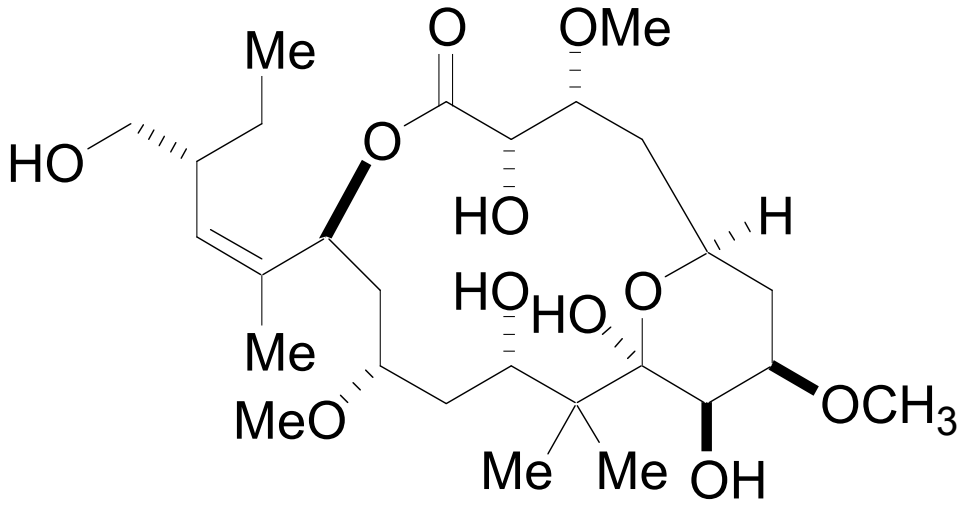
Total Synthesis of Peluroside A



-Isolated from a marine sponge, *mycole*

-Reported in 2000 by Northcote and co-workers

-A potent cytotoxic agent with paclitaxel-like microtubule-stabilizing activity

-First total synthesis by De Brabander in 2003

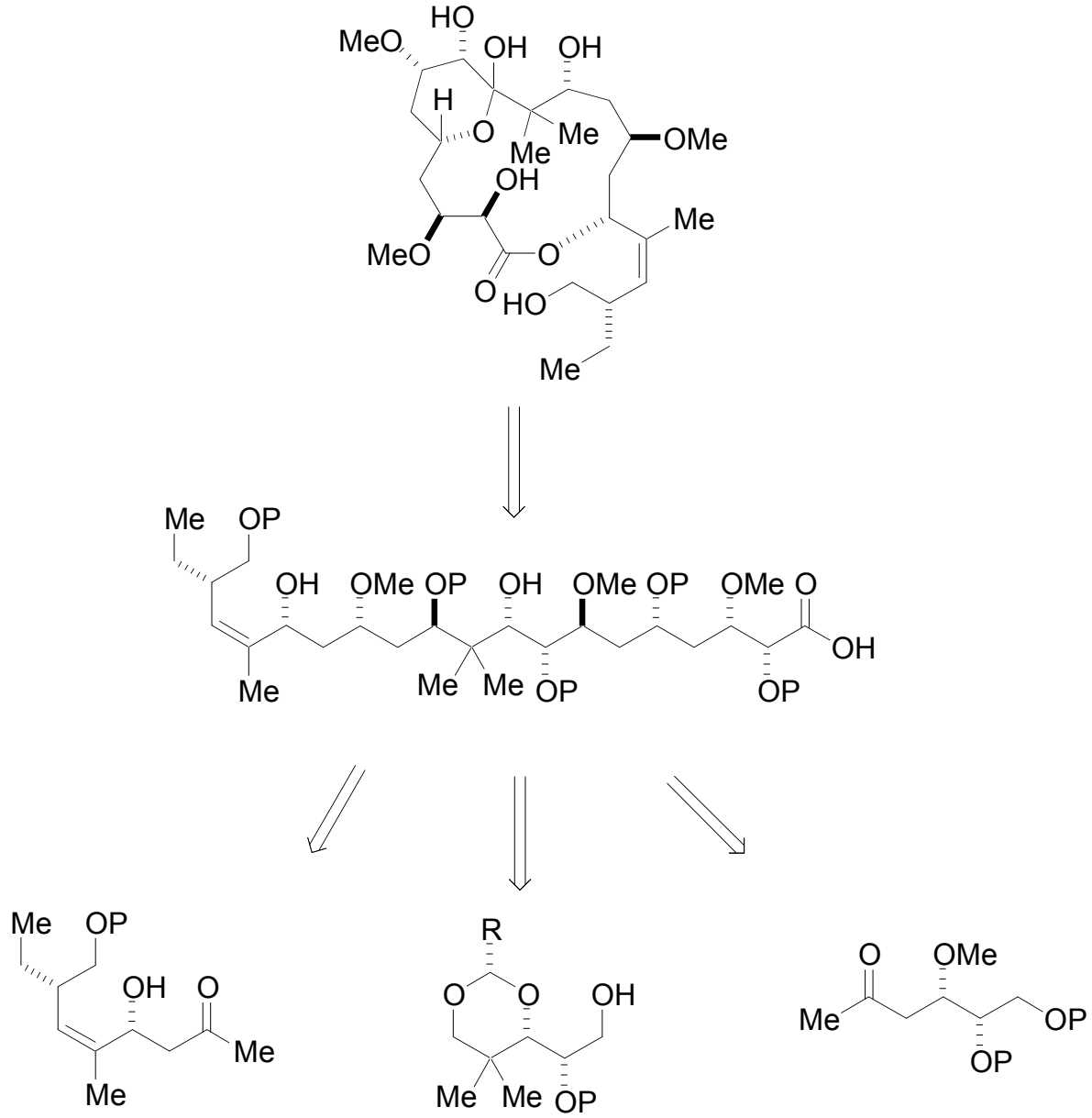
-Synthetic efforts by Crimmins, Ghosh, Paterson, Roush, Smith, and Taylor

Paterson, I; Di Francesco, M. E.; Kuhn, T. *Org. Lett*. **2003**, *5*, 599;
Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2003**, *42*, 1648.

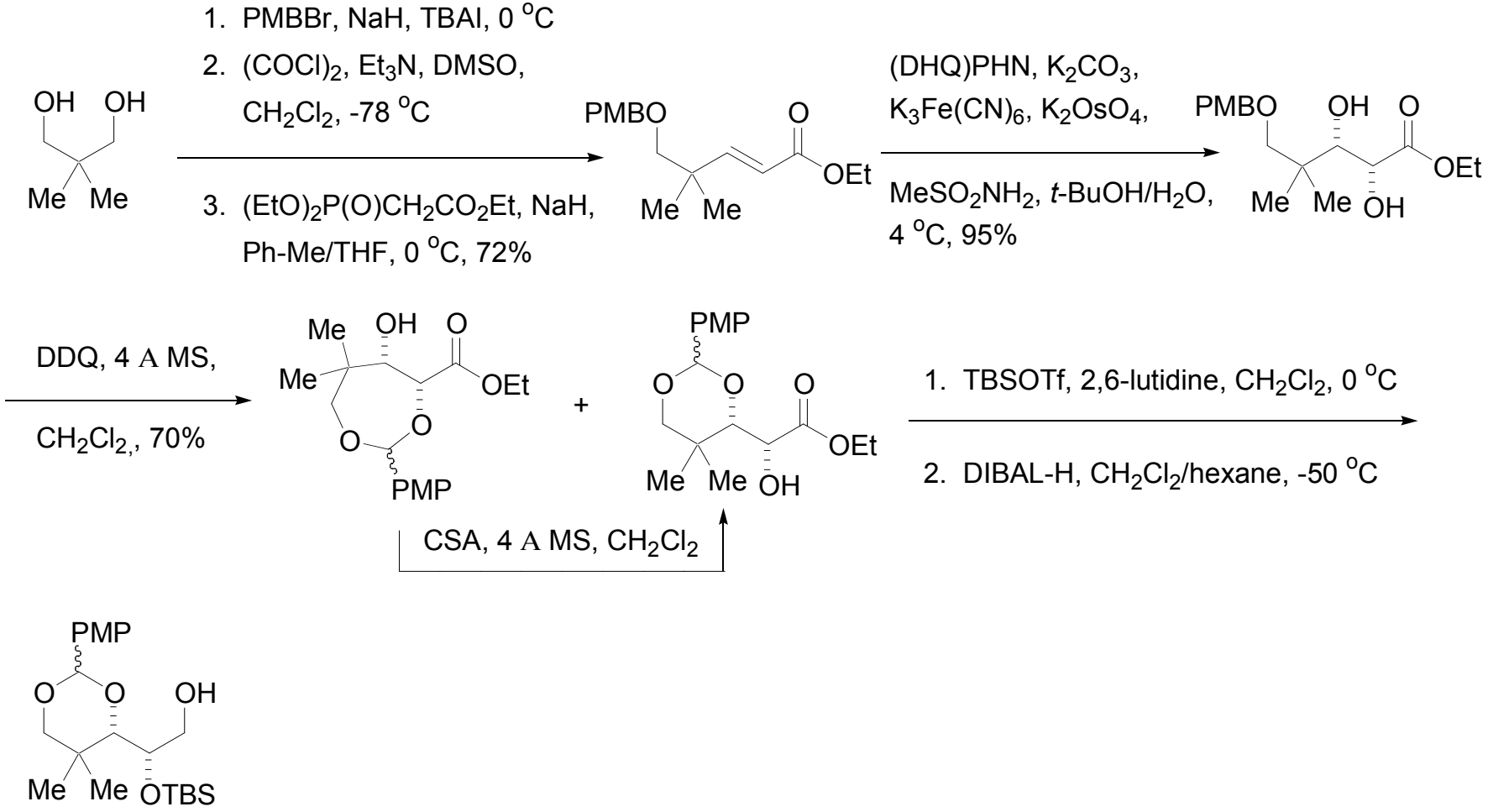
Jin, M.; Taylor, R. E. *Org. Lett.* **2003**, *5*, 4959;

Jin, M.; Taylor, R. E. *Org. Lett.* ASAP.

Paterson's Retrosynthetic Analysis

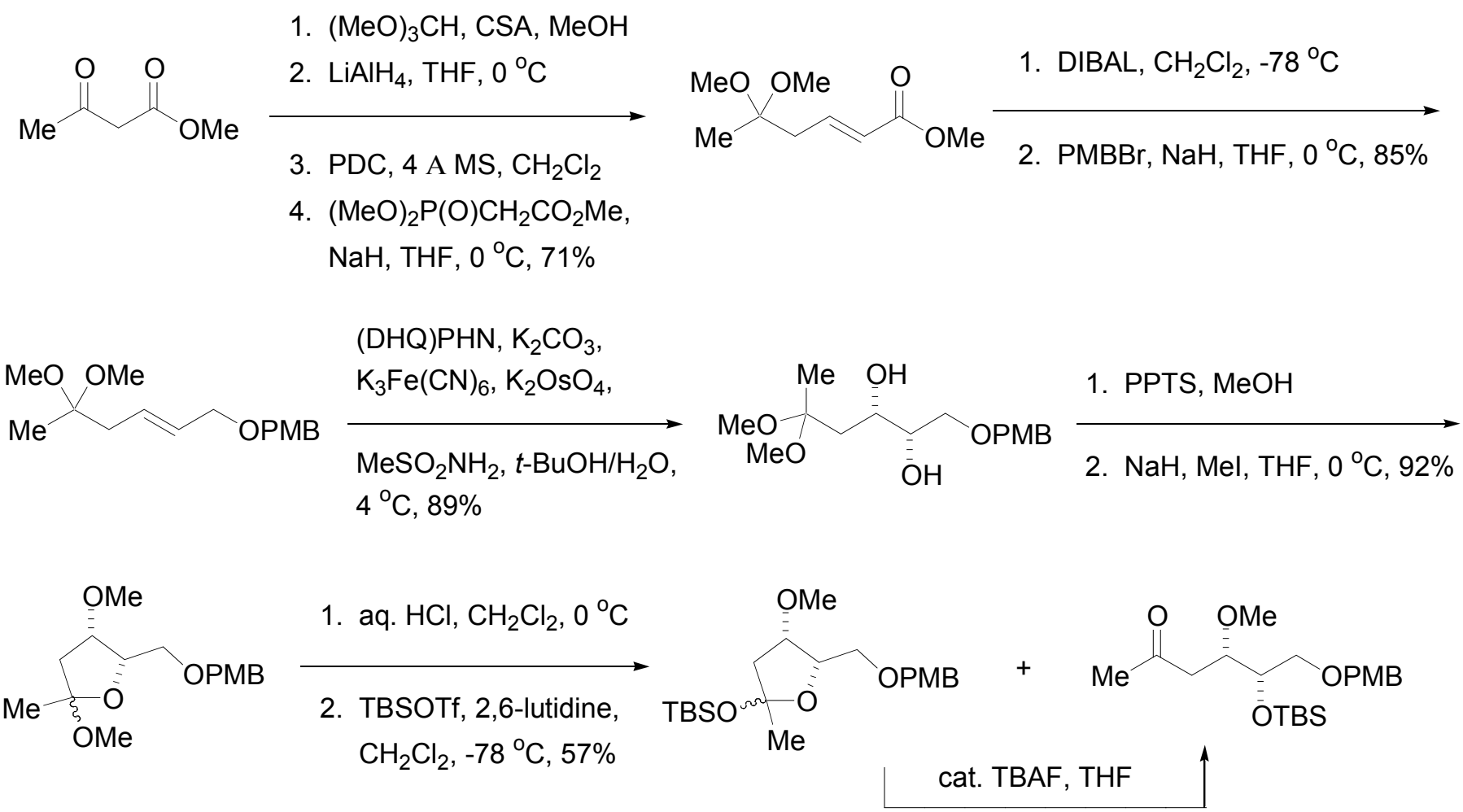


Paterson's Partial Synthesis

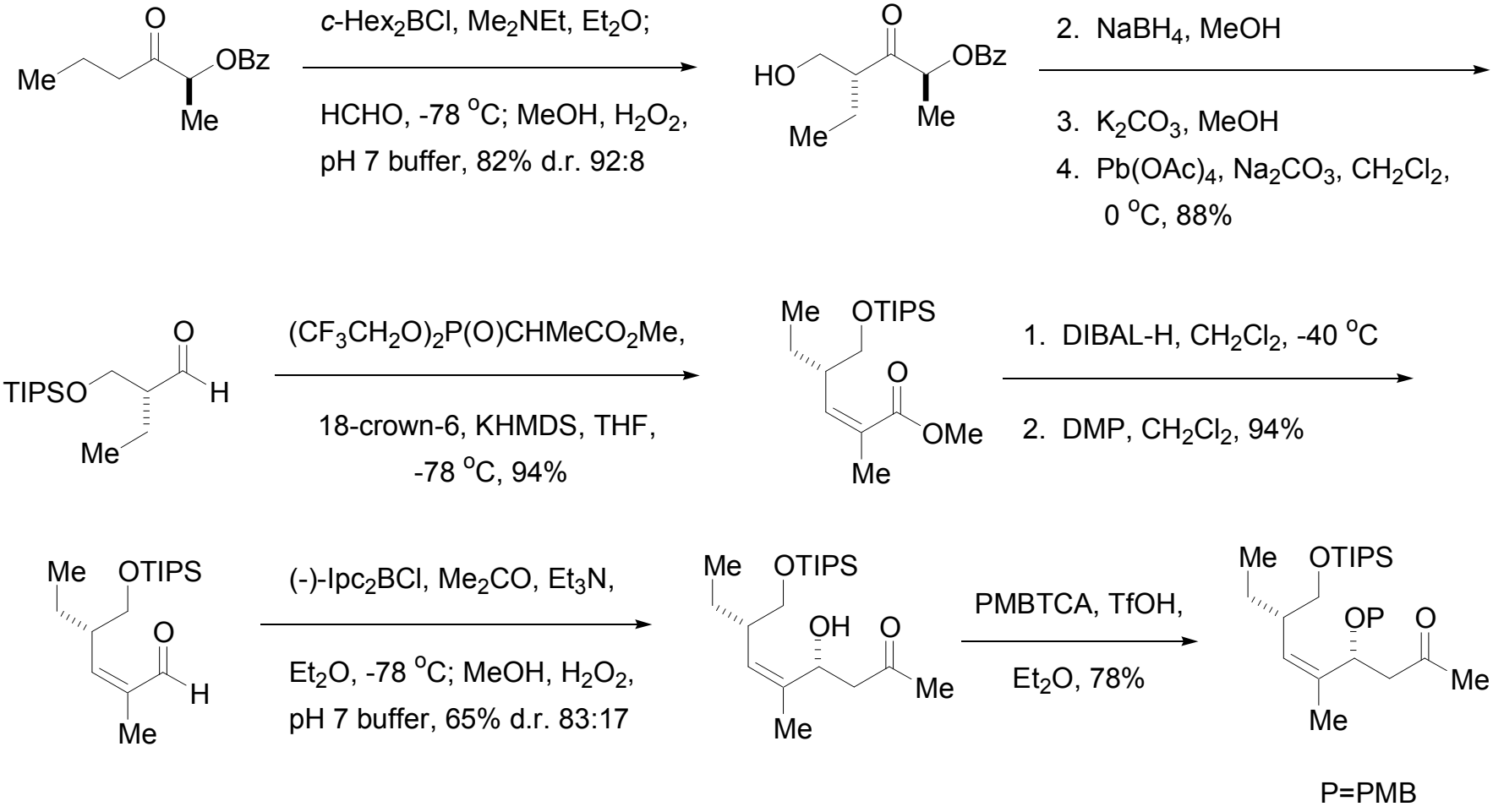


Paterson, I; Di Francesco, M. E.; Kuhn, T. *Org. Lett*. **2003**, *5*, 599.

Synthesis of Methyl Ketone

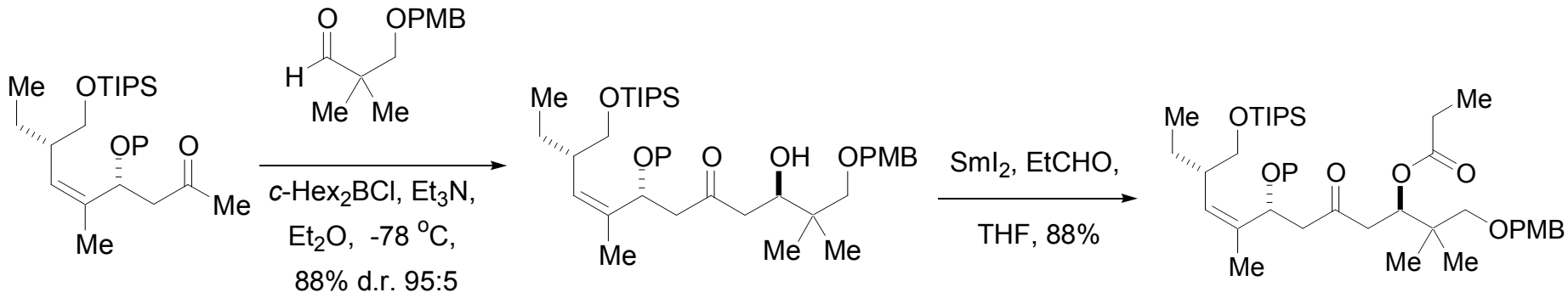


Another Methyl Ketone Fragment



Studies for Aldol Stereoinduction

Enolate Stereoinduction



P=PMB

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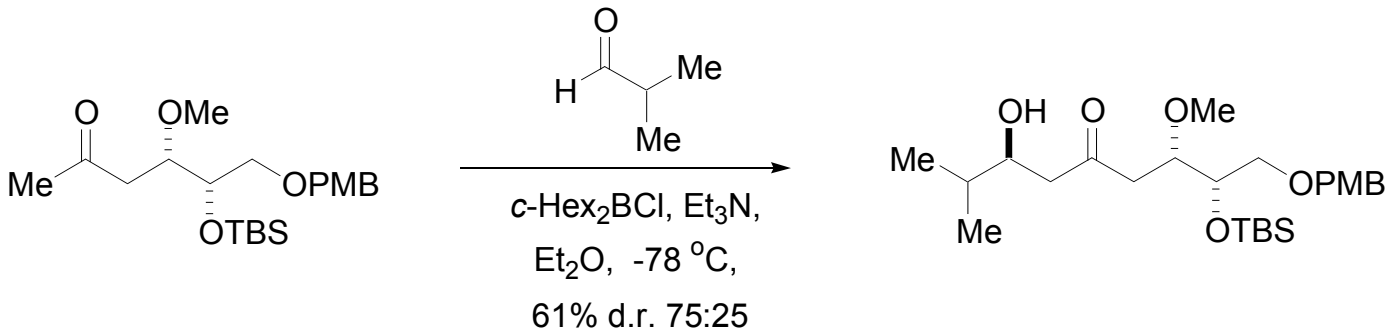
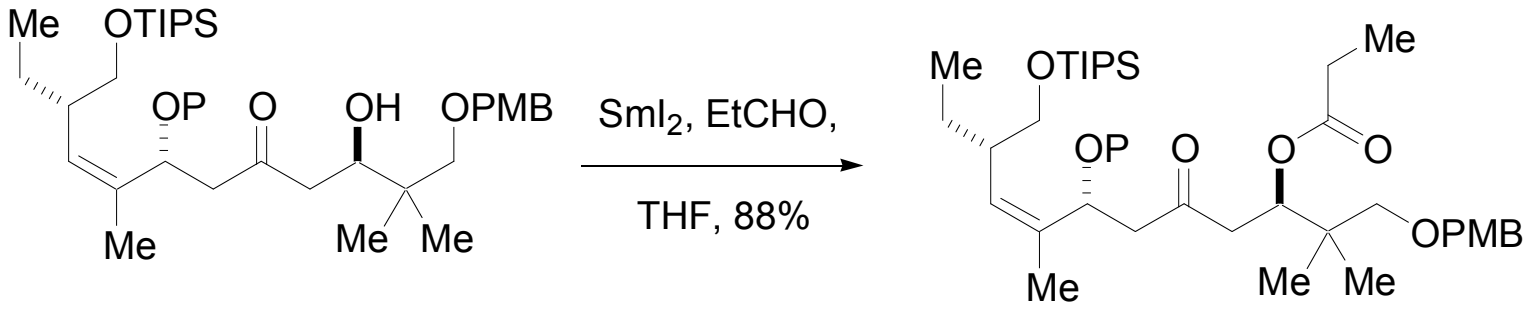


Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tet. Lett.* **1996**, *37*, 8585;
Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

Evans-Tishchenko Reduction



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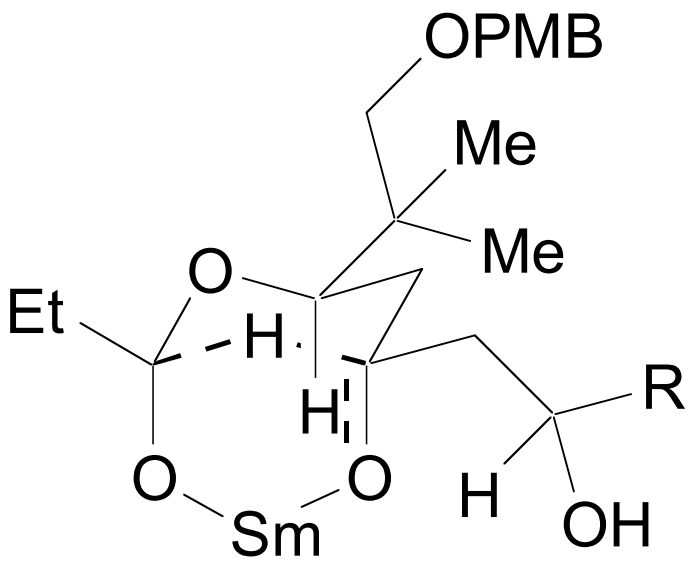
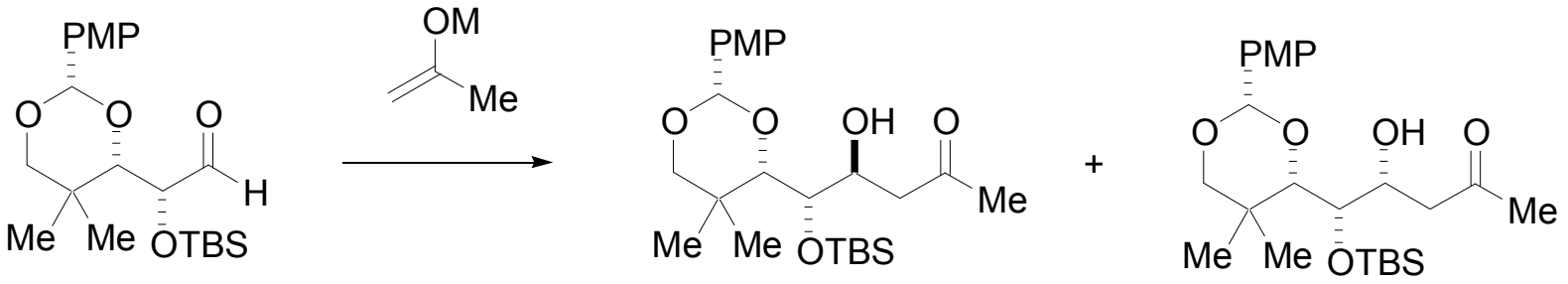


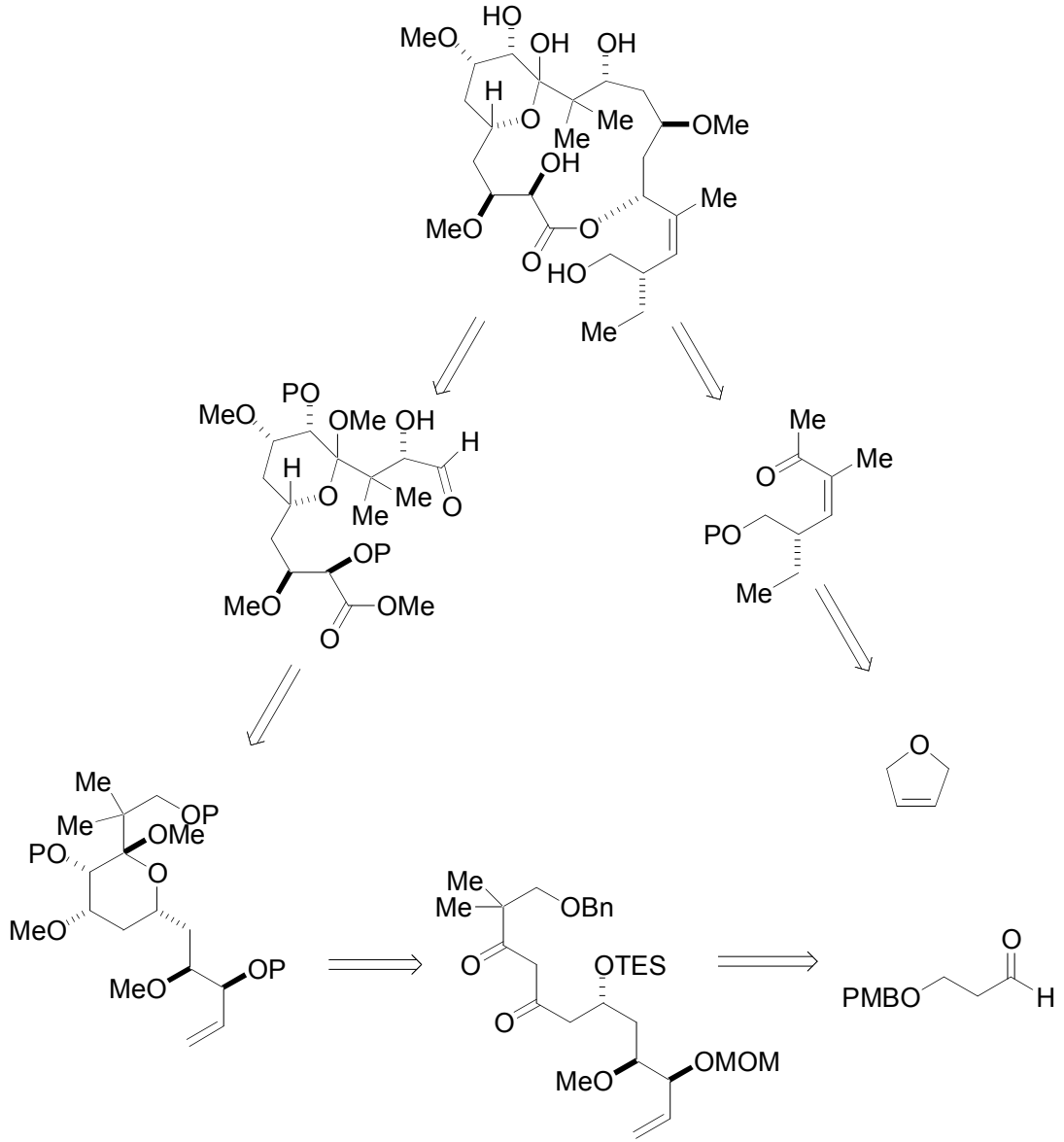
More Aldol Studies

Aldehyde Stereoinduction



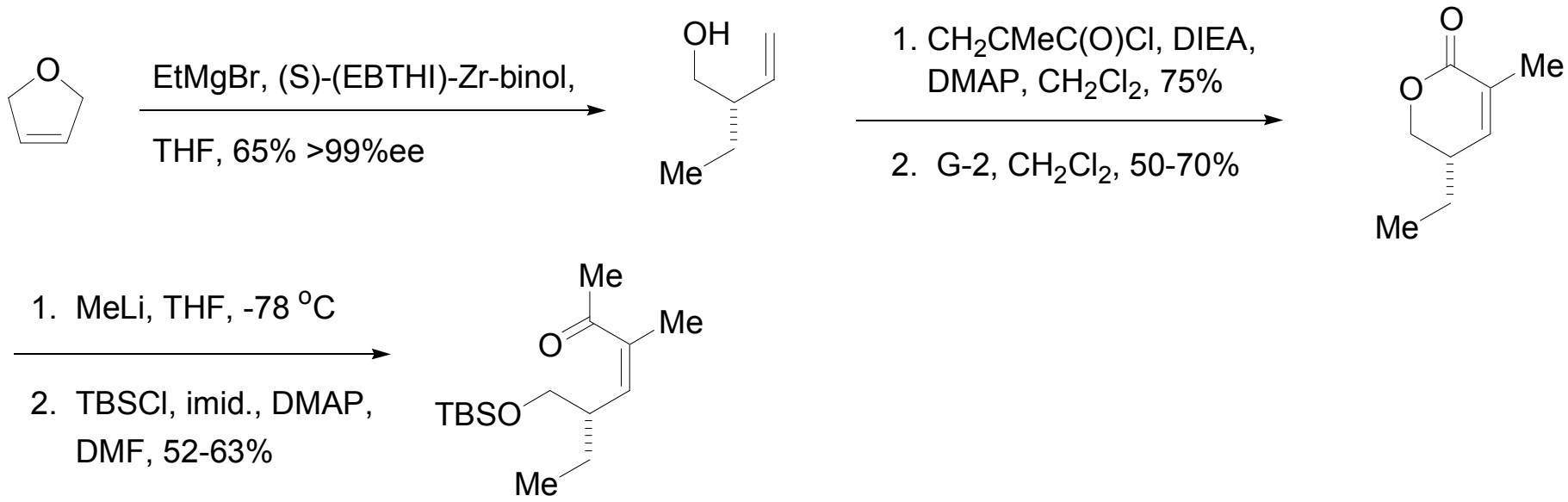
Reaction Conditions (-78 °C)	**Yield (%)**	**1,3-*anti* : 1,3-*syn***
c-Hex_2BCl, Et_3N, Et_2O	87	57:43
LiHMDS, THF	57	25:75
$SiMe_3$, BF_3-OEt_2, CH_2Cl_2	54	7:93
(-)-Ipc_2BCl, Et_3N, Et_2O	88	10:90
(+)-Ipc_2BCl, Et_3N, Et_2O	69	75:25

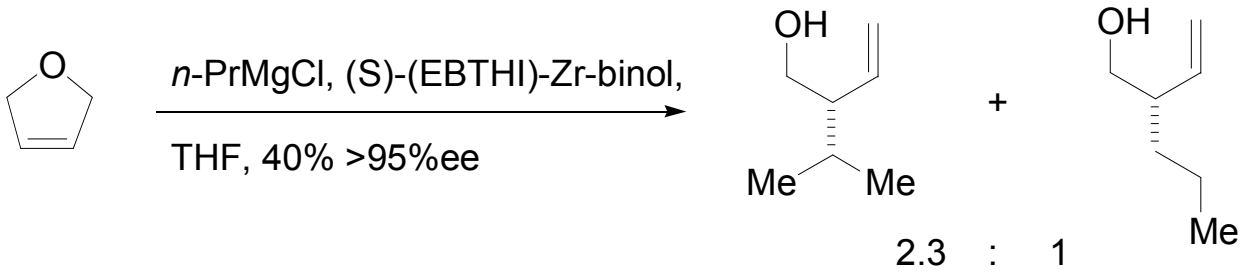
De Brabander's Retrosynthetic Analysis



Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2003**, *42*, 1648.

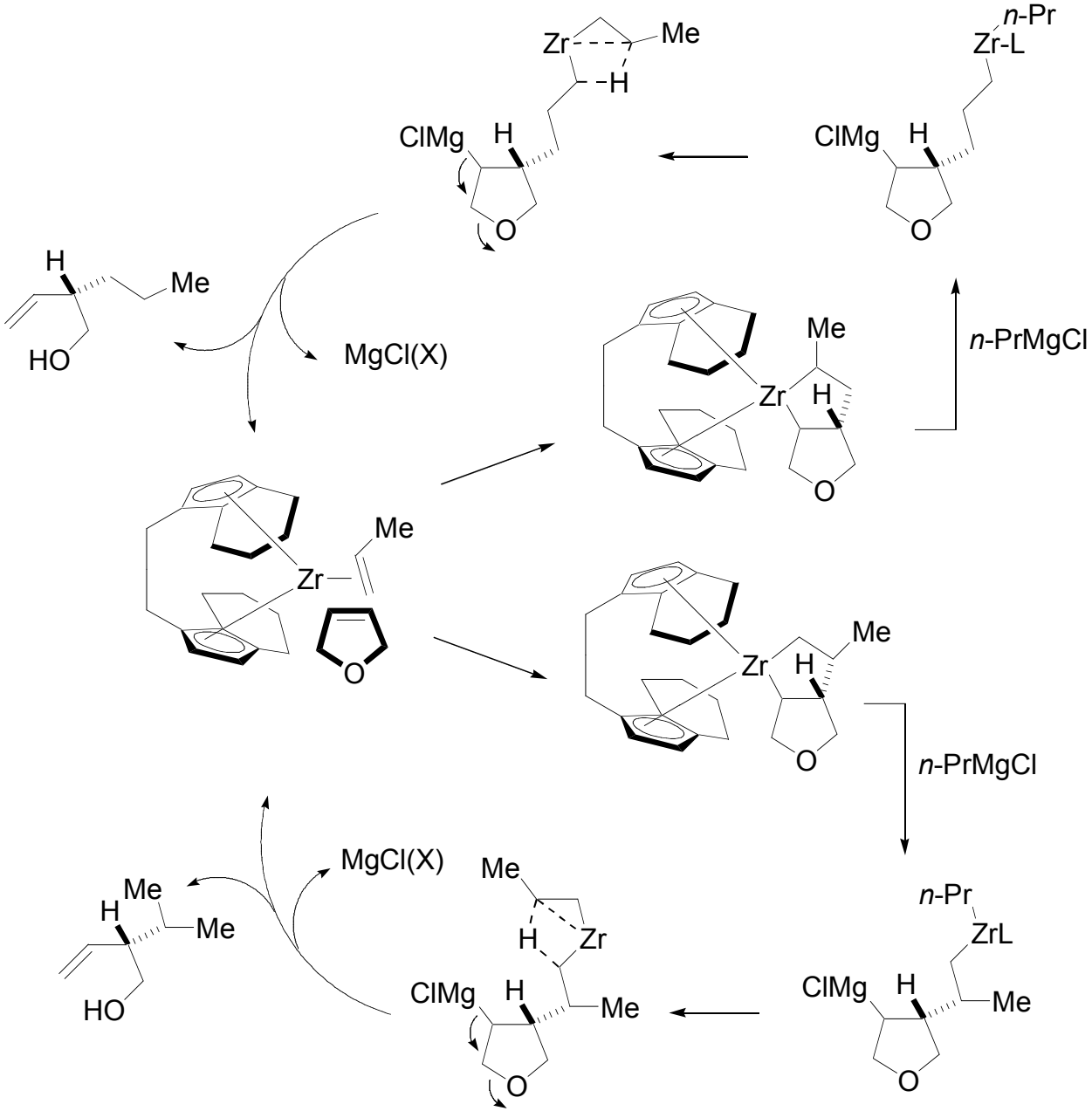
Synthesis of Methyl Ketone



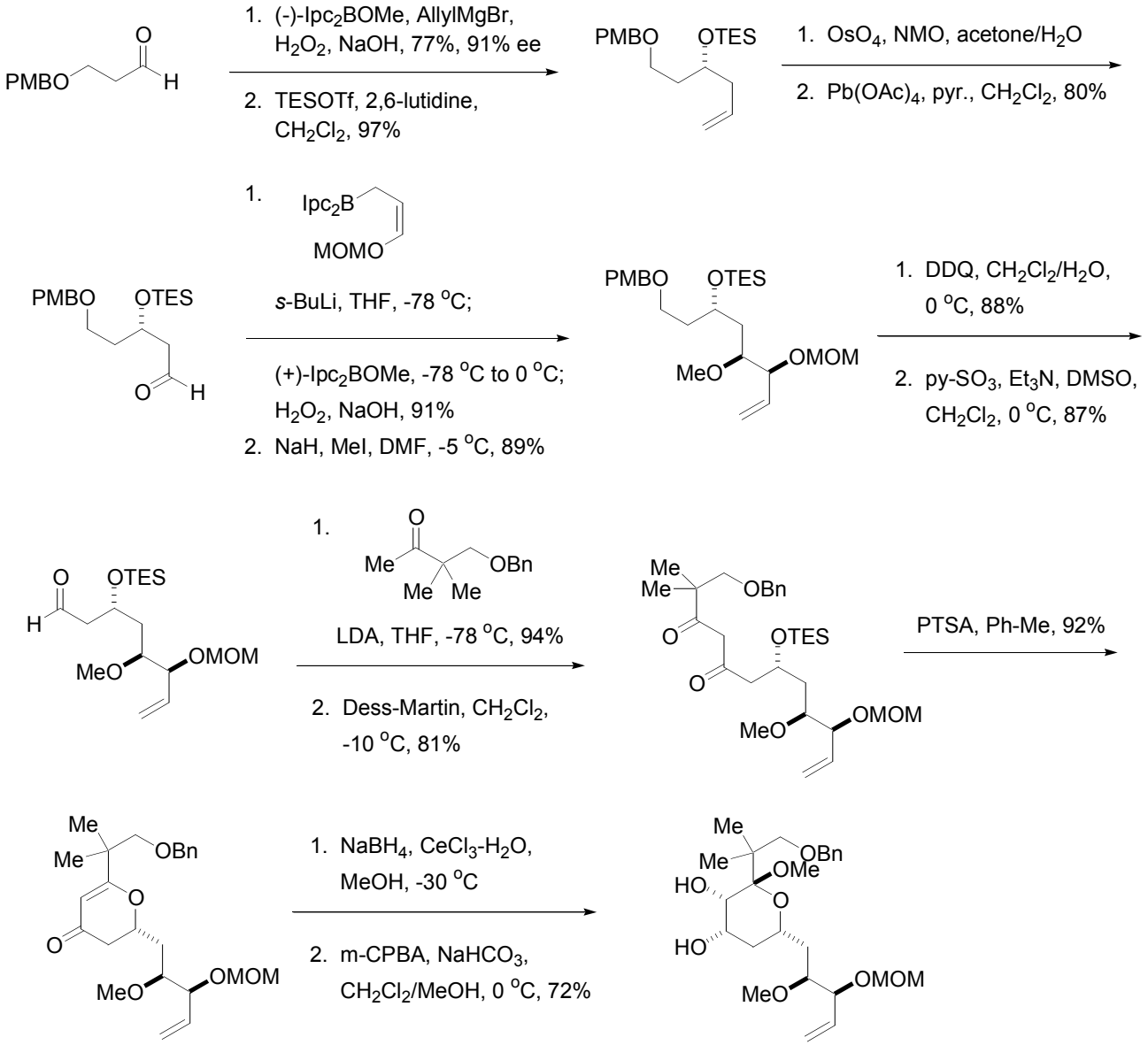


Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, 115, 6997;
Xu, Z.; Johannes, C. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302.

Carbomagnesation

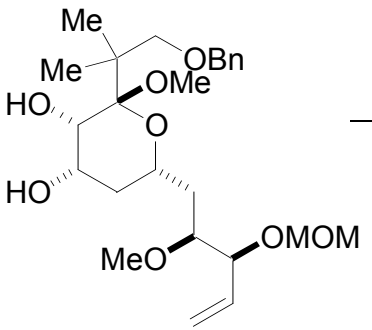


Synthesis of Pyran

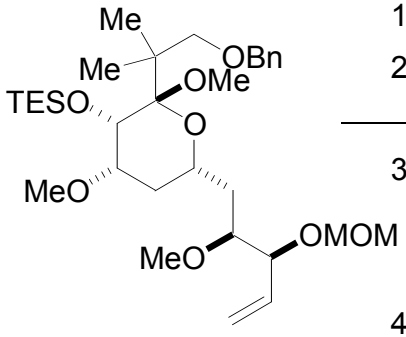


Smith III, A. B.; Minbiole, K. P.; Verhoest,M. S. *J. Am. Chem. Soc.* **2001**, *123*, 10942.

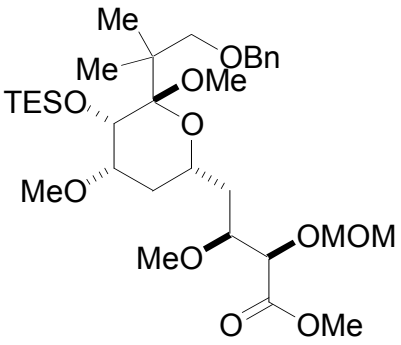
Completion of Aldehyde Fragment



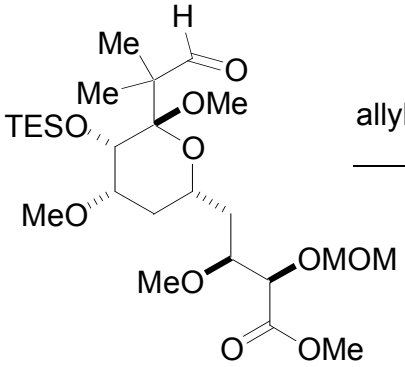
1. *t*-BuOK, MeI, THF, 0 °C
2. TESOTF, 2,6-lutidine, CH_2Cl_2, 75%



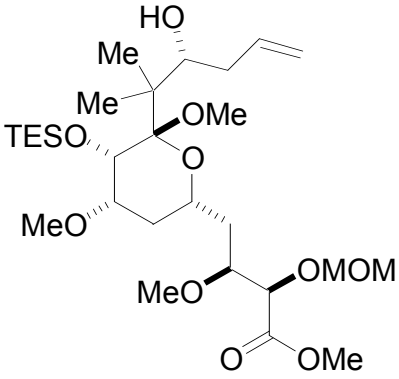
1. OsO_4, NMO, acetone/H_2O
2. $Pb(OAc)_4$, pyr., CH_2Cl_2
3. $NaClO_2$, NaH_2PO_4, 2-Me-2-butene, *t*-BuOH/H_2O
4. CH_2N_2, Et_2O, -10 °C, 80%



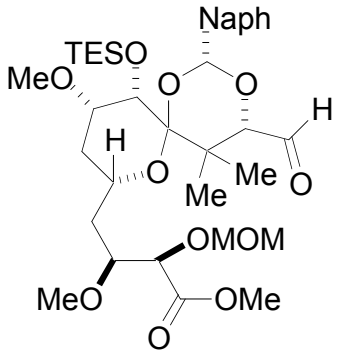
1. H_2, Pd/C, MeOH
2. py-SO_3, Et_3N, DMSO, CH_2Cl_2, 0 °C, 90%



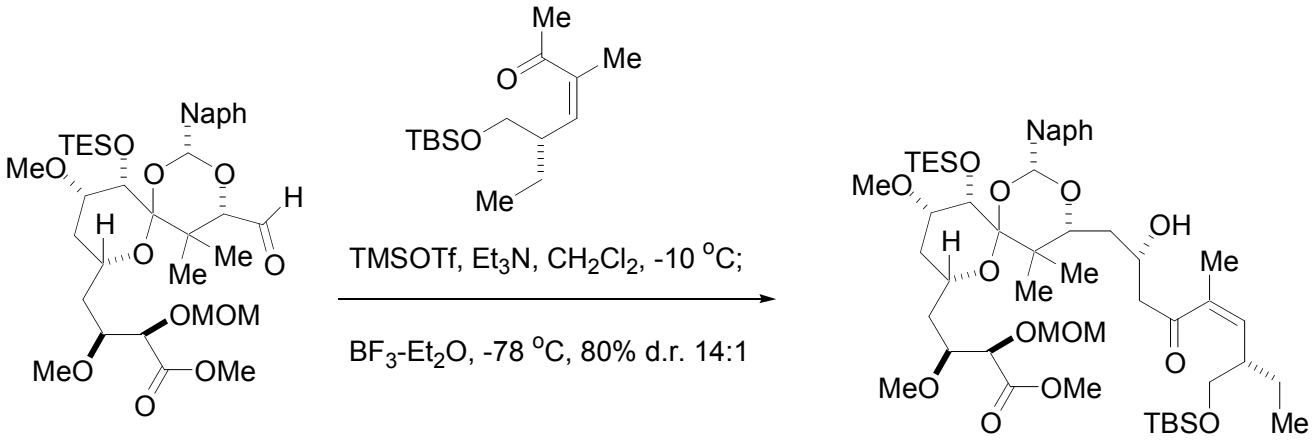
allylBEt_2, Et_2O, -10 °C, 94%



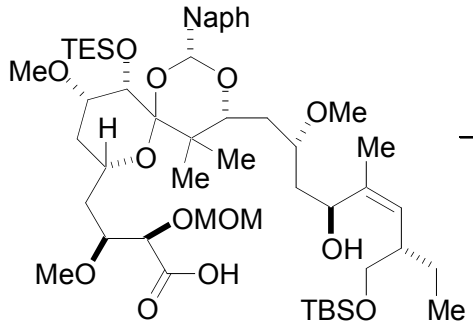
1. TESOTf, 2-naphthaldehyde, -78 °C; 2,6-lutidine, TESOTf, 0 °C, 81%
2. OsO_4, NMO, acetone/H_2O
3. $NaIO_4$ on silica gel, CH_2Cl_2, 90%



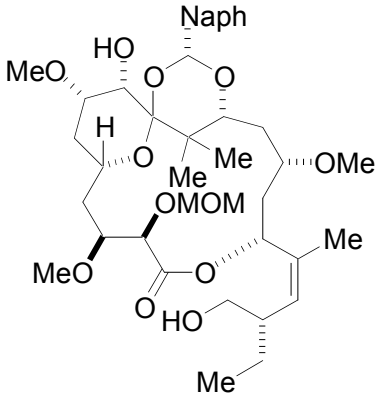
Aldol and a Roadblock



1. Me_3OBF_4, 1,8-bis(dimethyl-amino)naphthalene, CH_2Cl_2, 92%
2. (*S*)-B-Me-CBS, BH_3-SMe_2, CH_2Cl_2 -30 °C to RT; MeOH, 83% d.r.13:1
3. aq. LiOH, THF, RT (Quant.)

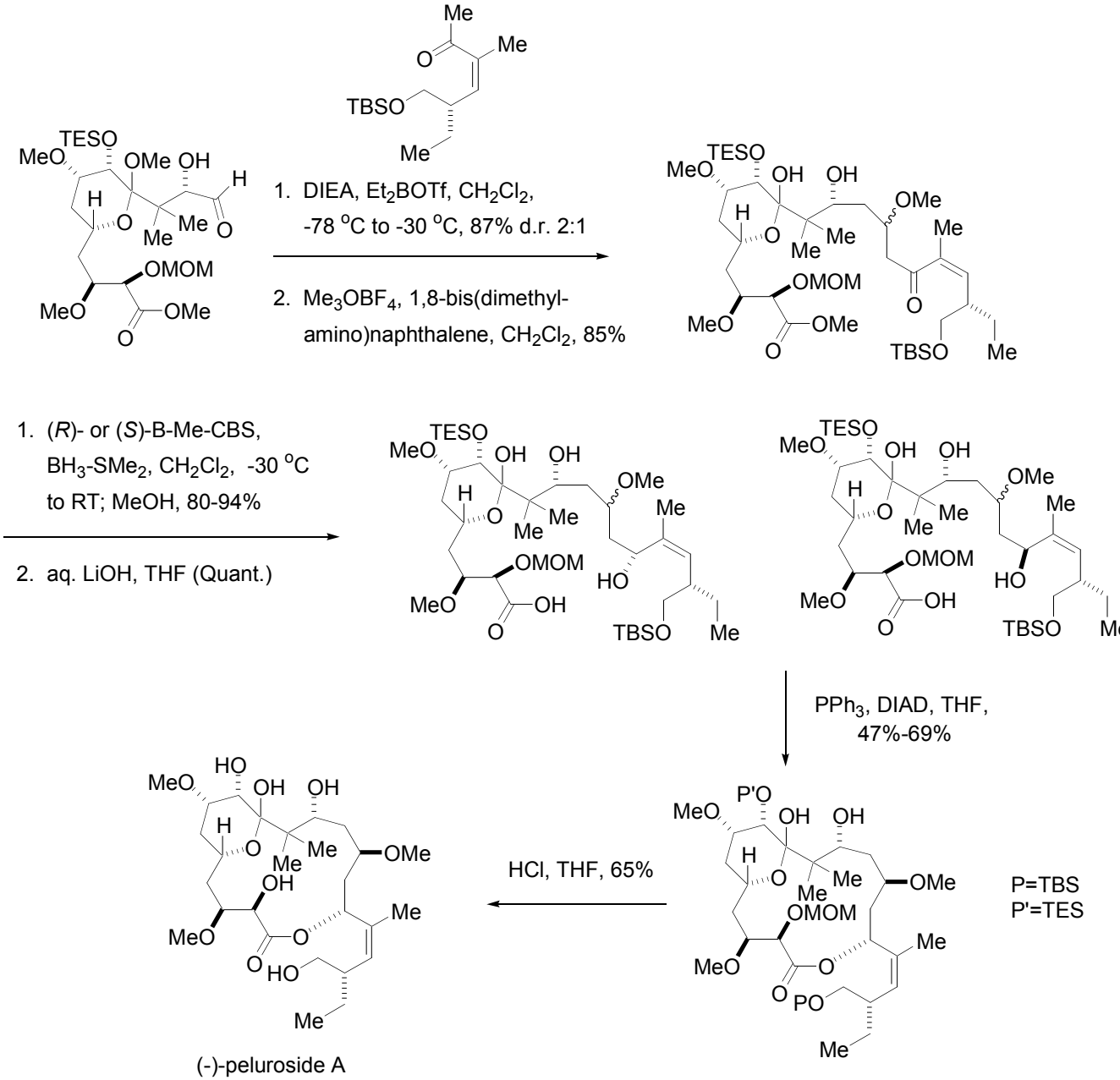


1. PPh_3, DIAD, THF, 40-50%
2. aq. HF, MeCN/H_2O, 88%

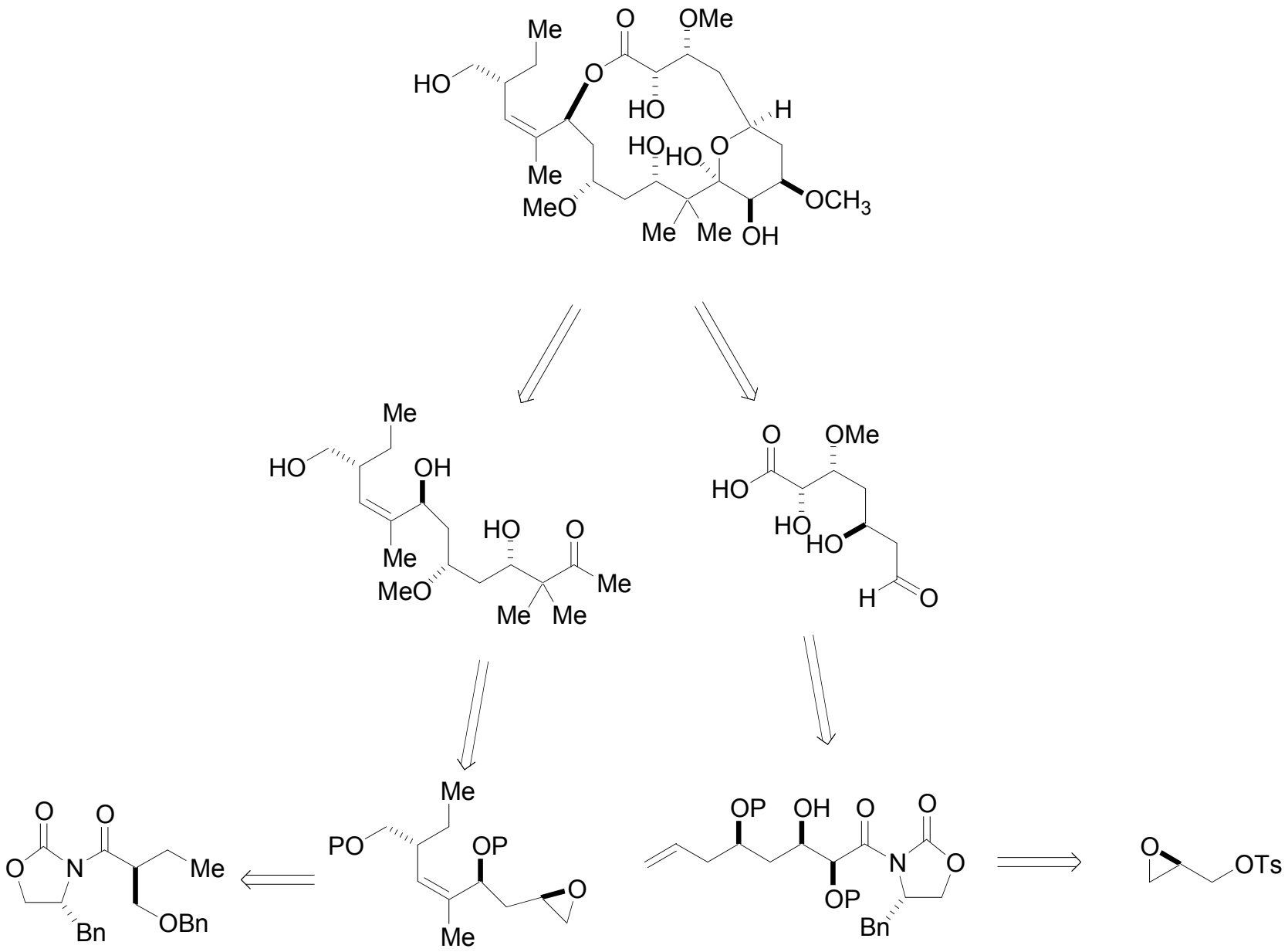


X-Ray confirmed incorrect C13 stereochemistry
Acetal also difficult to remove

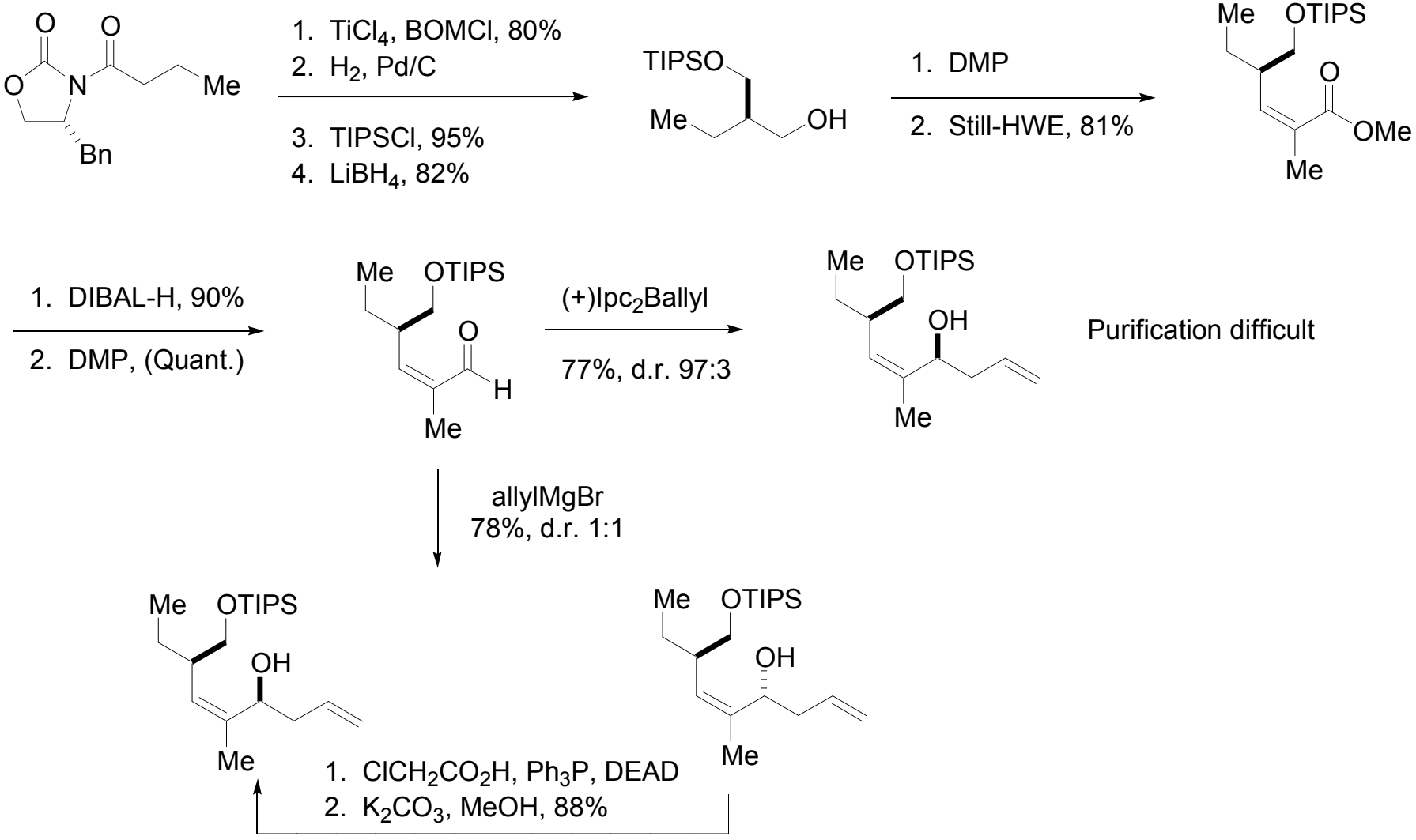
Back on Course



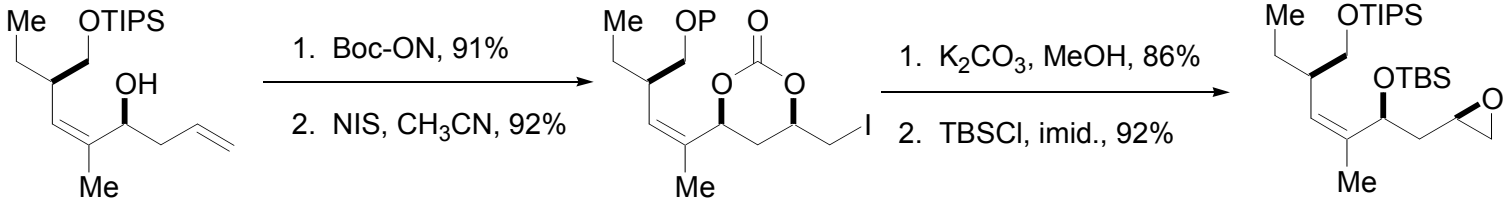
Taylor's Retrosynthetic Analysis



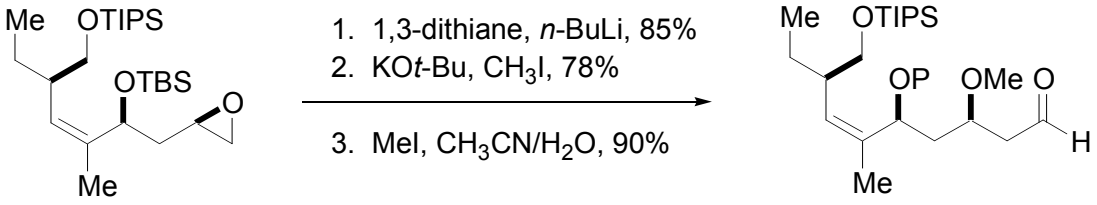
Synthesis of Methyl Ketone Fragment



Synthesis of Methyl Ketone Fragment



P=TIPS



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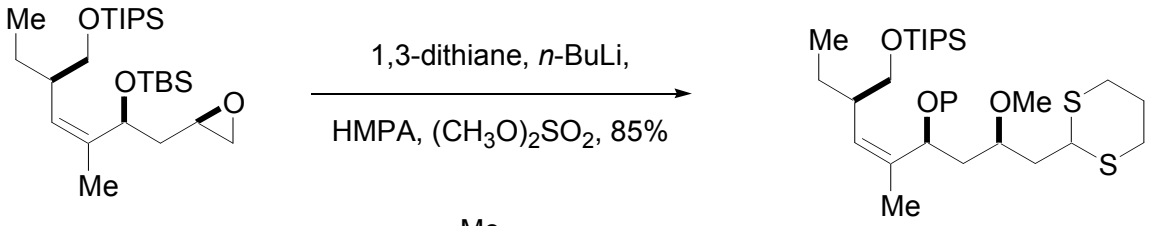
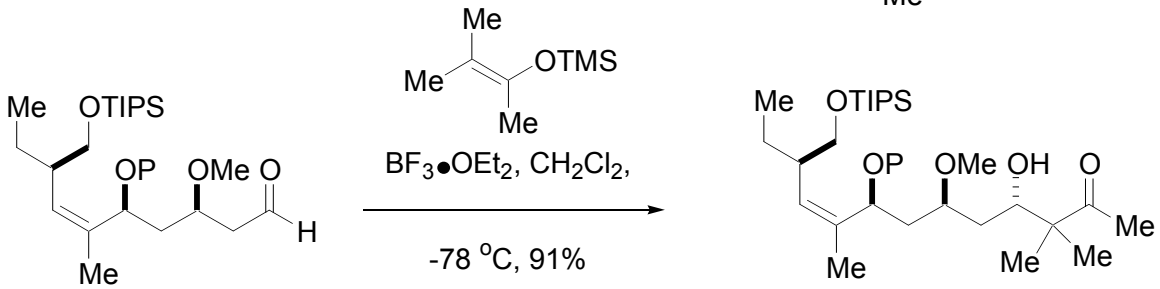
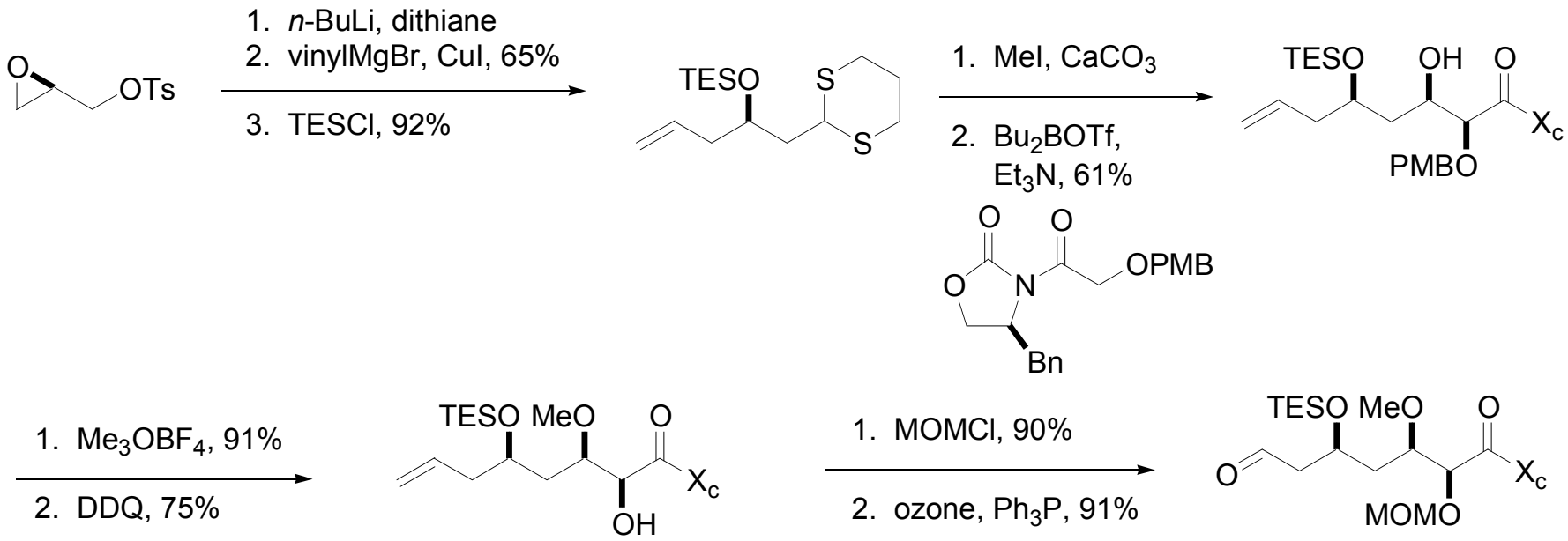




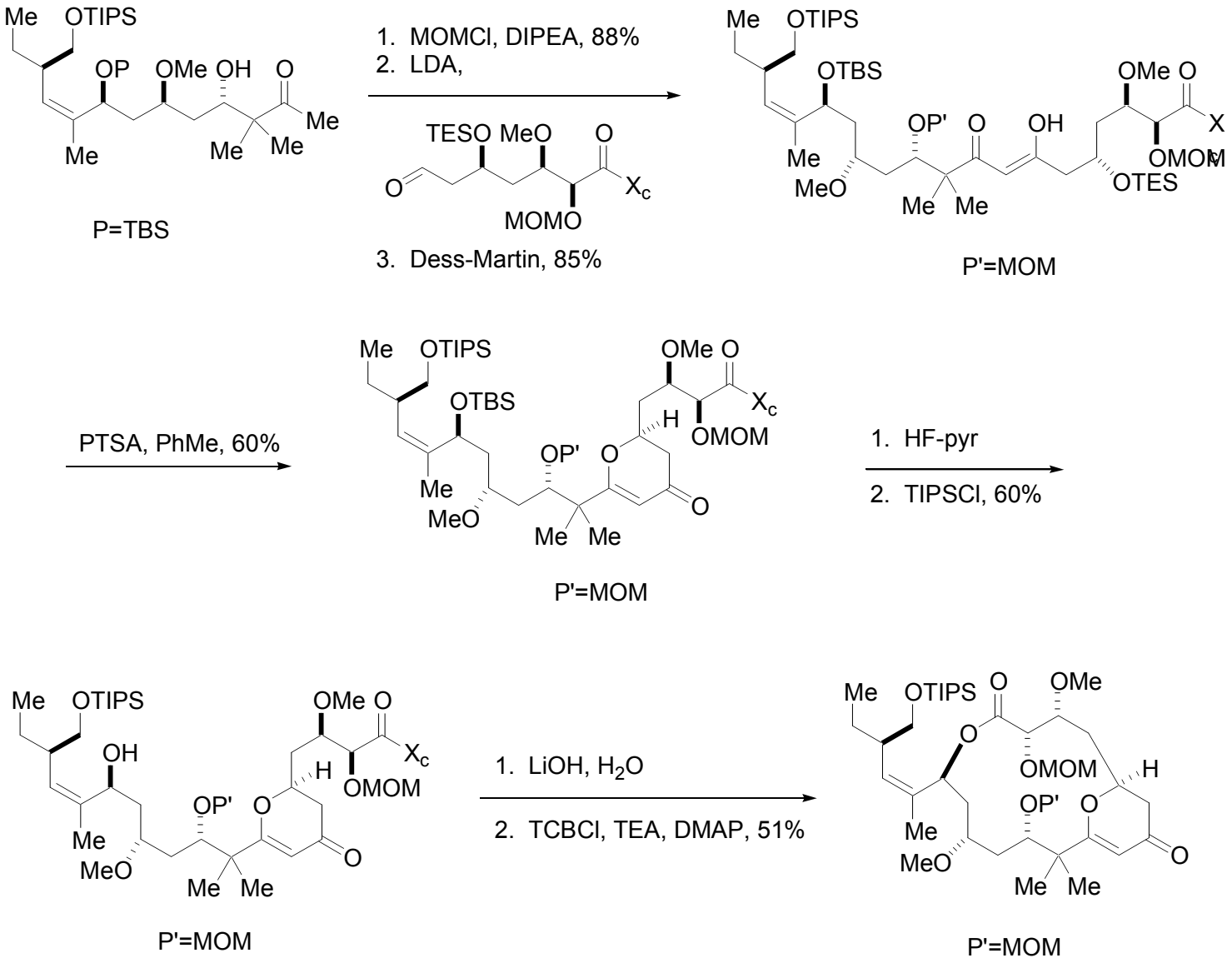
P=TBS

Bartlett, P. A.; Meadows, J. D.; Brown, E. G. *J. Org. Chem.* **1982**, *47*, 4013;
Duan, J. J-W.; Smith, A. B. III *J. Org. Chem.***1993**, *58*, 3703.

Synthesis of Aldehyde Fragment

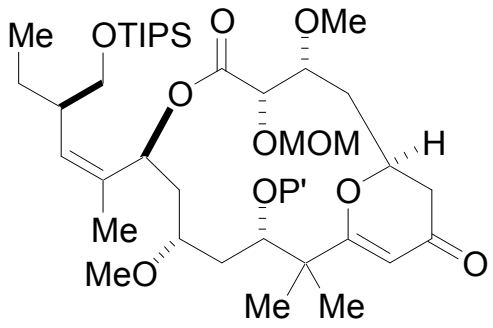


Aldol and Cyclizations



Inanaga, J.; Hirata, K.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

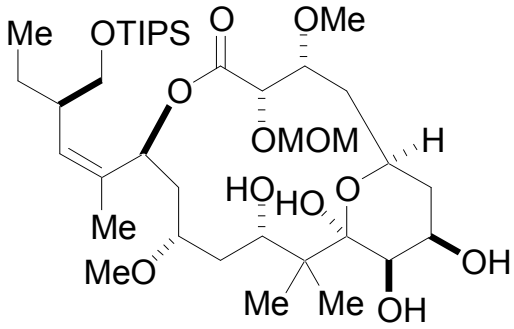
Completion of the Natural Product



P'=MOM

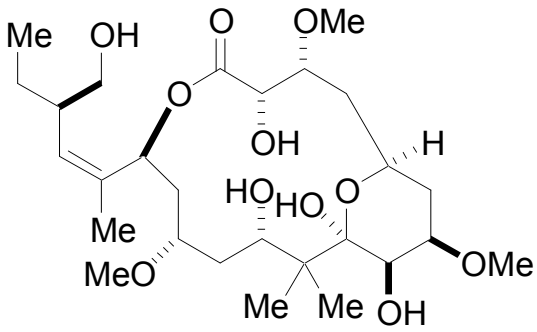
1. $NaBH_4$, $CeCl_3$

2. m-CPBA, 52%



1. Me_3OBF_4, 2,6-di-*t*-Bu-pyr

2. 4N HCl, 43%



(+)-peluroside A