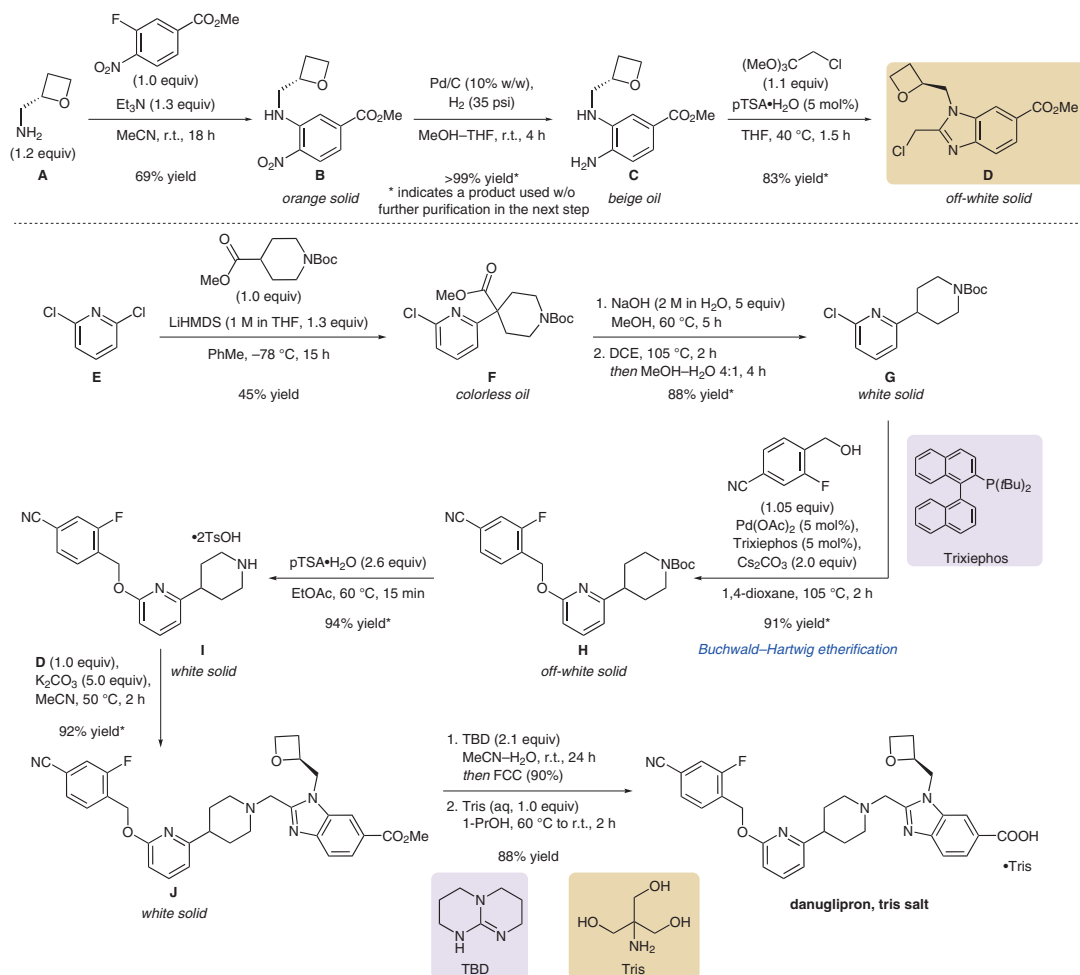


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A Small-Molecule Oral Agonist of the Human Glucagon-like Peptide-1 Receptor  
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## Synthesis of Danuglipron: An Orally Available GLP-1R Agonist



**Significance:** The glucagon-like peptide-1 receptor (GLP-1R) is a well-known target, playing a key role in metabolic health. Peptidic agonists have been approved for the treatment of type 2 diabetes and obesity. Danuglipron is the first orally available small-molecule GLP-1R agonist showing to decrease glucose levels in humans. A phase 1 clinical study has recently been completed.

**Comment:** A transformation of interest in the synthesis of danuglipron is the saponification of the methyl ester **J** to the corresponding acid in the penultimate step of the synthesis. Extensive evaluation of various conditions revealed that TBD is a suitable base for the chemoselective production of the acid without hydrolysis of the nitrile moiety.

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