Of cyclops and lilies: New strategy for the synthesis of cylcopamine, a potential cancer treatment

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(PhysOrg.com) -- In 1957, shepherds in Idaho (USA) discovered that when pregnant sheep ate lilies of the species Veratrum californicum (corn lily, California false hellebore), their lambs were born with only one eye in the center of their foreheads, like a cyclops. The trigger for this was found to be the alkaloid cyclopamine. Cyclopamine has proven to be an effective candidate for cancer therapy in adult humans and is now undergoing clinical trials.

A research team at the Universities of Leipzig (Germany) and Thessaloniki (Greece) has now developed a new synthetic pathway for the production of cyclopamine. As they report in the journal *Angewandte Chemie*, the scientists, led by Athanassios Giannis, are confident that their research results will help to broaden our understanding of the structure-activity relationships of cyclopamine and to develop cyclopamine analogues with tuned bioactivities.

Cyclopamine is the first inhibitor of the hedgehog signal-transduction pathway, which is used by cells to react to external signals. The signaling pathway is named for its ligand “hedgehog”, a signal protein that carries out an important function in embryonic development. Malfunction of this signaling pathway leads to massive deformations in the course of embryonic development, such as cyclopia, and can cause cancer in adults. Inhibition of this pathway is a new possible cancer treatment.

Until now, there has been no efficient synthesis for cyclopamine. The structure of this unusual steroidal alkaloid contains many peculiarities that make synthesis difficult. The German and Greek team has now overcome these difficulties to develop an efficient twenty-step synthetic strategy starting from commercially available dehydroepiandrosterone, a natural steroid hormone.

The strategy is based on biomimetic and diastereoselective transformations. The researchers achieved an overall yield of 1 %, which is a good result for such a tricky synthesis. In addition, small modifications in the reagents used allow this strategy to be used to produce cyclopamine analogues that do not occur in nature. The scientists aim to use these analogues to further examine the biological activity of this interesting natural product and then to adjust the activity to develop a new anti-tumor agent.

More information: Athanassios Giannis, Synthesis of Cyclopamine Using a Biomimetic and Diastereoselective Approach; Angewandte Chemie *International Edition*, doi: 10.1002/anie.200902520

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