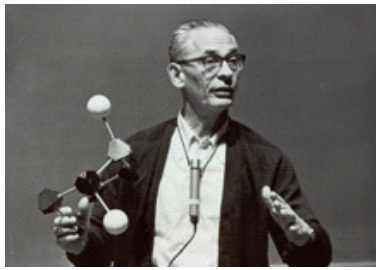
Henry Rapoport

Klement Foo



1918-2002
Professor of Chemistry, Emeritus
Berkeley

-born in Brooklyn, New York, of Russian descent
-B.S. in chemistry in 1940; M.S. in 1941; Ph.D in 1943 (MIT)
-worked briefly during WWII at Heyden Chemical Corporation on penicillin
-1945 studied morphine syntheis at NIH
-1946 appointed as instructor in UC Berkeley
-trained 253 students, out of which 103 were grad students.
-Coauthored with James Cason an organic chemistry lab textbook.
-436 papers and 33 patents.
-noted for TS of heterocyclic drugs like morphine, codeine, camptothecin and structural determination of saxitoxin.
-been a consultant to at least 43 companies
-students have commented that he is too fast to keep up as he writes with both hands.

1940s-1960s -structure elucidation; isolation; biosynthetic discussion, $NaBH_4$ reduction of esters; methods to make heterocycles.

Modified procedure to organolithium species

Anal.Chem. **1948**, *20*, 635

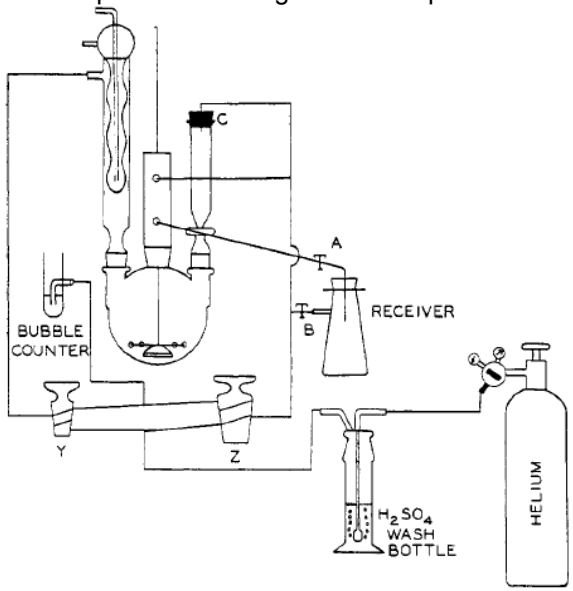


Figure 1. Assembly of Apparatus

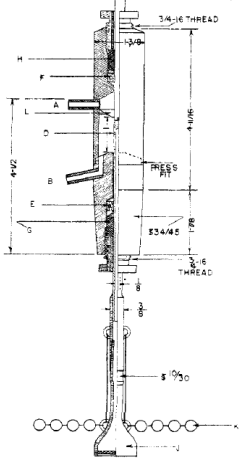
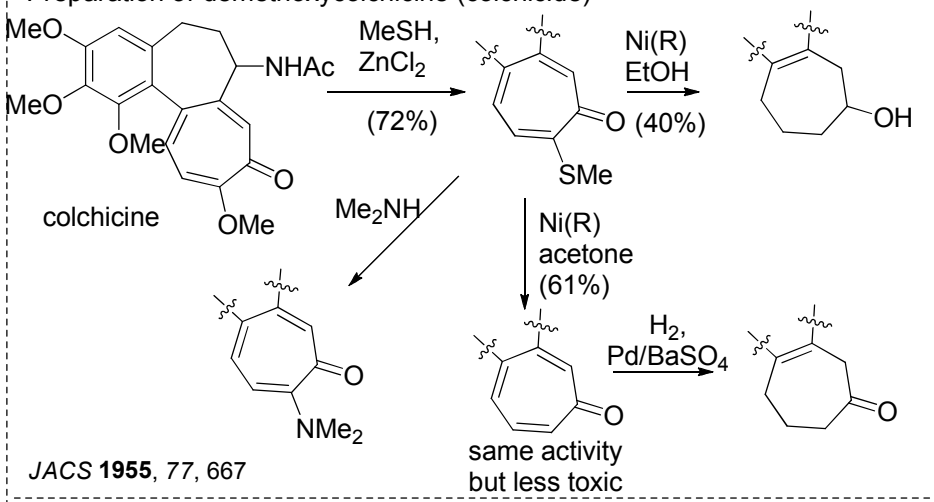


Figure 2. Diagram of Apparatus

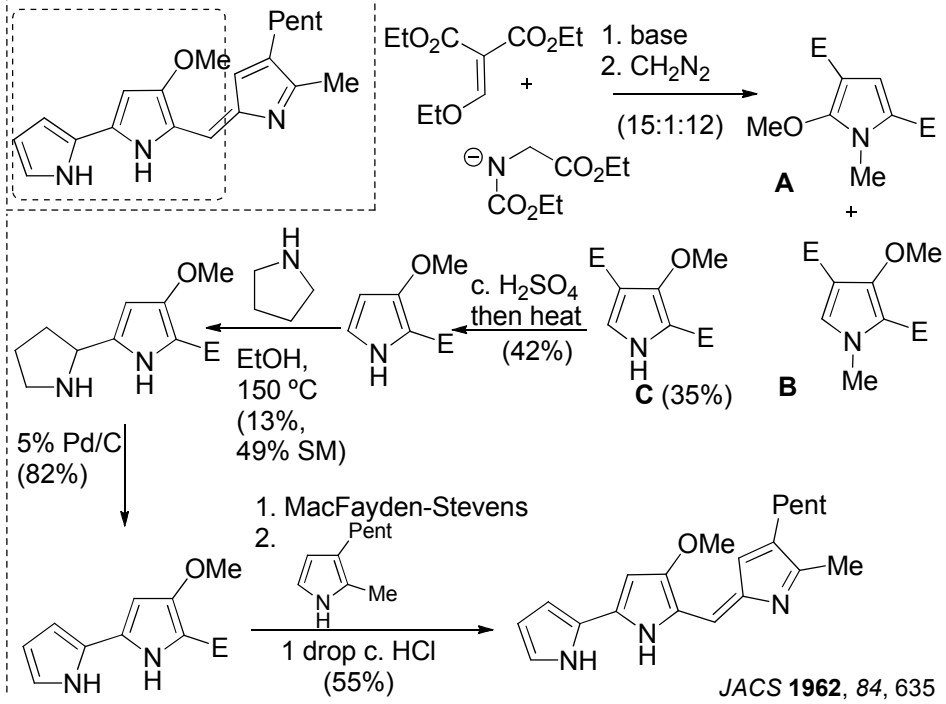
A. Helium tube
B. Filtrate outlet tube
C. Stirrer shaft
D. 2 holes, 1/16 inch diameter
E, F. Vico No. 402-2 ball bearings 1/4 × 11/16 inch
G, H. Graphite-lead-asbestos packing
J. Ace filter tube #610, 25-mm. diameter and porosity A (Ace Glass Co., Vineland, N. J.)
K. Hirschberg type stirrer of 18-gage Chromel wire
L. Baffle

Preparation of demethoxycolchicine (colchicide)



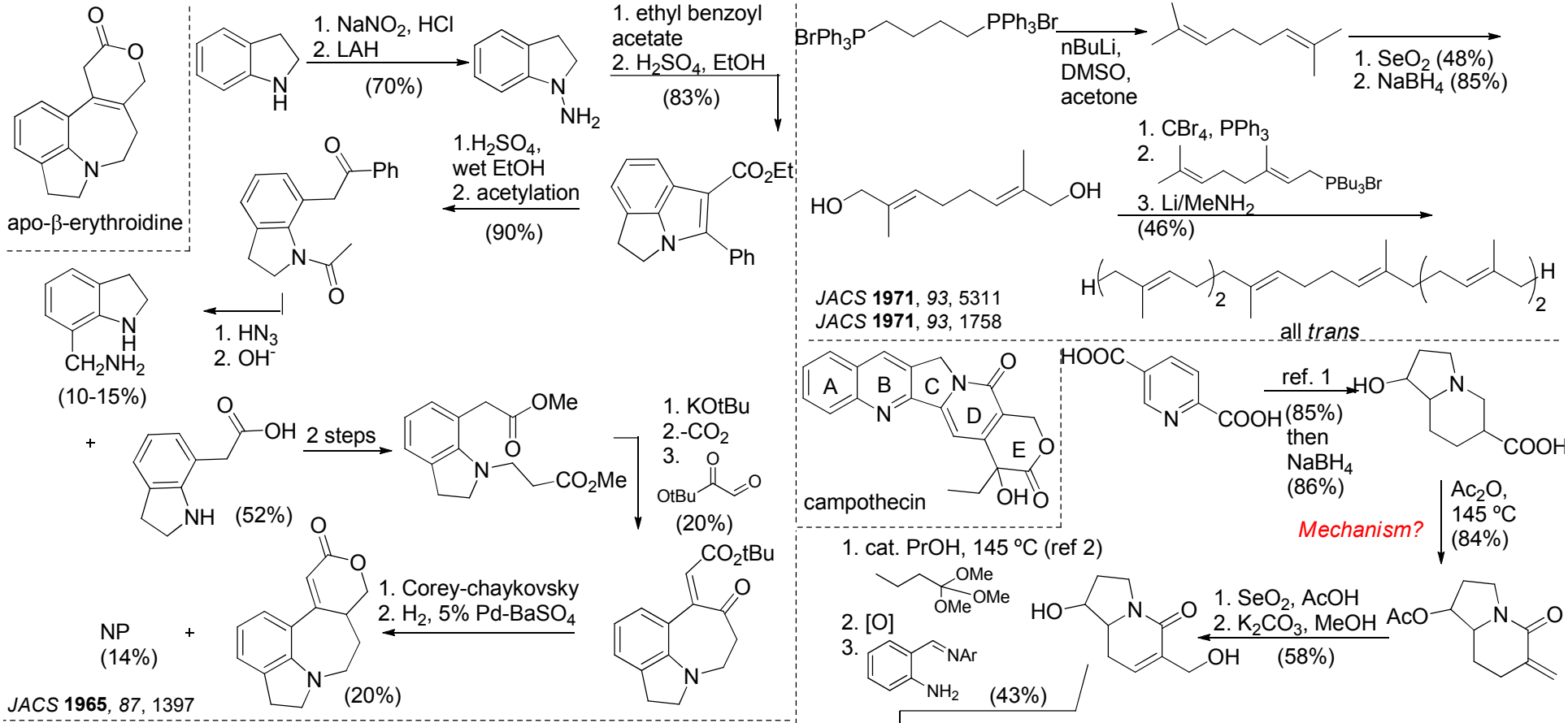
JACS **1955**, *77*, 667

Total synthesis: Prodigiosin (at this time structure was not fully established)



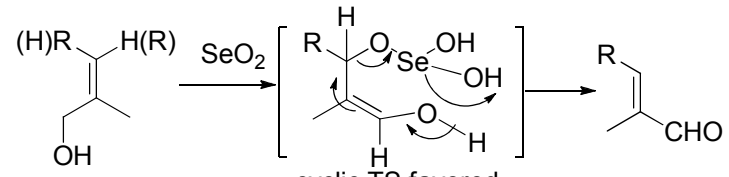
JACS **1962**, *84*, 635

Henry Rapoport



1970s - Obtained Xray structure of saxitoxin *JACS* **1975**, *97*, 6008
Review on Solid phase in organic synthesis *Acc. Chem. Res.* **1976**, *9*, 135
Aberrant Alkaloid Biosynthesis- In-vitro synthesis of unnatural nicotine analogs *JACS* **1971**, *93*, 7021

Stereochemistry of SeO_2 oxidation-application to squalene synthesis

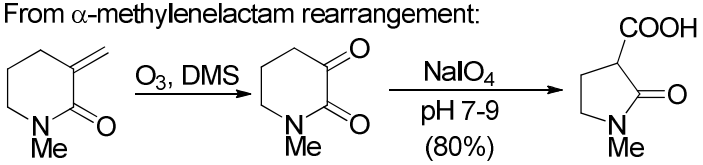


1. *JACS* **1972**, *94*, 8613; 2. *JOC* **1976**, *41*, 535
3. *Chem. Ber*. **1972**, *105*, 2126
this work: *JACS* **1972**, *94*, 8615. see Ke Chen GM "Campothecin" for more.

Henry Rapoport

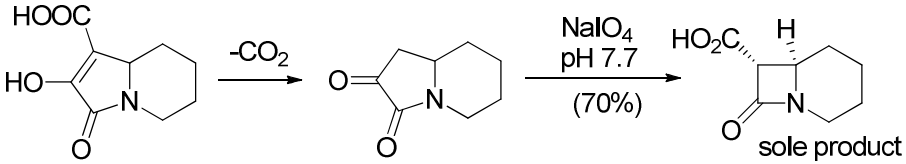
Klement Foo

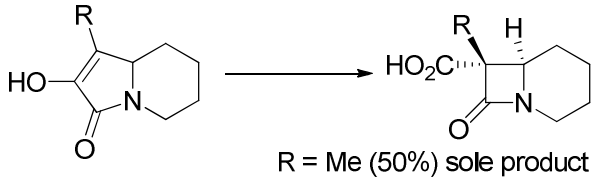
From α-methylenelactam rearrangement:



JACS **1972**, *94*, 3877

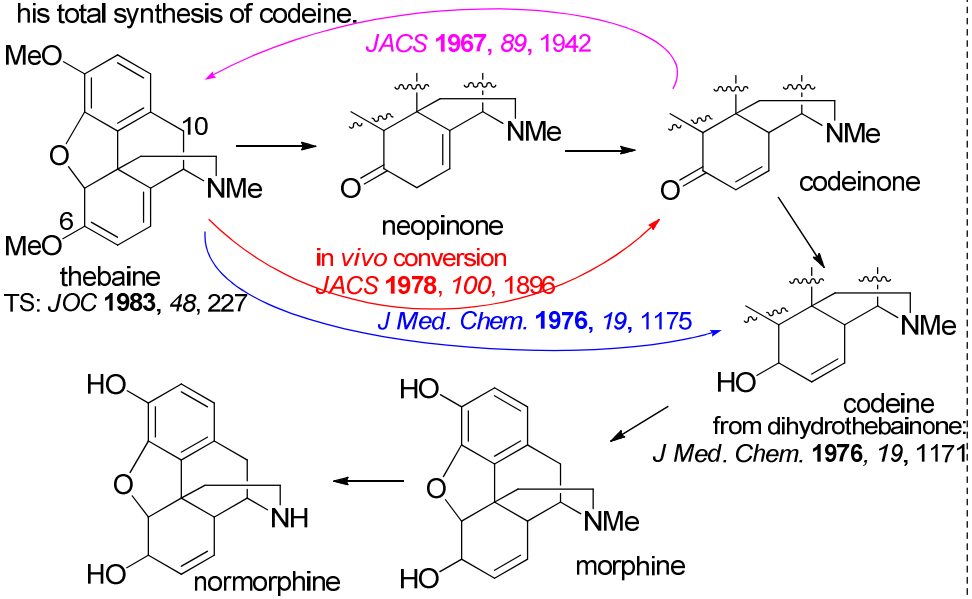
to make β-lactam





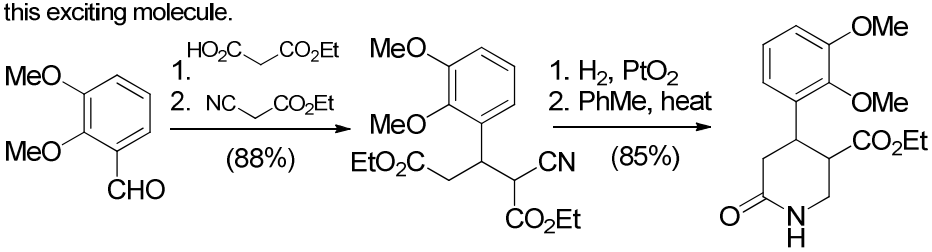
JOC **1975**, *40*, 1264

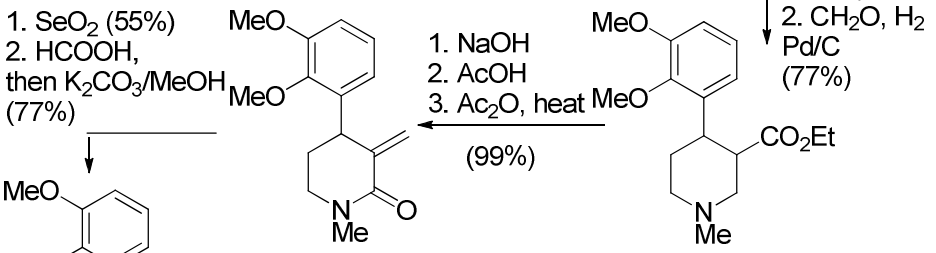
From α-methylenelactam rearrangement and Claisen strategy, ultimately led to his total synthesis of codeine.

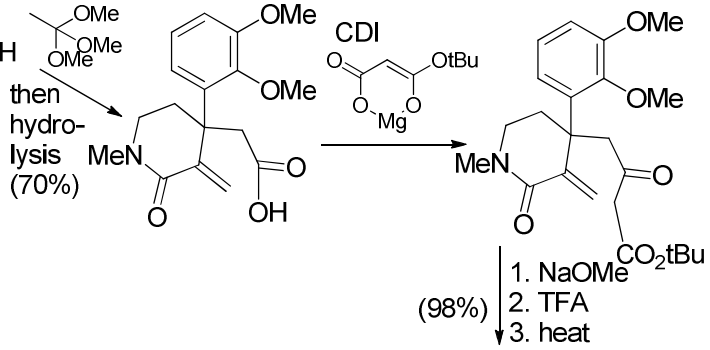


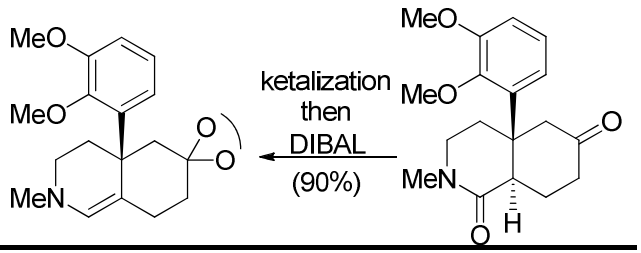
TS: *JOC* **1983**, *48*, 227

Completed total synthesis of thebaine in 1982, which combined with his 1976 J Med. Chem. paper constitutes his total synthesis of codeine. This J Med. Chem. paper was featured briefly in Ke Li "Morphine/Codeine" GM, together with many other syntheses of this exciting molecule.







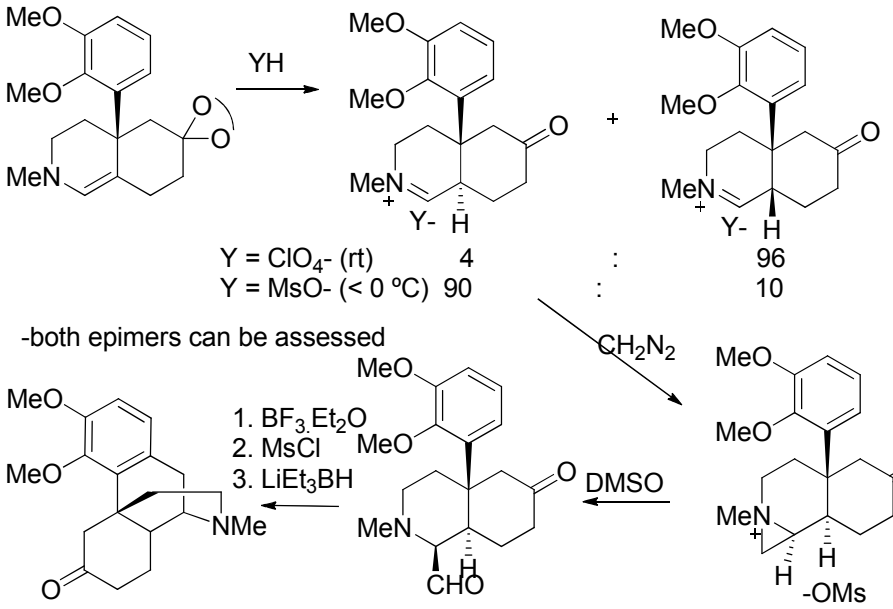


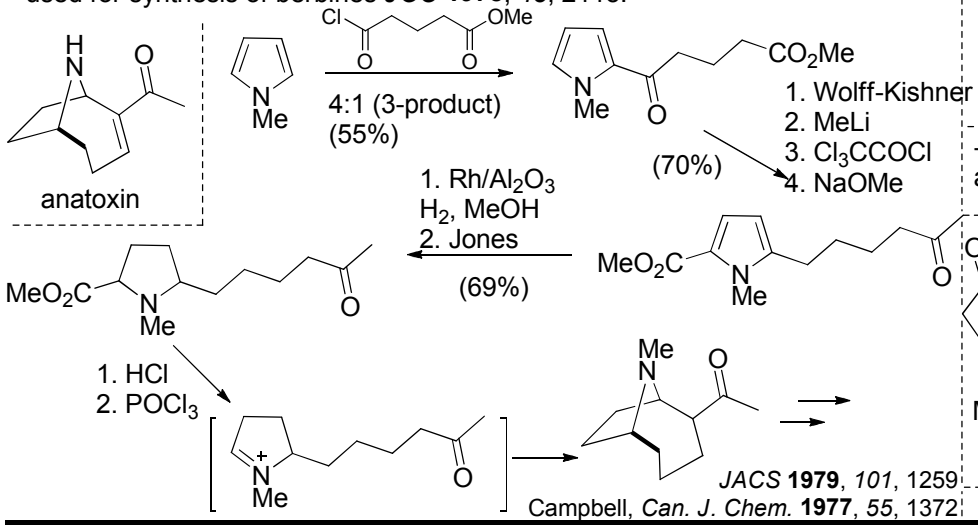
JOC **1981**, *46*, 5064
JOC **1982**, *47*, 1831
other analogs:
JACS **1976**, *98*, 6650

Comment:
many steps do not need purification.

Henry Rapoport

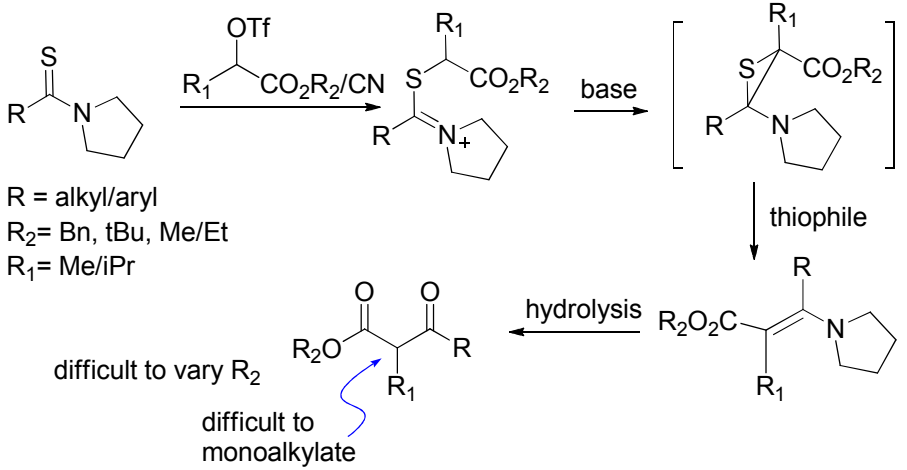
Klement Foo





1980s

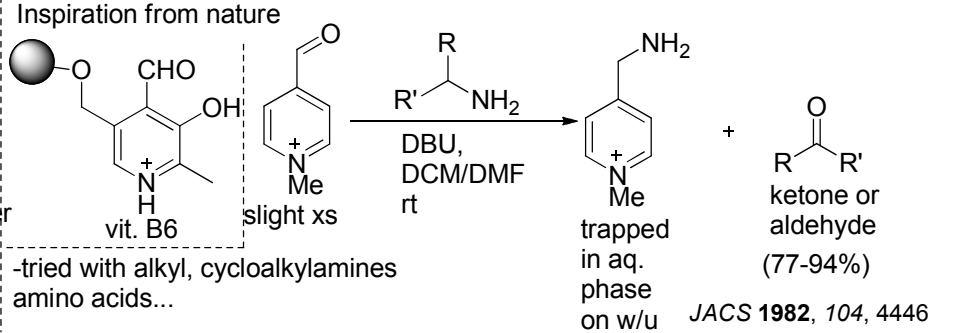
A twist on Eschenmoser sulfide contraction



-modified Eschenmoser thiophile reagent to (3-morpholinylpropyl)$_2$PPh

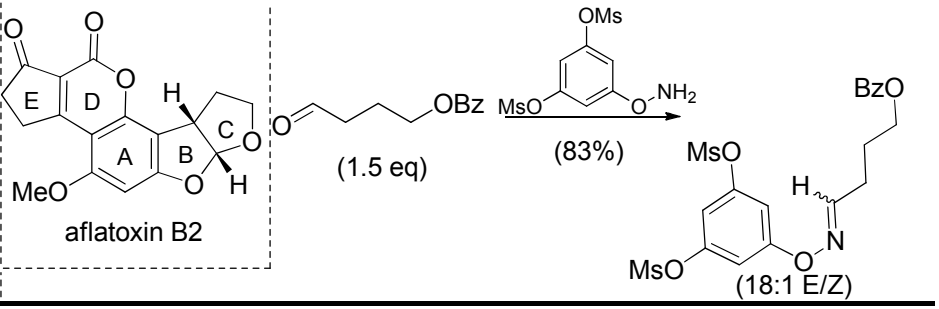
-vital to use triflate as bromide give little (R1≠H) or low yield. *JOC* **1981**, *46*, 3230

Inspiration from nature



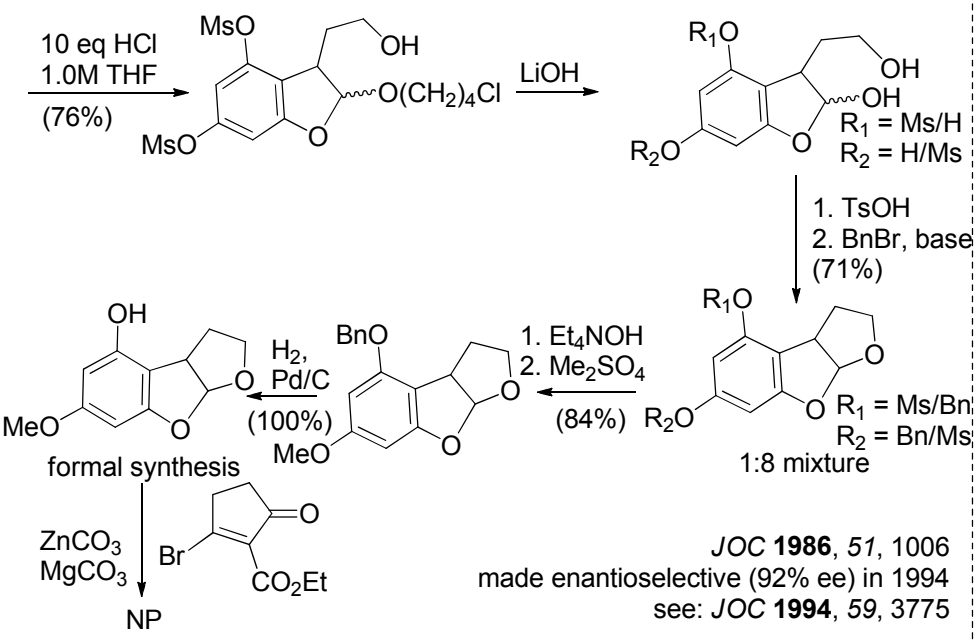
-tried with alkyl, cycloalkylamines amino acids...

JACS **1982**, *104*, 4446



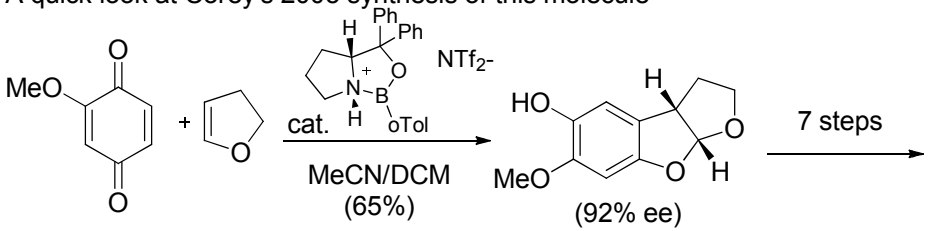
Henry Rapoport

Klement Foo

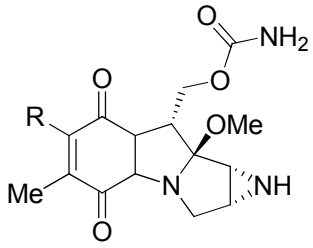


JOC **1986**, *51*, 1006
made enantioselective (92% ee) in 1994
see: *JOC* **1994**, *59*, 3775

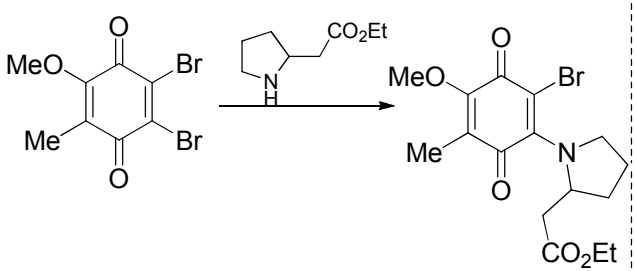
A quick look at Corey's 2005 synthesis of this molecule

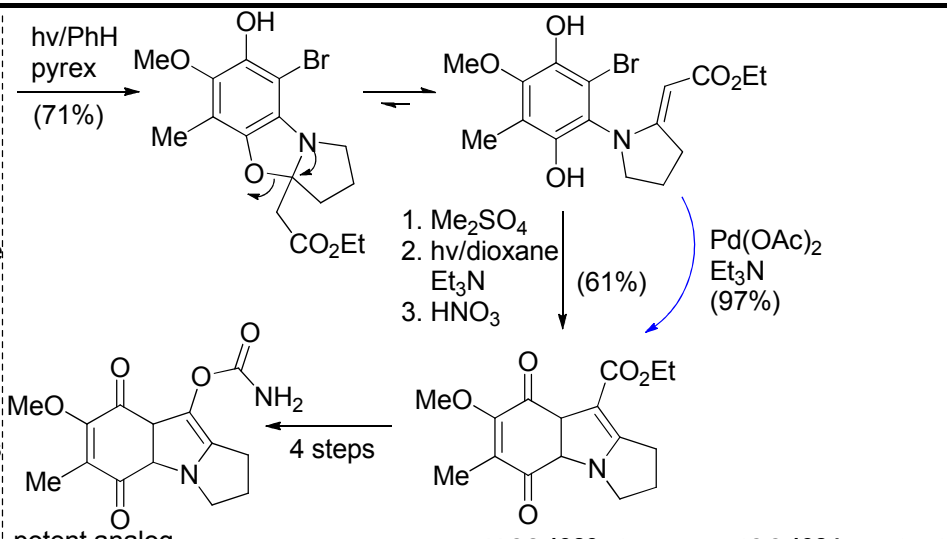


JACS **2005**, *127*, 11958

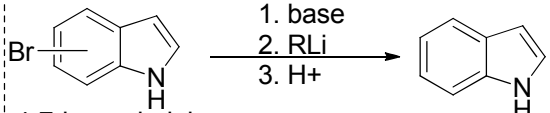


Mitomycin A (R=OMe)
C (R=NH_2)





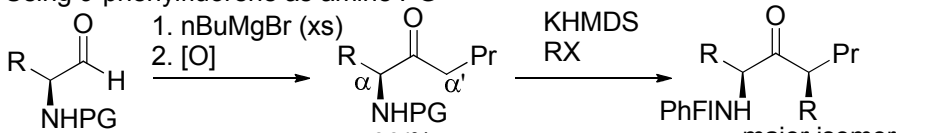
JACS **1983**, *105*, 2859; *JOC* **1984**, *49*, 1671
for iminium salt strategy: *JOC* **1981**, *46*, 2745; *JOC* **1982**, *47*, 2404
for aziridine installation: *JOC* **1985**, *50*, 4515

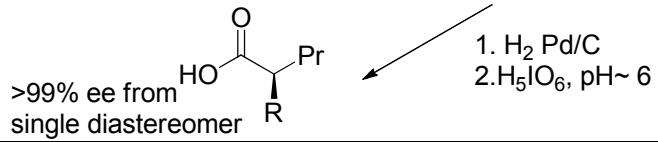


Base	RLi	% xchange
n/s-BuLi	n/s-BuLi	0
tBuLi	tBuLi	15-90*
MeLi	tBuLi	15-90*
NaH	tBuLi	30
MeMgBr	tBuLi	<15
KH	tBuLi	>90

* variable on Br position
JOC **1986**, *51*, 5106

Using 9-phenylfluorene as amine PG

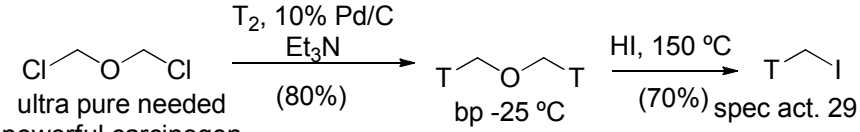




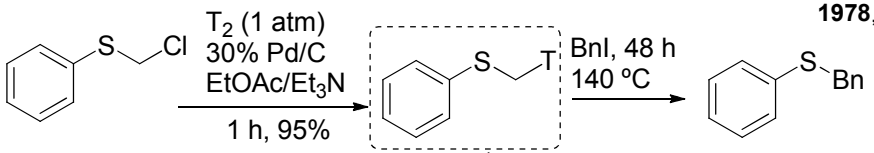
JACS **1987**, *109*, 236
JACS **1988**, *110*, 7447

one example of radiochemistry - new reagent precursor of CH_2TI

Previous:

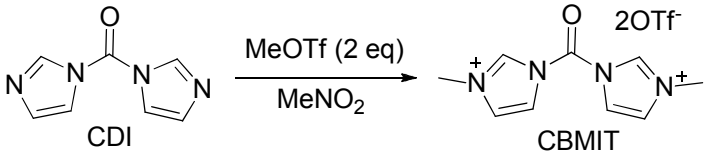


Wuersch, *J. Labelled Compd. Radiopharm.* **1978**, *14*, 355



JOC **1989**, *54*, 4689

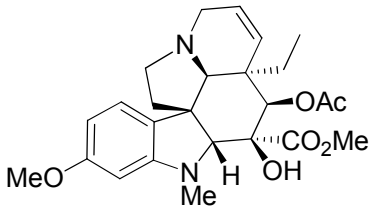
New coupling reagents



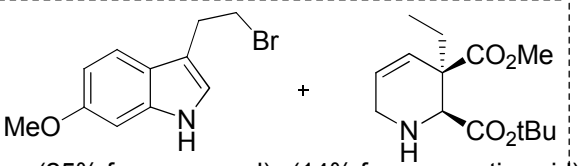
esterification of amino acids proceed 85-98% even with 2º ROH minimal loss of optical purity

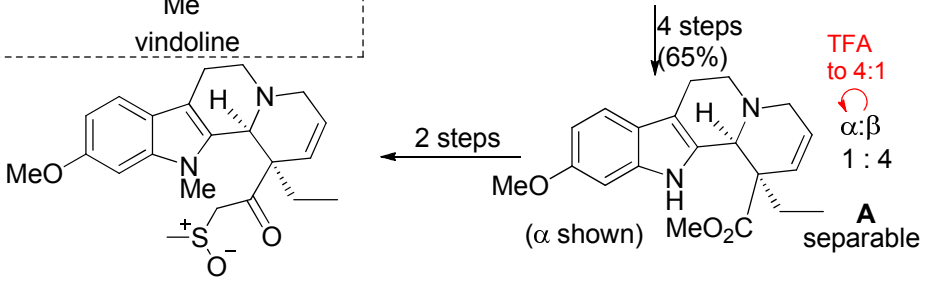
JACS **1989**, *111*, 4856

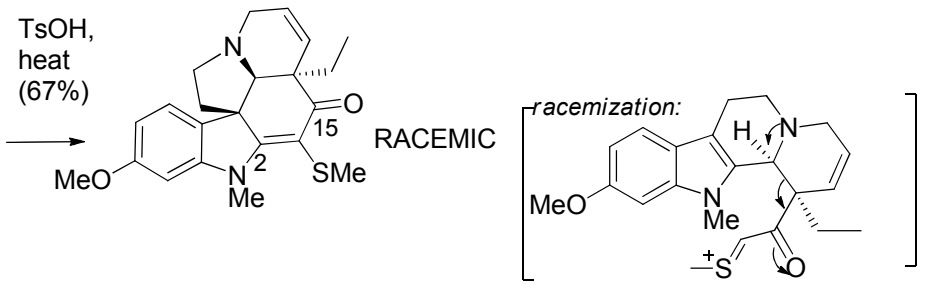
another new reagent: see *JOC* **1994**, *59*, 7503



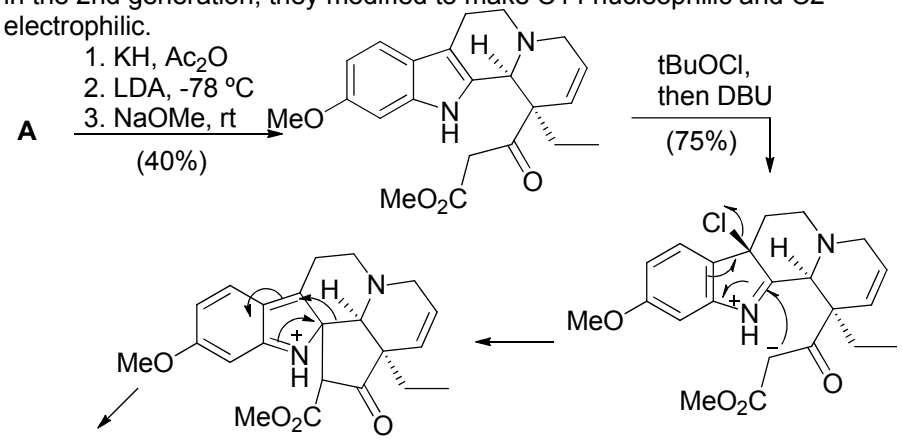
vindoline

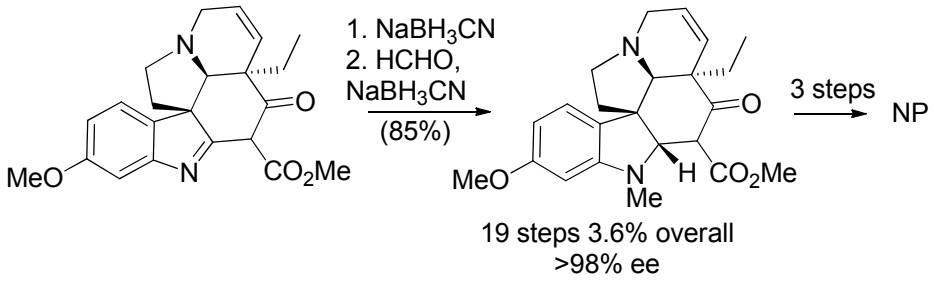






in the 2nd generation, they modified to make C14 nucleophilic and C2 electrophilic.



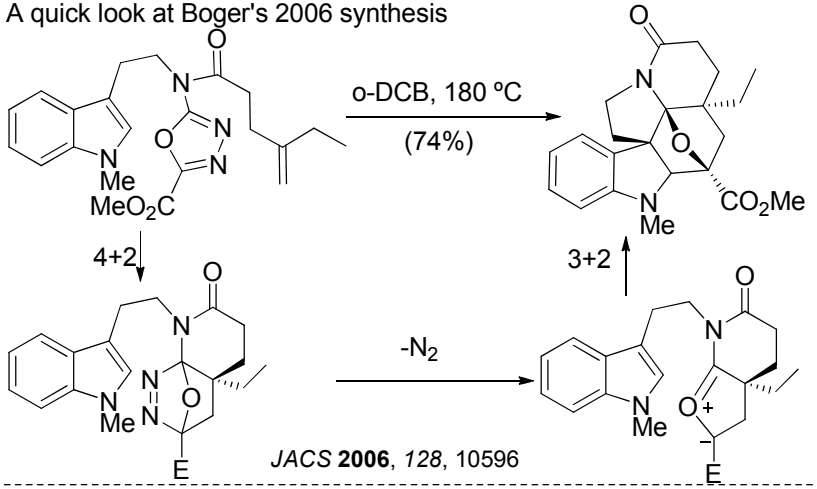


JOC **1986**, *51*, 3882; *JACS* **1987**, *107*, 1603
also discussed in Mitsos "Vindoline" GM
for vincamine TS: see *JOC* **1985**, *50*, 1239; *JOC* **1990**, *55*, 3068

Henry Rapoport

Klement Foo

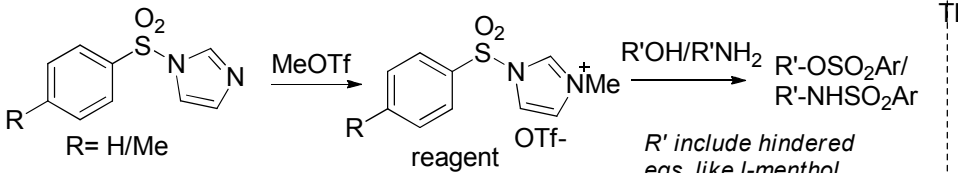
A quick look at Boger's 2006 synthesis



JACS **2006**, *128*, 10596

1990s

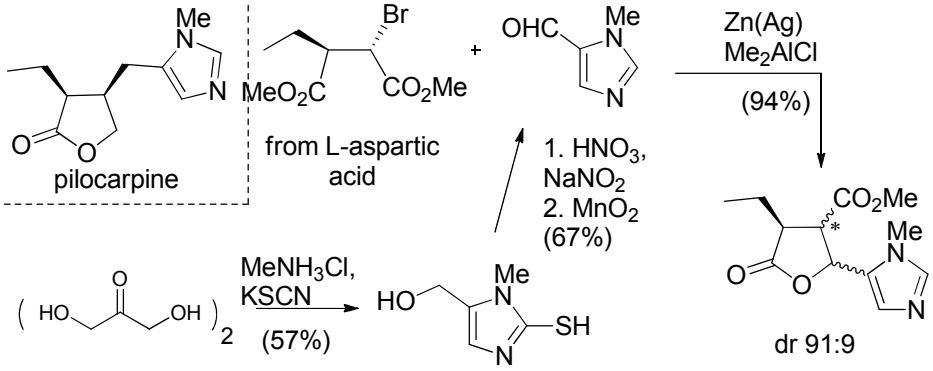
yet another new reagent

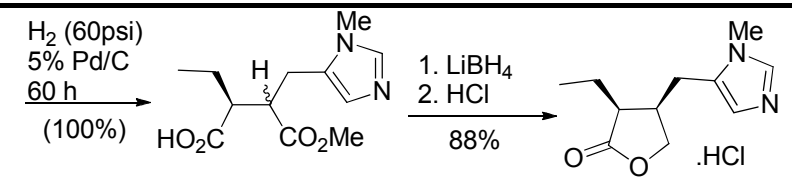


R' include hindered egs. like l-menthol. proline or diisopropylamine

-phloroglucinol in TsCl/pyr 60-70 ºC need days to obtain 60-70% product.
-this condition allows 100% in hours.

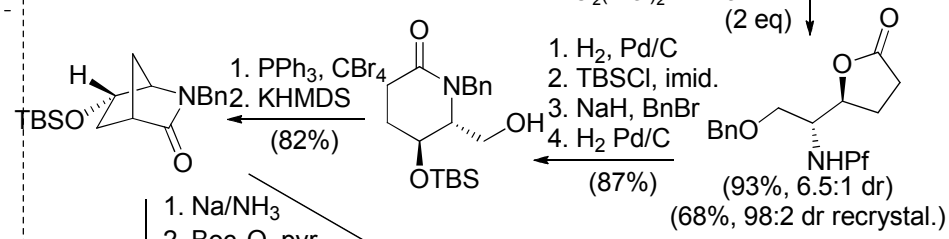
JOC **1992**, *57*, 4775



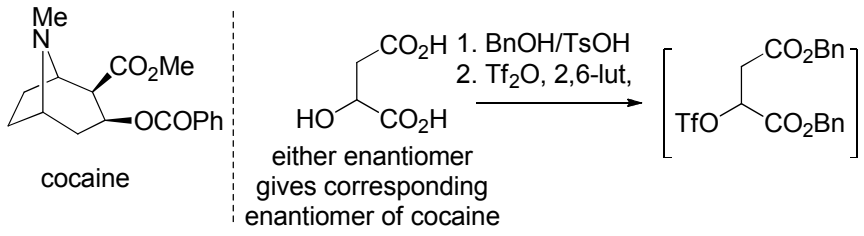


major isomer has right stereochem.
10 steps from L-aspartic acid (51% overall)

JOC **1993**, *58*, 1159

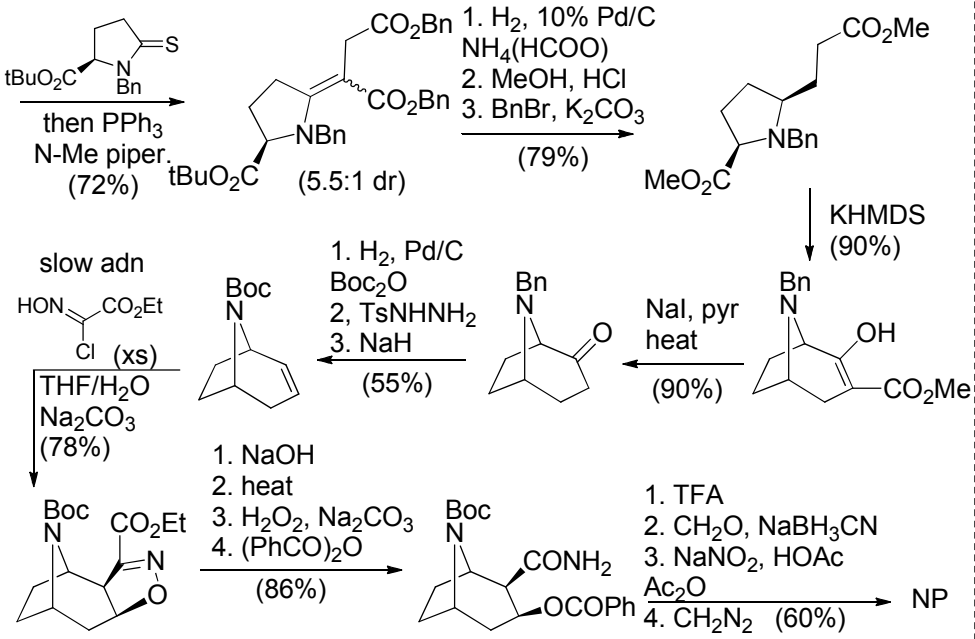


JOC **1995**, *60*, 4602



Henry Rapoport

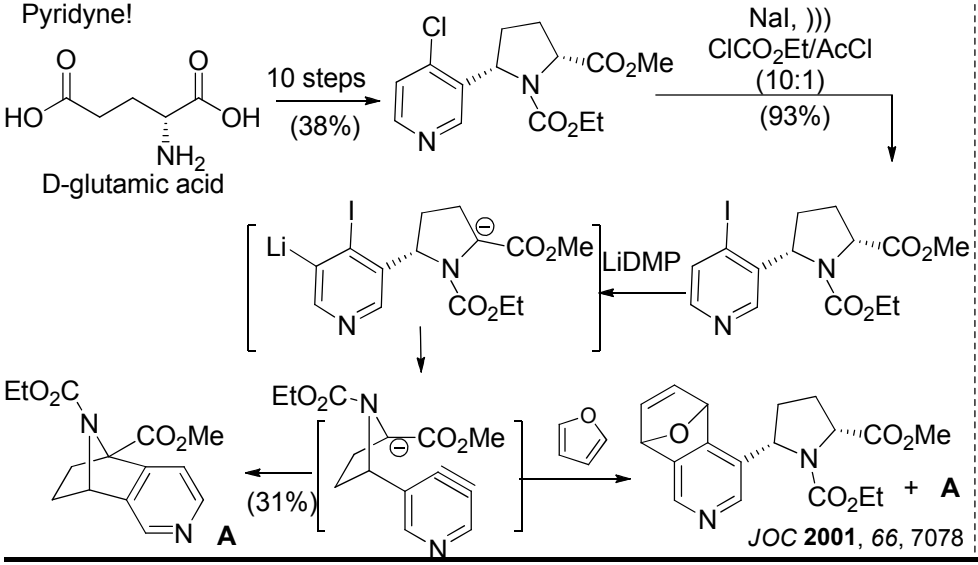
Klement Foo



JOC **1998**, *63*, 4069

2000s

Pyridyne!



JOC **2001**, *66*, 7078

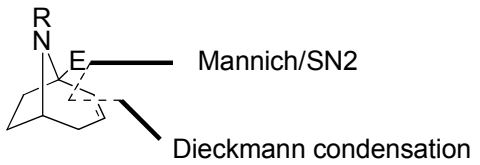
Summary:

Rapoport's favorite strategies:

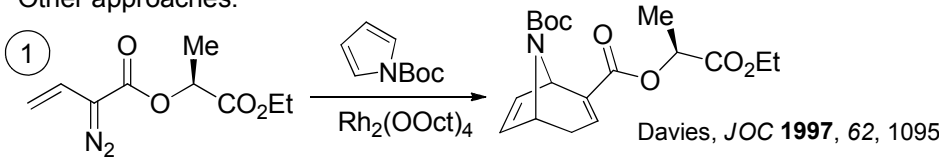
- decarbonylation of amino acid derivative and alkylation of iminium salts ('Mannich')
- Dieckmann condensation
- α-methylene lactam rearrangement
- Claisen rearrangement on (hetero)arenas

Not covered: synthesis of heterocycles like 1,4-disubstituted imidazoles, thiocoumarins, azaindoles, benzofurans...
also his contribution to structure elucidation, isolation of natural products, and radiolabelling.

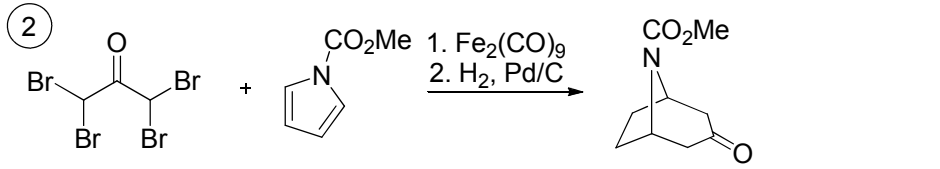
Bonus



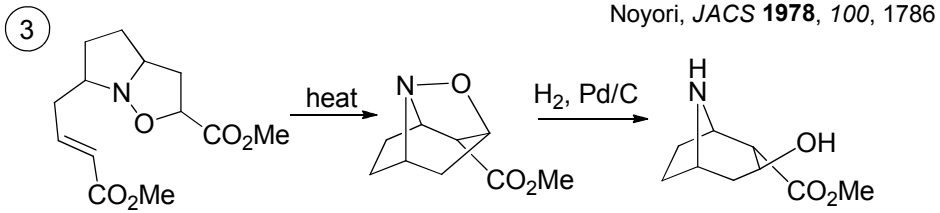
Other approaches:



Davies, *JOC* **1997**, *62*, 1095

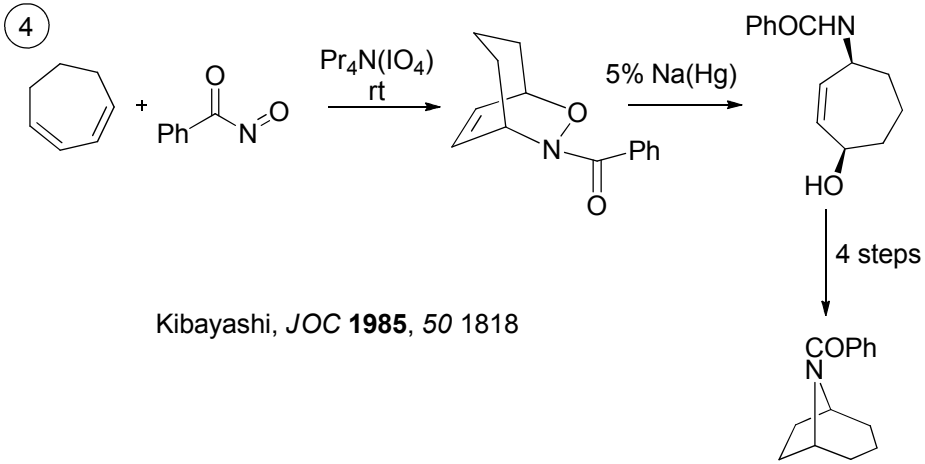


Noyori, *JACS* **1978**, *100*, 1786



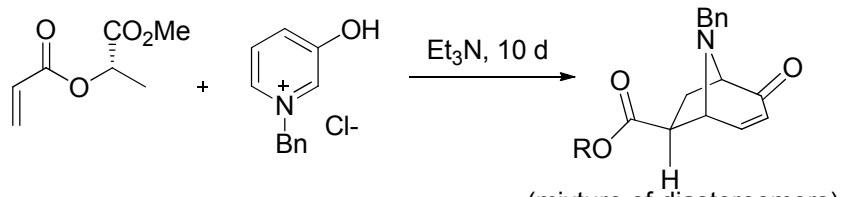
Tufariello, *JACS* **1979**, *101*, 2435
modified by Davis, *OL* **2010,** *12* 4118

4



Kibayashi, *JOC* **1985**, *50* 1818

5



(mixture of diastereomers)

Charlton, *JOC* **1995**, *60*, 8057