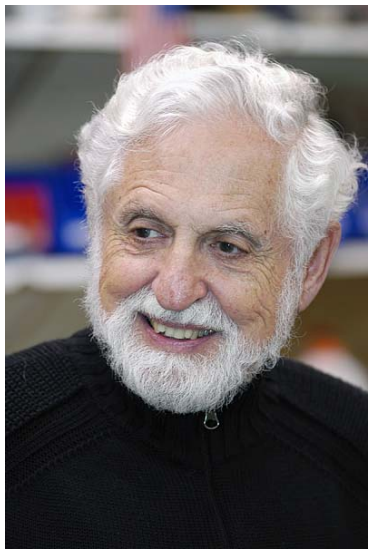
Carl Djerassi

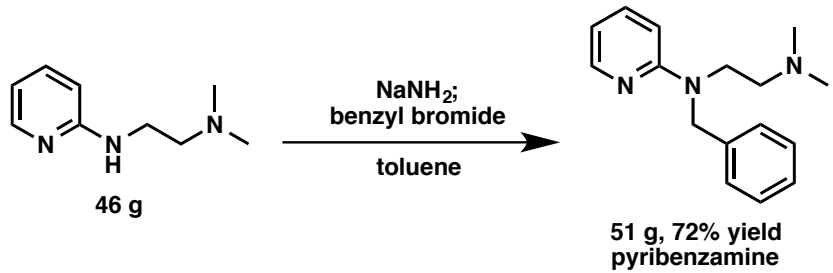
Chemistry Career in Review

October 24 2013

- **Born: October 29, 1923 in Vienna**
- **B.A.: Kenyon College, 1942**
- **Ph.D.: Wisconsin, 1945**
- **Ciba (1945-1949), Syntex (1949-1952)**
- **Wayne State (1952-1959)**
- **Stanford (1959-present)**
- **Zoecon (1970-1988)**
- **Professor Emeritus (2002)**

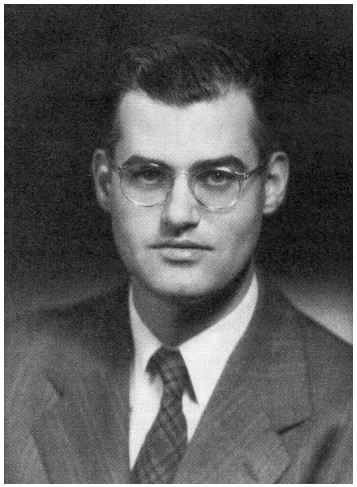


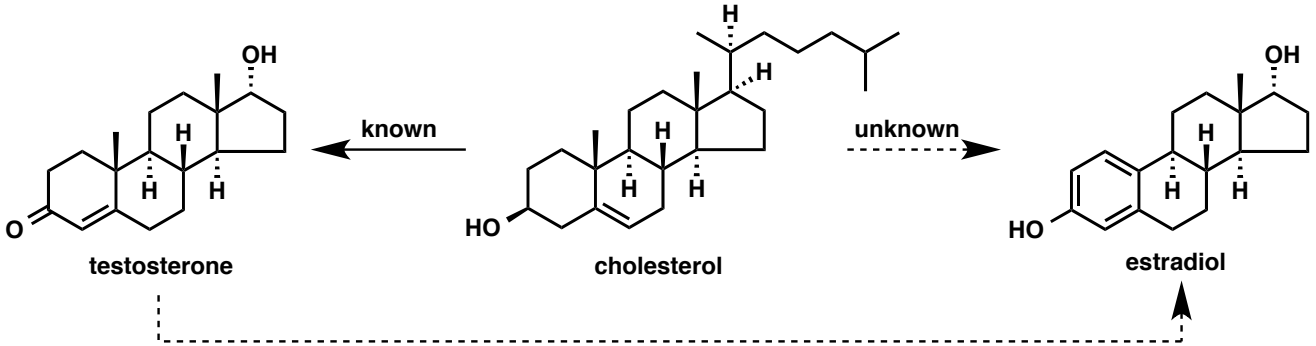
- **Born: October 29, 1923 in Vienna**
- **Lived in Vienna, Austria and Sofia, Bulgaria**
- **1939 flees Europe, moves to US (age 16)**
- **Tarkio College then Kenyon College; graduated in 1942**
- **Worked at CIBA Pharmaceutical Products in Summit, NJ**
  - **Synthesized pyribenzamine, first commercial antihistamine**



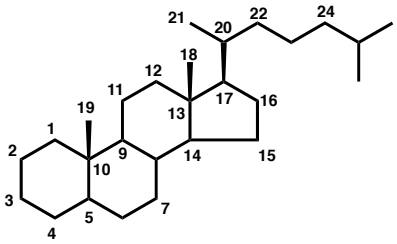
Huttrer, C. P.; Djerassi, C.; Beears, W. L.; Mayer, R. L; Scholz, C. R.. *J. Am. Chem. Soc.* **1946**, *68*, 1999.

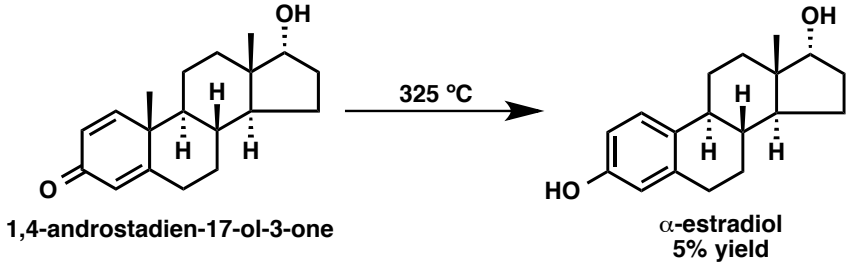
- **PhD from Wisconsin (1945, 22 years old); Advisor: Alfred. L. Wilds (pictured)**
- **Studied partial aromatization of androgenic steroids to estrogens**
- **Testosterone available from cholesterol, but estrone isolated from pregnant mare urine**
- **Studies previously done by Inhoffen, but lacking in details**





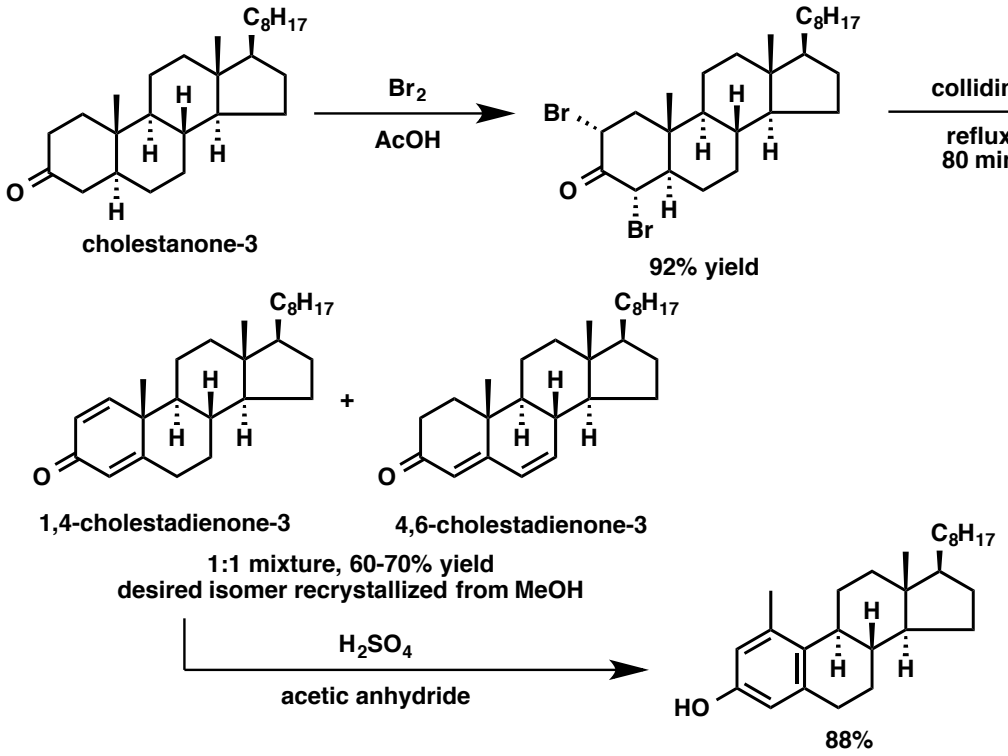
Inhoffen:





- **Goal: can one ring be selectively aromatized? Is there a route from male sex hormones to female sex hormones?**

- **Characterization by melting point, elemental analysis, and sometimes UV**
- **"Dienone-phenol rearrangement"**



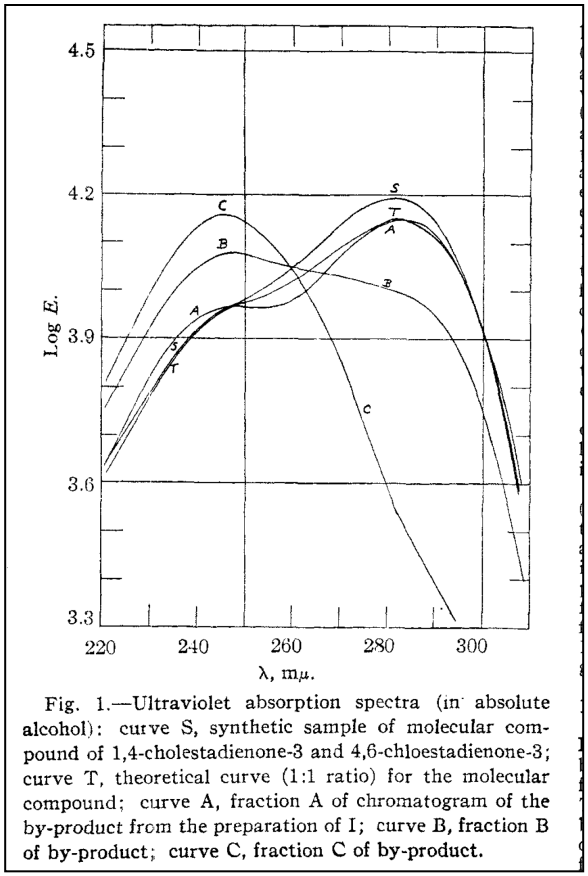
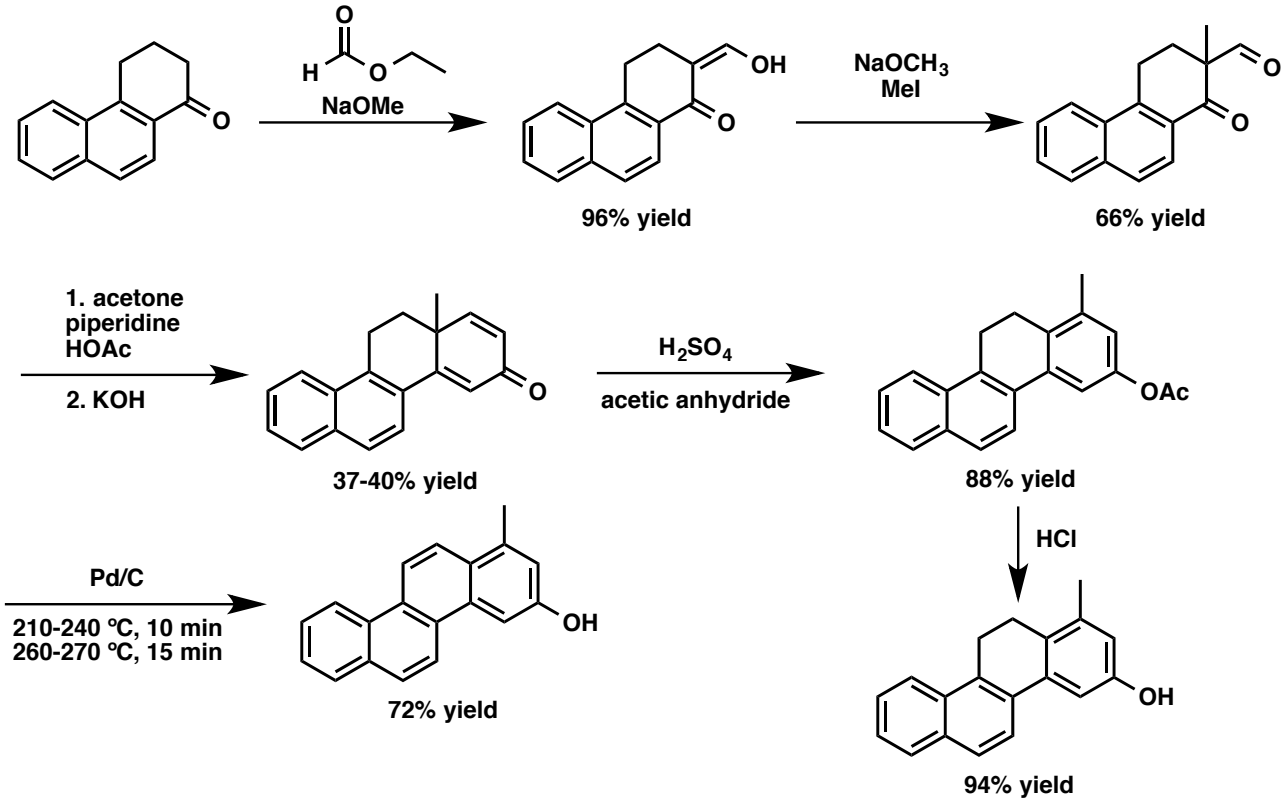


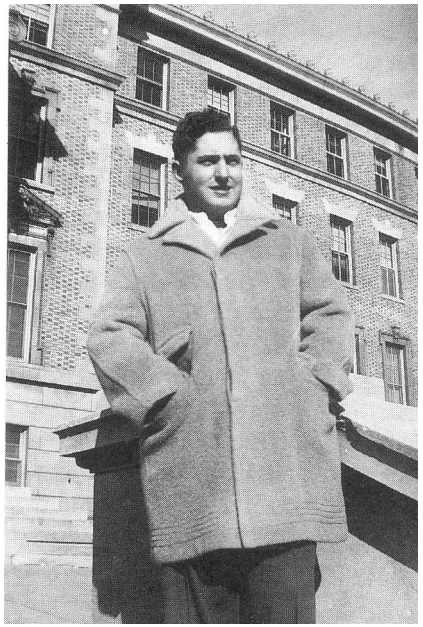
Fig. 1.—Ultraviolet absorption spectra (in absolute alcohol): curve S, synthetic sample of molecular compound of 1,4-cholestadienone-3 and 4,6-chloestadienone-3; curve T, theoretical curve (1:1 ratio) for the molecular compound; curve A, fraction A of chromatogram of the by-product from the preparation of I; curve B, fraction B of by-product; curve C, fraction C of by-product.

- **Confirms and improves upon study by Inhoffen**

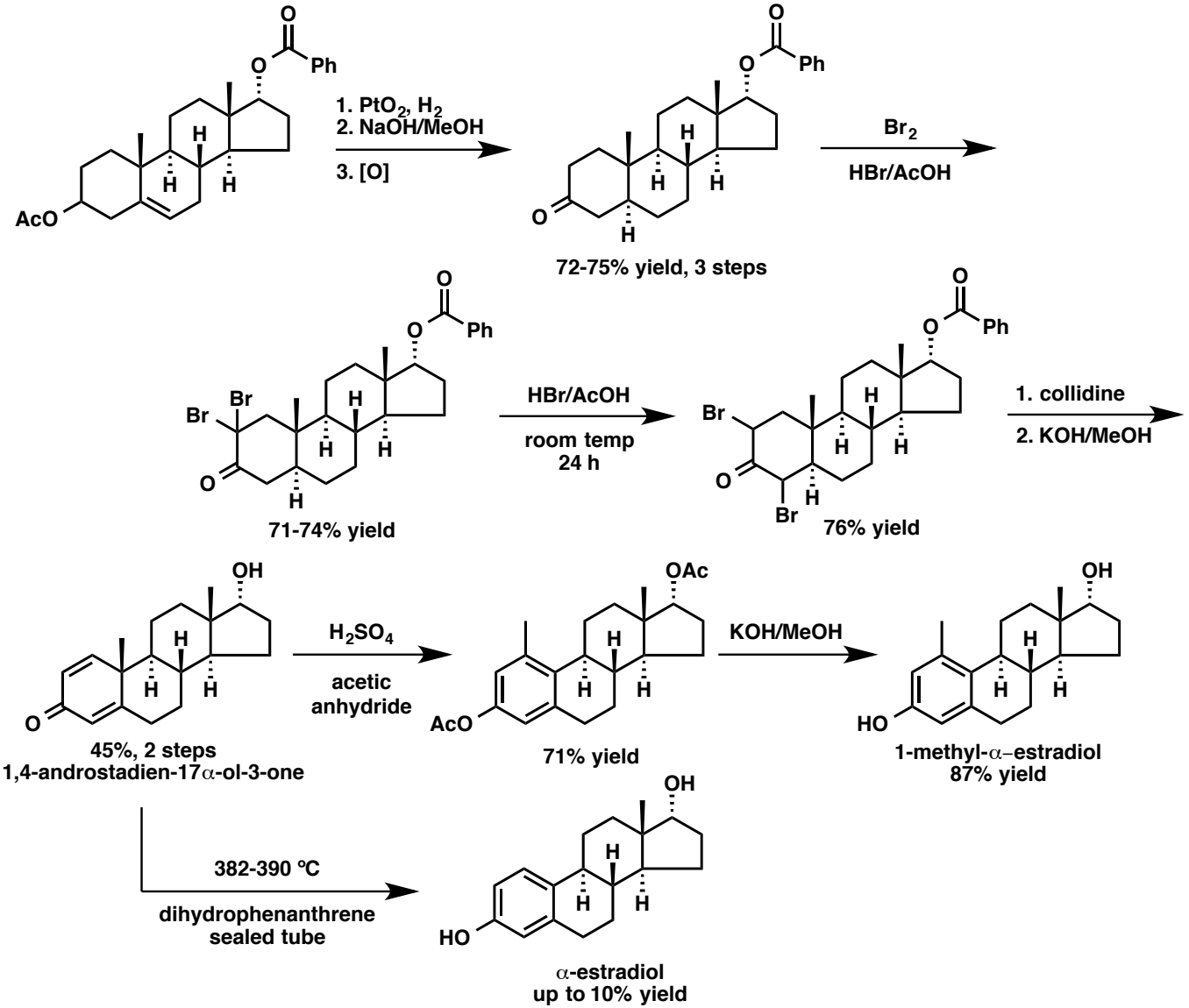
Wilds, A. L.; Djerassi, C. *J. Am. Chem. Soc.* **1946**, *68*, 1712.

■ Investigate rearrangement further





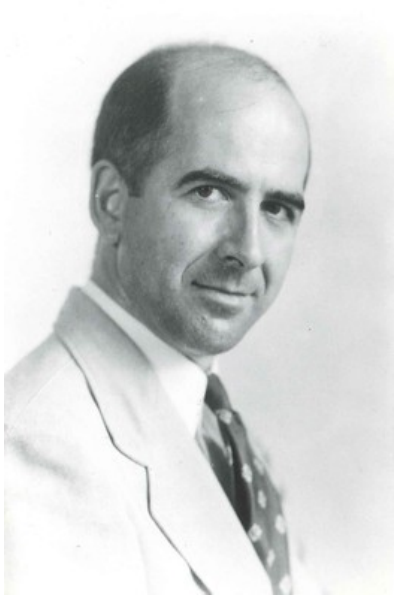
Wilds, A. L.; Djerassi, C. *J. Am. Chem. Soc.* **1946**, *68*, 1715.

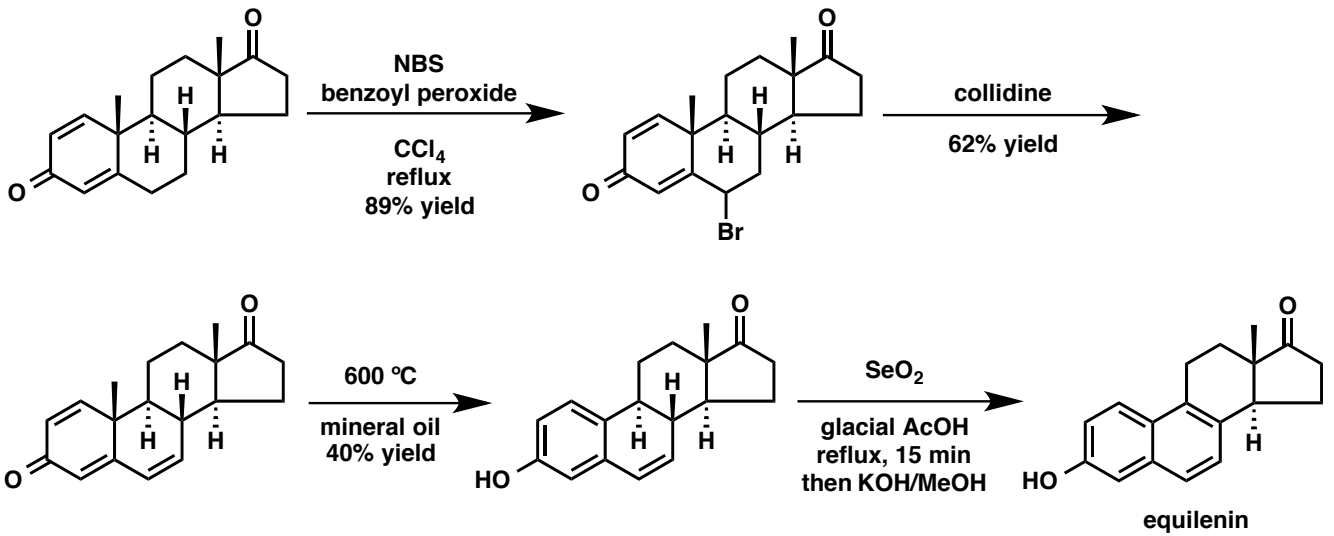


■ **Confirms and improves upon study by Inhoffen**

Wilds, A. L.; Djerassi, C. *J. Am. Chem. Soc.* **1946**, *68*, 2125.

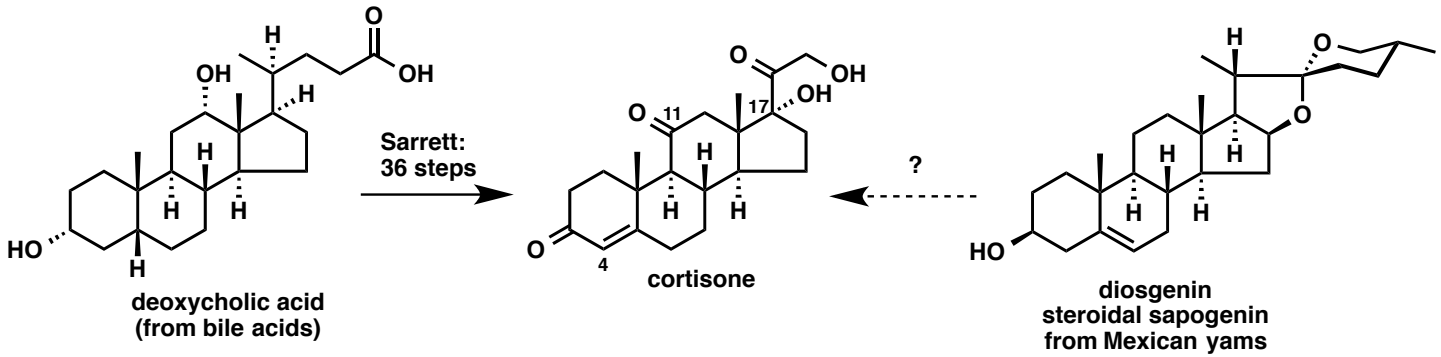
- **Returns to CIBA in NJ for 4 years, studies brominated steroids**
- **1949 joins Syntex in Mexico City**
- **Syntex:**
  - **Founded in 1944 by Russell E. Marker (Penn St.).**
  - **Isolate steroids from Mexican yam, synthesize hormones**
  - **Yams as steroid source leads to cheaper steroids**
- **Synthesis of equilenin**





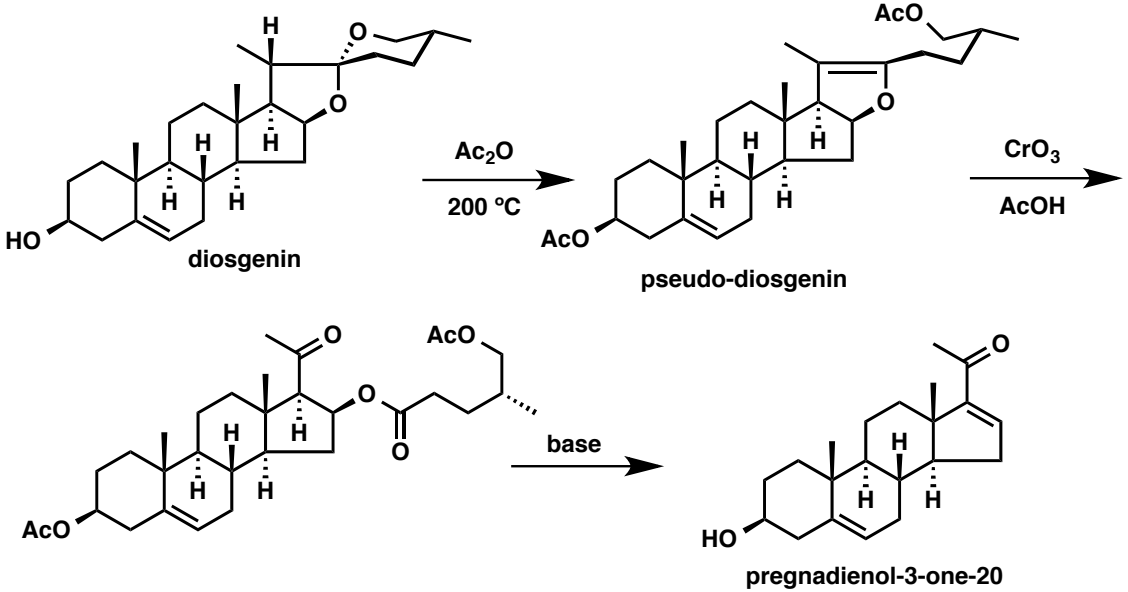
Kaufmann, St.; Pataki, J.; Rosenkranz, G.; Romo, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 4531.

- **Cortisone:**
  - **hormone released by the adrenal glands**
  - **suppresses immune system, thereby reducing pain and swelling**
- **Synthesized by Sarrett in 36 steps from deoxycholic acid**
- **Many research groups race to find a better route**
- **Syntex starts from diosgenin, available from Mexican yams**



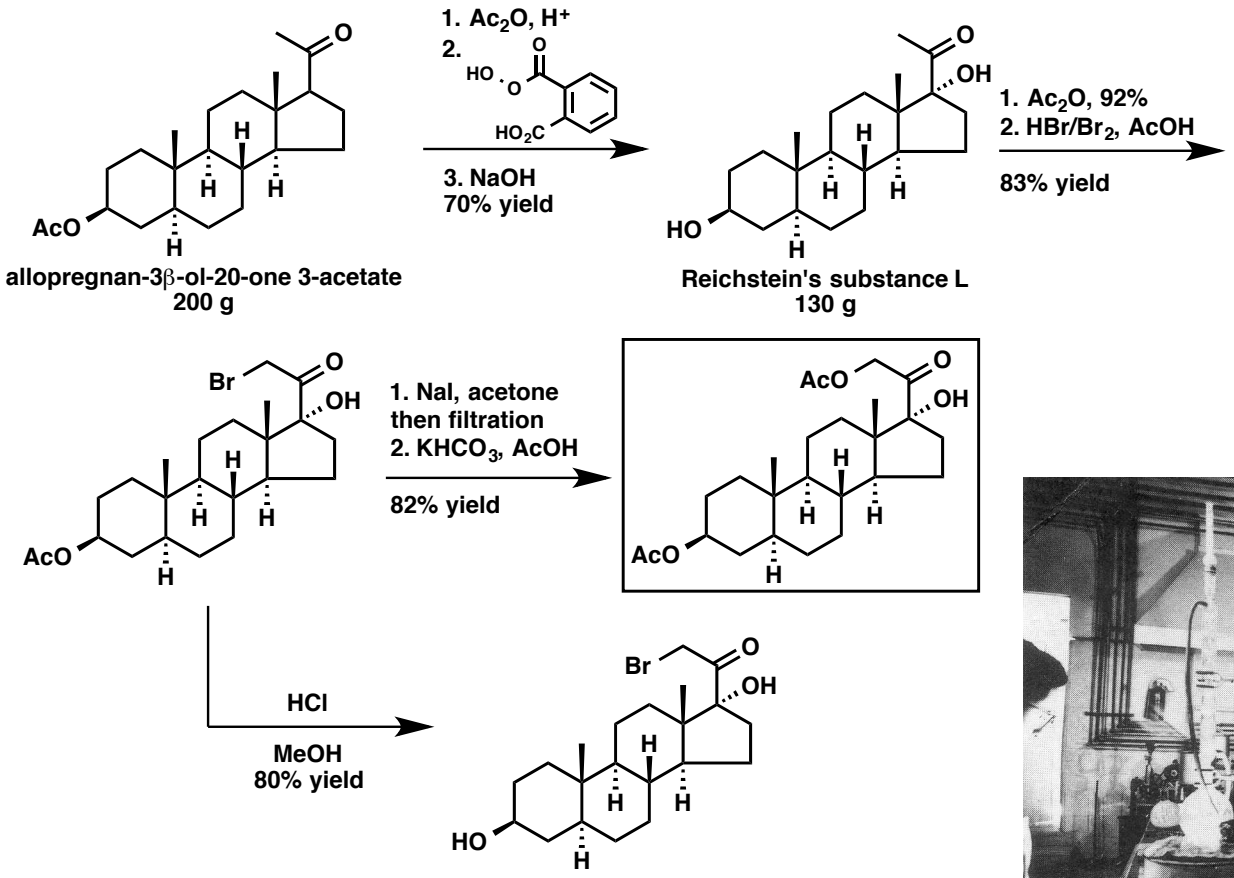
- **3 Challenges:**
  - **C17 side chain of D ring**
  - **A ring**
  - **C11 ketone of C ring**

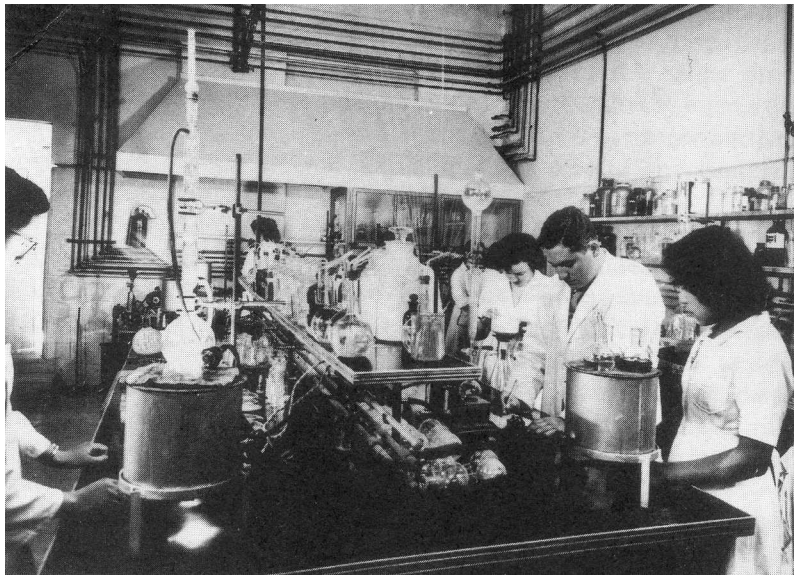
■ **1943: Russell Marker collects 10 tons of yams, synthesizes 3 kg of progesterone, worth $240,000 ($3 million in 2009)**



Marker, R. E. *J. Am. Chem. Soc.* **1939**, *61*, 3592.
Marker, R. E.; Rohrmann, E. *J. Am. Chem. Soc.* **1940**, *62*, 518.
Marker, R. E.; Tsukamoto, T.; Turner, D. L. . *J. Am. Chem. Soc.* **1940**, *62*, 2525.

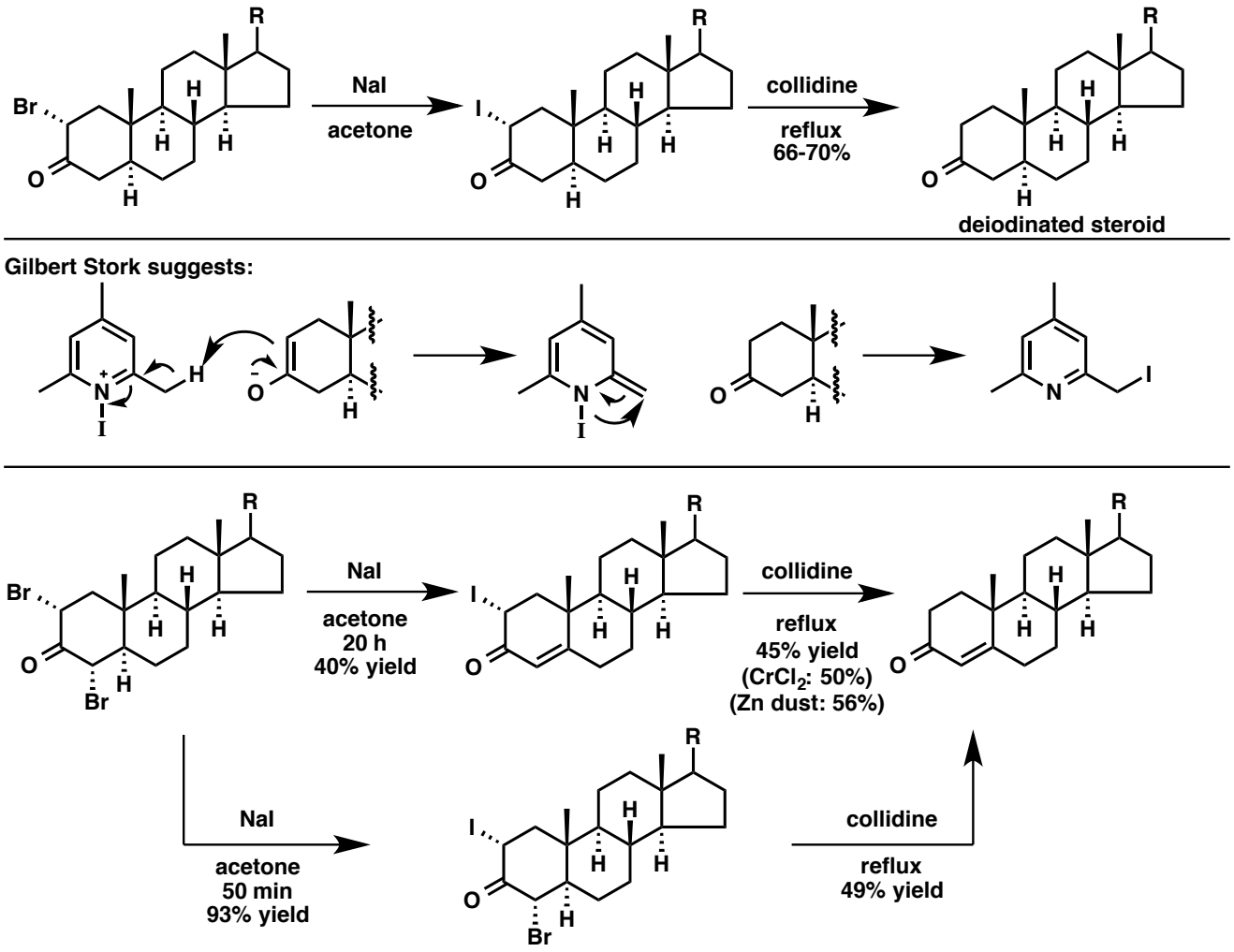
■ Applied Marker degradation





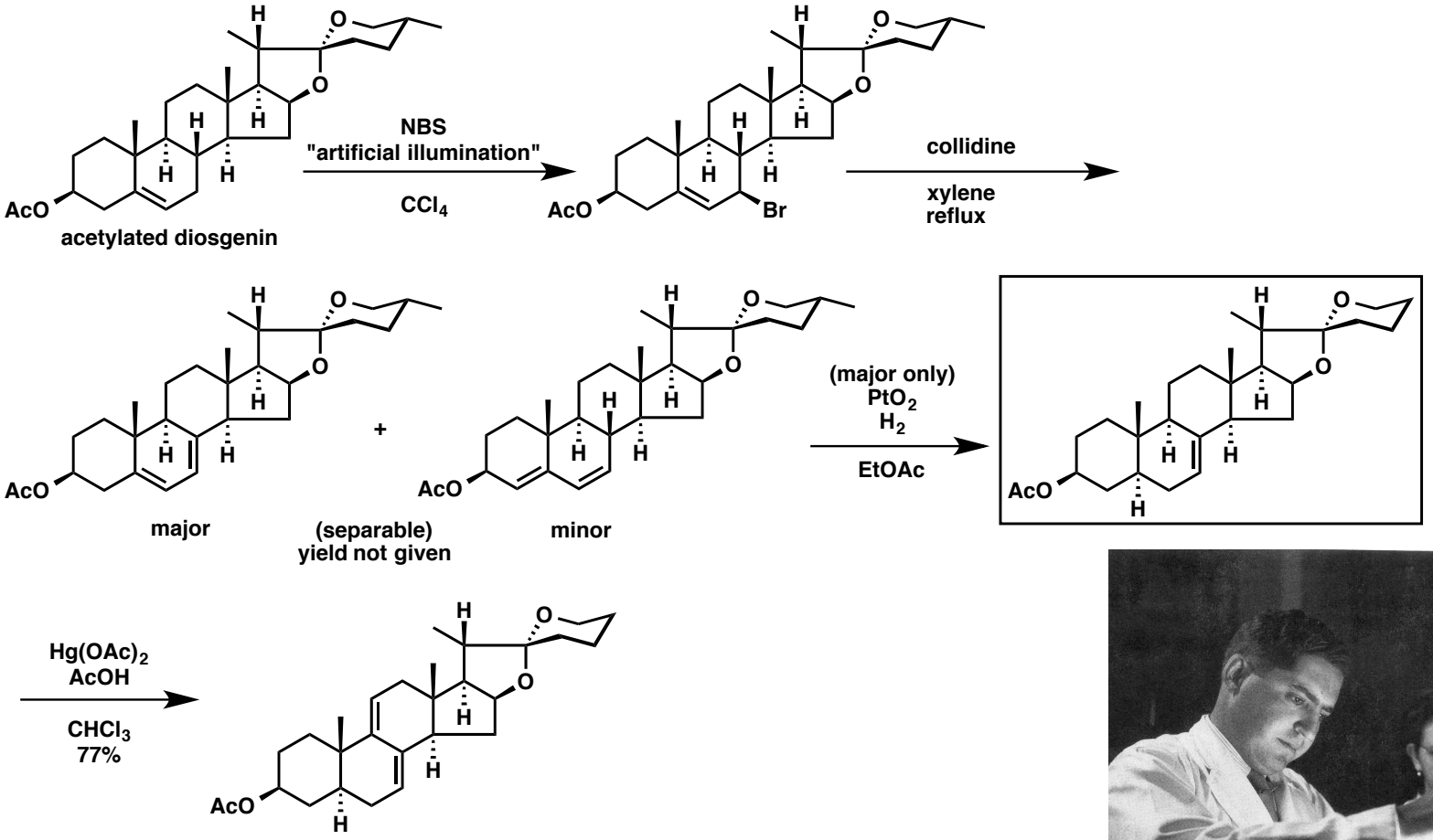
Rosenkranz, G.; Pataki, J.; Kaufmann, St.; Berlin, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 4081.

- **Bromination/Iodination to install unsaturation**
- **Deiodination with collidine**

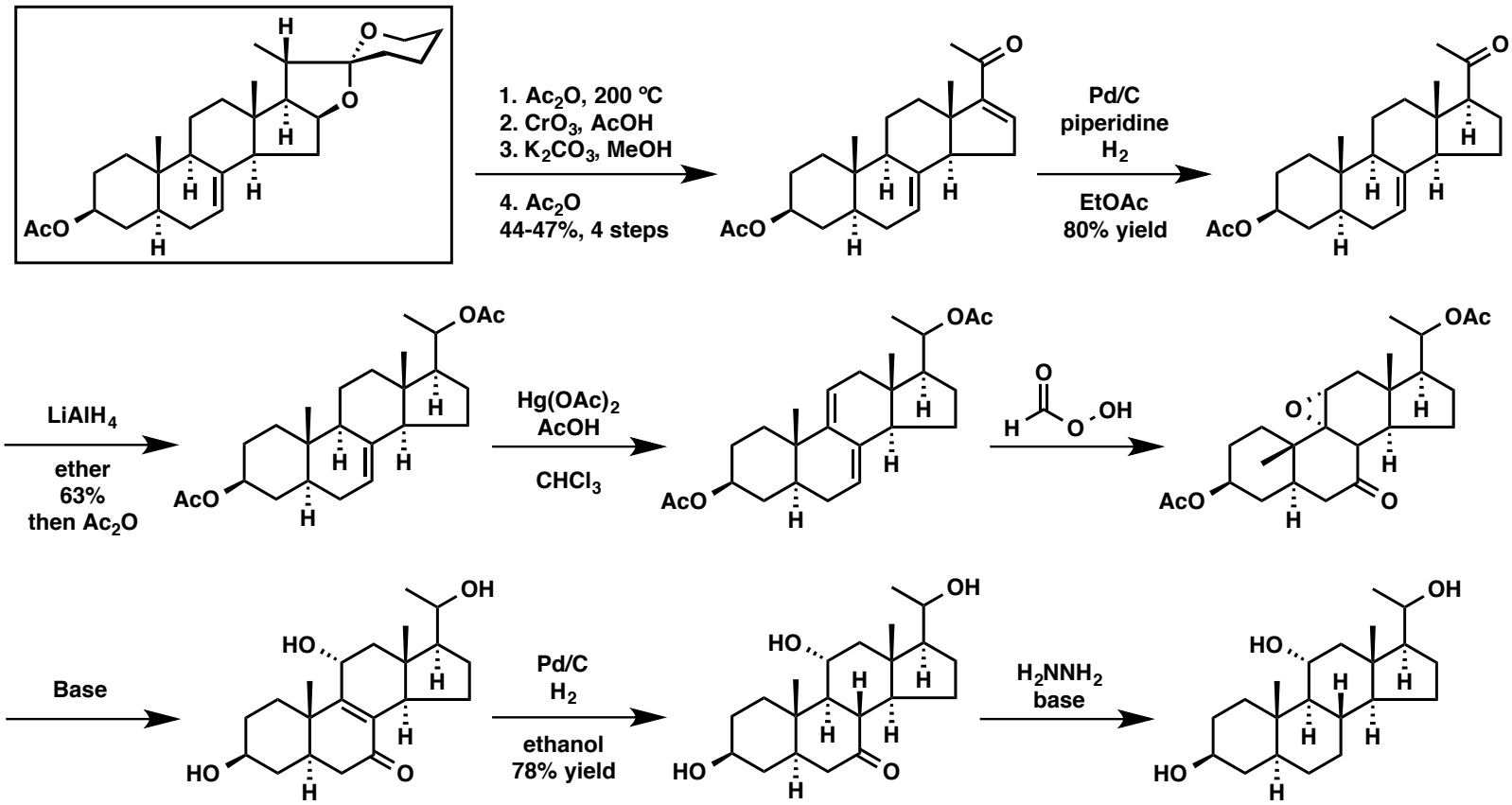


Rosenkranz, G.; Mancera, O.; Gatica, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 4077.

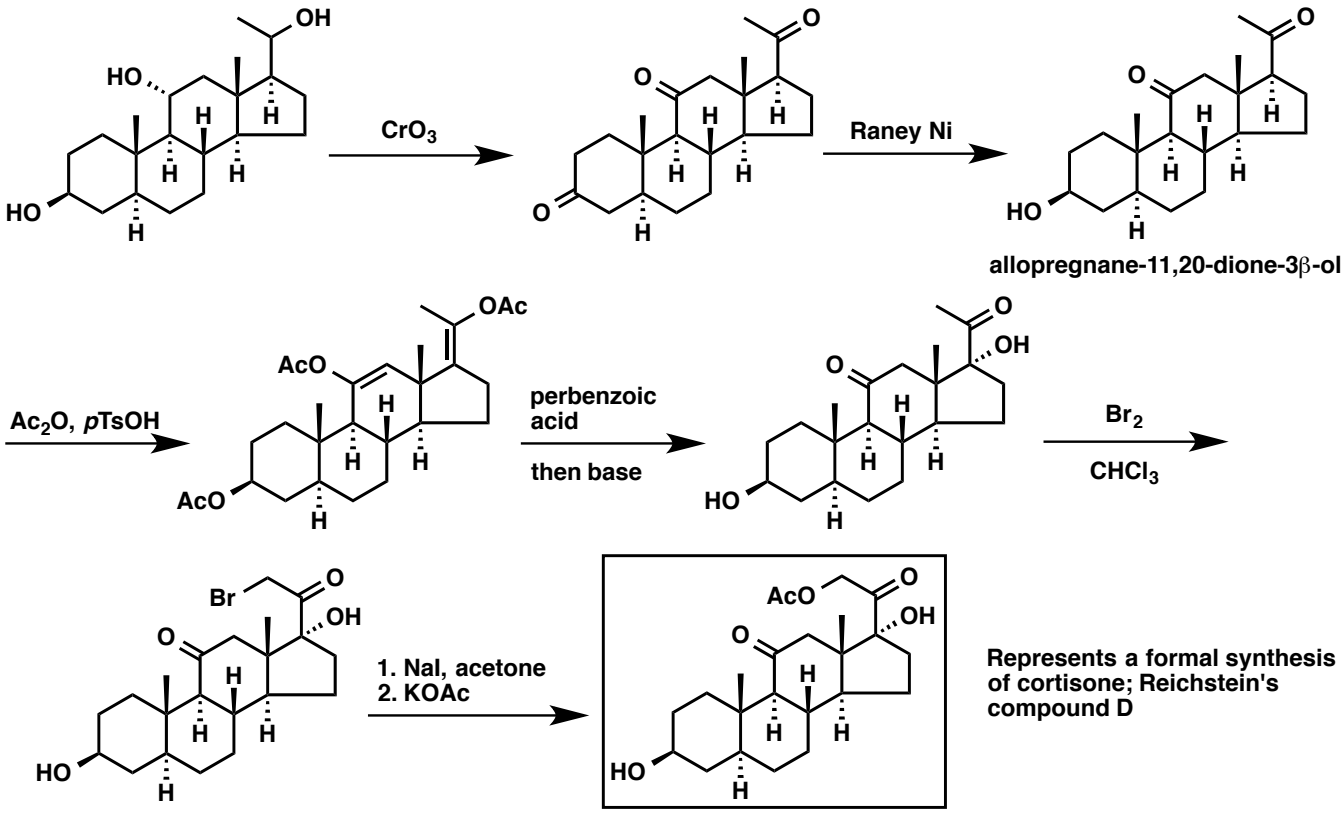
■ Study on acetylated diosgenin: access handle to C11



Rosenkranz, G.; Romo, J.; Batres, E.; Djerassi, C. *J. Org. Chem.* **1950**, *16*, 290.
Rosenkranz, G.; Romo, J.; Batres, E.; Djerassi, C. *J. Org. Chem.* **1950**, *16*, 298.

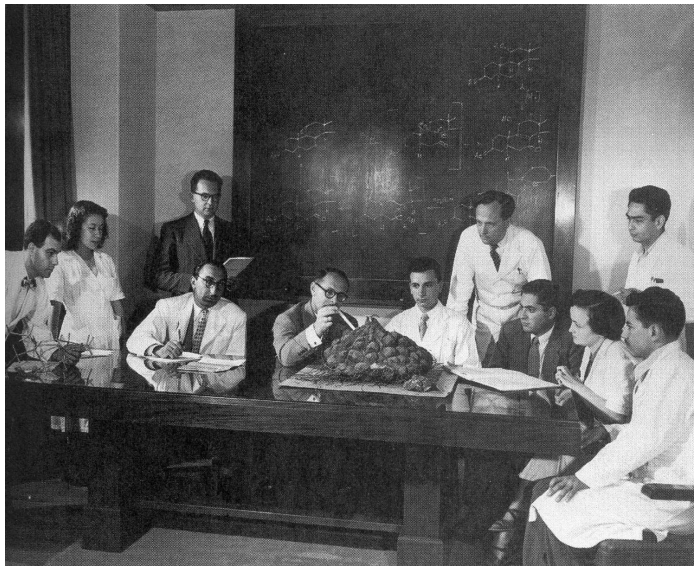


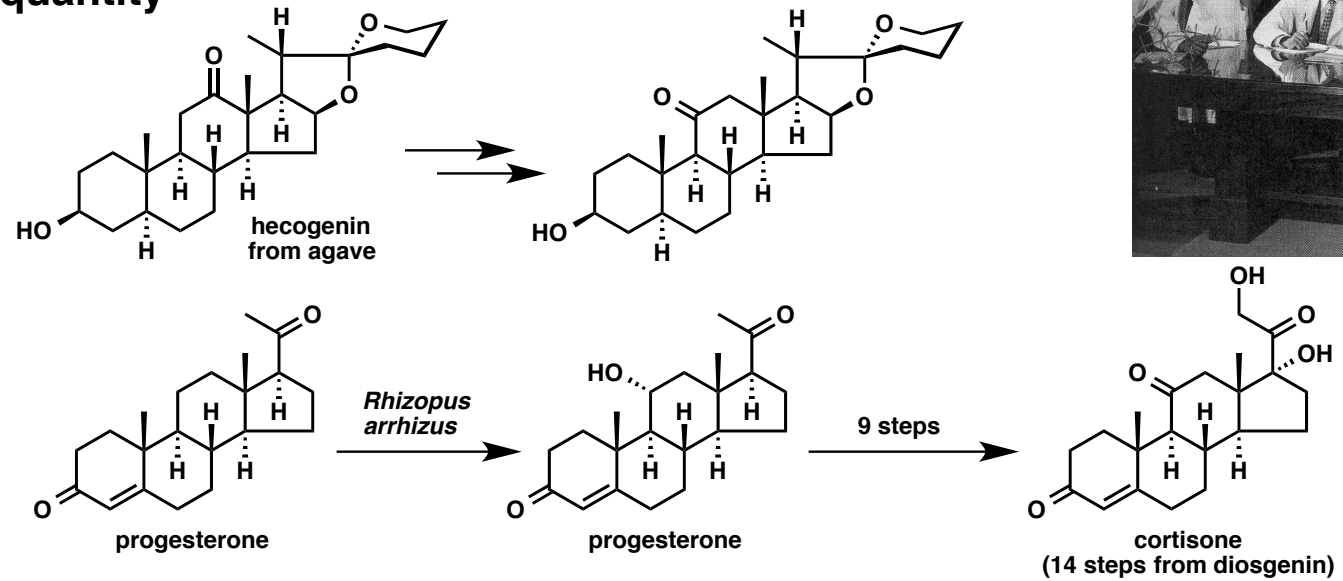
Djerassi, C. Rosenkranz, G.; Romo, J.; *J. Org. Chem.* **1951**, *16*, 754.
Stork, G. Romo, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 3546.
Romo, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 5489.



Djerassi, C. Rosenkranz, G.; Romo, J.; *J. Org. Chem.* **1951**, *16*, 754.
Stork, G. Romo, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 3546.
Romo, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 5489.

- **Syntex also finds route from hecogenin**
- **Upjohn discovers microbial oxidation at C11**
- **Requires tons of progesterone, Syntex is the only company that has the ability to supply that quantity**

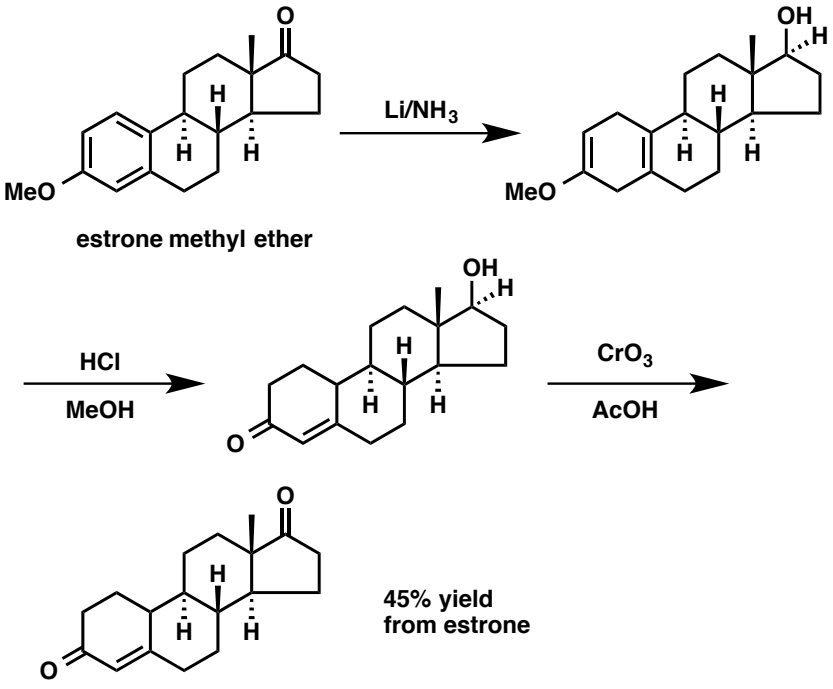


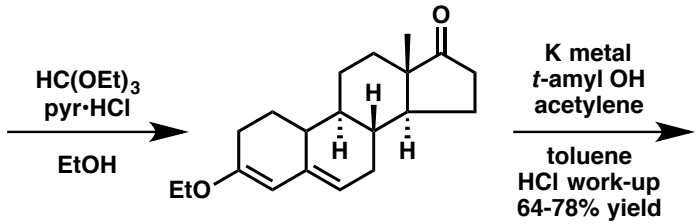


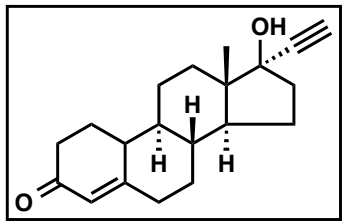
- "Our synthesis of cortisone from a plant raw material, rather than from animal-derived bile, not only made scientific headlines but even resulted in articles in *Fortune* and *Life*. The *Life* article showed us in a silly picture posed around a bare conference table supporting a huge Mexican yam from which we supposedly made cortisone. George Rosenkranz, the only person in that group over the age of 30, is holding a test tube of cortisone (my vague recollection is that the tube was filled with salt, because we had only made a minute quantity of cortisone at the time), and we seem to be mesmerized by the huge and somewhat ominous-looking yam."

Djerassi, C.; Ringold, H. J.; Rosenkranz, G. *J. Am. Chem. Soc.* **1951**, *73*, 5513.
Peterson, D. H.; Murray, H. C. *J. Am. Chem. Soc.* **1952**, *74*, 1871.
Mancera, O.; Zaffaroni, A.; Rubin, B. A.; Sondheimer, F.; Rosenkranz, G.; Djerassi, C. *ibid*. **1952**, *74*, 3711.

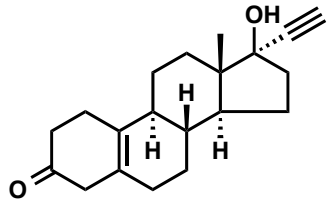
- **Progesterone: hormone that inhibits ovulation**
- **Investigated around time of the cortisone synthesis**
- **C19 methyl group important to biological activity; analogs lacking C19 group have significantly increased activity**
- **Syntex patents orally active norethindrone**







19-nor-17α-ethynyltestosterone (norethindrone)

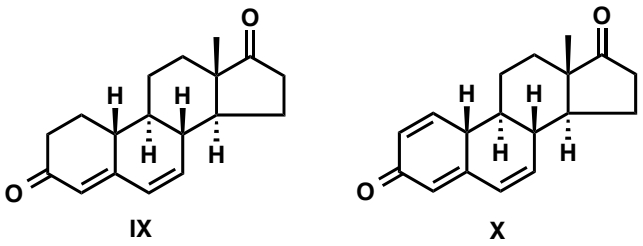


1953: Frank B. Colton of G. D. Searle & Co. patent norethynodrel; isomerizes to norethindrone in stomach acid

- **First effective oral contraceptive, but also effective in treating pain and bleeding**

Djerassi, C.; Miramontes, L.; Rosenkranz., G. *U.S. Patent 2744 122* (orig. appl. Nove 22, 1951)
Wilds, A. L.; Nelson, N. A. *J. Am. Chem. Soc.* **1953**, *75*, 5366.
Djerassi, C.; Miramontes, L.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc.* **1954**, *76*, 4092.

- **"In January 1952, I left sunny Mexico City and drove to cold, dirty, slushy Detroit. In the end, it was the most direct route to California, where I have now spent three decades."**
- **Absolute configuration by optical rotatory dispersion**
- **Optical rotatory dispersion: variation in optical rotation with change in wavelength of light**
- **Studies changes in rotation with respect to changes in structure of ketone steroids**



IX

X

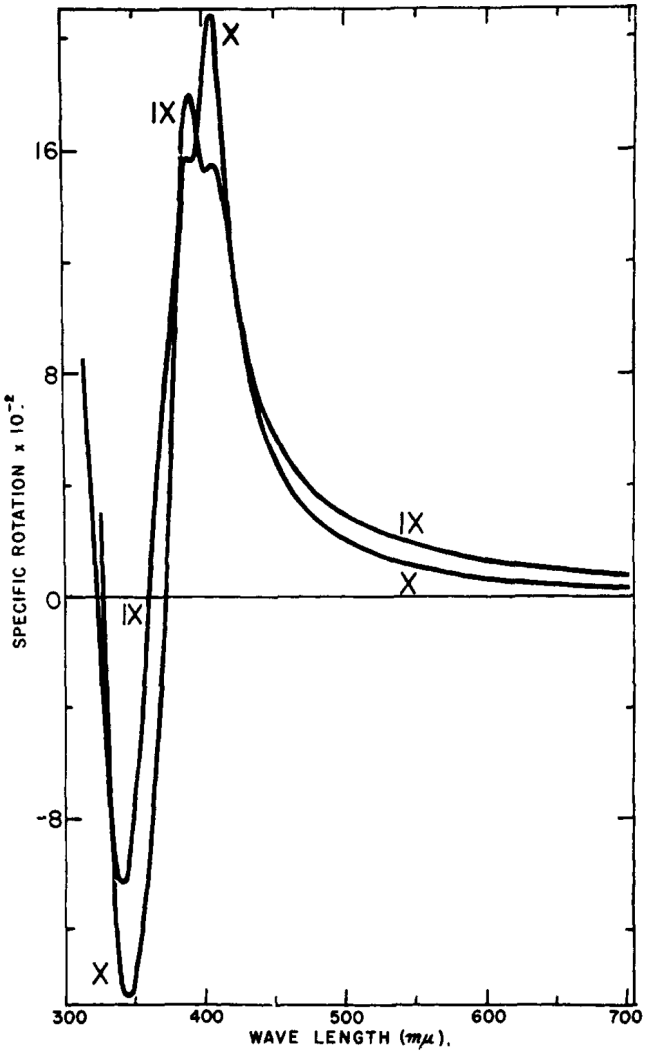
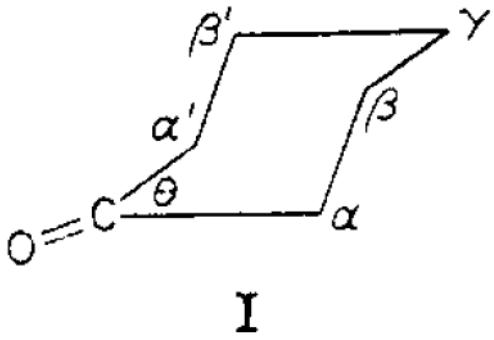


Fig. 3.—Rotatory dispersion curves of: $\Delta^{4,6}$-androstadiene-3,17-dione (IX) and $\Delta^{1,4,6}$-androstatriene-3,17-dione (X).

Djerassi, C. Foltz, E. W.; Lippman, A. E. *ibid.* **1952**, *77*, 4354.

■ **Octant rule: stereochemistry and conformation of substituted cyclohexanones vs Cotton effect**



I

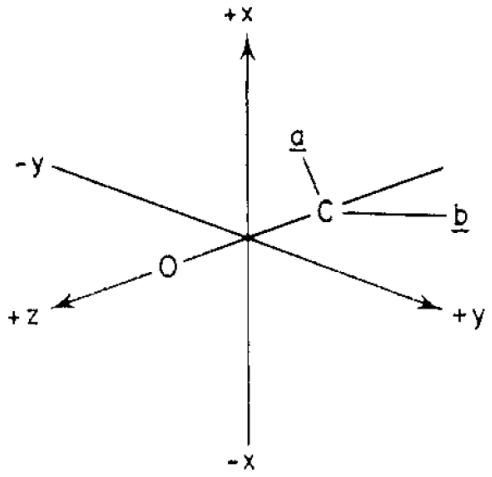


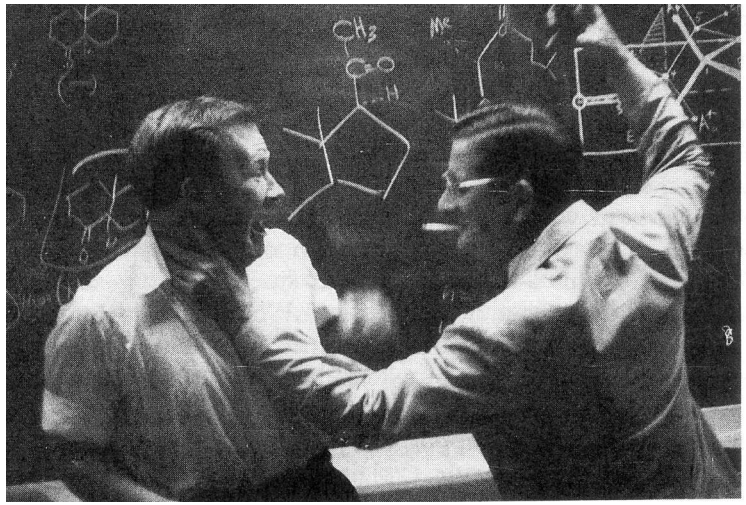
Fig. 1.

+ x − y − z	+ x + y − z
− x − y − z	− x + y − z

Back octants

+ x − y + z	+ x + y + z
− x − y + z	− x + y + z

Front octants



Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.

- **Invited by W. S. Johnson; moves into Stauffer building**
- **Studies circular dichroism applied to ketone steroids**
  - **differential absorption versus circularly polarized light**

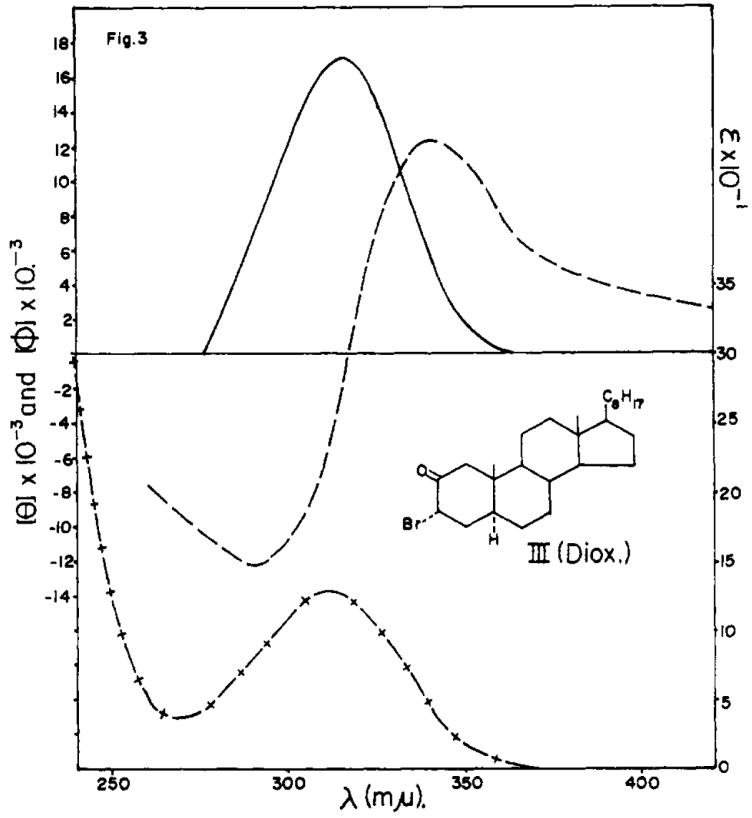
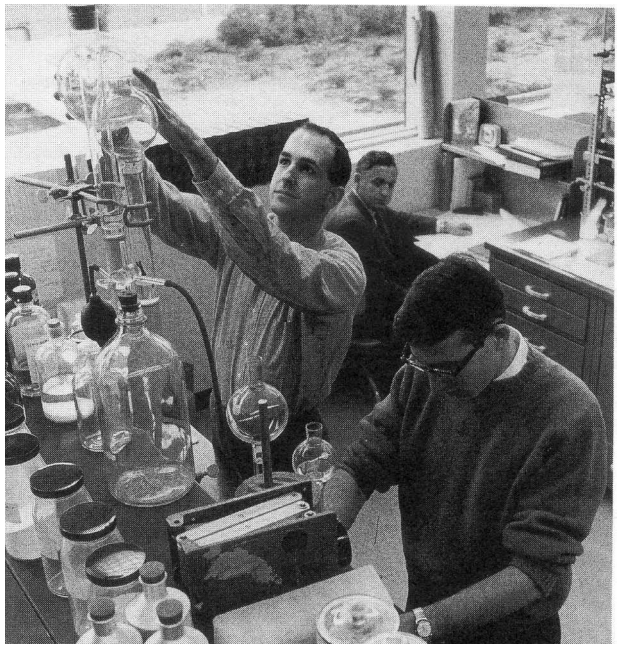
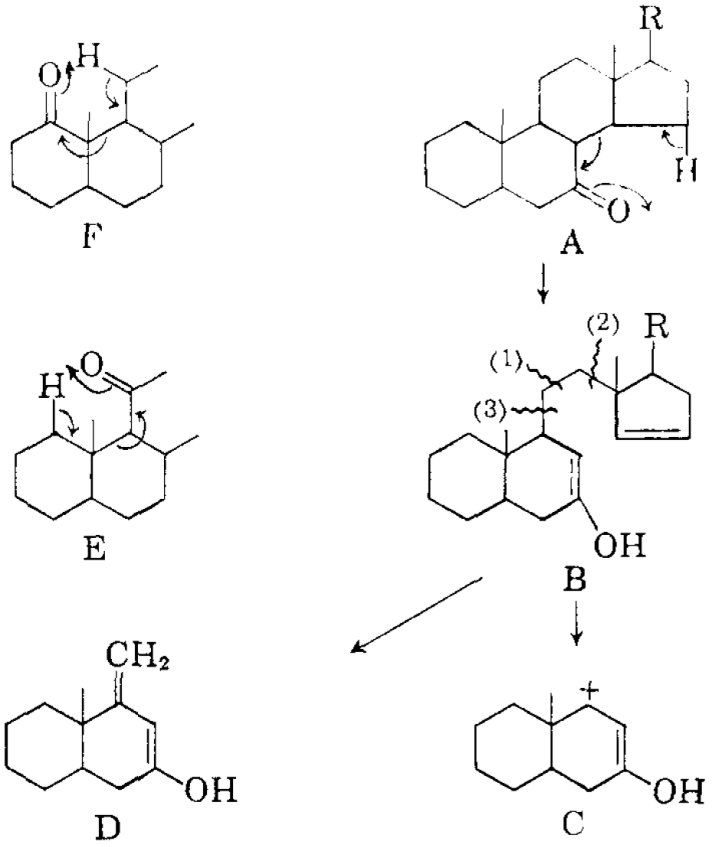


Fig. 3.—Circular dichroism (———), optical rotatory dispersion (– – – –) and ultraviolet absorption (– + – +) curves of 3α-bromocholestan-2-one (III) in dioxane solution.

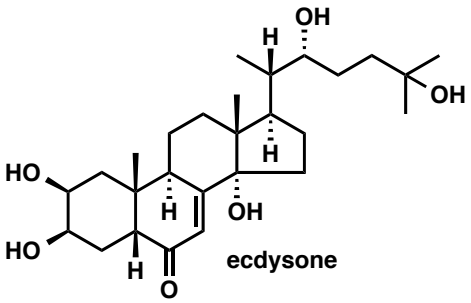


- **Mass spectrometry is a new analytical technique**
  - **Applied to small molecules**
  - **Studied fragmentation ions versus structure**
  - **Isotopic labeling studies**
- **Early studies with computer modeling**
- **Characterization of marine sterols**
- **Studies of phospholipids**

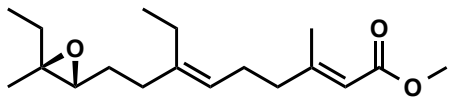


Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1430.

- **Zoe: life; con: control**
- **A new approach to pest control: Insect Growth Regulators (IGR)**
  - **Control/halt life cycle of insect and prevent reproduction**
  - **Does not affect crops, humans, and animals**
  - **Problems:**
    - **Natural hormones last for hours or are metabolized; make analogs**
    - **Does not actually kill pests, must deal with one generation**
    - **Some pests are most destructive when in early stages of life cycle**
      - **Target pests that are benign in early stages (e.g. mosquitos)**
- **1960's: Peter Karlson discovers ecdysone, hormone that controls molting**
  - **a complex steroid; too difficult for commercial purposes**
- **juvenile hormone (JH) discovered; C17 sesquiterpenoid and amenable to synthesis**

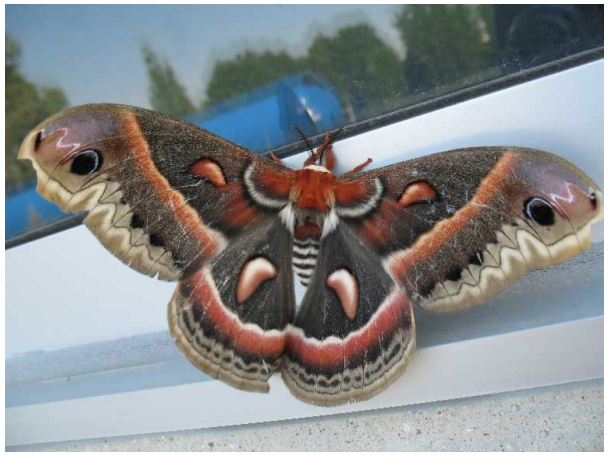


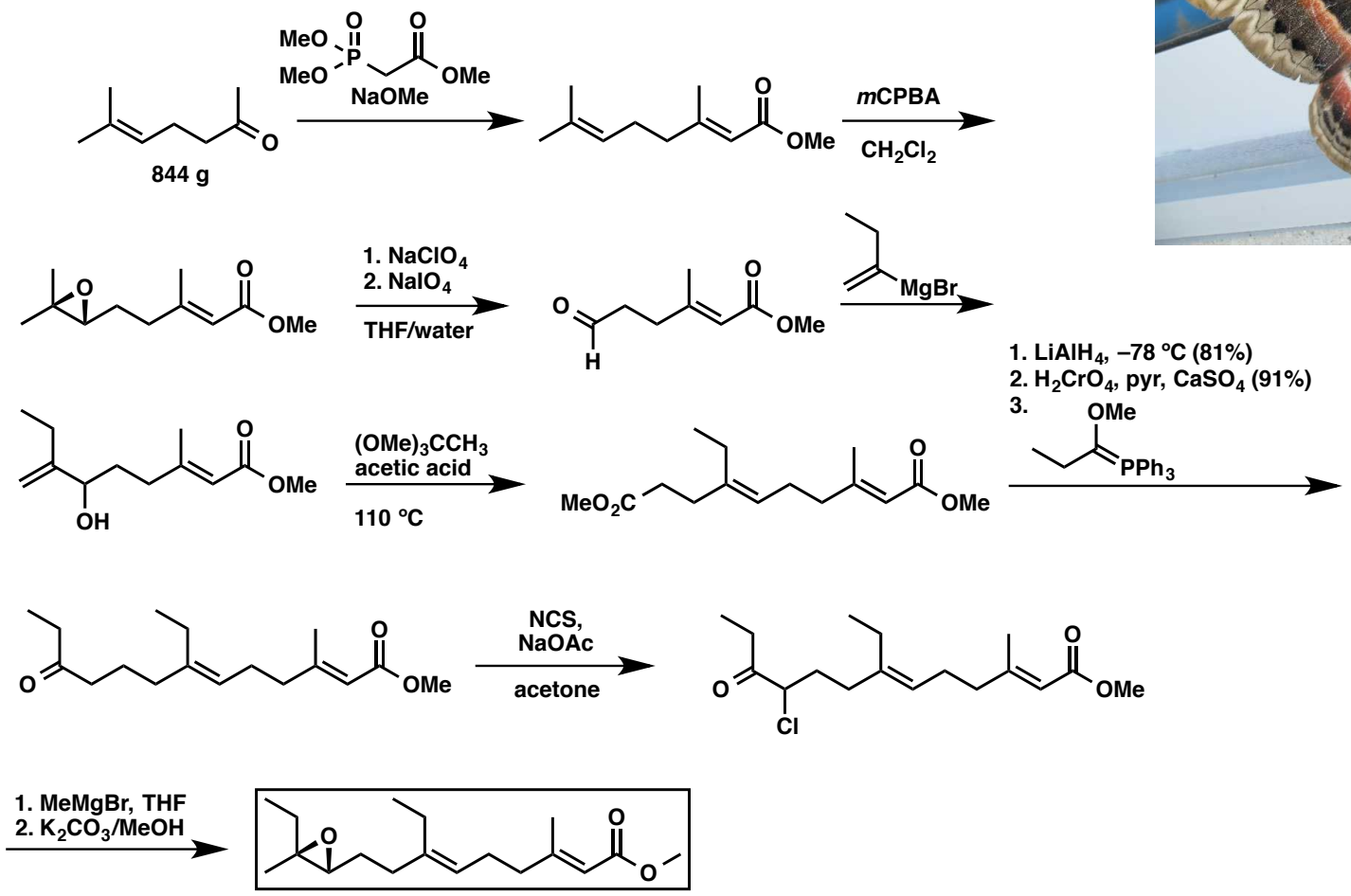
ecdysone



A Juvenile Hormone (JH)

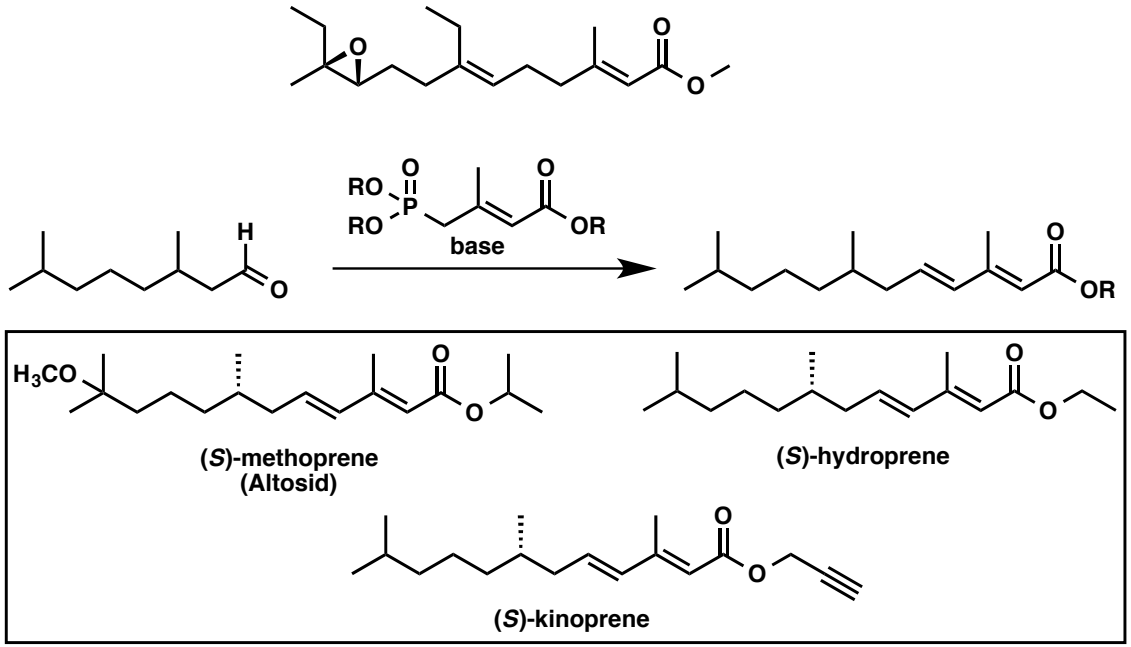
■ Synthesis of C-18 and C-17 Cecropia JHs





Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Am. Chem. Soc.* **1971**, *94*, 5374.
Anderson, R. J.; Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Am. Chem. Soc.* **1971**, *94*, 5379.

- **Synthesis of analog—observations of structure-activity relationship**
  - **ethyl ester more active than methyl; is hydrolyzed slower**
  - **hydration of C6 alkene does not affect activity**
  - **Introducing another alkene in conjugation improves activity**
  - **More effective without an epoxide**
- **(*S*)-methoprene (Altosid: Alto- from Palo Alto, -sid from Siddall)**
- **Proves to be most effective analog in original report**



Henrick, C. A.; Staal, G. B.; Siddall, J. B. *J. Agr. Food Chem.* **1973**, *21*, 354.

- **IRG pesticides are a huge success**
  - **Altosid: mosquitos**
  - **Extinguish: fire ants**
  - **Gentrol: fruit flies, roaches, bed bugs**
  - **Precor: fleas**
  - **Can even be used on silkworms to improve silk production**
- **Altosid approved by WHO for use in water cisterns**
- **Zoecon bought by Sandoz in 1983**

- **A career starting in 1942; still lectures and writes today**
- **Important contributions to organic chemistry—steroids, mass spectrometry, and optical rotation**
- **Impacts to society with regards to birth control pill and IGR pesticides**
- **Now known by general public for his science writing**
  - **“science-in-fiction” genre, ethics of scientific research**
- **Professor Emeritus at Stanford; lives in San Francisco, London, and Vienna**