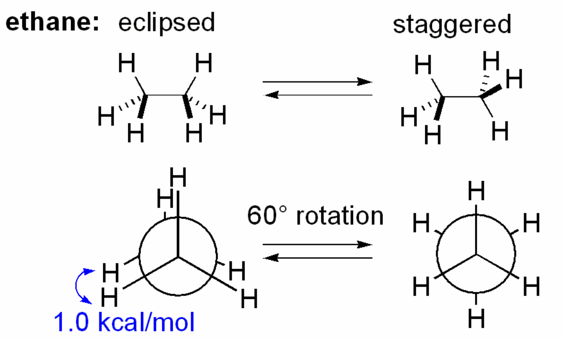
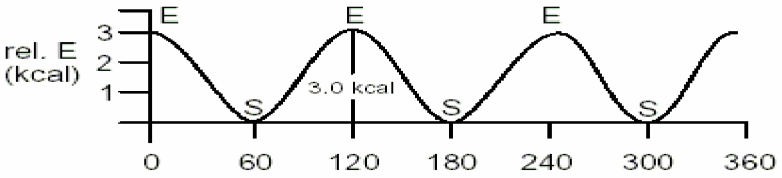
Conformational Analysis

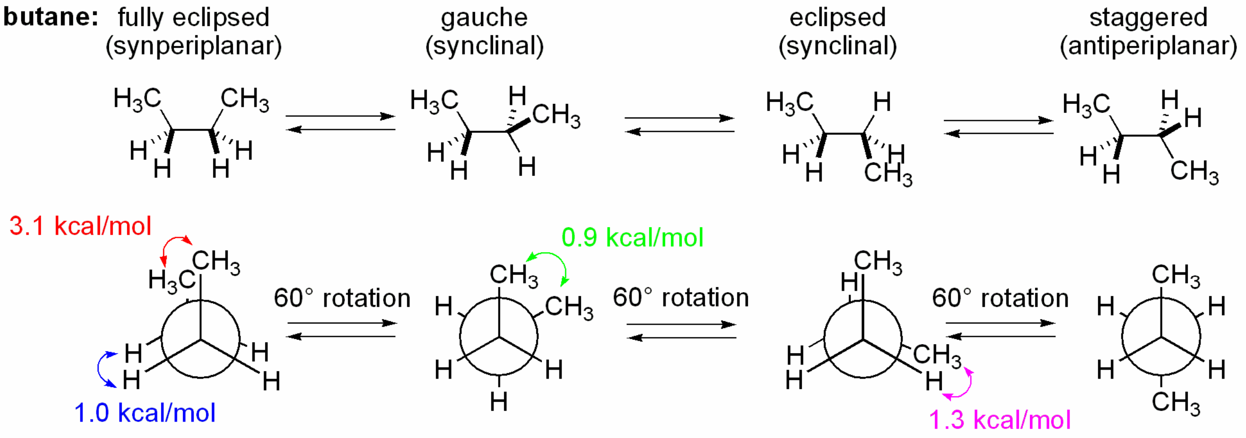
1. Acyclic Systems

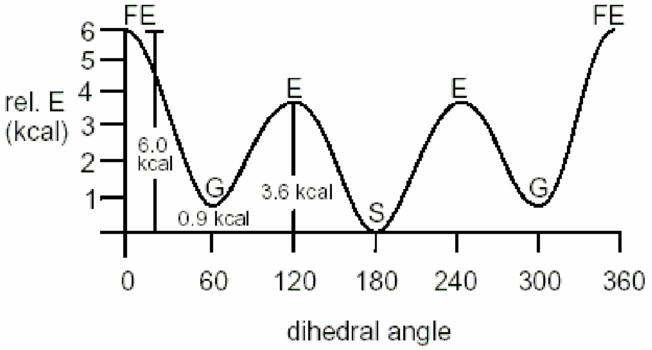
1.1. Saturated Systems





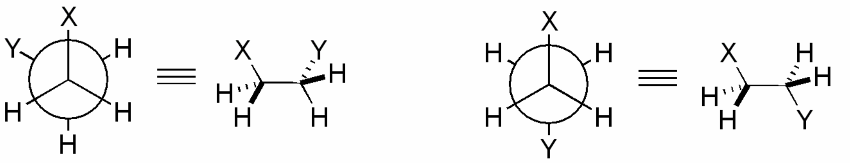
There are two extreme conformations, with a barrier for rotation of 3.0 kcal/mol.





The lowest energy conformation is the staggered conformation. However, this is not always the case.

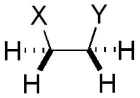
If X and Y are electronegative substituents, the gauche conformation is preferred (see discussion in part 3).



This is known as the **gauche-effect.**

$E_{gauche} < E_{staggered}$ if X = OH, OAc and Y = Cl, F

hierarchy of eclipsing interactions:



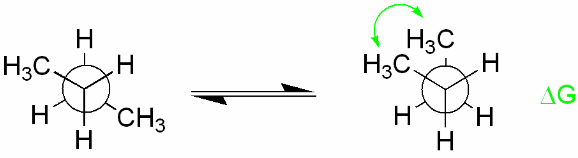
X - Y	energetic cost
H - H	+ 1.0 kcal/mol
H - Me	+ 1.4 kcal/mol
Me - Me	+ 3.1 kcal/mol
Cl - Cl	+ 3.6 kcal/mol

- steric contributions to torsional barrier in ethane have been estimated at no greater than 10% since H-atoms are barely within van der Waals distance

- major contribution to barrier has been ascribed to unfavorable overlap interaction between bond orbitals in the eclipsed conformation.

J. Chem. Phys. **1968**, *49*, 2592.
J. Am. Chem. Soc. **1990**, *112*, 6530.

butane: gauche interactions



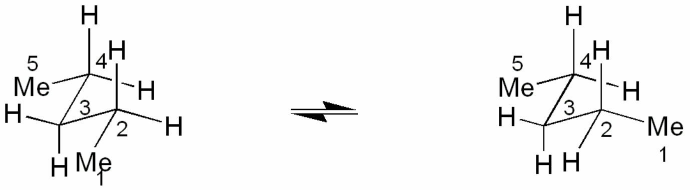
anti conformer *gauche* conformer

ΔG = + 0.9 kcal/mol

at rt for gas phase: K = 0.43
(corresponds to 70:30 *anti*:*gauche*)

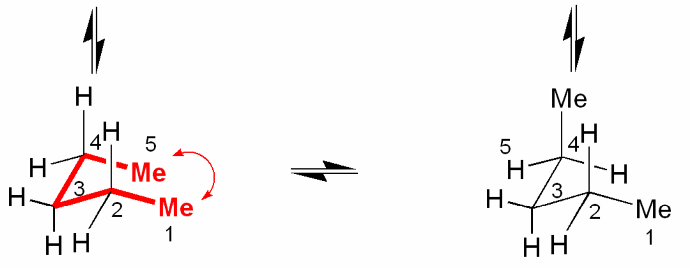
Experiment: Compton *J. Phys. Chem.* **1980**, *89*, 3587.
Calculation: Wiberg *J. Am. Chem. Soc.* **1988**, *110*, 8029.

pentane:



anti about C_{2-3}, *anti* about C_{3-4}
aa
ΔG_{rel} = 0

gauche about C_{2-3}, *anti* about C_{3-4}
ga
ΔG_{rel} = + 0.9 kcal/mol



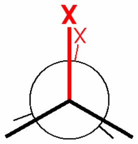
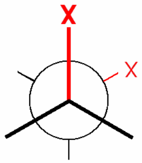
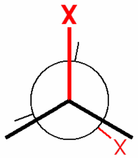
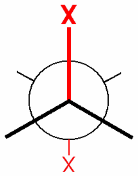
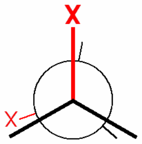
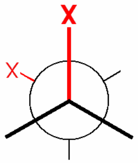
gauche about C_{2-3}, *gauche* about C_{3-4}
gg
ΔG_{rel} = + 5.5 kcal/mol

double gauche pentane

gauche about C_{2-3}, *gauche* about C_{3-4}
gg
ΔG_{rel} = + 1.8 kcal/mol

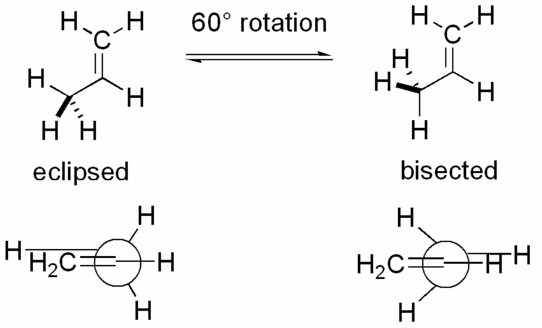
J. Am. Chem. Soc. **1961, ***83*, 2145.

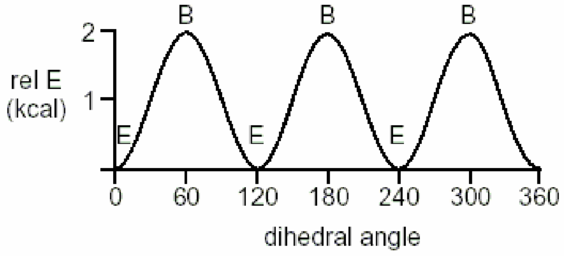
Conformational Descriptors

Conformation						
German name	ekliptisch planar-syn Atom-Atom	windschief schief-syn	teilweise verdeckt schief-anti	gestaffelt auf Lücke anti trans Atom-Lücke	teilweise verdeckt schief-anti	windschief schief-syn
English name	fully eclipsed	gauche skew	partially eclipsed	fully staggered anti opposed	partially eclipsed	gauche skew
Klyne/ Prelog (abbr.)	±synperiplanar ±sp	+synclinal +sc	+anticlinal +ac	±antiperiplanar ±ap	-anticlinal -ac	-synclinal -sc
angle	0°	60°	120°	180°	240°	300°

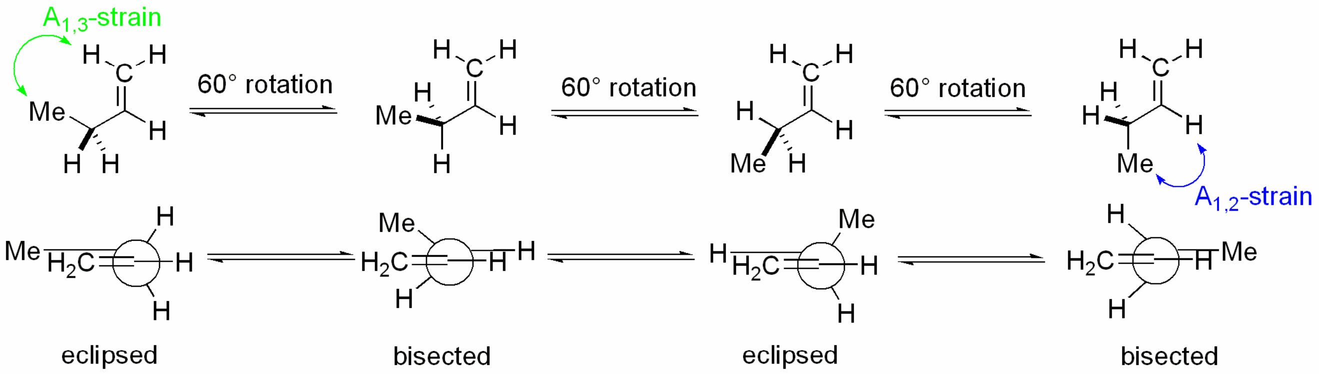
1.2. Allylic Systems: Allylic 1,2- and 1,3-Strain

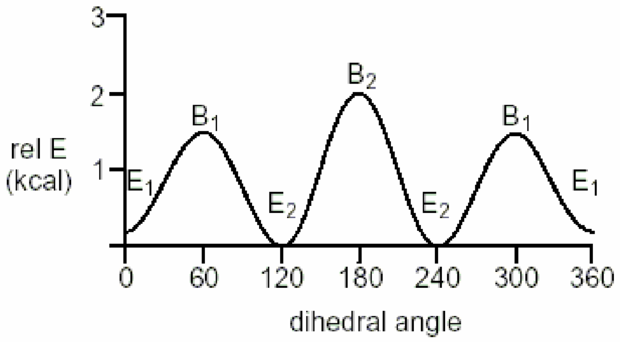
propene:



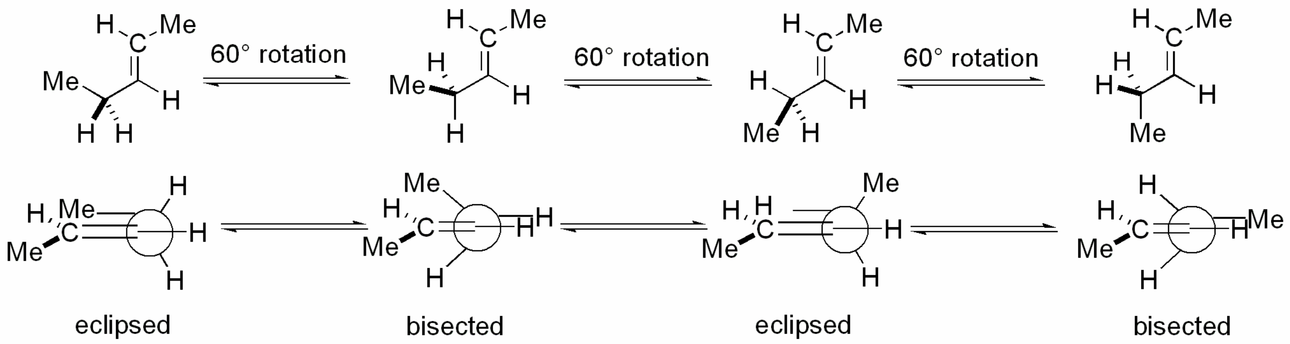


1-butene:

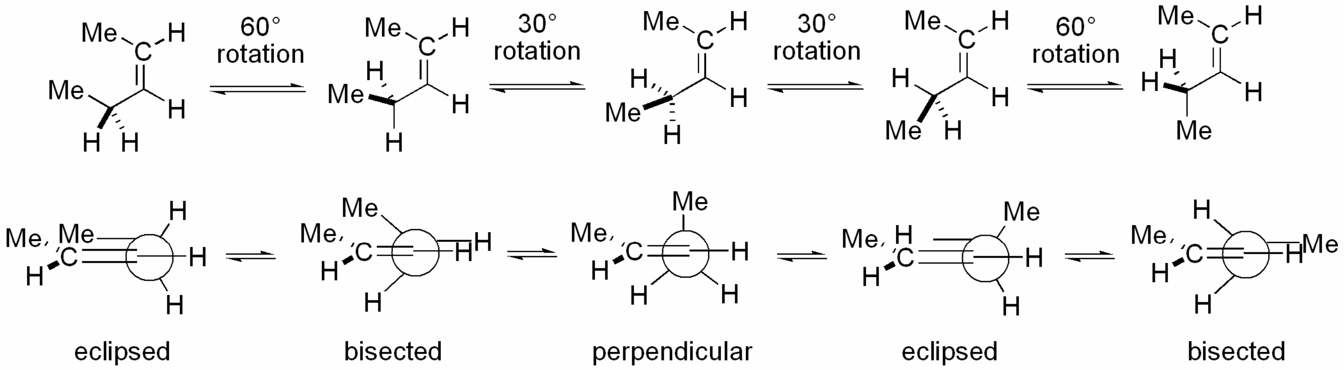


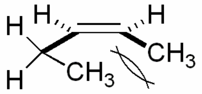


(*E*)-2-pentene:

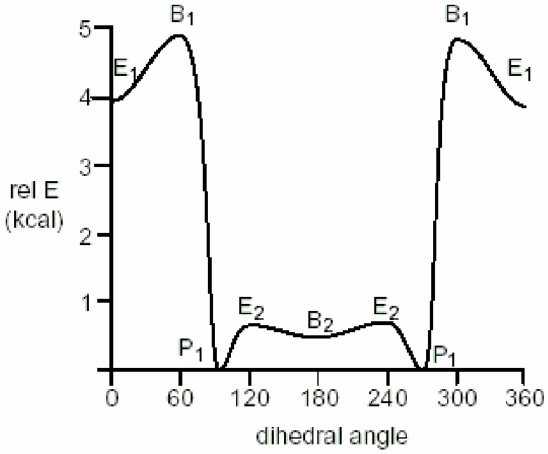


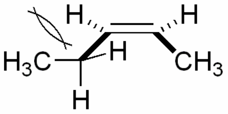
(*Z*)-2-pentene:





serious destabilizing interaction, often referred to as allylic 1,3-strain **($A_{1,3}$-strain)**





analogous H/CH_3-eclipsing interaction in the bisected conformation, often referred to as allylic 1,2-strain **($A_{1,2}$-strain)**

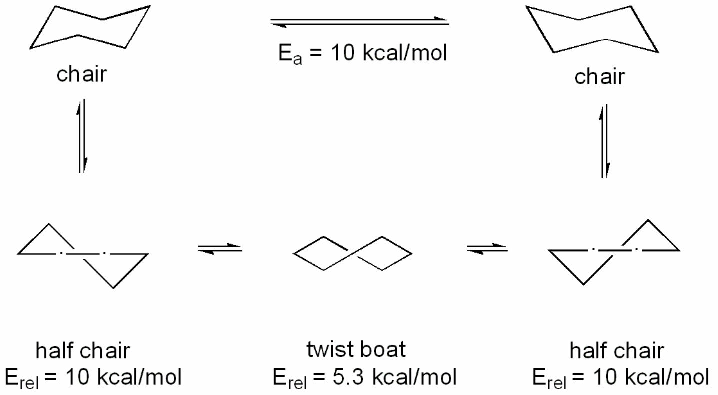
Allylic 1,3-strain is an important controlling factor in stereoselective transformations.

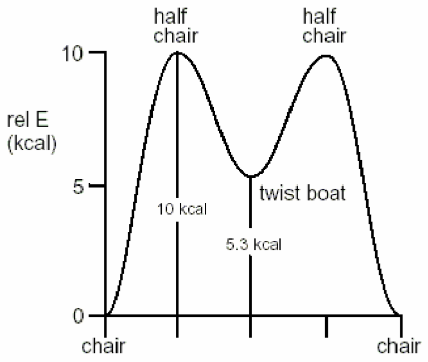
For a review, see: Hoffmann *Chem. Rev.* **1989**, *89*, 1841.
For computational calculations, see: Houk *J. Am. Chem. Soc.* **1991**, *113*, 5006.

2. Cyclic Systems

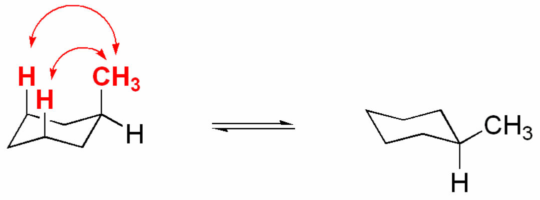
2.1. Cyclohexane Scaffold

cyclohexane:

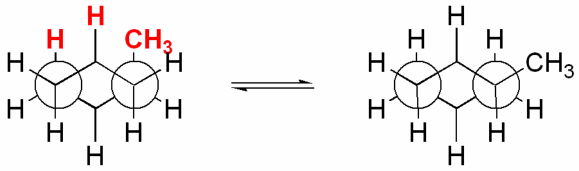




substituted cyclohexane:



two *gauche* butane interactions:
1,3-dixial interactions



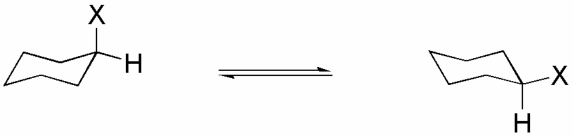
2 *gauche* butane interactions no *gauche* butane interactions

1,3-diaxial interactions:

R/R	ΔG [kcal/mol]
Me/H	0.9
Me/Me	3.7
OH/Me	2.4
OH/OH	1.9
OAc/OAc	2.0

A-values:

Definition of A-values: free energy difference (-ΔG°) between equatorial and axial substitution on a cyclohexane ring



preferred

$-\Delta G° =$ A-value

entry	substituent	A-value
1	CH_3	1.7
2	CH_2CH_3	1.7
3	$CH(CH_3)_2$	2.1
4	$C(CH_3)_3$	4.7
5	CH_2OH	1.7
6	CO_2Et	1.2
7	CN	0.2
8	$C \equiv C\text{-}H$	0.4
9	$CH = CH_2$	1.6
10	C_6H_5	2.8
11	$Si(CH_3)_3$	2.5
12	$Sn(CH_3)_3$	1.0
13	O_2CCH_3	0.7
14	OCH_3	0.6
15	N_3	0.5
16	F	0.3
17	Cl	0.6
18	Br	0.6
19	I	0.5

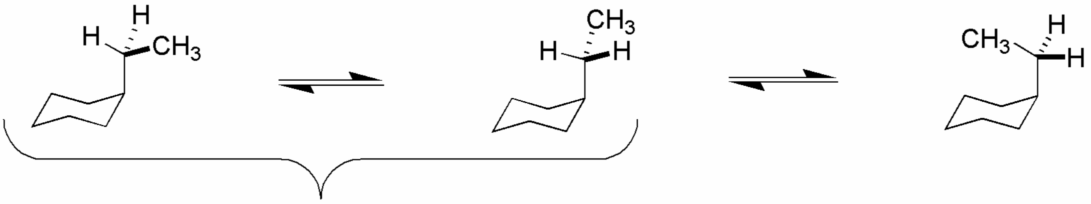
general comments:

- A-value is not exclusively a function of size (compare entries 16-19). For reference, *van der Waals* radii of halogens are: F = 1.5 Å; Cl = 1.7 Å; Br = 1.9 Å; I = 2.0 Å. In this regard, while the size of each of these does progressively increase, so do the length of the bonds to carbon: C-F = 1.4 Å; C-Cl = 1.8 Å; C-Br = 1.9 Å; C-I = 2.1 Å.

- Conformational energies of O-R vary little as a function of R.

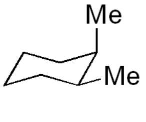
- sp^2 hybridized groups orient themselves in such a way that the flat face confronts the ring. For axial phenyl groups, this preference imposes steric crowding of *ortho* hydrogen atoms with both adjacent equatorial hydrogen atoms of the cyclohexane ring.
  For equatorial phenyl groups, the most stable conformer bisects plane of the cyclohexane chain. This avoids unfavorable interactions with equatorial hydrogens.

Branched alkyl groups rotate about the axial C-C bond so as to avoid unfavorable interactions that result by having the side chain over the ring. This is reflected in the entropy term ΔS of the free energy of the system.



dominant species

Energetic interactions can be used in an additive fashion:



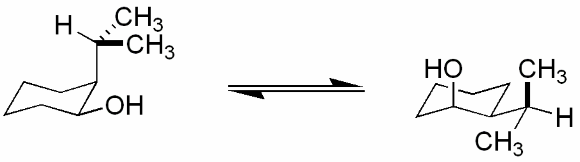
1

vs.

2

Calculated energy difference:

axial methyl group in **1** = 1.8 kcal/mol
⟶ favoring **2**



3 **4**

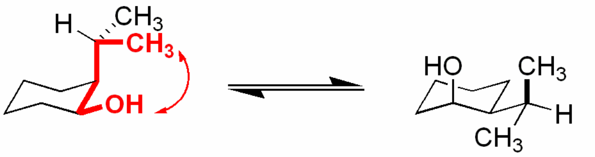
Calculated energy difference:

axial isopropyl group in **3** = 2.1 kcal/mol
axial hydroxyl group in **4** = 0.6 kcal/mol

ΔG = - 2.1- (- 0.6) = - 1.5 kcal/mol
⟶ favoring **4**

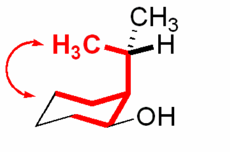
experimental value: ΔG = - 2.2 kcal/mol

Isopropyl group behaves as if it were larger than in cyclohexane. Explanation:



4

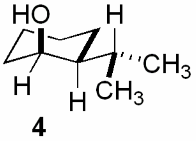
double *gauche* pentane-like interaction



3

double *gauche* pentane interaction

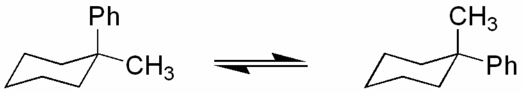
apart from axial hydroxyl group, no other serious interactions present



4

Problem:

Based on A-values, it is anticipated that the equilibrium shown below resides primarily on the right side, with calculated ΔG = - 1.0 kcal/mol.However, experiments indicate that the equilibrium is favored towards the left, with ΔG = + 2.0 kcal/mol.

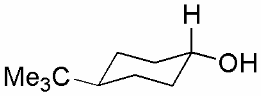


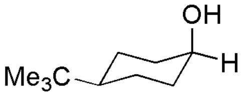
ΔG(calculated) = - 1.0 kcal/mol
ΔG(observed) = + 2.0 kcal/mol

Geminally substituted systems are not additive.

different reactivity for axial and equatorial substituents:

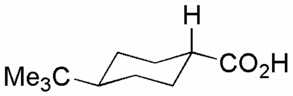
acetylation with Ac_2O/pyridine:

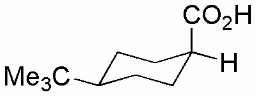




k_{rel} 1 0.27

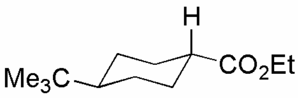
acid-catalyzed esterification:

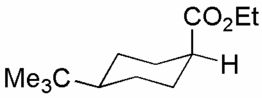




k_{rel} 1 0.05

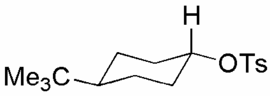
ester saponification:

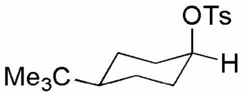




k_{rel} 1 0.05

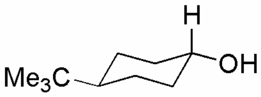
S_N2 displacement with $PhS^{\ominus}$:

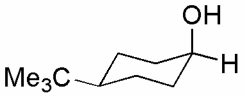




k_{rel} 1 0.03

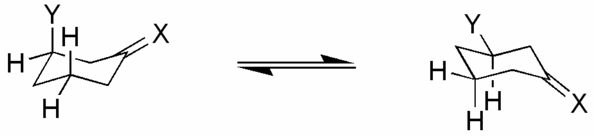
oxidation with Cr^{VI}:

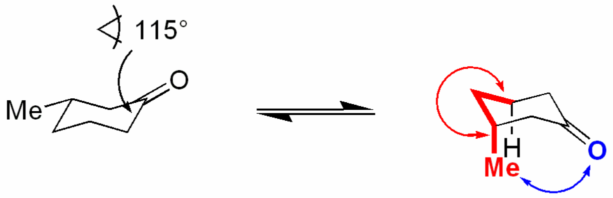




k_{rel} 1 3.2

cyclohexanone:



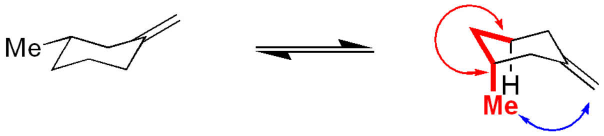


experimental: ΔG = + 1.4 kcal/mol

J. Am. Chem. Soc. **1962,** *84,* 2201.

gauche butane interaction = 0.9 kcal/mol
→ Me↔C=O interaction = 0.5 kcal/mol

interaction of axial methyl with C = O ~ 0.5 kcal/mol

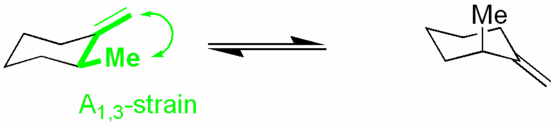


experimental: ΔG = + 0.8 kcal/mol

reason for lower energy difference than in cyclohexanone not clear

selected bond lengths

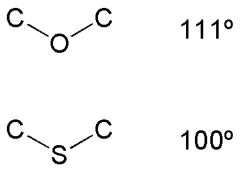
C–C	1.54
C–C$_{sp2}$	1.51
C=C	1.32
C–H	1.1
C–O	1.43
C–N	1.47
C–S	1.82
C–Cl	1.8
C–Br	1.9
C–I	2.1



experimental: ΔG = + 1.0 kcal/mol

methyl group behaves as if it were smaller:
- transdiaxial interactions are diminished
- A$_{1,3}$-strain

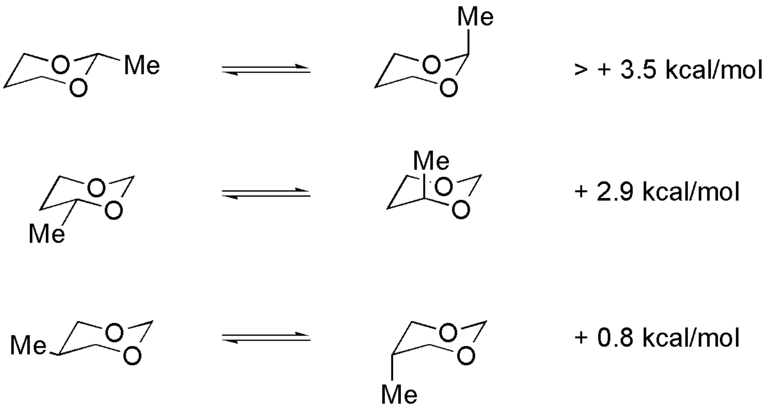
effect of the incorporation of heteroatoms in the cyclohexane ring:



C—C	1.54 Å
C—O	1.42 Å
C—S	1.82 Å

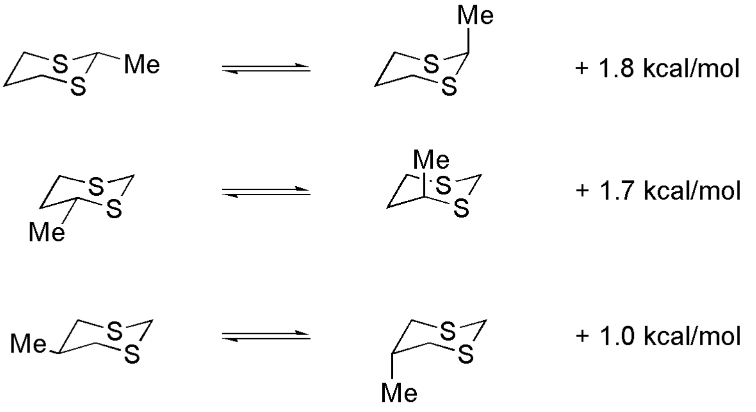
For a review, see: Eliel *Acc. Chem. Res.* **1970**, *3*, 1.

1,3-dioxanes:



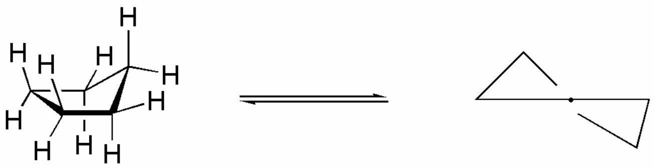
Eliel *J. Am. Chem. Soc.* **1968**, *90*, 3444.

1,3-dithianes:



Eliel *J. Am. Chem. Soc.* **1969**, *91*, 2703.

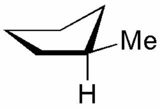
2.2. Cyclopentane Scaffold



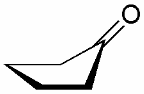
envelope
most stable form

energy barriers not high between conformations: conformationally flexible

position of substituents:

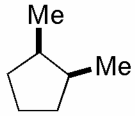


most stable by 0.9 kcal/mol
equatorial substitution preferred at flap of envelope

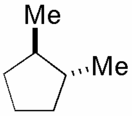


most stable position for carbonyl groups

Top. Stereochem. **1978**, *10,* 1

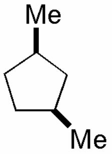


vs.

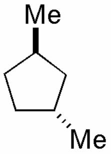


ΔG = - 1.8 kcal/mol

partially eclipsing



vs.

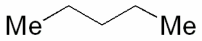


ΔG = + 0.5 kcal/mol

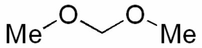
more stable by 0.5 kcal/mol

3. Stereoelectronic Effects

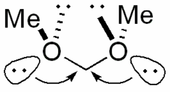
3.1. The Gauche Effect



lowest energy conformation
of pentane

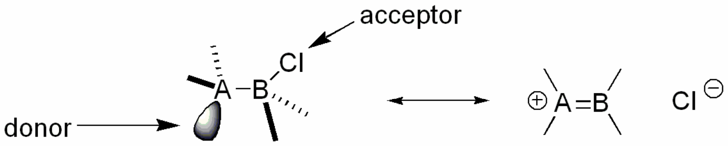


extended conformation
of simple acetal

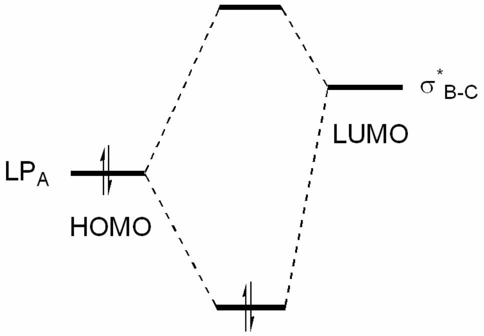


gauche conformation allows
donation into σ*

valence bond description:



MO description: HOMO-LUMO interaction

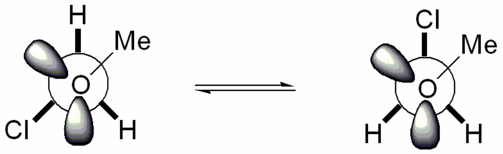


HOMO and LUMO interact by mixing:

- sensitive to energy difference between HOMO and LUMO
- geometrical constraints due to required overlap of orbitals

examples:

$ClCH_2OMe$



$n_O \longrightarrow \sigma^*_{C-H}$ $n_O \longrightarrow \sigma^*_{C-H}$

$n_O \longrightarrow \sigma^*_{C-H}$ $n_O \longrightarrow \sigma^*_{C-Cl}$

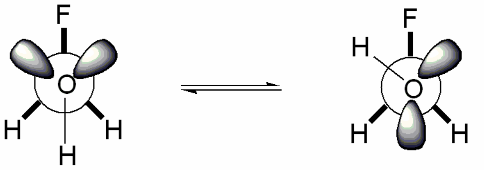
ΔG = - 2 kcal/mol

measured barrier: 4.2 kcal/mol
estimated barrier based on sterics: 2.0 kcal/mol

gauche contribution: 2.0 kcal/mol

J. Am. Chem. Soc. **1977,** *99,* 6752.

FCH_2OH



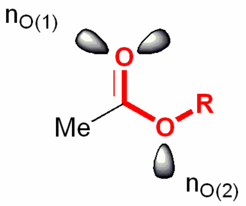
$n_O \longrightarrow \sigma^*_{C-H}$ $n_O \longrightarrow \sigma^*_{C-H}$

$n_O \longrightarrow \sigma^*_{C-H}$ $n_O \longrightarrow \sigma^*_{C-F}$

ΔG = -12.6 kcal/mol

Carbohydrate Res. **1979**, *69*, 1.

3.2. Conformation of Esters, Diazines

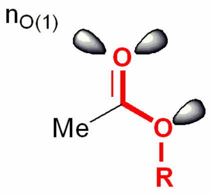


cis about C-O

two interactions are possible:

$n_{O(1)} \longrightarrow \sigma^*_{C\text{-}O}$

$n_{O(2)} \longrightarrow \pi^*_{C=O}$



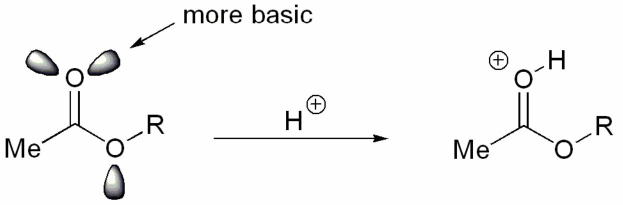
trans about C-O

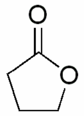
only one interaction is possible:

$n_{O(1)} \longrightarrow \sigma^*_{C\text{-}O}$

Chem. Phys. Lett. **1981,** *84,* 267.
Bull Chem. Soc. Jpn. **1970,** *43,* 2558.

Implications:

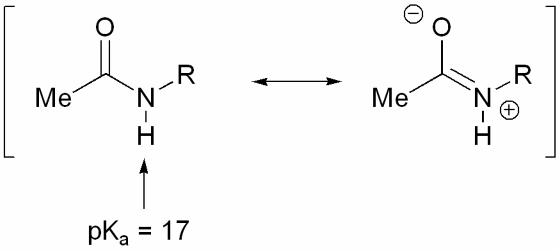
- 

- 

  trans arrangement enforced by ring:

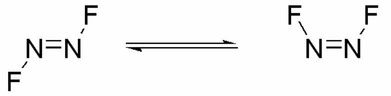
  lactones more reactive than esters, behave more like ketones in many reactions (e. g. easy reduction with $NaBH_4$ possible)

- similar stereoelectronic interaction can be used to explain the acidity of amides:



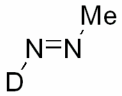
orbital interaction:

$\sigma_{N\text{-}H} \longrightarrow \sigma^*_{C=O}$

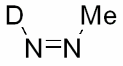


ΔG = - 3 kcal/mol

J. Chem. Phys. **1963,** *38,* 109.



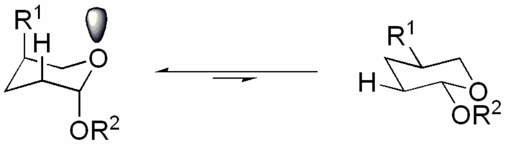
$\nu_{(N\text{-}D)} = 2317\ cm^{-1}$
$\nu_{(N\text{-}N)} = 1559\ cm^{-1}$



$\nu_{(N\text{-}D)} = 2188\ cm^{-1}$
$\nu_{(N\text{-}N)} = 1565\ cm^{-1}$

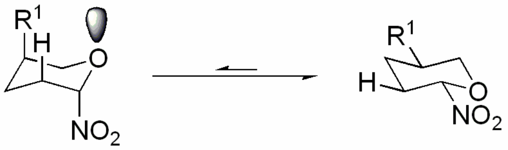
J. Am. Chem. Soc. **1979,** *101,* 2480.

3.3. Anomeric Effect



For a review, see: *Tetrahedron* **1992**, *48*, 5019.

polar, electronegative groups (e. g. OR, Cl) adjacent to oxygen prefer the axial position



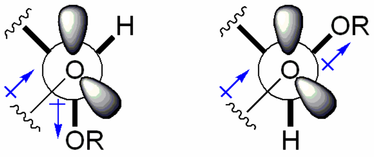
strongly electronegative or groups bearing a positive charge (R$_3$N$^{\oplus}$, NO$_2$, SOCH$_3$) adjacent to oxygen prefer the equatorial position: reverse anomeric effect

Perrin *Tetrahedron* **1995**, *51*, 11901.

Explanations for the anomeric effect:

dipole stabilization

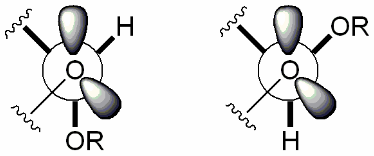
opposing dipoles, stabilizing



dipoles aligned, destabilizing

electrostatic repulsion

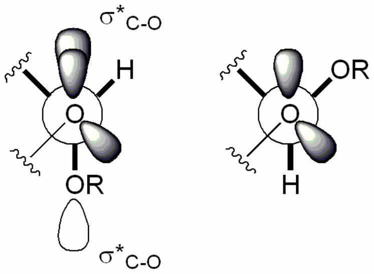
electrostatic repulsion between lone pairs and the electronegative substituent minimized



destabilizing electrostatic interaction between electronegative centers maximized (charge repulsion)

electronic stabilization

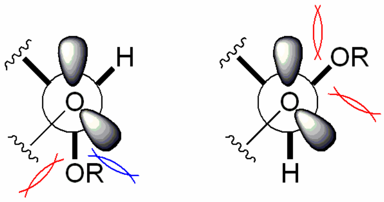
stabilizing n ⟶ σ^* orbital interaction due to delocalization of lone pair on oxygen into σ^*_{C-O} orbital (lower in energy than σ^*_{C-H})



no stabilization possible

gauche **interaction involving lone pairs**

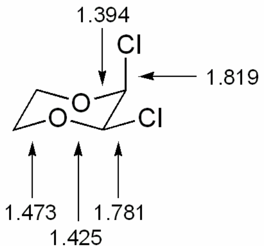
1 lone pair/OR *gauche* interaction
1 ring/OR *gauche* interaction
(0.35 kcal/mol)



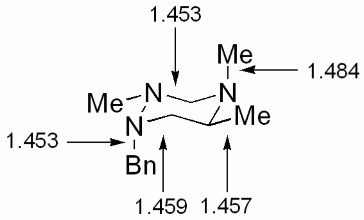
2 lone pair/OR *gauche* interaction
(would required them to be worth
1.2 kcal/mol)

examples:

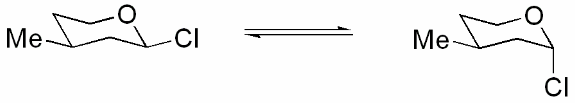
structural data: bond lenths [Å]



Top. Stereochem. **1967**, *4,* 39.

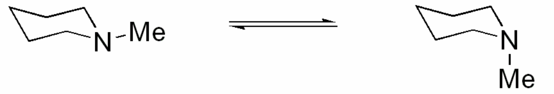


J. Chem. Soc. Perkin Trans. 2 **1980**, 1733.

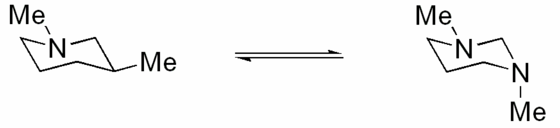


K = 32

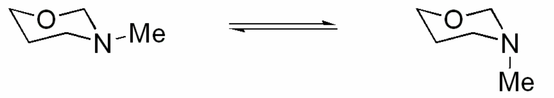
J. Org. Chem. **1967,** *32,* 607.



ΔG = + 1.5 kcal/mol

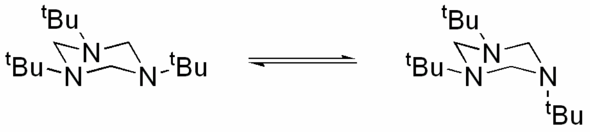


ΔG = + 0.7 kcal/mol



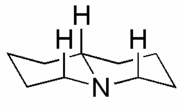
ΔG = - 0.16 kcal/mol

J. Chem. Soc. Perkin Trans. 2 **1970,** 1746.



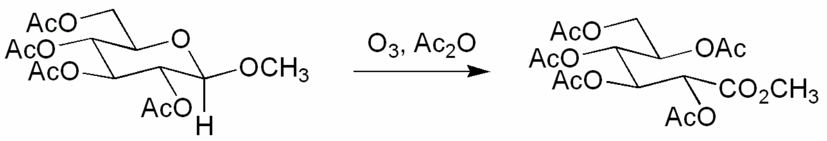
ΔG = - 0.35 kcal/mol

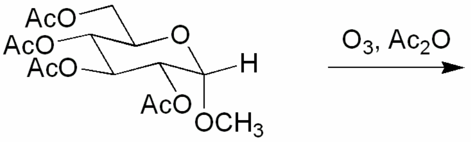
J. Chem. Soc. B, **1970**, 135.



Bohlmann bands: characteristic IR bands at 2700- 2800 cm^{-1}
for hydrogen at C(4), C(6) and C(10)

Chem. Ber. **1958,** *91,* 2157.
For a review, see: *Chem. Soc. Rev.* **1978,** 7399.





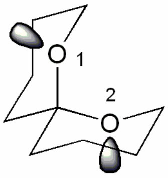
no reaction

Can. J. Chem. **1974**, *52*, 3651.

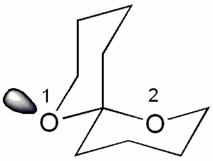
J. Am. Chem. Soc. **1980,** *102,* 6363

3.3.1. Bicyclic Ketals

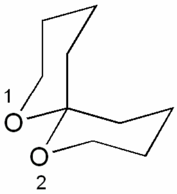
bicyclic ketals: interesting case with important synthetic consequences



1



2



3

O_1 anomer	- 1.3 kcal/mol	O_2 anomeric	- 1.3 kcal/mol	2 x CH_2 axial	2 x + 1.7 kcal/mol
O_2 anomer	- 1.3 kcal/mol	CH_2 axial	+ 1.7 kcal/mol		
O_1 axial	+ 0.7 kcal/mol	O_2 axial	+ 0.7 kcal/mol		
O_2 axial	+ 0.7 kcal/mol				

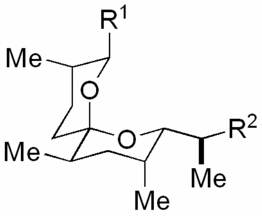
Σ - 1.2 kcal/mol Σ + 1.1 kcal/mol Σ + 3.4 kcal/mol

structure 1 is strongly preferred

J. Am. Chem. Soc. **1985,** *107,* 6393.

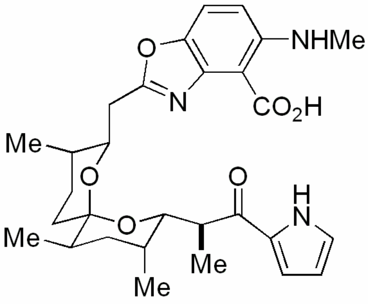
applications in total synthesis:

antibiotic A-23187 core



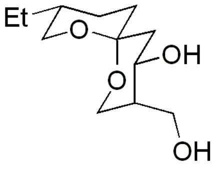
Evans *Tetrahedron Lett.* **1978**, *8*, 727.

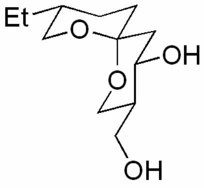
Calcimycin



J. Am. Chem. Soc. **1972**, *96*, 1932.

Talaromycins

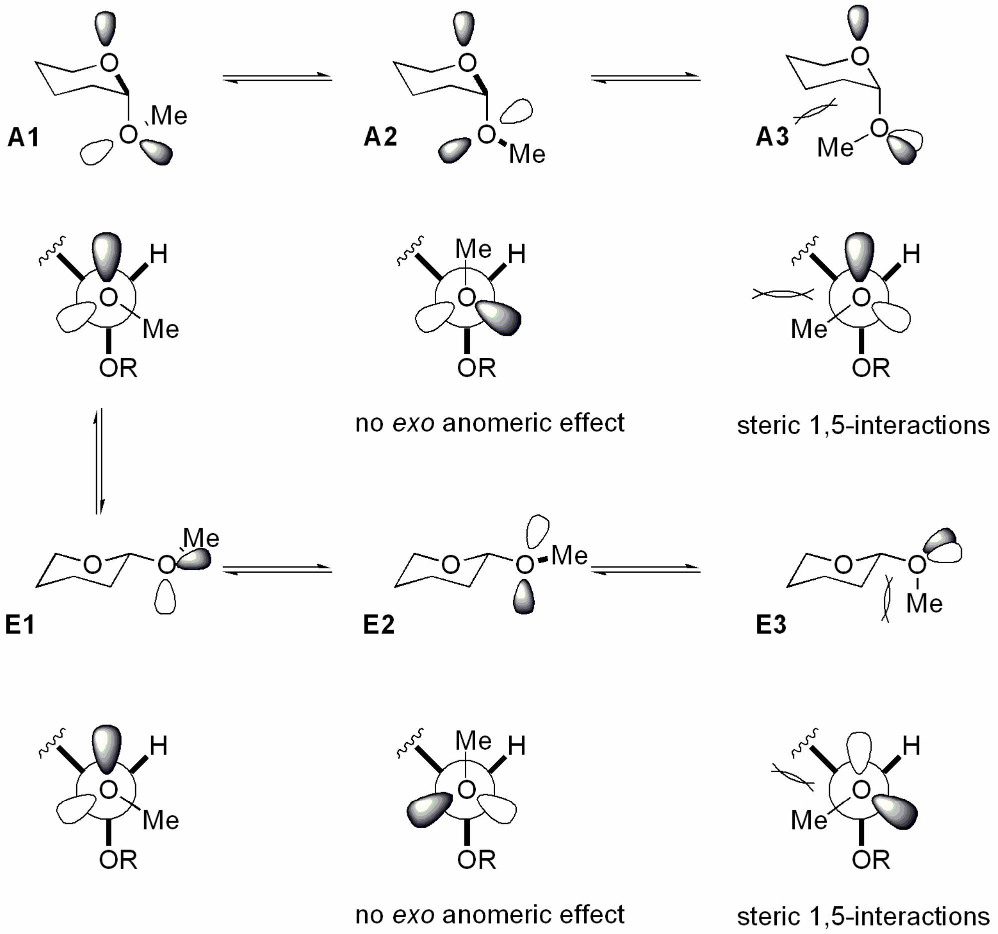




Schreiber *Tetrahedron Lett.* **1983**, *24*, 4781; *Tetrahedron Lett.* **1985**, *26*, 17.

3.3.2. Exo Anomeric Effect

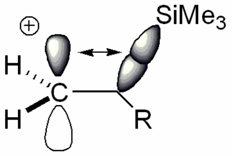
Kishi *J. Org. Chem.* **1991**, *56*, 6412.



For a discussion about the influence of *endo* and *exo* anomeric effects of the conformation of hexose and pentose nucleic acids, see: Eschenmoser *Helv. Chim. Acta* **1992**, *75*, 218.

3.4. β-Silyl Effect

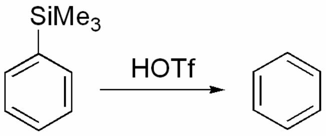
silicon stabilizes a positive charge on the β carbon

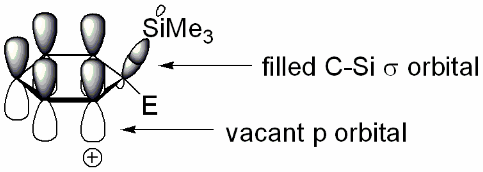


$\sigma_{C\text{-}Si} \longrightarrow p$

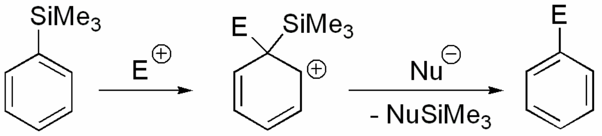
high stabilisation, rotational barrier around C-Si bond ca. 20 kcal/mol

aryl silanes undergo *ipso* substitution:



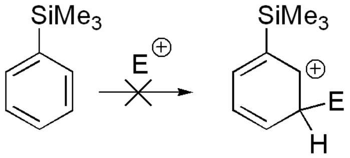


mechanism:

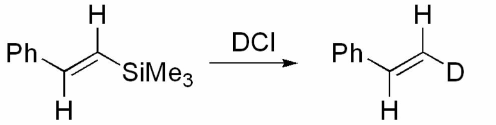


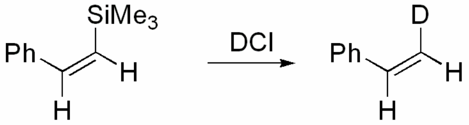
stabilized by β-silicon effect

incorrect:

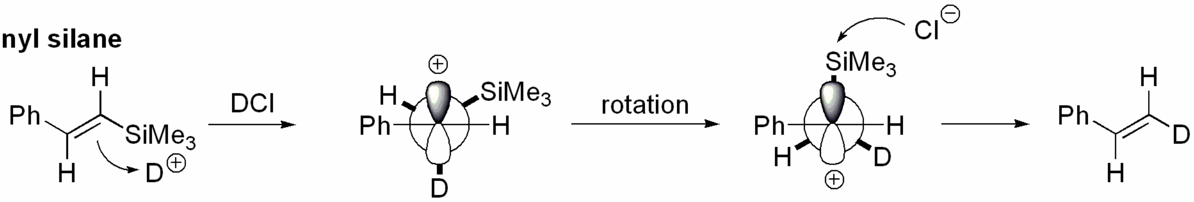


vinyl silanes offer a regio- and stereoselective route to alkenes:





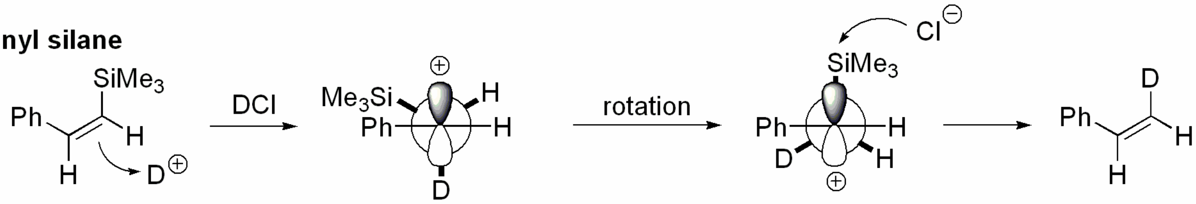
(*E*)-vinyl silane



deuteration from bottom face

correctly aligned stabilized by β-silicon effect

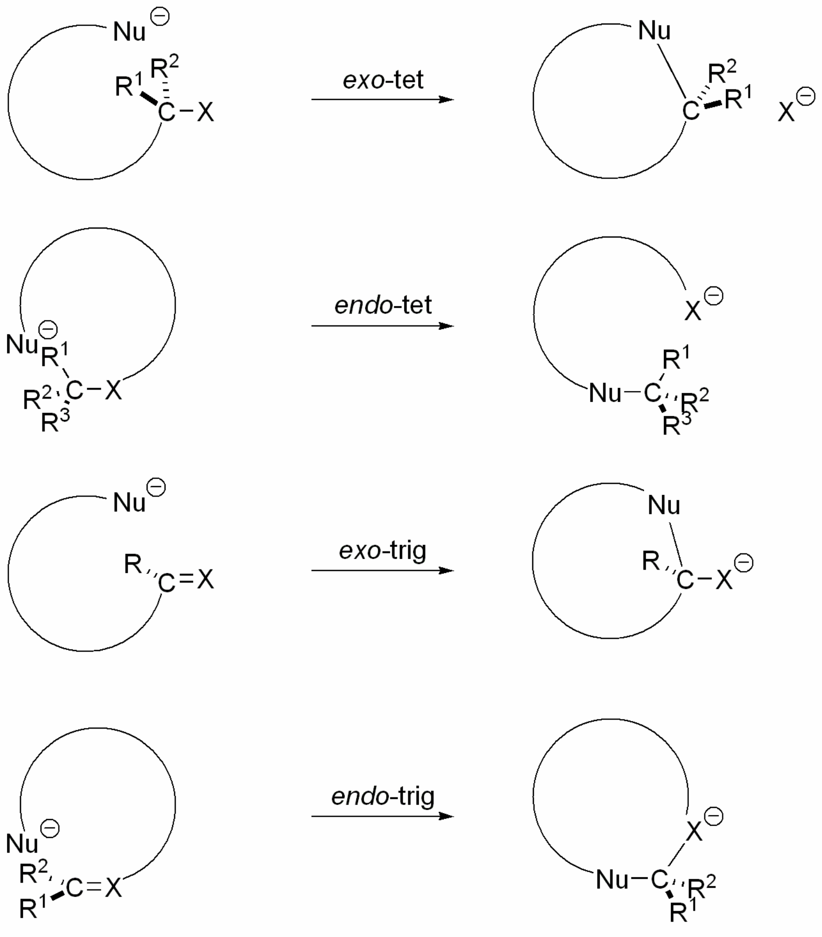
(*Z*)-vinyl silane



deuteration from bottom face

correctly aligned stabilized by β-silicon effect

3.5. Baldwin-Rules



3- to 7-*exo*-tet: all favoured

5- to 6-*endo*-tet: disfavoured

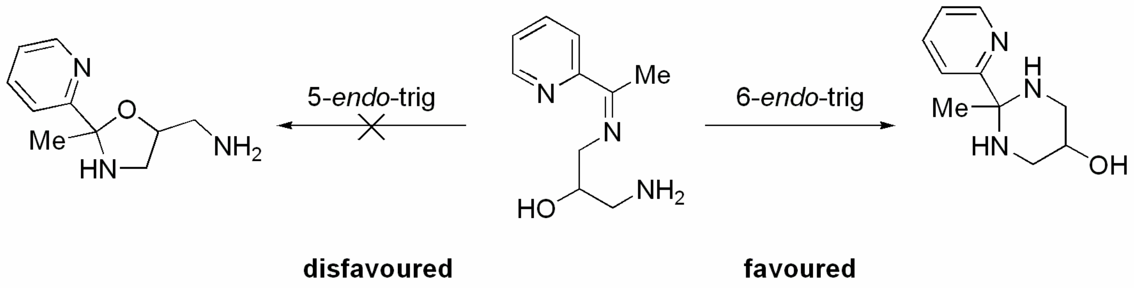
3- to 7-*exo*-trig: all favoured

3- to 5-*endo*-trig: disfavoured

6- to 7-*endo*-trig: favoured

Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734.

An example from the literature:

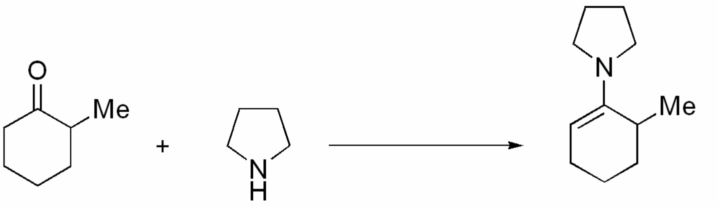


Acc. Chem. Res. **1993**, *26*, 476.

4. Cyclic Stereocontrol: Some Applications

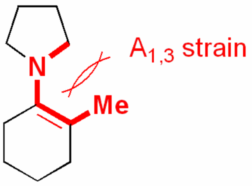
Careful analysis of steric and stereoelectronic effects allows the design of highly stereoselective reactions. Especially rings as rigidified systems allow to achieve high selectivities.

4.1. Minimalizing $A_{1,3}$ Interactions during Enamine Formation



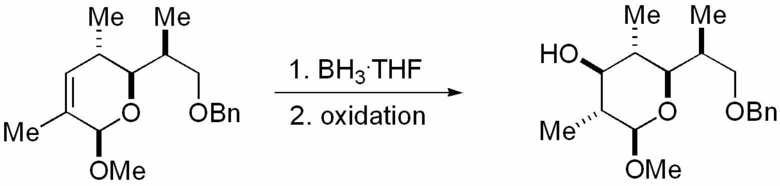
only observed isomer

higher substituted enamine not formed due to $A_{1,3}$-strain:

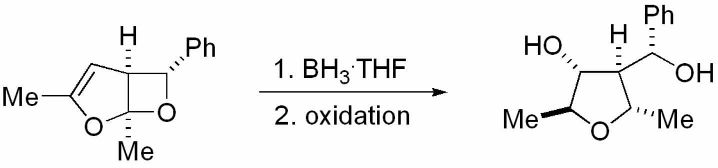


4.2. Cyclic Olefins: Stereoselective Hydroboration

synthesis of rifamycin:



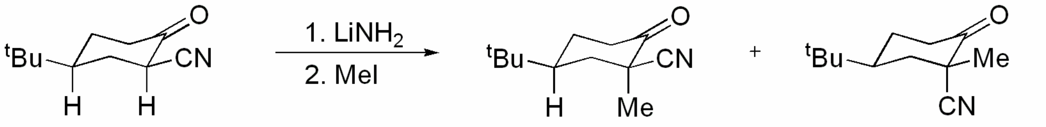
Danishefsky *J. Am. Chem. Soc.* **1987**, *109*, 862.



Schreiber *J. Am. Chem. Soc.* **1983**, *105*, 660.

4.3. Functionalization of Cyclic Enolates

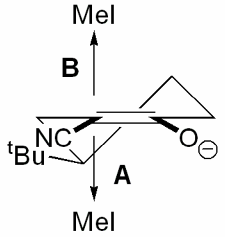
preferred axial alkylation of cyclic enolates due to stereoelectronic control



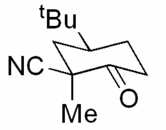
77 : 23

axial product **equatorial product**

explanation:

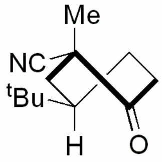


A: via chair directly to axial product



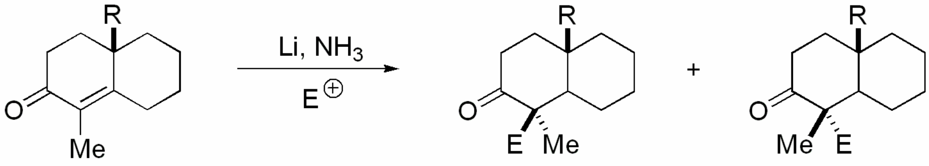
axial product

B: via less favourable twist boat to equatorial product



equatorial product

steric diaxial interactions can override stereoelectronic effect:

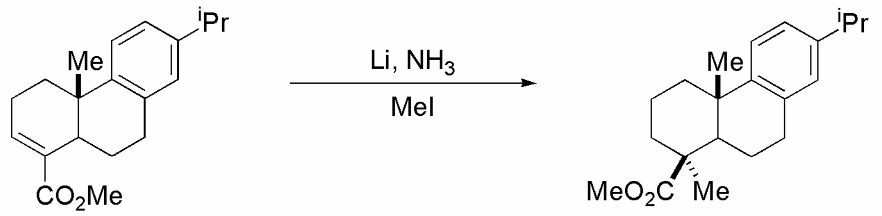


R	E$^{\oplus}$	dr
H	CD_3I	83:17
Me	EtI	5:95

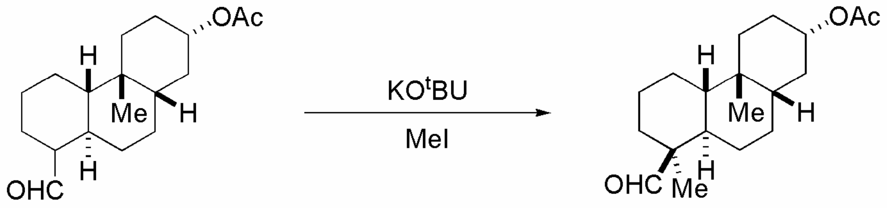
Tetrahedron Lett. **1967**, 1975.

for a definition of the terms convex and concave, see: Woodward *Tetrahedron* **1958**, *2*, 1

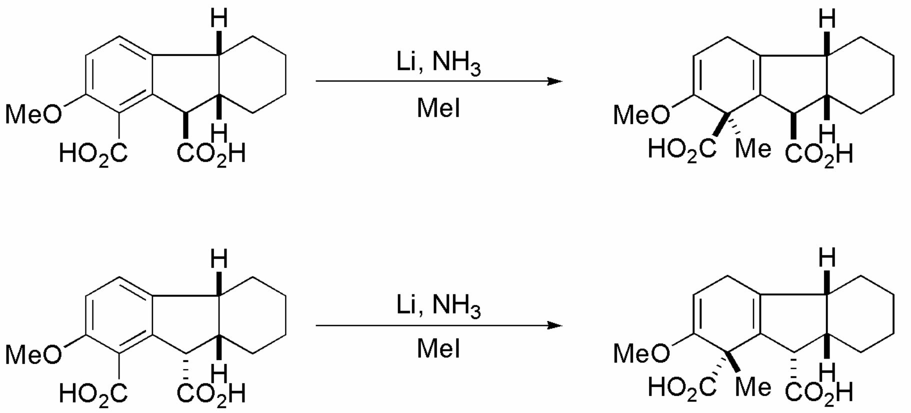
further examples of $A_{1,3}$ interaction in fused ring systems:



J. Org. Chem. **1977**, *42*, 2879.

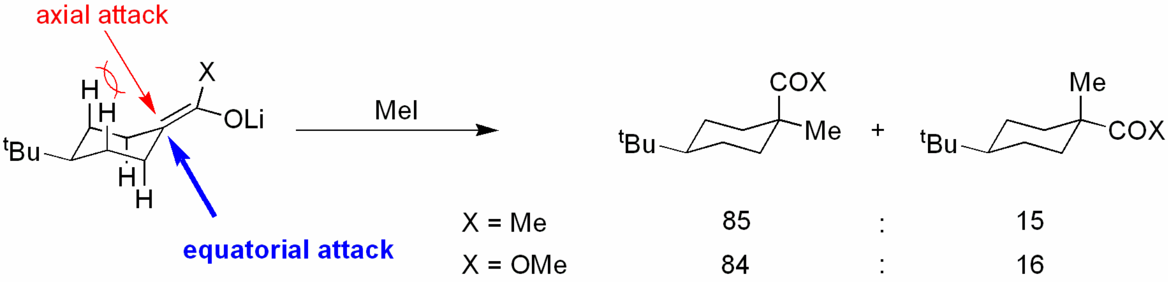


Ireland, *J. Org. Chem.* **1969**, *34*, 142.



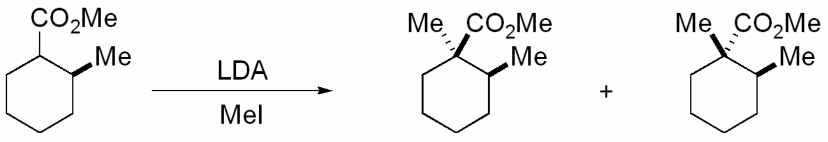
House, *J. Org. Chem.* **1976**, *41*, 2401.

exo-enolate alkylation in cyclohexane derivatives: equatorial attack is favored

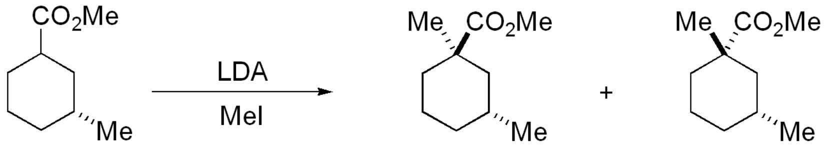


X = Me 85 : 15

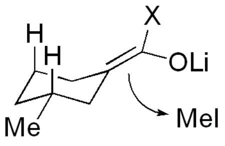
X = OMe 84 : 16



85 : 15



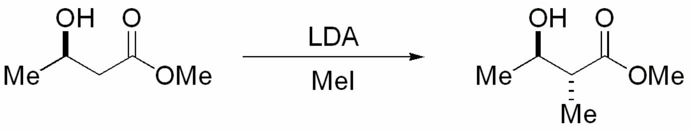
90 : 10

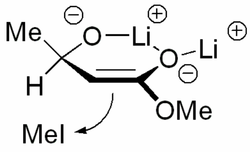


preferred

special cases:

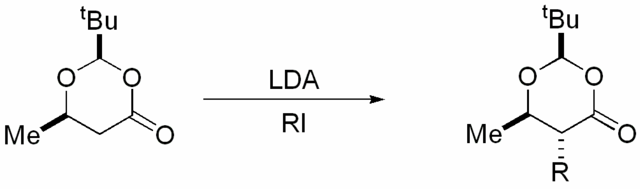
If the ring contains more than two sp^2 centers, the system is rigidified and can be considered as nearly flat for analysis.





bottom face accessible

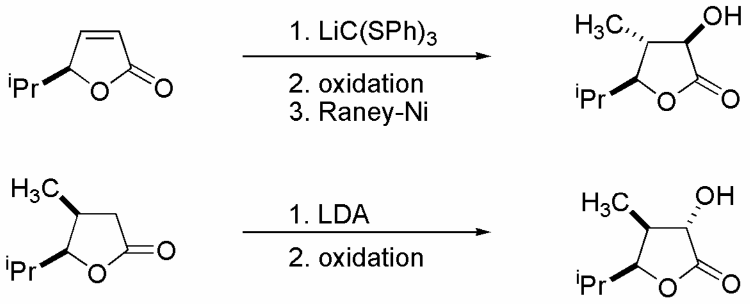
Fráter *Tetrahedron* **1984**, *40*, 1269.



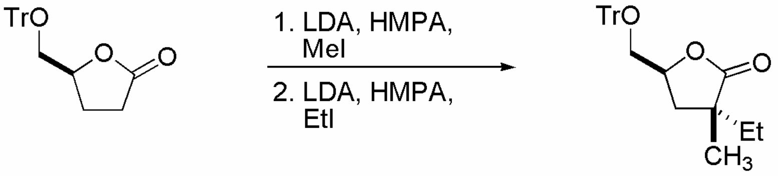
95% ds

Helv. Chim. Acta. **1986**, *69,* 1147.

enolate functionalisation in 5-membered rings:

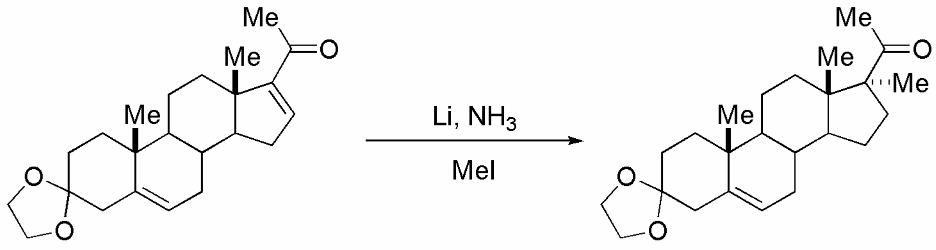


Stork *J. Am. Chem. Soc.* **1987**, *109*, 1564.



J. Org. Chem. **1988**, *53,* 4094.

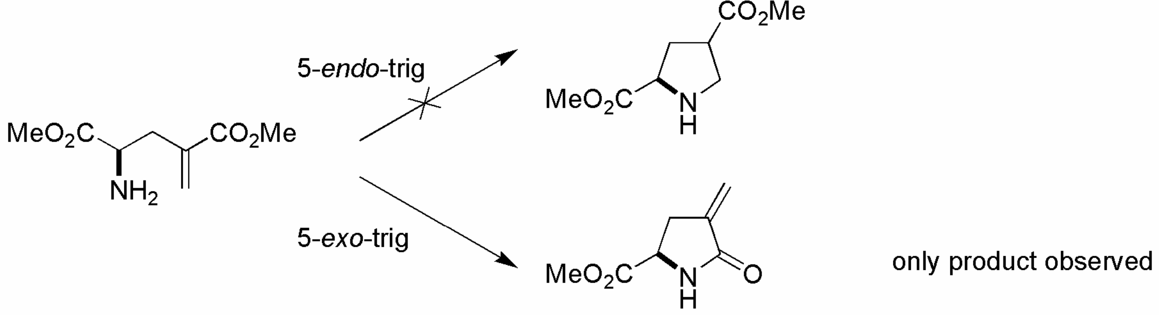
J. Org. Chem. **1983**, *48,* 3761.

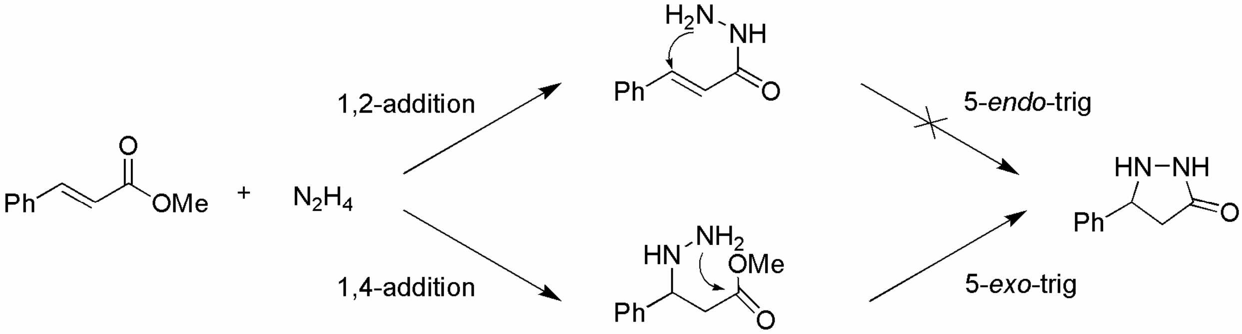


Tetrahedron Lett. **1964**, *20*, 357.

4.4. Stereoselective Cyclization (Baldwin Rules)

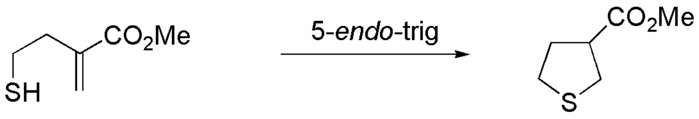
classical examples for the Baldwin rules:



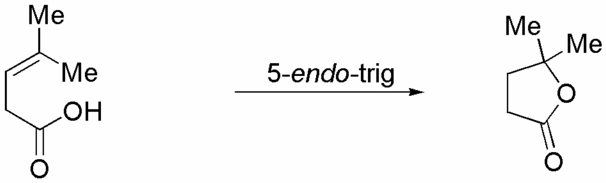


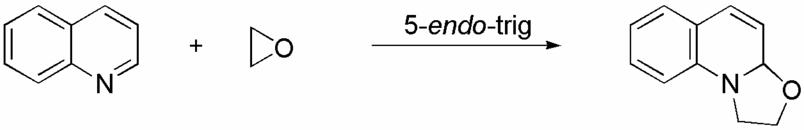
exceptions to the Baldwin rules:

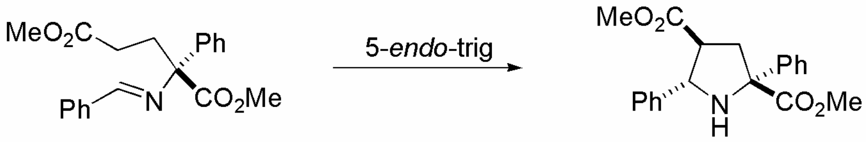
3rd row elements:



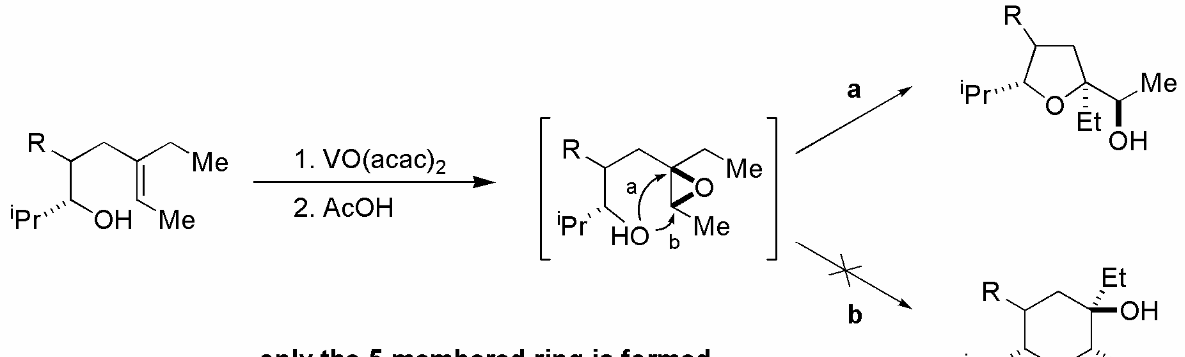
charged intermediates:



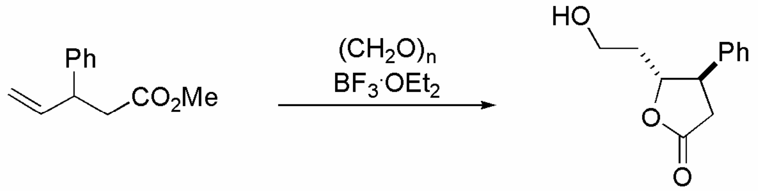




stereoselective cyclisation reactions following the Baldwin rules: some applications

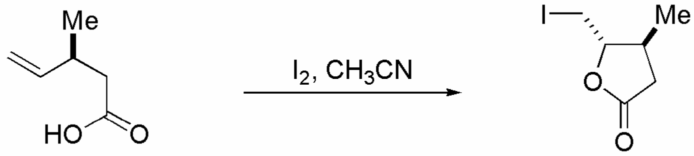


only the 5-membered ring is formed



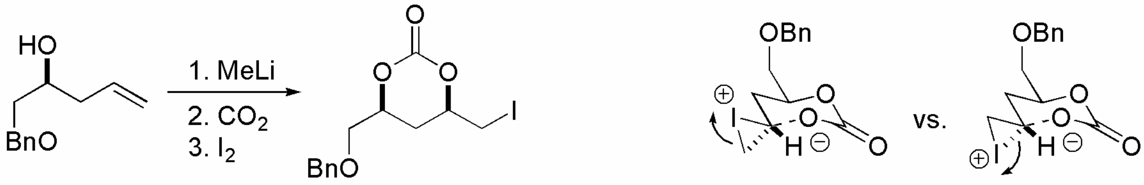
dr = 7:1

Bartlett *J. Am. Chem. Soc.* **1978**, *100*, 3950.
Still *J. Am. Chem. Soc.* **1980**, *102*, 2118.



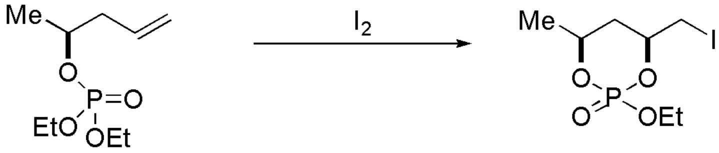
dr = 10:1

Tetrahedron Lett. **1982**, *23*, 3391.

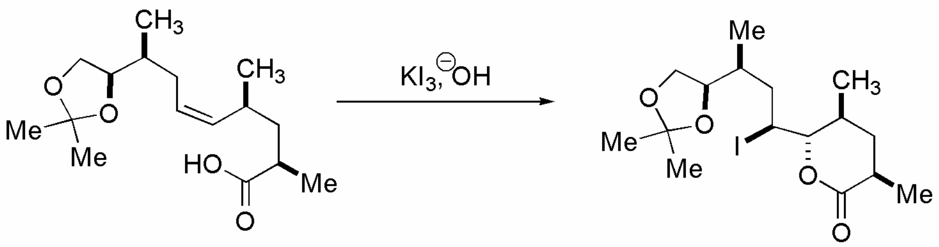


preferred

Lipshutz *J. Org. Chem.* **1984,** *49*, 1147.

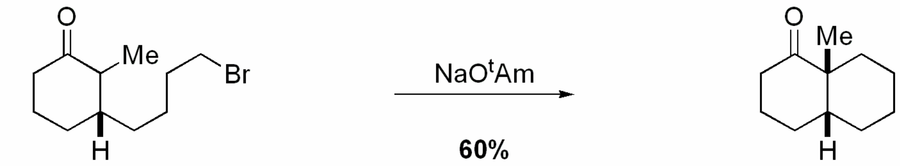


Bartlett *J. Am. Chem. Soc.* **1977**, *99*, 4829.

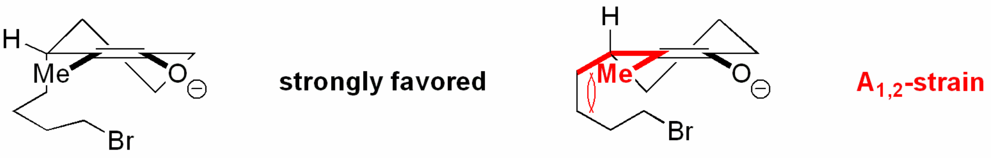


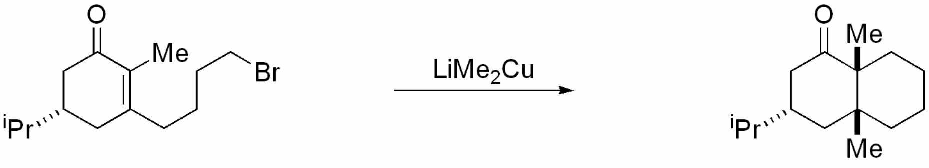
Still *J. Am. Chem. Soc.* **1980**, *102*, 2118.

further stereoselective cyclisation reactions:

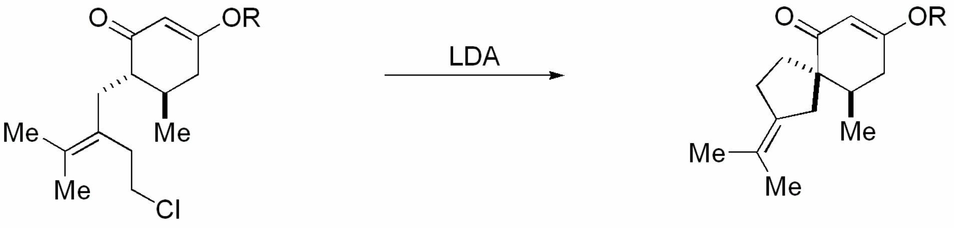


Tetrahedron **1961**, *16*, 45.

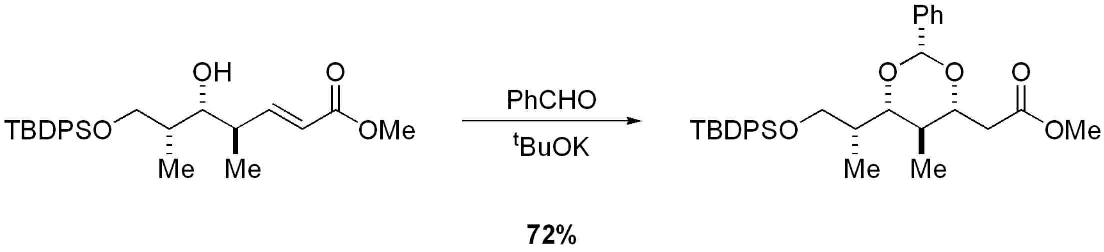




J. Am. Chem. Soc. **1975**, *97*, 107.



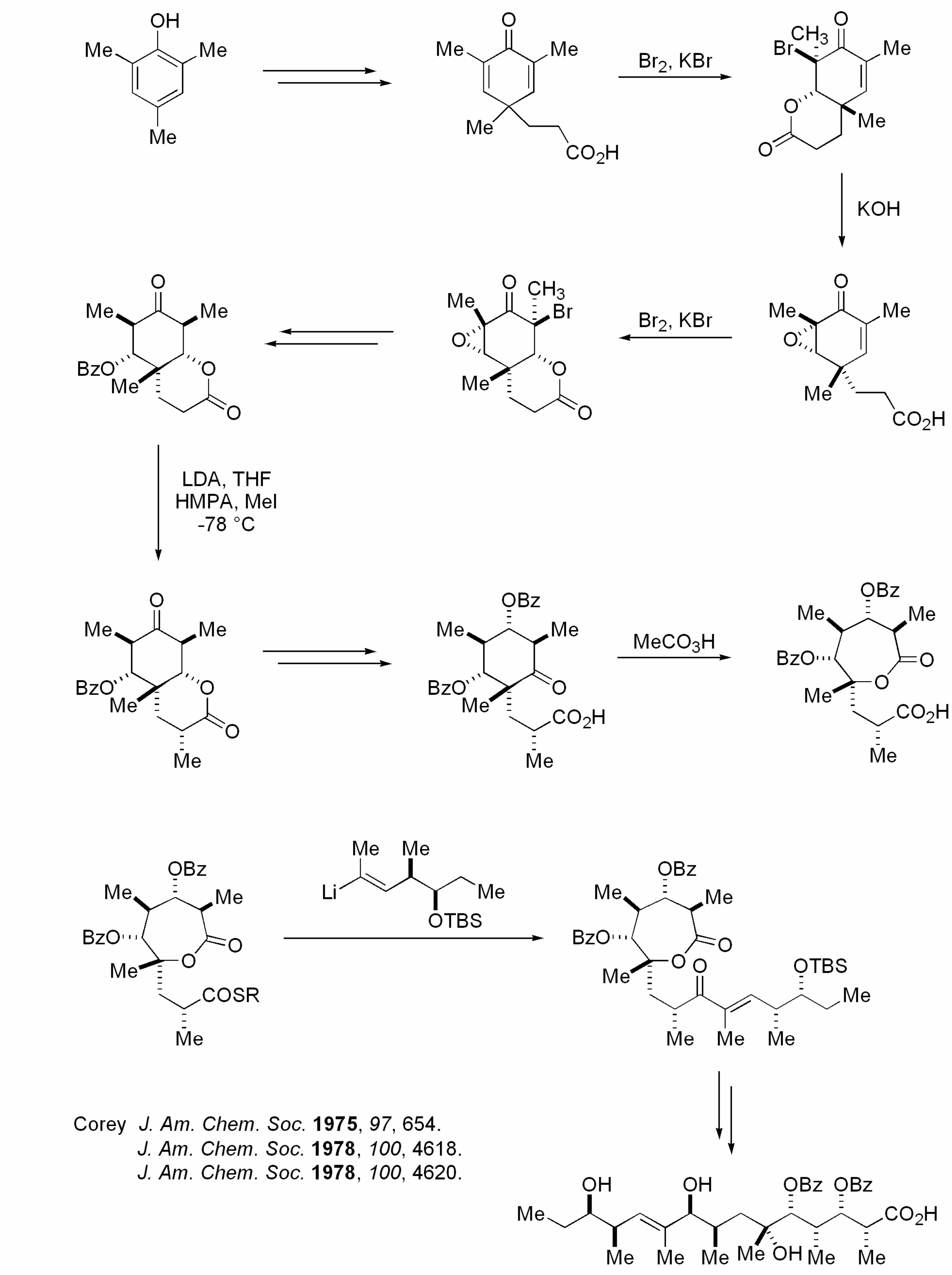
Stork *J. Am. Chem. Soc.* **1973**, *95*, 3414.



Evans *J. Org. Chem.* **1993**, *58*, 2446.

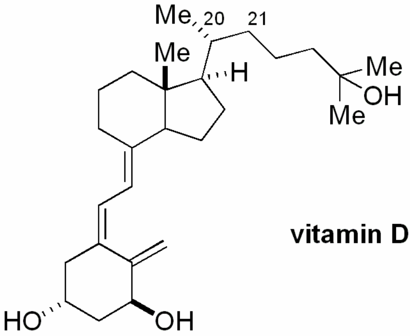
4.5. A Classic in Cyclic Stereocontrol - Synthesis of Erythronolide B

control of stereochemistry through functionalization of rigidified systems



Corey *J. Am. Chem. Soc.* **1975**, *97*, 654.
J. Am. Chem. Soc. **1978**, *100*, 4618.
J. Am. Chem. Soc. **1978**, *100*, 4620.

5. Conformation and Biological Activity: Vitamin D_3

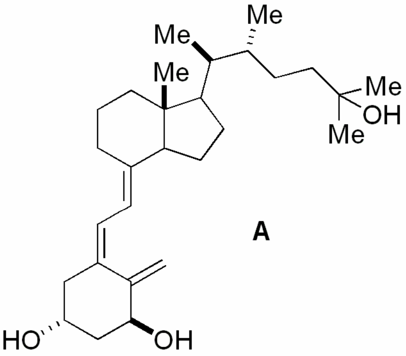


vitamin D_3

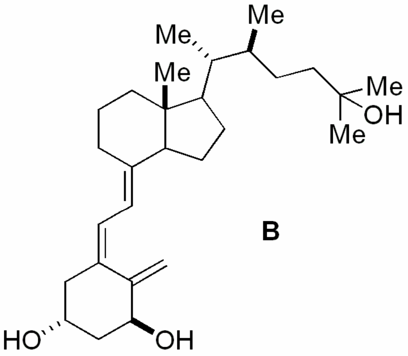
Multiple biological activities: calcium and phosphorus metabolism, cell differentiation, regulation of immune system

For a variety of reasons it would be beneficial to separate functions and generate analogs that lead to only one response. It has been found that the sidechain is in a different conformation when bound to vitamin D receptor (VDR) which regulates Ca metabolism than when bound to vitamin D binding protein (DBP). This suggests that the binding events can be controlled by modifying accessible sidechain conformations.

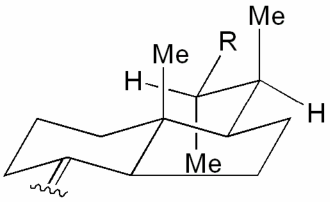
Thus by changing configuration at C20 and introducing an additional methyl group at C21 it has been found that structures are produced which differentiate activities towards the various receptors. For example, **A** binds more strongly to VDR and is devoid of activity towards DBP whereas **B** binds poorly to VDR but shows a high affinity for DBP. In contrary to vitamin D_3, which has a highly flexible sidechain, the sidechain of **A** and **B** is blocked in a specific conformation, allowing more selective binding.



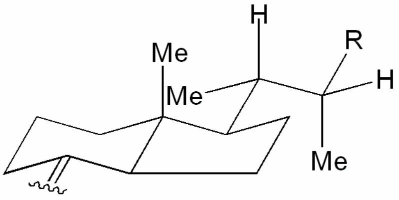
A



B



preferred conformation of **A**



preferred conformation of **B**

The natural vitamin D_3 shows nearly no difference in energy for conformations A and B

review: Hoffmann *Angew. Chem. Int. Ed.* **2000**, *39*, 2054.