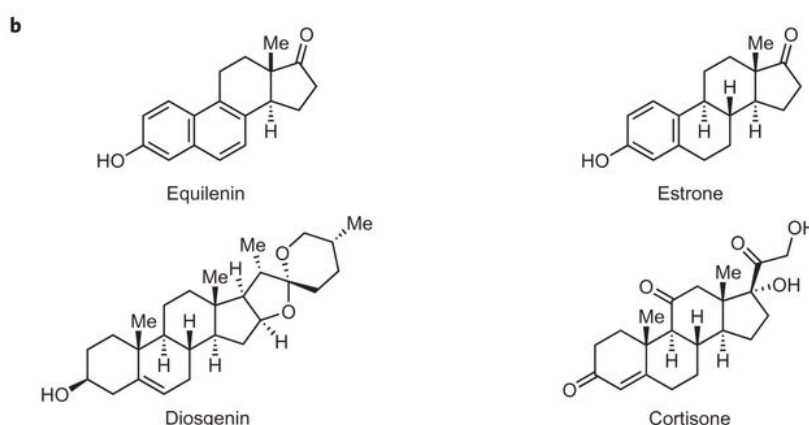
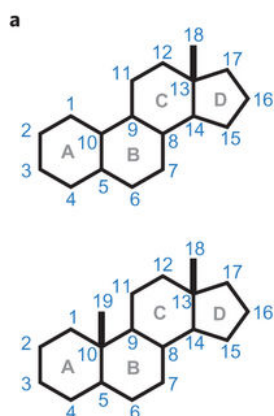
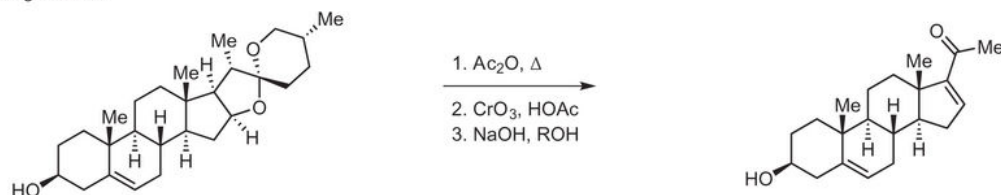


# Streamlined process opens drug development to a new class of steroids

September 25 2017

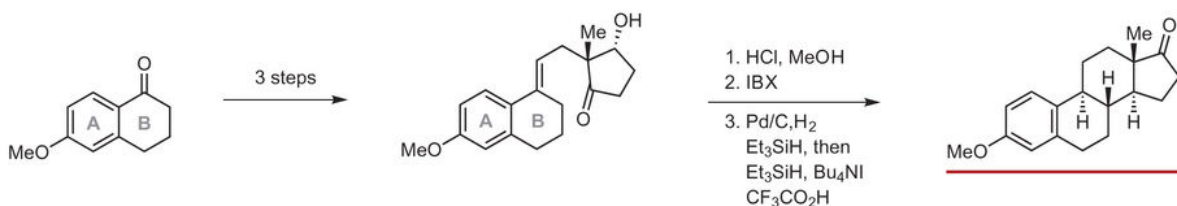


**c** Marker degradation:



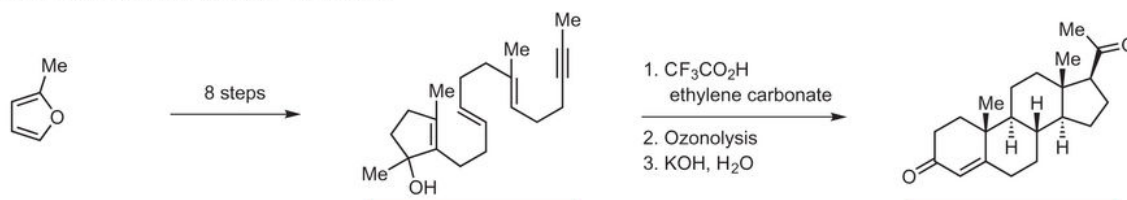
Not useful for ent-steroids and difficult to employ for highly oxygenated targets

Corey's asymmetric modification of the Torgov synthesis of oestrone methyl ether:



Challenges surface when targeting varied ABC tricyclic domains

Johnson's biomimetic synthesis of (±)-progesterone:



Limited utility for efficiently accessing functionalized/oxygenated steroidal targets

Introduction to steroid structure and synthesis. a, The general steroid tetracyclic skeleton. b, Examples of natural steroids. c, Selected approaches to steroid synthesis using semisynthetic and de novo strategies. Credit: (c) *Nature Chemistry* (2017). DOI: 10.1038/nchem.2865

Researchers at Dartmouth College have developed a technique to produce synthetic steroids that could pave the way for a cascade of new drug discoveries. The process, published in the journal *Nature Chemistry*, facilitates access to rare, mirror-image isomers of naturally occurring steroid structures.

The technique, based on a series of new chemical reactions, significantly reduces the expense and time needed to develop therapeutics from a pharmaceutically privileged yet underexplored collection of molecules.

"This is a fundamentally new molecular strategy for steroid construction," said Glenn Micalizio, the New Hampshire Professor of Chemistry at Dartmouth. "This technology allows the preparation of either [mirror-image](#) isomer with equal ease, but with unprecedented efficiency."

The core molecular structure of [steroids](#) is a proven backbone in [drug](#) development. More than 100 different steroid molecules are approved by the U.S. Food and Drug Administration as therapeutics for a wide range of symptoms and diseases including inflammation and pain, cancer and bacterial infection.

Steroidal therapeutics arguably make up the most successful class of medicine inspired by a natural product. All known drugs in this class share a common structure comprised of only one of two possible mirror

image skeletons - known as enantiomers. Such agents are typically available from chemical transformations of natural and readily available steroids.

According to researchers, molecules based on the unnatural mirror image isomer of steroids form the foundation of a vast collection of underexplored potential medicines. While these compounds share the basic drug-like physical properties of the natural class, they boast complementary 3-D structures with broad potential in the clinic.

"With this advancement, we now have the opportunity to investigate fertile regions of chemical space for the identification of untold numbers of unique, medically relevant agents," said Micalizio.

The process developed in the [Micalizio Laboratory at Dartmouth](#), produces steroidal structures of either enantiomer with what researchers describe as unprecedented efficiency. Using inexpensive and abundant starting materials, the new class of synthetics can be produced in as few as five chemical steps.

The advance is based on a chemical reaction discovered in 2014 by Micalizio that forges half of the steroid [structure](#). The breakthrough was made possible by inventing a simple procedure to advance these intermediates to steroid structures of either mirror image series.

While chemical synthesis has previously been described as a route to unnatural enantiomers of steroids, the process pioneered at Dartmouth allows scientists to more easily investigate their medicinal properties. Importantly, the time and cost of preparing collections of new compounds in this class - a requirement of most modern [drug discovery](#) efforts - has been drastically reduced.

"This is by far the most concise and flexible route to make a wide

variety of novel steroids," said Micalizio.

To show the value of the technology in [biomedical science](#), the research team demonstrated that one of the molecules prepared in their initial study has potent and selective growth inhibitory properties against three different human cancer cell lines.

"We're not just saying these things have potential," said Micalizio, "here is one example from the relatively small number of compounds that we produced that proves their potential value as anti-cancer agents."

Since synthetic mirror image isomers are not readily available from natural sources, pursuit of this class of drugs and their clinical value is dependent on the efficiency with which organic chemists can prepare them.

"The science of synthetic organic chemistry is an essential component of drug discovery, and advances in this field are directly responsible for our recent discovery," said Micalizio.

"Without the ability to create new collections of molecules, it is difficult to pursue many potentially exciting new directions in drug discovery. As such, advances in [chemical](#) synthesis, like this one, can have profound and rippling effects on biomedical science," Micalizio added

Building on the challenge to invent chemistry that fuels discovery in biomedical science, Micalizio's lab hopes to develop a new technology platform to explore unnatural isomers of steroids for the development of therapeutics.

**More information:** Wan Shin Kim et al, Synthetic nat- or ent-steroids in as few as five chemical steps from epichlorohydrin, *Nature Chemistry* (2017). [DOI: 10.1038/nchem.2865](https://doi.org/10.1038/nchem.2865)

Provided by Dartmouth College

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