Methodologies Relevant to the Synthesis of the Brevetoxins

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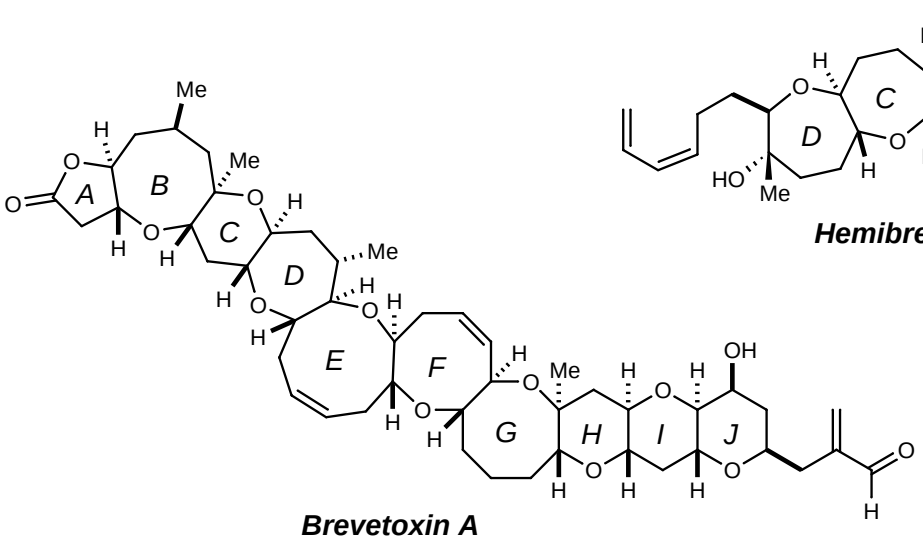
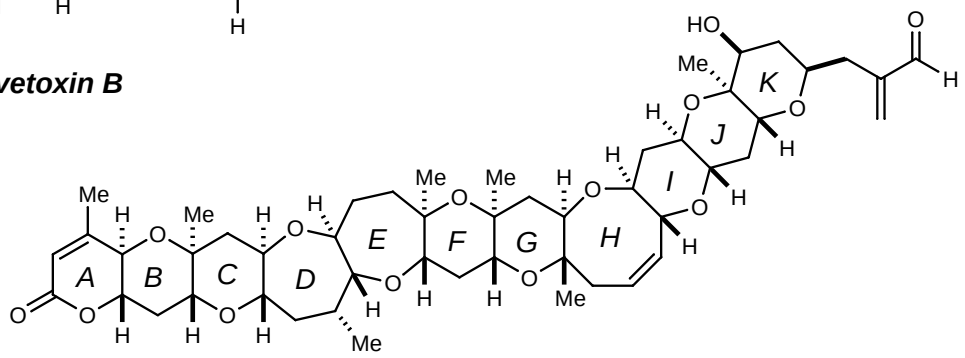
I. Background
II. Hemibrevetoxin B
    A. Approaches to the Construction of the A ring
    B. Approaches to the Construction of the B ring
    C. Approaches to the Construction of the C ring
    D. Approaches to the Construction of the D ring
    E. End Game
III. Brevetoxin B
IV. Brevetoxin A

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 A

Hemibrevetoxin B



Brevetoxin B

■ **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*.

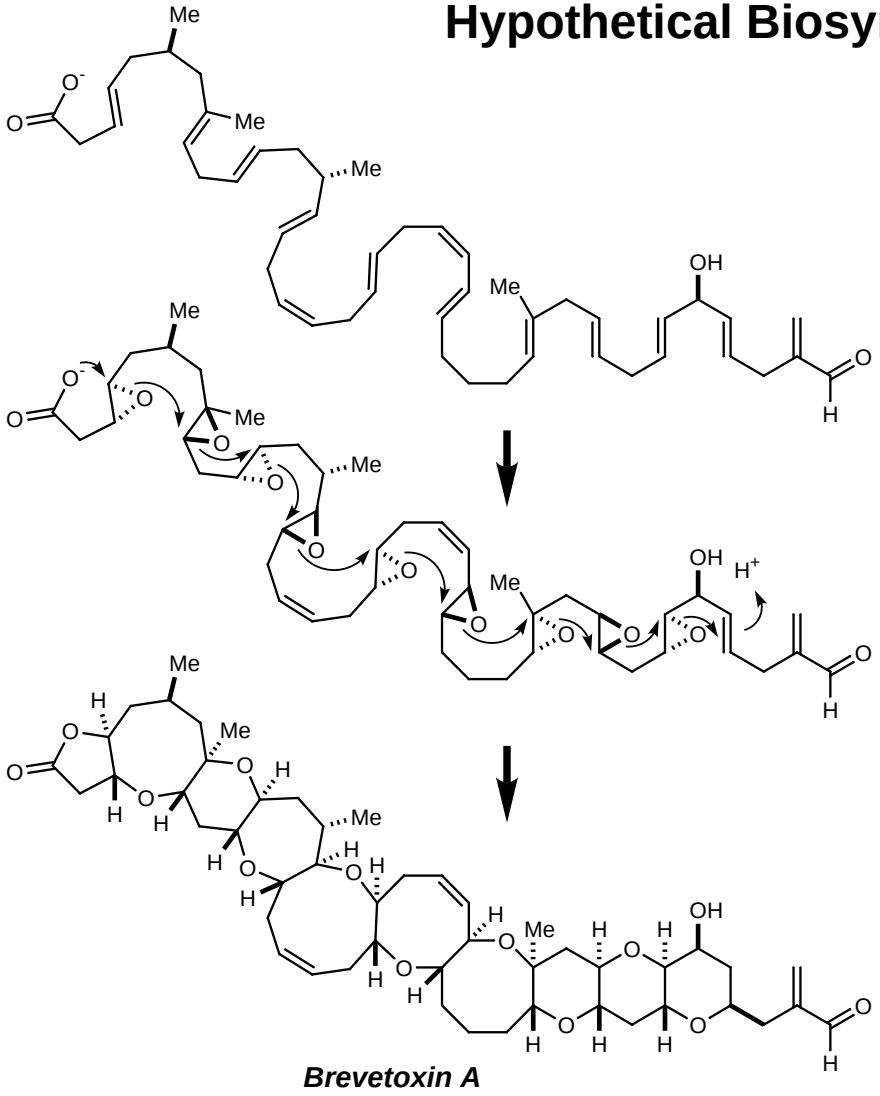
Structure determined from extensive 1D and 2D NMR analysis and comparison to brevetoxin A.

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

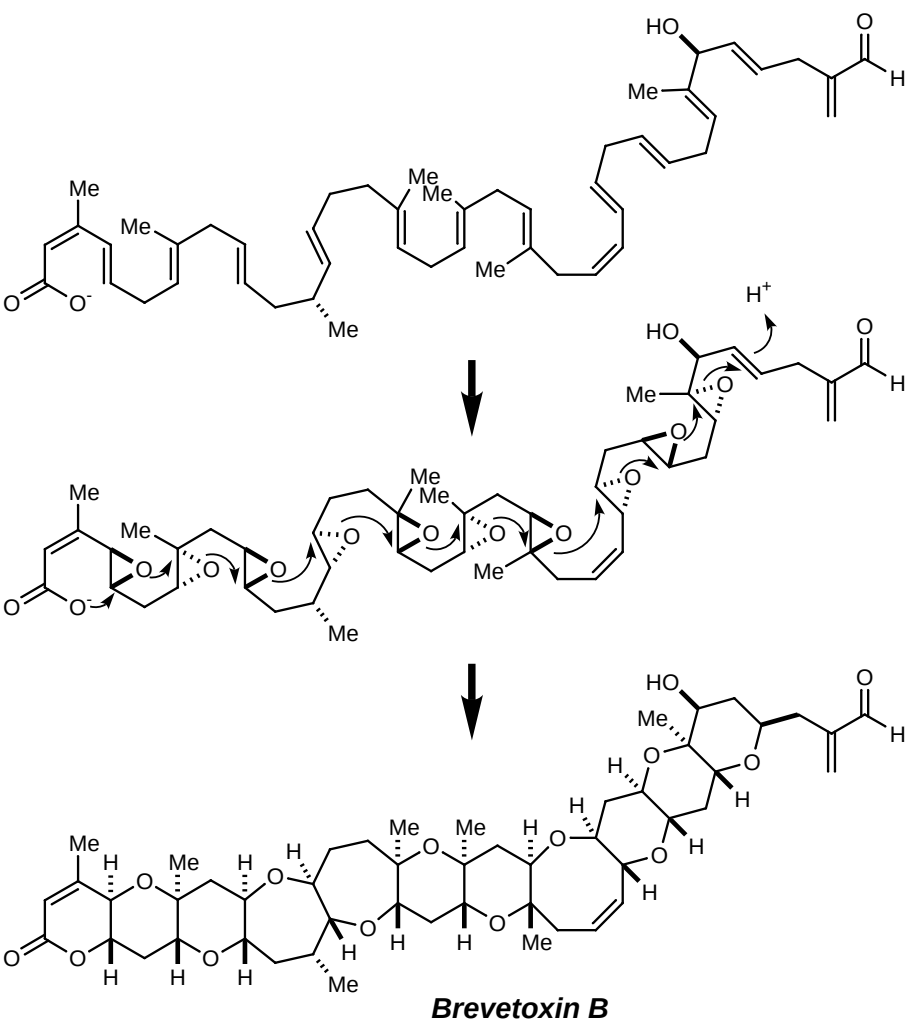
Total Syntheses: Nicolaou *J. Am Chem. Soc.* **1992**, *114*, 7935.; Nicolaou *J. Am Chem. Soc.* **1993**, *115*, 3558.
Yamamoto *Tet. Lett.* **1995**, *36*, 5777.
Nakata *Tet. Lett.* **1996**, *37*, 6365.

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

Hypothetical Biosynthesis of the Brevetoxins



Brevetoxin A



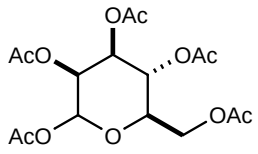
Brevetoxin B

"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."

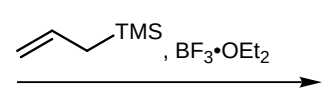
Nakanishi *J. Am.Chem. Soc.* **1989**, *111*, 6234.

Approaches to the Synthesis of the A Ring of Hemibrevetoxin B

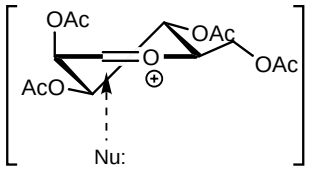
Sugar Derivatization:

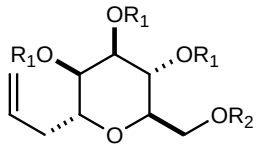


D-mannose pentaacetate



Diastereoselectivity = 6.8:1

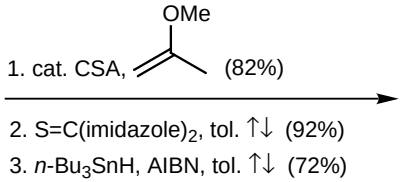


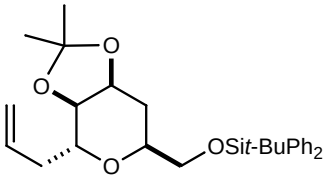


NaOMe, MeOH → $R_1 = R_2 = Ac$

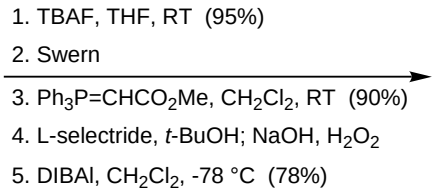
NaOMe, MeOH → $R_1 = R_2 = H$

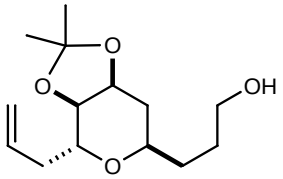
t-$BuPh_2SiCl$, imid., DMF → $R_1 = H$, $R_2 = t$-$BuPh_2Si$





Common intermediate in all 3 Nicolaou syntheses.

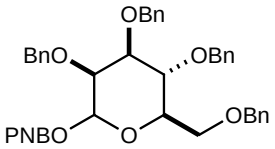


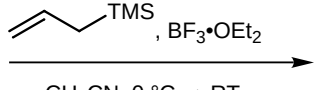


Intermediate in Nicolaou synthesis of brevetoxin A; used by Yamamoto for hemibrevetoxin B

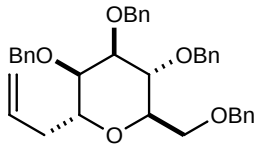
Nicolaou *J. Am. Chem. Soc.* **1989**, *111*, 6682.

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





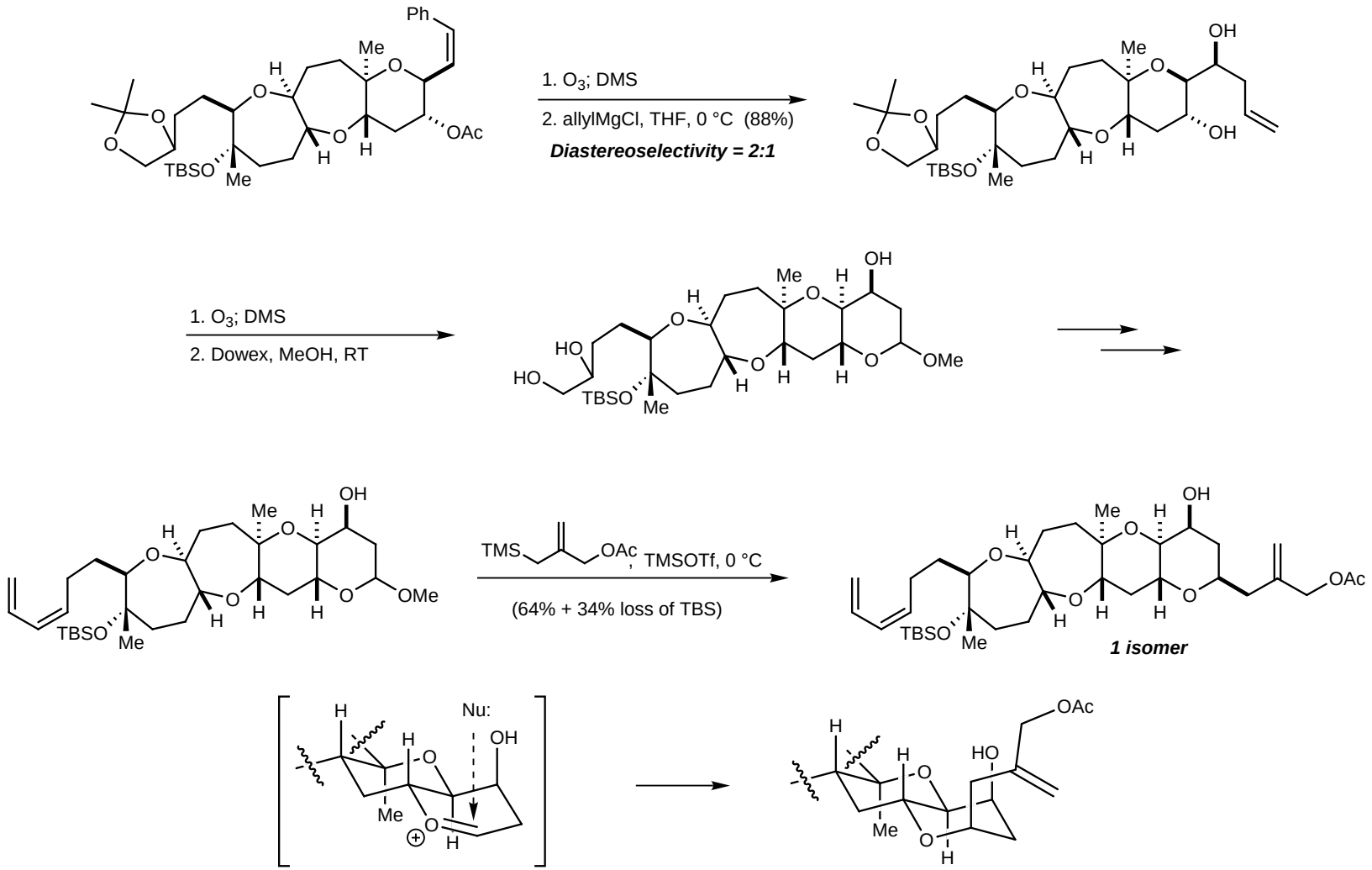
Diastereoselectivity > 10:1



Kishi *J. Am. Chem. Soc.* **1982**, *104*, 4976.

Approaches to the Synthesis of the A Ring of Hemibrevetoxin B

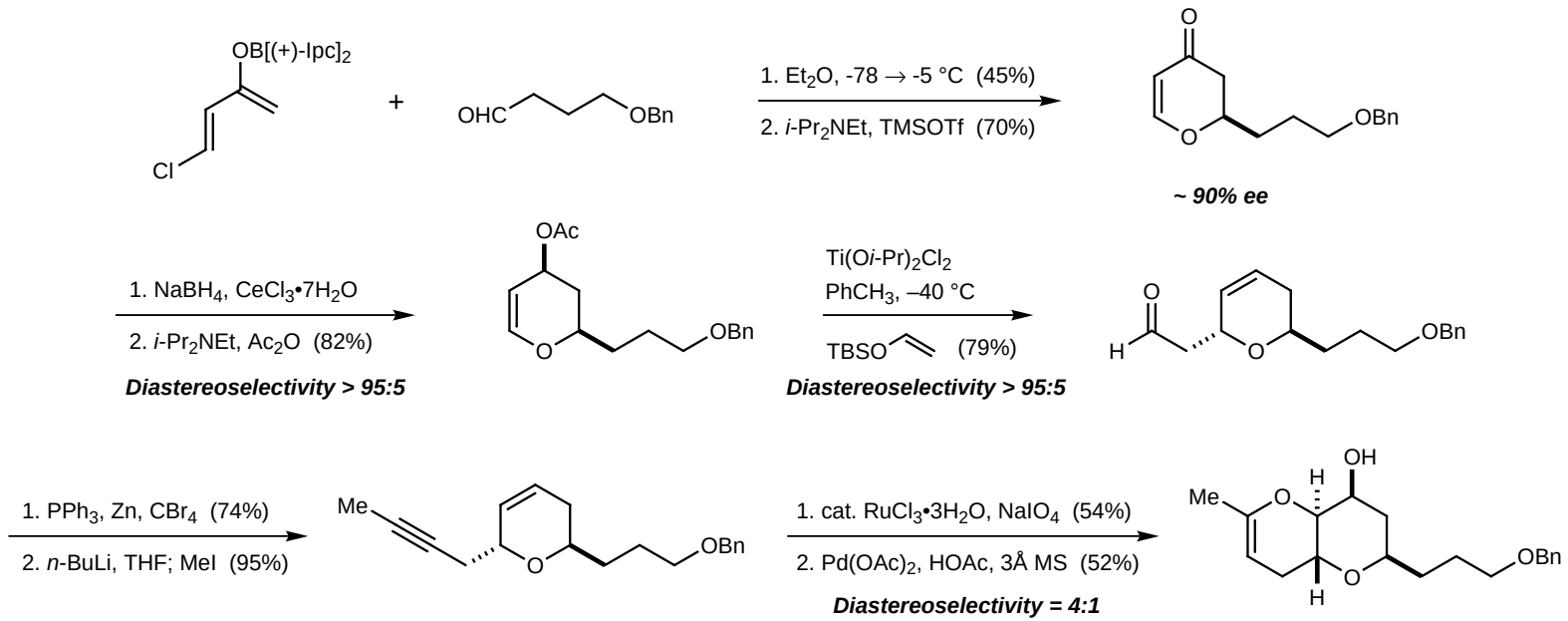
Late Stage Installation:



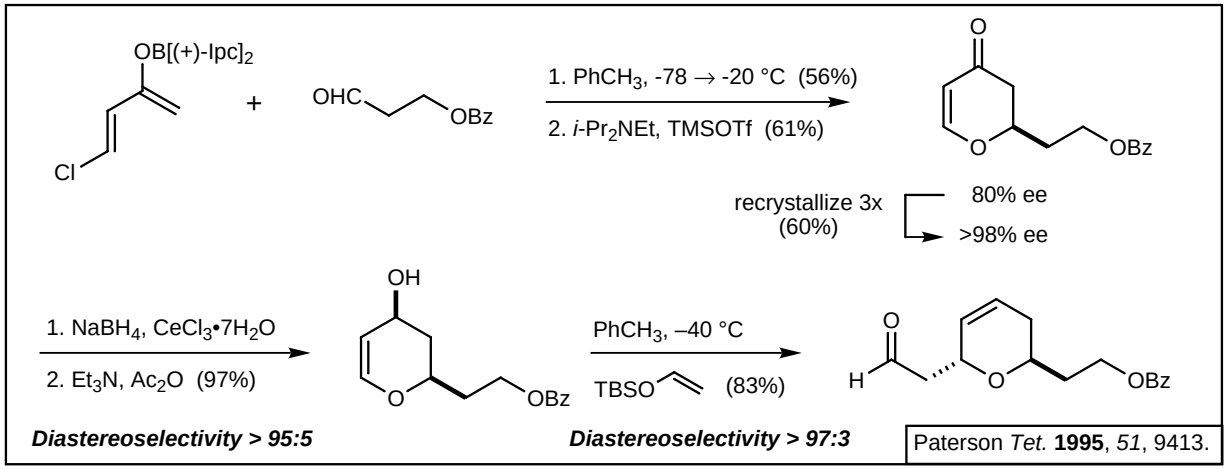
Nakata *Tet. Lett.* **1996**, *37*, 6365.

Approaches to the Synthesis of the A Ring of Hemibrevetoxin B

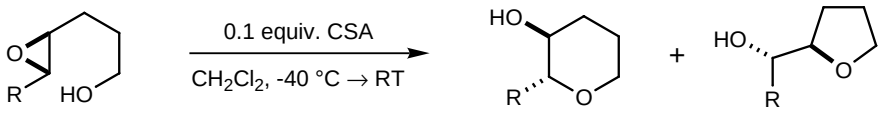
Asymmetric Aldol:



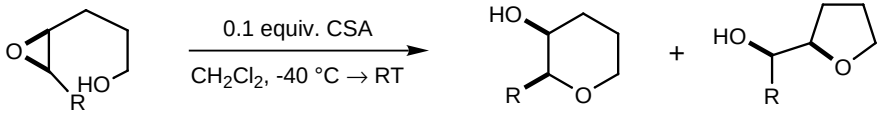
McDonald *J. Org. Chem.* **1997**, *62*, 6432.



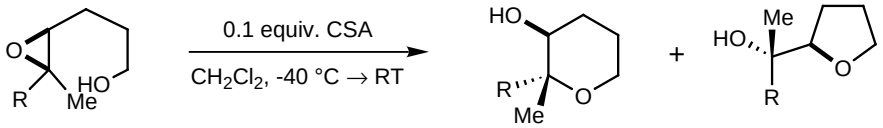
6-Endo Over 5-Exo Hydroxy Epoxide Opening



R	Ratio			Yield
$CH_2CH_2CO_2Me$	0	:	100	94%
E-CH=$CHCO_2Me$	60	:	40	96%
$CH=CH_2$	100	:	0	95%
$CH=CBr_2$	100	:	0	90%

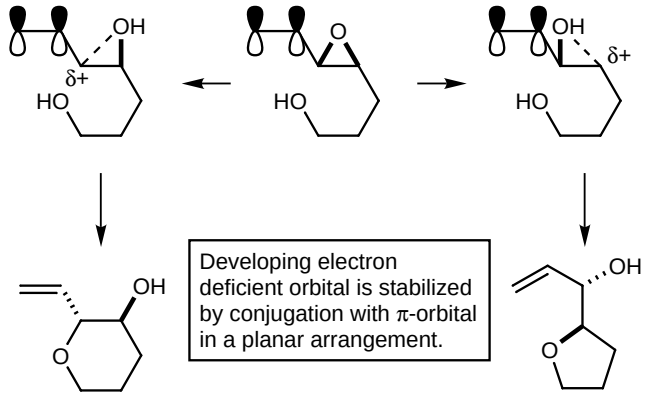


R	Ratio			Yield
E-CH=$CHCO_2Me$	0	:	100	86%
$CH=CH_2$	44	:	56	95%
E-CH=CHCl	76	:	24	94%
Z-CH=CHCl	33	:	67	92%
C≡CBr	0	:	100	87%



R	Ratio			Yield
E-CH=$CHCO_2Me$	66	:	34	92%
$CH=CH_2$	100	:	0	96%

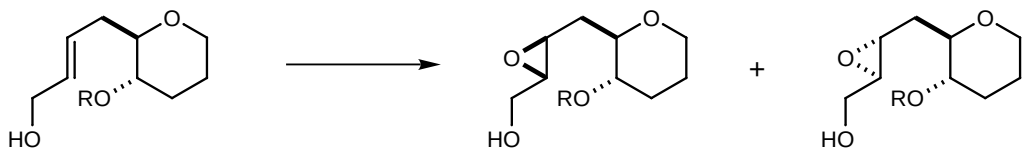
Authors' Explanation:



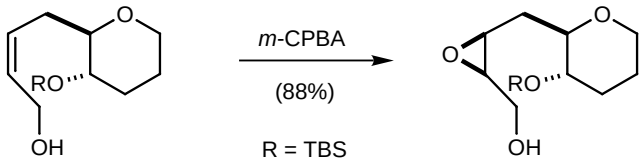
"In the absence of the π-orbital, both acid- or base-induced ring closures were expected to lead to the smaller ring, exo product on the basis of better antiparallel alignment of the incipient and rupturing bonds." (See: Stork *J. Am. Chem. Soc.* **1974**, *96*, 5270. Baldwin *J.C.S. Chem Commun.* **1976**,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

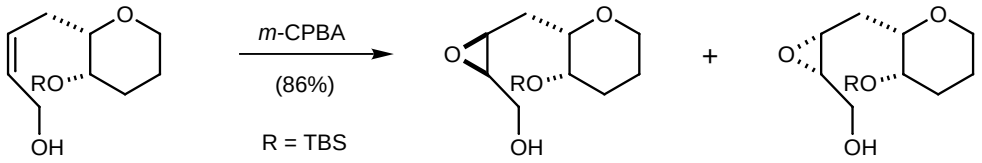
Nicolaou *J. Am. Chem. Soc.* **1989**, *111*, 5330.

Diastereoselective Epoxidation of Allylic Alcohols



R	Conditions	Ratio			Yield
Si*t*-BuPh$_2$	(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH	4.3	:	1	80%
Si*t*-BuPh$_2$	(-)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH	1	:	18	87%
Si*t*-BuPh$_2$	*m*-CPBA	2	:	1	89%
Si*t*-BuMe$_2$	(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH	5.2	:	1	78%
Si*t*-BuMe$_2$	(-)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH	1	:	19	92%
Si*t*-BuMe$_2$	*m*-CPBA	1	:	1	85%



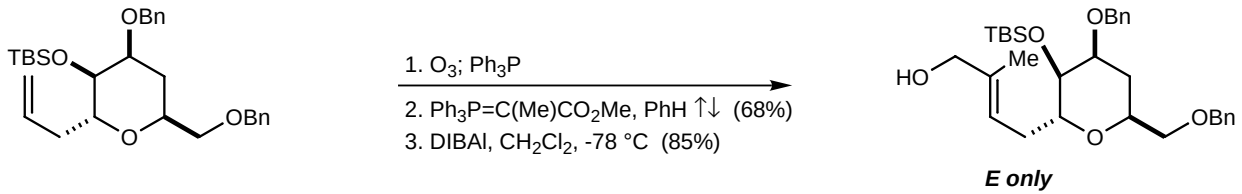


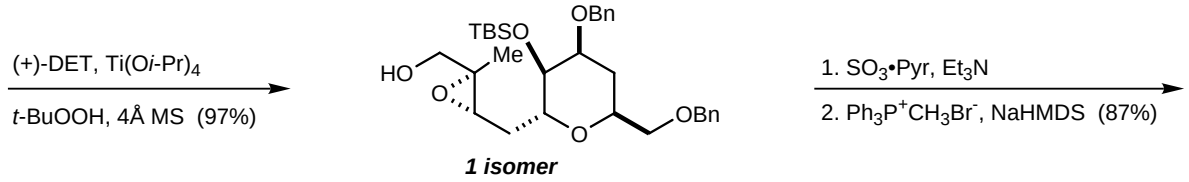
1 : 10

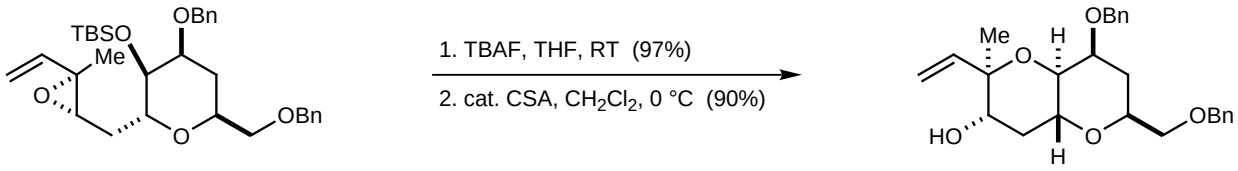
Nicolaou *J. Am. Chem. Soc.* **1989**, *111*, 5330.

Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

6-*Endo* Epoxide Cyclization:



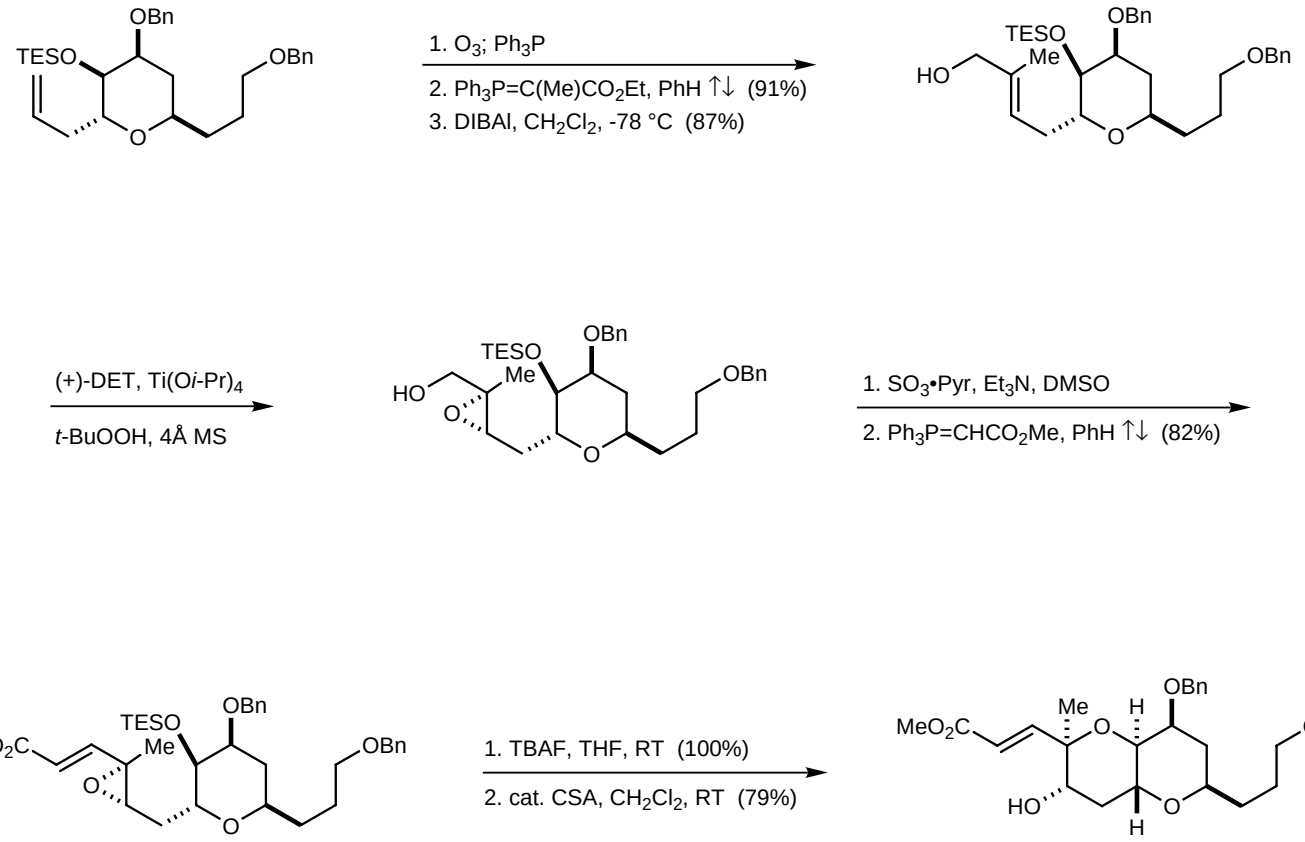




Nicolaou *J. Am. Chem. Soc.* **1993**, *115*, 3558.

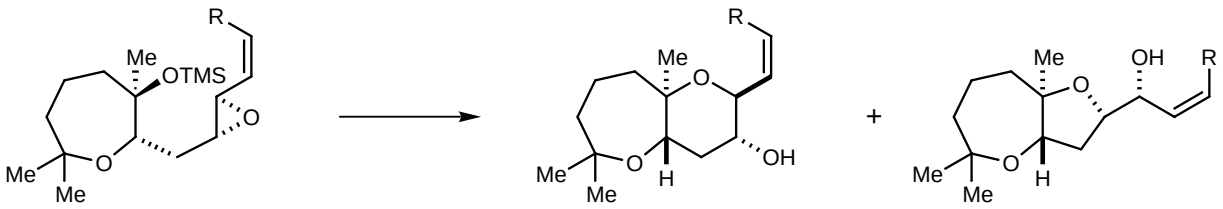
Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

6-*Endo* Epoxide Cyclization:



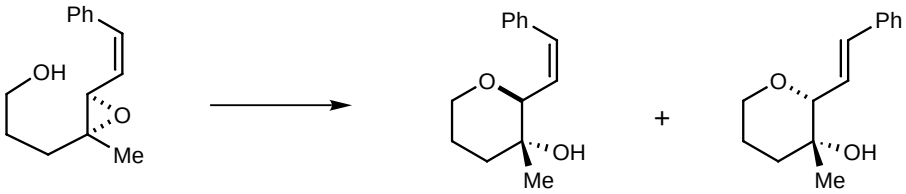
Yamamoto *Tet. Lett.* **1995**, *36*, 5777.

Modified 6-Endo Hydroxy Epoxide Opening



R	Reagents	Ratio			Yield
H	TBAF; cat. PPTS	1	:	1	86%
H	10:1 AcOH-H_2O	3.8	:	1	78%
Ph (*E*/*Z* = 1:8)	TBAF; cat. PPTS	1	:	0	86%

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



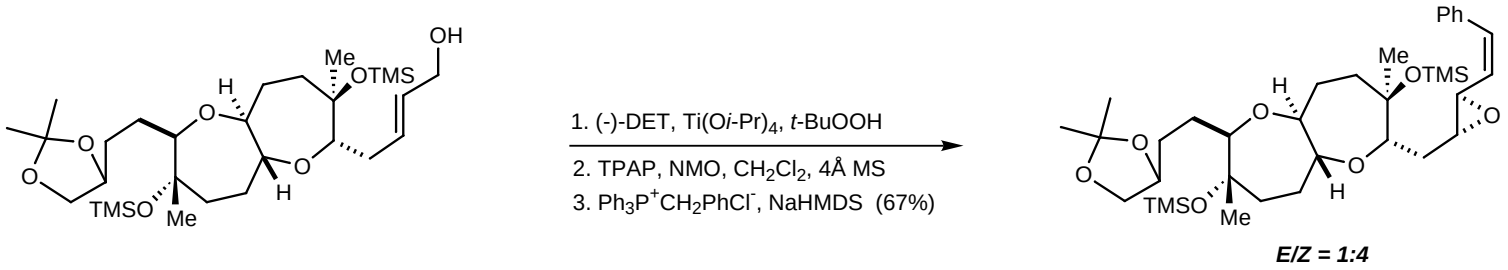
Conditions	Ratio			Yield
cat. PPTS, CH_2Cl_2, RT, 15 min	65 (*Z*/*E* = 7:1)	:	35 (*Z*/*E* = 1:2.5)	97%
cat. PPTS, CH_2Cl_2, -20 °C, 21 h	79 (*Z*/*E* = 15:1)	:	21 (*Z*/*E* = 1:2)	97%
cat. CSA, CH_2Cl_2, RT, 10 min	58 (*Z*/*E* = 5:1)	:	42 (*Z*/*E* = 1:3)	81%
cat. CSA, CH_2Cl_2, -78 °C, 1 h	90 (*Z*/*E* = 22:1)	:	10 (*Z*/*E* = 1:2)	100%
10:1 AcOH-H_2O	47 (*Z*/*E* = 8:1)	:	53 (*Z*/*E* = 1:10)	83%
10 equiv. NaH, DMSO, RT, 2.5 h	100 (*Z* only)	:	0	97%

Note: ***No 5-Exo products were observed.***

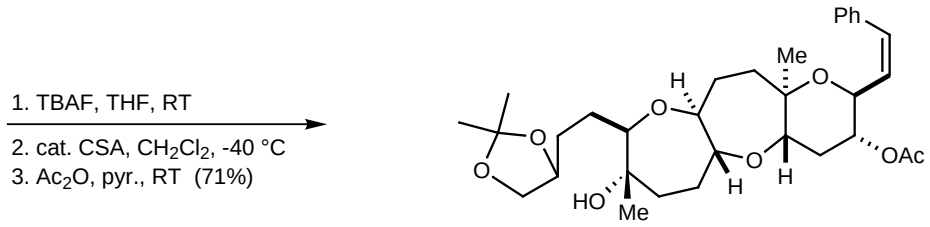
Nakata *Tet. Lett.* **1997**, *38*, 5545.

Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

Late Stage 6-*Endo* Epoxide Cyclization:

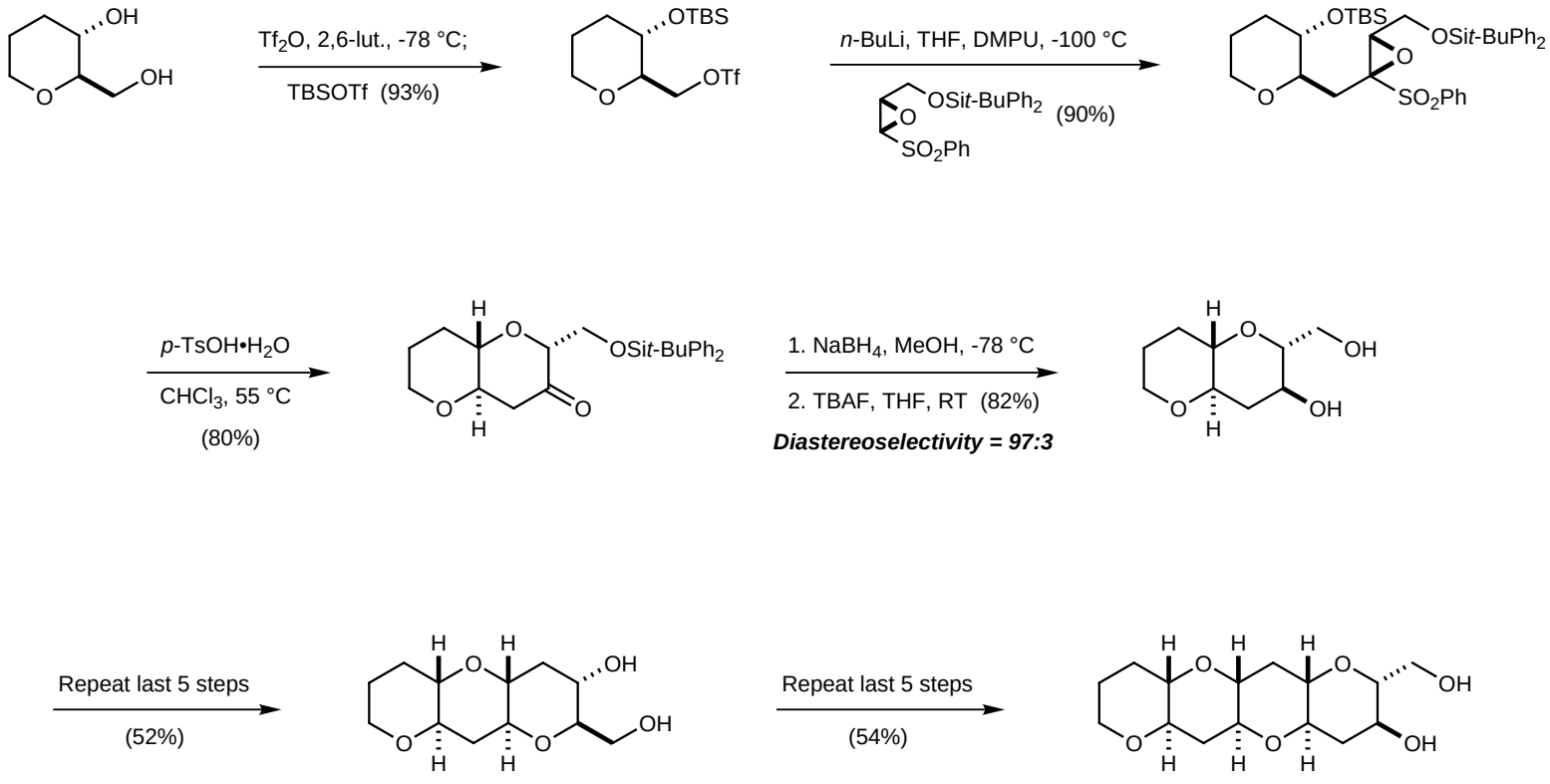


E/Z = 1:4



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

Reiterative Oxiranyl Anion Alkylation

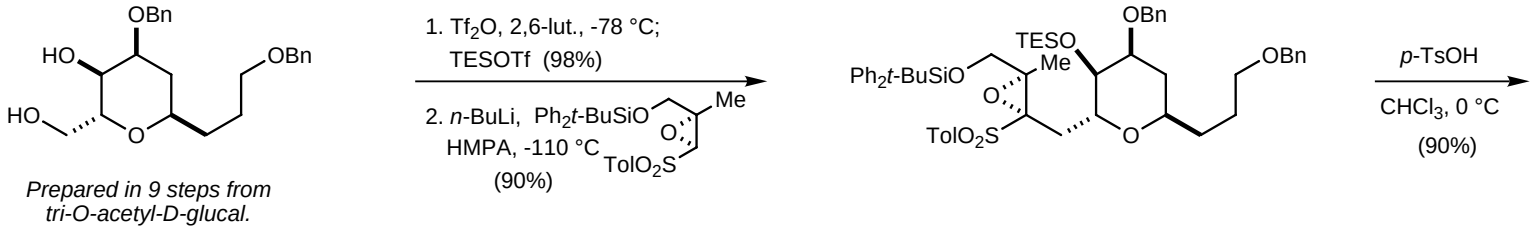


"The synthesis of such a ring system by Baldwin's rule-disfavored 6-*endo* mode of cyclization is receiving attention since such cyclization is considered to be a key step in the biosynthesis of polycyclic ethers."

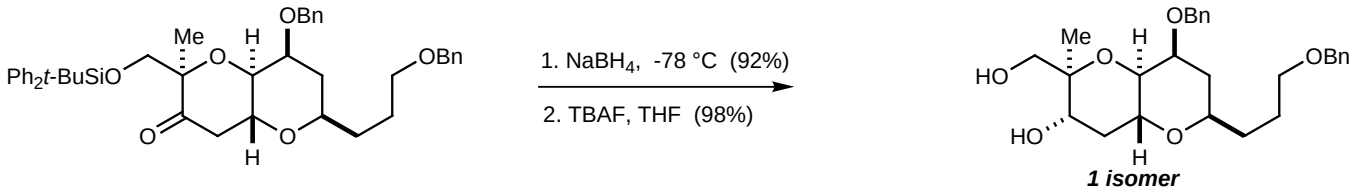
Mori *J. Am. Chem. Soc.* **1996**, *118*, 8158.

Approaches to the Synthesis of the B Ring of Hemibrevetoxin B

Oxiranyl Anion Alkylation Followed by 6-*Endo* Epoxide Cyclization:



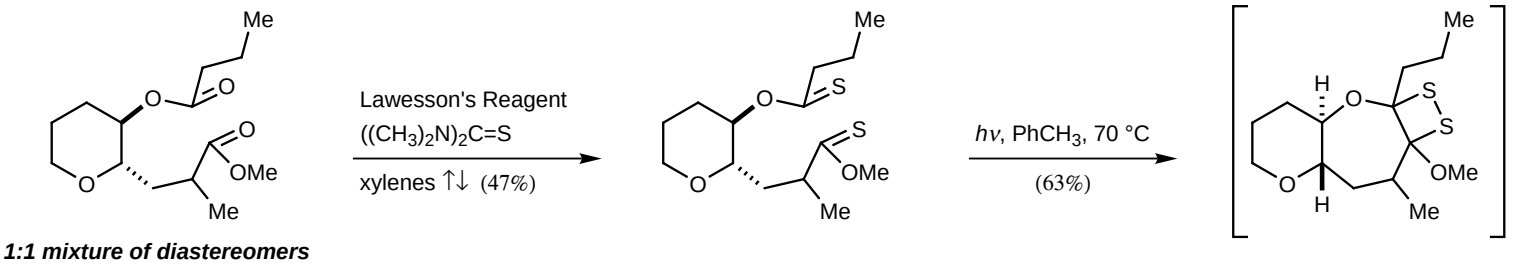
Prepared in 9 steps from tri-O-acetyl-D-glucal.



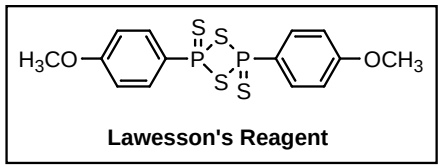
***1* isomer**

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

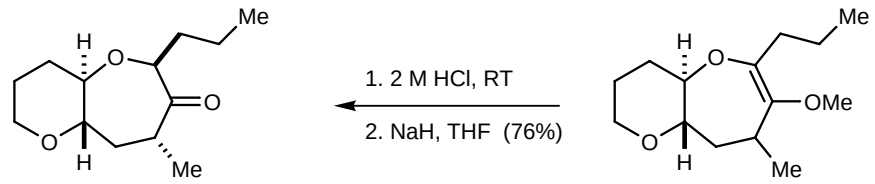
Photo-induced Cyclization of Dithionoesters



1:1 mixture of diastereomers



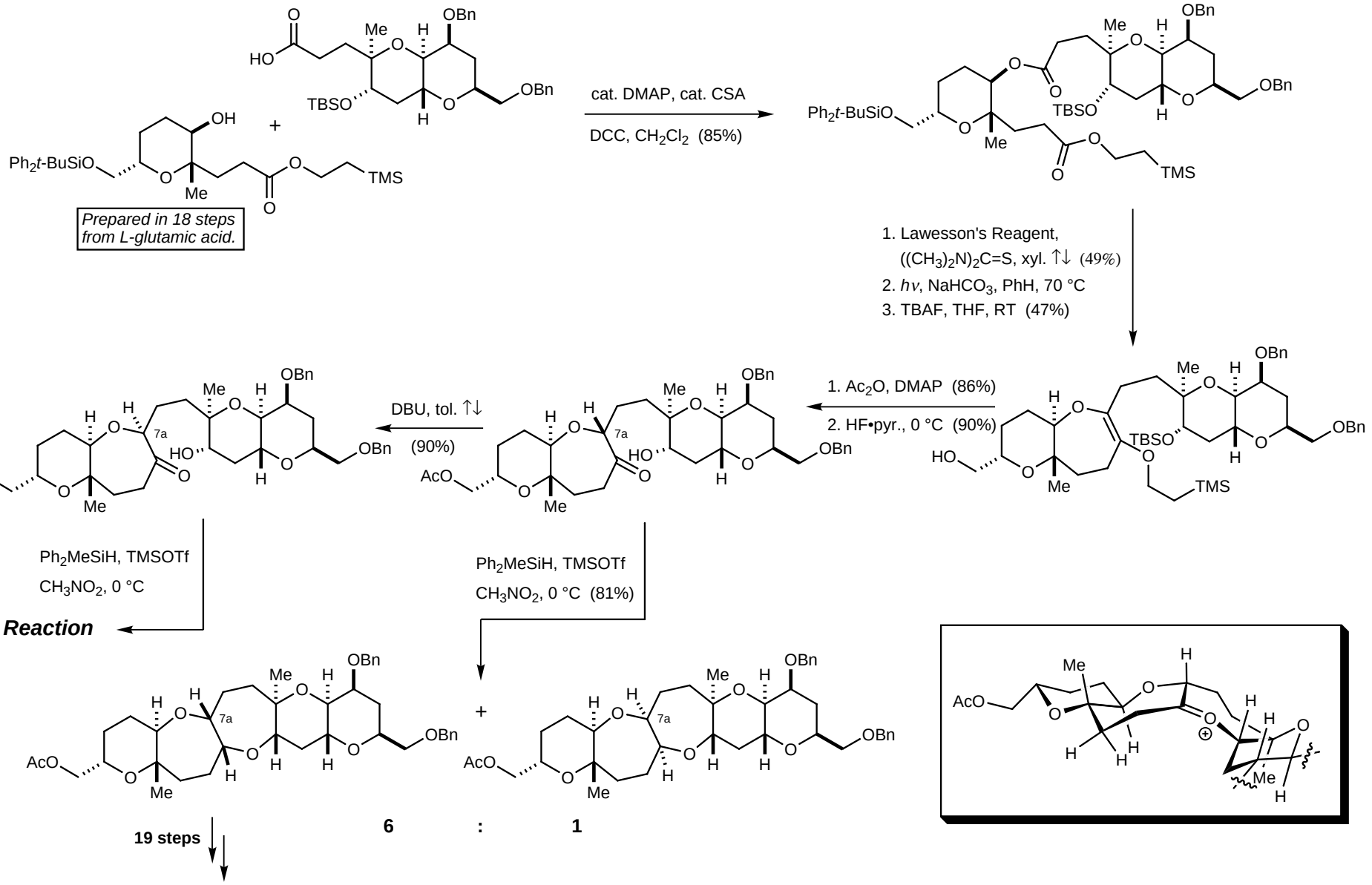
Lawesson's Reagent



1 isomer

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

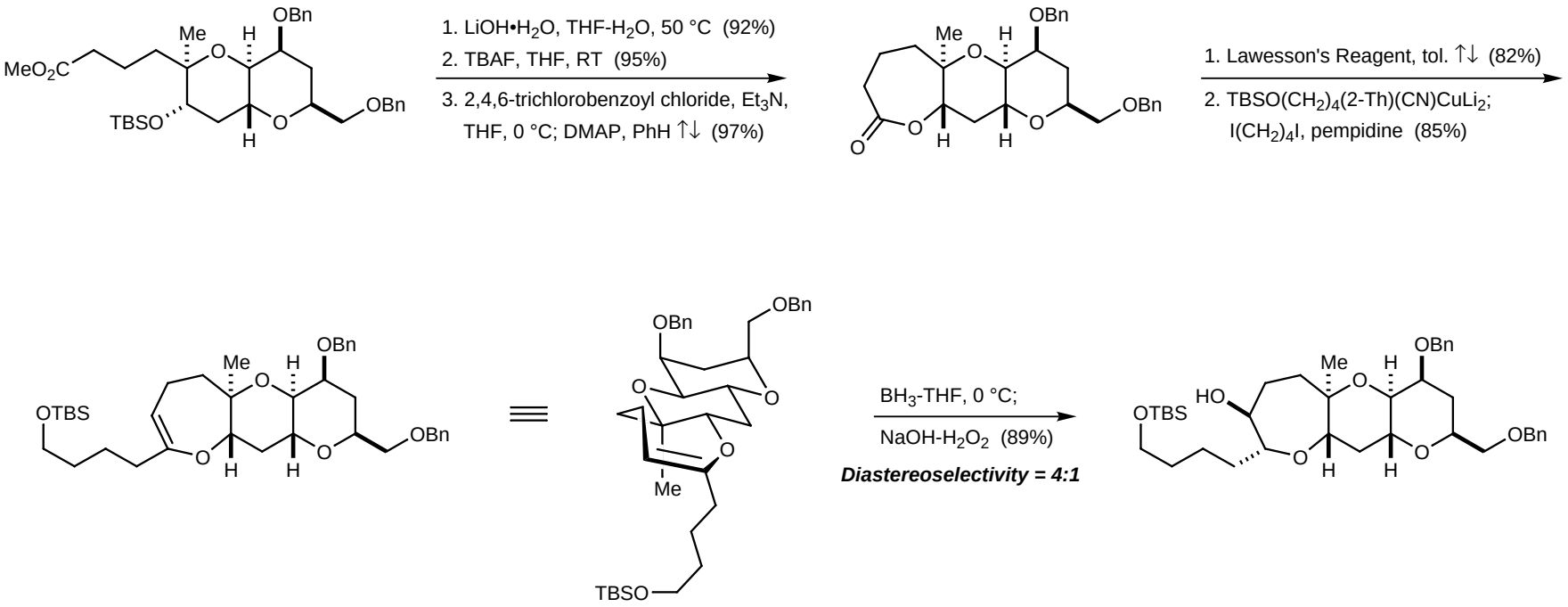
Failed Convergent Route to Hemibrevetoxin B



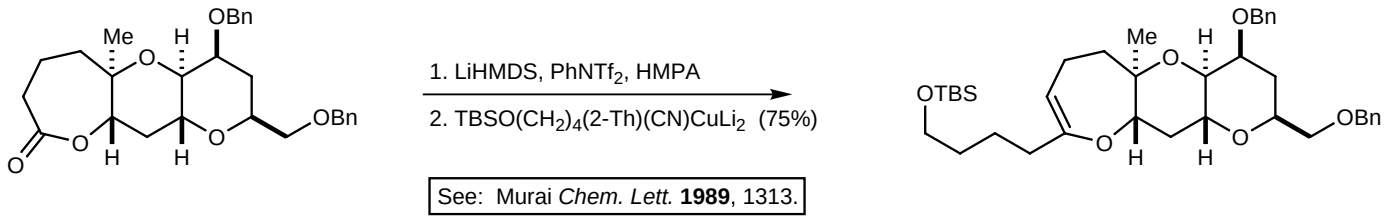
Nicolaou *J. Am. Chem. Soc.* **1993**, *115*, 3558.

Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

Thionolactone Alkylation:



Cross-Coupling of Enol Triflate:

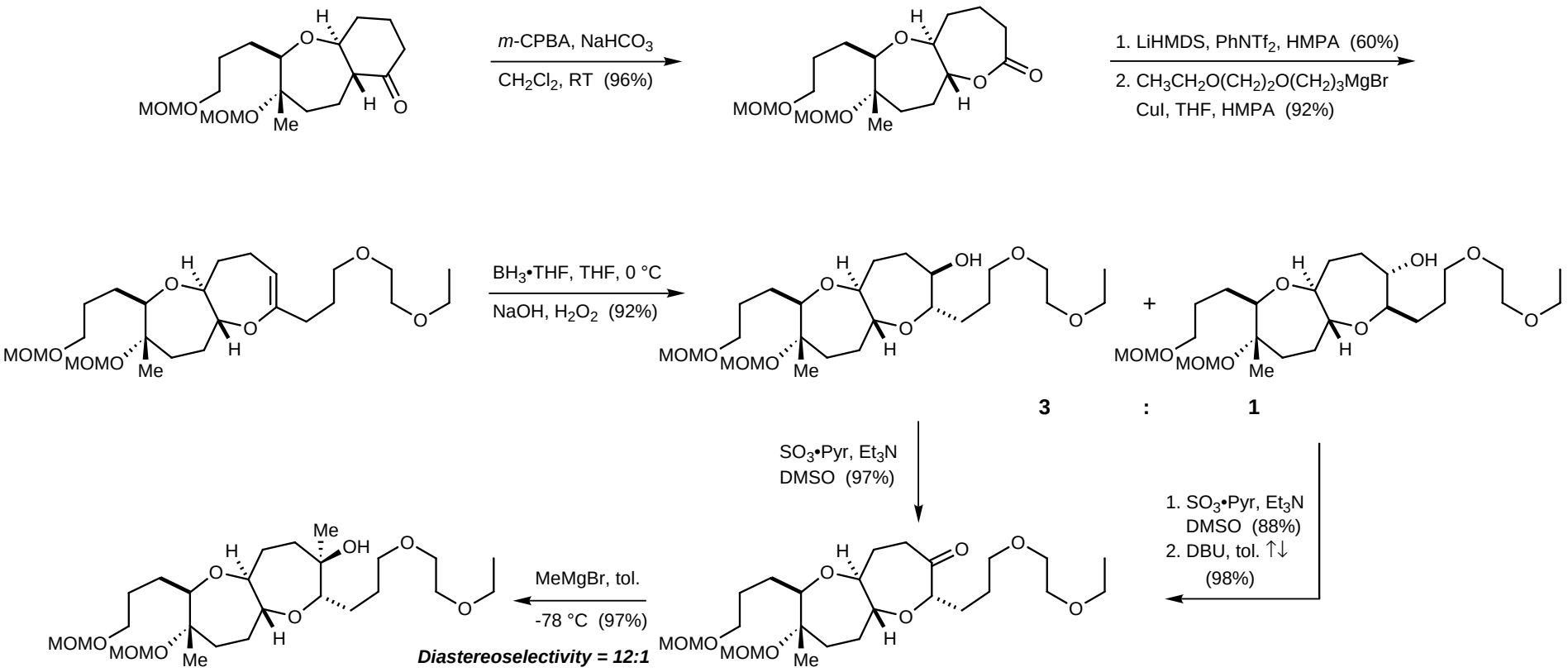


See: Murai *Chem. Lett.* **1989**, 1313.

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

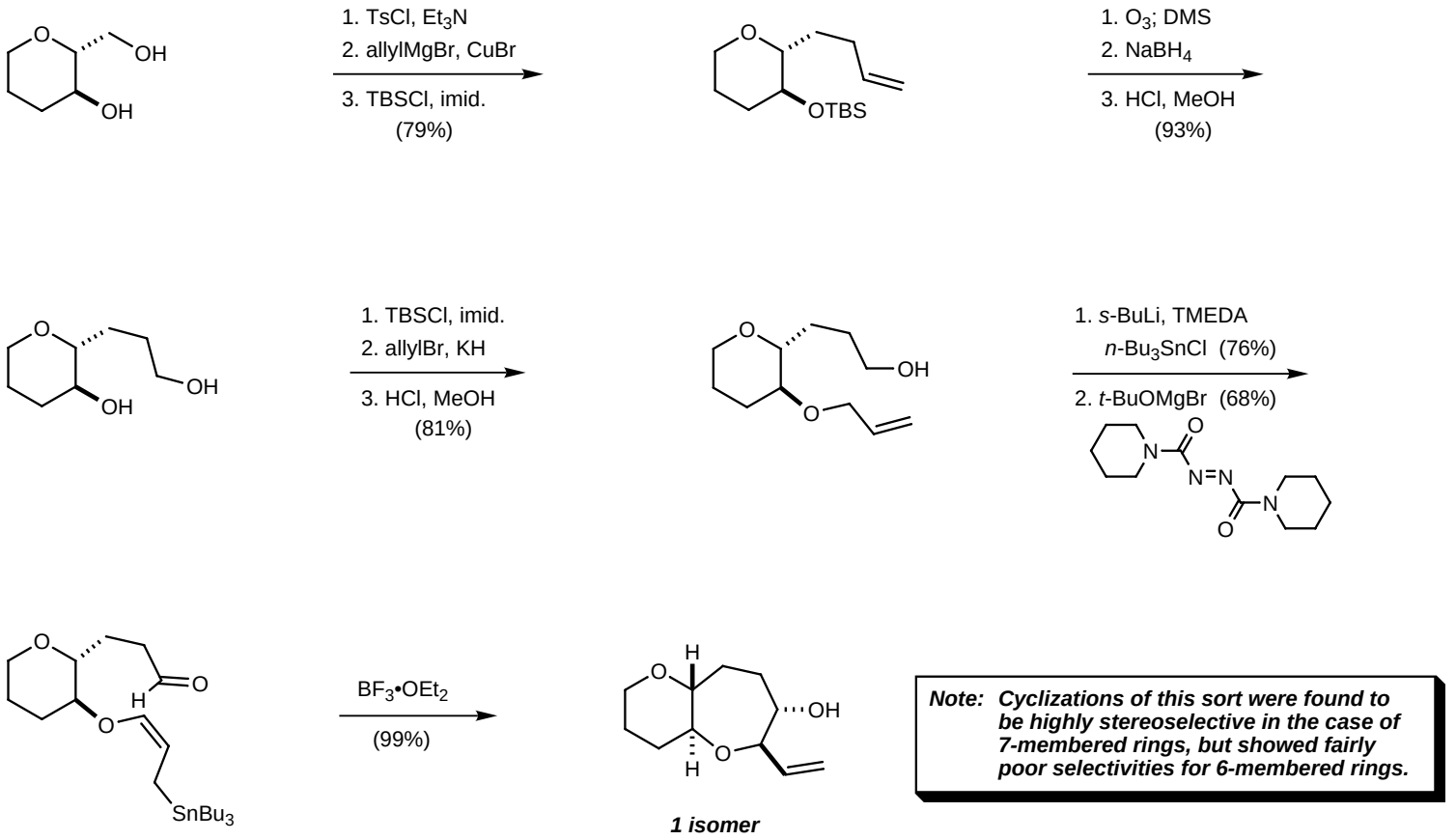
Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

Cross-Coupling of Enol Triflate:



Murai *Synlett* **1995**, 863.

Cyclization of ω-Tributylstannyl Ether Aldehydes

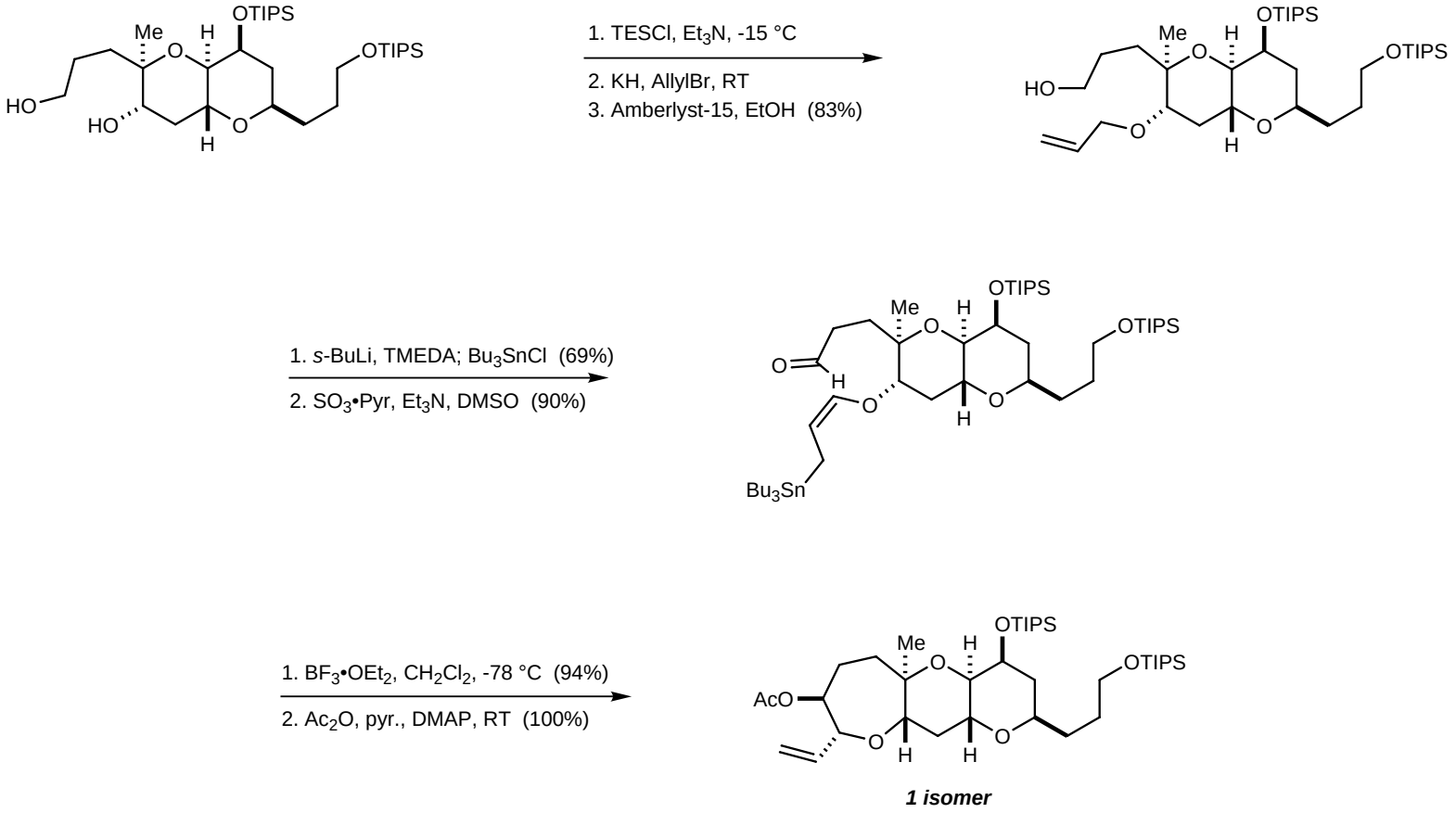


Note: ***Cyclizations of this sort were found to be highly stereoselective in the case of 7-membered rings, but showed fairly poor selectivities for 6-membered rings.***

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

Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

Allyl Tin Cyclization:

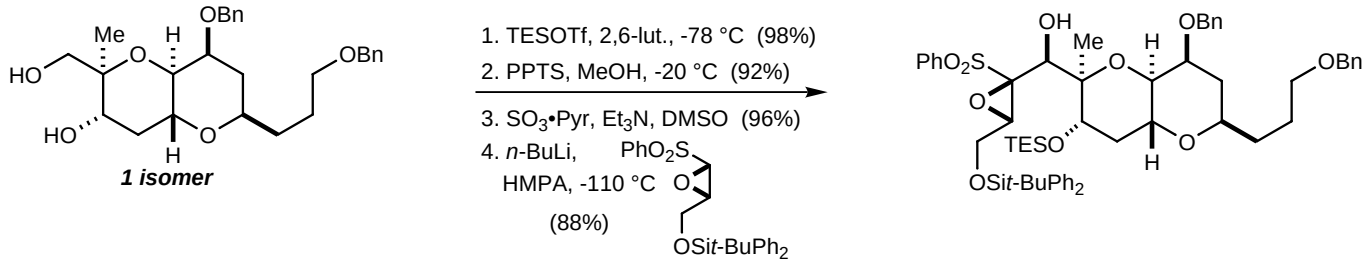


1 isomer

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

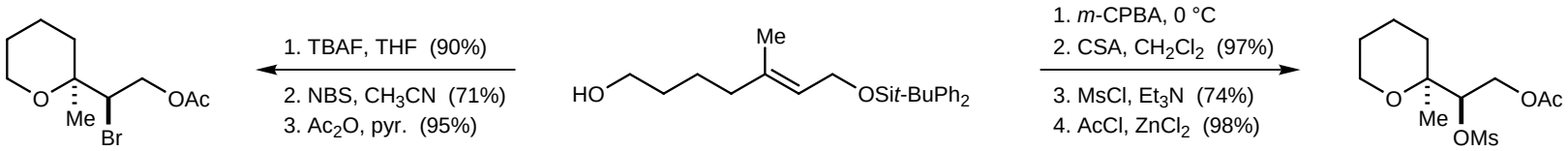
Approaches to the Synthesis of the C Ring of Hemibrevetoxin B

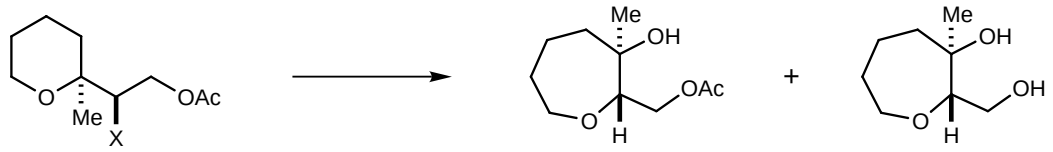
Oxiranyl Anion Alkylation
Followed by Ring Expansion:



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

Ring Expansion of Tetrahydropyrans





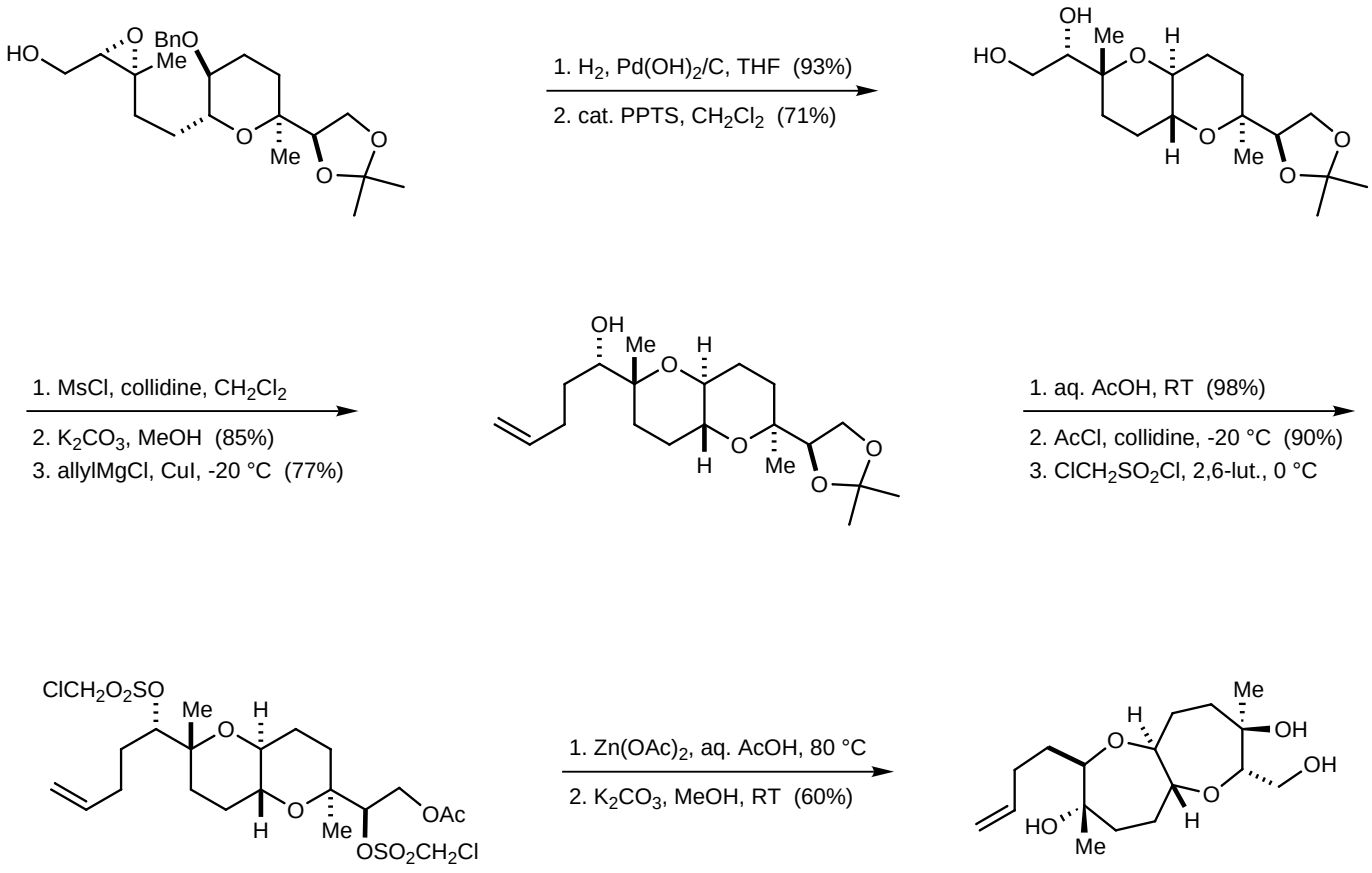
Note: ***In all cases a single stereoisomer was obtained.***

X	Reagent	% Yield	
OMs	Ag_2CO_3	17	0
OMs	AgOAc	47	37
OMs	$Zn(OAc)_2$	53	42
Br	Ag_2CO_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

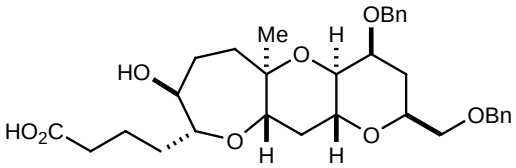
Double Ring Expansion:



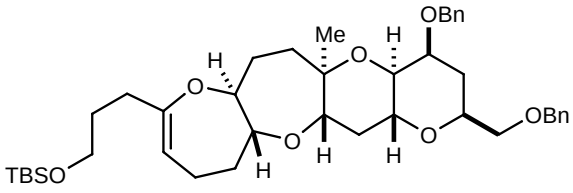
Nakata *Tet. Lett.* **1996**, *37*, 6365.

Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

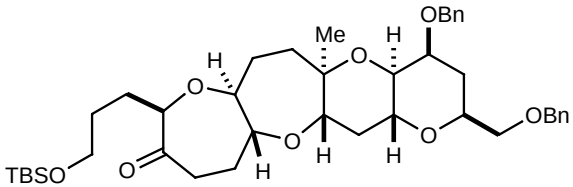
Cross-Coupling of Enol Triflate Followed by Hydroboration:



1. 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C; DMAP, PhH ↑↓ (80%)
2. LiHMDS, $PhNTf_2$, HMPA
3. $TBSO(CH_2)_3(2\text{-Th})(CN)CuLi_2$ (75%)



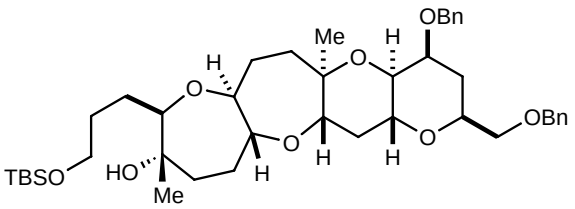
1. BH_3-THF, 0 °C; $NaOH\text{-}H_2O_2$ (94%)
2. Swern (90%)
3. cat. DBU, tol. ↑↓ (92%)



1 isomer

MeMgI, Et_2O (94%)

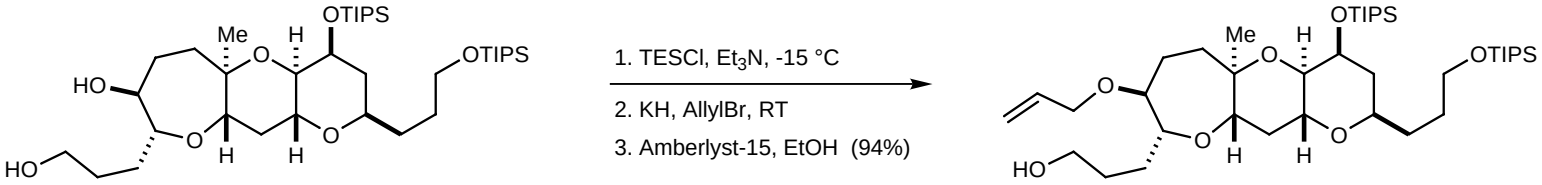
Diastereoselectivity = 3:2

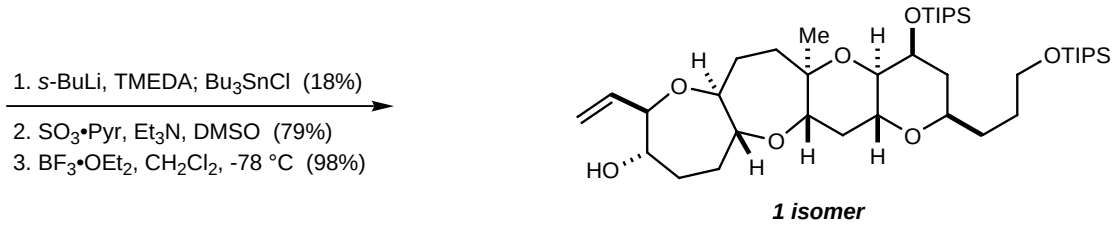


Nicolaou *J. Am. Chem. Soc.* **1993**, *115*, 3558.

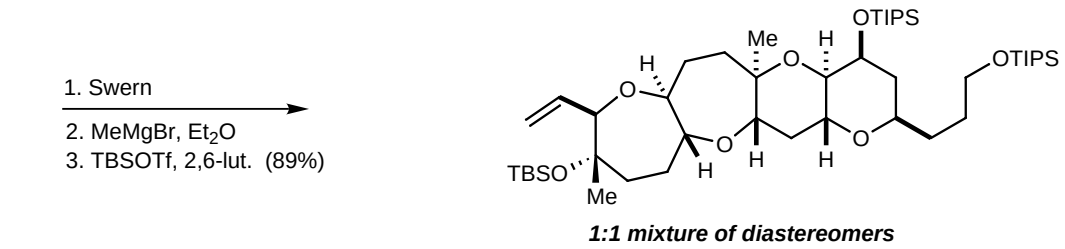
Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

Allyl Tin Cyclization:





1 isomer

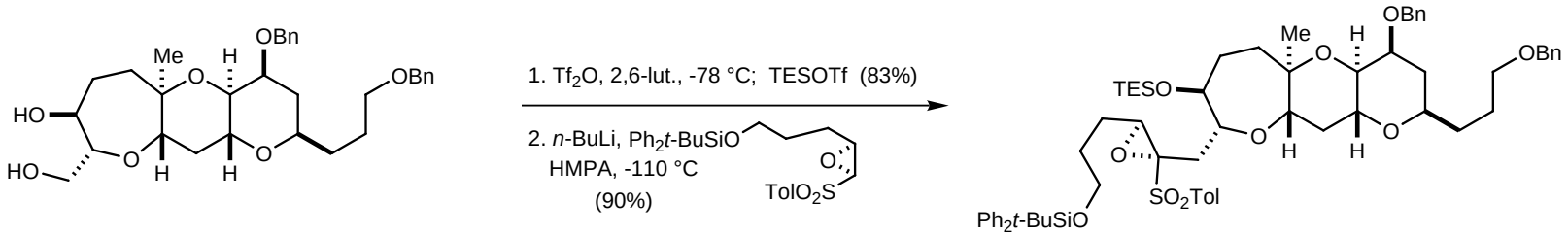


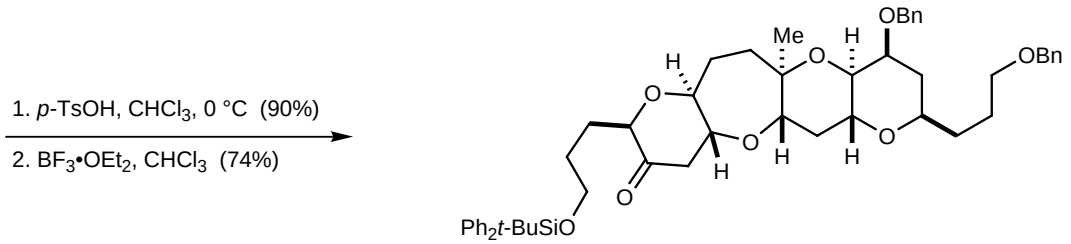
1:1 mixture of diastereomers

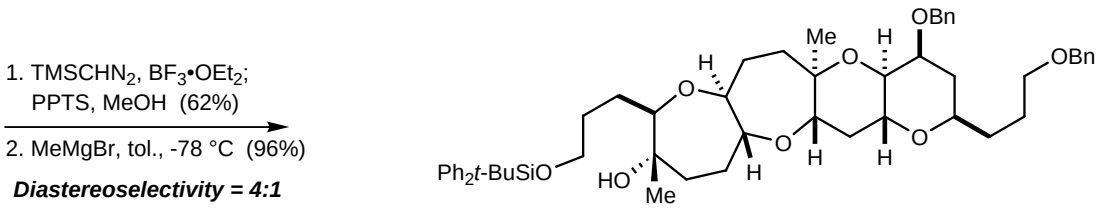
Yamamoto *Tet. Lett.* **1995**, *36*, 5777.

Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

Oxiranyl Anion Alkylation
Followed by Ring Expansion:



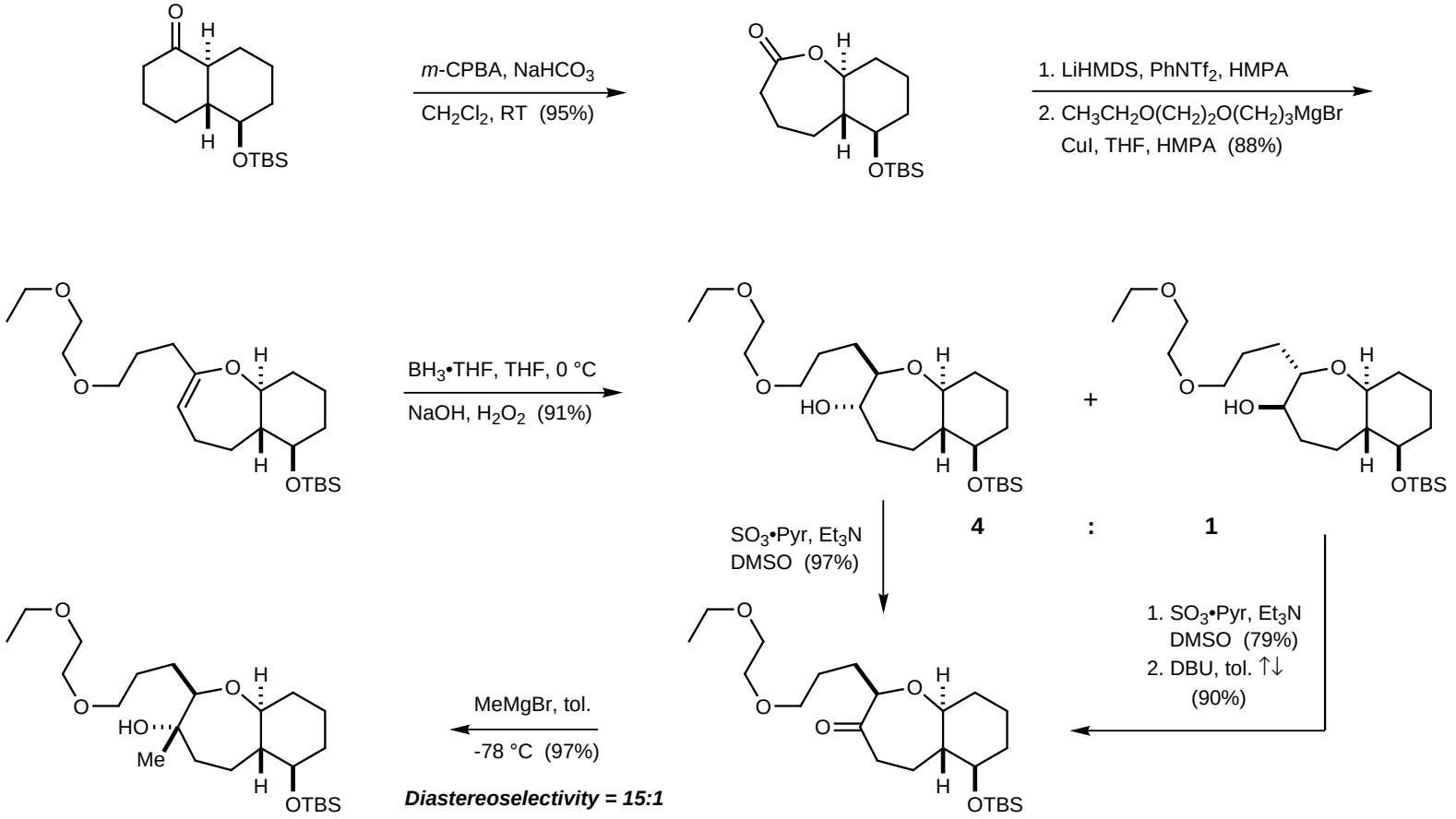




Mori *J. Am. Chem. Soc.* **1997**, *119*, 4557.

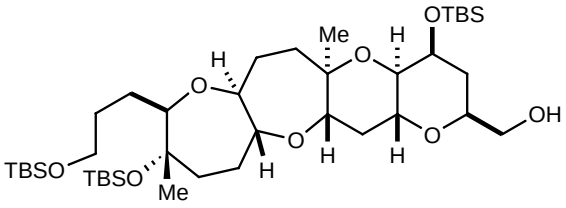
Approaches to the Synthesis of the D Ring of Hemibrevetoxin B

Cross-Coupling of Enol Triflate Followed by Hydroboration:

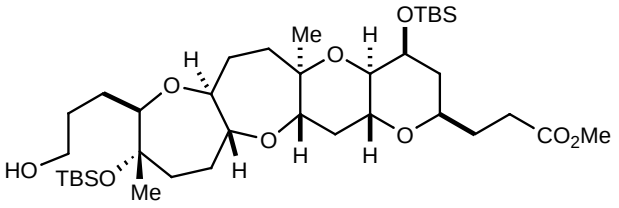


Murai *Synlett* **1995**, 863.

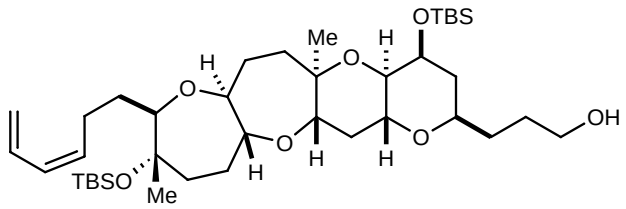
Completion of the Synthesis of Hemibrevetoxin B



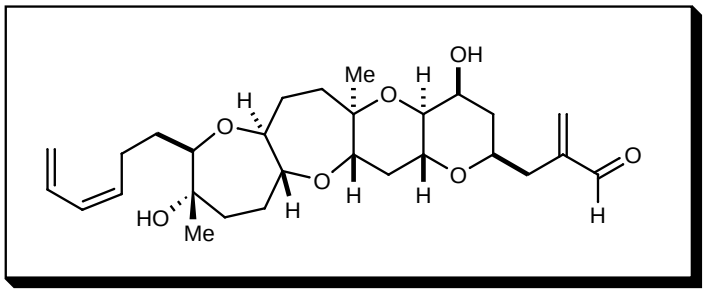
1. Swern
2. $Ph_3P{=}CHCO_2Me$, PhH (80%)
3. H_2, 5% Pd/C, EtOAc (95%)
4. cat. CSA, MeOH, 0 °C (86%)



1. Swern (90%)
2. $PhSe(CH_2)_3Ph_3P^+I^-$, *n*-BuLi (72%)
3. H_2O_2, $NaHCO_3$, THF (78%)
4. DIBAl, CH_2Cl_2, -78 °C (95%)



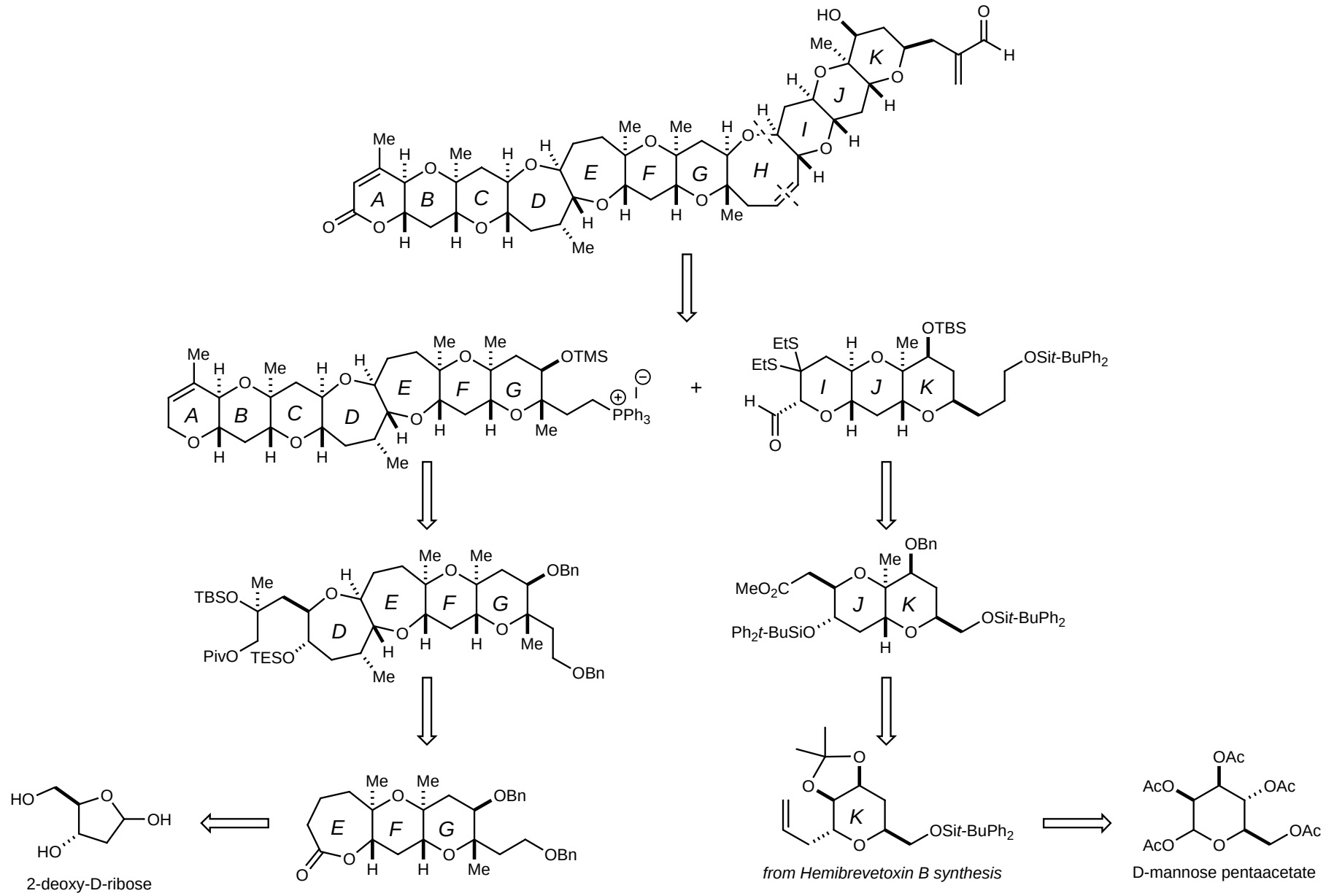
1. Swern
2. $Me_2(CH_2)N^+I^-$ (90%)
3. SiF_4, CH_3CN-CH_2Cl_2 (82%)



Hemibrevetoxin B

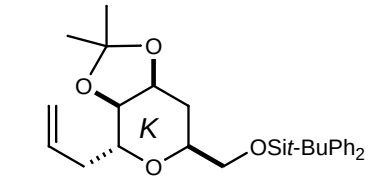
Nicolaou *J. Am. Chem. Soc.* **1993**, *115*, 3558.

Retrosynthetic Analysis of Brevetoxin B



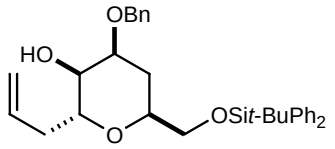
Nicolaou *J. Am. Chem. Soc.* **1995**, *117*, 10252.

Construction of the J Ring of Brevetoxin B



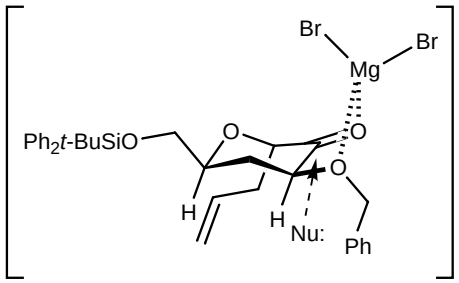
from Hemibrevetoxin B synthesis

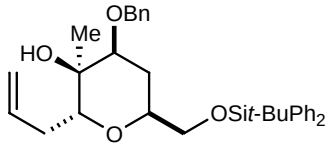
1. Amberlyst-15, MeOH, 60 °C (72%)
2. Bu_2SnO, MeOH; BnBr, CsF (74%)



1. Swern (100%)
2. $AlMe_3$, $MgBr_2$•OEt_2
   -50 °C (81%)

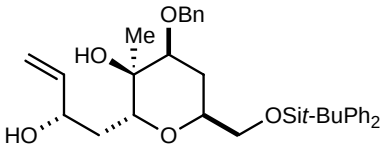
Diastereoselectivity = 3:1



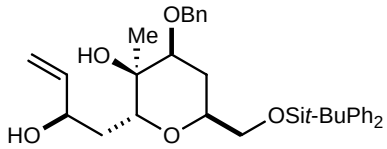


1. O_3; DMS, Ph_3P
2. CH_2=$CHMgBr$, 0 °C (89%)

Diastereoselectivity = 1:1

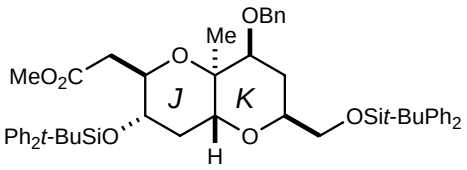


+



1. *t*-$BuPh_2SiCl$, imid., DMF (88%)
2. O_3; DMS, Ph_3P
3. Ph_3P=$CHCO_2Me$, PhH, RT (89%)
4. NaH, THF, RT (92%)

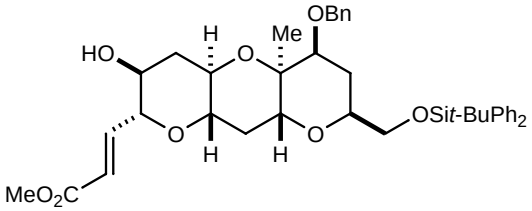
1. TMS- imid., CH_2Cl_2, 0 °C (85%)
2. O_3; DMS, Ph_3P
3. Ph_3P=$CHCO_2Me$, PhH, RT (85%)
4. NaH, THF, RT (72%)
5. Jones oxidation (69%)
6. $NaBH_4$, MeOH, 0 °C (85%)
7. *t*-$BuPh_2SiCl$, imid., DMF (89%)



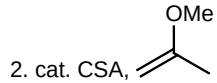
1 isomer

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

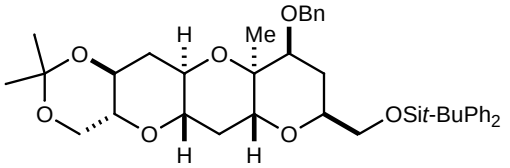
Refunctionalization of the IJK Fragment of Brevetoxin B



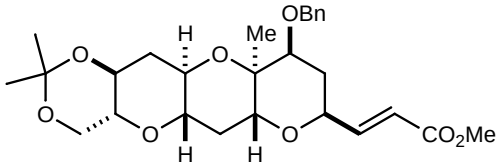
1. O_3; Ph_3P; $NaBH_4$ (95%)



2. cat. CSA, (89%)

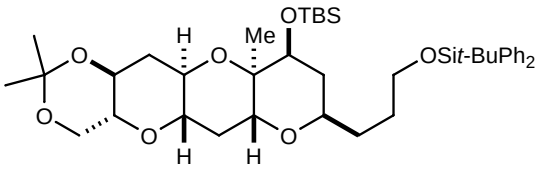


1. TBAF, THF, RT (97%)
2. Swern (100%)
3. $Ph_3P{=}CHCO_2Me$, PhH, RT (96%)

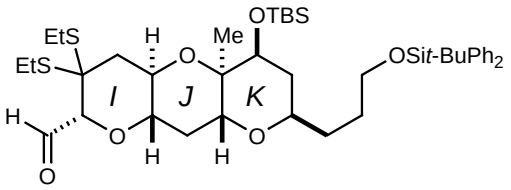


***E:Z* = 4:1**

1. H_2, $Pd(OH)_2$, EtOAc, RT (100%)
2. LAH, THF, 0 °C (92%)
3. *t*-$BuPh_2SiCl$, DMAP, CH_2Cl_2 (93%)
4. TBSOTf, 2,6-lut., 0 °C (100%)

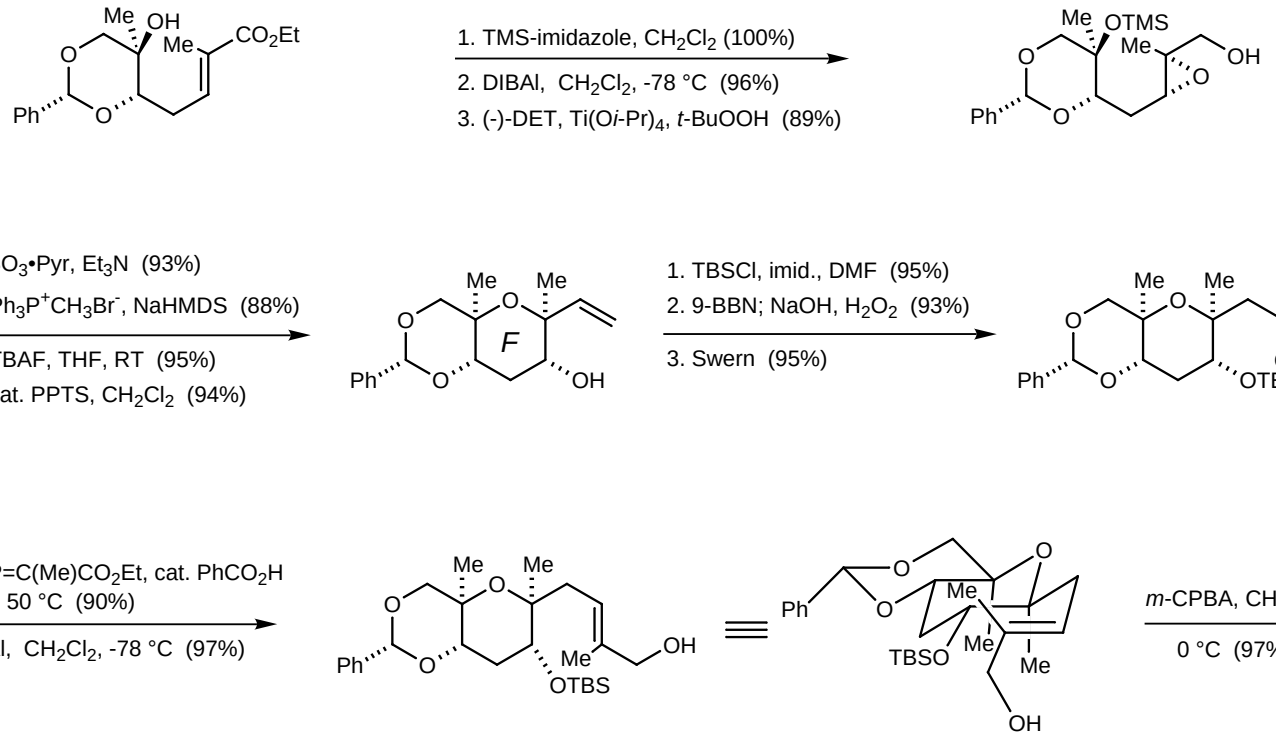


1. cat. CSA, CH_2Cl_2/MeOH, 0 °C (87%)
2. TBSCl, imid., DMF (94%)
3. TPAP, NMO (96%)
4. EtSH, $Zn(OTf)_2$; cat. CSA, MeOH (74%)
5. Swern (92%)

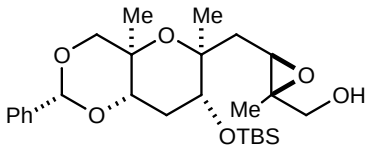


Nicolaou *J. Am. Chem. Soc.* **1989**, *111*, 6682.

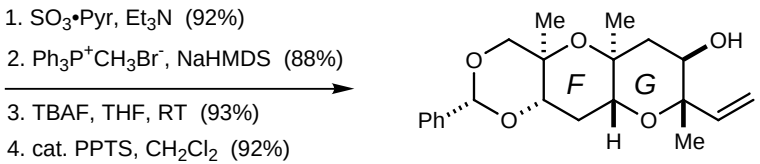
Construction of the F & G Rings of Brevetoxin B



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

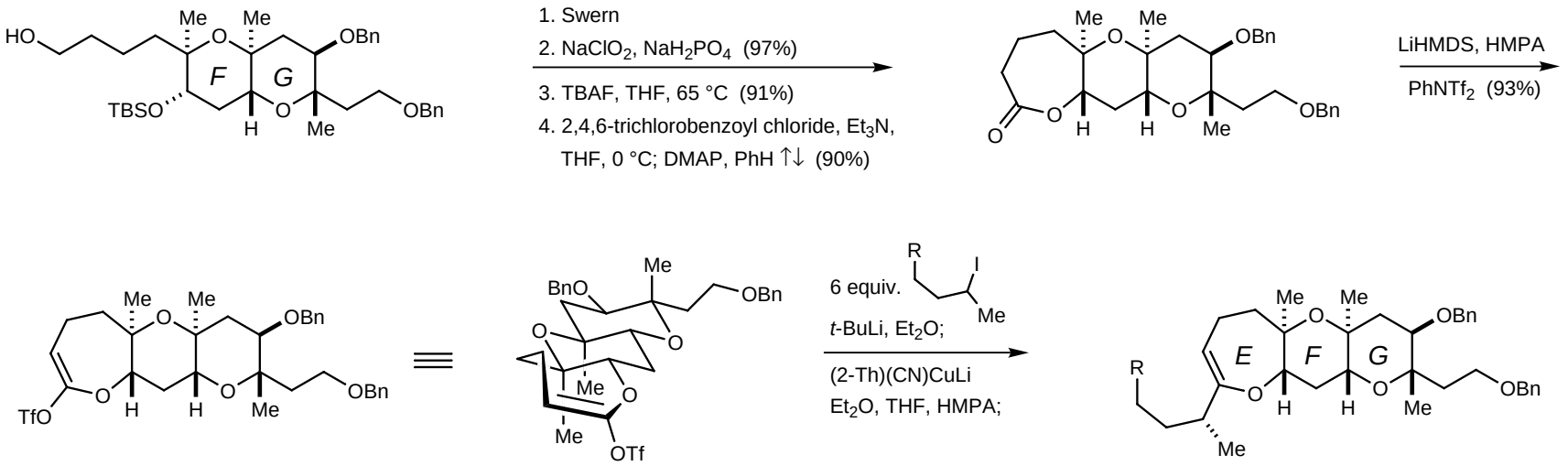


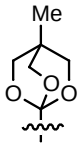
1 isomer

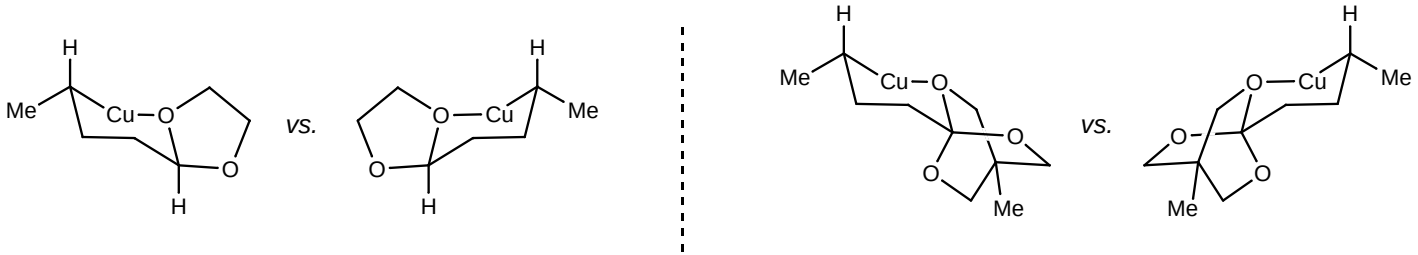


Nicolaou *Tet.* **1990**, *46*, 4517.

Construction of the EFG Fragment of Brevetoxin B

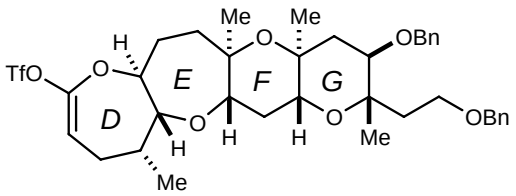


R	Ratio (Desired : Undesired)	Yield
CH_2OTBS	1 : 1.4	50%
	1 : 1.5	49%
	2.4 : 1	85%

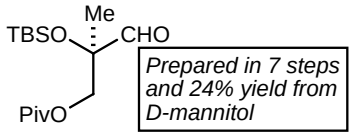


Nicolaou *J. Am. Chem. Soc.* **1995**, *117*, 10239.

Construction of the C-G Fragment of Brevetoxin B



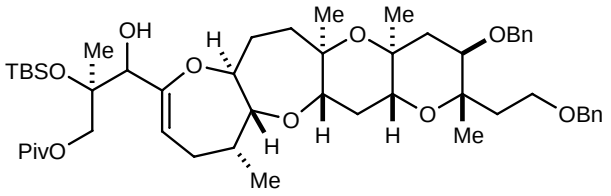
cat. $NiCl_2$, $CrCl_2$, DMF, ultrasound



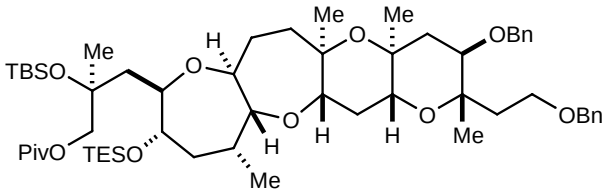
Prepared in 7 steps and 24% yield from D-mannitol

(66%)

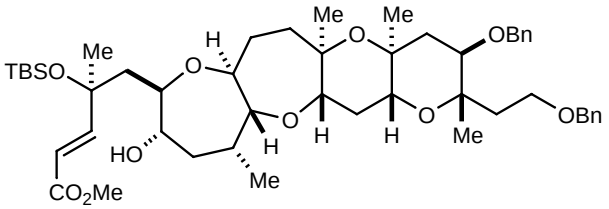
Diastereoselectivity = 5:1



1. KH, CS_2; MeI (89%)
2. cat. AIBN, *n*-Bu_3SnH (67%)
3. BH_3•THF; NaOH, H_2O_2 (82%)
4. TESOTf, 2,6-lut., -70 °C (96%)

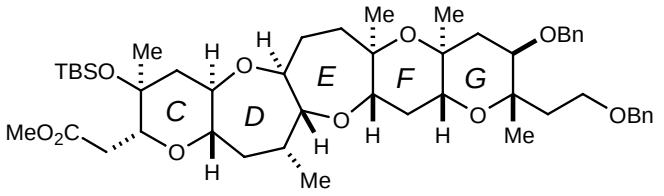


1. DIBAl, CH_2Cl_2, -78 °C (98%)
2. Dess-Martin periodinane (85%)
3. $(MeO)_2P(O)CH_2CO_2Me$, KHMDS (99%)
4. cat. CSA, MeOH, RT (100%)



KH, THF, RT

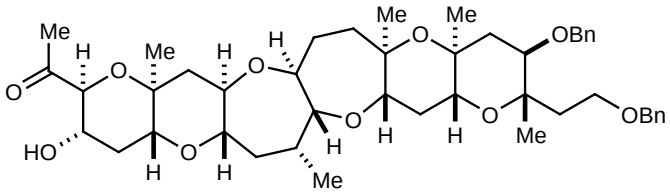
(90%)



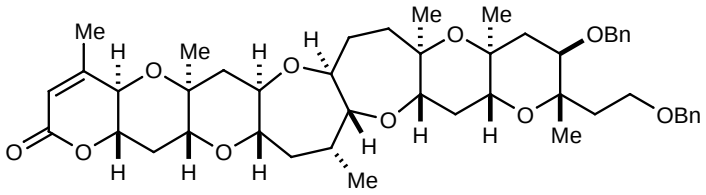
1 isomer

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

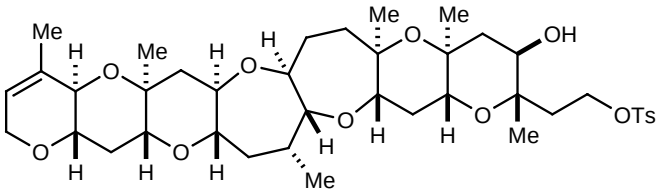
Construction of the A-G Fragment of Brevetoxin B



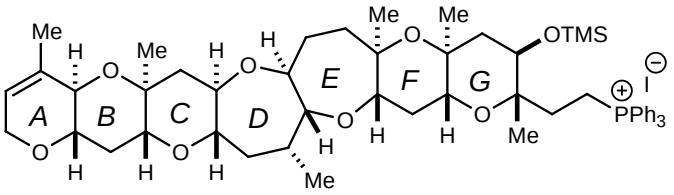
1. $BrCH_2COCl$, pyr. (81%)
2. $(MeO)_3P$, 90 °C
3. *i*-Pr_2NEt, LiCl, RT (89%)



1. DIBAl, CH_2Cl_2, -78 °C
2. BF_3•OEt_2, Et_3SiH, -10 °C (93%)
3. Li, liq. NH_3 (92%)
4. TsCl, pyr. (79%)

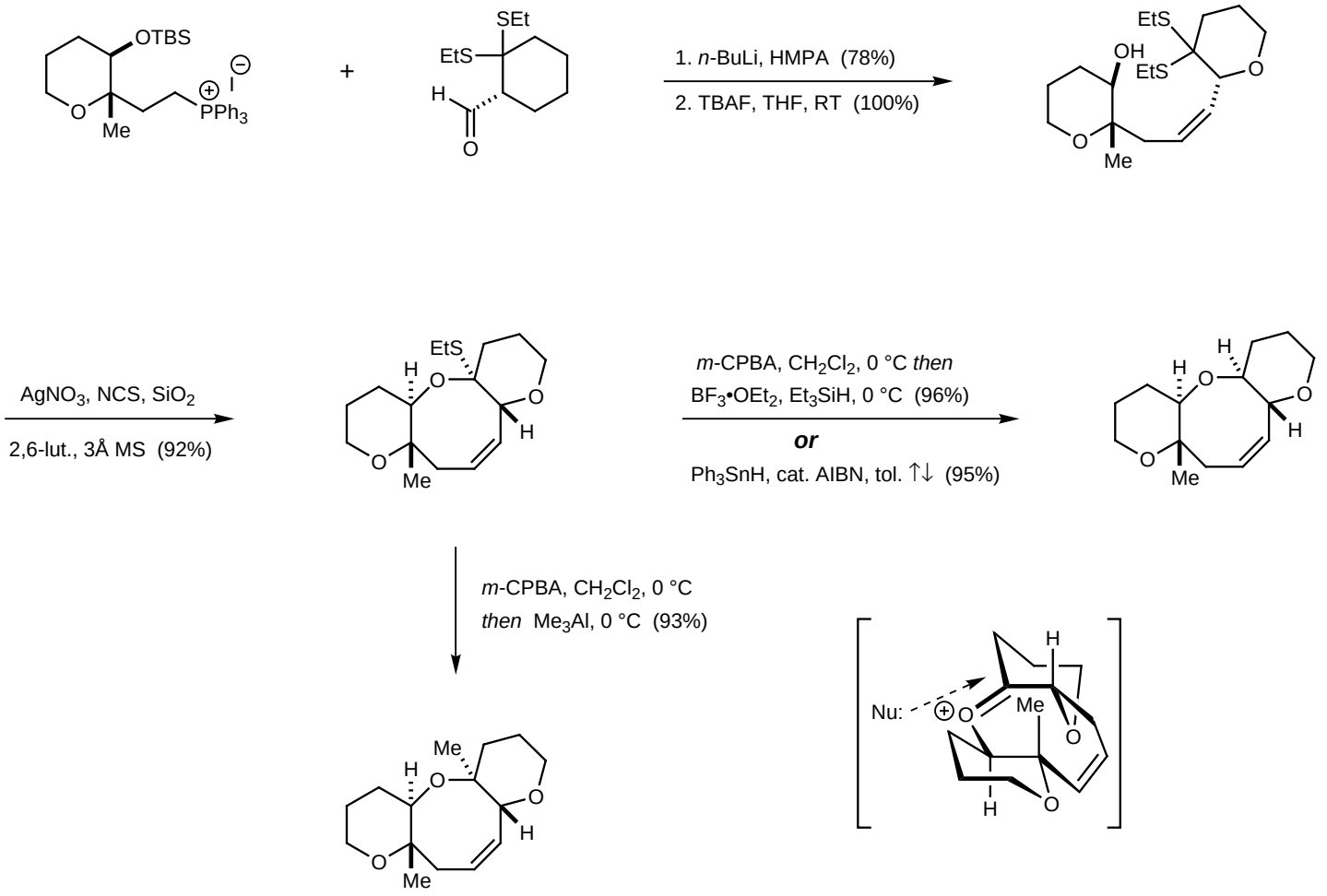


1. NaI, acetone, 60 °C
2. TMS-imidazole (96%)
3. PPh_3, CH_3CN ↑↓ (99%)



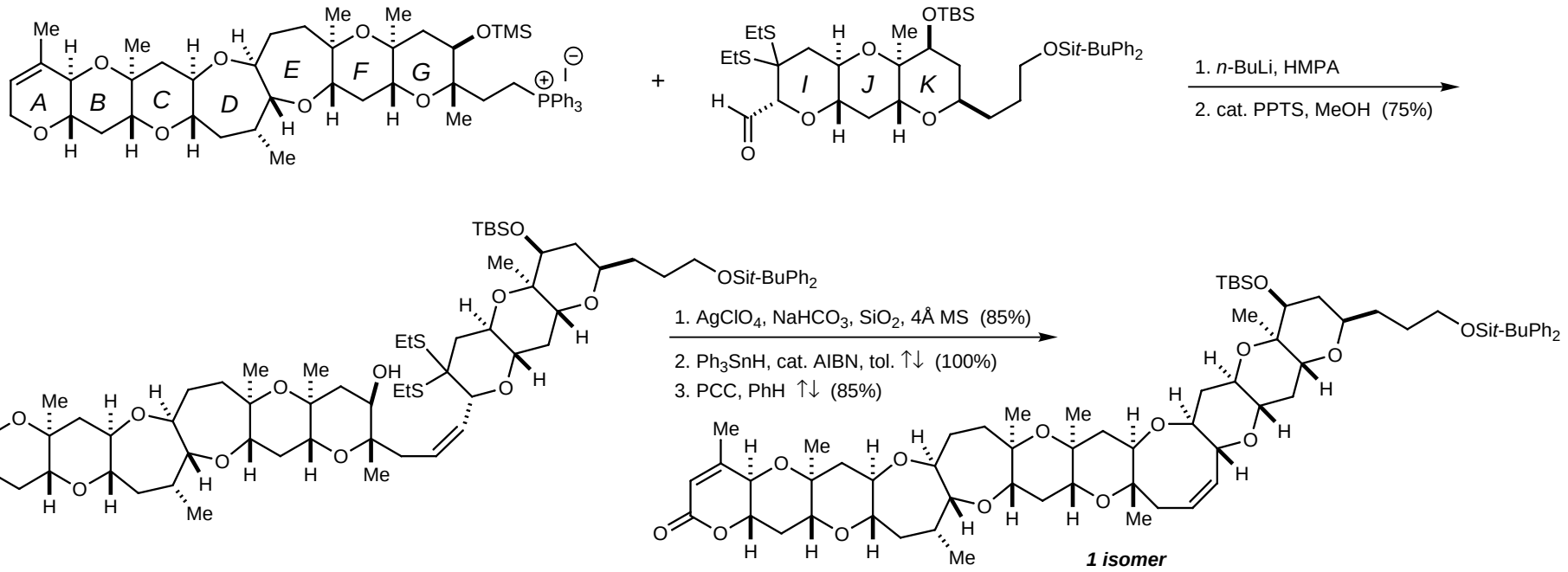
Nicolaou *J. Am. Chem. Soc.* **1995**, *117*, 10252.

Cyclization of Hydroxy Dithioketals

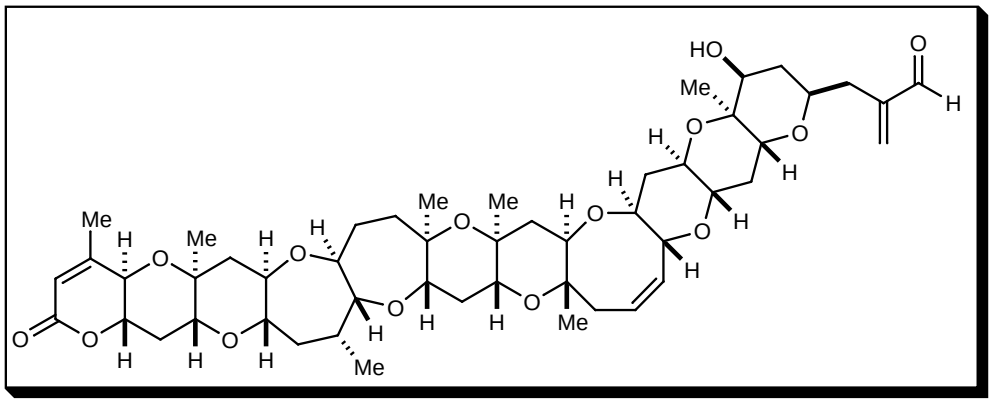


Nicolaou *J. Am. Chem. Soc.* **1989**, *111*, 5321.

Completion of the Synthesis of Brevetoxin B



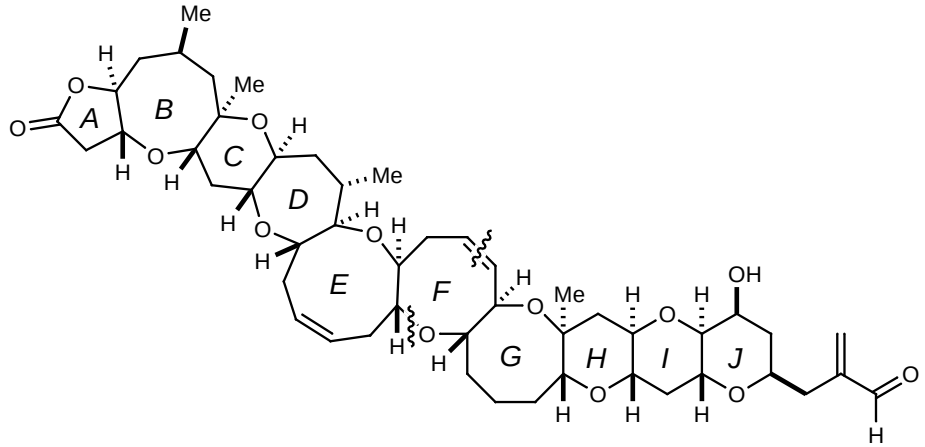
1. TBAF, THF, RT (69%)
2. Dess-Martin (100%)
3. $Me_2(CH_2)N^+I^-$, Et_3N (83%)
4. HF•pyr., CH_2Cl_2, 0 °C (91%)

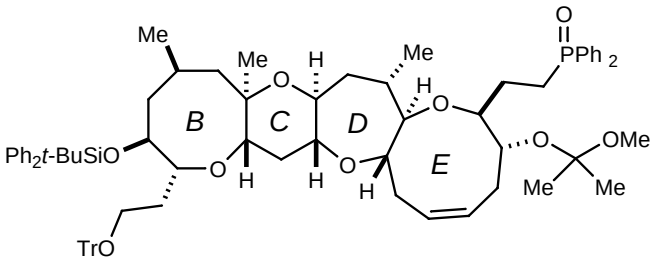


Brevetoxin B

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

Retrosynthetic Analysis of Brevetoxin A





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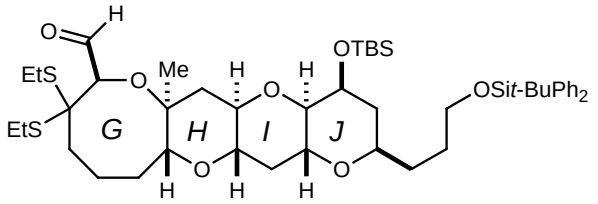
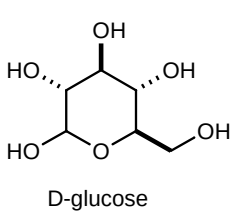
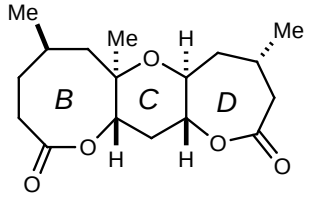
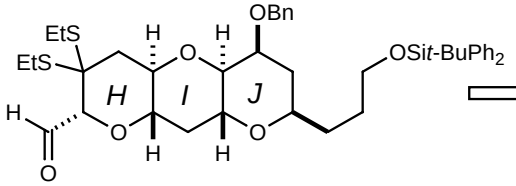
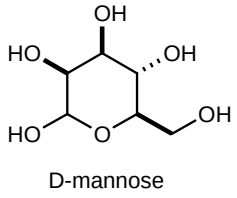




D-glucose



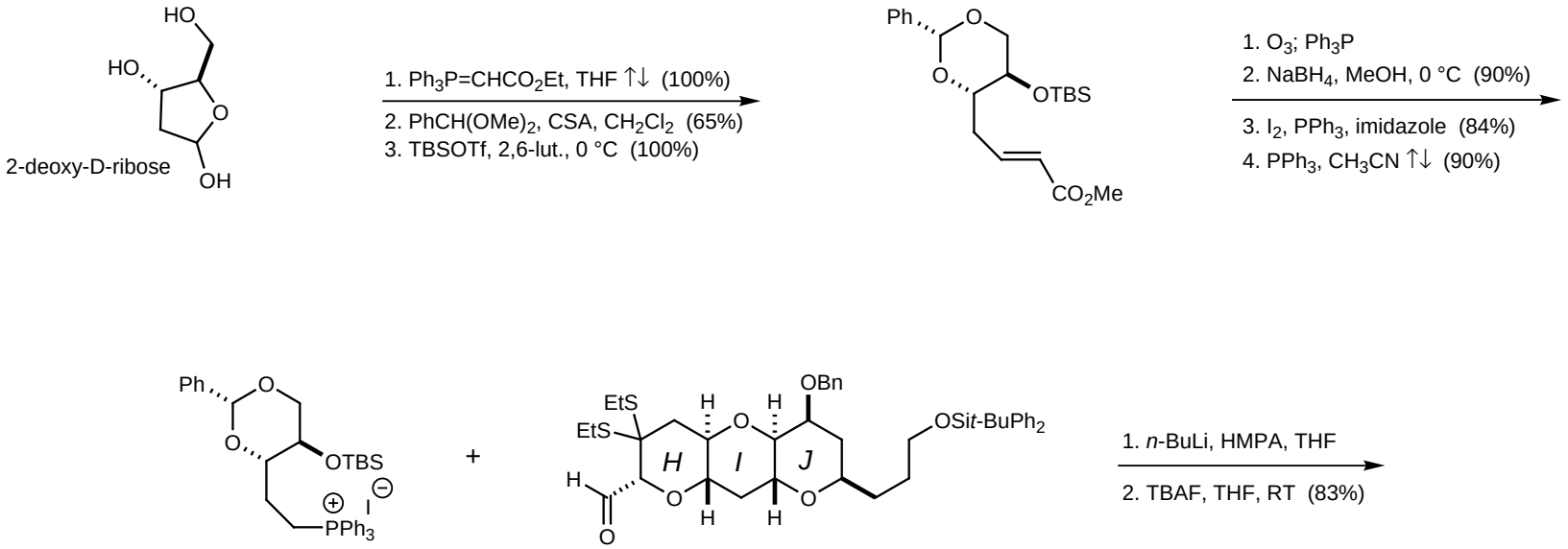


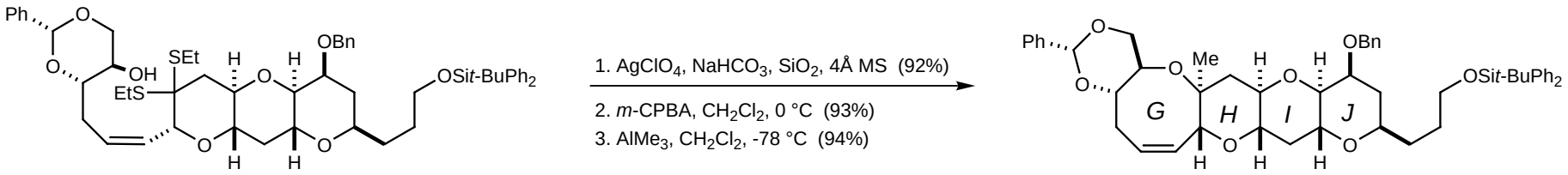


D-mannose

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

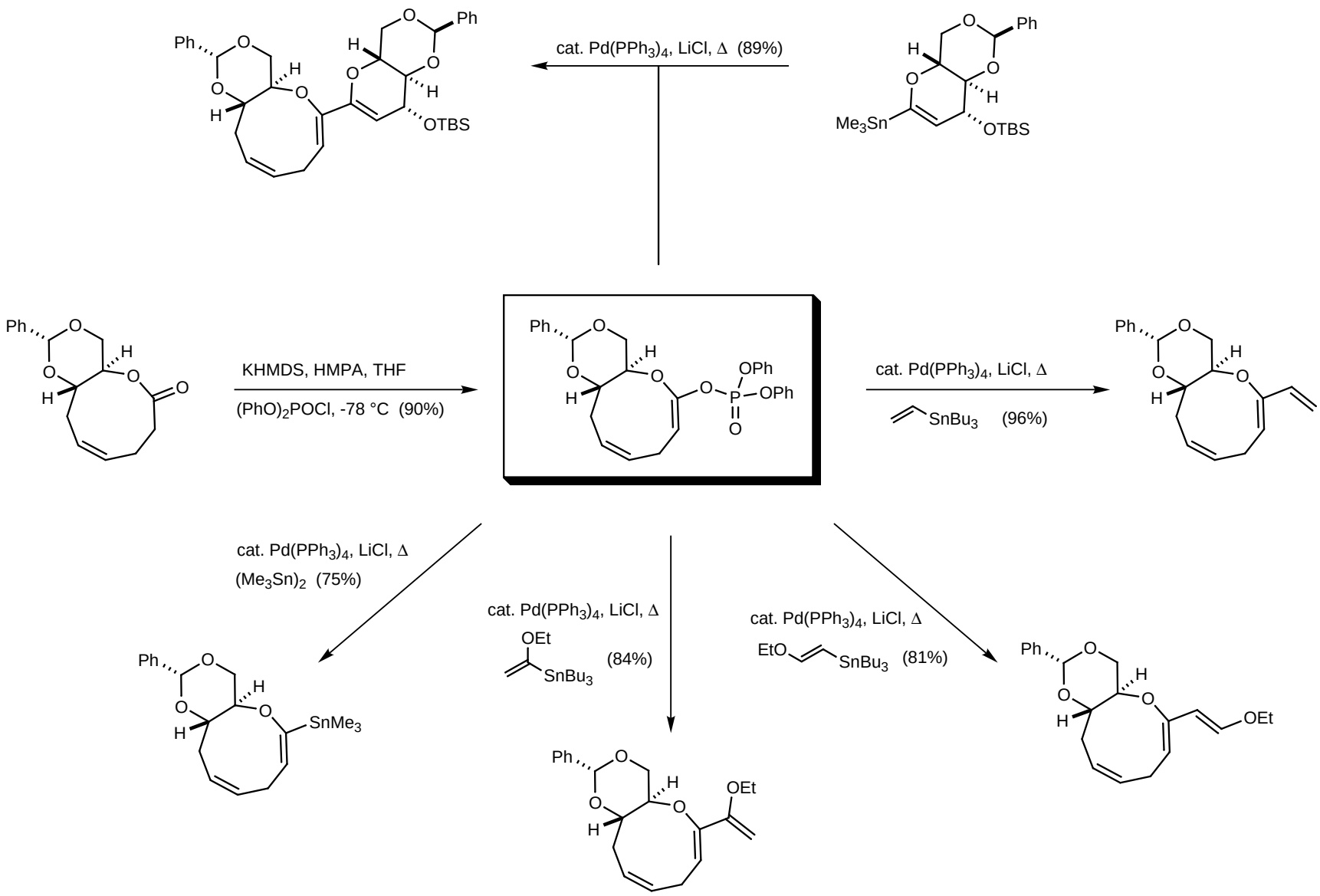
Construction of the G Ring of Brevetoxin A





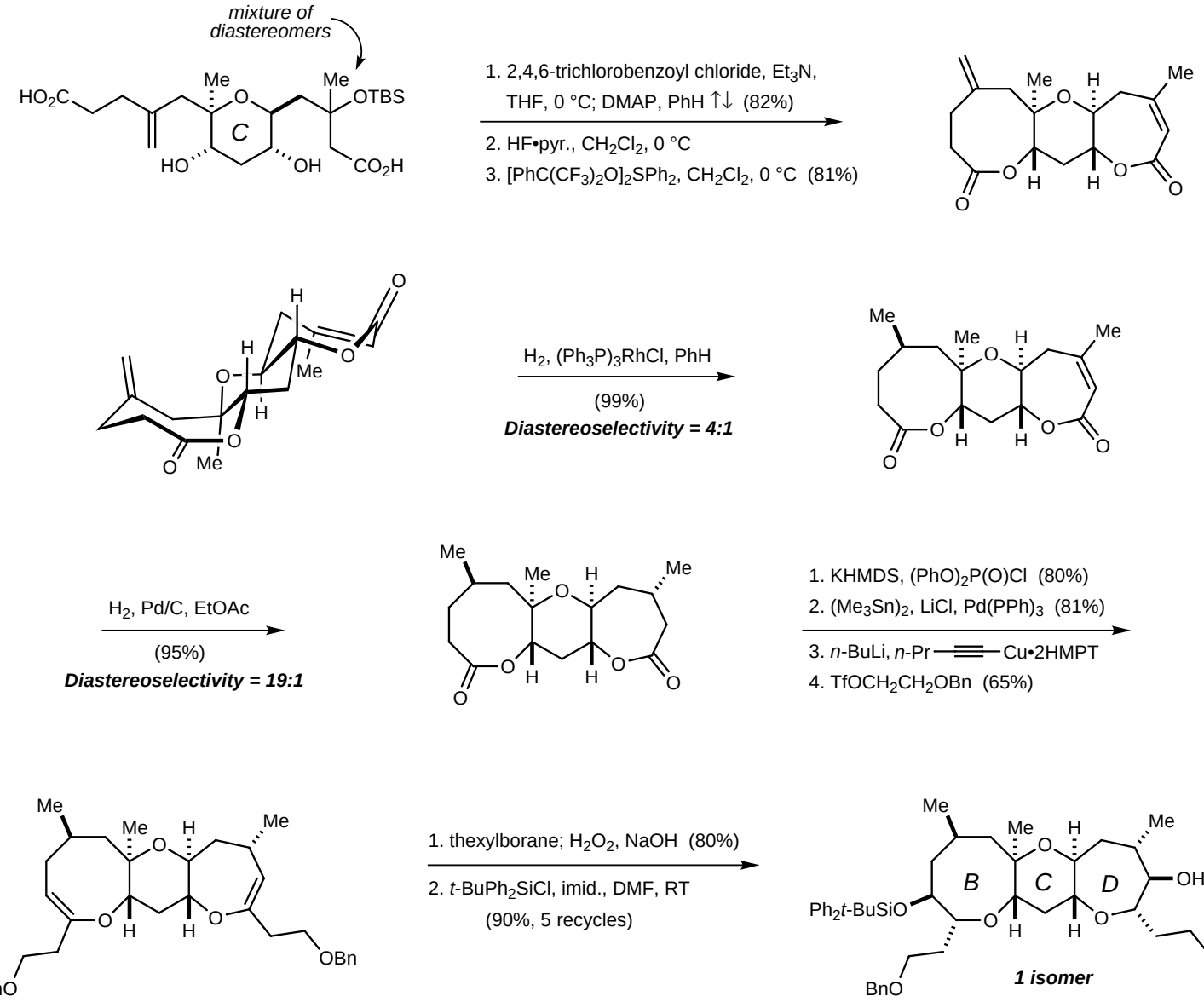
Nicolaou *Nature* **1998**, *392*, 264.

Cross-Coupling of Cyclic Ketene Acetal Phosphates



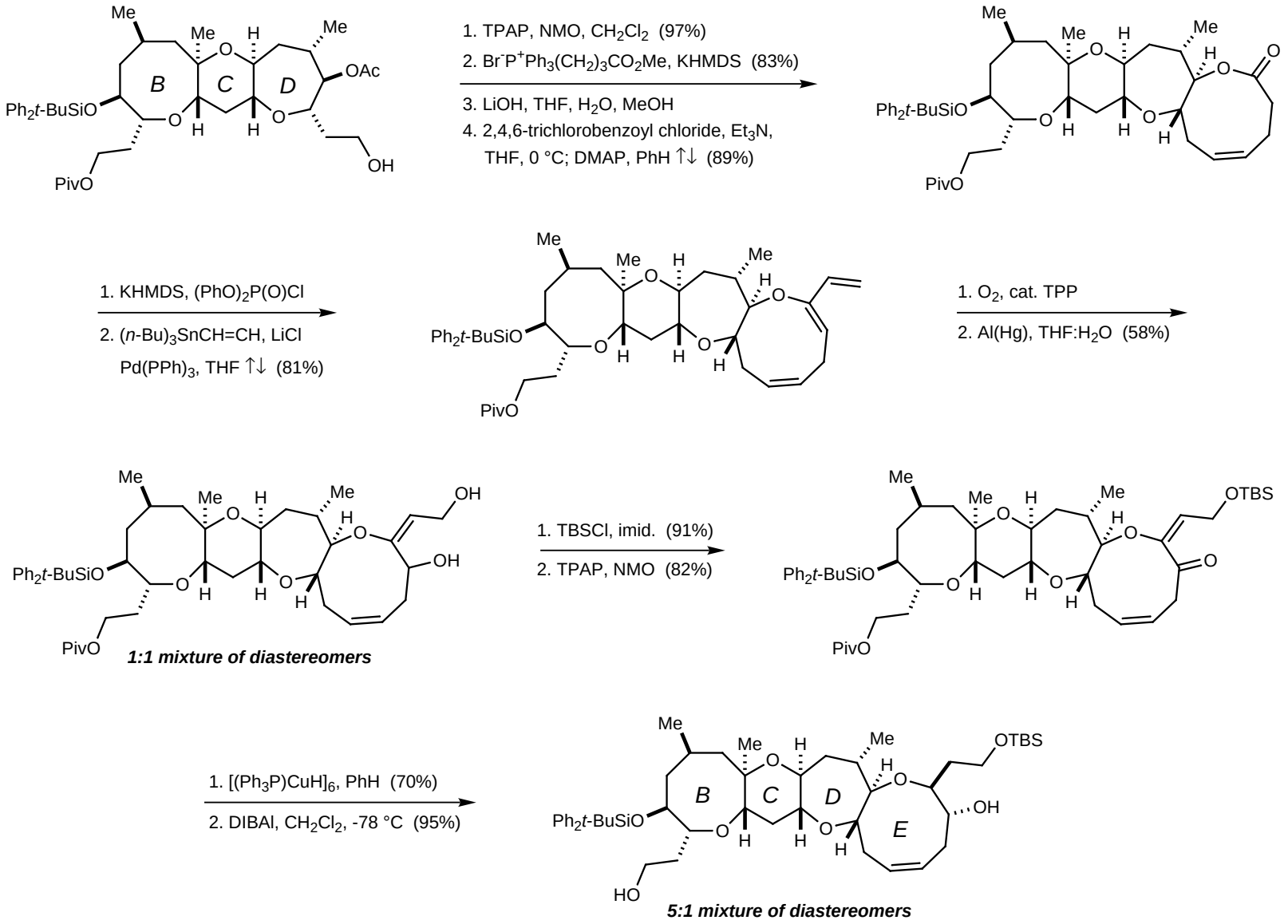
Nicolaou *J. Am. Chem. Soc.* **1997**, *119*, 5467.

Construction of the BCD Fragment of Brevetoxin A



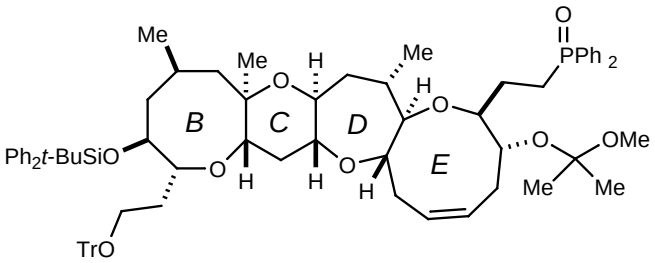
Nicolaou *Nature* **1998**, *392*, 264.

Construction of the E Ring of Brevetoxin A



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

Construction of the B-J Fragment of Brevetoxin A



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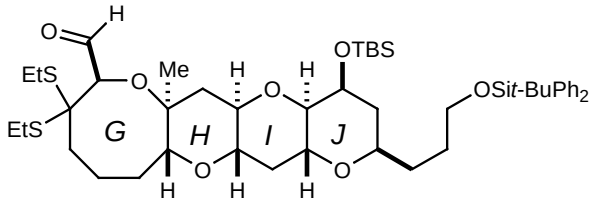
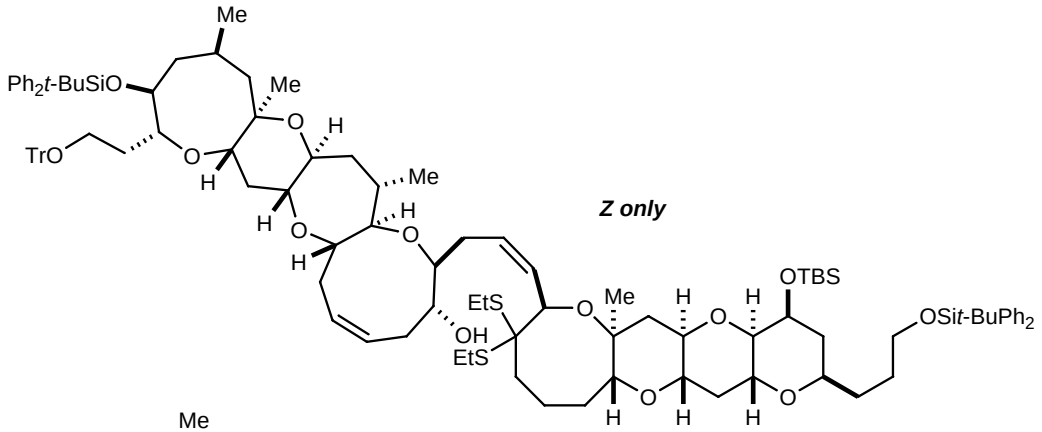
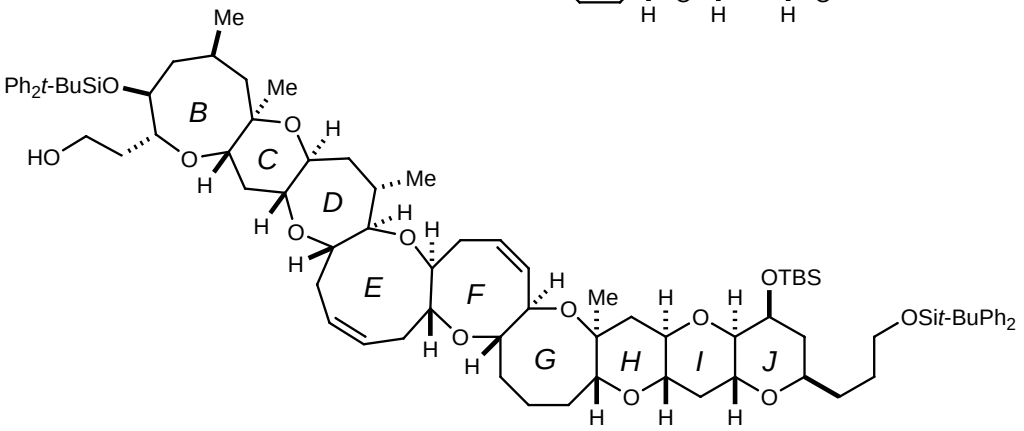


1. *n*-BuLi, -78 °C (75%)
2. KH, DMF
3. AcOH, THF (72%)

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.***

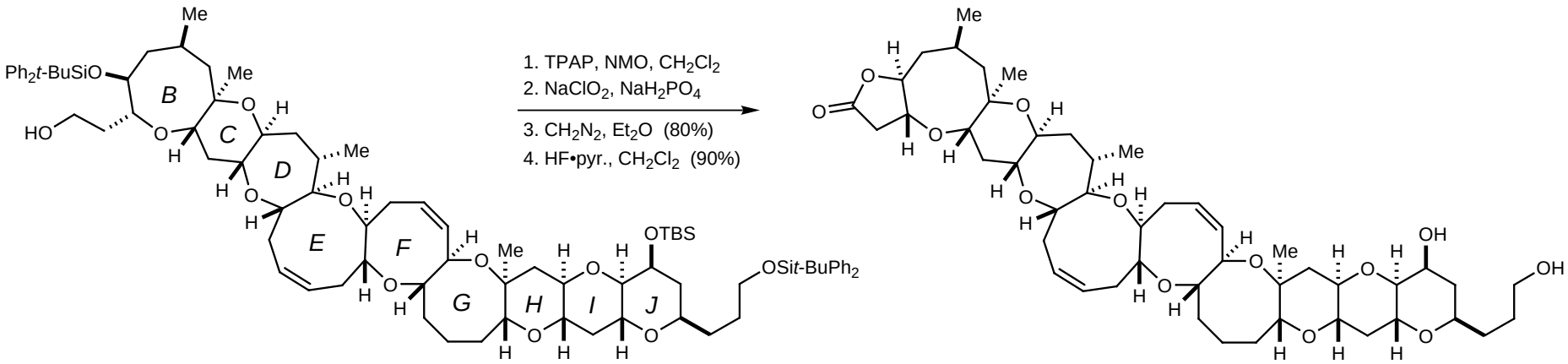


1. $AgClO_4$, $NaHCO_3$, SiO_2, 4Å MS (80%)
2. *m*-CPBA, CH_2Cl_2, 0 °C (85%)
3. BF_3•OEt_2, Et_3SiH, -78 °C (94%)

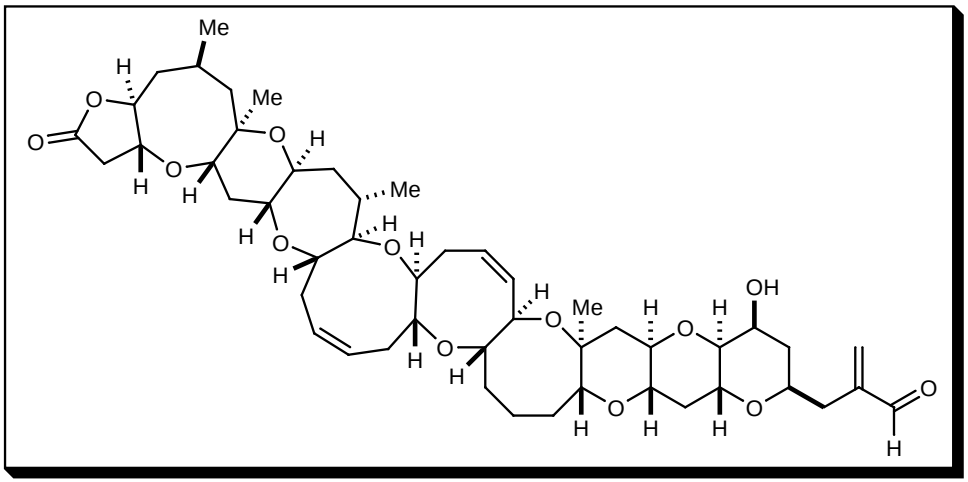


Nicolaou *Nature* **1998**, *392*, 264.

Completion of the Synthesis of Brevetoxin A



1. Dess-Martin (80%)
2. $Me_2(CH_2)N^+I^-$, Et_3N (90%)



Brevetoxin A

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

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%