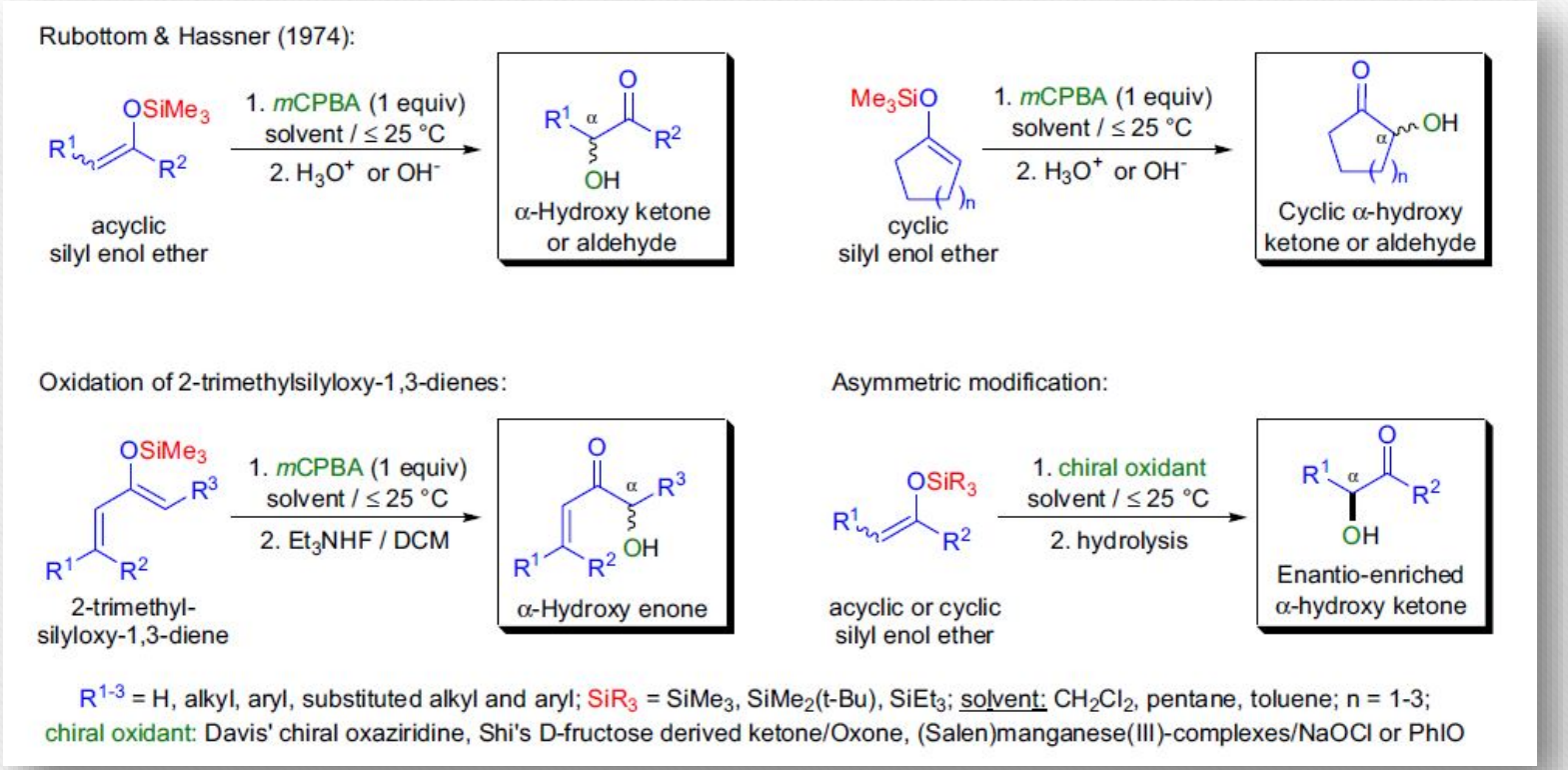
RUBOTTOM OXIDATION

In 1974, the research groups of G.M. Rubottom and A. Hassner independently developed a general and high-yielding preparation of ⟨ -hydroxy ketones (acyloins) and ⟨ -hydroxy aldehydes by the oxidation of silyl enol ethers with *m*CPBA. The first observation of this transformation, however, was made by A.G. Brook and co-workers the same year.[1] Today the ⟨ -hydroxylation of carbonyl compounds *via* the peroxyacid oxidation of the corresponding silyl enol ethers is known as the *Rubottom oxidation*.



The general features of this reaction are:

1) The silyl enol ether substrates can be prepared efficiently and regioselectively from ketones and aldehydes;

2) Both acyclic and cyclic enol ethers undergo the oxidation;

3) The oxidation readily takes place at or below room temperature (predominantly using dichloromethane as the solvent) and the reaction mixture is worked up with either acid or base to afford the ⟨ -hydroxyl carbonyl compounds in good yield;

4) The silyl enol ethers derived from ⟨ ,®-unsaturated ketones (2-trimethylsilyloxy- 1,3-dienes) are regioselectively oxidized at the more electron-rich double bond to afford ⟨ -hydroxy or ⟨ -acyloxy enones depending on the workup conditions;[4]

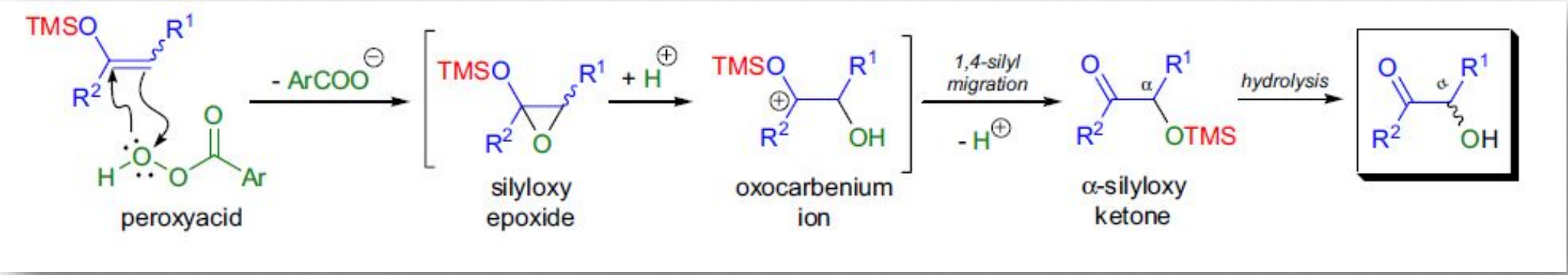
5) Often the initial product of the oxidation is the ⟨ -silyloxy carbonyl compound, which is readily hydrolyzed to the corresponding ⟨ -hydroxy derivative;

6) In the case of bicyclic silyl enol ethers, the reaction has to be buffered and the use of a completely non-polar solvent (e.g., pentane, toluene) is required to avoid the extensive hydrolysis of the starting material;

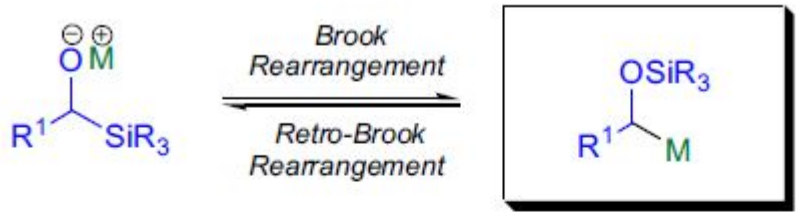
7) The introduction of the □-hydroxyl functionality is stereoselective in the case of bicyclic and polycyclic substrates. There are a number of modifications of the *Rubottom oxidation*, and they mainly differ in the applied oxidizing agent: 1) the use of chiral oxidants such as Davis' chiral oxaziridines, Shi's D-fructose-derived chiral ketone in combination with Oxone or manganese(III)-(Salen)complexes gives rise to enantiomerically enriched □-hydroxy ketones; 2) hydrogen peroxide efficiently oxidizes silyl enol ethers in the presence of MTO (methyltrioxorhenium) to give high yields of the corresponding □- hydroxy and □-silyloxy ketones; and 3) HOF-acetonitrile complex (made directly from F_2 and aqueous acetonitrile) not only oxidizes silyl enol ethers but also silyl ketene acetals (derived from esters) to afford □-hydroxy ketones and esters, respectively.

Mechanism: [18,1,19]

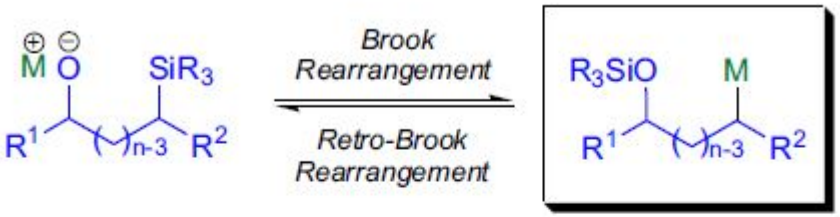
The *Rubottom oxidation* proceeds through the intermediacy of a silyloxy epoxide. The epoxide ring opens under the acidic conditions to afford a stable oxocarbenium ion, which undergoes a *1,4-silyl migration* (*Brook rearrangement*)[1] to give an ⟨ -silyloxy ketone. The ⟨ -silyloxy ketone is readily hydrolyzed to the product. Until recently the silyloxy epoxide could not be isolated or observed but when the oxidation was conducted with neutral epoxidizing agents, the silyloxy epoxide intermediate could be isolated.



[1,2]-Silyl migrations:



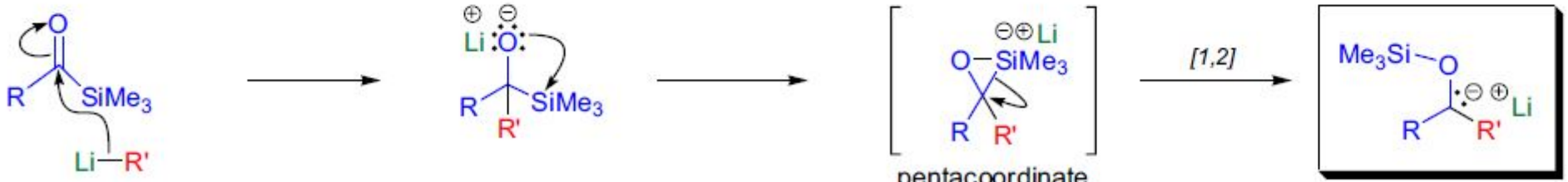
[1,n]-Silyl migrations:



$R^{1\text{-}2}$ = alkyl, aryl; SiR_3 = $SiMe_3$, $SiEt_3$, $SiMe_2t$-Bu, etc.; n = 2-5

Mechanism: [28,29,13,30-32,25]

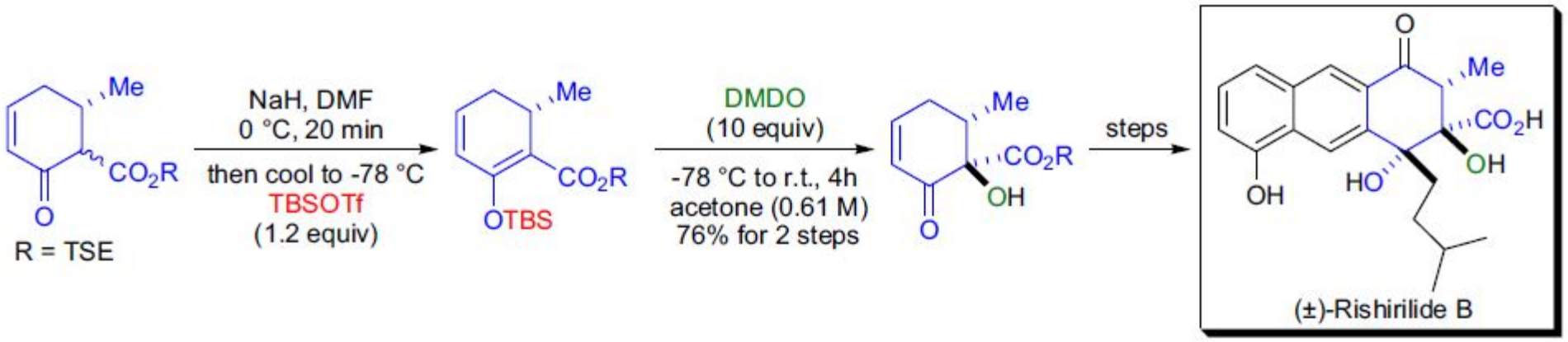
The mechanism is believed to involve a pentacoordinate-silicon atom.[30]



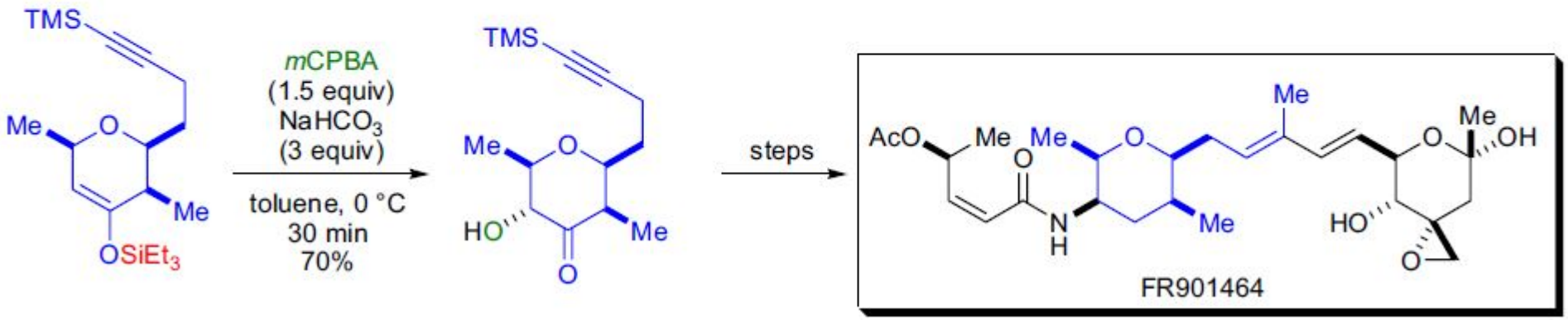
pentacoordinate
silicon intermediate

Synthetic Applications:

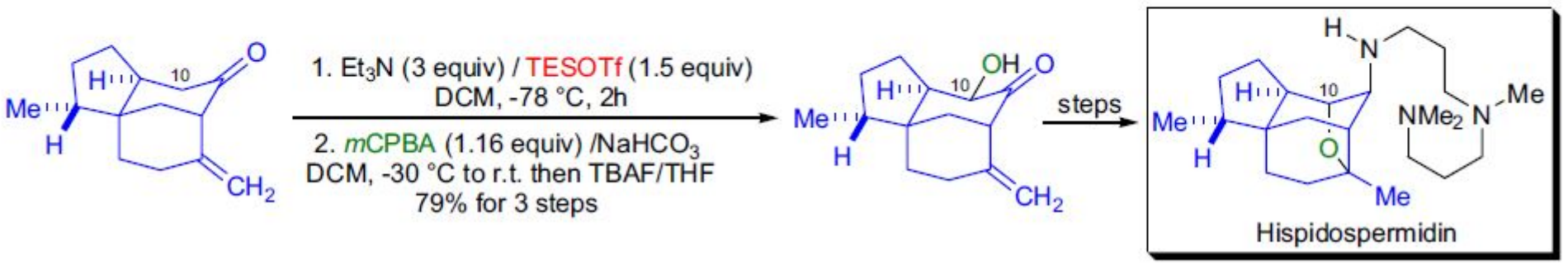
The highly potent antithrombotic (±)-rishirilide B was synthesized in the laboratory of S.J. Danishefsky.[20] One of the tertiary alcohol functionalities was introduced *via* the *Rubottom oxidation* of a six-membered silyl dienol ether with dimethyl dioxirane (DMDO). The oxidation was completely stereoselective, and it was guided by the proximal secondary methyl group. Subsequently, the enone was converted to the enedione, which was used as a dienophile in the key *intermolecular Diels-Alder cycloaddition* step.



The total synthesis of the antitumor antibiotic FR901464 was accomplished by E.N. Jacobsen et al.[21] The preparation of the central six-membered fragment was achieved *via* a highly *enantioselective hetero Diels-Alder reaction* between a diene and an aldehyde. The resulting silyl enol ether was subjected to a modified *Rubottom oxidation* condition (buffer and nonpolar solvent) with mCPBA to afford the desired α-hydroxy ketone with complete diastereoselectivity.



In the highly stereoselective synthesis of hispidospermidin, the oxygenation of the C10 position was achieved *via* a *Rubottom oxidation* by S.J. Danishefsky et al.[23] The tricyclic ketone was first converted to the TES enol ether, which was readily oxidized with *m*CPBA to give the corresponding α-hydroxy ketone as a single diastereomer.



Thank you