Ovatodiolides: Scalable protection-free syntheses, configuration determination, and biological evaluation against hepatic cancer stem cells

With the support by the National Natural Science foundation of China, the research team led by Prof. Chen Yue (陈悦) at the State Key Laboratory of Medicinal Chemical Biology, Nankai University, recently reported the first total synthesis, determination of the absolute configuration of the scaffold of ovatodiolide. Biological assays confirmed ovatodiolides can selectively ablate hepatic cancer stem cells (HCSCs). The research work was published in *Angew Chem Int Ed* (2019, 131: 10587—10590).

Liver cancer is one of the deadliest cancers in the world, the critical roles of HCSCs in tumorigenesis, metastasis, resistance to therapy and disease relapse have been well recognized. Ovatodiolide is a macrocyclic diterpenoid that was first isolated from the South Vietnamese plant *A. ovata* by Toubiana and his collaborators. The leaves of *Anisomeles indica Kuntze*or (*Labiatae*), a traditional Chinese medicine used for treating inflammation and hepatic disorders, are also rich in ovatodiolide. The written history of *Anisomeles indica* can be traced back to 1711 in the Qing dynasty of China. The selectivity of ovatodiolide against HCSCs makes ovatodiolide an interesting target for anti-CSC medicinal chemistry.

Recently, Chen's group reported the first asymmetric total synthesis of *ent*-ovatodiolide on a 1 g scale in 6 linear steps. The protecting group-free synthesis features a tandem ROM/RCM reaction to install the macrocycle fused butenolide ring and an allylboration/lactonization to build the α-methylene-γ-butyrolactone. The chemical syntheses have enable the determination of the hitherto unknown stereochemical configurations of this family of natural products. This efficient synthetic sequence can not only provide abundant ovatodiolide, but also result in several ovatodiolides (including isoovatodiolide and 4,5-epoovatodiolide) or derivatives for further biological assays.

More importantly, the research team discovered that isoovatodiolide exhibited superior HCSCs selectivity compared to ovatodiolide and the drug candidate ACT001 in decreasing CD133 protein expression. In the tumorsphere forming assay, the number of tumorspheres formed in the isoovatodiolide-treated group was around 15-fold less than the control group.

These properties are highly desirable for selecting HCSCs drug candidates in preclinical study. The highly productive total synthesis and exciting anti-HCSCs activities, along with the uncertain mechanism of action, warrant ovatodiolide as a promising beginning for the discovery of novel HCSCs-targeting drugs.

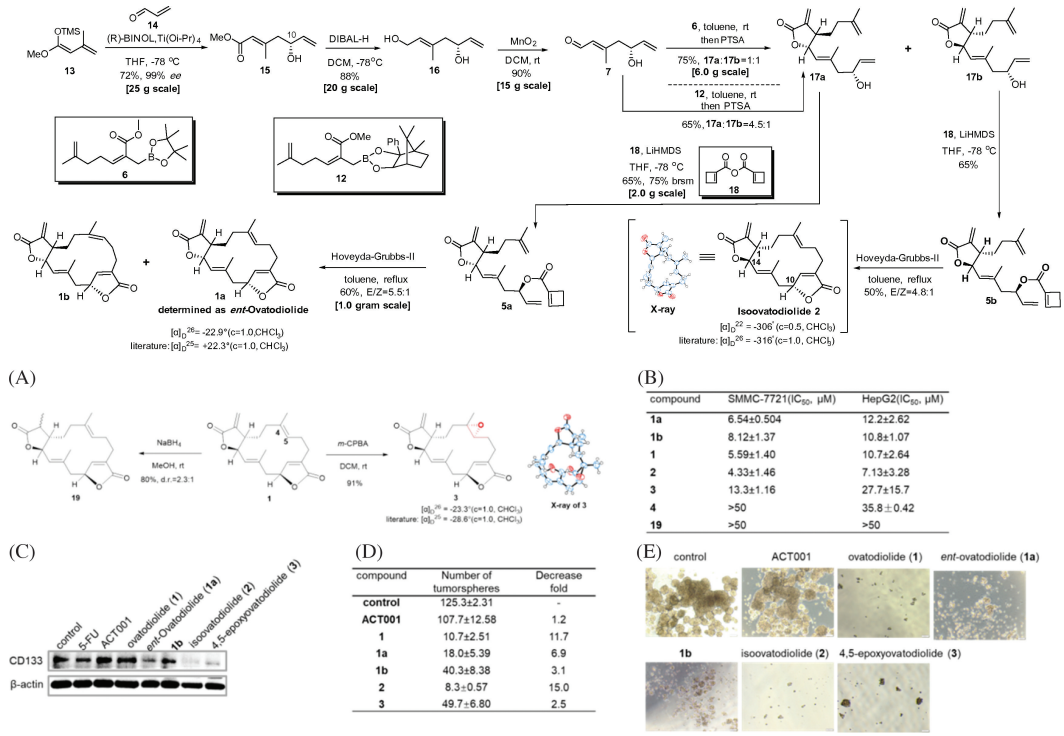

Figure Key steps in total synthesis of *ent*-ovatodiolide and biological results of ovatodiolides against HCSCs.