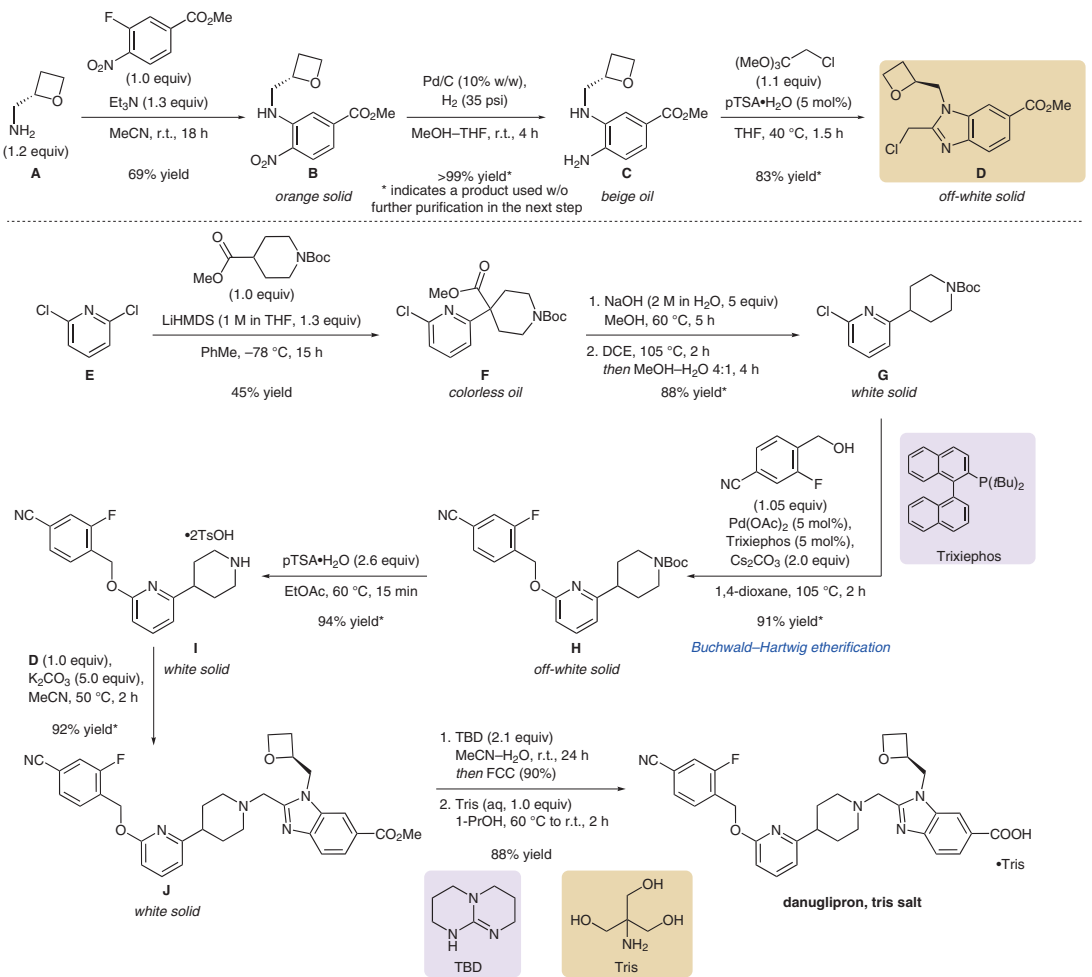
D. A. GRIFFITH*, D. J. EDMONDS, J.-P. FORTIN, A. S. KALGUTKAR, J. B. KUZMISKI, P. M. LORIA, A. R. SAXENA, S. W. BAGLEY, C. BUCKERIDGE, J. M. CURTO, D. R. DERKSEN, J. M. DIAS, M. C. GRIFFOR, S. HAN, V. M. JACKSON, M. S. LANDIS, D. LETTIERE, C. LIMBERAKIS, Y. LIU, A. M. MATHIOWETZ, J. C. PATEL, D. W. PIOTROWSKI, D. A. PRICE, R. B. RUGGERI, D. A. TESS (PFIZER WORLDWIDE RESEARCH, DEVELOPMENT, AND MEDICAL, CAMBRIDGE, USA)

A Small-Molecule Oral Agonist of the Human Glucagon-like Peptide-1 Receptor

J. Med. Chem. **2022**, *65*, 8208–8226, DOI: 10.1021/acs.jmedchem.1c01856.

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.

SYNFACTS Contributors: Antonia F. Stepan (Roche), Ferdinand H. Lutter (Janssen Pharmaceutica)
Synfacts 2022, 18(09), 1025 Published online: 18.08.2022
DOI: 10.1055/s-0041-1738304; **Reg-No.:** A00522SF

Category

Innovative Drug Discovery and Development

Key words

danuglipron

Buchwald–Hartwig etherification

benzimidazoles

chemoselective saponification

antidiabetics

PF-06882961

Synfact of the Month