UCLA Chemistry & Biochemistry

AMGEN®

presenting

The 2017
Amgen–UCLA Lectureship

with

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Amgen, Inc.

"Stereoselective Synthesis of a Chiral Lactone Precursor to AMG 232"

Abstract. AMG 232 is a small molecule therapy currently in clinical trials for the treatment of cancer. A stereodefined lactone intermediate, labeled **DLAC**, was identified as a key synthetic precursor to AMG 232. As such, we required a robust, isolable, and highly selective synthetic route to **DLAC** that would enable material for both clinical trials and commercial production. This presentation details process improvements toward the scalable synthesis of **DLAC** via development of a robust and highly-selective Ru(II)-catalyzed dynamic kinetic resolution. Key features of this work include the discovery of ruthenabicyclic complex RuCl[(*S*)-diapena][(*S*)-xylBINAP] ((*S*)-RUCY-xylBINAP) as a highly effective catalyst for ketone hydrogenation with respect to conversion, yield, selectivity, catalyst loading, and cycle time. This report discusses an important transesterification event to a more sterically hindered isopropyl ester prior to hydrogenation to curb unexpected product erosion during the reaction. Lastly, we detail process control of a deleterious carboxylic acid impurity in the starting material in order to optimize DKR catalyst performance. Comprehensive process improvements led to a 55% yield of **DLAC** over 7 steps; desired product was obtained in > 90 kg on 3 separate occasions.

Thursday, February 2, 2017

1:30 PM

Cram Conference Room – 3440 Molecular Sciences Bldg

For further information, contact David Gingrich at gingrich@chem.ucla.edu