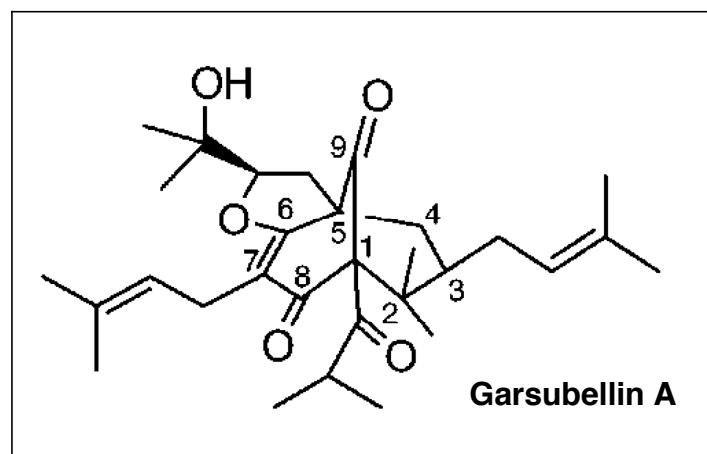


Total Synthesis of (\pm)-Garsubellin A

Akiyoshi Kuramochi, Hiroyuki Usuda, Kenzo Yamatsugu,
Motomu Kanai,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo

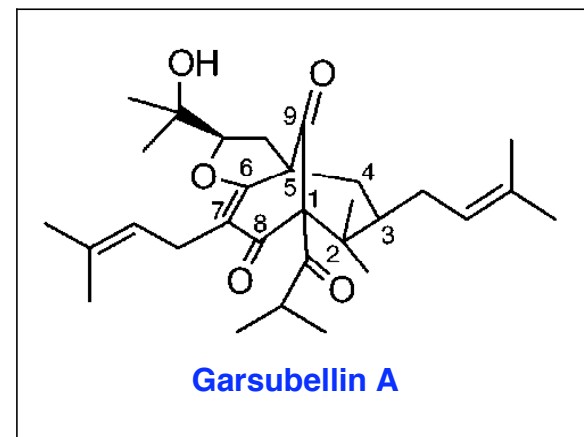
J. Am. Chem. Soc., **2005**, ASAP



Anthony Cuzzupe
October 15, 2005

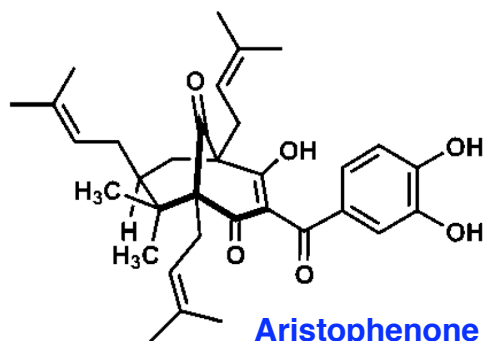
Isolation and Biological activity

- Structure of garsubellin A reported in 1997 by Fukuyama et al.
- Isolated from the wood of *Garcinia subelliptica* found on the Okinawan Islands of Japan
- Structurally, garsubellin A is a polyprenylated phloroglucin derivative containing a highly congested bicyclo [3.3.1]nonane-1,3,5-trione core fused to a tetrahydrofuran ring
- Potent inducer of choline acetyltransferase (ChAT), the enzyme responsible for biosynthesis of the neurotransmitter acetylcholine (ACh)
- Garsubellin A was found to increase ChAT activity in rat septal neurons by 154% at a 10 μ M concentration
 - May have therapeutic potential for treatment of neurodegenerative diseases such as Alzheimer's disease

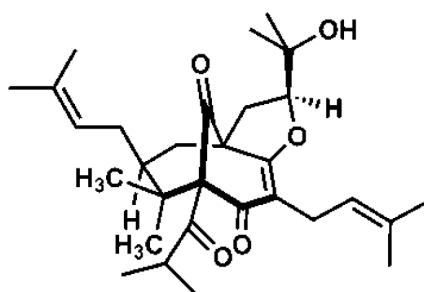


Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947

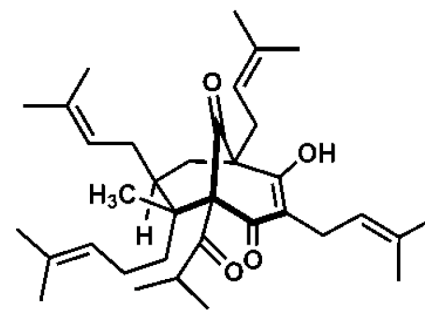
Some Bicyclic Natural Products from the *Guttiferae* Class



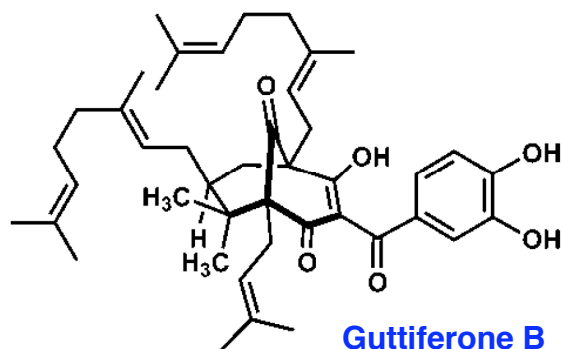
Aristophenone A
Antioxidant/Anticancer



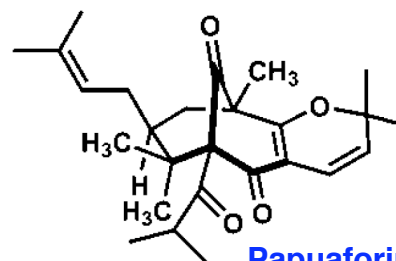
Garsubellin A
Antineurodegenerative



Hyperforin
Antidepressant



Guttiferone B
Anti HIV

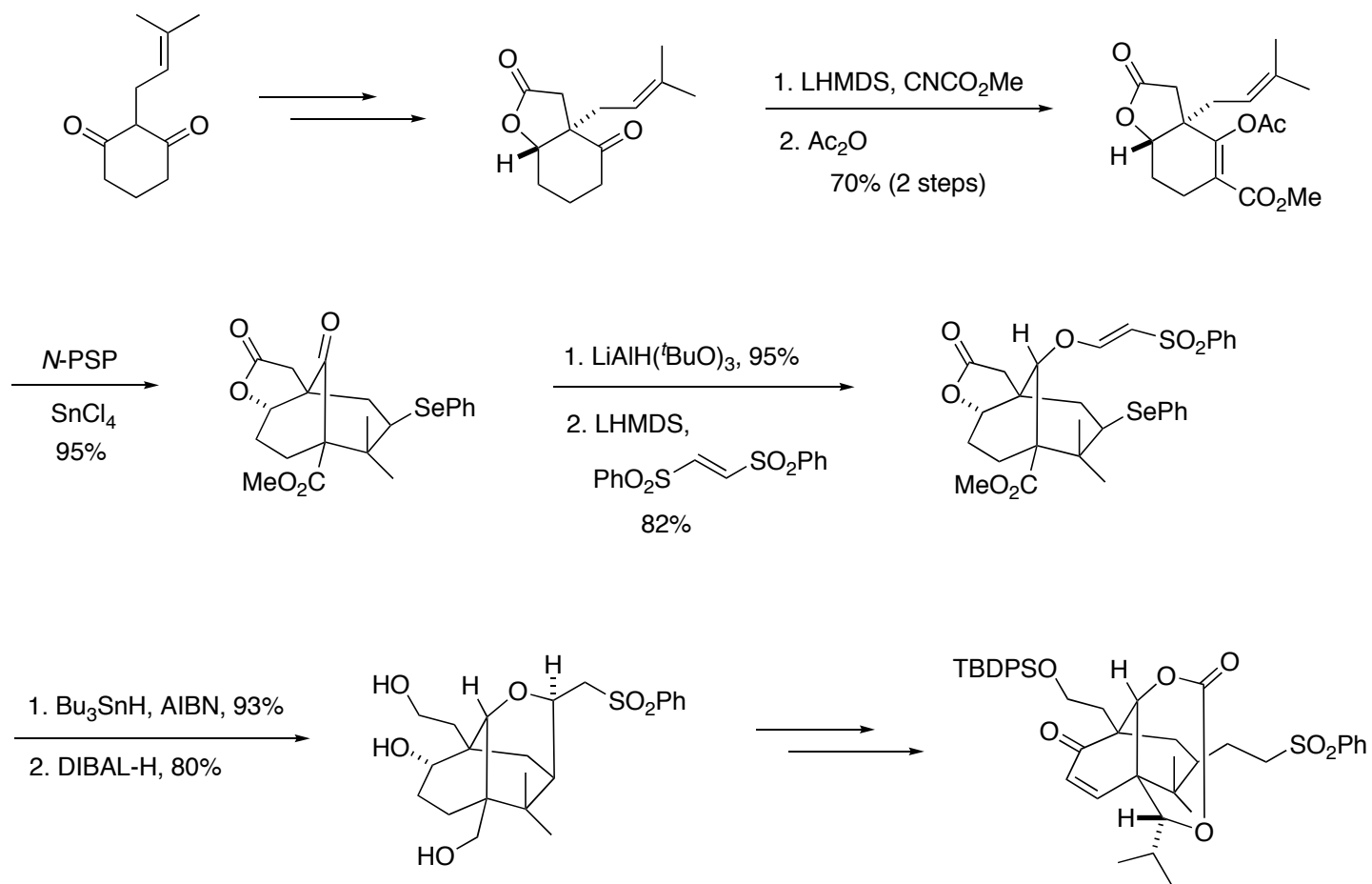


Papuaforin A
Anticancer/Antibacterial

- Despite their structural complexity and biological activities, this class of compounds (>50 members) has received little attention until the past five years, with only a handful of synthetic efforts aimed mainly at the common bicyclo[3.3.1]nonane core

Core Syntheses of Garsubellin A

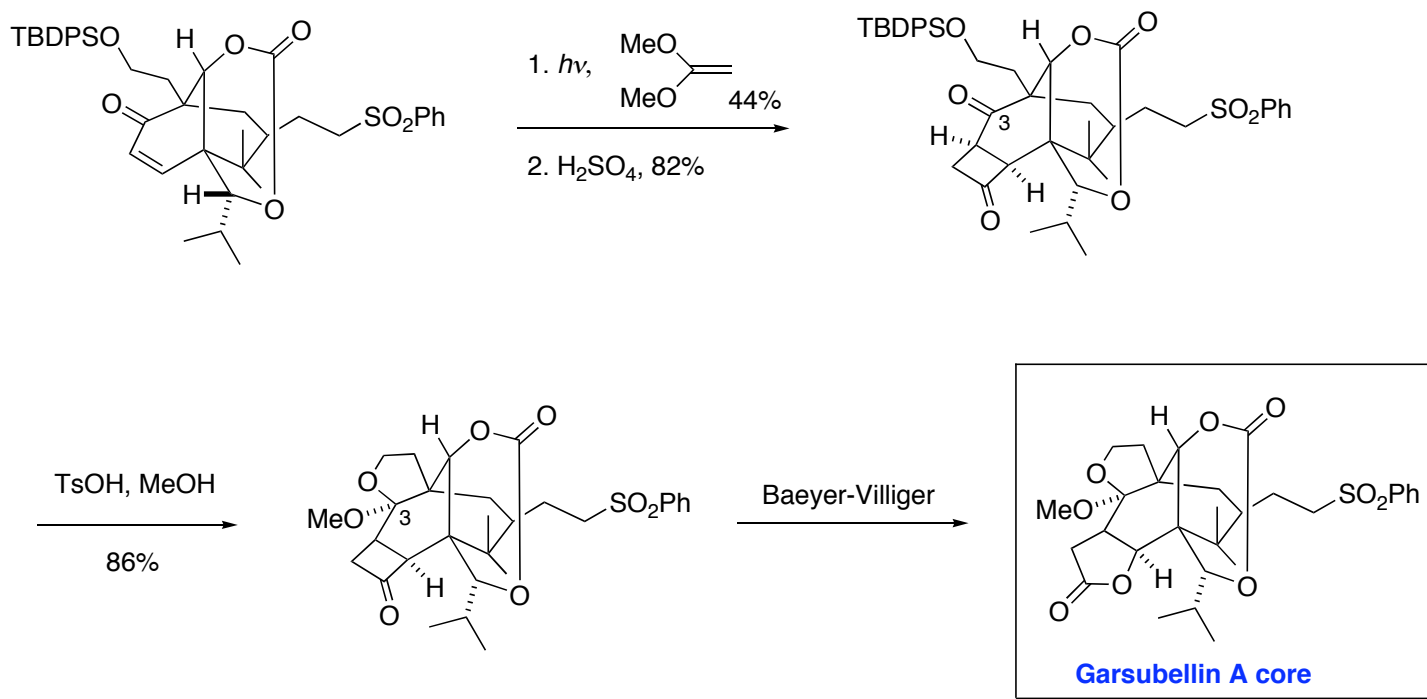
Nicolaou: Synthesis of the fully functionalized core using a selenocyclisation approach



Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724

Core Syntheses of Garsubellin A

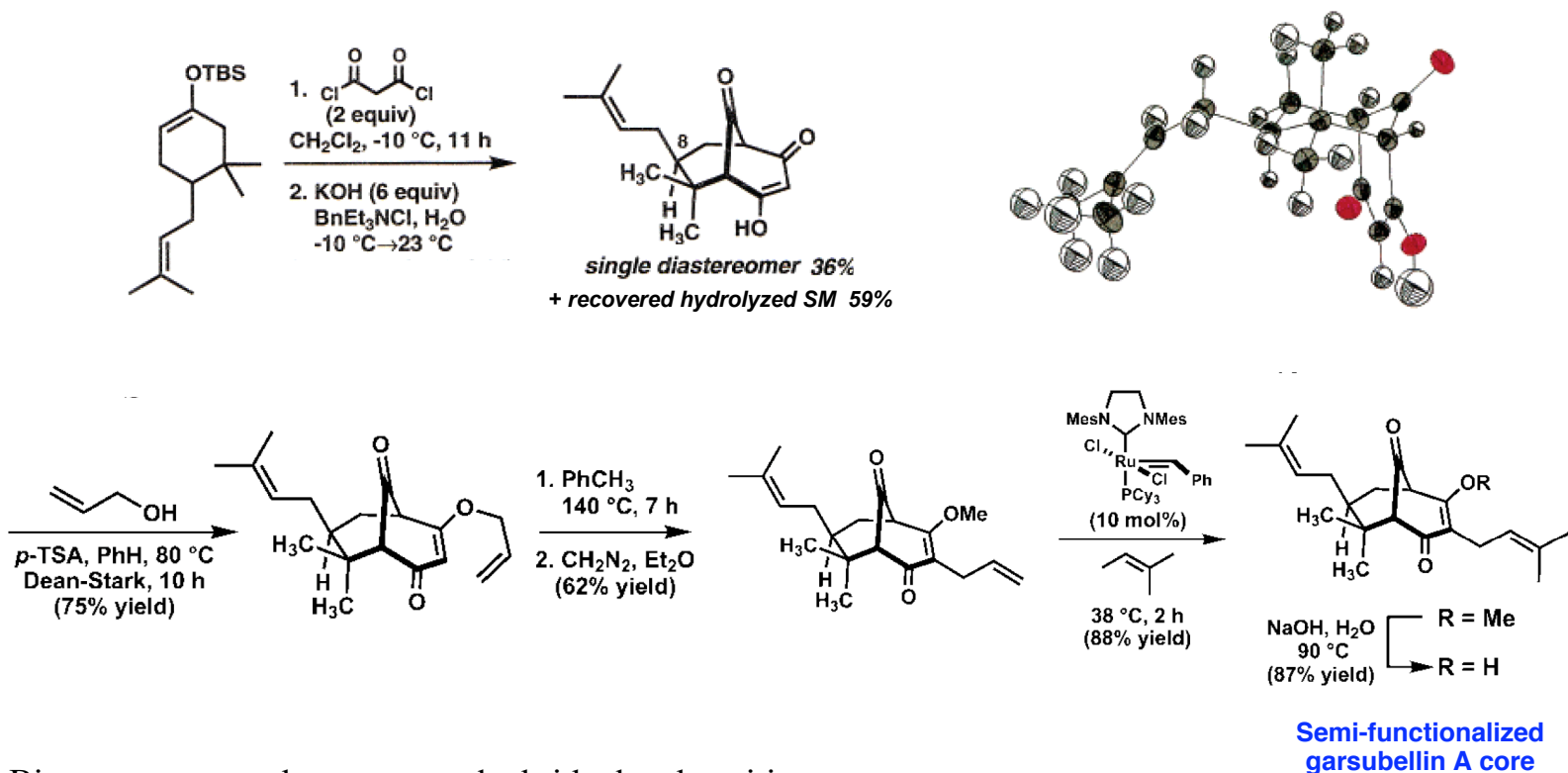
Nicolaou: Synthesis of the fully functionalized core using a selenocyclisation approach



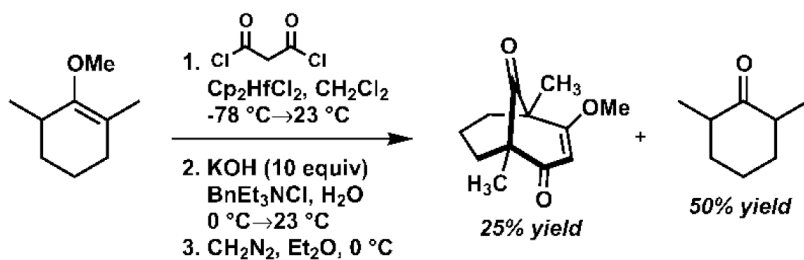
Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724

Core Syntheses of Garsubellin A

Stoltz: Synthesis of bicyclo[3.3.1]nonane core via a tandem Claisen-Dieckmann reaction of malonyl dichloride



Bis-quaternary carbon array at the bridgehead positions could also be accessed using this strategy:

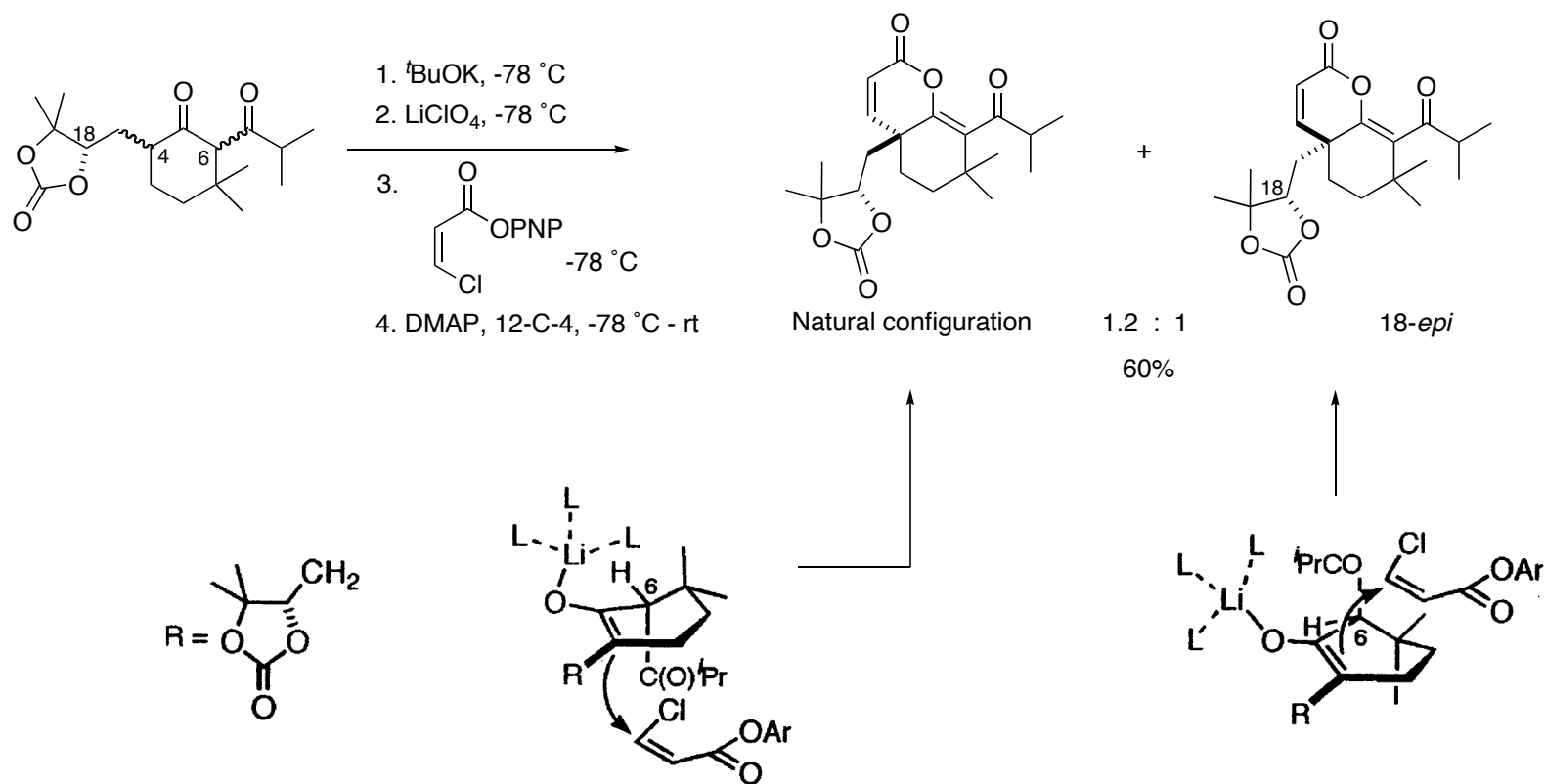


Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943

Core Syntheses of Garsubellin A

Shibasaki: Synthesis of 8-deprenyl-garsubellin A - lead-up to total synthesis

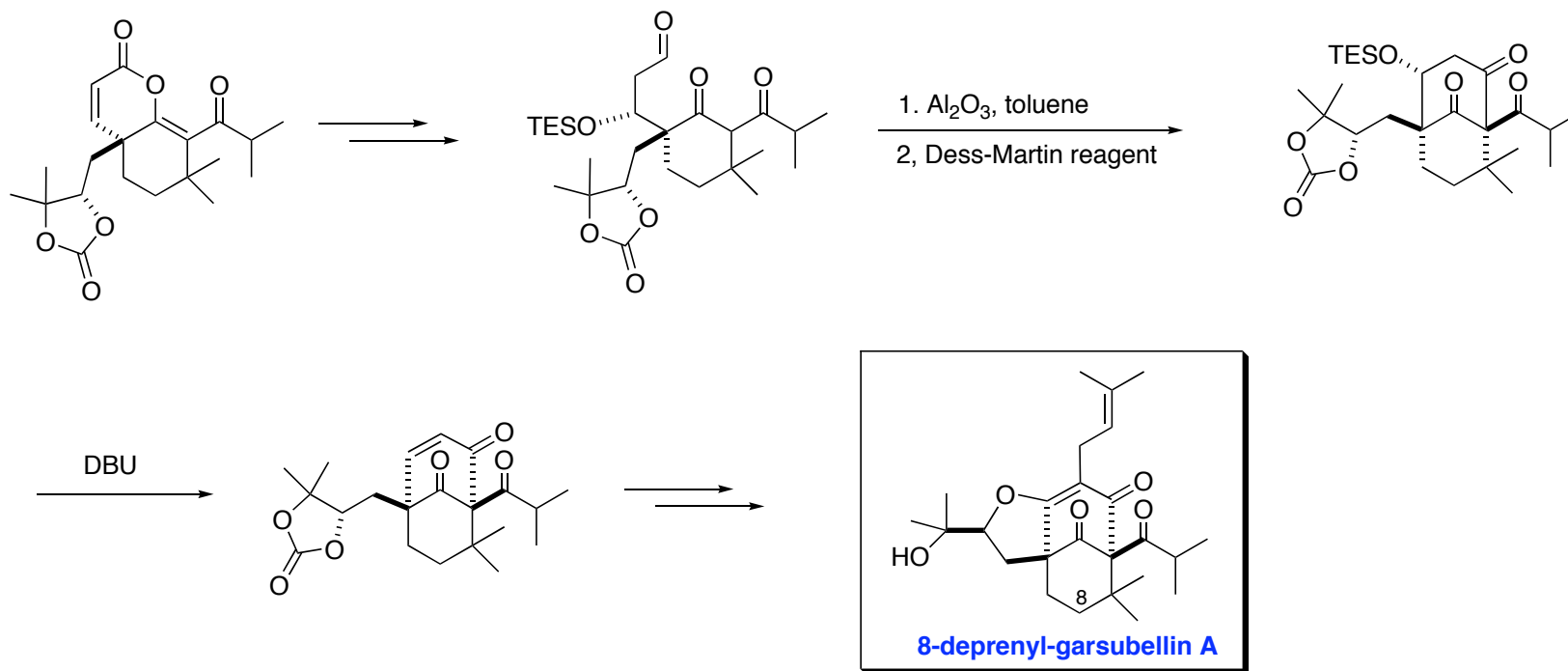
● One-pot lactone formation as key step



Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, 43, 3621

Core Syntheses of Garsubellin A

Shibasaki: Synthesis of 8-deprenyl-garsubellin A - lead-up to total synthesis

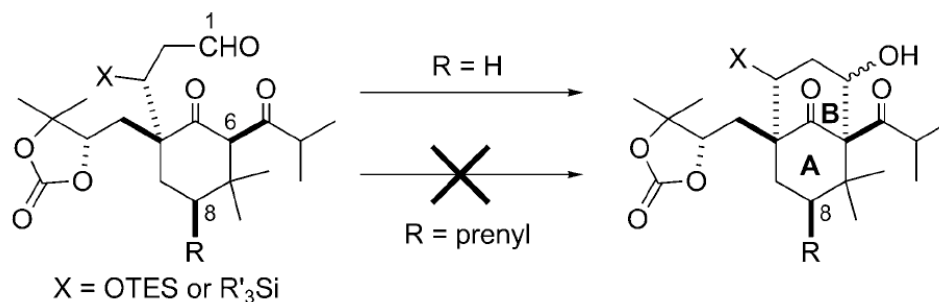


Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621

Total Synthesis of (\pm)-Garsubellin A

Retrosynthetic Analysis

- Construction of the quaternary carbon at C-6 via an intramolecular aldol-type reaction between C-1 and C-6 failed in the real system. Possibly due to destabilization of the reactive conformation for cyclization by the prenyl group.



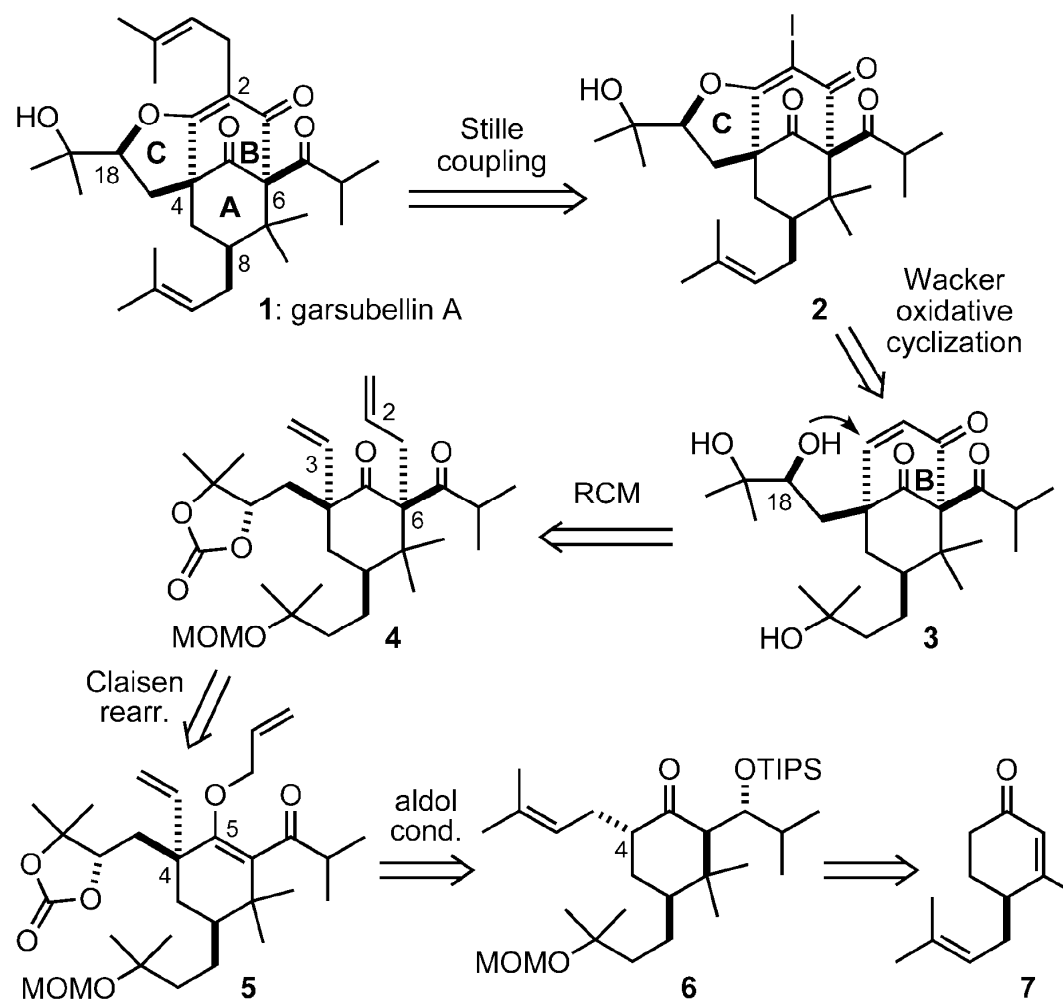
- These preliminary results called for a new synthetic approach

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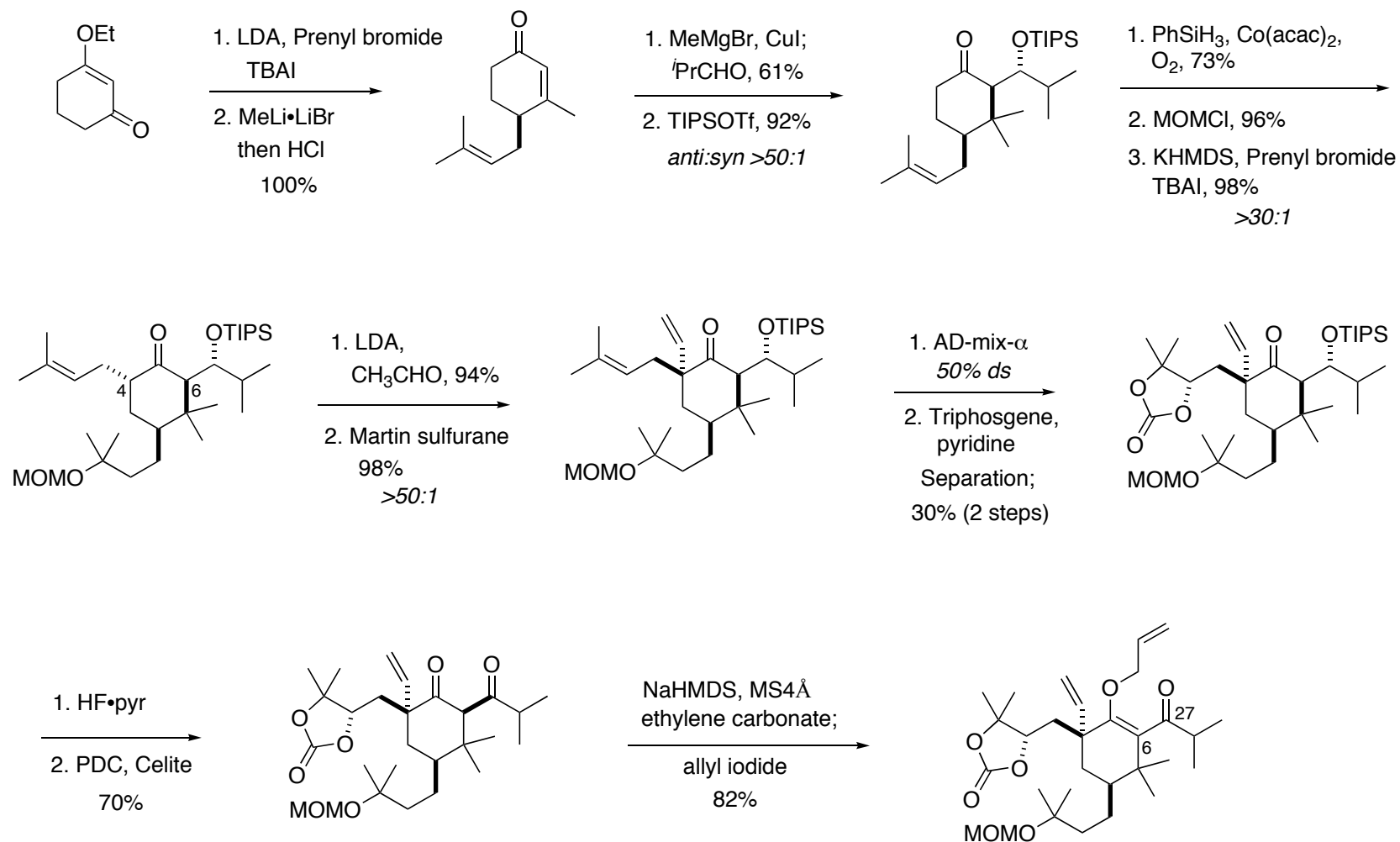
Retrosynthetic Analysis



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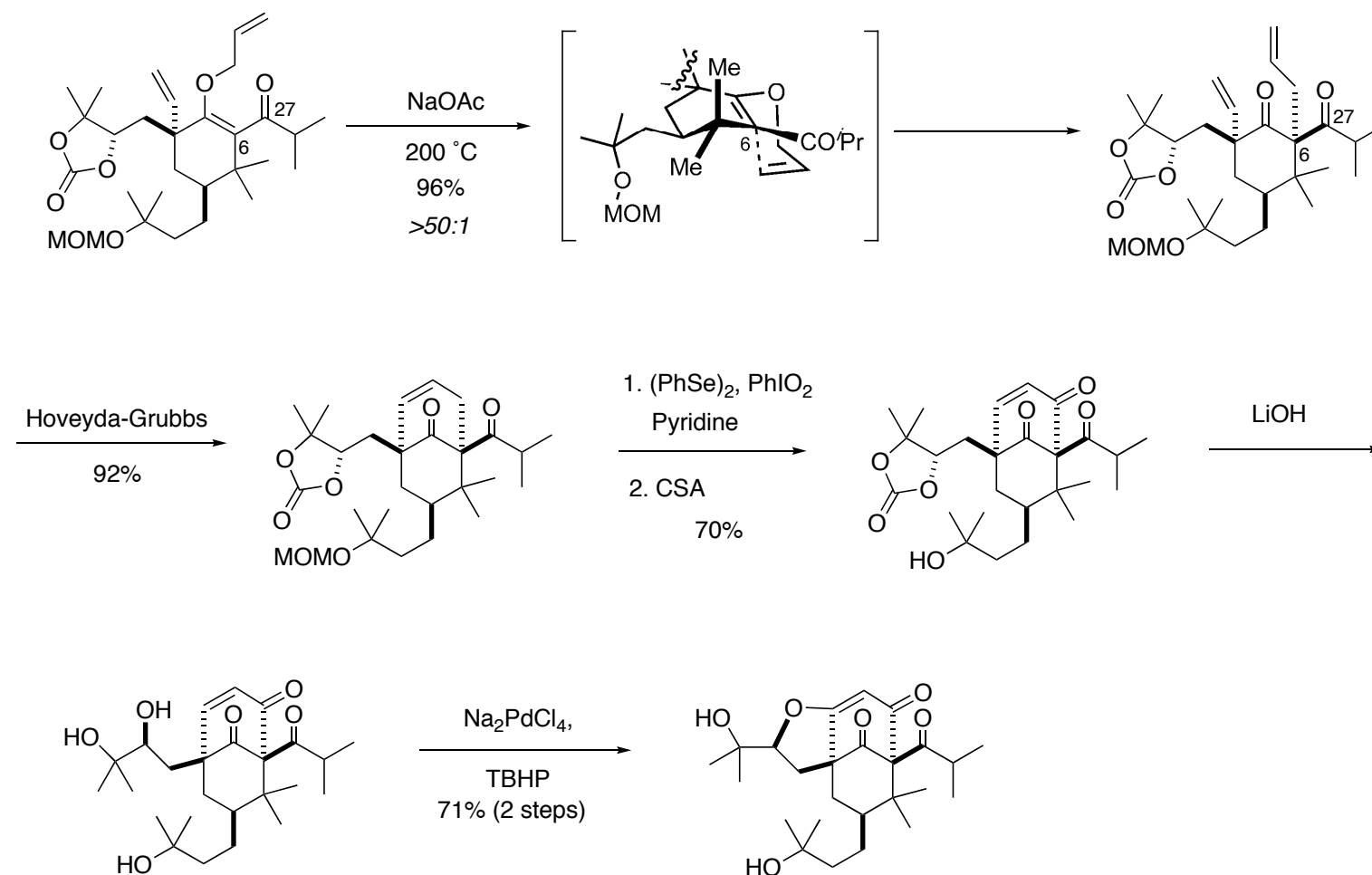
Total Synthesis of (±)-Garsubellin A



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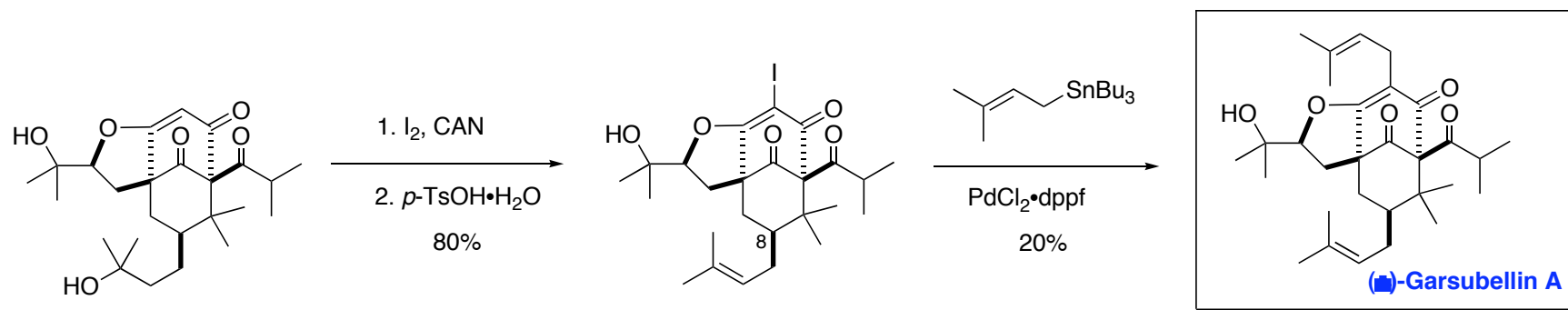
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Total Synthesis of (±)-Garsubellin A



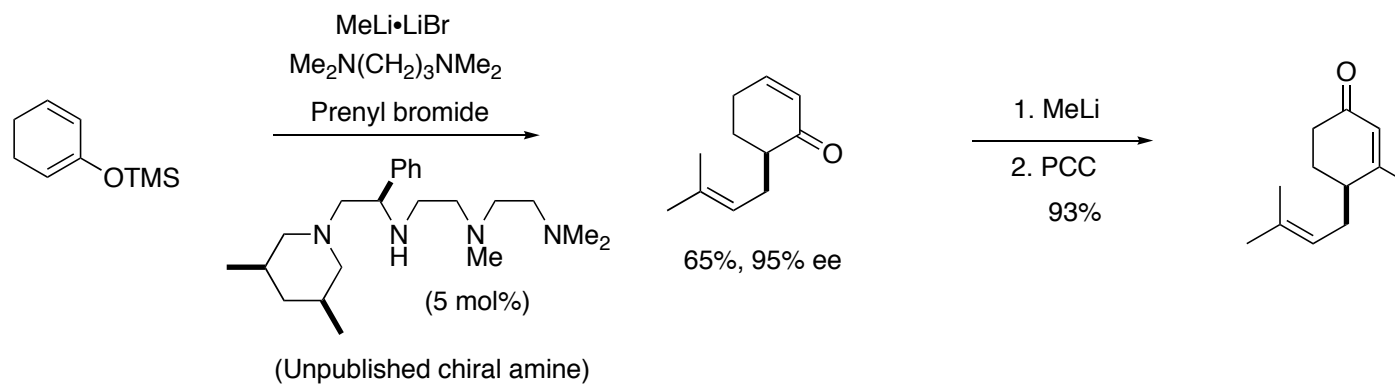
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Total Synthesis of (±)-Garsubellin A



24 Steps from commercial material,
0.4% overall yield

Application of Koga Alkylation to Asymmetric Synthesis of Garsubellin A



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Summary

- The first total synthesis of (\pm)-garsubellin A has been achieved
- Key steps in the synthesis included:
 - (1) Stereo- and regioselective introduction of the vinyl group at C-4 via aldol condensation
 - (2) Stereoselective allylation at C-6 via Claisen rearrangement
 - (3) Ring-closing metathesis for construction of the sterically congested B-ring
- Asymmetric synthesis of an early intermediate makes an asymmetric synthesis of garsubellin A possible