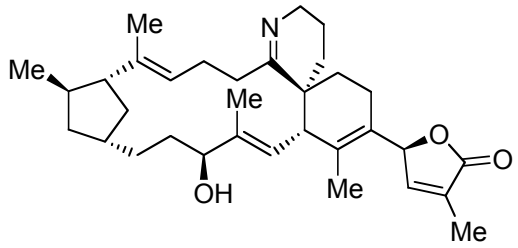
Enantioselective Total Synthesis of the Marine Toxin (–)-Gymnodimine Employing a Barbier-Type Macrocyclization

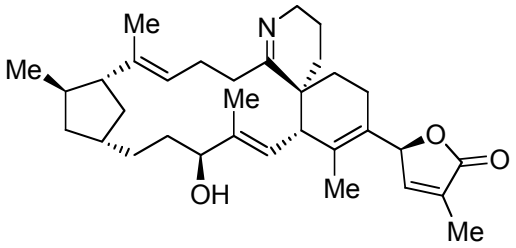
Angew. Chem. Int. Ed. **2009**, 48, 1–5



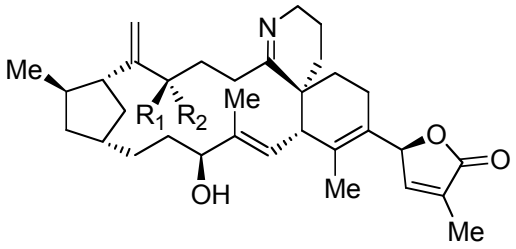
Current Literature Presentation
12SEP2009
Michael Yang

Gymnodimine Background

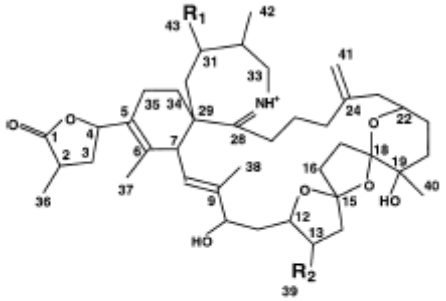
- Isolated from dinoflagelate *Karenia selliformis*
- Sensitize neurons to the effects of Okadaic acid
- Binds to muscle nicotinic acetylcholine receptors
- Causes neurotoxic shellfish poisoning
- Spiroimine toxins: gymnodimine analogues B and C, pinnatoxins, spirolides, pteriatoxins, prorocentrolide,



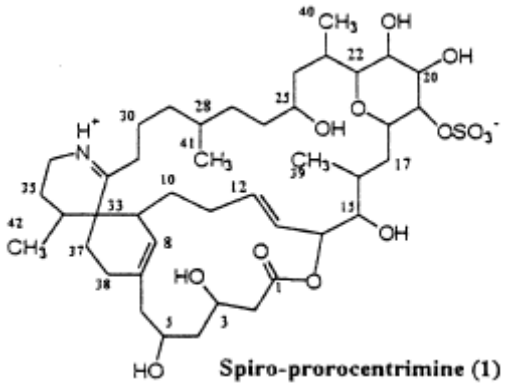
Gymnodimine A



Gymnodimine B: R_1 = H, R_2 = OH
Gymnodimine C: R_1 = OH, R_2 = H

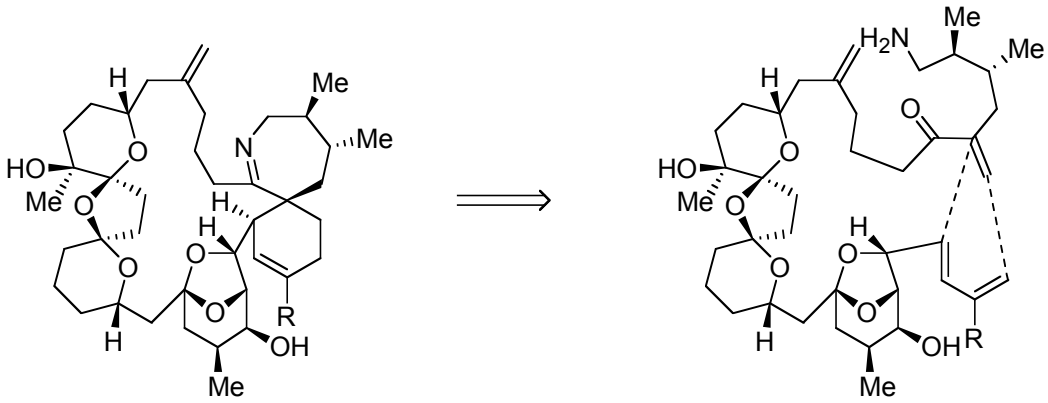


	Spirolide		R_1	R_2
1	A	$\Delta^{2,3}$	H	CH_3
2	B		H	CH_3
3	C	$\Delta^{2,3}$	CH_3	CH_3
4	D		CH_3	CH_3
5	13-desMe C	$\Delta^{2,3}$	CH_3	H



Spiro-prorocentrimine (1)

Formation of Spirocyclic Imines – The Diels-Alder Strategy - Kishi



Pinnatoxins

A: CO_2H

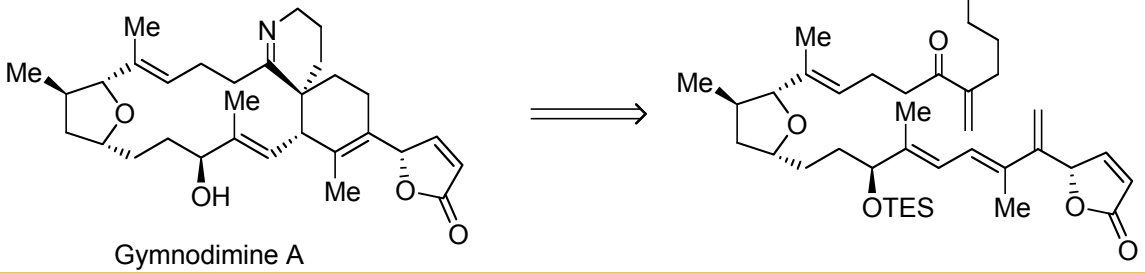
B: H_2N CO_2H

C: O CO_2H

Pteriatoxins

A: S OH NH_2 CO_2H

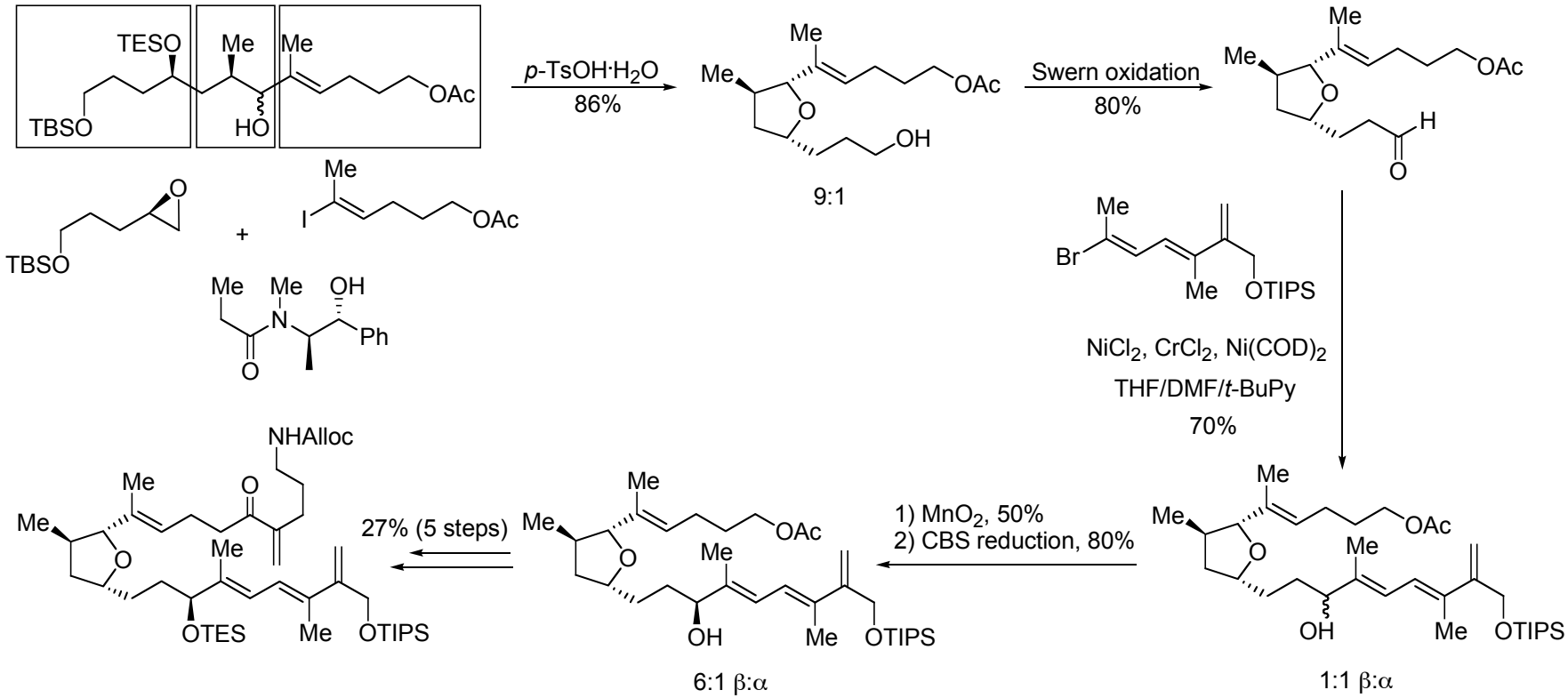
B/C: H_2N OH OH S



Gymnodimine A

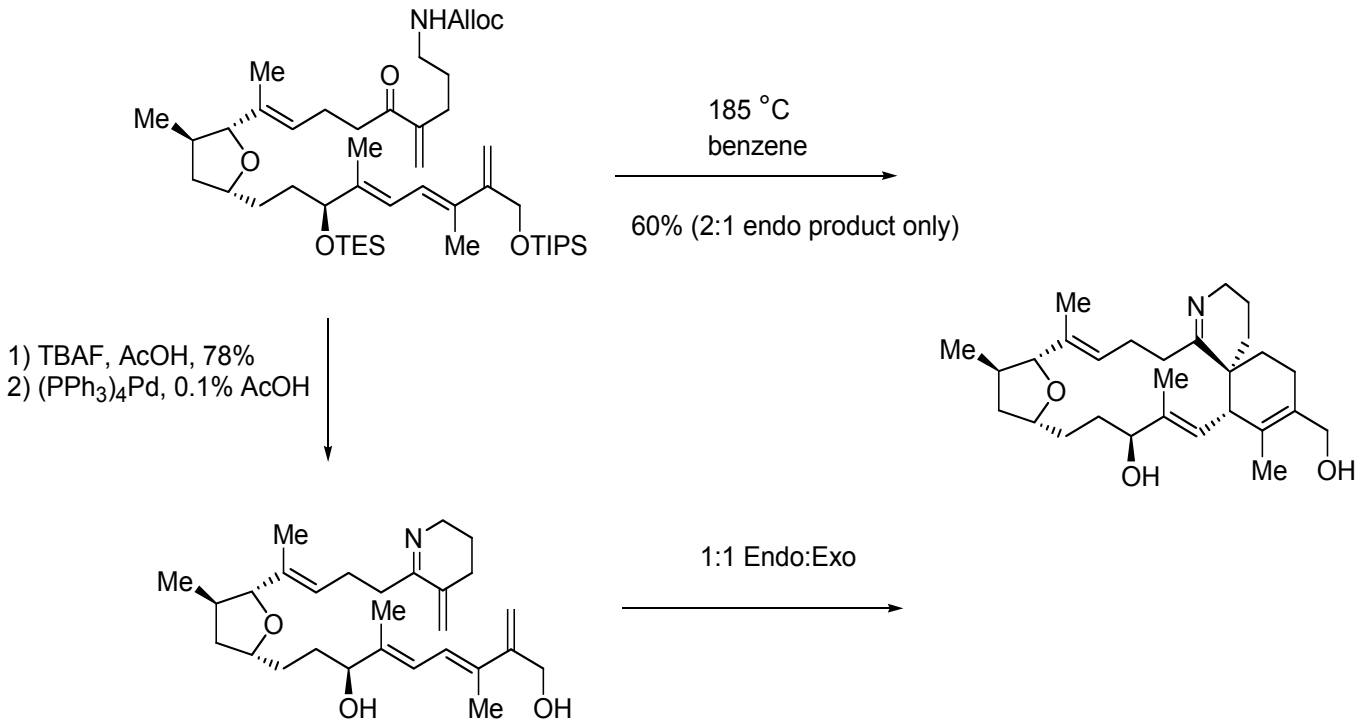
McCauley, J. A.; Nagasawa, N.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647-7648.
Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, 3997-4000.

Synthesis of Diels Alder Precursor – Kishi



Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, 3997-4000.

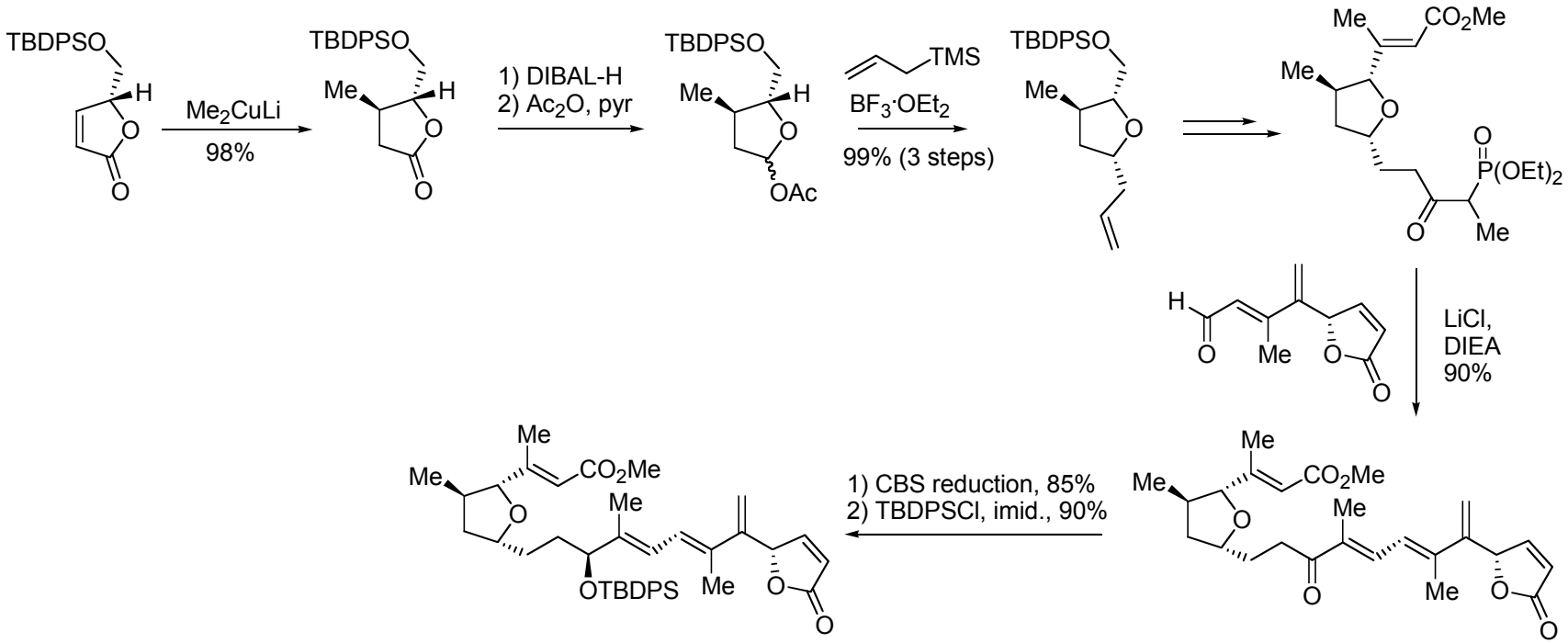
Gymnodimine – Diels Alder Strategy – Kishi



Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, 3997-4000.

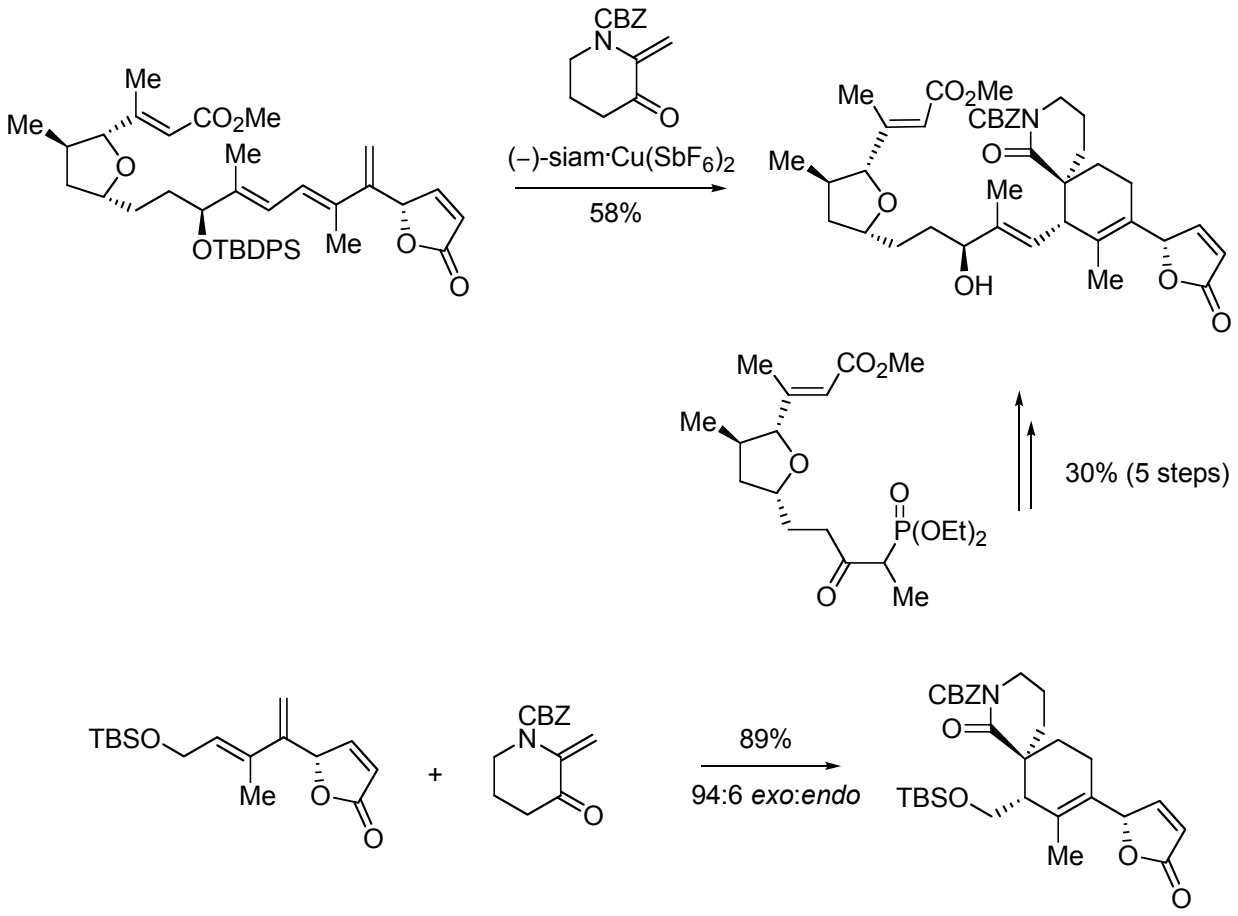
Murai THP and DA precursor

Retrosynthesis?



Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett.* **1997**, 1417-1419.
Ishihara, J.; Horie, M.; Tsujimoto, T.; Murai, A. *Synlett.* **2002**, 399-402.

Murai



Ishihara, J.; Horie, M.; Tsujimoto, T.; Murai, A. *Synlett.* **2002**, 399-402.

THF fragment – Iodoetherification - White

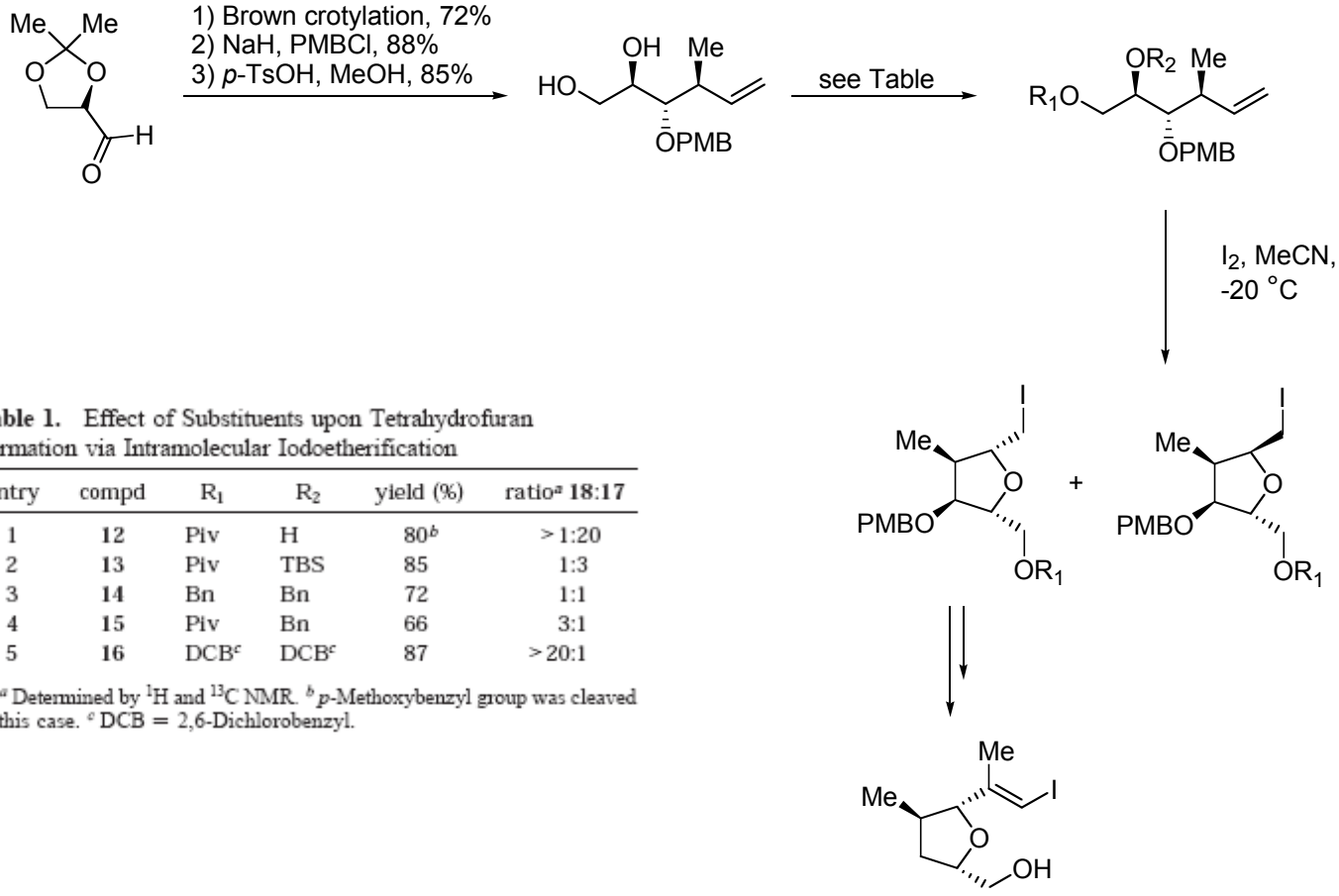


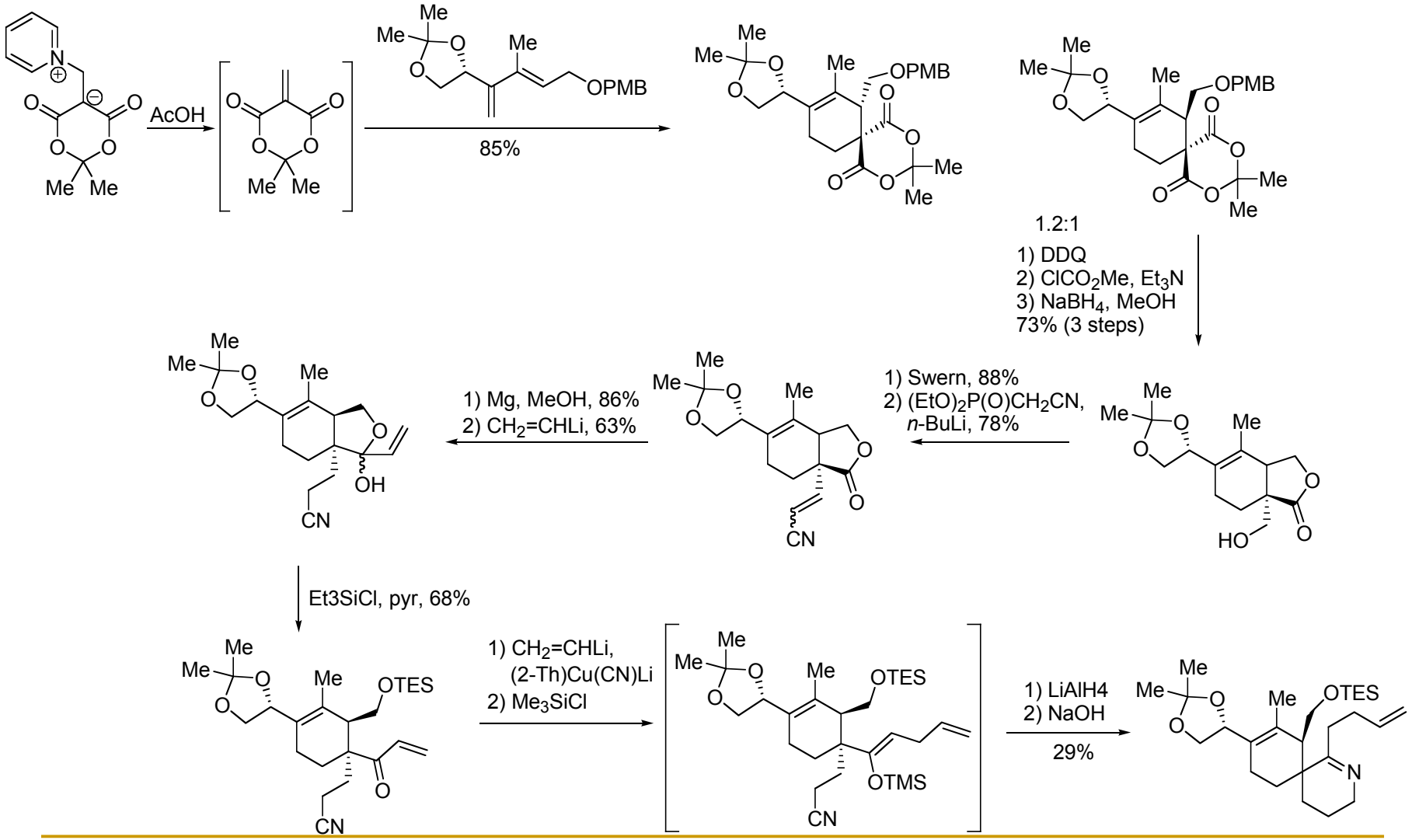
Table 1. Effect of Substituents upon Tetrahydrofuran Formation via Intramolecular Iodoetherification

entry	compd	R_1	R_2	yield (%)	ratio[a] **18:17**
1	**12**	Piv	H	80[b]	>1:20
2	**13**	Piv	TBS	85	1:3
3	**14**	Bn	Bn	72	1:1
4	**15**	Piv	Bn	66	3:1
5	**16**	DCB[c]	DCB[c]	87	>20:1

[a] Determined by ^{1}H and ^{13}C NMR. [b] *p*-Methoxybenzyl group was cleaved in this case. [c] DCB = 2,6-Dichlorobenzyl.

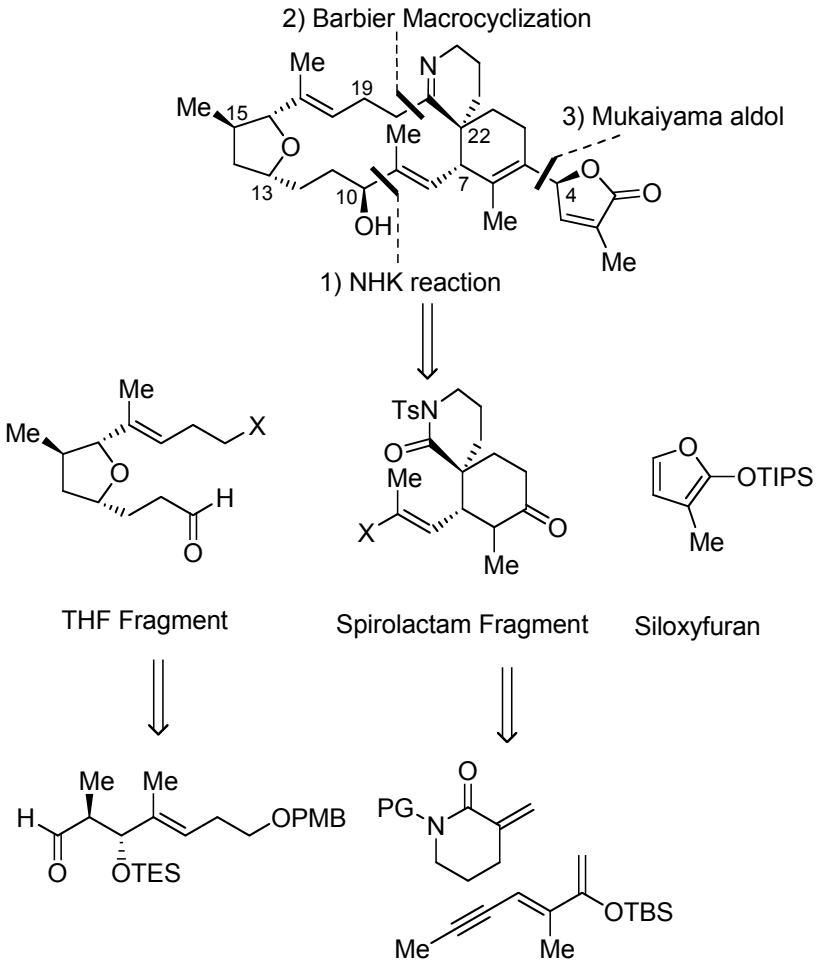
White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, 4109-4112.

Diels Alder - White

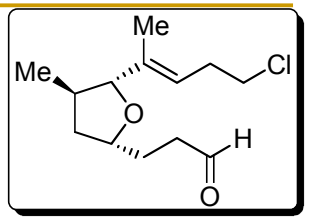


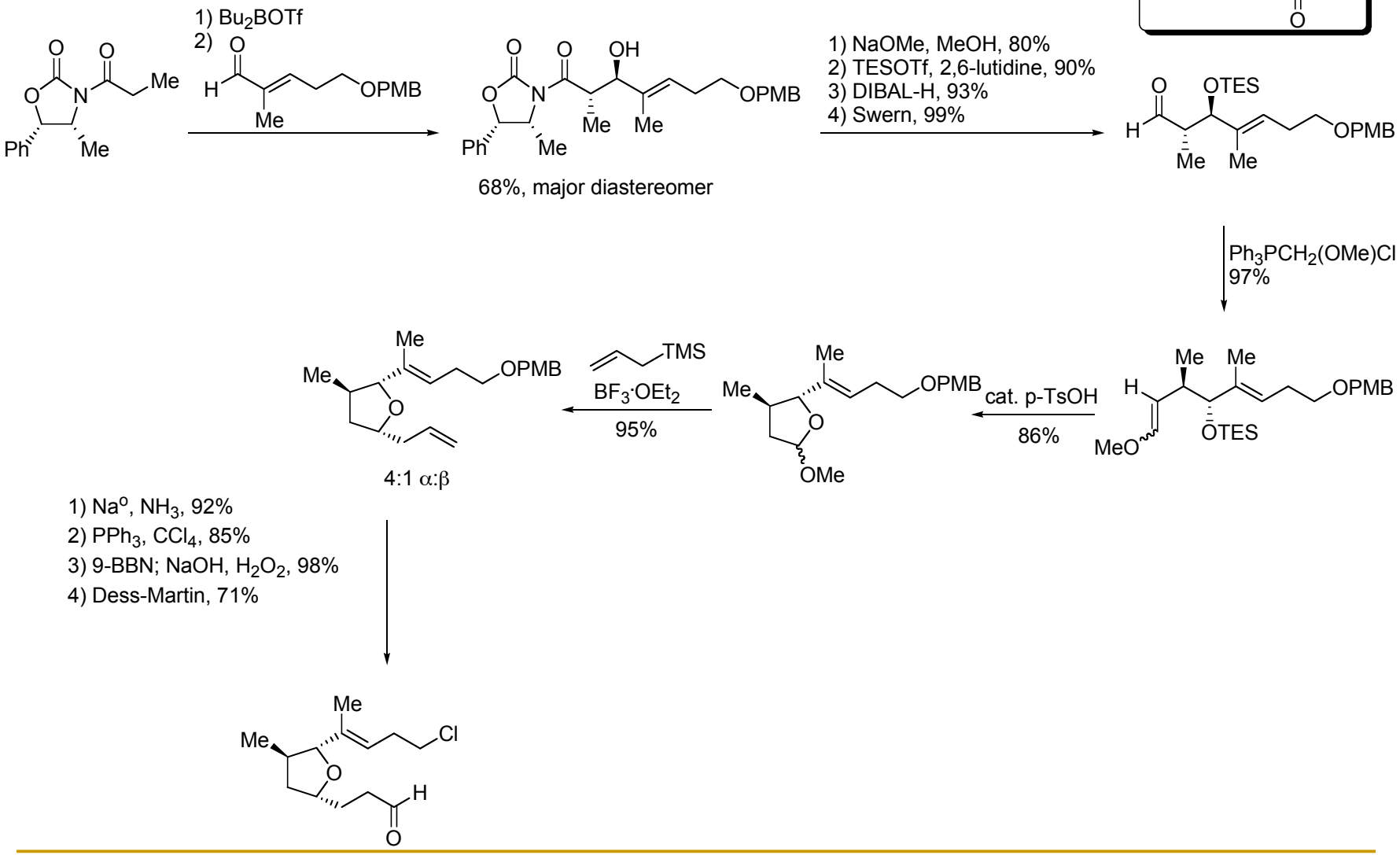
White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, 4983-4986.

Retrosynthetic Analysis – Romo



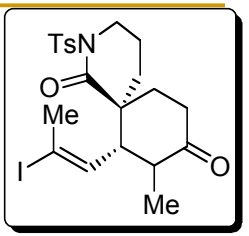
Synthesis of THF fragment – Romo

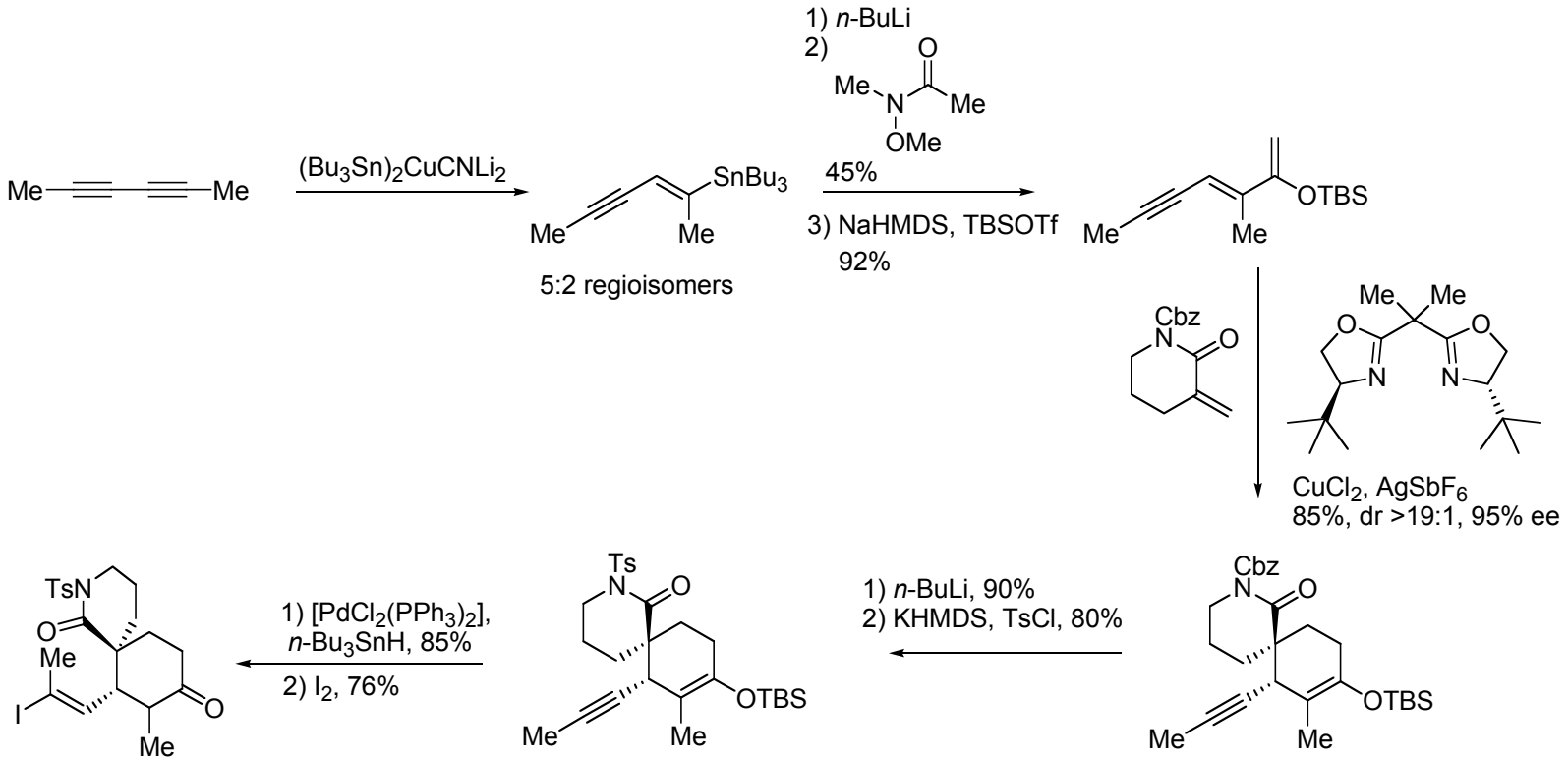




Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, 2, 763-766.

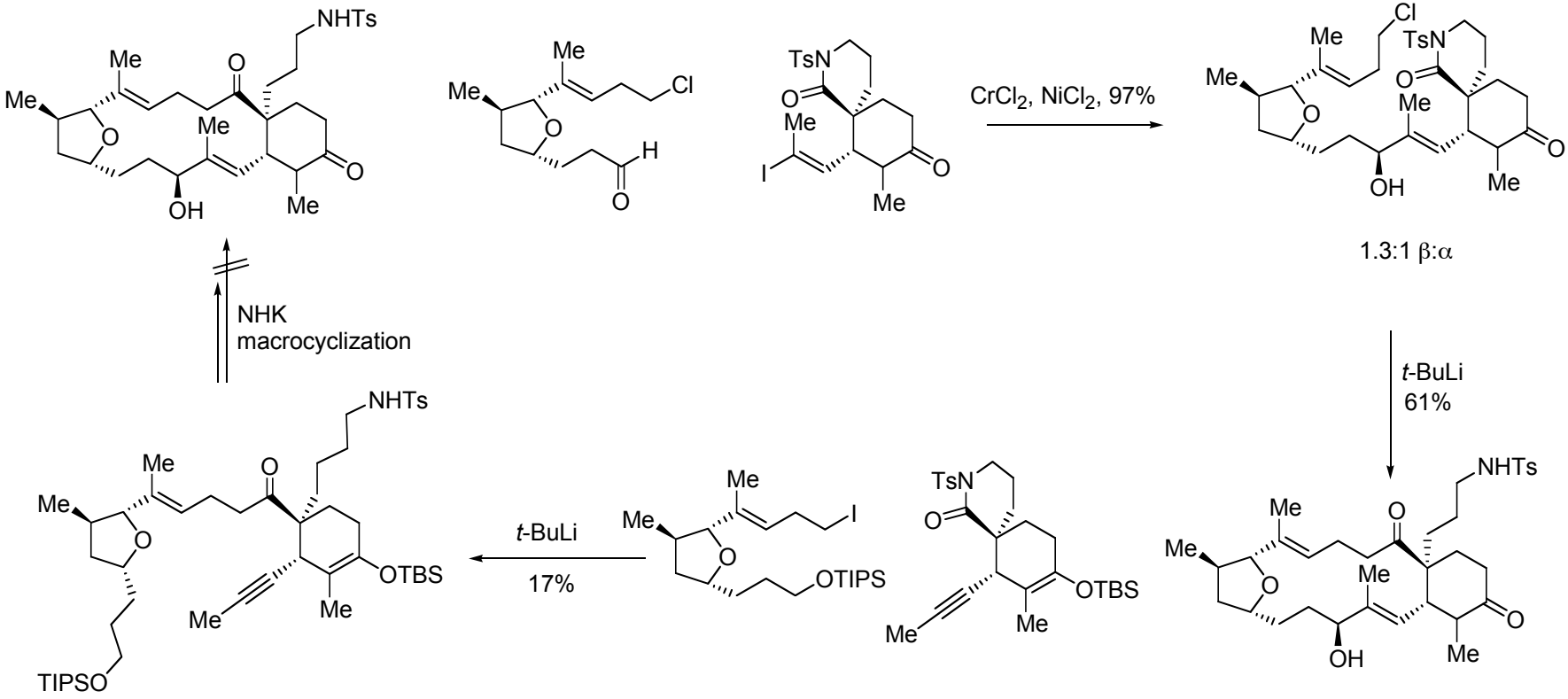
Synthesis of the spirolactam fragment – Romo



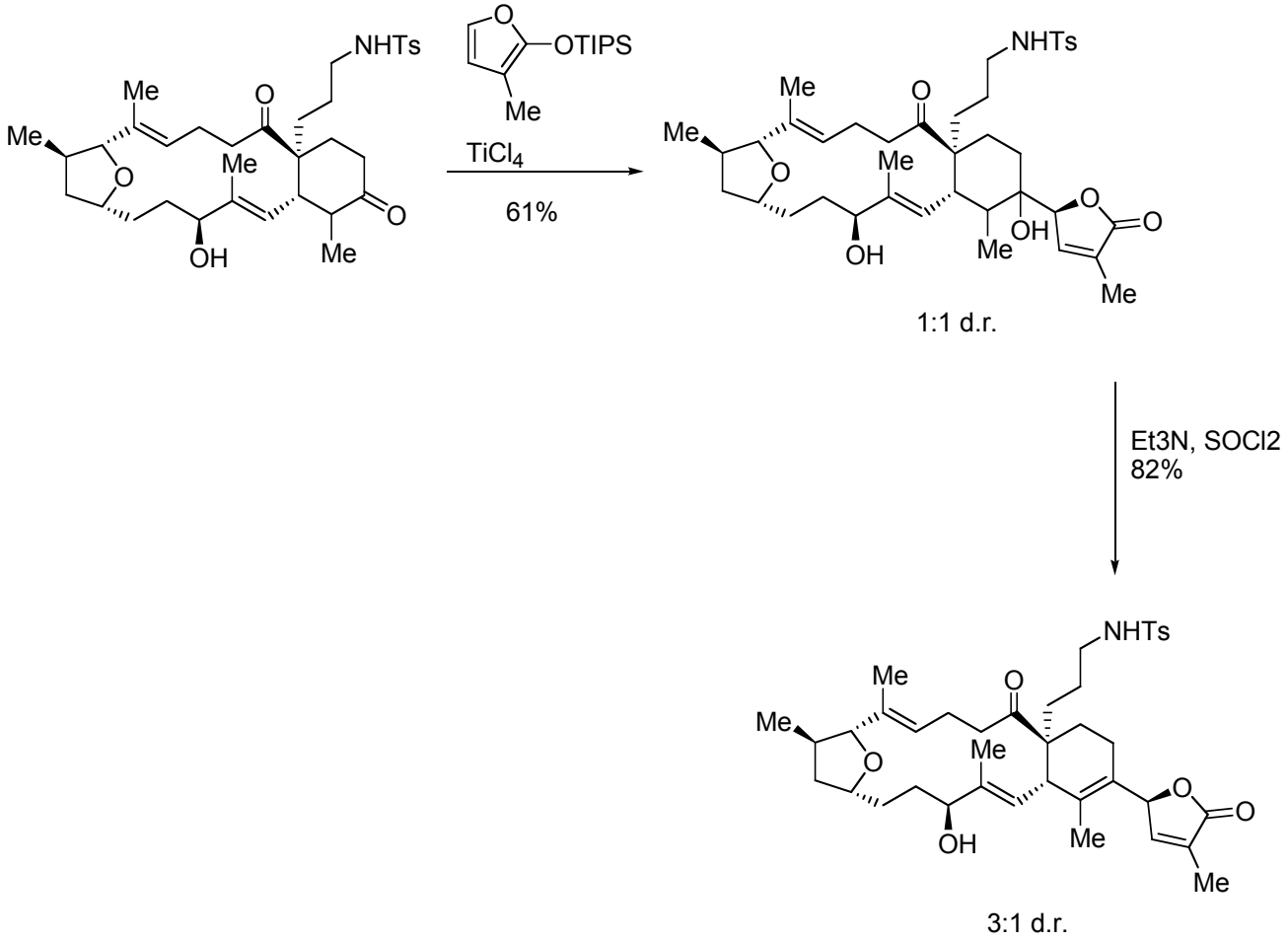


Kong K.; Moussa, Z.; Romo, D. *Org. Lett.* **2005**, 7, 5127-5130.

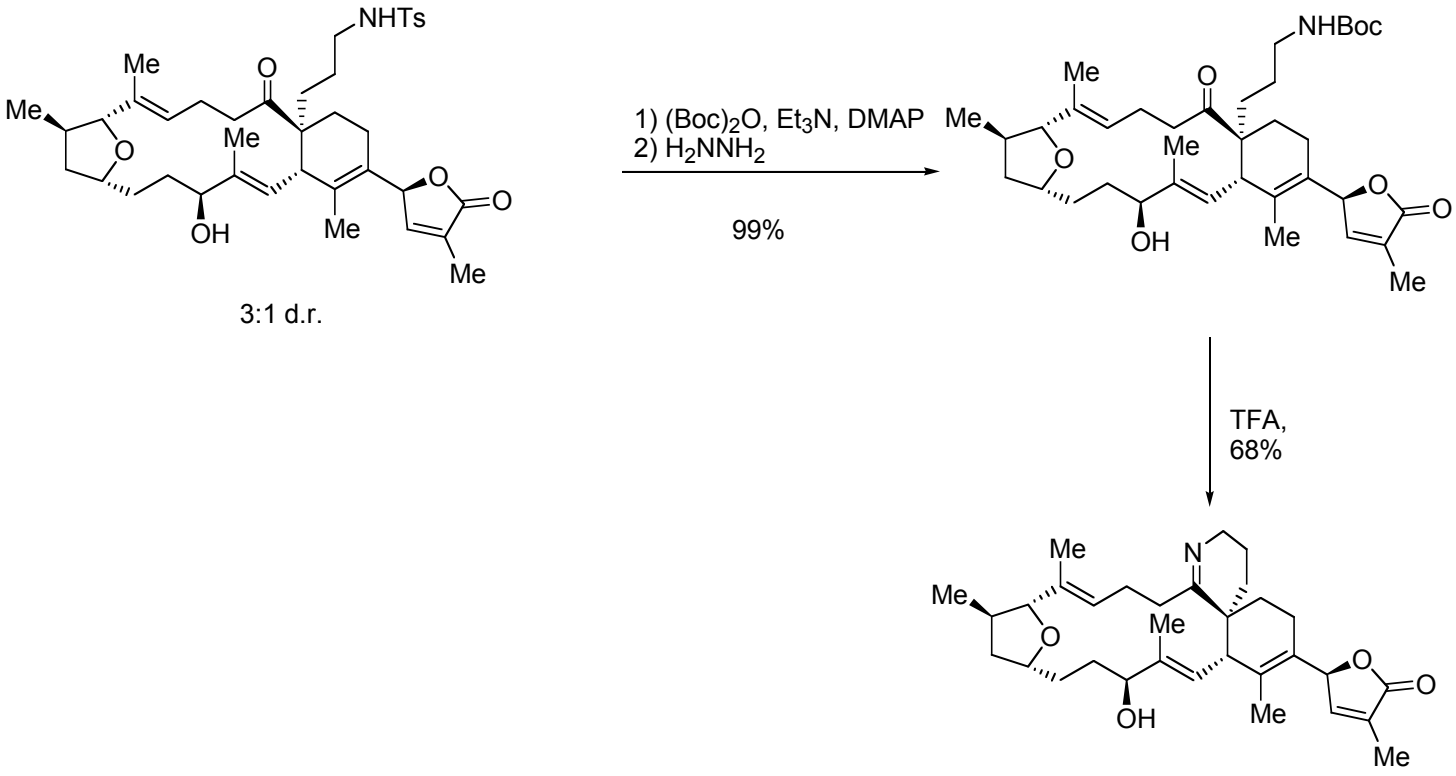
NHK reaction and Barbier Macrocyclization – Romo



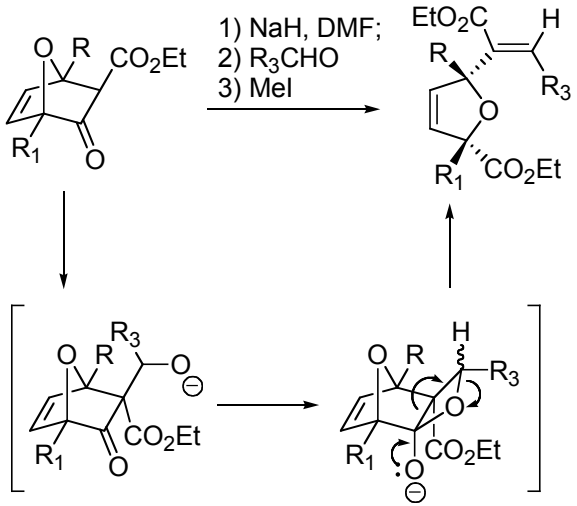
Vinylogous Mukaiyama Aldol – Romo



Romo


NHTs
Me
O
Me
Me
O
OH
Me
O
O
Me
3:1 d.r.
1) (Boc)2O, Et3N, DMAP
2) H2NNH2
99%
NHBoc
Me
O
Me
Me
O
OH
Me
O
O
Me
TFA,
68%
Me
N
Me
Me
O
OH
Me
O
O
Me

Synthesis of THF Fragment via Anionic Condensation, Fragmentation and Elimination – Rainier



Entry	Ketone	R	R^1	R^3	Furan	Yield	*E:Z*
1	**4**	OCH_3	CH_3	Ph	**5**	83%	0:1
2	**4**	OCH_3	CH_3	*i*-Pr	**6**	78%	0:1
3	**7**	H	H	Ph	**8**	56%	3:1
4	**7**	H	H	*i*-Pr	**9**	45%	1:2

Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, 27-29.

Summary