Construction of Two Vicinal Quaternary Carbons by Asymmetric Allylic Alkylation: Total Synthesis of Hyperolactone C and (-)-Biyouyanagin A**

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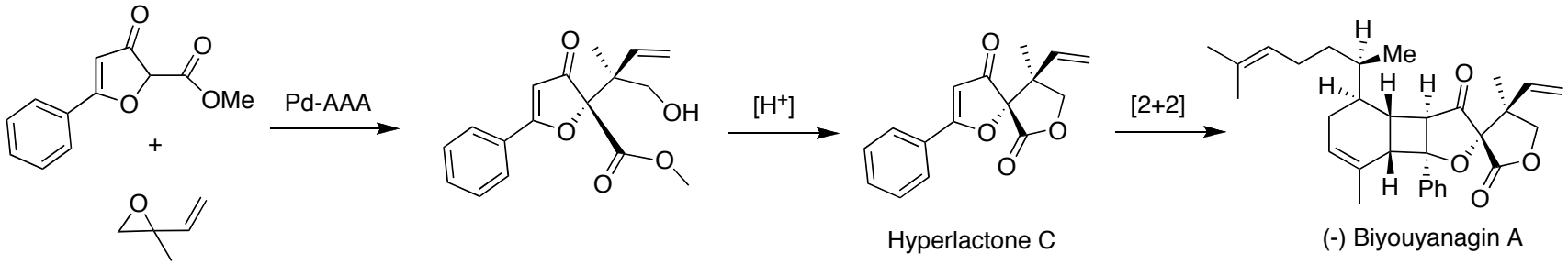
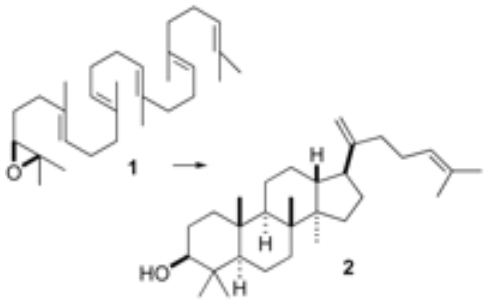
Jared Hammill

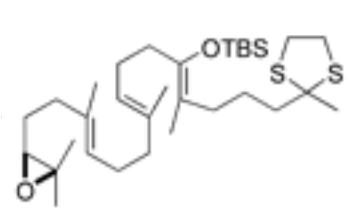
Current Literature presentation
10/3/09

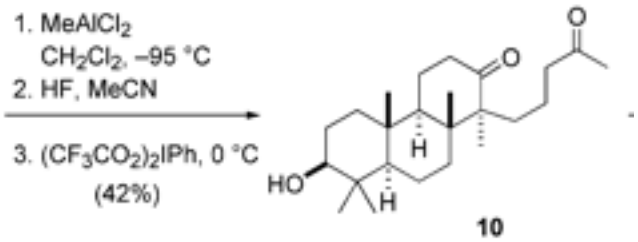


Constructing Contiguous Stereogenic Quaternary Carbons

- Carbocation Cascade



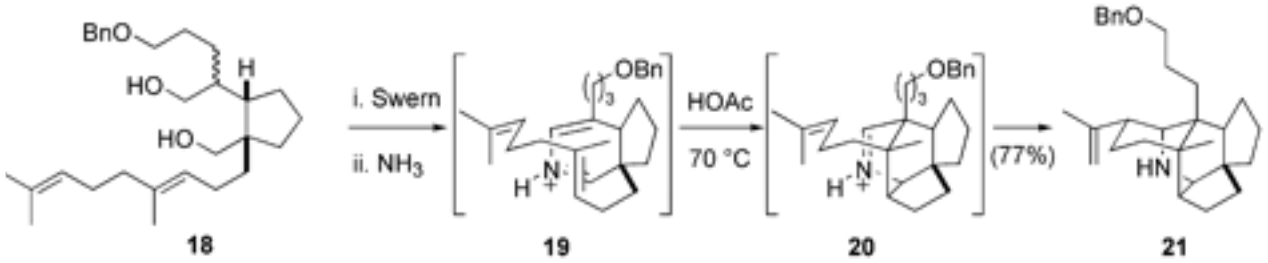




Corey, E. J. & Lin, S. (1996) J. Am. Chem. Soc. 118 , 8765-8766.

Johnson, W. S. (1976) Angew. Chem. Int. Ed. Engl. 15, 9-17

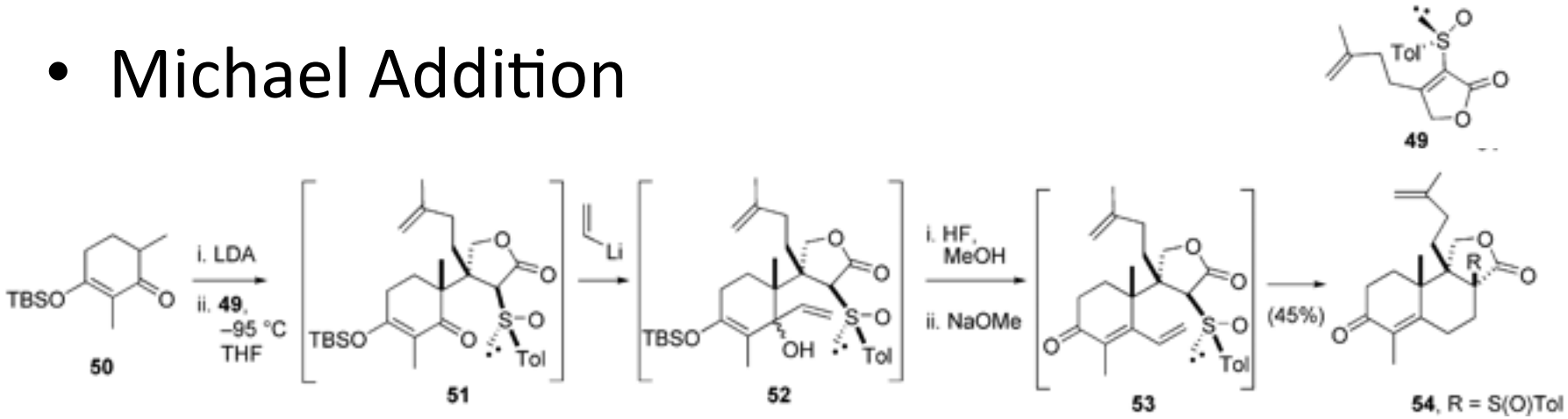
- Diels-Alder



Stafford, J. A. & Heathcock, C. H. (1990) J. Org. Chem. 55 , 5433-5434.

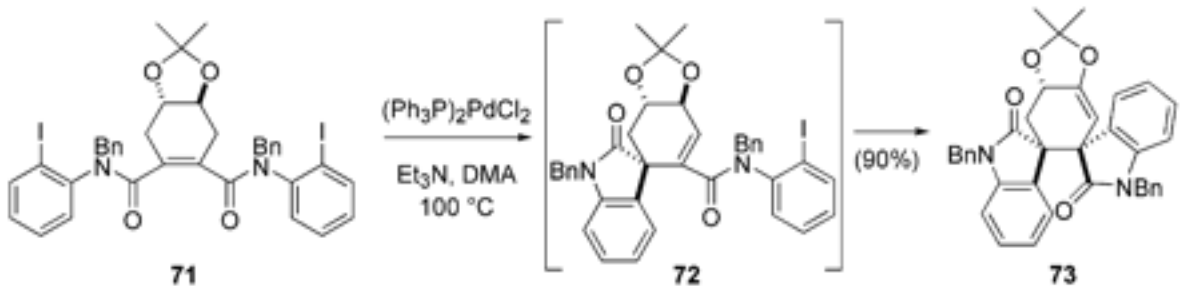
Quaternary Centers Cont.

- Michael Addition



Holton, R. A., Kennedy, R. M., Kim, H.-B. & Krafft, M. E. (1987) J. Am. Chem. Soc. 109 , 1597-1600.

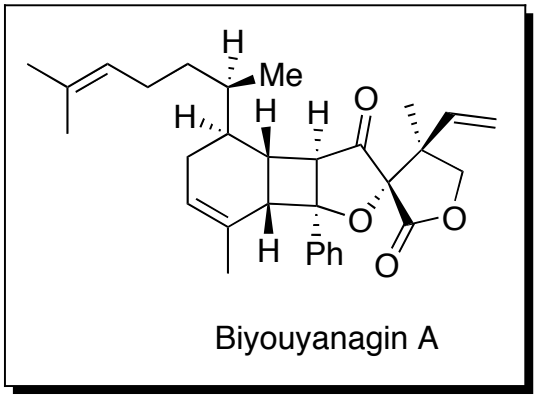
- Heck Cascade



Overman, L. E., Paone, D. V. & Stearns, B. A. (1999) J. Am. Chem. Soc. 121 , 7702-7703.

Further Reading: C. J. Douglas, L. E. Overman,PNAS, 2004, 101, 5363 & B. M. Trost, C. H. Jiang, Synthesis 2006, 369

Biyouyanagin A



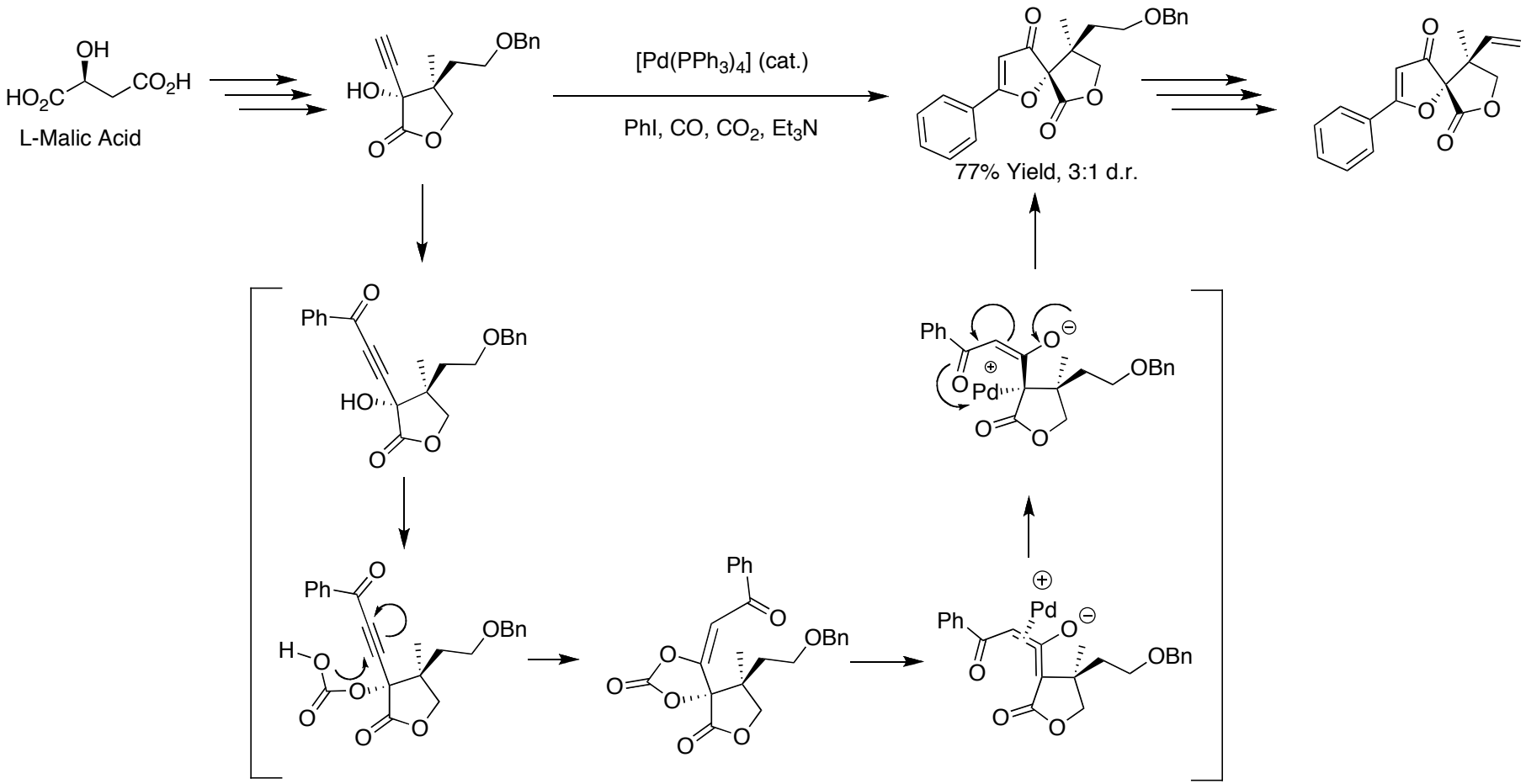
Biyouyanagin A

- Isolated in 2005 from *H. chinense L. var. salicifolium* a *Hypericum* species (St. John's Wort *H. perforatum*)
- Japanese folk medicine for "female disorders"
- Inhibitory activity and selectivity against HIV replication in H9 lymphocytes (EC_{50}=0.798 µg/mL, TI>31.3)
- Therapeutic Index (TI)=LD_{50}/EC_{50}

Images: flickr.com/photos/66631176@N00/178427005 K. C. Nicolaou, D., Sarlah, D. M. Shaw, Angew. Chem. Int. Ed. 2007, 46, 4708

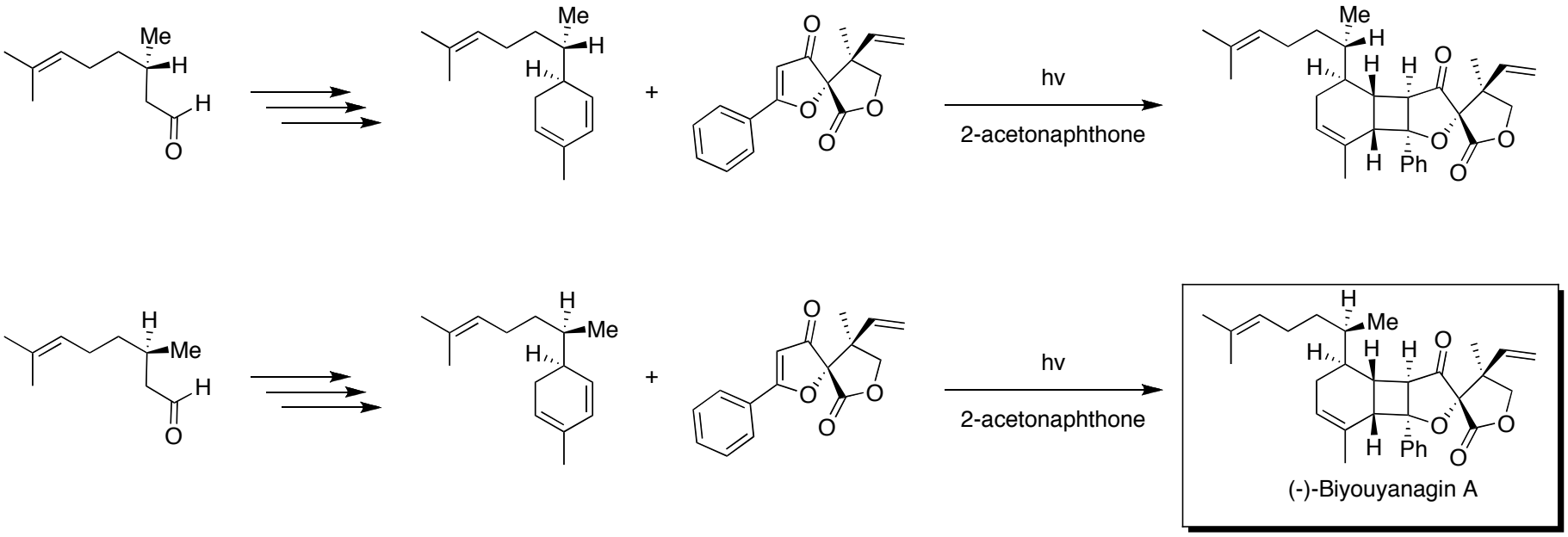
Previous Synthesis

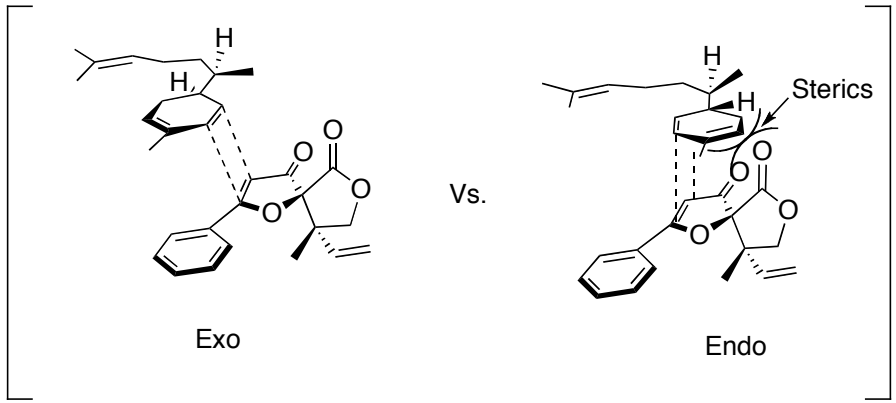
Total synthesis and structural revision by Nicolaou et at. in 2007



K. C. Nicolaou, D., Sarlah, D. M. Shaw, Angew. Chem. Int. Ed. 2007, 46, 4708

Nicolaou Synthesis





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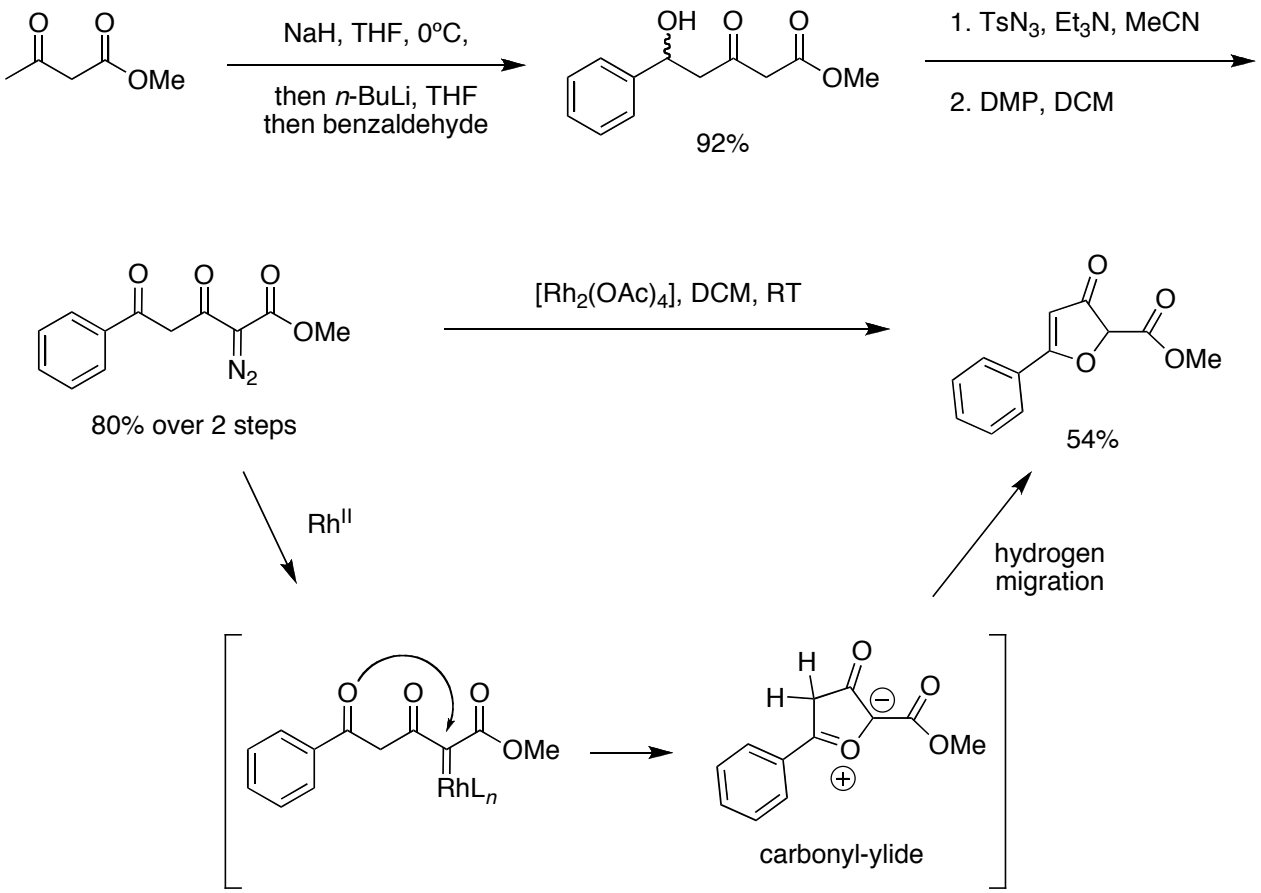
Title Paper

Goal: Use Pd-AAA reaction to provide a concise route to (-)-Biyouyanagin A



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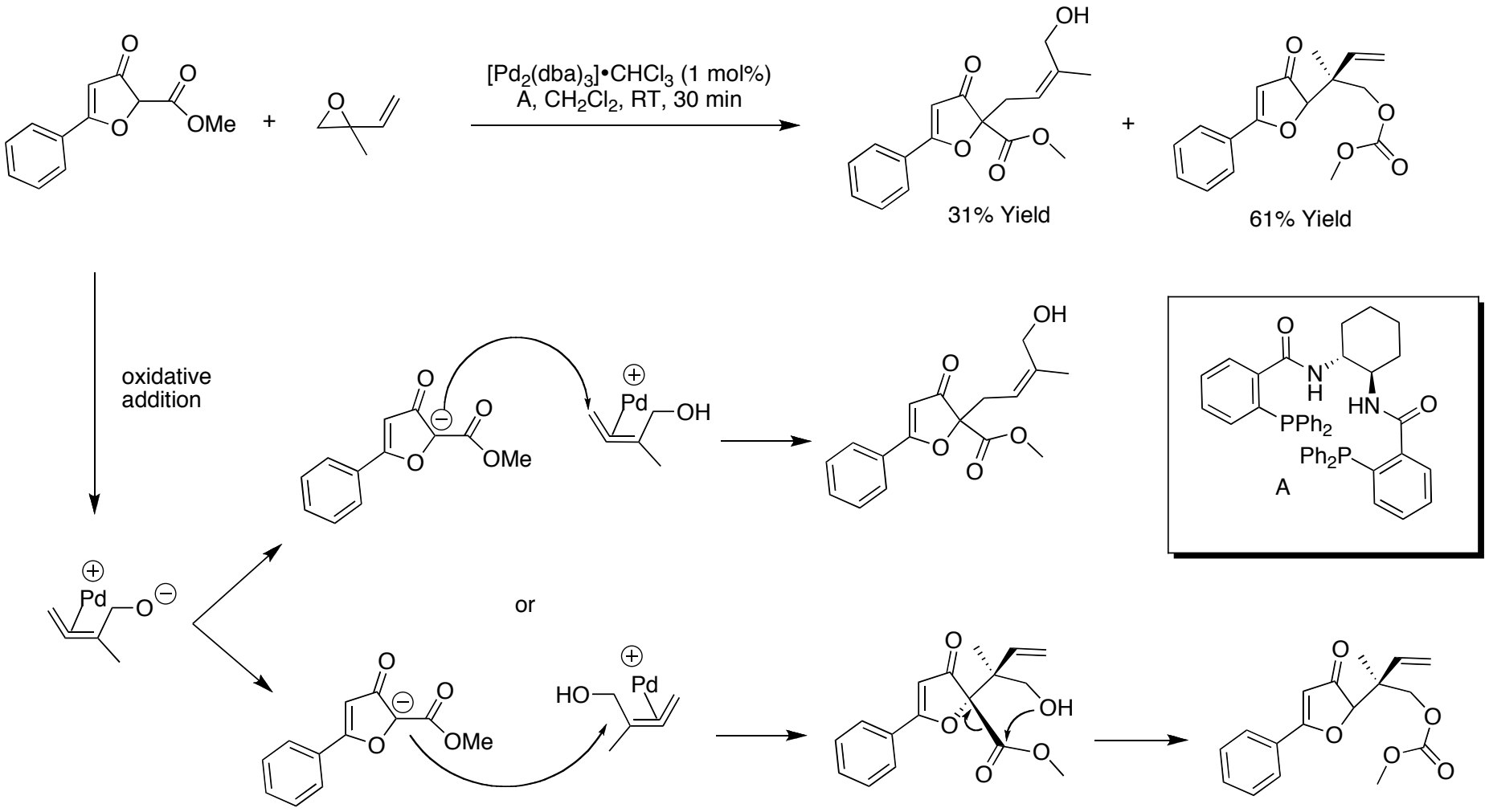
Pd-AAA Reaction



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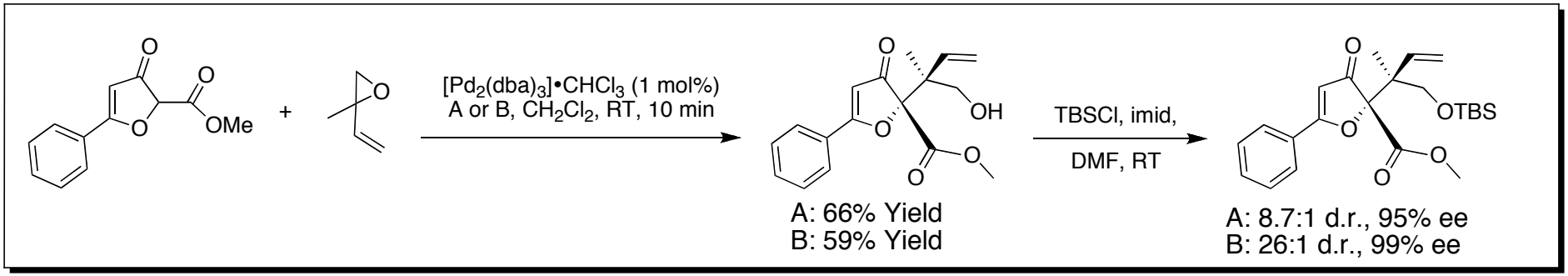
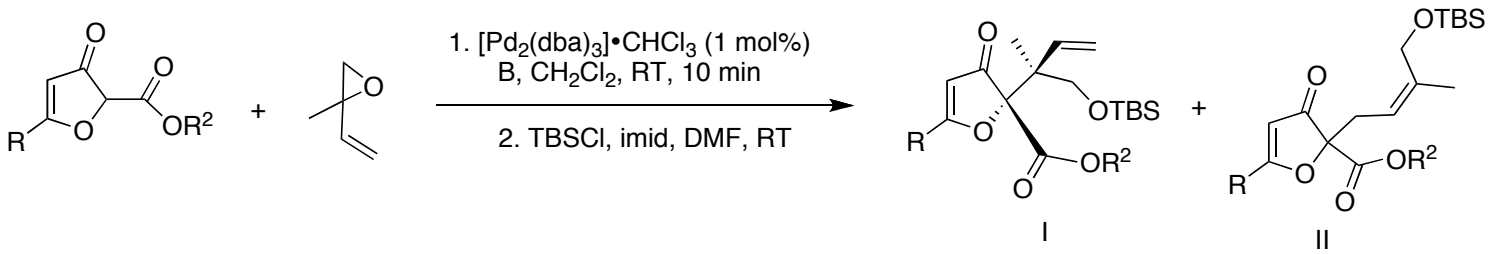
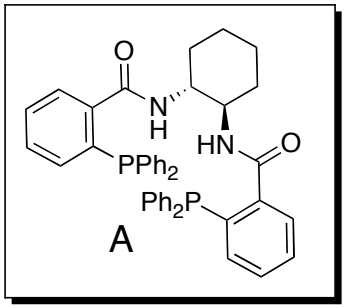
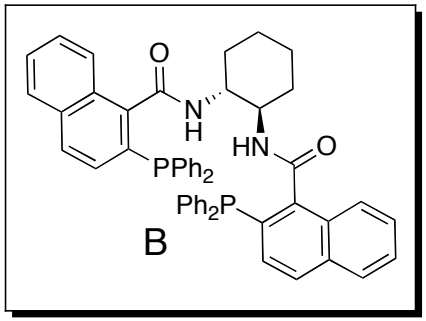
Pd-AAA Reaction





R	R^2	d.r. (I/II)	Product	Yield	ee	
Ph	Me	26:1 (2.1:1)	I	59	99	
Ph	Me	23:1	ent-I	54	99	*Used ent-B
p-$OMeC_6H_4$	Et	32:1 (1.8:1)	I	57	99	
p-ClC_6H_4	Et	53:1 (1.6:1)	I	68	99	
i-Pr	Me	8.3:1 (2.8:1)	I	55	99	
$(CH_2)_2OBn$	Me	56:1 (2.2:1)	I	48	99	





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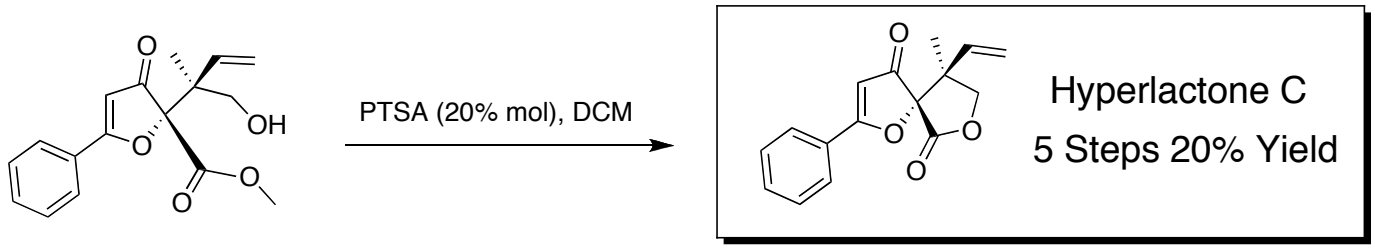
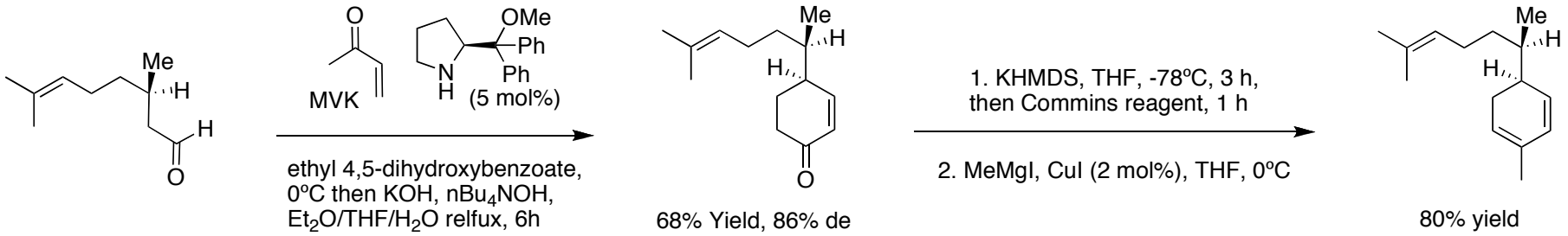
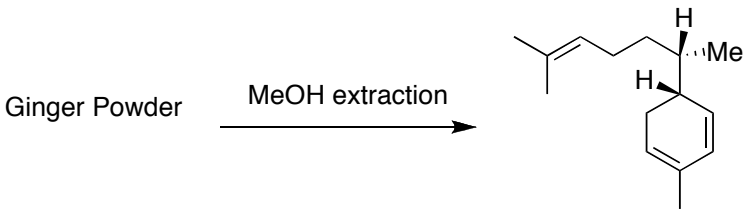
Hyperlactone C







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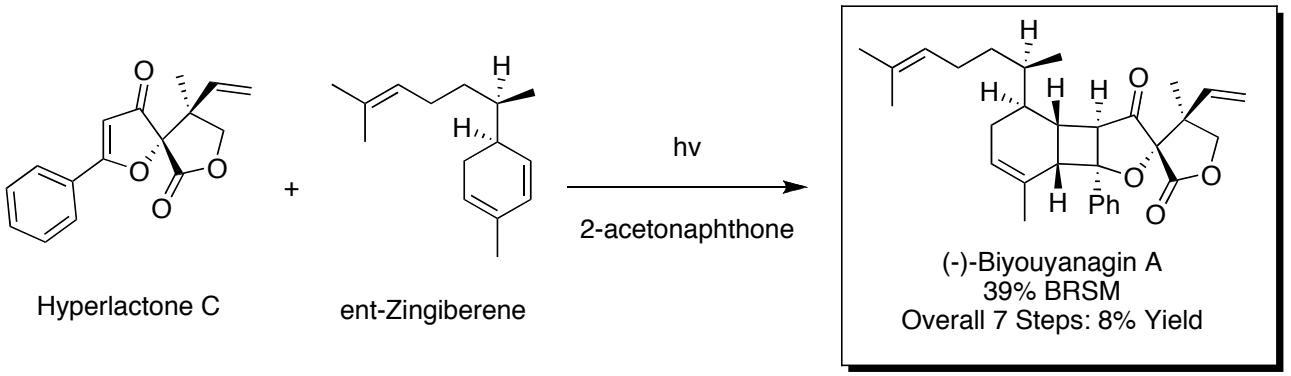
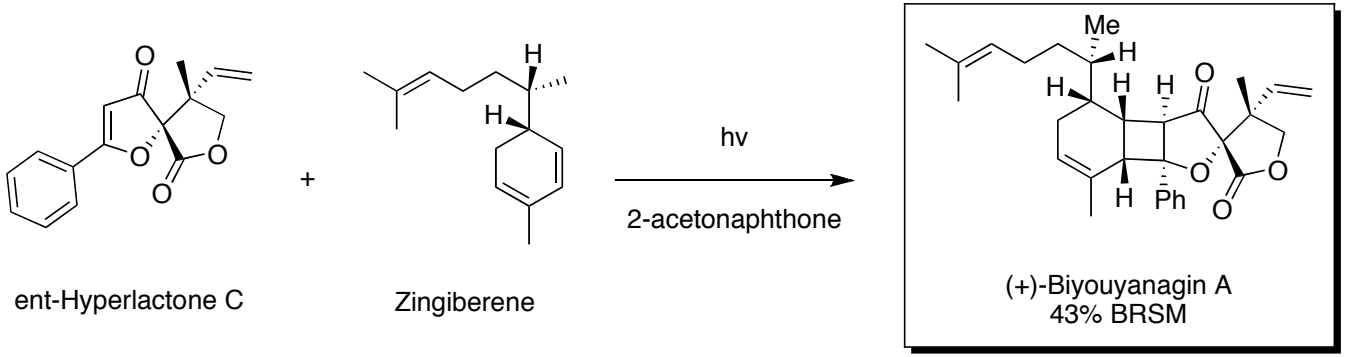
(-)-Biyouyanagin





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Conclusions

- Pd-AAA was successfully extended to construct two vicinal quaternary carbon centers in high diastereoselectivity (up to 56:1 d.r.) and excellent enantioselectivity (99% ee)
- Hyperlactone C was synthesized in 6 steps 20% Yield
- (-)-Biyouyanagin A was synthesized in 7 steps 8% Yield
- Enantiomers could be prepared by switching the chiral ligand and by changing the final coupling partner