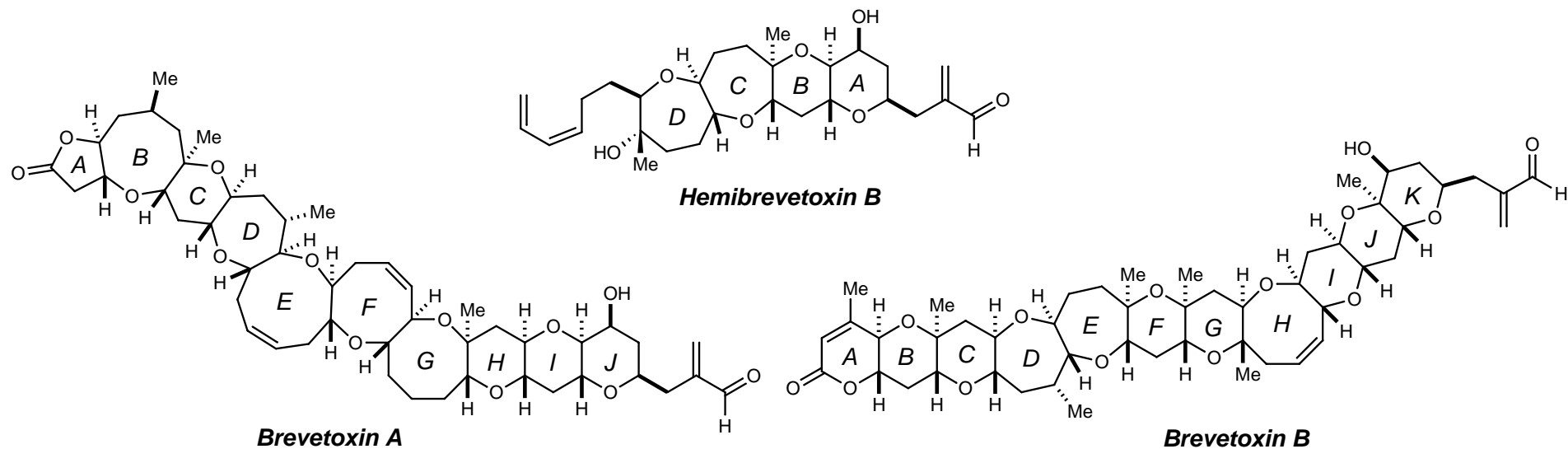


Methodologies Relevant to the Synthesis of the Brevetoxins

Duke M. Fitch
Evans Group Seminar
June 5, 1998

- I. Background
- II. Hemibrevetoxin B
 - A. Approaches to the Construction of the A ring
 - B. Approaches to the Construction of the B ring
 - C. Approaches to the Construction of the C ring
 - D. Approaches to the Construction of the D ring
 - E. End Game
- III. Brevetoxin B
- IV. Brevetoxin A

Leading References: Martín, J.D. *Chem. Rev.* **1995**, 95, 1953.
Nicolaou, K.C. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 589.
Nicolaou, K.C. *Classics in Total Synthesis*; VCH: New York, **1996**, 731.
Nicolaou, K.C. *Nature* **1998**, 392, 264.



■ **Brevetoxin B:**

Isolated in 1981 (Lin, Clardy, Nakanishi *J. Am Chem. Soc.* **1981**, 103, 6773.) from red tide dinoflagellate, *Gymnodinium breve*.

Structure determined using a combination of spectroscopic and X-ray crystallographic methods.

Potent, lipid soluble neurotoxin that binds to sodium channels of neurons, keeping them open, causing depolarization of the cell membrane.

Total Synthesis: Nicolaou *J. Am Chem. Soc.* **1995**, 117, 1171.; Nicolaou *J. Am Chem. Soc.* **1995**, 117, 10227.

■ **Brevetoxin A:**

Structure determined in 1986 using a combination of spectroscopic and X-ray crystallographic methods.

(Shimizu, Clardy *J. Am Chem. Soc.* **1986**, 108, 514.)

Most potent ichthyotoxin isolated from *Gymnodinium breve* with $LC_{100} = 4$ ng/ml to guppies.

Total Synthesis: Nicolaou *Nature* **1998**, 392, 264.

■ **Hemibrevetoxin B:**

Isolated in 1989 (Shimizu *J. Am Chem. Soc.* **1989**, 111, 6476.) along with A and C from *Gymnodinium breve*.

Structure determined from extensive 1D and 2D NMR analysis and comparison to brevetoxin A.

Causes characteristic rounding of cultured mouse neuroblastoma cells and exhibits cytotoxicity at 5 μ mol.

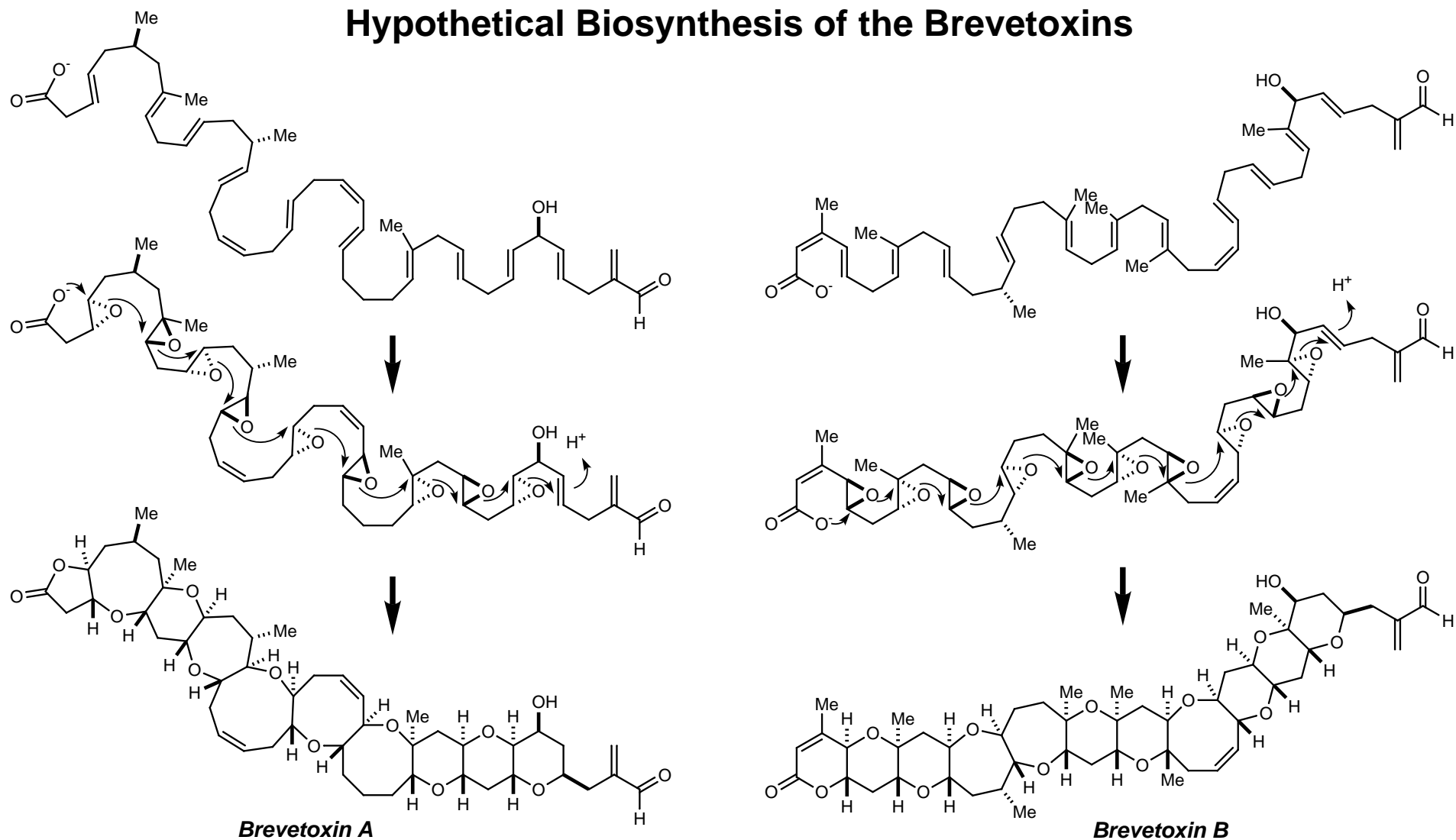
Total Syntheses: Nicolaou *J. Am Chem. Soc.* **1992**, 114, 7935.; Nicolaou *J. Am Chem. Soc.* **1993**, 115, 3558.

Yamamoto *Tet. Lett.* **1995**, 36, 5777.

Nakata *Tet. Lett.* **1996**, 37, 6365.

Formal Total Synthesis: Mori *J. Am Chem. Soc.* **1997**, 119, 4557.

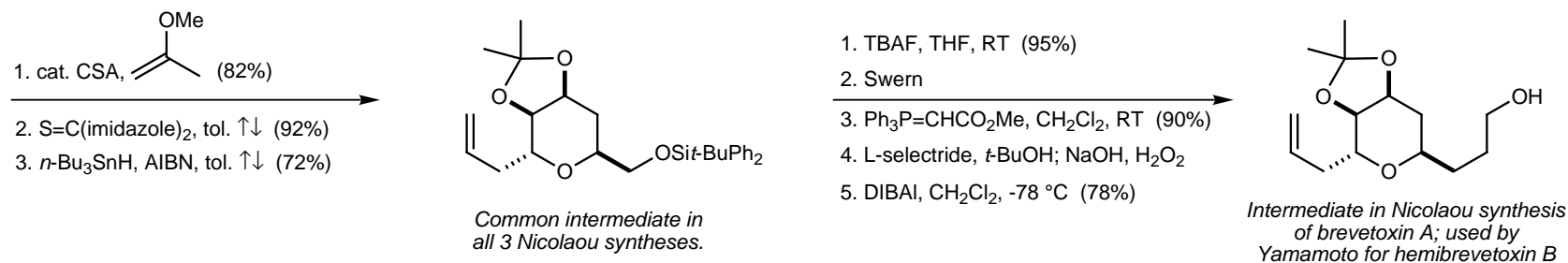
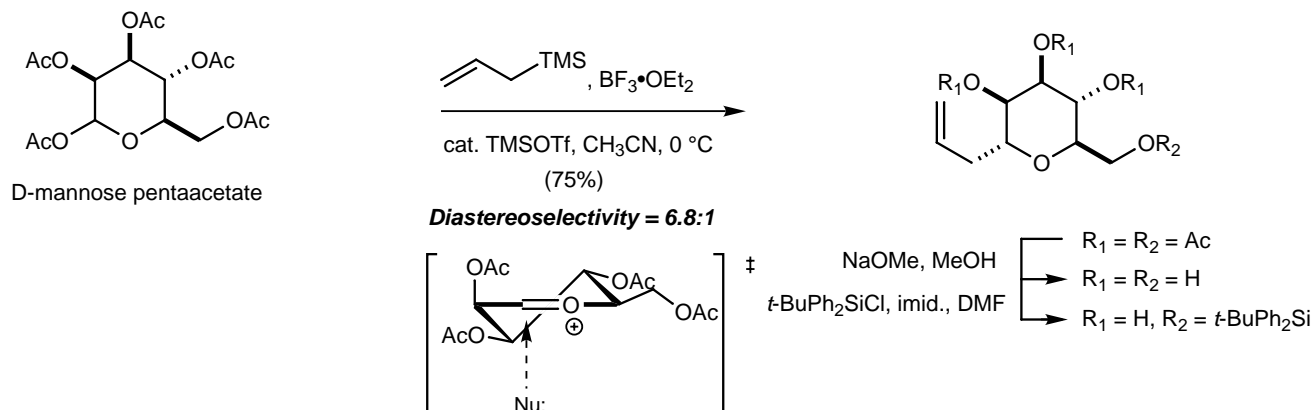
Hypothetical Biosynthesis of the Brevetoxins



"The cyclization cascade of the polyepoxides was proposed earlier (Nakanishi *Toxicon* **1985**, 23, 473) as an intriguing biogenetic scheme and should not be taken seriously; moreover, the origins of the oxygen atoms are unknown."

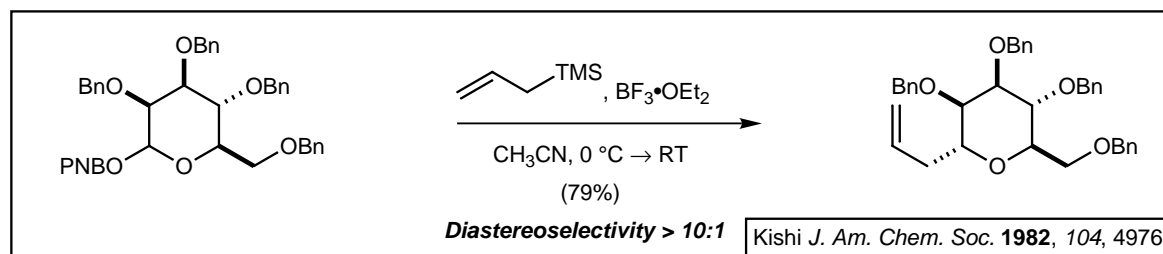
Approaches to the Synthesis of the A Ring of Hemibrevetoxin B

Sugar Derivatization:



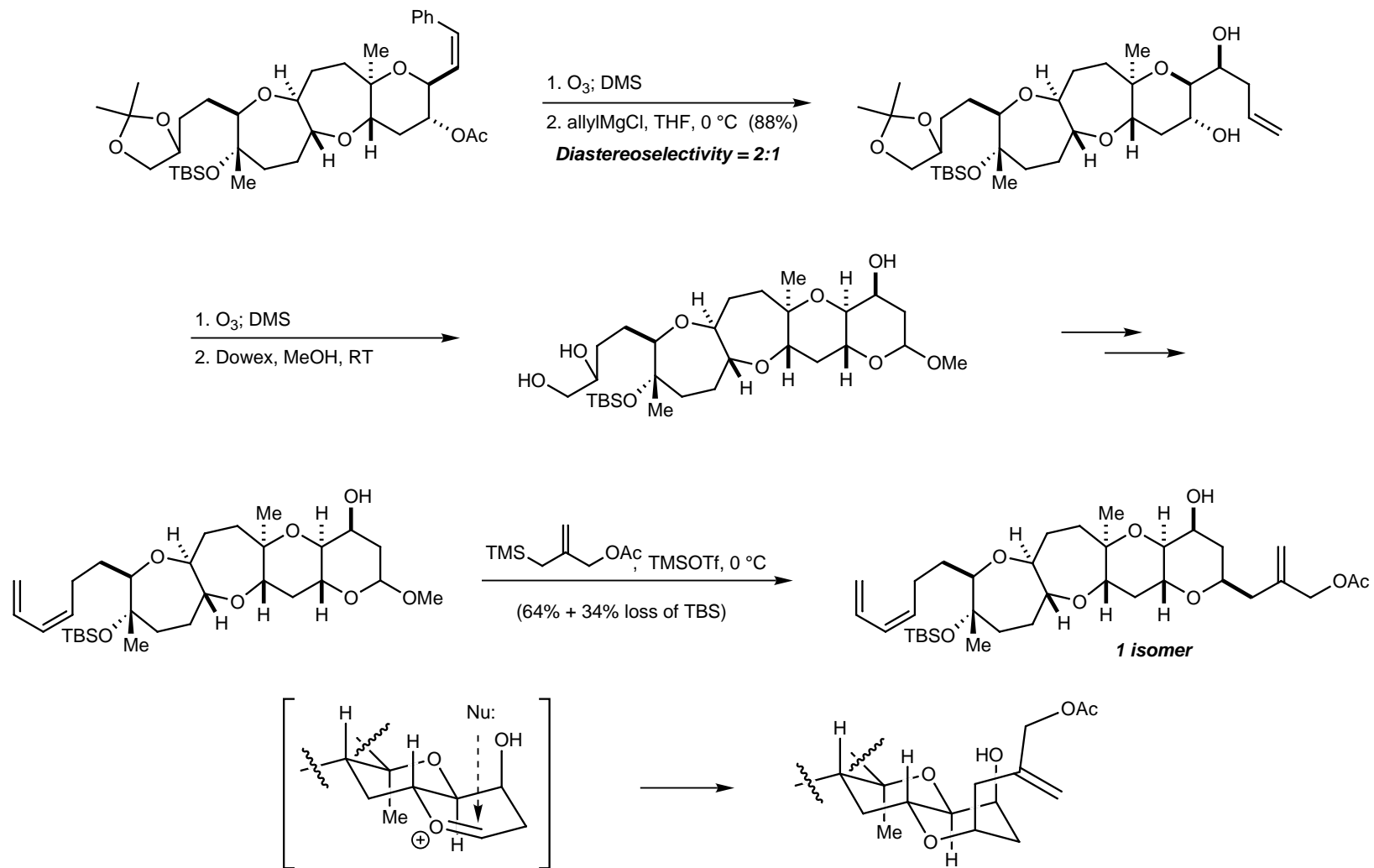
Nicolaou *J. Am. Chem. Soc.* **1989**, 111, 6682.

Nicolaou *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 299.



Approaches to the Synthesis of the A Ring of Hemibrevetoxin B

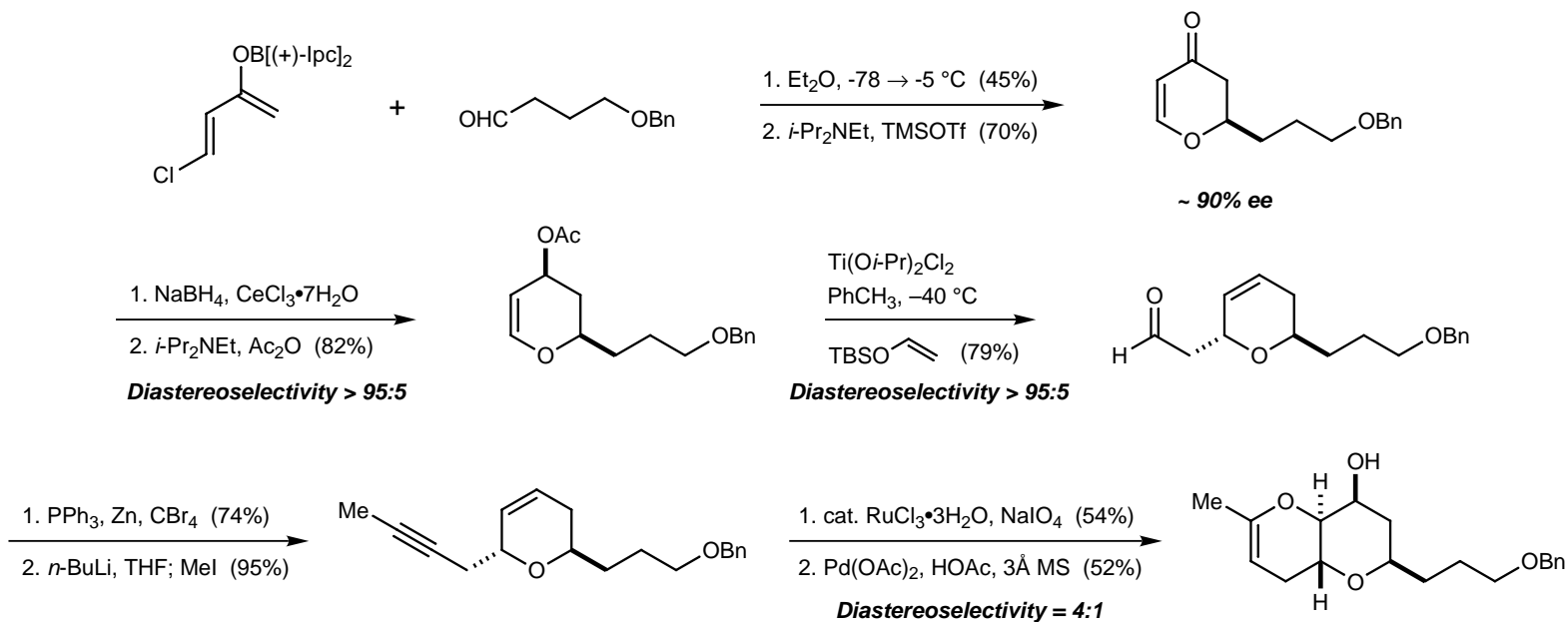
Late Stage Installation:



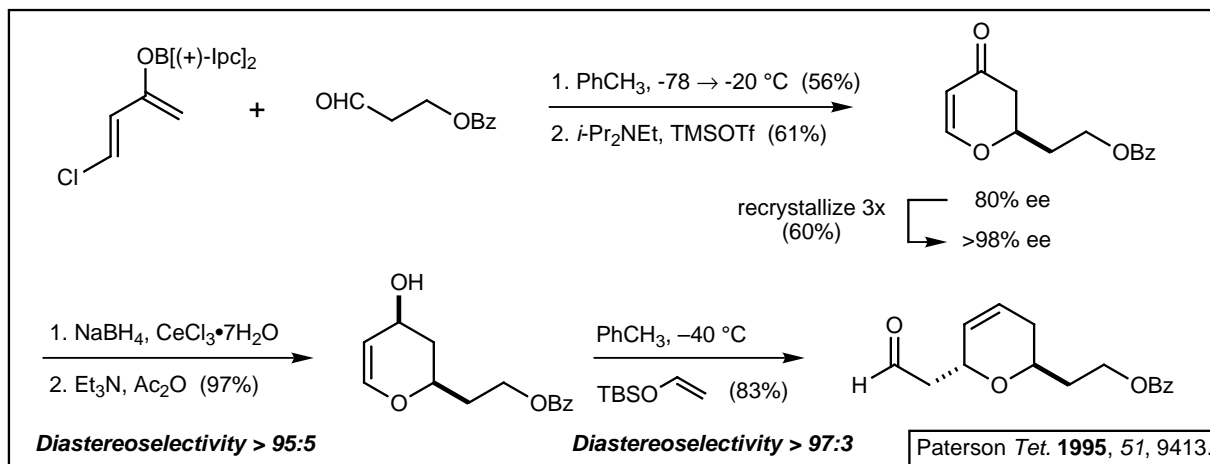
Nakata *Tet. Lett.* **1996**, 37, 6365.

Approaches to the Synthesis of the A Ring of Hemibrevetoxin B

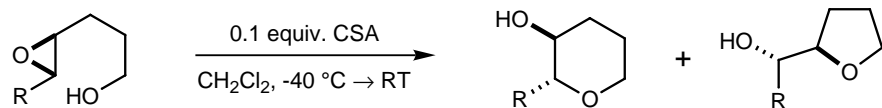
Asymmetric Aldol:



McDonald *J. Org. Chem.* **1997**, *62*, 6432.



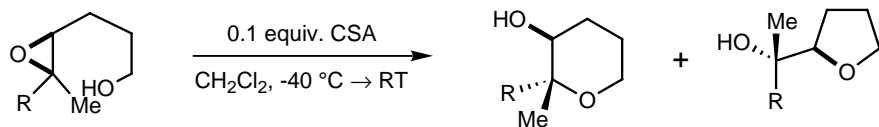
6-Endo Over 5-Exo Hydroxy Epoxide Opening



R	Ratio	Yield
CH ₂ CH ₂ CO ₂ Me	0 : 100	94%
<i>E</i> -CH=CHCO ₂ Me	60 : 40	96%
CH=CH ₂	100 : 0	95%
CH=CBr ₂	100 : 0	90%

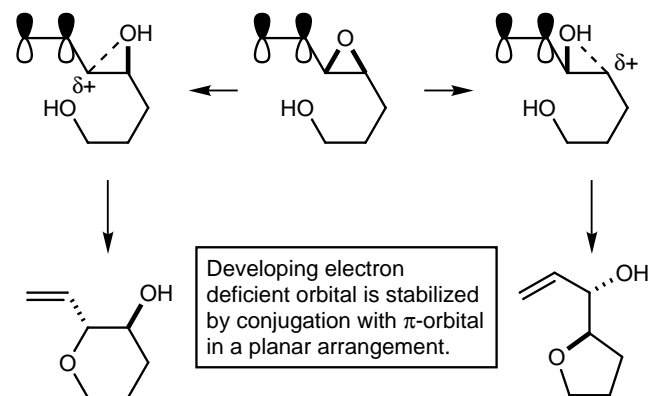


R	Ratio	Yield
<i>E</i> -CH=CHCO ₂ Me	0 : 100	86%
CH=CH ₂	44 : 56	95%
<i>E</i> -CH=CHCl	76 : 24	94%
<i>Z</i> -CH=CHCl	33 : 67	92%
C≡CBr	0 : 100	87%



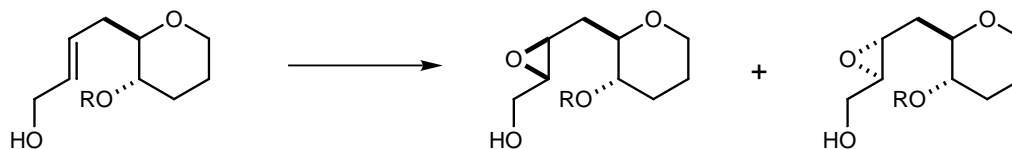
R	Ratio	Yield
<i>E</i> -CH=CHCO ₂ Me	66 : 34	92%
CH=CH ₂	100 : 0	96%

Authors' Explanation:

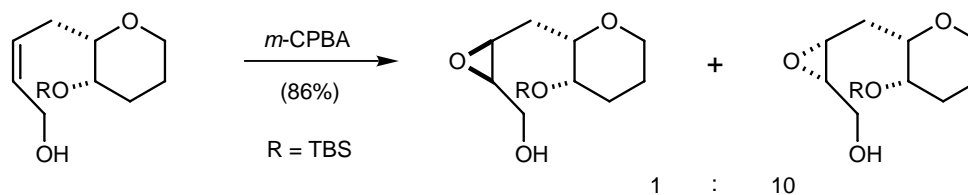
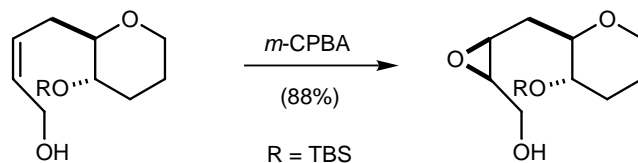


"In the absence of the π -orbital, both acid- or base-induced ring closures were expected to lead to the smaller ring, exo product on the basis of better antiparallel alignment of the incipient and rupturing bonds." (See: Stork *J. Am. Chem. Soc.* **1974**, *96*, 5270. Baldwin *J.C.S. Chem Commun.* **1976**, 734.)

Diastereoselective Epoxidation of Allylic Alcohols

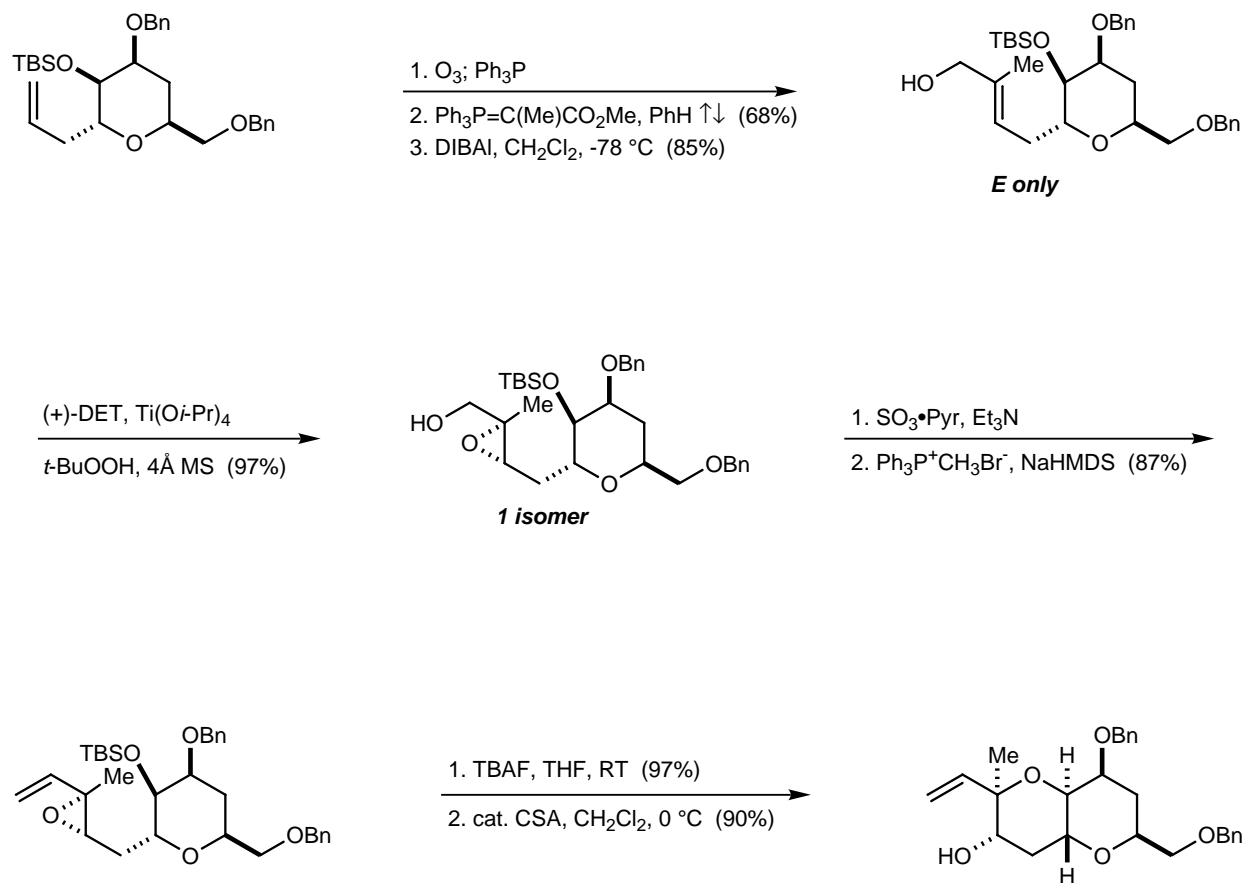


R	Conditions	Ratio	Yield
Si <i>t</i> -BuPh ₂	(+)-DET, Ti(O <i>i</i> -Pr) ₄ , <i>t</i> -BuOOH	4.3 : 1	80%
Si <i>t</i> -BuPh ₂	(-)-DET, Ti(O <i>i</i> -Pr) ₄ , <i>t</i> -BuOOH	1 : 18	87%
Si <i>t</i> -BuPh ₂	<i>m</i> -CPBA	2 : 1	89%
Si <i>t</i> -BuMe ₂	(+)-DET, Ti(O <i>i</i> -Pr) ₄ , <i>t</i> -BuOOH	5.2 : 1	78%
Si <i>t</i> -BuMe ₂	(-)-DET, Ti(O <i>i</i> -Pr) ₄ , <i>t</i> -BuOOH	1 : 19	92%
Si <i>t</i> -BuMe ₂	<i>m</i> -CPBA	1 : 1	85%



Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

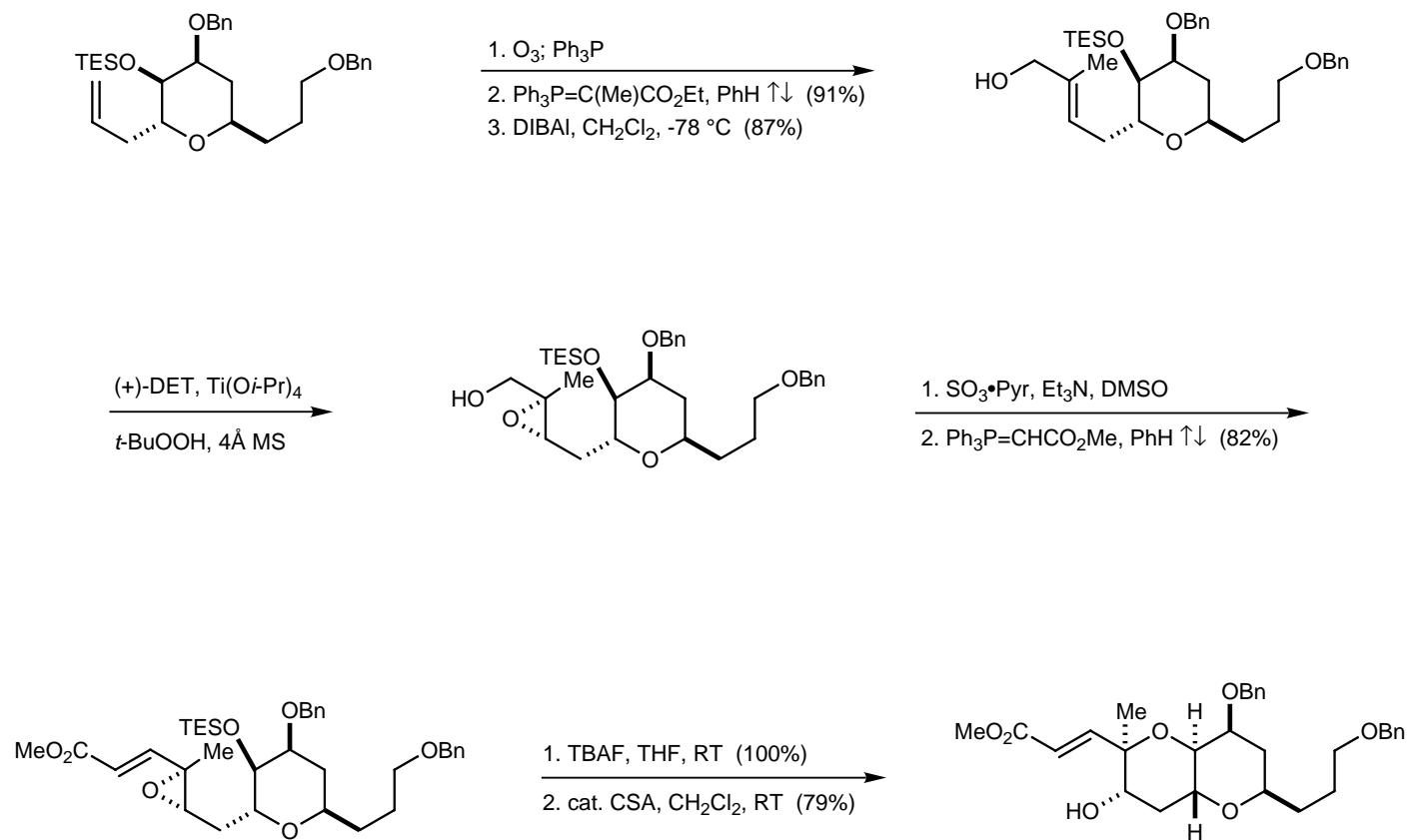
6-Endo Epoxide Cyclization:



Nicolaou *J. Am. Chem. Soc.* **1993**, *115*, 3558.

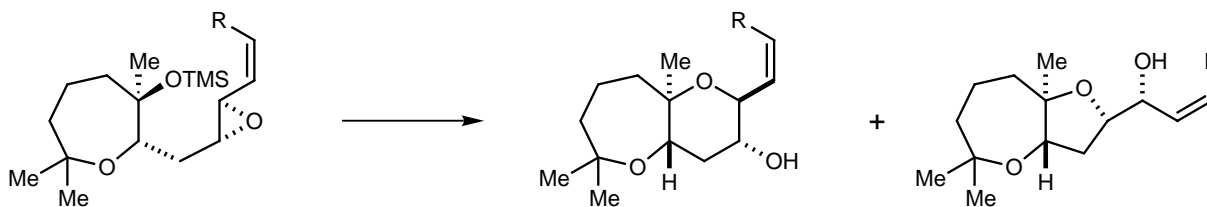
Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

6-Endo Epoxide Cyclization:



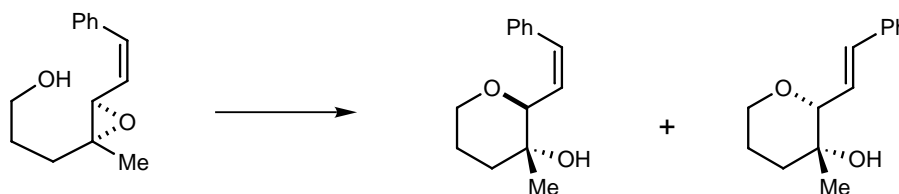
Yamamoto *Tet. Lett.* **1995**, 36, 5777.

Modified 6-Endo Hydroxy Epoxide Opening



R	Reagents	Ratio	Yield
H	TBAF; cat. PPTS	1 : 1	86%
H	10:1 AcOH-H ₂ O	3.8 : 1	78%
Ph (<i>E/Z</i> = 1:8)	TBAF; cat. PPTS	1 : 0	86%

Nakata *Chem. Lett.* **1996**, 487.



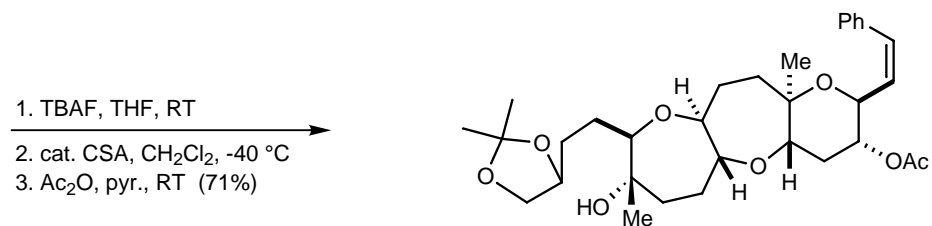
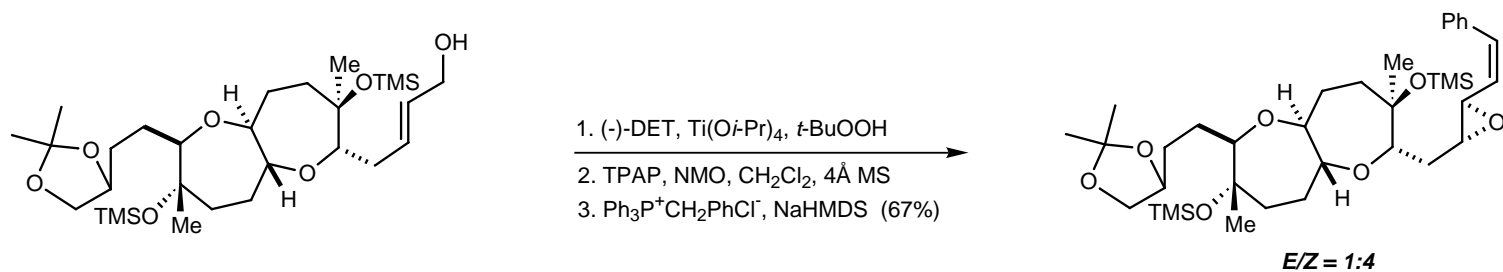
Conditions	Ratio	Yield
cat. PPTS, CH ₂ Cl ₂ , RT, 15 min	65 (<i>Z/E</i> = 7:1) : 35 (<i>Z/E</i> = 1:2.5)	97%
cat. PPTS, CH ₂ Cl ₂ , -20 °C, 21 h	79 (<i>Z/E</i> = 15:1) : 21 (<i>Z/E</i> = 1:2)	97%
cat. CSA, CH ₂ Cl ₂ , RT, 10 min	58 (<i>Z/E</i> = 5:1) : 42 (<i>Z/E</i> = 1:3)	81%
cat. CSA, CH ₂ Cl ₂ , -78 °C, 1 h	90 (<i>Z/E</i> = 22:1) : 10 (<i>Z/E</i> = 1:2)	100%
10:1 AcOH-H ₂ O	47 (<i>Z/E</i> = 8:1) : 53 (<i>Z/E</i> = 1:10)	83%
10 equiv. NaH, DMSO, RT, 2.5 h	100 (<i>Z</i> only) : 0	97%

Note: No 5-Exo products were observed.

Nakata *Tet. Lett.* **1997**, 38, 5545.

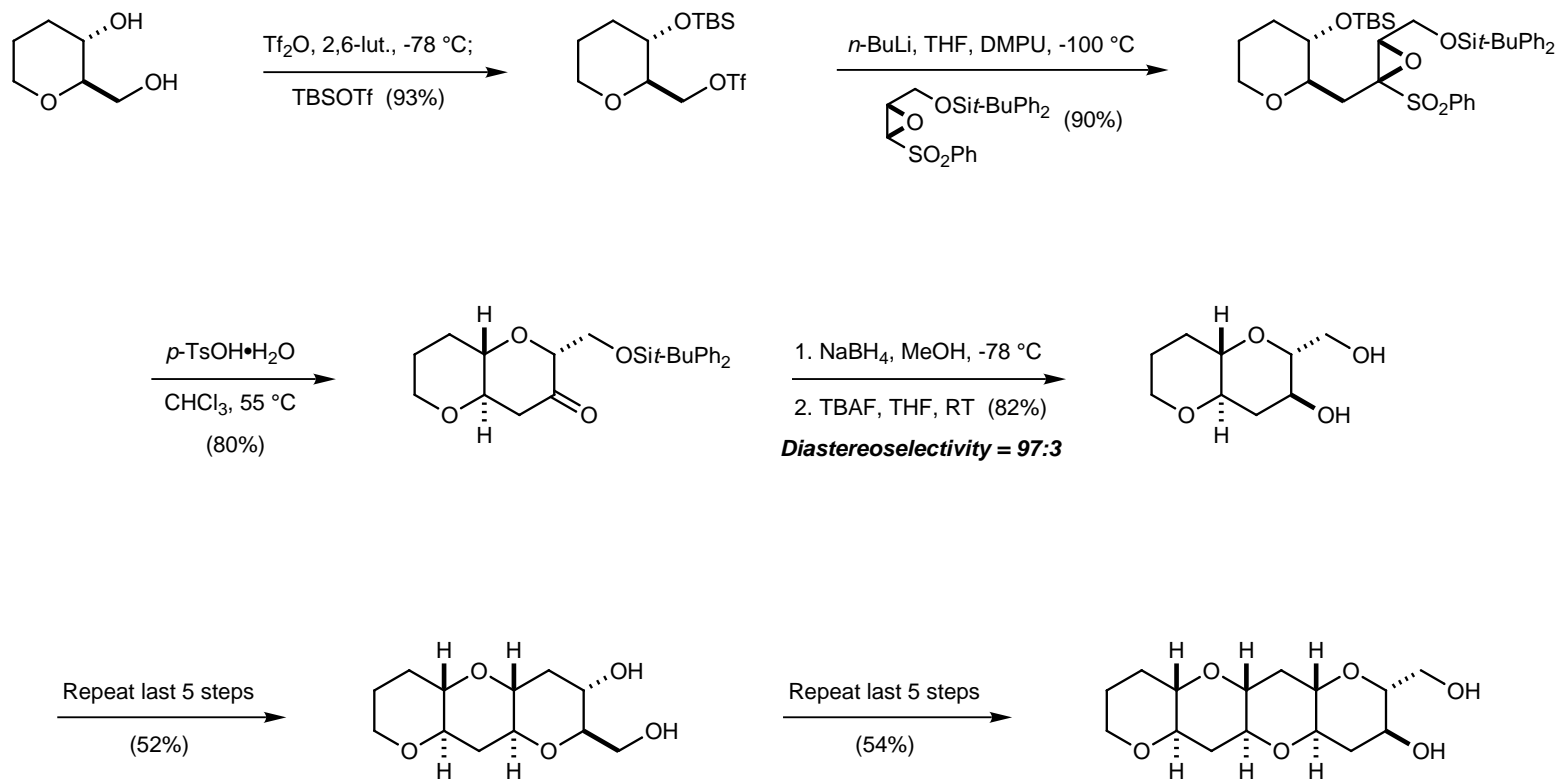
Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

Late Stage 6-*Endo* Epoxide Cyclization:



Nakata *Tet. Lett.* **1996**, 37, 6365.

Reiterative Oxiranyl Anion Alkylation

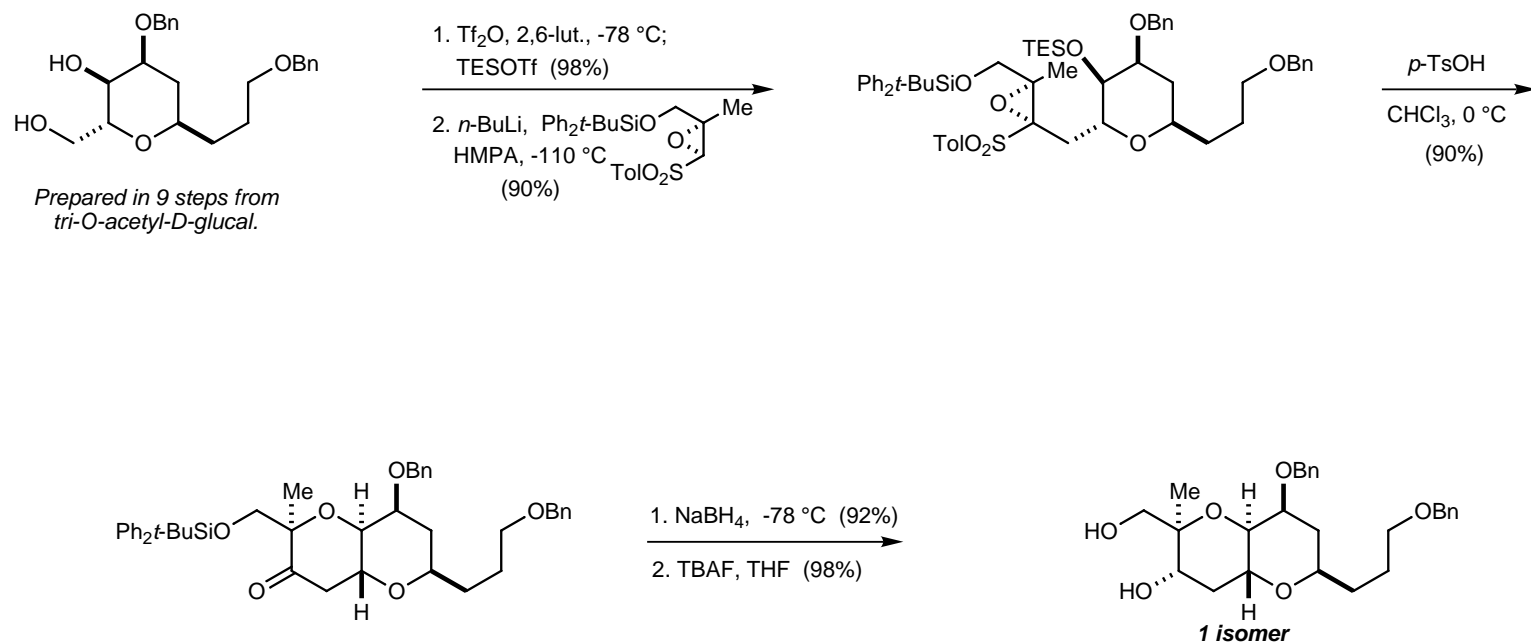


"The synthesis of such a ring system by Baldwin's rule-disfavored 6-*endo* mode of cyclization is receiving attention since such cyclization is considered to be a key step in the biosynthesis of polycyclic ethers."

Mori *J. Am. Chem. Soc.* **1996**, *118*, 8158.

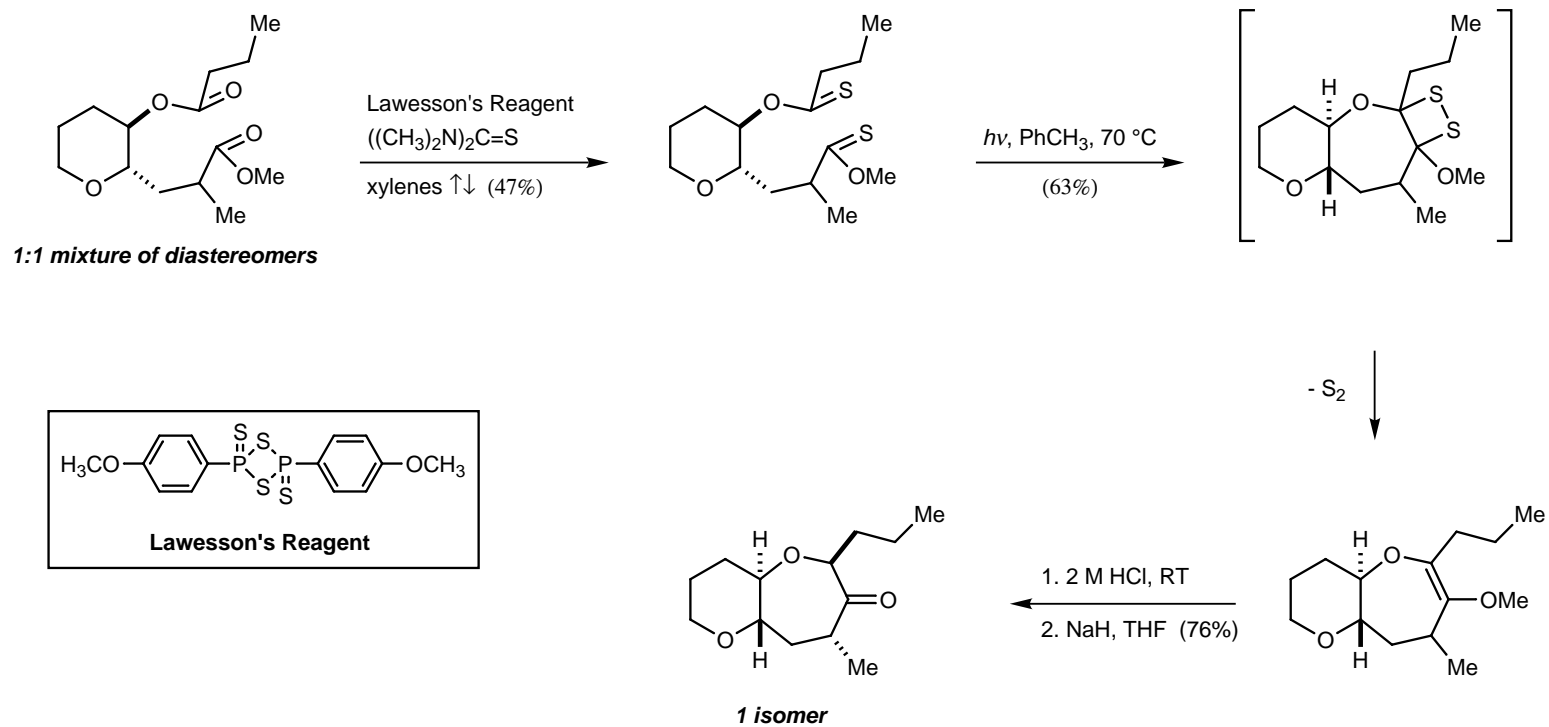
Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

Oxiranyl Anion Alkylation Followed
by 6-Endo Epoxide Cyclization:



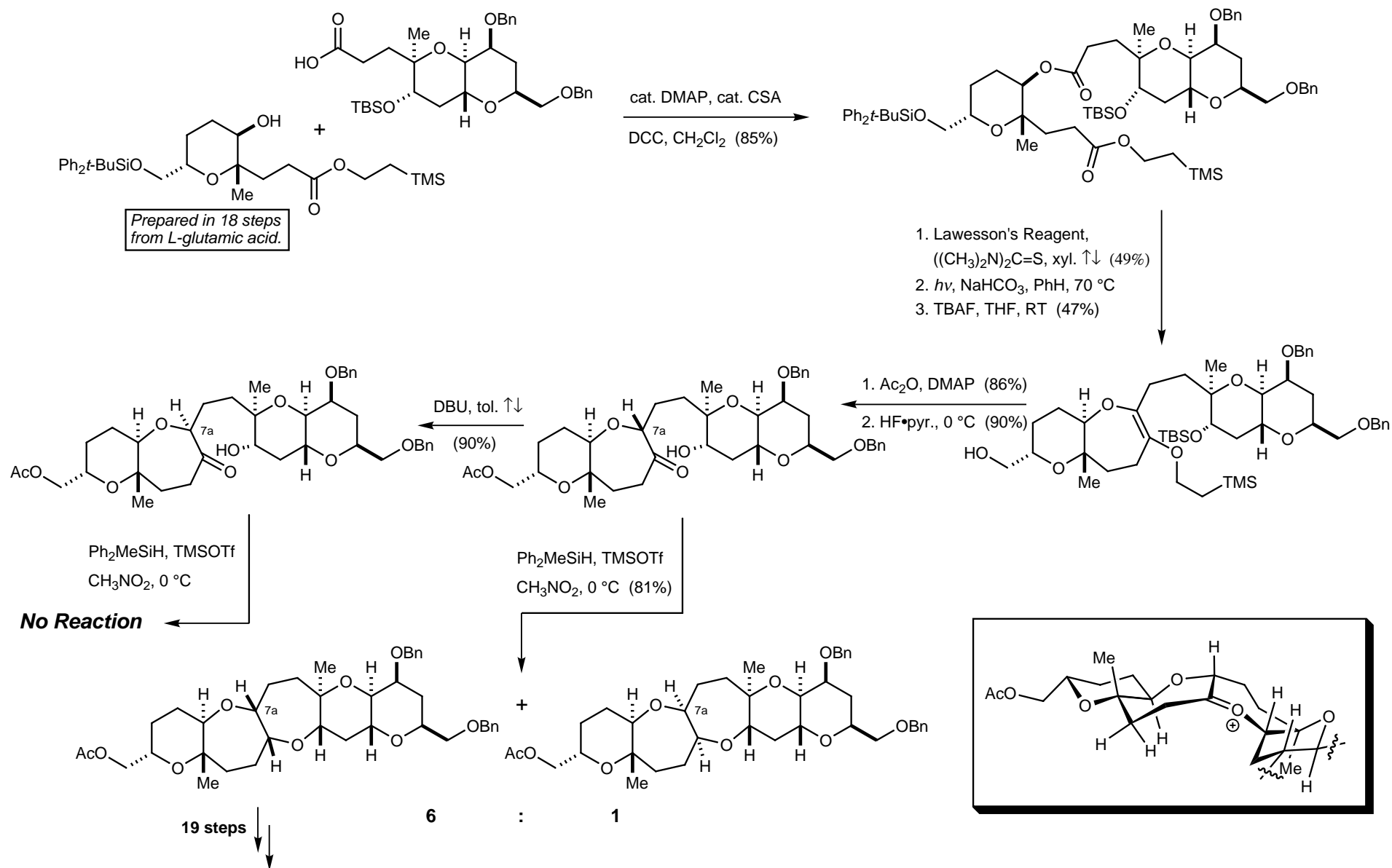
Mori *J. Am. Chem. Soc.* **1997**, *119*, 4557.

Photo-induced Cyclization of Dithionoesters



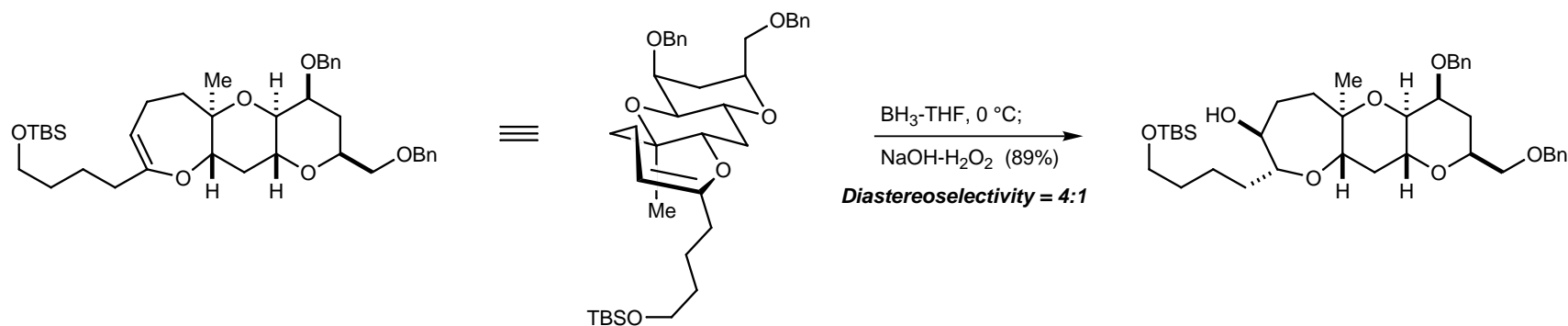
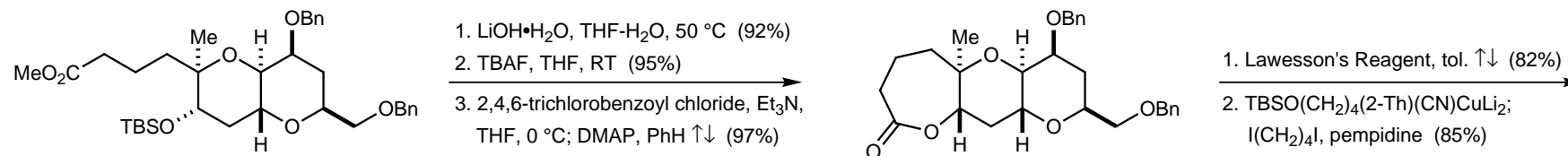
Nicolaou *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1362.

Failed Convergent Route to Hemibrevetoxin B

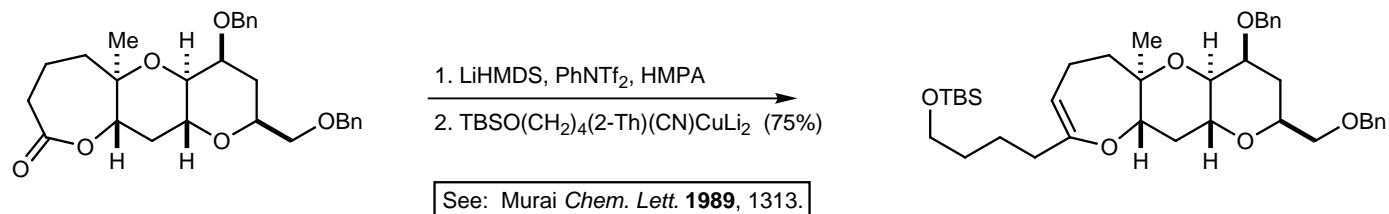


Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

Thionolactone Alkylation:

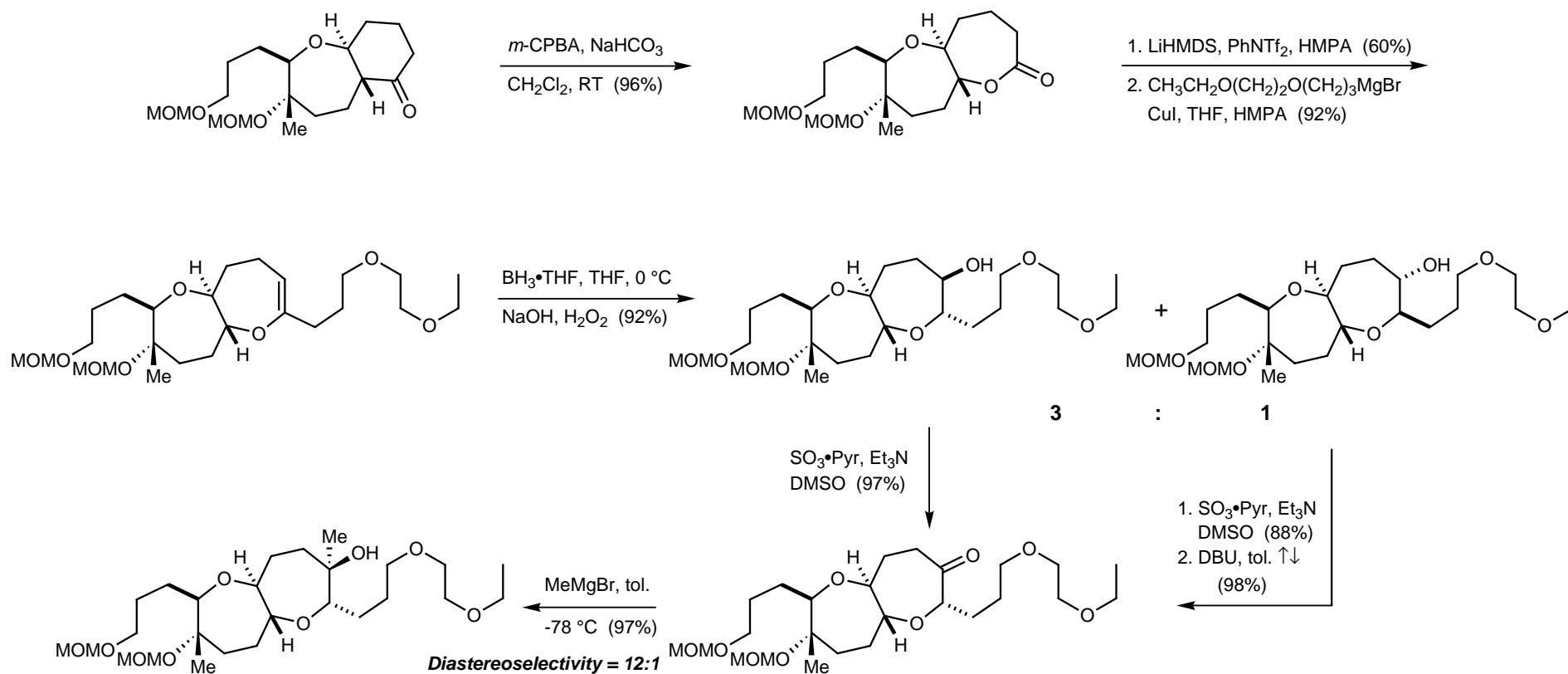


Cross-Coupling of Enol Triflate:



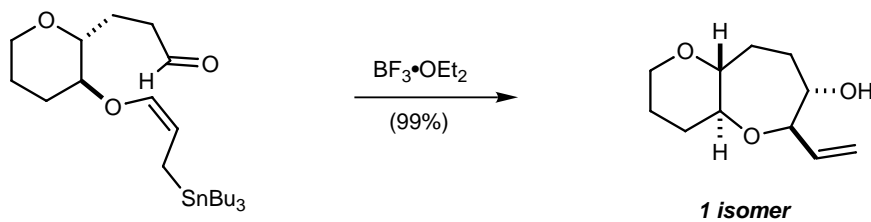
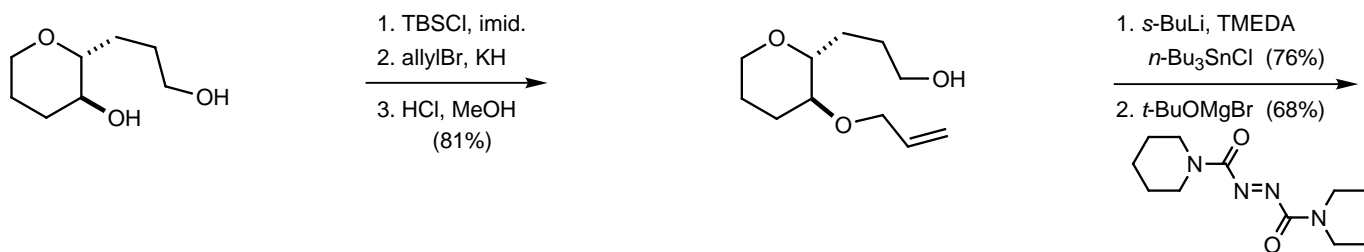
Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

Cross-Coupling of Enol Triflate:



Murai *Synlett* 1995, 863.

Cyclization of ω -Tributylstannyl Ether Aldehydes

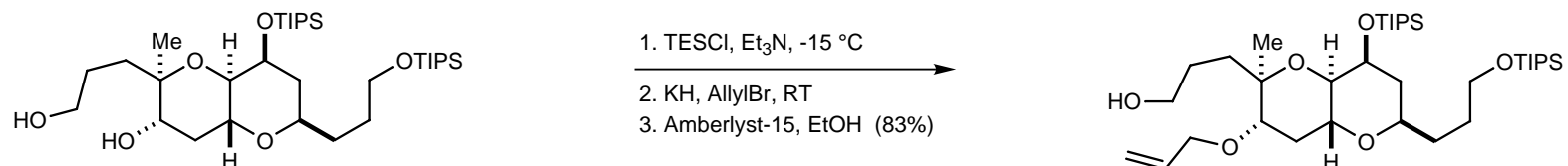


Note: Cyclizations of this sort were found to be highly stereoselective in the case of 7-membered rings, but showed fairly poor selectivities for 6-membered rings.

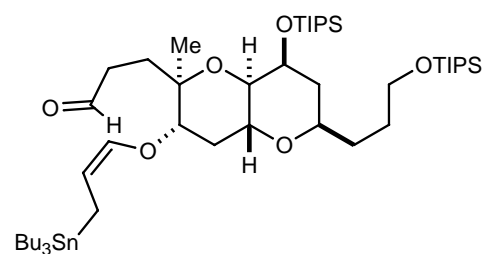
Yamamoto *Tet. Lett.* **1991**, 32, 7069.

Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

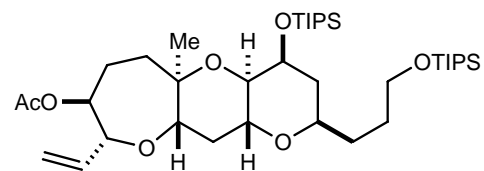
Allyl Tin Cyclization:



1. *s*-BuLi, TMEDA; Bu₃SnCl (69%)
2. SO₃•Pyr, Et₃N, DMSO (90%)



1. BF₃•OEt₂, CH₂Cl₂, -78 °C (94%)
2. Ac₂O, pyr., DMAP, RT (100%)

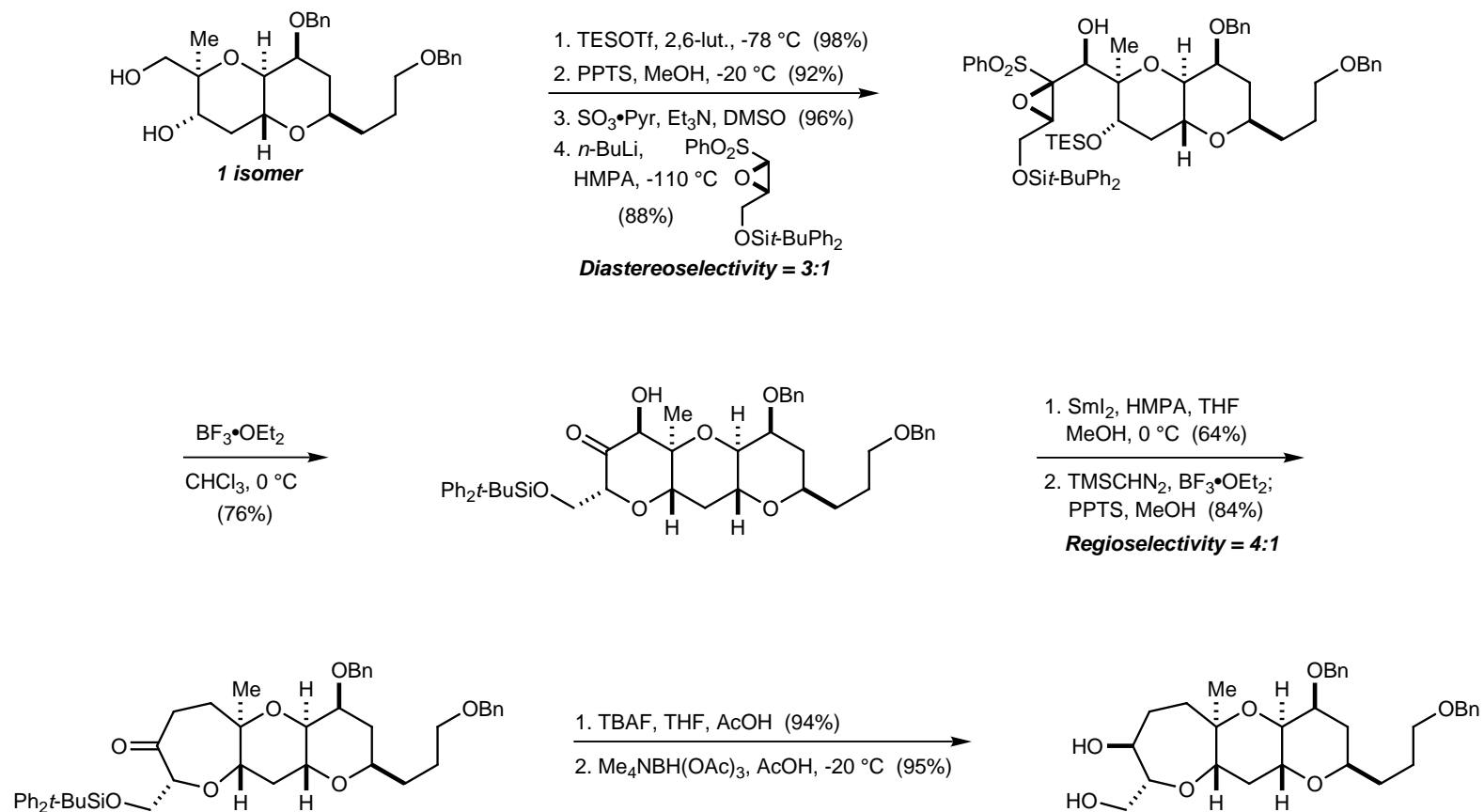


1 isomer

Yamamoto *Tet. Lett.* **1995**, 36, 5777.

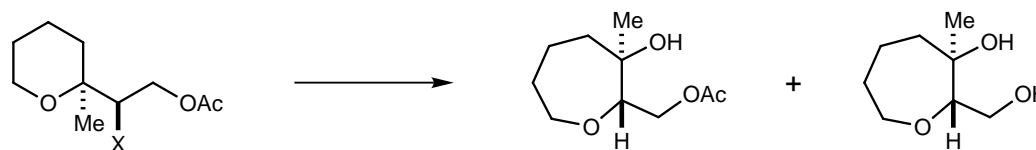
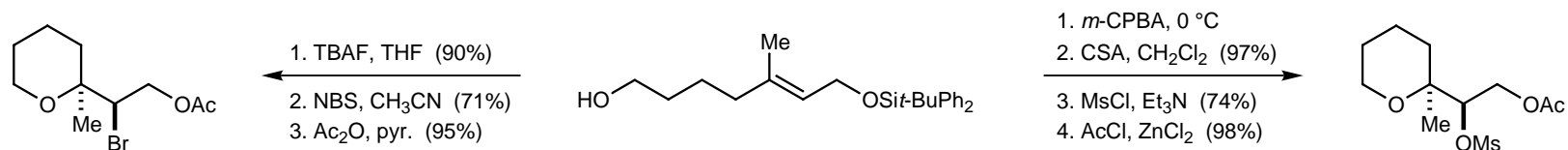
Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

Oxiranyl Anion Alkylation
Followed by Ring Expansion:



Mori *J. Am. Chem. Soc.* **1997**, *119*, 4557.

Ring Expansion of Tetrahydropyrans



Note: In all cases a single stereoisomer was obtained.

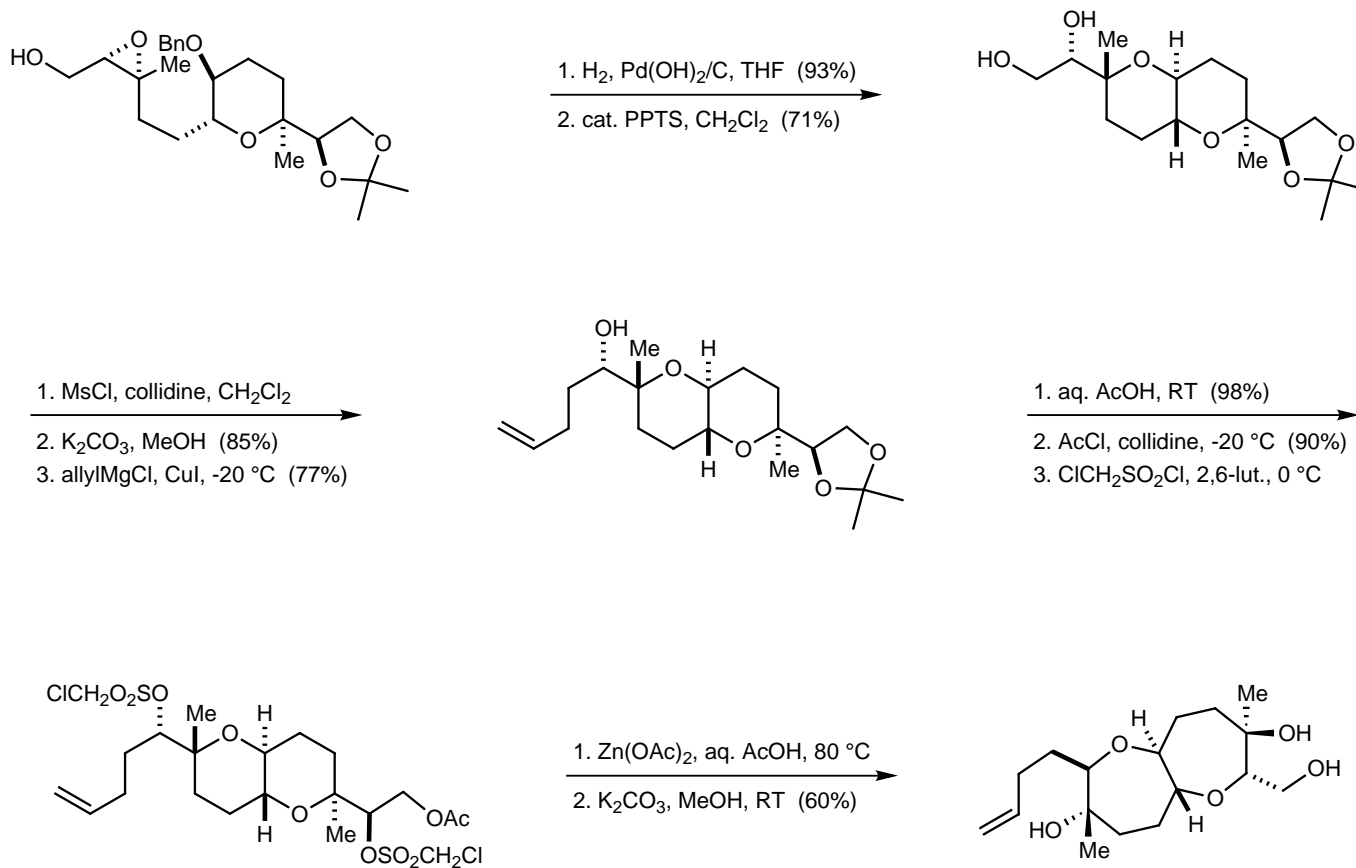
X	Reagent	% Yield	
OMs	Ag ₂ CO ₃	17	0
OMs	AgOAc	47	37
OMs	Zn(OAc) ₂	53	42

Br	Ag ₂ CO ₃	0	0
Br	AgOTf	31	7
Br	AgOAc	49	6
Br	Zn(OAc) ₂	16	15

Nakata *Tet. Lett.* **1996**, 37, 213.

Approaches to the Synthesis of the C & D Rings of Hemibrevetoxin B

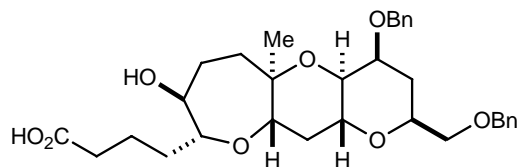
Double Ring Expansion:



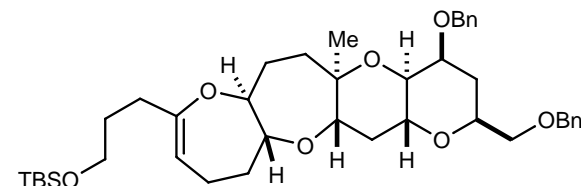
Nakata *Tet. Lett.* **1996**, 37, 6365.

Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

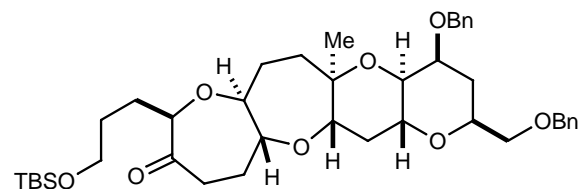
Cross-Coupling of Enol Triflate Followed by Hydroboration:



1. 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 0 °C; DMAP, PhH ↑↓ (80%)
2. LiHMDS, PhNTf₂, HMPA
3. TBSO(CH₂)₃(2-Th)(CN)CuLi₂ (75%)



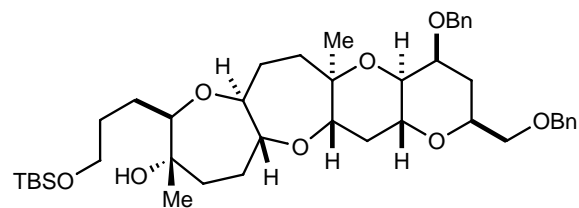
1. BH₃-THF, 0 °C;
NaOH-H₂O₂ (94%)
2. Swern (90%)
3. cat. DBU, tol. ↑↓ (92%)



1 isomer

- MeMgI, Et₂O (94%)

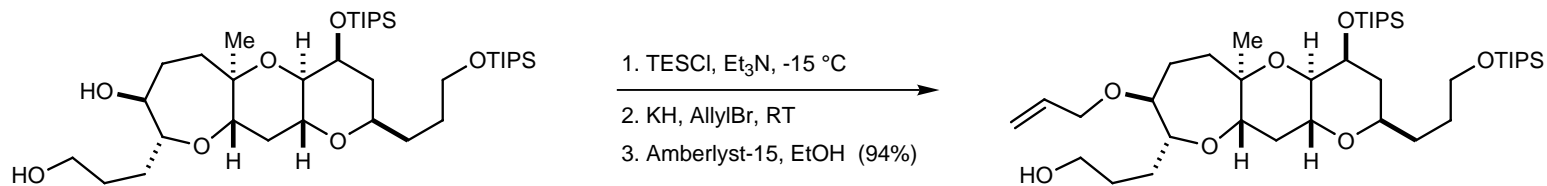
Diastereoselectivity = 3:2



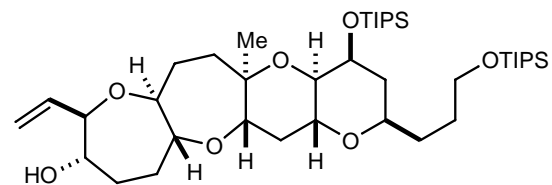
Nicolaou *J. Am. Chem. Soc.* **1993**, *115*, 3558.

Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

Allyl Tin Cyclization:

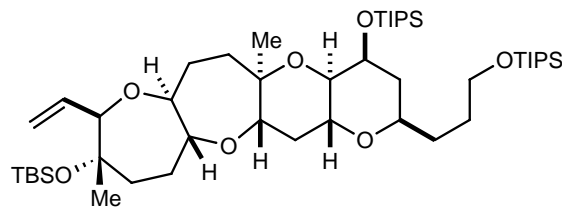


1. *s*-BuLi, TMEDA; Bu₃SnCl (18%)
2. SO₃•Pyr, Et₃N, DMSO (79%)
3. BF₃•OEt₂, CH₂Cl₂, -78 °C (98%)



1 isomer

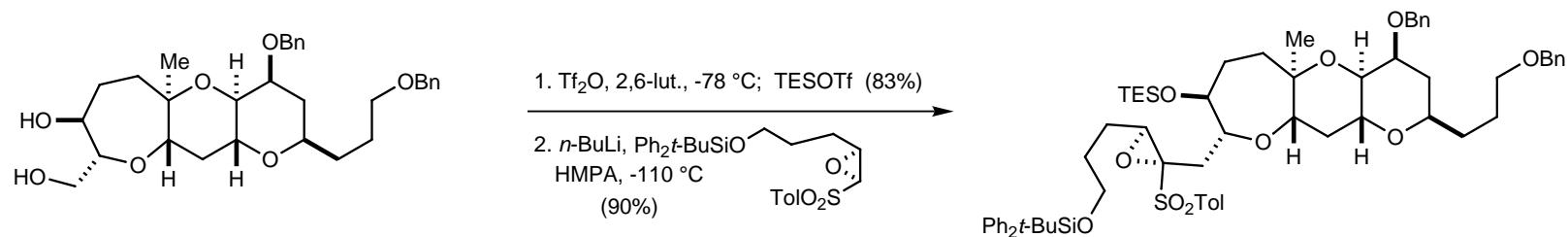
1. Swern
2. MeMgBr, Et₂O
3. TBSOTf, 2,6-lut. (89%)



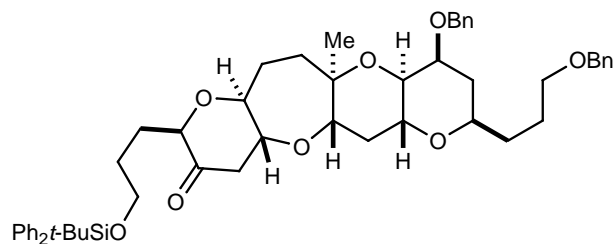
1:1 mixture of diastereomers

Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

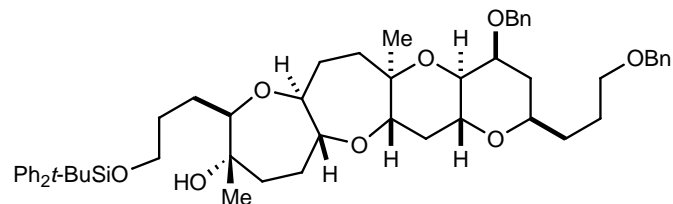
Oxiranyl Anion Alkylation
Followed by Ring Expansion:



1. $p\text{-TsOH}$, CHCl_3 , $0\text{ }^\circ\text{C}$ (90%)
2. $\text{BF}_3\cdot\text{OEt}_2$, CHCl_3 (74%)



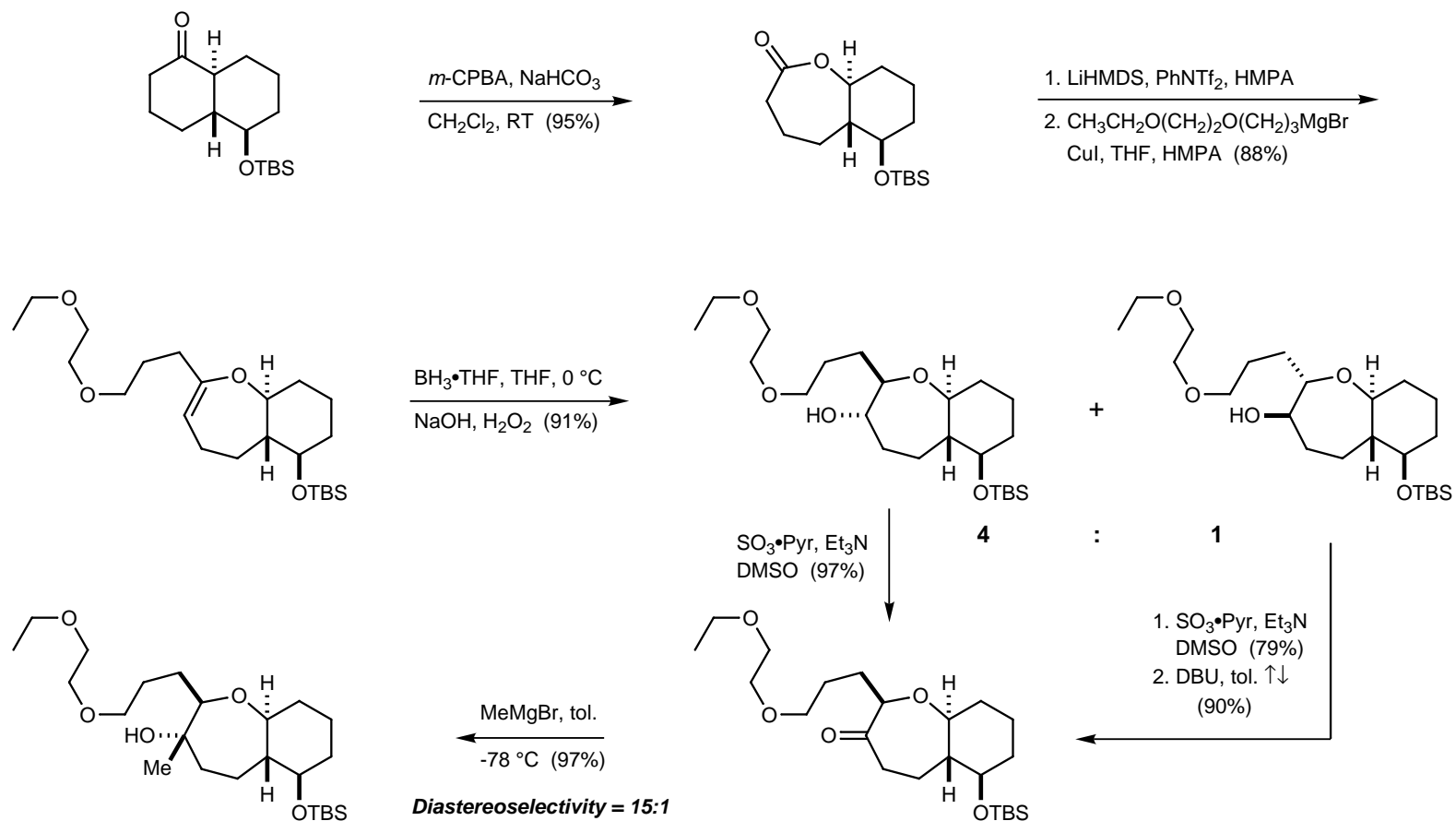
1. TMSCHN_2 , $\text{BF}_3\cdot\text{OEt}_2$;
PPTS, MeOH (62%)
2. MeMgBr , tol., $-78\text{ }^\circ\text{C}$ (96%)
Diastereoselectivity = 4:1



Mori *J. Am. Chem. Soc.* **1997**, 119, 4557.

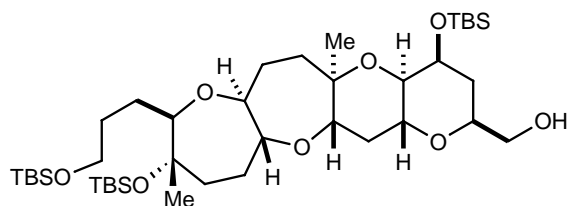
Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

Cross-Coupling of Enol Triflate
Followed by Hydroboration:

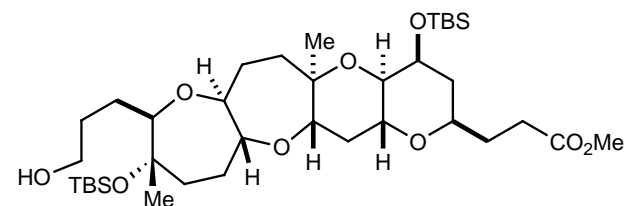


Murai *Synlett* 1995, 863.

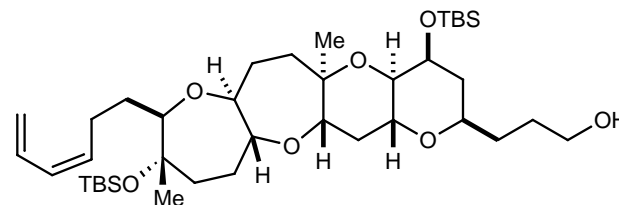
Completion of the Synthesis of Hemibrevetoxin B



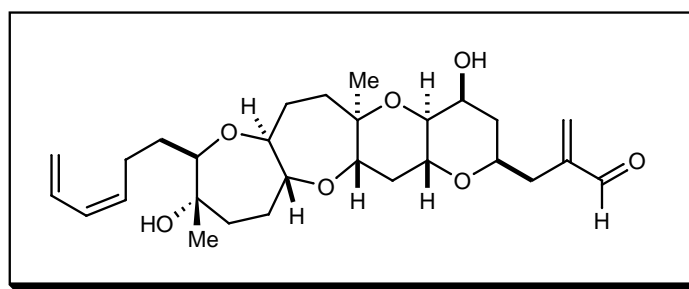
1. Swern
2. $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, PhH (80%)
3. H_2 , 5% Pd/C, EtOAc (95%)
4. cat. CSA, MeOH, 0 °C (86%)



1. Swern (90%)
2. $\text{PhSe}(\text{CH}_2)_3\text{Ph}_3\text{P}^+\text{I}^-$, *n*-BuLi (72%)
3. H_2O_2 , NaHCO₃, THF (78%)
4. DIBAL, CH₂Cl₂, -78 °C (95%)

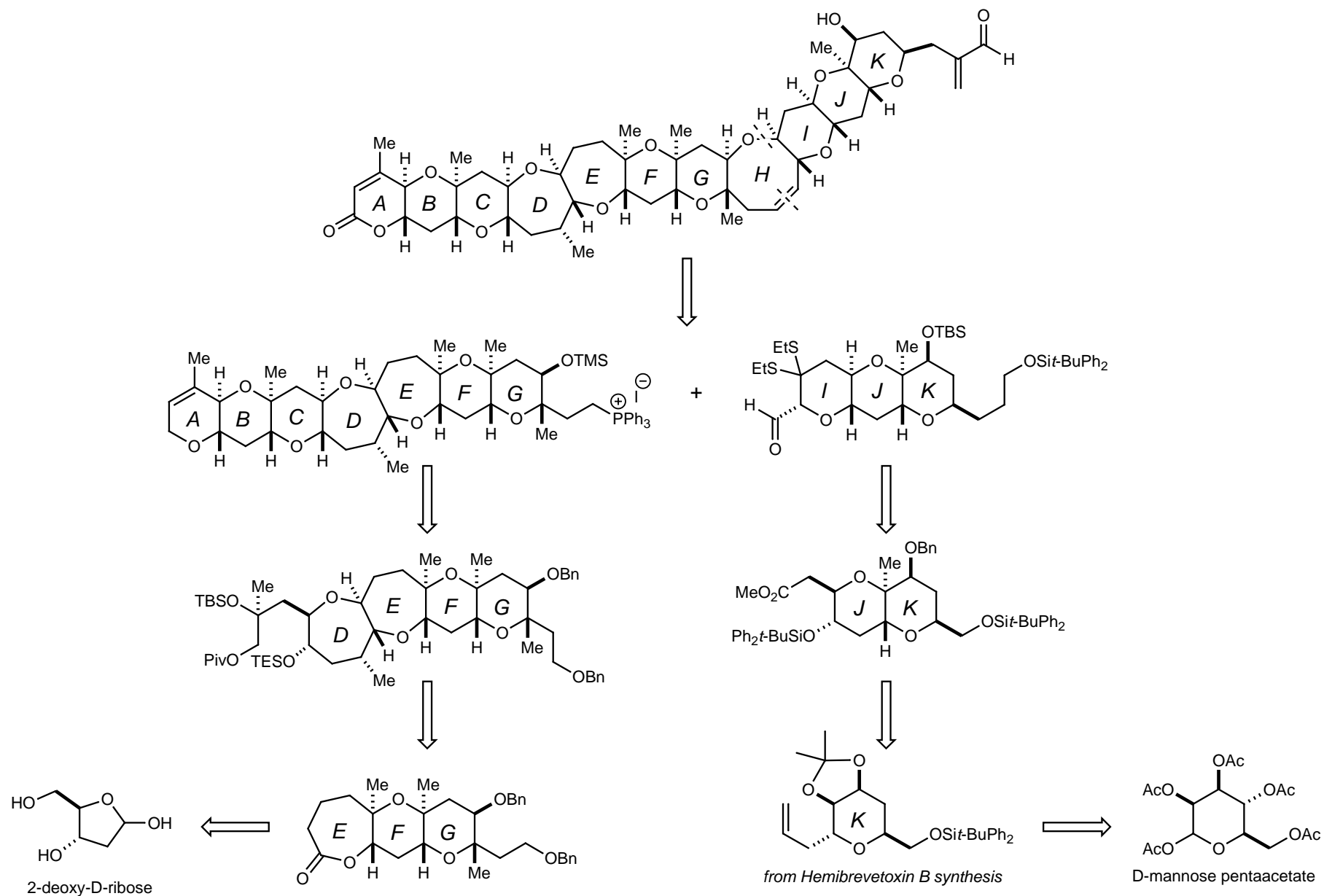


1. Swern
2. $\text{Me}_2(\text{CH}_2)\text{N}^+\text{I}^-$ (90%)
3. SiF_4 , CH₃CN-CH₂Cl₂ (82%)

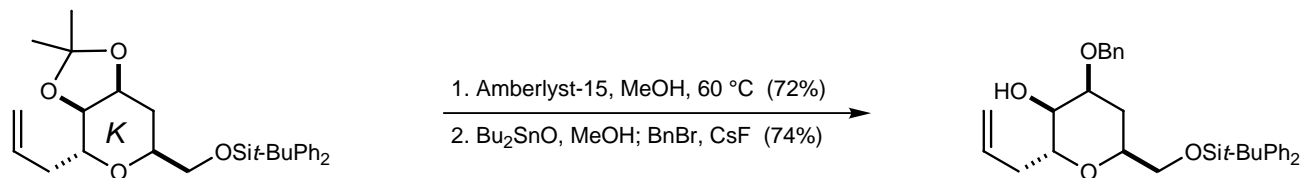


Hemibrevetoxin B

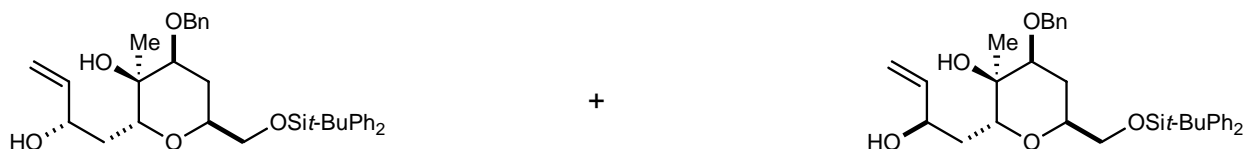
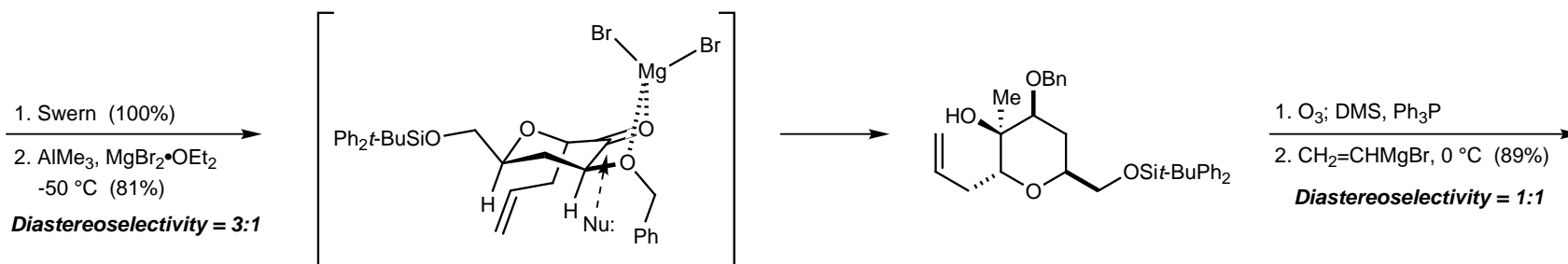
Retrosynthetic Analysis of Brevetoxin B



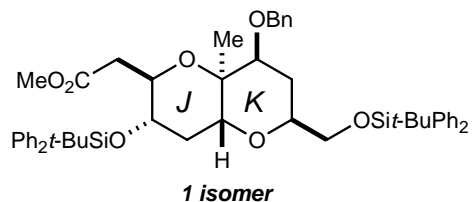
Construction of the J Ring of Brevetoxin B



from Hemibrevetoxin B synthesis



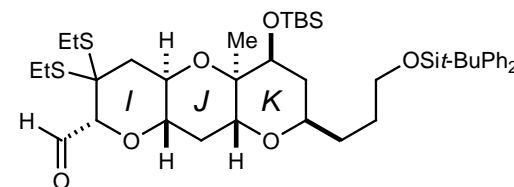
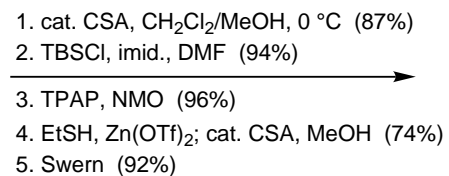
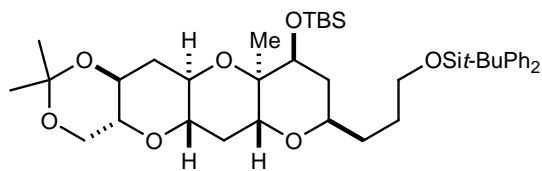
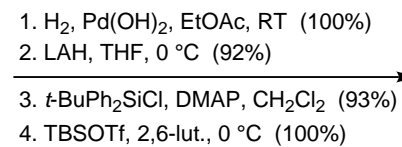
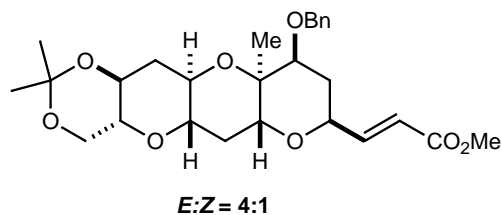
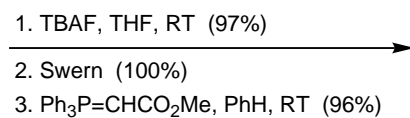
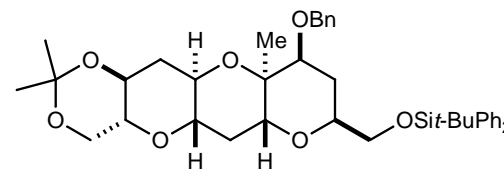
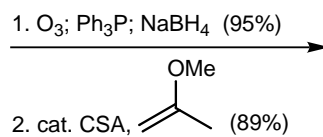
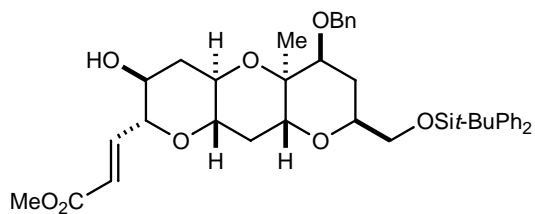
1. *t*-BuPh₂SiCl, imid., DMF (88%)
2. O₃; DMS, Ph₃P
3. Ph₃P=CHCO₂Me, PhH, RT (89%)
4. NaH, THF, RT (92%)



1. TMS-imid., CH₂Cl₂, 0 °C (85%)
2. O₃; DMS, Ph₃P
3. Ph₃P=CHCO₂Me, PhH, RT (85%)
4. NaH, THF, RT (72%)
5. Jones oxidation (69%)
6. NaBH₄, MeOH, 0 °C (85%)
7. *t*-BuPh₂SiCl, imid., DMF (89%)

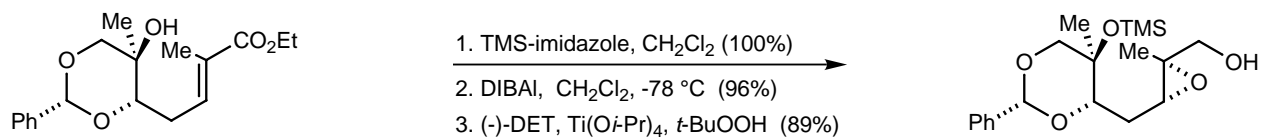
Nicolaou *J. Am. Chem. Soc.* **1989**, *111*, 6682.

Refunctionalization of the IJK Fragment of Brevetoxin B

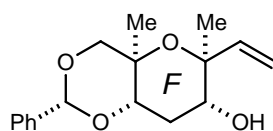


Nicolaou *J. Am. Chem. Soc.* **1989**, *111*, 6682.

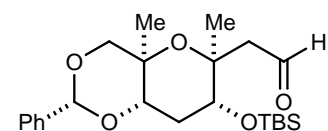
Construction of the F & G Rings of Brevetoxin B



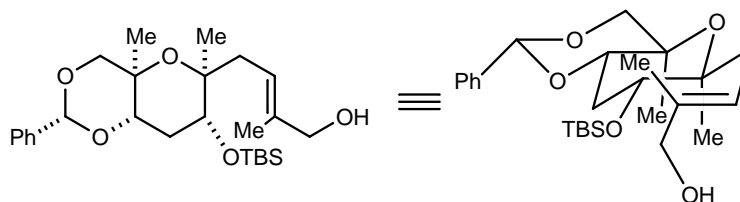
1. $\text{SO}_3 \cdot \text{Pyr}$, Et_3N (93%)
2. $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$, NaHMDS (88%)
3. TBAF, THF, RT (95%)
4. cat. PPTS, CH_2Cl_2 (94%)



1. TBSCl, imid., DMF (95%)
2. 9-BBN; NaOH, H_2O_2 (93%)
3. Swern (95%)

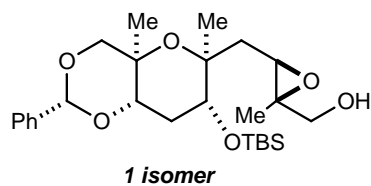


1. $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$, cat. PhCO_2H , PhH, 50°C (90%)
2. DIBAL, CH_2Cl_2 , -78°C (97%)

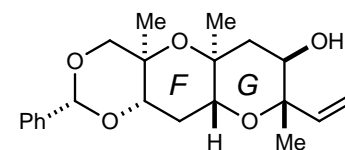


- $m\text{-CPBA}$, CH_2Cl_2 , 0°C (97%)

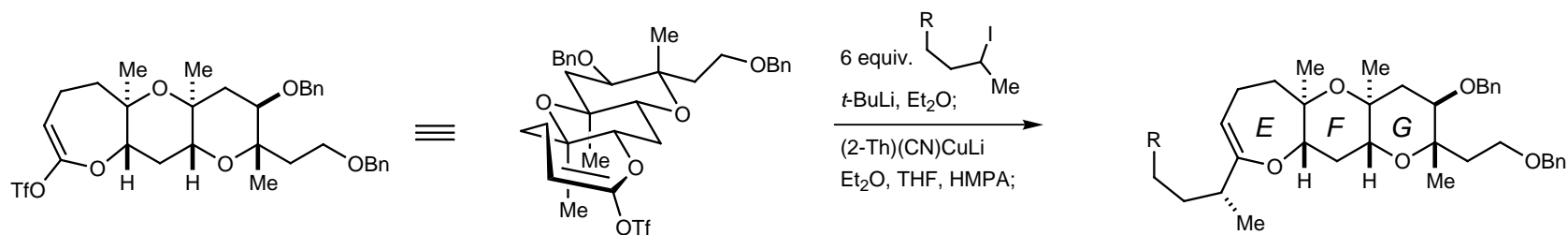
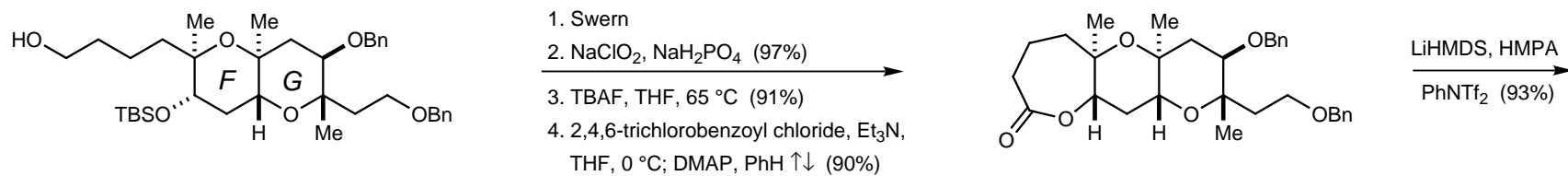
Note: Sharpless epoxidation afforded an unfavorable mixture of diastereomeric epoxides.



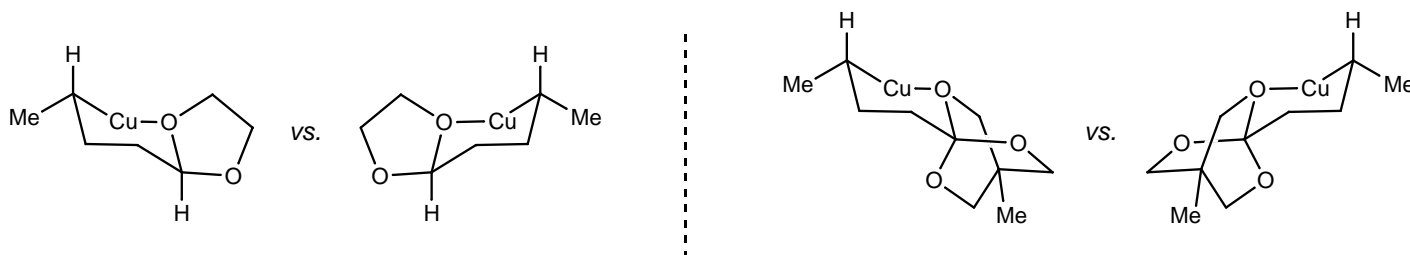
1. $\text{SO}_3 \cdot \text{Pyr}$, Et_3N (92%)
2. $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$, NaHMDS (88%)
3. TBAF, THF, RT (93%)
4. cat. PPTS, CH_2Cl_2 (92%)



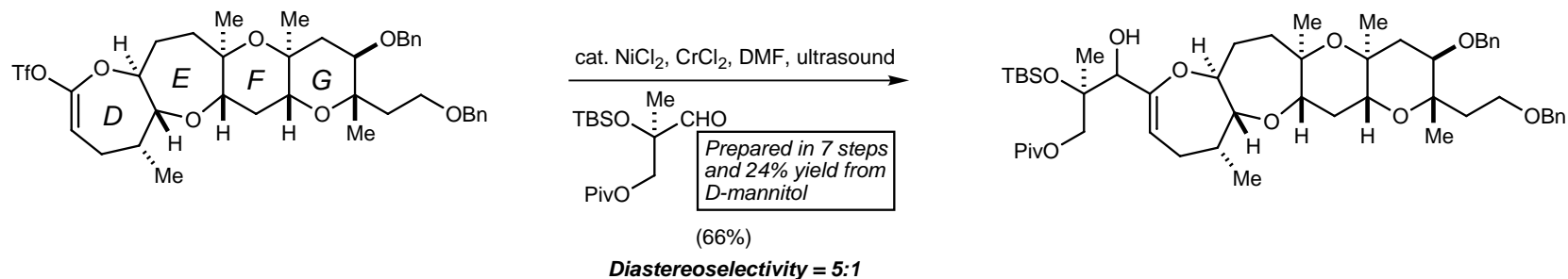
Construction of the EFG Fragment of Brevetoxin B



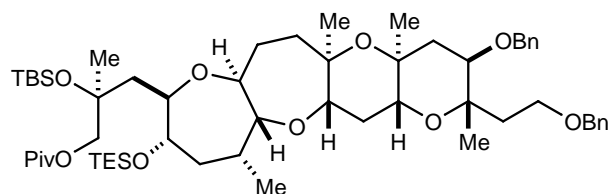
R	Ratio (Desired : Undesired)	Yield
CH_2OTBS	1 : 1.4	50%
	1 : 1.5	49%
	2.4 : 1	85%



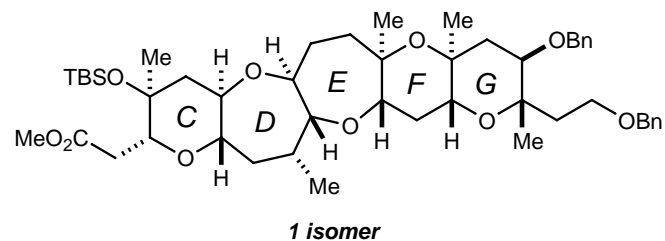
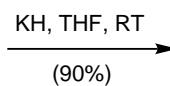
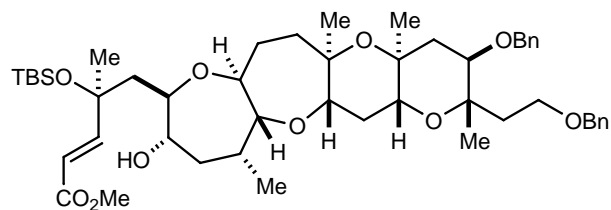
Construction of the C-G Fragment of Brevetoxin B



1. KH, CS_2 ; MeI (89%)
2. cat. AIBN, $n\text{-Bu}_3\text{SnH}$ (67%)
3. $\text{BH}_3 \cdot \text{THF}$; NaOH, H_2O_2 (82%)
4. TESOTf, 2,6-lut., -70°C (96%)

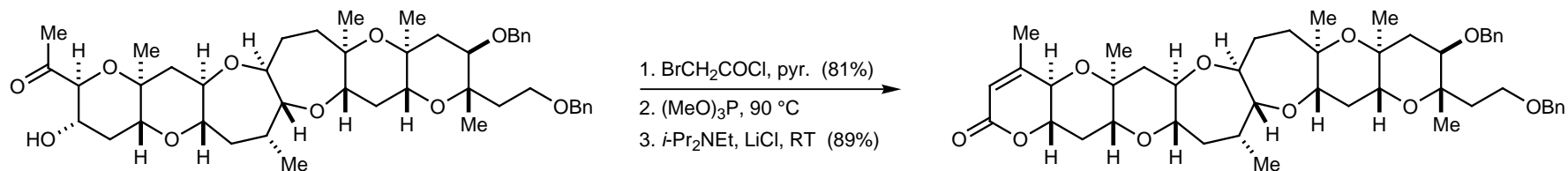


1. DIBAL, CH_2Cl_2 , -78°C (98%)
2. Dess-Martin periodinane (85%)
3. $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, KHMDS (99%)
4. cat. CSA, MeOH, RT (100%)

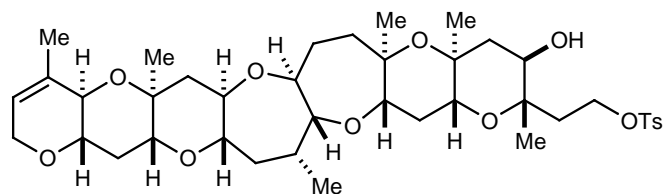


Nicolaou *J. Am. Chem. Soc.* **1995**, *117*, 10239.

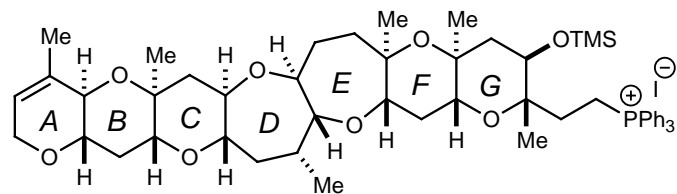
Construction of the A-G Fragment of Brevetoxin B



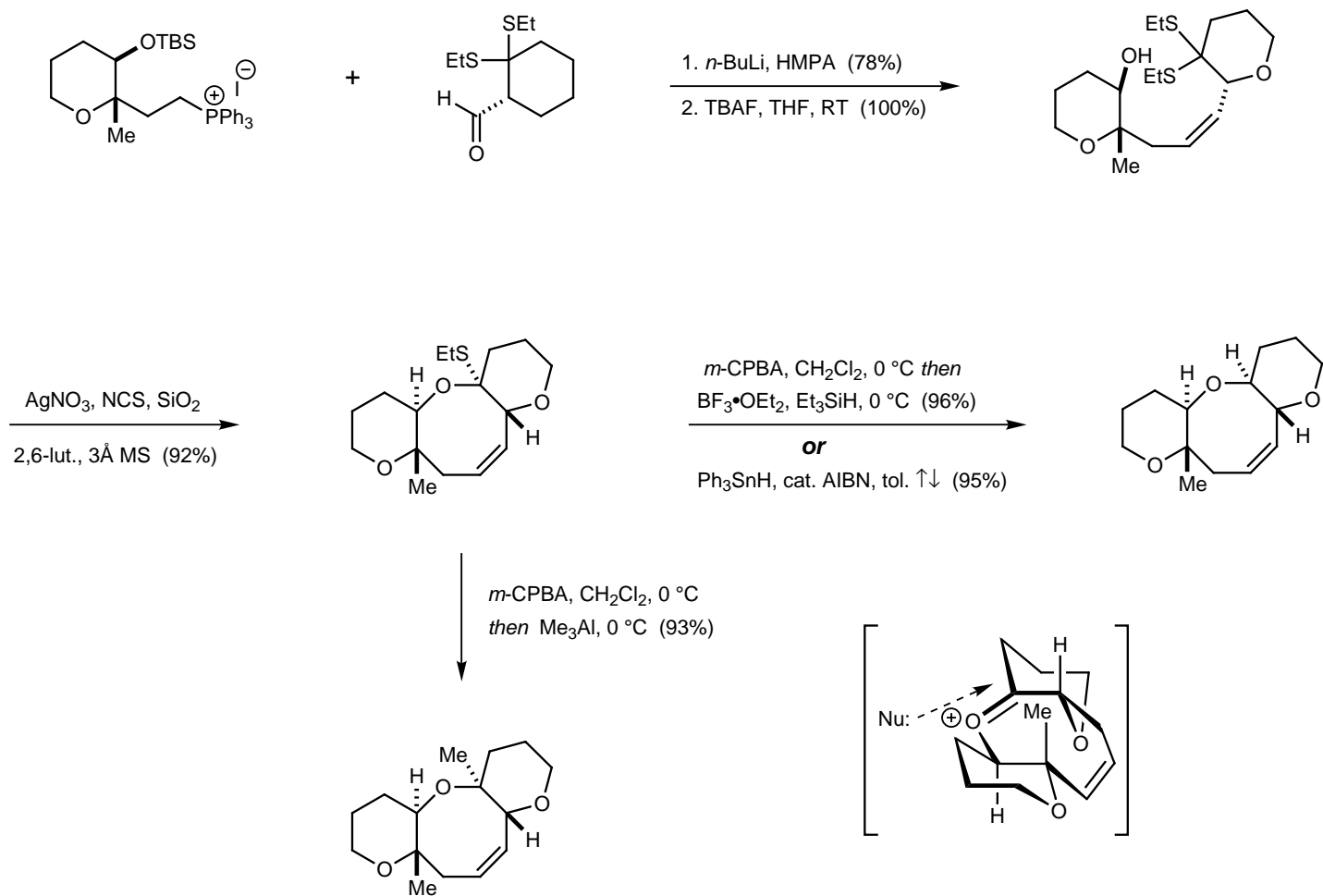
1. DIBAL, CH_2Cl_2 , -78 °C
 2. $\text{BF}_3 \cdot \text{OEt}_2$, Et_3SiH , -10 °C (93%)
 3. Li, liq. NH_3 (92%)
 4. TsCl, pyr. (79%)



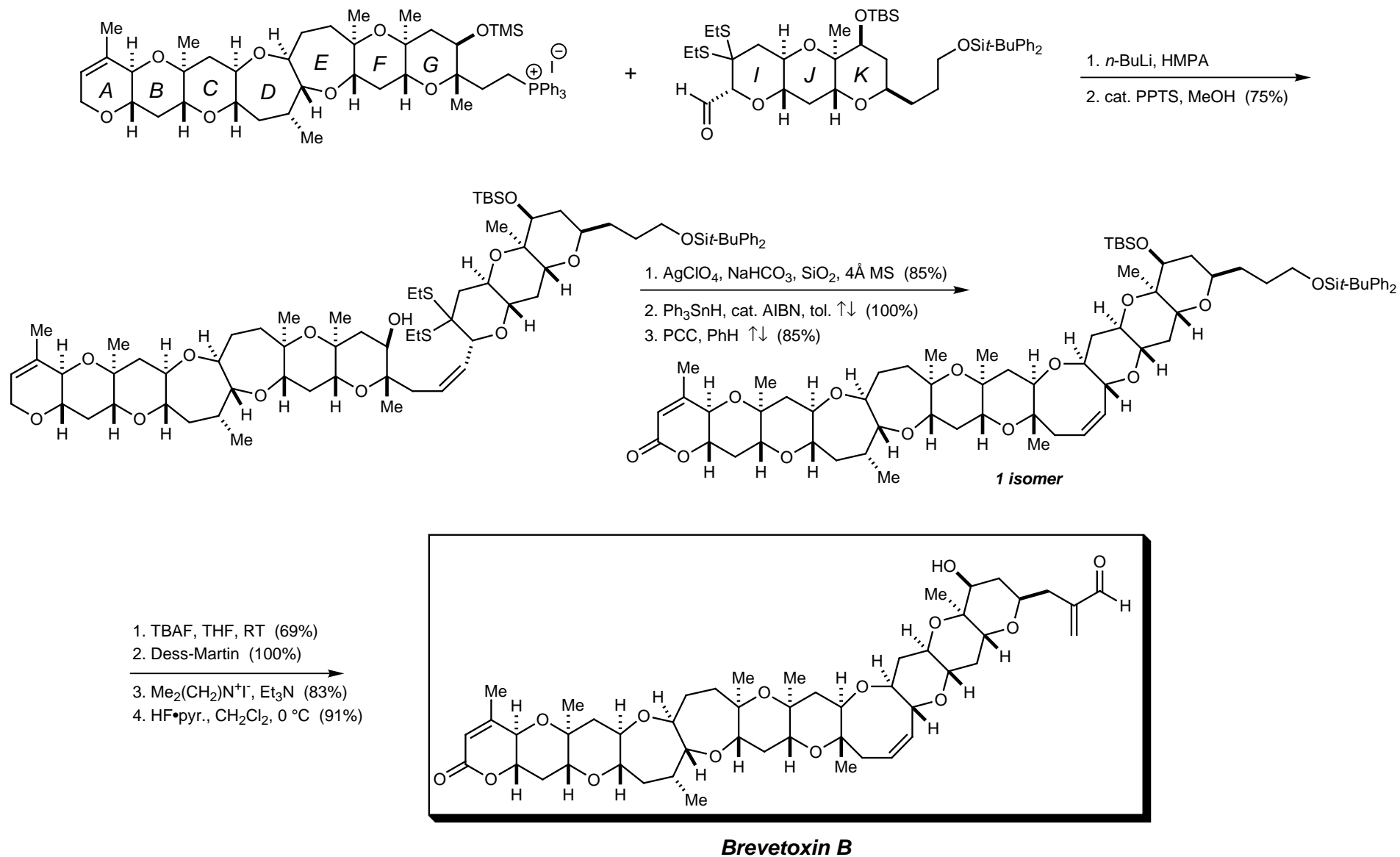
1. NaI, acetone, 60 °C
 2. TMS-imidazole (96%)
 3. PPh_3 , CH_3CN $\uparrow\downarrow$ (99%)



Cyclization of Hydroxy Dithioketals

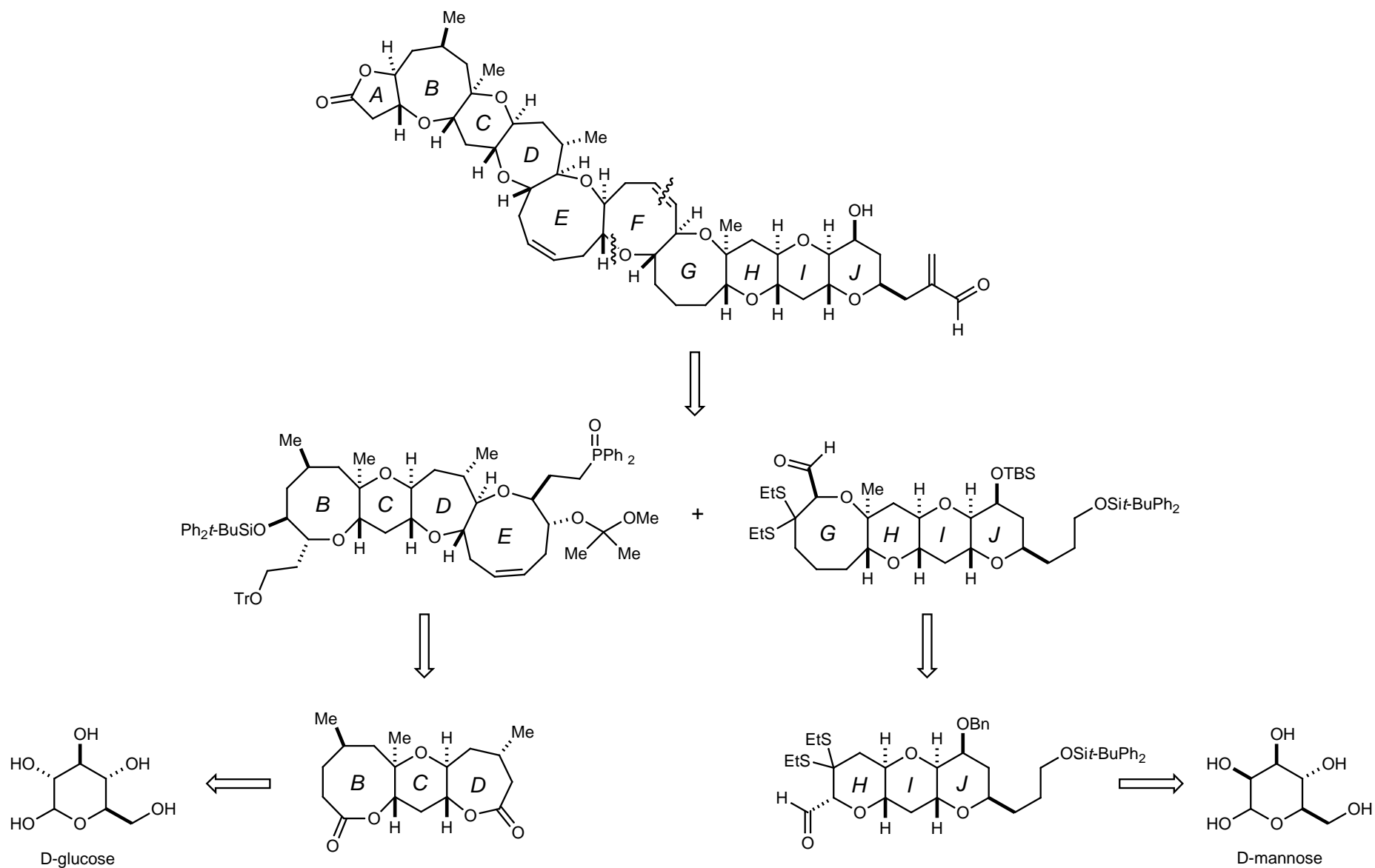


Completion of the Synthesis of Brevetoxin B



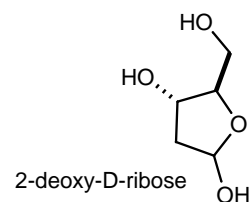
Nicolaou *J. Am. Chem. Soc.* **1995**, *117*, 10252.

Retrosynthetic Analysis of Brevetoxin A

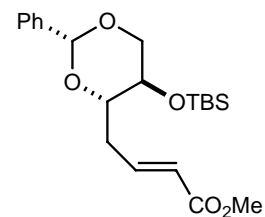


Nicolaou *Nature* **1998**, 392, 264.

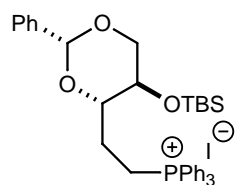
Construction of the G Ring of Brevetoxin A



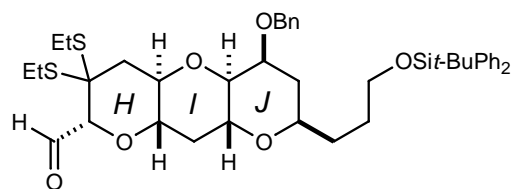
1. $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, THF $\uparrow\downarrow$ (100%)
2. $\text{PhCH}(\text{OMe})_2$, CSA, CH_2Cl_2 (65%)
3. TBSOTf, 2,6-lut., 0 °C (100%)



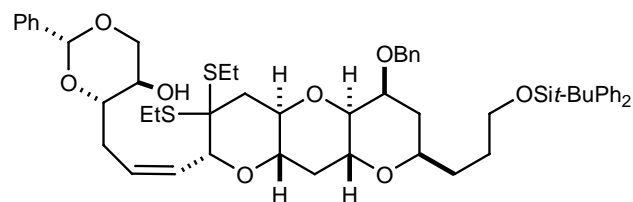
1. O_3 ; Ph_3P
2. NaBH_4 , MeOH, 0 °C (90%)
3. I_2 , PPh_3 , imidazole (84%)
4. PPh_3 , CH_3CN $\uparrow\downarrow$ (90%)



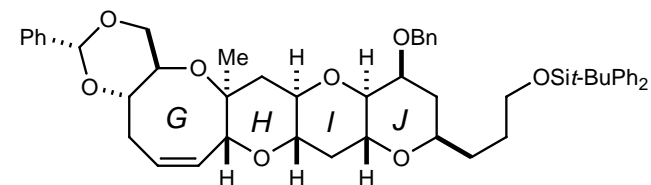
+



1. *n*-BuLi, HMPA, THF
2. TBAF, THF, RT (83%)

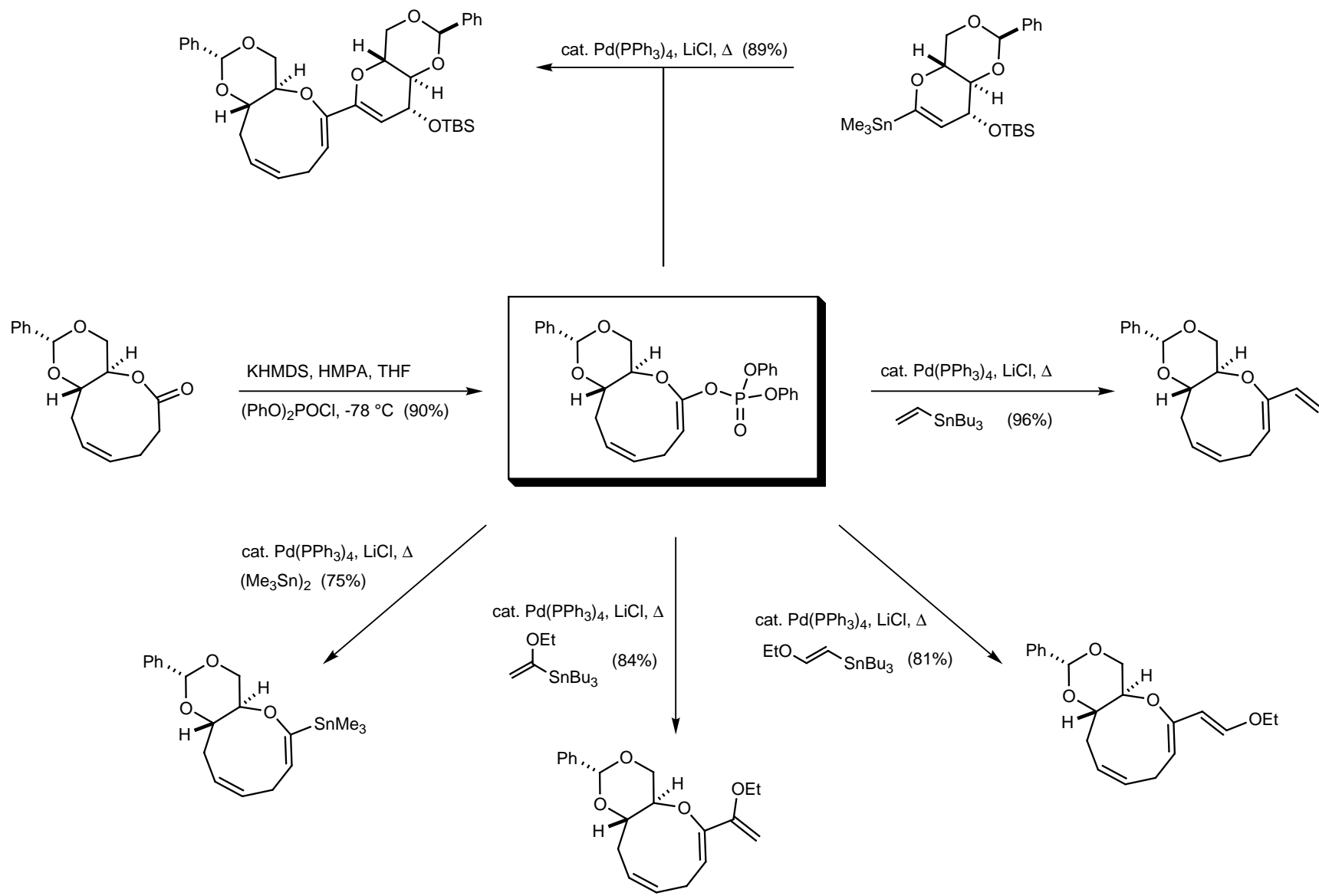


1. AgClO_4 , NaHCO_3 , SiO_2 , 4 Å MS (92%)
2. *m*-CPBA, CH_2Cl_2 , 0 °C (93%)
3. AlMe_3 , CH_2Cl_2 , -78 °C (94%)



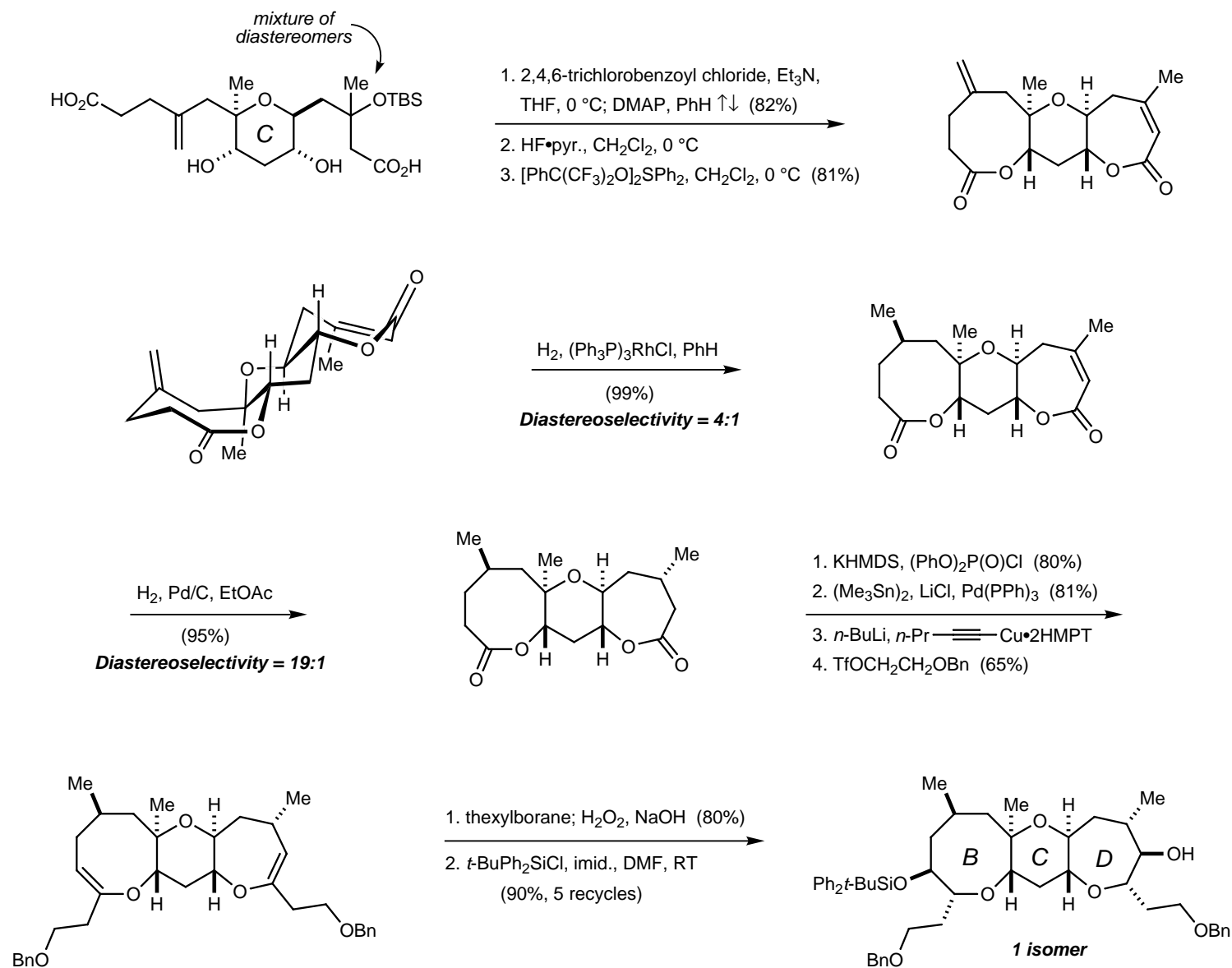
Nicolaou *Nature* **1998**, 392, 264.

Cross-Coupling of Cyclic Ketene Acetal Phosphates



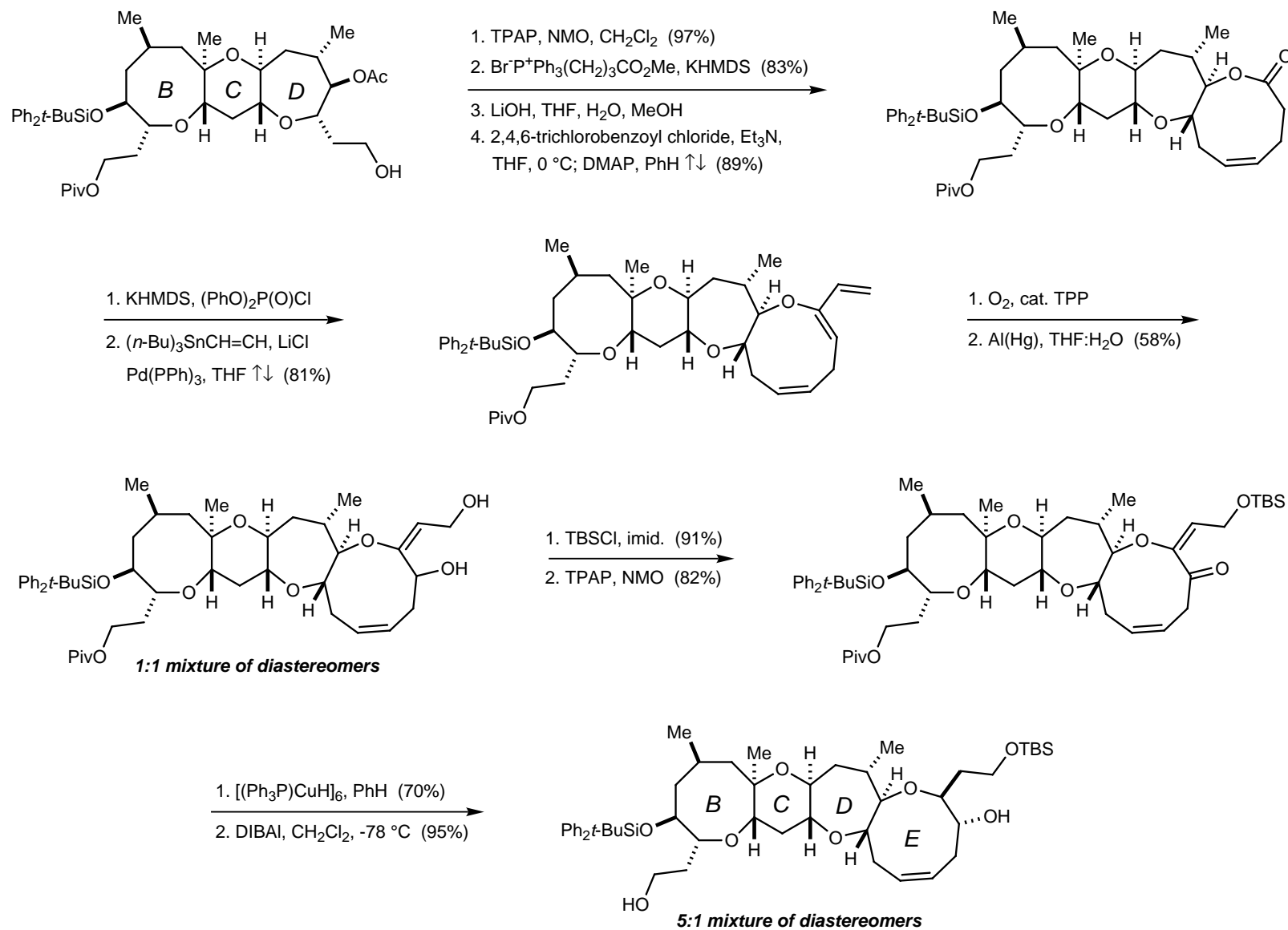
Nicolaou *J. Am. Chem. Soc.* **1997**, *119*, 5467.

Construction of the BCD Fragment of Brevetoxin A

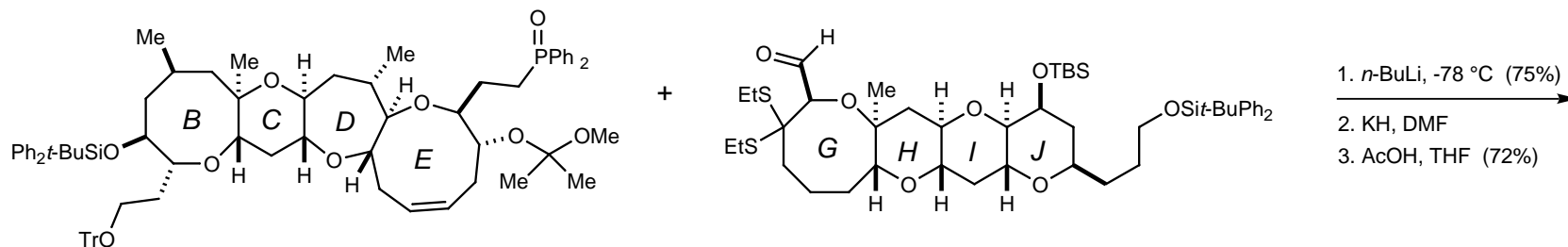


Nicolaou *Nature* **1998**, 392, 264.

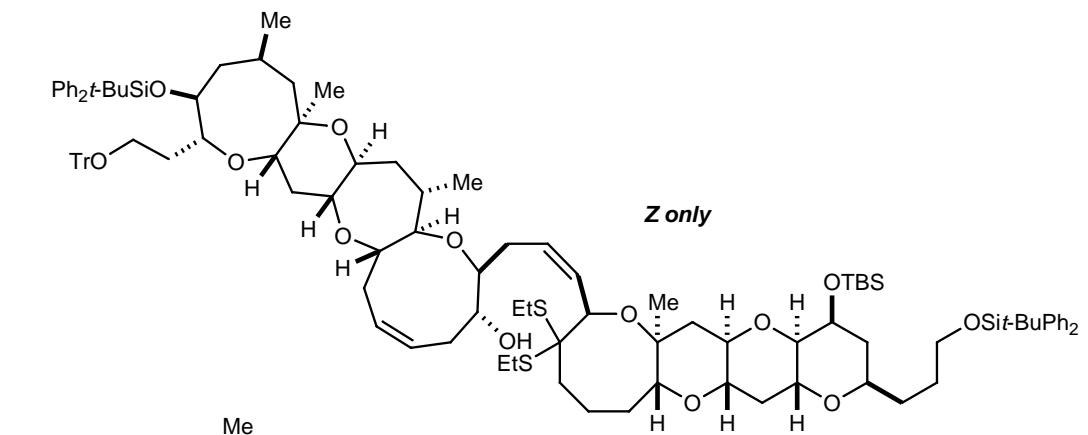
Construction of the E Ring of Brevetoxin A



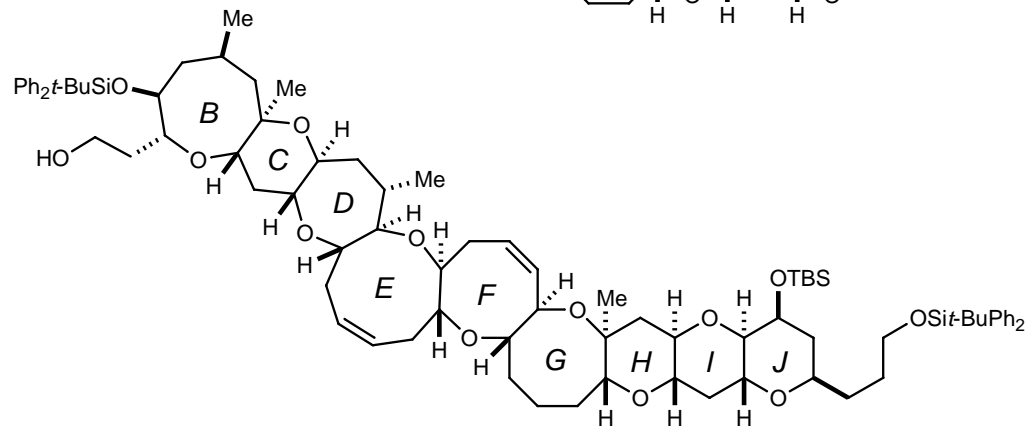
Construction of the B-J Fragment of Brevetoxin A



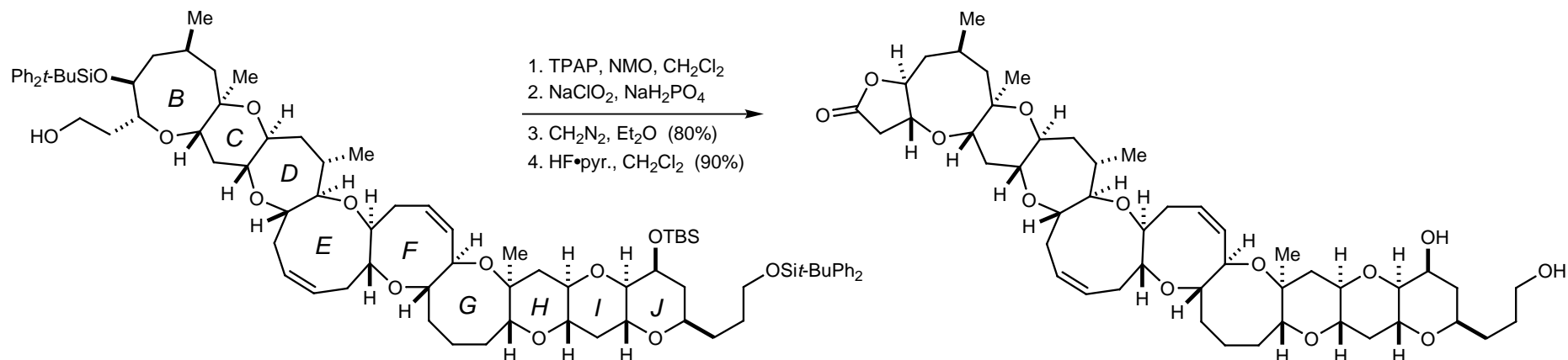
Note: Use of a phosphonium ylide instead of the phosphine oxide showed no reaction. In addition, the MOP protecting group on the E ring was found to be essential for good Z selectivity.



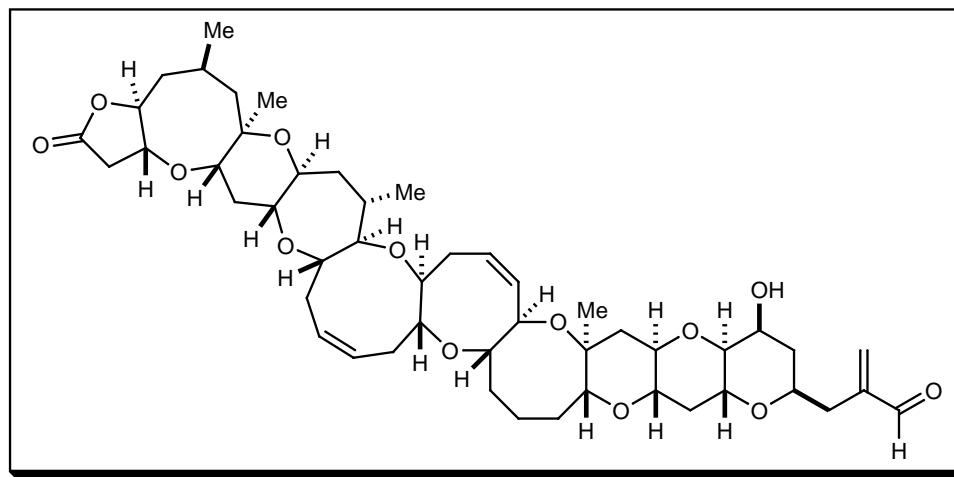
1. AgClO₄, NaHCO₃, SiO₂, 4Å MS (80%)
2. *m*-CPBA, CH₂Cl₂, 0 °C (85%)
3. BF₃•OEt₂, Et₃SiH, -78 °C (94%)



Completion of the Synthesis of Brevetoxin A



1. Dess-Martin (80%)
2. Me₂(CH₂)N⁺I⁻, Et₃N (90%)



Brevetoxin A

Tale of the Tape

Hemibrevetoxin B	Total Steps	Longest Linear Sequence	Overall Yield	Average Yield
Nicolaou	56	56 Steps	0.0487%	87%
Yamamoto	58	58 Steps	0.0197%	86%
Nakata	60	60 Steps	0.0606%	88%
Mori	59	41 Steps	????	????
Brevetoxin B (Nicolaou)	132	84 Steps	0.0324%	91%
Brevetoxin A (Nicolaou)	127	66 Steps	0.0237%	88%