Total Synthesis of (±)-Garsubellin A

Akiyoshi Kuramochi, Hiroyuki Usuda, Kenzo Yamatsugu,
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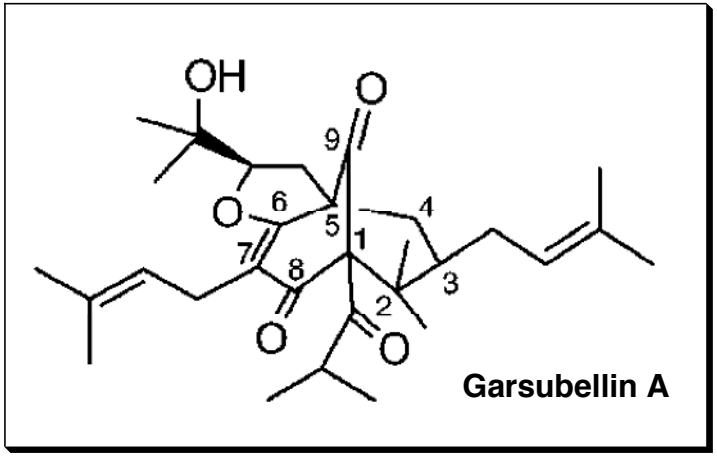
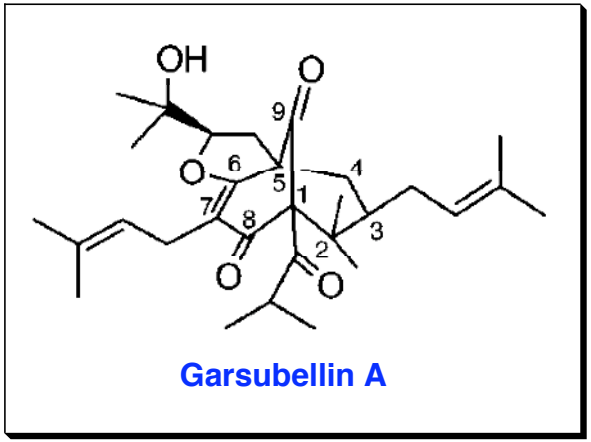


Garsubellin A

Anthony Cuzzupe
October 15, 2005

Isolation and Biological activity



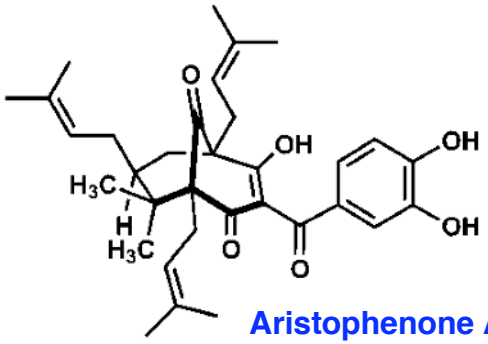
Garsubellin A

- 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 μM concentration

  → May have therapeutic potential for treatment of neurodegenerative diseases such as Alzheimer's disease

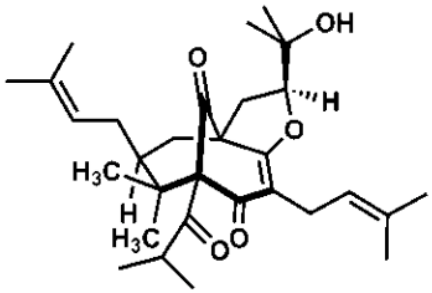
Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947

Some Bicyclic Natural Products from the *Guttiferae* Class



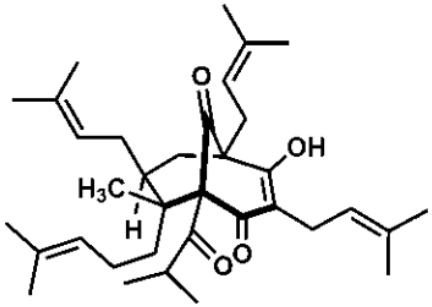
Aristophenone A

Antioxidant/Anticancer



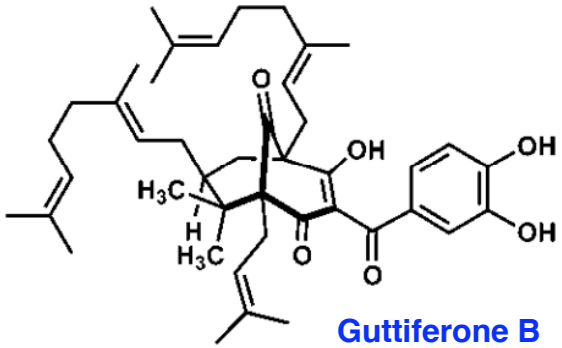
Garsubellin A

Antineurodegenerative



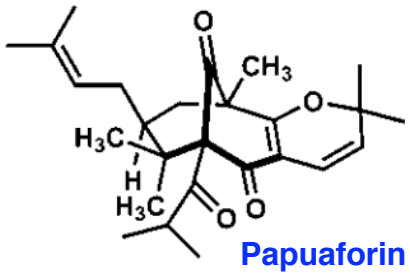
Hyperforin

Antidepressant



Guttiferone B

Anti HIV



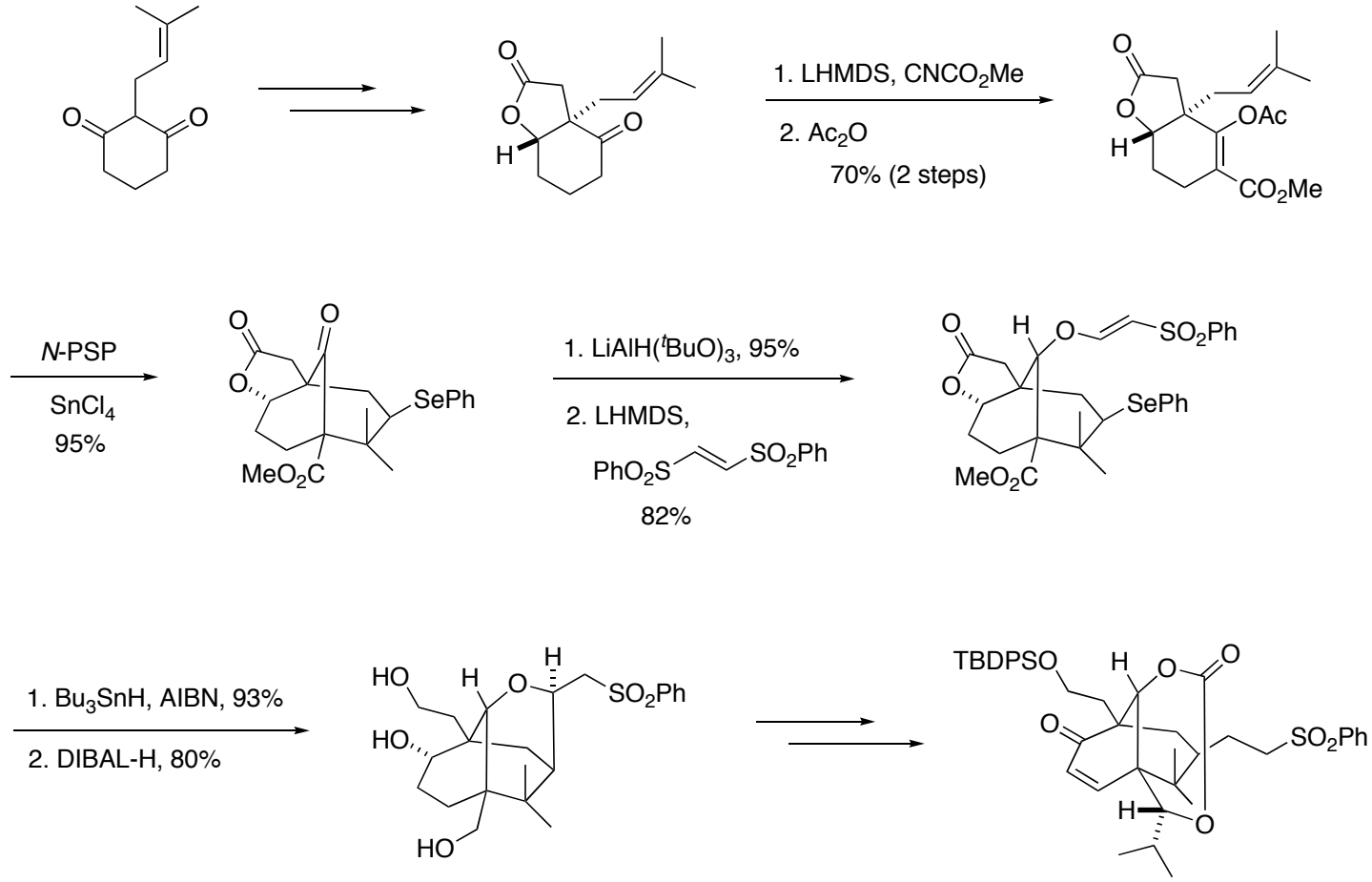
Papuaforin A

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



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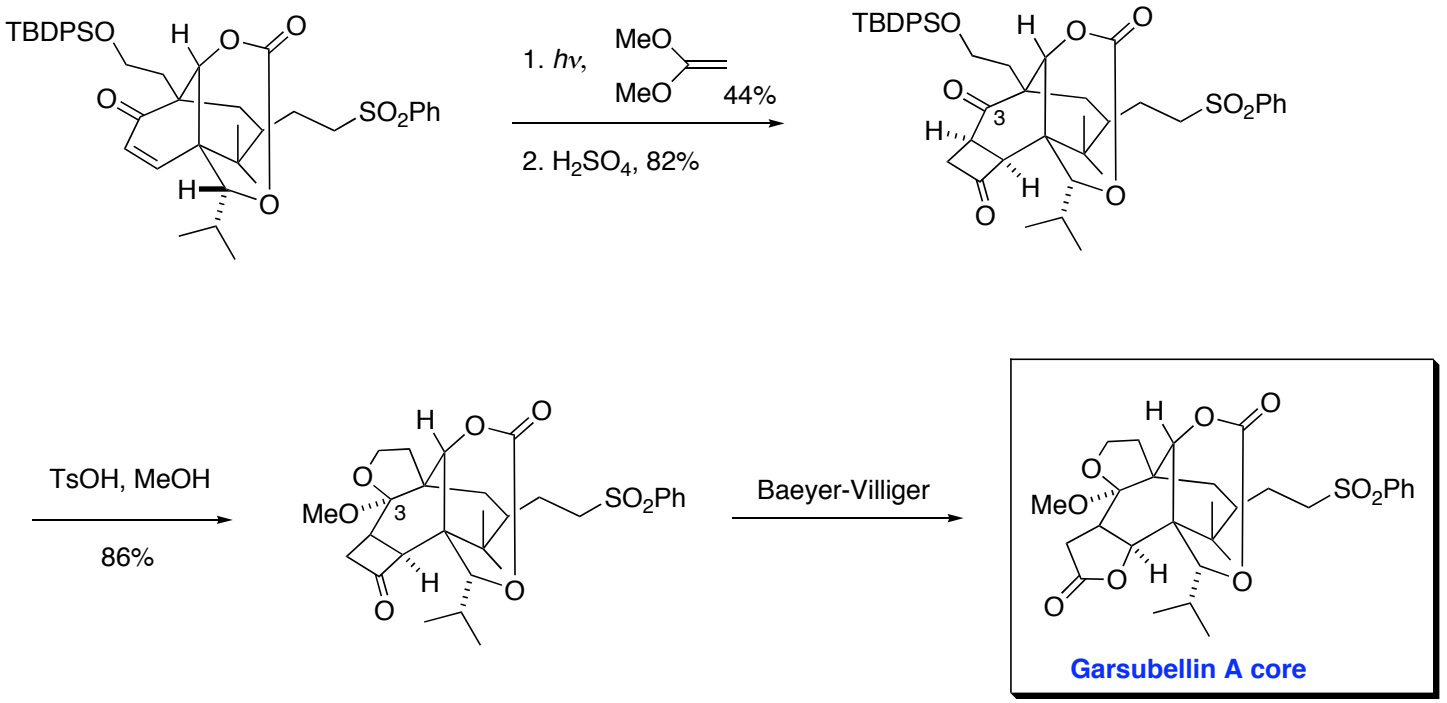
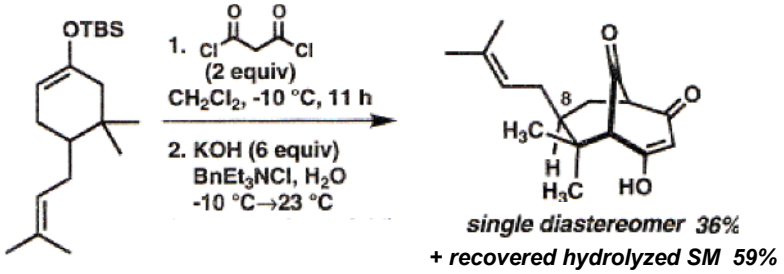
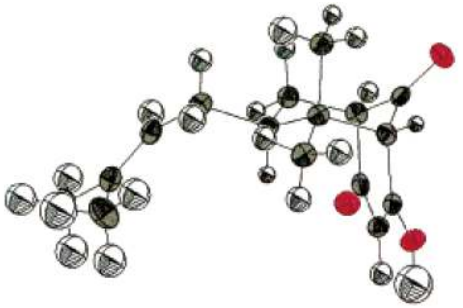


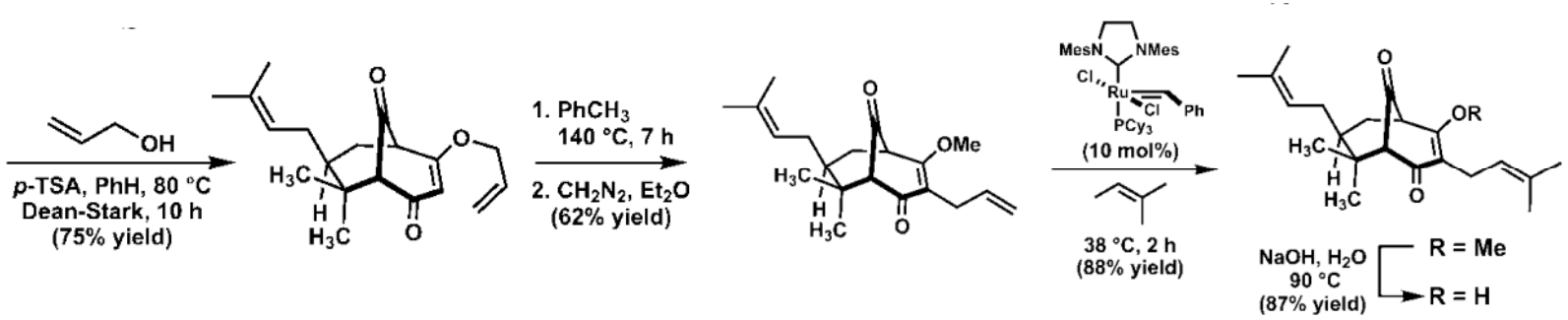
Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724

Core Syntheses of Garsubellin A

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

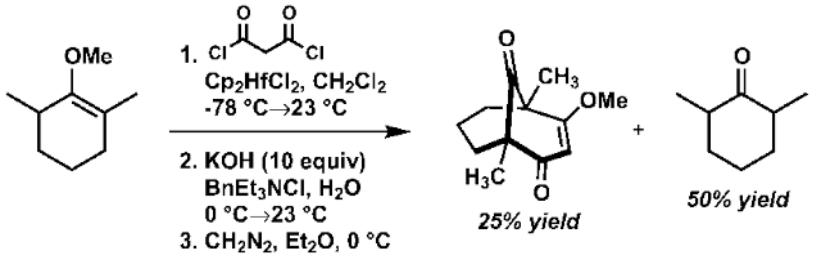






Semi-functionalized garsubellin A core

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

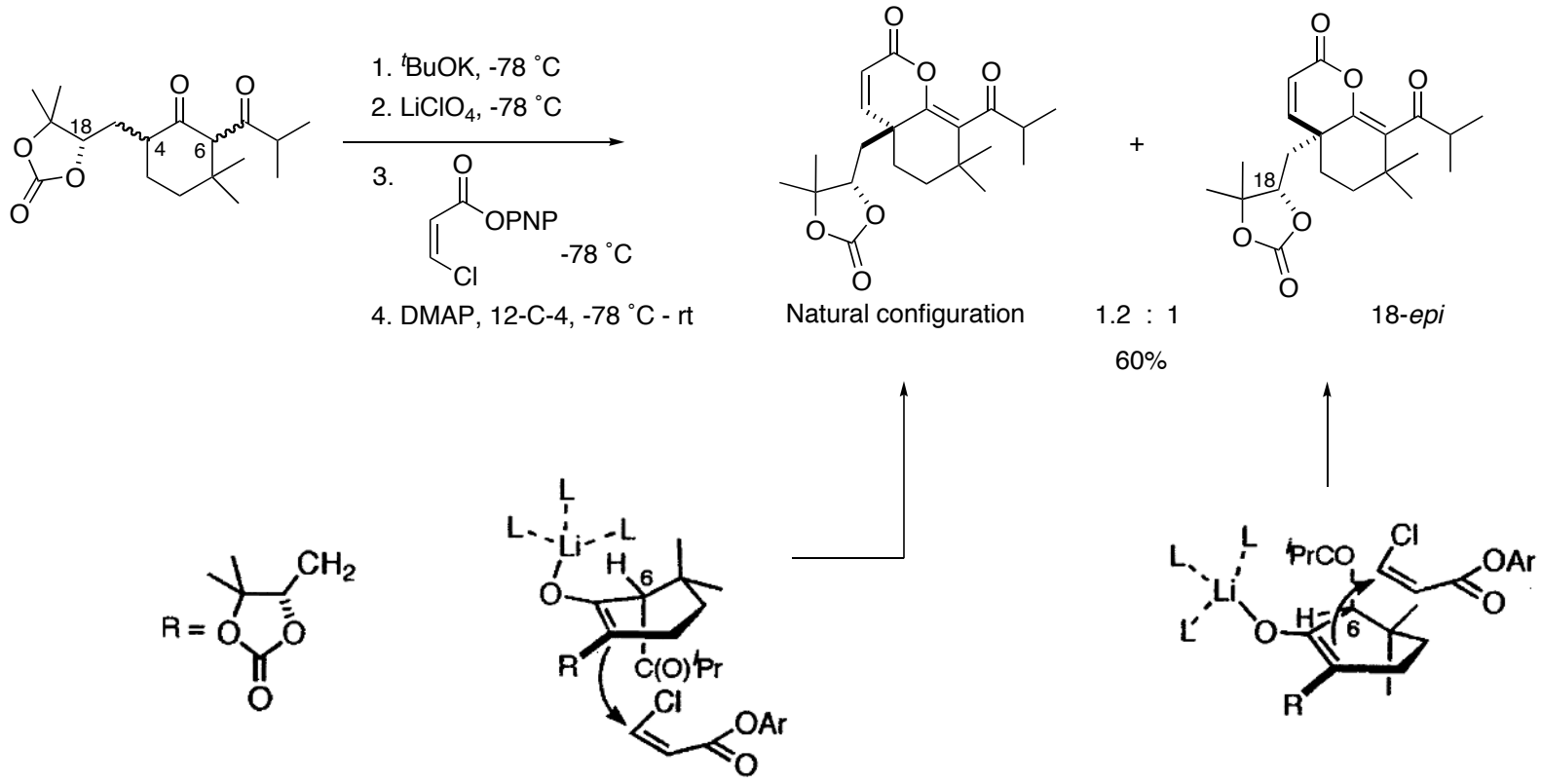


Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943

Core Syntheses of Garsubellin A

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

- One-pot lactone formation as key step



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Core Syntheses of Garsubellin A

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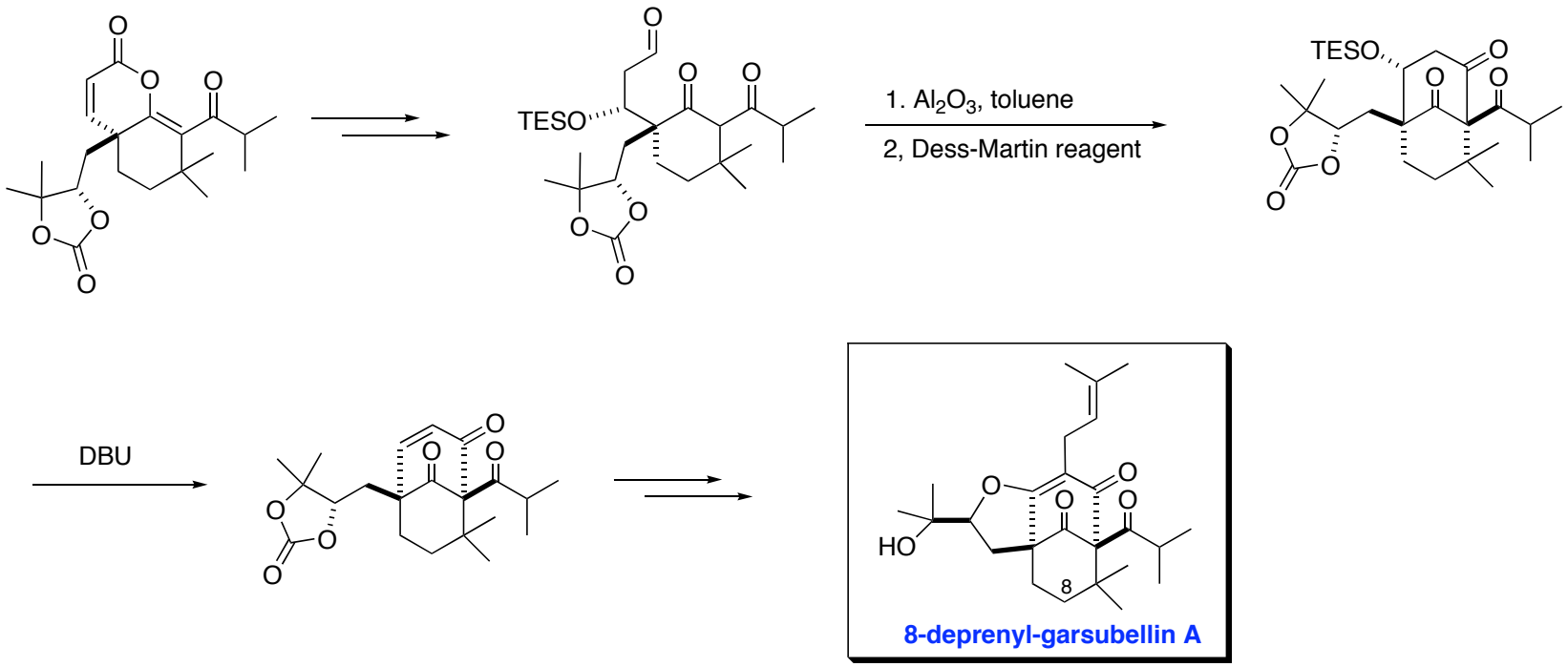

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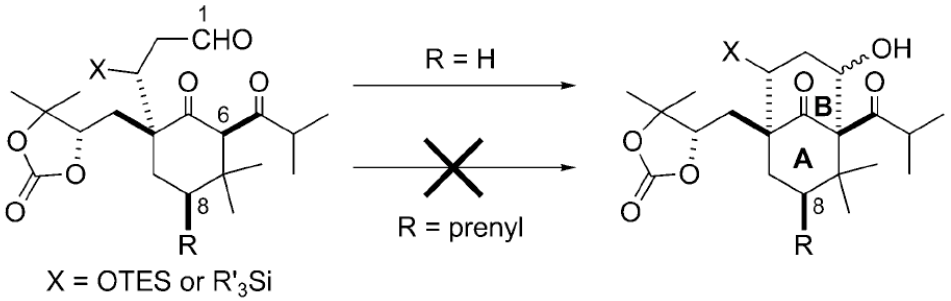
Total Synthesis of (±)-Garsubellin A
Retrosynthetic Analysis

- 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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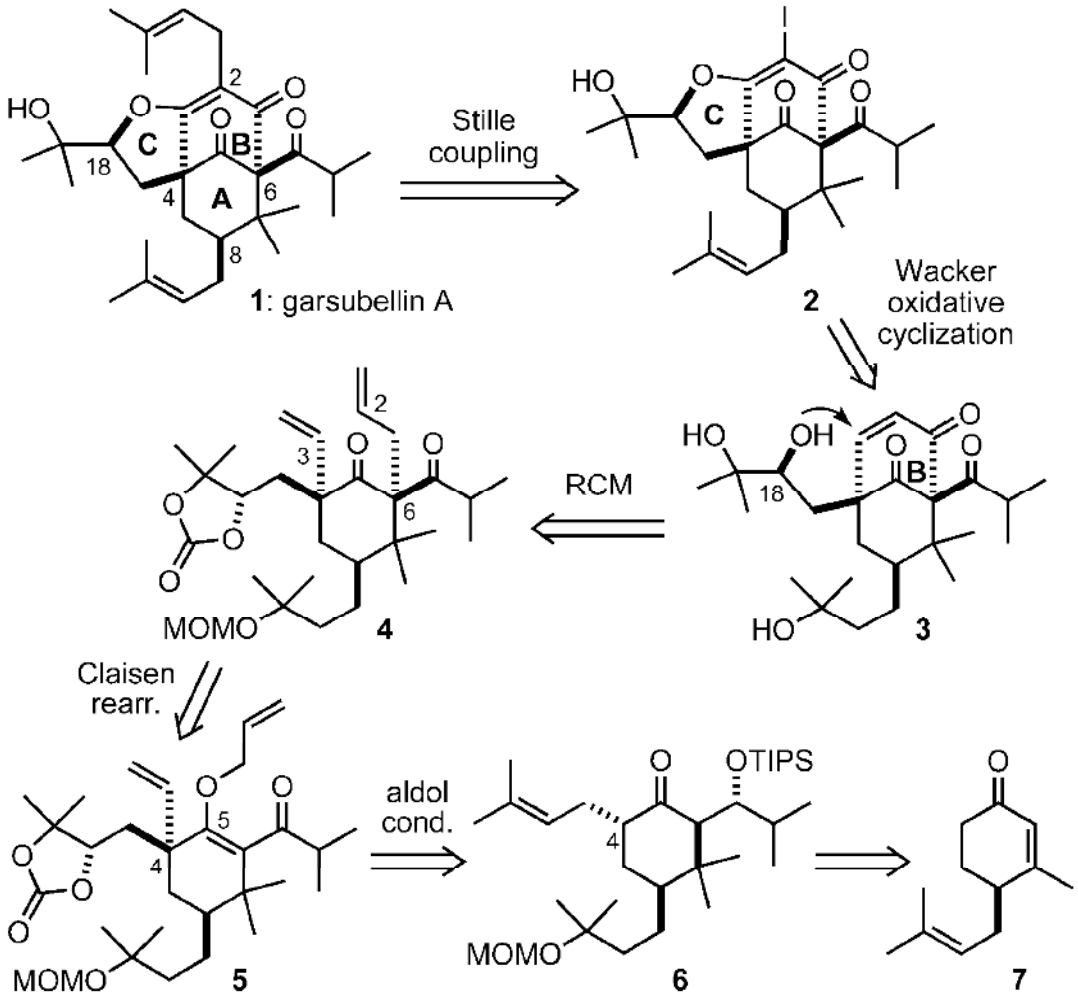

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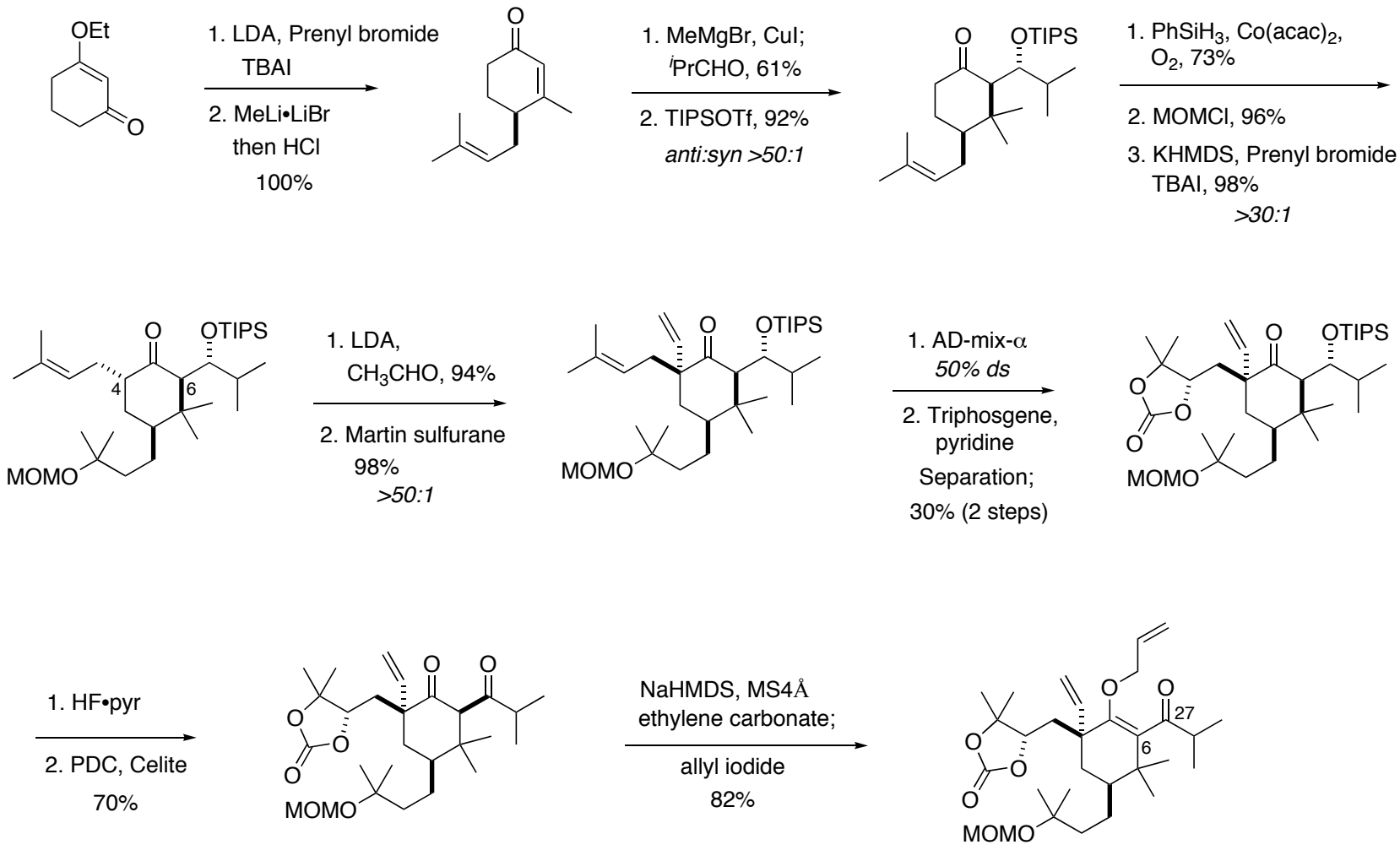

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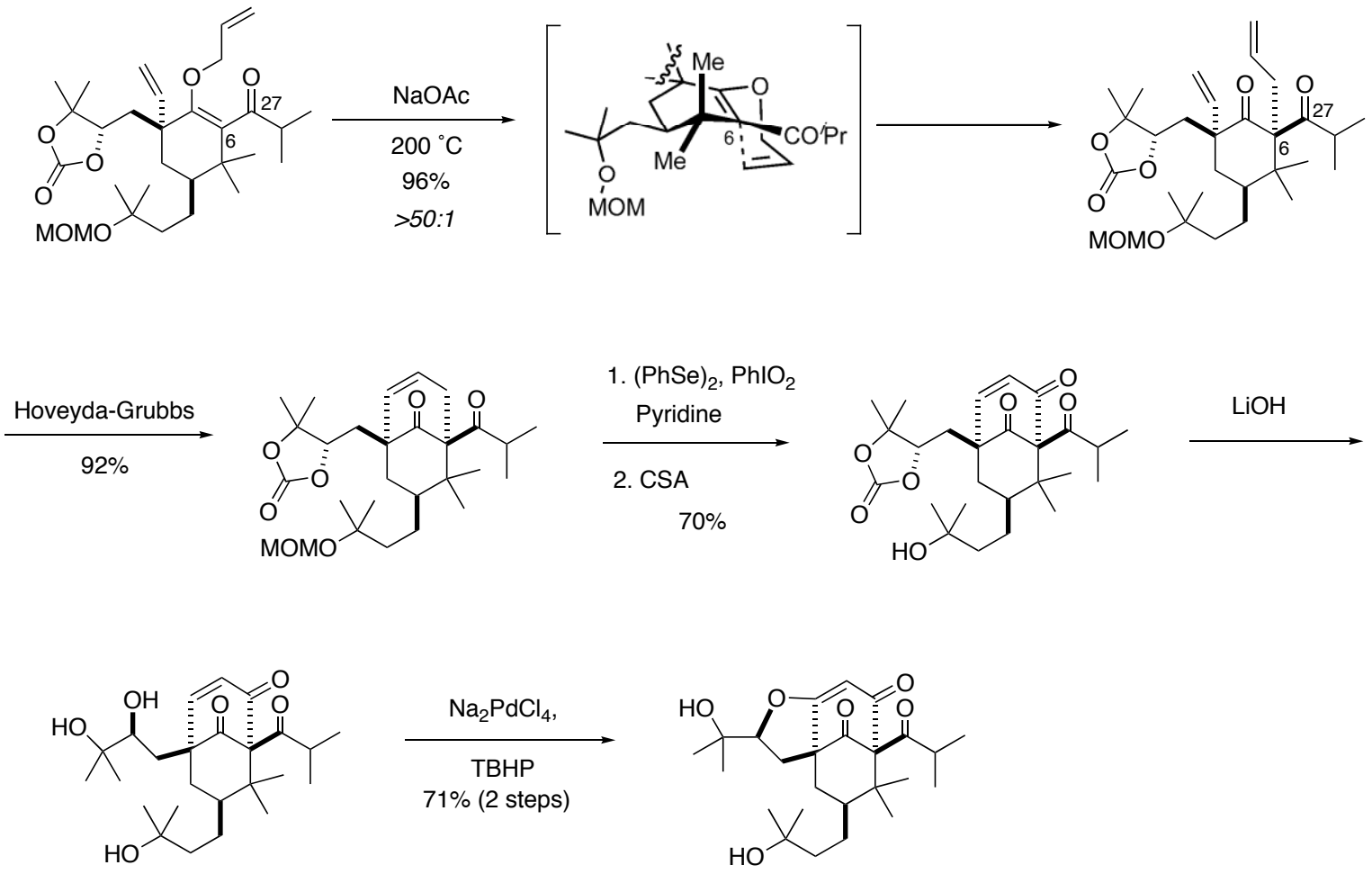

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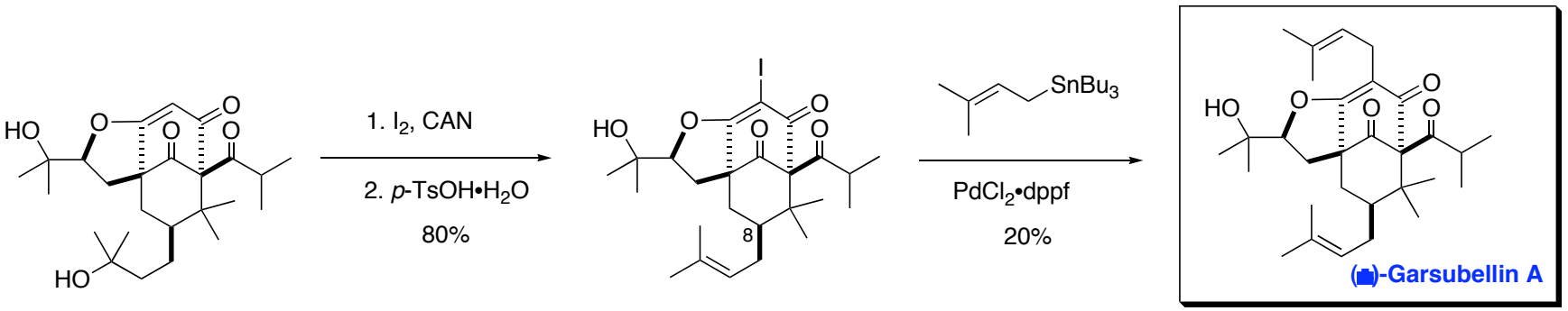
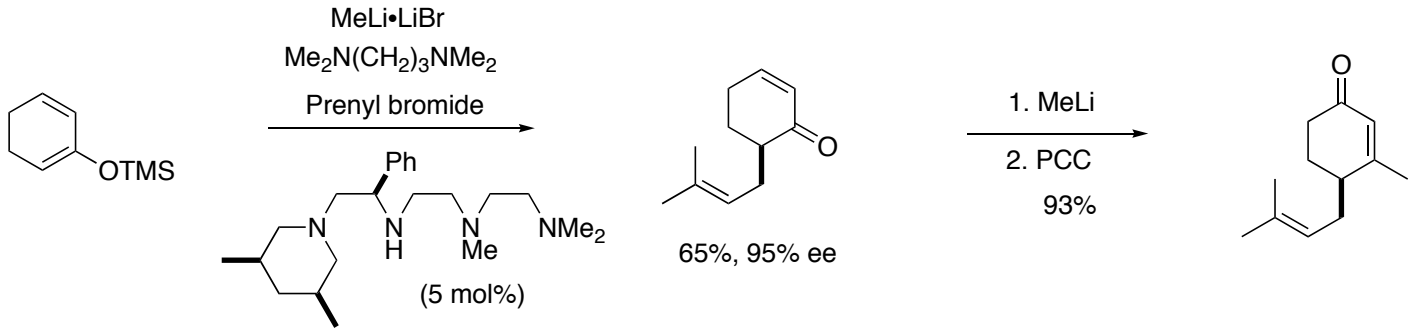


24 Steps from commercial material,
0.4% overall yield

Application of Koga Alkylation to Asymmetric Synthesis of Garsubellin A



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Summary

- The first total synthesis of (±)-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