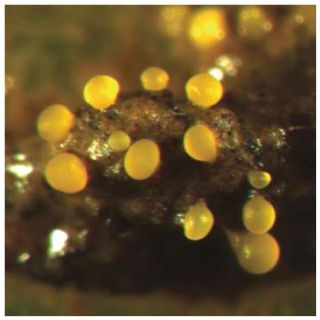
Tubulysin Core

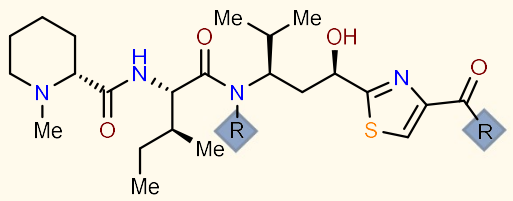
Bristol Myers Squibb™

Properties:

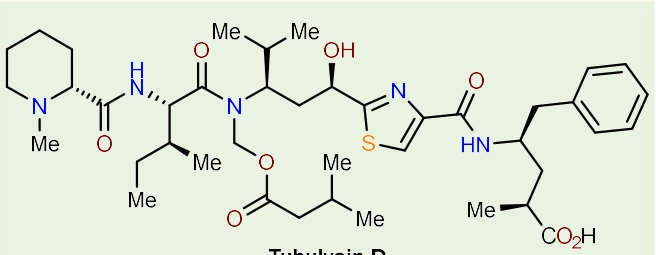
- Microtubule-destabilizing cytotoxic peptides isolated from myxobacteria.
- Research aimed particularly at incorporating this molecules into antibody−drug conjugate-based therapeutics.
- Synthetic research could provide the foundation for an eventual commercial synthesis of this class of compounds while also producing quantities of material to enable further SAR development.

Org. Process Res. Dev. ASAP. https://doi.org/10.1021/acs.oprd.2c00010





Tubulysin family

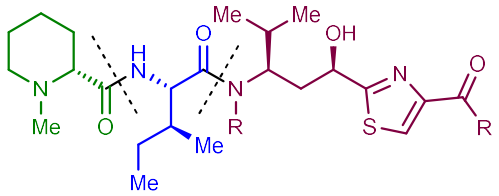


Tubulysin D

Chemical background:

***N*-methyl-D-pipecolic acid (Mep)**

tubuvaline (Tuv)



isoleucine (Ile)

Previous synthetic efforts

- Several syntheses exist. The most important ones from Ellman, Nicolaou and Wipf.
- There has been little work on *N*-alkylated tertiary amides in the Tuv substructure.
- Studies have clearly highlighted the difficulty of forming *N*-alkylated Ile-Tuv tertiary amides.
- Development efforts from AstraZeneca show three cycles of amidation are required to achieve satisfactory conversion.

Process developement

- For a commercially viable route, ensuring the stability of the intermediates was critical, especially with respect to stereochemical purity.
- convergent sequence leading to an advanced tubulysin tripeptide intermediate that proceeds in eight steps and 22.4% overall yield utilizing only one silica gel chromatographic purification.
- Eight-step sequence was easily performed on the decagram scale because of the crystalline nature of all of the isolated intermediates except one.

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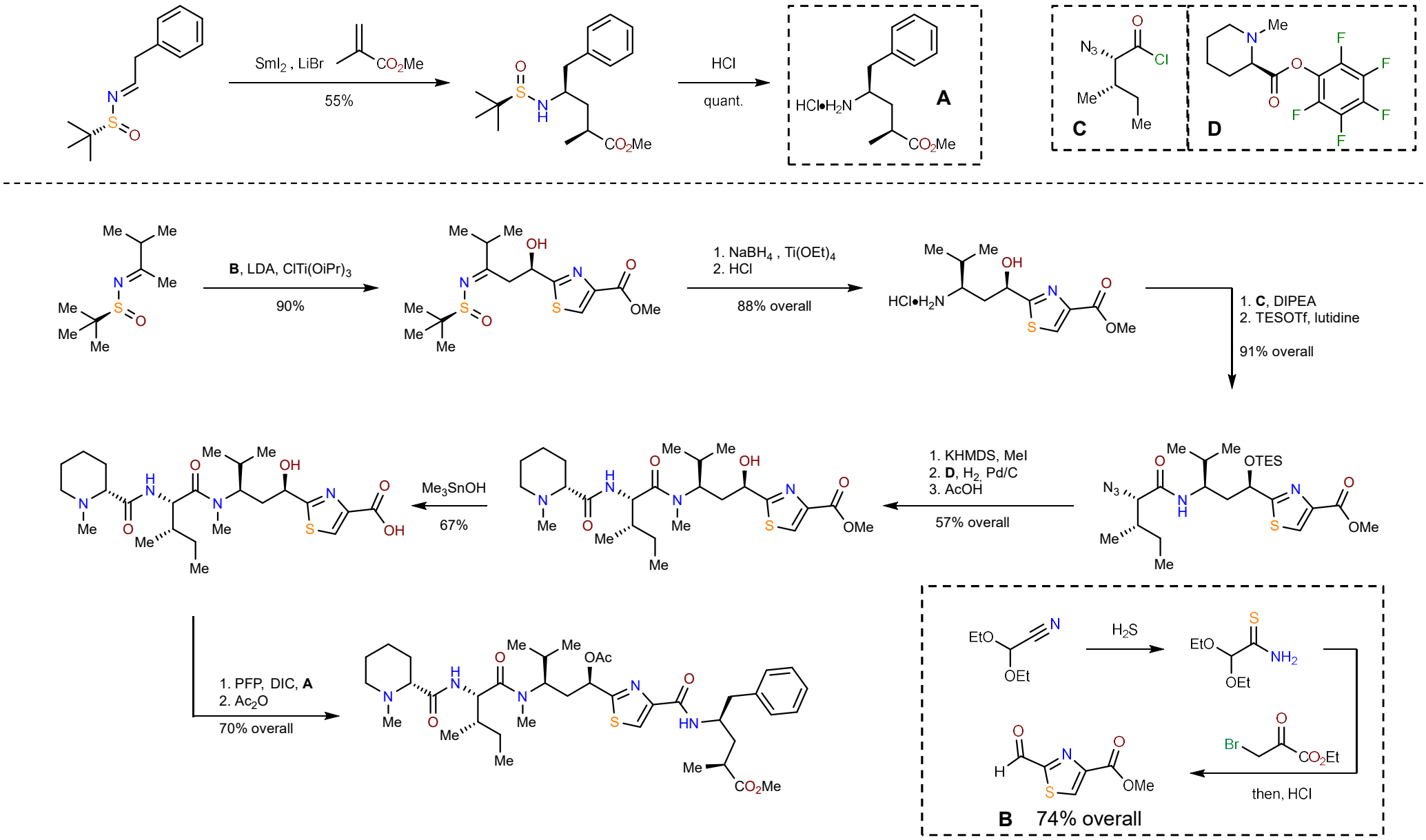
Ellman's synthesis:



J. Am. Chem. Soc. **2006**, *128*, 16018−16019. https://doi.org/10.1021/ja067177z

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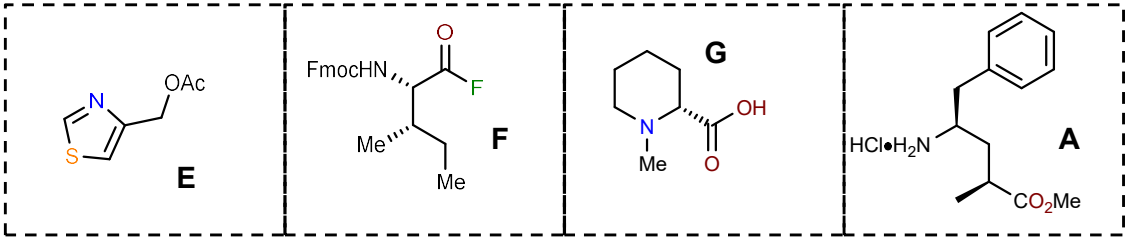
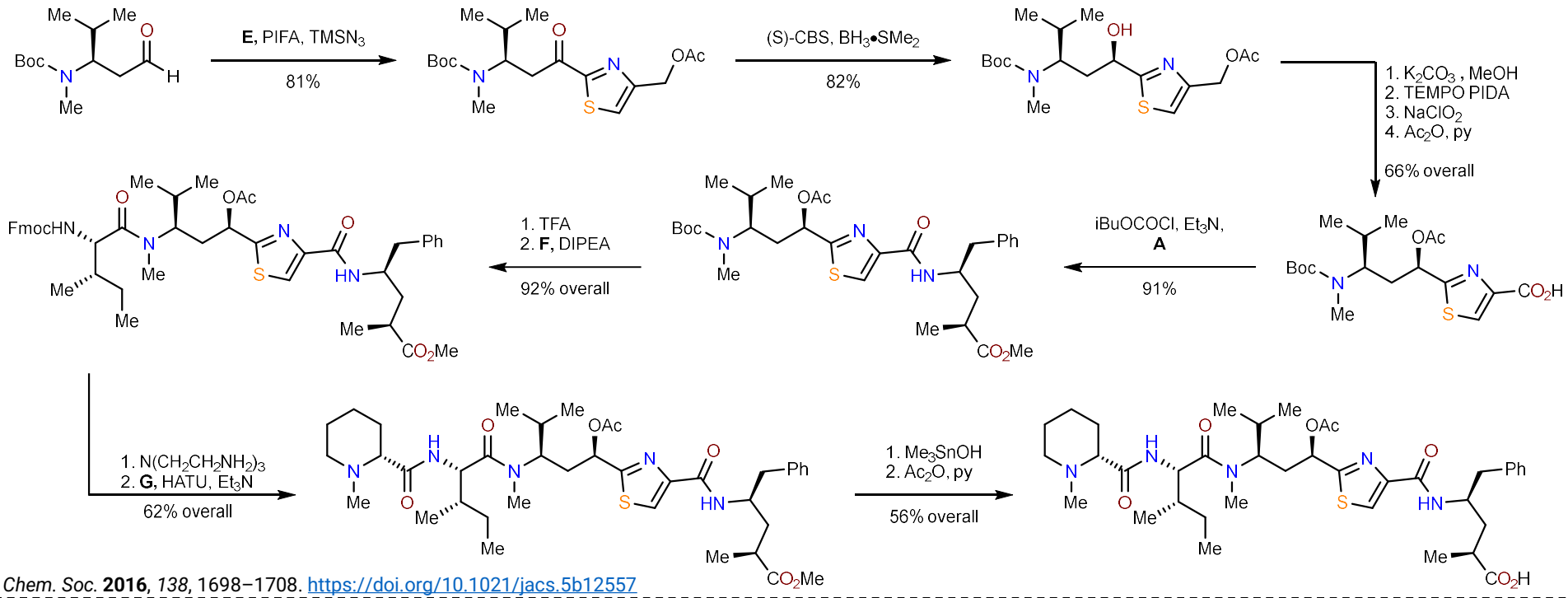
Nicolaou's synthesis:

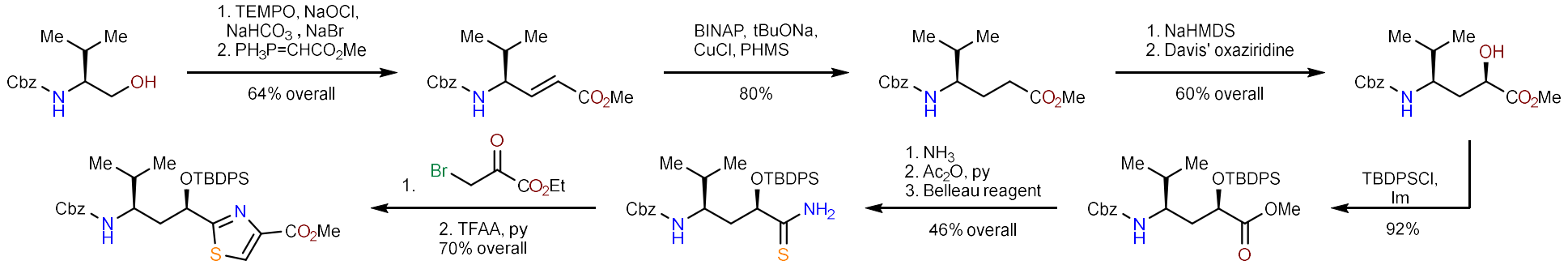




J. Am. Chem. Soc. **2016**, *138*, 1698−1708. https://doi.org/10.1021/jacs.5b12557

Wipf's synthesis:

Org. Lett. **2004**, *6*, 4057−4060. https://doi.org/10.1021/ol048252i



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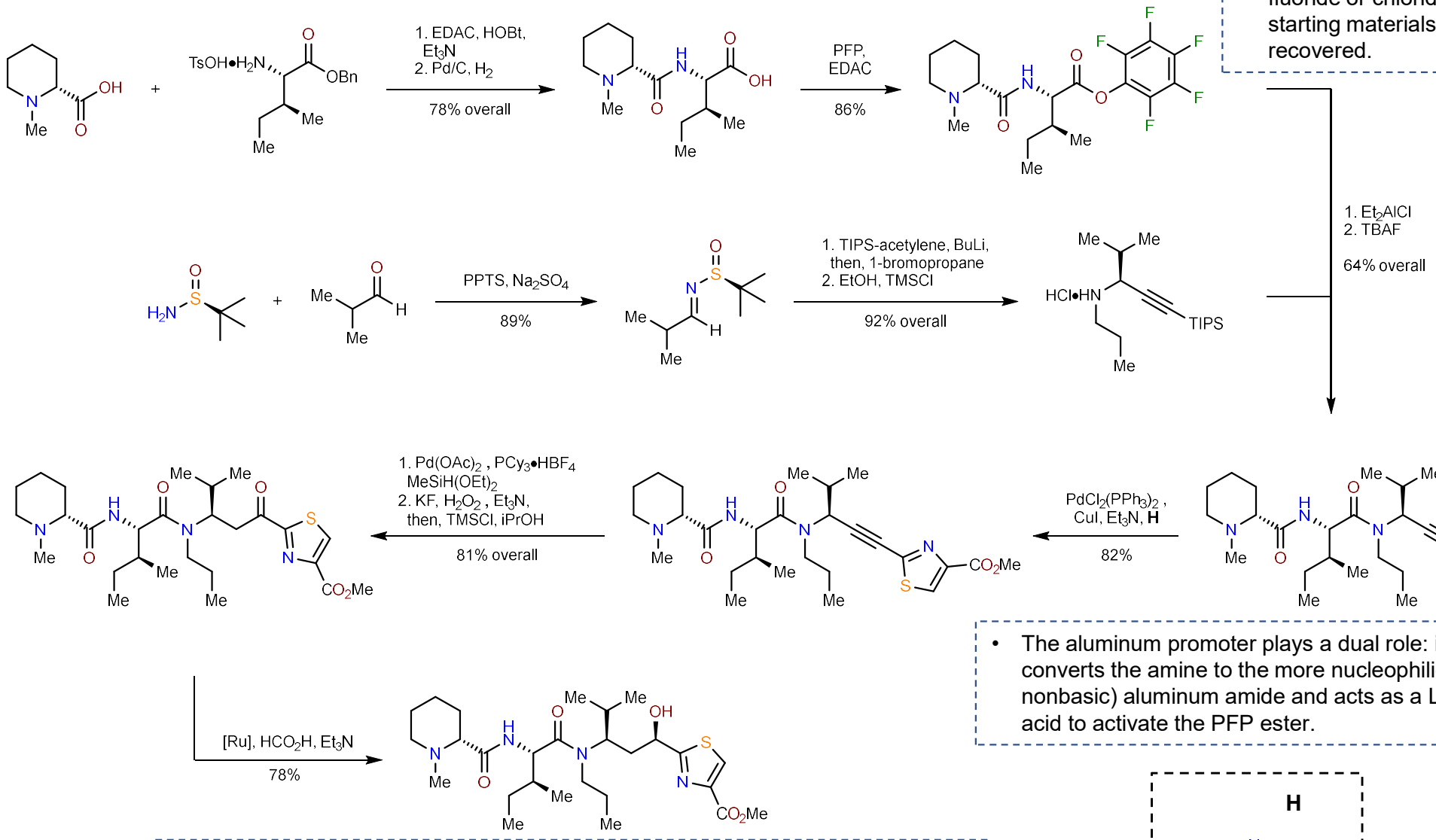
Process route:

- Activation with pentafluorophenol, which is stable and containes a chromophore for visualization by HPLC.
- Activation method critical to avoidepimerization. With acyl fluoride or chloride the starting materials were recovered.



- The aluminum promoter plays a dual role: it converts the amine to the more nucleophilic (but nonbasic) aluminum amide and acts as a Lewis acid to activate the PFP ester.

- The vinyl silane would prove to be more stable than the corresponding boron analogue. Moreover, close literature precedent for the desired transformation was not found with boron, while transition-metal-catalyzed hydrosilylations on similar substrates were known.

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