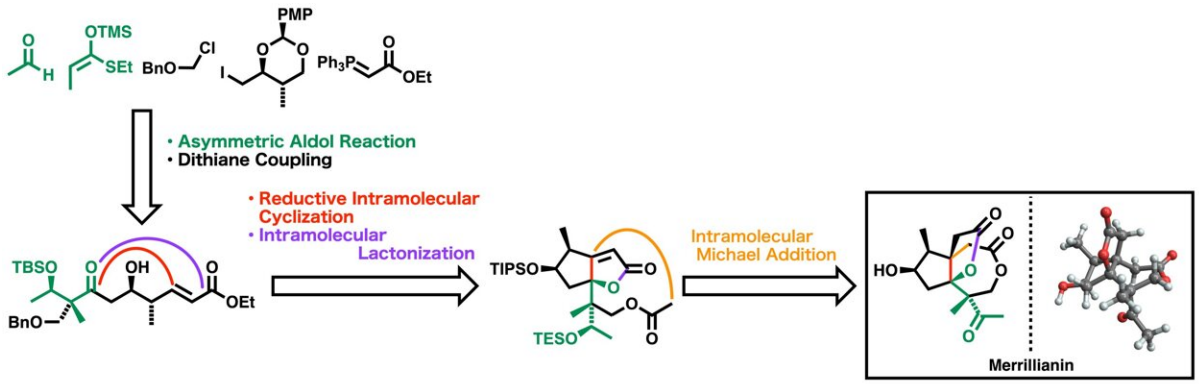
Scientists achieve first total synthesis of potentially anti-rheumatic sesquiterpene merillianin

February 15 2024



The artificial synthesis of merrillianin opens doors to developing drugs for treating nervous system diseases such as rheumatism and neuralgia. Credit: Isamu Shiina, TUS Japan

An avenue that scientists are currently exploring for the development of novel pharmaceuticals involves the synthesis of bioactive compounds found in Chinese herbal medicine. This collaborative effort, combining traditional knowledge with modern scientific methods, focuses on pharmaceutically relevant compounds found in medicinal plants for large-scale synthesis.

An important compound in this context is merrillianin, a type of illicium

sesquiterpene that was isolated in 2002 from the fruit of Illicium merrillianum, a plant that belongs to the same genus as star anise. Illicium sesquiterpenes are naturally occurring compounds that hold promise for treating nervous system diseases.

However, merrillianin has a complex structure with a central arrangement of six consecutive stereogenic carbon centers, including three quaternary carbon stereogenic centers and three rings fused to two carbons. This complexity has posed challenges for the artificial synthesis of merrillianin, leading to limited progress in its practical application since its isolation.

In a breakthrough study published in the journal *Organic Letters*, a research group led by Assistant Professor Takatsugu Murata and Professor Isamu Shiina from Tokyo University of Science (TUS) succeeded in synthesizing merrillianin, opening doors to its artificial synthesis almost 20 years after the compound was isolated.

"Illicium sesquiterpenes are a group of compounds that are expected to be effective against neurological diseases, but their highly oxidized and ring-fused structures have made it difficult to synthesize them artificially. However, we have synthetic technique and knowledge about the synthesis of highly complicated compounds such as taxol," says Dr. Murata.

"Therefore, we wanted to perform the world's first artificial synthesis of merrillianin, which is expected to have anti-rheumatic activity, and create a lead compound that can contribute to the treatment of neurological diseases."

Merrillianin can be obtained with yields as high as 80% via the Wacker-type oxidation of a dilatone. However, the challenge lies in efficiently preparing the precursor compounds for the dilatone. To address this, the

researchers employed a total of 30 reaction steps, covering the synthesis of precursors to the final production of merrillianin. The process commences with the Mukaiyama aldol reaction, which involves enol silyl ether and acetaldehyde.

This reaction leads to the creation of a dithioacetal, a compound that includes a quaternary carbon stereogenic center. Subsequently, the dithioacetal undergoes a series of reactions with an iodo compound, resulting in the formation of α, β-unsaturated ester possessing an aldol structure.

The next steps involve a reductive intramolecular cyclization of this compound to cyclopentane, followed by an intramolecular Michael's reaction for the formation of tricyclic dilactone with a total yield of 1.6%. Tricyclic dilactone is a key intermediate for the commercial production of a wide variety of Illicium sesquiterpene compounds, including merrillianin.

The researchers point out that if merrillianin has high bioactivity, the amount required for treatment would be very little. (According to the isolation report, 3 mg of merrillianin was isolated from 30 kg of fruit.) Interestingly, it would be possible to examine its bioactivity using the synthetic version prepared by the group.

The synthesis method also revealed the absolute configuration of merrillianin, which, so far, had only known relative configurations. The proposed synthesis method for merrillianin represents another milestone for the research group, which previously succeeded in synthesizing the naturally occurring tanzawaic acid B found in the fungus Penicillium citrinum that has the potential for developing antibiotics against multidrug-resistant bacteria.

The research group's ongoing dedication to synthesizing compounds with

interesting biological activities holds promise for future discoveries in the field of drug development. Species of the Illicium genus have been used as medicinal herbs for the treatment of conditions like rheumatoid arthritis and traumatic injuries, and the synthesis of merrillianin could also contribute to advancements in these areas.

"The proposed synthesis method for merrillianin will help develop suitable drugs to treat nervous system diseases such as rheumatism, and neuralgia, improving neurological disease prognosis and enhancing patient quality of life," concludes Prof. Shiina.

More information: Isamu Shiina et al, Total Synthesis of the Sesquiterpene (−)-Merrillianin, *Organic Letters* (2023). DOI: 10.1021/acs.orglett.3c03877

Provided by Tokyo University of Science