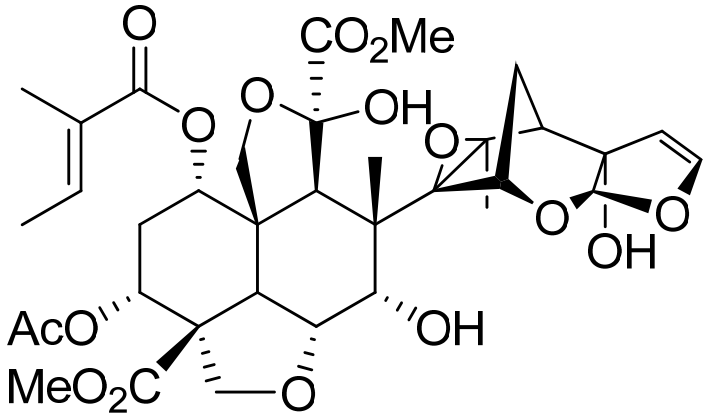
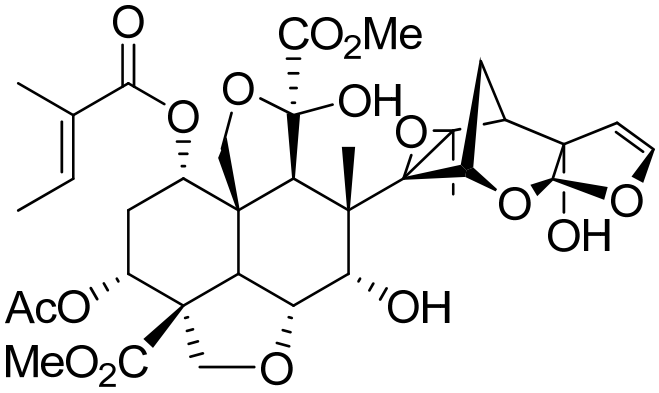
Synthesis of Azadirachtin: A Long but Successful Journey



Gemma E. Veitch, Edith Beckmann, Brenda J. Burke, Alistair Boyer, Sarah L. Maslen, and Steven V. Ley
Angew. Chem. Int. Ed. 2007, Early View
And
Gemma E. Veitch, Edith Beckmann, Brenda J. Burke, Alistair Boyer, Carles Ayats, and Steven V. Ley
Angew. Chem. Int. Ed. 2007, Early View

Current Literature
Chenbo Wang @ Wipf Group
Aug 18th, 2007

Azadirachtin

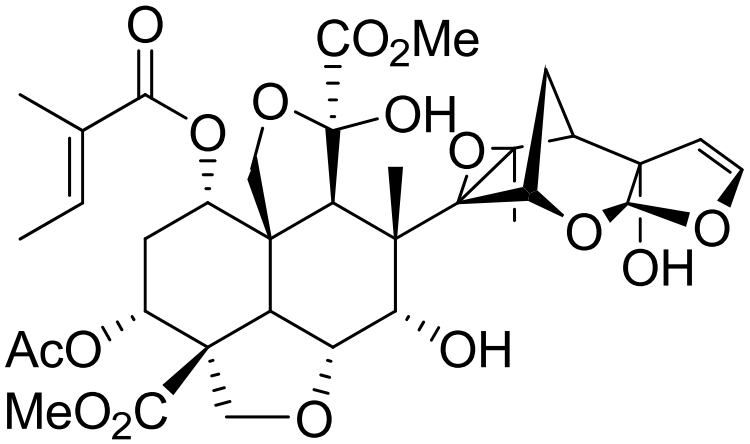


- Azadirachtin was isolated from the seed of Indian neem tree *Azadirachta indica* (0.2 to 0.8 percent by weight) in 1968.
- It acts as an antifeedant and growth disruptor against over 200 species of insect yet displays very low mammalian toxicity (LD_{50}(rat) > 5g/kg).
- Its structure was elucidated in 1987.
- Commercially available: 10 mg@$137

Butterworth, J. H. et al *Chem. Commun.* **1968**, 23 – 24.

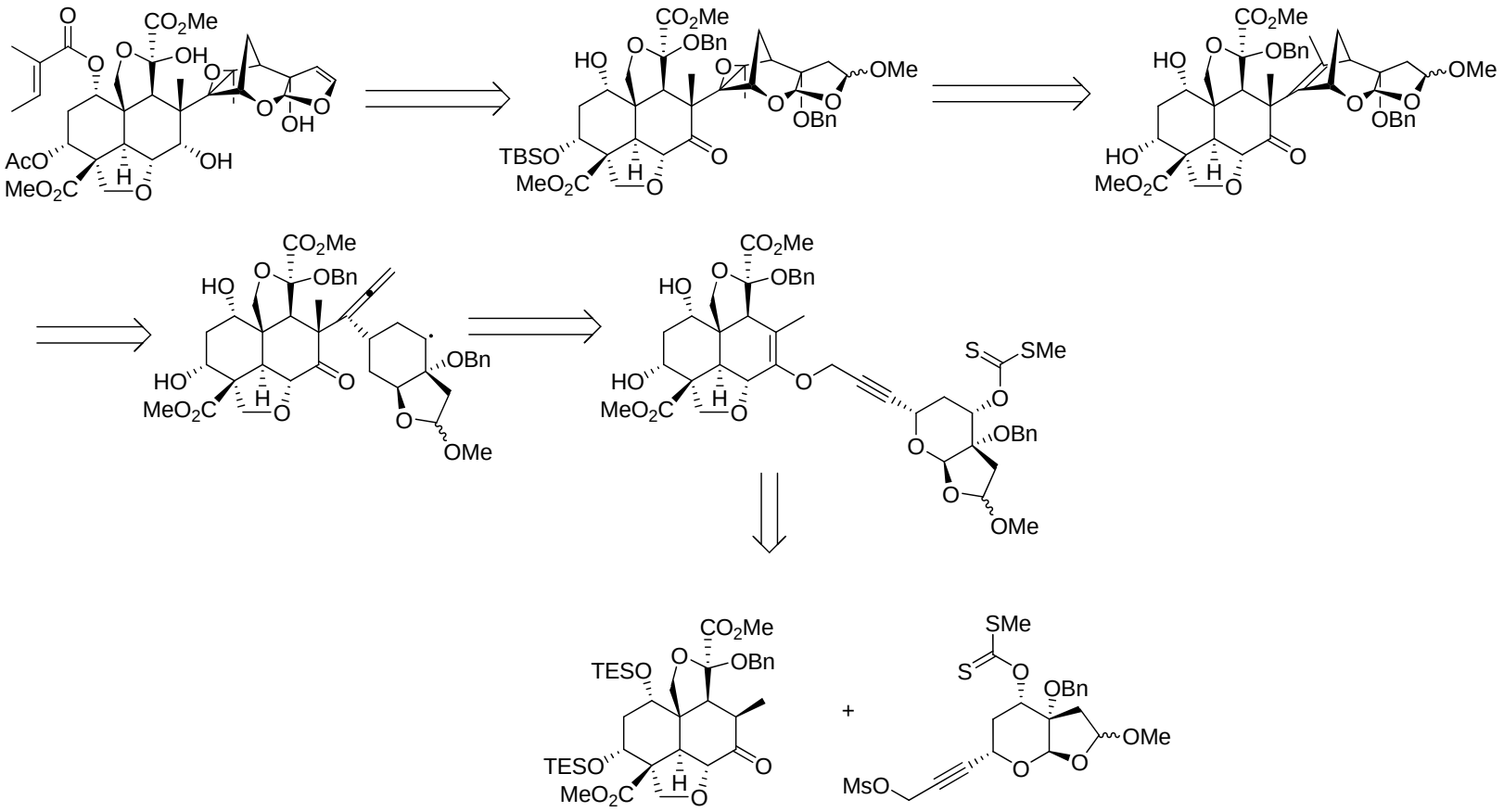
Kraus, W et al *Tetrahedron* **1987**, *43*, 2817 – 2830

Azadirachtin: Structural Features



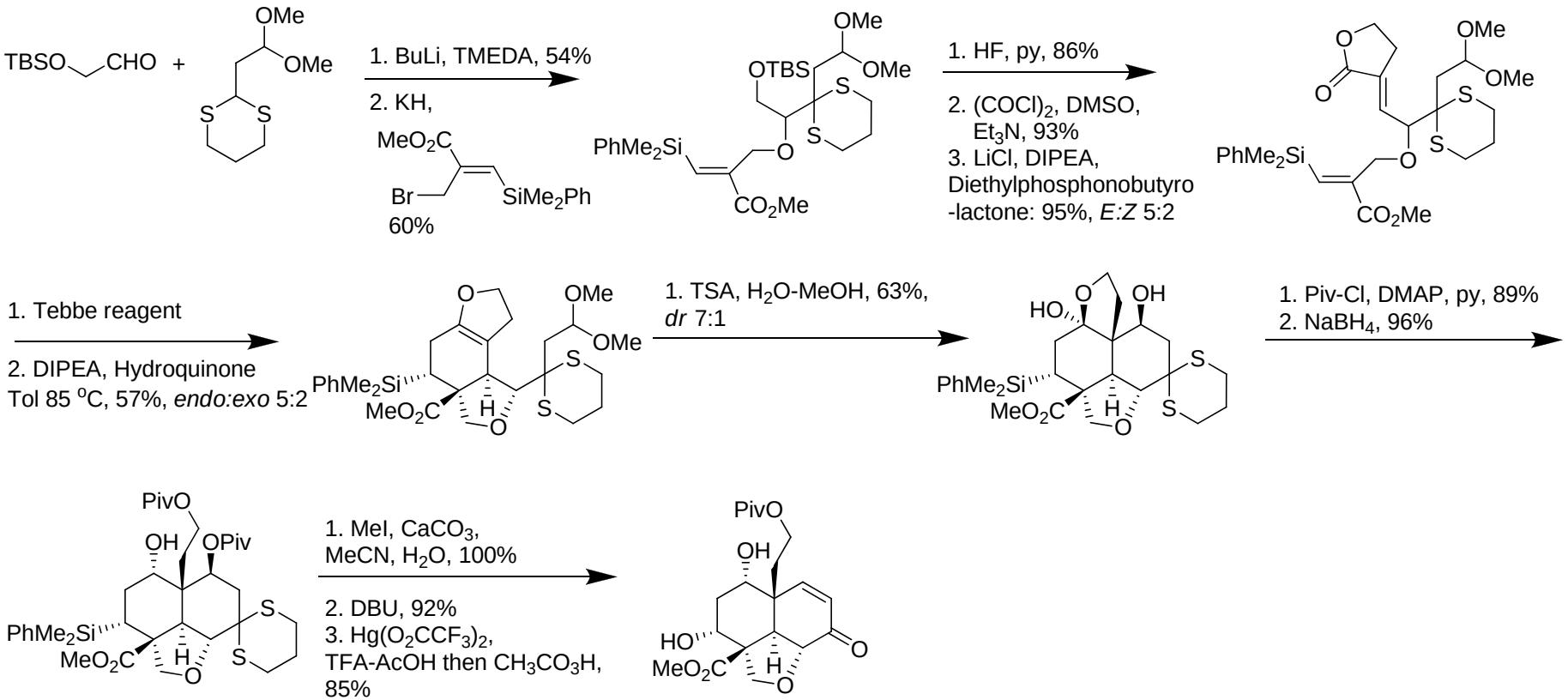
- Sixteen contiguous stereogenic centers, seven quaternary carbons
- Highly oxygenated
- Sensitive functionalities (enol ether and epoxide)

Retrosynthesis



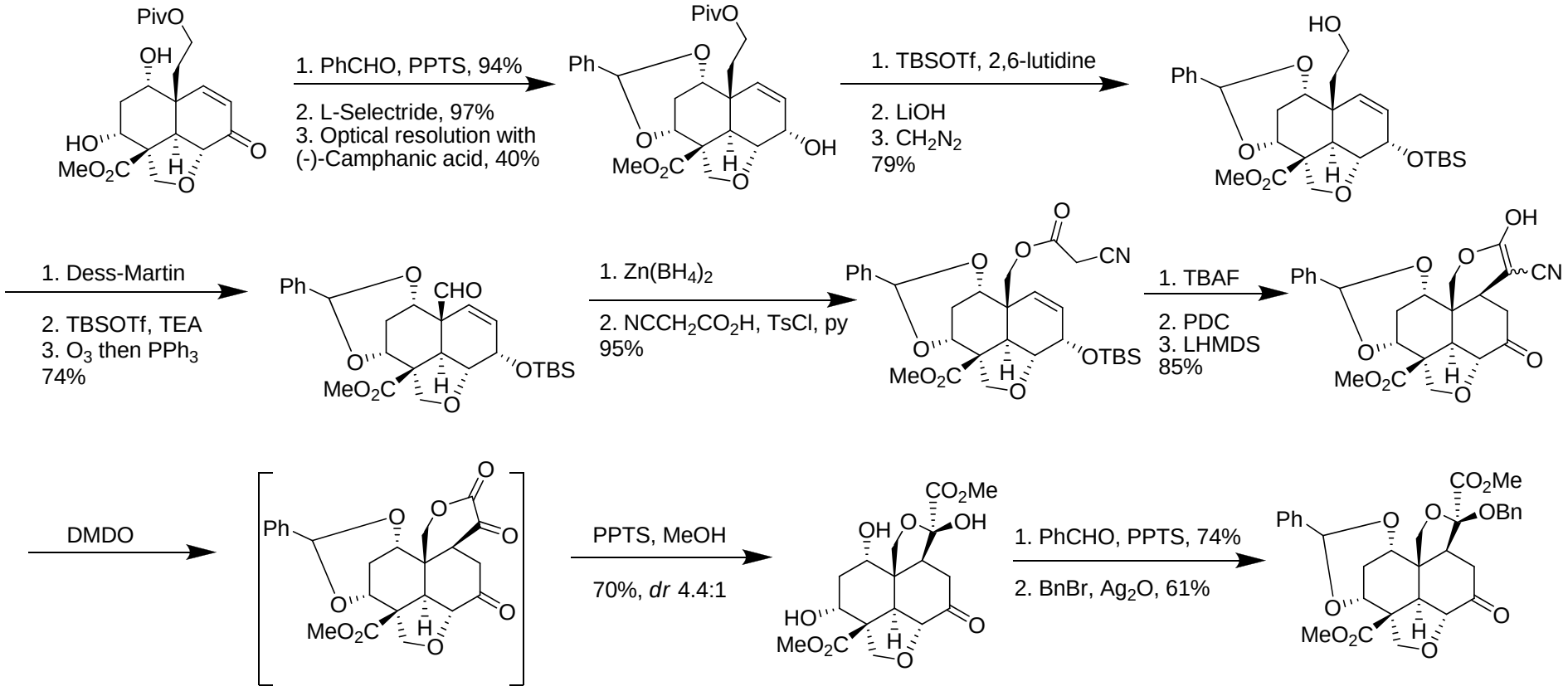
- Key tranformations:
  - Methy acetal protection of the enol ether functionality
  - Radical cyclization to provide the bridged ring system
  - O-alkylation followed by Claisen rearrangement to install the C8 quartenary center

Preparation of Left Hand Fragment



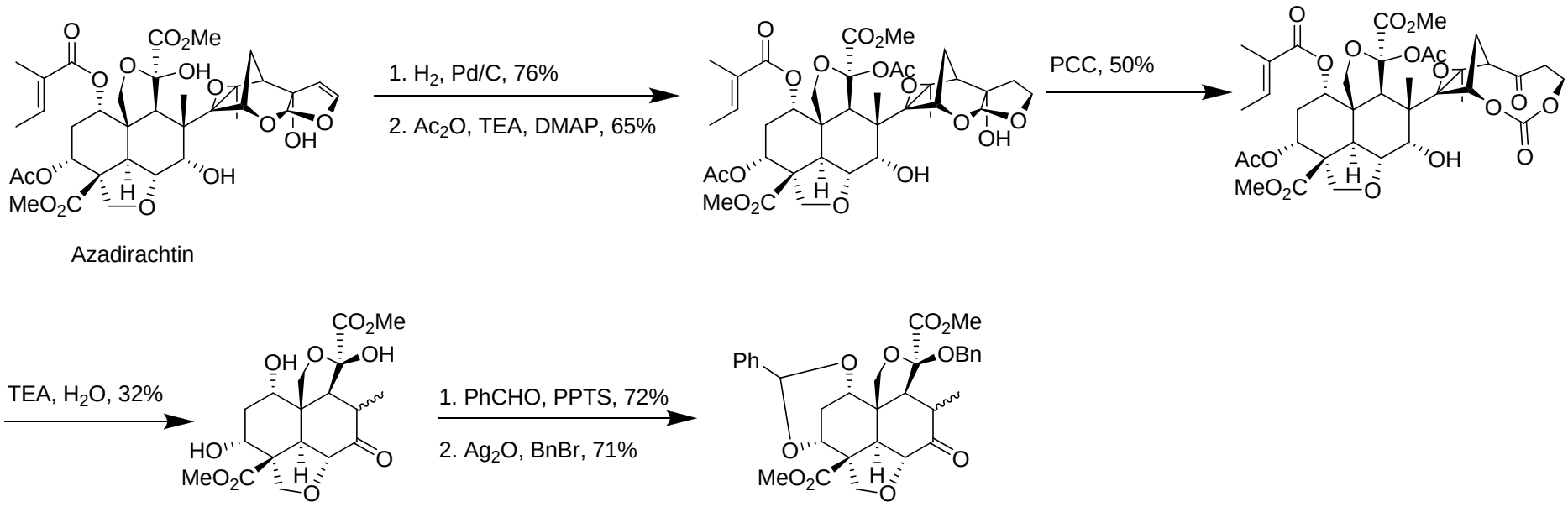
Kolb, H. C. et al. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735

Preparation of Left Hand Fragment (cont.)



30 steps, 0.12% overall yield

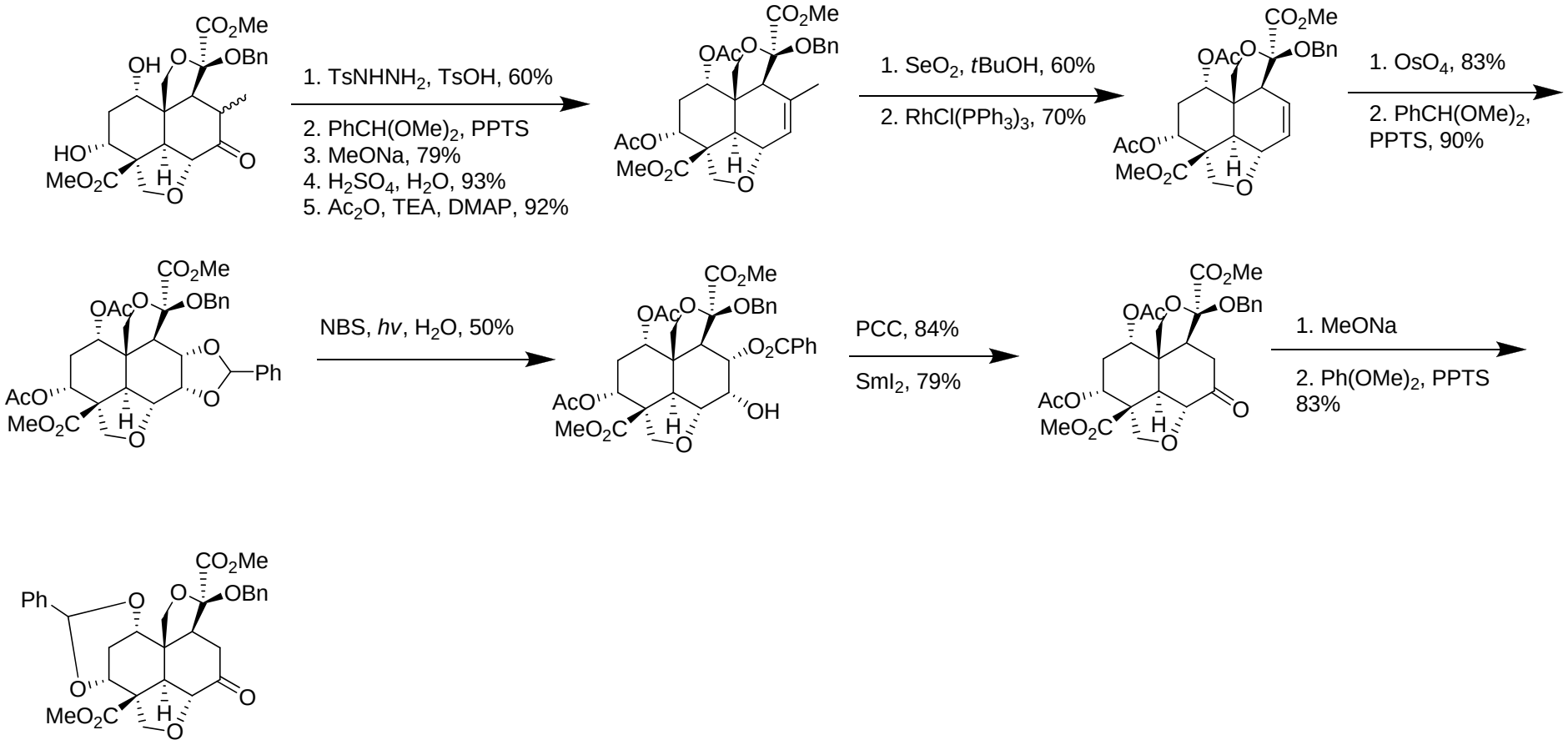
Degradation Study



Azadirachtin

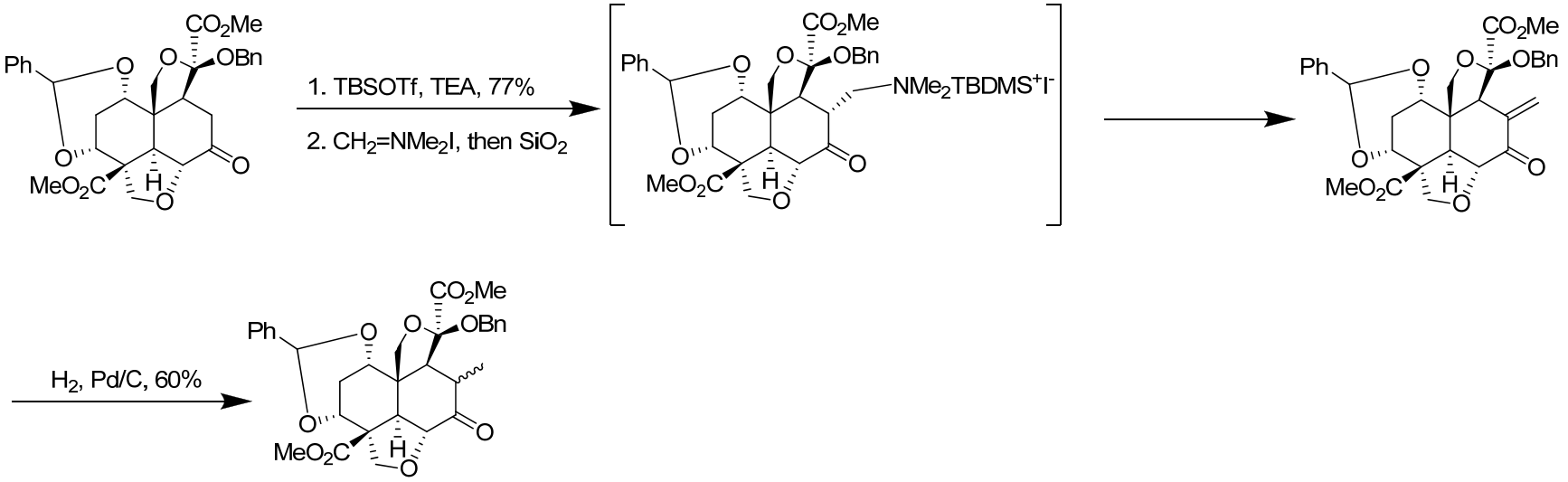
Ley, S. V. et al *Tetrahedron*, **1993**, *49*, 1675

Demethylation of the C-8 Position



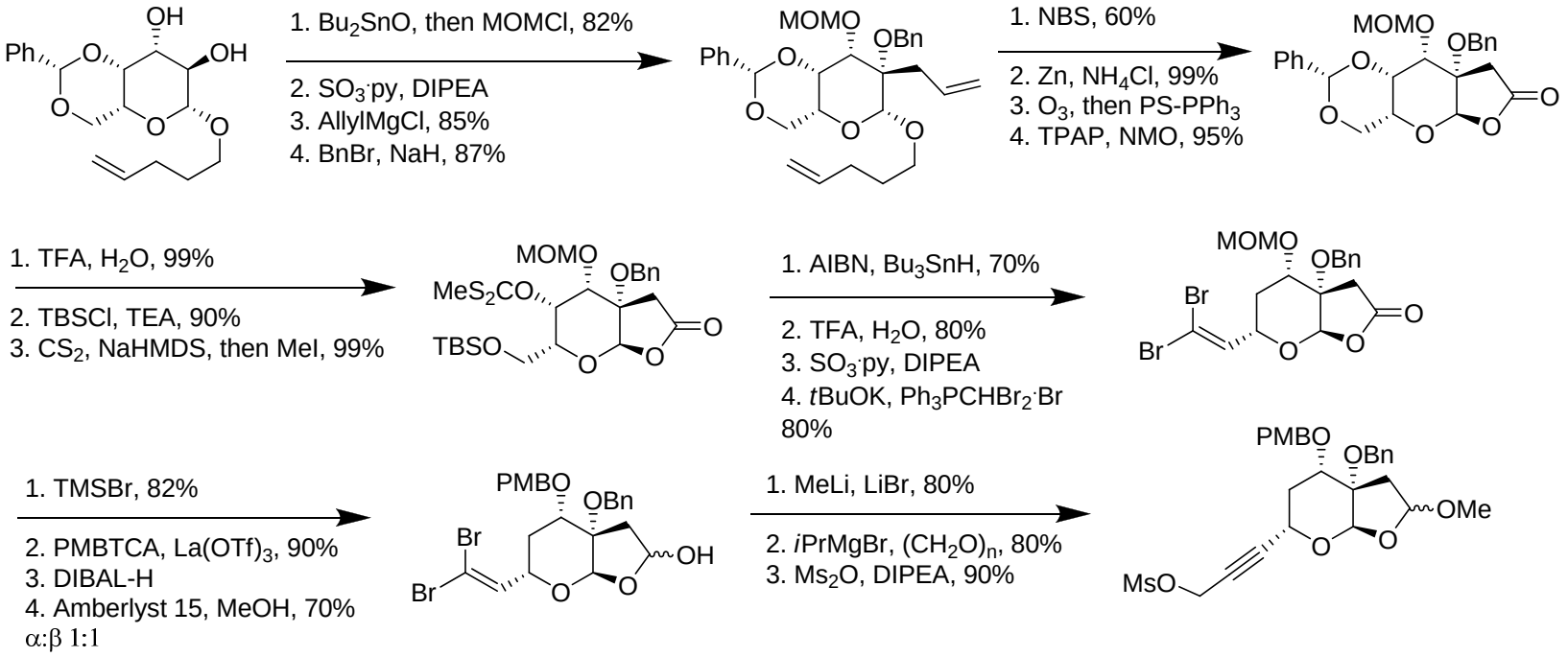
Koot, W. J. et al *Tetrahedron*, **1995**, *51*, 2077

Methylation of the C-8 Position



3 steps, 46%

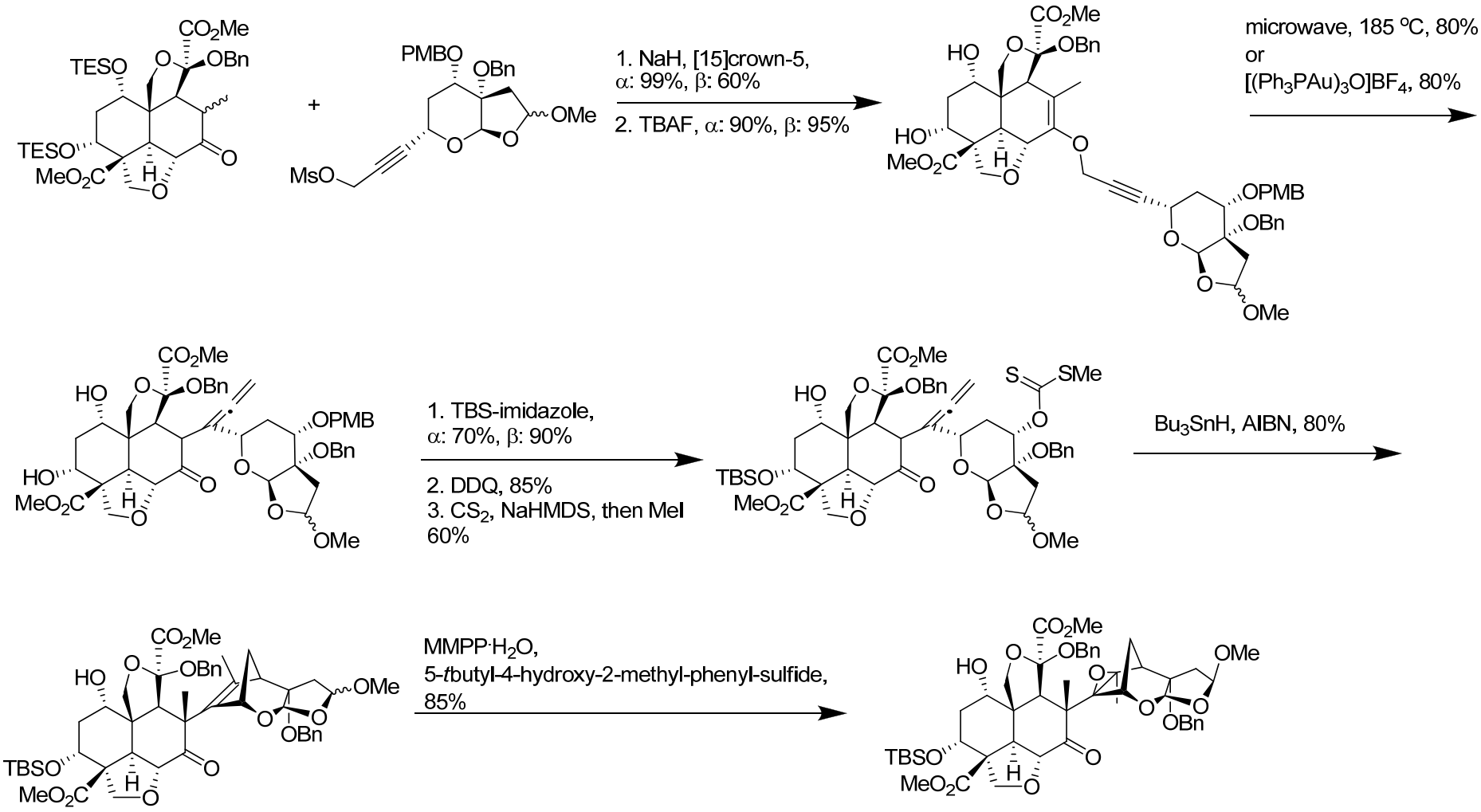
Preparation of Right Hand Fragment



22 steps, 4.1%

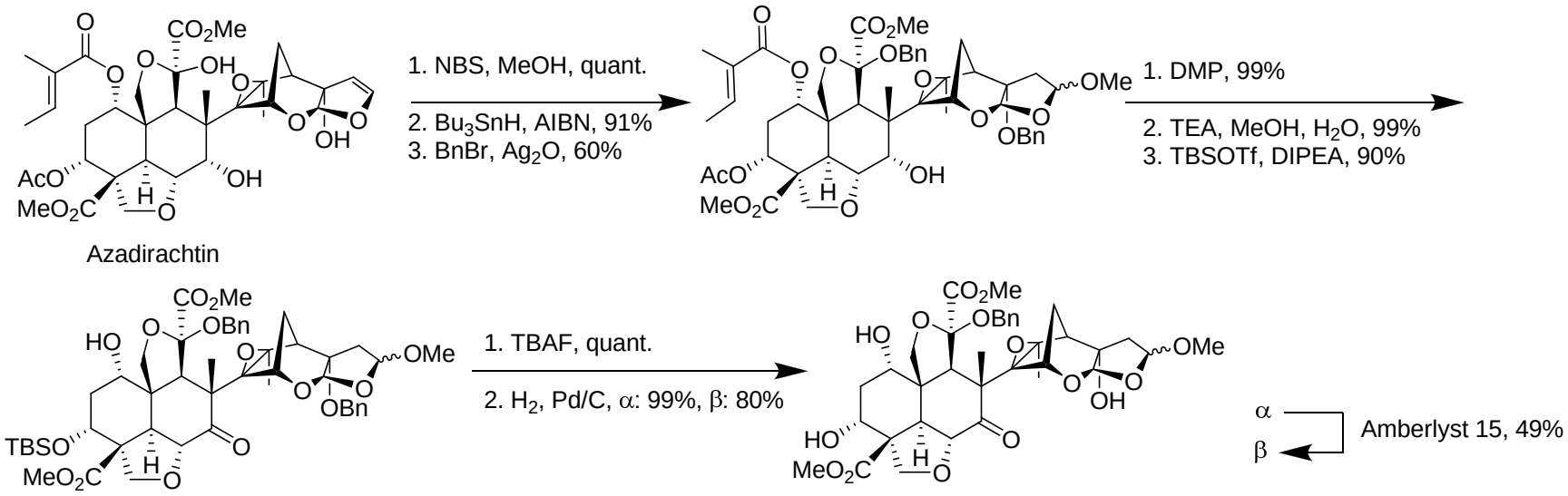
Veitch, G. et al *Angew. Chem. Int. Ed.* Early View

Fragment coupling



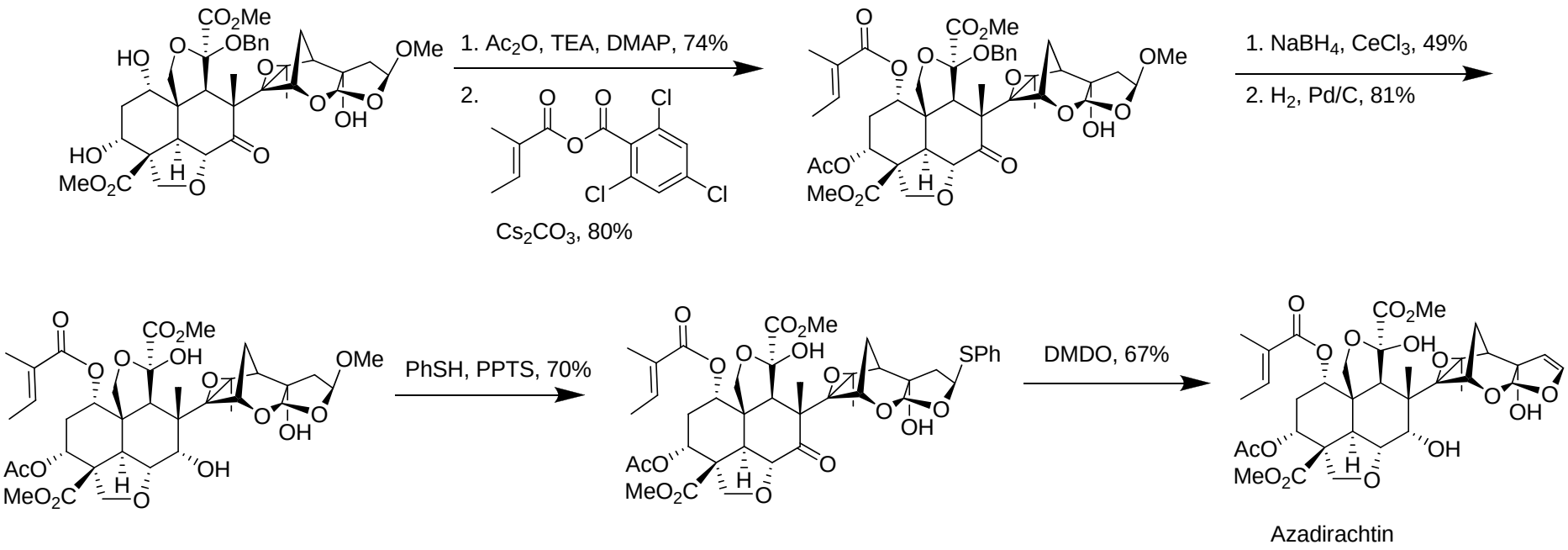
8 steps, 17%

A Relay Route to Azadirachtin



Azadirachtin

End Game



6 steps, 11%

Summary

- The authors have demonstrated a feasible pathway for the synthesis of azadirachtin: “22 years in the making”.
- 47 linear steps, 0.0010% overall yield
- Key steps include a Claisen rearrangement for the formation of C8-C14 bond and a radical cyclization to form the bridged ring system.
- End game relies on an intermediate prepared by the degradation of the target molecule.