Total Synthesis of Steroids

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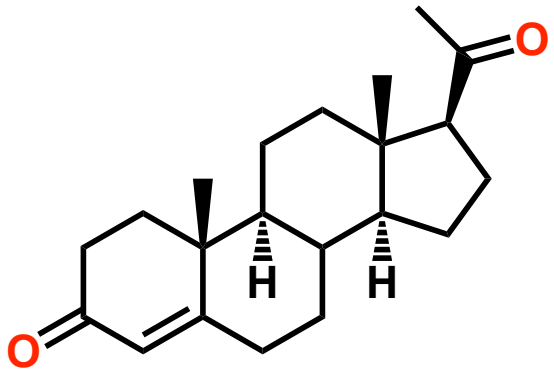
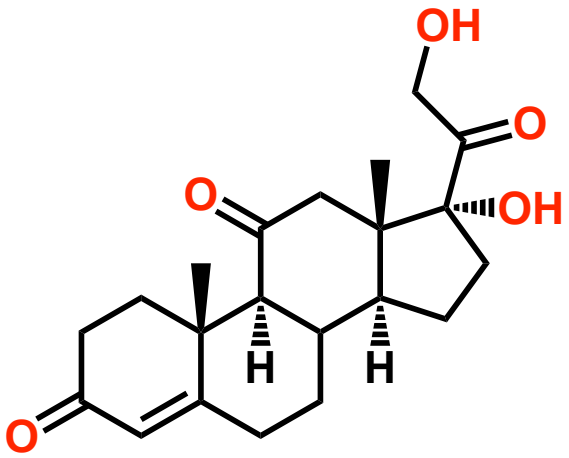
CH-588 Course on Organic Synthesis

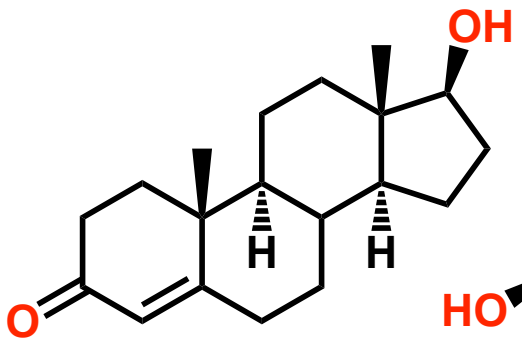
Birth of Commercial Synthesis of Steroids



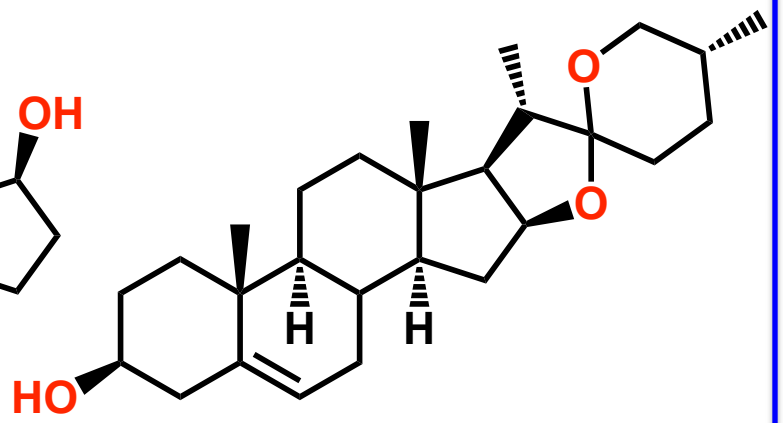
Progesterone



Cortisone



Testosterone



Diosgenin

In drug discovery program, 1930's were considered as 'The decade of the Sex harmones'

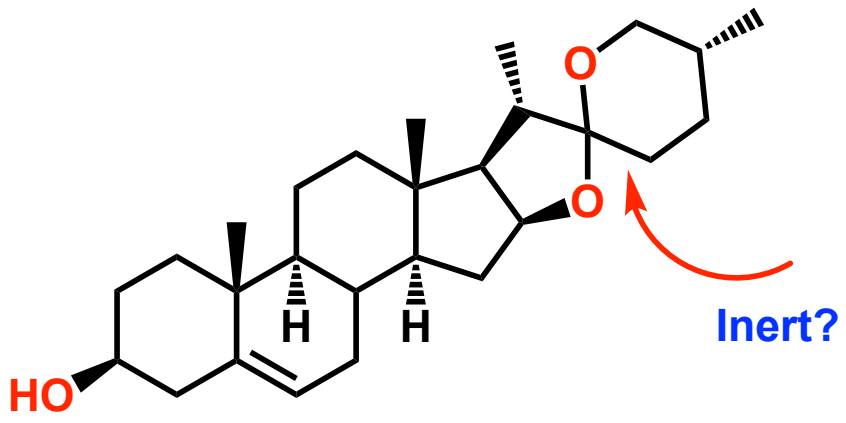
Molecular structures of male sex harmone 'testosterone', female sex harmone 'estrone' and pregnancy harmone 'progesterone' were determined and used as drugs.

Much attention was focused on 'progesterone' because of its medicinal properties in the treatment of menstrual disorders.

Unfortunately, the high cost associated with 'progesterone' restricted its use as a drug.

The cost of progesterone and other related steroids fell dramatically in 1940's with the creation of a Mexican company.

Steroids from Diosgenin



Diosgenin

In 1938, Russell Marker from Penn State University, proposed the correct structure for 'diosgenin', a plant steroid isolated from *sarsaparilla*.

The side chain of 'diosgenin' was initially considered as inert but Marker could cleave that using a clever reaction.

In 1944, Russell Marker achieved the first practical synthesis of 'progesterone' from diosgenin.

As the cost of this route is expensive, Marker started looking at other sources to get 'diosgenin'.

In his search for better source for diosgenin, he appointed several botanists and launched plant collection trips in South Western States of America.

This low-cost process of making 'progesterone' became useful in making the anti-inflammatory drug 'cortisone'

In 1941, while going through a botany textbook, he saw a picture of 'dioscorea' that grows in Mexico

The root of this plant weighs about '100 Kilos'

Marker's Mexican Journey & Entrepreneurship

In 1942, he went to Mexico by bus and took 2 bags with large roots of this plant and returned. Unfortunately, it was stolen during the bus trip itself

He bribed a policeman and recovered a 50 pound root to Penn State University

Back at Penn State, he could isolate 'diosgenin' in satisfactory yield from this root.

As this research program was funded by Parke-Davis, he approached them to commercialize this process.

Not only they refused, other pharma companies also refused

He thought that the only way to succeed is to do it himself

He went to Mexico again, collected 10 tons of this root, and talked to a local small scale extractor and asked him to extract the root with alcohol and give the syrup

He gave him one third of the syrup and came to New York with the remaining.

He converted this syrup into 80 Kgs of 'progesterone'

He sold 1 g of 'progesterone' for 80 US $

He decided then to form a company to start this manufacturing and he thought the best place to do would be Mexico

He found two entrepreneurs Somlo and Lehmann and together they signed an agreement to form a new company called 'Syntex'

Marker's Degradation Process

Now, they could sell 'progesterone' for 50 $ per gram

In 1944, Marker then resigned from Penn State University and moved to Syntex .

In 1945, there was a dispute in profit sharing and Marker left the company. As he himself was doing the whole work with coding the reagents, the other two couldn't repeat this process.

Marker moved out in 1946 and started a new company 'Botanica-mex'

He was with this company until retirement

Meanwhile, Syntex was looking for someone who will continue this work

They found 'George Rosengranz', who revived this work and 'Syntex' again started selling 'progesterone'

He extended this work to other steroids like testosterone etc.,

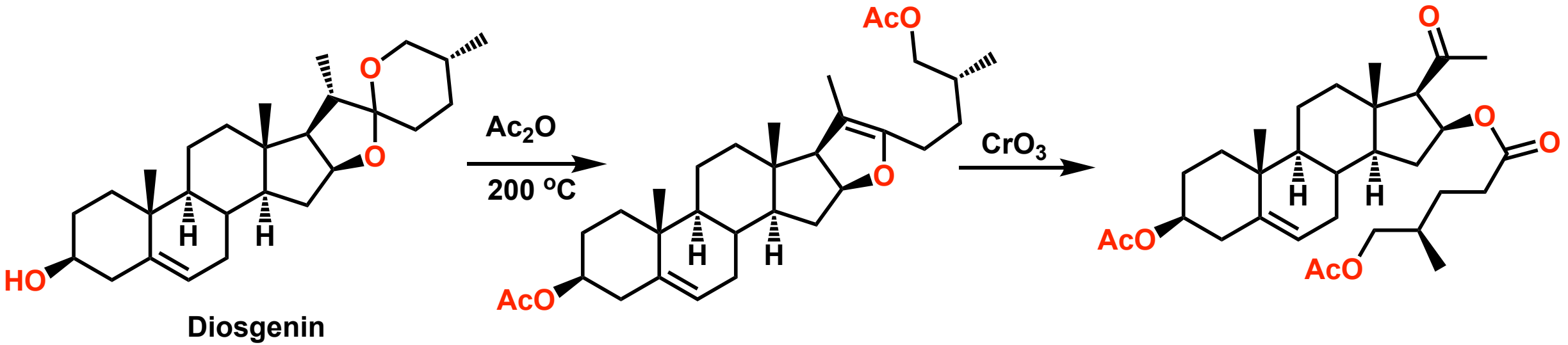
Syntex also later collaborated with Prof. Carl Djerassi

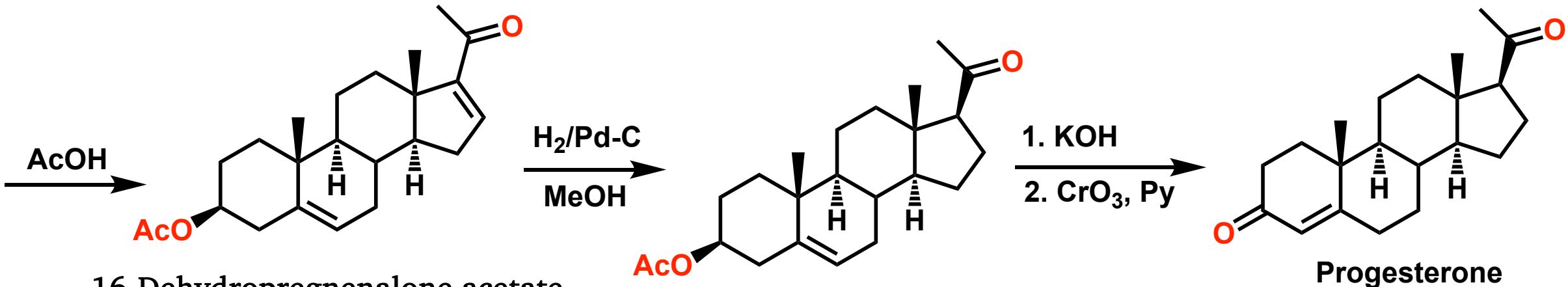
Carl Djerassi succeeded in converting 'diosgenin' to 'cortisone'

Existing Merck process took 36 steps to make 'cortisone'

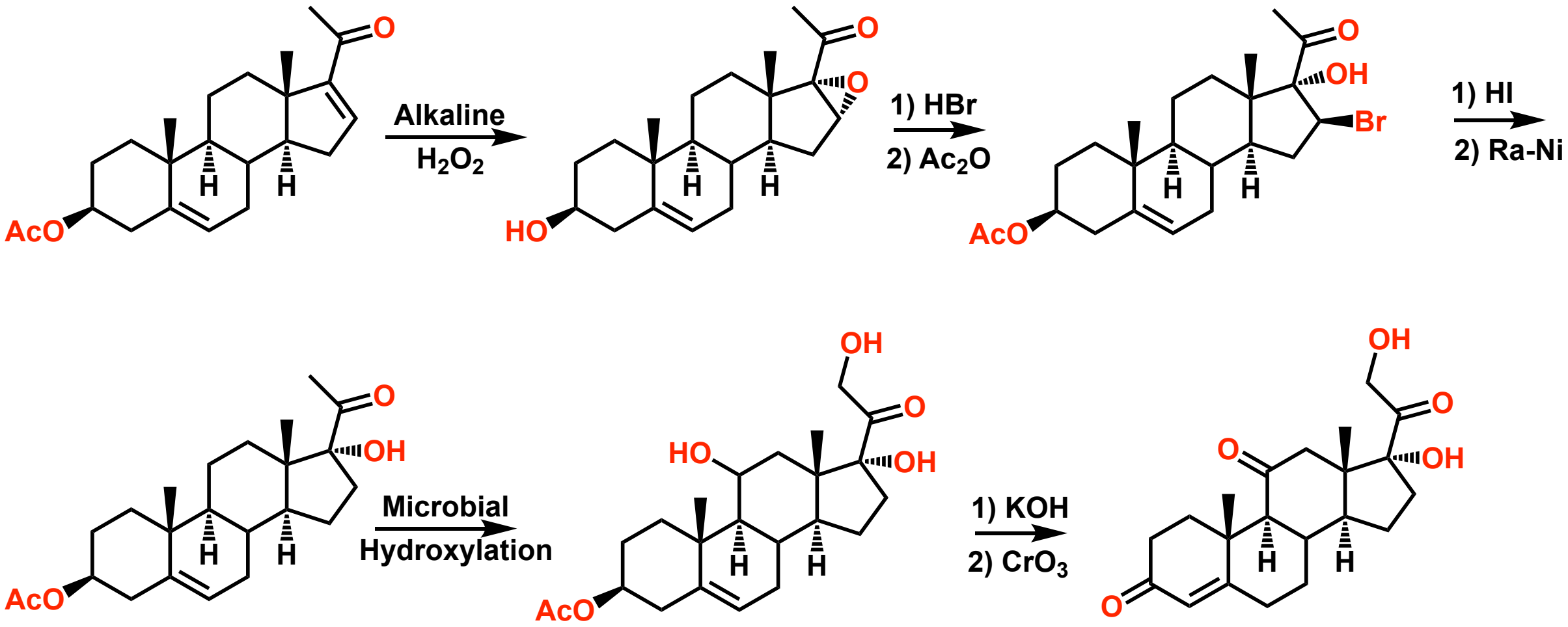
Upjohn Co., invented a new microbiological process to oxidise progesterone and the product could be easily converted to 'cortisone'

Marker's Modified Degradation Process

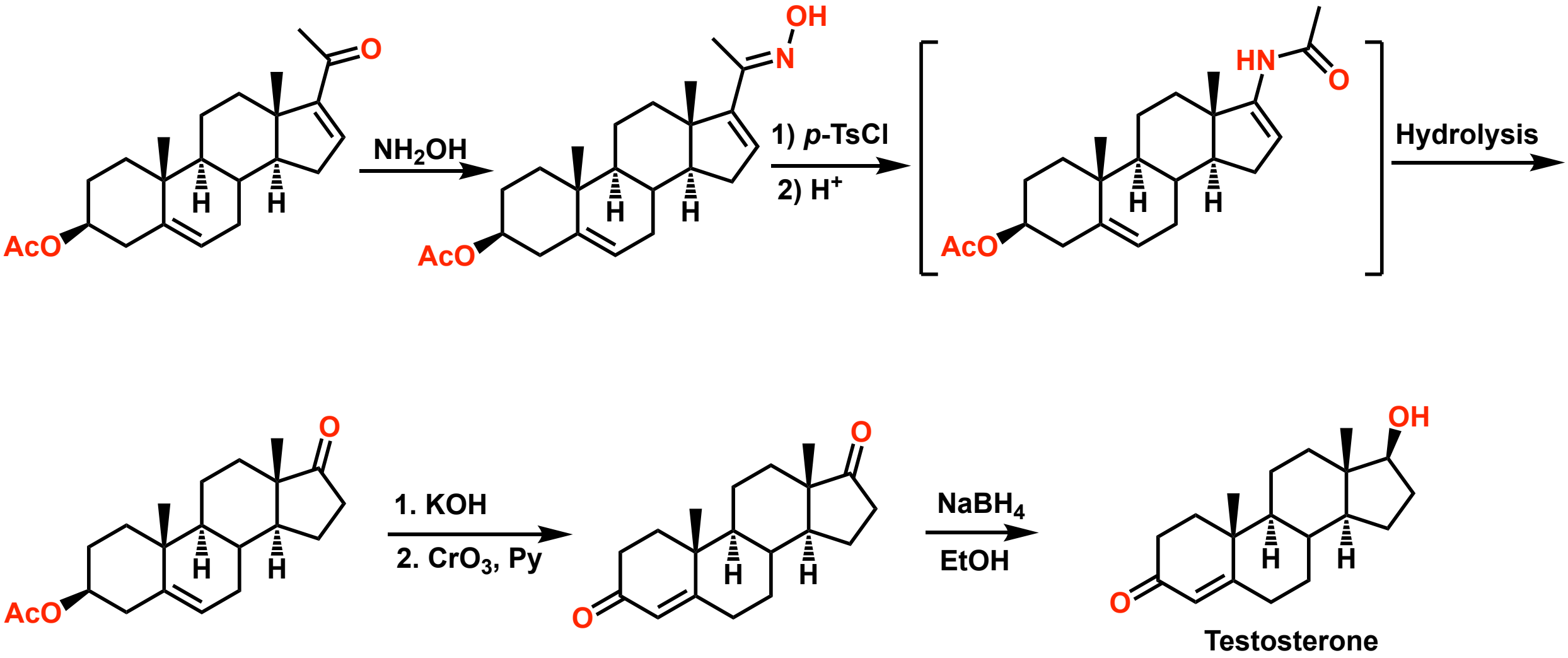




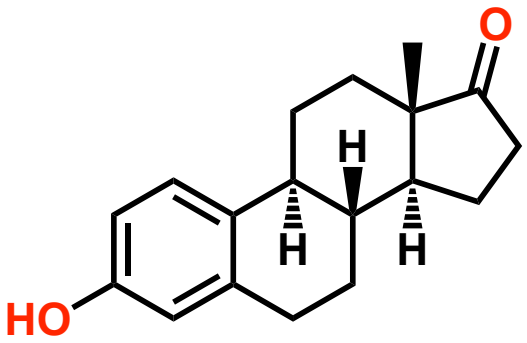
16-DPA to Cortisone



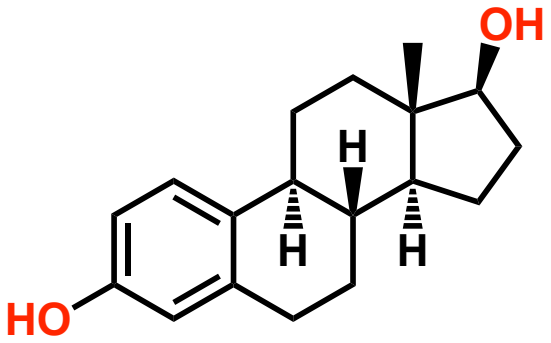
16-DPA to Testosterone



Total Synthesis of Estrone



Estrone



Estradiol

Estrone is excreted in the form of estrone sulfate in urine

First steroid harmone to be discovered in 1929

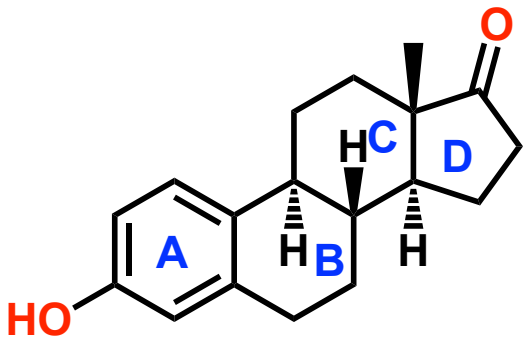
Four contiguous chiral centers

Angular methyl group

Trans-Anti-Trans ring junctions

Trans hydrindanone system

Torgov's Synthesis of Estrone



Estrone

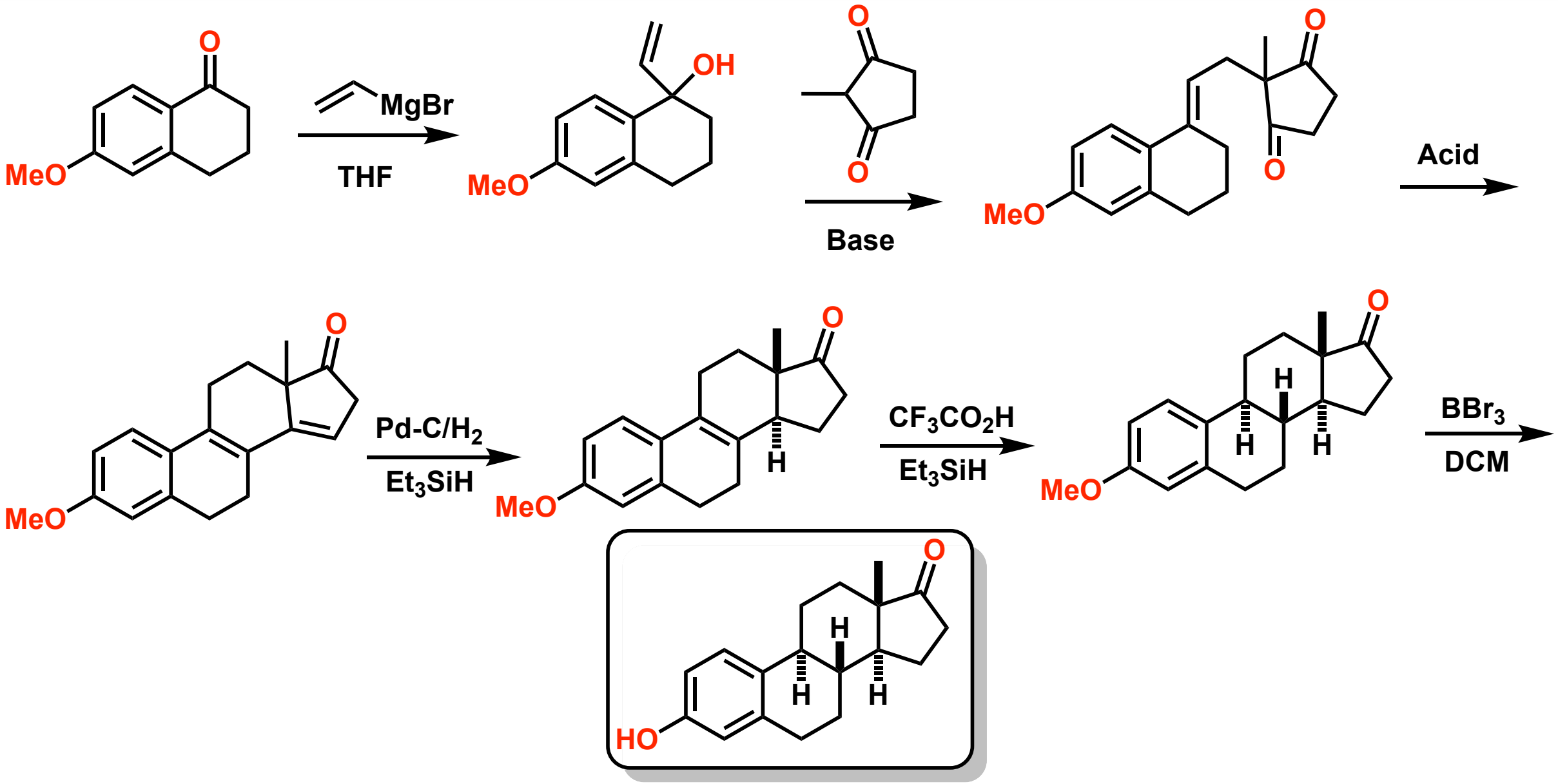
Strategy used is AB ⟶ ABD ⟶ ABCD

6-Steps Total Synthesis

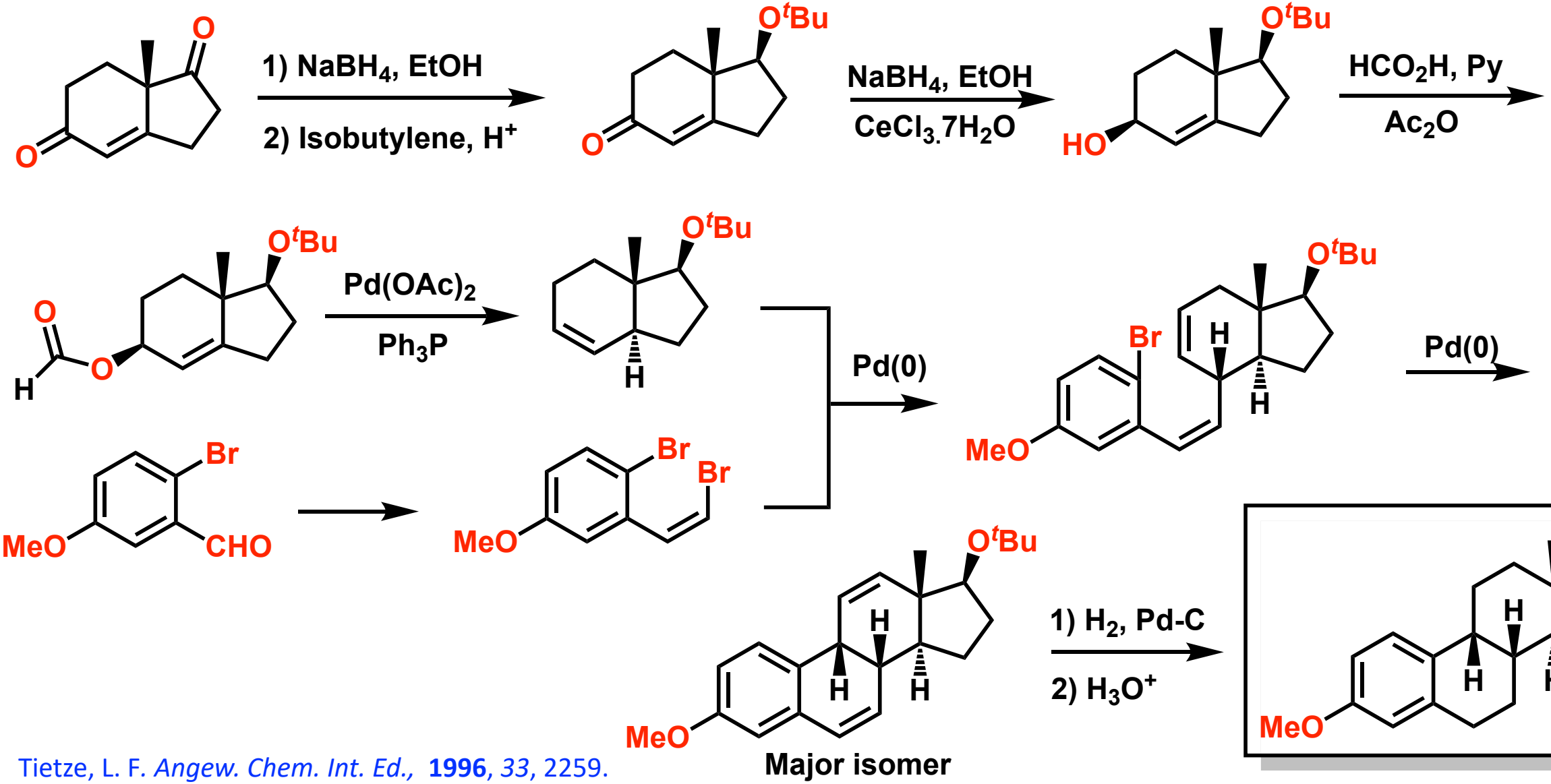
Key reactions are: Acid catalyzed cyclization & Stereoselective reduction

Torgov., ***Tetrahedron Lett.*, 1963**, *4*, 1553.

Torgov's Synthesis of Estrone



Tietze's Synthesis of Estradiol Methyl Ether



Tietze, L. F. *Angew. Chem. Int. Ed.*, **1996**, *33*, 2259.