A more concise way to synthesize tetrodotoxin

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A small international team of researchers has developed a way to synthesize tetrodotoxin (TTX) using far fewer steps than prior methods. In their paper published in the journal *Science*, the group describes their process and the steps they took to improve its efficiency.

TTX is most well-known for its association with pufferfish—the fish do not make the toxin though; it is biosynthesized by bacteria that infect the creature. The bacteria also infect other less well-known species, who also coopt the chemical as a means of defense. Prior research has shown that the reason TTX is so toxic to humans and other animals is that it blocks voltage-gated sodium channels in the membranes of nerve cells, resulting in disruption of signals, which leads to paralysis and death as organs fail.

Since its discovery, TTX has been used as a learning tool in the bioscience community. It has also been the subject of analgesic research—if a way could be found to control application of the chemical in the body, it could be used to eliminate neural activity, resulting in numbness and the absence of pain.

Because of its potency and the role it can play in disrupting neuronal activity, scientists have taken great interest in TTX. They have put much effort into recreating it in the lab. But because the chemical is so complex, it took years of work—it wasn't until 1972 that a method was devised. Unfortunately, that method was quite complex—versions of it involve conducting 25 to 67 steps. It was also inefficient, yielding just 1%.

In this new effort, the researchers have rethought some of the steps involved and have found a way to reduce the steps to 22 and bring the efficiency up to 11%. Cutting down the number of steps reduces the time and cost involved, and the researchers note that their process can by scaled up to manufacturing standards. They also note that the reactions used in the process are quite versatile, which means it could be used to make TTX derivatives that are perhaps less toxic and more useful.

More information: David B. Konrad et al, A concise synthesis of tetrodotoxin, *Science* (2022). DOI: 10.1126/science.abn0571