Total Synthesis of Thapsigargins

Thapsigargin is a complex densely oxygenated sesquiterpene lactone, which functions as a selective and irreversible subnanomolar inhibitor of sarco/endoplasmic reticulum Ca\(^{2+}\) ATPases. Importantly, a prodrug of this natural product, Mipsagargin, is currently in late-stage clinical trials for the treatment of multiple cancers. Nevertheless, the limited availability of the material from natural sources, coupled with an estimated demand of one metric ton per annum, provides a compelling mandate to develop a practical total synthesis of this agent. This seminar will focus on the development of a concise, efficient and scalable synthesis of thapsigargin and related members of the family from commercially available (R)-(–)-carvone. Notably, the strategy is inspired by nature’s carbon-carbon bond formation sequence, which facilitates the construction of a highly functionalized sesquiterpene lactone skeleton in five steps via an enantioselective ketone alkylation and a diastereoselective pinacol cyclization.