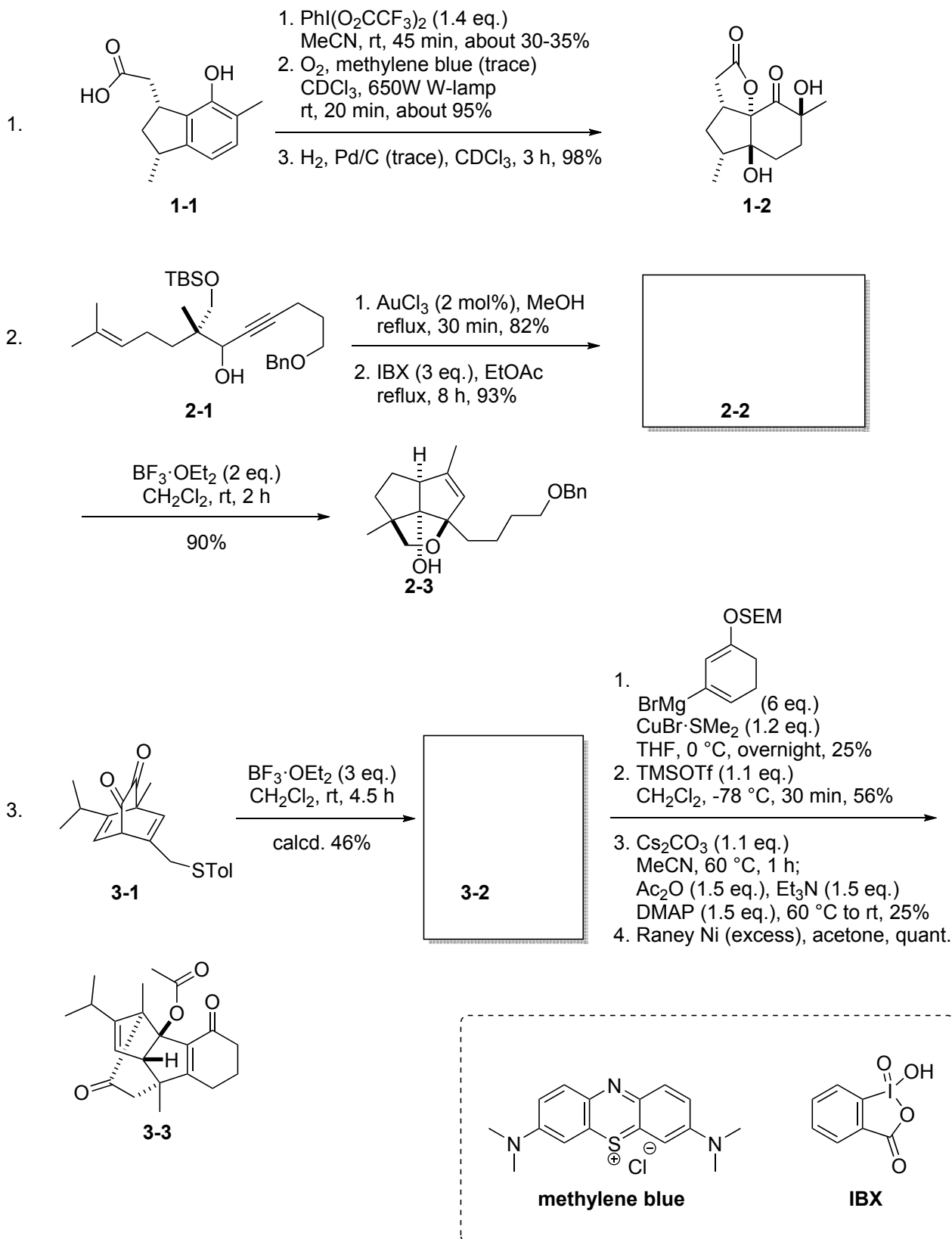


Problem Session (7)

2016/02/27 MASANORI NAGATOMO

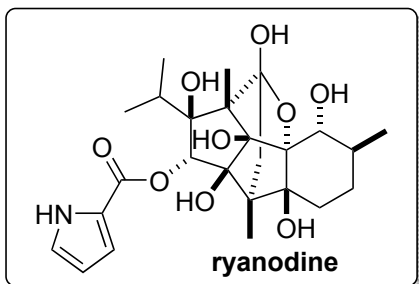
Please fill in the blanks and explain reaction mechanisms



Problem Session (7)- Answer

2016/02/27 MASANORI NAGATOMO

Topic: Studies toward Total Synthesis of Ryanodine



Isolation:

roots and stems of *Ryania speciosa Vahl*
Folkers, K. et al. *J. Am. Chem. Soc.* **1948**, 70, 3086.

Biological Activity:

modulation of Ca^{+2} release channel (ryanodine receptor)
Sutko, J. L. et al. *Pharmacol. Rev.* **1997**, 49, 53.

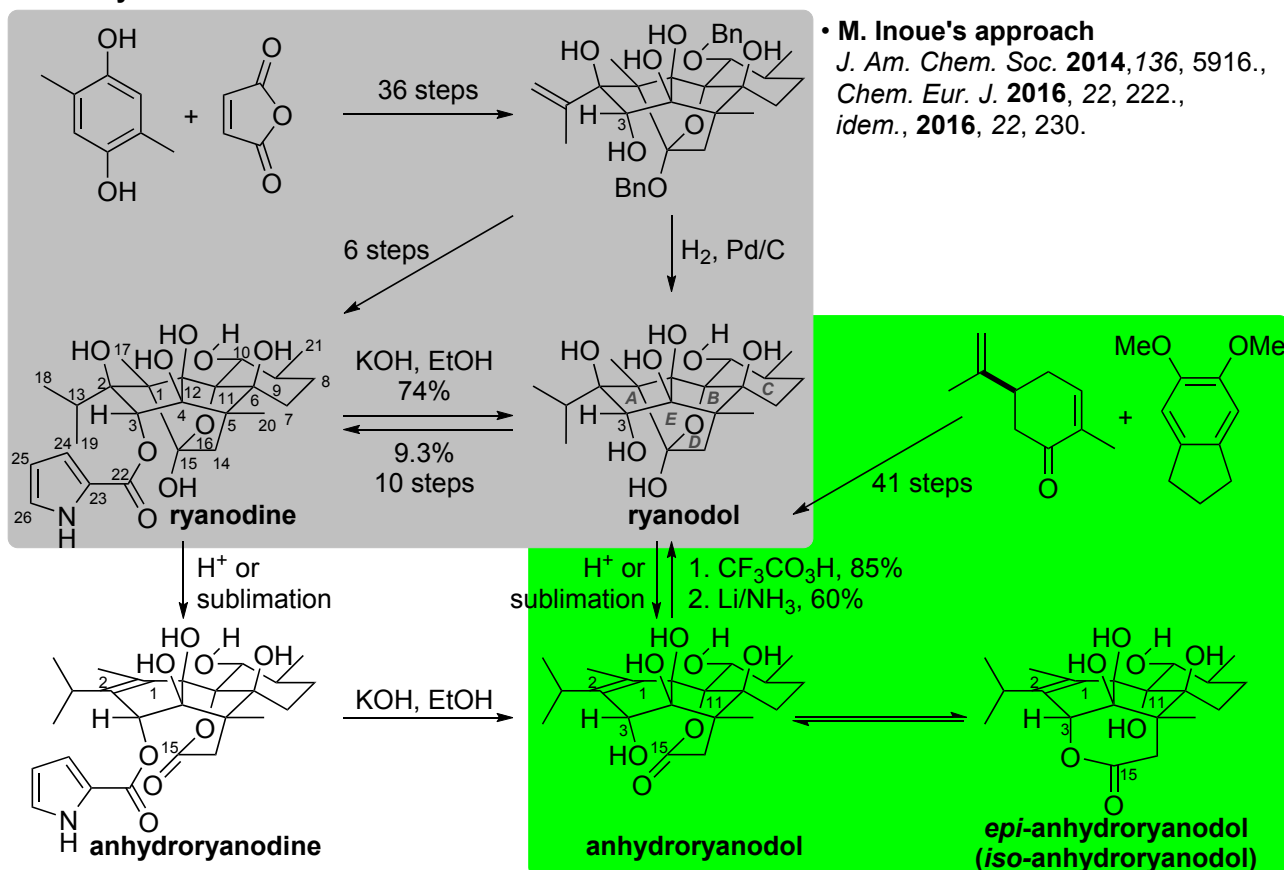
Structure Elucidation:

a) Wiesner, K. *Adv. Org. Chem.* **1972**, 8, 295.

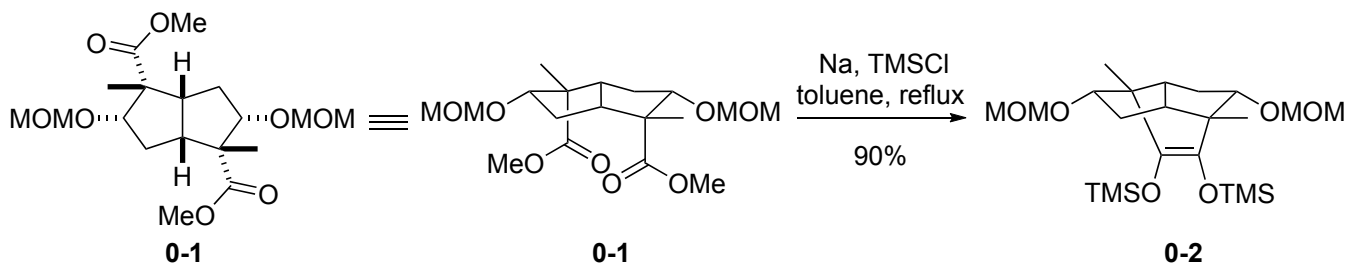
Structural Features:

1H-pyrrole-2-carboxylate ester at the C3-position &
complex five fused rings (ABCDE-rings) with 11 contiguous stereocenters.

• Total synthesis



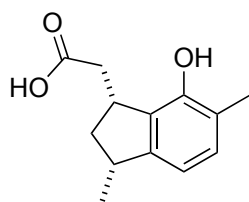
• Others approach



Sieburth, S. McN. et al. *Tetrahedron Lett.* **1994**, 35, 8127.

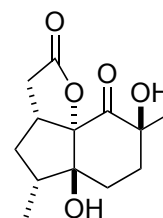
See also: 150124_PS_Masanori_NAGATOMO_Tricyclo[5.3.0.0]decane.pdf

1.



1-1

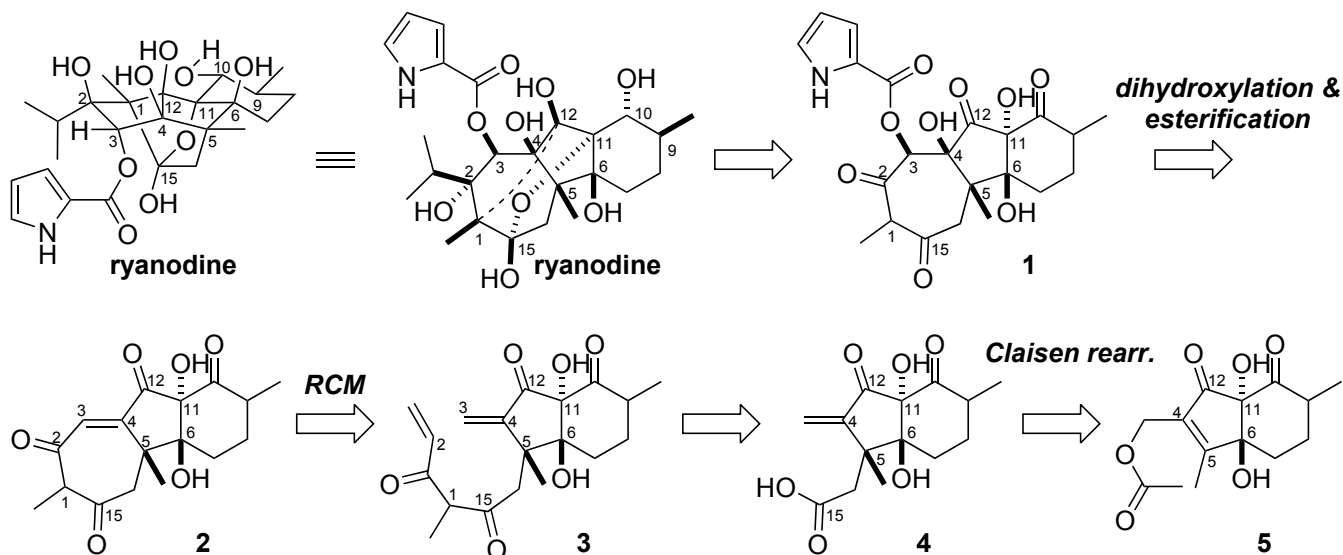
1. $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ (1.4 eq.)
MeCN, rt, 45 min, about 30-35%
2. O_2 , methylene blue (trace)
 CDCl_3 , 650W W-lamp (350—3,000 nm)
rt, 20 min, about 95%
3. H_2 , Pd/C (trace), CDCl_3 , 3 h, 98%



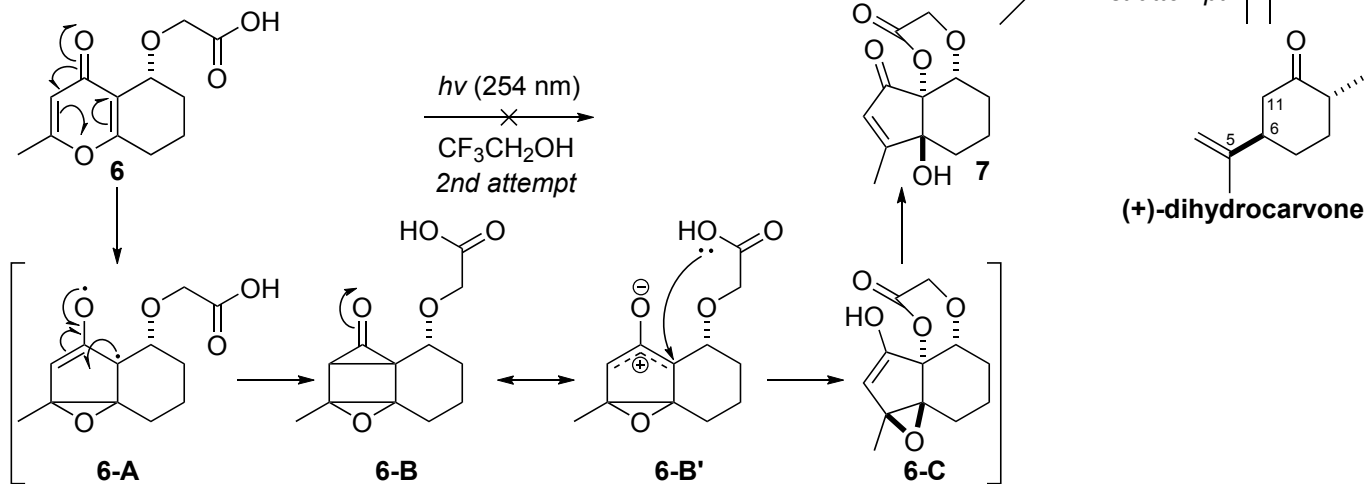
1-2

"Application of phenolic oxidation chemistry in synthesis: preparation of the BCE ring system of ryanodine"
John L. Wood,* Jens K. Graeber and Jon T. Njardarson *Tetrahedron* **2003**, *59*, 8855.

• The first Wood's retrosynthesis of ryanodine



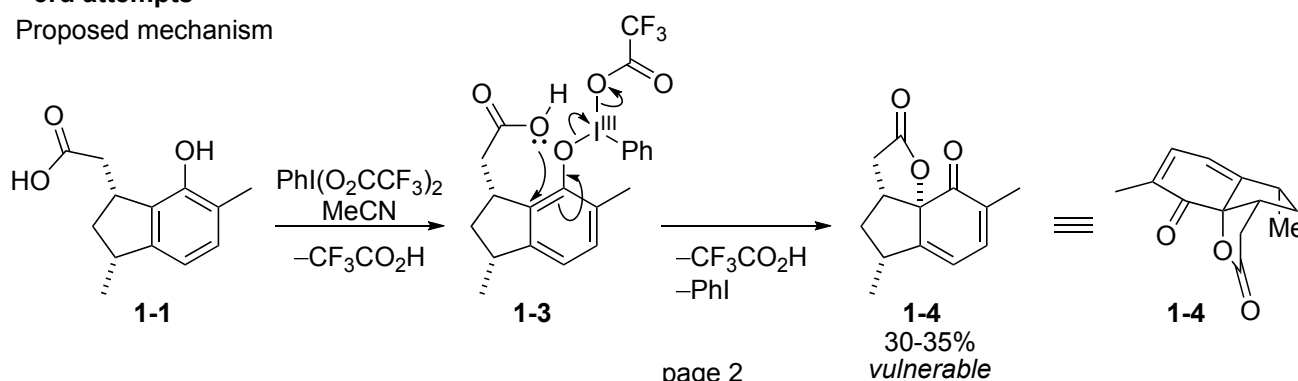
• 1st and 2nd attempts



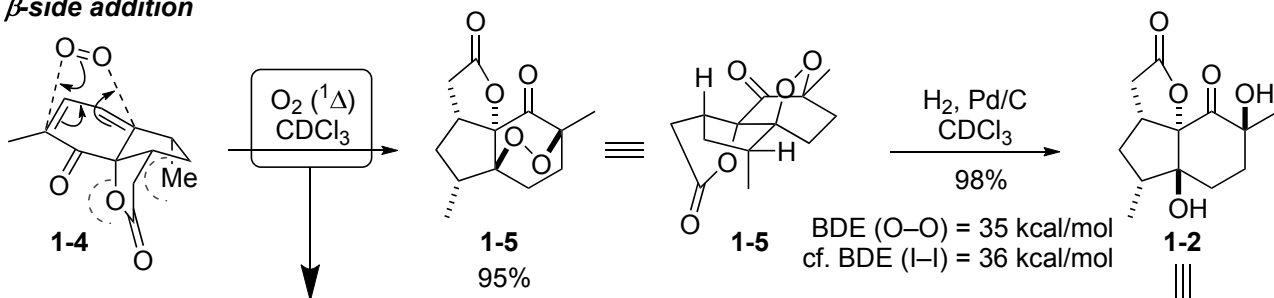
Jens K. Graeber Ph.D. Thesis, Yale University, 2003. (J. L. Wood Group)

• 3rd attempts

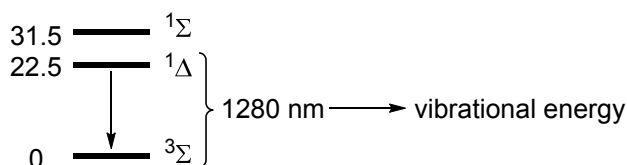
Proposed mechanism



***β*-side addition**

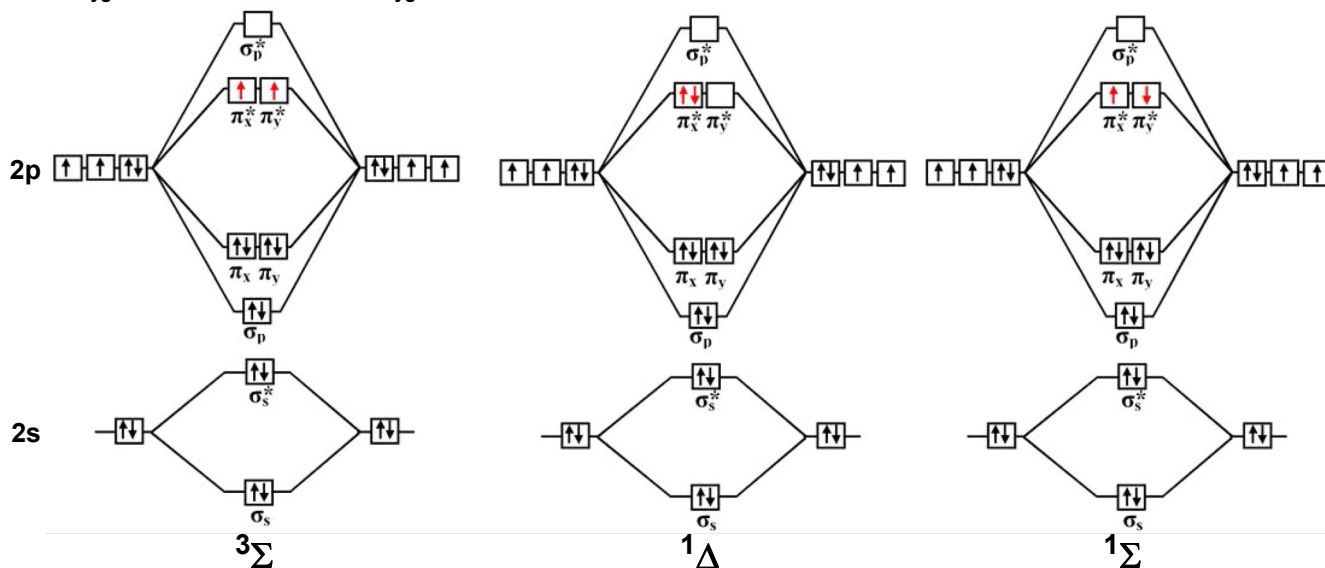


Energy (kcal/mol)

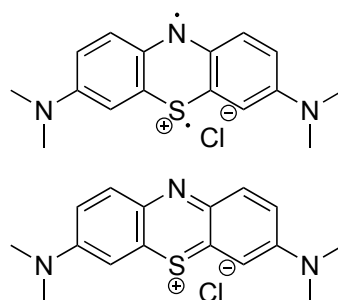
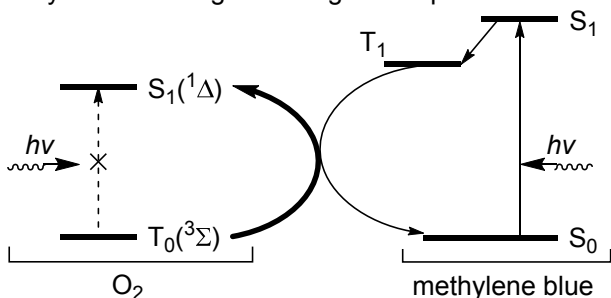


atomic-orbital of an oxygen atom molecular orbital atomic-orbital of an oxygen atom

molecular orbital diagram of O_2



Intersystem crossing from singlet to triplet state:



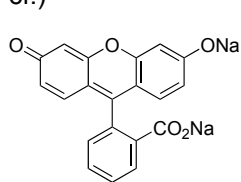
T_1 absorbance range = 550–700 nm
quantum yield (Φ) = 0.52 (in EtOH)
triplet energy (E_r) = 32.0 kcal/mol

Direct excitation of O_2 from triplet to singlet state is spin-forbidden.

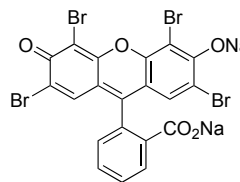
Lifetime of O_2 ($^1\Delta$)

Solvent	Lifetime (ms)
H ₂ O	3.8
D ₂ O	62.0
CH ₃ OH	10.0
CHCl ₃	264.0
CDCl₃	740.0
(CH ₃) ₂ C=O	50.0
(CD ₃) ₂ C=O	723.0
C ₆ H ₆	30.0
C ₆ D ₆	630.0
Freon-113	15,800.0
(F ₂ CICCFCl ₂)	

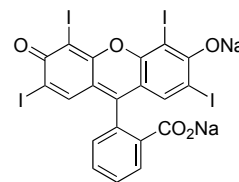
cf.)



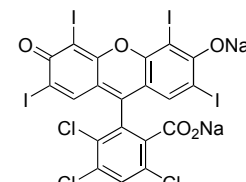
Φ = 0.03
 E_r = 47.2



absorbance range = 480–550 nm
 Φ = 0.37
 E_r = 45.5



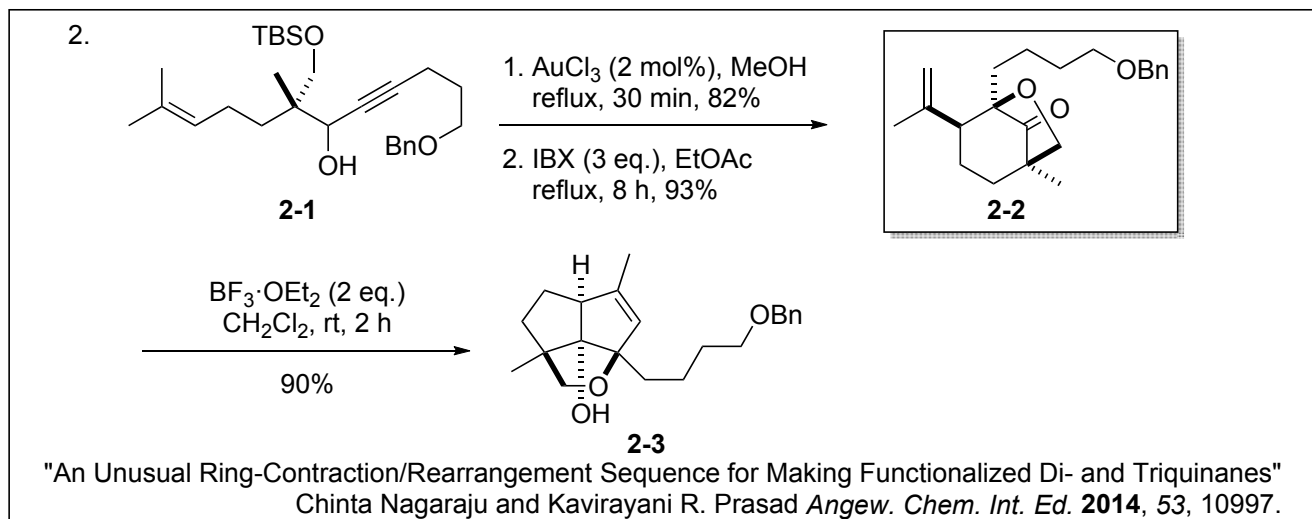
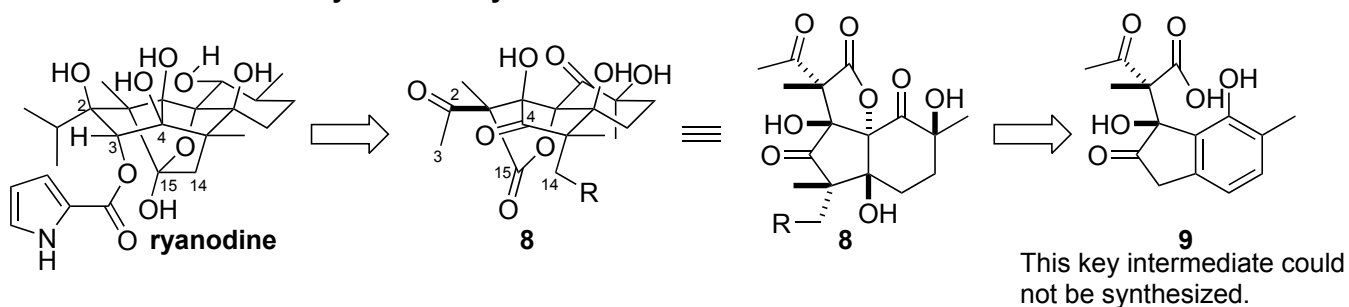
Φ = 0.69



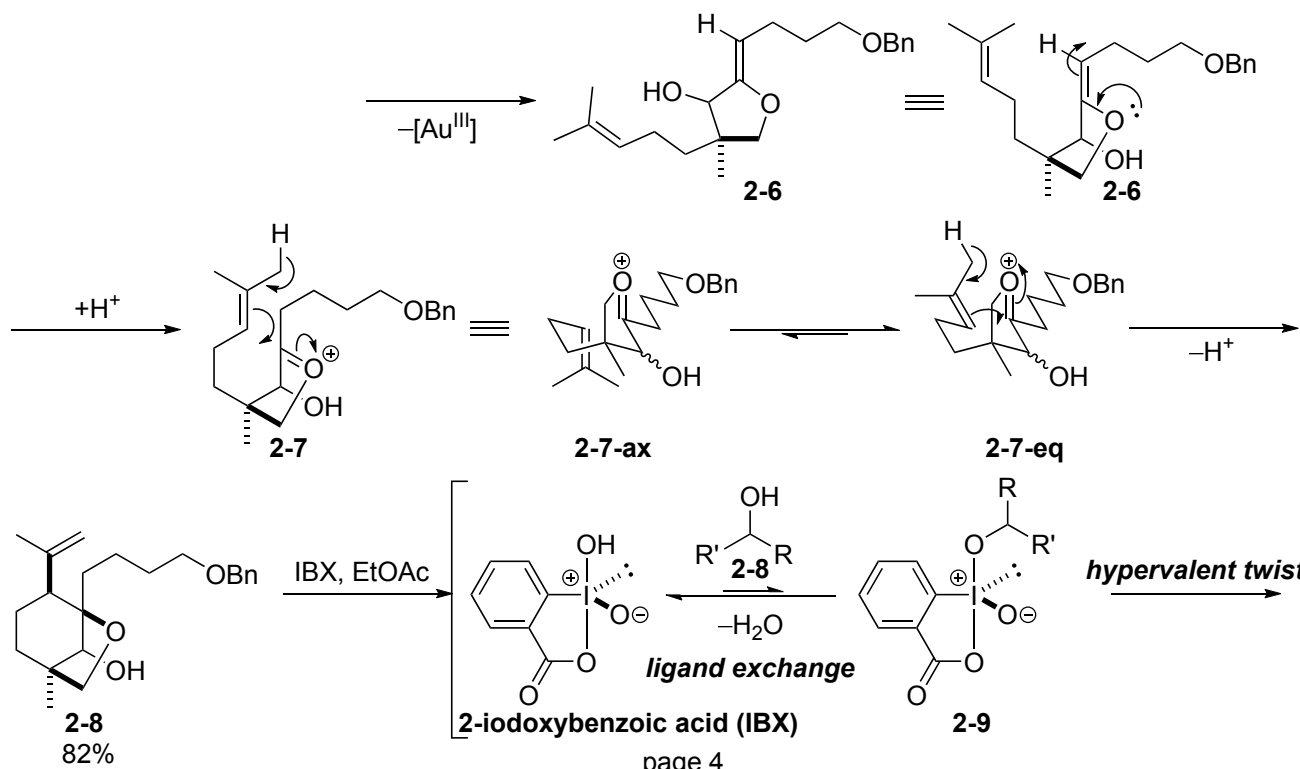
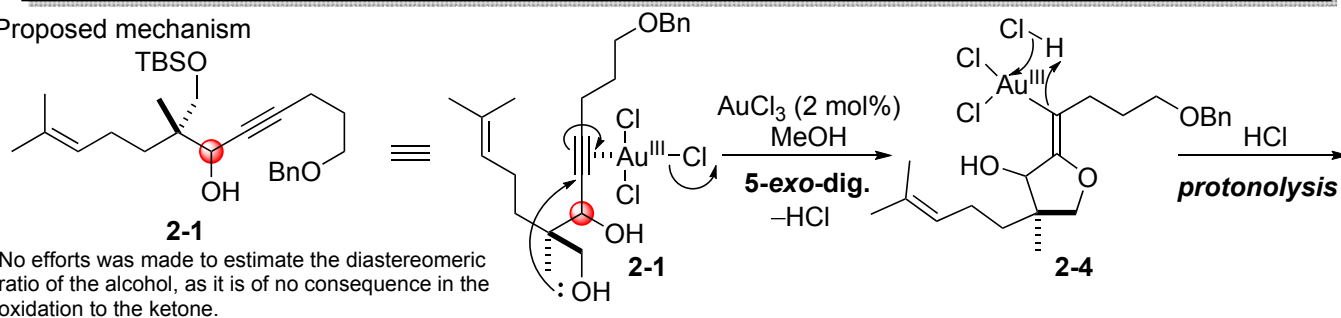
Φ = 0.68
 E_r = 42.0

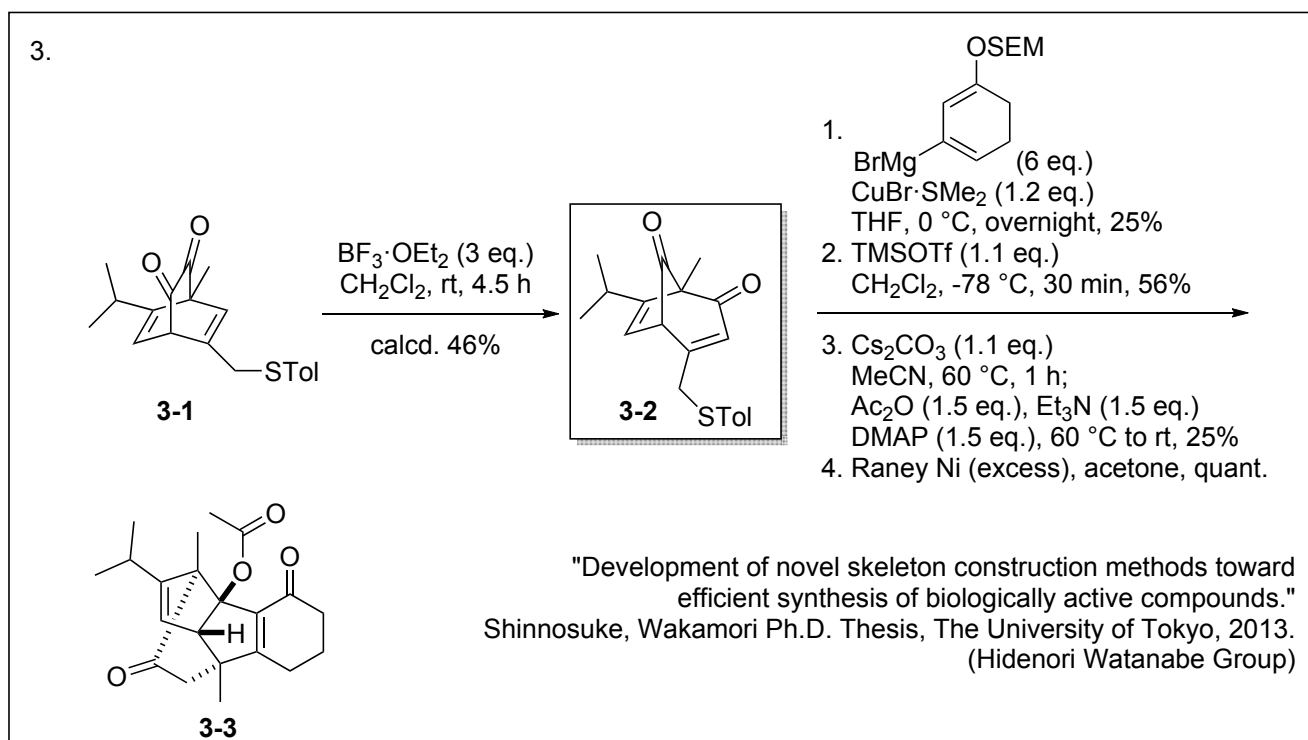
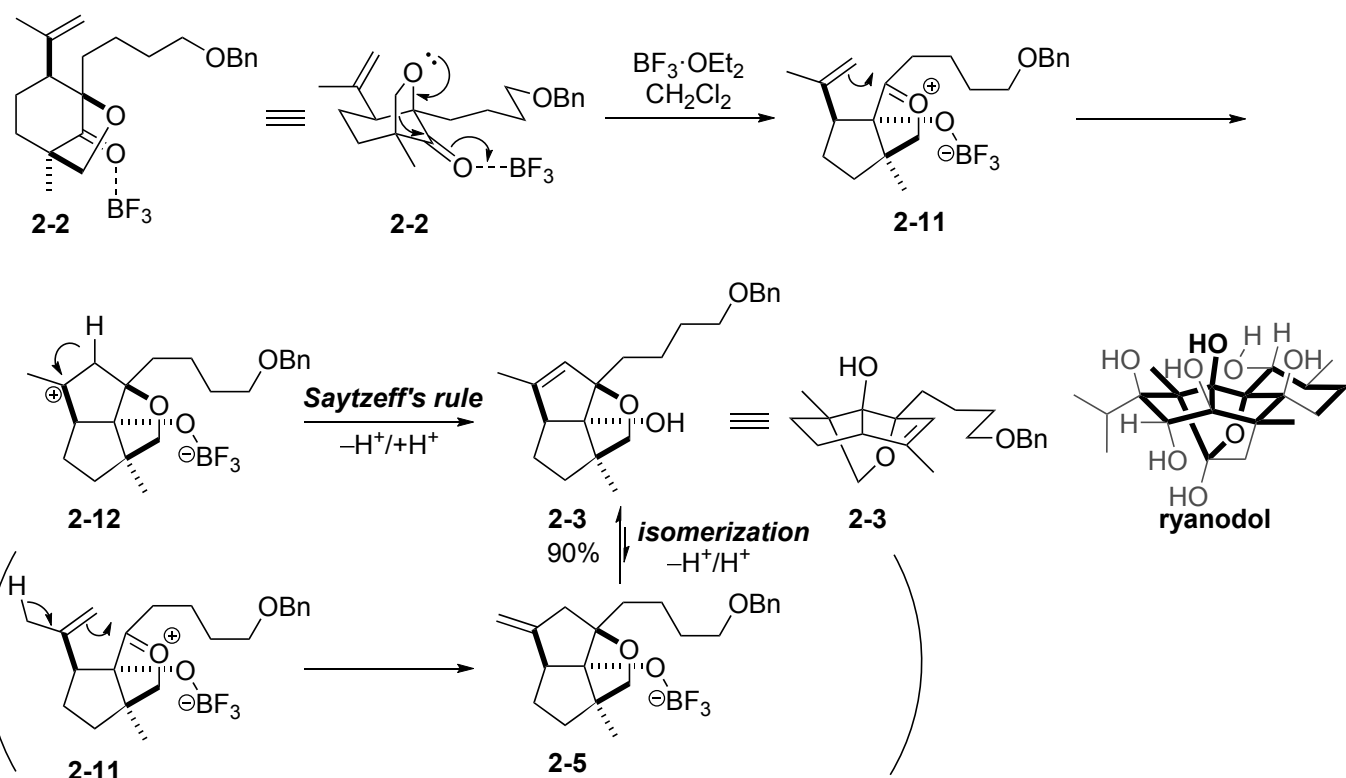
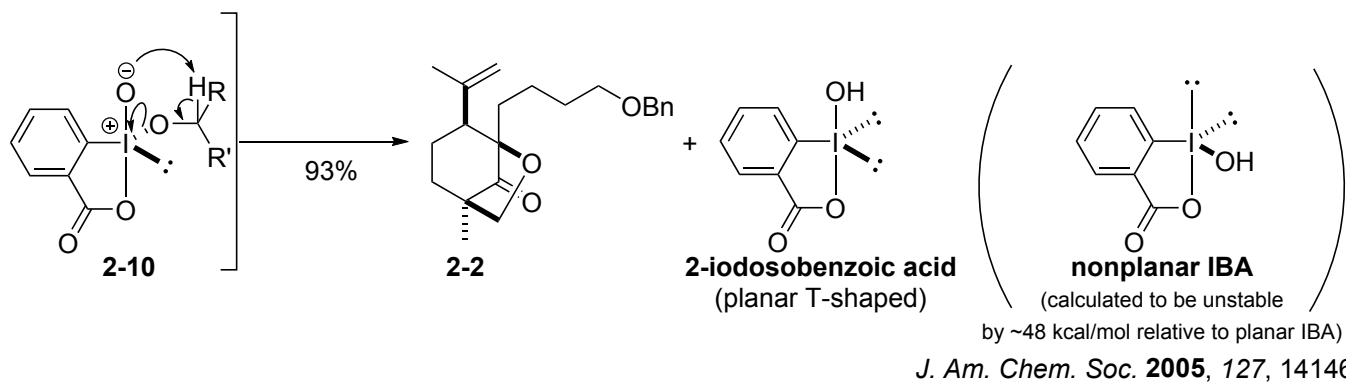
(in this case Φ = # O_2 ($^1\Delta$) generated / # photons absorbed)

• The second Wood's retrosynthesis of ryanodine

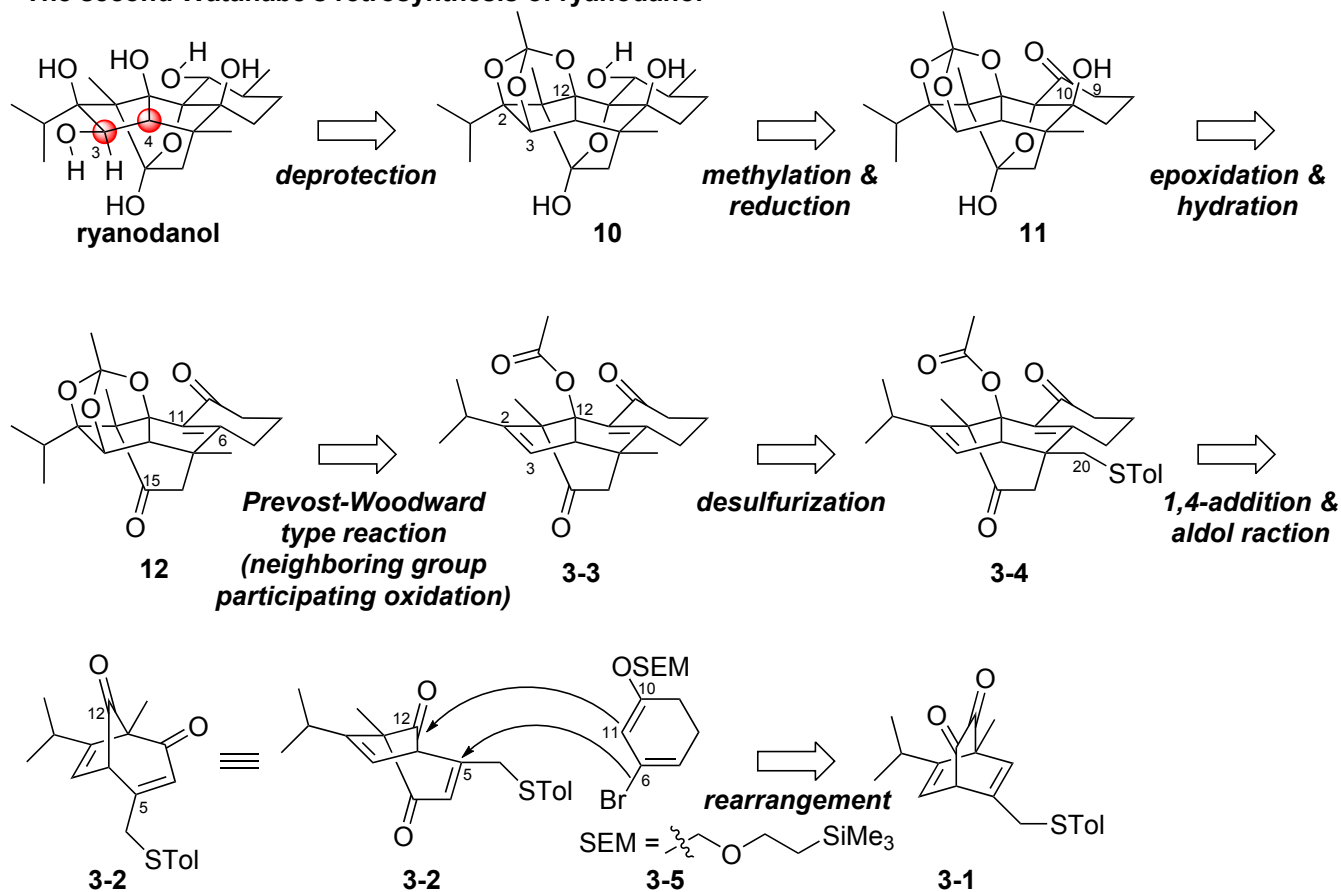


Proposed mechanism

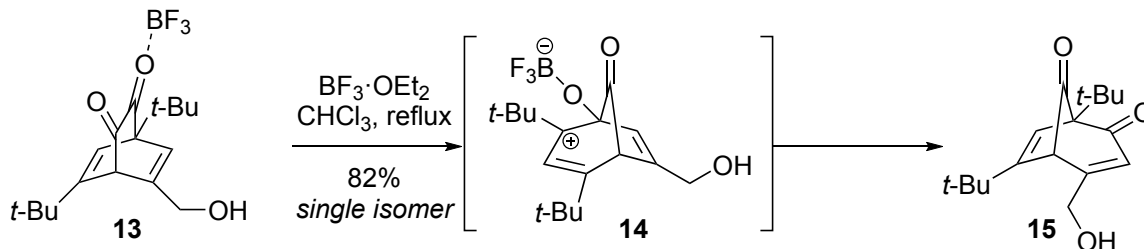




• The second Watanabe's retrosynthesis of ryanodanol

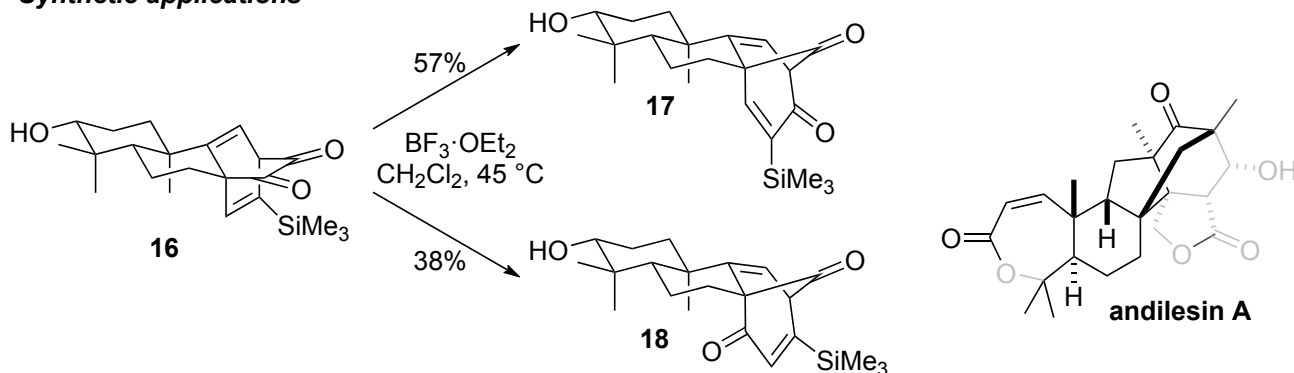


Prospects of success



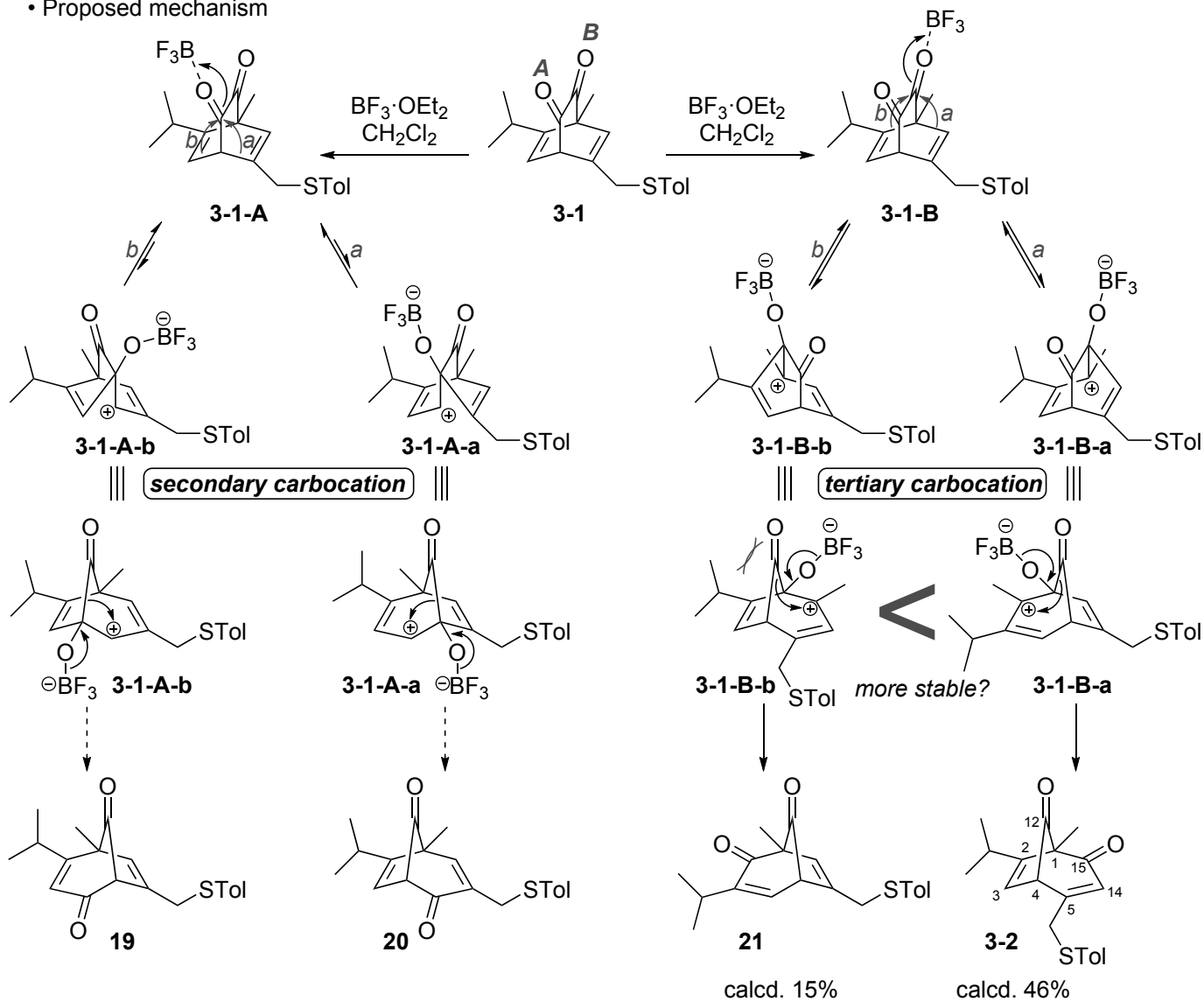
V. Nair, G. Anilkumar, G. K. Eigendorf, P. G. Willard, *Tetrahedron Lett.* **1996**, 37, 8271.

Synthetic applications

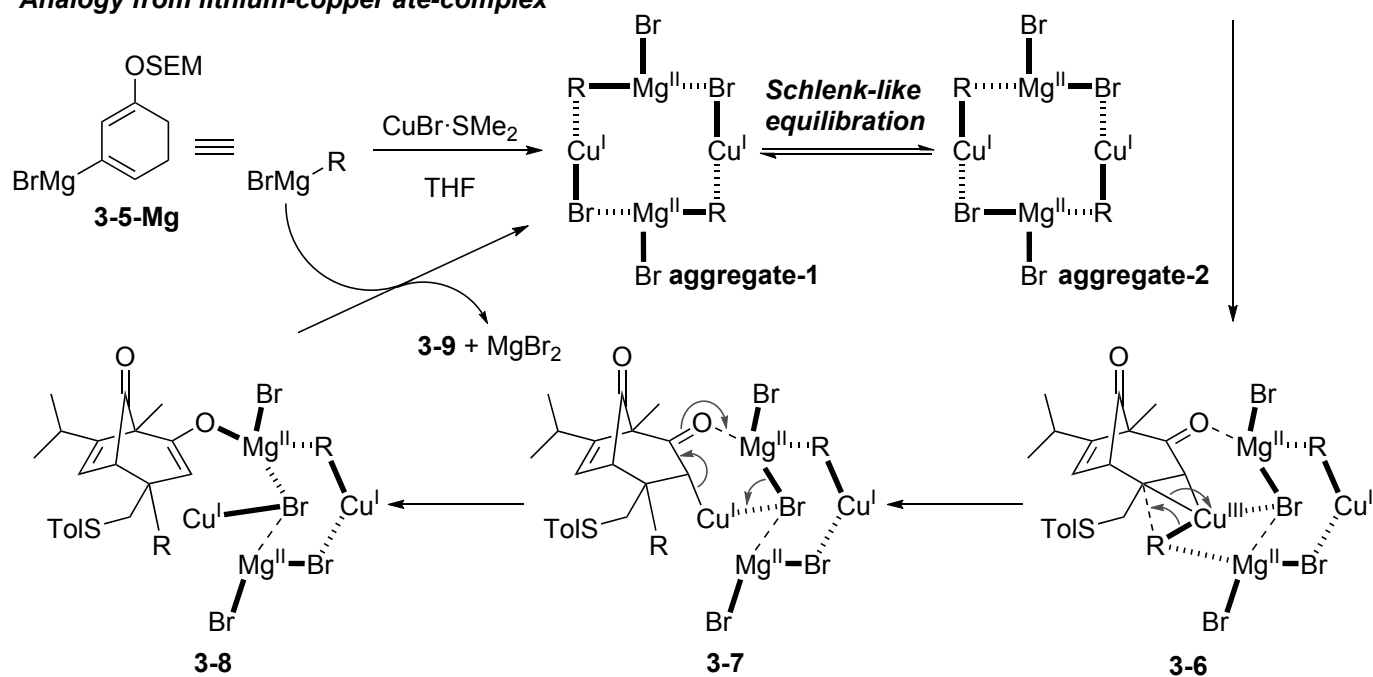


L. Song, G. Zhu, Y. Liu, B. Liu, S. Qin, *J. Am. Chem. Soc.* **2015**, 137, 13706.

• Proposed mechanism



Analogy from lithium-copper ate-complex



See, mechanisms in case of lithium-copper ate-complex

a) *Angew. Chem. Int. Ed.* **2000**, 39, 3750.

b) *J. Am. Chem. Soc.* **2007**, 129, 7208.

c) *J. Am. Chem. Soc.* **2007**, 129, 7210.

