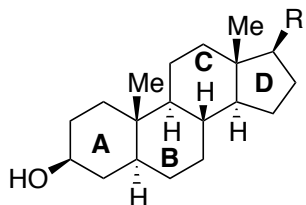


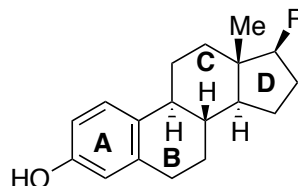
CHEM 330

Topics Discussed on Sept 30

Steroids: hormones involved in the regulation of a large number of biological processes and possessing the general structure shown below:



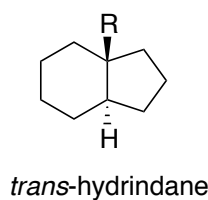
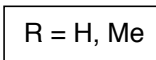
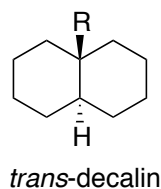
"ordinary" steroids exhibit an aliphatic A-ring. Group R may be many things



estrone: a typical aromatic A-ring steroid. These steroids are important female hormones

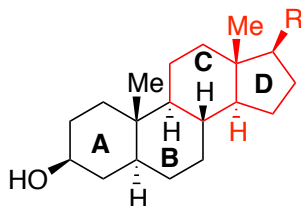
Difficulties encountered in the isolation of steroid hormones from natural sources and consequent interest in a chemical synthesis of such compounds starting in the 1940's

Trans-decalin and trans-perhydroindane ("hydrindane") subunits of steroids

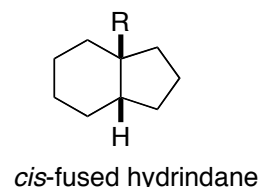
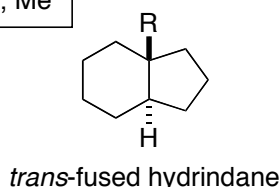
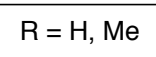
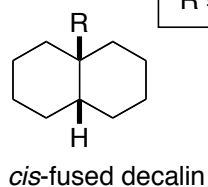
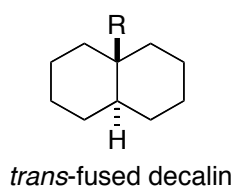


Strained nature of *trans*-hydrindane due to bond angle distortion (make models!!) as a source of many difficulties associated with early syntheses of steroids

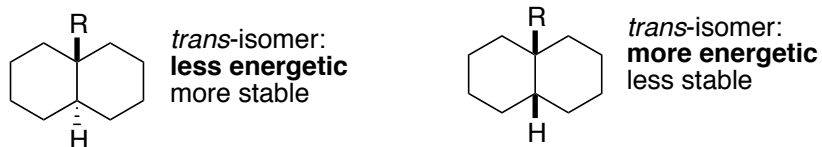
Problematic formation of a *trans* junction between rings C and D of steroids



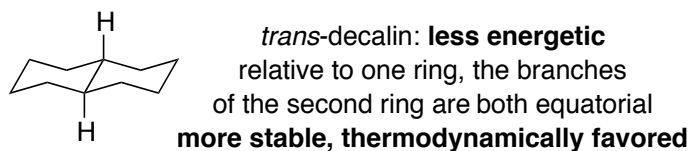
Decalins and perhydrohydrindanes: *cis* and *trans* ring fusion



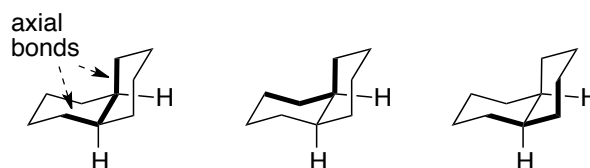
Energetically **favorable** *trans*-ring fusion in decalin (especially when R = Me)



Reasons for the greater energy content of *cis*- vs. *trans*-decalin: presence of three additional *gauche*-butane type interactions:

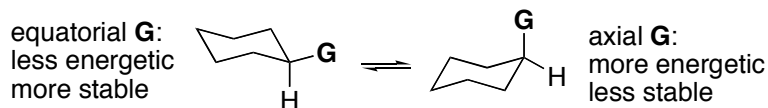


cis-decalin: **more energetic**
relative to one ring, one branch of the
second ring is axial. This results in 3 *gauche*-
butane interactions that are absent in the
trans-isomer, and that add up to:
 $3 \times 0.9 \text{ kcal/mol} = 2.7 \text{ kcal/mol}$
less stable, thermodynamically disfavored



reminder

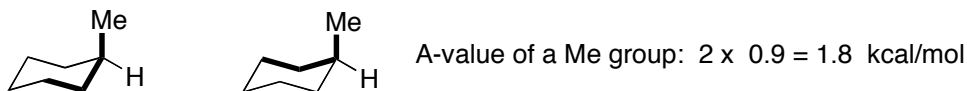
A-value of a group, **G** (see table of A-values on CHEM 330 website, "handouts" page): the energy difference between the equatorial and axial conformation of a monosubstituted chair-cyclohexane carrying group **G**:



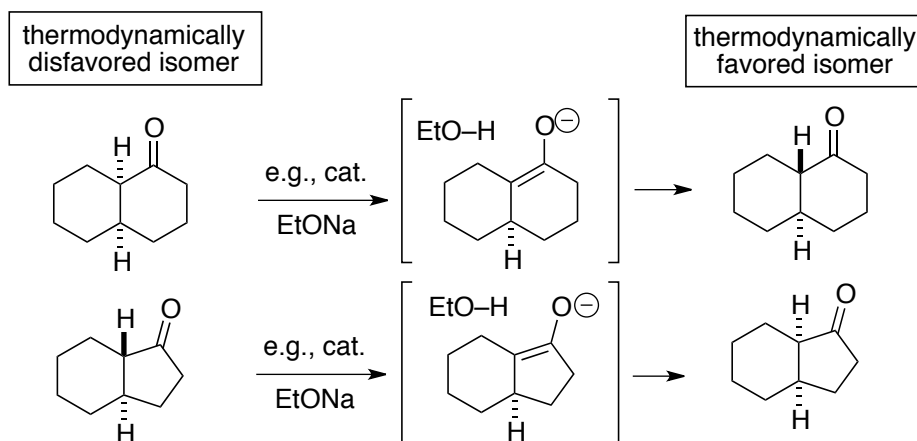
The energy difference
between the two
conformers is the
A-value of group **G**

The A-value of a group **G** as twice the magnitude of a *gauche*-butane interaction in a system such as $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-G}$. For example, the A-value of a Me group is. ca. 1.8 kcal/mol, because:

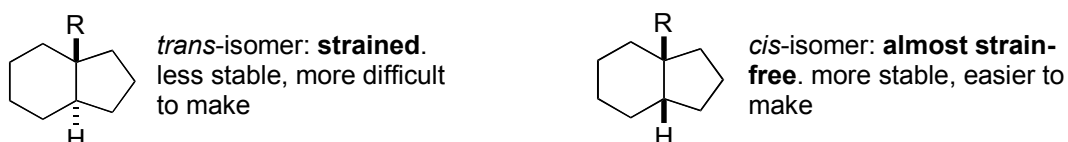
- *gauche*-butane contains 0.9 kcal/mol more energy than *anti*-butane (energy minimum)
- an axial Me group experiences *two* *gauche*-butane interactions with ring carbons:



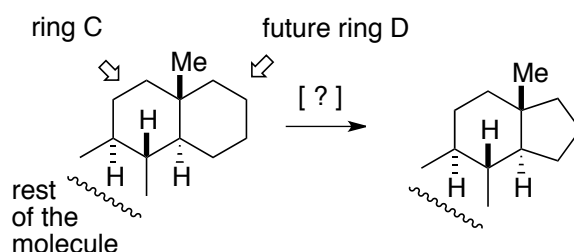
Facile isomerization of *cis*-decaline ketones to the *trans*-isomer and of *trans*-hydrindane ketones to the *cis*-isomer under mildly basic conditions:



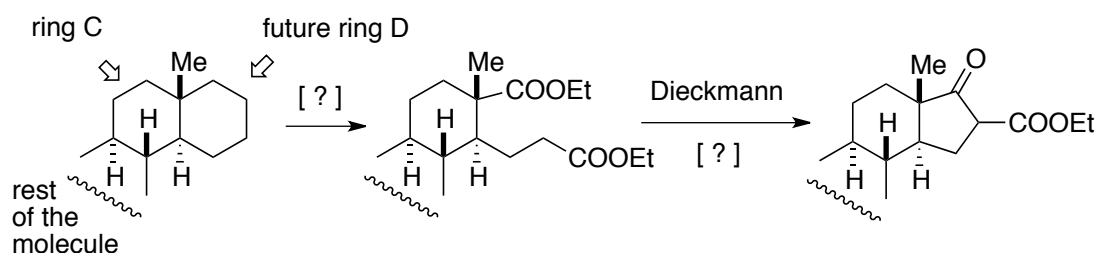
Energetically **unfavorable** *trans*-ring fusion in hydrindane (especially when R = Me) due to bond angle strain (make molecular models!!)



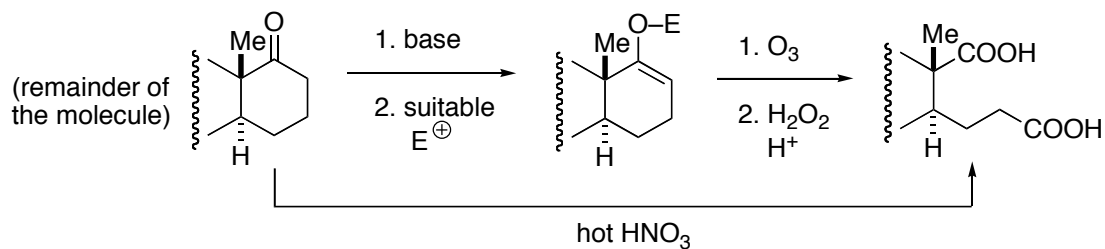
Pre-1970's approach to the creation of the C-D ring system of a steroid: prepare such a molecular subunit in the form of *trans*-decalin, then somehow contract the 6-membered ring into a 5-membered ring to form the *trans*-hydrindane!



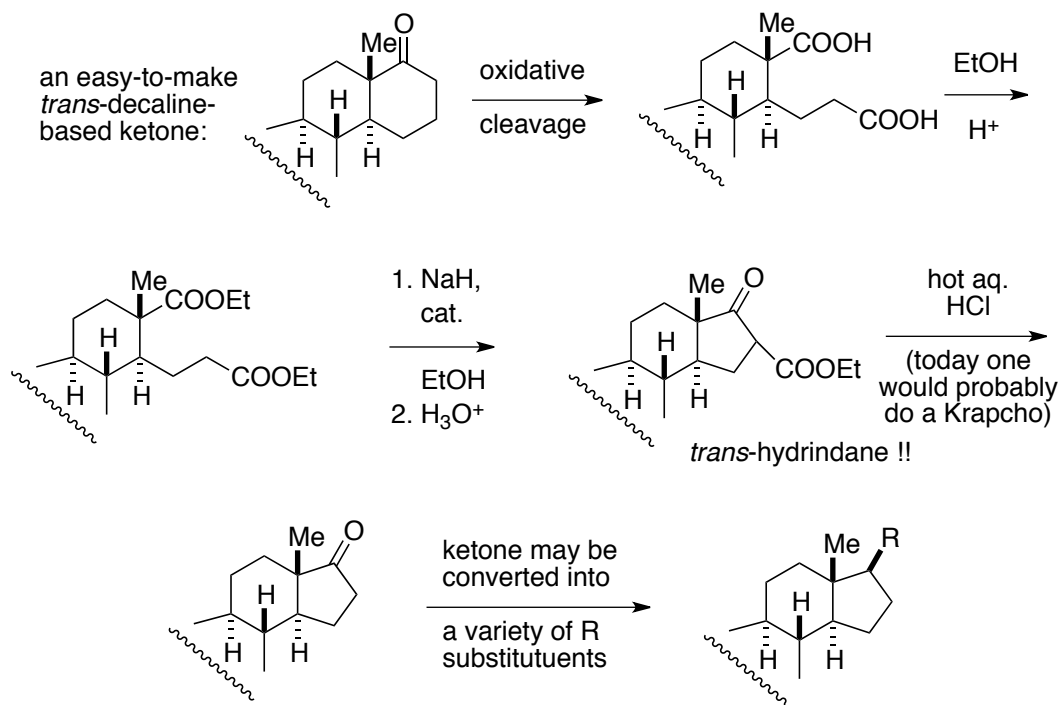
Approach to the creation of the C-D ring system of a steroid: prepare such a molecular subunit in the form of *trans*-decalin, then somehow break the ring to form a diester and carry out a Dieckmann condensation to build a 5-membered ring!



Oxidative ring cleavage of cyclic ketones, e.g., by ozonolysis of enol derivatives or by treatment with hot concentrated HNO_3

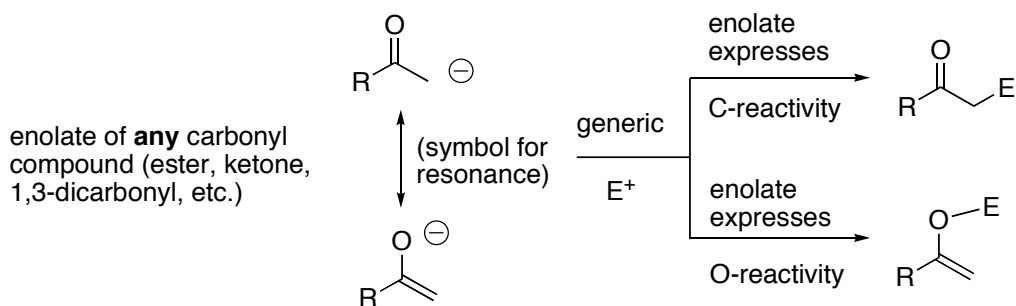


Claisen-Dieckmann avenue to *trans* C-D ring motifs of steroids, e.g:



Significance of enolate alkylation reactions, leading to the formation of new C–C bonds, in the synthesis of compounds of current biomedical interest

Reaction of enolates with electrophilic agents (" E^+ "): the question of C- vs. O-reactivity:



"Ambident" character of enolates = their ability to react at C as well as at O

Importance of the products resulting from C- and O-reaction of enolates in contemporary organic chemistry

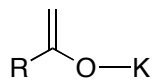
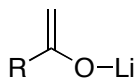
Principle: a multitude of factors, some of them rather subtle, control the C- vs. O-reactivity of an enolate. Three such factors that have a major influence on the reactivity of enolates are, in order of increasing importance:

- the nature of the metallic counterion that accompanies the enolate (significant)
- the solvent (very significant)
- the nature of the electrophile that reacts with the enolate (most significant)

Influence of the metallic counterion: C-reactivity is more pronounced in enolates incorporating more electronegative, and consequently more strongly Lewis acidic, metal ions, such as Li^+ . O-reactivity is more pronounced in enolates containing more electropositive, less strongly Lewis acidic metal ions such as K^+

Li is smaller and more electronegative than K, therefore:

- short, stronger O–Mt bond
 - less strongly polarized
 - lower e^- density around O
- greater C-reactivity**



- long, weaker O–Mt bond
 - more strongly polarized
 - higher e^- density around O
- greater O-reactivity**