Making puffer fish toxin in a flask

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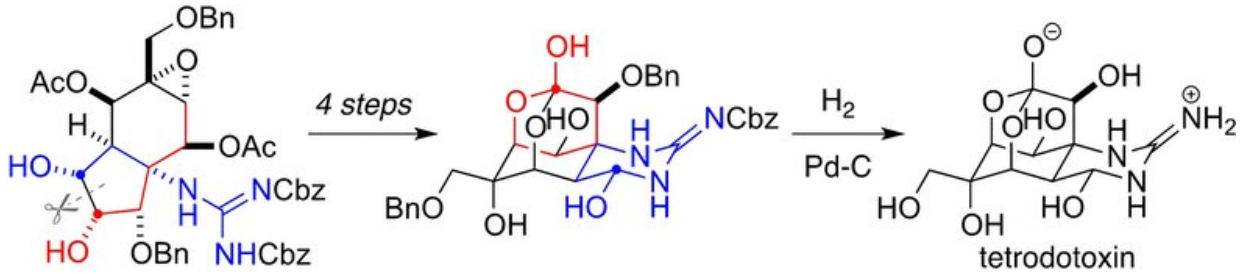

Credit: Angewandte Chemie

In Japan, puffer fish is considered a delicacy, but the tickle to the taste buds comes with a tickle to the nerves: fugu contains tetrodotoxin, a strong nerve toxin. In low doses, tetrodotoxin is shown in clinical trials to be a replacement for opioids for relieving cancer related pain. In the journal *Angewandte Chemie*, scientists have introduced a new route for the total synthesis (complete production of a natural product from current materials) of tetrodotoxin.

Eating fugu initially elicits a light prickling in the mouth, which can have a relaxing or euphoric effect—assuming the cook knows what he or she is doing. If the fish is incorrectly prepared, things can end badly: Tetrodotoxin blocks the voltage-gated sodium channels, and thus nerve impulses. This may result in paralysis and even difficulty breathing. In the EU, the importation and preparation of fugu as food is forbidden. In Japan and other countries, a number of strict laws regulate the

preparation and consumption of puffer fish products. However, there are occasional deaths.

In very low doses, tetrodotoxin is a pain-reliever and could be used to treat severe pain, such as in the treatment of cancer. Early clinical studies are underway. It is thus important to develop a simple, reliable synthetic method to provide access to tetrodotoxin and structurally related compounds—for research and eventually robust and inexpensive production.

Tetrodotoxin has a unique, highly complex, cage-like structure (a tricyclic orthoester) as well as a cyclic guanidine component. Guanidine is an important component of many biological molecules, including arginine. The tetrodotoxin framework is highly oxidized and has five hydroxy groups (–OH) as substituents. A number of different total syntheses of tetrodotoxin have previously been published, including one from researchers led by Satoshi Yokoshima at the Nagoya University (Japan) in 2017. Now Yokoshima and his team have introduced another, novel total synthesis.

The key step is a Diels-Alder reaction between a known starting compound (an enone) and a silicon-containing component (a siloxyldiene) to make a tricyclic intermediate with the right spatial (steric) arrangement to allow for proper attachment of the hydroxy groups and later, construction of the "cage." Formation of the guanidine component begins with introduction of an amino group—either by a conventional four-step method or a three-step reaction sequence based on a newly developed conversion of a terminal alkyne to a nitrile. Finally, the "bridges" needed for formation of the cage are built up over several steps. A cross-coupling reaction was used for introducing a carbon substituent (hydroxymethyl group) on the cage. Employing other components for the cross coupling reaction might lead to producing structurally related molecules.

More information: Keigo Murakami et al. Total Synthesis of Tetrodotoxin, *Angewandte Chemie International Edition* (2020). DOI: 10.1002/anie.201916611

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