

Further Reading: G.R.J. Thatcher (ed.), *The Anomeric Effect and Related Stereoelectronic Effects*. ACS Symposium Series #539, **1993**.

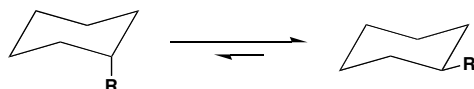
Review: Juaristi, E., Cuevas, G., *Tetrahedron*, **1992**, 48(24), 5019-5087.

Historical Aspects of the Anomeric Effect

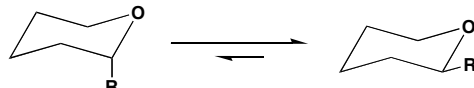
First observed in 1955 by J.T. Edward and in 1958 by R.U. Lemieux.

Both were studying carbohydrate chemistry and noticed a preference for alkoxy and acetyl groups to reside in the axial position. Edward proposed that the lone pairs on the ring oxygen were contributing to the effect.

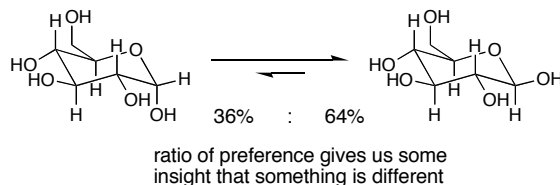
alkyl substituted cyclohexanes prefer equatorial orientation over axial



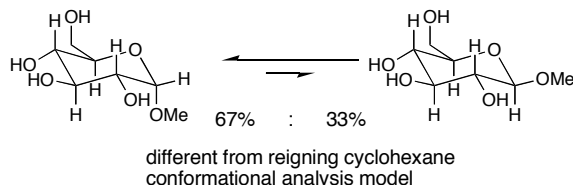
alkyl substituted tetrahydropyrans show this same preference



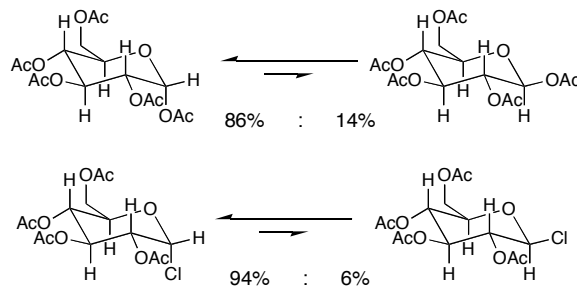
the anomeric carbon of the most abundant natural sugar, D-glucopyranose, also prefers an equatorial orientation.



conversion into a methyl ether at the anomeric carbon produces a different result from the above

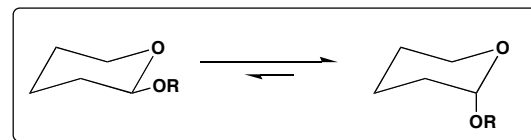


substitution with more electronegative groups changes the observed ratio to a greater extent



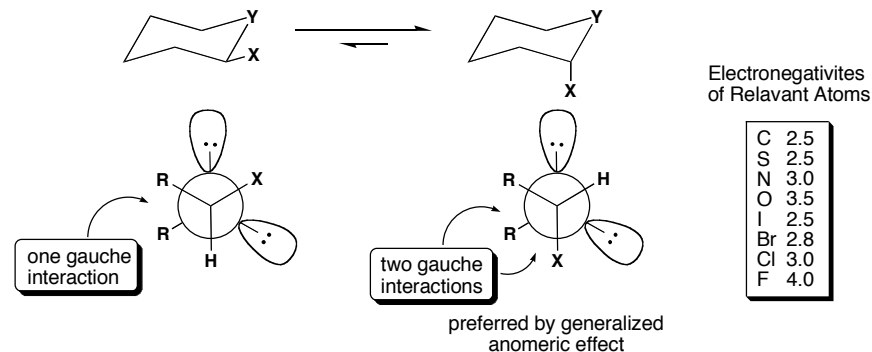
Anomeric Effect Defined (IUPAC):

Originally defined as the thermodynamic preference for polar groups bonded to C-1 (the anomeric carbon of a glycopyranosyl derivative) to take up an axial position.



-OR has an axial preference in a C1 substituted tetrahydropyran

This effect is now considered to be a special case of a general preference (the **generalized anomeric effect**) for gauche conformations about the bond C-Y in the system X-C-Y-C where X and Y are heteroatoms having nonbonding electron pairs, commonly at least one of which is nitrogen, oxygen, sulfur or fluorine.



$$\Delta\Delta G^{\circ}_{\text{anomeric effect (stabilization)}} = \sum \Delta G^{\circ}_{(\text{heterocycle})} - \sum \Delta G^{\circ}_{(\text{steric})}$$

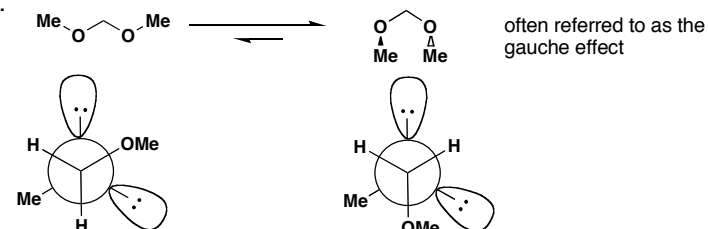
Franck, R.W., *Tetrahedron*, **1983**, 39, 3251.

electronic factor

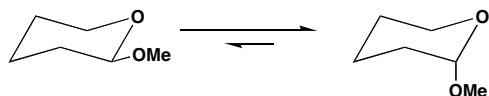
steric factor

For the anomeric stabilization to effect the conformation at all it must be more stabilizing than the sum of all of the steric factors

Linear Example:



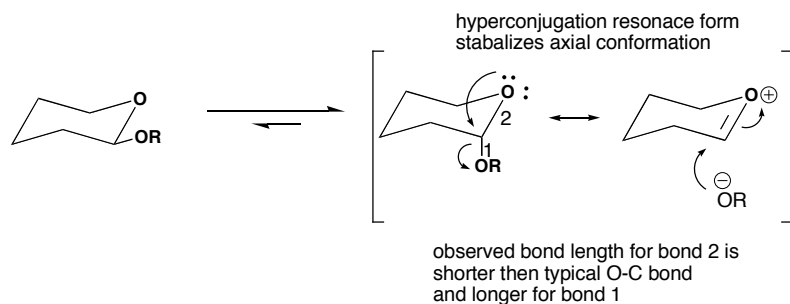
Solvent also plays a role: Increase in anomeric stabilization associated with low solvent dipole



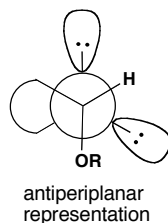
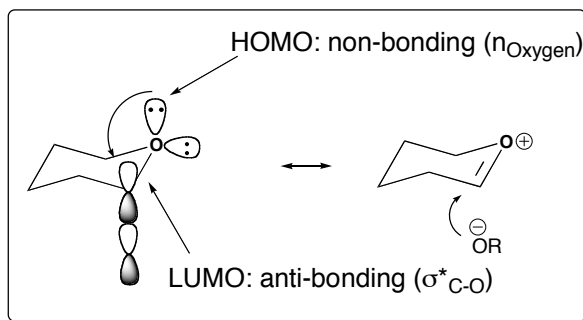
Solvent	Dipole	% axial
CCl ₄	2.2	83
benzene	2.3	82
CHCl ₃	4.7	71
acetone	20.7	72
MeOH	32.6	69
MeCN	37.5	68
H ₂ O	78.5	52

Lemieux, R.U., et al. *Can. J. Chem.* **1969**, 47, 4427.

Most widely accepted explanation for the anomeric effect:

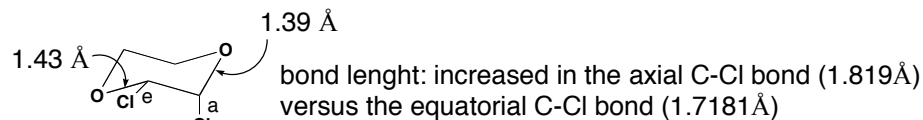


Closer Examination of Orbitals:

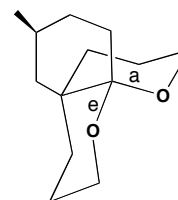


This model is referred to as Antiperiplanar Lone Pair Hypothesis or **ALPH**

Further Evidence:



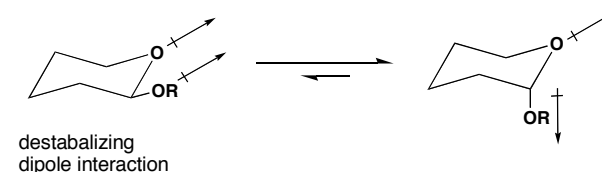
Romers, C., et al. *Topics Stereochem.*, **1969**, 4, 39.



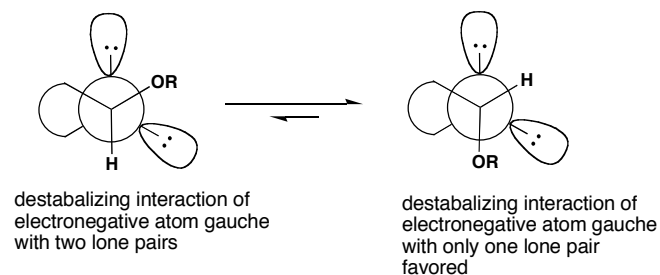
axial bond also observed to be longer than equatorial bond in this constrained case

Other Explanations:

Dipole Stabilization: Opposing dipoles are stabilizing relative to aligned dipoles

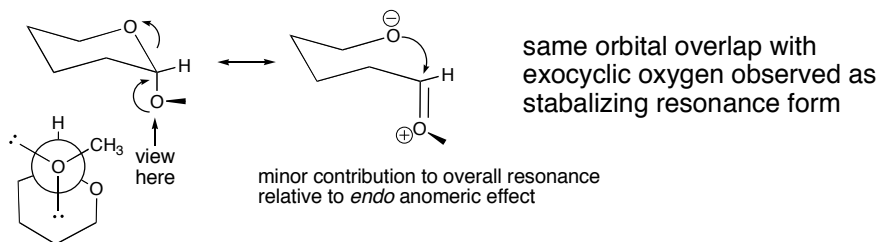


Electrostatic Repulsion: Decreased electrostatic interactions are favored

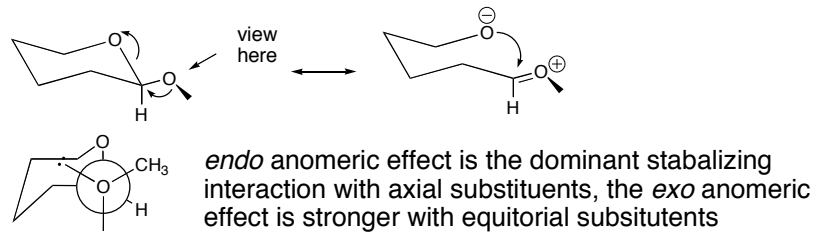


Net Anomeric Effect probably due to a combination of factors

The Exo-Anomeric Effect:



also can be stabilizing with equatorial substituents

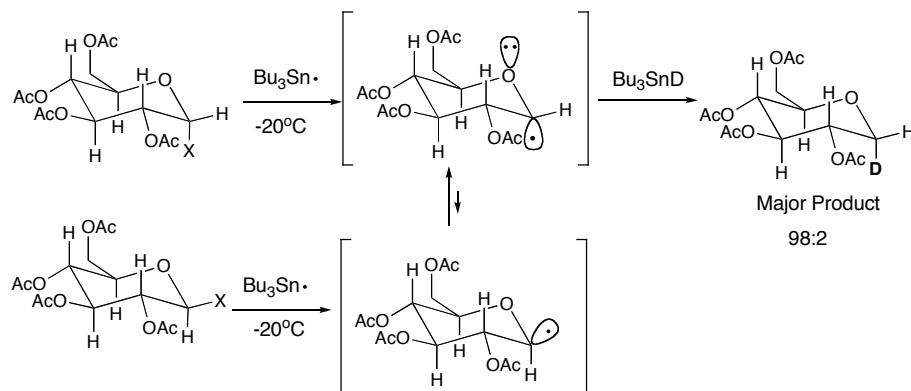


$$\text{Anomeric Effect} = (\text{exo-AE}_{\text{eq}}) - (\text{exo-AE}_{\text{ax}} + \text{endo-AE}_{\text{ax}})$$

endo anomeric effect is absent in the equatorial conform so this term is zero

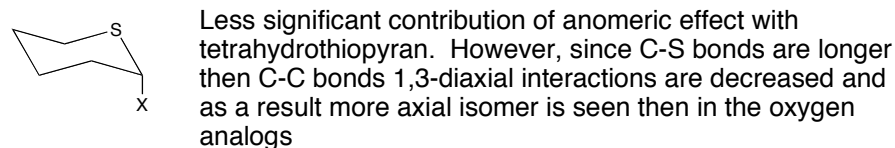
Praly, J. P., Lemieux, R.U., *Can. J. Chem.* **1987**, 65, 213.

Anomeric Effect of Radicals:

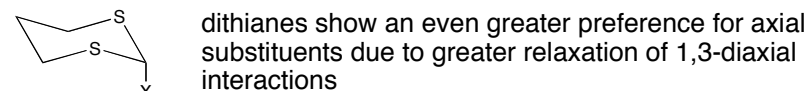
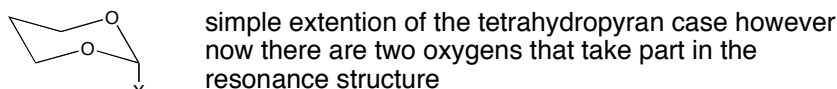


Giese, B., Dupuis, J., *Tetrahedron Lett.*, **1983**, 25, 1349.

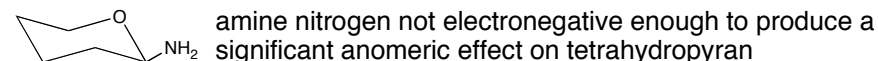
Effect is observed in tetrahydrothiopyran:



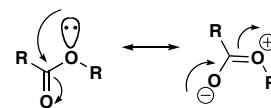
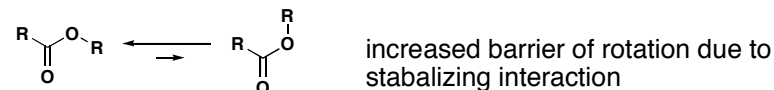
Effect is observed in dioxanes and dithianes:



Effect is very minimal with amine nitrogens:

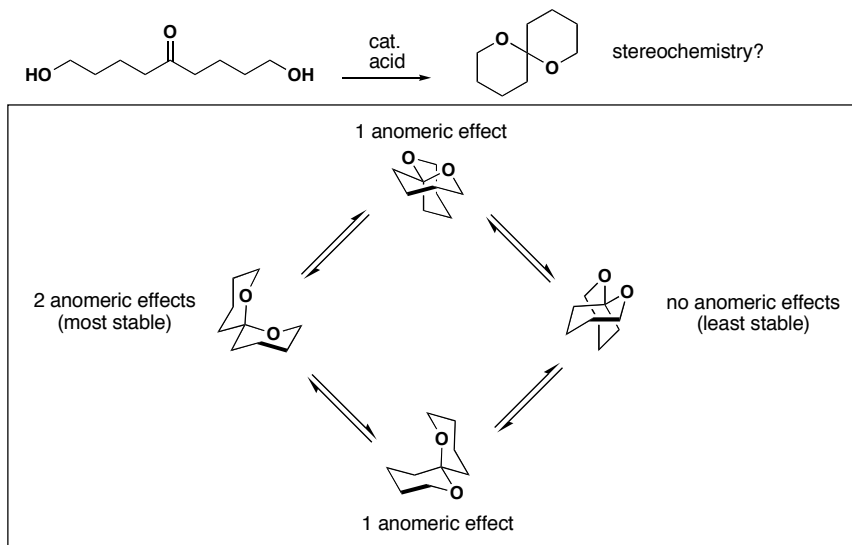
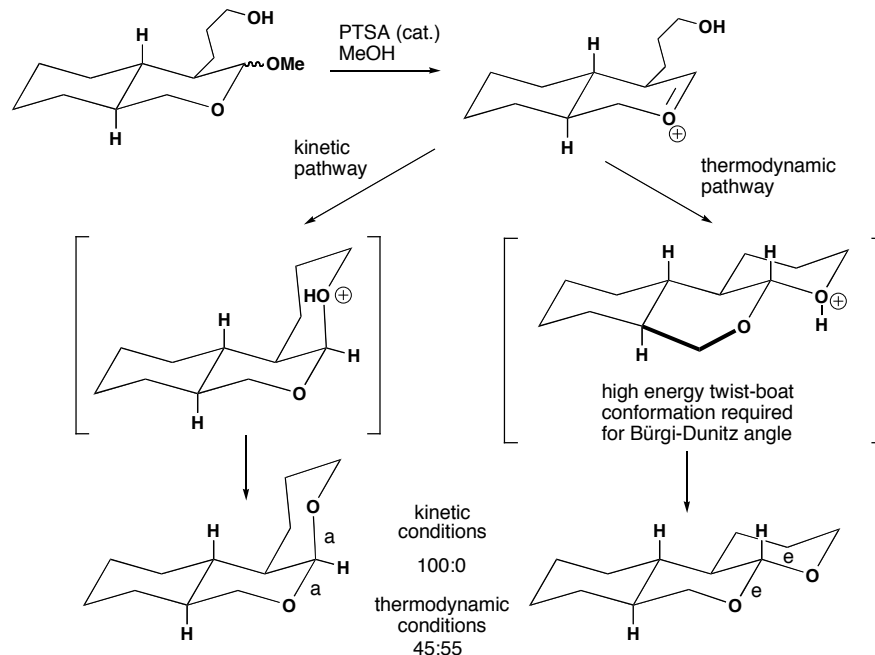
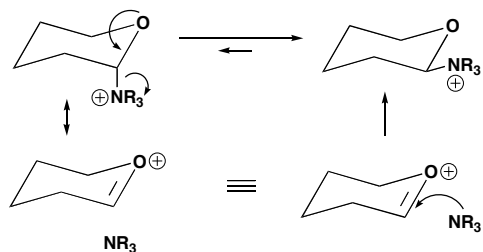


Structures with N-C-X bonds where X is a strongly electronegative substituent on piperidine are not stable so the effect cannot be studied on these systems

Effects at sp^2 centers:

Spiroketals: found in many natural productsreviews: Perron, F., Albizati, K.F. *Chem.Rev.* **1989**, 89, 1617-1661Brimble, M.A., Furkert, D.P. *Current Organic Chemistry*, **2003**, 7, 1461-1484.

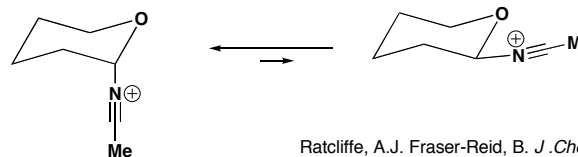
structural conformations that depend on the anomeric effect

General considerations for spiroketal ring systems.
Actual outcome will also be dependent on substituents**Anomeric Control of Product Distribution:**G.R.J. Thatcher (ed.), *The Anomeric Effect and Related Stereoelectronic Effects*. ACS Symposium Series #539, **1993**.**The Reverse Anomeric Effect: Fact or Fiction?**Preference for equatorial position with positively charged-electronegative substituents C. L. Perrin, *Tetrahedron*, **1995**, 51, 11901.

highly debated in the literature

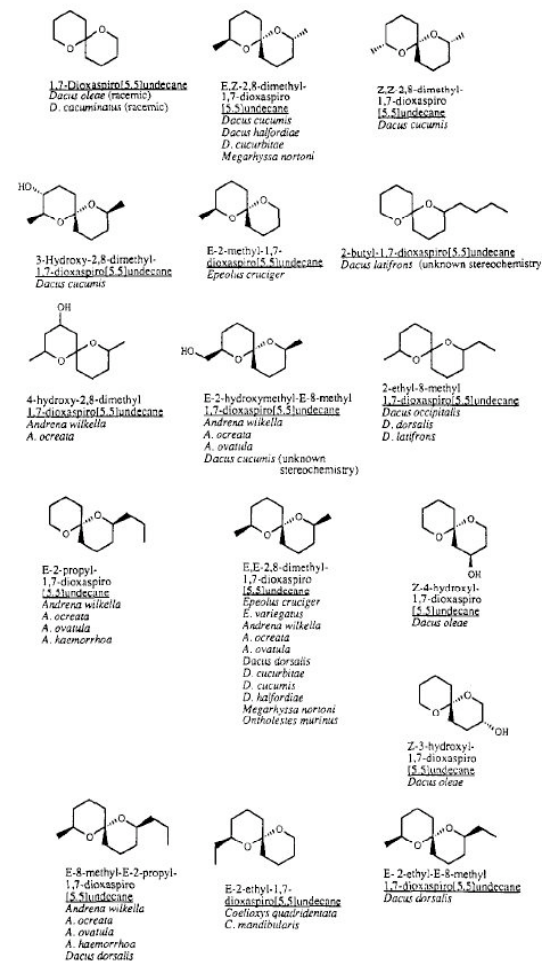
- often the charged species studied are bulky and sterics have a greater contribution
- dipole interactions in equatorial state are not stabilizing (evidence for this model)
- no lone pair on axial substituent to contribute to the *exo*-anomeric effect
- the axial structure is weak (favored by elimination) and unlikely to exist, only the equatorial isomer is preferred as a result

interesting exception:

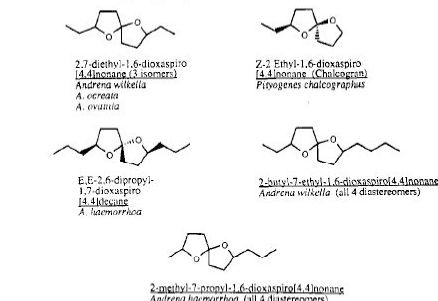
Ratcliffe, A.J. Fraser-Reid, B. *J. Chem. Soc. Perkin Trans. 1* **1990**, 747-750.

Brief Sampling of Simple Spiroketal Natural Products:

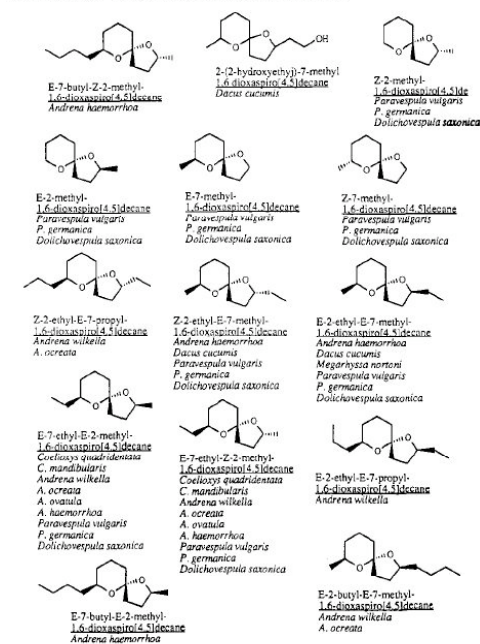
SCHEME 7. Spiro[5.5] Insect Pheromones



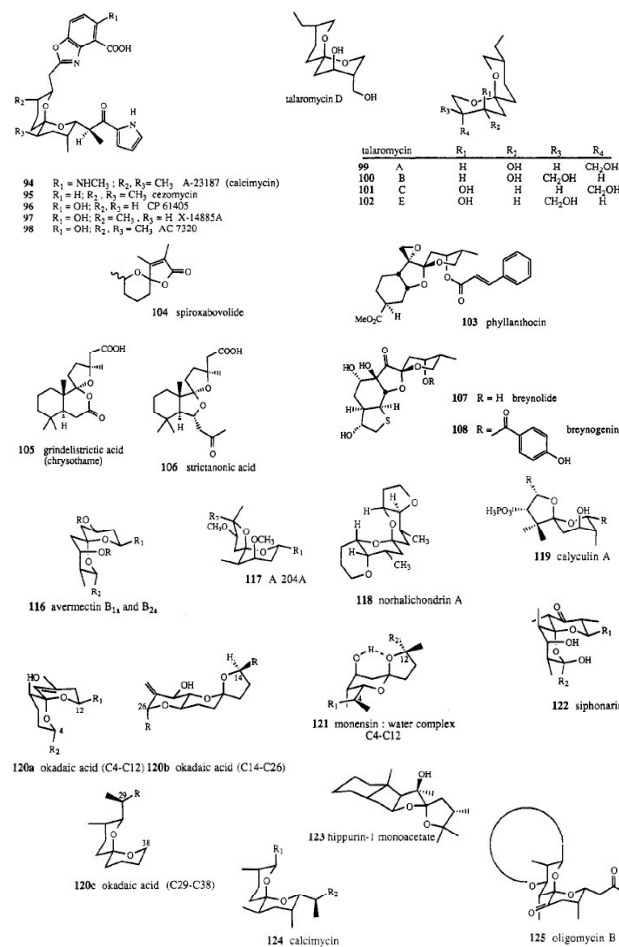
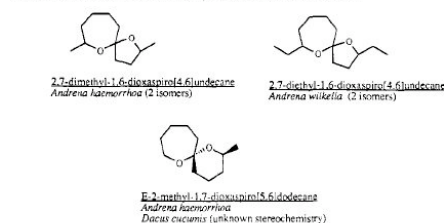
SCHEME 8. Spiro[4.4] Insect Pheromones



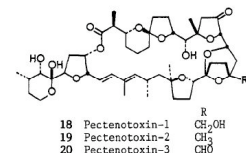
SCHEME 9. Spiro[4.5] Insect Pheromones



SCHEME 10. Spiro[n.6] Insect Pheromones



Non-Anomeric spiroketal:



Agric. Biol. Chem., 1986. 50, 2693

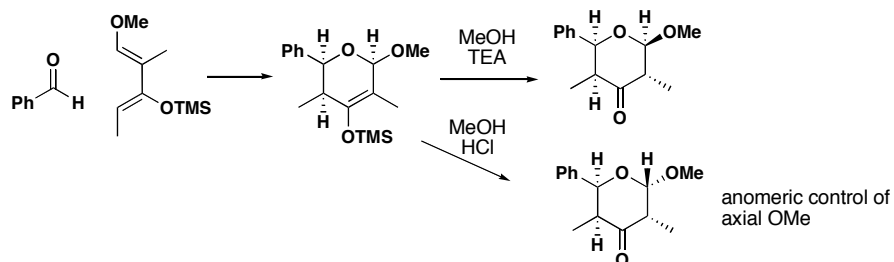
Org. Lett., 2004, 6(21), 3849-3852.

Table 1. Relative Proportions of the Spiroketal Products with Different Acid Promoters^a

entry	acid promoter	pK _a H ₂ O (DMSC)	reaction time	12 (%)	19 (%)	26 (%)	11 (+27) (%)
1	PPTS (20 mol %)	5.21 (3.4)	10 min	53	18	29 ^b	
2	TsOH (20 mol %)	-1.3	10 min	51	21	28	
3	TsOH (20 mol %)	-1.3	70 min	70	10	<2	
4	ClCH ₂ CO ₂ H (80 mol %)	2.86	4 h	29	22	49 ^b	
5	HCOOH (40 mol %)	3.77	4 h	29	28	43	
6	AcOH (100 mol %) ^b	4.76 (12.3)	6 h	34	26	40	
7	AcOH (3300 mol %)	4.76 (12.3)	21 h	65	35	<2	

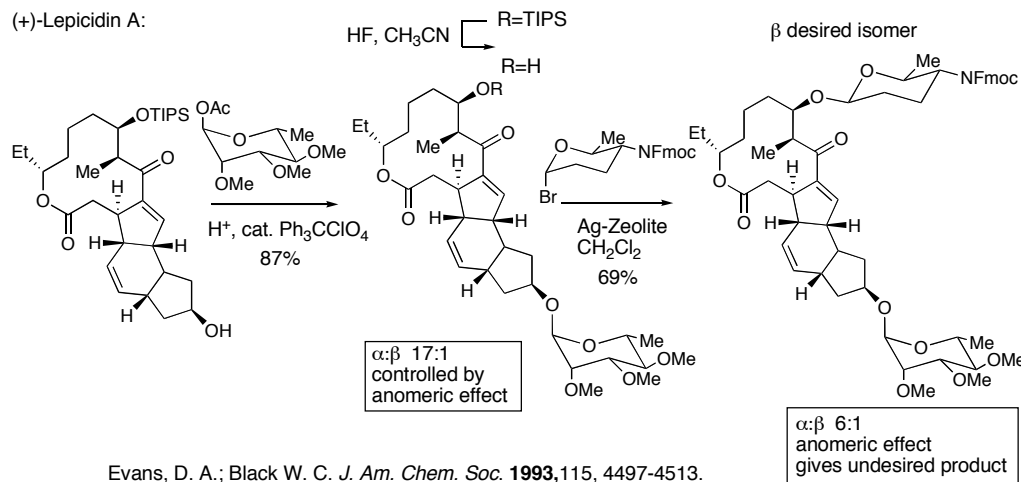
From: Perron, F., Albizzati, K.F. *Chem.Rev.* 1989, 89, 1617-1661

How can we use the anomeric effect?

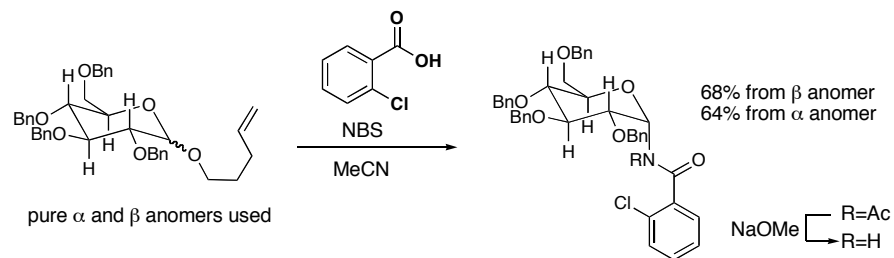


Danishefsky, S. Langer, M. *J. Org. Chem.* **1985**, 50, 3674-3676.

(+)-Lepicidin A:

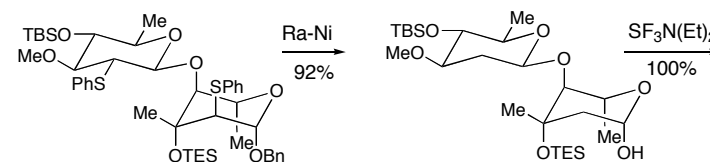
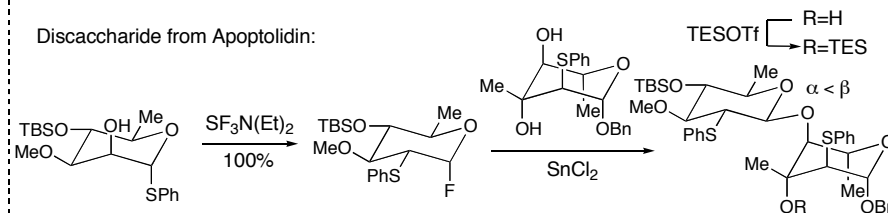


Evans, D. A.; Black W. C. *J. Am. Chem. Soc.* **1993**, 115, 4497-4513.

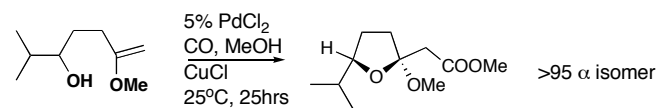
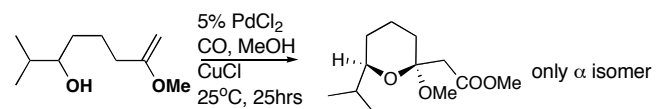


Ratcliffe, A.J. Fraser-Reid, B. *J. Chem. Soc. Perkin Trans. 1* **1990** 747-750.

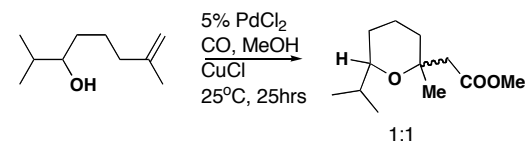
Disaccharide from Apoptolidin:



Nicolaou, K.C. et. al. *J. Am. Chem. Soc.* **2001**, 125, 15433-15442.



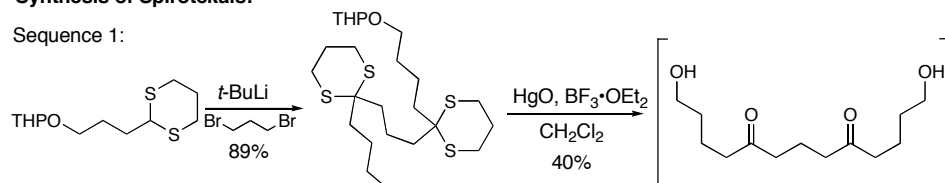
whereas:



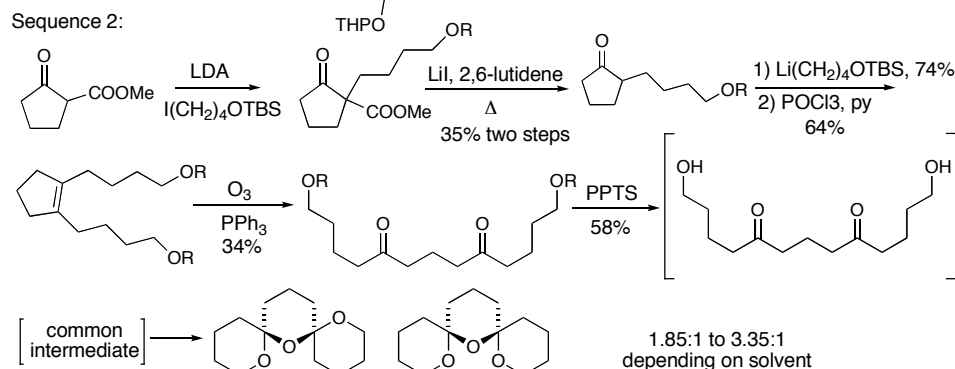
Semmelhack, M.F., et al. *Pure & Appl. Chem.*, **1990**, 62(10), 2035-2040.

Synthesis of Spirotekals:

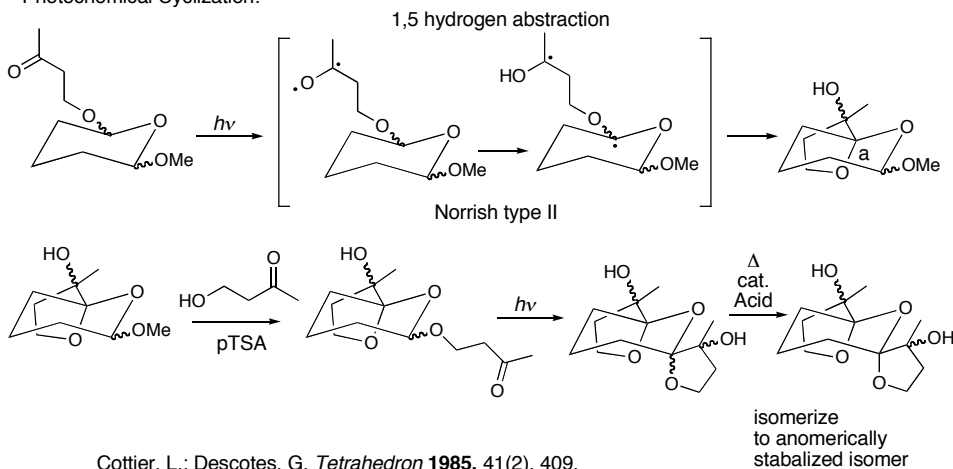
Sequence 1:



Sequence 2:

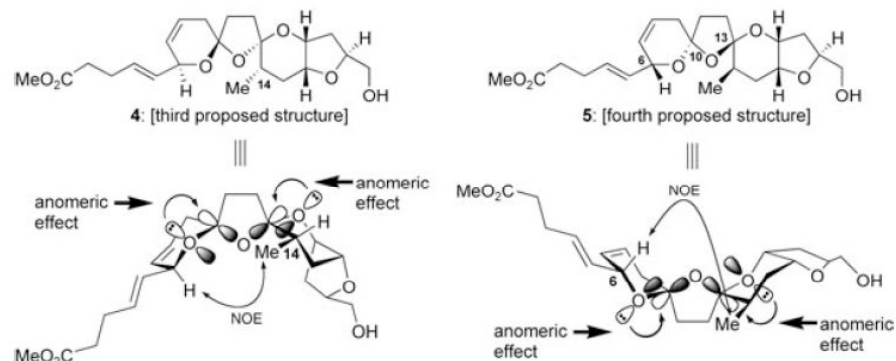
McGarvey, G.J., Stepanian, M.W. *Tet. Lett.*, **1996**, 37(31), 5461-5466.

Photochemical Cyclization:

Cottier, L.; Descotes, G. *Tetrahedron* **1985**, 41(2), 409.

Azaspiracid:

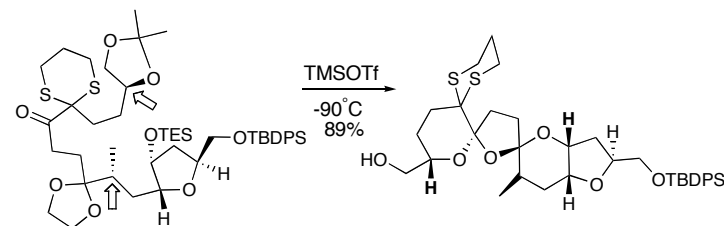
both forms show anomeric stabilization



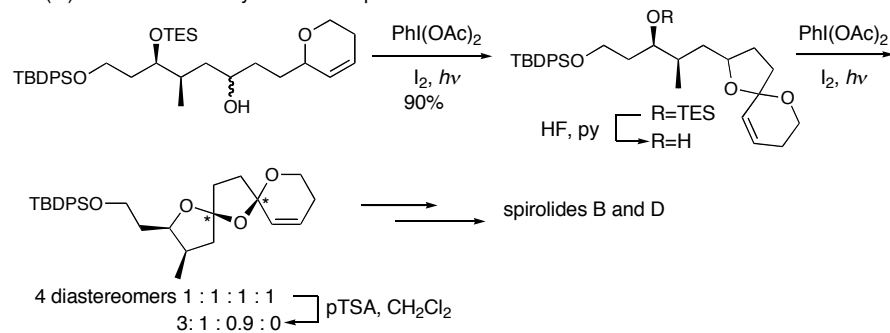
incorrect structure originally targeted and synthesized

correct structure as compared to natural product

key spiroketal step:

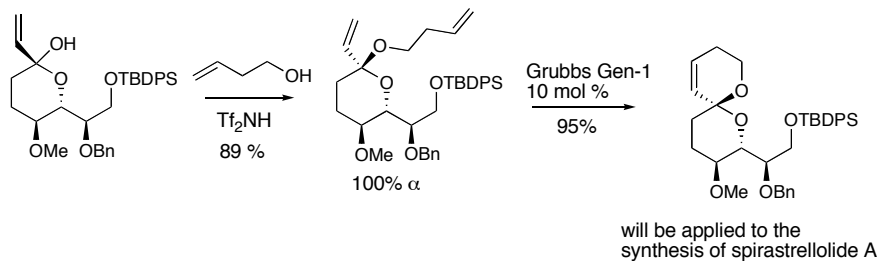
Nicolaou, K.C., et al. *Angew. Chem. Int. Ed.* **2004**, 43, 4318-4324.

Iodine(III) mediated radical cyclization to Spiroacetals:

Brimble, M. A. *Molecules*. **2004**, 9, 394-404

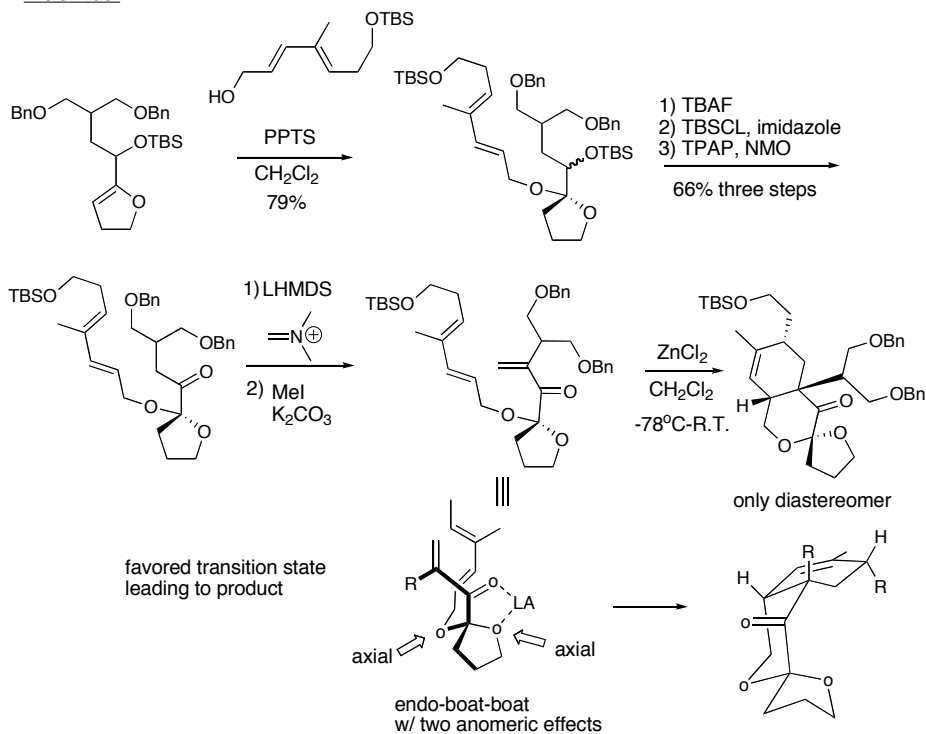
Examples of Spiroketal Tethering:

Olefin Metathesis



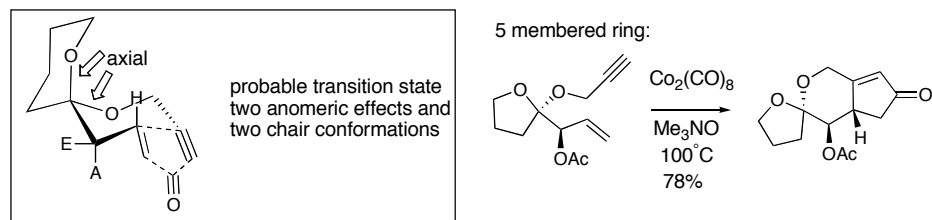
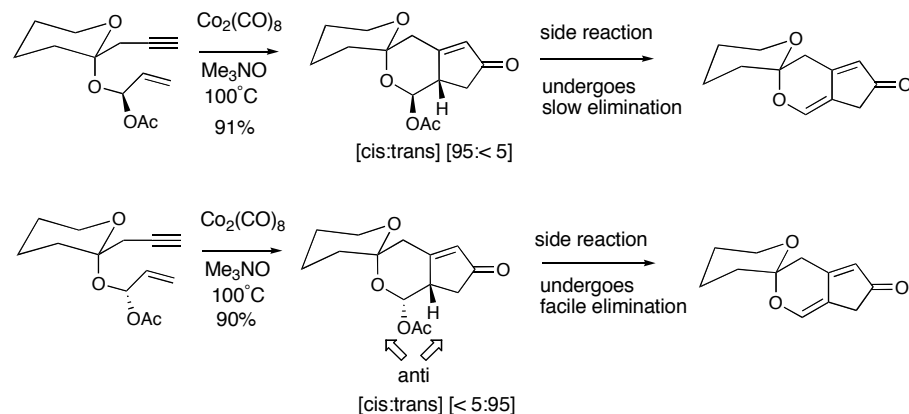
Liu, J., Hsung, R. P., *Org. Lett.* **2005**, 7(11), 2273-3376.

Diels Alder

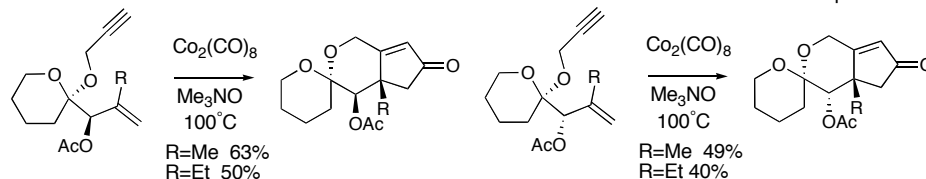


Wang, J., Hsung, R. P., Ghosh, S.K. *Org. Lett.* **2005**, 6(12), 1939-1942.

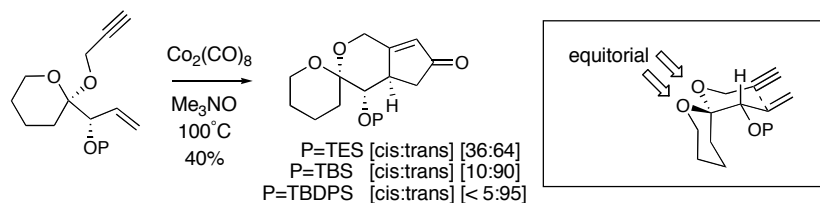
Pauson-Khand



anomeric control dominates stereochemical outcome even if substituent is forced into axial position



finally able to force selectivity with bulky silyl group - sterics beat anomeric effect



Ghosh, S.K., Hsung, R.P., Liu, J. *J. Am. Chem. Soc.* **2005**, 127, 8260-8261.