

Total Synthesis and Stereochemical Reassignment of Mandelalide A

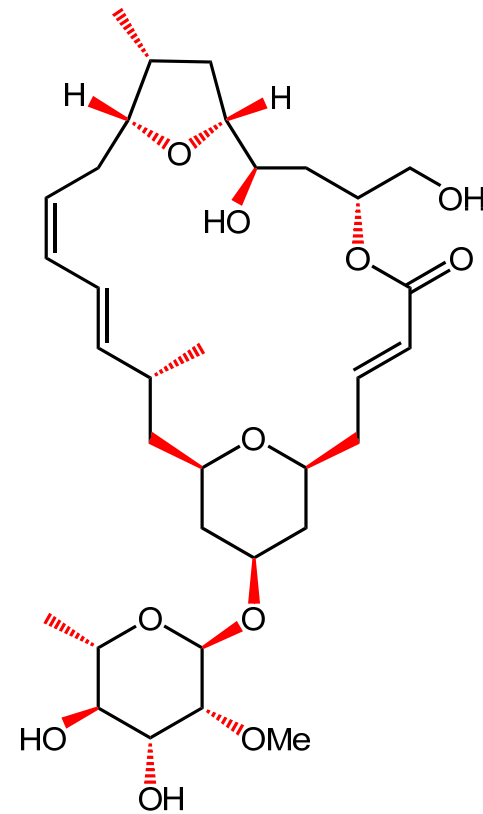
Reporter: Lian-Jin Liu
Checker: Wen-Xue Huang
Date: 25/11/2014

Zheng-Shuang Xu *et al.* *Angew. Chem. Int. Ed.* **2014**, *53*, 6533–6537

Contents

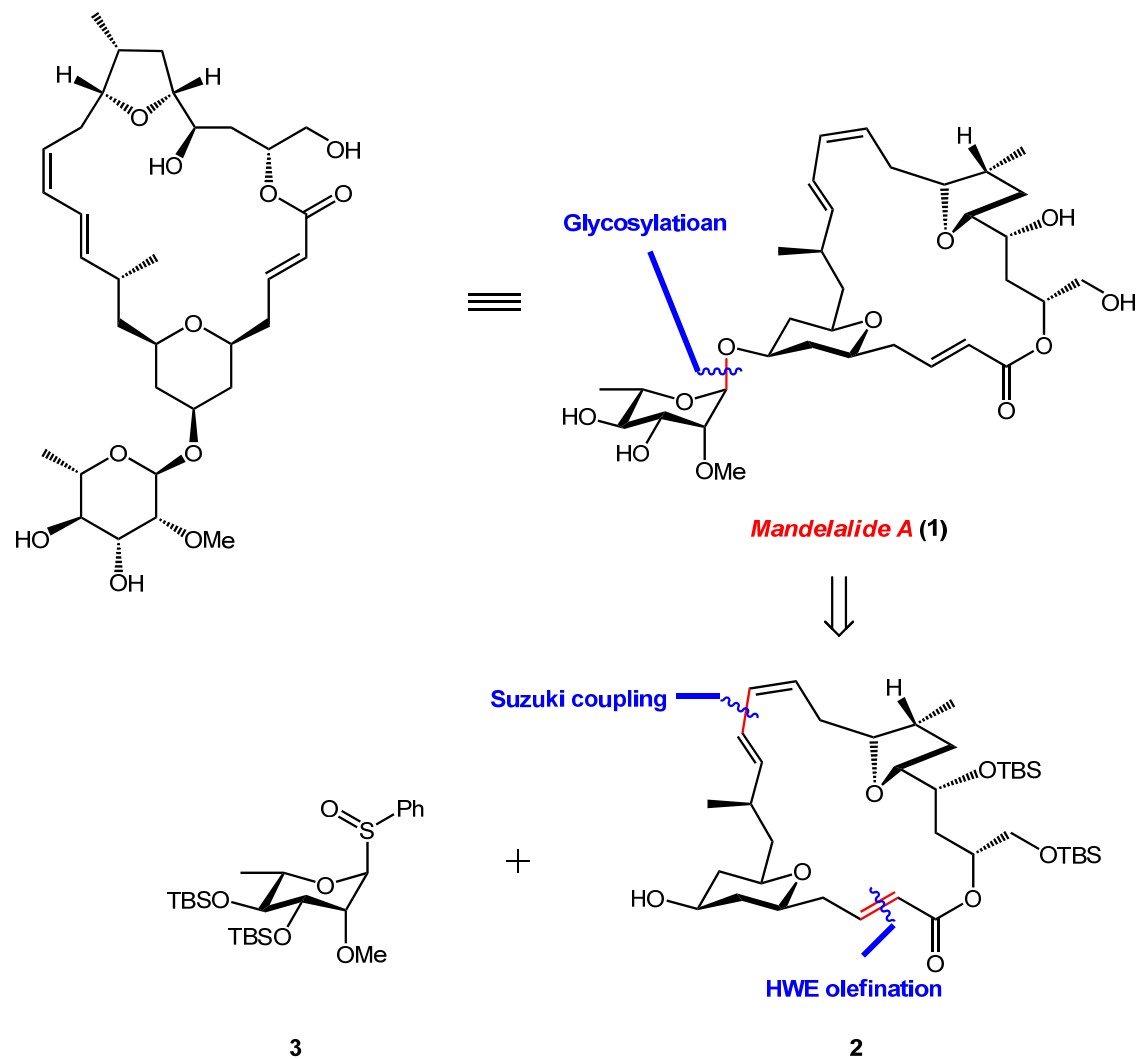
- ❖ **Introduction**
- ❖ **Total synthesis by Xu's group**
- ❖ **Total synthesis by Fürstner's group**
- ❖ **Summary**

➤ Introduction

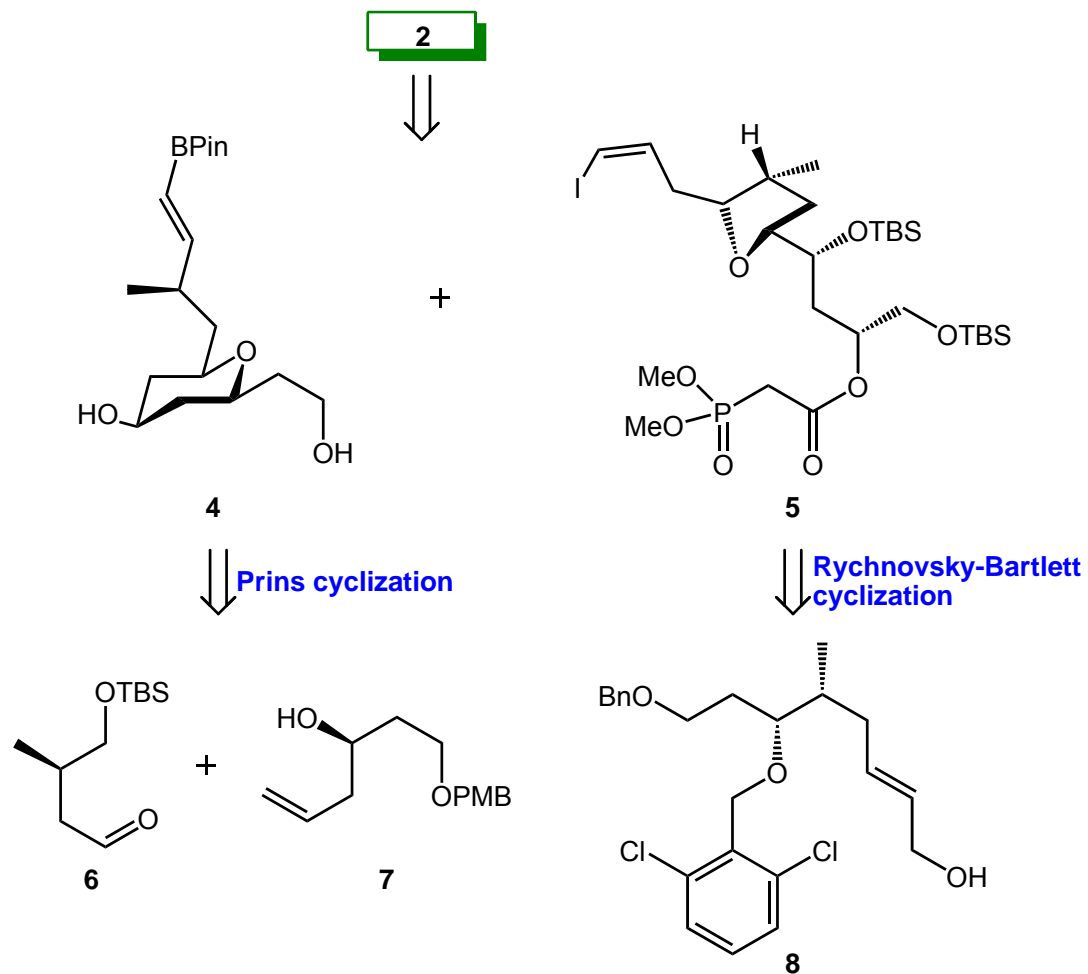


Mandelalide A

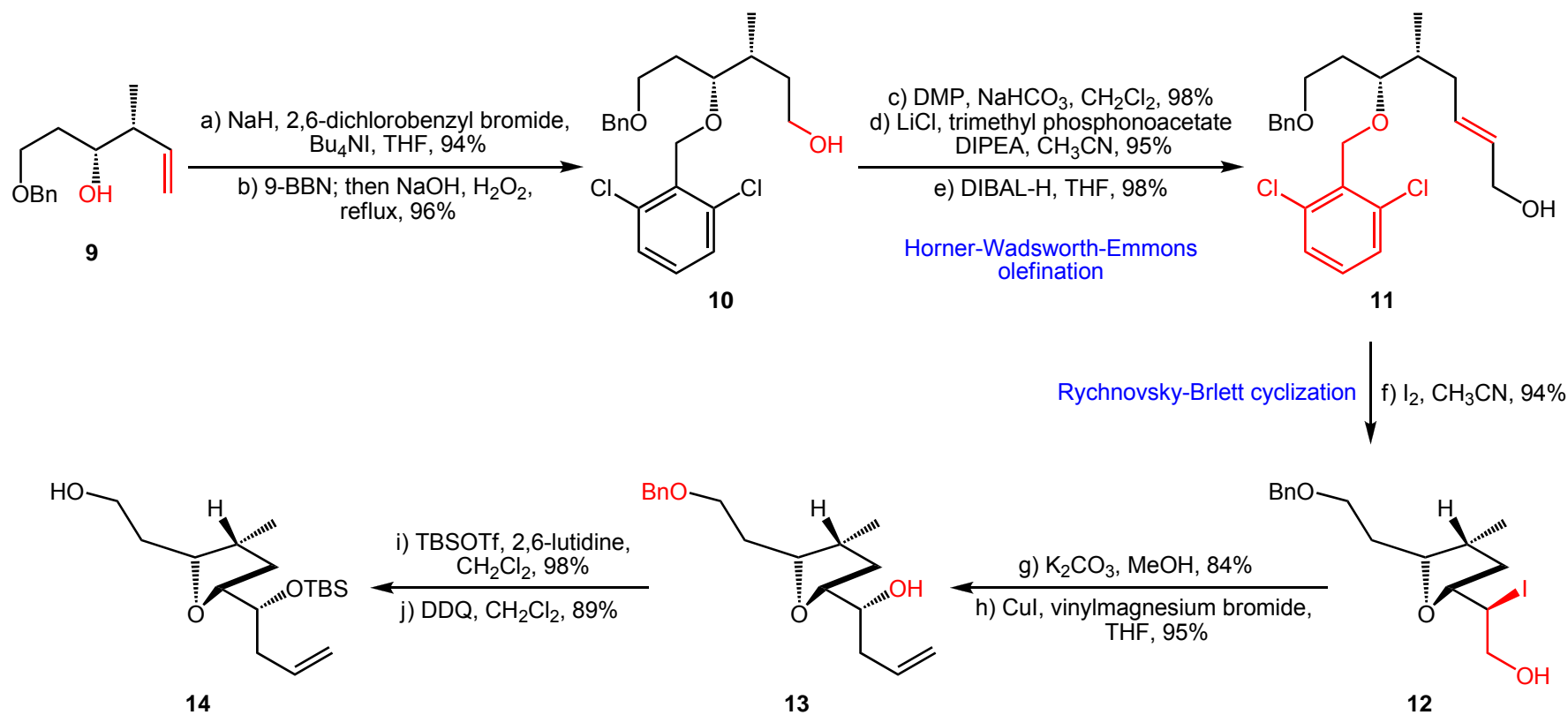
► Total synthesis by Xu's group



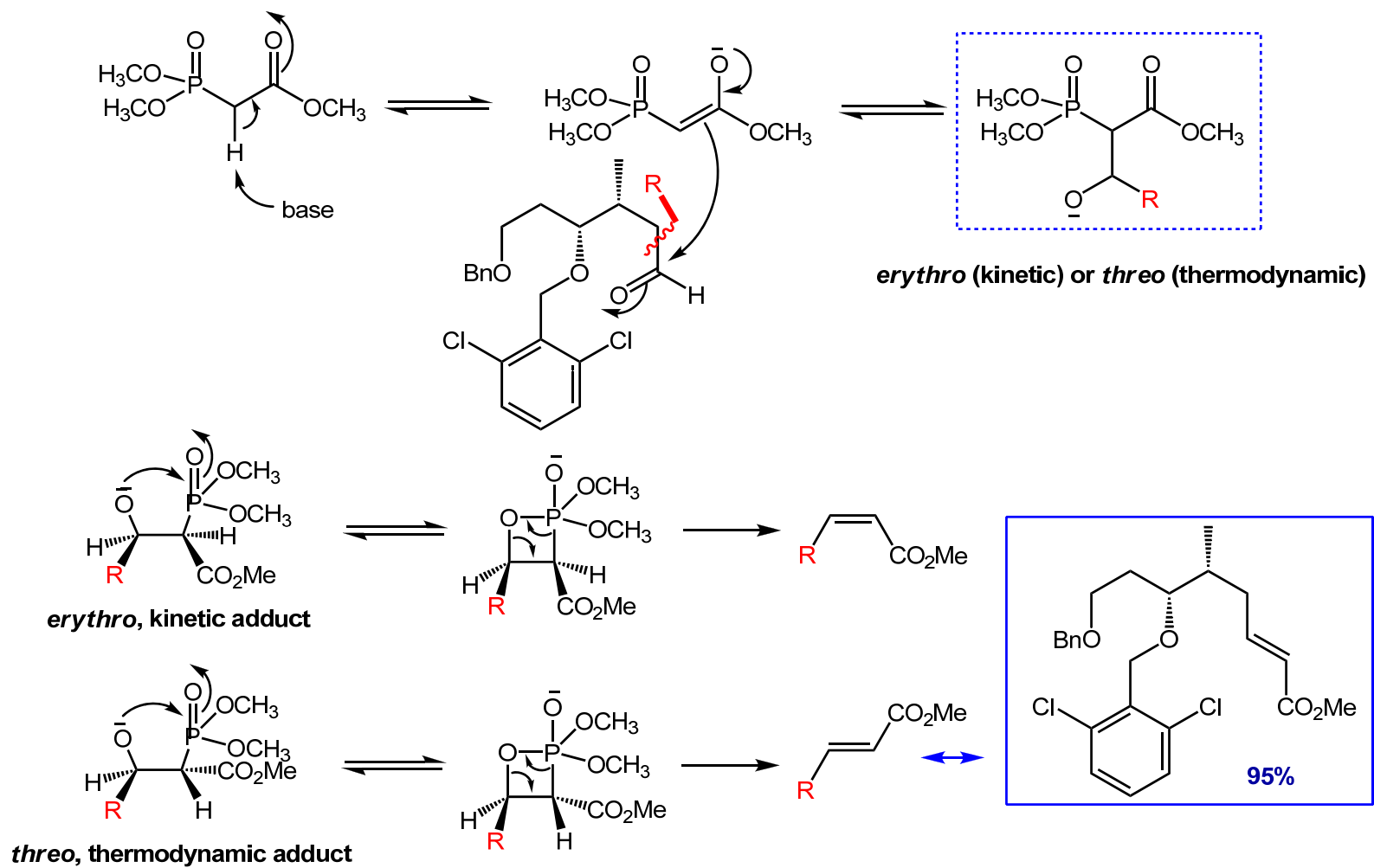
➤ Total synthesis by Xu's group



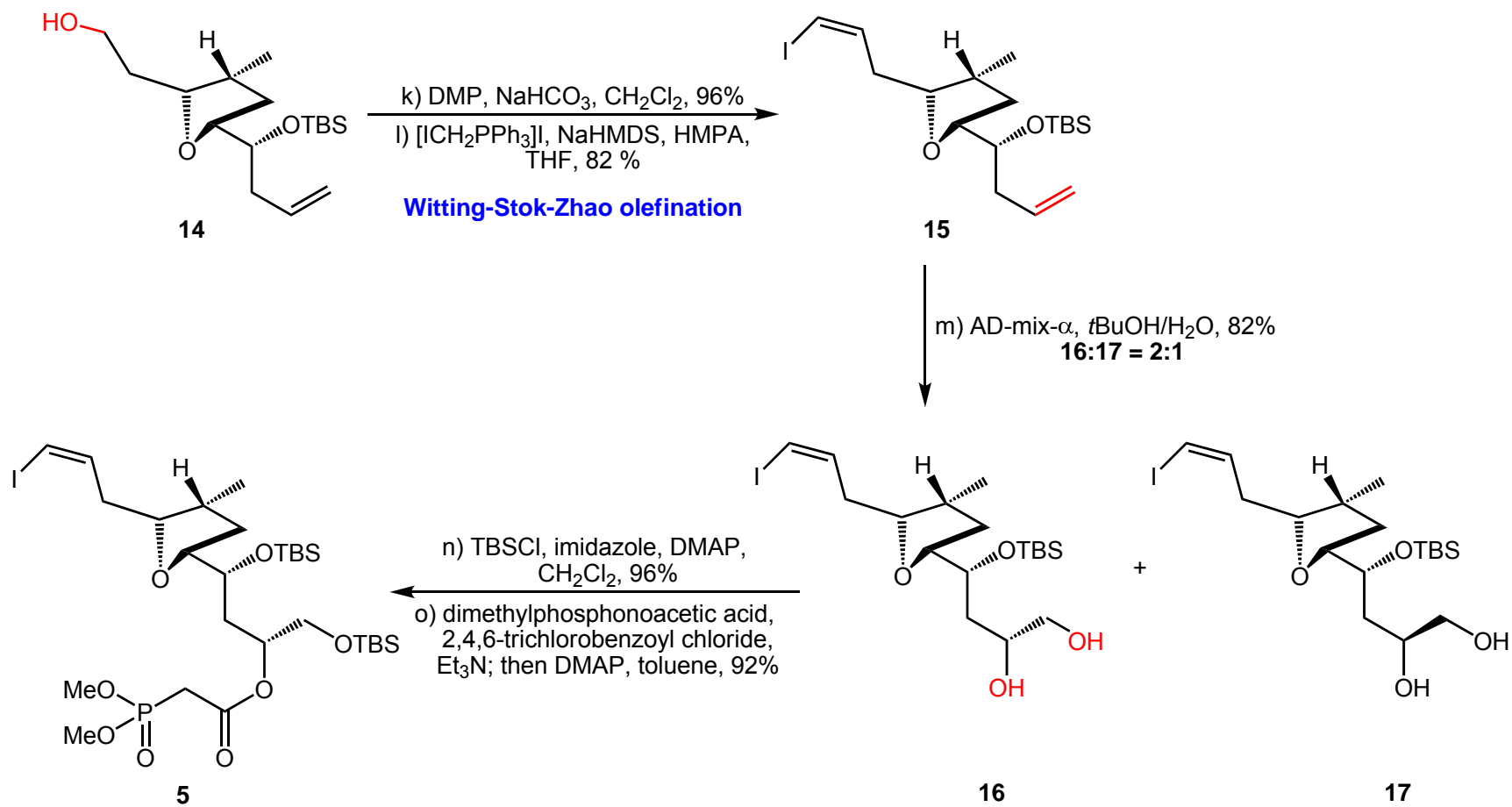
► Total synthesis by Xu's group



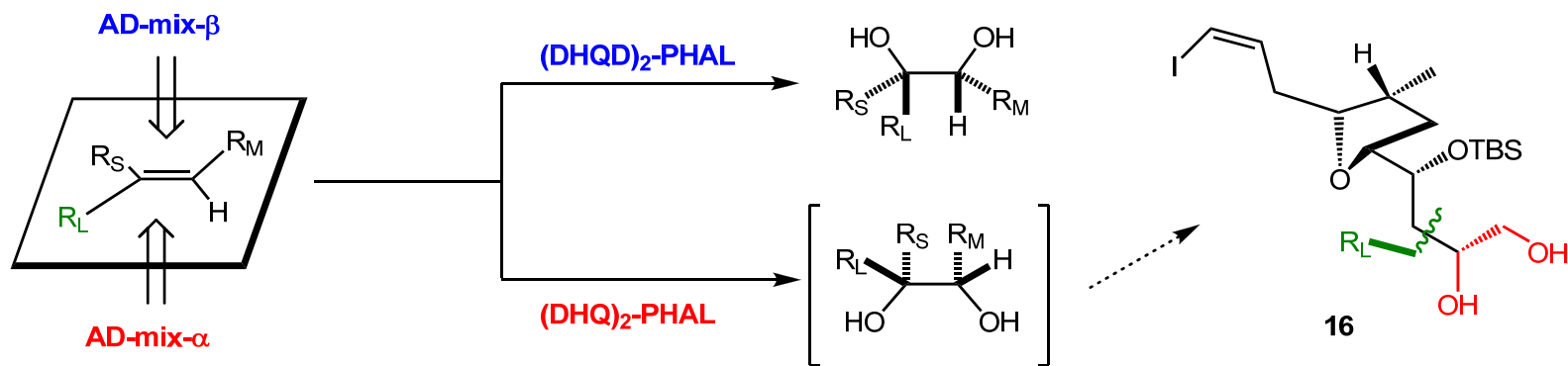
Horner-Wadsworth-Emmons olefination



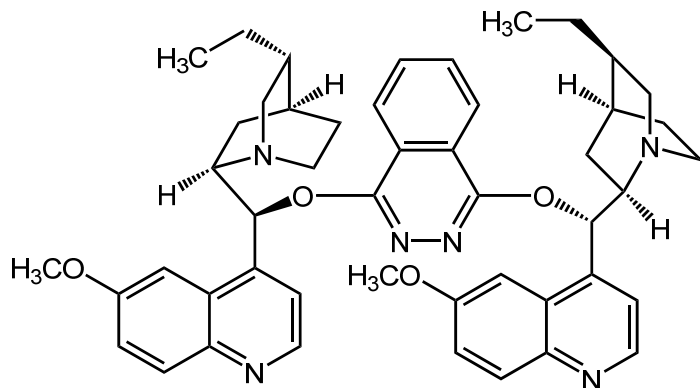
► Total synthesis by Xu's group



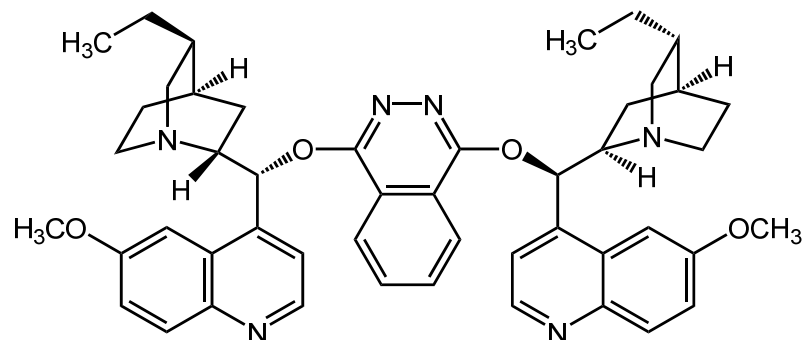
Sharpless dihydroxylation



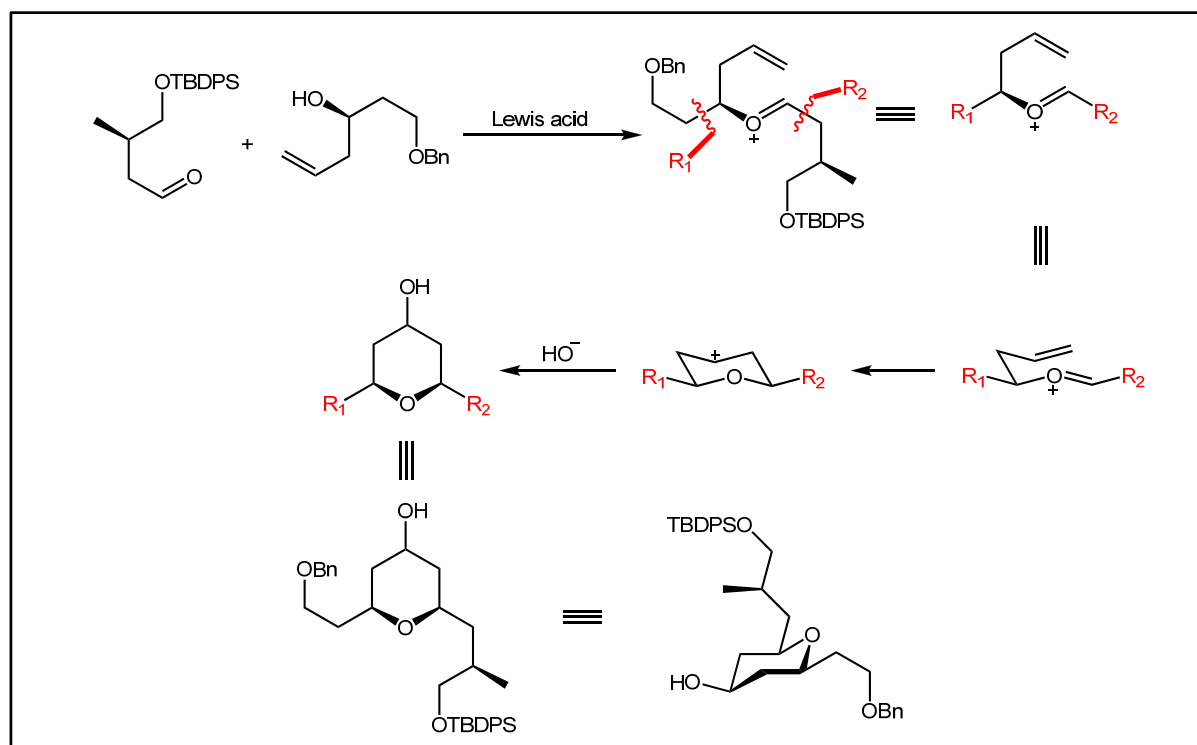
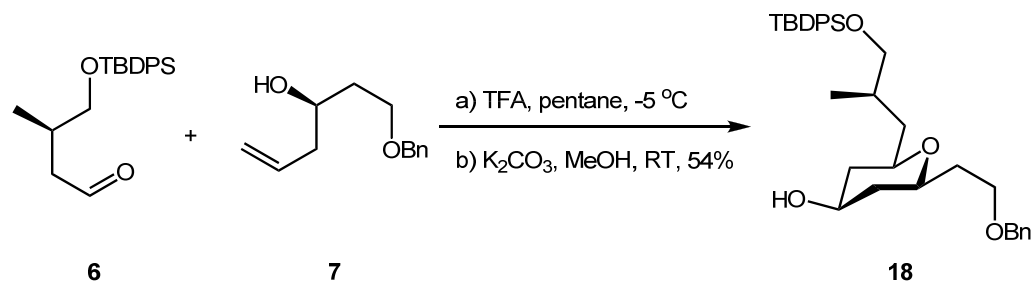
$(DHQD)_2\text{-PHAL}$ = 1,4-bis(9-O-dihydroquinidine)phthalazine



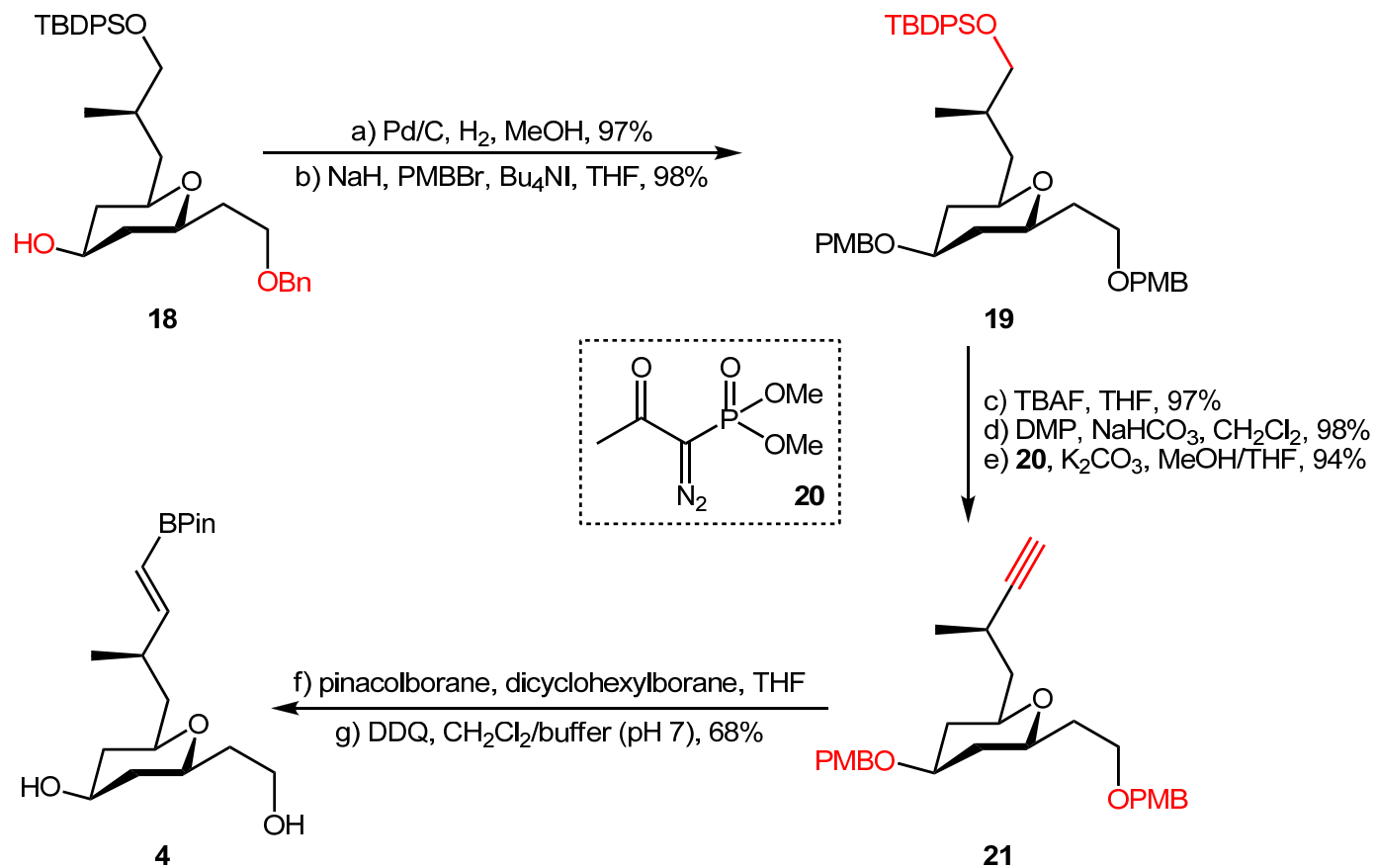
$(DHQ)_2\text{-PHAL}$ = 1,4-bis(9-O-dihydroquinine)phthalazine



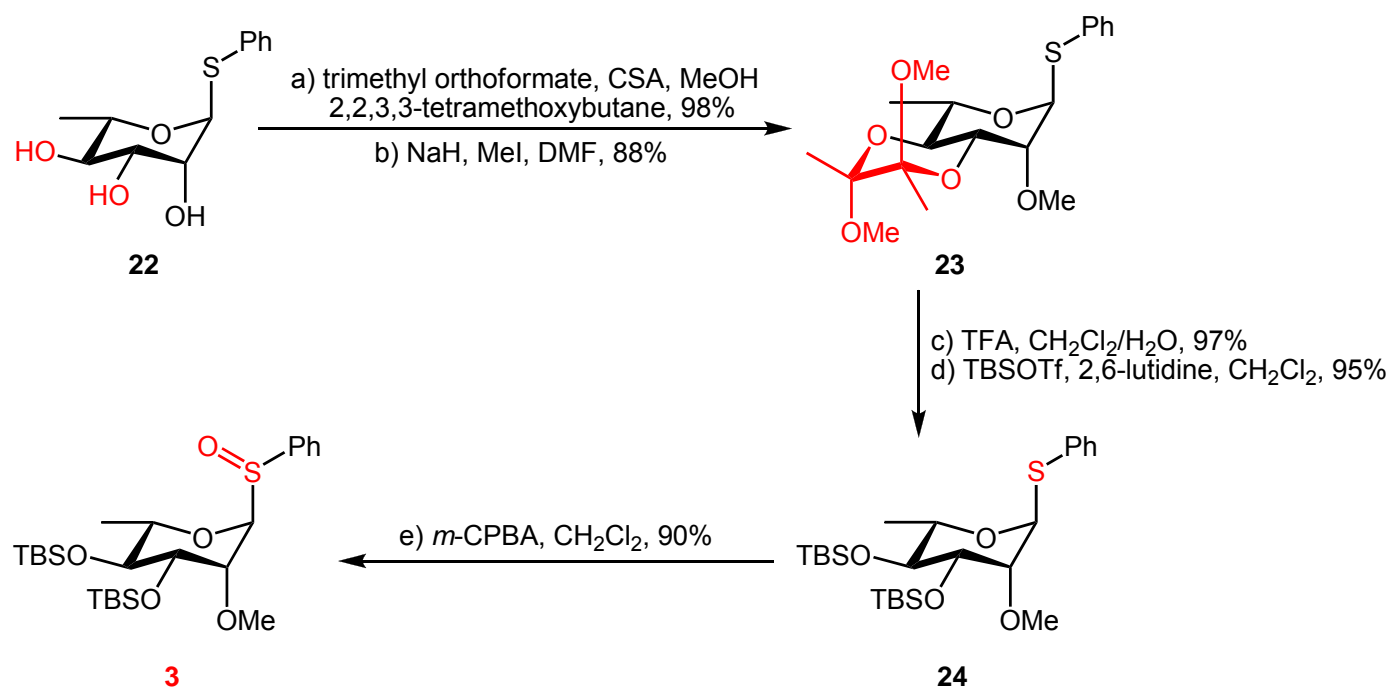
Prins cyclization of aldehyde **6** and homoallylic alcohol **7**



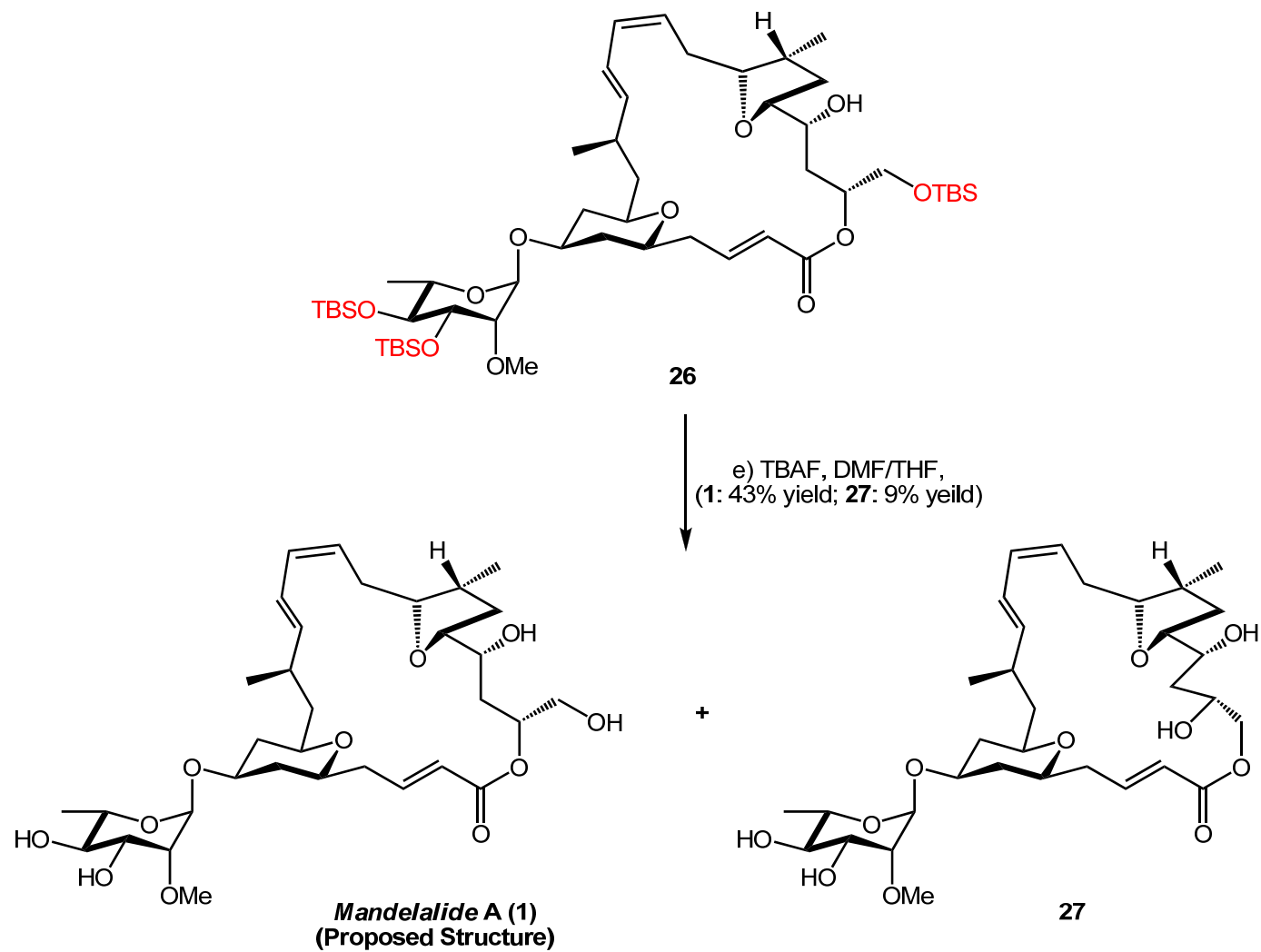
► Total synthesis by Xu's group



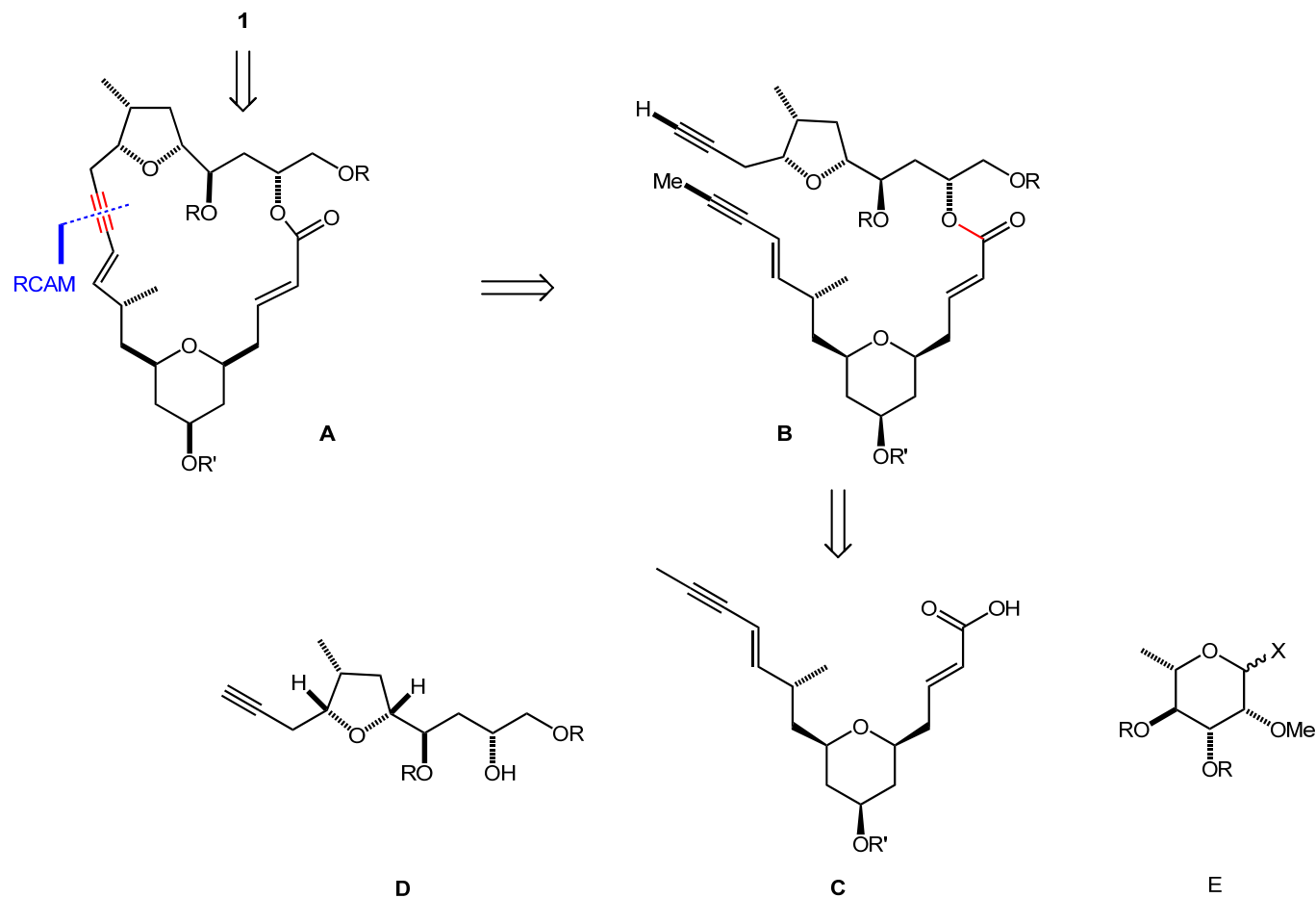
➤ Total synthesis by Xu's group



► Total synthesis by Xu's group

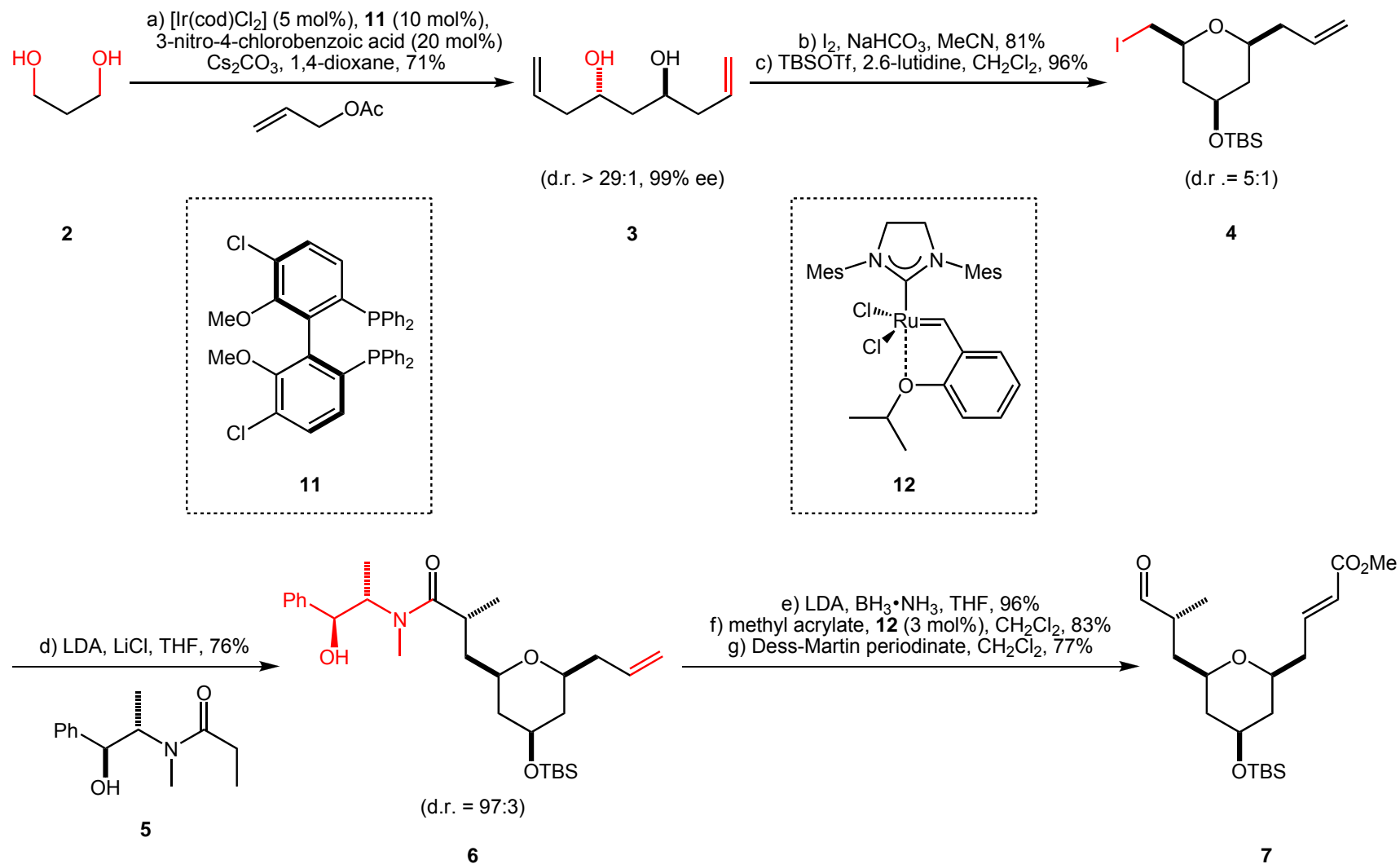


► Total synthesis by Fürstner's group

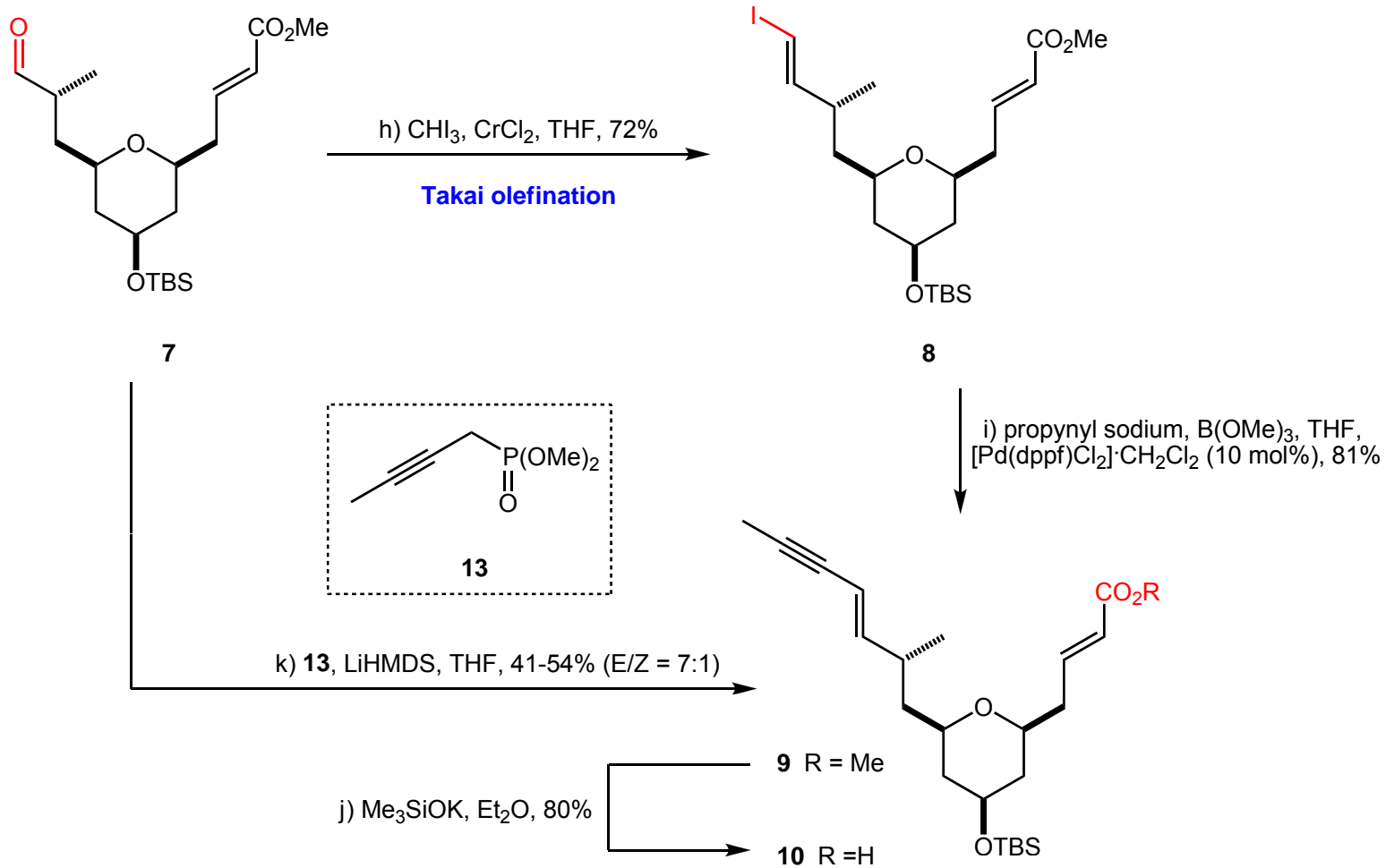


A. Fürstner *et al.* *Angew. Chem. Int. Ed.* **2014**, 53, 4217–4221

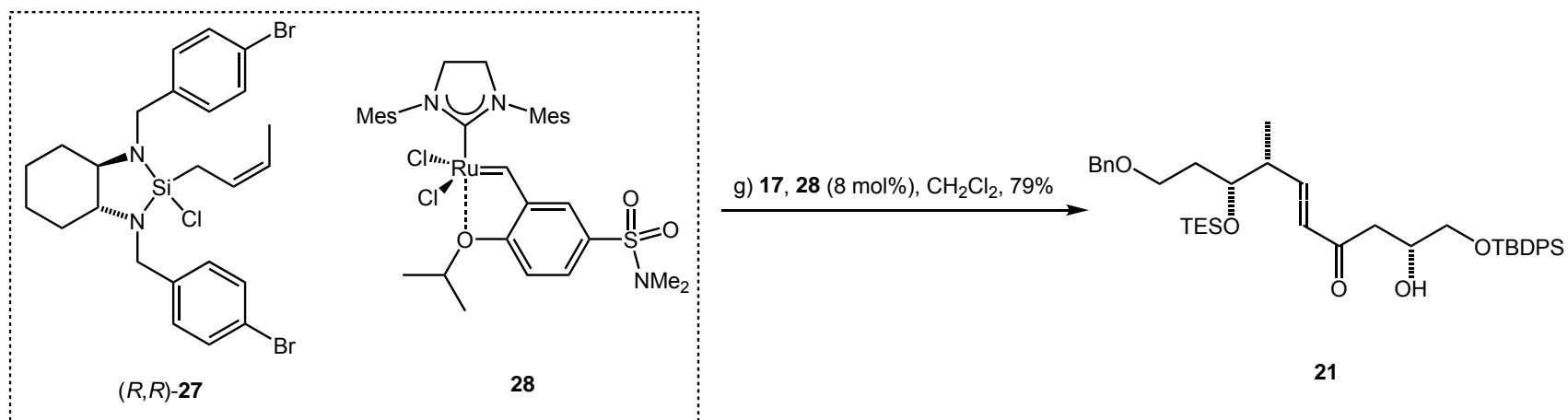
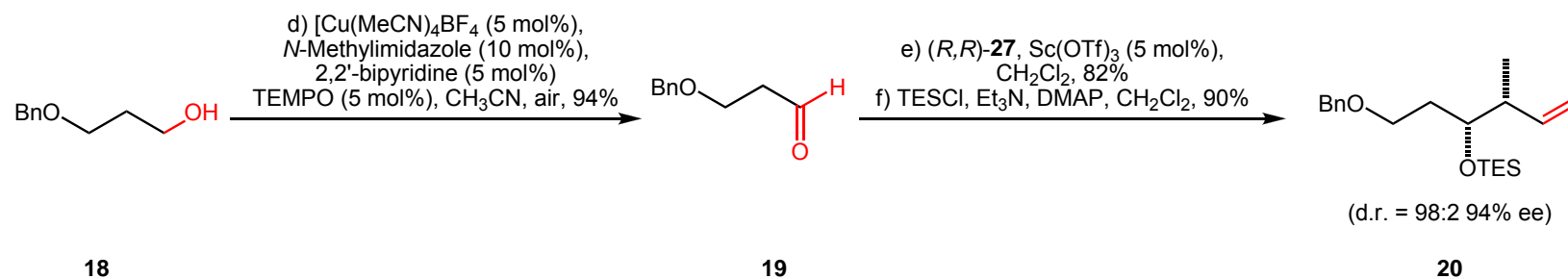
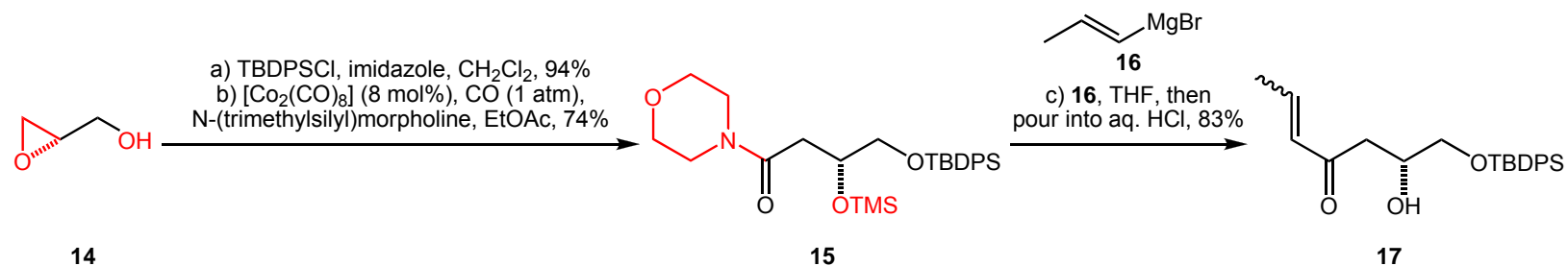
► Total synthesis by Fürstner's group



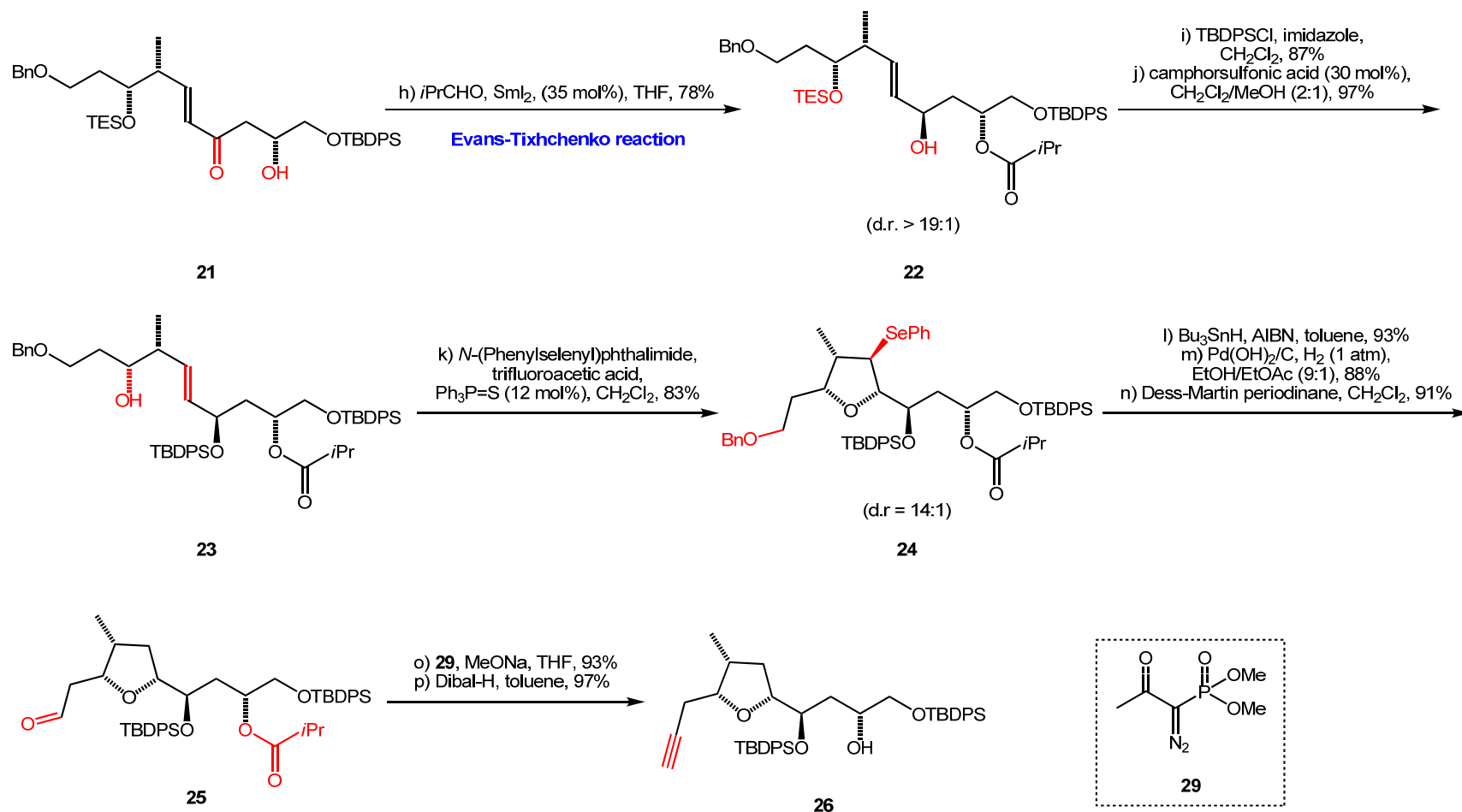
► Total synthesis by Fürstner's group



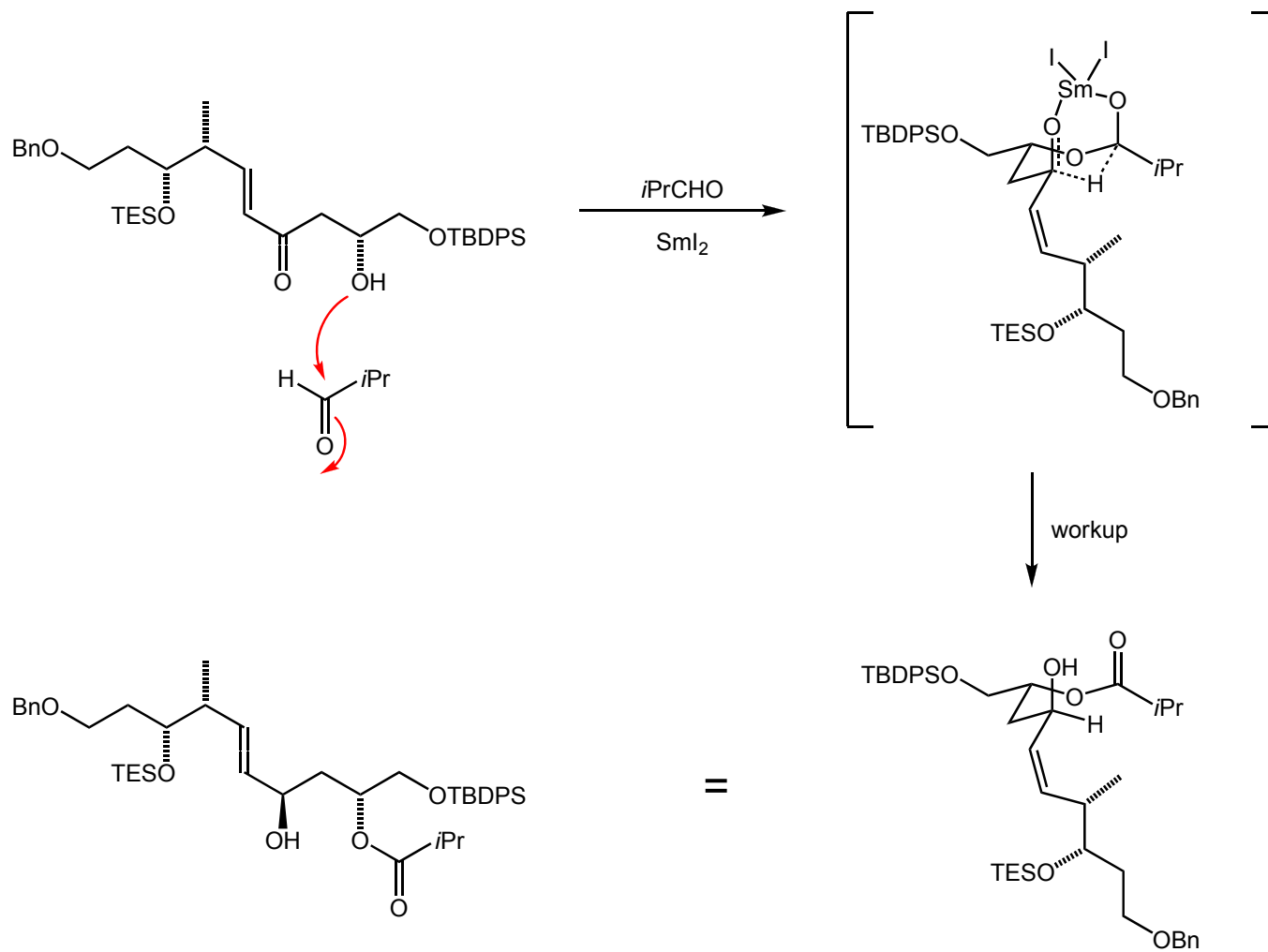
► Total synthesis by Fürstner's group



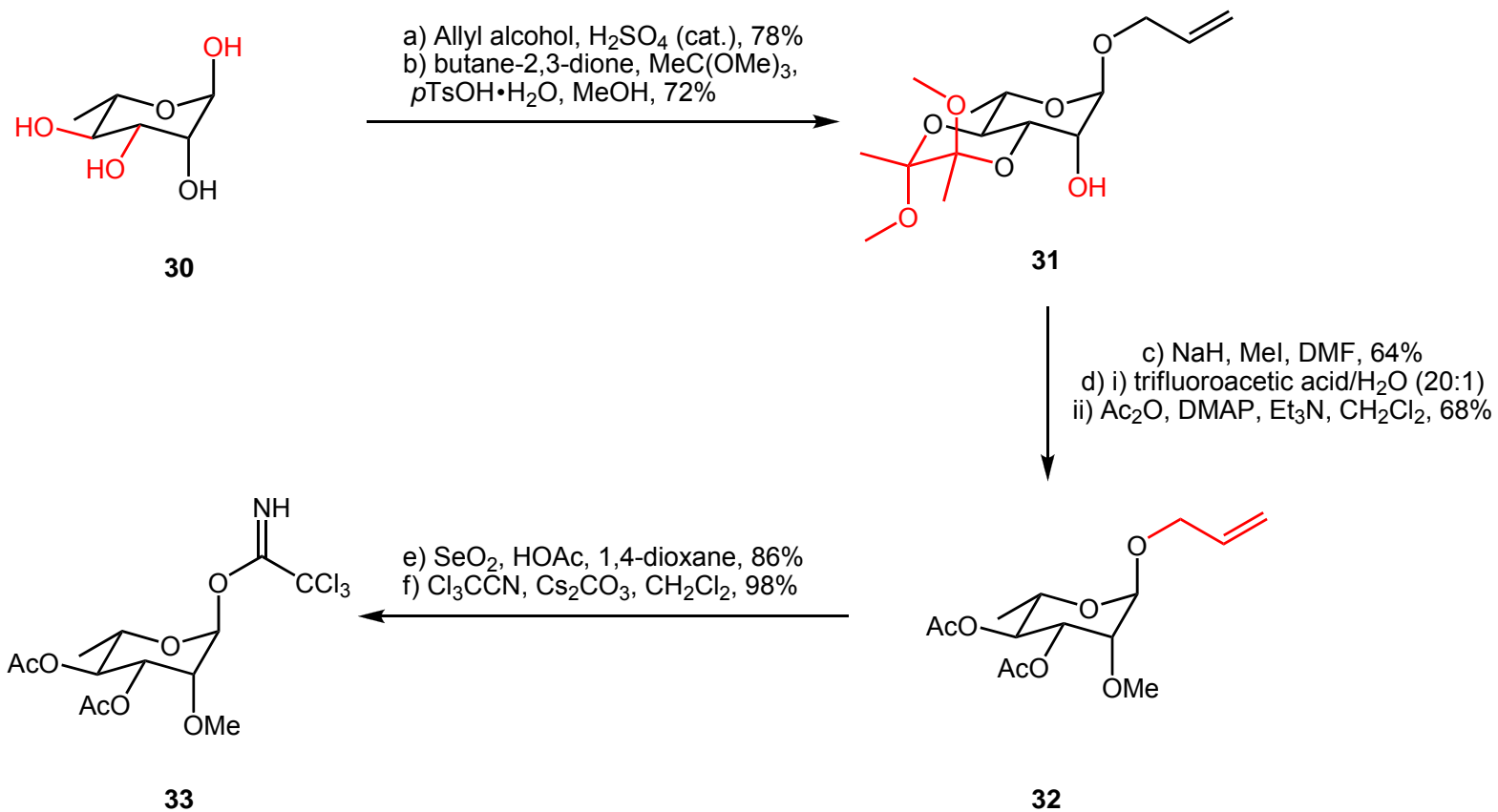
► Total synthesis by Fürstner's group



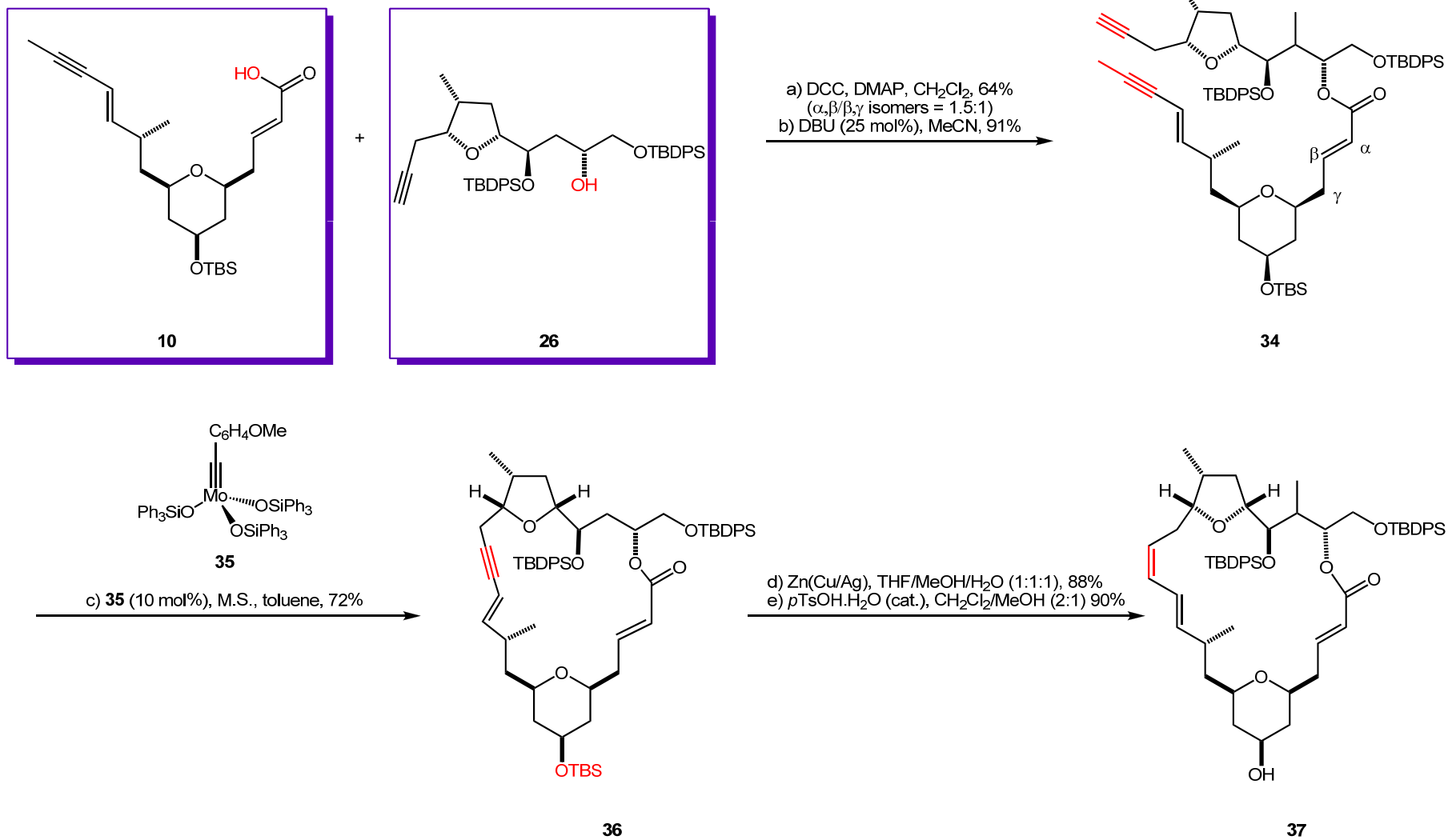
Evans-Tishchenko reaction



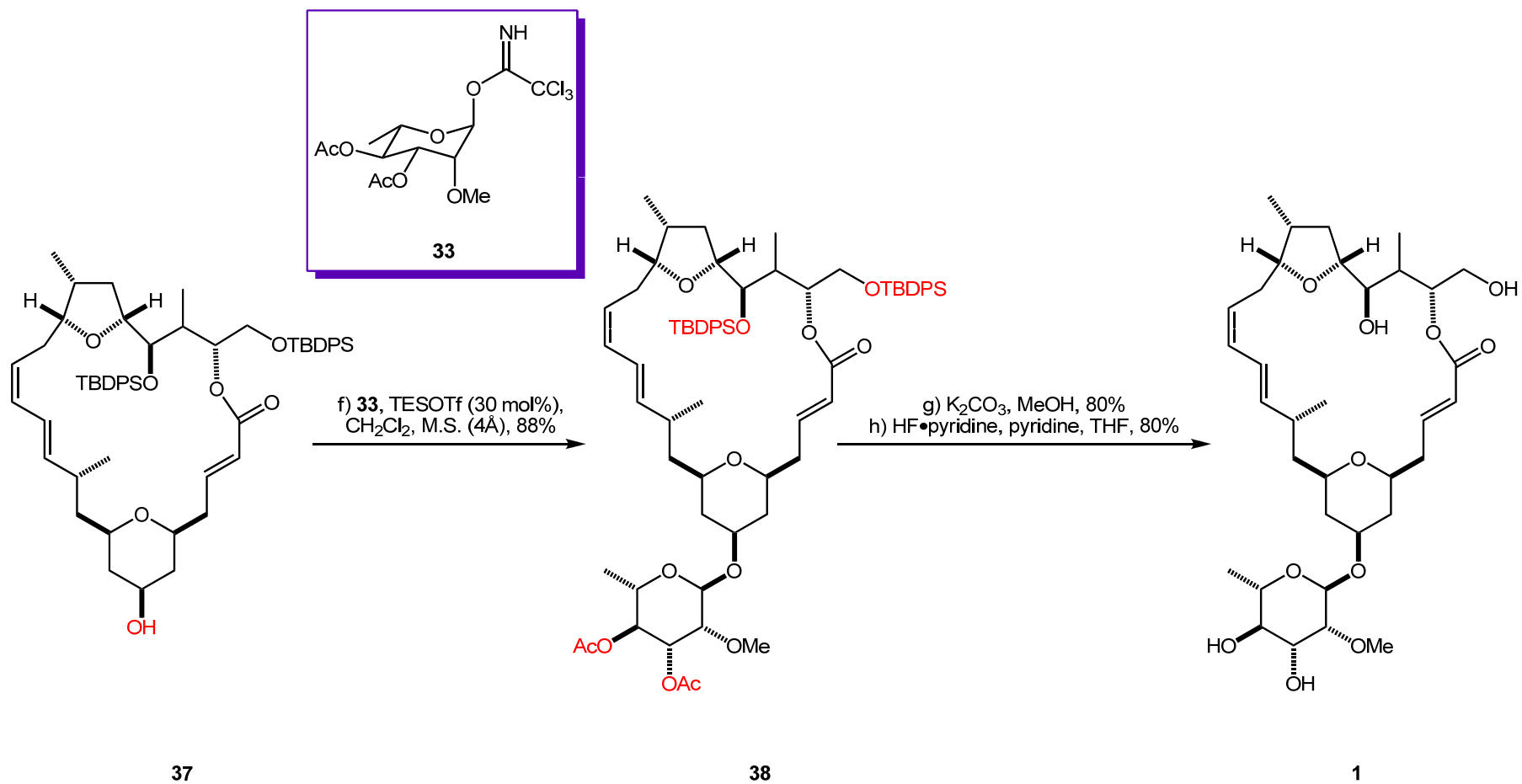
➤ Total synthesis by Fürstner's group



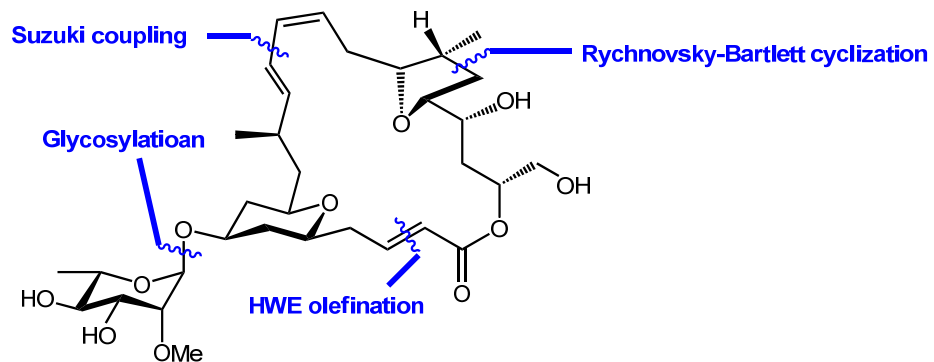
➤ Total synthesis by Fürstner's group



► Total synthesis by Fürstner's group

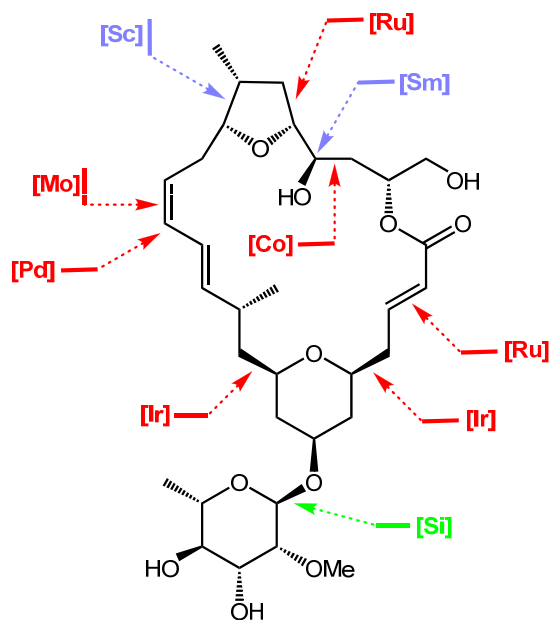


► Summary



Xu's group

1. Convergent approach
2. 20 steps.



Fürstner's group

1. Catalysis-based total synthesis.
2. 21 steps, 4.5% overall yield.

Mandelalide A (1) is an extraordinary glycosylated macrolide that was recently isolated from a new species of *Lissoclinum* ascidian, collected from Algoa Bay, South Africa. Intriguing structural features of mandelalide A include a 24-membered α,β -unsaturated macrolactone, which entails a conjugated diene, a trisubstituted tetrahydrofuran (THF) moiety, and a trisubstituted tetrahydropyran (THP) fragment appended with an unusual carbohydrate unit. Furthermore, a total of nine stereogenic centers are present in the carbon backbone of mandelalide A. Mandelalide A exhibited potent cytotoxicity to human NCI-H460 lung cancer cells (IC_{50} : 12 nM) and mouse Neuro-2A neuroblastoma cells (IC_{50} : 29 nM). We have been engaged in a program devoted to the total synthesis of biologically active marine natural products. Herein, we disclose the total synthesis of mandelalide A and the resulting reassignment of the stereochemical configuration of the natural product.

In summary, we have achieved the total synthesis of the proposed structure of mandelalide A. The convergent approach features a highly diastereoselective Prins cyclization for the construction of the tetrahydropyran subunit and Rychnovsky–Bartlett cyclization for the preparation of the tetrahydrofuran moiety. Suzuki coupling, Horner–Wadsworth–Emmons macrocyclization, and glycosylation also served as key reactions for the total synthesis. The application of this strategy to the synthesis of mandelalide B is in progress, and the results will be reported in due course.