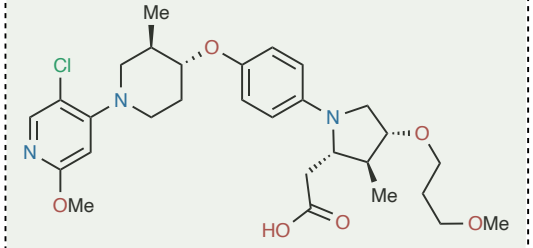
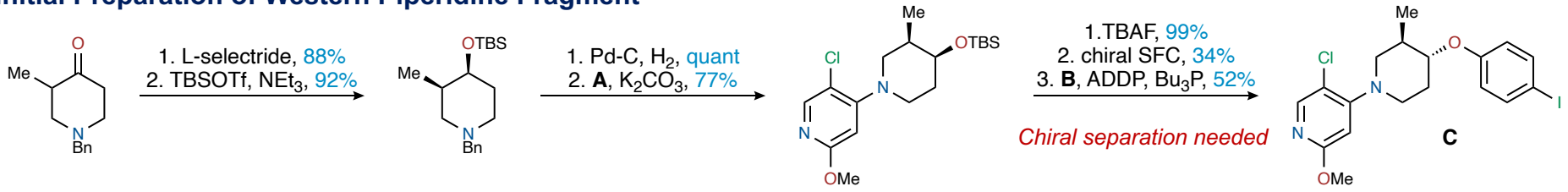
GPR40 Agonist I

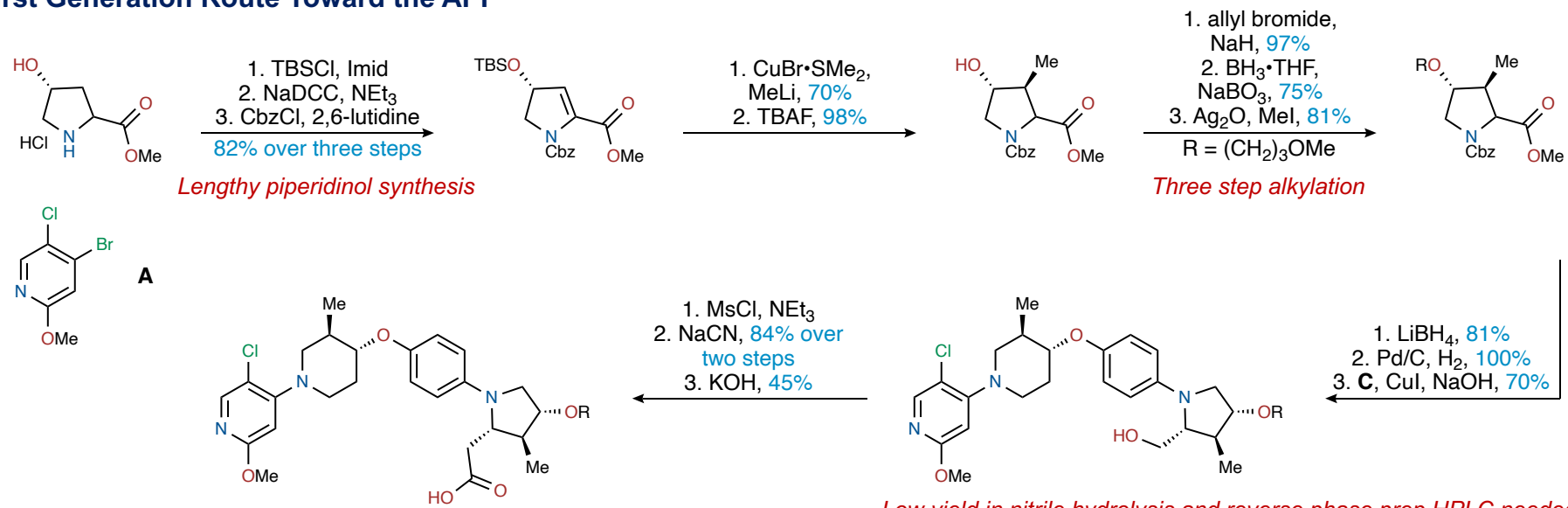
- GPR40 is a free fatty acid receptor. It is expressed in the pancreas and modulates insulin secretion stimulated by glucose.
- GPR40 Agonist compound 1 is an agonist that acts as a positive allosteric modulator (AgoPAM) which is responsible for increasing the affinity of an agonist.
- These drugs are developed for the treatment of type two diabetes mellitus.
- Mechanism of action: stimulates glucose-dependent insulin and GLP-1 secretion
- In vivo, the drug has lowered plasma glucose levels in rats in an oral challenge model and more of the compound was needed for toxicological testing.



Initial Preparation of Western Piperidine Fragment



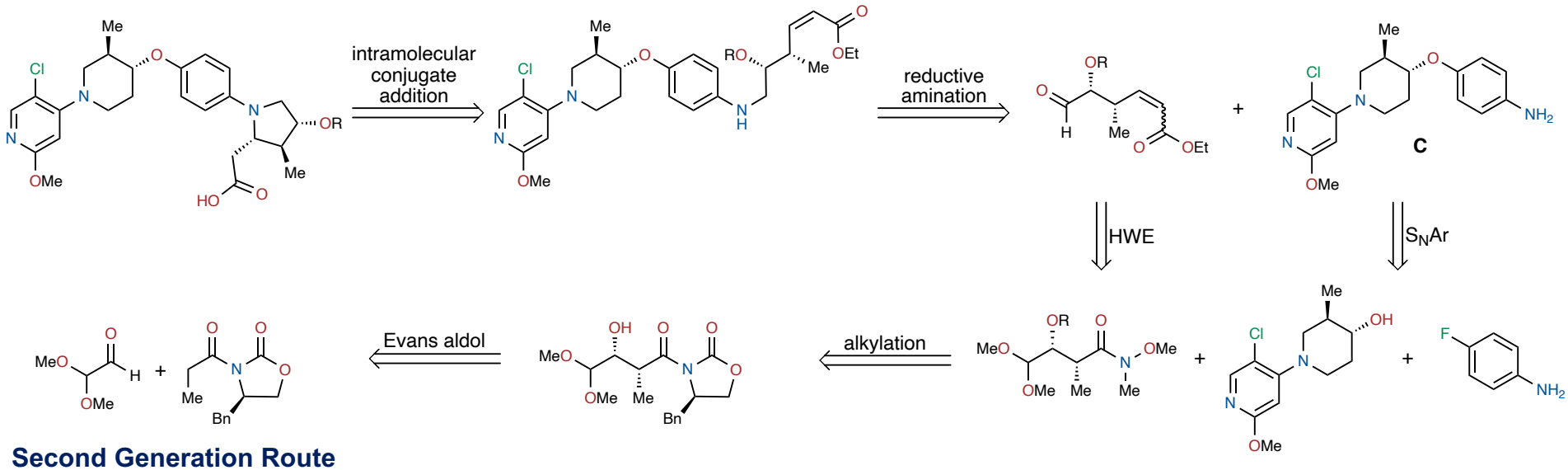
First Generation Route Toward the API



Hou, X. *Org. Process Res. Dev.* **2023**, *27*, 1317. https://doi.org/10.1021/acs.oprd.3c00077

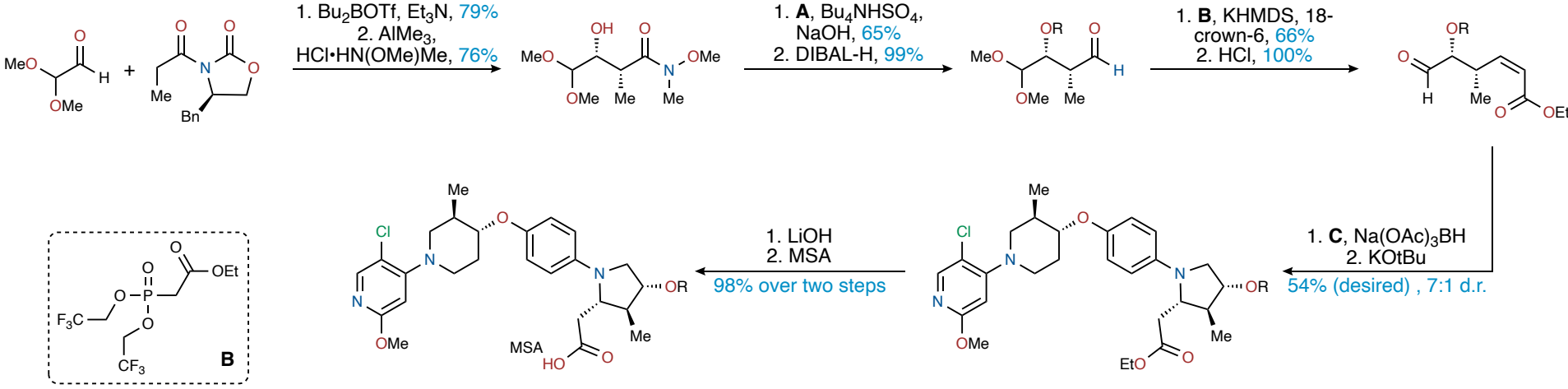
GPR40 Agonist I

Second Generation Retrosynthesis



Second Generation Route

Bu_2BOTf availability issues — *A no longer available* — *Expense of B and long lead time*



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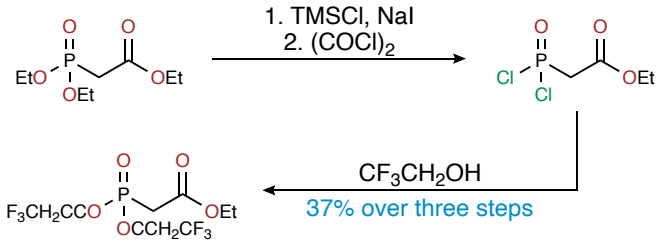
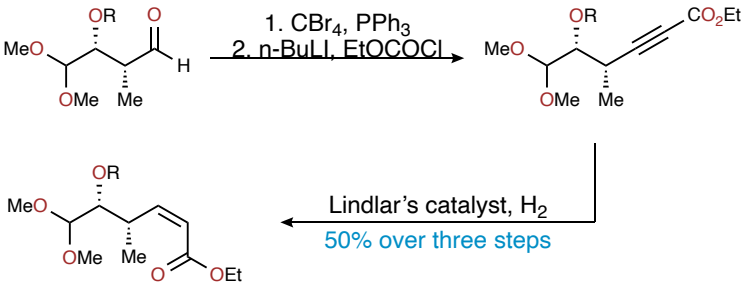
GPR40 Agonist I

Still-Gennari Phosphonate Preparation



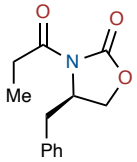
Sealed tube needed first step and low yielding

13% overall step increase, scalable and reproducible



Phosphonate Preparation Via Corey-Fuchs

Optimized Route Toward API



> 100g of API produced

30% overall yield to make the aldehyde

Five columns to two in route

Cryogenic conditions decreased from five to one

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