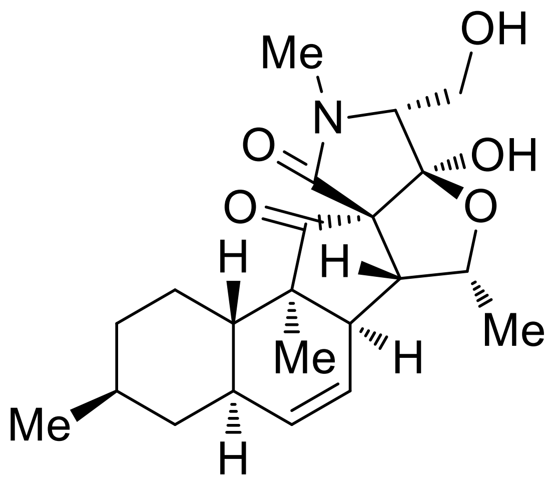
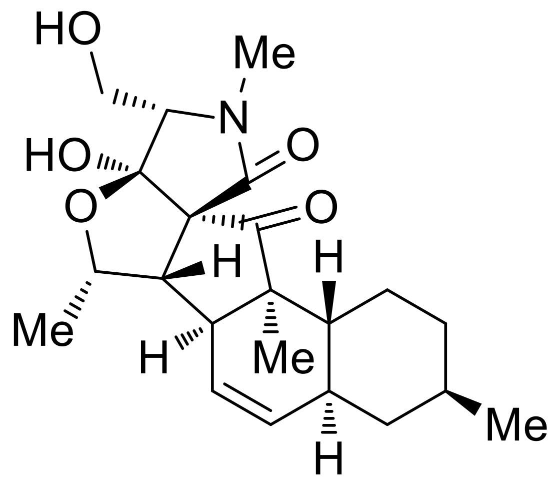
Total Synthesis of (−)-Fusarisetin A

Jun Deng, Bo Zhu, Zhaoyong Lu, Haixin Yu, and Ang L. *JACS.* **2012**, *134*, 920-923



proposed structure of fusarisetin A

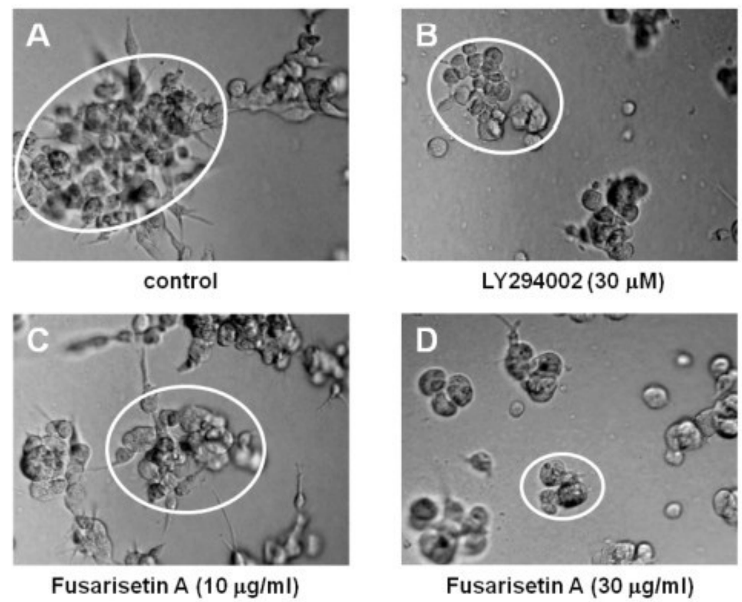


revised structure of fusarisetin A

Yongzhao Yan
Current Lit.
2012.2.18

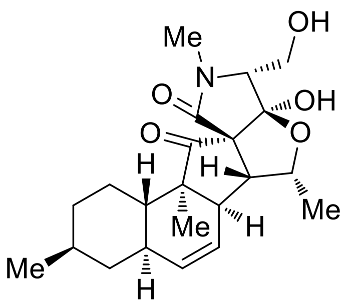
Isolation & Biological Activity

- Isolated from a fraction of fungus *Fusarium* sp. FN080326[a]
- Fungus *Fusarium* sp. FN080326 was isolated from a soil sample in Korea.[a]
- Results showed that ***Fusarisetin* A** inhibits the development of acinar morphogenesis, cell migration, and invasion in MDA-MB-231 cells.[a]
- The molecular target of ***Fusarisetin* A** is different from other compound and is not related to well-known signal pathways for bioactivitites.[a]

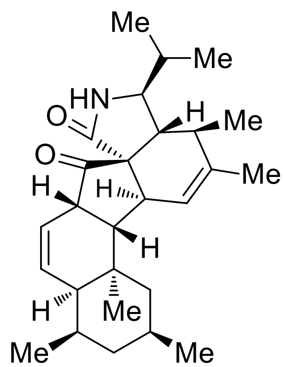


a) Jang, J.-H.; Asami, Y.; Jang, J.-P.; Kim, S.-O.; Moon, D. O.; Shin, K.-S.; Hashizume, D.; Muroi, M.; Saito, T.; Oh, H.; Kim, B. Y.; Osada, H.; Ahn, J. S. *J. Am. Chem. Soc.* **2011**, 133, 6865.
b) Picture of *Fusarium verticillioides,* from Wikipedia.

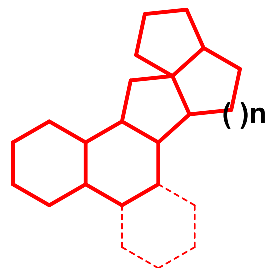
Structurally Similar Metabolites

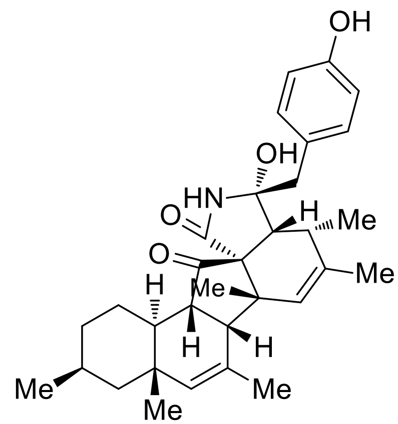


Fusarisetin **A**

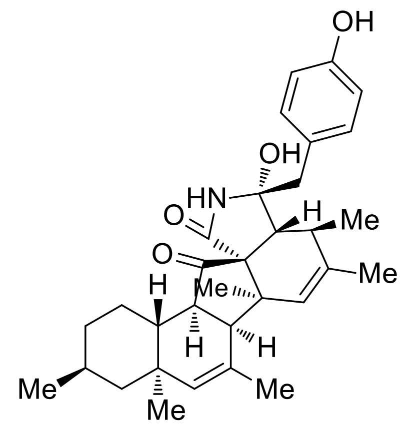


chaetochalasin **A**[a]





phomopsichalasin[b]



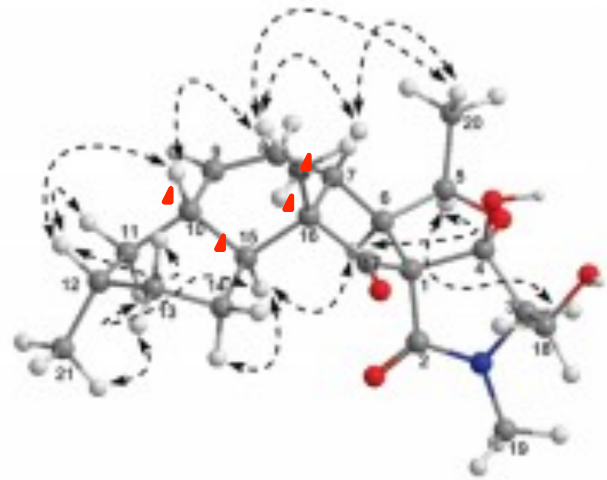
diaporthichalasin[c]

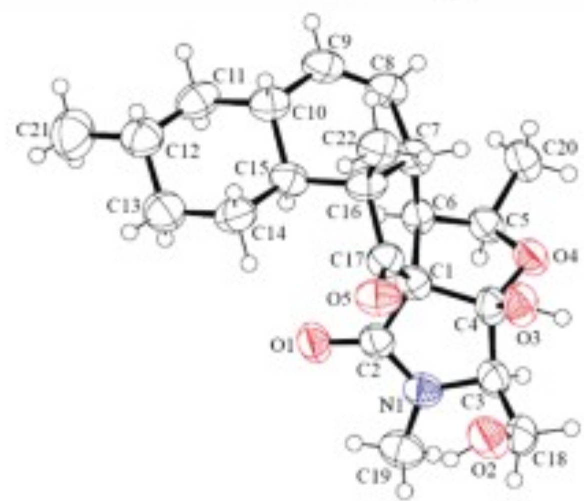
- 5,5,5-angular tricycle motif.
- 6,6,5,5,5-fused pentacyclic ring system, 10 stereocenters.
- Chaetochalasin A displayed cytotoxicity against human tumor cell line.[a]
- Diaporthichalasin exhibited significantly potent inhibition of CYP3A4 with an IC_{50} value of 0.626 µM.[c]

a) Oh, H.; Swenson, D. C.; Gloer, J. B. *Tetrahedron Lett.* **1998**, 39, 7633.
b) Horn, W. S.; Simmonds, M. S. J.; Schwartz, R. E.; Blaney, W. M. *Tetrahedron* **1995**,51, 3969.
c) Pornpakakul, S.; Roengsumran, S.; Deechangvipart, S.; Petsom, A.; Muangsin, N.; Ngamrojnavanich, N.; Sriubolmas, N.; Chaichit, N.; Ohta, T. *Tetrahedron Lett.* **2007**, 48, 651.

Structure Elucidation

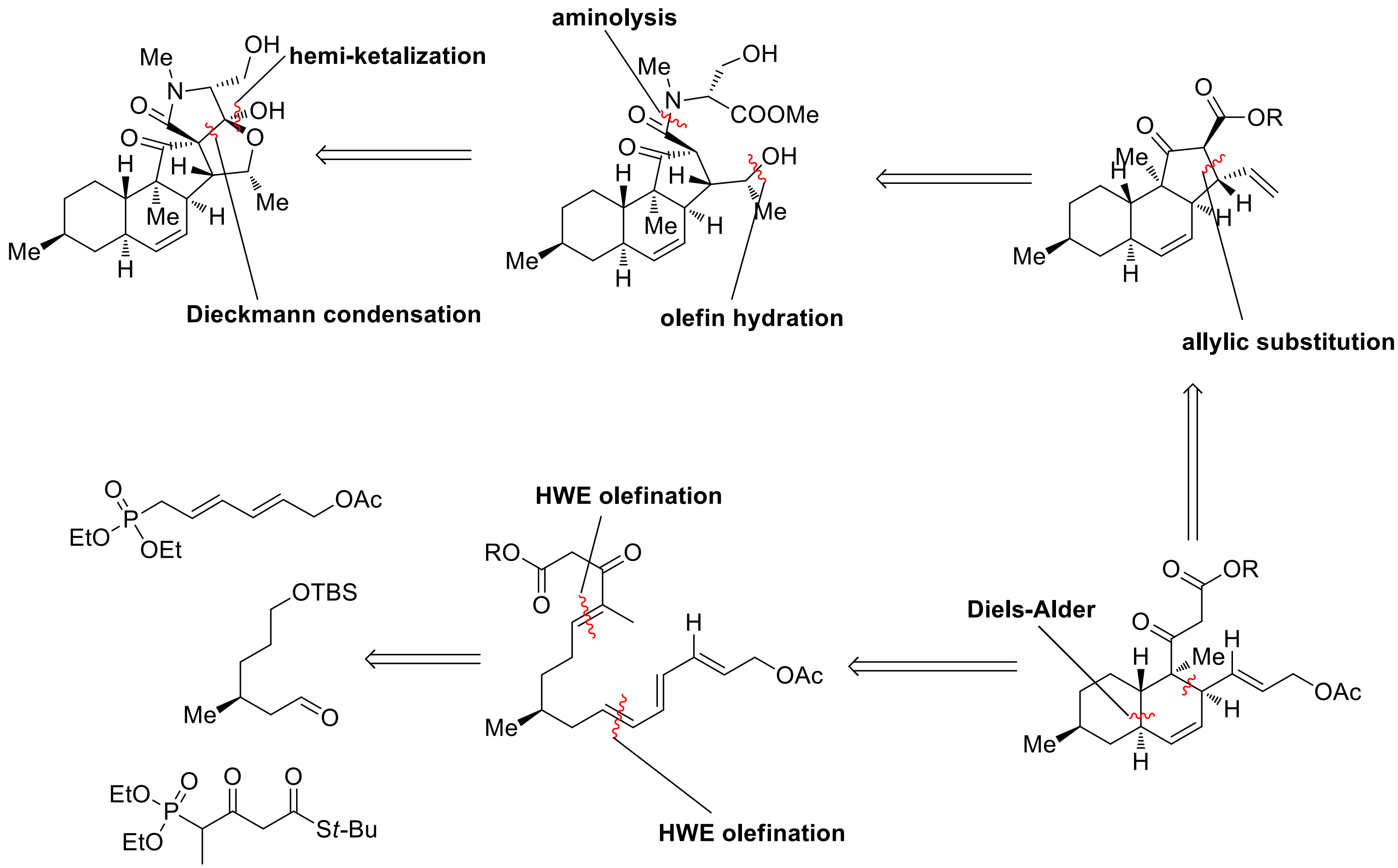
- The structure of 1 was determined in detail by 2D NMR and circular dichroism spectroscopy and X-ray analysis.[a]
- Trans junction of the decalin ring system and the cis junction between the tricyclic and decalin ring systems.[a]
- The configuration of C1 is confirmed by the 3D X-ray stucture. [a]





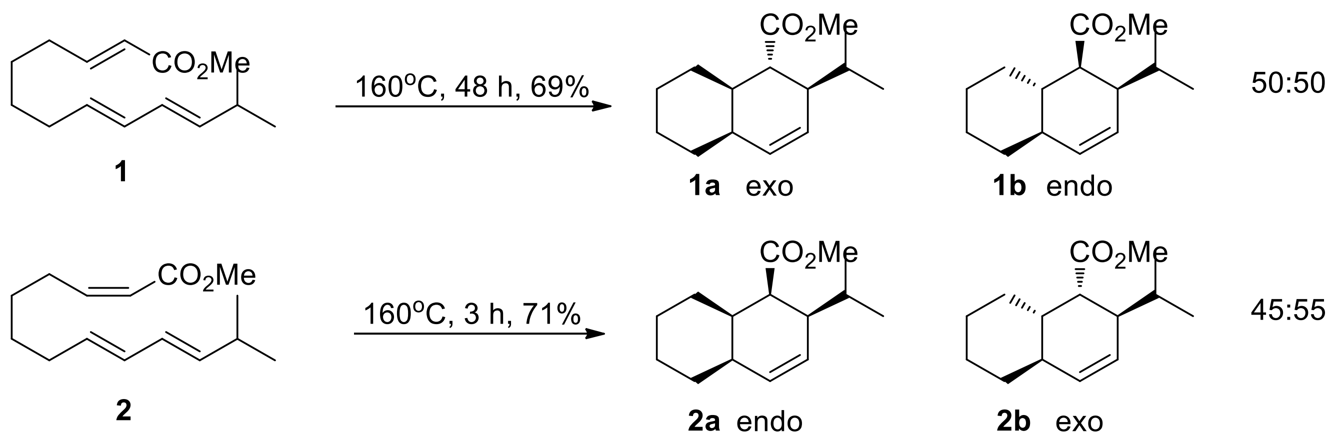
a) Jang, J.-H.; Asami, Y.; Jang, J.-P.; Kim, S.-O.; Moon, D. O.; Shin, K.-S.; Hashizume, D.; Muroi, M.; Saito, T.; Oh, H.; Kim, B. Y.; Osada, H.; Ahn, J. S. *J. Am. Chem. Soc.* **2011**, 133, 6865.

Retrosynthetic Analysis



a) Deng J.; Zhu B.; Lu Z.; Yu H.; Li A., *J. Am. Chem. Soc.*, **2012**, *134* , 920–923.

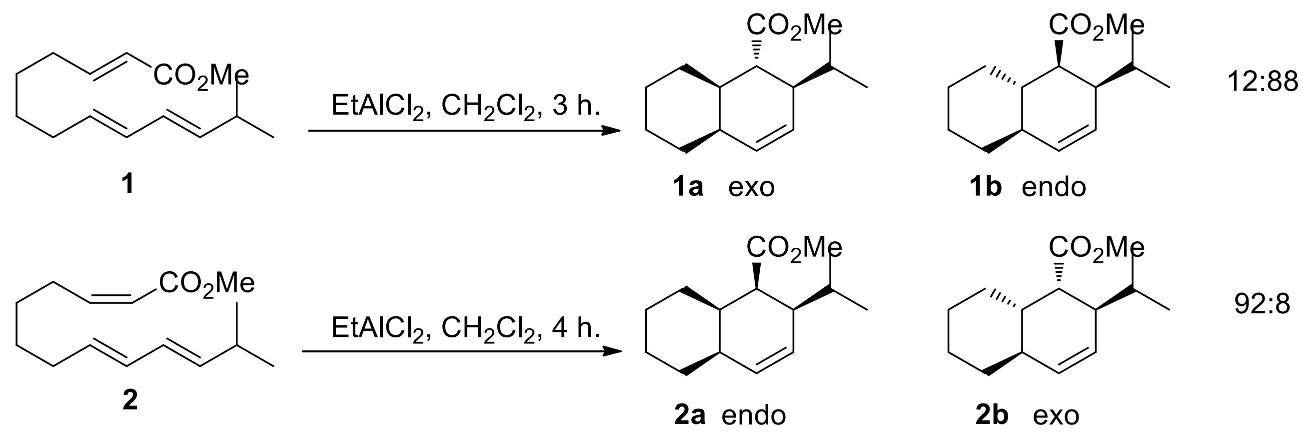
Intramolecular Diels-Alder Reaction



- Under thermo condition, product selectivity is independent with dienophile stereochemistry.[a,b]

a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, 103, 5200.
b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, 47, 4825.

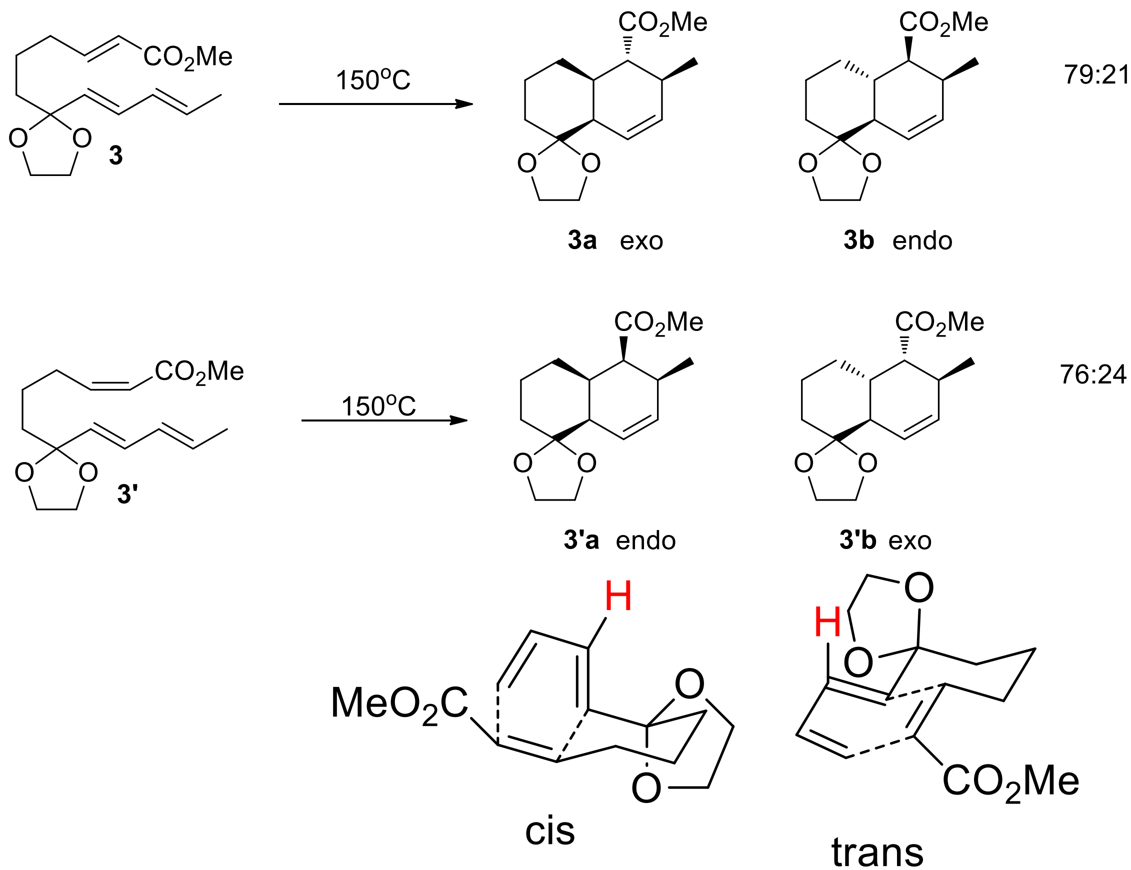
Intramolecular Diels-Alder Reaction



- In the presence of $EtAlCl_2$, the major product of each cyclization is endo-product. [a,b]

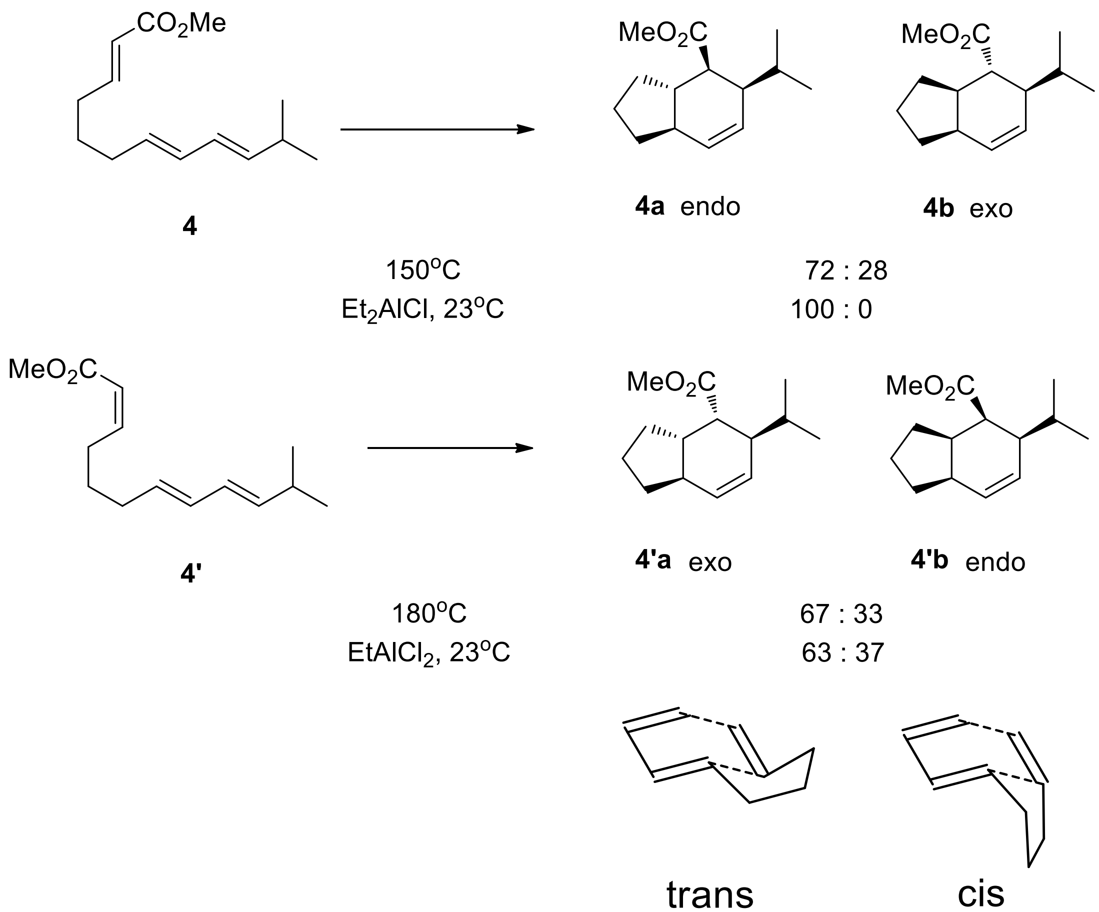
a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, 103, 5200.
b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, 47, 4825.

Intramolecular Diels-Alder Reaction



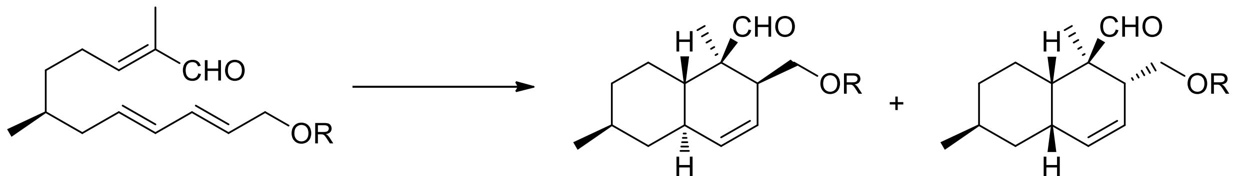
a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, 103, 5200.
b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, 47, 4825.

Intramolecular Diels-Alder Reaction



a) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, 104, 2269.
b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, 47, 4825.

Intramolecular Diels-Alder Reaction



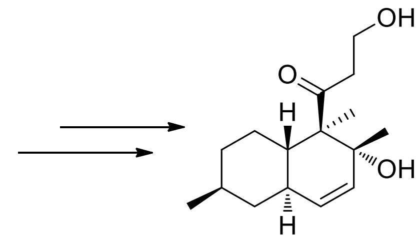
5

5a endo

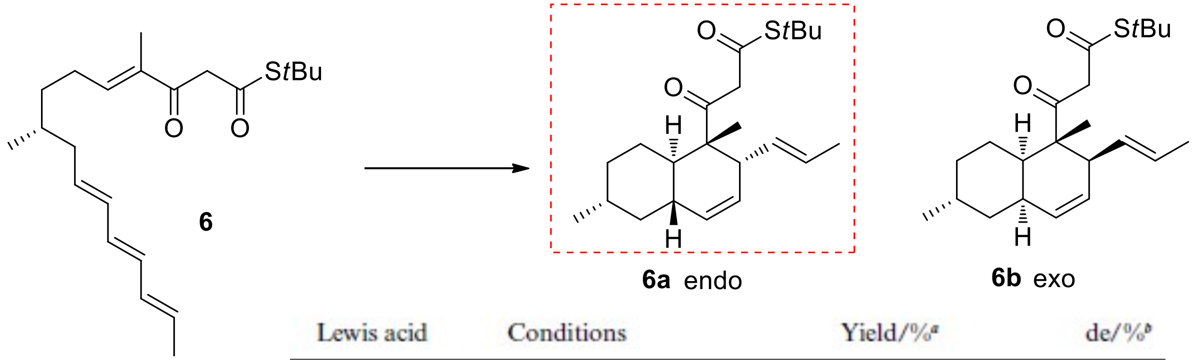
5b exo

Toluene, 150°C, 36%	**5a**:**5b** = 2:1
CH_2Cl_2, Et_2AlCl, 78%	**5a**:**5b** = 10:1

5a



aspermytin A



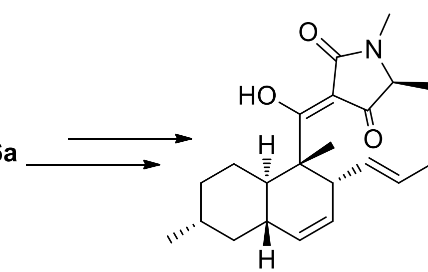
6

6a endo

6b exo

Lewis acid	Conditions	Yield/%[a]	de/%[b]
$ZnCl_2$	CH_2Cl_2, rt	No reaction	—
$EtAlCl_2$	CH_2Cl_2, −78 °C	Decomposition	—
$MeAlCl_2$	CH_2Cl_2, −78 °C	Decomposition	—
Me_2AlCl	CH_2Cl_2, −78 °C	35	>95
Me_3Al	CH_2Cl_2, −78 °C	41	>95
$LiClO_4$	Et_2O, rt	70	85
$BF_3 \cdot Et_2O$	CH_2Cl_2, −78 °C to 0 °C	71	>95

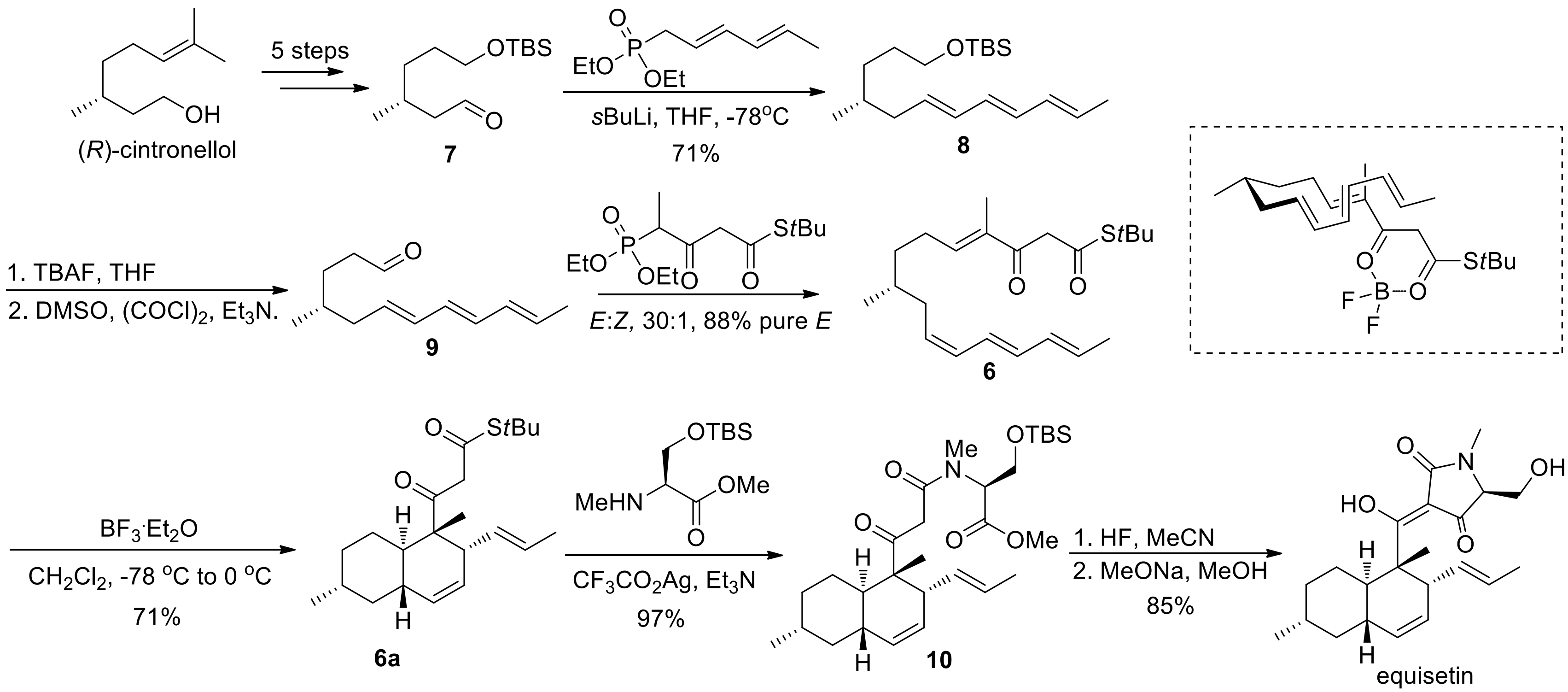
6a



equisetin

a) Inoue, A.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2010**, 51, 3966.
b) Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Biomol. Chem.* **2005**, 3, 274.

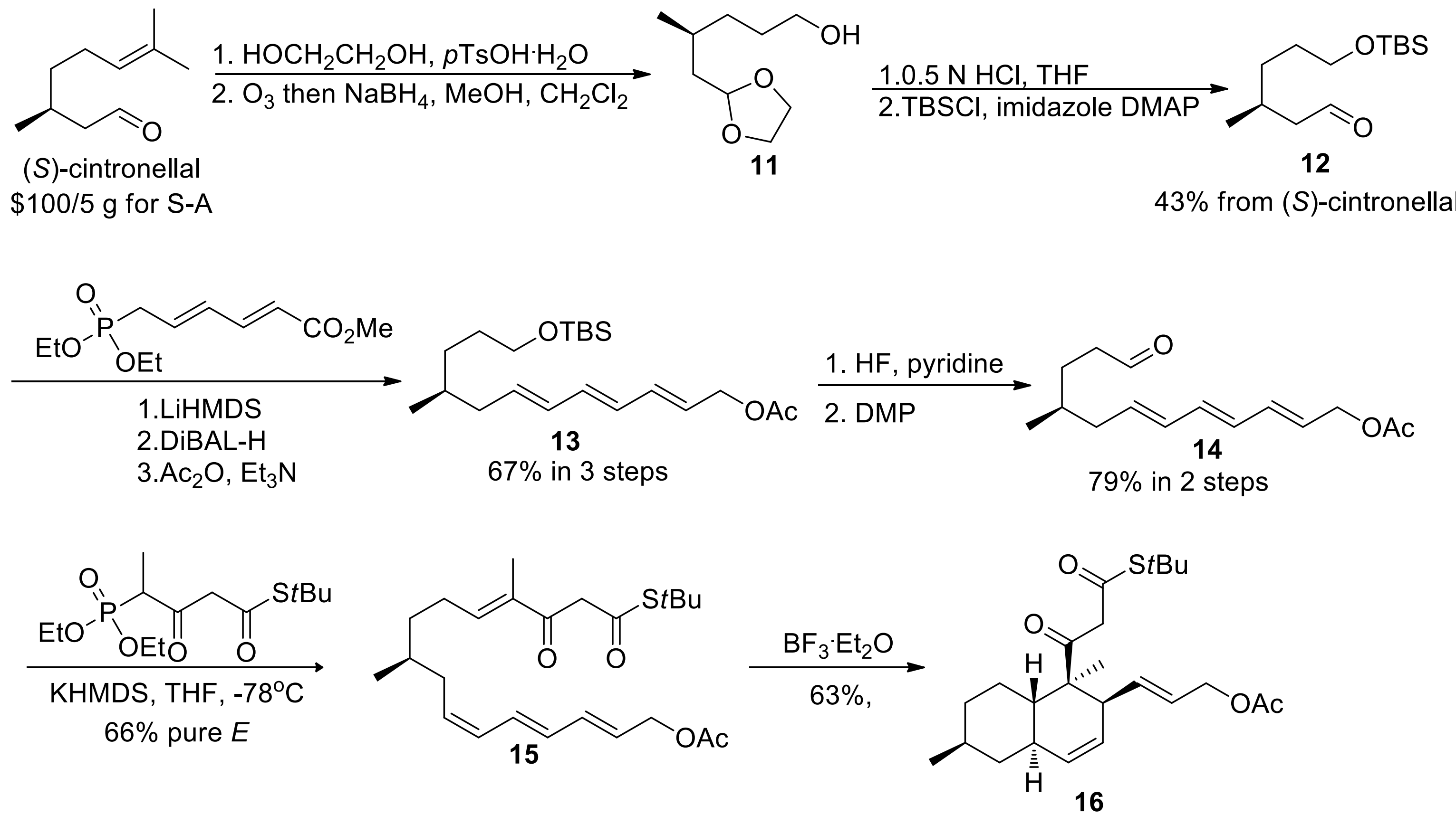
Total Synthesis of Equisetin



a) Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Lett.* **2000**, 2, 3611.

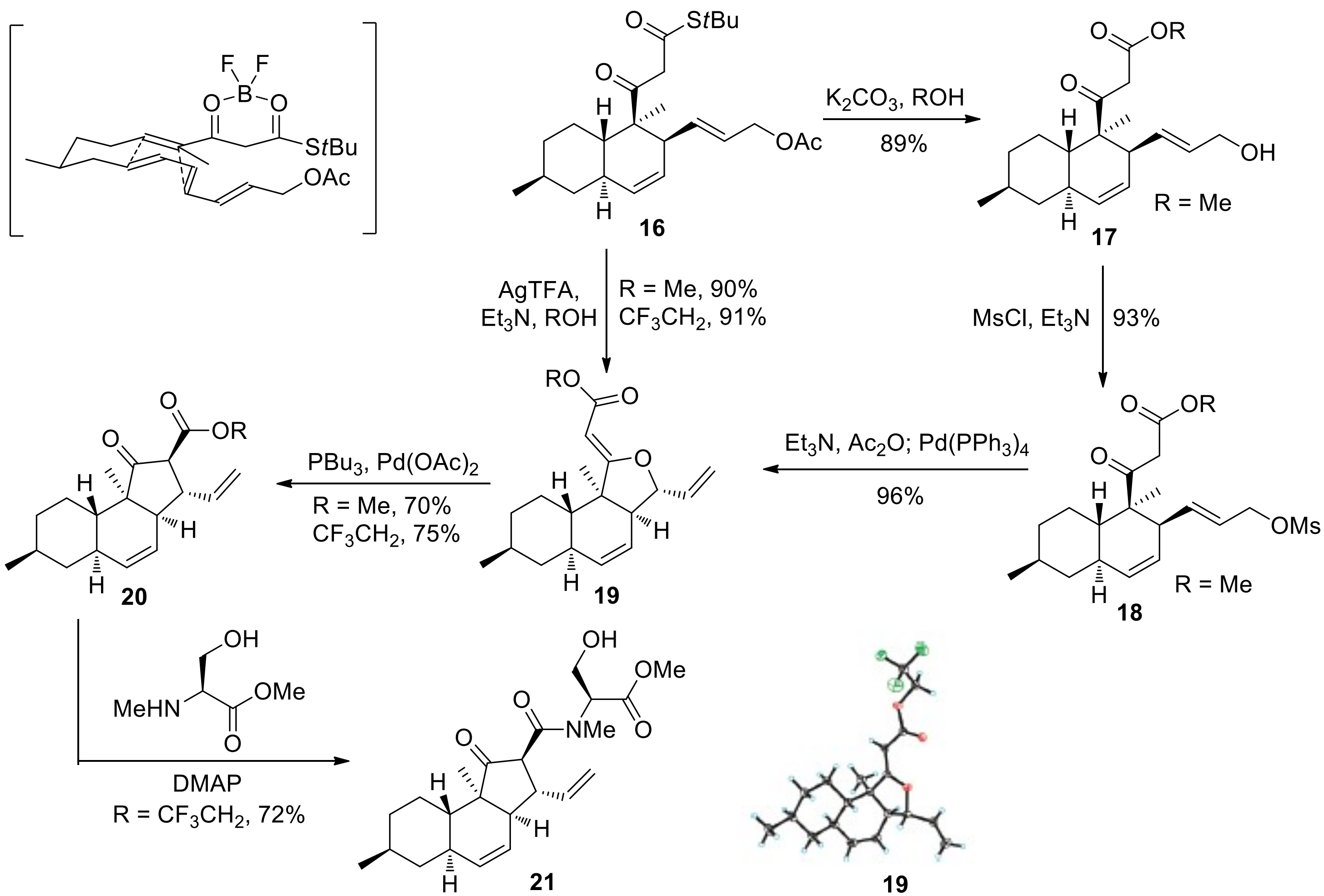
b) Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Biomol. Chem.* **2005**, 3, 274.

Total Synthesis of (−)-Fusarisetin A



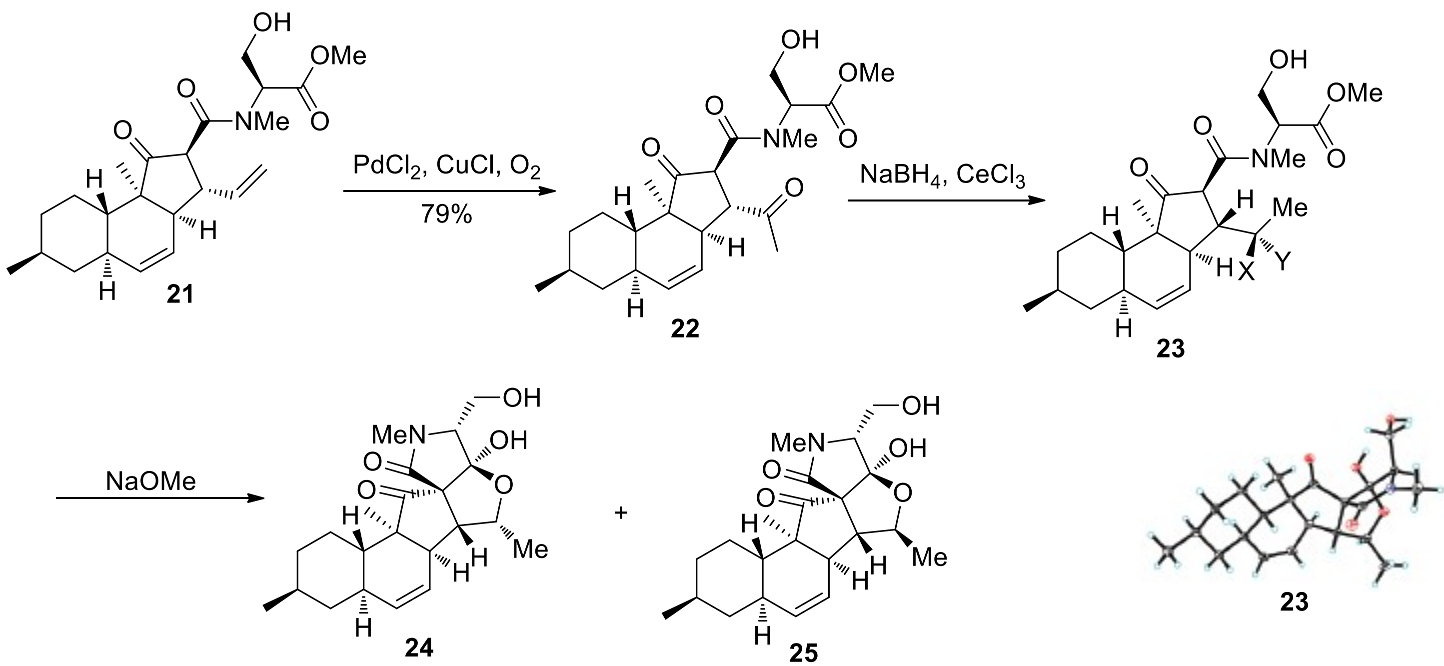
a) Deng J.; Zhu B.; Lu Z.; Yu H.; Li A., *J. Am. Chem. Soc.*, **2012**, *134* , 920–923.

Total Synthesis of (−)-Fusarisetin A



a) Deng J.; Zhu B.; Lu Z.; Yu H.; Li A., *J. Am. Chem. Soc.*, **2012**, *134* , 920–923.

Total Synthesis of (–)-Fusarisetin A



proposed structure of fusarisetin A
ent-fusarisetin A
41%

5-*epi*-*ent*-fusarisetin A
8%

a) Deng J.; Zhu B.; Lu Z.; Yu H.; Li A., *J. Am. Chem. Soc.*, **2012**, *134* , 920–923.

Summary

- First total synthesis of enantiomer fusarisetin A
- 17 steps, yield 1.5%
- Featured with a Lewis acid-promoted intramolecular Diels-Alder reaction, a Pd-catalyzed O-C allylic rearrangement, a chemoselective Wacker oxidation and a Dieckmann condensation/hemiketalization.