Strategies and Synthesis of Contrathermodynamic Spiroketals

Timothy Chang
SED Group Meeting
3/27/07

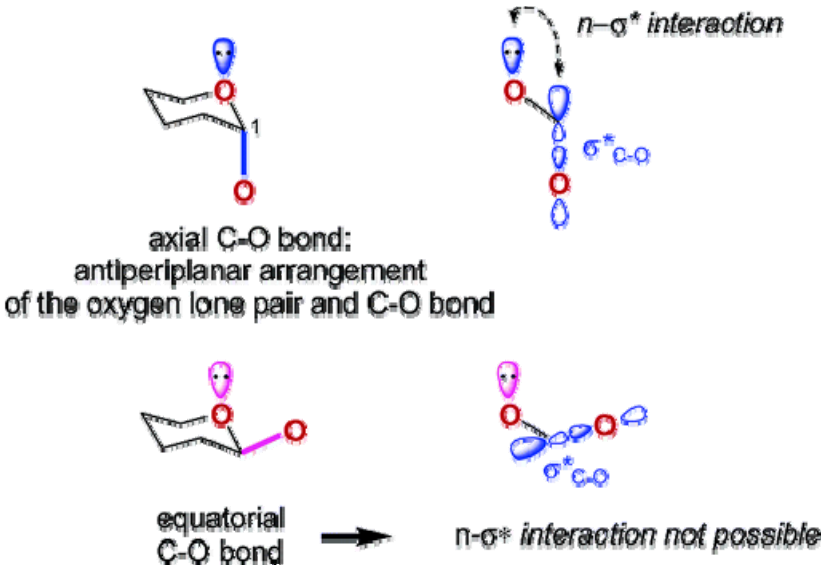
Outlines

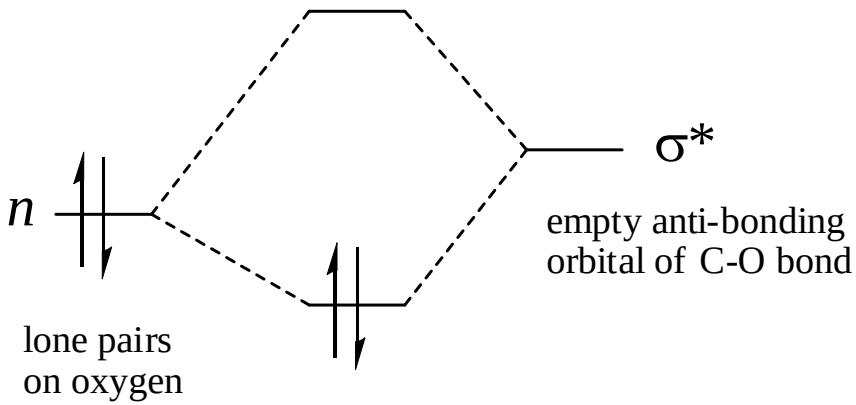
- Anomeric effect: discovery and origin
- Anomeric effect in [5.5] ([6,6]) and [5.4] ([6,5]) spiroketal systems
- Anomeric-nonanomeric dichotomy / definitions
- Examples of “nonanomeric” spiroketal in nature
- Target orientated synthesis:

  CD ring system of Spongistatin (Evans, Smith, Patterson, Heathcock, Crimmins and Roush)
- Stereocontrolled methods (Rychnovsky and Tan)

Anomeric Effect: Discovery and Origin

-First observed by J. T. Edward in 1955 and studied by R. U. Lemieux
-The term “anomeric effect” is first introduced in the 133rd National Meeting of the American Chemical Society at San Francisco (1958).
“The tendency of an electronegative substituent at C(1) of a pyranoid ring to assume the axial rather than the equatorial orientation, in contrast to predictions based solely on steric grounds.”

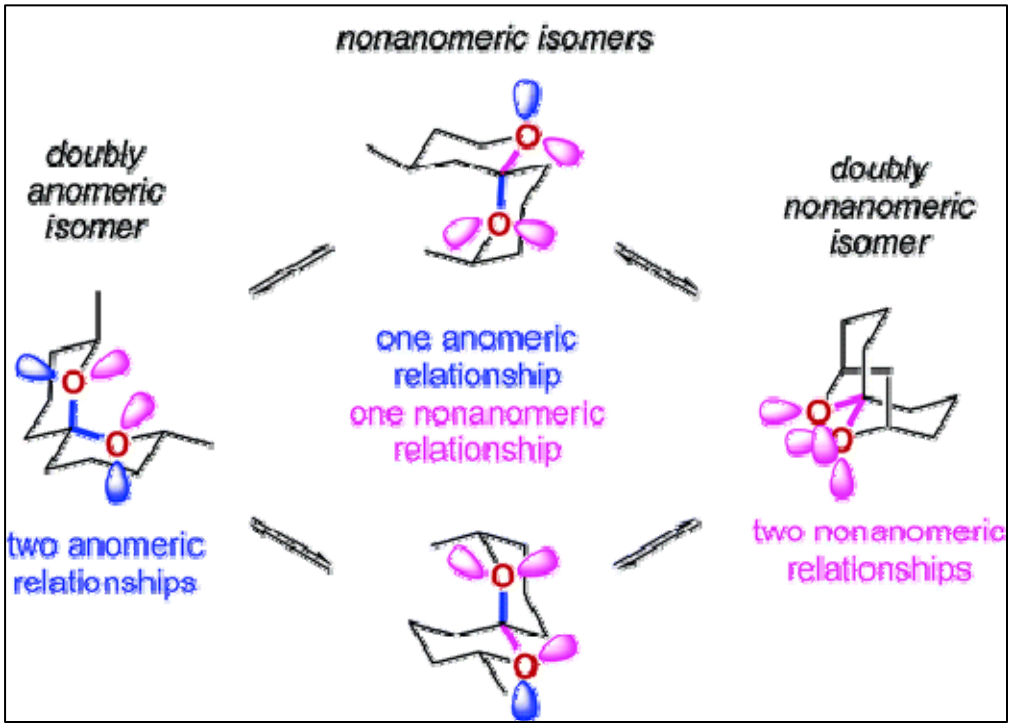


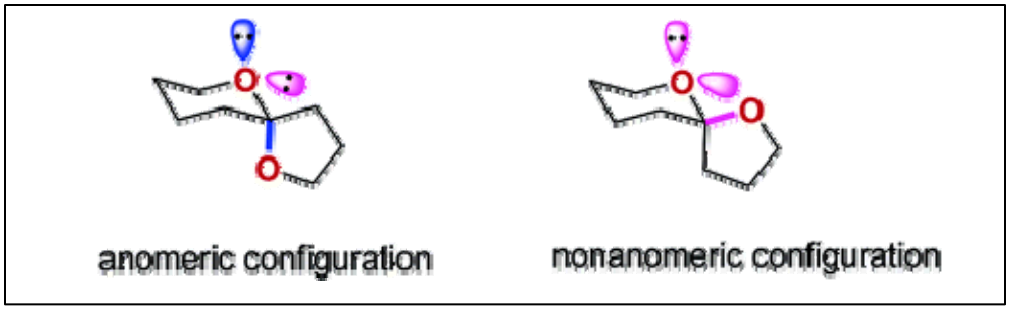


Stabilization: ~ 1.4 – 2.4 kcal/mol per interaction

Juaristi, E.; Cuevas G. *Tetrahedron* **1992**, *48*, 5019
Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005**, *105*, 4406

Anomeric Effect in [5.5] and [5.4] System

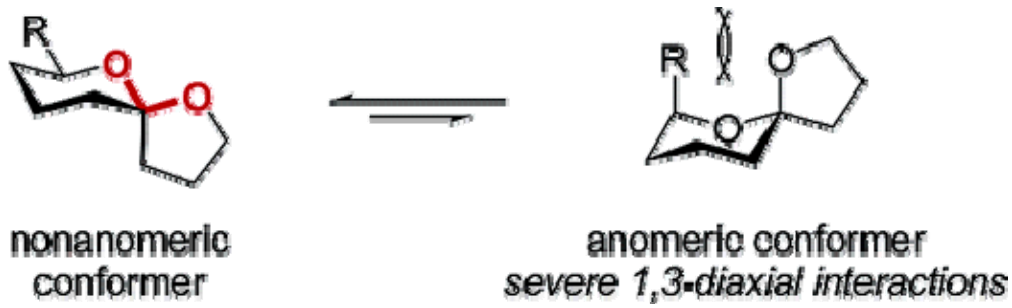




Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005**, *105*, 4406

Meaningful Anomeric-Nonanomeric Dichotomy

1. Clear difference between anomeric and nonanomeric configuration as in six-membered ring system where axial/equatorial bonds are often well defined. Five-membered ring undergoes rapid pseudorotation.
2. Conformational locking is required to stabilize the nonanomeric structures.



Additional factors that help stabilize nonanomeric conformers in nature:
-Intramolecular hydrogen bonding
-Coordination to a metal cation
-Macrocyclic ring constraint

Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005**, *105*, 4406

Definitions

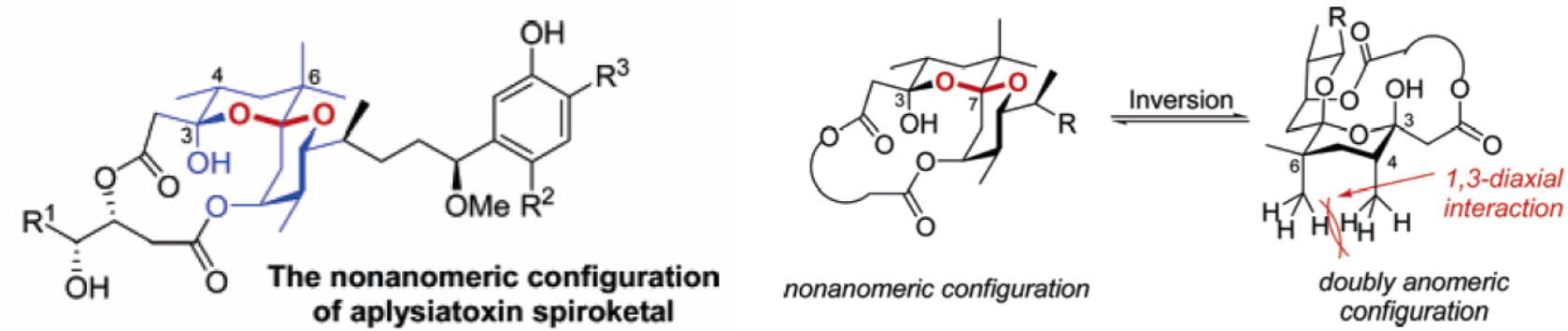
Contrathermodynamic spiroketal

A. Spiroketal that defies the law of thermodynamic?

B. Spiroketal with less than maximum number of possible anomeric stabilization?

C. The less thermodynamically favored isomer of spiroketal.

The conformation of aplysiatoxin with one anomeric stabilization is more stable than the conformation with two anomeric stabilizations. Must consider multiple factors.

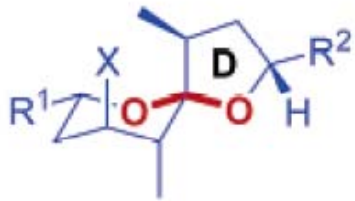


Nonanomeric

Spiroketal isomers that have less than maximum possible number of anomeric stabilization

Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005**, *105*, 4406

Nonanomeric [5.4] Spiroketals in Nature

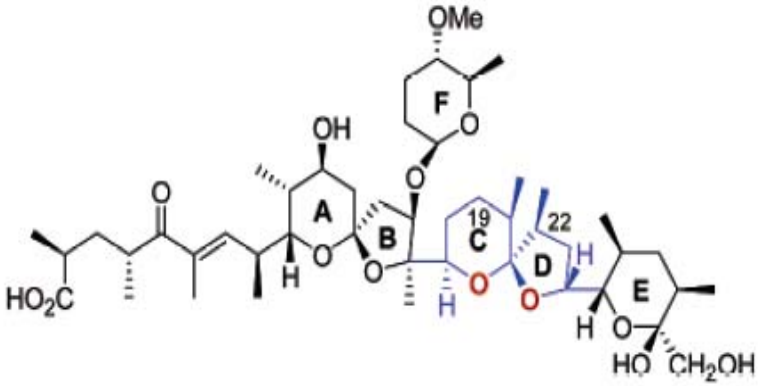


The nonanomeric configuration of the CD ring segment

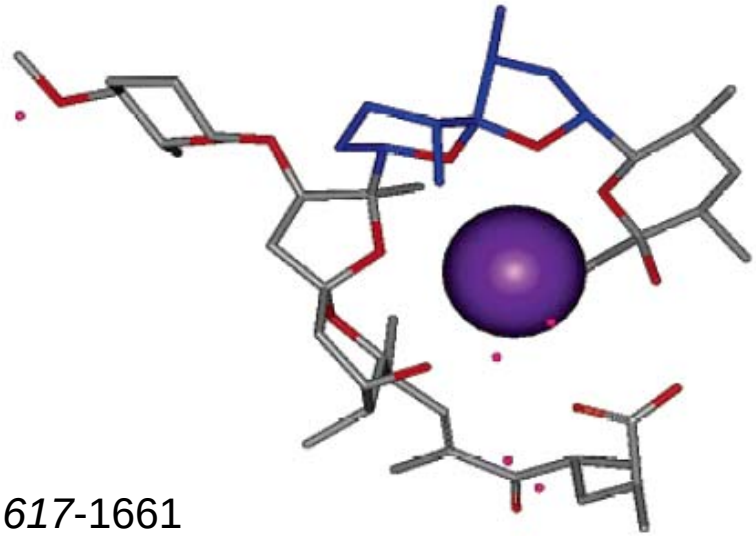
-Nonanomeric spiroketals are common in insect pheromones, polyketide antibiotics and marine toxins.

-Endusamycin belongs to a class of polyketide ionophore antibiotics which are microbial metabolites produced by *Streptomyces*

-Biological properties related to ion transportations across biological membranes



Endusamycin (CP-63.517)

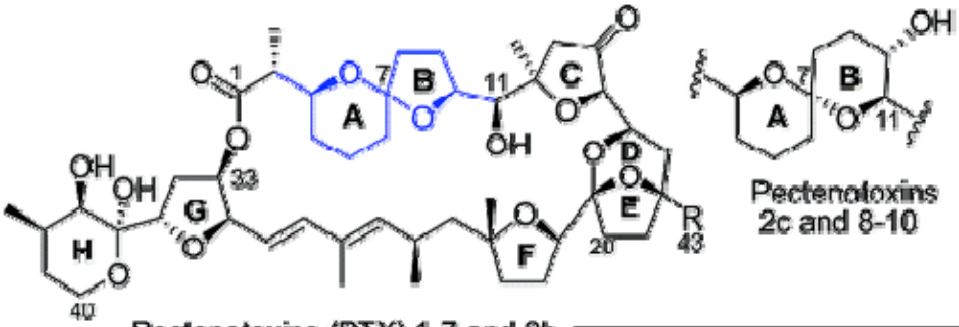


Endusamycin rubidium salt

Perron, F.; Albizati K. *Chem. Rev.* ***1989,*** 89*, 1617*-1661

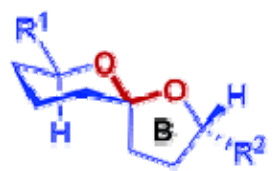
Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005***, 105*, 4406

Nonanomeric [5.4] Spiroketals in Nature



Pectenotoxins (PTX) 1-7 and 2b

Pectenotoxins 2c and 8-10



The nonanomeric configuration of the AB ring segment in pectenotoxins 1-3 and 6

	R	C_7
28: PTX1	CH_2OH	*R*
29a: PTX2	CH_3	*R*
29b: PTX2b	CH_3	*S*
29c: PTX2c	CH_3	*S*
30: PTX3	CHO	*R*
31: PTX4	CH_2OH	*S*
32: PTX5	unidentified	
33: PTX6	COOH	*R*
34: PTX7	COOH	*S*
35: PTX8	CH_2OH	*S*
36: PTX9	COOH	*S*
37a-d: PTX10; PTX11, PTX11b, PTX11x	*Structures not fully elucidated*	

<u>Pectenotoxins 1-3 and 6</u>

-Marine natural products

-Isolated from the Scallop *Patinopecten yessoensis*

-C_7 configuration is *R*

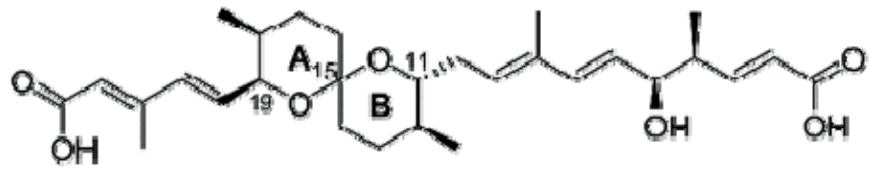
-Significant cytotoxicity against a variety of lung, colon and breast cancer cell lines.

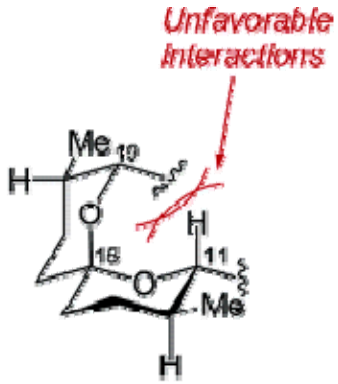
-Nonanomeric isomers are major isolated products

-Appear to be more cytotoxic than the anomeric congeners

Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005**, *105*, 4406

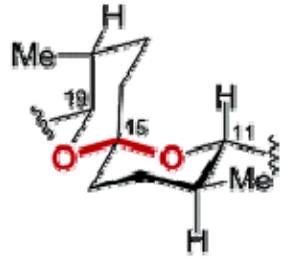
Nonanomeric [5.5] Spiroketals in Nature





99: Spirofungin A (15*R*)

The nonanomeric spiroketal configuration in Spirofungin B

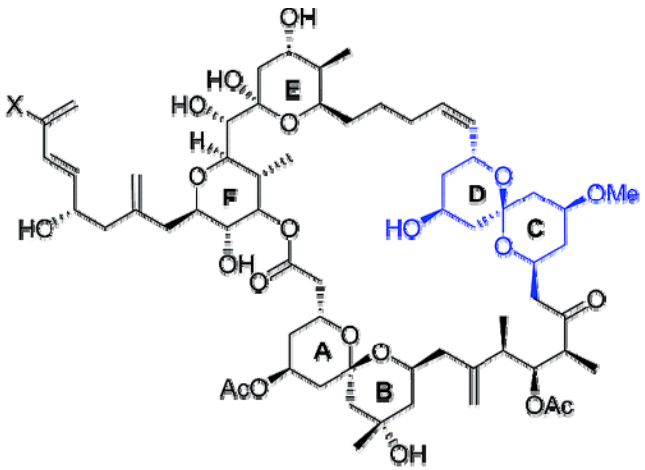


100: Spirofungin B (15*S*)

<u>Spirofungin A and B</u>
-Polyketide Antibiotics
-Collected in Australia Otway National Park
-Isolated as 4:1 (A:B) mixture from the extract of *Streptomyces violaceusniger* Tu 4113

Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005**, *105*, 4406

Nonanomeric [5.5] Spiroketals in Nature



	X
112: Spongistatin 1 = Altohyrtin A	Cl
113: Spongistatin 2 = Altohyrtin C	H
114: Altohyrtin B	Br

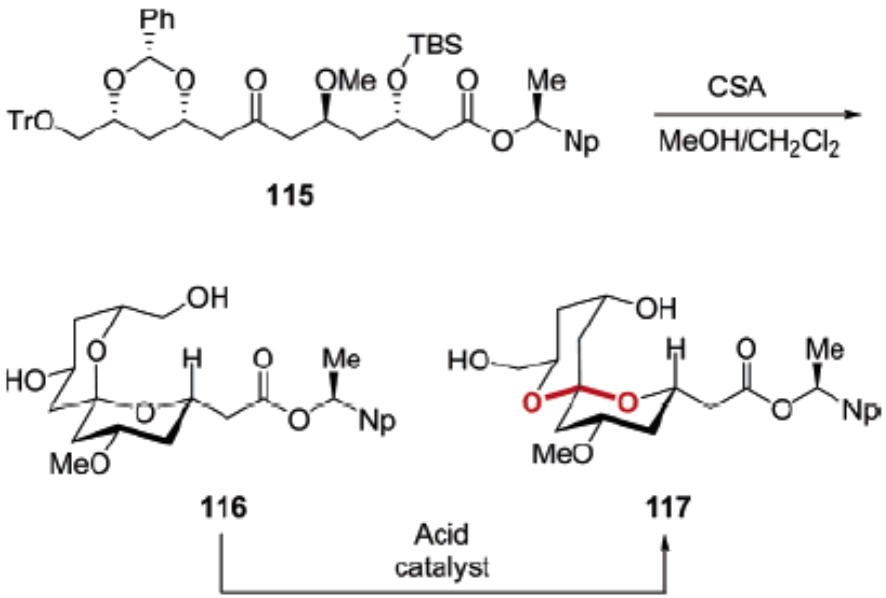
The nonanomeric configuration of the CD ring in spongistatins

<u>Spongistatins</u>

-Marine natural product
-Very active antitumor compounds
-Spongistatin 1, the most active member, has IC_{50} ~ 0.13 nM in average against the NCI's panel of 60 cancer cell lines!
-42-membered macrolactone
-Two spiroketal units
-Why is CD ring nonanomeric?
-Intramolecular hydrogen bonding
-Conformational constraints imposed by the macrocyclic structure

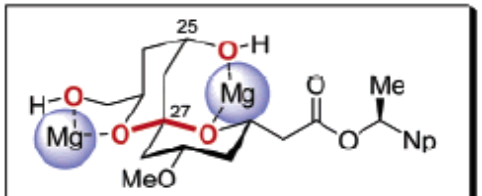
Aho, J.; Pihko, P.; Rissa, T. *Chem. Rev.* **2005**, *105*, 4406

Synthesis of the CD Ring in Spongistatin Evans



Entry	Acid	Solvent	Time	**116**:**117**
1	CSA	$MeOH/CH_2Cl_2$	24h	6:1
2	CSA	CH_2Cl_2	3h	1:1
3	$ZnBr_2$	CH_2Cl_2	1h	1:2.3
4	$Mg(O_2CCF_3)_2$	CH_2Cl_2	3h	1:2.6
5	$ZnCl_2$	CH_2Cl_2	3h	1:4.3

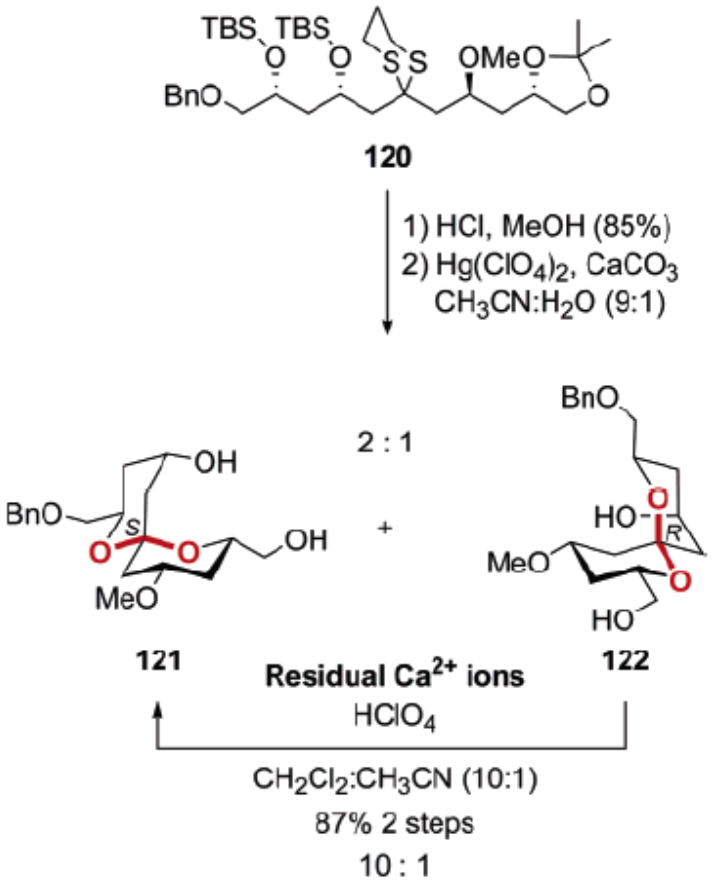
Strategy:
Stabilize the nonanomeric structure by metal chelation and thus favor it in the equilibration.



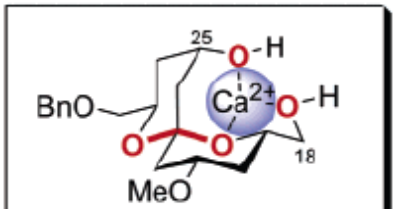
117, dimagnesium complex

Evans *et. al. Angew. Chem. Int. Ed.* **1997**, *36*, 2744

Synthesis of the CD Ring in Spongistatin Smith



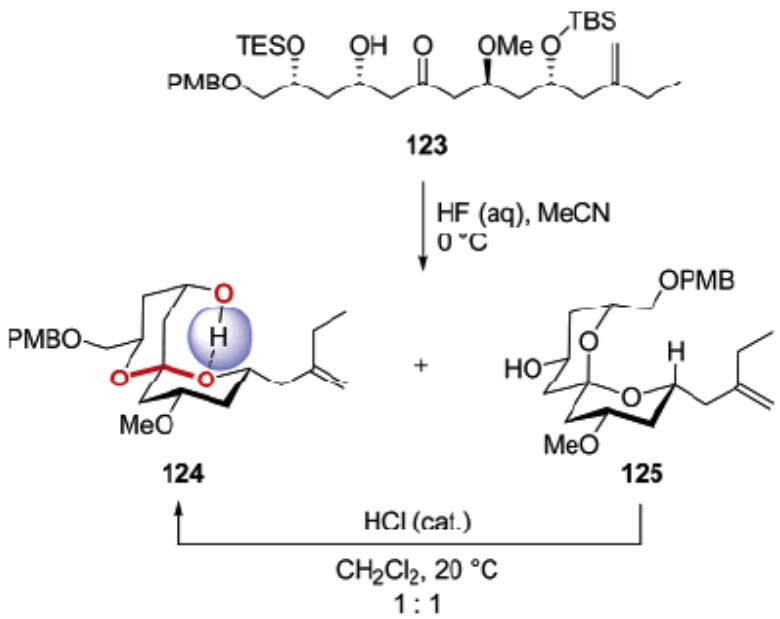
Same strategy as Evans:
Stabilize the nonanomeric structure by chelating calcium ions and thus favor it in the equilibration.



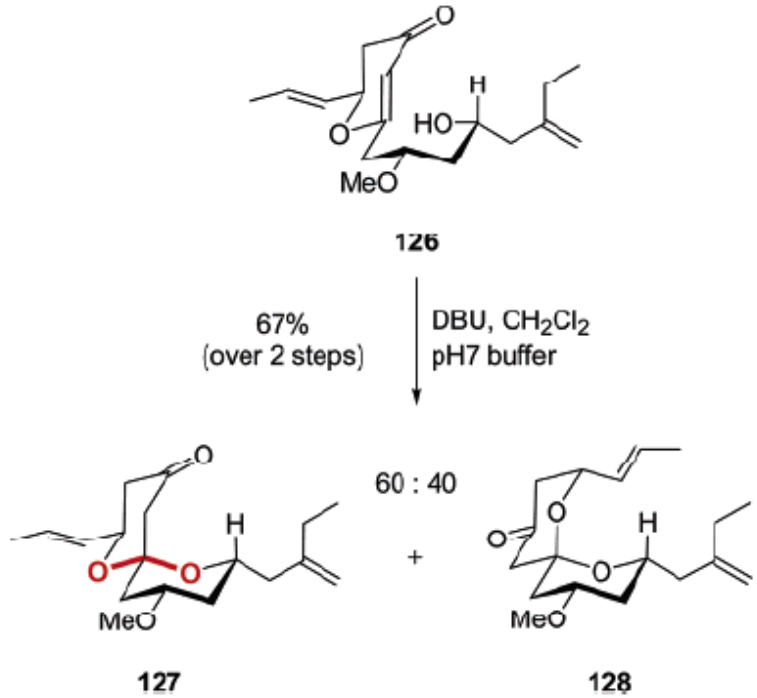
121, calcium complex

Smith *et. al. Angew. Chem. Int. Ed.* **2001**, *40*, 191.

Synthesis of the CD Ring in Spongistatin Paterson



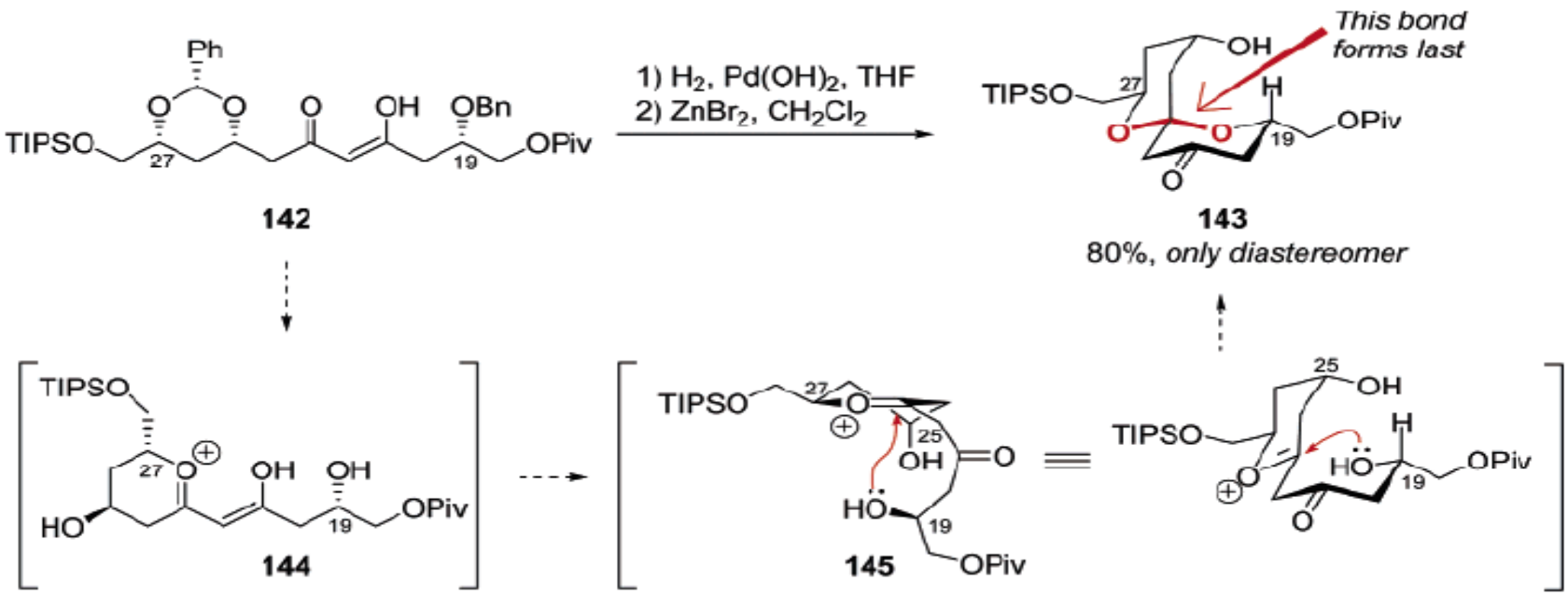
Strategy:
Stabilize the nonanomeric structure by hydrogen bonding
Only obtain 1:1 mixture



Strategy:
Hetero-Michael cyclization
Axial attack (chair transition state)
“Kinetic control”

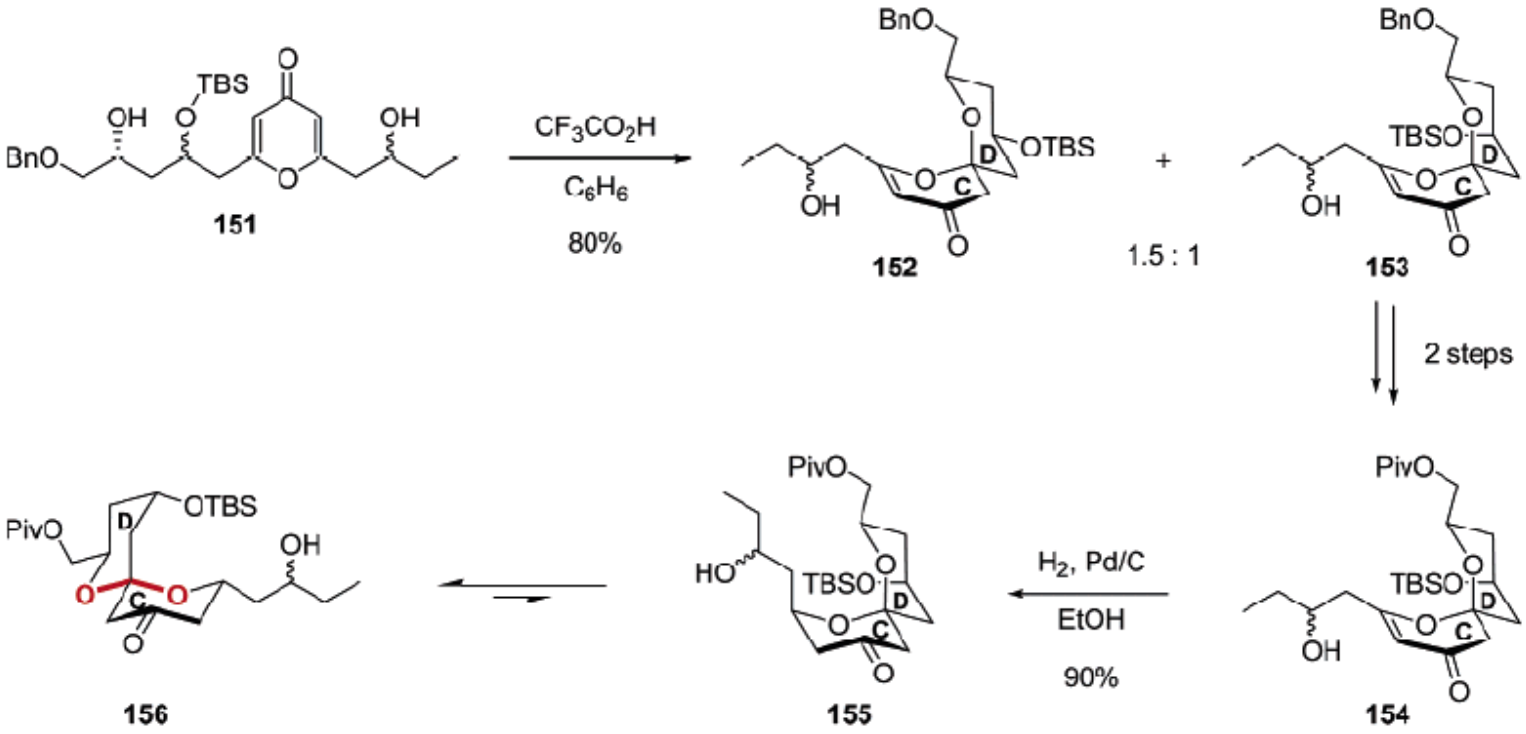
Paterson *et. al. Tetrahedron Lett.* **1997**, *38*, 8911; *Tetrahedron Lett.* **2002**, *43*, 3285

Synthesis of the CD Ring in Spongistatin Heathcock



Heathcock *et. al. J. Am. Chem. Soc.* **2003**, *125*, 12836

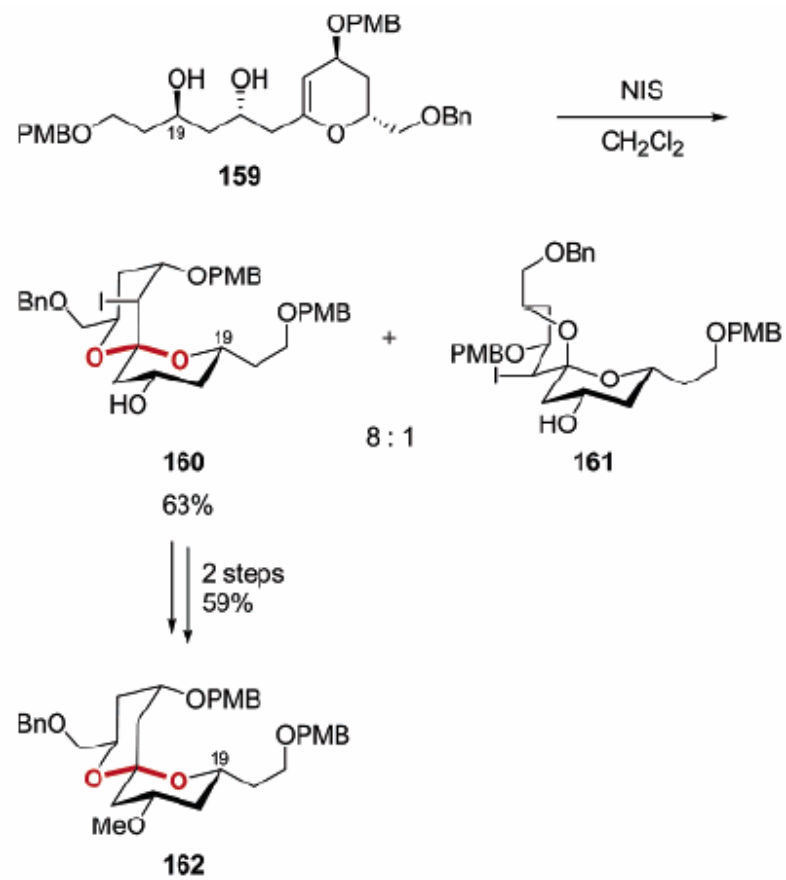
Synthesis of the CD Ring in Spongistatin
Crimmins



154-155: Stereoselective hydrogenation
Approach from convex face
155-156: Ring inversion due to severe 1,3-diaxial interaction

Crimmins *et. al. Org. Lett*. **2000**, *2*, 957

Synthesis of the CD Ring in Spongistatin Roush



Strategy:
-Iodo-spiroketalization
-159 is activated by NIS (steric control)
-Axial attack by C_{19} hydroxyl group through chair transition state

Roush *et. al. Org. Lett.* **2002**, *4*, 3719

Summary of the Strategies

- Thermodynamic equilibration:

  Metal chelation (Evans, Smith)

  Hydrogen bonding (Paterson)
- Hetero Michael cyclization (Paterson)
- Stereoselective hydrogenation followed by steric induced ring inversion (Crimmins)
- Iodo-spiroketalization (Roush)

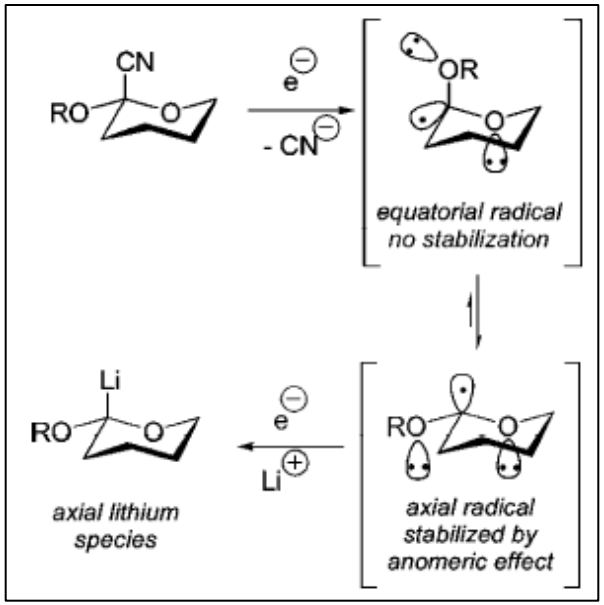
- Most of these strategies are case specific.
- Stereoseletivity is only moderate in many instances
- Iterative recycling and equilibration maybe necessary to afford reasonable yield

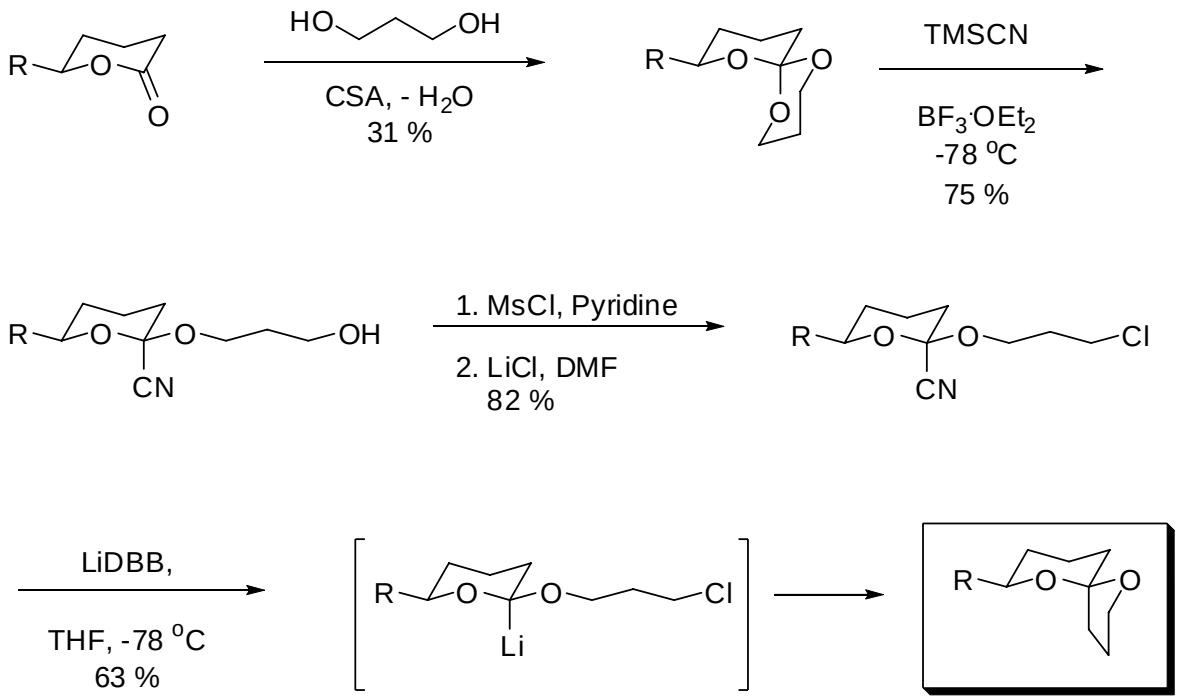
Challenges:

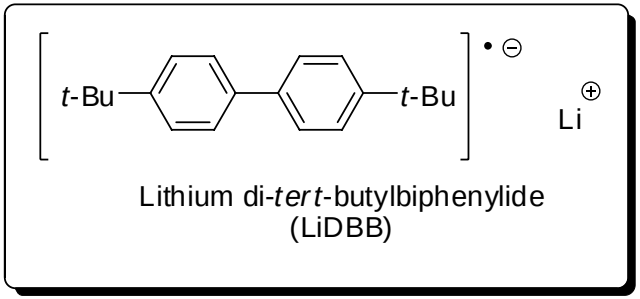
Development of general and stereocontrolled approaches to contrathermodynamic (nonanomeric) spiroketals.

Rychnovsky's Reductive Cyclization

Make use of anomeric effect



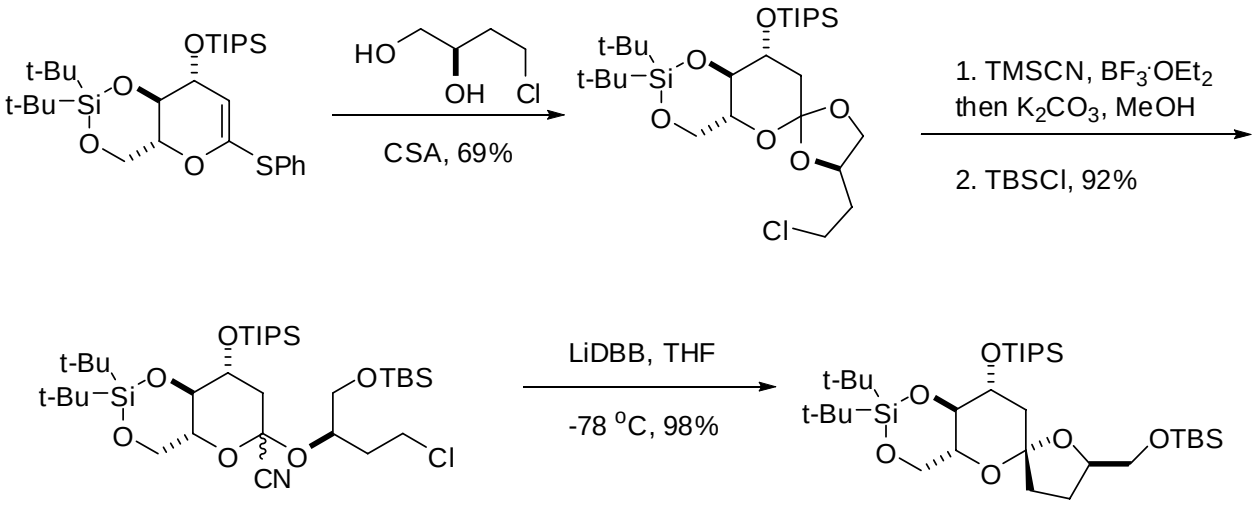


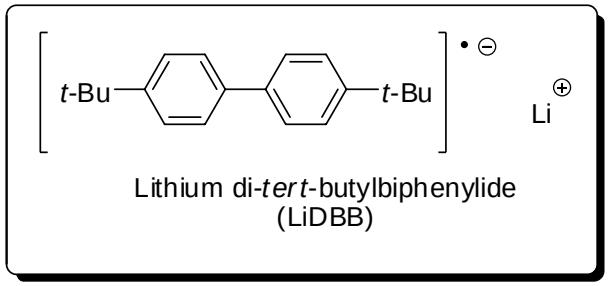


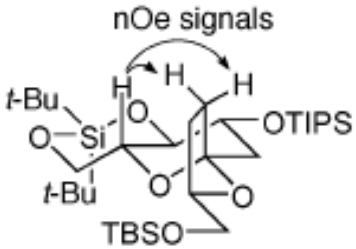
Lithium di-*tert*-butylbiphenylide
(LiDBB)

Rychnovsky *et. al. J. Am. Chem. Soc.* **1992**, *114*, 8375
Rychnovsky *et. al. J. Am. Chem. Soc.* **2005**, *127*, 528

Rychnovsky's Reductive Cyclization Optimized Procedure

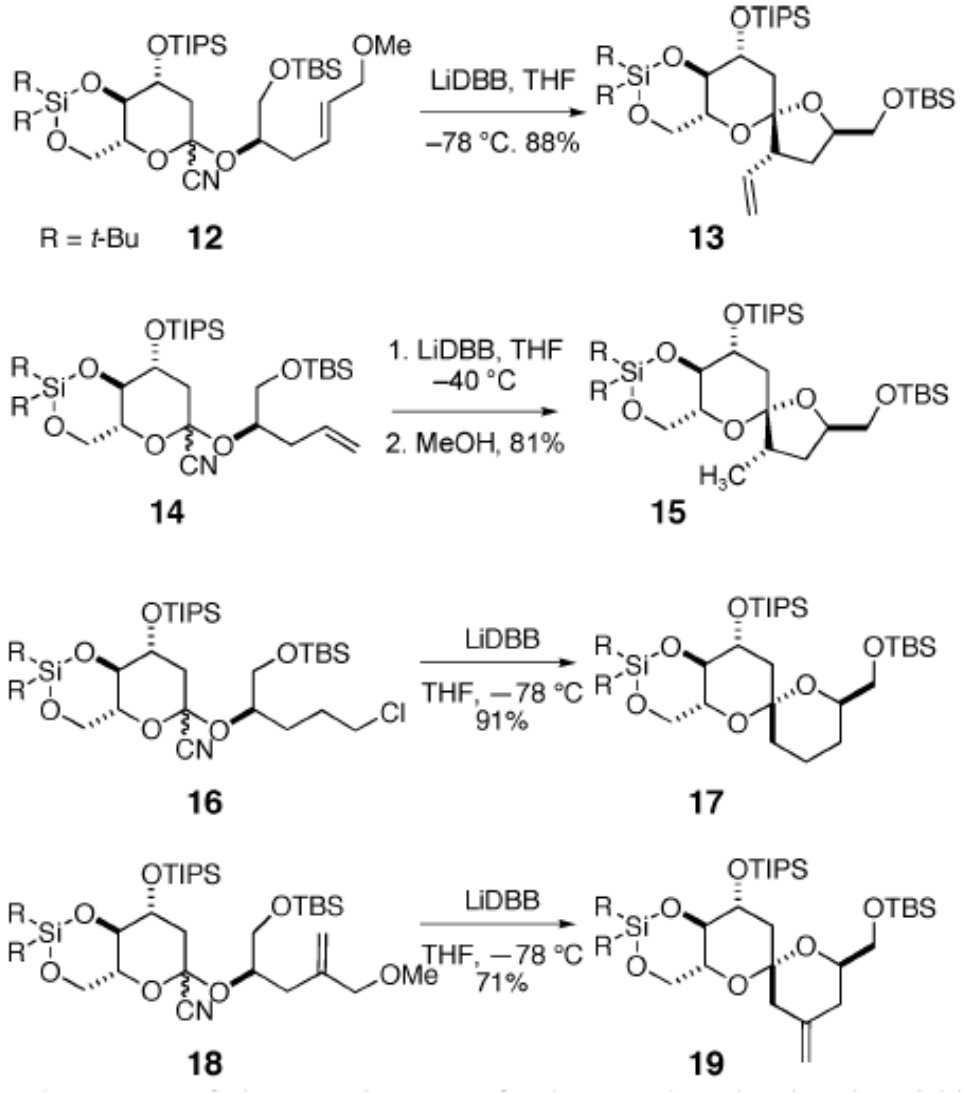






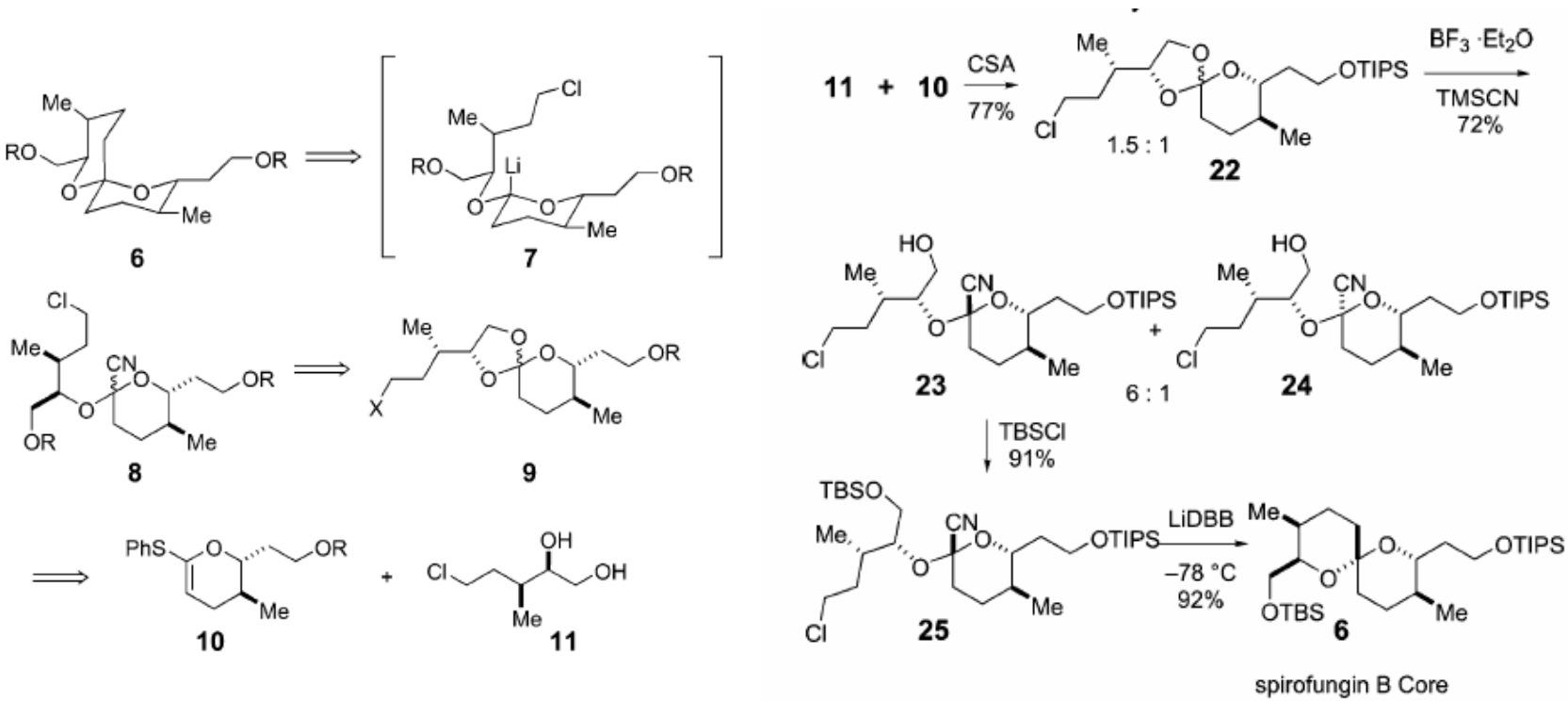
Rychnovsky *et. al. J. Am. Chem. Soc.* **2005**, *127*, 528

Reductive Cyclization: Scope



Rychnovsky *et. al. J. Am. Chem. Soc.* **2005**, *127*, 528

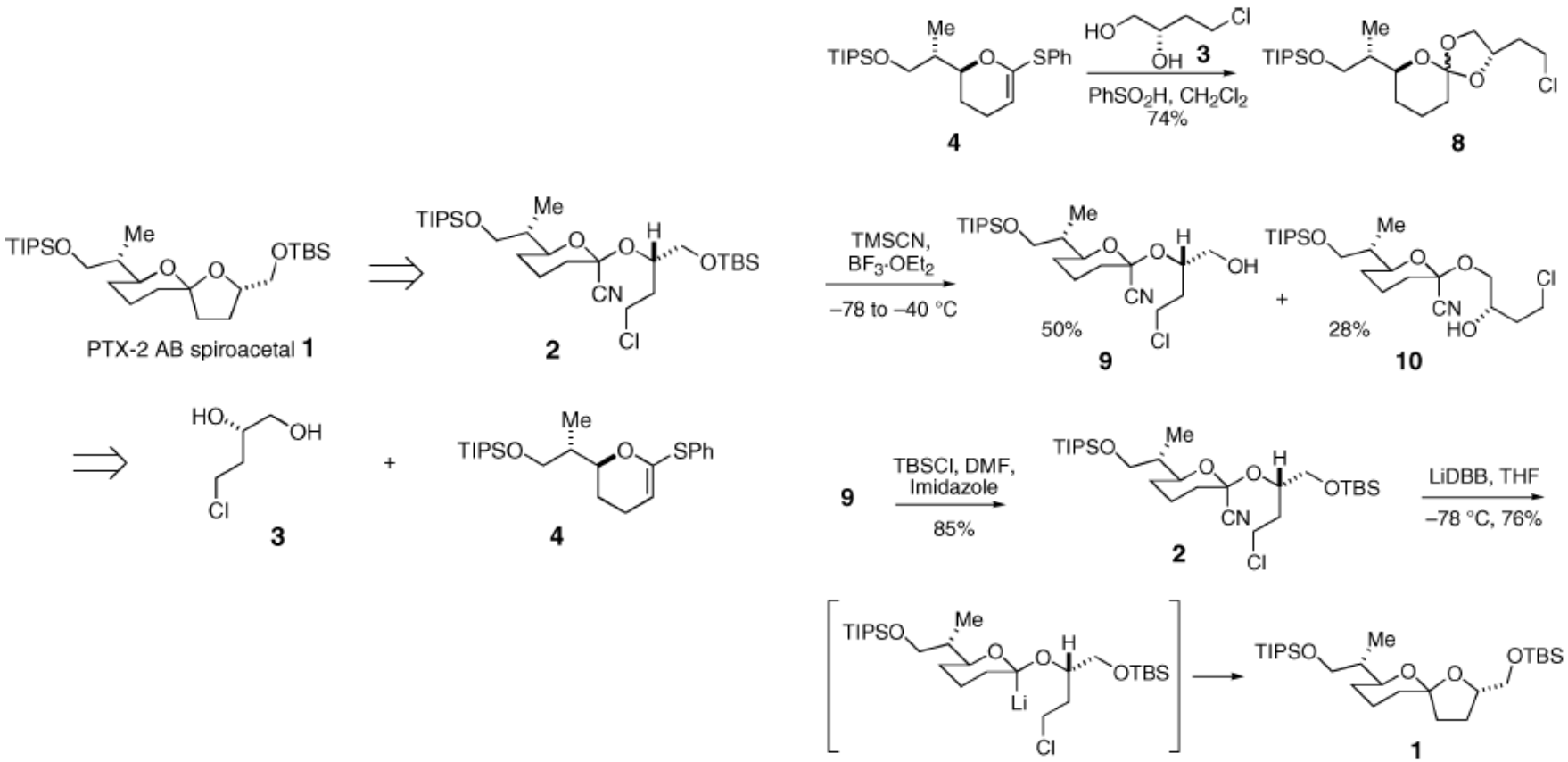
Rychnovsky's Reductive Cyclization: Synthesis of Spirofugin B Core



First key disconnect is the axial C-C bond rather than C-O bond

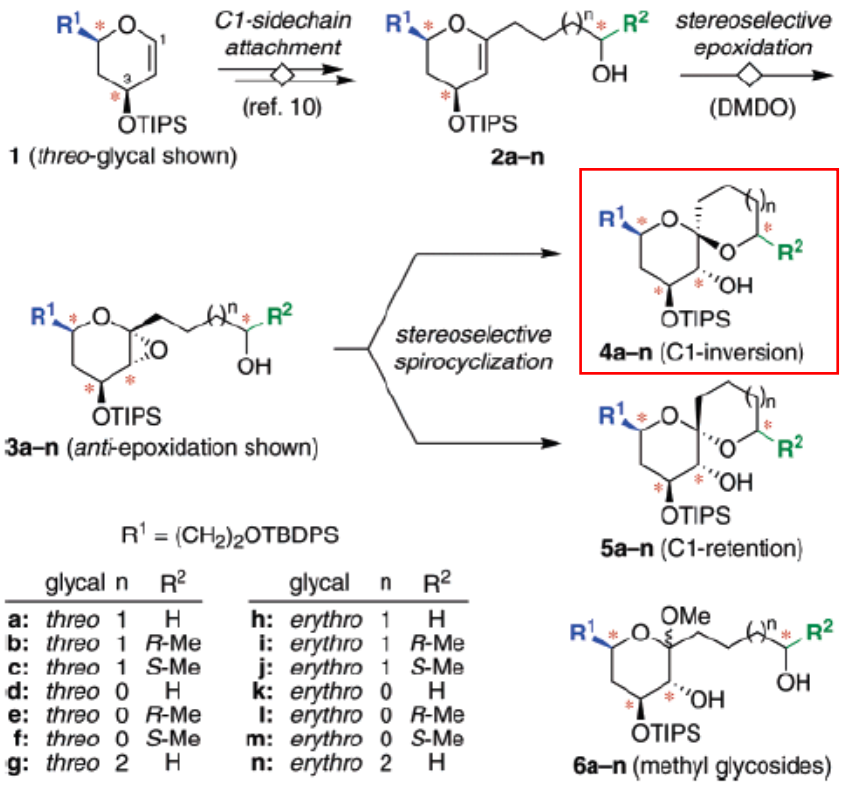
Rychnovsky *et. al. Org. Lett.* **2005**, *7*, 1873

Rychnovsky's Reductive Cyclization: Synthesis of PTX-2 AB Ring



Rychnovsky *et. al. Org. Lett.* **2007**, *9*, 711

Tan's Methanol-Induced Kinetic Spirocyclization



	glycal	n	R^2		glycal	n	R^2
a:	*threo*	1	H	**h:**	*erythro*	1	H
b:	*threo*	1	*R*-Me	**i:**	*erythro*	1	*R*-Me
c:	*threo*	1	*S*-Me	**j:**	*erythro*	1	*S*-Me
d:	*threo*	0	H	**k:**	*erythro*	0	H
e:	*threo*	0	*R*-Me	**l:**	*erythro*	0	*R*-Me
f:	*threo*	0	*S*-Me	**m:**	*erythro*	0	*S*-Me
g:	*threo*	2	H	**n:**	*erythro*	2	H

- Configuration at anomeric carbon is controlled by the initial stereoselective epoxidation
- Surprise! Excess MeOH leads to C1-inversion
- Lower conc. and other alcohols are less effective (more undesired C1-retention spiroketals and methyl glycoside)
- Mechanism probing:

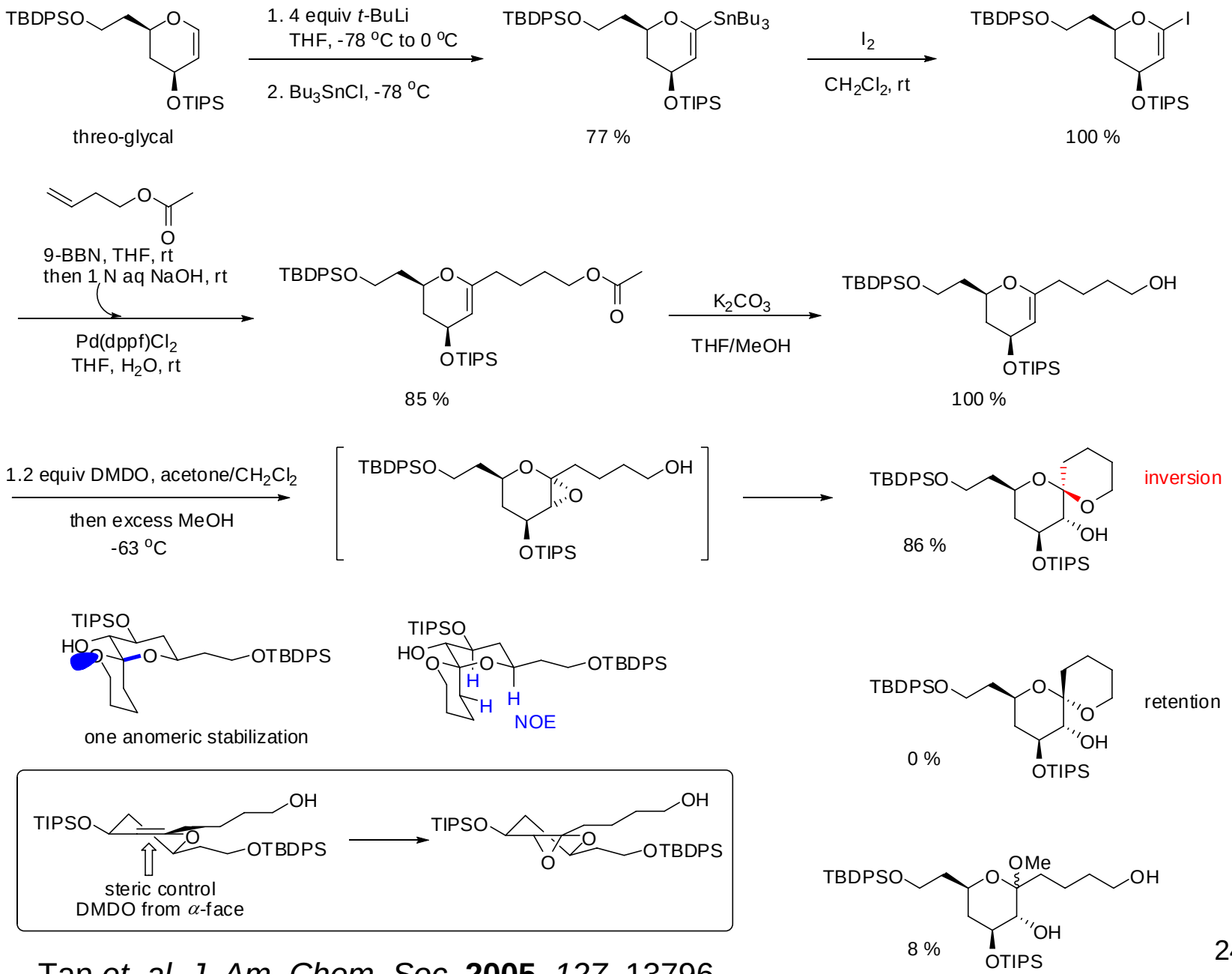
  Under reaction conditions,

  5a ~~→~~ 4a (5a is not intermediate)

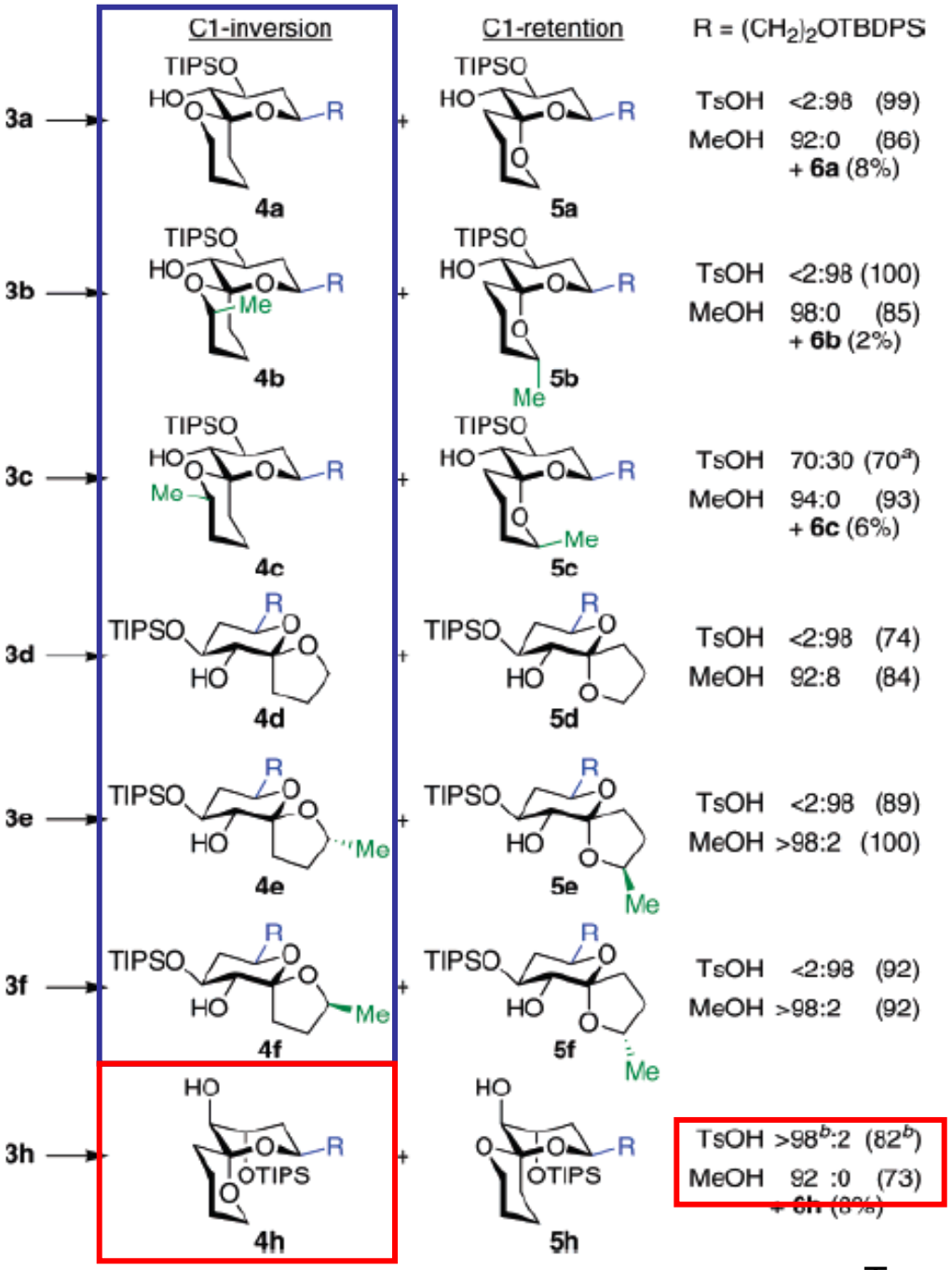
  6a → 6a (6a is not intermediate)

  Polar aprotic solvent did not induce cyclization (MeOH hydrogen bonding catalysis?)

Tan *et. al. J. Am. Chem. Soc.* **2005**, *127*, 13796



Tan *et. al. J. Am. Chem. Soc.* **2005**, *127*, 13796



threo-Glycal series

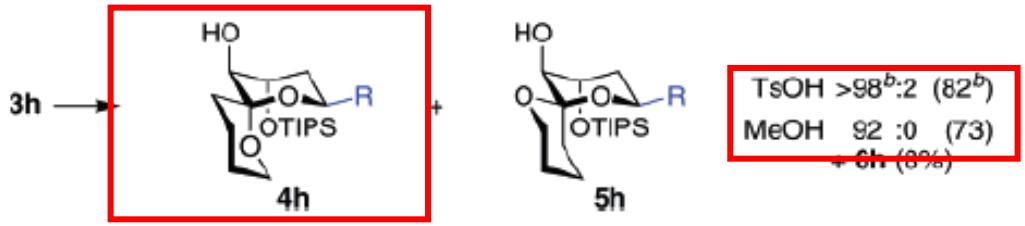
- Contrathermodynamic spiroketal is the kinetic product (MeOH-induced)
- Excellent diastereoselectivity
- High yield
- Access to thermodynamically more stable spiroketal under acidic equilibration (TsOH)

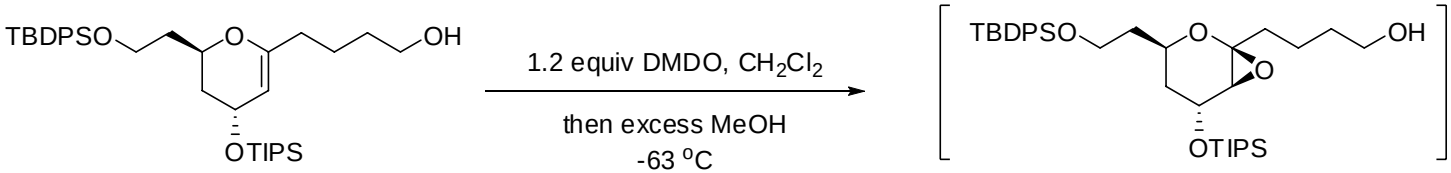
erythro-Glycal series

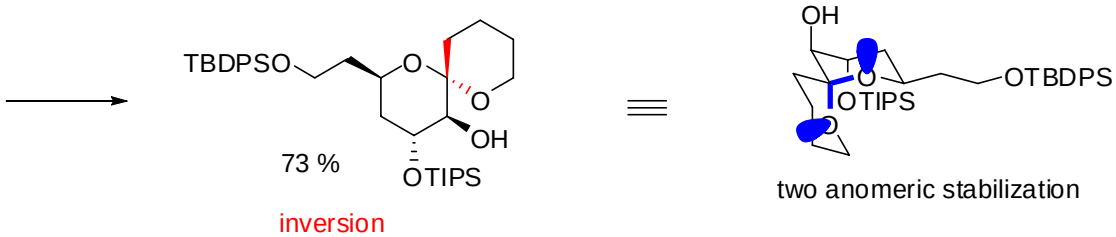
- 4h has two anomeric stabilizations
- Problem: kinetic product is the same as thermodynamic product
- The key is the stereochemistry of epoxidation in the *erythro*-glycal series

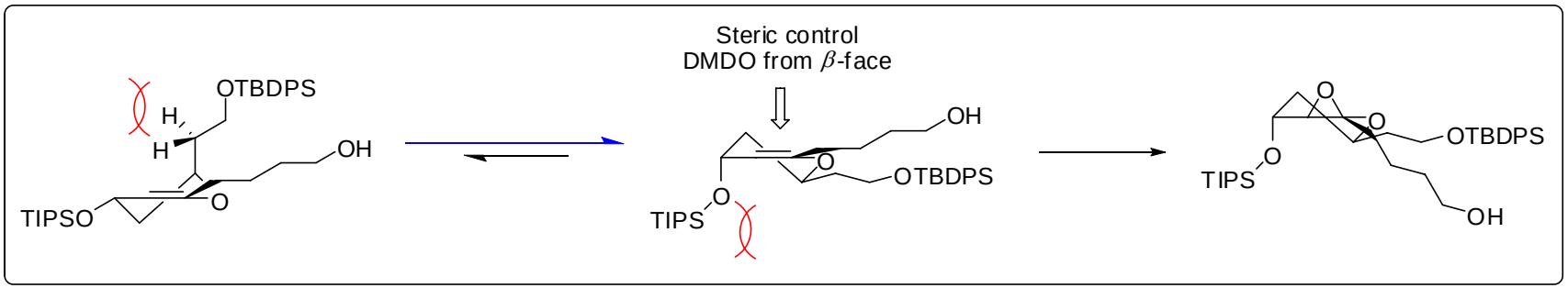
Tan *et. al. J. Am. Chem. Soc.* **2005**, *127*, 13796

Stereochemical Outcome of Epoxidation is Crucial



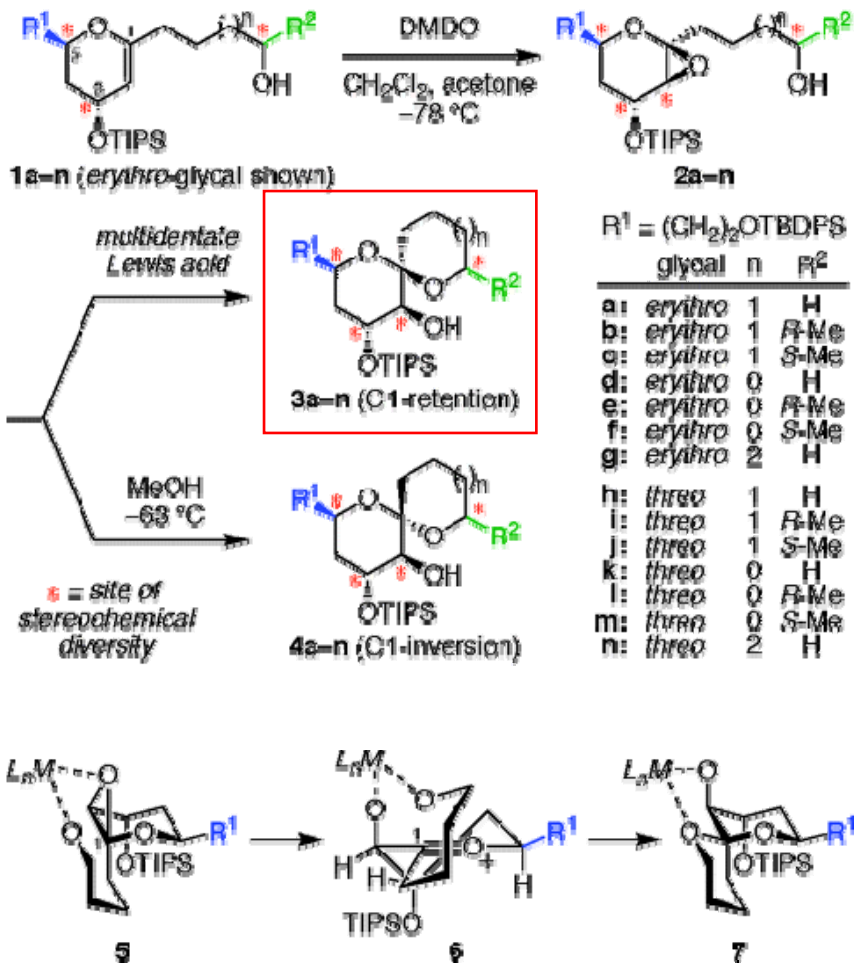






Rentention of configuration at anomeric carbon is required to obtain contrathermodynamic spiroketal

Ti(O*i*-Pr)$_4$-Mediated Kinetic Spirocyclization



- No Lewis Acid 3a:4a = 1:3
- With Ti(O*i*-Pr)$_4$ 3a:4a = >98:2
- Dual roles of Ti(O*i*-Pr)$_4$
  1. activate epoxide
  2. guide the hydroxyl attack
- Reaction condition of the spirocyclization step:
  2 equiv of Ti(O*i*-Pr)$_4$, -78 ^{o}C; then 0 ^{o}C, ≤ 1h
- Probing the mechanism:
  Under reaction conditions, 4a $\not\rightarrow$ 3a (suggesting kinetic control)

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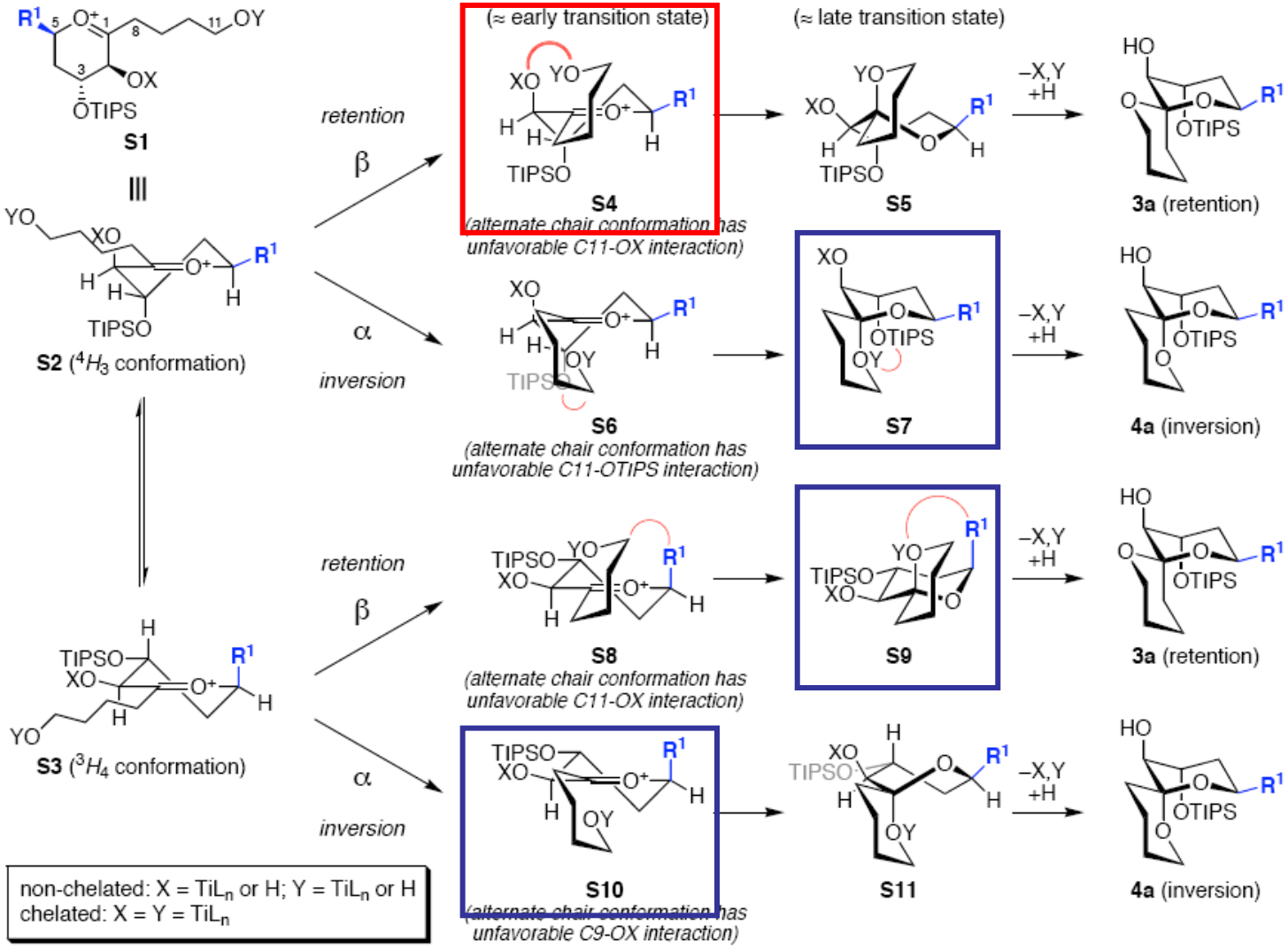
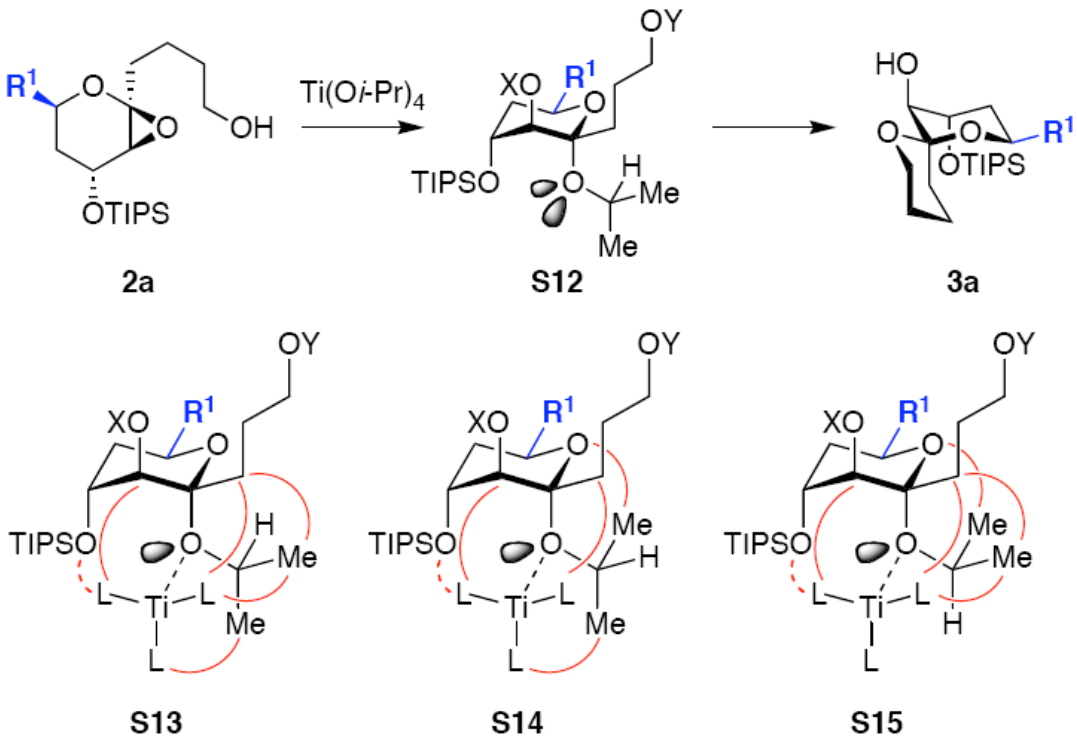
Rationalize Your Results!



Metal chelation through early transition state S4

Double Inversion?



Four unfavoured *syn*-pentane-like interactions in each case

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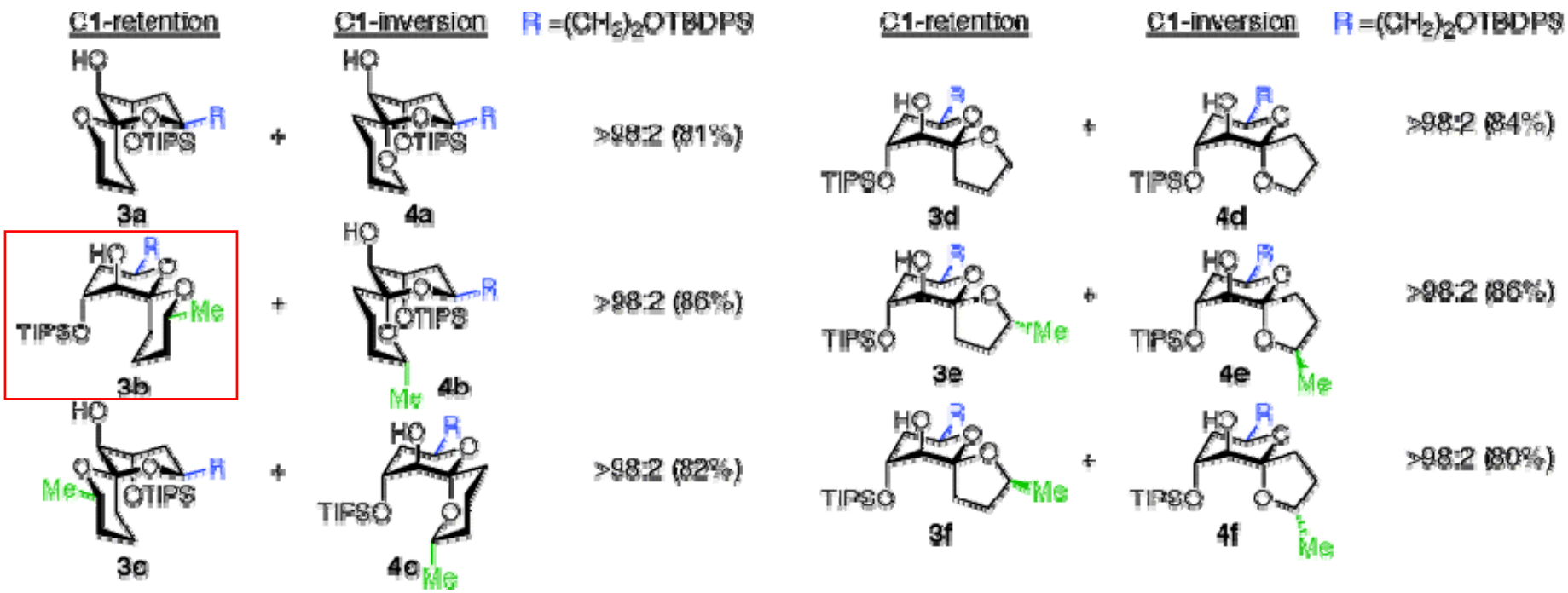
Scope



3b has no anomeric stabilization

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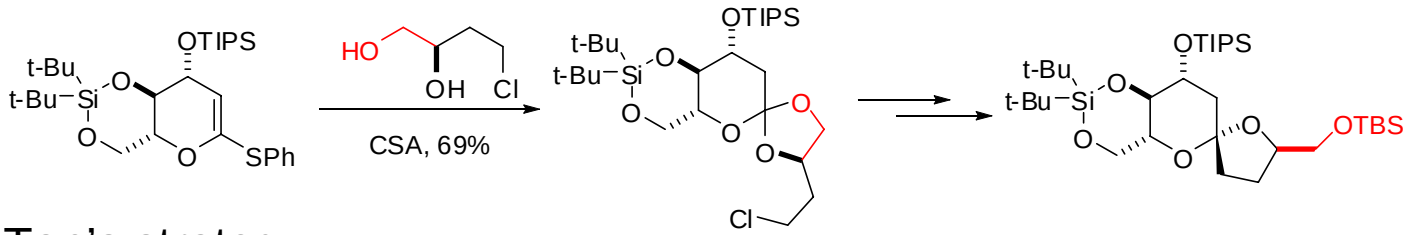
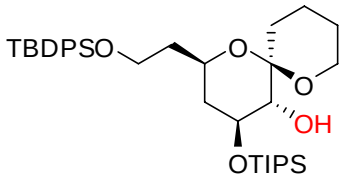
Conclusion

- Stereocontrolled synthesis of spiroketal is still very challenging
- Limited number of approaches with generality and diversity
- Rychnovsky's strategy:
  Has demonstrated its utility in natural product synthesis
  Functional group compatibility with radical?
  Introduces a CH_2OH group



- Tan's strategy:
  Introduces a hydroxyl group



Application to other substitution pattern?
Awaits to be tested in natural product synthesis