Enantioselective Total Synthesis of Roridin E

Seungbin Park,[a] Sang J. Chung*[a]

[a]*Department of Biopharmaceutical Convergence, Sungkyunkwan University, Suwon, 16419, Republic of Korea.*
E-mail: sjchung@skku.edu

Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer which has no effective therapeutic options. So, the development of new therapeutic agents for the treatment of TNBC has become an urgent medical need. Type D trichothecene which mycotoxin is highly potent for the development of anti-breast cancer drugs. Roridin E, a kind of type D trichothecene, showed IC_{50} value of less than 50 pM against TNBC cell lines.[1] Therefore, Roridin E has potential for development as a therapeutic agent for TNBC.

We have developed an enantioselective total synthesis of Roridin E divided into verrucarol domain and macrocyclic ring domain. A key feature of verrucarol synthesis is catalytic asymmetric alkylation of β-keto esters that allows formation of a highly enantioselective quaternary stereocenter. Phase transfer *N*-spiro C_2-symmetric chiral quaternary ammonium salt *(S,S-1)* catalyst was used to facilitate the direct stereo controlled formation of key core bicyclic lactone which enabled efficient and concise total synthesis. Macrocyclic ring part was synthesized from L-threonine which is easily commercially available. The present synthesis is based on Sandmeyer reaction, Horner-Wadsworth-Emmons reaction, DIBAL-H reduction of α,β-unsaturated ketone and Jones oxidation. We have completed synthesis of Roridin E for the development of therapeutic candidates targeting TNBC.

References

[1] Seoung Rak, Lee.; Soonja, Seok.; Rhim, Ryoo.; Sang Un, Choi.; Ki Hyun Kim. *J. Nat. Prod.* **2019***, 82, 1,* 122–128.