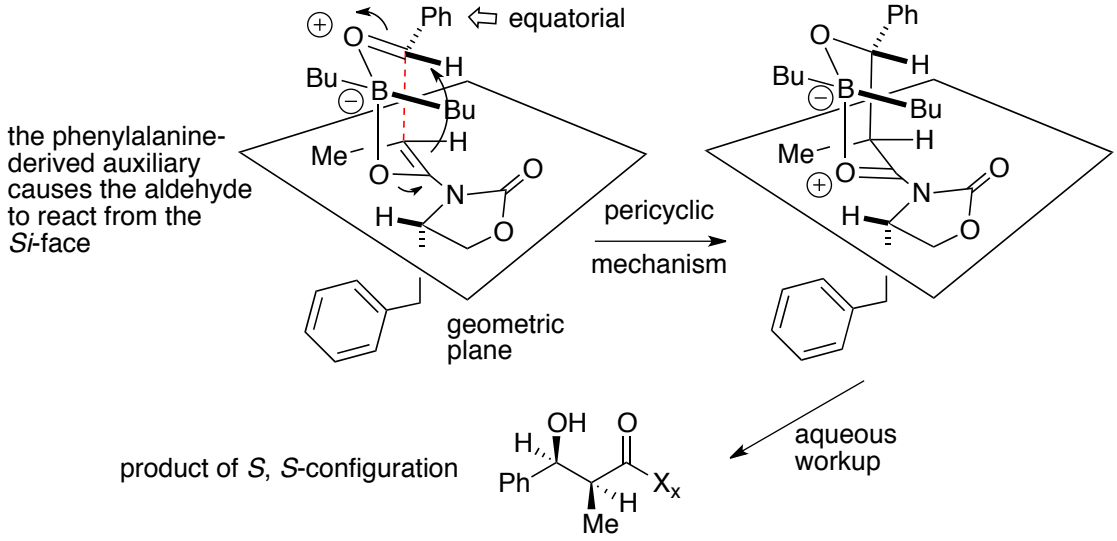
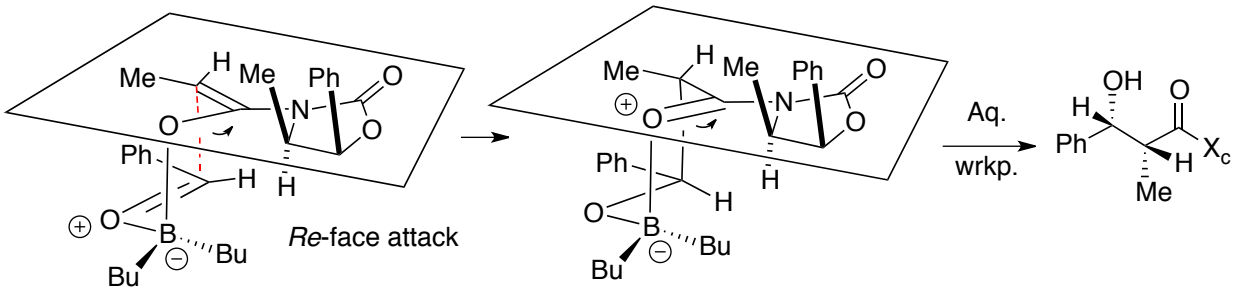
CHEM 330

Topics Discussed on Nov. 18

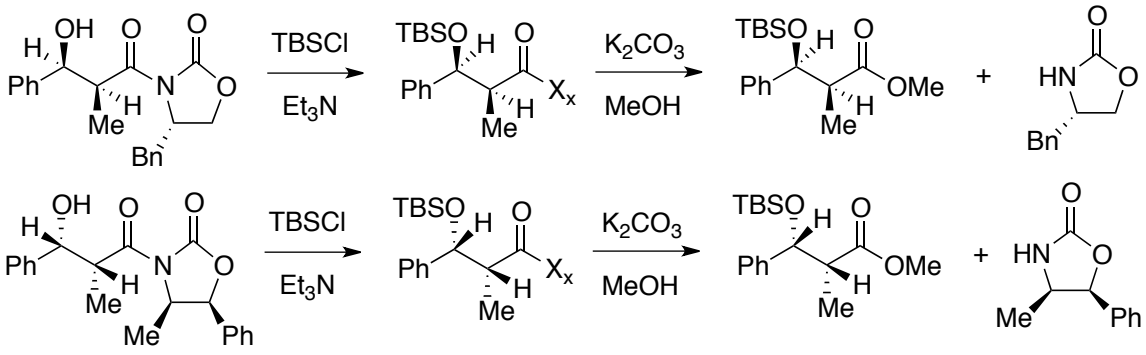
Principle: the Evans auxiliary derived from (L)-phenylalanine causes the aldehyde to react from the *Si* face:



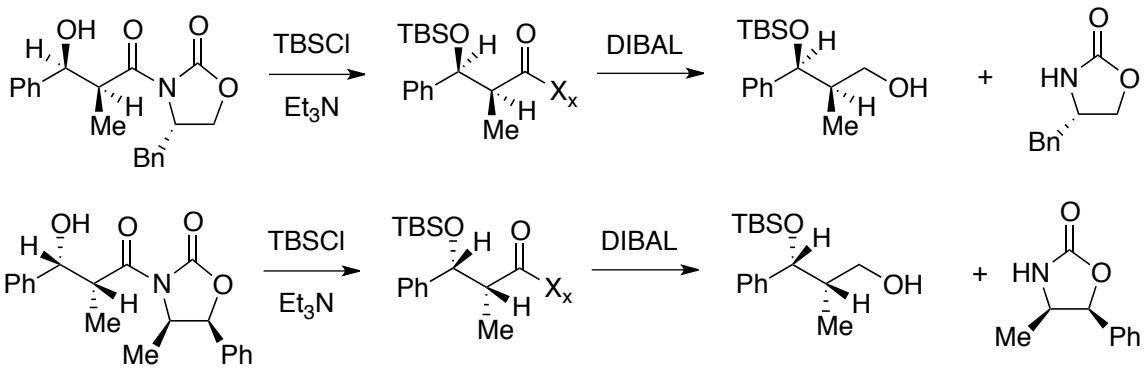
Principle: the Evans auxiliary derived from norephedrine causes the aldehyde to react from the *Re* face:



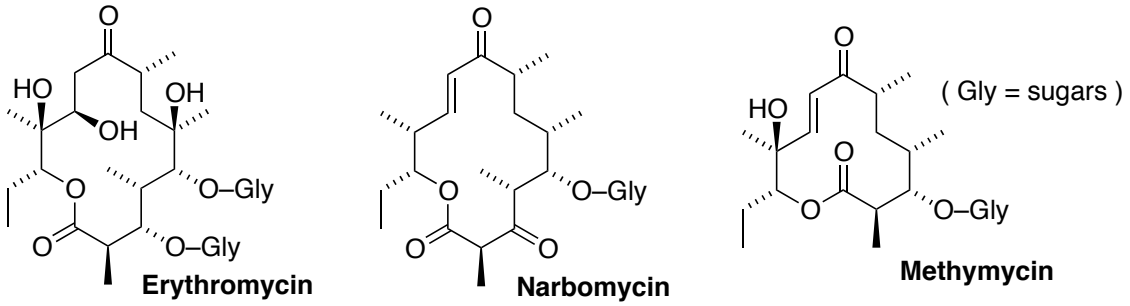
Release of X_c from Evans aldol products by treatment with, e.g., $MeOH/K_2CO_3$ after protection of the OH group:



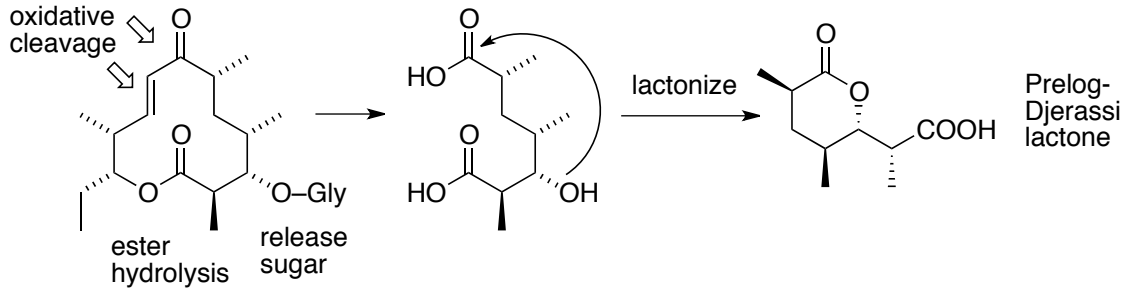
Reduction of Evans aldol products (e.g., with DIBAL) after protection of the OH group:



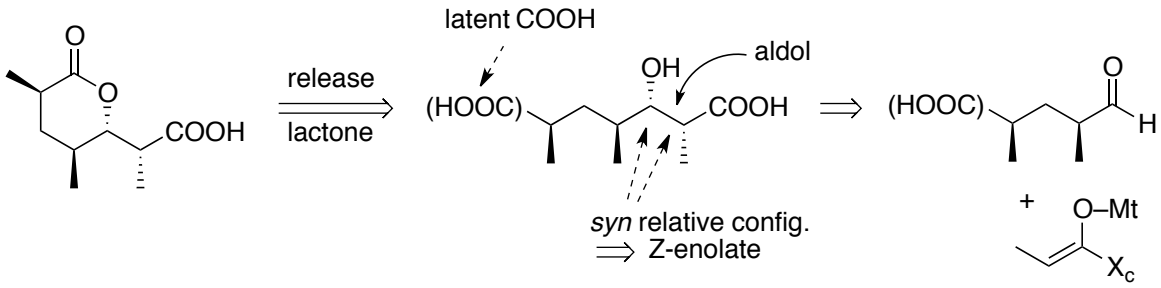
Application of the Evans aldol technology: macrolide antibiotics



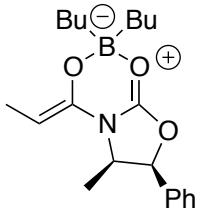
The Prelog-Djerassi lactone ("PDL"): a product of chemical degradation of narbomycin and methymycin that may be used as a template for the synthesis of macrolide analogs



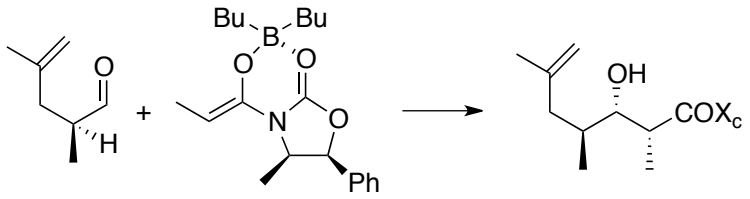
Retrosynthetic logic for the Prelog-Djerassi lactone:



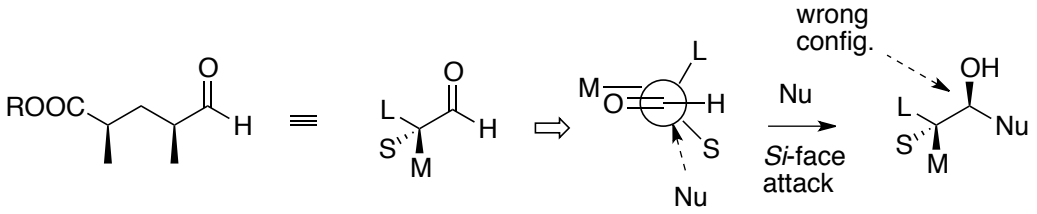
Choice of X_c in the above enolate: the desired aldol product is the one arising through *Re*-face attack on the aldehyde. Therefore, the above reaction requires the Evans auxiliary derived from norephedrine:



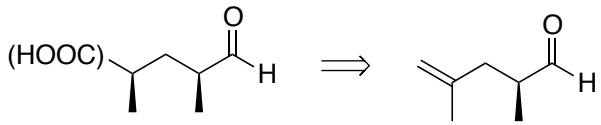
Stereochemical aspects of the aldol step in the synthesis of the Prelog-Djerassi lactone: interplay of innate stereochemical preferences of substrate and reagent



- Conduct of the above aldol reaction under conditions of *substrate control* could be problematic, because:
  - (i) the desired product must form through addition of the enolate to the *Re*-face of the aldehyde
  - (ii) the aldehyde has only C/H substituents at the α-stereogenic carbon, so its reactivity may be predicted using the Cram-Felkin model
  - (iii) the Cram-Felkin model predicts preferential nucleophilic attack from the *Si*-face of the CHO group:



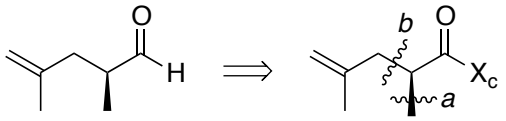
Nature of the precursor of the latent COOH group: while many choices are possible, experiment showed that an olefinic linkage constituted the best option:



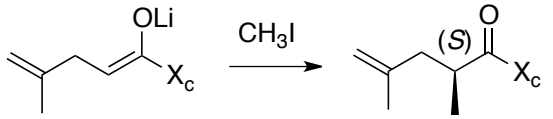
The COOH group may be introduced by hydroboration-oxidation of the olefin, followed by further oxidation of the resultant primary alcohol.

Important: the hydroboration step must occur diastereoselectively, so as to induce the desired configuration of the second Me group.

Enantioselective preparation of the above aldehyde by alkylation of an Evans enolate: two options available:

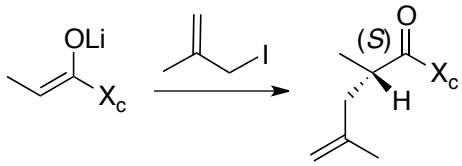


option *a*: cause the appropriate (*Z*)-Evans enolate to react with CH_3–I:



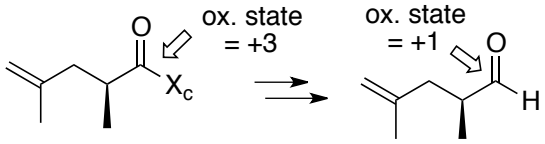
the chiral auxiliary must direct the incoming CH_3I to the **top face** of the enolate

option *b*: cause the (*Z*)-enolate of a propionyl Evans imide to react with a suitable allyl iodide:



the chiral auxiliary must direct the incoming electrophile to the **bottom face** of the enolate

important: in either case, redox operations are necessary to elaborate the alkylated Evans complex to the desired aldehyde:

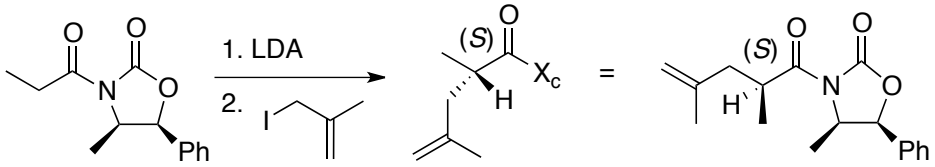


redox operations are required to complete the synthesis of the aldehyde

Principle of convergency: it is generally best to assemble molecules by inducing the union of fragments of approximately equal size. This frequently leads to a more efficient synthesis.

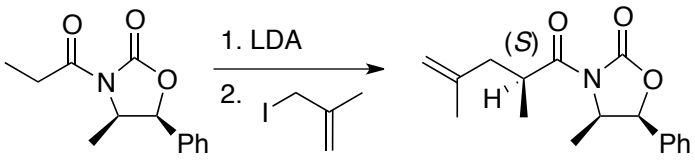
Option *b* above as the more convergent of the two

Requirement for the Evans auxiliary derived from norephedrin for the implementation of the above approach:

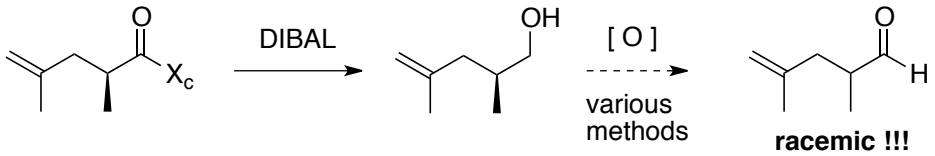


The Evans synthesis of the Prelog-Djerassi lactone: see Evans, D. A., *et al.*, *Tetrahedron Lett.* **1982**, *23*, 807, for complete details

High level of stereoselectivity observed during the initial alkylation step:



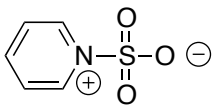
The redox sequence: facile DIBAL reduction of the alkylation product to a primary alcohol but problematic oxidation of the latter to an aldehyde (e.g., with PCC or other oxidants) due to racemization of the product:



DMSO as a potential oxidant: the S atom in DMSO is present at the oxidation state of 0, but the favorable oxidation state of S in organic compounds is –2

Kinetic stability of DMSO and consequent requirement for a suitable form of activation in order to express its oxidizing properties

The Parekh-Doering oxidation: activation of DMSO with the pyridine-sulfur trioxide complex:



pyridine-sulfur trioxide complex