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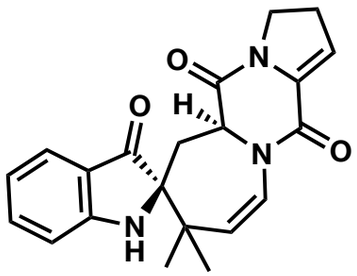
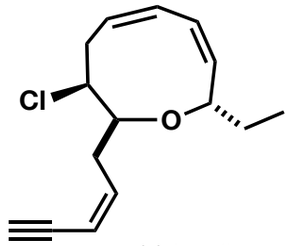
2002

Literature Talk, Birte Schröder, 08.06.2016, AK Gaich Group Seminar

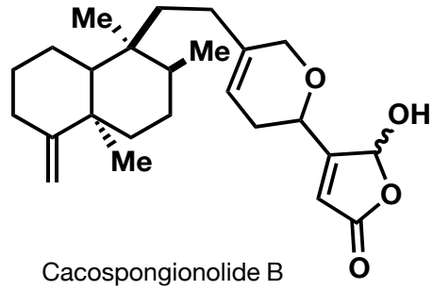
Detailed Syntheses



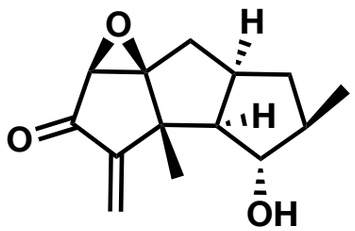
(+) Austamide



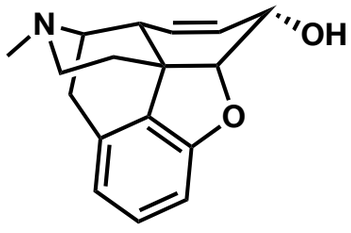
(+)-brasilenyne



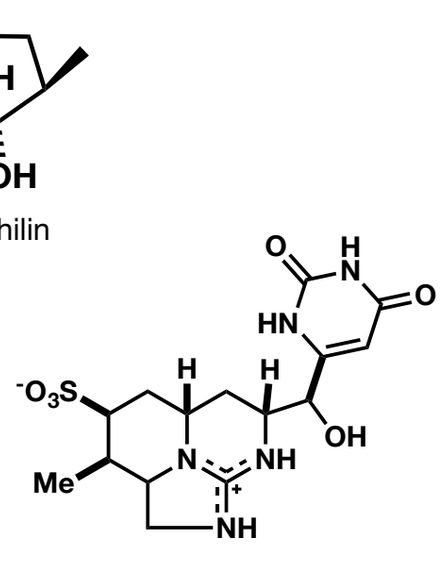
Cacospongionolide B



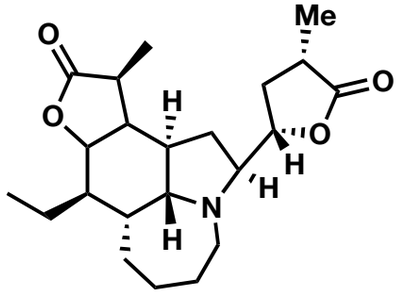
Hypnophilin



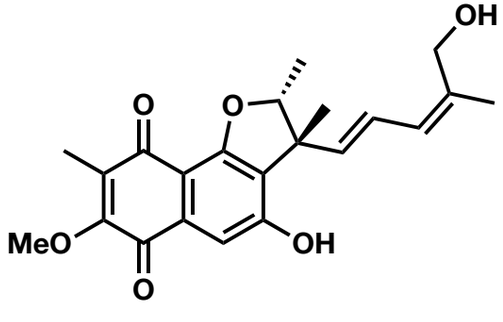
(-) Morphine



7-Epicylindrospermopsin

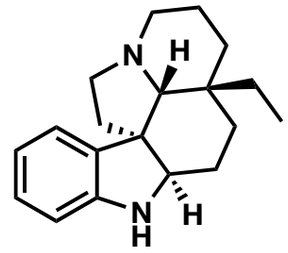


(-) Tuberostemonine

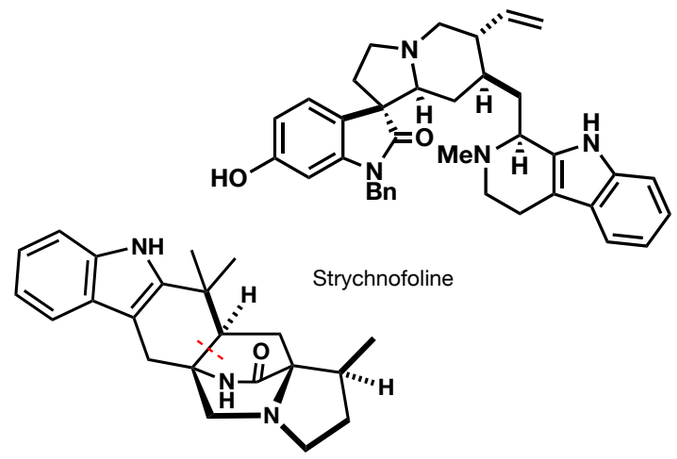


Furaquinocin E

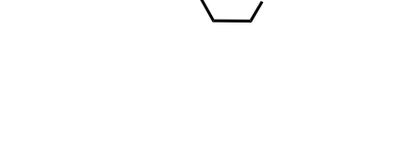
Key steps



(+) Aspidospermidine



Strychnofoline



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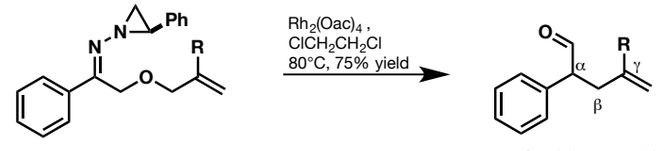
Methodologies

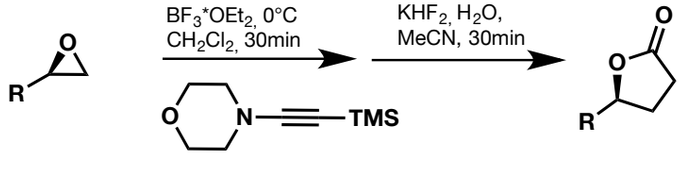
1. Rh-catalyzed Bamford-Stevens/Claisen rearrangement



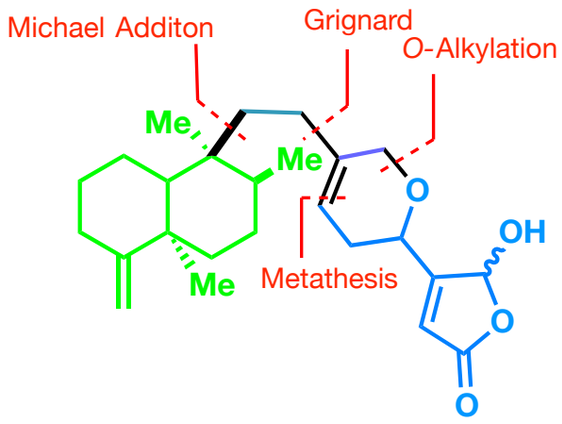
Eschenmoser hydrazone

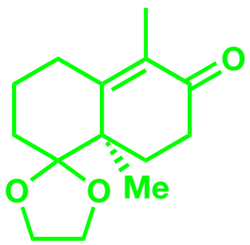
dr = 3:1 up to > 20:1

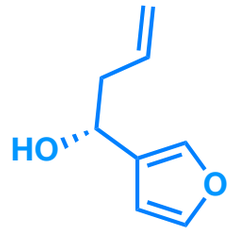
2. Synthesis of γ-butanolides

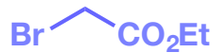


M. L. Snapper: Cacospongionolide B





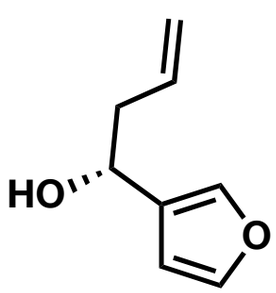




- Structural Features:
  - γ-hydroxybutenolide
  - *trans*-decalin system with a quaternary stereo center
  - 6 stereocenters:
    - 2 quaternary stereocenter

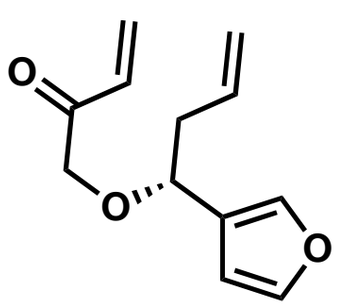
- Key step:
  - three-step coupling sequence

J. Am. Chem. Soc. **2002**, *124*, 11584.



1

1. NaH, THF, 0°C to rt
   $BrCH_2CO_2C_2H_5$, 0°C
   84% brsm
2. LiOH, MeOH/H_2O
   (3:1), rt
3. Weinreb amide, 86%
4. vinyl-MgBr, THF, 83%



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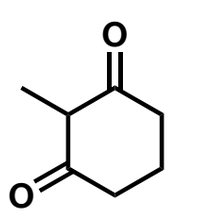

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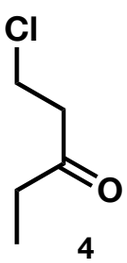
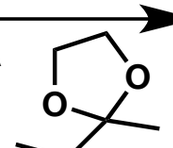


4

1. Et_3N, EtOAc
2. S(-) Phenylalanine
   HOAc, 120°C, 2h
3. CSA



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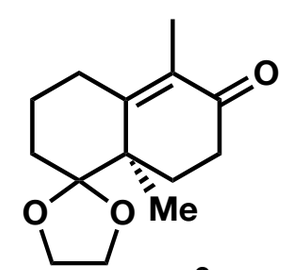

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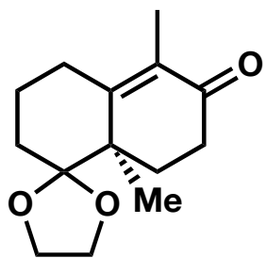
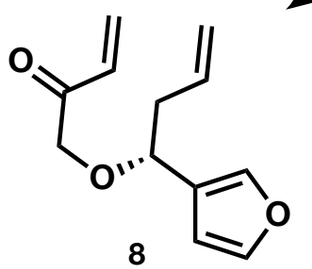
R. Uma *Tet. Lett.* **1984**, *25*, 5825.

M. L. Snapper: Cacospongionolide B



7

5. Li/NH_3, t-BuOH, -33°C
then Et_2O, -78°C, 70%



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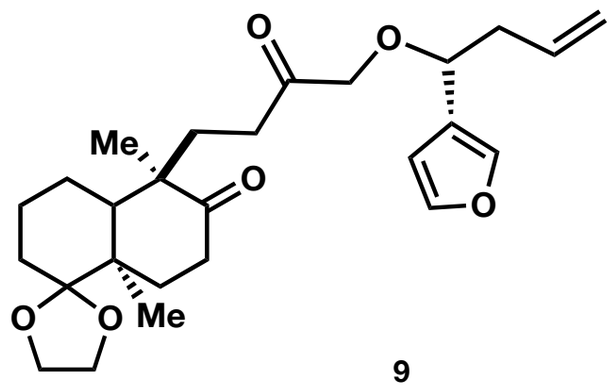
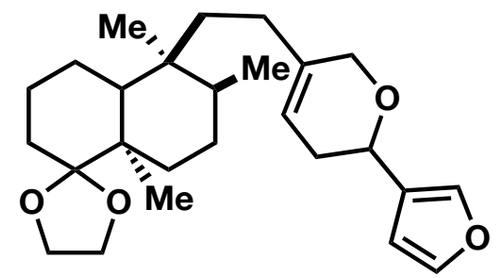


9

6. $Ph_3P{=}CH_2$, DMSO,
75°C, 60%
7. $Cy_3P(iMes)(Cl)_2Ru{=}CHPh$,
CH_2Cl_2, rt, 91%

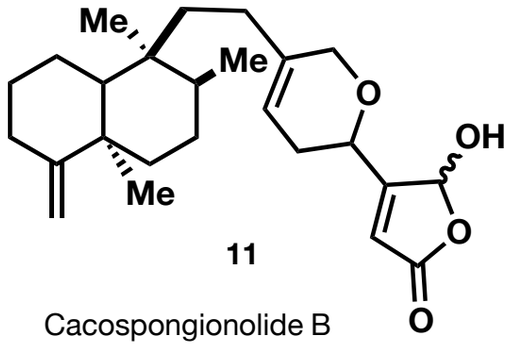
8. $[(COD)RhCl]_2$, *(R)*-BINAP,
H_2 (3 atm), CH_2Cl_2, 30°C
91%, dr = 3.3:1



10

9. 1 M HCl/THF (1:2)
rt, 90%
10. $Ph_3P{=}CH_2$, DMSO
75°C, 84%

11. O_2, rose bengal,
D*i*PEA, 150 W tungsten
filament lamp, CH_2Cl_2,
-78°C, 69%



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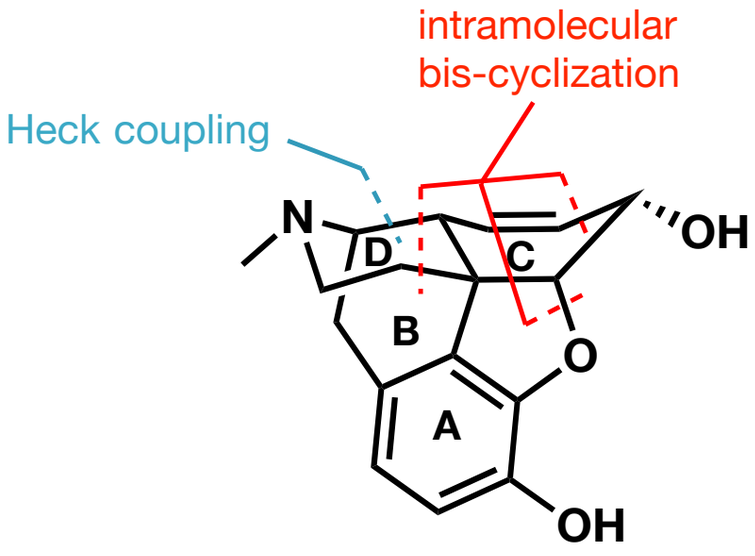
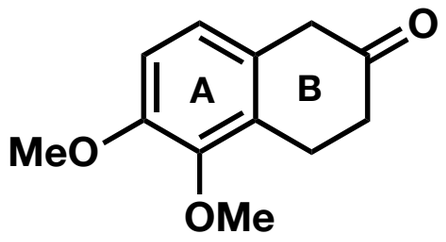
Cacospongionolide B

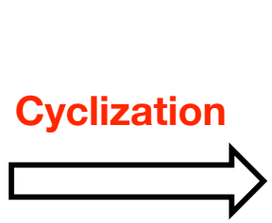
(-) Morphine

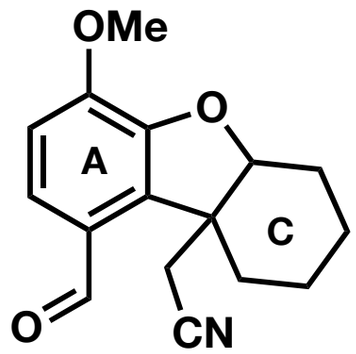


(-) Morphine



B.M. Trost: 7 (13) steps, 15.4 %

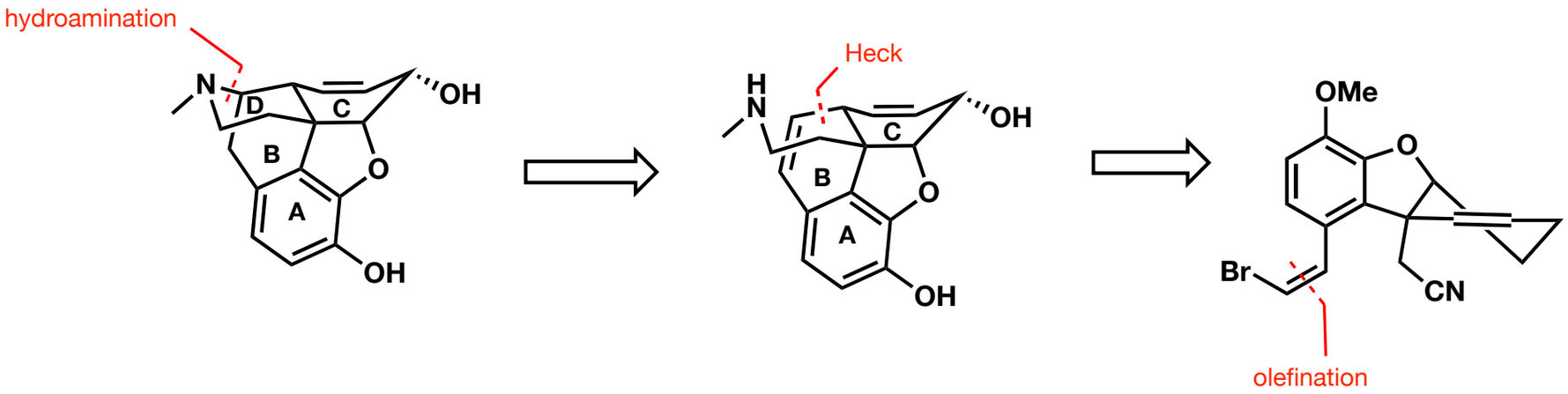


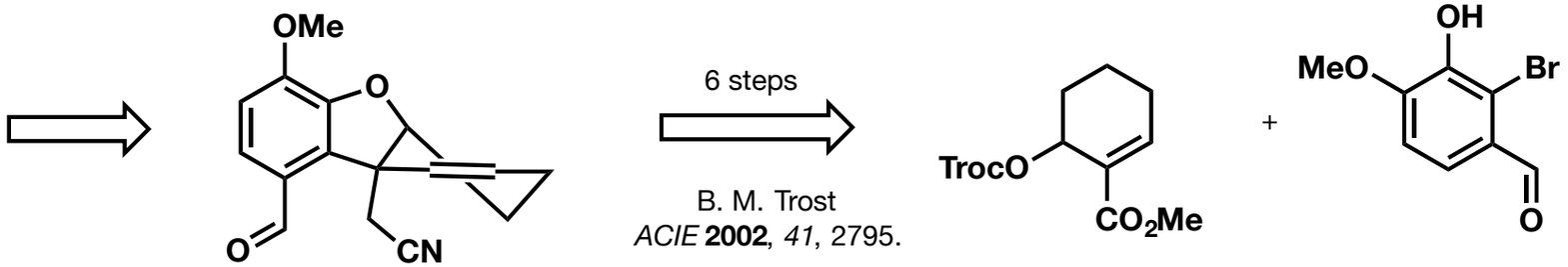


D. F. Taber: 23 (27) steps, 0.77 %

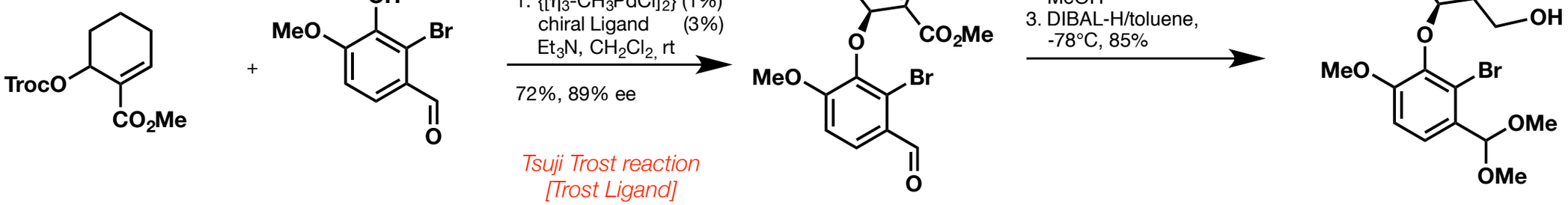
- Structural Features:
  - pentacyclic ring system
  - bridged piperidine ring
  - compact array of functionality
  - 5 contiguous stereocenters:
    - 1 quaternary stereocenter
- Landmark synthesis was in 1952 by Gates (today: at least 18 TS)

B. M. Trost: (-) Morphine



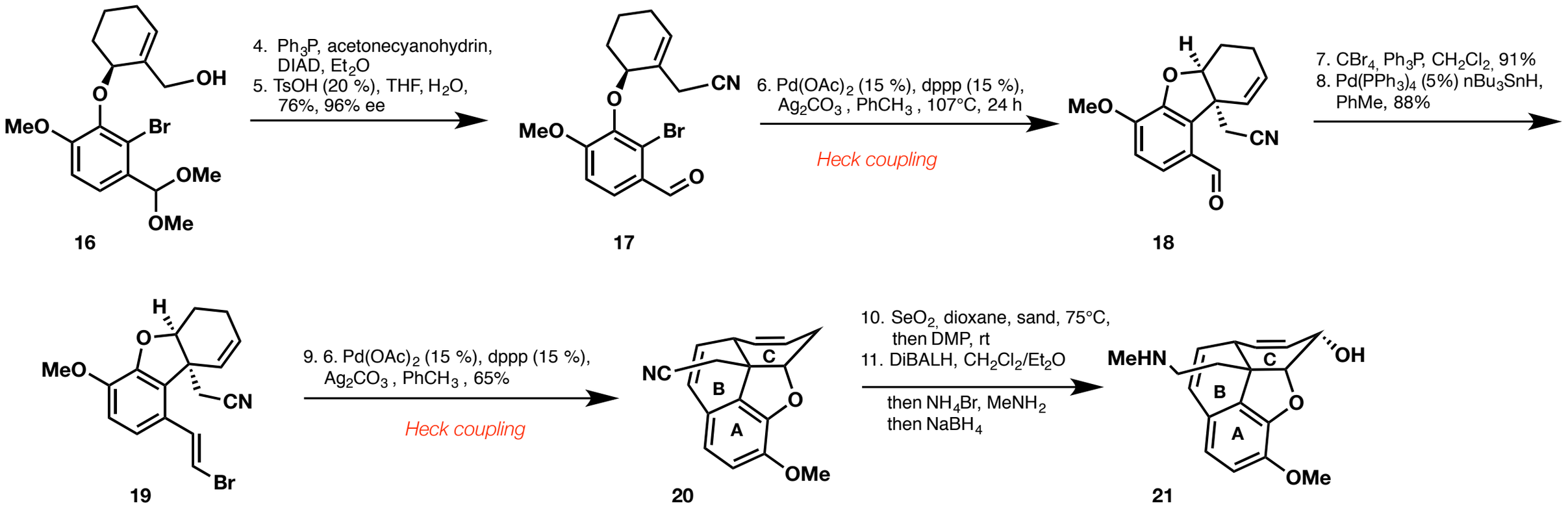


J. Am. Chem. Soc. **2002**, *124*, 14542.

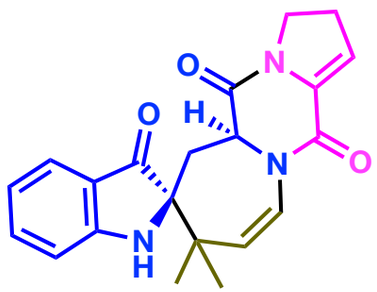


12 **13** **14** **15**

B. M. Trost: (-) Morphine



E. J. Corey: (+) Austamide



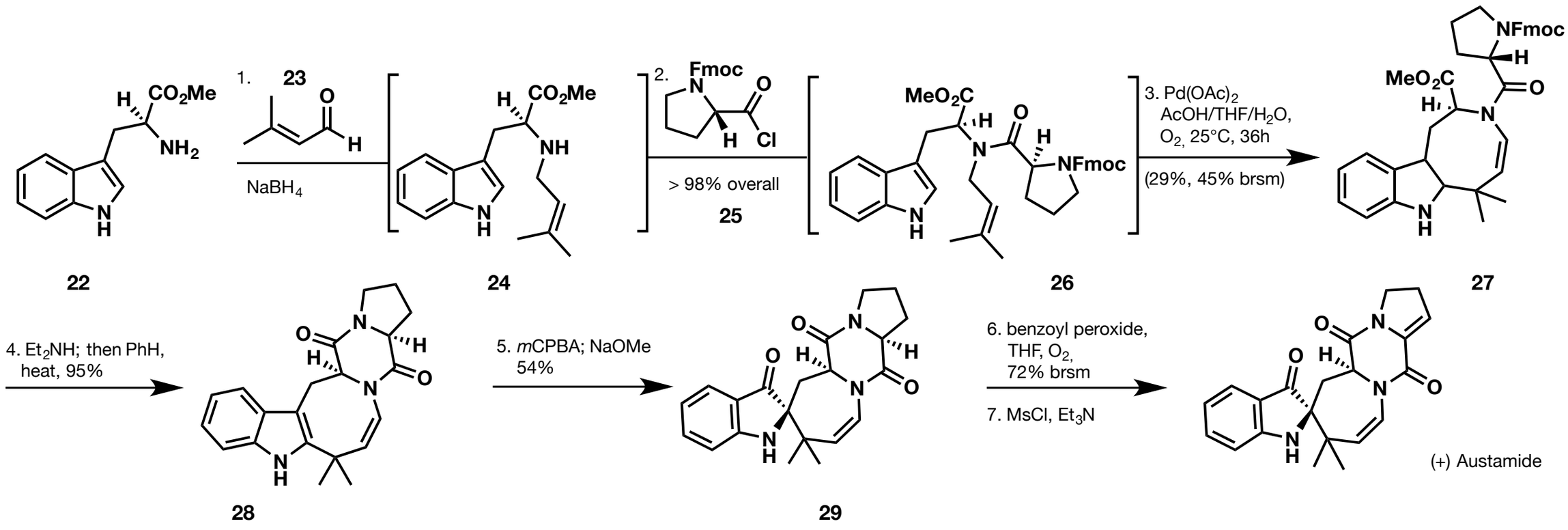
(+) Austamide

J. Am. Chem. Soc. **2002**, *124*, 7904.

- Structural Features:
  - indoloazocine tricyclic subunit
  - diketopiperazine
  - 2 stereocenters:
    - 1 heteroatom-based spiro stereocenter

- Key steps:
  - Pd-mediated cyclization

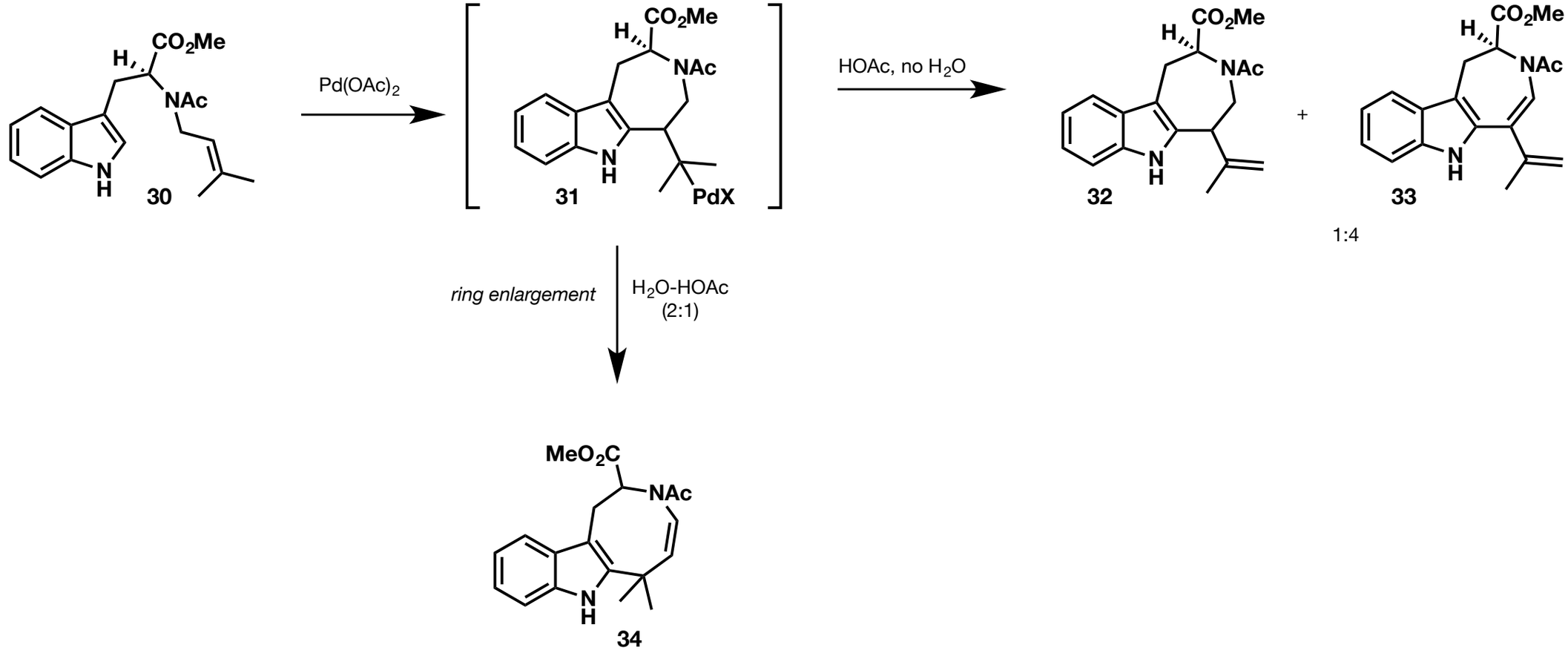
- Previous Synthesis: Kishi Group, racemic, 29 steps



E. J. Corey: (+) Austamide

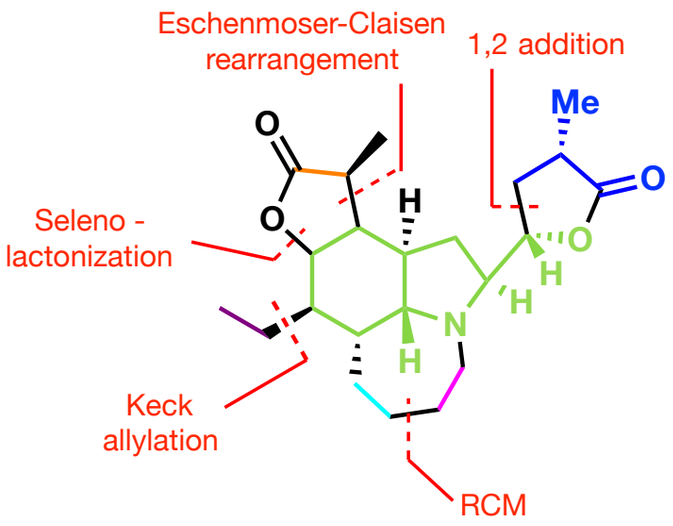
Studies towards the key step:

1. in absence of acetic acid: no cyclization occurs
2. in absence of water: major product is dihydroindoloazepine xxx (4:1)
3. similiar results are obtained starting from performed chloromercury derivative but the rate is faster!

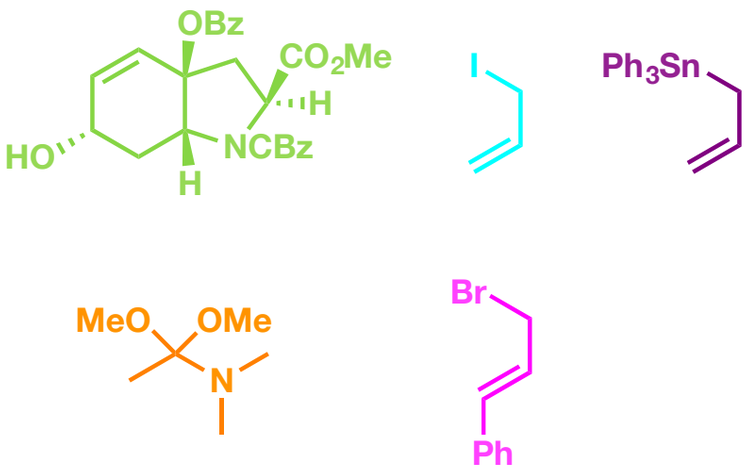


4. Additional significant mechanistic details are missing:
   the methoxycarbonyl of the tryptophan subunit is crucial for the cyclization

P. Wipf: (-) Tuberostemonine



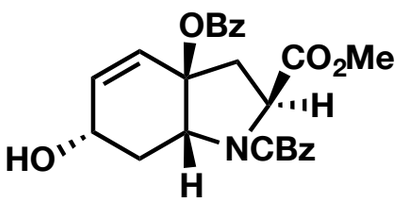
(-) Tuberostemonine



J. Am. Chem. Soc. **2002**, *124*,14848.

- Structural Features:
  - pentacyclic ring system
  - azepane ring
  - γ-butyrolactone
- 10 stereocenters:
  - 6-membered ring with only stereogenic carbon centers

- Key steps:
  - 1,2 addition of a lithiated *ortho*-ester
  - RCM to form the azepane
  - Eschenmoser-Claisen rearrangement



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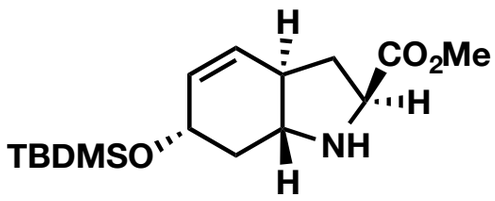
1. $Pd_2(dba)_3CHCl_3$, NEt_3, HCOOH, PBn_3, THF, 65 °C, 93%
2. TBDMSCl, imid., DMAP, CH_2Cl_2 , 97%
3. Et_3SiH, $Pd(OAc)_2$, NEt_3, CH_2Cl_2 , rt



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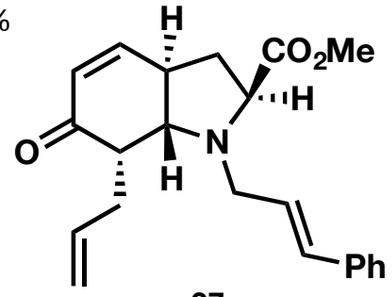
4. cinnamyl bromide, K_2CO_3 , K_2CO_3, toluene, 60°C, 96%
5. TBAF, THF, rt, 96%
6. TPAP, NMO, CH_2Cl_2, 88%
7. KHMDS, allyl iodide, -90°C, 66%



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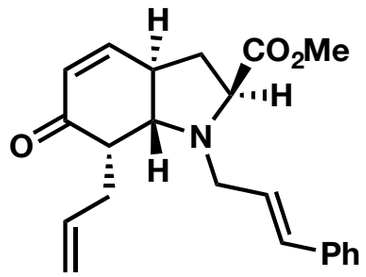
P. Wipf: (-) Tuberostemonine



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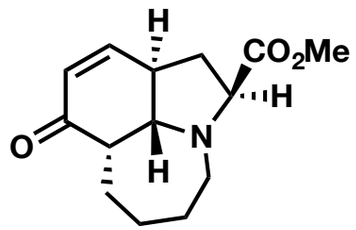
8. **A**, CH_2Cl_2, reflux, 92%
9. PhSH, NEt_3, CH_2Cl_2
10. $(PPh_3)_3RhCl$, H_2, EtOH/CH_2Cl_2 , rt

11. DBU, CH_2Cl_2, rt 89%



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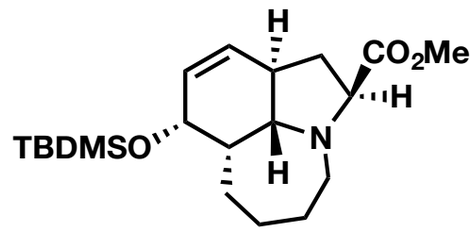
12. $CeCl^*{}_7H_2O$, $NaBH_4$, THF/MeOH
13. TBDSMCl, imid., DMAP CH_2Cl_2, rt, 79%



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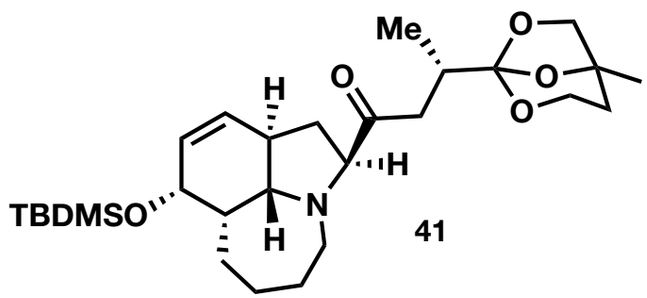
14. MeNH(OMe)*HCl, Me_2AlCl CH_2Cl_2, rt
15. **B**, LiDBB, 93%

1,2 addition



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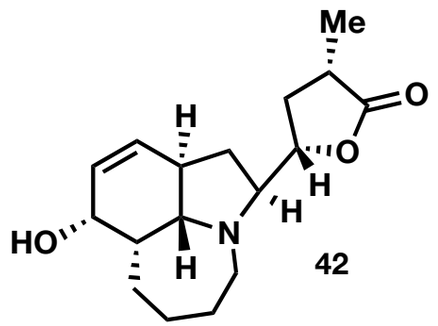
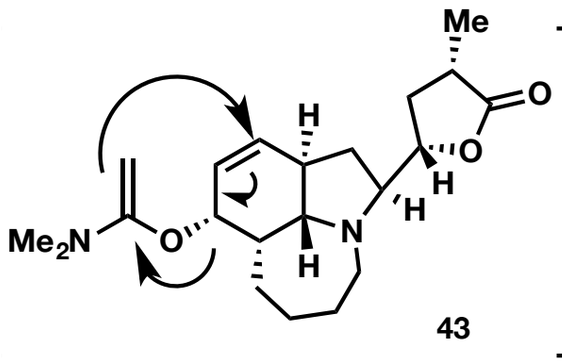
16. L-Selectride, THF, -78°C
17. TsOH, MeOH, 70%



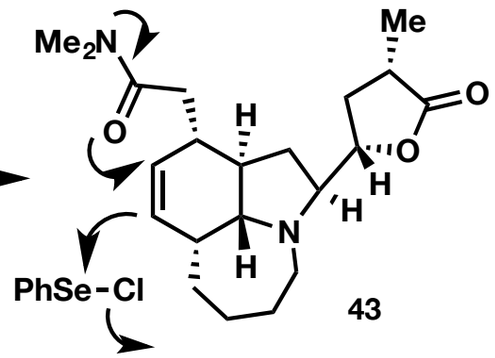
42

18. *N,N*-Dimethylacetamide dimethyl acetal, xylenes, 135°C, 78%

Eschenmoser-Claisen



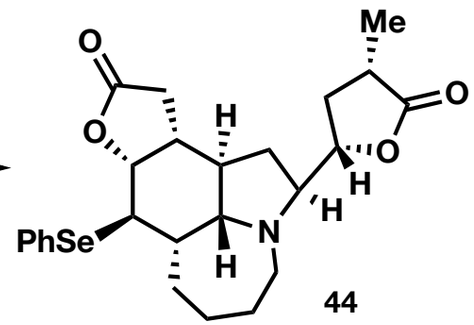
43



43

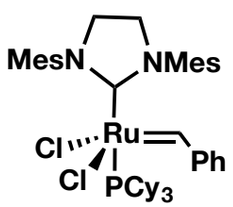
19. PhSeCl, MeCN/H_2O, 0°C, 67%

Seleno-lactonization

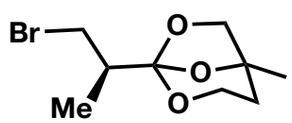


44

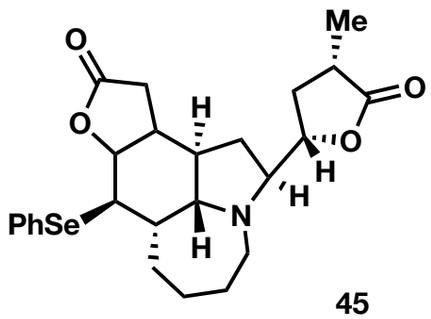
A:



B:

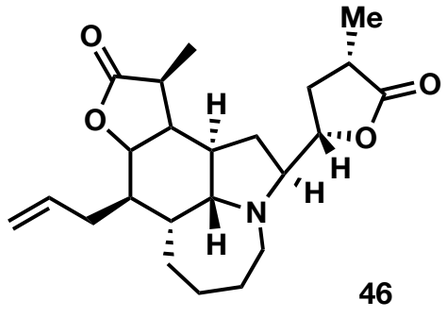


P. Wipf: (-) Tuberostemonine



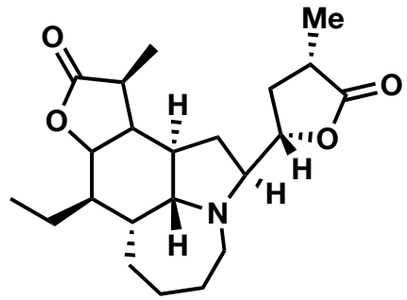
45

20. AIBN, allyltriphenyltin (neat), 95°C, 70%
21. LDA, HMPA, THF, -78°C; MeI, 76% brsm



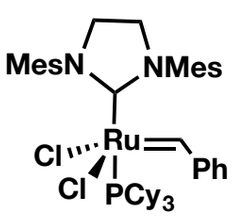
46

22. A, allyltritylamine, DIEA, 110°C, 85%
23. TsOH, **C**, CH_2Cl_2 reflux, ethylene,81%
24. Pd/C, H_2 (1 atm), MeOH, 97%

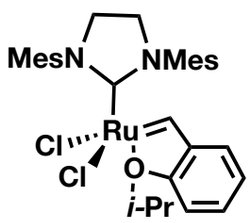


(-) Tuberostemonine

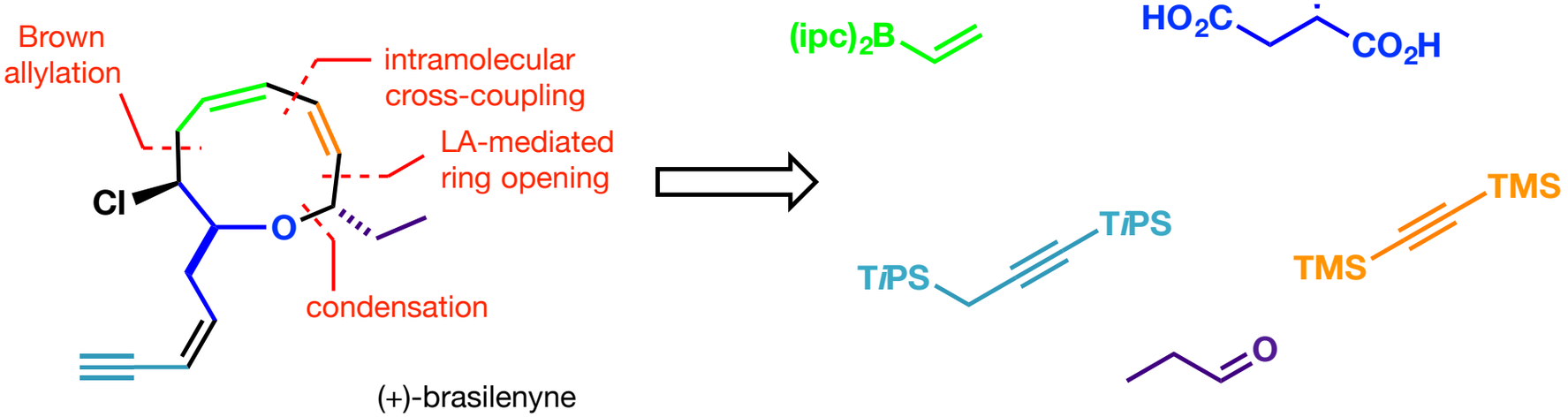
A:



C:



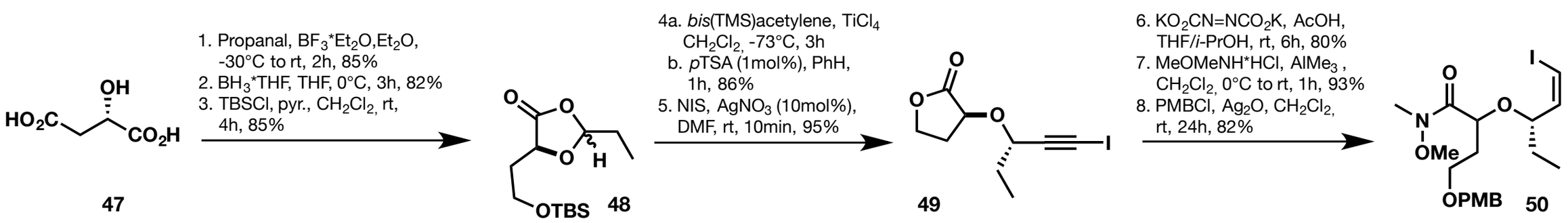
S. Denmark: (+) Brasilenyne



J. Am. Chem. Soc. **2002**, *124*, 15196.

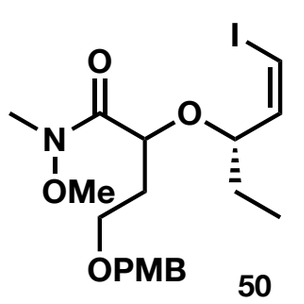
- Structural Features:
  - nine-membered cyclic ether skeleton
  - 1,3-*cis,cis*-diene unit
  - 3 Stereocenters

- Key steps:
  - intramolecular cross-coupling



L-(S)-malic acid

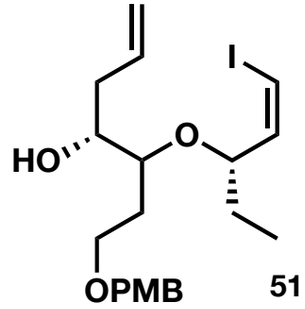
S. Denmark: (+) Brasilenyne



50

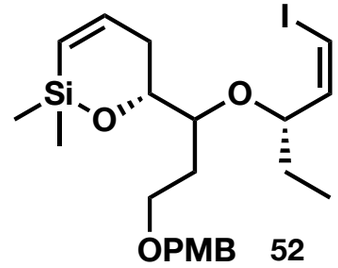
9. DIBAL-H, CH_2Cl_2, -73°C, 3h, 87%
10. allylB(Ipc)$_2$, Et_2O, -100°C, 2h, 89%

Brown Allylation



51

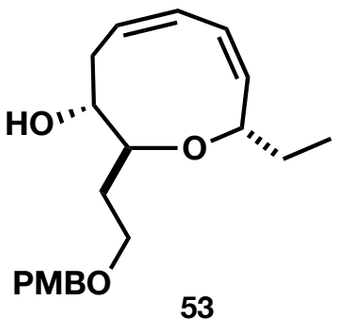
11. chlorodimethylvinylsilane, Et_3N, CH_2Cl_2, 0°C to rt, 30min, 91%
12. Schrock's catalyst (5mol%), PhH, rt, 1h, 92%



52

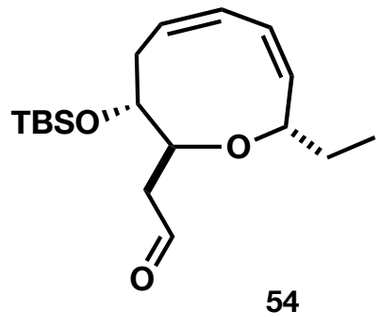
13. [allylPdCl]$_2$ (7.5 mol%), TBAF, rt, 60h, 61%

silicon-assisted intramolecular cross-coupling



53

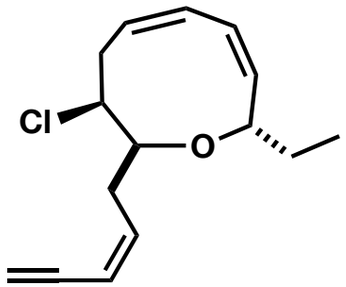
14. TBSOTf, pyr., DMAP (10%mol), CH_2Cl_2, 0°C to rt, 2h., 88%
15. DDQ, CH_2Cl_2/H_2O (19/1), rt., 30min, 84%
16. DMP, CH_2Cl_2, rt, 2h, 83%



54

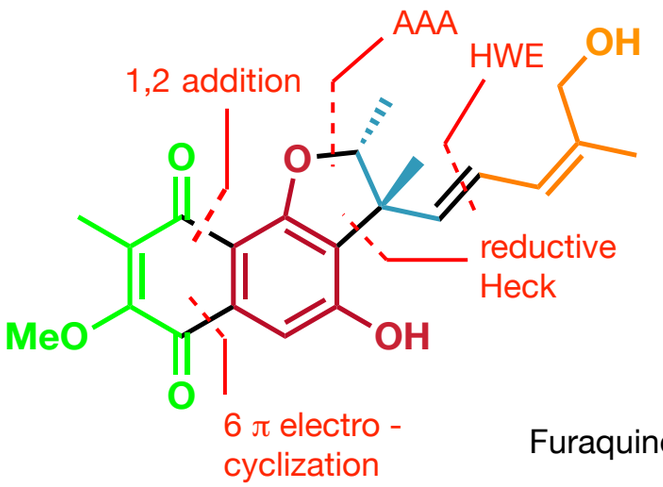
17. 1,3-bis(triisopropylsilyl)propyne, nBuLi, THF, -74°C to rt, 8h, 83% (Z/E = 6/1)
18. TBAF, THF, 0°C, 1.5h, 93%
19. CCl_4, (n-Oct)$_3$P, toluene, 65°C, 12h, 92%

Peterson-Olefination

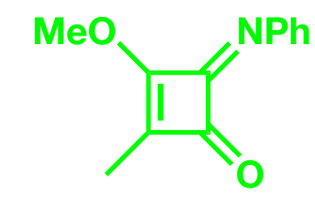


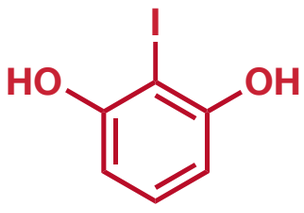
(+)-brasilenyne

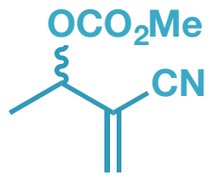
B. M. Trost: Furaquinocin E

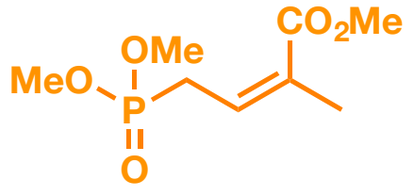


Furaquinocin E



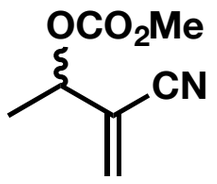






J. Am. Chem. Soc. **2002**, *124*, 16116.

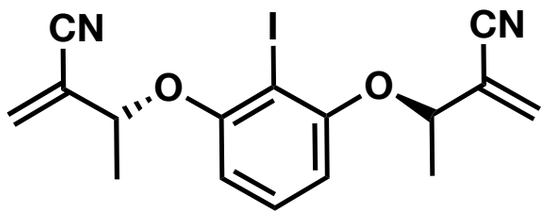
- Structural Features:
  - nine-membered cyclic ether skeleton
  - 1,3-*cis,cis*-diene unit
  - 3 Stereocenters
- Key steps:
  - intramolecular cross-coupling



55

1. **A**, $Pd_2(dba)_3$*$CHCl_3$ (1 mol%)
   ligand(*R,R*)-**B** (2.65mol%),
   CH_2Cl_2, rt, 97%, dr 92/8

Triple AAA

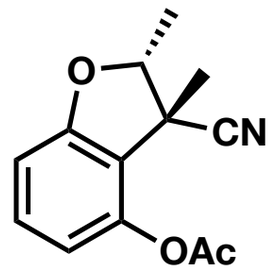


56

2. a) $PdCl_2(CH_3CN)_2$ (10mol%)
   HCOOH, PMP, DMP, 50°C

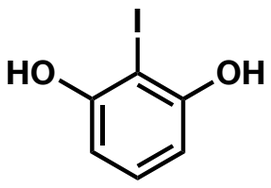
b) Ac_2O, TEA, DMAP, CH_2Cl_2,
rt, 81%, 87% ee

Reductive Heck



57

A:



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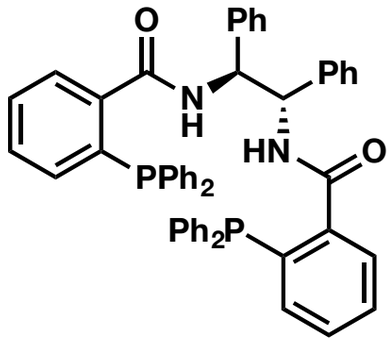
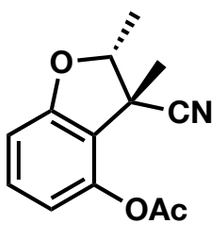
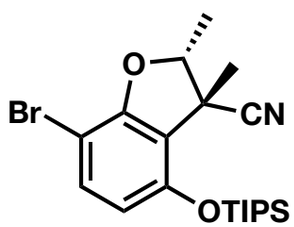


B. M. Trost: Furaquinocin E



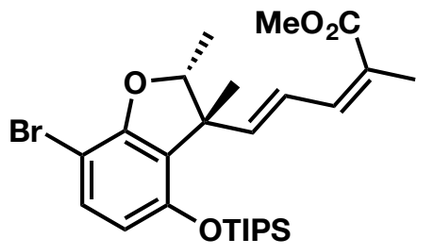
57

3. NaOMe, MeOH, rt, 94%
4. TIPSOTf, TEA, CH_2Cl_2, 96%
5. NBS, THF, rt, 92%



58

6. a) DIBAL-H, CH_2Cl_2, -78°C
   b) **C**, LiHMDS, THF, 0°C, 89%



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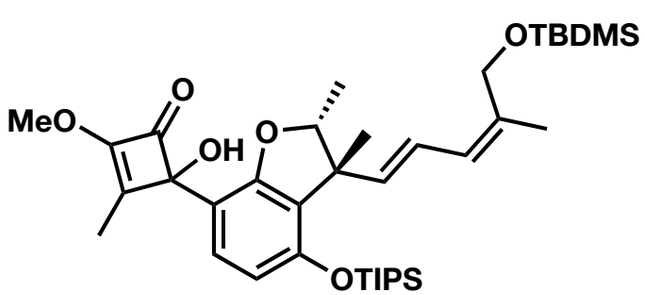
7. a) DIBAL-H, CH_2Cl_2, -78°C
   b) TBDMSCl, imid., CH_2Cl_2, reflux, 89%
8. a) nBuLi, THF, -78°c
   b) **D**,THF, -78°C
   c) oxalic acid, THF/H_2O, 50%



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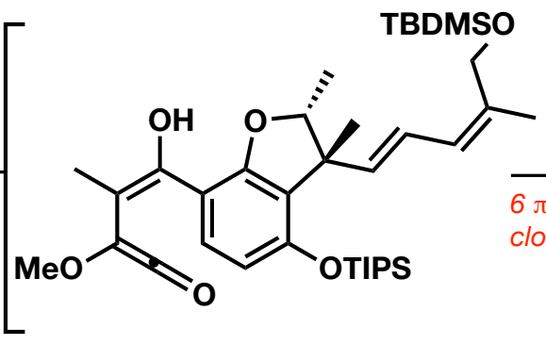
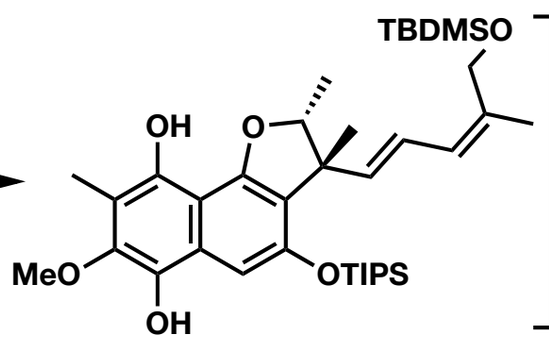
9. a) PhMe, 110°C

4 π ring opening



60

6 π ring closure

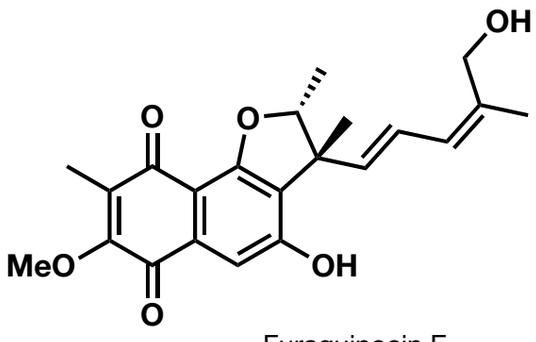


61

b) air, rt, 64%

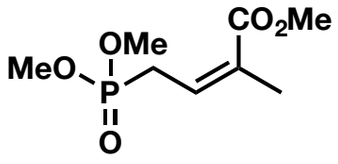
10. TBAF, THF, 0°C, 65%

Moore-Liebeskind naphtoquinone synthesis

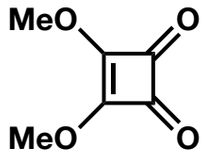


Furaquinocin E

C:

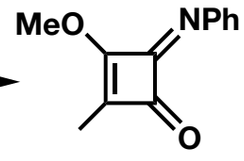


D:

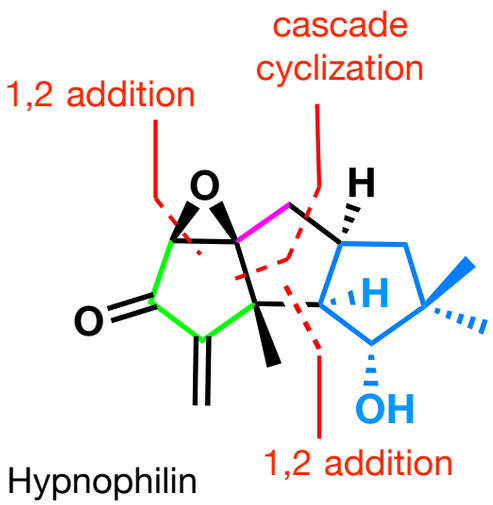


1. a) MeLi, THF, -100°C
   b) TFAA, -78°C,
   c) aniline, -78°C to -15°C

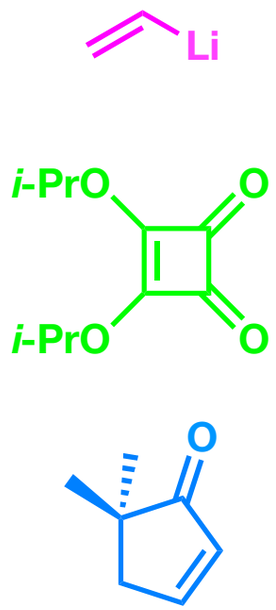
53%



L. A. Paquette: Hypnophilin



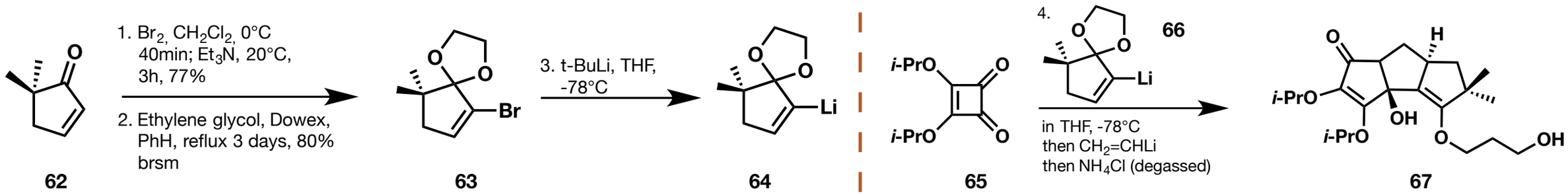
Hypnophilin



J. Am. Chem. Soc. **2002**, *124*, 9199.

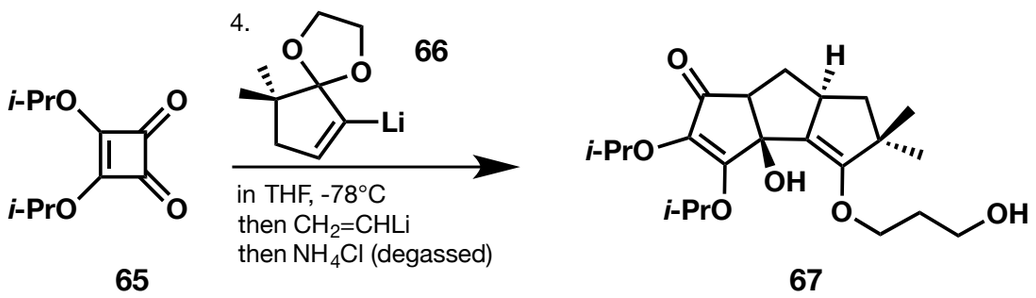
- Structural Features:
  - linear fused triquinane system
  - uncommon Michael acceptor
  - 6 stereocenters:
    - 5 contiguous stereocenters
    - 1 quaternary stereocenter

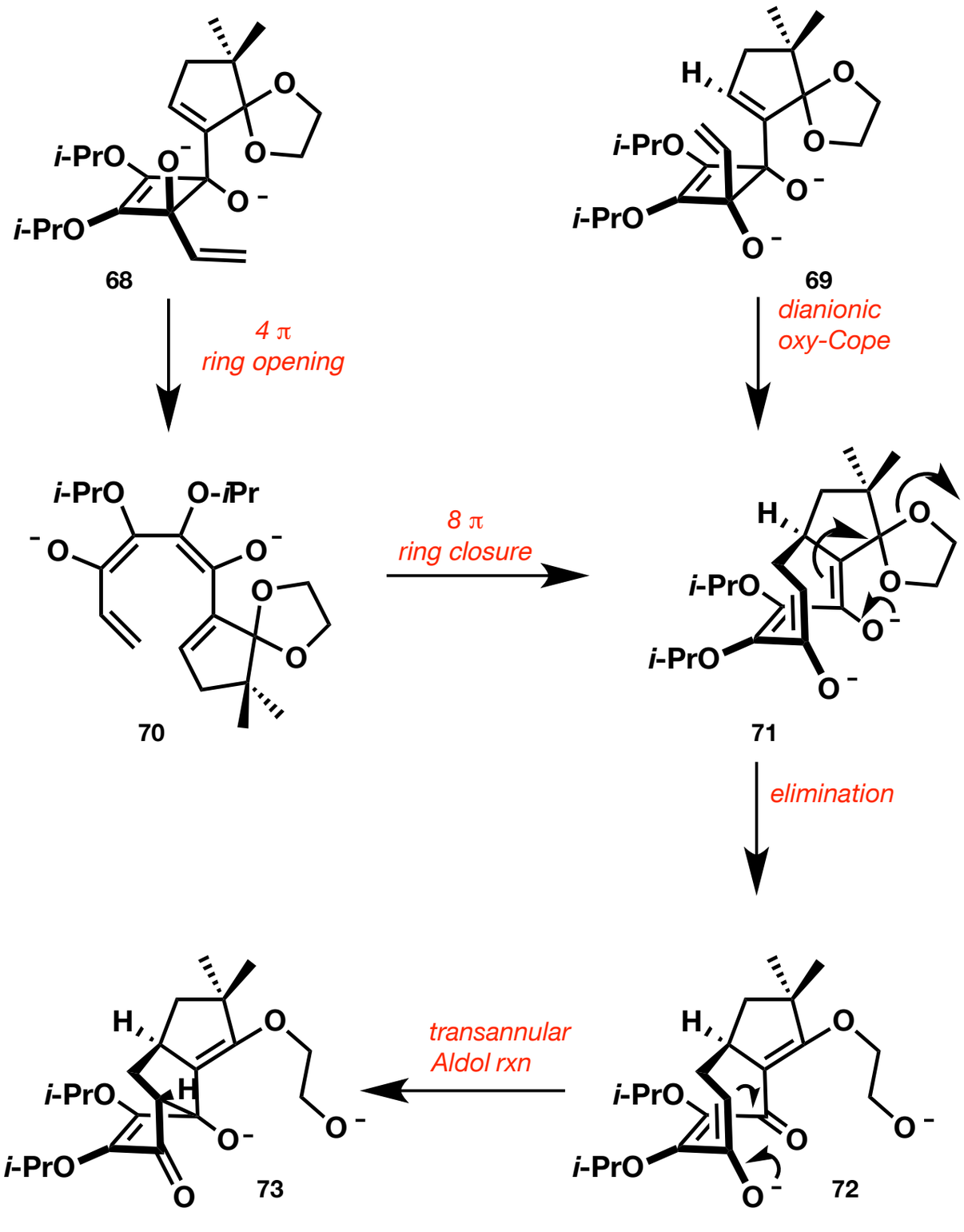
- Key steps:
  - cascade cyclization with diisopropyl squarate



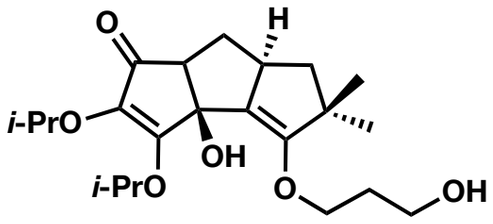
L. A. Paquette: Hypnophilin

A closer look at the key step:



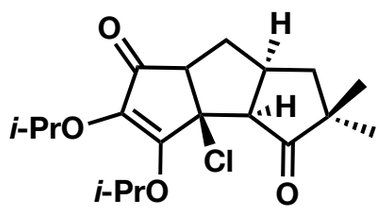


L. A. Paquette: Hypnophilin



67

5. 10% H_2SO_4, o/n, rt, 24% over two steps
6. MsCl, Et_3N, DMAP, rt, o/n, 72%



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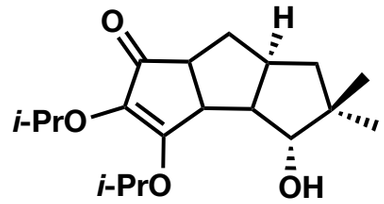
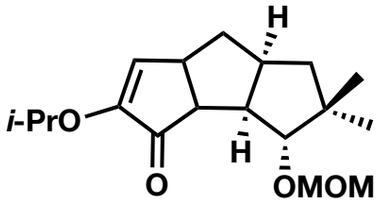
7. Li, NH_3, THF, -78°C, 1.5h, Li benzoate, -78°C, 72%



75

8. LAH, THF, -10°C, 5min then 1 M HCl, 76%
9. MOMCl, DiPEA, CH_2Cl_2 rt, o/n, quant. yield



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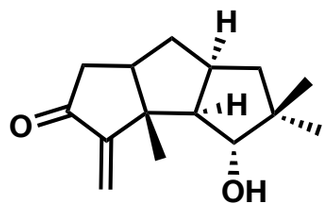
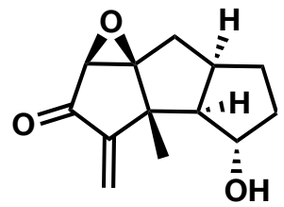
10. LDA, HMPA, THF, MeI, rt, o/n, 95%
11. MeLi, Et_2O, 0°C, 2h, then 30% H_2SO_4, THF, reflux, 10h, 85%

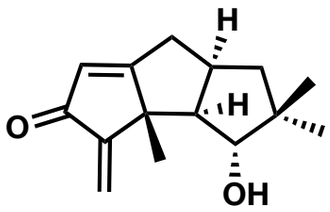


77

12. LDA, DMPU, THF, TMSCl, $Pd(OAc)_2$, MeCN, rt, o/n, 60%
13. K_2CO_3, 30% H_2O_2, H_2O, CH_2Cl_2, rt, 3h, 80% brsm

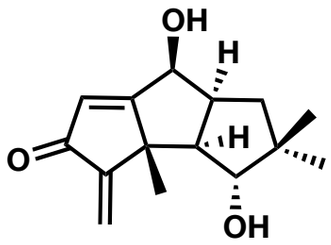


Hypnophilin



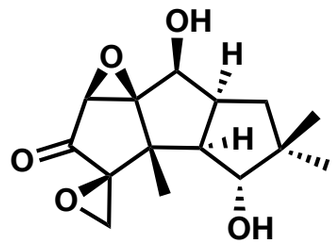
78

13. KOtBu, DME, -78°C to rt, 10% aq HOAc
14. mCPBA, CH_2Cl_2, DBU, PhH, 48% over two steps



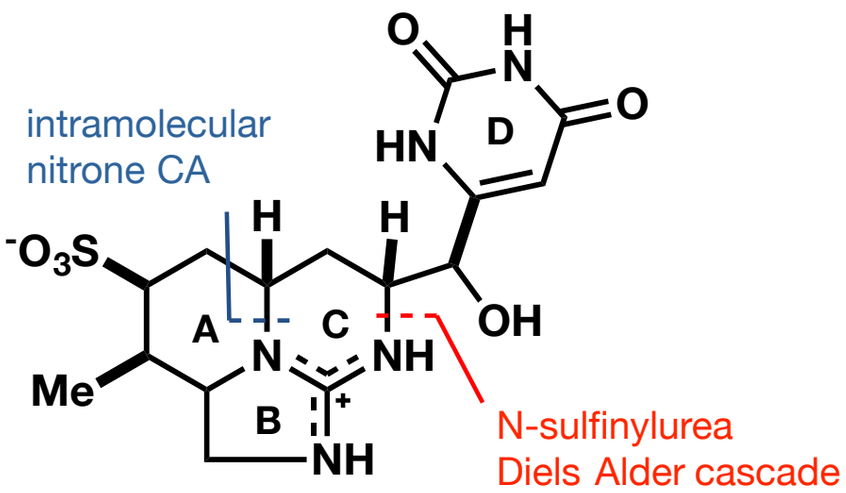
79

15. Ac_2O, DMAP, pyr. , 98%
16. LiOH, THF, 30% H_2O_2

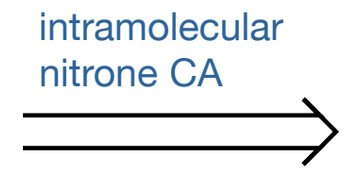


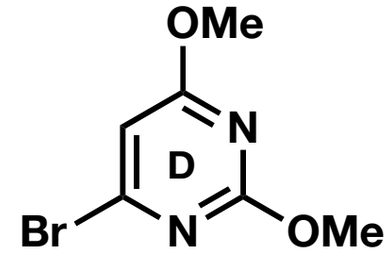
Coriolin

7-Epicylindrospermopsin

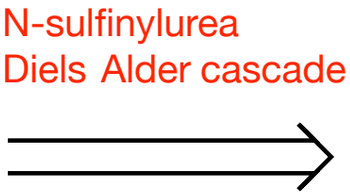


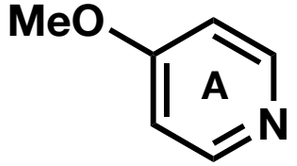
7-Epicylindrospermopsin





J. D. White

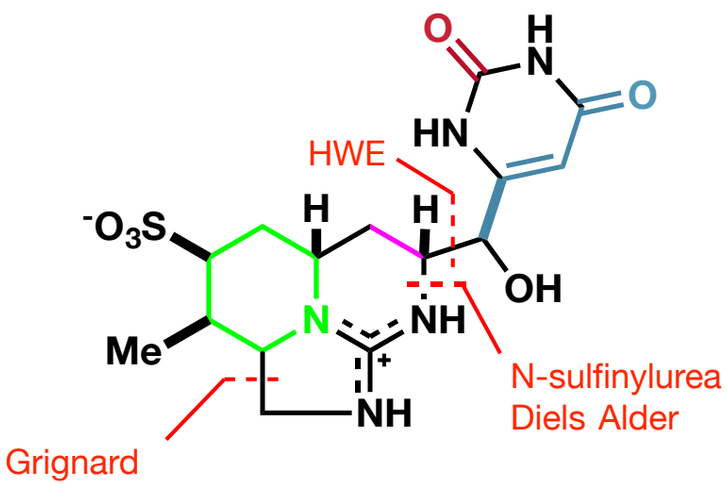


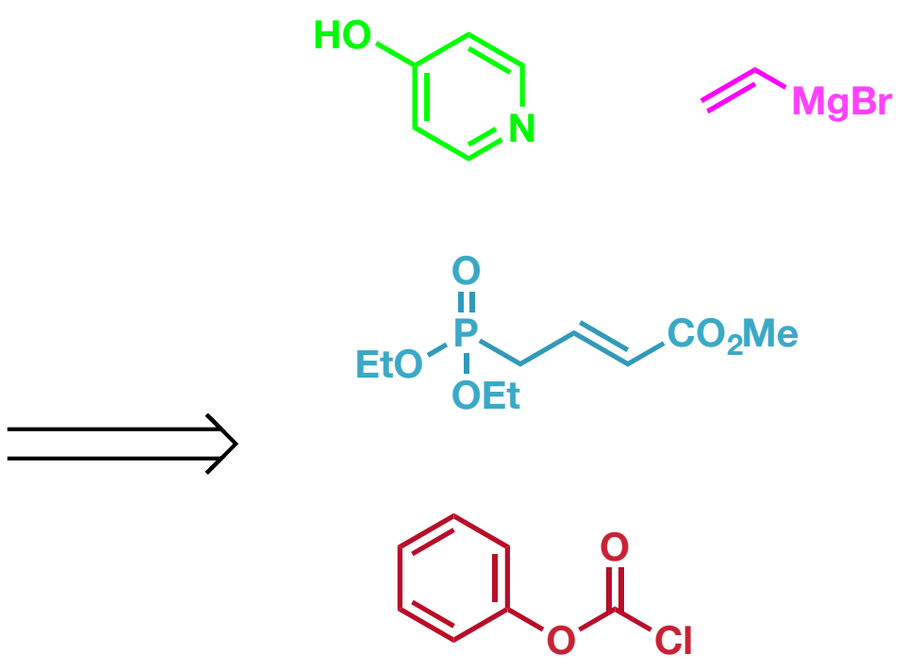


S. M. Weinreb

- Structural Features:
  - polycyclic ring skeleton
  - unusual enolic uracil D-Ring
  - guanidine C-Ring
  - 7 stereocenters

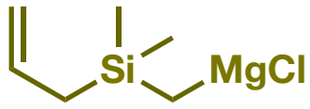
S. M. Weinreb: 7-Epicylindrospermopsin

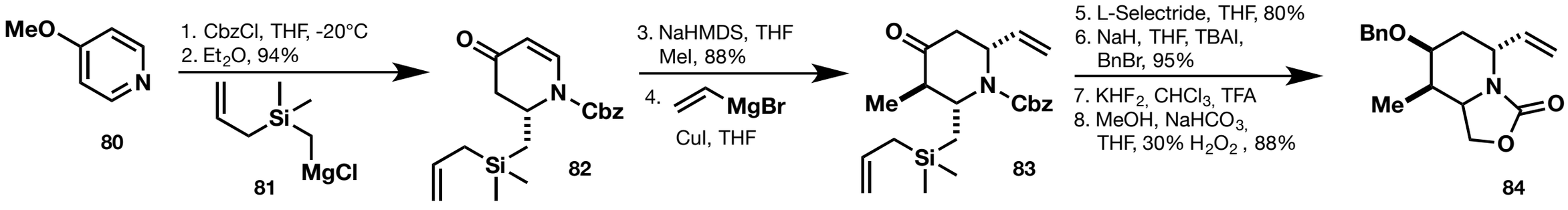




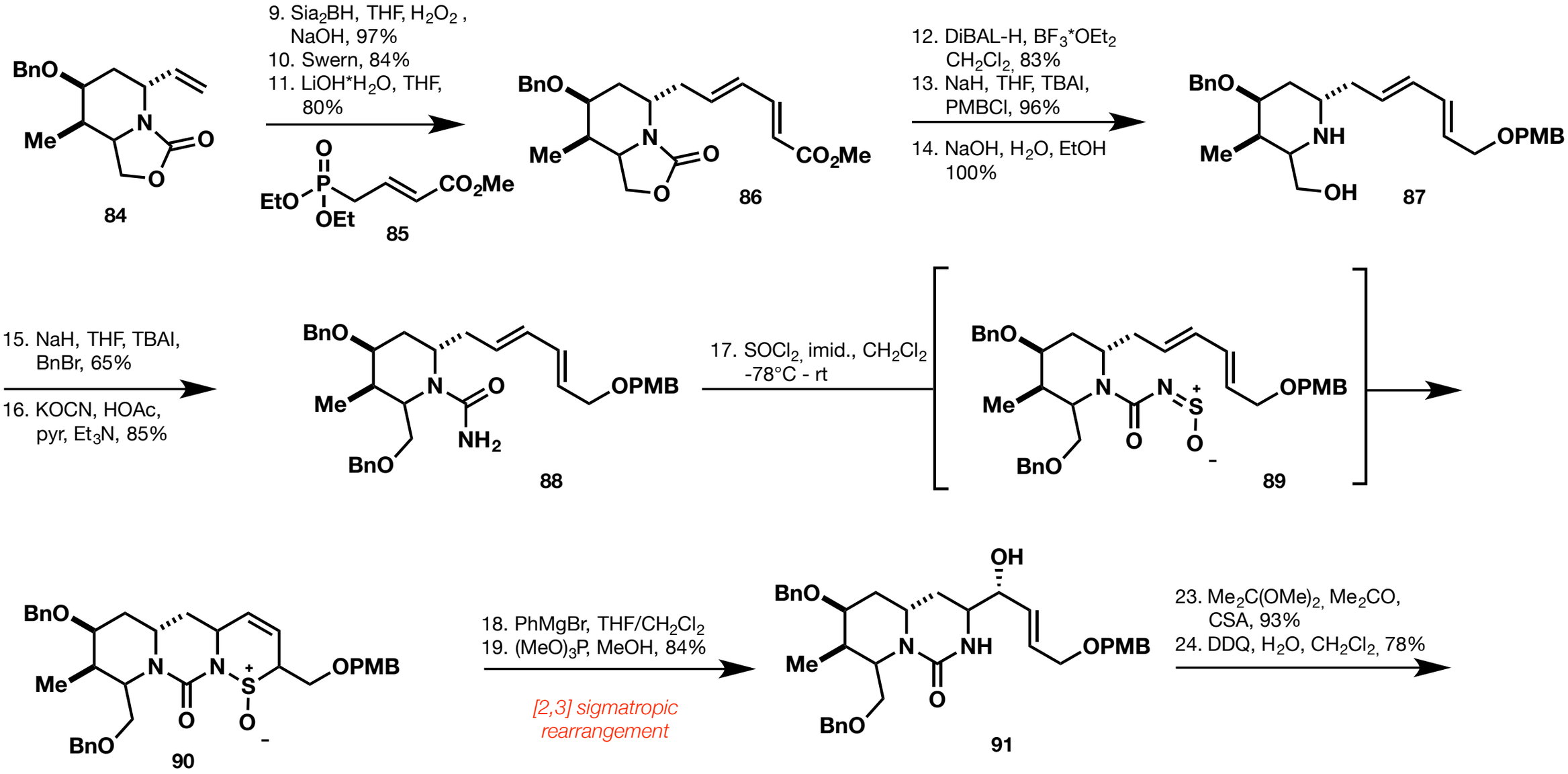
7-Epicylindrospermopsin

J. Am. Chem. Soc. **2002**, *124*, 3939.

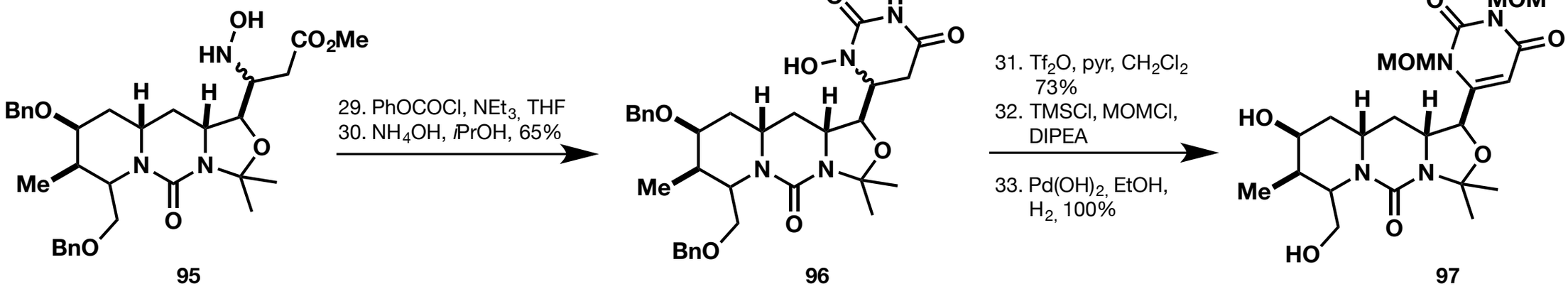


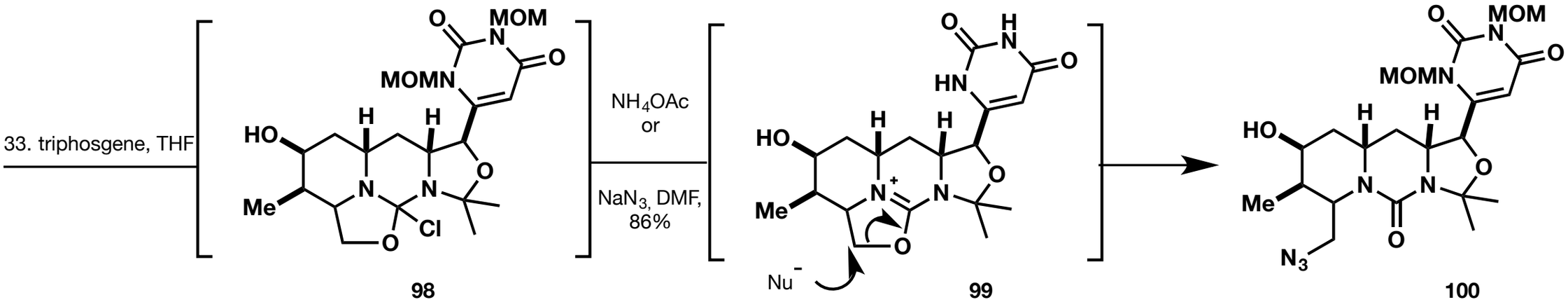


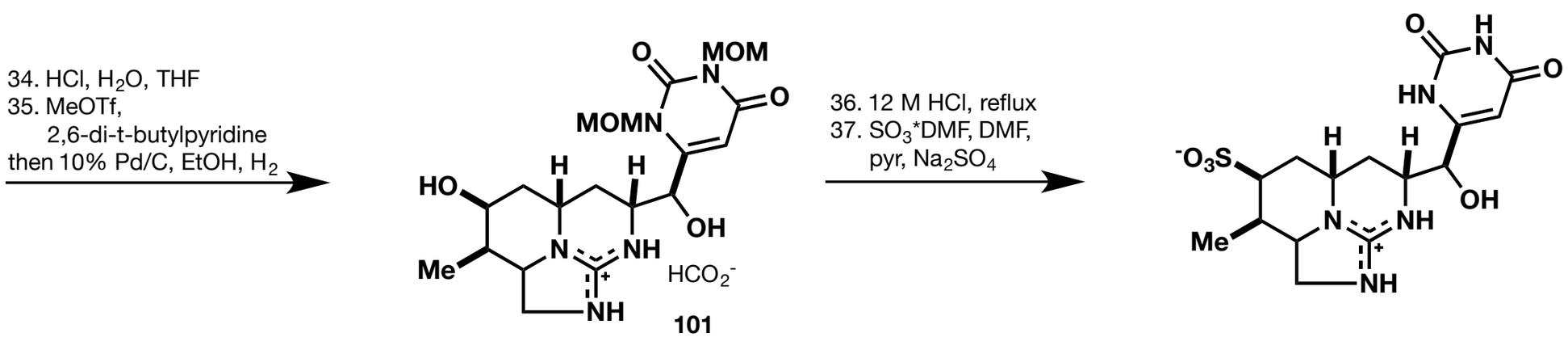
S. M. Weinreb: 7-Epicylindrospermopsin



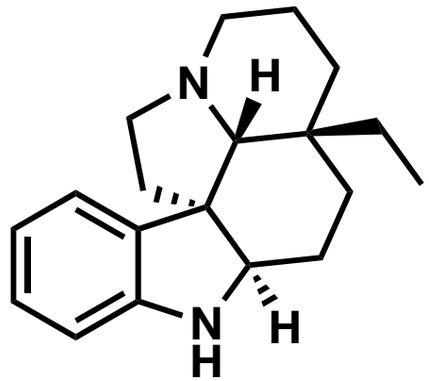
S. M. Weinreb: 7-Epicylindrospermopsin





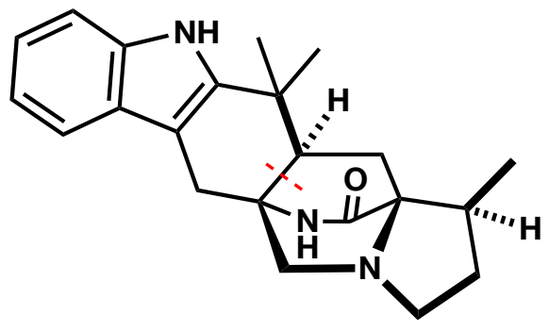


Key steps in Total Synthesis

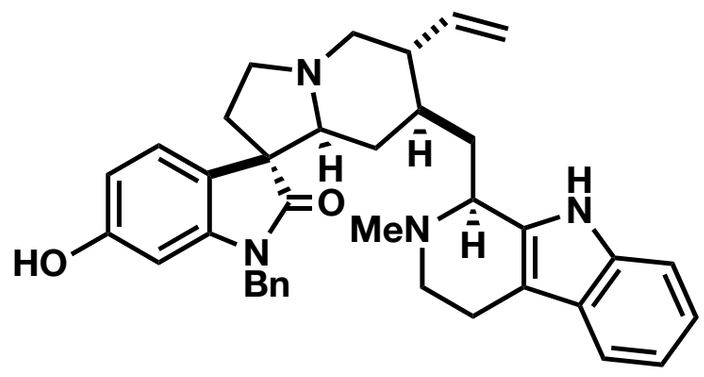


(+) Aspidospermidine

JACS 2002

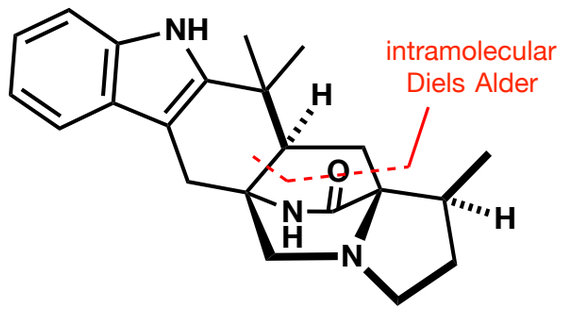


VM55599

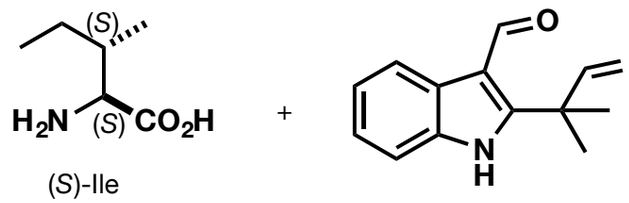


Strychnofoline

Williams Group: (-)VM55599

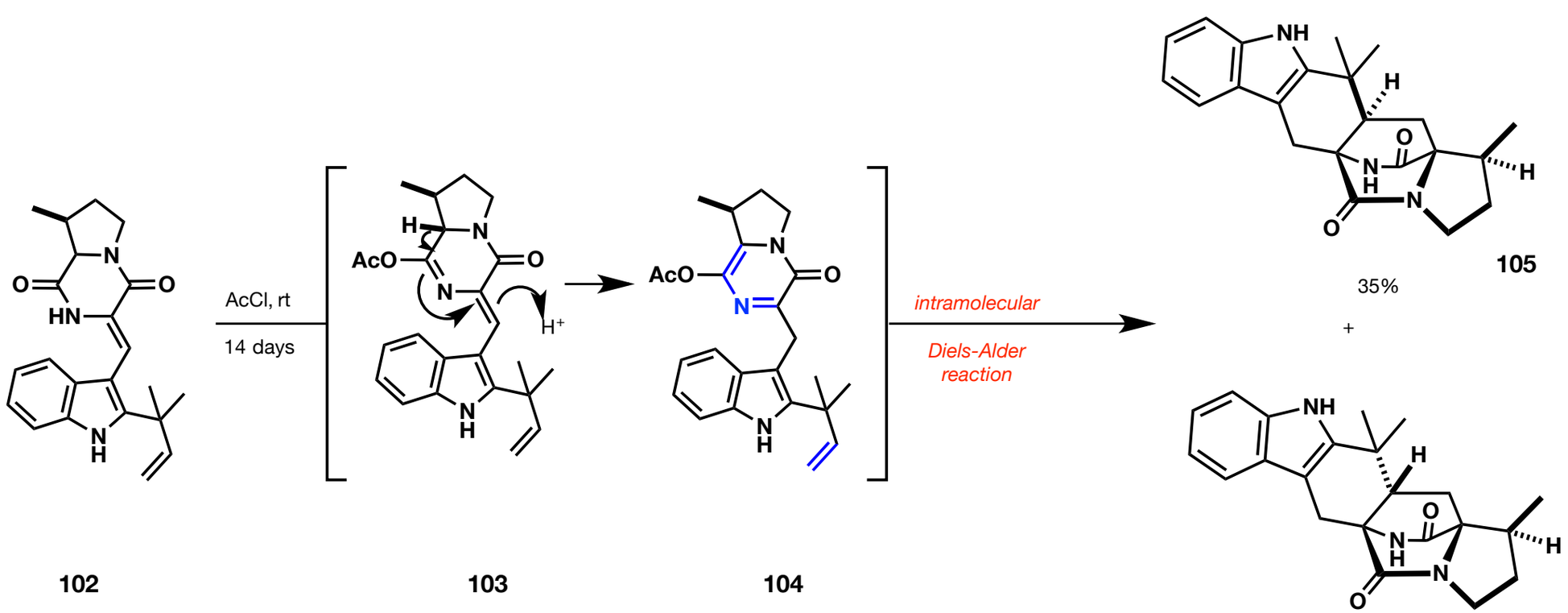


VM55599



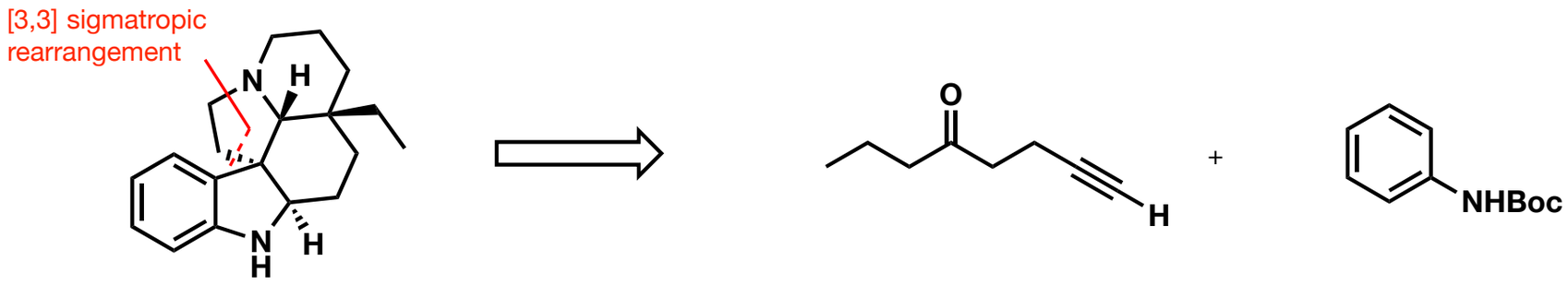
- Key step:
  Intramolecular Diels Alder cycloaddition

J. Am. Chem. Soc. **2002**, *124, 2556*.



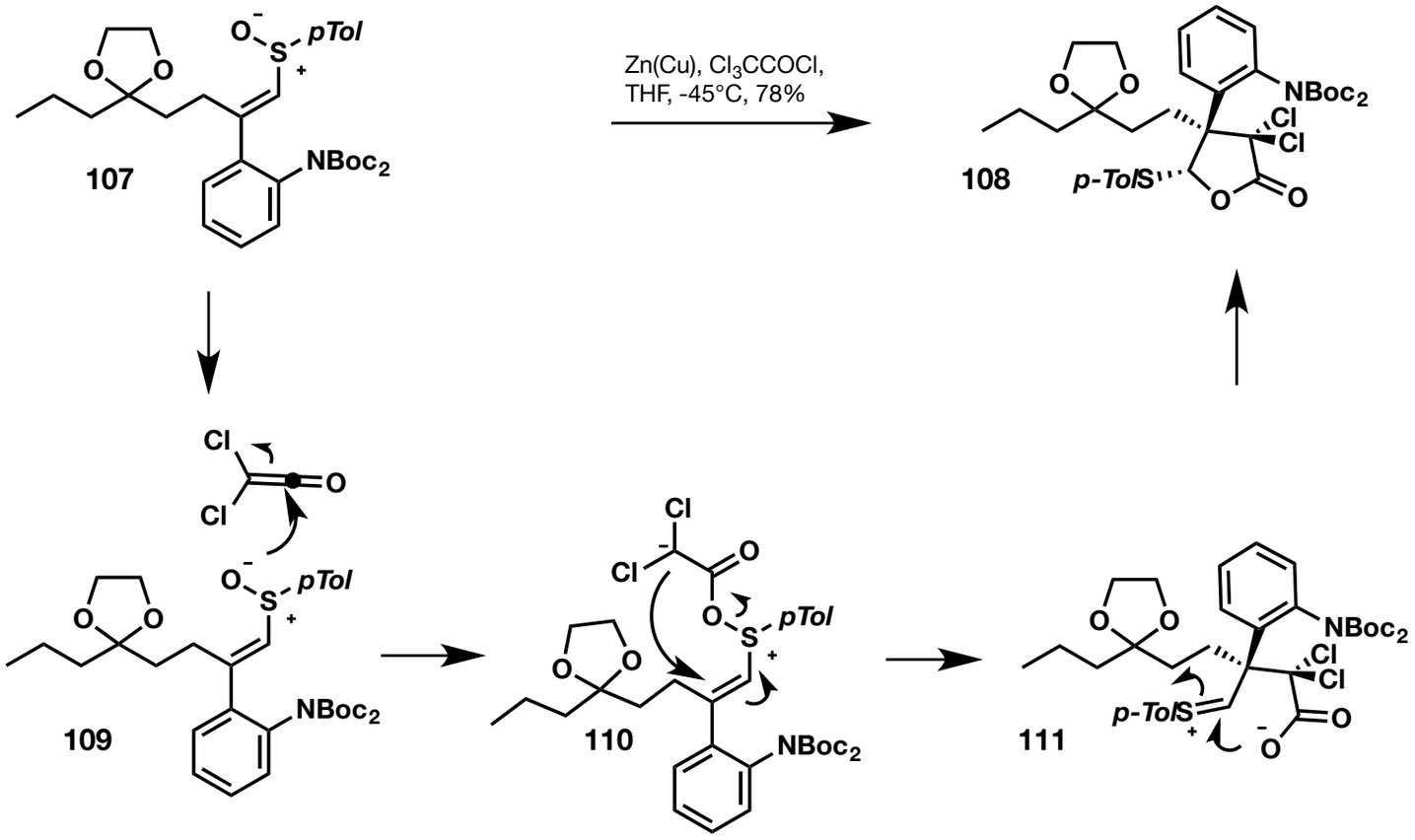
102 **103** **104**

Marino Group: (+) Apsidospermidine

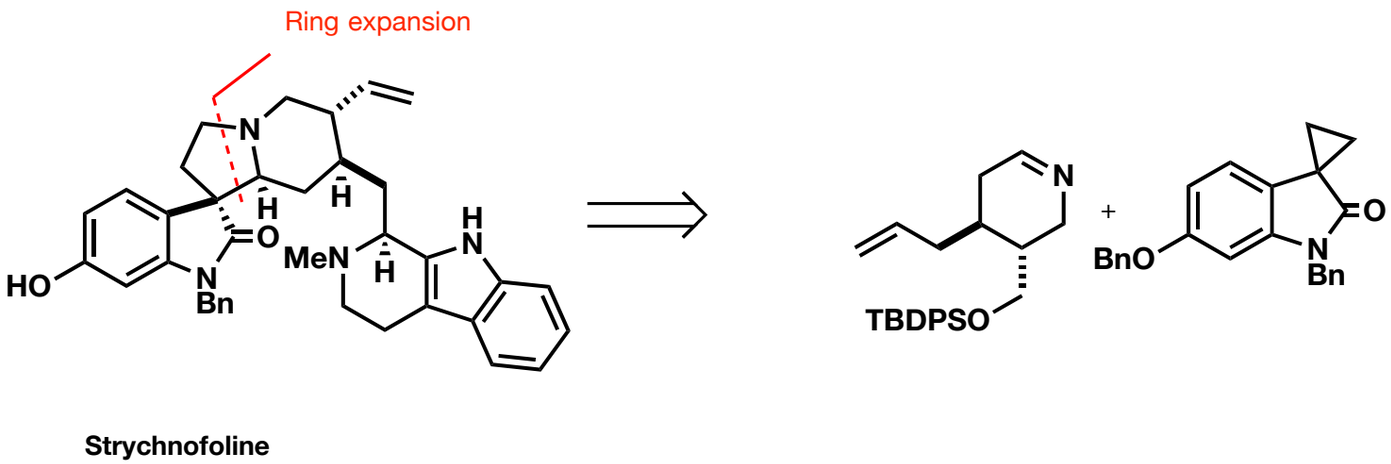


- <u>Key step:</u>
  [3,3]-sigmatropic rearrangement with of chiral vinyl sulfoxid with a ketene

J. Am. Chem. Soc. **2002**, *124,13398.*



Careirra Group: Strychnofoline

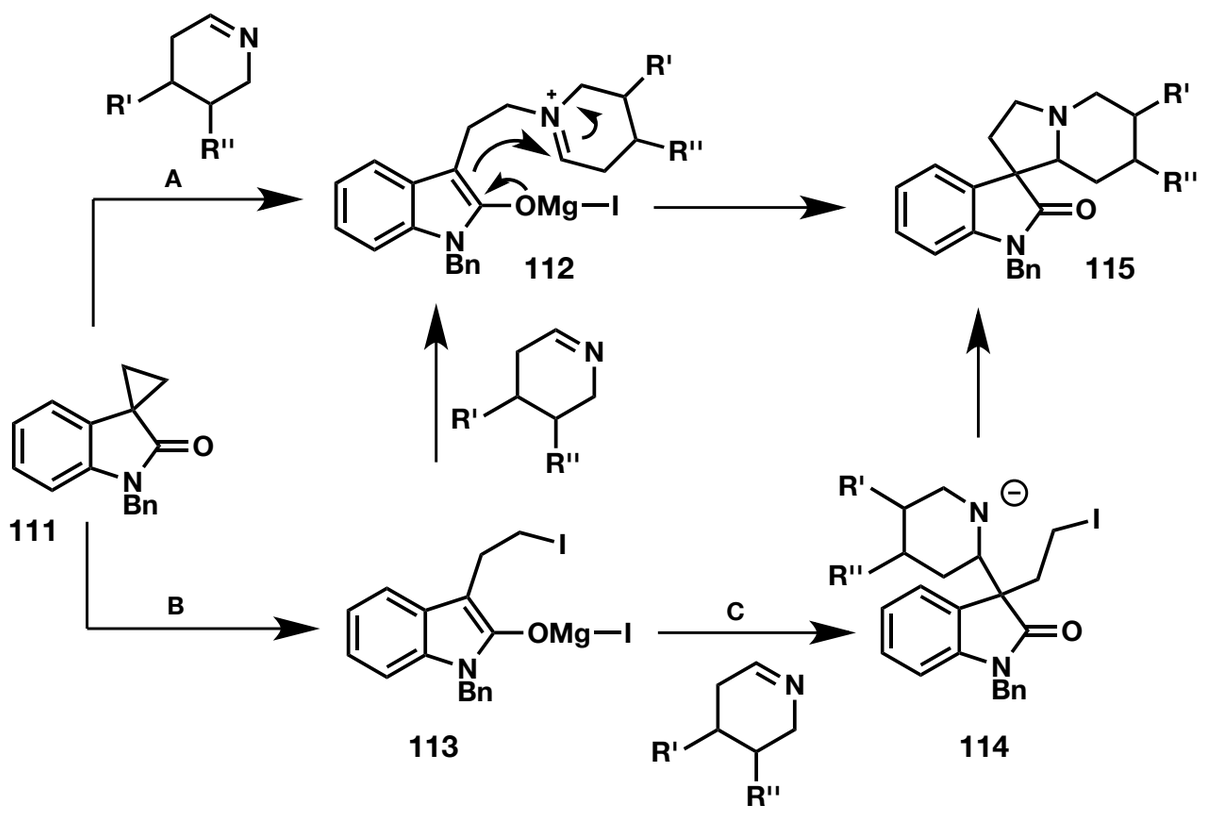


Strychnofoline

J. Am. Chem. Soc. **2002**, *124,14826.*

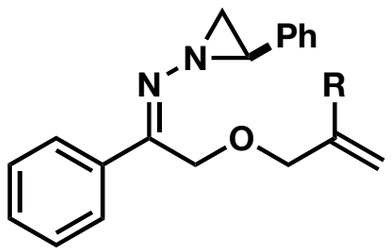
- <u>Key step:</u>
  Ring expansion reaction

Proposed pathways:

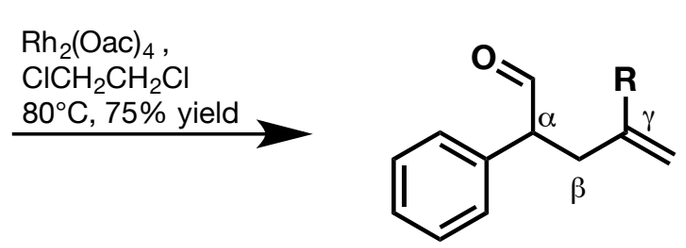


Methodology

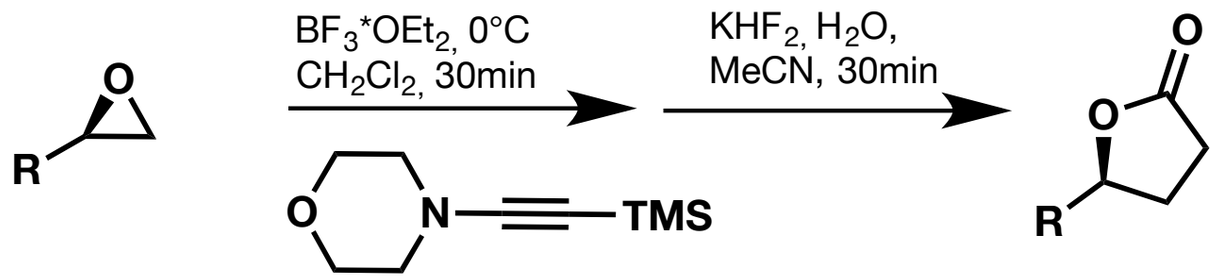
JACS 2002



Eschenmoser hydrazone



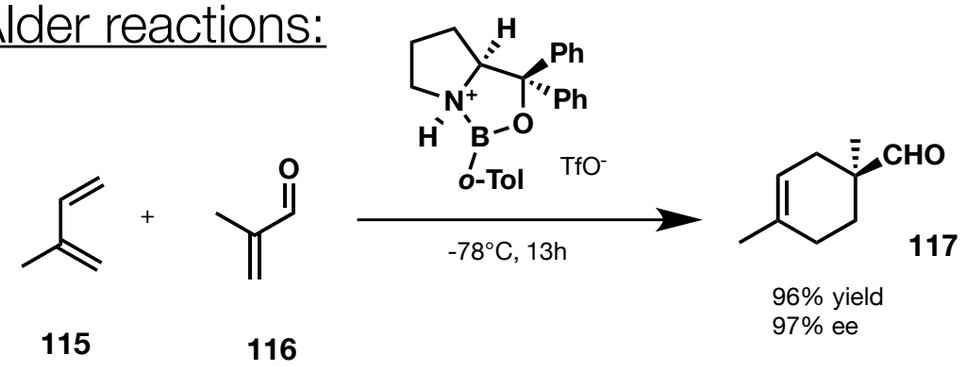
dr = 3:1 up to > 20:1



JACS 2002: Methodology

1) <u>Oxazaborolidines in enantioselective Diels-Alder reactions:</u>

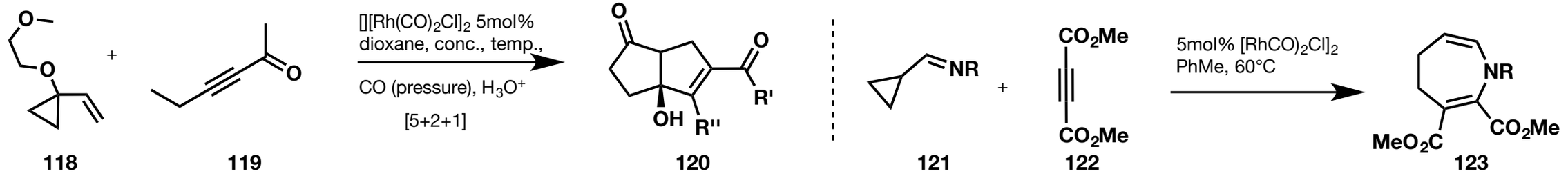
- broad substrate scope
- high ee values



J. Am. Chem. Soc. **2002**, *124, 9992.*

2) <u>Wender</u>

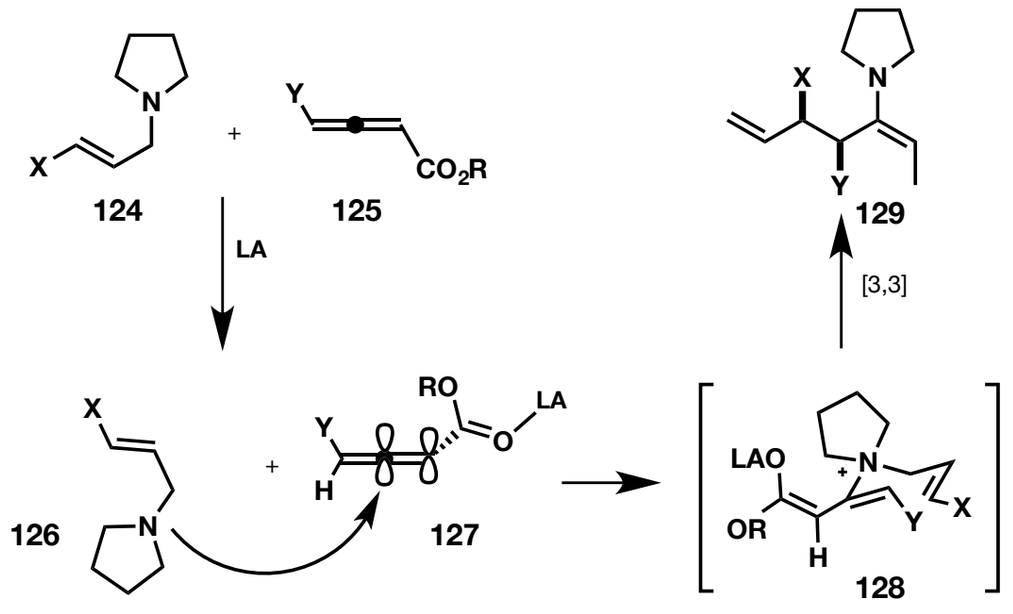
- [5+2+1] Cycloaddition
- Aza-[5+2] Cycloaddition



J. Am. Chem. Soc. **2002**, *124, 2876.*

3) <u>Allenoate-Claise Rearrangement</u>

- addition across H —> (*E*) - enamine favored
- depending on (*E*) vs. (*Z*) in the starting: *anti* vs. *syn*

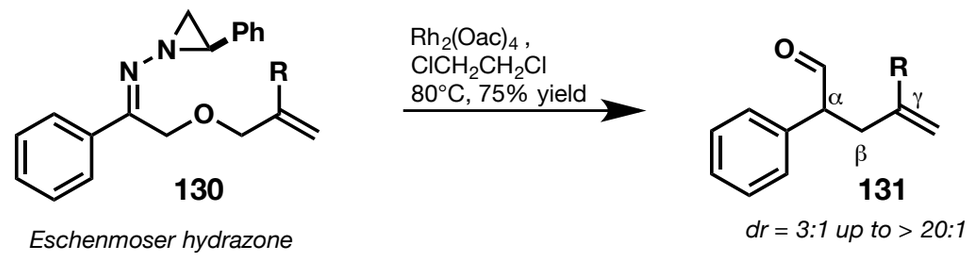


J. Am. Chem. Soc. **2002**, *124, 13646.*

Tandem Rh-catalyzed Bamford-Stevens/Claisen rearrangement sequence

Synthesis of α, γ – unsatured aldehydes

- modification of the *Claisen* rearrangement
- improvement: stereoselective preparation of (Z)-isomer
- utilization of non-carbonyl stabilized diazo compounds
- works in high *dr*, good yields and a broad range of substrates (R = H, Ar, alkyl, acyclic, cyclic)
- Retron: *Eschenmoser* hydrazone

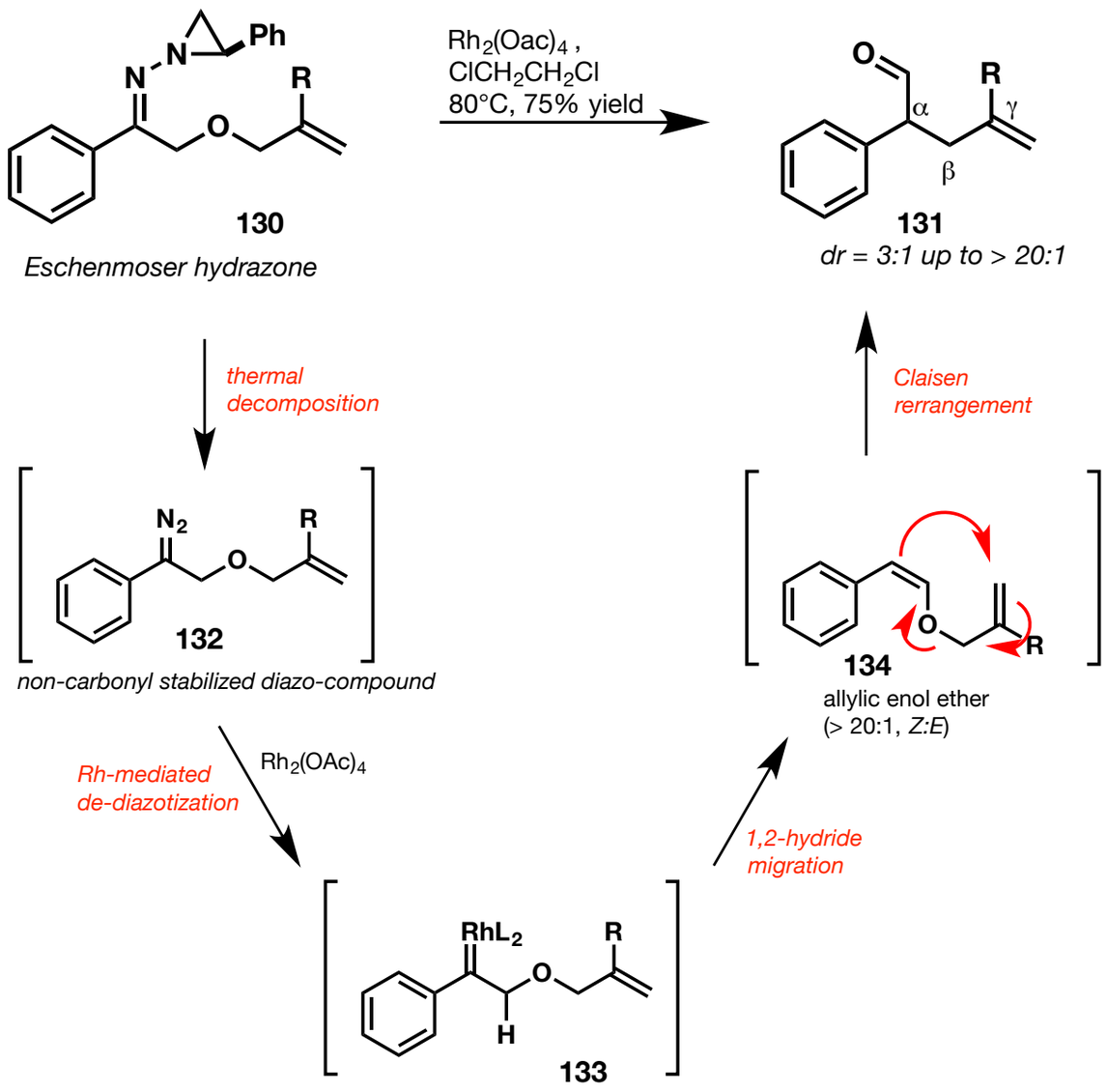


Eschenmoser hydrazone

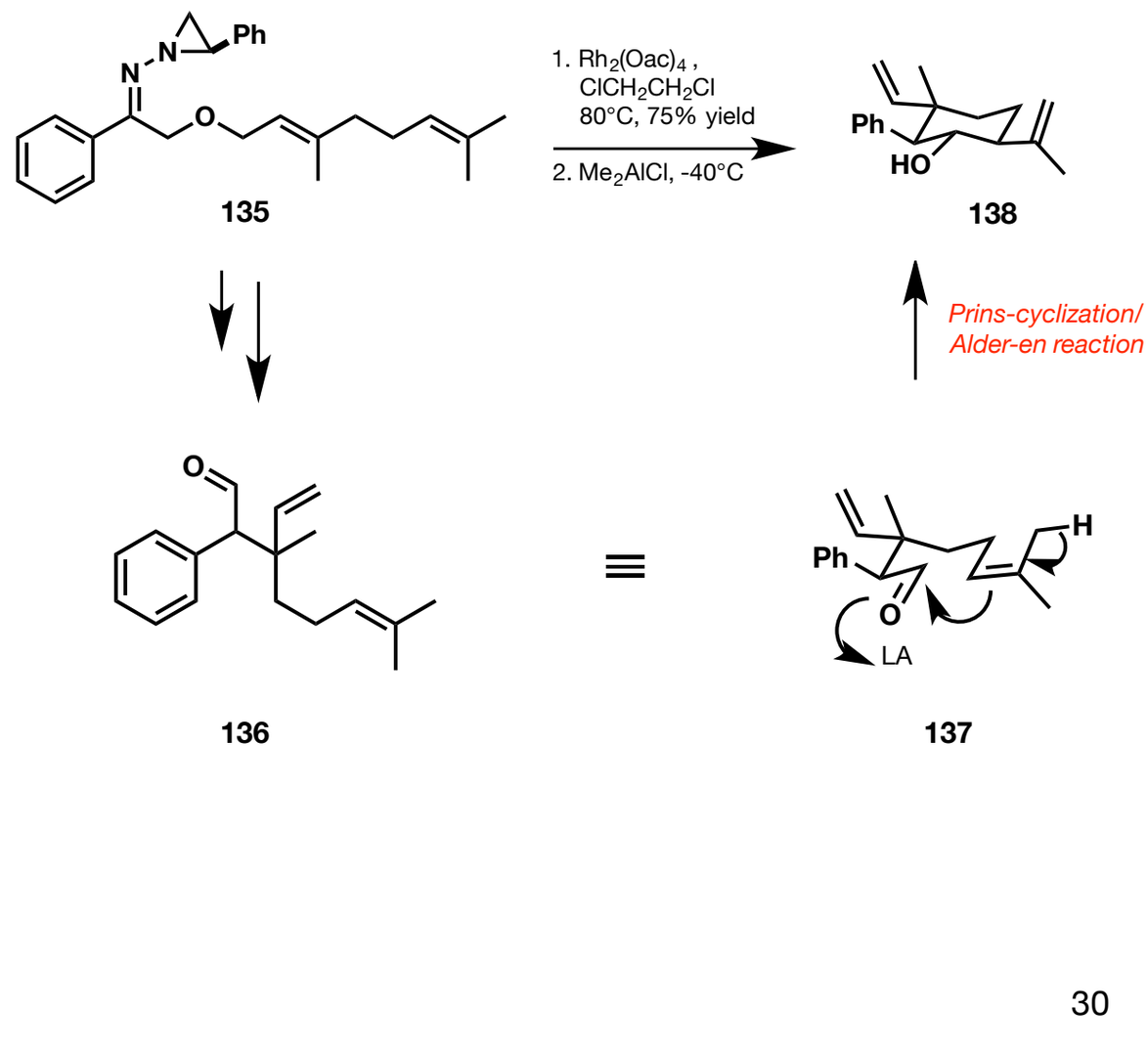
dr = 3:1 up to > 20:1

J. Am. Chem. Soc. **2002**, *124*, 12426.

Proposed mechanism:

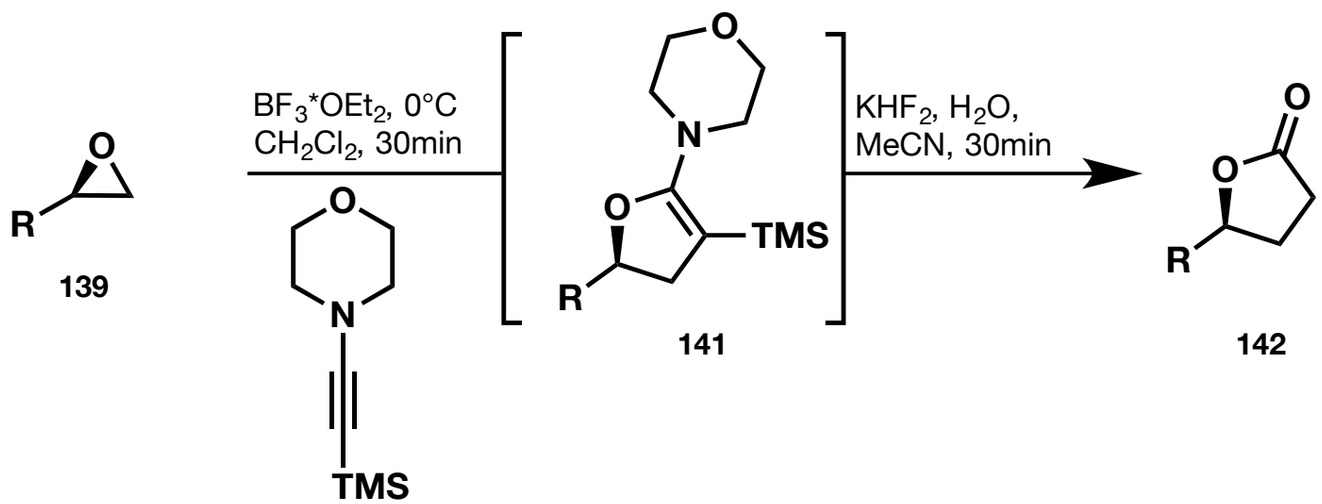


Nice feature:



Conversion of terminal epoxides into γ-butanolides

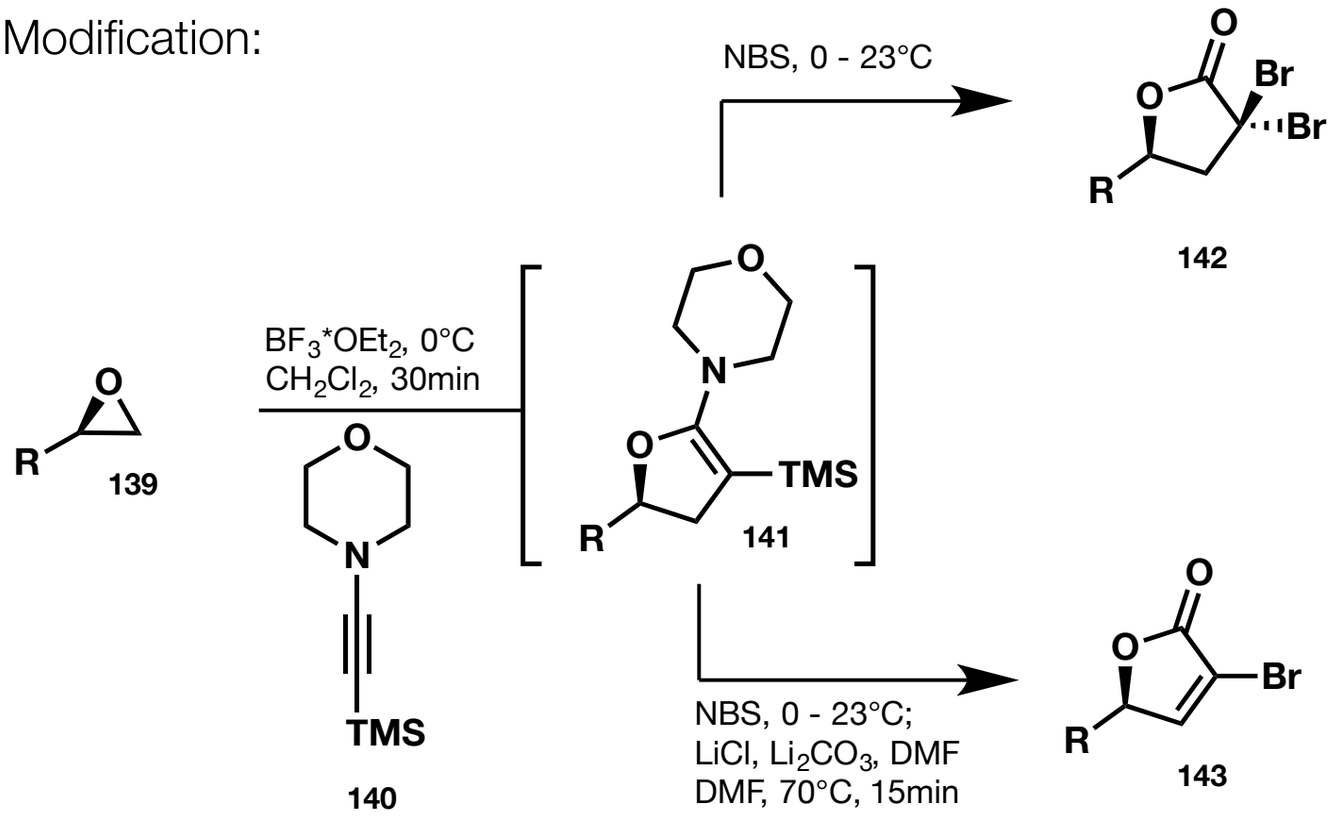
- single step: Lewis acid-mediated epoxide opening of 1-morpholino-2-trimethylsilyl acetylene
- mild reaction conditions
- enantiomerically enriched epoxides can be converted into enantiomer pure γ-butanolides without loss of optical purity



R = allyl, -OPh, different alcohols, alkylhalides, esters, ….

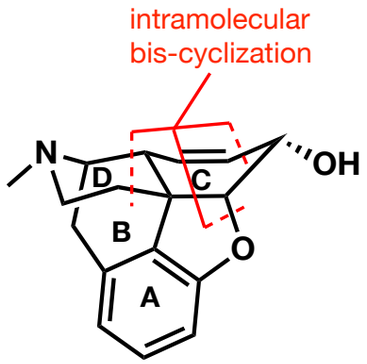
J. Am. Chem. Soc. **2002**, *124*, 2457

Modification:

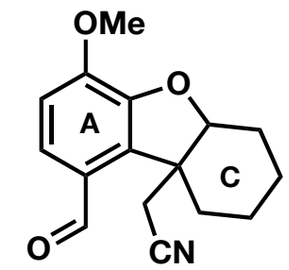


Thank you for your kind attention!

D. F. Taber: (-) Morphine



(-) Morphine



D. F. Taber: 23 (27) steps, 0.77 %

- Key step:

intramolecular bis-cyclization

J. Am. Chem. Soc. **2002**, *124*, 12416.