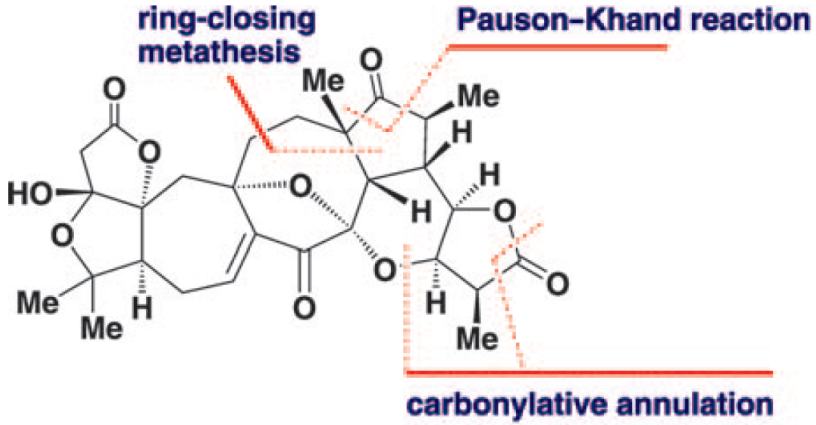
Dead Ends and Detours

Diastereoselective Total Synthesis of (±)-Schindilactone A

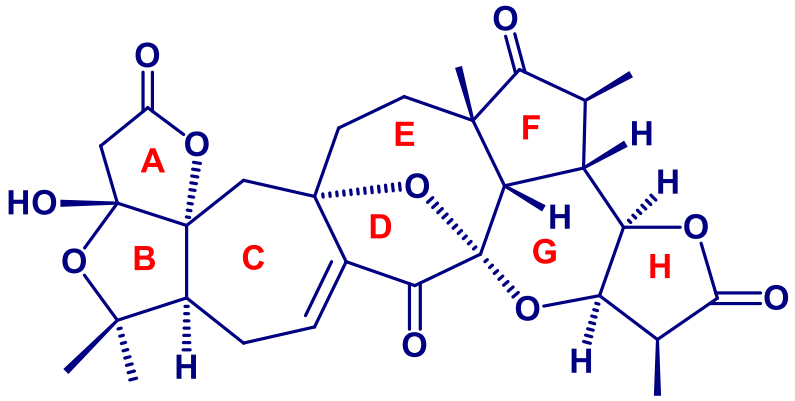


schindilactone A

Current Literature
Jie Xu
08.06.11

Xiao, Q.; Ren, W.; Chen, Z.; Sun, T.; Li, Y.; Ye, Q.; Gong, J.; Meng, F.; You, L.; Liu, Y.; Zhao, M.; Xu, L.; Shan, Z.; Shi, Y.; Tang, Y.; Chen, J.; Yang, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 7373 – 7377

Isolation



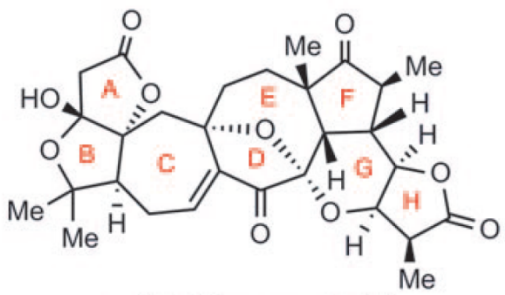
Schindilactone A

Schisandraceae

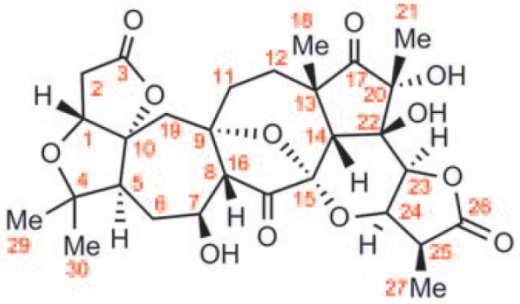
- ***Schisandraceae has been used in China for the treatment of rheumatic lumbago and related diseases.***
- ***Structure was determined by 1D and 2D NMR, X-ray spectroscopic data.***
- ***Some of the family members possess biological activities for inhibiting hepatitis, tumors and HIV-1.***

Sun, H.; *et. al. Org. Lett.* **2007**, *9*, 2079 – 2083.
Sun, H.; *et. al. J. Nat. Prod. Rep.* **2008,** *25,* 871 – 891.
Sun, H.; *et. al. J. Nat. Prod.* **1996,** *59,* 525 – 527.

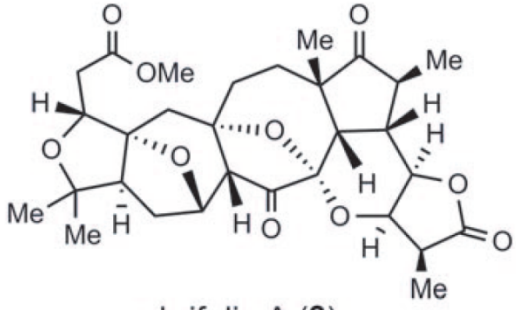
Structure Feature



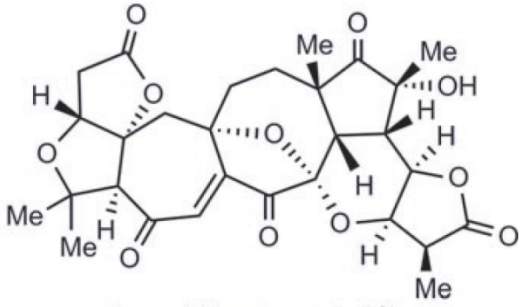
schindilactone A (**1**)



micrandilactone A (**2**)



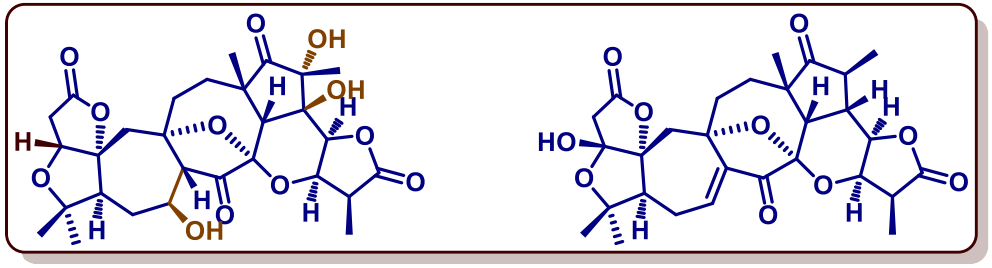
rubrifolin A (**3**)



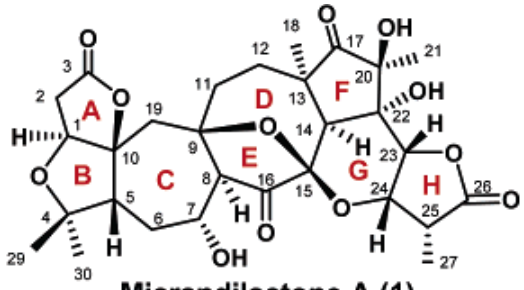
henridilactone A (**4**)

- ***Consisted of 5,6,7,8-membered rings, including lactone, furan, pyran***
- ***Highly oxygenated framework bearing 12 stereogenic centers, eight of which are contiguous chiral centers located in the FGH tricyclic ring system***
- ***An oxa-bridged ketal that lies within an unprecedented 7–8 fused carbocyclic core.***

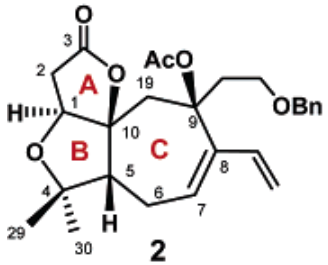
First Generation Synthesis



Micrandilactone A **Schindilactone A**



Micrandilactone A (1)



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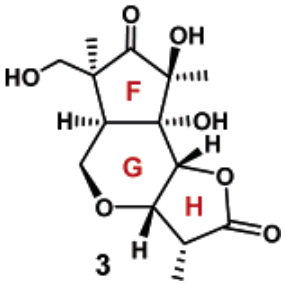
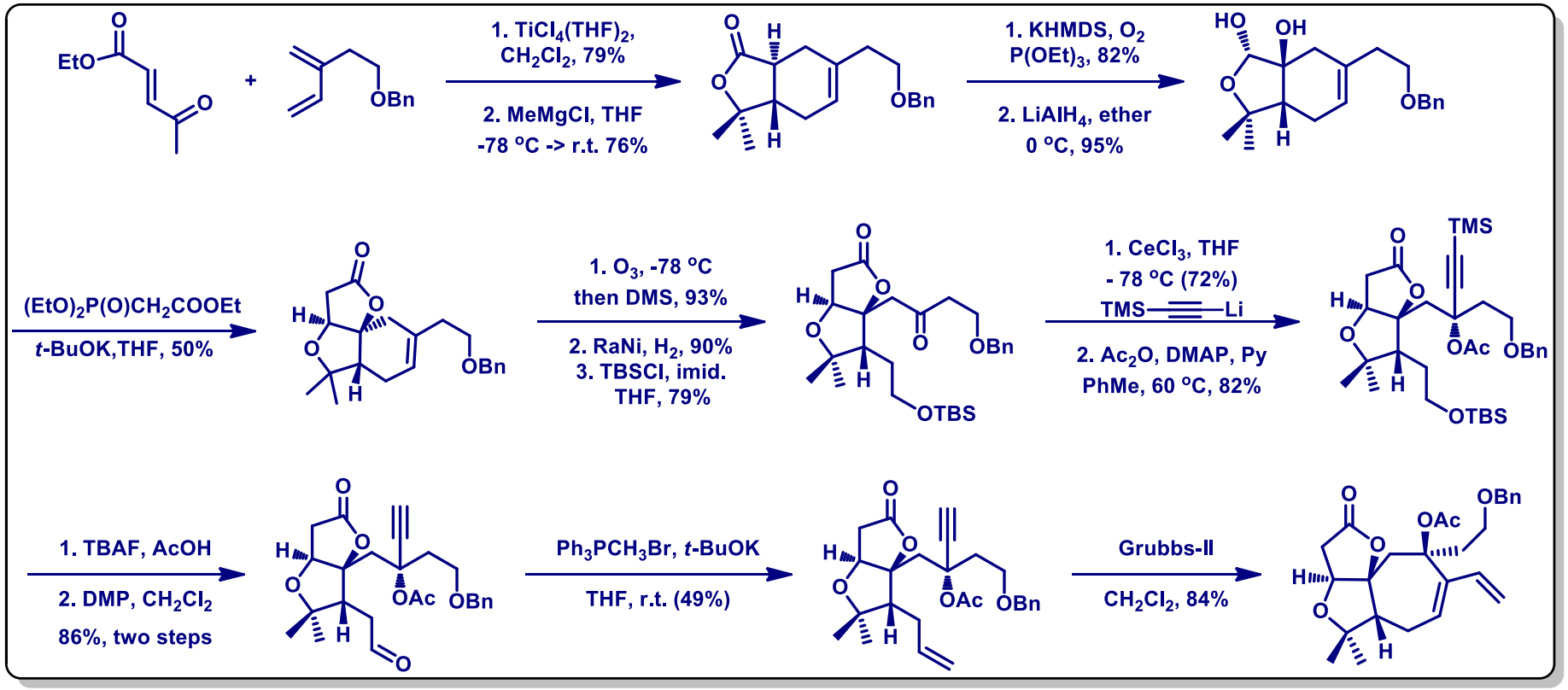


3

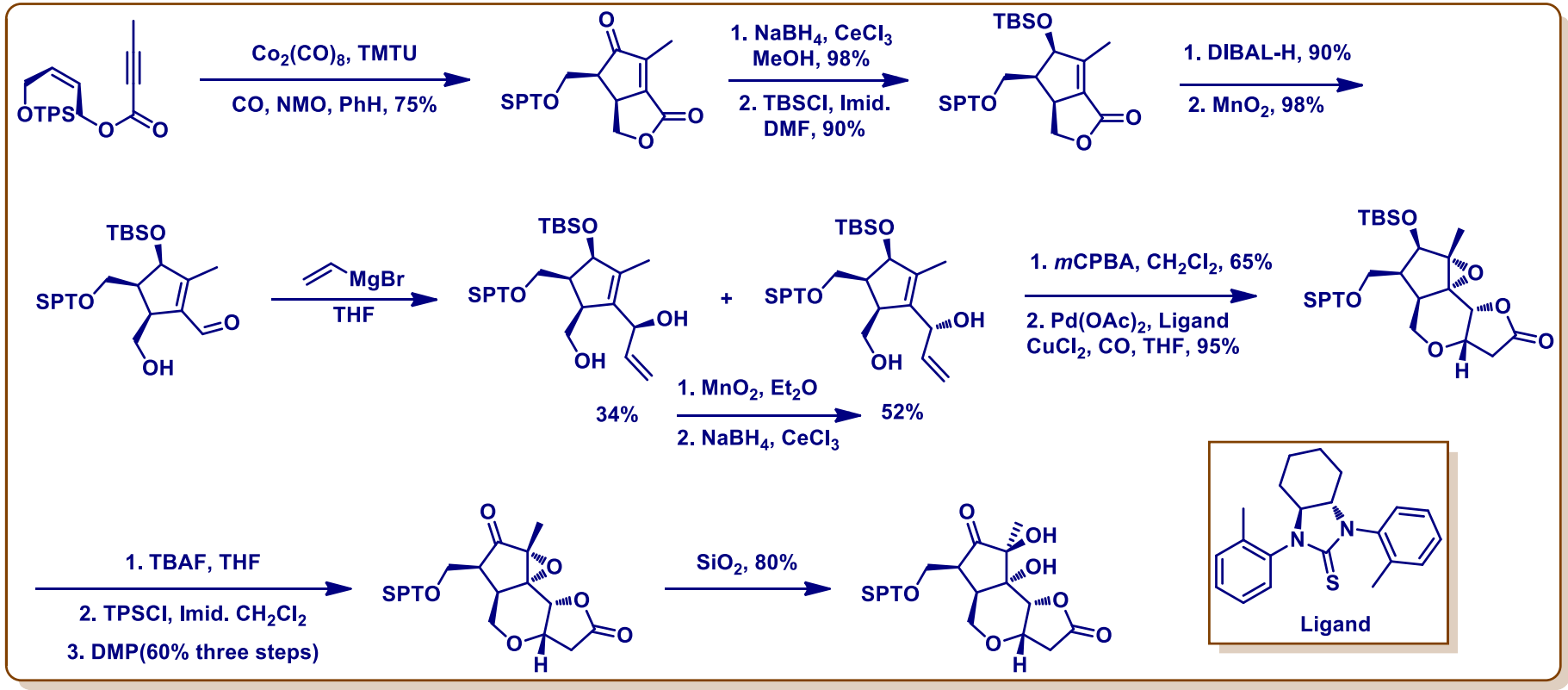
Yang. Z., *et. al. Org. Lett.* **2006**, *8*, 107 – 110.

Syntheis of ABC Ring



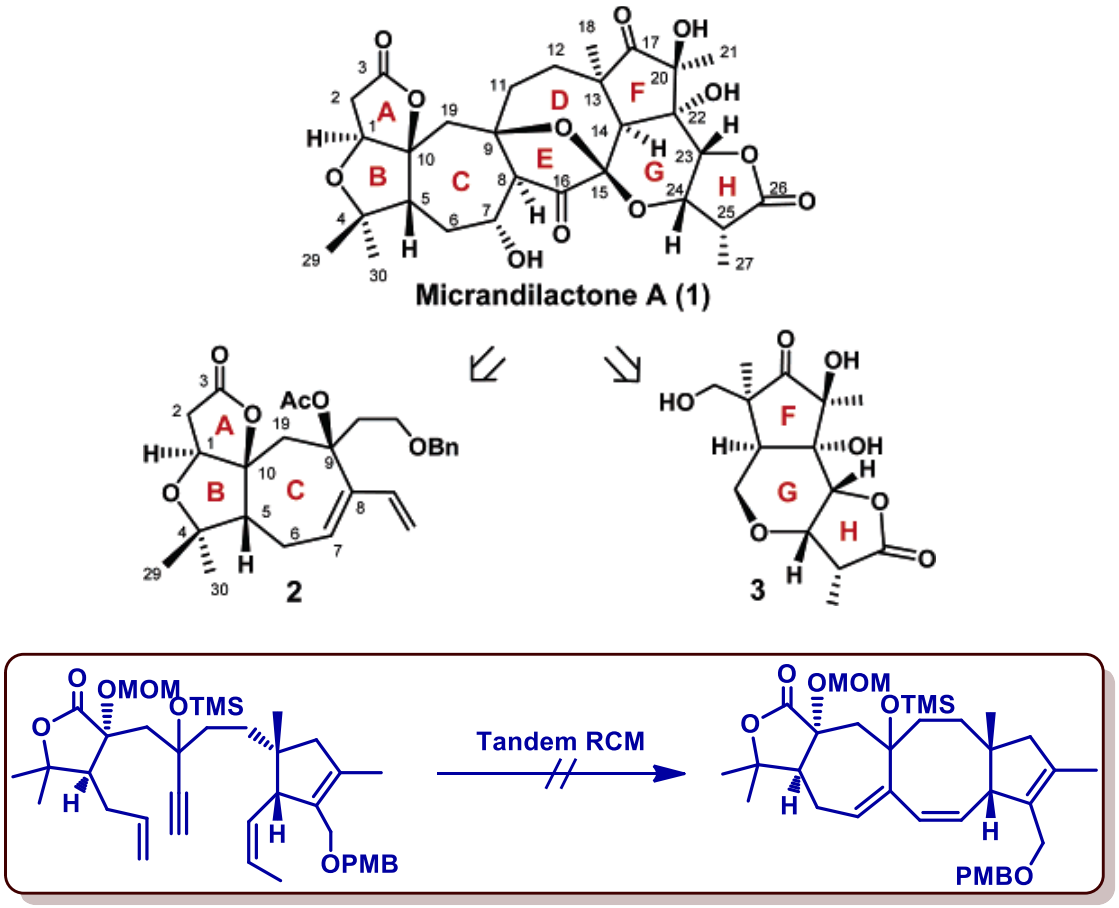
Yang. Z., *et. al. Org. Lett.* **2006**, *8*, 107 – 110.

Syntheis of FGH Ring



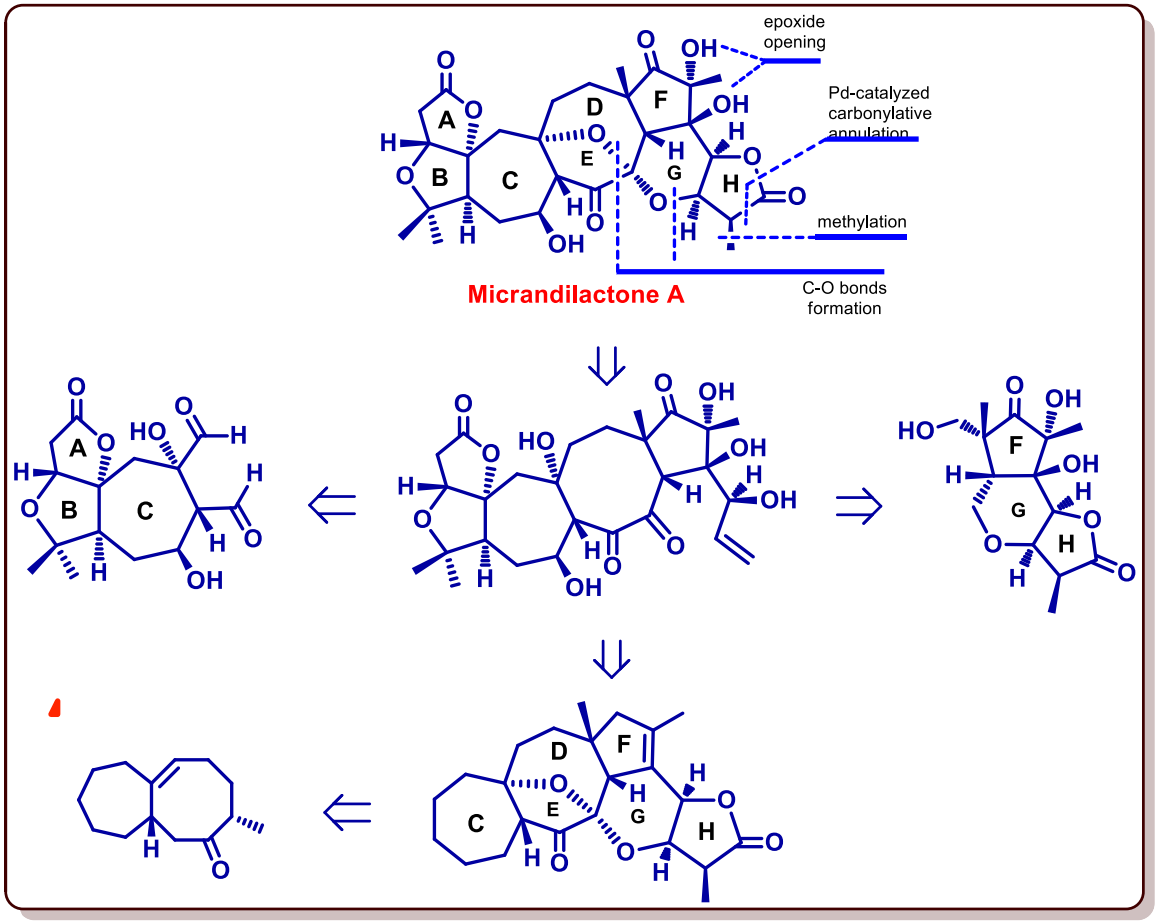
Yang. Z., *et. al.* *Org. Lett.* **2005**, *7*, 885 – 888.

Coupling Strategy

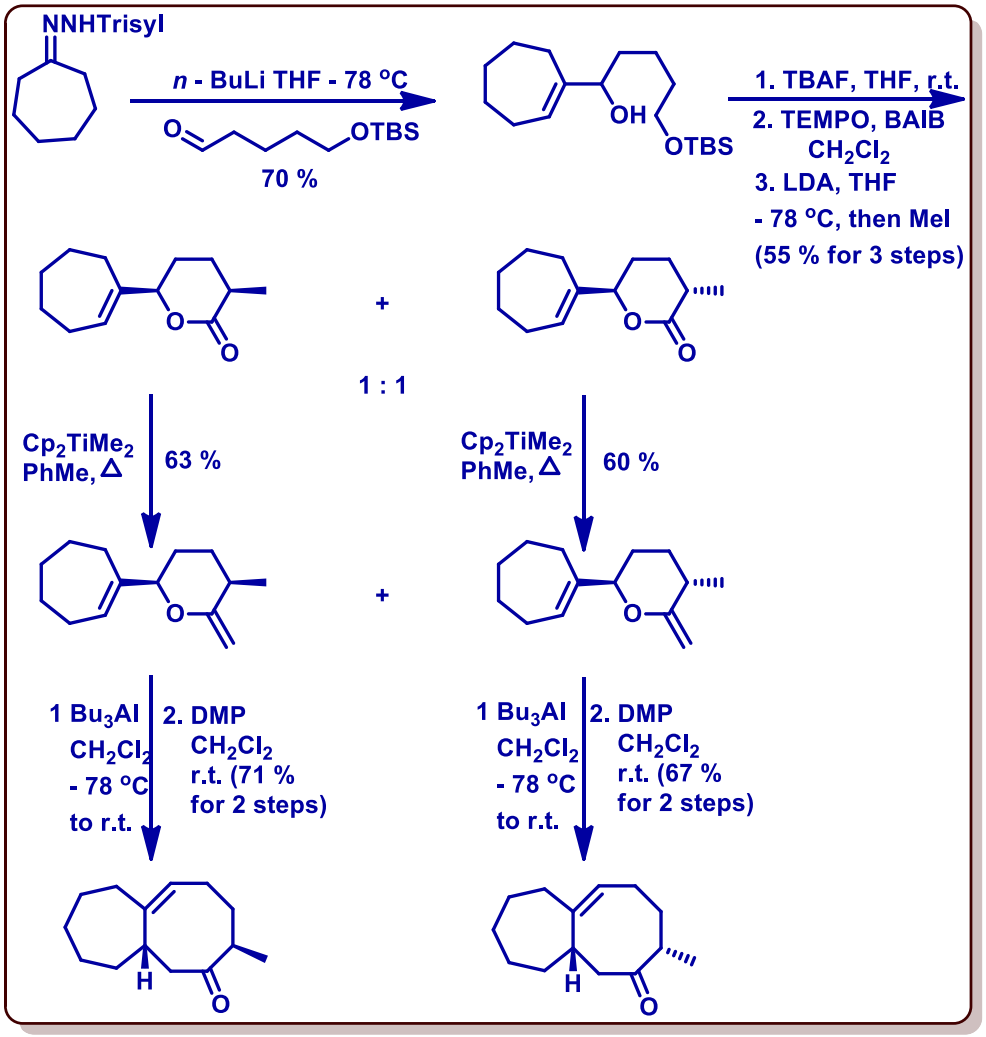


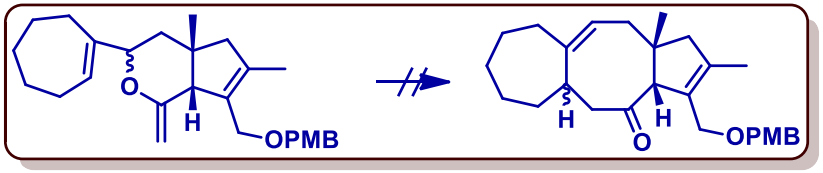
Yang. Z., *et. al.* *Org. Lett.* **2008**, *10*, 665 – 668.

Second Generation Synthesis

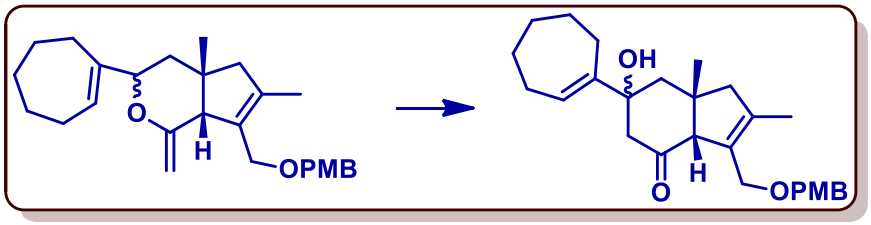


Sigmatropic Rearrangement



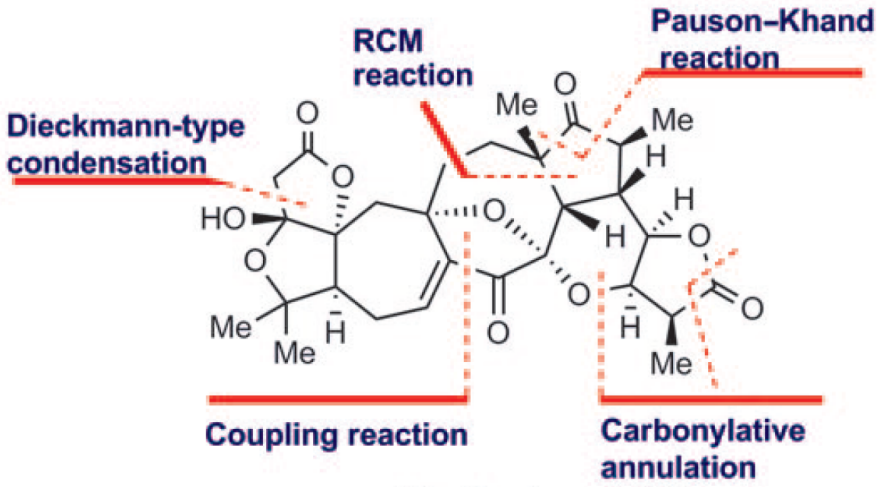


Ferrier Rearrangement



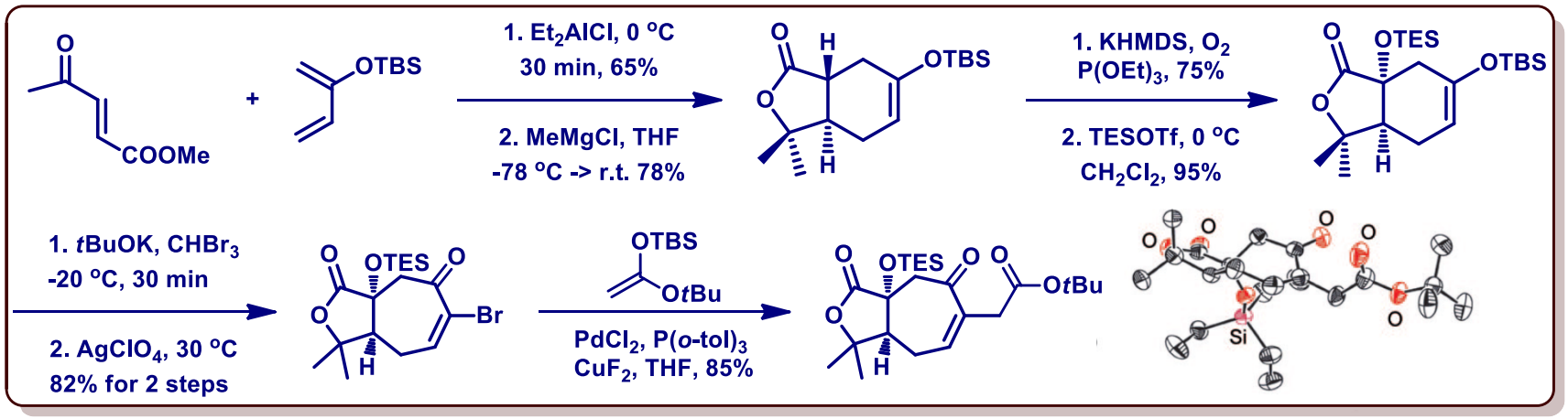
Yang. Z., *et. al. Org. Lett.* **2008**, *10*, 665 – 668.

Third Generation Synthesis



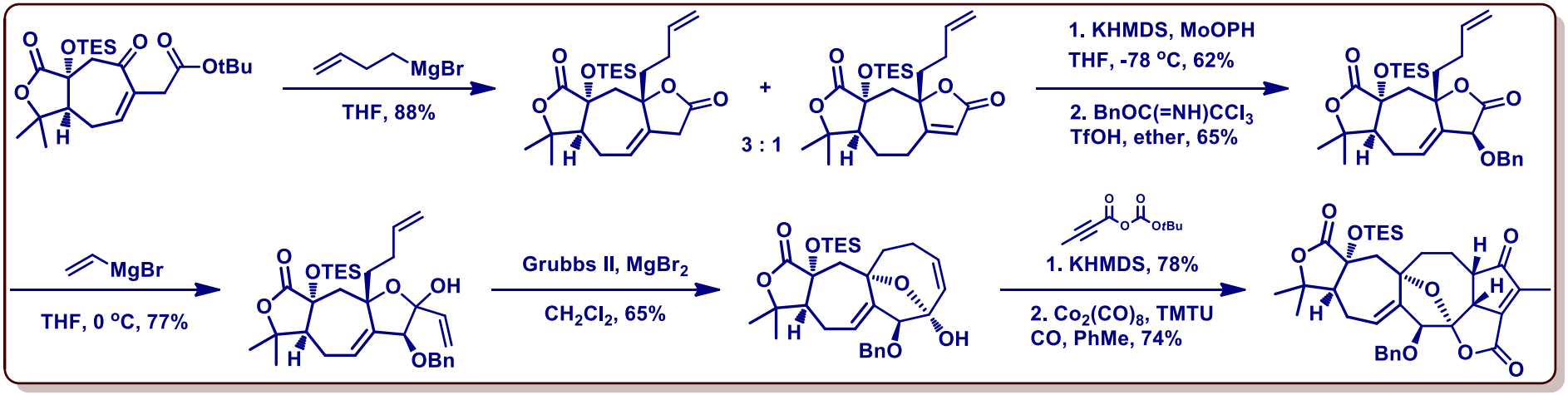
- ***Convergent to Linear***
- ***Oxygen Bridge Formation ahead of Eight Member Ring***

Seven Member Ring



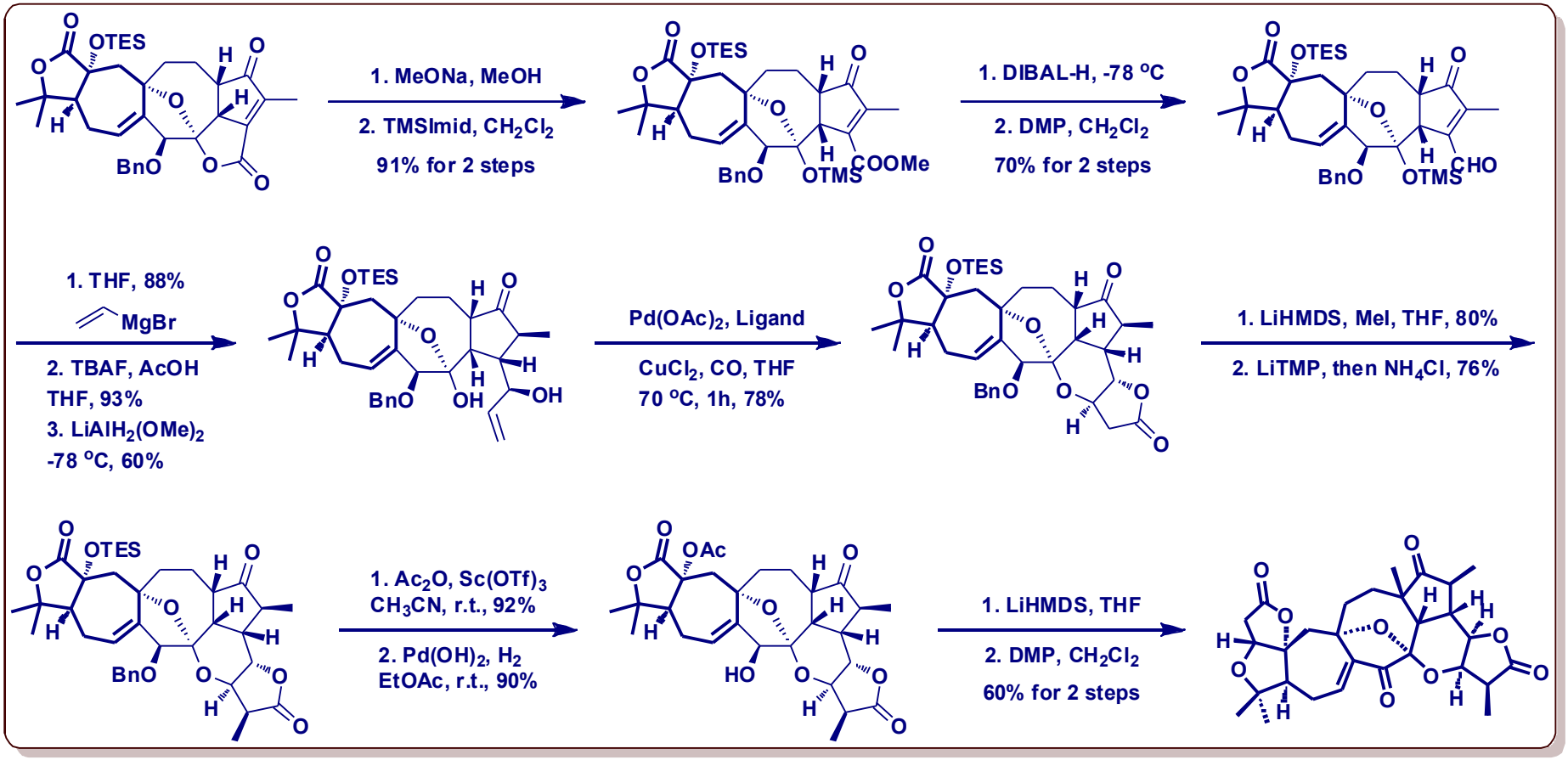
- ***Intermolecular Diels–Alder reaction to set up the B ring system;***
- ***Silvermediated cyclopropane rearrangement to generate the C ring rather then enyne metathesis.***

Eight Member Ring Construction



- ***RCM reaction for the diastereoselective formation of fully the functionalized eight-membered CDE ring system;***
- ***Thiourea/cobalt-catalyzed PKR for the stereoselective construction of the F ring;***

End Game



- ***Thiourea/palladium-catalyzed carbonylative annulation for the stereoselective synthesis of the GH ring system;***
- ***Dieckmann-type condensation to generate the A ring.***

Summary

- *29 Steps, 0.2% yield*
- *Ring-Closing Metathesis*
- *Thiourea/cobalt-catalyzed Pauson–Khand reaction*
- *Thiourea/palladium-catalyzed carbonylative annulation reaction*