Synthesis of the Zoanthamine Alkaloids

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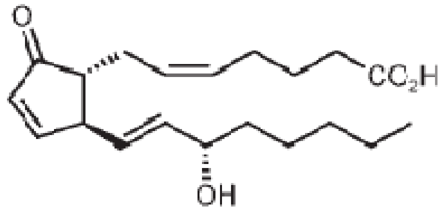
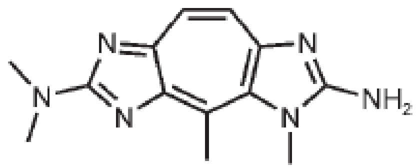
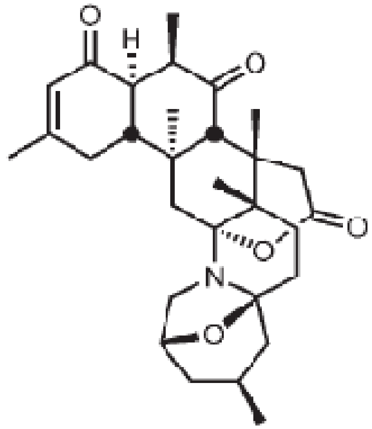
Natural Products Isolated from the Zoanthids



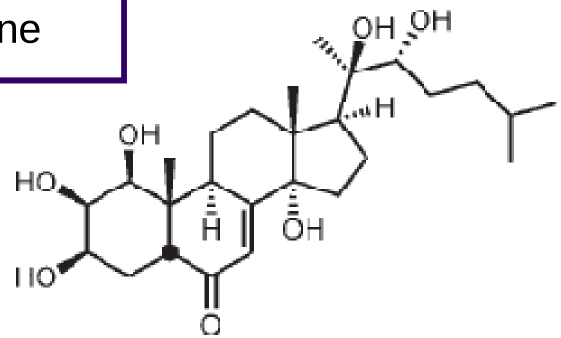
PGA_2



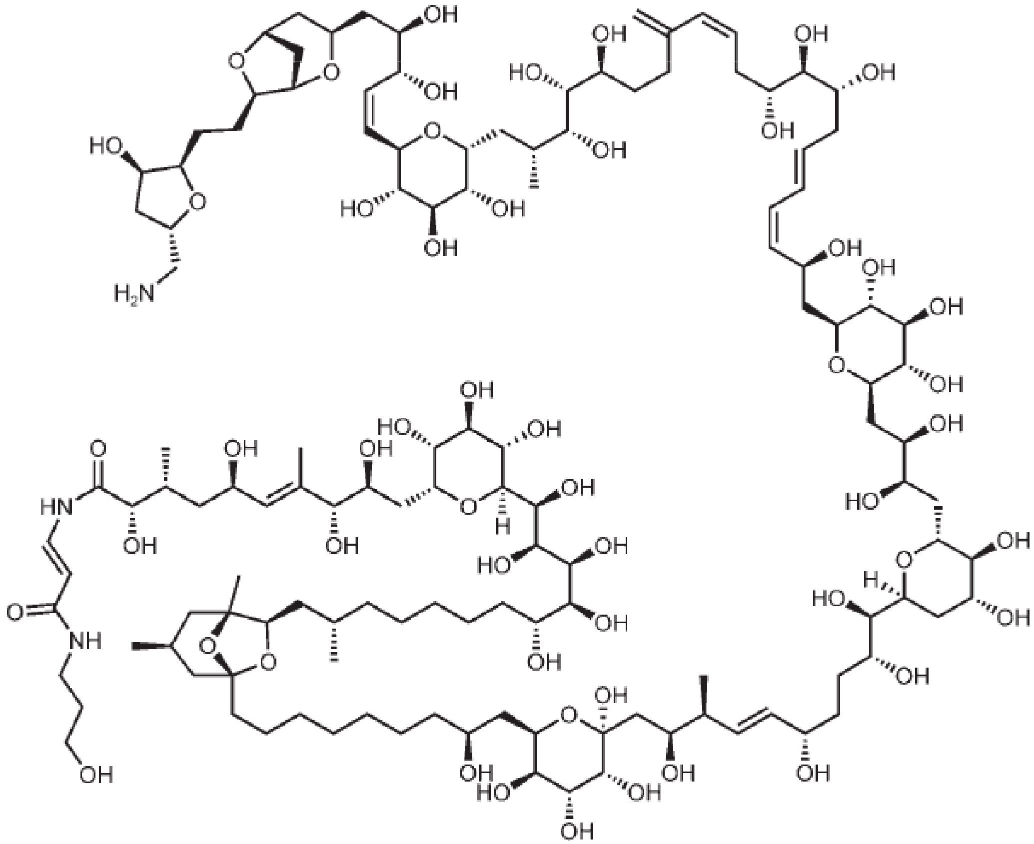
Zoanthoxanthin



Zoanthamine



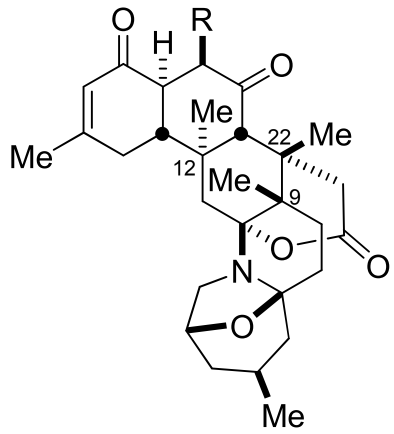
Zoanthusterone



Palytoxin

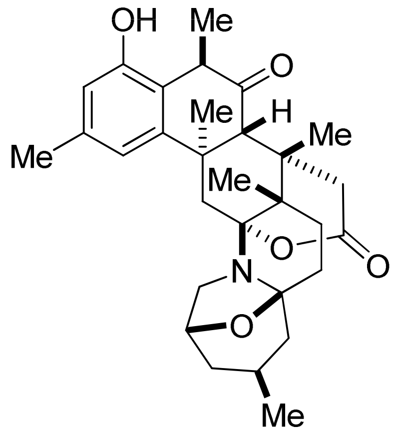
Zoanthamine Alkaloids: Isolation and Biological Activity

- Zoanthamine:
  - Isolation: Rao and Faulker, 1984 off the coast of India
  - Biological activity: Inhibits ear inflammation in mice



R = Me, Zoanthamine
R = H, Norzoanthamine

- Norzoanthamine:
  - Isolation: Uemura, 1995 from the coast of islands south of Japan
  - Biological activity:
    - Prevents osteoporosis in vivo in ovarieoctimized mice
    - Cytoxicity against P388 murine leucemia cells
    - Inhibits human platelet aggregation



Zoanthenol

- Zoanthenol:
  - Isolation: Norte, 1996 in the Canary Islands
  - Biological activity: Inhibits human platelet aggregation

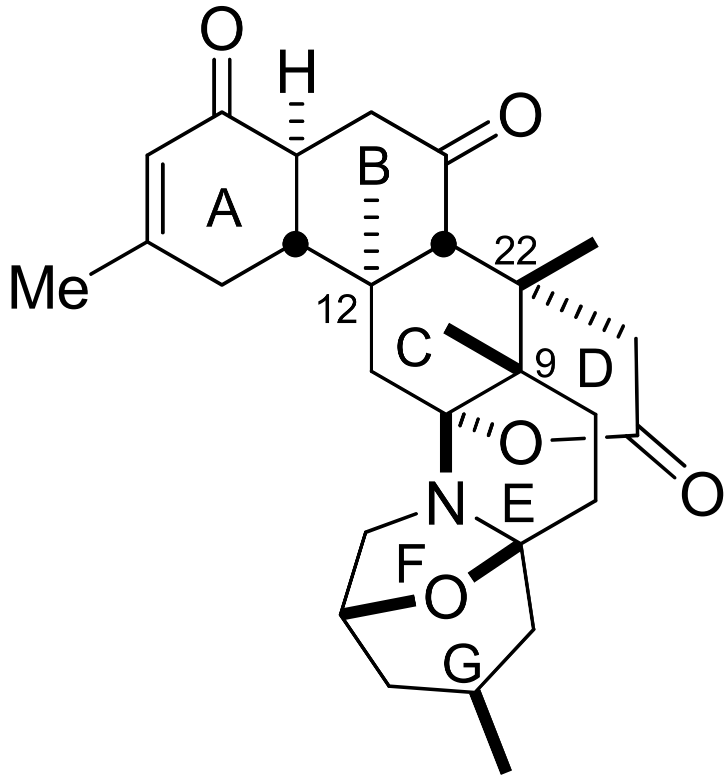
Synthetic Efforts Towards Norzoanthamine

Total synthesis:

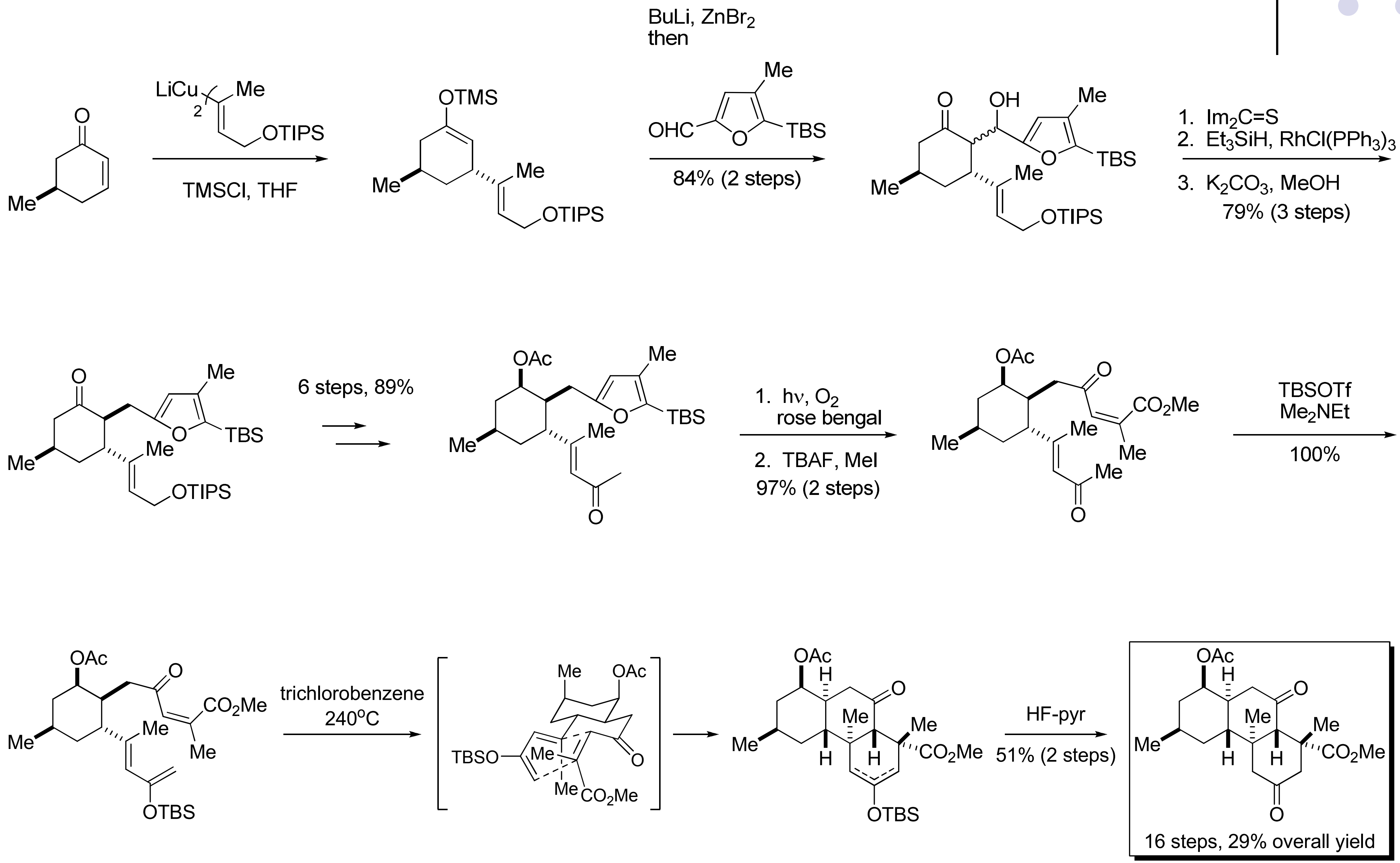
- Miyashita, Norzoanthamine-2004

Partial syntheses:

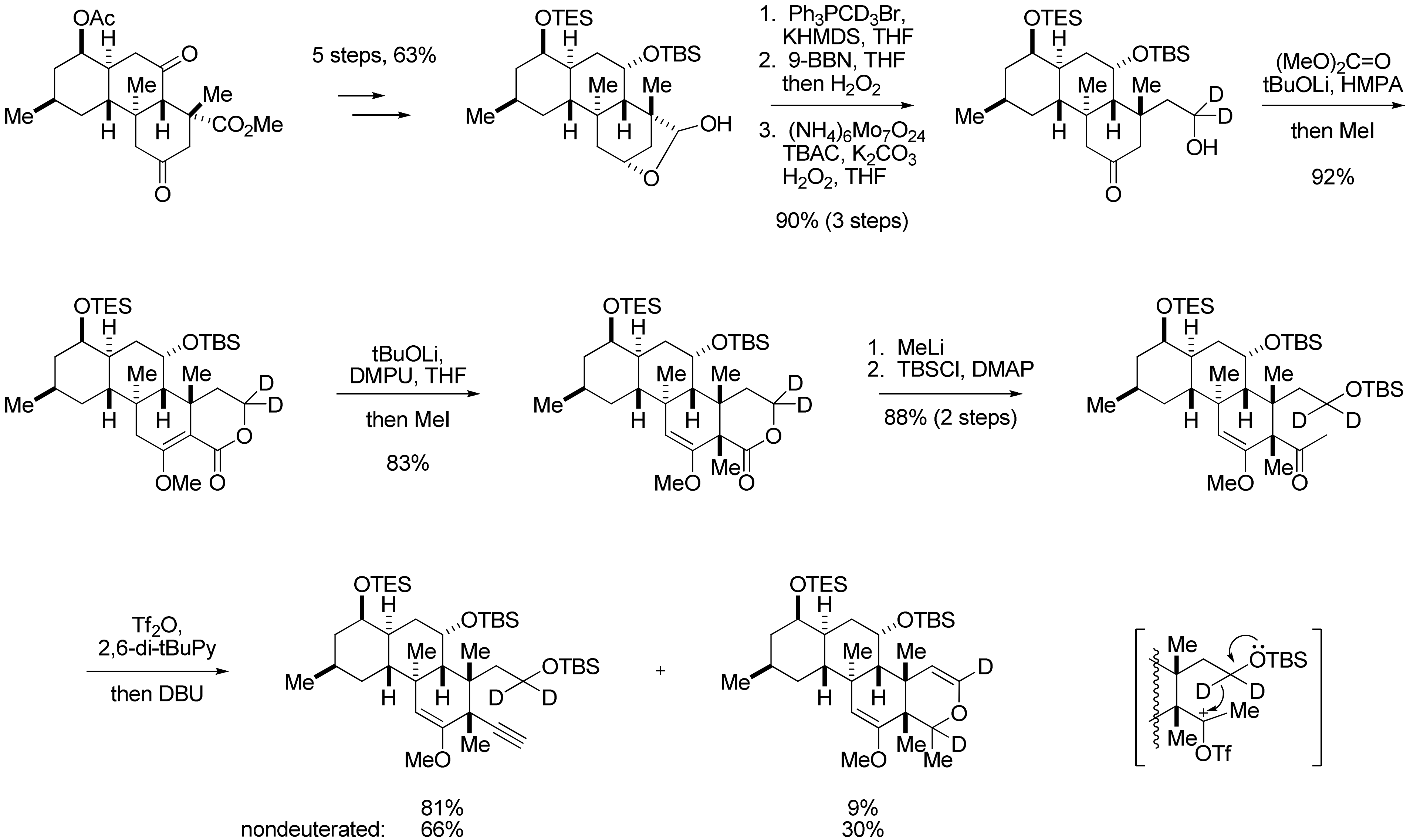
- Tanner
- Williams
- Uemura
- Stoltz
- Theodorakis
- Kobayashi



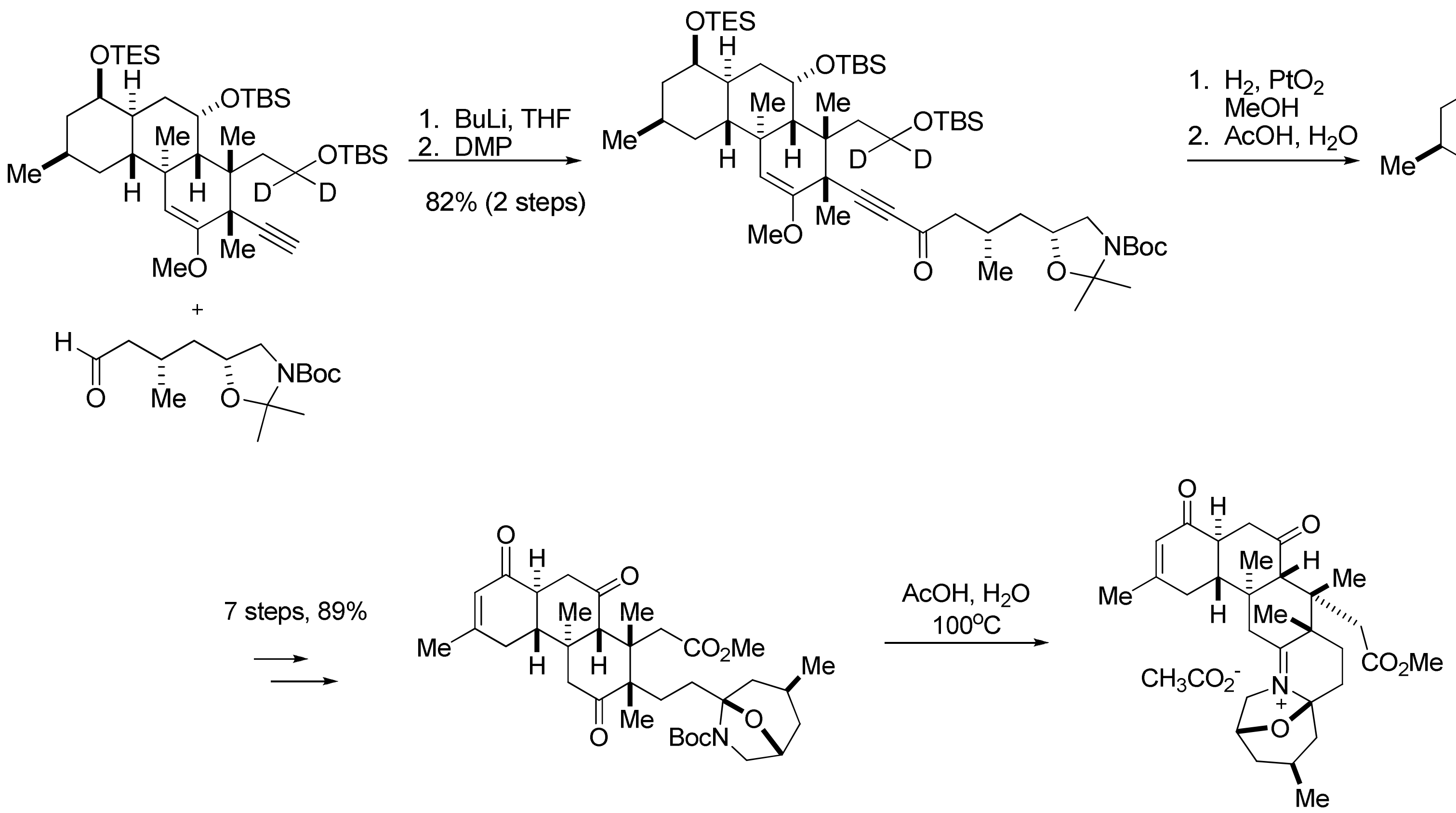
Miyashita's Synthesis of Norzoanthamine: Synthesis of the ABC Ring System



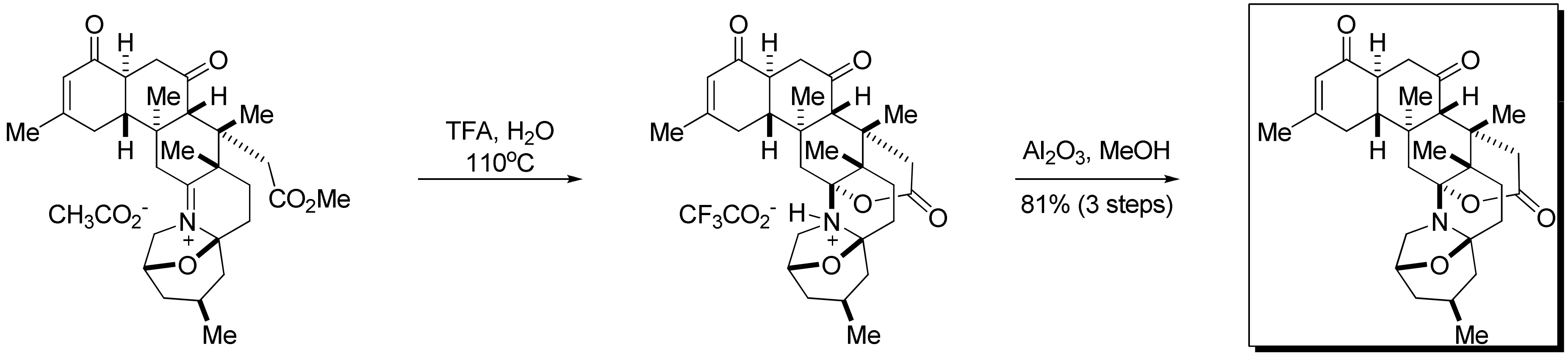
The Kinetic Isotope Effect…Not Just for Inorganic Chemists



Construction of the DEFG Rings



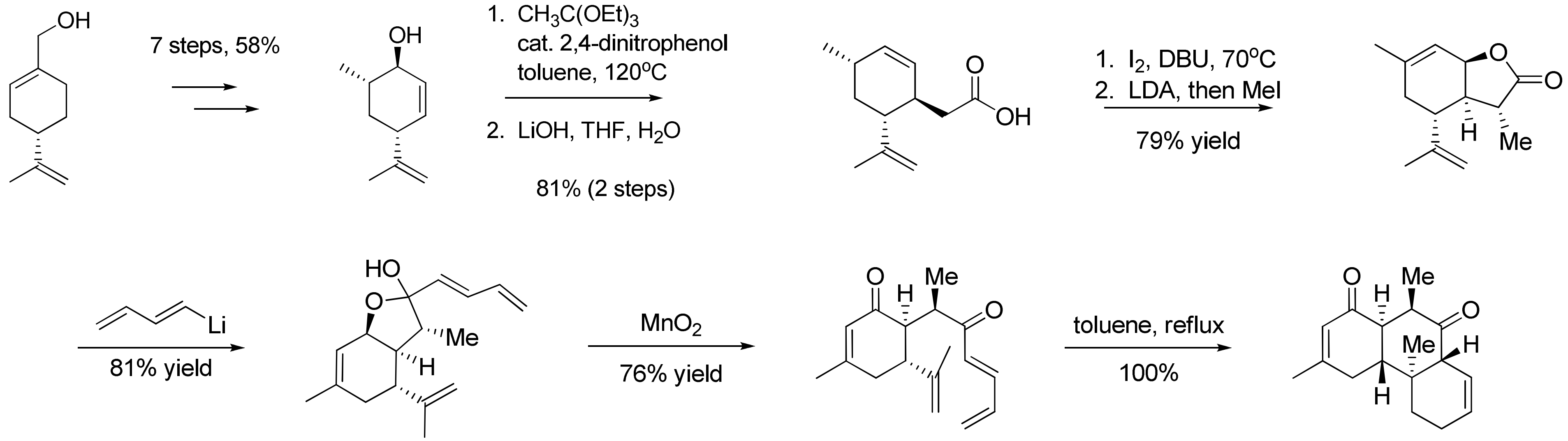
Completion of Norzoanthamine

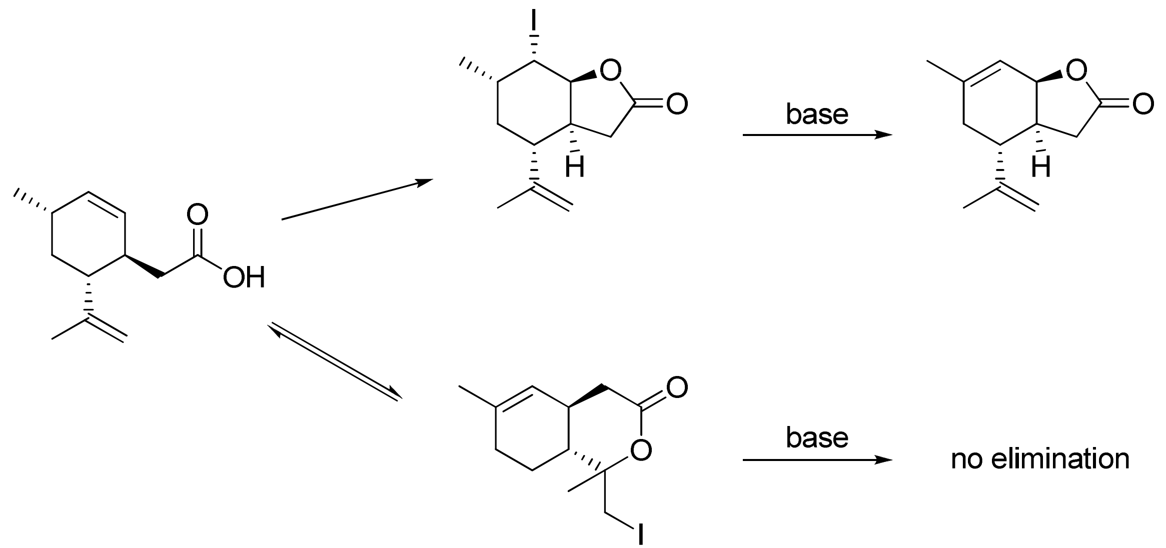


Norzoanthamine,

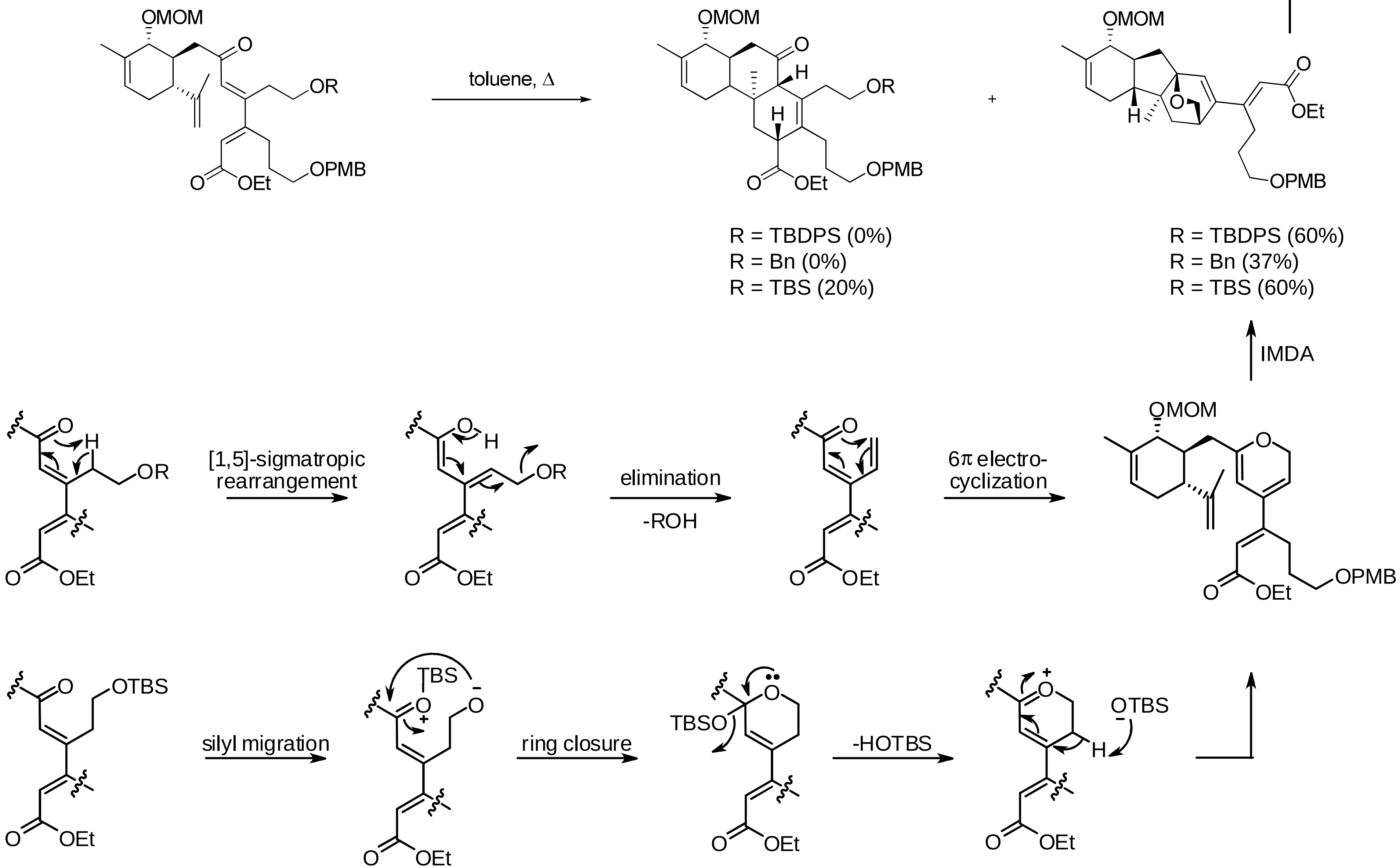
- 41 steps, 3.5% overall yield (average of 92% yield per step)
- Key steps:
  - IMDA to set stereochemistry at C-12 and C-22
  - Use of kinetic isotope effect for installation of alkyne
  - Bis-aminoacetalization for the construction of the DEFG rings

Tanner's Approach to the ABC Ring System: Model Studies on the IMDA Reaction

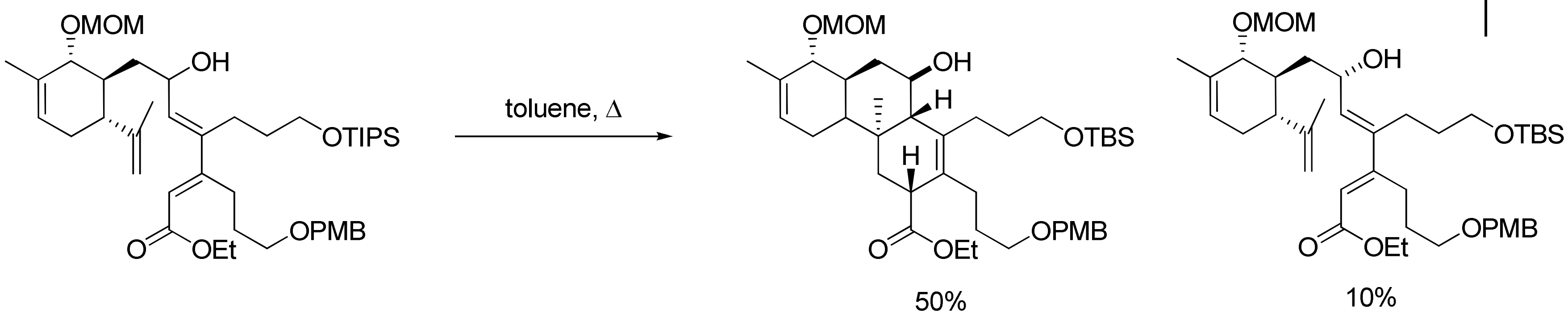


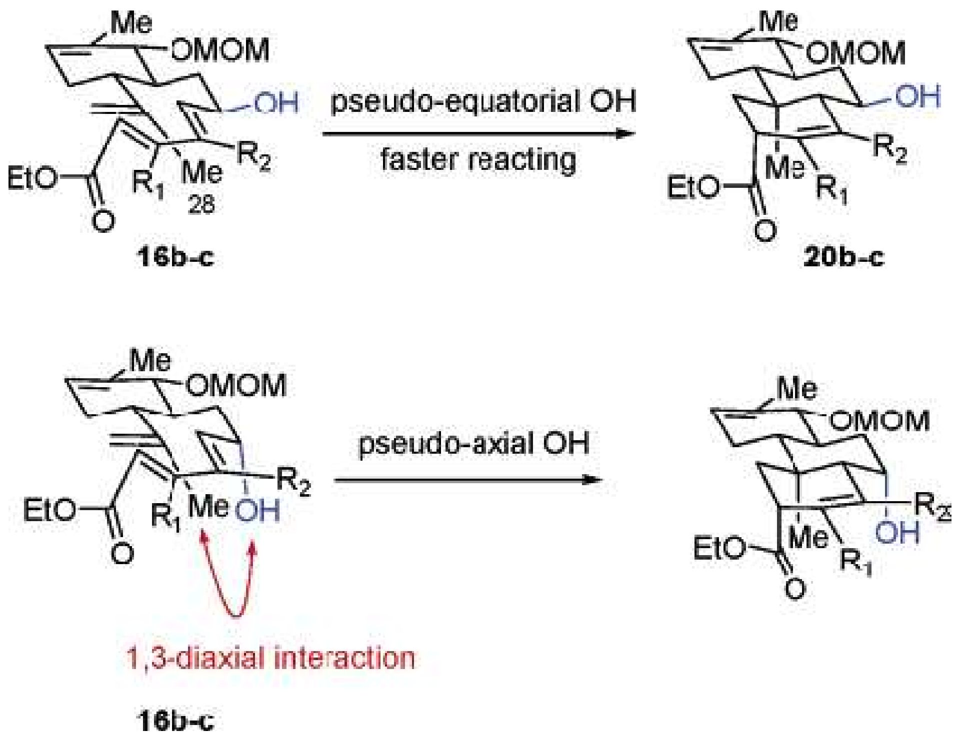


An Unexpected Product from the IMDA Reaction

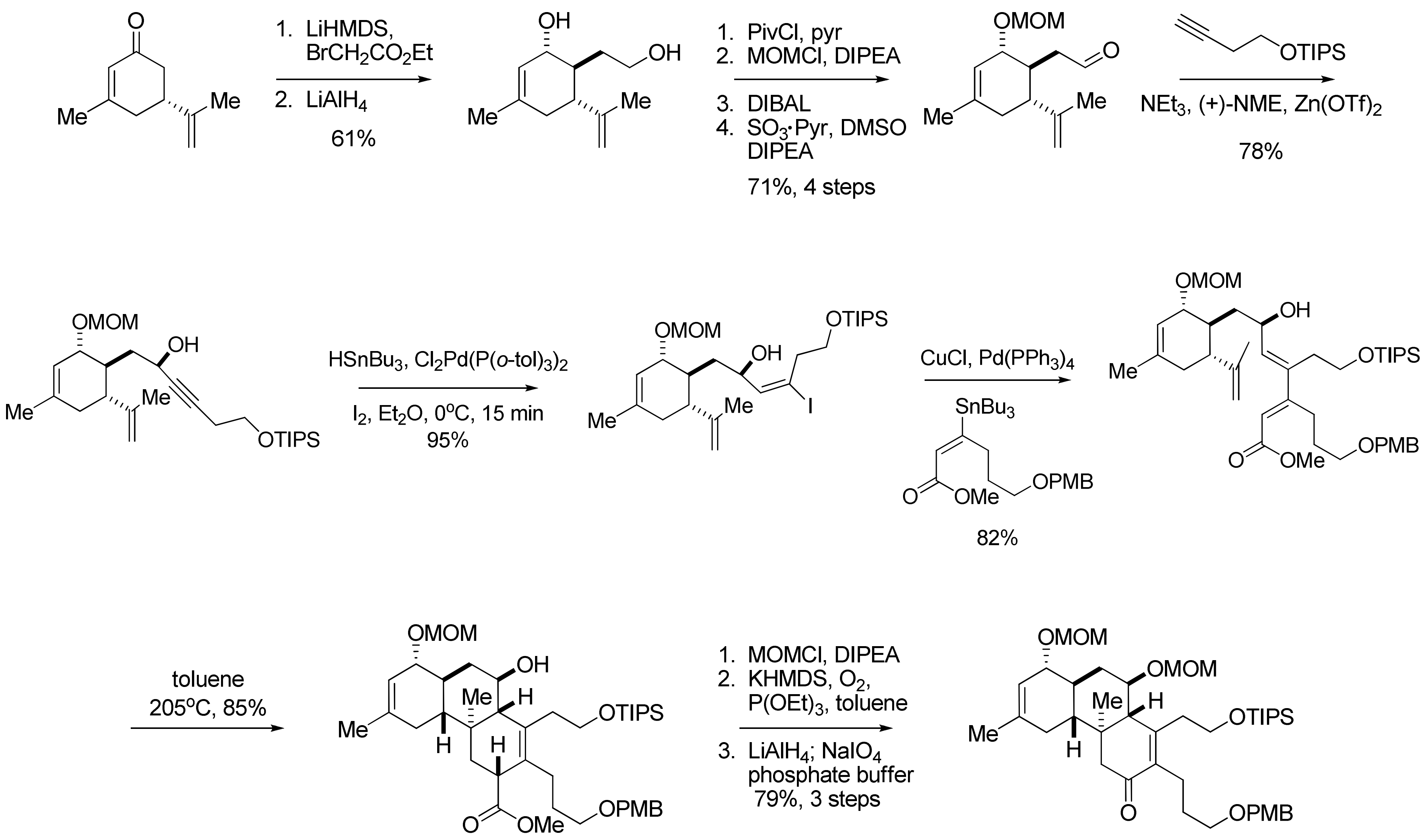


Getting the IMDA Reaction to work

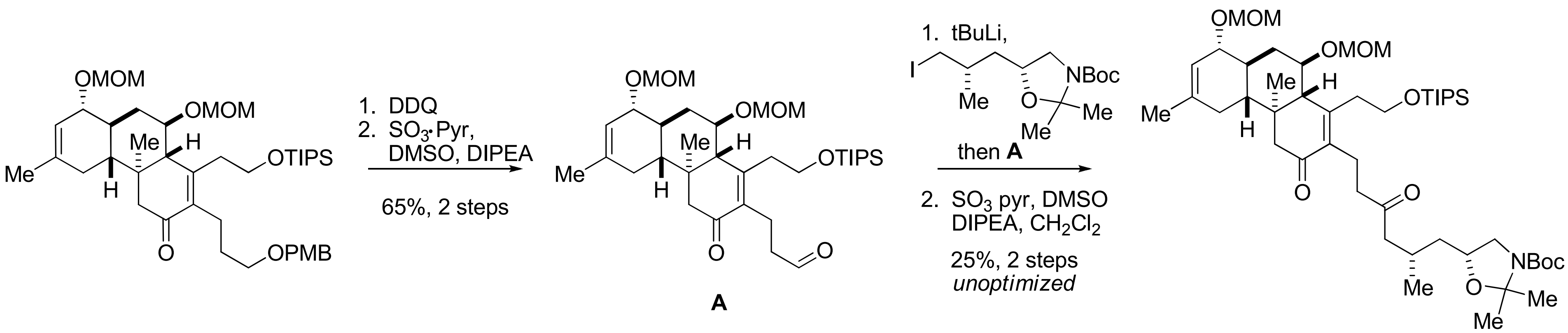




Revised Synthesis of the ABC Ring Fragment

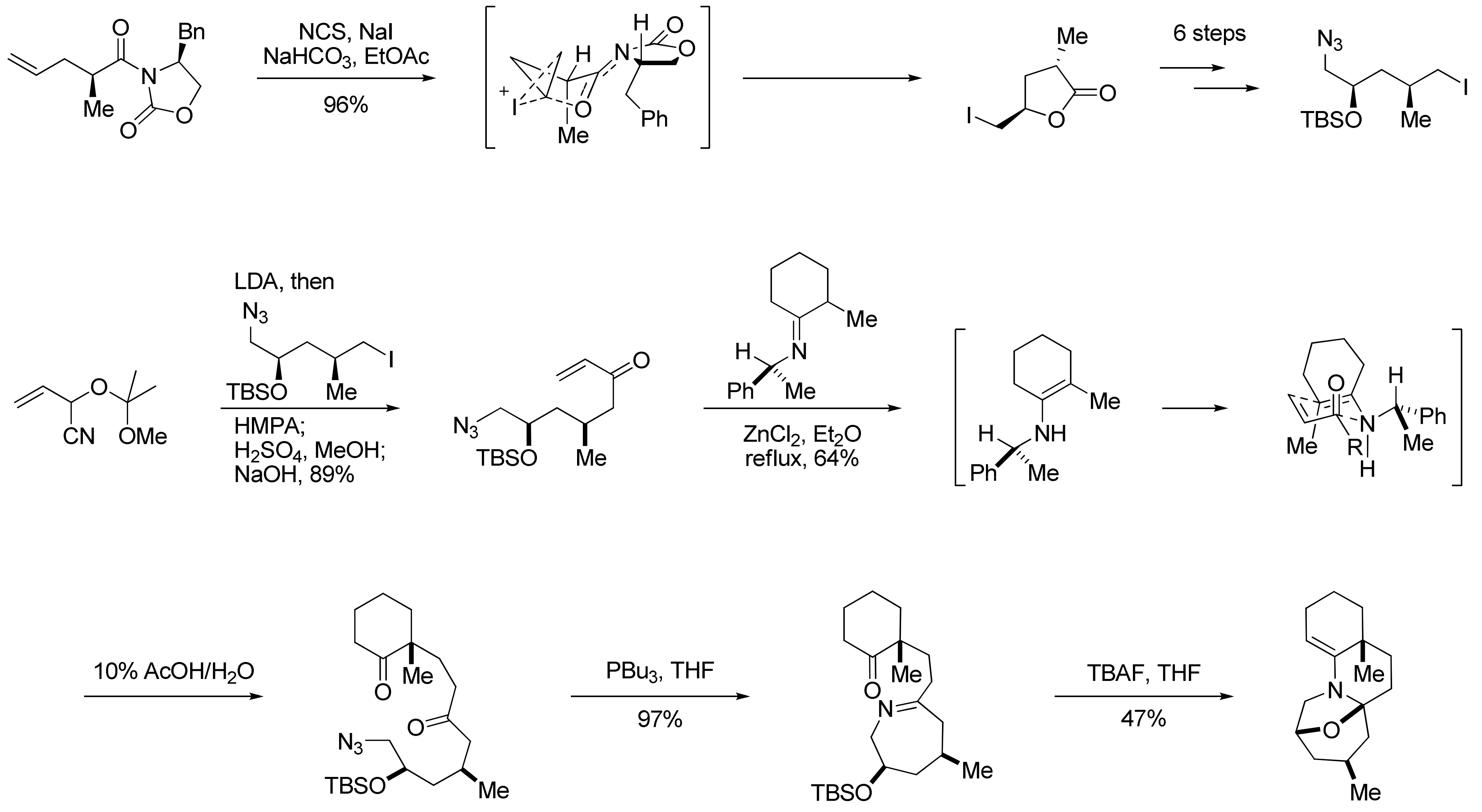


Coupling of the Fragments



- Key vinyl stannane prepared in 18 steps from (*S*)-carvone in 6%overall yield.
- Key steps: sterically demanding Stille coupling, IMDA reaction to form tricycle
- Coupling of tricyle and fragment A affords the entire carbon frame work

Williams' Approach to the DEFG Ring System



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