A Sakurai-Prins-Ritter Sequence for the Three-Component Diastereoselective Synthesis of 4-Amino Tetrahydropyrans

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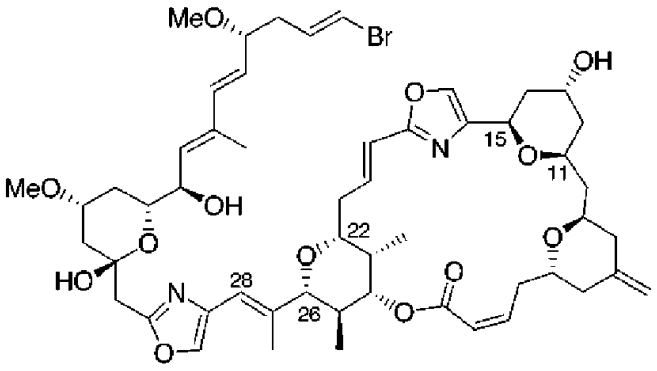
Colorado State University

J. Am. Chem. Soc. **2006**, *128*, 16480-16481.

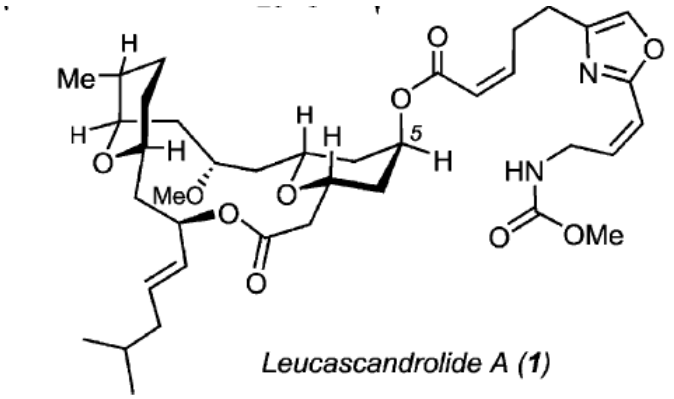
Current Literature Presentation on Jan. 6th, 2007
Shuli Mao

Tetrahydropyrans as Backbones of Natural Products



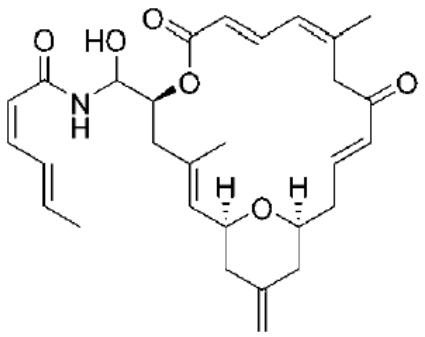
(+)-Phorboxazole A (1)

Potent antimitotic agents
Mean GI50 value: 1.58 X 10-^{9} M
against NCI panel of 60 tumor cell lines



Leucascandrolide A (1)

Potent cytotoxicity against
KB and P388 tumor cell lines



(-)-Zampanolide

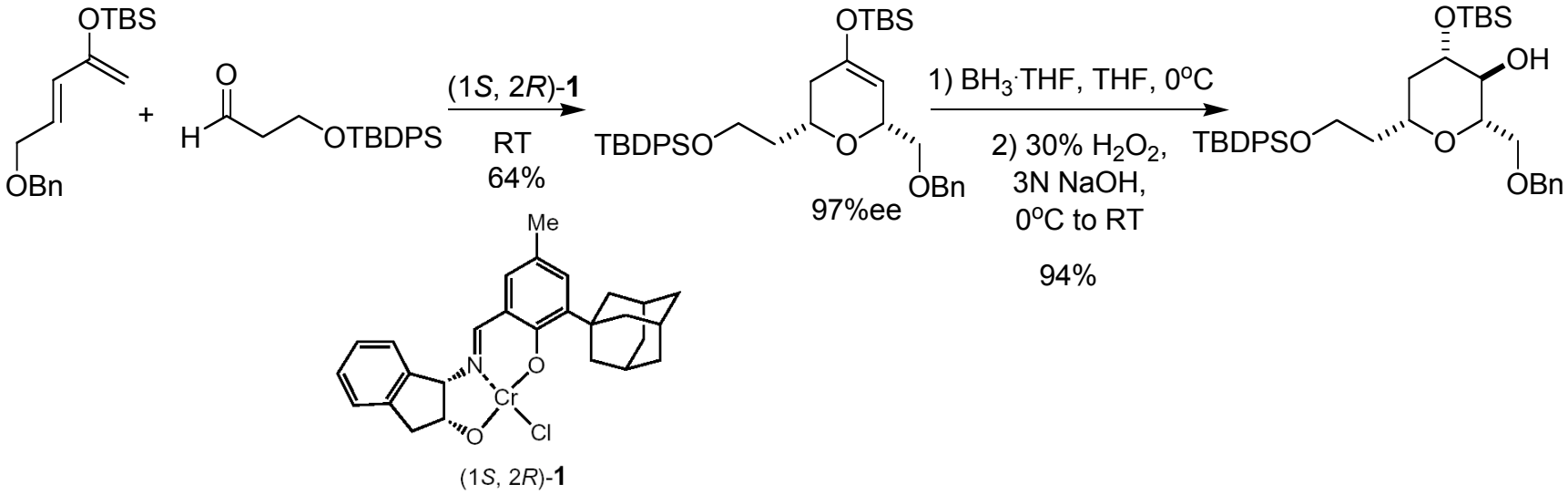
IC_{50}=1-5 nM against several tumor cell lines

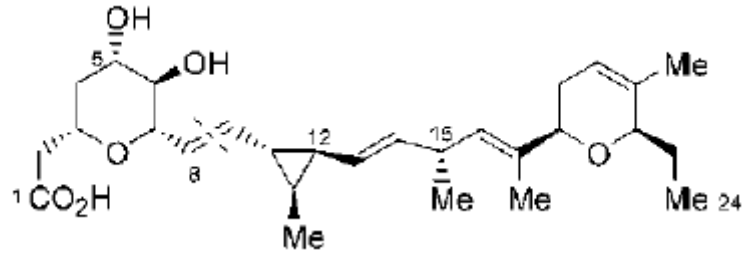
Approaches to Tetrahydropyran Skeleton

- Hetero-Diels-Alder Cyclizations (C-C and C-O formation)
- Cyclizations onto Epoxides (C-O formation)
- Cyclizations onto Oxocarbenium Ions (C-C formation)
- Other Methods

Review: Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045.

[4+2] Hetero-Diels-Alder Approach

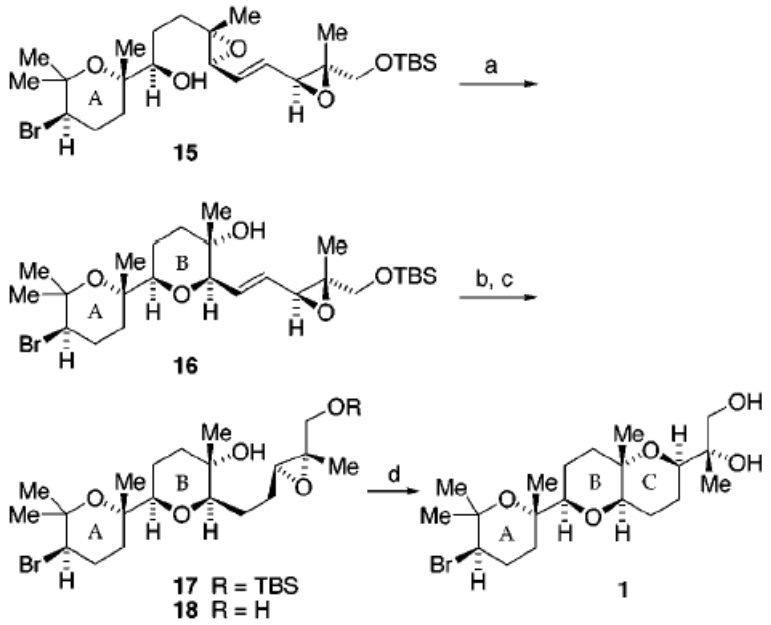




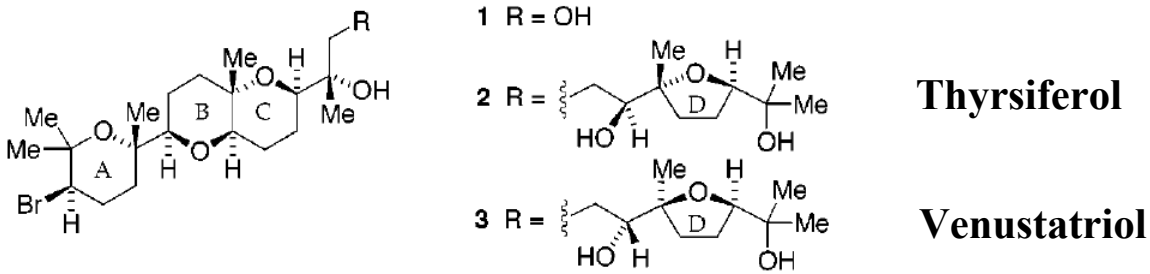
(+)-Ambruticin

Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.

Cyclizations onto Epoxides



[a] (a) cat. PPTs, CH_2Cl_2, 0 °C, 1 h (70%). (b) H_2NNH_2, H_2O_2, EtOH, 30 h (70%). (c) Bu_4NF, THF (90%). (d) $Ti(O\text{-}i\text{-}Pr)_4$, toluene, 50 °C, 2 h (58%).

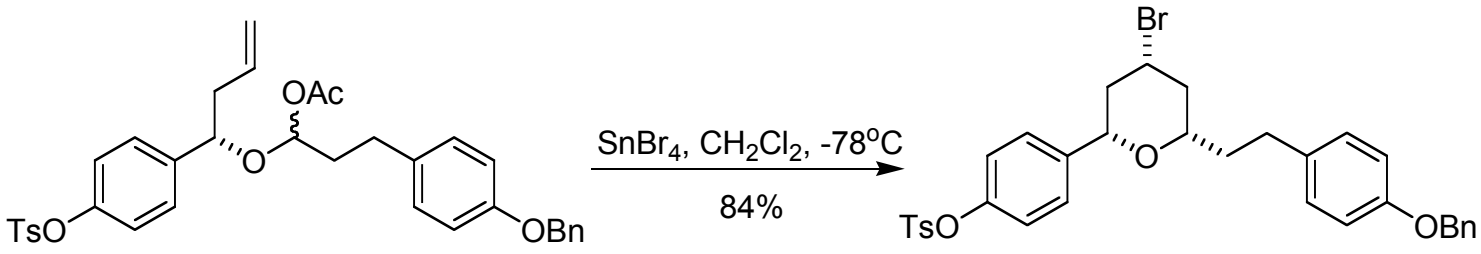


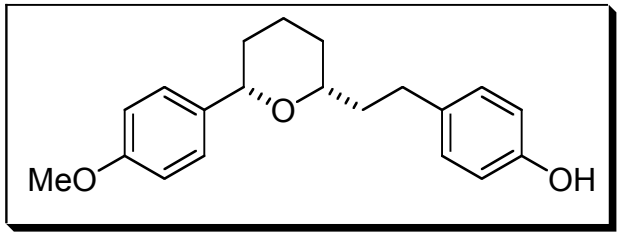
Thyrsiferol

Venustatriol

McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593.

Cyclizations onto Oxocarbenium Ions

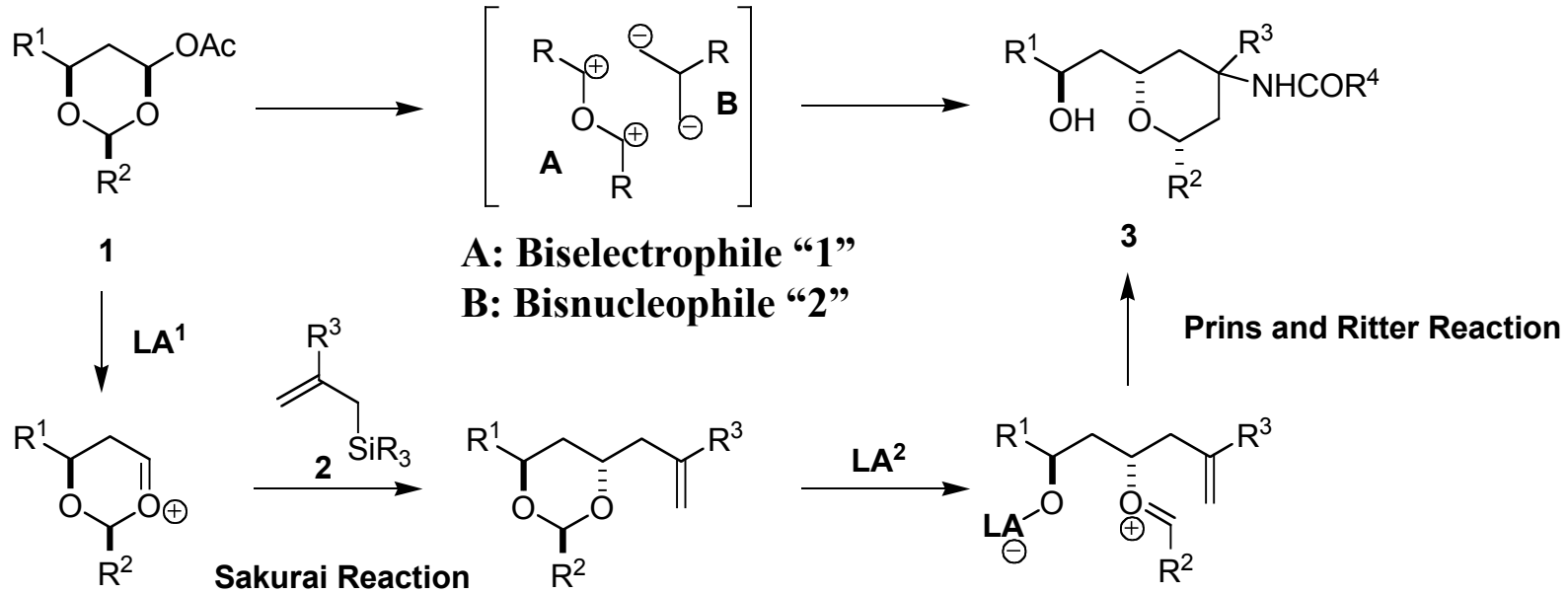




(-)-Centrolobine

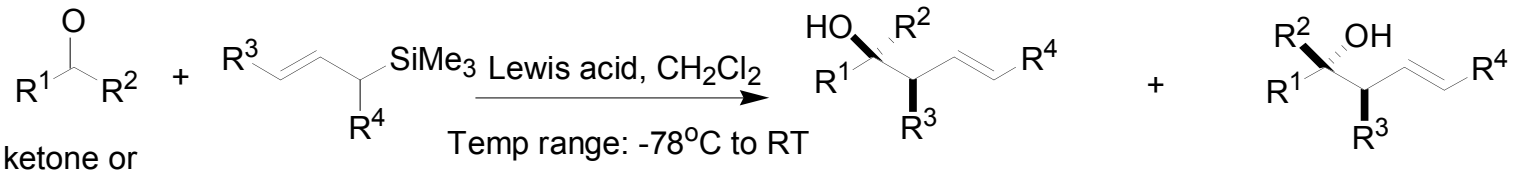
Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919.

[3+3] Cyclocondensation Approach



Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480.

Sakurai Reaction



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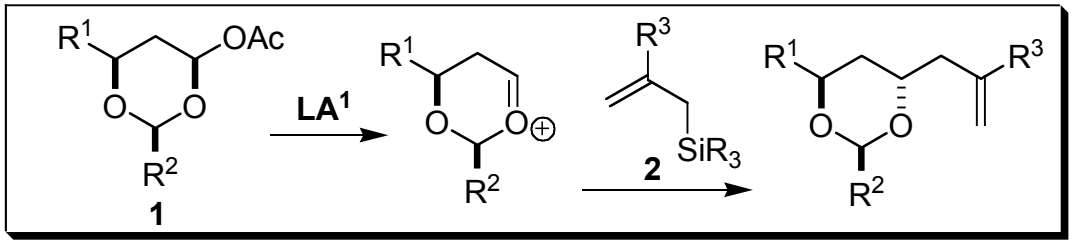
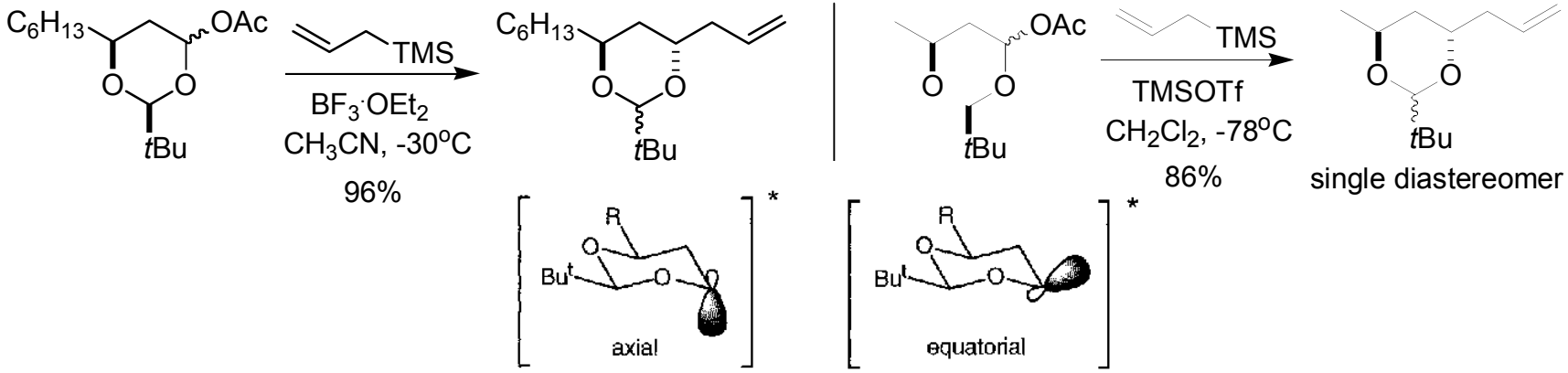


1,3-*anti* relationship

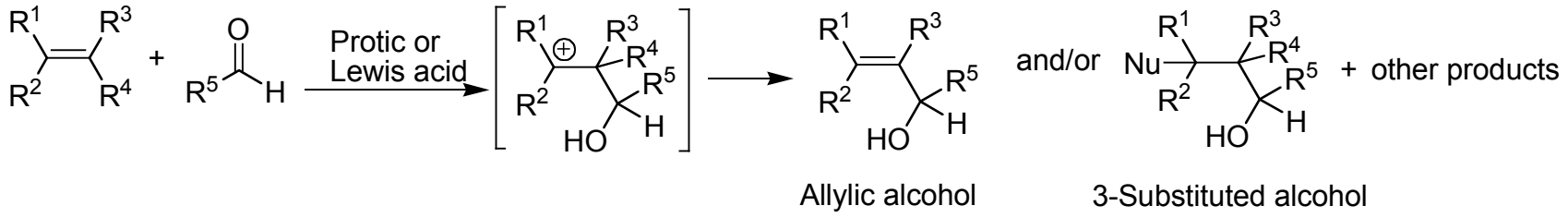


favored

Rychnovsky, S. D.; Skalitzky, D. J. *Synlett* **1995**, 555.

Boons, G.-J.; Eveson, R.; Smith, S.; Stauch, T. *Synlett* **1996**, 536.

Prins Reaction



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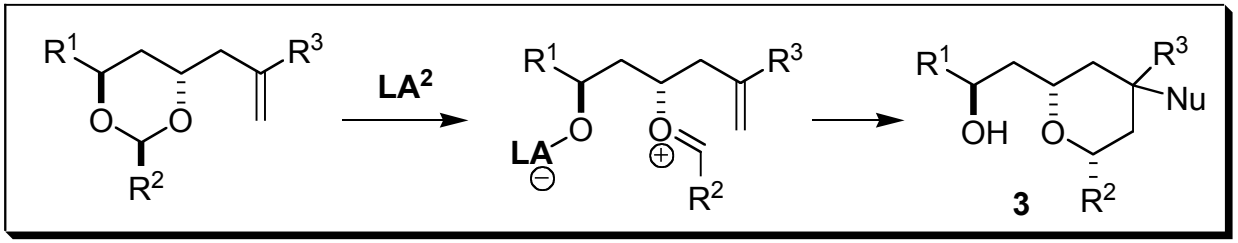
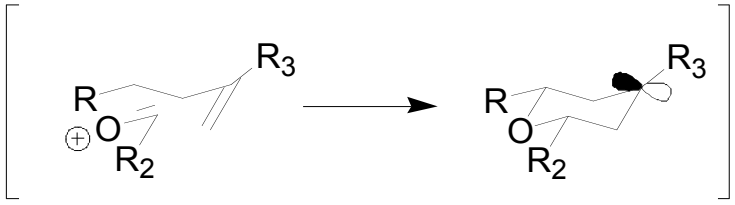
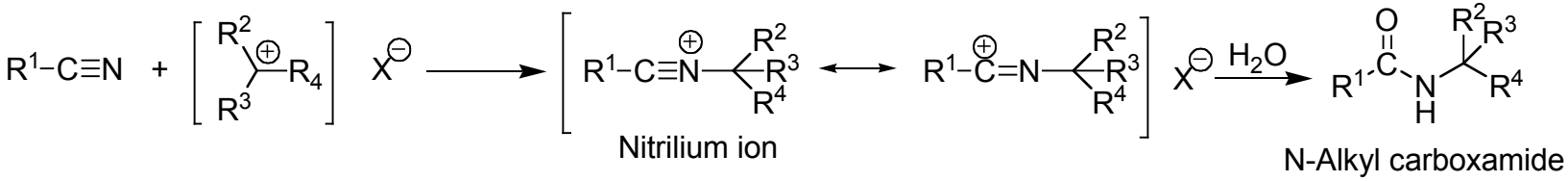


Rational for 2,6-***cis*** tetrahydropyran formation:



Ritter Reaction



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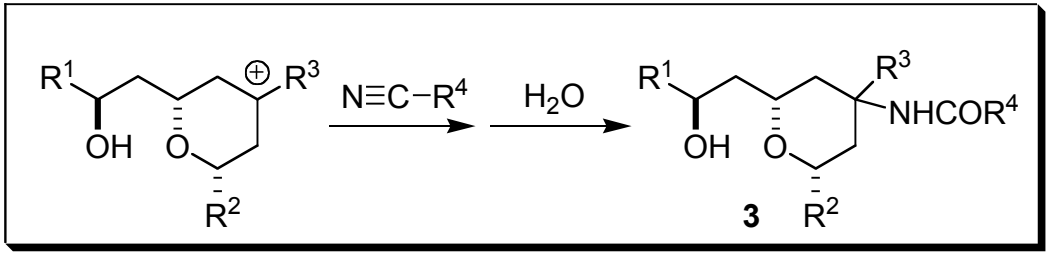
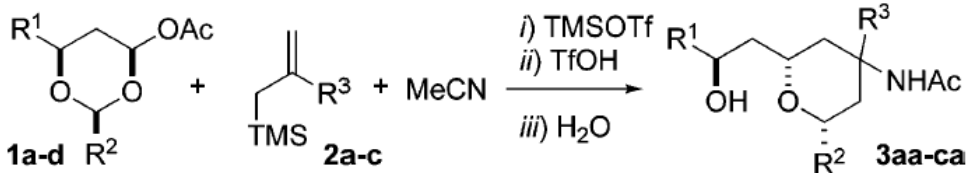
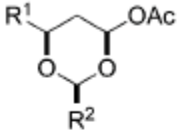
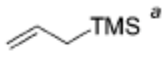
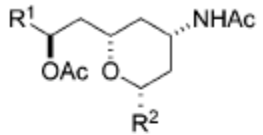
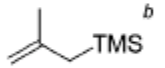
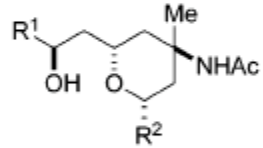
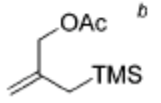
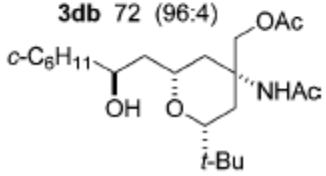


Stereochemistry depends on **R³**

Sequential Sakurai-Prins-Ritter Reactions



Entry	1,3-Dioxane	Allyl silane	Product, yield (%) (dr)
		 [a] **2a**	
1	**1a**: R^1= *c*-C_6H_{11}; R^2=*t*-Bu		**3aa** 79 (97:3)
2	**1b**: R^1= *c*-C_6H_{11}; R^2=*n*-Pr		**3ba** 80 (97:3)
3	**1c**: R^1= $Ph(CH_2)_2$; R^2=*t*-Bu		**3ca** 77 (97:3)
4	**1d**: R^1= $Ph(CH_2)_2$; R^2=*n*-Pr		**3da** 75 (98:2)
5	**1e**: R^1= $PivO(CH_2)_2$; R^2=$(CH_2)_3Cl$		**3ea** 59 (90:10)
		 [b] **2b**	
6	**1a**		**3ab** 88 (97:3)
7	**1b**		**3bb** 71 (97:3)
8	**1c**		**3cb** 80 (96:4)
9	**1d**		**3db** 72 (96:4)
		 [b] **2c**	
10	**1a**		**3ac** 61 (99:1)[c]

[a] Procedure A: (i) TMSOTf (1 equiv), −45 °C; (ii) TfOH (2 equiv), −45 to −15 °C; (iii) Ac_2O, −15 to 0 °C, CH_2Cl_2/MeCN (1:1). [b] Procedure B: (i) TMSOTf (1 equiv), −45 °C; (ii) TfOH (2 equiv), −45 to 0 °C;(iii) $NaHCO_3$, MeCN; see Supporting Information for details. [c] Tertiary alcohol **8** was isolated in 8% yield as a 1:1 mixture of diastereomers at the 4-position.

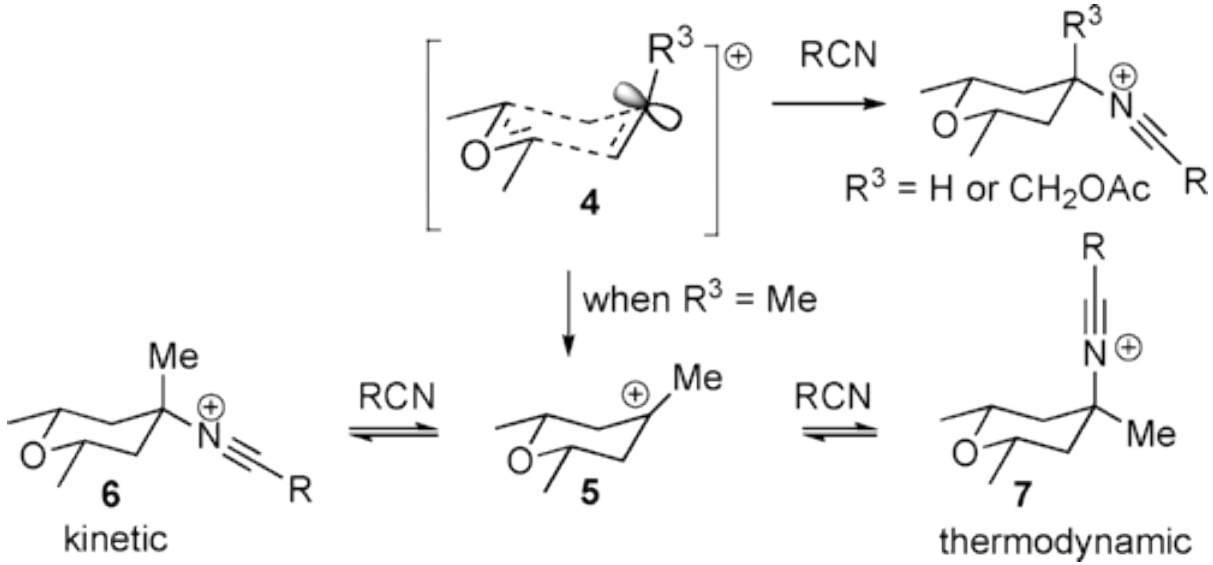
Stereochemistry Rational

Alder's model:

1) THP cation **4** has an increased stability relative to the open-chain oxocarbonium ion due to delocalization. The calculated optimal geometry for delocalization places the H atom at **C4** in a pseudoaxial position.

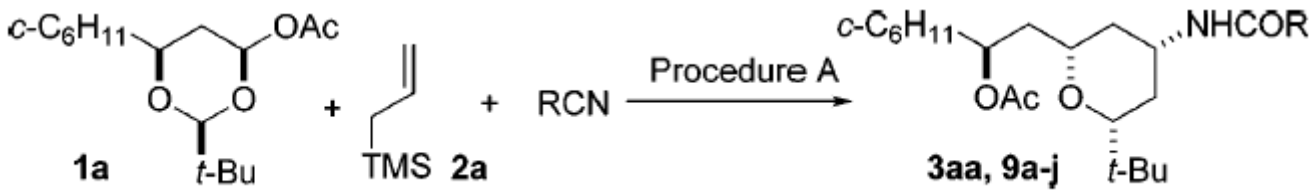
2) 4-Methyl substituted THP cation **5** is much more stable than **4**.

3) Destabilization of the intermediate tertiary cation was observed if 4-methyl was replaced by 4-acetoxymethyl substituent.



Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960.
Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480.

Nitriles Scope

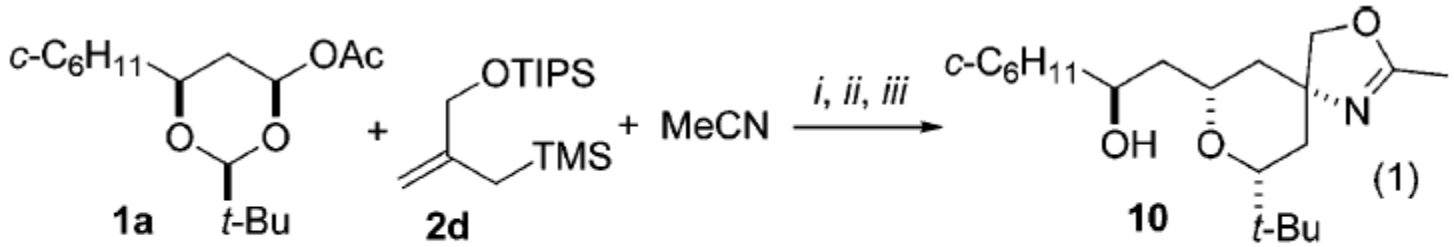


entry	product	R	dr	yield (%)
1	**3aa**	Me	97:3	79
2	**9a**	Et	96:4	84
3	**9b**	*i*-Pr	94:6	81
4	**9c**	*t*-Bu	95:5	71
5	**9d**	CH_2F	99:1	83
6	**9e**	CH_2Cl	97:3	79
7	**9f**	CH_2Br	95:5	89
8	**9g**	CH_2OMe	94:6	66[a]
9	**9h**	vinyl	98:2	75[a]
10	**9i**	allyl	95:5	42
11	**9j**	Ph	93:7	77

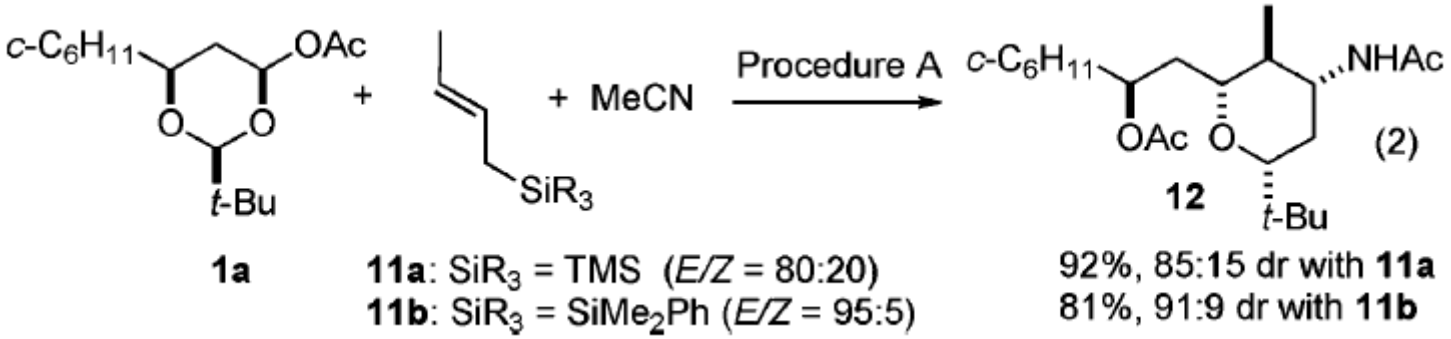
[a] Isolated yield after aqueous workup and acetylation of unpurified reaction mixture with Ac_2O/Py/DMAP.

Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480.

Extension of Sakurai-Prins-Ritter Reactions



i) TMSOTf, CH_2Cl_2, -78 °C; *ii*) MeCN, TfOH, -45 to 0 °C; *iii*) $NaHCO_3$



Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480.

Conclusions

- Another THP formation method was developed using a sequential Sakurai-Prins-Ritter Reactions
- Reactions involved are all diastereoselective
- The introduction of the amide made further functionalization possible
- Up to four new stereocenters may be controlled from a single stereocenter present in the starting material