Regiospecific and Stereoselective Synthesis of (±)-Reserpine and (-)-Reserpine

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Presented by Steve Rossi
February 28, 2012
Gilbert Stork

• Born December 31, 1921
• B.S. University of Florida (1942)
• Ph.D. University of Wisconsin (1945) under Samuel M. McElvain

• 1946, Joined the Harvard Faculty
• 1948, Associate Professor at Harvard
• 1953, Associate Professor at Columbia
• 1955, Professor at Columbia
• 1967, Eugene Higgins Professor
• 1993, Professor Emeritus
Reserpine

- First isolated from Rauwolfia Serpentina (Indian Snakewood) in 1952
- Early uses included “insanity,” fever, and snakebites
- Current medicinal uses
  - Antipsychotic
  - Antihypertensive
  - Dyskinesia (Huntington’s Disease)
Previous Total Synthesis

- 1956, First Synthesis by Woodward
  - 19 Steps
- 1985, Martin
  - 20 Steps
- Diels-Alder as the primary source of ring closure
- 1997, Hanessian
Retrosynthesis
Route A

HO – vinyl + vinyl – ME

NBS

EtO

O3

Br

Ph3PO

Me

O

THF

Br

LDA

TBSCI

HMPA

Me

O2N

DBU

B2H6

EtO

NaOAc

H2O2

MeOTF

Br

CO2Et

CO2Et

O

TBS

TBS

tBu

HO

TBS

tBu

3
Route A

- 4.5: 1 Selectivity at * Chiral Center
- 11% Yield through 9 Steps
- Want to Increase Selectivity
- ....Route B
Route B

1) MSCI, Py
2) CsOAc

1) LAH
2) TsCl, Py

TBSCI
Imidazole

LHMDS
TMSCI

TMSO

1) O₃
2) PPh₃
CH₂N₂

HF

MeO₂C
OH

CHO

MeO₂C
OMe

CHO

MeO₂C
OMe

CHO

MeO₂C
OMe

CHO
Route B

- 9.2% Overall Yield
- 14 Steps
- 100% Selectivity
Route C

- Bicyclic System
- Moderate Diels-Alder Reactivity
- Successful Synthesis
- No Yields Reported
Final Steps to Reserpine
Conclusion

• 3 Viable, Novel Total Synthesis of Reserpine

• Individual Steps Generally High Yielding for Route B

• “Unique” Approach
Questions?