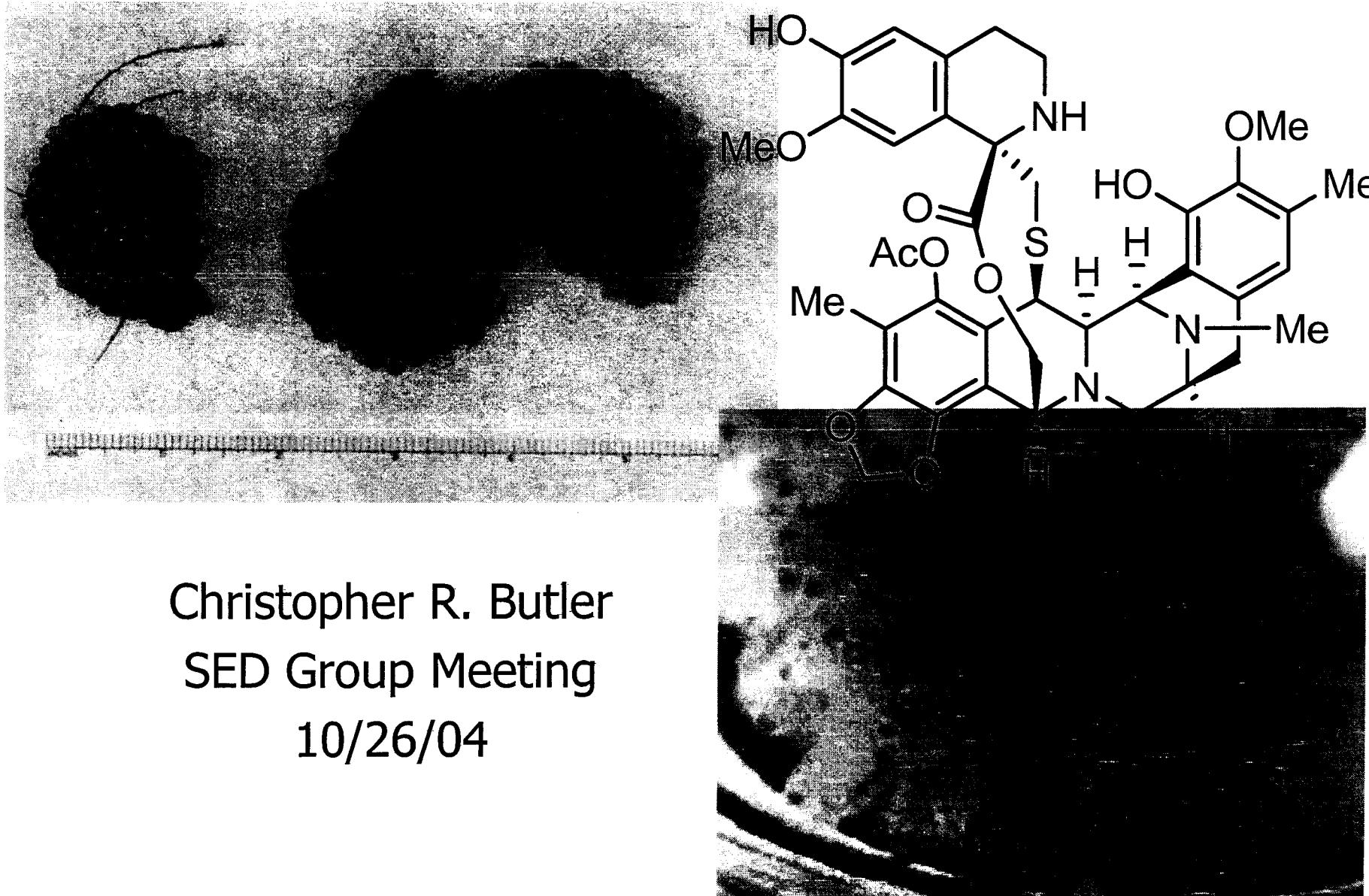


Ecteinascidin 743



Christopher R. Butler
SED Group Meeting
10/26/04

Isolation/History

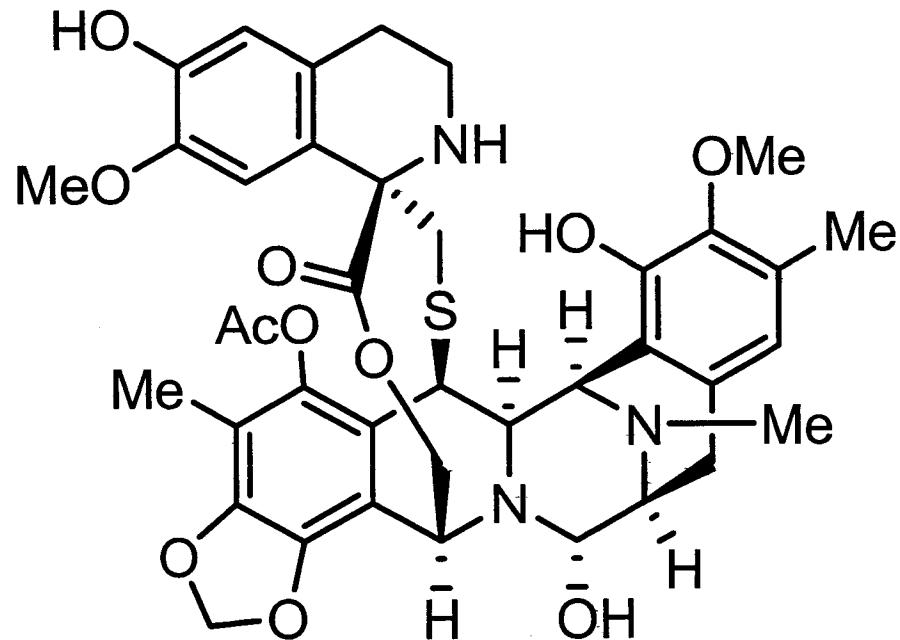
- 1970- *Ecteinascidia turbinata* (Mangrove Tunicate) extracts tested against leukemic mice. Afforded 50% cure rate.
- 1986- Prof. Rinehart and Tom Holt at UIUC isolated and elucidated the structure of Ecteinascidin 743 (ET 743).
- 1996- First Total Synthesis by Corey, Gin, Martinez.

Sigel, M. M.; Wellham, L. L.; Lichter, W.; Dudeck, L. E.; Gargus, J. L.; In *Food-Drugs from the Sea*, Youngken, H. W., ed., Marine Technological Society, Washington, D.C., 1970, pp 281-294.

Rinehart, K. L.; Holt, T. G.; Fergeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, Jr., T. J.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Siegler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijen, C. J. P.; Gade, G. *Journal of Natural Products* 1990, 53, 771-792

Corey, E.J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* 1996, 118, 9202-9203

ET 743-Reasonable Drug Candidate?



MW: 769.26

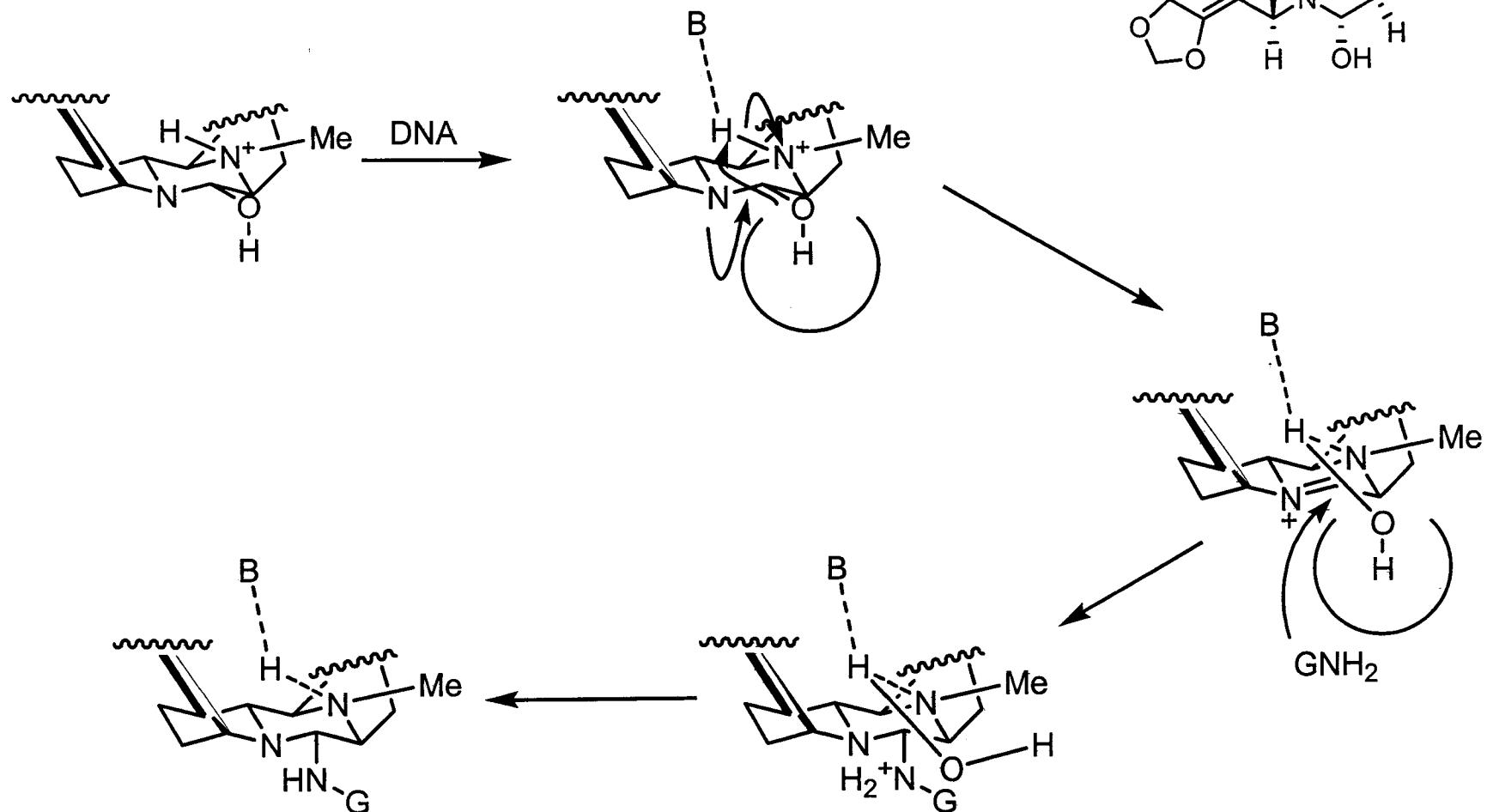
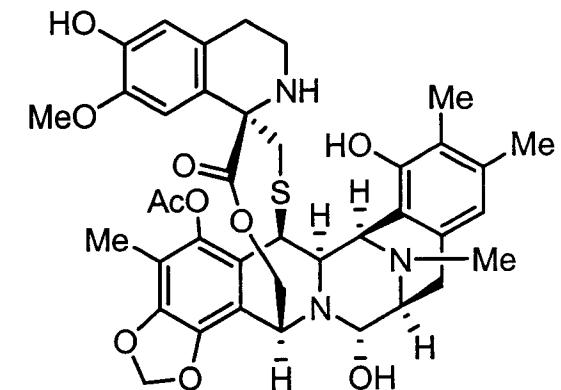
C₃₉H₄₃N₃O₁₁S

3 Hydrogen Acceptors, 4 Hydrogen Donors

Bio-activity (Summary)

- ET-743 (trabectedin, Yondelis®) found to cause objective remission >8-11 months for a variety of soft tissue sarcomas
- Toxicity a non-issue, as PK/PD doses demonstrate viability of chronic administration.
- Being tested in a combination with Paclitaxel, cisplatin, and others
- Currently in Phase II FDA trials

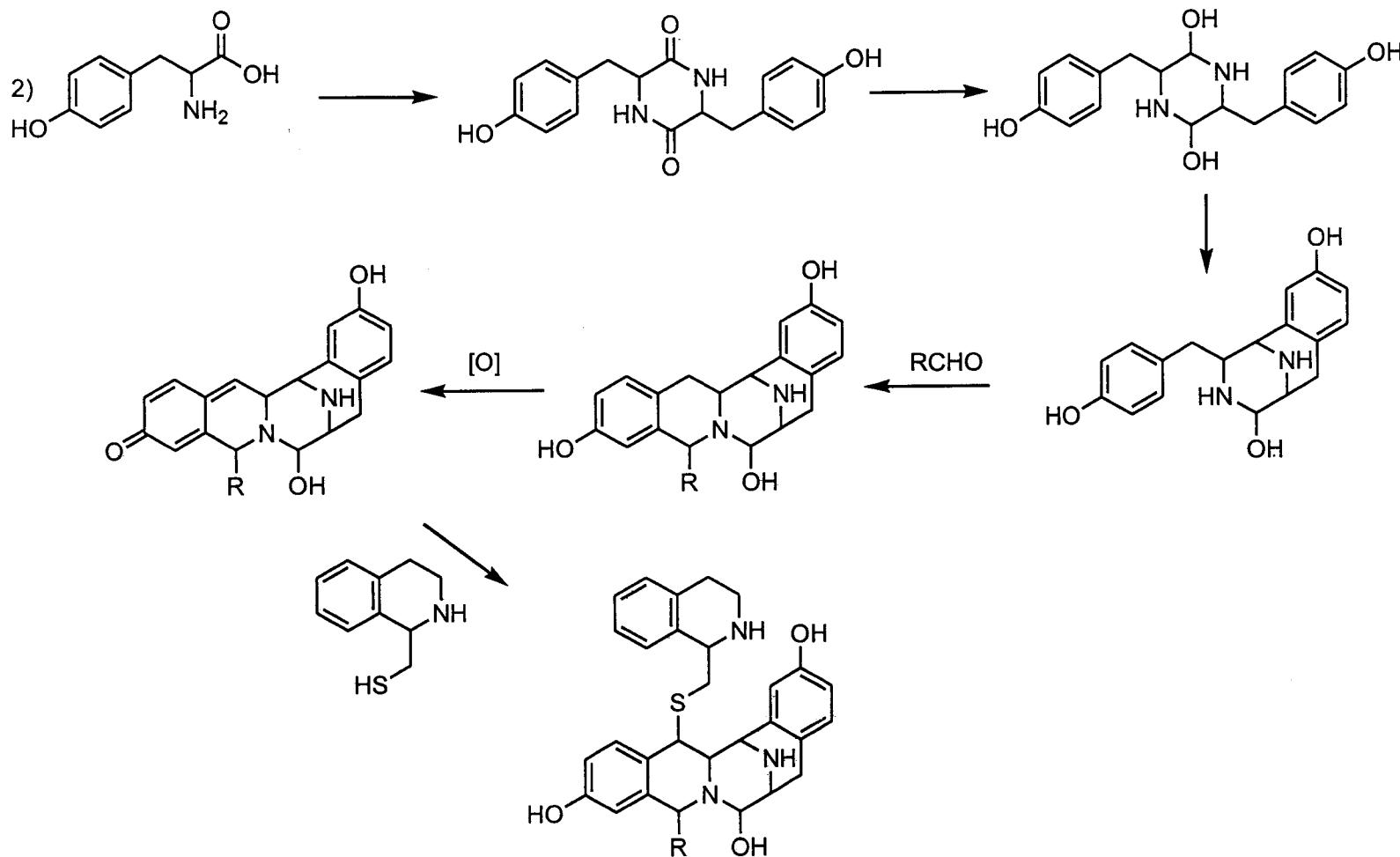
Mechanism of Action



Attempted (and Successful) Syntheses

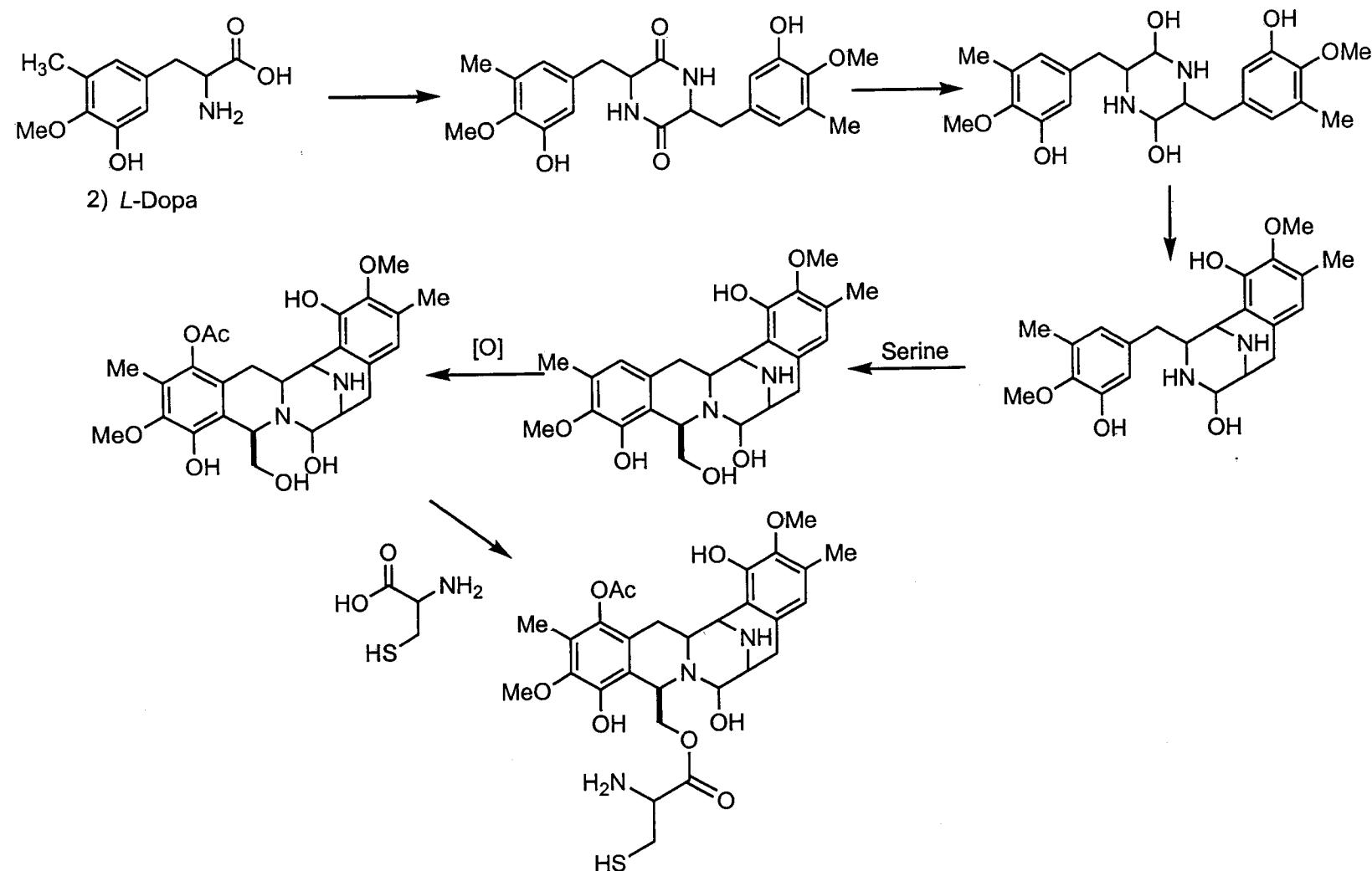
- 1996- Corey, 1st Total Synthesis
- 2000- Corey- New Route (kind of...)
- 2000- Pharma Mar, Commercial Synthesis
- 2002- Fukuyama, Total Synthesis
- 2002- Danishefsky, Partial Synthesis
- 2003- Williams, Partial Synthesis

Proposed Biosynthesis



Rinehart, K. L.; Holt, T. G.; Fergeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, Jr., T. J.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Siegler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijen, C. J. P.; Gade, G. *Journal of Natural Products* **1990**, *53*, 771-792

Empirical Biosynthesis

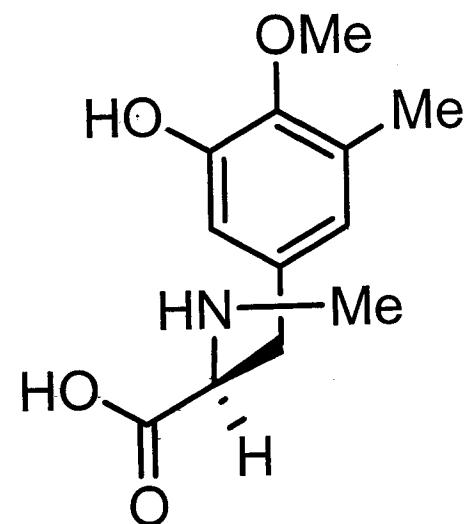
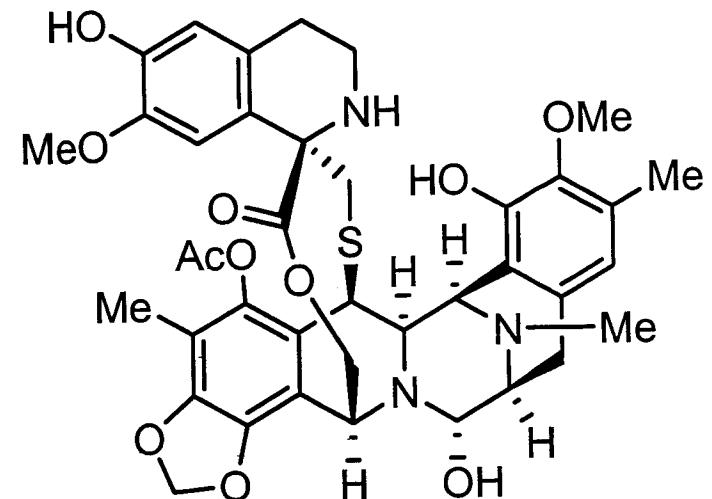
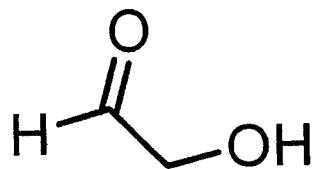
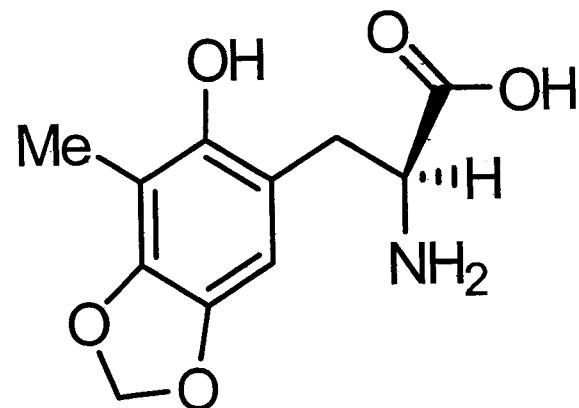
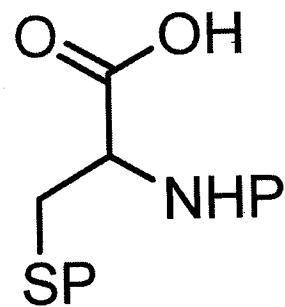
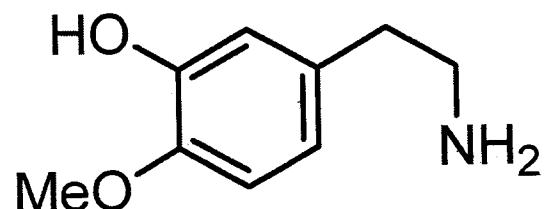


Kerr, R. G.; Miranda, N. F. *J. Nat. Prod.* 1995, 58, 1616-1621.

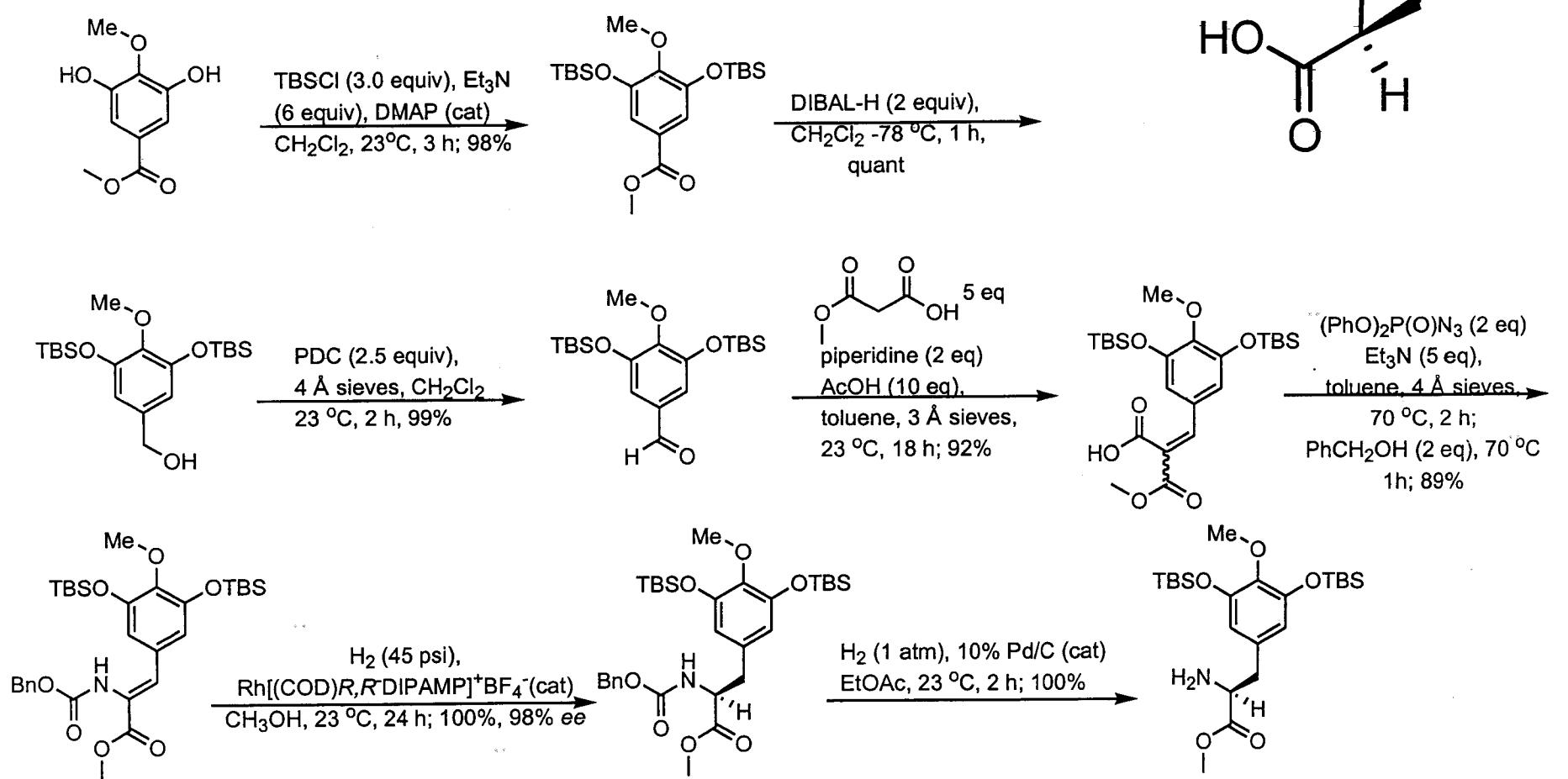
8

Morales, J. J.; Rinehart, K. L. 1995 International Chemistry Congress Pacific Basin Societies, Honolulu, Dec 17-22, 1995 Abstract
ORGN 184

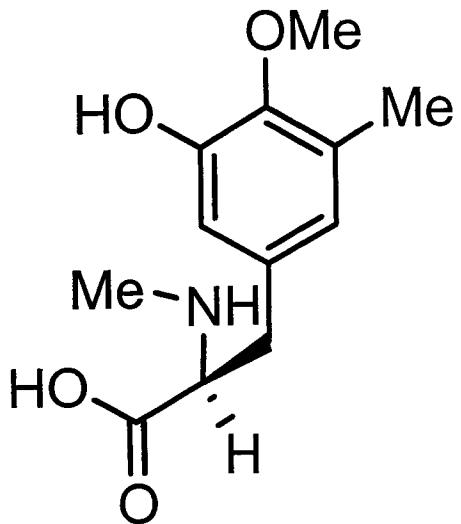
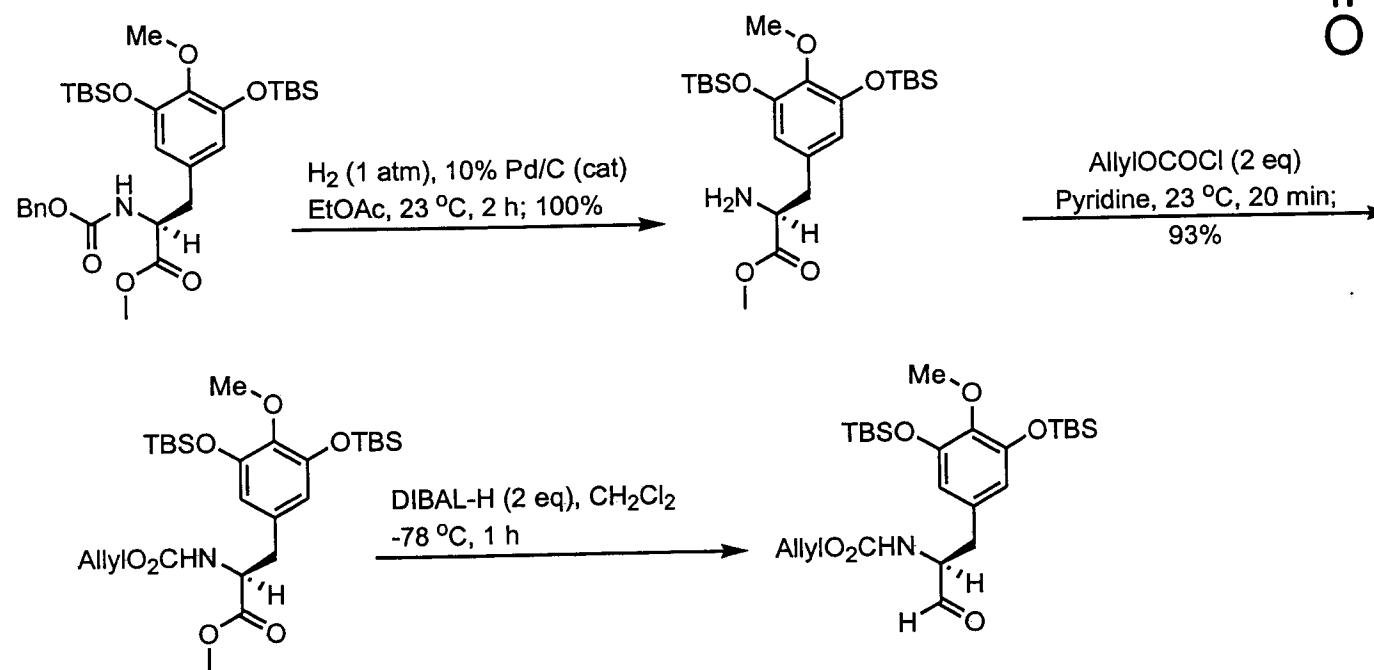
Retrosynthetic Analysis



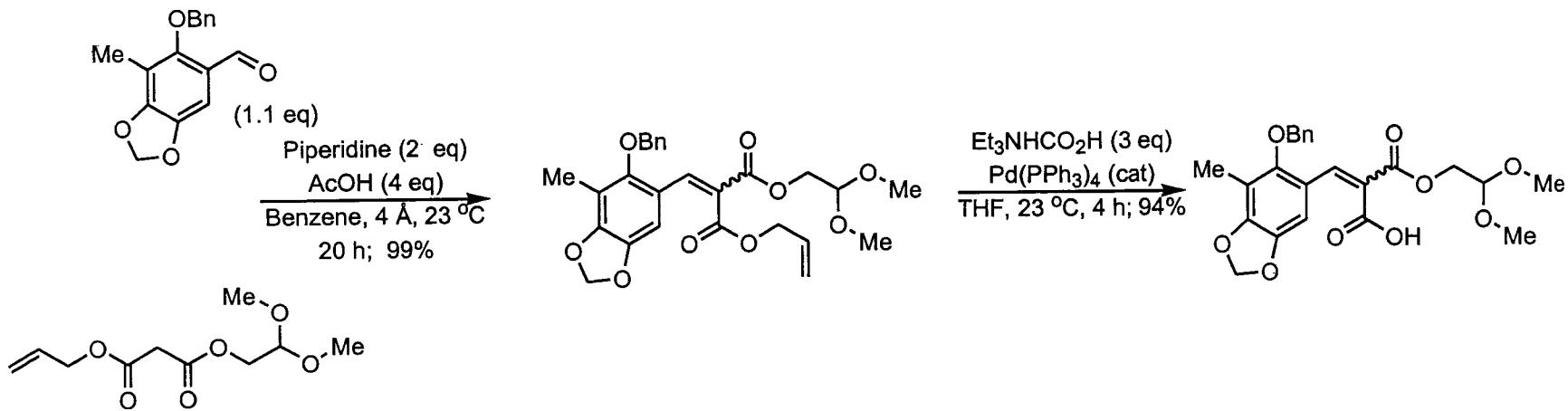
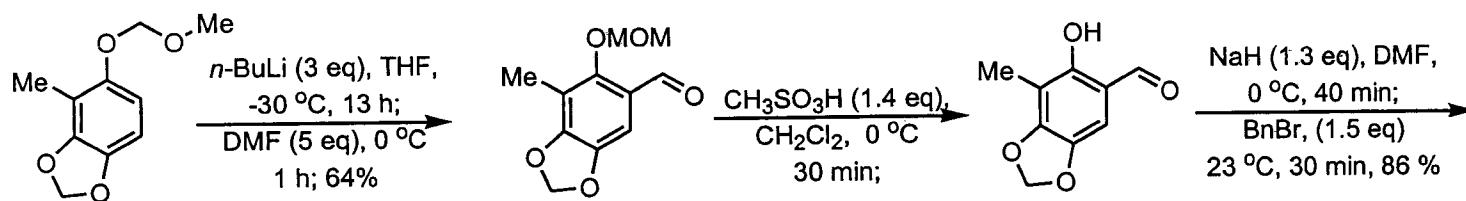
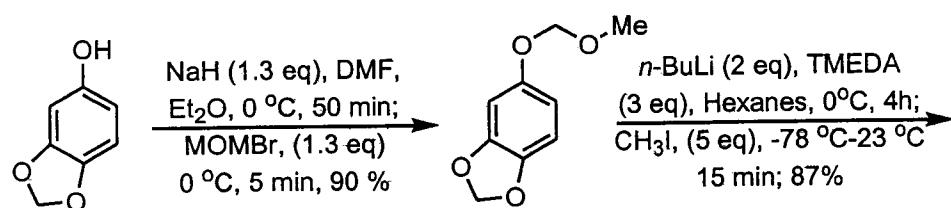
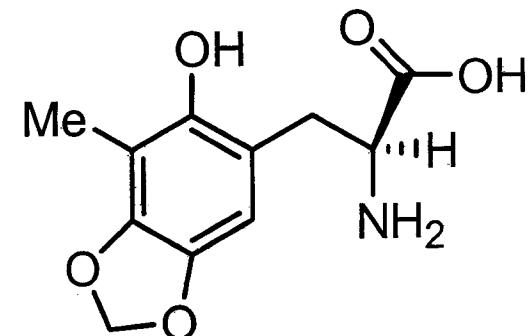
Commencement



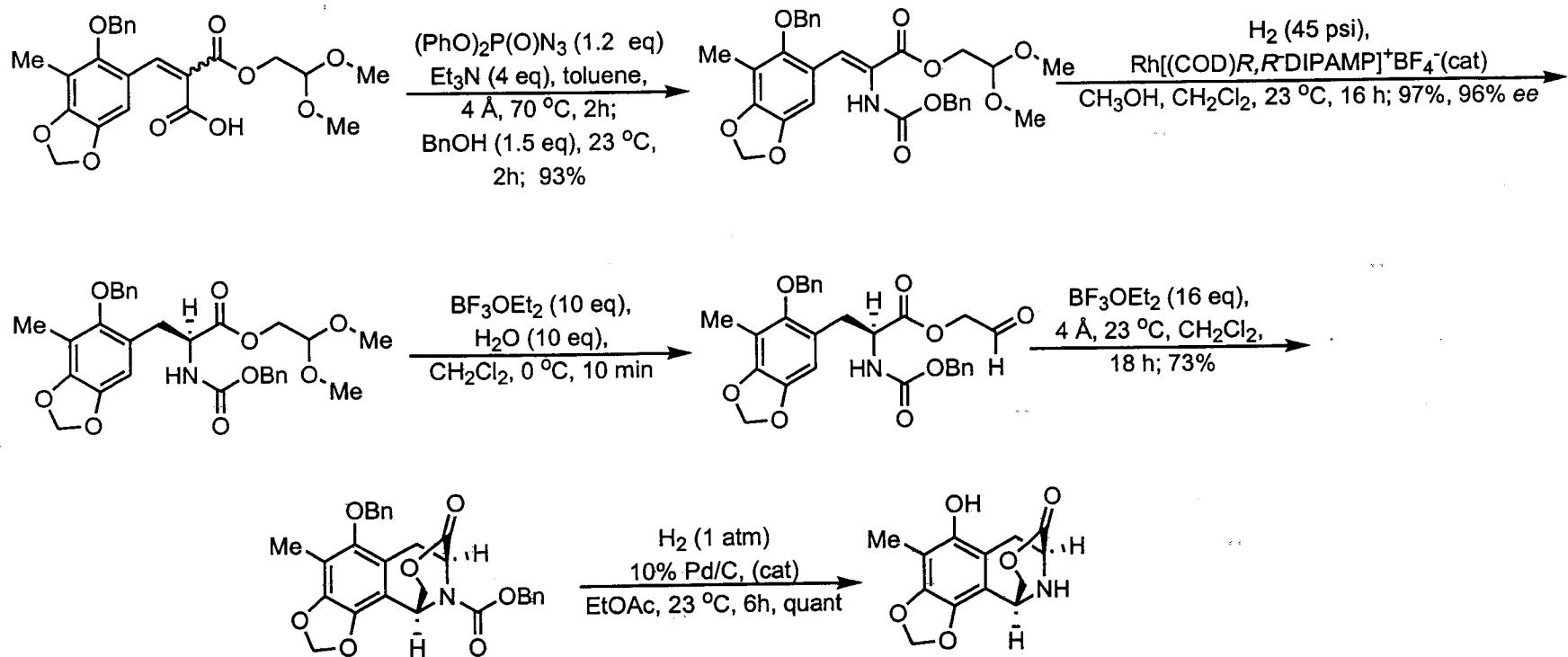
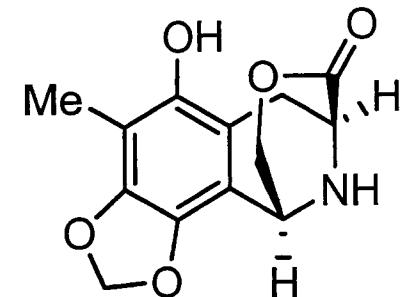
Eastern Front - Part II



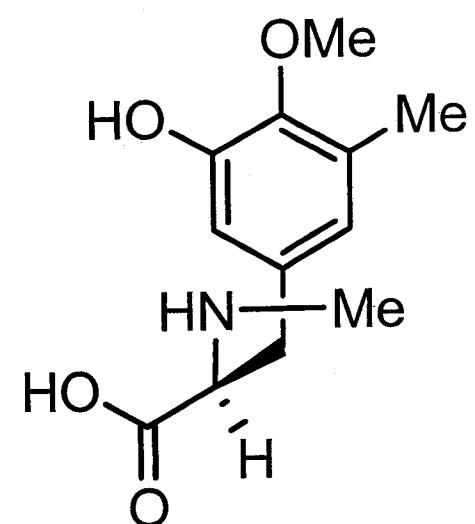
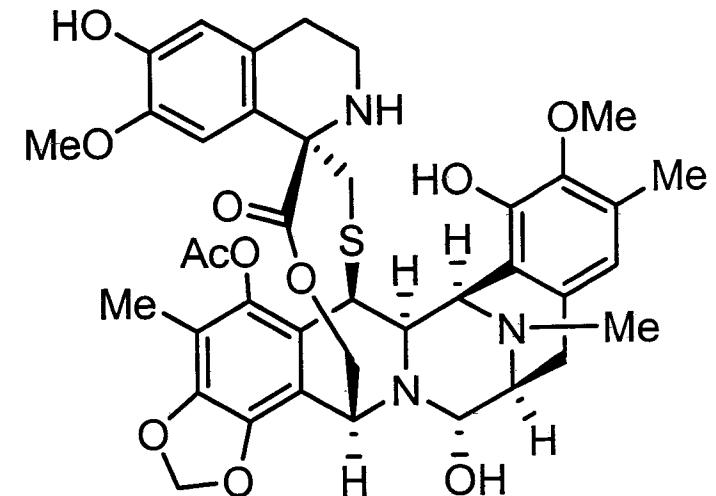
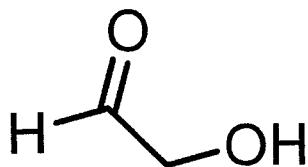
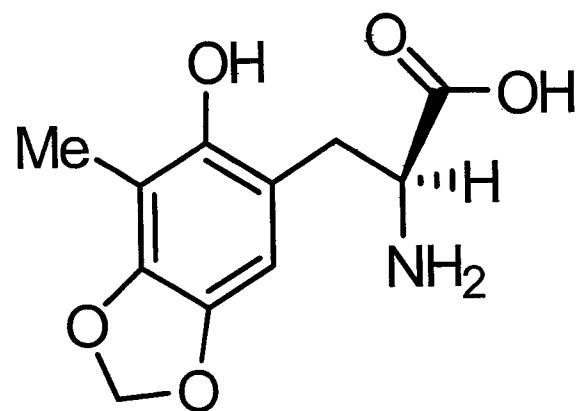
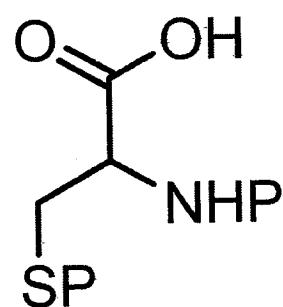
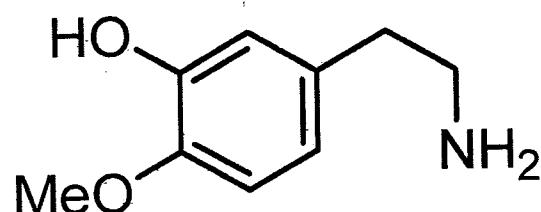
Western Half—Part I



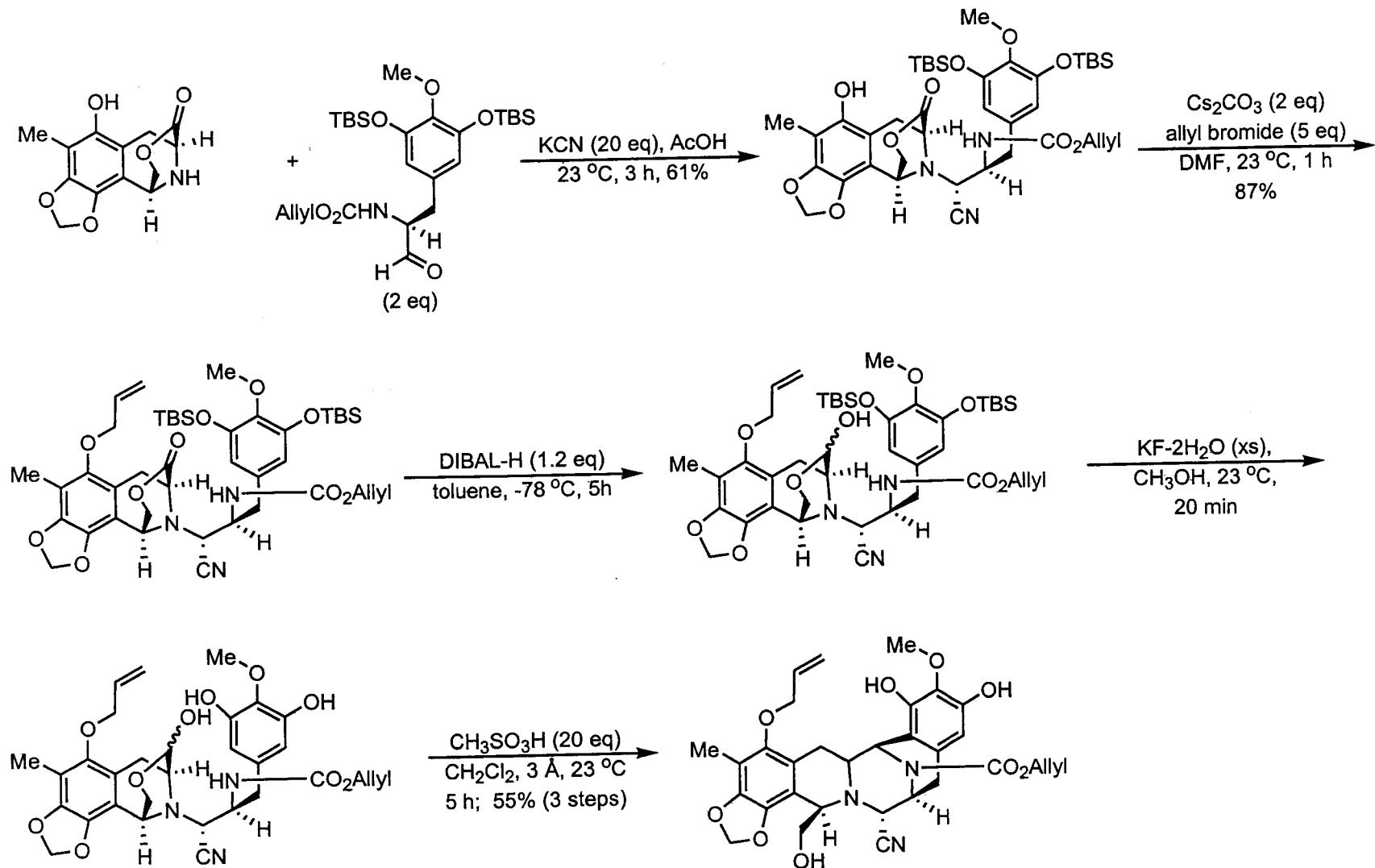
1st Pictet-Spengler



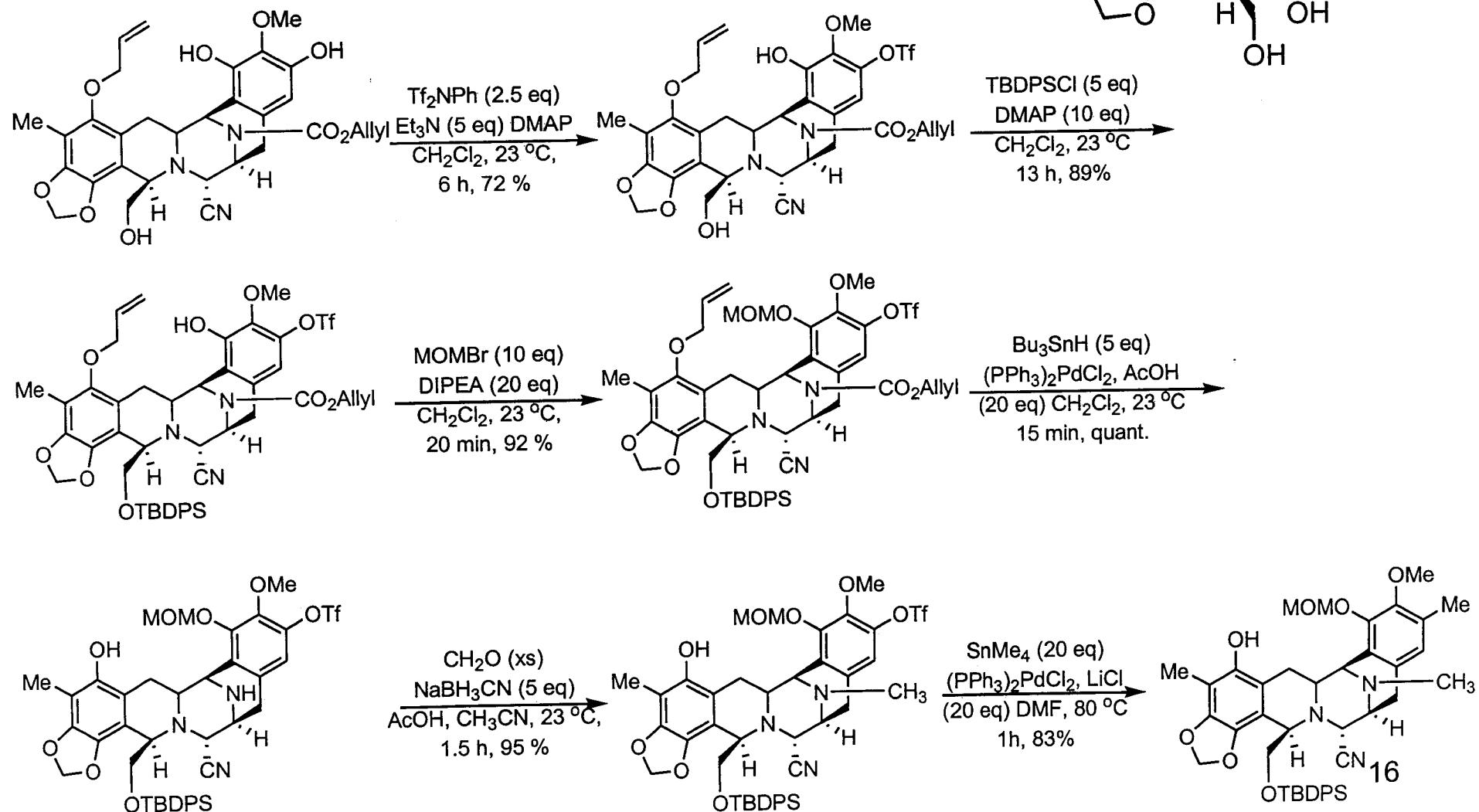
Retrosynthetic Analysis



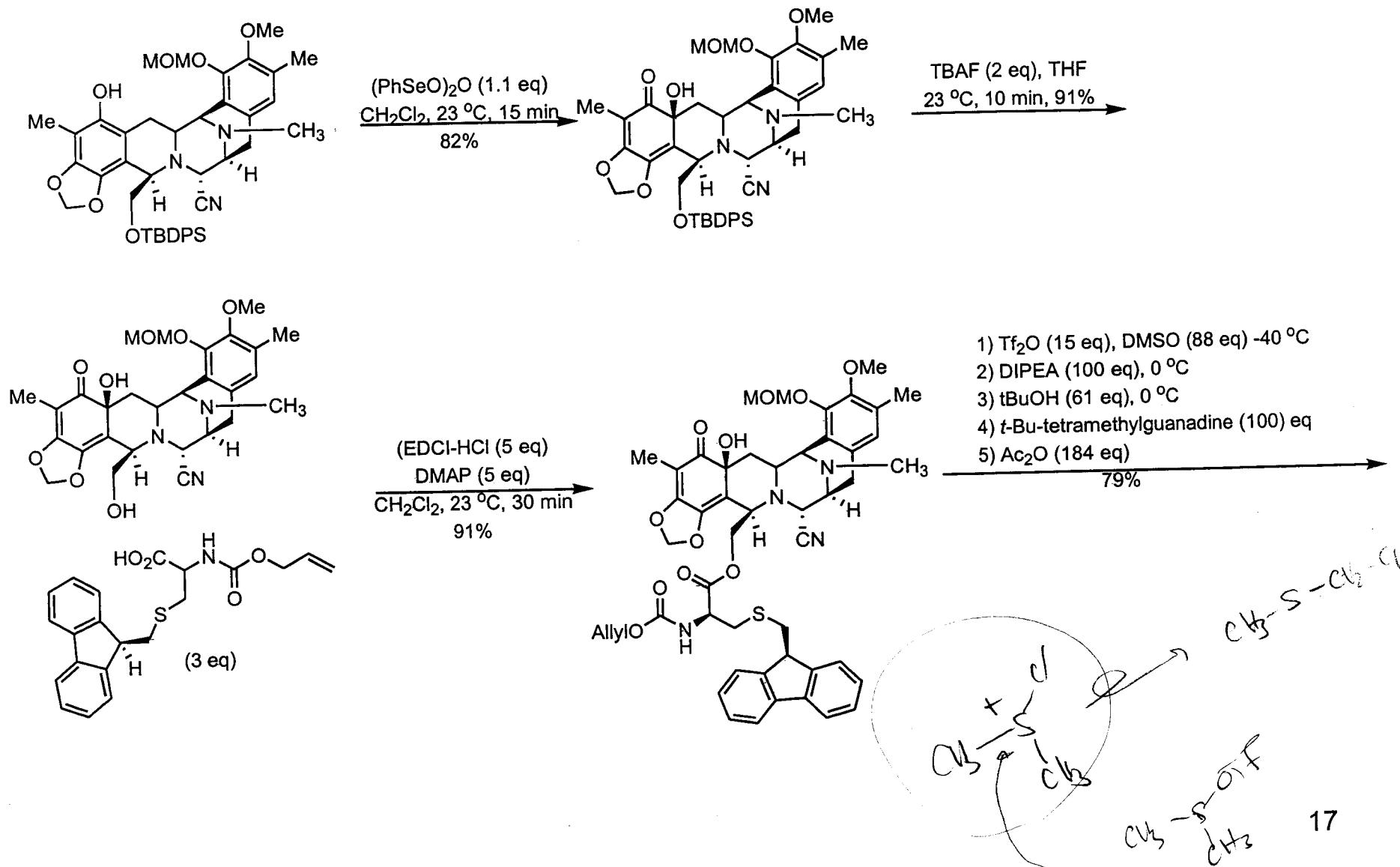
Pentacycle Formation



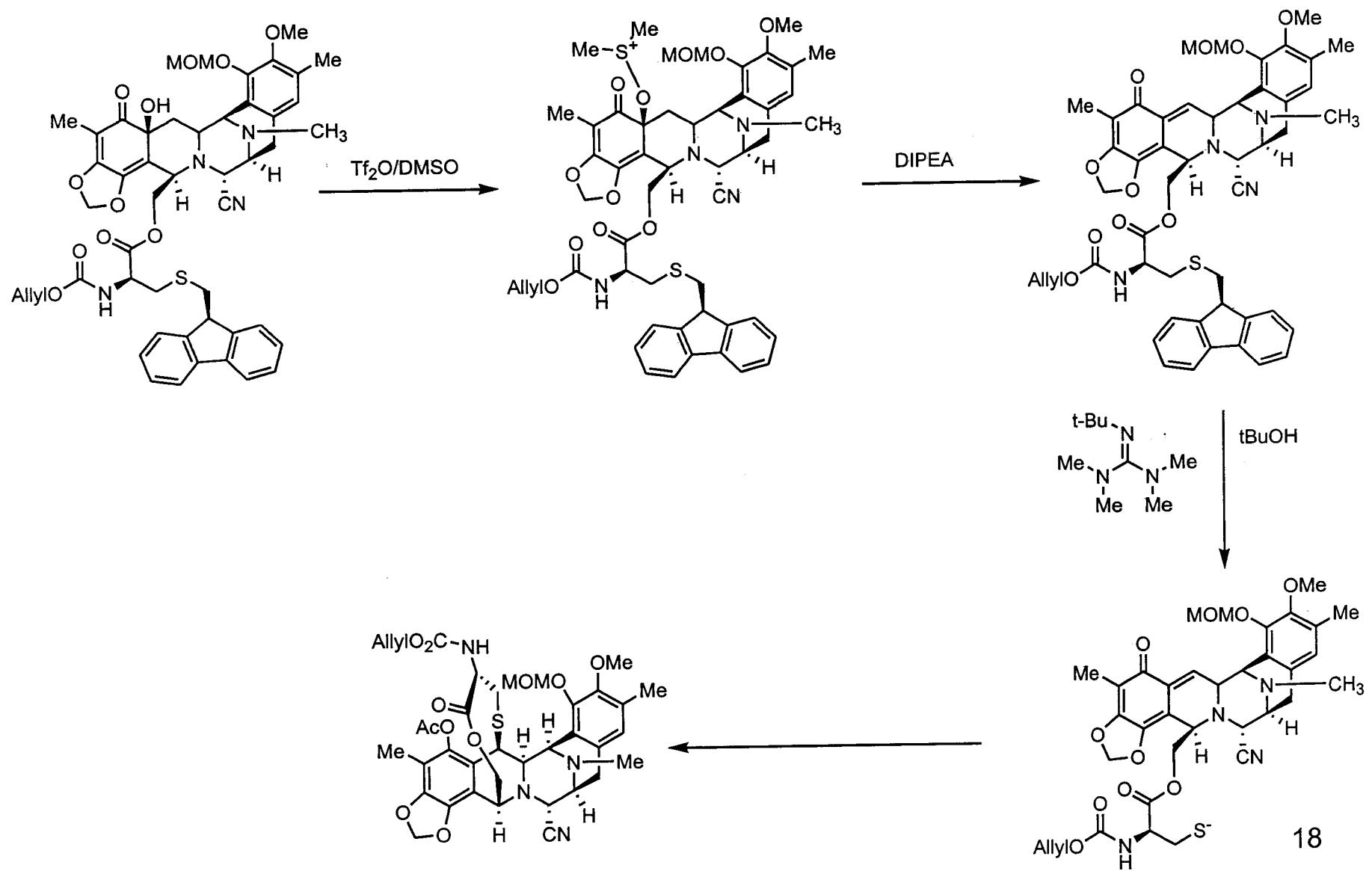
A Few Manipulations...



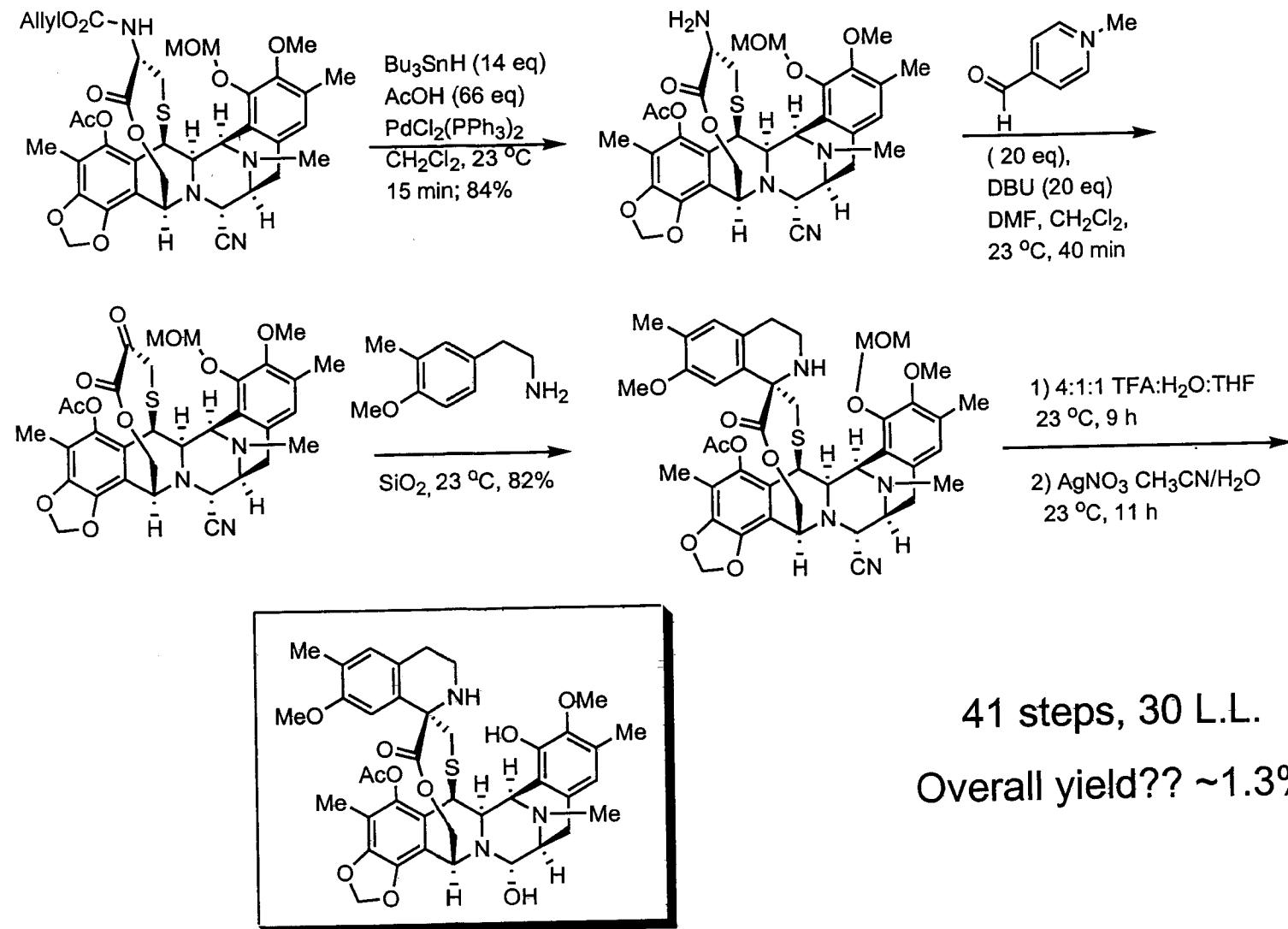
Elaboration of the Pentacycle



Bridge Building



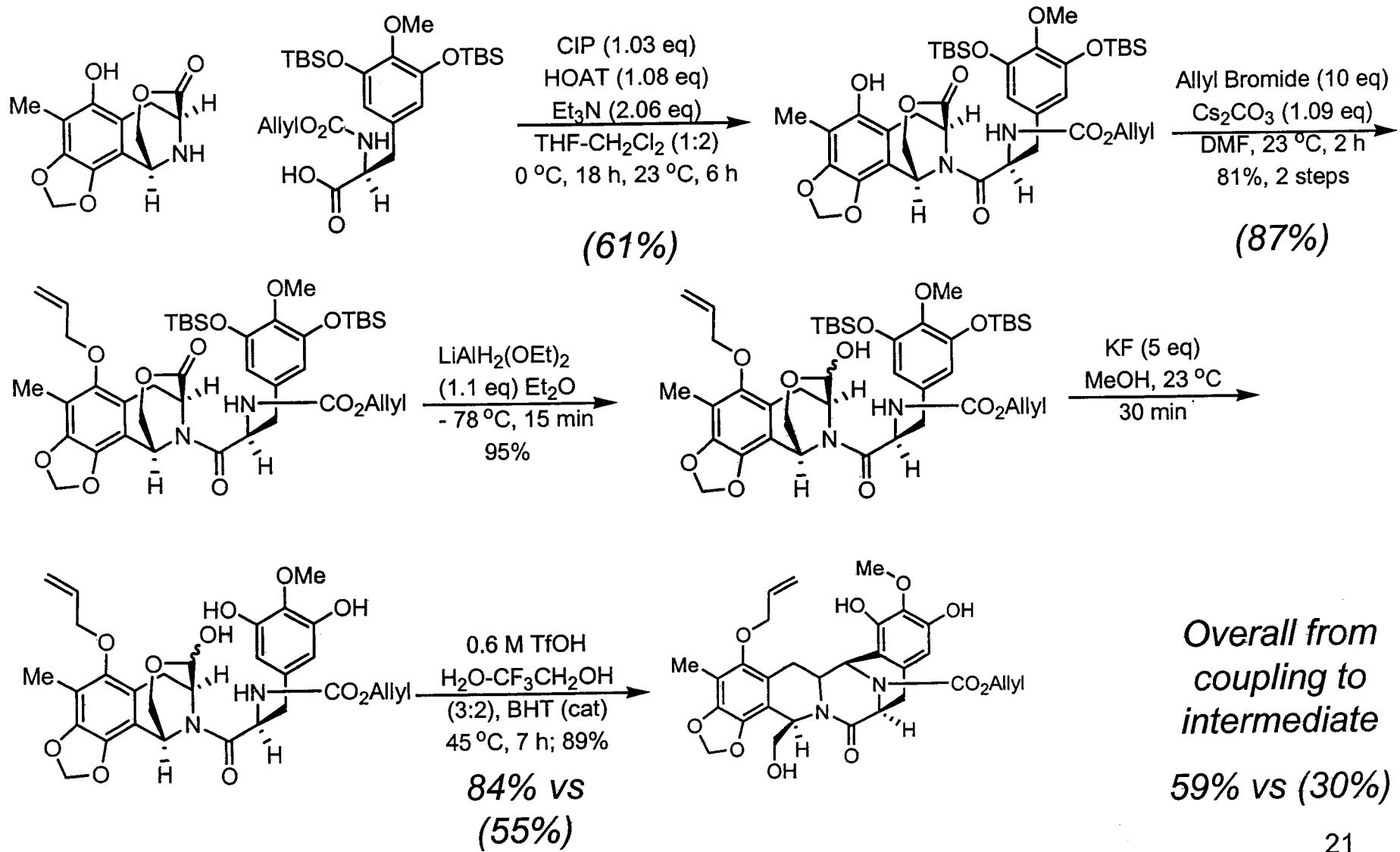
Endgame



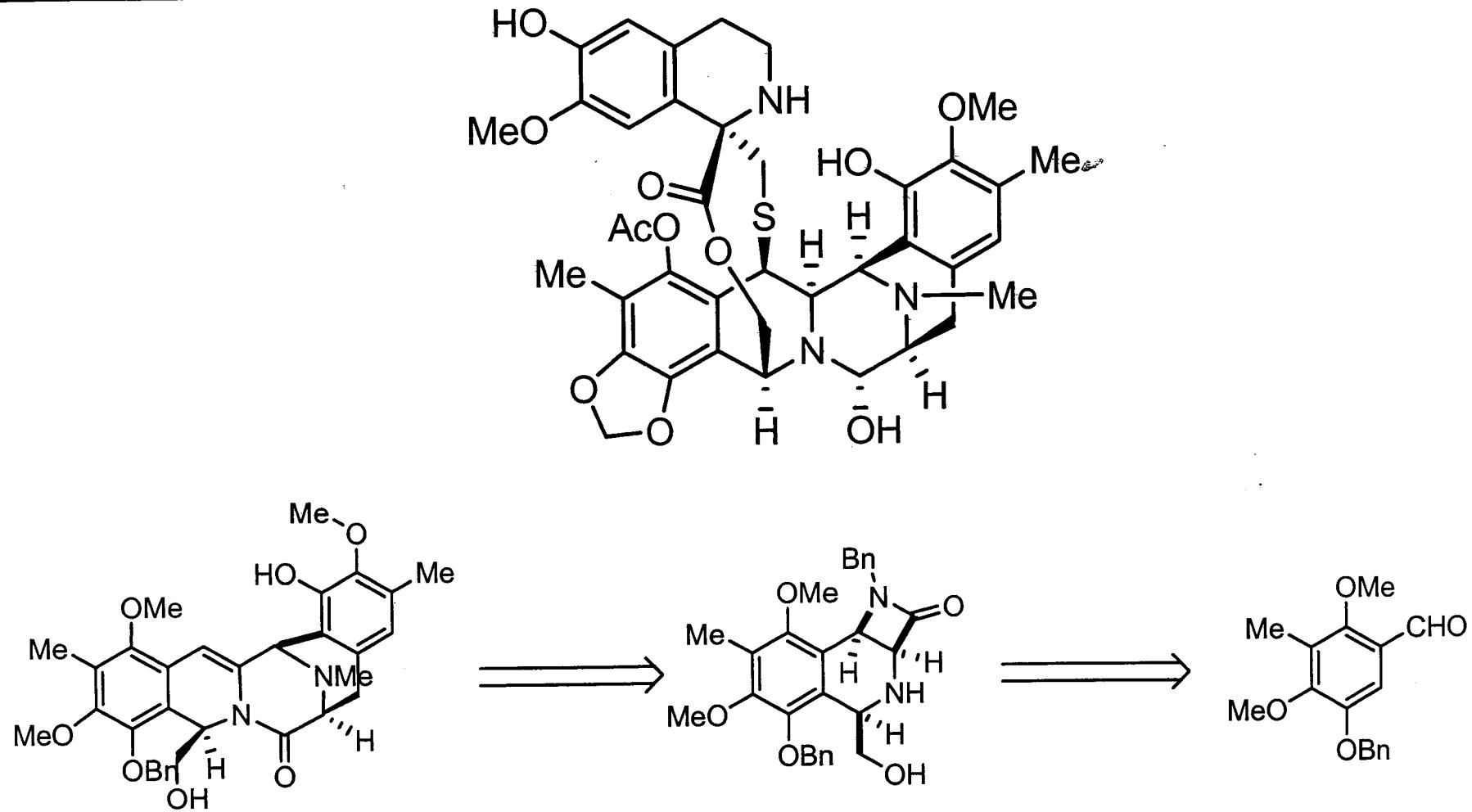
Corey Summary

- First total synthesis
- Follows proposed biosynthesis, uses 2 diastereoselective Pictet-Spengler rxns, 1 Mannich to set main rings
- Lots of PG manipulations 17 (41%)...
- Put together molecule in 24 steps
- Equally convergent and linear

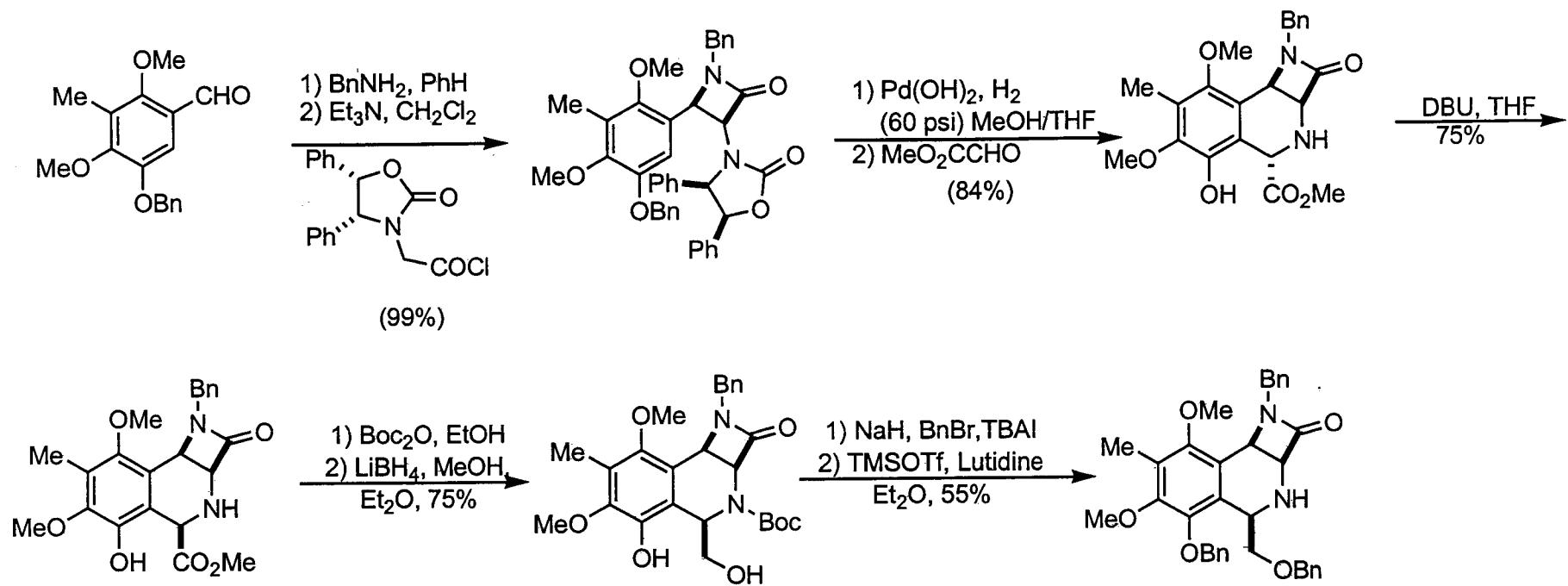
Improvement??



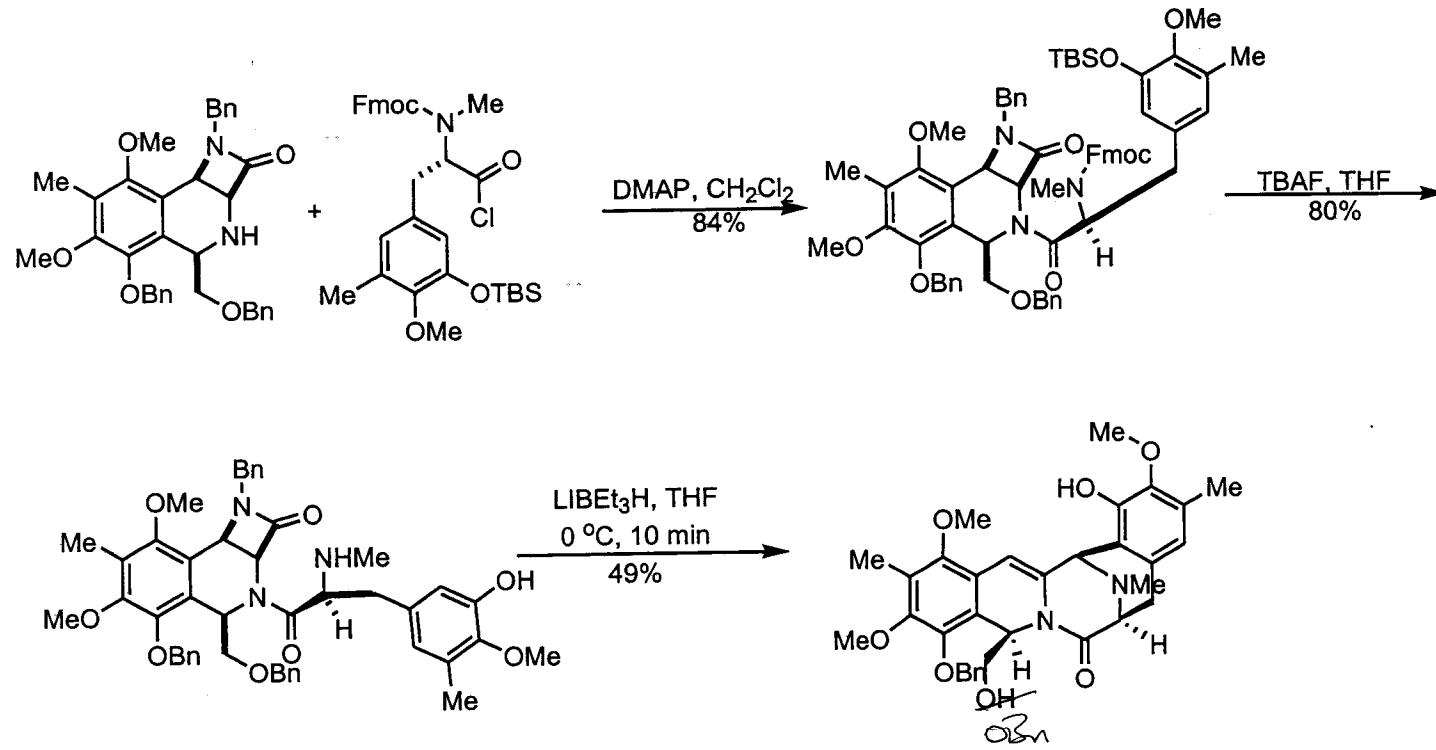
Williams Partial Synthesis



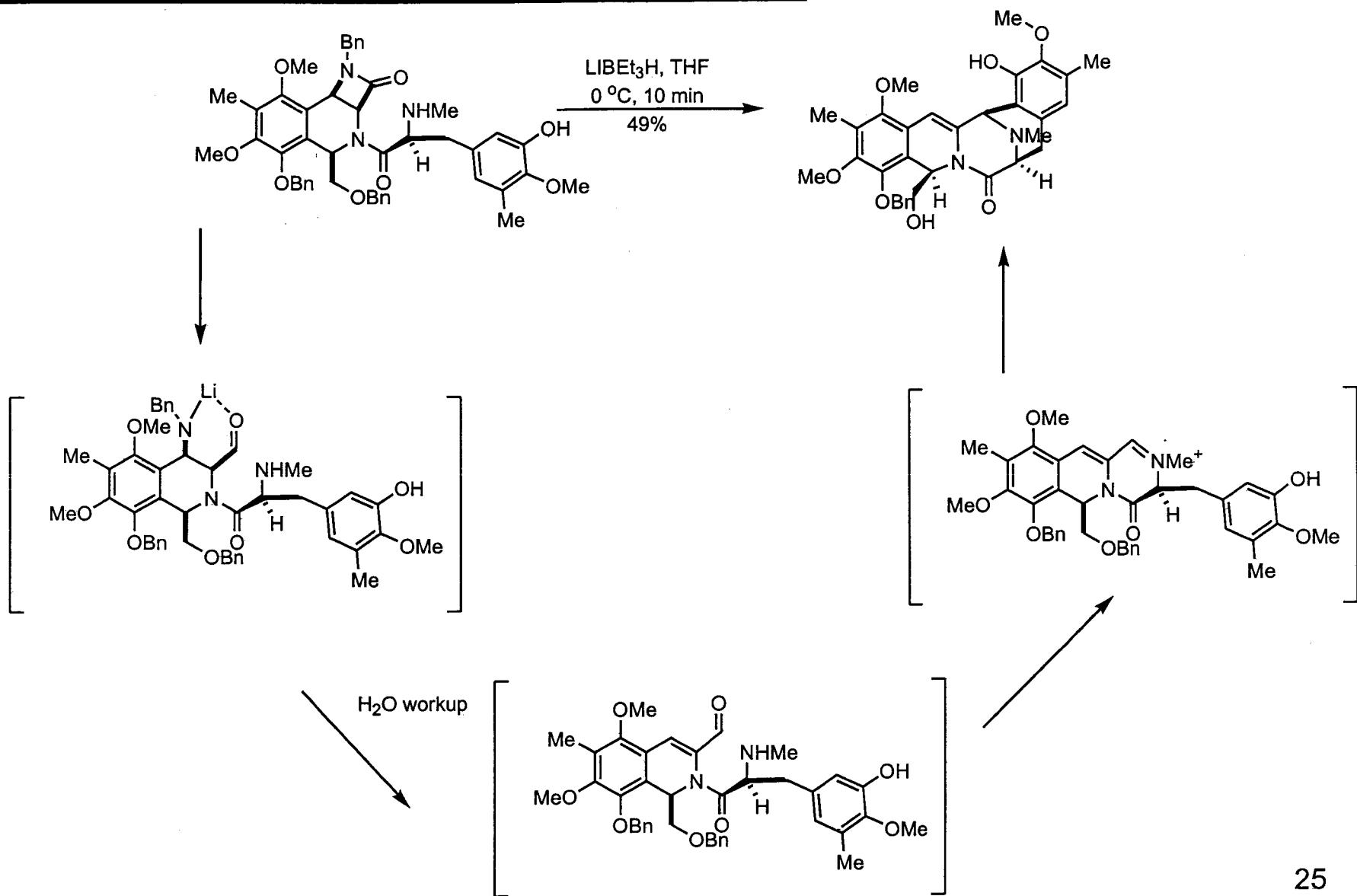
Staudinger/Pictet-Spengler



Coupling... and then:



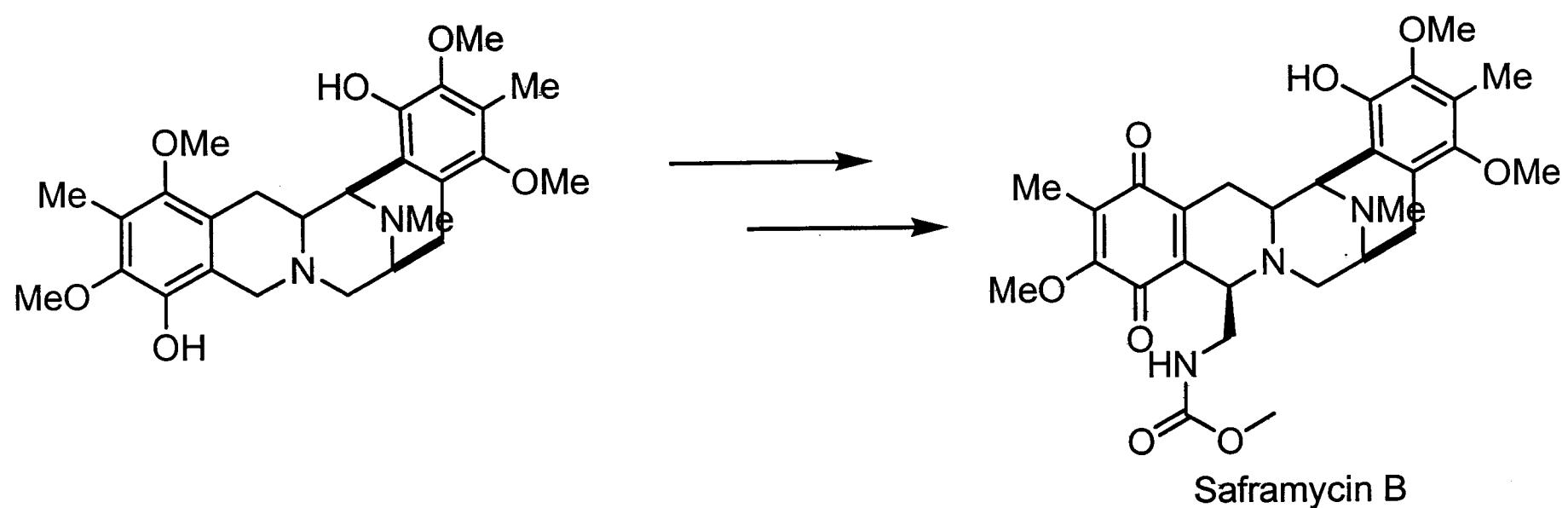
That last step...



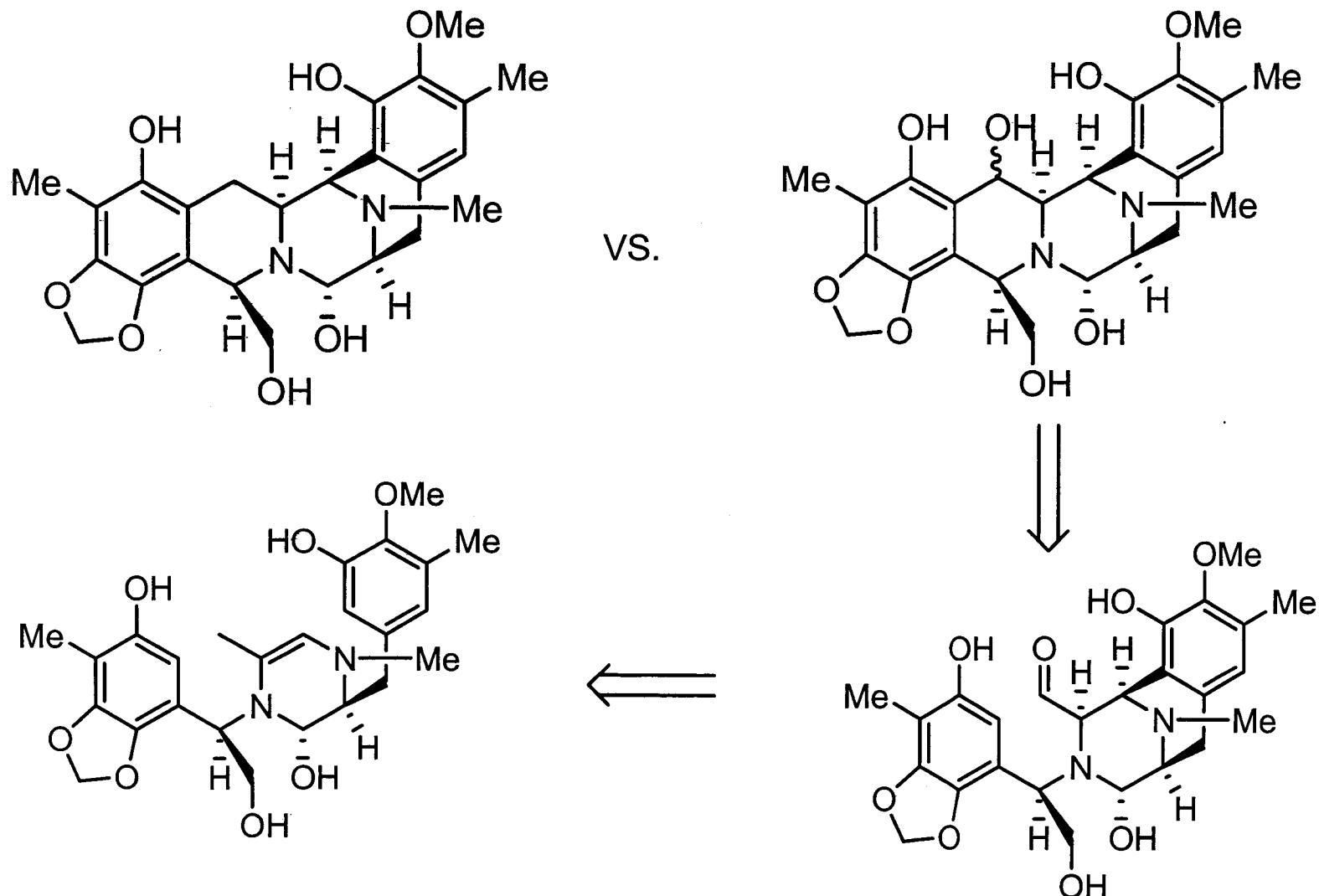
Williams Summary

- 12 steps, 12% yield
- Uses chiral auxillary, then destroys chiral center.
- 3 very powerful steps sandwiching many FG interconversions.
- Epimerization... Seems ill-used
- PG's: 4 steps (33%)

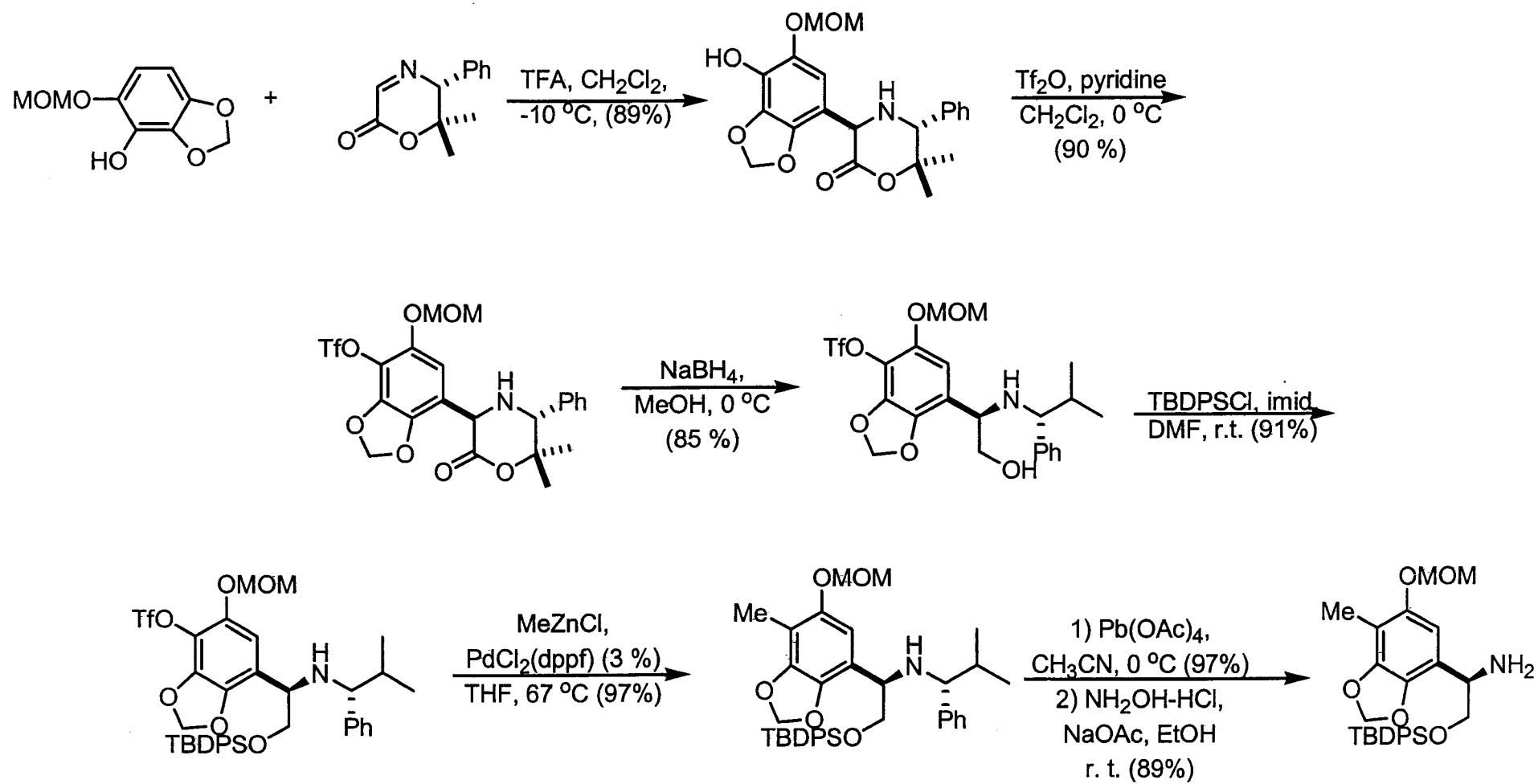
Fukuyama – Saframycin B



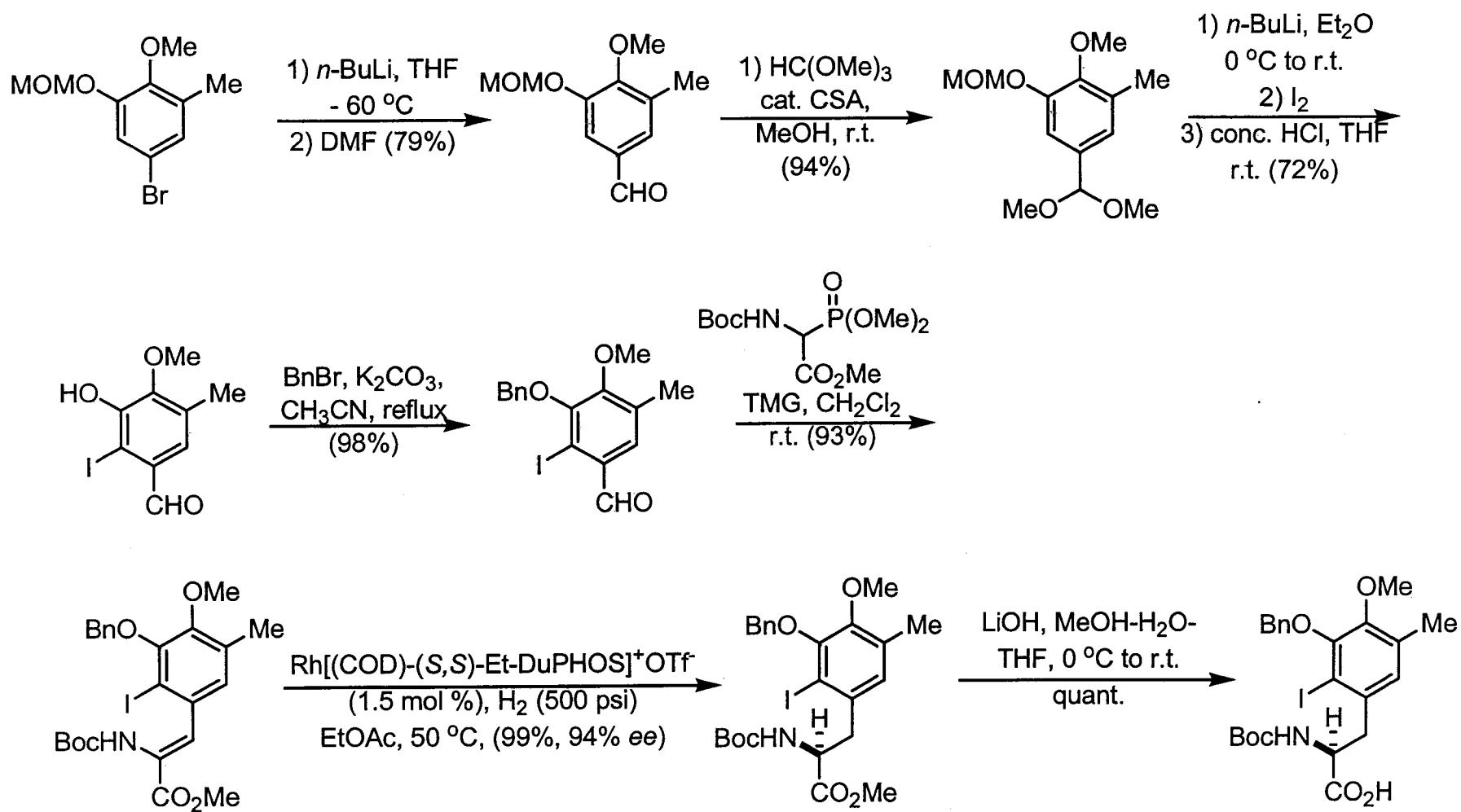
Fukuyama's Total Synthesis



Amino Acid I

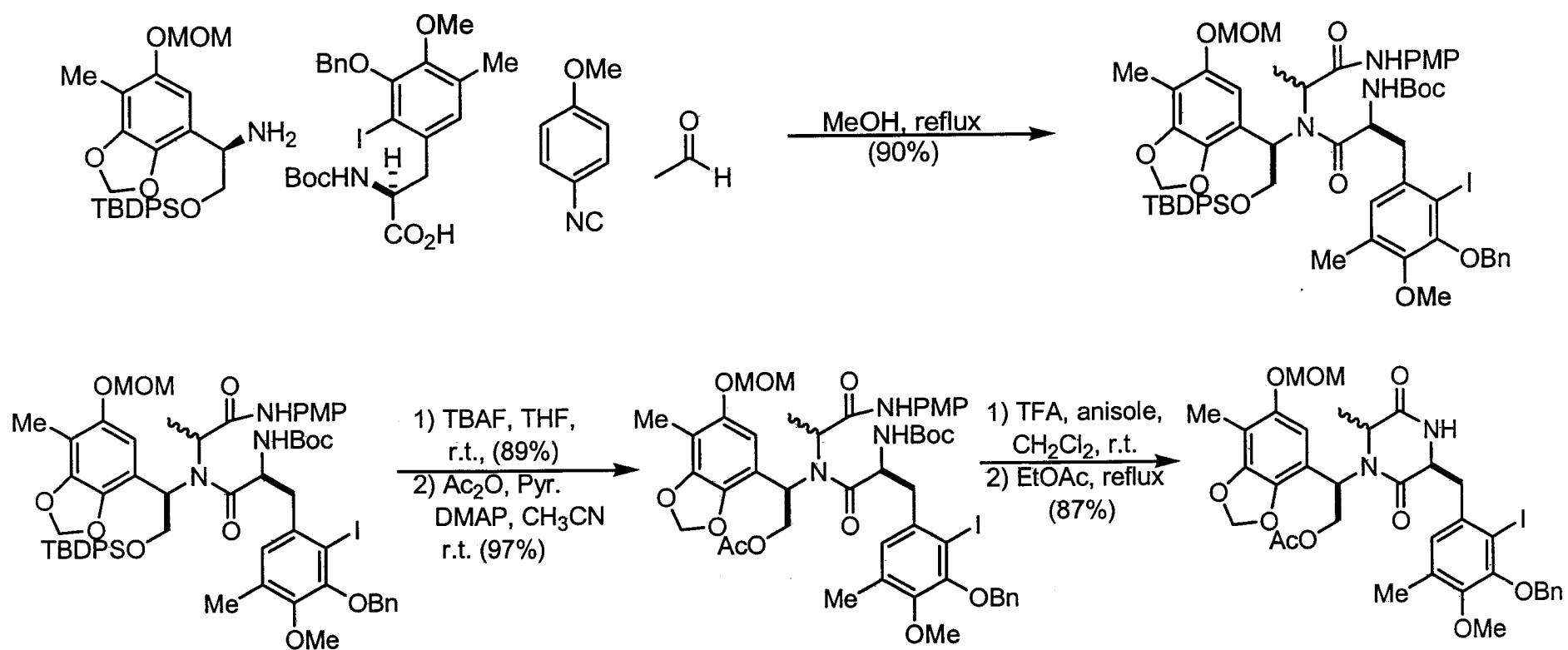


Amino Acid II

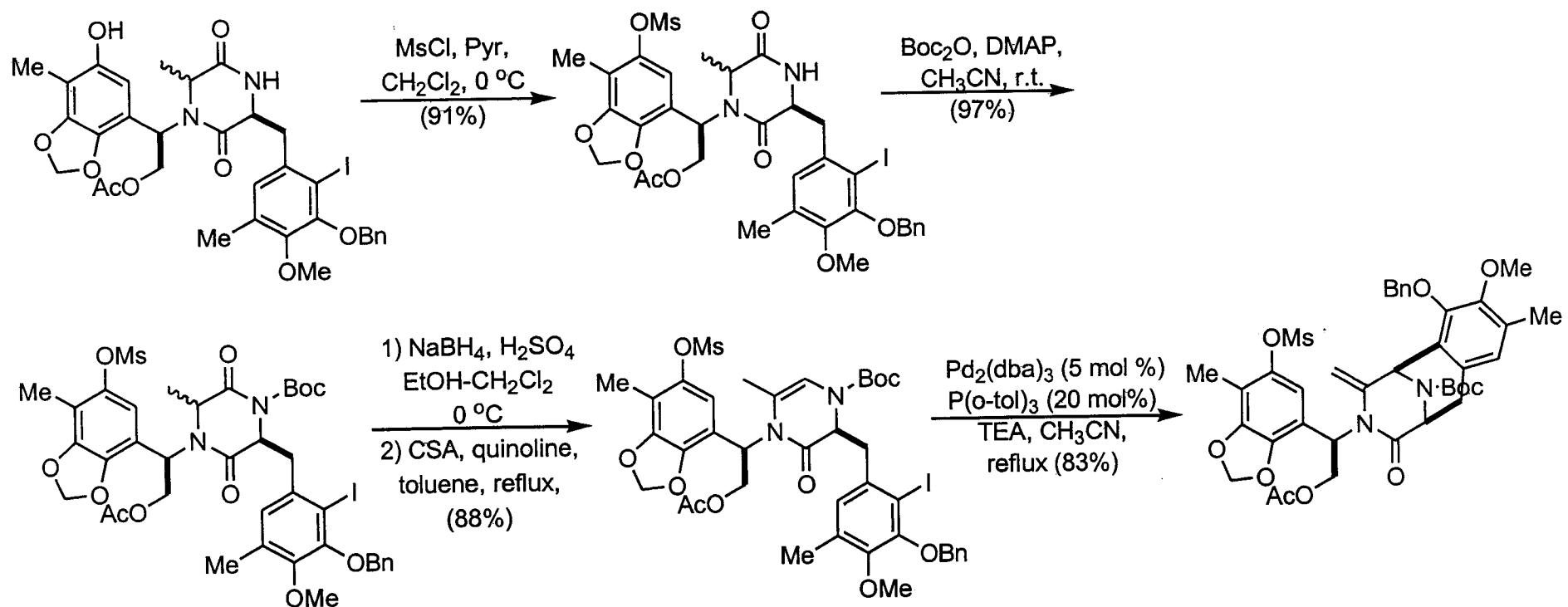


30

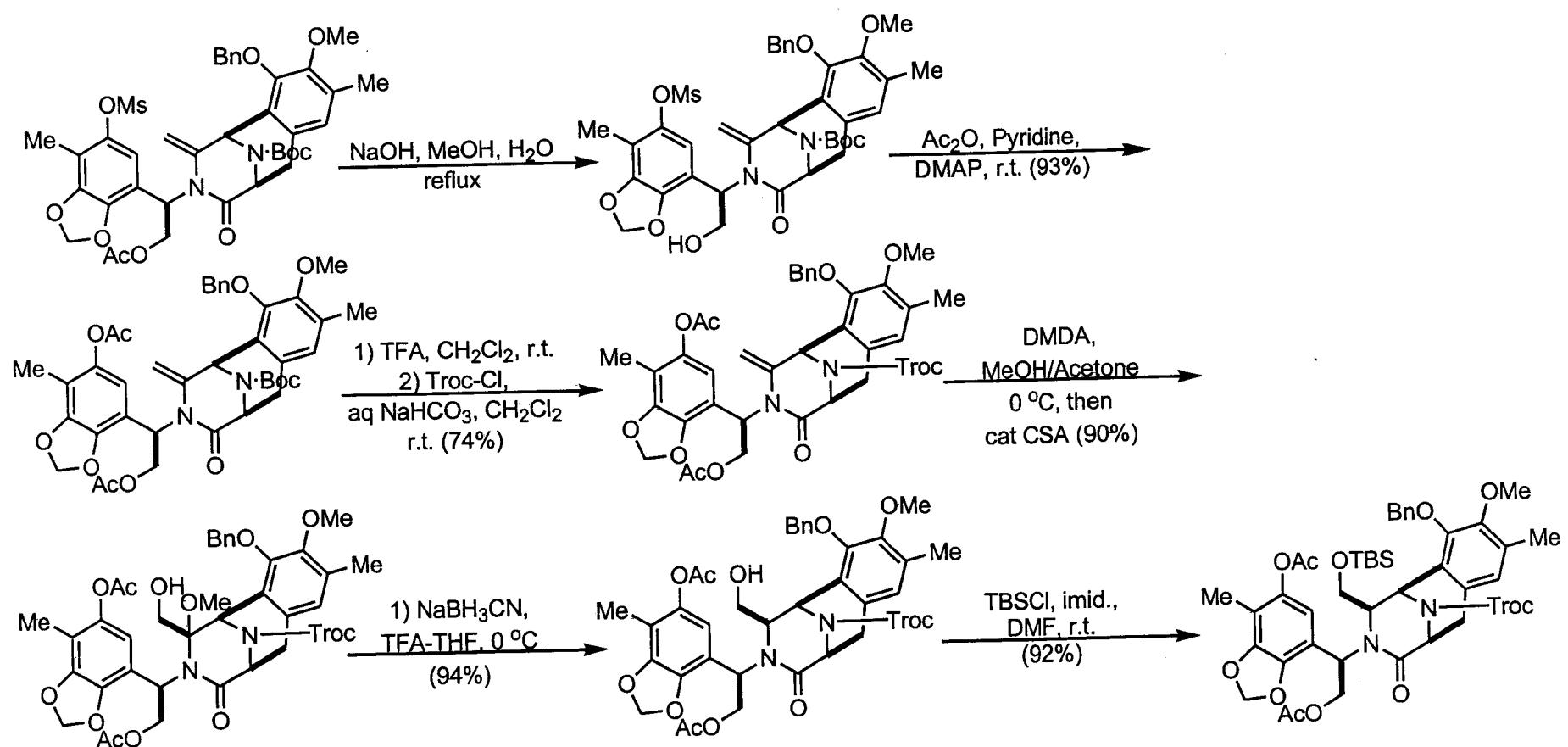
Le Ugi...



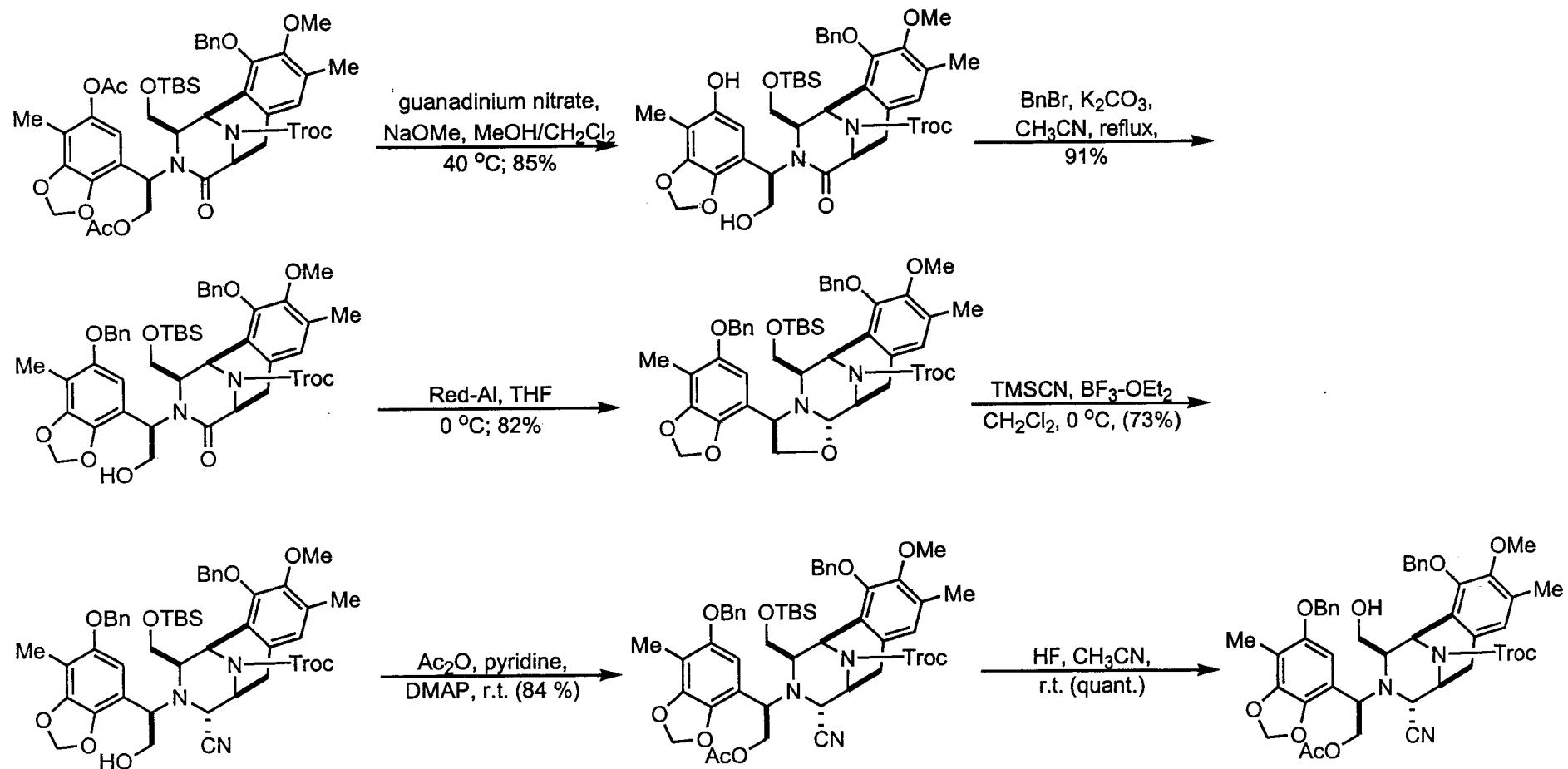
Heck Coupling



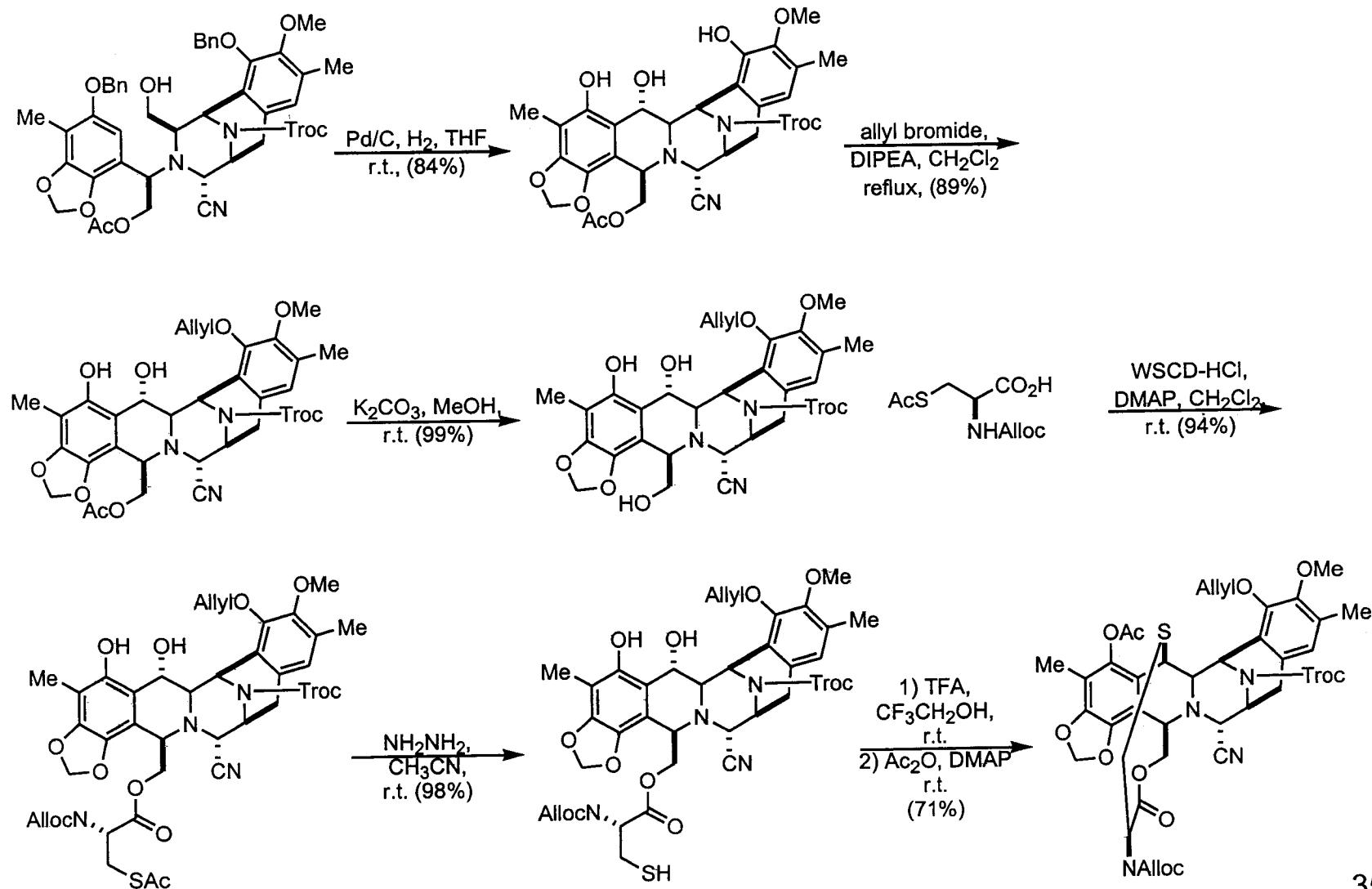
Epoxidation/Ring Opening



Installation of Cyano-group

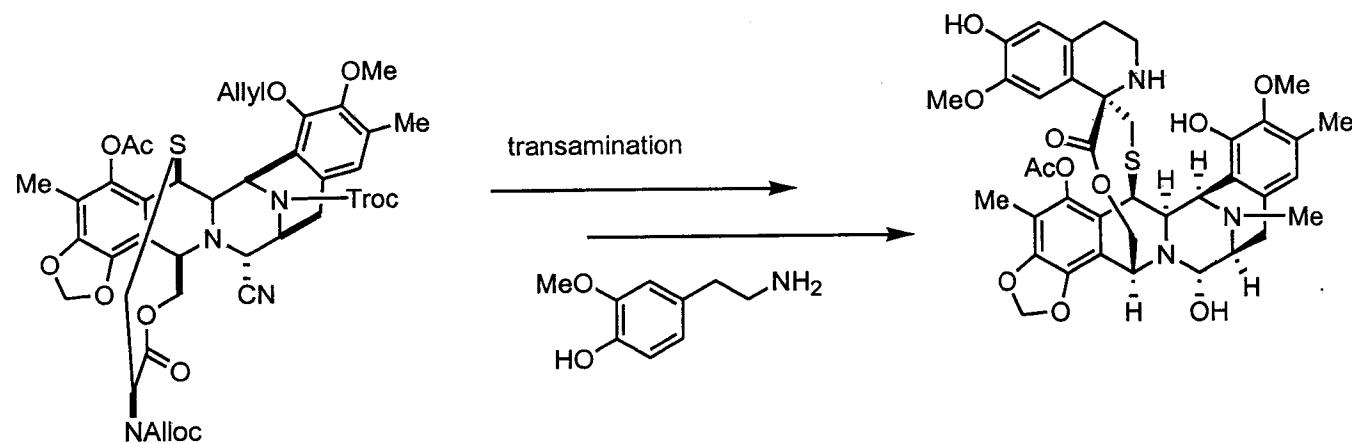


Pentacycle Formation



Endgame

Followed Corey protocol, 6 steps (overall 37%)

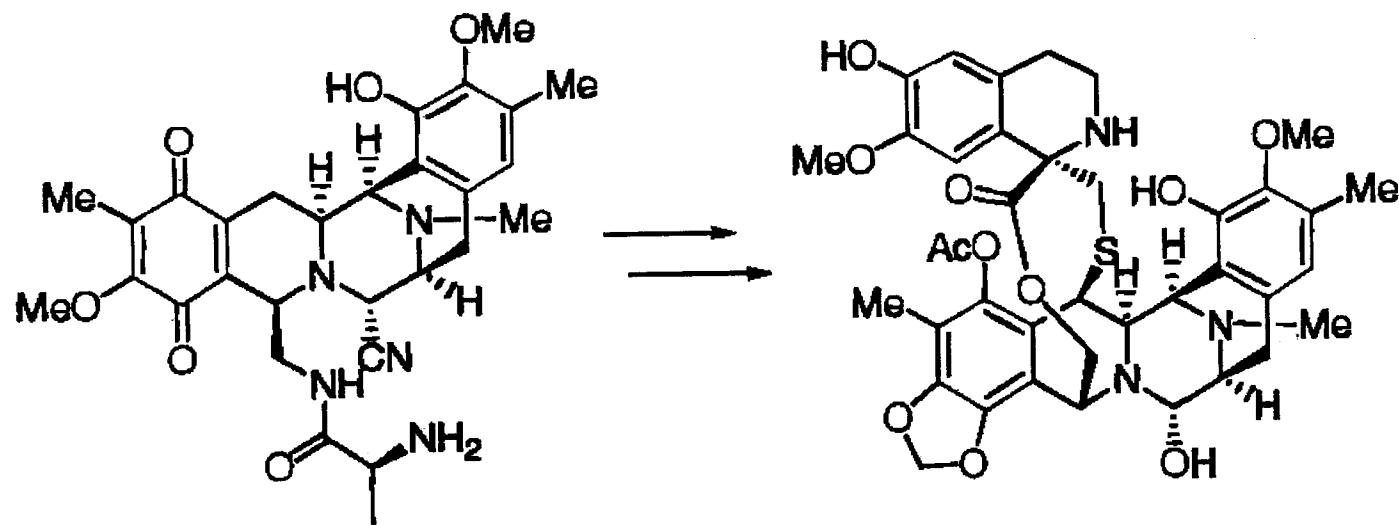


Overall 52 steps, (45 longest linear) (overall 0.7%)

Fukuyama Summary

- Somewhat different strategy, used Ugi, Heck, E_aS reactions to set pentacycle.
- Primarily used chiral induction to set centers (after 1 auxillary, and 1 chiral catalyst)
- Overall sense of “steppy-ness”, although only 16 P.G. steps (30% of steps).
- Very linear

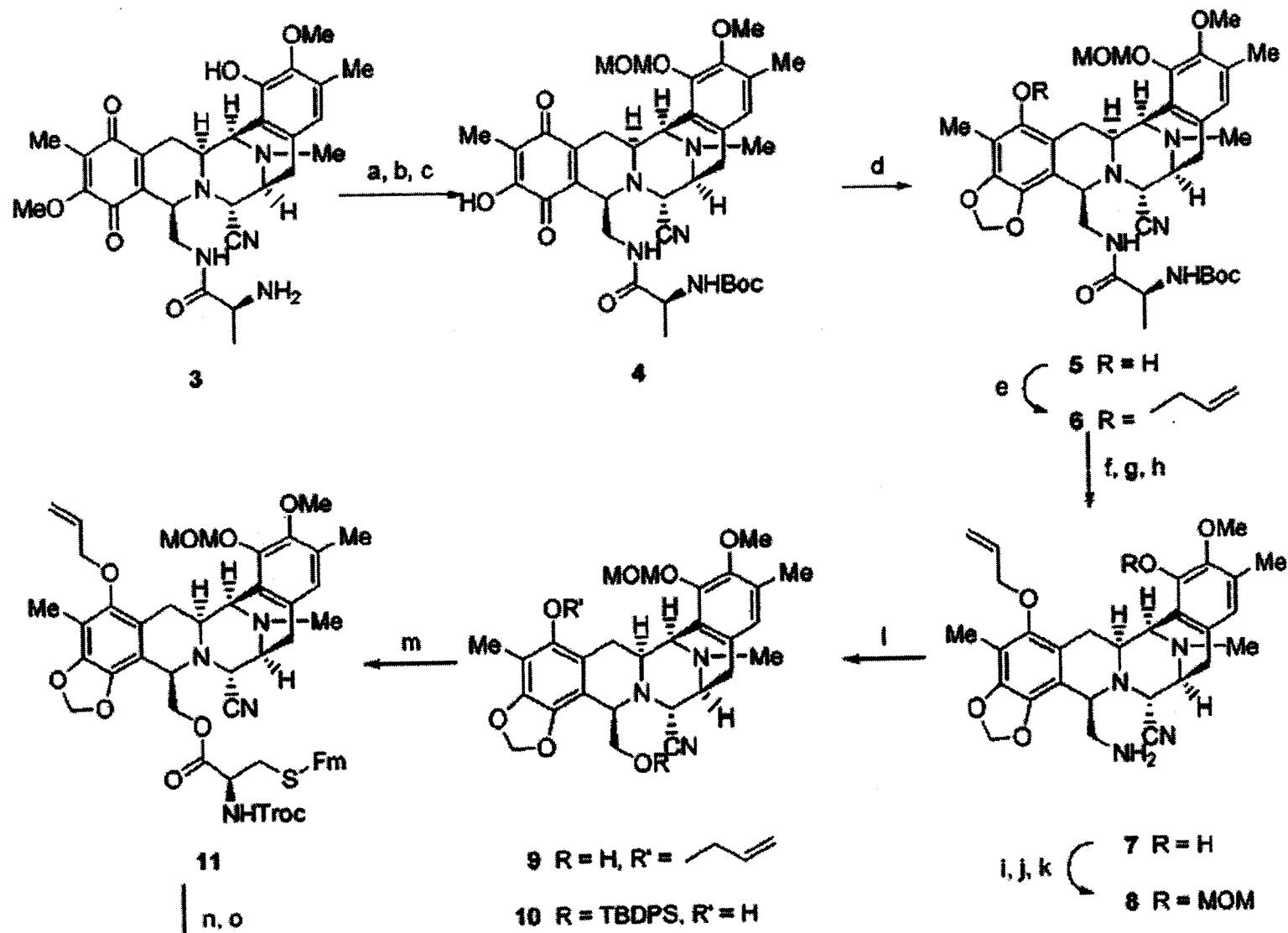
Pharma Mar Semi-Synthesis



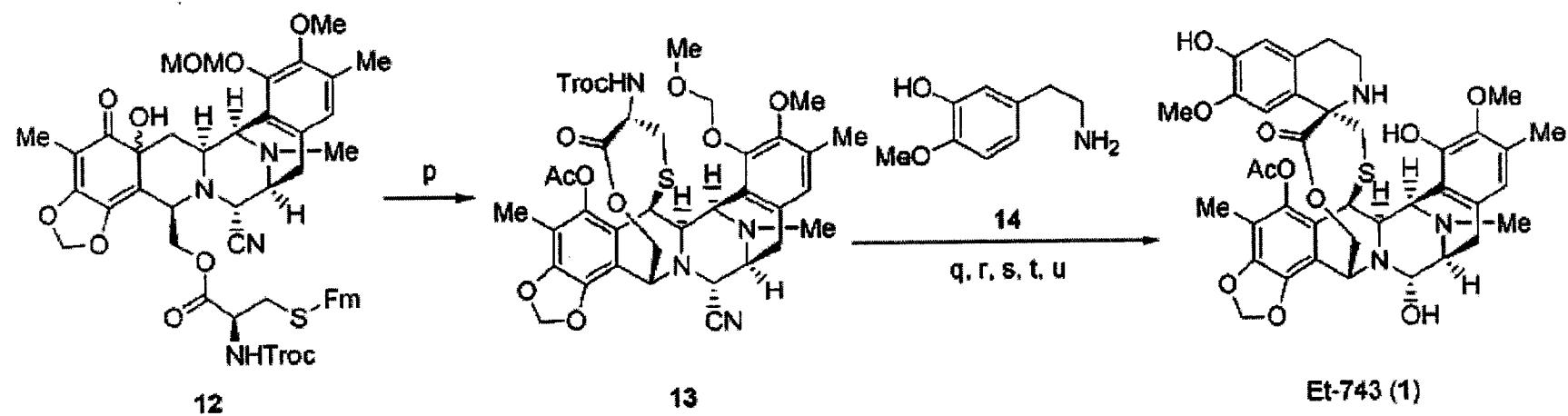
Cyanosafracin B, available in kilogram quantities from the fermentation of
Psuedomonas Fluorescens.

Pharma Mar Semi-Synthesis

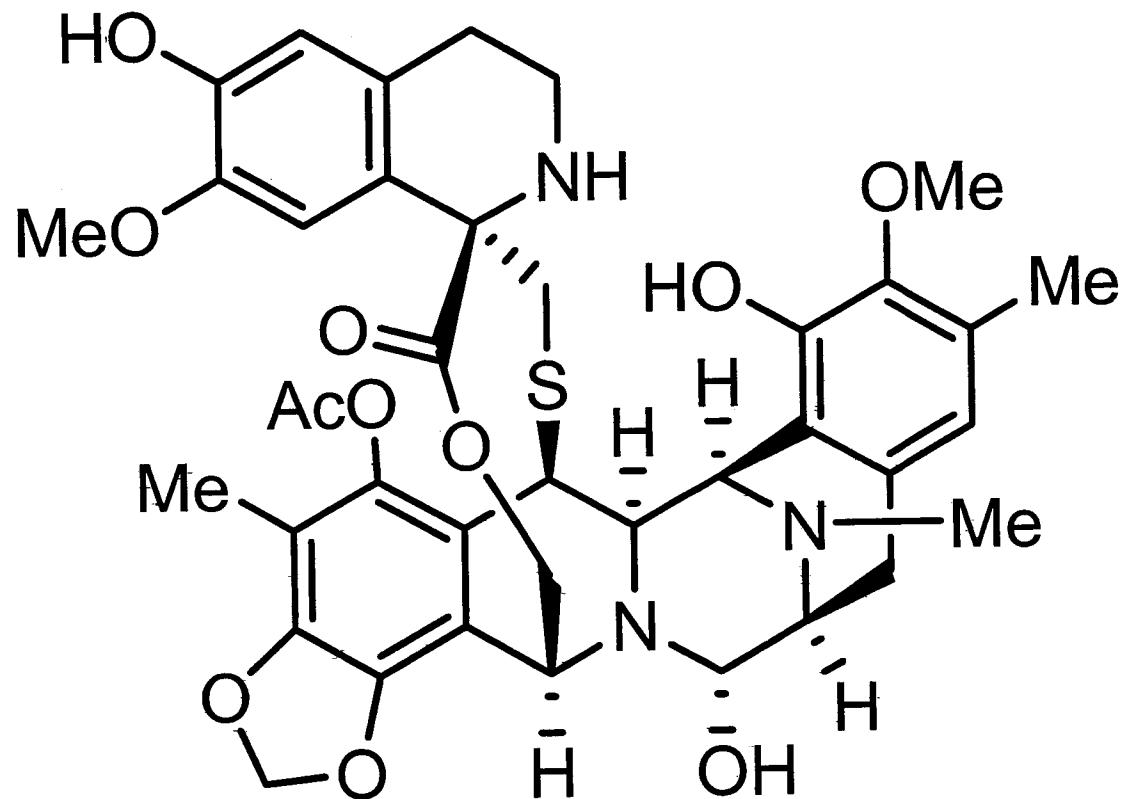
Scheme 1^a



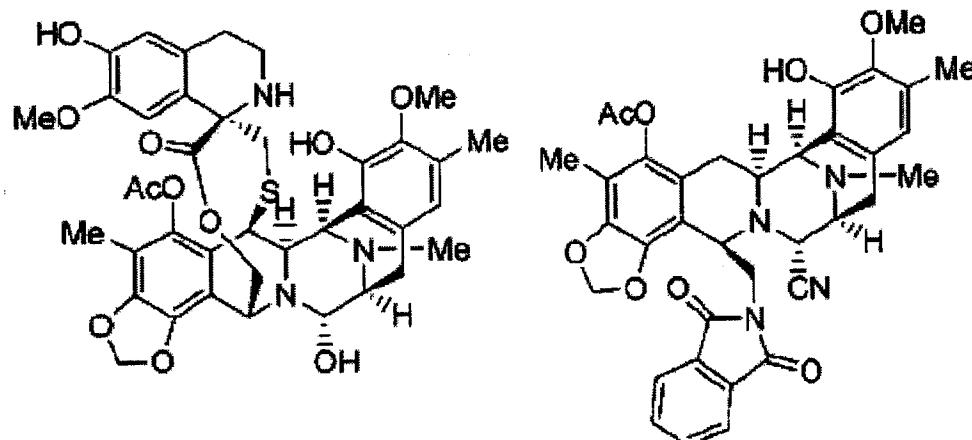
Look Familiar??



El Fin...



Outlook



ET-743 (1)

Phthalascidin (2)

