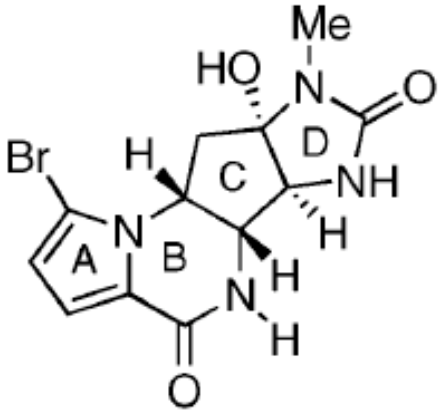
Asymmetric Total Synthesis of (-)-Agelastatin A Using Sulfinimine (*N*-Sulfinyl Imine) Derived Methodologies

Presented by: Jie Huang
February 2005



(-)-Agelastatin A **1**

References:

Franklin A. Davis and Jianghe Deng, *Organic Letters*, ASAP
Franklin A. Davis and Jianghe Deng, *Organic Letters*, **2004**, 2789-2792
Franklin A. Davis and Yongzhong Wu, *Organic Letters*, **2004**, 1269-1272

Isolation and Bioactivities

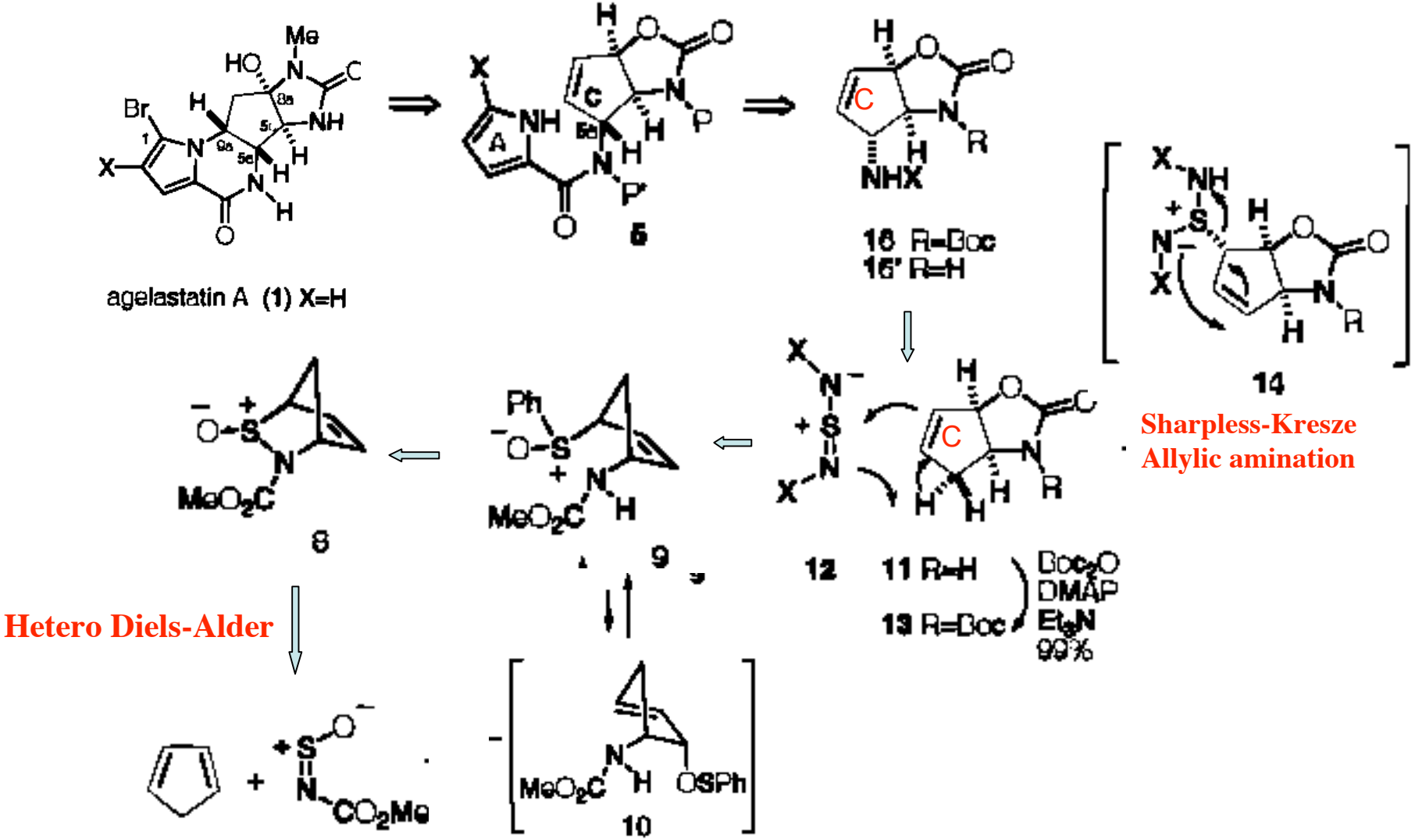
Isolation:

from axinellid marine spong *Agelas Dedromorpha in 1993*
and from West Australian spong *Cymbastela sp*. in 1998

Bioactivities

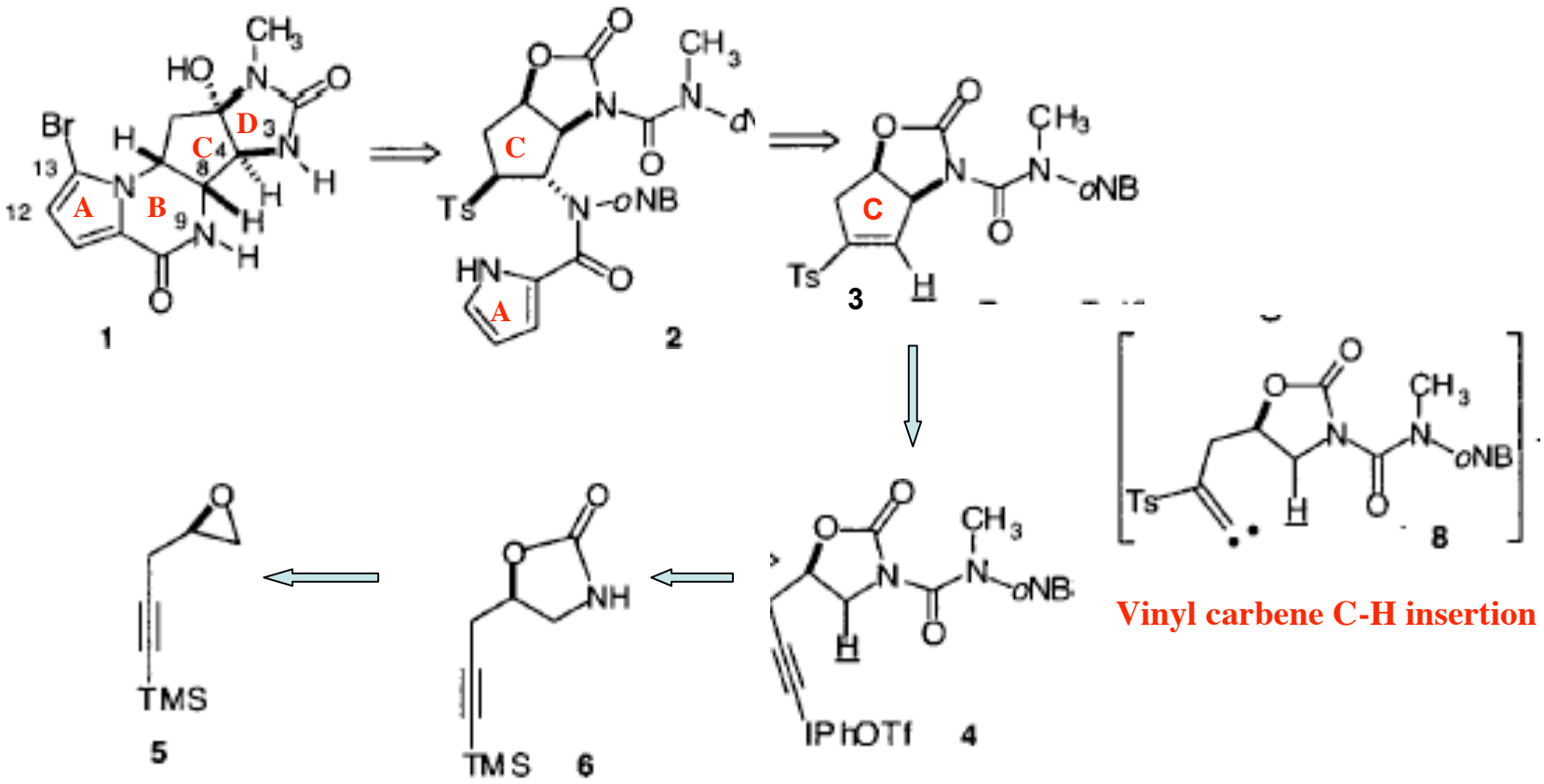
- inhibiting the growth of L1210 Leukemia in mice
- against human KB nasopharyngeal tumor cell lines
- selectively inhibit GSK-3β (Glycogen Synthase Kinase- 3β)
  preventing Alzheimer's disease
  inhibiting neuronal apoptosis after stroke
- functioning as an insulin mimetic
- potent insecticidal activity against beet army worm larvae and corn rootworm

First racemic total synthesis:



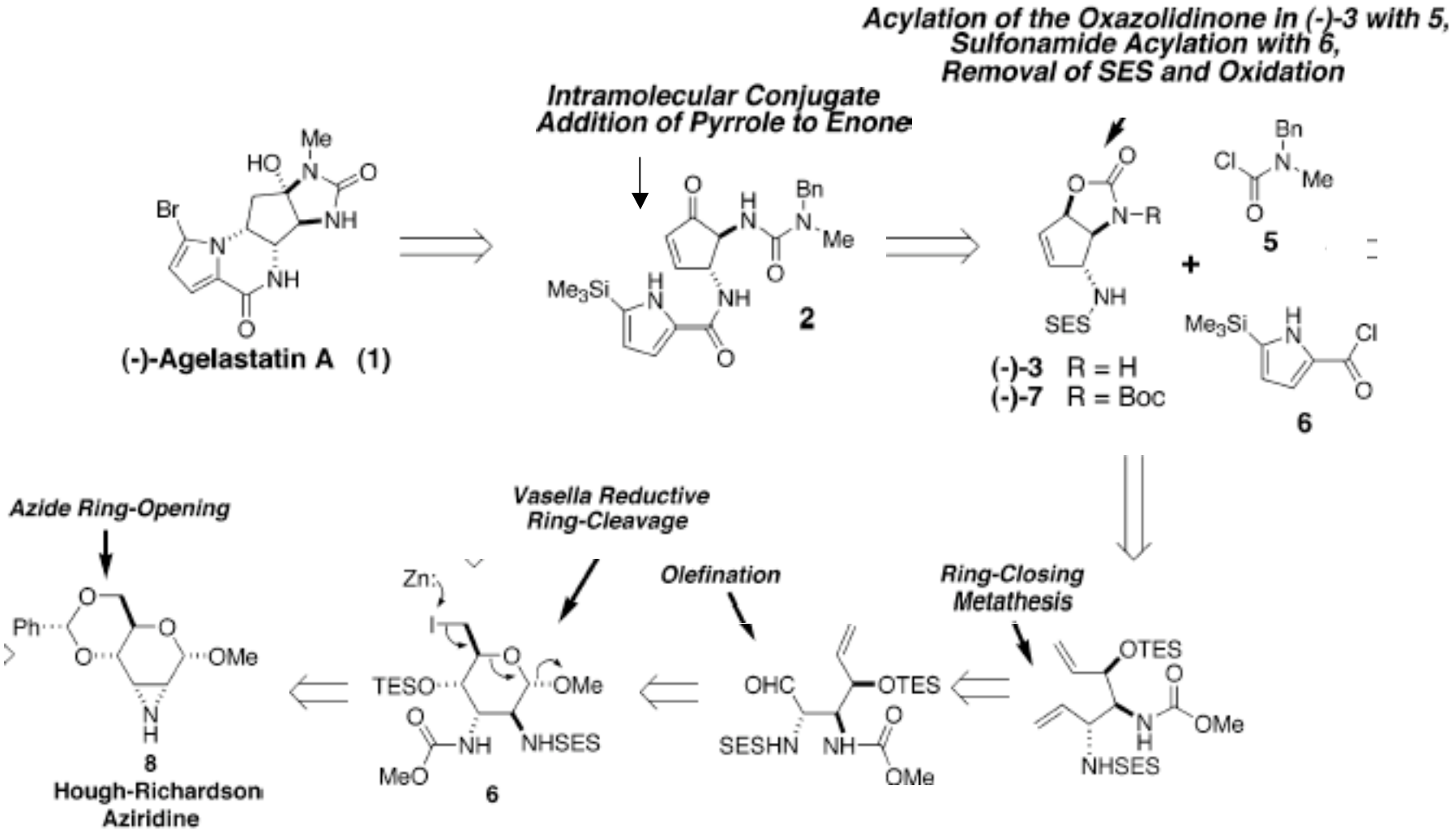
Stein, D.; Anderson, G. T.; Chase, C. E.; Koh, Y. H.; Weinreb, S. M. *J. Am.Chem. Soc*. **1999**, *121*, 9574

First enantioselective total synthesis:



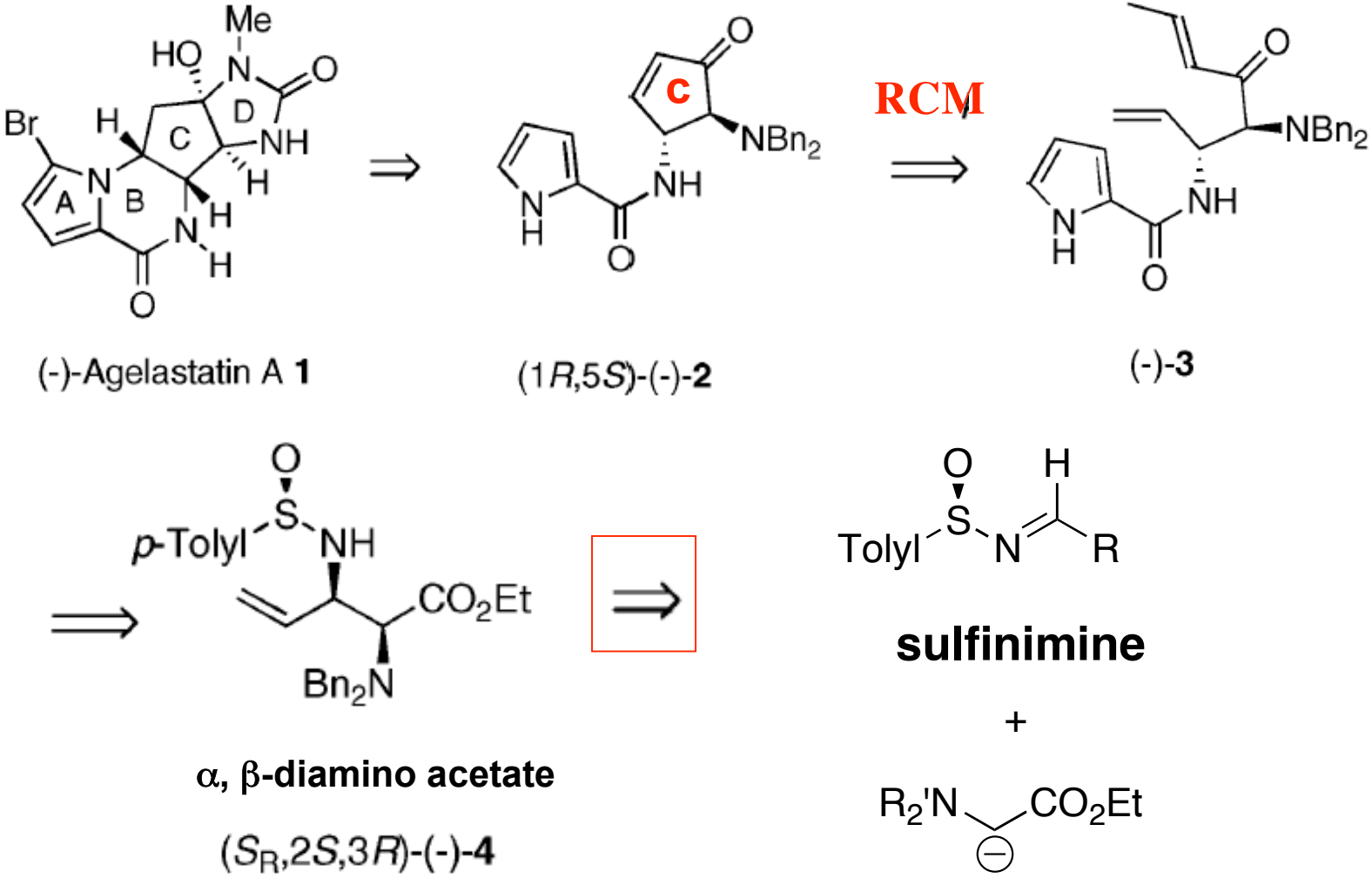
Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060
Feldman, K.S.; Saunders, J. C.; Laci Wrobleski, M. *J. Org. Chem.* **2002**, 7096

Another asymmetric total synthesis



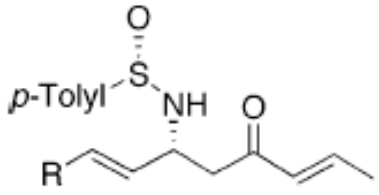
Domosoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615;
Hale, K. J.; Domostoj, M. M.; tocher, D. A.; Irving, I.; Scheinmann, F. *Org. Lett.* **2003**, 2927

Davis' Total Synthesis Strategy

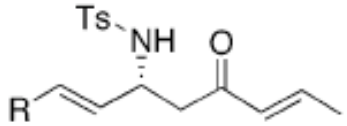


Franklin A. Davis and Jianghe Deng, *Organic Letters*, ASAP

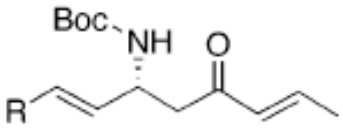
Synthesis of (*R*)-(+)-4-Aminocyclopentenone Using Ring-Closing Metathesis (RCM) of Amino Ketodiene



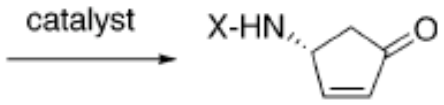
(S_S,*R*)-(+)-**6**



(*R*)-(-)-**7**



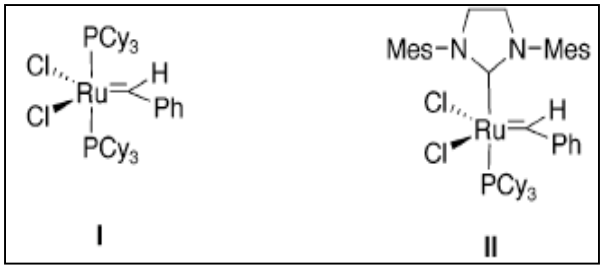
(*R*)-(-)-**8**



Aminocyclopentenone

(*R*)-(+)-**1**: X = Boc
(*R*)-(+)-**9**: X = *p*-TolyS(O)
(R)-(+)-**10**: X = Ts

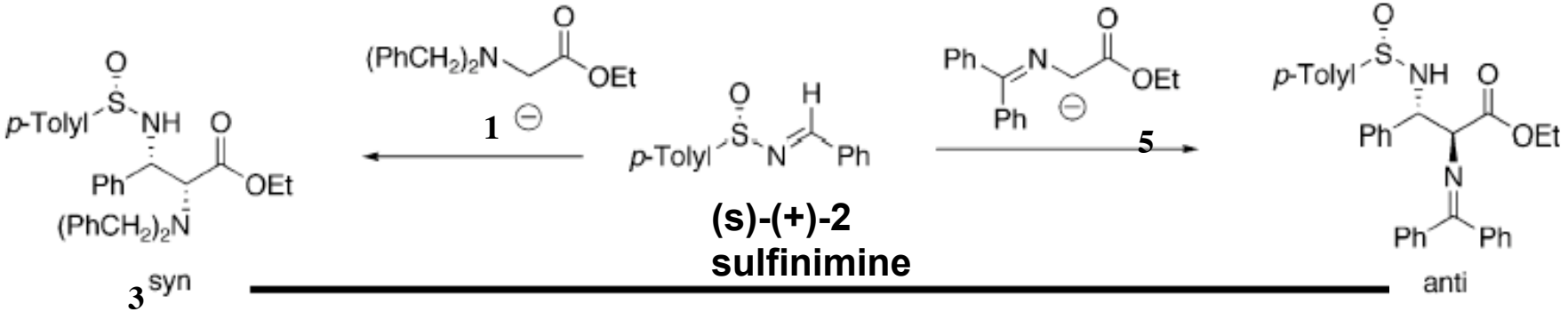
a) R = H; b) R= Me



entry	amino ketodiene	catalyst	product yield(%)
1	6a	I	NR
2		II	85
3	6b	I	NR
4		II	25
5	7a	I	94
6		II	95
7	7b	I	NR
8		II	8
9	8a	I	97
10		II	97
11	8b	I	NR
12		II	21

Franklin A. Davis and Yongzhong Wu, *Organic Letters*, **2004**, 1269-1272

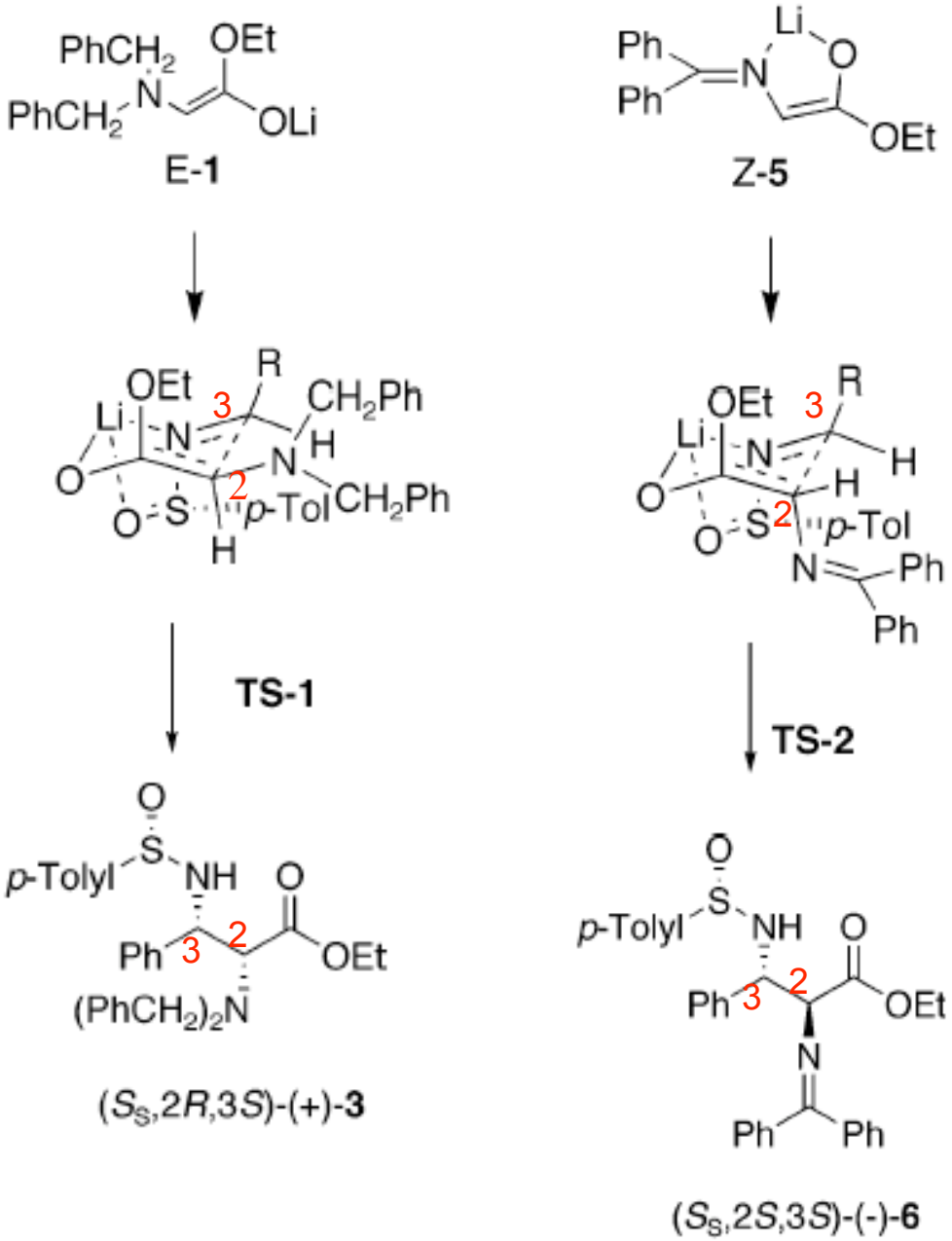
Asymmetric Synthesis of *Syn*- and *Anti*-α,β-diamino Acetate from Sulfinimine and Glycine Enolates



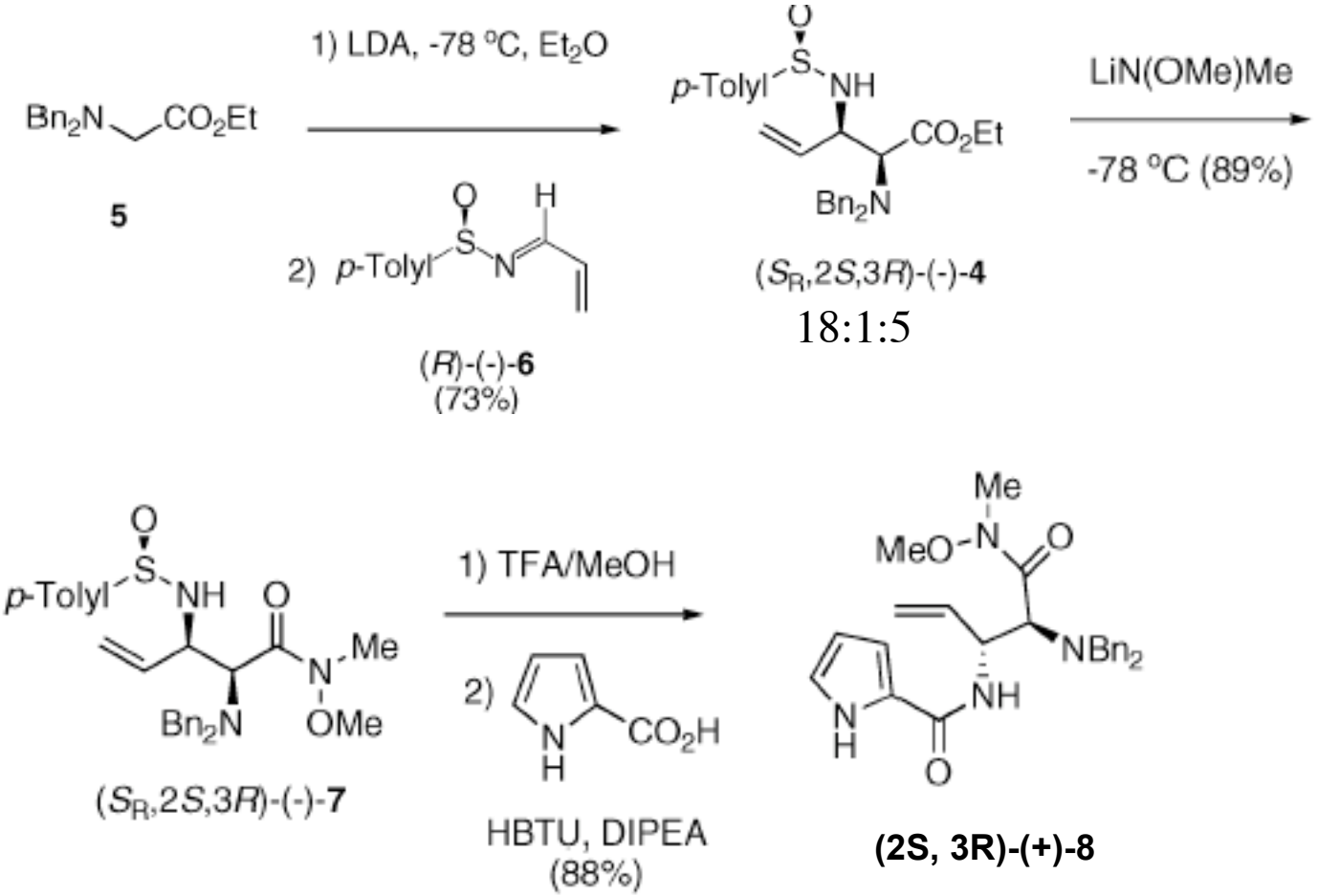
entry	glycine	conditions base/equiv/solvent	α,β-diamino ester (isomer ratio)[a] % isolated yield[b]
1	1	LDA/1.6/THF	(+)-**3** (20:3:2:4) 30[c]
2		LDA/5.0/THF	(20:3:2:3) 68
3		LDA/5.0/Et_2O	(20:4:3:0) 50
4		LiHMDS/5.0/THF	(20:2:2:4) 65
5		NaHMDS/5.0/THF	(20:7:6:7) 80[c]
6		KHMDS/5.0/THF	(20:3:10:6) 76[c]
7	5	LDA/1.1/THF	(−)-**6** (10:0:5:3) 36
8		LDA/1.6/THF	(100:0:2:2) 89
9		LDA/2.0/THF	(10:0:4:3) 34

Franklin A. Davis and Jianghe Deng, *Organic Letters*, **2004**, 2789-2792

Proposed Transition State

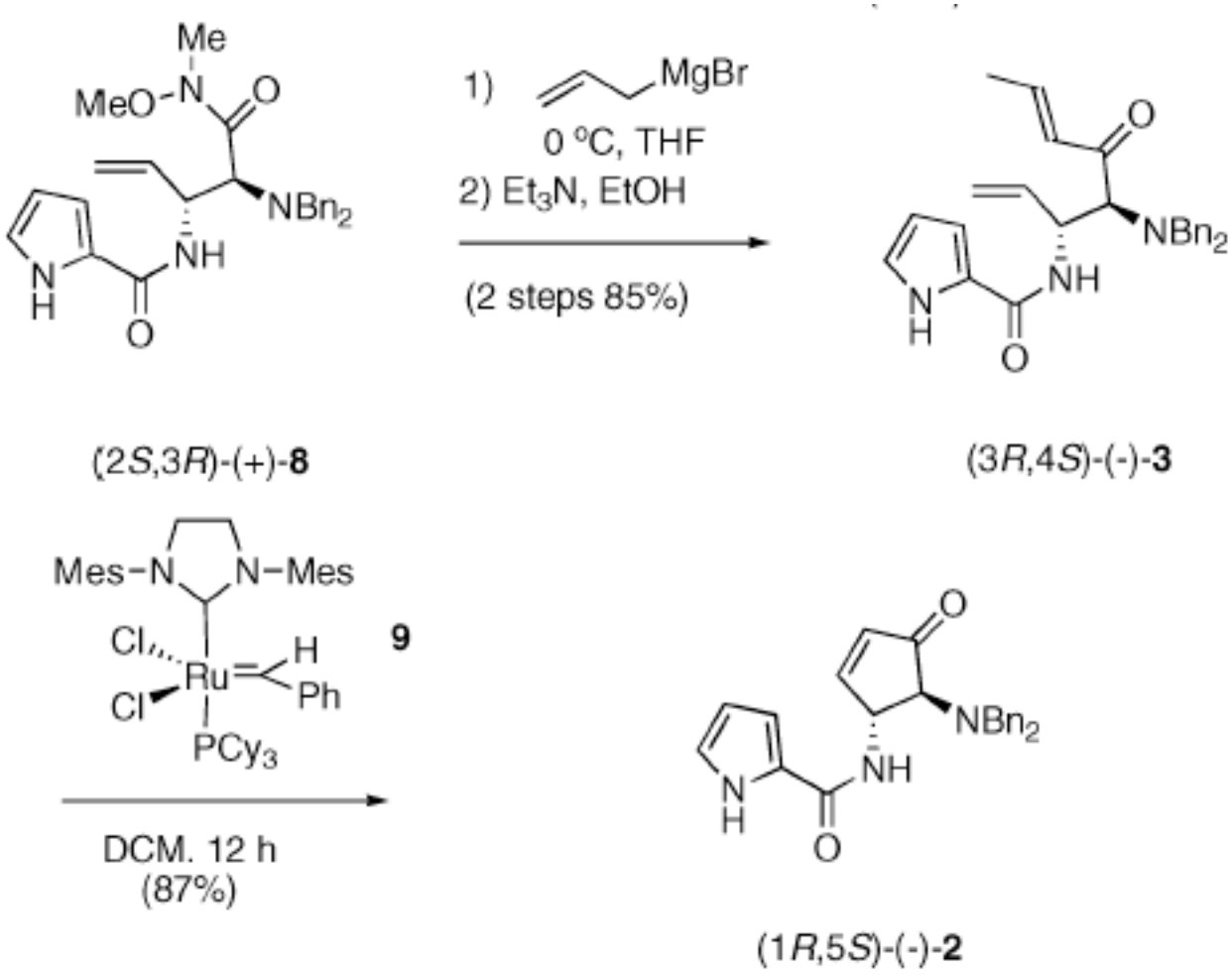


Total Synthesis of (-)-Agelastatin A



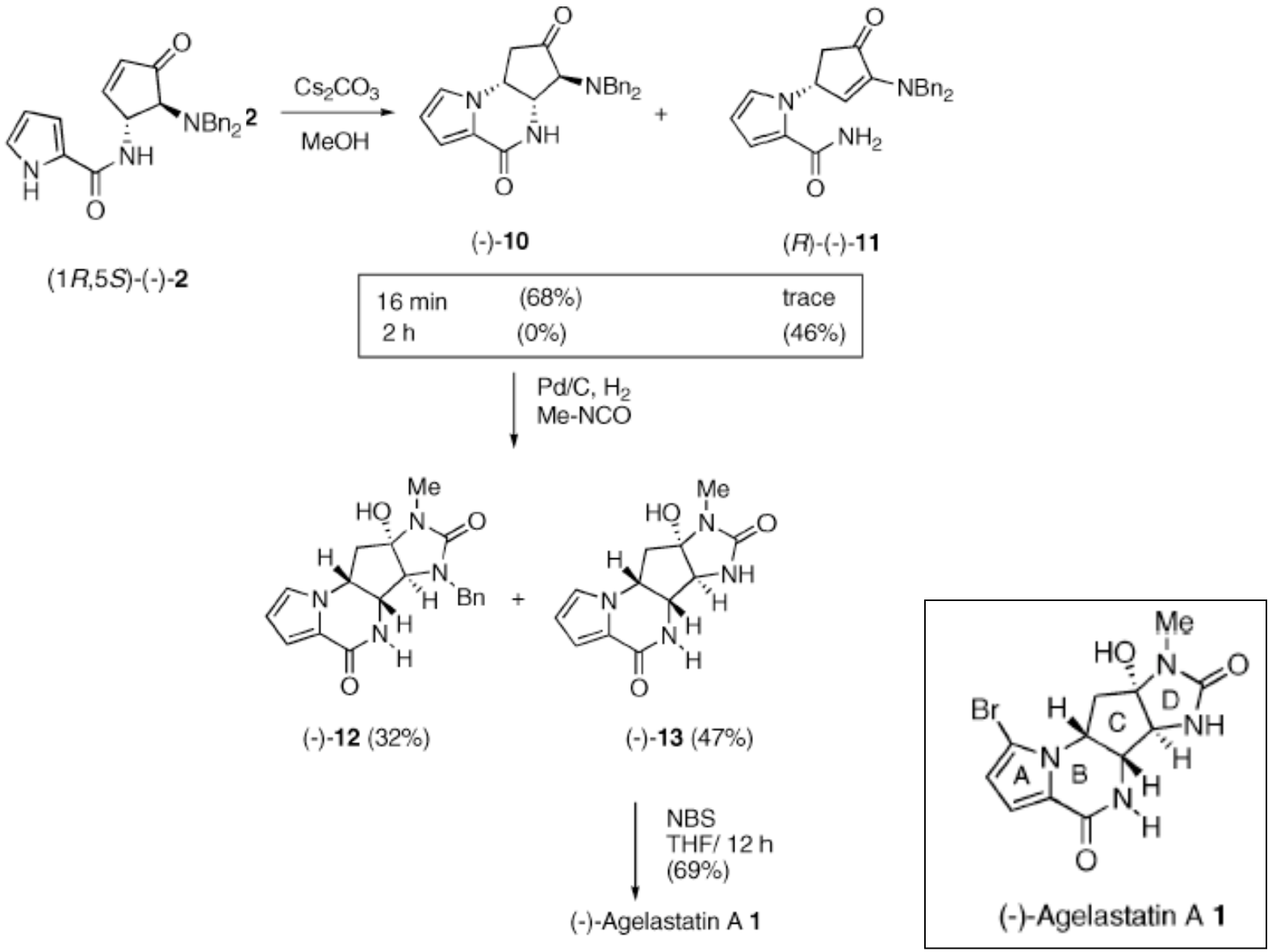
Franklin A. Davis and Jianghe Deng, *Organic Letters*, ASAP

Total Synthesis of (-)-Agelastatin A



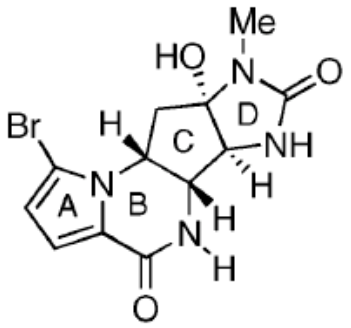
Franklin A. Davis and Jianghe Deng, *Organic Letters*, ASAP

Total Synthesis of (-)-Agelastatin A

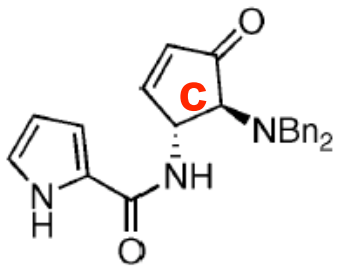


Franklin A. Davis and Jianghe Deng, *Organic Letters*, ASAP

Conclusions

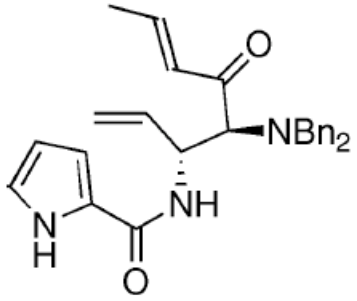


(-)-Agelastatin A **1**

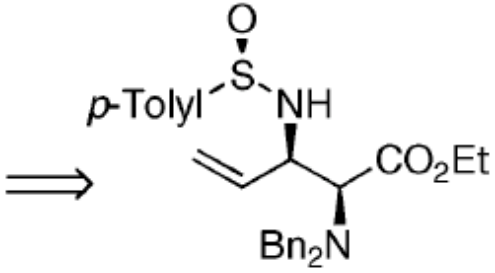


(1*R*,5*S*)-(-)-**2**

RCM

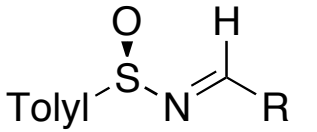


(-)-**3**



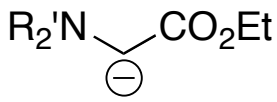
α, β-diamino acetate

(S_R,2*S*,3*R*)-(-)-**4**



sulfinimine

+



11 steps (9% overall yield)
Weinreb: (14 steps, ~7%)
Feldman: (11 steps, 5%)