Synthesis of a SIRT1 Inhibitor

Significance: SIRT1 deacetylates the p53 tumor suppressor protein, a key transcriptional regulator of genes involved in cell cycle regulation, apoptosis, and DNA repair. The target molecule is a potent SIRT1 inhibitor. The key step in the synthesis of the (S)-eutomer depicted is the stereospecific [3,3]-sigmatropic rearrangement of the divinylcyclopropane intermediate F derived from aldehyde D via a Horner–Wadsworth–Emmons (HWE) reaction.

Comment: Twelve examples of the HWE–[3,3]-sigmatropic rearrangement cascade leading to cyclohepta[b]indoles are described. The temperature required for the [3,3]-sigmatropic rearrangement varies from room temperature to 140 °C, depending on the structure of the indole divinylcyclopropane. For an earlier synthesis of the racemic target and its chiral HPLC resolution, see: A. D. Napper et al. J. Med. Chem. 2005, 48, 8045.