The transformation of an advanced synthetic intermediate into a whole family of naturally occurring molecules

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A research collaboration between A*STAR and the University of Oxford has generated a simple and efficient approach for assembling organic molecules that show promise as therapeutic drugs. The team drew on a strategy favored by the pharmaceutical industry, devising a synthetic route to an advanced intermediate that, late in the synthesis, could be diversified into five target molecules.

"Late stage divergence from a versatile intermediate enables rapid access to a diverse range of drug-like molecules for drug discovery," explains Jayasree Seayad from the A*STAR Institute of Chemical and Engineering Sciences, who co-led the work alongside Darren Dixon from Oxford.

The team used an iridium-catalyzed reaction to synthesize five diverse members of a family of naturally occurring molecules—aspidosperma alkaloids—derived from a flowering plant endemic to South America. Their method enabled each target molecule to be synthesized in fewer than ten steps from simple, readily available materials.

Pivotal to the synthesis was the creation of a suitably advanced intermediate. The team chose a nitrogen- and oxygen-containing cyclic compound known as a δ-lactam. Treatment with the iridium catalyst and a reducing agent, removed the oxygen atom from this stable compound, helping convert it into a highly reactive enamine. The enamine molecule

then reacted with its own tail, triggering a cascade of bond-forming reactions to produce a pentacyclic target molecule called minovine and a quadracyclic natural product vincaminorine.

"The enamine intermediate undergoes two different reaction pathways in a cascade manner to form two skeletally distinct natural alkaloids in a single-pot." Seayad says.

By making simple, one-step changes to the stable δ-lactam advanced intermediate before converting it into the reactive enamine, the team could also synthesize several other aspidosperma alkaloids.

As with any complex organic molecule, each of the target molecules made by the team can exist in two possible forms, known as enantiomers, which are mirror images. One form is found in nature, while the other is not—and both exhibit quite different chemical responses.

To interact with the body as intended, most such drug molecules are also produced in a single-enantiomer form. Currently, the team's approach produces both possible enantiomers in equal quantities. "The next step in our work will be to expand this synthetic strategy to selectively synthesize these natural alkaloids," Seayad says.

More information: Peng Wen Tan et al. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates, *Angewandte Chemie International Edition* (2016). DOI: 10.1002/anie.201605503

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