

Global Focus on Knowledge

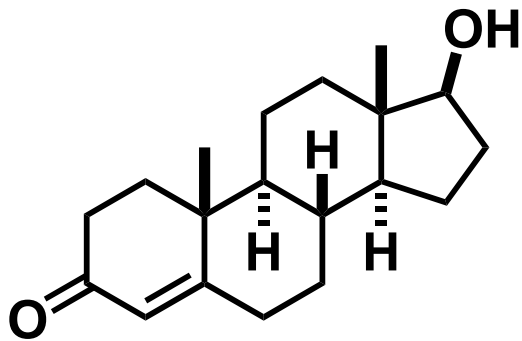
**From the Big Bang to a Green Planet:
The 13.7-Billion-Year Journey of Matter**

Nov 19: Matter and Biological Functions

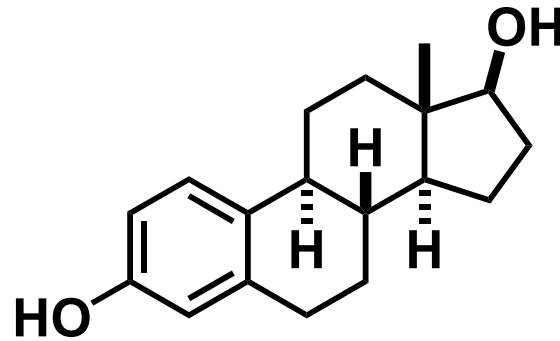
**Masakatsu Shibasaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo**

Landmark Substances Discovered in Vivo, Early 20th Century

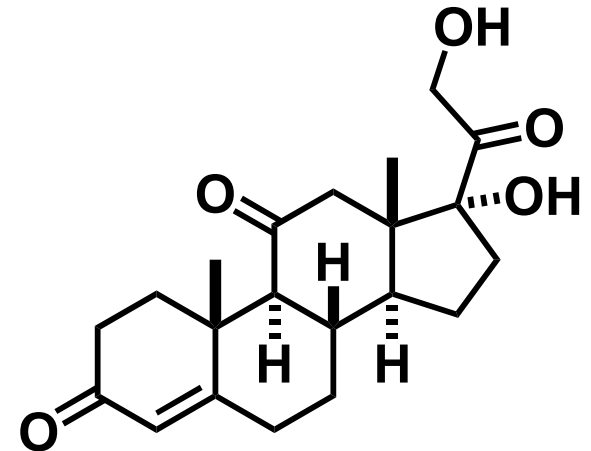
“Steroid Hormones”



Testosterone
Human (male)



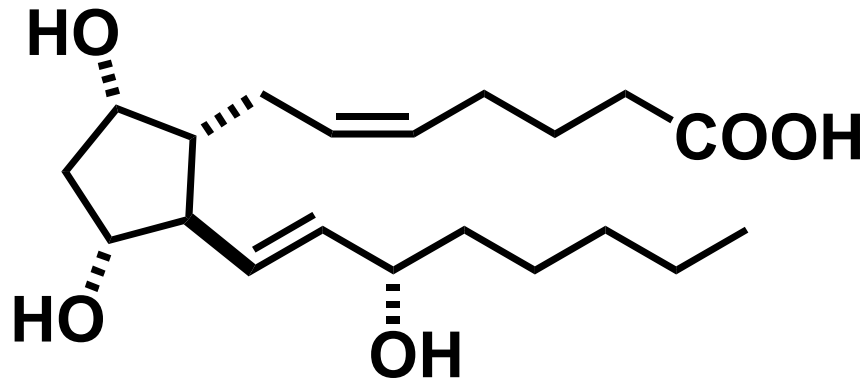
Estradiol
Human (female)



Cortisone
(Mammalian)

Landmark Substances Discovered in Vivo, Early 20th Century

“Prostaglandins”

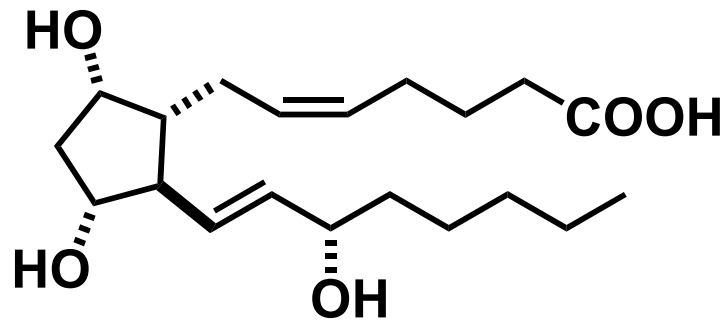


Prostaglandin F_{2α}

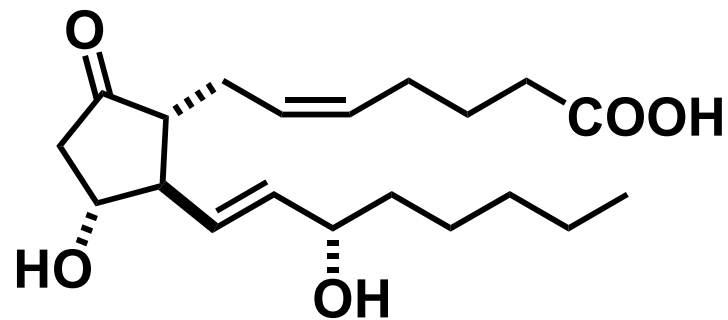
Lead-up to Identification of Prostaglandin $F_{2\alpha}$

- New substances exhibiting high rate of bioactivity found in human semen and sheep seminal vesicles (early 1930s).
- Thought at the time to be produced in the prostate gland, these substances were named prostaglandins. (PGs were later shown to be produced in the vesicular glands.)
- No information on these substances for 20 years.
- Final characterization in 1963.

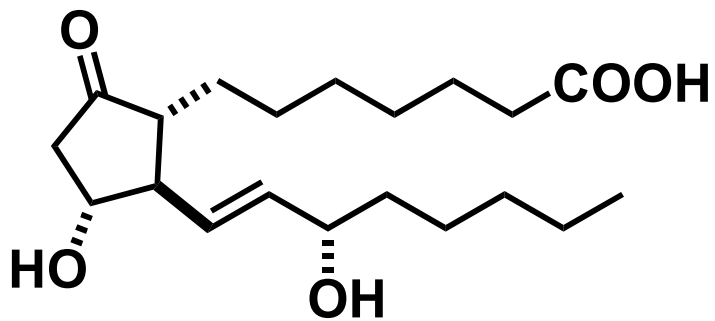
Prostaglandins Found In Vivo



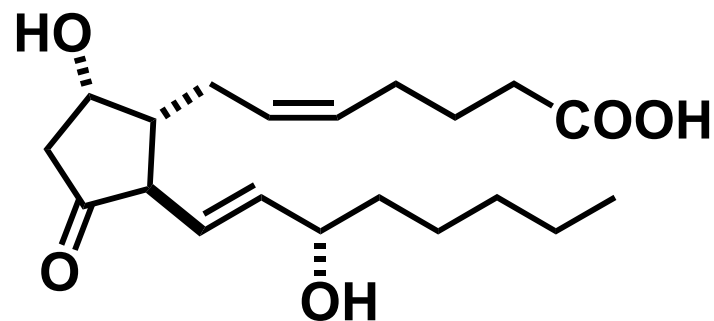
PGF₂α



PGE₂

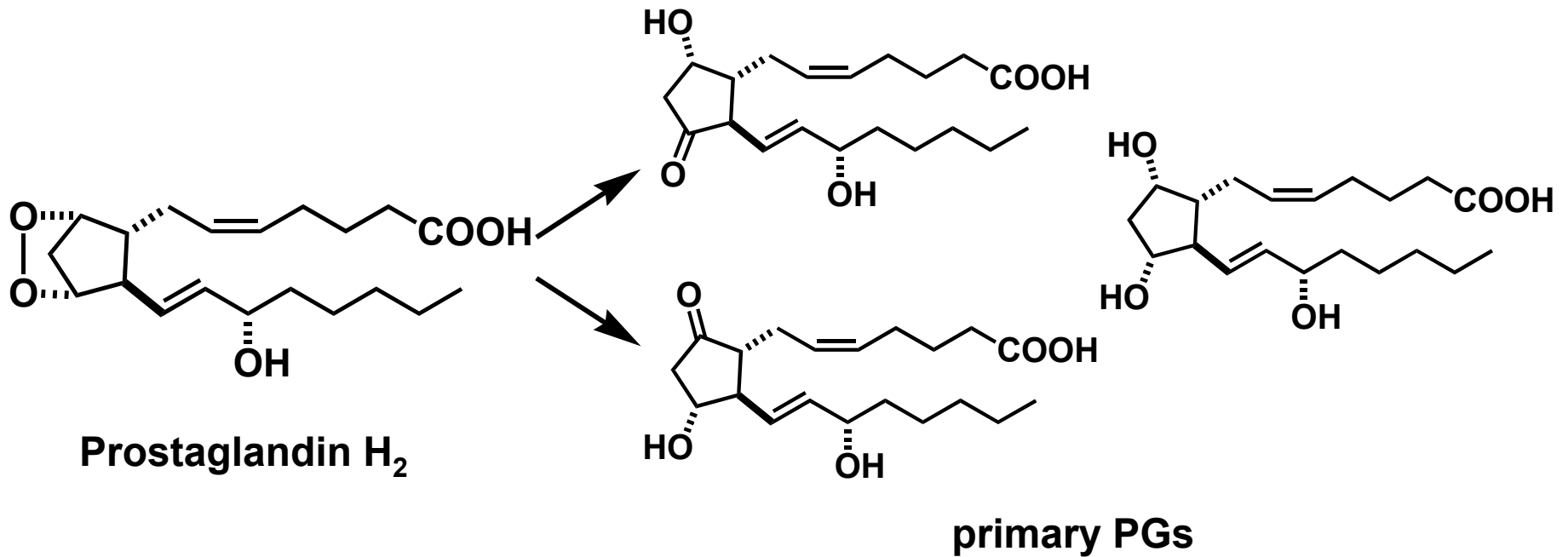
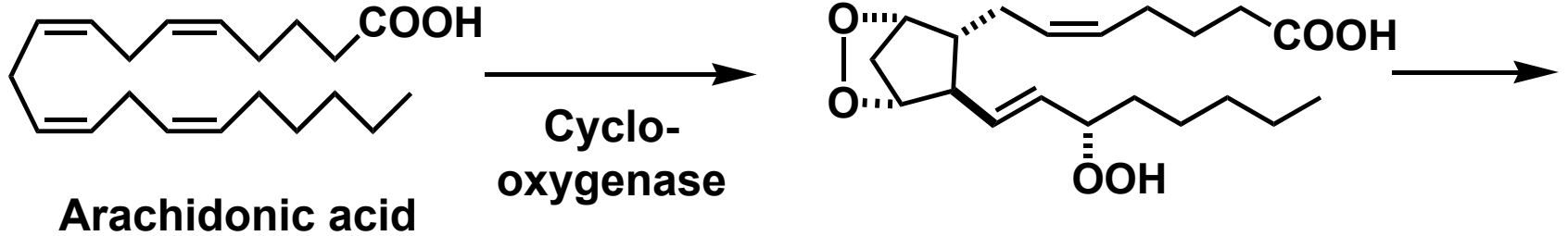


PGE₁

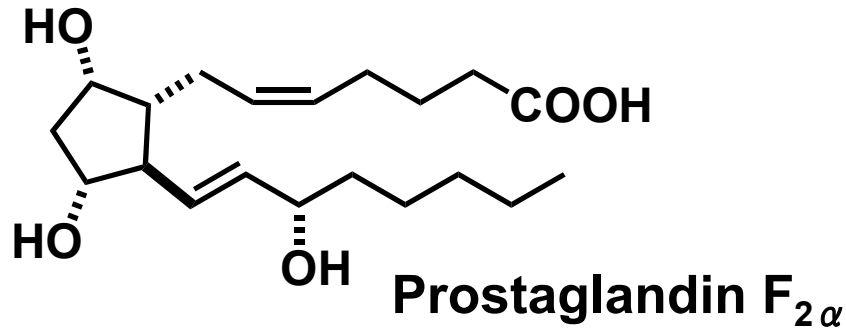


PGD₂

How Are Prostaglandins Synthesized Biologically?



Physiological Functions of Prostaglandins and Some Medical Applications

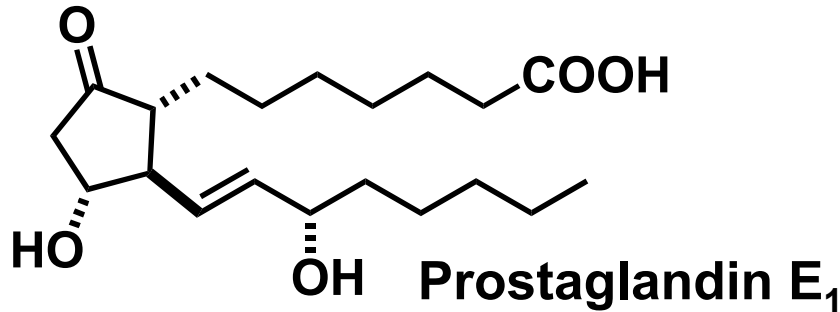


**Physiological
Function**

**Uterine
contraction**

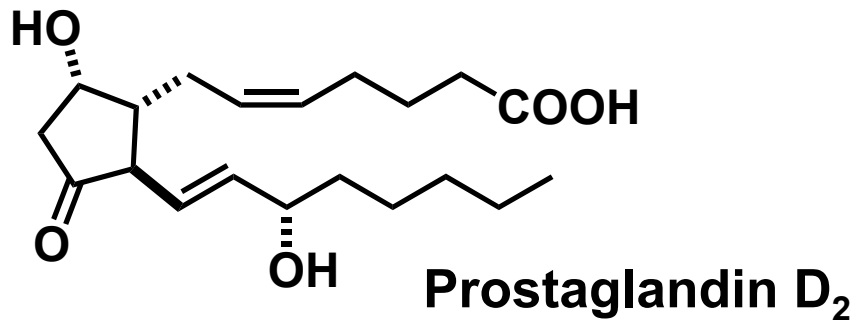
**Medical
Application**

**Use at
childbirth**



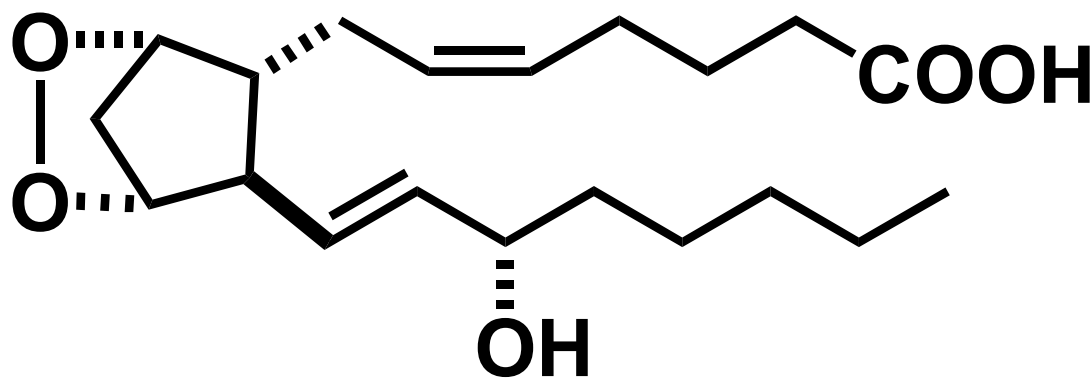
**Inhibits platelet
aggregation**

**Occlusion in
peripheral blood
vessels**



Hypnotic

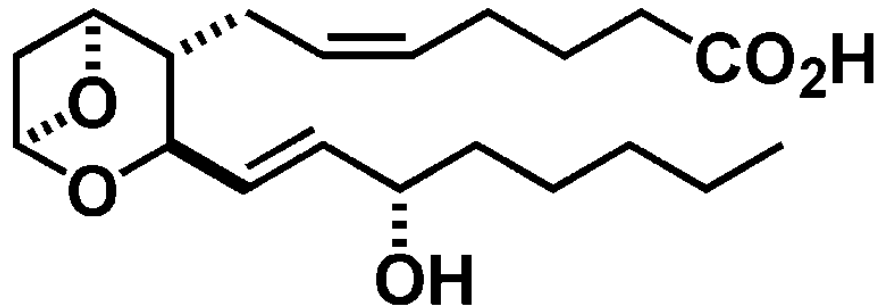
Isolation and Physical Characterization of Unstable Prostaglandin



Prostaglandin H₂

Isolation and Physical Characterization of Unstable Prostaglandin

In platelet

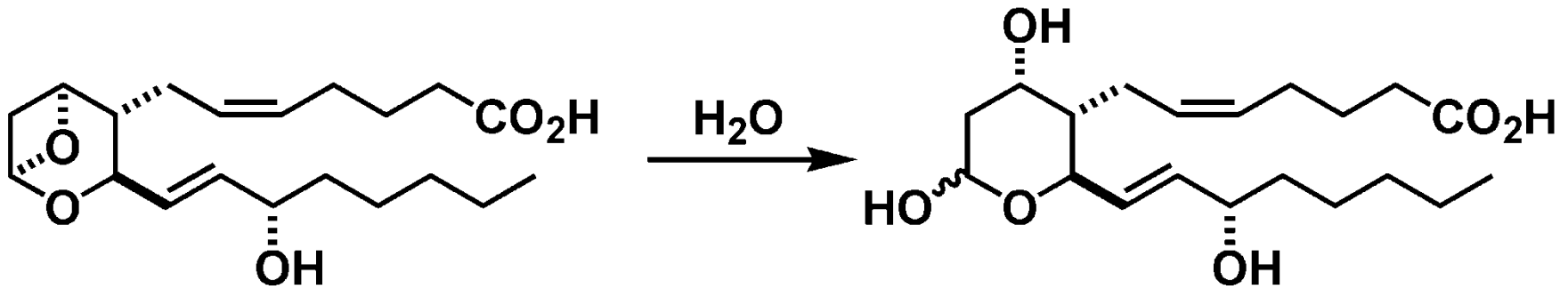


Thromboxane A₂

Half-life in water of 30 seconds

No substance more potent in inducing platelet aggregation

Isolation and Physical Characterization of Unstable Prostaglandin

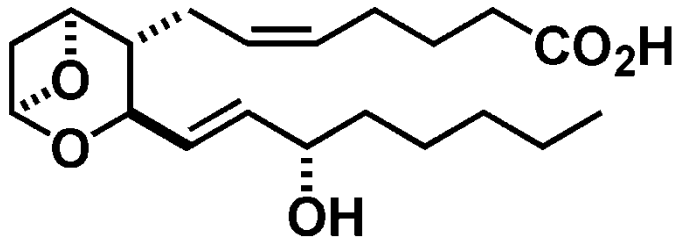
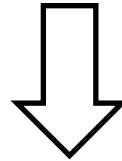


Thromboxane A₂

Thromboxane B₂

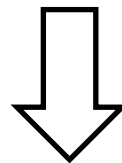
Physiological activity
extinguished

Most Potent Substance Inducing Platelet Aggregation



Thromboxane A₂

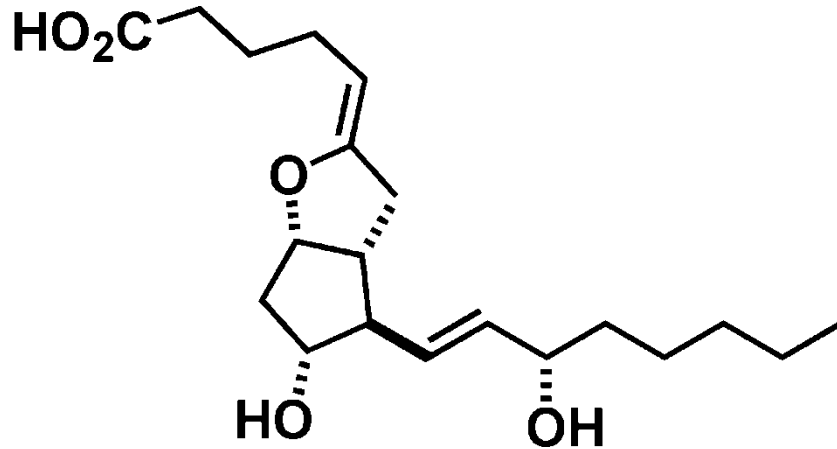
**Biogenic homeostasis
unsustainable**



Task

Existence suggested of a substance more potent than any other in inhibiting platelet aggregation

Isolation and Physical Characterization of Unstable Prostaglandin

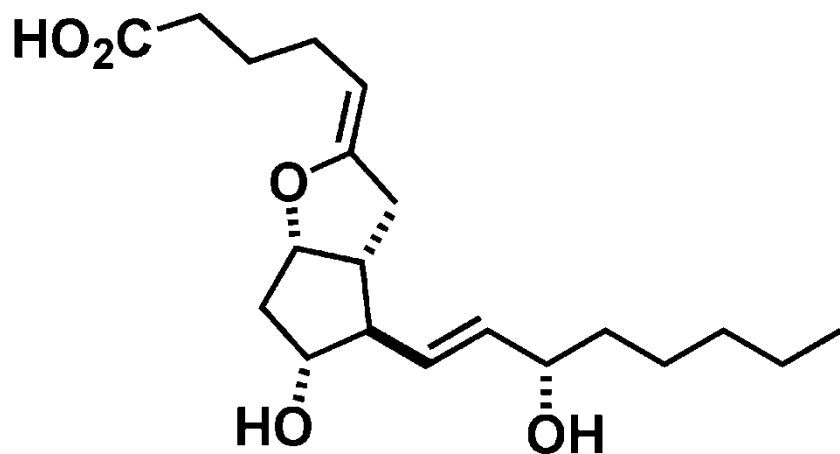


Prostaglandin I₂ found to be biosynthesized in arterial walls

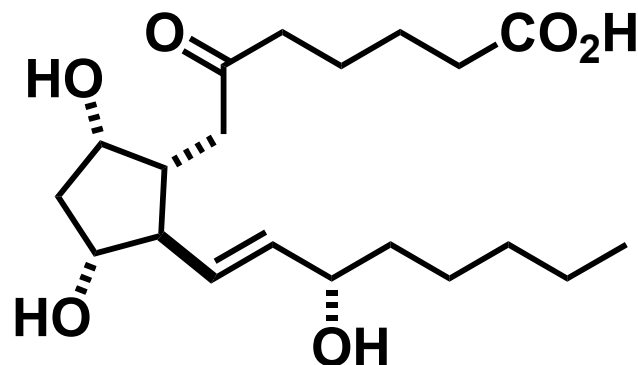
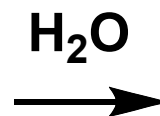
Half-life in water of 5 seconds

No substance more potent in inhibiting platelet aggregation

Isolation and Physical Characterization of Unstable Prostaglandin

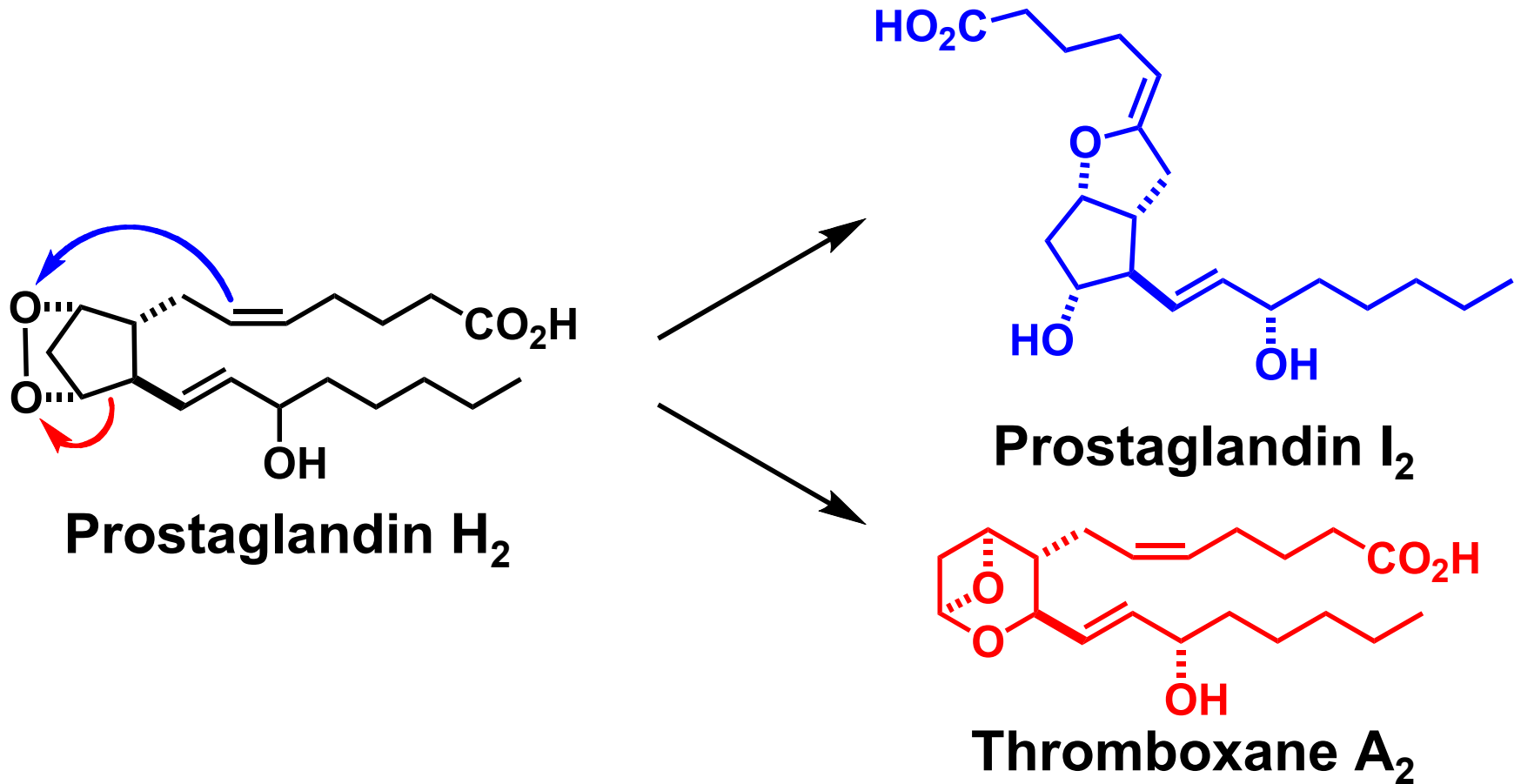


Prostaglandin I₂



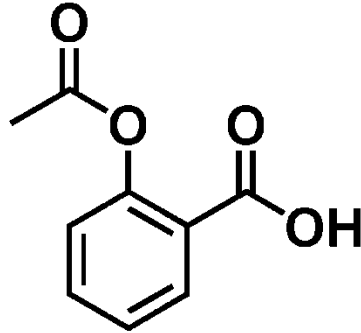
Physiological activity
extinguished

Isolation and Physical Characterization of Unstable Prostaglandin



Substances having completely opposite physiological functions biosynthesized from the same intermediate substance!!

Aspirin: A Landmark Pharmaceutical

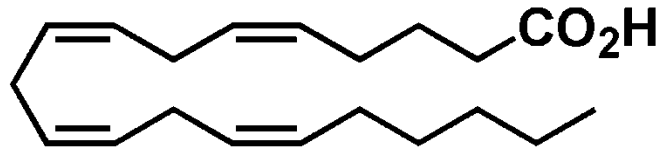


A prophylactic for heart attacks

— Studies of one million American subjects

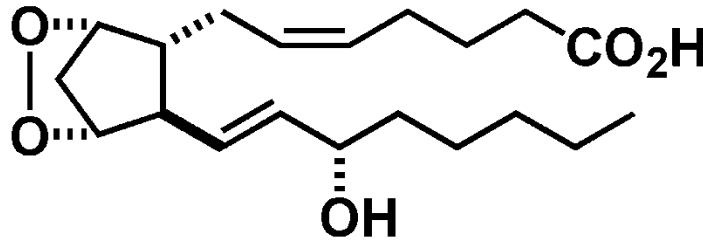
Why ?

How Aspirin Works Biologically



Arachidonic acid

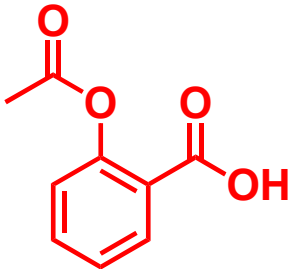
Cyclooxygenase



Thromboxane A₂

Prostaglandin E₂

Prostaglandin I₂



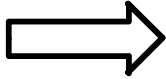
Aspirin

is a cyclooxygenase inhibitor

The 50-Year Scientific Quest for SRS-A

What is SRS-A?

(A slow-reacting substance of anaphylaxis)

- Bronchial smooth muscle contraction
 - Venular smooth muscle contraction
 - Increased neutrophil chemotactic factor production
 - Increased vascular permeability
- 
- Bronchial asthma
 - Allergic reactions
 - Sustaining inflammatory reaction

Scientific Contributions to Characterization of SRS-A

- 1938–40, Feldberg & Kellaway

Discovery of a slow-reacting smooth-muscle stimulating substance in guinea pig ileum

- 1979, B. Samuelsson, Karolinska Institute, Sweden

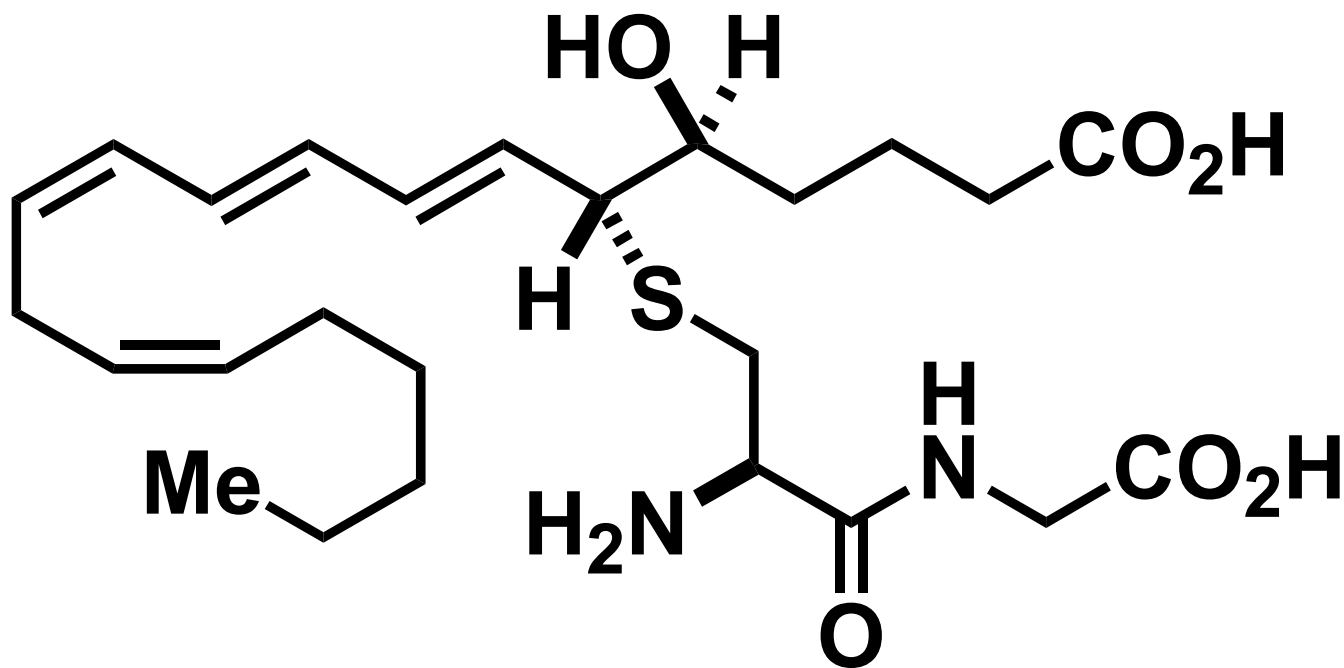
Report of isolation of SRS-A as a precursor of arachidonic acid and a structural formula inferred from results of multiple transformations

- 1979–80, E.J. Corey, Harvard University

Success in world's first pure chemical synthesis of SRS-A and its final characterization

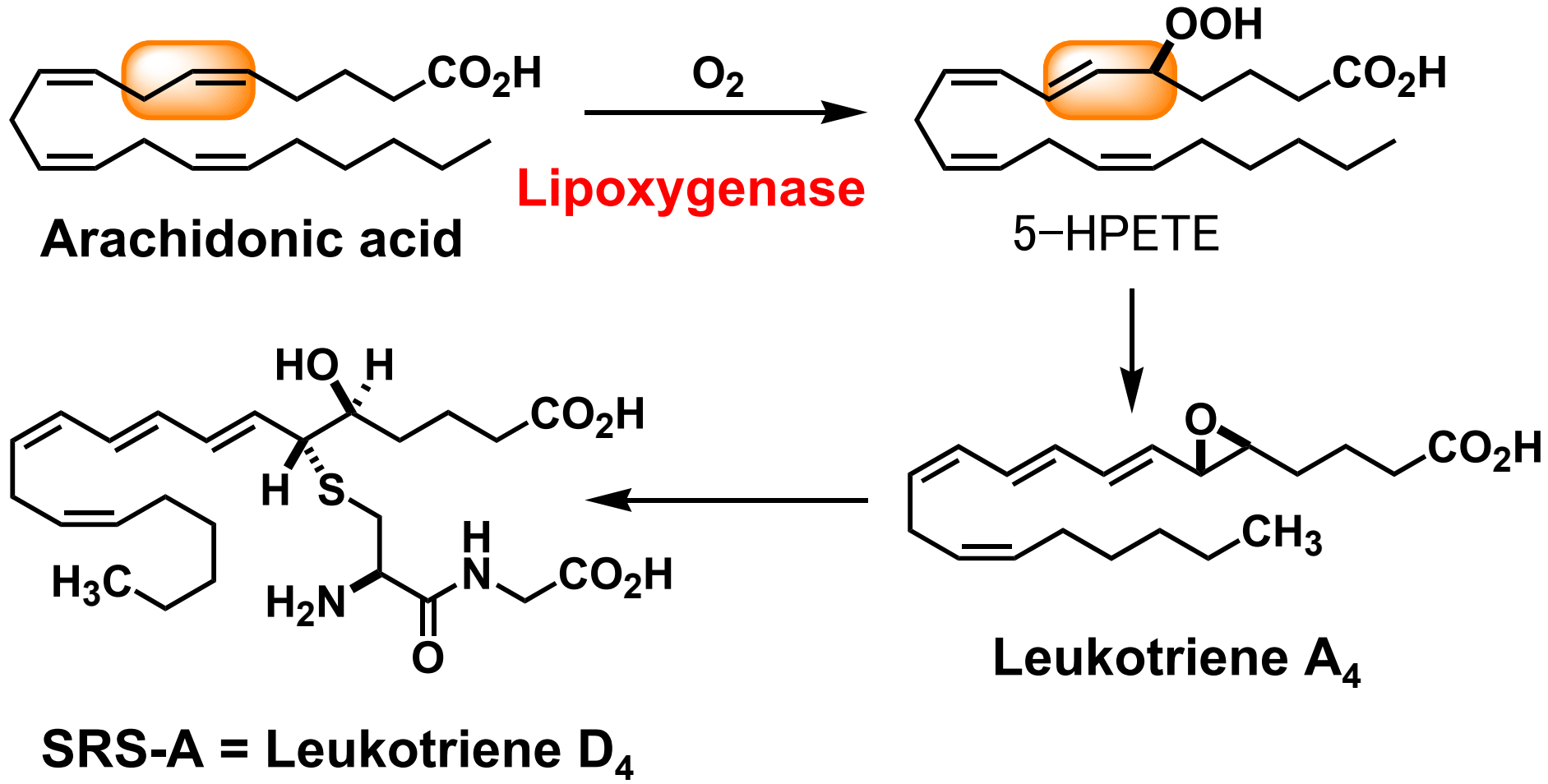
Physical Characterization of SRS-A

Joint research by Harvard University and
the Karolinksa Institute of Sweden

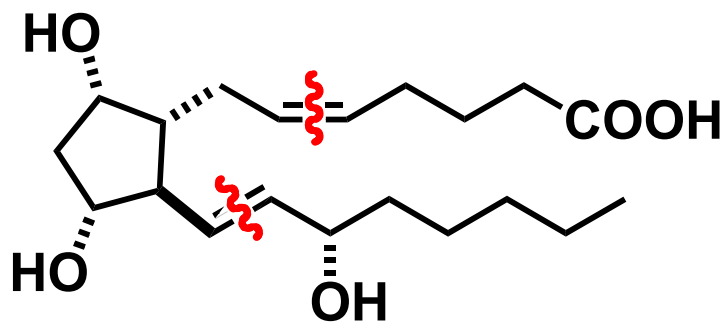


SRS-A

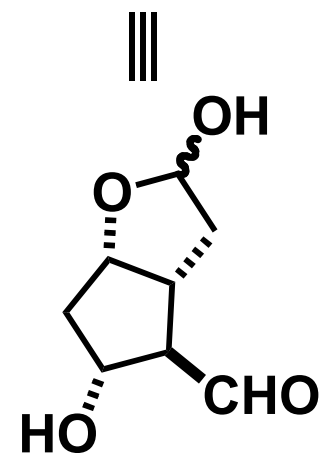
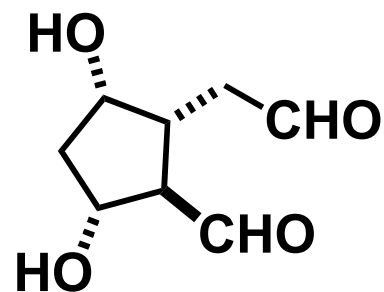
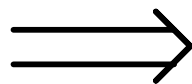
How Is SRS-A Synthesized Biologically?



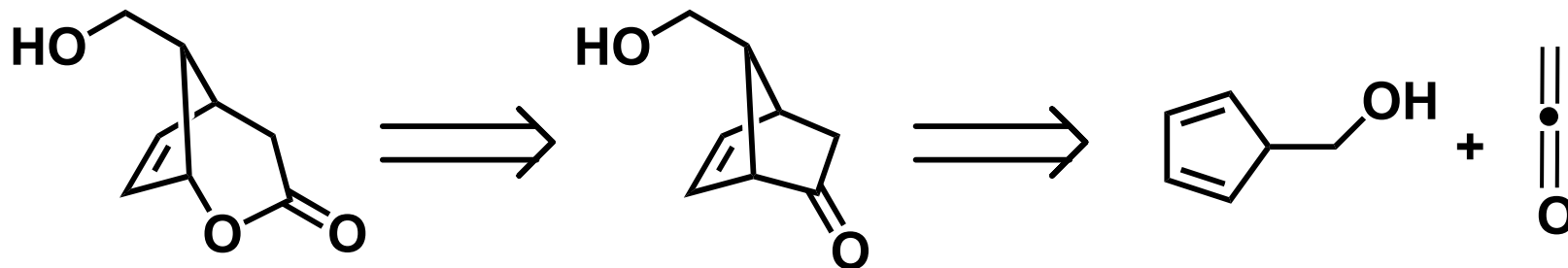
Pure Chemical Synthesis Dramatically Advancing Prostaglandin Studies



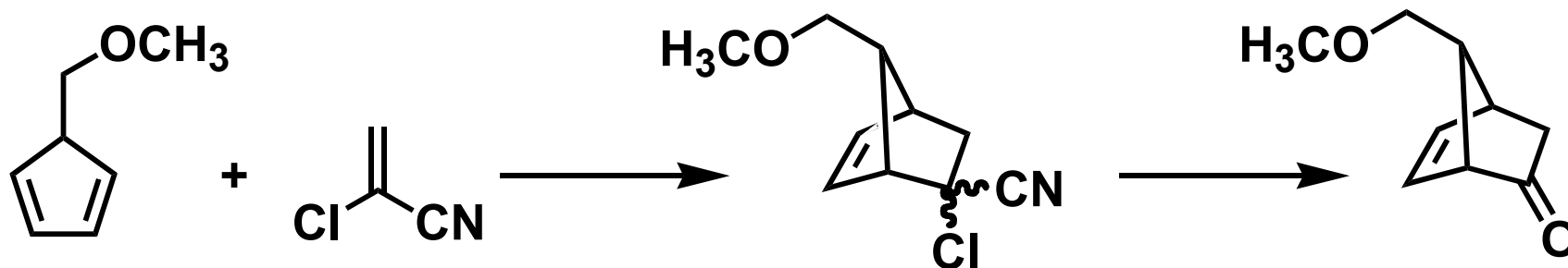
Prostaglandin $F_{2\alpha}$



Pure Chemical Synthesis Dramatically Advancing Prostaglandin Studies

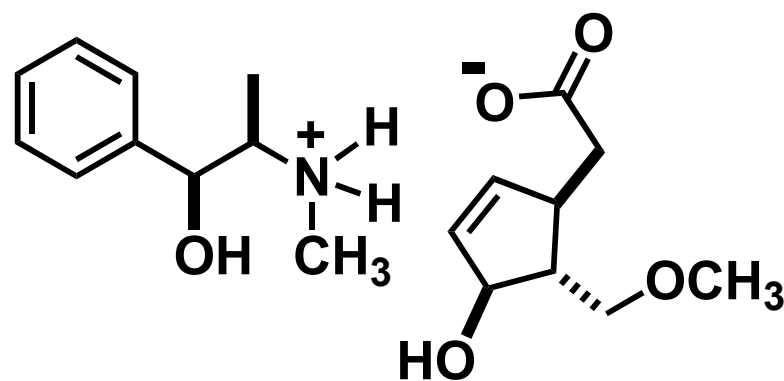
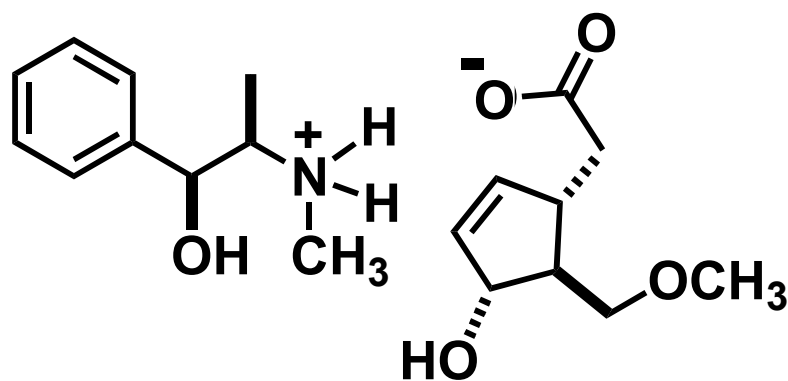


Observed synthesis



Chiral Prostaglandins: Left-Handed and Right-Handed Substances

Optical resolution



Idealized synthesis \Rightarrow Catalytic asymmetric synthesis