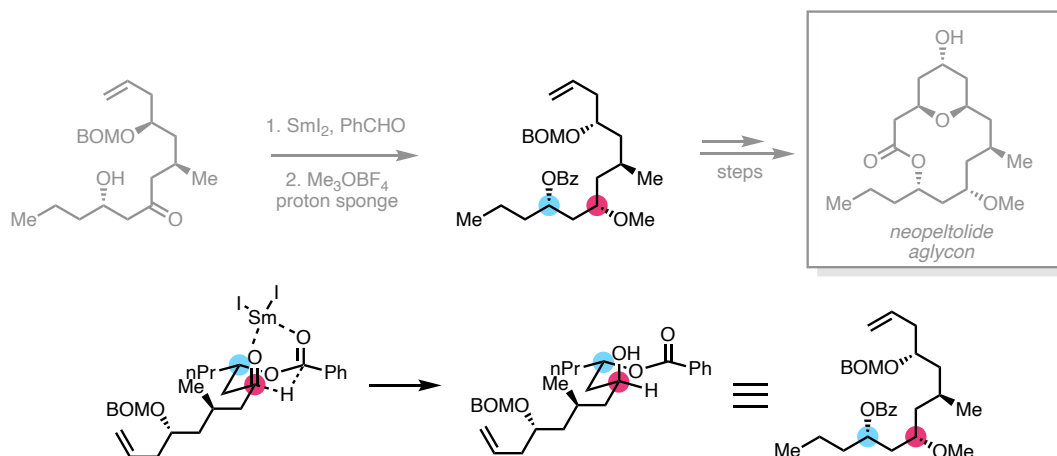
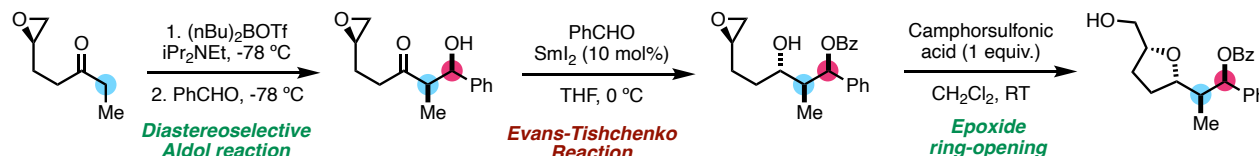


- Identify the intermediate in Taylor and co-workers' synthesis of the aglycon portion of neopeltolide (*Org. Lett.* **2008**, *10*, 5047–5050). Additionally, rationalize the observed diastereoselectivity. (Proton sponge, 1,8-bis(dimethylamino)naphthalene) [★]

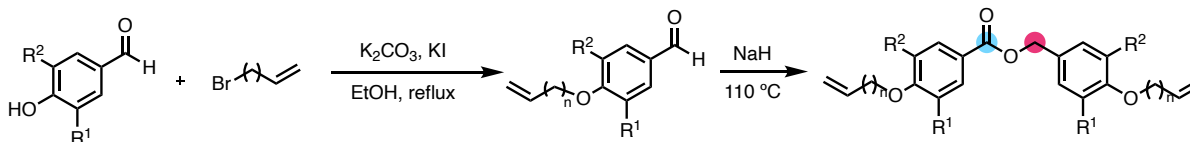


The diastereoselective outcome can be predicted by considering the hydride transfer transition state, where the molecule assumes a cyclohexane-like conformation and 1,3-diaxial strain is minimized by placing the substituents at the equatorial positions.

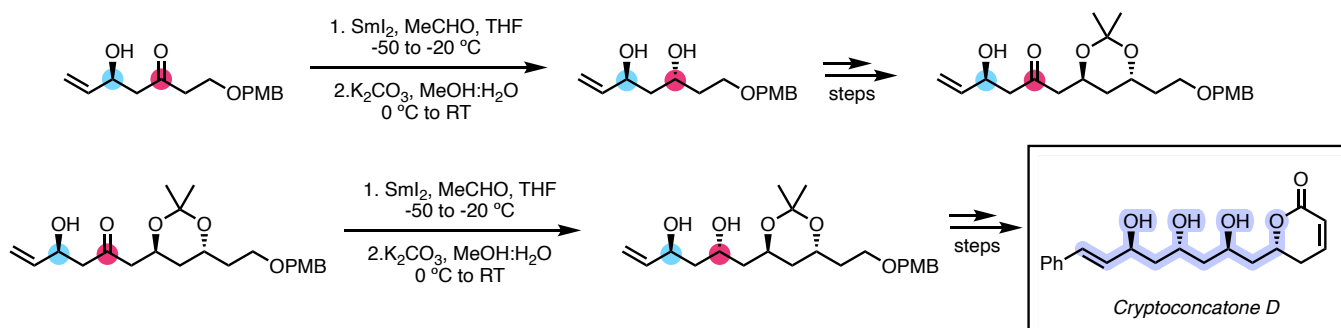
- Identify the intermediates of the following synthetic sequence and identify the type of transformation involved. [★★]



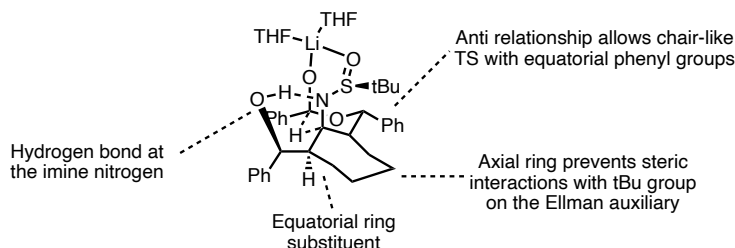
- In 2020, Chen, Xie and co-workers (*Green Chem.* **2020**, *22*, 1542–1547) developed the polymer species in figure. Identify a possible synthesis (including conditions) of the monomer precursor. [★]



- The team of Kirsch reported the synthesis of Cryptoconcatone C, a natural product polyketide (*J. Org. Chem.* **2022**, *87*, 14899–14908). Identify the missing intermediates and locate the fragment structure in the final molecule. [★]

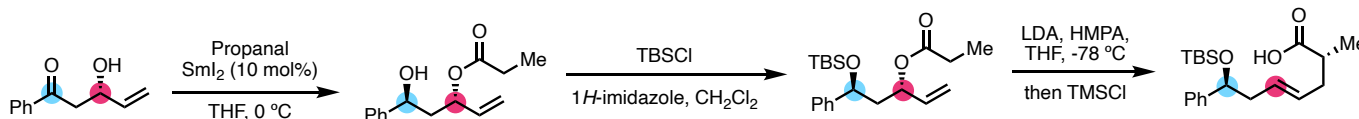


5. Houk and McGlacken reported the following transformation, which proceeds with remarkable diastereoselectivity. Describe the possible steps of the transformation that can account for the stereochemical outcome and provide a rationalization of it (*Org. Lett.* **2021**, 23, 6372–6376). [★★★]

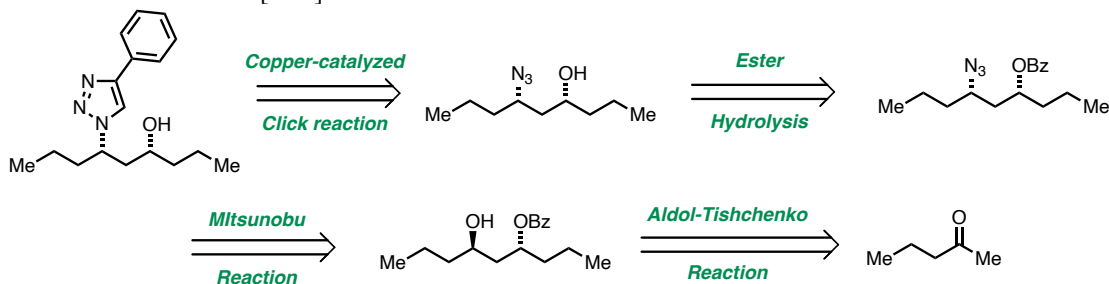


In general, aldol reactions are reversible and can therefore offer opportunity for “Curtin-Hammett-like” regimes, where the relative energy of subsequent irreversible steps decides the final reaction outcome. In this case, the energy of the transition state of the hydride transfer.

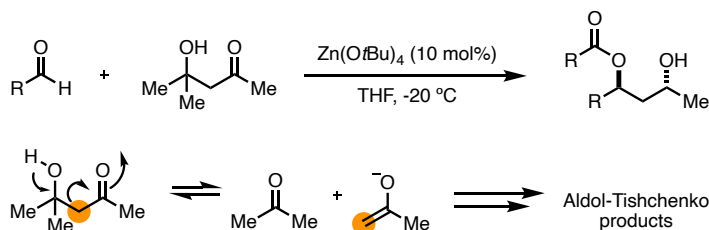
6. Identify the starting material, intermediates, and reaction conditions of the following synthetic sequence (HMPA, hexamethylphosphoramide; LDA, lithium diisopropylamide; TBS, *tert*-butylphenylsilyl; TMS, trimethylsilyl). [★★]



7. Propose a synthetic strategy of the following molecule, starting from butanal and 2-pentanone, which involves the Evans-Tishchenko reaction. [★★]



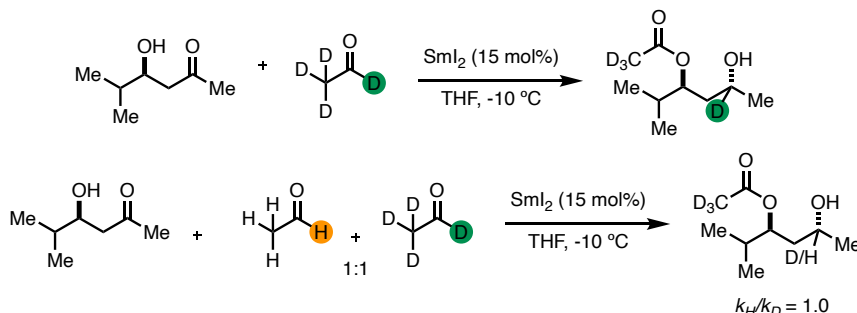
8. Schneider and co-workers reported the following transformation. Explain the mechanism underlying the transformation (*Chem. Commun.* **2001**, 1218–1219). [★★]



Aldols (3-hydroxycarbonyl compounds) can easily undergo retro-aldol reaction and generate back the carbonyl electrophile (in this case acetone) and an enolate. The generated enolate can undergo aldol condensation with the more reactive aldehyde,

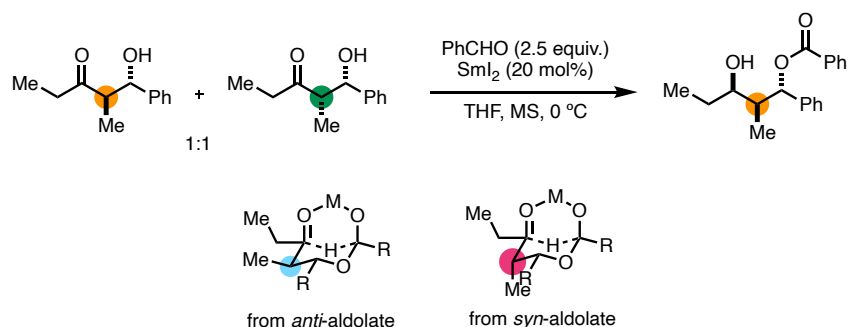
accounting for the overall transformation. The first nucleophilic addition reaction is followed by the Tishchenko reaction, which affords the corresponding 1,3-hydroxy compounds.

9. In their seminal publication in 1990 (*J. Am. Chem. Soc.* **1990**, *112*, 6447-6449), Evans and Hoveyda observed the following: (a) Complete deuterium incorporation; (b) Absence of kinetic isotope effect when deuterated acetaldehyde was used. Explain the mechanistic conclusions that can be drawn. [★★]



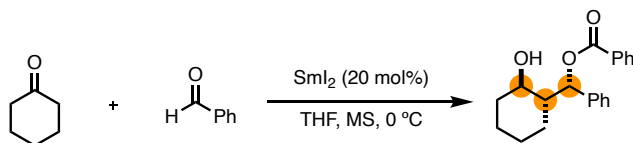
Complete incorporation of deuterium confirms the aldehyde to be the exclusive hydride source in the reaction. Competition experiment between ^1H -acetaldehyde and ^2D -acetaldehyde shows no kinetic isotope effect. This is compatible with hydride transfer not being rate-determining step. Likely, the rate-determining step involves samarium-mediate hemiacetal formation.

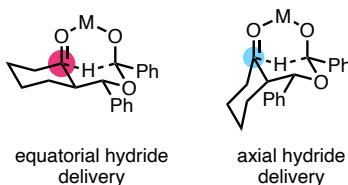
10. Upon subtle modification from the original Evans-Hoveyda conditions (*J. Org. Chem.* **1999**, *64*, 843-853), epimerization of the α -carbonyl position was observed. Rationalize this observation. [★★]



Aldol starting materials have the ability to undergo enolization, thereby epimerizing the α -carbonyl position. This creates a mobile equilibrium between the *syn*- and *anti*-aldolate. If we analyze the potential chair-like transition states for the *syn* and *anti* intermediates, we observed that the *syn* aldolate imposes the methyl substituent to adopt an axial position, causing increased 1,3-diaxial strain. Therefore, this scenario falls under a Curtin-Hammett regime, where the reaction sinks to the *anti* reaction product due to irreversibility of the hydride transfer step.

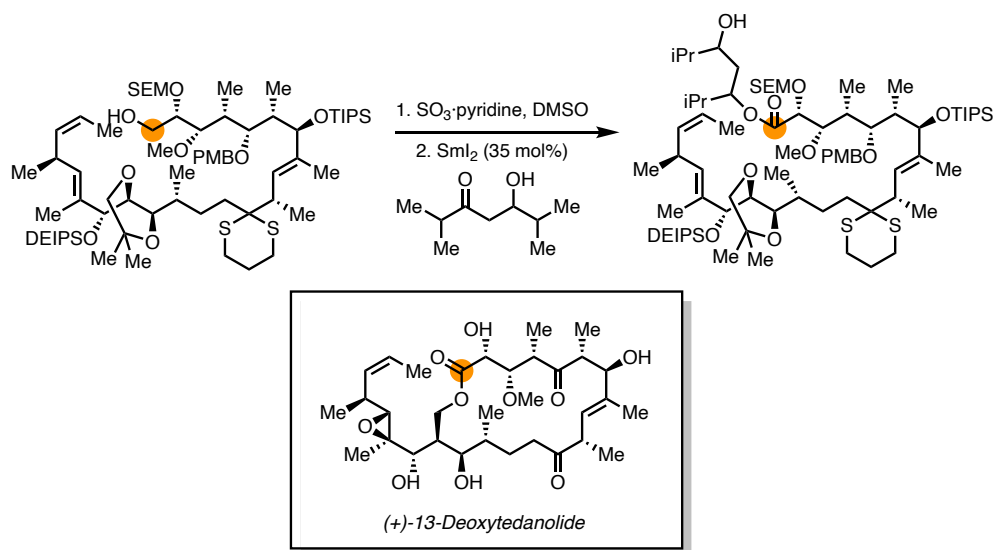
11. Rationalize the observed relative stereochemistry in the following reaction (*J. Org. Chem.* **1999**, *64*, 843-853). [★★★]





Also in this case, the initial aldol step is believed to be reversible and maintains an active equilibrium between the two diastereoisomers. In this case, empirical observation revealed that axial hydride transfer at the Tishchenko step is energetically favorable, compared to an equatorial one.

12. Hypothesize why the Tishchenko reaction was used to achieve the overall aldehyde oxidation (*J. Am. Chem. Soc.* **2003**, *125*, 350-351). (DEIPS, diethylisopropylsilyl; PMB, para-methoxybenzyl; SEM, trimethylsilylethoxymethyl, TIPS, triisopropylsilyl) [★★]



The literature is characterized by paucity of methods to oxidize alcohols to carboxylic acids and derivative. Often, these methods use harsh conditions (e.g. potassium permanganate, CrO_3 in sulfuric acid, sodium chlorite), which are incompatible with highly functionalized substrates. Therefore, the combination of Parikh-Doering oxidation (with DMSO as terminal oxidant), followed by Tishchenko reaction, offers an exceptionally mild method to oxidizing the alcohol for the required macrolactonization.