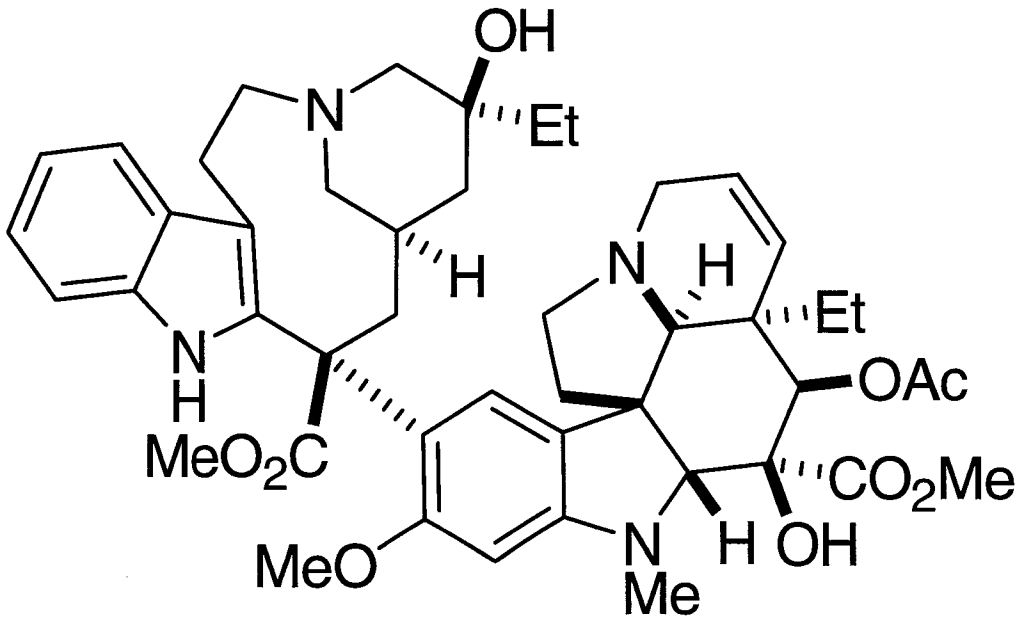
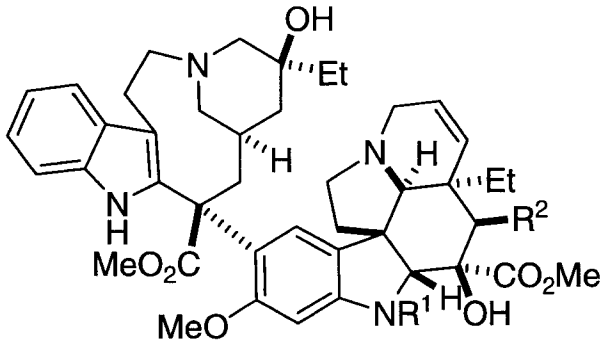
Ramzi F. Sweis
05-20-03

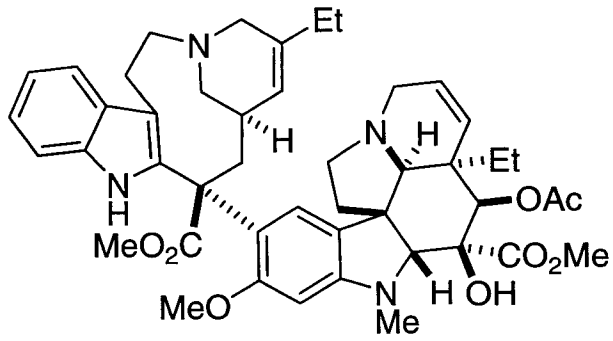
Bisindole Alkaloids: The Total Synthesis of (+)-Vinblastine



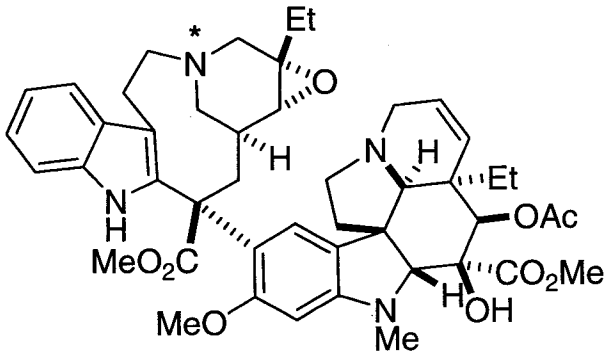
Some Bisindole Alkaloids



R^1	R^2	
Me	OAc	*Vinblastine*
Me	H	*Deacetoxyvinblastine*
Me	OH	*Deacetylvinblastine*
H	OAc	*Demethylvinblastine*

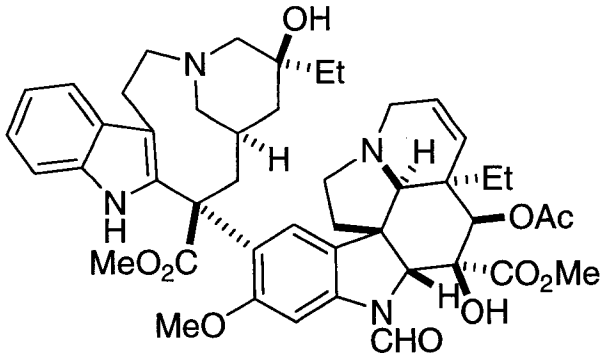


Anhydrovinblastine

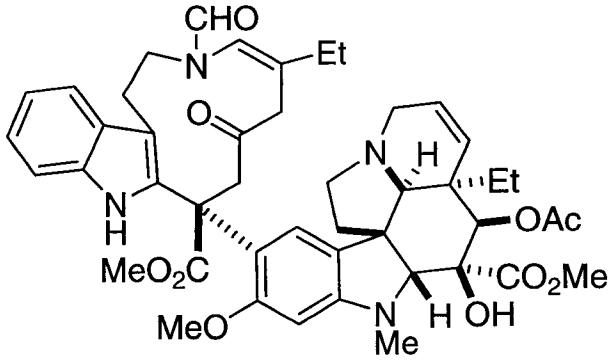


Leurosine
(Pleurosine : * N-oxide)

More alkaloids (over 90) have been isolated from C. Roseaus than from any other plant



Vincristine
isolated in 0.0003% yield, the lowest level of any medicinally useful alkaloid produced on a commercial basis

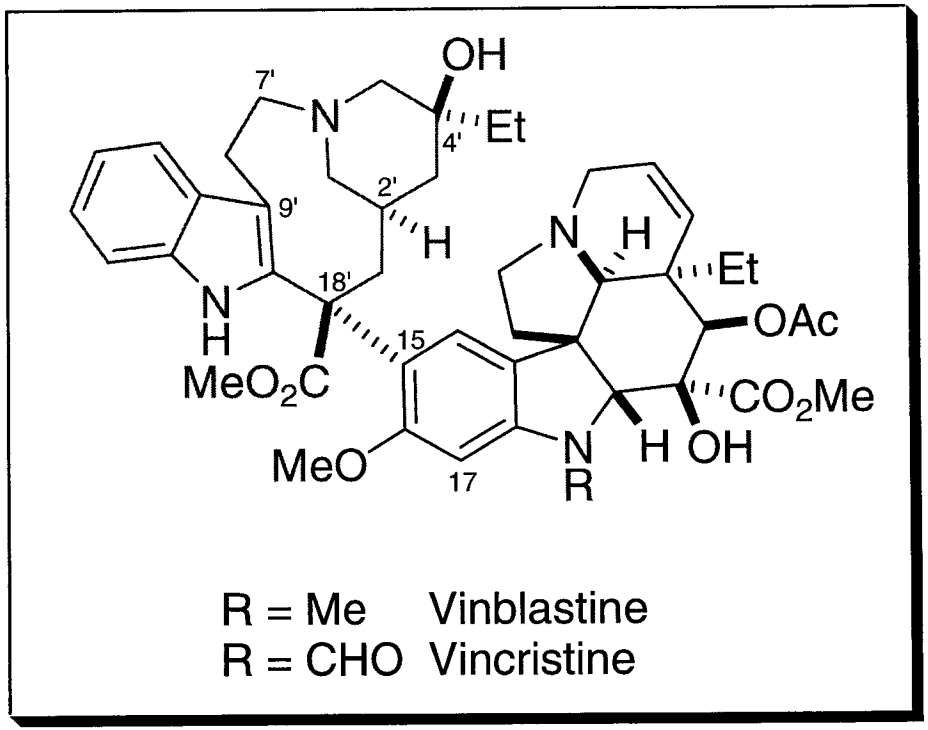


Catharine

Isolation and Biological Properties

- First isolated from Catharanthus roseus in 1958. Structure solved in 1966
- Vinblastine and Vincristine ("Vinca dimers") generally produced from Vinca rosea
- Is a prominent agent in cancer chemotherapy
- Natural abundance has provided the synthetic studies on this compound
- Five syntheses to date. Four employ bottom half (Vindoline) from natural sources

Top Half – Carbomethoxyvelbamine
Bottom Half - Vindoline



R = Me Vinblastine
R = CHO Vincristine

Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N.Y. Acad. Sci.* **1958**, *76,* 882.
Svoboda, G. H.; Neuss, N.; Gorman, M. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, *48*, 659.
Moncrief, J. W.; Lipscomb, W. N. *Acta Crystallogr.* **1966**, *21*, 311.

Some Data on Vinblastine and Vincristine

Usage

- Vinblastine is a component of the regimen of choice for treatment of metastatic testicular cancer
- Also used as a component in a regimen to treat Hodgkin's disease, Kaposi's sarcoma, and carcinoma of the breast
- Vincristine is a standard component of regimens used in the treatment of acute lymphocytic leukemia in children
- Both Vinblastine and Vincristine are administered by intravenous injection due to the poor bioavailability
- An typical dose of vinblastine is 5.5 - 7.4 mg administered weekly.

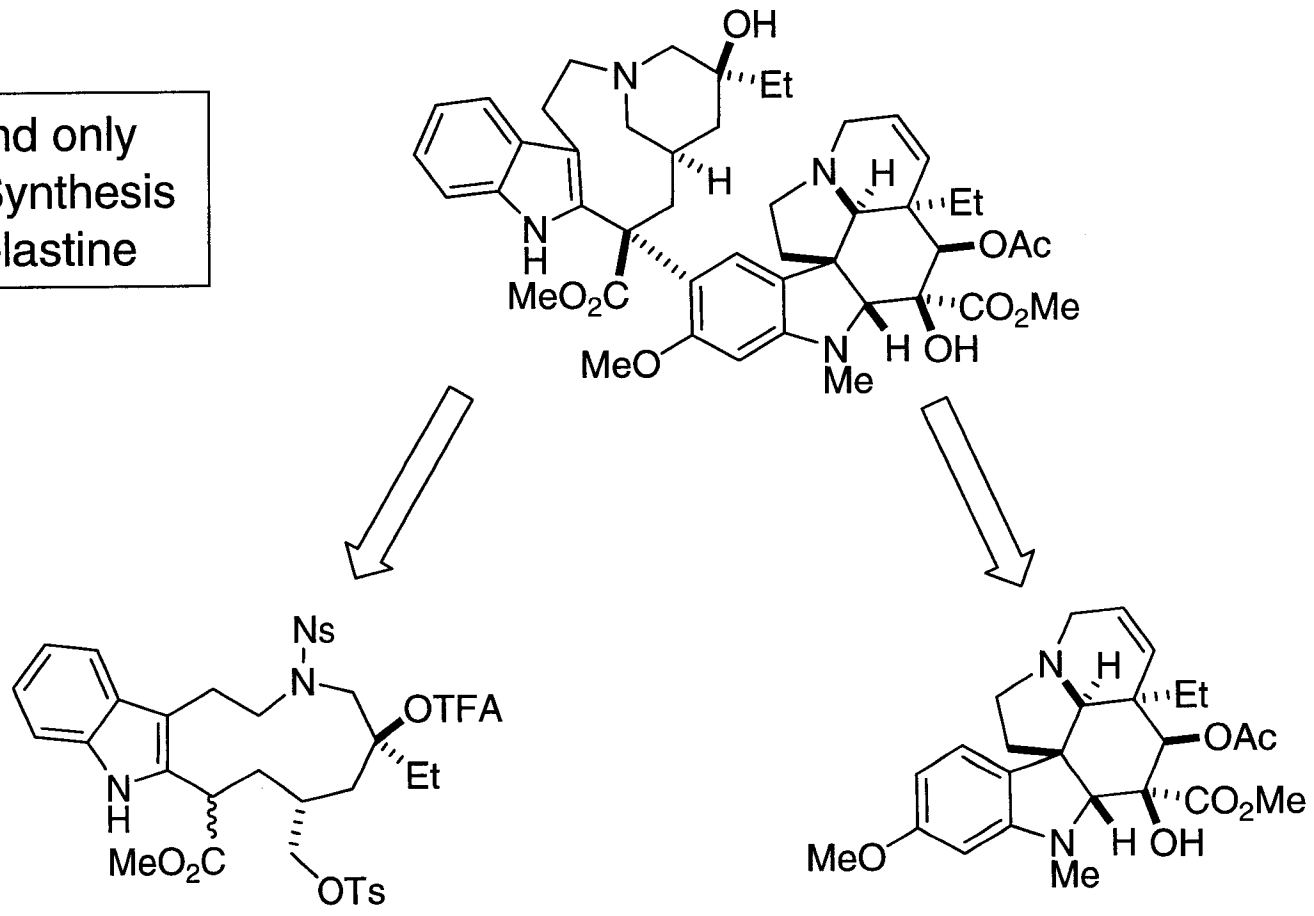
Biological Mode of Action

- Vinblastine and Vincristine interefere with the mitotic process arresting cells in metaphase
- They interact with proteins essential for microtubule formation and thus spindle generation is suppressed.

The *Alkaloids, Vol 37* (Ed.: A. Brossi), Academic Press, New York, 1990.

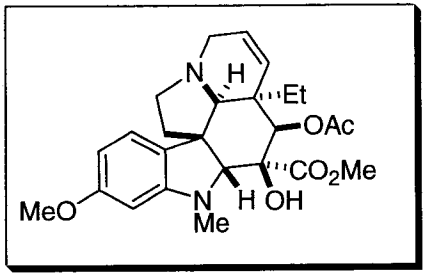
Fukuyama Synthesis

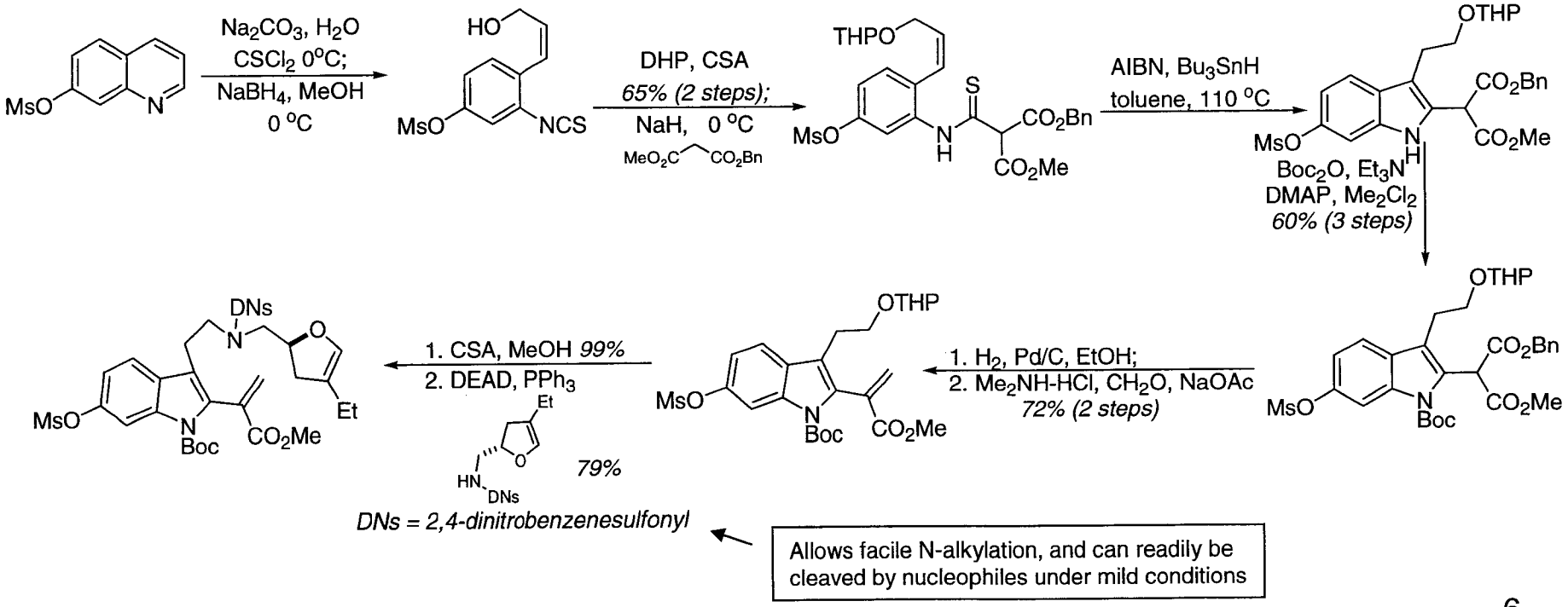
First and only
Total Synthesis
of Vinblastine



Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

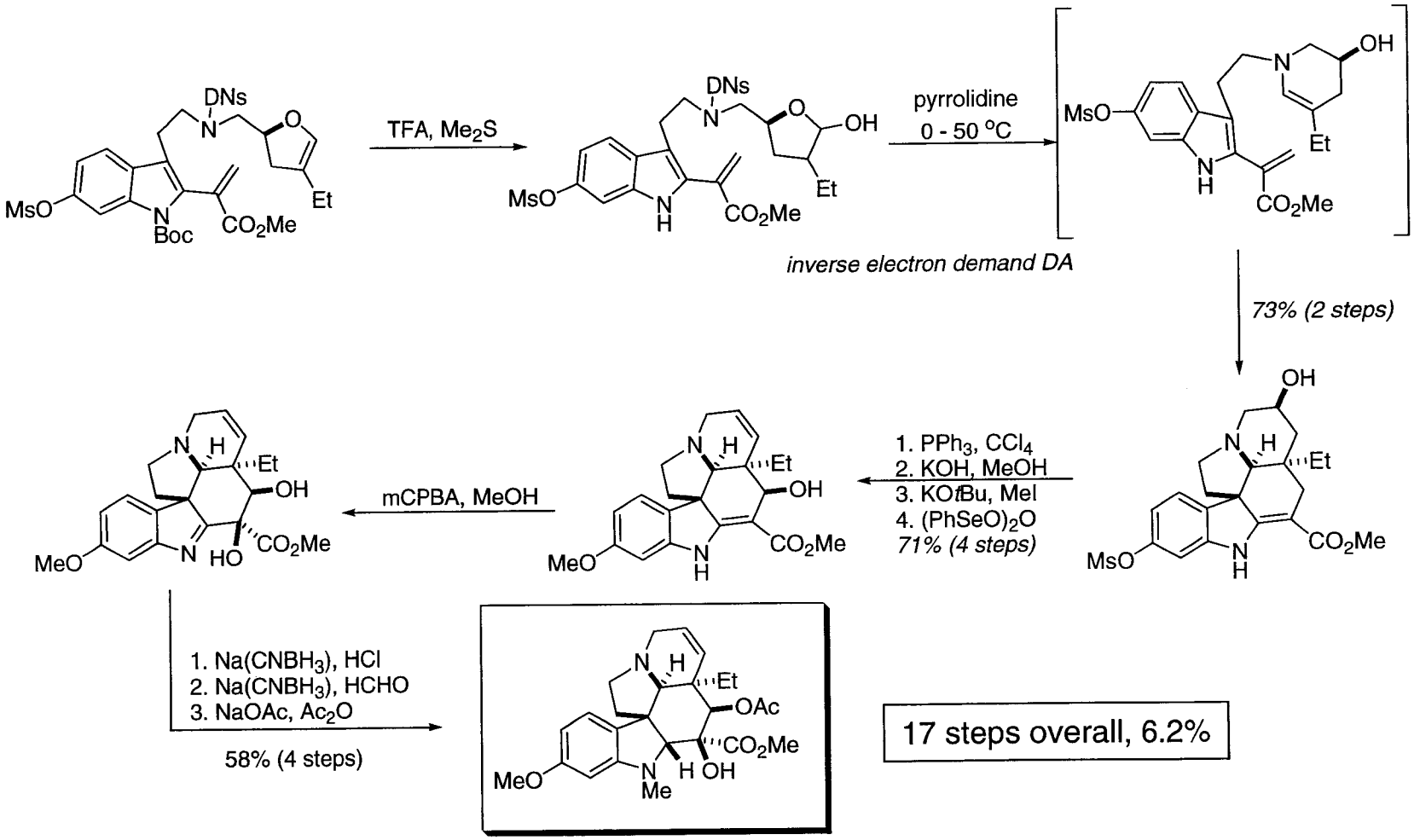
Synthesis of Vindoline Half





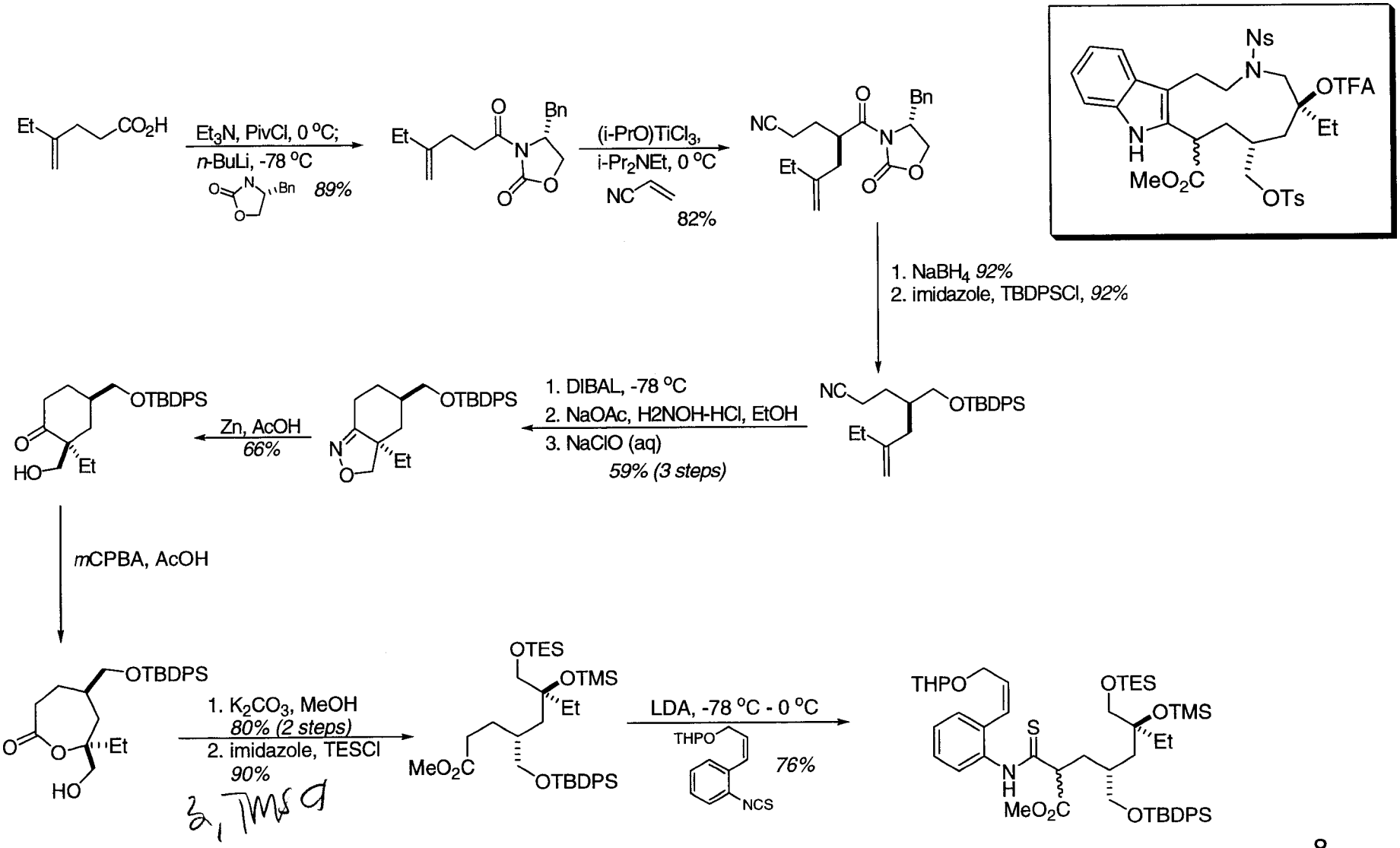
Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.
Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, 883.

Completion of Vindoline Half



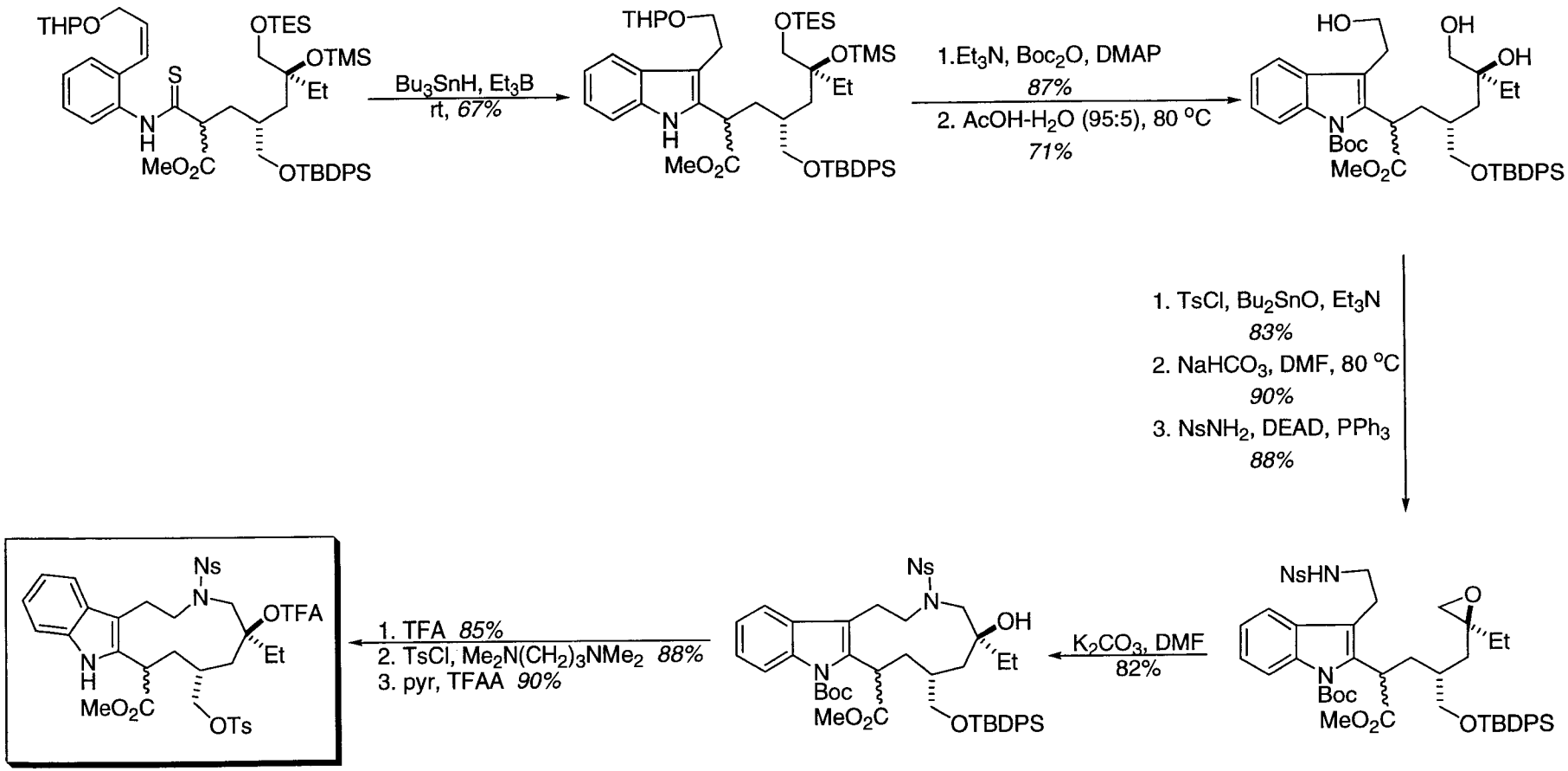
Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.
Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, 883.

Synthesis of Top Half



Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

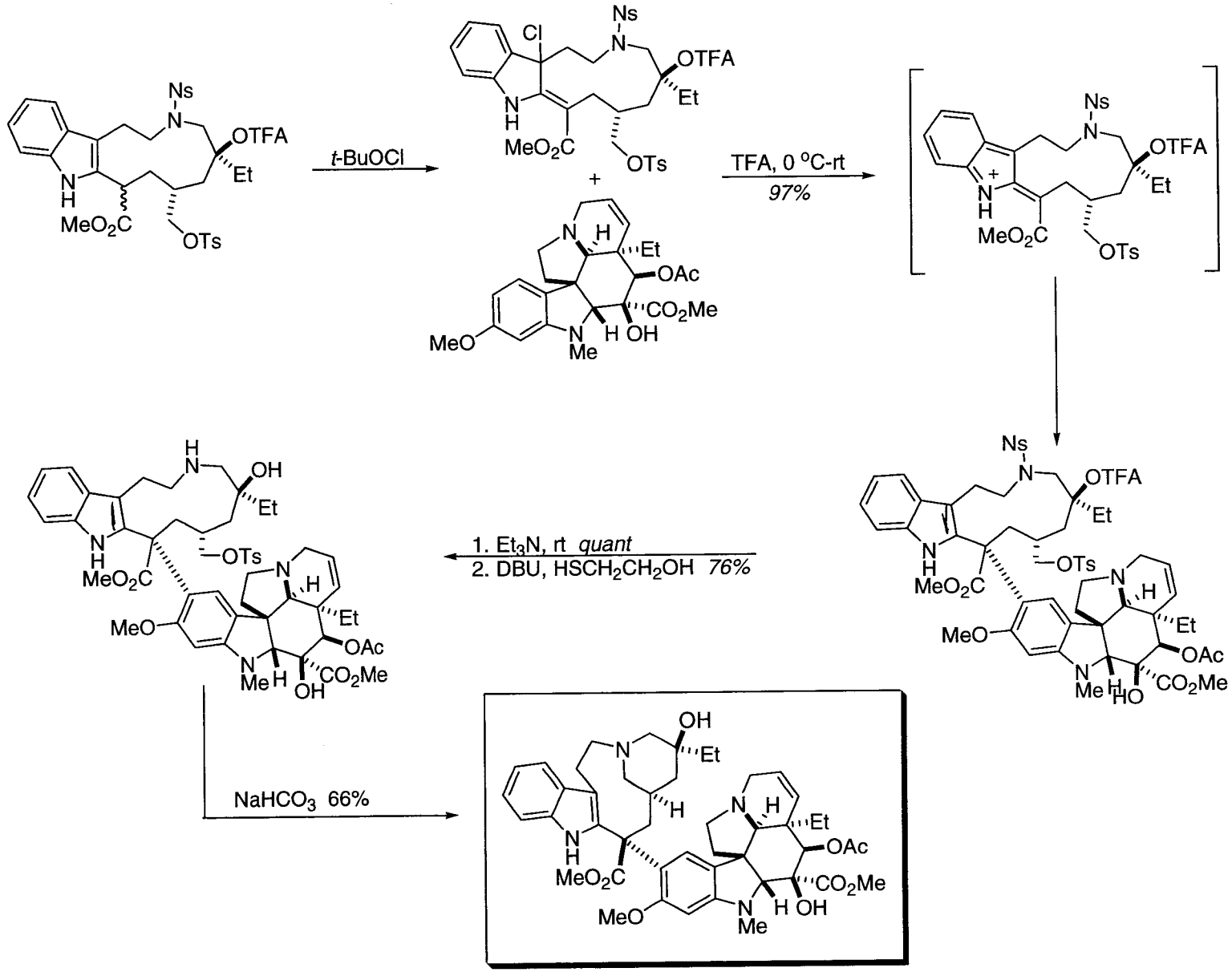
Completion of Top Half



Overall yield for this 22 step sequence: 2.0 %

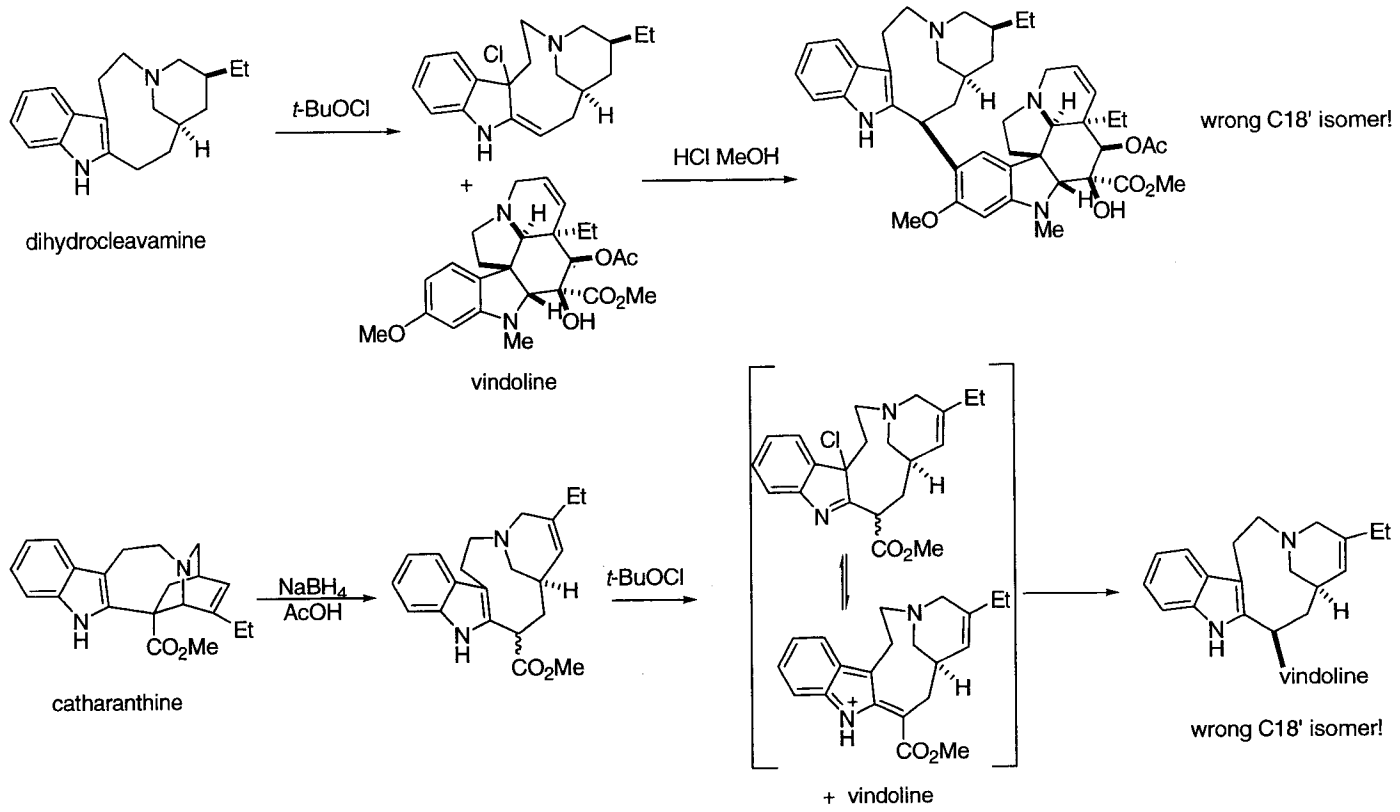
Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

Coupling of the Two Subunits



Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

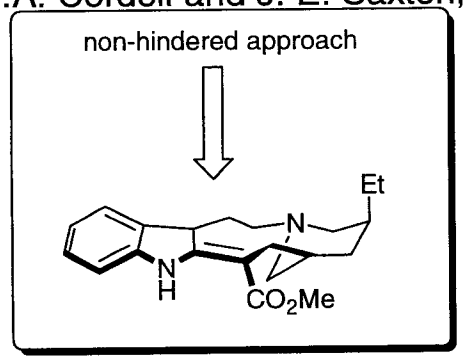
44 Years Between Discovery & Synthesis



"it is very unlikely that any natural dimer could be obtained in this way"

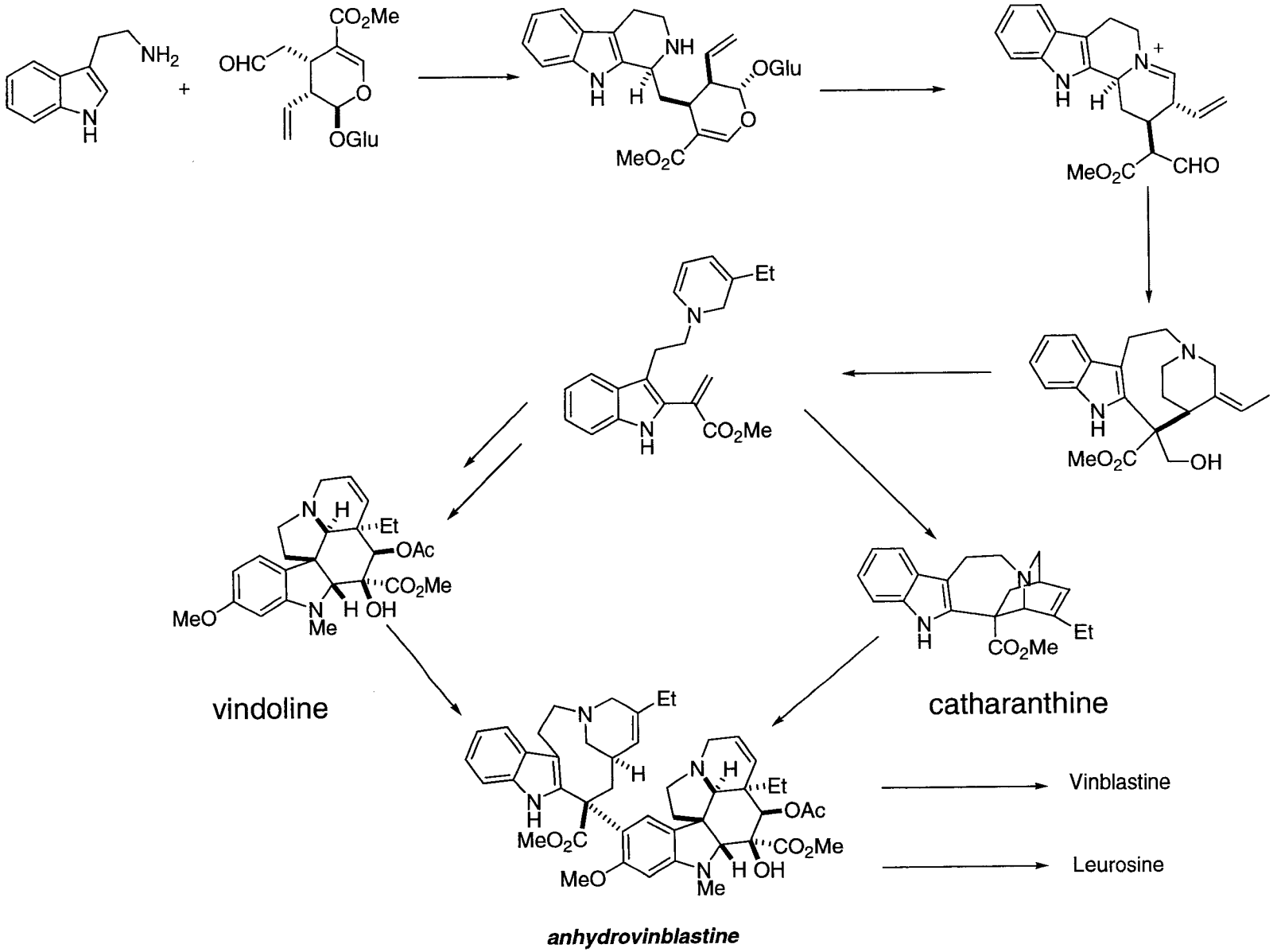
G.A. Cordell and J. E. Saxton, in "The Alkaloids", Vol. 20, 1981.

Why?



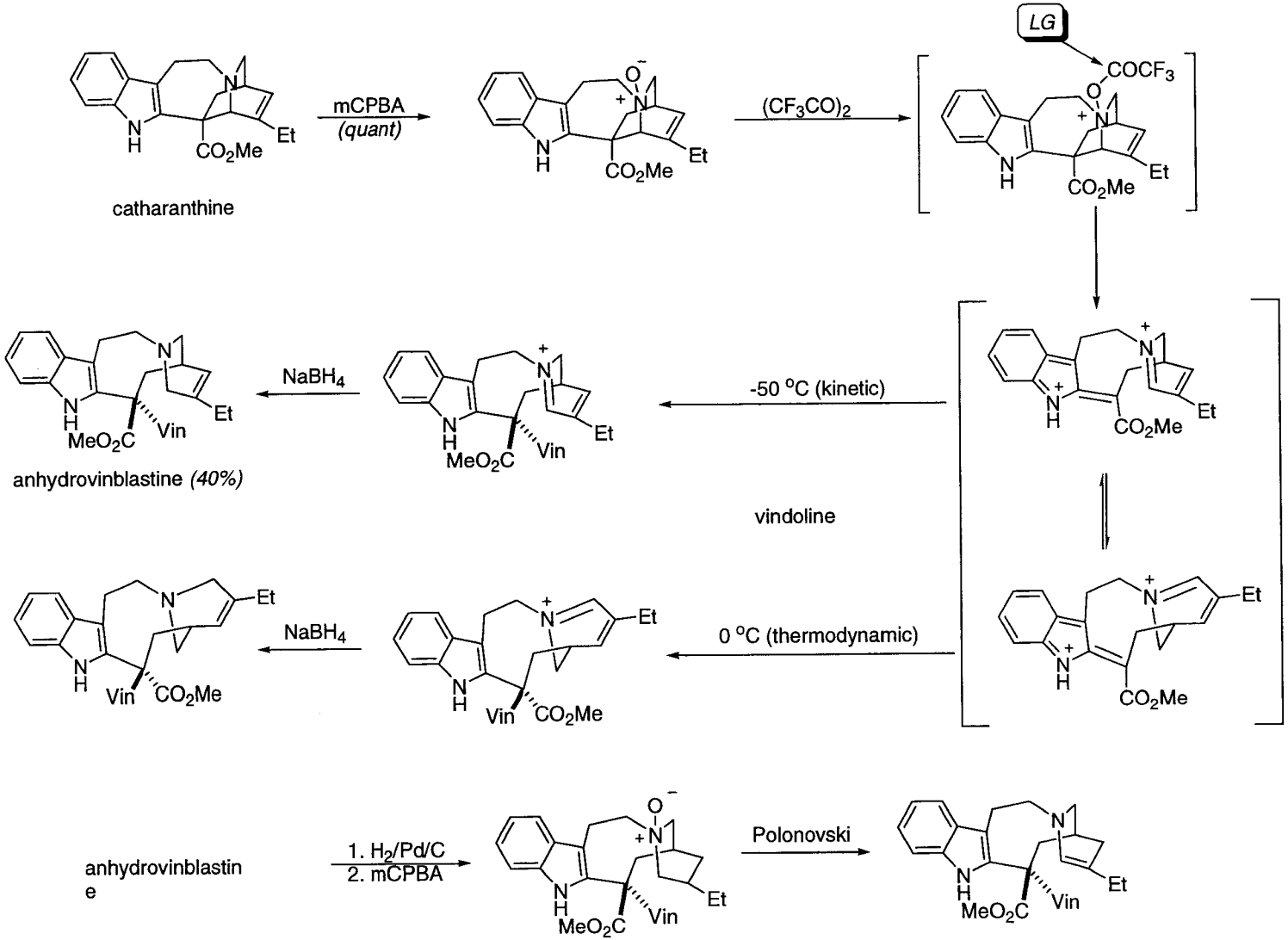
Nuess, N.; Gorman, M.; Cone, N. J.; Huckstep, L. L. *Tetrahedron Lett.* **1968**, 783.
Rahman, A-ur.; Basha, A.; Ghazala, M. *Tetrahedron Lett.* **1976**, 2351.

Biosynthesis of Vinblastine



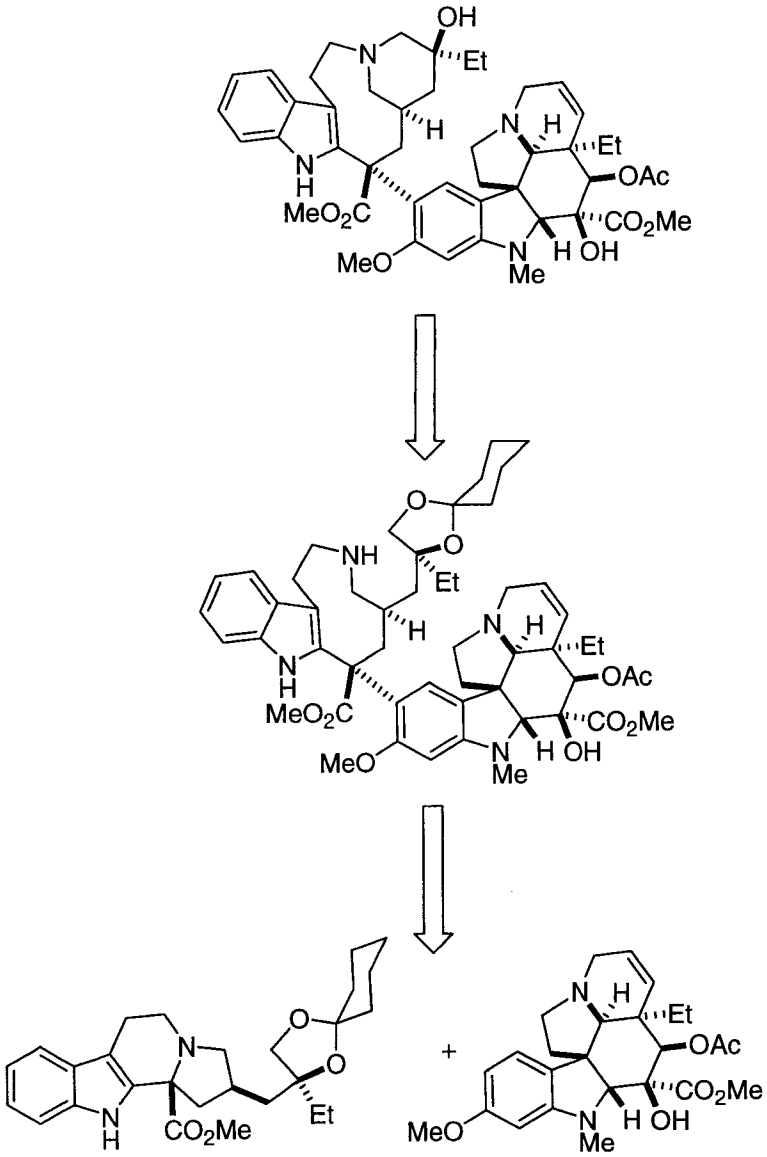
First Synthesis: Biomimetic Approach

Instead of the chloroindolenine approach, leaving group is placed on nitrogen in form of N-oxide



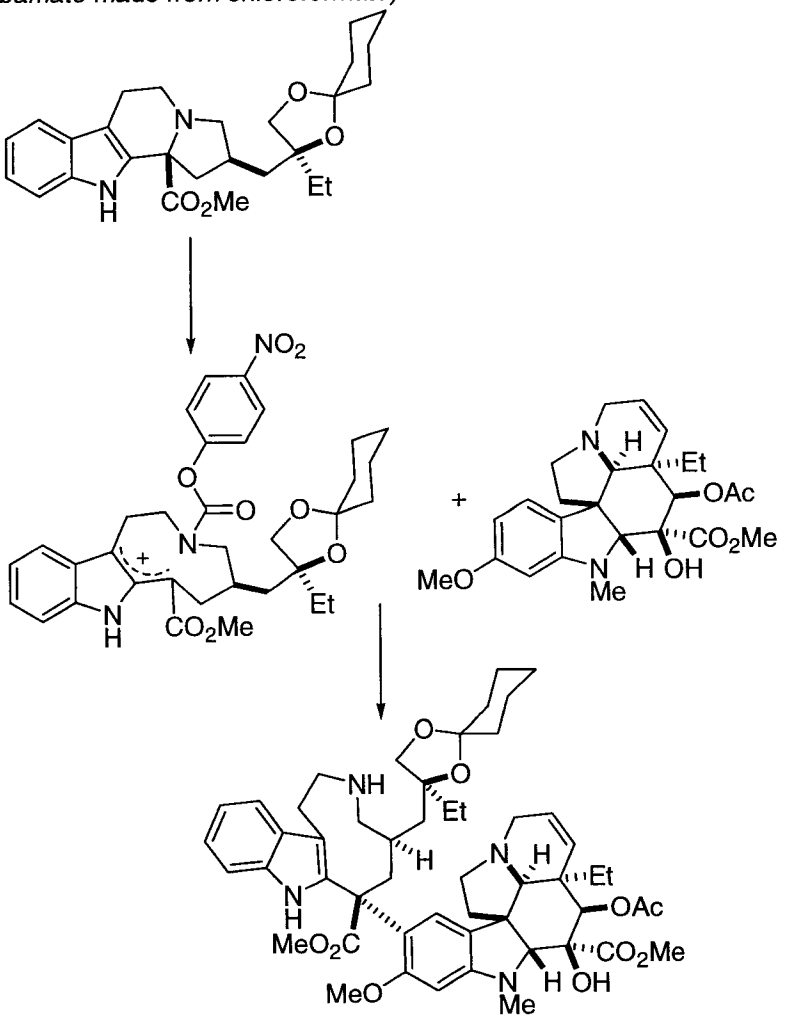
Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Poteir, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243

Non-Oxidative Approach to Coupling



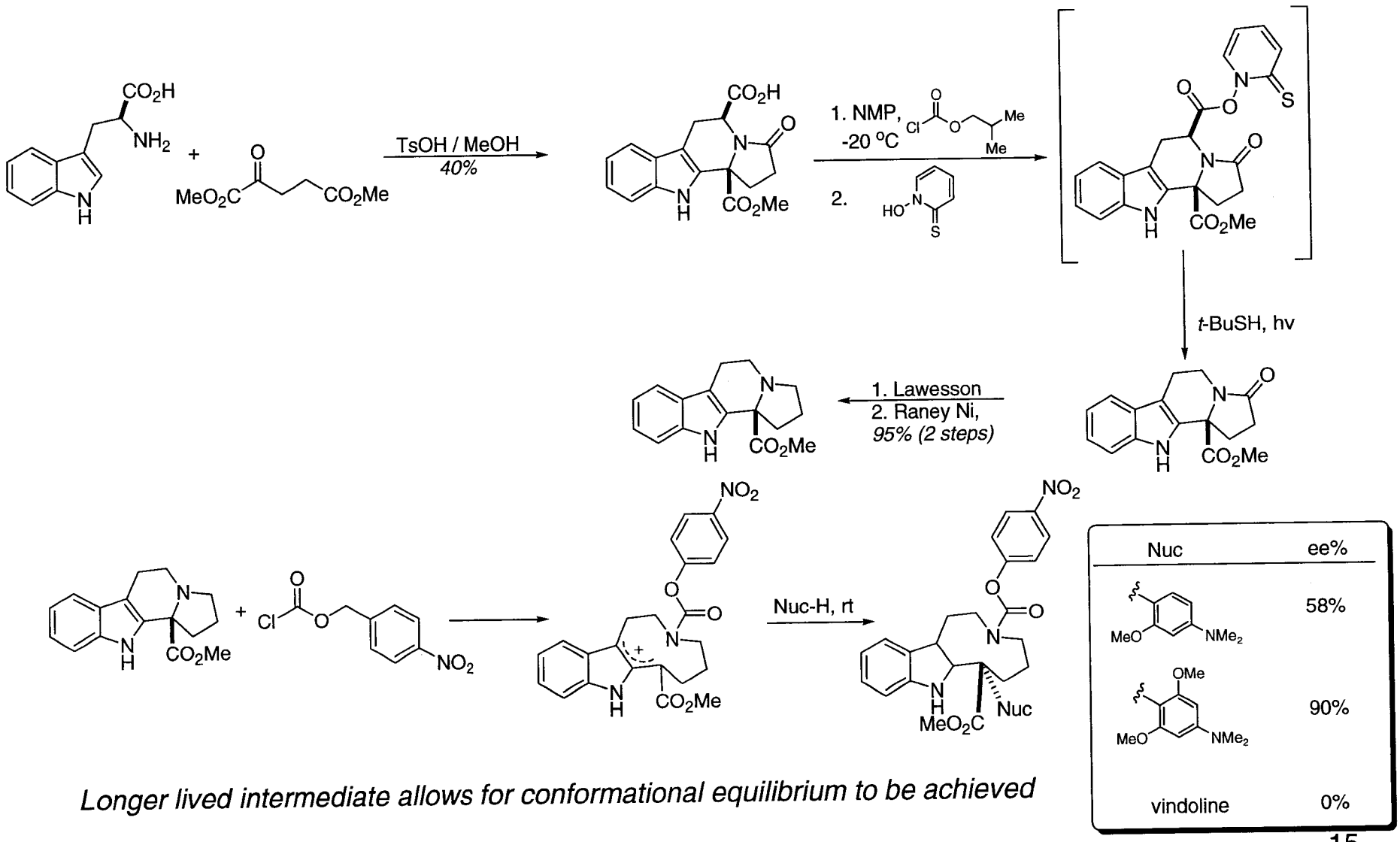
Generate a delocalized cation through a tertiary amine leaving group

(carbamate made from chloroformate)



Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.

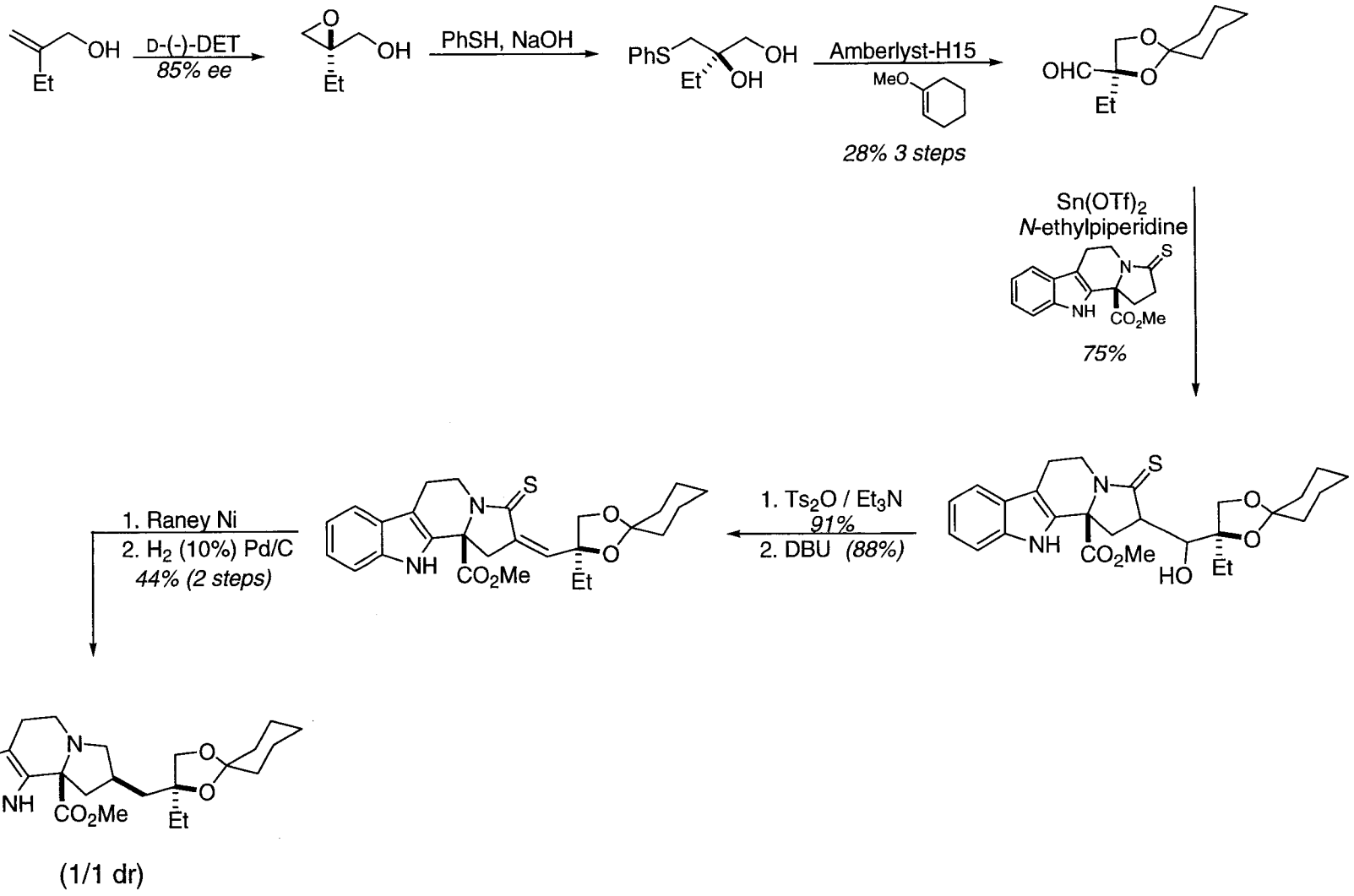
Studies on C18' Stereoselectivity



Longer lived intermediate allows for conformational equilibrium to be achieved

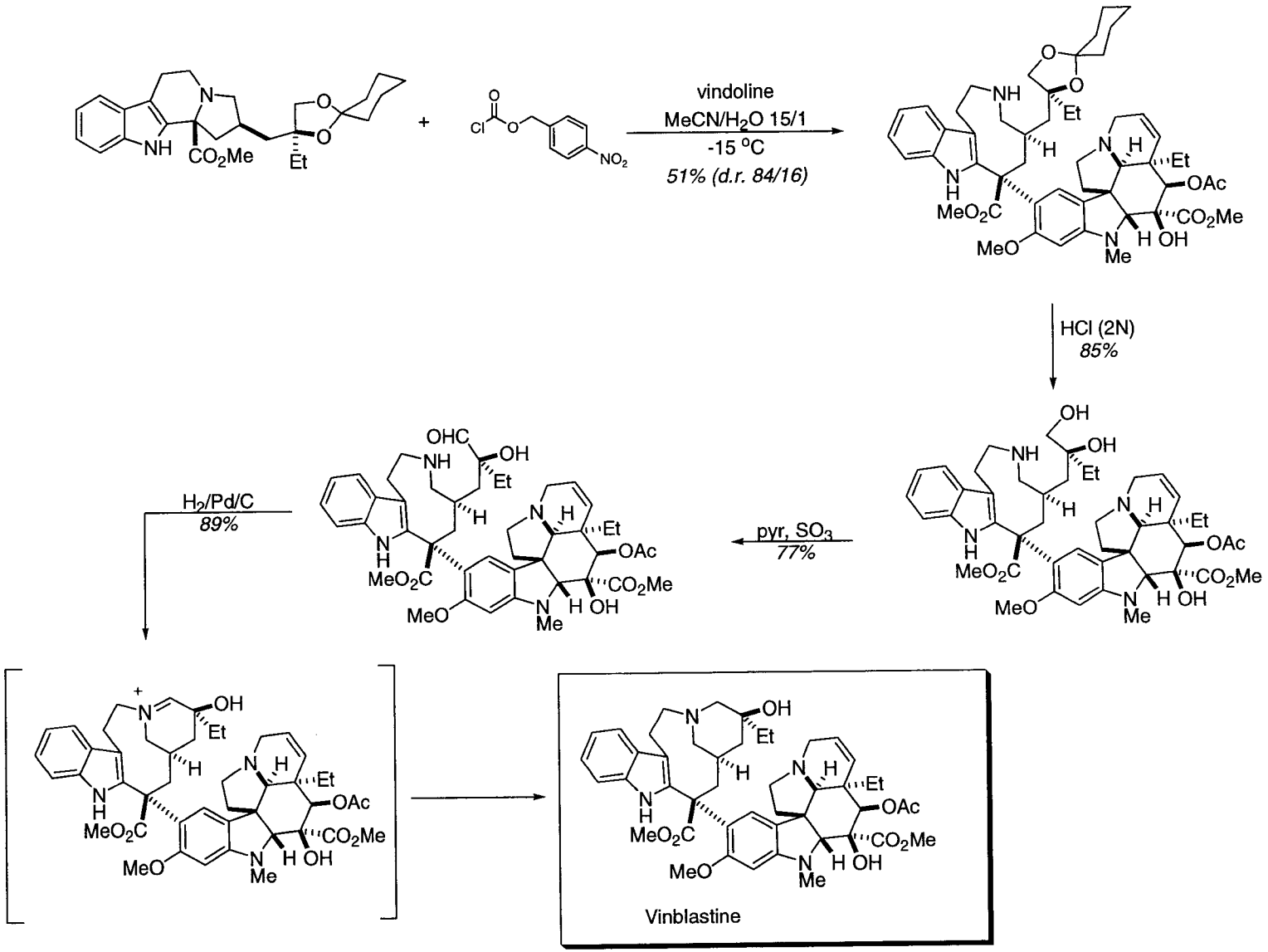
Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.

Synthesis of Vinblastine



Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.

Final Coupling Step

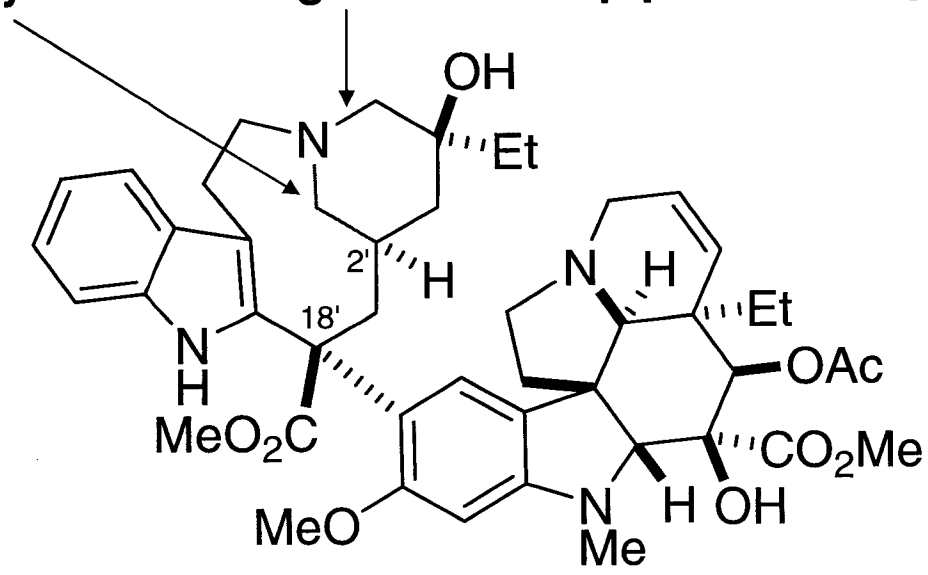


Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.

Final Analysis

Different approaches to address the key C18' stereochemical issue

Both Fukuyama and Magnus formed piperidine ring last



Poteir's biomimetic strategy utilizes catharanthine

Demonstration of how difficult it is to reproduce nature even with known pathway