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

![Diagram of pericyclic mechanism](image)

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

![Diagram of pericyclic mechanism](image)

Release of $X_c$ from Evans aldol products by treatment with, e.g., MeOH/K$_2$CO$_3$ 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 $\alpha$-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:

\[
\text{\begin{align*}
\text{H} & \quad \Rightarrow \\
\text{O} & \quad \text{C} \\
& \quad \text{X}_c \\
\end{align*}}\]

option a: cause the appropriate (Z)-Evans enolate to react with CH\textsubscript{3}–I:

\[
\text{O} \quad \text{Li} \\
\text{H} \quad \text{X}_c \\
\text{C} \quad \text{CH}_3 \quad \text{I} \\
\text{O} \quad \text{X}_c \\
\text{H} \\
\]

the chiral auxiliary must

direct the incoming CH\textsubscript{3}I
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:

\[
\text{O} \quad \text{Li} \\
\text{H} \quad \text{X}_c \\
\text{C} \quad \text{I} \\
\text{O} \quad \text{X}_c \\
\text{H} \\
\]

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:

\[
\text{ox. state} = +3 \\
\text{ox. state} = +1 \\
\]

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:

\[
\text{N} \quad \text{O} \quad \text{O} \\
\text{Ph} \quad \text{H} \\
\begin{align*}
1. \text{LDA} \\
2. \text{I} \\
\text{Ph} \\
\end{align*}
\]


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:

\[
\begin{align*}
\text{O} & \quad \text{N} & \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

1. LDA
2. \text{DIBAL}

\[
\begin{align*}
\text{O} & \quad \text{N} & \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

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:

\[
\begin{align*}
\text{N} & \quad \text{S} & \text{O} \\
\oplus & \quad \ominus & \ominus \\
\end{align*}
\]

\text{pyridine-sulfur trioxide complex}

racemic !!!