The Beaver as Chemist: Total Synthesis of Enantiomerically Pure Nupharamine Alkaloids from Castoreum

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(PhysOrg.com) -- Castoreum, the dried scent glands of the Canadian beaver, was once one of the most valuable scent components derived from animals. Castoreum contains a complex mixture of substances, including a number of compounds known as nupharamine alkaloids. Many of these have been structurally characterized. Researchers working with Horst Kunz at the University of Mainz (Germany) have now, as they report in the journal *Angewandte Chemie*, determined the stereochemistry (precise spatial structure) of another castoreum component by using a total synthesis. A total synthesis is the complete chemical synthesis of a complex organic natural substance from simple, easily attainable starting materials.

Beavers use their fat- and pheromone-containing gland secretions to groom their fur and to mark their territory. In the past, the resin-like content of the dried glands was used as medicine to treat various complaints, such as cramps, “hysteria”, and nervousness. In antiquity it was even used to treat epilepsy. Castoreum’s effectiveness can be explained by the salicylic acid it contains—aspirin is also based on this substance. Castoreum was once in such demand that the beaver was threatened with extinction. Today, there are special beaver farms where the beavers rub their secretions off onto special collection containers. In addition, castoreum is now only used for homeopathic remedies and in some perfumes.

The team from Mainz undertook the synthesis of a minor component (5-(3'-furyl)-8-methylindolizidine), which makes up less than 0.0002% of castoreum. In principle, the structure of this nupharamine is known. It has an indolizidine skeleton (a special ring system made of one six-membered and two five-membered rings). However, one detail has remained unknown: the stereochemistry at one of the carbon atoms of the six-membered ring. The four bonds of a carbon atom point toward the corners of a tetrahedron. If there are four different bonding partners, there are two possible spatial arrangements possible, which are mirror images of each other. This type of carbon center is called "chiral".

One of the two possible versions of the nupharamine, the cis-trans form, has previously been produced enantioselectively. The German team has now achieved the enantioselective total synthesis of both versions—the all cis form for the first time. To do this they used a carbohydrate as a chiral auxiliary. This is a molecule that is attached to a starting material in order to shield one side of the molecule in subsequent reaction steps so that only the desired stereochemical form of the product is formed.

Spectroscopic and mass-spectrometric analyses of both synthetic products and the nupharamine isolated from natural castoreum showed that the all-cis form is identical to the natural product.

More information: Horst Kunz, Universität Mainz, Stereoselective Synthesis of Enantiomerically Pure Nupharamine Alkaloids from Castoreum, *Angewandte Chemie International Edition*, doi: 10.1002/anie.200805606

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