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 mutiple 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**

SmI_2 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 CH_2I_2, ICH_2CH_2I, or I_2.

-Reactions are generally performed with an excess of samarium diiodide, degassed reagents and solvents, and in dry THF containing an antioxidant.

-Catalytic amounts of SmI_2 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 SmI_2. 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 SmI_2 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-sustituted carbonyls, cyclopropyl ketones, epoxides, amine oxides, sulfoxides, phosphine oxides, sulfones, sulfonates, nitro, nitroso, and azo compounds, allyl acetates, and isoxazoles.

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

SmI_2 Reduction Potential

-Samarium diiodide is a polyvalent single electron reducing agent.

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

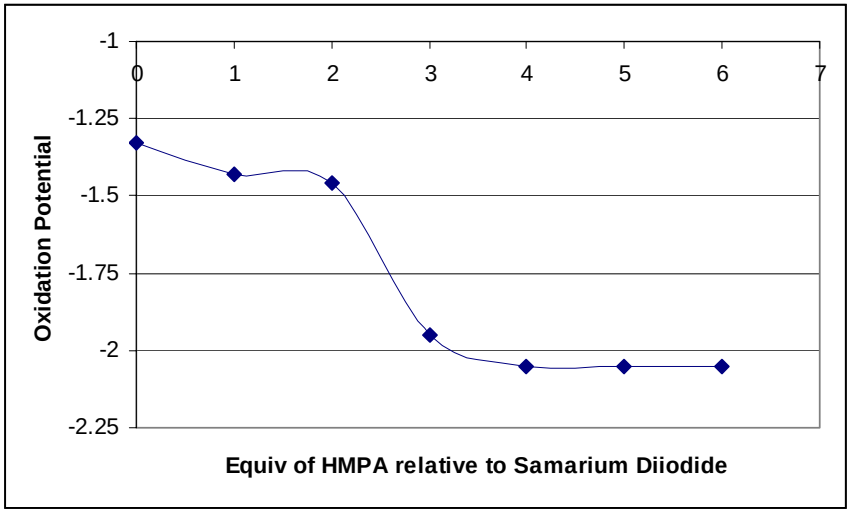
-The reduction potential of SmI_2 can be increased by the addition of HMPA, and LiBr or LiCl.

-The addition of transition metal increases the rate of several SmI_2 reactions.
(Kagan, H. B. *Synlett* **1996**, 633)

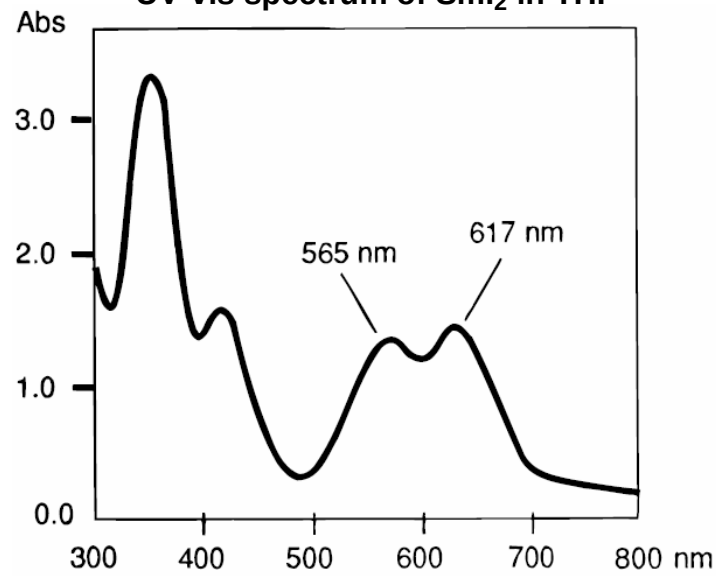
-Changes in protic solvents can alter the rates of SmI_2 mediated reactions and in some cases alter the mechanism.

-Visible light increases the reduction potential of SmI_2. (Ogawa, A. *J. Am. Chem. Soc.* **1997**, 2745)

Effects on the E^o of SmI_2 with HMPA



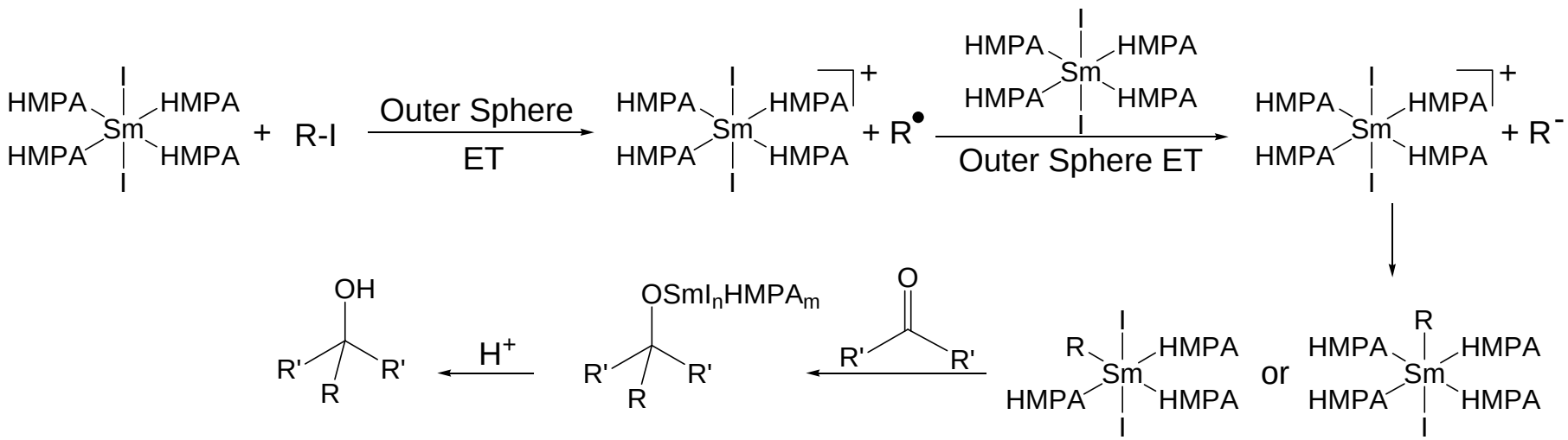
UV-vis spectrum of SmI_2 in THF



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

SmI_2 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.

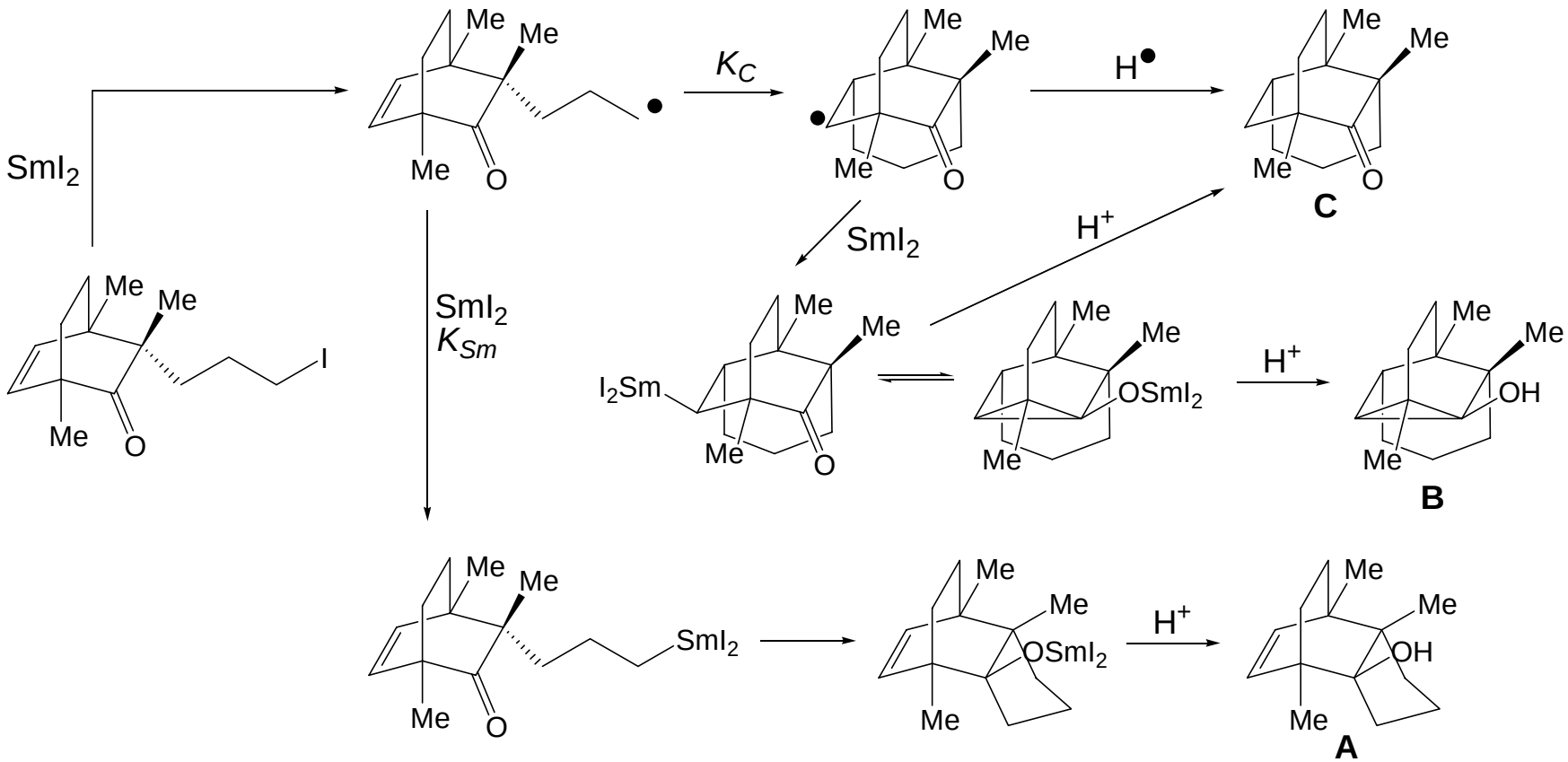
-The replacemed of HMPA with LiBr predominately leads to the Pinacol product via inner sphere electron transport/reduction of the ketone via formation of $SmBr_2$.

-Replacement of HMPA with HMDS leads to the formation of $[Sm(HMDS)_2]_2$, which has a redox potential inbetween SmI_2 and $[Sm(HMPA)_6]I_2$. $[Sm(HMDS)_2]_2$ reacts faster with alkyl halides and ketones via change in mechanism towards an inner sphere ET process.

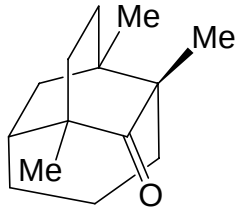
Molander, G. *J. Am. Chem. Soc.* **1987**, 6556.
Curran, D. P. *Synlett* **1992**, 943.
Flowers, R. A. *Org. Lett.* **1999**, 2133.
Flowers, R. A. *J. Am. Chem. Soc.* **2000**, 7718.
Flowers, R. A. *J. Am. Chem. Soc.* **2002**, 6895.
Flowers, R. A. *J. Am. Chem. Soc.* **2002**, 14663.
Flowers, R. A.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

Intramolecular SmI_2 Barbier Reactions

Basic Mechanism



SmI_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%



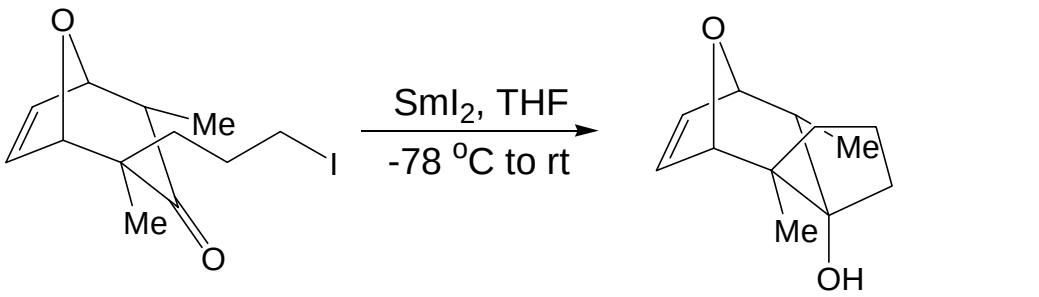
D

Reactions performed with 2 equiv of SmI_2 and 20 equiv of HMPA

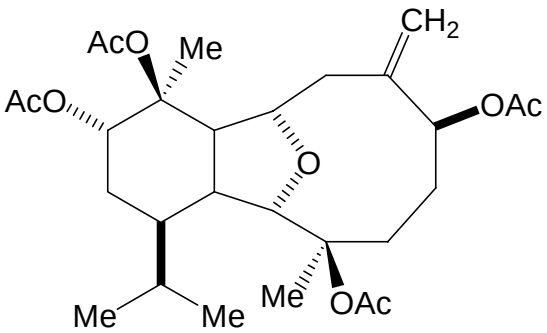
Curran, D. P. *Tetrahedron* **1997,** 9023
Krief, A. *Chem. Rev.* **1999**, 745
Molander, G. A. *J. Org. Chem.* **1991**, 4112

Intramolecular SmI_2 Barbier Reactions

Eunicellin and Muscone

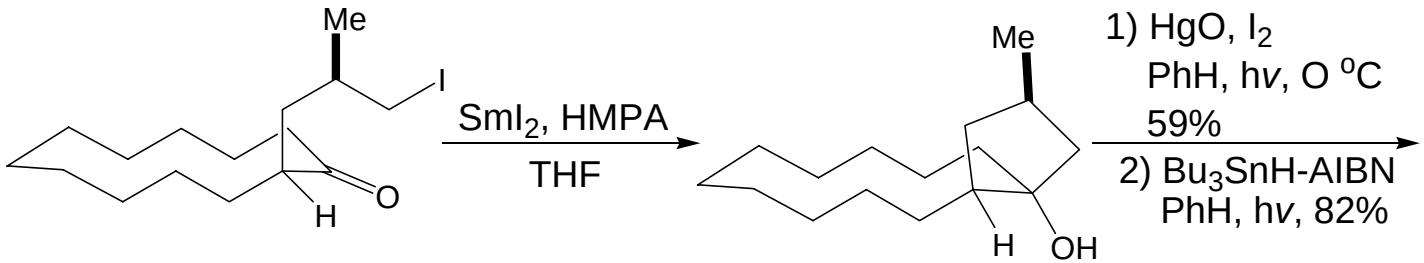


88% Single Diastereomer

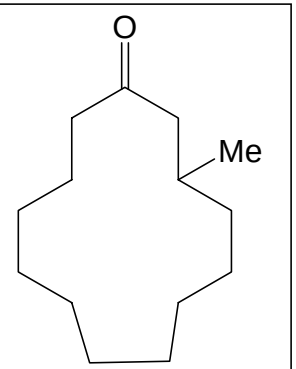


Eunicellin

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



90% Single Diatereomer

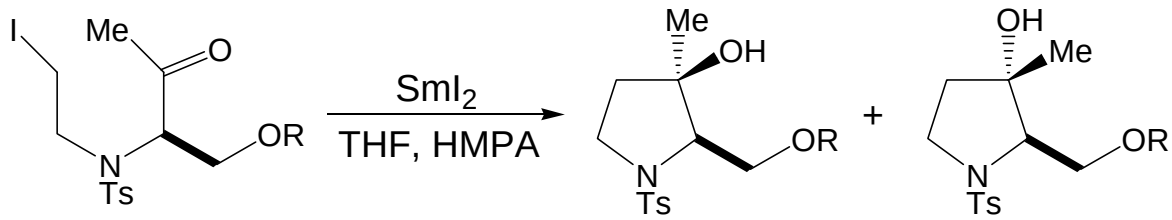


(+/-) Muscone

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

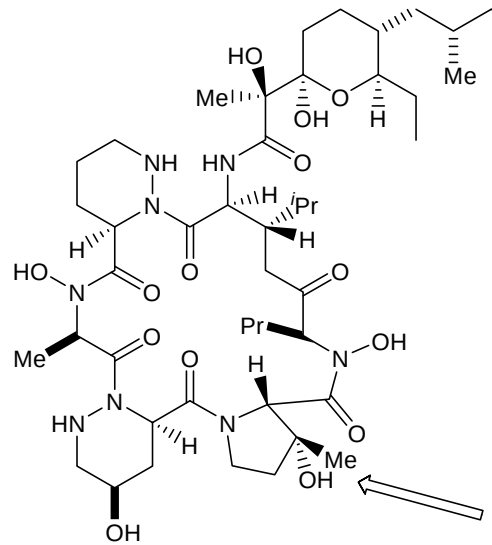
Intramolecular SmI_2 Barbier Reactions

Polyoxypeptin A



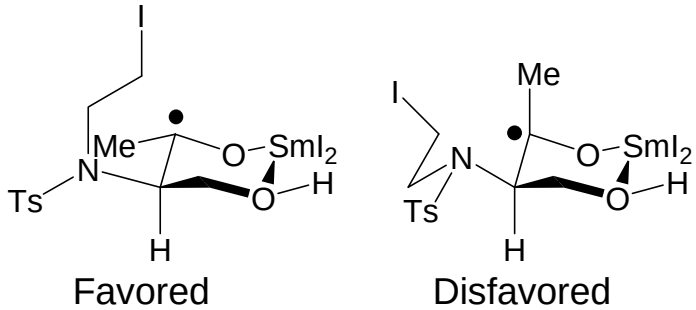
A **B**

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



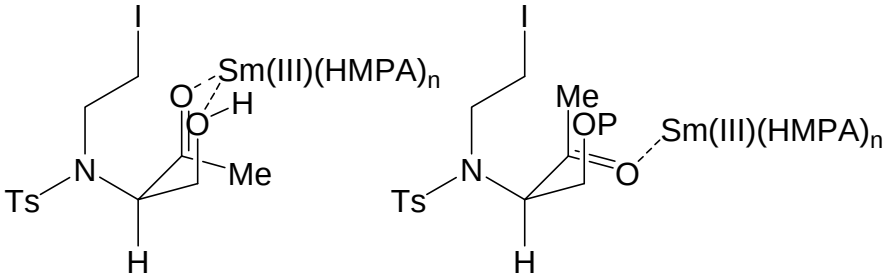
Polyoxypeptin A

Hamada's Explanation



Favored Disfavored

Procter's Explanation

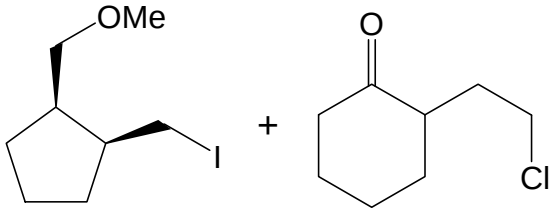


-Mechanism might proceed through a *bis*-radical stucture

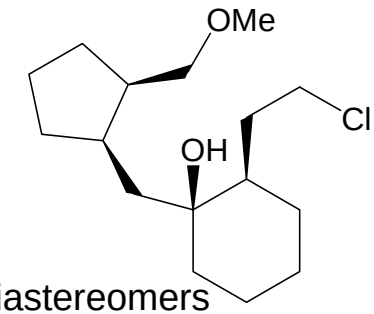
Hamada, Y. *Tetrahedron Letters* **2002**, 4695
Procter D. *Chem. Rev.* **2004**, 3371

Intramolecular SmI_2 Barbier Cyclizations

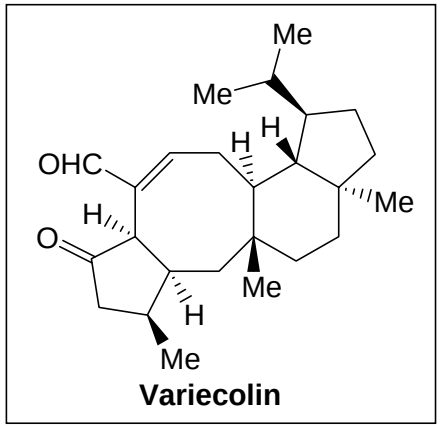
Synthetic Studies Towards Variecolin



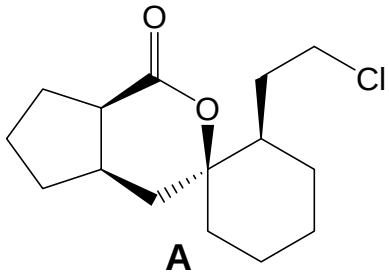
SmI_2, cat. NiI_2
THF, 72%



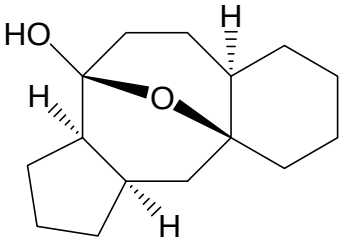
1:1 Mixture of diastereomers due to racemic starting materials



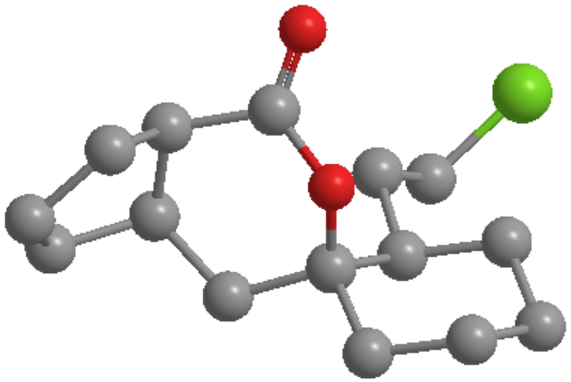
$RuCl_3$, $NaIO_4$
MeCN, CCl_4, H_2O
65%



SmI_2, NiI_2
hv, THF
63%



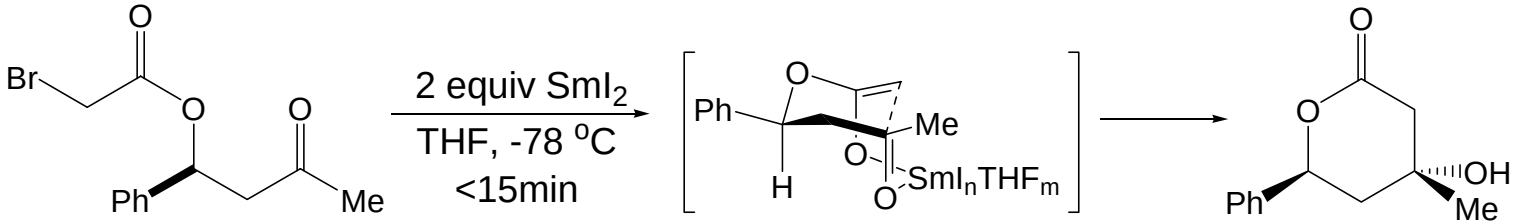
Model of Intermediate **A**



Molander, G. *Org. Lett.* **2001**, 2257
For increased reaction rates with NiI_2 see: Kagan, H. *Synlett* **1996**, 633
For increasing reducing ability of SmI_2 with visible light see: Ogawa A. *J. Am. Chem. Soc.* **1997**, 2745

SmI_2 Reformatsky reactions

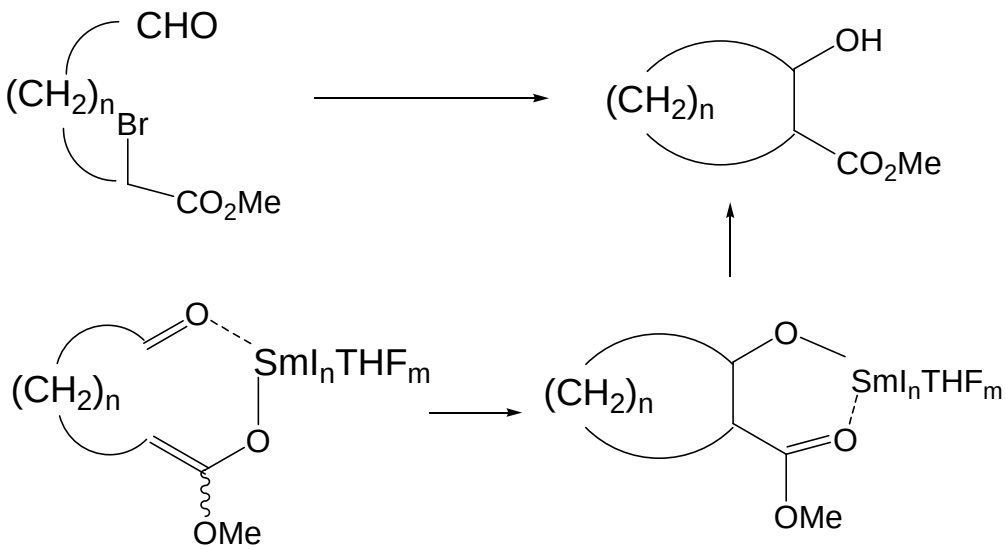
Basic Mechanism



95%. Single Diastereomer

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

-Due to Sm(III)'s ionic radius, high coordination number, and high oxophilicity: SmI_2 has been used succesfully as a chelation element to bring two reaction centers in proximity for the formation of large ring.

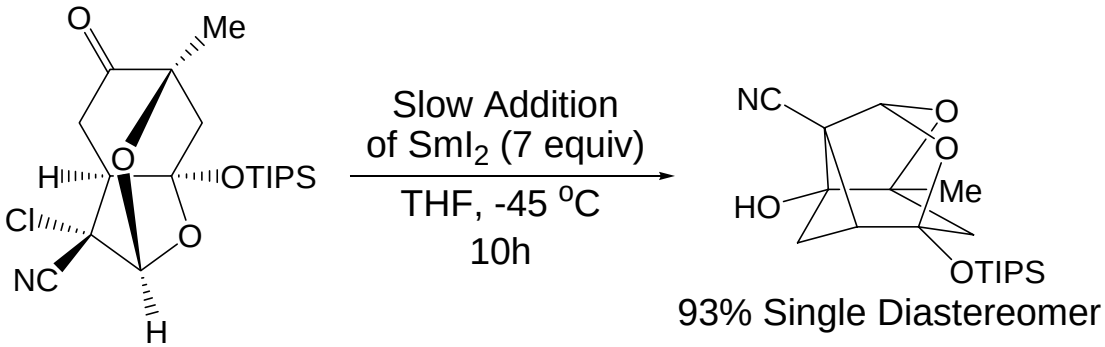


n	Ring Size	Yield
6	8	68%
7	9	70%
9	11	74%
12	14	82%
13	15	82%

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

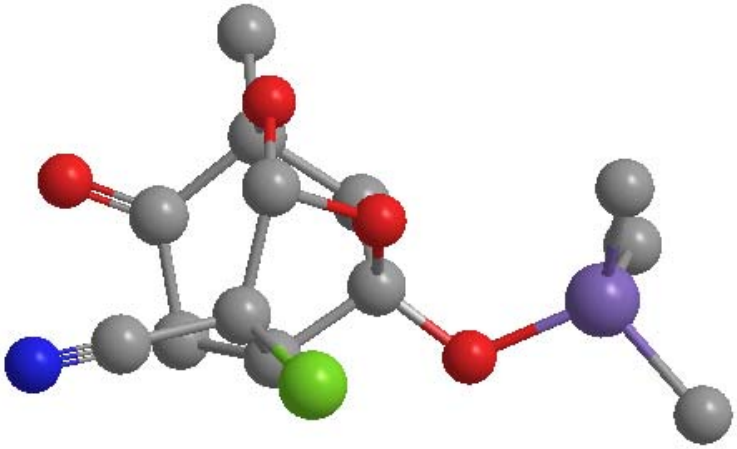
SmI_2 Intramolecular Reformatsky reactions

(+/-) Paeoniflorigenin and Paeoniflorin

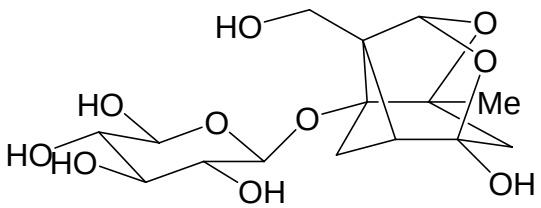


93% Single Diastereomer

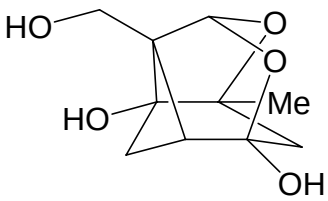
Chem 3D w/ MM2 energy minimization



-Product of the cyclization is base sensitive. Retro-Aldol is observed upon treatment of product with Et_3N.



Paeoniflorin

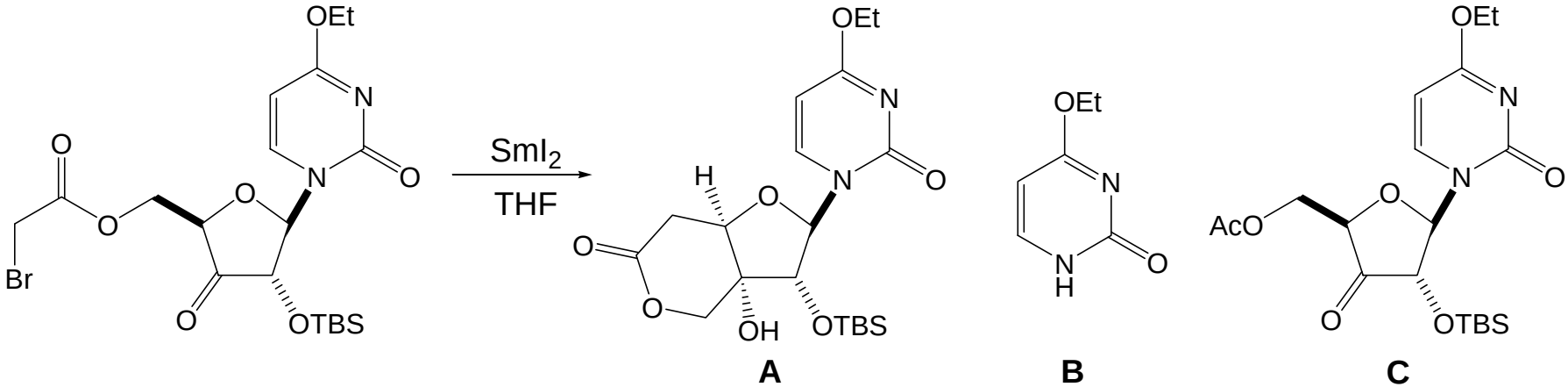


Paeoniflorigenin

Corey, E. J. *J. Am. Chem. Soc.* **1993**, 8871

SmI_2 Intramolecular Reformatsky reactions

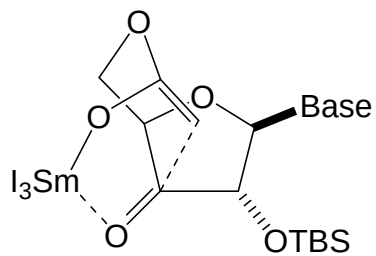
Uridine Derivatives

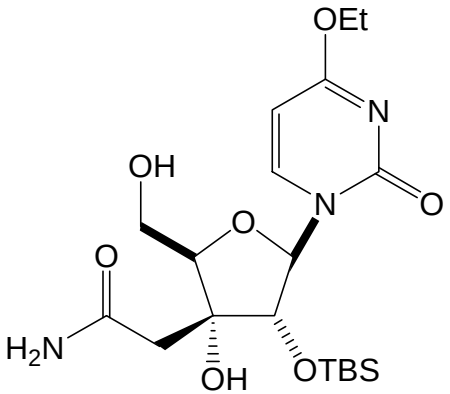


Product Distribution

Conditions	Product Yields
rt w/ Zn	**C** 22%
rt	**A** 71%
0 ^{o}C	**A** 75%
-78 ^{o}C	**A** 90%
-78 ^{o}C w/ HMPA	**A** 76%, **B** 11%

Plausible Transition State





Uridine Derivatives

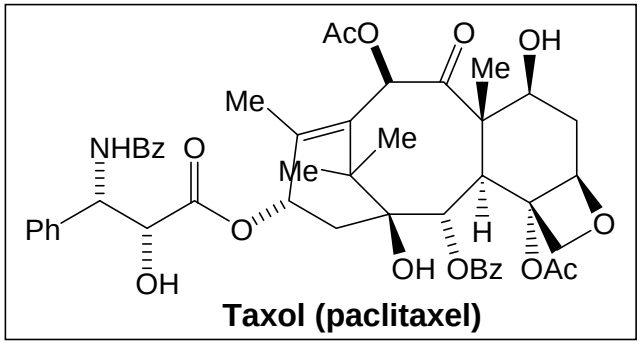
-Substrate is Base sensitive

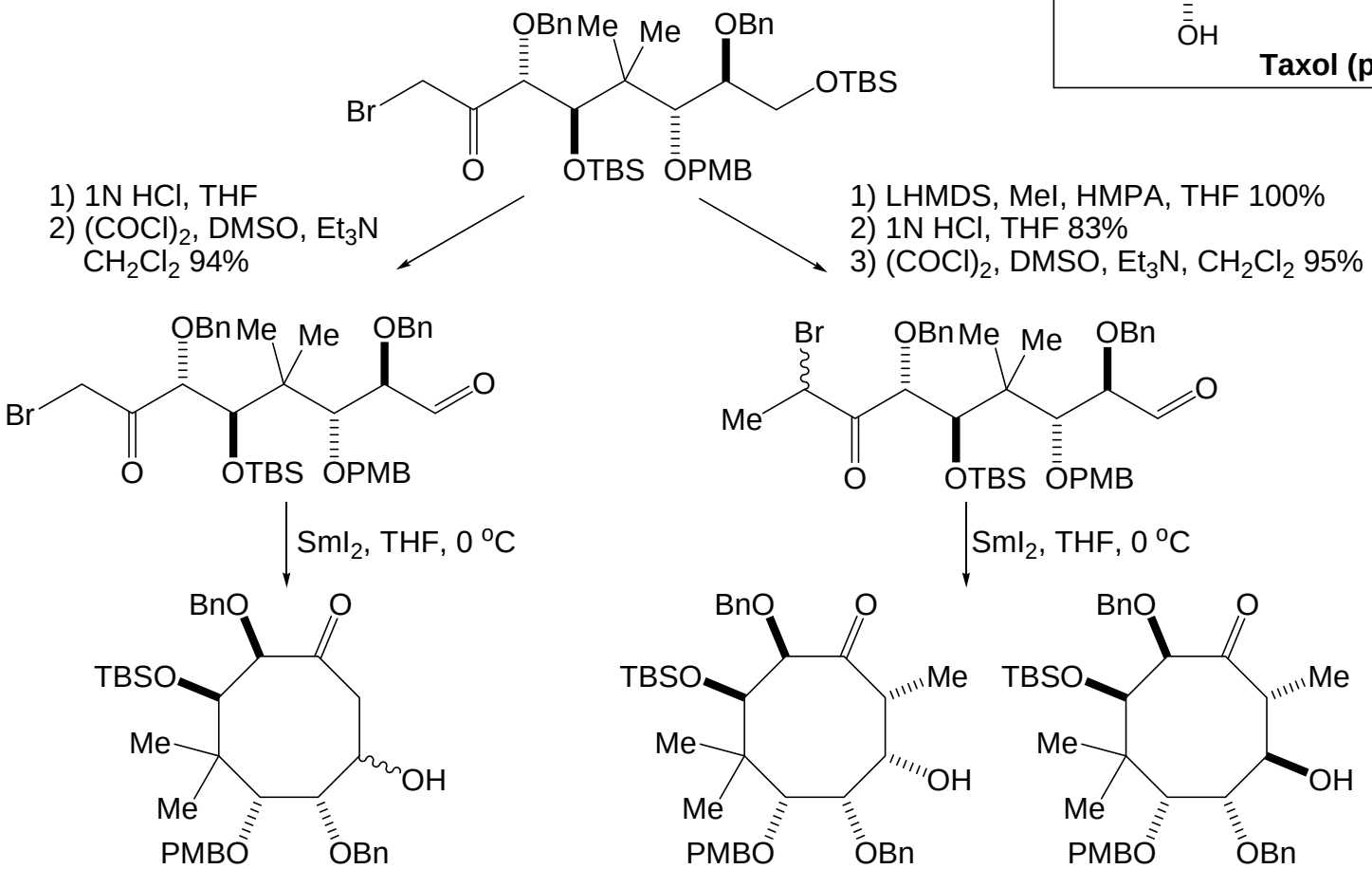
-Uridine Derivatives have been shown to be potent antitumor agents both *in vitro* and *in vivo*

Matsuda A. *J. Org. Chem.* **1997**, 1368

SmI_2 Intramolecular Reformatsky reactions

Taxol-Mukaiyama





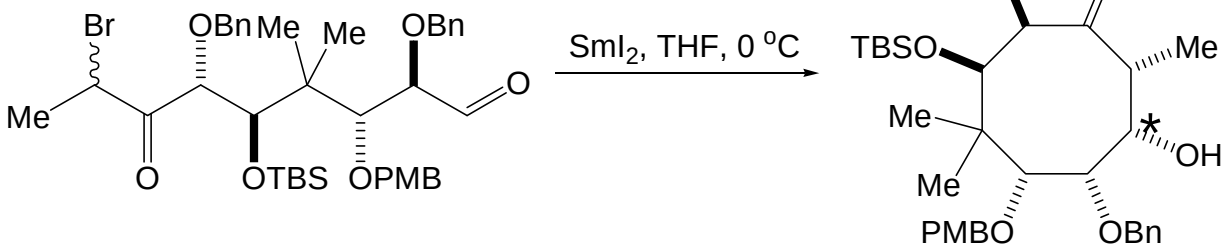
87% dr 65:35

70% dr 83:17

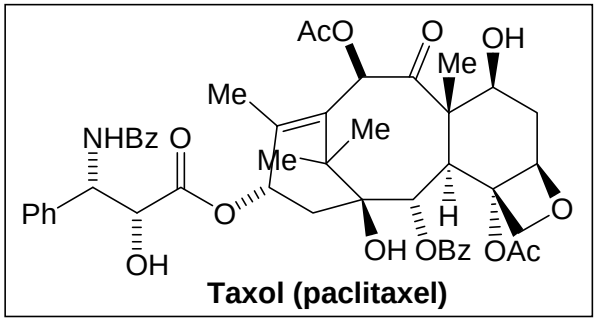
Mukaiyama, T. *Chem. Eur. J.* **1999**, 121

SmI_2 Intramolecular Reformatsky reactions

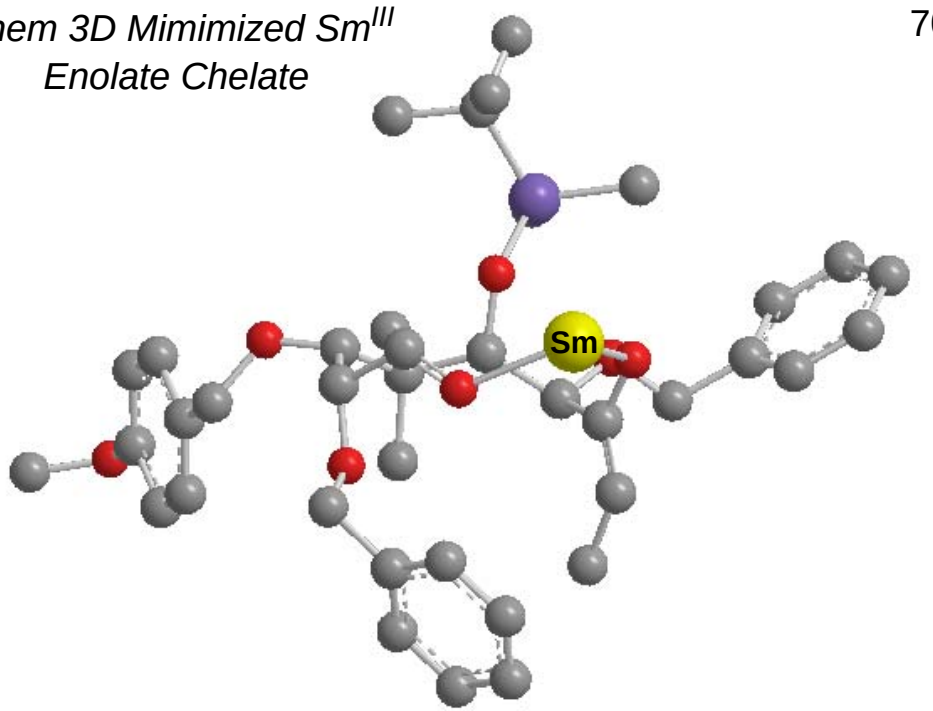
Taxol-Mukaiyama



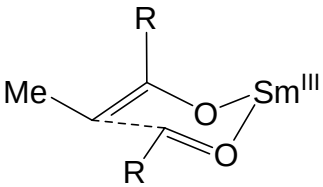
70% dr 83:17



Chem 3D Mimimized Sm^{III} Enolate Chelate



Simplified Chair Transition State

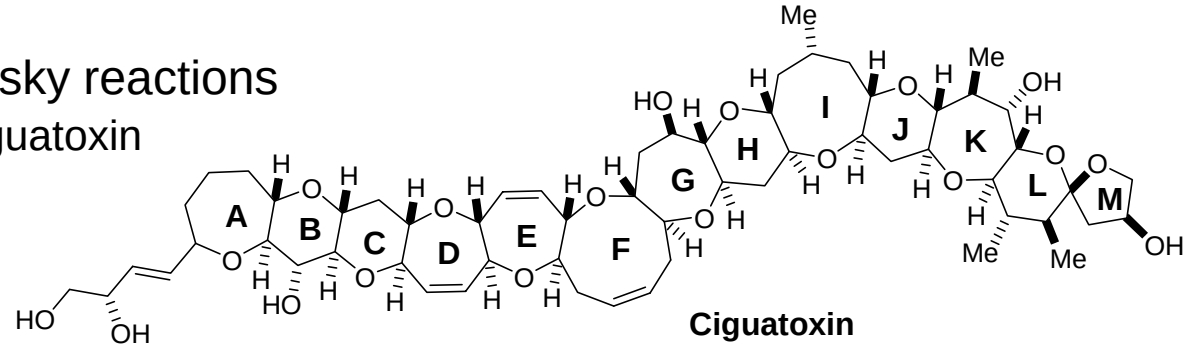


-Preliminary modeling suggest reaction preceeds through *E*-enolate

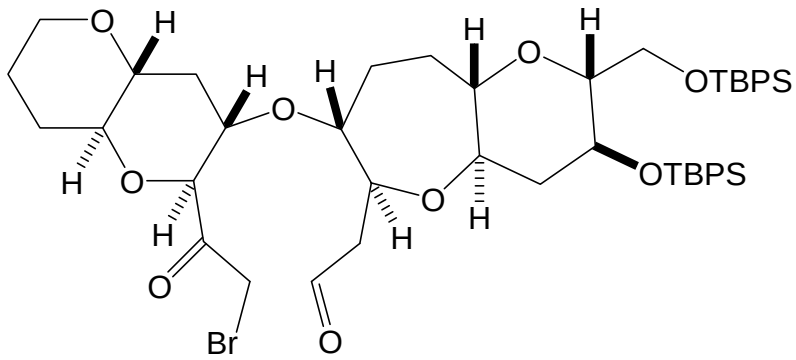
Mukaiyama, T. *Chem. Eur. J.* **1999**, 121

SmI_2 Intramolecular Reformatsky reactions

Model Studies Toward Ciguatoxin

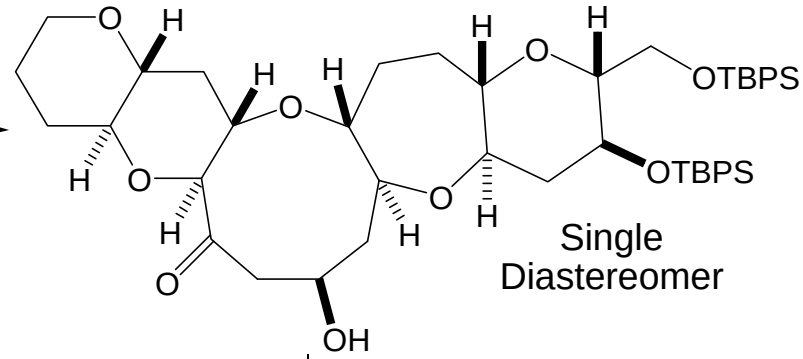


Ciguatoxin



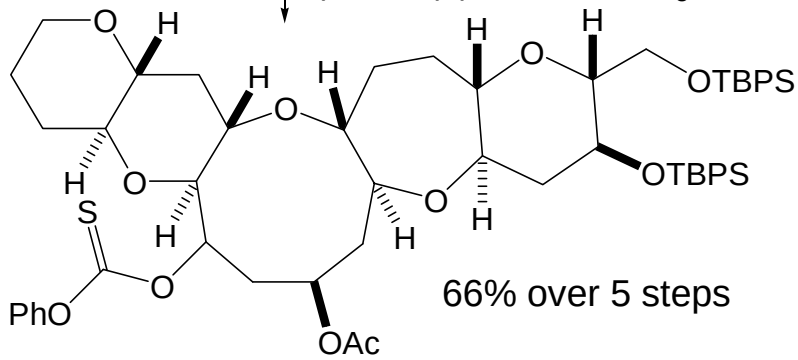
SmI_2, THF

-78 ^oC

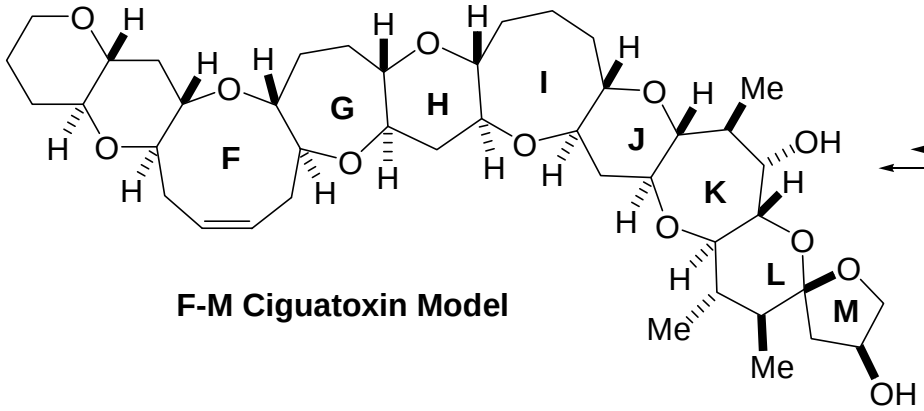


Single Diastereomer

1) Ac_2O, DMAP, 0 ^oC
2) $NaBH_4$, CH_2Cl_2/MeOH
3) PhOC(S)Cl, DMAP, CH_3CN, rt



66% over 5 steps

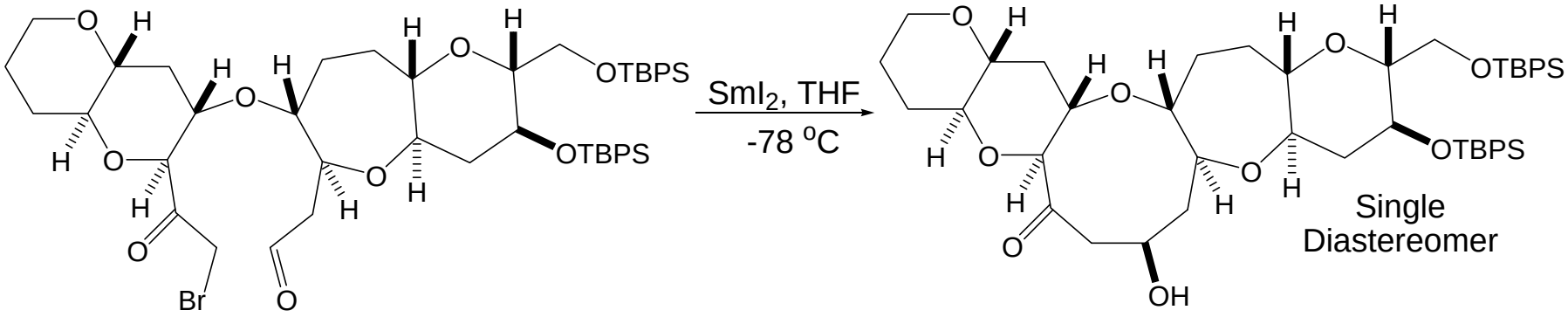


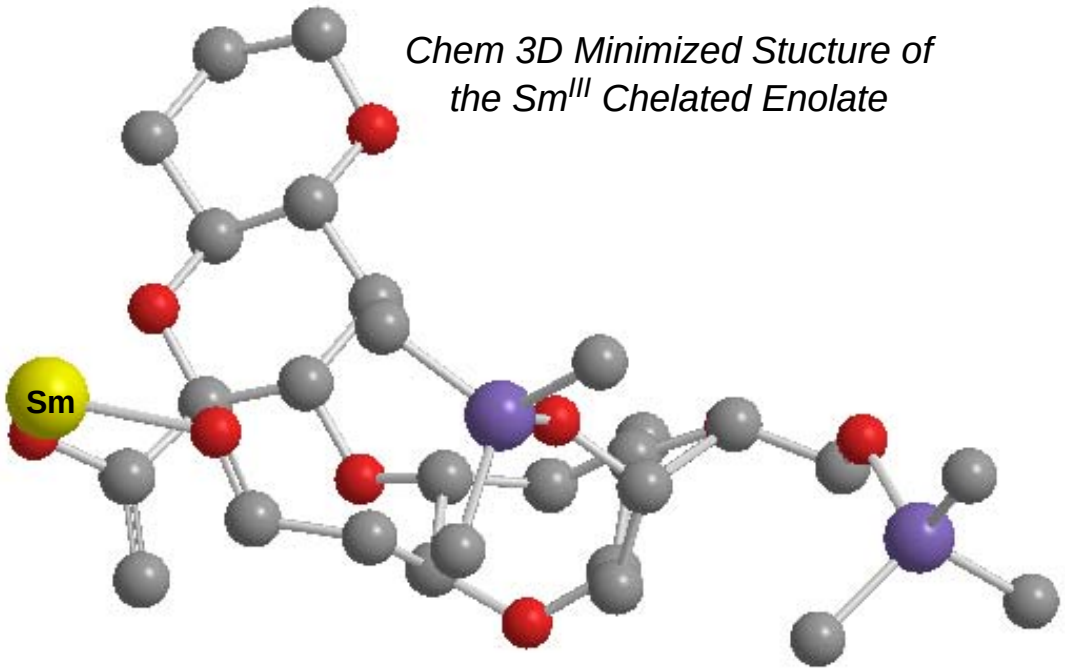
F-M Ciguatoxin Model

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

SmI_2 Intramolecular Reformatsky reactions

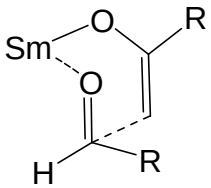
Model Studies Toward Ciguatoxin





Chem 3D Minimized Stucture of the Sm^{III} Chelated Enolate

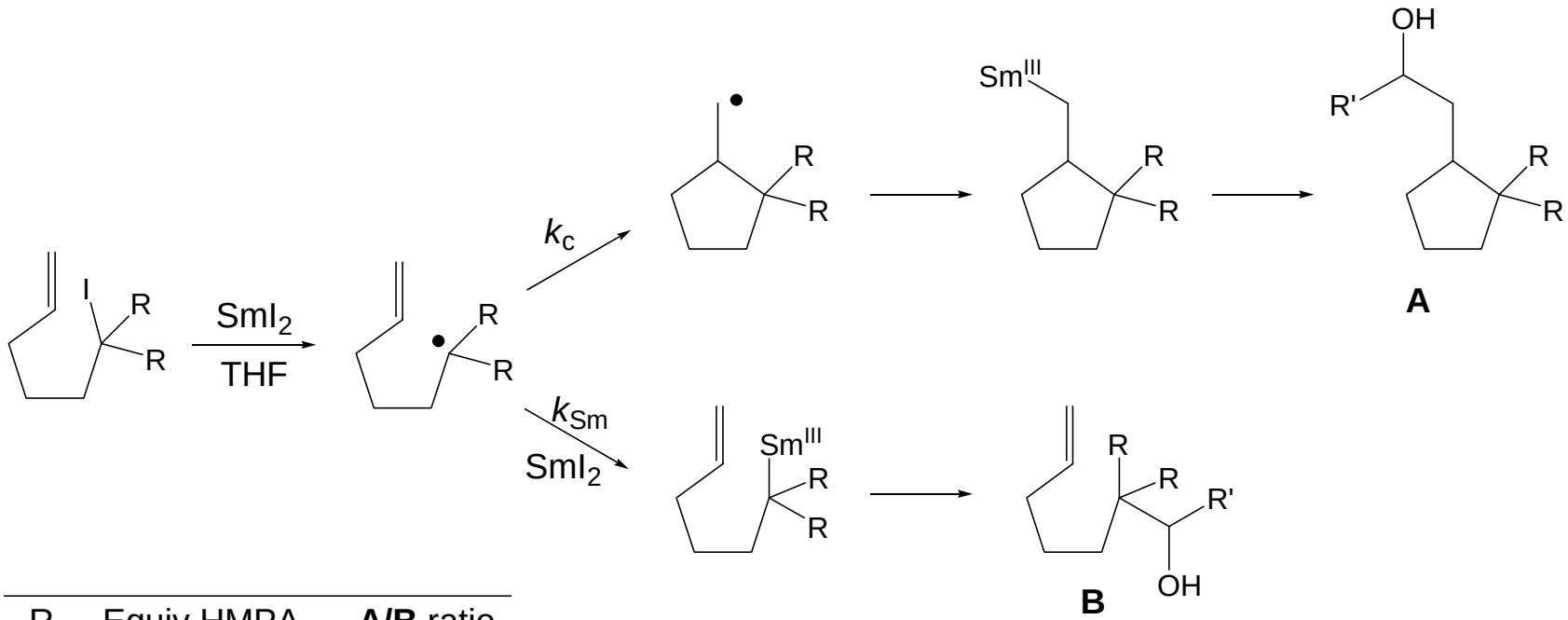
Simplified Conformation



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

SmI_2 Radical-Alkene and Alkyne Cyclizations

Basic Mechanism

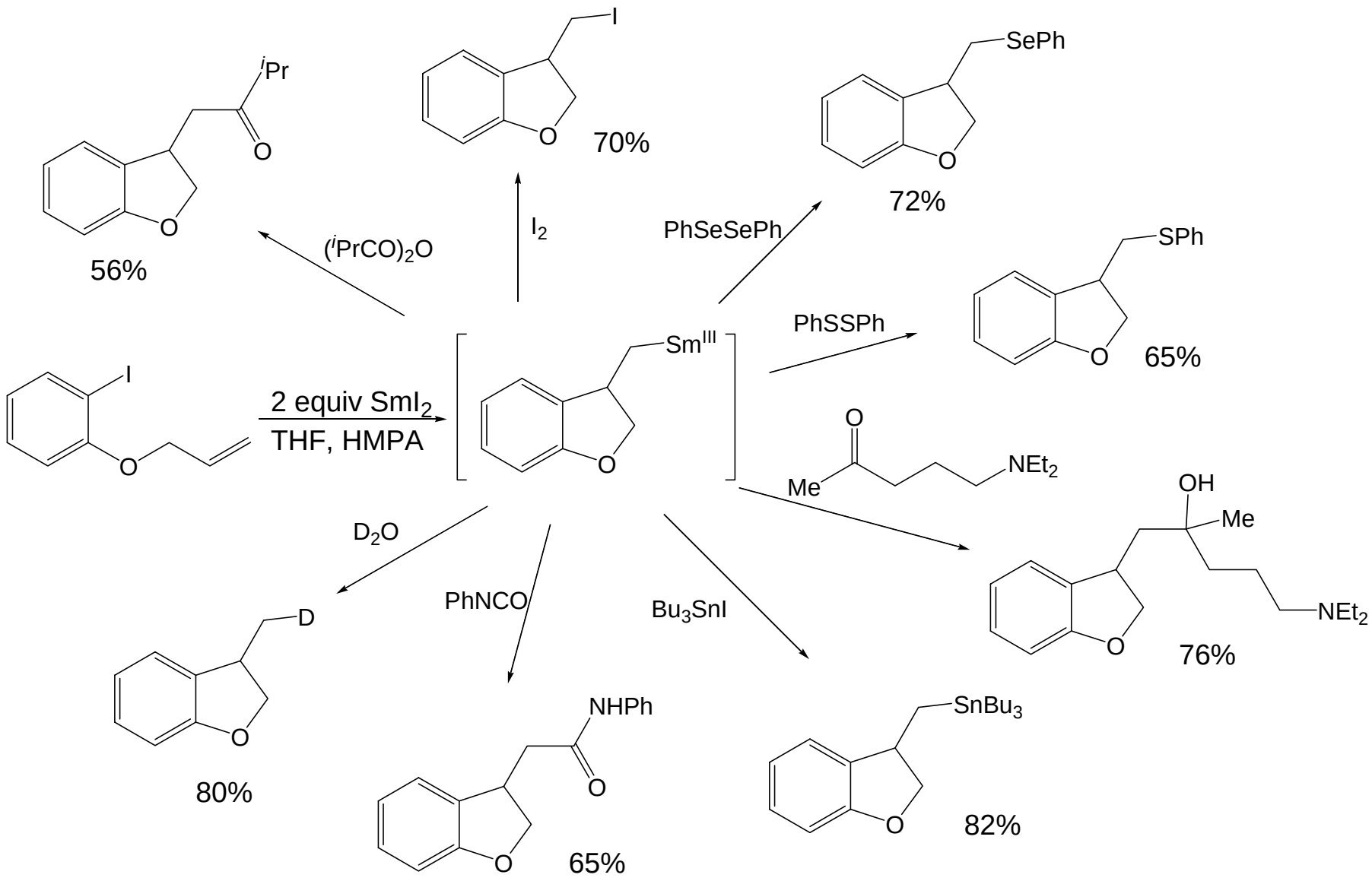


R	Equiv HMPA	**A/B** ratio
H	2.3	08/92
H	3.2	34/66
H	3.7	50/50
H	5	56/44
H	7	52/48
Me	0	0/100

Curran, D. *Tetrahedron Lett.* **1993**, 1717.
For a review on the mechanism of SmI_2 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.

SmI_2 Radical-Alkene and Alkyne Cyclizations

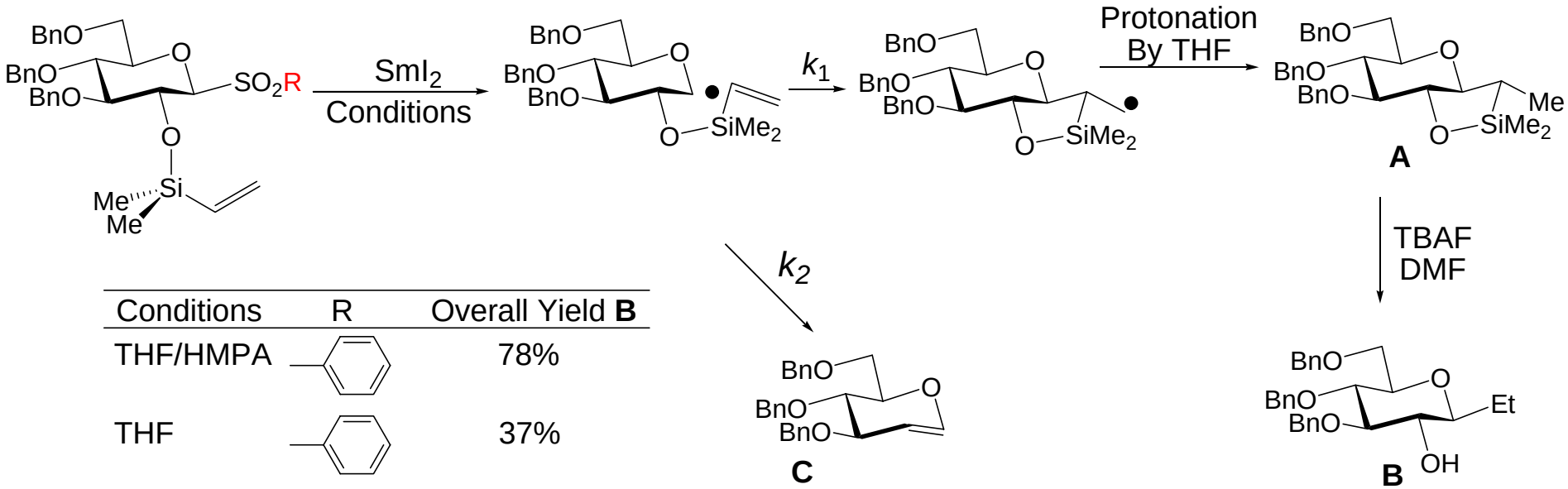
Synthetic Utility of Intermediate Organo-Samarium Compounds

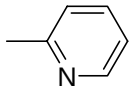


Molander, G. *Chem. Rev.* **1996**, 307
Procter, D. J. *Chem. Rev.* **2004**, 3371

SmI_2 Radical-Alkene Cyclizations

C-Glycoside Formation



Conditions	R	Overall Yield **B**
THF/HMPA		78%
THF		37%
THF		80%

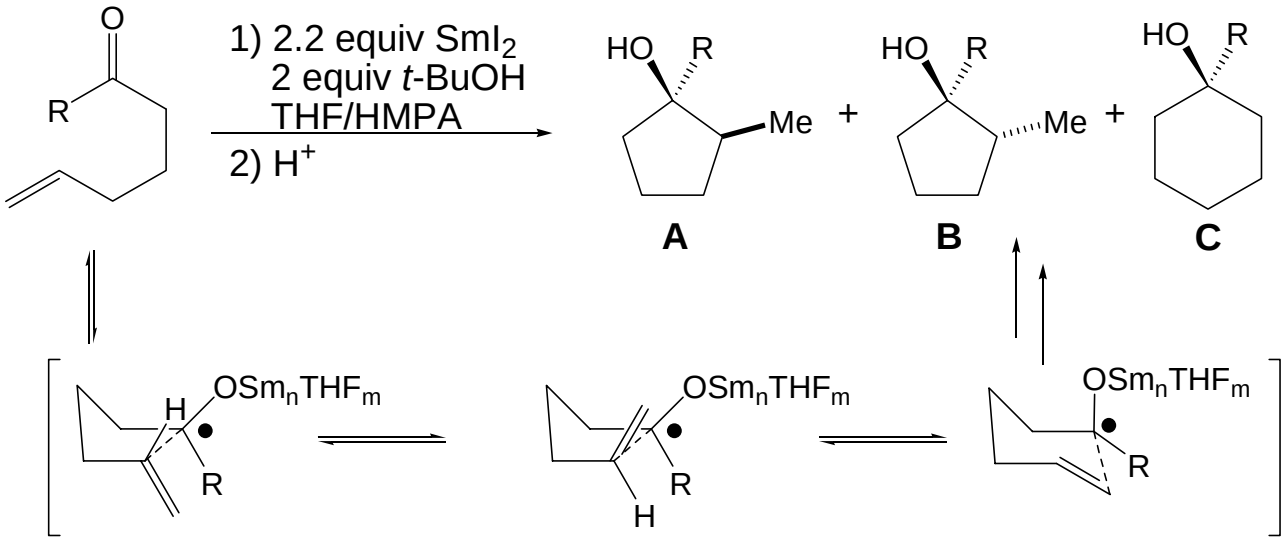
-Authors propose 2-pyridyl group lowers LUMO thus facilitates inital sulfone cleavage

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

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

SmI_2 Radical Carbonyl-Alkene Cyclizations

Basic Mechanism



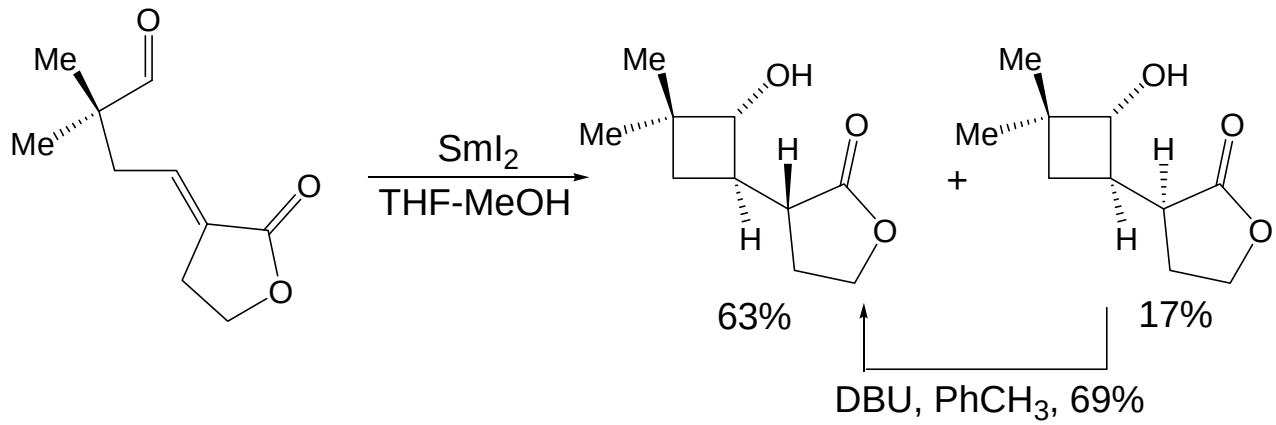
R	% isolated Yield of **A** and **B** (diast ratio, **A**:**B**)	**%** Yield **C**	Reaction Time
Me	86 (>150:1)	-	15 min
i-Pr	85 (23:1)	3	30 min
t-Bu	78 (3:1)	4	8 h
Ph	48 (1<150)	-	2 h

-Carbonyl reduction by SmI_2 is well documented

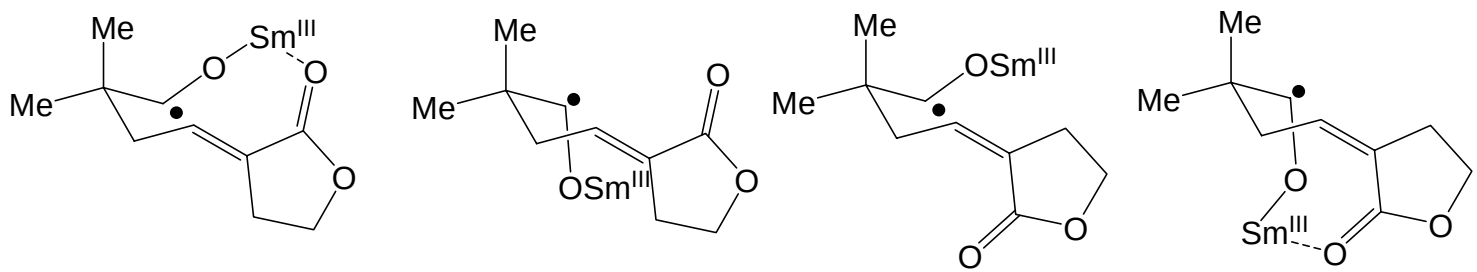
Molander, G. *J. Org. Chem.* **1995**, 872.
Curran, D. P. *Synlett* **1992**, 943
Rajapaksa, H. *Group Seminar* **6-1998**

SmI_2 Radical Carbonyl-Alkene Cyclizations

Basic Mechanism, an Example of an Activated Alkene



Transition States

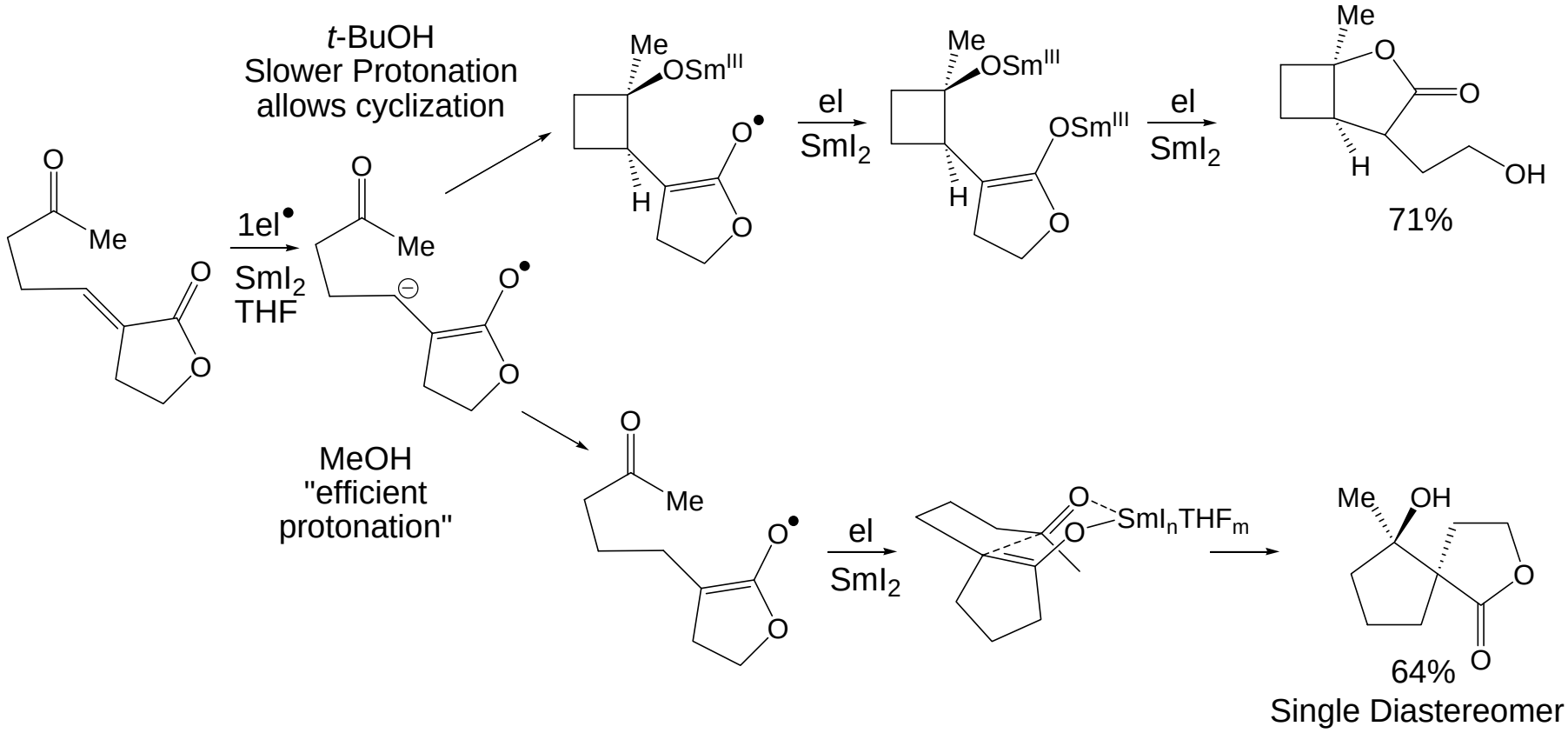


A **B** **C** **D**

Procter, D. J. *Org. Lett.* **2003**, 4811

SmI_2 Radical Carbonyl-Alkene Cyclizations

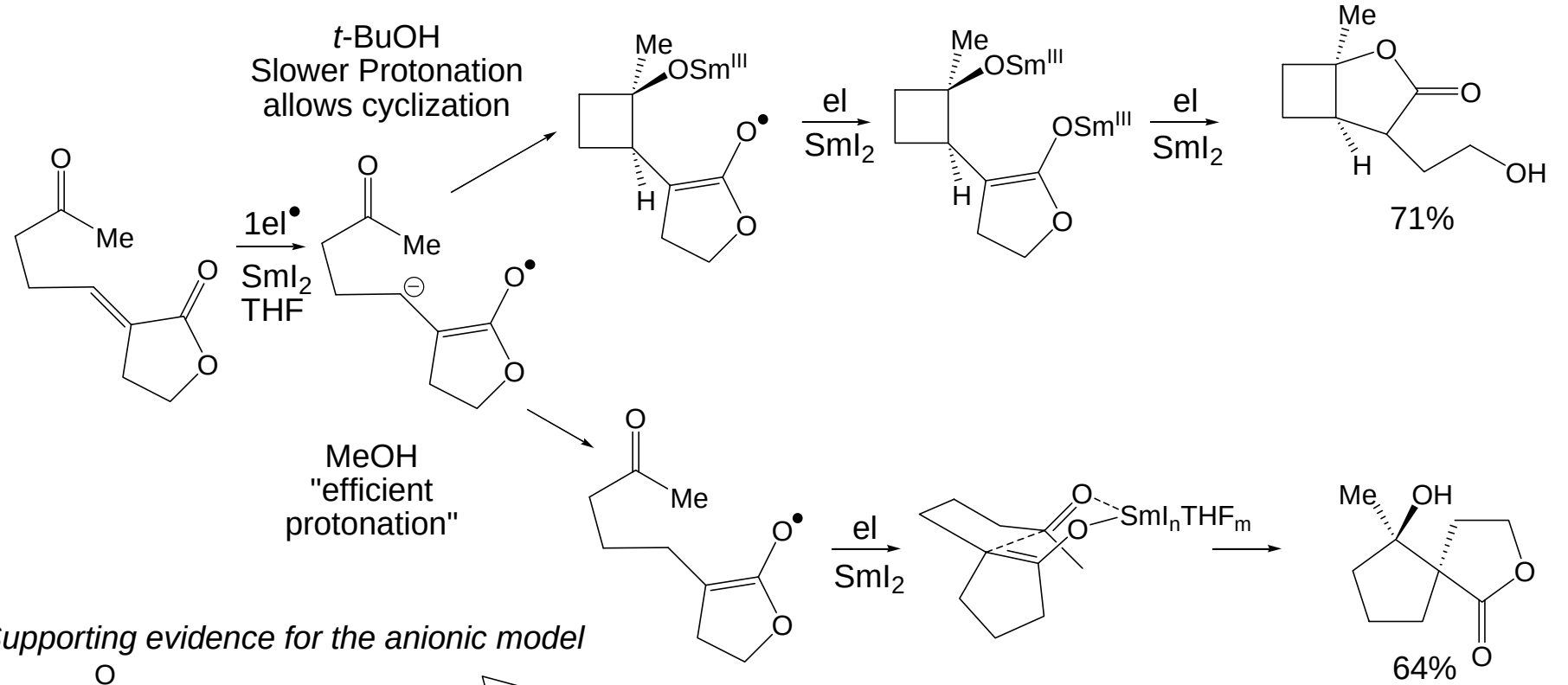
Basic Mechanism, an Example of an Activated Alkene



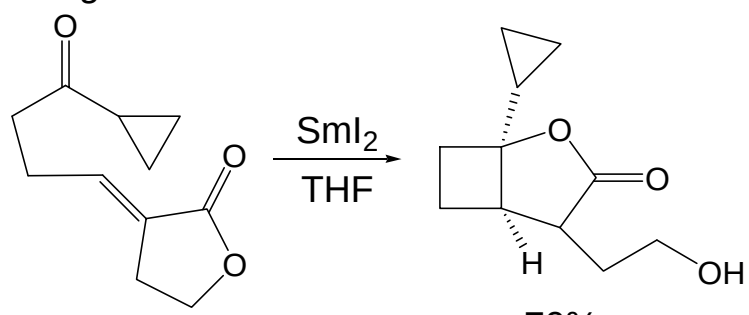
Procter, D. J. *Org. Lett.* **2003**, 4811

SmI_2 Radical Carbonyl-Alkene Cyclizations

Basic Mechanism, an Example of an Activated Alkene



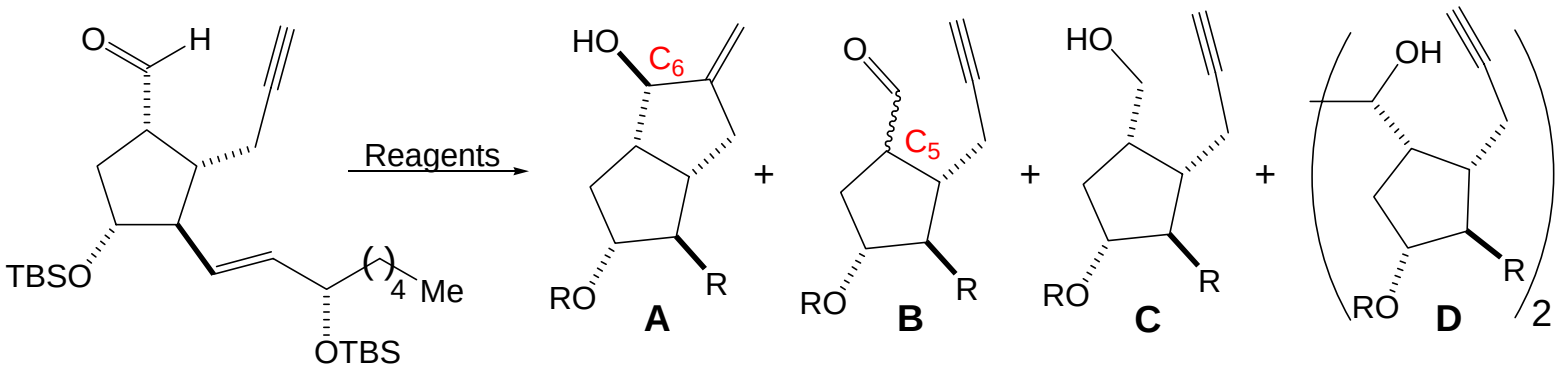
Supporting evidence for the anionic model



Procter, D. J. *Org. Lett.* **2003**, 4811

SmI_2 Radical Carbonyl-Alkyne Cyclizations

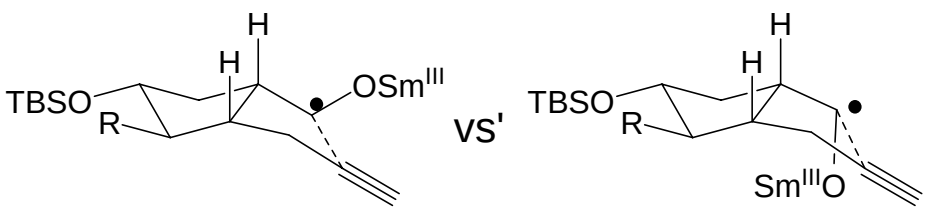
Isocarbacyclin

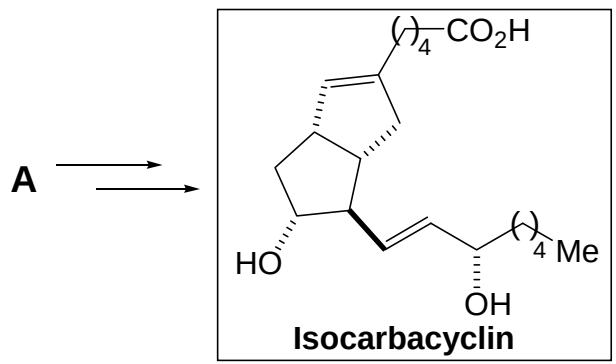


Reagents	**A** (C_6 dr)	**B** (C_5 dr)	**C**	**D**
Zn,TMSCl, 2,6 Lutidine, in THF, at reflux	28% (ND mix)	51% (1:1)	-	-
Li-Naphthalene, *t*-BuOH, in THF at -70 ^{o}C	65% (ND mix)	15% (1:2)	3%	-
SmI_2, *t*-BuOH, in THF at -70 ^{o}C	71% (9:1)	-	8%	8%
h*v*, Et_3N, in CH_3CN at rt	60% (2:1)	20% (ND)	-	-

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

Plausible Transition States

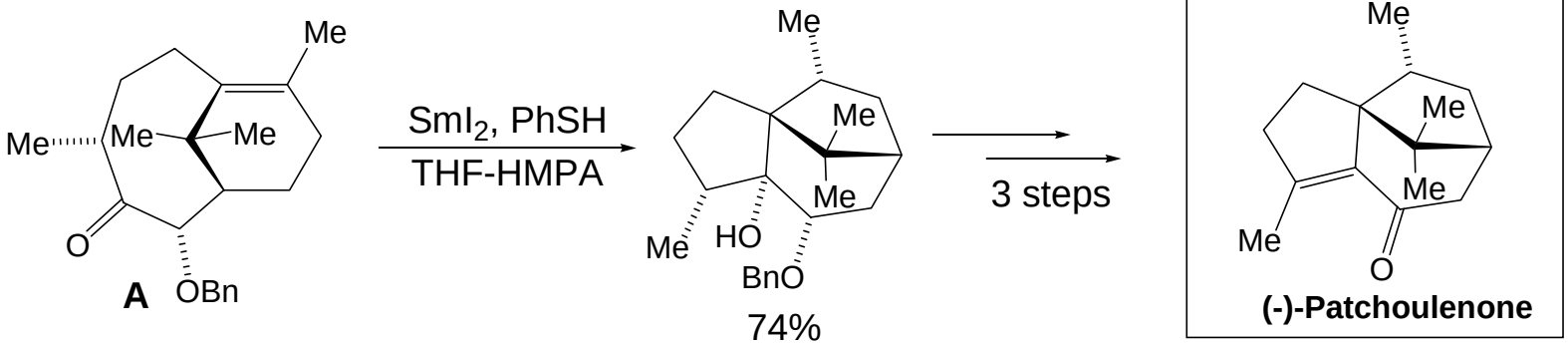




Noyori, R. *Tetrahedron* **1990**, 6689.
Procter, D. *Chem. Rev.* **2004**. 3371.

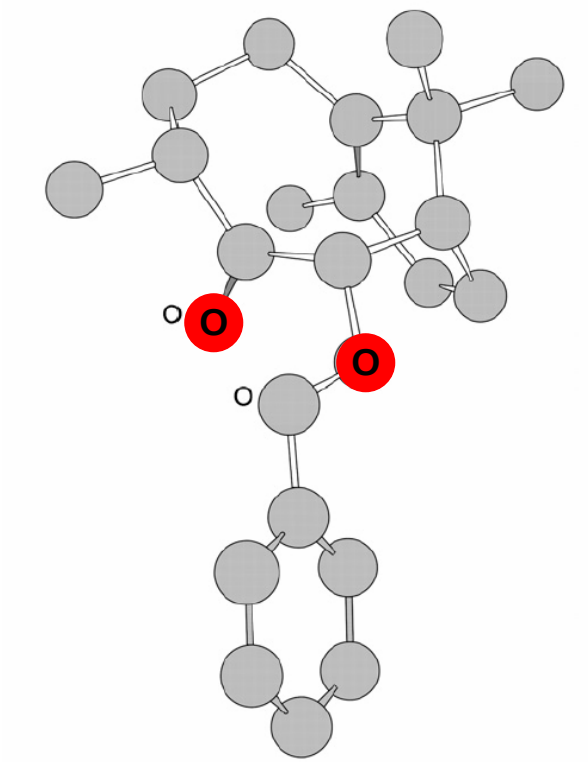
SmI_2 Radical Carbonyl-Alkene Cyclizations

(-)-Patchoulenone

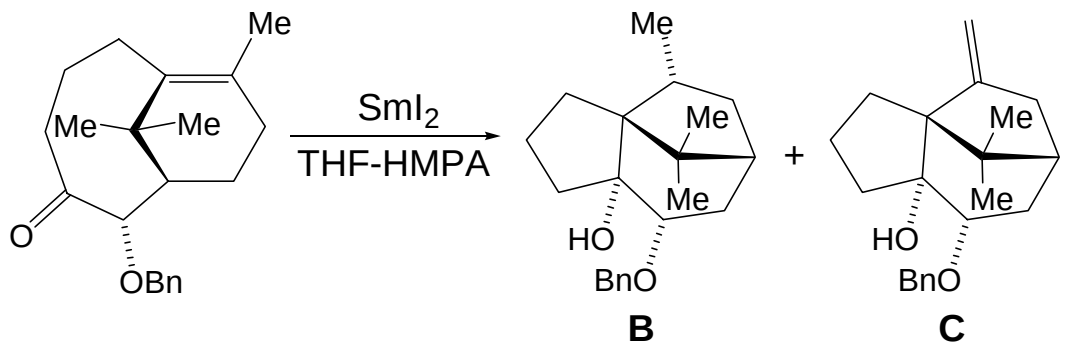


74%
Single Diastereomer

*X-Ray Structure of **A***



Model Studies, effects of PhSH additive



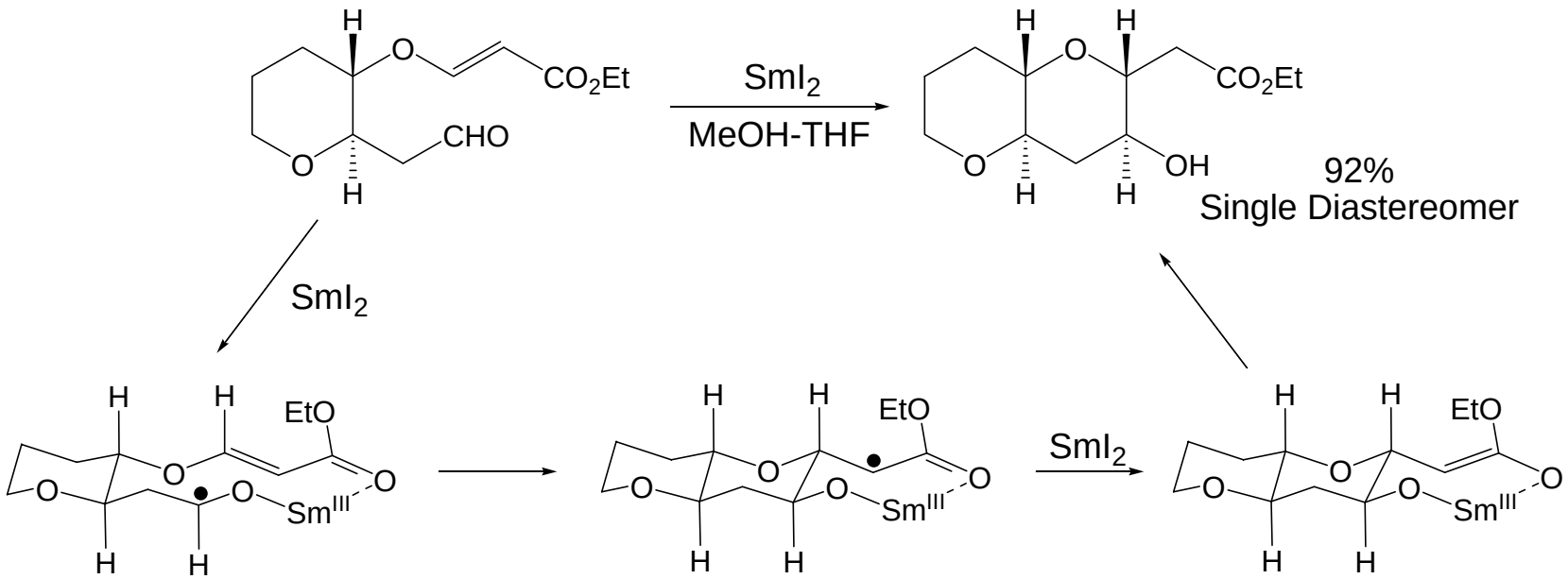
Additive	Yield **B**	Yield **C**
None	39%	54%
PhSH	71%	0%

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

Banwell, M. G. *New J. Chem.* **2003**, 50.

SmI_2 Radical Carbonyl-Alkene Cyclizations

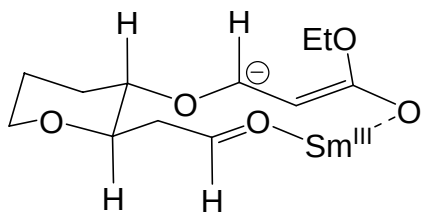
trans-Fused Polytetrahydropyrans



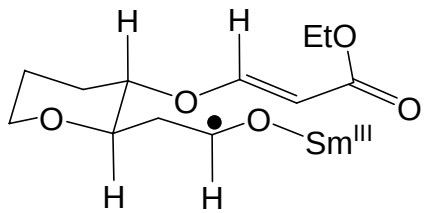
-Issues with similtaneous binding of ketyl radical and conjugated ester, geometerical constraints?

-Alternated Possibilities

Procter's Alternative



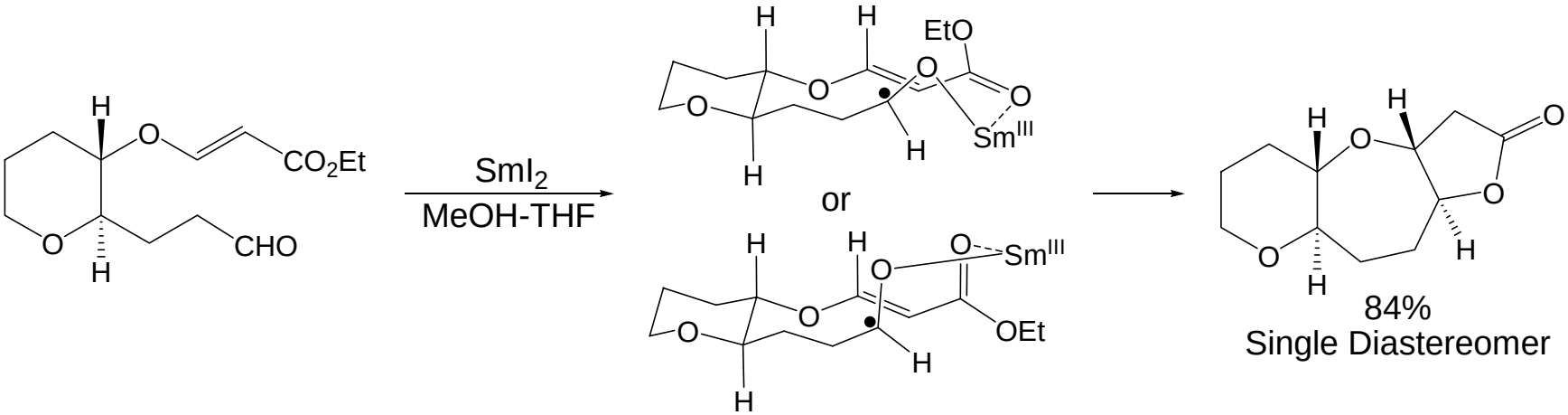
Non-Chelation



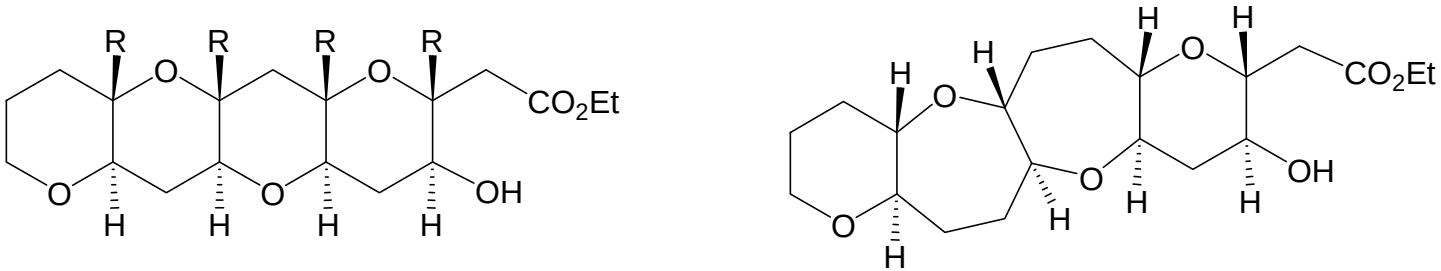
Hori, N. *Tetrahedron Lett.* **1999**, 2811
Hori, N. *Org. Lett.* **1999**, 1099
Hori, N. *Tetrahedron* **2002**, 1853
Suzuki, K. *Tetrahedron Lett.* **2002**, 8653

SmI_2 Radical Carbonyl-Alkene Cyclizations

trans-Fused Polytetrahydropyrans



Iterative Cyclizations produces Polytetrahydropyrans and Oxepanes



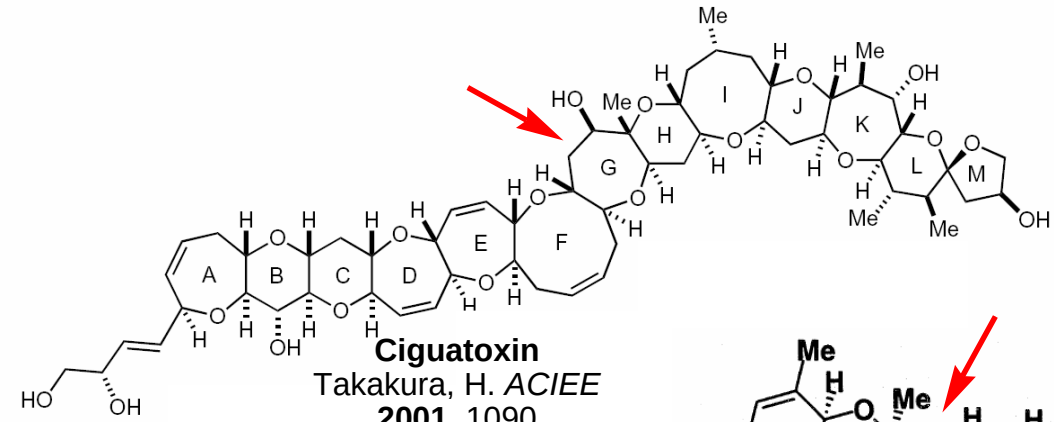
R= Me or H

-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

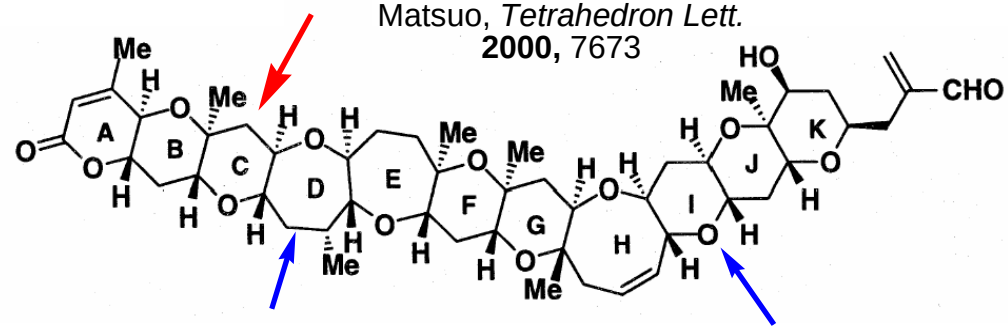
SmI_2 Radical Carbonyl-Alkene Cyclizations

Natural Product Synthesis and Synthetic Studies

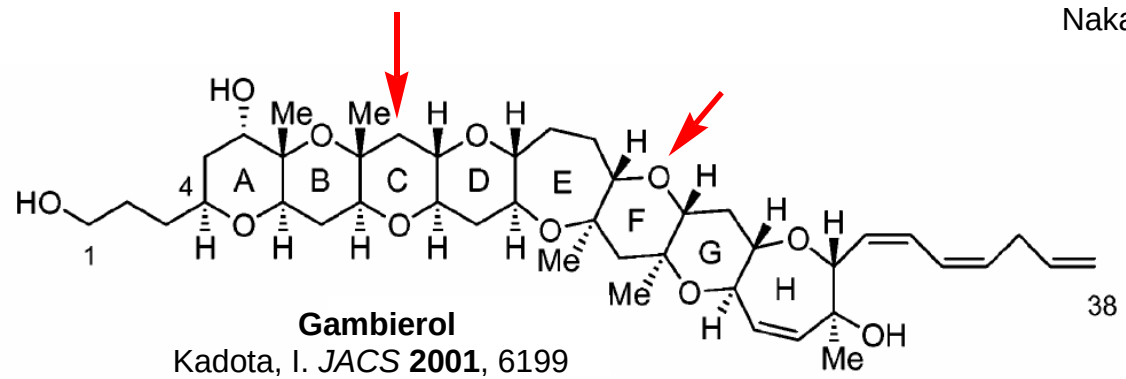


Ciguatoxin
Takakura, H. *ACIEE*
2001, 1090

Brevetoxin B
Matsuo, *Tetrahedron Lett.*
2000, 7673



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

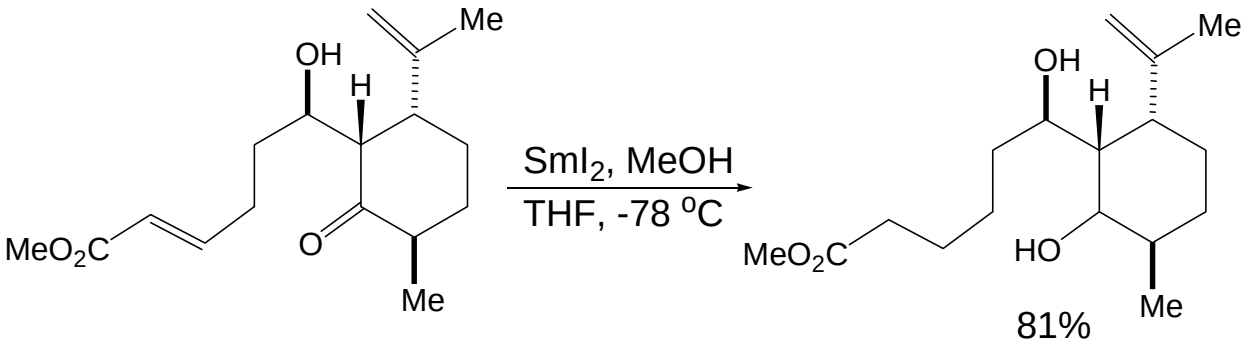


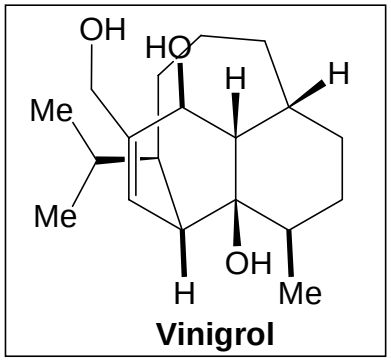
Gambierol
Kadota, I. *JACS* **2001**, 6199
Kadota, I. *JACS* **2001**, 11893

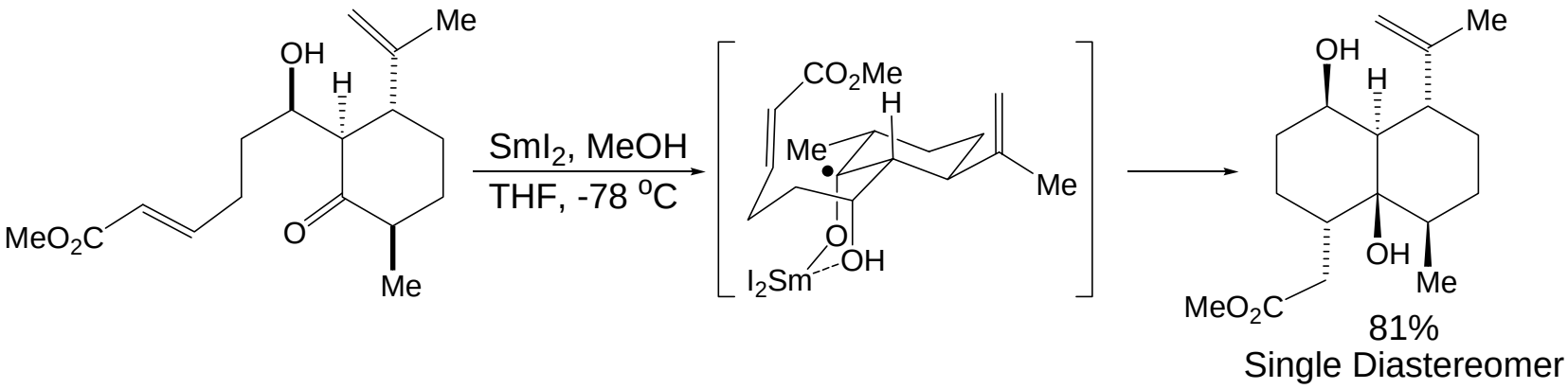
Also, the D and E ring of the A-F fragment of Yessotoxin. Suzuki, K. *Org. Lett.* **2002**, 3943

SmI_2 Radical Carbonyl-Alkene Cyclizations

Synthetic Studies Toward Vinigrol



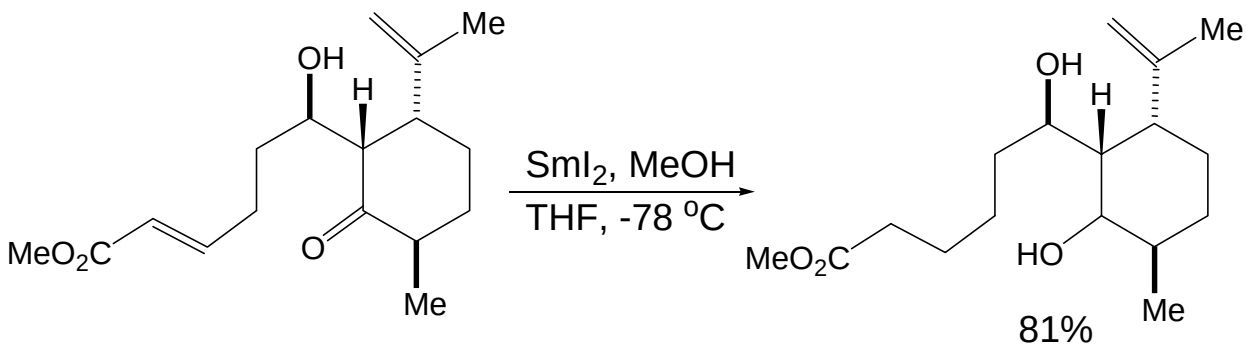


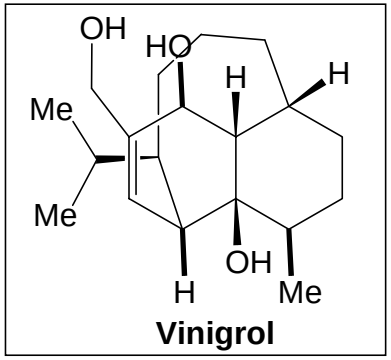


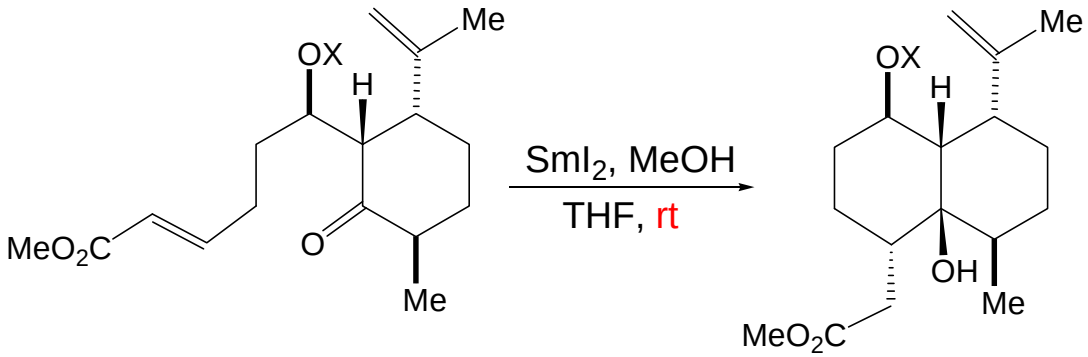
Matsuda, F. *Synlett* **1996**, 1057

SmI_2 Radical Carbonyl-Alkene Cyclizations

Synthetic Studies Toward Vinigrol

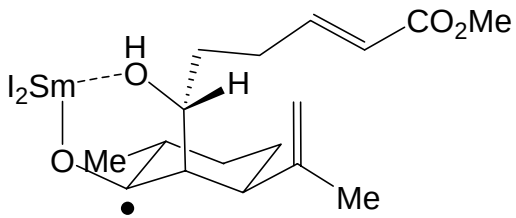




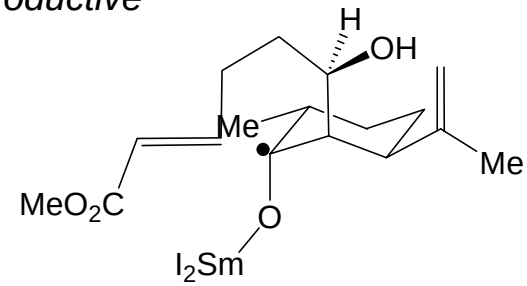


X	Yield
H	45%
Ac	85%

Non-productive



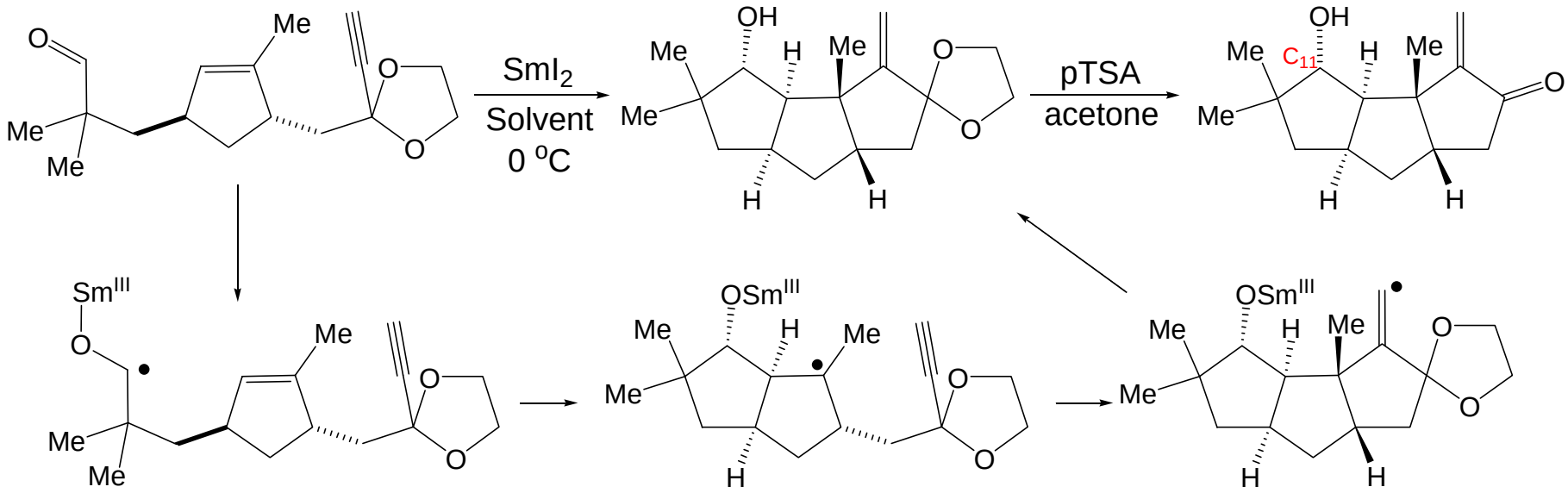
Productive



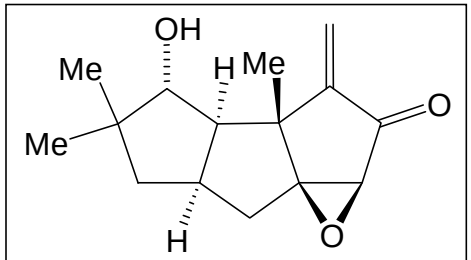
Matsuda, F. *Synlett* **1996**, 1057

SmI_2 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%



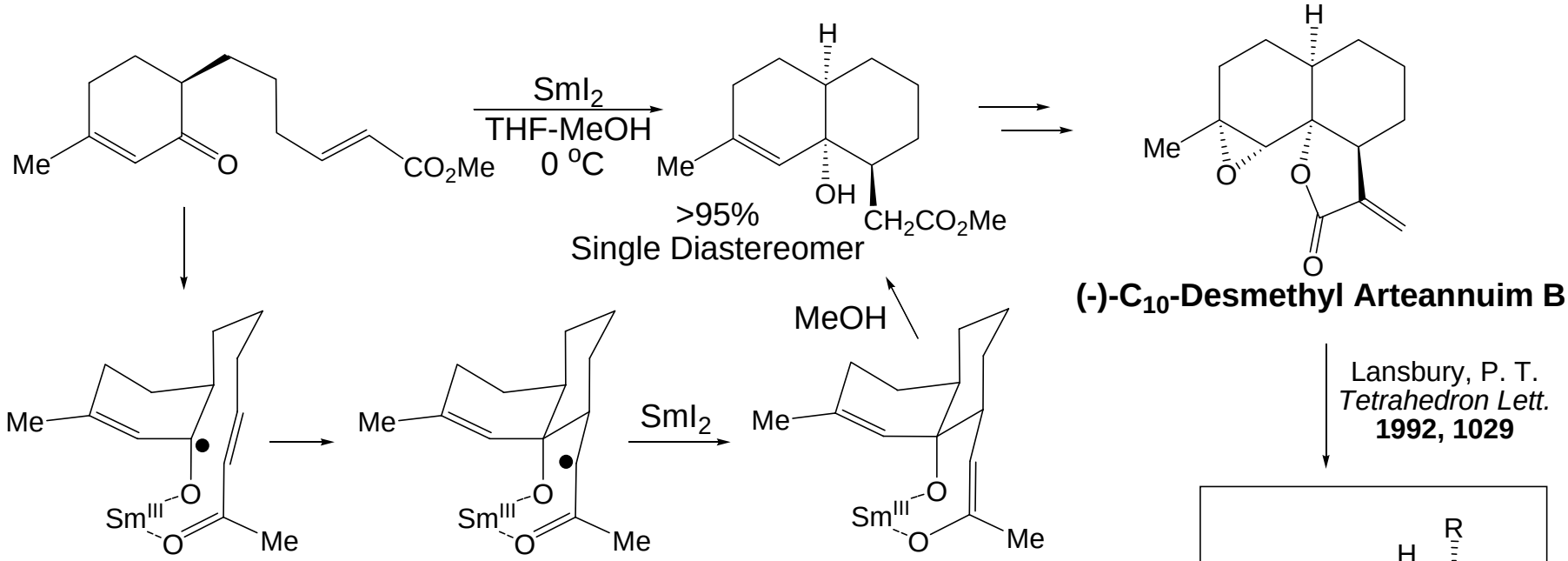
Hypnophilin

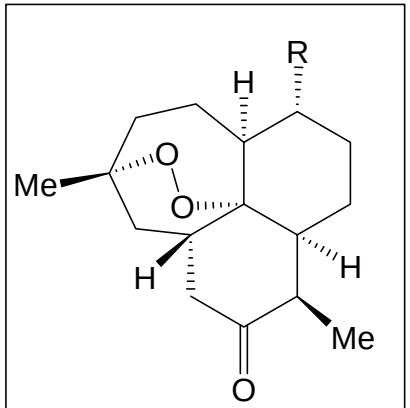
-Addition of D_2O lead to *no* incorporation of deuteriumin products.

Curran, D. P. *J. Am. Chem. Soc.* **1988**, 5064

SmI_2 Radical Carbonyl-Alkene Cyclizations

(-)-C_{10}-Desmethyl Arteannuim B





R=Me or H
Artemisinin

-α,β-unstaturated 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.

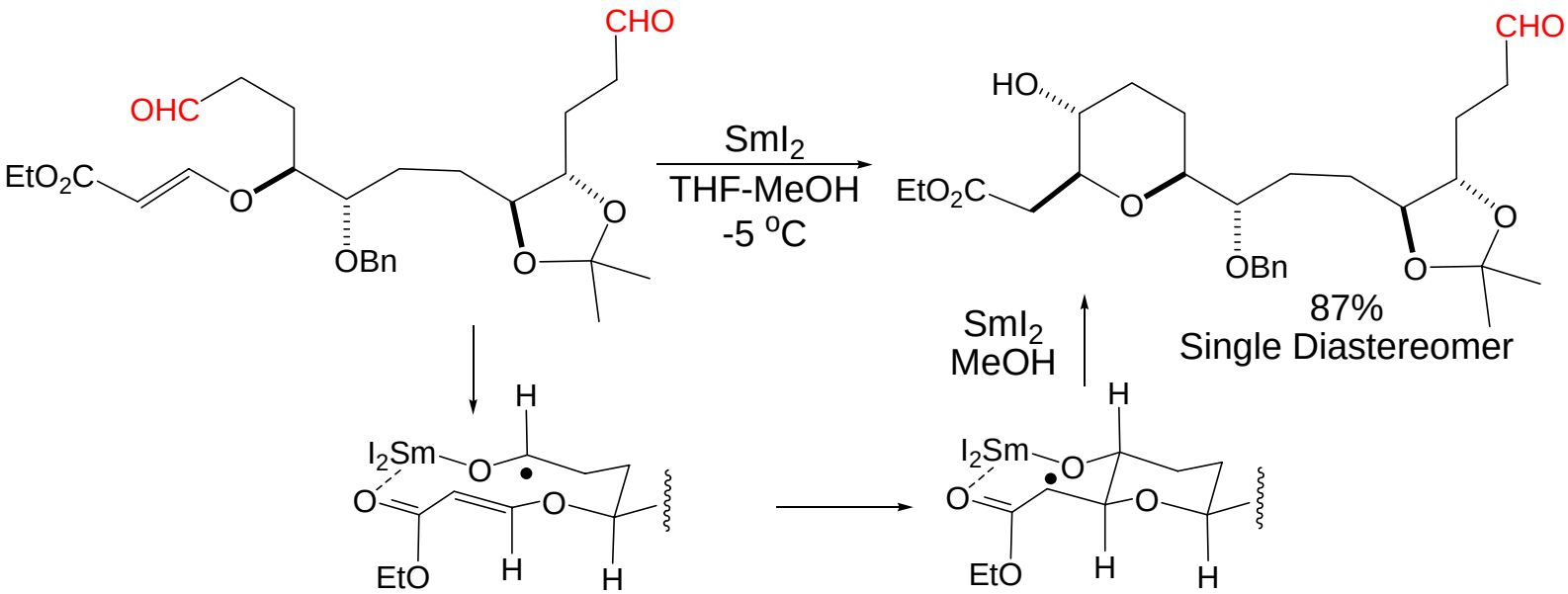
-Reaction required degassed solvents and slow separate addition of MeOH and SmI_2.

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

Little, R. D. *J. Org. Chem.* **1996**, 3240

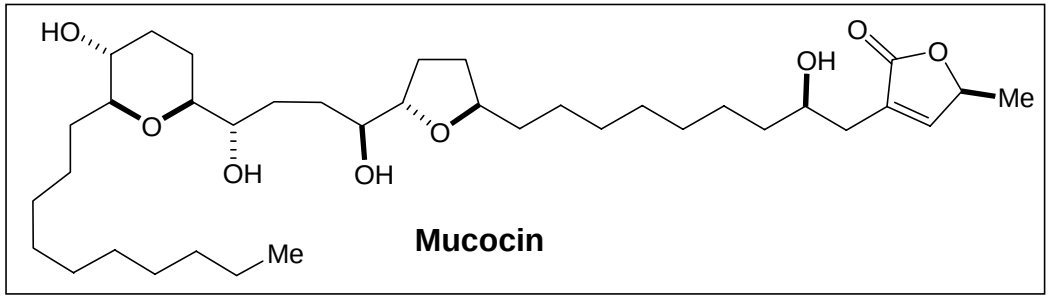
SmI_2 Radical Carbonyl-Alkene Cyclizations

Mucocin



-Survival of second aldehyde suggests inital SmI_2 reduction is reversible

-Increasing reaction time or using larger amounts of SmI_2 leads to Pinacol-type coupling and reduction products.

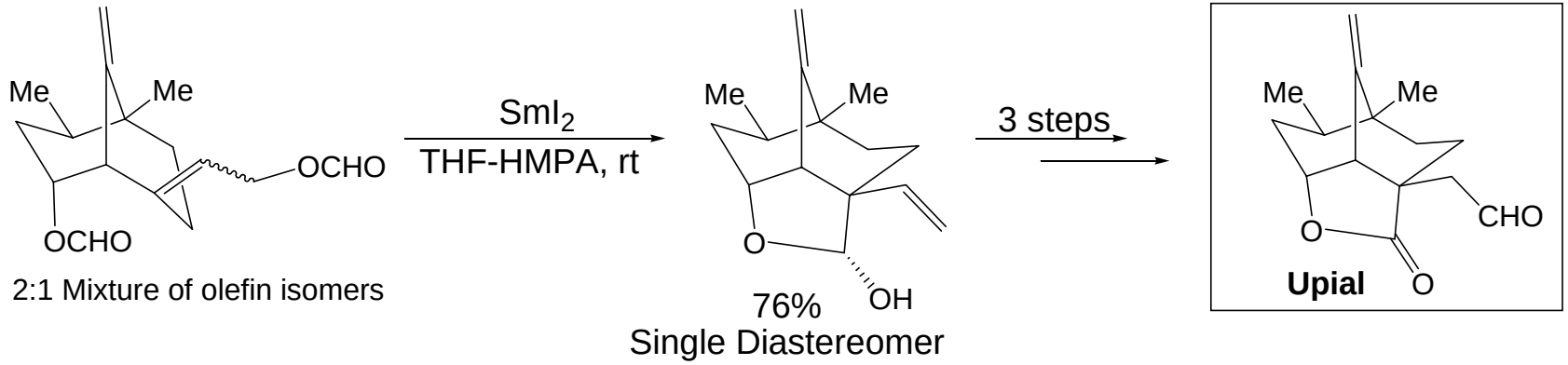


Mucocin

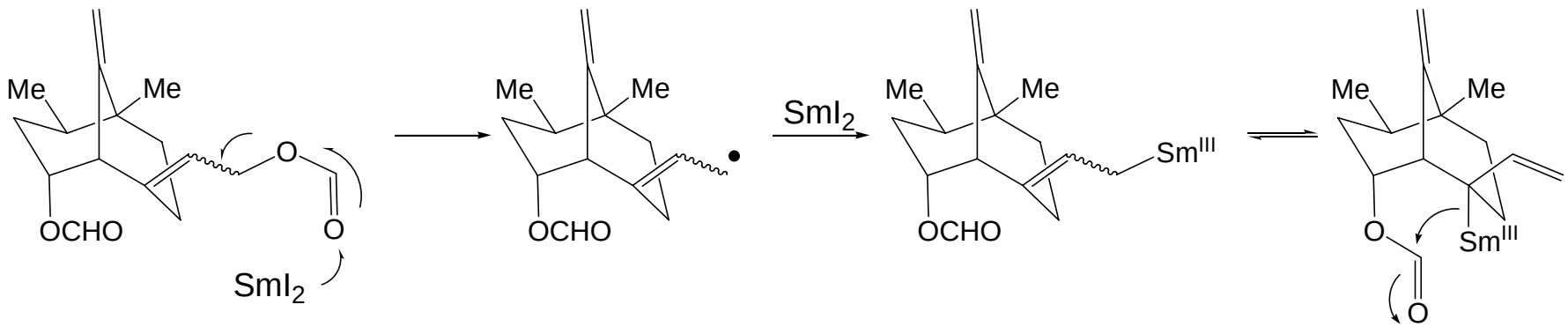
Nakata, T. *ACIEE* **2002**, 4751
Curran, D. P. *Synlett* **1992**, 943

SmI_2 Radical Carbonyl-Alkene Cyclizations

Upial



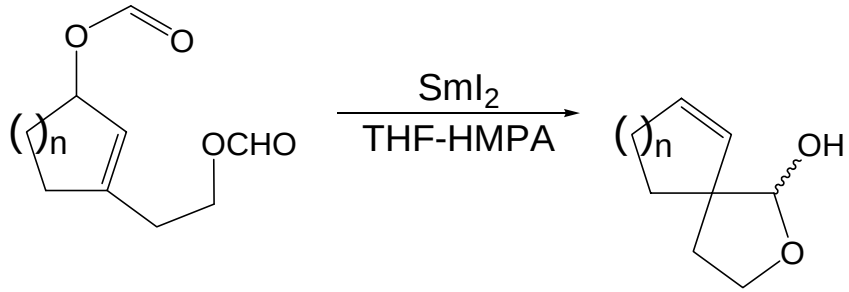
Proposed Mechanism



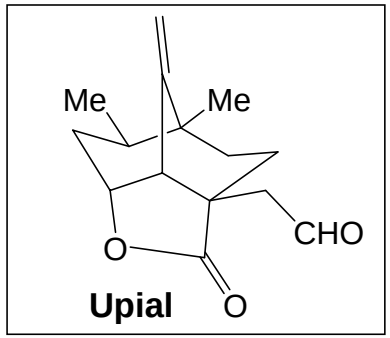
Nagaoka, H. *Tetrahedron Lett.* **1993**, 1504.
Shibuya, K. *J. Chem. Soc. Chem. Commun.* **1991**, 1545.
Procter, G. *Chem. Rev.* **2004**, 3371.

SmI_2 Radical Carbonyl-Alkene Cyclizations

Model Studies: Upial

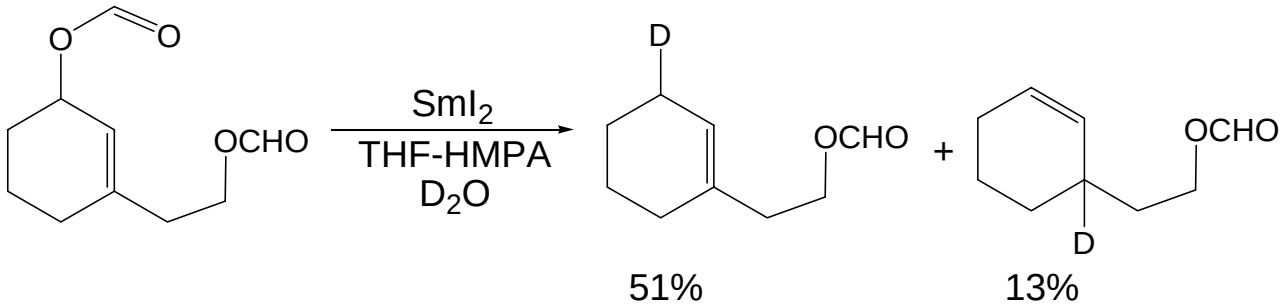


n	Yield
1	55%
2	73%
3	76%



Without HMPA product yields were 5-10%

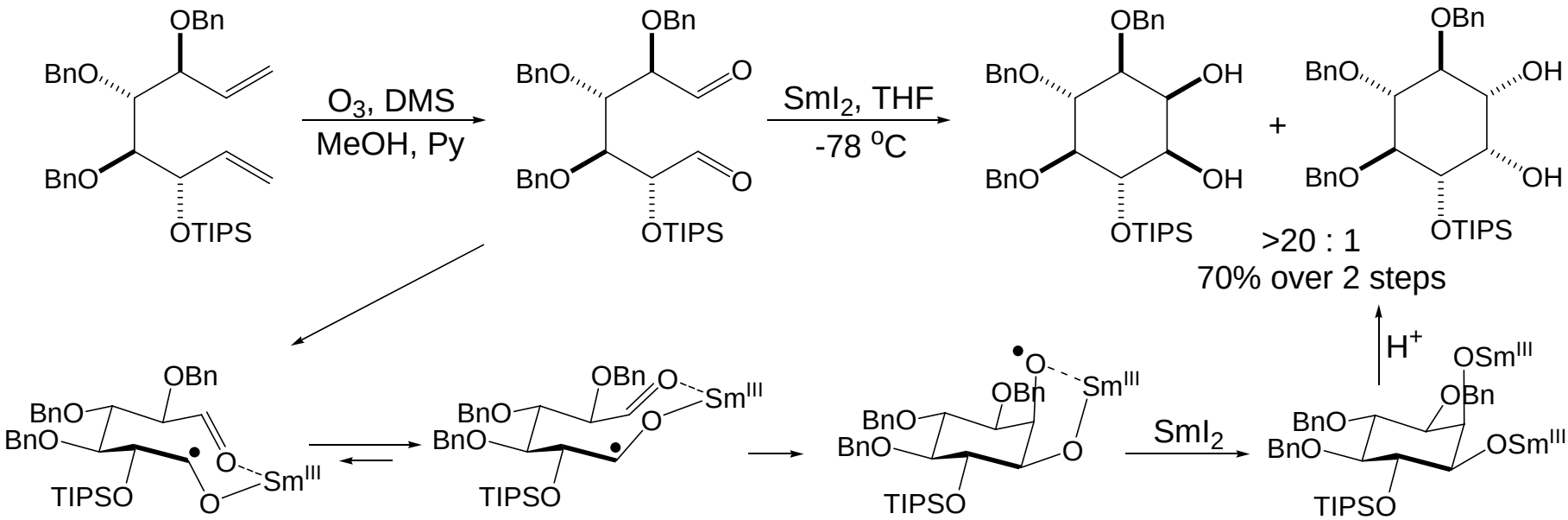
Supporting Evidence

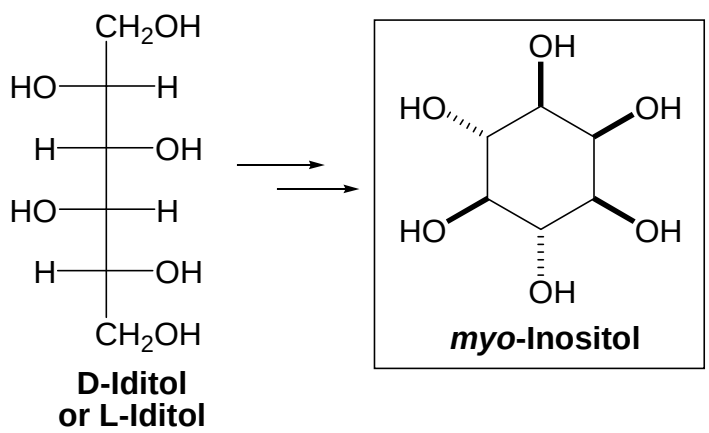


Shibuya, K. *J. Chem. Soc. Chem. Commun.* **1991**, 1545.
Proctor, G. *Chem. Rev.* **2004**, 3371.

SmI_2 Intramolecular Pinacol Couplings

Basic Mechanism, *myo*-Inositol





D-Iditol or L-Iditol

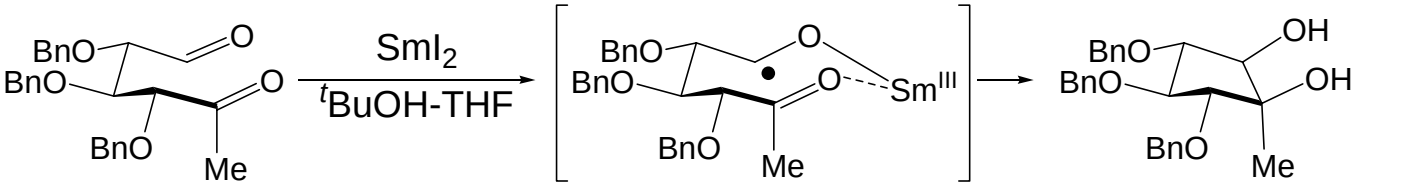
-Attractive alternative to $TiCl_3$-Zn/Cu, Mg(Hg)-$TiCl_4$, or Ytterbium pinacol couplings.

-Predominately gives cis-diol trans to α-substitution

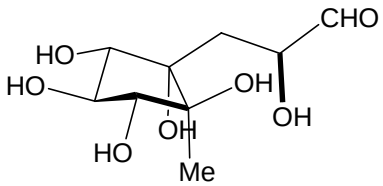
Kornienko, A. *Tetrahedron Asymmetry* **1998**, 2783.
Chiara, J. L. *Terahedron Letters* **1994,** 1969.
Chiara J. L. *Tetrahedron Letters* **1991**, 1125.
Guidot J. P. *Tetrahedron Letters* **1994**, 6671.
Molander, G. A. *J. Am. Chem. Soc.* **1989**, 8236.
dodong, U. K. *J. Org. Chem.* **1988**, 2132.

SmI_2 Intramolecular Pinacol Couplings

Caryose and a Jojoba Bean Disacchride

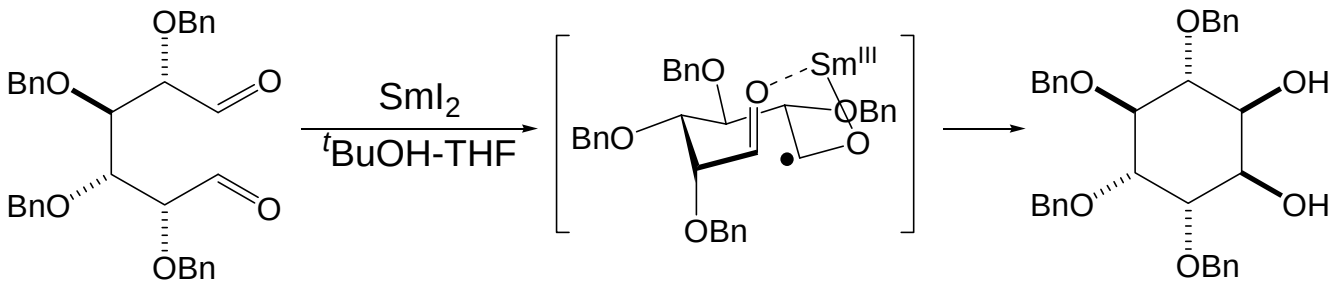


93:7 mixture of cis-Diols
64% Yield

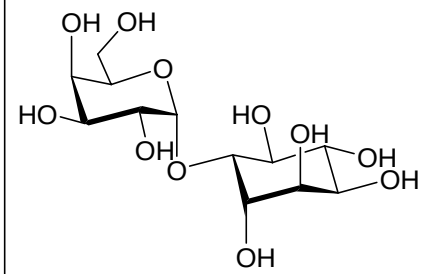


Caryose

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



Single Diastereomer
40% with Oxidation

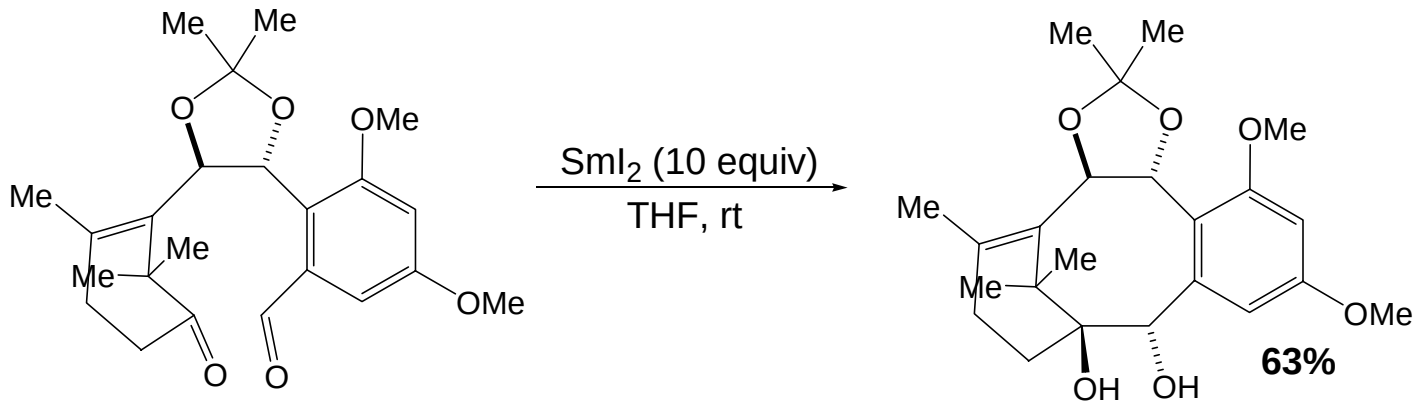


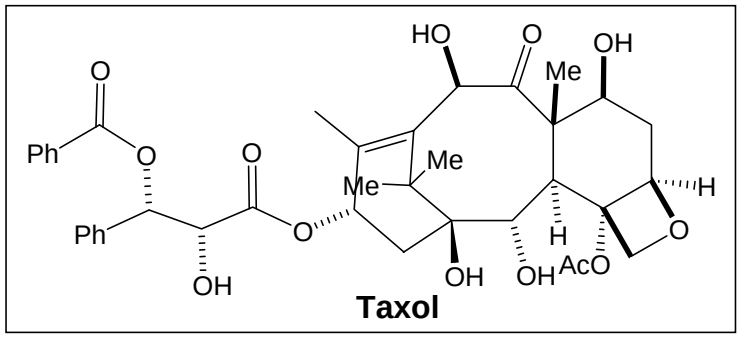
A Jojoba Bean Disaccharide

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

SmI_2 Intramolecular Pinacol Couplings

Synthetic Studies Toward Taxol





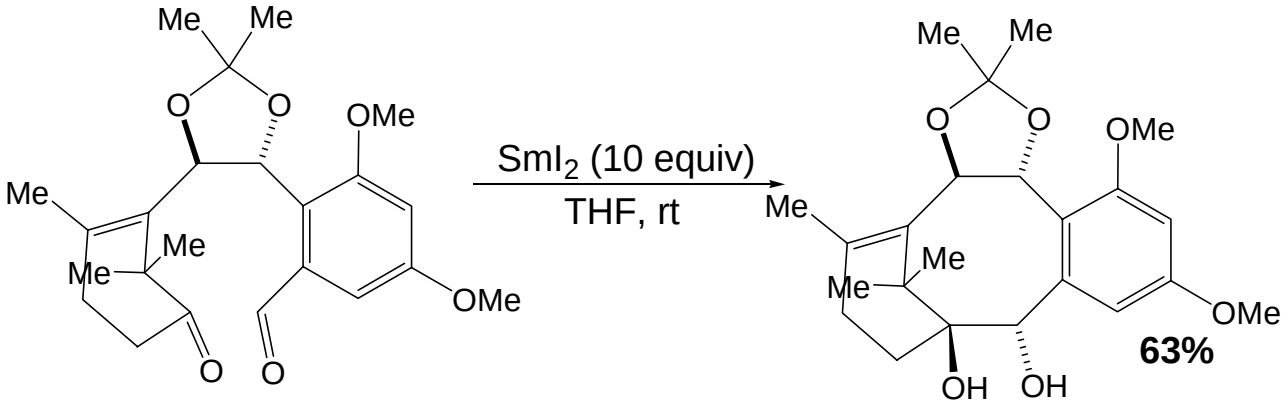
-Performing reaction at -78 ^{o}C leads to reduction

-Corresponding Pinacol with $TiCl_4$/Zn produces pdt in 33% yield.

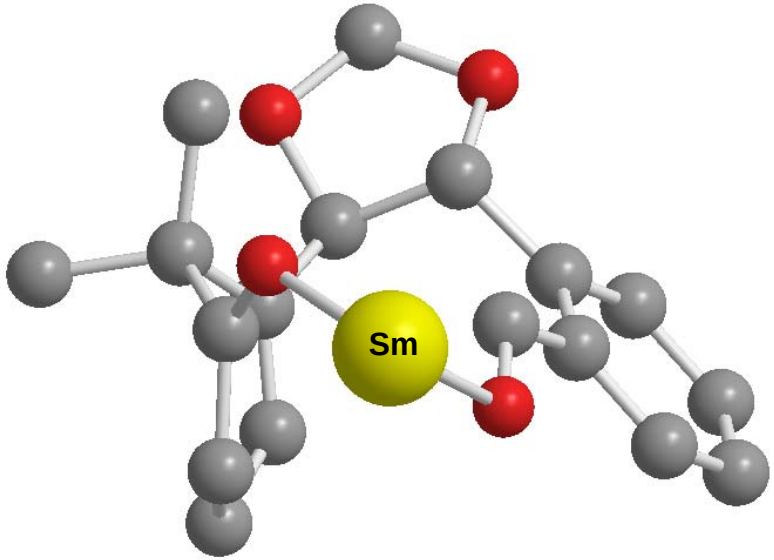
Swindell, C. S. *J. Org. Chem.* **1996**, 1109.
Swindell, C. S. *Tetrahedron* **1996**, 2321.
Arseniyadis, S. *tetrahedron Lett.* **1993**, 1137.

SmI_2 Intramolecular Pinacol Couplings

Synthetic Studies Toward Taxol



Sm-Chelated Models Minimized Energies



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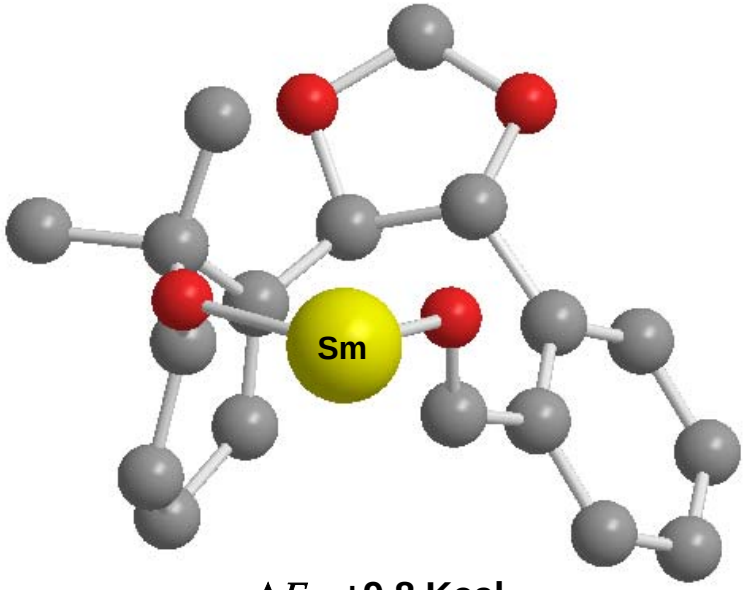


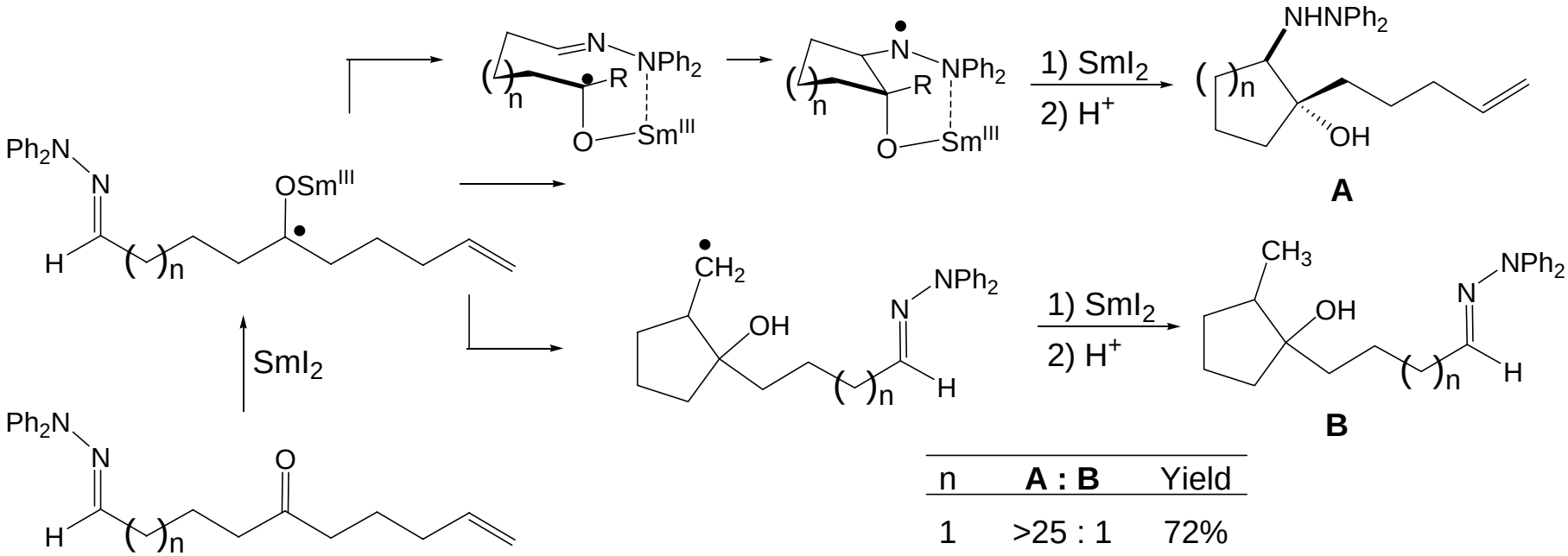
$\Delta E =$ **+9.8 Kcal**

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.

SmI_2 Intramolecular Reductive Coupling of Carbonyl-Hydrazones

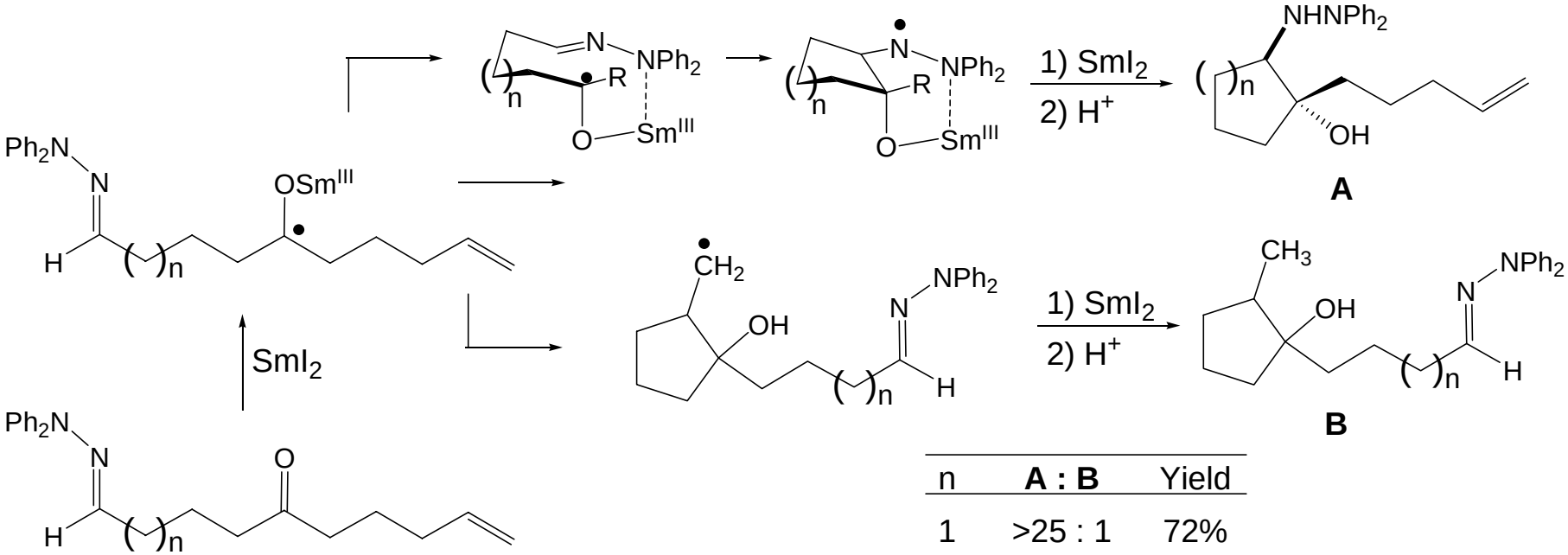
Basic Mechanism, An Example



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

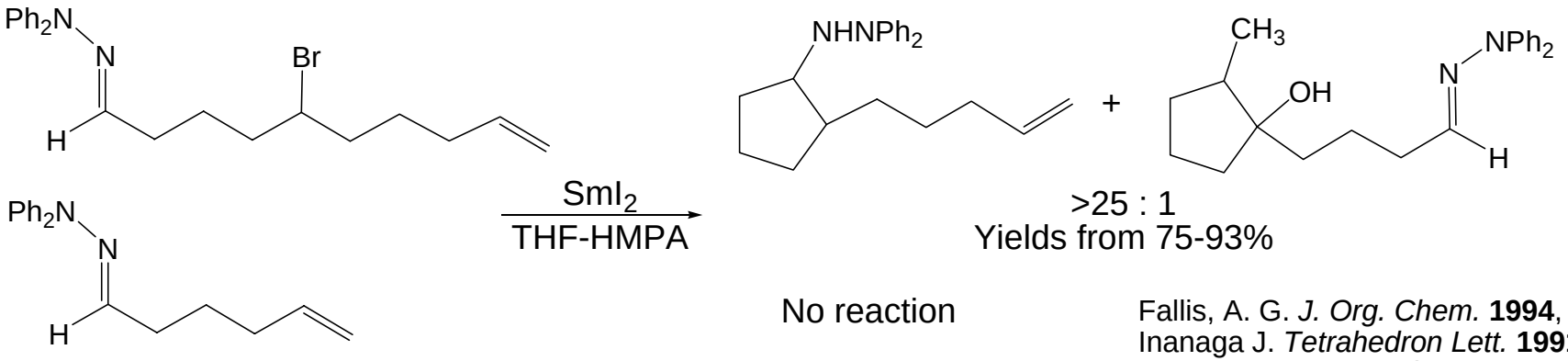
SmI_2 Intramolecular Reductive Coupling of Carbonyl-Hydrazones

Basic Mechanism, An Example



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

Additional Evidence



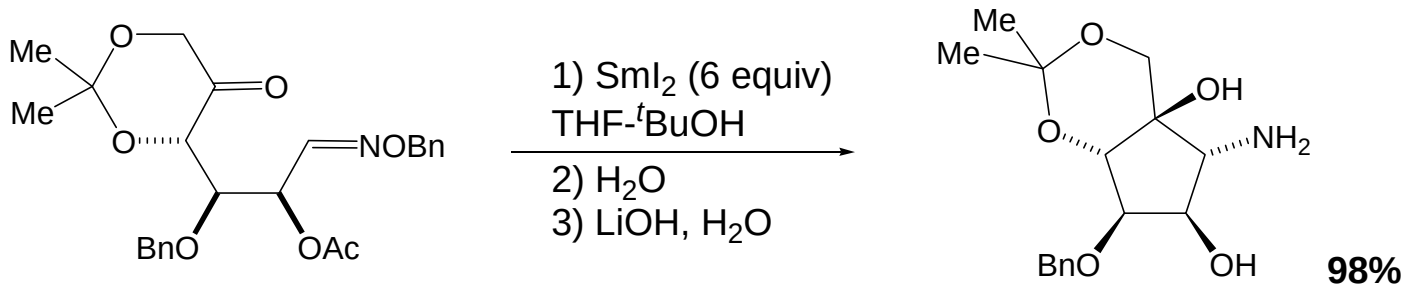
>25 : 1
Yields from 75-93%

No reaction

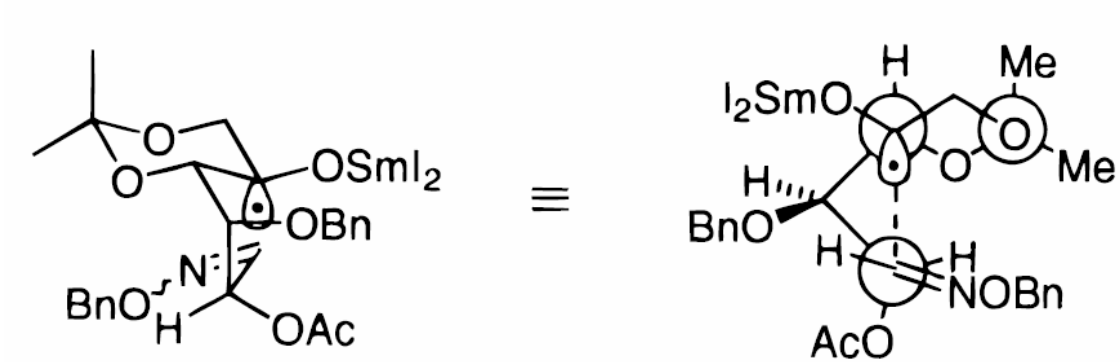
Fallis, A. G. *J. Org. Chem.* **1994**, 6514.
Inanaga J. *Tetrahedron Lett.* **1991**, 3555.
Fallis A. G. *J. Am.. Chem.. Soc.* **1994**, 7447.

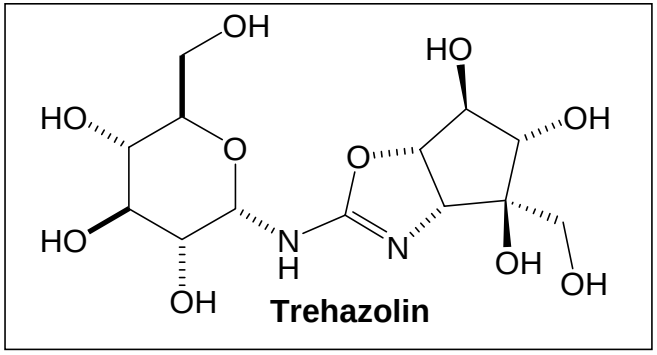
SmI_2 Intramolecular Reductive Coupling of Carbonyl-Oximes

Synthesis of Trehazolin



Proposed Transition States

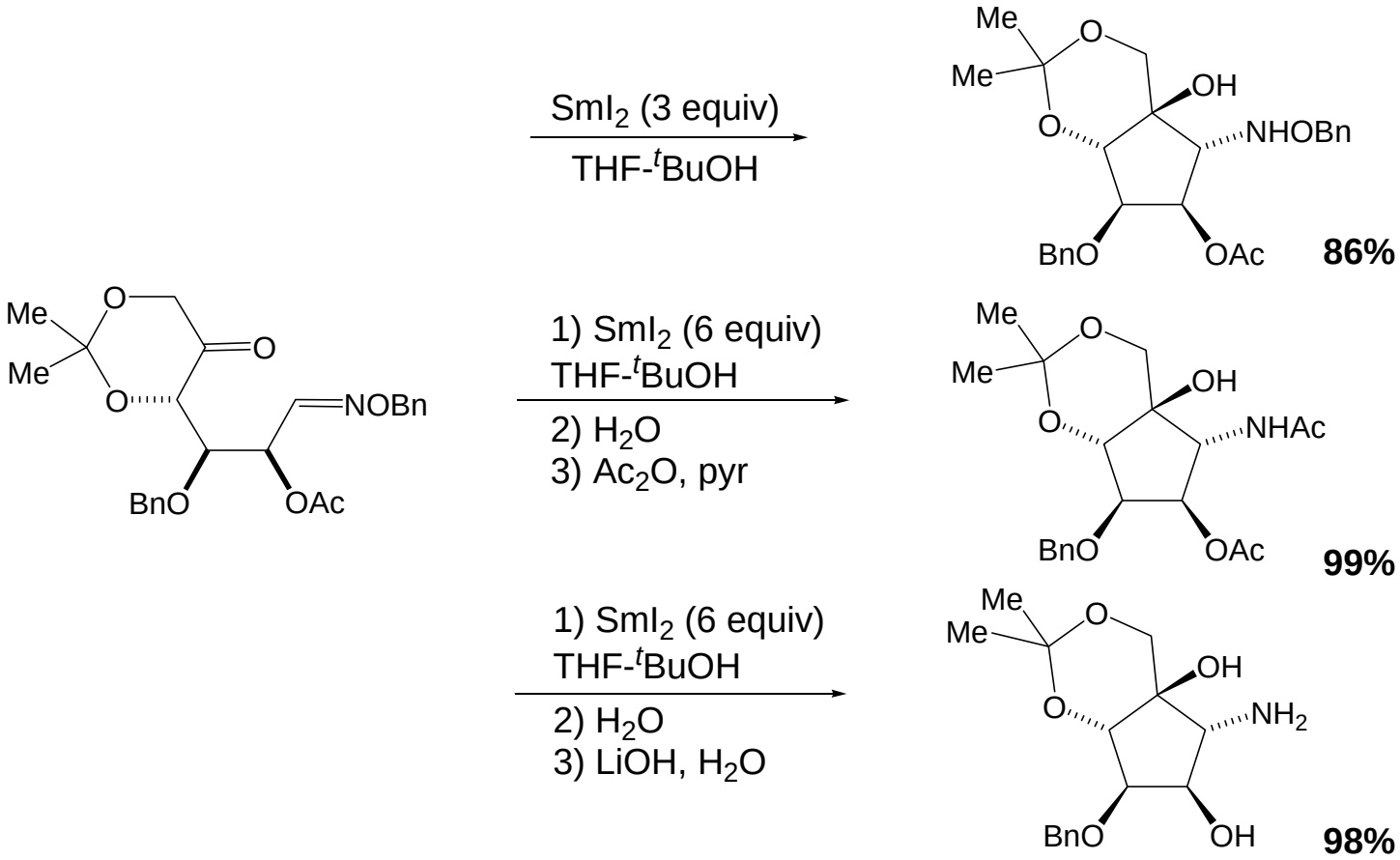




Chiara, J. L *Org. Lett.* **1999**, 1705.
Giese, B. *J. Org. Chem.* **1998,** 5877.
Chiara, J. L. *Synlett* **1999**, 1551.

SmI_2 Intramolecular Reductive Coupling of Carbonyl-Oximes

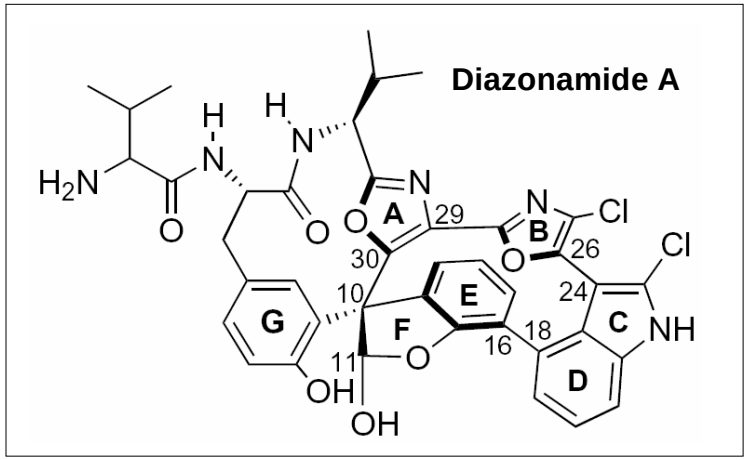
Synthesis of Trehazolin

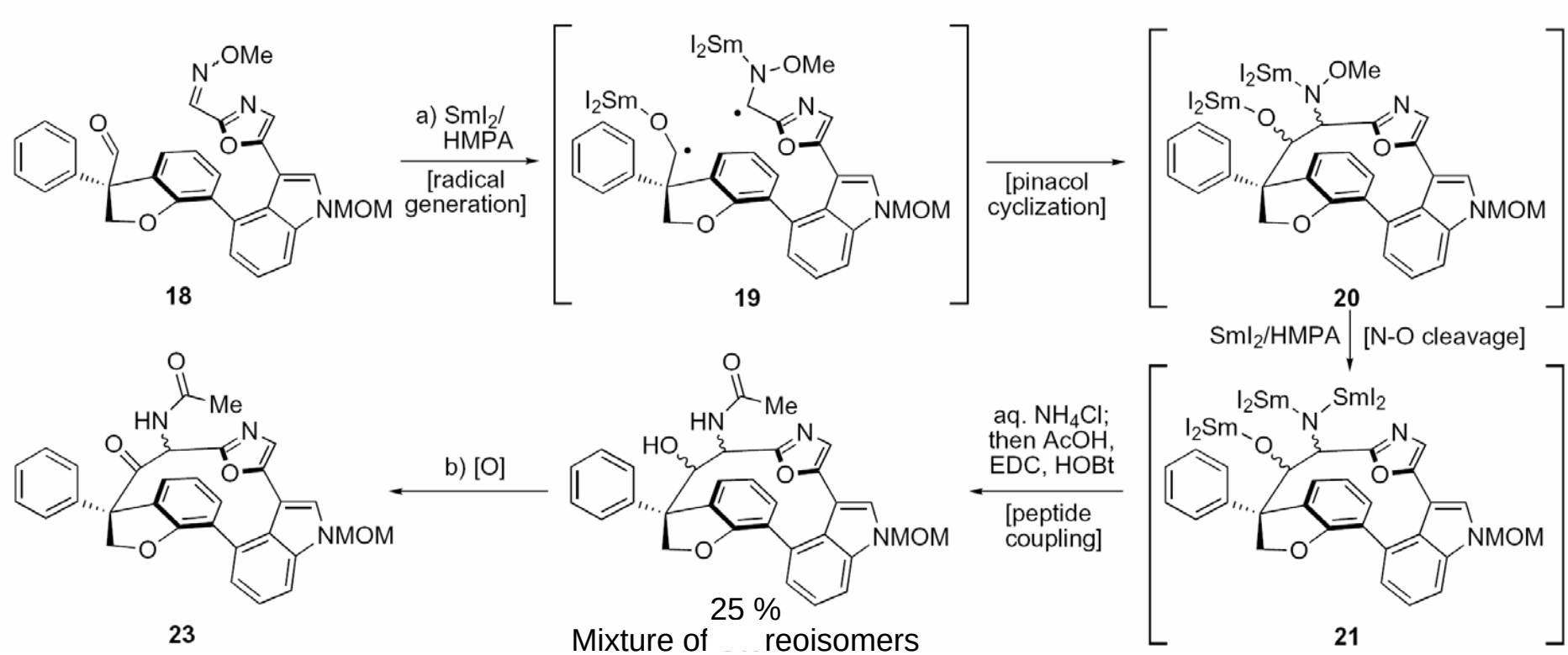


Chiara, J. L *Org. Lett.* **1999**, 1705.
Giese, B. *J. Org. Chem.* **1998,** 5877.
Chiara, J. L. *Synlett* **1999**, 1551.

SmI_2 Intramolecular Reductive Coupling of Carbonyl-Oximes

Synthesis of Diazonamide A



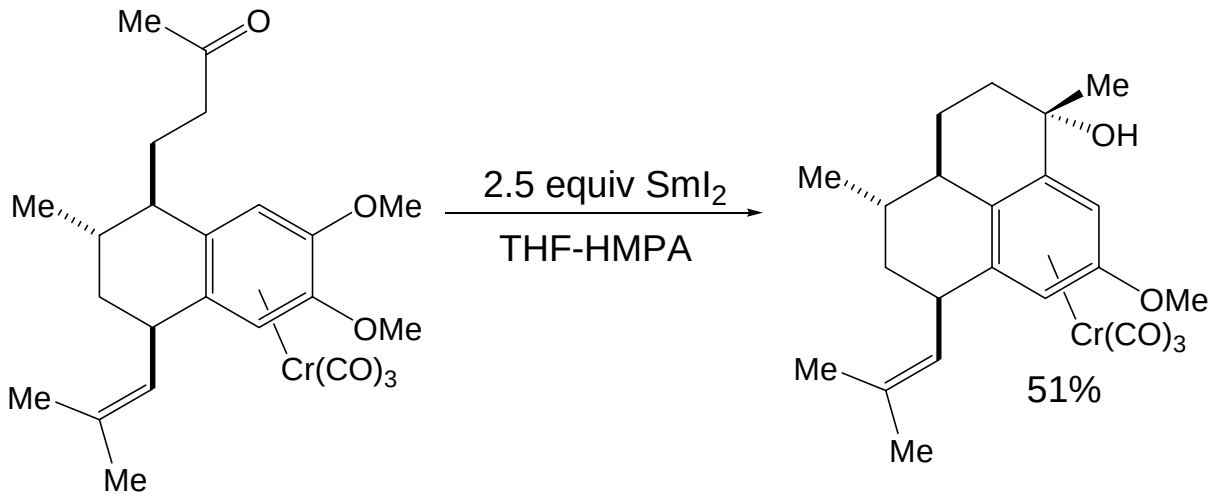


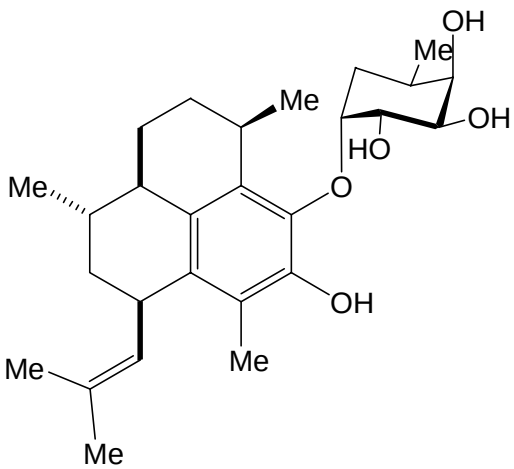
-No reaction in the absence of HMPA

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

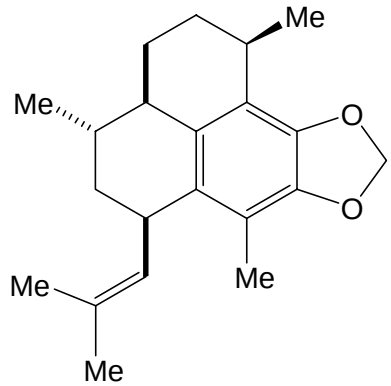
SmI_2 Intramolecular Reductive Arene-$Cr(CO)_3$-Carbonyl Cyclizations

Synthetic Studies Towards Pseudoterosin G and Helioporin E





Pseudoterosin G

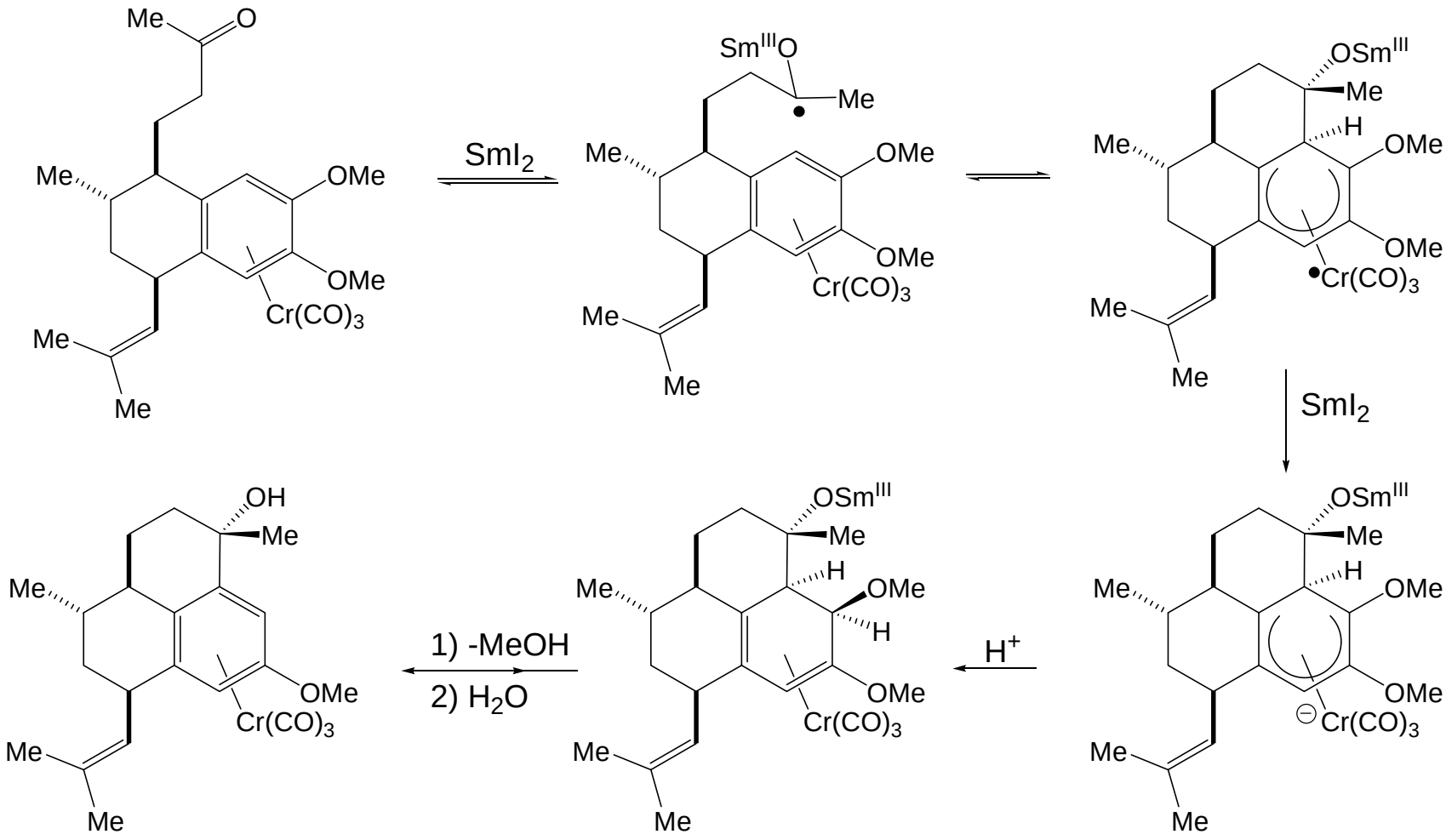


Helioporin E

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.

SmI_2 Intramolecular Reductive Arene-$Cr(CO)_3$-Carbonyl Cyclizations

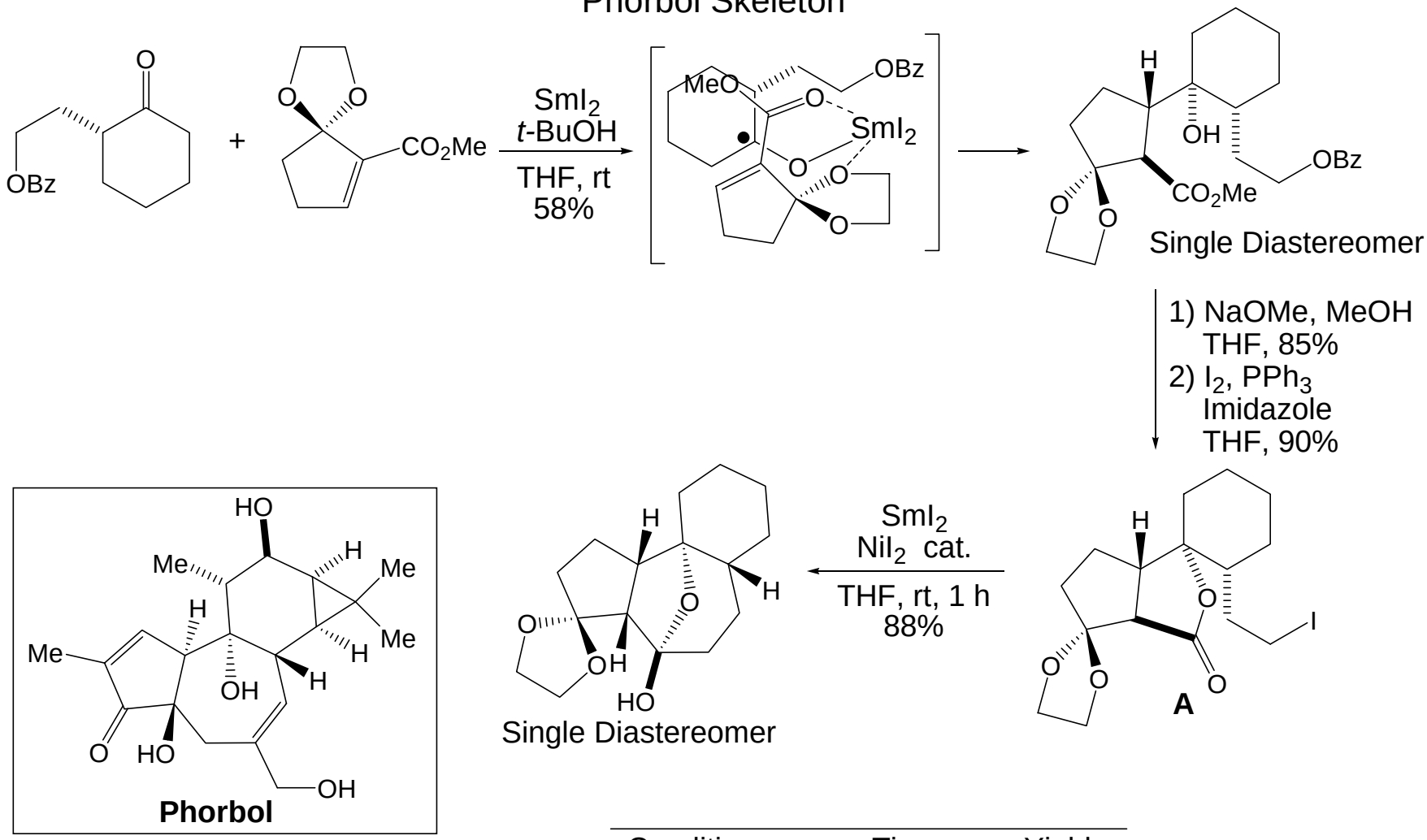
Mechanism



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



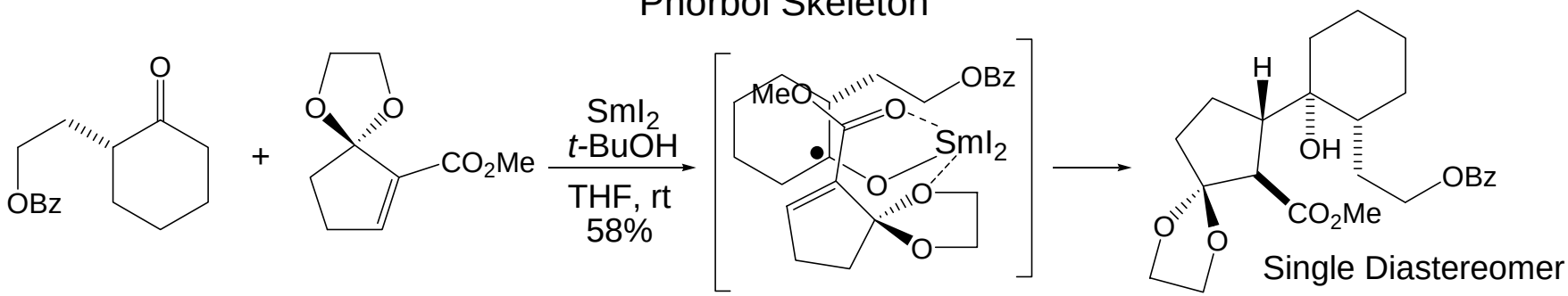
Conditions	Time	Yield
No Additve	5-7h	43-68%
With NiI_2	1h	82-88%

Little D. *Org. Lett.* **2000**, 2873

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

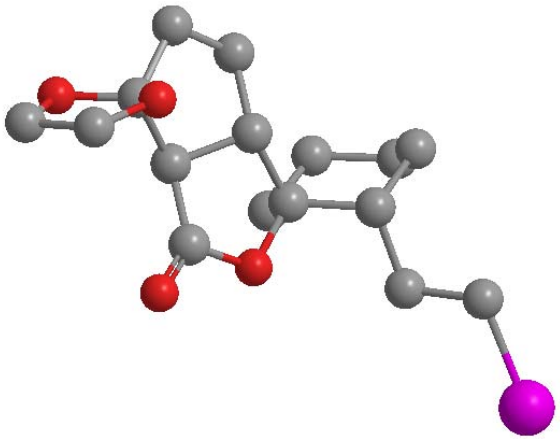
Carbonyl-Olefin Reductive Coupling/Intramolecular SmI_2 Barbier Cyclization

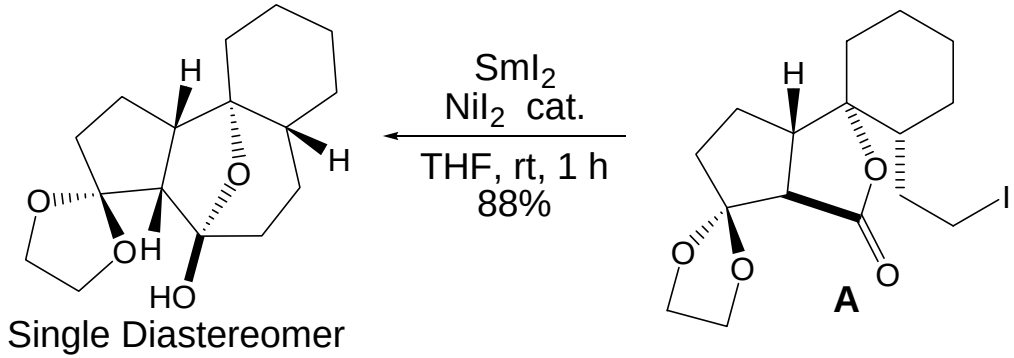
Phorbol Skeleton



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

Model of Intermediate **A**





Conditions	Time	Yield
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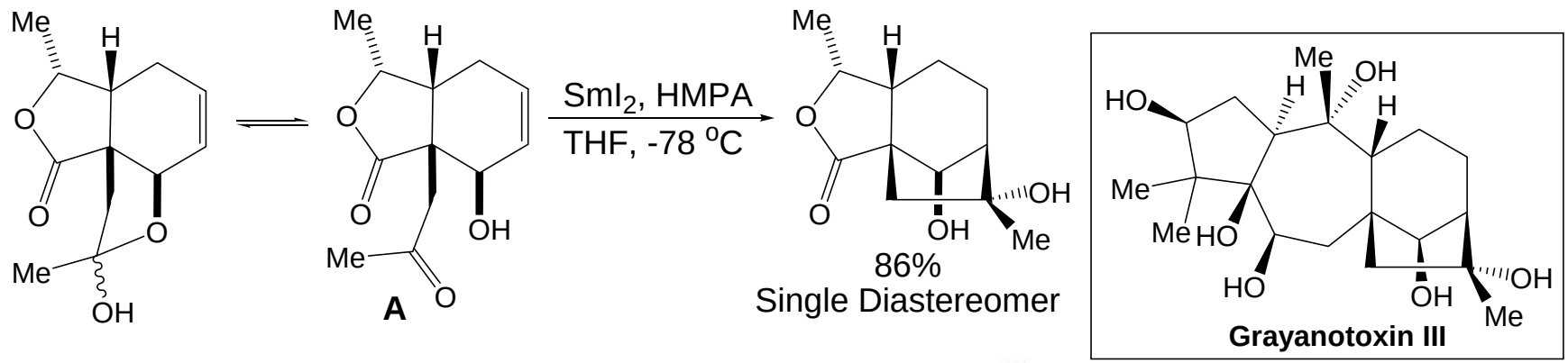
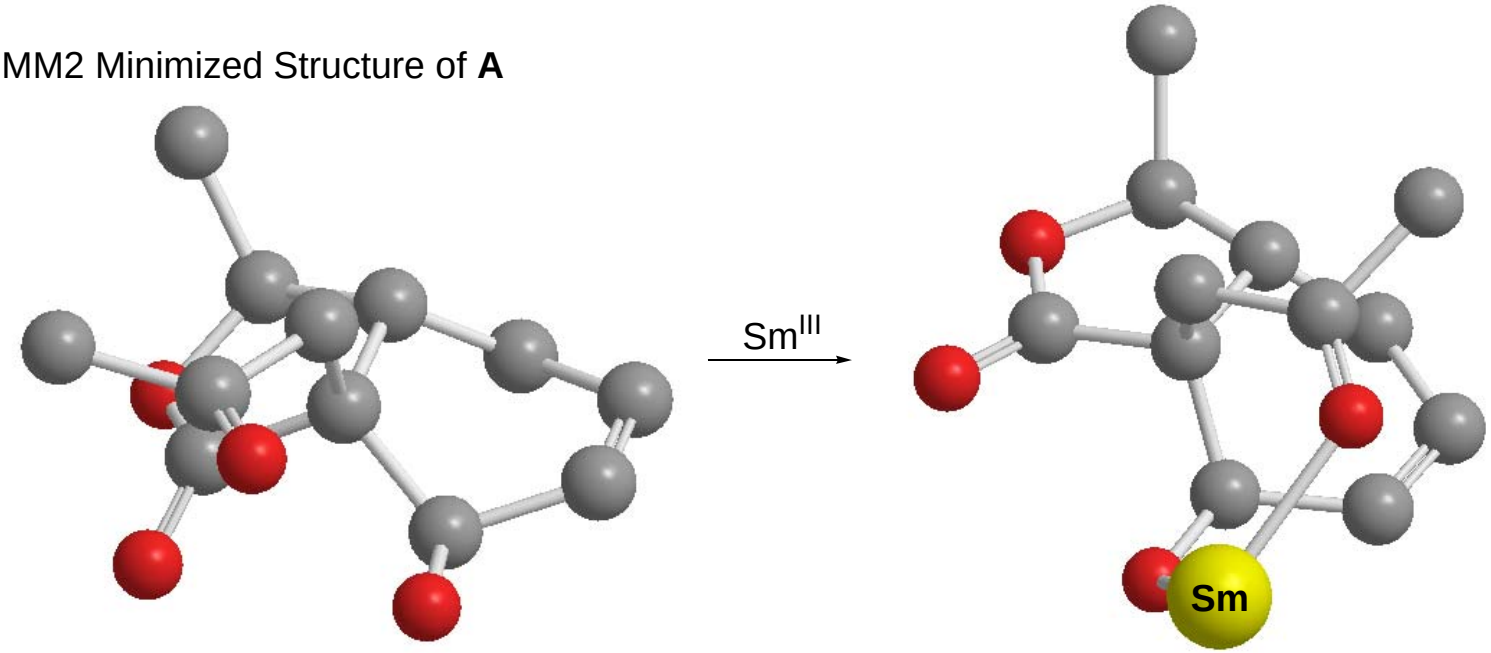
Little D. *Org. Lett.* **2000**, 2873
For increased reaction rates with NiI_2 see: Kagan, H. *Synlett* **1996**, 633

Reductive Carbonyl Conjugate and Pinacol Cyclizations

Grayanotosin III



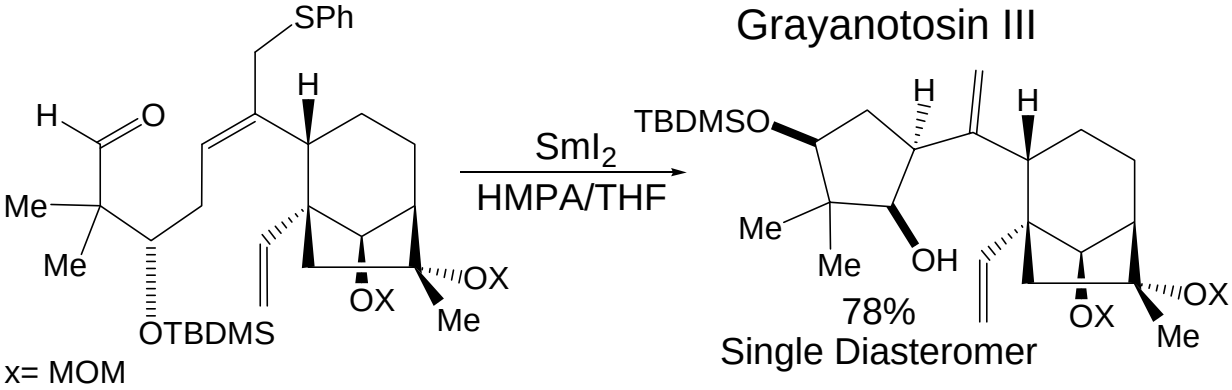
MM2 Minimized Structure of **A**

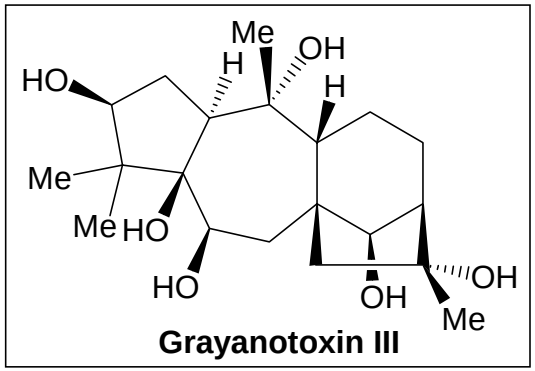


Shirahama, H. *J. Org. Chem.* **1994**, 5532

Reductive Carbonyl Conjugate and Pinacol Cyclizations

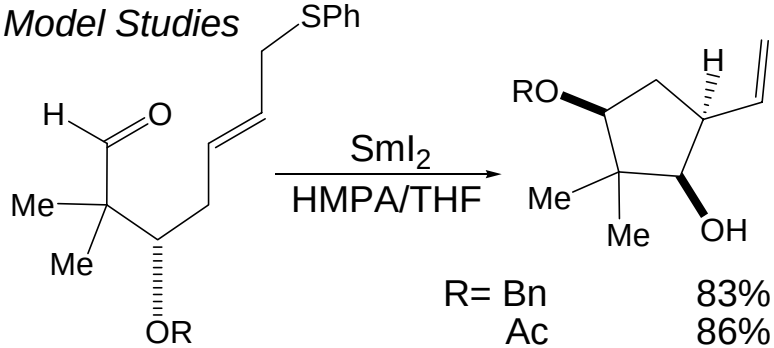
Grayanotosin III



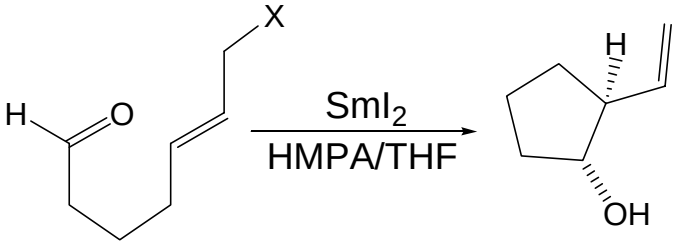


-Both *E* and *Z*-allyl sulfides gave the same product in similar yields

Model Studies

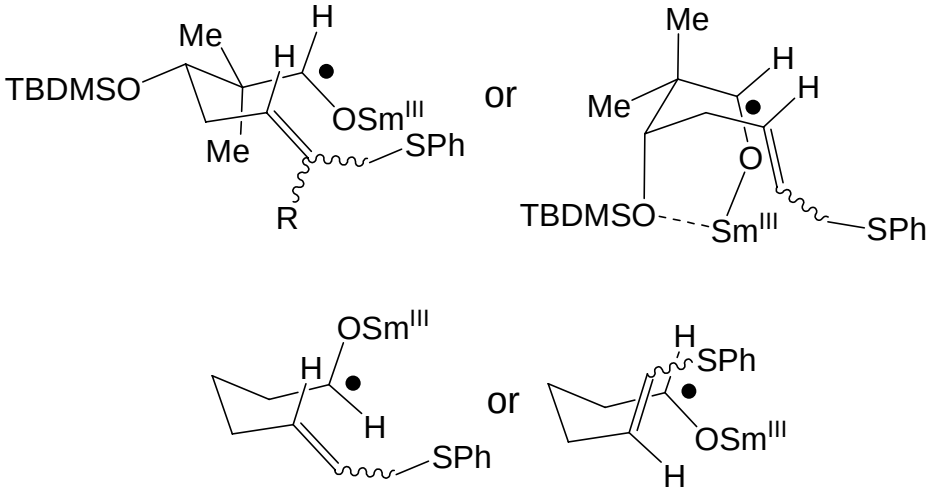


R= Bn	83%
Ac	86%
TBDMS	91%



X= SPh	47%
SO_2Ph	78%

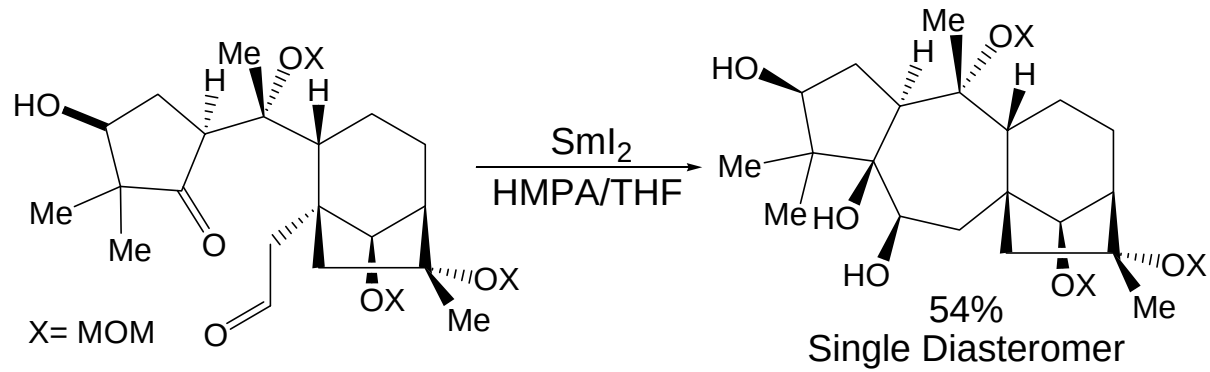
Plausible Transition States

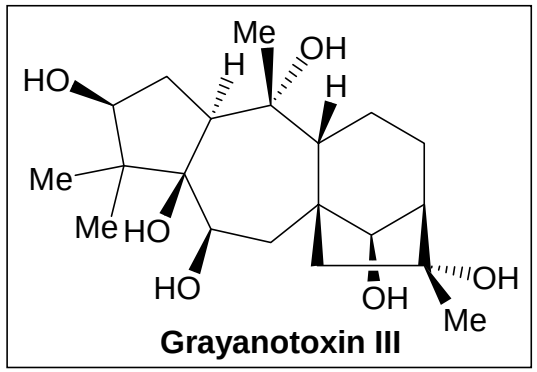


Kan, T. *J. Org. Chem.* **1994**, 5532.
Kan, T. *J. Org. Chem.* **1994**, 5113.

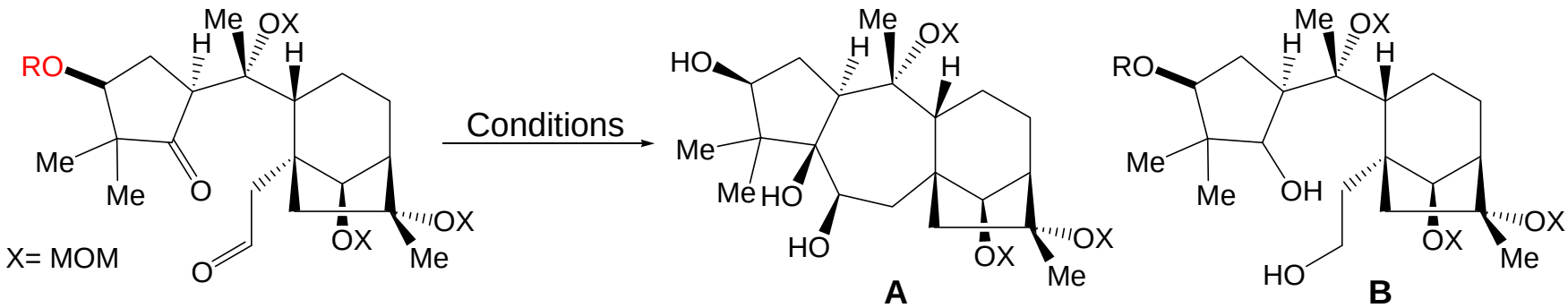
Reductive Carbonyl Conjugate and Pinacol Cyclizations

Grayanotosin 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

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

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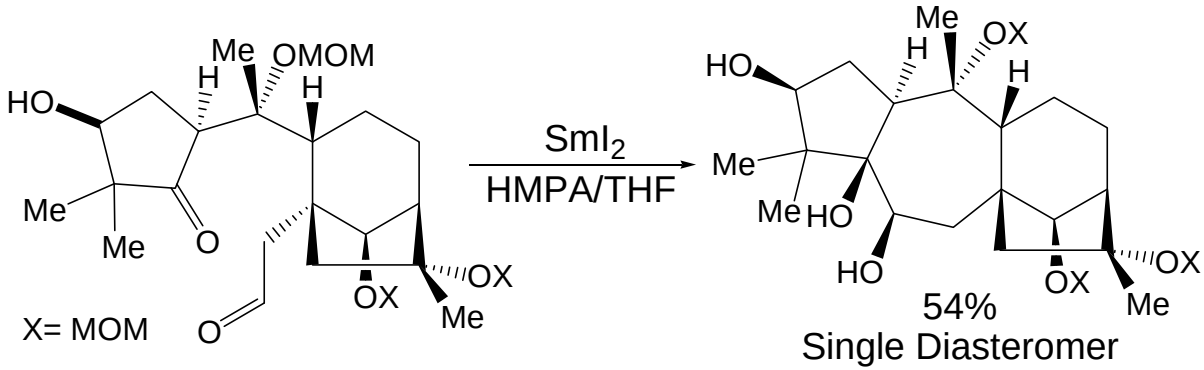
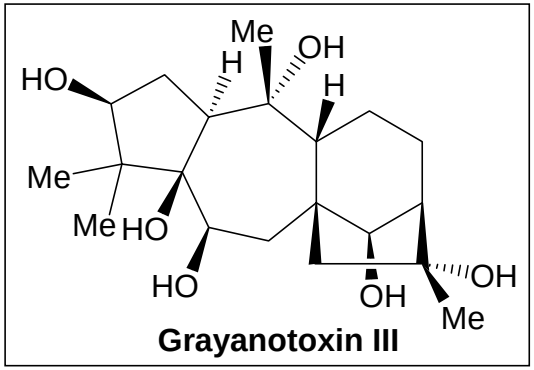
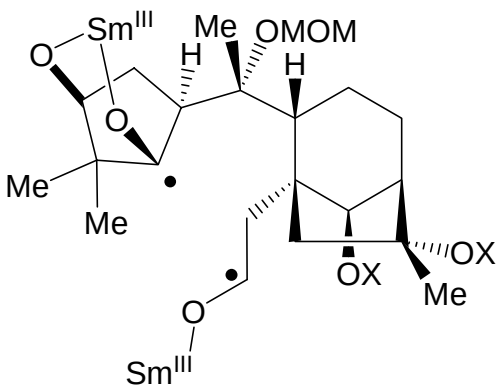
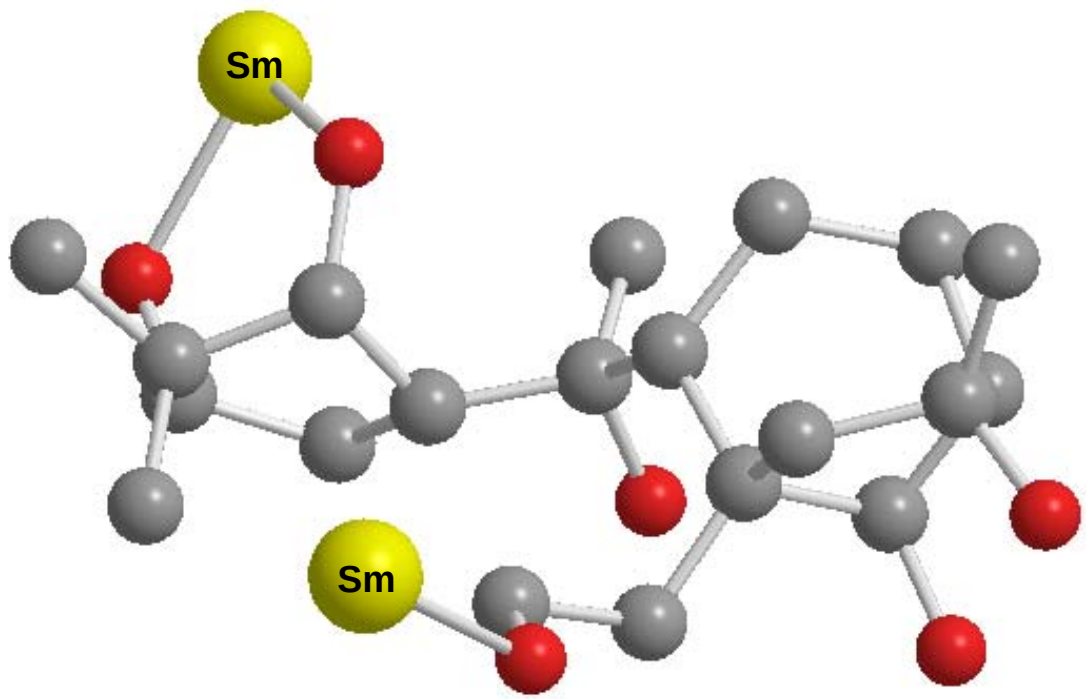




Potential Stereochemical Model





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Concluding Remarks

Benifits 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 succesfully in multiple total synthetic endeavors as a mild single electron chelating reducting agent.

-Due to samarium diiodide's large ionic radius, high coordination number, and high oxophilicity samarium diiodide has been used succesfully 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 uncertainity in the mechanism of the transformations limits the stereochemical predictive potential of the reagent.