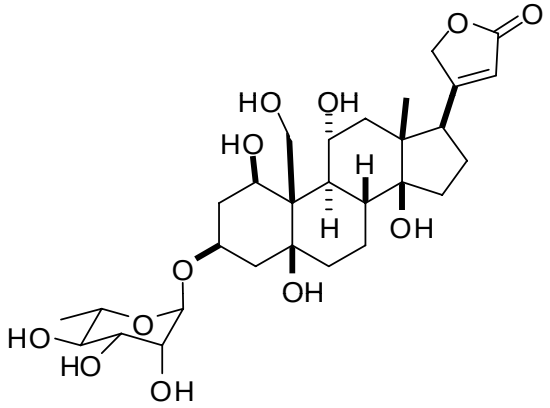
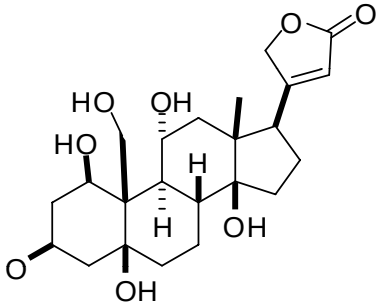
Synthesis of the Steroidal Natural Product Ouabain and Aglycone Ouabagenin



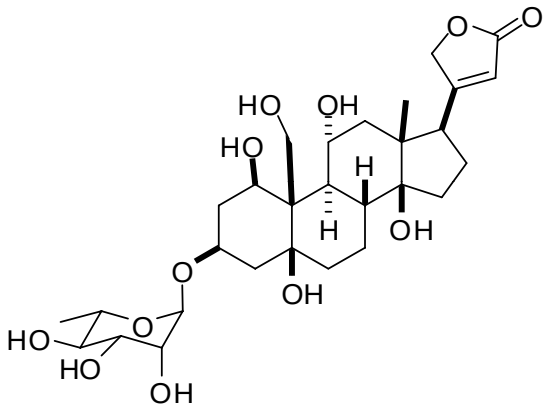
Ouabain



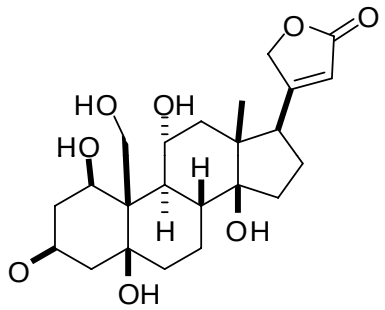
Ouabagenin

Matt Haley
February 20, 2008

Background



Ouabain



Ouabagenin

Acokanthera oblongifolia

-isolated from the African ouabio tree (*Acokanthera ouabio*) in 1888 by Arnaud

-cardiac glycoside elicits effect by binding to myocardial Na^+, K^+-ATPase (responsible for regulating intracellular Na^+ transport

-used in Africa to make poison arrows

-unique steroid structure:

- -sugar at the 3β position
- -β butenolide ring at C17

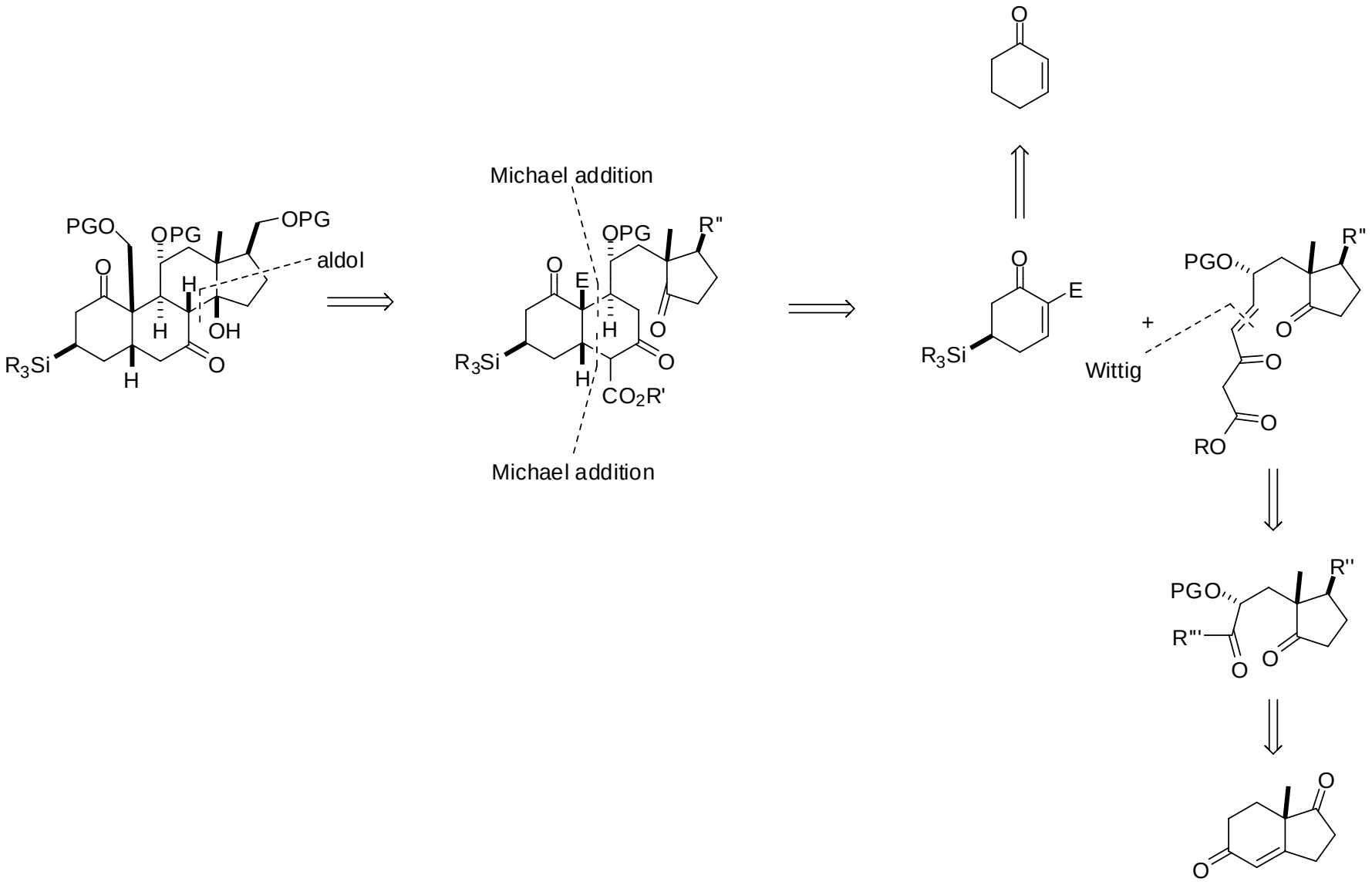
Synthetic Efforts to Date

-completed total synthesis of ouabain and ouabagenin reported by Deslongchamps in 2008

-completed tetracyclic core reported by Overman in 1998

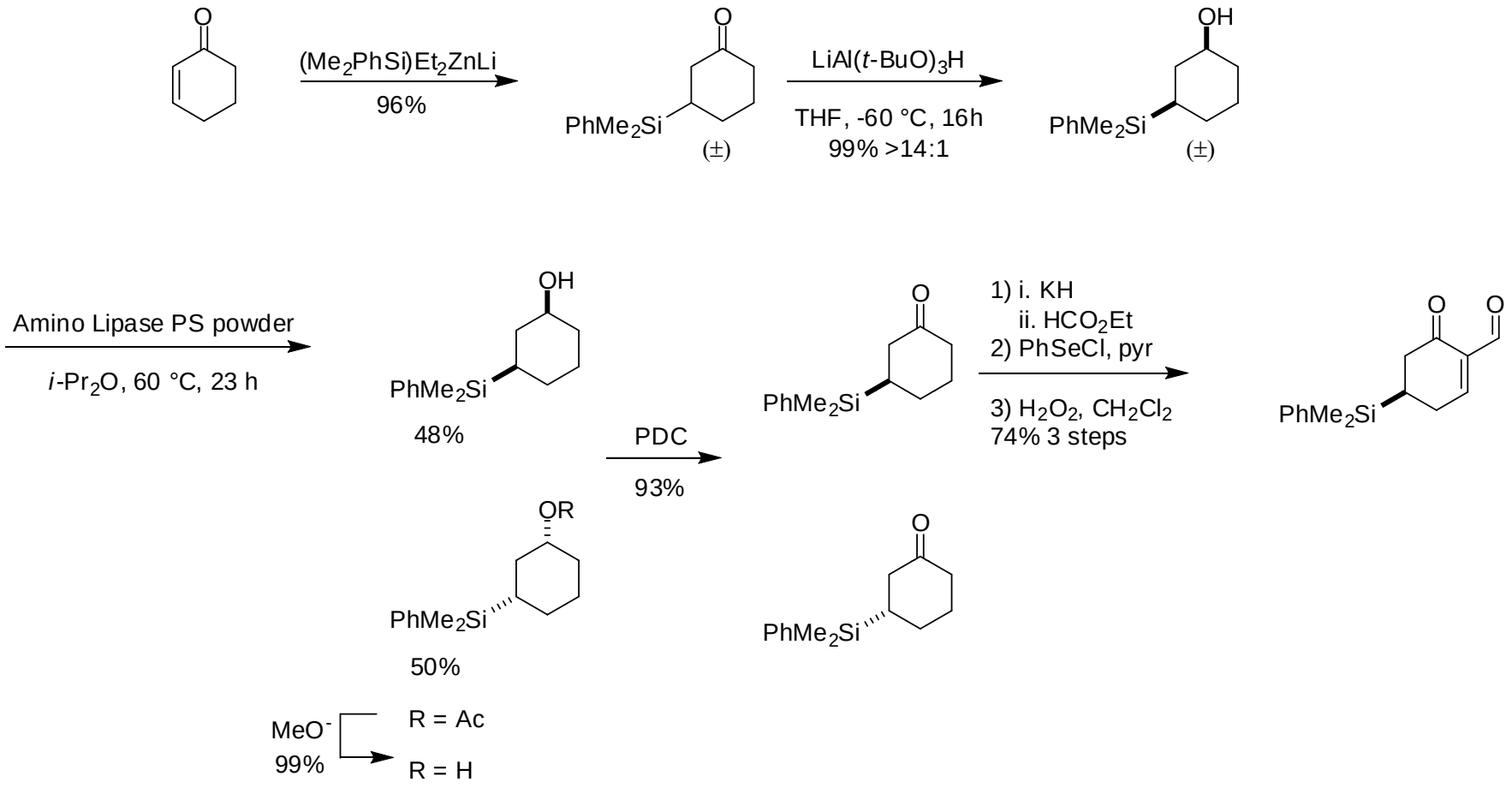
-studies towards AB bicyclic fragment reported by Jung in 2003

Deslongchamps' Retrosynthetic Analysis



Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272

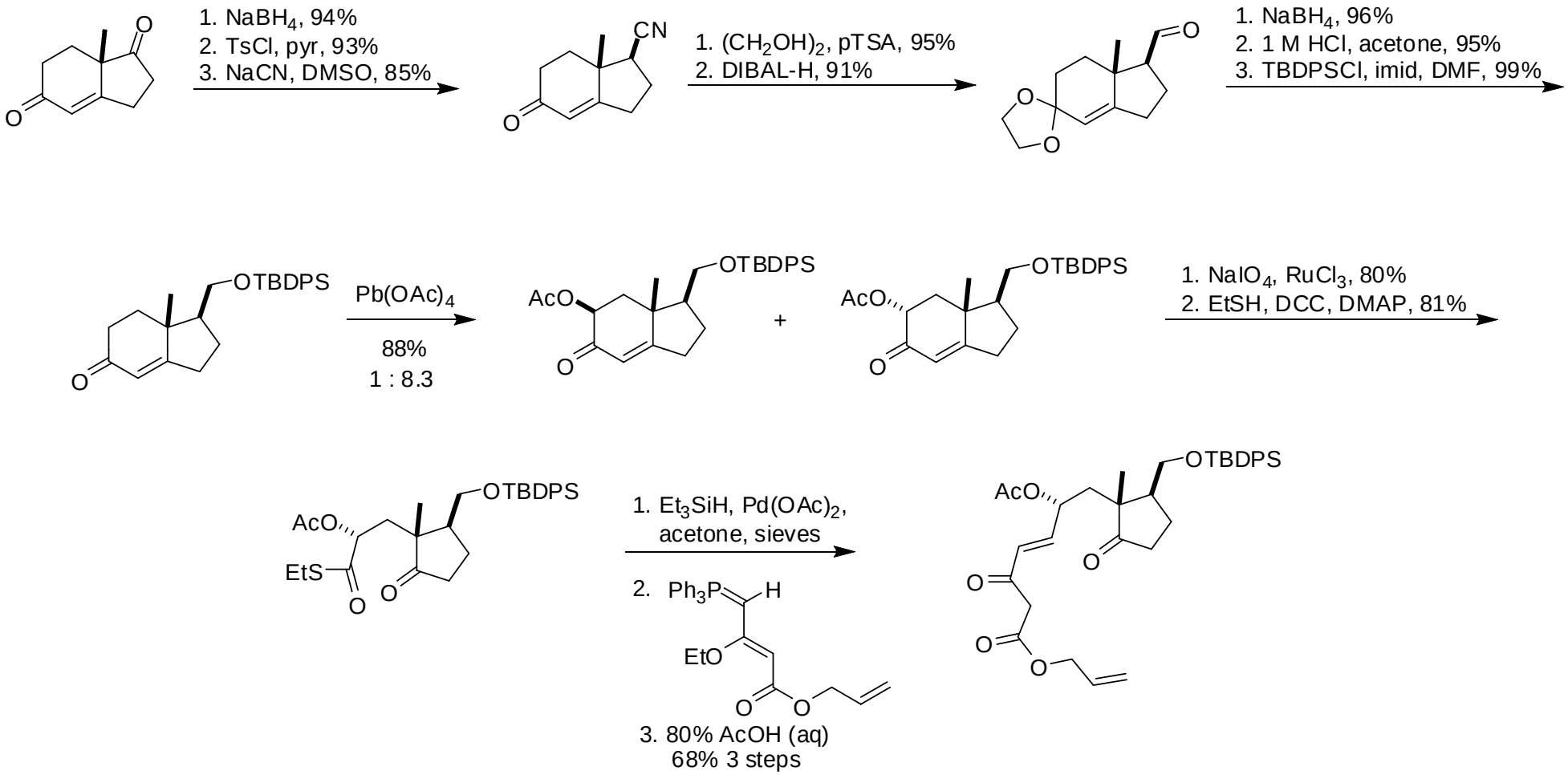
Synthesis of Cyclic Enone



Sarakinos, G.; Corey, E. J. Org. Lett. 1999, 1, 811

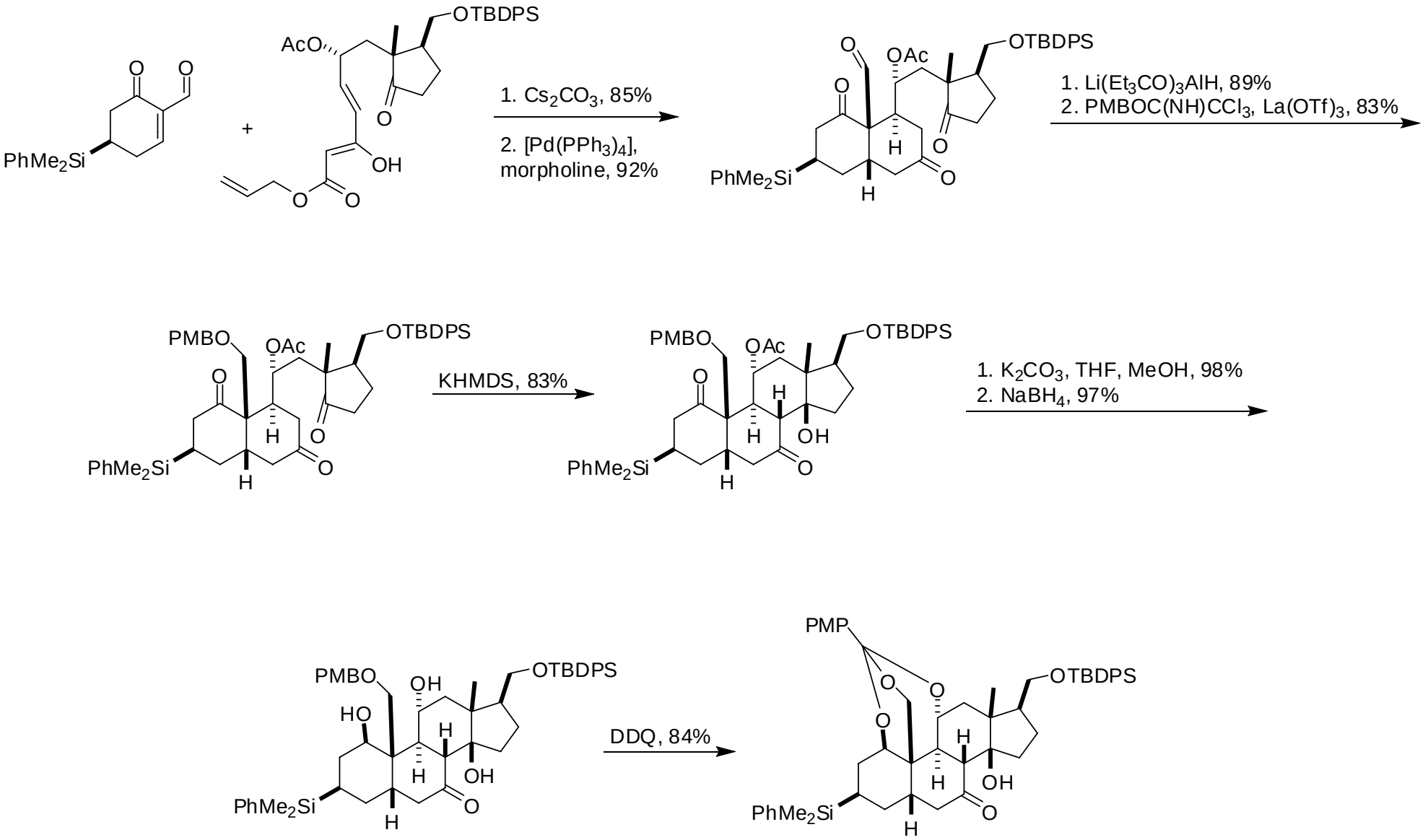
Trudeau, S.; Deslongshamps, P. J. Org. Chem. 2004, 69, 832

Synthesis of Cyclic Enone



Yang, Z.; Shannon, D.; Truong, V-L.; Deslongshamps, P. Org. Lett. 2002, 4, 4693

Synthesis of Ouabagenin



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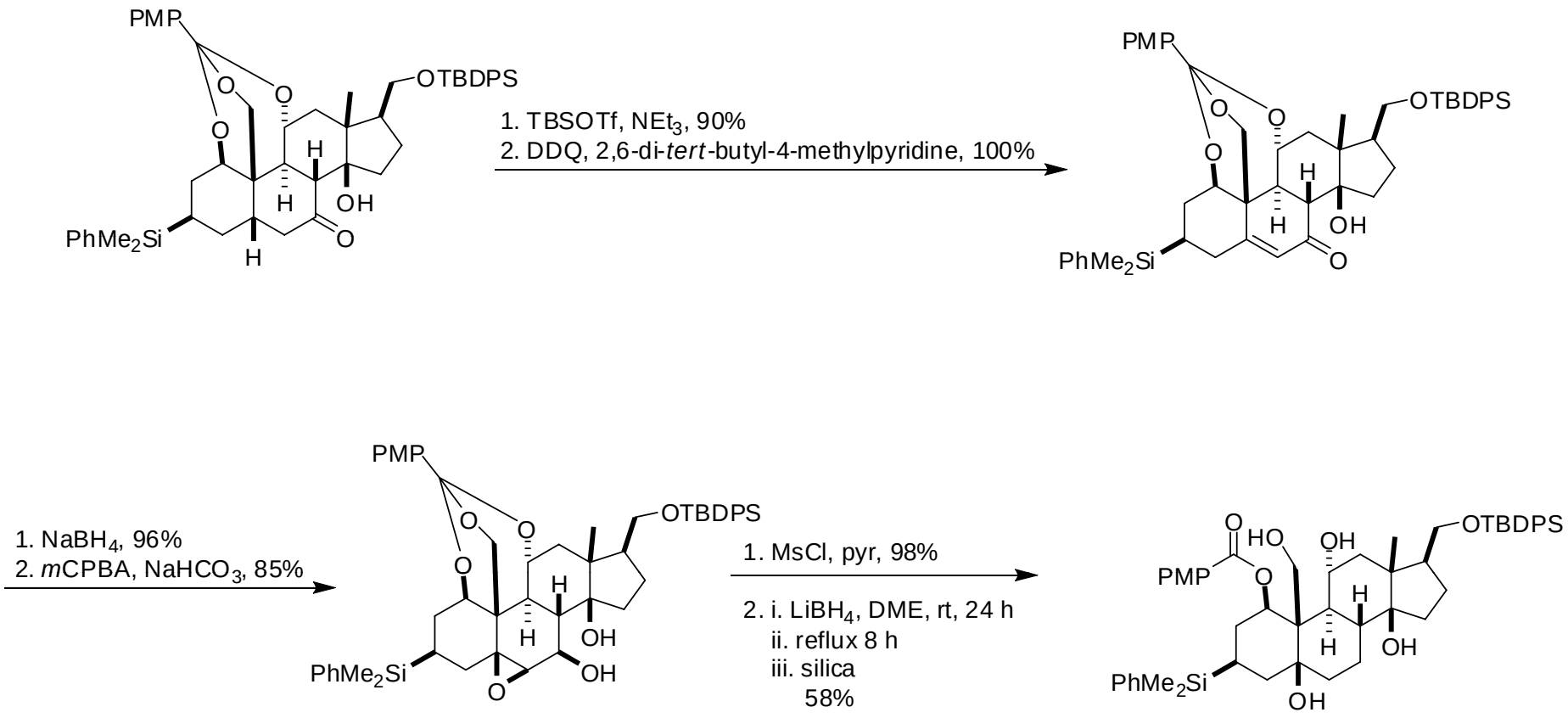
Synthesis of Ouabagenin



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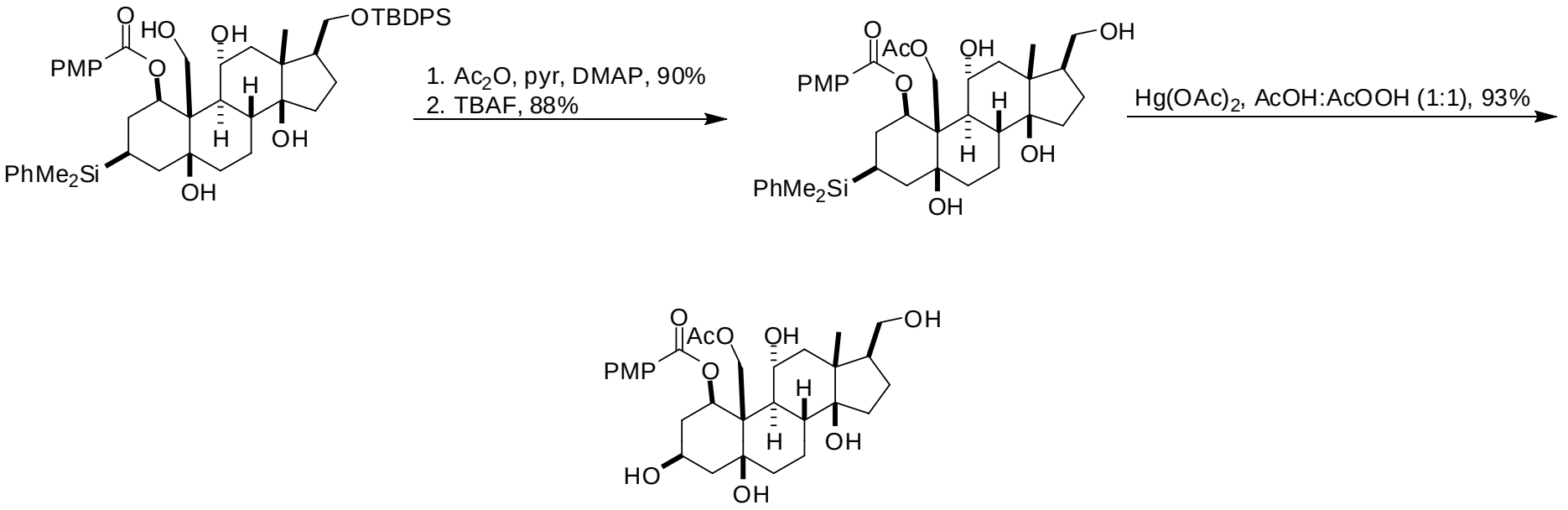
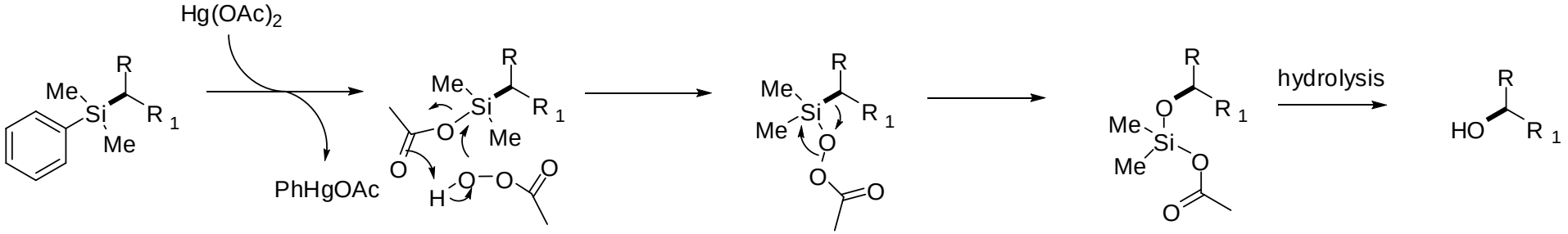
Synthesis of Ouabagenin



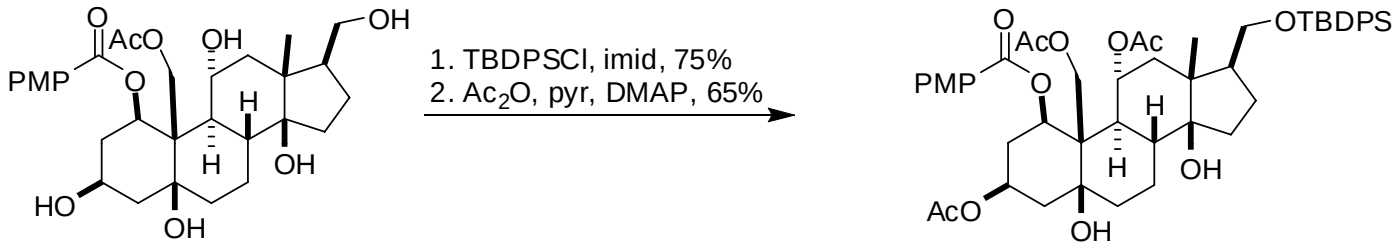
Tamao oxidation:

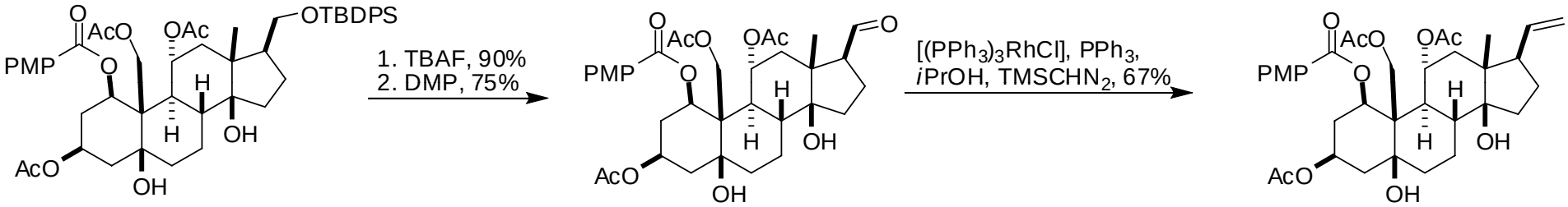


Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272

Jones, G. R. *Tetrahedron*, **1996**, *52*, 7599

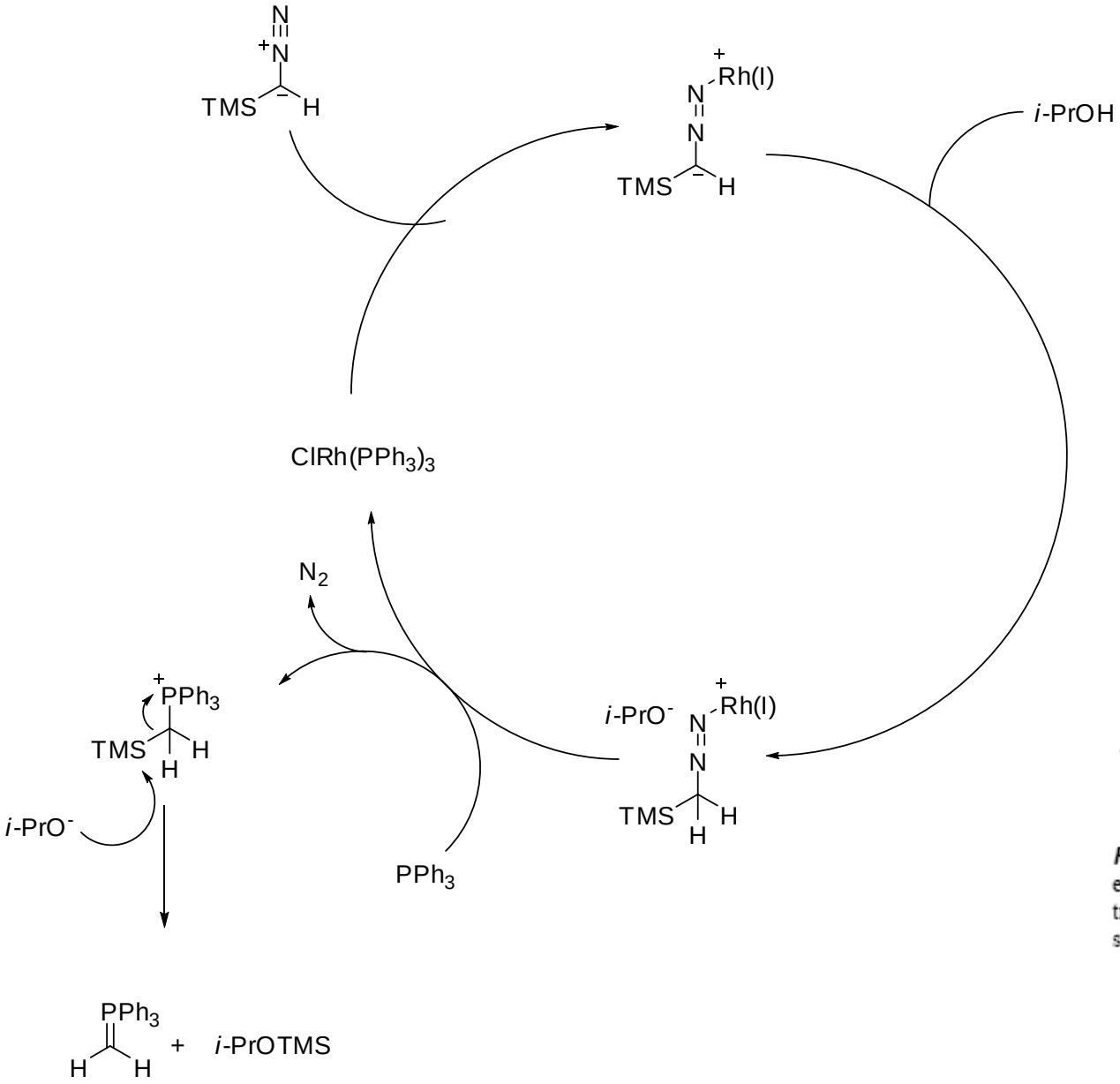
Synthesis of Ouabagenin





Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272

Rhodium Catalyzed Methylenation



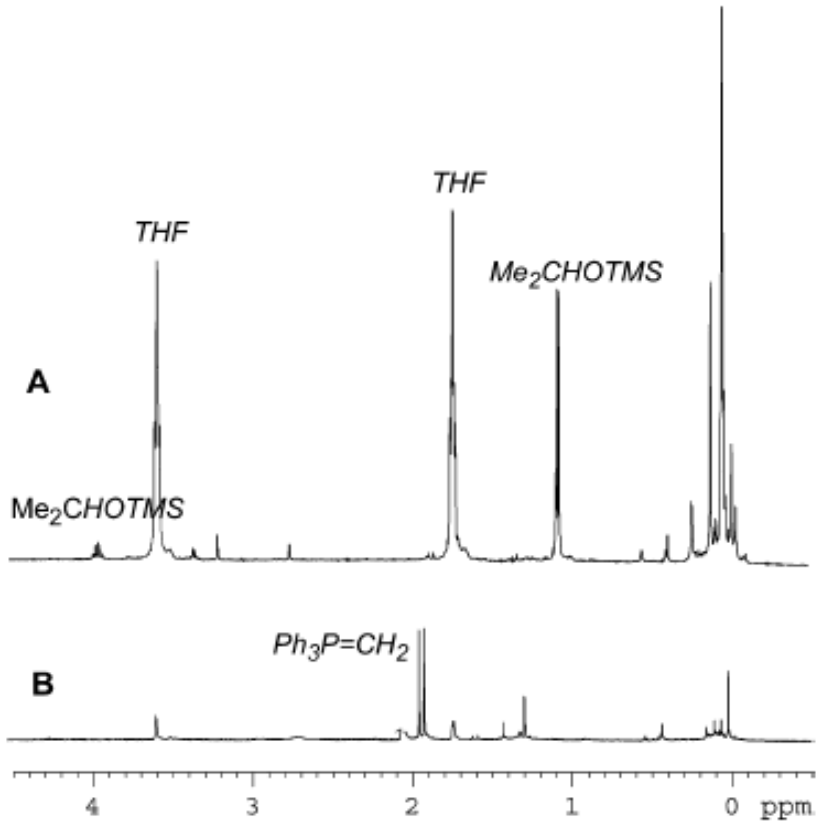
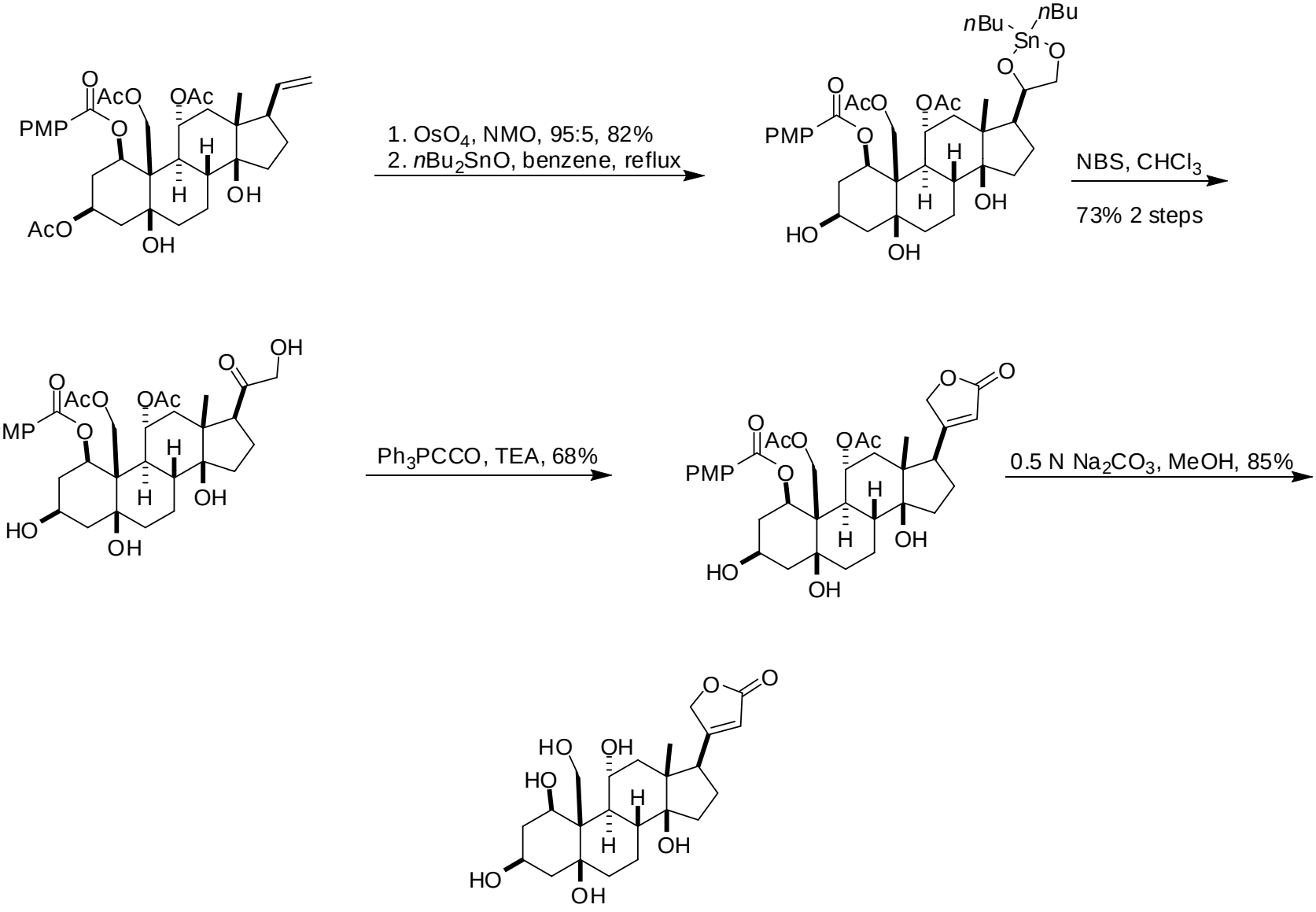


Figure 2. ^{1}H NMR spectra showing the formation of methylenetriphenylphosphorane in d_8-THF from trimethylsilyldiazomethane, 2-propanol, triphenylphosphine, and chlorotris(triphenylphosphine)rhodium. (A) Initial spectrum. (B) After partial evaporation under argon.

Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320

Synthesis of Ouabagenin

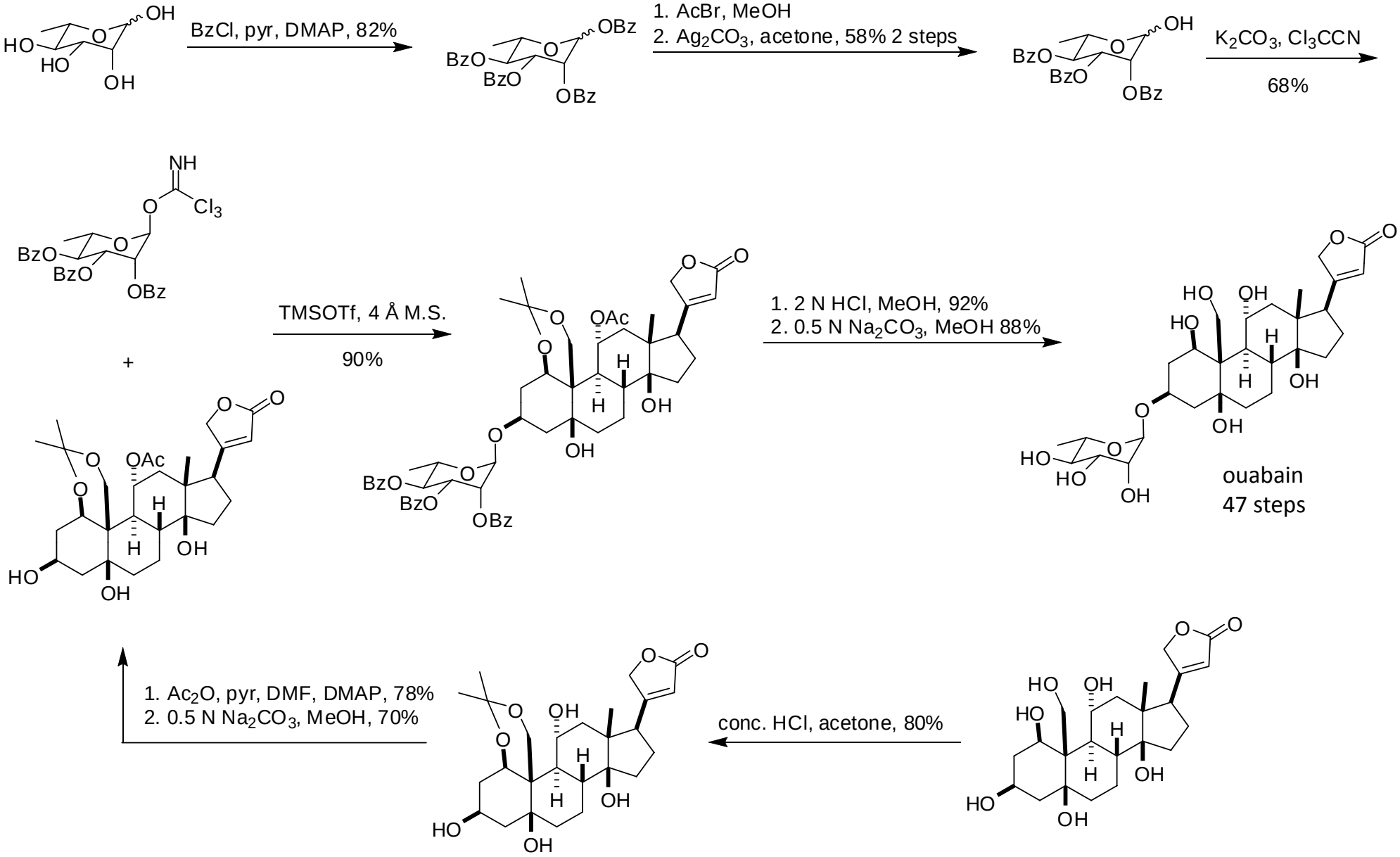


ouabagenin

41 steps

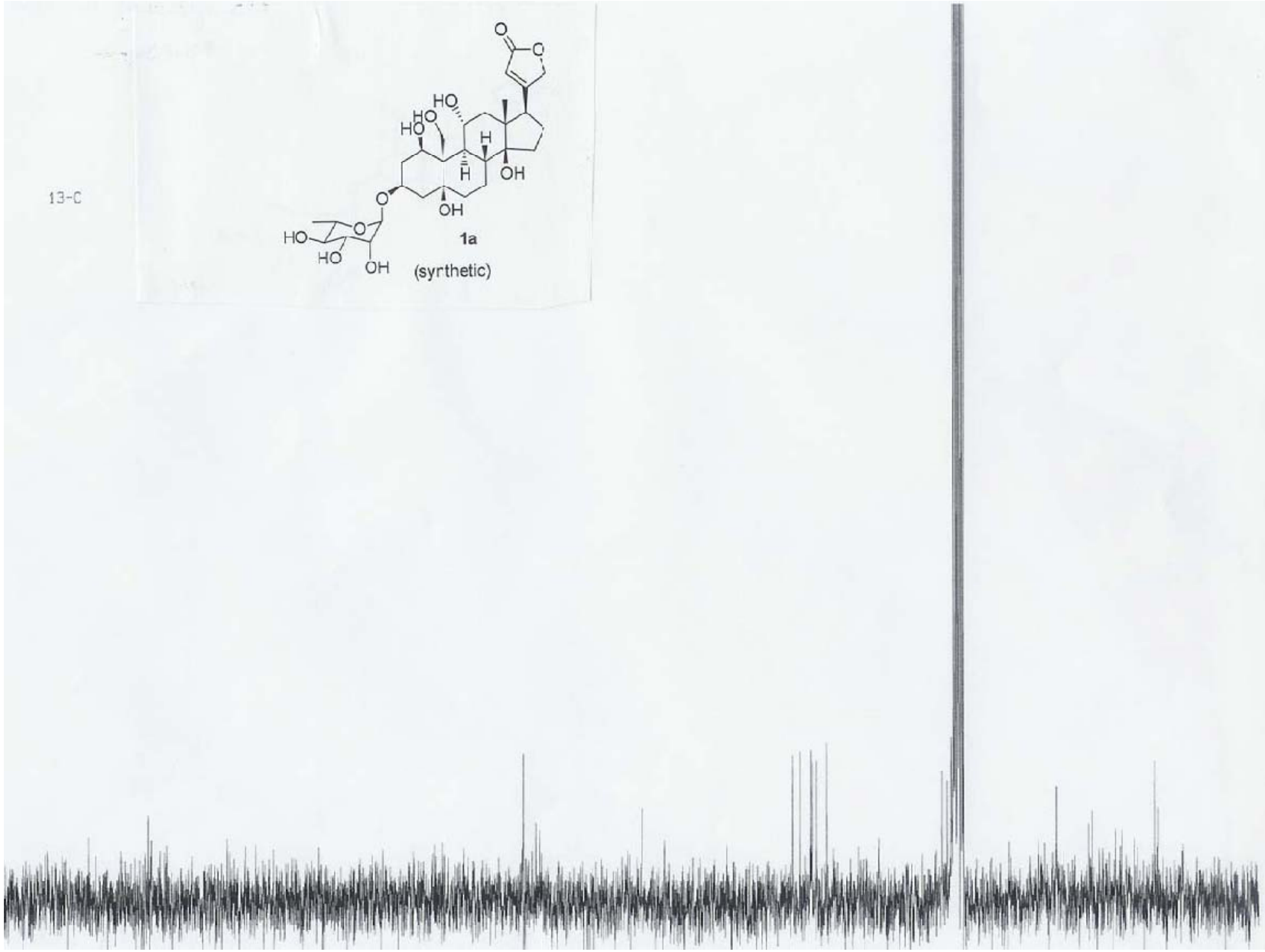
Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272

Synthesis of Ouabain



Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272

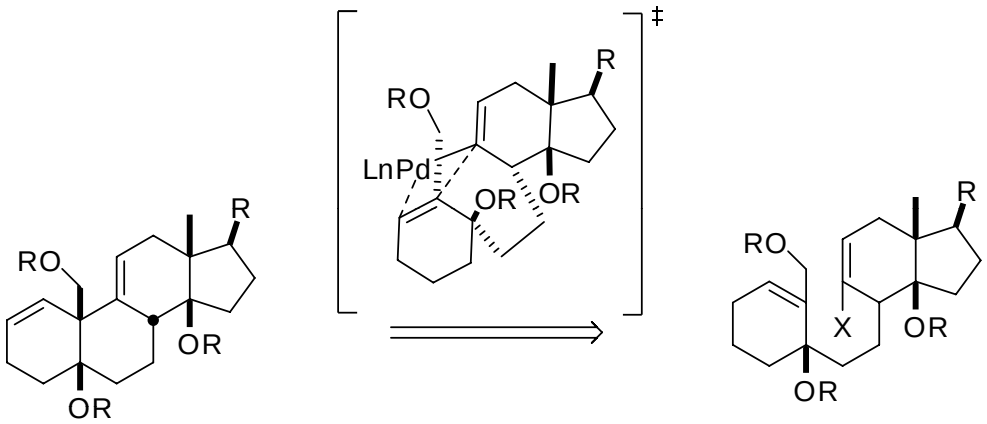
C^{13} of Synthetic Sample of Ouabain



Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272

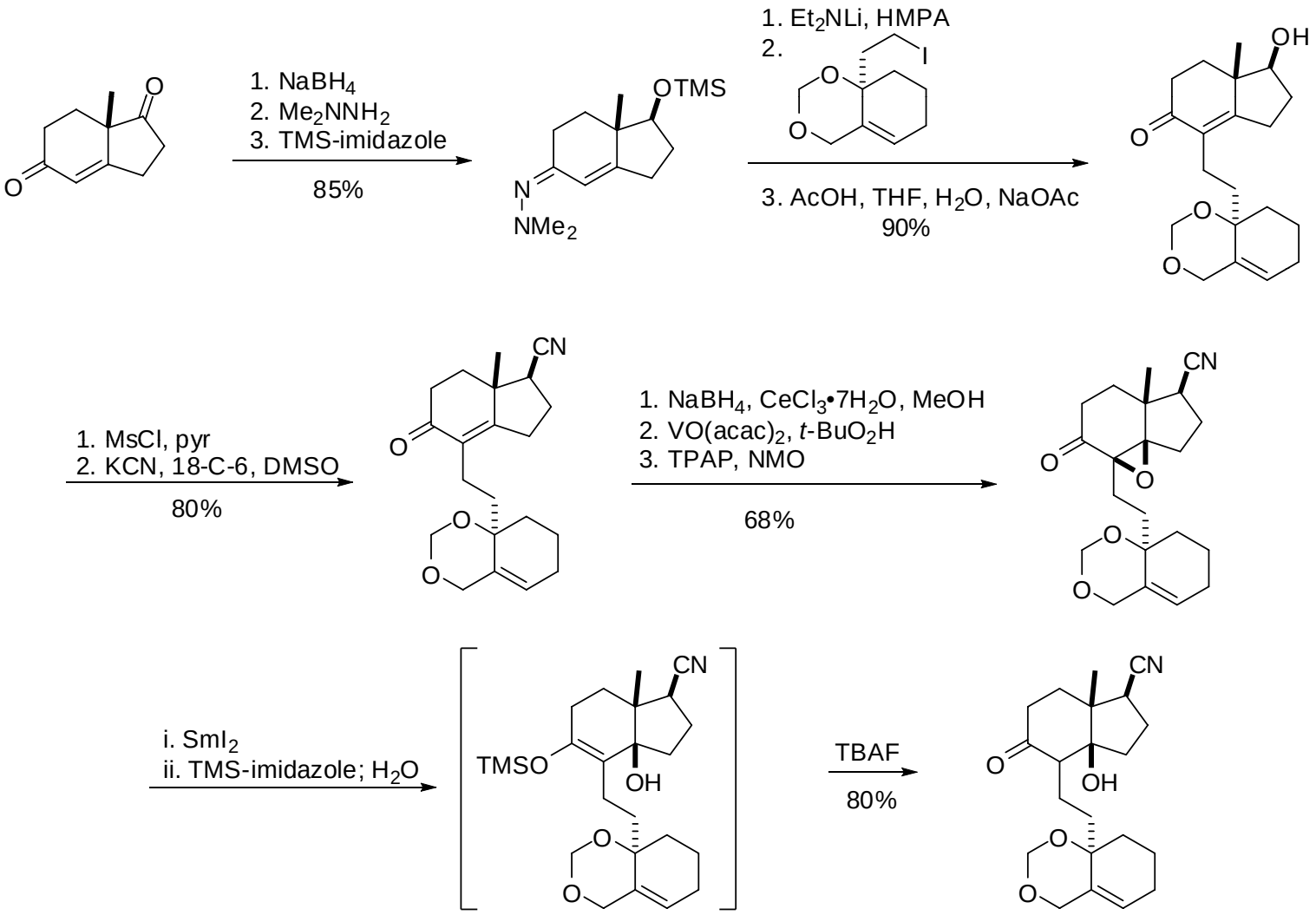
Overman Synthetic Efforts

Intramolecular Heck Approach:



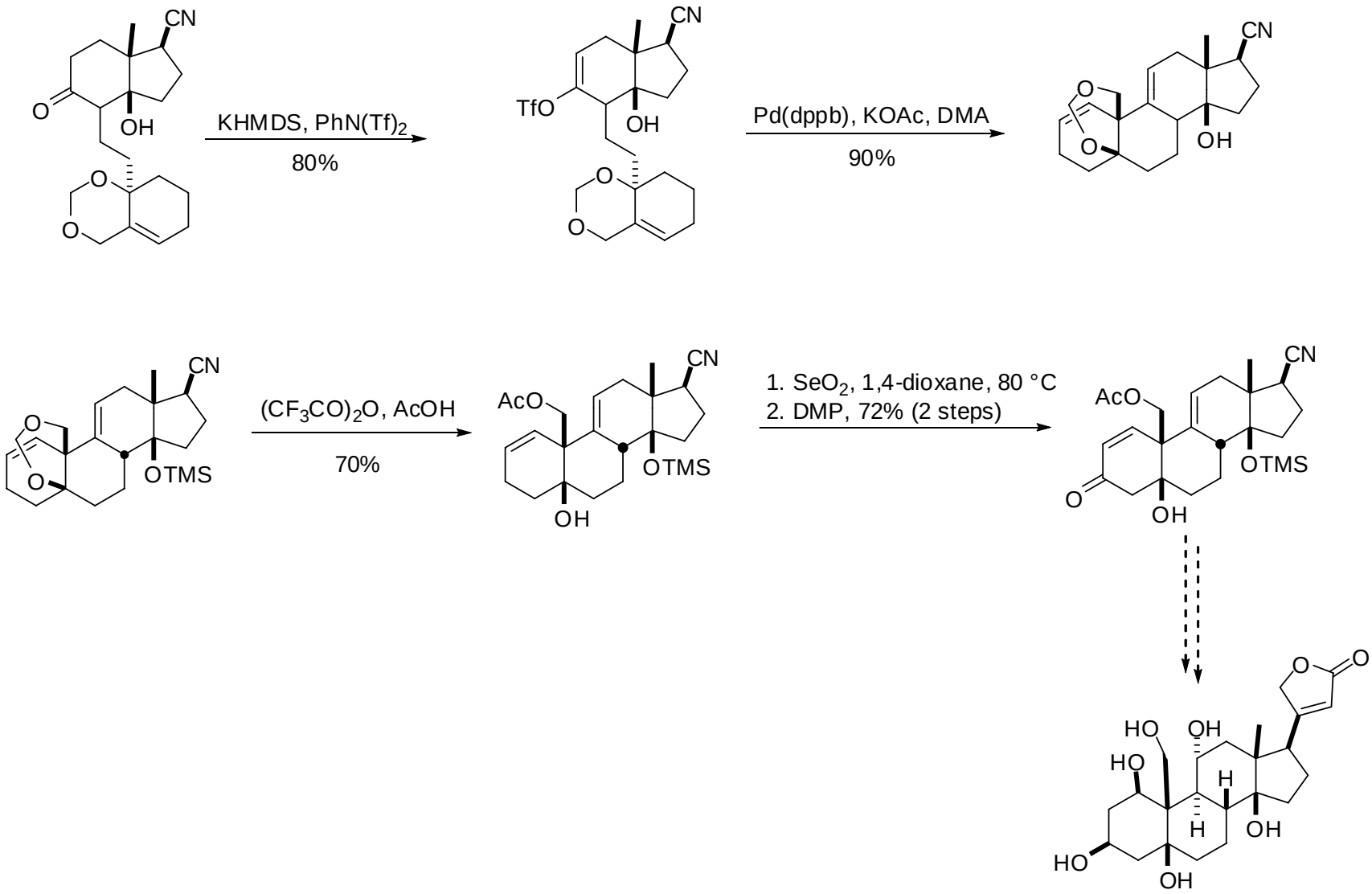
Overman, L. E.; et al. *J. Org. Chem.* **1996**, *61*, 6760

Overman Synthetic Efforts



Rucker, P. V; Overman, L. E. *Tetrahedron Let.* **1998**, *39*, 4643

Overman Synthetic Efforts



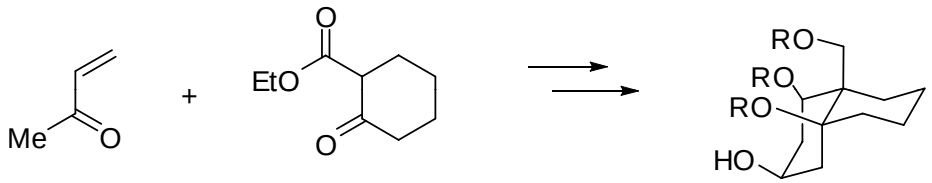
Ouabagenin

Rucker, P. V; Overman, L. E. *Tetrahedron Let.* **1998**, *39*, 4643

Rucker, P. V; Overman, L. E. *Heterocycles* **2000**, *52*, 1297

Jung Synthetic Efforts

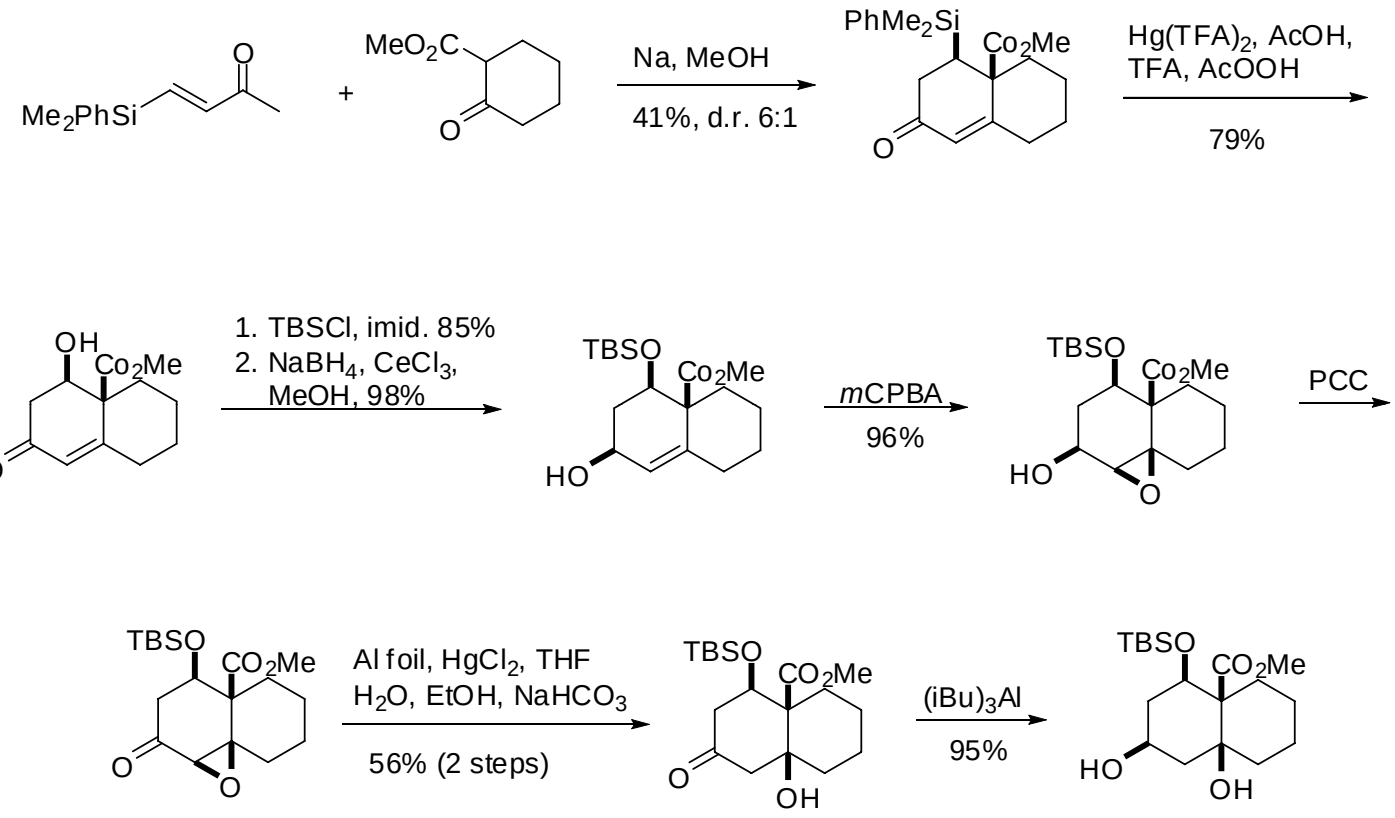
Robinson Annulation Approach:



Jung, M. E; Piizzi, G. *Org. Let.* **2003**, *5*, 137

Jung Synthetic Efforts

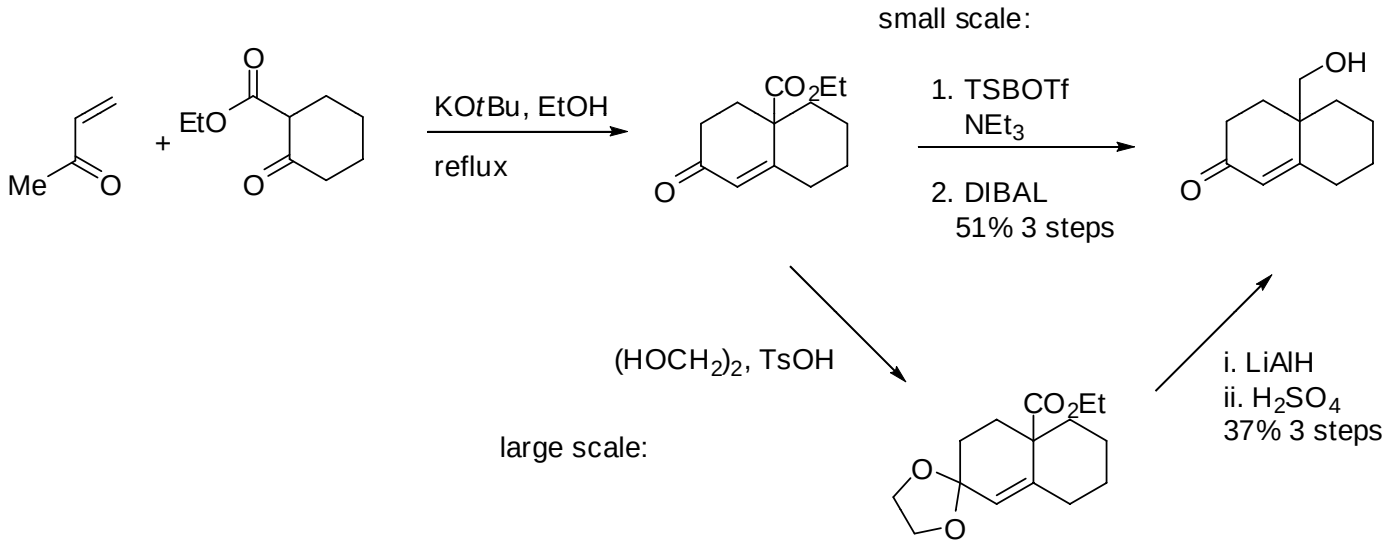
First Attempt:



Jung, M. E; Piizzi, G. *Org. Let.* **2003**, *5*, 137

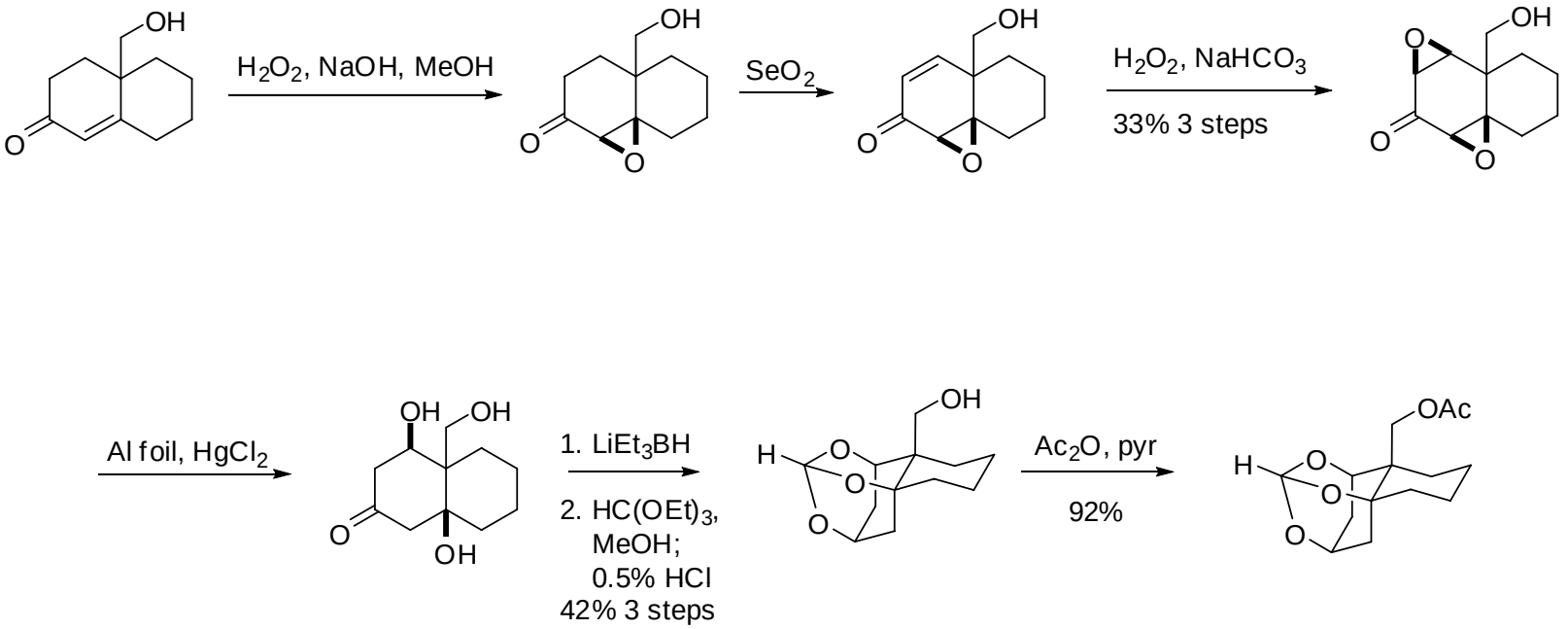
Jung Synthetic Efforts

More Successful Approach:



Jung, M. E; Piizzi, G. *Org. Let.* **2003**, *5*, 137

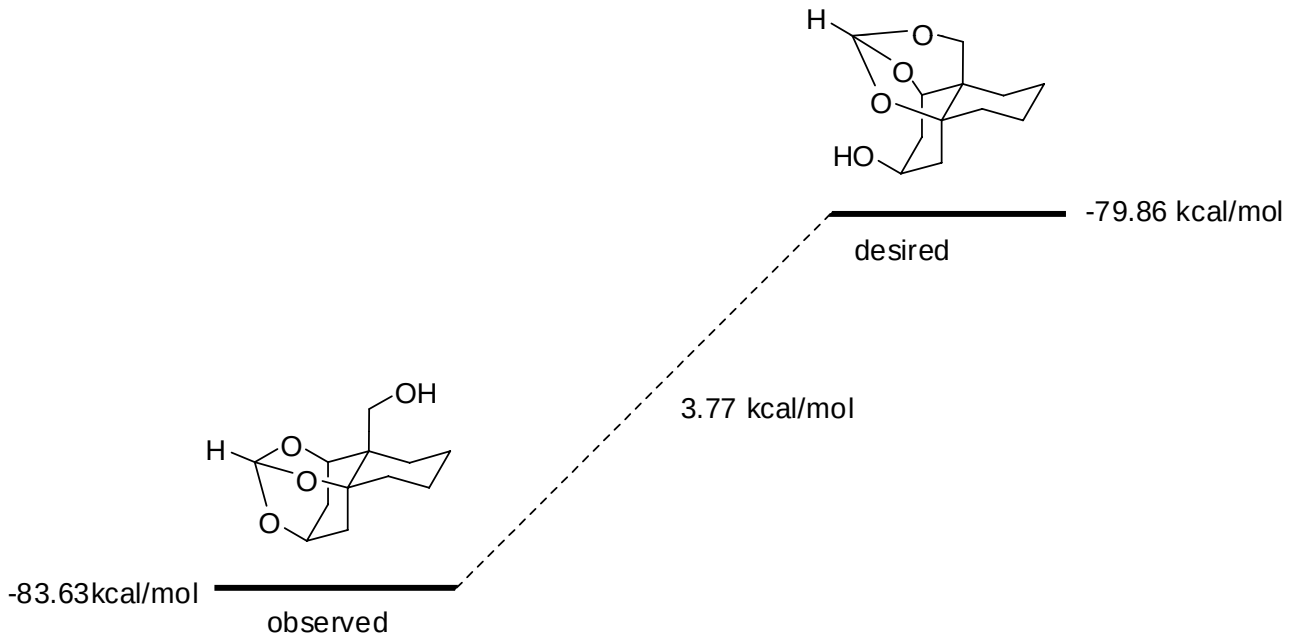
Jung Synthetic Efforts



Jung, M. E; Piizzi, G. *Org. Let.* **2003**, *5*, 137

Jung Synthetic Efforts

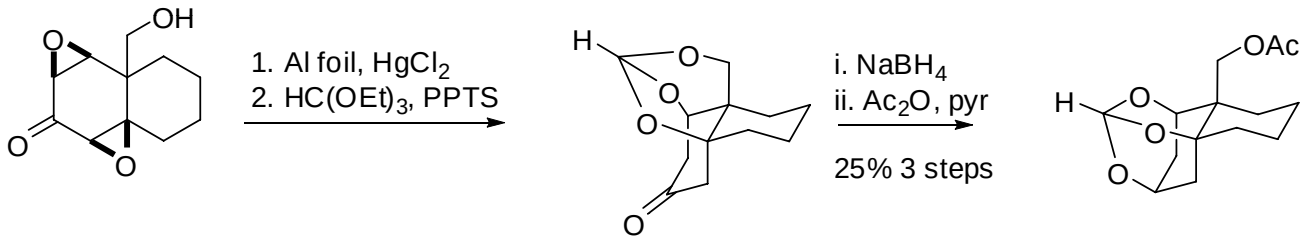
MM2 Calculations:



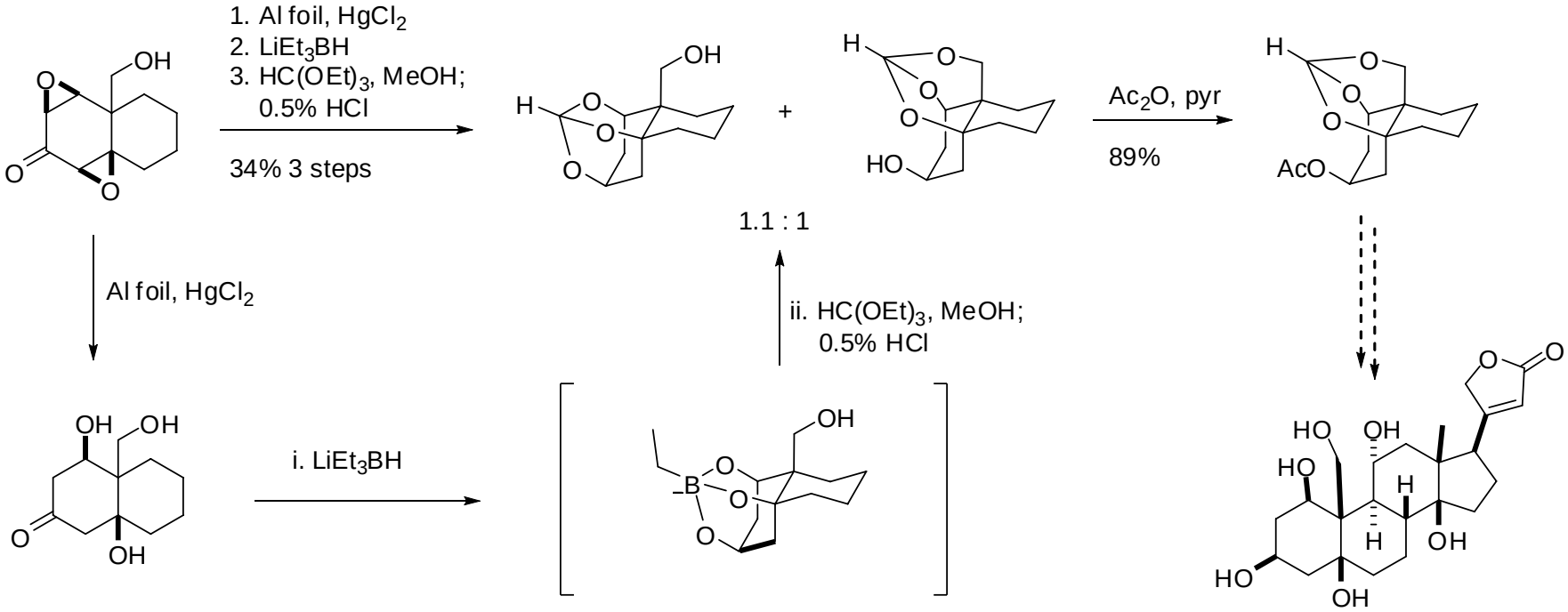
Jung, M. E; Piizzi, G. *Org. Let.* **2003**, *5*, 137

Jung Synthetic Efforts

changing step sequence:



use of boron chelate:



Jung, M. E; Piizzi, G. *Org. Let.* **2003**, *5*, 137

Ouabagenin