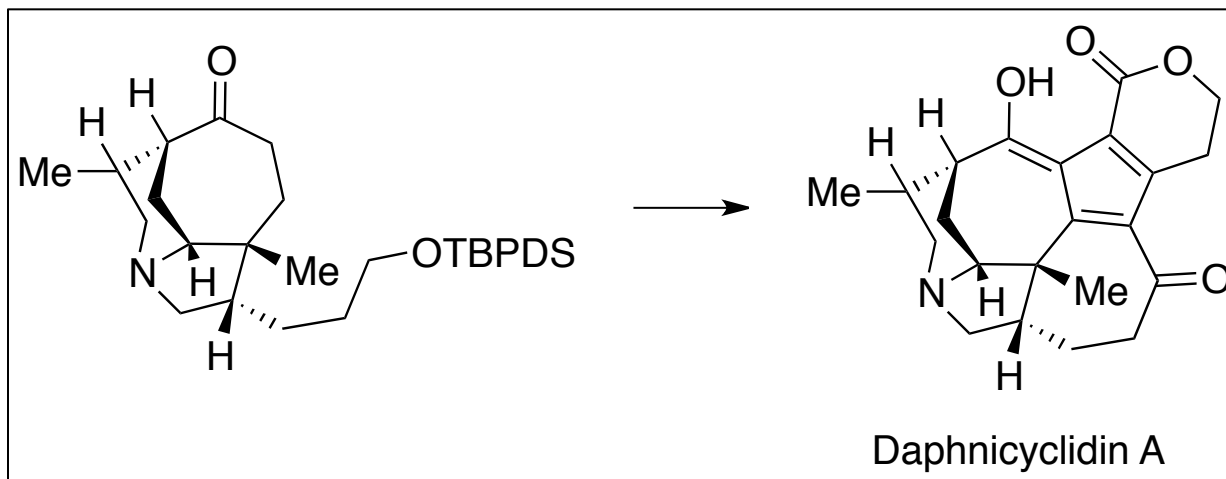


Stereocontrolled Synthesis of the Tricyclic ABC Ring System of Daphnicyclidin A



Mondal, P. K., Bawel, S. A., Nag, P. P., Williams, D. A.; *Org. Lett.*, ASAP
DOI: 10.1021/ol5005092

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Daphniphyllum alkaloids

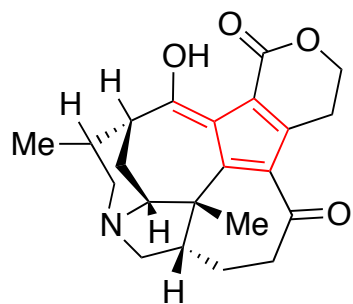
- *Daphniphyllum* alkaloids are isolated from *Daphniphilaceae* (e.g. *D. teijsmanni*)
- Plants are distributed in east and southeast Asia
- First reported isolation of a *Daphniphyllum* alkaloid (daphnimacrine) in 1909 by Yagi
- Over 200 alkaloids isolated so far from 13 species of the genus *Daphniphyllum*
- Alkaloids are generated from six molecules of mevalonic acid via a squalene-like intermediate
- *D.* alkaloids are neurotoxic and target directly the central nervous system, resulting in depression of voluntary movement as well as respiratory function
- Notable constituents of plants used in traditional chinese medicine for treatment of inflammation and other diseases



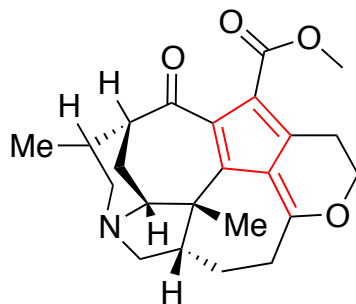
Daphniphyllum teijsmanni

Daphnicyclidines

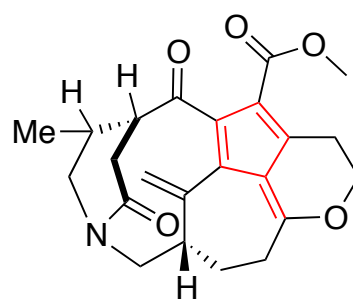
- First isolated in 2001 by Kobayashi and *co-workers*
- Highly modified Daphniphyllum alkaloids
- Unprecedented fused-hexa- or pentacyclic skeletons
- Categorised in 3 subgroups, based on the connectivity associated with the fulvene core



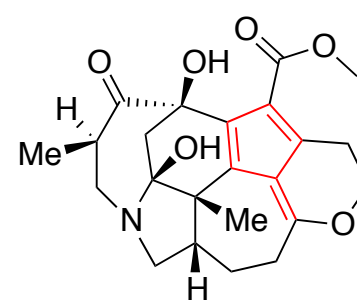
Daphnicyclidin A



Daphnicyclidin D



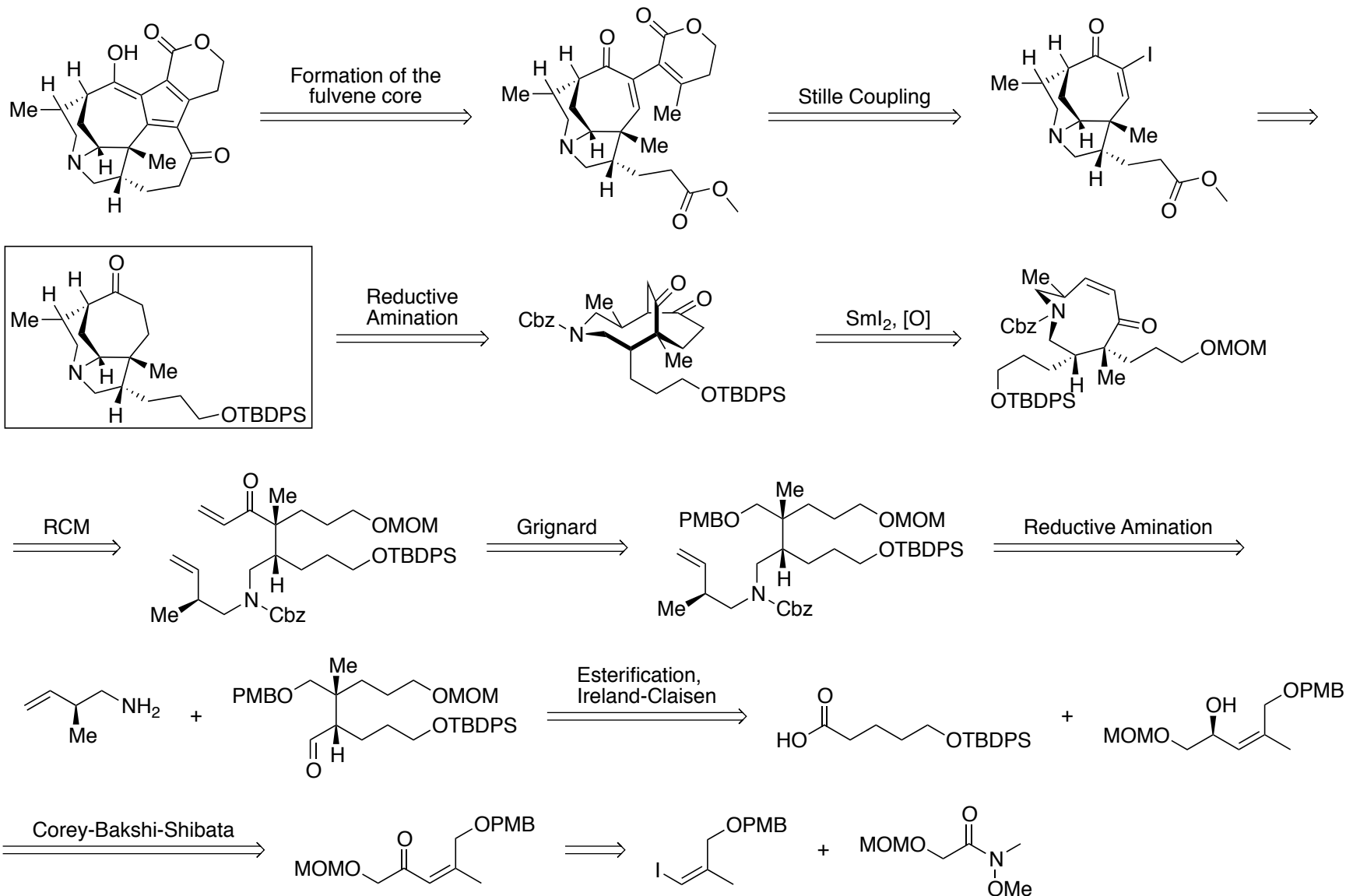
Daphnicyclidin J



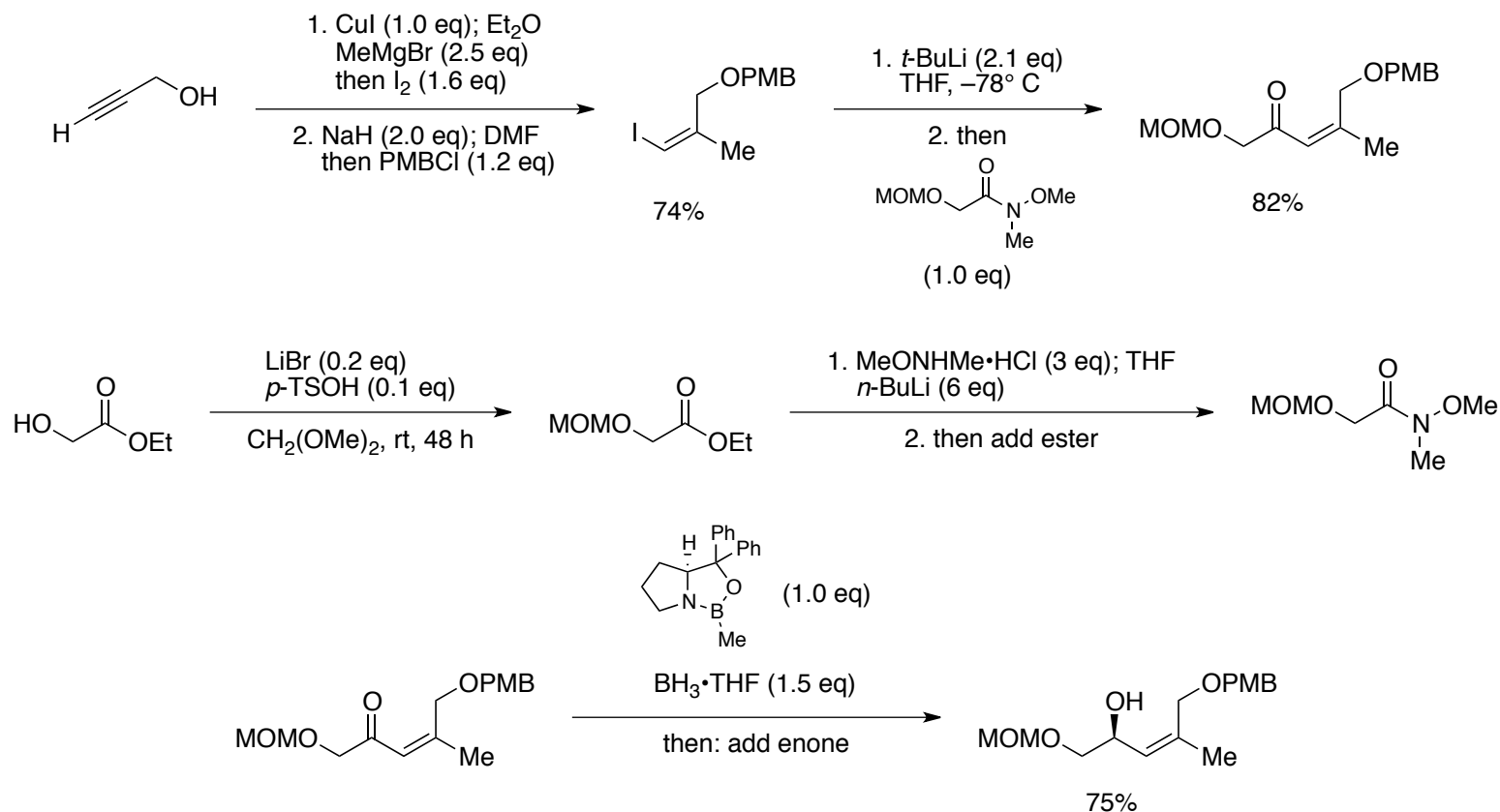
Daphnicyclidin K

Kobayashi, J., Inaba, Y., Shiro, M., Yoshida, N., Morita, H.; *J. Am. Chem. Soc.*, **2001**, *123*, 11402-11408

Retrosynthetic Pathway

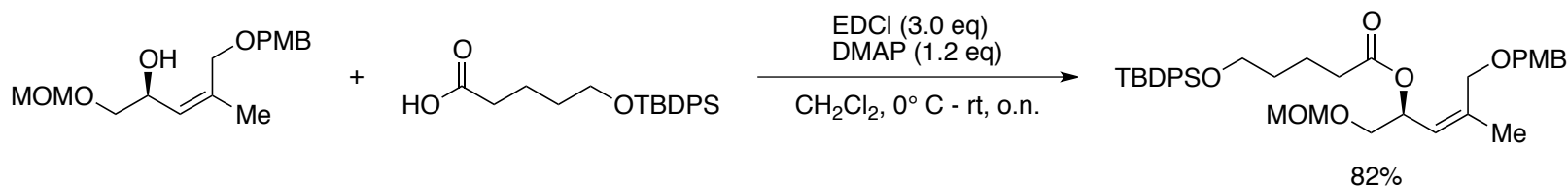


Synthesis of starting (S)-alcohol

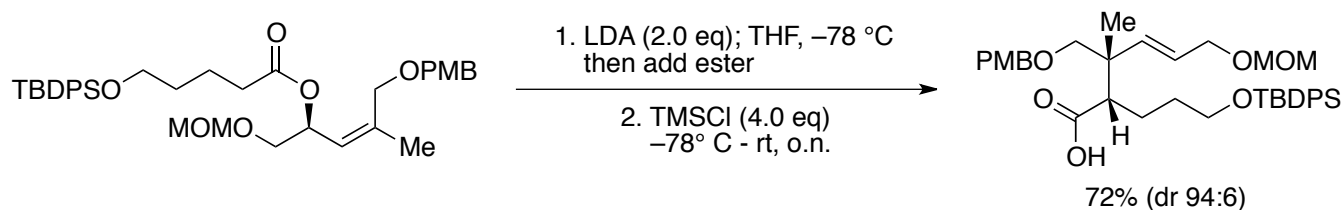


Stereochemical outcome of reaction verified by modified Mosher ester analysis, which also indicated high asymmetric induction ($\geq 99\%$ ee)

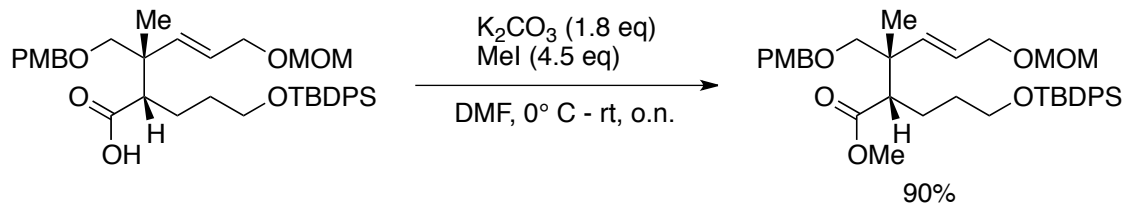
Ireland-Claisen Rearrangement

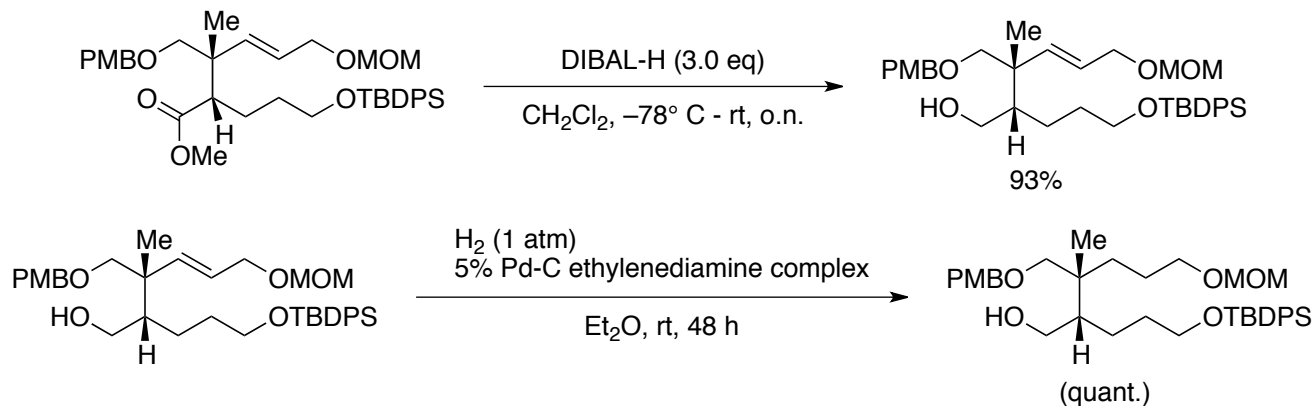


The carboxylic acid was prepared from valerolactone by methanolysis (83%), protection (96%) and hydrolysis



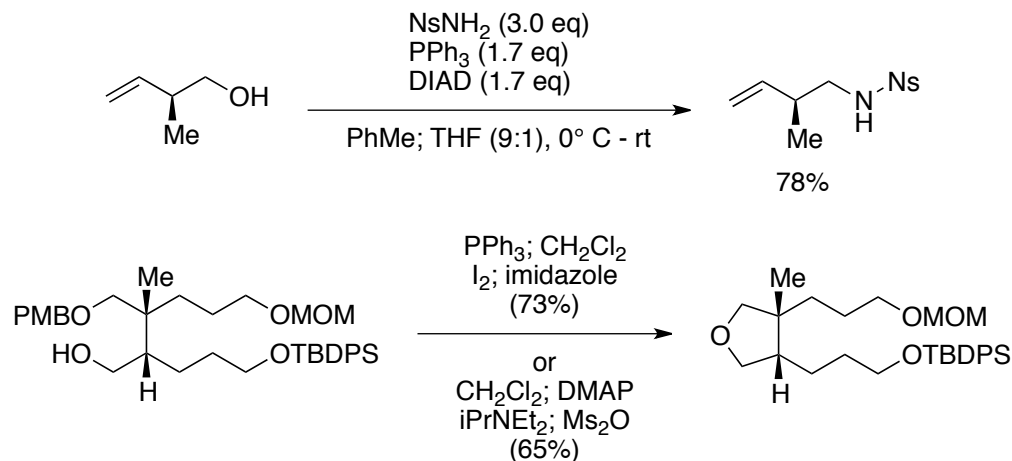
The stereoselectivity of the process was evaluated with DDQ, which directly provided the *cis*-disubstituted lactone.



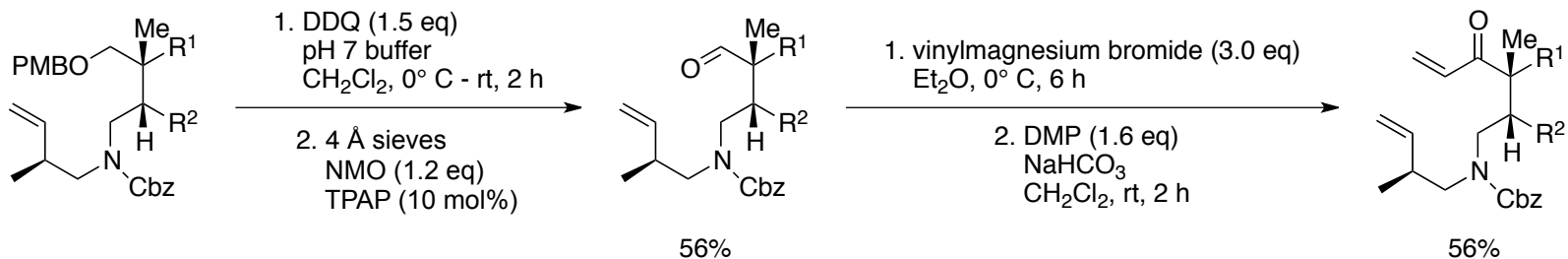
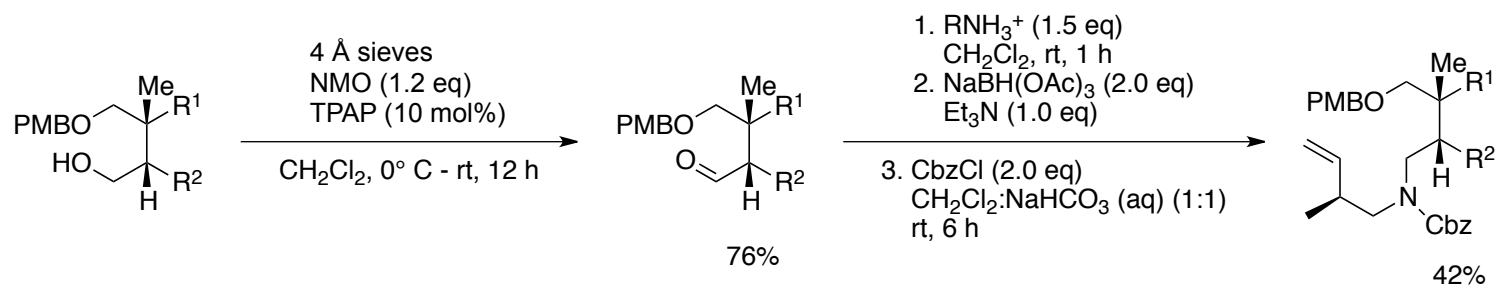
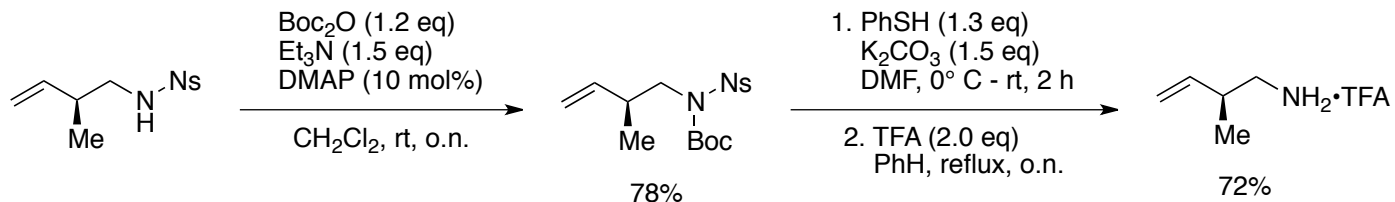


Modified version of the catalyst diminished loss of PMB ether by use of 5% Pd-C (THF byproduct)

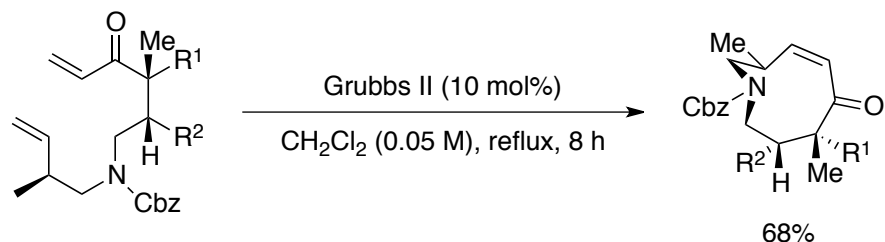
Introduction of Amino Moiety (N-alkylation, Fukuyama-Mitsunobu)



Introduction of Amino Moiety (Transamination)

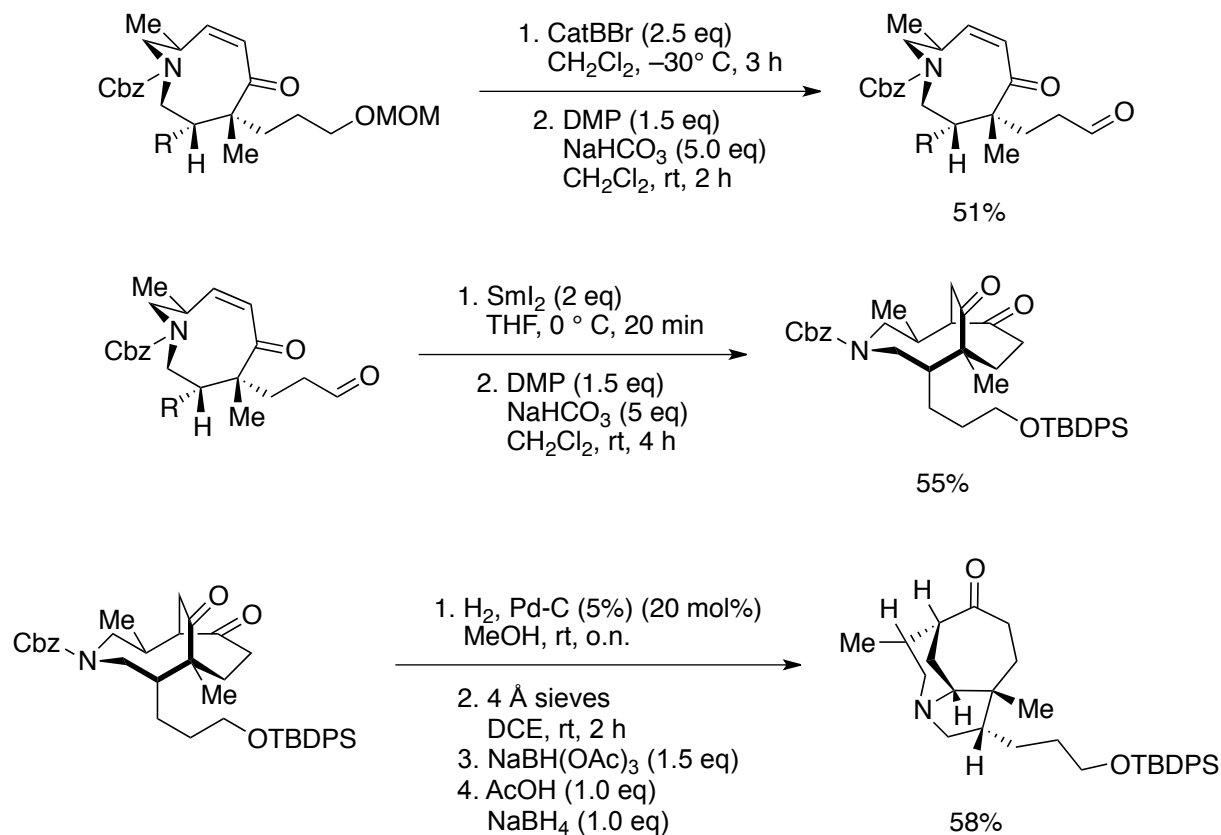


Ring-Closing Metathesis (9-Membered Ring)



- (RCM that yield 9-membered rings are very rare)
- Unusual and unexplored *Z*-hexahydro-(1*H*)-azocine
- Grubbs I was ineffective
- More reactive catalysts resulted in faster consumption of starting material increasing amount of intermolecular reactions
- Precursor allylic alcohol proved to be much less effective substrate, poor yields for RCM

Installing the ABC-Tricyclic System



Reduction of the diketone provided the secondary amine along with the hemiaminal from transannular attack as well as the reduced tricycle

Yu, C., Liu, B., Hu, L.; *Tetrahedron Lett.*, **2000**, *41*, 819–822

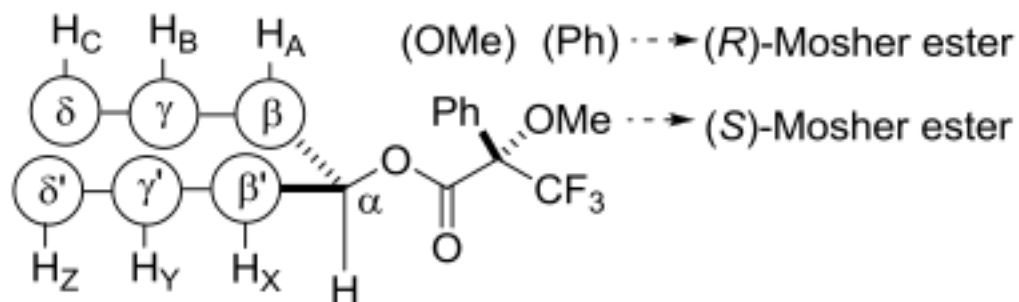
Nguyen, T. M., Siefert, R. J., Mowrey, D. R., Lee, D.; *Org. Lett.*, **2002**, *4*, 3959–3962

Conclusion and Outlook

- Enantiocontrolled pathway of a tricyclic nitrogen containing system as a significant motif representing the ABC system of Daphnicyclidin A
- Preparation of a nine-membered *Z*-hexahydro-(1*H*)-azocine
- Reductive cyclisation of a novel 4-azabicyclo[5.3.2]dodecane system
- 25 linear steps (0.25% overall yield)
- Further studies to incorporate findings for a convergent total synthesis of Daphnicyclidin A are planned

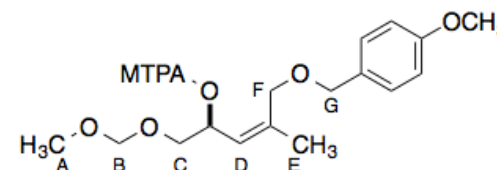
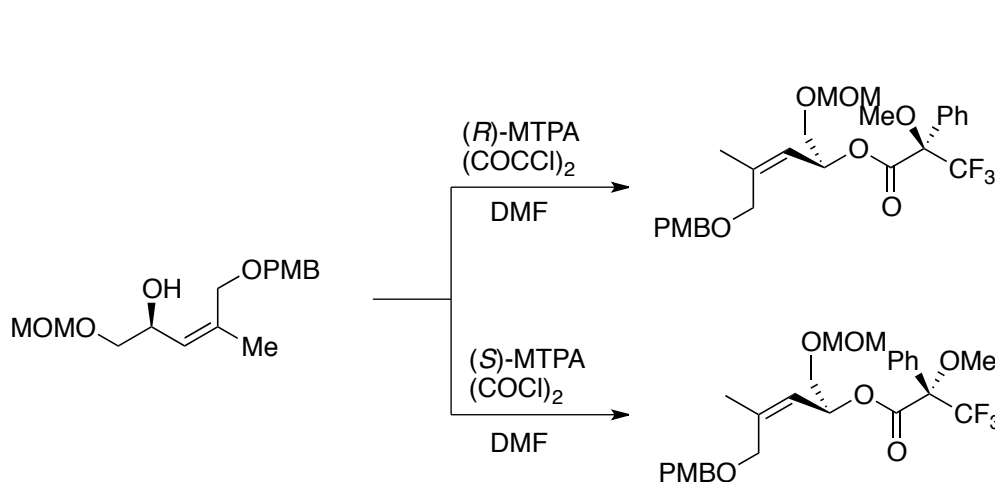
Thank you for your attention

Confirmation of Alcohol Stereochemistry via Mosher Ester Analysis



$$H_A, H_B, H_C: \delta_S - \delta_R = +ve$$

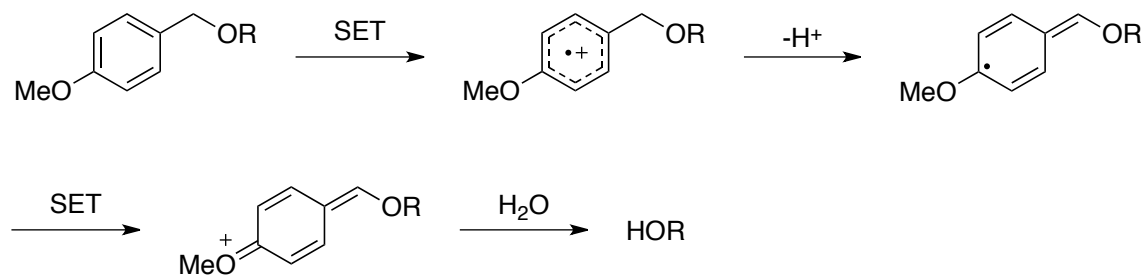
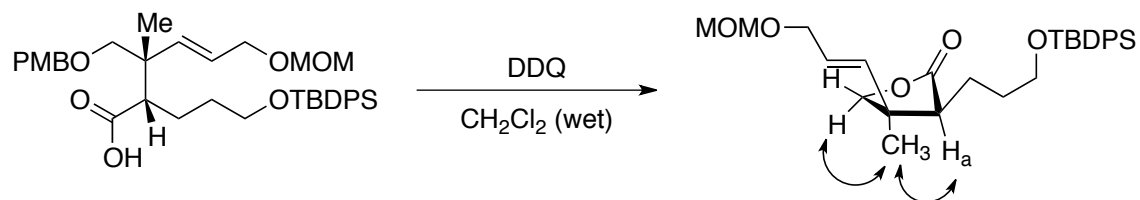
$$H_X, H_Y, H_Z: \delta_S - \delta_R = -ve$$



Proton	δ_S (Hz)	δ_R (Hz)	$\delta_S - \delta_R$ (Hz)
A	1141.211	1140.936	+0.275
B	1589.329	1589.329	+0.000
D	1566.395	1612.951	-46.556
E	514.888	552.119	-10.231
G	1328.293	1330.250	-1.957

Ohtani, I.; Kusumi, T.; Ishitsuk, M. O.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147–3150

Stereoselectivity of the Ireland–Claisen Rearrangement (DDQ)



Williams, D. R., Wals, M. J., Miller, N. A.; *J. Am. Chem. Soc.*, **2009**, *131*, 9038–9045