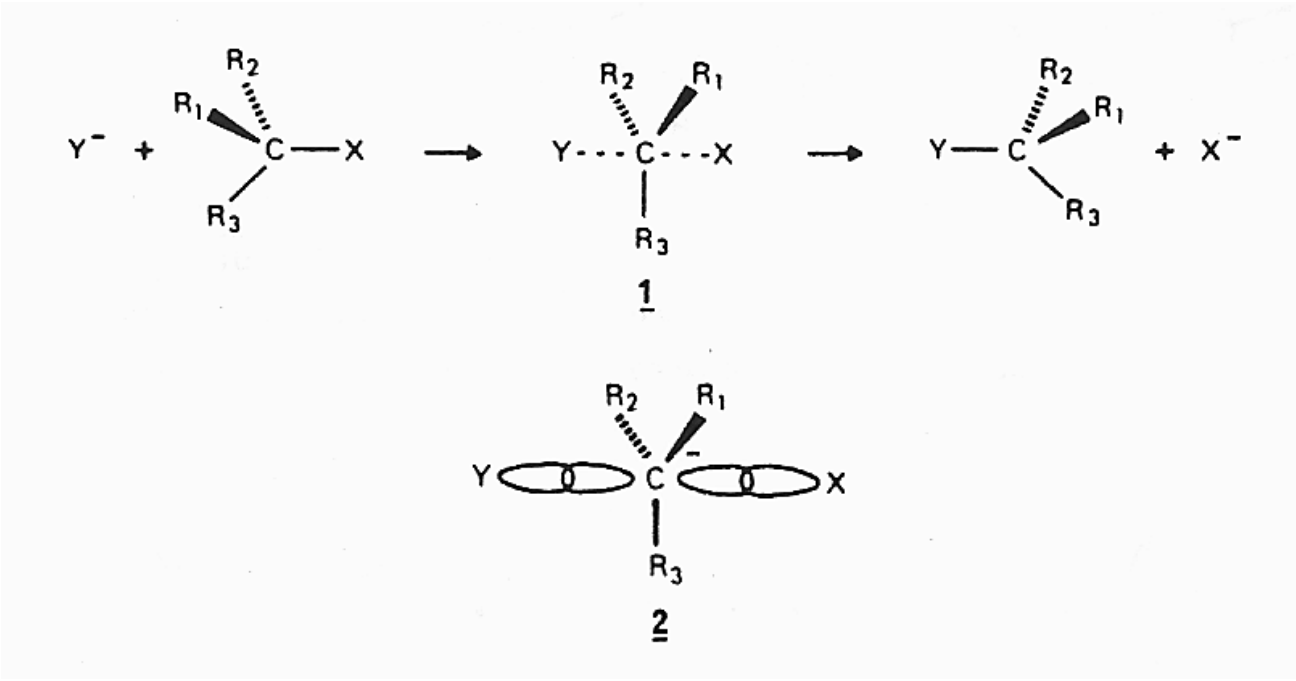
SECTION 2

Antiperiplanar Hypothesis

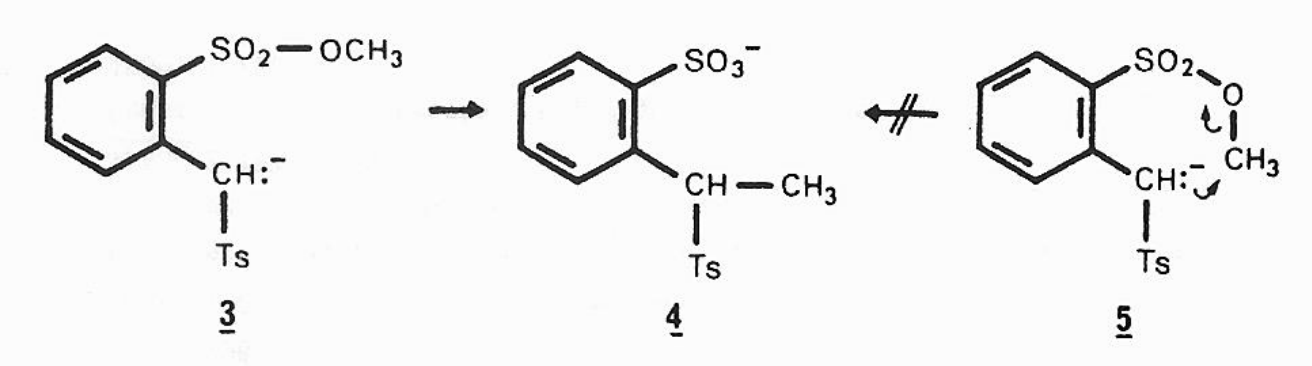
and Reactions at Saturated Carbons

(2018)

Stereochemical Course of SN_2 Reaction



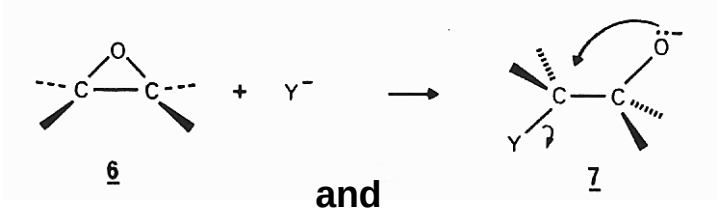
Experimental Evidence for the SN_2 Pathway



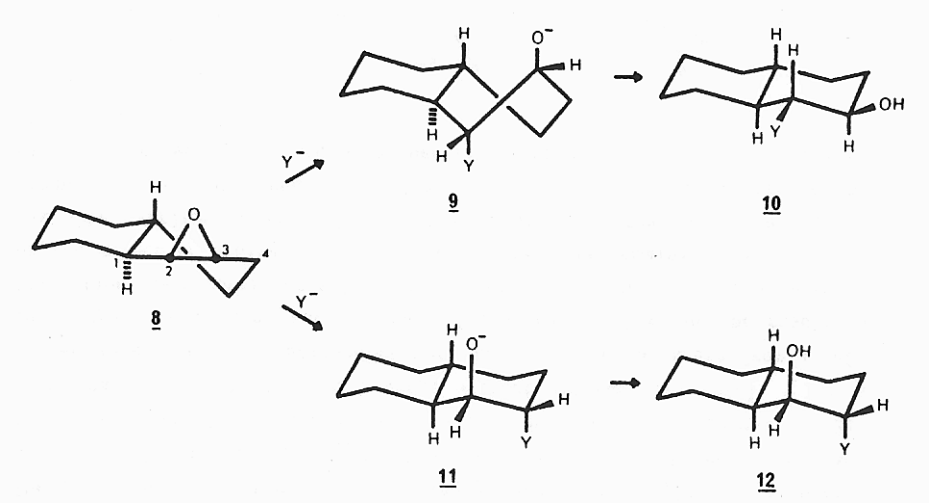
3 gives the expected product 4 via an intermolecular process rather than the « formally appealing » intramolecular process (5 to 4) using appropriately labelled starting material.

A. ESCHENMOSER *et al.* *Helv. Chim. Acta* 1970, *53,* 2059.

Opening of Epoxide (an Intramolecular SN_2 Reaction)



and



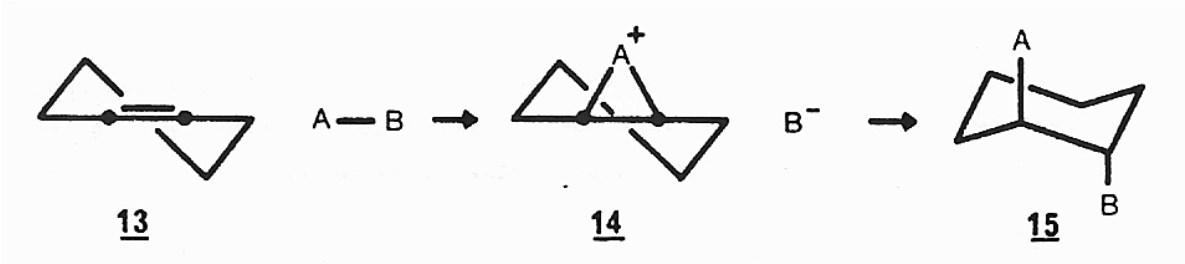
1. **Nu attack at C_2 of 8 gives 10 via the twist-boat intermediate 9 after a conformational change (reverse process is identical)**
2. **Nu attack at C_3 of 8 gives 12 via the chair intermediate 11**

Both pathways are stereoelectronically controlled but

8 to 11 to 12 is preferred because it is lower energy (less steric interaction)

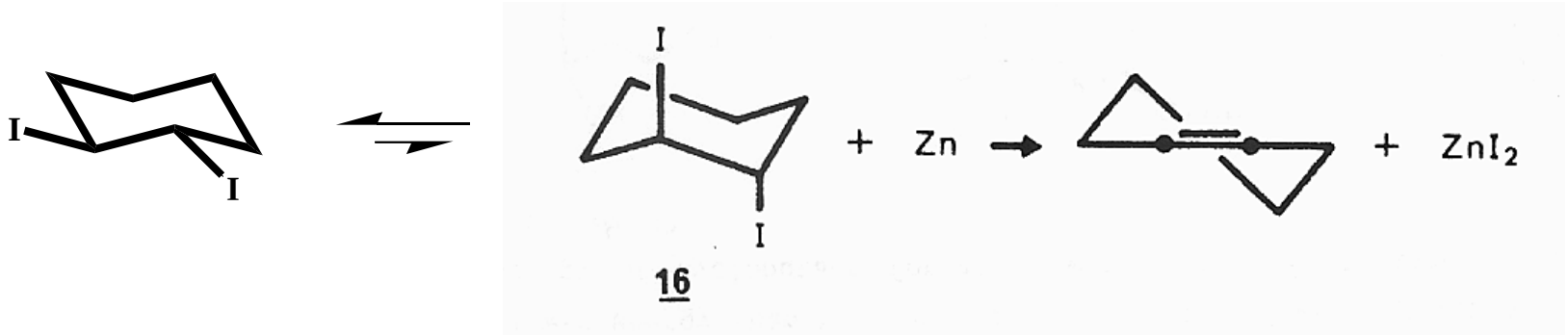
E. TOROMANOFF *et al.* *Bull. Soc. Chim. Fr.* 1961, 2758.

Addition of Electrophilic Reagents (A-B) on Cyclohexene

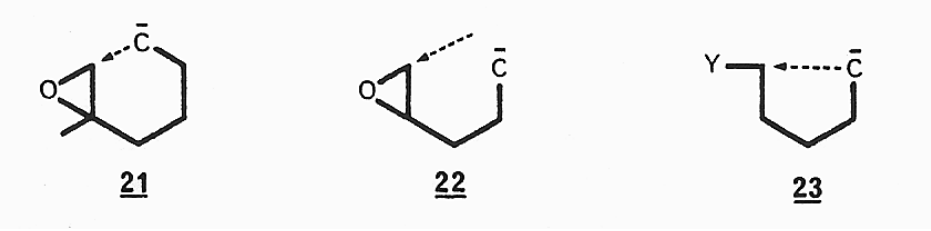


A — B
H — X (X = halogens)
X — X (X = halogens)
NO — Cl
I — N_3
$Hg(OAc)_2$ + H_2O (ROH)

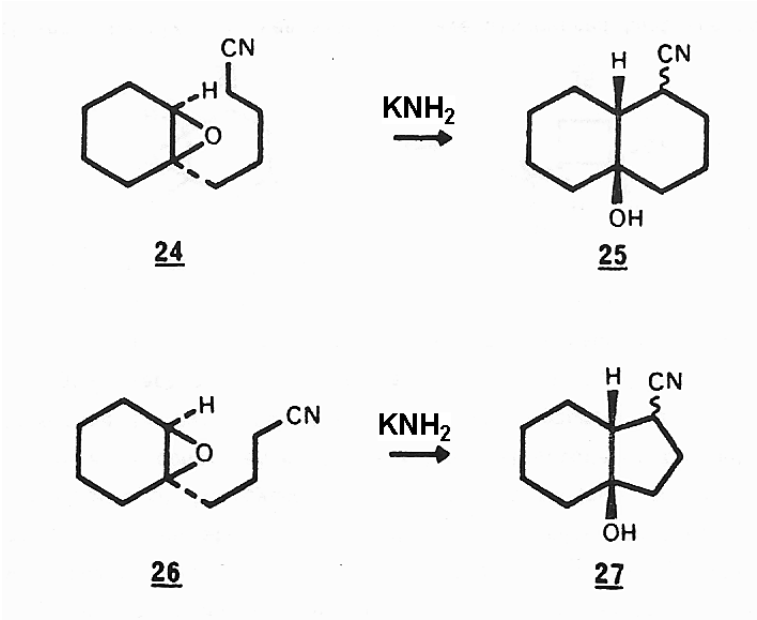
The reverse process takes place with the same stereoelectronic control.



Intramolecular Epoxide Opening to Yield 5- or 6-Membered Ring



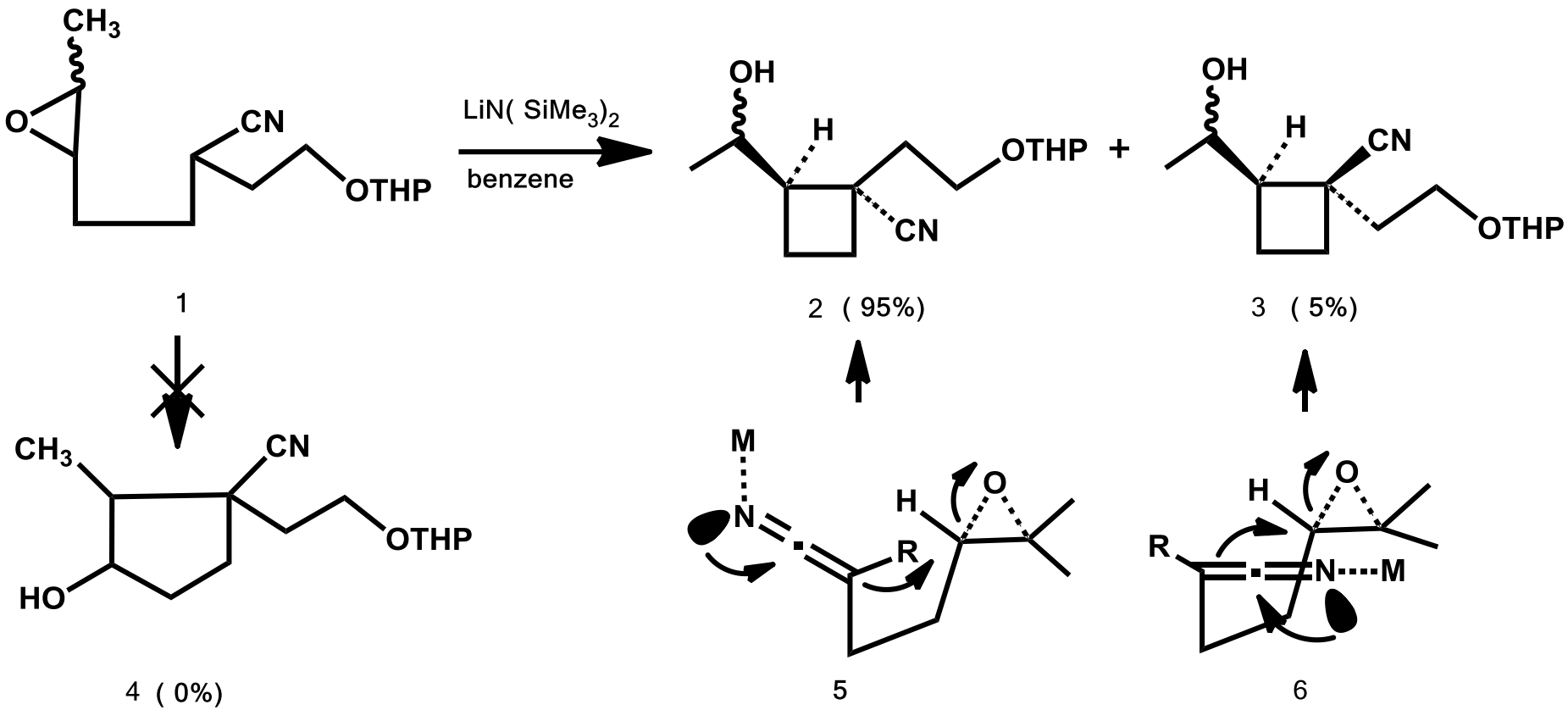
1. **6-membered is favored in 21 (also less subsituted)**
2. **considerable bond distortion in 22**
3. **no particular constraint in 23**



24 → 25
faster (easier) than
26 → 27

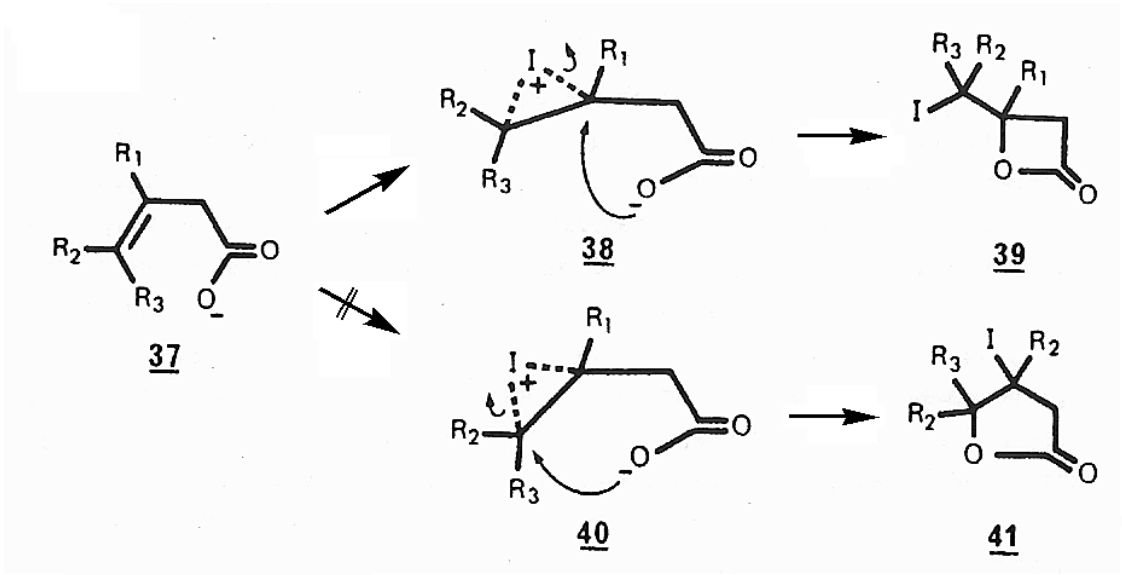
G. STORK *et al.* *J.Am.Chem.Soc.* 1974, *96,* 5268.

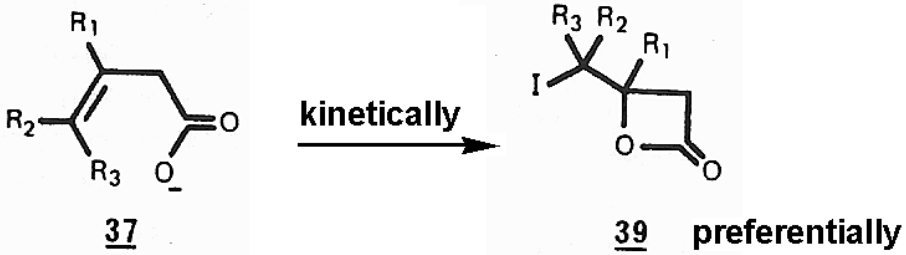
Intamolecular Epoxide Opening to Yield 4 rather than 5-Membered RIng



G. STORK *et al.* *J.Am.Chem.Soc.* 1974, *96,* 5270.

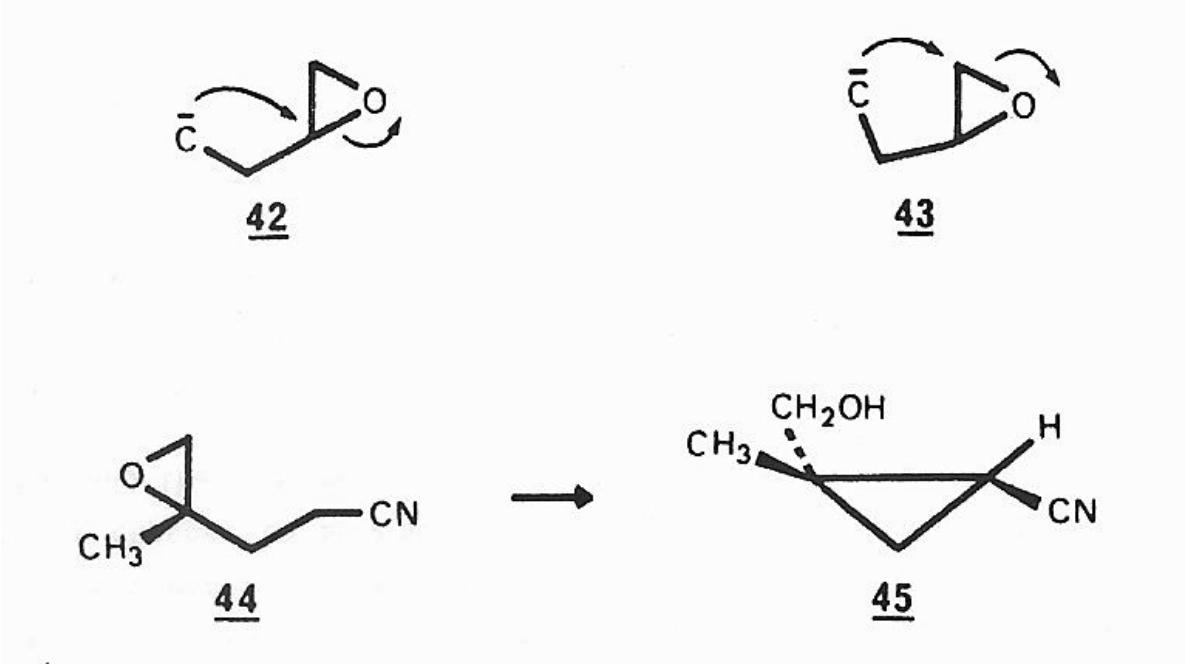
Iodolactonization 4-Preferred to 5-Membered Ring





W.E. BARNETT *et al. J. Org. Chem.* 1975, *40,* 2843.

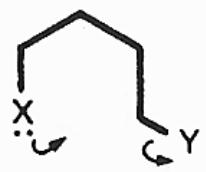
Cyclopropane Formation Preferred Over Cyclobutane Formation



Cyclopropane (42) is produced in preference to a cyclobutane (43) regardless of the relative degree of substitution of the oxirane ring because 44 gave only 45.

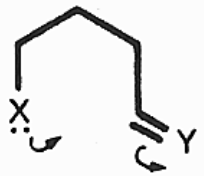
G. STORK *et al.* *J.Am.Chem.Soc.* 1974, *96,* 5270.

Baldwin Rules for Ring Closure (nomenclature)



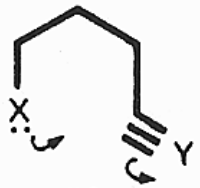
49

5-*exo*-tet



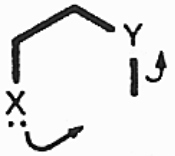
50

5-*exo*-trig



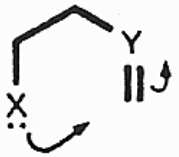
51

5-*exo*-dig



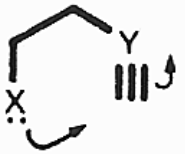
52

5-*endo*-tet X



53

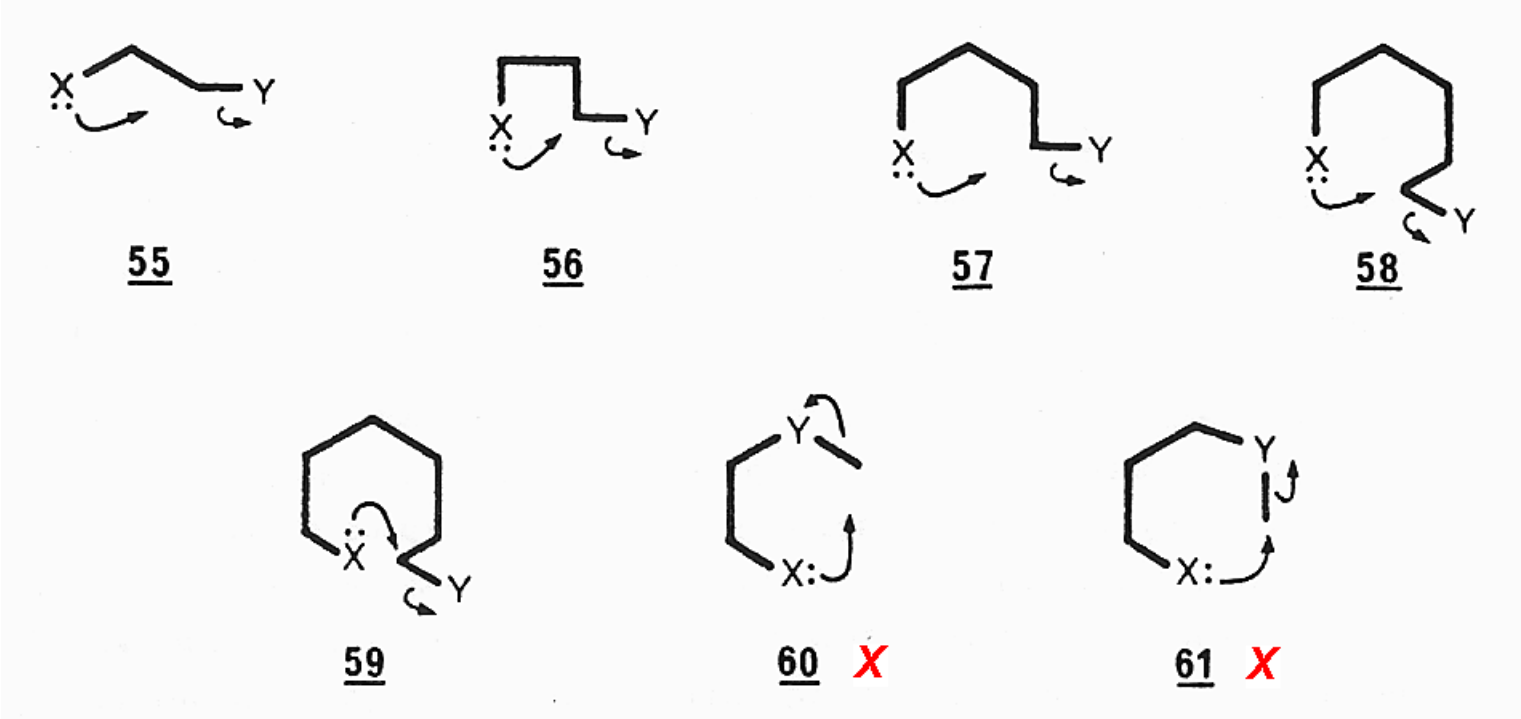
5-*endo*-trig X



54

5-*endo*-dig X

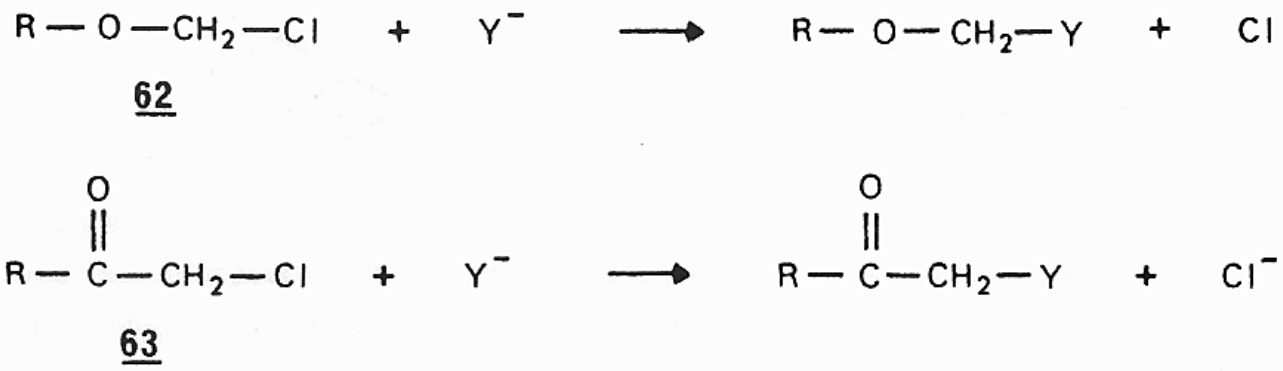
Baldwin Rules for Ring Closure in Tetrahedral Systems



1. 3-*exo*-tet to 7-*exo*-tet (55-59) are all favored
   relative ease: 55 > 56 > 57 > 58 > 59
2. However when Y is part of an oxirane ring
   the order is 55 > 56 > 57 < 58
3. 5-*endo*-tet (60) and 6-*endo*-tet (61) are disfavored
4. 61 corresponds to Eschenmoser experiment

J.E. BALDWIN. ***J.Chem.Soc., Chem.Commun.*** **1976, 738.**

SN_2 Displacement of α-Cl-ether and α-Cl-ketone



62

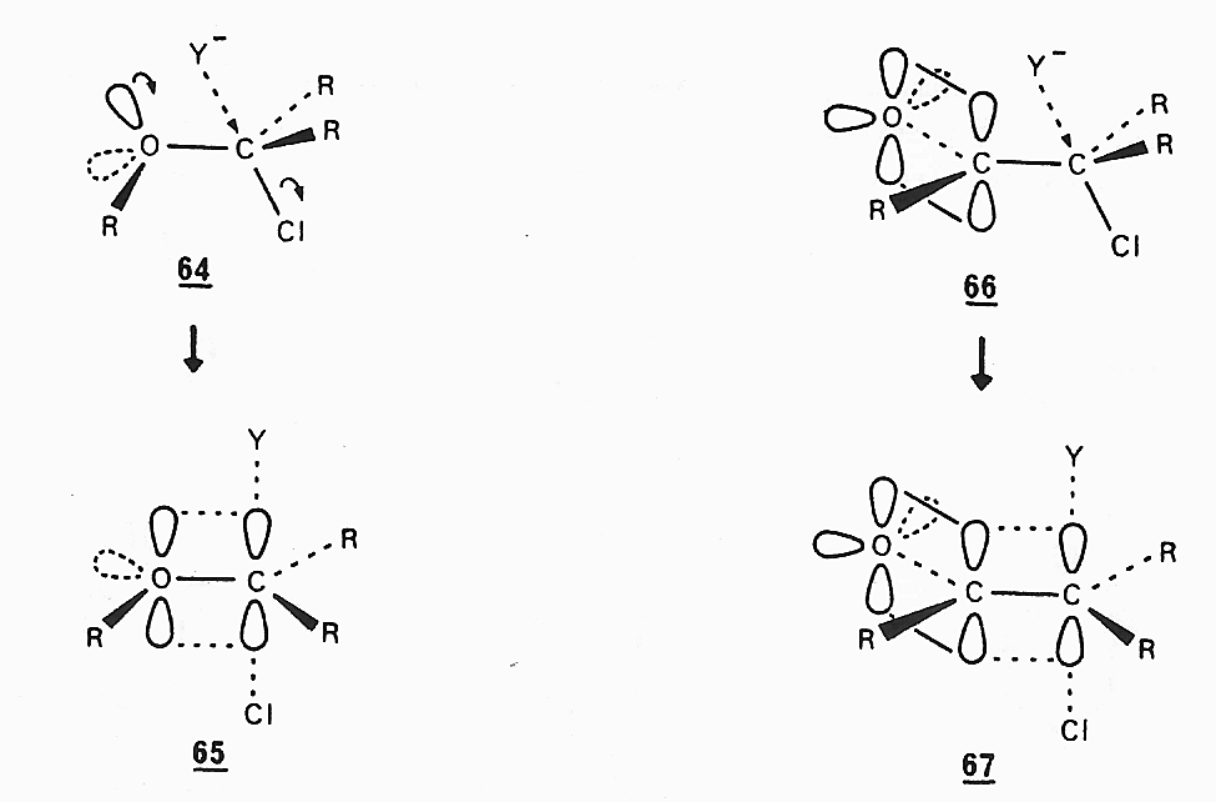
63

The rate of SN_2 reaction is greatly enhanced in α-haloethers 62 and in α-haloketones 63. This enhancement should however occur only when the oxygen atom in 62 has an electron pair antiperiplanar to the C–Cl bond (cf. 64 ⇢ 65). Similarly, in an α-haloketone the π system of the carbonyl group must be parallel to the C–Cl bond (cf. 66 ⇢ 67) (20).

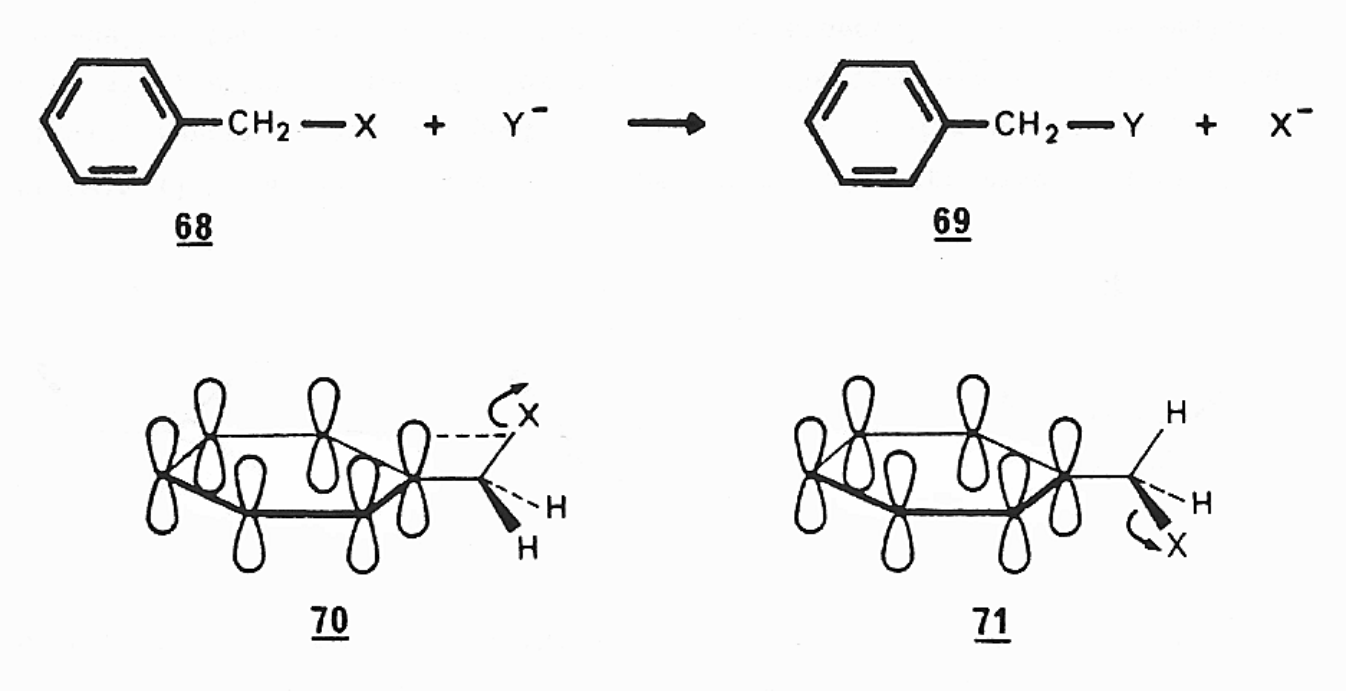
64 → 65 and 66 → 67 are shown on next slide.

Stereoelectronic Effect at TS in the Preceding Displacement Reactions

α-Cl-ether **α-Cl-ketone**

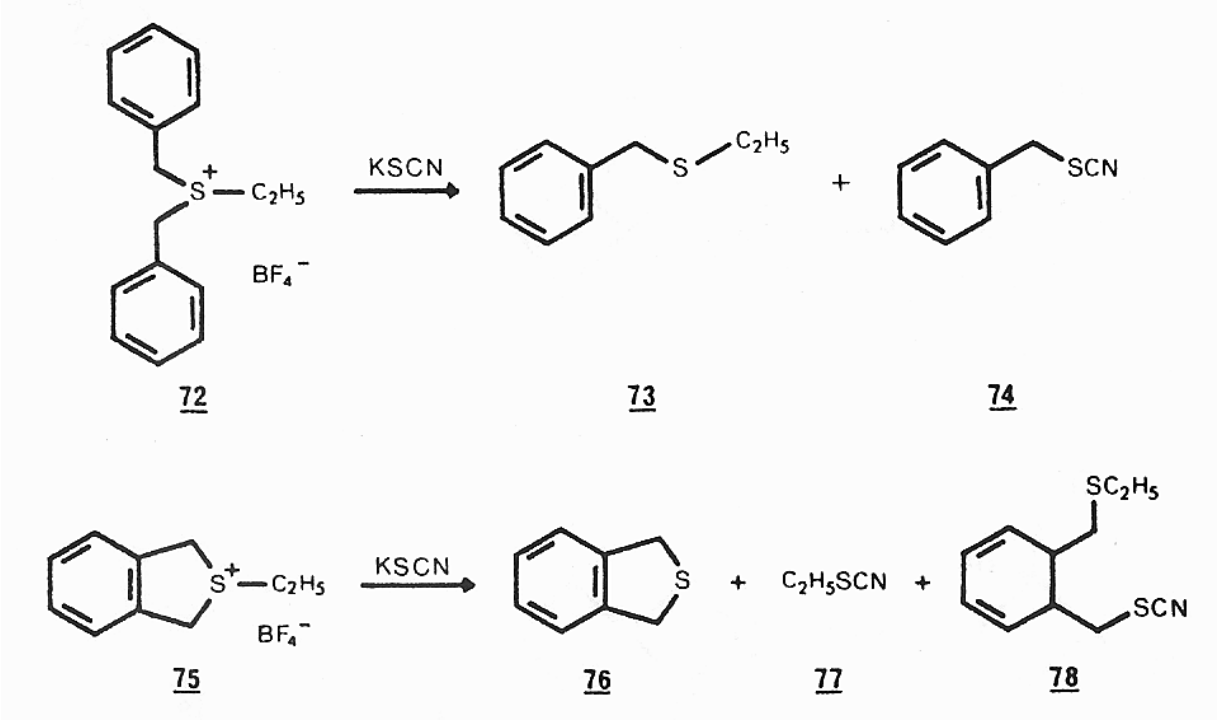


Displacement in Benzylic Substrates



1. **Bimolecular substitution in benzyl substrates (68 to 69) takes place with ease via conformation 70**
2. **Conformation 71 is disfavored**

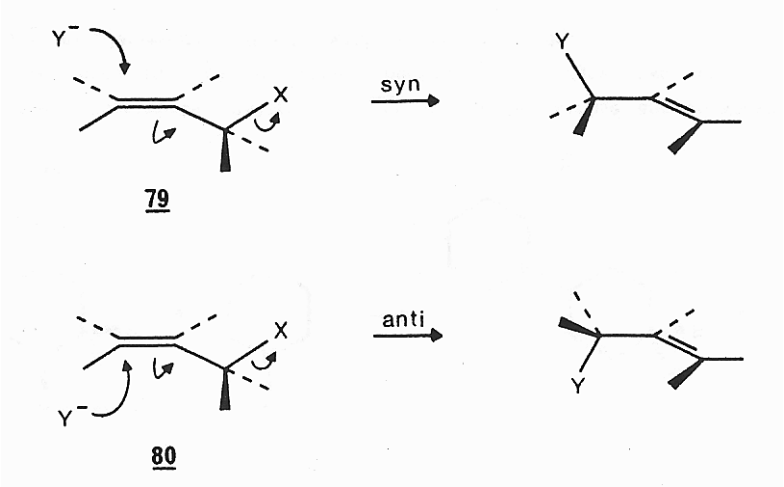
SN_2 Displacement on Sulfonium Salts



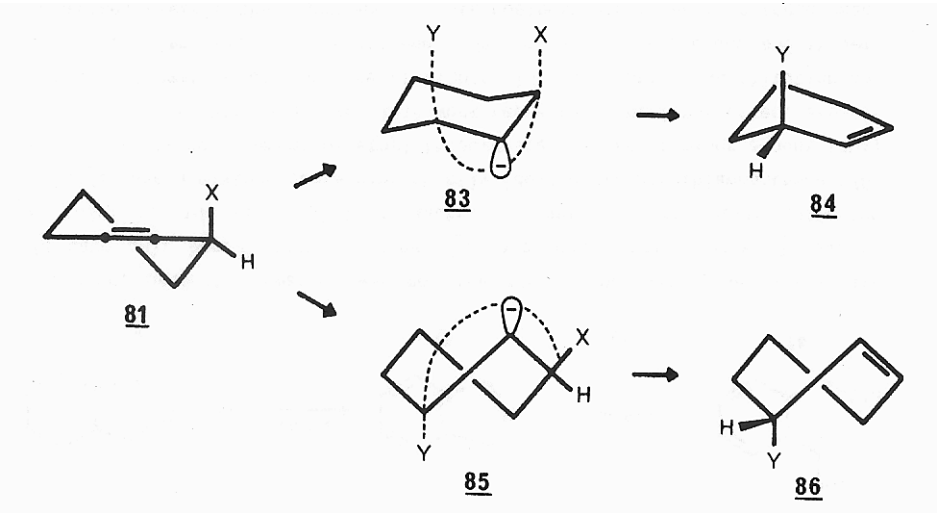
1. **Reaction on 72 is 8000 faster than that on 75**
2. **72 can take conformation 70 (previous slide)**
3. **75 is locked in the unreactive conformation 71, displacement takes place preferentially on the ethyl group to give 76**

J.F. KING *et al.* *J.Chem.Soc., Chem.Commun.* 1979, 1131.

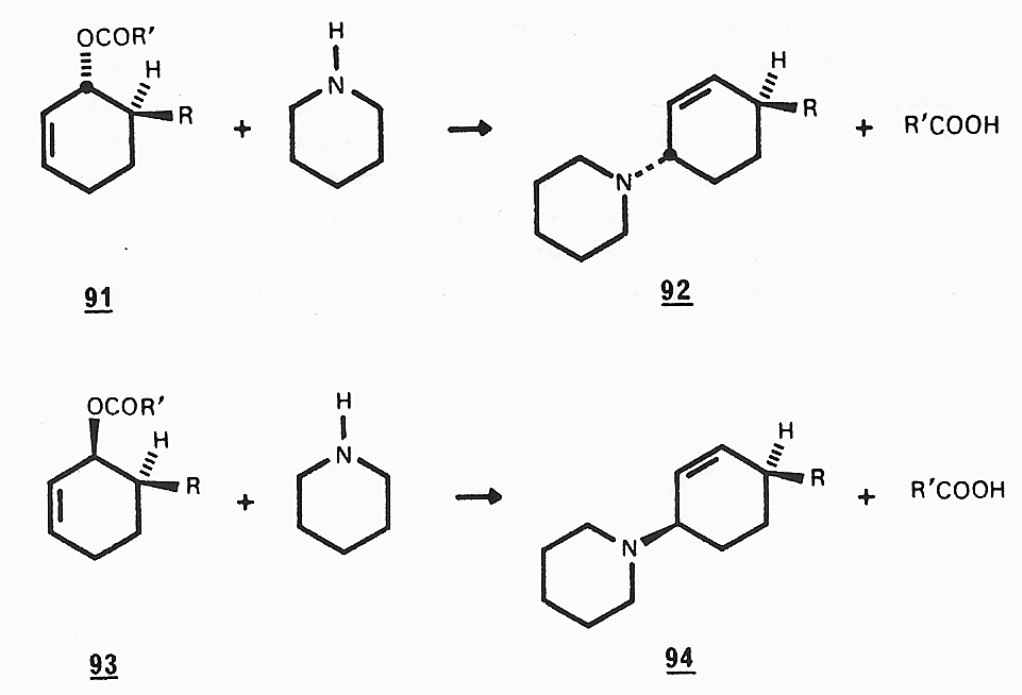
Syn and *Anti* Displacement in Allylic System



Based on the antiperiplanar lone pair hypothesis, *syn* is preferred over *anti* displacement.



SN_2' Takes Place via the *Syn* Mode

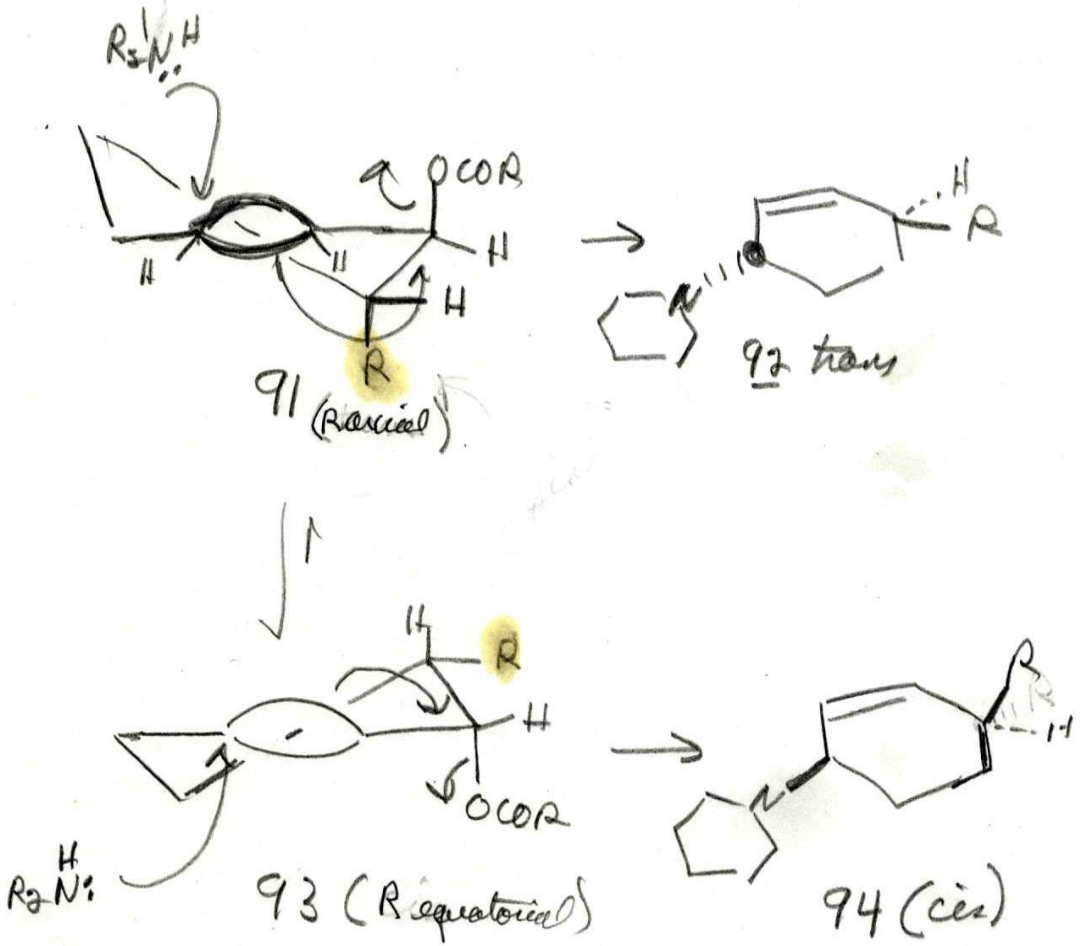


91 (R = CH_3, $CH(CH_3)_2$ or $C(CH_3)_3$ and R' = $Cl_2C_6H_3$-) reacts with piperidine to give the *syn* SN_2' product 92. Also,

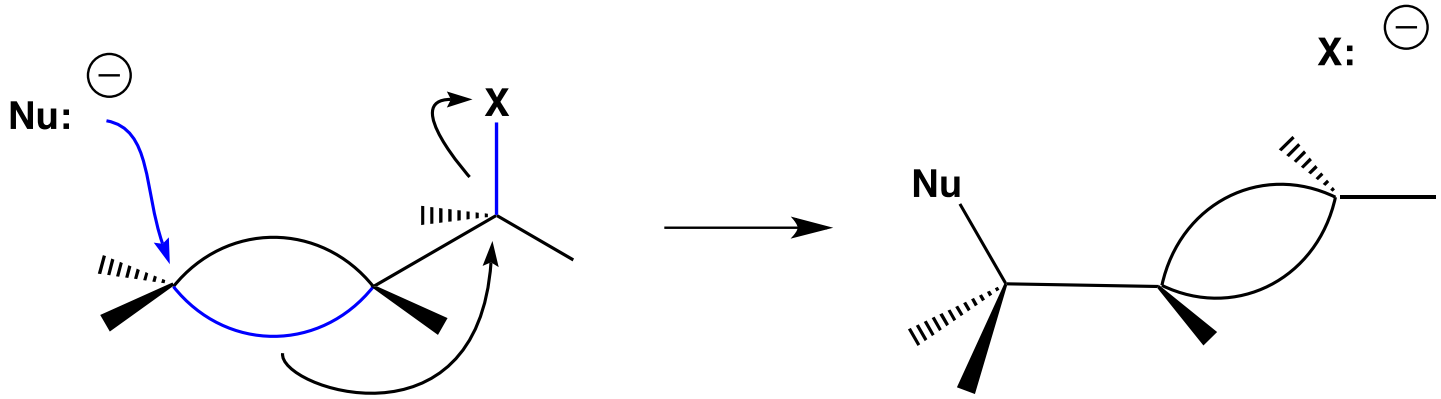
91 and 93 (R = $CH(CH_3)_2$, R' = $C_6H_2(CH_3)_3$), gave *syn* SN2' products 92 and 94 respectively.

G. STORK *et al.* *J.Am.Chem.Soc.* 1953, *75,* 4119; 1956, *78,* 4609; 1977, *99,* 3850, 8373.

K.H. OVERTON *et al.* *J.Chem.Soc., Chem.Commun.* 1977, 722.


R2NH
OCOR
H
H
R
91 (R axial)
92 trans
H
R
93 (R equatorial)
94 (cis)

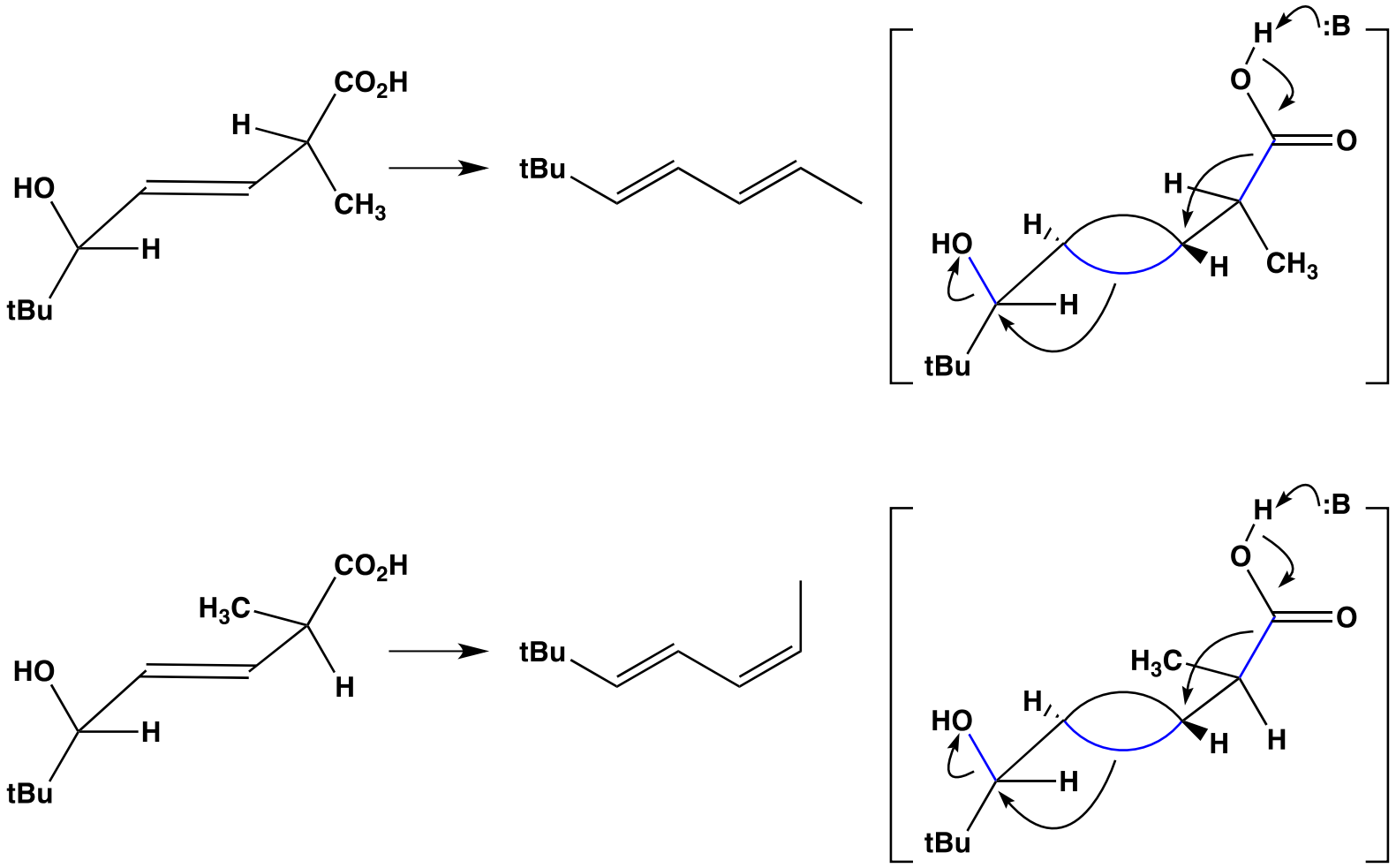
$S_N2´ / E2´$ Reaction (SYN Pathway)



R. M. Magid, Tetrahedron, 1980, 36, 1901.

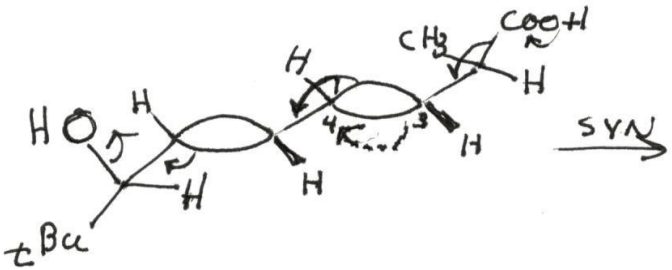
E. Vogel, G. Caravatti, P. Franck, P. Aristoff, C. Moody, A.-M. Becker, D. Felix, A. Eschenmoser, Chem. Lett. 1987, 219.

Stereoselectivity of E' Elimination Reactions

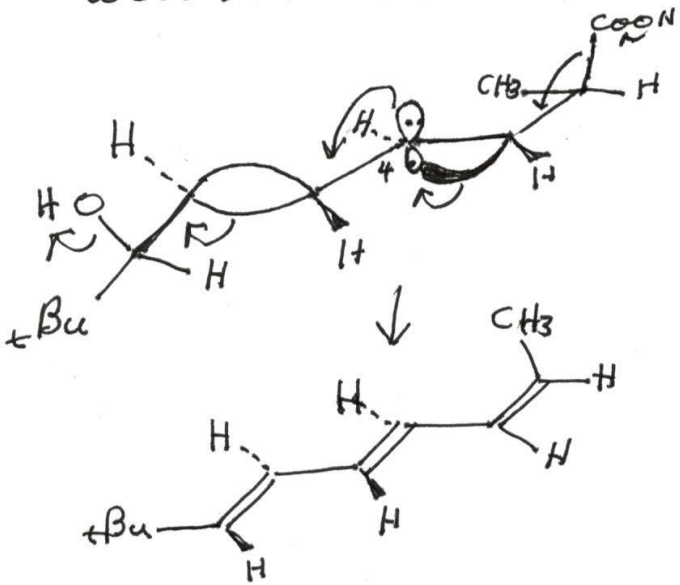


E. Vogel, G. Caravatti, P. Franck, P. Aristoff, C. Moody, A.-M. Becker, D. Felix, A. Eschenmoser, Chem. Lett. 1987, 219.

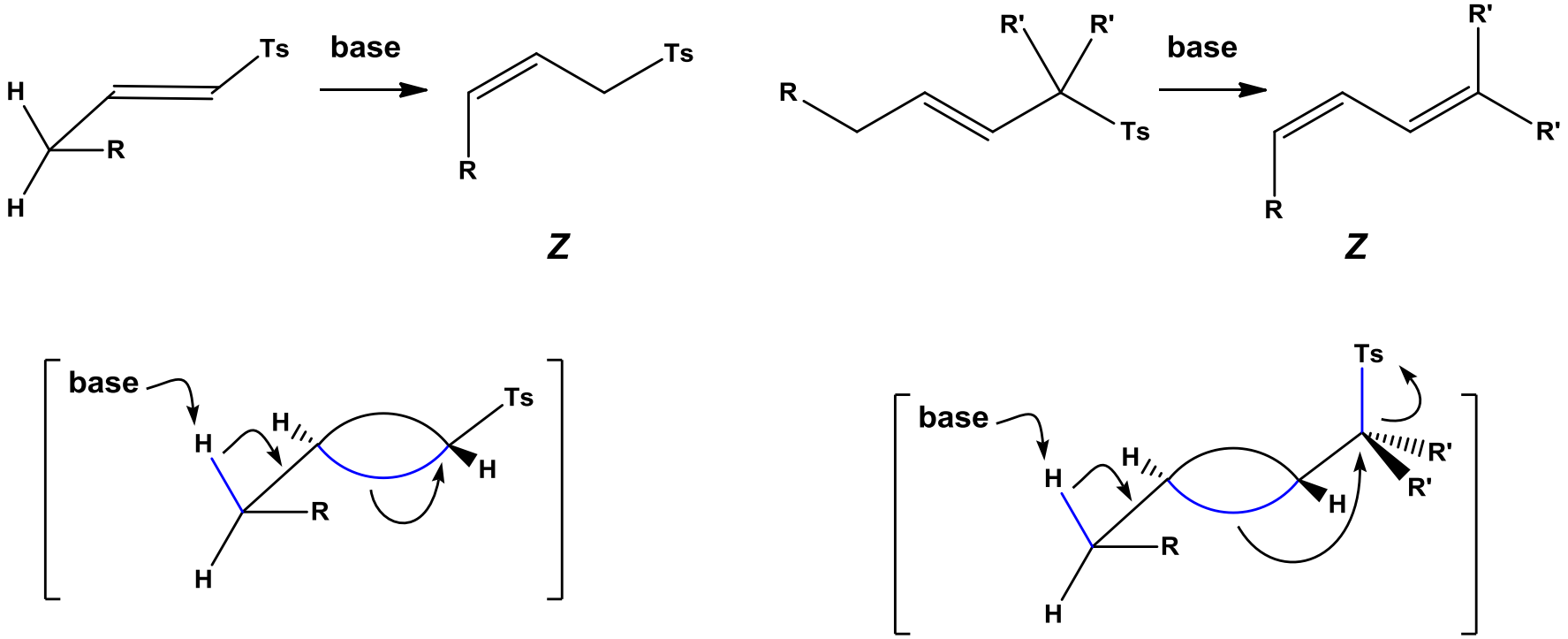
Eschenmoser has also observed



But, it can also be an elimination ANTI with inversion at C4.

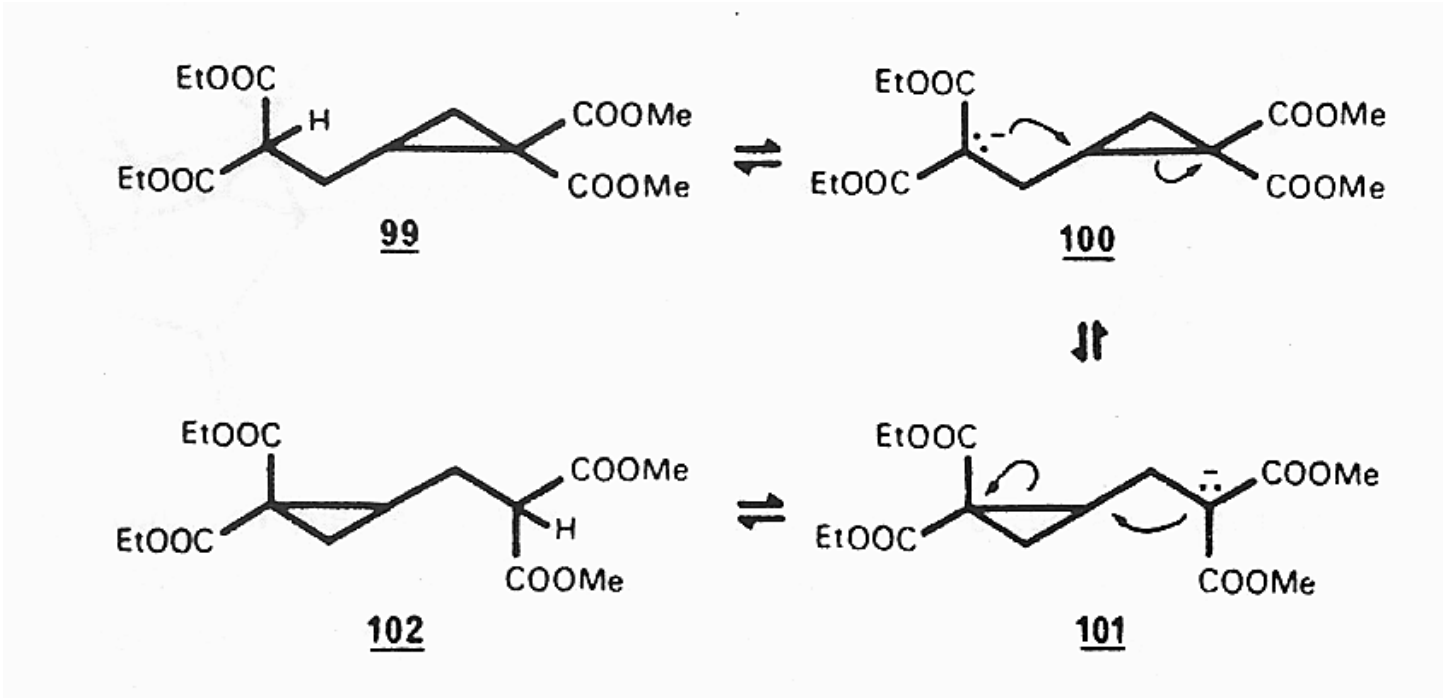


Preferred Formation of Z-olefin due to Syn Effect



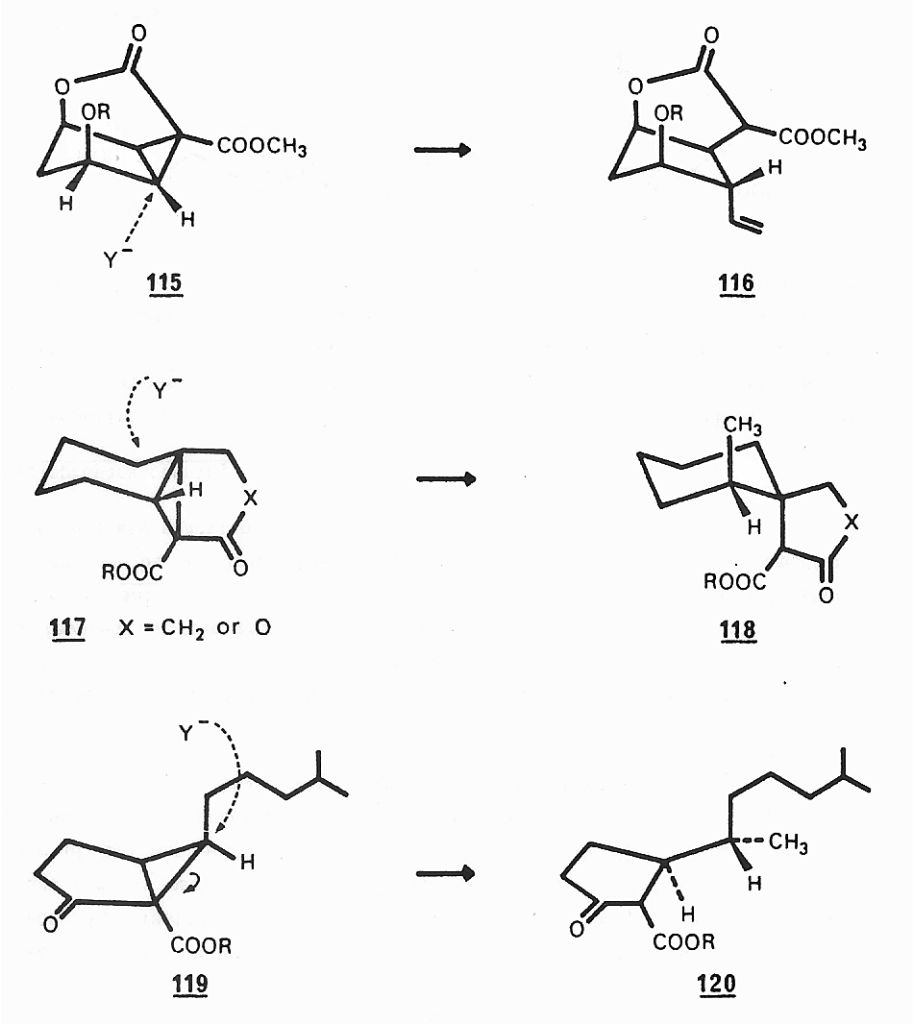
K. Inomata, J. Synth. Org. Chem. Jpn, 2009, 67, 1172.

Cyclopropane Opening



DANISHEFSKY *et al.* *J.Chem.Soc., Chem.Commun.* 1973, 81.

Cyclopropane Opening by Cuprate Addition



E.J. COREY *et al.*

***J.Am.Chem.Soc.* 1972, *94,* 4014.**

C.H. HEATHCOCK *et al.*

***Tet. Lett.* 1975, 529.**

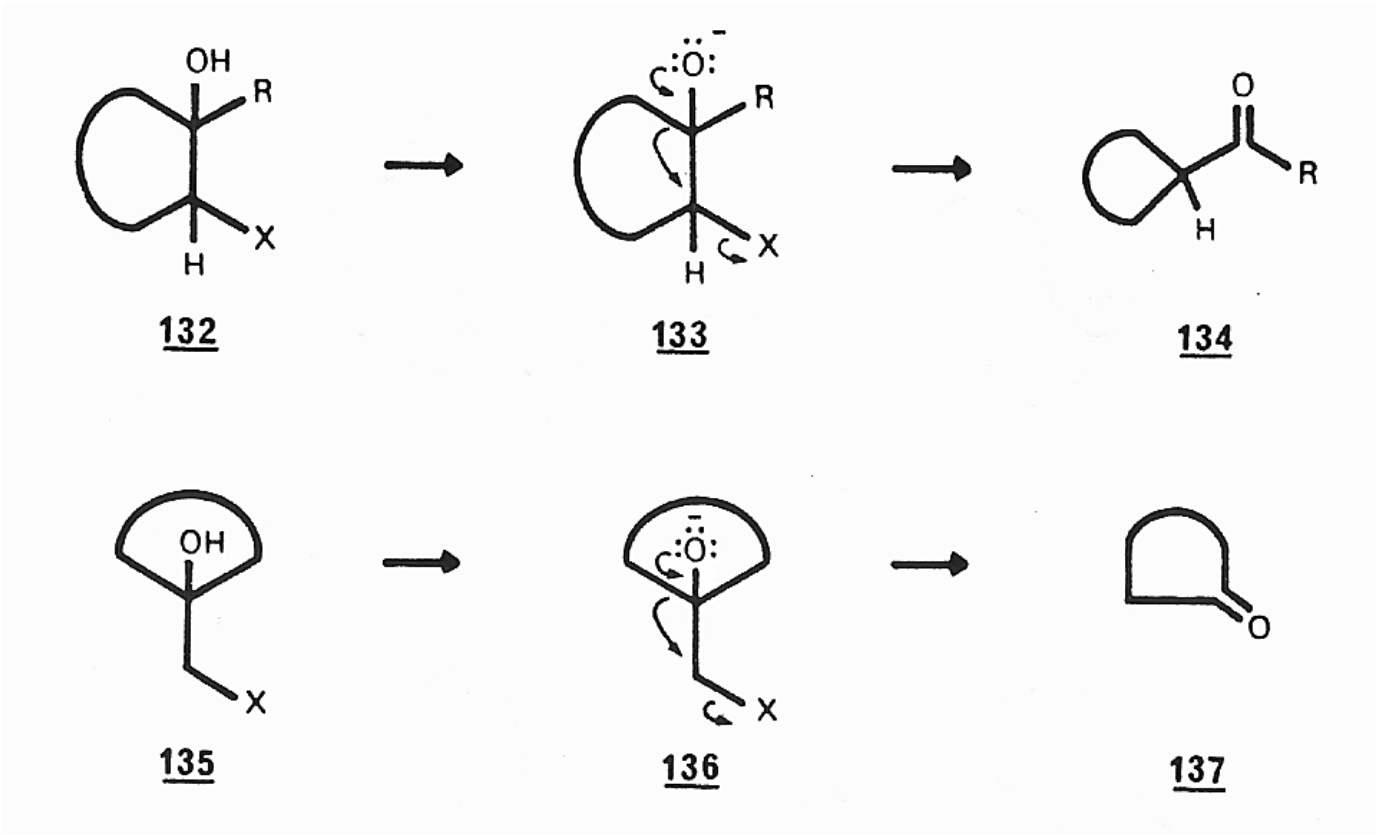
B.M. TROST *et al.*

***Tet. Lett.* 1976, 3857.**

MOLECULAR REARRANGEMENT

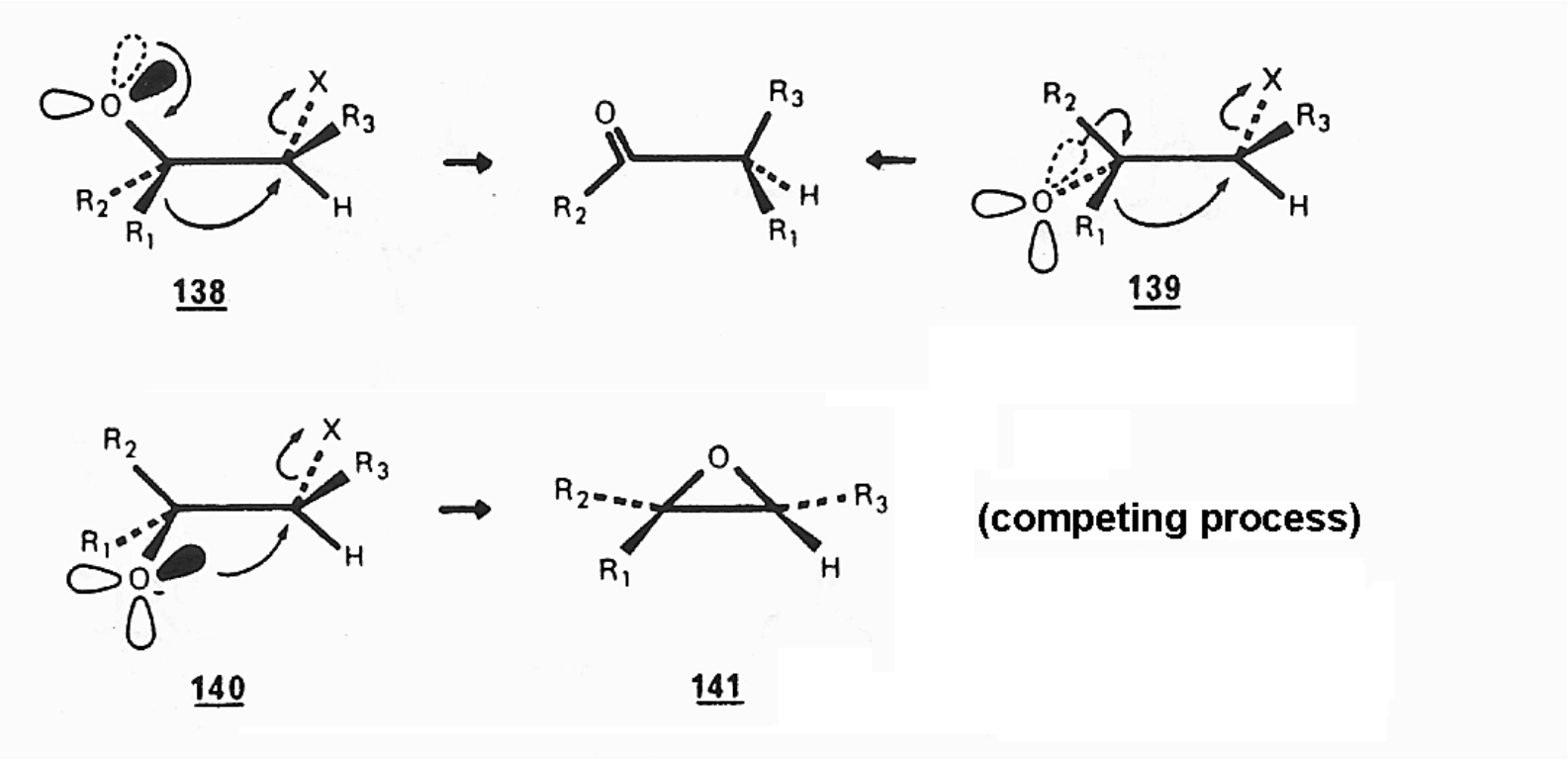
Ring Contraction or Expansion:

2 Consecutive Intramolecular SN_2 Displacements

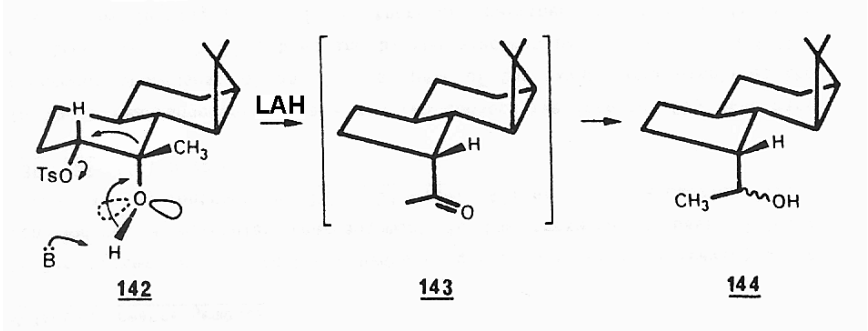


MOLECULAR REARRANGEMENT

Migrating Group Always Oriented Antiperiplanar to the Leaving Group



Specific Examples of Rearrangement

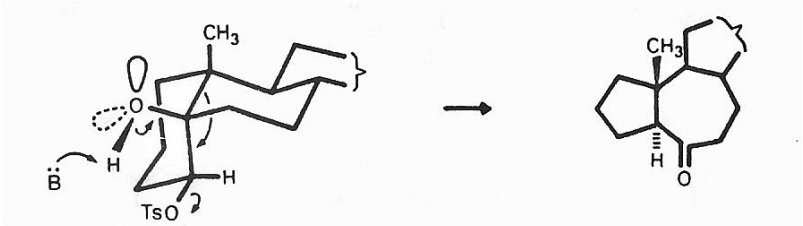


142 143 144

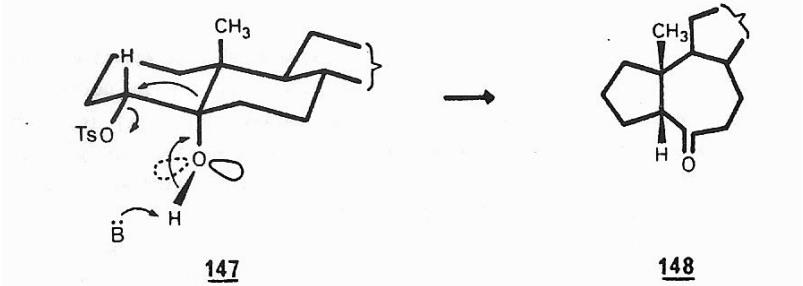
G. BÜCHI *et al.*

J.Am.Chem.Soc. 1960, *82,* 2327.

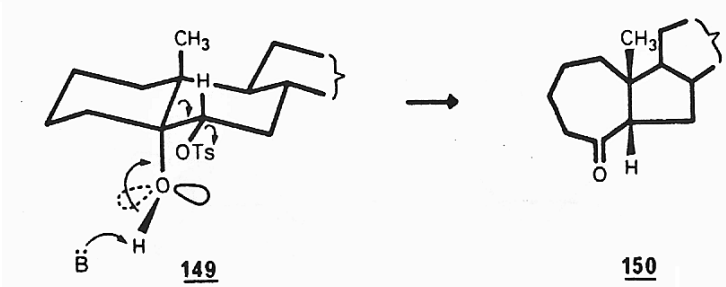
Steroids Derivatives



145 146



147 148

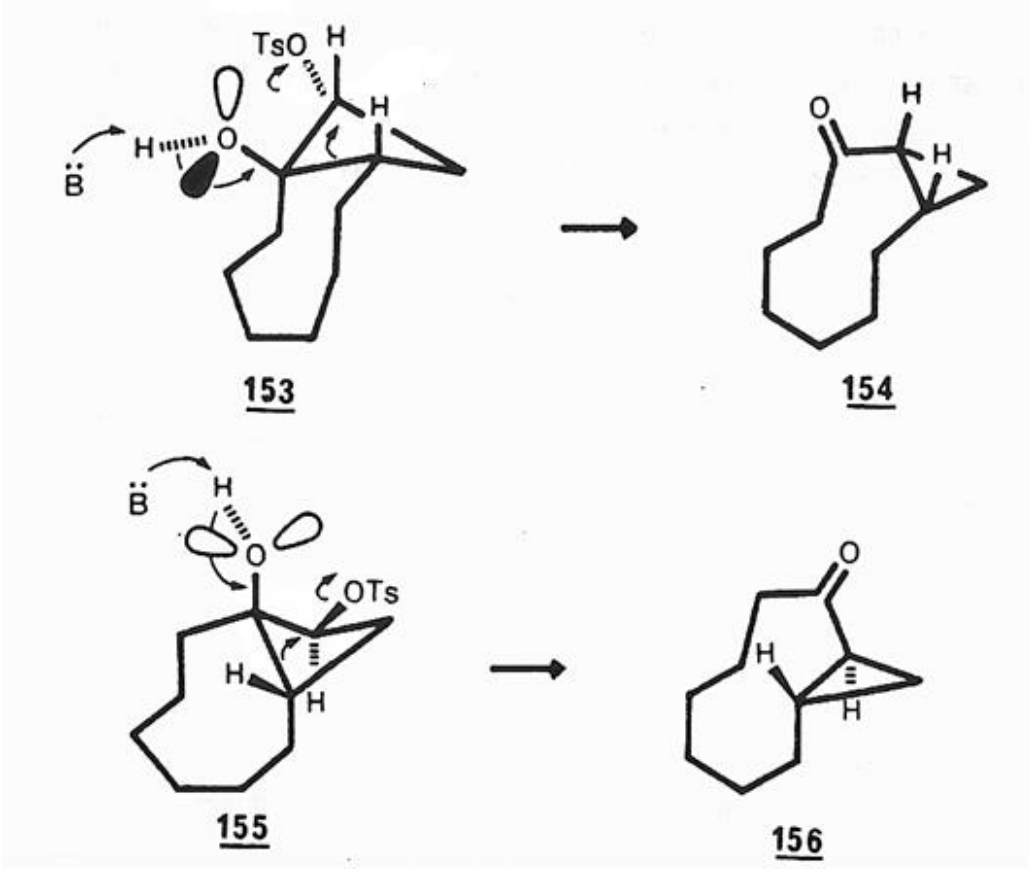


149 150

Y. MAZUR *et al.*

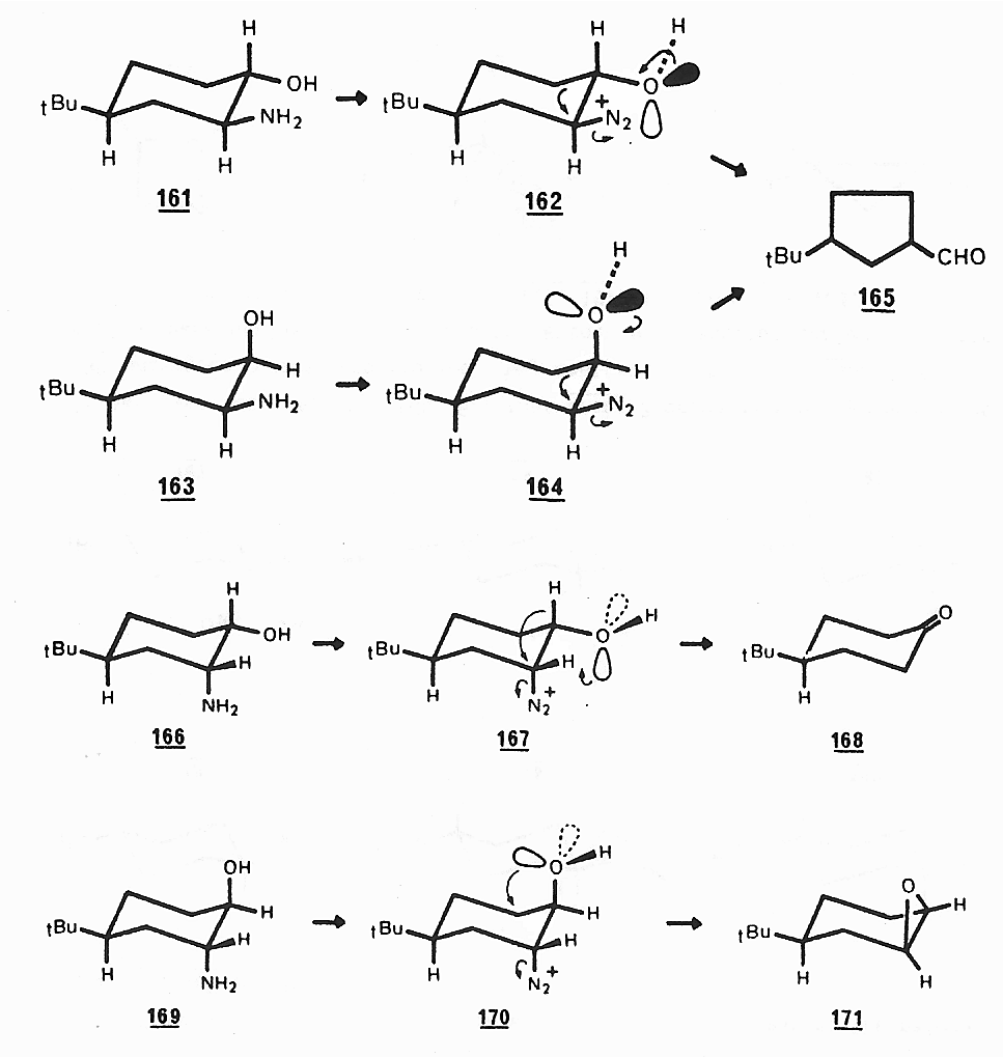
Tetrahedron 1968, *24,* 5337.

Cyclobutane to Cyclopropane Ring



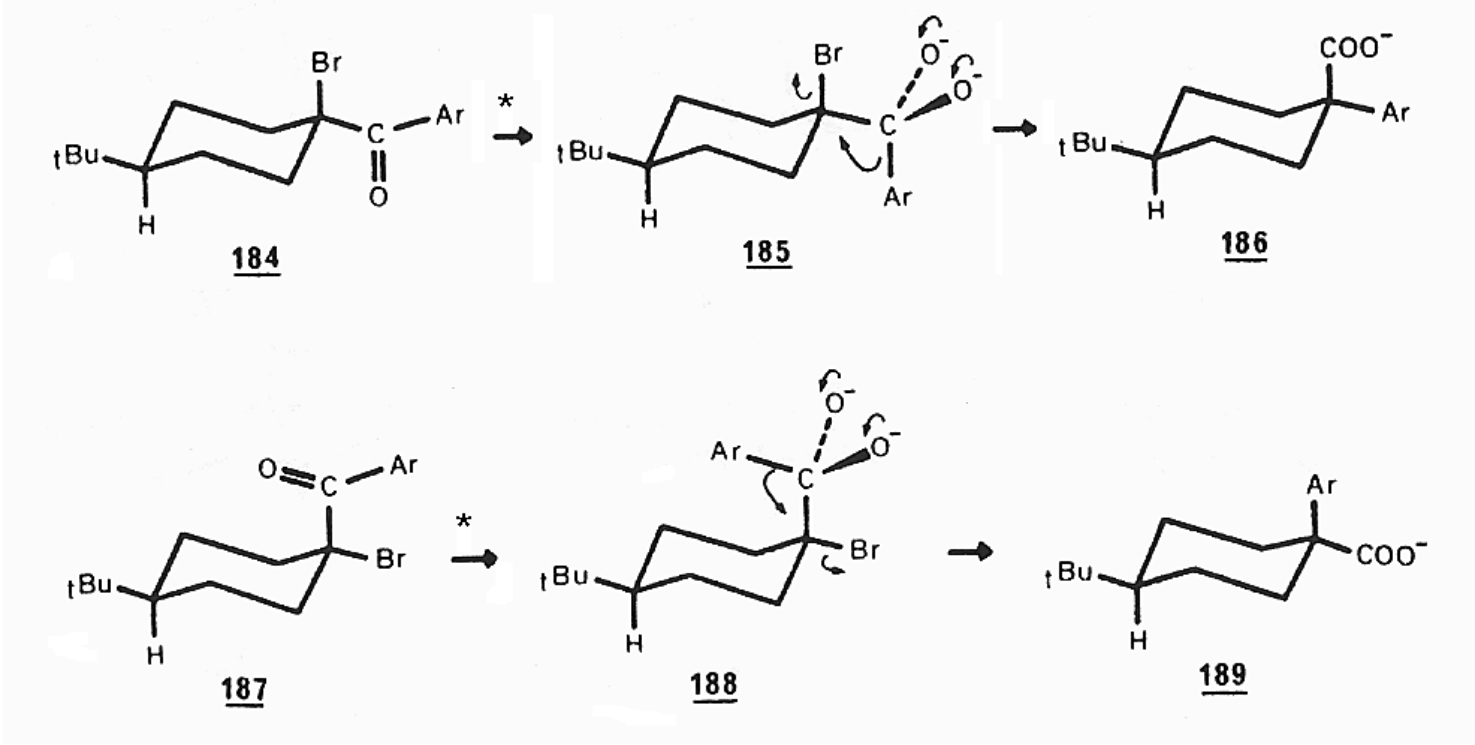
J.V. PAUKSTELIS *et al.* *Tetrahedron Lett.* 1970, 3691.

Diazotization with Nitrous Acid of Amino-alcohol



H. FAVRE, D. GRAVEL. *Can.J.Chem.* 1961, *39,* 1548; 1963, *41,* 1452.

Quasi-Favorski Rearrangement

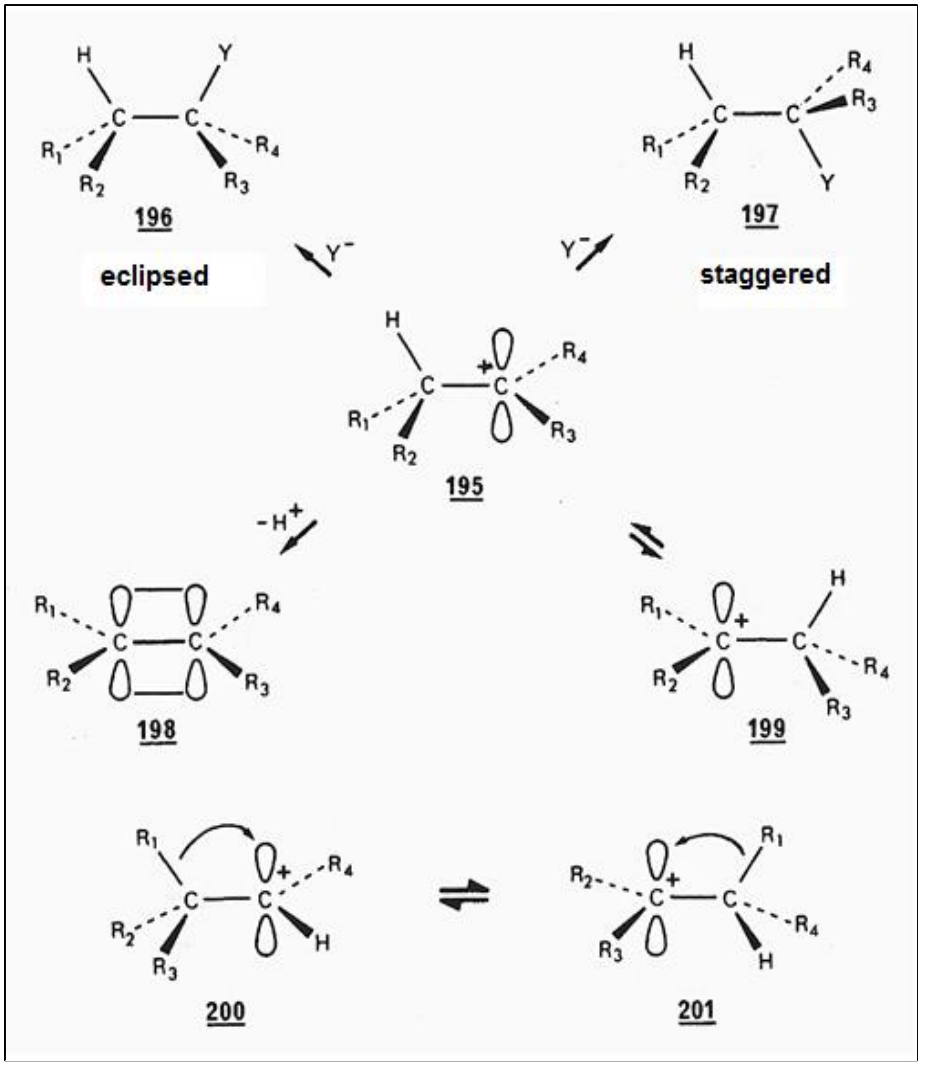


*** Refluxing xylene in the presence of sodium hydroxide.**

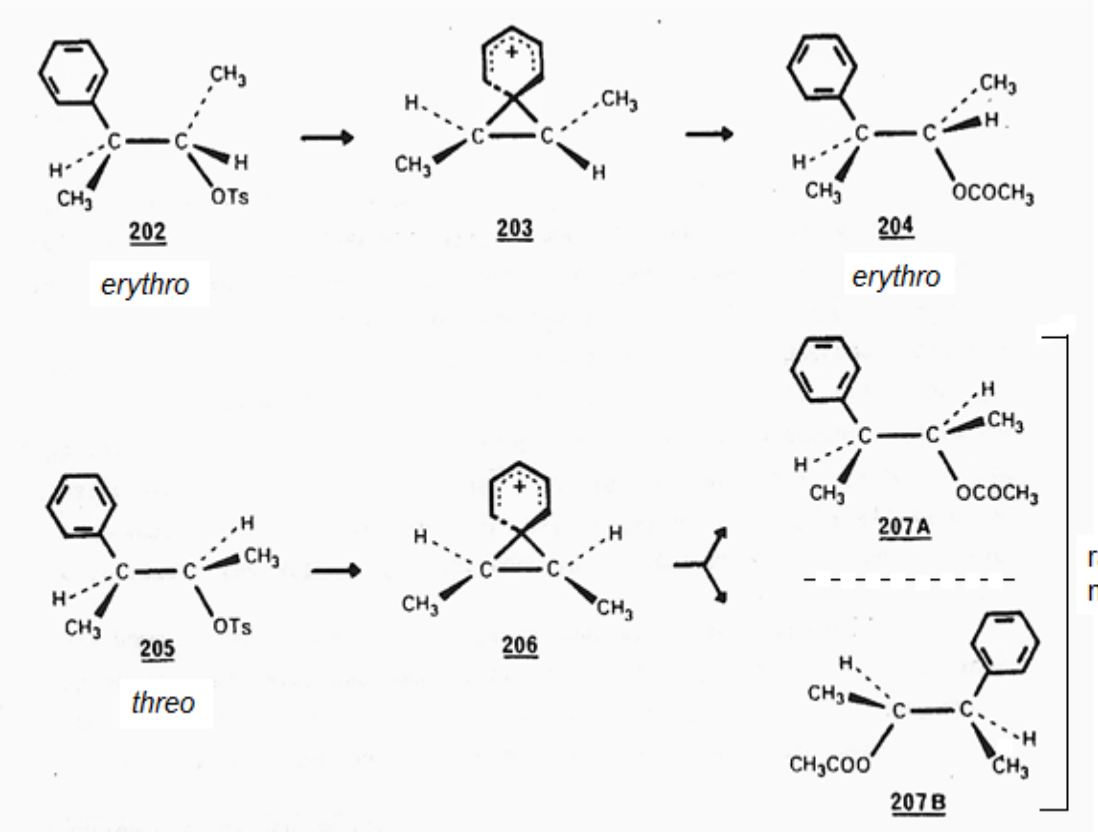
W.S. JOHNSON. ***Acc.Chem.Res.*** **1968, 1.**

Reaction at Carbonium Ion (general)

For instance, the attack of a nucleophile Y^- from above or below the plane of a carbonium ion having the conformation **195** will, if $R_3 \neq R_4$, give two diastereomers in conformations **196** and **197** respectively. Carbonium ion **195** can also form a double-bond ($\rightarrow$**198**) by the loss of a proton because the C-H bond is properly aligned with the p-orbital of the carbonium ion. For the same reason, it can also undergo a migration of the hydrogen atom with its electron pair to give the rearranged carbonium ion **199**. Similarly, in skeletal rearrangement such as the Wagner-Meerwein or the pinacol transposition, the migrating alkyl group must be that which is properly aligned as shown by **200** and **201**.



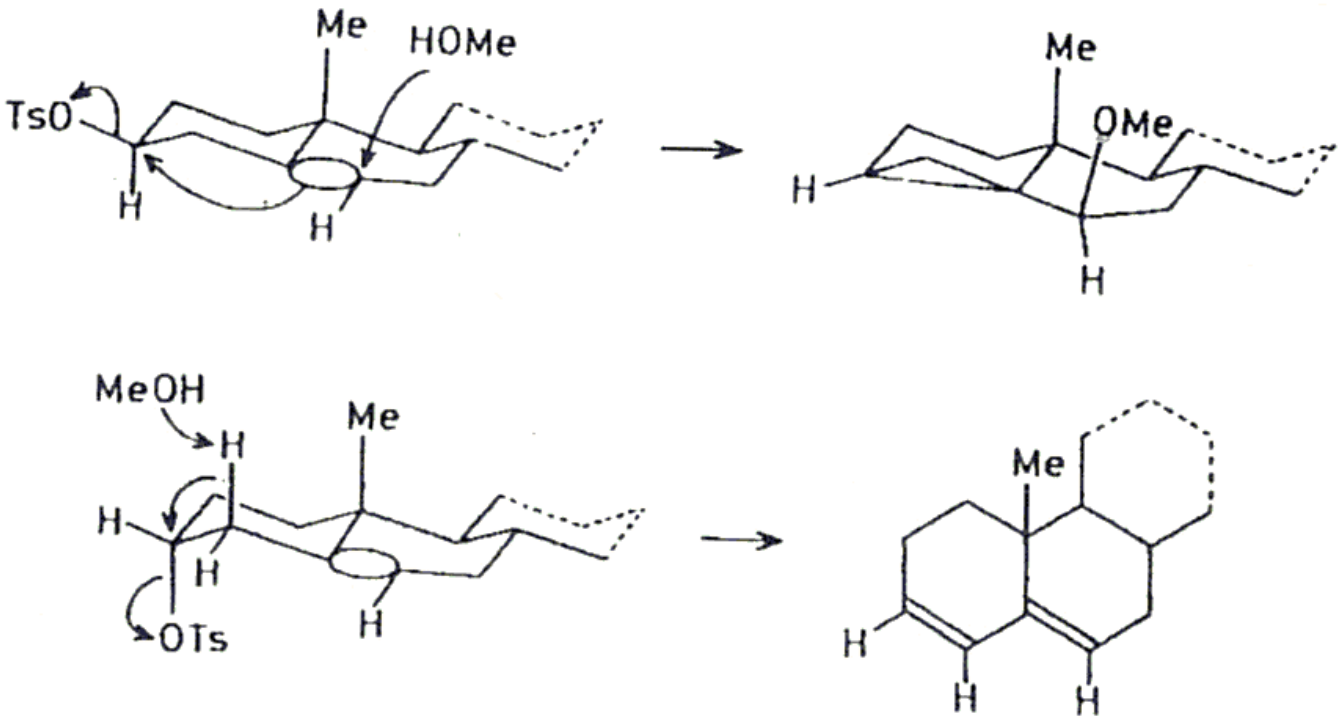
Neighboring Group Participation in Solvolysis Reactions



1. ***Erythro*-tosylate 202 in acetic acid gave *erythro*-acetate 204 via chiral bridged ion 203**
2. ***Threo*-tosylate 205 gave a racemic mixture of *threo* products 207A and 207B via the achiral intermediate 206**

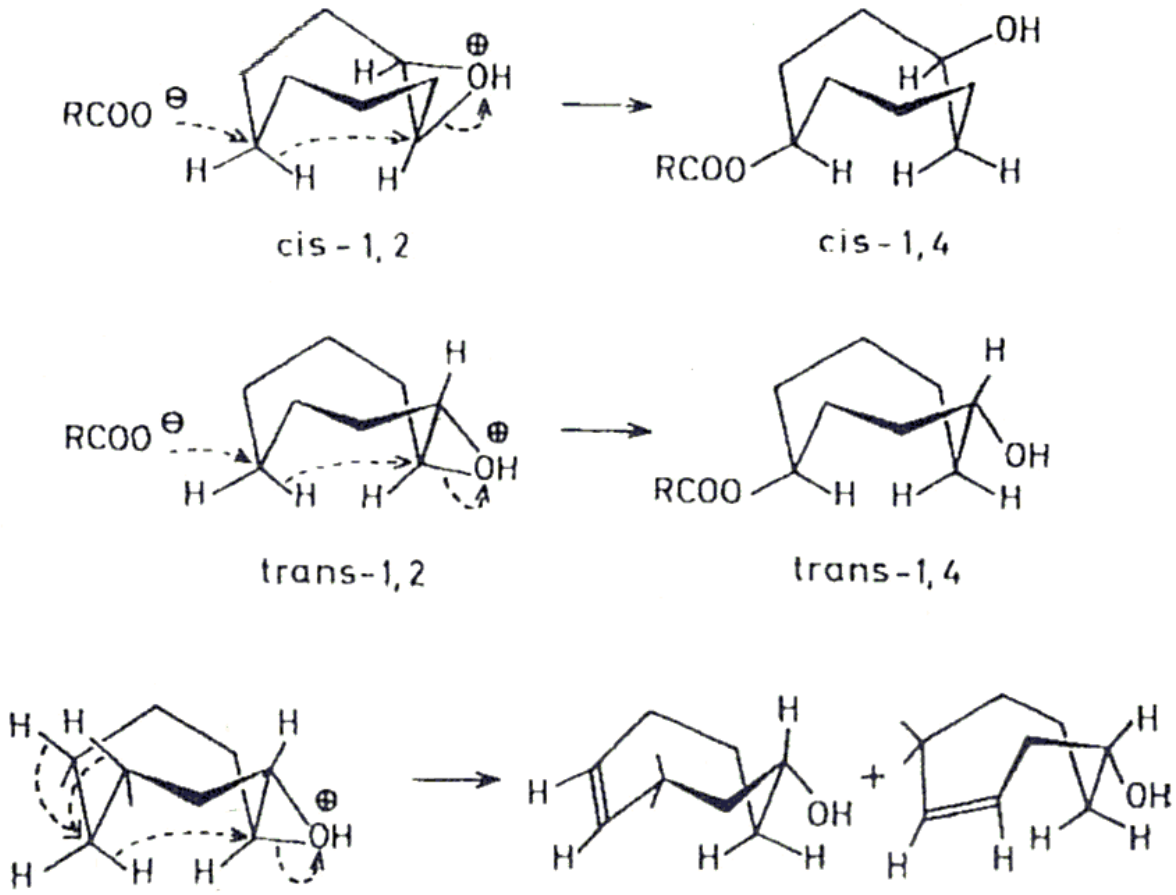
D.J. CRAM. *J.Am.Chem.Soc.* 1949, *71,* 3863.

Reactivity of Isomeric Cholesterol 3-Tosylates



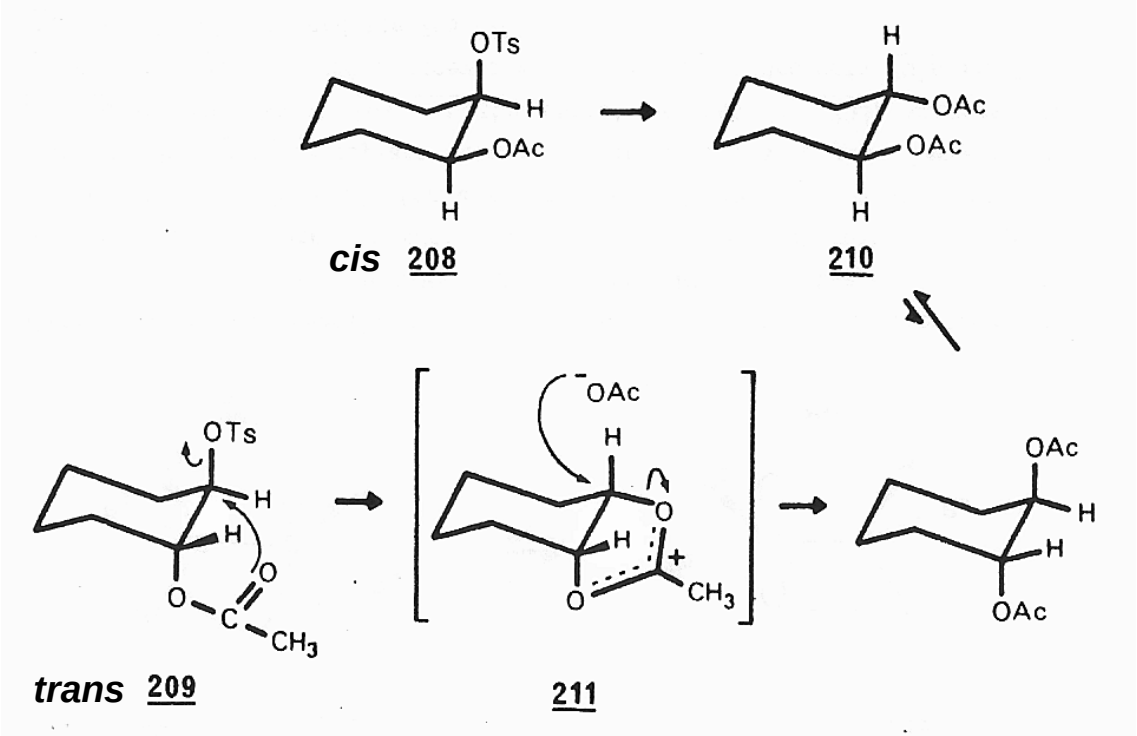
TARLE, M.; BORCIC, S.; SUNCO, D.E. *J.Org.Chem.* 1975, *40,* 2954.

Formolysis of *cis*- and *trans*-Cyclooctane Epoxides



COPE, A.C.; GIRSAR, M.J.; PETERSON, P.E. *J.Am.Chem.Soc.* 1959, *81,* 1640.

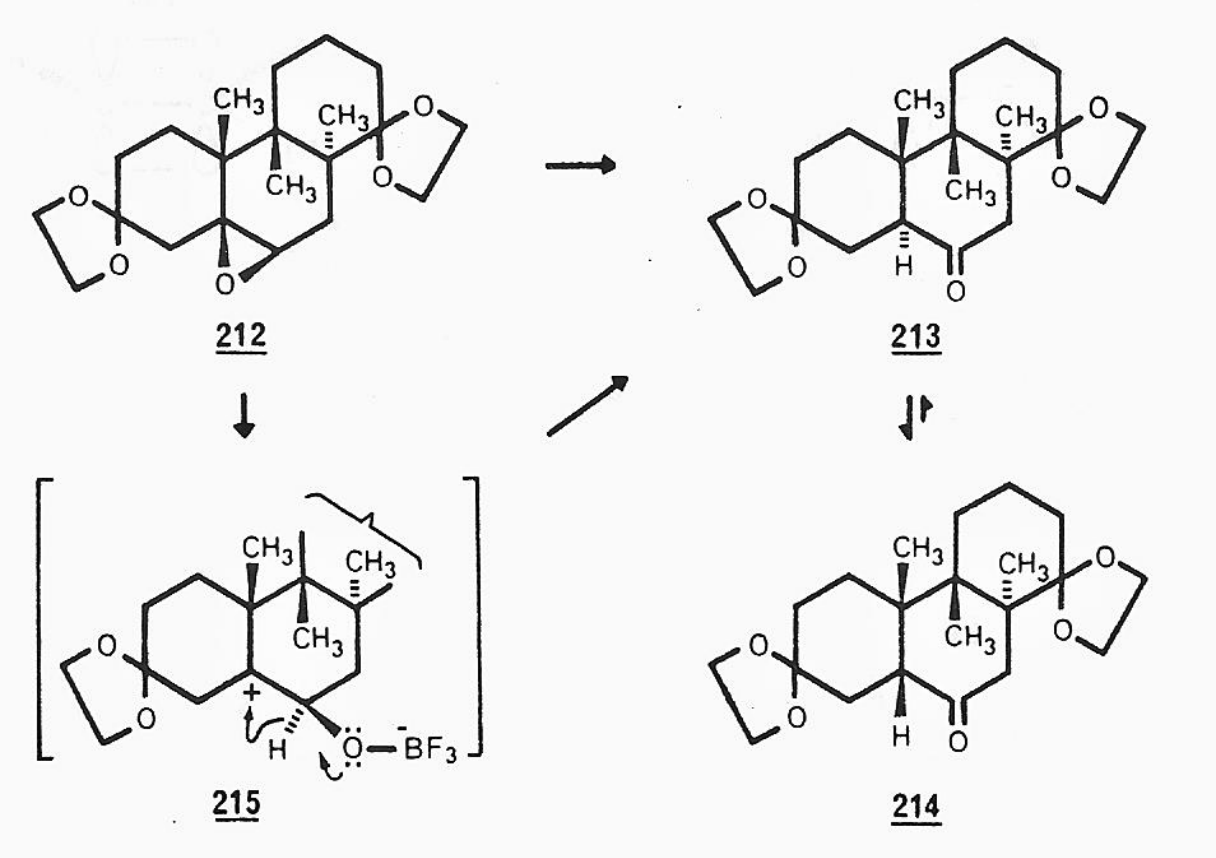
Acetate can Undergo Neighboring Group Participation



1. **Solvolysis of *cis* and *trans* 208 and 209 gave the same *trans*-diacetate 210**
2. **208 undergoes a classic SN_2 displacement by OAc^-**
3. **209 gave 210 via the cyclic acetoxonium intermediate 211**
4. **Interestingly, solvolysis of *trans* isomer 209 is 700 times faster than the *cis* isomer 208**

S. WINSTEIN *et al*. *J.Am.Chem.Soc.* 1948, *70,* 816.

Stereocontrolled Hydrogen Transfer in Epoxide Opening

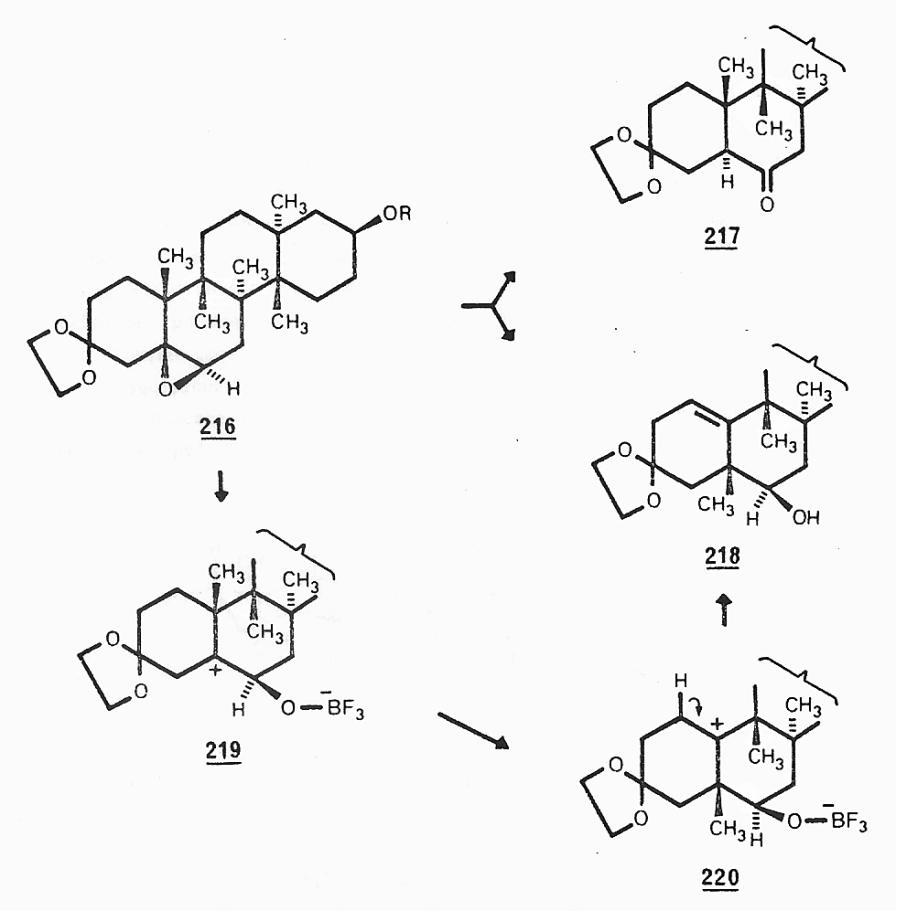


BF_3 catalyzed rearrangement of β-epoxide 212 gave only *trans*-ketone 213 via the intermediate 215.

The *cis* product 214 can be obtained by isomerization of 213.

R.E. IRELAND *et al*. *J.Am.Chem.Soc.* 1972, *94,* 3652.

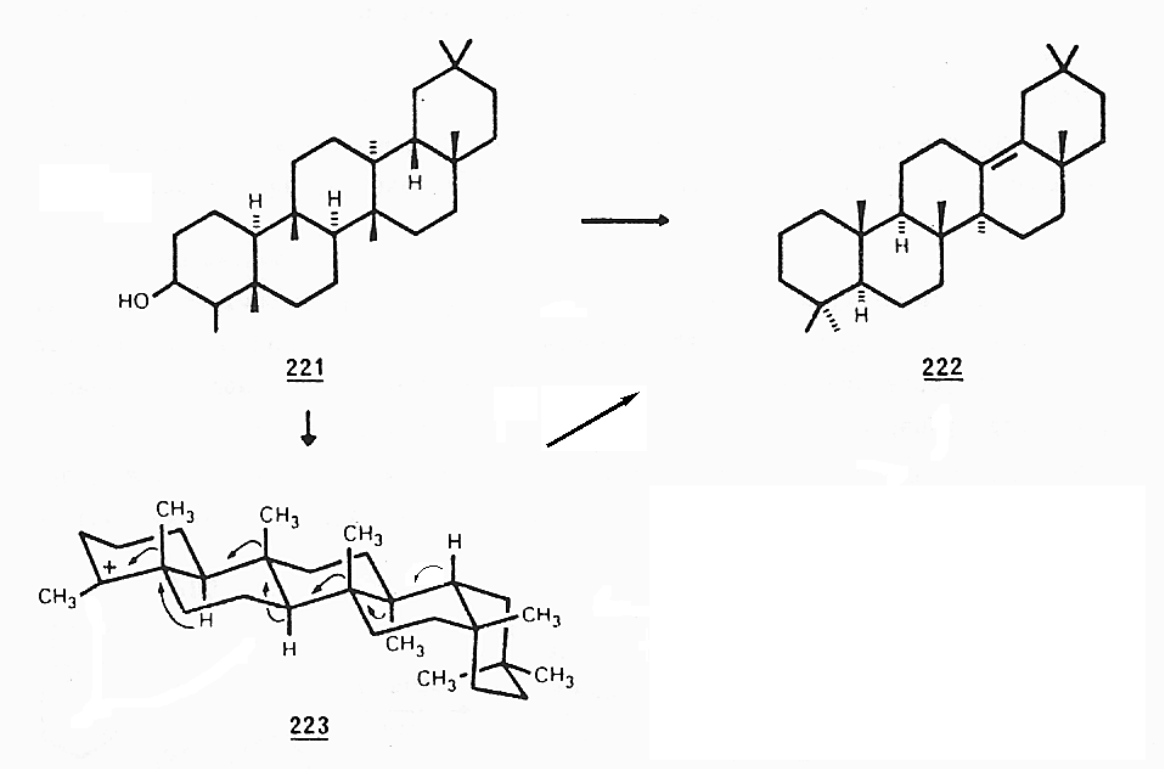
Stereocontrolled Migration of Hydrogen or Methyl Groups in Epoxide Opening



1. On treatment with BF_3-etherate, 216 gave a mixture of 217 and 218
2. 217 is obtained by internal hydrogen transfer on 219
3. 218 is obtained by CH_3 migration on 219 to produce first 220

R.E. IRELAND *et al*. *J.Org.Chem.* 1977, *42,* 1276.

A Spectacular Case of Methyl Migration from 3-β-Friedelanol



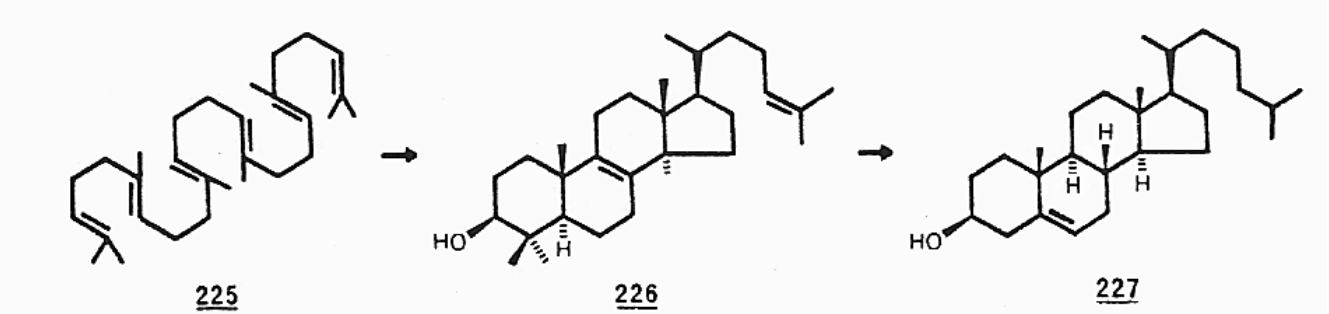
Acid-catalyzed transformation of 221 gives 222 via six stereoelectronically controlled 1,2 shifts followed by loss of a proton.

COREY *et al*. *J.Am.Chem.Soc.* 1956, *78,* 5041.

DUTLER, JEGER, RUZICKA. *Helv.Chim.Acta* 1955, *38,* 1268.

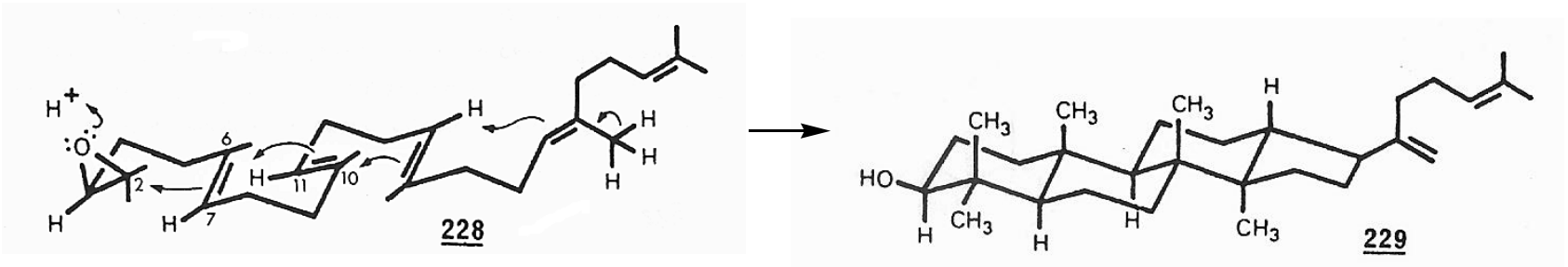
Biogenesis of Cholesterol is Stereoelectronically Controlled

The enzyme-catalyzed polycyclization of squalene produces first lanosterol which is later converted into cholesterol.



squalene **lanosterol** **cholesterol**

The stereochemical course of this biological cyclization can be illustrated by considering the transformation of squalene oxide (228) (an intermediate in the biosynthesis of cholesterol) into dammaradienol 229.
This transformation is simpler than the squalene-lanosterol conversion which involves some rearrangements of carbon atoms.



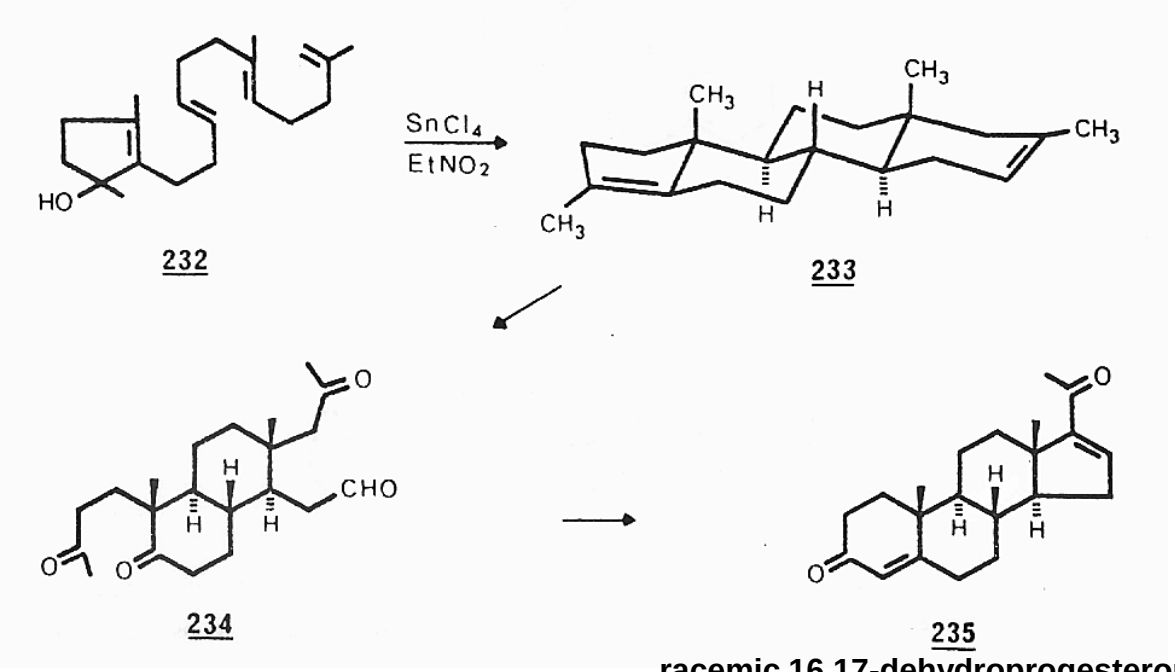
STORK *et al*. *J.Am.Chem.Soc.* 1955, *77,* 5068.

ESCHENMOSER, RUZICKA, JEGER, ARIGONI. *Helv.Chim.Acta* 1955, *38,* 1890.

ESCHENMOSER, STORK *et al*. *Helv.Chim.Acta* 1957, *40,* 291.

Polycyclization can take place without the Need of Enzymes.

The First Synthesis of a Steroid *via* the So-called « Biomimetic » Polyene Cyclization.



232 233 234 235

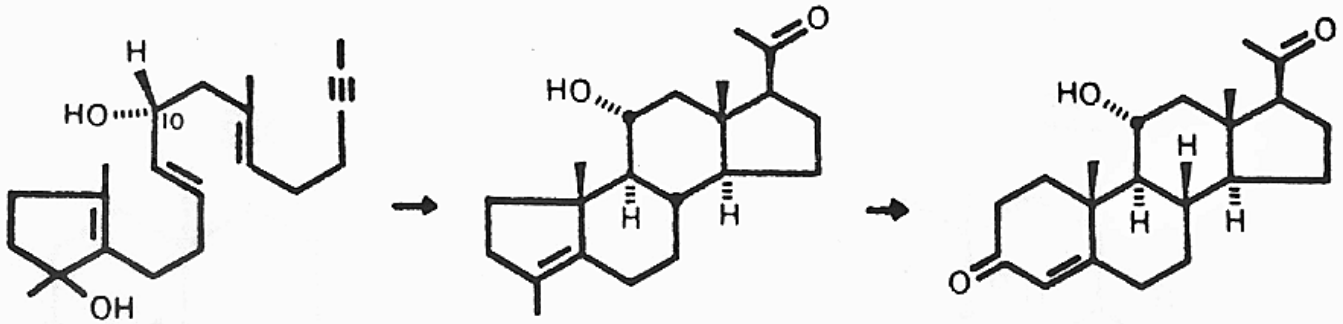
racemic 16,17-dehydroprogesterone

Cyclization of the racemic allylic alcohol ***232*** at -80°C furnished the racemic tetracyclic *bis*-olefin **233** in 70% yield. Ozonolysis of **233** gave the bicyclic triketone aldehyde **234** which underwent under acidic conditions a double intramolecular aldol cyclodehydration to produce racemic 16,17-dehydroprogesterone **235**. This represents the first synthesis of a steroid *via* the now so-called « biomimetic » polyene cyclization method.

A Review: W.S. JOHNSON. *Angew.Chem.Int.Ed.* 1976, *15,* 9.

Synthesis of Optically Active 11α-Hydroxy Progesterone

In another study (93), cyclization of optically active substrate 244 gave optically active tetracyclic product 245 with the same optical purity. Since, 245 was converted into 11α-hydroxyprogesterone (246), this work constitutes a total asymmetric synthesis of that steroid. This remarkable asymmetric control is due to the chiral center at C-10 of 244: the relative orientation of the hydroxyl group in the transition state of the cyclization process, controlled by stereoelectronic factors, is such that it yields a product (245) having an equatorial secondary alcohol.

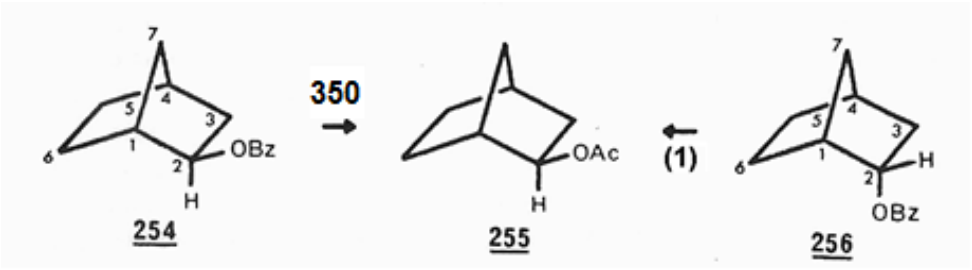


244 245 246

W.S. JOHNSON. *J.Am.Chem.Soc.* 1977, *99,* 8341.

The Famous Norbornyl Cation Produced by Solvolysis

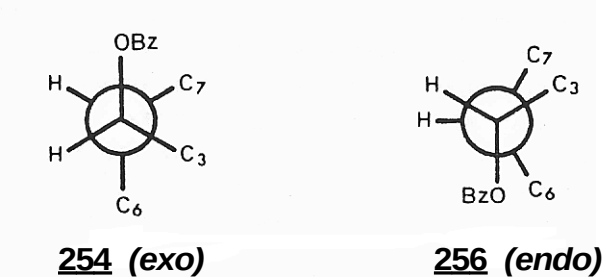
Bridged (non-classical) cation (Winstein) versus the rapidly equilibrating classical carbonium ions (Brown)



Results:

254 ***(exo)*** — **rate 350** → racemic **255**

256 ***(endo)*** — **rate 1** → racemic **255**



254 ***(exo)*** **256** ***(endo)***

W.S. WINSTEIN. ***J.Am.Chem.Soc.*** **1952, *74*, 1147, 1154.**

H.C. BROWN. ***Acc.Chem.Res.*** **1973, *6*, 377.**

Of interest, it has been shown that 1-methyl-1-cyclohexyl cation **1** has previously been shown **(ref. 1)** to exist in two different isomeric structures called hyperconjomers which are in equilibrium. The completely flat intermediate ion **D** is higher in energy and corresponds to an energy barrier between the two hyperconjomers. The so-called ICH isomer is more stable as it is stabilized by hyperconjugation of the neighbouring axial hydrogens. The ICC isomer is less stable as it is stabilized by the C_2–C_3 and C_5–C_6 bond hyperconjugation. Nucleophilic addition would then take place either α on ICC or β on ICH.

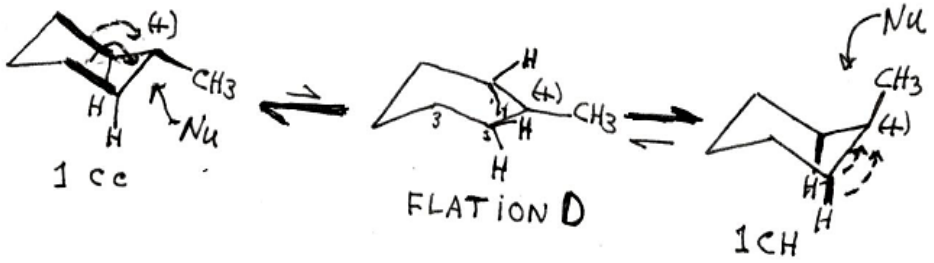
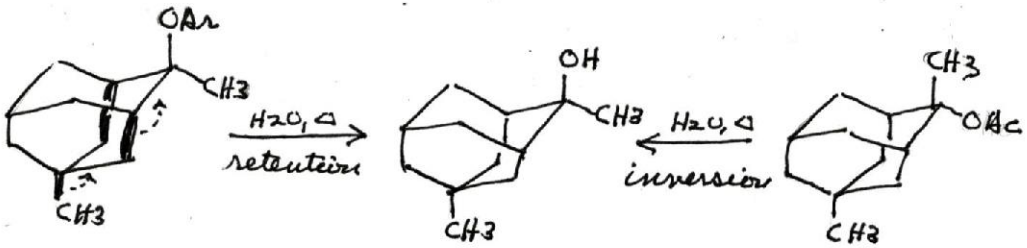


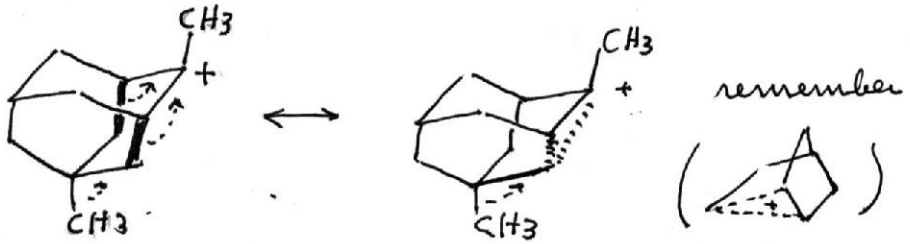
Fig. 4 The two hyperconjomers of 1-methyl-1-cyclohexyl cation.

Ref. 1: A. Rauk, T. S. Sorensen and P. von R. Schleyer. *J. Chem. Soc., Perkin Trans 2*, 2001, 869-874.

Evidence for "Hyperconjugation"

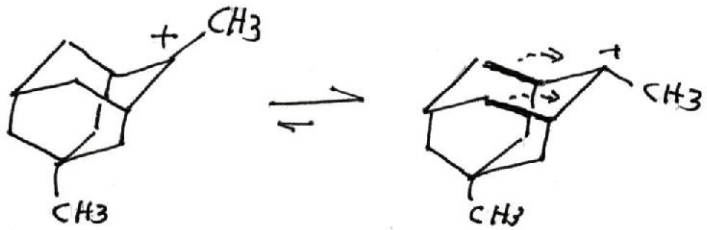


Thus



more stable

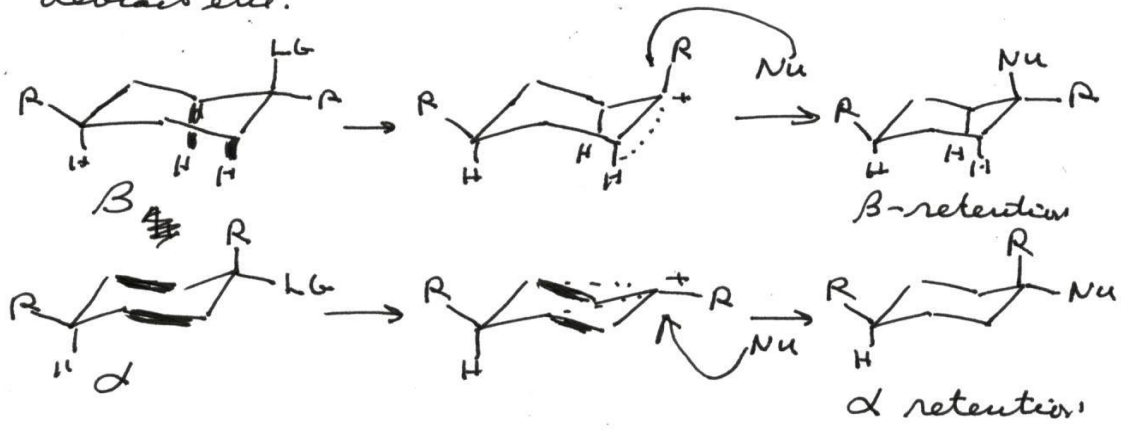
↑↓



planar — less stable

Bone, Pritt, Whiting
J. Chem. Soc. Perkin Trans 2, 1975, 1447

Rauck et al indique que les réactions d'addition devrait être.



Weinstein, Holness J.A.C.S. 1955, 77, 5562