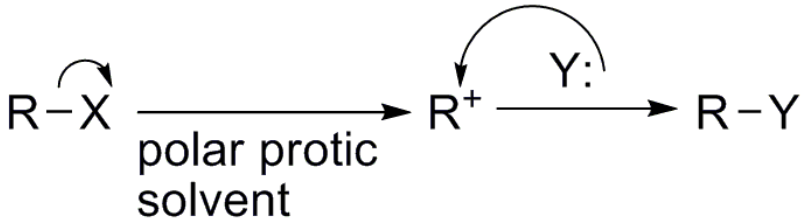
S_N1 Reactions and Antitumor Retinoids



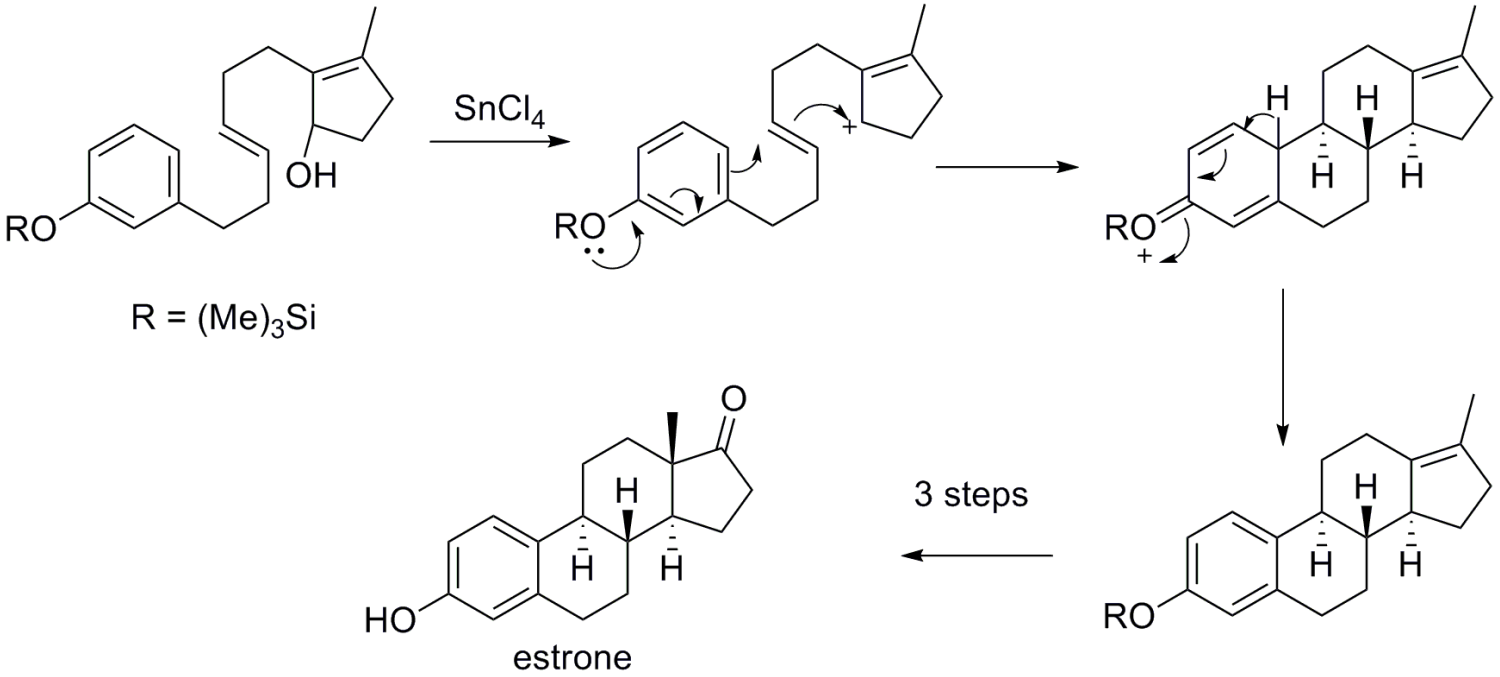
The S_N1 substitution reaction is a two step process in which the carbocation intermediate is formed by loss of a leaving group, and is subsequently attacked by a nucleophile to form the final product. The reaction has the following major characteristics:

- **Since the formation of the cation is usually rate-limiting, the reaction exhibits first-order kinetics (rate = k_1[substrate]) and only occurs if R^+ is stable**
- **The reaction is usually performed in polar protic solvents that stabilize the cation, so the nucleophile is often the solvent**
- **Because the cation is planar chiral substrates undergo racemization**
- **Because carbocations readily rearrange, the reaction often occurs with rearrangement of the carbon skeleton**

Because of substrate, rearrangement, racemization, and nucleophile limitations the S_N1 reaction is usually avoided by synthetic chemists.

There are exceptions!!

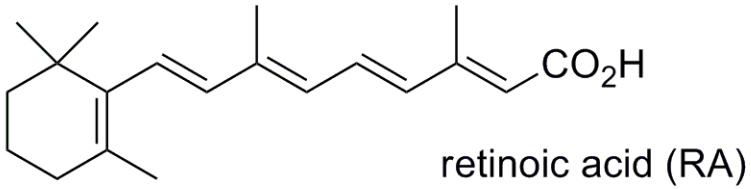
Steroid synthesis



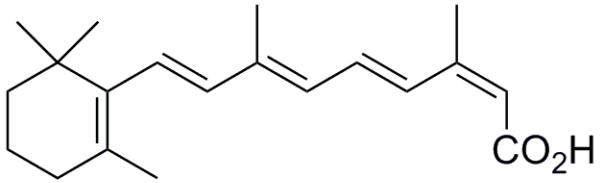
The multi-ring structure of steroids can be readily made by intramolecular S_N1 processes. In this example the Lewis acid $SnCl_4$ induces cleavage of the C-O bond of the initial allylic alcohol to form a cation that undergoes a concerted intramolecular attack to form two rings with the correct relative stereochemistry at three asymmetric centers. The steroid estrone can be synthesized in three additional steps after the ring-forming reaction.

Retinoid Synthesis

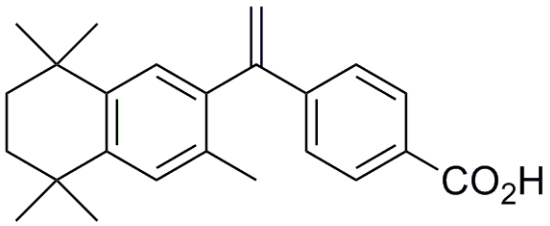
Retinoids



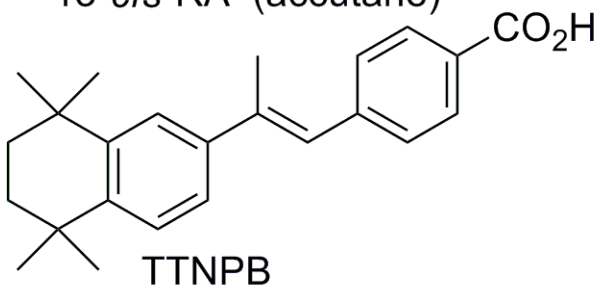
retinoic acid (RA)



13-*cis*-RA (accutane)



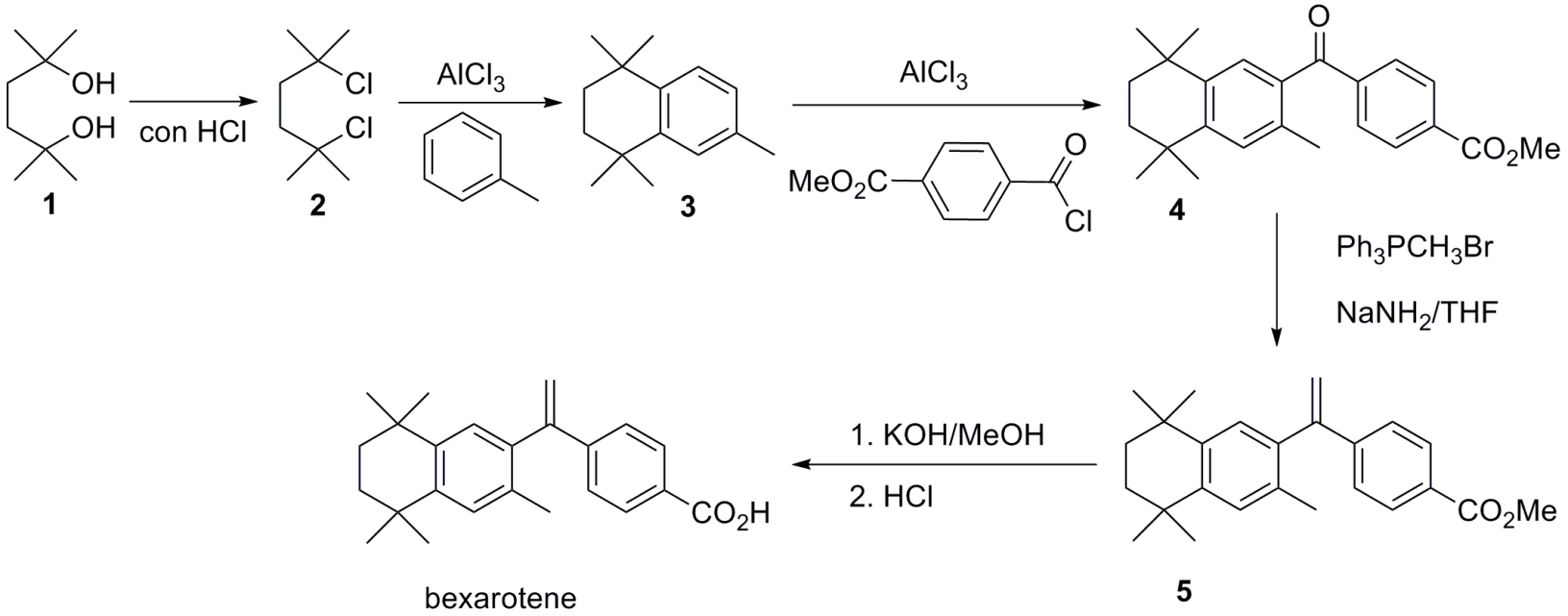
bexarotene



TTNPB

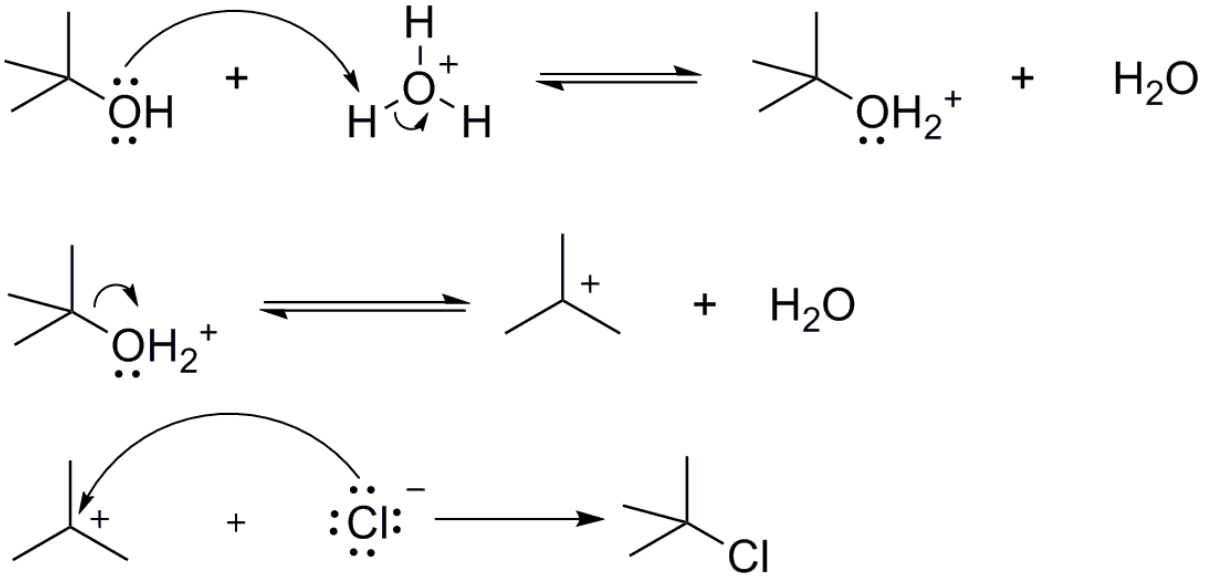
Retinoids are natural and synthetic compounds that mimic retinoic acid (RA) in some of its biological functions. They bind to retinoic acid receptors and retinoid X receptors that play a role in cell differentiation. Retinoids have been used in a number of medical applications including acne treatment and anti-tumor drugs. Bexarotene is an FDA-approved treatment for cutaneous T-cell lymphoma (CTCL). The synthesis of this and related retinoid drugs makes use of S_N1 chemistry.

The synthesis of bexarotene includes three steps that make use of carbocation chemistry. In this experiment the first step, the conversion of diol, 1, into the dichloro compound, 2, will be investigated.



Next semester the chemistry of the subsequent two steps, the Friedel-Crafts alkylation that converts 2 into 3 and the Friedel-Crafts acylation that converts 3 into 4 , will be investigated. Both of these reactions also involve carbocation chemistry.

The reaction of tertiary alcohols with concentrated HCl to generate tertiary alkyl chlorides is a well-known example of S_N1 chemistry. The mechanism of the reaction is shown below.



The mechanism of the conversion of 1 into 2 is similar. You will write the mechanism of the reaction as part of the report for this experiment. The reaction itself is very straightforward. It makes use of the high solubility of the reactant in the aqueous HCl solution, protonation of the alcohol to convert it into a good leaving group, and the very low solubility of the product in the aqueous solvent.

Experimental Hints

1. **This reaction will be complete in one lab day, but you may have to wait until the following week to take a melting point and IR spectrum after the compound has thoroughly dried.**
2. **The reactant is soluble in the concentrated hydrochloric acid, but you have to be careful to swirl/stir the reaction mixture vigorously to get it all into solution before the product starts to precipitate.**
3. **The product is very insoluble in water and can be washed with significant amounts of water and aqueous $NaHCO_3$ solution to remove traces of HCl.**
4. **The product is somewhat soluble in MeOH, so the last rinse with MeOH must be done with ice-cold solvent, and the rinse must be done rapidly.**
5. **Allow the compound to dry thoroughly before taking a melting point or IR spectrum. If you do either of these before the compound is sufficiently dry, you may come to the conclusion that the product is impure when it is only wet.**