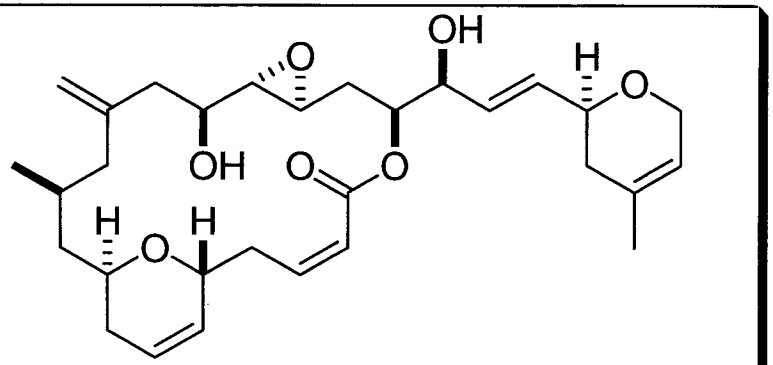
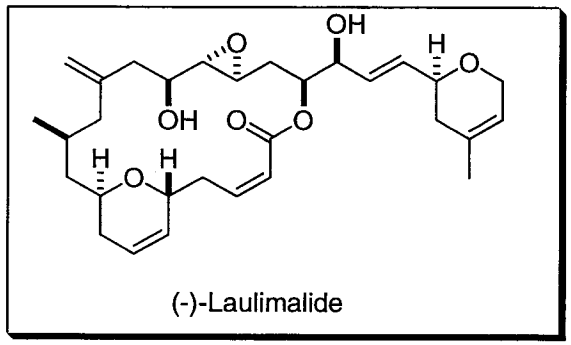
Selected Syntheses of Laulimalide



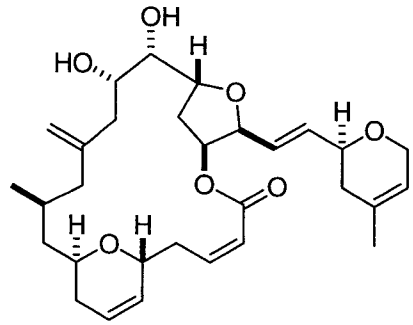
(-)-Laulimalide

Steve Tymonko
12/10/02

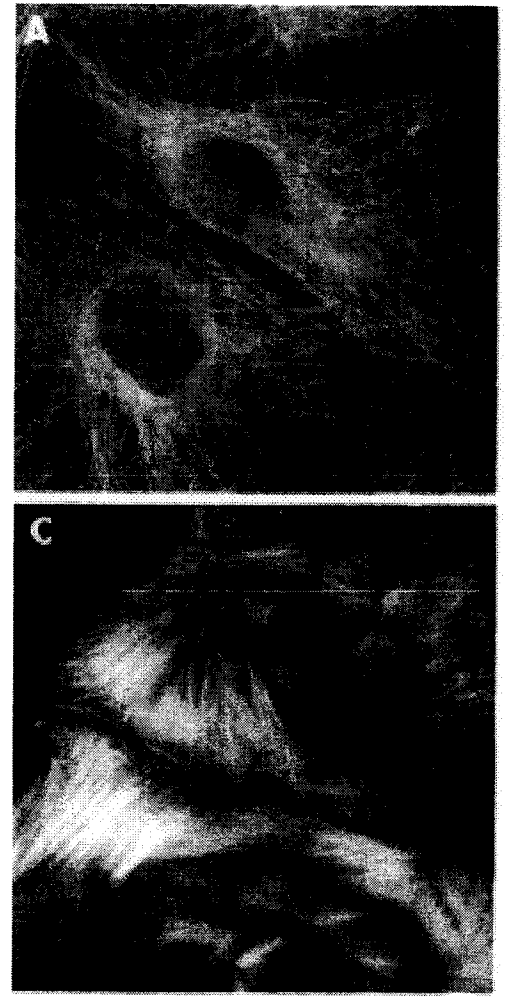
Laulimalide: Potent Anti-Tumor Agent



(-)-Laulimalide



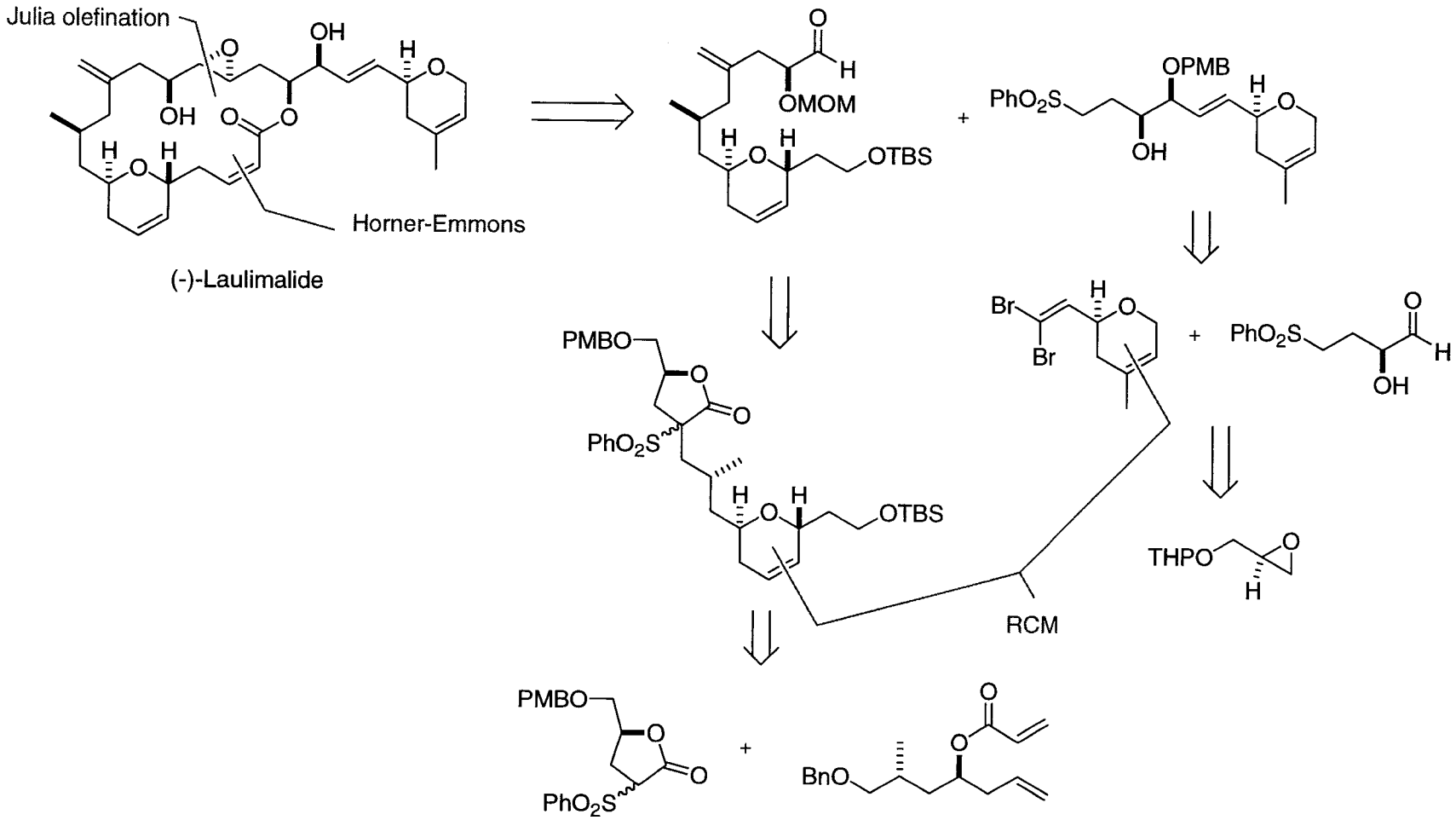
isolaulimalide



- First isolated in 1988 from *Spongia mycofijiensis*
- Structure initially determined by NMR
- X-ray confirmation of absolute configuration in 1996
- IC_{50} = 10-50 μM in several lines of cancer cells
- Active against multi-drug resistant cell line
- Promotes tubulin polymerization

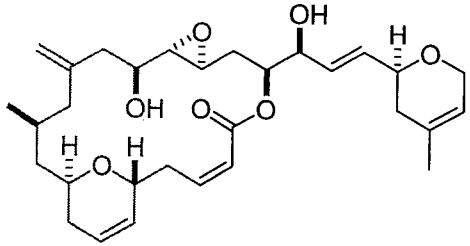
Quinoa, E.; Kakou, Y.; Crews, P. J. *J. Org. Chem.* **1988**, *53*, 3642
Jefford, C.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159.
Mooberry, S. et. Al. *Cancer Res.* **1999**, *59*, 653.

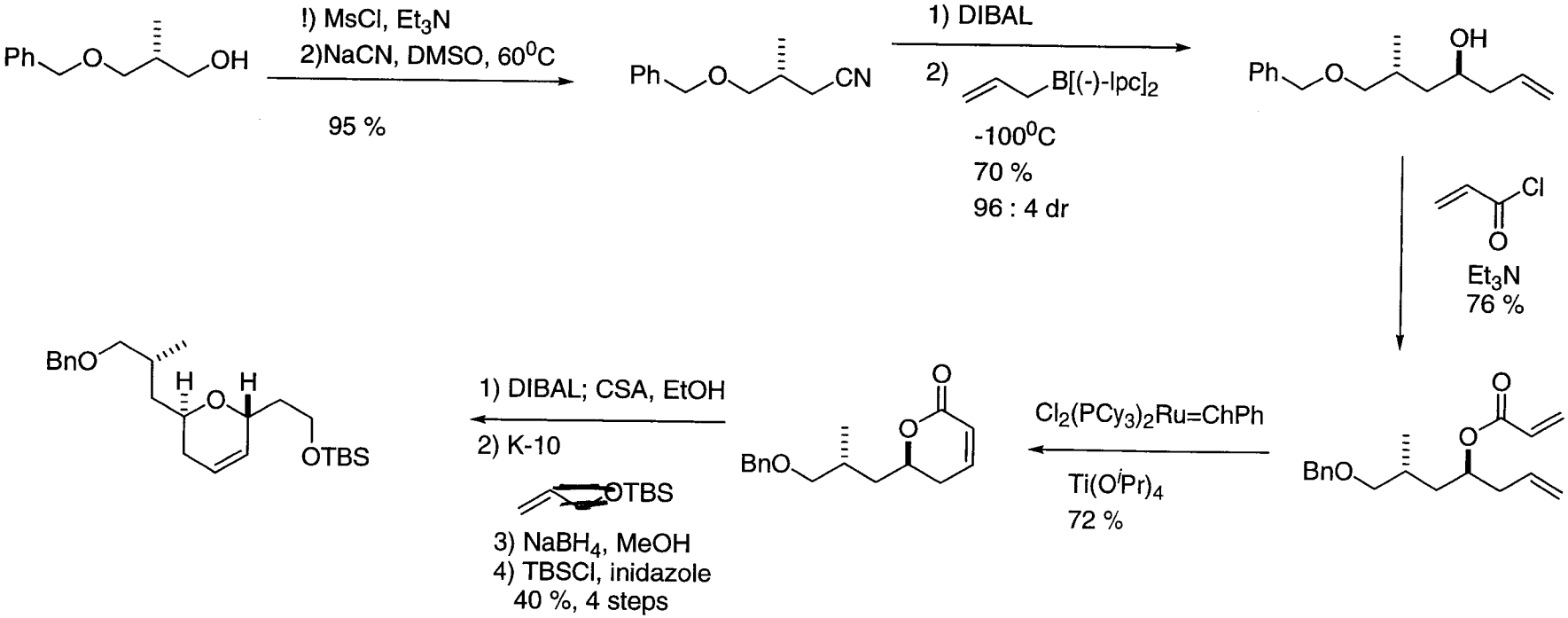
Ghosh: Retrosynthesis



Ghosh, A.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027

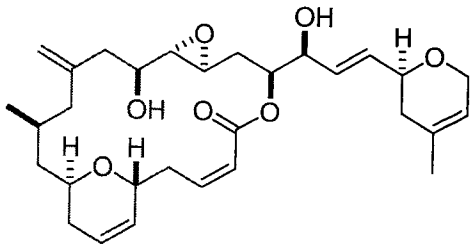
Ghosh: C_3-C_{16} Fragment

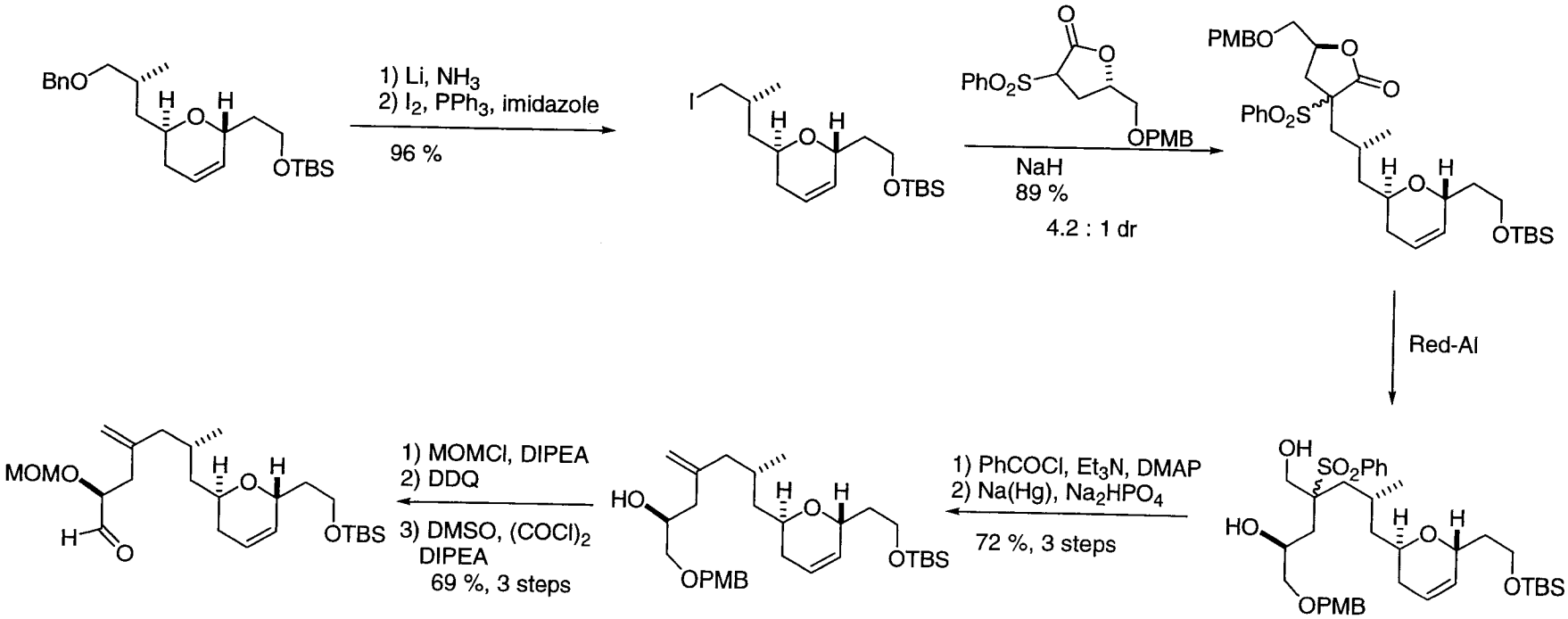




Ghosh, A.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027
Ghosh, A.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 2319

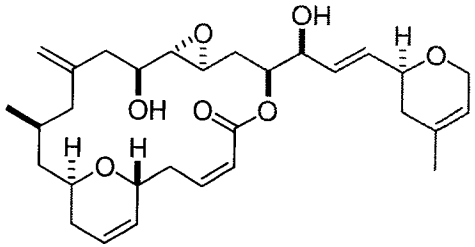
Ghosh: C_3-C_{16} Fragment Cont.

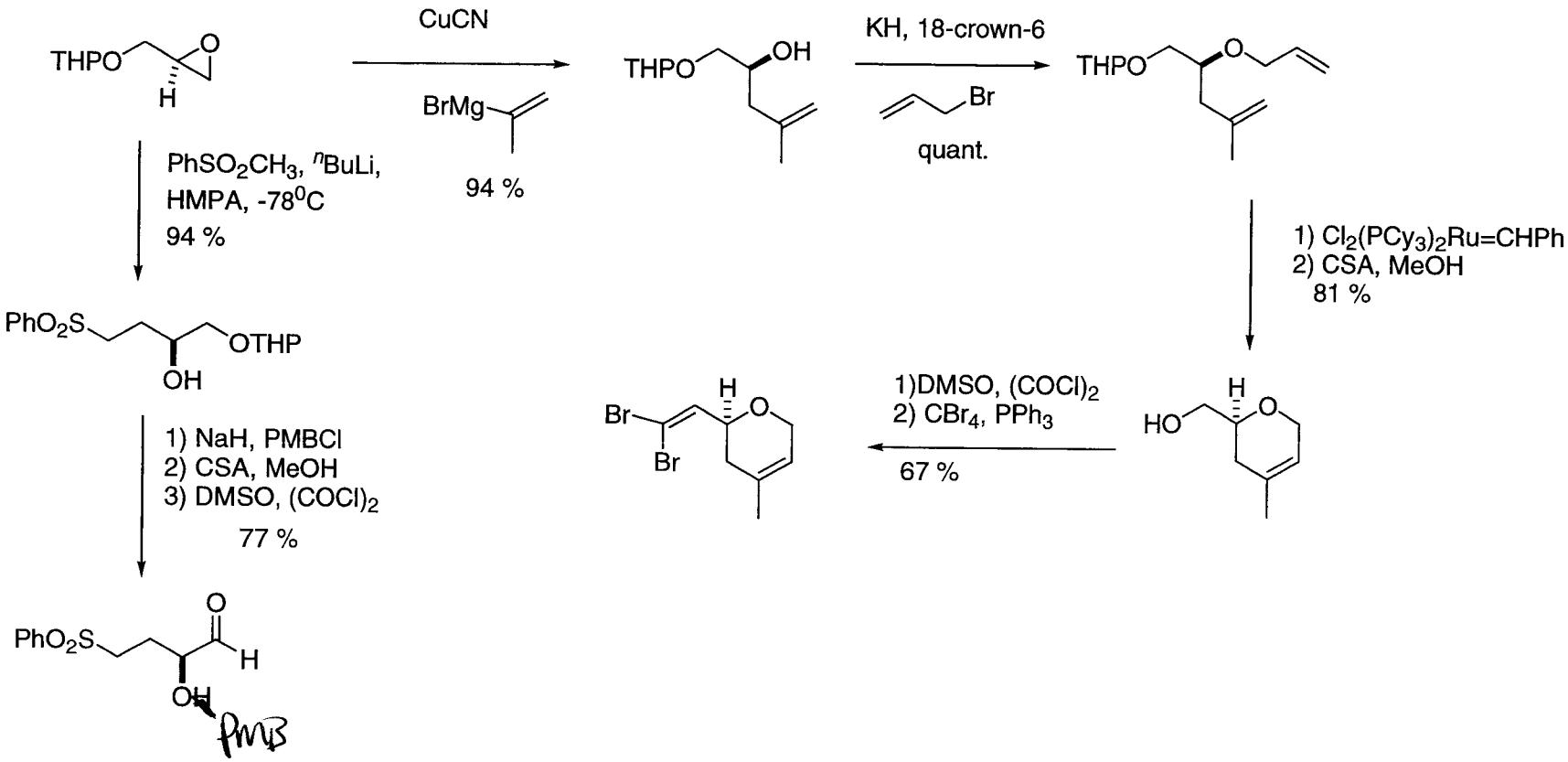




Ghosh, A.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027
Ghosh, A.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 2319

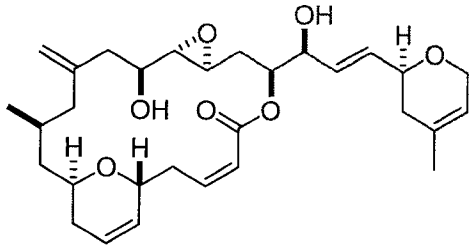
Ghosh: C_{17}-C_{27} Fragment

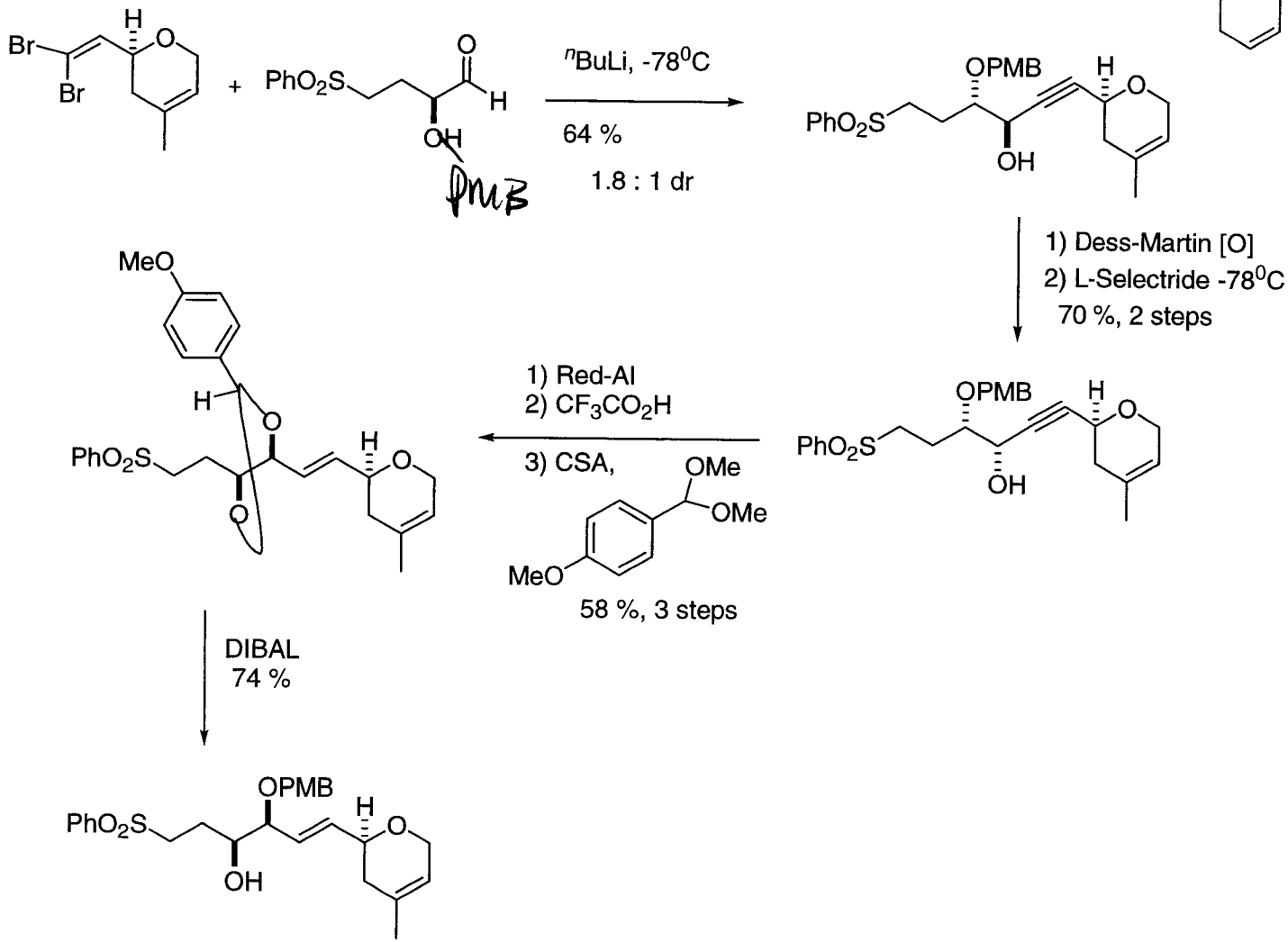




Ghosh, A.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027
Ghosh, A.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 4705

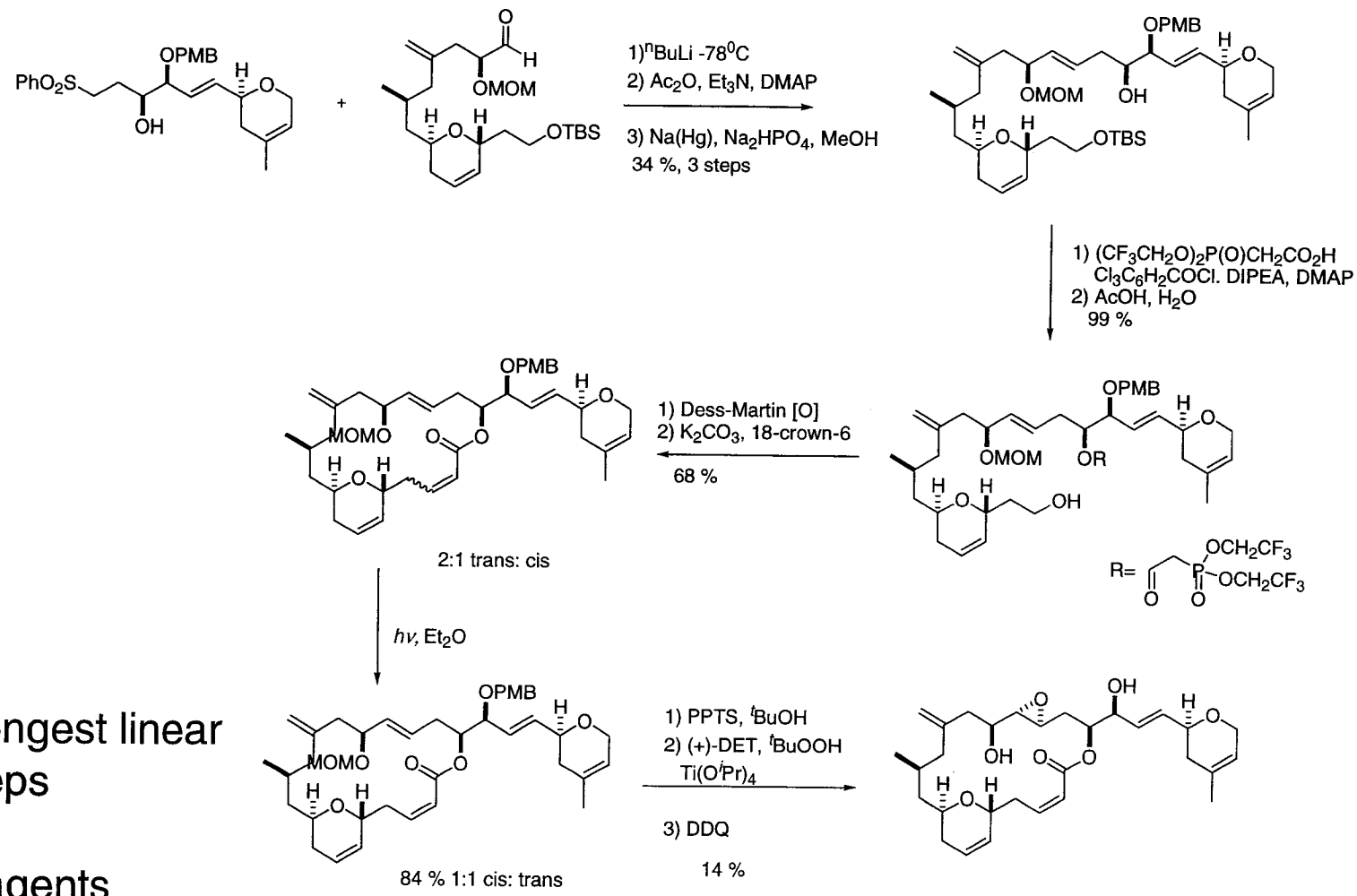
Ghosh: C_{17}-C_{27} Fragment Cont.





Ghosh, A.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027
Ghosh, A.; Wang, Y. *Tetrahedron Lett.* **2000**, *41*, 4705

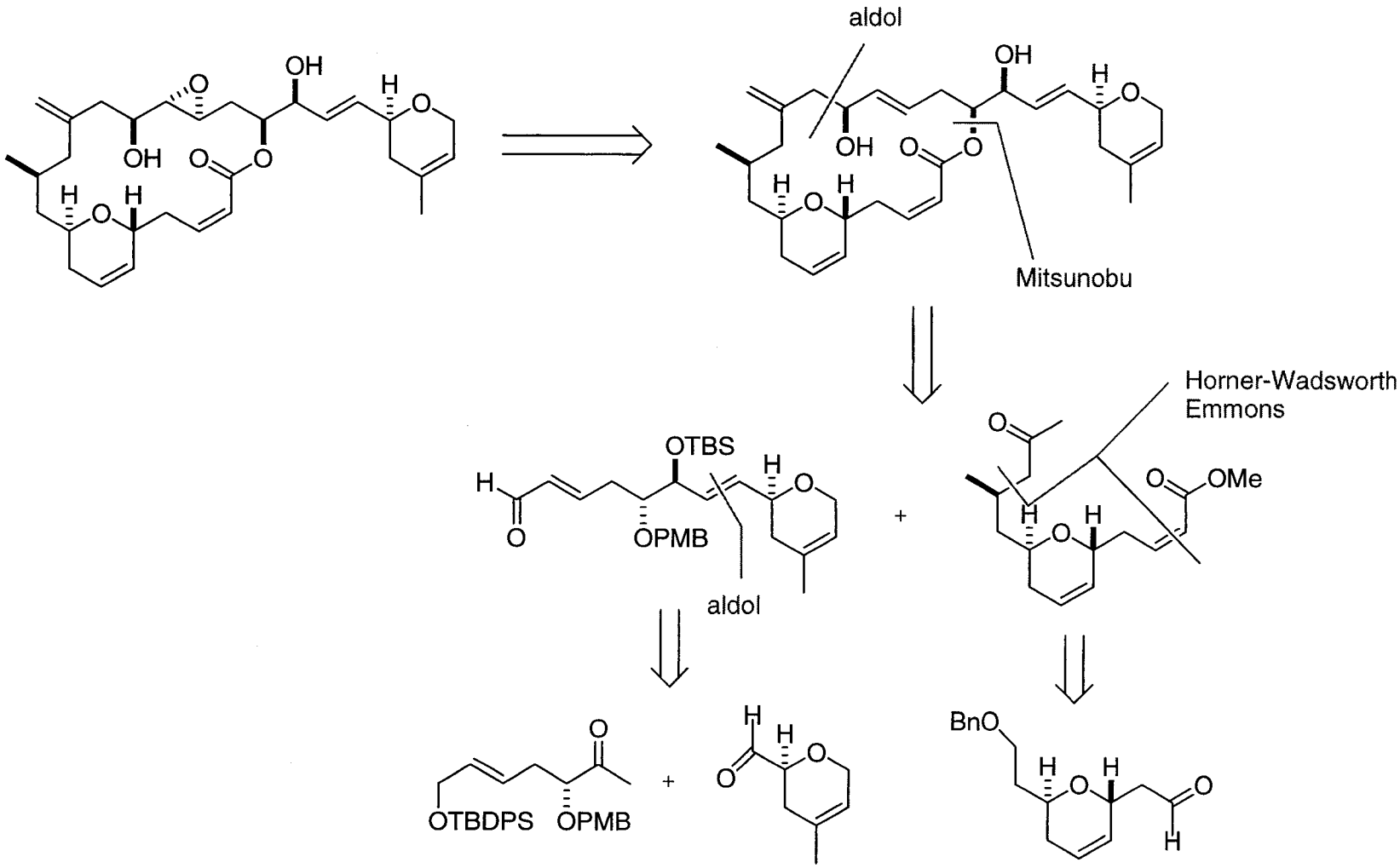
Ghosh: Completion



30 steps longest linear
47 total steps
0.2% yield
2 chiral reagents
3 chiral pool materials

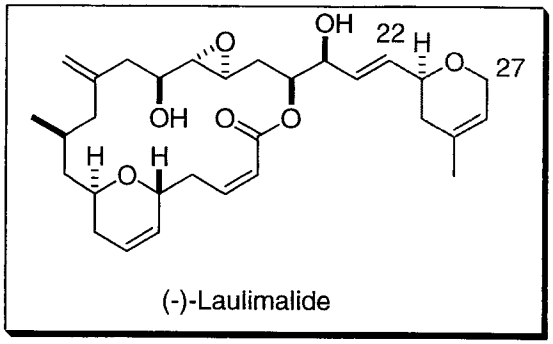
Ghosh, A.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027

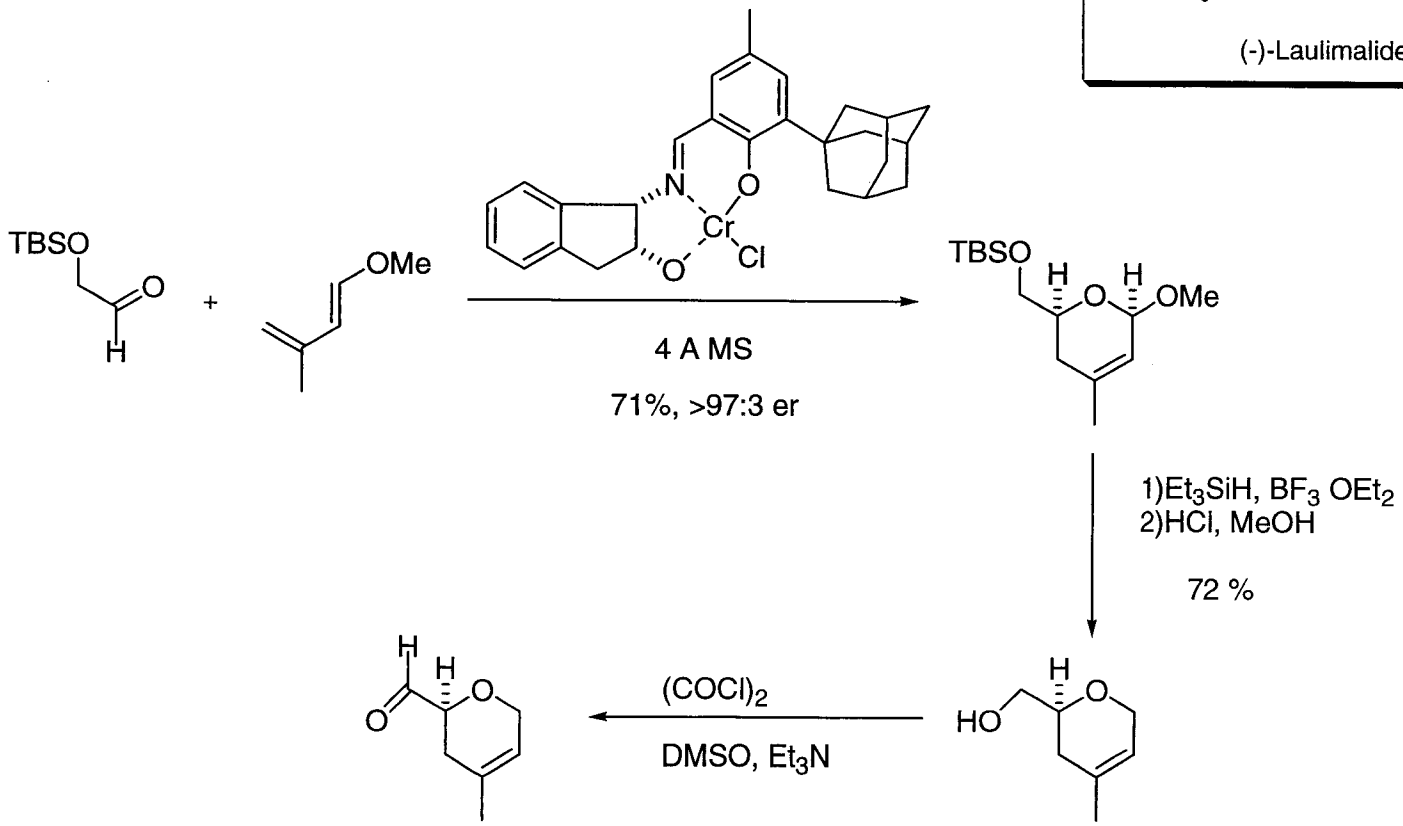
Paterson: Retrosynthesis



Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149

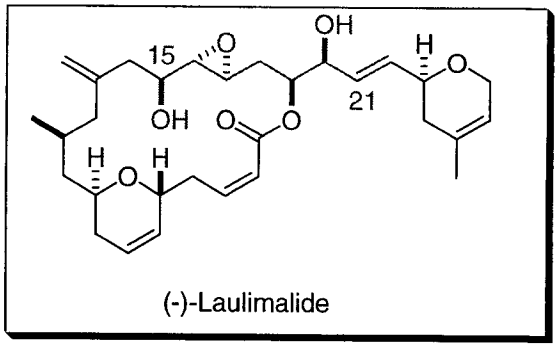
Paterson: C_{22}-C_{27} Fragment

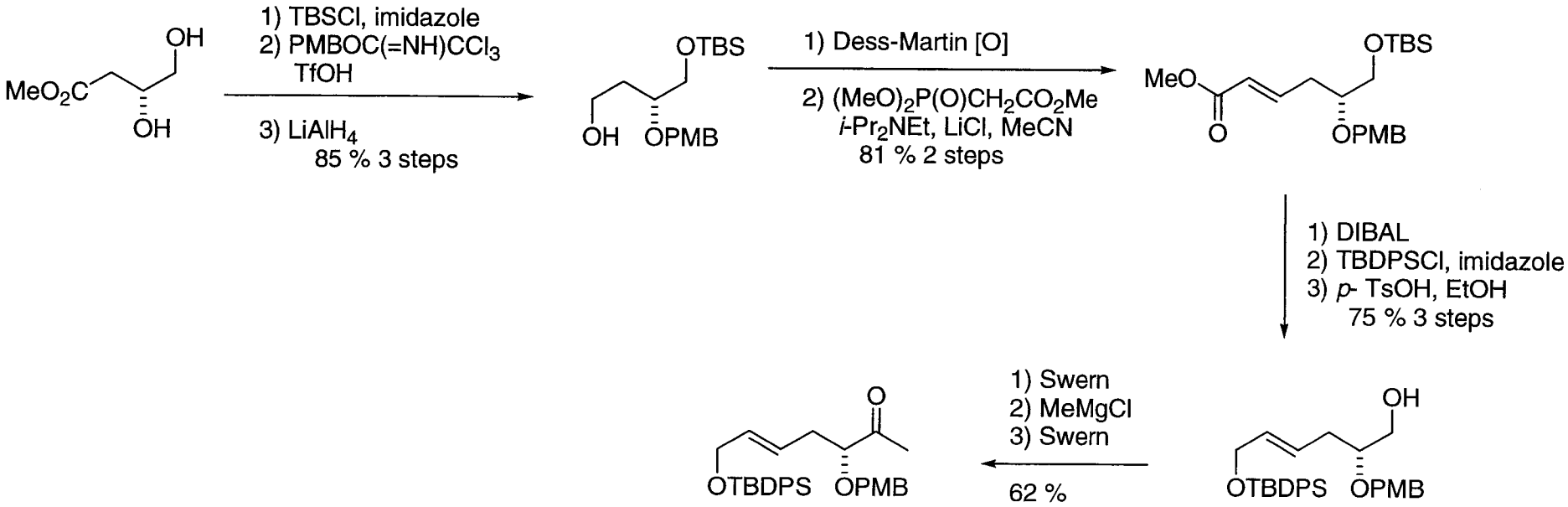




Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149

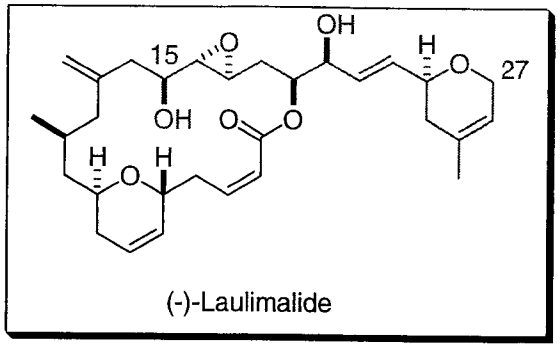
Paterson: C_{15}-C_{21} Fragment

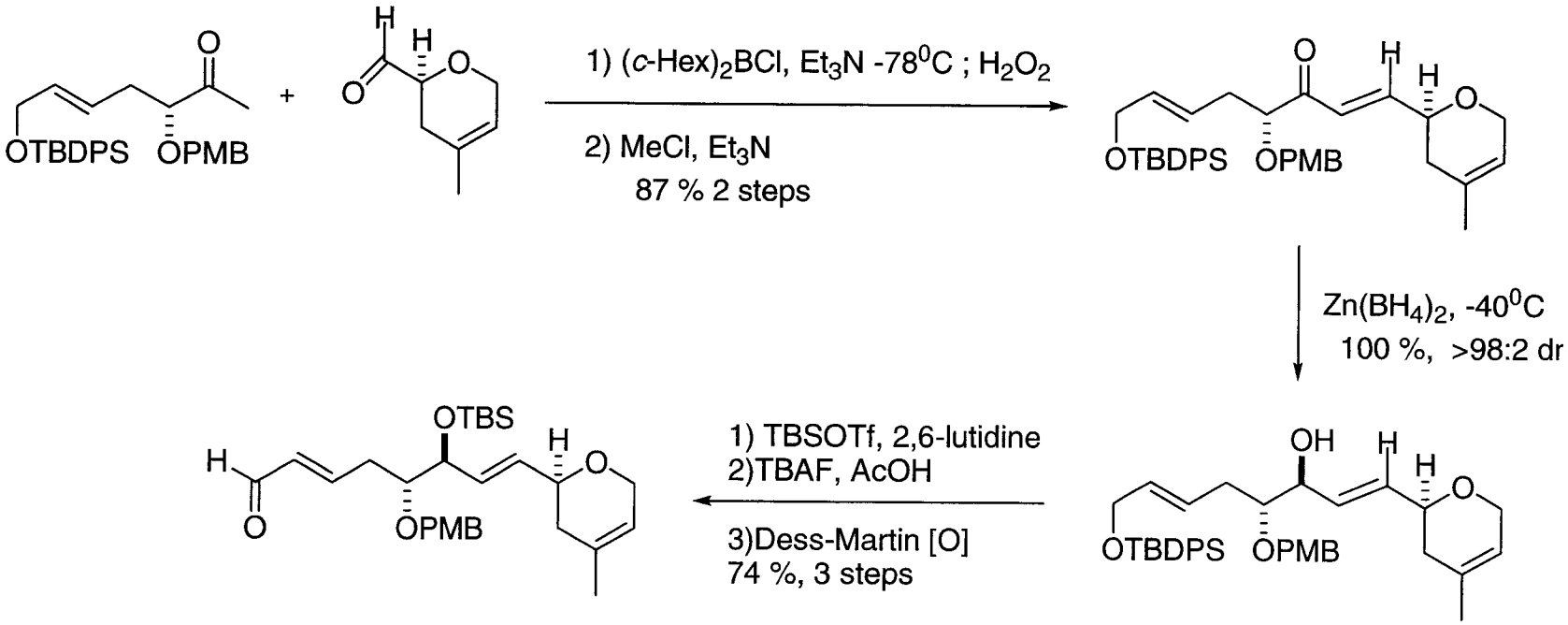




Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149

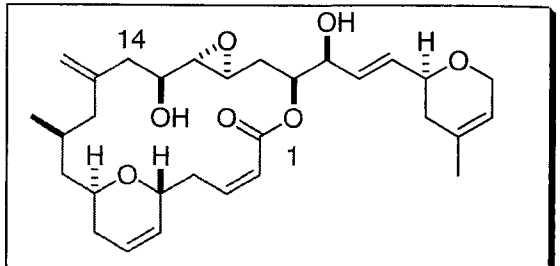
Paterson: C_{15}-C_{27} Fragment



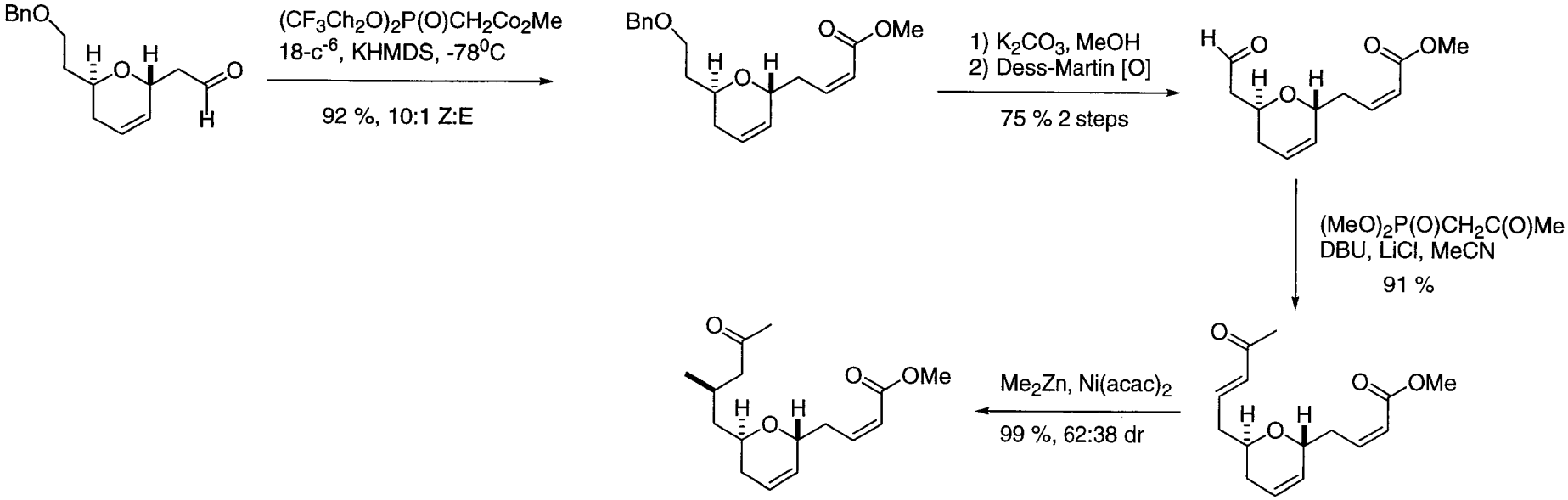


Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149

Paterson: C_1-C_{14} Fragment

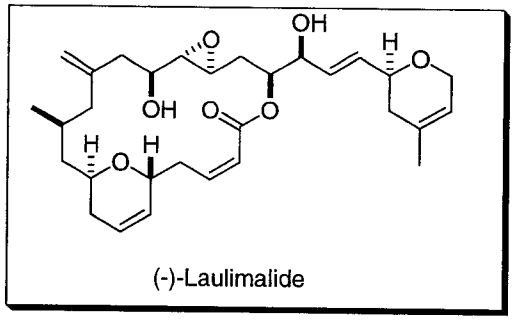


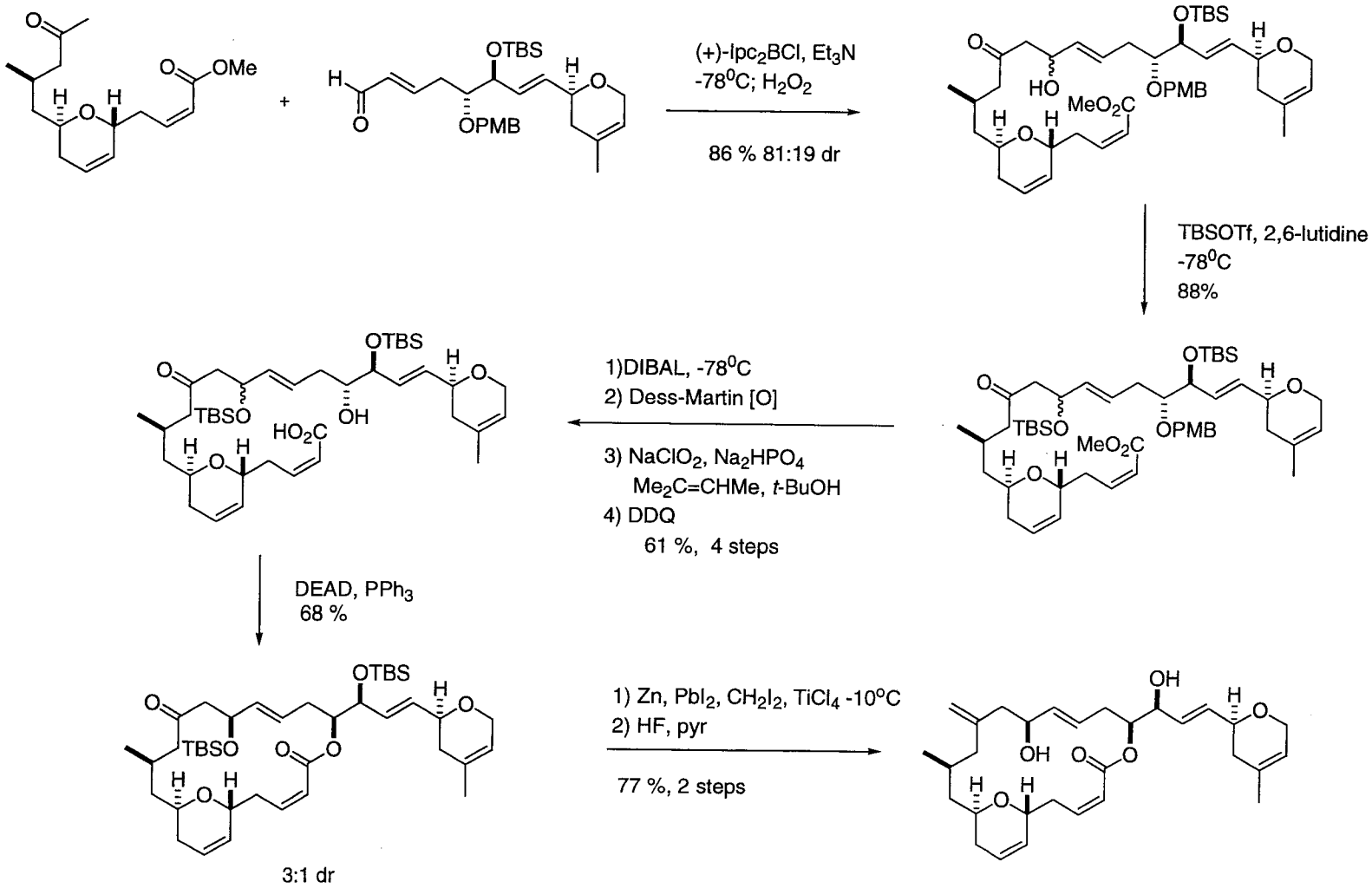
(-)-Laulimalide



Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149

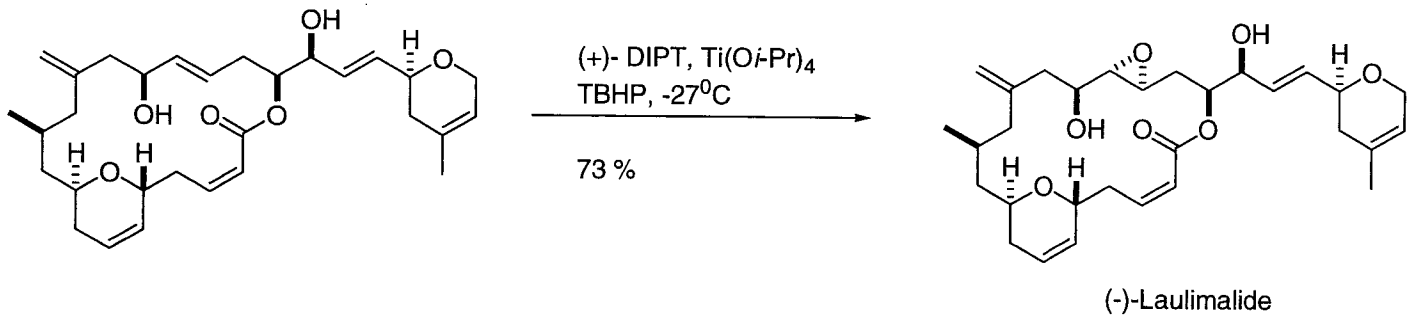
Paterson: Macrocycle





Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149

Paterson: Completion

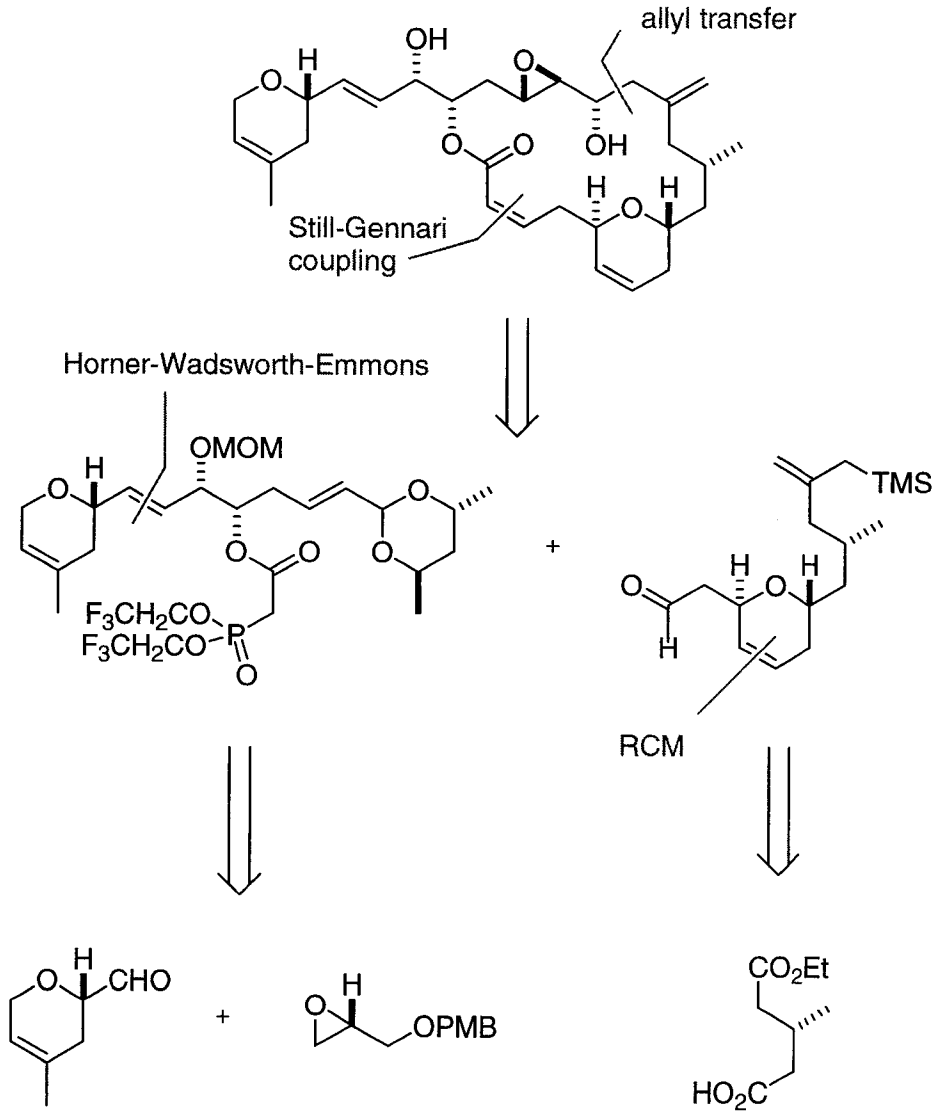


(-)-Laulimalide

- 27 steps longest linear
- 36 total steps
- 2.9% yield
- 3 chiral reagents
- 2 chiral pool materials

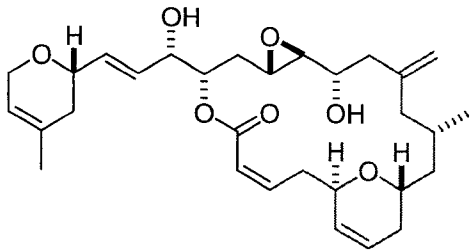
Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149

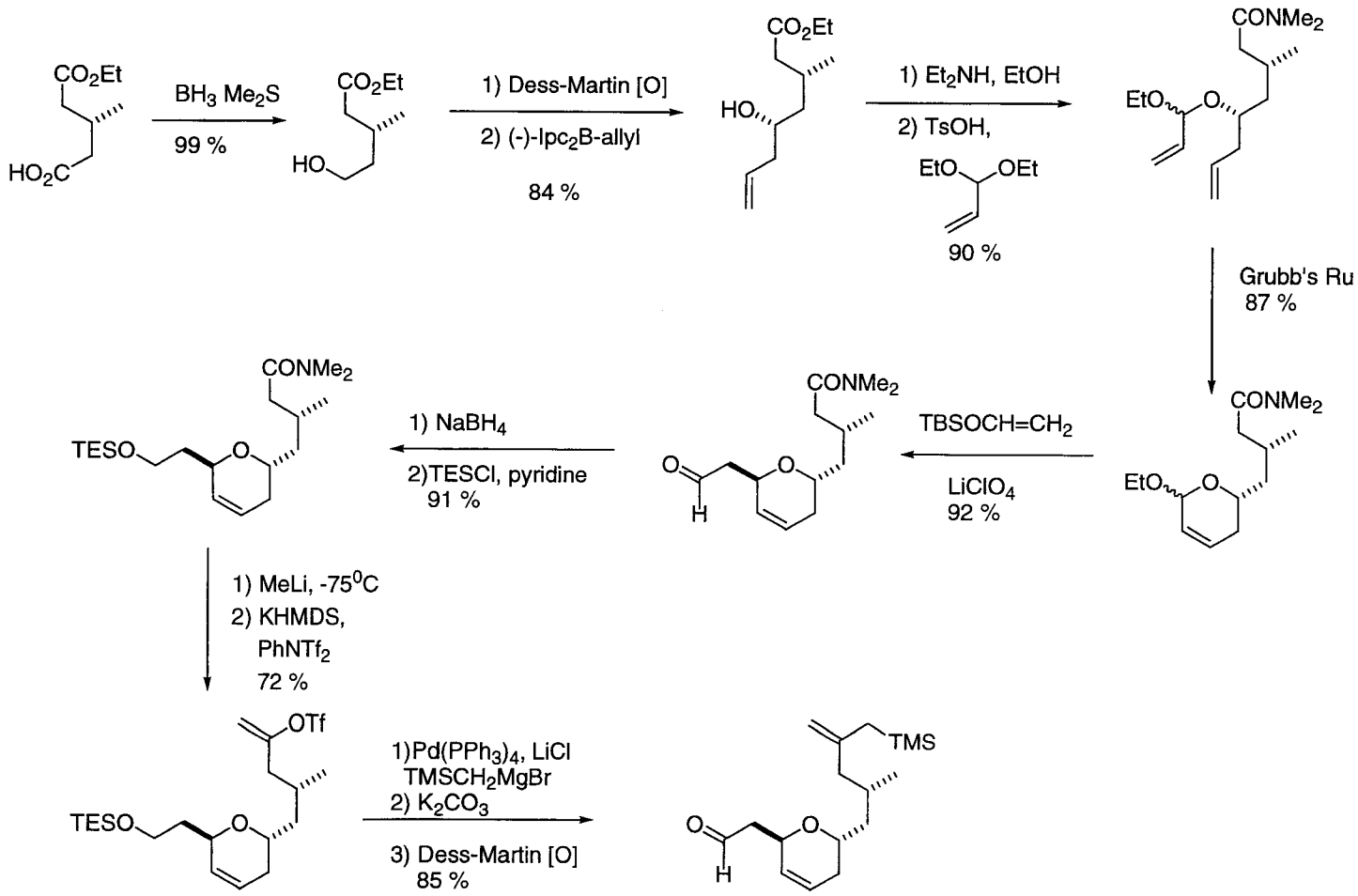
Mulzer: Retrosynthesis



Enev, V.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764

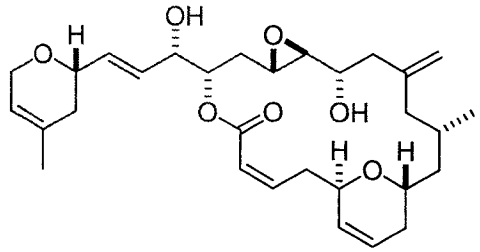
Mulzer: C_3-C_{14} Fragment

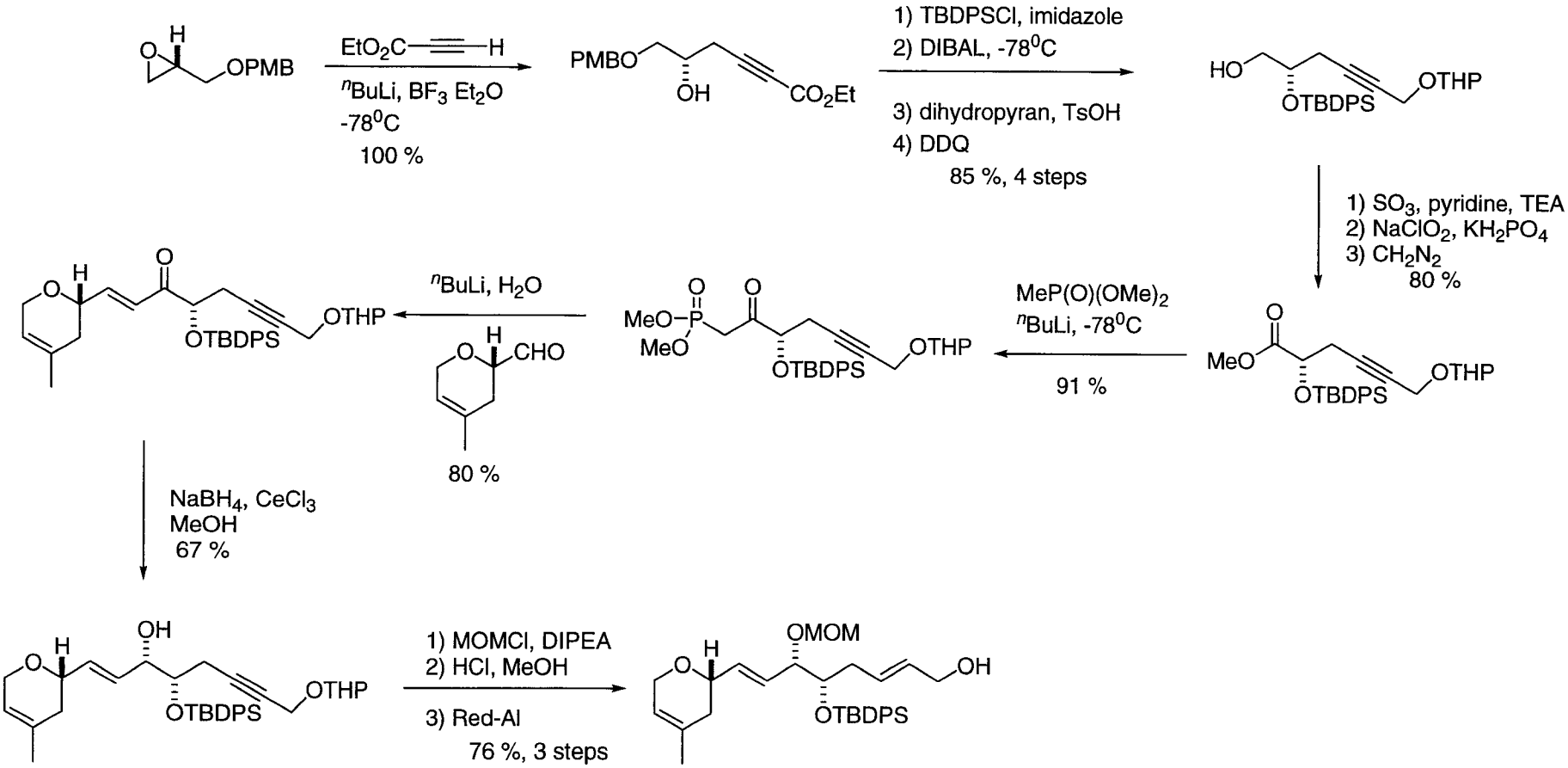




Enev, V.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764

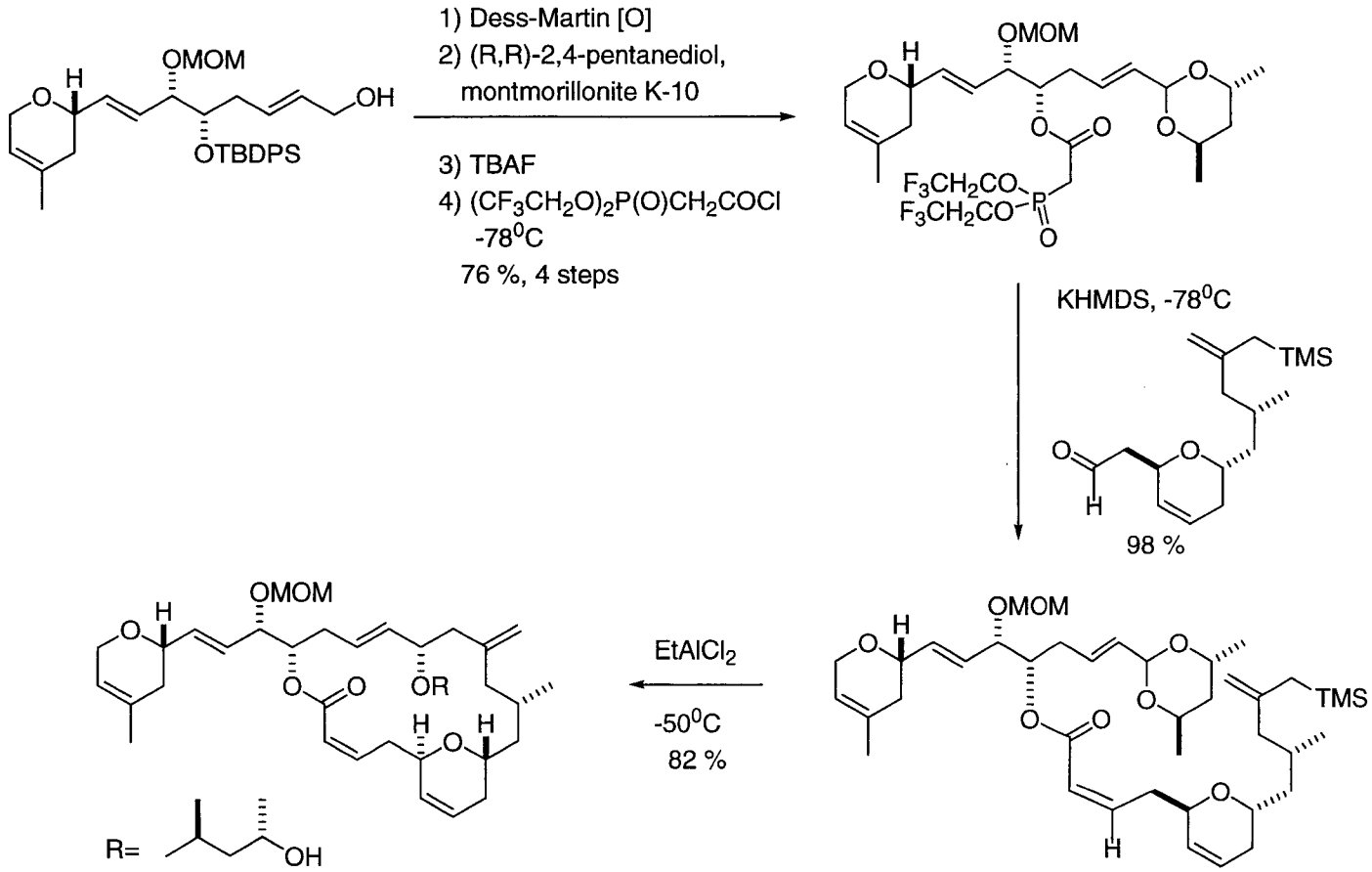
Mulzer: C_{15}-C_{27} Fragment





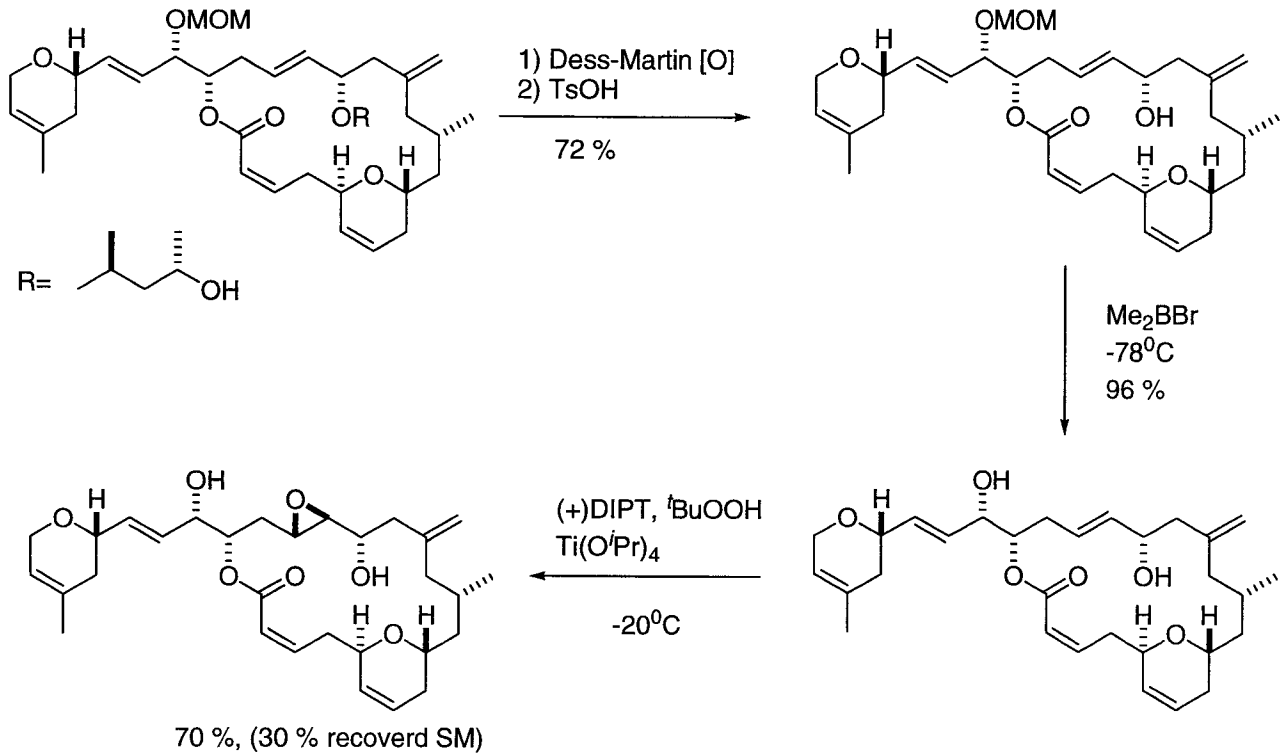
Dorling, K.; Ohler, E.; Mulzer, J. *Tetrahedron Lett.* **2000**, *41*, 6323

Mulzer: Macrocyclization



Enev, V.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764
Mulzer, J.; Ohler, E.; Enev, V.; Hanbauer, M. *Adv. Synth. Catal.* **2002**, *344*, 573

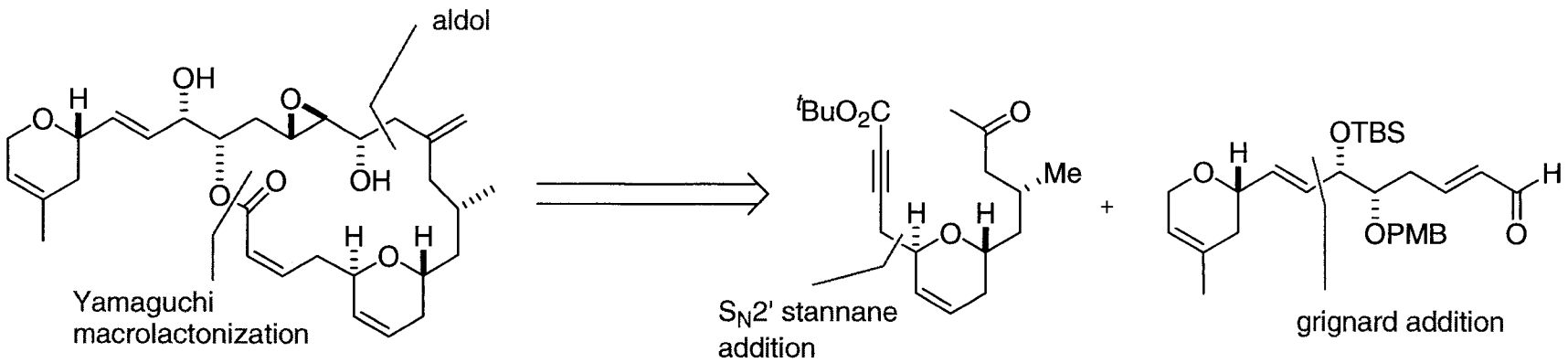
Mulzer: Completion

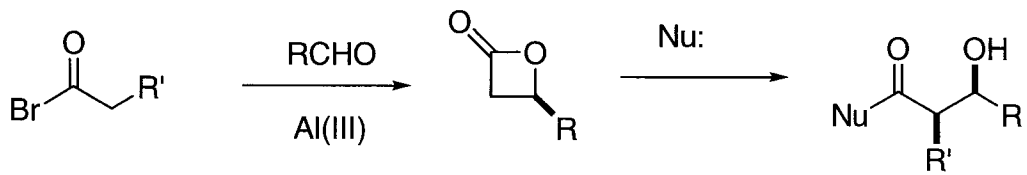


19 steps longest linear
39 total steps
21% yield
2 chiral reagents
3 chiral pool materials

Enev, V.; Kaehlig, H.; Mulzer, J. *J. Am. Chem. Soc.* **2001**, *123*, 10764
Mulzer, J.; Ohler, E. *Angew. Chem. Int. Ed.* **2001**, *40*, 3842

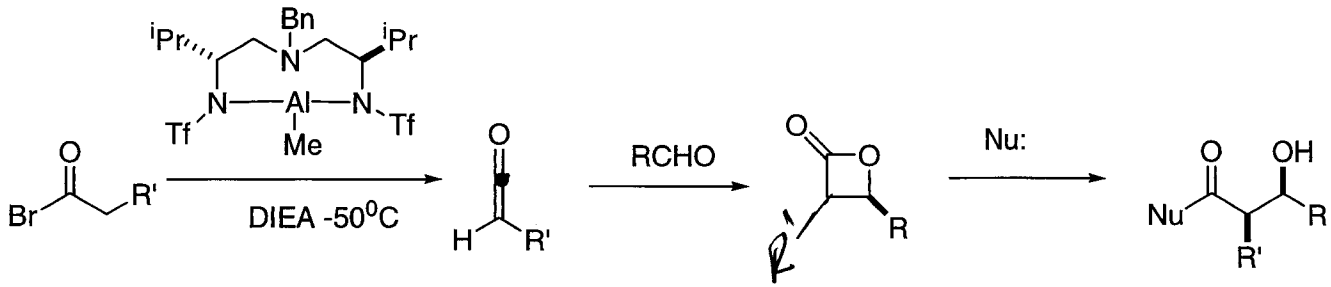
Nelson: Retrosynthesis





Nelson, S.; Cheung, W.; Kassick, A.; Hilifiker, M. *J. Am. Chem. Soc.* **2002**, *124*, 13654

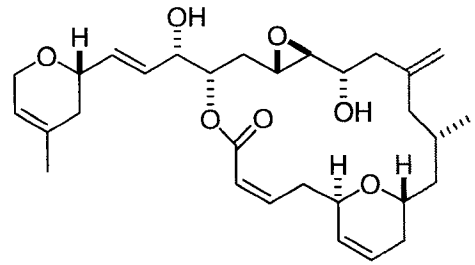
Nelson: Catalytic AAC

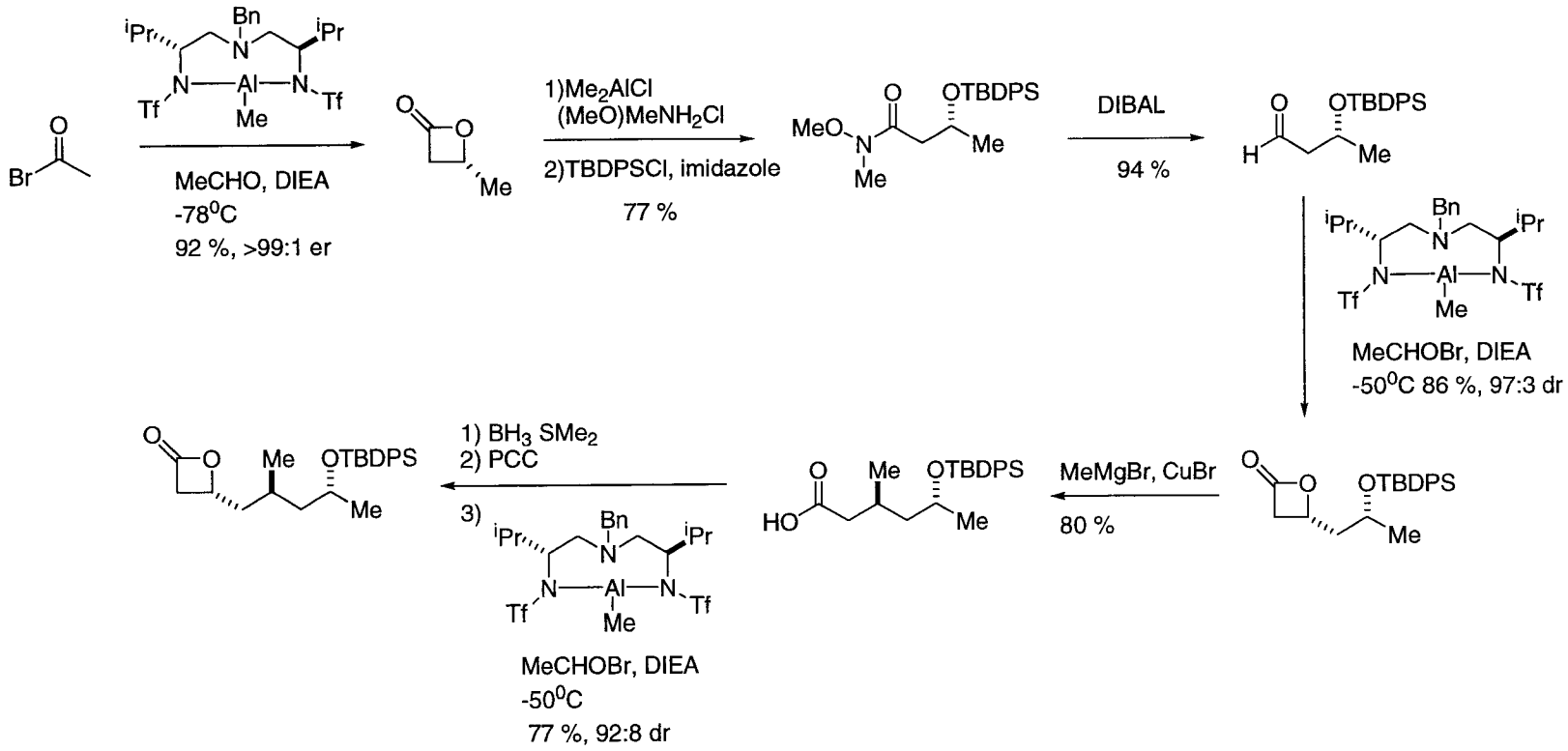


R	R'	yield, %	er	cis:trans
$BnOCH_2$	H	91	96:4	—
$C_{10}H_{21}$	H	91	95: 5	—
$BnOH_2C$—≡—	H	86	96: 4	—
$BnOCH_2$	Me	78	97: 3	88:12
Me—≡—	Me	90	95: 5	99:1
4-$(NO_2)C_6H_4$	Me	90	99: 1	99: 1

Nelson, S.; Peelen, T.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742
Nelson, S.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883.

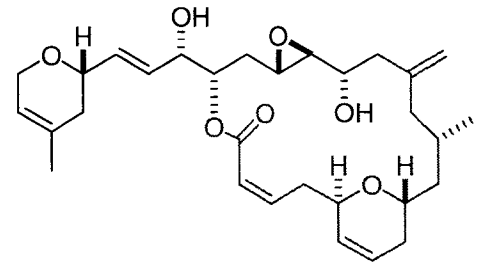
Nelson: C_7-C_{14} Fragment

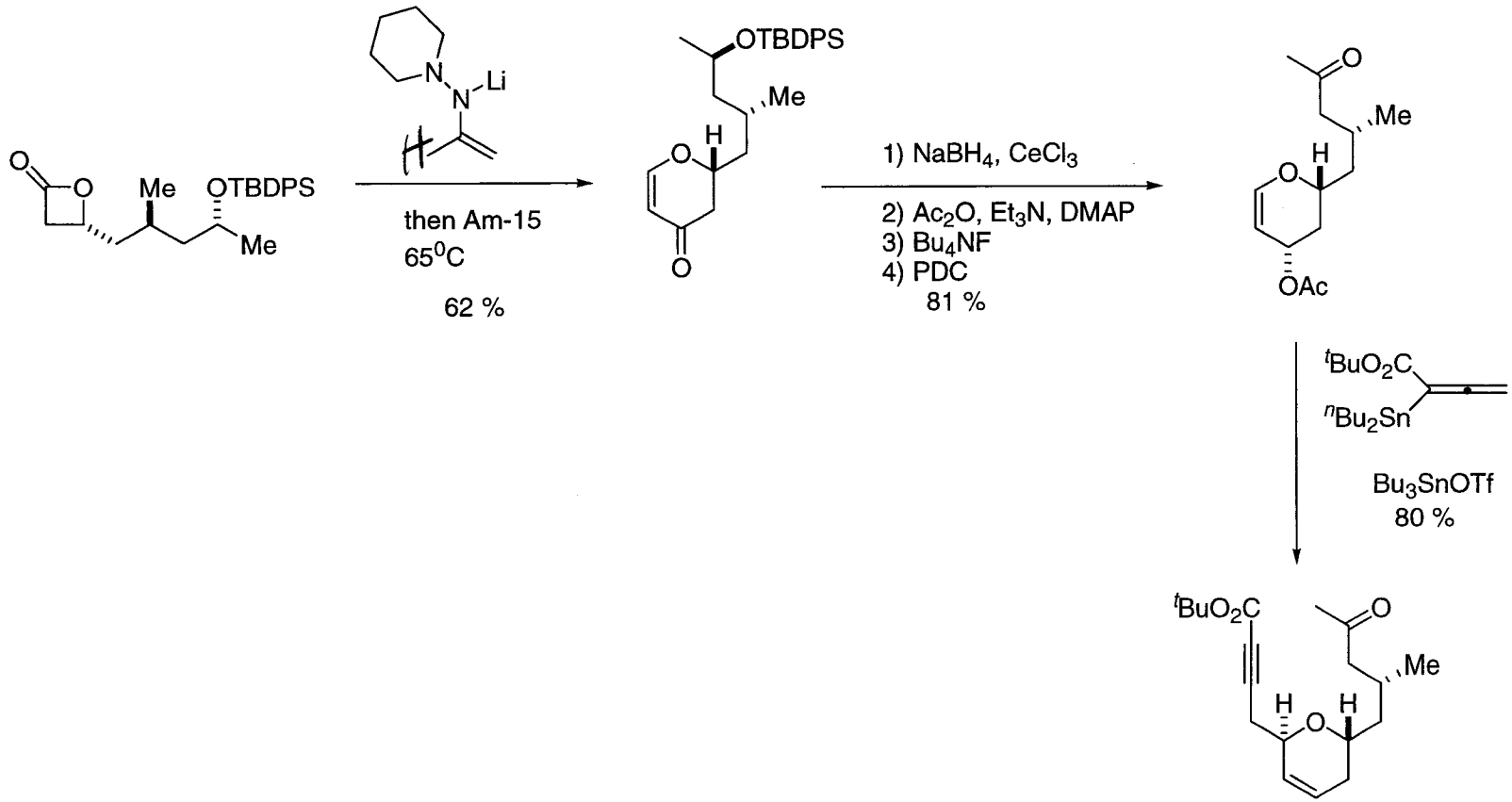




Nelson, S.; Cheung, W.; Kassick, A.; Hilifiker, M. *J. Am. Chem. Soc.* **2002**, *124*, 13654

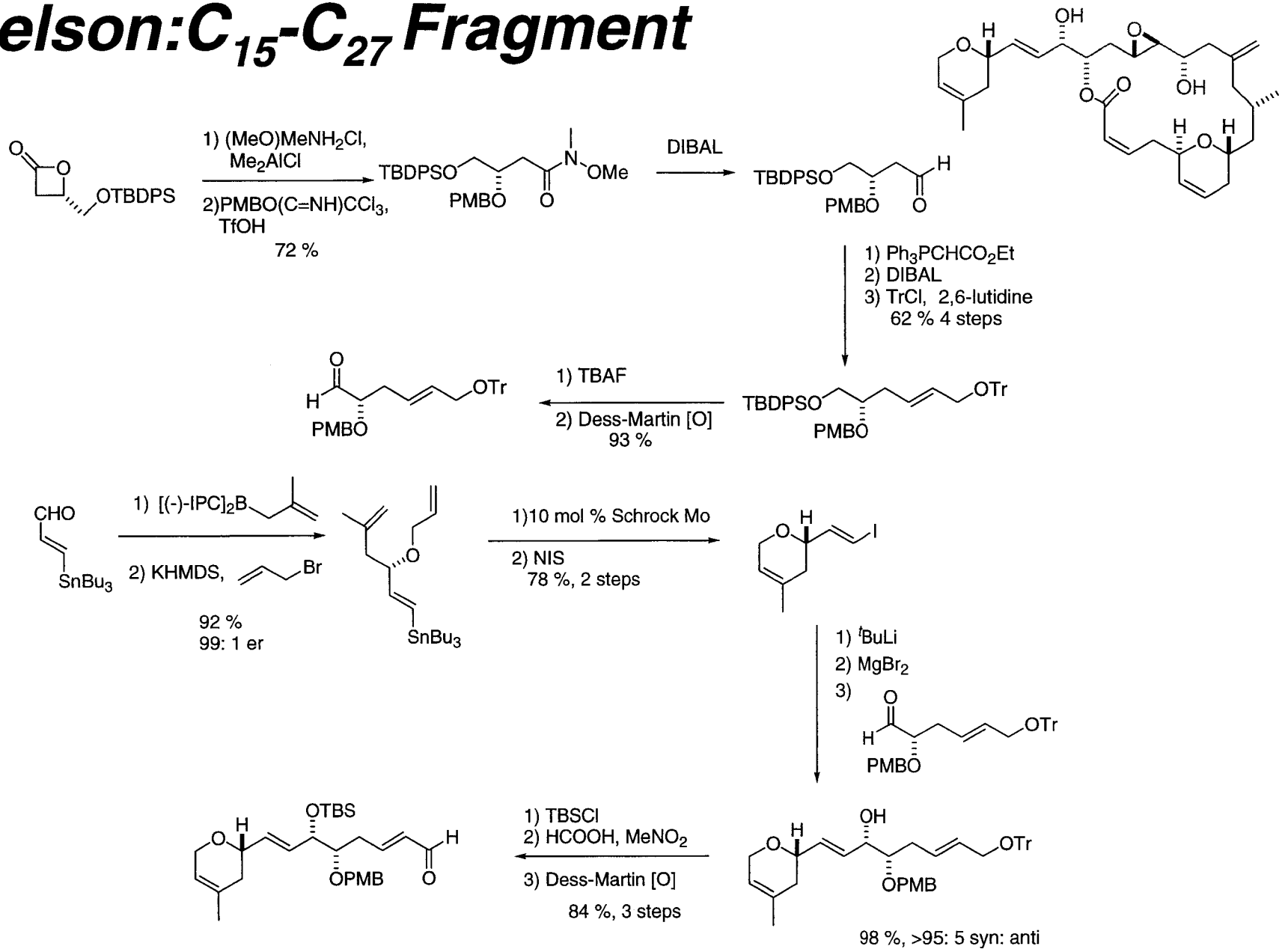
Nelson: C_1-C_{14} Fragment





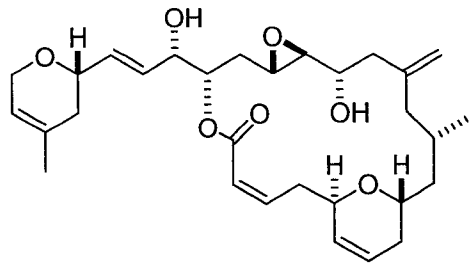
Nelson, S.; Cheung, W.; Kassick, A.; Hilifiker, M. *J. Am. Chem. Soc.* **2002**, *124*, 13654
Zipp, G.; Hilifiker, M.; Nelson, S. *Org. Lett.* **2002**, *4*, 1823

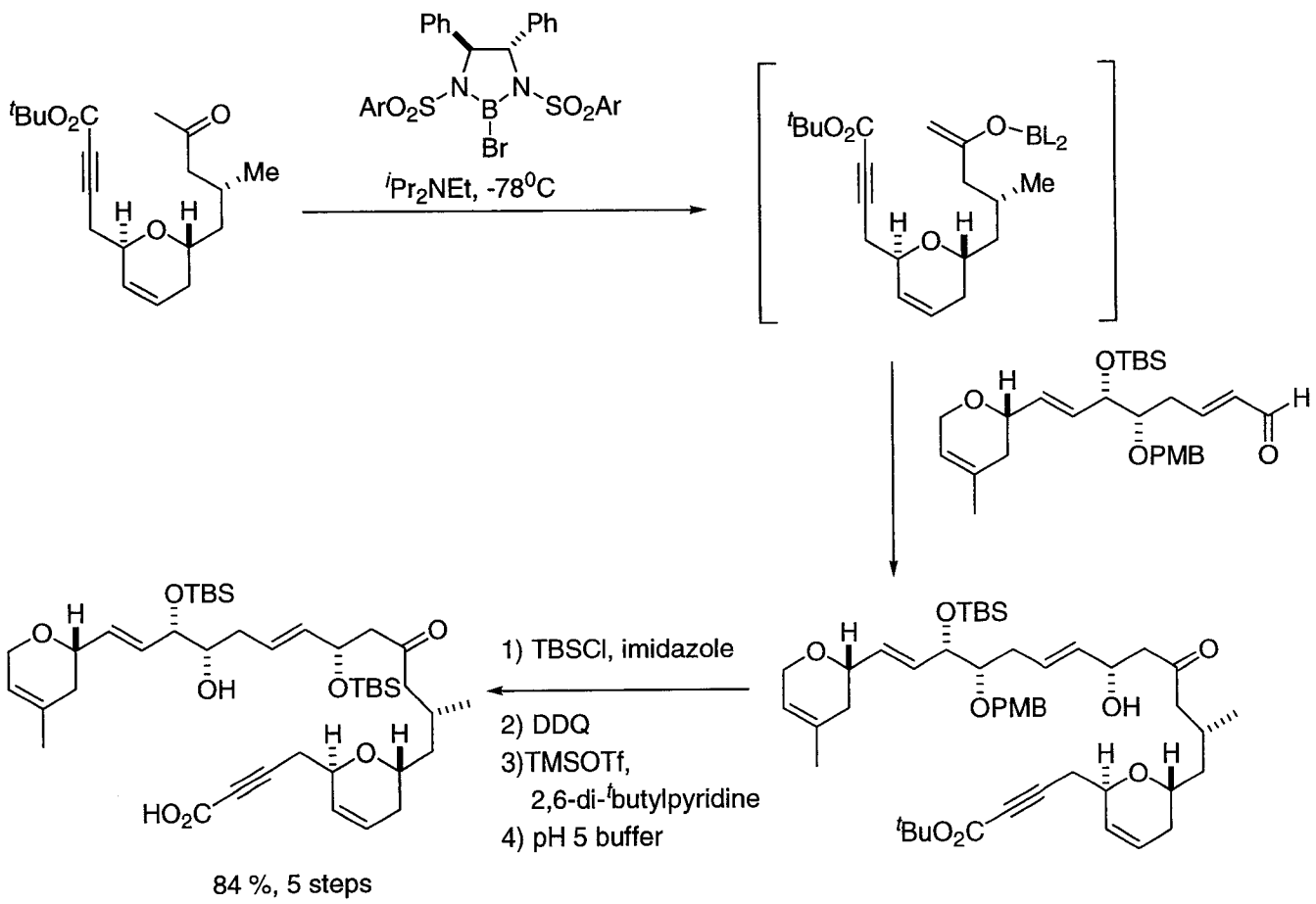
Nelson: C_{15}-C_{27} Fragment



Nelson, S.; Cheung, W.; Kassick, A.; Hilifiker, M. *J. Am. Chem. Soc.* **2002**, *124*, 13654

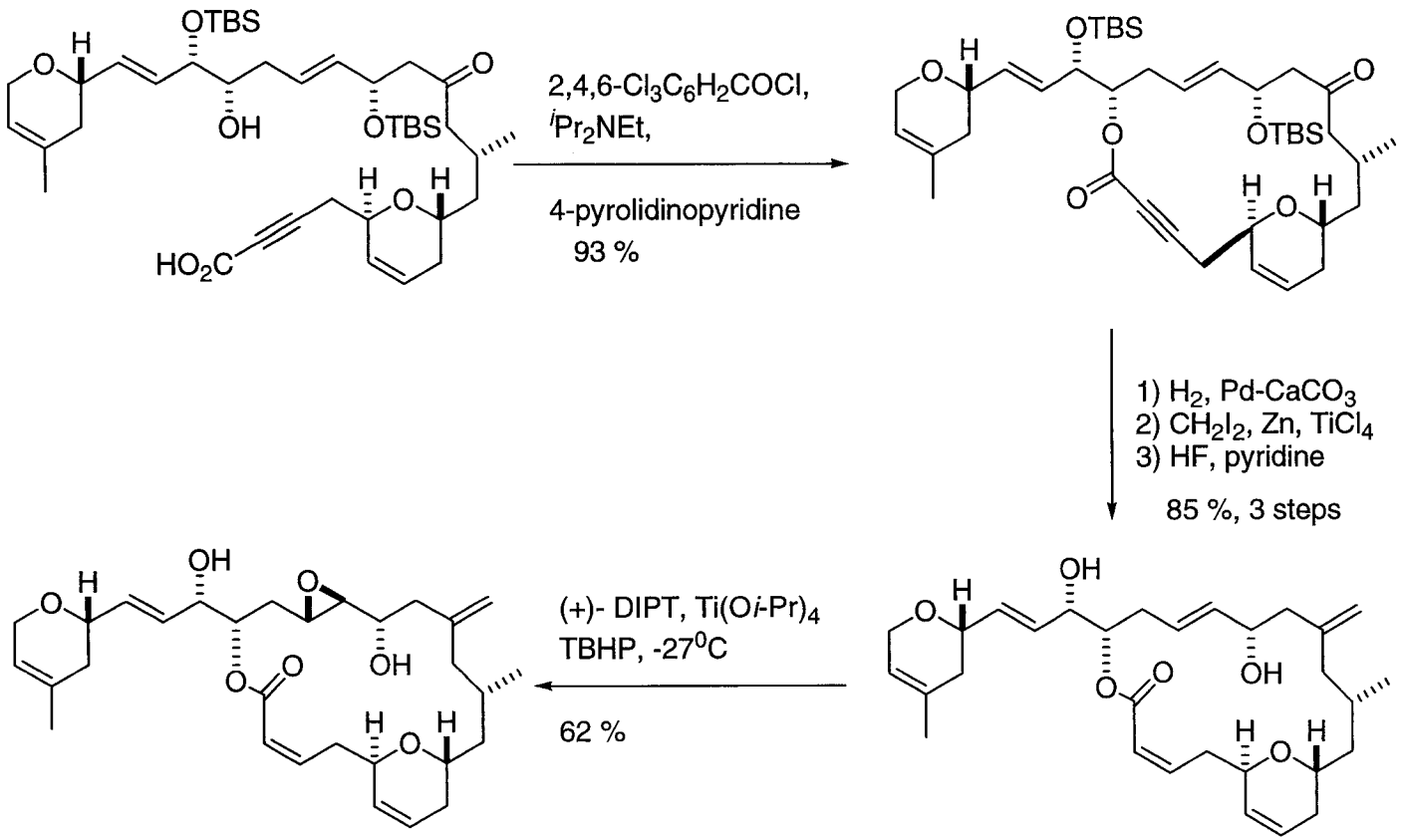
Nelson: Coupling





Nelson, S.; Cheung, W.; Kassick, A.; Hilifiker, M. *J. Am. Chem. Soc.* **2002**, *124*, 13654

Nelson: Completion

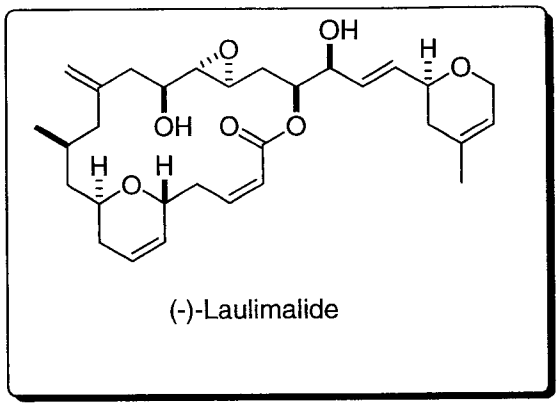


(-)-Laulimalide

25 steps longest linear
43 total steps
5.8% yield
7 chiral reagents
0 chiral pool materials

Nelson, S.; Cheung, W.; Kassick, A.; Hilifiker, M. *J. Am. Chem. Soc.* **2002**, *124*, 13654

Comparison of Syntheses



(-)-Laulimalide

	Ghosh	Paterson	Mulzer	Nelson
Longest Linear	30 steps	27 steps	19 steps	25 steps
Total Steps	47 steps	36 steps	39 steps	43 steps
Yield	0.2%	2.9 %	21 %	5.8 %
Chiral Reagent	2	3	2	7
Chiral Pool	3	2	3	0