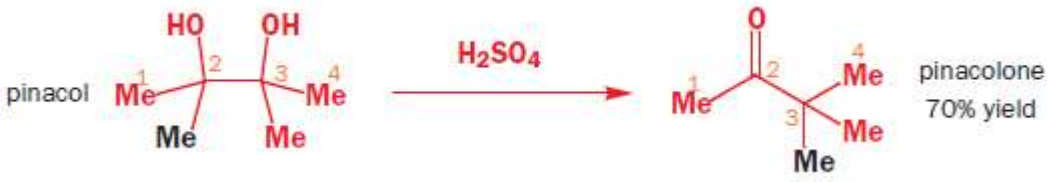
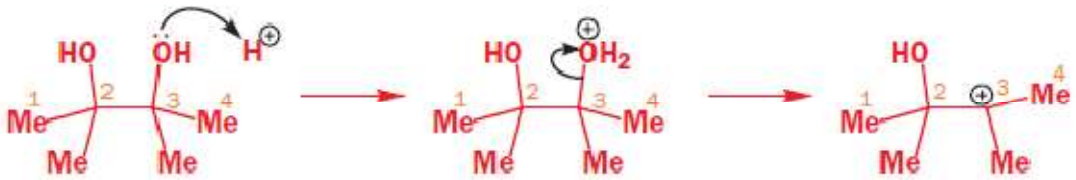
## The pinacol rearrangement:

Is the reaction of **1,2-diol 'pinacol**, formed from acetone' with **acid**, gives **pinacolone** by **rearrangement**.



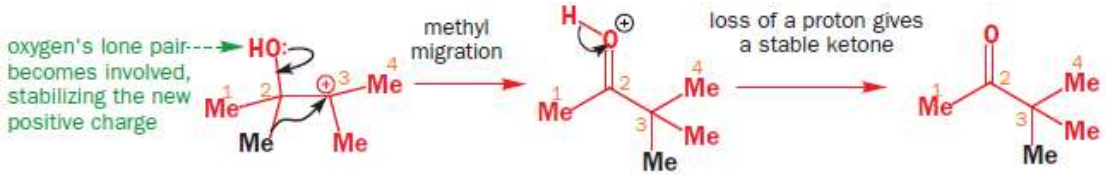

## Mechanism:

Firstly **protonation of one of the hydroxyl groups** then it leaves as water, giving the **carbocation**.




The **carbocations rearrange** by **alkyl shifts** to get **more stable** but this **carbocation** is already **tertiary**, and there is **no ring strain**, so why should it rearrange?

Here **have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom**. That **oxygen is very good at stabilizing a positive charge on an adjacent atom**, and **somewhat less good at stabilizing a positive charge two atoms away**. **By rearranging, the first-formed carbocation gets the positive charge into a position where the oxygen can stabilize it, the loss of a proton from oxygen then gives a stable ketone**.

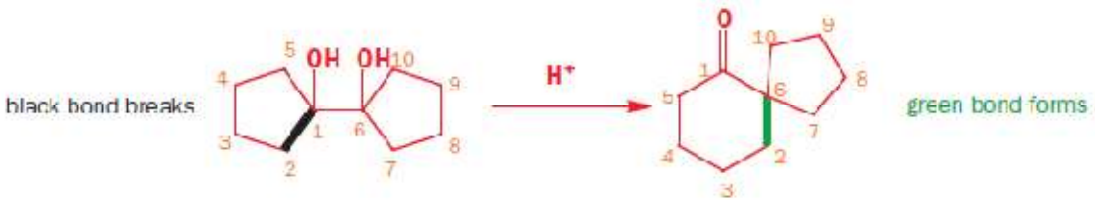



**Note:** Unlike **sulfur**, which **stabilizes a charge 2 atoms away better than it stabilizes a charge on an adjacent atom**.

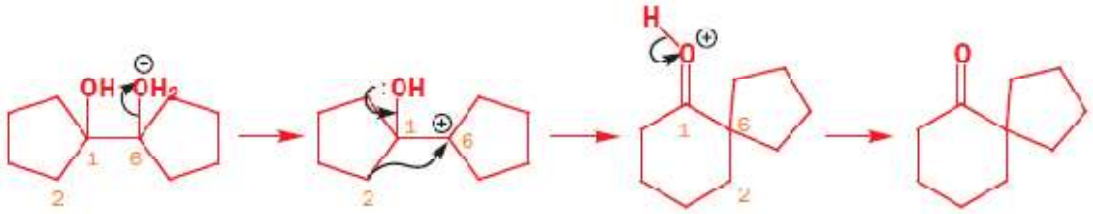
-You can view the **pinacol rearrangement** with a '**push**' and a '**pull**'. The **carbocation formed by the departure of water 'pulls' the**

**migrating group across at the same time as the oxygen's lone pair 'pushes' it**. A particularly valuable type of **pinacol rearrangement** forms **spirocyclic ring systems** (**Spirocycles are pairs of rings joined at a single carbon atom**).

**Example:** The atom 2 has migrated from atom 1 to atom 6.

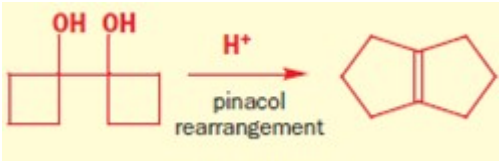



**Mechanism:** It doesn't matter which hydroxyl group you protonate or which adjacent C–C bond migrates they are all the same. **One five-membered ring** expands to a **six-membered ring** but the reason this reaction happens is the **formation of a carbonyl group**, as in **pinacol rearrangements**.

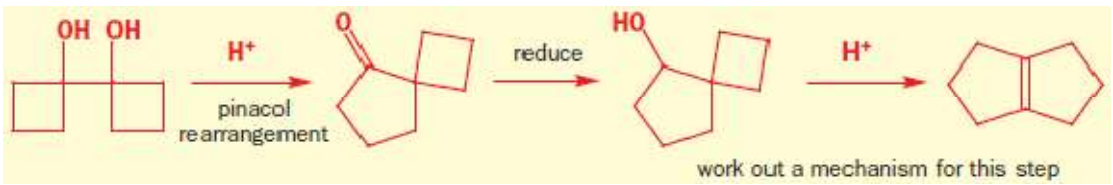


**Use The pinacol reaction in the synthesis:**

**Example:** Synthesis of the bicyclic alkene starts with a pinacol reaction.



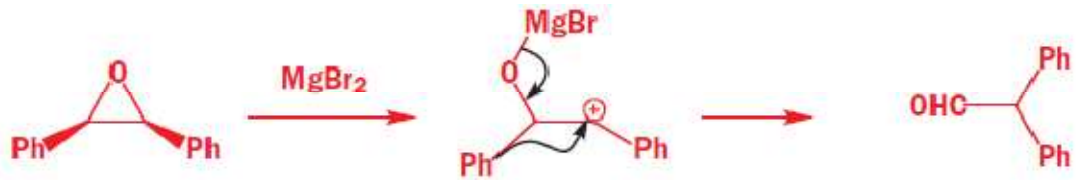

The '**pinacol' dimer from cyclobutanone rearranges with the expansion of one of the rings to give a cyclopentanone fused spiro to the remaining four-membered ring. Reduction of the ketone then gives an alcohol that rearranges to the alkene in acid**.



- The mechanism for this transformation is initiated by **protonating the alcohol** and allowing **water to leave to give a cation**.

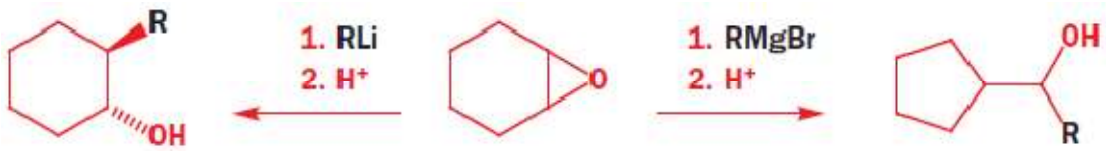
**Epoxides rearrange with Lewis acids in a pinacol fashion:**

The intermediate cation in a pinacol rearrangement can formed from an epoxide, and **treating** **epoxides** with **acid (**such as **$MgBr_2$)**.

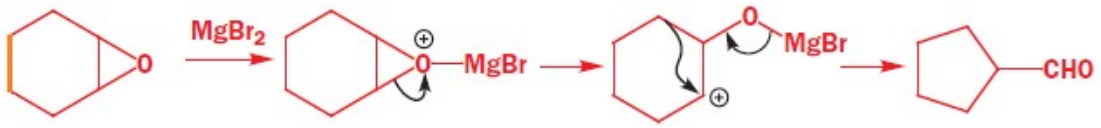



**Note: Rearrangement of epoxides** with **magnesium salts** means that **opening epoxides with Grignard reagents can give surprising results**.

**Examples:**




**Mechanism:**



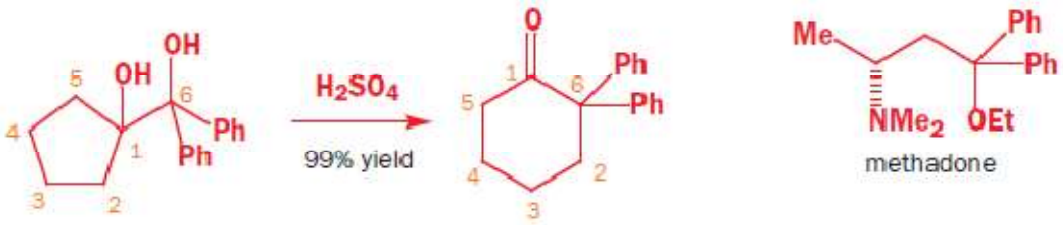

**Note:** The **alkyllithium reaction** is quite straightforward as long as the alkyllithium is free of lithium salts. A clue to what has happened with the Grignard reagents comes from the fact that treating this **epoxide with just $MgBr_2$ (no RMgBr) gives an aldehyde**. With a **Grignard reagent**, rearrangement occurs faster than addition to the epoxide, and then the **Grignard reagent adds to the aldehyde**.

**The pinacol rearrangements choice of the migrating group:**

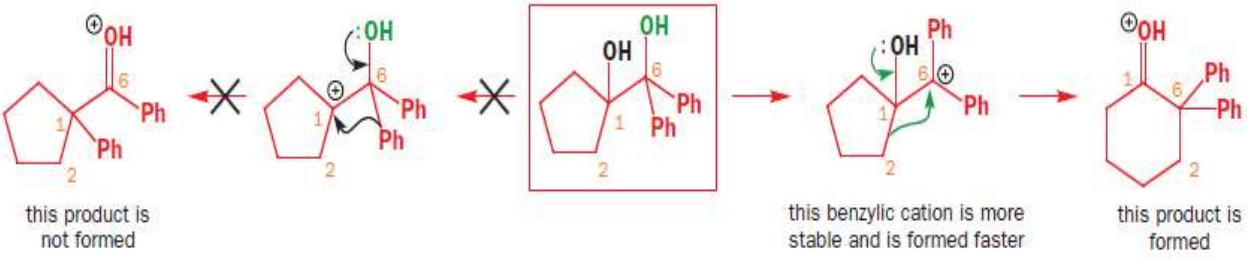
When **diols** and **epoxides** are **symmetric**, it **does not matter which hydroxyl group is protonated and leaves, which end the epoxide opens, nor which group migrates**. When an **unsymmetrical diol** or **epoxide rearranges**, it is important which way the reaction goes. The **reaction leaves behind a more stable cation**.

**Note: unsymmetrical diol** gives the **ring-expanded ketone**, a starting material for the synthesis of analogues of the drug methadone.

**Example:**




**Mechanism:** This product is formed because the **green OH group leaves more readily than the black because the carbocation stabilized by two phenyl groups forms more readily than the carbocation stabilized by two alkyl groups.** The **migration step follows without selectivity as both alkyl groups on the black alcohol are the same**.

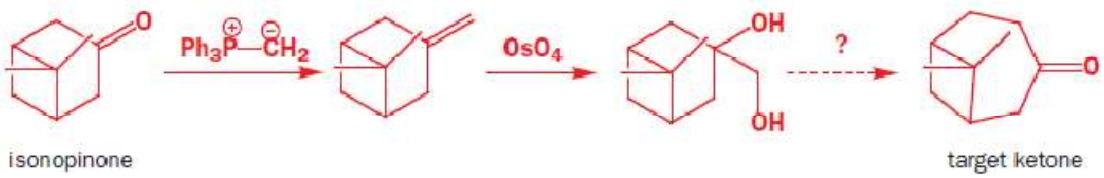



- Most **unsymmetrical diols** or **epoxides** give **mixtures of products upon rearrangement**. The problem is that there is a **choice of two leaving groups** and **two alternative rearrangement directions**, and only for certain substitution patterns is the choice clear cut.

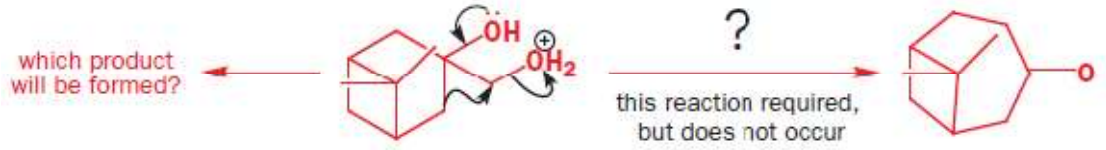
**Semipinacol rearrangements are pinacol reactions with no choice about which way to go:**

In 1971, French chemists needed this **seven-membered cyclic ketone**. A reasonable starting material to use is this diol because it can be made in two steps from the natural product **isonopinone.**

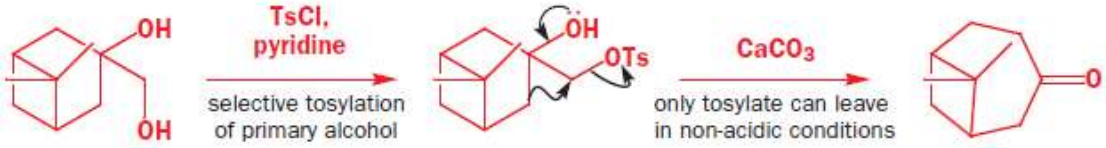
**Example:**



The reaction they needed for the **last stage** is a **pinacol rearrangement** the ***primary*** **hydroxyl group** needs **persuading to leave** as the **ring expands**. The problem is that the **tertiary hydroxyl group is much more likely to leave since it leaves behind a more stable carbocation**.

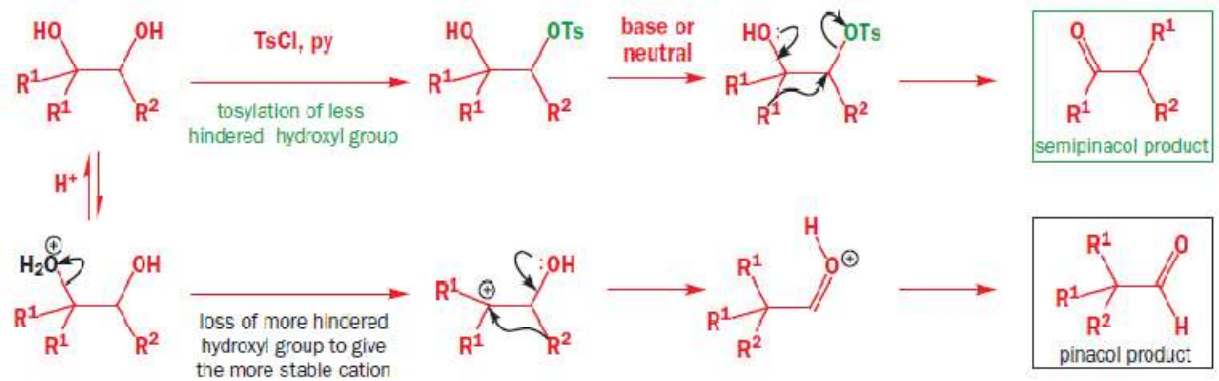



The solution to this problem is to force the **primary hydroxyl group** to be the **leaving group** by **making it into a tosylate**. The **primary hydroxyl group reacts more rapidly with TsCl** than the **tertiary** one because it is **less hindered**. A **weak base** is now all that is needed to **make the compound rearrange in what is known as a semipinacol rearrangement**.

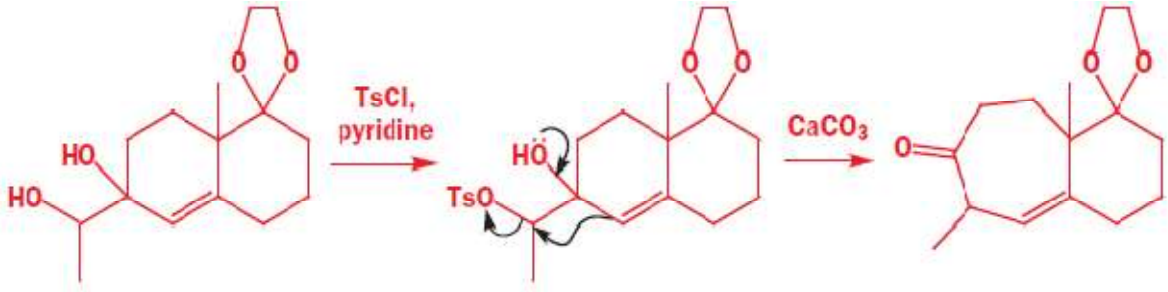



Semipinacol rearrangements are rearrangements in which a hydroxyl group provides the electrons to 'push' the migrating group across, but the 'pull' comes from the departure of leaving groups other than tosylate in example, but typically also halide or nitrogen ($N_2$). Since tosylation occurs at the less hindered hydroxyl group of a diol, not only can semipinacol rearrangements be more regioselective than pinacol rearrangements, but their regioselectivity may be in the opposite direction.

**Examples:**

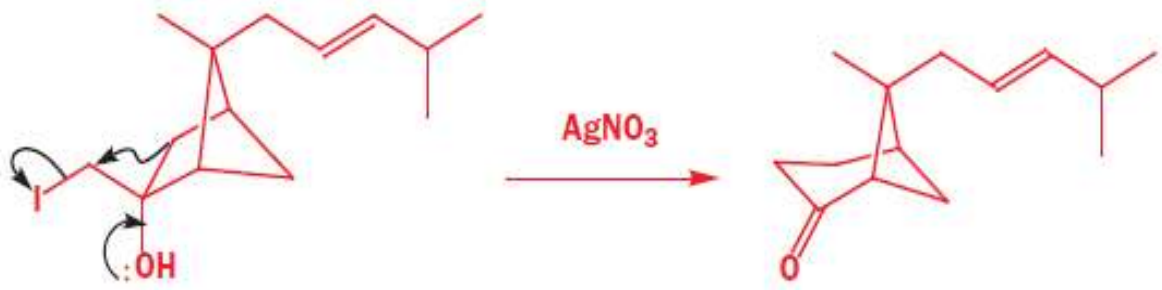


**Example:** Corey exploited this in a synthesis of the natural product longifolene. He needed to persuade an easily made 6,6-fused ring system to undergo rearrangement to a ring-expanded ketone. a normal acid-catalyzed **pinacol rearrangement is no good the tertiary, allylic hydroxyl group is much more likely to ionize, and the acid-sensitive protecting group would be hydrolyzed too**. **Tosylation of the secondary alcohol in the presence of the tertiary is possible, and semipinacol rearrangement gives the required ketone**.




**Note:** The **leaving group** need **not be tosylate**: in the following example, part of a synthesis of bergamotene (a component of valerian root oil and the aroma of Earl Grey tea), a 2-iodo alcohol rearranges.

**Example:**

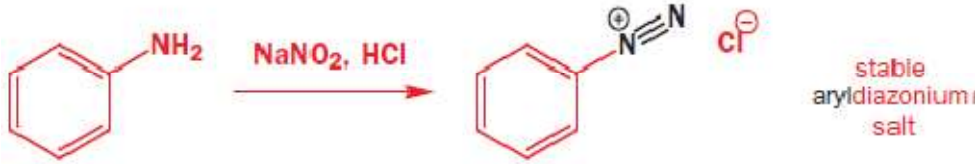



**Note:** Treating **2-halo alcohols** with **base** is a **good way to make epoxides**. Using **$AgNO_3$** to **improve iodide's leaving ability without increasing the nucleophilicity of the hydroxyl group favors rearrangement at the expense of epoxide formation**. There would certainly be a danger of **epoxide formation in strong base**.

**Semipinacol rearrangements of diazonium salts:**

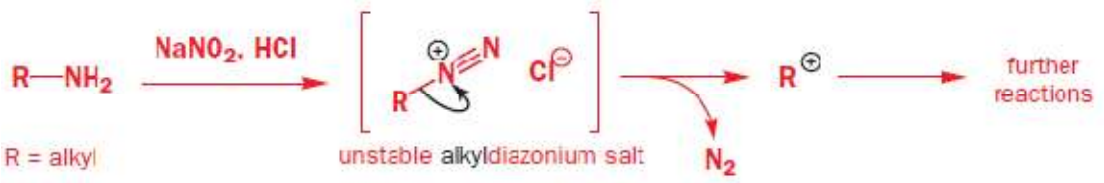
**Aromatic amines** can be **converted** to **diazonium salts** by **treatment** with **acidic sodium nitrite**.

**Example:**



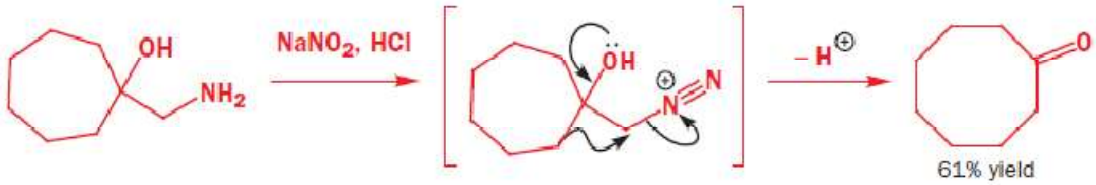

**Note: Aryldiazonium salts are stable but alkyldiazonium salts are not**: **nitrogen gas is the best leaving group**, **and, when it goes, it leaves behind a carbocation**.

**Mechanism:**

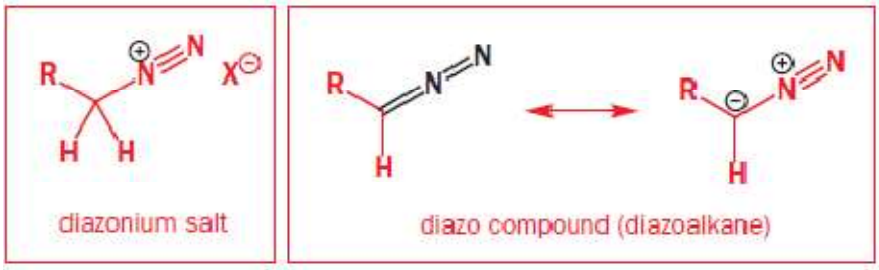



One of the 'further reactions' this **carbocation can undergo is rearrangement**. If the starting **amine is a 2-amino alcohol**, the **cation can be stabilized by a semipinacol rearrangement**. Semipinacol rearrangements of diazonium salts derived from 2- amino alcohols are sometimes called **Tiffeneau–Demjanov rearrangements**.

**Example:**

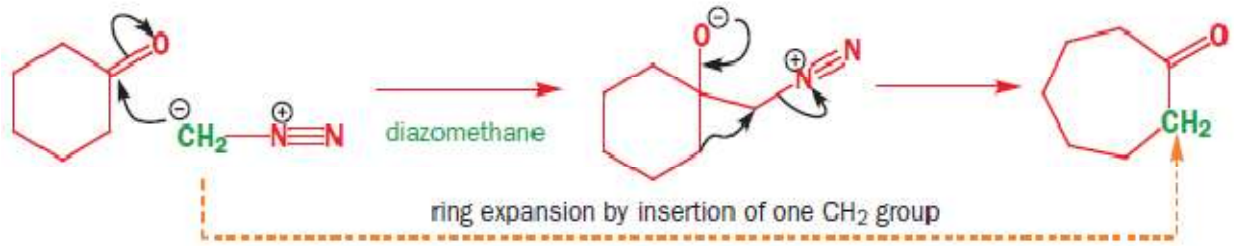



While **alkyldiazonium salts** are **unstable**, their conjugate bases, **diazoalkanes**, are **stable enough to be prepared and are nucleophilic towards carbonyl compounds**. **Diazoalkanes are neutral compounds having one fewer proton** than **diazonium salts** and **are delocalized structures with a central sp nitrogen atom**.



When **diazomethane adds to a ketone, the product undergoes a ring expansion by rearrangement** of the same type of intermediate.

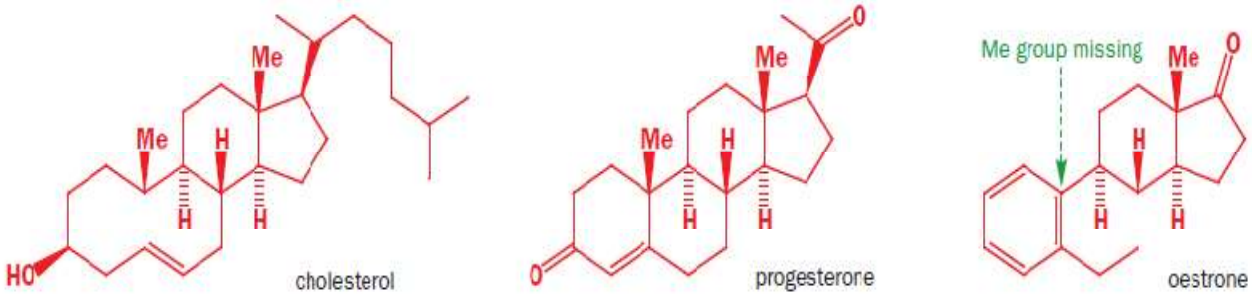
**Example:**




**Note:** The problem with reactions like this is that **both the starting material and product are ketones**, so they work cleanly only if the starting material is **more reactive than the product**. **Cyclohexanone is more reactive as an electrophile than either cyclopentanone or cycloheptanone**, so it **ring expands cleanly to cycloheptanone**. **But expansion of cyclopentanone to cyclohexanone is messy and gives a mixture of products**.

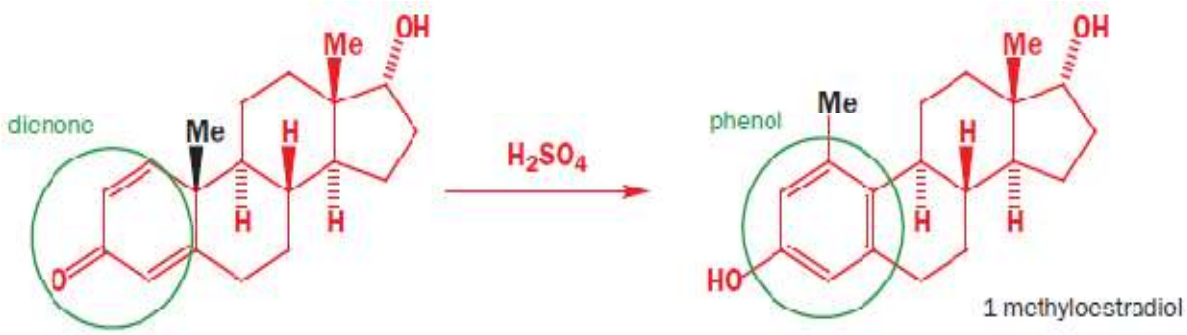
**The dienone–phenol rearrangement:**

The female sex hormone **oestrone** is the **metabolic product** of another hormone, **progesterone**, itself made in the body from **cholesterol**.




Oestrone lacks one of progesterone's methyl groups, probably removed in the body as $CO_2$ after oxidation. In 1946, Carl Djerassi, a man whose work led directly to the invention of the contraceptive pill, showed that another derivative of cholesterol could be rearranged to the oestrone analogue 1-methyloestradiol notice how the methyl group has this time migrated to an adjacent carbon atom. At the same time, the dienone has become a phenol.

**Example:**




This **type of rearrangement** is known helpfully as a **dienone phenol rearrangement**, and we can consider it quite simply as a type of **reverse pinacol rearrangement**. **Pinacol and semipinacol rearrangements** are driven by the **formation of a carbonyl group**. The **rearranged cation is stabilized by being next to oxygen, and it can rapidly lose $H^+$ to give a carbonyl compound**. In the key step of a **dienonephenol rearrangement, a protonated carbonyl compound rearranges to a tertiary carbocation**.

**Mechanism:** The reaction is driven from **dienone to phenol because the product cation can rapidly undergo elimination of $H^+$ to become aromatic**.