New method allows easy, versatile synthesis of lactone molecules

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Chemists at Scripps Research have unveiled a method for turning cheap and widely available chemicals known as dicarboxylic acids into potentially very valuable molecules called lactones.

Lactone structures are common in biologically active natural molecules; they can be found, for example, in vitamin C and in the bacterial-derived antibiotic erythromycin. Chemists have long had techniques for synthesizing lactones, but these techniques are quite limited in what they can produce. The achievement, reported May 26, 2022, in *Science*, makes the construction of diverse, complex lactones easier than ever.

"This method should be very broadly useful for developing new pharmaceuticals, polymer materials, perfumes and many other chemical products—we're already getting queries from interested manufacturers," says Jin-Quan Yu, Ph.D., the Frank and Bertha Hupp Professor of Chemistry at Scripps Research.

Yu and his laboratory are renowned for their innovations in molecule building, especially with regard to "C-H activation." This involves the use of specially designed catalyst molecules to remove a hydrogen (H) atom from a carbon (C) atom on an organic molecule, and to replace the hydrogen atom with a more complex cluster of atoms.

The general goal is to develop a set of methods for doing C-H activation selectively to any chosen carbon atom on a starting molecule—and the dream is to use those methods to turn cheap and relatively simple molecules into complex and valuable drugs, plastics and other molecules.

In this case, Yu and his team aimed to perform particularly difficult, site-selective C-H activations to convert cheap and readily available dicarboxylic acids into highly valuable lactones. Dicarboxylic acids, despite their complicated-seeming name, are relatively simple molecules, and are ideal starting materials for many types of chemical synthesis. But chemists attempting C-H activation of dicarboxylic acids have traditionally faced steep hurdles.

"C-H activations at sites on a dicarboxylic acid that are far away from

one of its carboxyl groups have been very difficult to date," Yu says. "Being able to target distant carbons and/or nearer carbons, selectively by catalyst control, has seemed an impossible dream."

The feat achieved by Yu and his team, including first author Sam Chan, Ph.D., a Croucher Foundation Postdoctoral Fellow in the Yu lab, was a set of methods employing palladium-based catalysts to freely achieve C-H activations on easy- and hard-to-reach carbons on a dicarboxylic acid.

"Over the past two decades, we managed to develop good methods for C-H activation two carbons away from a carboxyl, but now with our new methods we can also reach one more carbon away, and with the freedom to choose between the two sites, we can readily access new chemical space in drug discovery," Yu says. "In addition, the remaining carboxyl group on the dicarboxylic acid can be used to make further modifications, so essentially with this approach one can build a very broad range of complex lactone compounds."

Yu and his team demonstrated the ease and utility of their new methods by synthesizing—from cheap dicarboxylic acids—two complex natural lactones, a fungal molecule called myrotheciumone A, which has been investigated for anticancer properties, and the plant lactone pedicellosine.

The chemists are now using the new methods to generate hundreds of diverse lactone structures, whose properties—and potential to be developed into future pharmaceuticals—they are exploring in collaboration with the laboratory of Ben Cravatt, Ph.D., the Gilula Chair of Chemical Biology at Scripps Research.

"We are also using our methods to develop improved processes for ton-scale production of lactones used by chemical products manufacturers," Yu says.

More information: Hau Sun Sam Chan et al, Catalyst-controlled site-selective methylene C–H lactonization of dicarboxylic acids, *Science* (2022). DOI: 10.1126/science.abq3048