2-arylpropanoic acids and its derivatives, known as profens, are important drug molecules marketed globally as painkiller medication, of which the (S)-form is biologically active. Currently established production processes are based on multi-step chemical synthetic pathways that suffer from poor atom economy. The development of an enzymatic pathway to result in a milder, more environmentally benign process was therefore investigated. Styrene oxide isomerase (SOI) was identified as a key enzyme for our proposed pathway. Unfortunately, it was found that SOI possessed only mild activity towards profen drug precursor epoxides. To overcome this problem, we performed structure-independent semi-rational directed evolution to engineer an SOI with enhanced activity towards drug precursor epoxides. After two rounds of iterative saturation mutagenesis, the enhanced mutant showed more than 10-fold increase in $k_{cat}/K_m$ for the (S)-precursor epoxide. This mutant could be utilized in a chemoenzymatic cascade to produce several (S)-profen drugs in high conversion and enantiomeric excess. We then performed a third round of mutagenesis to engineer a triple mutant with higher (S)-selectivity. This study could be a good starting point for the development of novel enantiospecific enzyme cascades around the unique isomerization reaction.