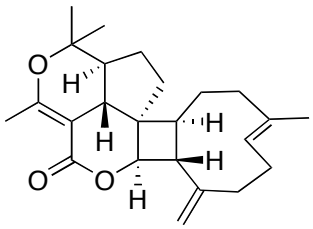
Total Synthesis of Antheliolide A



Antheliolide A

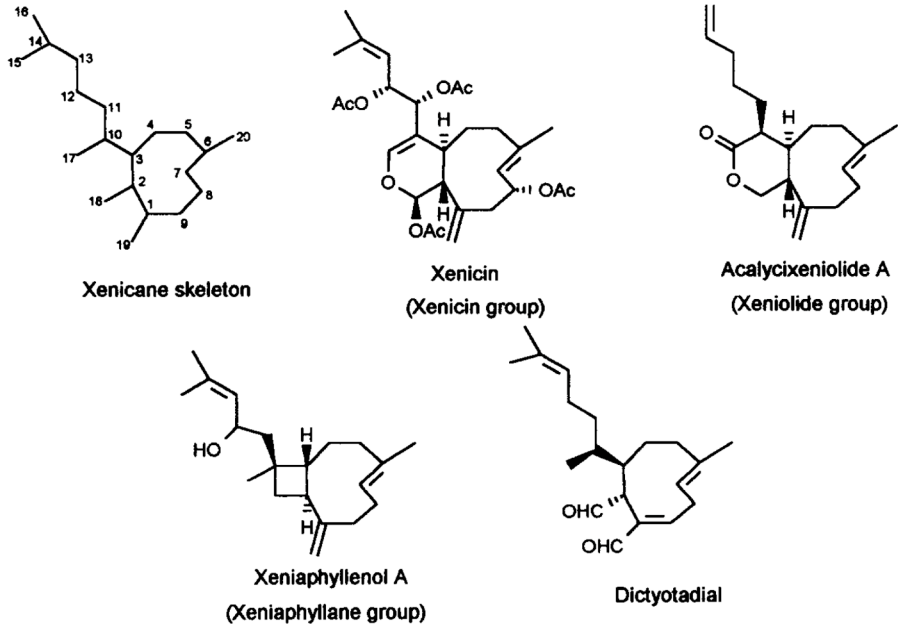
Chandra Sekhar Mushti, Jae-Hun Kim and
E.J. Corey

JACS, ASAP

10/28/06

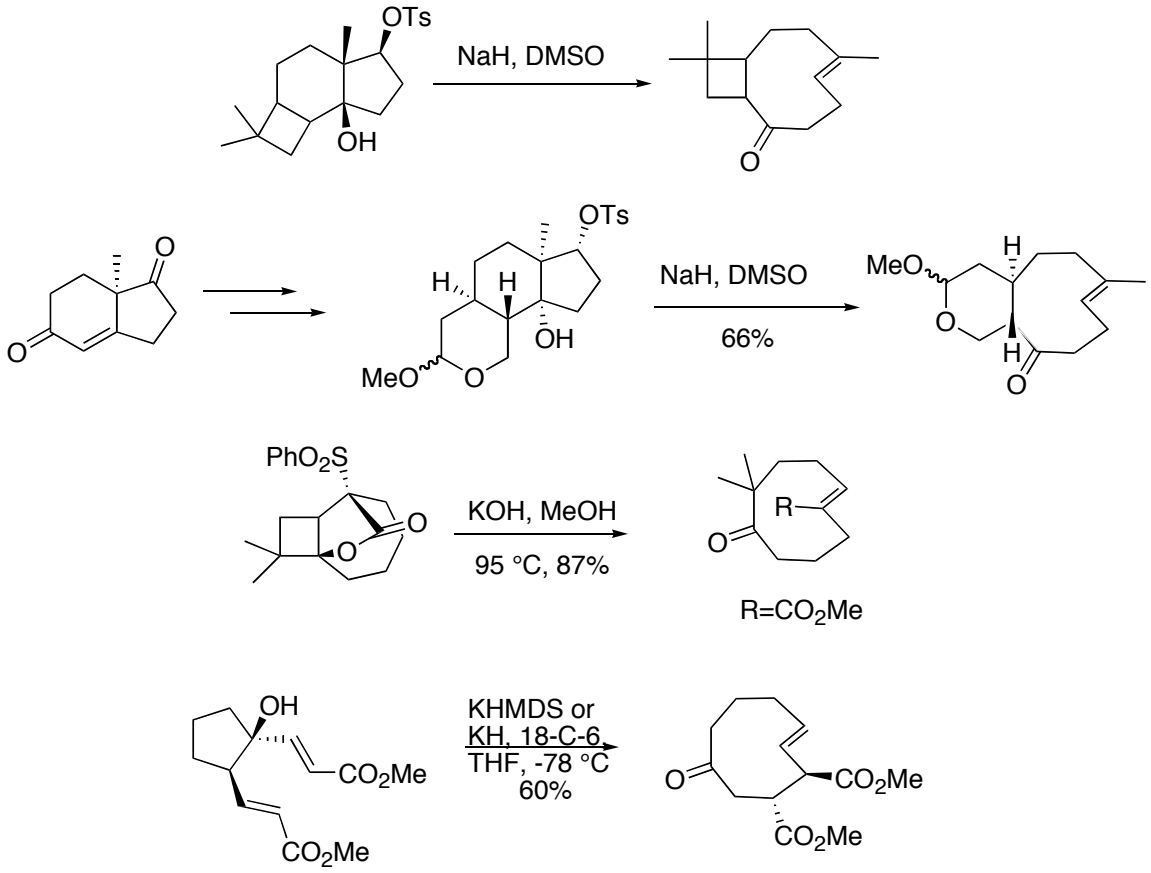
Xenicane Family of Natural Products

- A class of diterpenes and norditerpenes isolated from marine organisms
- Have shown cytotoxicity, anti-inflammatory and antifungal activites.
- First in the family was isolated in 1977 and since a hundred xenicanes have been discovered
- This family can be divided into four main groups



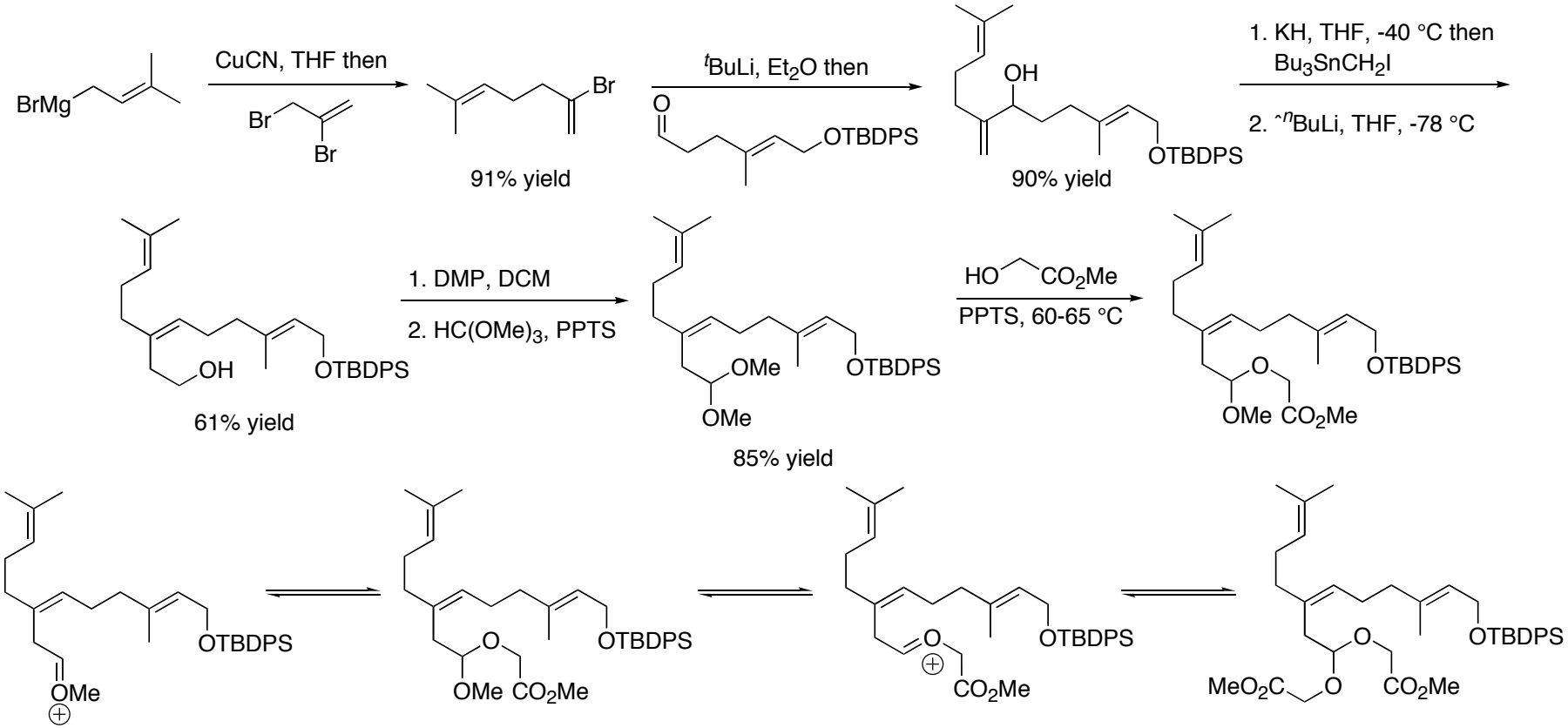
Liu, G.; Smith, T. C.; Pfander, H., *Tet. Lett.,* **1995,** 4979

Synthesis of *trans*-Cyclononenes



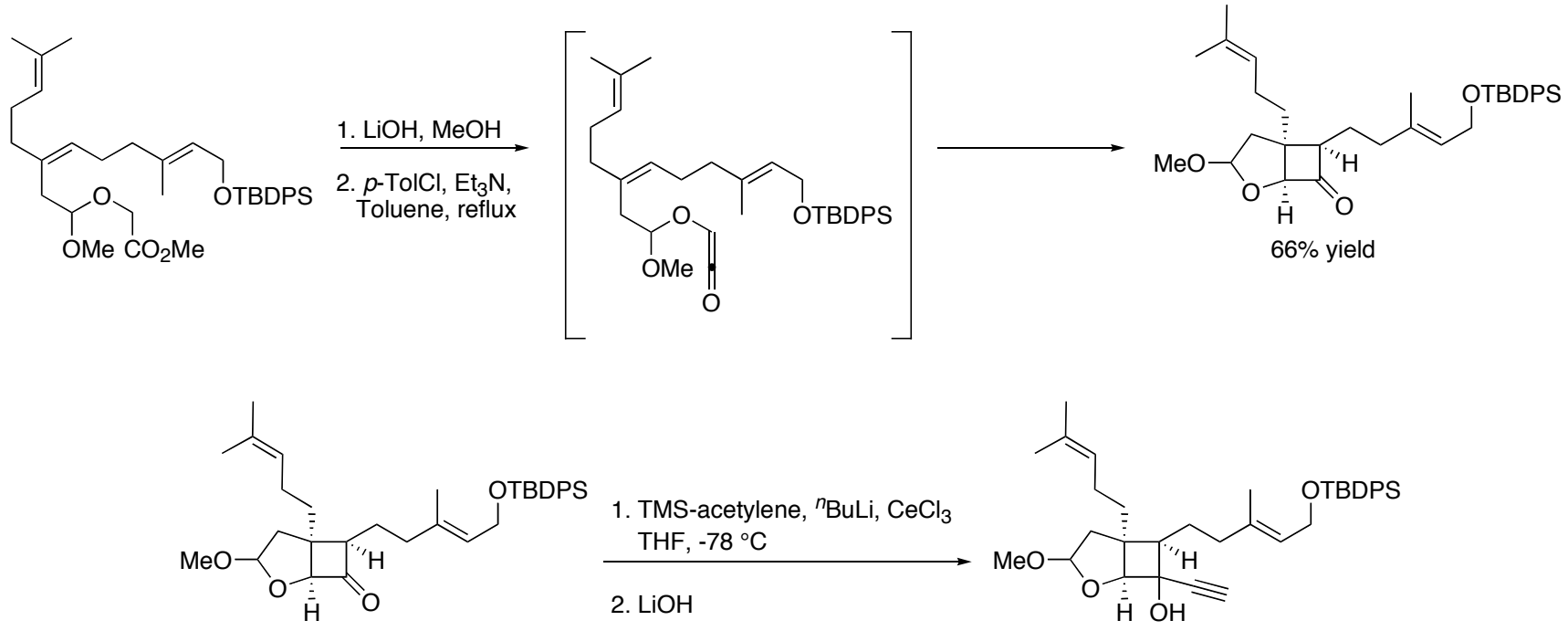
Corey, E. J.; Mitra, R. B.,;Uda, H. *J. Am. Chem. Soc.* **1964**, 485
Liu, G.; Smith, T. C.; Pfander, H. *Tet. Lett.* **1995,** 4979
Kende, A. S.; Kaldor, I. *Tet. Lett.,* **1989**, 7329
Von Zezschiwitz, P.; Viogt, K.; Noltemeyer, M.; de Meijere, A. *Synthesis,* **200,** 1327

Synthesis of Mixed Acetal



Preparation of the Racemic Mixed Acetal Methyl Ester 7. To a mixture of dimethyl acetal (4.15 g, 7.77 mmol) and methyl glycolate (9 mL, 116.6 mmol, 15 equiv), pyridinium tosylate (58 mg, 0.233 mmol, 3 mol %) was added and the reaction was heated in a preheated oil bath whose temperature was maintained between 60 to 65 °C. The biphasic reaction mixture was vigorously stirred and continuously purged with a slow stream of dry N_2 gas to remove the MeOH generated during the reaction. The reaction was continued at the same temperature until the reaction mixture became homogenous (usually within 1.5 to 2 h). ….. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 1:0 → 9:1 to give racemic mixed acetal methyl ester 7 (3.34 g, yield 73%) and 664 mg of starting dimethyl acetal 6 along with aldehyde, which can be recycled to the dimethyl acetal by treating methyl orthoformate and PPTS as before.

The “Magic” HPLC

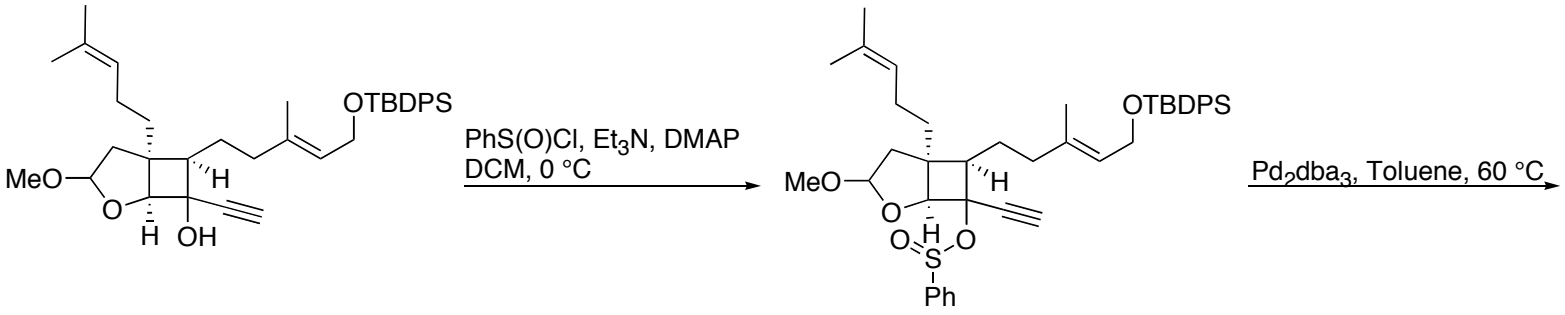


We were pleased to find that the two enantiomers of (±)-**9** were separated with remarkable facility on a Chiral Technologies OD-H HPLC column with 97:3 hexane−*i*-PrOH as eluent because of greatly different retention times (baseline separation with the two enantiomers typically eluting at 4.75 and 6.14 min). This separation was performed on a 4.2 g sample to afford each of the oily enantiomers of **9** in pure form and >99.9% ee.[11] Each of the

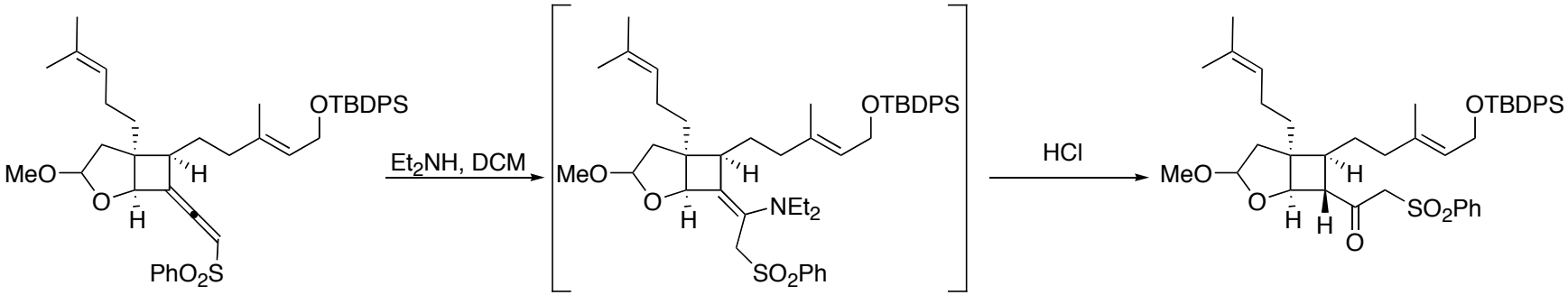
(11) This separation was accomplished in one pass using a 2 cm diameter OD-H column available from Chiral Technologies, Inc.

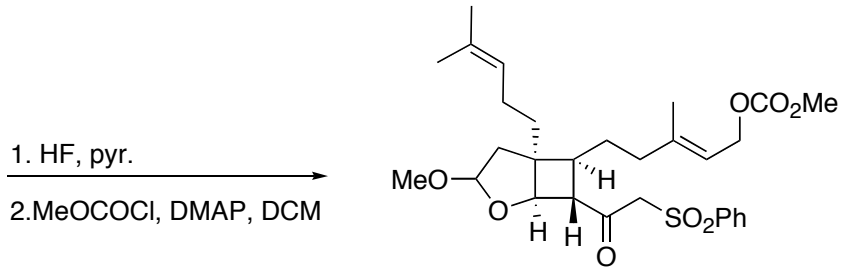
In 1 ml this is 7.2 M

Alkyne Oxidation

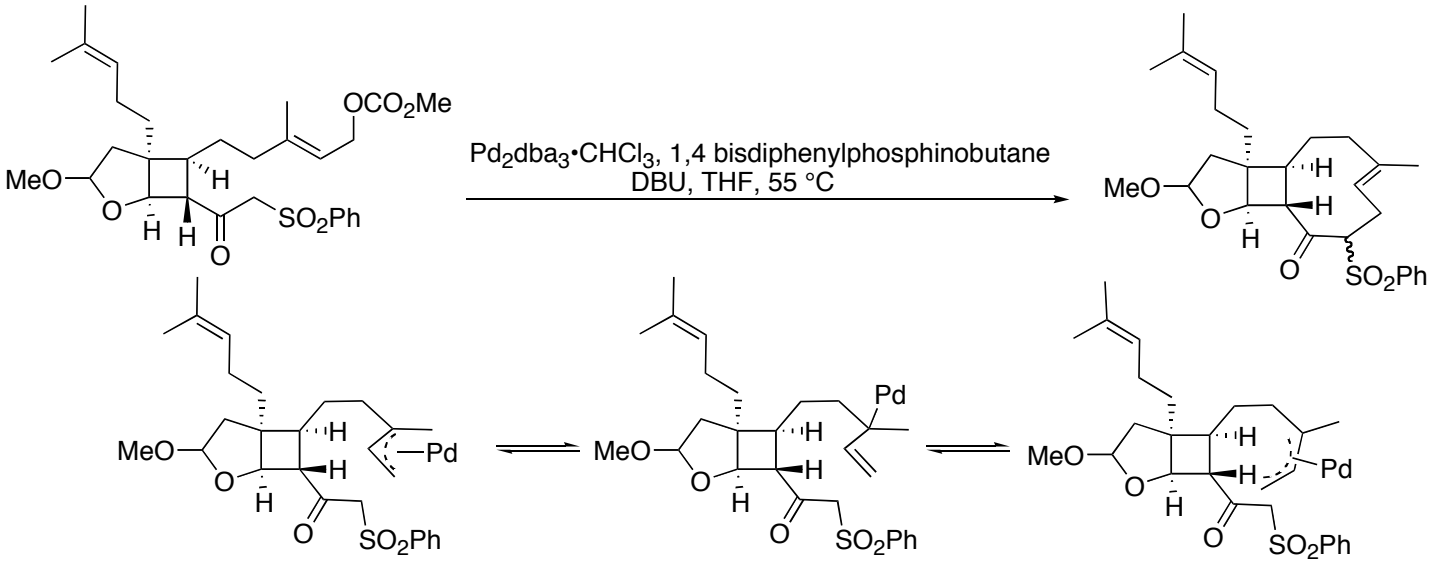


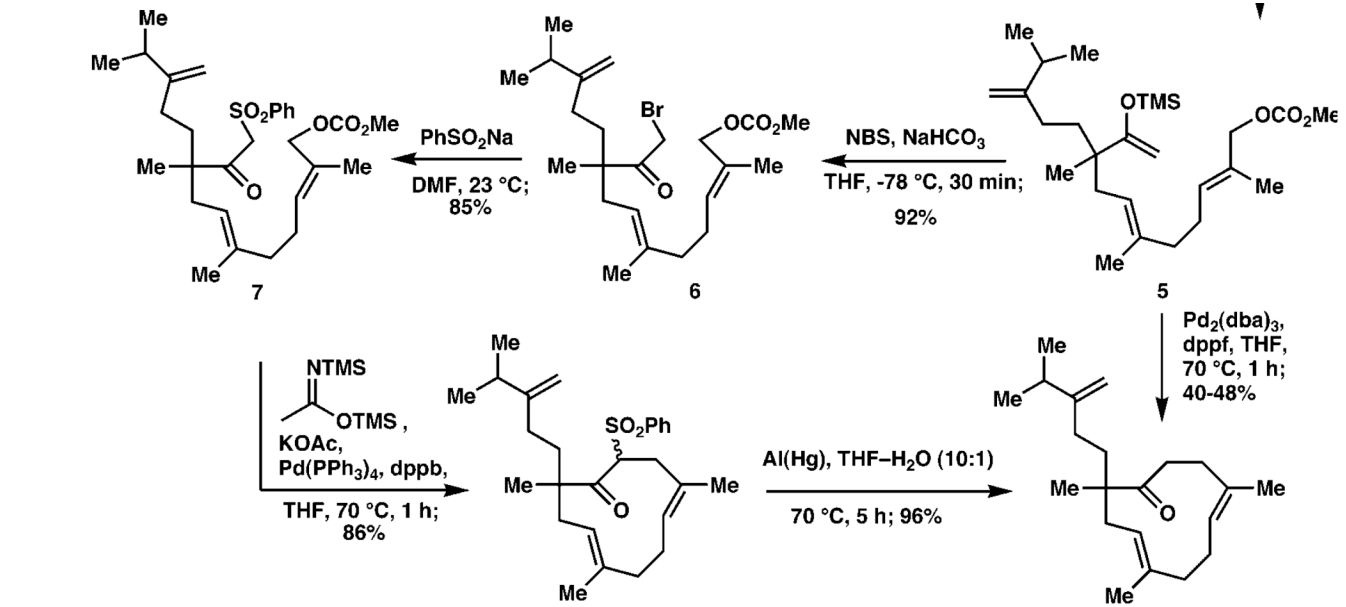
87% yield (3 steps)





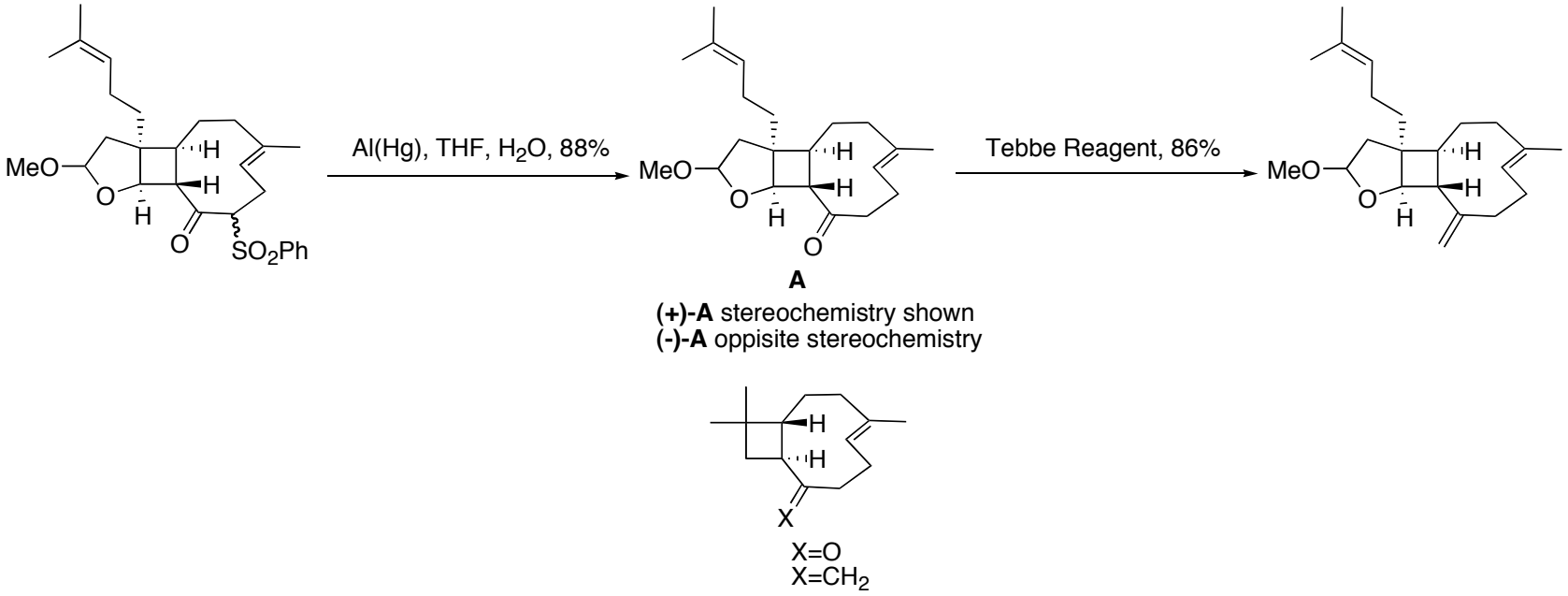
An Unusually Pd-Allyl Ring-Closure





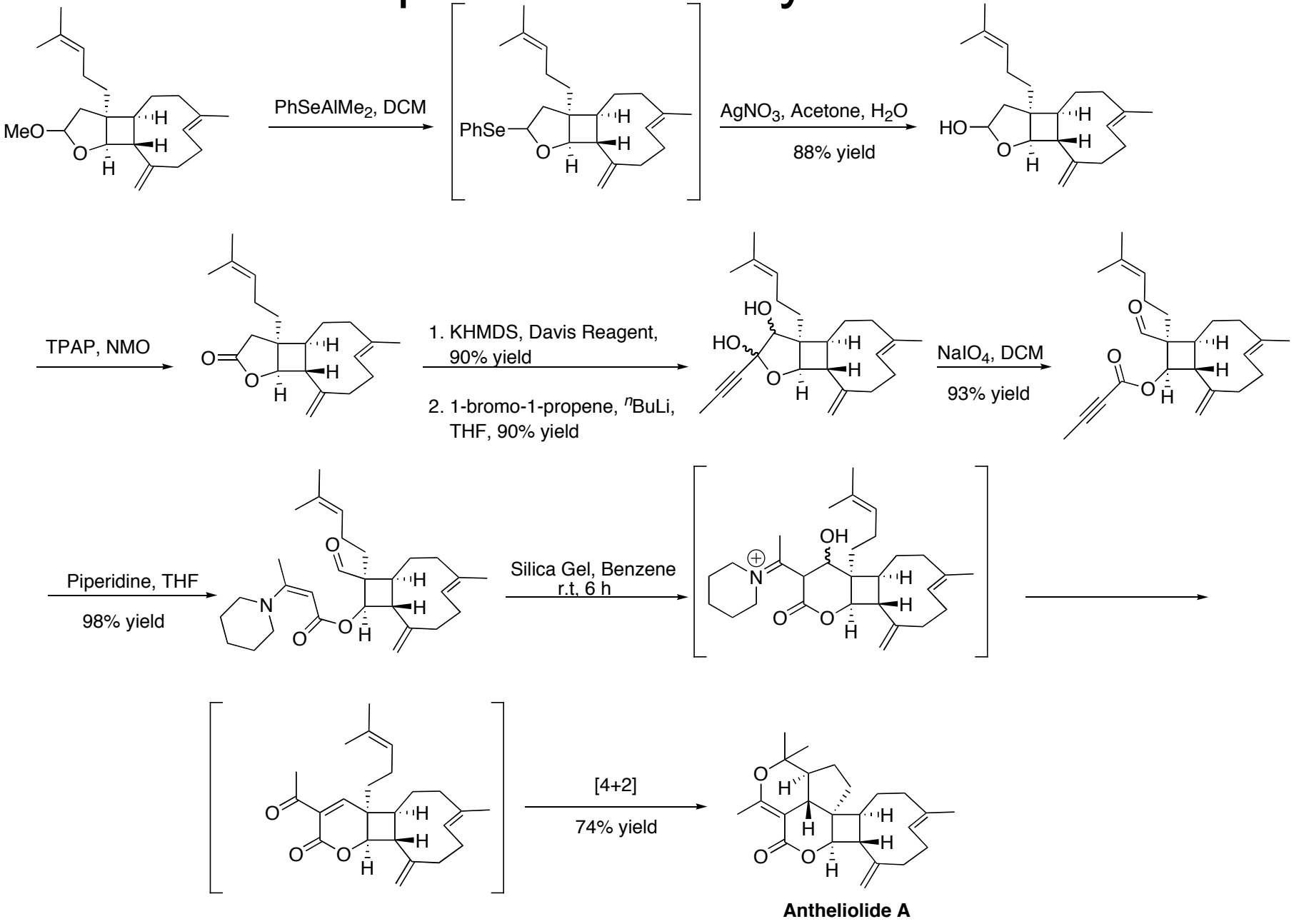
Hu, T.; Corey, E.J., *Org. Lett.* **2002,** 2441

Absolute Stereochemistry by Comparing Optical Rotation



Starting with the enantiomer of **9** with the shorter retention time (4.75 min) we obtained the dextrorotatory form of **13** ($[\alpha]^{23}_{D}$ +34 in $CHCl_3$) to which we assign the absolute stereochemistry shown in Scheme 1. From the enantiomer of **9** with the longer retention time (6.14 min) we obtained the levorotatory product, ketone *ent*-**13** ($[\alpha]^{23}_{D}$ −34 in $CHCl_3$). These assignments were made by comparison with a close model, the known levorotatory bicyclic ketone **19** ($[\alpha]_{D}$ −72 in $CHCl_3$) that had been correlated with naturally occurring β-caryophyllene (**20**).[15,16]

Completion of the Synthesis



Antheliolide A

Conclusion

Many of the steps used in the synthesis of antheliolide A described above have implications beyond the present work, as well as being of crucial importance to the success of this project. These include (1) formation of the mixed acetal **7**, (2) the diastereoselective bicyclization to form **8** in which stereocenters are correctly established at each carbon of the four-membered ring, (3) the chain extension **8** → **11**, (4) the efficient closure of the nine-membered ring of **12**, (5) the mild oxidative cleavage sequence **14** → **17**, and (6) the successful and quick formation of the last three rings of **1** from aldehyde **17** via **18**. It seems logical that the one-step conversion of **18** to **1** occurs via the intermediate **21** by [2 + 4]-cycloaddition which is made even more facile by steric acceleration. The same pathway may be involved in the biosynthesis of **1**. The approach described above for the synthesis of **1** is completely different from that employed in these laboratories earlier for the construction of the structural relative β-caryophyllene.[27]

- This synthesis had a number of interesting steps as listed above.
- The desire or need to separate the enantiomers at such an earlier stage (10 steps in to the synthesis, 15 steps remaining) is not addressed.
- The origin of the selectivity and high yield of the Pd-allylation reaction needs to be addressed.