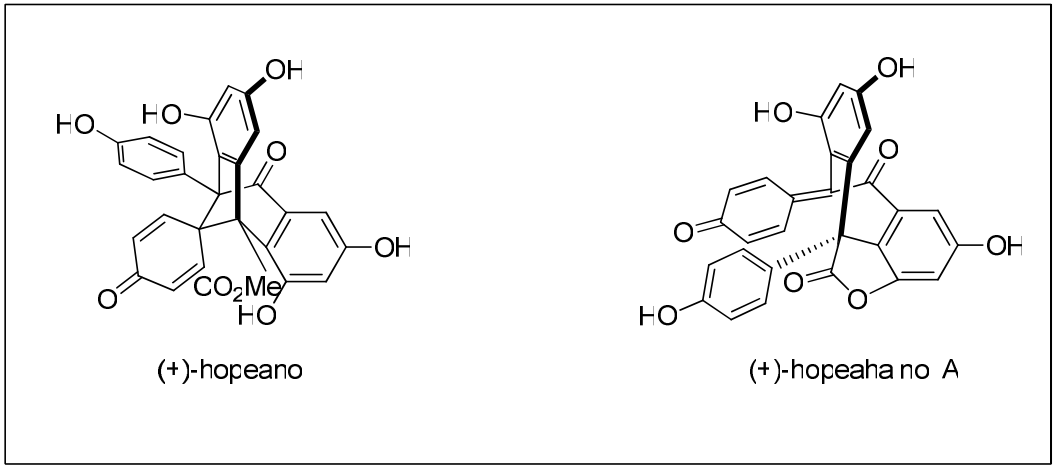
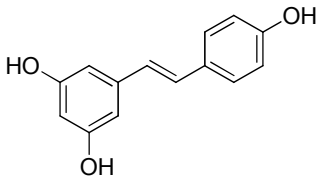
Total Synthesis and Biological Evaluation of the Resveratrol-Derived Polyphenol Natural Products Hopeanol and Hopeahainol A

Nicolaou, K. C.; Kang, Q.; Wu, T. R.; Lim, C. S.; Chen, D. Y.-K.
J. Am. Chem. Soc. ASAP, DOI: 10.1021/ja102623j

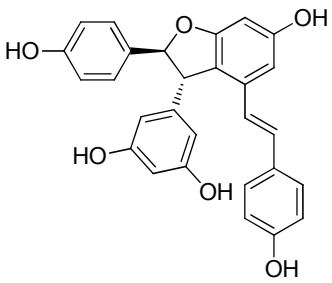


Resveratrol and Related Natural Products

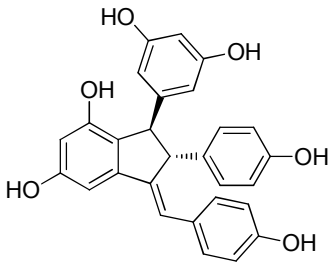


Resveratrol

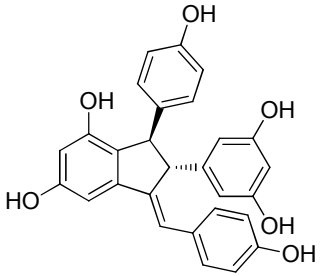
- Most widely distrubuted polyphenol, isolated from over 70 different plants
-Wide variety of biological activity
  anti-inflammatory, antiaging, antitumor, cardiovascular, and nureoprotective
-Substantial concentration in red wine ~3-5 mg in 750 mL
-"French paradox", balanced consumption of red wine may neutralize hramful nutritional effects of foods high in fat and cholesterol.



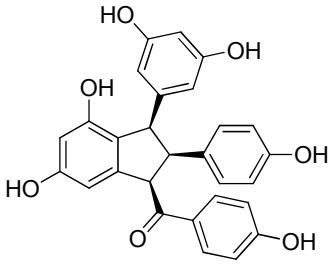
ε-viniferin



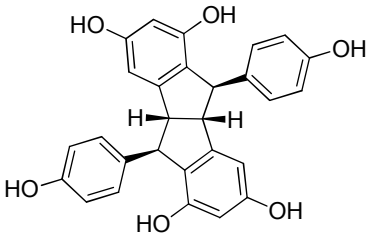
ampelopsin D



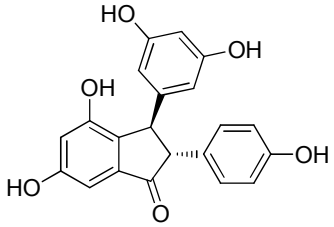
quadrangularin A



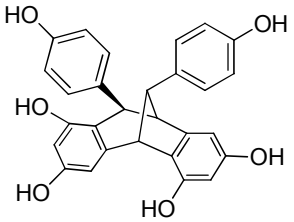
caraphenol B



pallidol



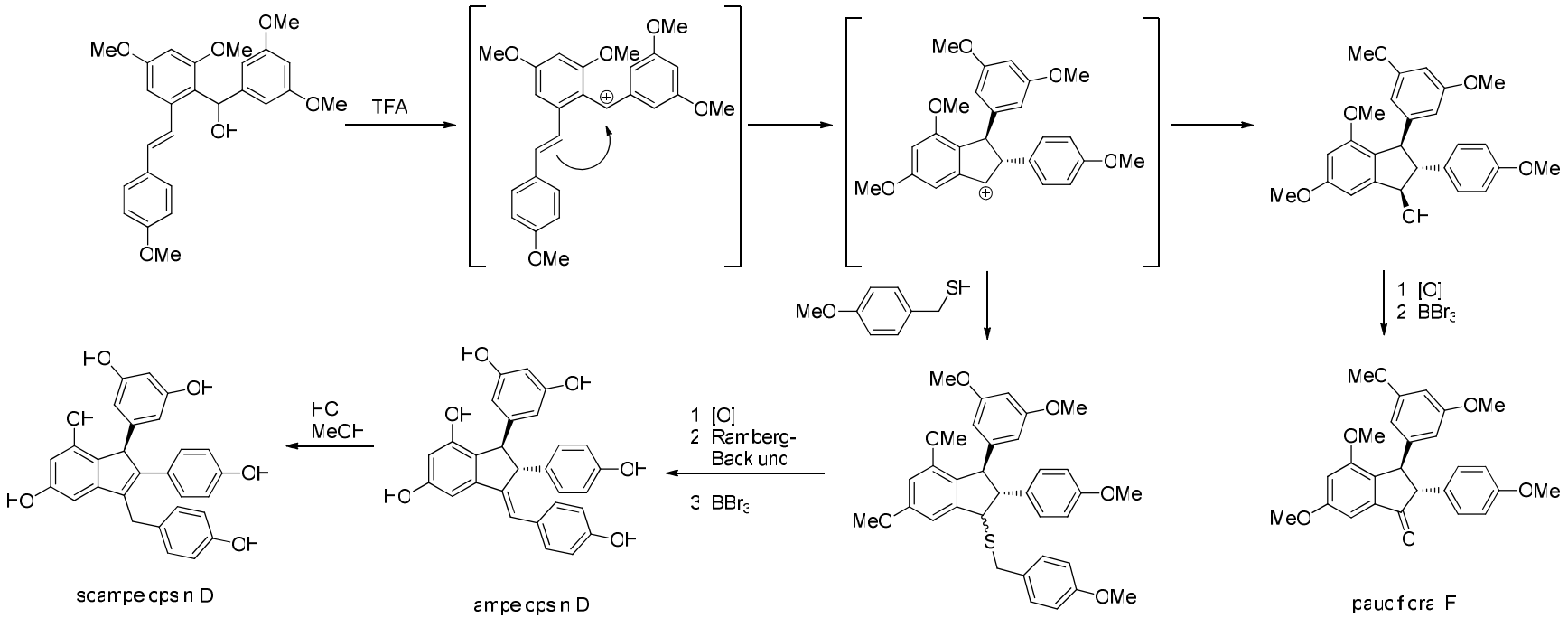
paucifloral F



ampelopsin F

Snyder S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L.. *J. Am. Chem. Soc.* **2009**, *131*, 1753
Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem. Int. Ed.* **2007***, 46*, 8186

Synder's Cascade approach towards Resveratrol derivatives



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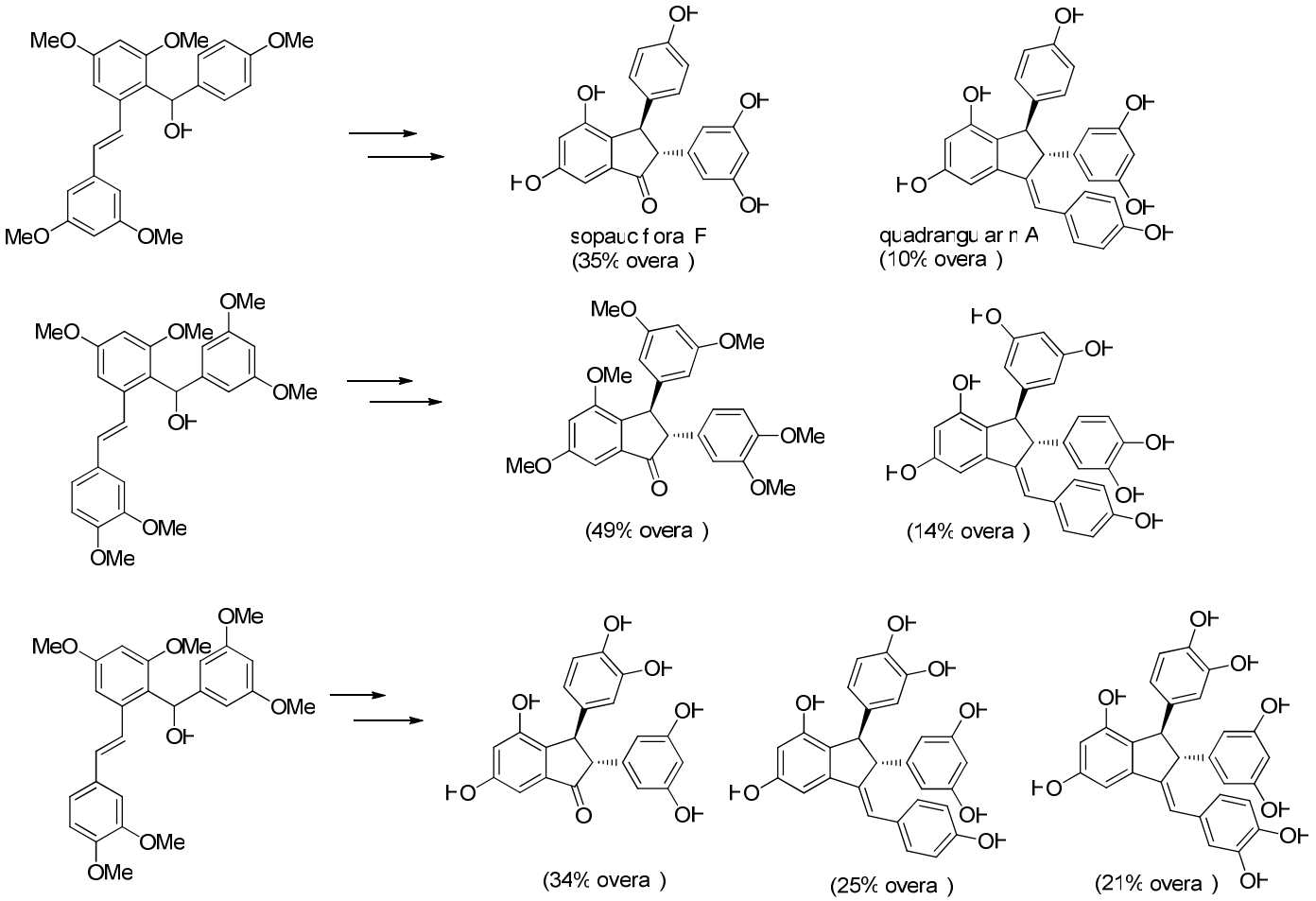
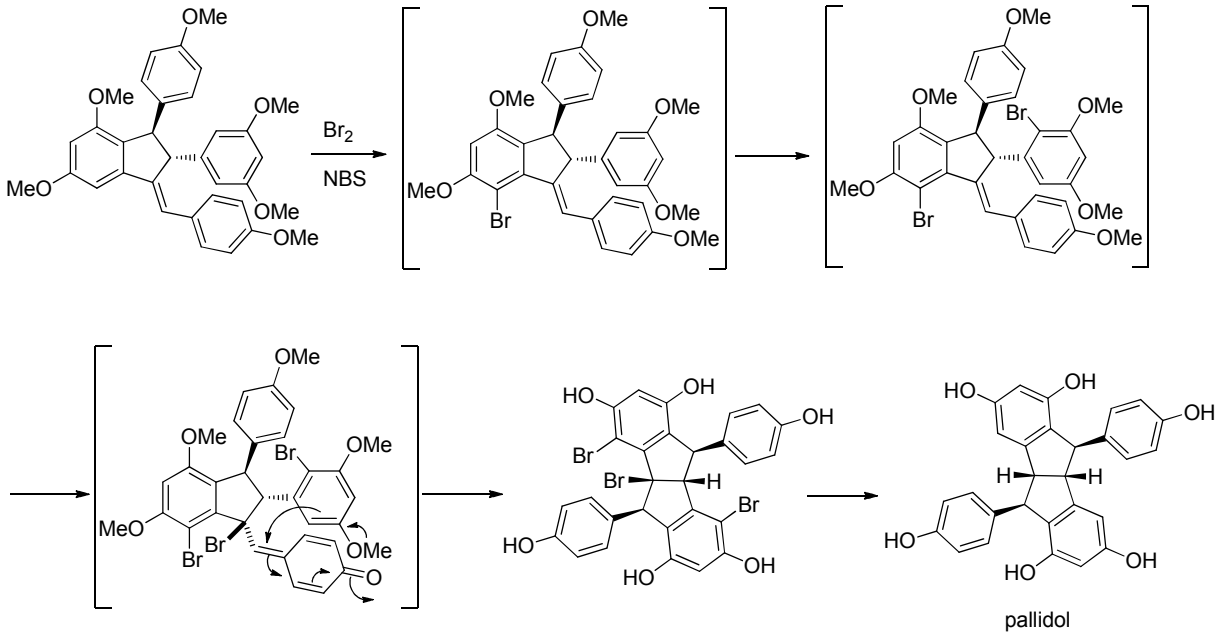
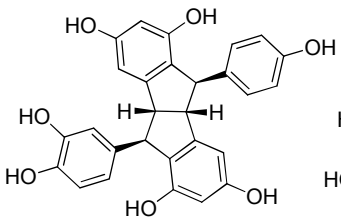
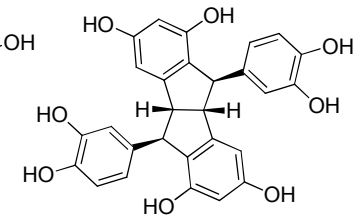


Synder's Cascade approach towards Resveratrol derivatives

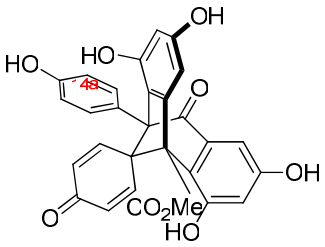






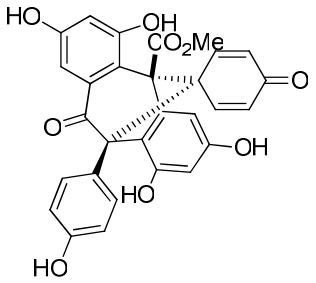
- Over 20 natural products and natural product-like analogues synthesized, using 4 common intermidiates or their derivatives

Isolation and Structure Elucidation

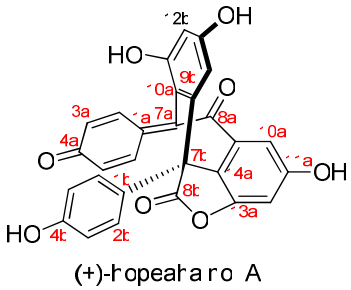


(+)-hopearo

≡



- Isolated by Tan and co-workers, in 2006, from bark of *Hopea exalata*, in China.
- 12.4 mg isolated from 1.8 kg of dry bark
-Structure elucidated by NMR studies
- Cytotoxic properties with IC_{50} 0.52-19.36 μM



(+)-hopeahaaro A

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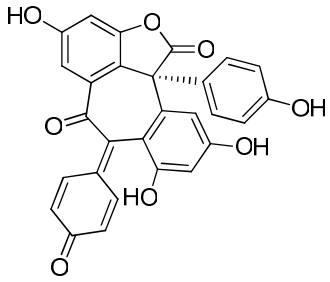
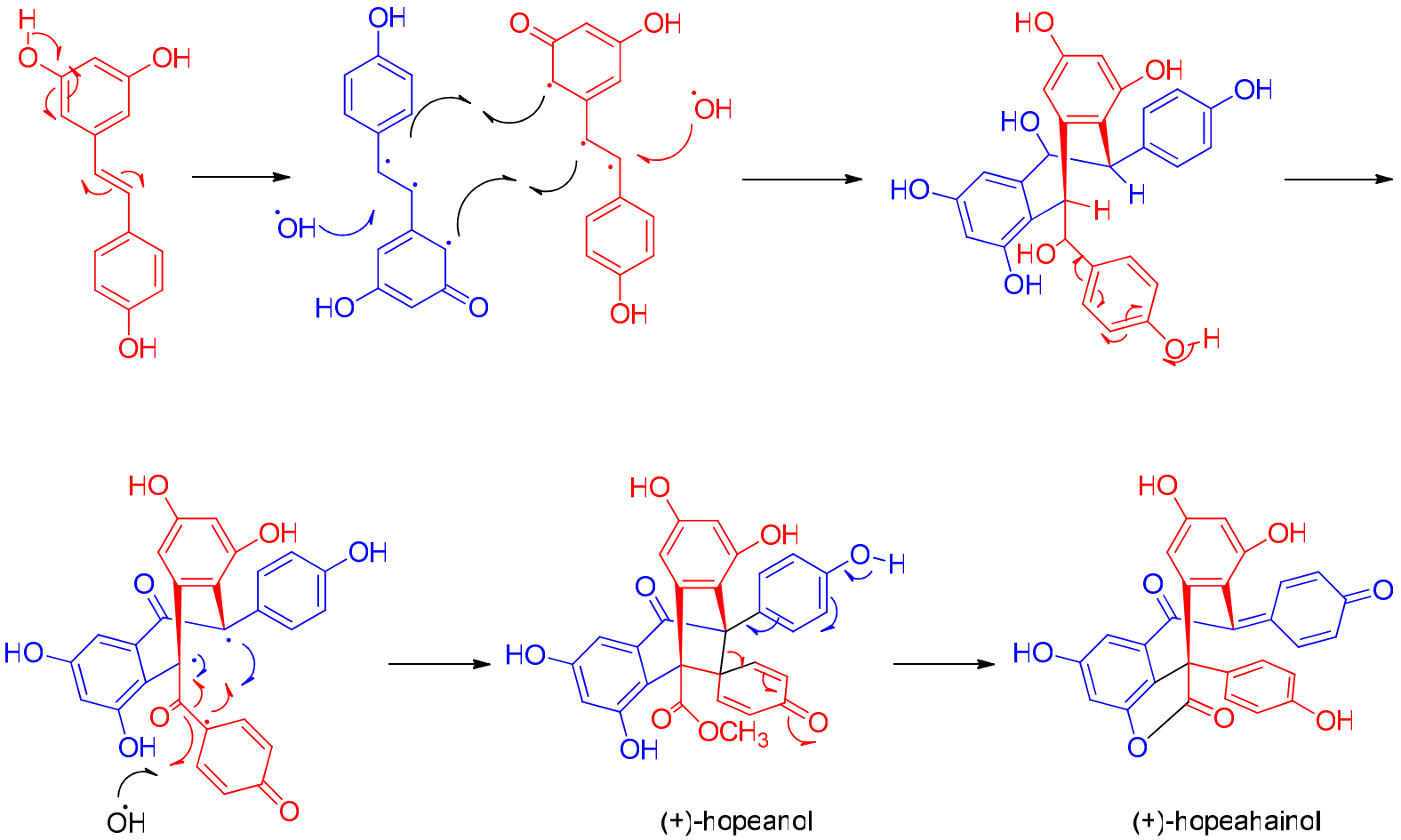


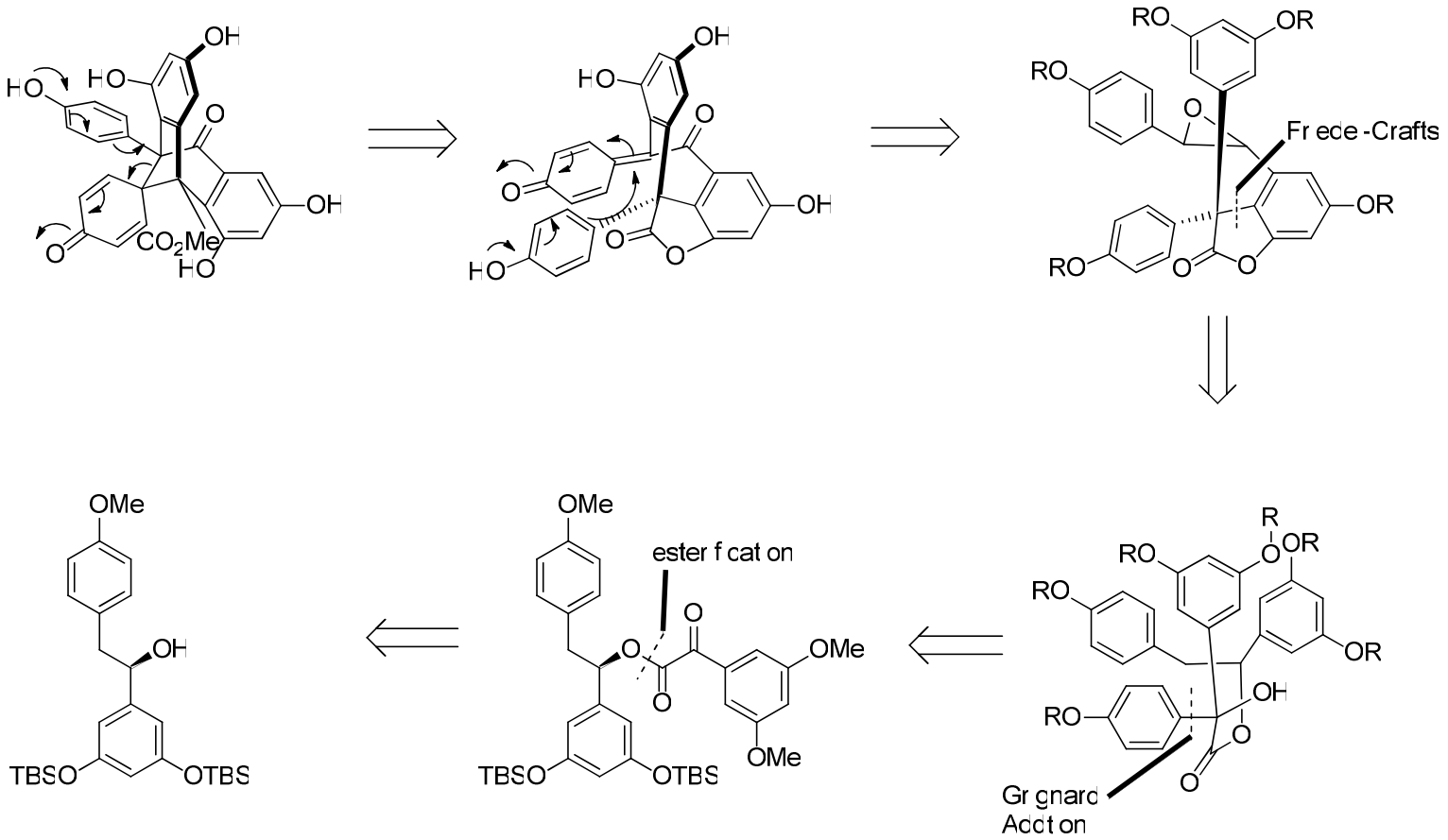
- Isolated by Tan and co-workers, in 2008, from bark of *Hopea hainanensis*, in China.
- 73 mg isolated
-Structure elucidated by NMR studies, and X-ray
- Acetylchloinesterase inhibitory property IC_{50} 4.33 μM

Ge, H. M.; Xu, C.; Wang, X. T.; Huang, B.; Tan, R. X. *Eur. J. Org. Chem.* **2006**, 5551.
Ge, H. M.; Zhu, C. H.; Shi, D. A.; Zhang, Xie, D. A.; Yang, J.; Ng, S. W.; Tan, R. X. *Chem. Eur. J.* **2008**, *14*, 376

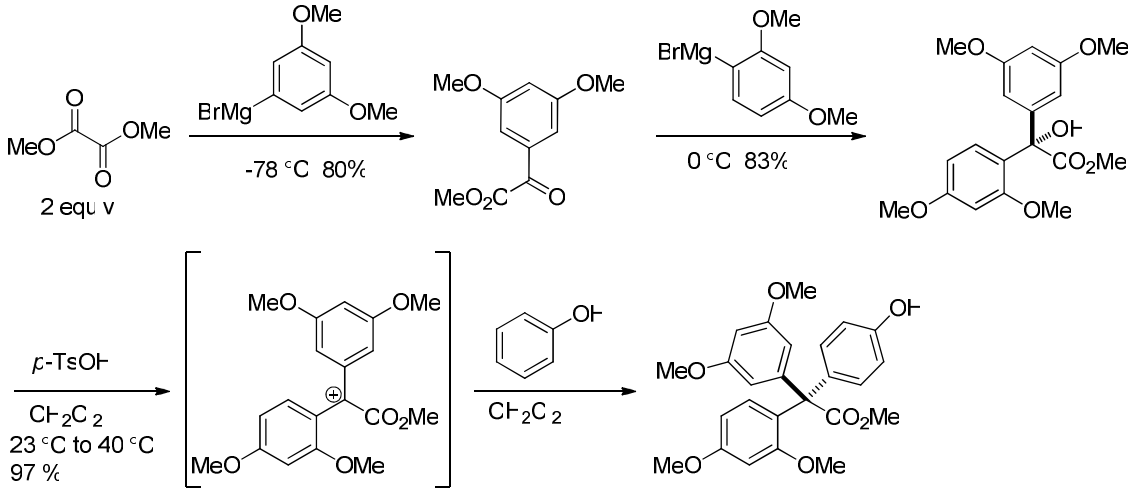
Biosynthesis

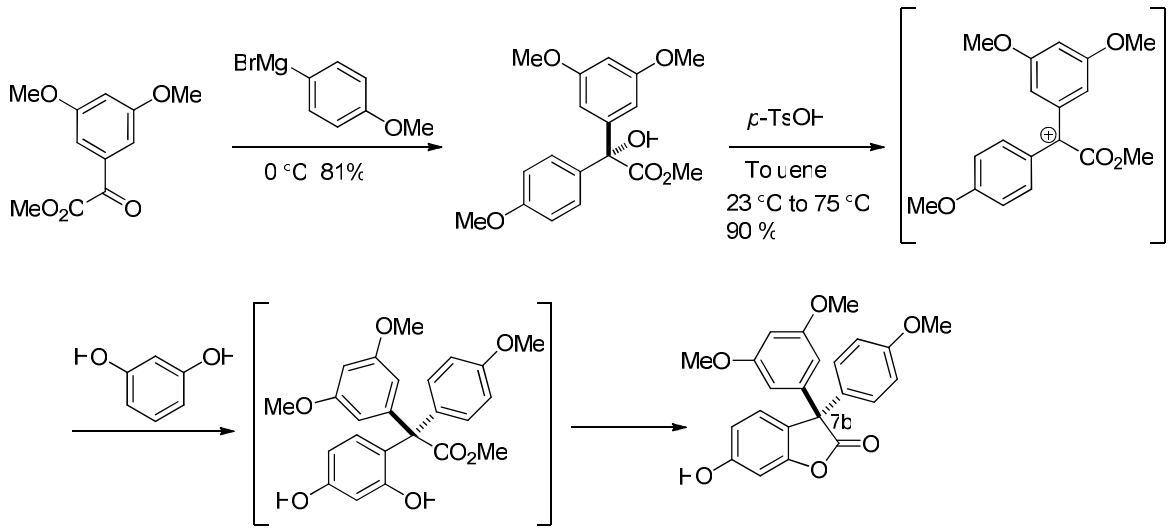


Retrosynthesis



Model Studies for Construction of C7b Quaternary Center





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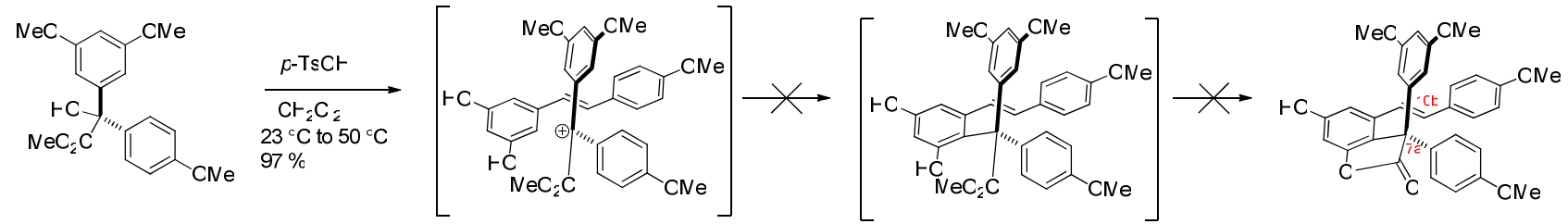
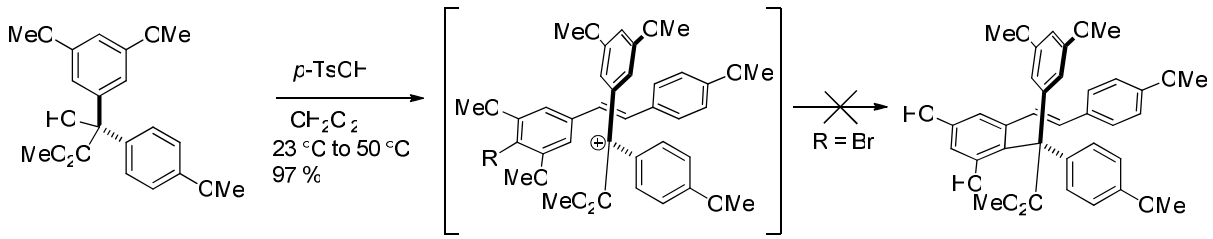
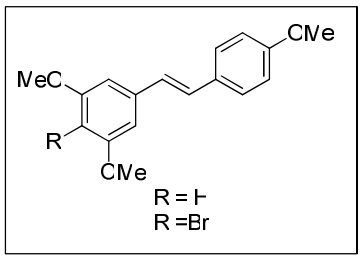
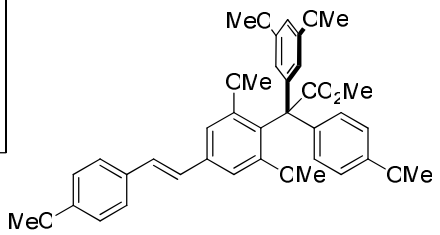


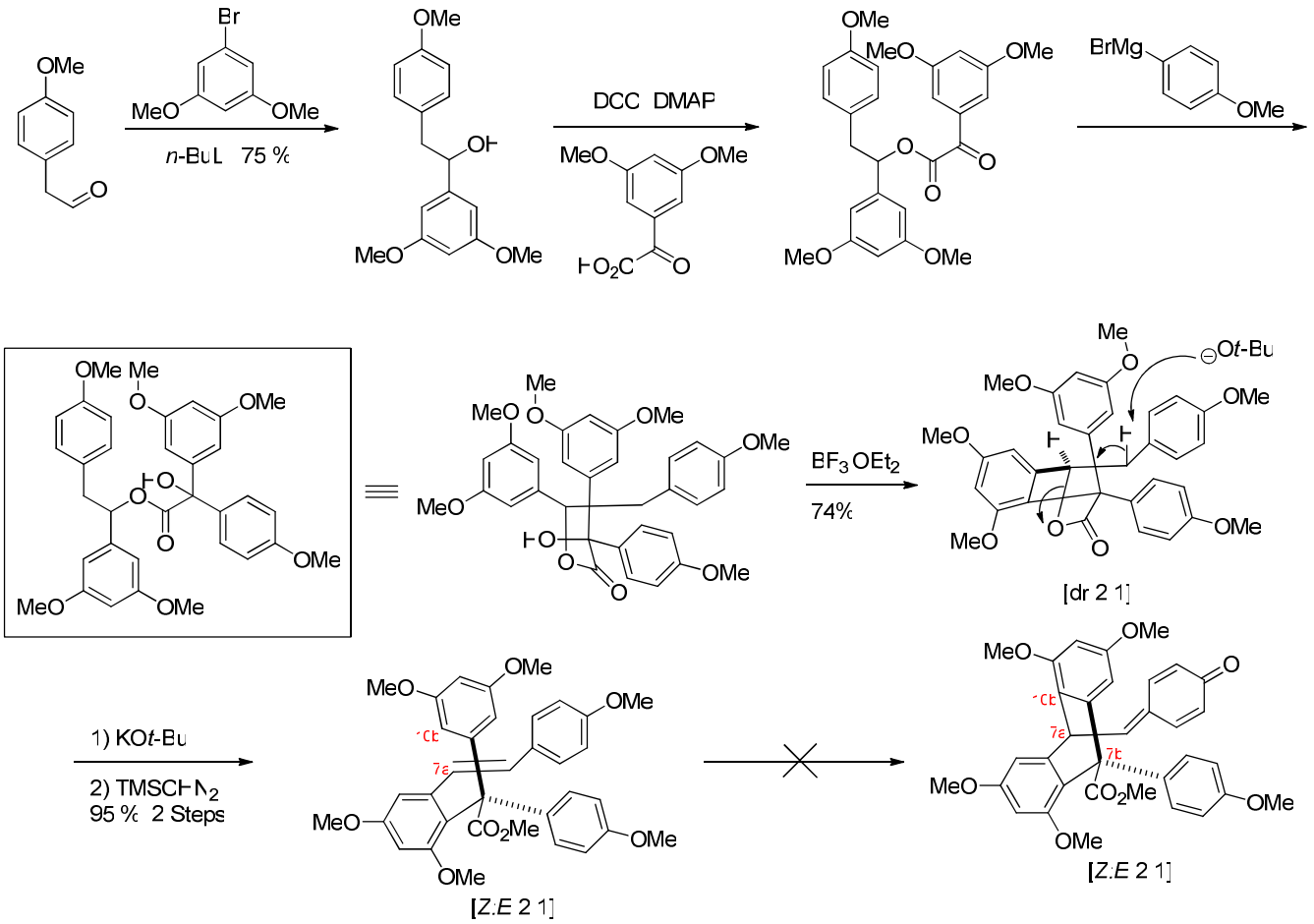




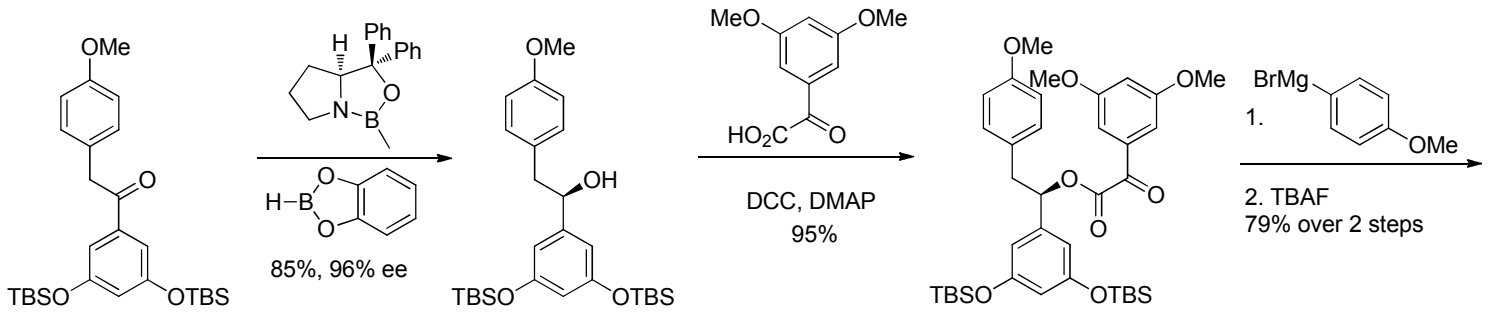


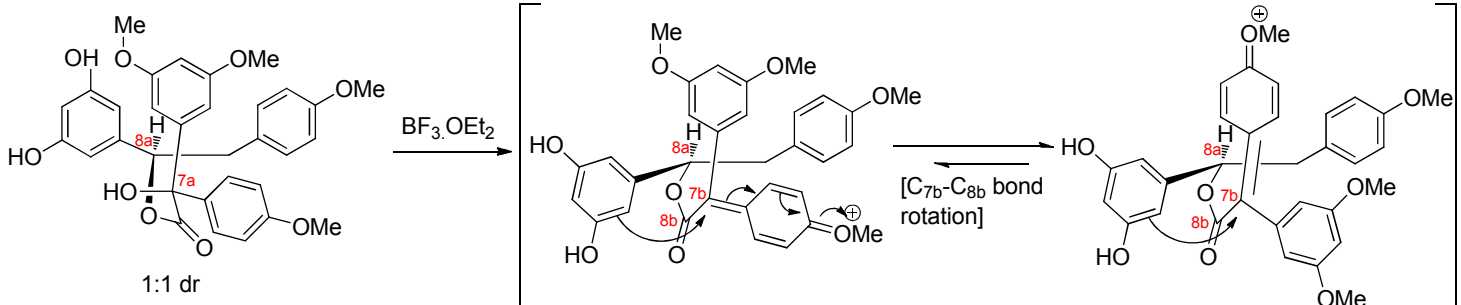
- Incorporation of entire backbone of hopeahainol A
- Undesired regioisomer formed
- Intramolecular Friedel-Crafts reaction

Intramolecular Friedel-Crafts approach for C7b Quaternary Center



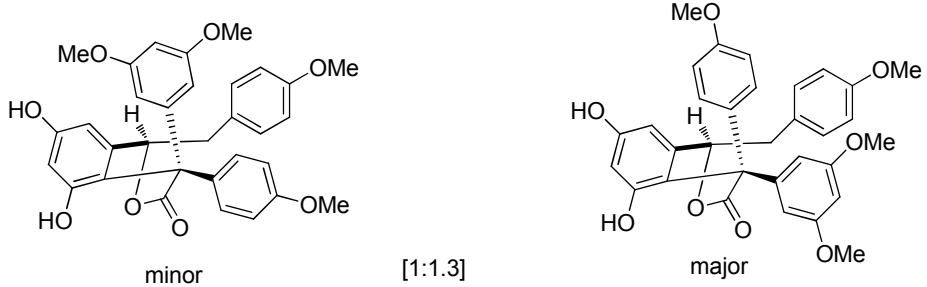
Total Synthesis of Hopeanol and Hopeahainol A





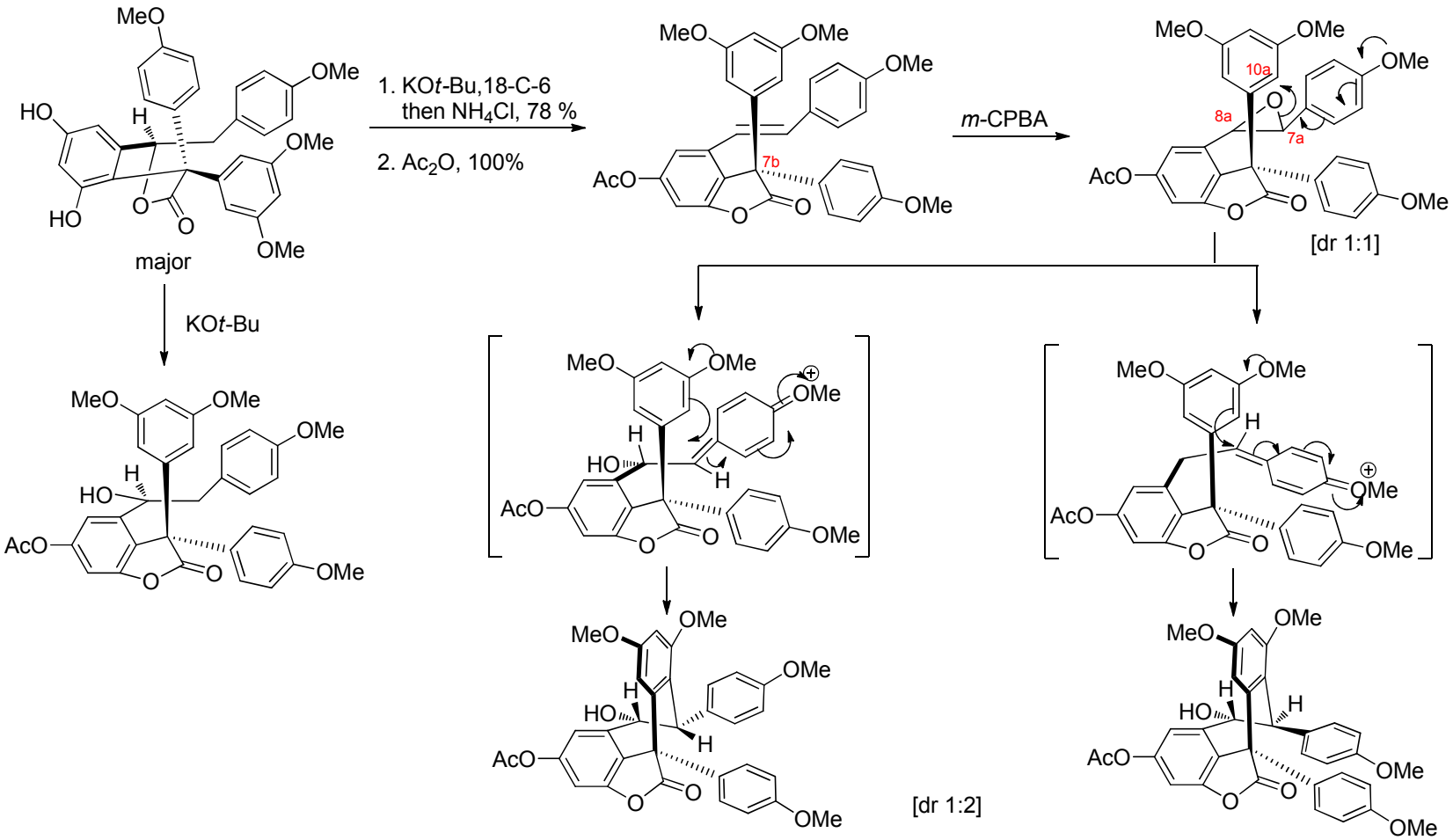
1:1 dr

promoter	yield (%)	ratio
$BF_3.OEt_2$	86	1:1.3
$TiCl_4$	0	--
$Ti(O\textit{i}\text{-}Pr)_4$	0	--
$AlCl_3$	trace	1:1
Me_2AlCl	0	--
$ZnCl_2$	0	--
p-TsOH.H_2O	65	1:2.4
TFA	85	1:1.2
$CeCl_3$	0	--
$Sc(OTf)_3$	91	1:1.5
$Yb(OTf)_3$	88	1:1.5



[1:1.3]

Total Synthesis of Hopeanol and Hopeahainol A



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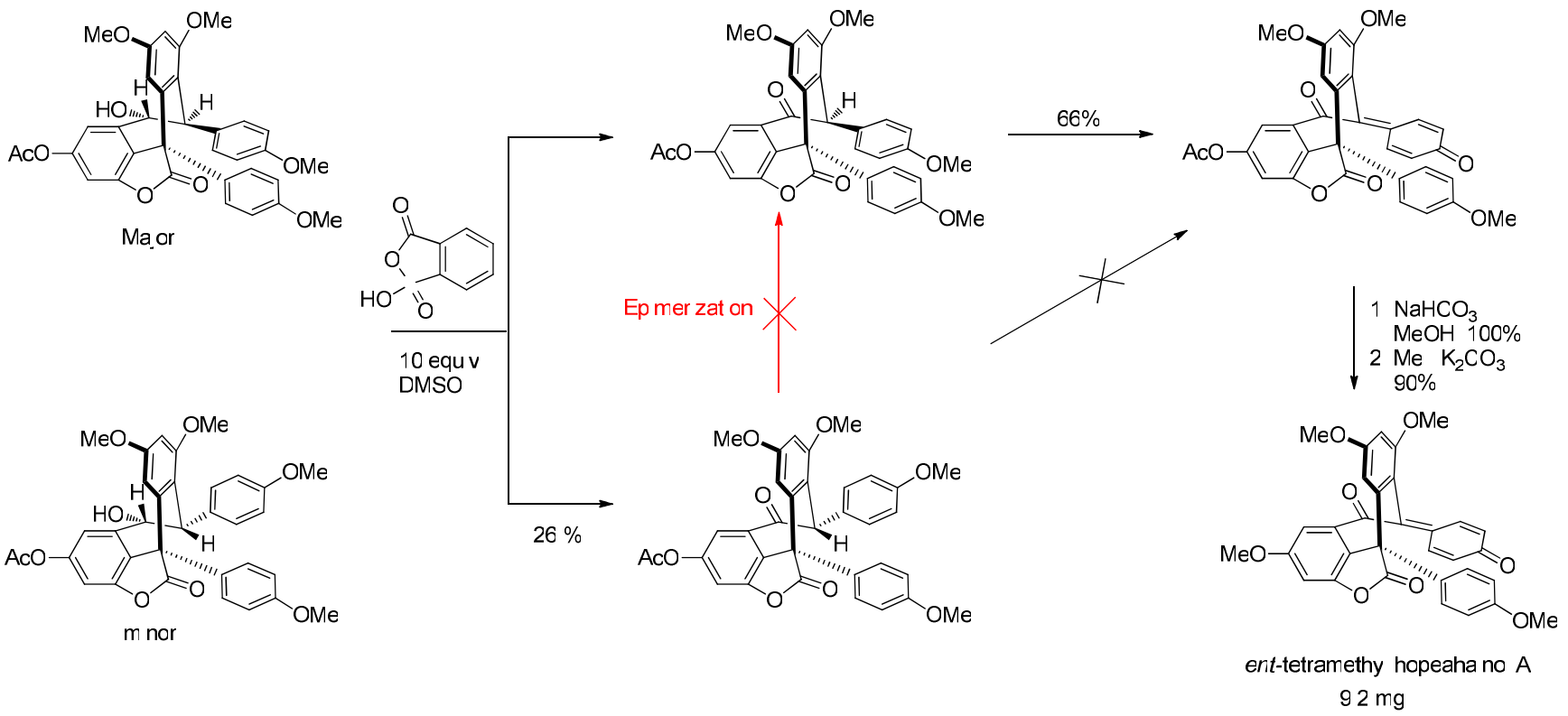
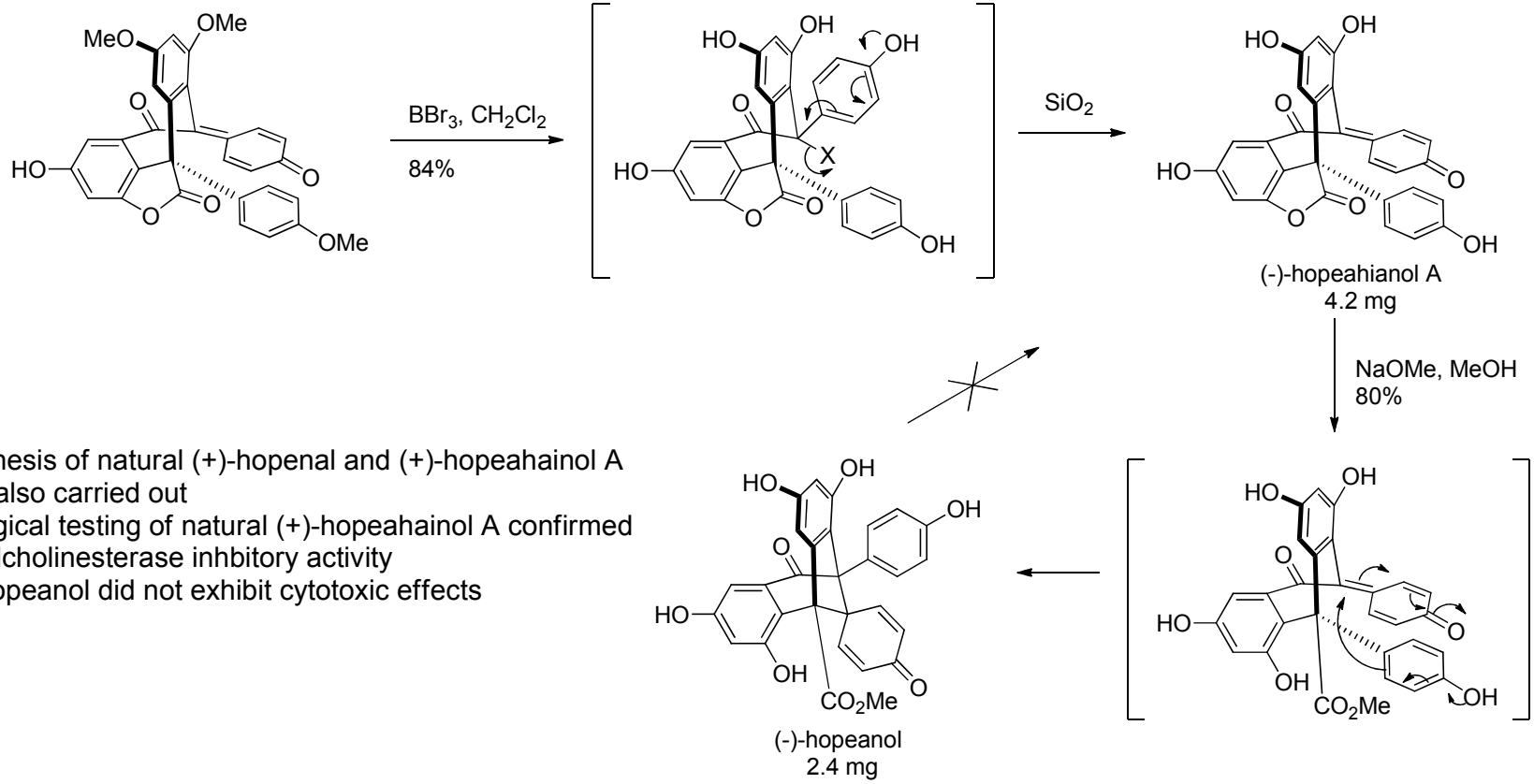


Total Synthesis of Hopeanol and Hopeahainol A



- Synthesis of natural (+)-hopenal and (+)-hopeahainol A was also carried out
-Biological testing of natural (+)-hopeahainol A confirmed acetylcholinesterase inhbitory activity
-(+)-hopeanol did not exhibit cytotoxic effects

Conclusions

- Total synthesis of both isomers of hopeanol and hopeahainol A was achieved using cascade reactions
- Synthetic (+)-hopeanol did not exhibit any cytotoxic effect
- Suggests hopeahainol as a biosynthetic precursor of hopeanol
- Further design and synthesis of related compounds for treatment of cancer and Alzheimer's disease.