Team Challenge #11
Presenter: Keary Engle

Low-density lipoprotein cholesterol (LDL-C) is commonly referred to as "bad" cholesterol. High-serum LDL-C is an established risk factor for atherosclerosis and a known biomarker for increased risk of coronary heart disease (CHD). Statins (*e.g.*, Lipitor and Crestor) are common frontline treatments to lower LDL-C. In some cases, however, these drugs do not lower LDL-C to safe levels. In these cases, other options are needed.

One strategy that has been pursued is inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), which has been shown to decreases serum LDL-C lelvels. Pfizer recently reported prodrug **P1**, a small moleucle inhibitor of PCSK9.

For this Team Challenge, you are part of a process chemistry team focused on meeting the multikilogram supply needs for clinical evaluation of **P1**. Working with your team, propose an efficient, scalable, and stereoselective route to access **P1**. You are not permited to use a computer for this Team Challenge but may ask Keary regarding commercial availability of starting materials. *Bonus:* Identify the active form of **P1**. Why might a prodrug approach have been pursued in this case?

Piotrowski, D. W.; Kamlet, A. S. et al., J. Am. Chem. Soc. 2016, 138, 4818-4823.

Piotrowski, D. W. et al., J. Org. Chem. 2017, 82, 869-886.

Piotrowski, D. W. et al., Org. Process Res. Dev. 2017, 21, 1990-2000.