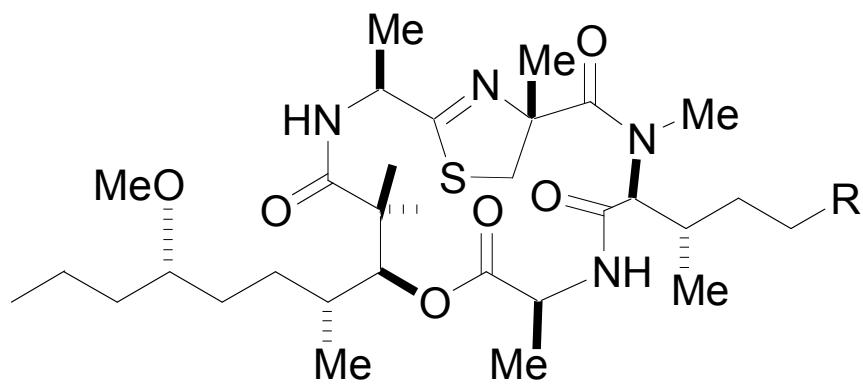


Total Synthesis of Halipeptins A and D



R = OH: halipeptin A
R = H: halipeptin D

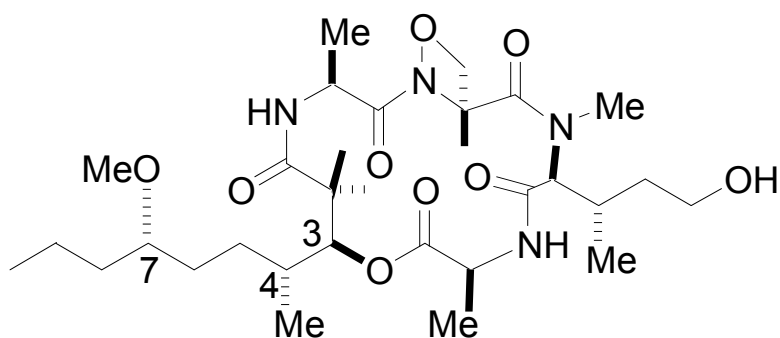
Isolation of the Halipeptin Family



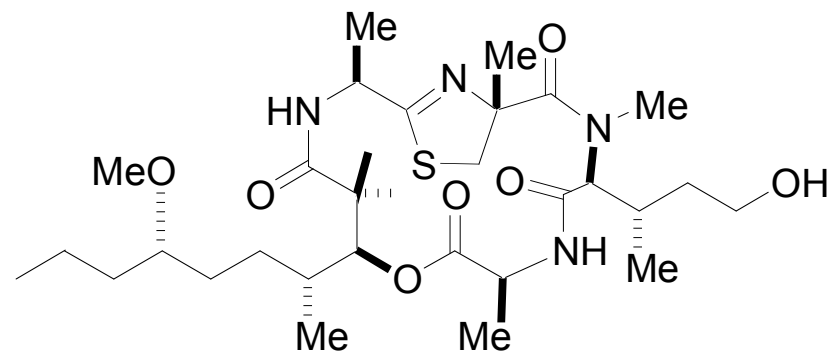
- Halipeptins A and B were isolated in 2001 by the Gomez-Paloma group from the sponge *Haliclona* sp. Halipeptin C was isolated in 2002 also by Gomez and Paloma.
 - Halipeptin D was isolated in 2003 by Faulkner and Manam from a different sponge, *Leiosella* cf. *arenifibrosa*.
 - Halipeptin A is noted for its potent anti-inflammatory activity, rivaling in potency commercially available anti-inflammatory drugs, possibly without the side effects.
 - Halipeptin D exhibits potent cytotoxic properties against an oncology diverse panel of tumor cell lines, particularly against the human colon cancer cell line.
-

Structural Determinations

- Initially, structure of halipeptin A was misassigned as containing an unusual oxazetidione-type structural motif:



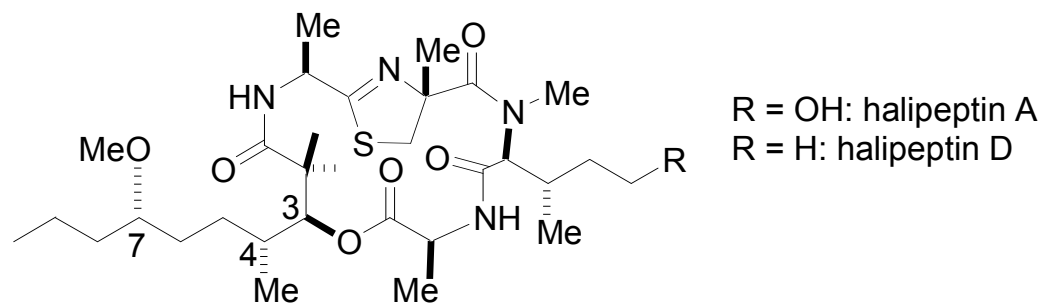
originally proposed structure of halipeptin A



currently proposed structure of halipeptin A

- It was not until the isolation of halipeptin C that the structure was corrected
- Neither Gomez-Paloma or Faulkner-Manam could assign with certainty the stereochemistries at C-3 and C-4, although the former group did conclude the stereochemistry at C-7 to be (S).

Synthetic Challenges of the Halipeptins



- Striking number of methyl groups situated on and around the periphery of the macrocyclic depsipeptide ring
- Constrains on the macrocycle by the thiazoline ring
- Potential for epimerization of the 3 stereocenters next to the carbonyl and thiazoline moieties
- Uncertainties in configurations of C-3, C-4, and C-7 demand flexible strategies for the construction of key intermediates

Synthetic Efforts

- Partial syntheses:

-  2003: Snider and Duvall

-  2003: De Riccardis and Izzo

-  2004: De Riccardis and Izzo

-  2004: Hamada and coworkers

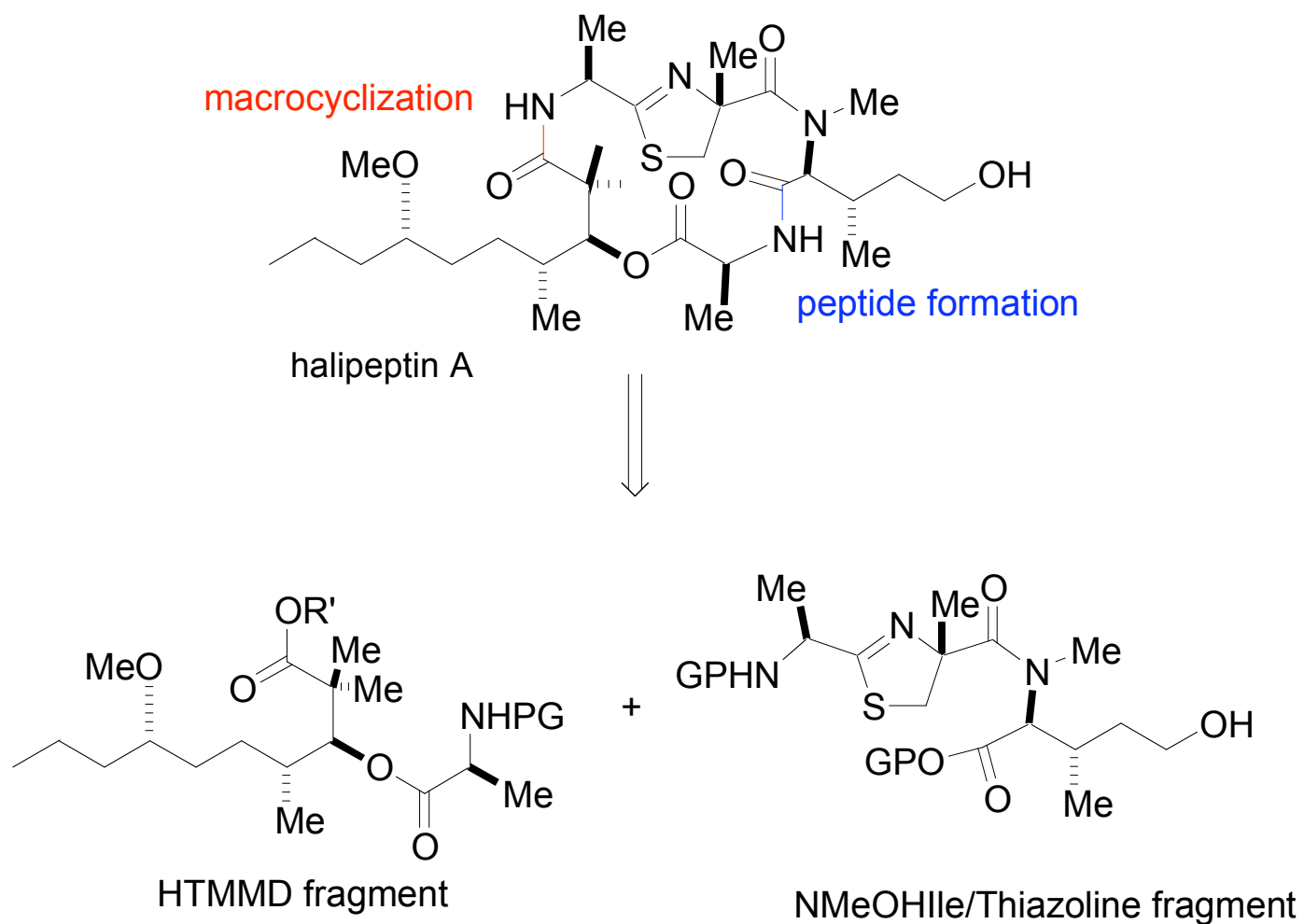
- First total synthesis of halipeptin A in 2005 by Ma and coworkers

Yu, S., Pan, X., Ma, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 135-138.

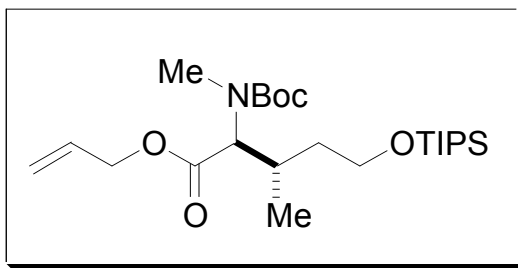
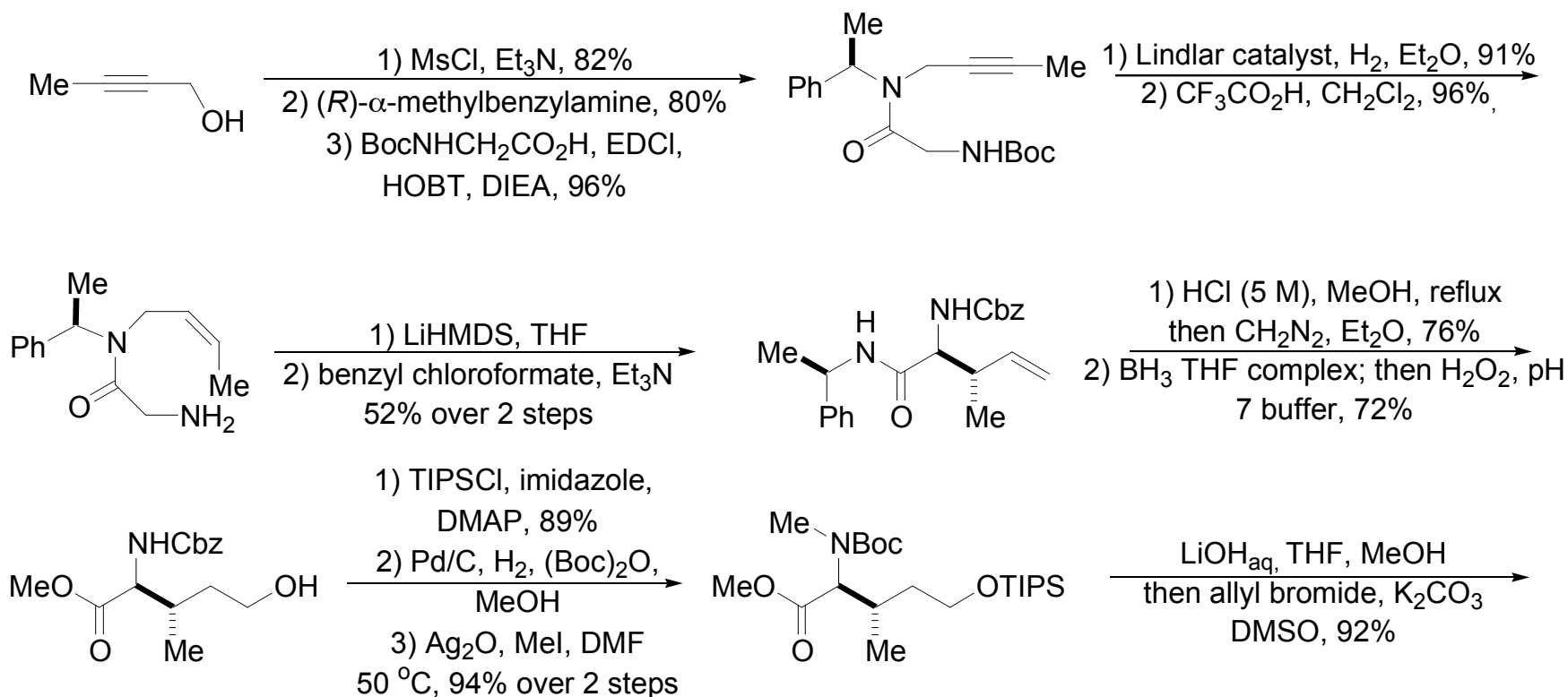
- Total synthesis of halipeptins A and D in 2006 by Nicolaou and coworkers

Nicolaou, K. C., Lizos, D. E., Kim, D. W., Schlawe, D., de Noronha, R. G., Longbottom, D. A., Rodriguez, M., Bucci, M., Cirino, G. *J. Am. Chem. Soc.* **2006**, *128*, 4460-4470.

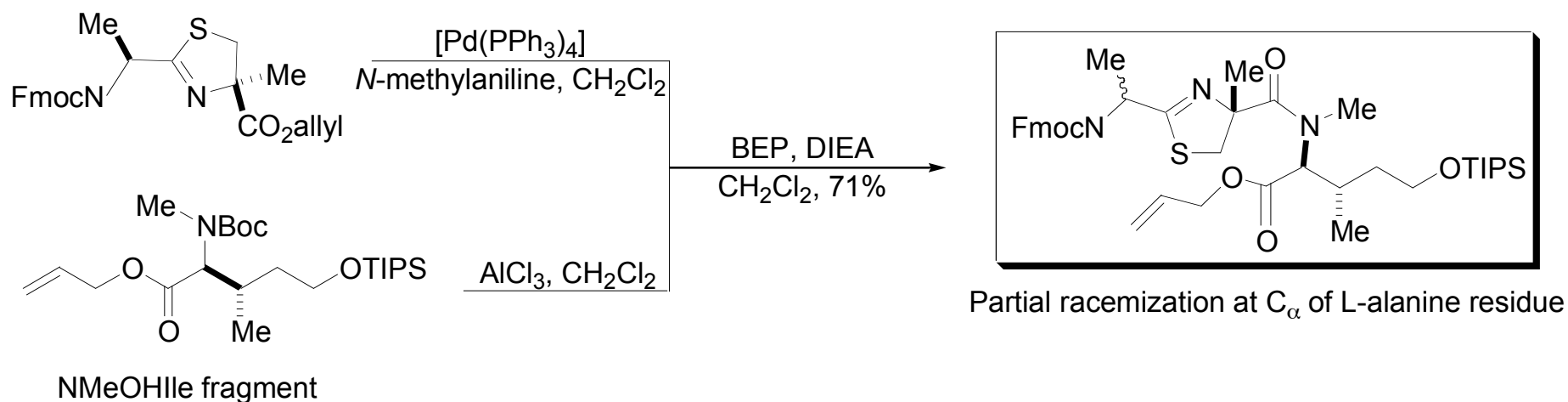
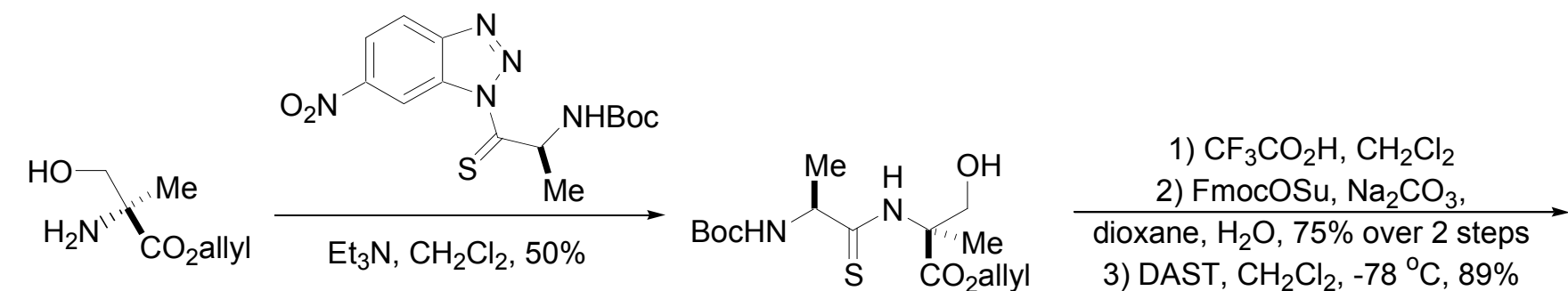
Ma's Retrosynthesis



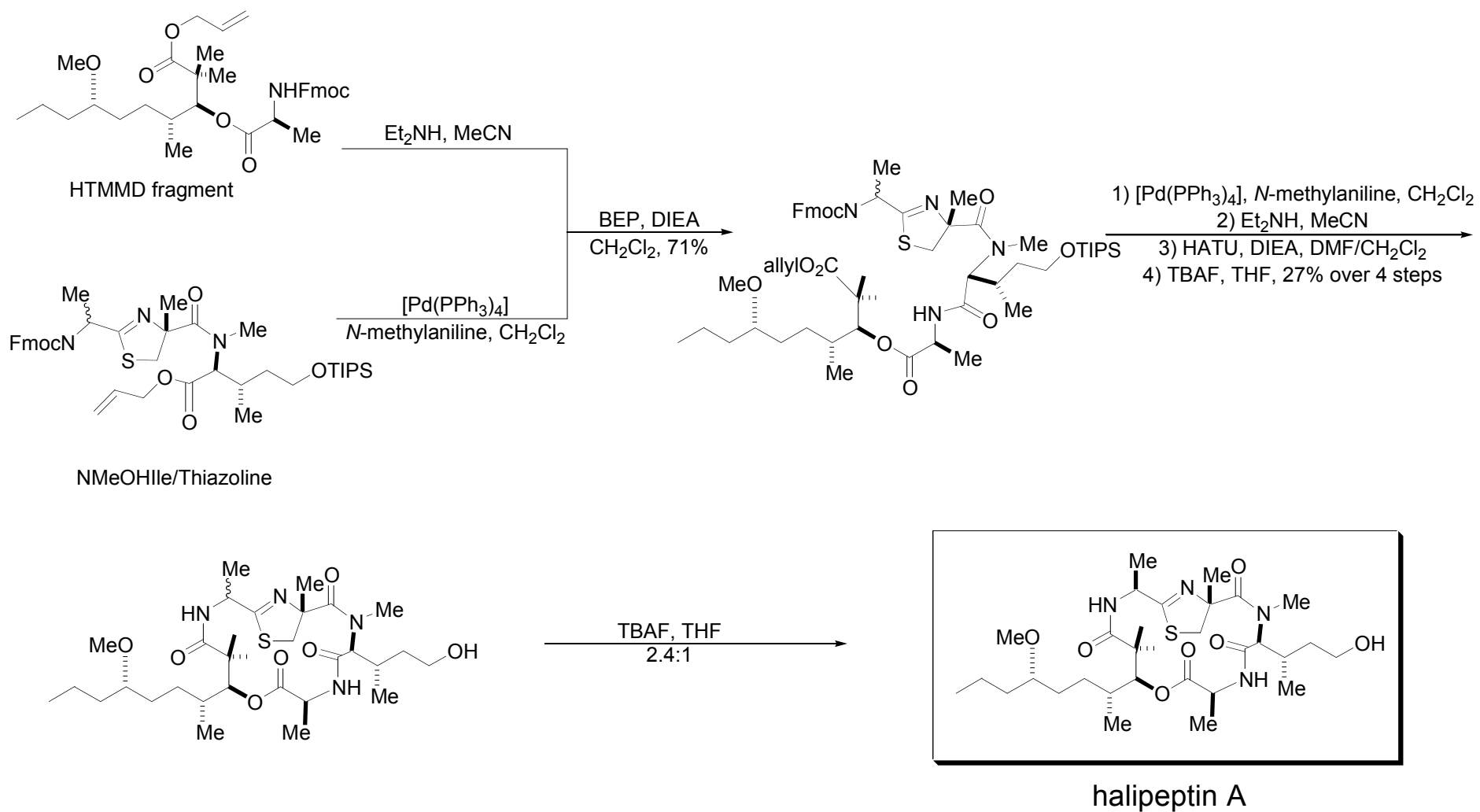
NMeOHle Fragment Assembly



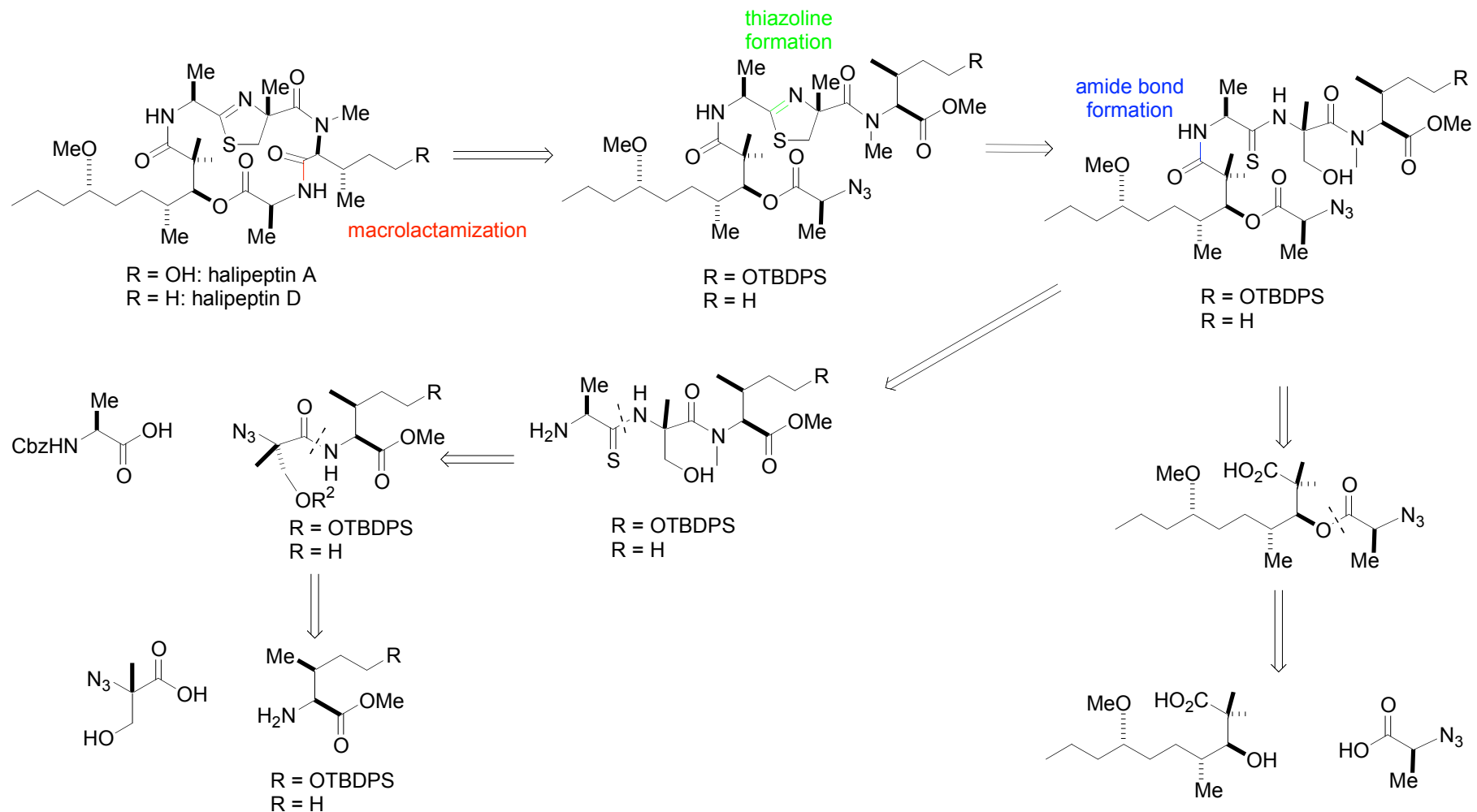
Thiazoline Formation and Coupling to NMeOHlle Fragment



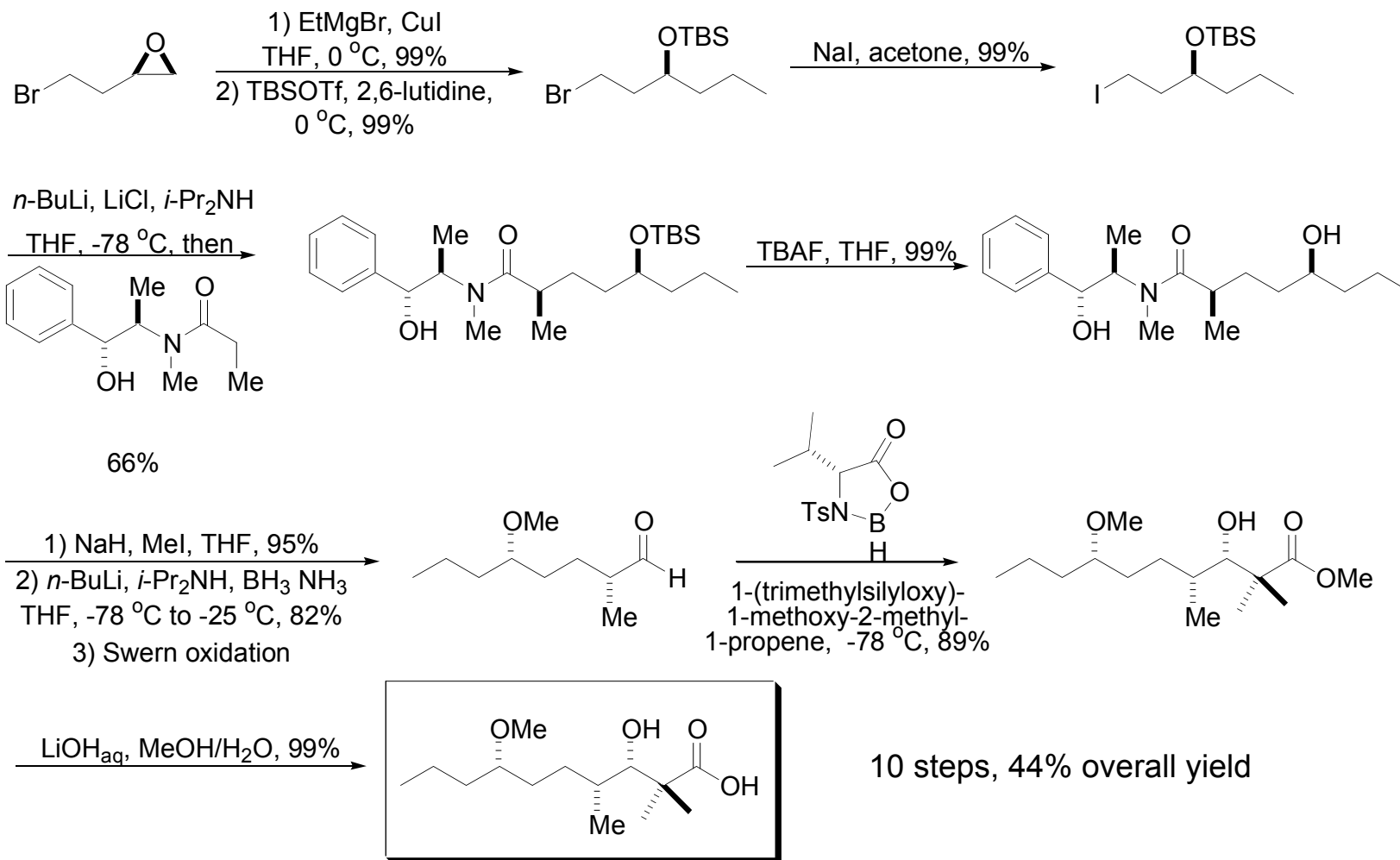
Completion of Synthesis



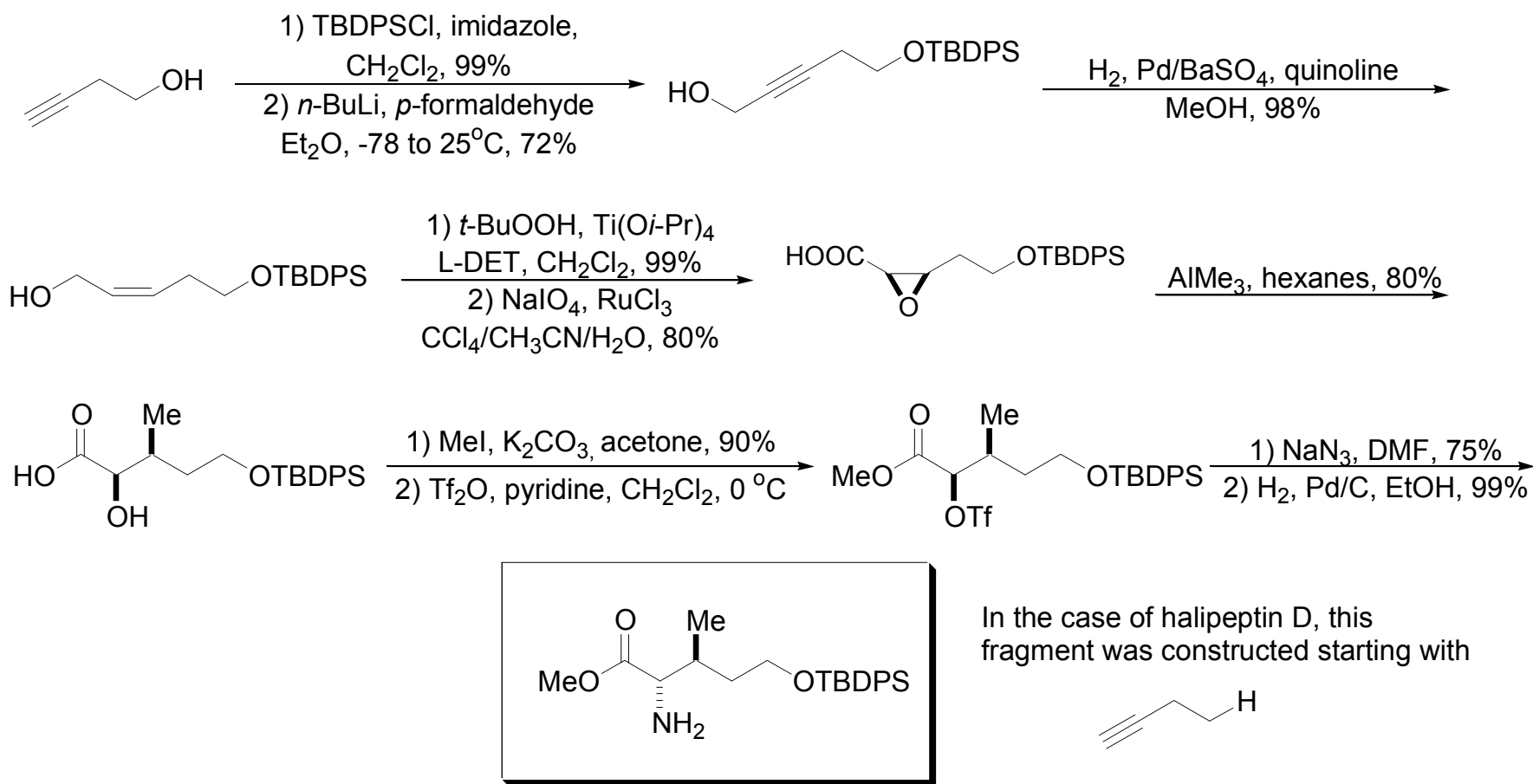
Nicolaou's Retrosynthesis



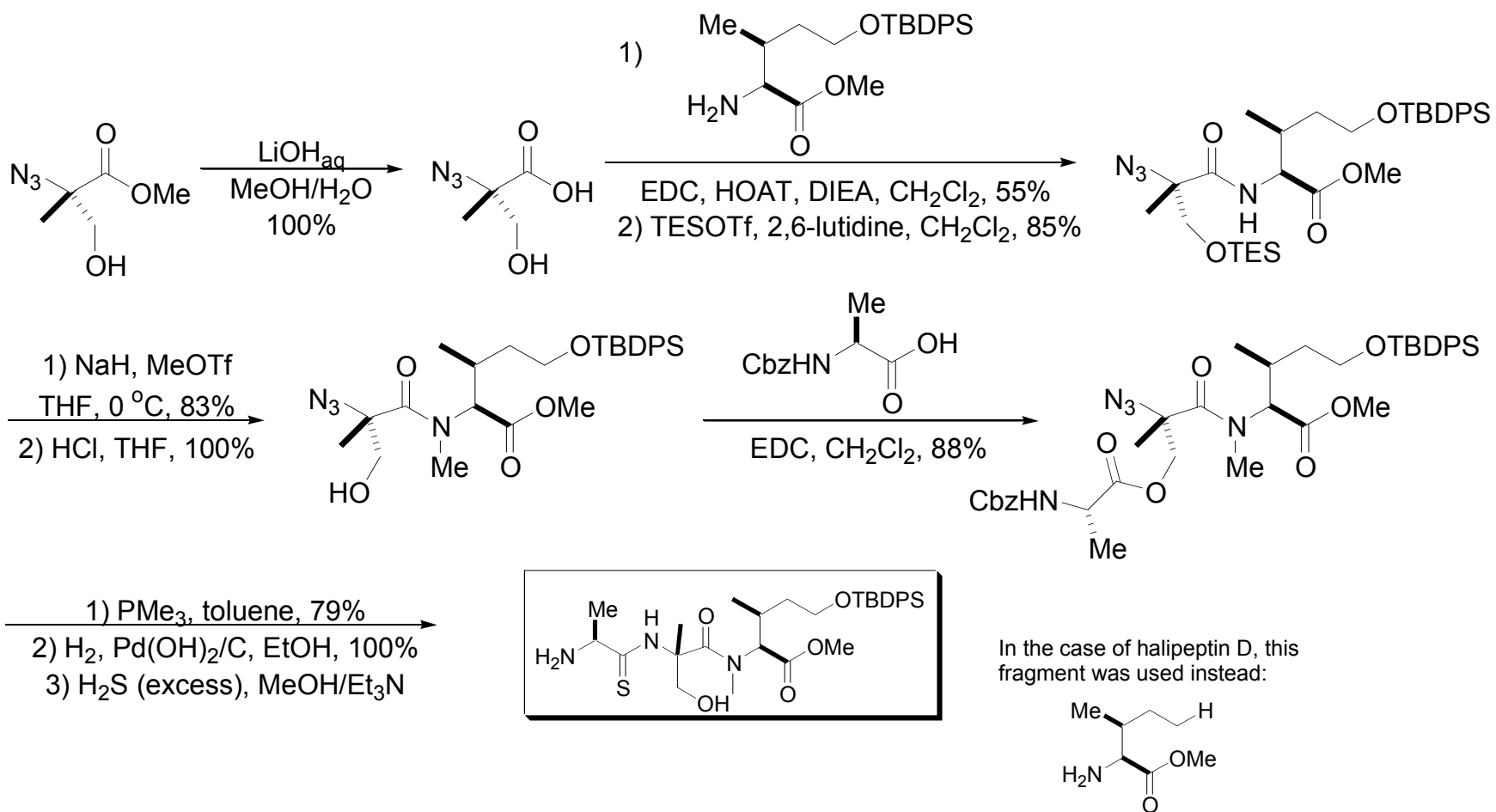
Hydroxydecanoic Acid Fragment Assembly



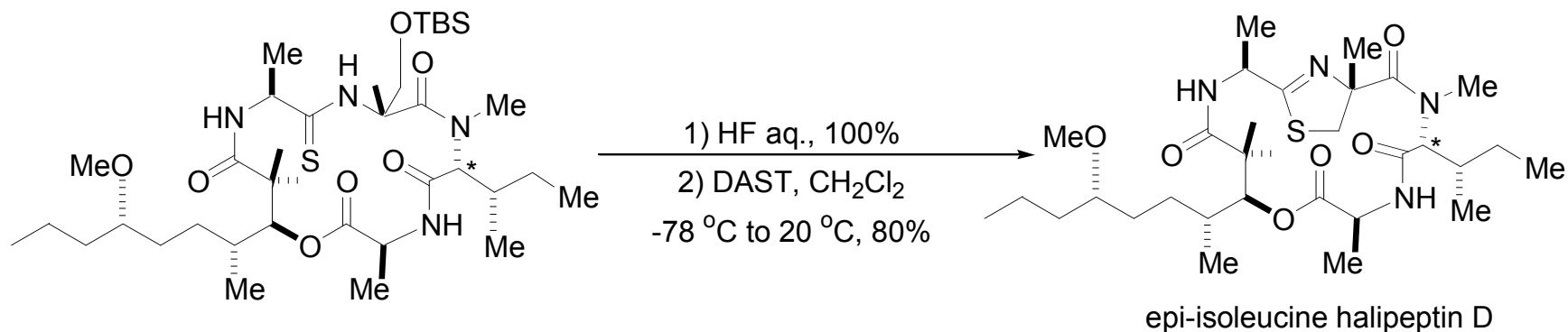
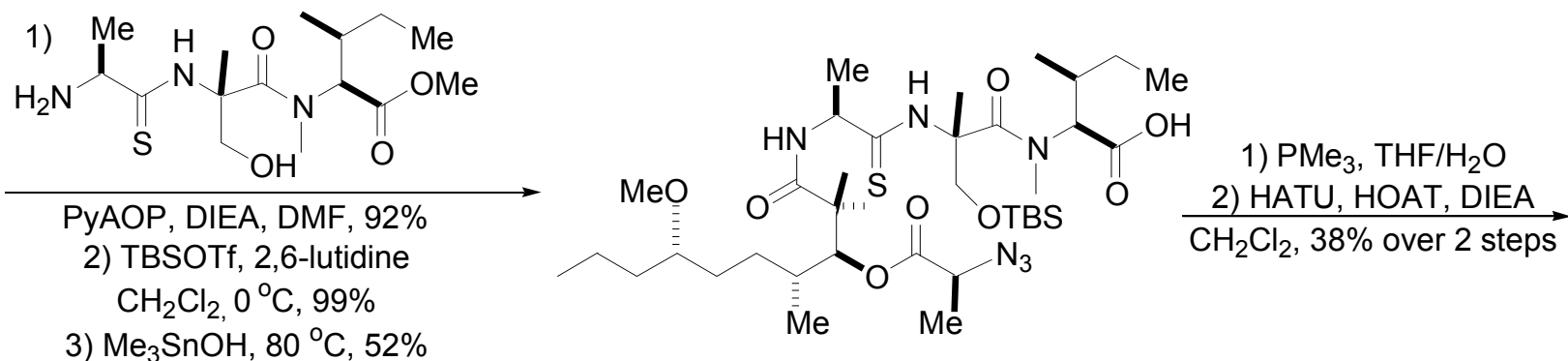
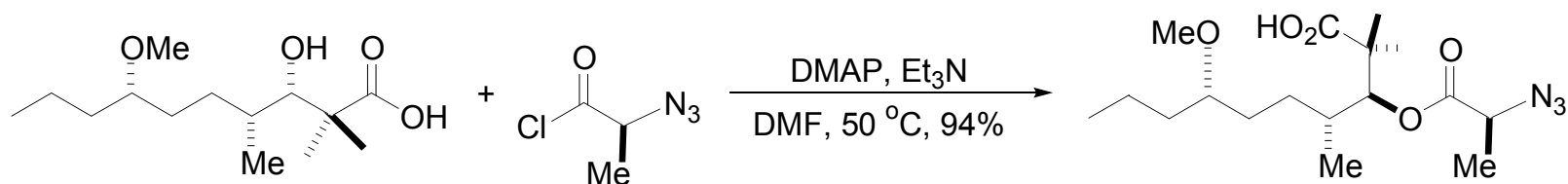
Hydroxy-isoleucine Methyl Ester Fragment Assembly



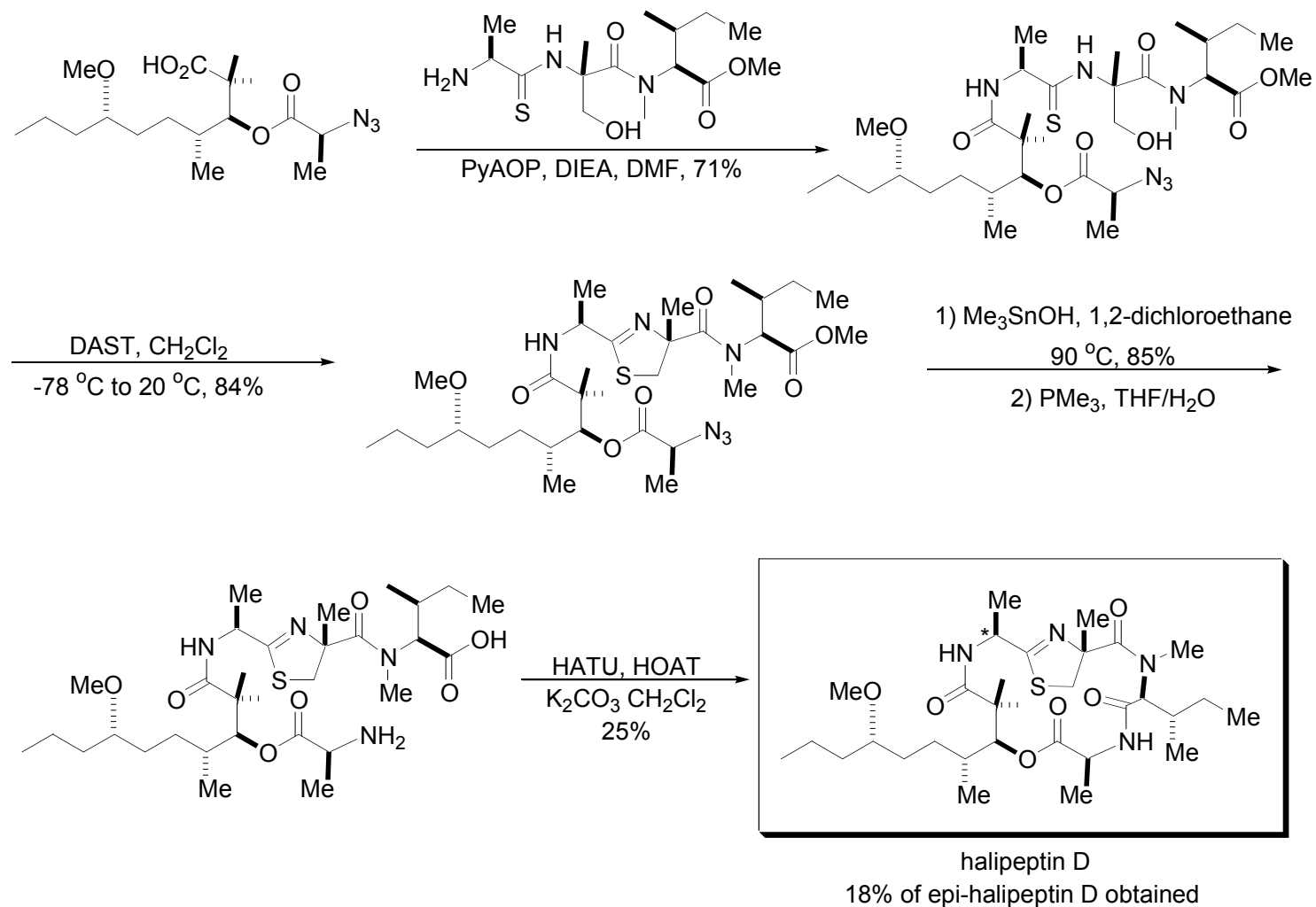
Assembly of Building Blocks into Thioamide



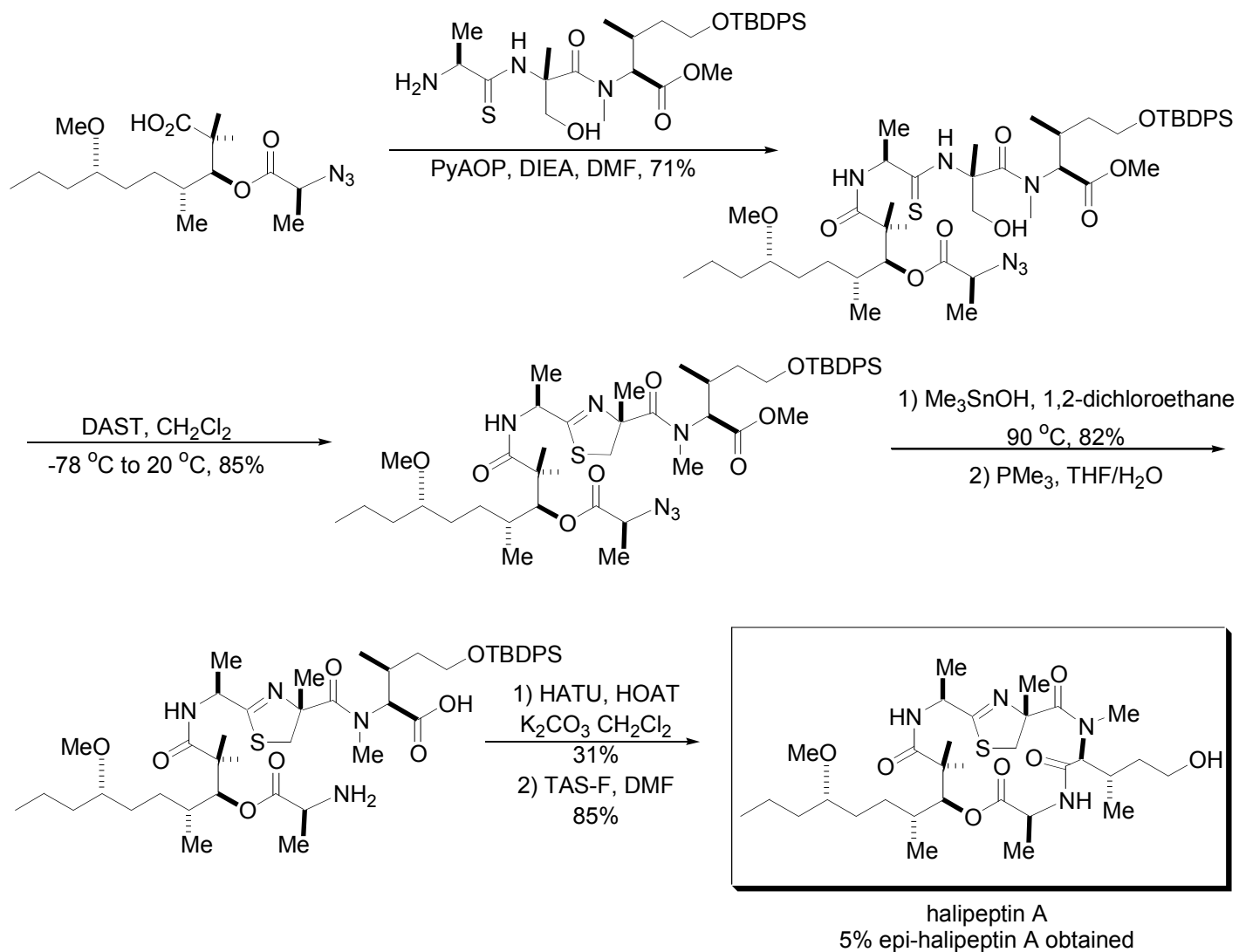
First Attempt at Synthesis of Halipeptin D



Revised Completion of Synthesis of Halipeptin D

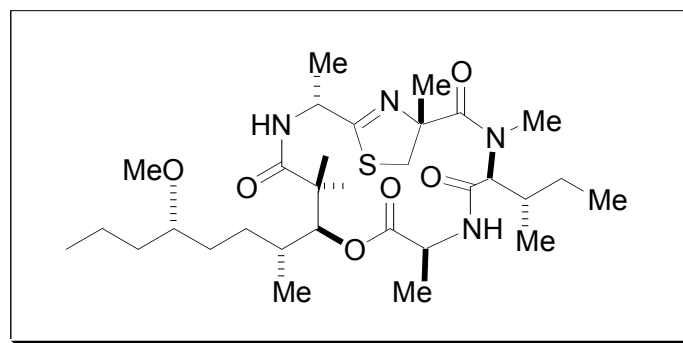
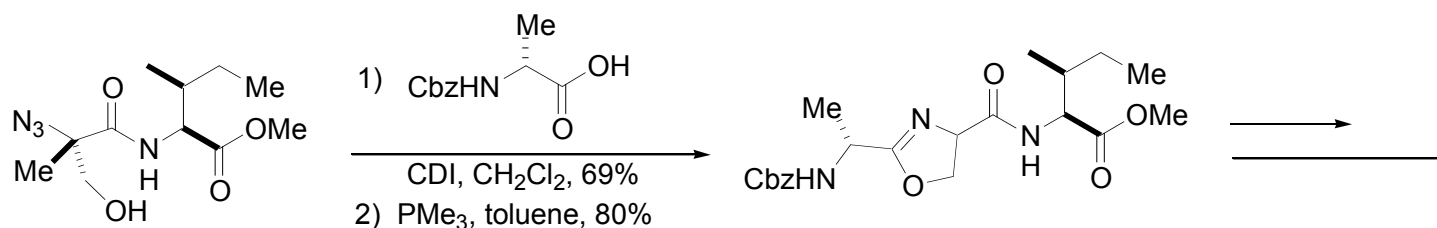


Completion of Halipeptin A



Synthesis of Halipeptin Analogue: *epi*-halipeptin D

- More stable than naturally occurring halipeptin D



Biological Evaluations of Synthetic Halipeptins A and D and Analogues

- Halipeptin A, halipeptin D, oxazoline D, *epi*-oxazoline D, *epi*-halipeptin D, *epi*-halipeptin A all tested for cytotoxic and anti-inflammatory properties
 - None exhibited potent cytotoxic properties, despite previous report by Faulkner-Manam
 - Halipeptin A, halipeptin D and *epi*-oxazoline D had the most potent anti-inflammatory properties, with *epi*-oxazoline D exhibiting the most potency.

