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 levels. Pfizer recently reported prodrug P1, a small molecule 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 permitted 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?

![Chemical Structure of P1](image)