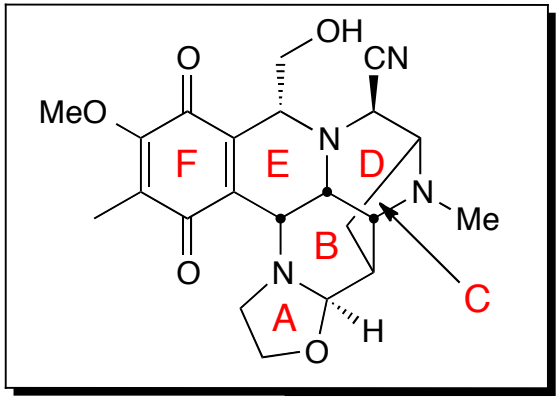
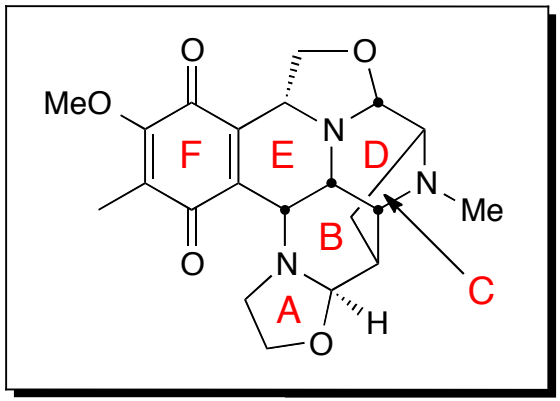
Asymmetric [C+NC+CC] Coupling Entry to the Naphthyridinomycin Natural Product Family: Formal Total Synthesis of Cyanocycline A and Bioxalomycin β2

Philip Garner, H. Ümit Kaniskan, Charles M. Keyari, and Laksiri Weerasinghe
J. Org. Chem. **2011**, ASAP

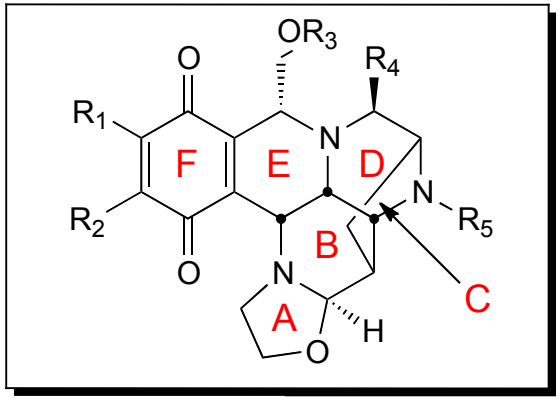




Brandon Parks
Wipf Group Current Literature
June 18th, 2011

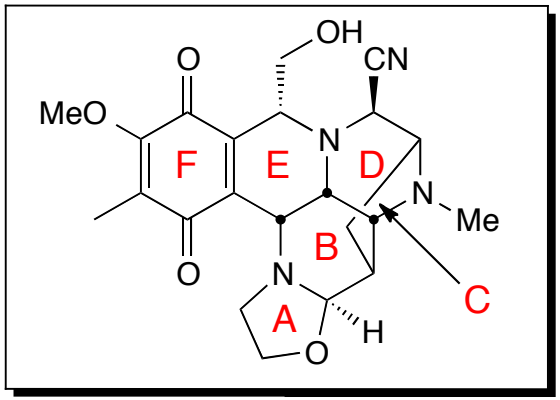
Napthyridinomycin Family

- Belongs to a family of tetrahydroisoquinoline alkaloids
- Isolated primarily from different species of *Streptomyces*
- Members of family are known “antitumor antibiotics”
- Key Features:
  - Hexacyclic core framework
  - Quinone functionality
  - Piperazine system
  - Oxazolidine fragment

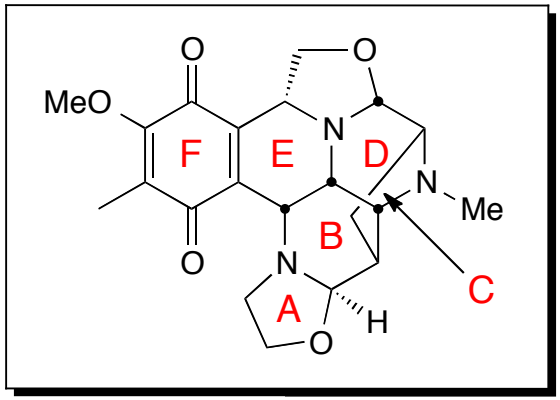


Scott, J.D.; Williams, R.M. *Chem. Rev.* **2002**, *102*, 1669-1730.
Ingh, K.; Sun, S.; Kluepfel, D. *Dev. Ind. Microbiol. Ser.* **1976**, *17*, 209-221.
Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676-2690.
Wipf, P.; Grace, H.C.; Kim, S.H. *Tetrahedron* **2006**, *62*, 10507-10517.

Cyanocycline A and Bioxalomycin β2



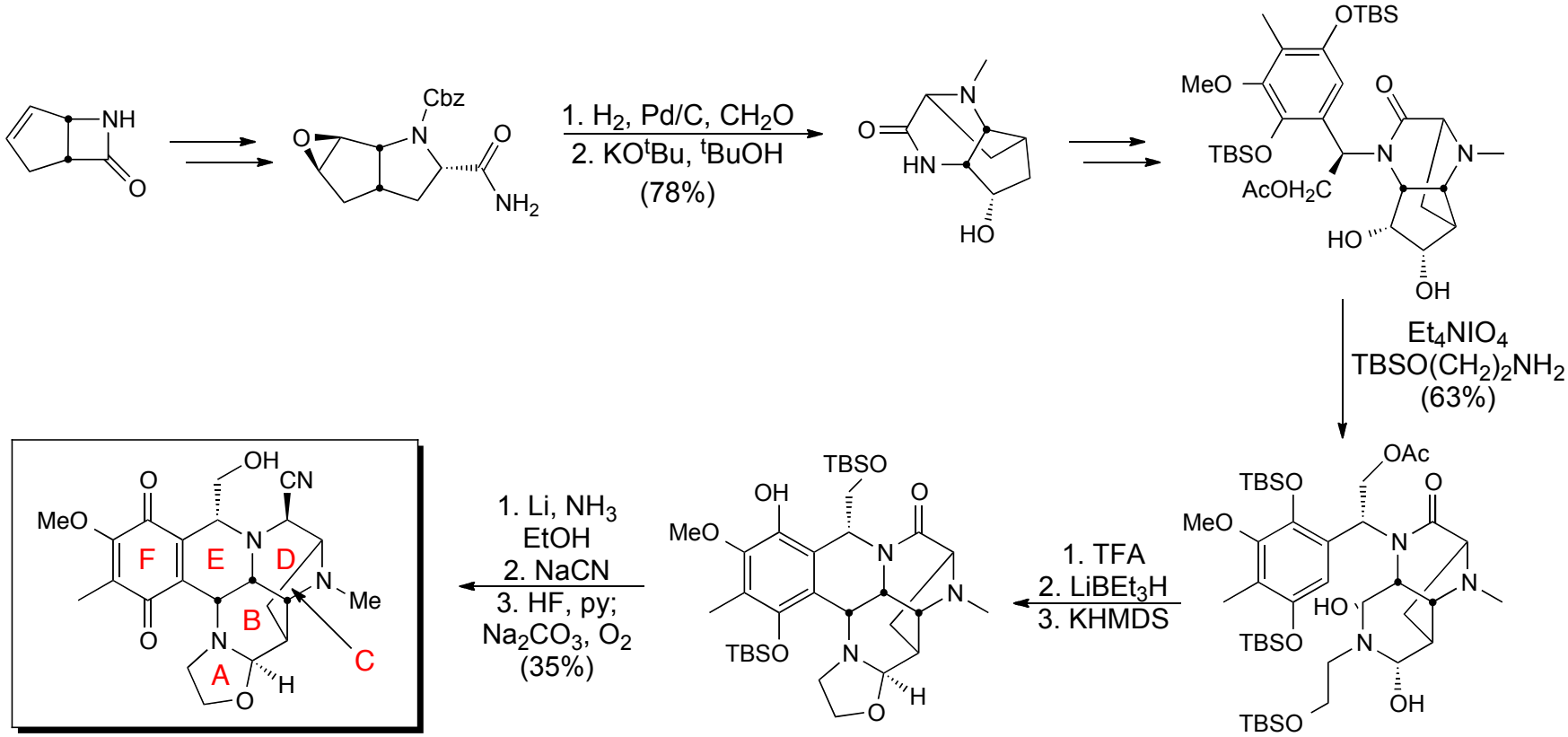
Cyanocycline A



Bioxalomycin β2

- 2 prior total syntheses of cyanocycline A have been completed:
  - Evans (1985 and 1987)
  - Fukuyama (1987 and 1992)
  - Wipf (partial – 2006)

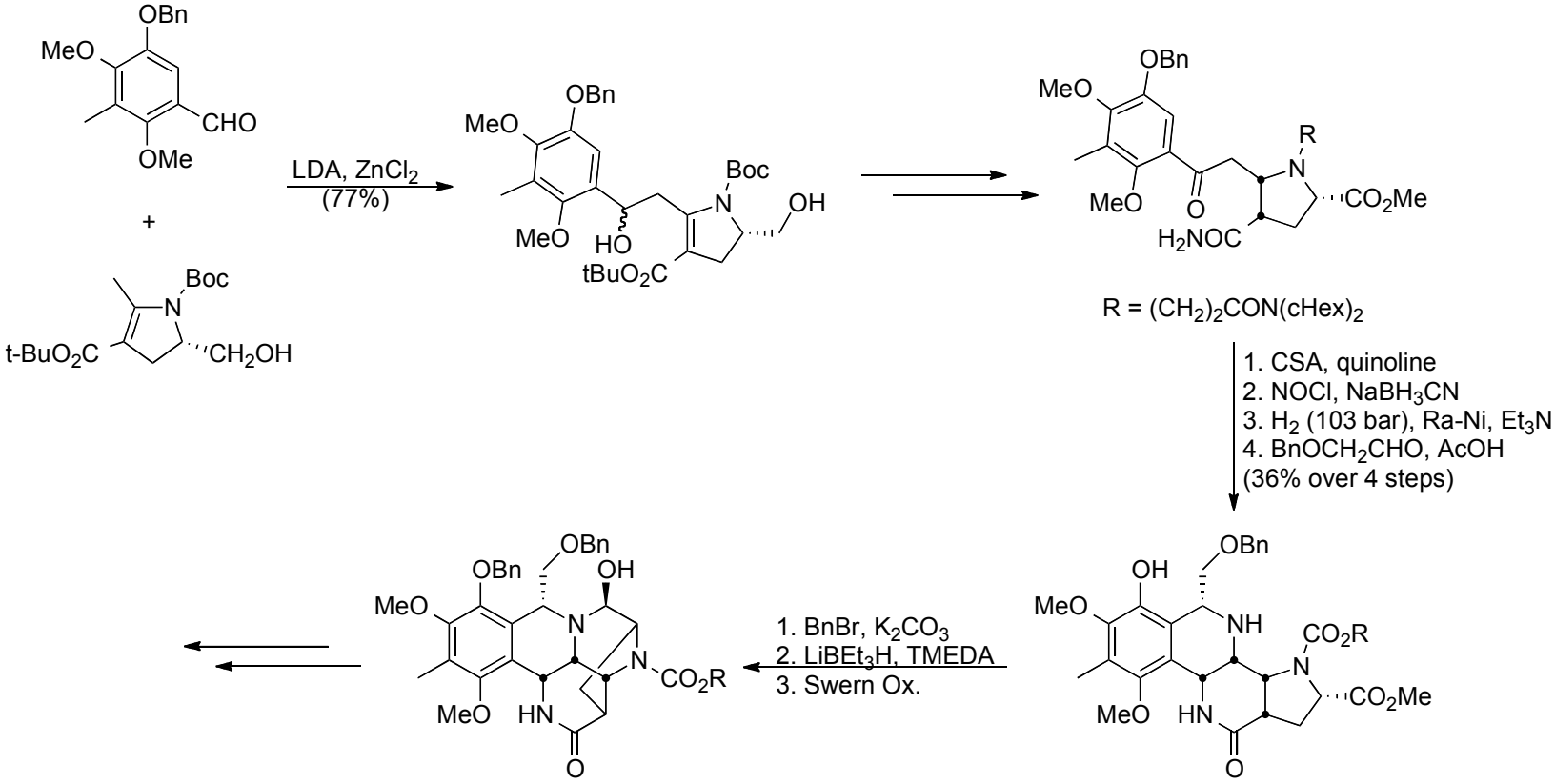
Evans' Total Synthesis of Cyanocycline A



- 31 steps, 1.8% overall
- Key Reactions:
  - Pictet Spengler and epoxide opening

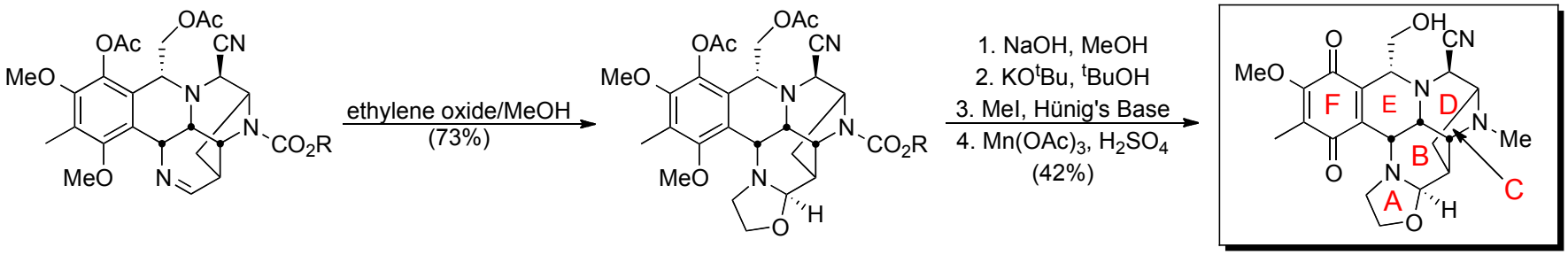
Evans, D.A.; Biller, S.A. *Tet. Lett.* **1985**, *26*, 1907-1910.
Evans, D.A.; Illig, C.R.; Saddler, J.C. *JACS*, **1986**, *108*, 2478-2479

Fukuyama's Total Synthesis of Cyanocycline A



Fukuyama, T.; Li, L.; Laird, A.A.; Frank, R.K. *JACS*, **1987**, *109*, 1587-1589

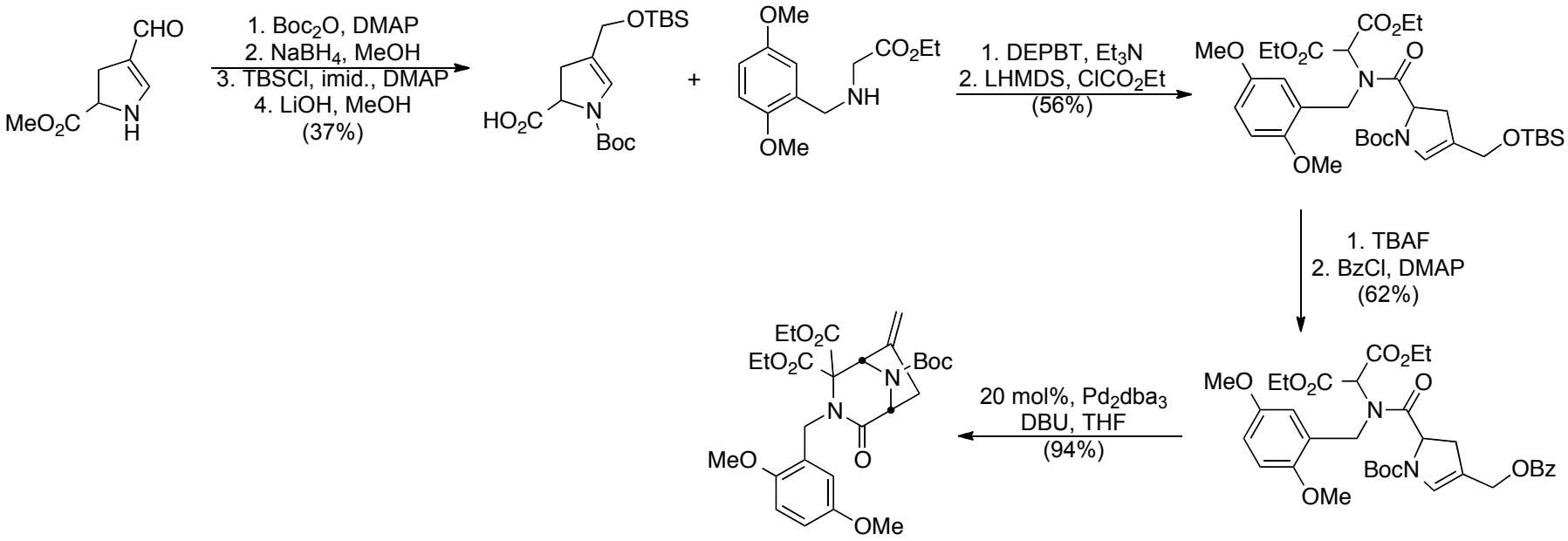
Fukuyama's Completion of Cyanocycline A



- 29 steps, 1.1% overall

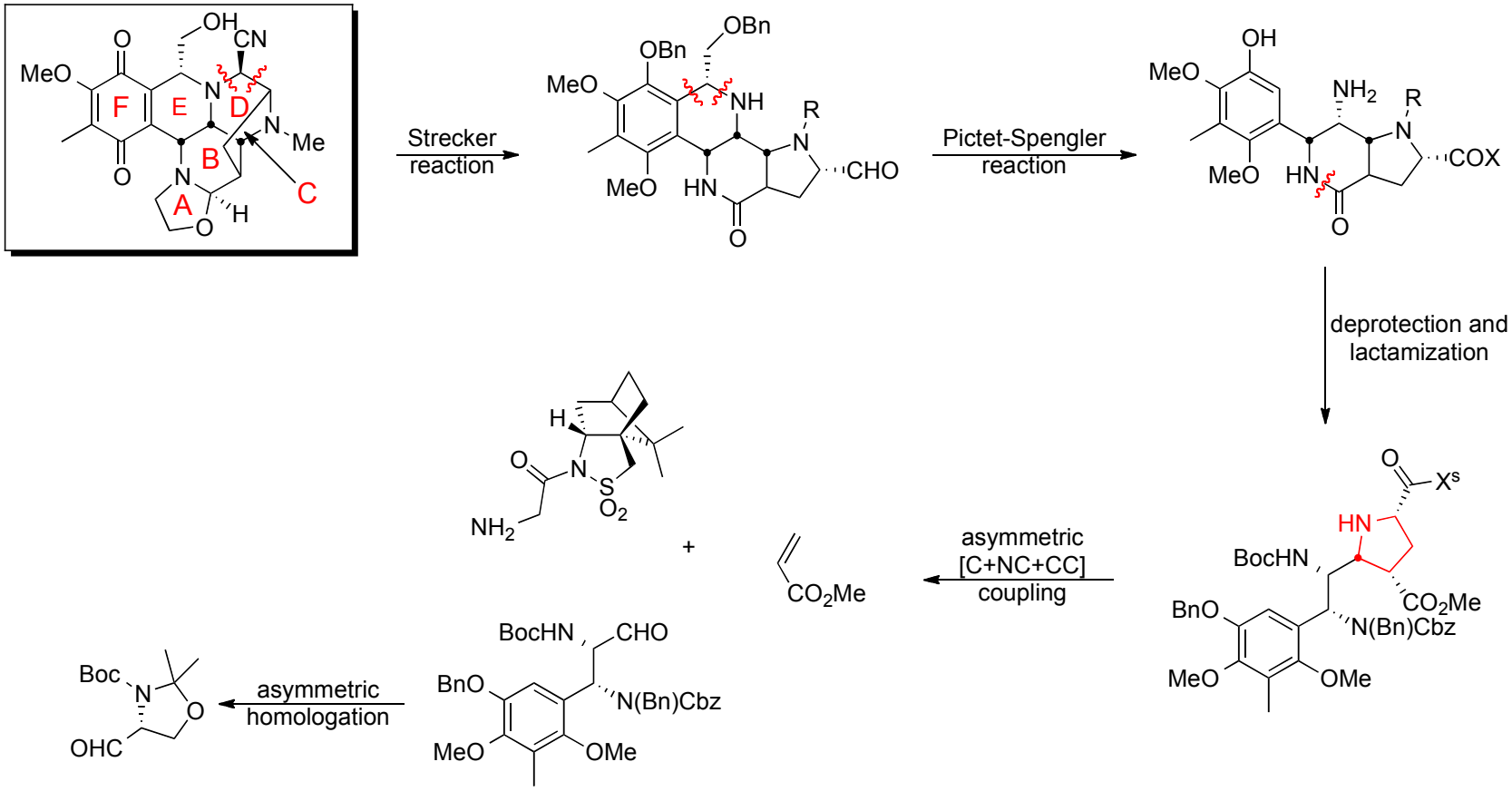
- Key Reactions:
  - Zinc di-enolate coupling
  - Nitrosyl chloride oxidation/oxime formation
  - Carbamate protecting group
  - Pictet-Spengler

Wipf Approach Towards Diazabicyclo[3.2.1]octane Core



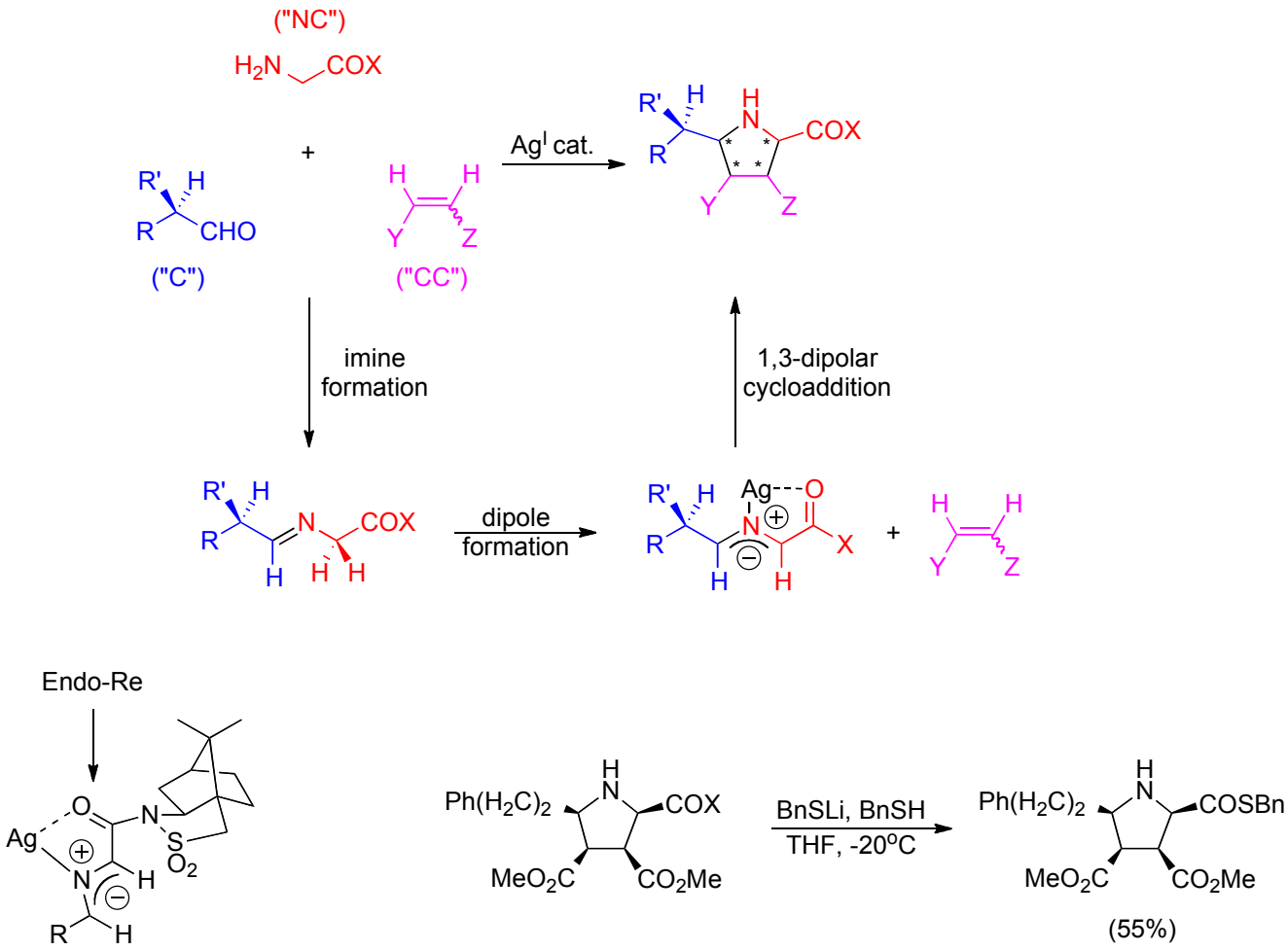
Wipf, P.; Grace, H.C.; Kim, S.H. *Tetrahedron* **2006**, *62*, 10507-10517.

Garner's Retrosynthetic Scheme



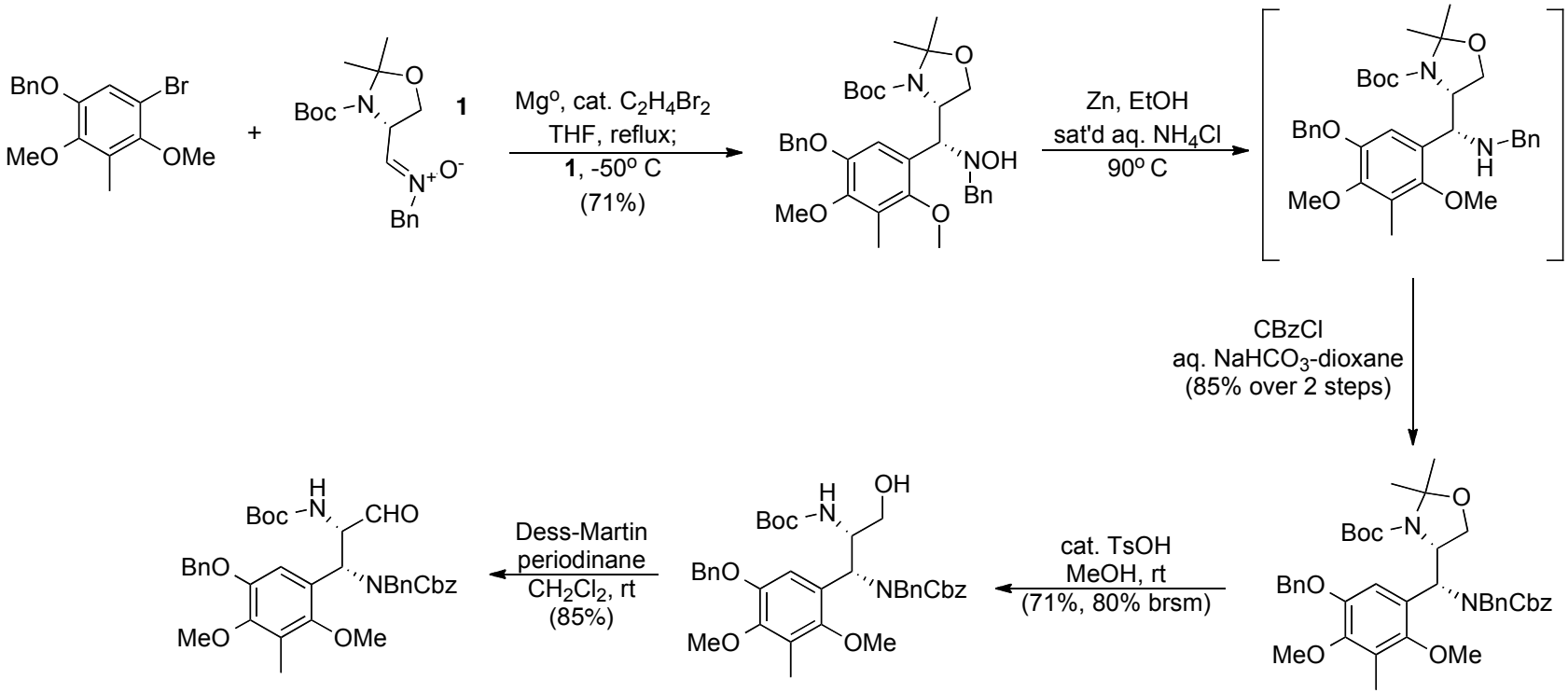
Garner, P.; Kaniskan, H. Ü.; Keyari, C.M.; Weerasinghe, L. *JOC*, **2011**, *ASAP*

Key Asymmetric [C+NC+CC] Coupling

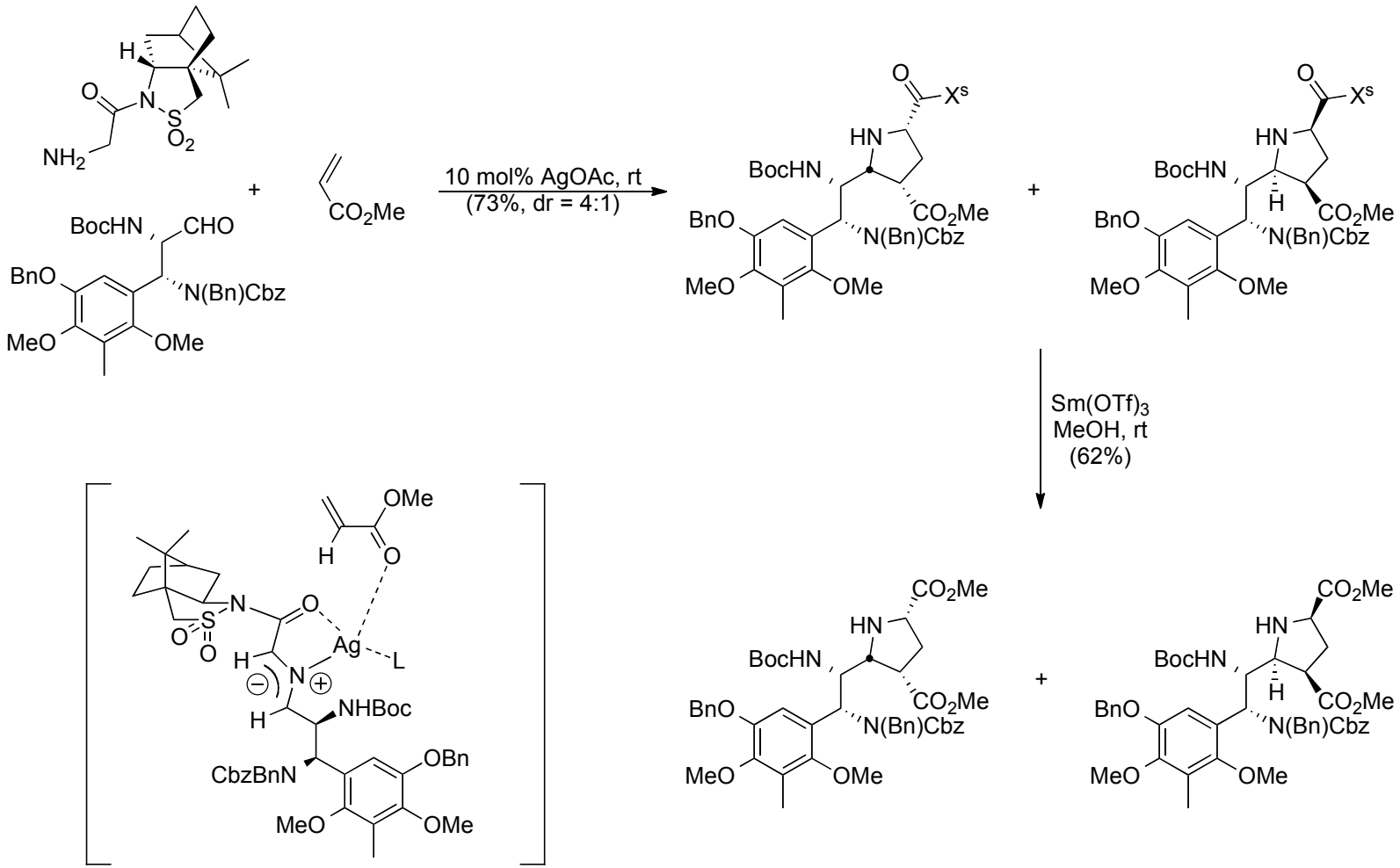


Garner, P.; Kaniskan, H.Ü.; Hu, J.; Youngs, W.J.; Panzner, M. *Org. Lett.* **2006**, *8*, 3647-3650.

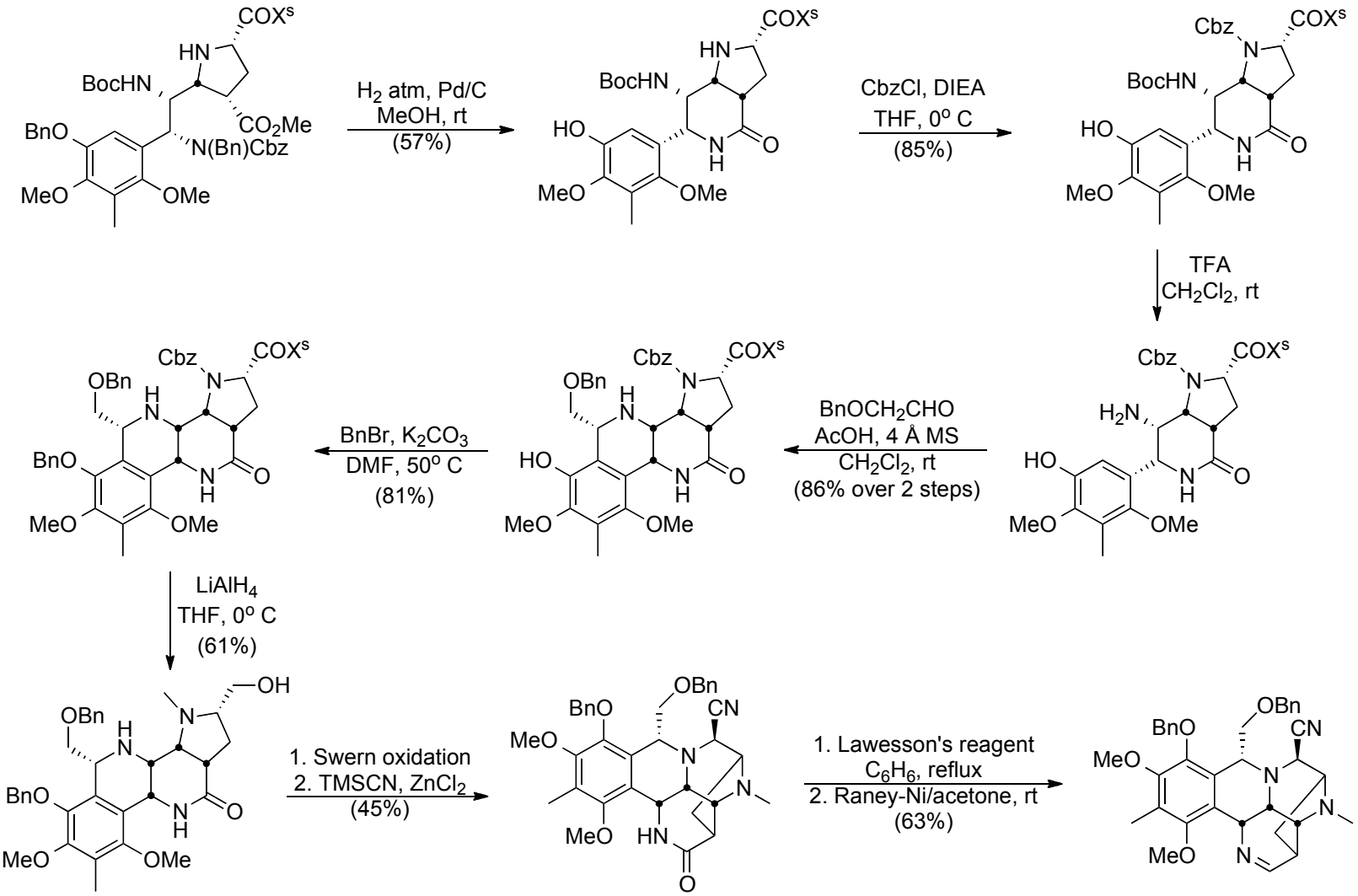
Garner's Total Synthesis of Cyanocycline A



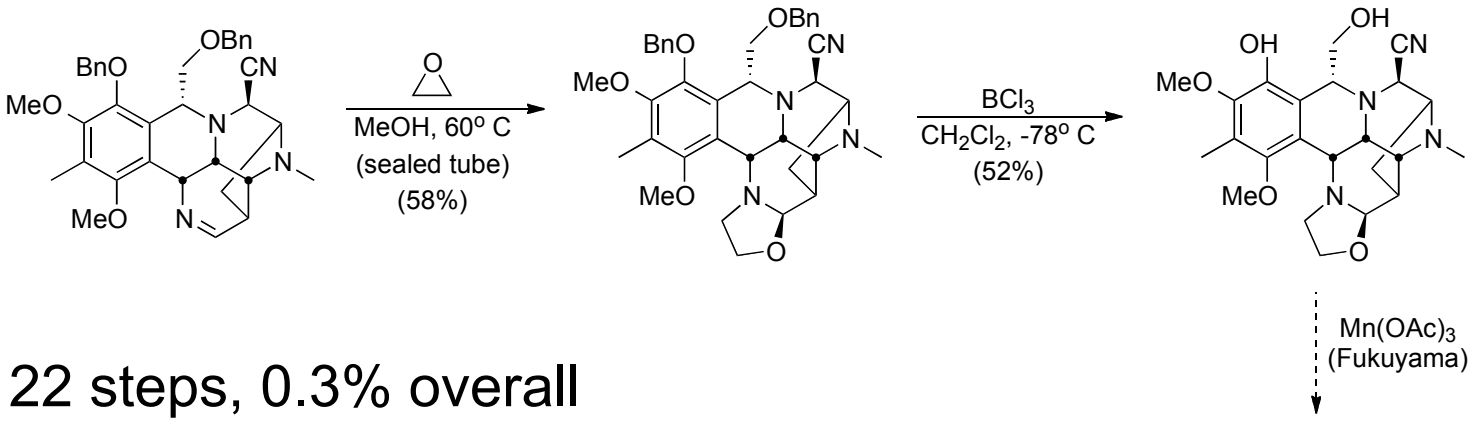
Garner's [C+NC+CC] Coupling

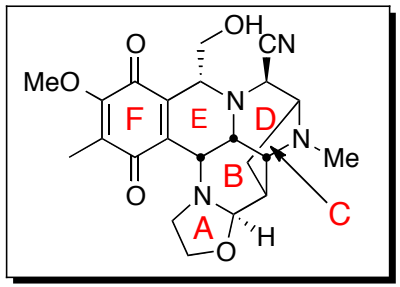


Garner's End Game



Garner's Formal Completion of Cyanocycline A





- 22 steps, 0.3% overall
- Key Reactions:
  - Stereoselective Grignard addition
  - [C+NC+CC] coupling
  - Pictet-Spengler
  - Late stage "D" ring closure

Conclusions

- Formal synthesis of bioxalmycin β2 and 3rd completed synthesis (formal) of cyanocycline A
- Currently the shortest synthesis although lower yielding than previous syntheses
- Novel [C+CN+CC] coupling reaction utilized