Literature Report 2

Total Synthesis of (+)-Dalesconol A and B

Reporter: Fan-Jie Meng
Checker: Bo Song
Date: 2017-05-02

Zhao, G.; Xu, G.; Qian, C.; Tang, W. *J. Am. Chem. Soc.* **2017**, *139*, 3360.

CV of Wenjun Tang

Education:

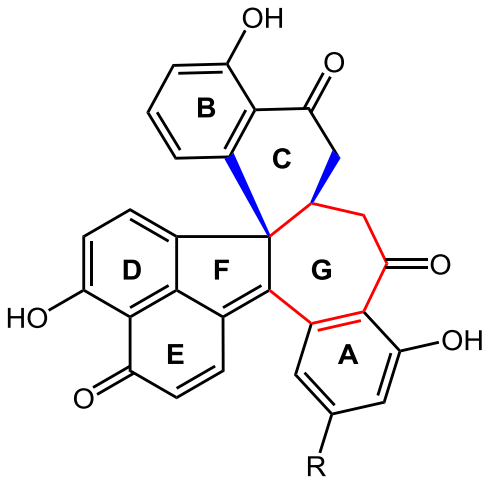
- 1991–1995 B. Eng., East China University of Sciences and Technology
- 1995–1998 M.S., Shanghai Institute of Organic Chemistry
- 1998–2003 Ph.D., The Pennsylvania State University
- 2003–2005 Postdoc., The Scripps Research Institute

Research:

- Design and development of novel, efficient, and practical chiral catalytic reactions
- Total synthesis of complex and biologically active natural products
- Development of efficient, economical, and green chemical processes for pharmaceutically important molecules

Contents

Dalesconol

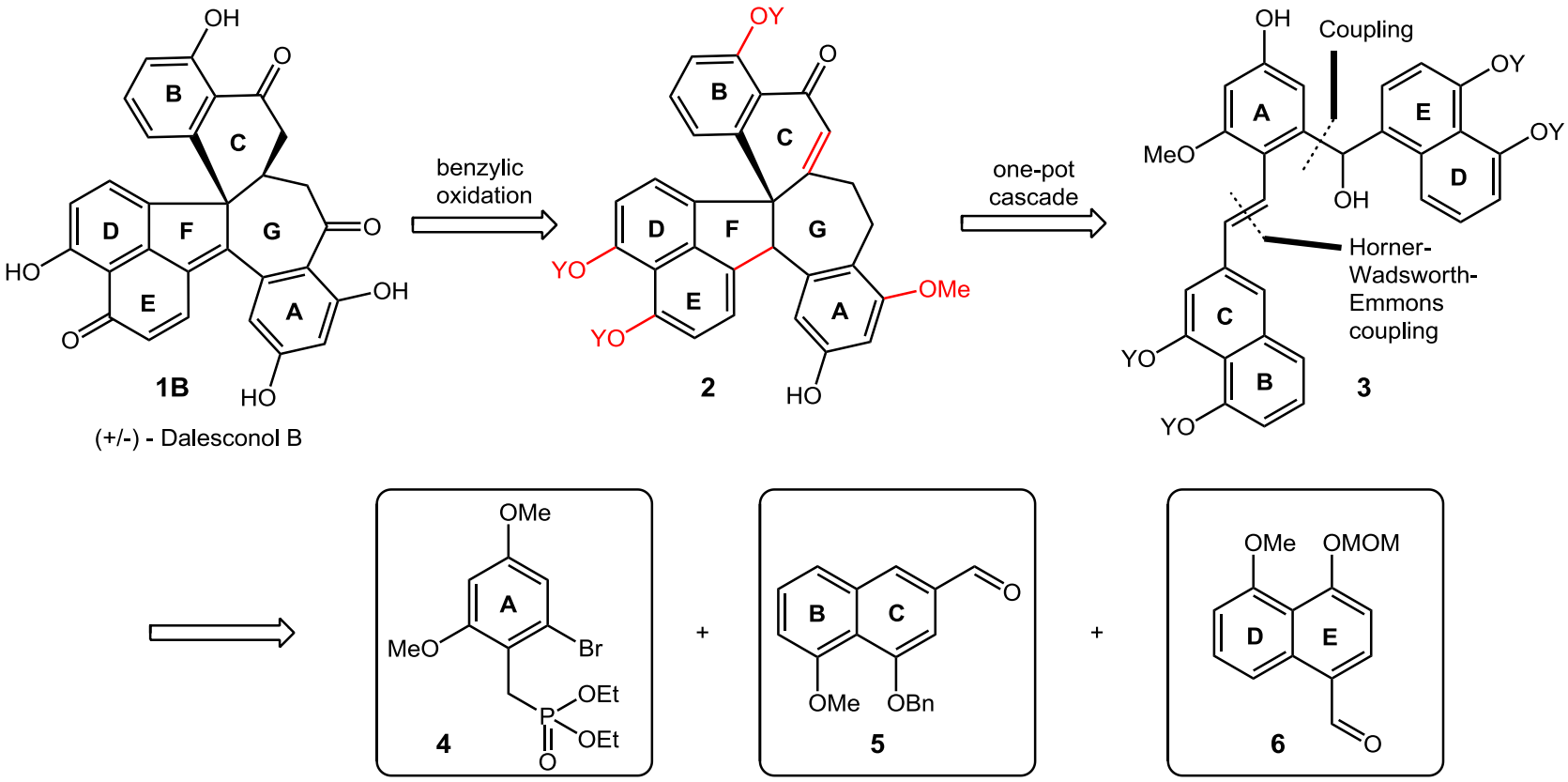


1: R = H, (+)-Dalesconol A
2: R = OH, (+)-Dalesconol B

Characters:

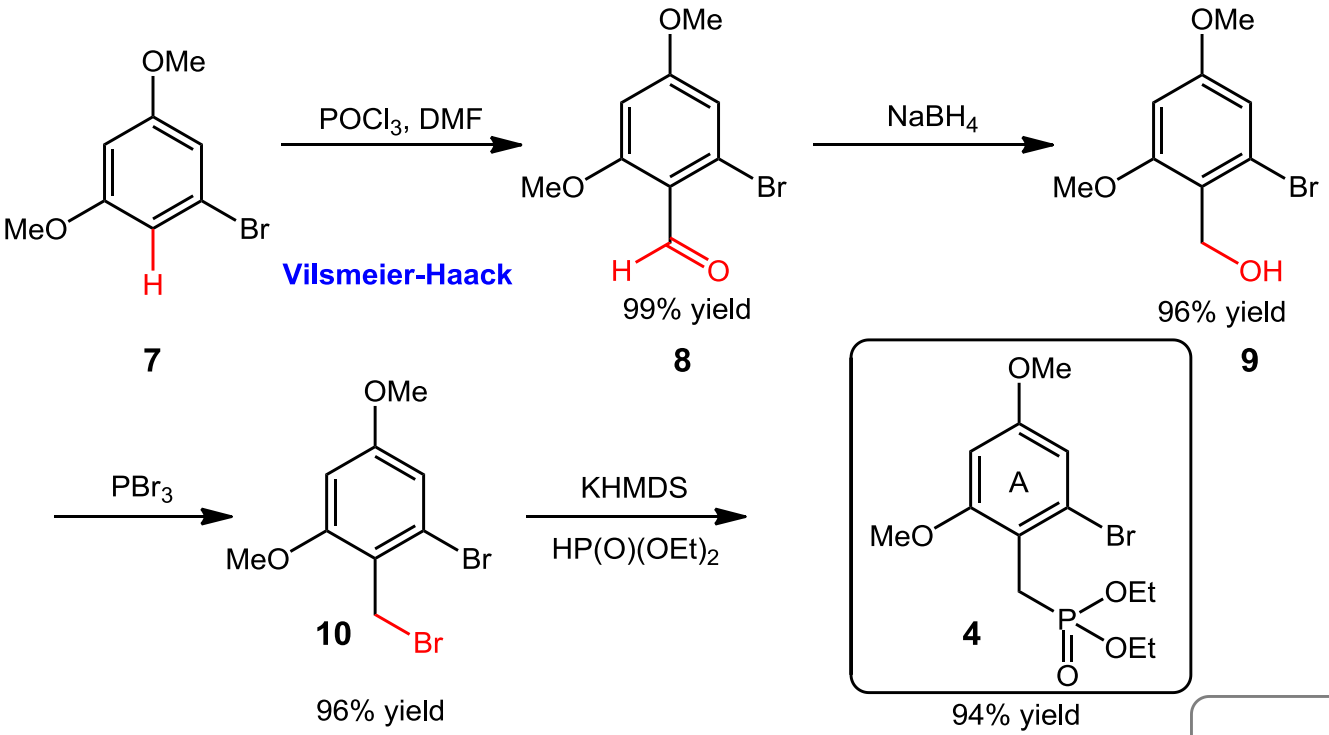
- Seven fused rings of various sizes
- Two stereogenic centers including one sterically congested all-carbon quaternary center
- Dalesconol exhibited strong inhibition of acetylcholine esterase, Dalesconol A (IC_{50} = 0.16 μg/mL^{-1}, SI > 500) and B (IC_{50} = 0.25 μg/mL^{-1}, SI > 320)
- Both compounds showed modest antitumor activities

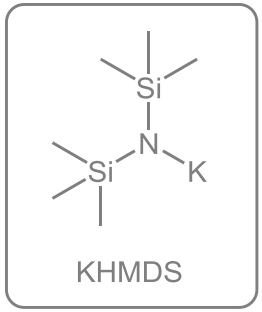
Total Synthesis of Dalesconol B by Snyder



Snyder, S. A.; Sherwood, T. C.; Ross, A. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 5146.

Total Synthesis of Dalesconol B by Snyder





Vilsmeier, A.; Haack, A. *Chem. Ber.* **1937,** *60*,119.

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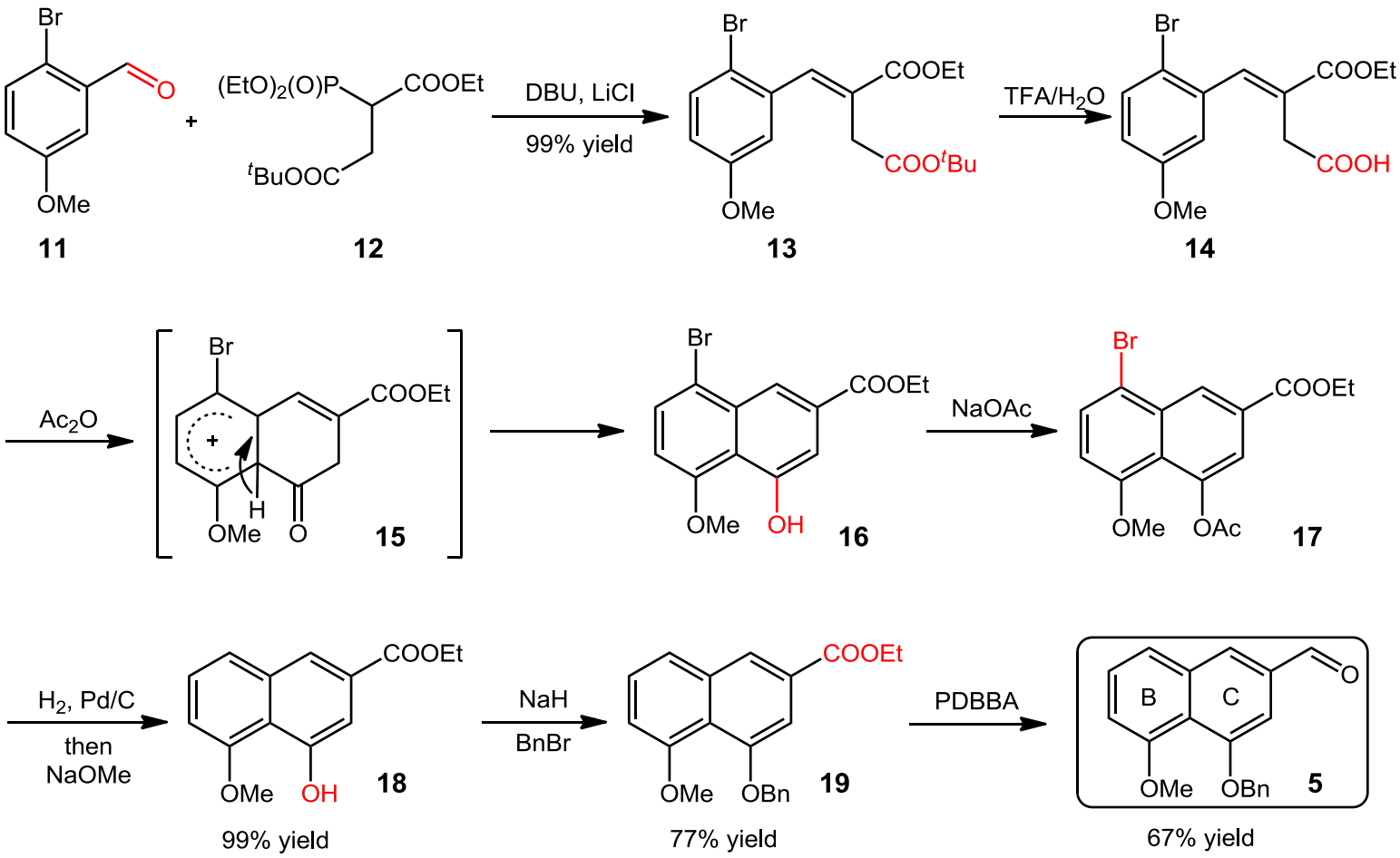

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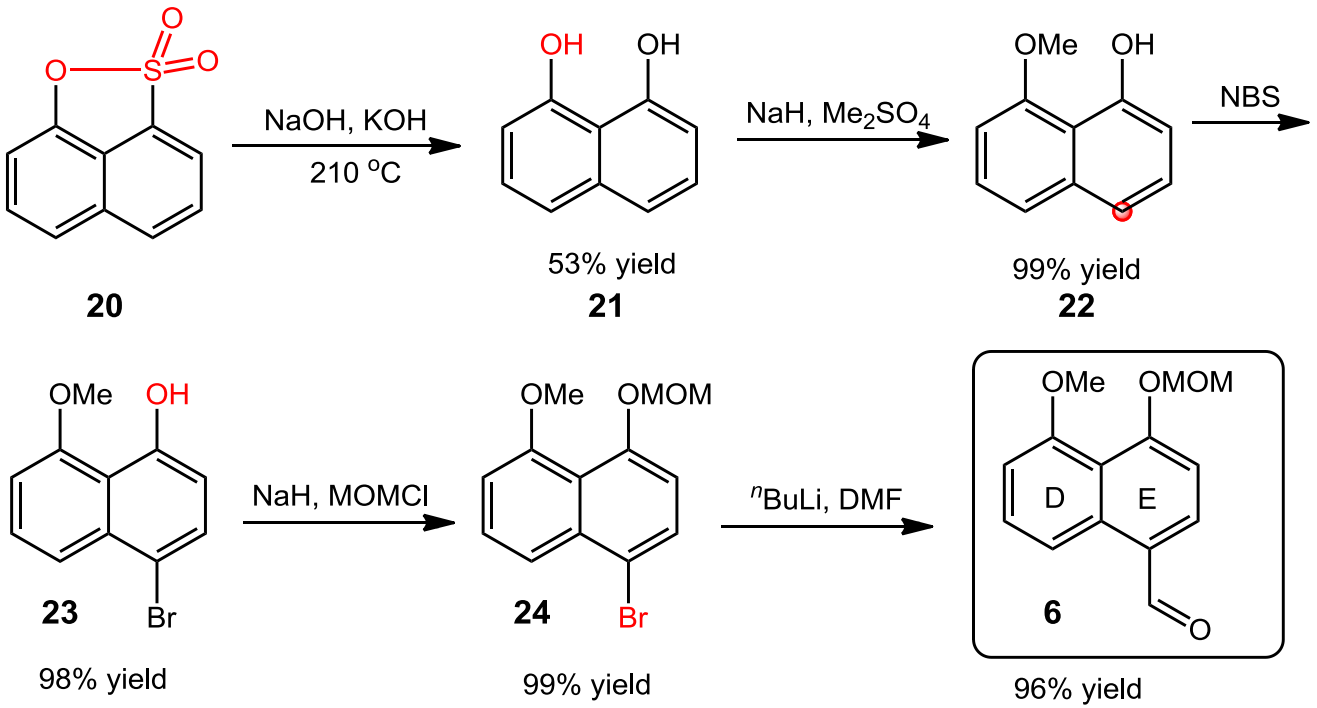

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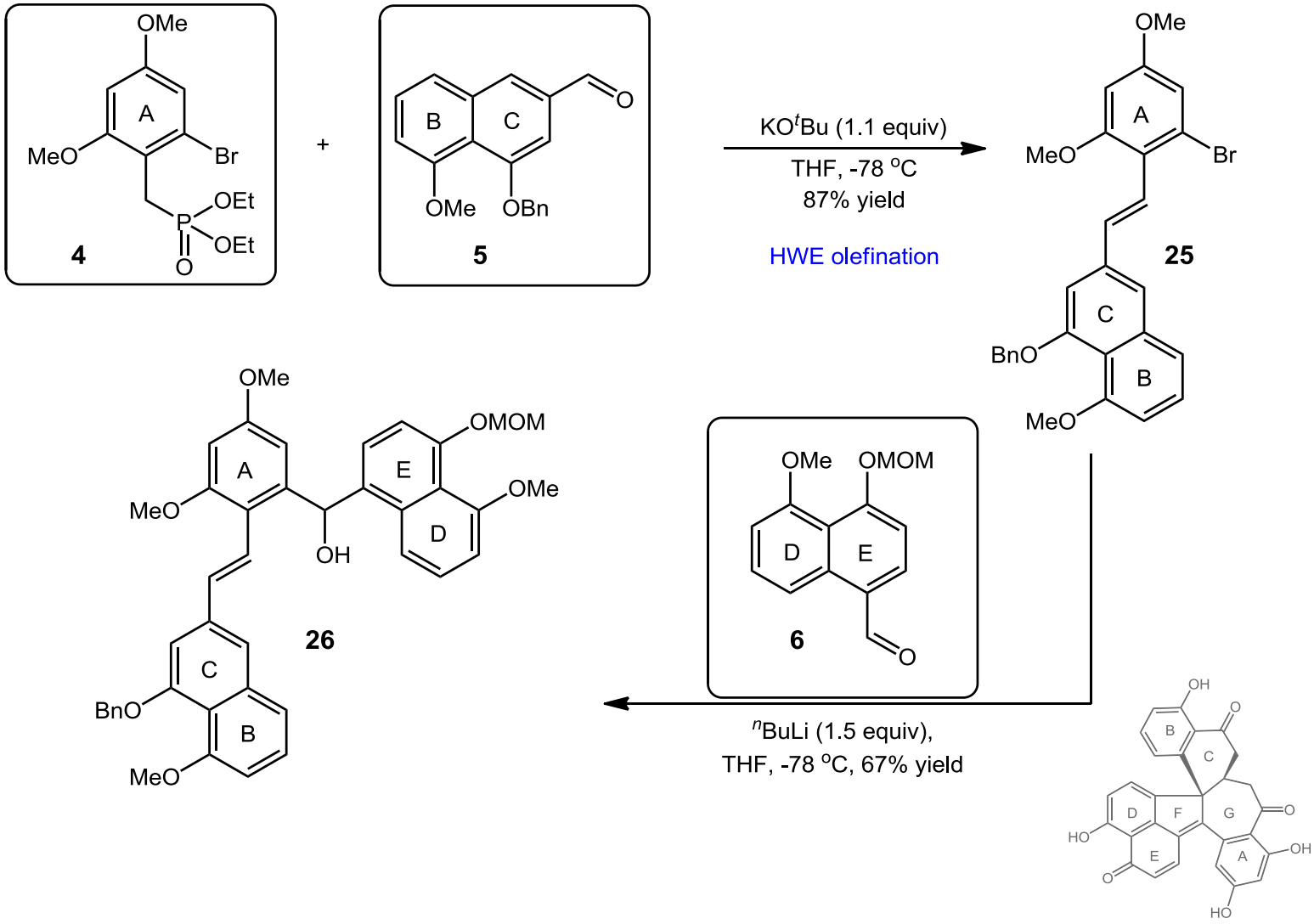

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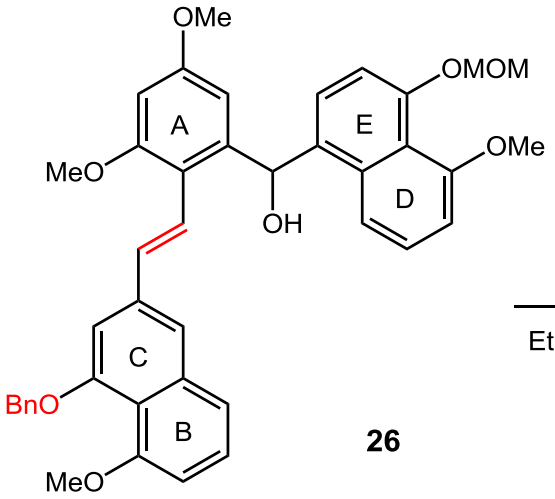

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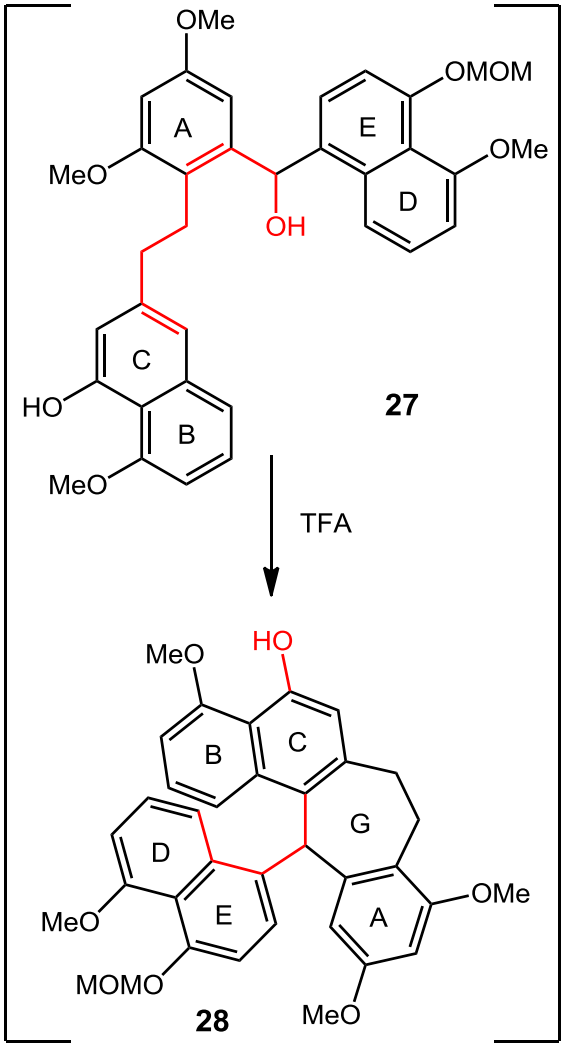
H_2, Pd/C

EtOAc/EtOH (2/3)



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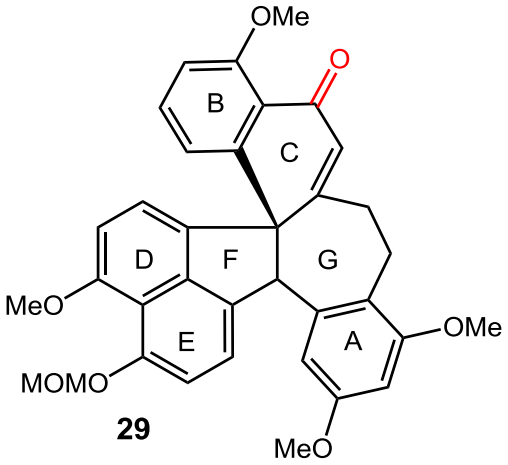
$PhI(OAc)_2$



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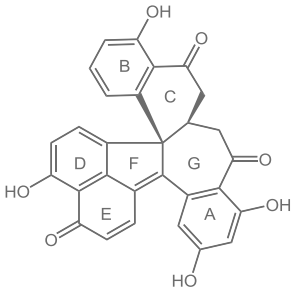

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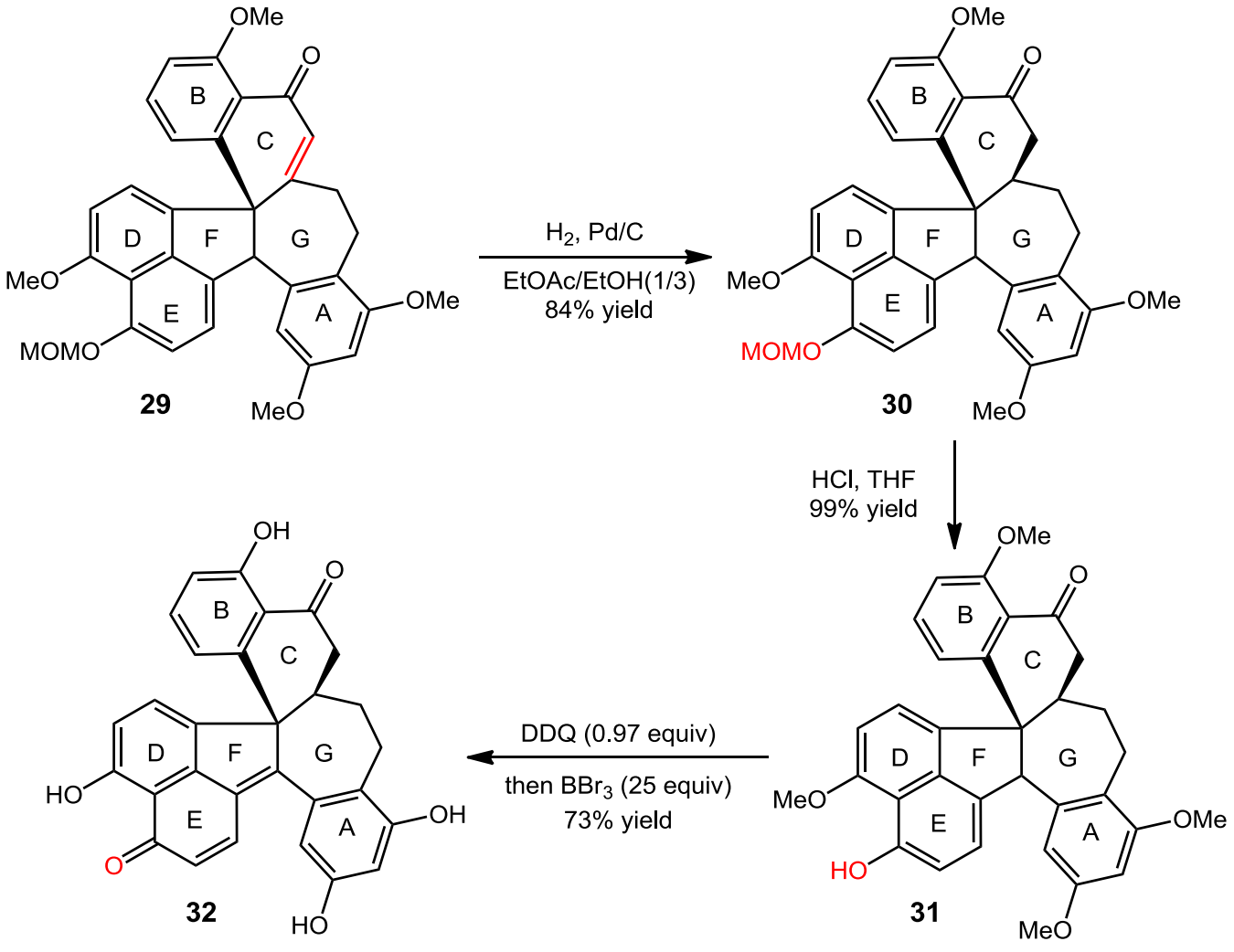

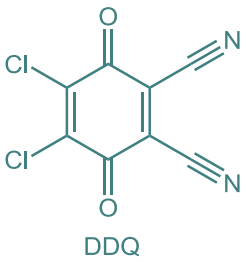

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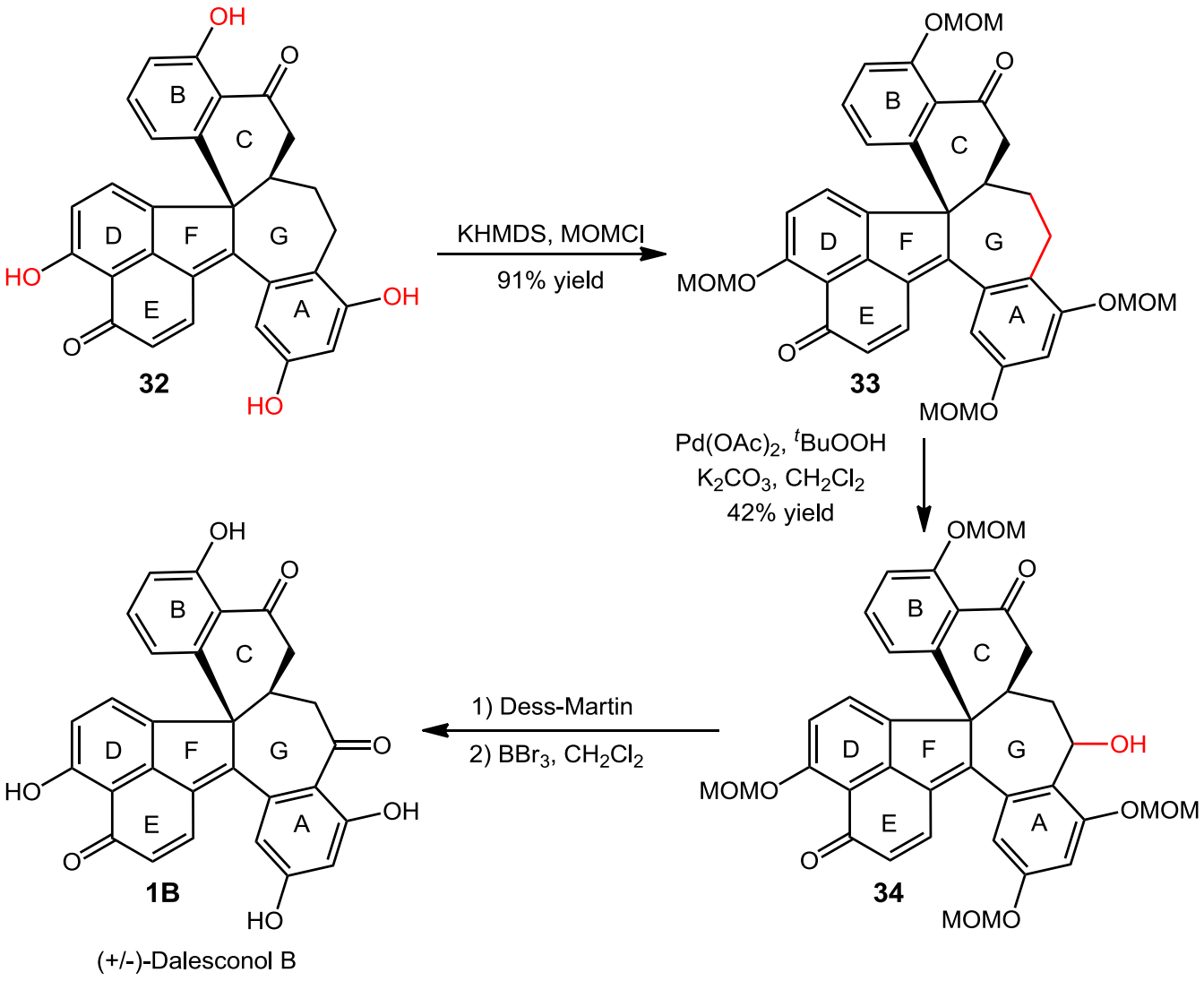
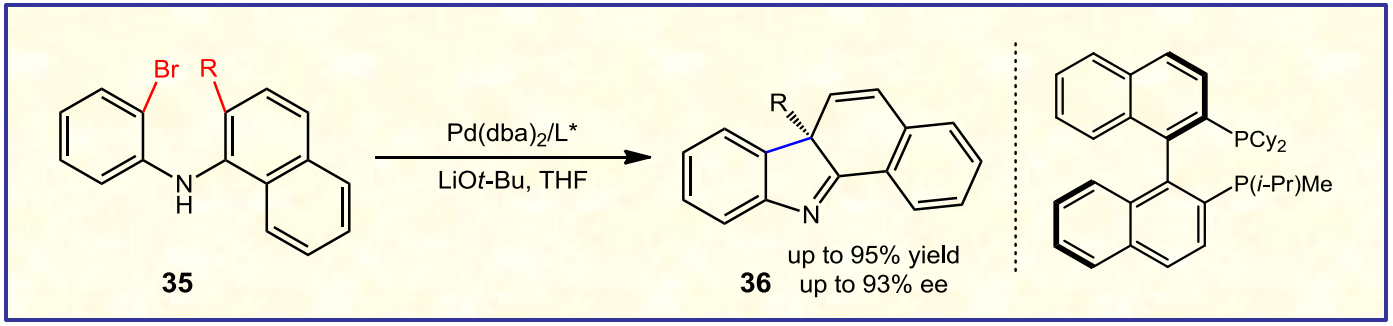
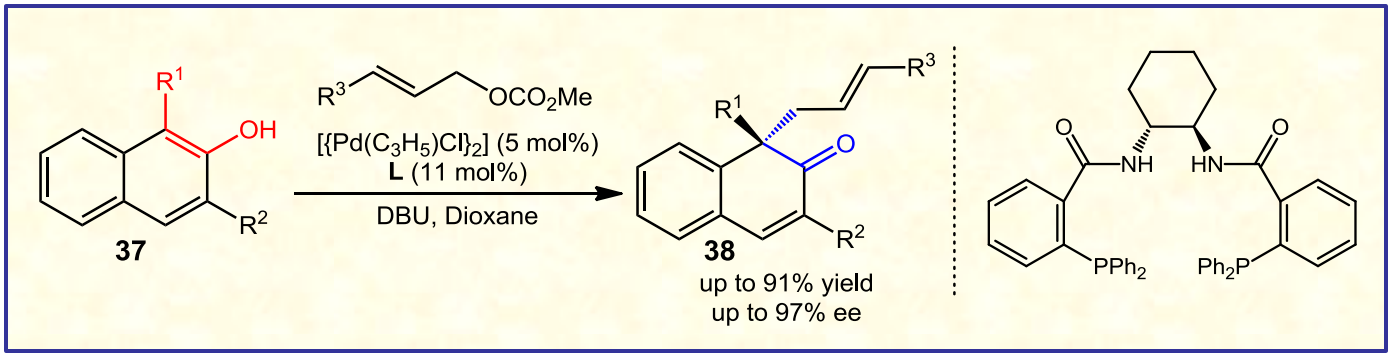


Asymmetric Dearomative Cyclization

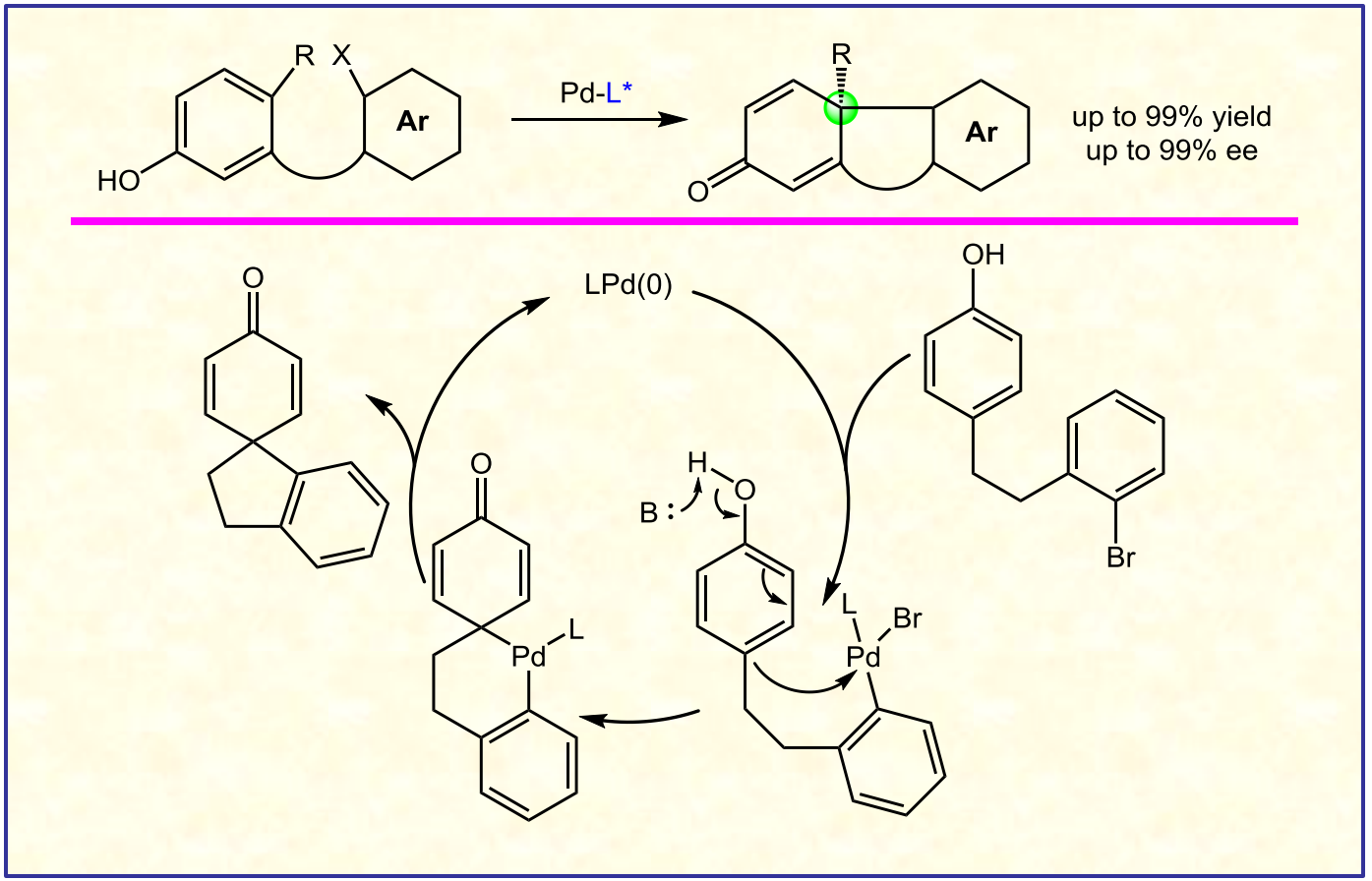


García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6676.



Zhuo, C. X.; You, S.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 10056.

Asymmetric Dearomative Cyclization



Rousseaux, S.; Garcia-Fortanet, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282.

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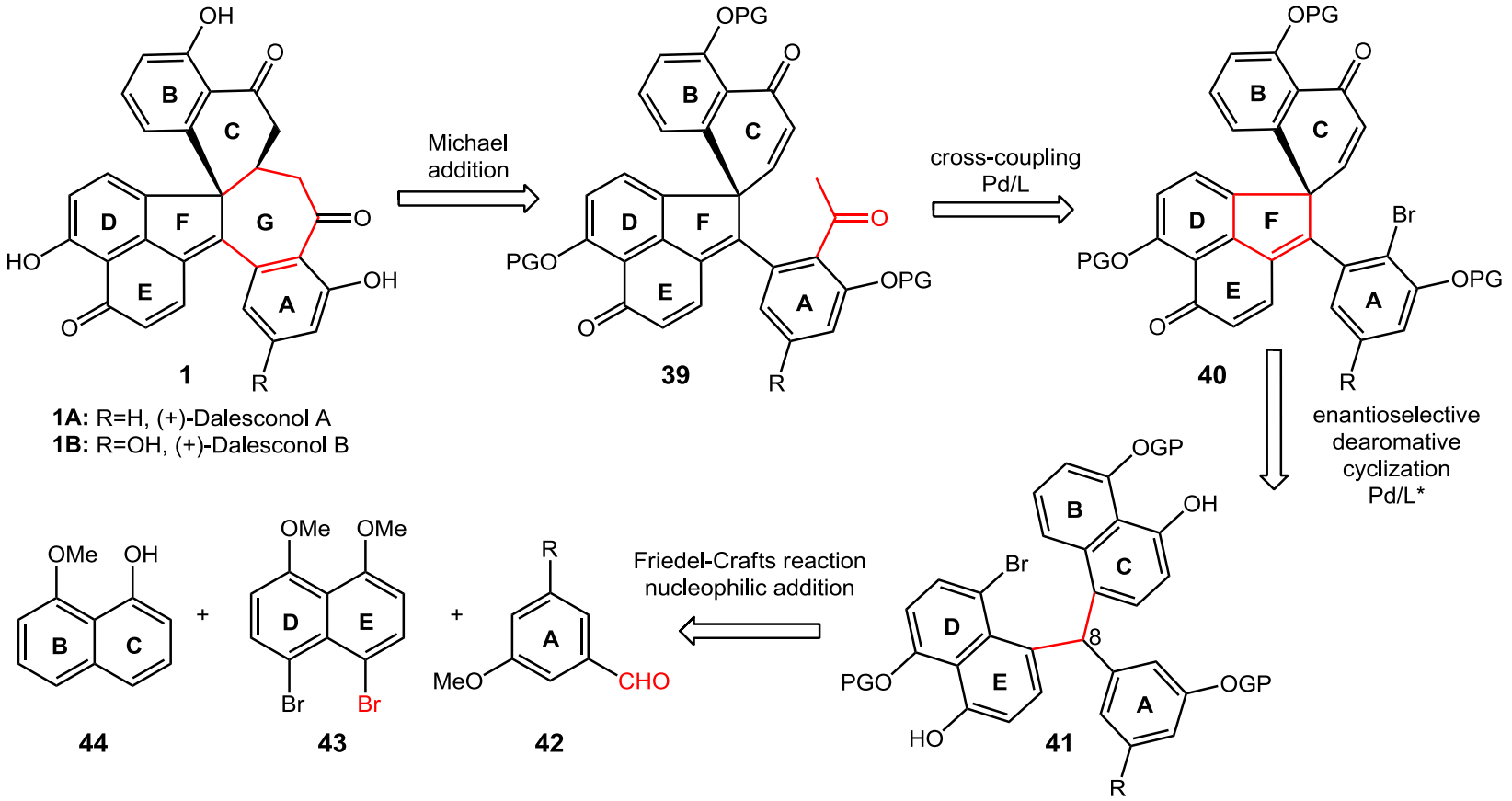
Retrosynthesis of (+)-Dalesconol



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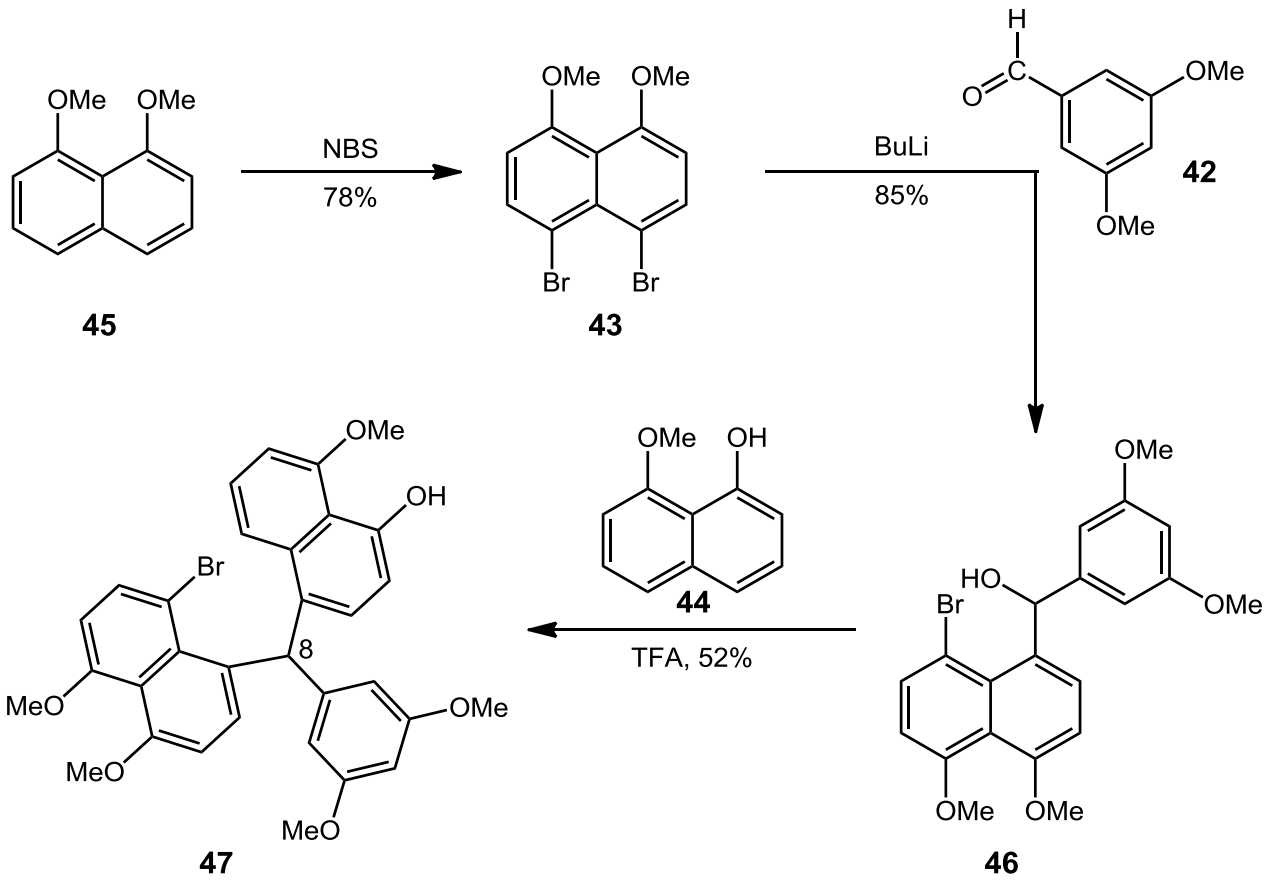

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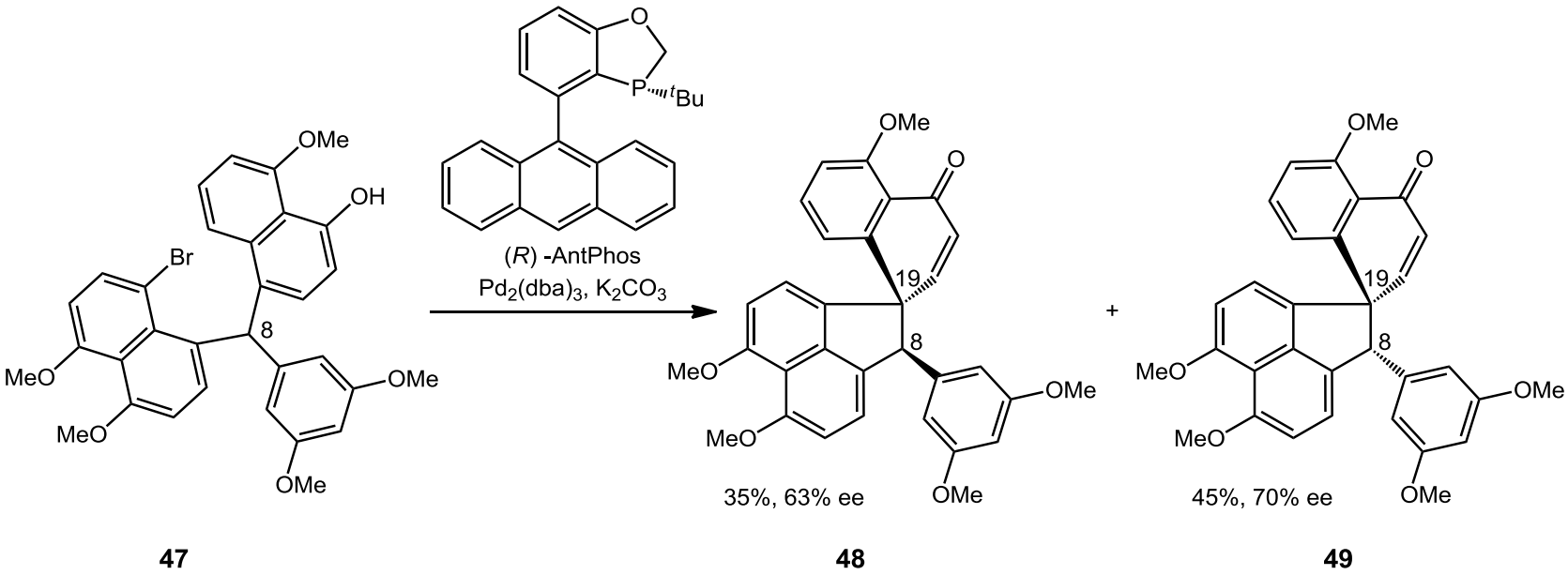

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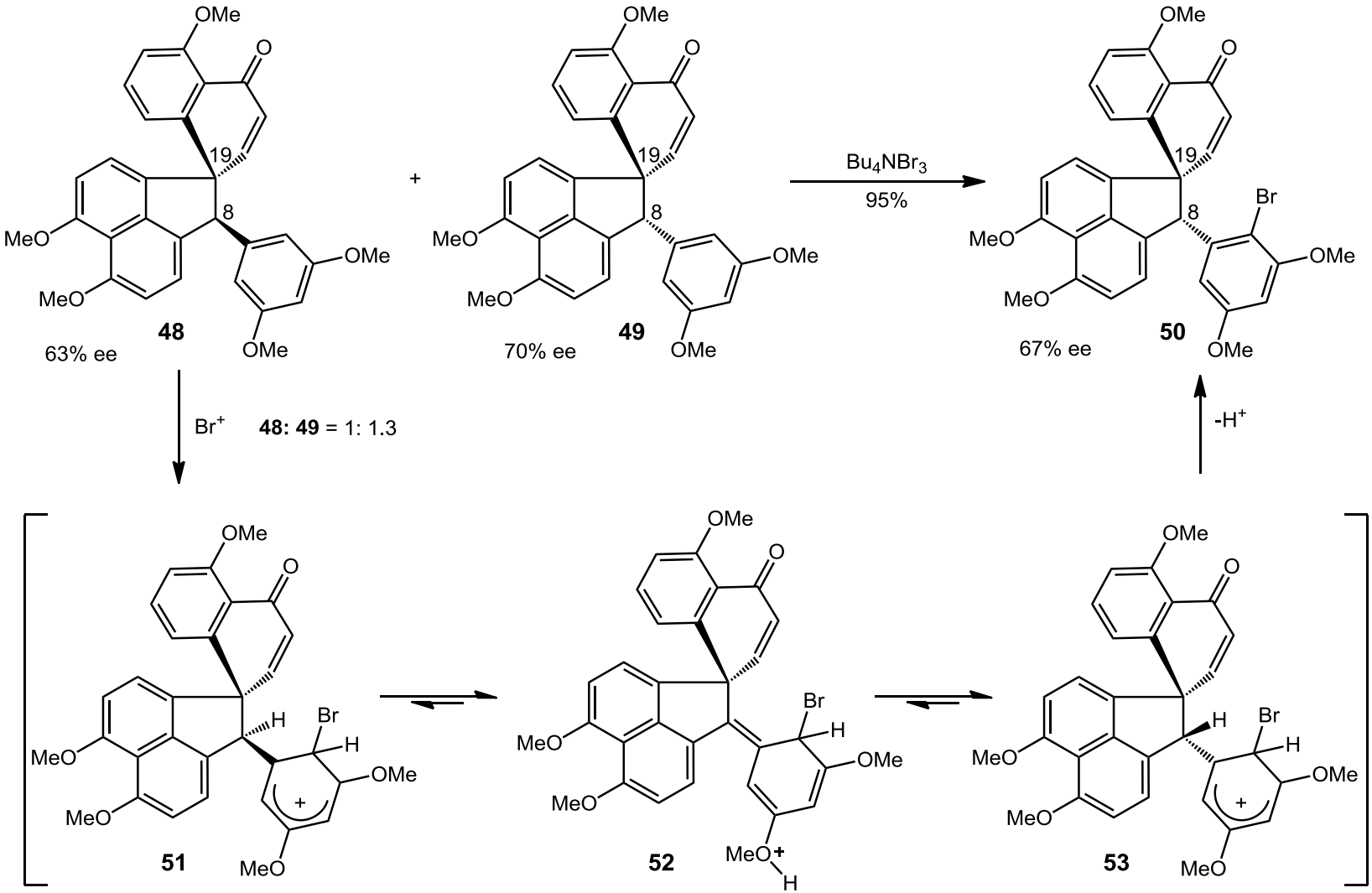
Total Synthesis of (+)-Dalesconol B by Tang



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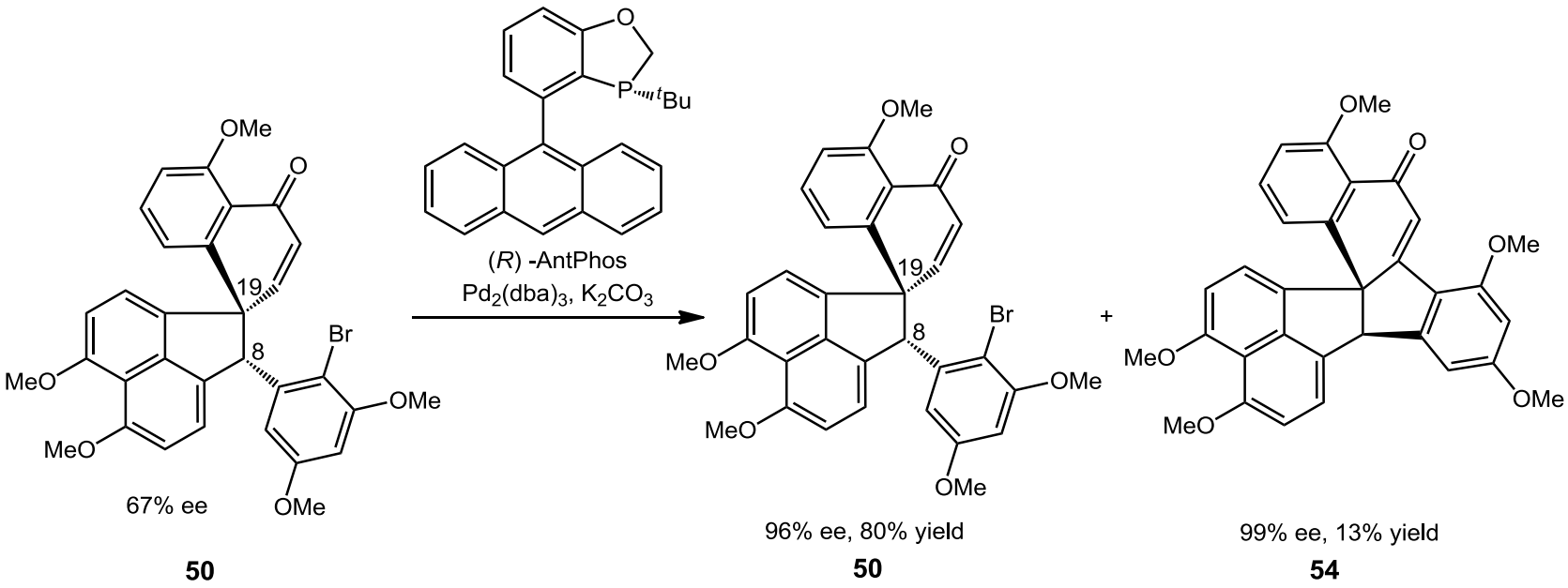

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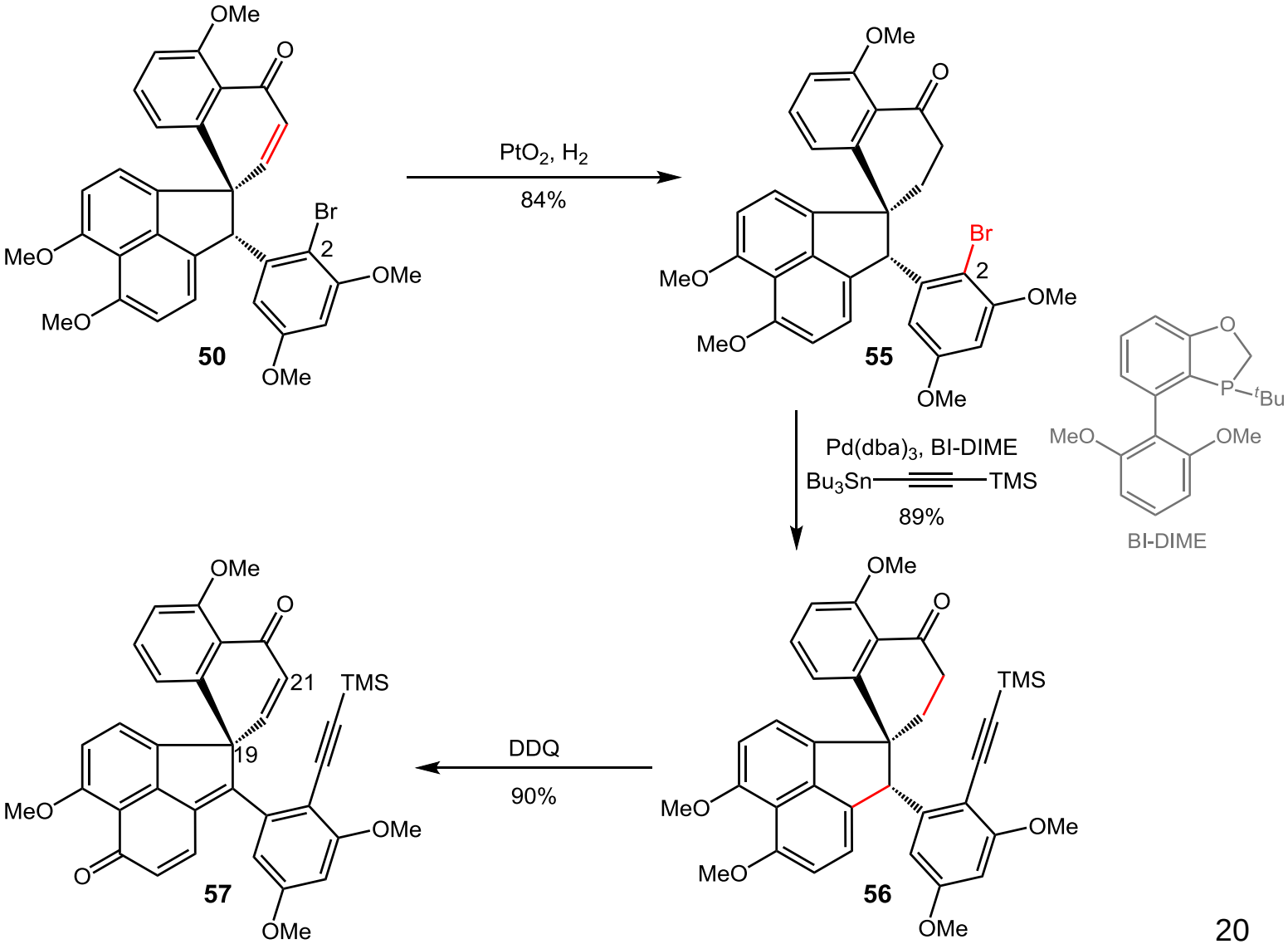

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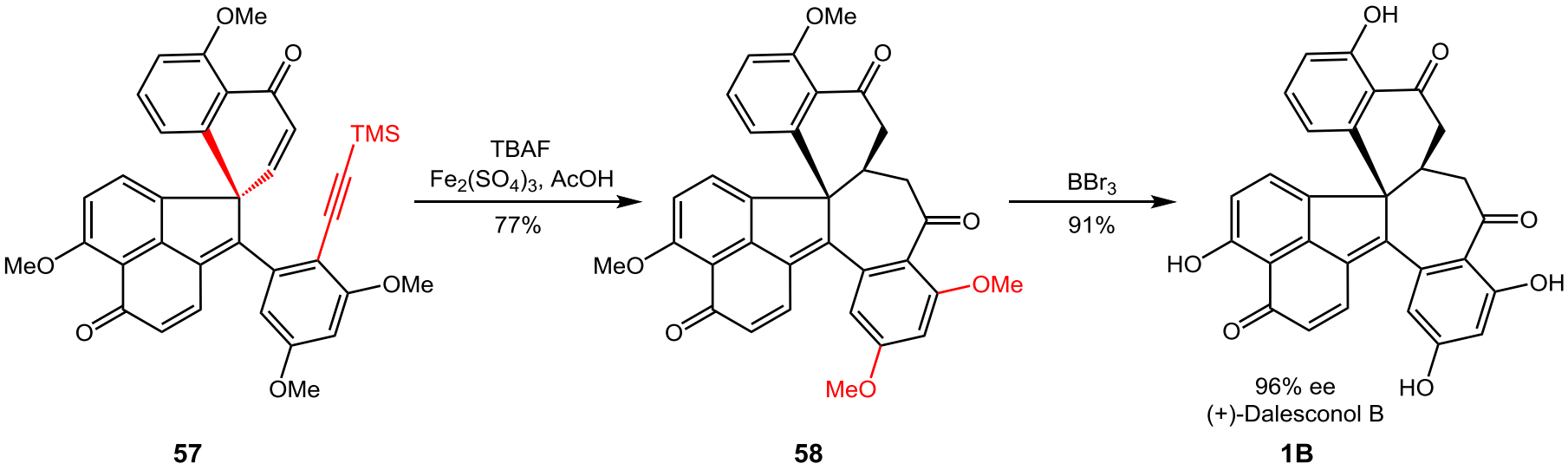

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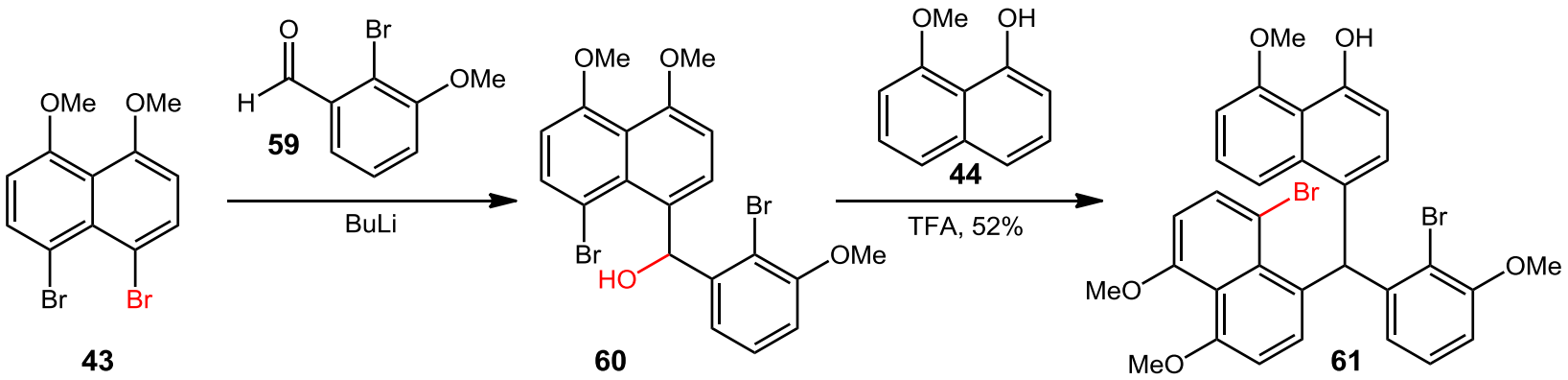
Total Synthesis of (+)-Dalesconol A by Tang



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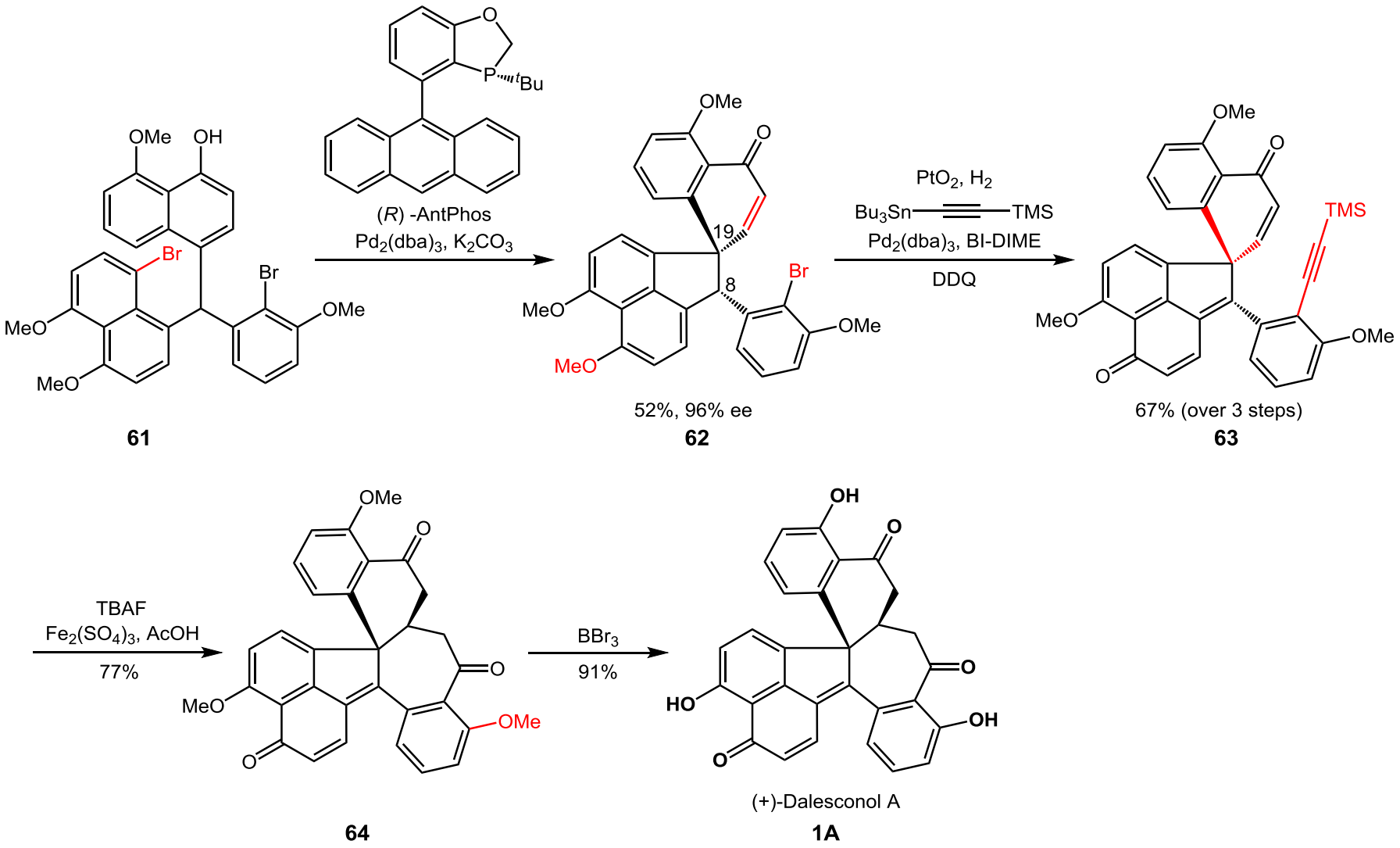
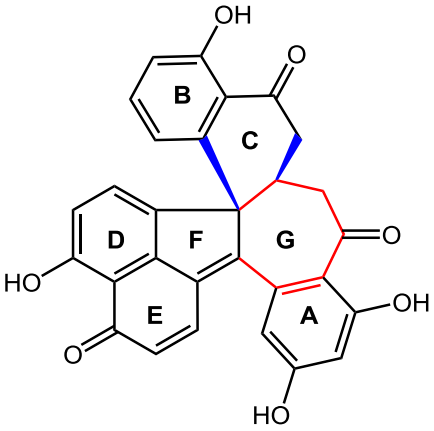


Summary



(±)-Dalesconol B

- **15 Steps, 1.3 % overall yield**
- **The first total synthesis of Dalesconol**
- **Tandem Friedel–Crafts/oxidation ring closure**
- **Benzylic oxidation**

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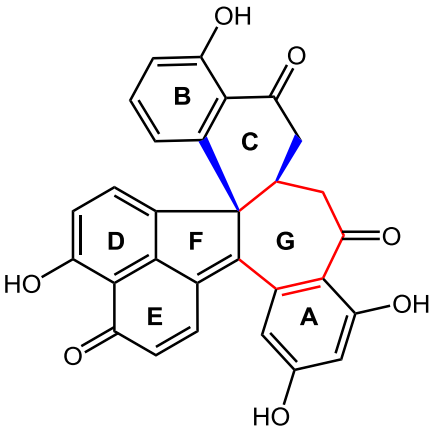

(+)-Dalesconol B

- **11 Steps, 9.9 % overall yield (Dalesconol B)**
- **9 Steps, 10.6 % overall yield (Dalesconol A)**
- **The first enantioselective synthesis of Dalesconol**
- **Palladium-catalyzed dearomative cyclization−kinetic resolution cascade**
- **Tandem hydrolysis−Michael addition ring closure**

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The First Paragraph

Initially isolated by Tan and co-workers in 2008 from mantisassociated fungus Daldinia Eschscholzii, Dalesconol A and B are two unusual polyketides that exhibit strong immuno-suppressive activities comparable to that of clinically used cyclosporine A，but with superior selective index values for their noncytotoxic nature. Interestingly, both natural dalesconol A and B are scalemic mixtures with an excess of their (−)-enantiomers, a consequence dictated by laccase during the atropselective coupling of naphthol radicals in their biosynthesis. Intriguingly, both scalemic mixtures of natural dalesconol A and B provided more potent immunosuppressive activities than their enantiomers. Structurally, dalesconol A and B possess an architecturally unique and highly dense carbon skeleton containing seven fused rings of various sizes and two stereogenic centers including one sterically congested all-carbon quaternary center.

The First Paragraph

The only total syntheses of racemic dalesconol A and B were accomplished beautifully by Snyder and co-workers by employing a key one-pot cationic cyclization−intramolecular oxidative coupling cascade through a sequence of 15 linear steps and 25 overall steps. An efficient enantioselective syntheses of dalesconol A and B would not only help provide ample optically pure samples for further elucidation of their biological mechanism but also provide valuable analogs for discovering new immunosuppressants. Herein we report the concise and first enantioselective syntheses of (+)-dalesconol A and B.

The Last Paragraph

In conclusion, we have accomplished the first enantioselective syntheses of immunosuppressants (+)-dalesconol A and B in a highly efficient and concise manner, which features an unprecedented enantioselective palladium-catalyzed dearomative cyclization−kinetic resolution cascade to install the sterically congested chiral all-carbon quaternary center, an effective sterically hindered Stille coupling, a powerful DDQ oxidation to furnish all requisite unsaturation, and a tandem hydrolysis−Michael addition ring closure sequence. Both Dalesconol A and B can be prepared within 9 steps from commercially available starting materials with a scalable synthetic route, which should facilitate the discovery and the development of new immunosuppressants.

Acknowledgment

Thanks For Your Kind Attention !