Total Synthesis of Batrachotoxin

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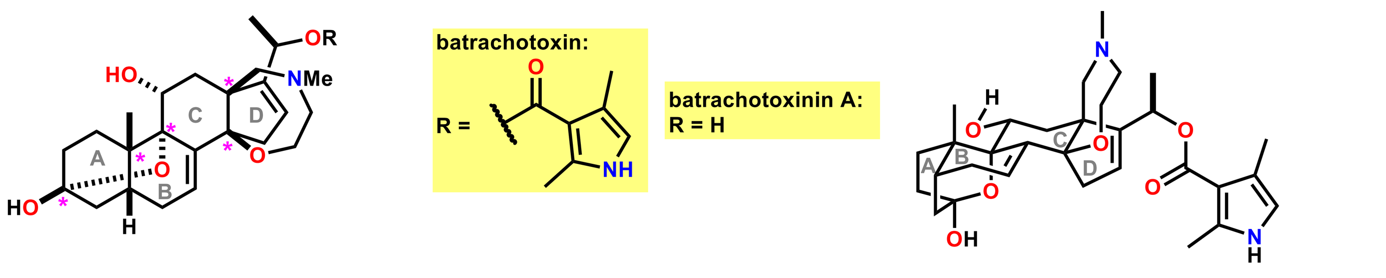
1. Introduction



Isolation of batrachotoxin:
- Poison dart frogs *Phyllobates* sp.[1]
- Birds *Pitohui* sp.[2]

Biological activity of batrachotoxin:
- Neurotoxicity, LD_{50} = 2 μg/kg (mice)[1b]

Structural features:
- Five tetra-substituted carbons
- *cis*-Fused AB/CD rings
- Cyclic hemiacetal
- Seven-membered oxazepane ring

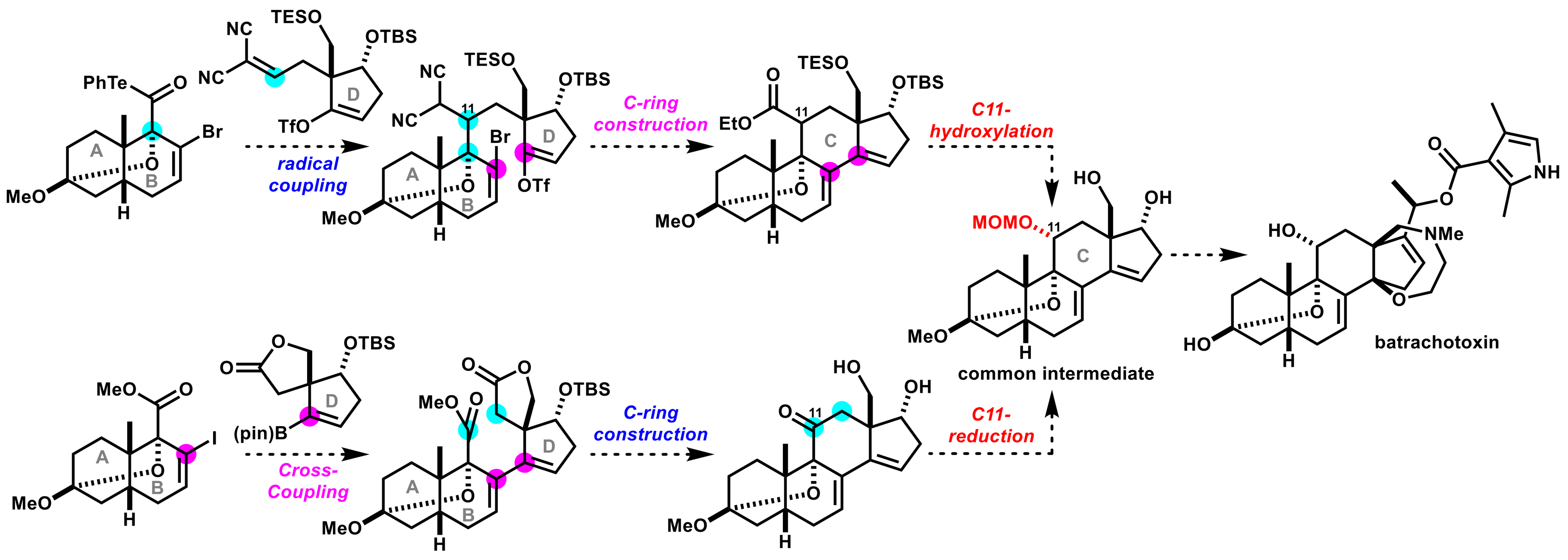
Total syntheses

batrachotoxinin A:
- Wehrli, 1973 (46 steps)[3]
- Kishi, 1998 (48 steps)[4]
- Luo, 2020 (17 steps)[5]

batrachotoxin:
- Du Bois, 2016 (24 steps)[6]

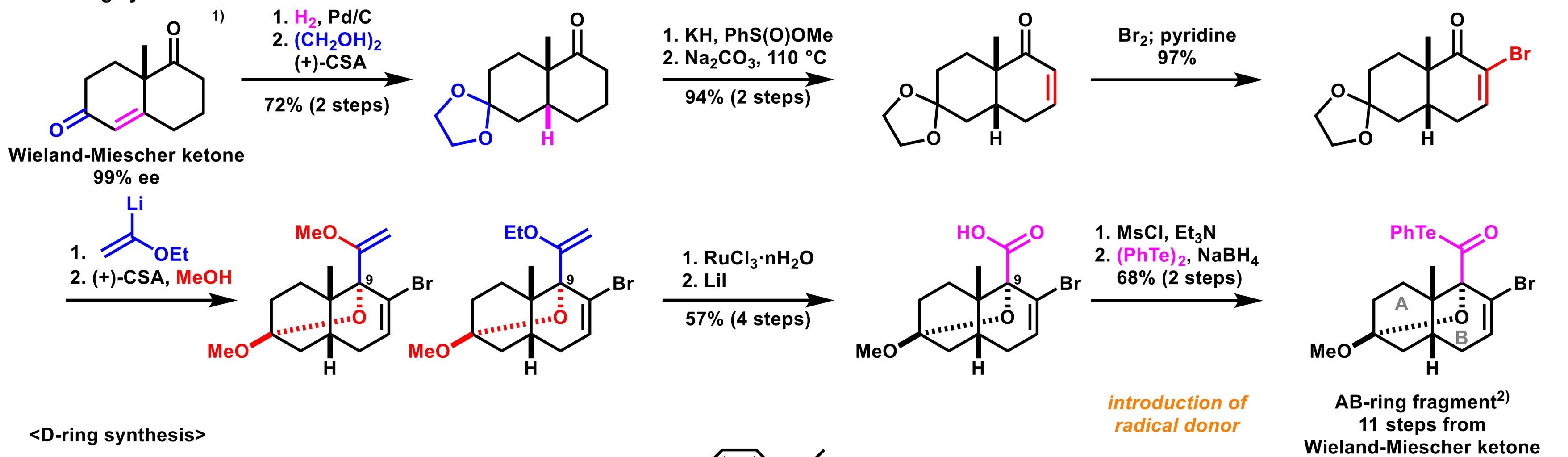
1) (a) Witkop, B. et al. *Experientia* **1963**, *19*, 329.
(b) Witkop, B. et al. *J. Am. Chem. Soc.* **1965**, *87*, 124.
2) Daly, J. W. et al. *Science* **1992**, *258*, 799.
3) (a) Wehrli, H. et al. *Helv. Chim. Acta* **1973**, *56*, 139.
(b) Wehrli, H. et al. *Helv. Chim. Acta* **1972**, *55*, 1151.
4) Kishi, Y. et al. *J. Am. Chem. Soc.* **1998**, *120*, 6627.
5) Luo, T. et al. *J. Am. Chem. Soc.* **2020**, *142*, 3675.
6) Du Bois, J. et al. *Science* **2016**, *354*, 865.

2. Synthetic Plans

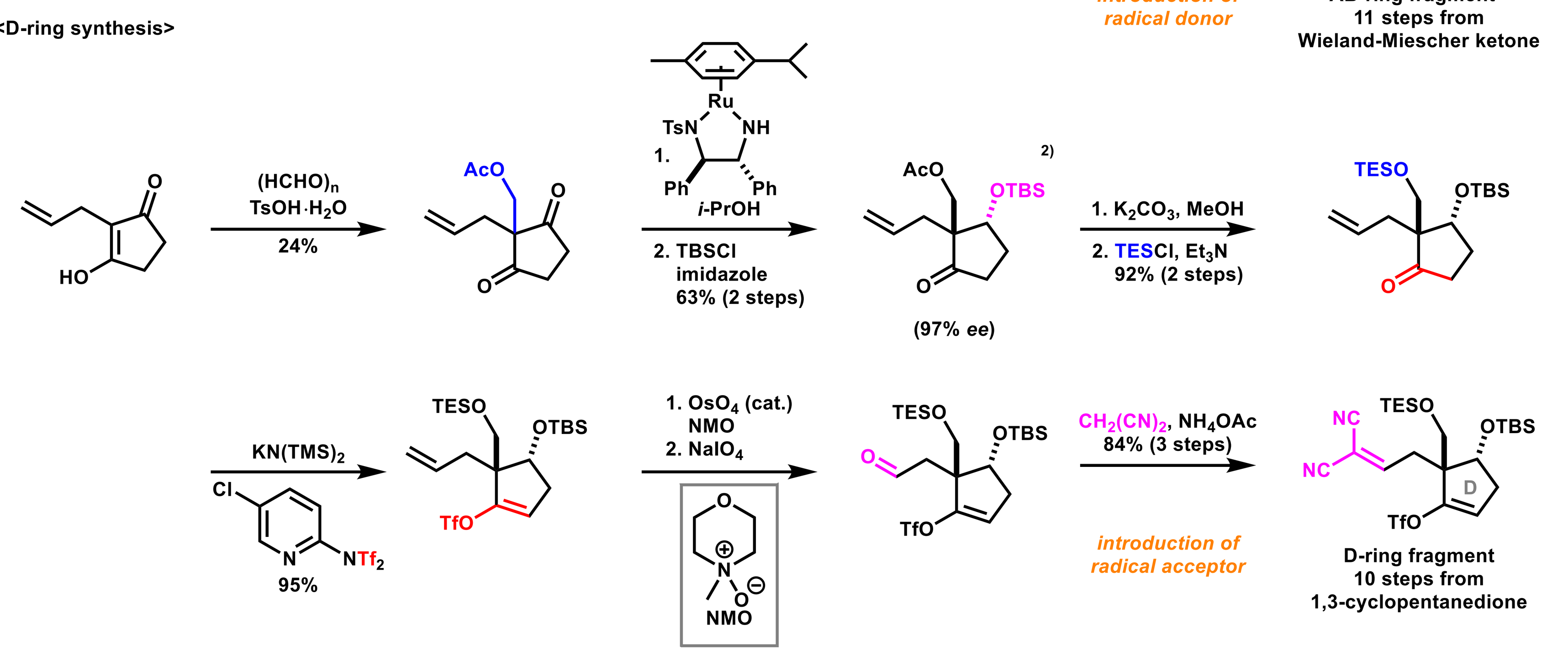


3. Preparation of Fragments

<AB-ring synthesis>

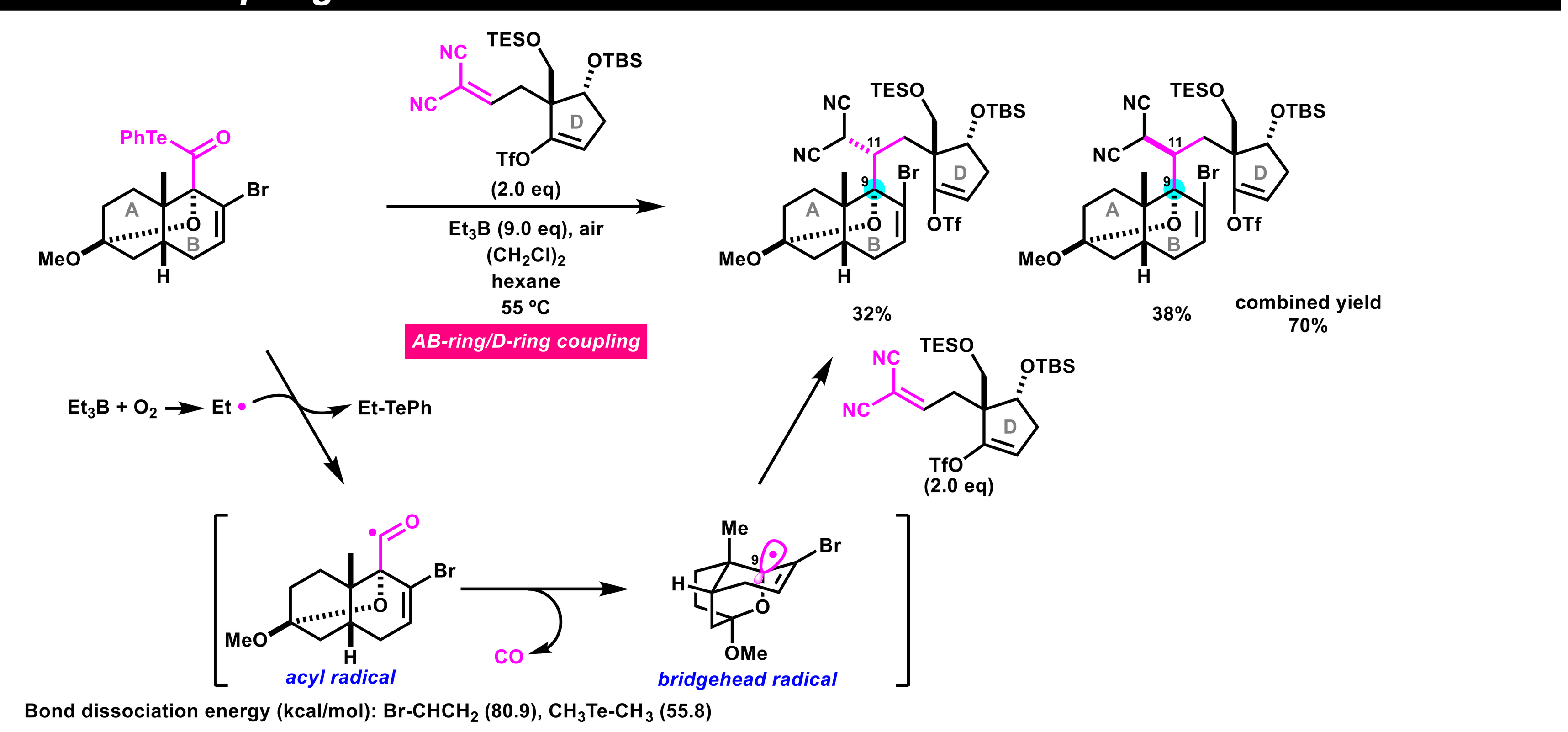


<D-ring synthesis>



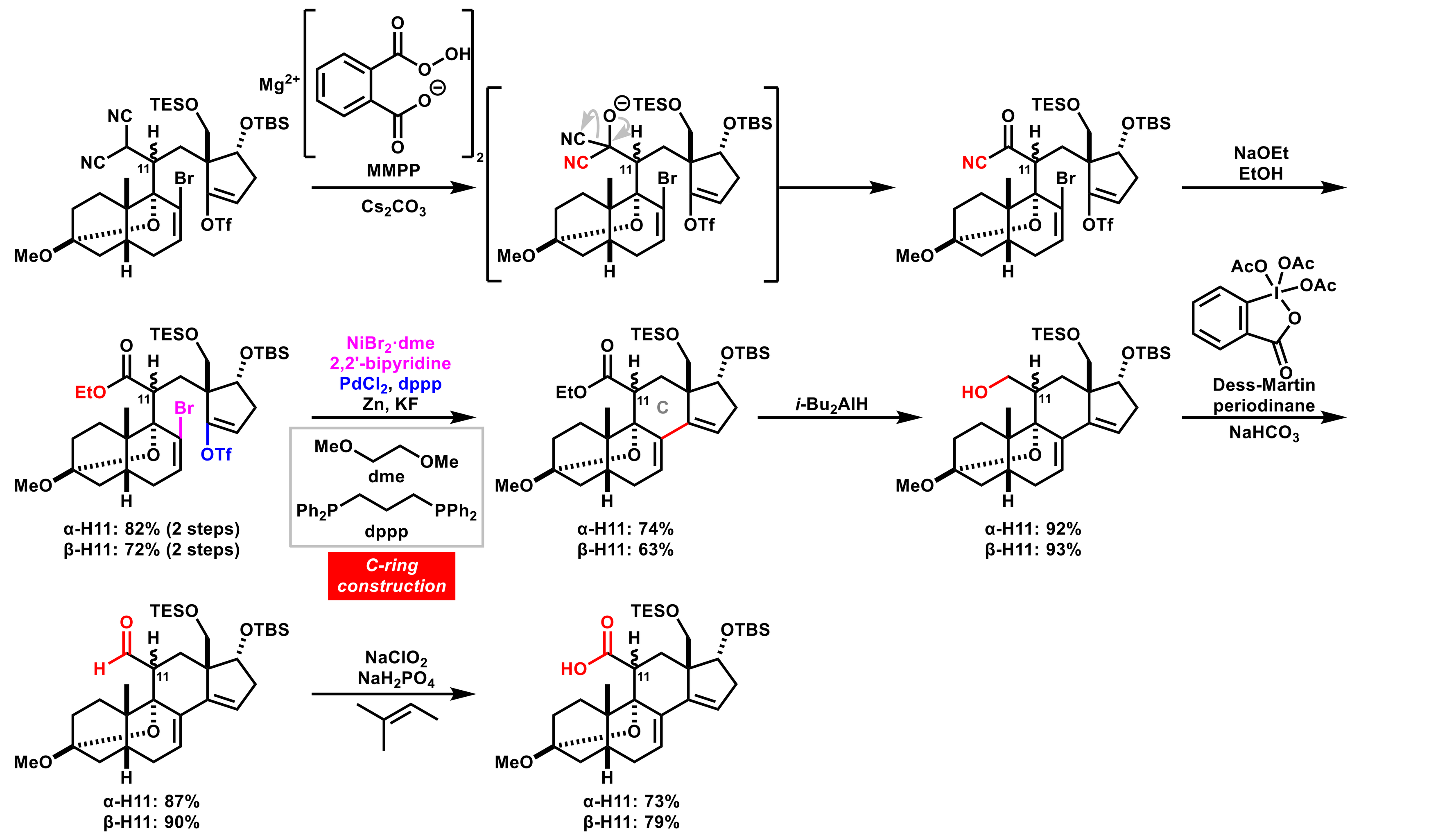
1) Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J.; Viózquez, S. F.; Guillena, G.; Nájera, C. *Org. Synth.* **2011**, *88*, 330−341.
2) Sakata, K.; Wang, Y.; Urabe, D.; Inoue, M. *Org. Lett.* **2018**, *20*, 130−133.

4. Radical Coupling

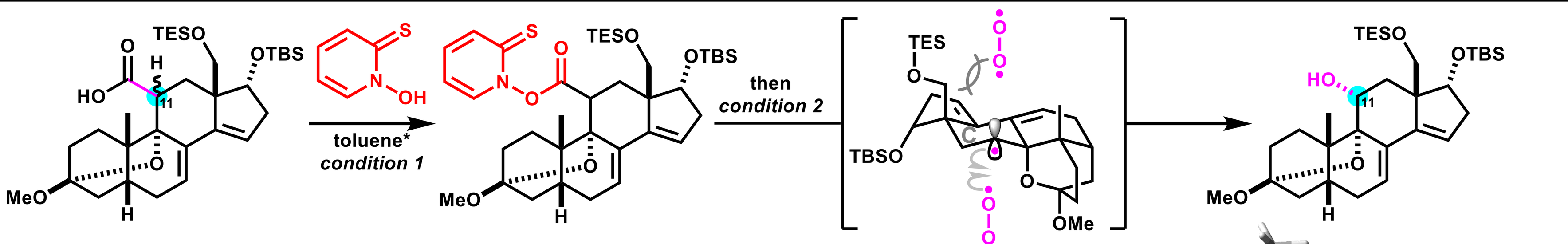


Bond dissociation energy (kcal/mol): Br-$CHCH_2$ (80.9), CH_3Te-CH_3 (55.8)

5. C-ring Construction

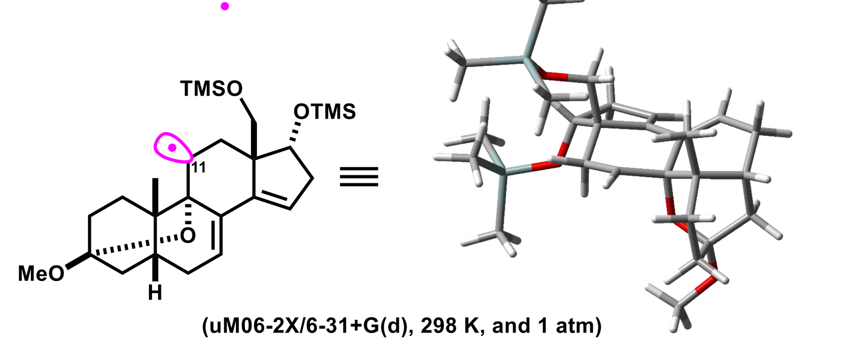


6. Decarboxylative Hydroxylation



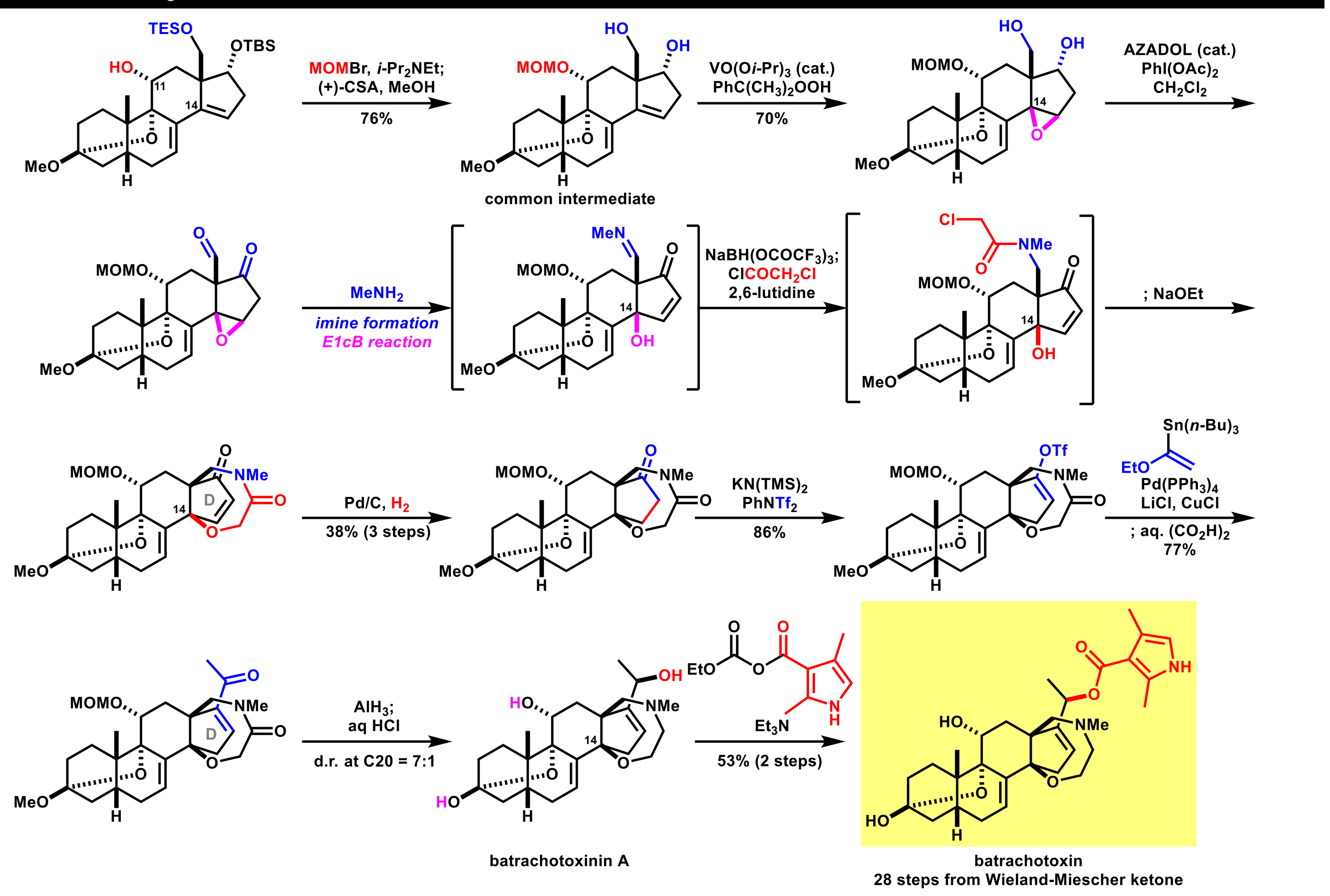
entry	SM	condition 1	condition 2	yield
1	α-H11	EDCI·HCl	*t*-BuSH Hg lamp	36%
2	α-H11	EDCI *t*-BuSH	Hg lamp	42%
3	α-H11	EDCI *t*-BuSH	O_2 (1 atm) 100 °C	42%
4	β-H11	EDCI *t*-BuSH	O_2 (1 atm) 100 °C	25%

* O_2 was bubbled through the solvent for 10 min before the reaction.

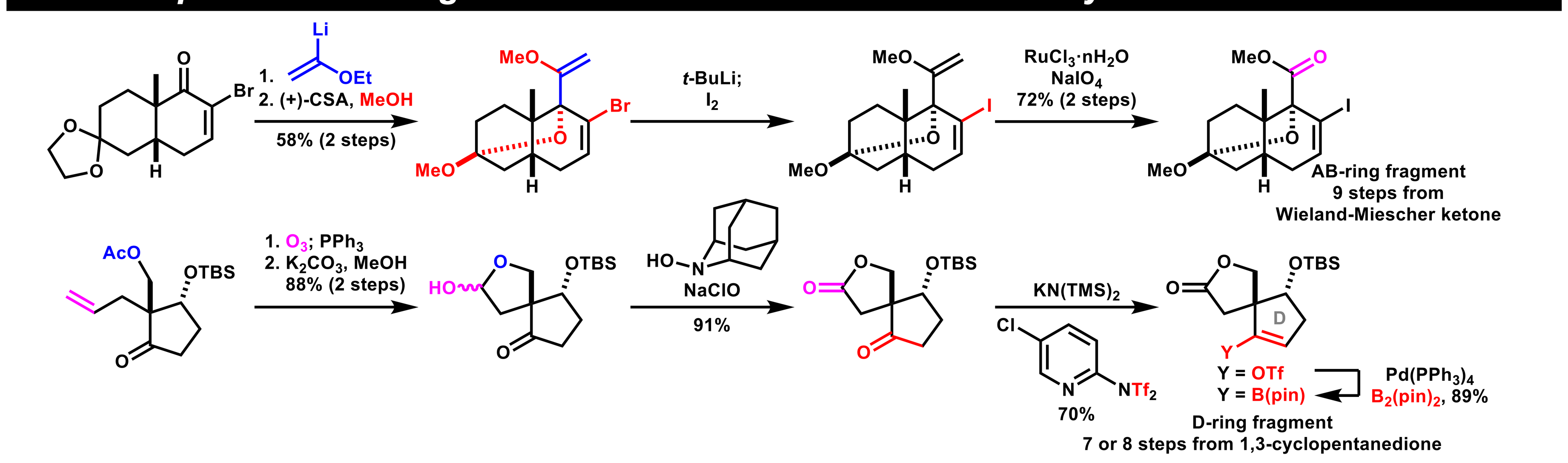


(uM06-2X/6-31+G(d), 298 K, and 1 atm)

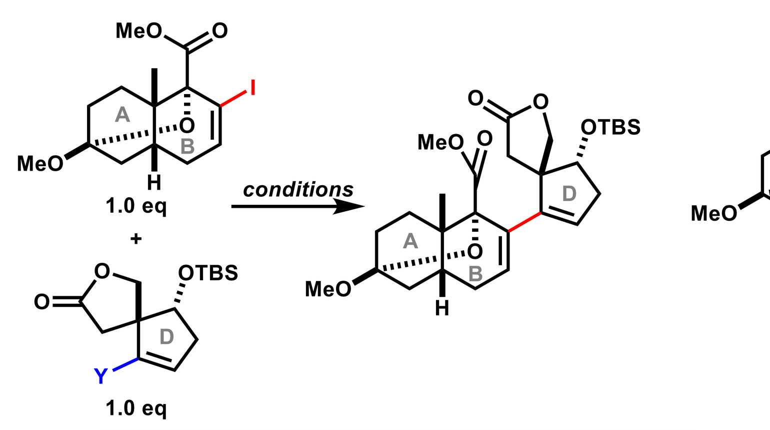
7. Total Synthesis of Batrachotoxin



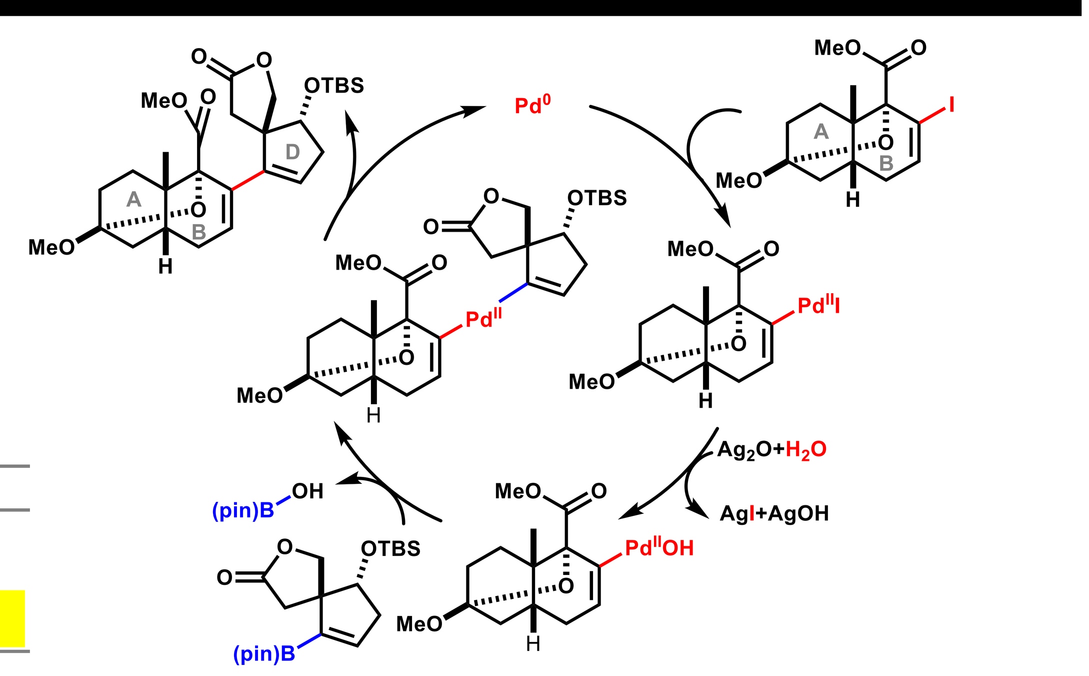
8. Preparation of Fragments for the Second Generation Synthesis



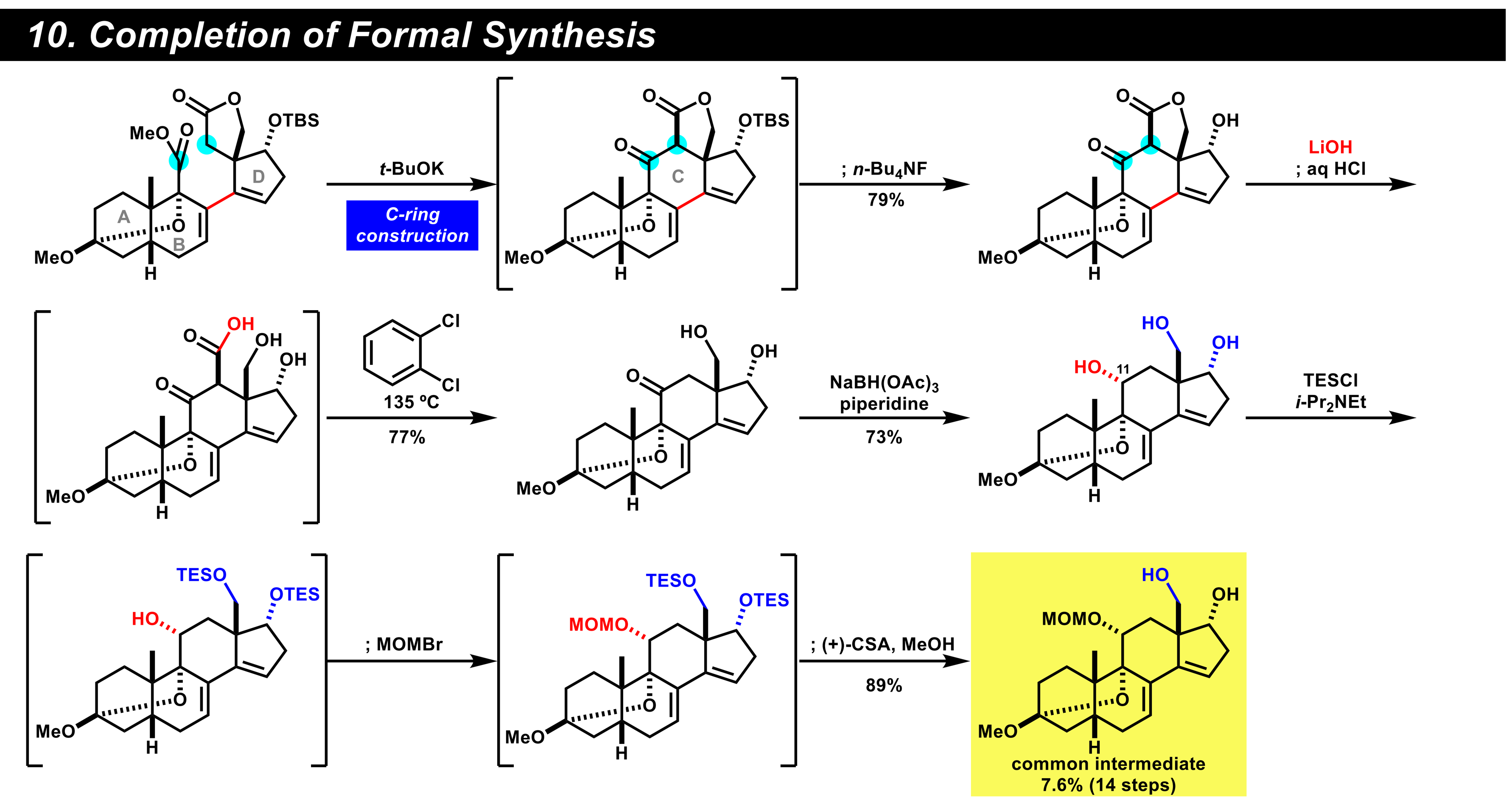
9. Cross-Coupling



entry	Y	conditions	yield
1	OTf	$NiBr_2$-diglyme, 2,2'-bpy $PdCl_2$, dppp, Zn DMF, 80 °C	18%
2	B(pin)	$Pd(PPh_3)_4$, Ag_2O THF/H_2O, 27 °C	70%



10. Completion of Formal Synthesis



11. Summary