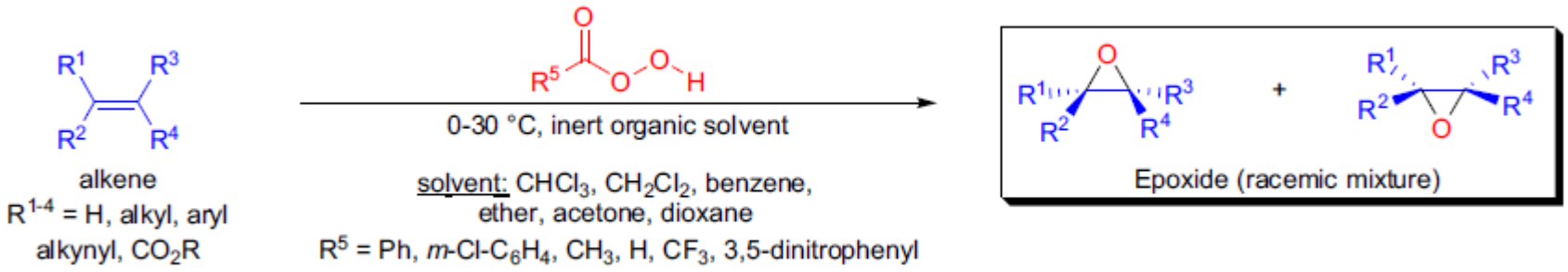
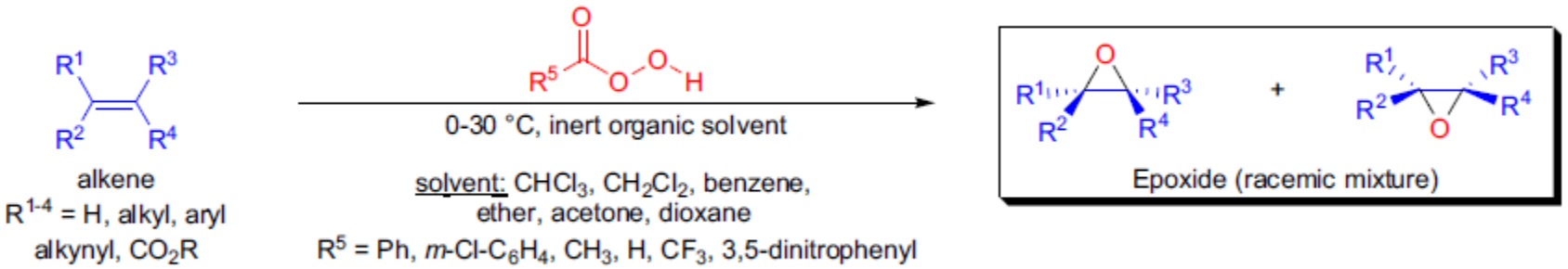
PRILEZHAEV REACTION

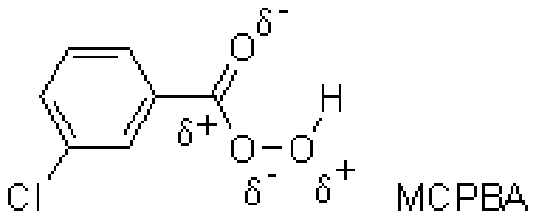


chenjingrong

In 1909, N. Prilezhaev was the first to use peroxycarboxylic acids to oxidize isolated double bonds to the corresponding oxiranes (epoxides).

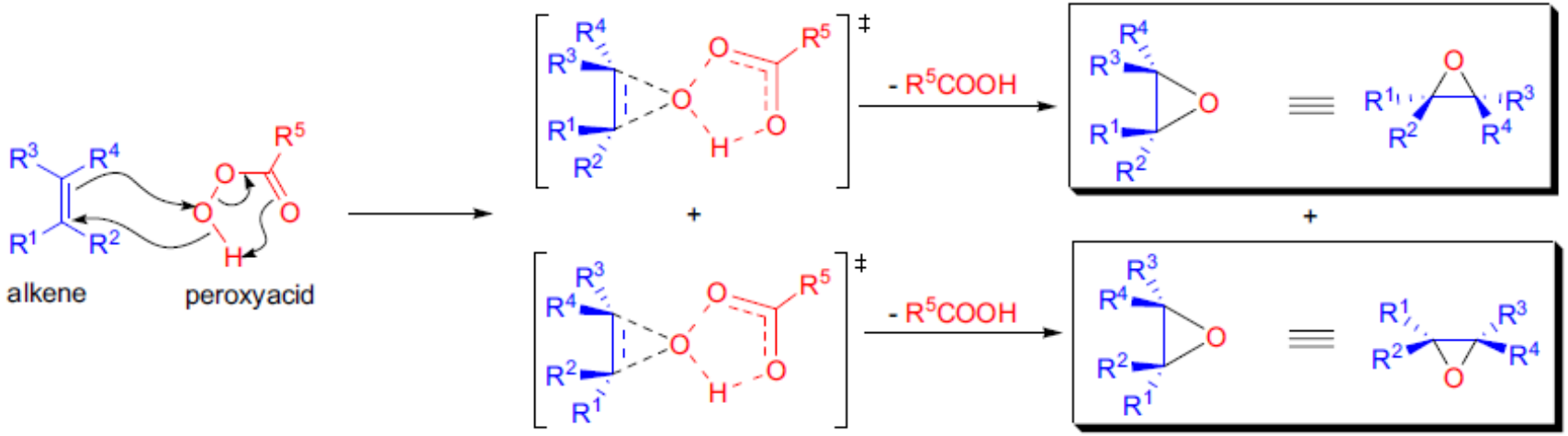


Peracids tend to adopt an intramolecularly hydrogen-bonded conformation in solution, and the high degree of polarisation results in an electrophilic oxygen atom that is able to add to alkenes.



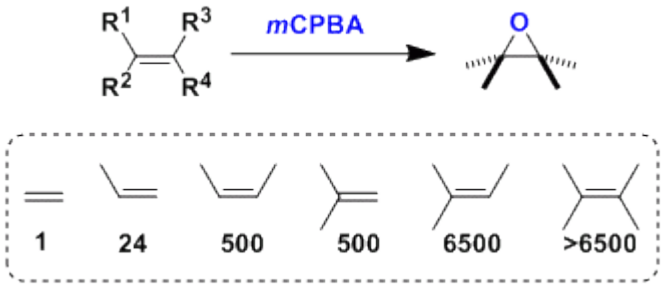
The epoxidation of an alkene with peracid to give an oxirane. The commercial available mCPBA is a widely used reagent for this conversion, while magnesium mono-perphthalate and peracetic acid are also employed

The *Prilezhaev reaction* is stereospecific, and a *syn* addition of the oxygen to the double bond is observed in all cases. This observation supports the assumption that the epoxidation of alkenes by peroxyacids is a concerted process. The reaction takes place at the terminal oxygen atom of the peroxyacid, and the π HOMO of the olefin approaches the σ^* LUMO of the O-O bond at an angle of 180° (butterfly transition structure).



1) the reaction is stereospecific, since the stereochemistry of the alkene substrate is retained in the epoxide product (*trans* alkene yields the *trans* epoxide, while *cis* alkene affords *cis* epoxide);

2) the reaction rate increases if the substituents on the alkene are electrondonating and decreases if they are electron-withdrawing;



3) an electron-withdrawing substituent (R_5) on the peroxyacid increases the rate of epoxidation;

4) substrates with multiple isolated double bonds can be epoxidized regioselectively, since the more electron-rich double bond reacts faster with the peracid (terminal alkenes are the least reactive, so a disubstituted alkene is selectively epoxidized in the presence of a terminal one);

5) alkenes that have preexisting chiral centers theoretically give rise to two diastereomeric epoxides, but in practice high diastereoselectivities may be achieved by preferentially epoxidizing the less sterically hindered face of the alkene

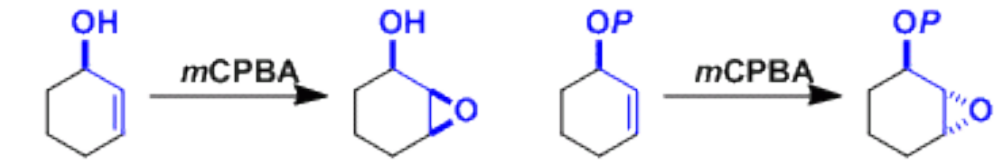
6) alkenes with no chiral centers give rise to a 1:1 mixture of enantiomeric epoxides

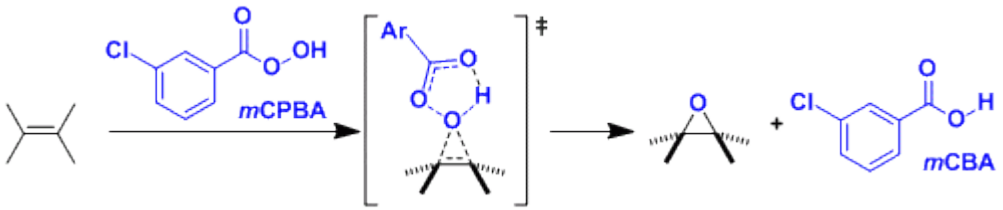
7) the steric demand of the peroxyacid is almost negligible, so even very sterically hindered substrates maybe epoxidized;

8) cup-shaped molecules are usually epoxidized from the less hindered convex side;

9) if a functional group adjacent to the double bond can coordinate to the peroxyacid, the natural steric bias will be overridden and the epoxidation will occur from that face of the double bond where the coordinating functional group is located (e.g., OH>CO_2H>CO_2R>OCOR) and this phenomenon is called the *neighboring group effect*;

When there is a free stereogenic hydroxyl group near the olefin, the hydrogen bond between the OH group and the reagent leads to diastereoselective epoxidation (the Henbest rule). When the OH group is protected, opposite diastereoselectivity is observed.





Henbest Rule: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Chem. Rev. 1993, 93, 1307. DOI: 10.1021/cr00020a002

10) the reagent peroxyacids can be prepared (by reacting carboxylic acids with hydrogen peroxide) or purchased from commercial sources;

11)most widely used peroxyacid is *m*CPBA, which is a relatively stable solid with good solubility in most organicsolvents;

12) less frequently used (and not very stable) peroxyacids are generated *in situ* (e.g., peroxyacetic and performic acid);

13) the peroxyacids are much less acidic than the carboxylic acids, so acid-catalyzed side reactions(e.g., epoxide ring-opening) are rare;

14) when the product is very acid sensitive, the reaction mixture needs to be buffered since the by-product is a strong carboxylic acid;

15) epoxidations with *m*CPBA are usually carried out at or below ambient temperature, and a mildly basic work-up ensures the removal of the benzoic acid by-product from the epoxide product;

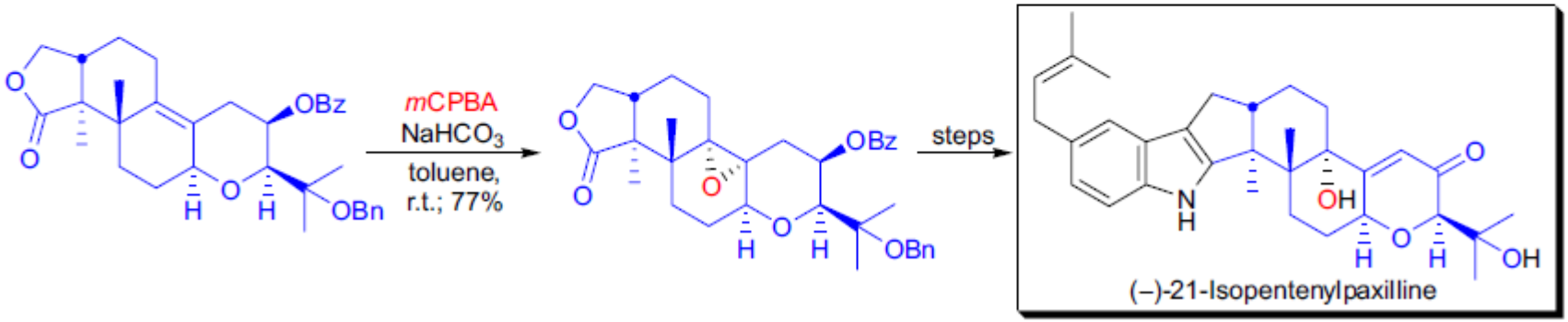
16) the reaction tolerates most functional groups, but free amines are readily oxidized, so they must be protected;

17) ketones may undergo a competing *Baeyer-Villiger oxidation*;

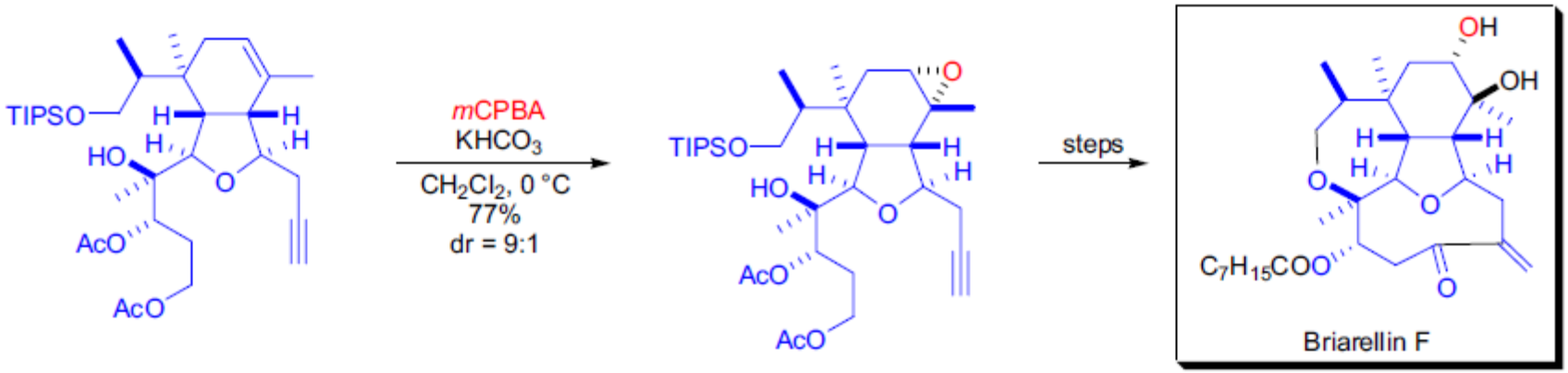
18) ⟨ ,®-unsaturated esters are epoxidized, while ⟨ ,®-unsaturated ketones remain unchanged under the reaction conditions;

19) alkynes react 10^3 times slower than alkenes, so alkenes are selectively epoxidized in the presence of alkynes.

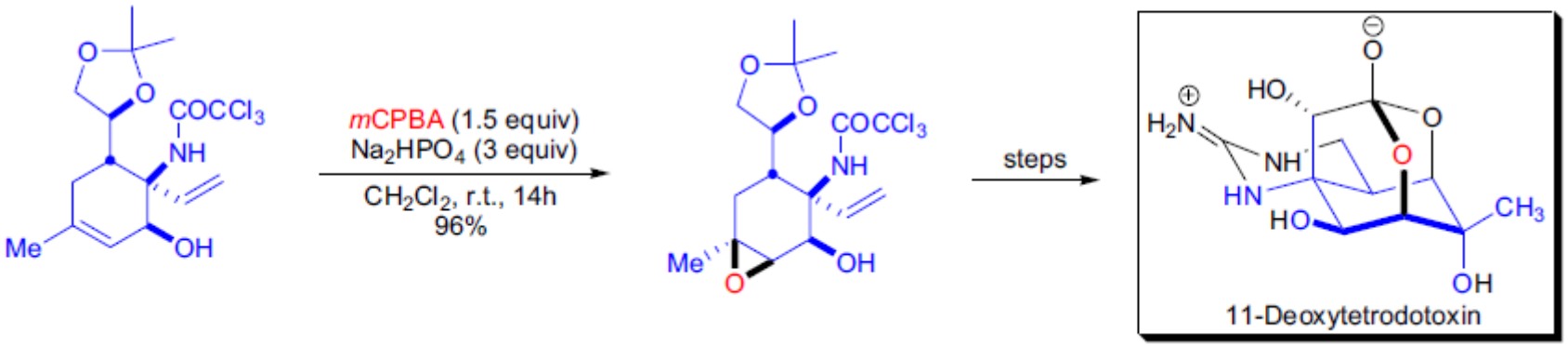
A *diastereoselective epoxidation* of a tetrasubstituted double bond was accomplished with *m*CPBA in the total synthesis of (–)-21-isopentenylpaxilline by A.B. Smith et al.[48] The tetracyclic lactone substrate containing the tetrasubstituted double bond was exposed to *m*CPBA in toluene at room temperature. The reaction mixture also contained sodium bicarbonate to neutralize the by-product *m*-chloro benzoic acid. The epoxidation exclusively took place from the less hindered α-face of the molecule. At a later stage, this epoxide was converted to the γ-hydroxy enone moiety present in the natural product.



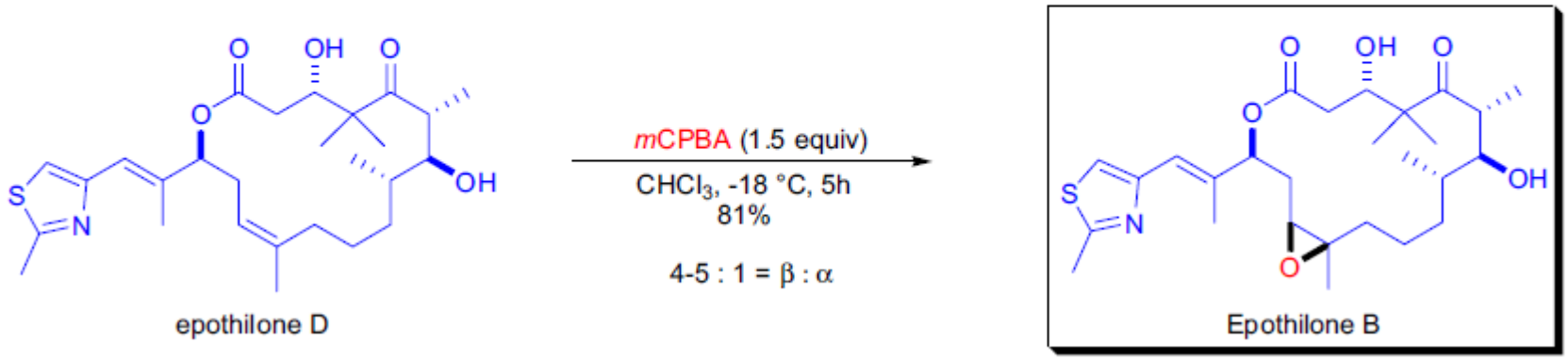
During the first total synthesis of briarellin diterpenes, briarellins E and F, L.E. Overman and co-workers utilized the large reactivity difference between a triple and a double bond in peroxyacid oxidations to selectively epoxidize a trisubstituted double bond in the presence of a terminal alkyne.[49] The epoxidation with *m*CPBA was carried out in DCM in the presence of a base to afford the α-epoxide in a 9:1 diastereomeric ratio.



The *hydroxyl group-directed epoxidation* was utilized by M. Isobe et al. in their total synthesis of 11-deoxytetrodotoxin.[50] The six-membered cyclic allylic alcohol was treated with *m*CPBA in the presence of a phosphate buffer to afford an almost quantitative yield of the desired β-epoxide.



The final step in J. Mulzer's total syntheses of epothilones B and D was the oxidation of the C12-C13 double bond of epothilone D *via* a highly diastereoselective *Prilezhaev reaction* to obtain epothilone B.[51] The same *m*CPBA oxidation endgame was chosen by R. E. Taylor et al. in the total synthesis of these two natural products.[52]



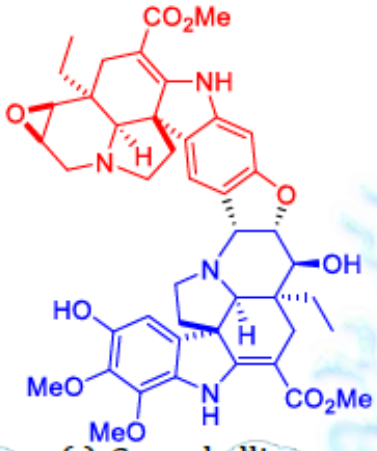
epothilone D

Epothilone B

Summary of (-)-Conophylline

- Isolated from Tabernaemontana divaricata (Apocynaceae) in 1992
- Potent anticancer drug; also show positive result on the treatment of diabetes mellitus type 1.
- Dimer of two indole subunits (shown as red and blue below), each of which has a pentacyclic aspidosperma skeleton

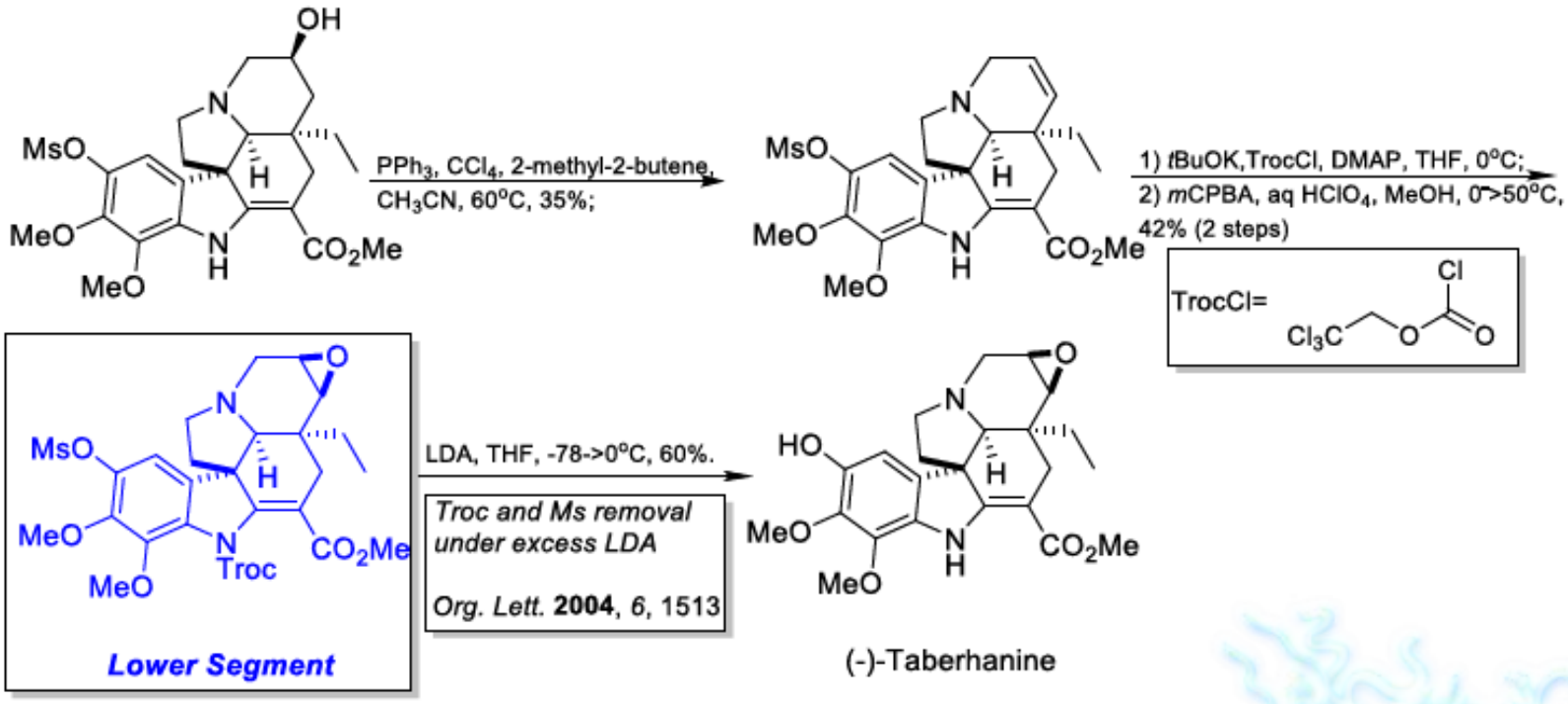
Apocynaceae



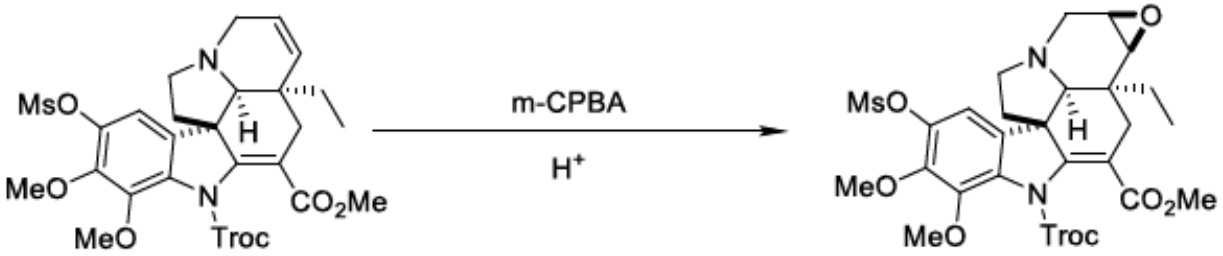
(-)-Conophylline

Tetrahedron Lett. **1992**, *33*, 969

Synthesis of the Lower Segment and (-)-Taberhanine

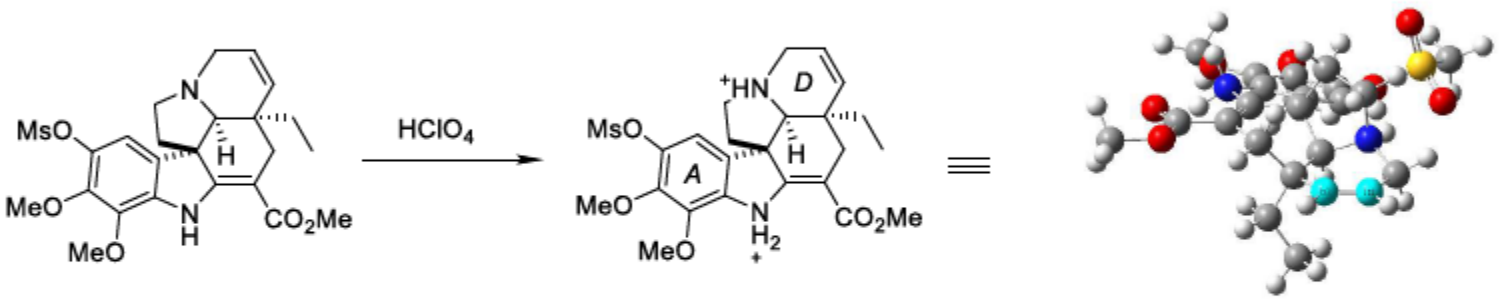


- Could you justify the selectivity of the epoxidation reaction in the last step of the synthesis?



hint: notice that the reagent accesses from the concave face

Stereoselectivity in the epoxidation step



"The structure of the molecule containing the aspidospermane ring system in the conformation with the lowest energy shows that the rings A (beznen ring) and D (N-heterocyclohexene) are nearly planar. We presume that during the oxidation m-CPBA is inserted between rings A and D, parallel to ring A, and then t***he ensuing pi-pi interaction will stabilize the transient state effected by the oxidation***."

However, in aspidosperma's system, the stereoselectivity remains even there is no pi-pi interaction. ***My proposal, according to the computational study*, suggest the origin of the stereoselectivity is actually the combined effects of torsional strain and steric effect during the transitional state.***

Sharpless, Jacobsen, and Shi asymmetric epoxidation