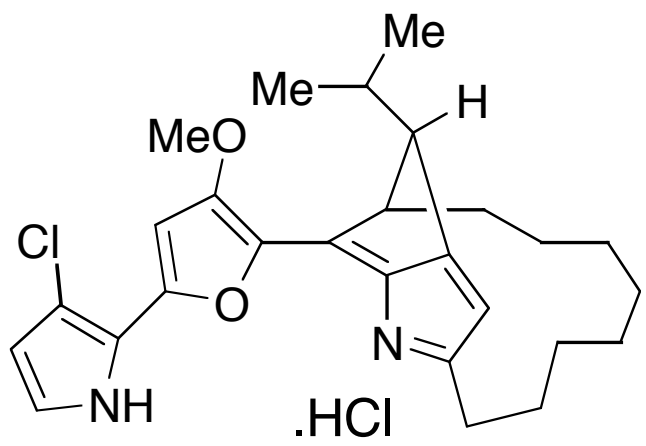
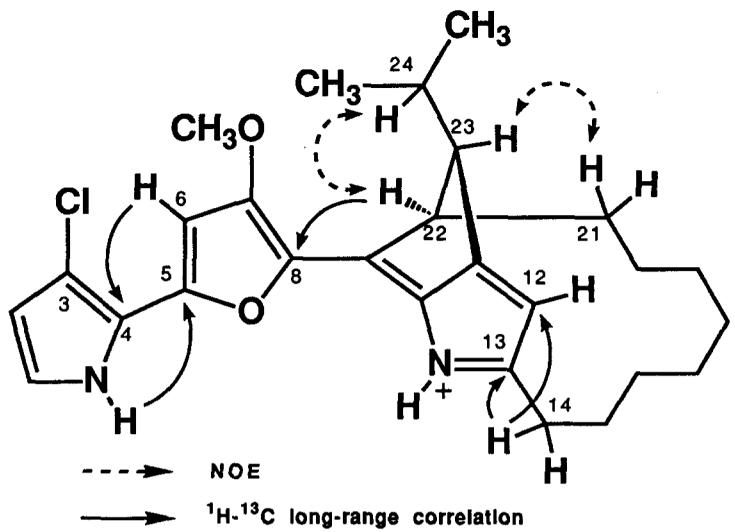
Selected Syntheses of Roseophilin

Tommy Bui
02-10-04



Isolation of Roseophilin and Its Biological Activities

- Isolated from the culture broth of Streptomyces griseoviridis in 1992
- Molecular formula: $C_{27}H_{33}ClN_2O_2$, m/z 453.2303, MH^+
- Structural determination by NMR spectroscopy
- Relative stereochemistry was established by NOEs
- Absolute configuration was determined through synthesis.

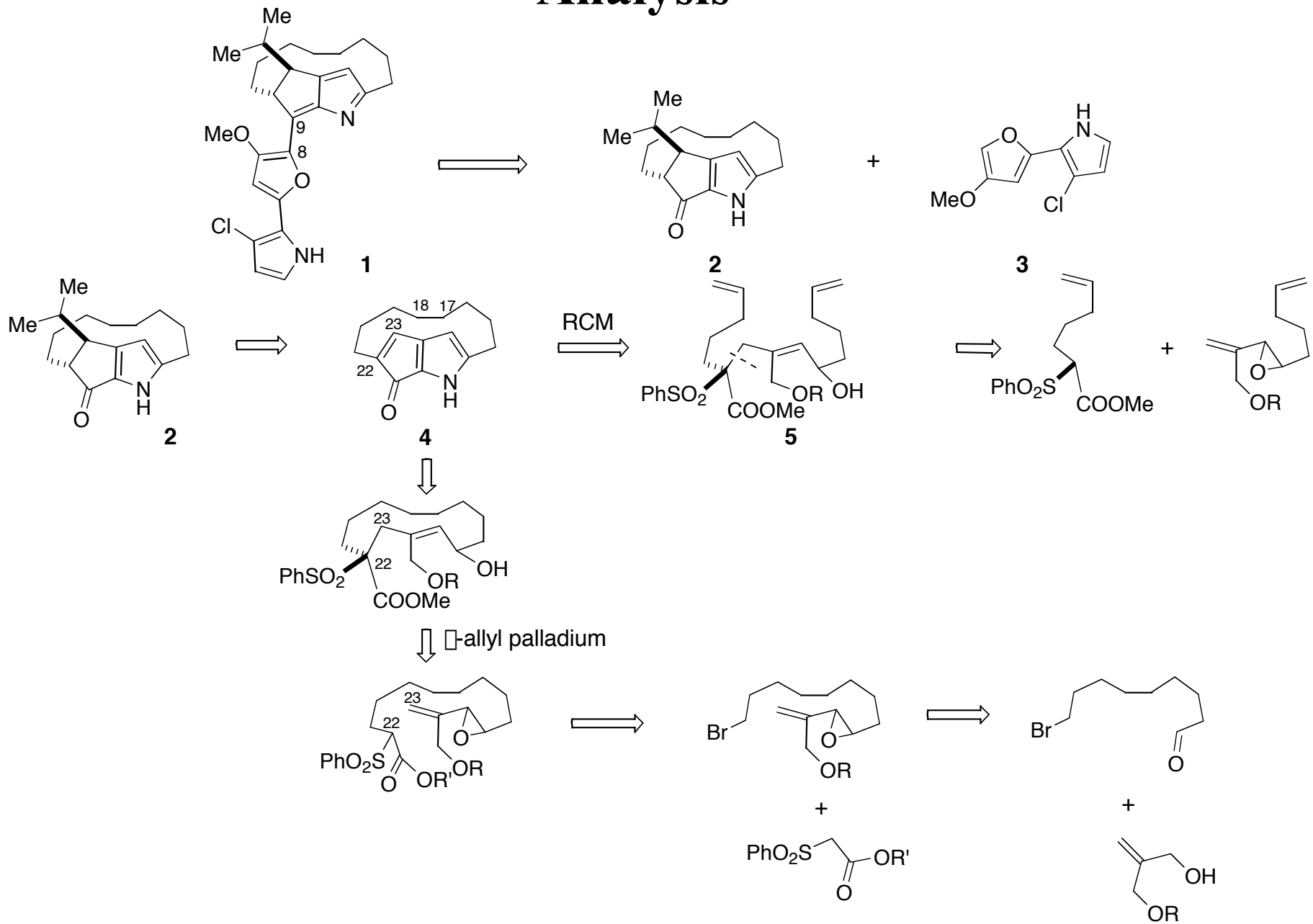


- Showed strong cytotoxicity against human leukemia cells (IC_{50}, 0.34 μM) and human carcinoma cells (IC_{50}, 0.88 μM).

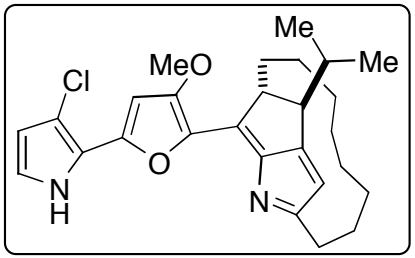
- The mechanism of action is still unknown.

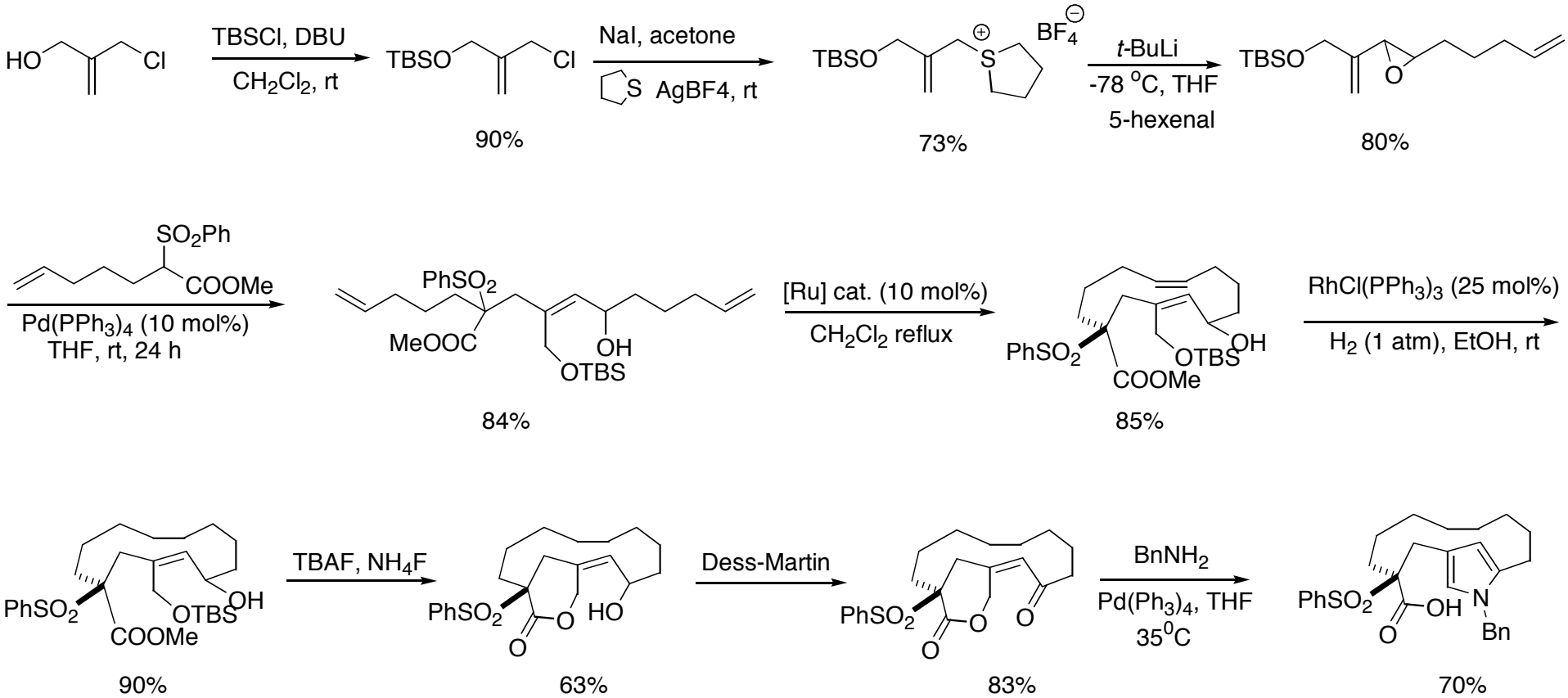
Seto, H. et al. *Tetrahedron Lett.* 1992, 33, 2701

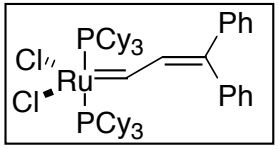
Furstner's Synthesis of Roseophilin: Retro Synthetic Analysis



Furstner Synthesis: Forward Synthesis 1

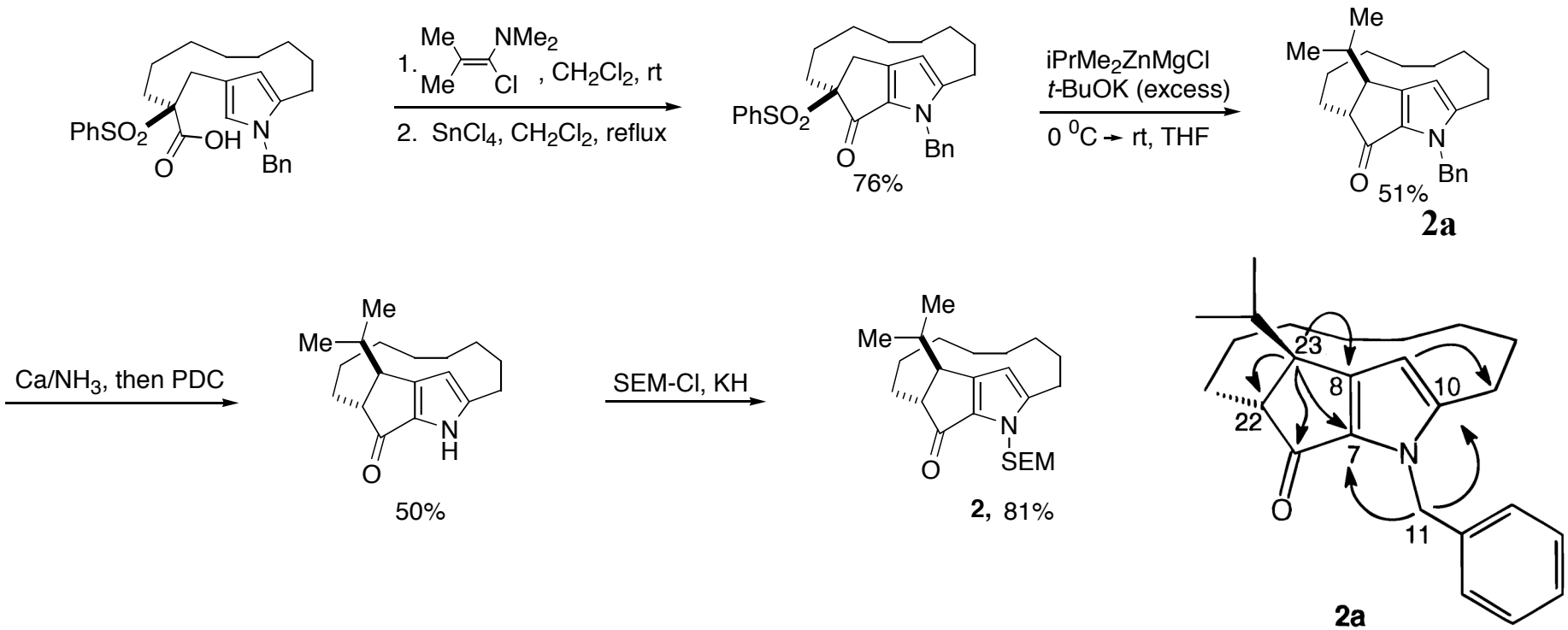




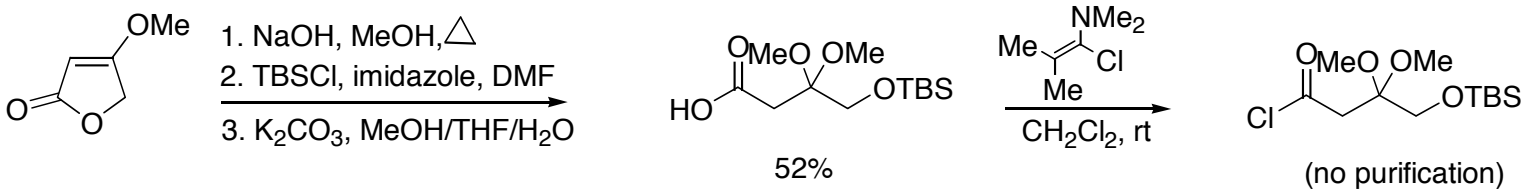


Furstner, A. et al. *J. Am. Chem. Soc.* 1998, 120, 2817.

Furstner Synthesis: Forward Synthesis 2



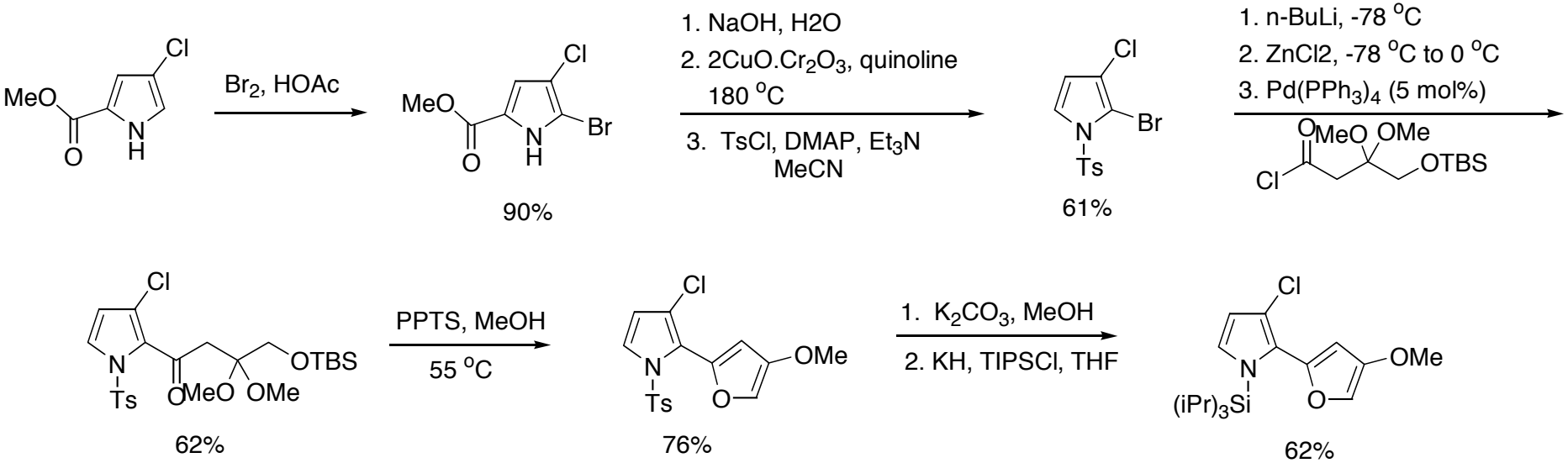
Synthesis of pyrrolylfuran:



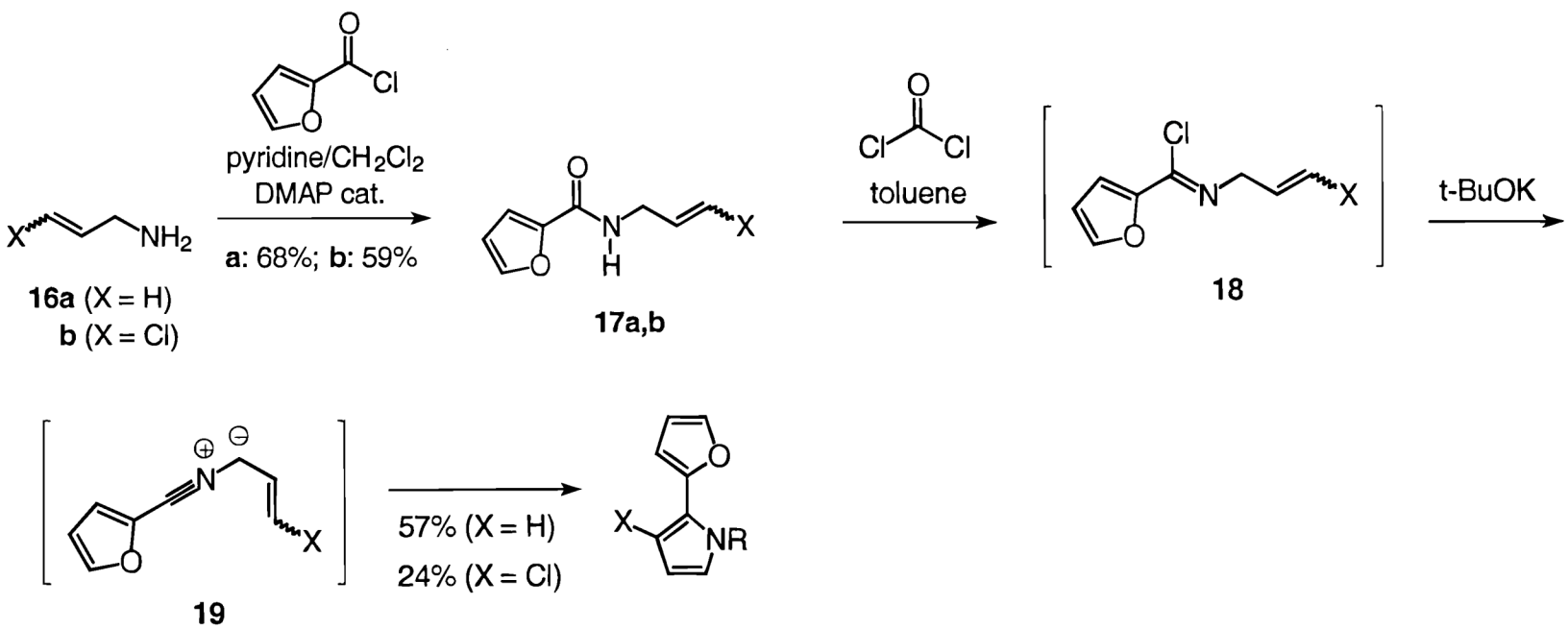
Furstner, A. et al. *J. Am. Chem. Soc.* 1998, 120, 2817.

Furstner, A. et al. *J. Org. Chem.* 1999, 64, 2361.

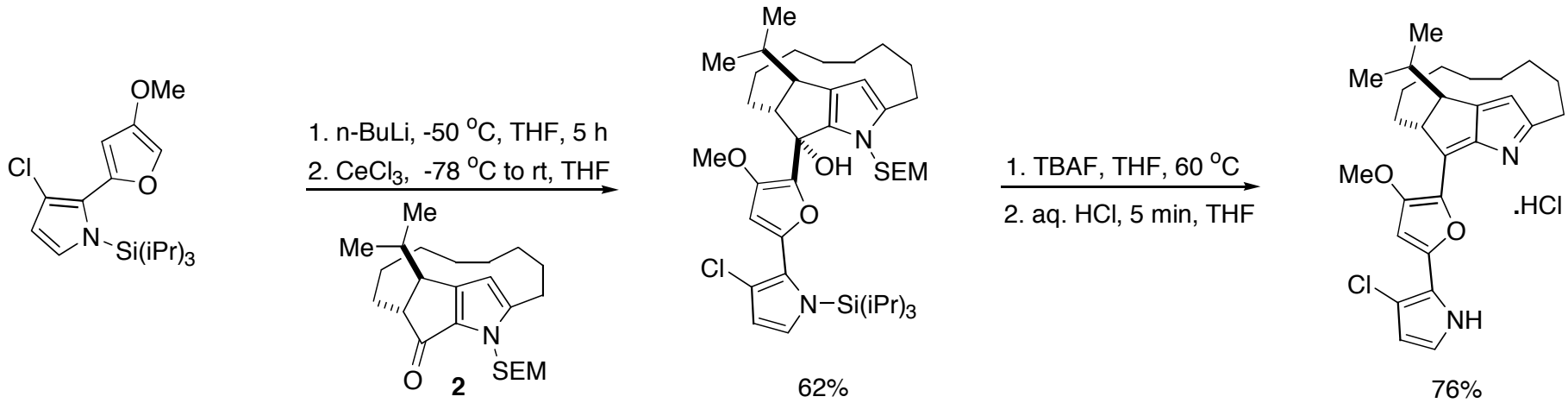
Furstner Synthesis: Forward Synthesis 3



Alternative synthesis of pyrrolylfuran derivatives:

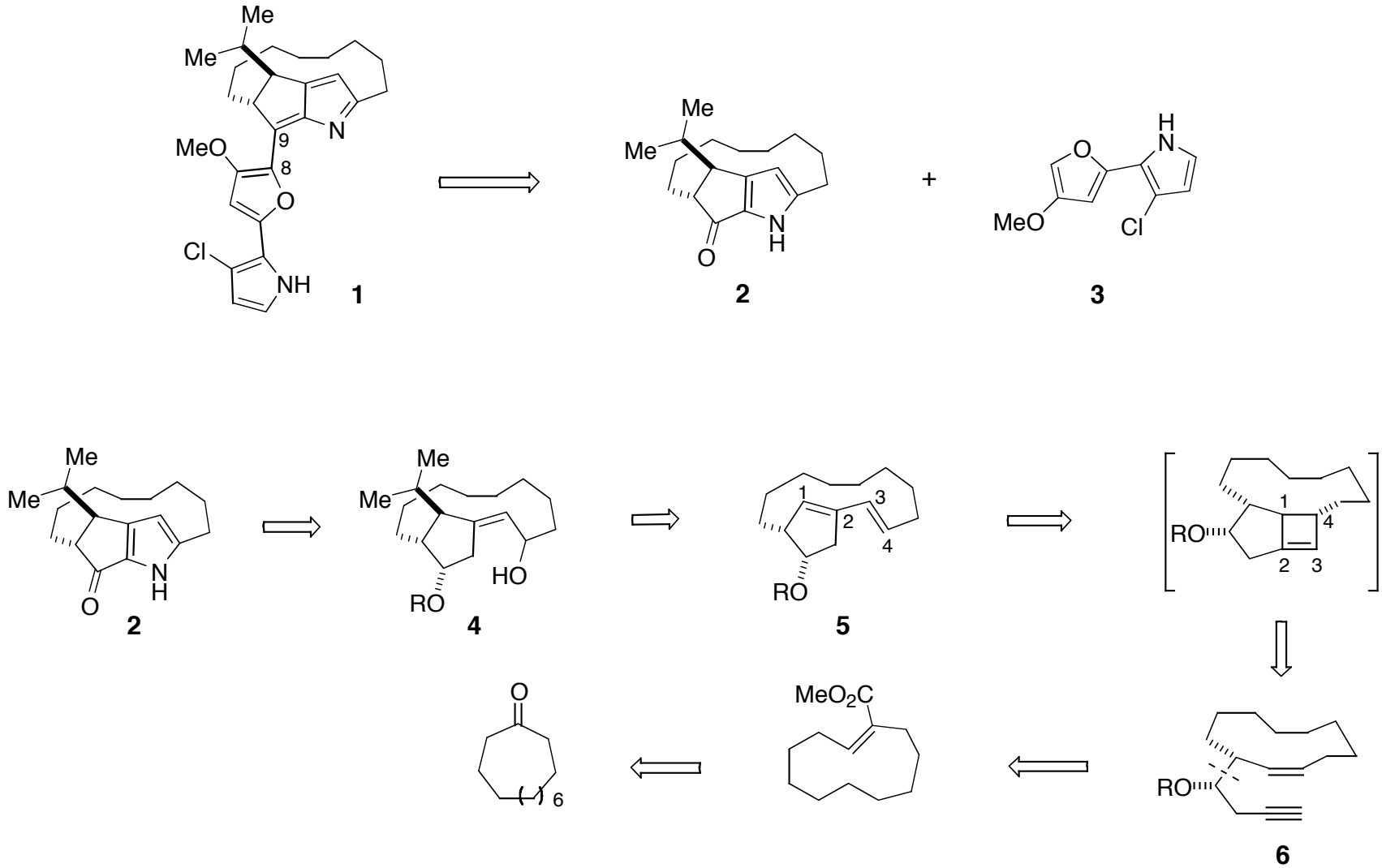


Completion of the Total Synthesis



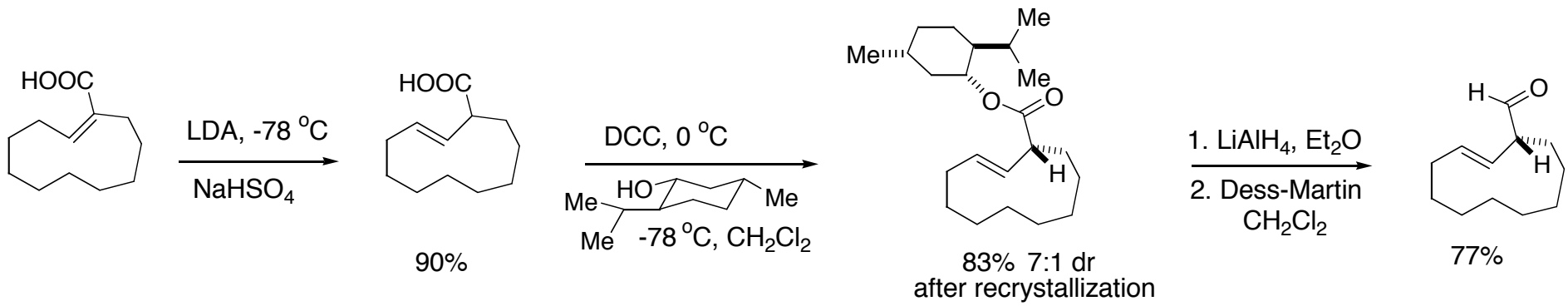
Less than 1% overall yield
Total of 29 steps from known start
7.4 mg isolated yield

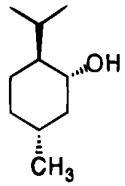
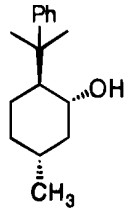
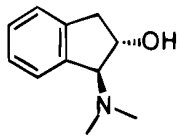
Trost Formal Synthesis of Roseophilin: Retro Synthesis



Trost Synthesis: Forward Synthesis 1

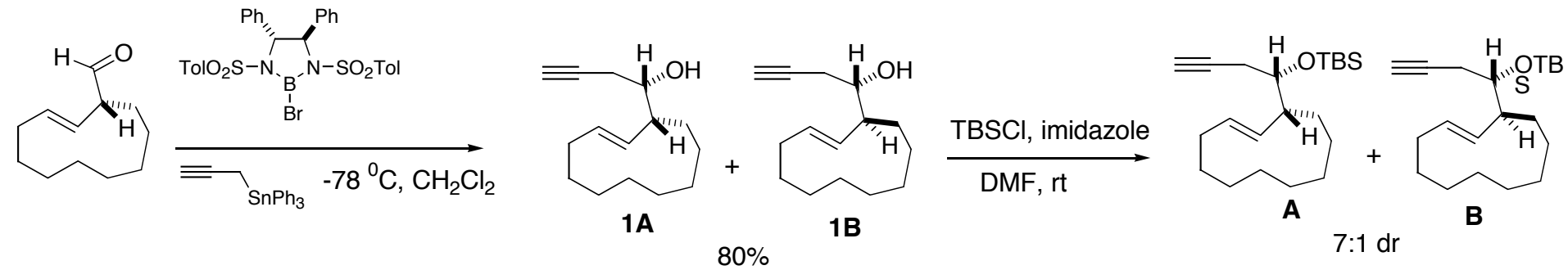
Asymmetric synthesis of the macrocyle:

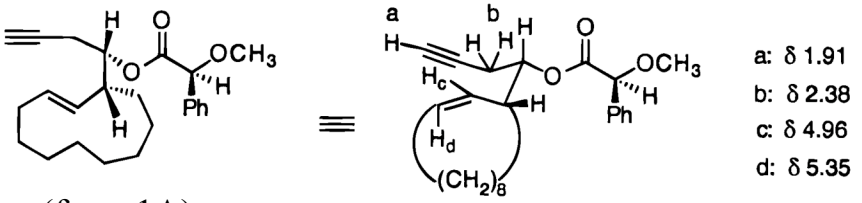


Entry	ROH	Solvent	Temp (°C)	dr
1		CH_2Cl_2	0°	3.8:1
		CH_2Cl_2	-78°	4.7:1
		pentane	-78°	1.5:1
2		CH_2Cl_2	0°	1.5:1
3		CH_2Cl_2	0°	1.5:1

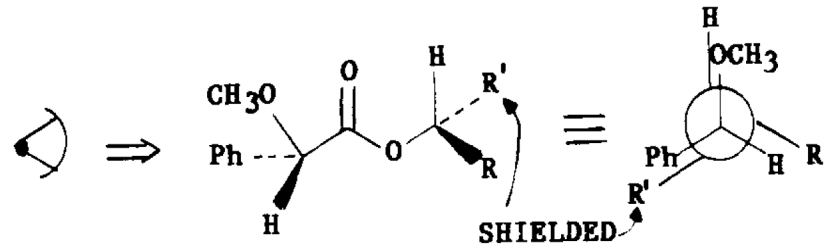
Trost, B. M. et al. *J. Am. Chem. Soc.* 2000, 122, 3801.

Trost Synthesis: Forward Synthesis 2

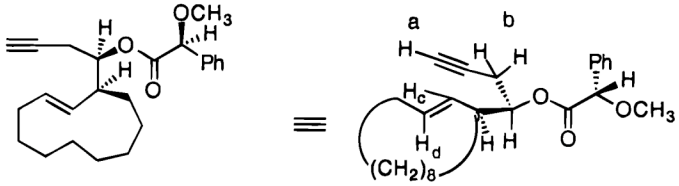




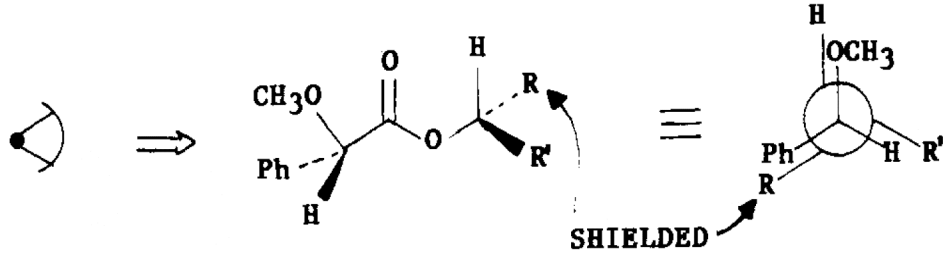
(from 1A)



1



(from 1B)

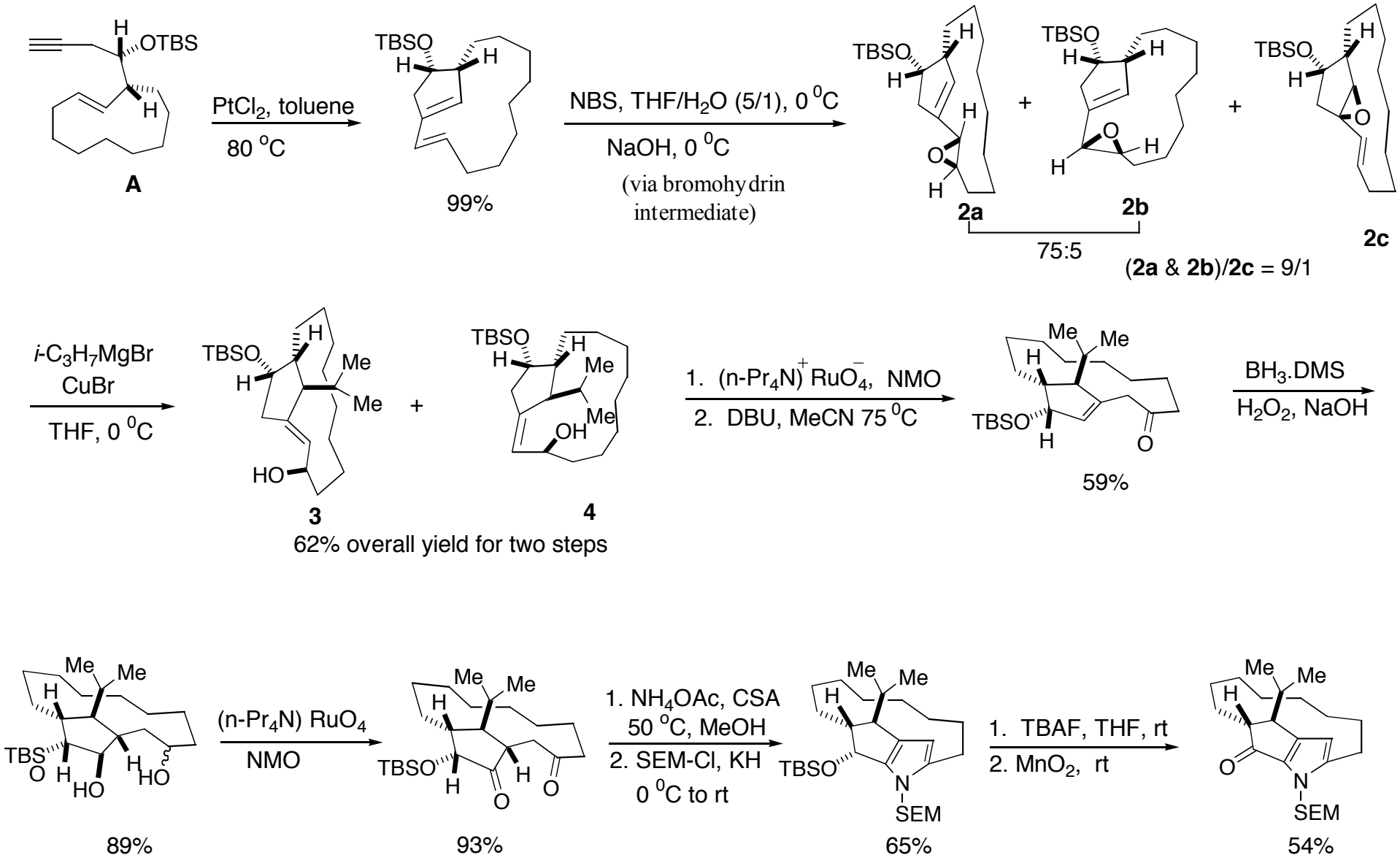


2

Trost, B. M. et al. *J. Am. Chem. Soc.* 2000, 122, 3801.

Trost, B. M. et al. *J. Org. Chem.* 1986, 51, 2370.

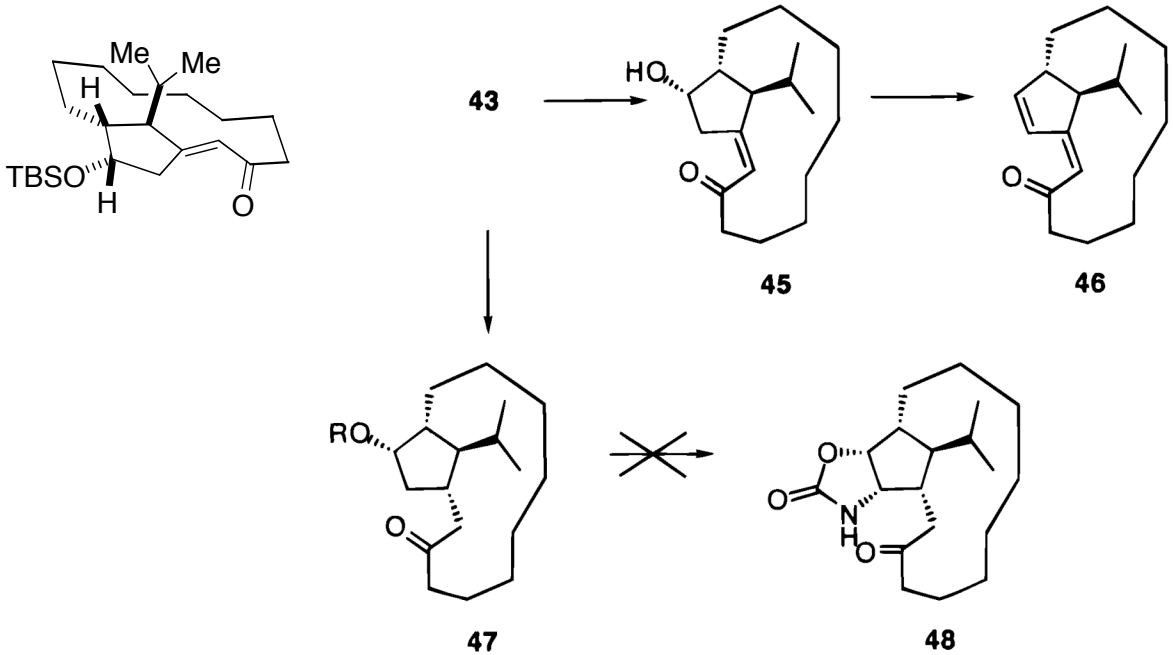
Trost Synthesis: Forward Synthesis 3



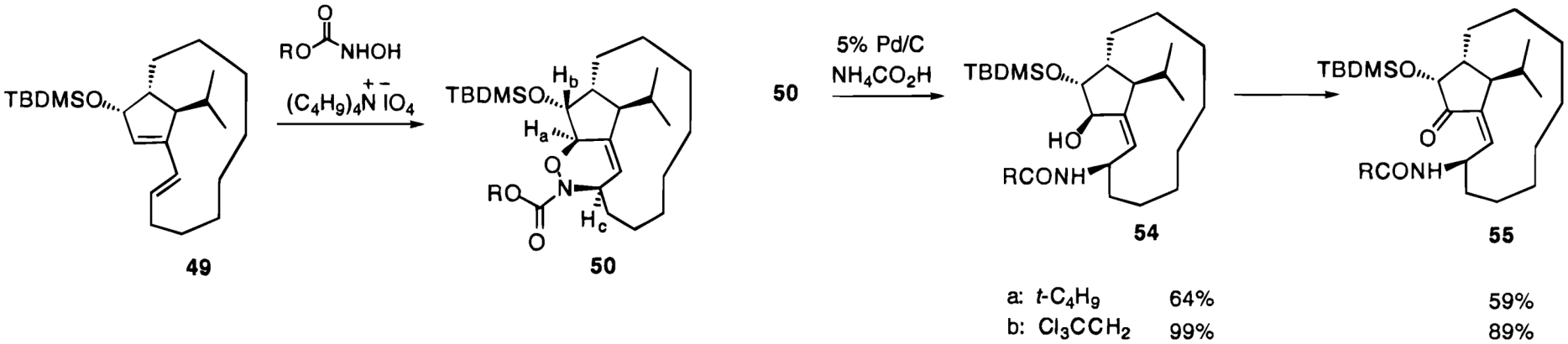
Trost, B. M. et al. *J. Am. Chem. Soc.* 2000, 122, 3801.

Trost Synthesis: Other Failed Attempt to Synthesize the Pyrrole Unit

C-H insertion of acylnitrene:

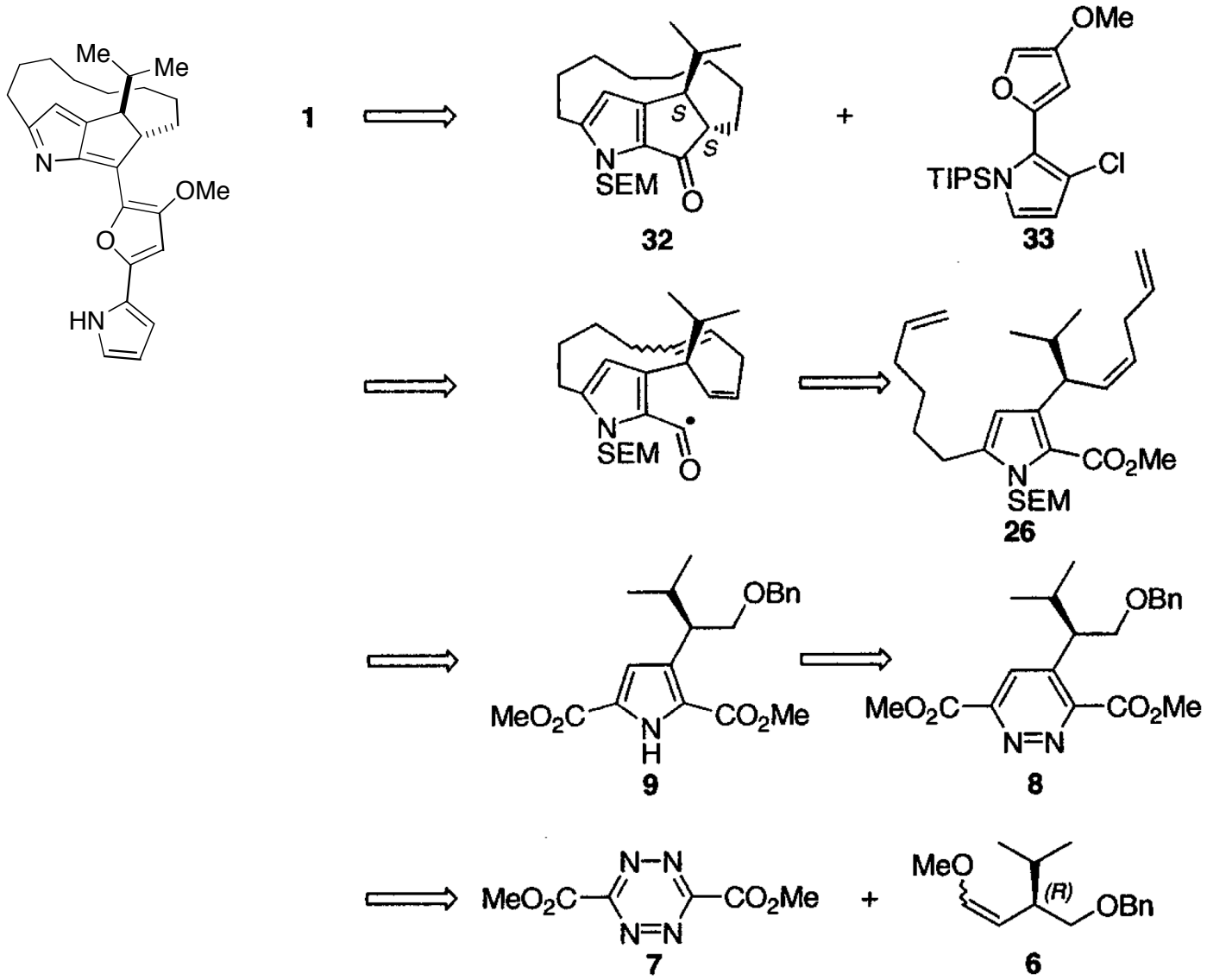


Hetero Diels-Alder reaction:

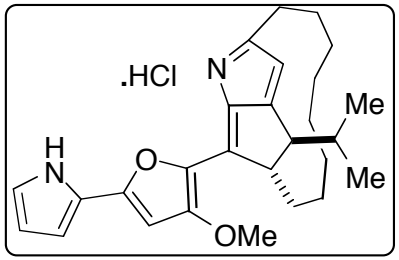


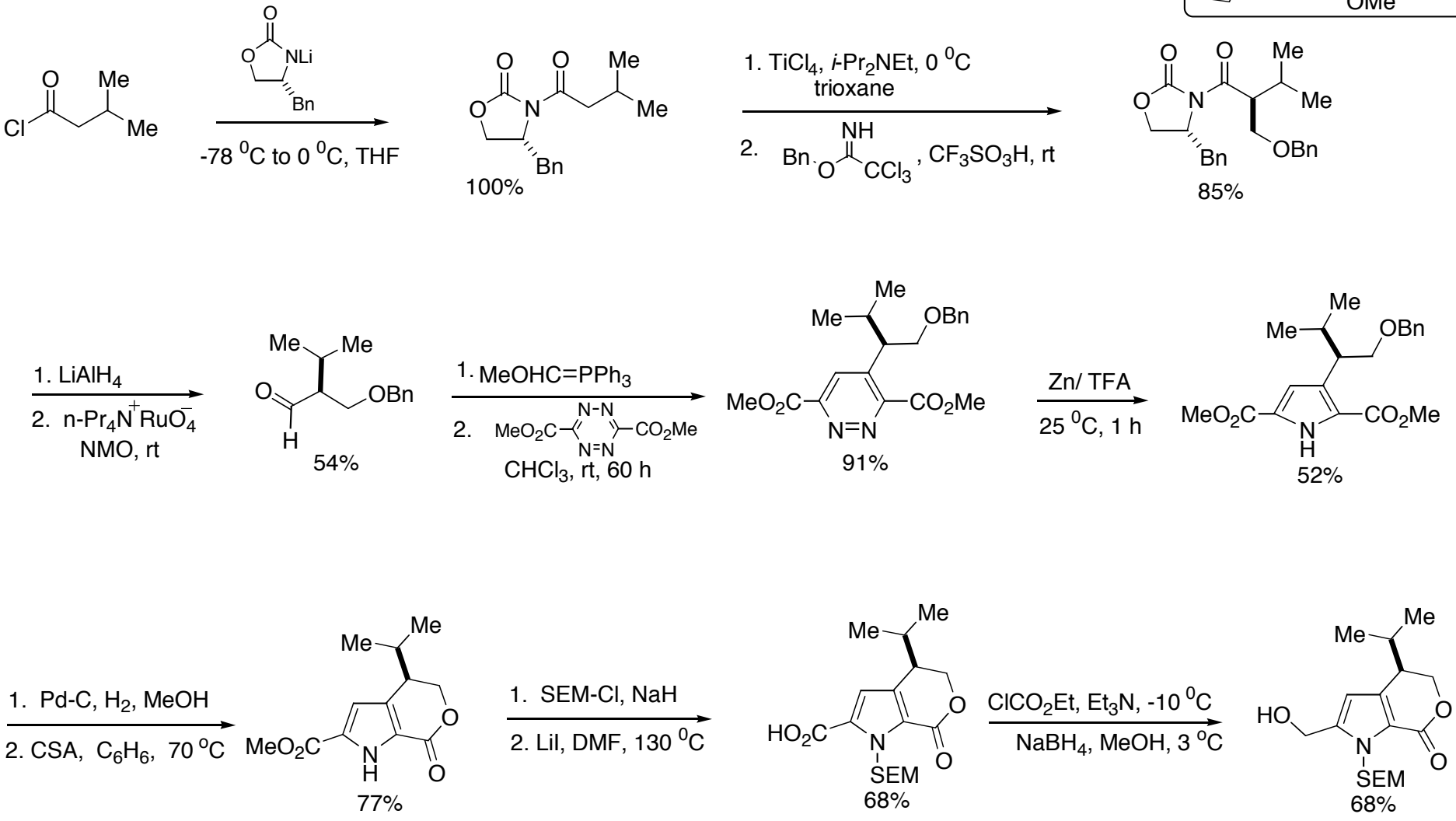
Trost, B. M. et al. *J. Am. Chem. Soc.* 2000, 122, 3801.

Asymmetric Synthesis of Roseophilin: Retro Synthetic Analysis



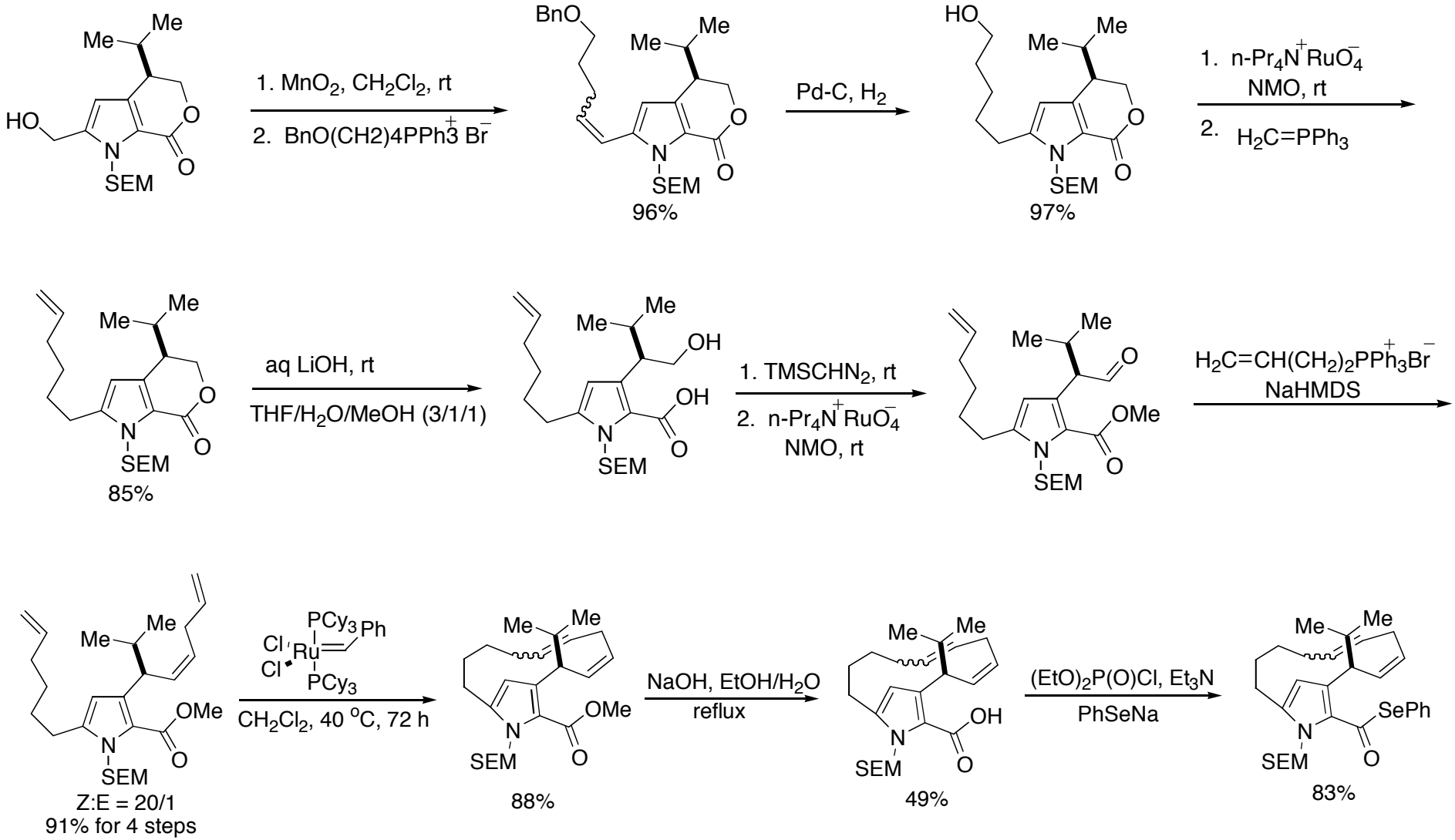
Boger Synthesis: Forward Synthesis 1





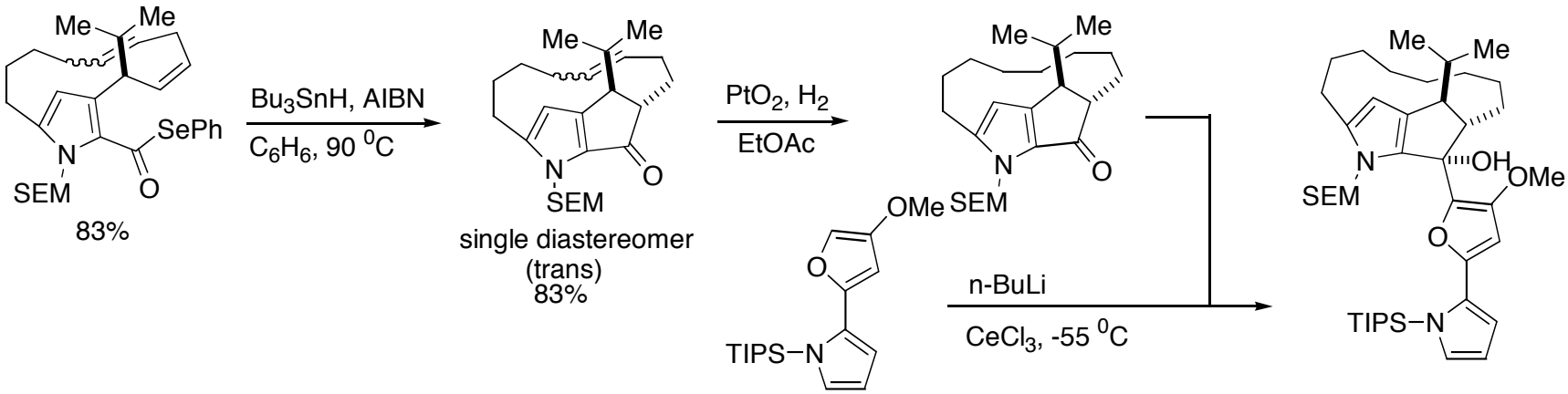
Boger, D.L. et al. *J. Am. Chem. Soc.* 2001, 123, 8515.

Boger Synthesis: Forward Synthesis 2



Boger, D.L. et al. *J. Am. Chem. Soc.* 2001, 123, 8515.

Boger Synthesis: Forward Synthesis 3



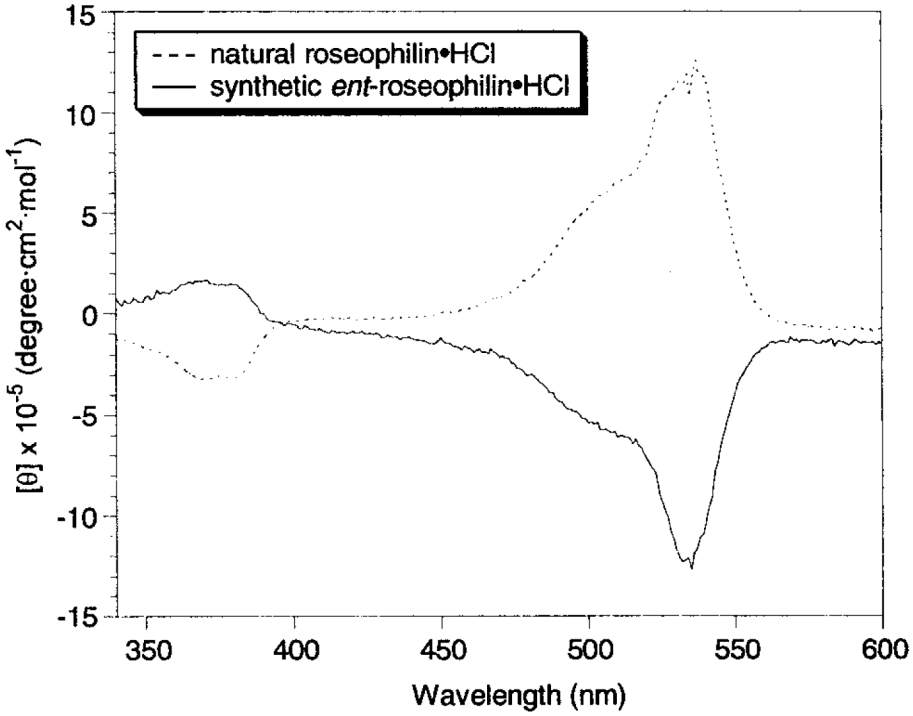


Figure 2. CD spectrum of (+)-**1**·HCl and *ent*-(−)-**1**·HCl in MeOH.

$[\alpha]_D^{25}$ = -5100, (MeOH) synthetic roseophilin

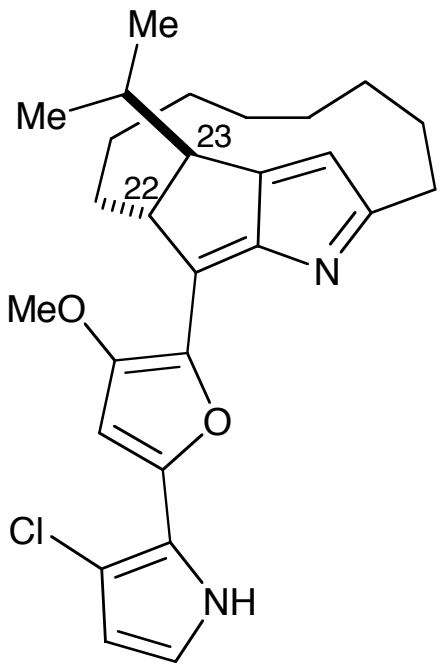
$[\alpha]_D^{25}$ = + 5500, (MeOH) natural roseophilin

Boger, D.L. et al. *J. Am. Chem. Soc.* 2001, 123, 8515.

Summary

Furstner's synthesis:

C22-C23 bond: π allyl palladium chemistry
Pyrrole moiety: π allyl palladium chemistry
Isopropyl group: cuprate addition
The marcrocycle: employed either RCM or
π allyl palladium chemistry
Bicyclic azafulvene: made from a keto pyrrole
precursor



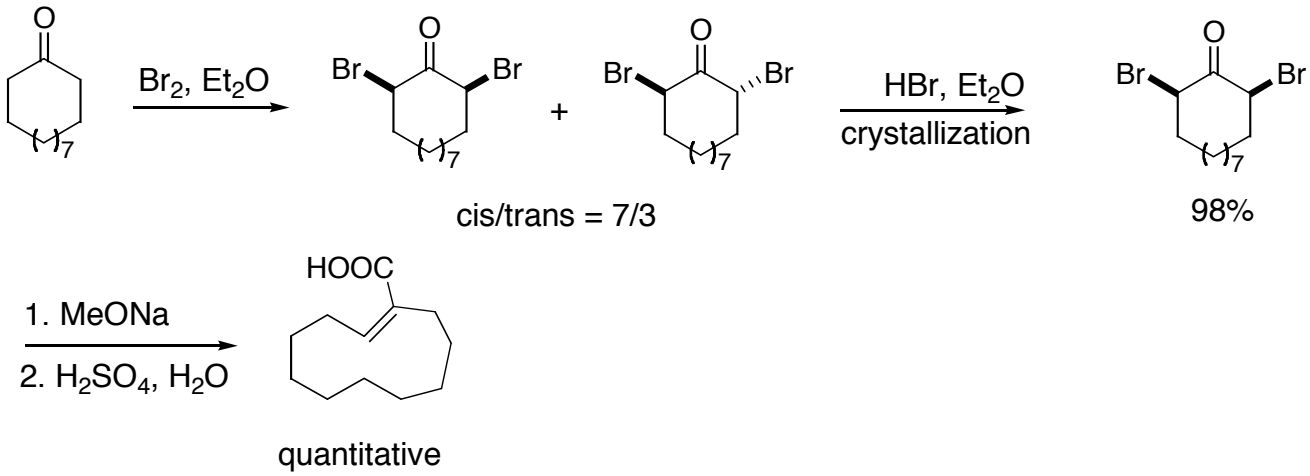
Trost's synthesis:

Pyrrole moiety: Paal Knor condensation
Isopropyl group: cuprate addition
The marcrocycle: enyne metathesis (ring expansion).

Boger's synthesis:

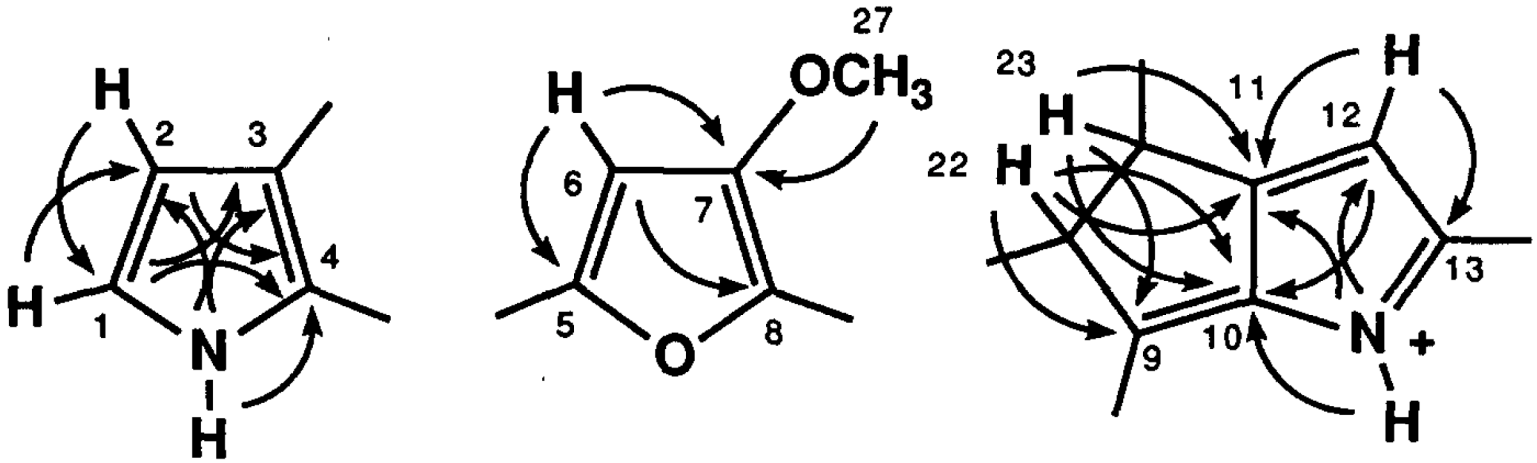
Pyrrole moiety: inverse electron demand Diels Alder reaction
Pyrrolyl cyclopentanone: acyl radical-alkene cyclization
Isopropyl group: cuprate addition
The marcrocycle: employed RCM
Established the absolute configuration of the natural product.

Synthesis of Macrocycle



Garbisch, E. W. JOC 1968, 33, 2157

1H-13C Long-Range Correlations



HOBr cis 1,4 additions