Glecaprevir was identified as a potent hepatitis C virus (HCV) protease inhibitor, and an enabling synthesis was required to support the preclinical evaluation and subsequent Phase I clinical trials. The key steps in the enabling route involved a ring-closing metathesis (RCM) reaction to form the 18-membered macrocycle and a challenging fluorination step to form a key difluoromethyl-substituted cyclopropyl amino acid. To support the late-stage clinical trials and subsequent commercial launch, a large-scale synthetic route to glecaprevir was required. The large-scale synthetic route to the macrocycle employed a unique intramolecular etherification reaction as the key step, avoiding the scalability limitations of the ring-closing metathesis (RCM) reaction of the enabling route. The large-scale route to the difluoromethyl-substituted cyclopropyl amino acid avoided the fluorination challenges by constructing the amino acid from a commercially available difluoromethyl-substituted hemi-acetal. The key steps in the amino acid synthesis were a Knoevenagel condensation, a Corey-Chaykovsky cyclopropanation, a Curtius rearrangement, and a chiral resolution. Subsequent coupling of the macrocycle to the amino acid containing sidechain produced glecaprevir in 16% overall yield.

PHOTOENZYMATIC CATALYSIS - USING LIGHT TO REVEAL NEW ENZYME FUNCTIONS

Enzymes are exquisite catalysts for chemical synthesis, capable of providing unparalleled levels of chemo-, regio-, diastereo- and enantioselectivity. Unfortunately, biocatalysts are often limited to the reactivity patterns found in nature. In this talk, I will share my groups efforts to use light to expand the reactivity profile of enzymes. In our studies, we have exploited the photoexcited state of common biological cofactors, such as NADH and FMN to facilitate electron transfer to substrates bound within enzyme active sites. In other studies, we found that enzymes will electronically activate bound substrates for electron transfer. In the presence of common photoredox catalysts, this activation can be used to direct radical formation to enzyme active sites. Using these approaches, we are able to develop biocatalysts to solve long-standing selectivity challenges in chemical synthesis.

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