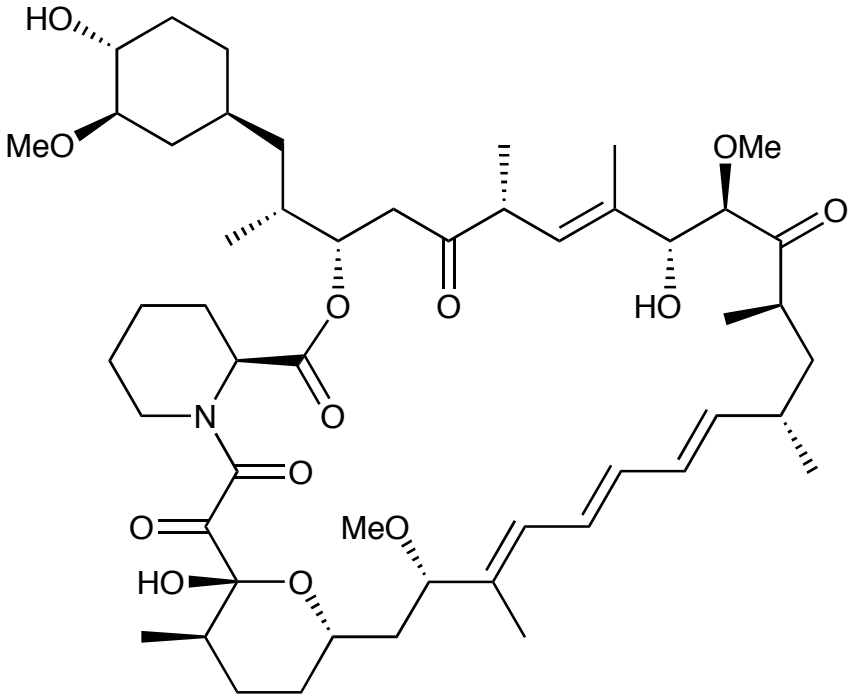
Total Synthesis of Rapamycin



Isolation and Structure Determination:

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Total Syntheses:

Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419.

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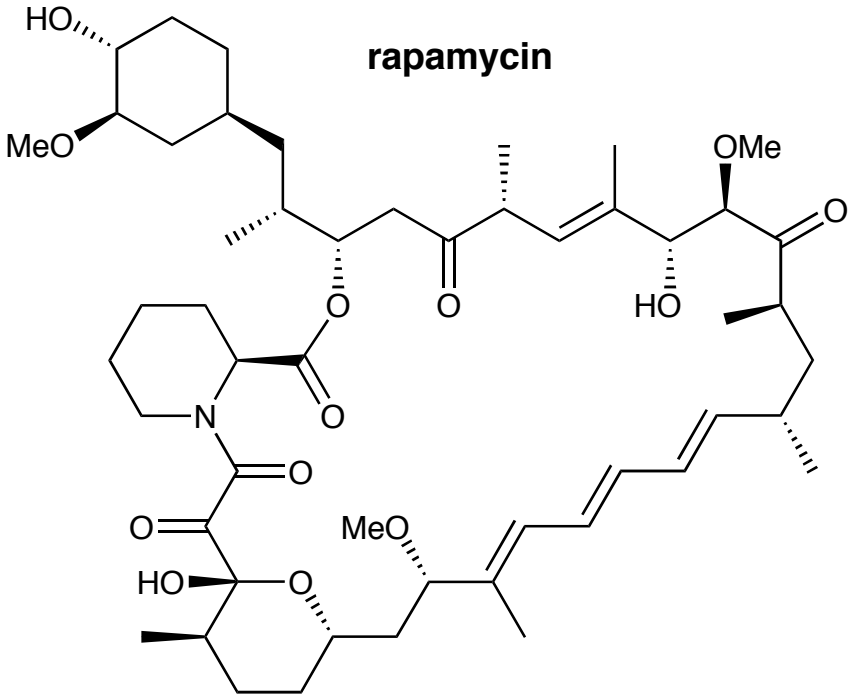
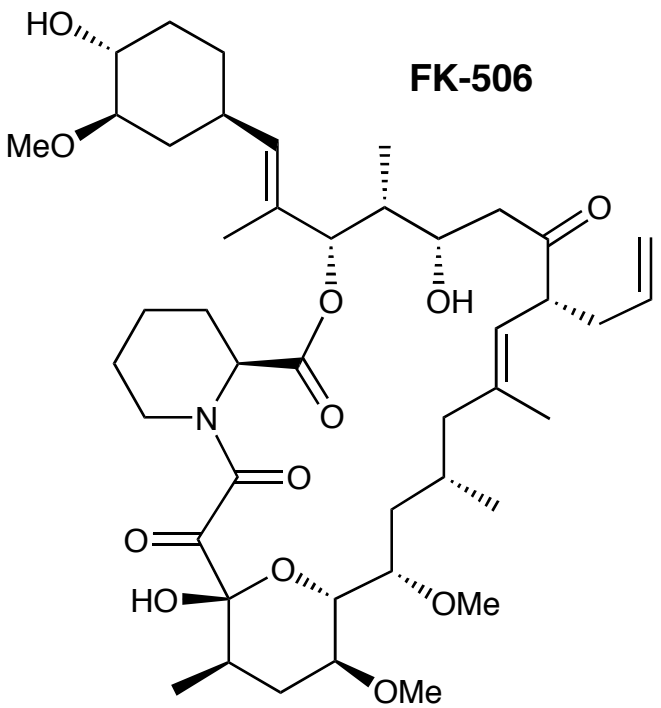
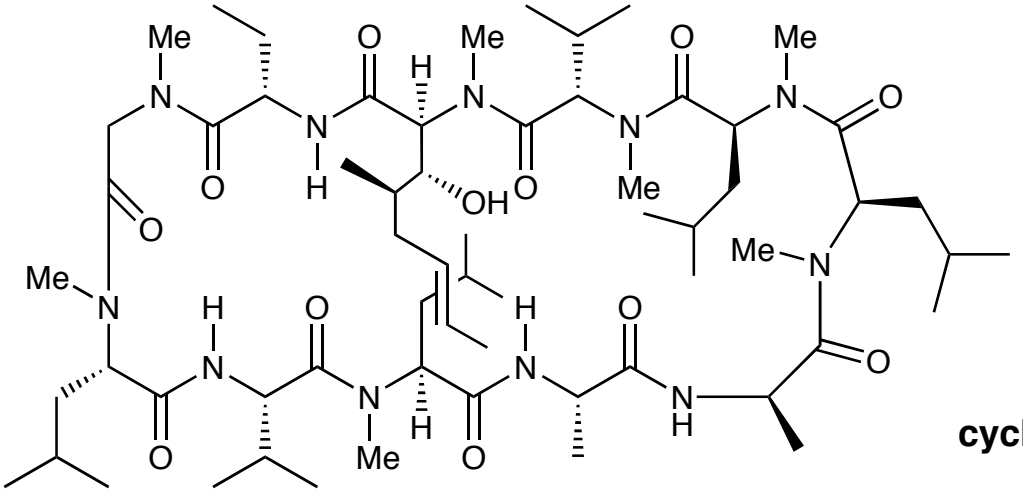
Immunomodulators



rapamycin

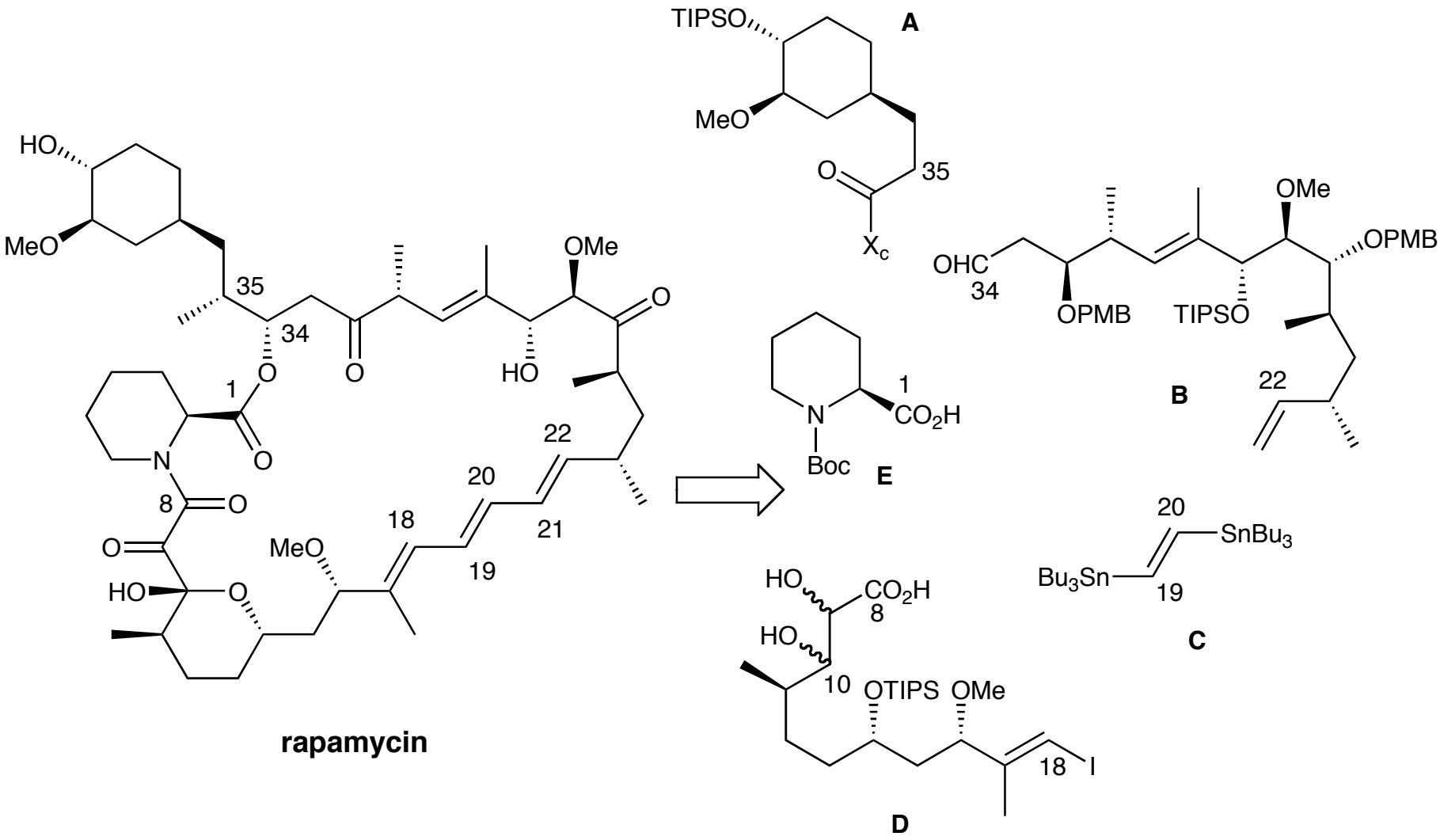


FK-506

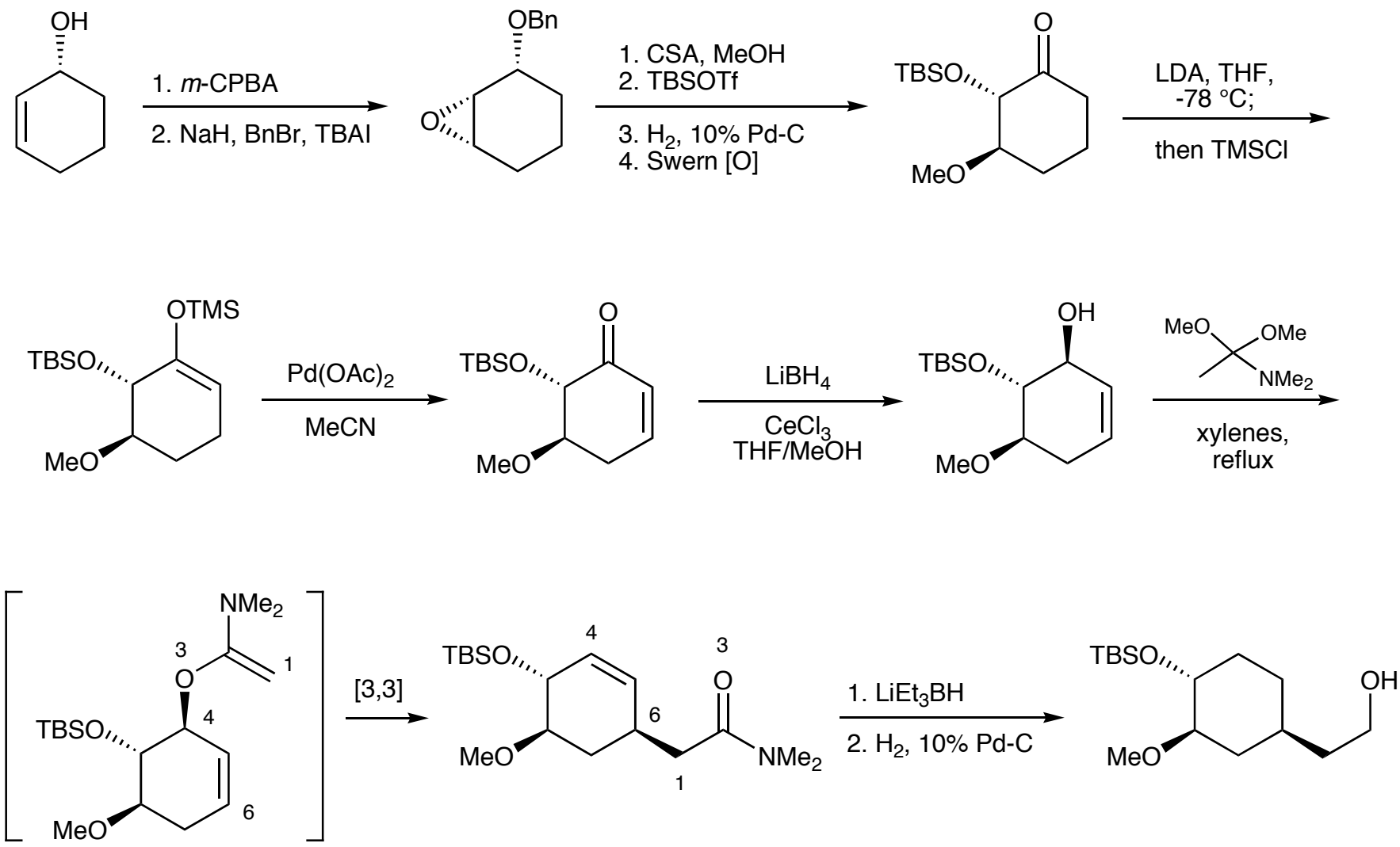


cyclosporin A

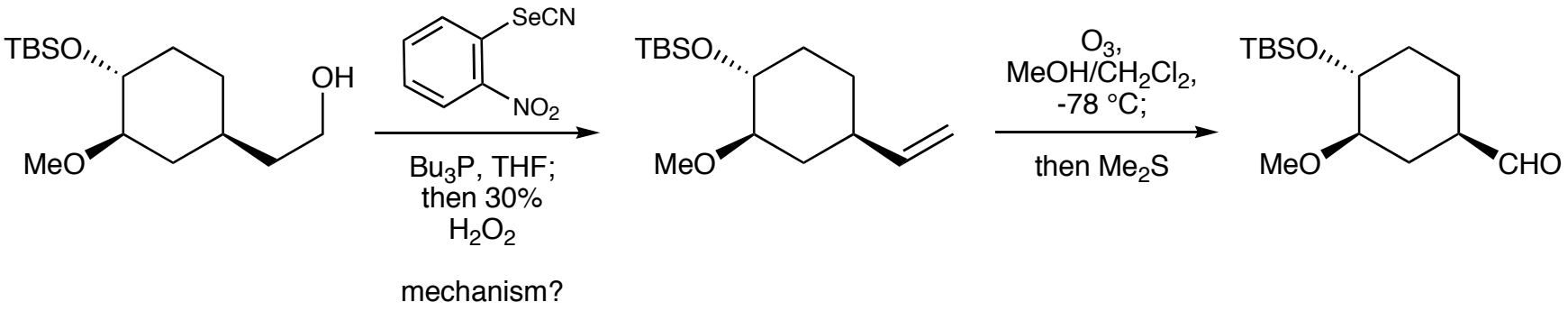
KCN's Retrosynthetic Analysis of Rapamycin

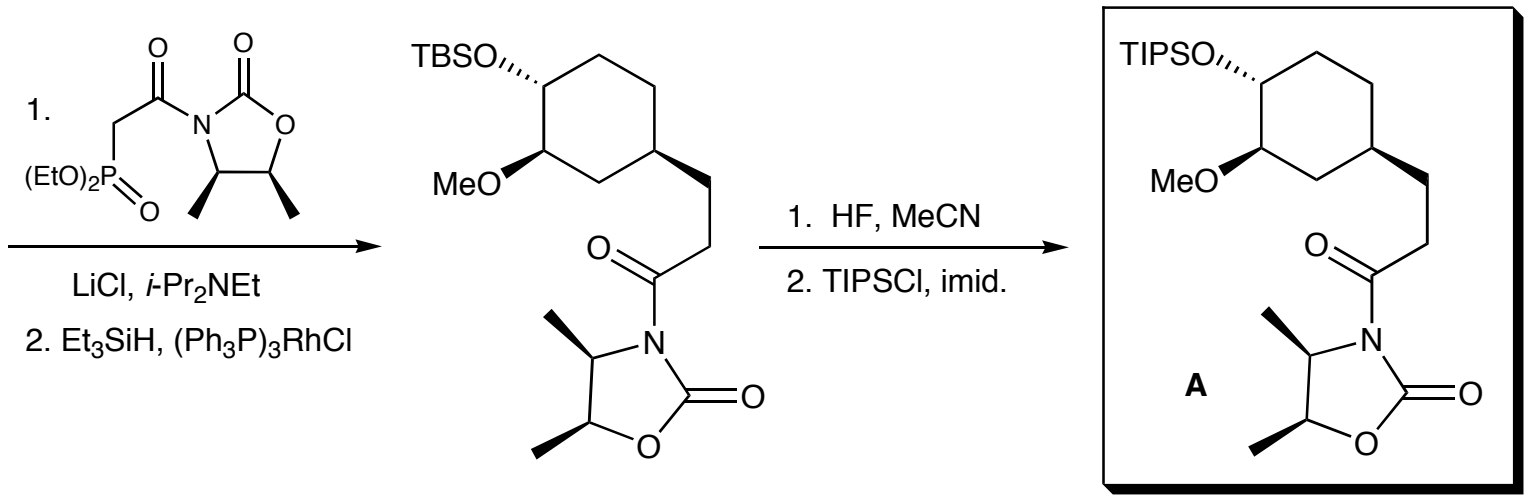


Synthesis of Oxazolidone A

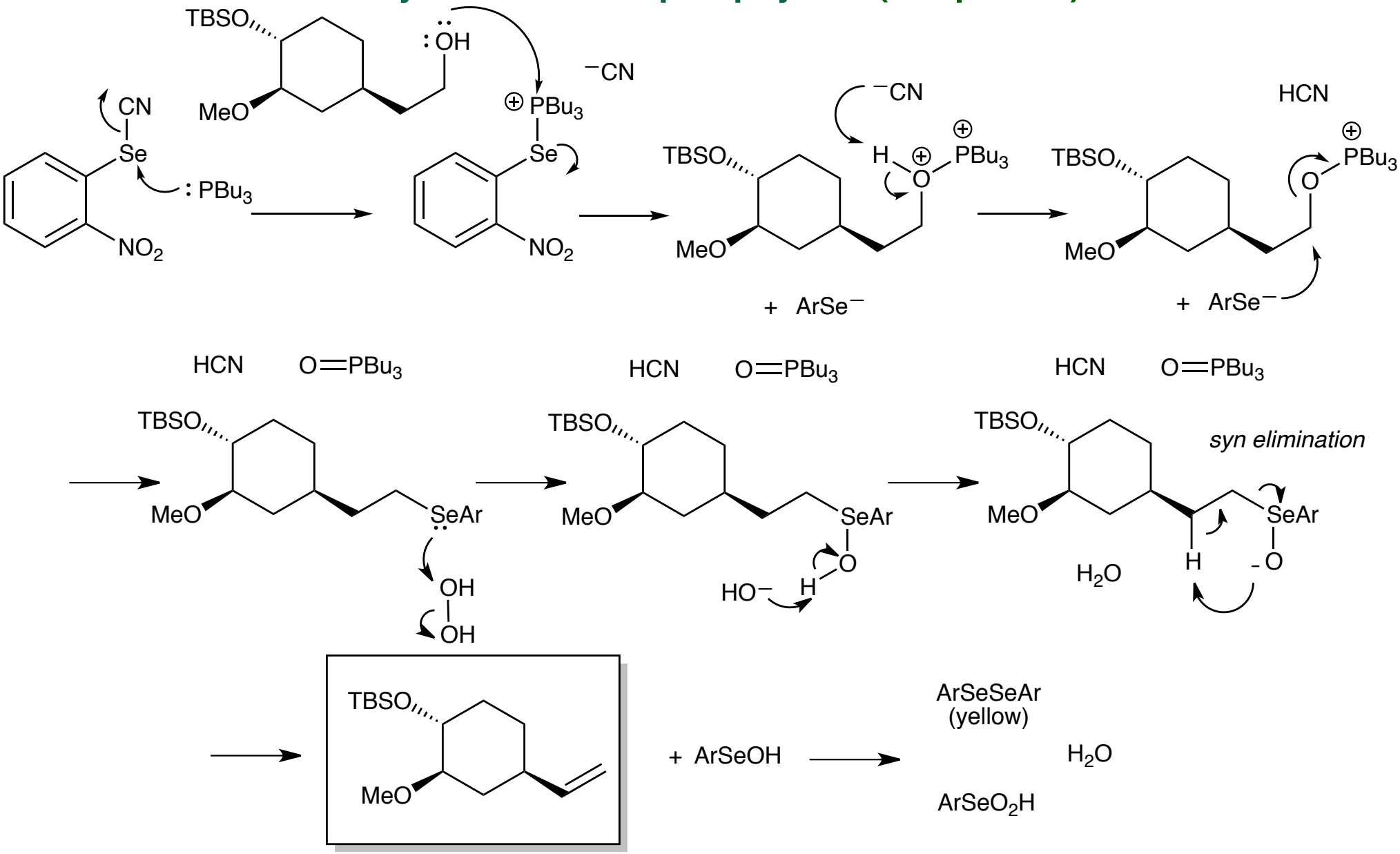


Synthesis of Oxazolidone A (continued)



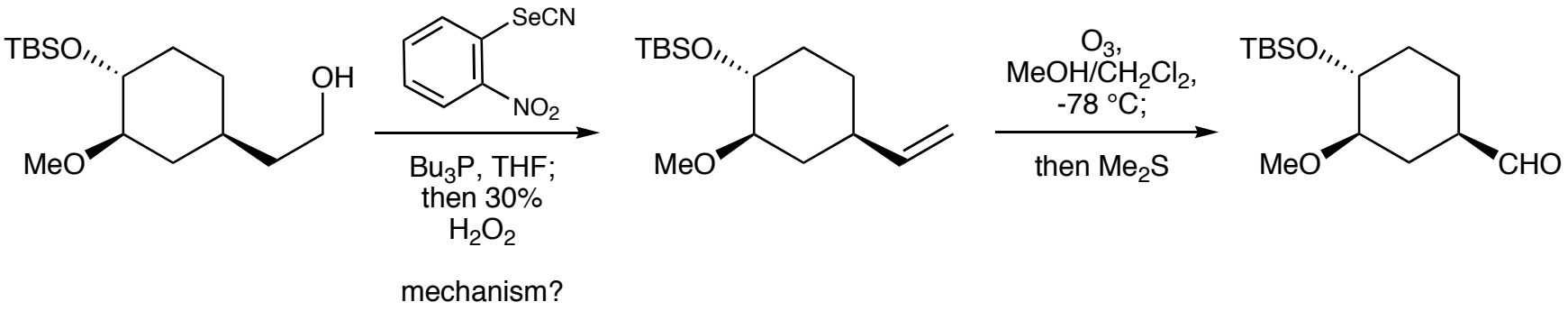


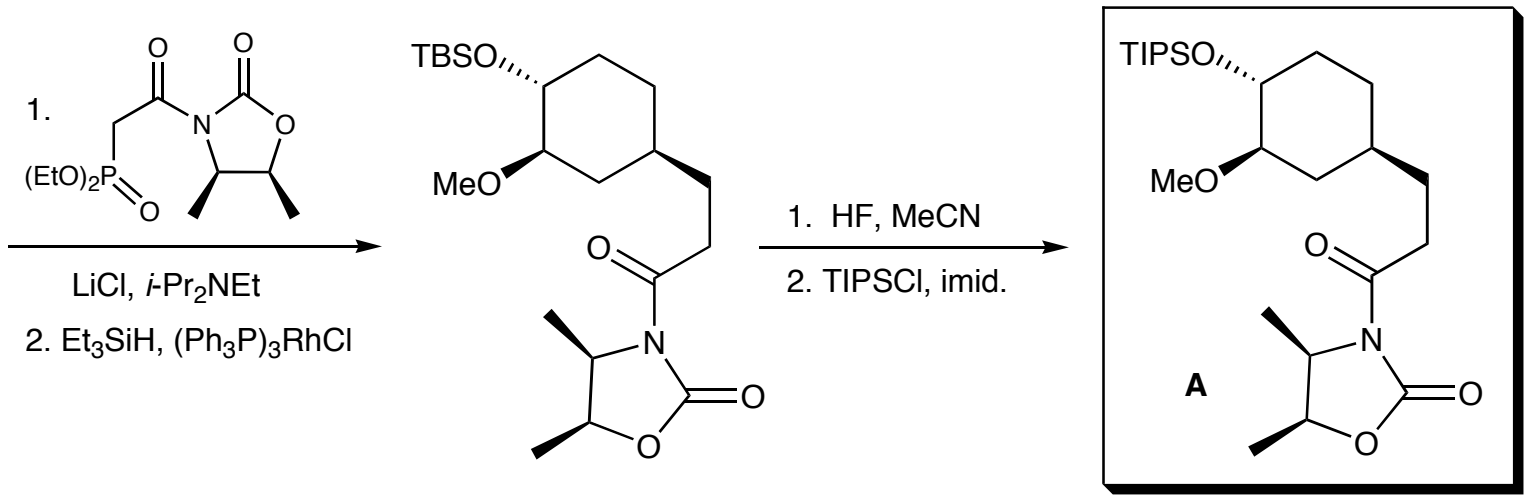
Methyl Homosecodaphniphyllate (Chapter 26)



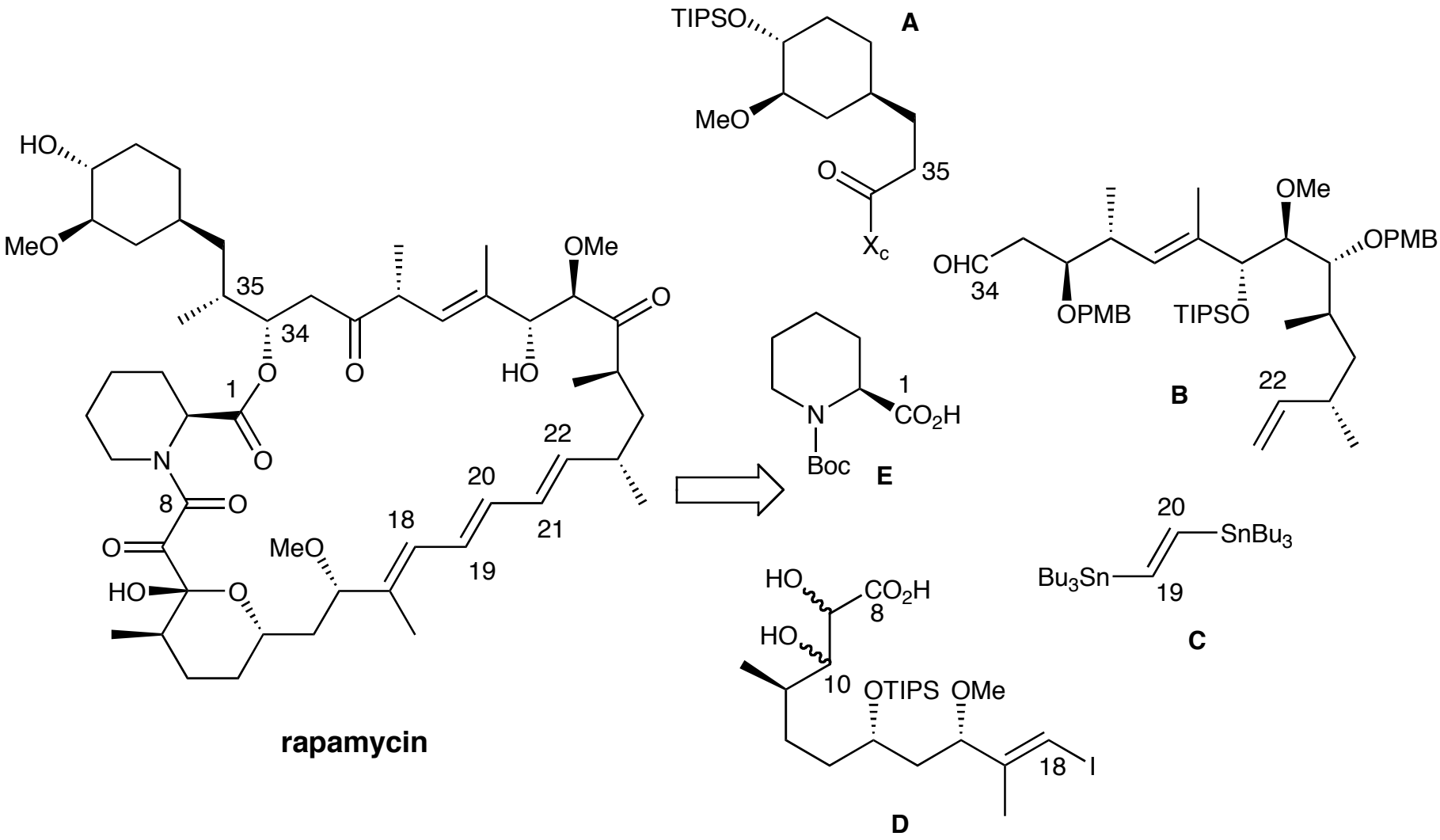
Ruggeri, R. B.; Hansen. M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734–8736.
Also see: Heathcock, C. H. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 665–804.

Synthesis of Oxazolidone A (continued)

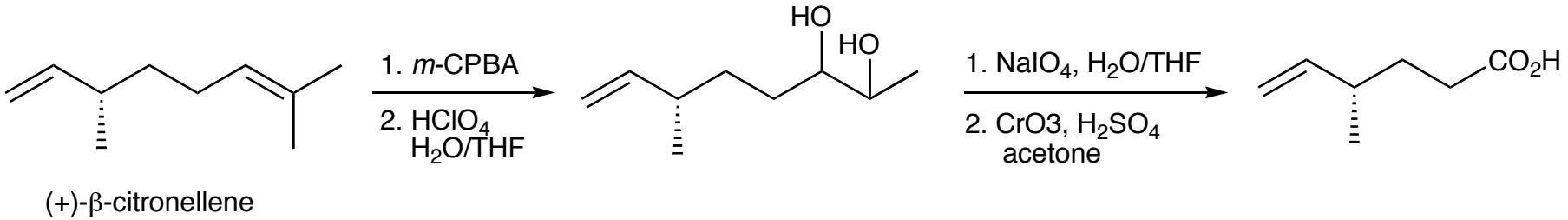




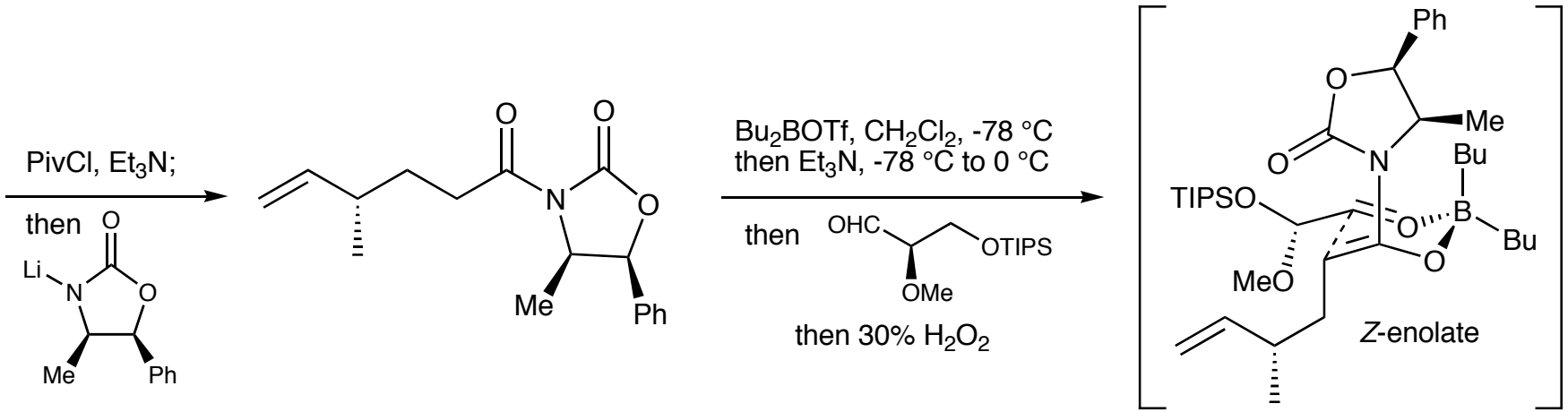
KCN's Retrosynthetic Analysis of Rapamycin

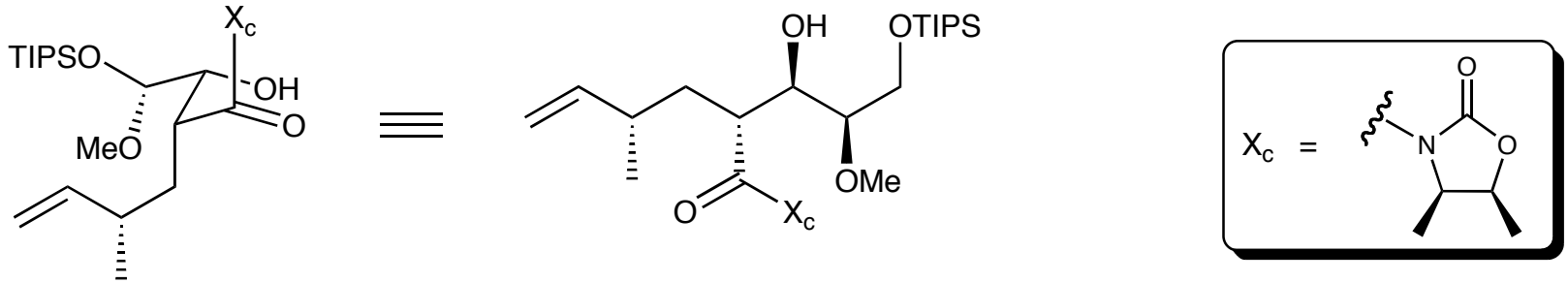


Synthesis of Subunit B

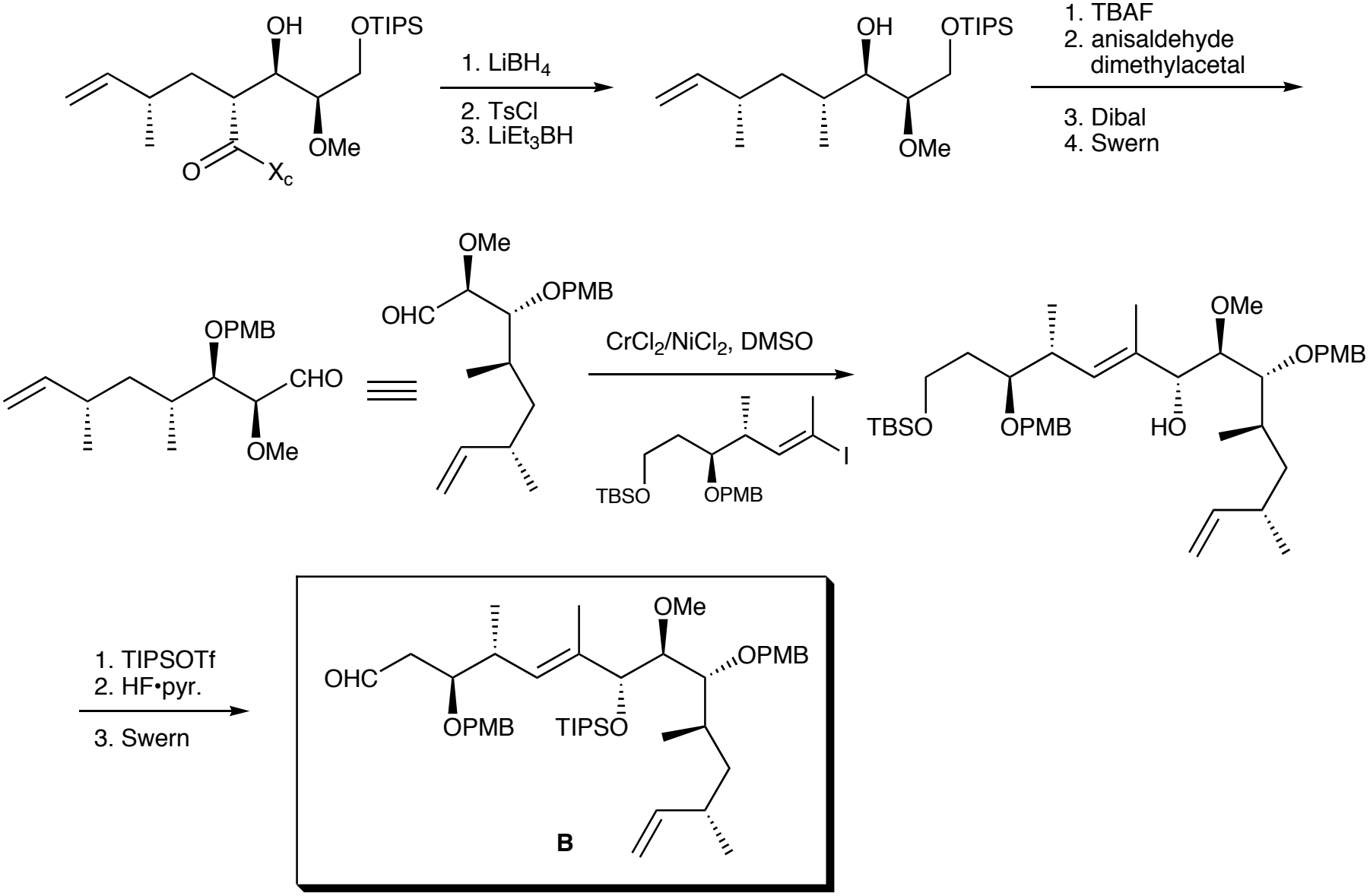


(+)-β-citronellene

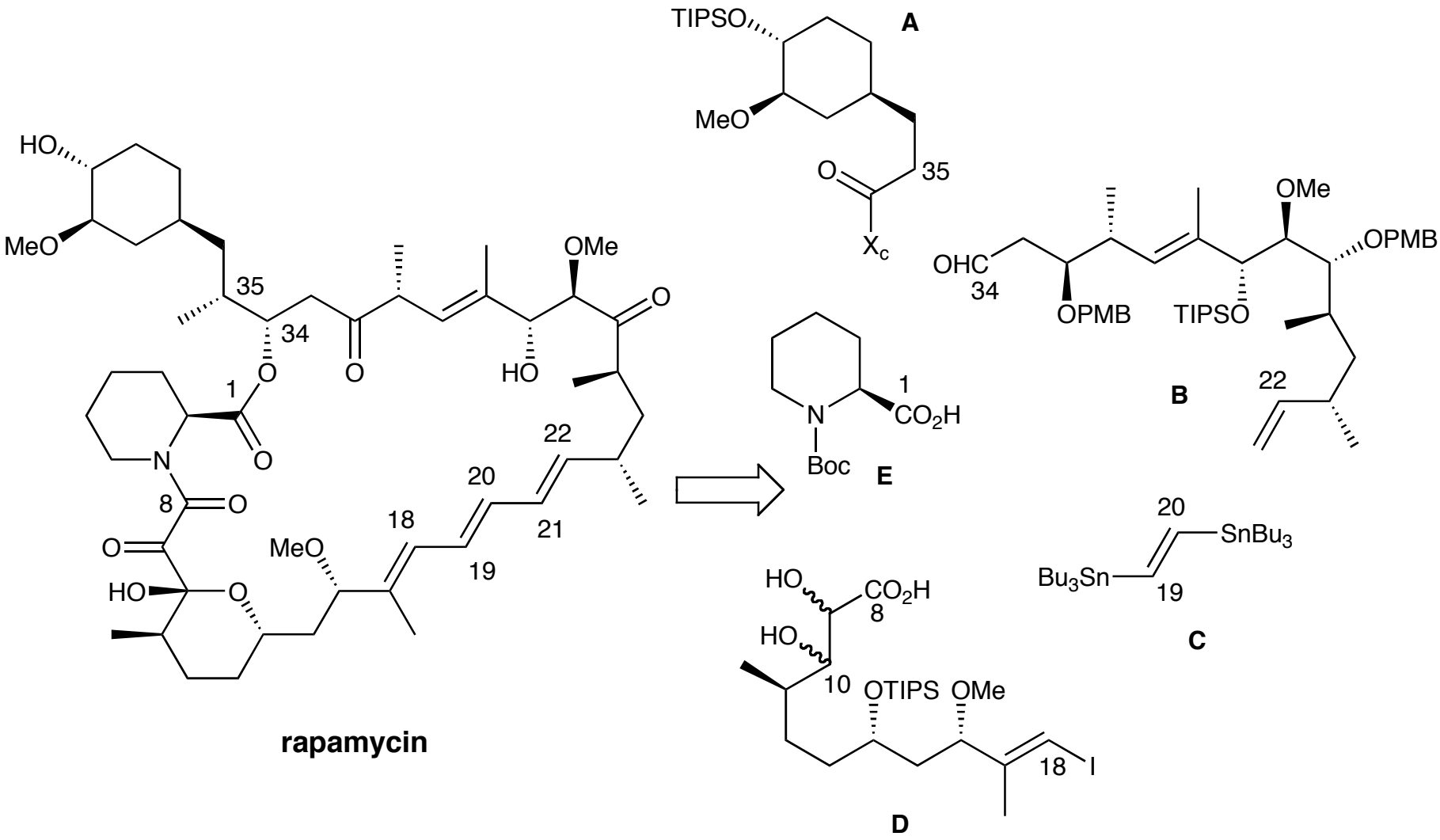




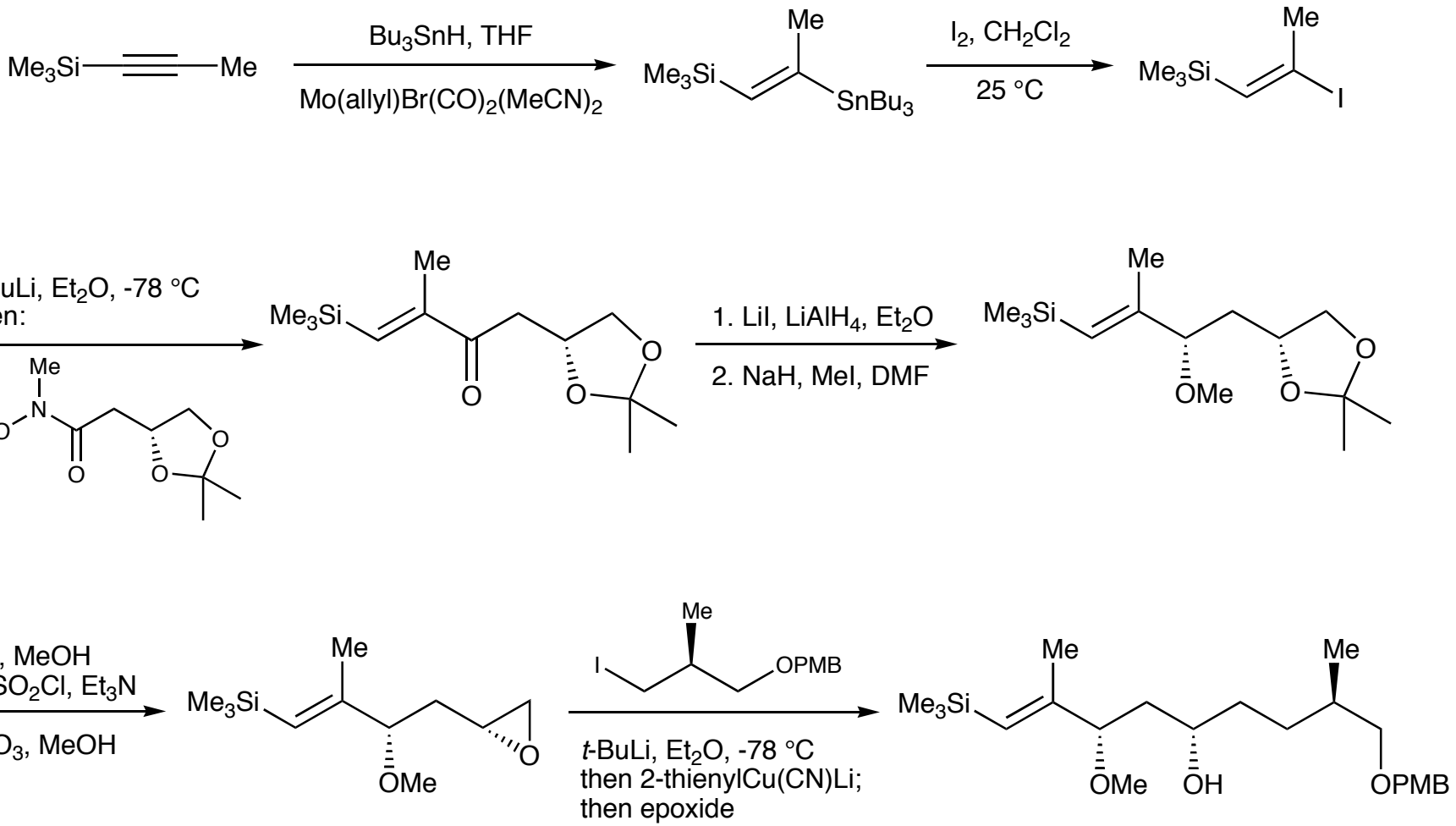
Synthesis of Subunit B (continued)



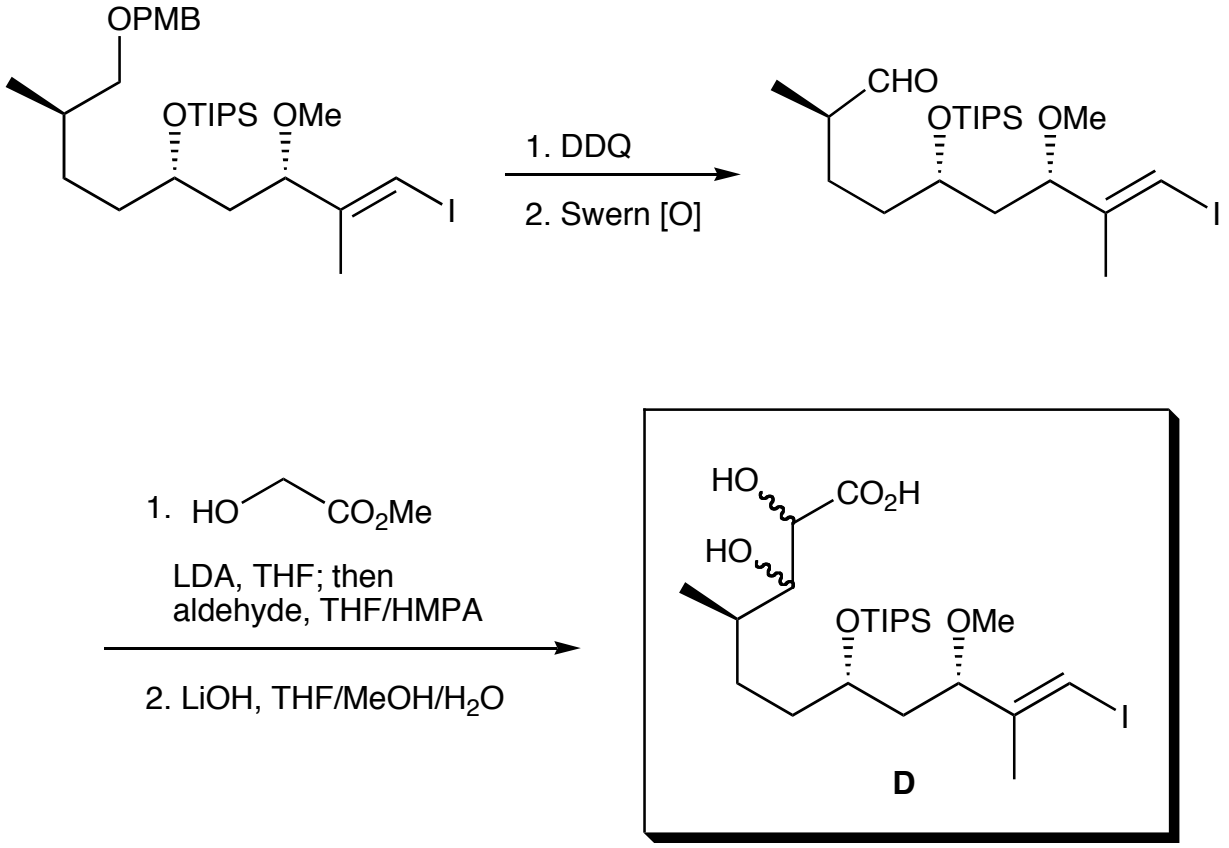
KCN's Retrosynthetic Analysis of Rapamycin



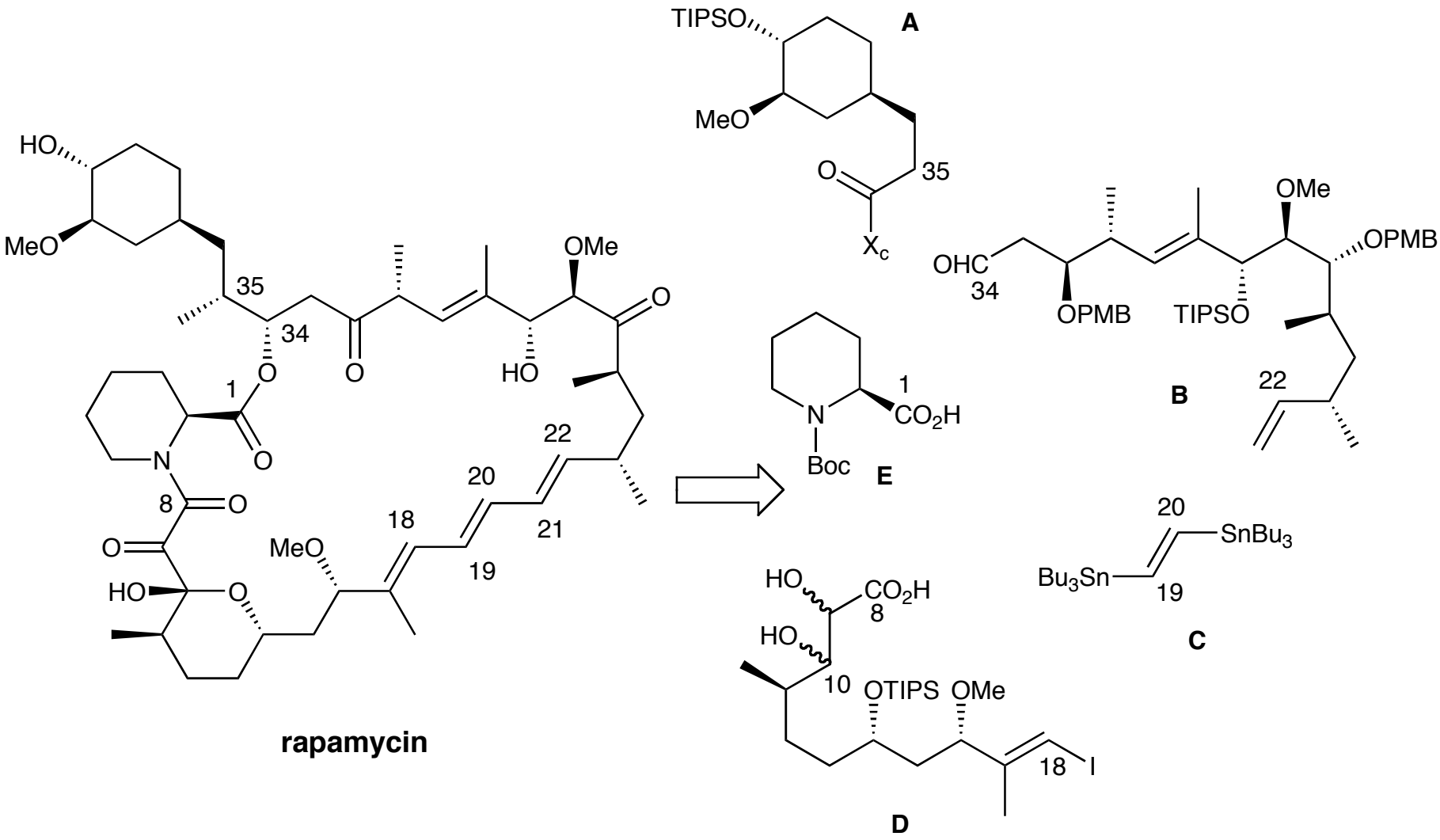
Synthesis of Vinyliodide D



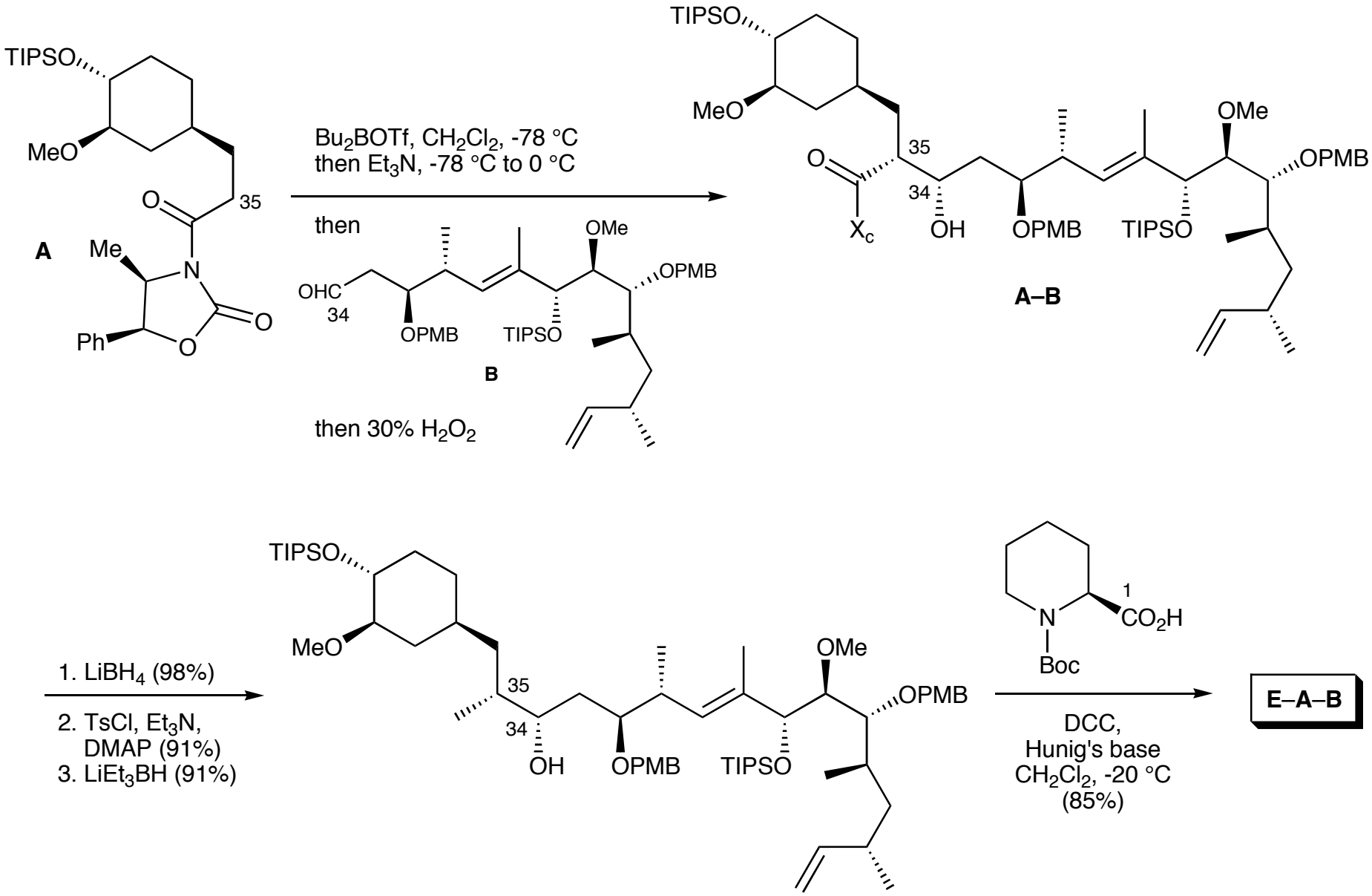
Synthesis of Vinyliodide D (continued)



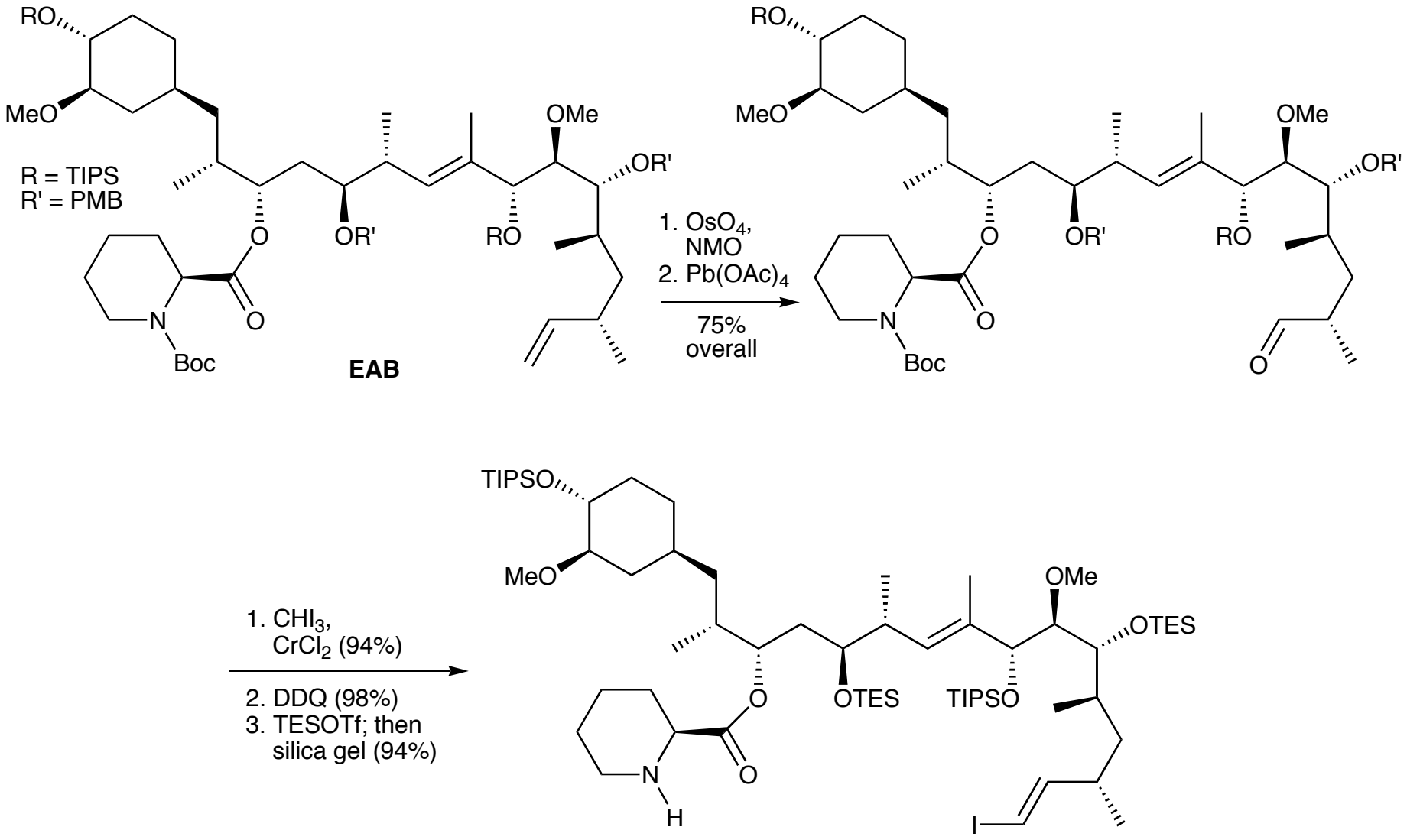
KCN's Retrosynthetic Analysis of Rapamycin



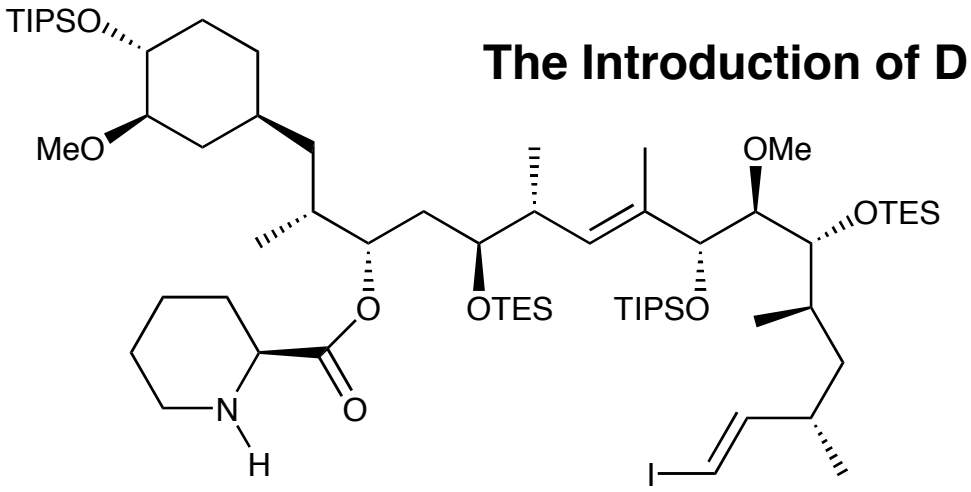
The Union of A + B + E



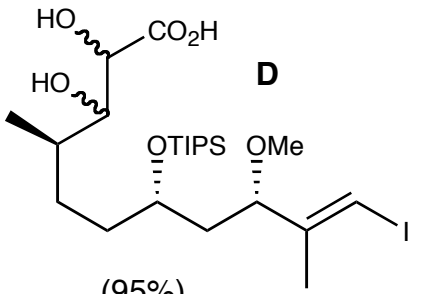
Elaboration of EAB



The Introduction of D

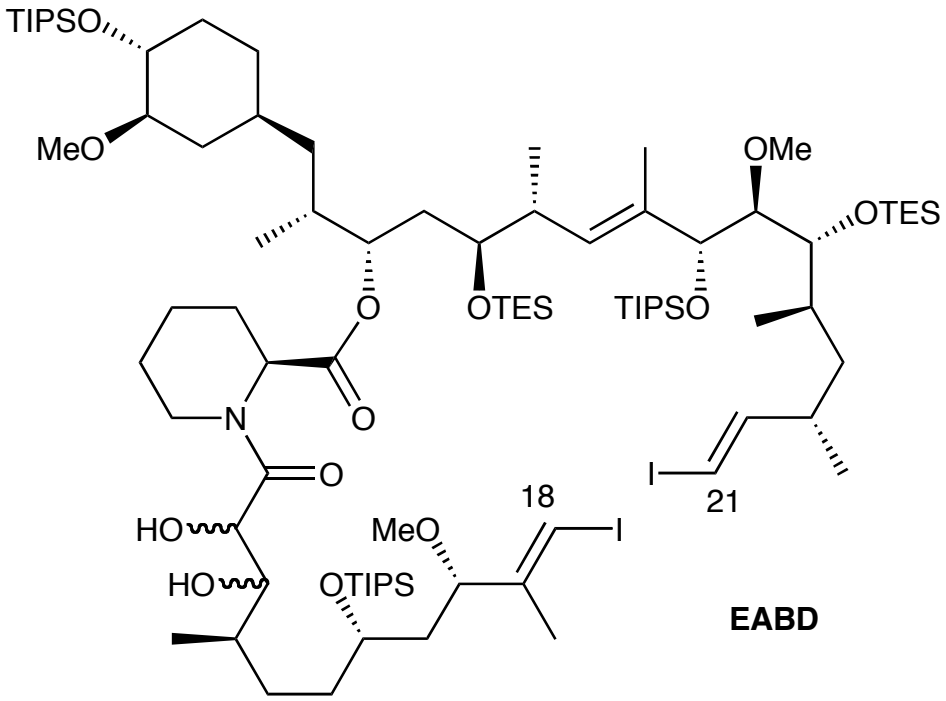


DIC, HOBT



D

(95%)

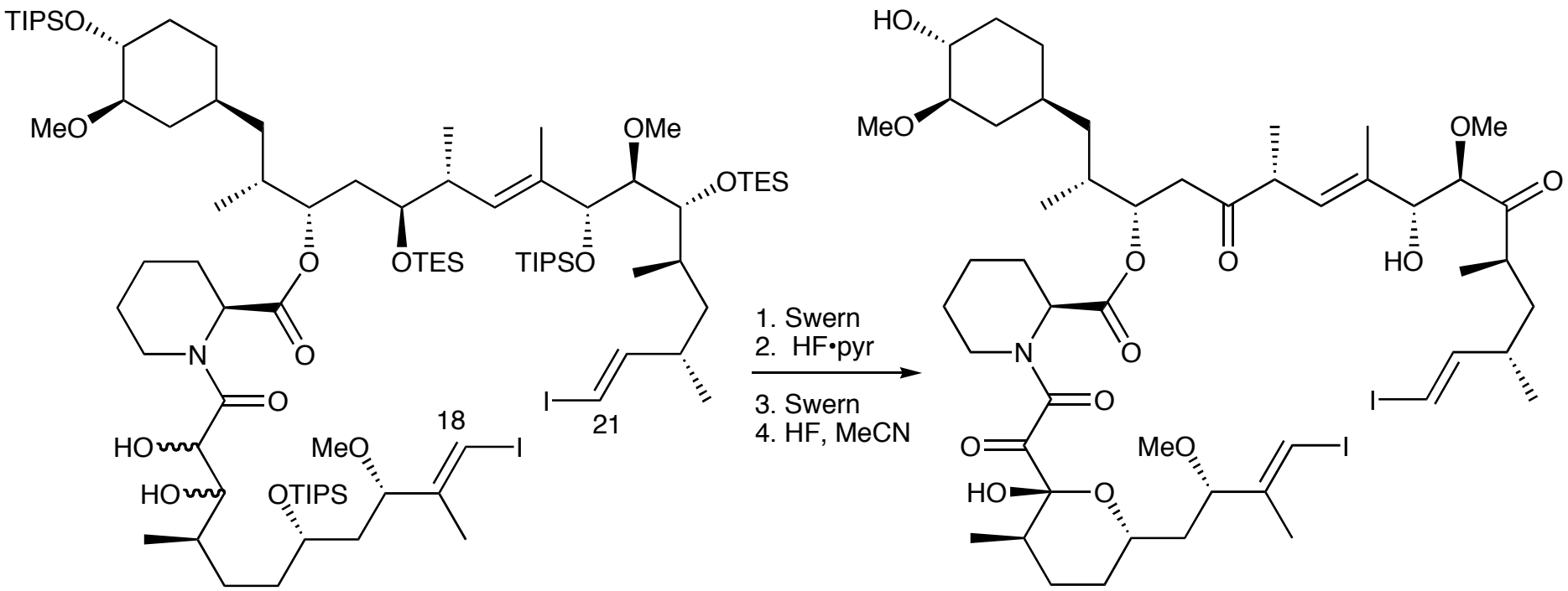


EABD

introduce C-19—C-20, adjust the oxidation state of the "D" fragment, and remove the protective groups

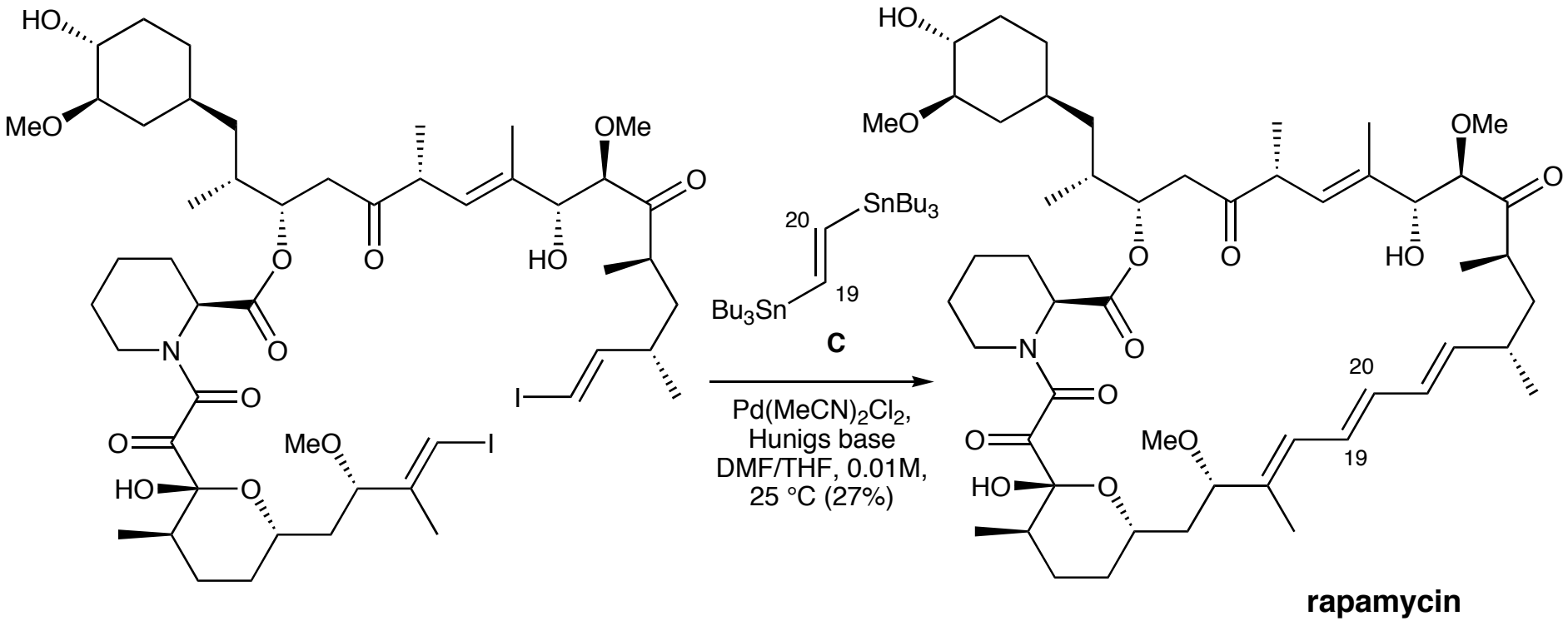
rapamycin

The End Game – Tricarbonyl Formation



Note: the first HF step removes the TES groups and the second HF step removes the TIPS groups

The End Game – The "Stitching" Stille Reaction



Summary

- Completed the first total synthesis of (-)-rapamycin.
  - The longest linear sequence from an article of commerce consists of thirty-seven steps.
  - The longest linear sequence from our five sub-targets is sixteen steps.
  - Total steps: 102

- Instructional applications of the Stille reaction, oxidation chemistry, chiral auxiliaries, organosilicons, protective groups, etc.