

Concise Syntheses of (+)-Macrosphelides A and B: Studies on the Macro-Ring Closure Strategy

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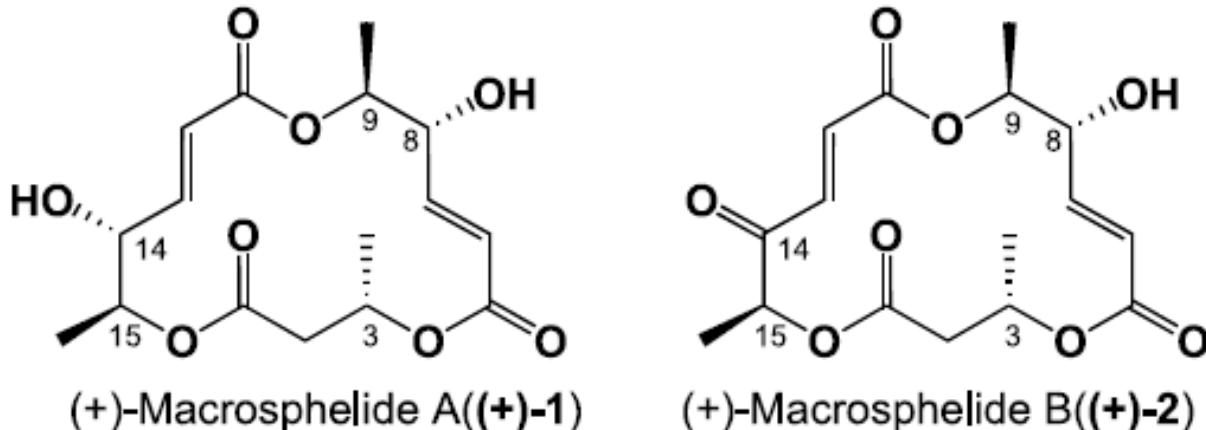
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Macrosphelides



The macrosphelides strongly inhibit the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells.

Macrosphelide A also proved to be orally active against lung metastasis of B16/BL6 melanoma in mice (50 mg/kg).

Importantly, **1** did not inhibit the growth of various mammalian cell lines (0.2 mg/mL) or microorganisms (1 mg/mL) in vitro.

No acute toxicity was observed upon intraperitoneal injection into BDF1 mice.

Isolation of the natural compounds

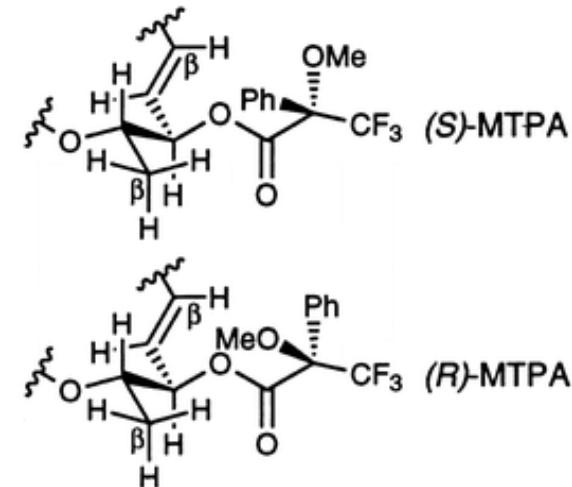
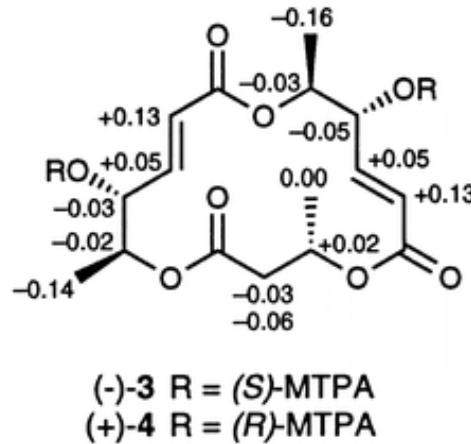
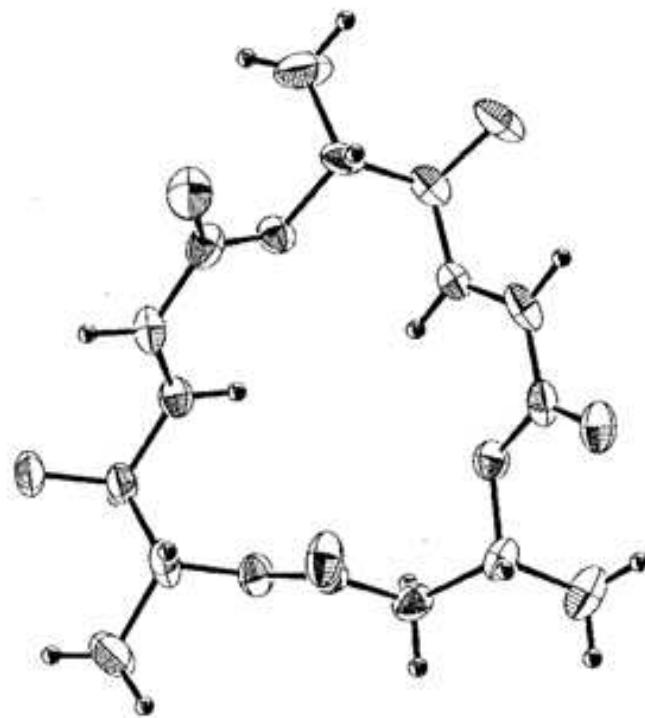
- From a culture broth of the fungus *Microsphaeropsis* sp. FO-5050 by the Omura group



- From *Periconia byssoides* separated from the sea hare *Aplysia kurodai* by the Numata group

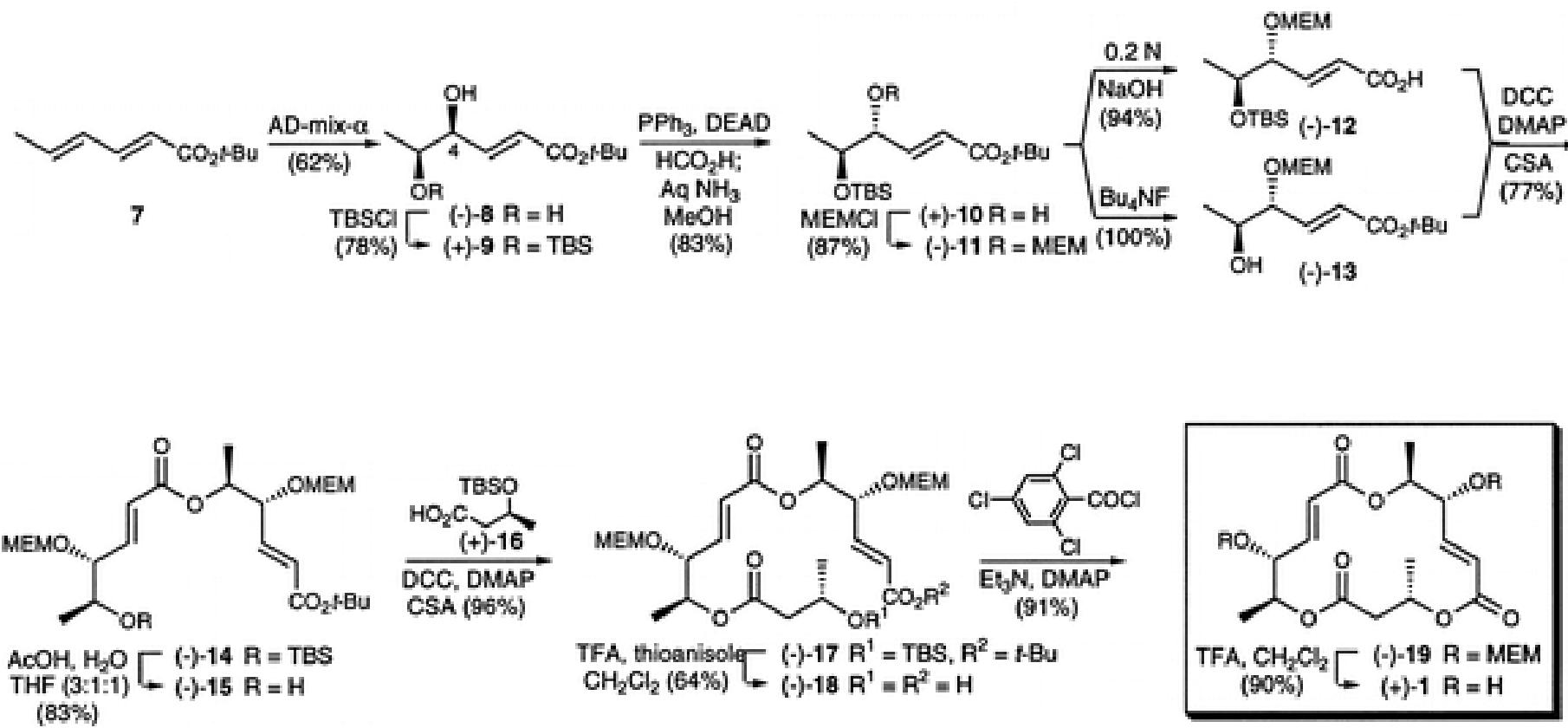


Structural determination



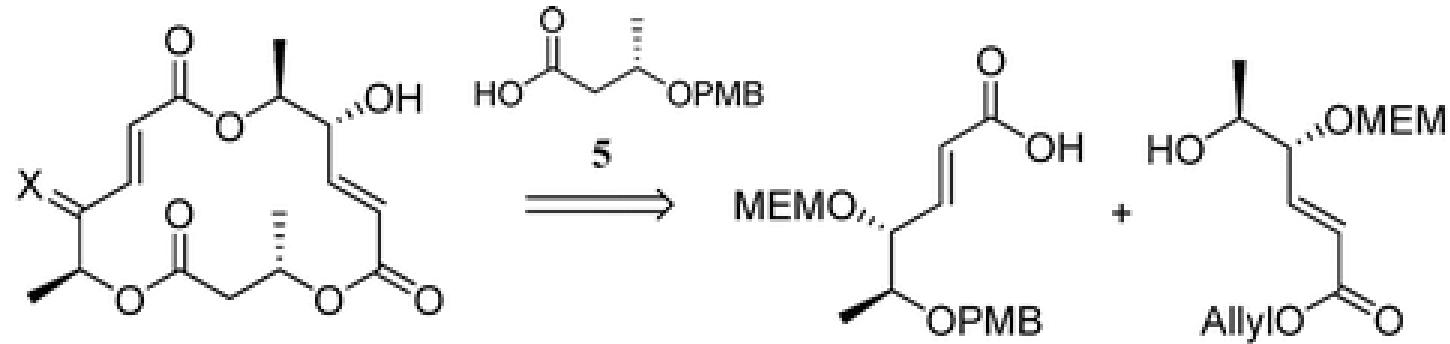
the bis(Mosher ester) derivatives

First synthesis of (+)-macrosphelide A



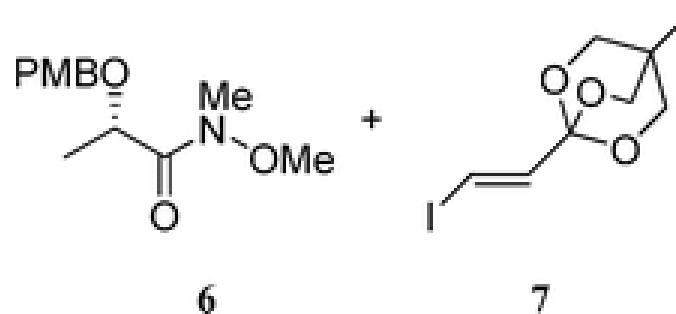
11 steps, 10.6 % overall yield (82 %/step)

Retrosynthetic analysis

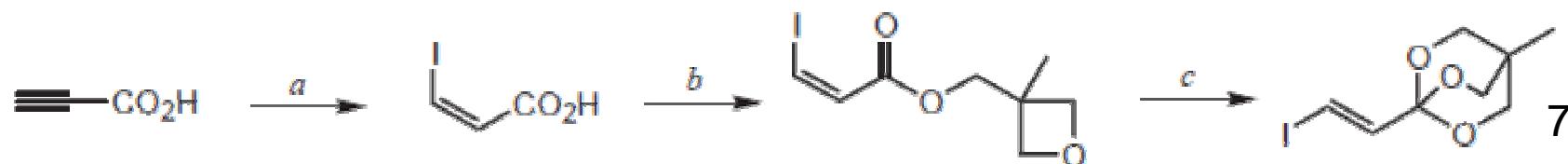


$\text{X} = \beta\text{-OH, H; (+)-macrospheleide A (1)}$
 $\text{X} = \text{O; (+)-macrospheleide B (2)}$

\Downarrow *trans vinylogous ester anion addition*

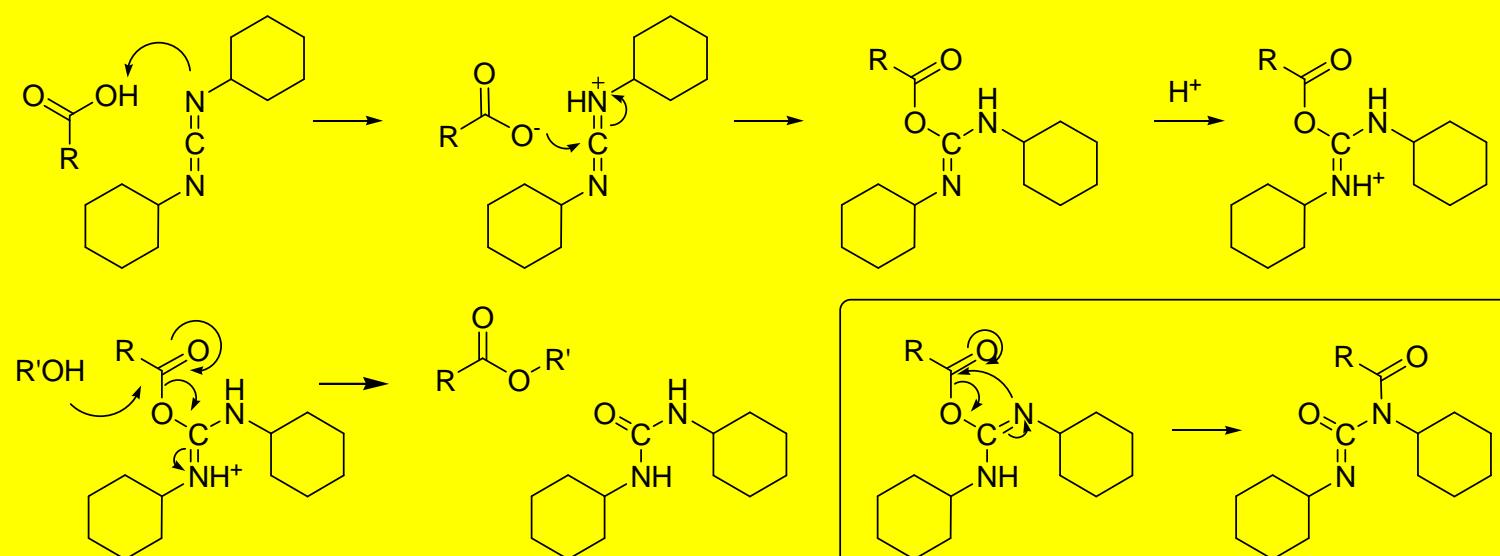


Preparation of fragment 7



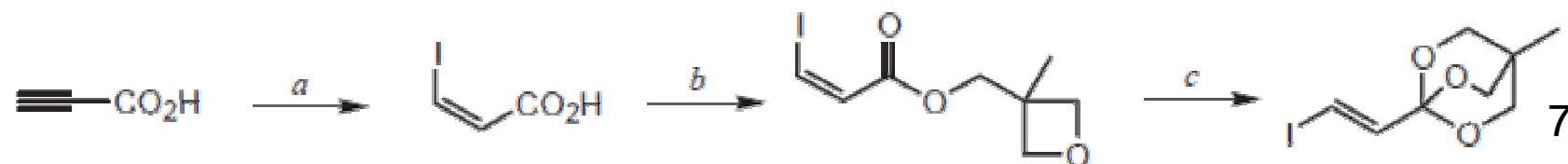
Reaction conditions: (a) 57% HI , H_2O , 85°C , 90%; (b) 3-methyl-3-hydroxymethylloxetane, DCC, DMAP, CH_2Cl_2 , rt, 95%; (c) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -15°C , 73%.

Steglich esterification

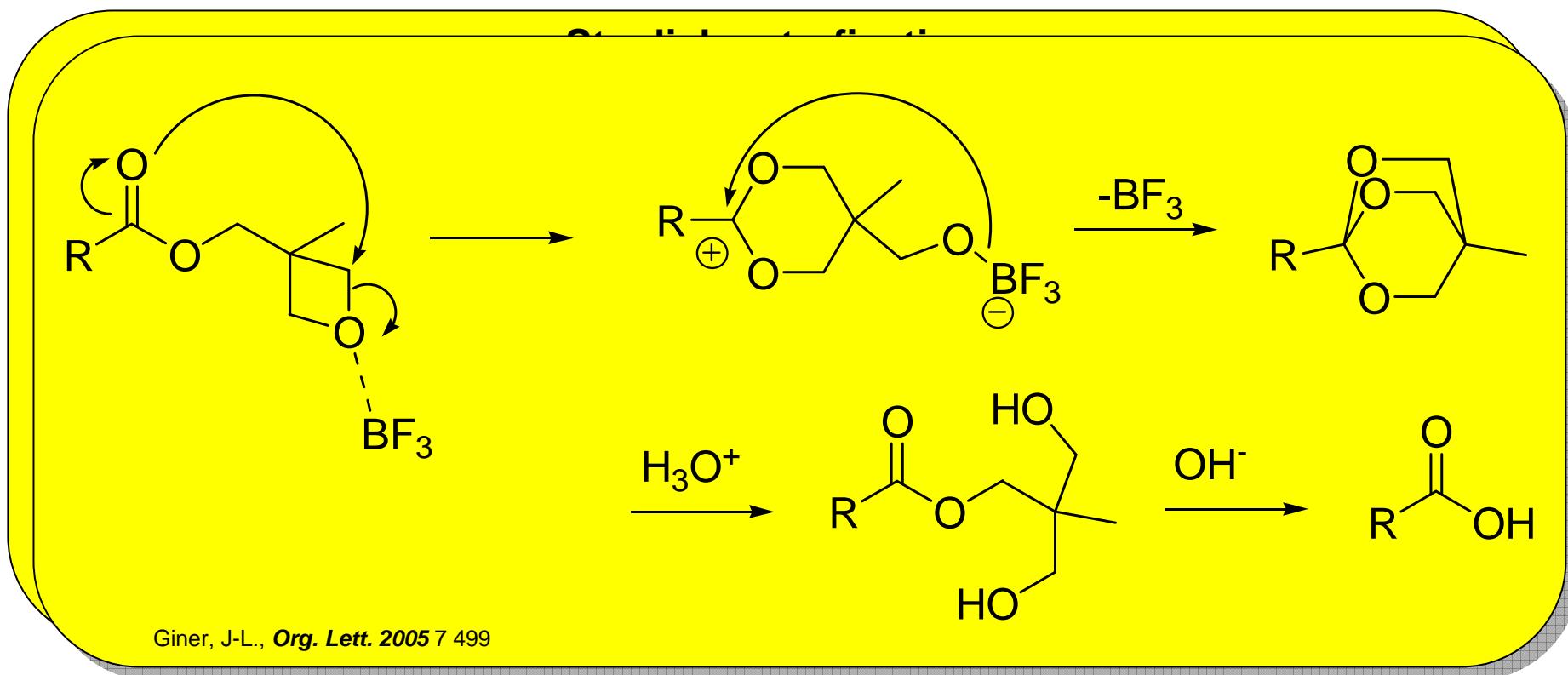


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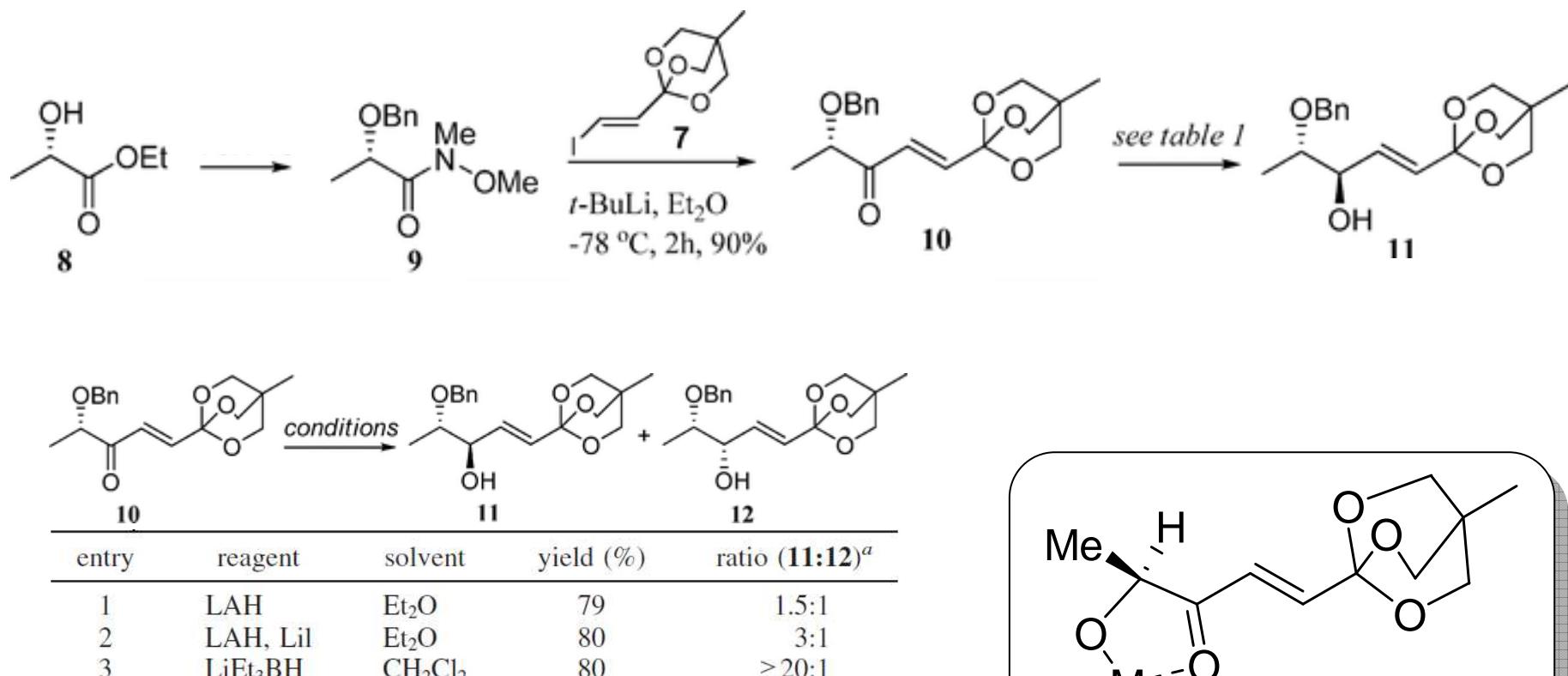
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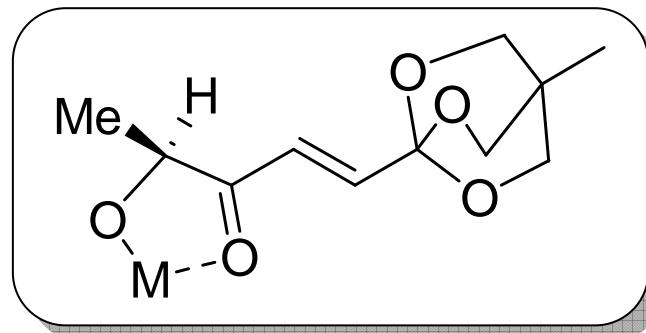
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Diastereoselective reduction through chelation control



^a Diastereomeric ratio was determined by ¹H NMR.

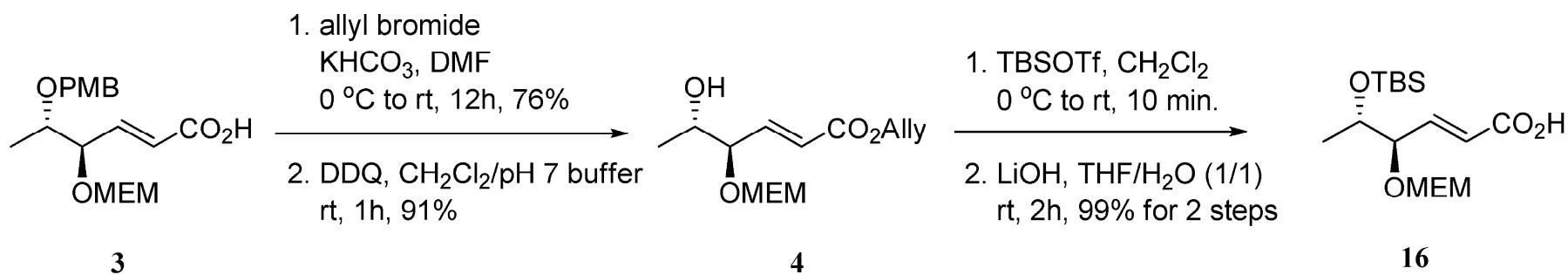
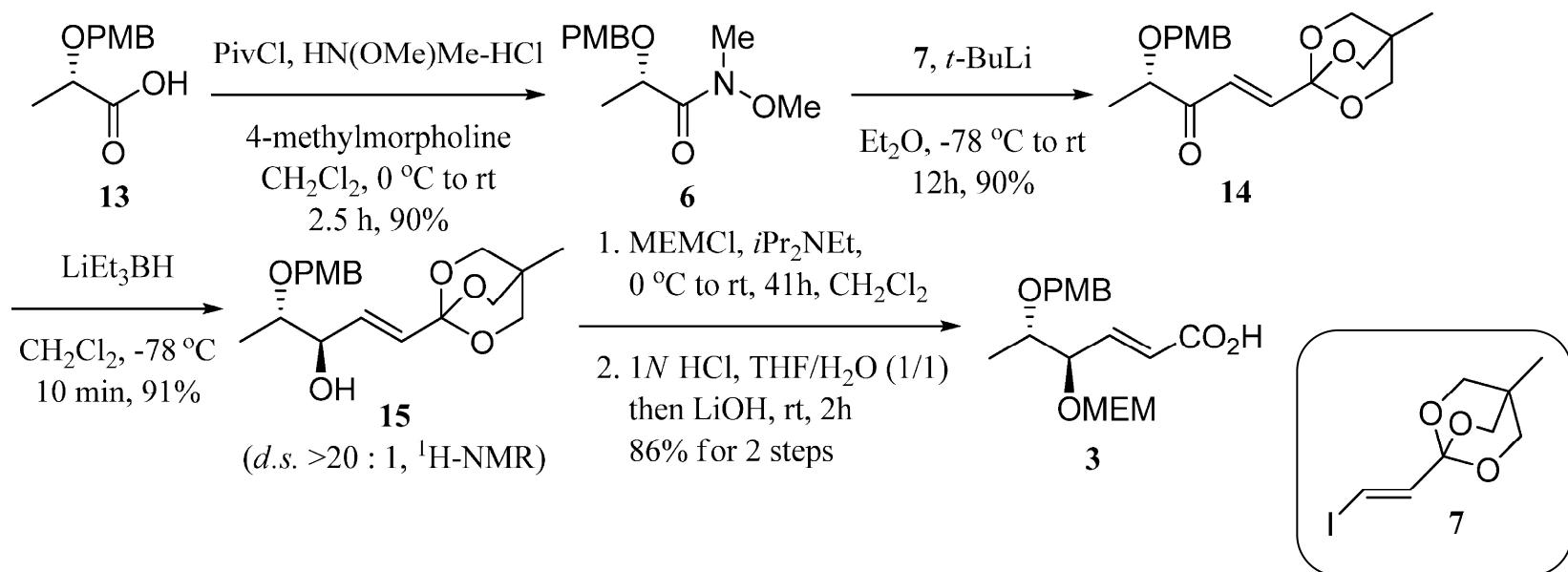


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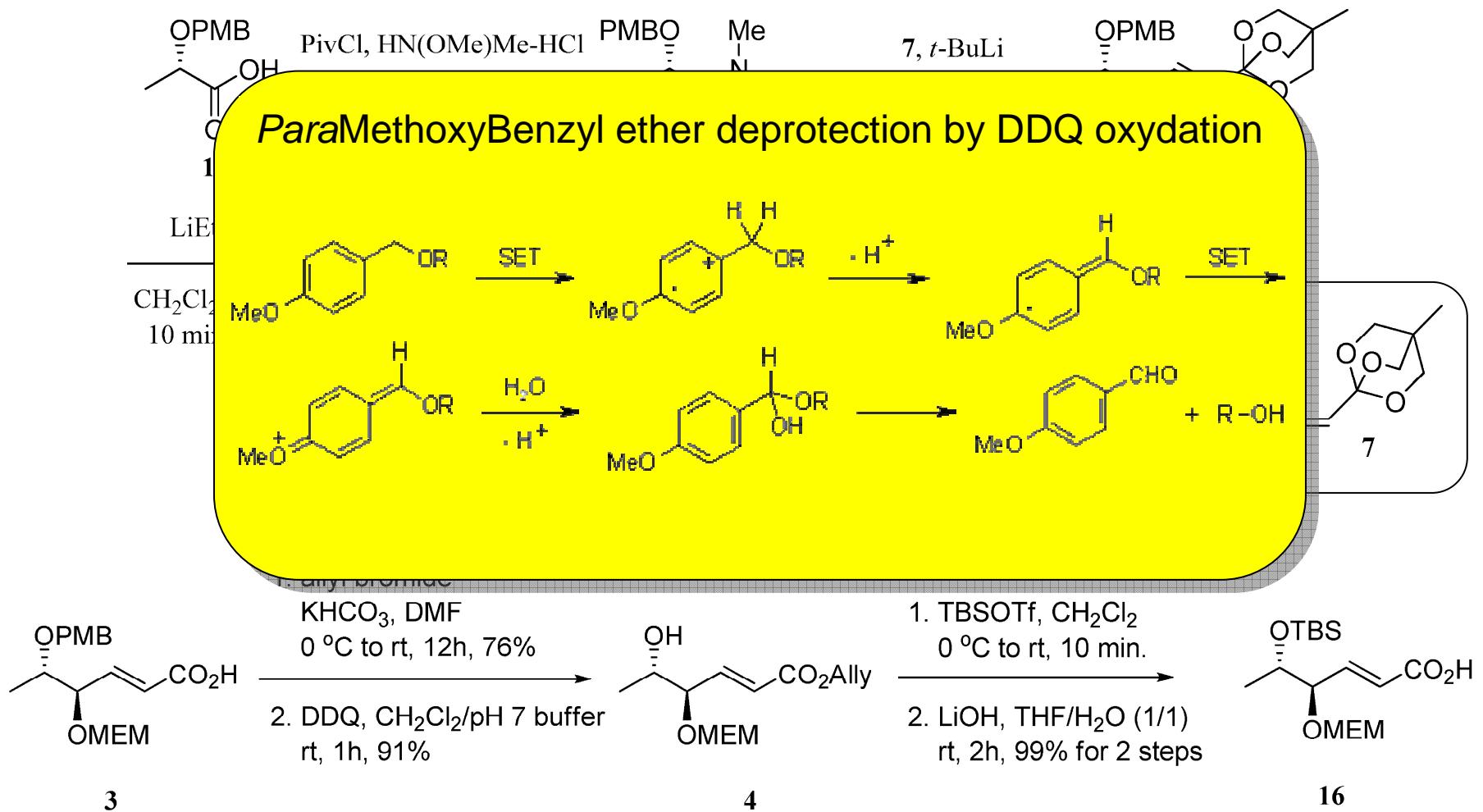
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Preparation of key fragment 3



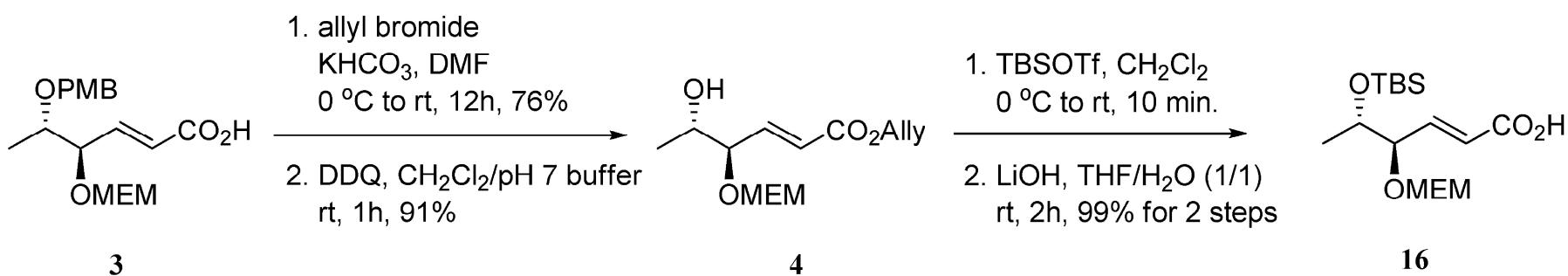
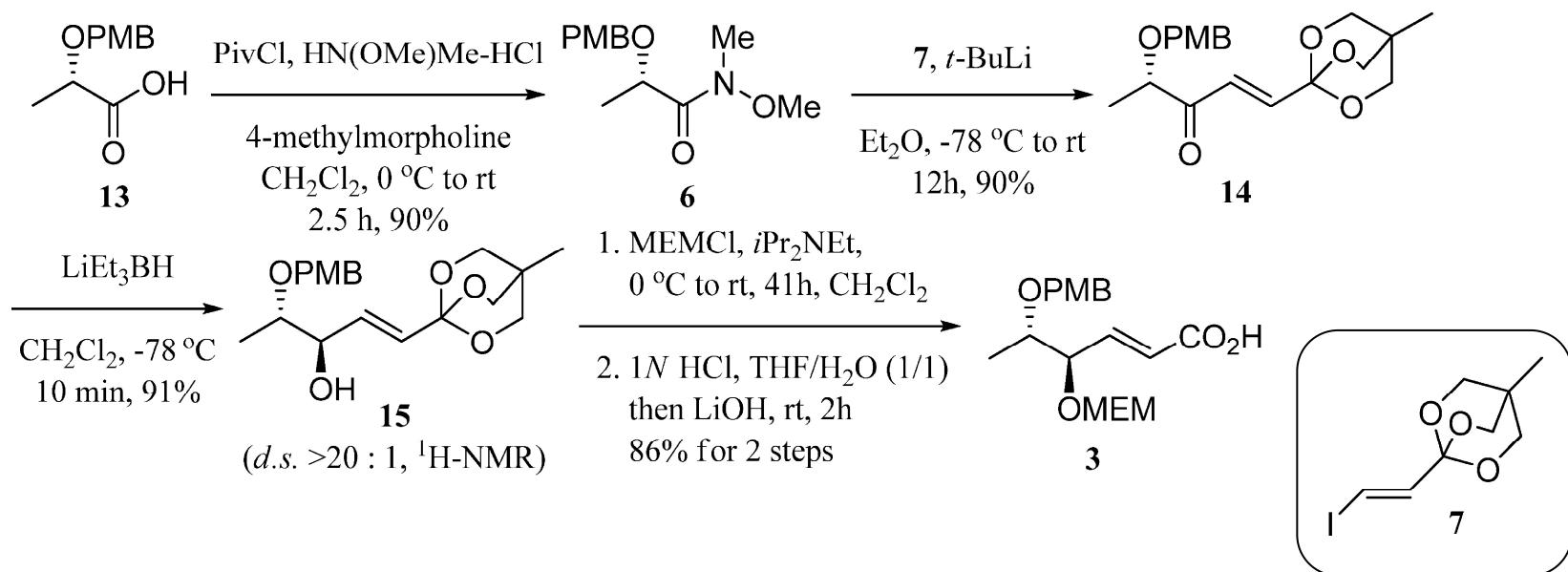
syn. $[\alpha]_D^{22} = -33.5$ (*c* 0.21 in CHCl₃)
lit. $[\alpha]_D^{22} = -30.0$ (*c* 0.62 in CHCl₃)

Preparation of key fragment 3



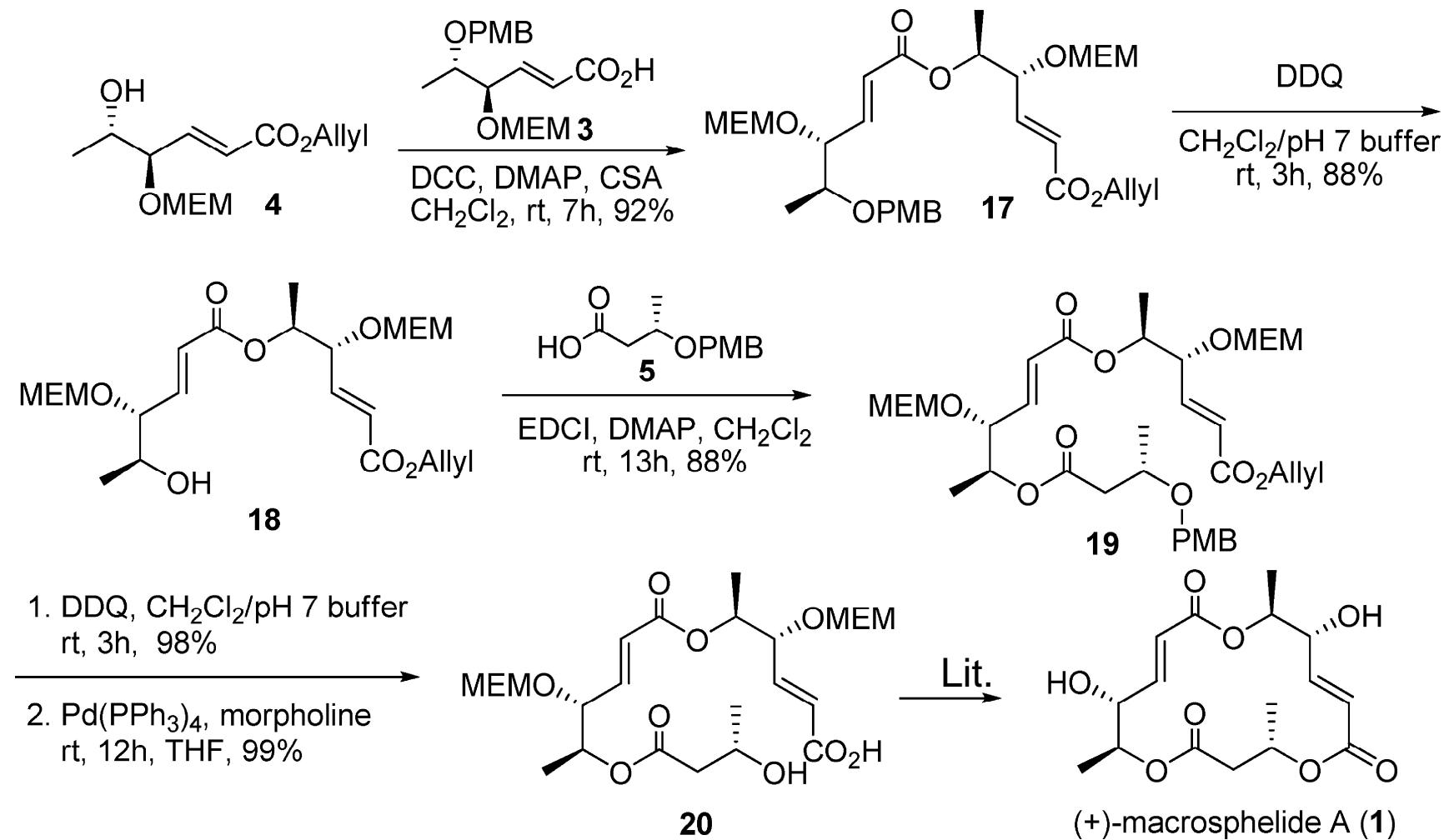
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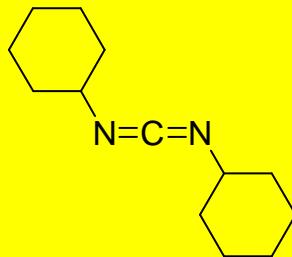
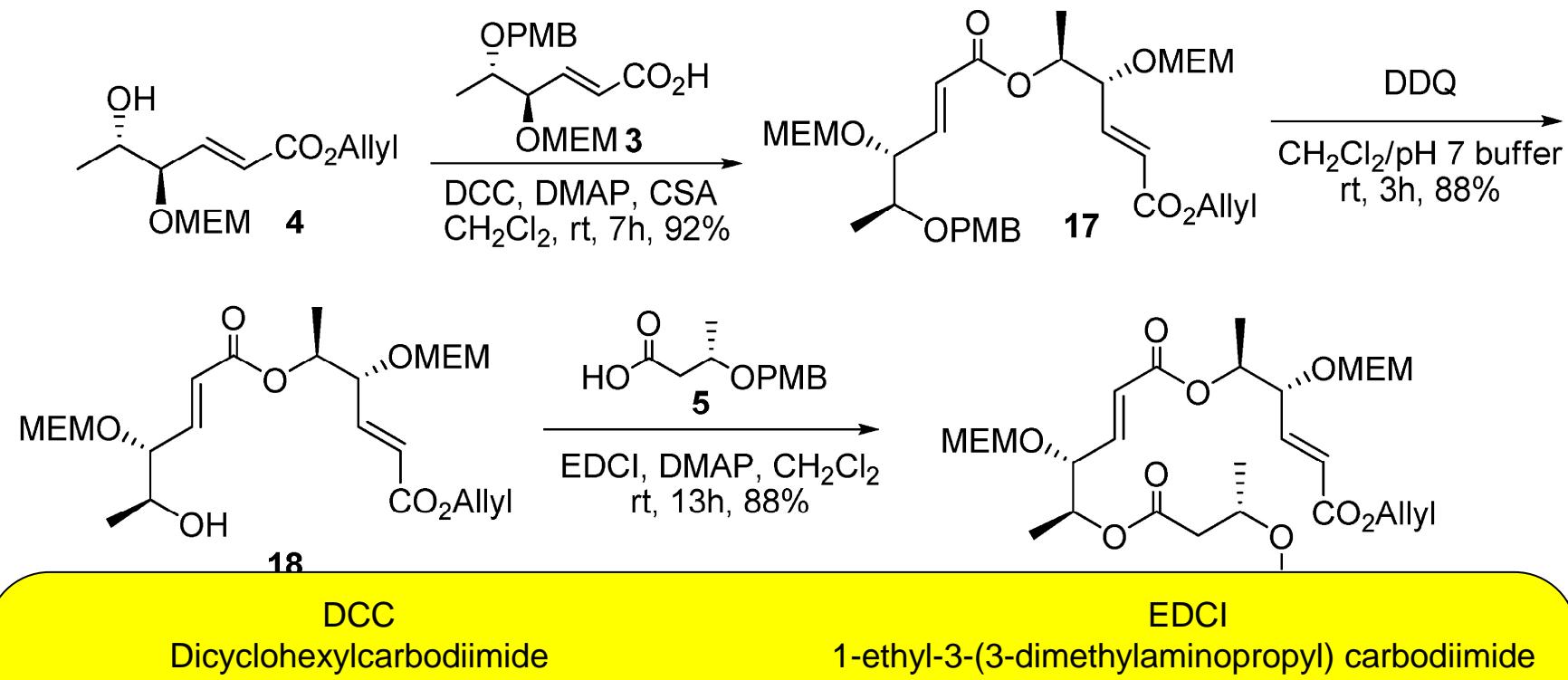
Synthesis of (+)-Macrosphelide A



Boden, E. P.; Keck, G. E. *J. Org. Chem.* 1985 50 2394,

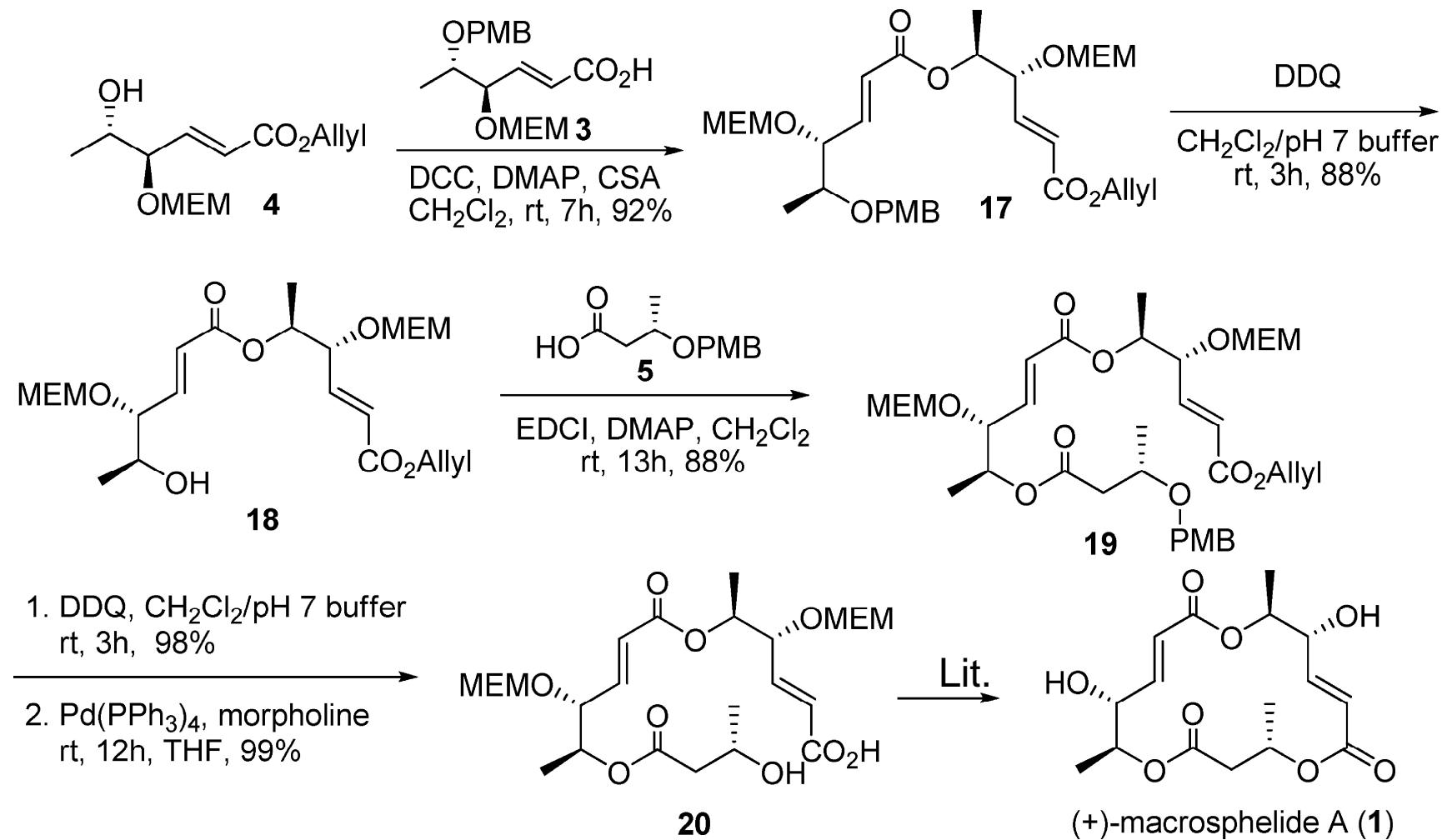
Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III
J. Am. Chem. Soc. 1997 119 10247

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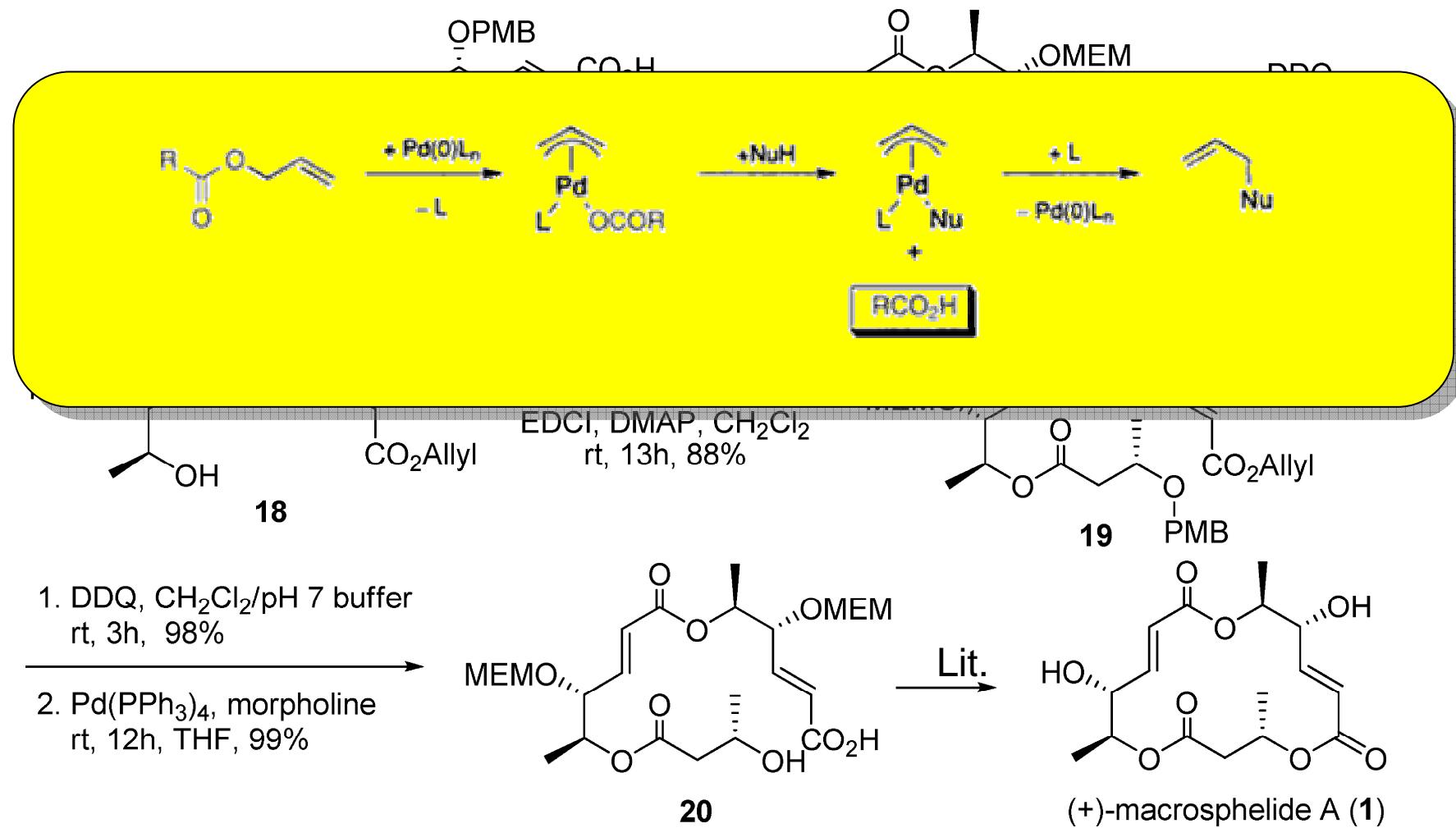
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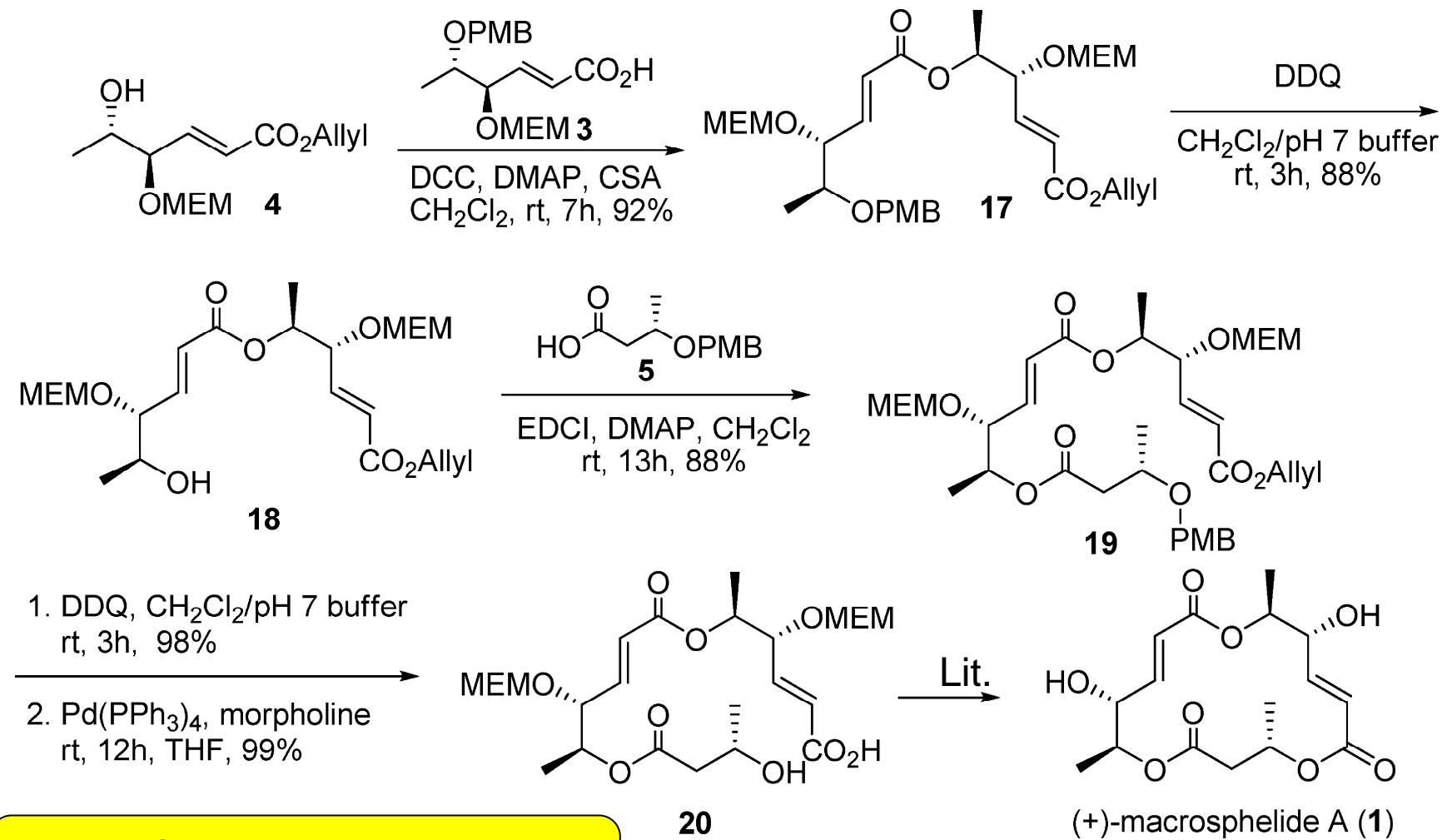
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Synthesis of (+)-Macrosphelide A



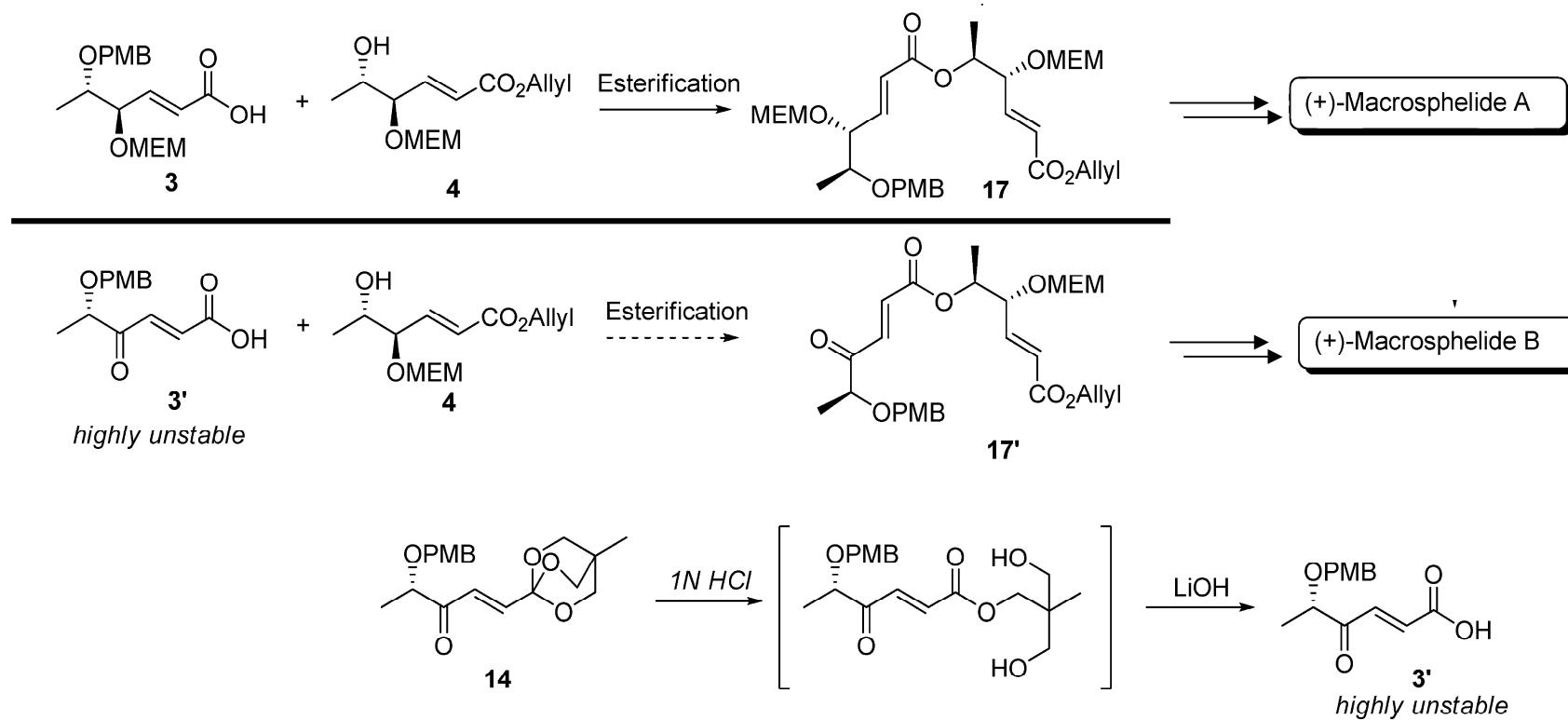
Formal Synthesis: 12 linear step,
30% overall yield (90%/step)

Boc
Sur

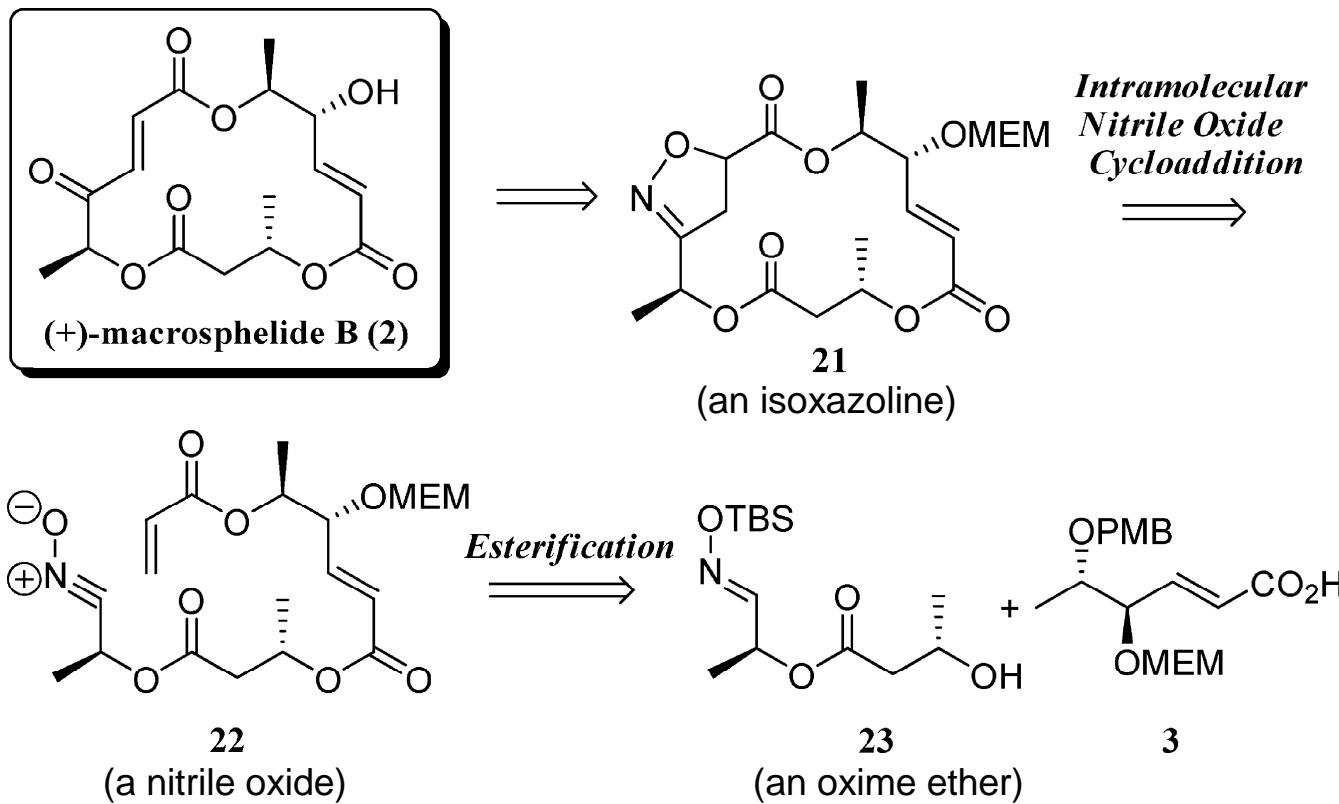
J. Am. Chem. Soc. 1997 119 10247

Komiyama, K.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III

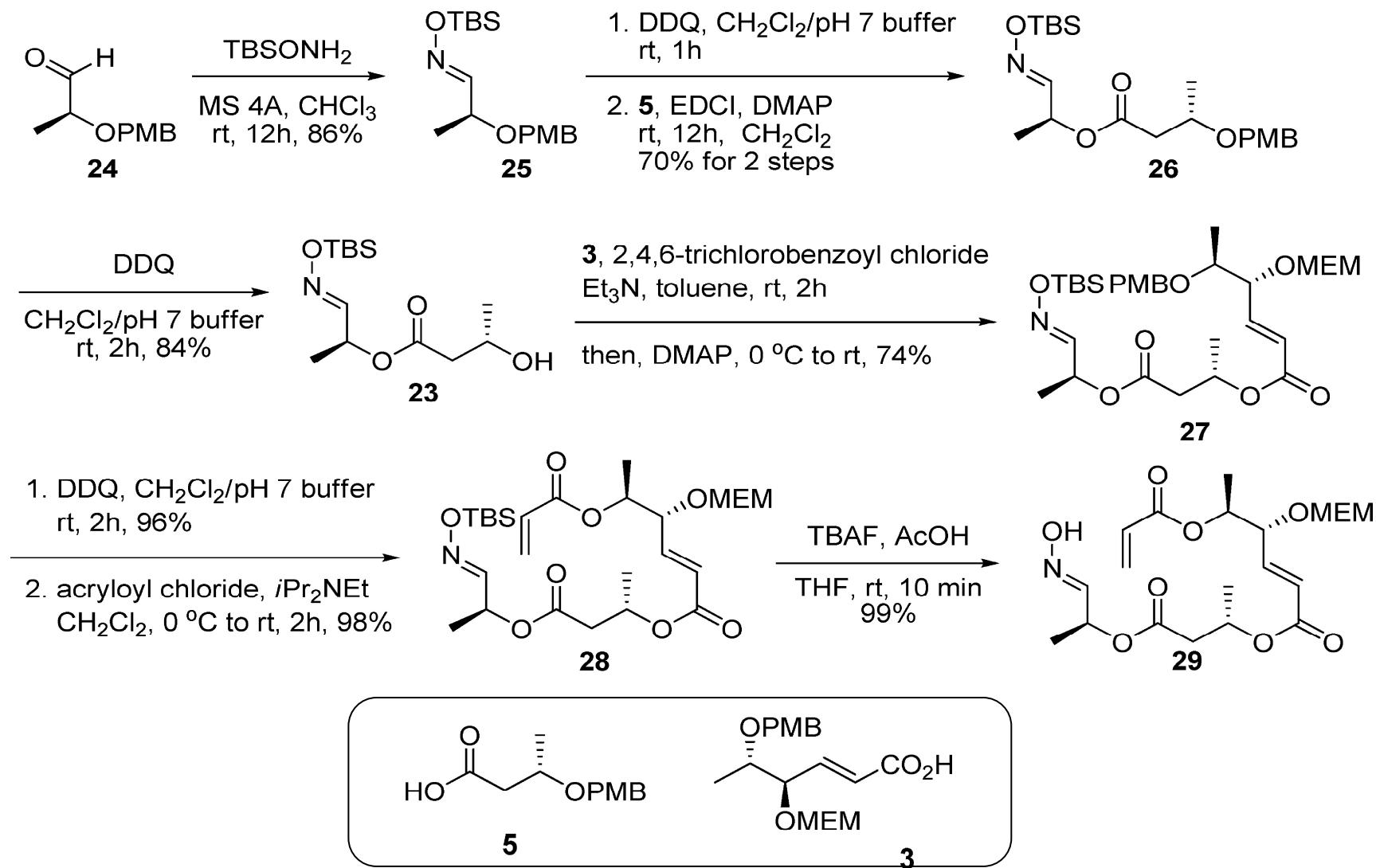
Planning (+)-Macrosphelide B



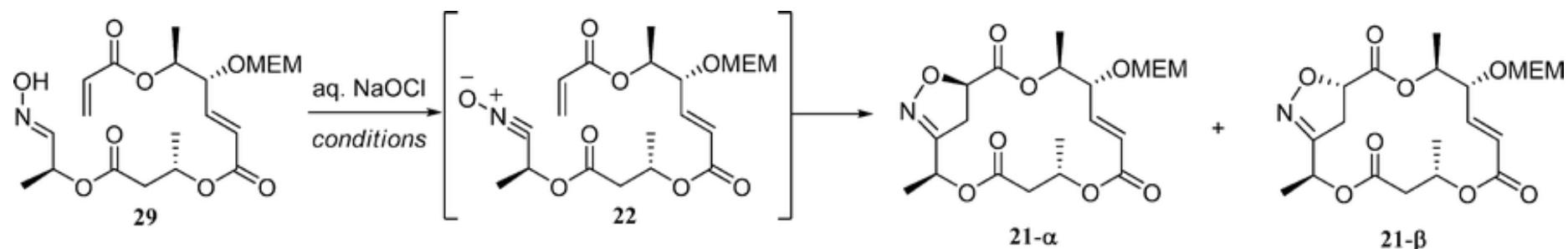
New approach to macrocyclisation



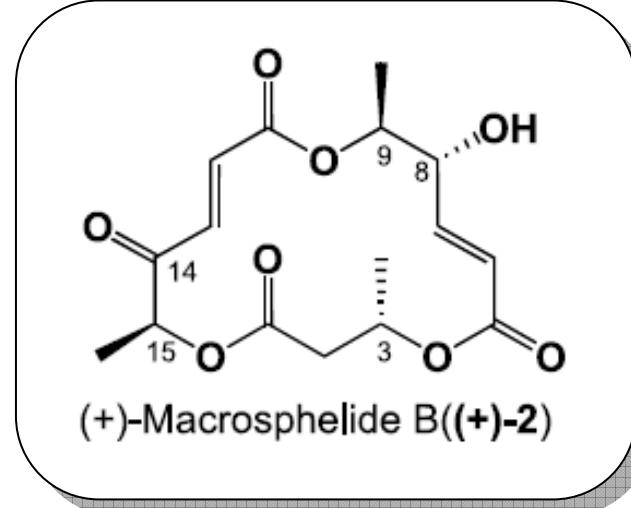
Preparation of macrocyclisation precursor



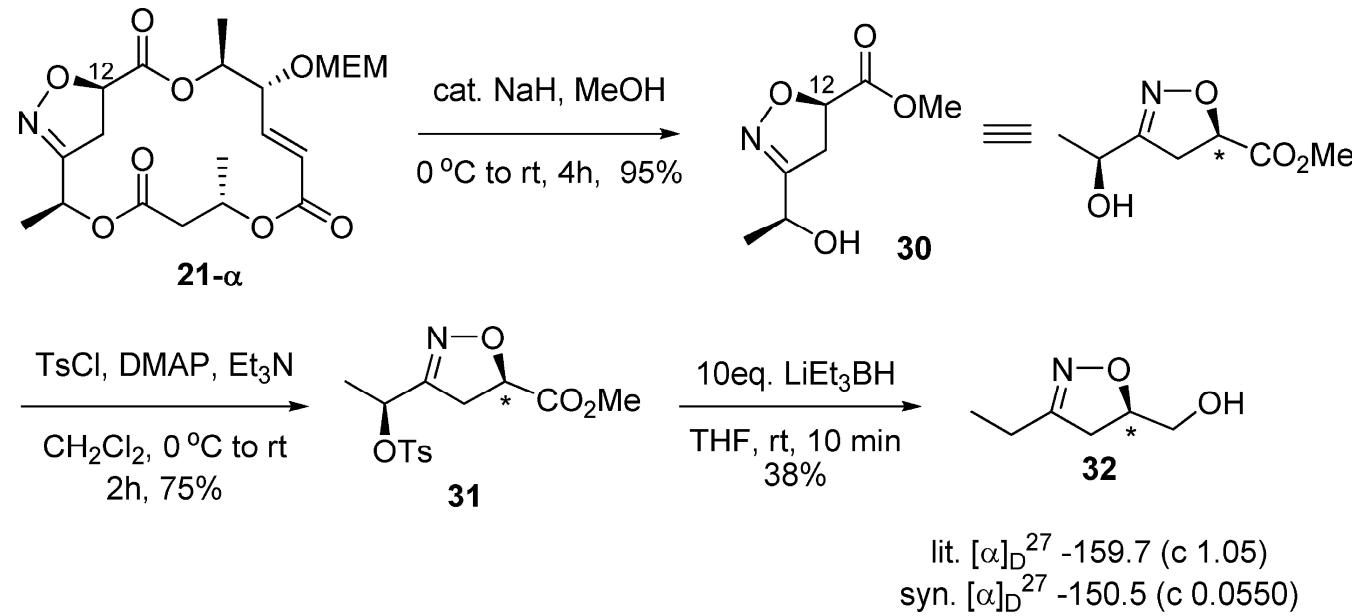
INOC: Intramolecular Nitrile Oxide-olefine Cycloaddition



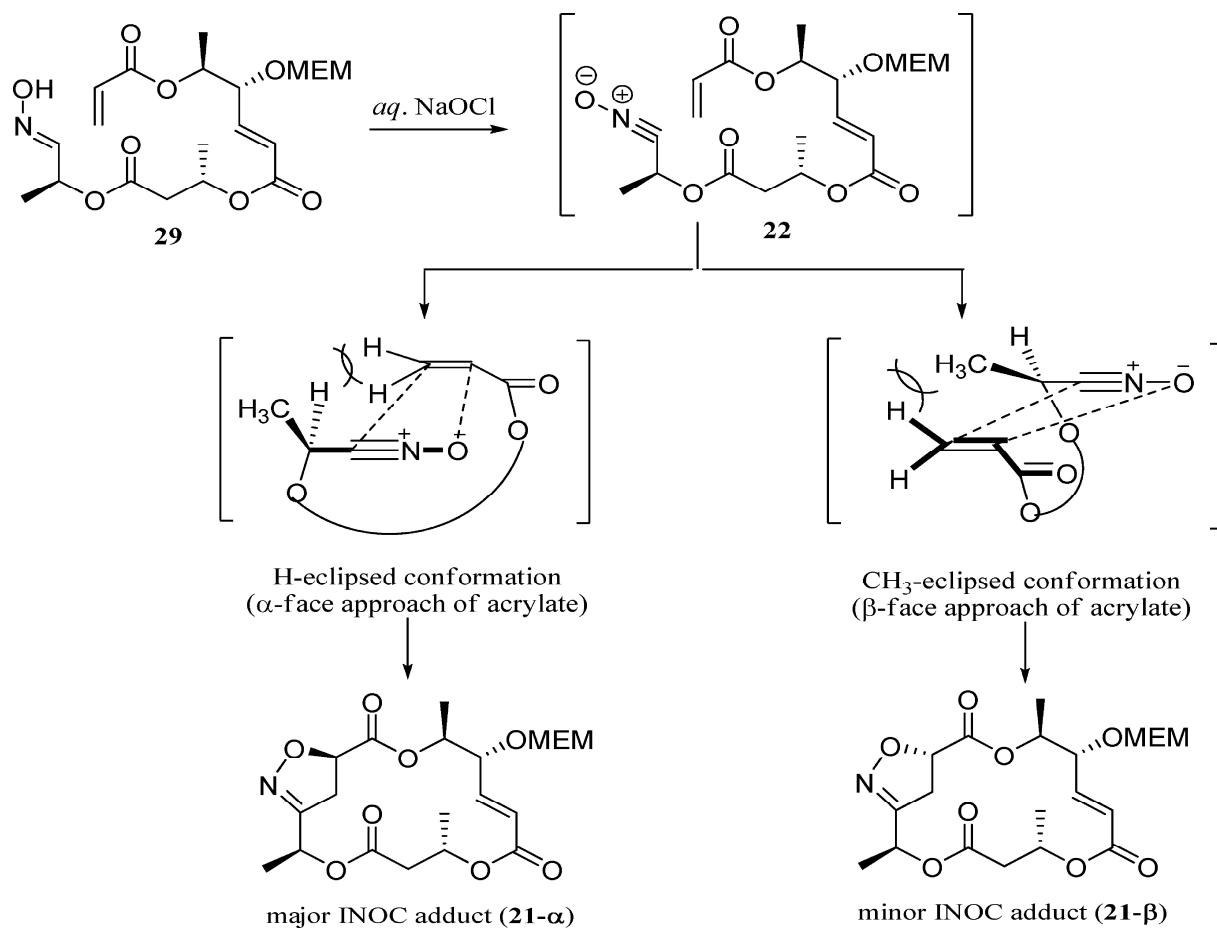
entry	solvent	temperature (°C)	ratio (21- α :21- β)	yield (%)
1	CH ₂ Cl ₂	rt	66:33	96
2	CH ₂ Cl ₂	-78	no reaction	—
3	CH ₂ Cl ₂	-30	83: 17	50
4	CH ₂ Cl ₂	-15	83: 17	79
5	CH ₂ Cl ₂	40	54: 46	37
6	THF	-15	88: 12	47
7	benzene	-15	93: 17	22
8	1,4-dioxane	rt	91: 9	89



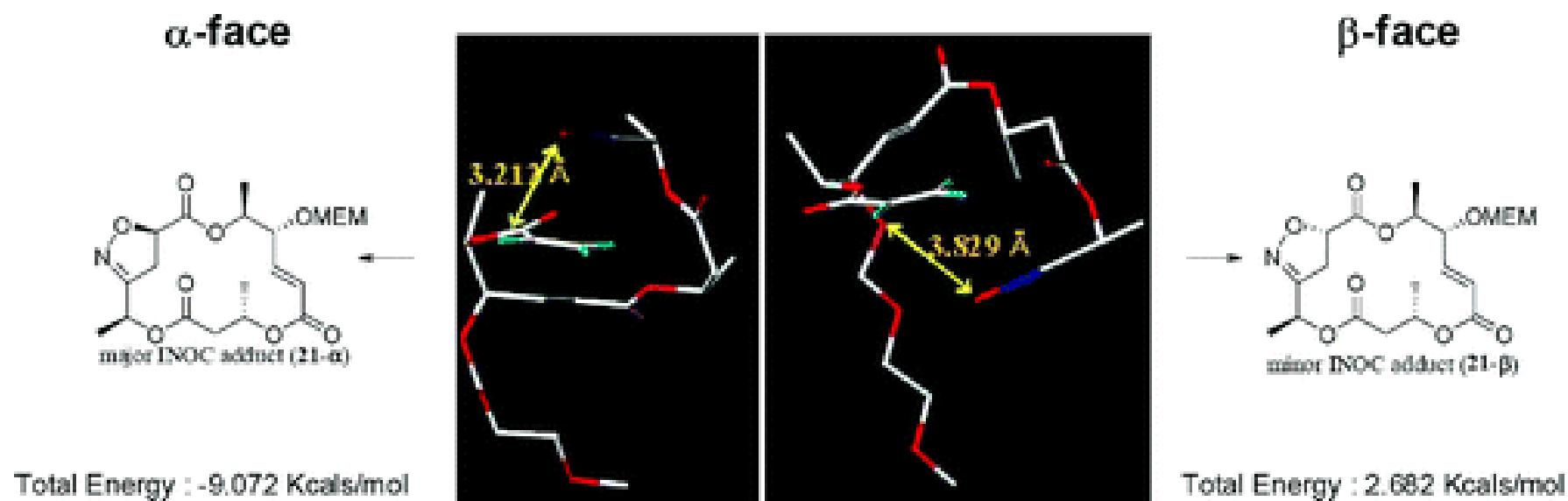
Determination of absolute configuration of the major diastereomer



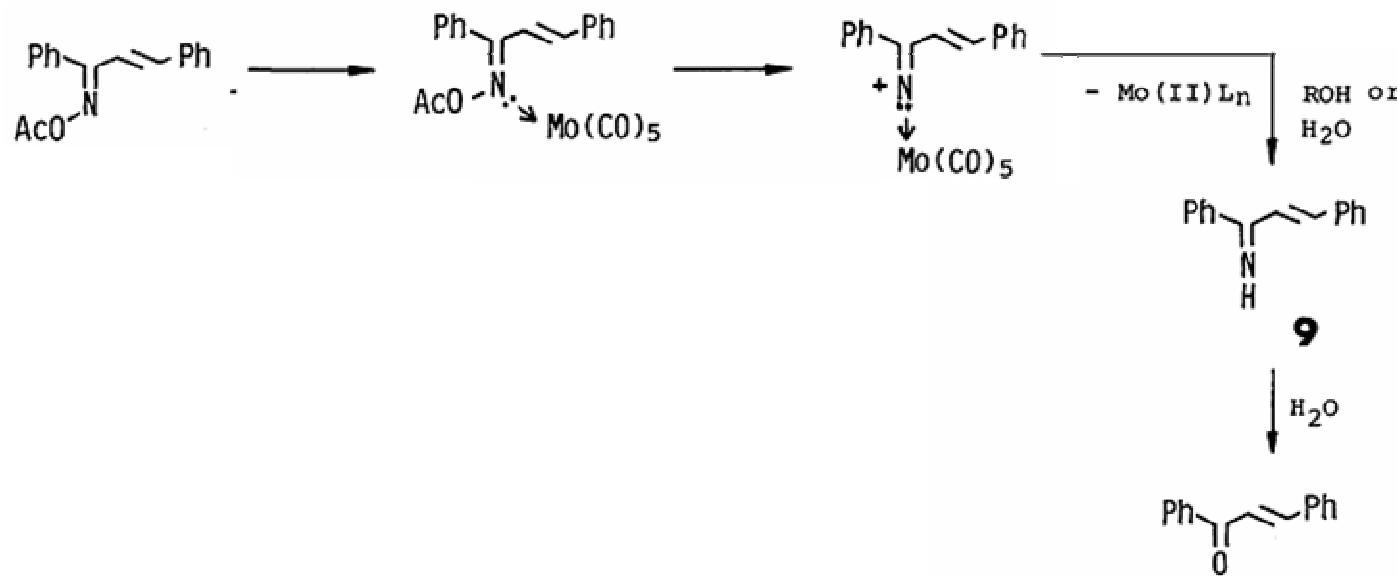
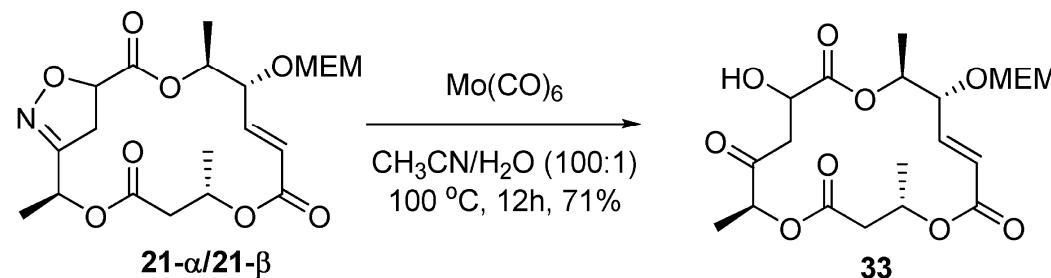
Transitions states in the [3+2] dipolar cycloaddition



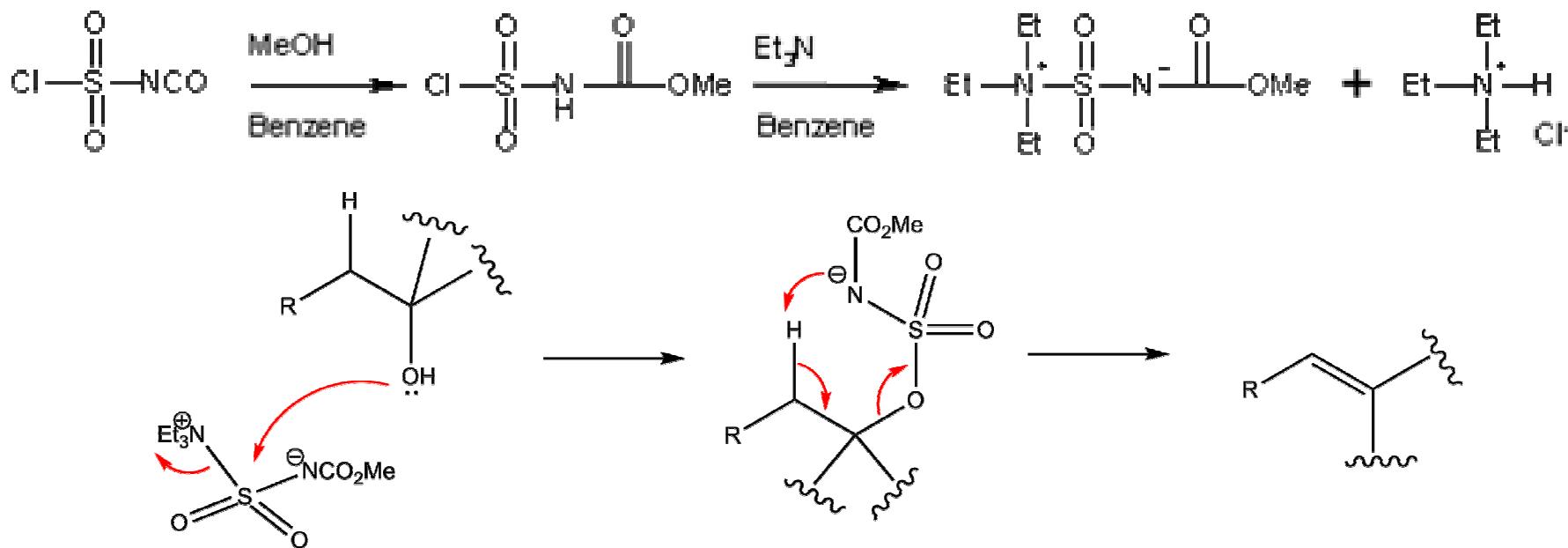
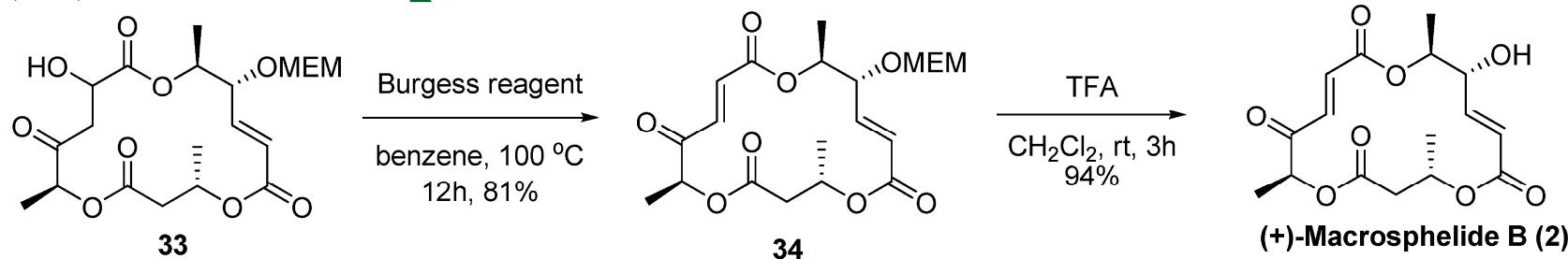
Transitions states in the [3+2] dipolar cycloaddition



Completing the synthesis of (+)-Macrosphelide B



Completing the synthesis of (+)-Macrosphelide B



Completing the synthesis of (+)-Macrosphelide B

Conclusion

(+)-Macrosphelide A: 12 linear steps, 30% overall yield (90%/step)

Vinylogous ester anion addition

Chelation-controlled carbonyl reduction

Standard macrolactonisation

(+)-Macrosphelide B: 13 linear steps, 20% overall yield (88%/step)

Vinylogous ester anion addition

Chelation-controlled carbonyl reduction

INOC macrocyclisation