The Bryostatins & Analogues:

A Study in Macrocyclizations

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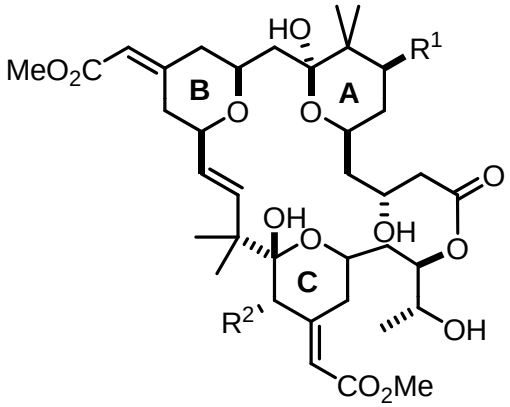
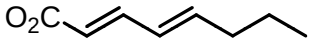
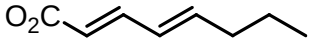
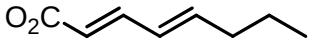
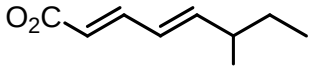
4 June 2008

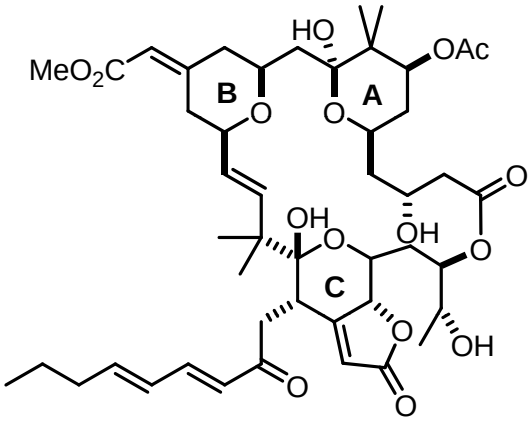
The Bryostatins

- Originally isolated (1968) by Pettit from marine bryozoan *Bugula neritina* – an invertebrate filter feeder
- Structure not elucidated until 1982 (Pettit)
- Potent antineoplastic activity against murine P388 lymphocytic leukemia and other tumors
- Bryostatin 1 in clinical trials as chemotherapy agent
- C ring proposed to play critical role in receptor recognition

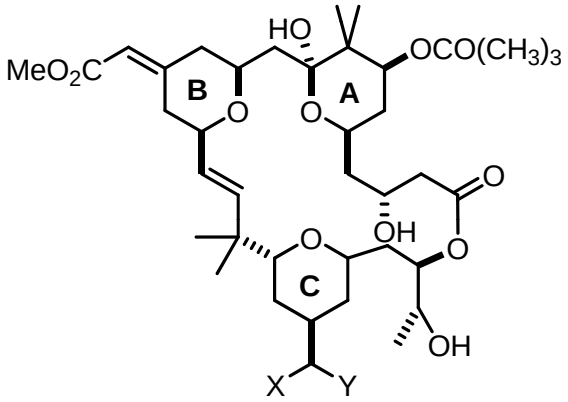
The Bryostatins



Bryostatin #	R^1	R^2
1	O_2CCH_3	
2	OH	
4	$O_2CC(CH_3)_3$	$O_2CCH_2CH_2CH_3$
5	$O_2CC(CH_3)_3$	O_2CCH_3
6	$O_2CCH_2CH_2CH_3$	O_2CCH_3
7	O_2CCH_3	O_2CCH_3
8	$O_2CCH_2CH_2CH_3$	$O_2CCH_2CH_2CH_3$
9	O_2CCH_3	$O_2CCH_2CH_2CH_3$
10	$O_2CC(CH_3)_3$	H
11	O_2CCH_3	H
12	$O_2CCH_2CH_2CH_3$	
13	$O_2CCH_2CH_2CH_3$	H
14	$O_2CC(CH_3)_3$	OH
15		O_2CCH_3
18	$O_2CC(CH_3)_3$	H

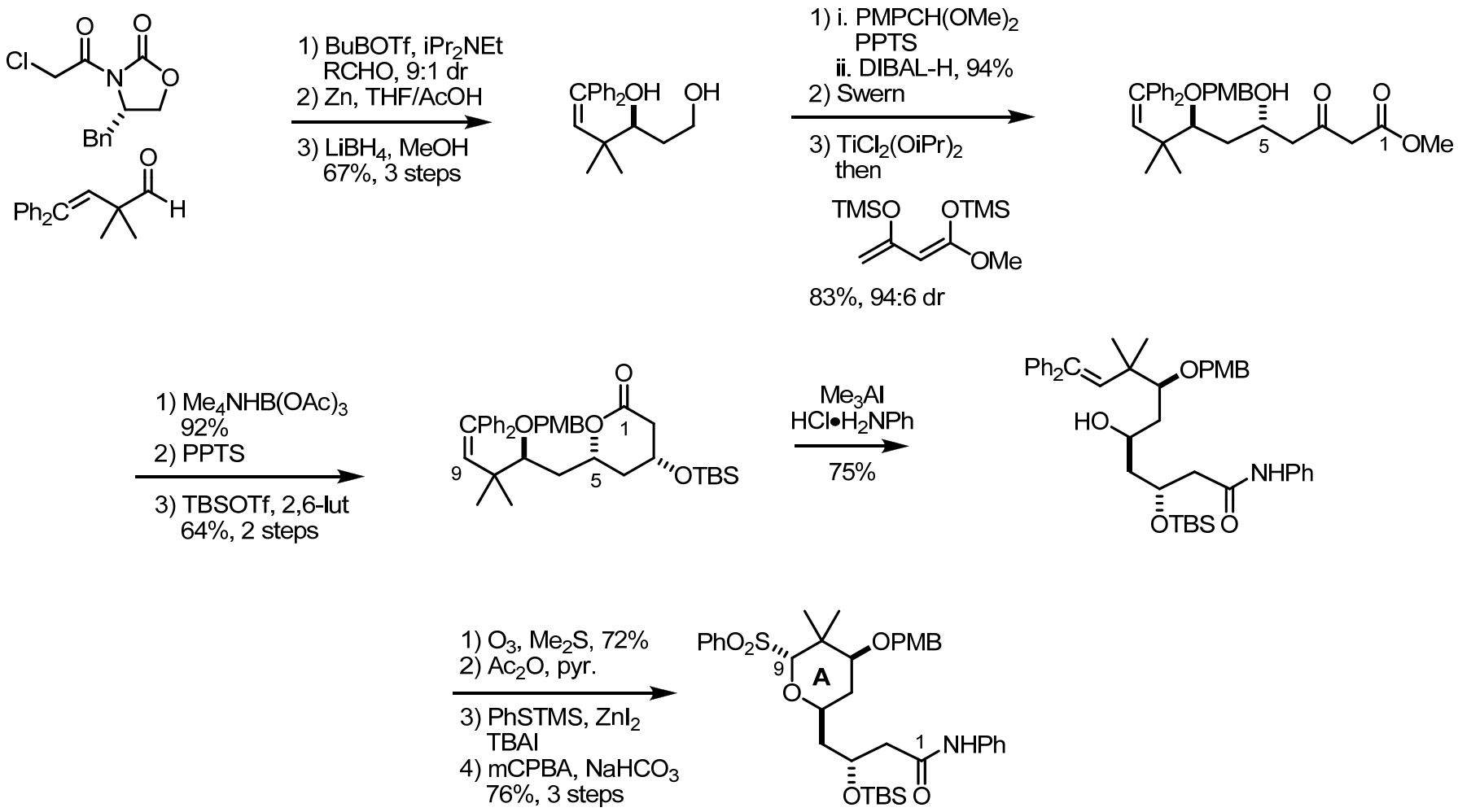


Bryostatin 3



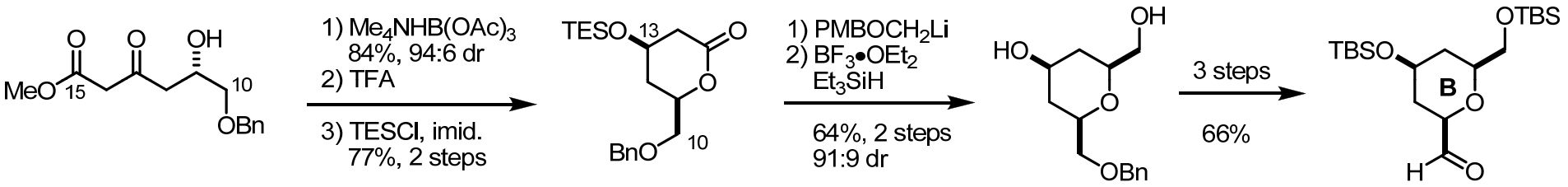
Bryostatin #	X	Y
16	H	CO_2Me
17	CO_2Me	H

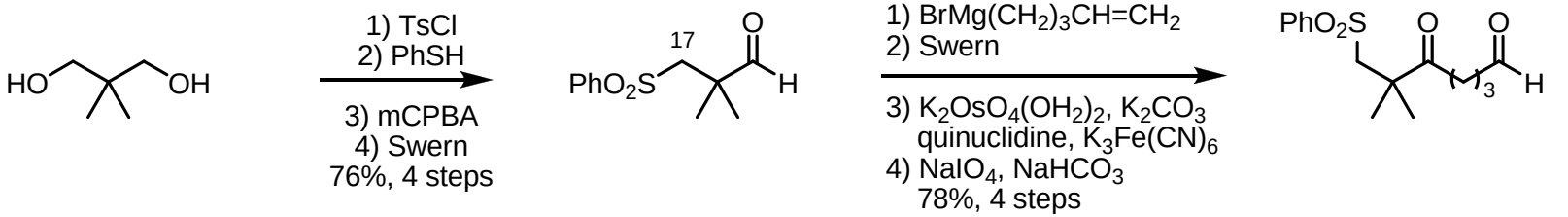
Bryostatin 2 – A Ring

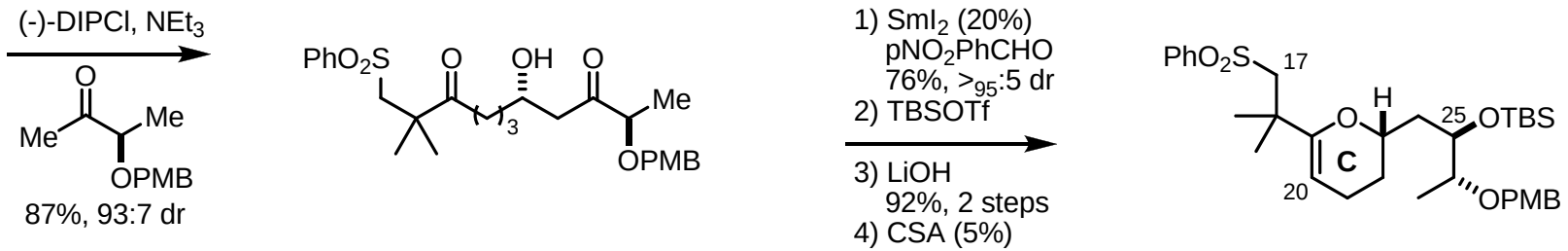


Evans, D.; Carter, P.; Carreira, E.; Charette, A.; Prunet, J.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540-7552.

Bryostatin 2 – B & C Rings

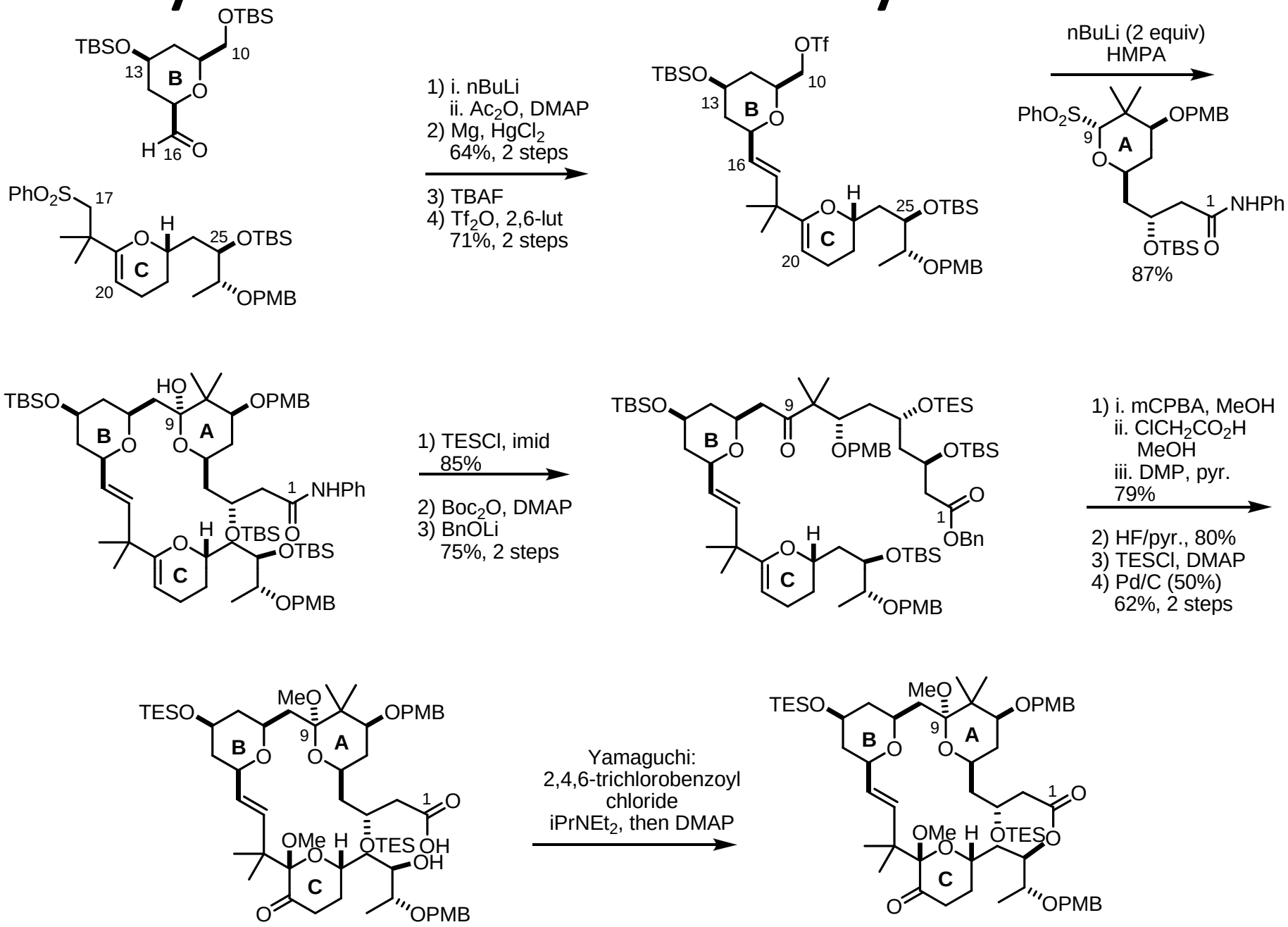






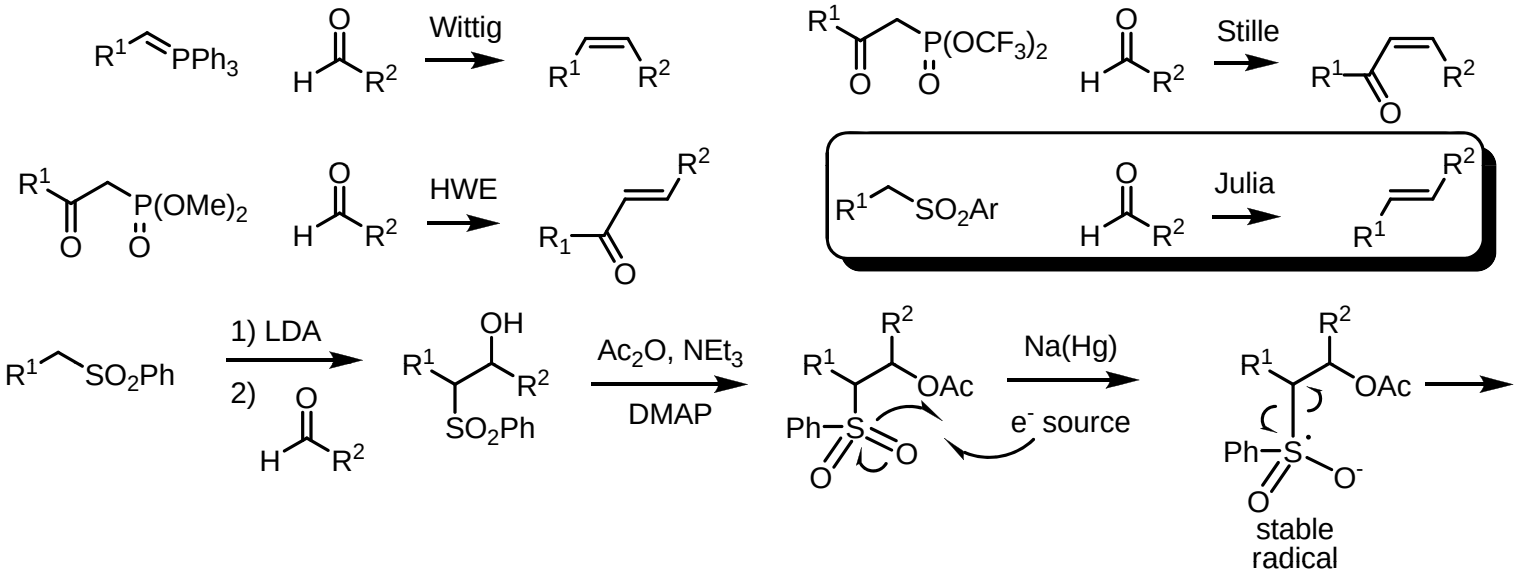
Evans, D.; Carter, P.; Carreira, E.; Charette, A.; Prunet, J.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540-7552.

Bryostatin 2 - Macrocyclization



Evans, D.; Carter, P.; Carreira, E.; Charette, A.; Prunet, J.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540-7552.

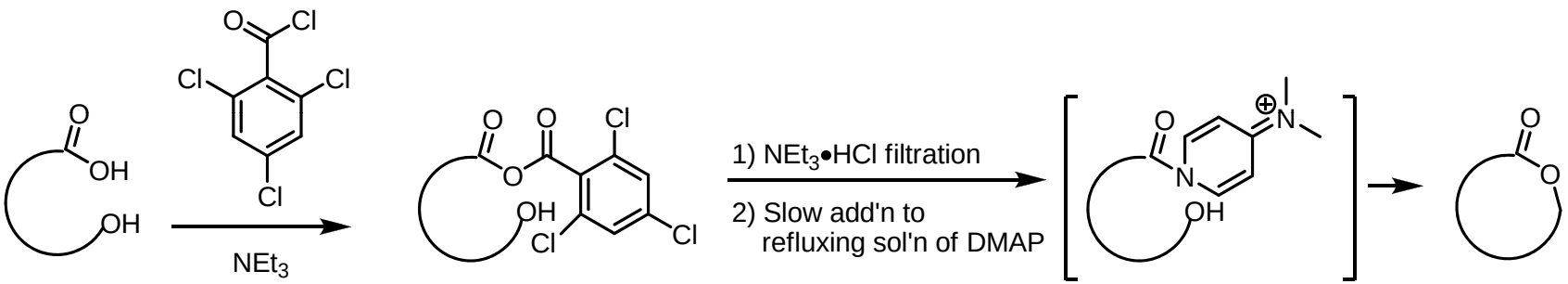
Julia Olefination



Plesniak, K.; Zarecki, A.; Wicha, J. *Topics in Current Chemistry*; 2007; pp. 163-250.

Yamaguchi Esterification

"Classical" Yamaguchi Conditions:



“Used in more than 200 synthetic applications”

“Modified Yamaguchi Conditions:” Preform mixed anhydride, add excess DMAP at rt w/o slow dilution

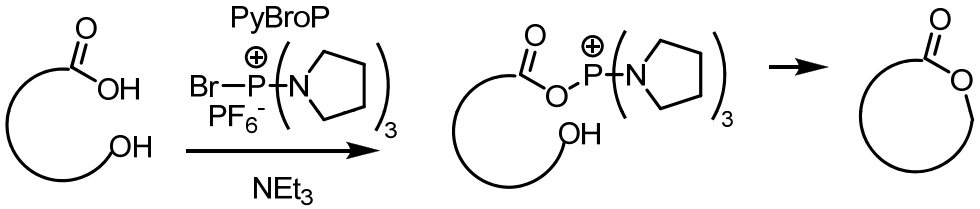
“Yonemitsu’s Conditions:” Add DMAP with acid chloride directly from beginning w/o heat (less basic conditions)

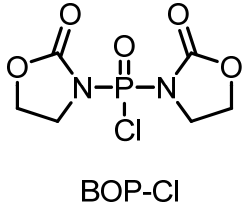
* In absence of these conditions, α, β-unsaturated acids were converted into β, γ-unsaturated lactones (i.e. double bond moved *out of* conjugation).

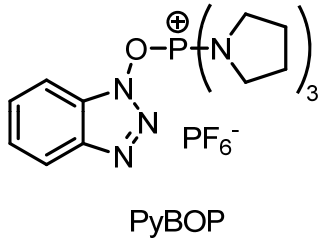
Parenty, A.; Moreau, X.; Campagne, J. *Chem. Rev.* **2006**, *106*, 911-939.

Other Lactone Formations

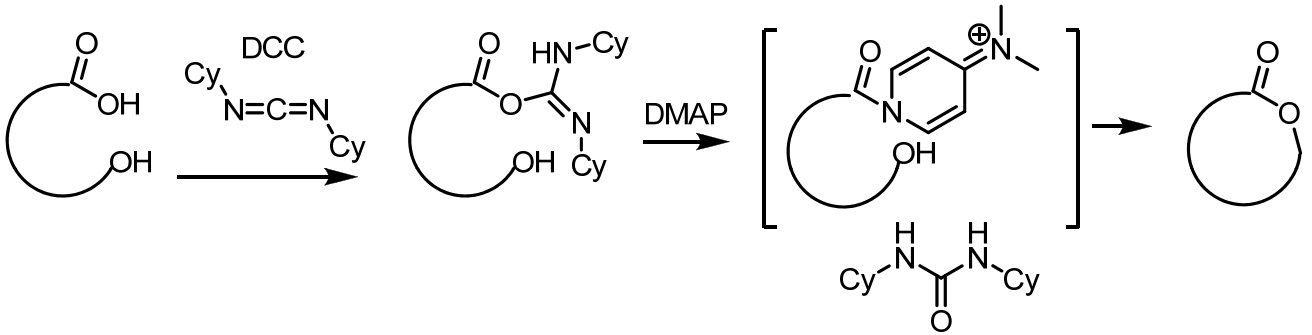
Mixed Phosphorous Anhydride:

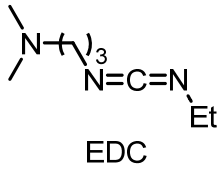




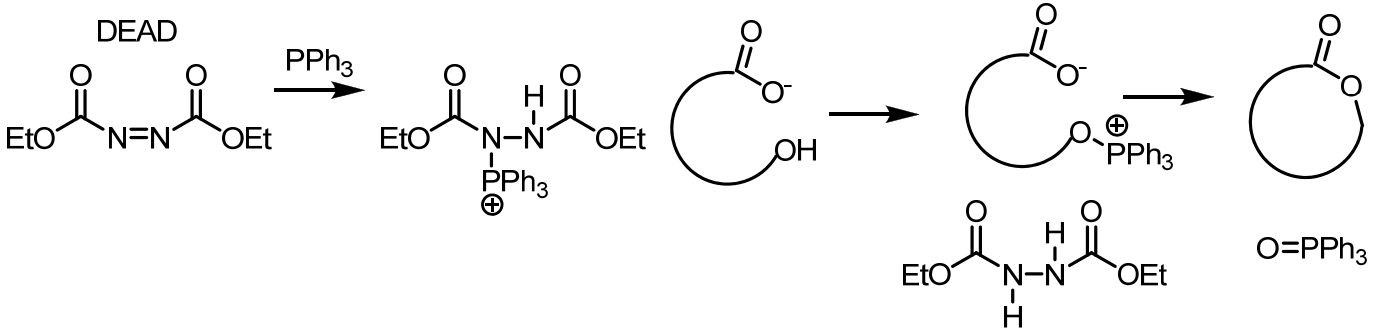


Carbodiimides:





Azodicarboxylates (alcohol activation):



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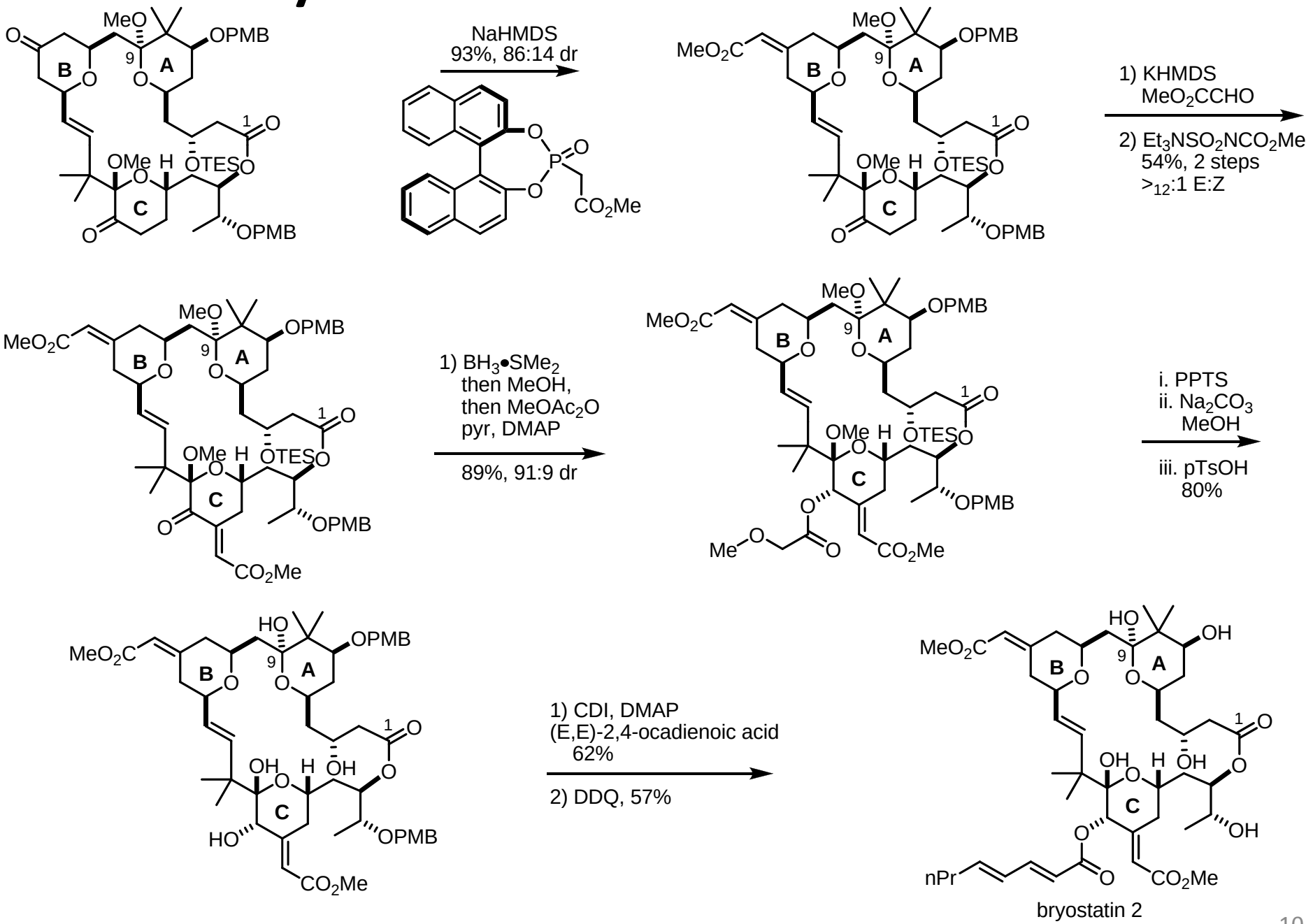
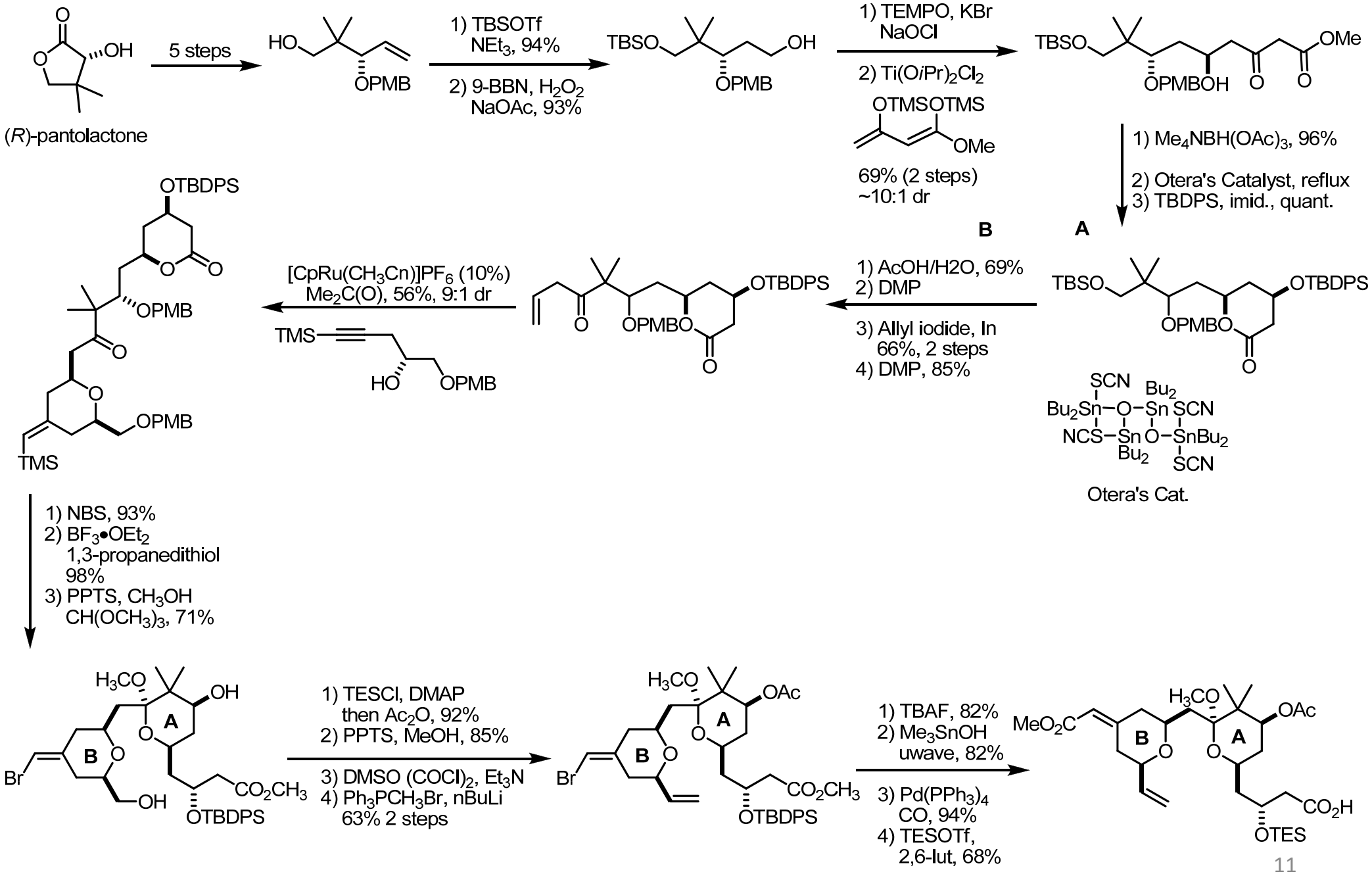
Bryostatin 2 – End Game



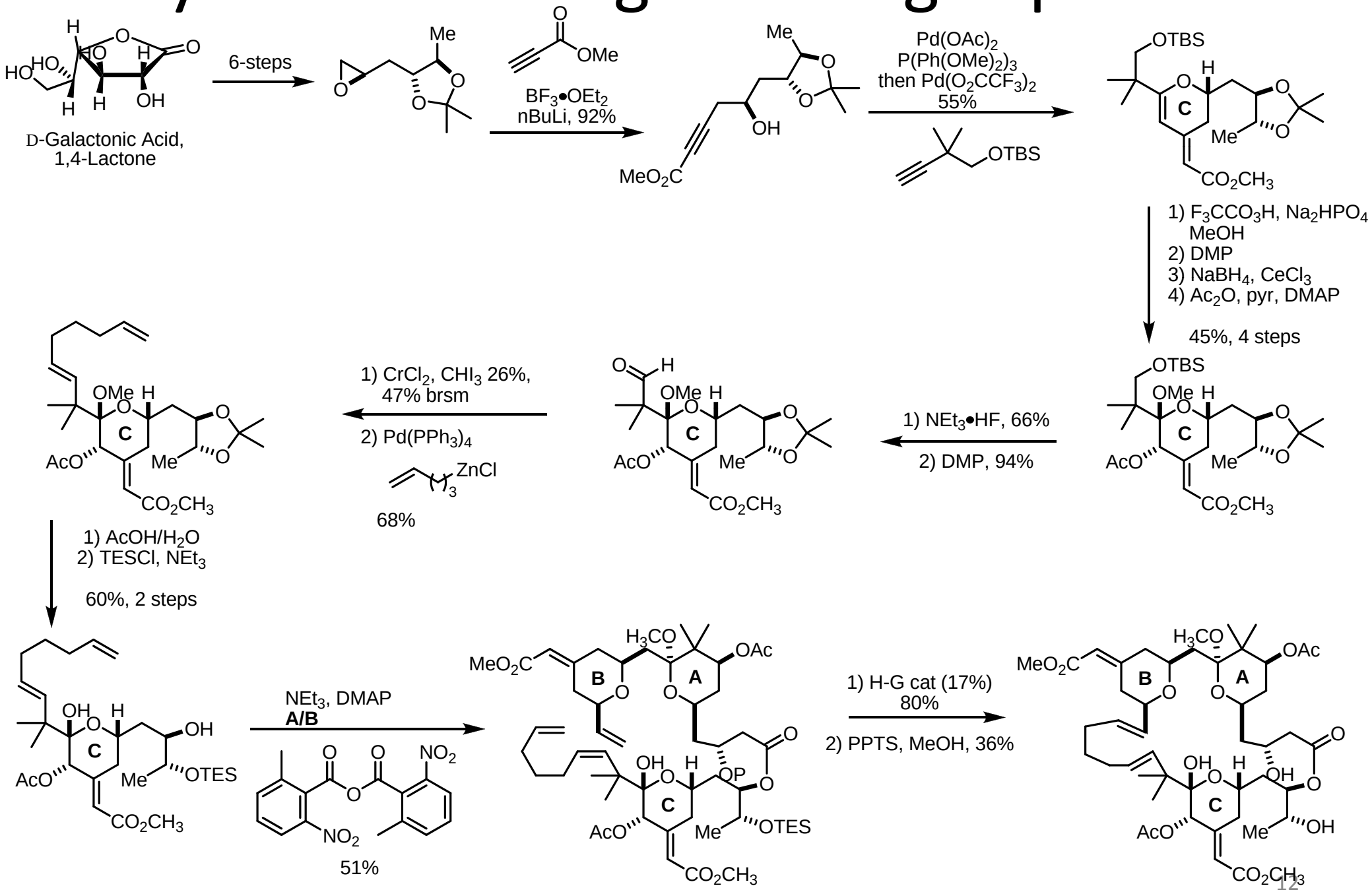
Evans, D.; Carter, P.; Carreira, E.; Charette, A.; Prunet, J.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540-7552.

Bryostatin Analogue – Ring Expansion



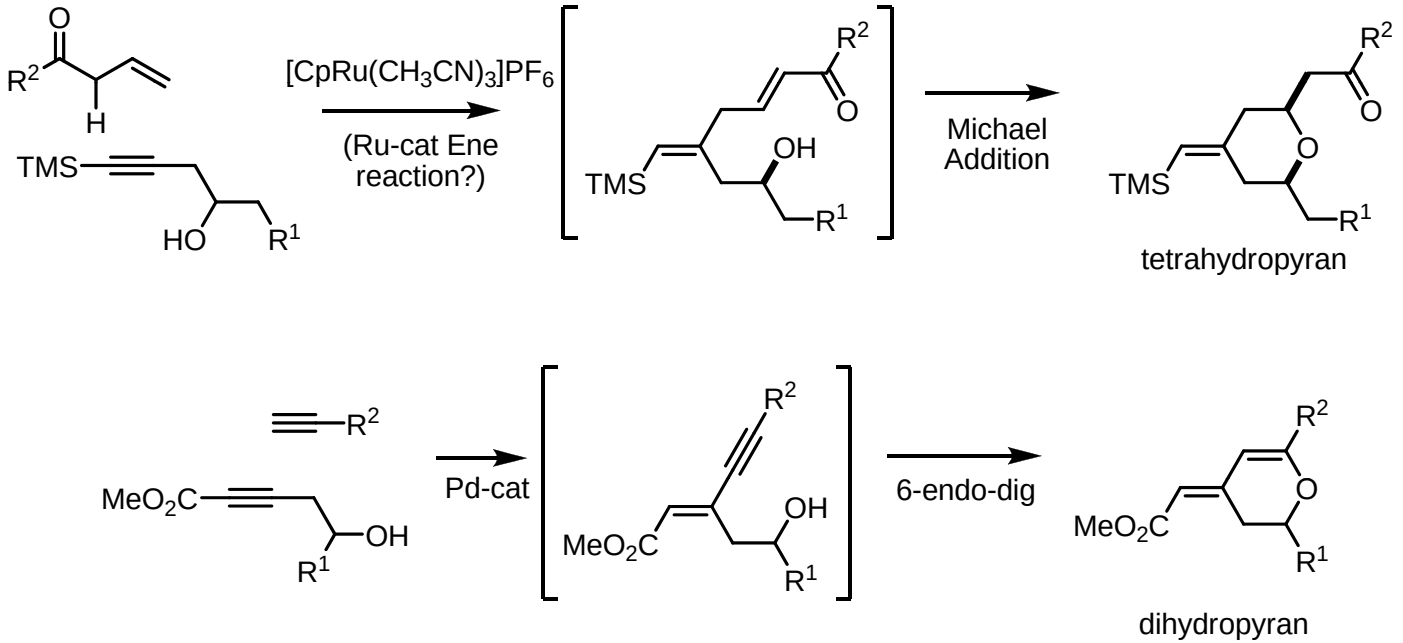
Trost, B.; Yang, H.; Thiel, O.; Frontier, A.; Brindle, C. *J. Am. Chem. Soc.* **2007**, *129*, 2206-2207.

Bryostatin Analogue – Ring Expansion



Trost, B.; Yang, H.; Thiel, O.; Frontier, A.; Brindle, C. *J. Am. Chem. Soc.* **2007**, *129*, 2206-2207.

Pyran Formation



Trost, B.; Yang, H.; Wuitschik, G. *Org. Lett.* **2005**, *7*, 4761-4764.
Trost, B.; Frontier, A. *J. Am. Chem. Soc.* **2000**, *122*, 11727-11728.

Metathesis

olefin reactivity ↑

Type I - Rapid homodimerization, homodimers consumable

Type II - Slow homodimerization, homodimers sparingly consumable

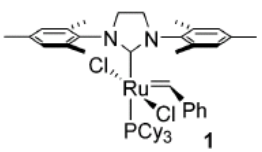
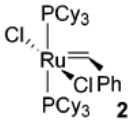
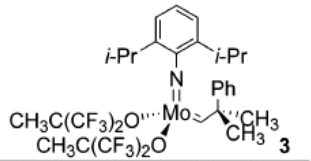
Type III - No homodimerization

Type IV - Olefins inert to CM, but do not deactivate catalyst (Spectator)

Reaction between two olefins of Type I = *Statistical CM*

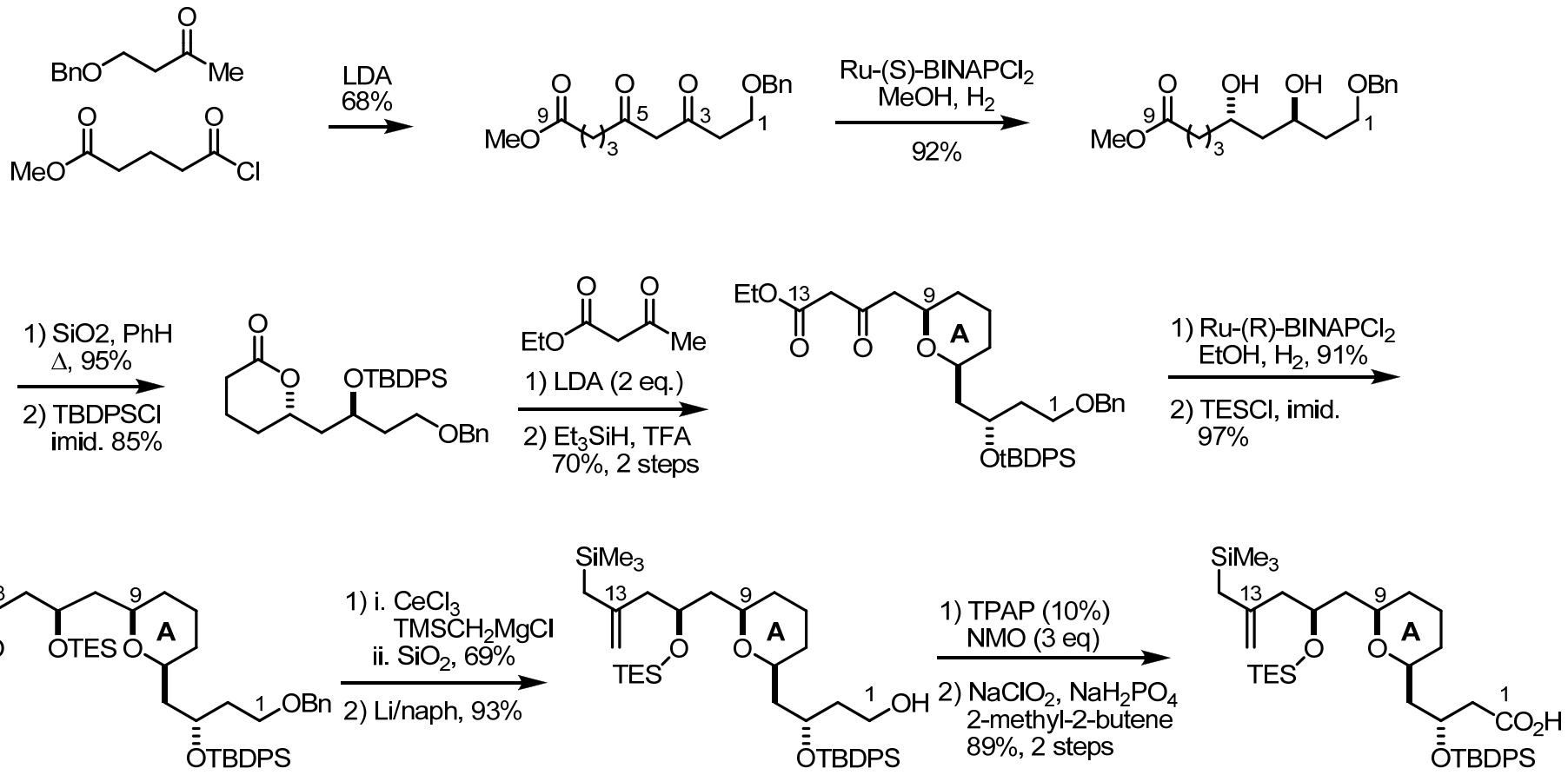
Reaction between two olefins of same type (non-Type I) = *Non-selective CM*

Reaction between olefins of two different types = *Selective CM*

Olefin type	 1	 2	 3
Type I (fast homodimerization)	terminal olefins,[6] 1° allylic alcohols, esters,[6h,20] allyl boronate esters,[6f] allyl halides,[6f,6i] styrenes (no large ortho substit.),[6c,d,f,i] allyl phosphonates,[6d] allyl silanes,[25] allyl phosphine oxides,[6h] allyl sulfides,[6h] protected allyl amines[6h]	terminal olefins,[8] allyl silanes,[14,18,19] 1° allylic alcohols, ethers, esters,[8,19,21] allyl boronate esters,[10f] allyl halides[17]	terminal olefins,[11a,b,12,14] allyl silanes[11b]
Type II (slow homodimerization)	styrenes (large ortho substit.),[6d,f] acrylates,[6b,i] acrylamides,[6c] acrylic acid,[6c] acrolein,[6b,24] vinyl ketones,[6b] unprotected 3° allylic alcohols,[6f,h] vinyl epoxides,[6b] 2° allylic alcohols, perfluorinated alkane olefins[6b,23]	styrene,[16] 2° allylic alcohols, vinyl dioxolanes,[8] vinyl boronates[8]	styrene,[11a,11b] allyl stannanes[15]
Type III (no homodimerization)	1,1-disubstituted olefins,[6a,g] non-bulky trisub. olefins,[6a,g] vinyl phosphonates,[6d] phenyl vinyl sulfone,[22] 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)	vinyl siloxanes[16]	3° allyl amines,[14] acrylonitrile[12]
Type IV (spectators to CM)	vinyl nitro olefins, trisubstituted allyl alcohols (protected)	1,1-disubstituted olefins,[8] disub. α,β-unsaturated carbonyls, 4° allylic carbon-containing olefins,[8] perfluorinated alkane olefins,[8] 3° allyl amines (protected)[14]	1,1-disubstituted olefins[11a]

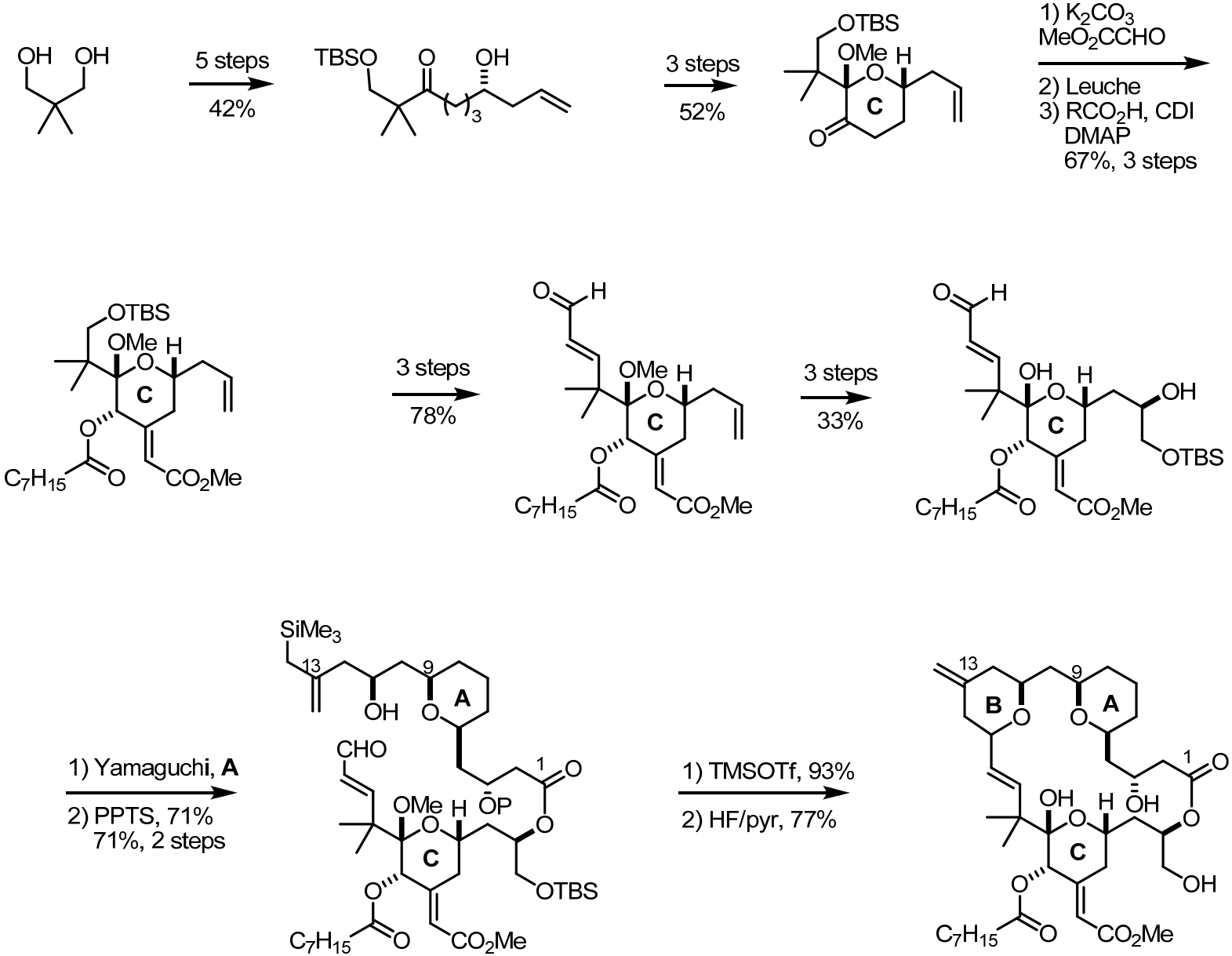
Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.
Debra J. Wallace *Angewandte Chemie International Edition*. **2005**, *44*, 1912-1915.

Bryostatin Analogue – Prins Strategy



Wender, P. A.; DeChristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658-6659.

Bryostatin Analogue – Prins Stragegy



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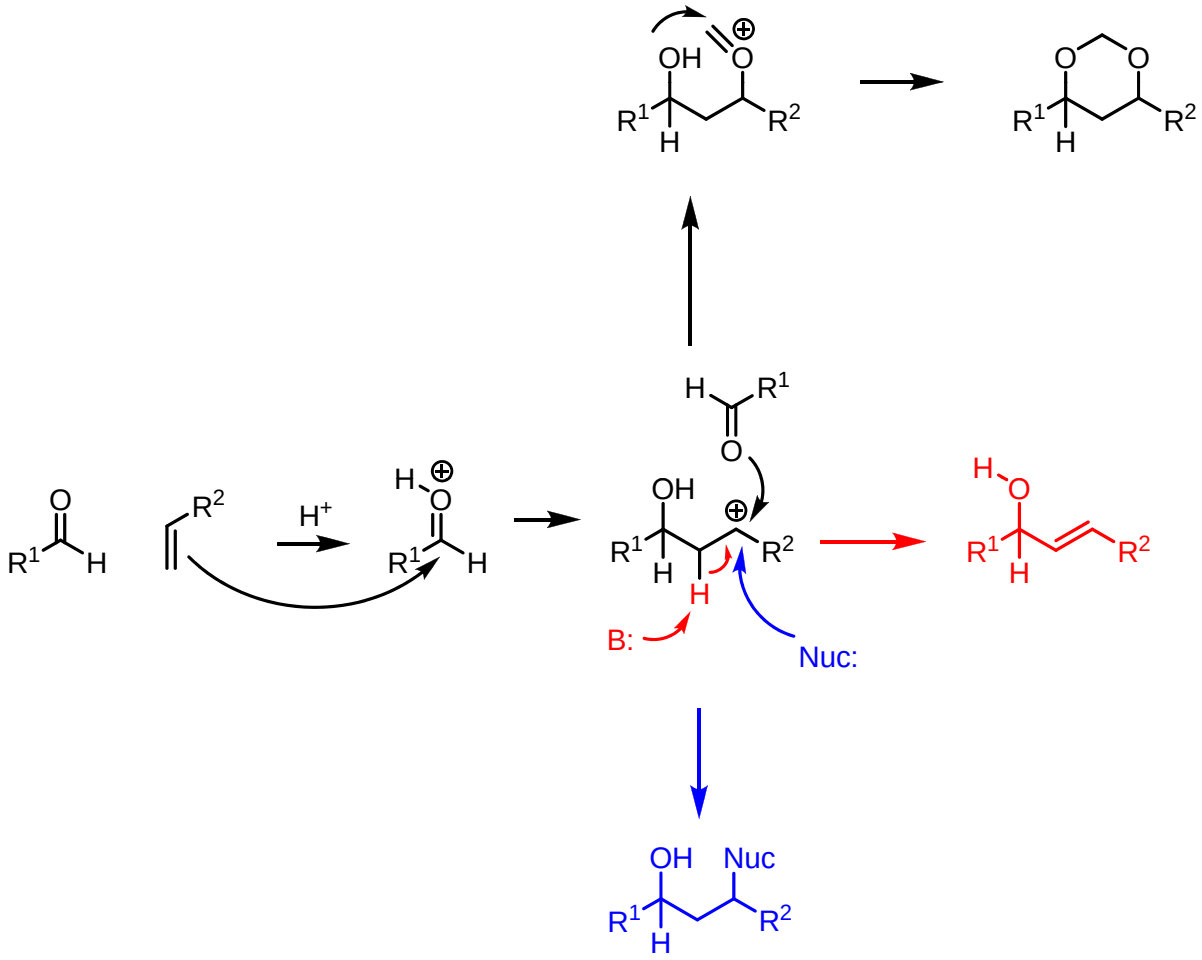
Prins Reaction



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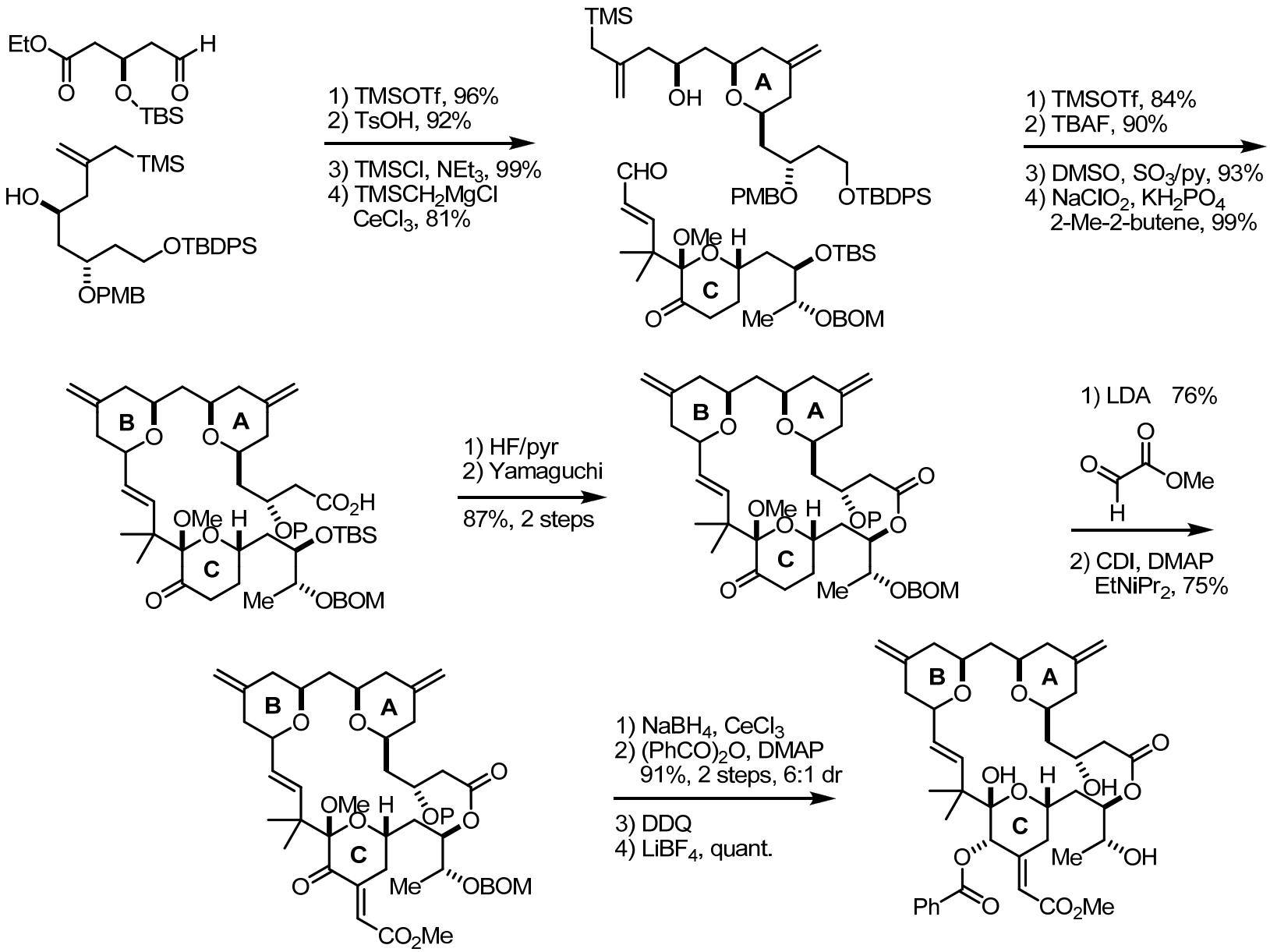
Bryostatin Analogue – Double Annulation



Keck, G. E.; Kraft, M. B.; Truong, A. P.; Li, W.; Sanchez, C. C.; Kedei, N.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **2008**, *130*, 6660-6661.