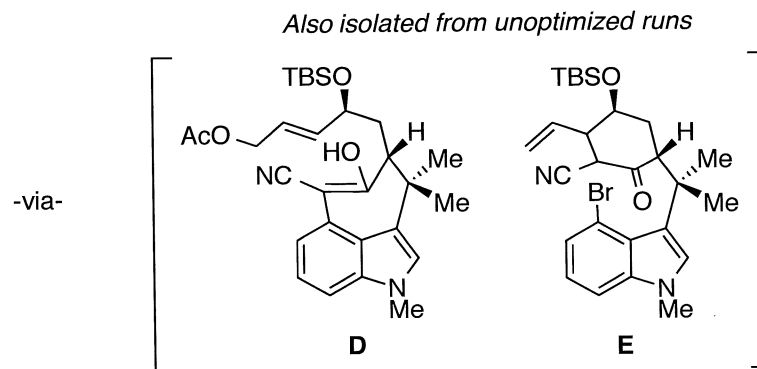
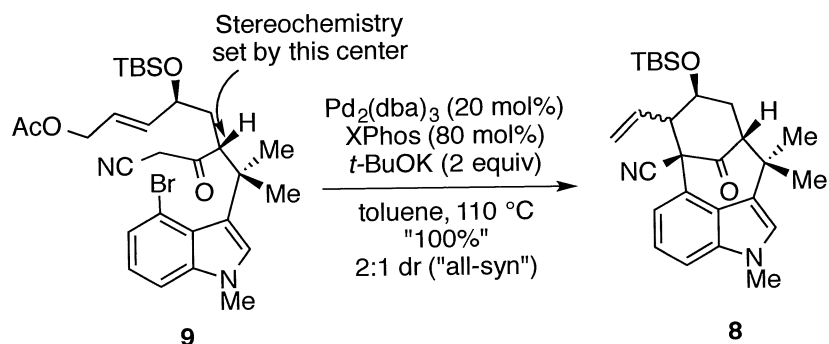
\*MeCN, LDA  
 THF,  $-78\text{ }^{\circ}\text{C}$   
 then  
 TBSOTf,  
 2,6-lutidine  
 $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^{\circ}\text{C}$

Tandem  
Annulation  
Precursor



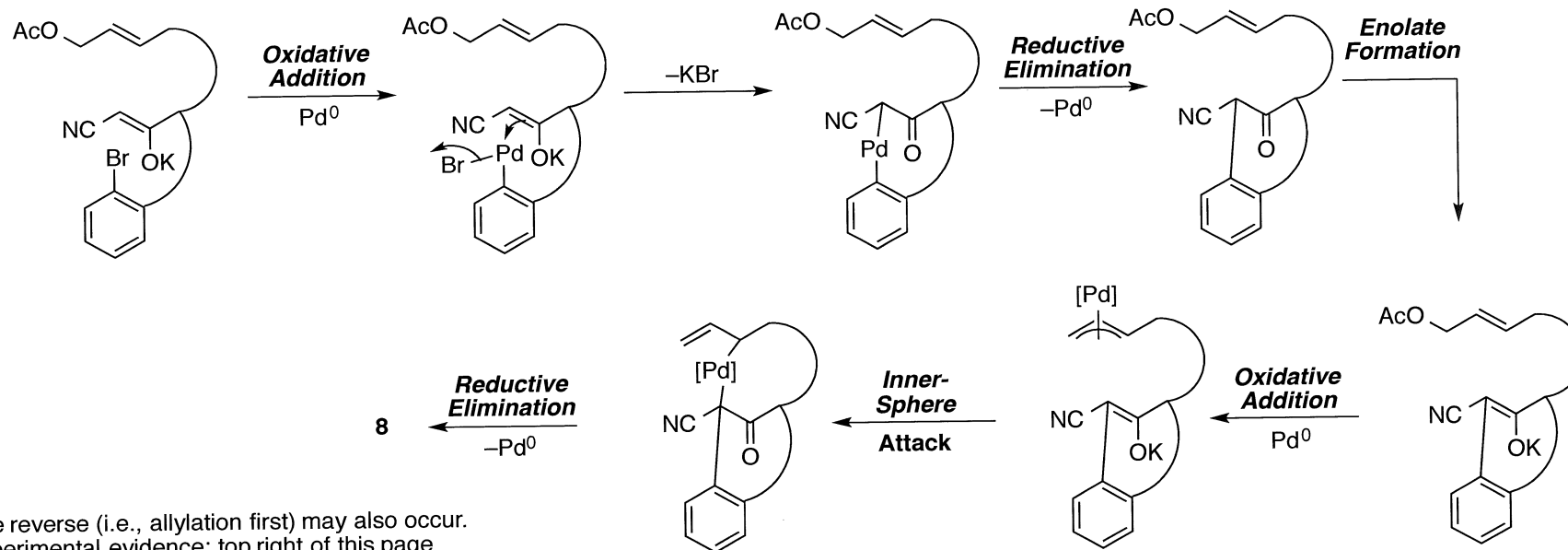
9





Either cyclization can proceed first.  
 Subjecting **E** to the reaction conditions gives a 10:1 dr, which is why the authors suggest allylation first is preferred over arylation first.

**9 to 8:**



The reverse (i.e., allylation first) may also occur.  
 Experimental evidence: top right of this page

Hard nucleophiles in the **Tsuji-Trost reaction** attack palladium in its coordination sphere rather than the carbon allyl fragment in an outer-sphere fashion.

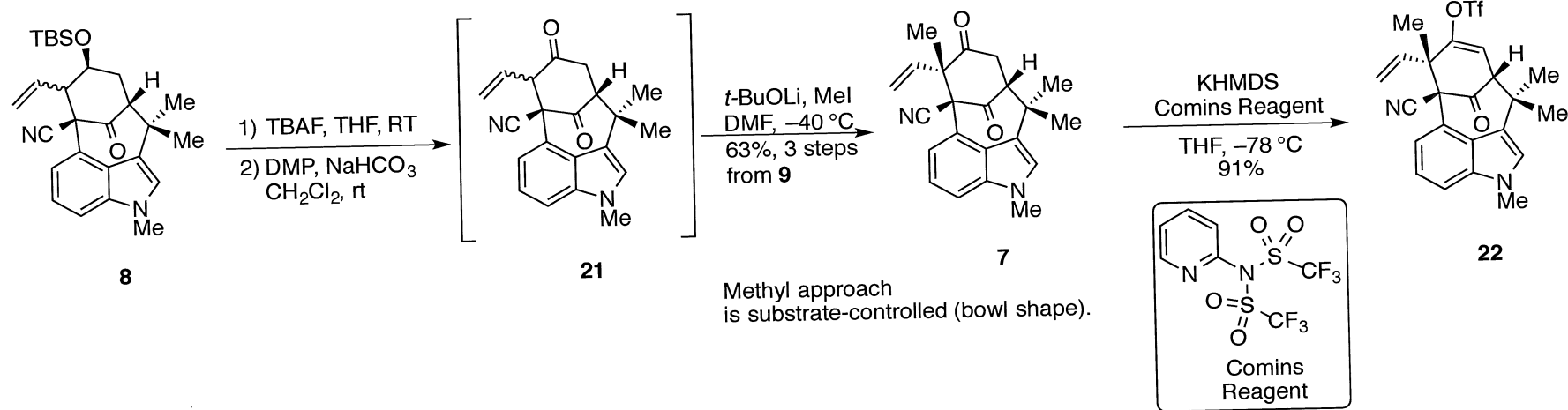
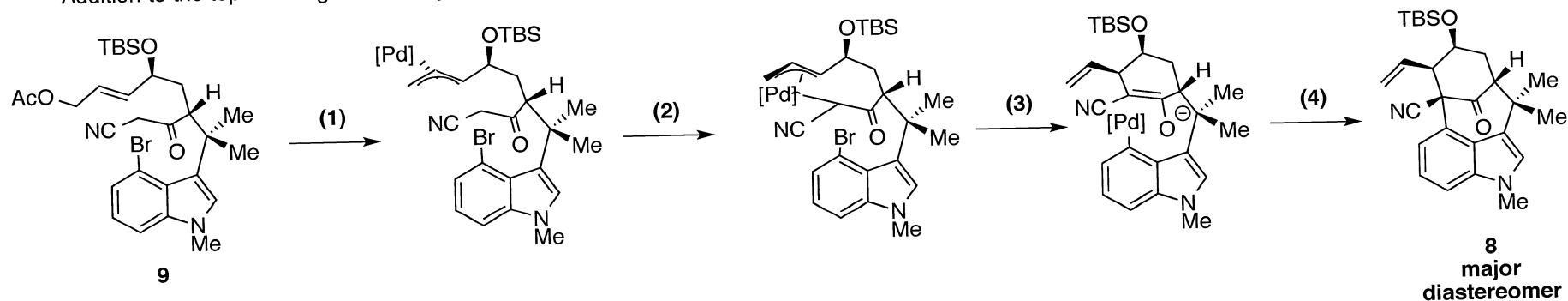
More on the (slightly) preferred stereochemistry for **8**:

1) Explicit "upward" facing proton directs the allyl-containing fragment "down." Also, bulky -OTBS fragment promotes *anti* oxidative addition of the allyl acetate.

2) Addition of enolate *via* coordination of Pd then

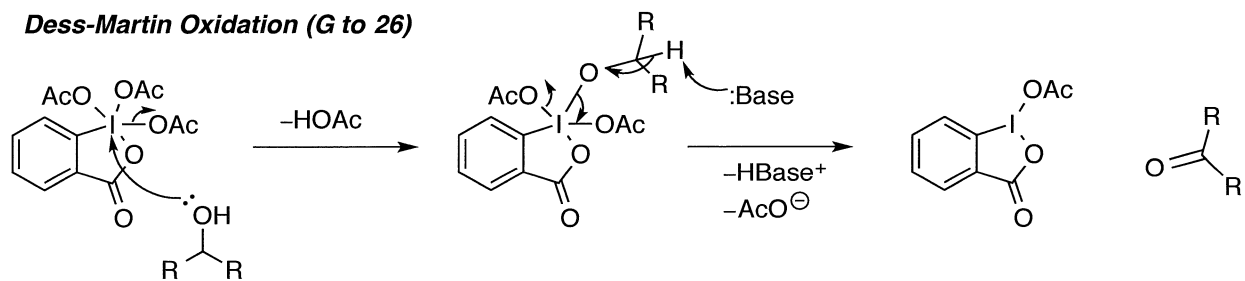
3) Reductive elimination gives the all *syn* product. Base in solution gives enolate then

4) The original stereocenter directs the second enolate addition from the "bottom" face only  
-Addition to the top face is geometrically unfeasible.

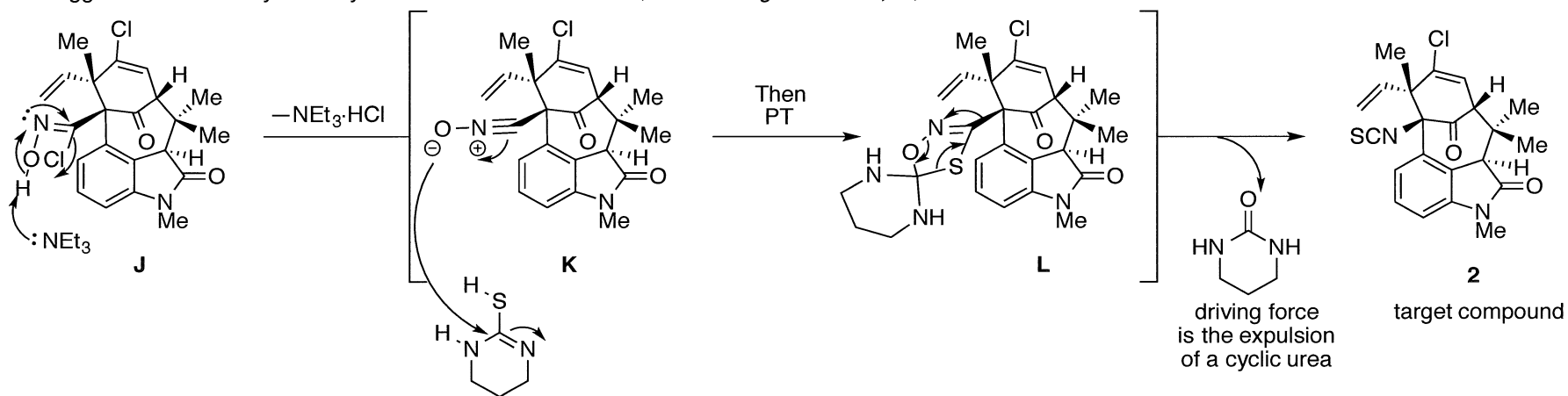




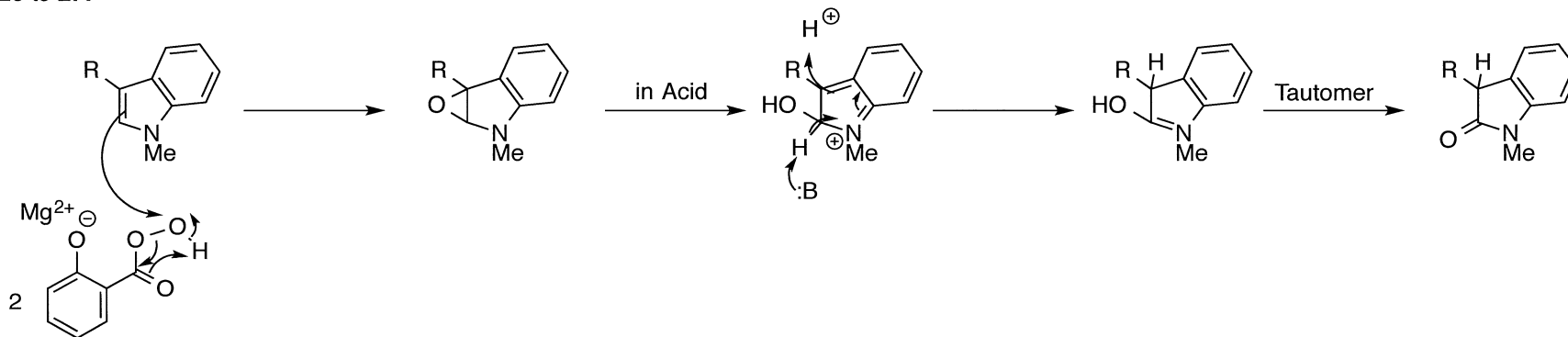
**Dess-Martin Oxidation (G to 26)**



suggestion of isothiocyanate synthesis mechanism: Radom, L. *et al. Org. Lett.* **2009**, *11*, 1325–1328.



**26 to 27:**



magnesium monoperoxyphthalate  
(MMPP)