

Samarium(II) Iodide Mediated Cyclizations in Natural Product Synthesis

The Kagan Reagent Part II

An Evans Group Afternoon Seminar

Keith Fandrick

Seminar outline:

- Introduction and Background
- Intramolecular Barbier Reaction
- Intramolecular Reformatsky Reaction
- Radical Alkene and Alkyne Cyclizations
- Carbonyl-Alkene Reductive Cyclizations
- Intramolecular Pinacol Couplings
- Intramolecular Reductive Couplings of Carbonyls and Hydrazones
- Total Synthetic endeavors utilizing multiple SmI_2 cyclizations

Primary References

- Procter, D. J. *Chem. Rev.* **2004**, 3371.
Krief, A. *Chem. Rev.* **1999**, 745.
Molander, G. *Chem. Rev.* **1996**, 307.
Molander, G. *Chem. Rev.* **1992**, 29.
Curran, D. R. *Synlett* **1992**, 943.
Rajapakse, H. *Evans Group Seminar* **1998**

SmI₂ Discovery and Background

Introduction

- Samarium diiodide was first reported by Kagan in 1977. Kagan reported the preliminary deoxygenation of epoxides and sulfoxides, chemoselective reduction of aldehydes in the presence of ketones, dehalogenations, and couplings between ketones and alkyl halides. (Kagan, H. B. *Nouv. J. Chim.* **1977**, 5. Kagan, H. B. *J. Am. Chem. Soc.* **1980**, 2693)
- Samarium diiodide is the subject of >20 reviews and >850 publications.
- Samarium diiodide is commercially available as an anhydrous powder (5g, \$185) or as a 0.1 M solution in THF (100mL, \$32). (Aldrich catalog **2003-2004**)
- Samarium diiodide can be prepared from Sm metal and CH₂I₂, ICH₂CH₂I, or I₂.
- Reactions are generally performed with an excess of samarium diiodide, degassed reagents and solvents, and in dry THF containing an antioxidant.
- Catalytic amounts of SmI₂ can be used with the addition of mischmetall (alloy of lanthanides [La 33%, Ce 50%, Nd 12%, Pr 4%, Sm and other lanthanides 1%]) to regenerate SmI₂. The use of catalytic amounts of Sm(II) and mischmetall is more cost effective. The alloy is unreactive to carbonyls and simple to use.
- The normal work-up usually requires acidic conditions. However, Rochelle's salt and potassium carbonate can be used for acid sensitive substrates. (Little D. *J. Org. Chem.* **1996**, 3240)
- THF appears to be the proton source for the termination of radical cascades. If a second reduction with additional equivalent of SmI₂ occurs the proton source is generally the alcoholic co-solvent. (Curran D. P. *J. Am. Chem. Soc.* **1988**, 5046)
- Samarium diiodide chemoselectively reduces: organic halides, carbonyls, α -hetero-substituted carbonyls, cyclopropyl ketones, epoxides, amine oxides, sulfoxides, phosphine oxides, sulfones, sulfonates, nitro, nitroso, and azo compounds, allyl acetates, and isoxazoles.

SmI₂ Reduction Potential

-Samarium diiodide is a polyvalent single electron reducing agent.

-The reduction potential (E°) of Sm⁺²/Sm⁺³ in water is -1.55 V compared to Na⁰/Na⁺¹ of -2.77 V.

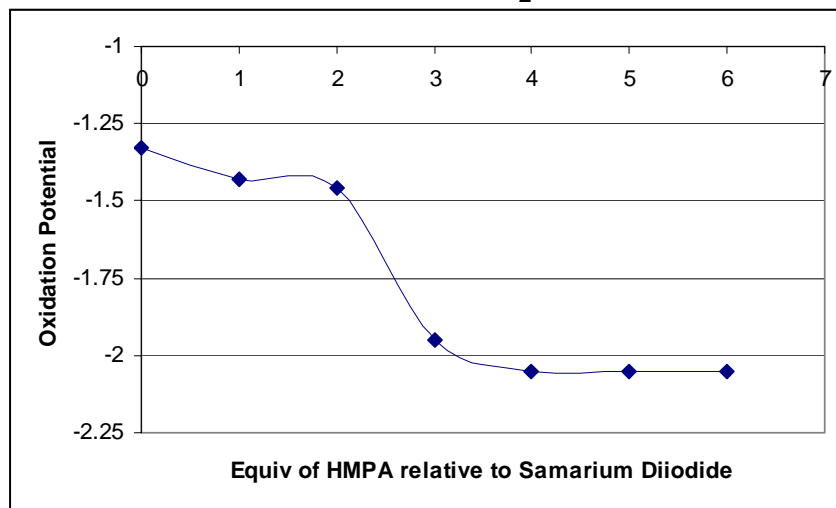
-The reduction potential of SmI₂ can be increased by the addition of HMPA, and LiBr or LiCl.

-The addition of transition metal increases the rate of several SmI₂ reactions.
(Kagan, H. B. *Synlett* **1996**, 633)

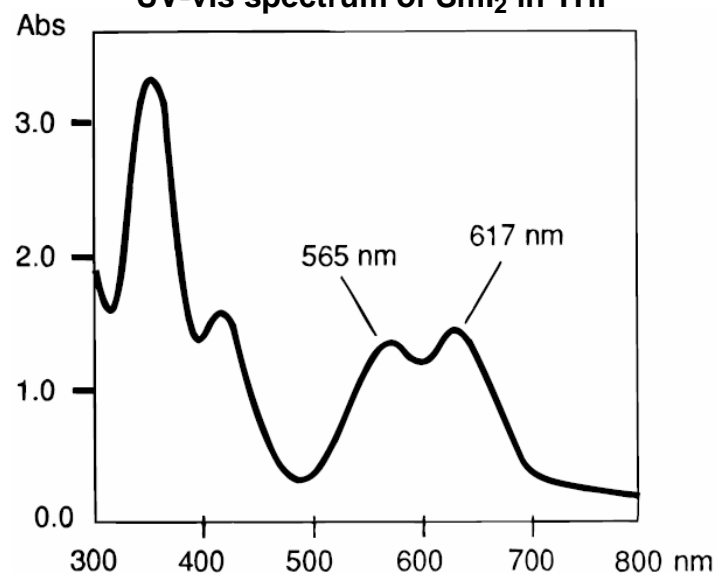
-Changes in protic solvents can alter the rates of SmI₂ mediated reactions and in some cases alter the mechanism.

-Visible light increases the reduction potential of SmI₂. (Ogawa, A. *J. Am. Chem. Soc.* **1997**, 2745)

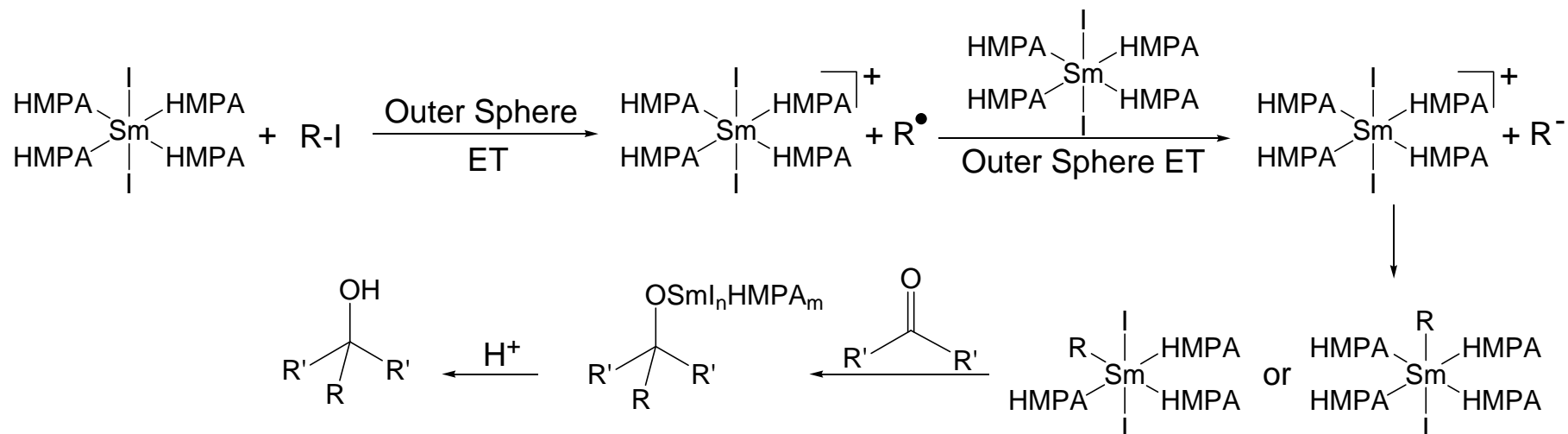
Effects on the E° of SmI₂ with HMPA



UV-vis spectrum of SmI₂ in THF



SmI₂ Barbier Reaction Basic Mechanism



-Reduction of the ketone followed by substitution of alkyl-halide with ketyl-radical ruled out by Kagan, because the use of chiral alkyl-halides leads to racemic products.

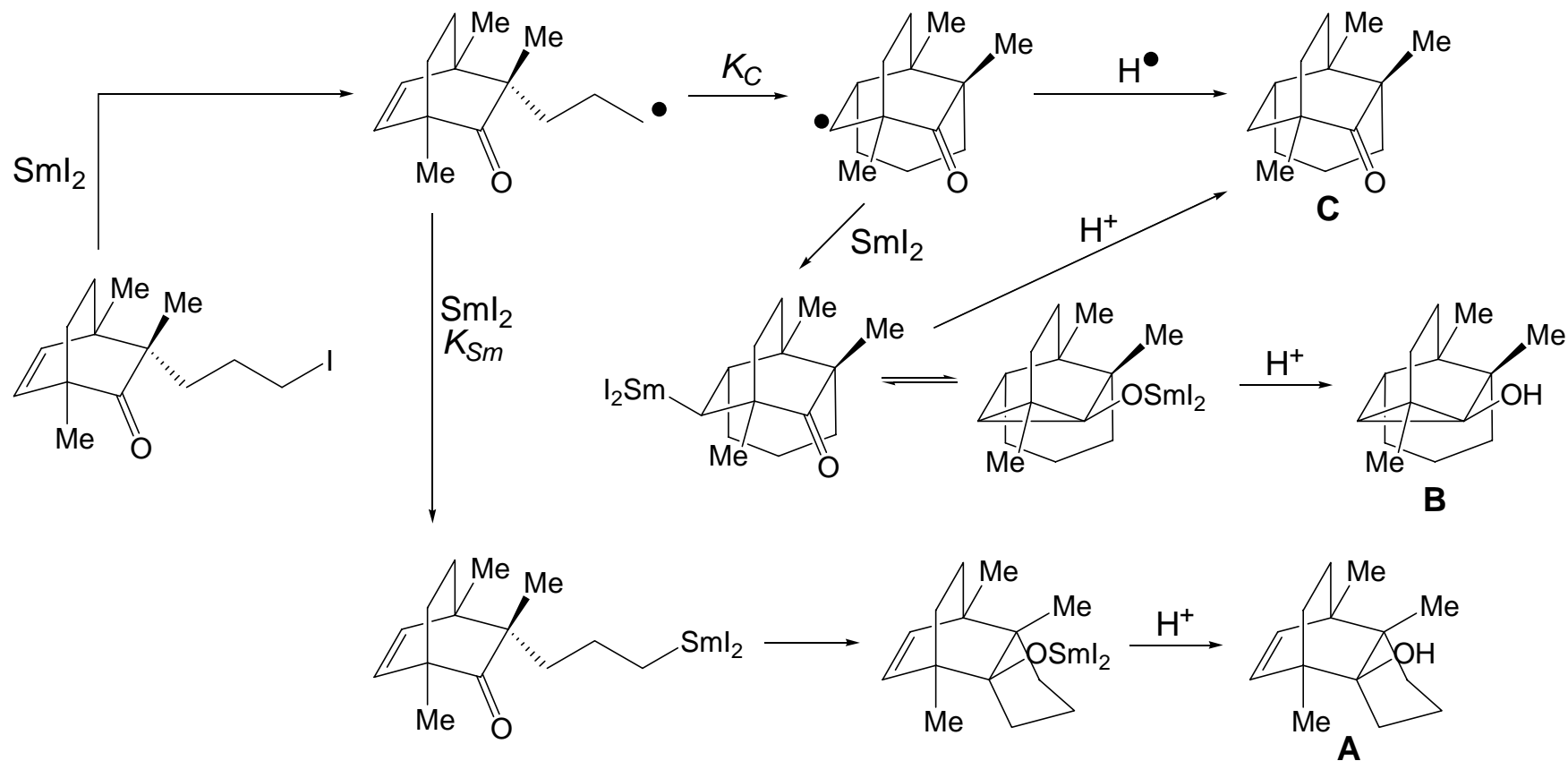
-The replacement of HMPA with LiBr predominately leads to the Pinacol product via inner sphere electron transport/reduction of the ketone via formation of SmBr₂.

-Replacement of HMPA with HMDS leads to the formation of [Sm(HMDS)₂]₂, which has a redox potential inbetween SmI₂ and [Sm(HMPA)₆]₂. [Sm(HMDS)₂]₂ reacts faster with alkyl halides and ketones via change in mechanism towards an inner sphere ET process.

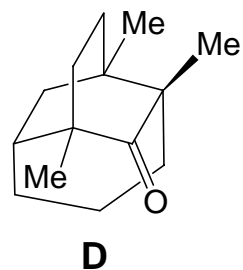
- Molander, G. *J. Am. Chem. Soc.* **1987**, 6556.
 Curran, D. P. *Synlett* **1992**, 943.
 Flowers, R. A. *Org. Lett.* **1999**, 2133.
 Flowers, R. A. *J. Am. Chem. Soc.* **2000**, 7718.
 Flowers, R. A. *J. Am. Chem. Soc.* **2002**, 6895.
 Flowers, R. A. *J. Am. Chem. Soc.* **2002**, 14663.
 Flowers, R. A. *J. Am. Chem. Soc.* **2004**, 6891.

Intramolecular Sml₂ Barbier Reactions

Basic Mechanism



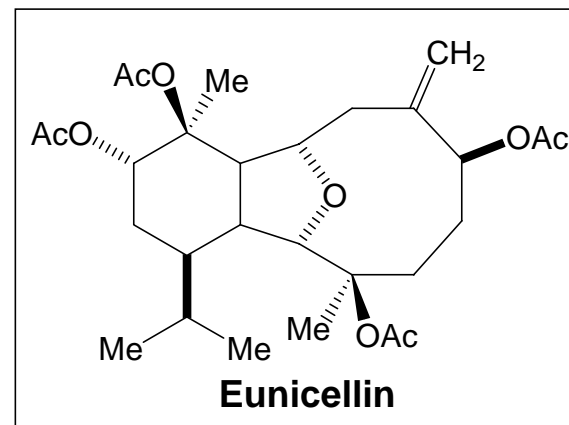
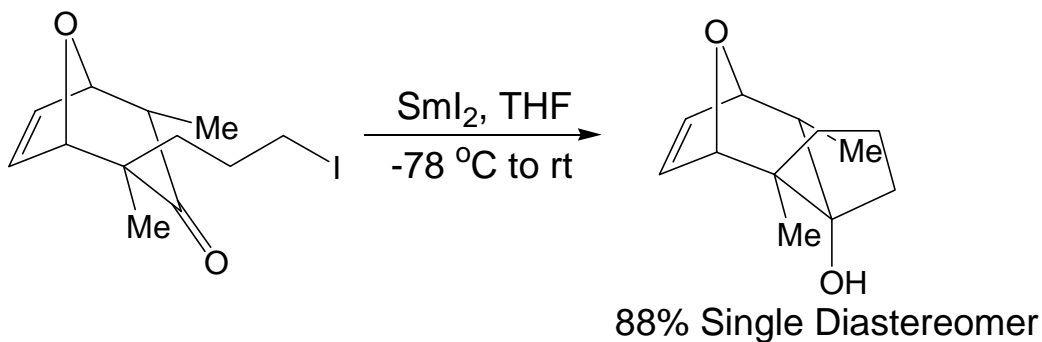
Sml ₂ (M)	A	B	C	D
0.01	64%	21%	11%	4%
0.03	42%	42%	11%	5%
0.05	27%	55%	13%	5%
0.07	20%	59%	15%	6%



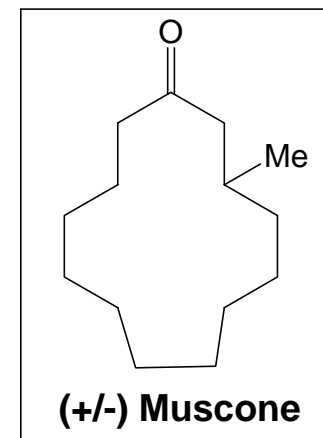
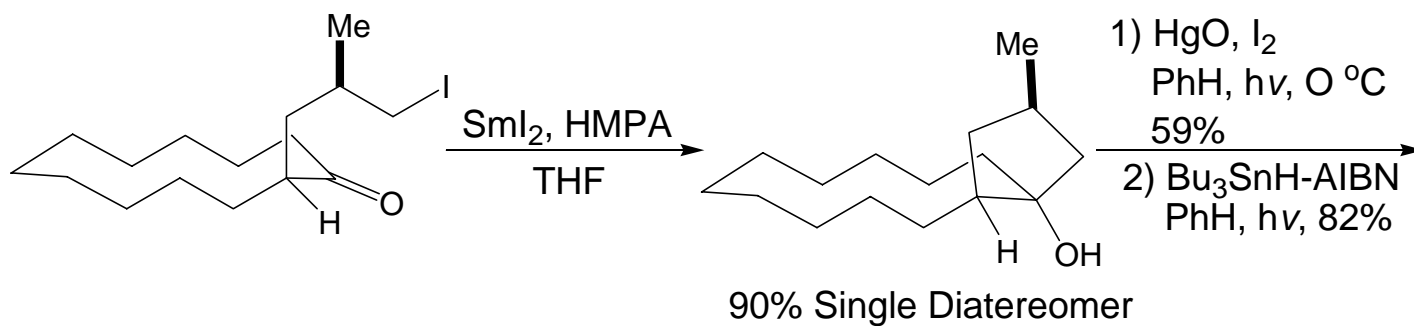
Reactions performed with 2 equiv of Sml₂ and 20 equiv of HMPA

Curran, D. P. *Tetrahedron* **1997**, 9023
 Krief, A. *Chem. Rev.* **1999**, 745
 Molander, G. A. *J. Org. Chem.* **1991**, 4112

Intramolecular SmI_2 Barbier Reactions Eunicellin and Muscone

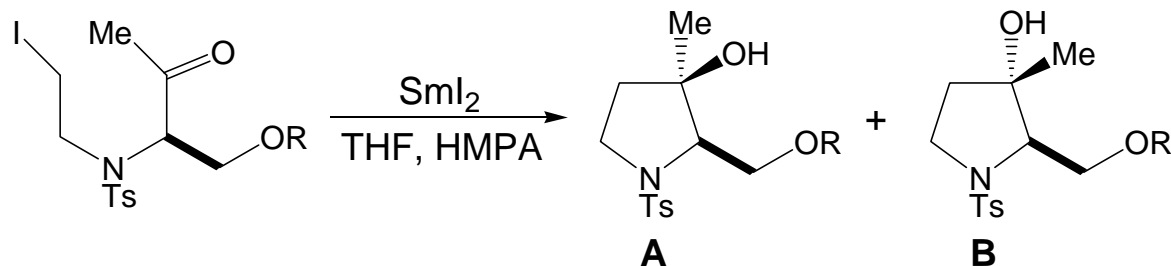


Hoffman, M. R. *Tetrahedron* **1997**, 4331

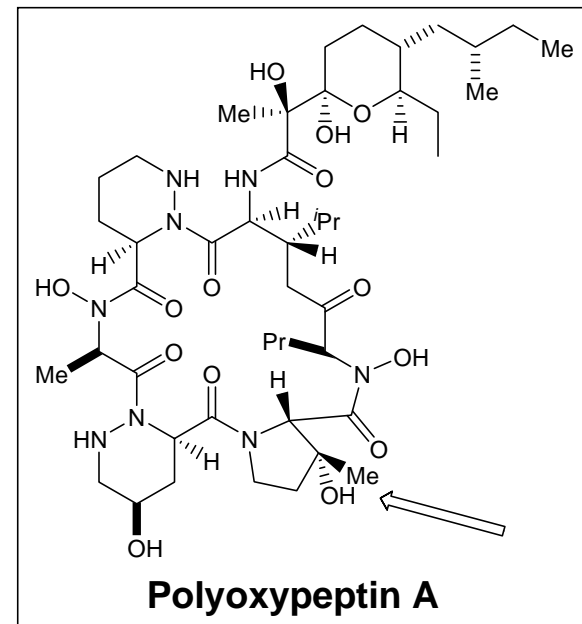


Suginome, H. *Tetrahedron* **1987**, 3963

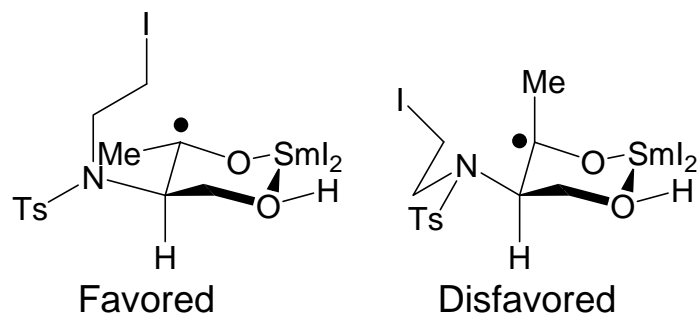
Intramolecular SmI₂ Barbier Reactions Polyoxypeptin A



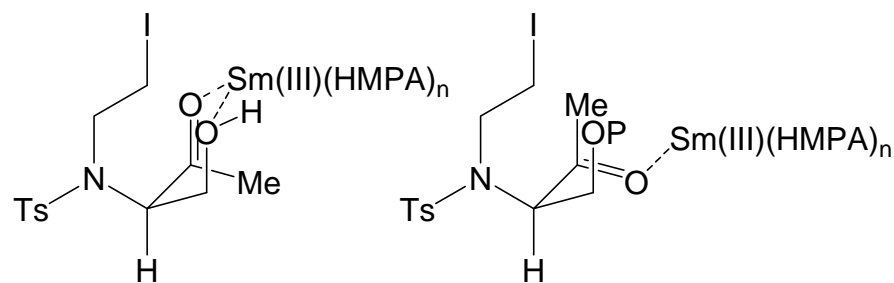
R	Yield	A:B
TBDPS	76%	13:87
Tr	45%	31:69
H	75%	97:3



Hamada's Explanation

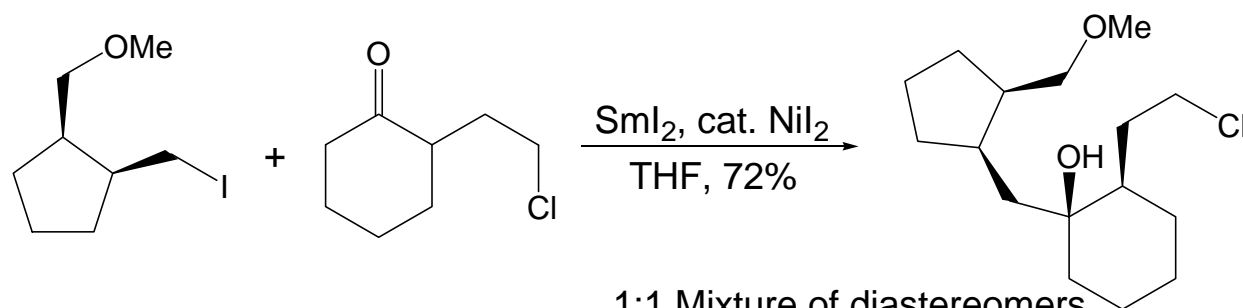


Procter's Explanation

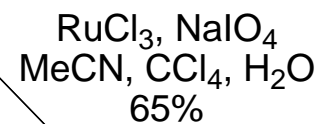


-Mechanism might proceed through a *bis*-radical structure

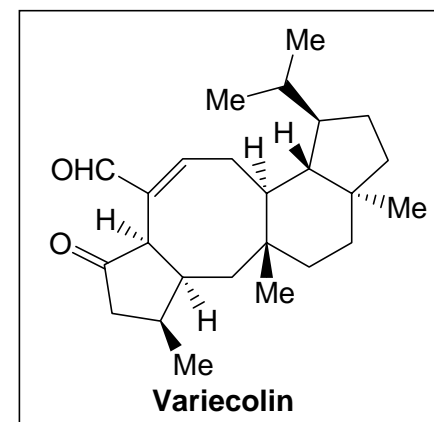
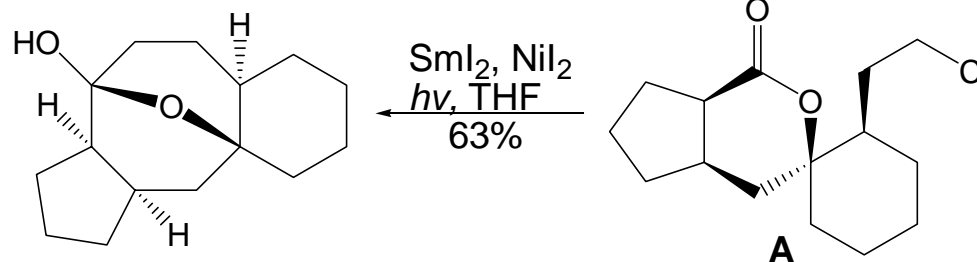
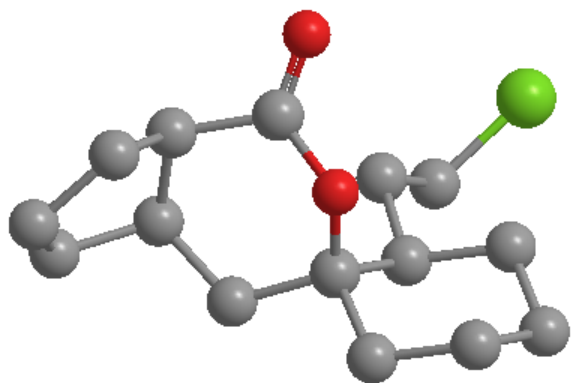
Intramolecular $S_{\text{M}}1_2$ Barbier Cyclizations Synthetic Studies Towards Variecolin



1:1 Mixture of diastereomers
due to racemic starting
materials



Model of Intermediate A

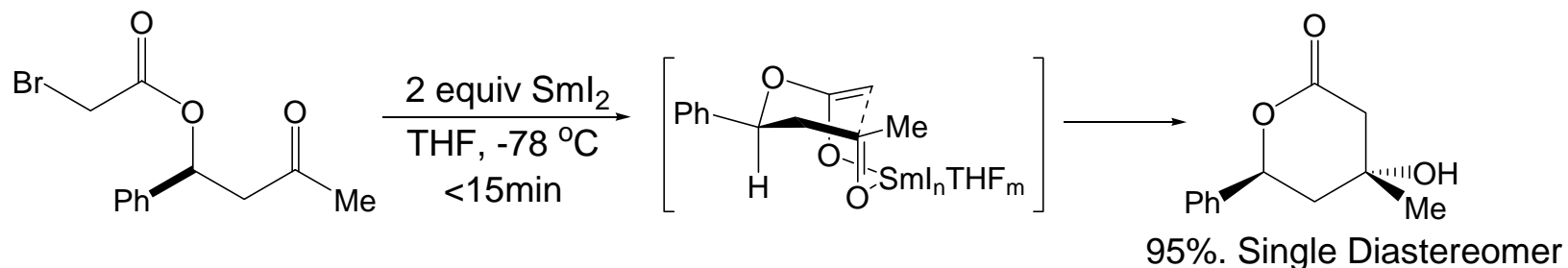


Molander, G. *Org. Lett.* **2001**, 2257

For increased reaction rates with NiI_2 see: Kagan, H. *Synlett* **1996**, 633

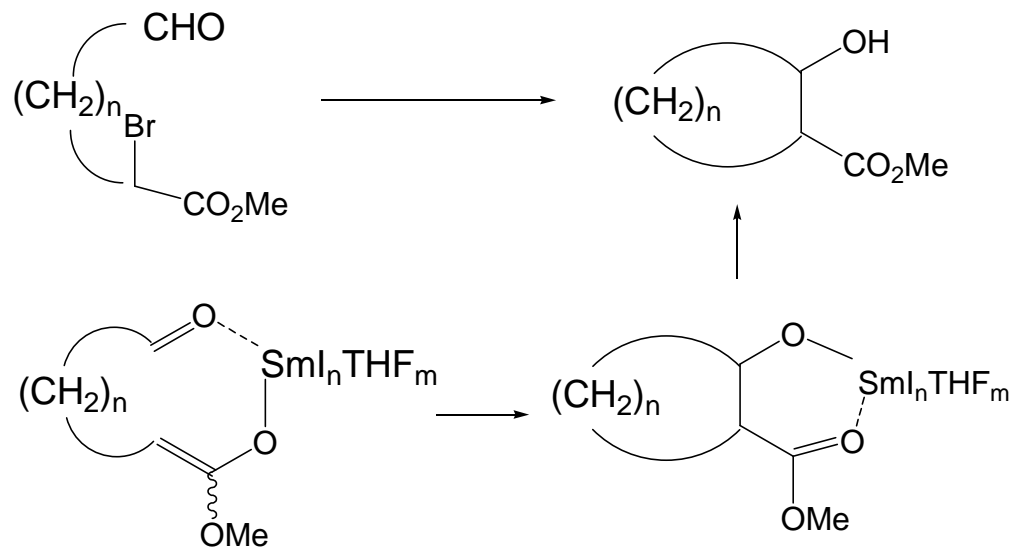
For increasing reducing ability of $S_{\text{M}}1_2$ with visible light see: Ogawa A. *J. Am. Chem. Soc.* **1997**, 2745

SmI₂ Reformatsky reactions Basic Mechanism



Molander, G. A. *J. Am. Chem. Soc.* **1987**, 6556

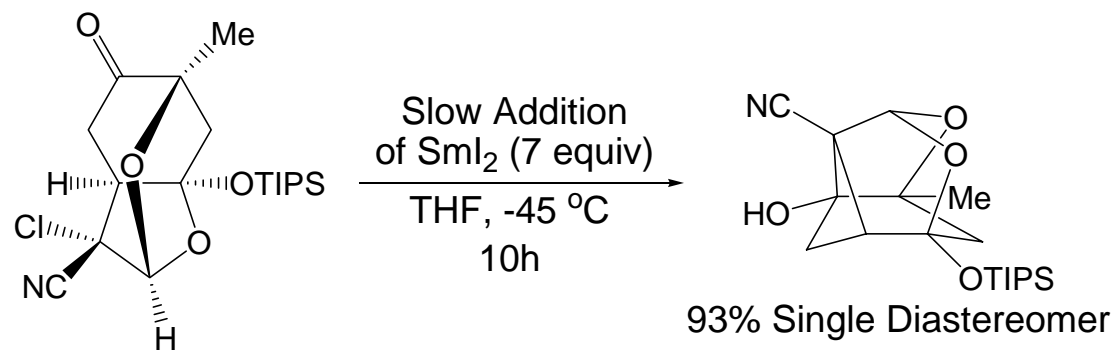
-Due to Sm(III)'s ionic radius, high coordination number, and high oxophilicity: SmI₂ has been used successfully as a chelation element to bring two reaction centers in proximity for the formation of large ring.



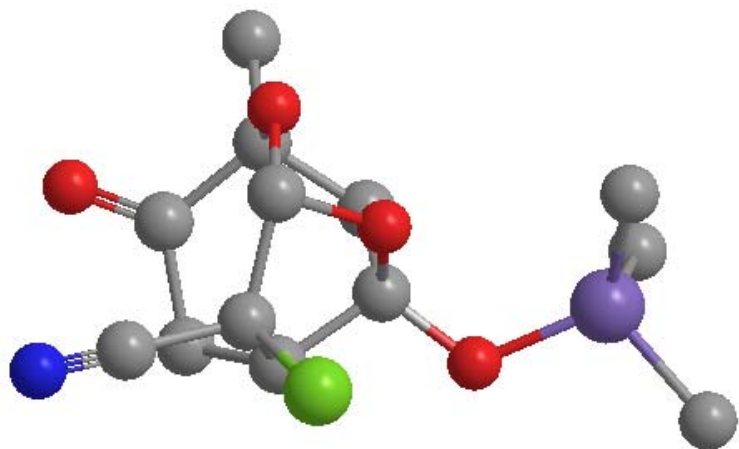
n	Ring Size	Yield
6	8	68%
7	9	70%
9	11	74%
12	14	82%
13	15	82%

Inanaga, J. *Tetrahedron Lett.* **1991**, 6371

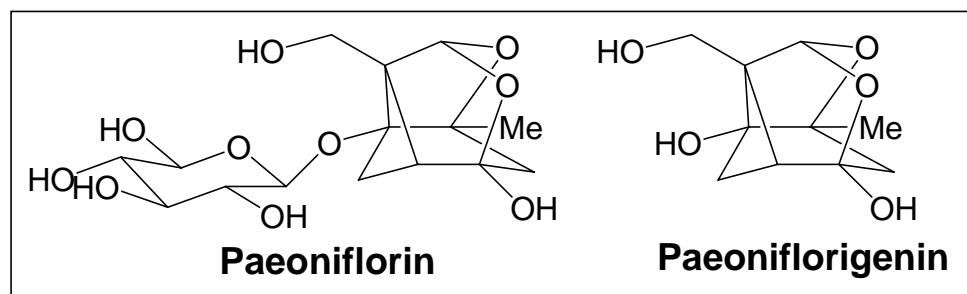
Sml₂ Intramolecular Reformatsky reactions (+/-) Paeoniflorigenin and Paeoniflorin



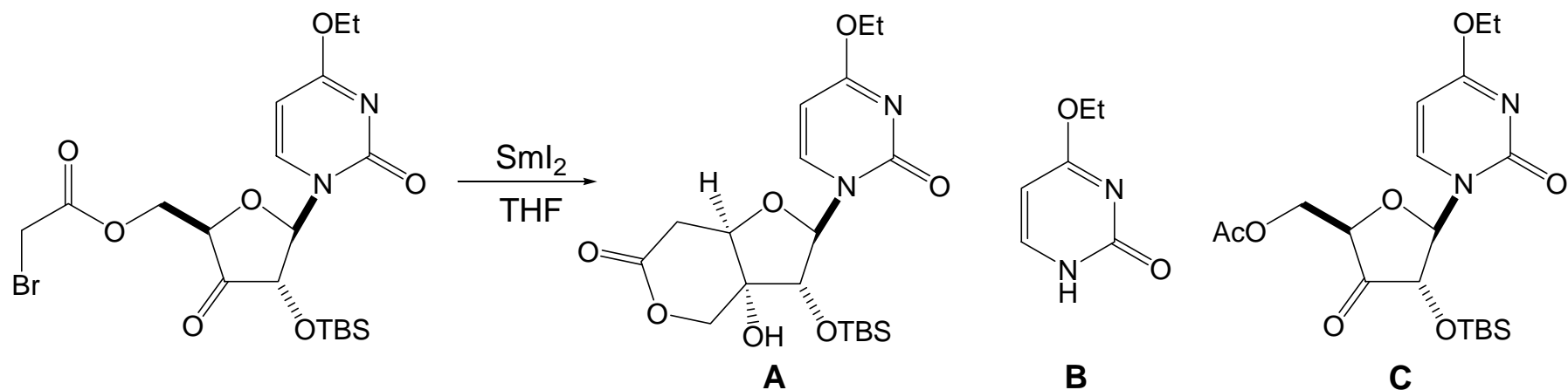
Chem 3D w/ MM2 energy minimization



-Product of the cyclization is base sensitive. Retro-Aldol is observed upon treatment of product with Et₃N.



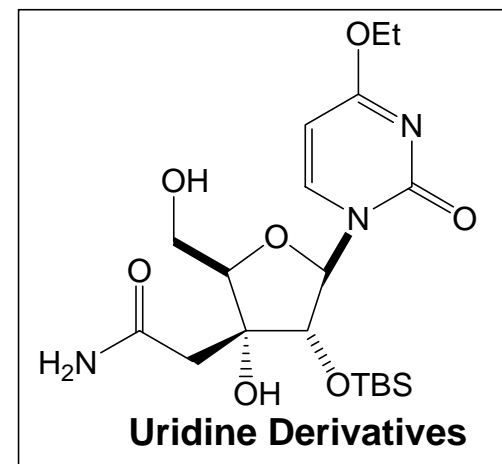
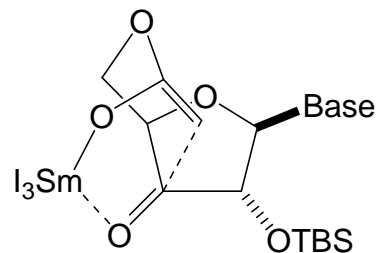
SmI₂ Intramolecular Reformatsky reactions Uridine Derivatives



Product Distribution

Conditions	Product Yields
rt w/ Zn	C 22%
rt	A 71%
0 °C	A 75%
-78 °C	A 90%
-78 °C w/ HMPA	A 76%, B 11%

Plausible Transition State

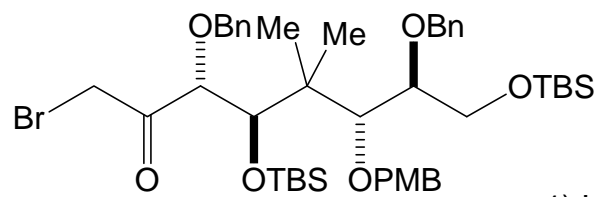
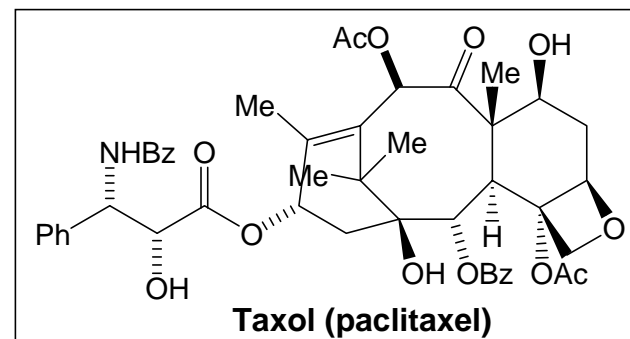


-Substrate is Base sensitive

-Uridine Derivatives have been shown to be potent antitumor agents both *in vitro* and *in vivo*

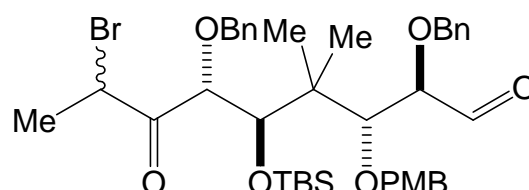
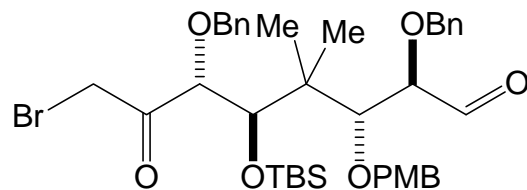
Sml₂ Intramolecular Reformatsky reactions

Taxol-Mukaiyama



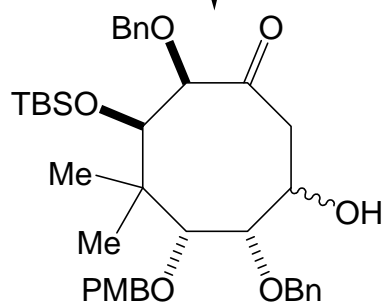
1) 1N HCl, THF
2) (COCl)₂, DMSO, Et₃N
CH₂Cl₂ 94%

1) LHMDS, MeI, HMPA, THF 100%
2) 1N HCl, THF 83%
3) (COCl)₂, DMSO, Et₃N, CH₂Cl₂ 95%

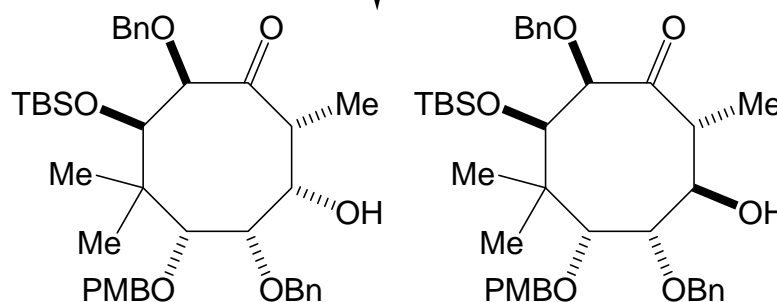


Sml₂, THF, 0 °C

Sml₂, THF, 0 °C

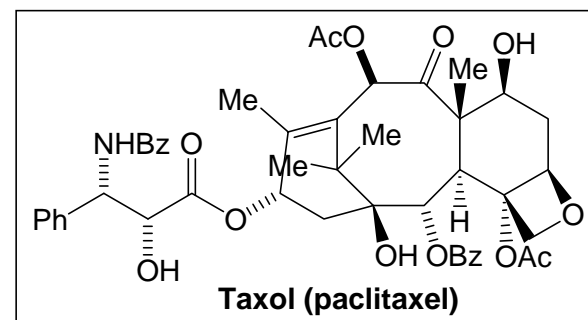
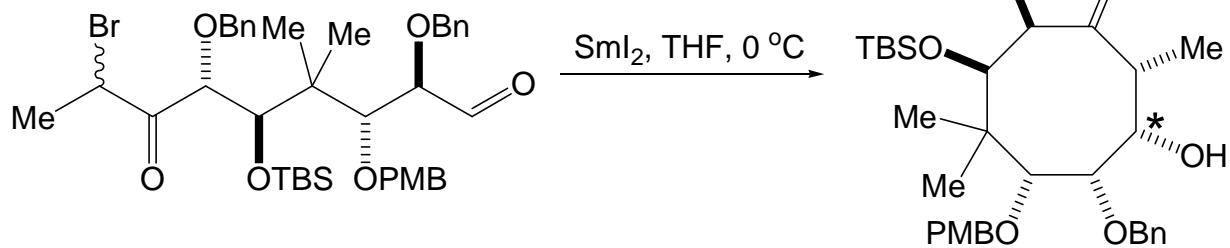


87% dr 65:35



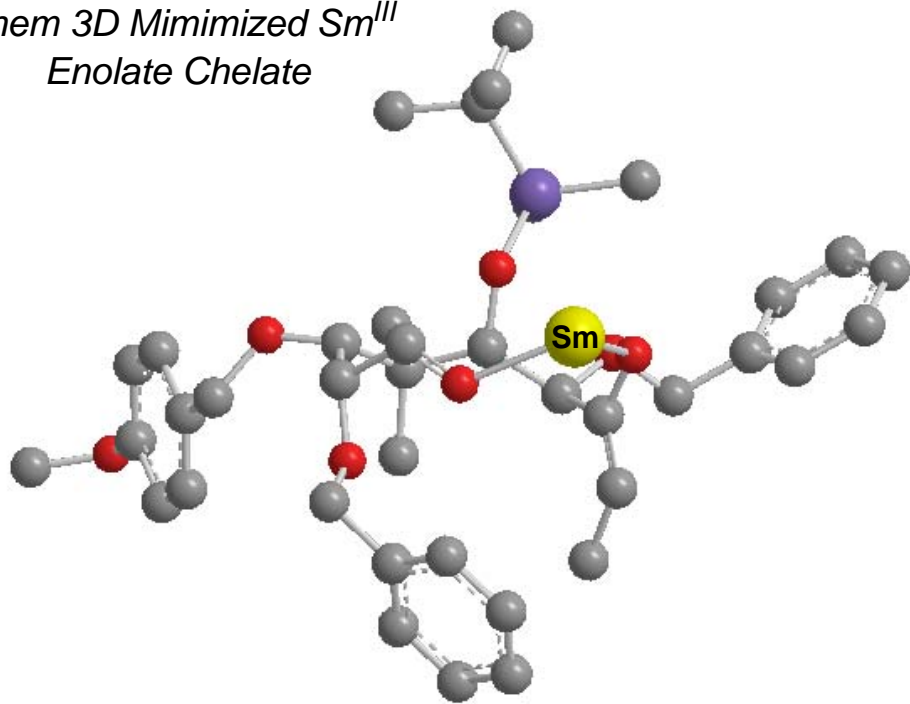
70% dr 83:17

Sml₂ Intramolecular Reformatsky reactions
Taxol-Mukaiyama

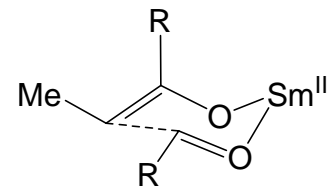


70% dr 83:17

Chem 3D Mimimized Sm^{III}
Enolate Chelate

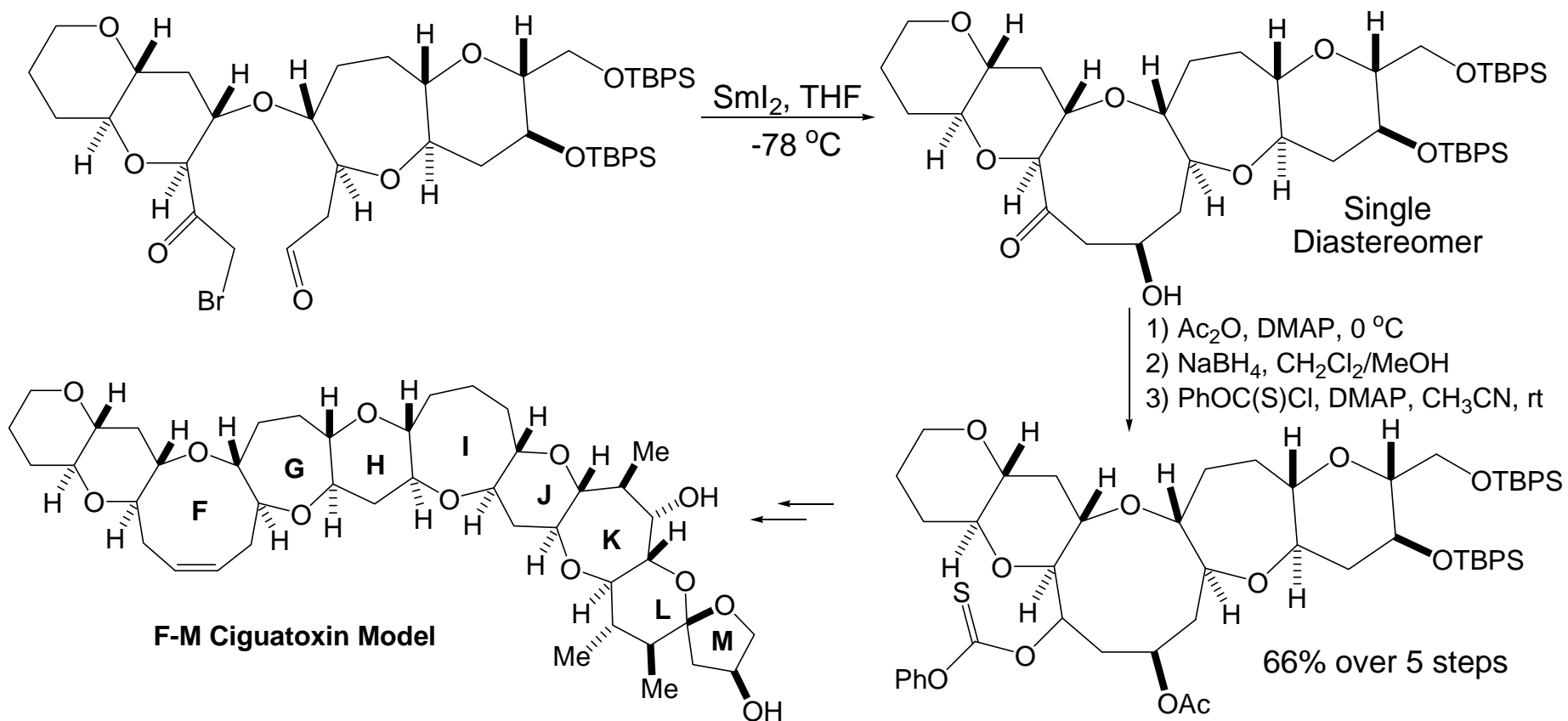
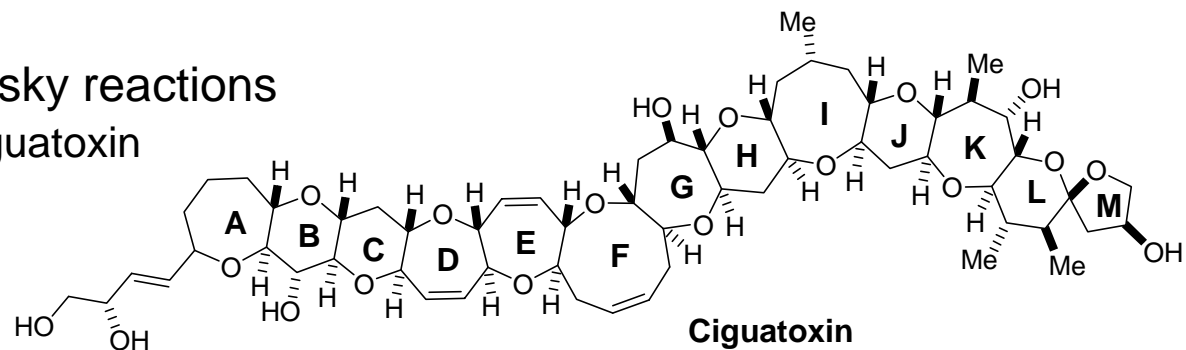


Simplified Chair Transition State



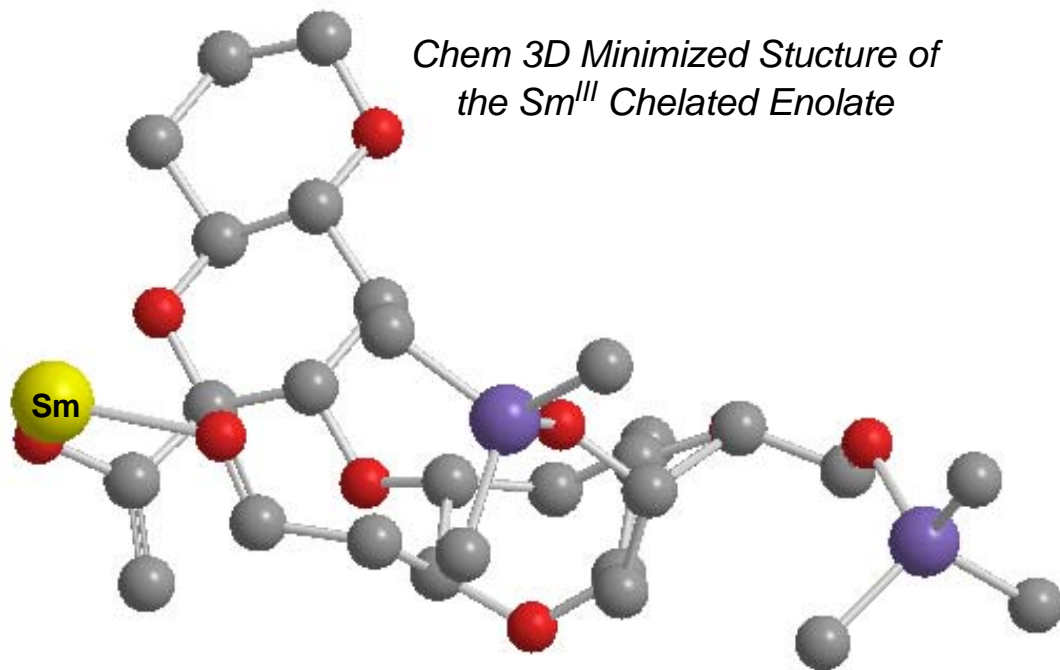
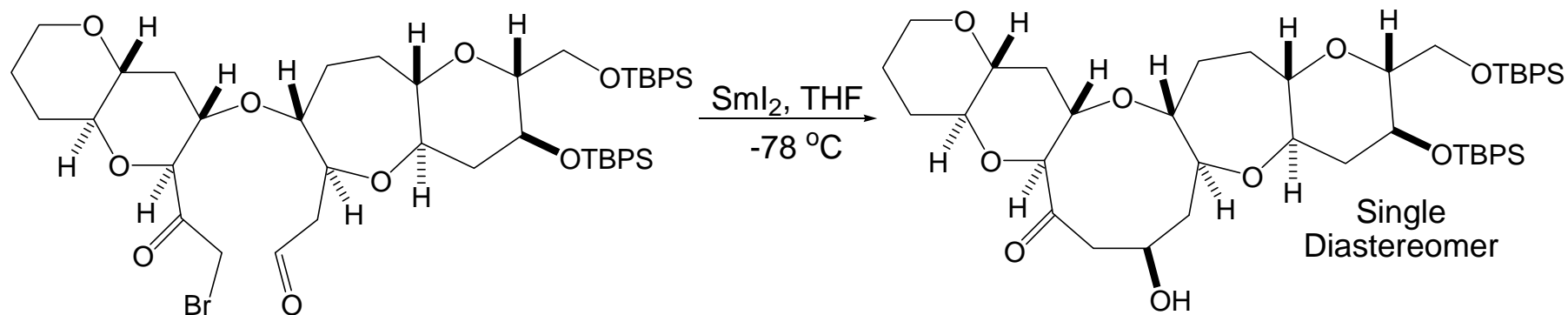
-Preliminary modeling suggest reaction proceeds through *E*-enolate

Sml₂ Intramolecular Reformatsky reactions Model Studies Toward Ciguatoxin

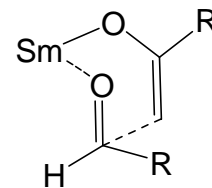


Inoue, M. *ACIEE* 1998, 965
Inoue, M. *JOC* 1999, 9416

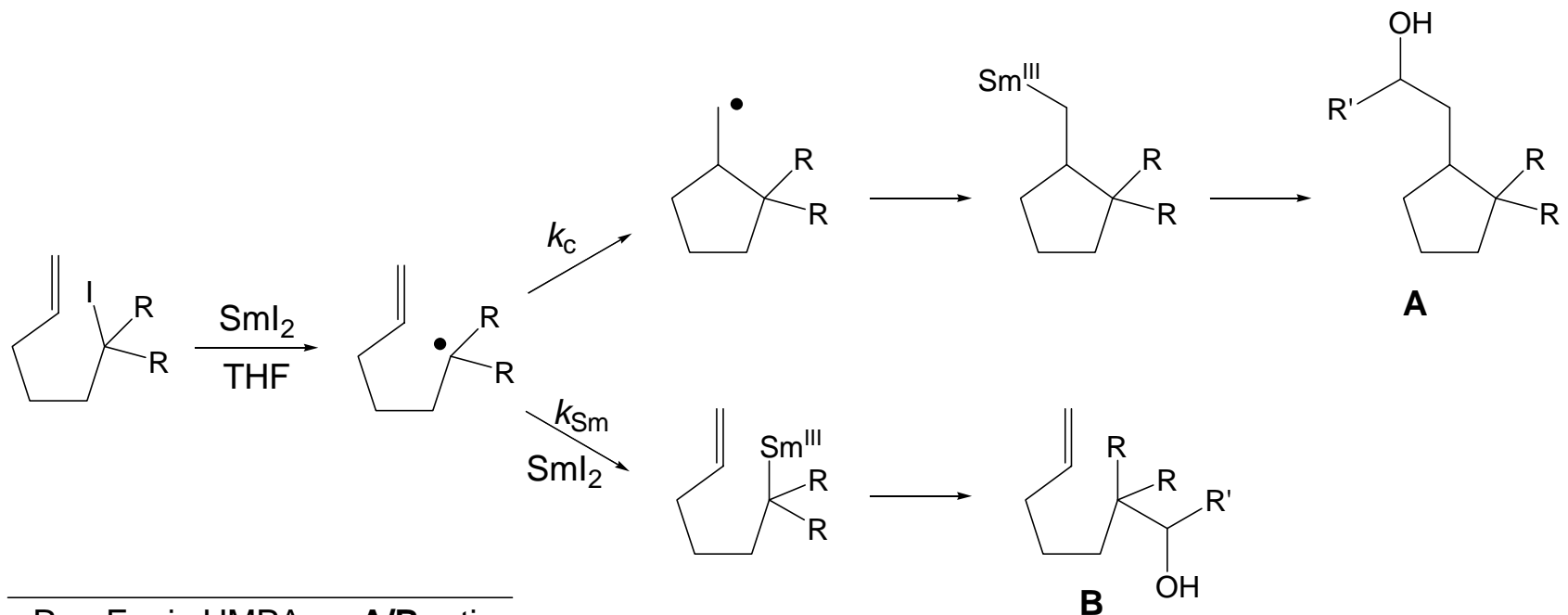
SmI₂ Intramolecular Reformatsky reactions Model Studies Toward Ciguatoxin



Simplified Conformation



SmI₂ Radical-Alkene and Alkyne Cyclizations Basic Mechanism



R	Equiv HMPA	A/B ratio
H	2.3	08/92
H	3.2	34/66
H	3.7	50/50
H	5	56/44
H	7	52/48
Me	0	0/100

Curran, D. *Tetrahedron Lett.* **1993**, 1717.

For a review on the mechanism of SmI₂ reactions see:

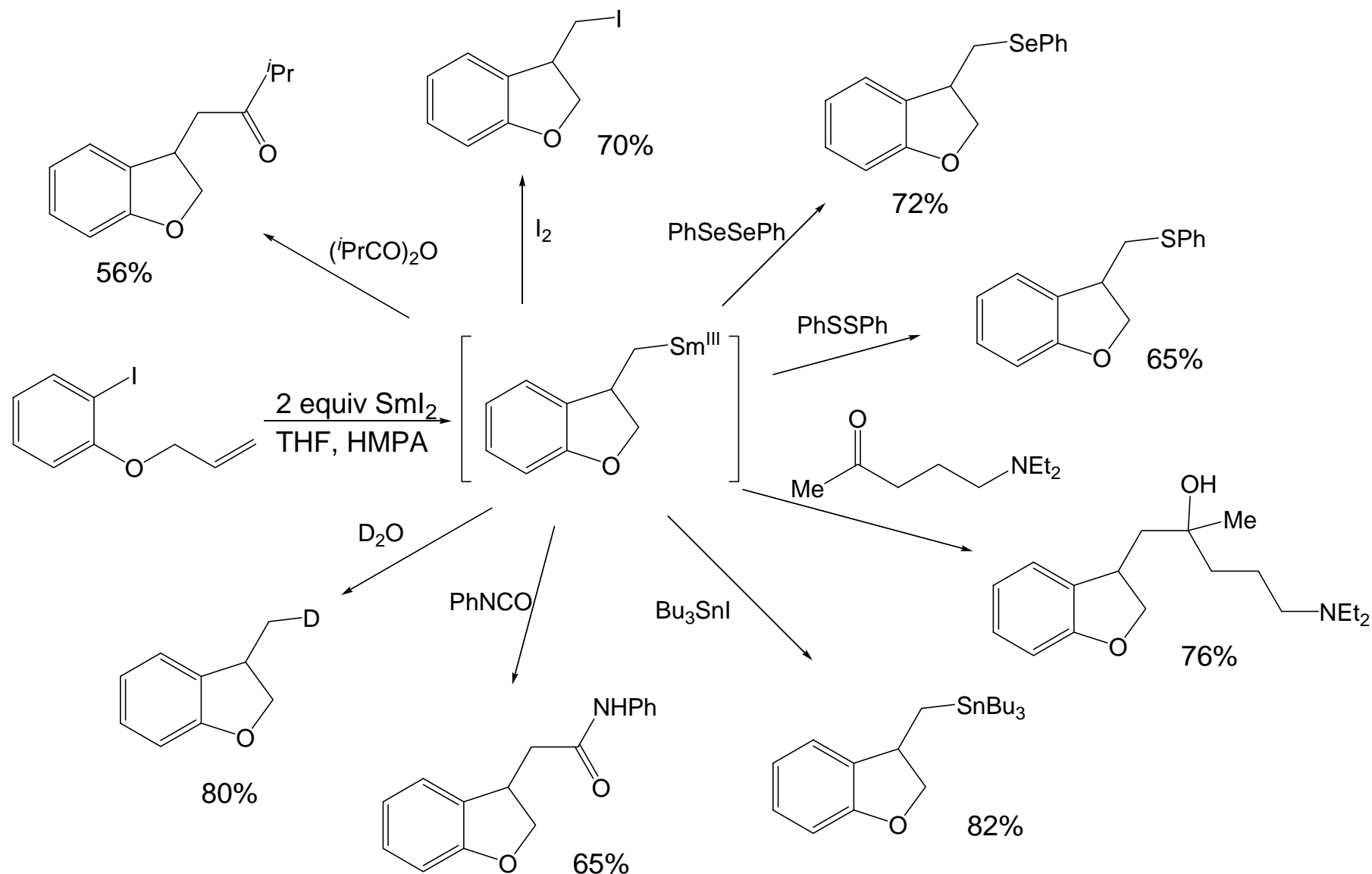
Curran, D. *Synlett* **1992**, 943.

For a review of coupling of organic halides and carbonyl compounds see:

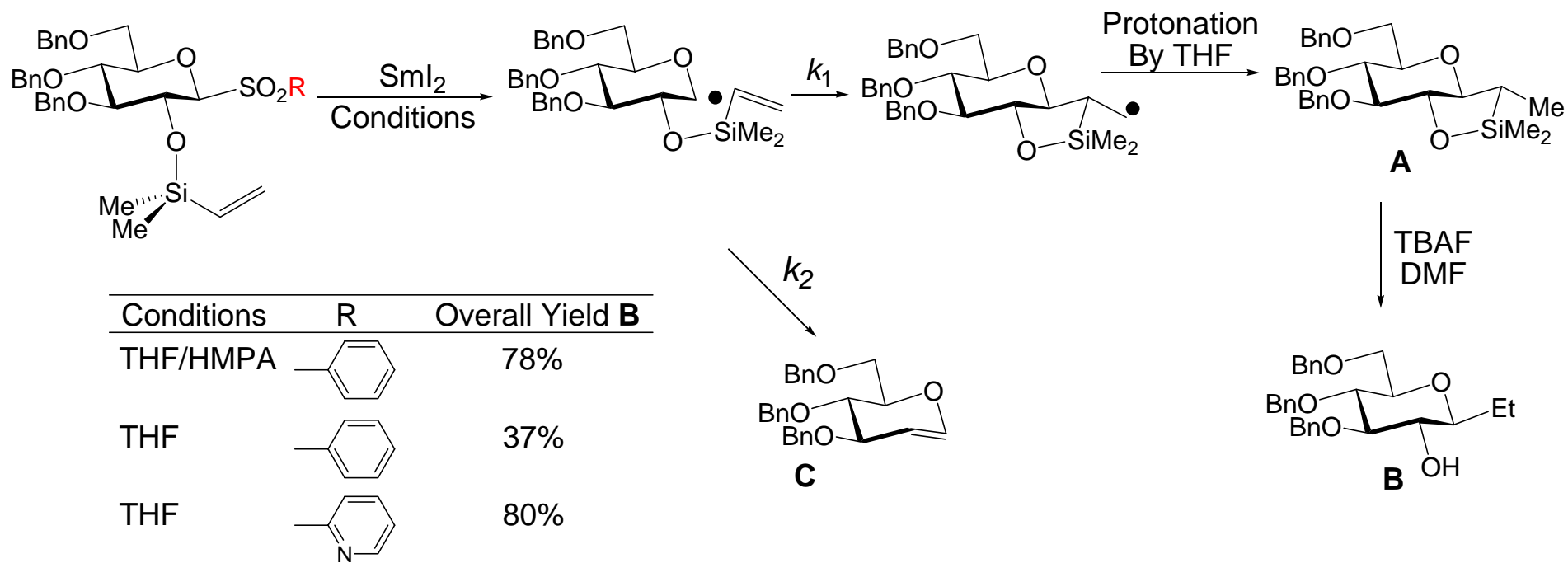
Krief, A. *Chem. Rev.* **1999**, 745.

Sml₂ Radical-Alkene and Alkyne Cyclizations

Synthetic Utility of Intermediate Organo-Samarium Compounds



Sml₂ Radical-Alkene Cyclizations C-Glycoside Formation

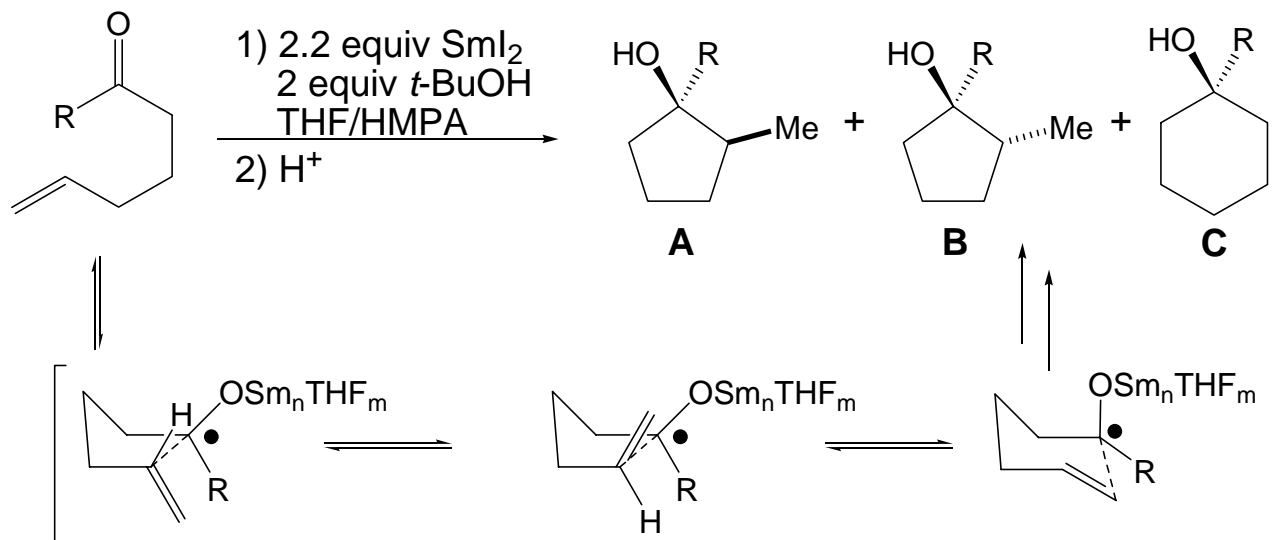


-Authors propose 2-pyridyl group lowers LUMO thus facilitates initial sulfone cleavage

-Possibility of 2-pyridyl group serving as a chelating point, thus facilitating inner sphere electron transport process for initial sulfone cleavage.

Beau, J.-M. *ACIEE* **1994**, 1383.
For the use of 2-pyridine as a chelation point see: Yamamoto, H. *JACS* **2004**, 4128.

SmI₂ Radical Carbonyl-Alkene Cyclizations Basic Mechanism



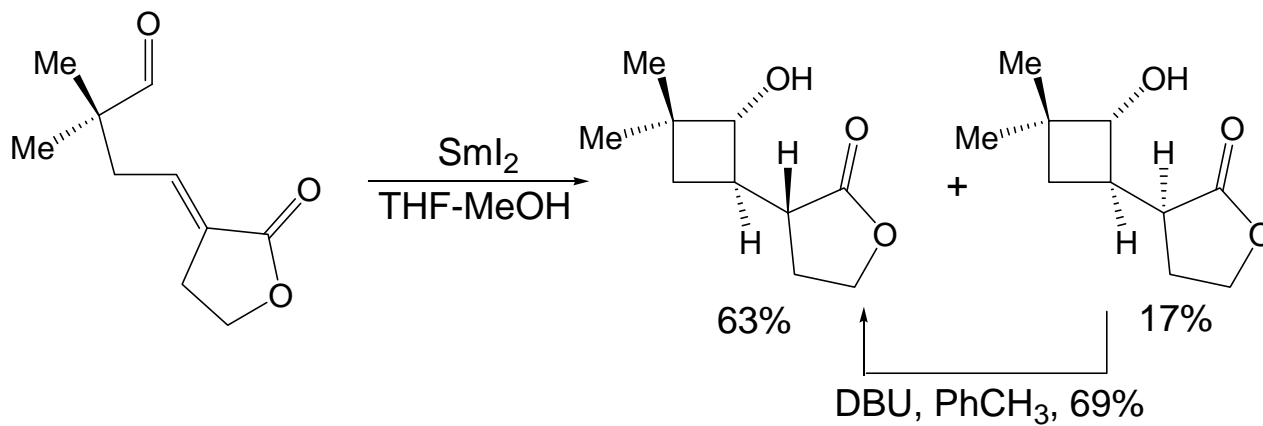
R	% isolated Yield of A and B (diast ratio, A : B)	% Yield C	Reaction Time
Me	86 (>150:1)	-	15 min
<i>i</i> -Pr	85 (23:1)	3	30 min
<i>t</i> -Bu	78 (3:1)	4	8 h
Ph	48 (1<150)	-	2 h

-Carbonyl reduction by SmI₂ is well documented

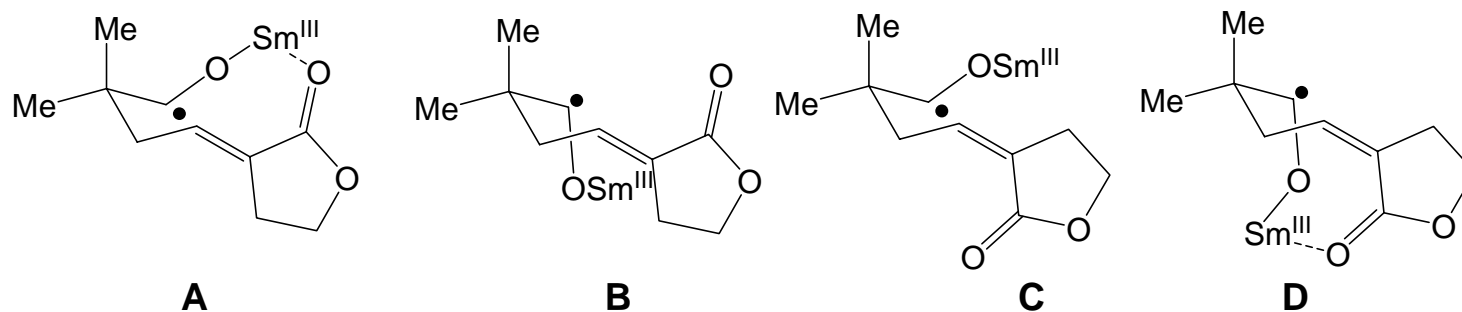
Molander, G. J. *Org. Chem.* **1995**, 872.
 Curran, D. P. *Synlett* **1992**, 943
 Rajapaksa, H. *Group Seminar* **6-1998**

SmI₂ Radical Carbonyl-Alkene Cyclizations

Basic Mechanism, an Example of an Activated Alkene

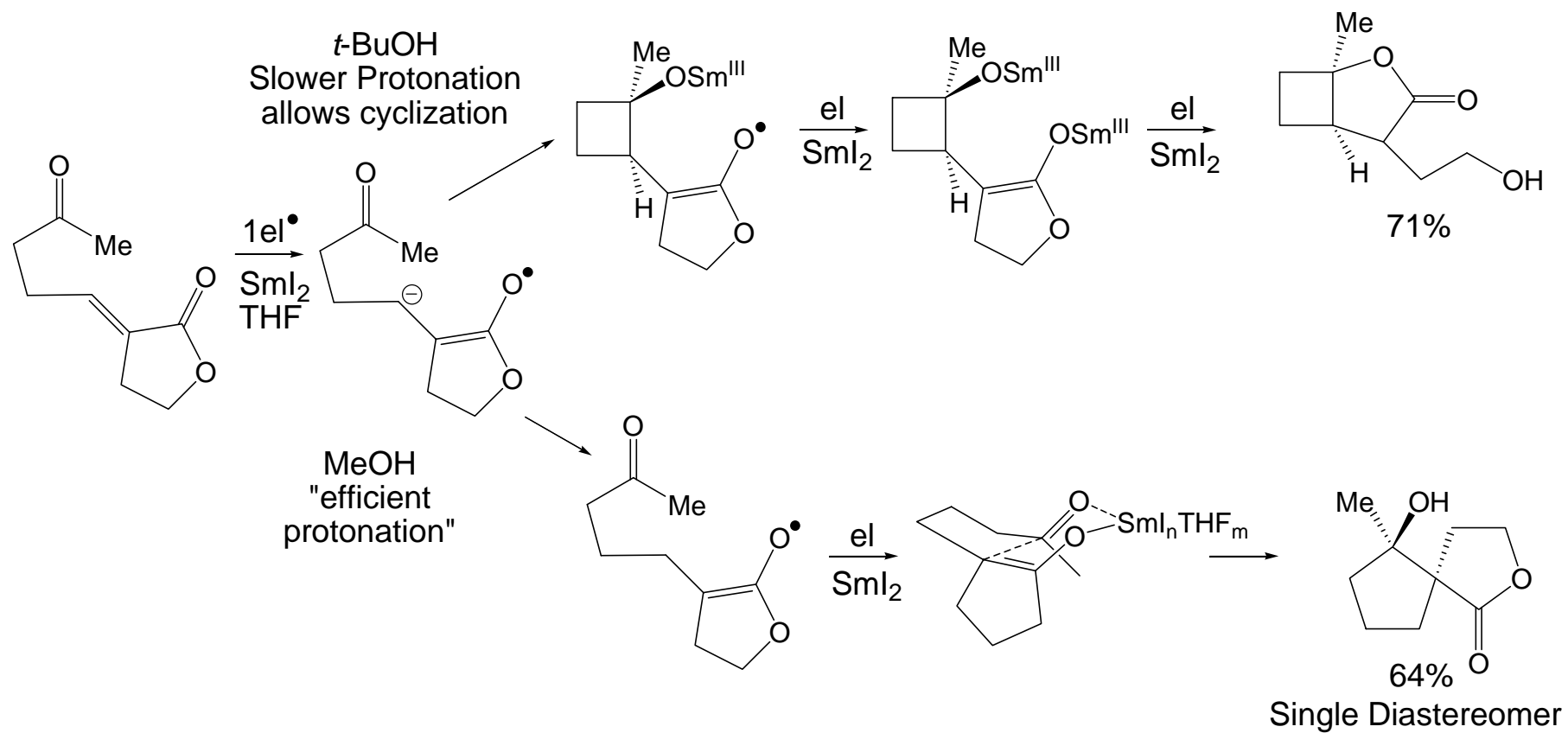


Transition States



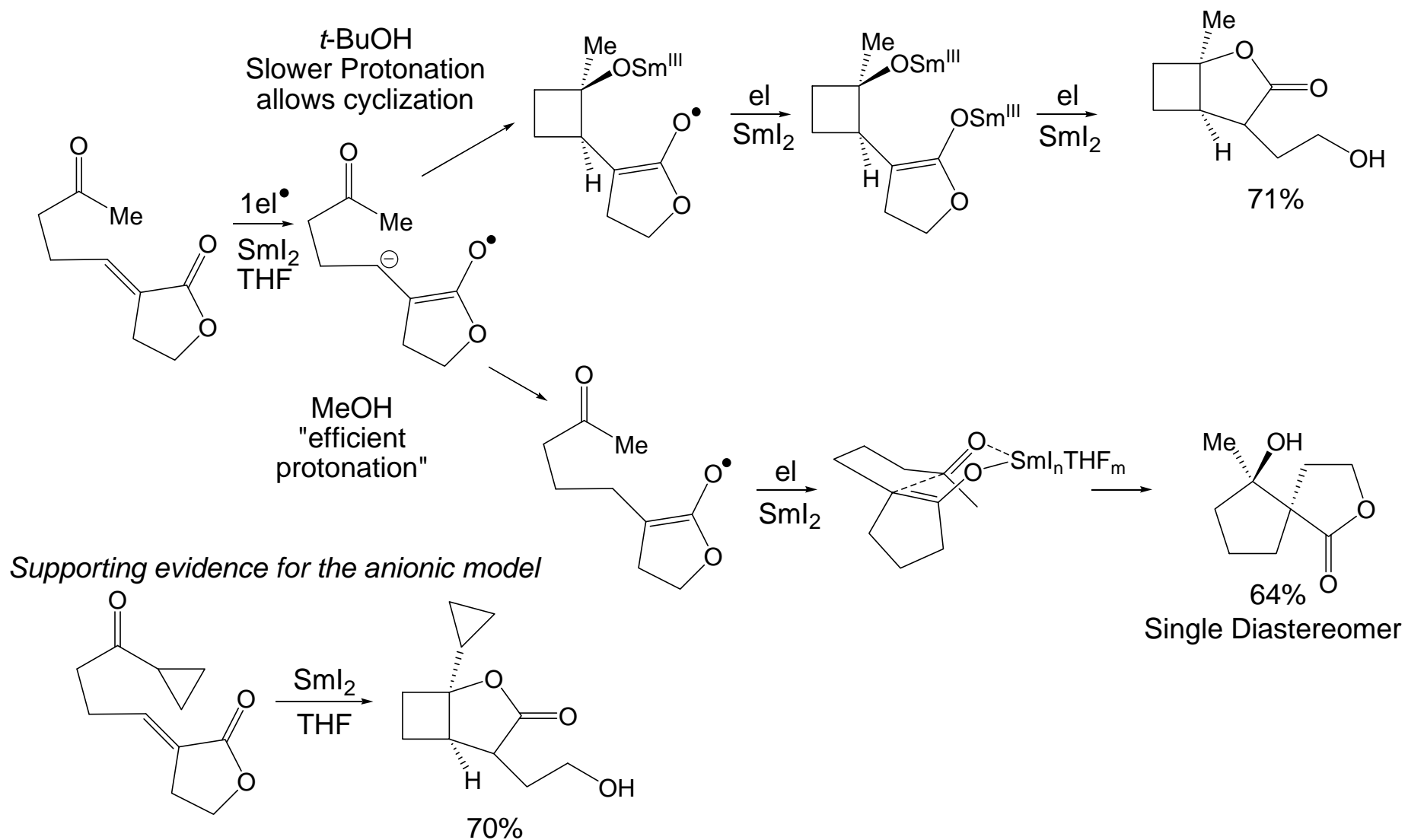
Sml₂ Radical Carbonyl-Alkene Cyclizations

Basic Mechanism, an Example of an Activated Alkene

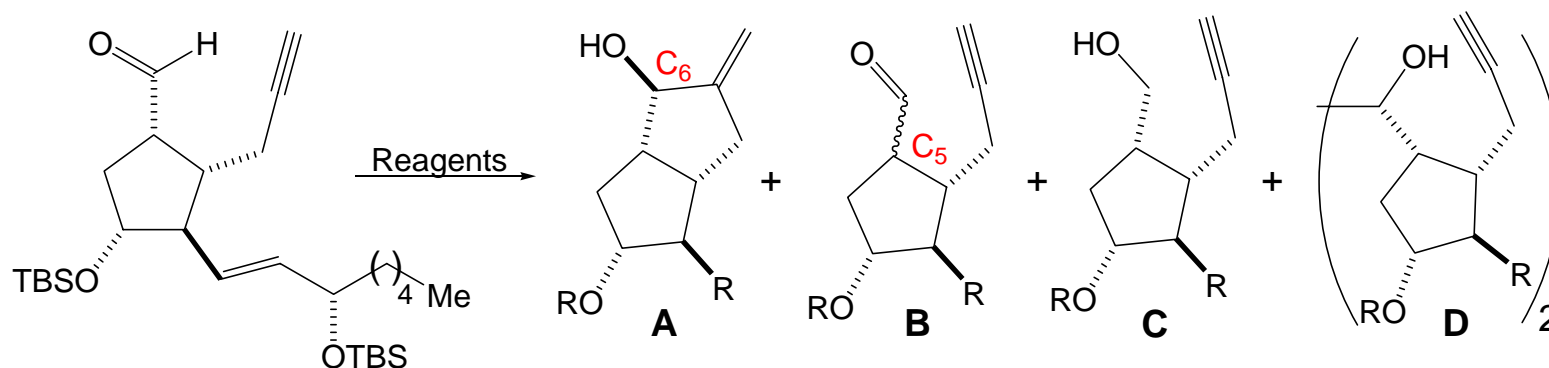


SmI₂ Radical Carbonyl-Alkene Cyclizations

Basic Mechanism, an Example of an Activated Alkene



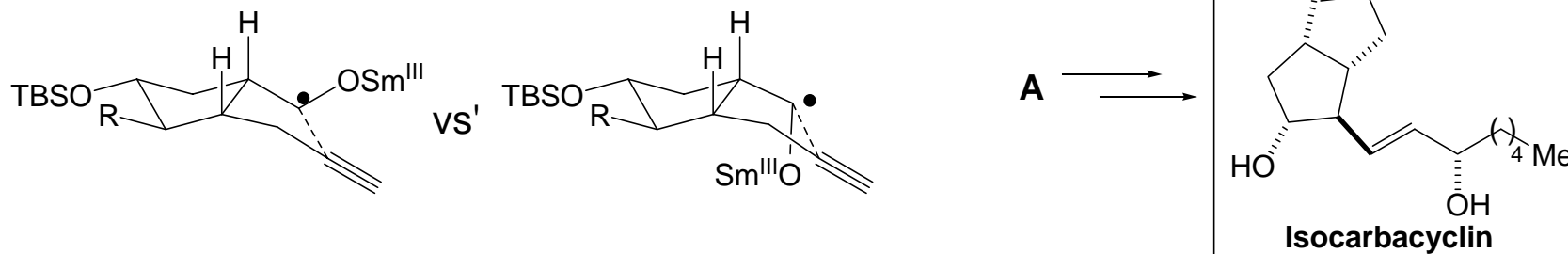
Sml₂ Radical Carbonyl-Alkyne Cyclizations Isocarbacyclin



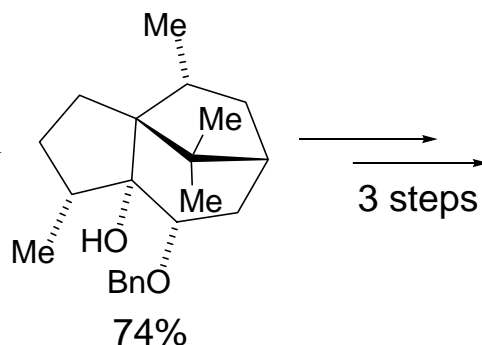
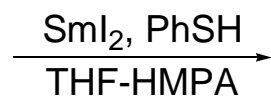
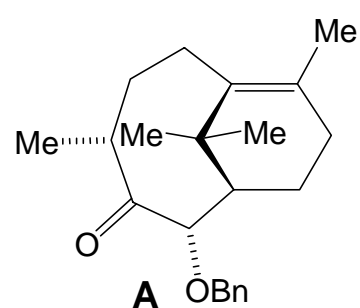
Reagents	A (C ₆ dr)	B (C ₅ dr)	C	D
Zn, TMSCl, 2,6 Lutidine, in THF, at reflux	28% (ND mix)	51% (1:1)	-	-
Li-Naphthalene, <i>t</i> -BuOH, in THF at -70 °C	65% (ND mix)	15% (1:2)	3%	-
Sml ₂ , <i>t</i> -BuOH, in THF at -70 °C	71% (9:1)	-	8%	8%
hν, Et ₃ N, in CH ₃ CN at rt	60% (2:1)	20% (ND)	-	-

ND denotes mixture was defined as an "epimeric mixture" at the defined stereocenter

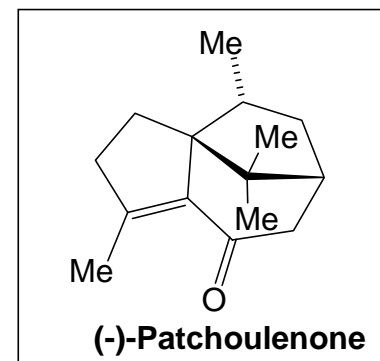
Plausible Transition States



Sml₂ Radical Carbonyl-Alkene Cyclizations (-)-Patchoulenone

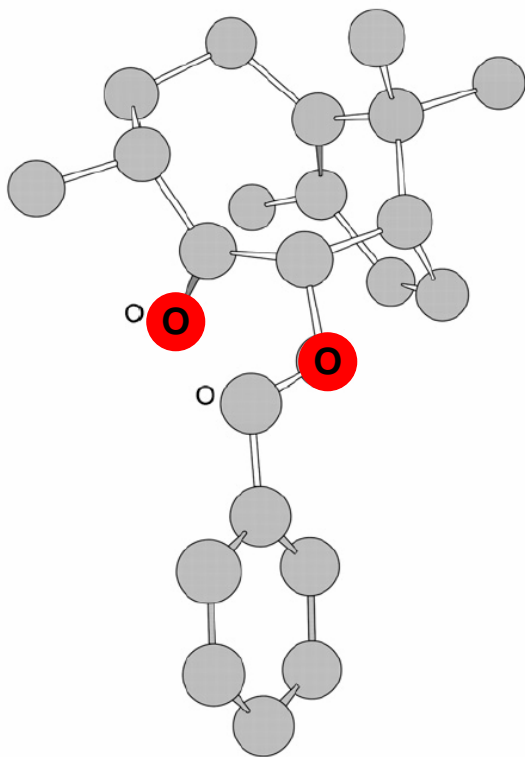


3 steps

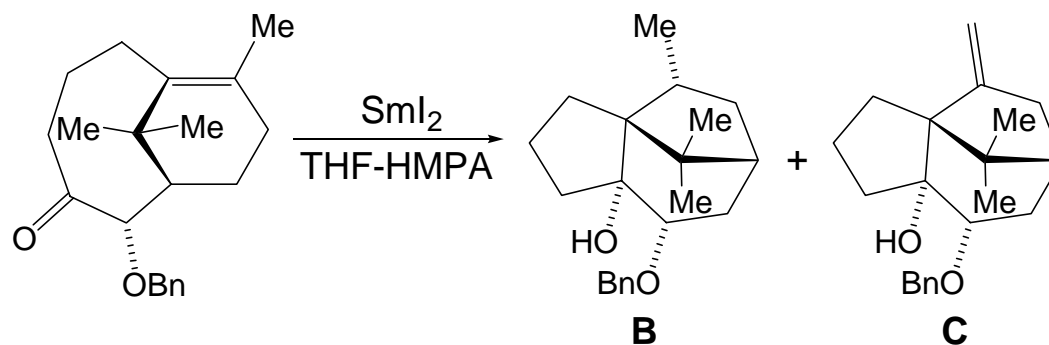


Single Diastereomer

X-Ray Structure of **A**



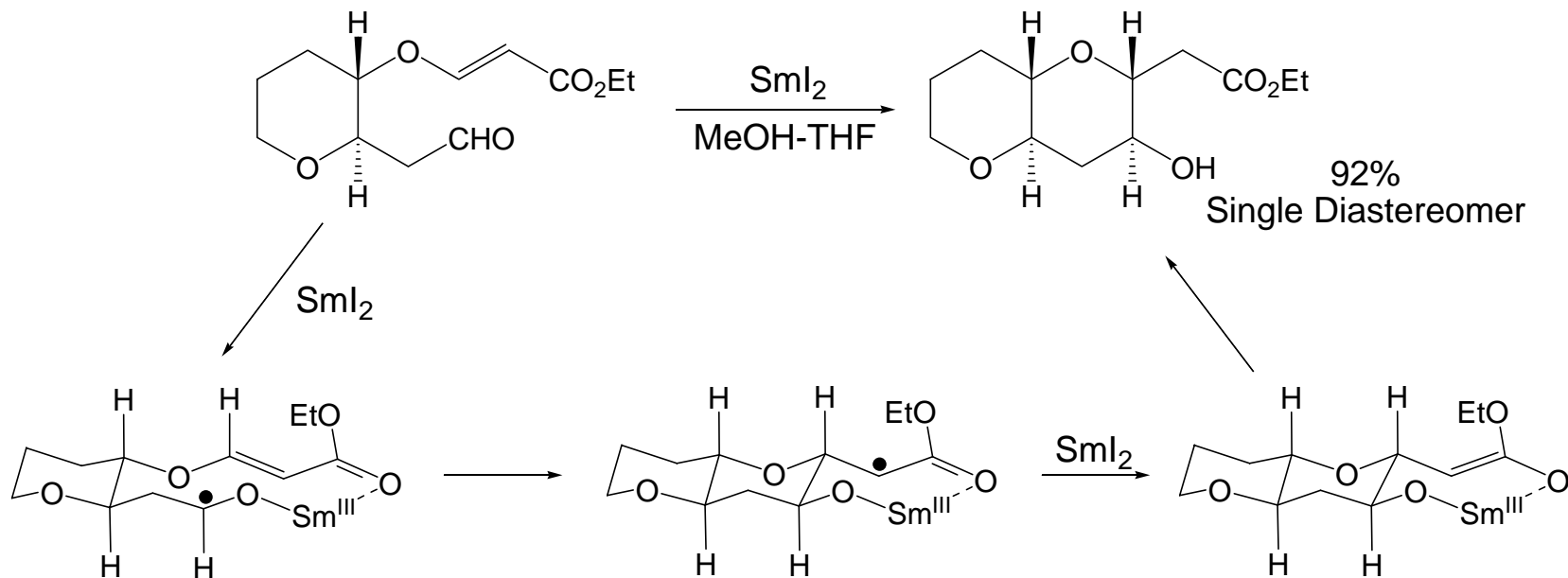
Model Studies, effects of PhSH additive



Additive	Yield B	Yield C
None	39%	54%
PhSH	71%	0%

-Prins, carbonyl-ene, and Paterno-Buchi reactions proved to be inferior methods in the synthesis

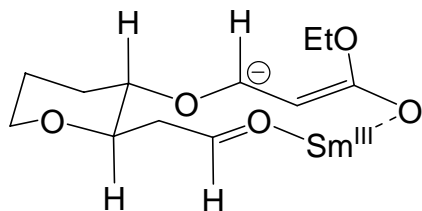
Sml₂ Radical Carbonyl-Alkene Cyclizations *trans*-Fused Polytetrahydropyrans



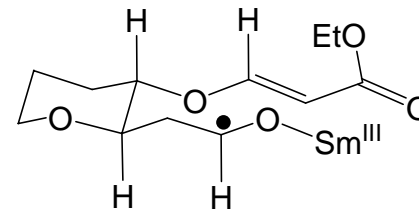
-Issues with simultaneous binding of ketyl radical and conjugated ester, geometrical constraints?

-Alternated Possibilities

Procter's Alternative

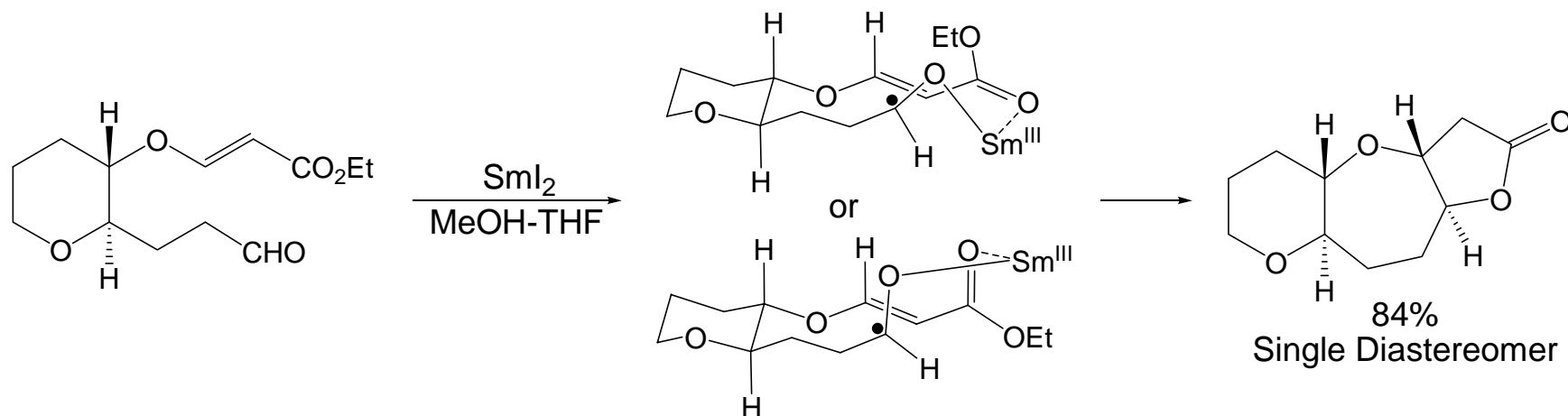


Non-Chelation

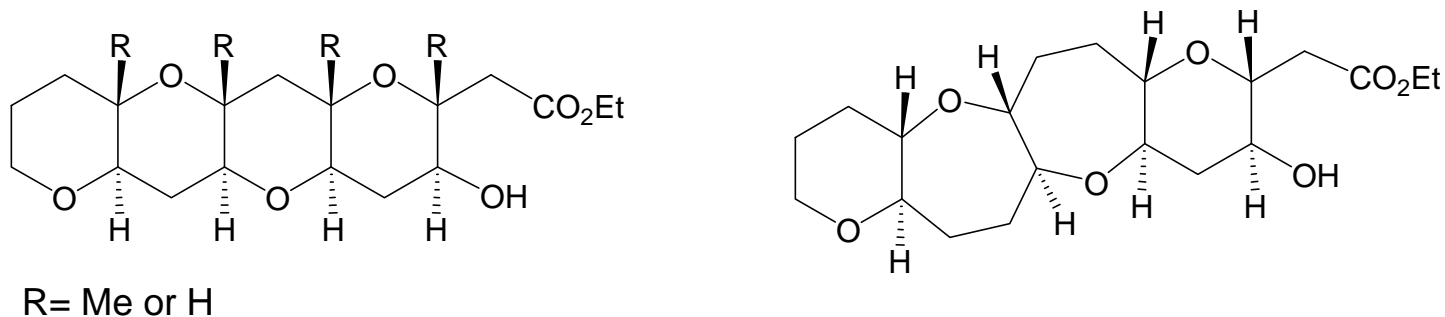


Hori, N. *Tetrahedron Lett.* **1999**, 2811
 Hori, N. *Org. Lett.* **1999**, 1099
 Hori, N. *Tetrahedron* **2002**, 1853
 Suzuki, K. *Tetrahedron Lett.* **2002**, 8653

SmI₂ Radical Carbonyl-Alkene Cyclizations *trans*-Fused Polytetrahydropyrans



Iterative Cyclizations produces Polytetrahydropyrans and Oxepanes

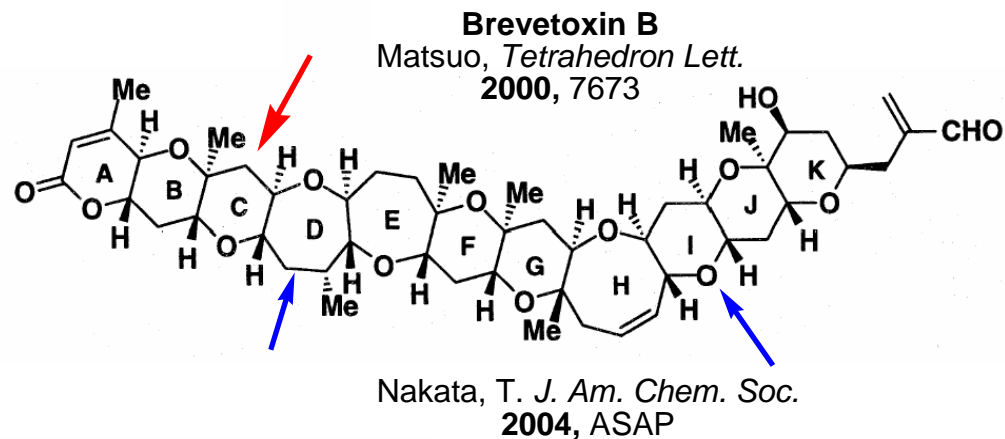
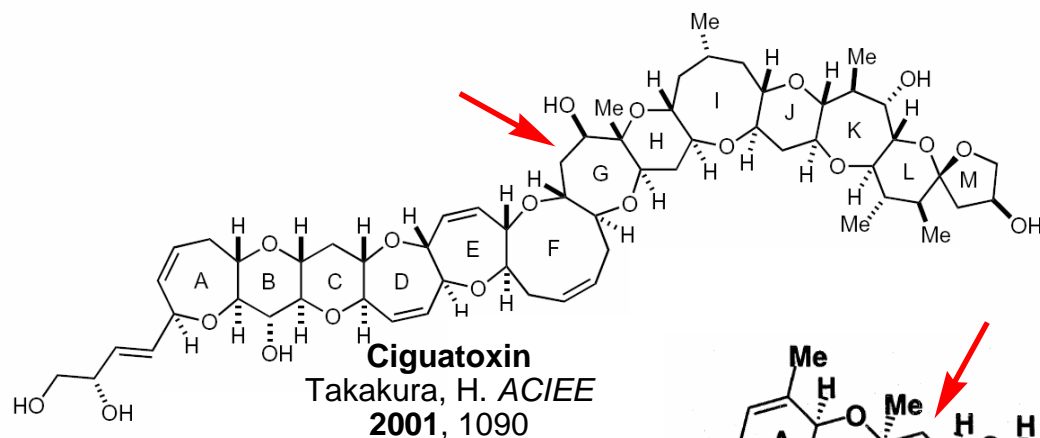


-Cyclizations proceed in high yield (>80%) and with complete stereocontrol

Hori, N. *Tetrahedron Lett.* **1999**, 2811
 Hori, N. *Org. Lett.* **1999**, 1099
 Hori, N. *Tetrahedron* **2002**, 1853
 Suzuki, K. *Tetrahedron Lett.* **2002**, 8653

Sml₂ Radical Carbonyl-Alkene Cyclizations

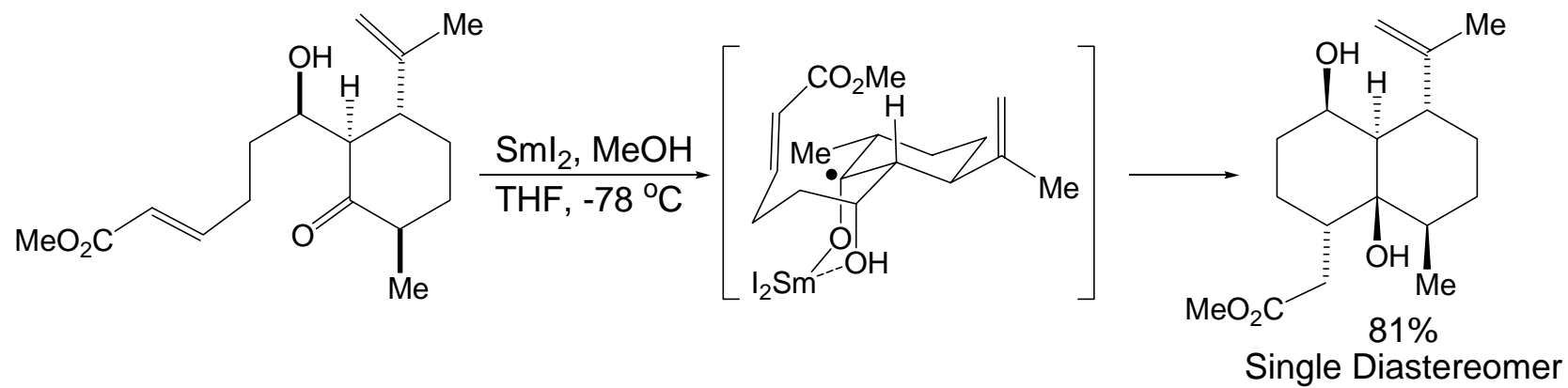
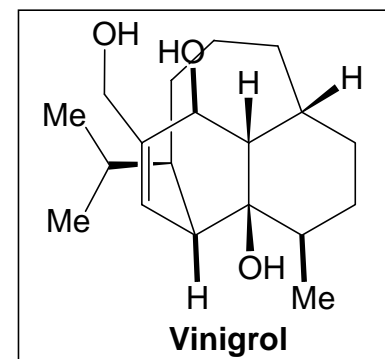
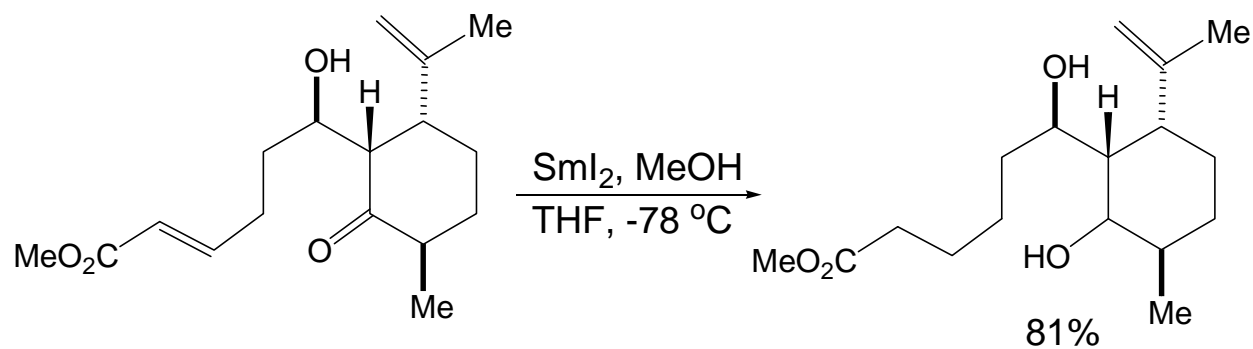
Natural Product Synthesis and Synthetic Studies



Nakata, T. *J. Am. Chem. Soc.* **2004**, ASAP

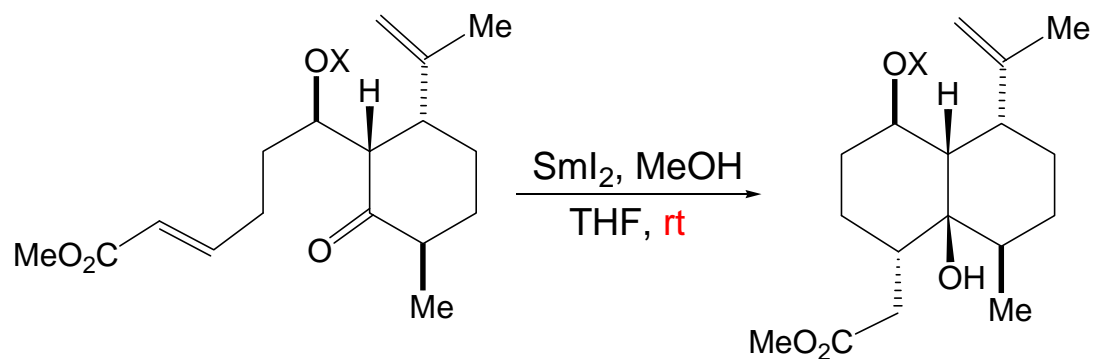
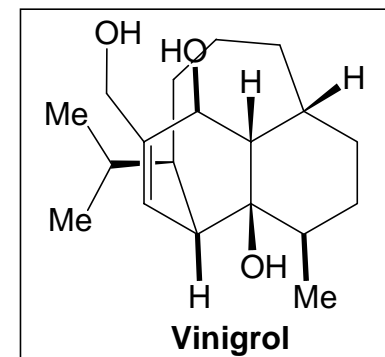
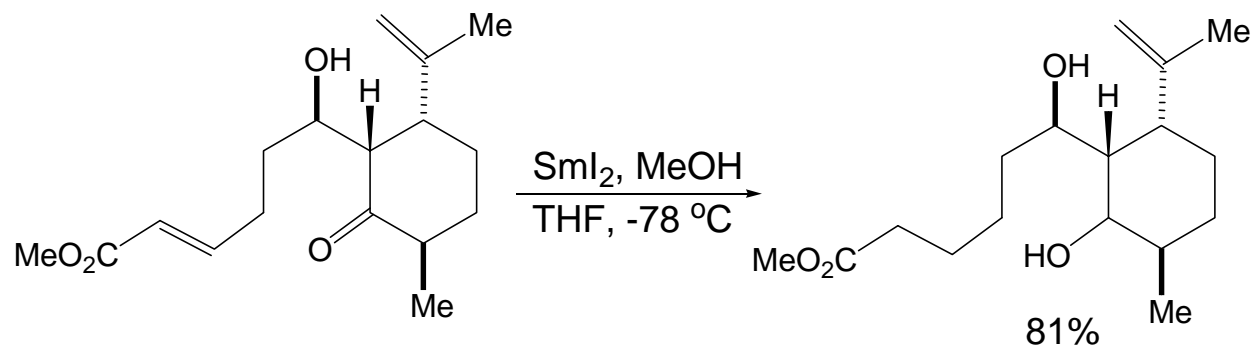
Also, the D and E ring of the A-F fragment of Yessotoxin. Suzuki, K. *Org. Lett.* **2002**, 3943

Sml₂ Radical Carbonyl-Alkene Cyclizations Synthetic Studies Toward Vinigrol



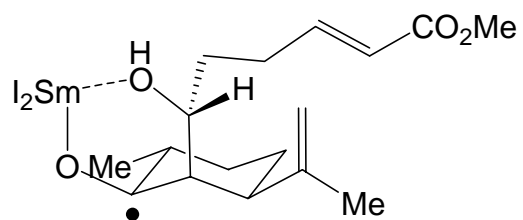
Sml₂ Radical Carbonyl-Alkene Cyclizations

Synthetic Studies Toward Vinigrol

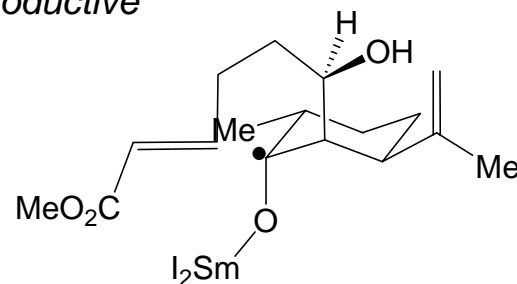


X	Yield
H	45%
Ac	85%

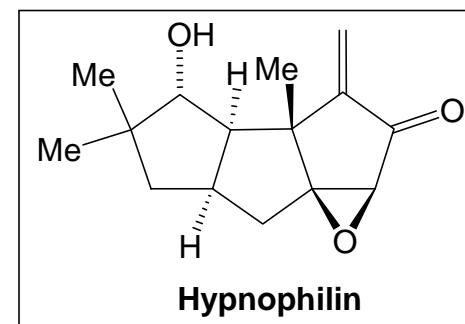
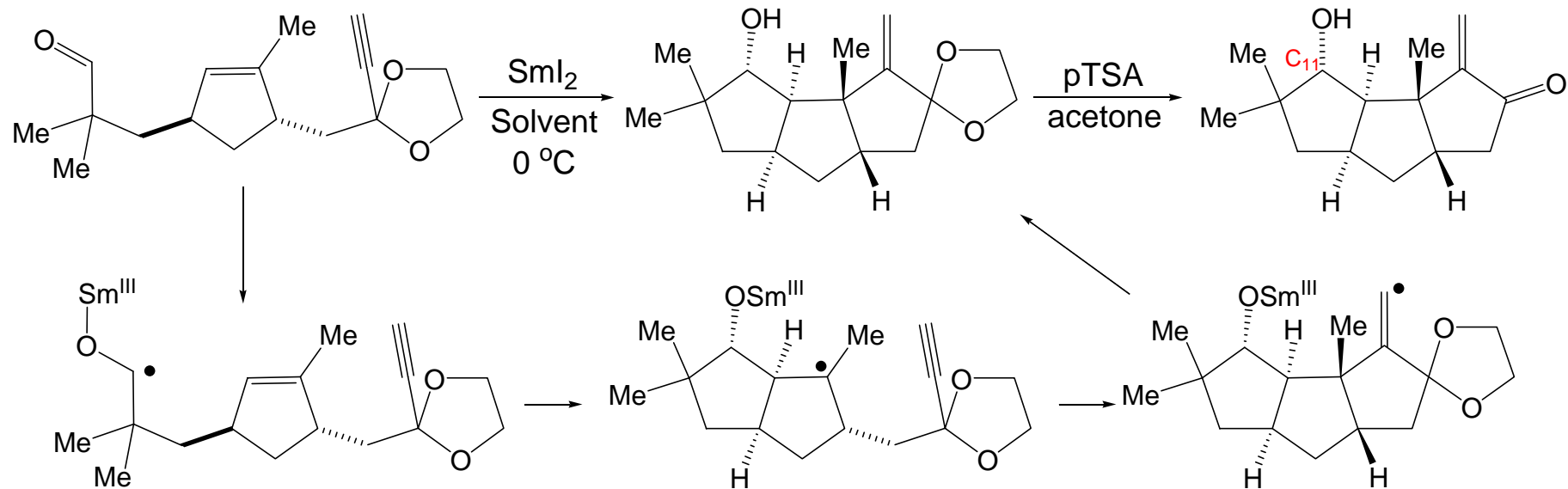
Non-productive



Productive



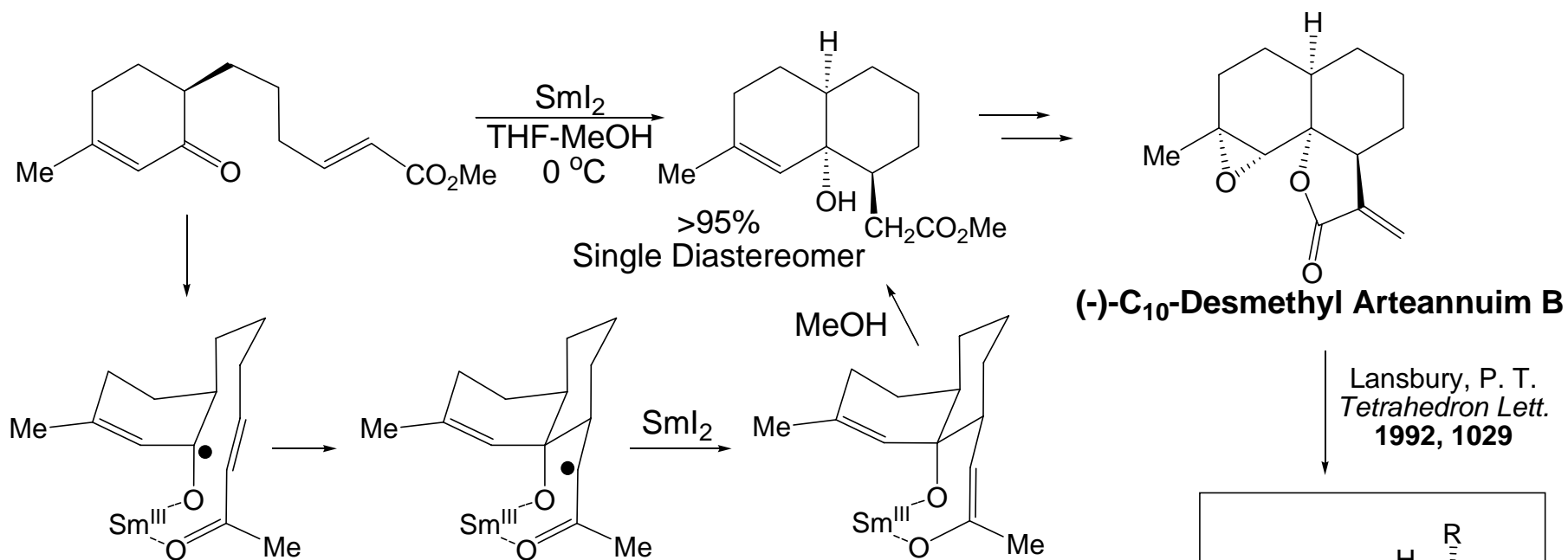
SmI₂ Radical Carbonyl-Alkene Cyclizations (+/-) Hypnophilin



Solvent	Pdt	epi-C ₁₁	Reduction	Yield of ketone
THF	11%	-	18%	NA
THF/HMPA	91%	-	9%	63%
THF/DMPU	87%	9%	4%	69%

-Addition of D₂O lead to *no* incorporation of deuterium in products.

SmI₂ Radical Carbonyl-Alkene Cyclizations (-)-C₁₀-Desmethyl Arteannuim B

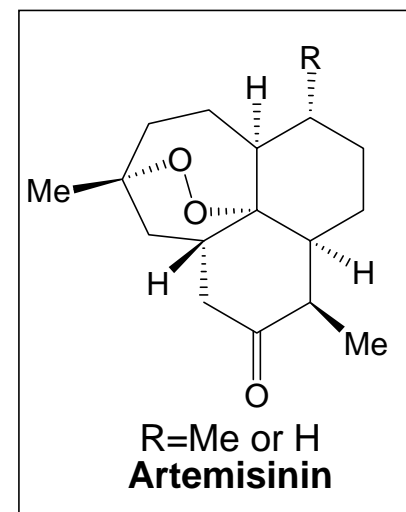


- α,β -unsaturated ester harder to reduce (E_p -2.45 V) than enone (E_p -2.2 V)

-Performing reaction at -78 °C leads to reduction of enone to allylic alcohol.

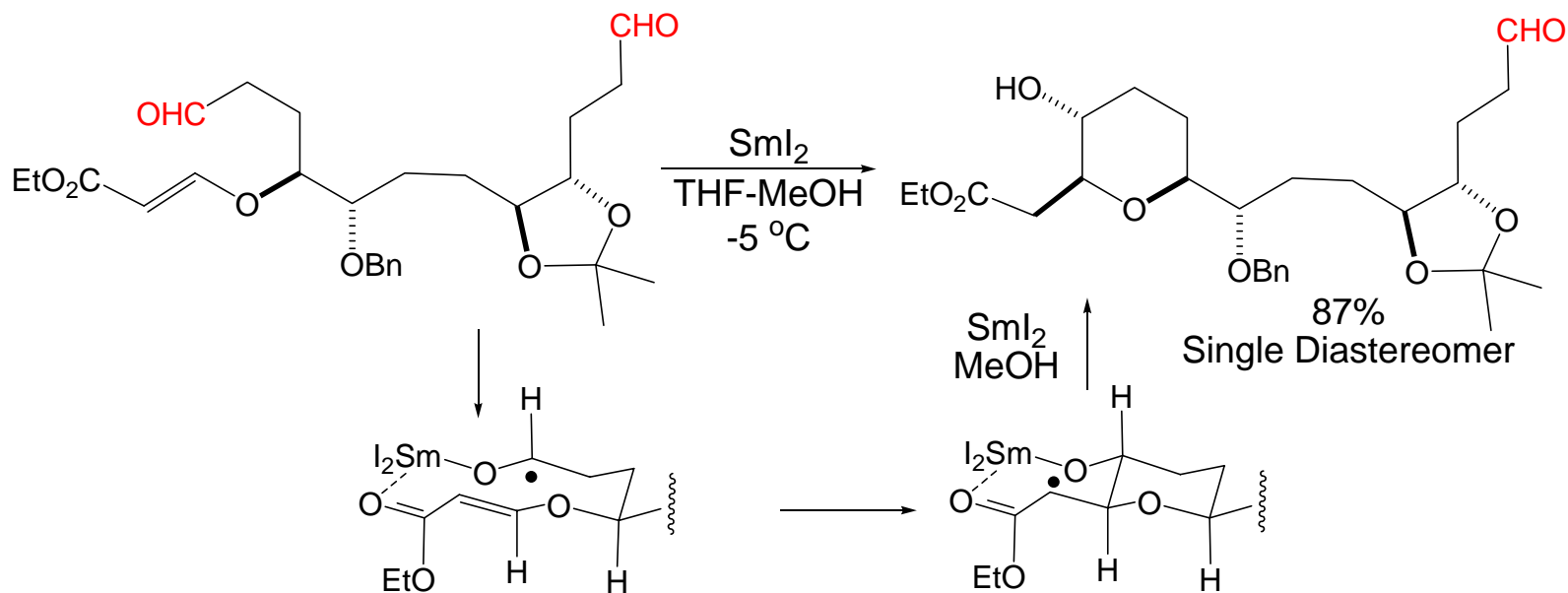
-Reaction required degassed solvents and slow separate addition of MeOH and SmI₂.

-Initial product acid sensitive, utilizing Rochelle's salt and a medium of 10% potassium carbonate significantly improved yields.



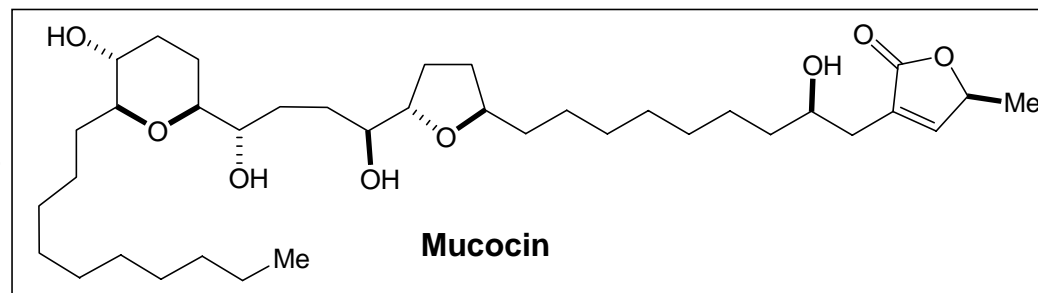
Sml₂ Radical Carbonyl-Alkene Cyclizations

Mucocin

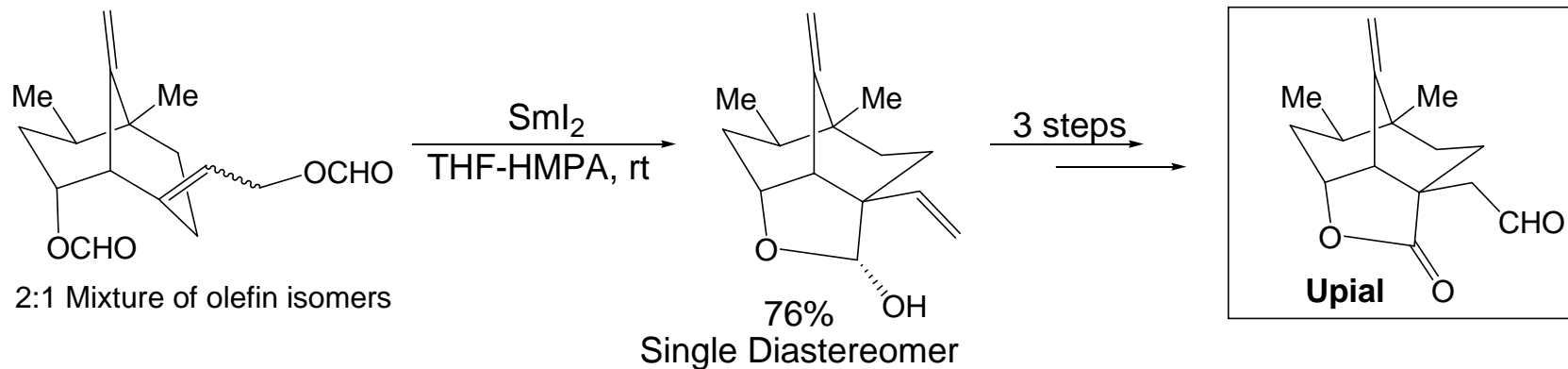


-Survival of second aldehyde suggests initial Sml₂ reduction is reversible

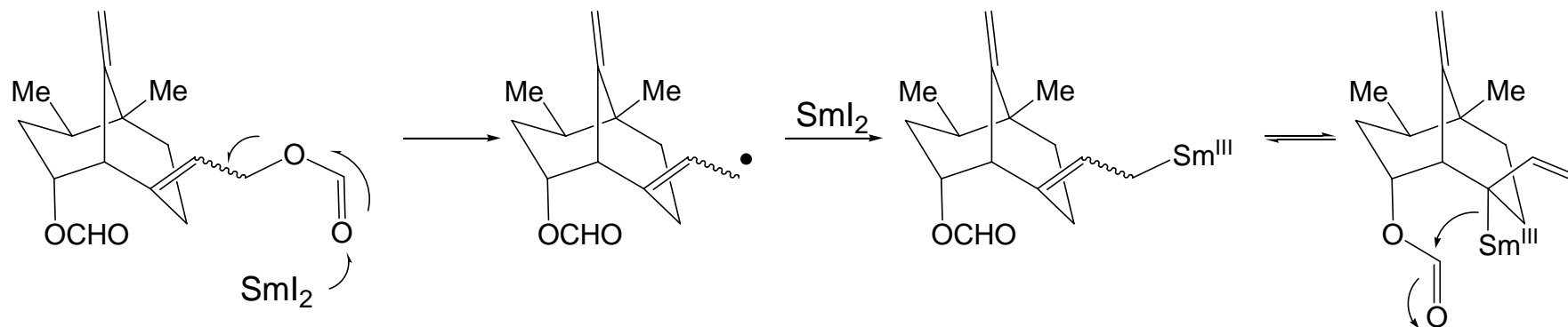
-Increasing reaction time or using larger amounts of Sml₂ leads to Pinacol-type coupling and reduction products.



SmI₂ Radical Carbonyl-Alkene Cyclizations Upial

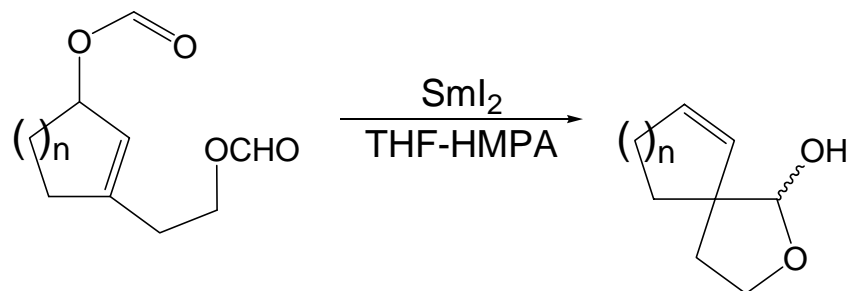


Proposed Mechanism



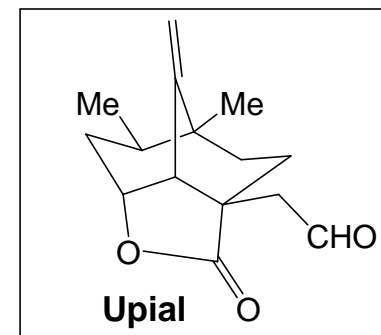
Nagaoka, H. *Tetrahedron Lett.* **1993**, 1504.
Shibuya, K. *J. Chem. Soc. Chem. Commun.* **1991**, 1545.
Procter, G. *Chem. Rev.* **2004**, 3371.

Sml₂ Radical Carbonyl-Alkene Cyclizations Model Studies: Upial

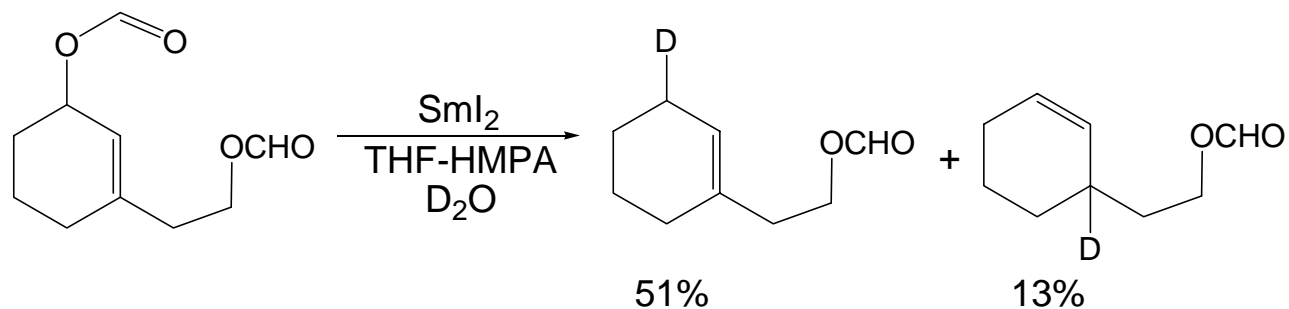


n	Yield
1	55%
2	73%
3	76%

Without HMPA product yields were 5-10%



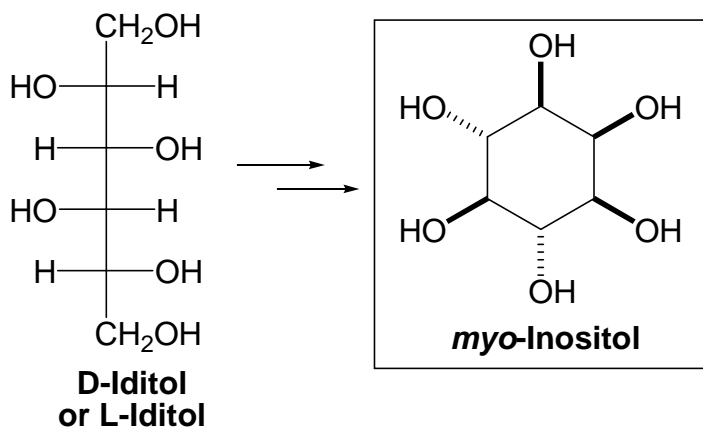
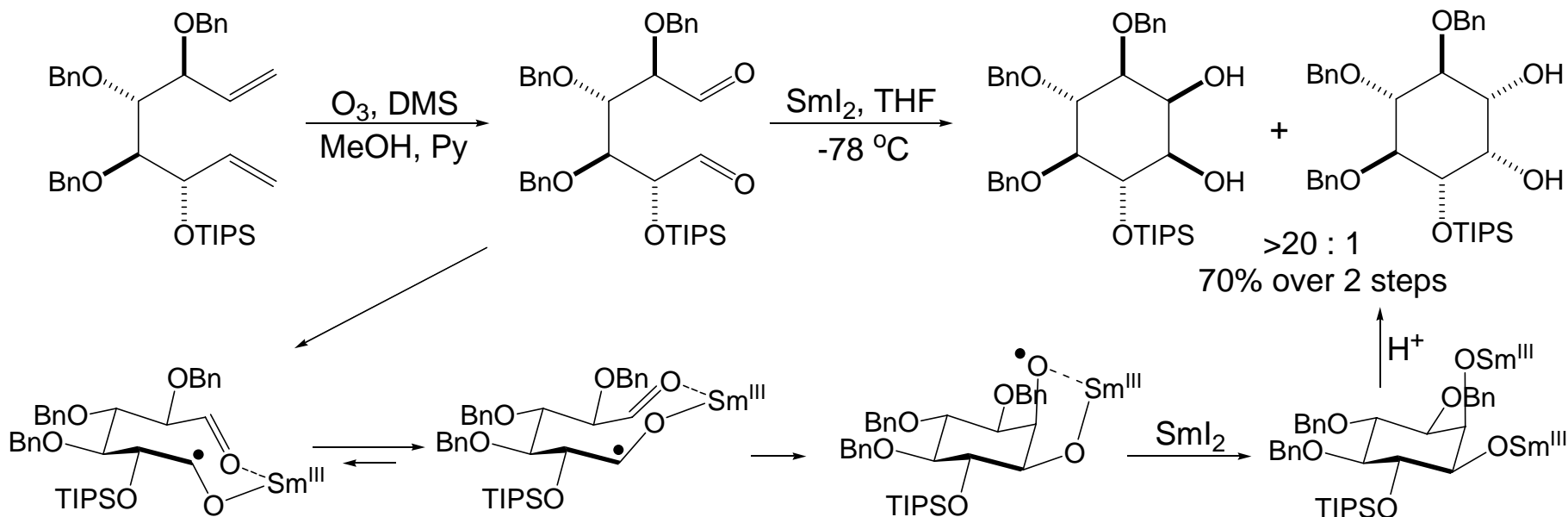
Supporting Evidence



Shibuya, K. *J. Chem. Soc. Chem. Commun.* **1991**, 1545.
Proctor, G. *Chem. Rev.* **2004**, 3371.

SmI₂ Intramolecular Pinacol Couplings

Basic Mechanism, *myo*-Inositol

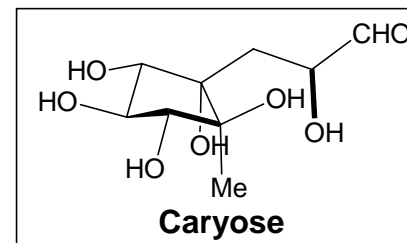
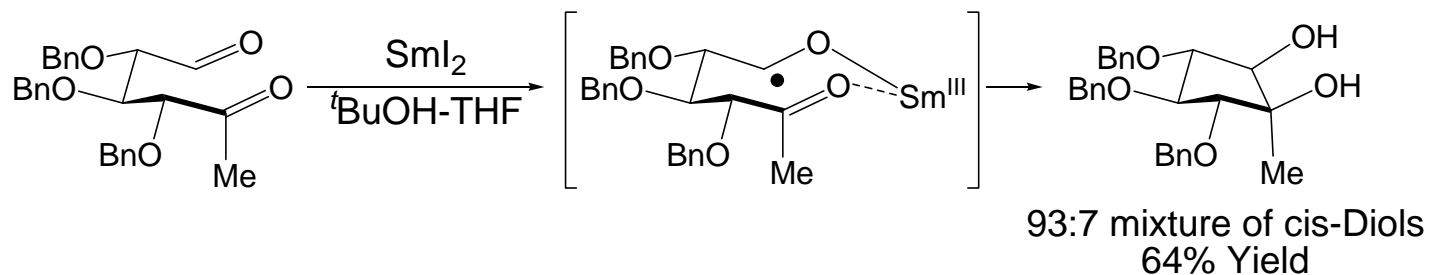


-Attractive alternative to TiCl₃-Zn/Cu, Mg(Hg)-TiCl₄, or Ytterbium pinacol couplings.

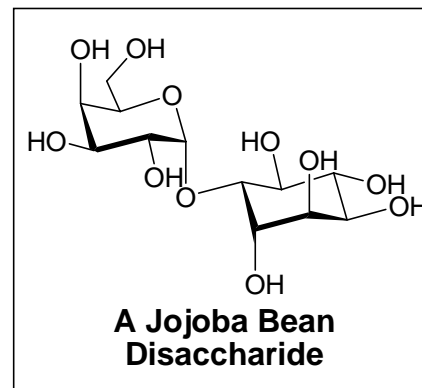
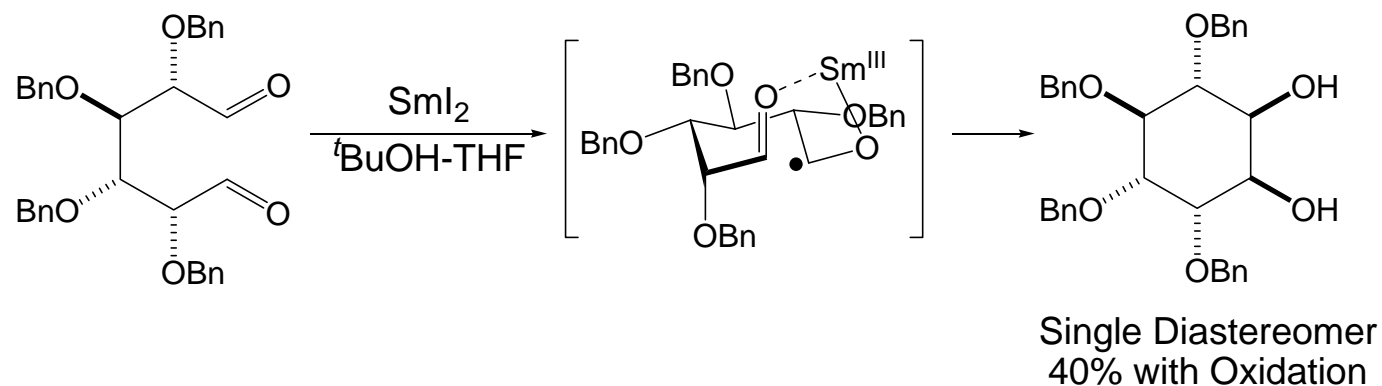
-Predominately gives cis-diol trans to α-substitution

Kornienko, A. *Tetrahedron Asymmetry* **1998**, 2783.
 Chiara, J. L. *Tetrahedron Letters* **1994**, 1969.
 Chiara J. L. *Tetrahedron Letters* **1991**, 1125.
 Guidot J. P. *Tetrahedron Letters* **1994**, 6671.
 Molander, G. A. *J. Am. Chem. Soc.* **1989**, 8236.
 dodong, U. K. *J. Org. Chem.* **1988**, 2132.

Sml₂ Intramolecular Pinacol Couplings Caryose and a Jojoba Bean Disacchride

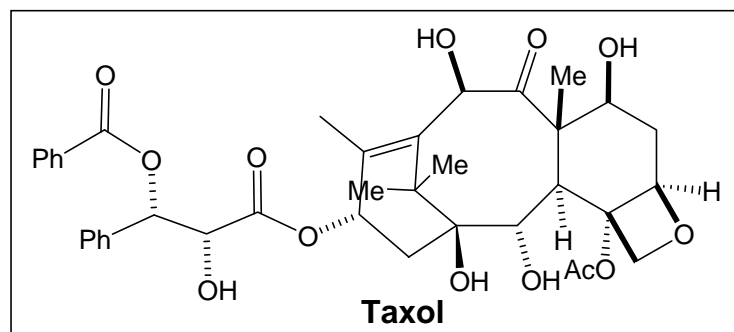
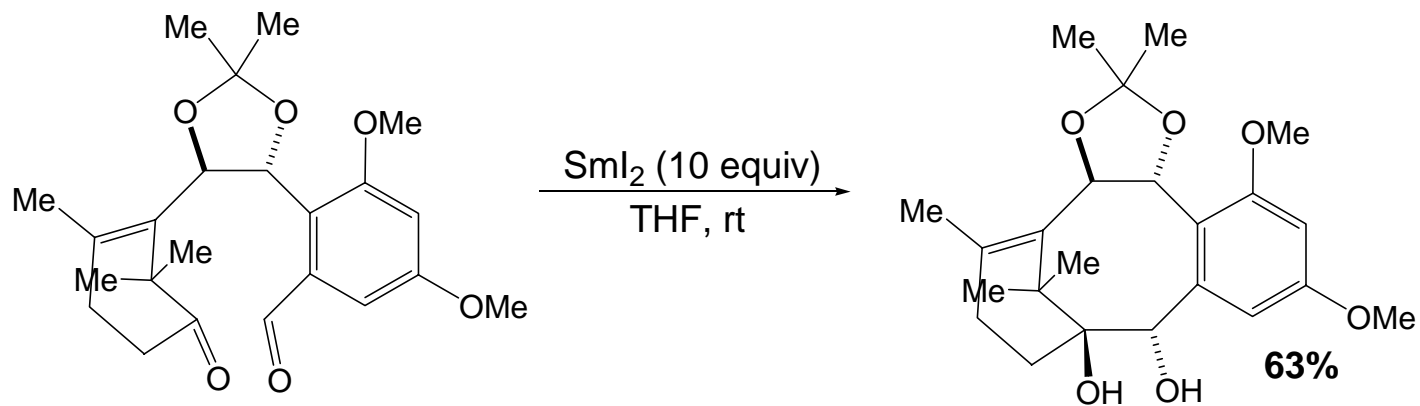


Adinolfi, M. *Tetrahedron* **1997**, 11767



Kornienko, A. *Carbohydrate Research* **1998**, 144.

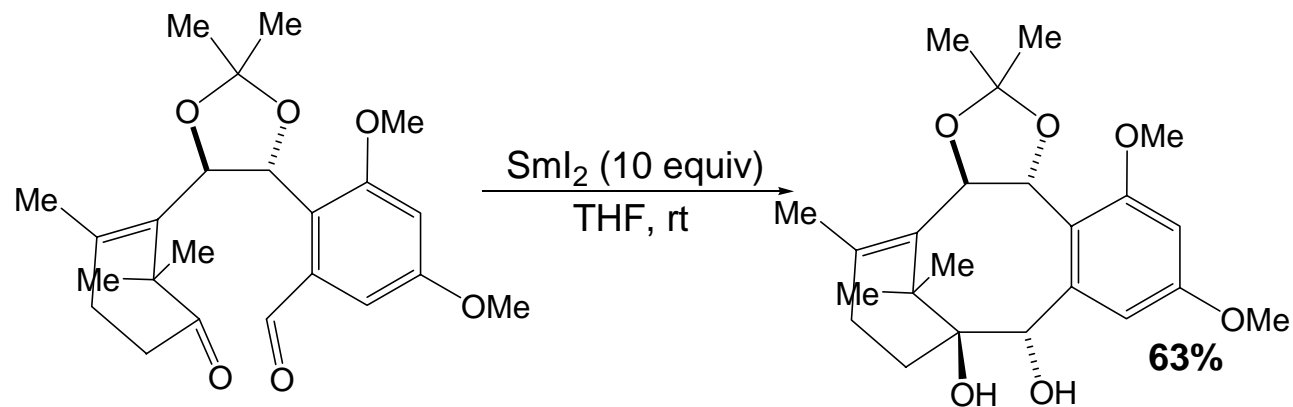
Sml₂ Intramolecular Pinacol Couplings Synthetic Studies Toward Taxol



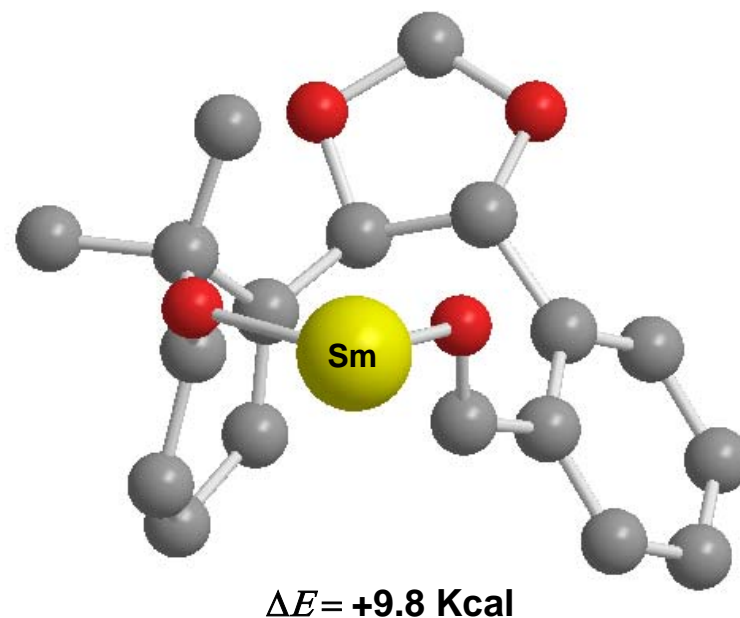
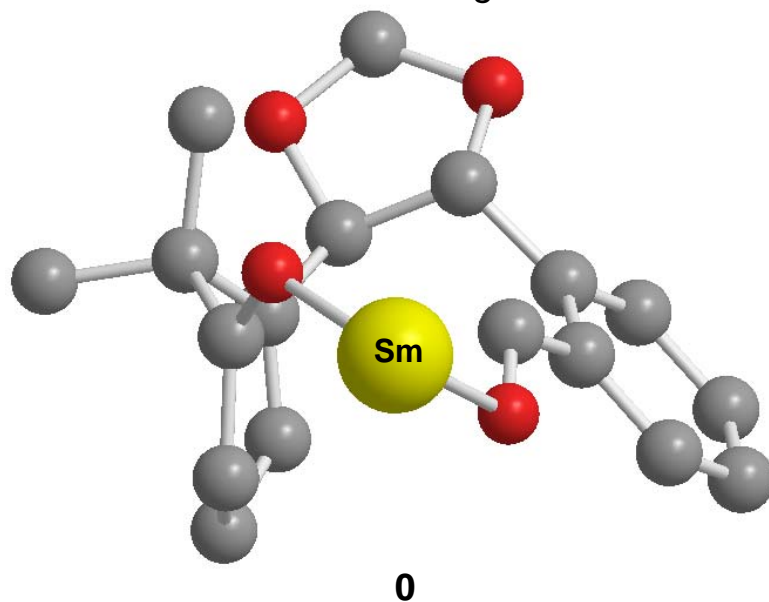
- Performing reaction at -78 °C leads to reduction
- Corresponding Pinacol with TiCl₄/Zn produces pdt in 33% yield.

Swindell, C. S. *J. Org. Chem.* **1996**, 1109.
Swindell, C. S. *Tetrahedron* **1996**, 2321.
Arseniyadis, S. *tetrahedron Lett.* **1993**, 1137.

SmI_2 Intramolecular Pinacol Couplings Synthetic Studies Toward Taxol



Sm-Chelated Models Minimized Energies

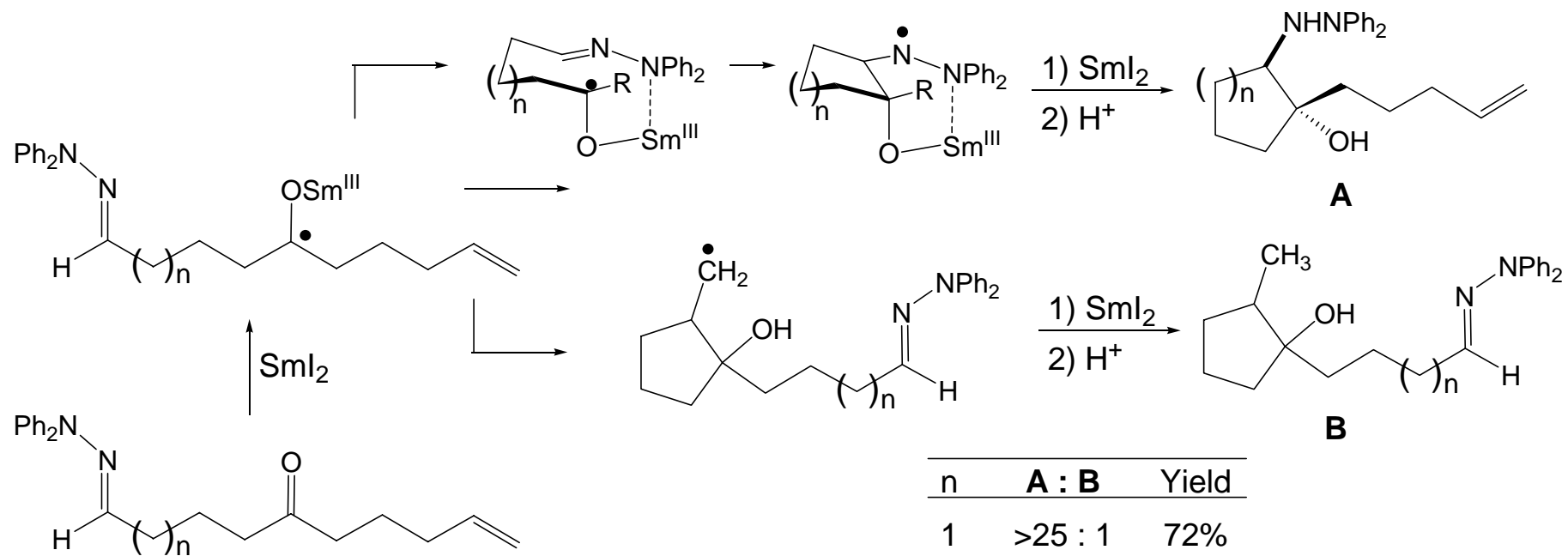


Minimized structures Utilizing Molecular Mechanics in Spartan 04',
Ground State conformers and restricting carbonyl-carbonyl
distance at 3.0 Å.

Swindell, C. S. *J. Org. Chem.* **1996**, 1109.
Swindell, C. S. *Tetrahedron* **1996**, 2321.
Arseniyadis, S. *tetrahedron Lett.* **1993**, 1137.

SmI₂ Intramolecular Reductive Coupling of Carbonyl-Hydrazones

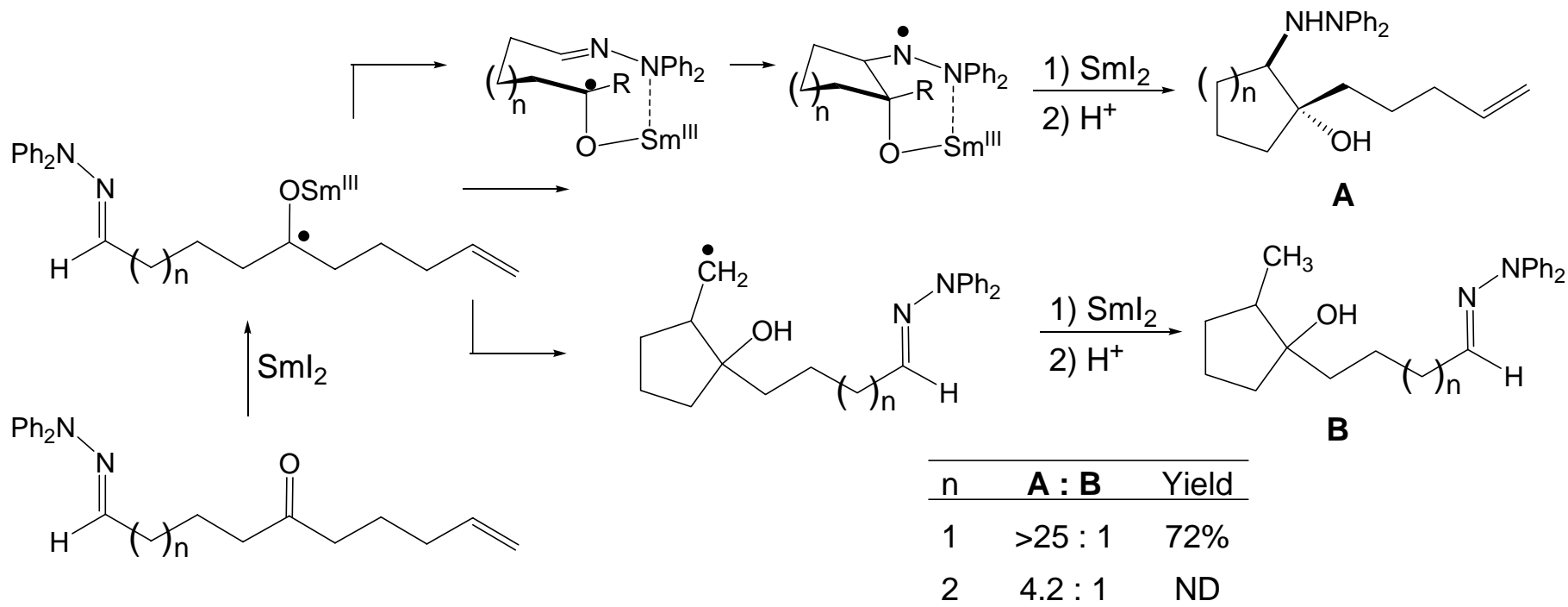
Basic Mechanism, An Example



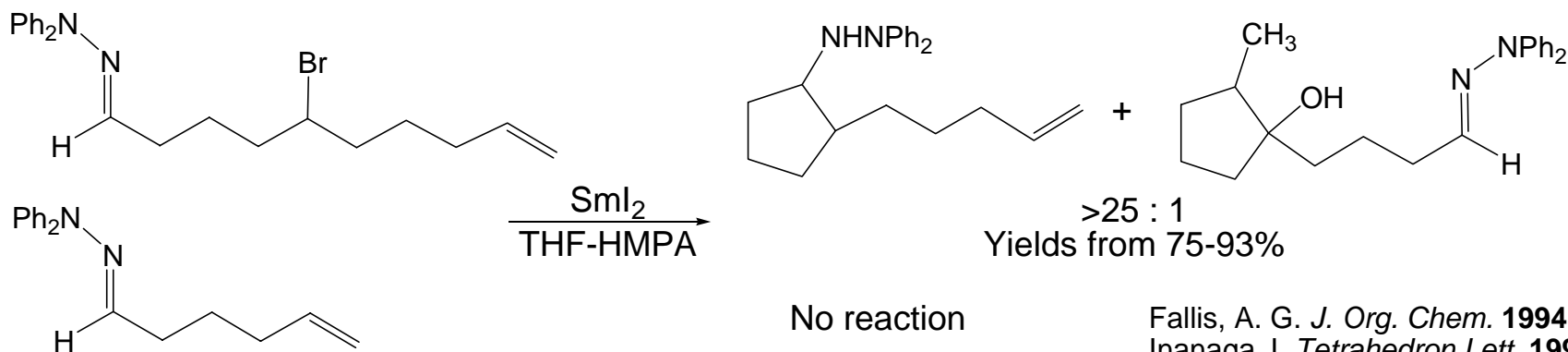
n	A : B	Yield
1	>25 : 1	72%
2	4.2 : 1	ND

Sml₂ Intramolecular Reductive Coupling of Carbonyl-Hydrazones

Basic Mechanism, An Example



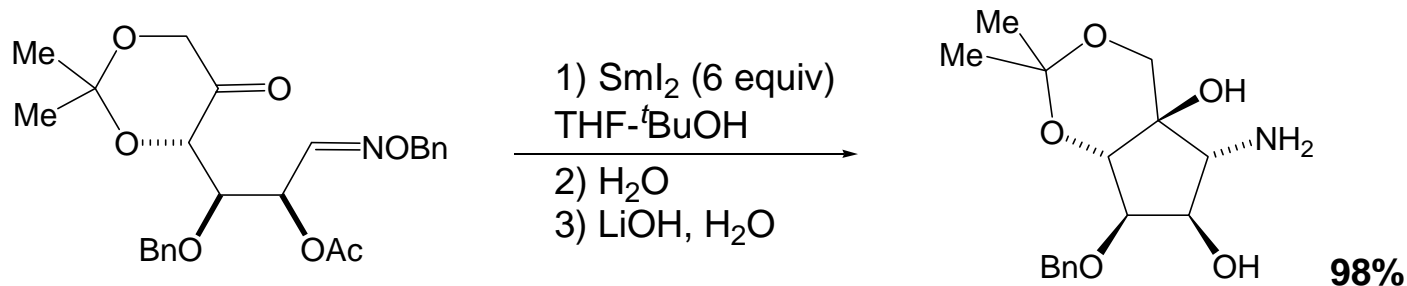
Additional Evidence



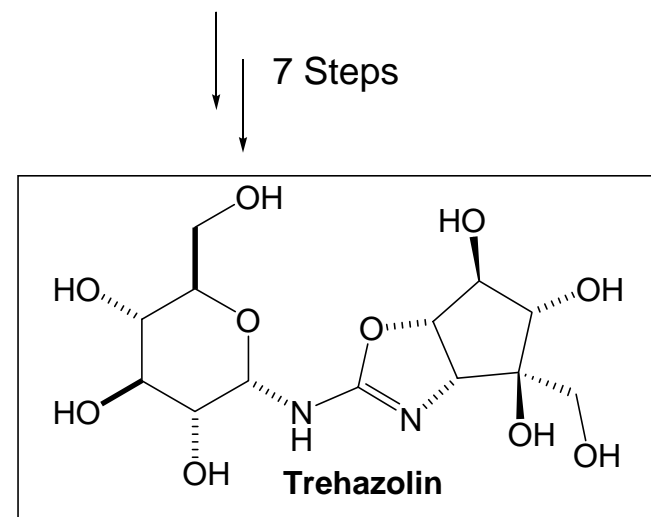
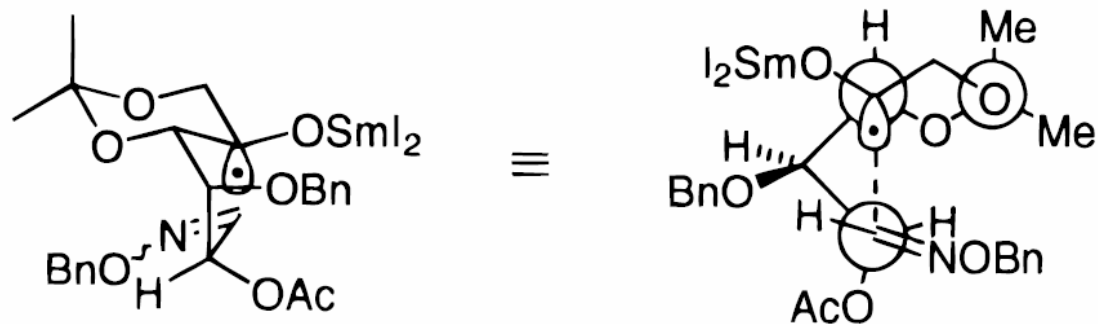
>25 : 1
Yields from 75-93%

Fallis, A. G. *J. Org. Chem.* **1994**, 6514.
Inanaga J. *Tetrahedron Lett.* **1991**, 3555.
Fallis A. G. *J. Am. Chem. Soc.* **1994**, 7447.

Sml₂ Intramolecular Reductive Coupling of Carbonyl-Oximes Synthesis of Trehazolin

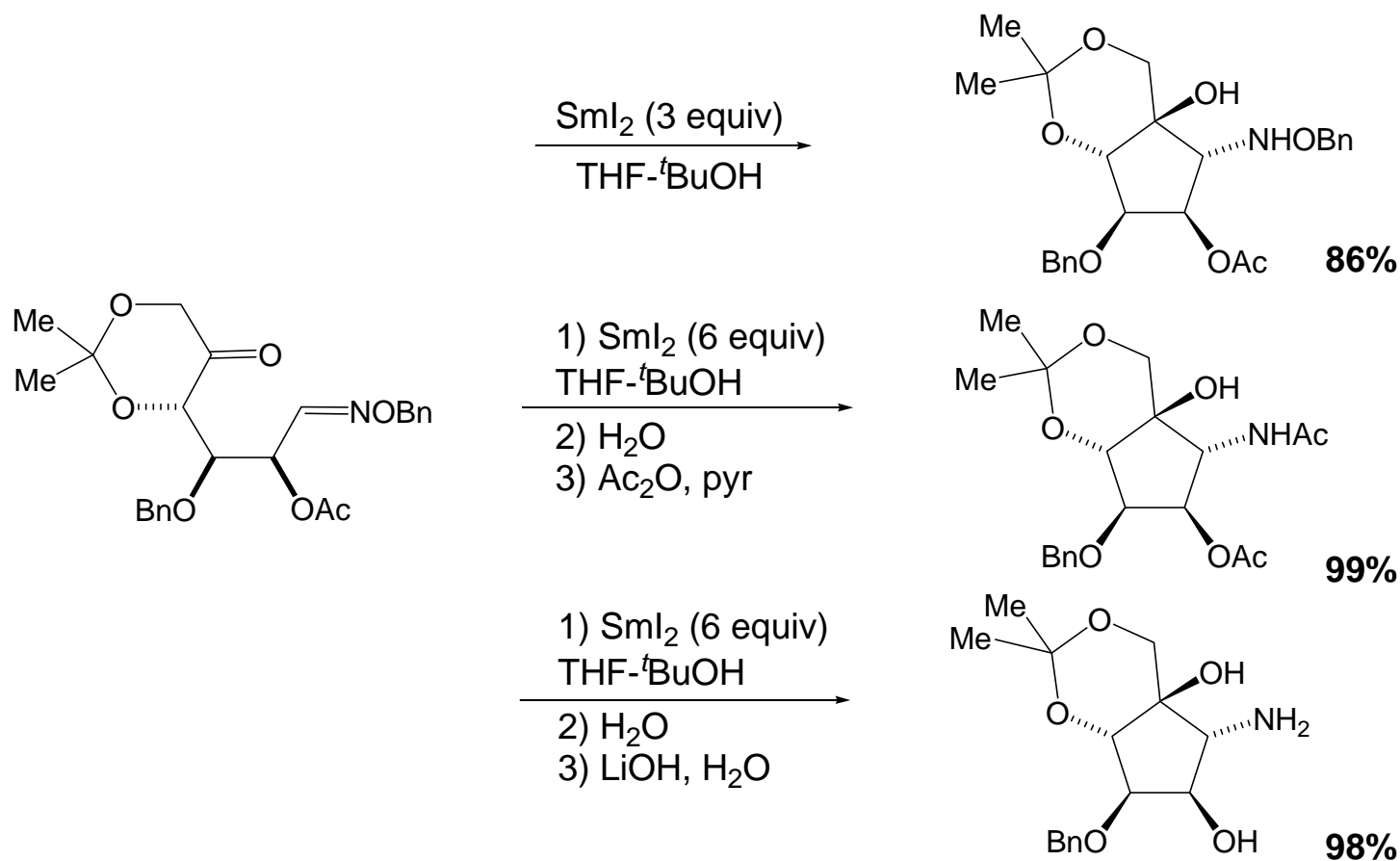


Proposed Transition States



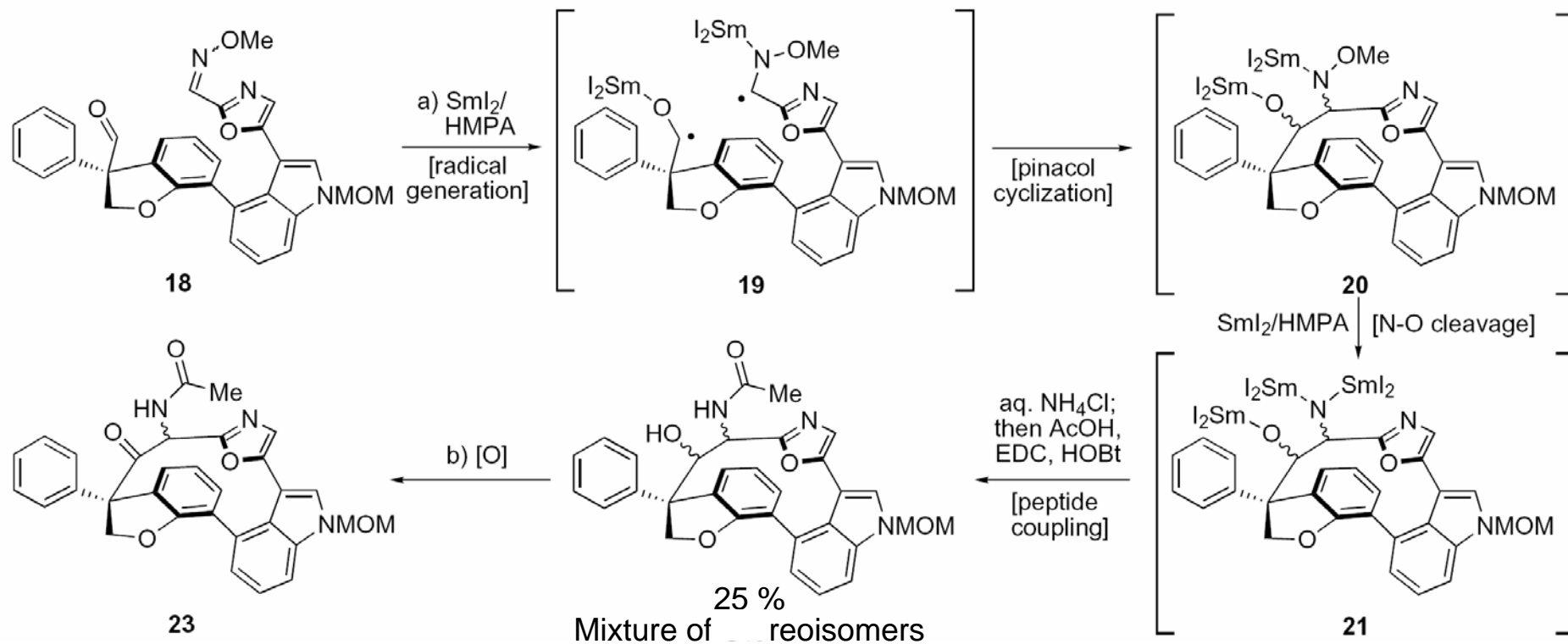
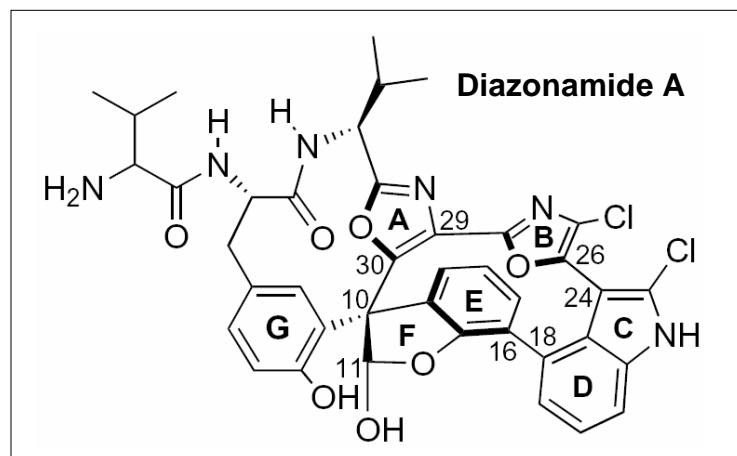
Chiara, J. L. *Org. Lett.* **1999**, 1705.
Giese, B. *J. Org. Chem.* **1998**, 5877.
Chiara, J. L. *Synlett* **1999**, 1551.

Sml₂ Intramolecular Reductive Coupling of Carbonyl-Oximes Synthesis of Trehazolin



Chiara, J. L. *Org. Lett.* **1999**, 1705.
Giese, B. *J. Org. Chem.* **1998**, 5877.
Chiara, J. L. *Synlett* **1999**, 1551.

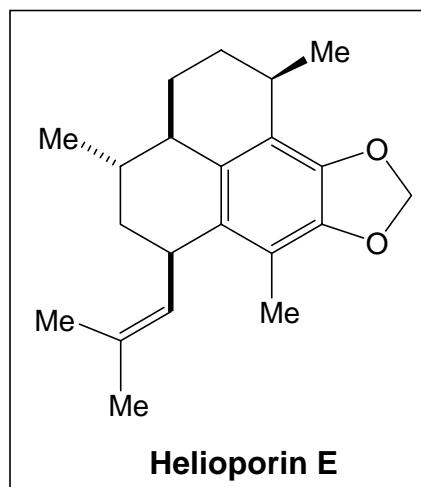
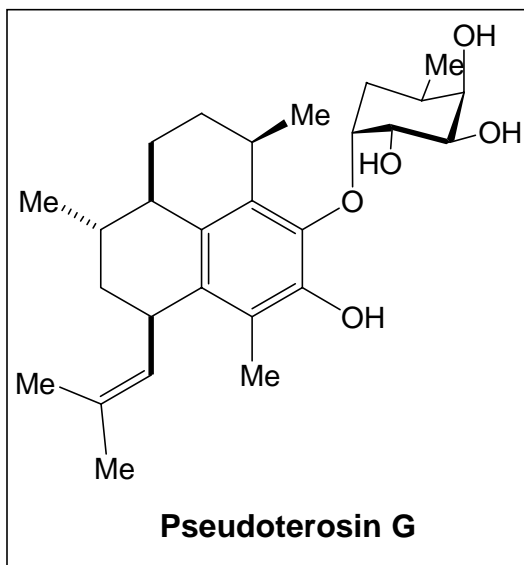
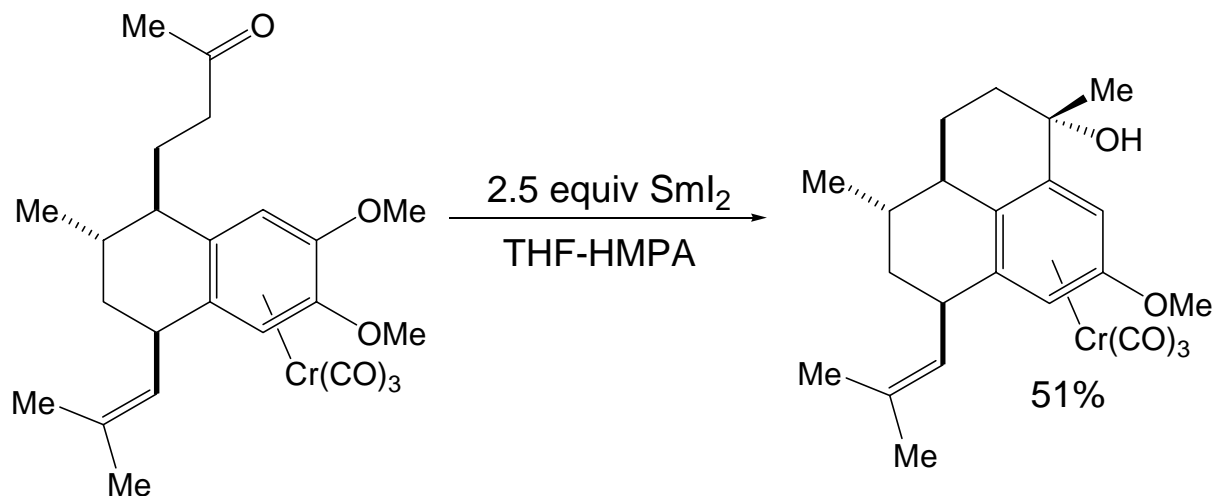
Sml₂ Intramolecular Reductive Coupling
of Carbonyl-Oximes
Synthesis of Diazonamide A



-No reaction in the absence of HMPA

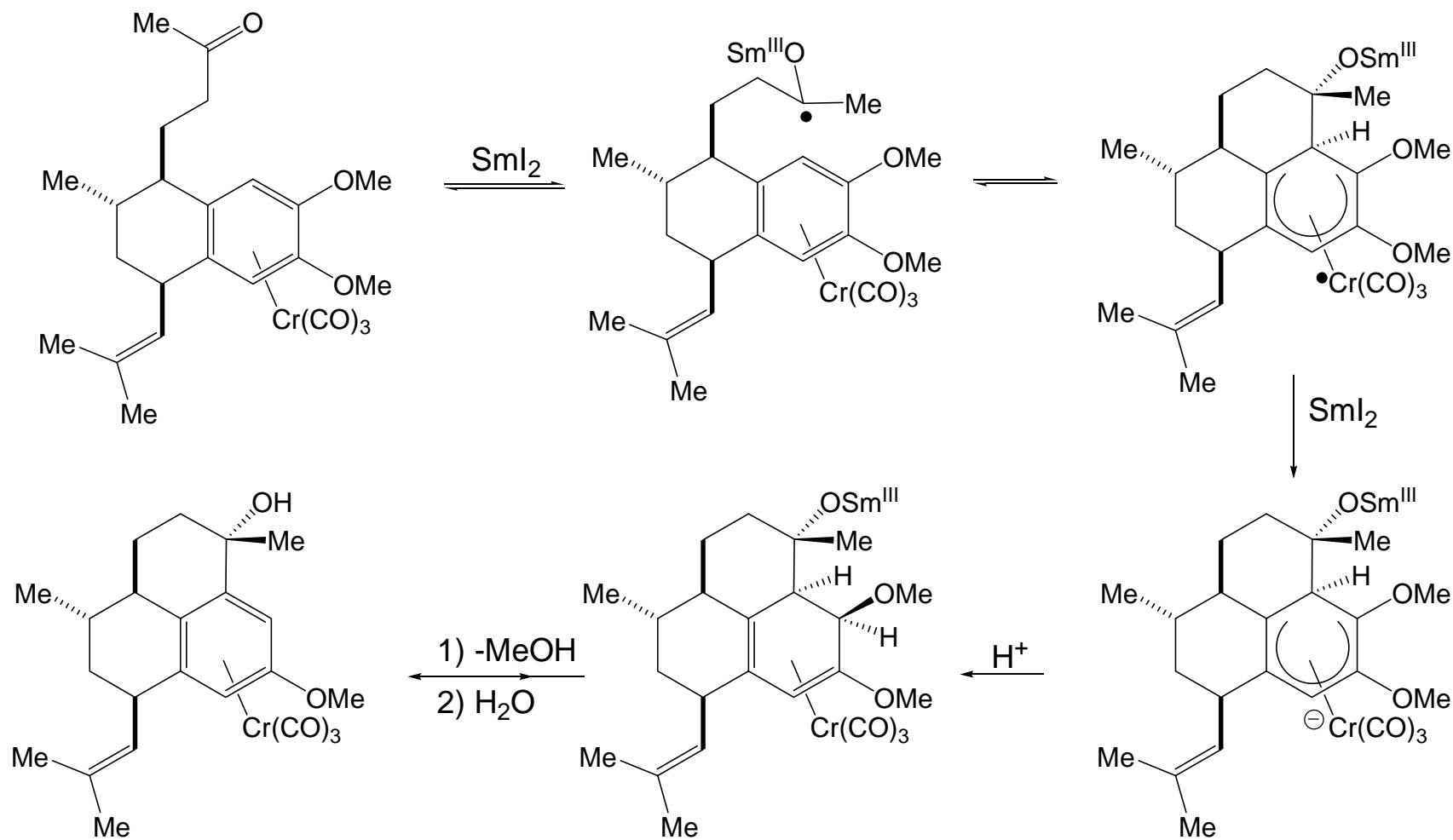
Nicolaou, K. C. *ACIEE* **2001**, 4705.
Nicolaou, K. C. *ACIEE* **2003**, 1753.

Sml₂ Intramolecular Reductive Arene-Cr(CO)₃-Carbonyl Cyclizations Synthetic Studies Towards Pseudoterosin G and Heliopirin E



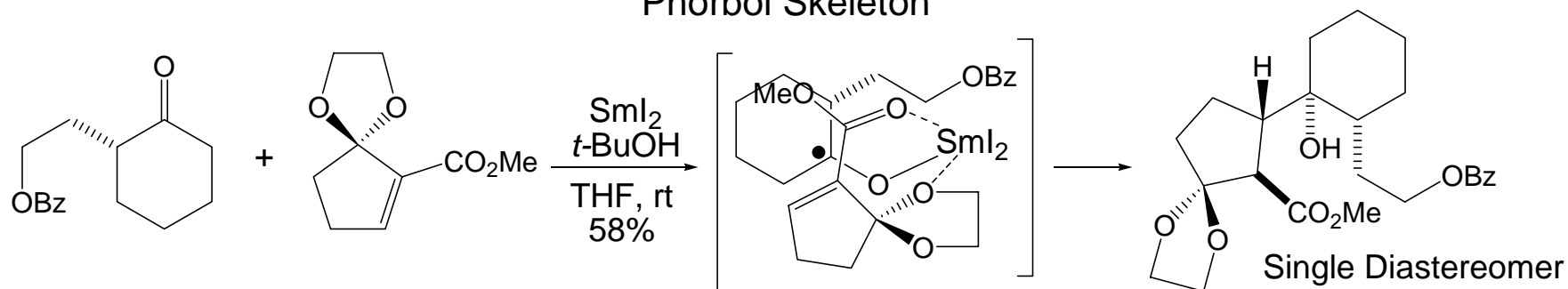
Schmalz, H.-G. *Tetrahedron Lett.* **1996**, 1947.
Schmalz, H.-G. *J. Org. Chem.* **1995**, 2383.
Higa, T. *Tetrahedron* **1993**, 811.
Fenical, W. J. *Org. Chem.* **1990**, 4916.

SmI₂ Intramolecular Reductive Arene-Cr(CO)₃-Carbonyl Cyclizations Mechanism

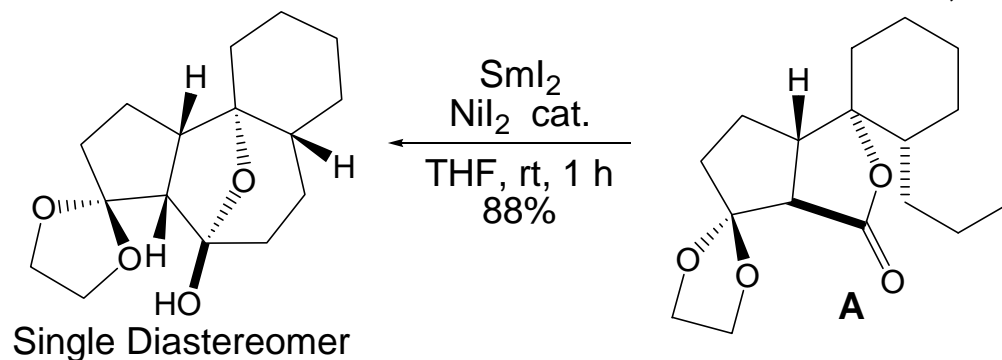
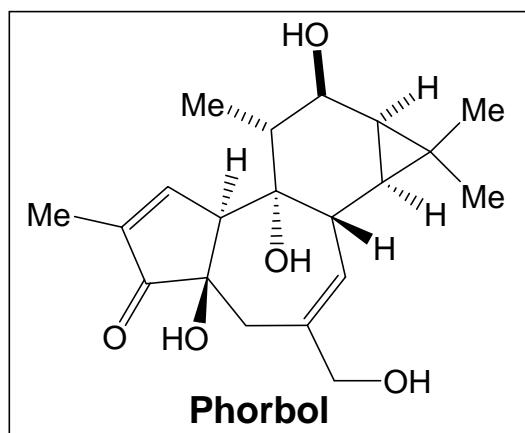


Schmalz, H.-G. *Tetrahedron Lett.* **1996**, 1947.
Schmalz, H.-G. *J. Org. Chem.* **1995**, 2383.

Carbonyl-Olefin Reductive Coupling/Intramolecular SmI_2 Barbier Cyclization Phorbol Skeleton

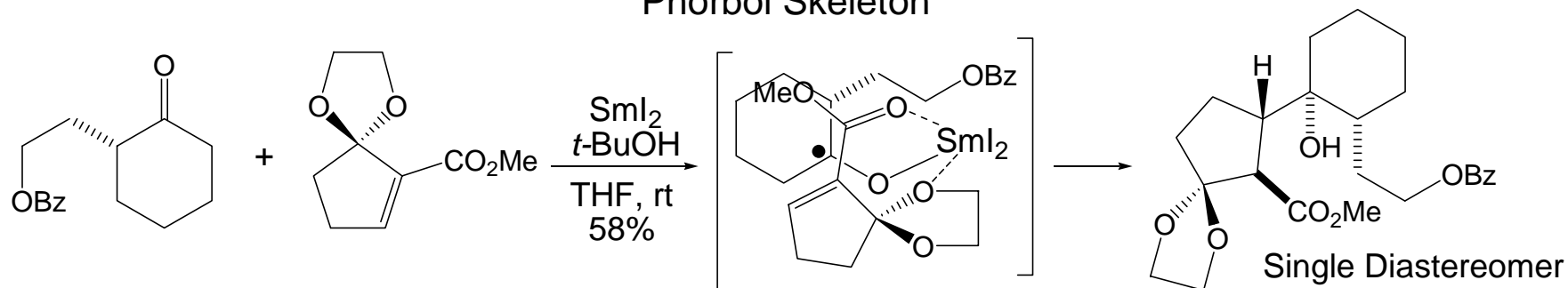


1) NaOMe, MeOH
THF, 85%
2) I_2 , PPh_3
Imidazole
THF, 90%

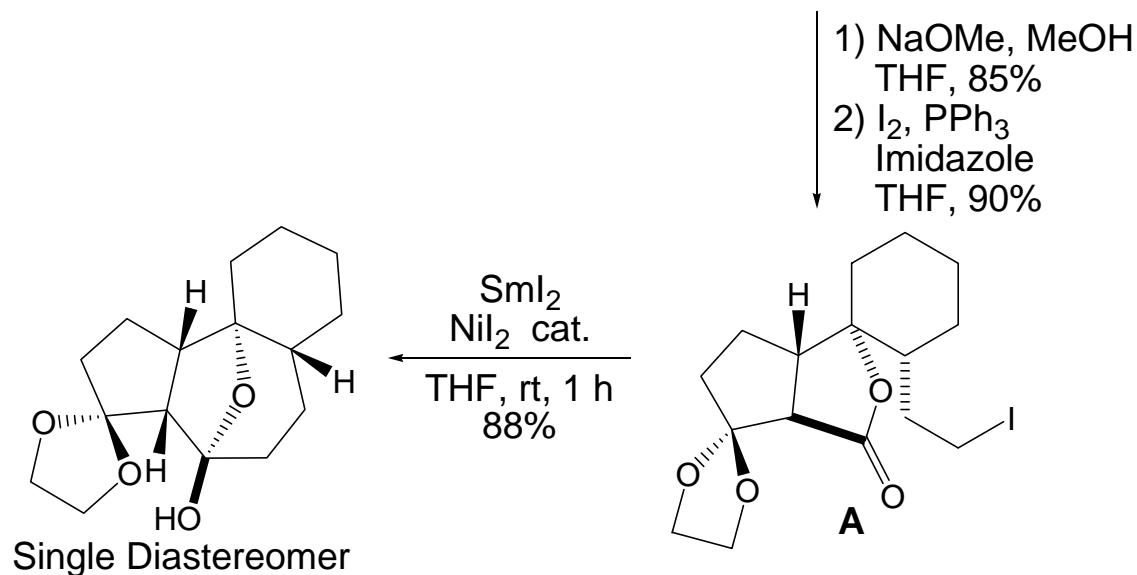
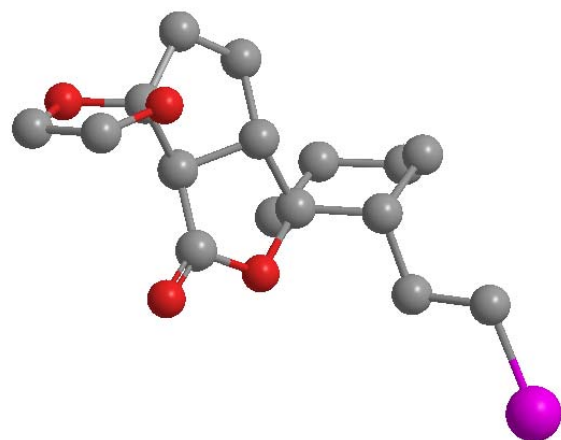


Conditions	Time	Yield
No Additive	5-7h	43-68%
With Nil_2	1h	82-88%

Carbonyl-Olefin Reductive Coupling/Intramolecular SmI₂ Barbier Cyclization Phorbol Skeleton

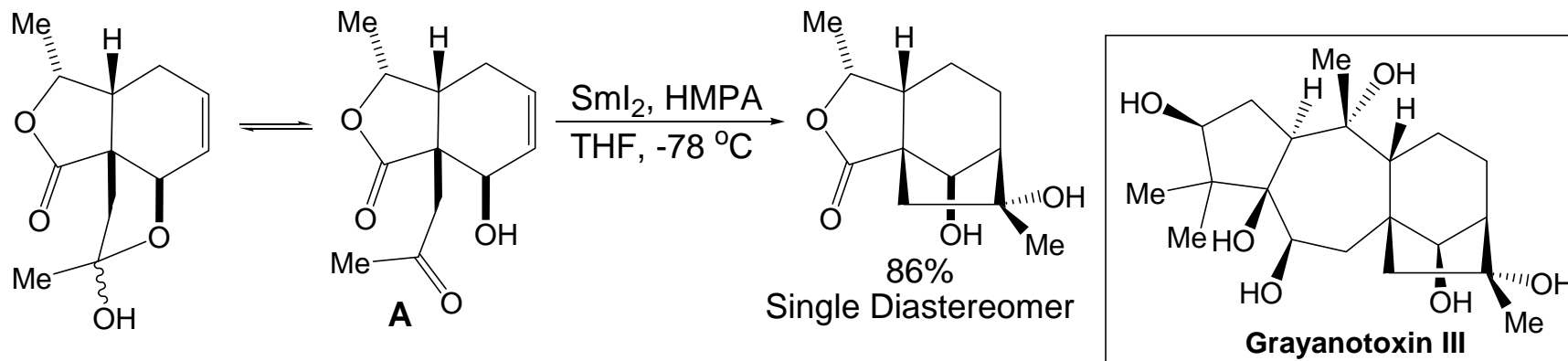


Model of Intermediate A

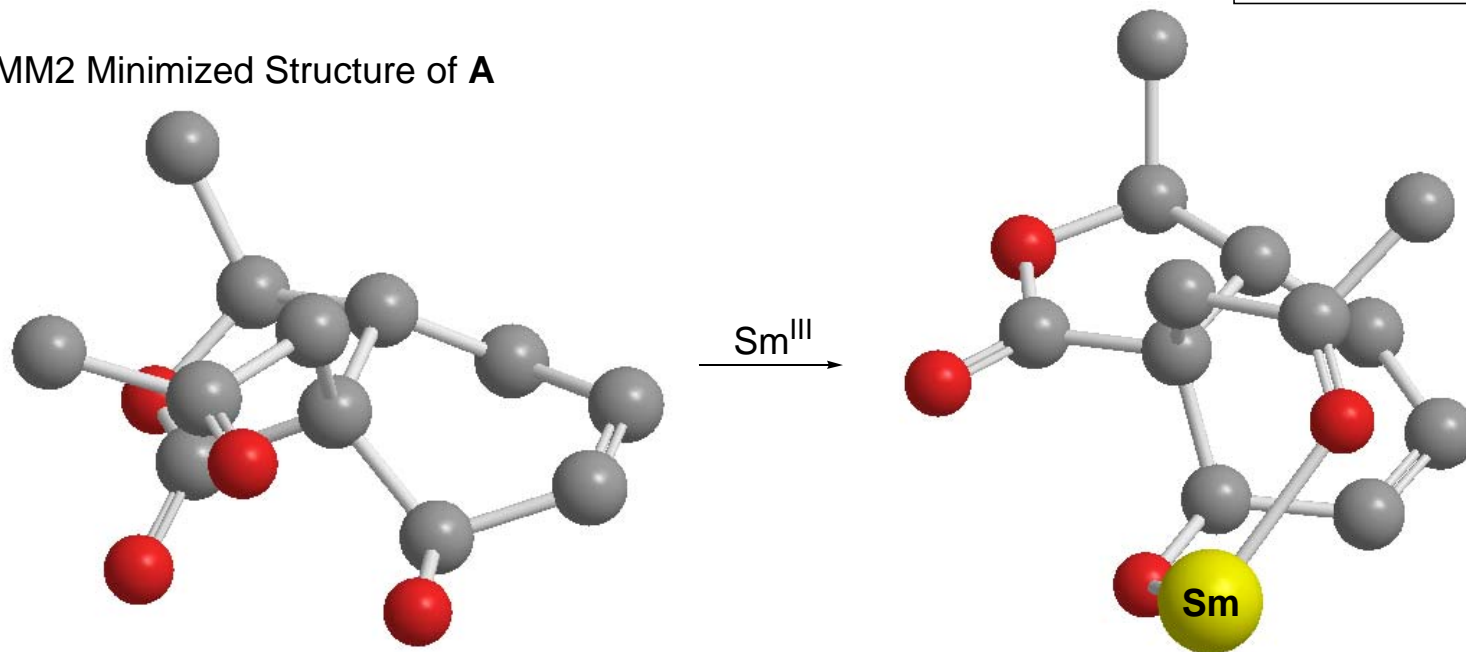


Conditions	Time	Yield
No Additive	5-7h	43-68%
With NiI ₂	1h	82-88%

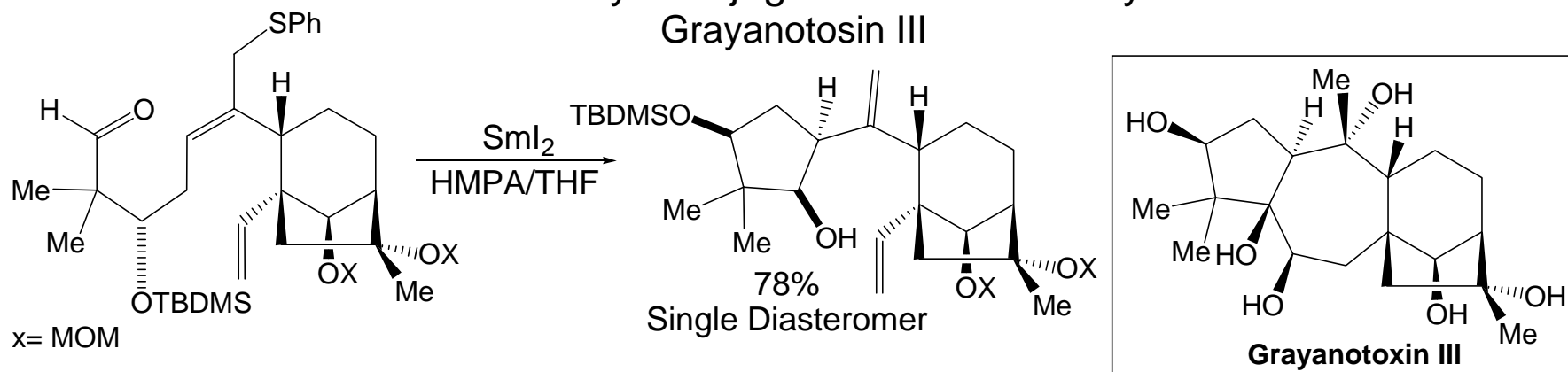
Reductive Carbonyl Conjugate and Pinacol Cyclizations Grayanotosin III



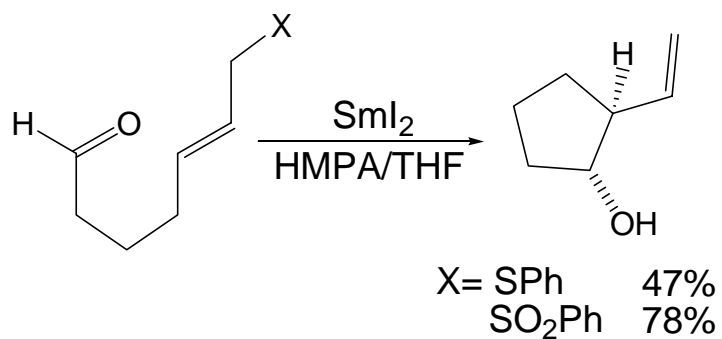
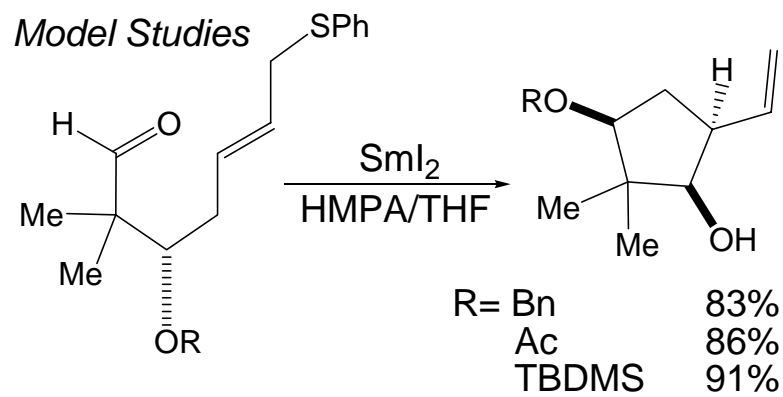
MM2 Minimized Structure of A



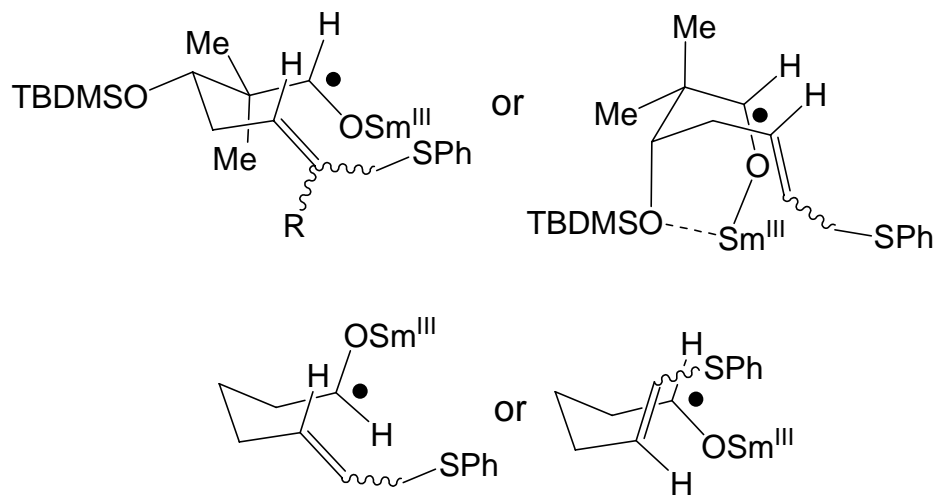
Reductive Carbonyl Conjugate and Pinacol Cyclizations Grayanotosin III



-Both *E* and *Z*-allyl sulfides gave the same product in similar yields

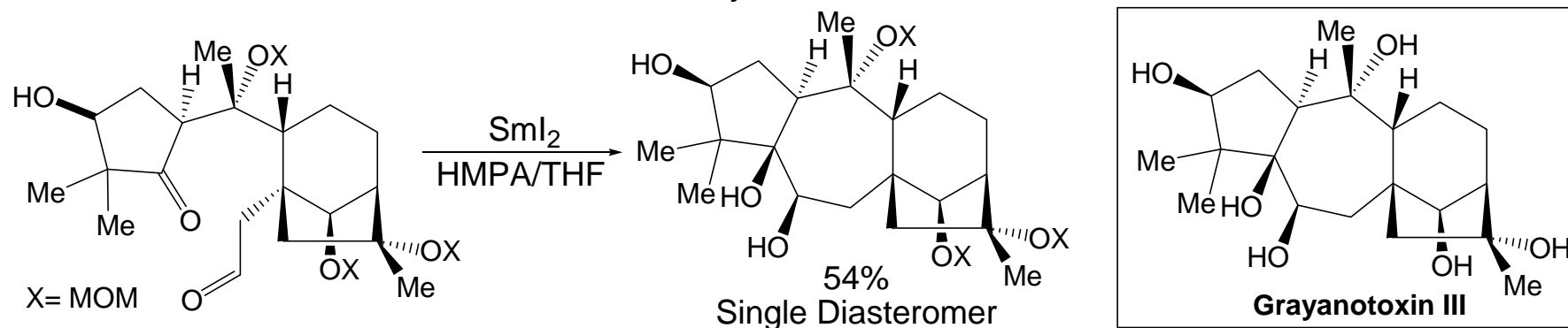


Plausible Transition States

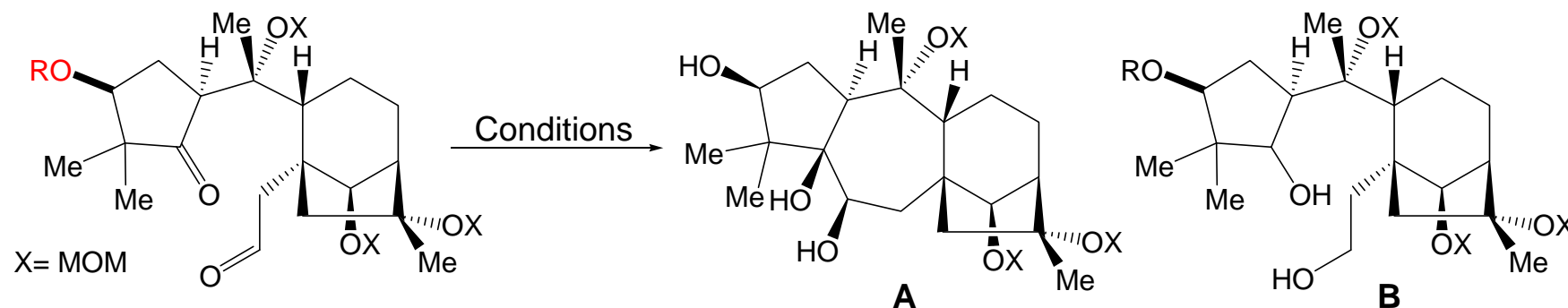


Kan, T. *J. Org. Chem.* **1994**, 5532.
Kan, T. *J. Org. Chem.* **1994**, 5113.

Reductive Carbonyl Conjugate and Pinacol Cyclizations Grayanotoxin III

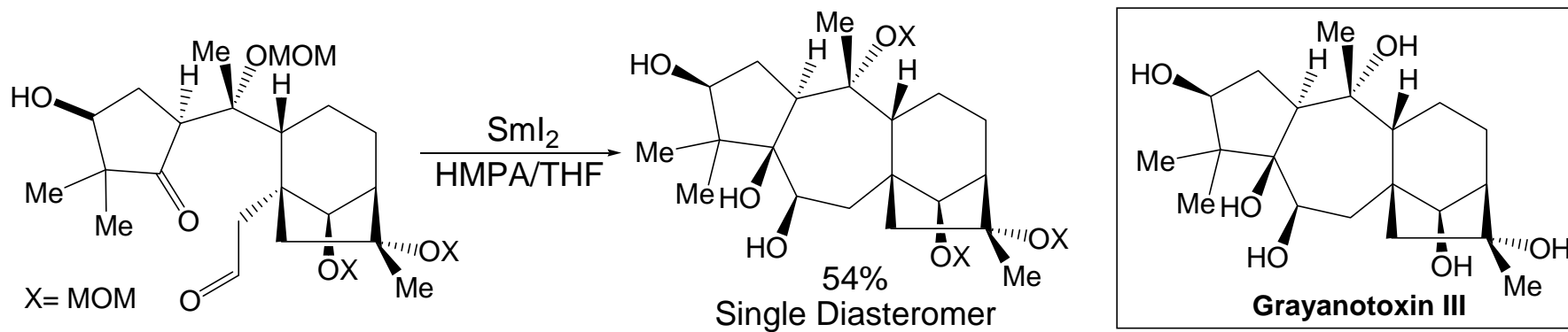


Model Studies

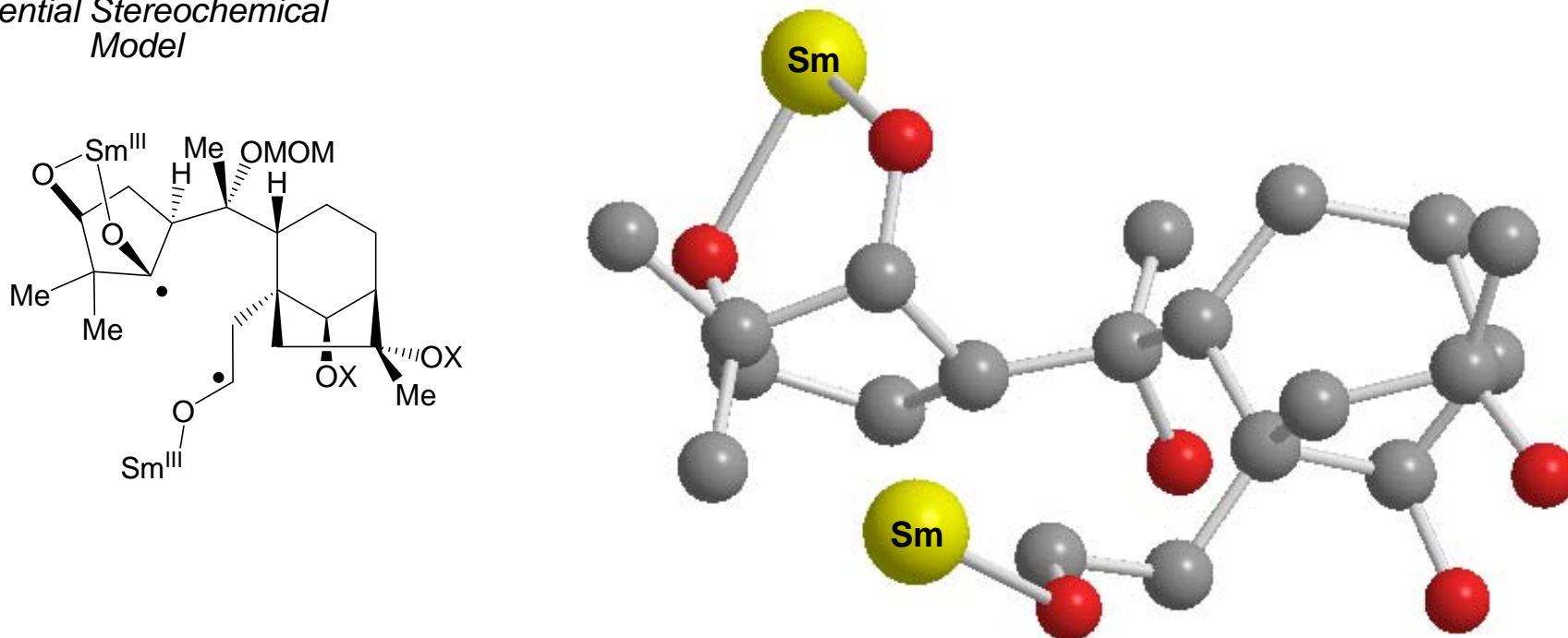


Conditions	R	%A	%B
Titanium-pinacol	NA	decomposition	
SmI_2 , HMPA-THF	MOM	ND	Sole prd
SmI_2 , HMPA-THF	H	50%	ND

Reductive Carbonyl Conjugate and Pinacol Cyclizations Grayanotoxin III



Potential Stereochemical Model



Kan, T. *J. Org. Chem.* **1994**, 5532.
Kan, T. *Synlett*, **1991**, 391.

Concluding Remarks

Benefits of Samarium Diiodide Cyclizations

- Samarium diiodide shows great functional group tolerance.
- The redox potential of SmI_2 can be altered by changes in: solvent, co-solvents, ligands, additives, light, and counter ions. This allows fine tuning of the one electron reduction so that relative rates of functional group reductions can be estimated and controlled. (For the reduction potential of several functional groups see: Fry, A. J. *Synthetic Organic Electrochemistry*, 2nd ed.; John Wiley and Sons: New York, 1989.)
- Samarium diiodide has been used successfully in multiple total synthetic endeavors as a mild single electron chelating reducing agent.
- Due to samarium diiodide's large ionic radius, high coordination number, and high oxophilicity samarium diiodide has been used successfully as a chelating element to bring two reacting centers in proximity to form large ring systems.
- Samarium diiodide has been shown to be a superior alternative to traditional methods for Barbier, Pinacol, Reformatsky, Carbonyl-Alkene, and Carbonyl-Alkyne cyclizations.

Drawbacks of Samarium Diiodide Cyclizations

- The uncertainty in the mechanism of the transformations limits the stereochemical predictive potential of the reagent.