The Petasis-Ferrier Union/Rearrangement

SED Group Meeting

01-22-08

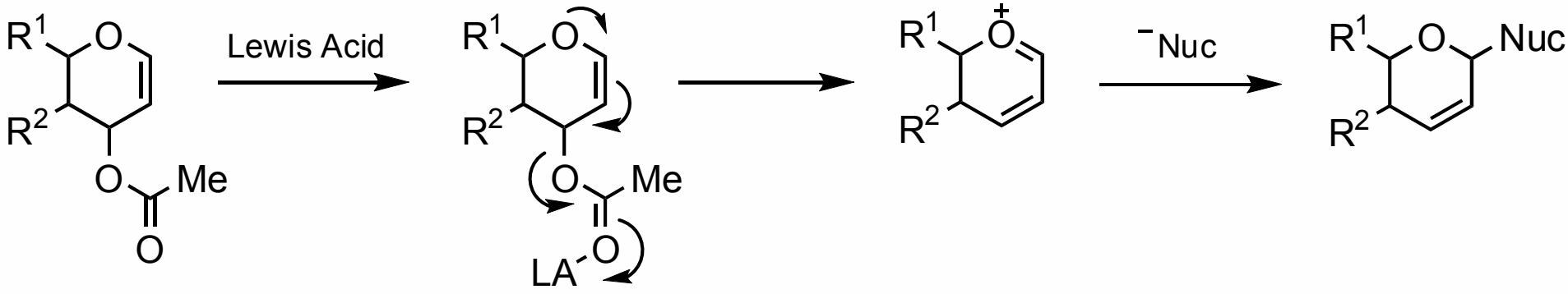
Larry Wolf

Outline

- **Ferrier Type I and Type II**
- **Petasis-Ferrier Rearrangement**
  - Scope and Mechanism
- **(+)-Phorboxazole A**
- **(-)-Clavosolide A**
- **Petasis-Ferrier Derivative**
- **Conclusions**

Ferrier Type I & II

Type I



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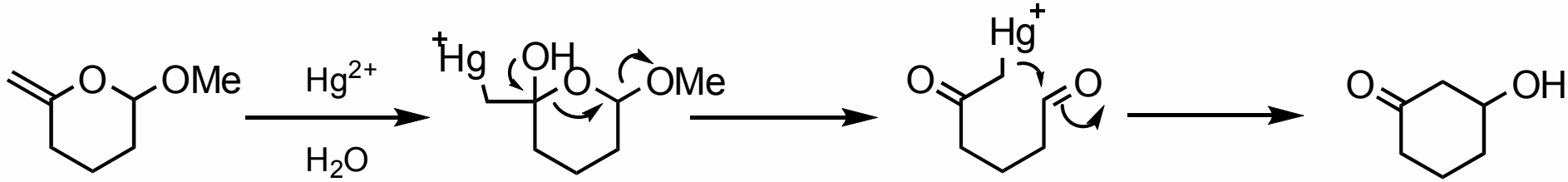
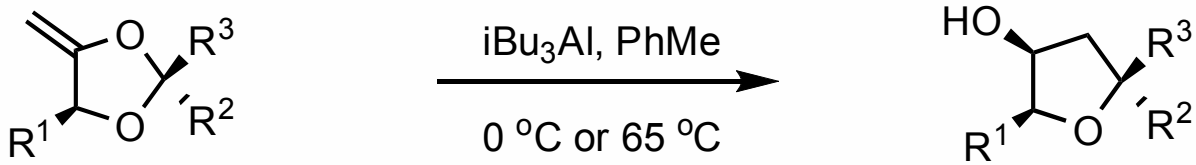
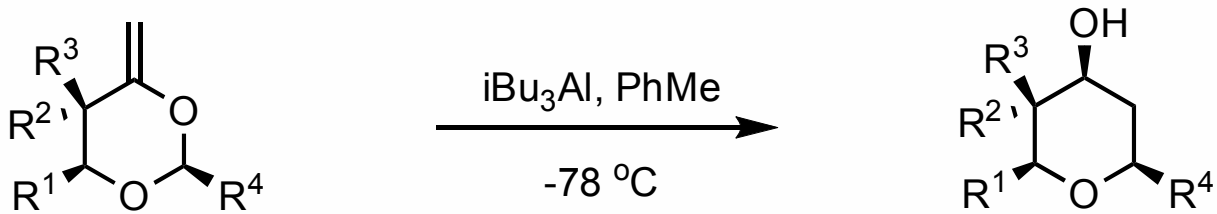


Petasis-Ferrier



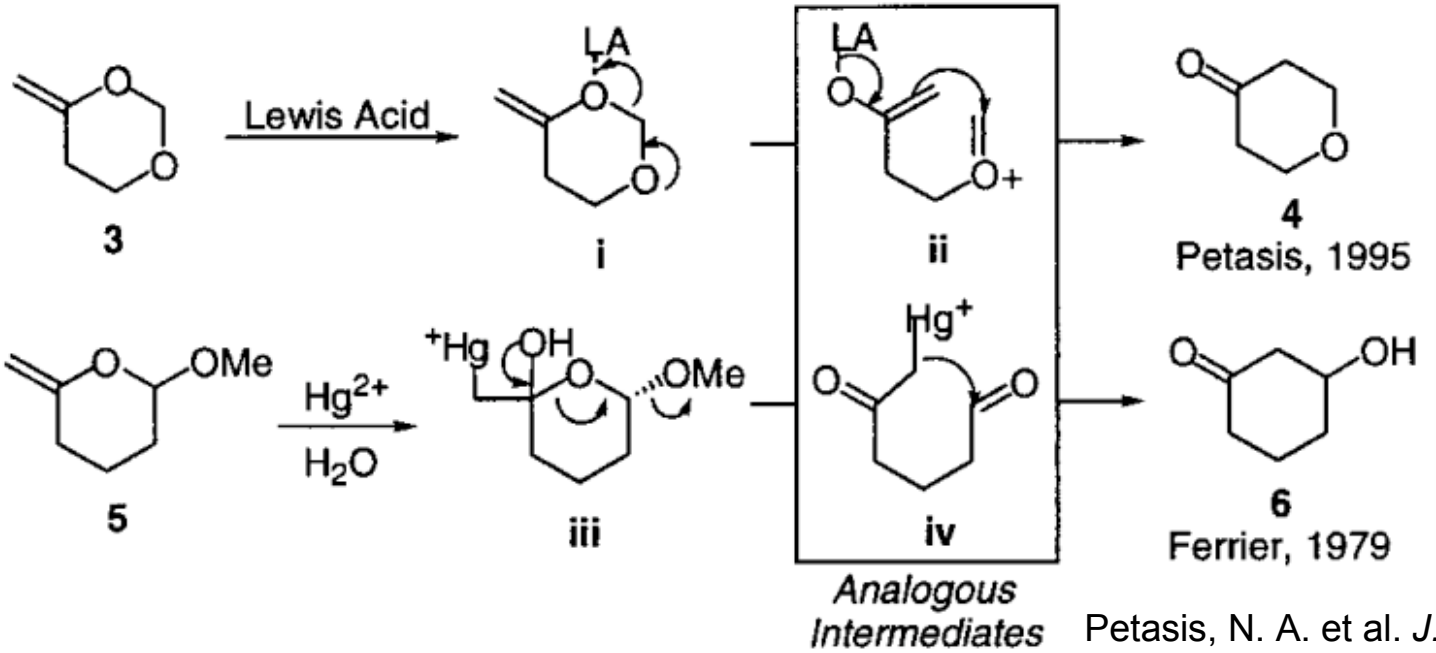
10 examples

50-91% yields



8 examples

81-96% yields

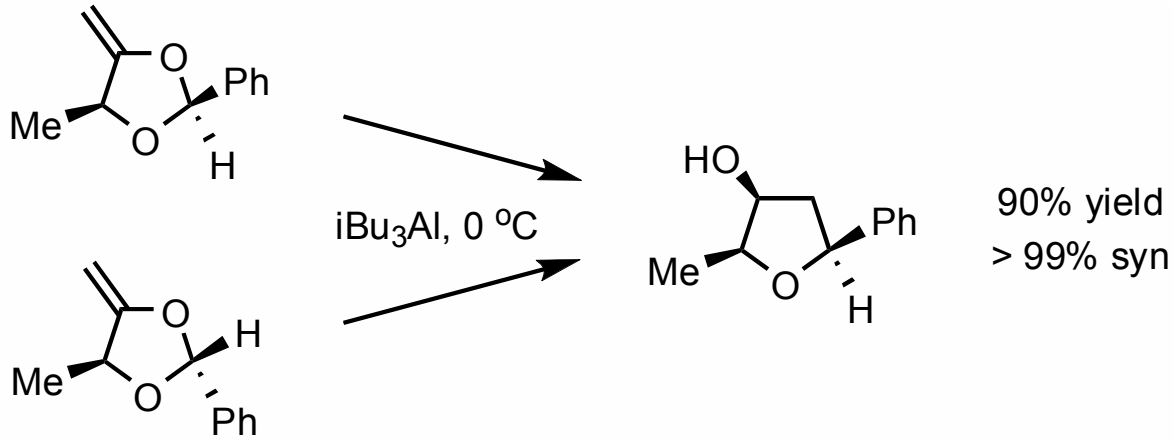


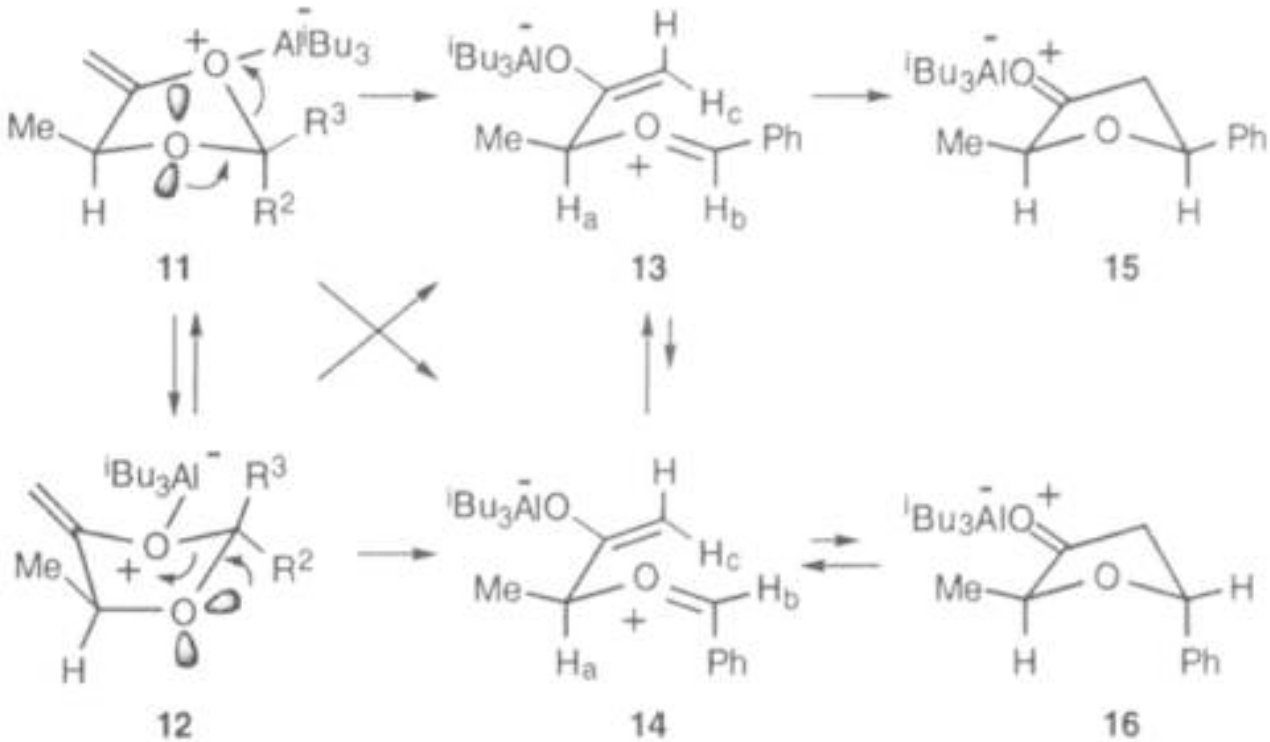
Petasis, N. A. et al. *J. Am. Chem. Soc.* **1995**, *117*, 6394

Petasis, N. A. et al. *Tett. Lett.* **1996**, *37*, 141

Smith, A. B. III et al. *J. Am. Chem. Soc.* **2001**, *123*, 10942

Mechanism





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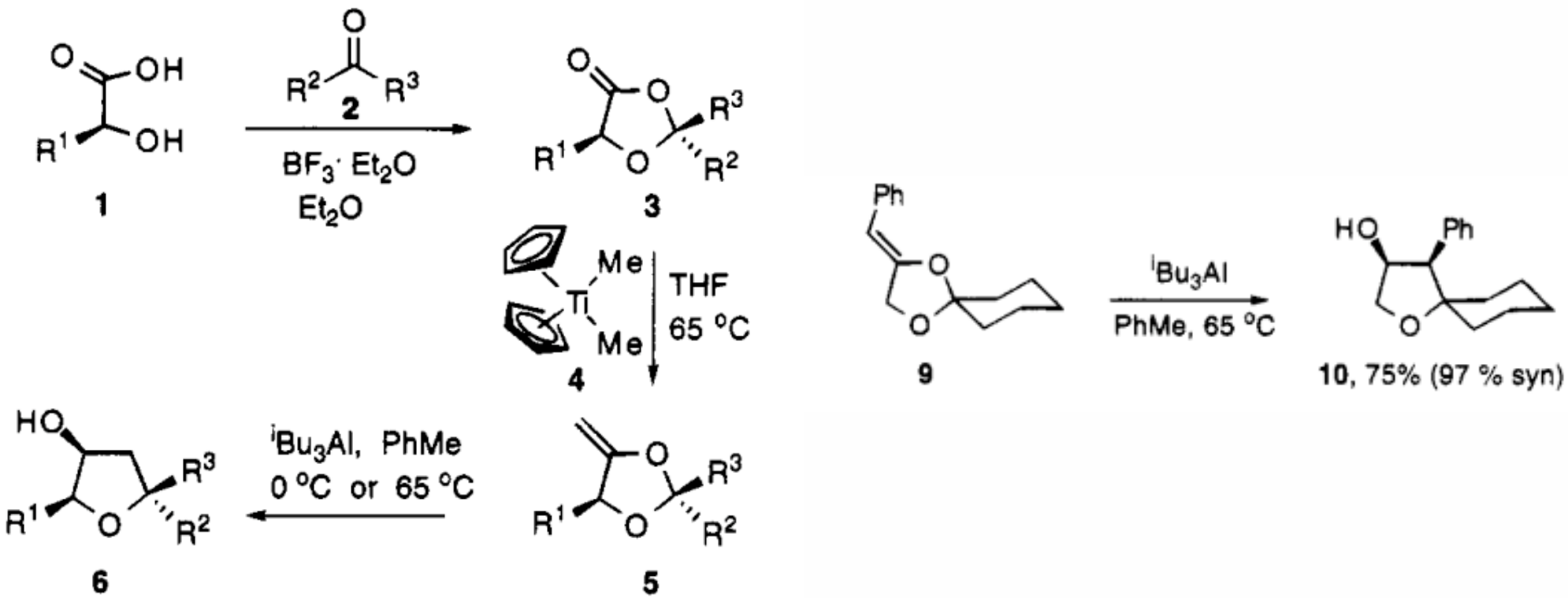
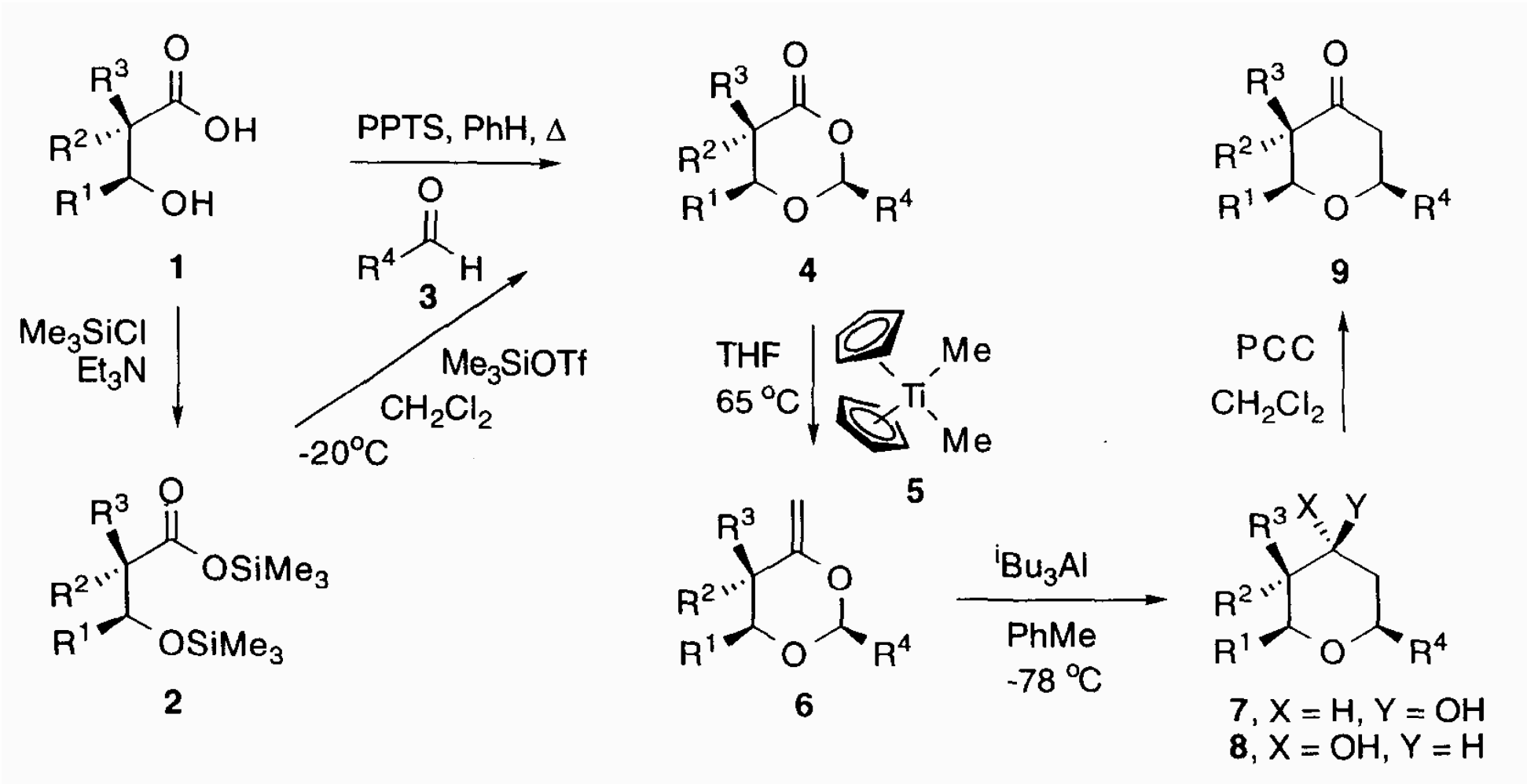
Convergency in P-F Sequence



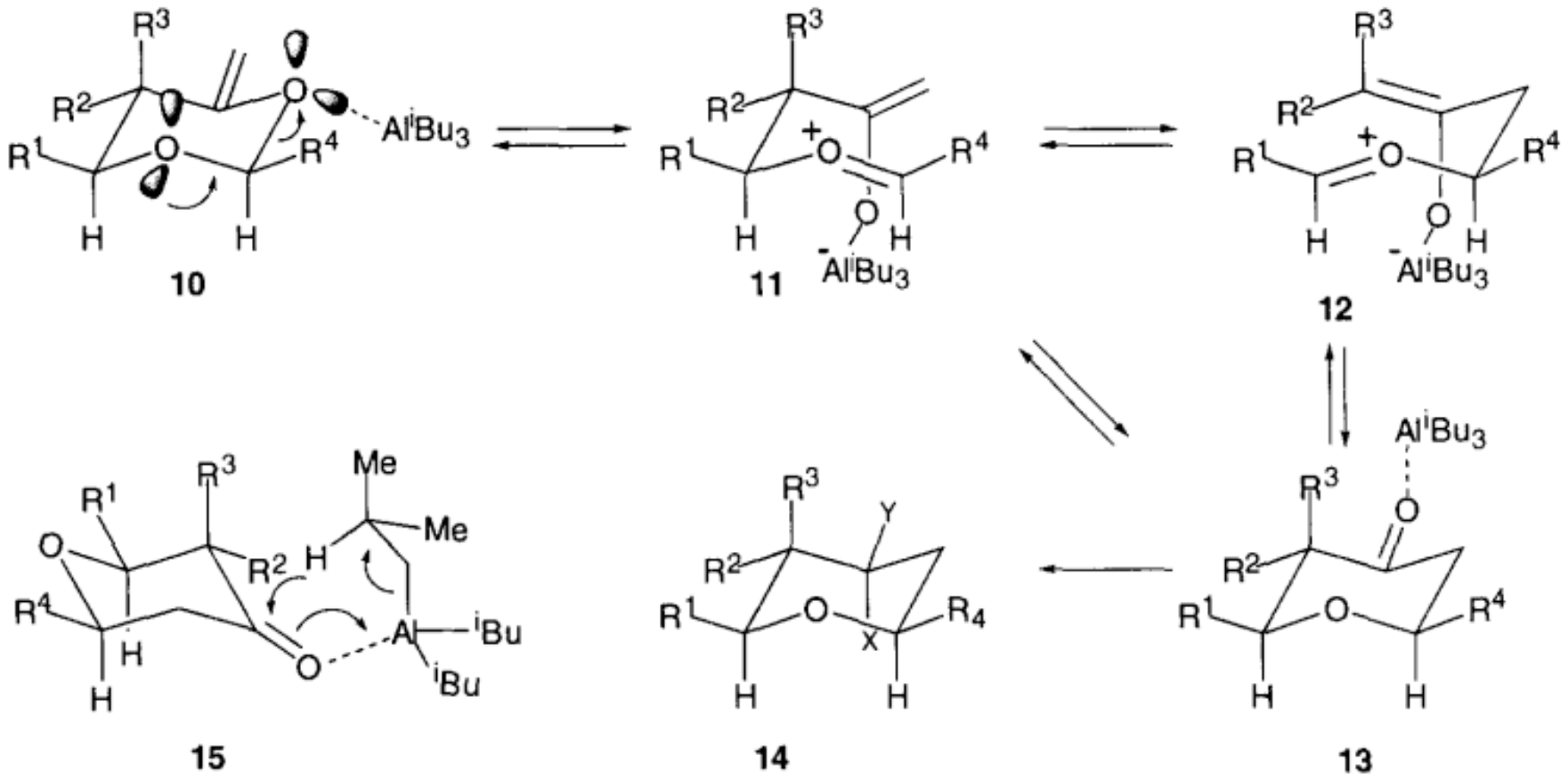
Petasis, N. A. et al. *J. Am. Chem. Soc.* **1995**, *117*, 6394

Six-membered 4-oxygenated tetrahydropyrans



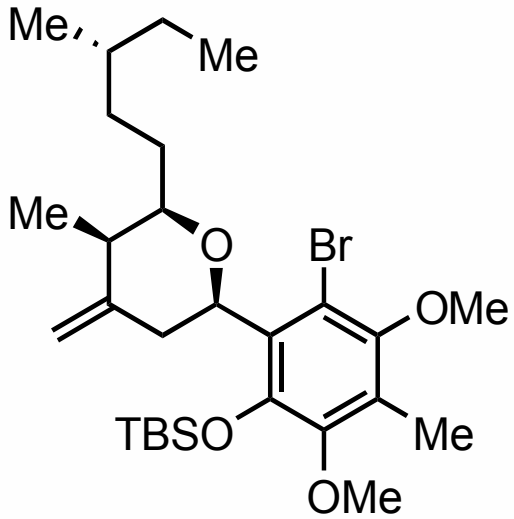
Petasis, N. A. et al. *Tett. Lett.* **1996**, *37*, 141

Mechanism



Petasis, N. A. et al. *Tett. Lett.* **1996**, *37*, 141

Problem

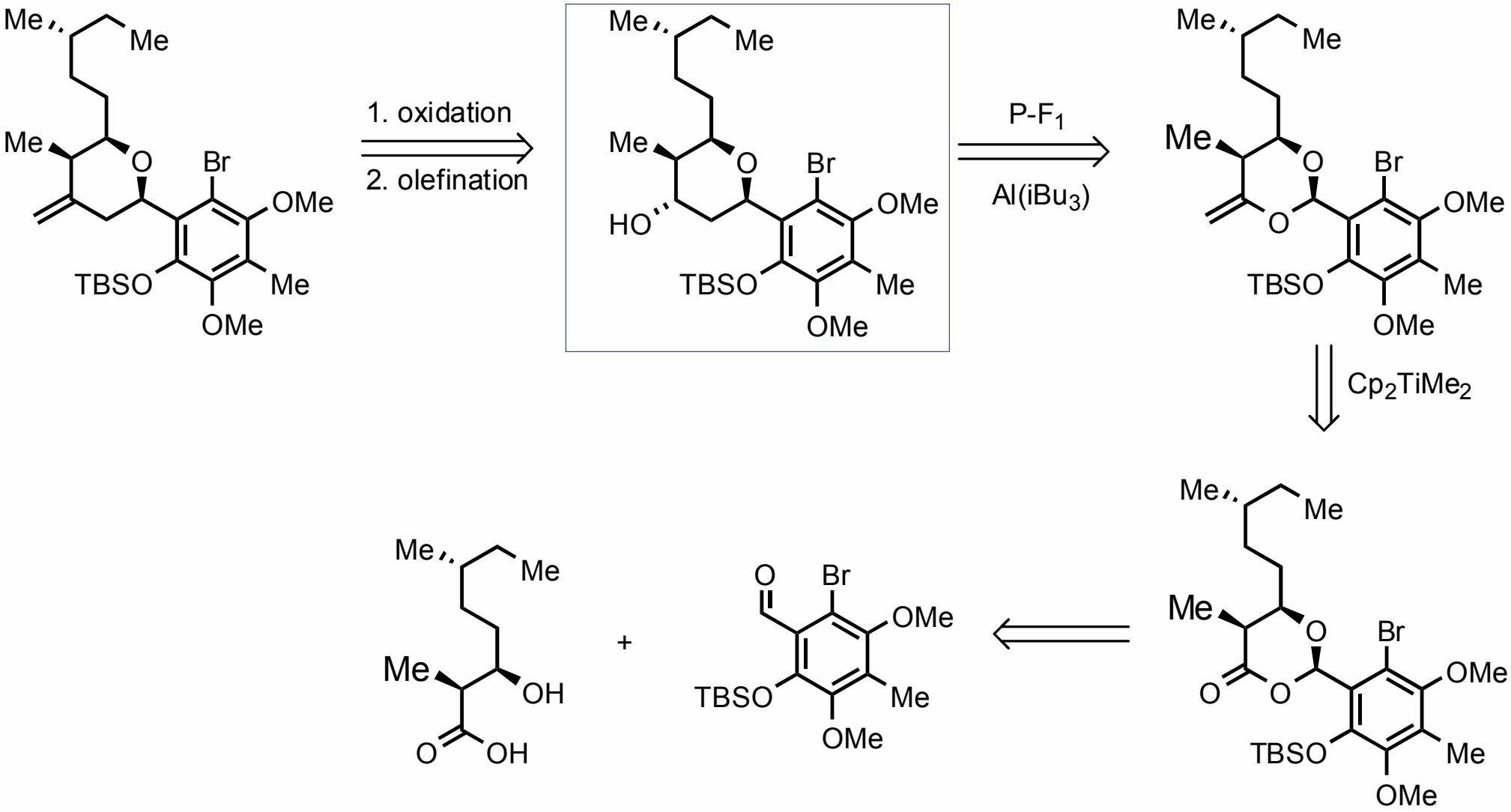


⟹ ?

Can you propose 2 retrosyntheses of the above molecule by exploiting the P-F rearrangement from a common intermediate to 2 sets of aldehydes and β-hydroxy acids?

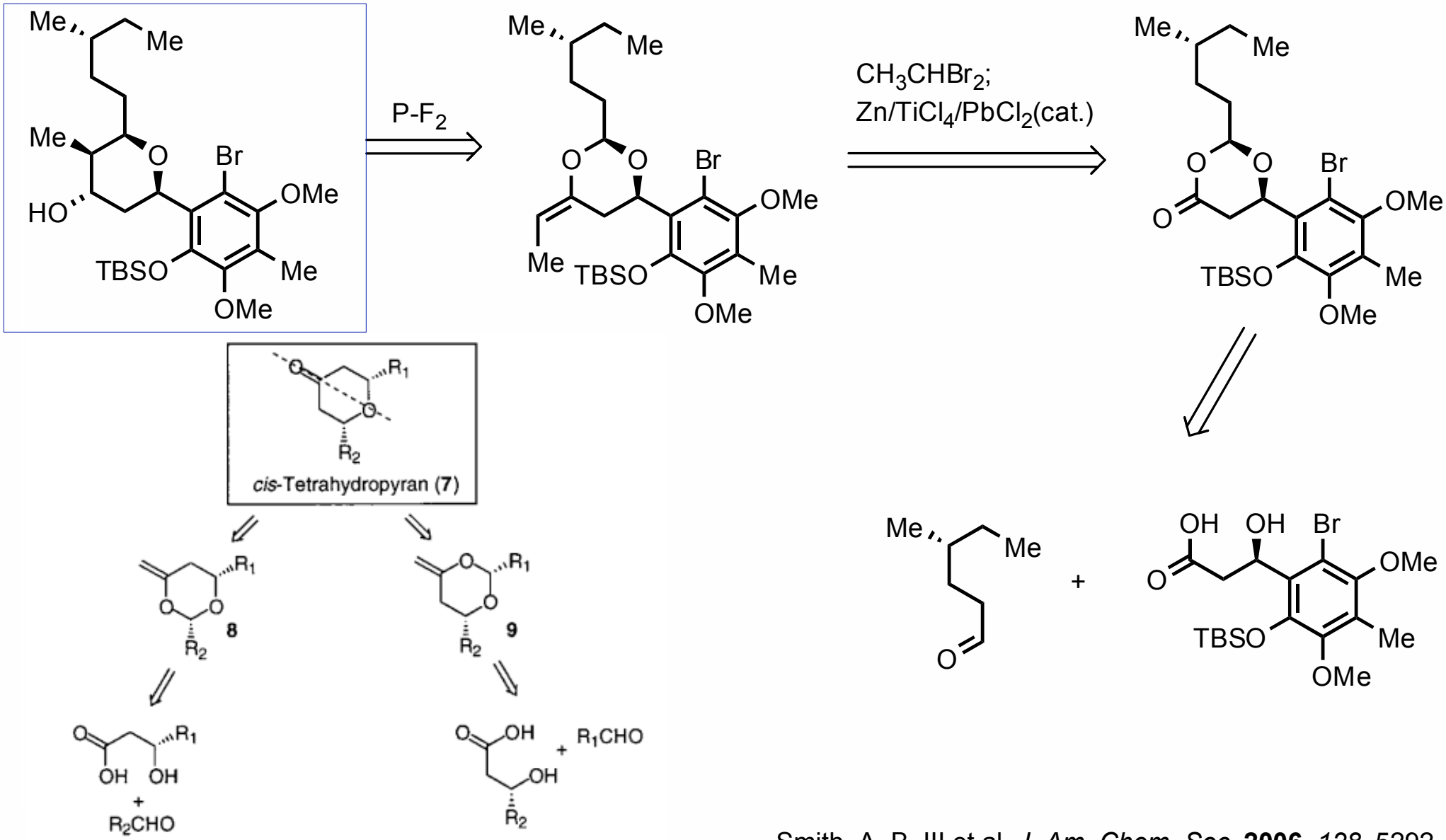
Smith, A. B. III et al. *J. Am. Chem. Soc.* **2006**, *128*, 5292

Answer P-F_1



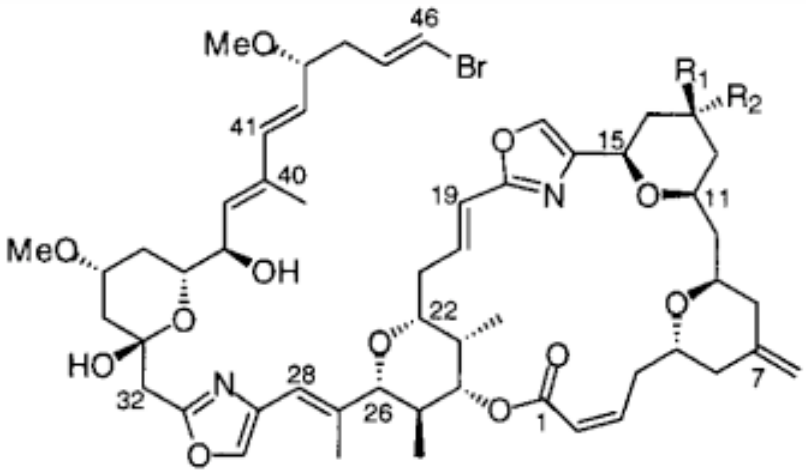
Smith, A. B. III et al. *J. Am. Chem. Soc.* **2006**, *128*, 5292

Answer P-F_2

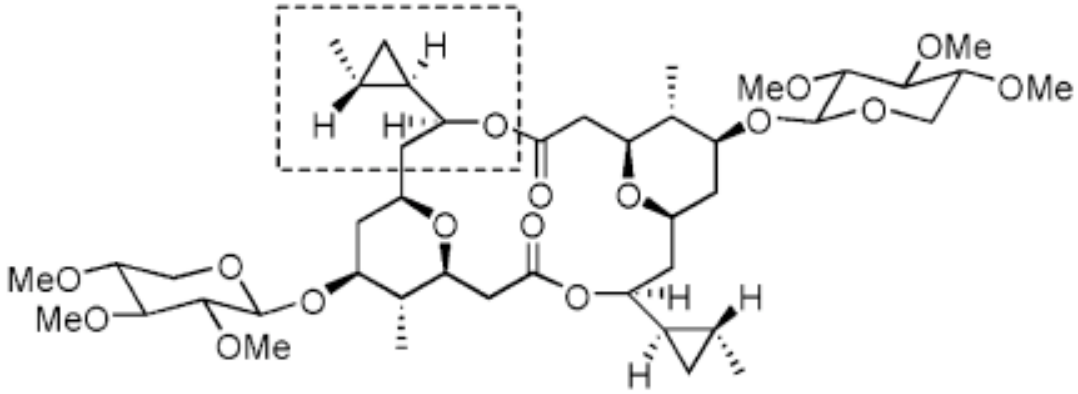


Smith, A. B. III et al. *J. Am. Chem. Soc.* **2006**, *128*, 5292

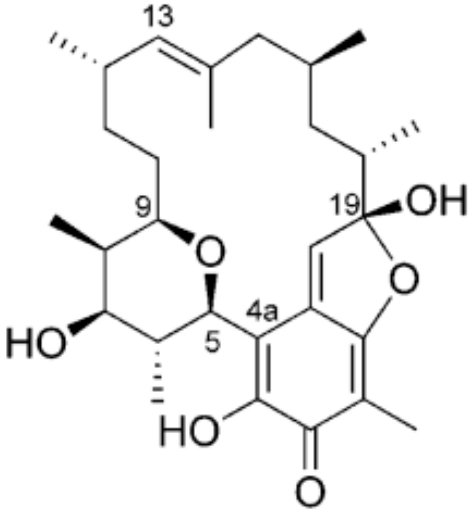
Application to Natural Products



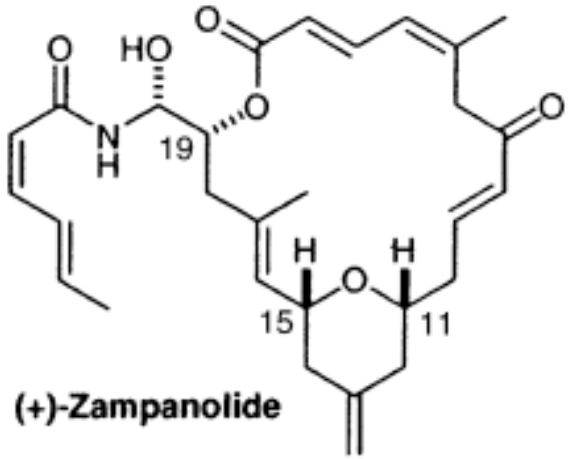
(+)-Phorboxazole A (**1**) R_1 = H, R_2 = OH
(+)-Phorboxazole B (**2**) R_1 = OH, R_2 = H



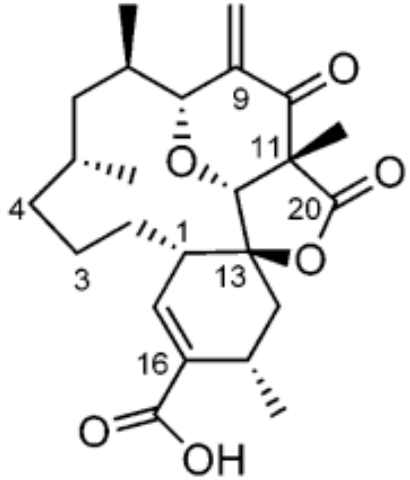
Clavosolide A (**1**) (Revised)



Kendomycin (−)-**1**

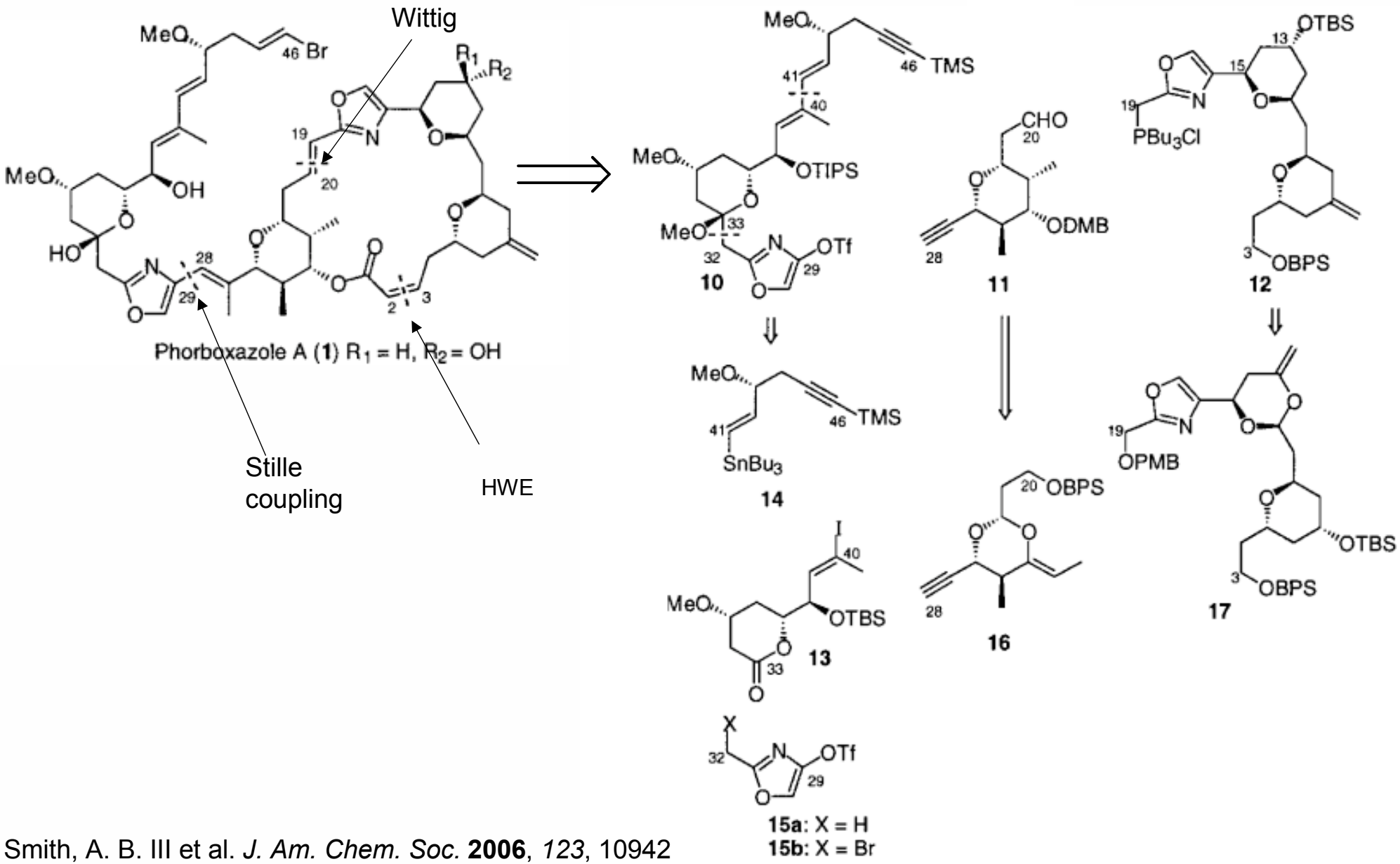


(+)-Zampanolide



Okilactomycin (**1**)

Phorboxazole



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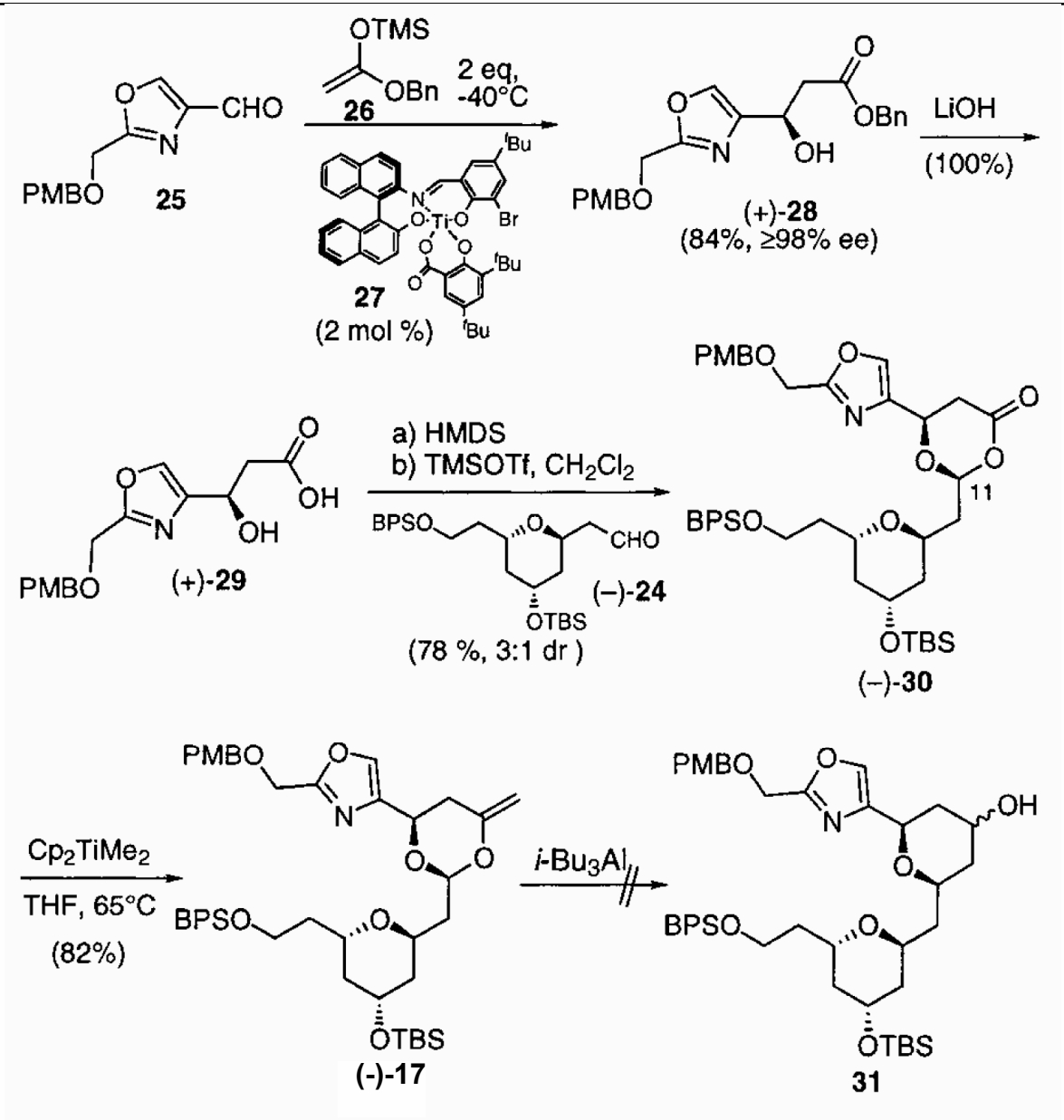
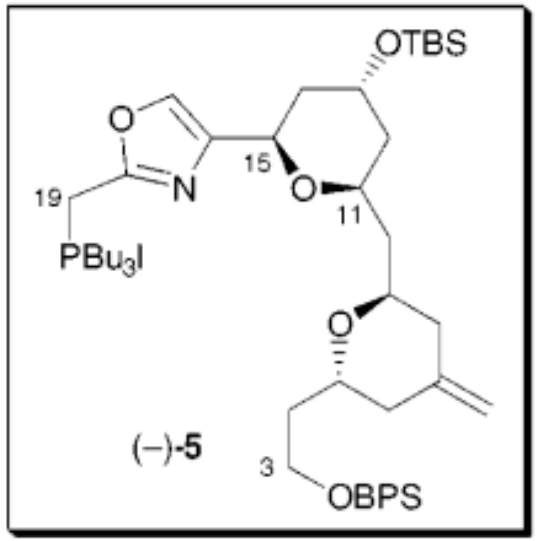
Petasis' conditions





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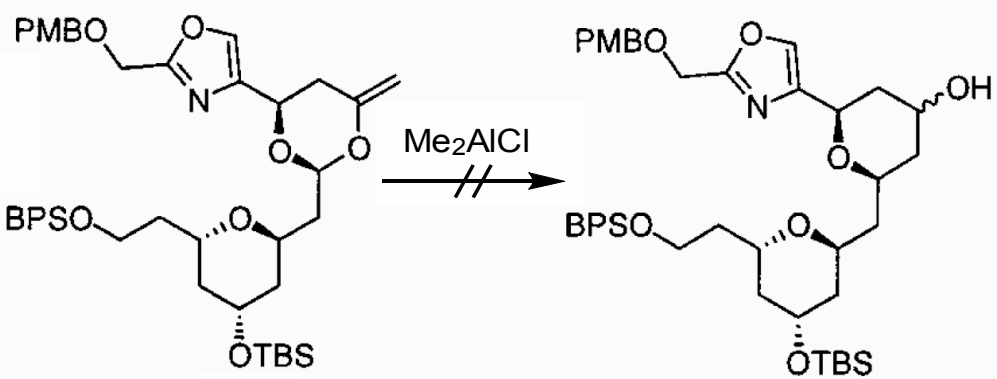
Optimization of Petasis' Protocol

37 R_1=OBPS, R_2=O
38 R_1=OBPS, R_2=(OH, H)
39 R_1=Ph, R_2=O
40 R_1=Ph, R_2=(OH, H)

Lewis Acid	R_1=Ph	R_1=OBPS
i-Bu_3Al	87%	85%
$ZnCl_2$	25%	0%
Me_2AlCl	**95%**	**92%**
$MeAlCl_2$	60%	-
$BF_3{\cdot}Et_2O$	0%	-
$TiCl_4$	0%	-
$TiCl_2(O\textit{i}\text{-}Pr)_2$	0%	-
$SnCl_4$	0%	-



(-)-17 **31**

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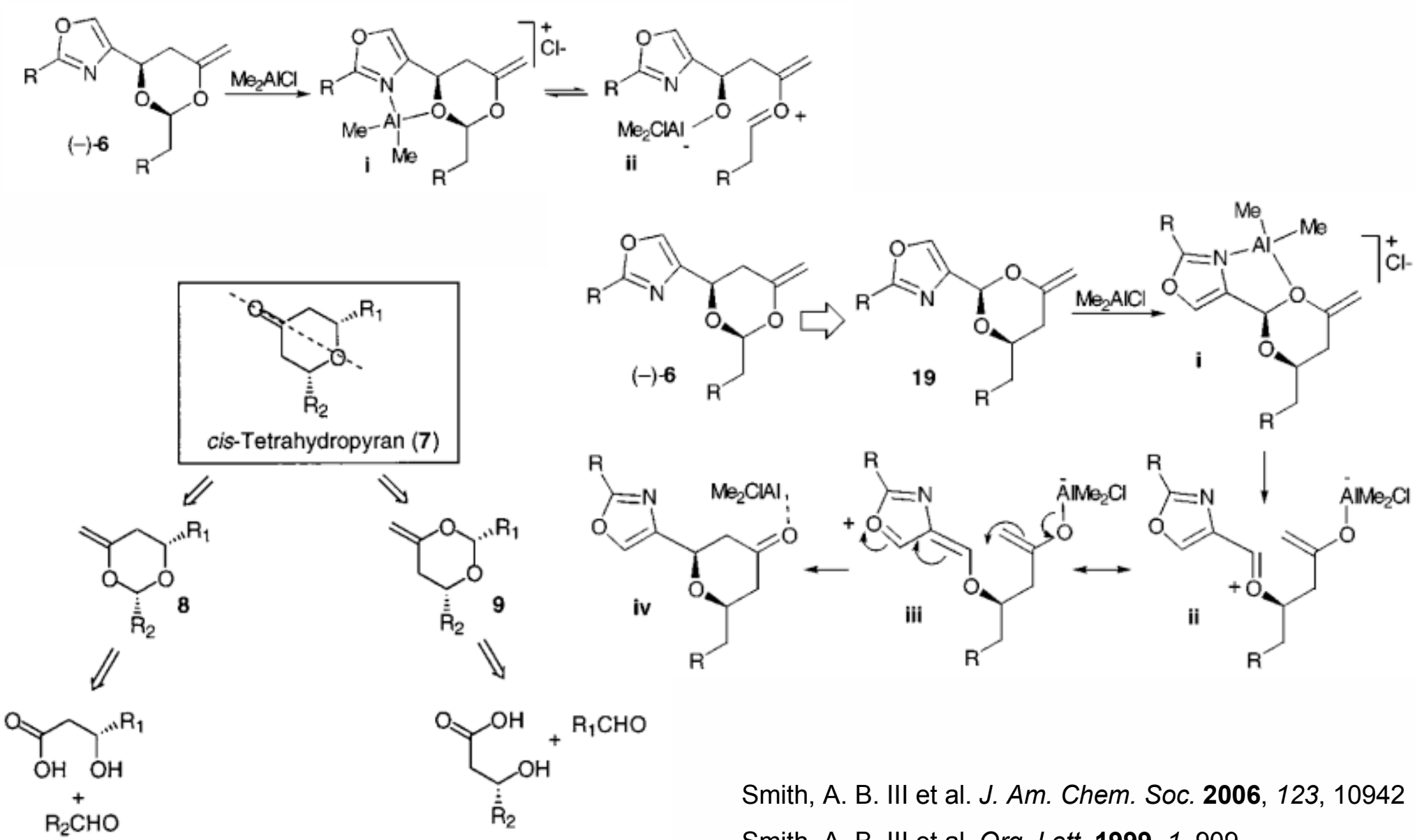
Flexibility of P-F rearrangement



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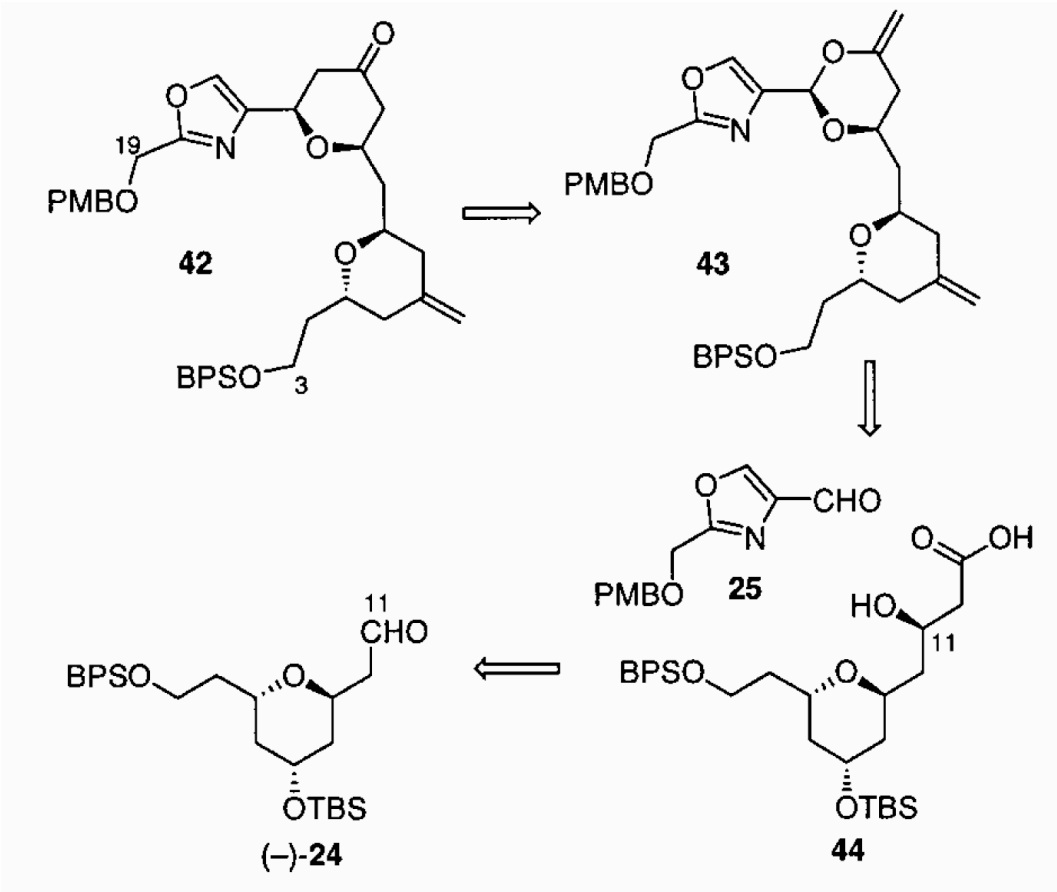
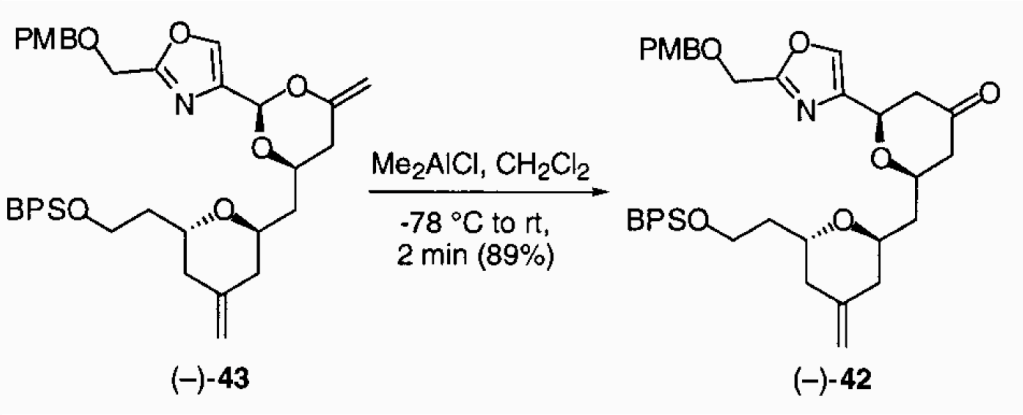
Smith, A. B. III et al. *Org. Lett.* **1999**, *1*, 909

Revised Strategy





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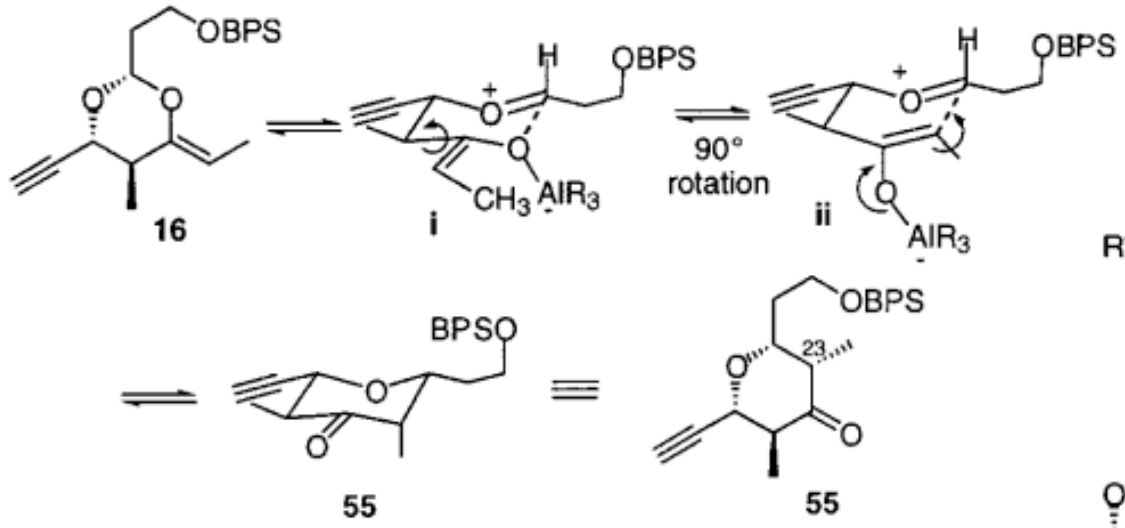
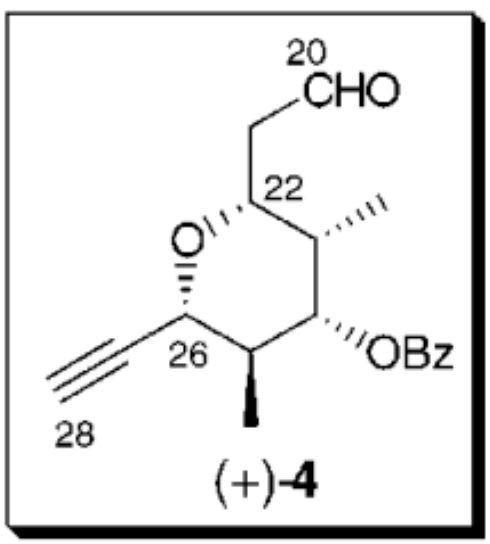
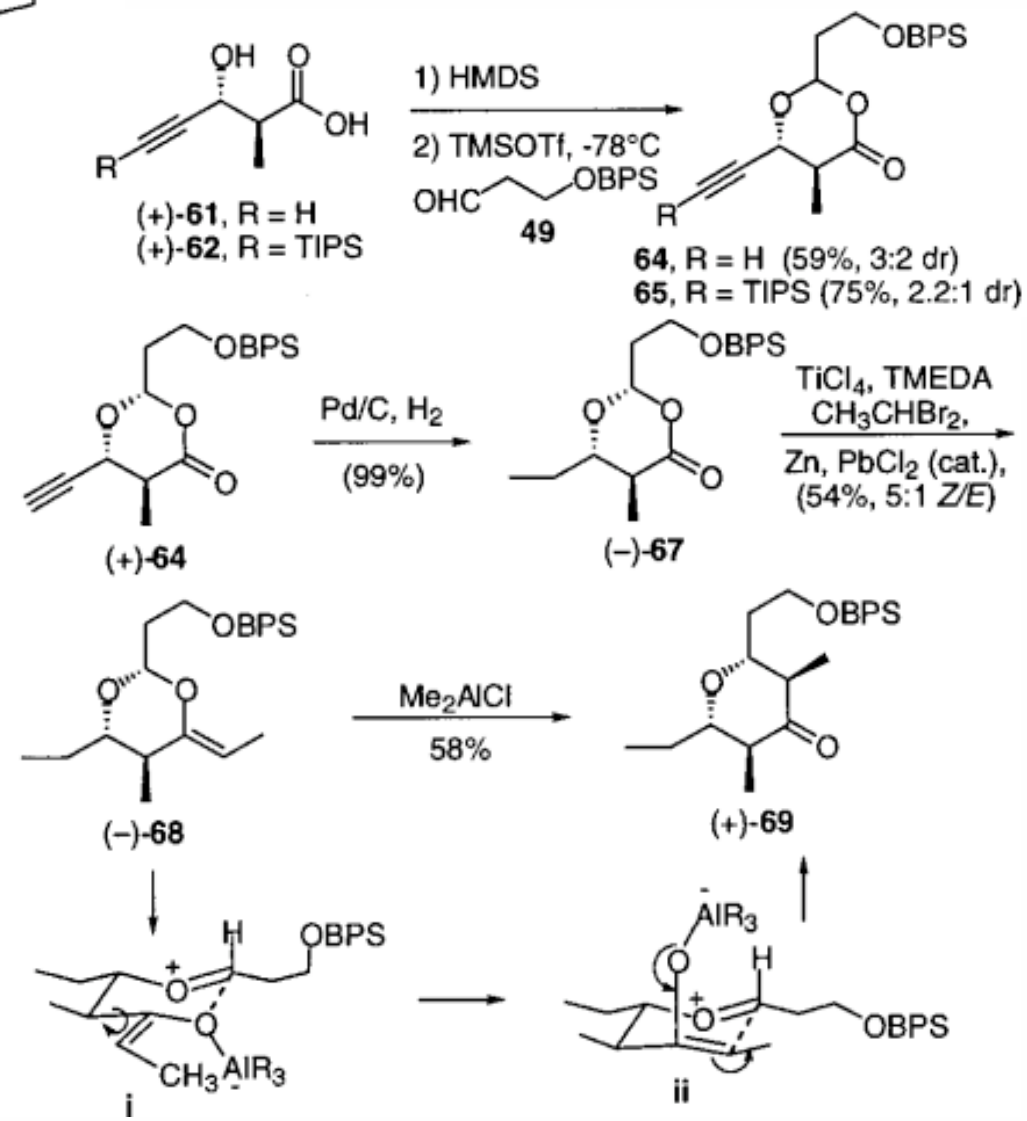
Intermediate X







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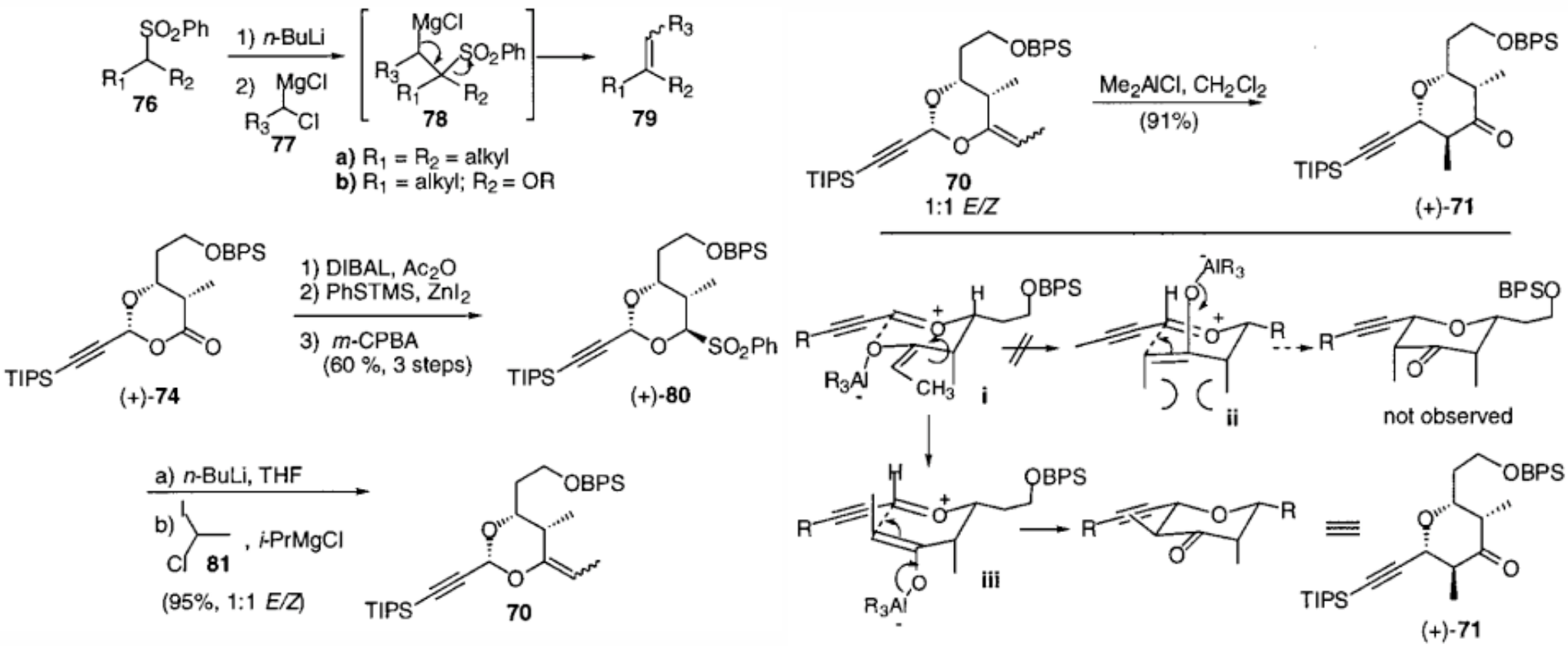
New Olefination Strategy



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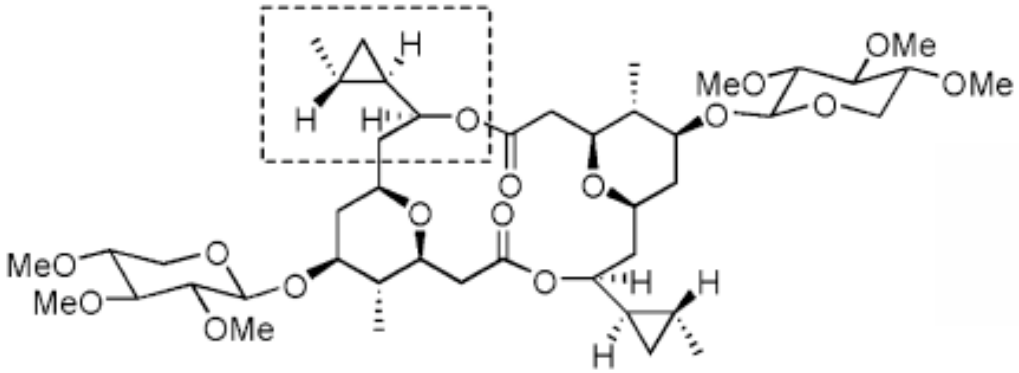
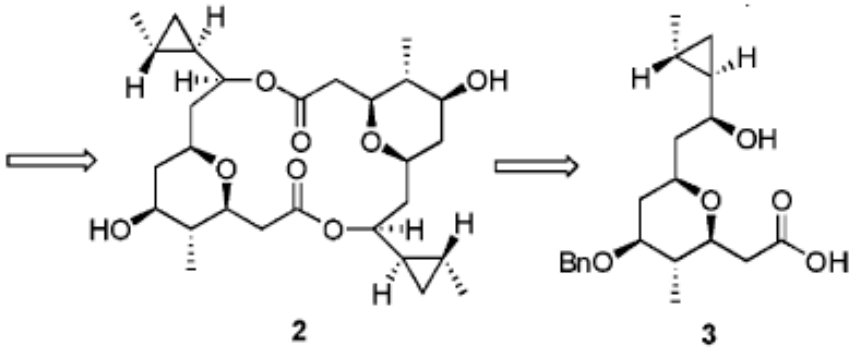
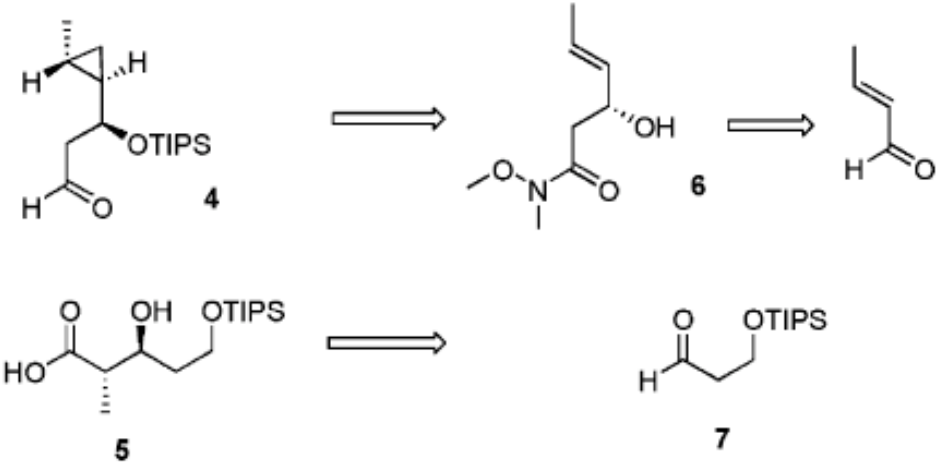
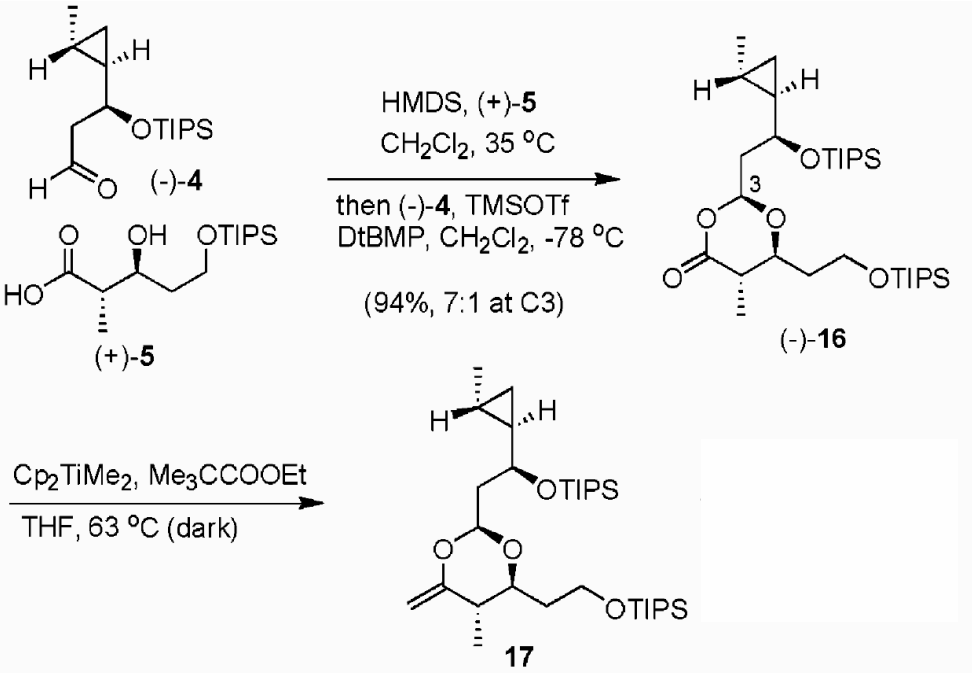
Clavosolide



Clavosolide A **(1)** (Revised)

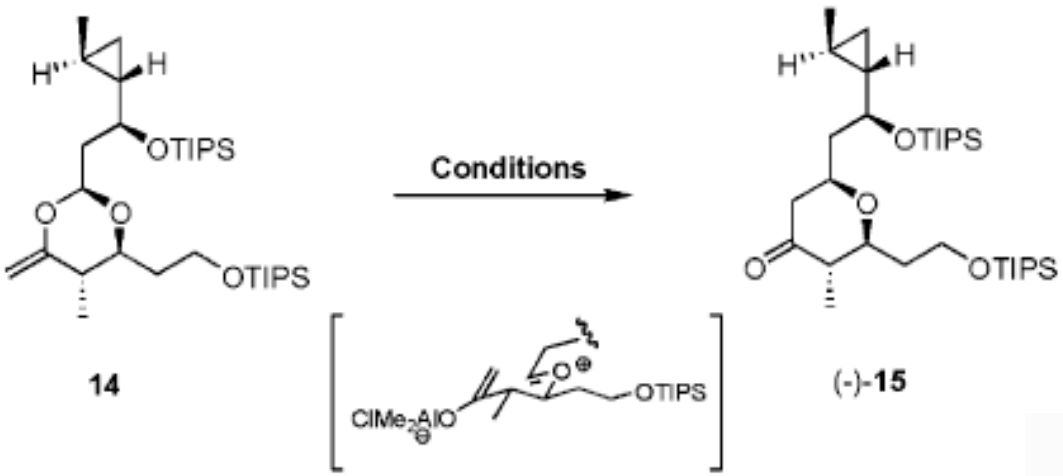




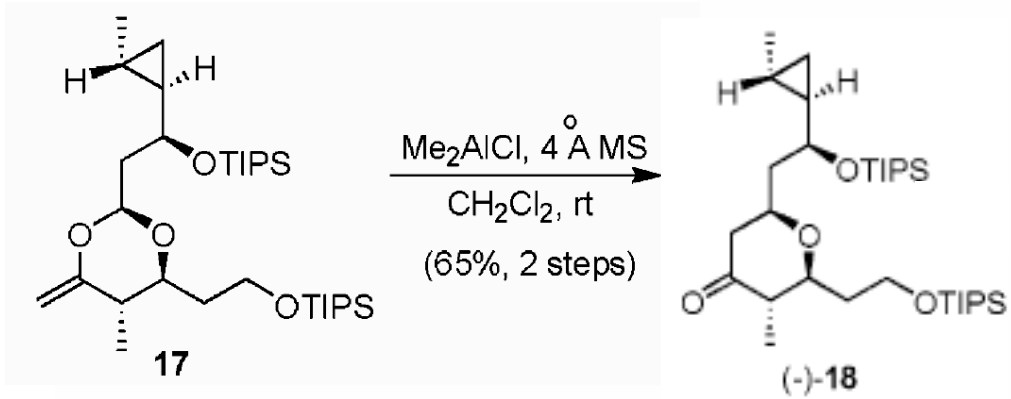


Smith. A. B. III et al. *Org. Lett*. **2006**, *8*, 3315

Rearrangement

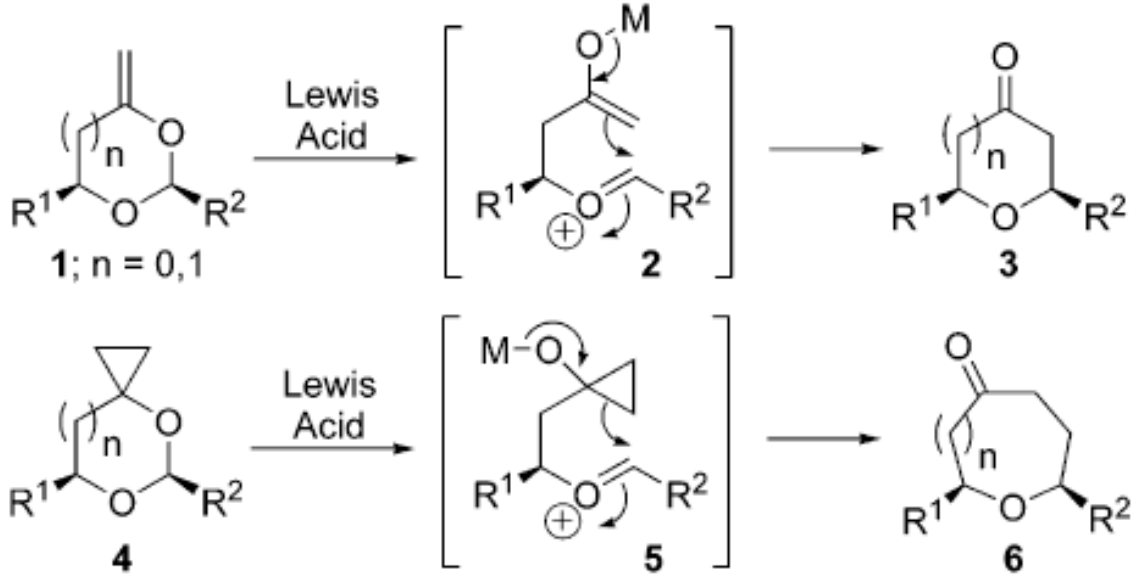


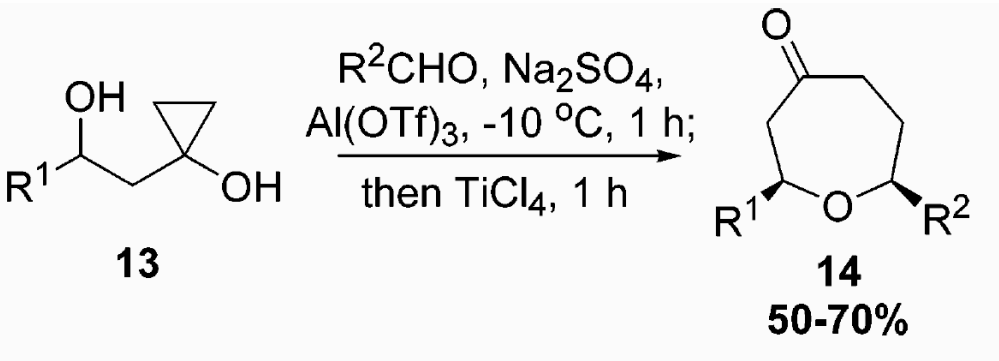
Me_2AlCl (equiv)	Cs_2CO_3 (equiv)	Conditions	Yield
2.6	1.6	-78 °C / 1h	Decomp.
1.3	1.6	-78 °C / 1h	No rxn.
1.3	1.6	0 °C / 5 min	40%
1.3	1.6	rt / 15 min	30%
1.1	-	rt / 1 min	31%
1.1	-	rt / 1 sec	60%

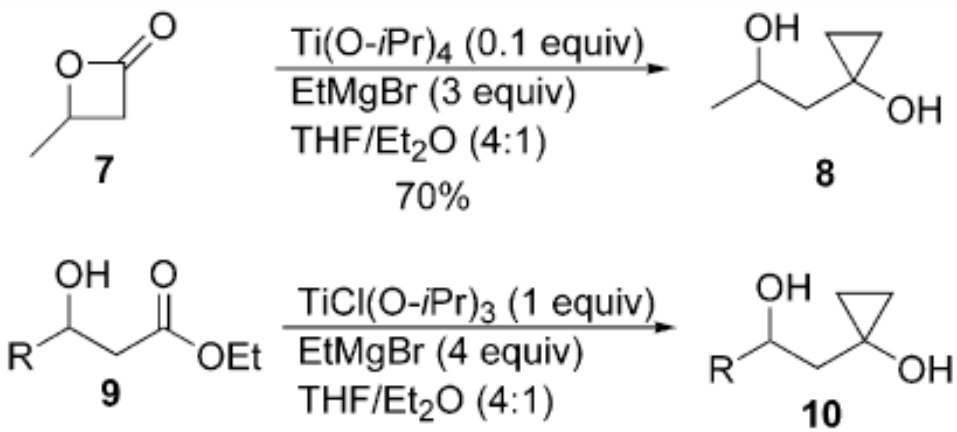


Smith. A. B. III et al. *Org. Lett*. **2006**, *8*, 3315

A derivative of P-F rearrangement





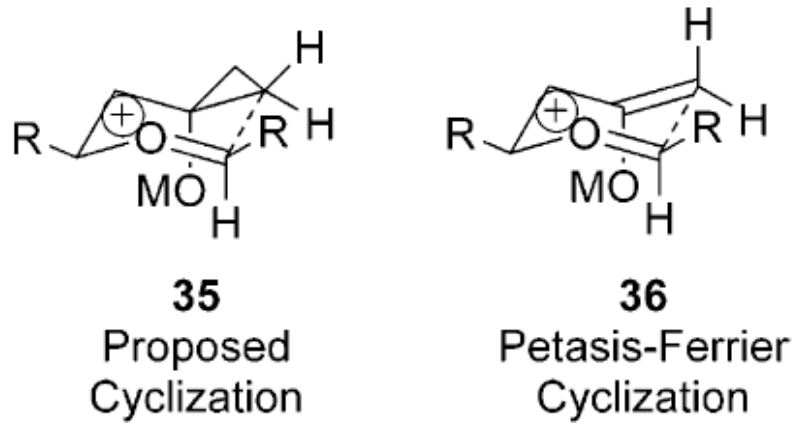


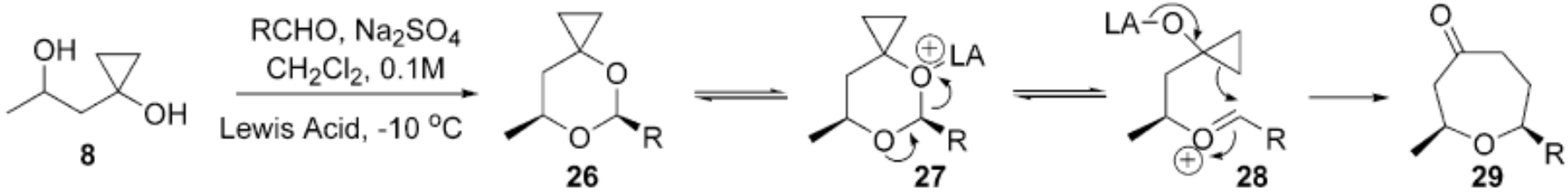
R	Yield
$CH(CH_3)_2$ (**10a**)	51%
$(CH_2)_2CH_3$ (**10b**)	51%

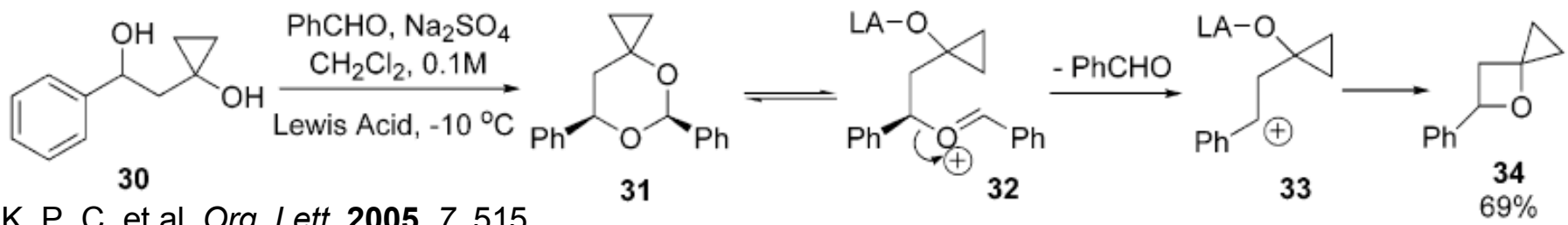
Minibiole K. P. C. et al. *Org. Lett.* **2005**, *7*, 515

Scope and Mechanism

diol \ RCHO	15	16	17
8	12 (55%)	18 (51%)	19 (55%)
10a	20 (69%)	21 (62%)	22 (70%)
10b	23 (66%)	24 (71%)	25 (71%)







Minibiole K. P. C. et al. *Org. Lett.* **2005**, *7*, 515

Conclusions

- **P-F reaction allows access to 2,6-*cis*-fused tetrahydropyrans in a highly convergent and stereoselective manner**
- **A number of natural products exhibit the P-F retron**
- **The P-F reaction has not been exploited outside of the Smith labs**

Other Natural Products

(-)-Kendomycin

Smith, A. B. III, et al. *J. Am. Chem. Soc*. **2006**, *128*, 5292

(+)-Zampanolide and (+)-Dactylolide

Smith, A. B. III, et al. *J. Am. Chem. Soc.* **2002**, *124*, 11102

(-)-Okilactomycin

Smith, A. B. III, et al. *J. Am. Chem. Soc*. **2007**, *129*, 14872

Spongistatin

Smith, A. B. III, et al. *Org. Lett*. **2004**, *6*, 3637