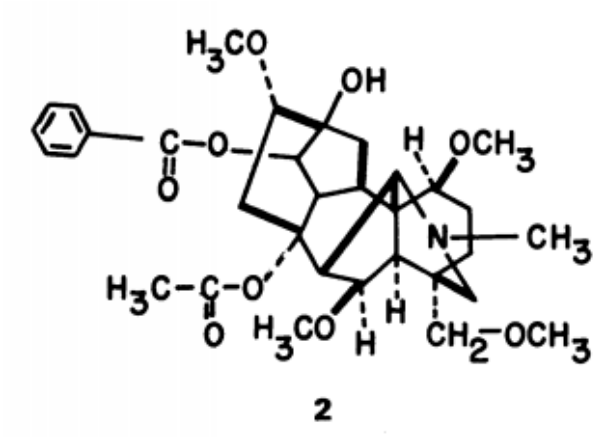
Aconitine-type Alkaloids

C19- and C18- norditerpenoid alkaloids



Lindsey R. Cullen

SED Group Meeting 6/24/14

Aconitum and *Delphinium* Natural Products

Aconitum
Common name: "Wild Monkshood"

Terms (used interchangably):

- aconite alkaloids
- *Aconitum* or *Delphinium* alkaloids
- C19-norditerpenoid alkaloids
- delphinine alkaloid

Delphinium

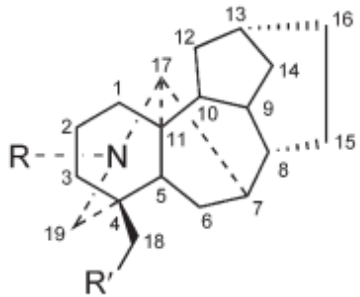
by 2008, 672 individual, naturally occurring C19-diterpenoid alkaloids had been isolated from 315 species of plants (but may contain repeats…)

92% of known C19-diterenoid alkaloids were isolated from the *Aconitum* and *Delphinium* genera

Wang, F. –P.; Chen, Q. –H.; Liang, X. –T. in *The Alkaloids: Chemistry and Biology, Vol 67* (Eds. Cordell, G. A.), Elsevier, New York, **2009**, pp 1-78.
Wang, F. –P.; Chen, Q. –H.; Lui, X. –Y. *Nat. Prod. Rep.* **2010**, *27*, 529.

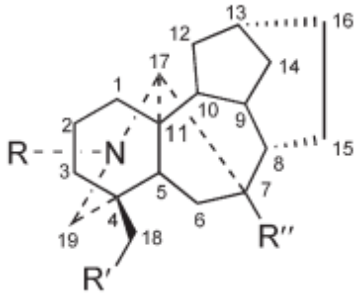
Aconotine Classifications

6 general subclasses:



Aconitine-type (A)

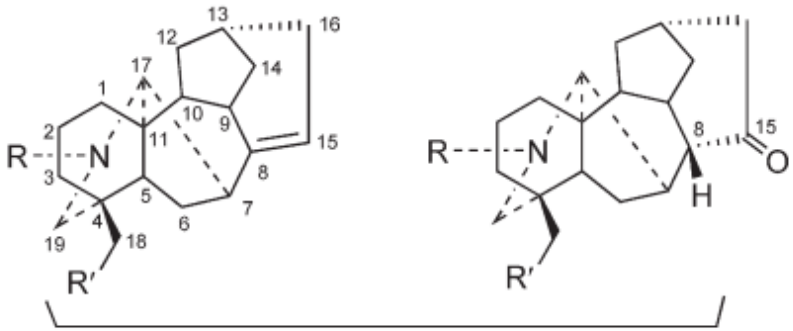
(~351)



oxygenated at C7

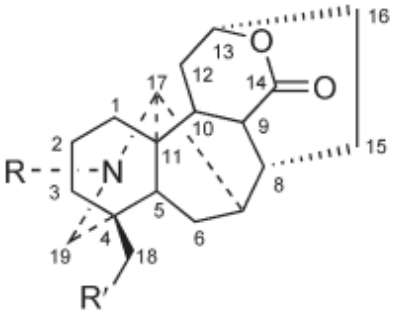
Lycoctonine-type (B)

(~284)



Pyro-type (C)

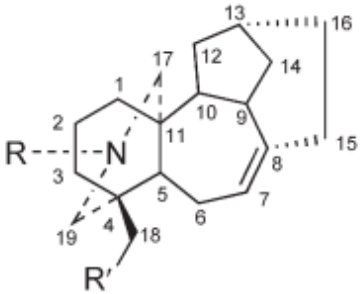
(~8)



Lactone-type (D)

(~12)

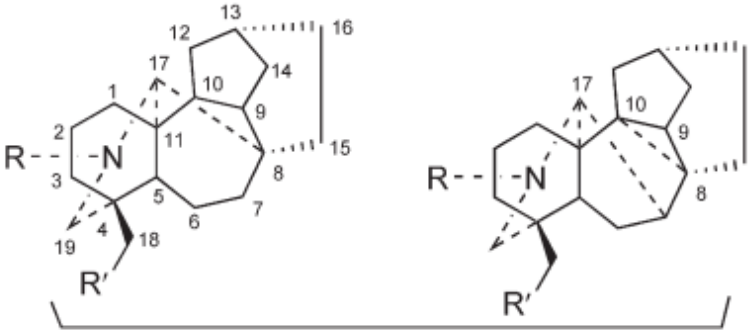
Baeyer-Villiger of C14 ketone



7, 17-*Seco*-type (E)

(~12)

Missing C17-C7 bridge



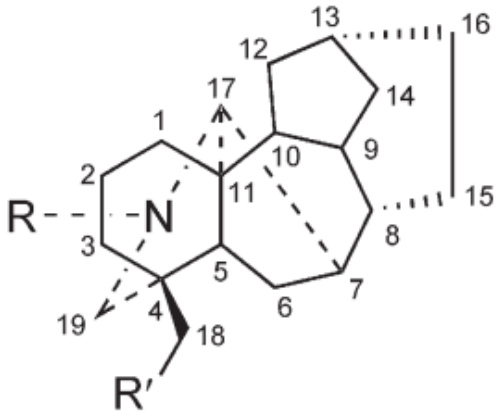
Rearranged-type (F)

(~5)

Wang, F. –P.; Chen, Q. –H.; Liang, X. –T. in *The Alkaloids: Chemistry and Biology, Vol 67* (Eds. Cordell, G. A.), Elsevier, New York, **2009**, pp 1-78.

Wang, F. –P.; Chen, Q. –H.; Lui, X. –Y. *Nat. Prod. Rep.* **2010**, *27*, 529.

Features of Aconitine-type Alkaloids



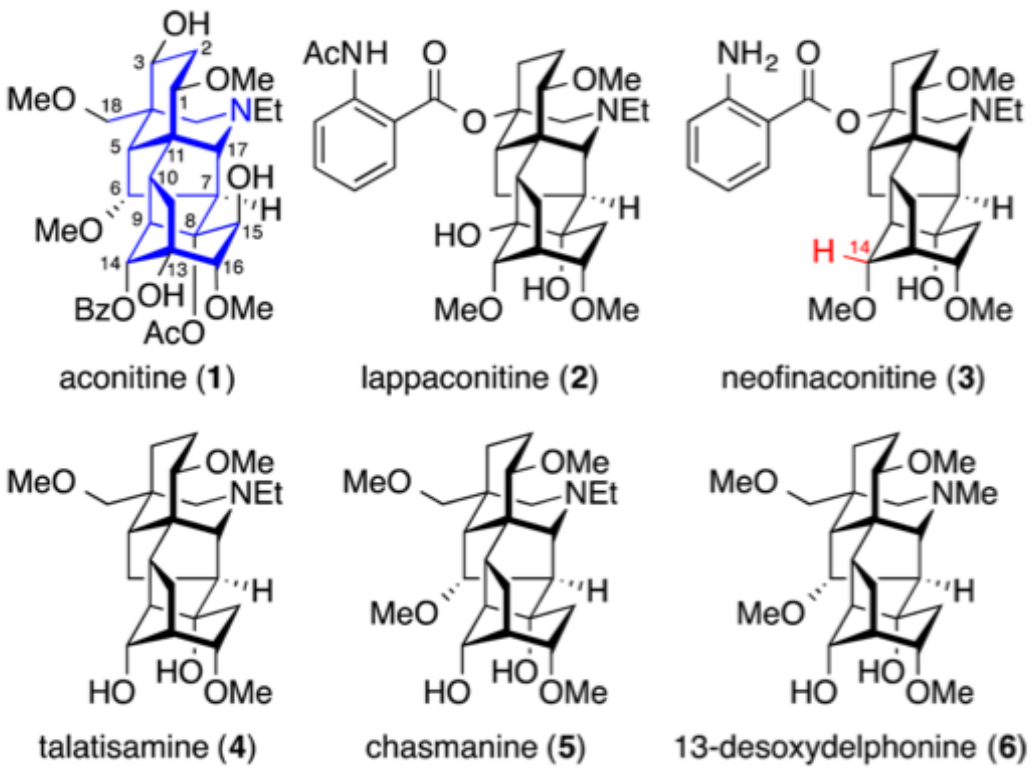
Aconitine-type (A)

(~351)

- typically oxygenated at C-1, C-6, C-8, C-14, C-16, and C-18
- typically only OH and OMe (C-1, C-16, C-18)
- ester groups can varied widely (C-8, C-14)
- most have an N-ethyl (very rare to be NH)
- characteristic hexacyclic core

A related class of C18-norditerpenoid alkaloids exist which lack the C18 carbon atom

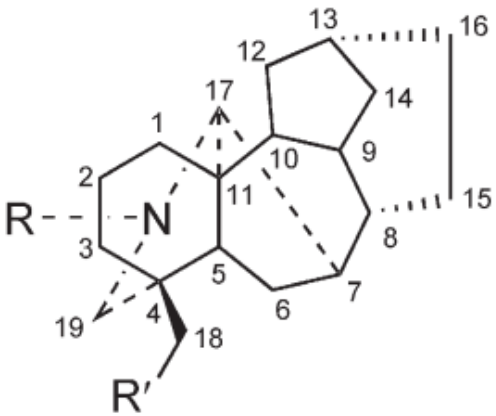
(see lappaconitine **2** and neofinaconitine **3**)



Wang, F. –P.; Chen, Q. –H.; Liang, X. –T. in *The Alkaloids: Chemistry and Biology, Vol 67* (Eds. Cordell, G. A.), Elsevier, New York, **2009**, pp 1-78.

Wang, F. –P.; Chen, Q. –H.; Lui, X. –Y. *Nat. Prod. Rep.* **2010**, *27*, 529.

Pharmacological Activity



Aconitine-type (A)

(~351)

Originate in traditional Chinese medicine called "Cao-Wu" (78 different species have be used in this medicine)

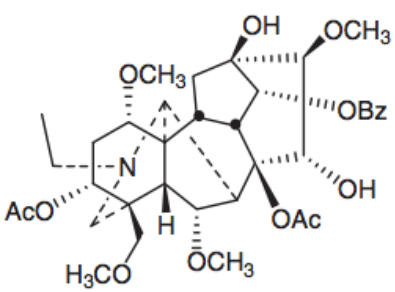
Representative biological activities include

- anti-inflammatory (although worse than NSAIDs)
- analgesic (w/o tolerance or physical dependence)
- antiarrhythmic

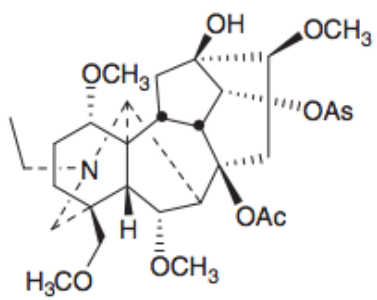
Disrupts sodium channels = some are horrible toxins (can elicit arrhythmias)

Used in China as non-narcotic analgesics

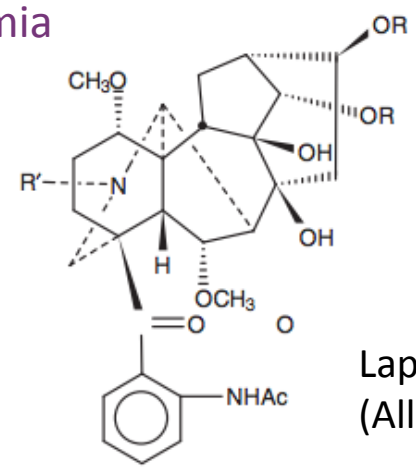
Flaconitine (3-acetylaconitine) (**264**)



Crassicauline A (**210**)



Used in China and Russia to treat arrhythmia



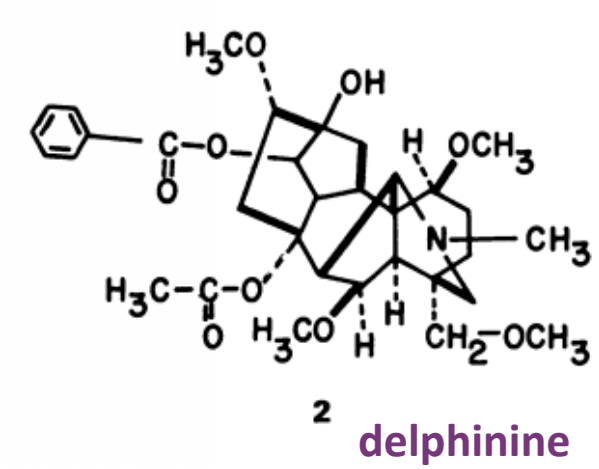
Lappaconitine (Allapinin)

Wang, F. –P.; Chen, Q. –H.; Liang, X. –T. in *The Alkaloids: Chemistry and Biology, Vol 67* (Eds. Cordell, G. A.), Elsevier, New York, **2009**, pp 1-78.

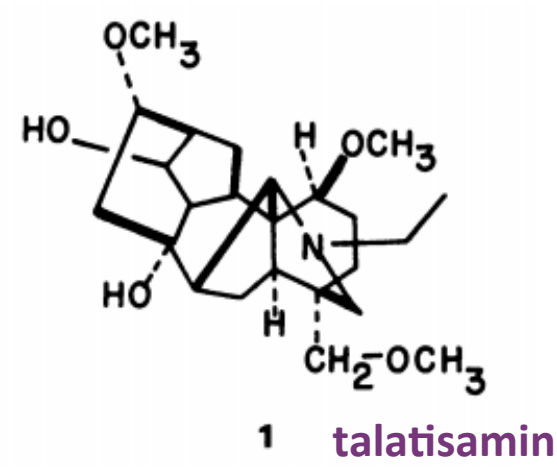
Wang, F. –P.; Chen, Q. –H.; Lui, X. –Y. *Nat. Prod. Rep.* **2010**, *27*, 529.

Challenging Targets for Total Synthesis

1. Weisner's Total Synthesis of Talitisamine

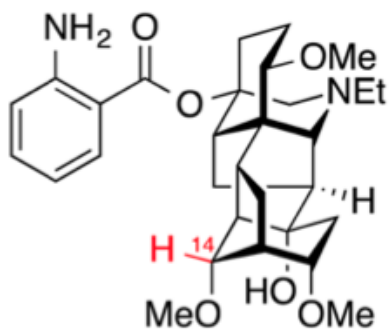


2 **delphinine**



1 **talatisamine**

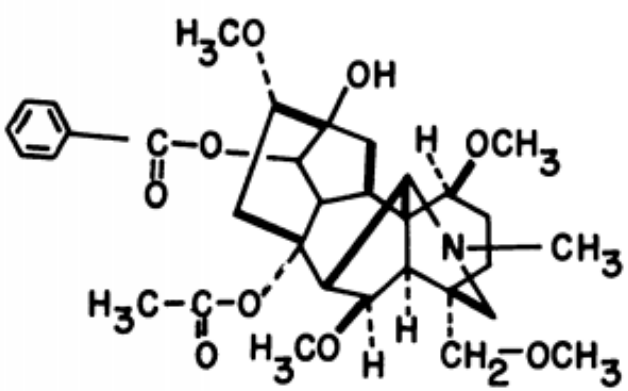
2. Gin's Total Synthesis of Neofinaconitine



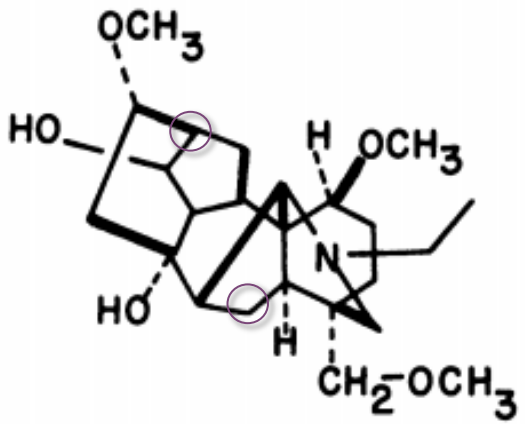
neofinaconitine (**3**)

Wiesner's Strategy

"…it was clear that with its bridged hexacyclic skeleton and seven substituents the delphinine fortress could not be taken by direct assault of inexperienced troops" - Karel Wiesner



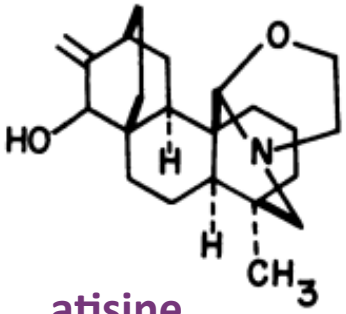
2 **delphinine**



1 **talatisamine**

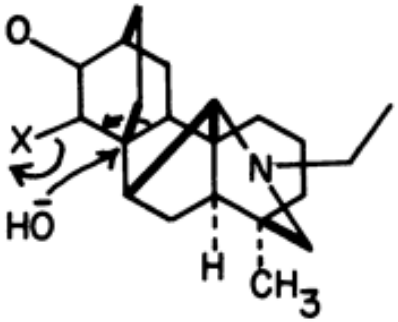
<u>Hypothesis:</u> Does the delphinine system originate from the related atisine natural products?

Subsequent isolation is consistent with this:

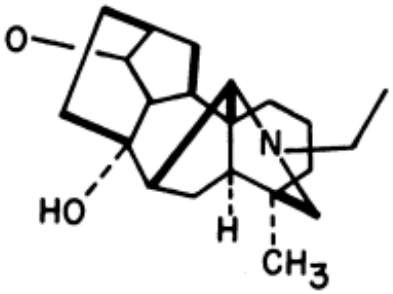


atisine

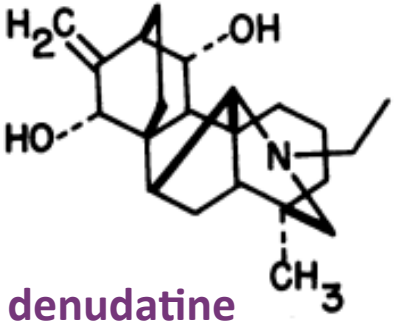
3



4



5

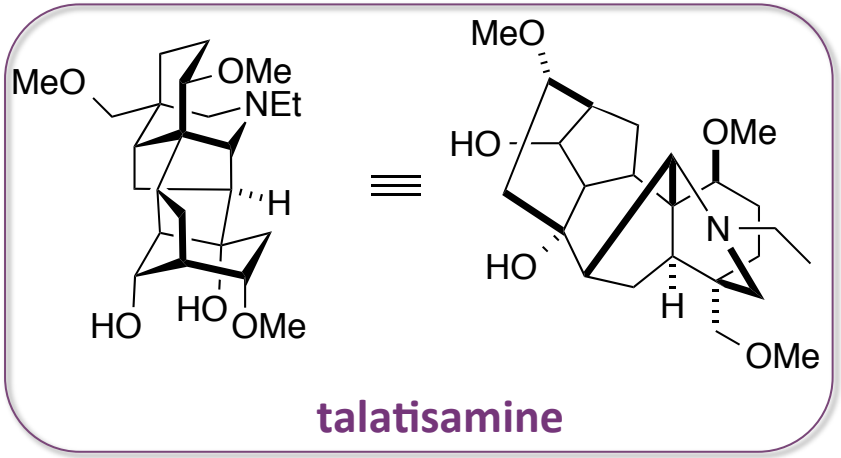


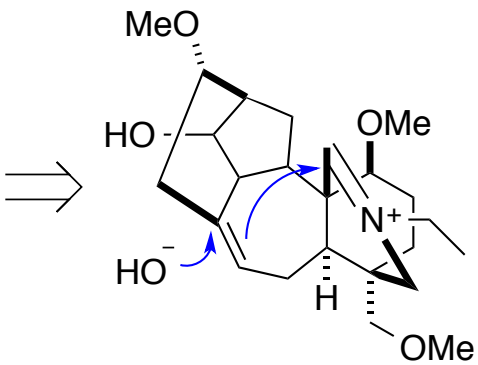
denudatine

6

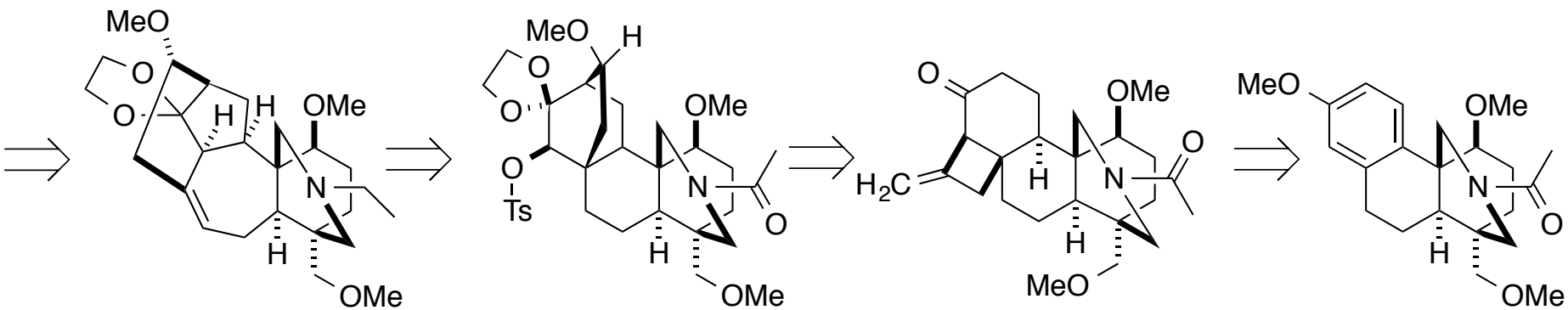
Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Wiesner's Retrosynthesis





oxidation to imine & spontaneous closure



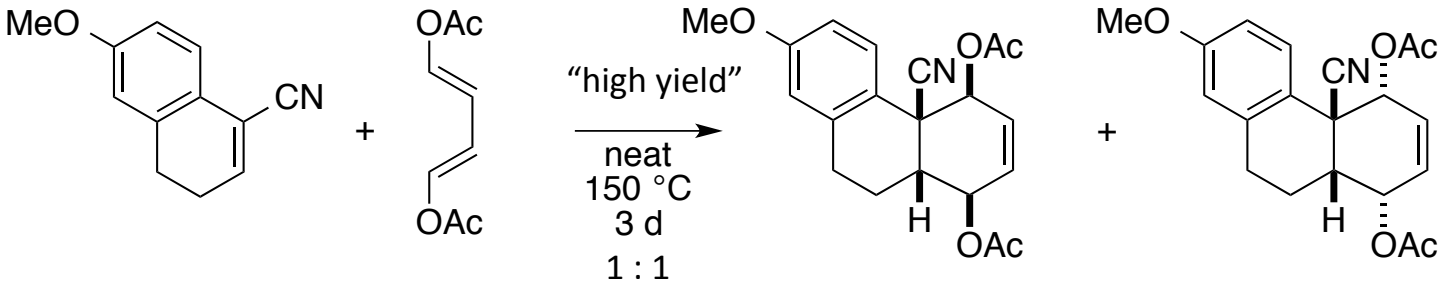
rearrangment of atisine skeleton

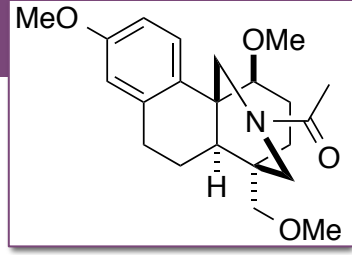
[2+2]-ketene photocycloaddition

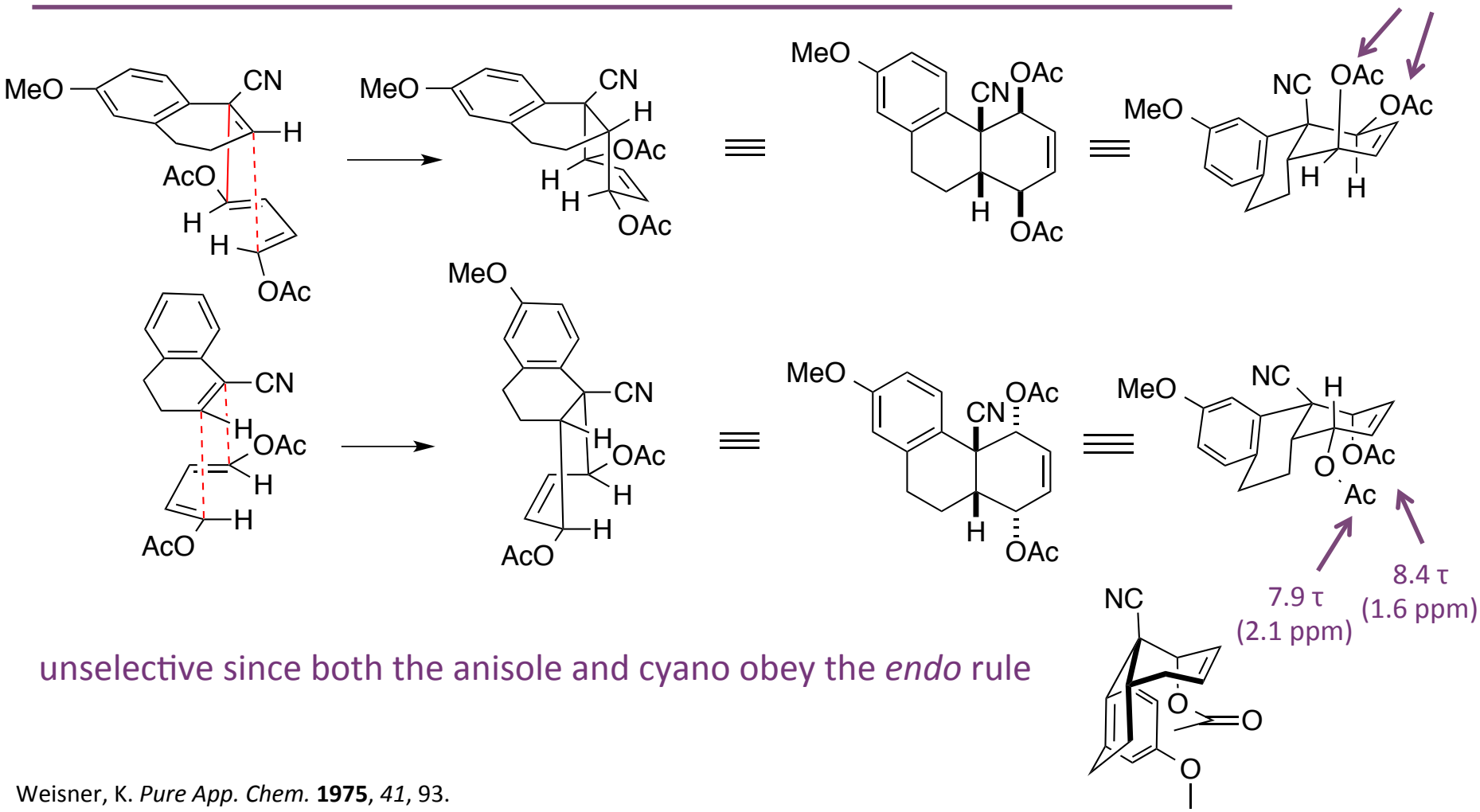
Birch reduction of "aromatic intermediate"

Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Synthesis of the "Aromatic Intermediate"



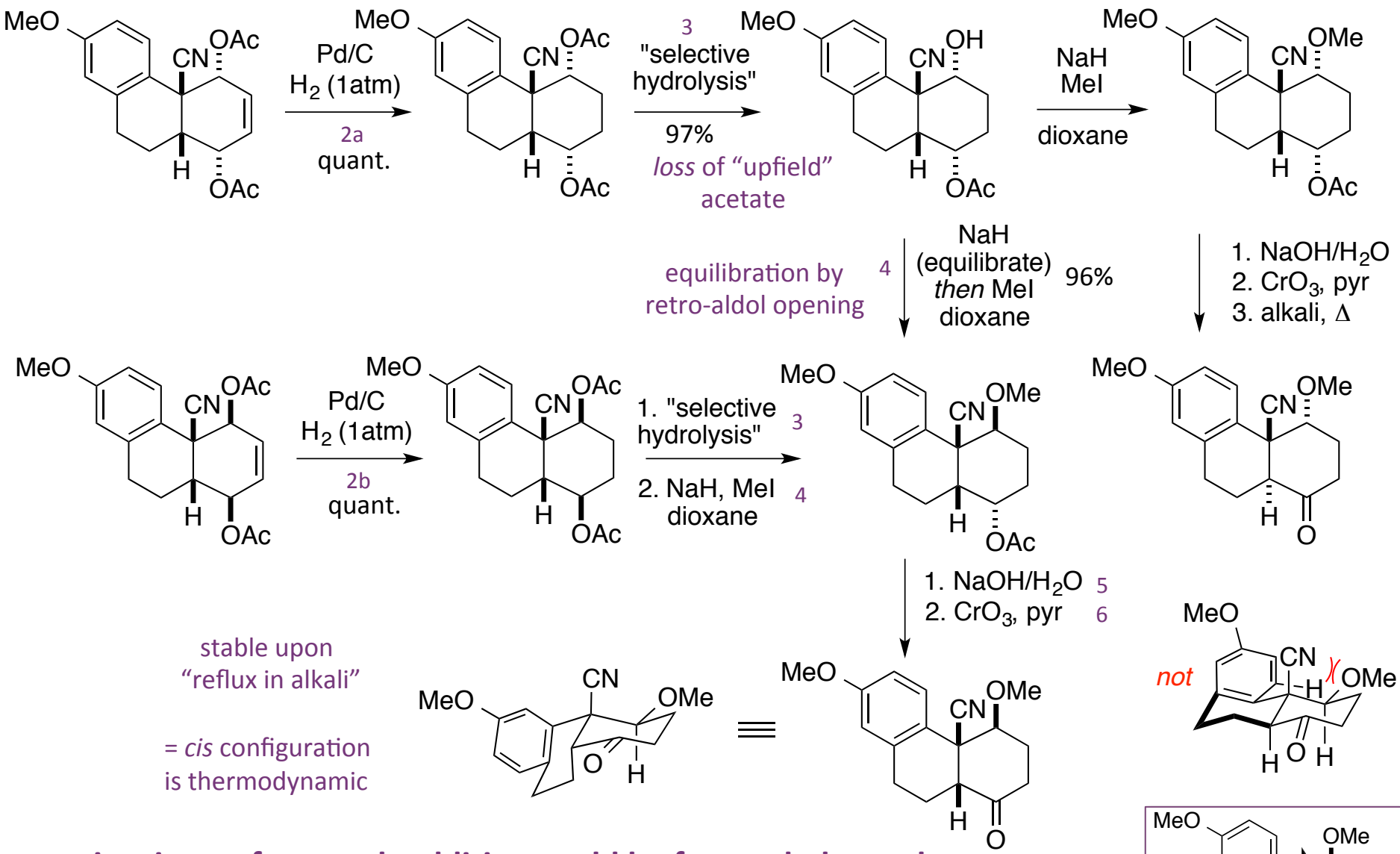




unselective since both the anisole and cyano obey the *endo* rule

Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

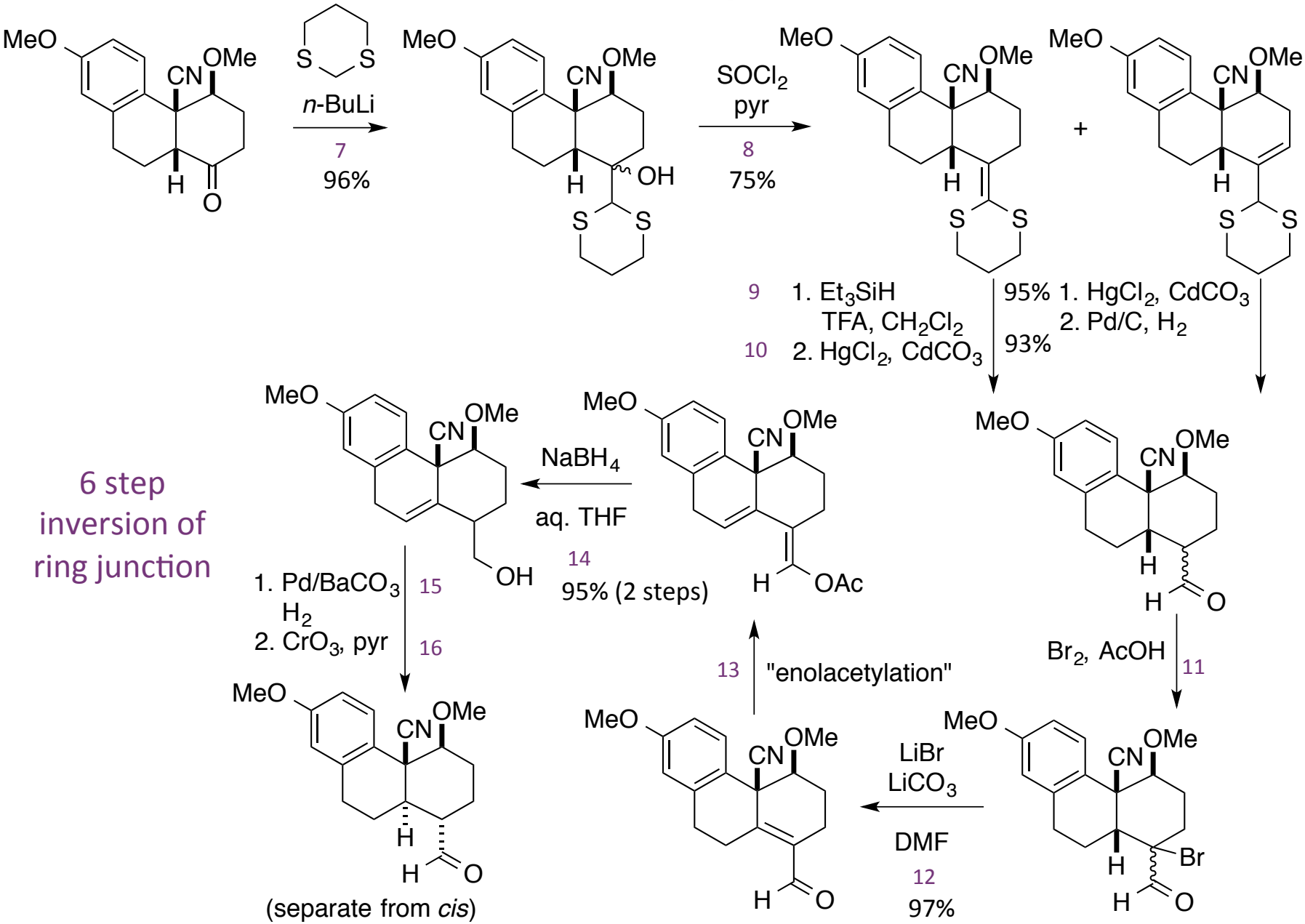
Determining Structure of Decalin Systems



isomeric mixture from cycloaddition could be forwarded together but favors *cis* decalin

Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

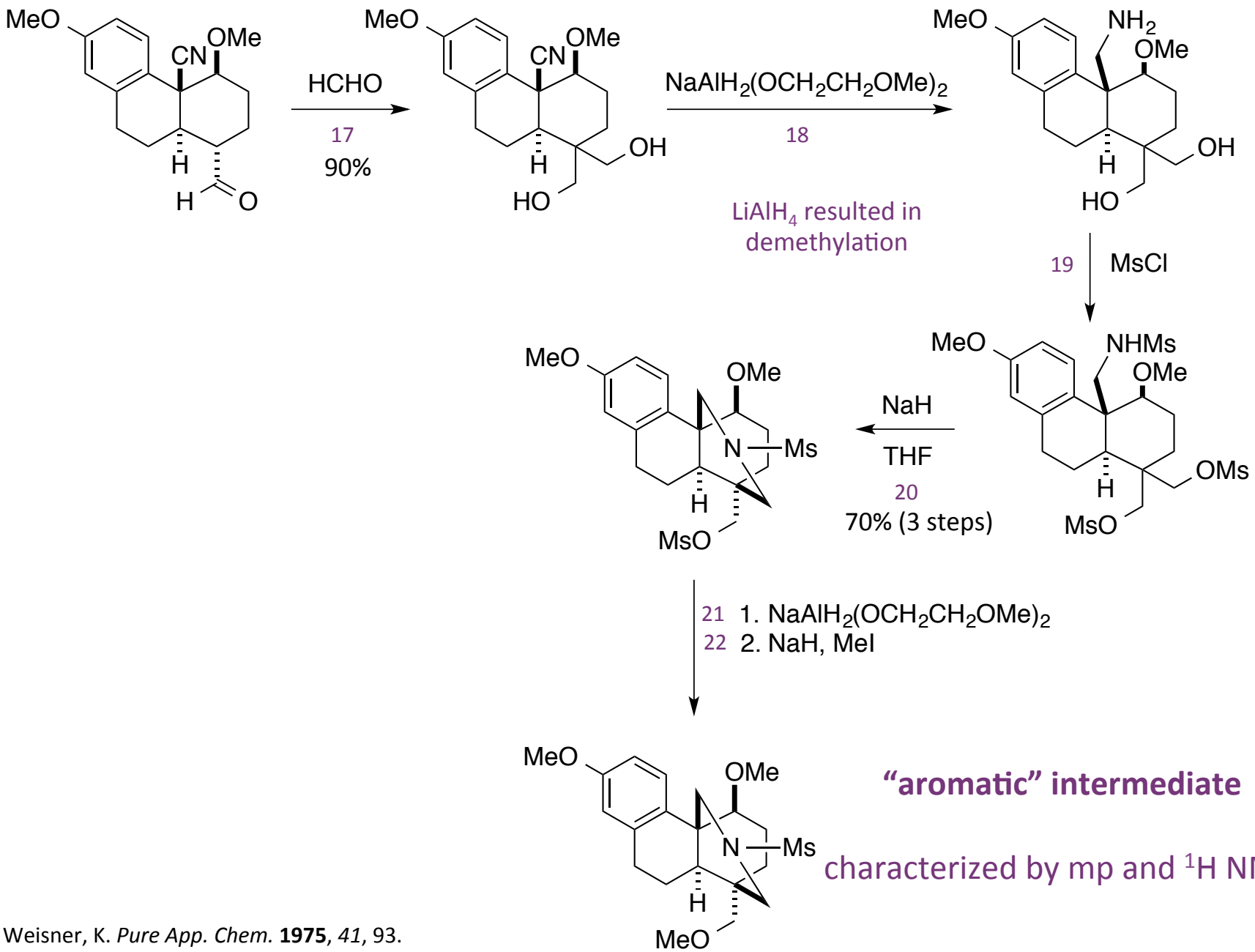
Interconverting *cis* to *trans*



6 step inversion of ring junction

Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Synthesis of the "Aromatic" Intermediate

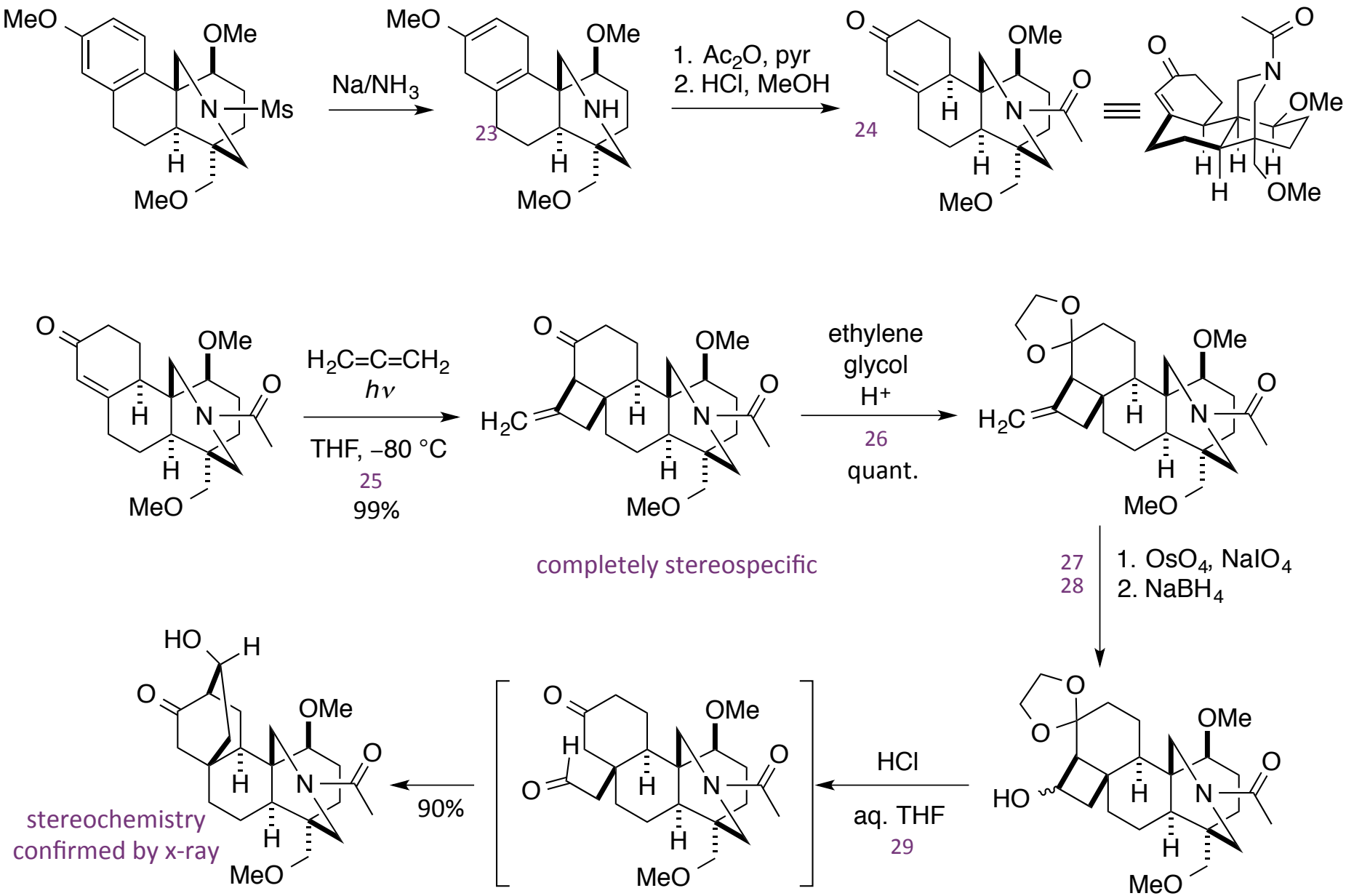


"aromatic" intermediate

characterized by mp and ^{1}H NMR

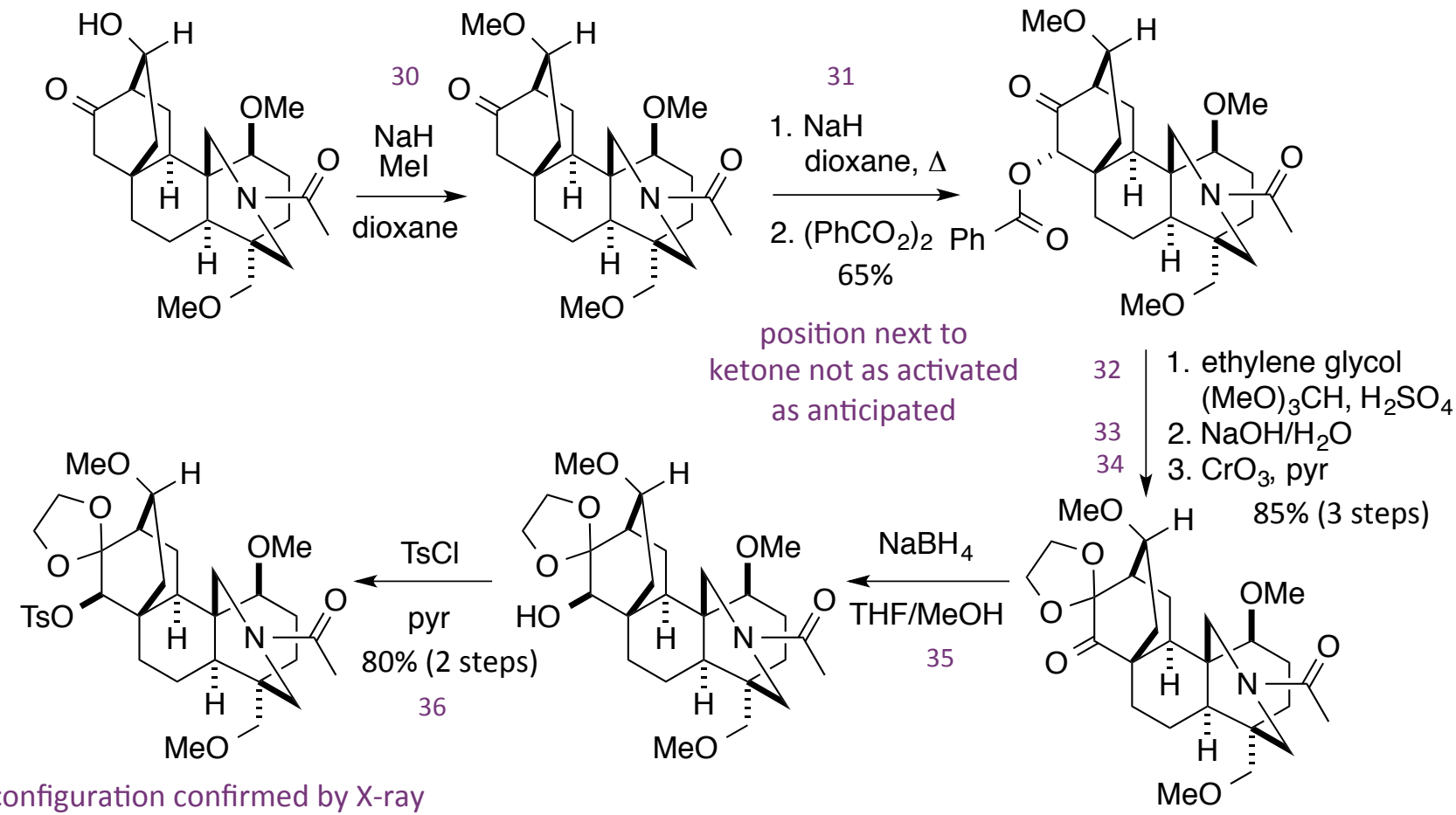
Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Photochemical Approach to Atisine Skeleton



Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Set Up for Final Rearrangement

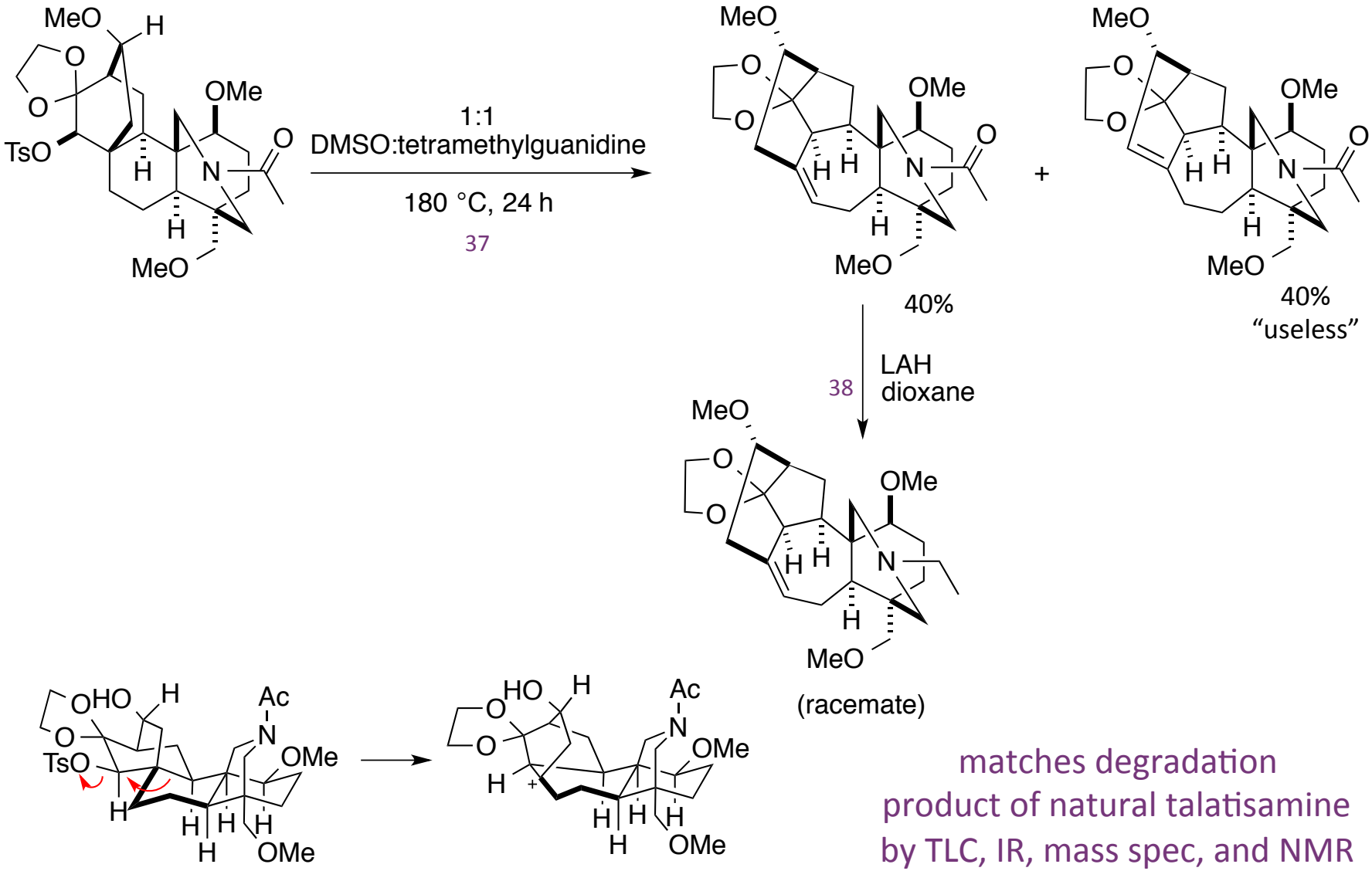


epimeric tosylate also prepared from benzoate & characterized (does not rearrange)

6 step interconversion to get proper configuration for rearrangement

Weisner, K.; Tsai, T. Y. R.; Huber, K.; Bolton, S. E. *J Am. Chem. Soc.* **1974**, *96*, 4990.
Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

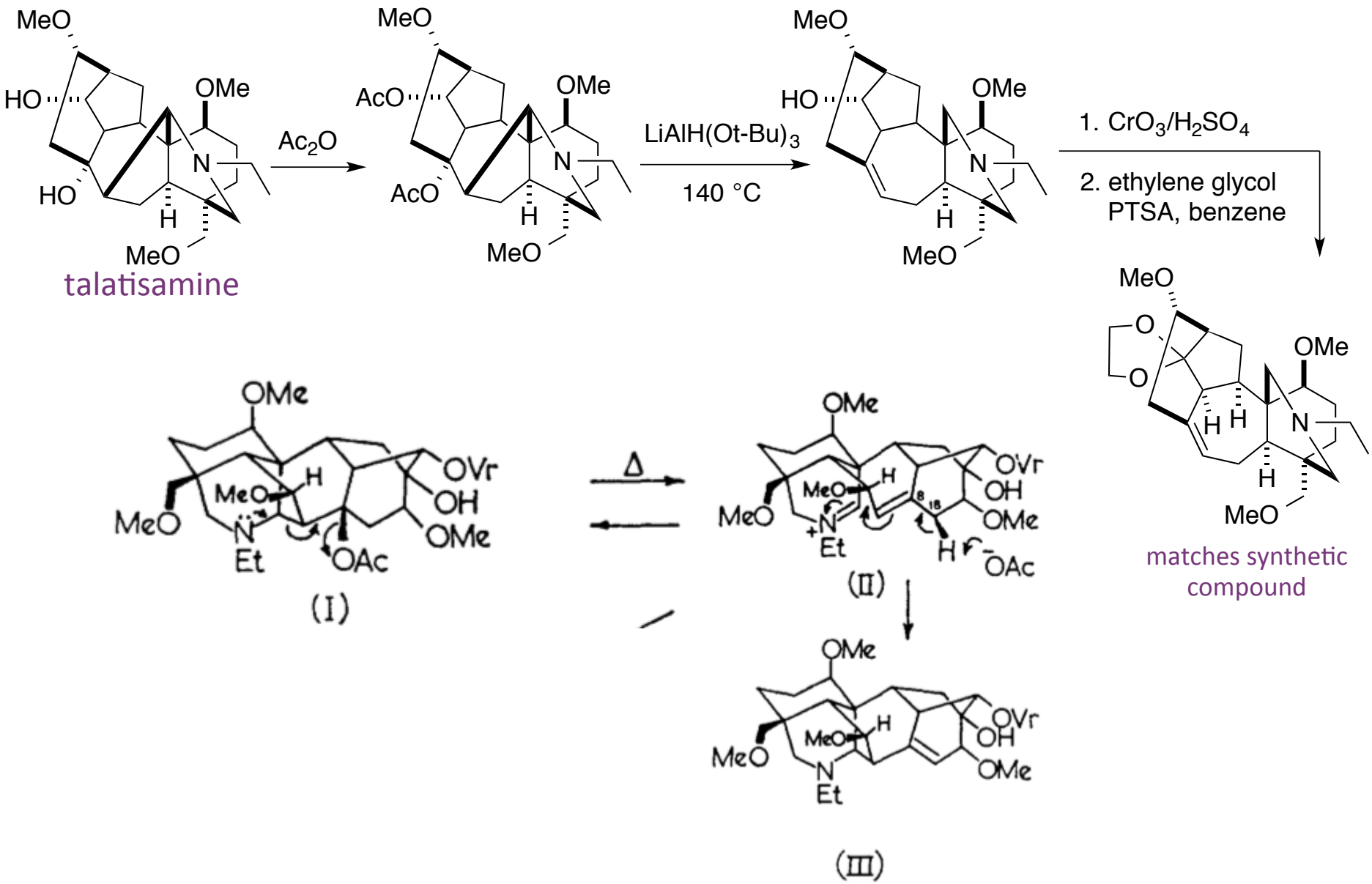
Rearrangement of Atisine Skeleton



matches degradation product of natural talatisamine by TLC, IR, mass spec, and NMR

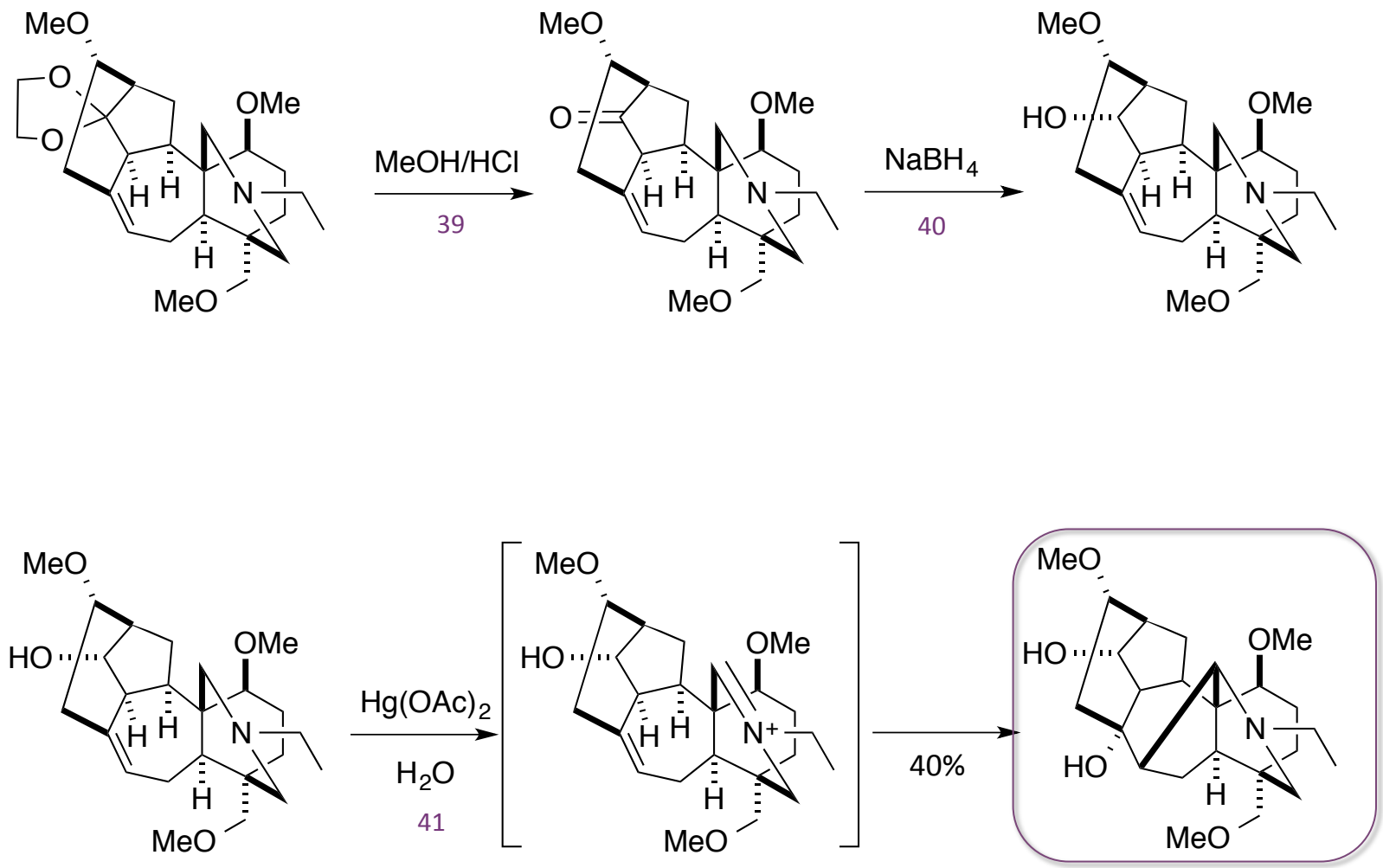
Weisner, K.; Tsai, T. Y. R.; Huber, K.; Bolton, S. E. *J Am. Chem. Soc.* **1974**, *96*, 4990.
Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Same sequence backwards from Talatisamine



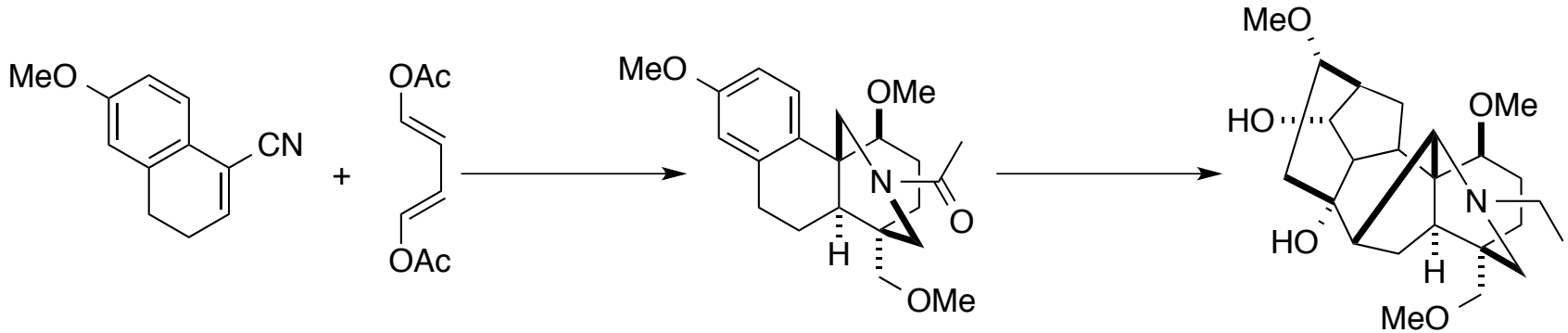
Edwards, O. E. *Chem. Commun.* **1965**, 318.
Edwards, O. E.; Fonzes L.; Marion, L. *Can. J. Chem.* **1966**, *44*, 583.

End Game: Closure of the "B" Ring



Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

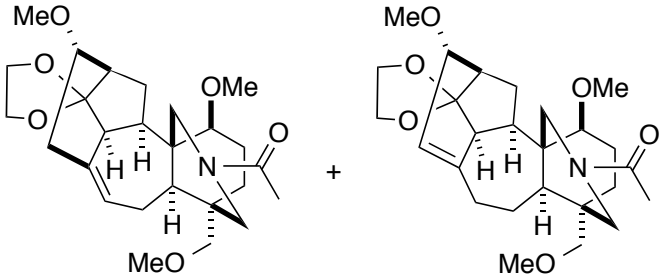
Summary



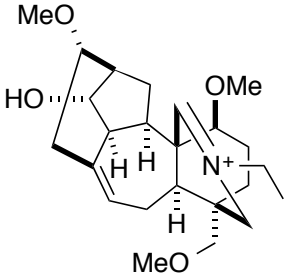
First synthesis of delphinine-type alkaloid (41 linear steps)

<u>Problems with efficiency due to:</u>

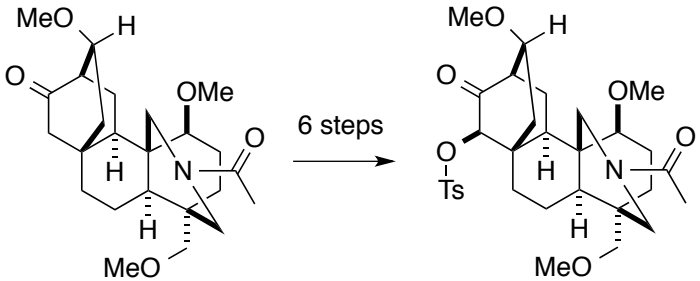
- Equal formation of "useless" double-bond isomer in rearrangement



- Low yield (40%) in final step due to unspecific oxidation



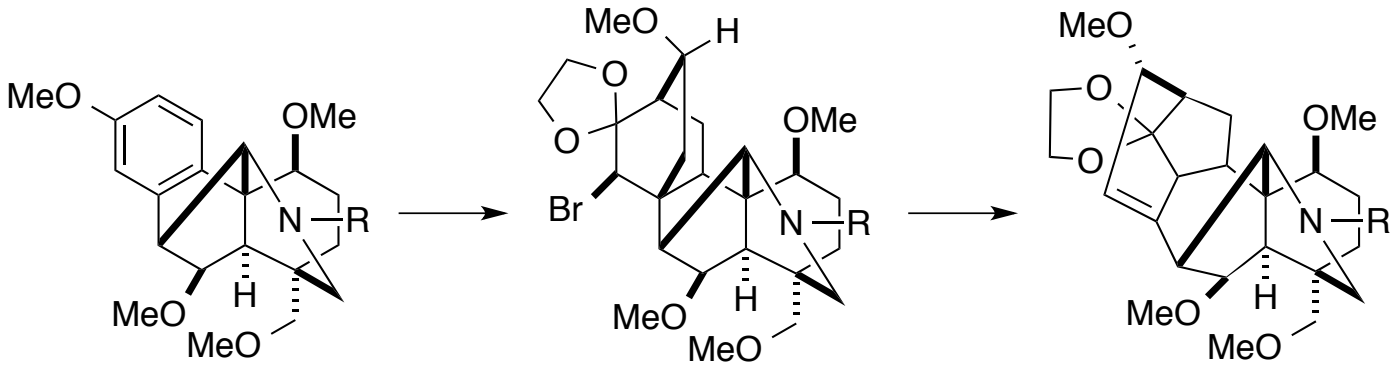
- Lengthy introduction of β–toxyloxy group



Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Next Generation Synthesis: Chasmanine

Change the approach to build the "B" ring first into the "aromatic intermediate"

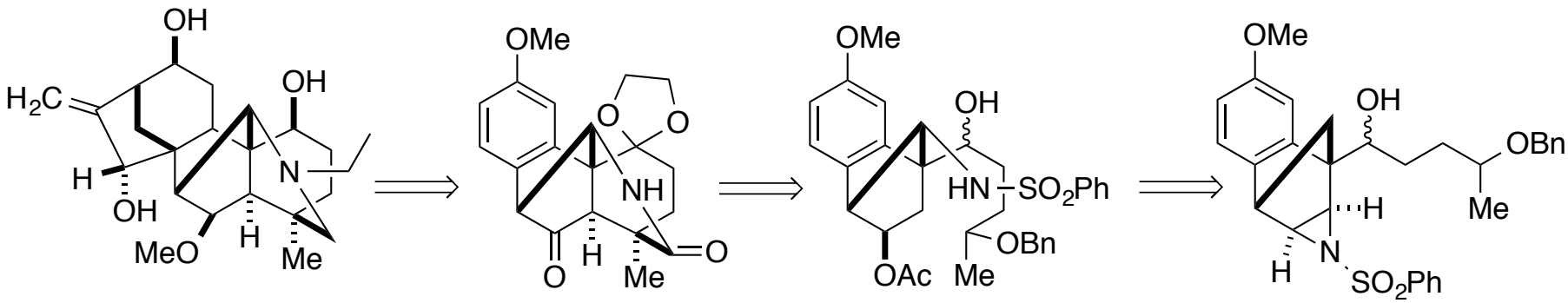


How do you build this?

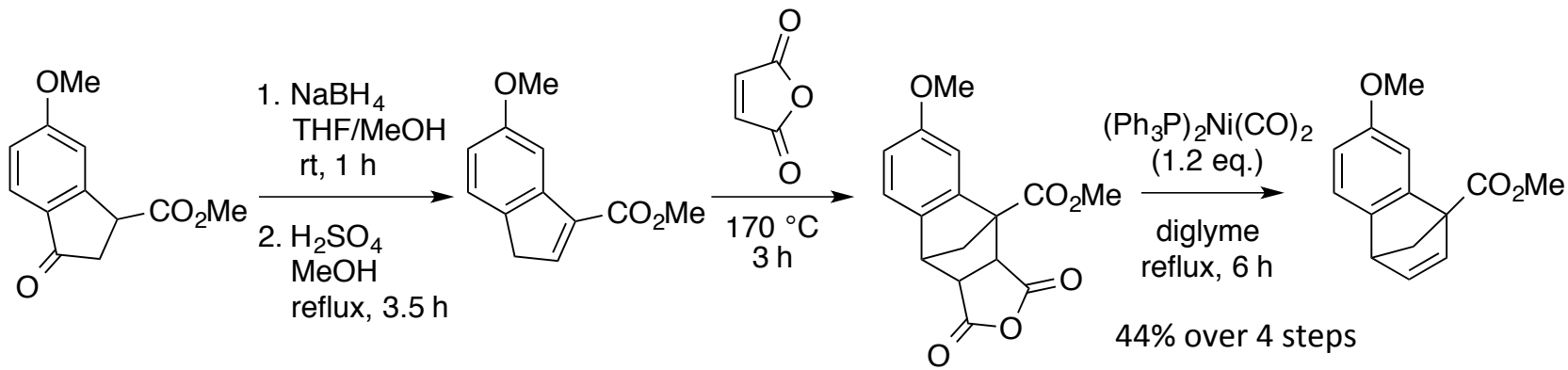
Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Synthesis of Napelline

Change the approach to build the "B" ring first into the "aromatic intermediate"



napelline



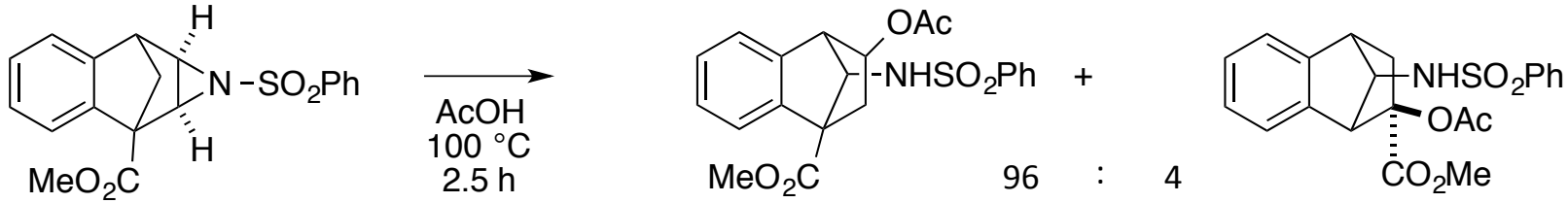
44% over 4 steps

Development of an aziridine acetolysis/rearrangement would be ideal since the starting olefin is easily prepared

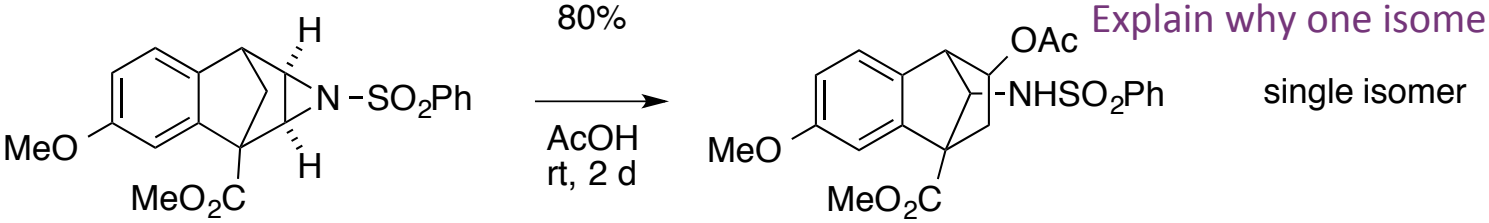
Weisner, K. *Pure App. Chem.* **1975**, *41*, 93.

Group Problem

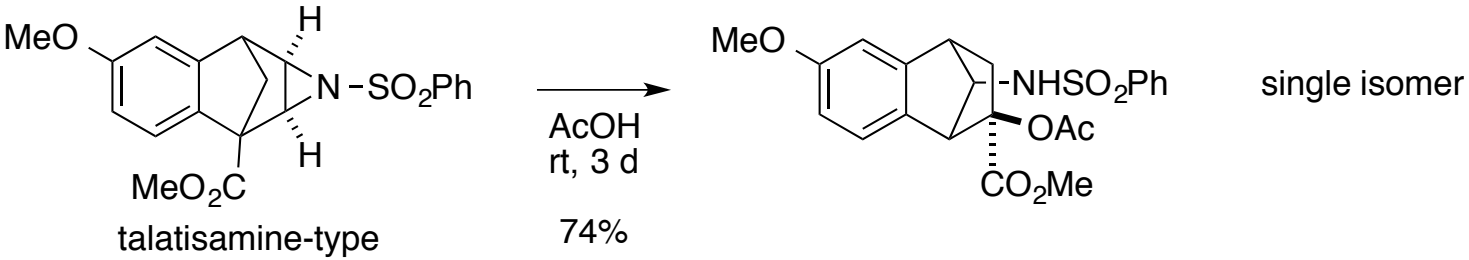
Provide a mechanism that explains the following observations:

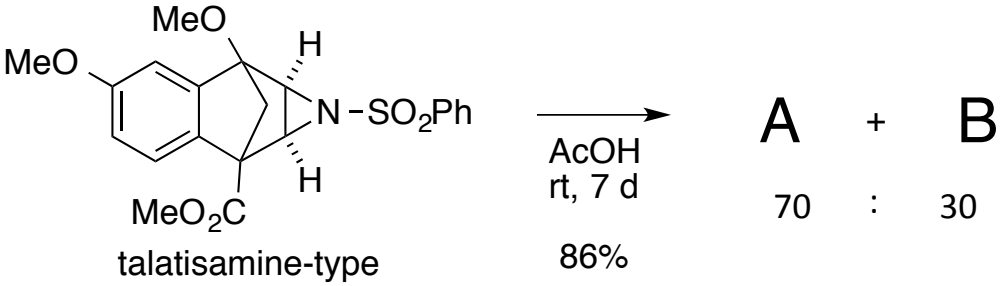


Explain why one isomer is favored.



Why does the position of the methoxy group affect which product is observed?

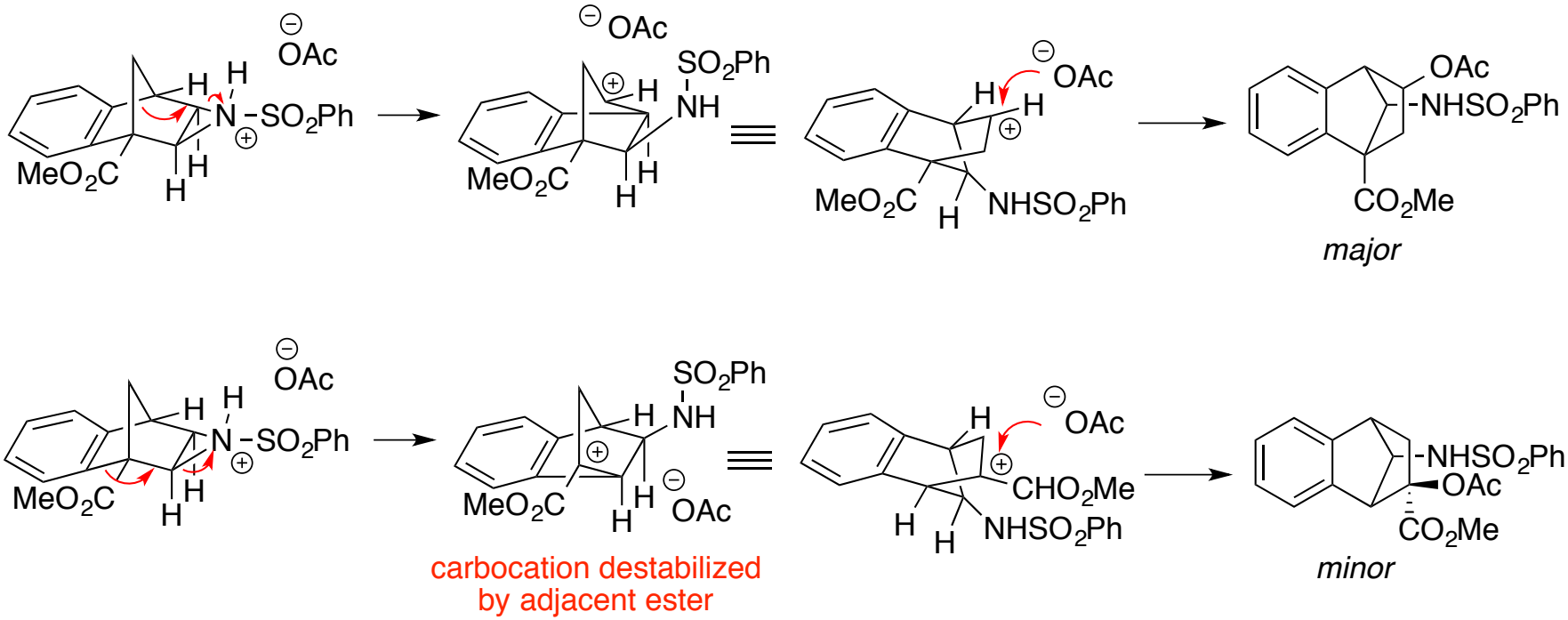




Draw anticipated structures for A and B.

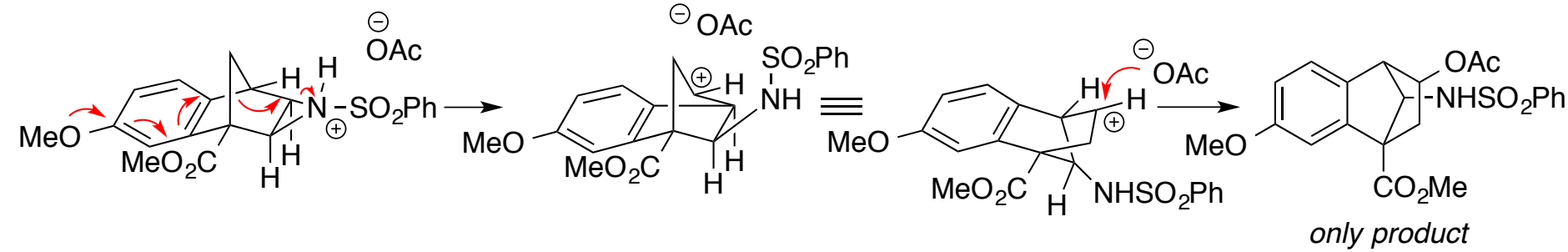
Weisner, K.; Ho, P. –T.; Jain, R. C.; Lee, S. F.; Oida, L. S.; Philipp, A. *Can. J. Chem.* **1973**, *51*, 1448.

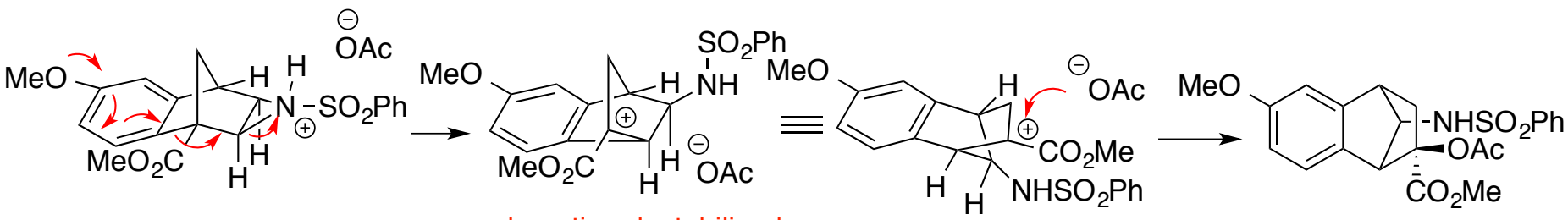
Group Problem



Weisner, K.; Ho, P. –T.; Jain, R. C.; Lee, S. F.; Oida, L. S.; Philipp, A. *Can. J. Chem.* **1973**, *51*, 1448.

Methoxy position impacts migratory aptitude

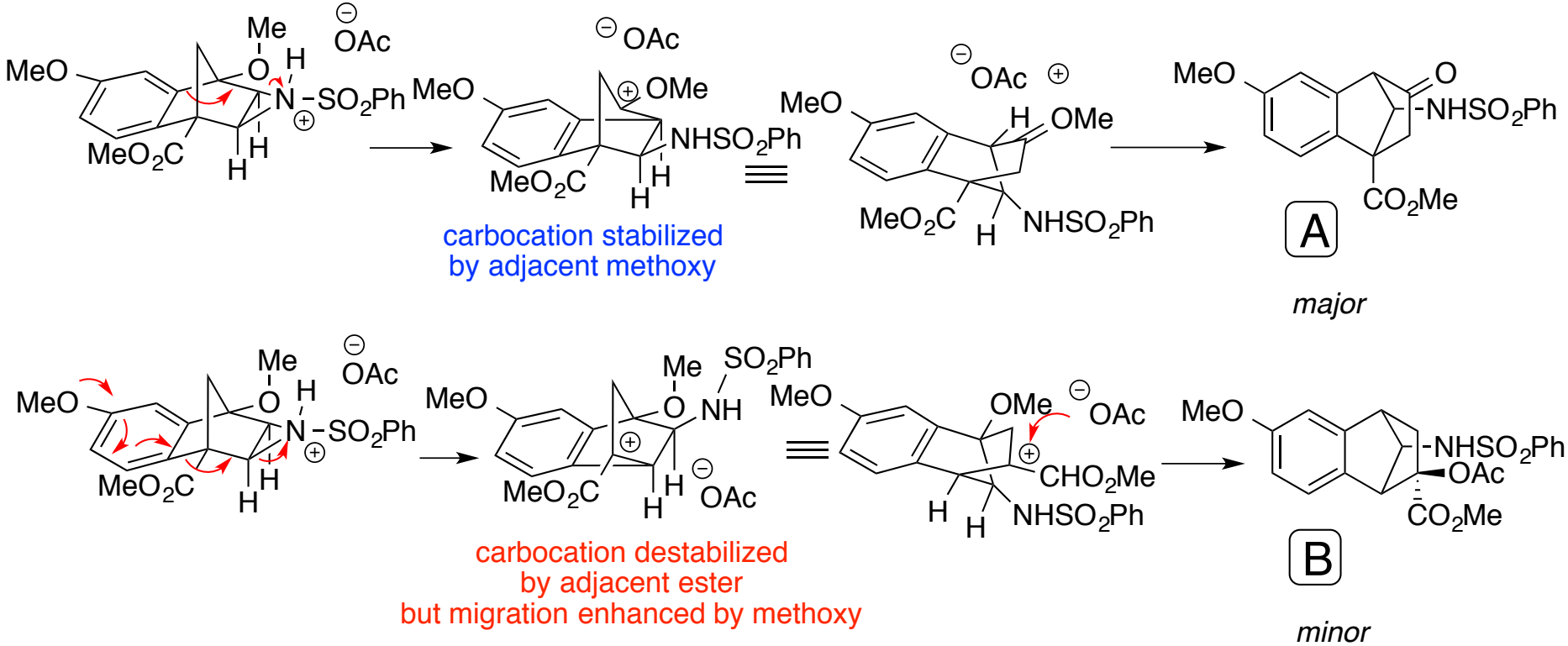




carbocation destabilized
by adjacent ester
but migration enhanced by methoxy

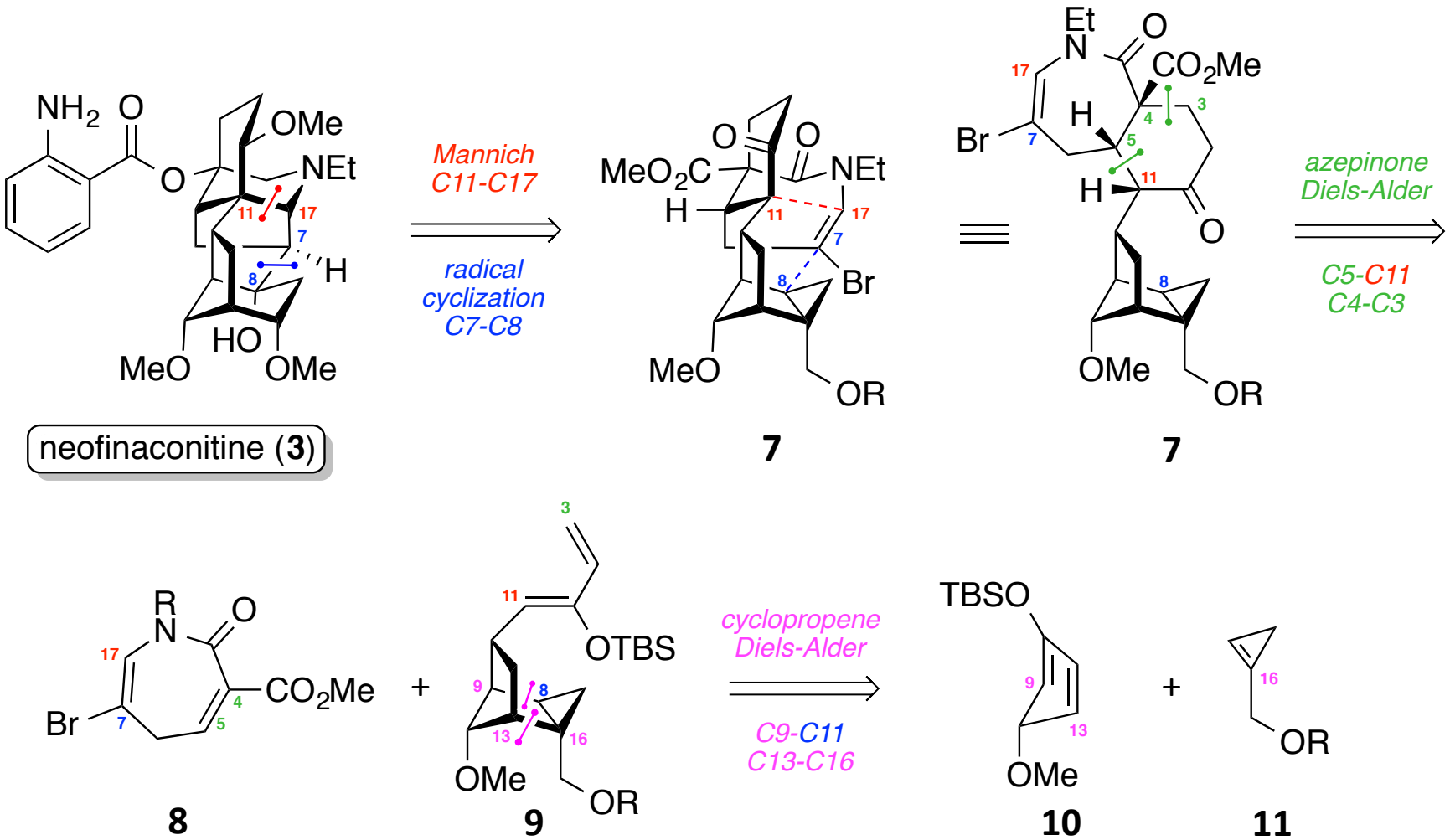
Weisner, K.; Ho, P. –T.; Jain, R. C.; Lee, S. F.; Oida, L. S.; Philipp, A. *Can. J. Chem.* **1973**, *51*, 1448.

Bridgehead methoxy favors desired isomer



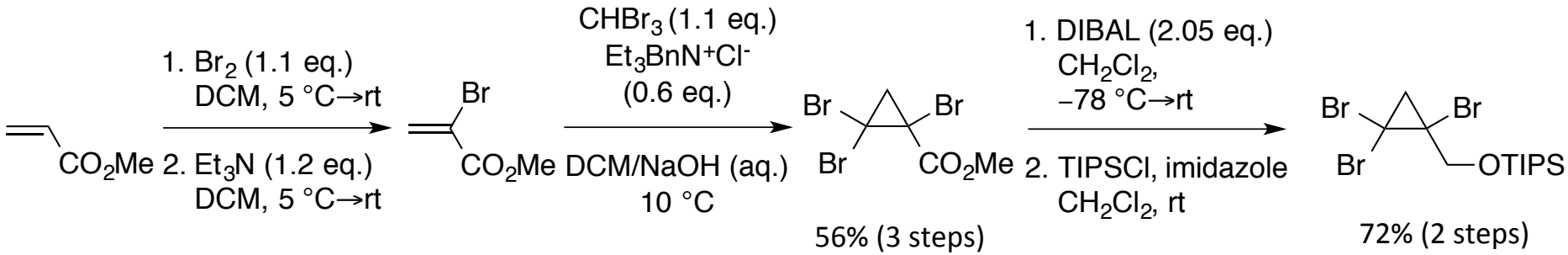
Weisner, K.; Ho, P. –T.; Jain, R. C.; Lee, S. F.; Oida, L. S.; Philipp, A. *Can. J. Chem.* **1973**, *51*, 1448.

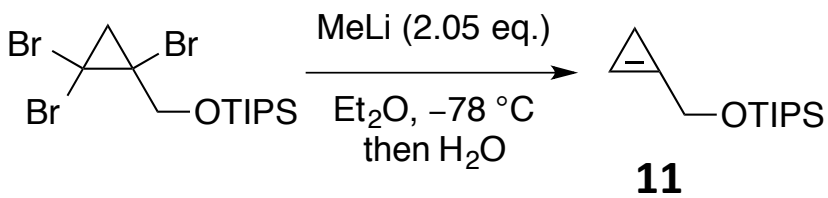
Gin's Retrosynthesis



Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Cyclopropene DA: Starting Material Synthesis





Isolated as a crude oil, used immediately due to rapid Alder-ene dimerization

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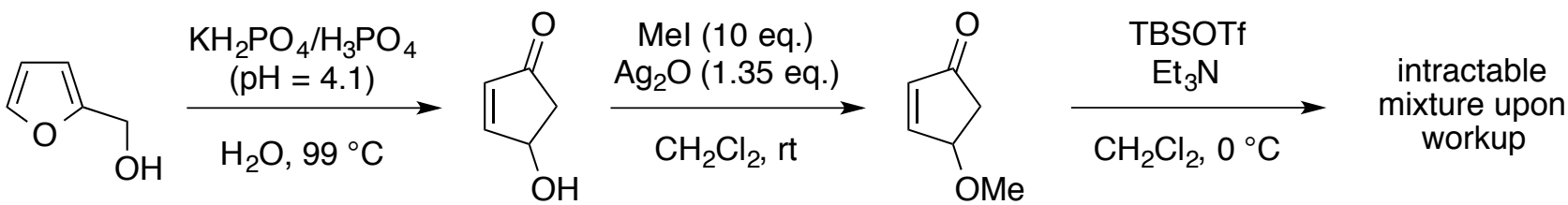
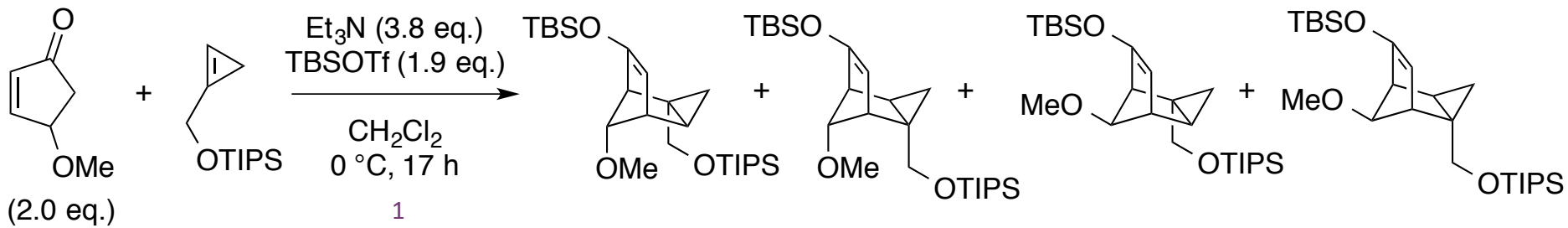


Cyclopentadiene could not be isolated after aqueous workup

Al Dulayymi, A. R.; Al Dulayymi, J. R.; Baird, M. S.; Gerrard, M. E. *Tetrahedron* **1996**, *52*, 3409.
Cuuran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983.
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

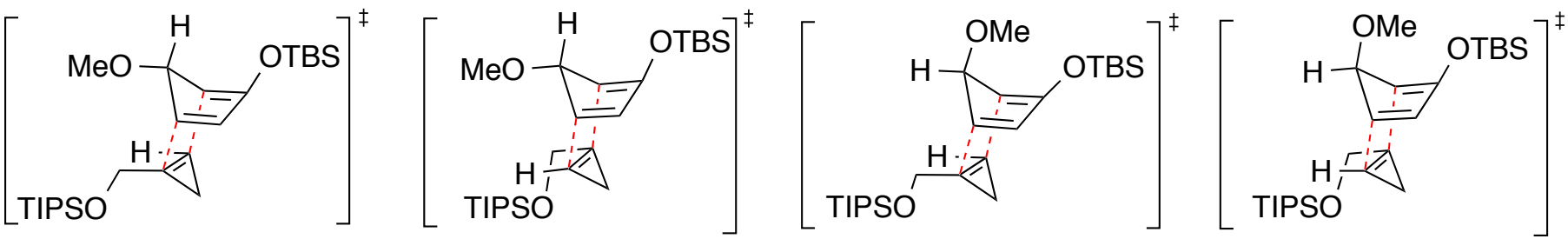
Cyclopropene-Cyclopentadiene Diels-Alder Reaction



5.4 : 9.5 : 1 : 1.5

"contra-steric" approach (major)

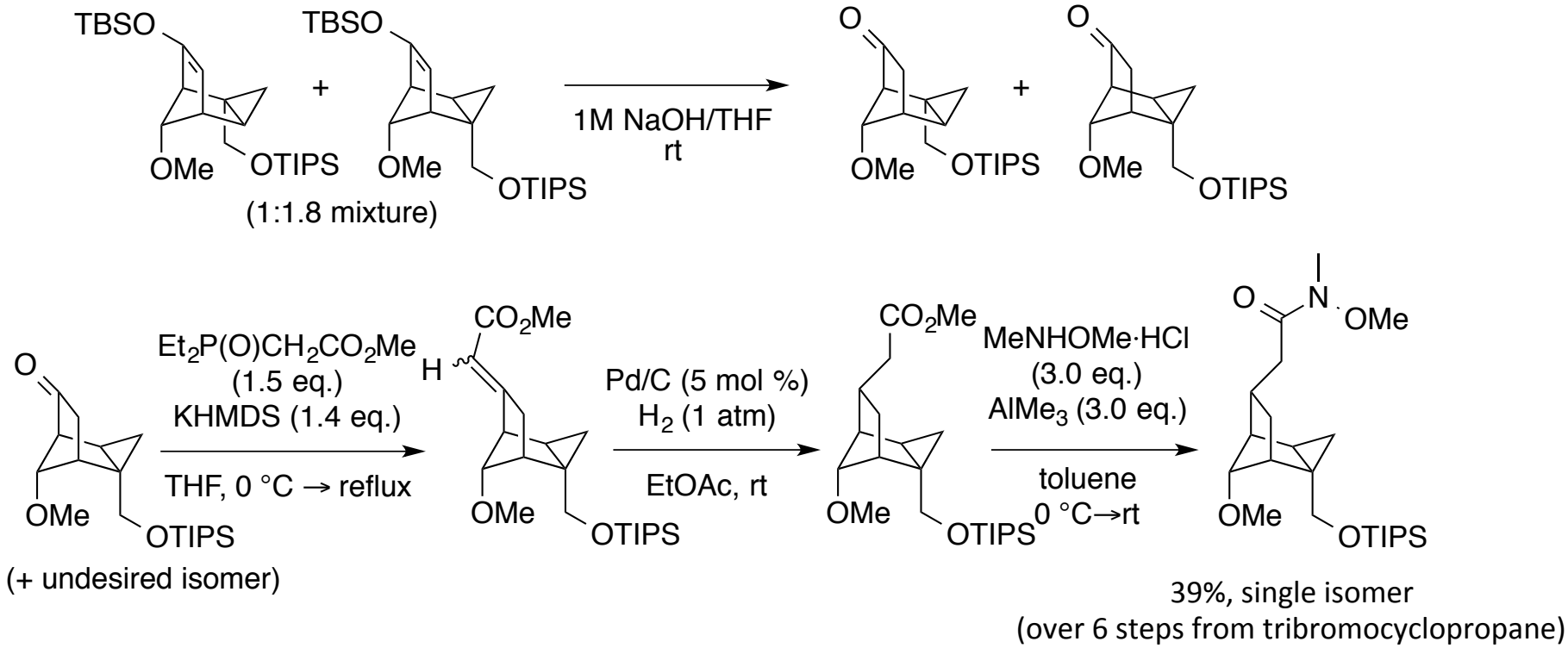
less-hindered approach (minor)

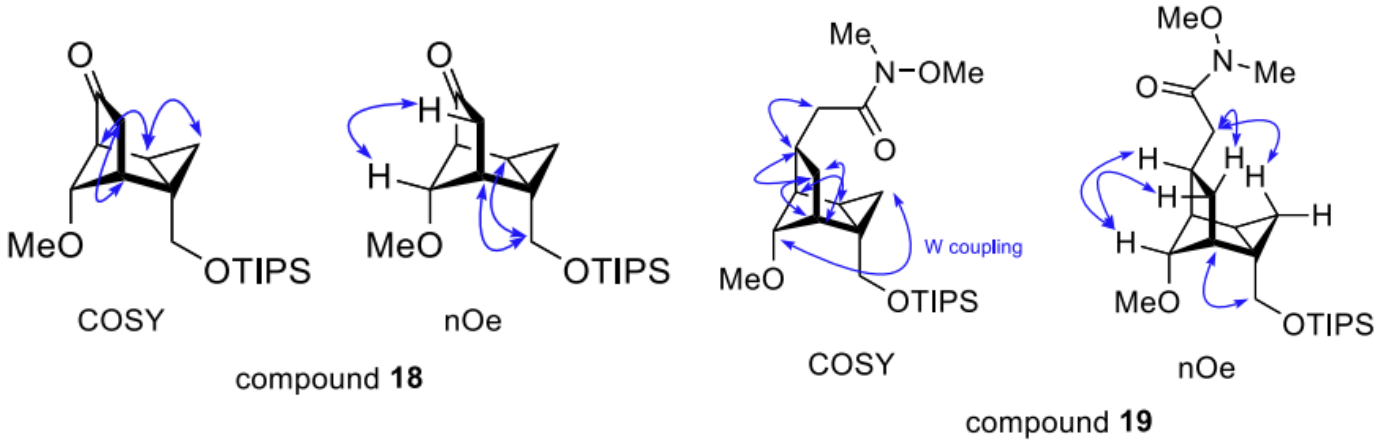


All isomers due to *endo* approach of the cyclopropene, however the diastereoselectivity is poor

Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

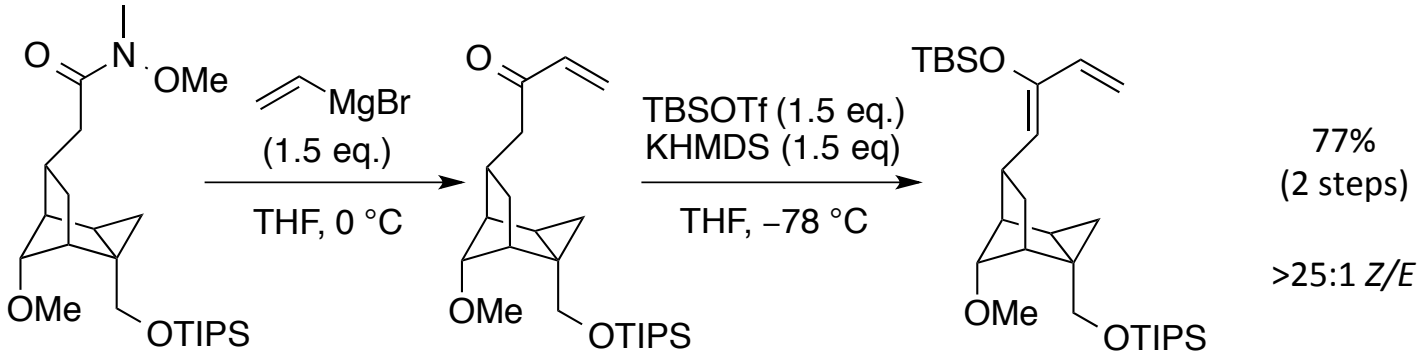
Further Elaboration of Tricyclic Core

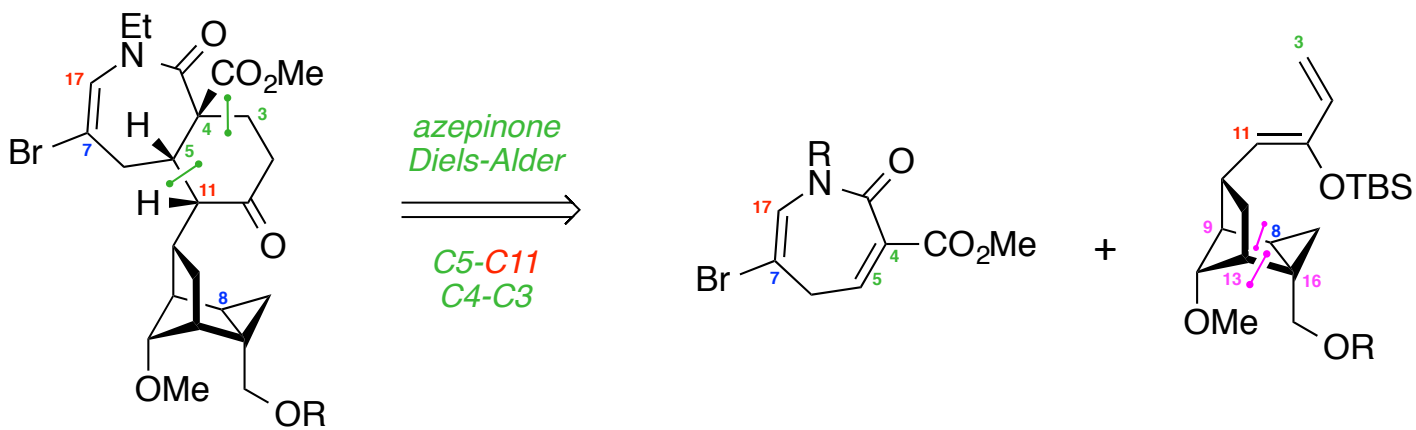




Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

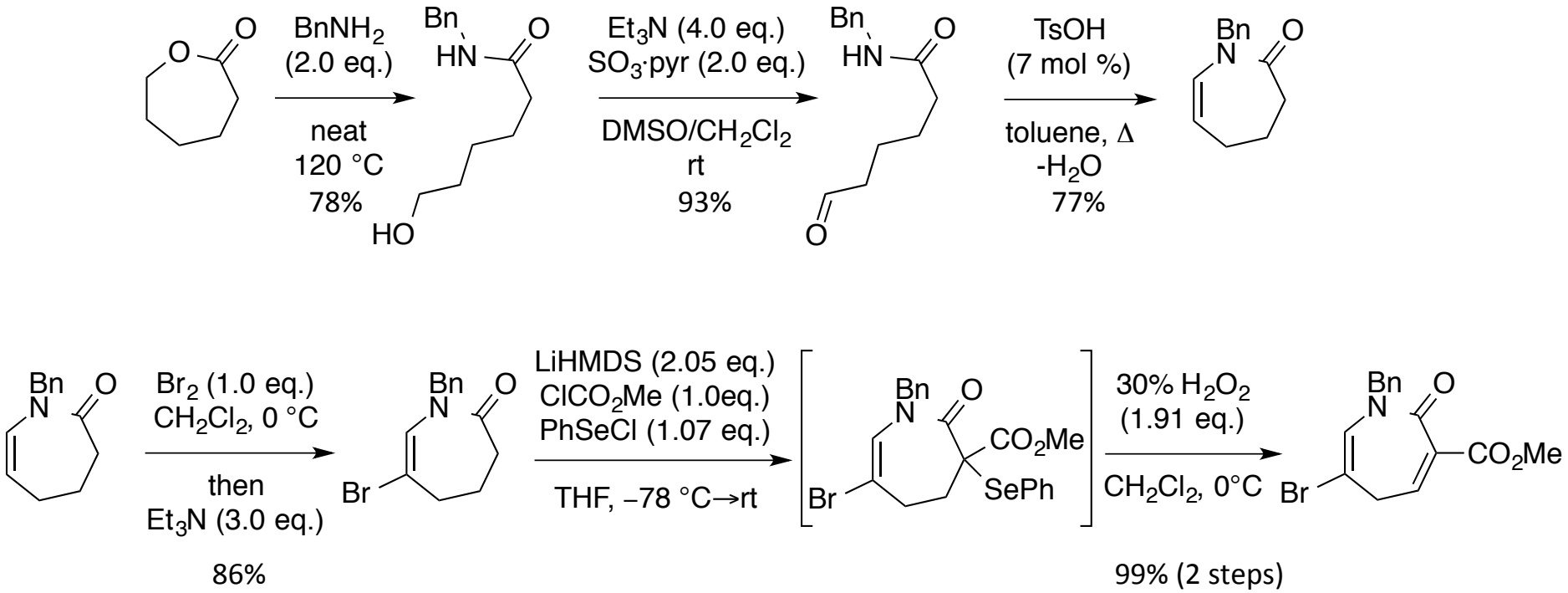
Formation of Diene





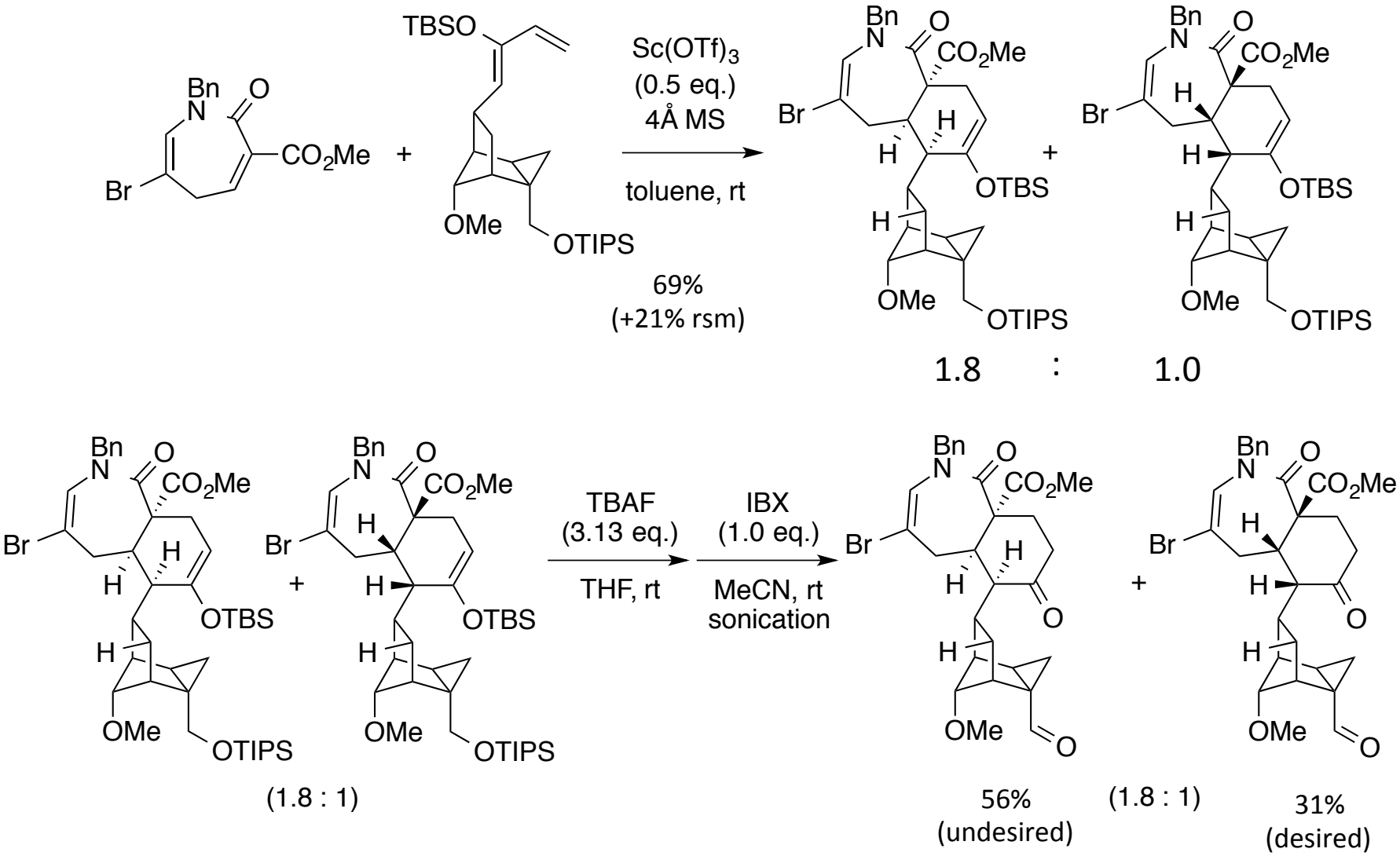
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Azepinone Synthesis



Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Unprecented Azepinone/Siloxydiene Diels-Alder Reaction

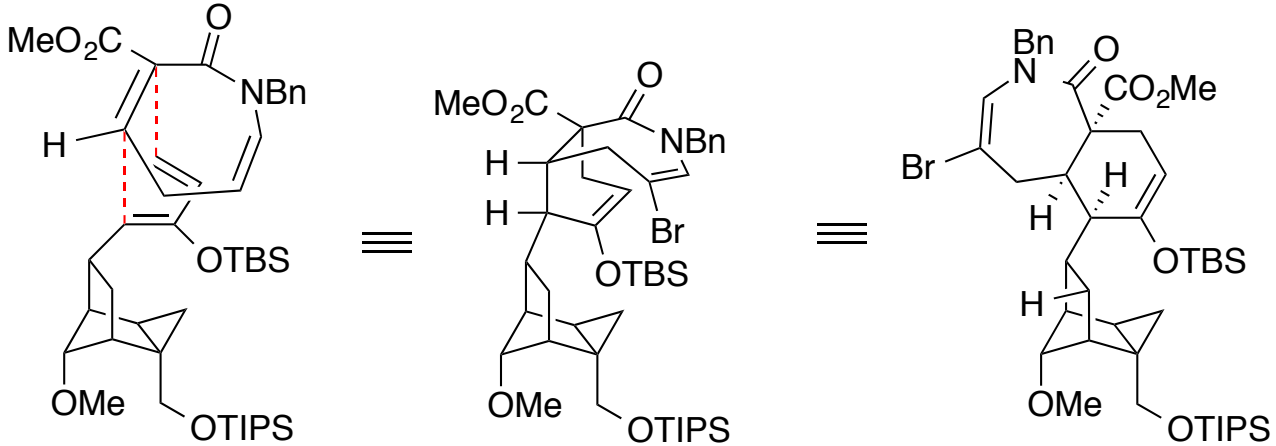


Complete regioselectivity and *endo* selectivity, poor diastereoselectivity

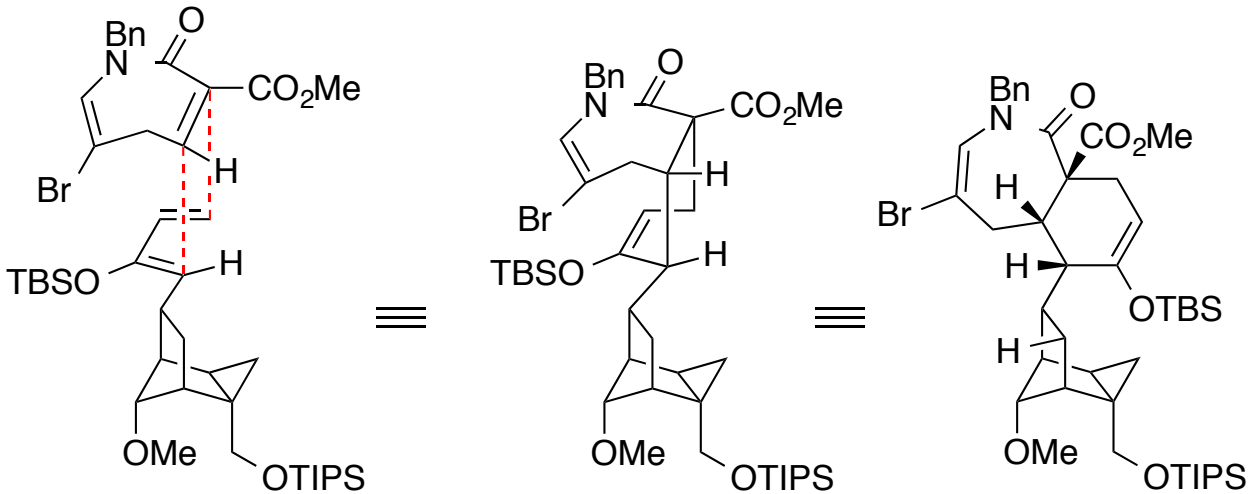
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Stereochemical Outcome of Diels-Alder Reaction

Favored diastereomer (undesired):

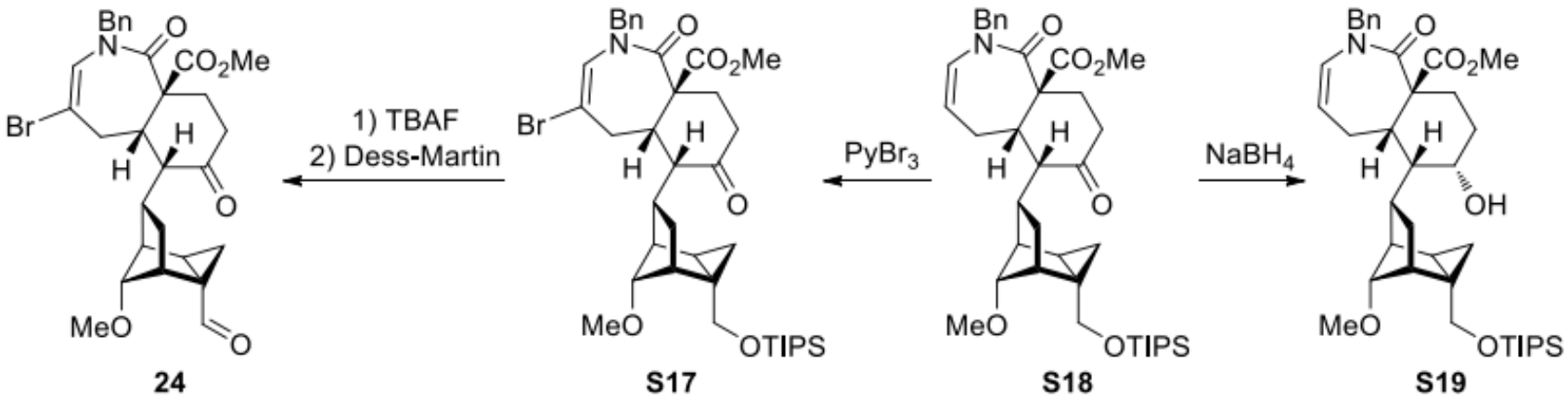


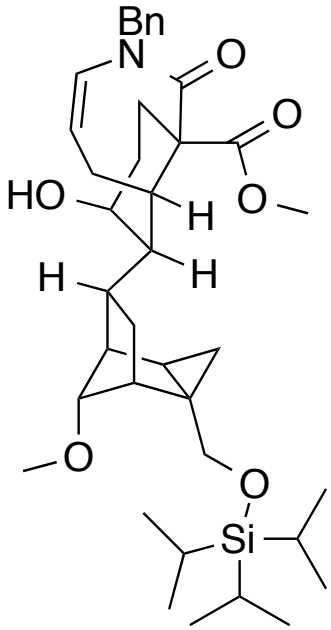
Slightly Less Favored diastereomer (desired):

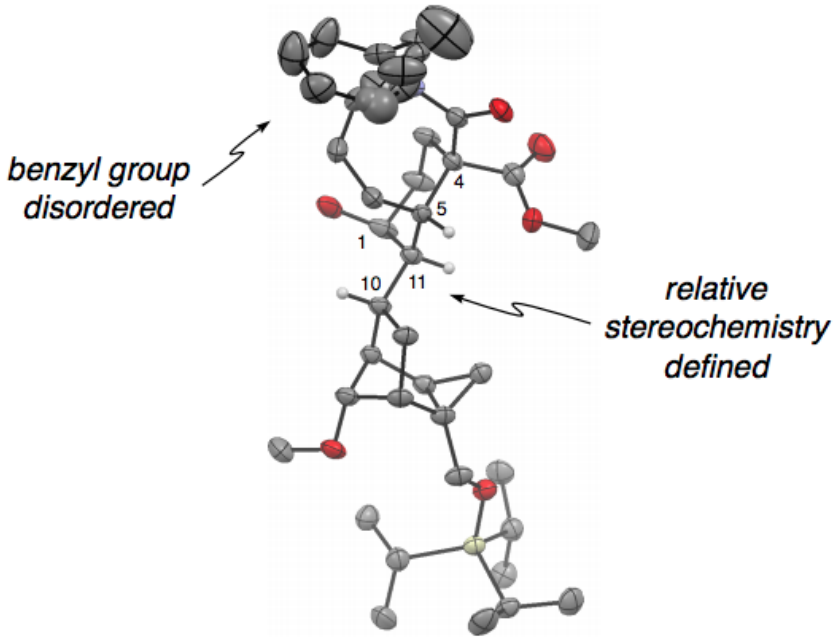


Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Stereochemical Assignment of Cycloadduct



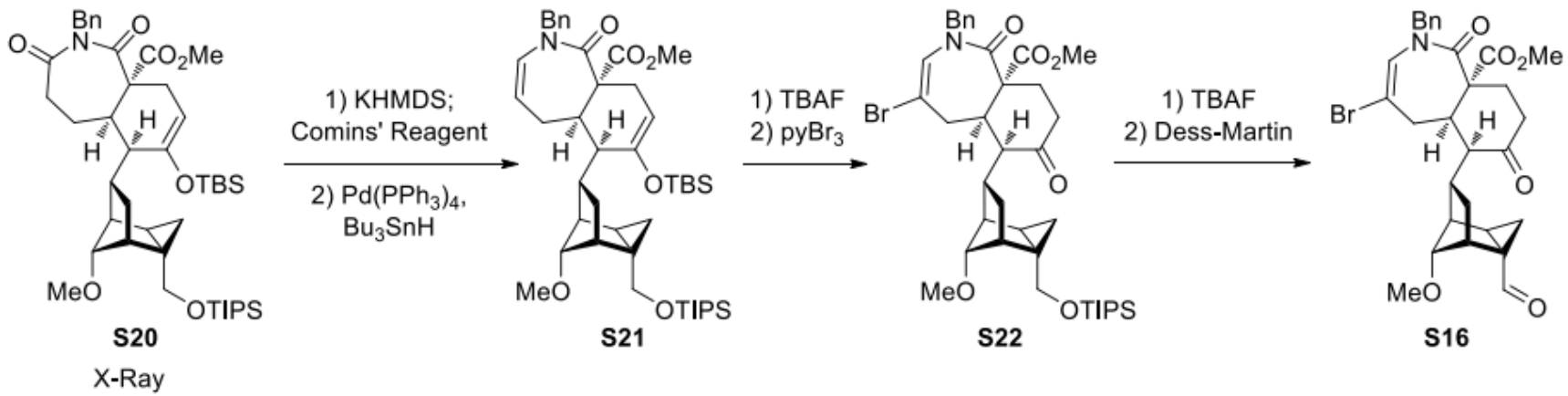


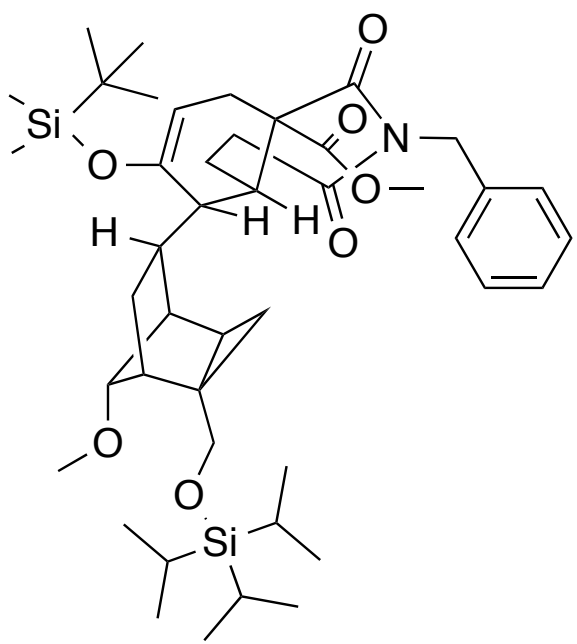


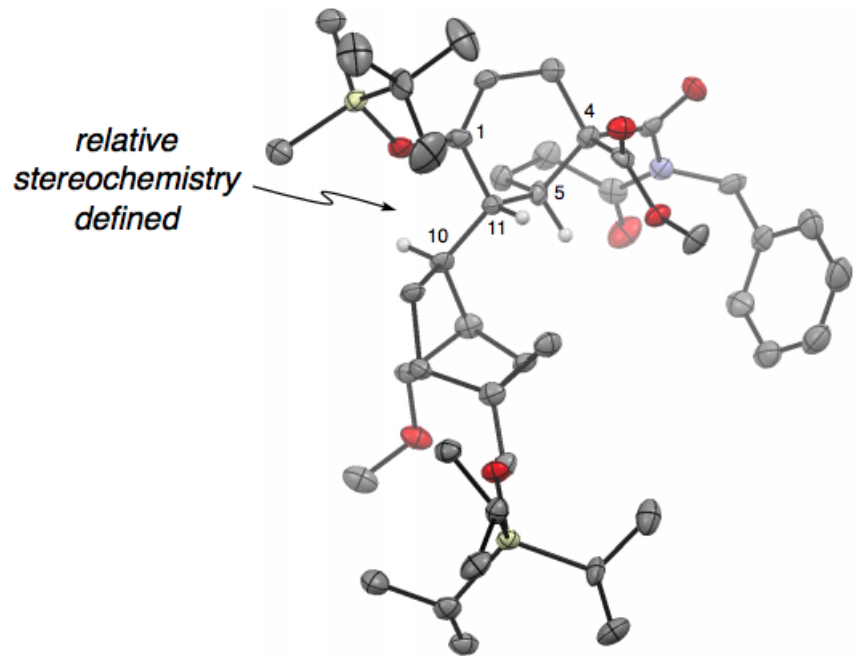
Single crystal x-ray structure of alcohol S19.

Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Stereochemical Assignment of Undesired Cycloadduct



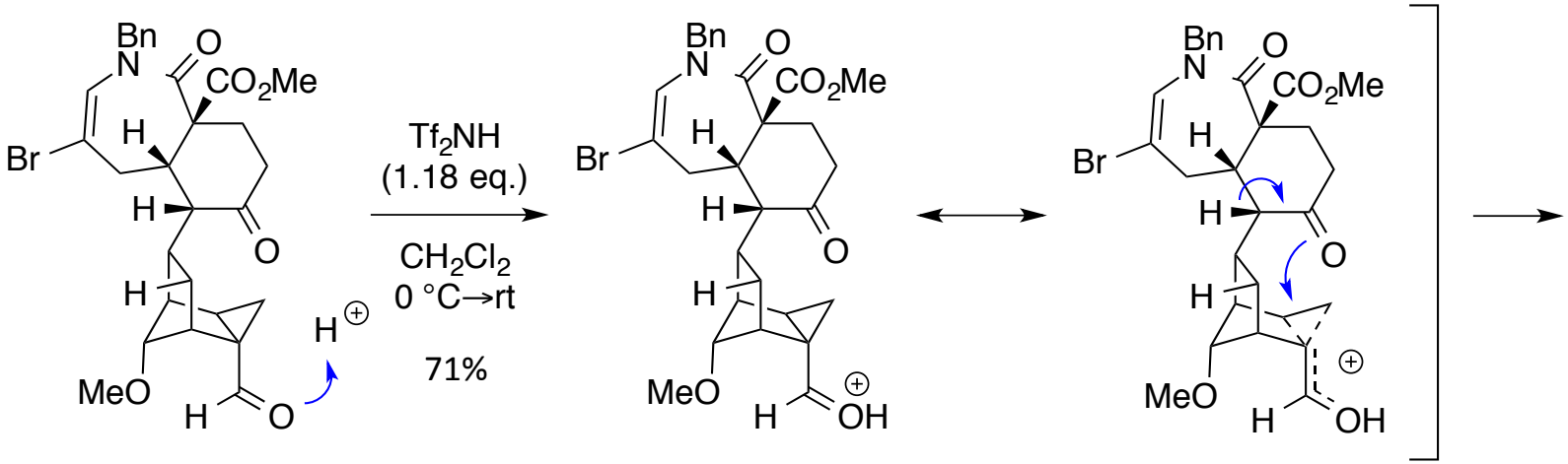




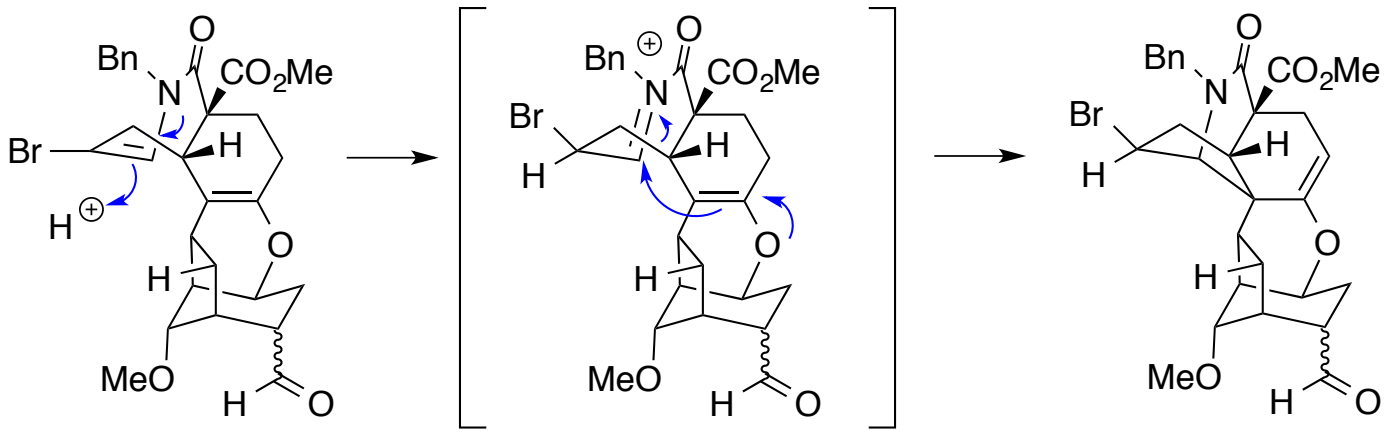
Single crystal x-ray structure of imide S20.

Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Mannich-Type *N*-Acyliminium Cyclization

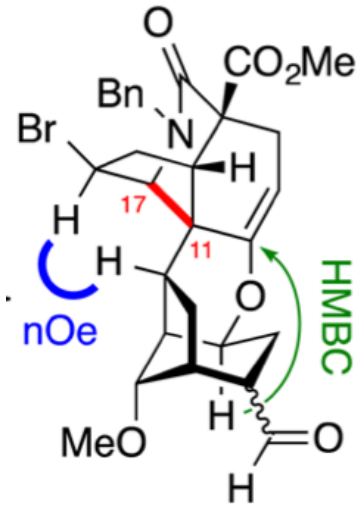


cyclopropylcarbinyl oxocarbenium



Stalls at enol ether with weaker acids (TFA)

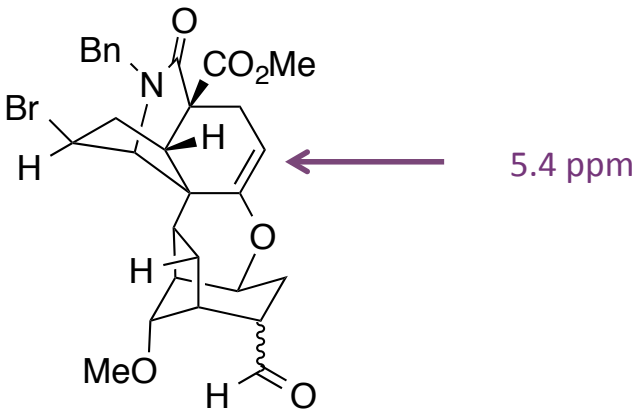
Strong acid (Tf_2NH) can protonate enamide through acyl iminium



29

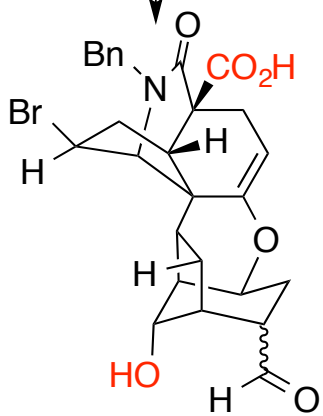
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Attempts to Hydrolyze an Enol Ether

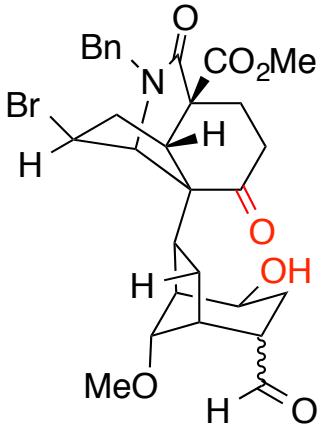


5.4 ppm

12 N HCl
60 °C



not

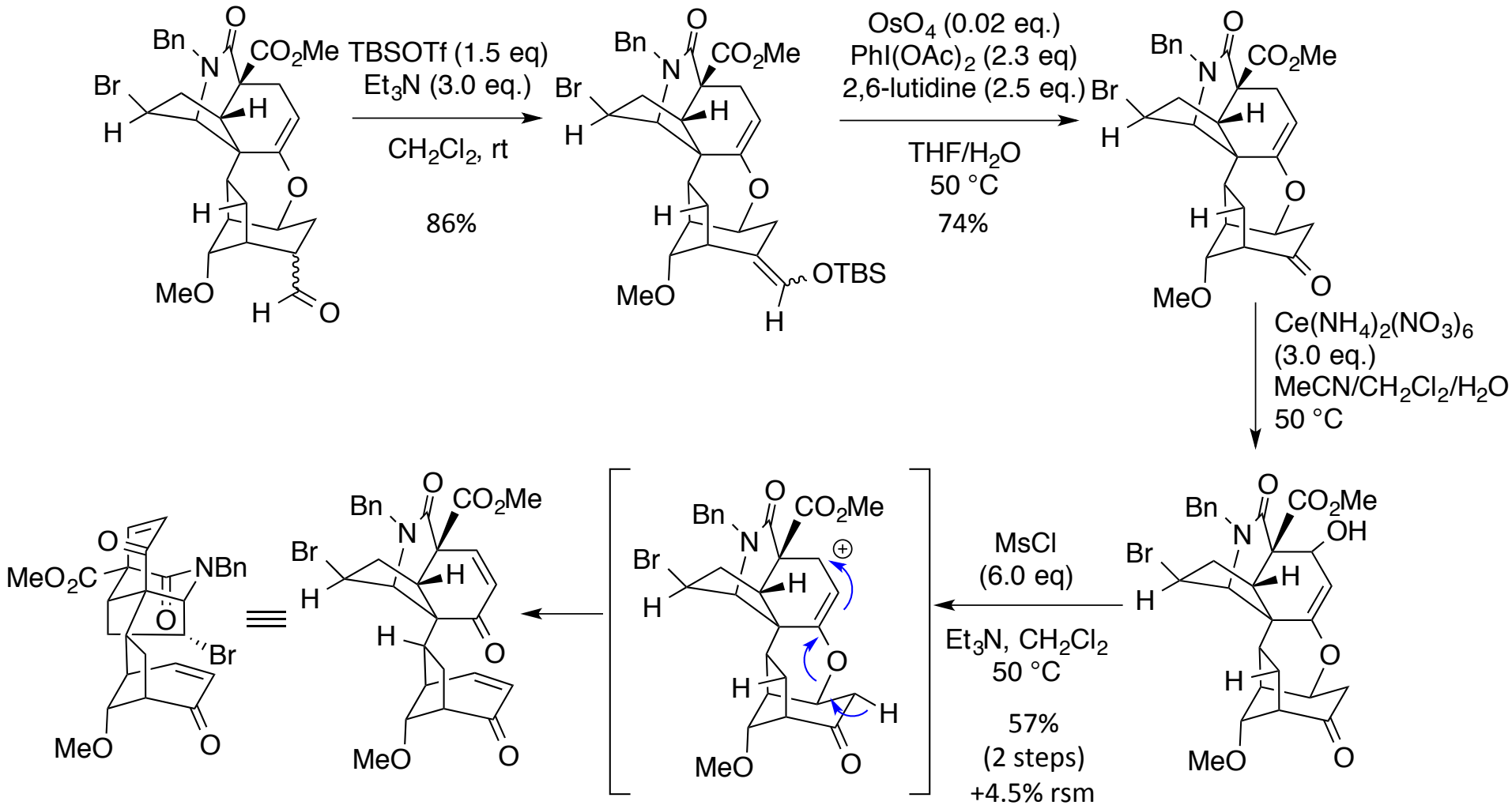


Stalls at enol ether with weaker acids (TFA)

Strong acid (Tf_2NH) can protonate enamide through acyl iminium

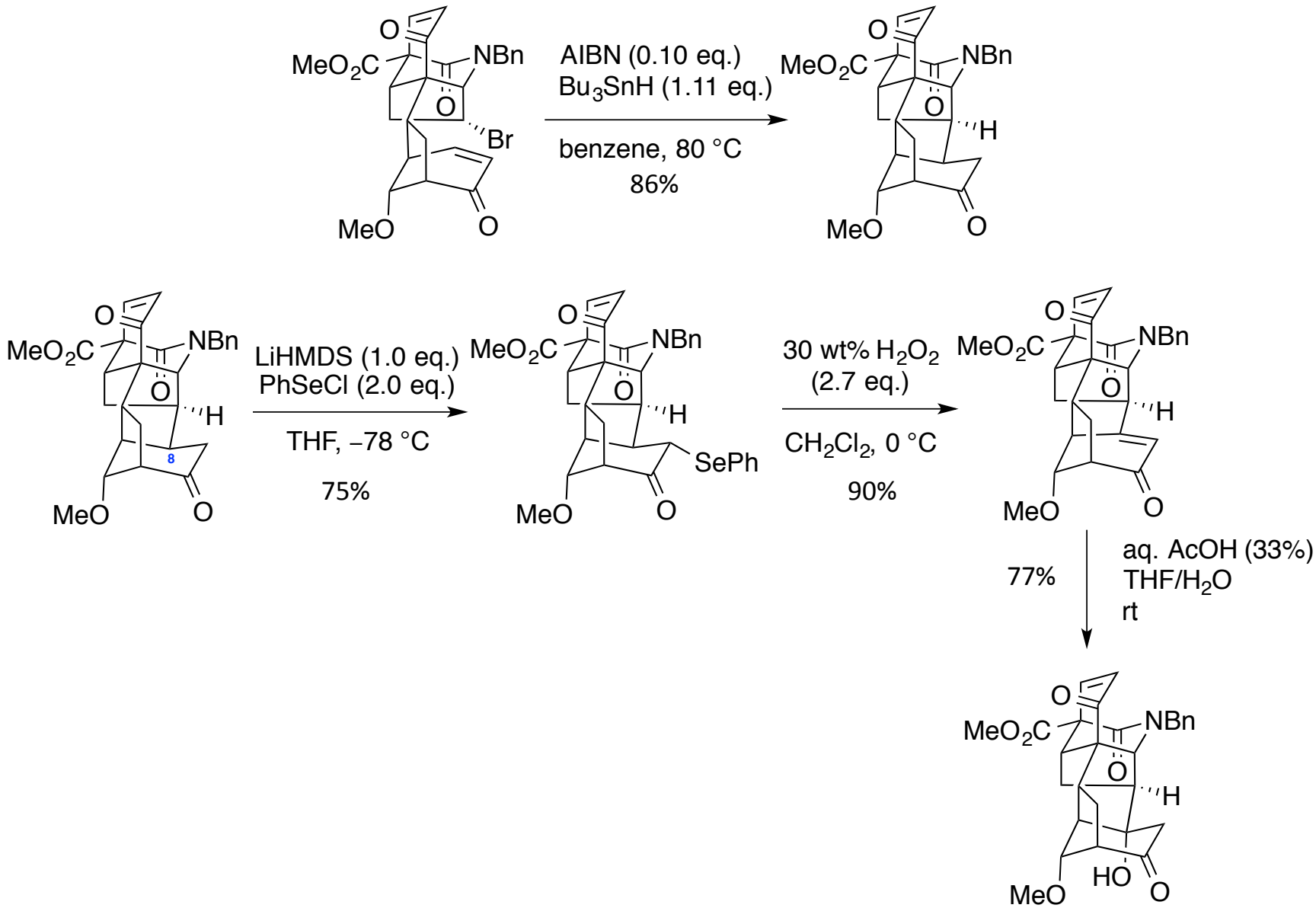
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Set-Up for Radical Cyclization



Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

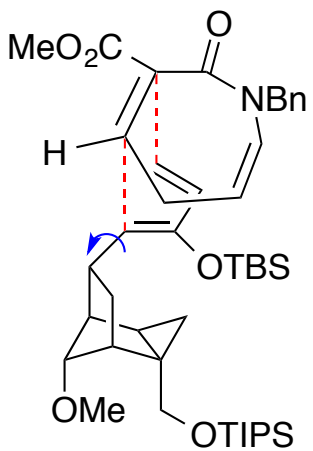
Radical Cyclization and C-8 Oxygenation

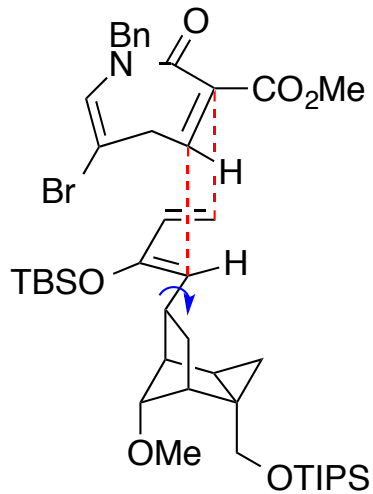


Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

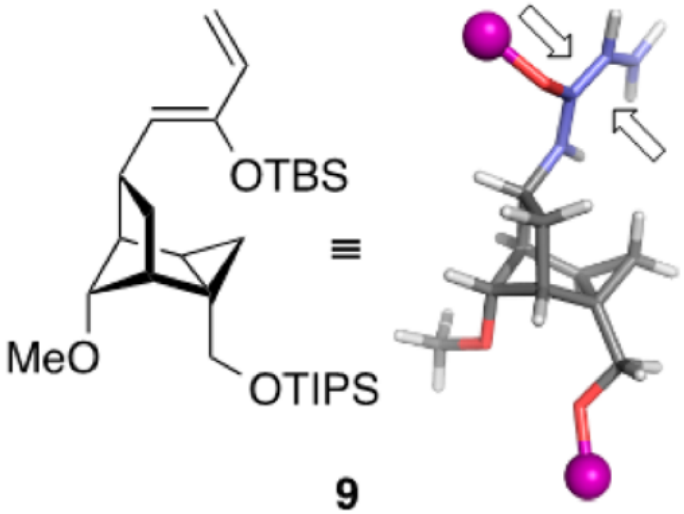
Second-Generation Cycloaddition

Poor diastereofacial selectivity due to ease of rotation of diene portion

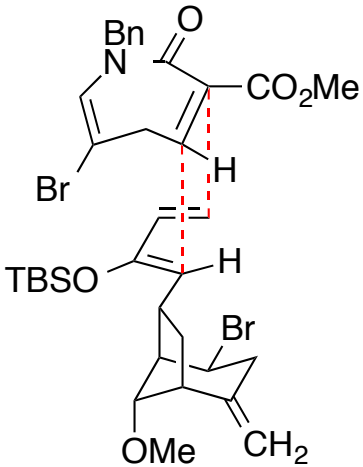


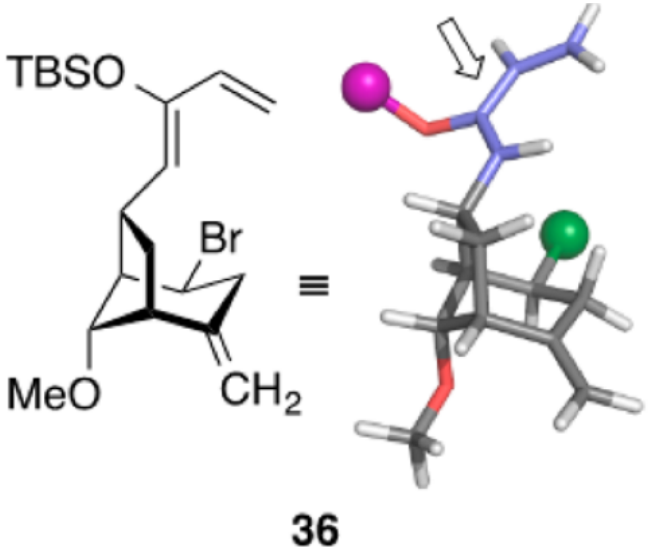


undesired 1.8 : 1 desired



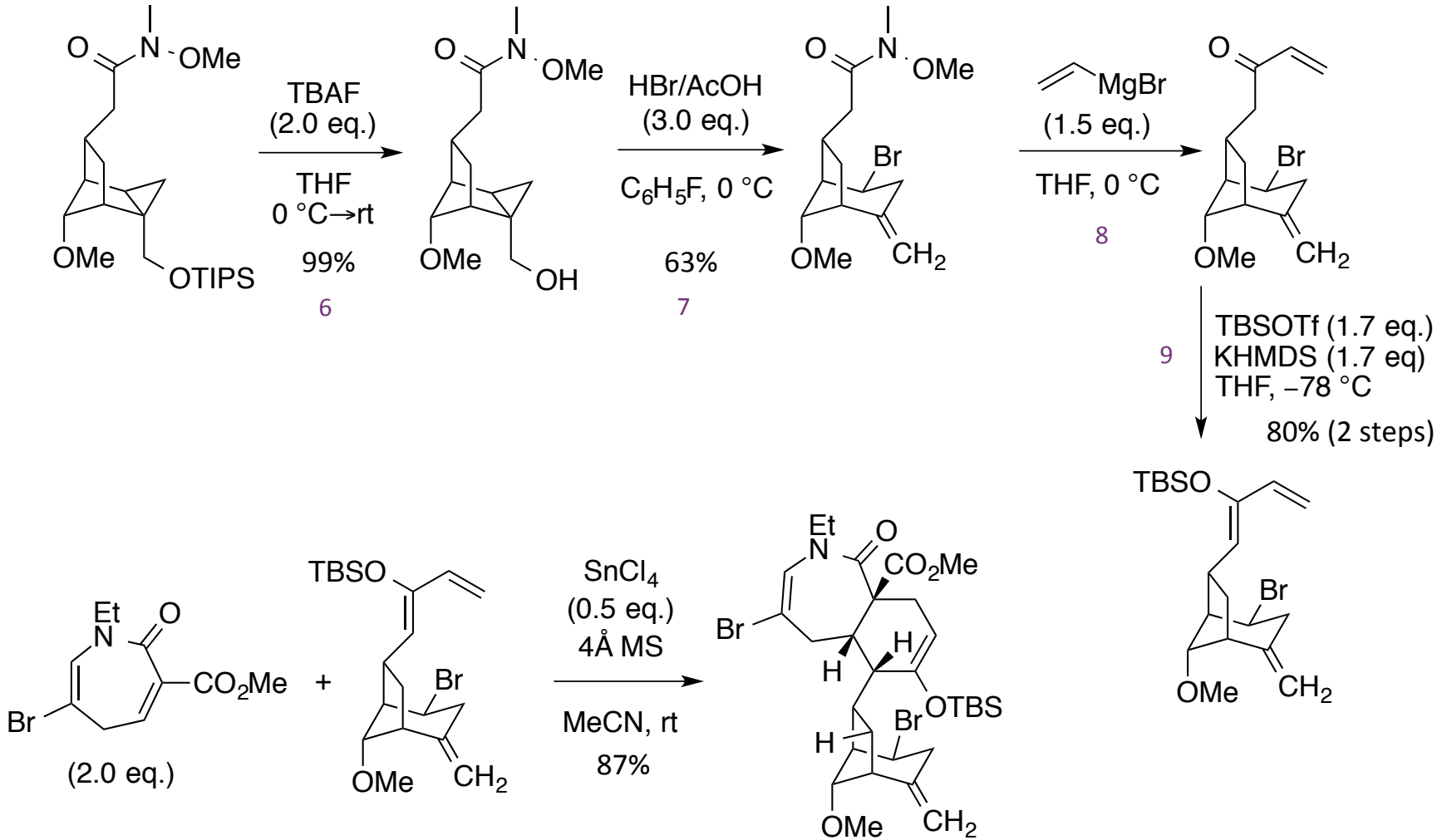
Improved diastereofacial selectivity *without* disrupting excellent *endo* and regioselectivity?





Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

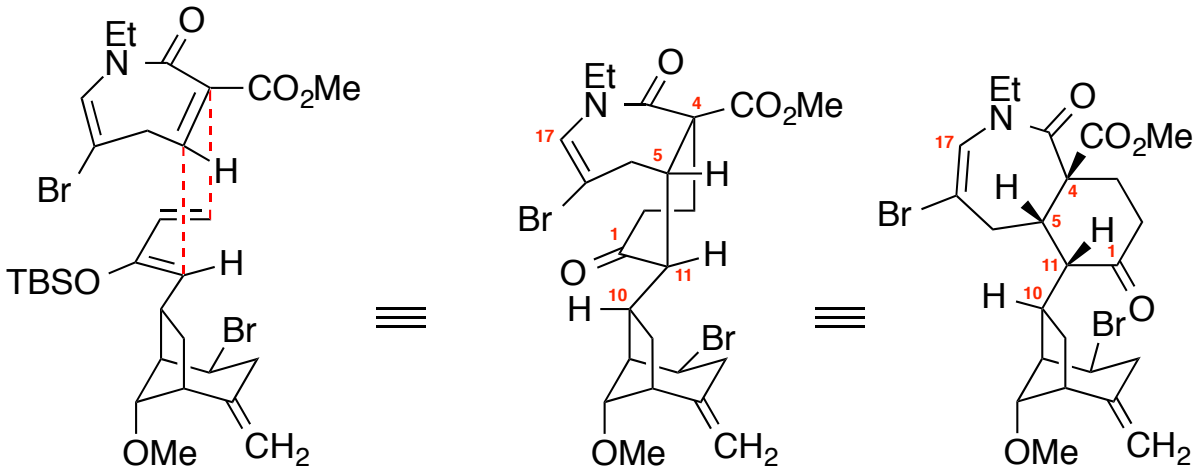
Synthesis of Alternative Siloxydiene

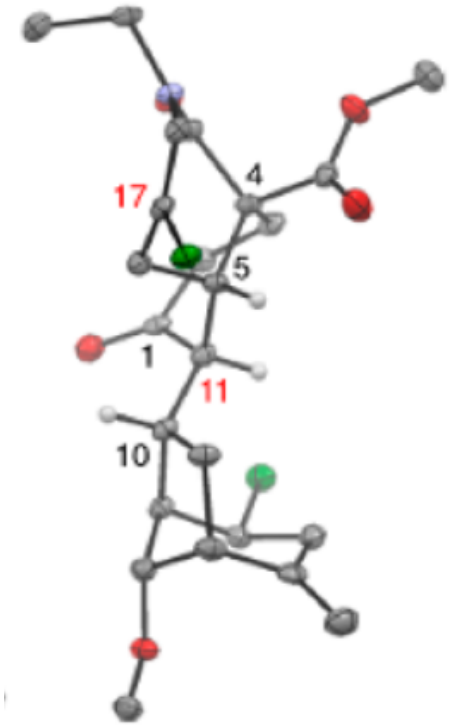


Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

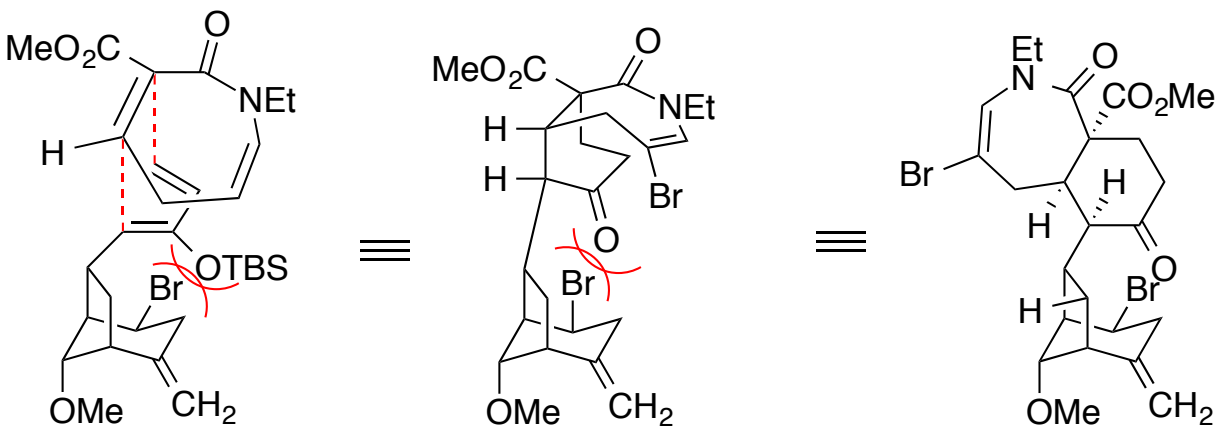
Stereochemical Outcome of Diels-Alder Reaction

Favored diastereomer (desired):



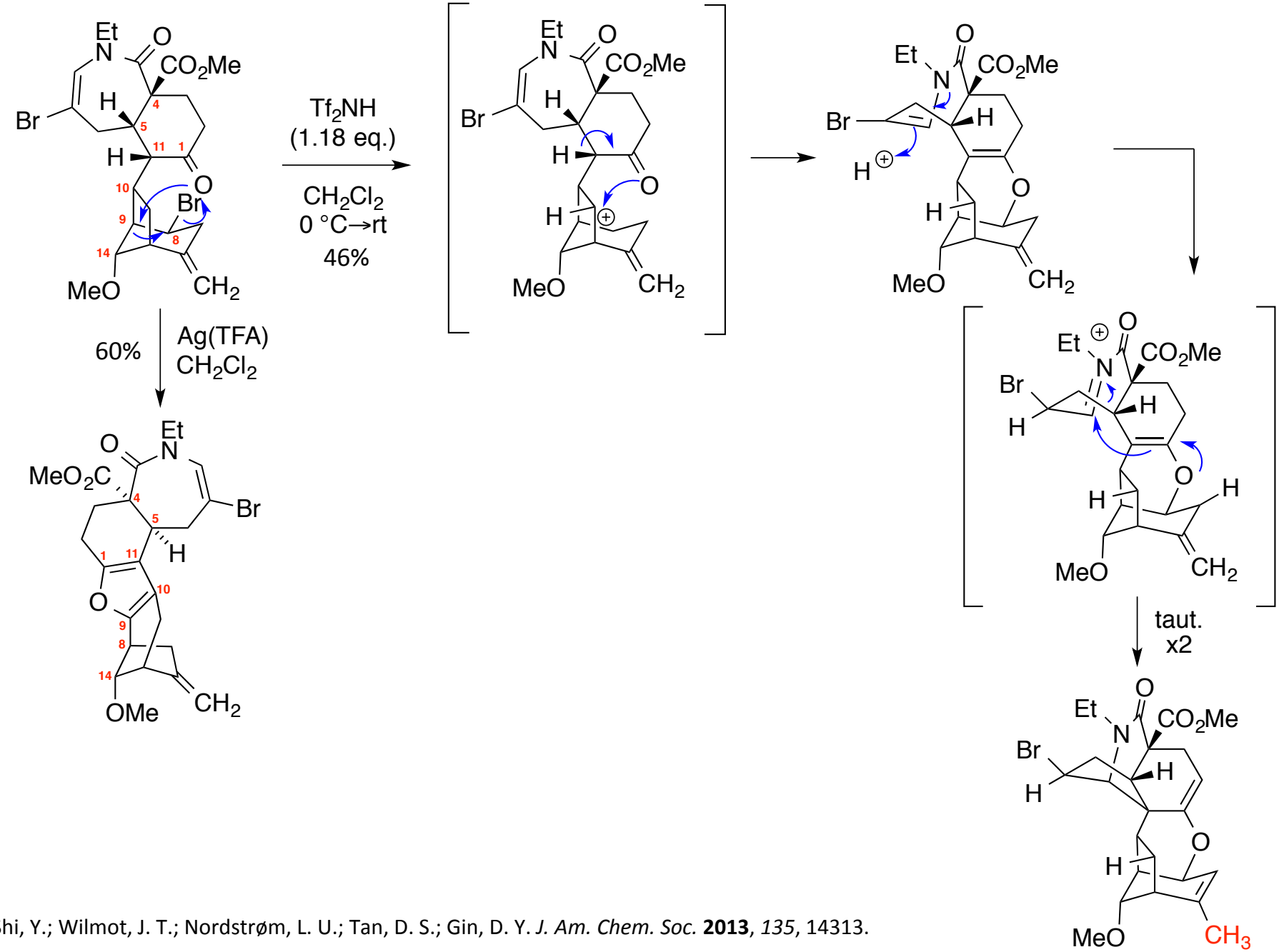


Disavored diastereomer (not observed):



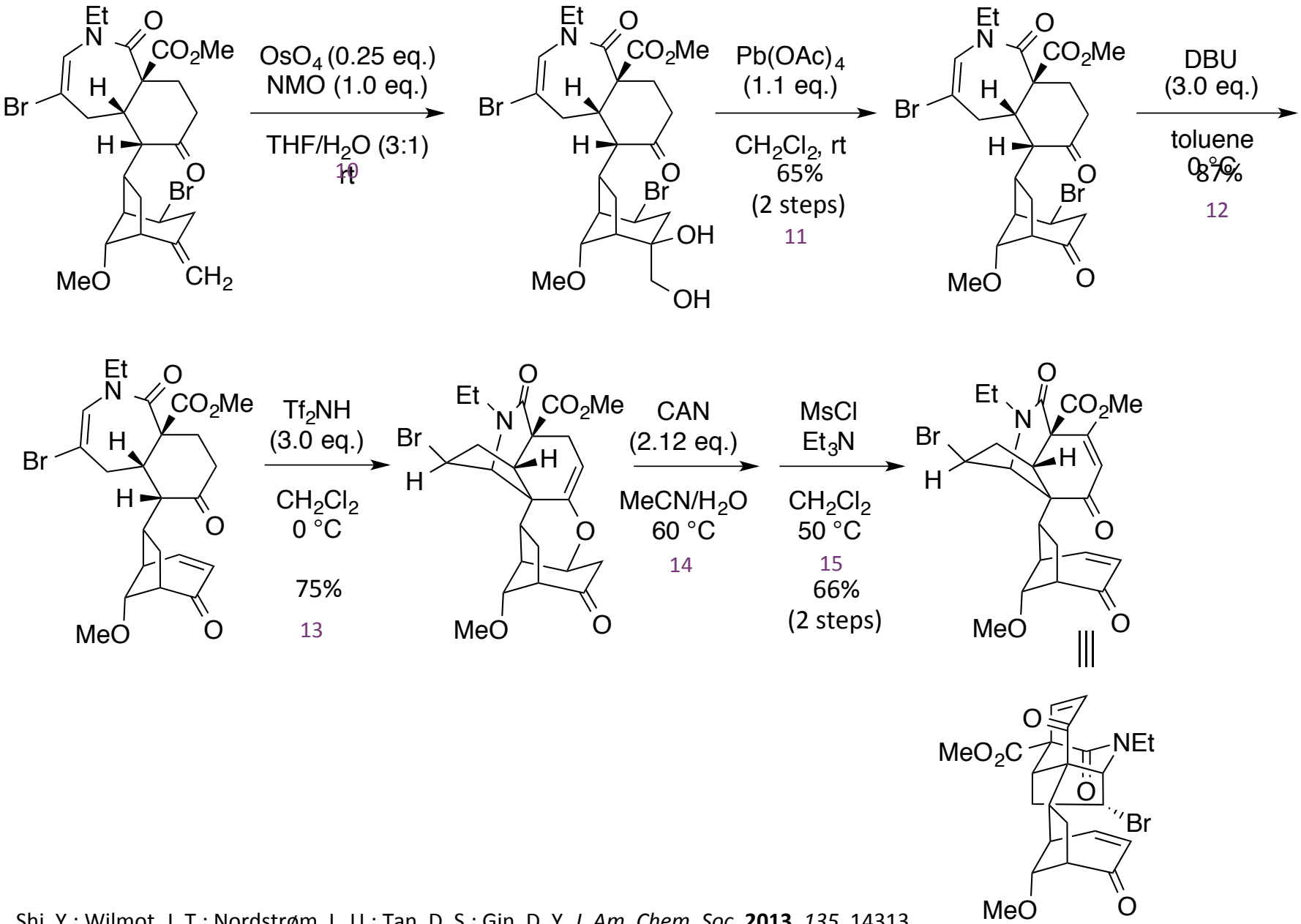
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Problematic Acyl Iminium Cyclization



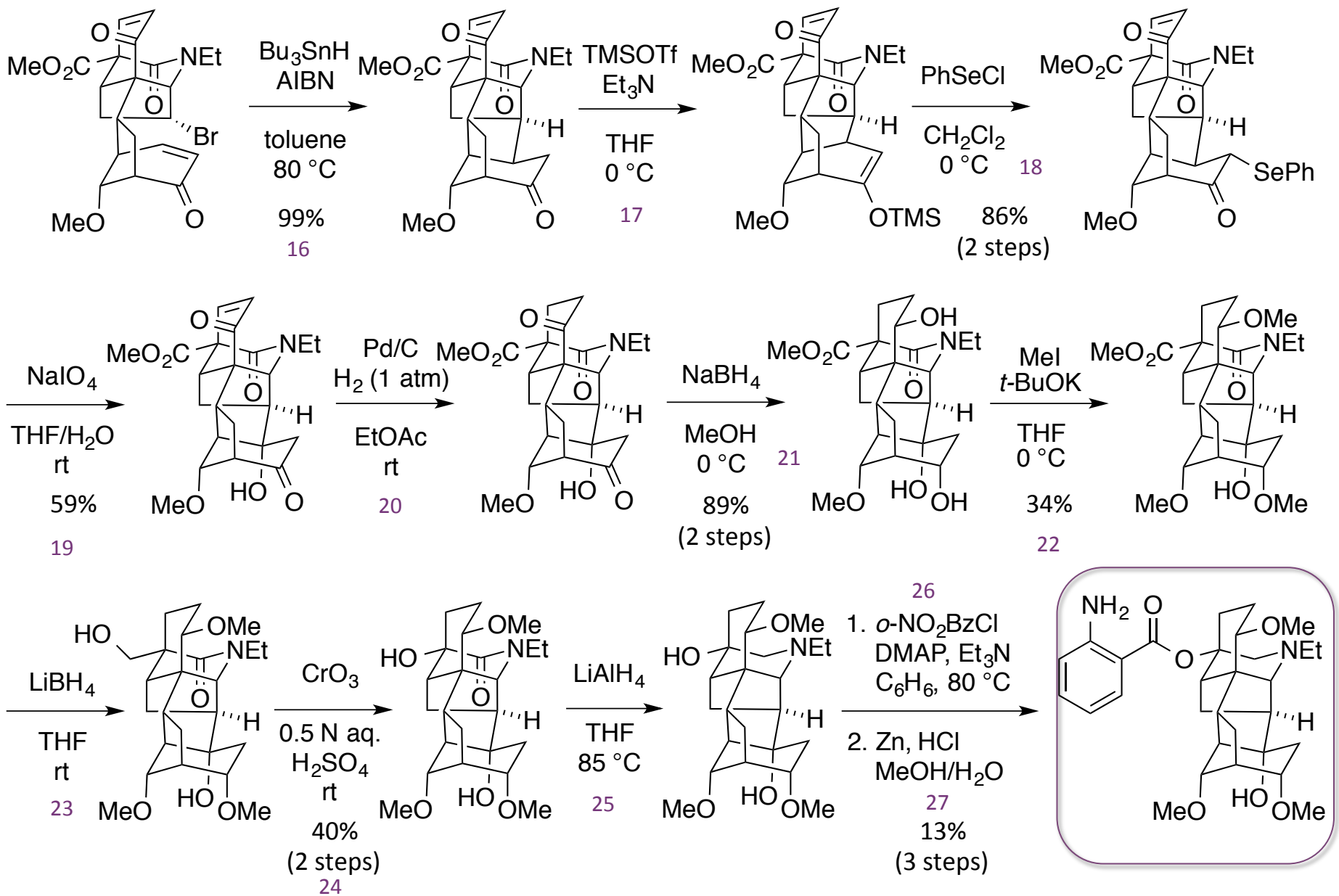
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

Manipulation Back to Original Acyl Iminium Cyclization



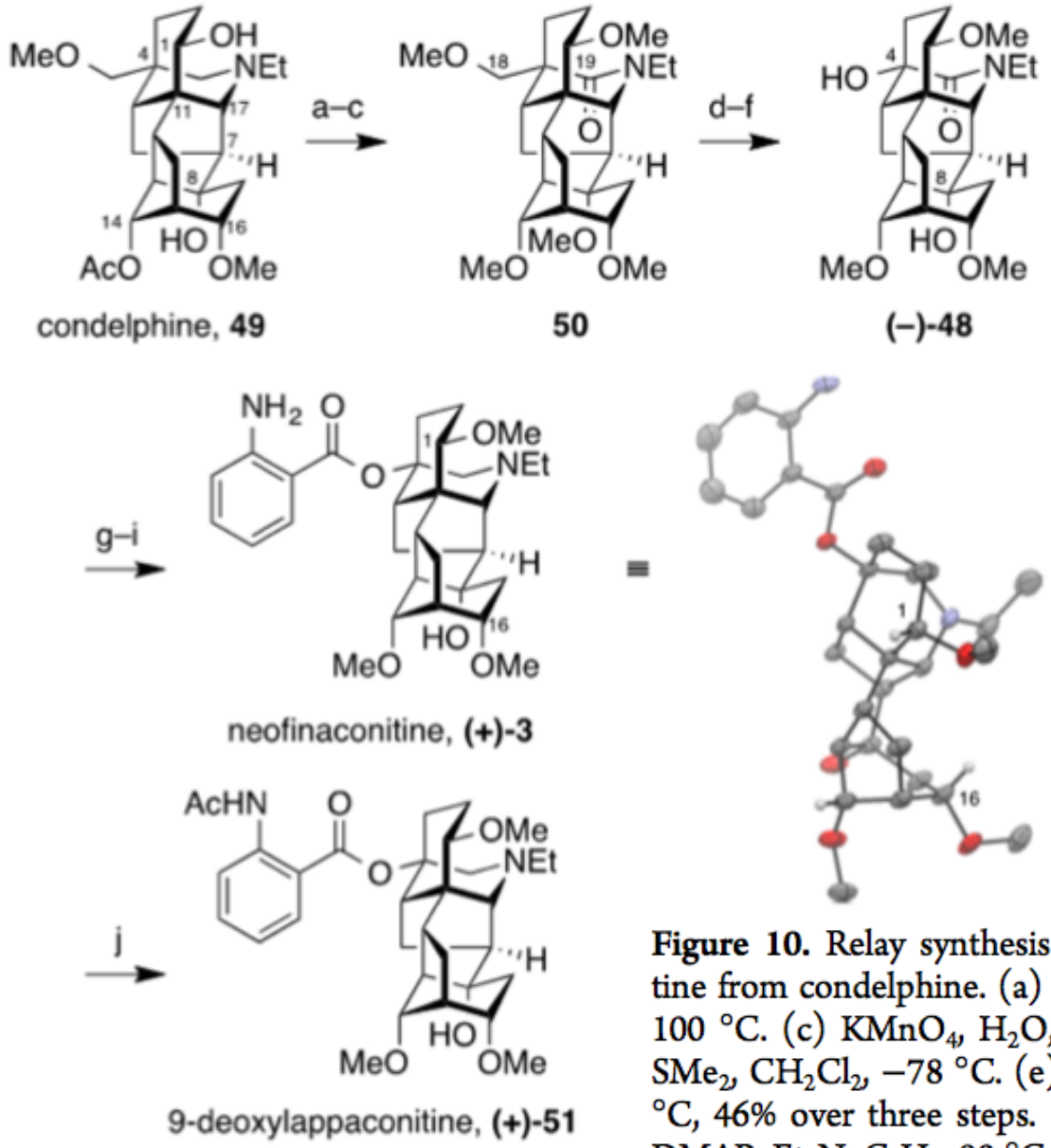
Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

End Game = Add Functionality!



Shi, Y.; Wilmot, J. T.; Nordstrøm, L. U.; Tan, D. S.; Gin, D. Y. *J. Am. Chem. Soc.* **2013**, *135*, 14313.

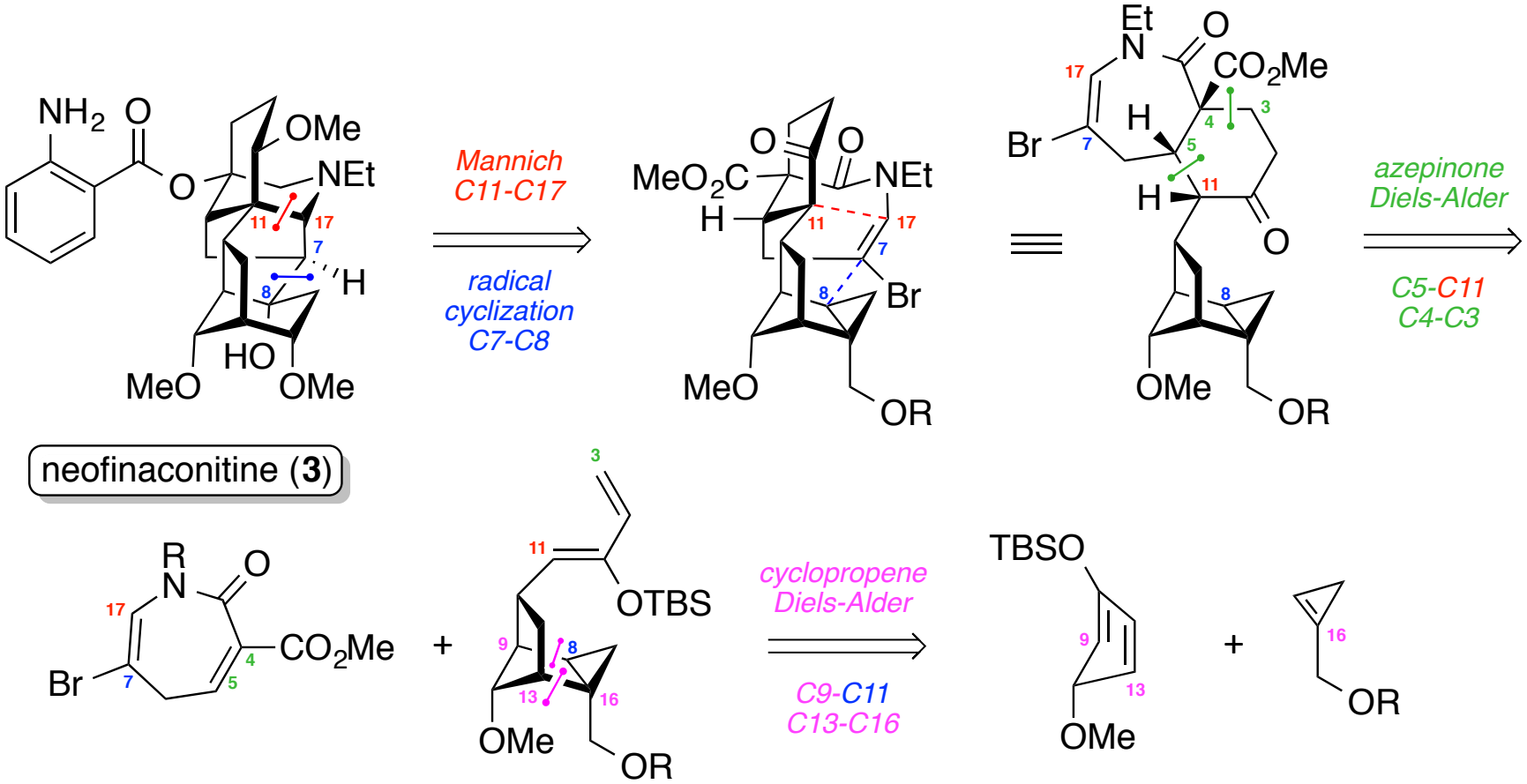
Confirmation of Structure by Relay Synthesis



condelphine available from Aldrich!
$185.00 / 20 mg

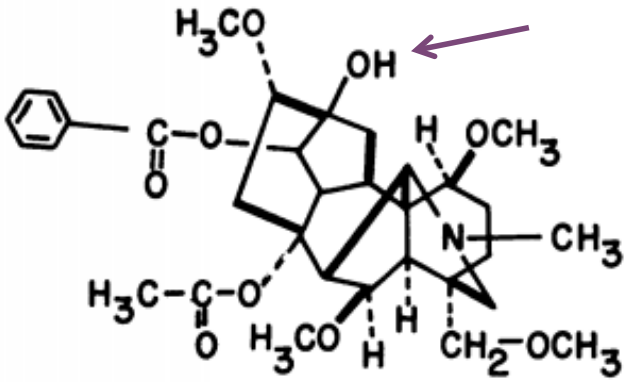
Figure 10. Relay synthesis of neofinaconitine and 9-deoxylappaconitine from condelphine. (a) NaOH, H_2O, EtOH. (b) NaH, MeI, THF, 100 °C. (c) $KMnO_4$, H_2O, CH_2Cl_2, 54% over three steps. (d) $BBr_3 \cdot SMe_2$, CH_2Cl_2, −78 °C. (e) CrO_3, 0.5 N H_2SO_4. (f) 0.5 N H_2SO_4, 80 °C, 46% over three steps. (g) $LiAlH_4$, THF, 80 °C. (h) *o*-NO_2BzCl, DMAP, Et_3N, C_6H_6, 80 °C. (i) Zn, HCl, MeOH, H_2O, 70% over three steps. (j) Ac_2O, pyridine, 91%.

Summary of Gin's Synthesis

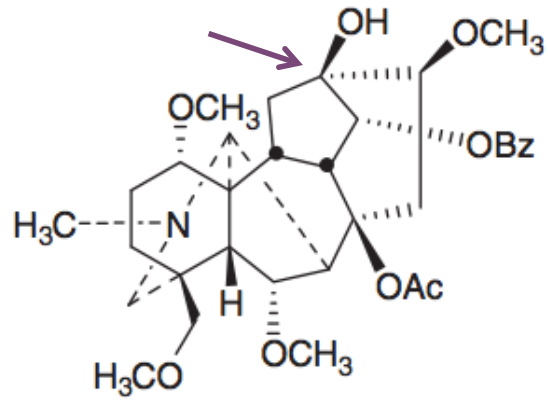


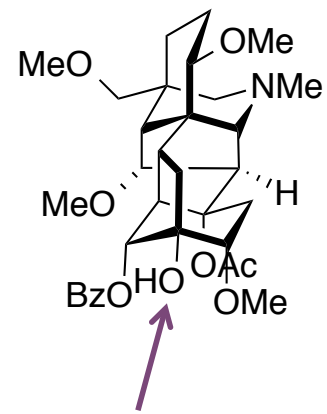
- Significantly shorter synthesis than Wiesner (27 steps)
- Convergent approach possible through cycloadditions (although selectivity is still an issue)
- A lot of functional group manipulation is still needed after the hexacyclic core is formed

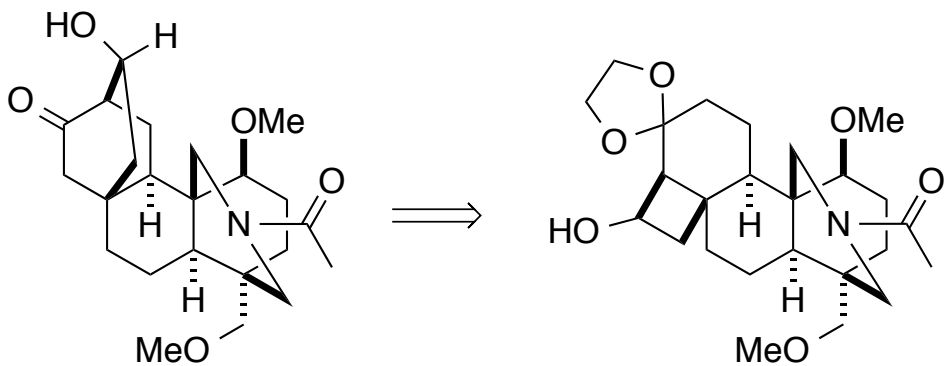
Still Cannot Make Delphinine

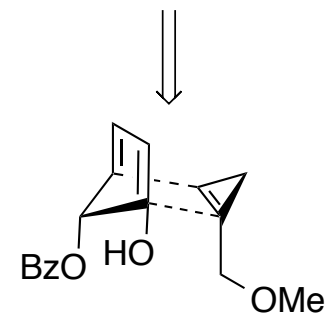


delphinine









C13-oxygenation is problematic to both routes. The congested oxygenation patterns for each member of this natural product family end up necessitating new routes each time.