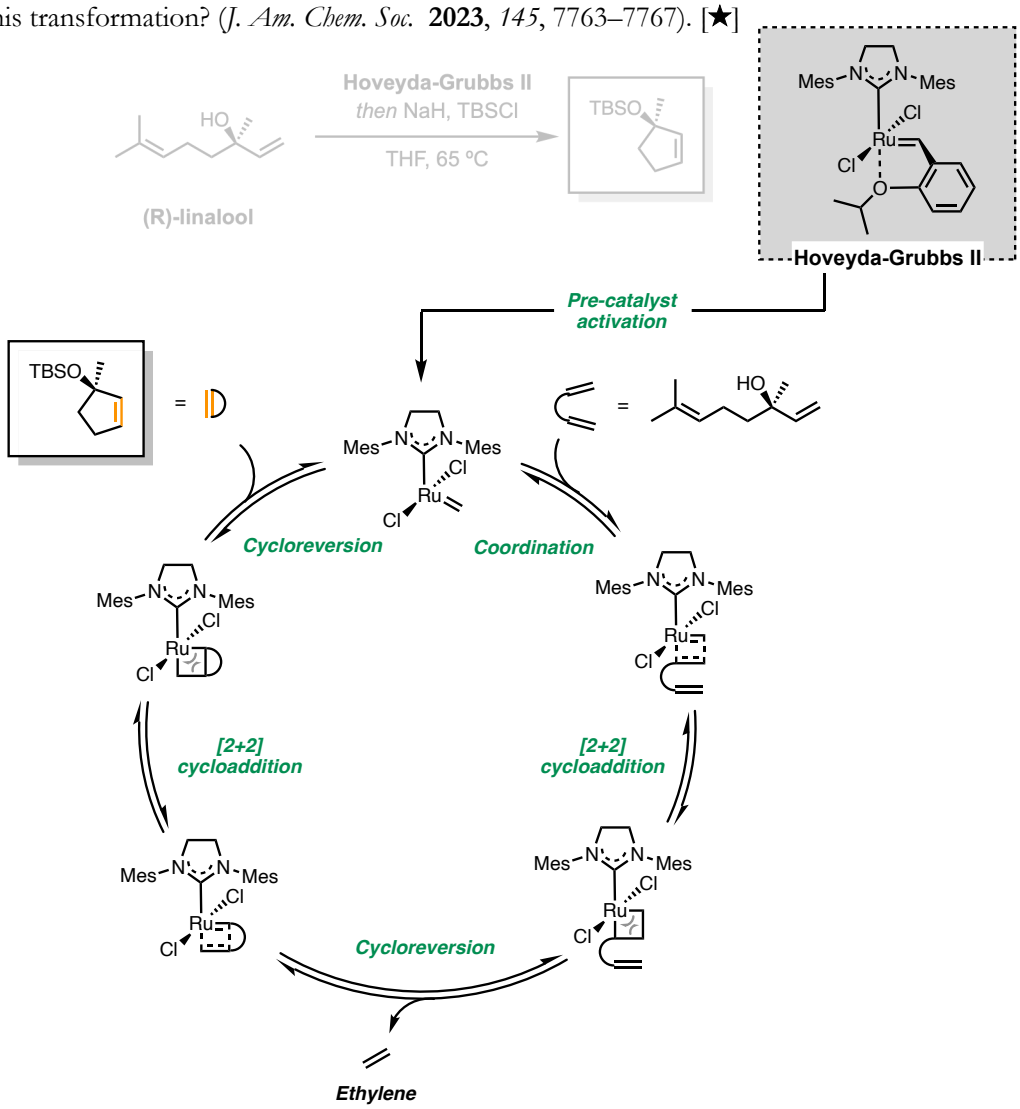
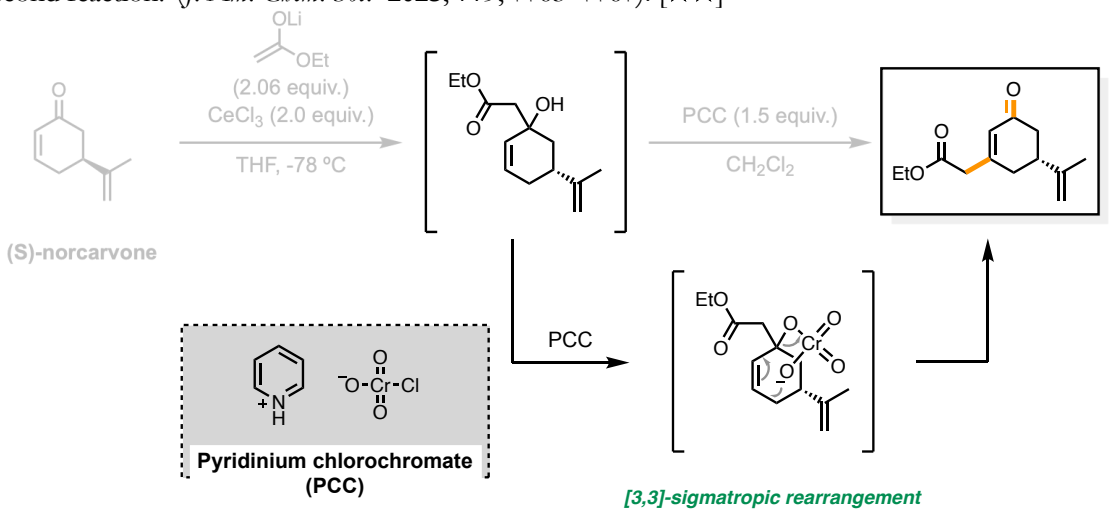
1. Propose and explain a plausible mechanism for the following catalytic cycle. Draw the structure of the catalyst employed. What is the name of this transformation? (*J. Am. Chem. Soc.* **2023**, *145*, 7763–7767). [★]



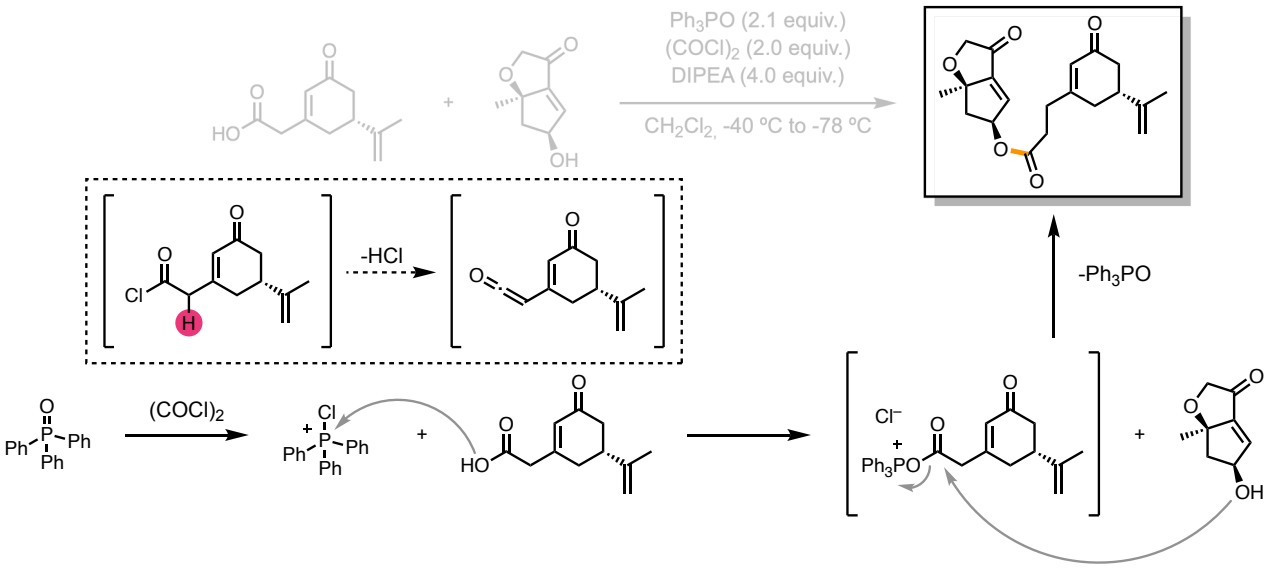
This reaction is known as a ring closing metathesis (RCM). See "prorocentin problem set" for a more detailed explanation of the mechanism.

2. Draw the structure of the intermediate and propose a plausible mechanism for the following transformation. What is the name of the second reaction? (*J. Am. Chem. Soc.* **2023**, *145*, 7763–7767). [★★]



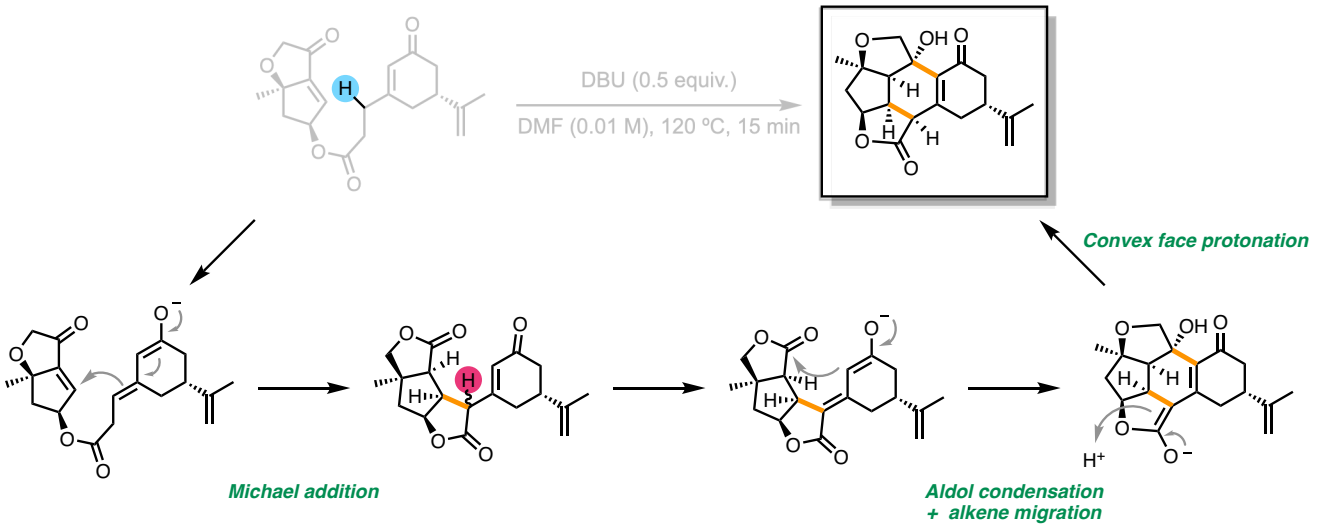
Addition of the lithium enolate, using $CeCl_3$ as Lewis acid, affords the corresponding allylic alcohol. Then, treatment of the latter with PCC results in the formation of the corresponding enone via Babler-Dauben oxidation. In this reaction, the intermediate chromate ester undergoes a [3,3]-sigmatropic rearrangement to produce the desired enone.

3. Identify the product and propose a plausible mechanism (*R. Soc. Open Sci.* **2018**, *5*, 171988). [★★]



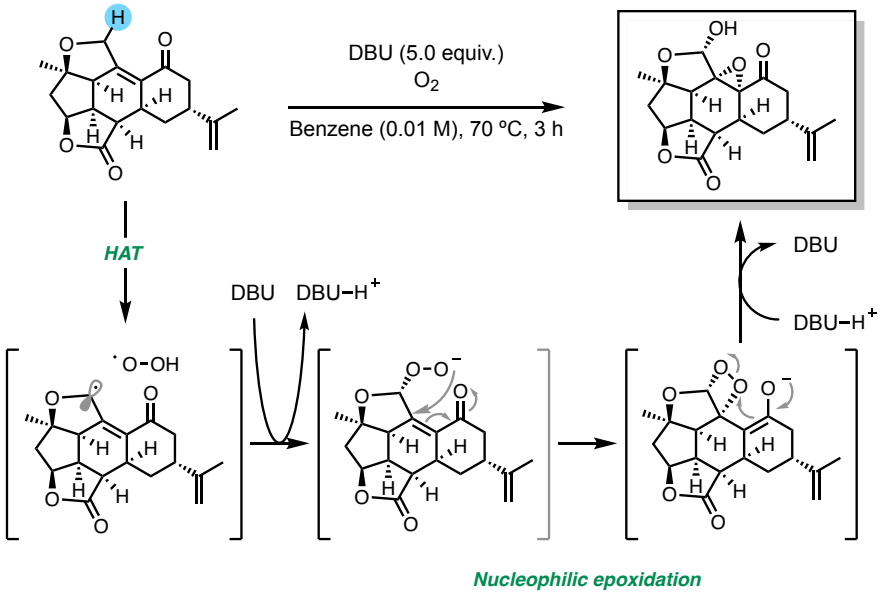
In the depicted esterification reaction, the authors found out that the conversion of the acid motif to the corresponding acyl chloride center was more challenging than they expected. The reason was the rapid decomposition of the acyl chloride through an elimination pathway that led to a highly reactive ketene intermediate. As solution, the authors employed specific conditions reported by Sun and coworkers, where the combination of triphenylphosphine and oxalyl chloride activates the acid center towards the nucleophilic attack of the alcohol. Triphenylphosphine oxide plays the role of an excellent leaving group, giving the ester product in short times and very good yields.

4. Identifying the product of the following transformation and propose a plausible mechanism. What is the role of DBU? Are you able to name the reactions involved? (*J. Am. Chem. Soc.* **2023**, *145*, 7763–7767). [★★★]



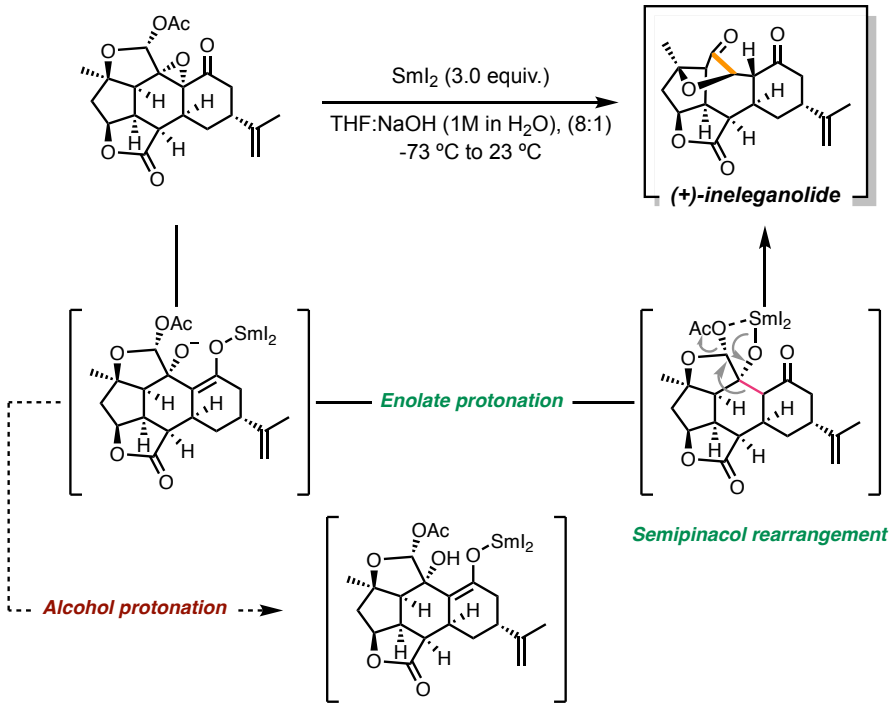
In this step, catalytic amounts of DBU are enough to activate this cascade process, where the desired pentacycle product was formed via Michael addition followed by a subsequent aldol condensation. This last aldol condensation step results in the migration of the alkene moiety, forming another aldol structure and setting the final structure of the desired product. The most acidic protons are labelled with different colors.

5. Propose a plausible mechanism for the following transformation. What is the role of oxygen in this reaction? (*J. Am. Chem. Soc.* **2023**, *145*, 7763–7767). [★★]



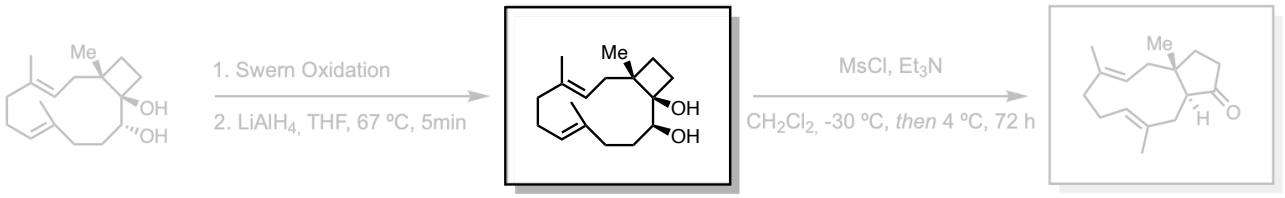
For this step, the authors proposed that triplet oxygen can act as a hydrogen atom abstractor, affording an allylic radical species. After radical recombination, and DBU-mediated deprotonation, a peroxide anion center is formed. The latter then adds in nucleophilic fashion to *β*–position of the enone, followed by a cleavage to produce the corresponding epoxide. Finally, DBU–H$^+$-mediated protonation results in the desired product.

6. **(Endgame)** Propose a plausible mechanism for the final step in the Total Synthesis of this episode. What is the name of this transformation? (*J. Am. Chem. Soc.* **2023**, *145*, 7763–7767). [★★★]



For the final step, the authors suggested that the reaction proceeds via opening of the epoxide moiety. After extensive screening of conditions, they discovered that by increasing the basicity of the reaction media, the protonation of the samarium enolate is favored over the protonation of the tertiary alcohol center. Thus, a final semipinacol rearrangement takes place, forming the **(+)-ineleganolide** natural product.

6.1. **BONUS:** Now that you have identified the above transformation, draw the structure of the missing intermediate and propose a plausible for the second step. These steps have been extracted from the Total Synthesis of Isoedunol and *β*-Araneosene reported by Kingsbury and Corey in 2005. Rationalize why the Swern oxidation step is necessary to afford this product. (*J. Am. Chem. Soc.* **2005**, *127*, 13813–13815).



Tiffeneau was the first one who, in 1923, created the term "semipinacol" to describe a special type of pinacol rearrangement. In the classical pinacol rearrangement, the diol system is conformed by two tertiary centers, while in the semipinacol version the diol motif possesses a tertiary and a secondary center. Thus, the resulting rearrangement consists in an unusual 1,2–migration towards the secondary center (upon efficient activation of such center), rather than the tertiary one. In both transformations, the stereoinformation of the final product is governed by the stereoelectronic effect, and an antiperiplanar orientation between the migratory group and the leaving group is required.

An example of this feature can be observed in the Total Synthesis of Isoedunol and *β*-Araneosene reported by Kingsbury and Corey. In the depicted example, the rigidity of the 12-membered ring blocks the antiperiplanar orientation of different C–C bonds towards the secondary C–O bond. Thus, the conversion of the *trans*-diol into the *cis*-diol is required in order to favor the correct orientation for the formation of the desired product.