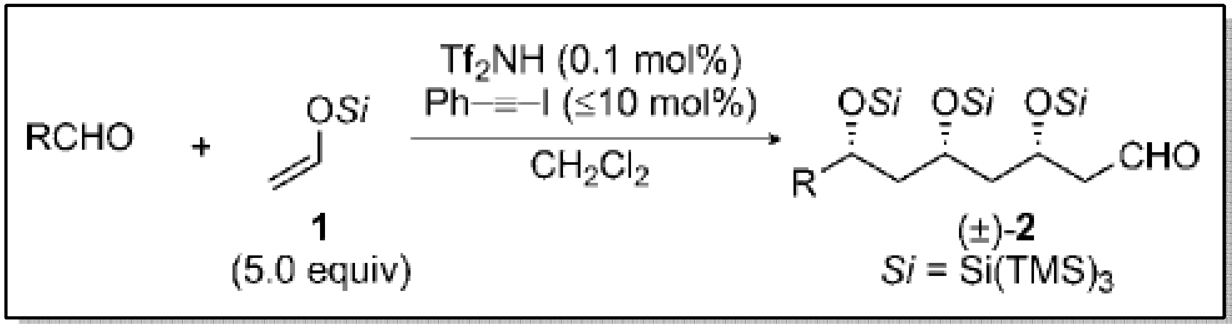
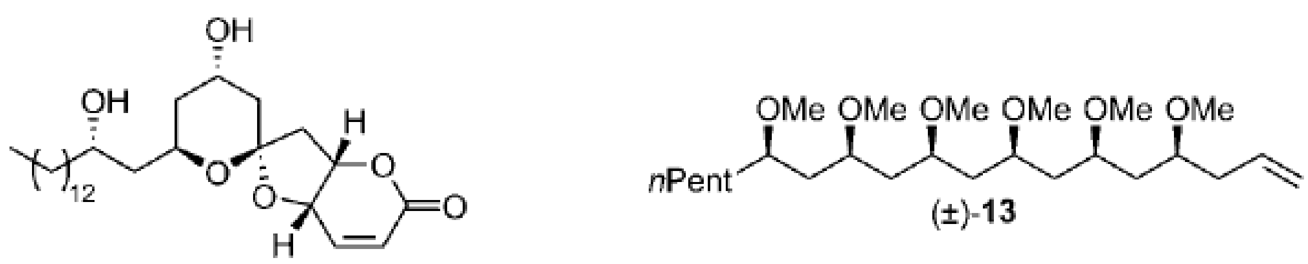
Rapid Total Syntheses Utilizing "Supersilyl" Chemistry

*Brian J. Albert, Yousuke Yamaoka, and Hisashi Yamamoto**

Angewandte Chemie - Early View





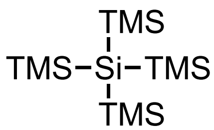
EBC-23

***Tolypothrix* hexaether**

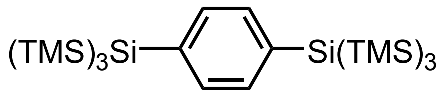
Nolan Griggs, Ph.D.

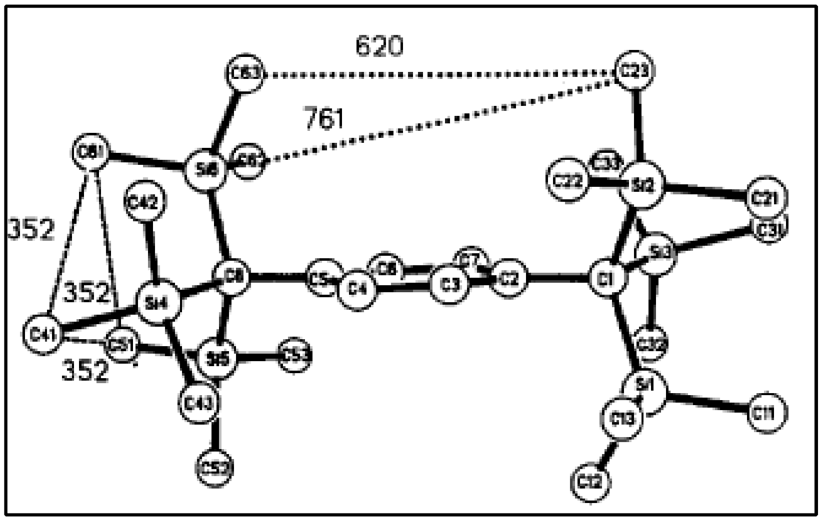
Current Literature - 02/26/2011

Introduction to "Supersilyl" Chemistry

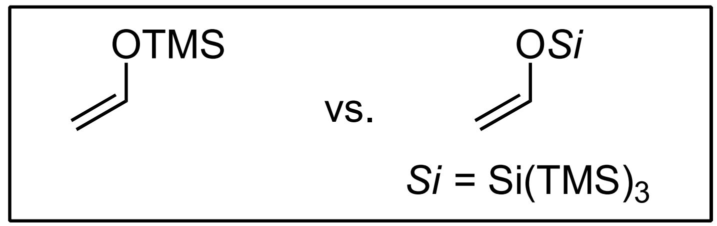


- First synthesized by Gilman: Gilman, H.; Smith, C.L. *J. Am. Chem. Soc.* **1964**, *86*, 1454





Bock, H.; Meuret, J.; Baur, R.; Ruppert, K.
J. Organomet. Chem. **1993**, *446*, 113-122.

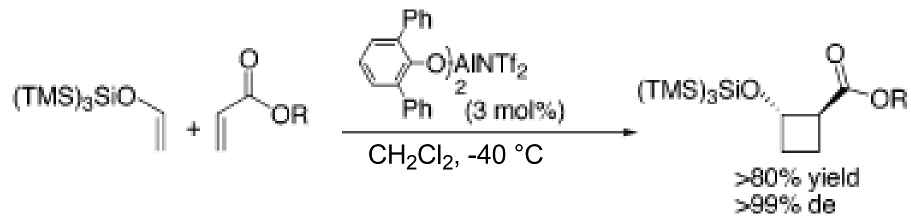


... selectivities observed for [2 + 2] cycloadditions and aldol reactions with supersilyl-substituted enol ethers cannot be attributed to electronic effects but are due to the steric bulk and the umbrella like structure created by the $Si(SiMe_3)_3$ group.

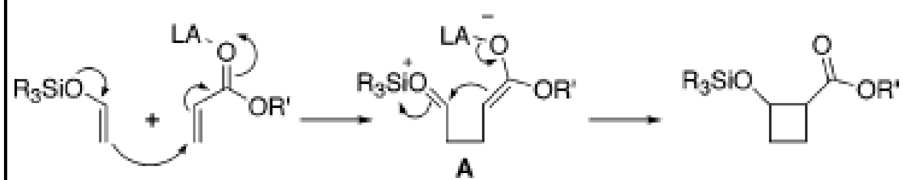
Laub, H. A.; Yamamoto, H.; Mayr, H.
Org. Lett. **2010**, *12*(22), 5206-5209

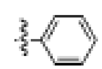
For use in radical chemistry, see: Postigo, A.; Kopsov, S.; Ferreri, C.; Chatgilialoglu, C.
Org. Lett. **2007**, *9*(25), 5159-5162 and references therein.

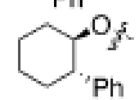
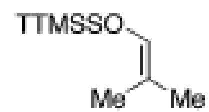
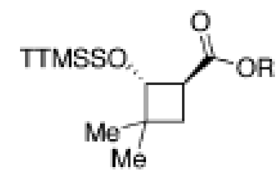
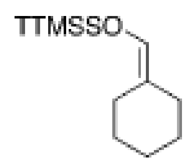
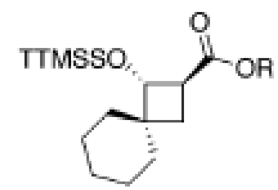
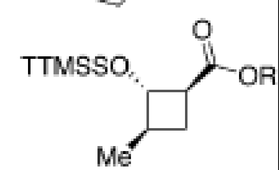
Diastereoselective [2+2] Cyclizations



Scheme 1. Proposed Michael-Aldol Mechanism for [2 + 2] Cyclization



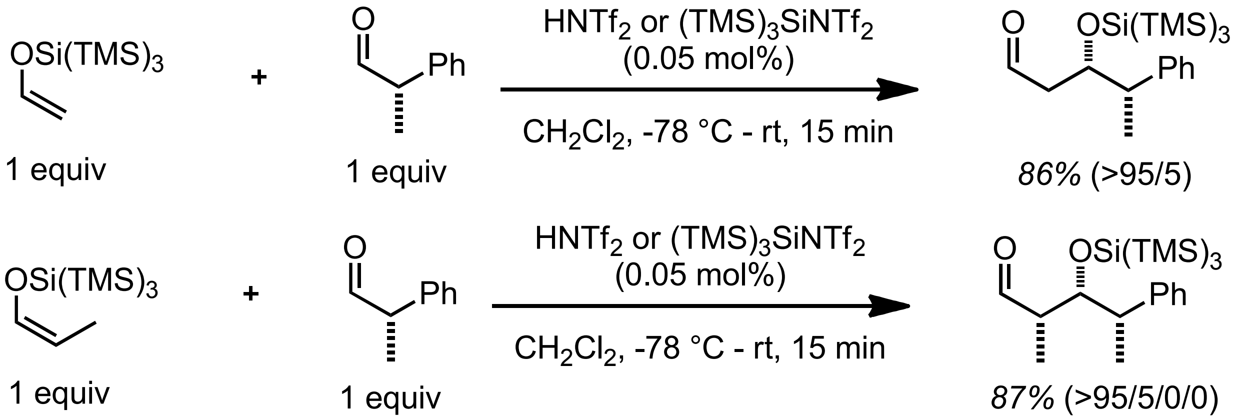
entry	*Si*	R	% yield[b] (trans/cis)[c]
1	TBS		0
2	TIPS		0
3	$SiMe_2TMS$		7 (1.5/1)
4	TTMSS		45 (2/1)
5	TTMSS		58 (5/1)

entry	substrate	R	% yield[b] (trans/cis)[c]	major product
1		Ph	84 (10/1)	
2[d]		Ph	82 (10/1)	
3[e]			81 (>99/1/0/0)[f]	
4		Ph	91 (>99/1)	
5		Ph	81 (25/1)	
6		Ph	94 (>99/1)	
7		Ph	93 (>99/1, 10/1[g])	

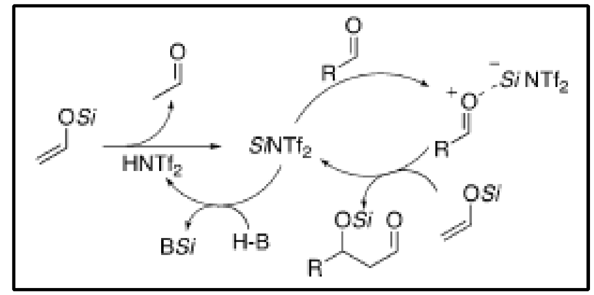
Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2005**, *7*(14), 3127-3129

Use of "Supersilyl" Groups in the Crossed Aldol Reaction

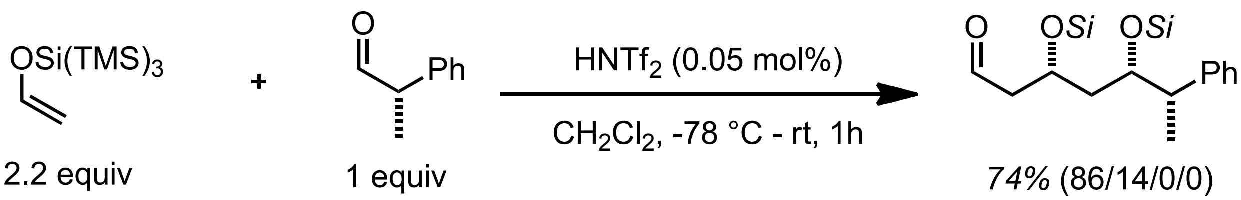
Mukaiyama aldol reactions:

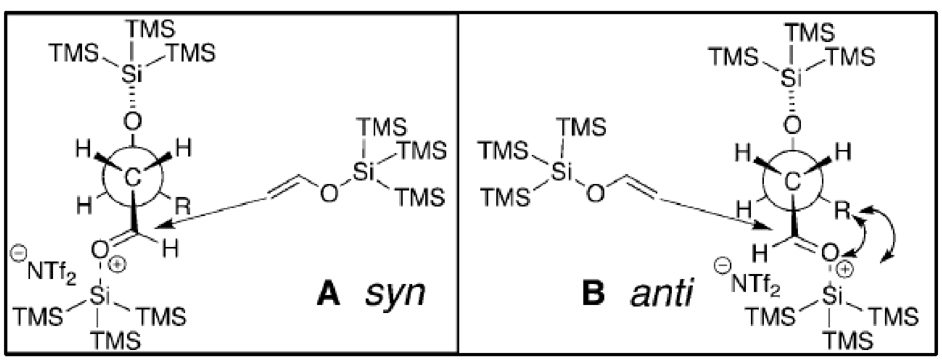


Formation of Silyltriflamide and Its "Self-Repair" Ability:



Cascade Mukaiyama aldol reactions:



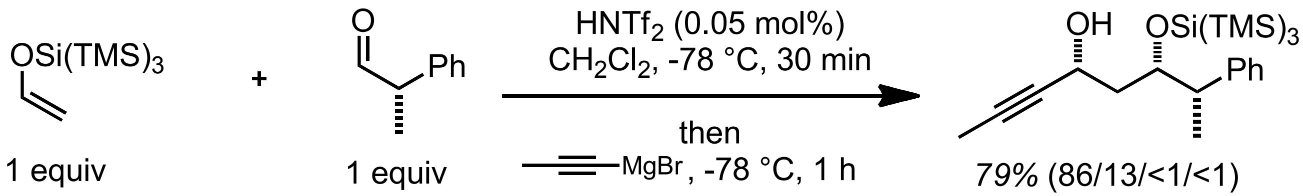


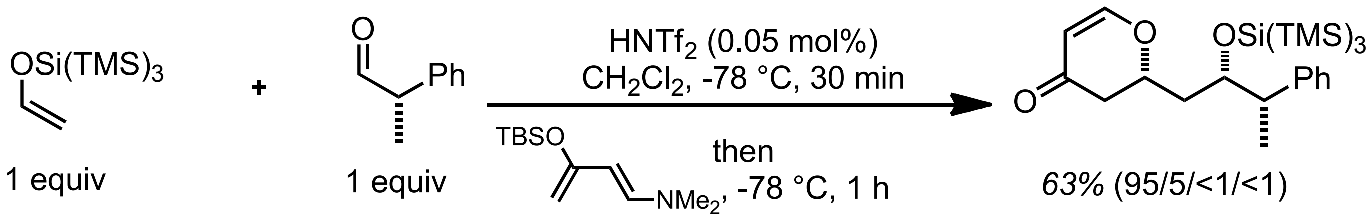
"The $(TMS)_3Si$ group is distinctive in that it combines the highest Lewis acidity as a silicon catalyst, high nucleophilic reactivity as a silyl-enolether, and large steric bulk for superior diastereoselection."

Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*(1), 48-49.

Further Development of Aldol Methodology

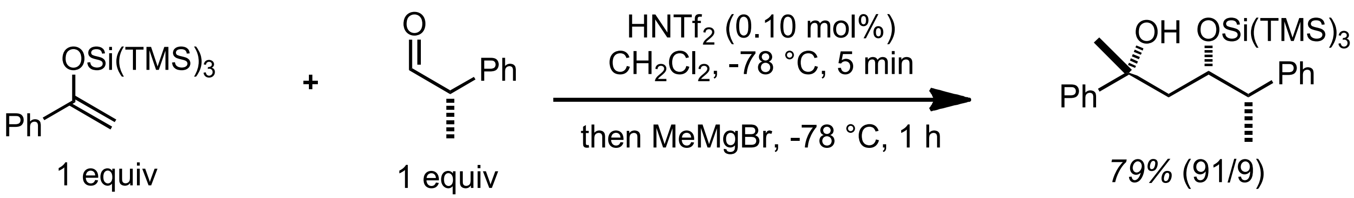
Diastereoselective Sequential Reactions in One Pot:





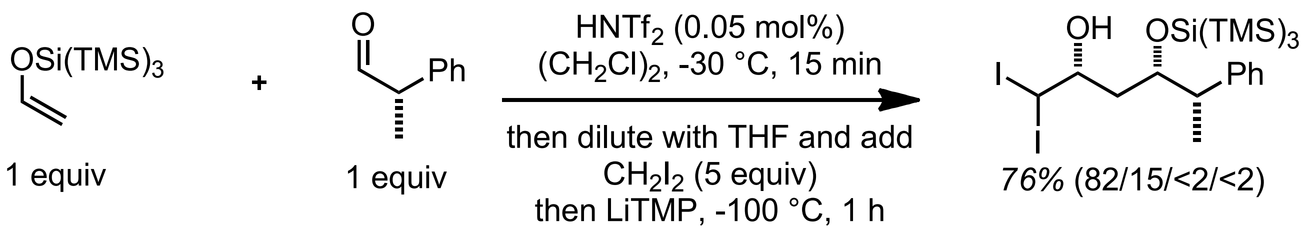
Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*(10), 2762-2763.

Diastereoselective Sequential Reactions in One Pot (ketones):



Boxer, M. B.; Akakura, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*(5), 1580-1582.

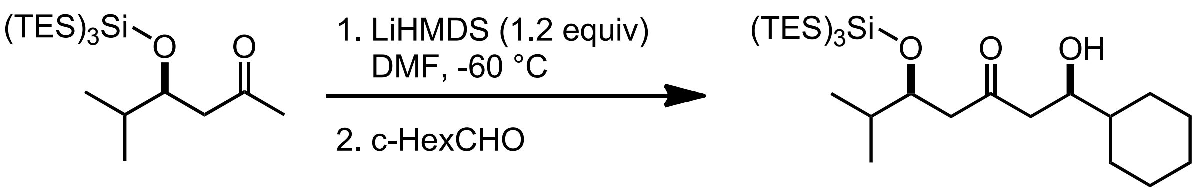
Diastereoselective Aldol-Polyhalomethyllithium Additions:

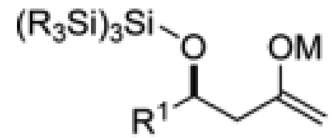


Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2008**, *10*(3), 453-455.

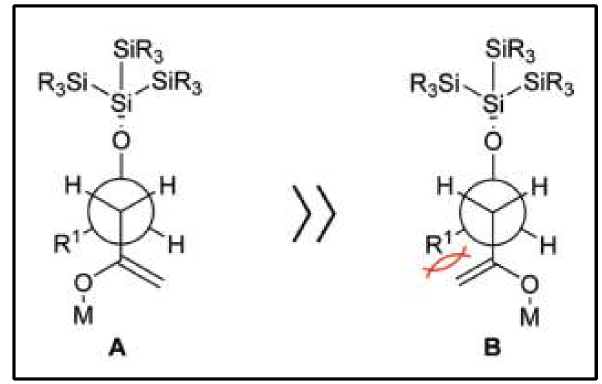
1,5 Stereoinduction in Aldol Reactions

1,5-Syn Aldol reactions:

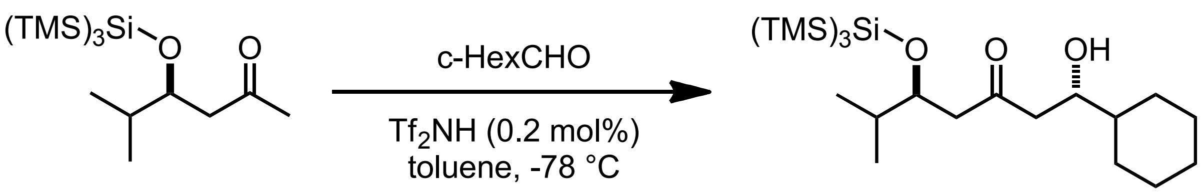




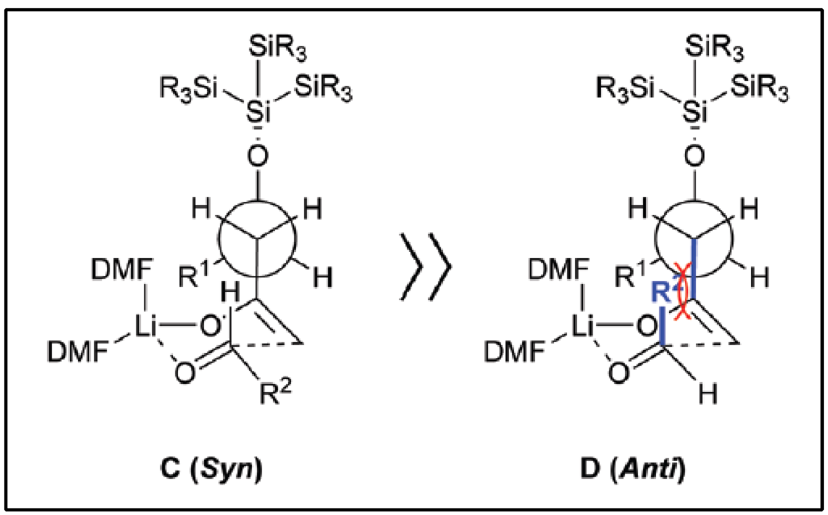
80% (95:5 *syn/anti*)

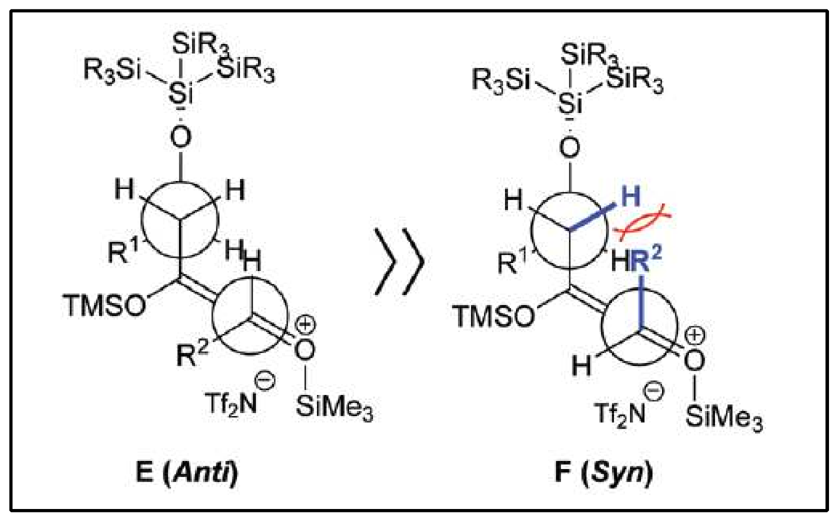


1,5-Anti Aldol reactions:



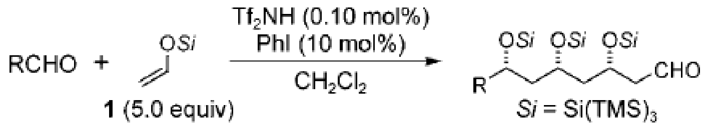
87% (97:3 *syn/anti*)

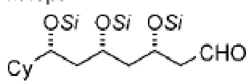
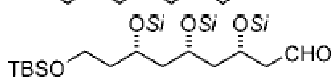
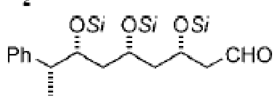


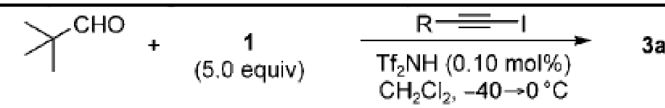


Yamaoka, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*(15), 5354-5356.

Triple-Aldol Cascade - Rapid Assembly of Polyketides



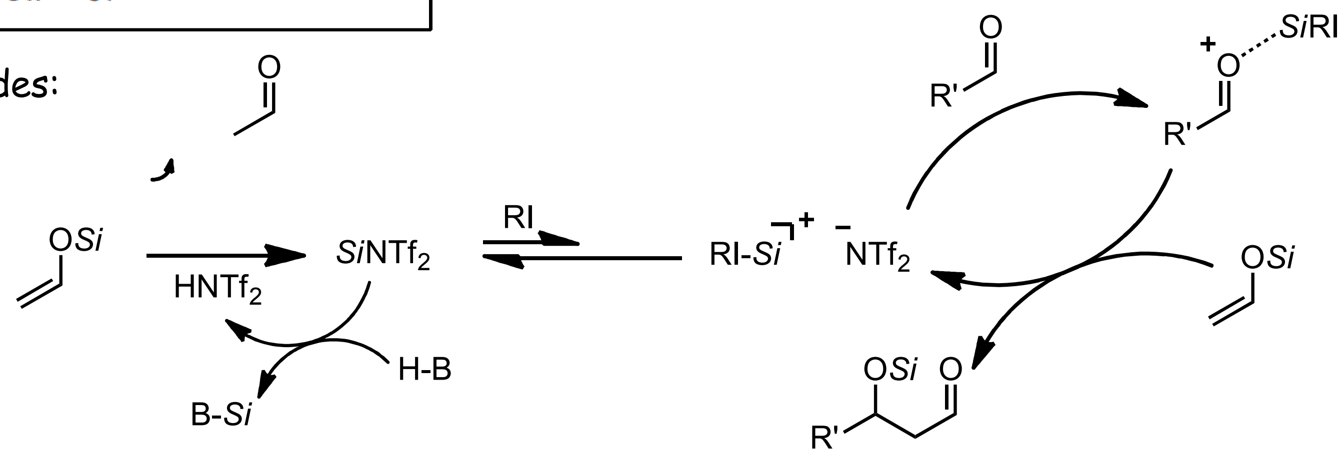
Entry	Product		Yield [%][a]	d.r.[b]
1		3b	84	79:10:9:<2
2		3c	87	81:9:8:<2
3		3d	75	81:9:8:<2
4		3e	87	71:14:12:2
5[c]		3f	89	87:8:3:2
6		3g	54	–[d]
7[e]		3h	57	–[d]



Entry	R [mol %]	Yield [%][a]
1	Ph (10)	80
2	Ph (2.0)	71
3	Ph (0.5)	65
4	Ph (0.1)	56
5	*t*Bu (0.5)	85
6	*t*Bu (0.1)	77

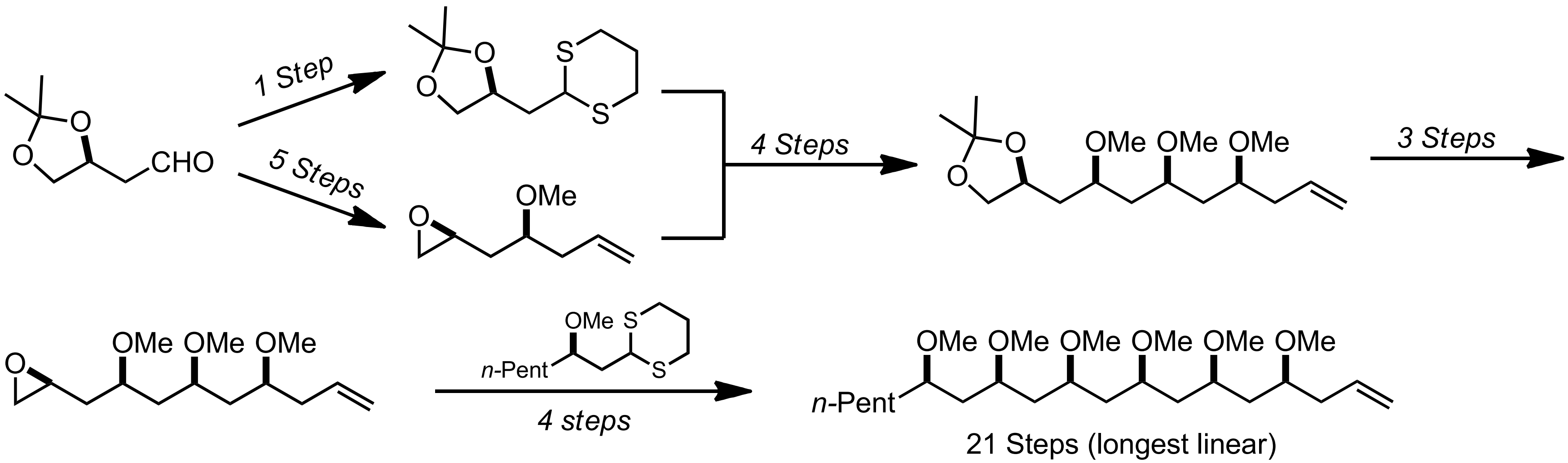
[a] Yield of combined isolated diastereomers.

Proposed role of organoiodides:

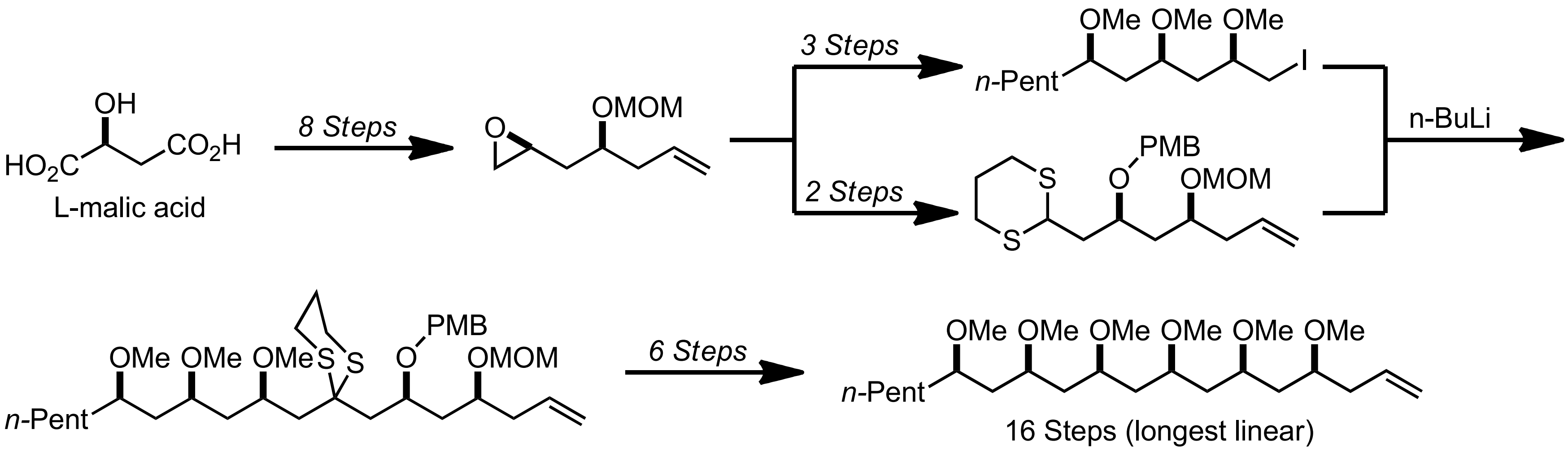


Albert, B. J.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 2747-2749

Tolypothrix Hexaether; Previous Total Syntheses

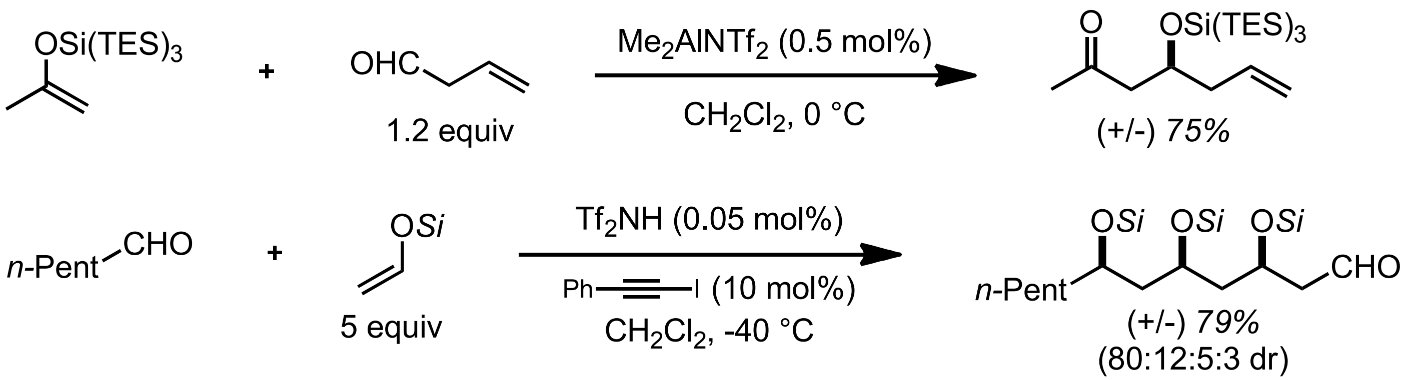


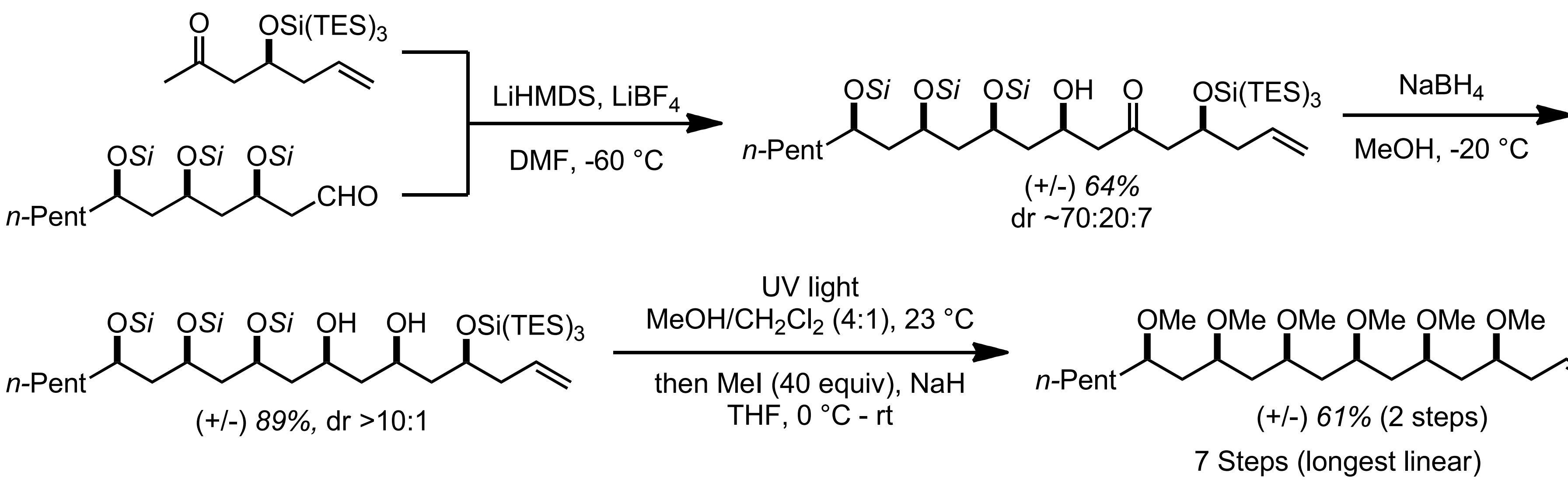
Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631-637.



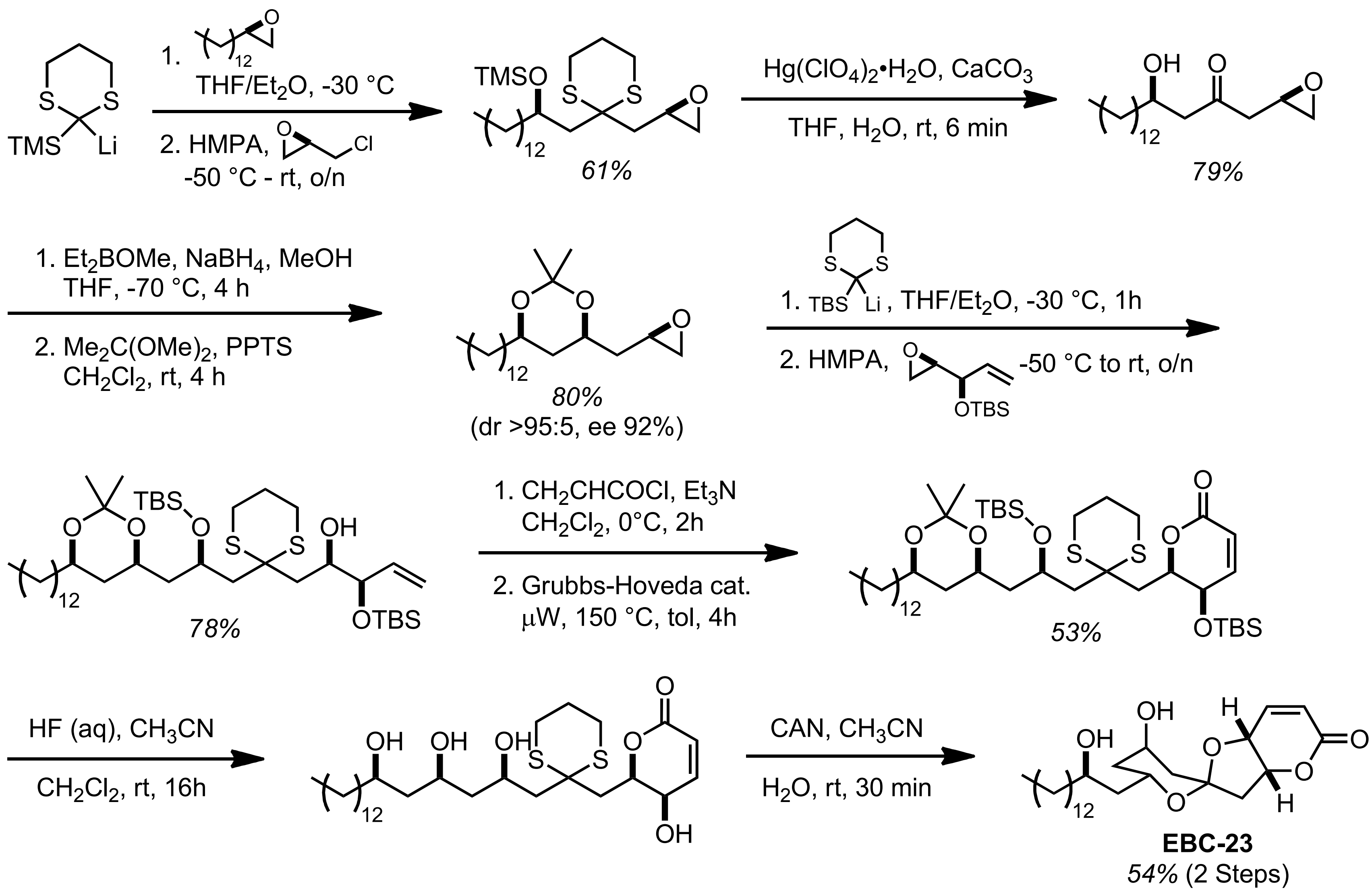
Lui, K.; Arico, J.W.; Taylor, R. *J. Org. Chem.* **2010**, *75*, 3953-3957

Tolypothrix Hexaether; Yamamoto's Total Synthesis





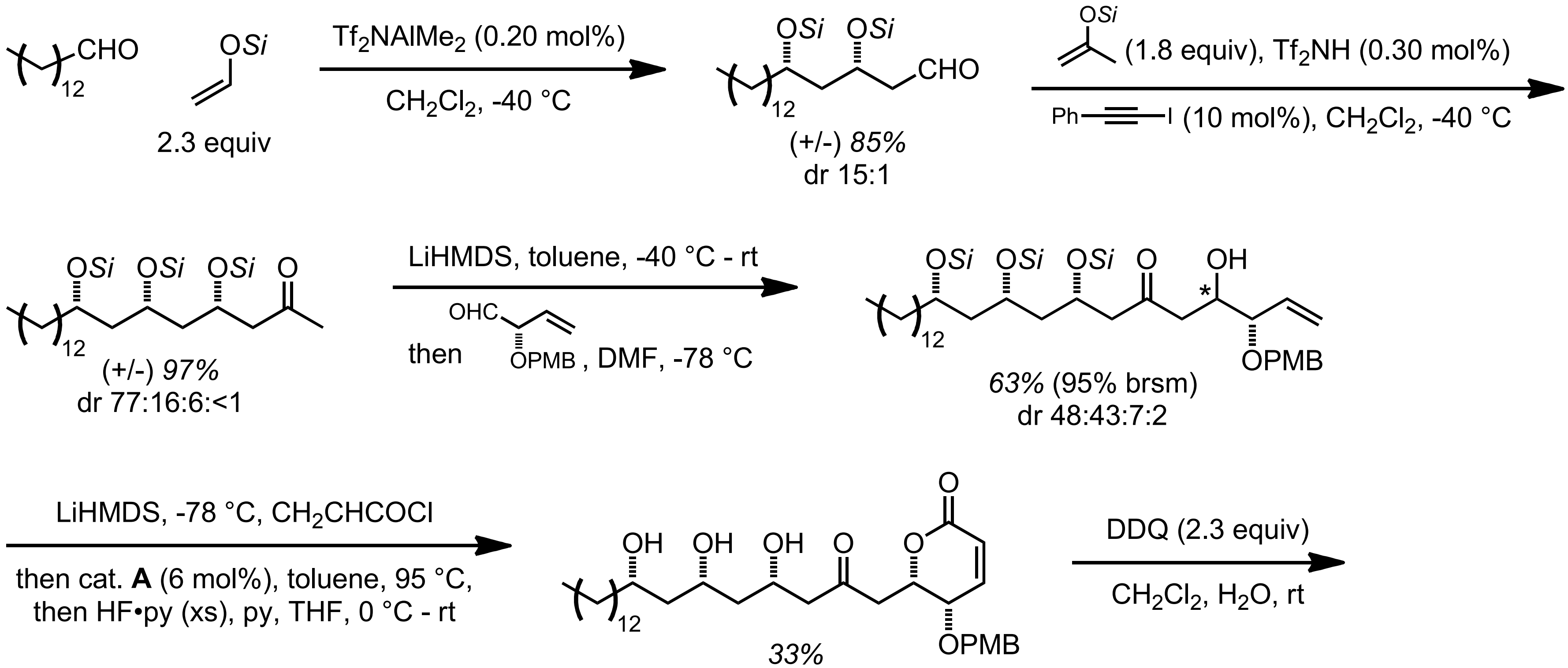
Anti-cancer Agent EBC-23; Previous Total Synthesis

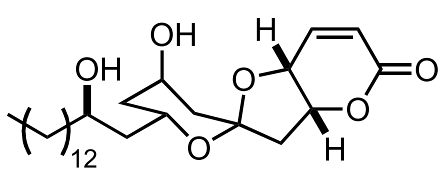


Williams, Craig M. and co-workers, *J. Am. Chem. Soc.* **2008**, *130*, 15262 - 15263

11 total linear steps
Overall yield = 8.6%

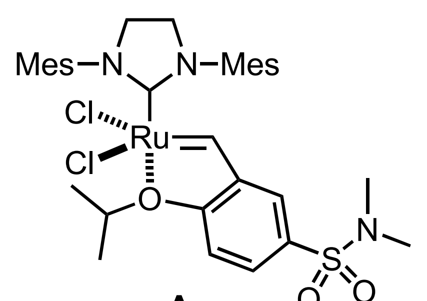
Anti-cancer Agent EBC-23; Yamamoto's Total Synthesis





EBC-23
72%

7 steps (longest linear)
Overall yield = 12%



A
Zhan Catalyst - 1B

Available from Strem Chemicals

Patents: US 2007/0043180A1
WO 2007/003135A1

Other uses: *ACIE* **2009**, *48*, 7428 - 7431.