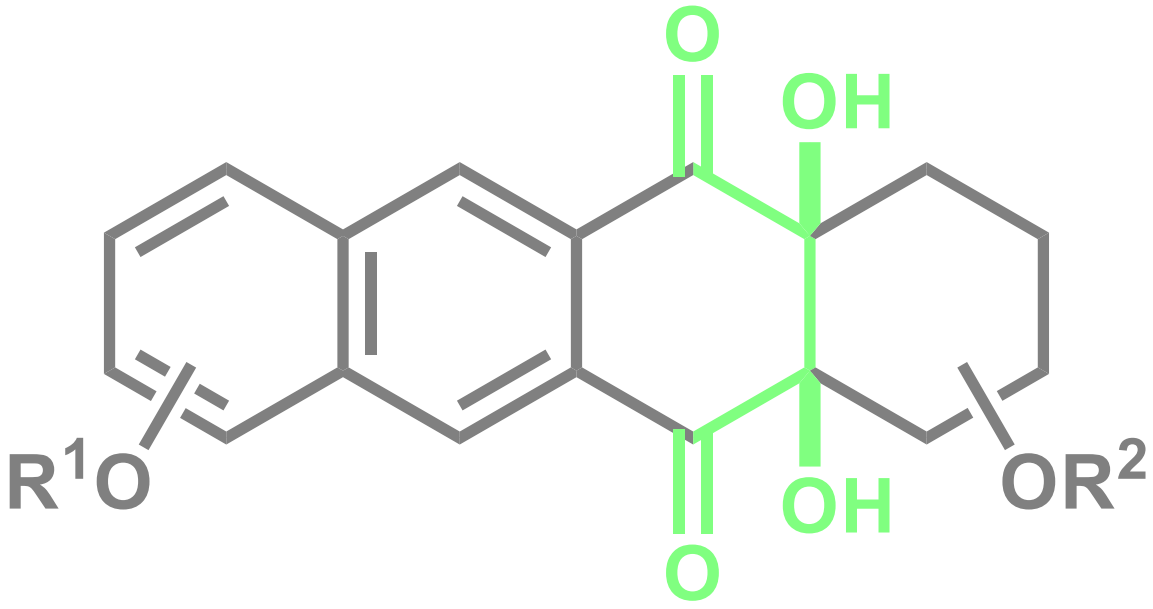
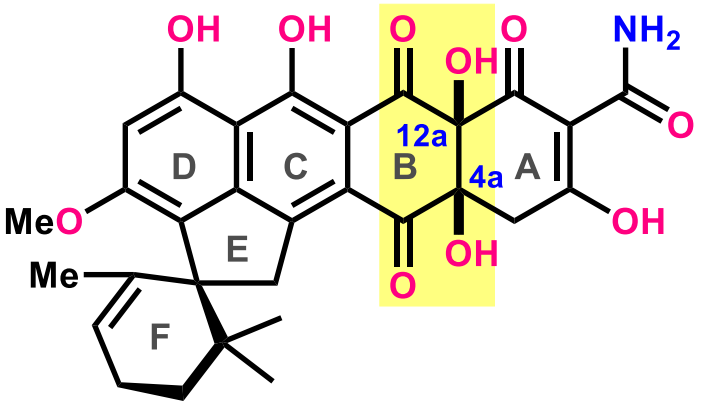
Construction of Polyketides Bearing Bridgehead Diols



2017.10.7
Haruka Fujino

Polyketides Bearing Diol Motif



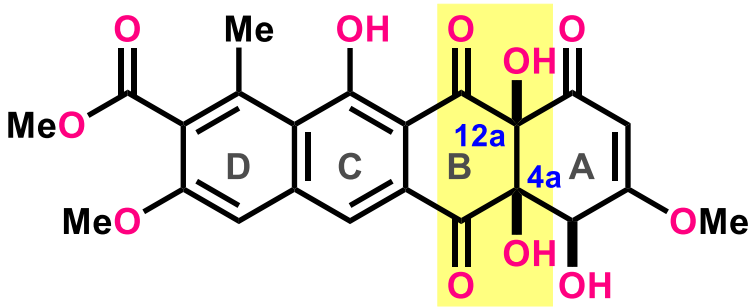
viridicatumtoxin B

isolation:
from *Penicillium* sp. FR11
Kim, W. G. *et al. J. Antibiot.* **2008**, *61*, 633.

bioactivity:
antimicrobial against Gram-positive bacteria

mode of action:
inhibition of UPP synthase
(= inhibition for bacterial petidoglycan synthesis)

one total synthesis:
Nicolaou, K. C. *et al.*
Angew. Chem. Int. Ed. **2013**, *52*, 8736.



tetracenomycin C

isolation:
from *Actynomycetas* sp. FR11
Weber, W. *et al. Arch. Microbiol.* **1979**, *121*, 111.

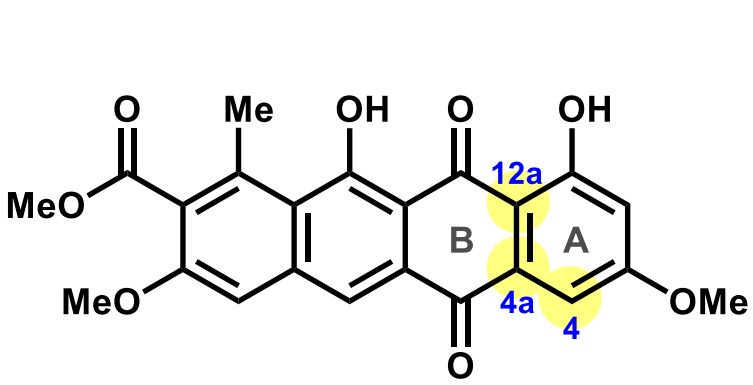
bioactivity:
antimicrobial against Gram-positive bacteria
cytotoxic activity against L1210 leukemia cells

mode of action:
inhibition of 30S ribosome unit
(= inhibition of bacterial protein synthesis)

one total synthesis:
Suzuki, K. *et al.*
Angew. Chem. Int. Ed. **2017**, *56*, 12608.

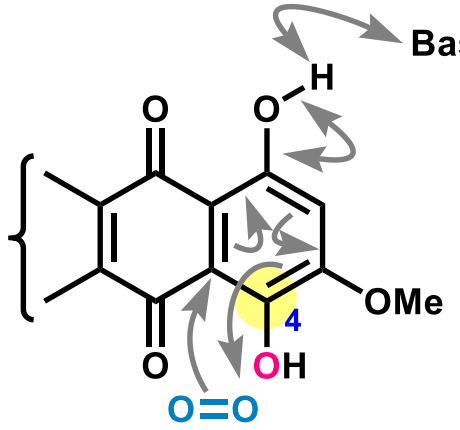
synthetic challenges:
regiocontrolled installation of oxygenated substituents on the ABCD tetracyclic core
streocontrolled construction of the angular *cis*-diol (C4a, C12a)

Proposed Biosynthesis of Angular *Cis*-diol [1)]

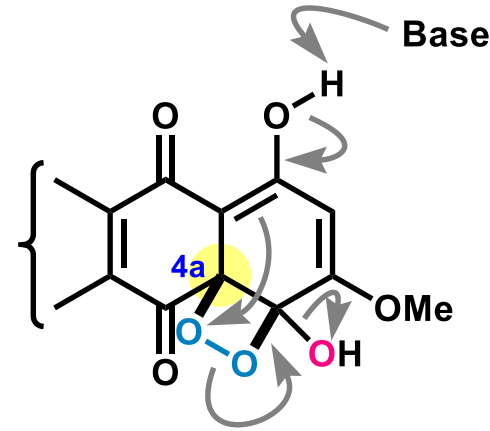


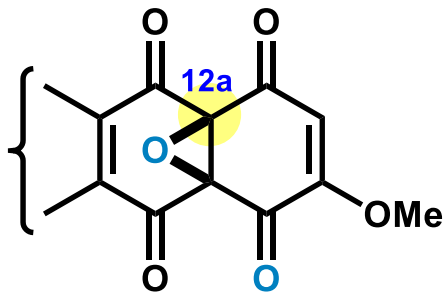
tetracenomycin A2
<several total syntheses>

O=O +
NAD(P)H
– H_2O
+ $NAD(P)^+$



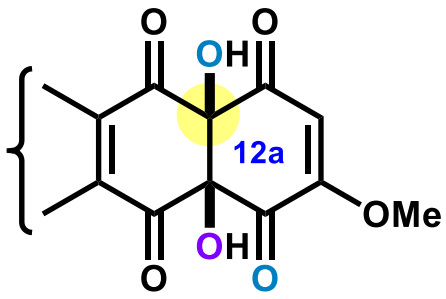
O=O



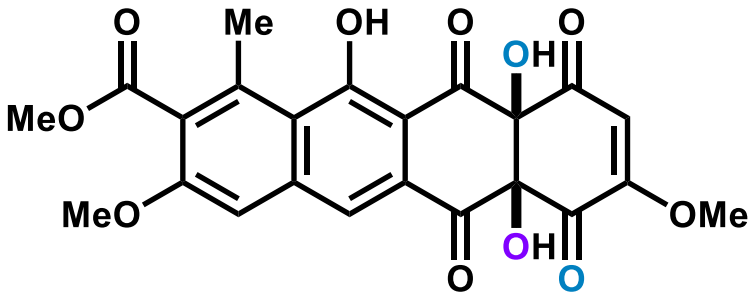


H_2O

cis opening of epoxide !?



H^+ +
NAD(P)H
– $NAD(P)^+$



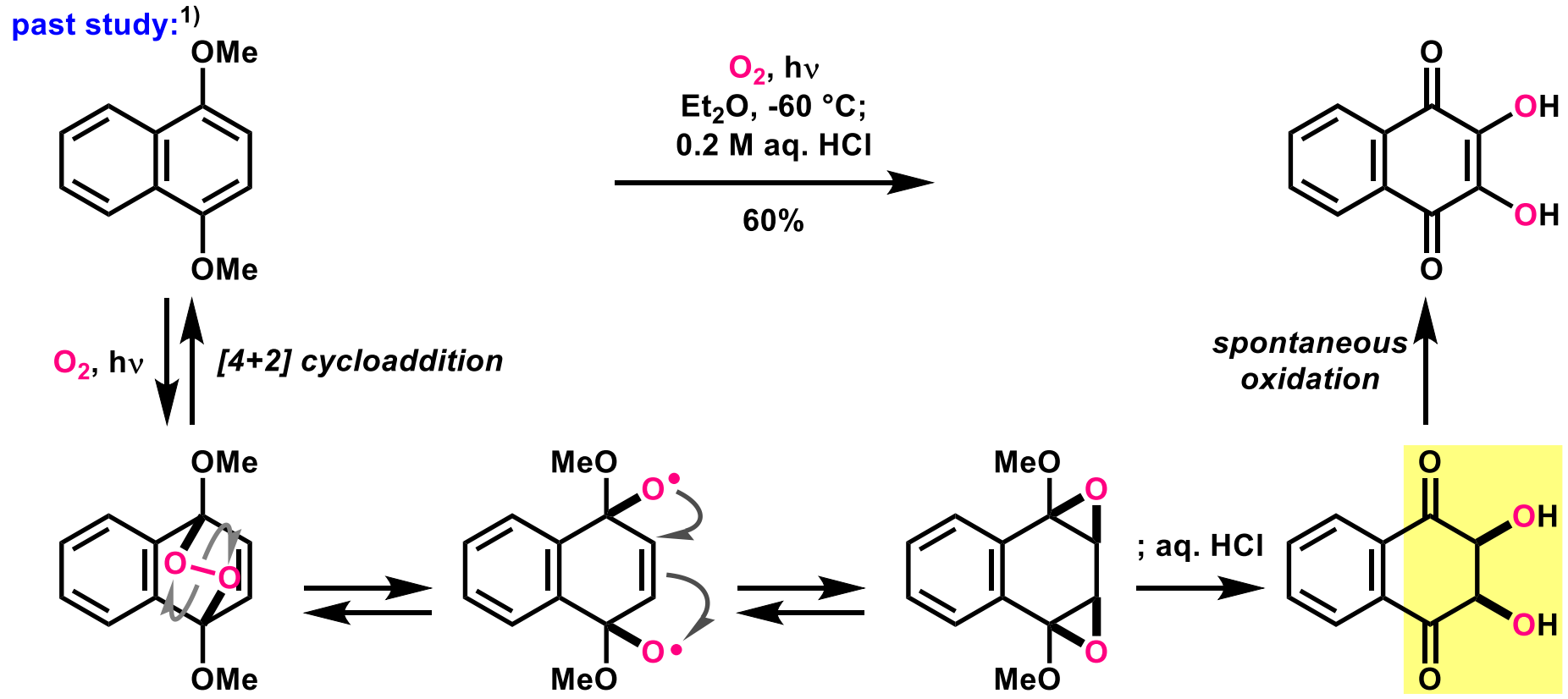
tetracenomycin C
<no total synthesis before 2017>

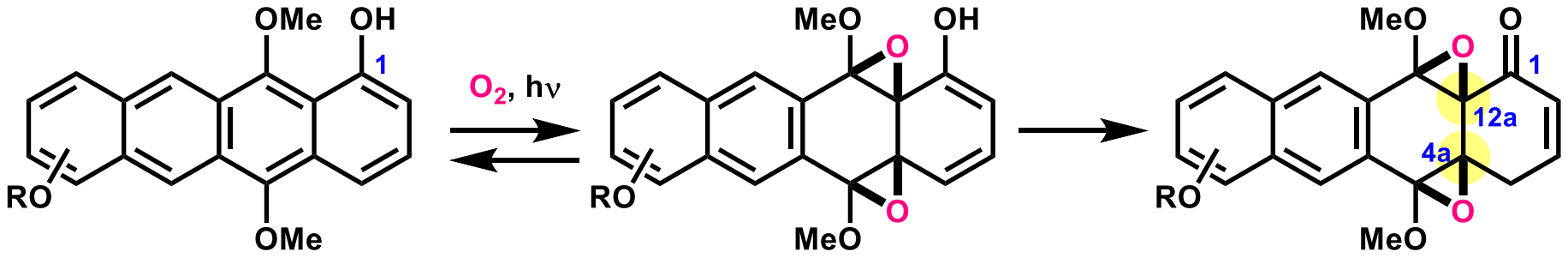
1) Rafanan, Jr., E. R. Hutchinson, C. R.; Shen, B. *Org. Lett.* **2000**, *2*, 3225.

Contents

Contents

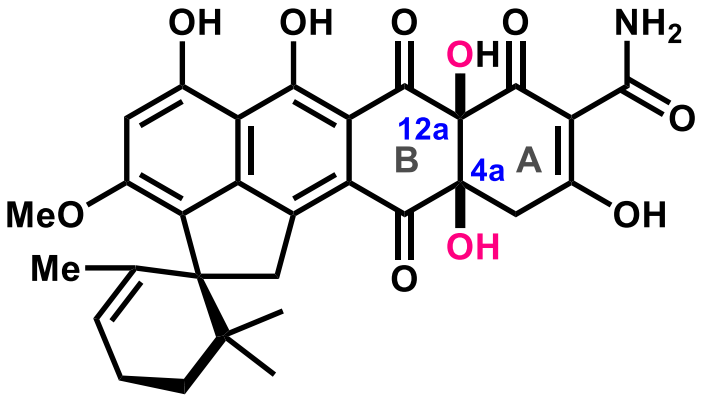
Singlet-oxygen Promoted Functionalization



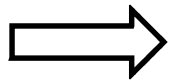


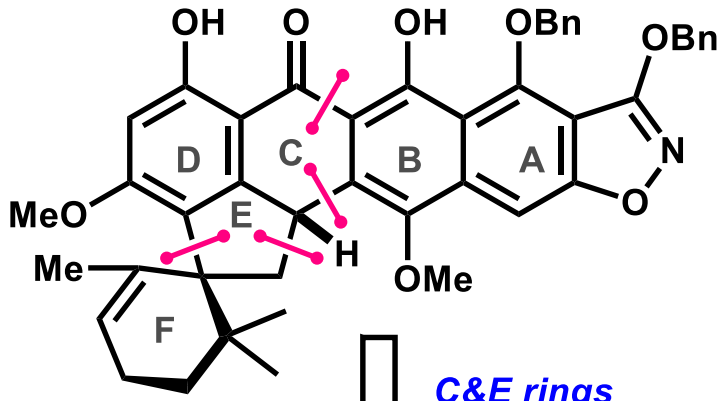
1) Rigaudy, J.; Deletang, C.; Basselier, J.-J. *C. R. Acad. Sci. Paris* **1969**, *268*, 344.

Nicolaou's First-generation Retrosynthetic Analysis[1)]

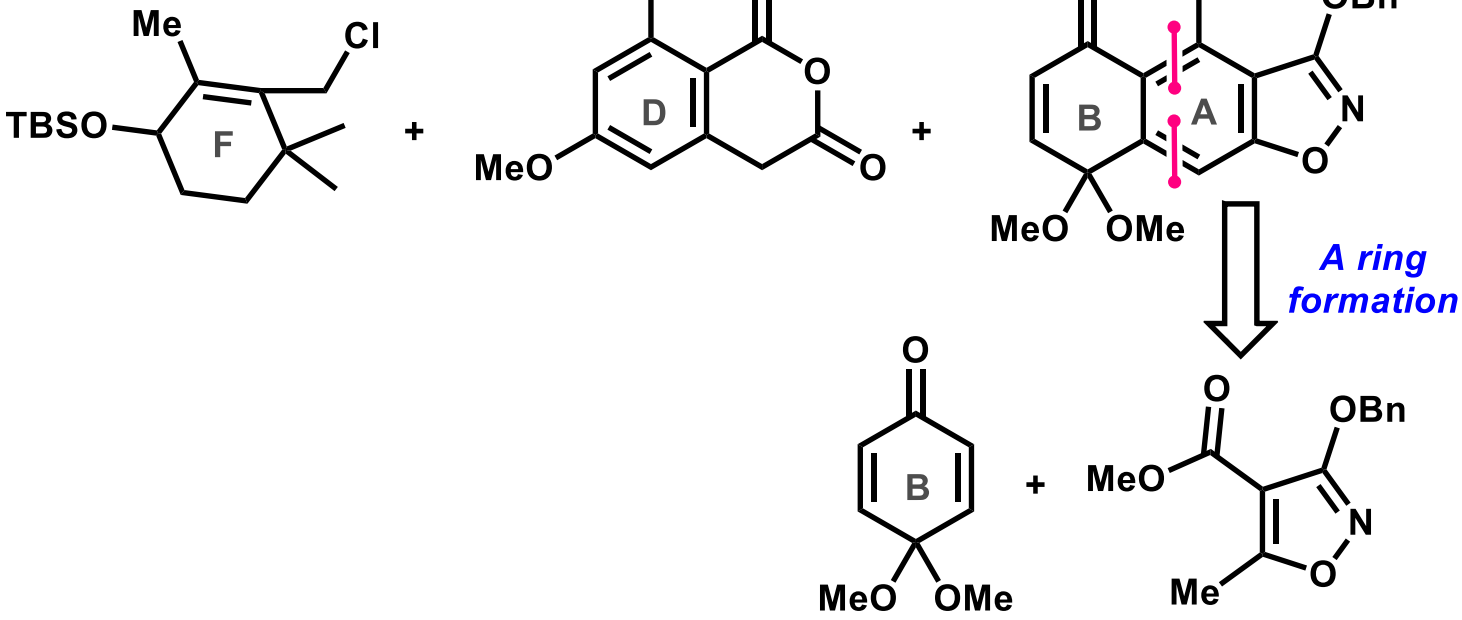


rac-viridicatumtoxin B



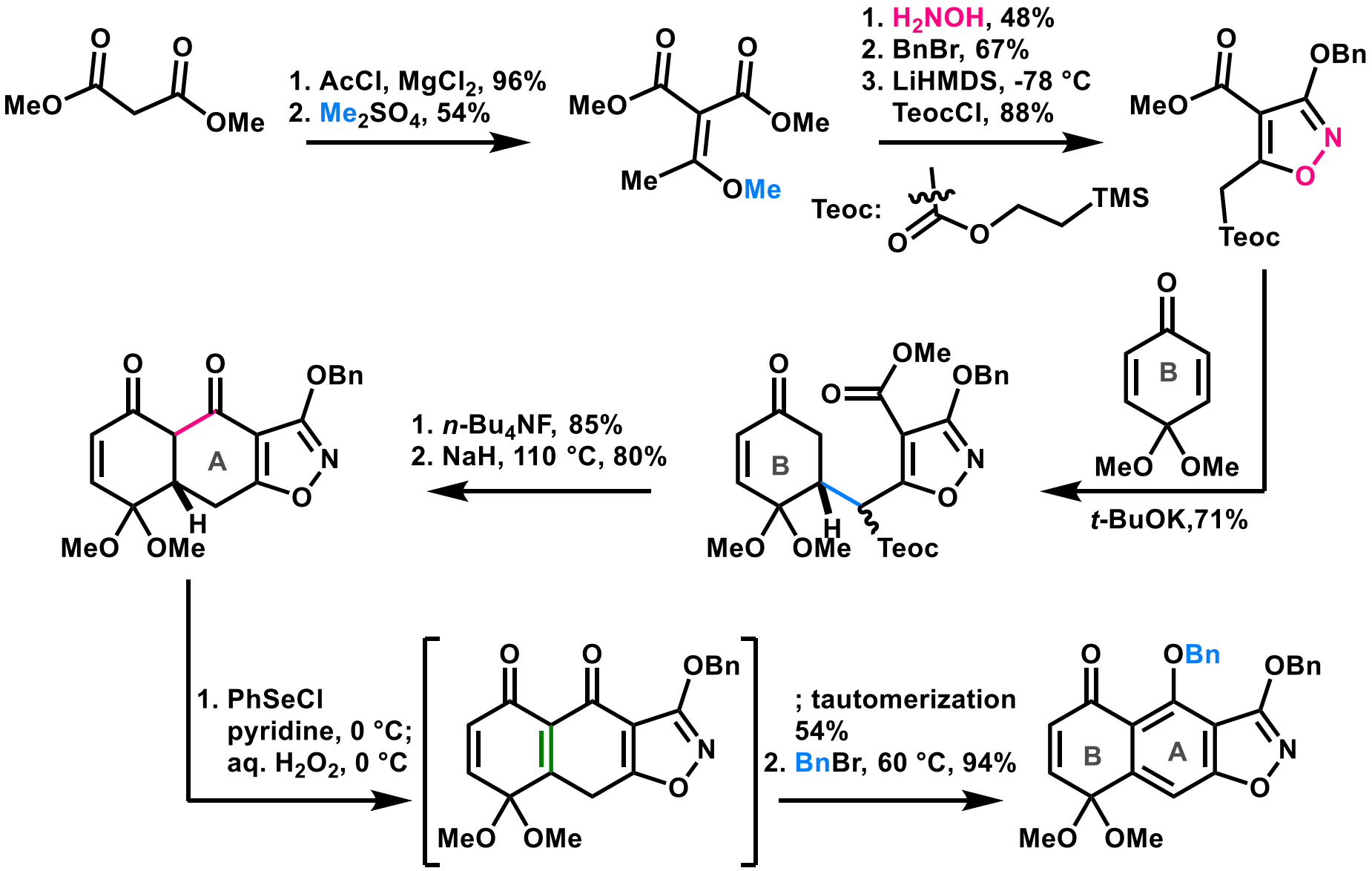


C&E rings formation



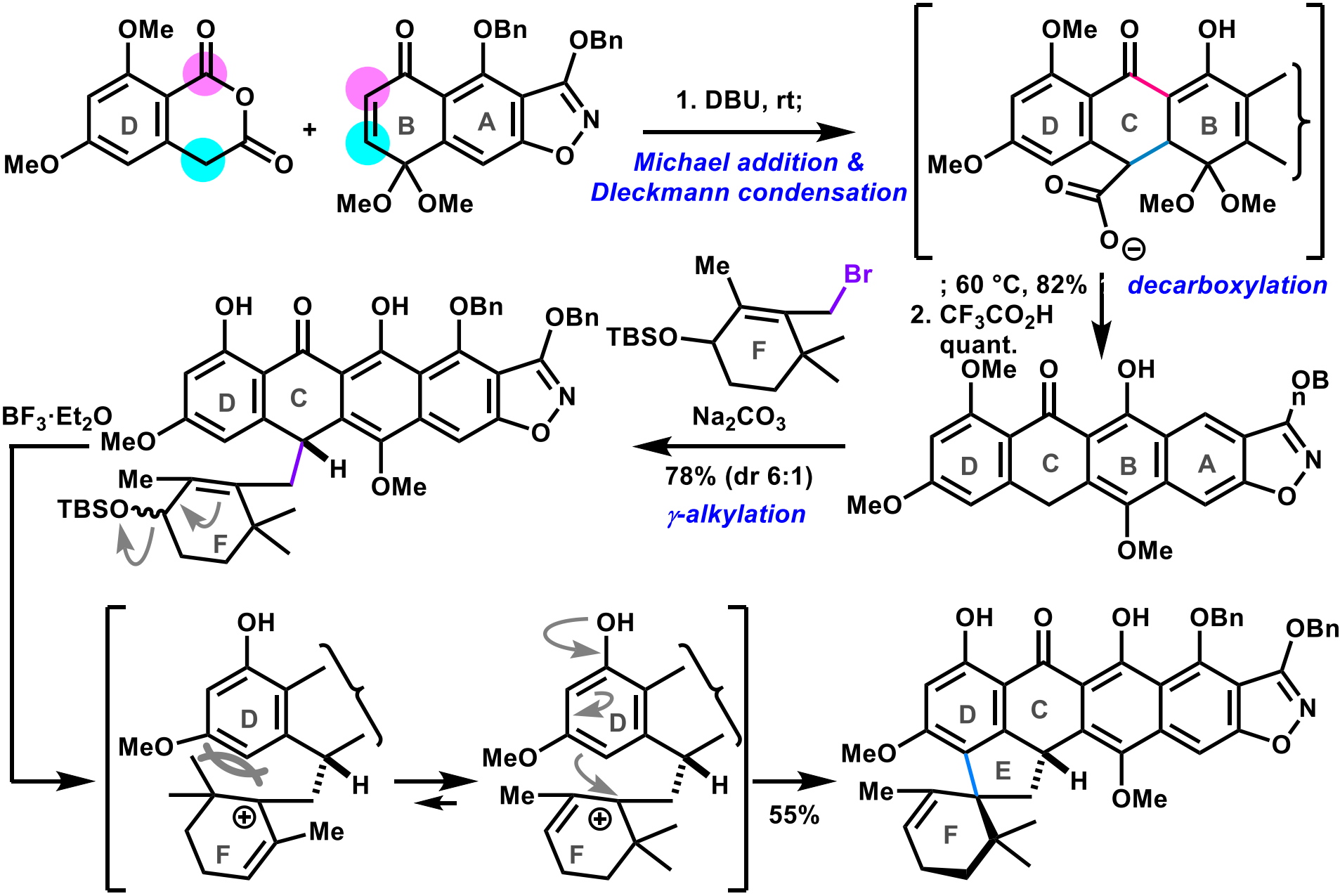
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Synthesis of AB-quinone Monoketal [1)]



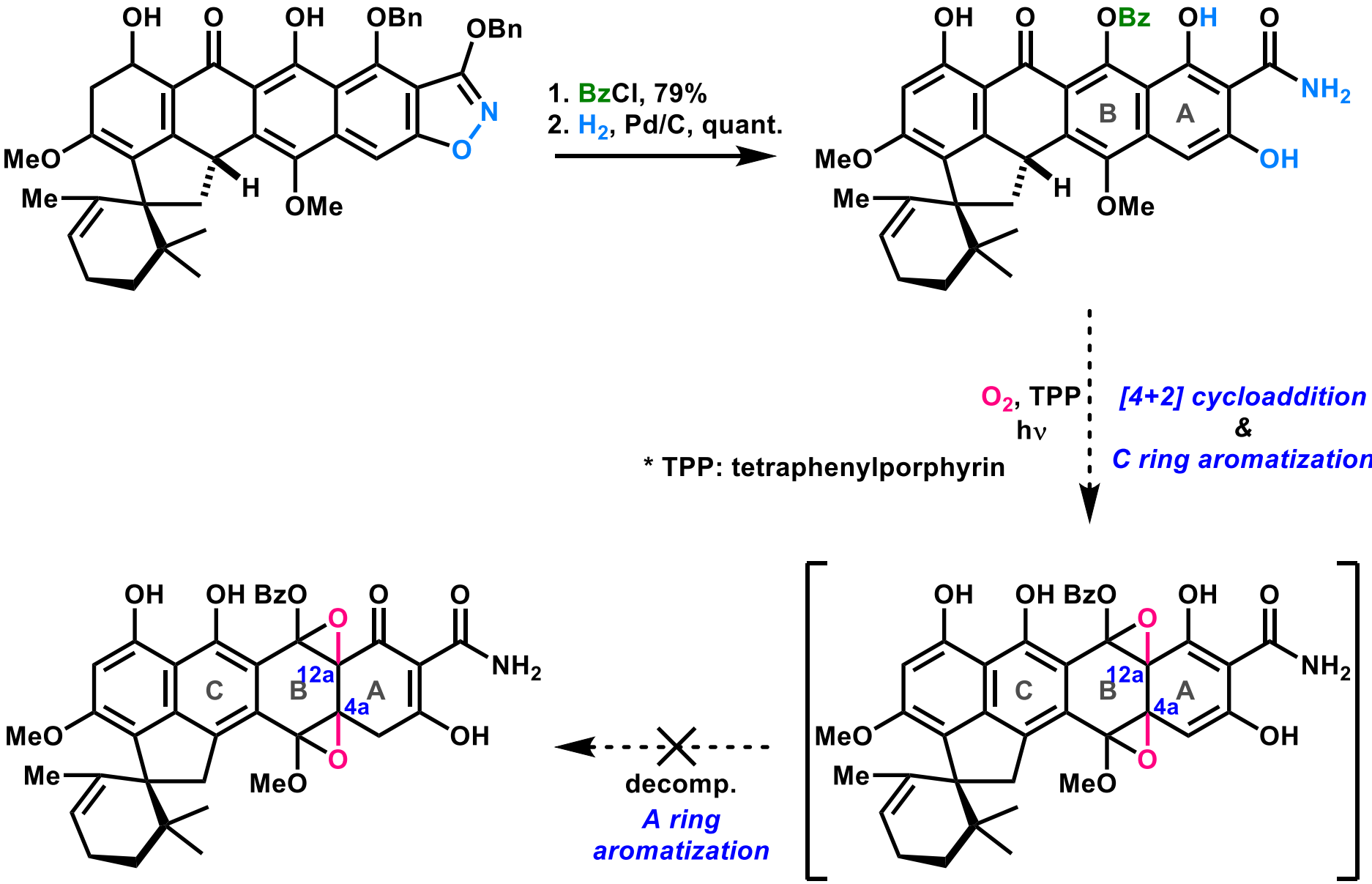
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Construction of Heptacyclic Core[1)]



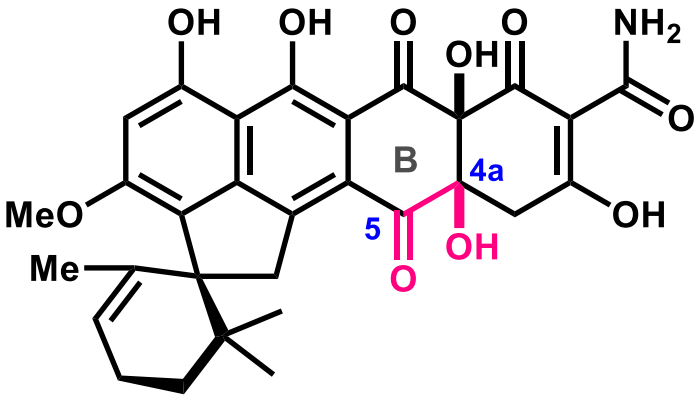
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Attempted C4a/C12a Oxidation by Singlet-oxygen[1)]



1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

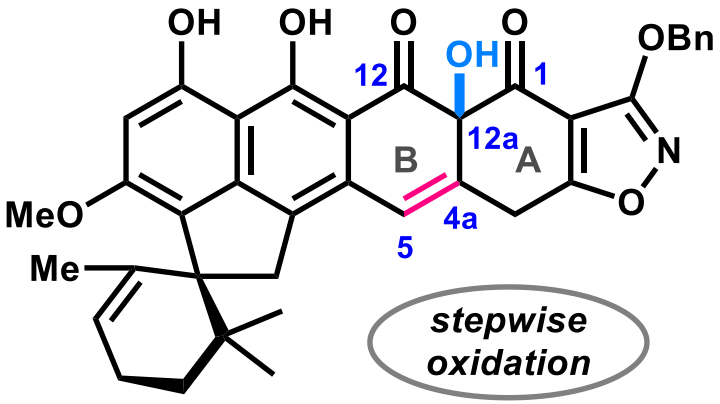
Nicolaou's Second-generation Retrosynthetic Analysis[1)]



rac-viridicatumtoxin B

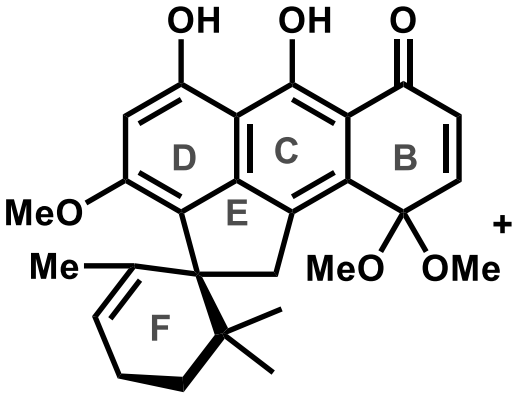
[O]

dihydrxylation of C4a=C5 olefin



stepwise oxidation

[O] *C12a oxidation*



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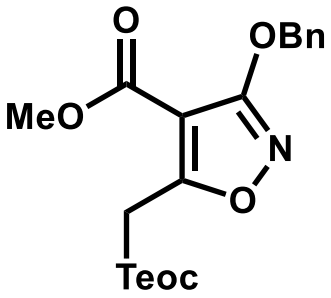
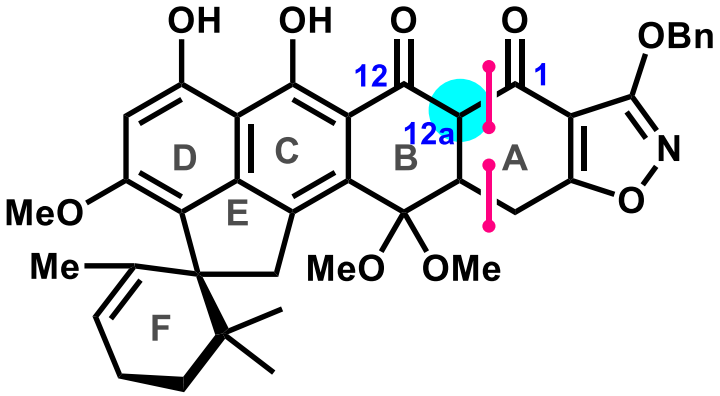
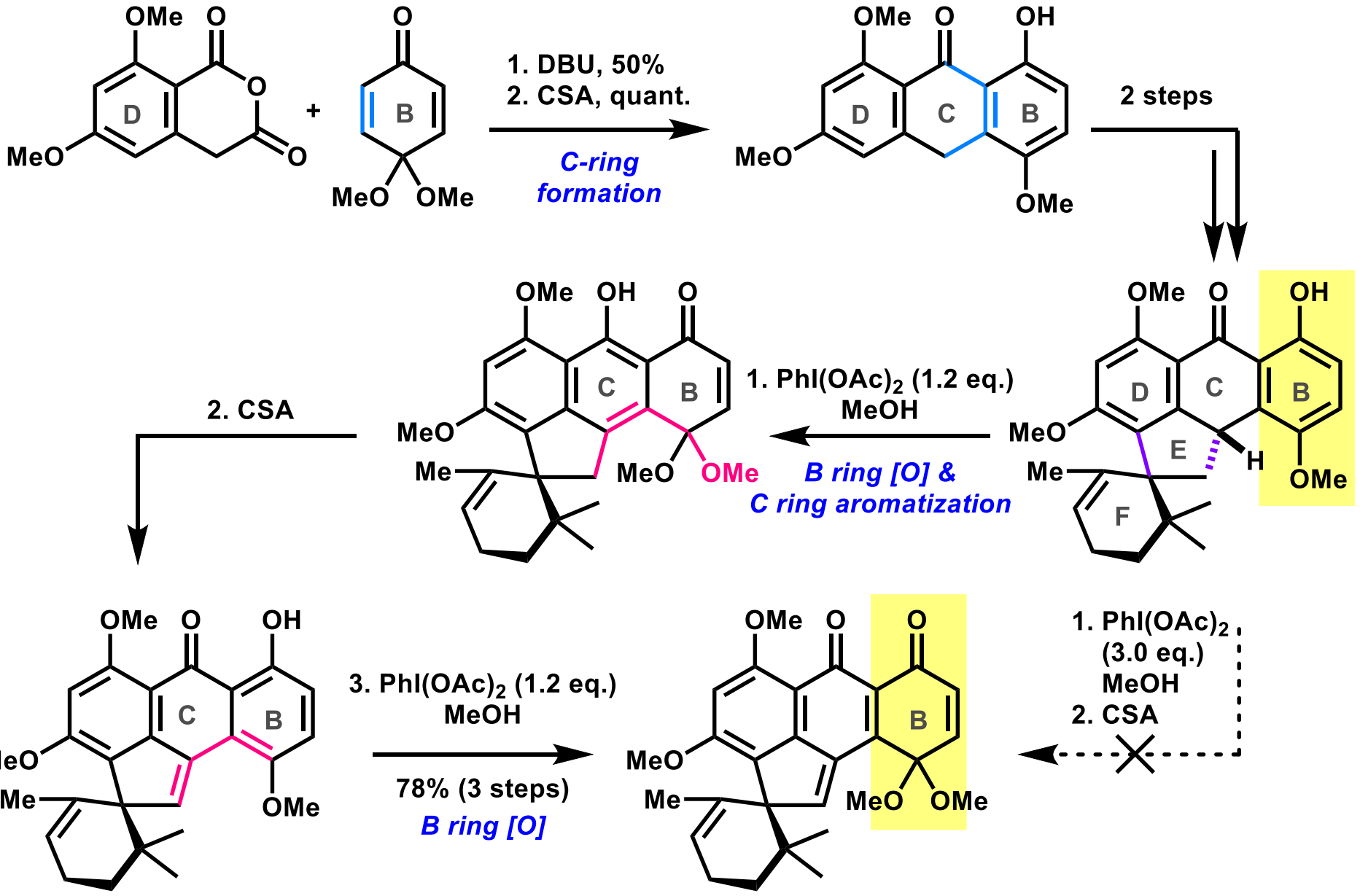


A ring formation



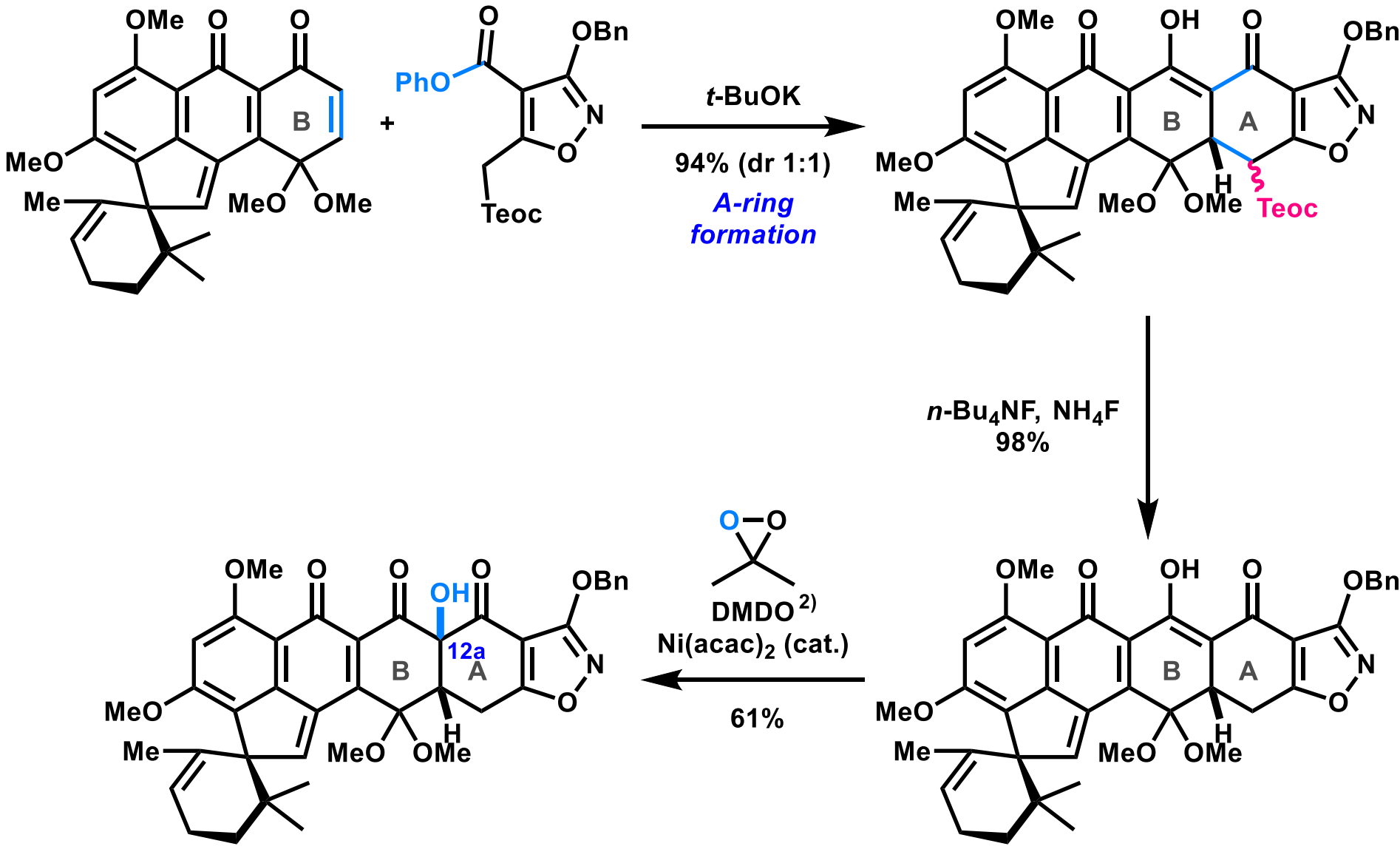
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

BCDEF-ring Construction[1)]



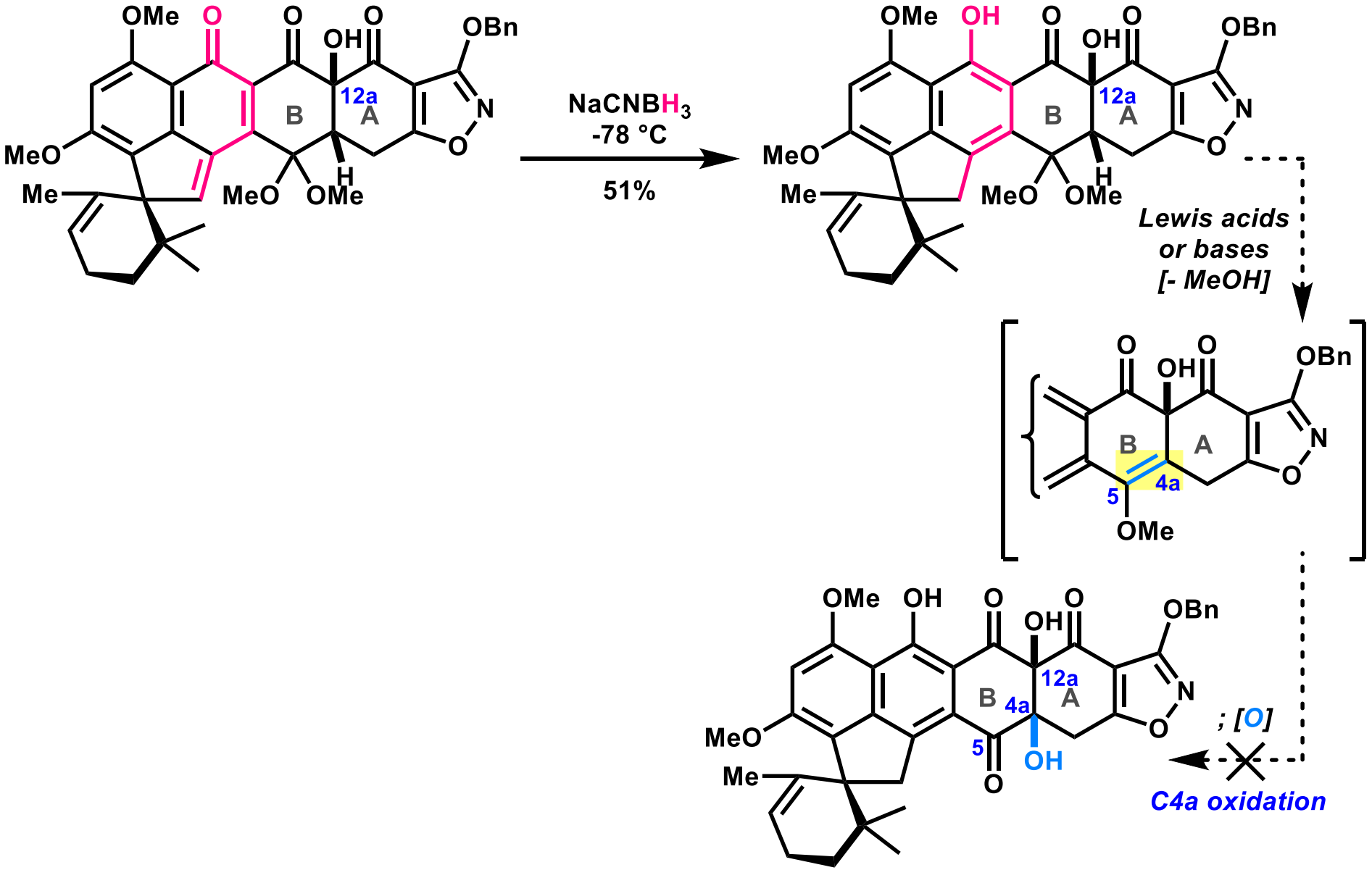
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

A-ring Formation and C12a Oxidation [1)]



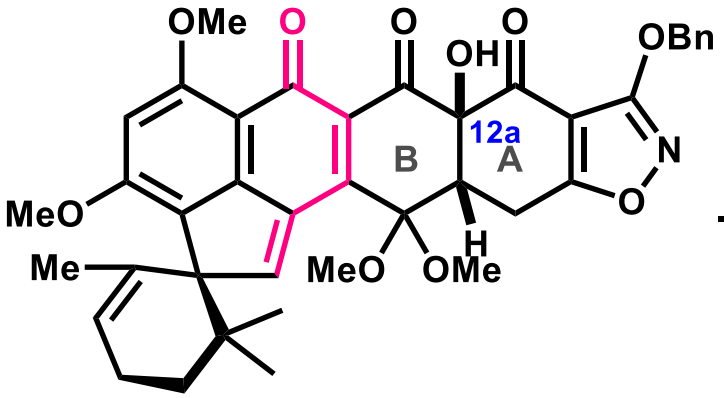
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.
2) Adam, W.; Smerz, A. K. *Tetrahedron* **1996**, *52*, 5799.

Attempted C4a-C5 Olefination[1)]

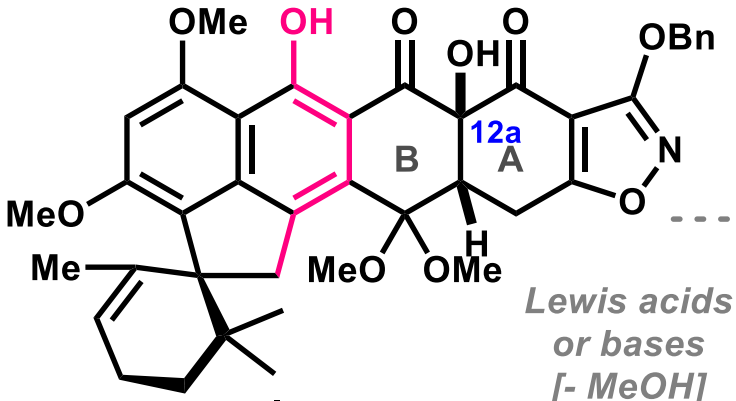


1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

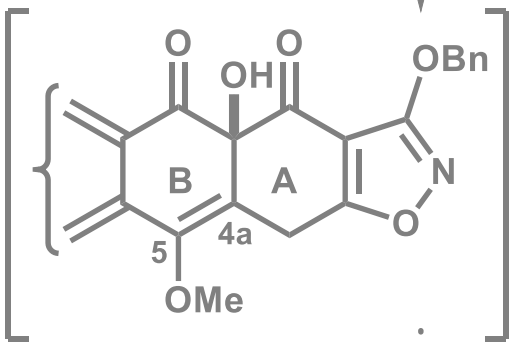
Attempted C4a-C5 Olefination [1)]



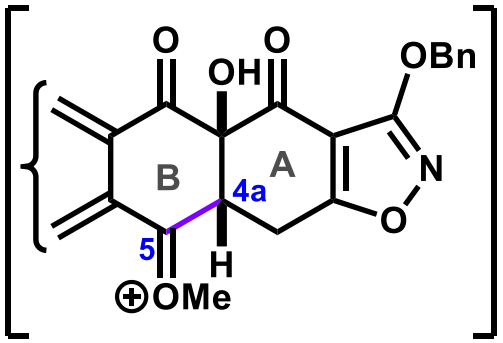
$NaCNBH_3$
-78 °C
51%



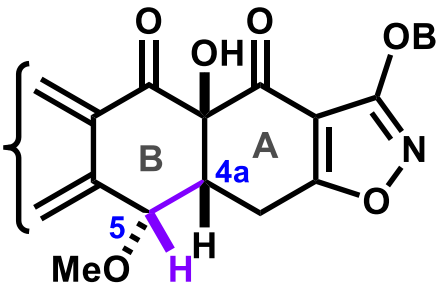
Lewis acids or bases [- MeOH]



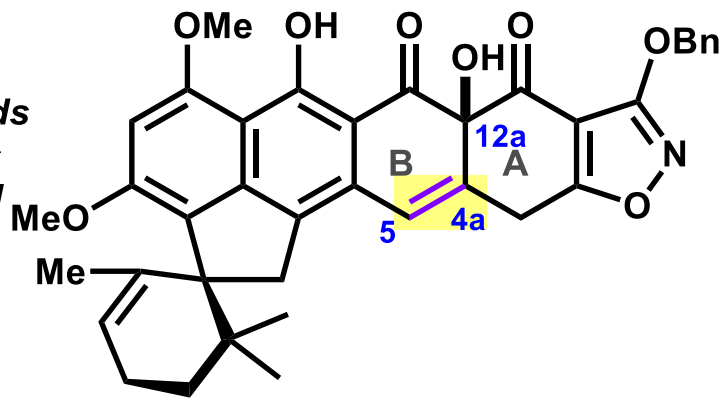
$H^{\oplus}$

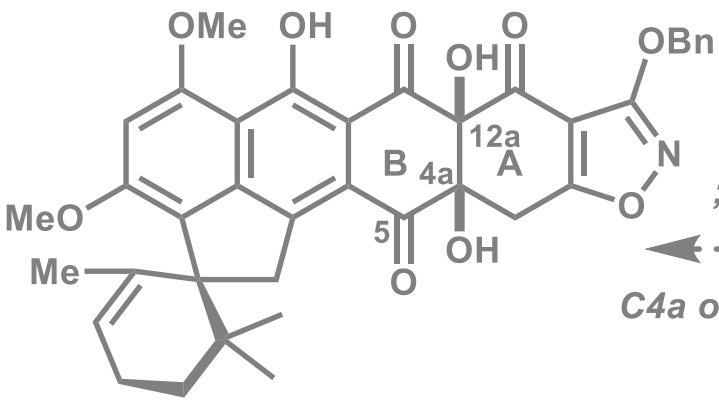


$NaCNBH_3$
72% (dr 1.3:1)



Lewis acids or bases [- MeOH]



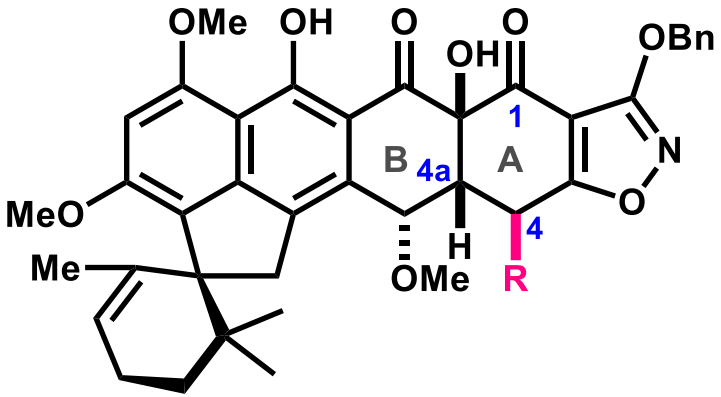


; [O]

C4a oxidation

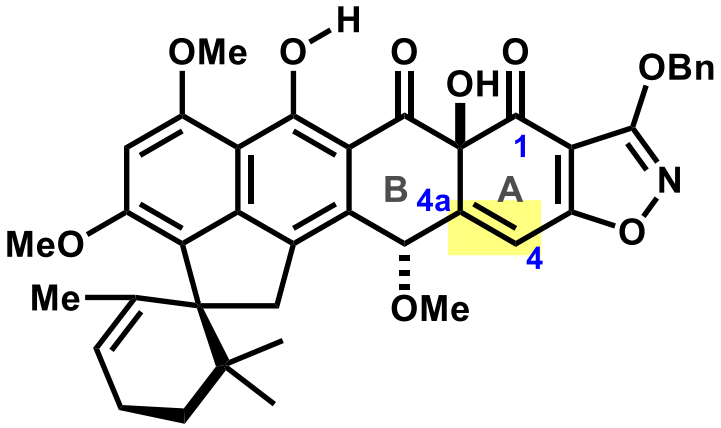
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Attempted C4-C4a Olefination[1)]



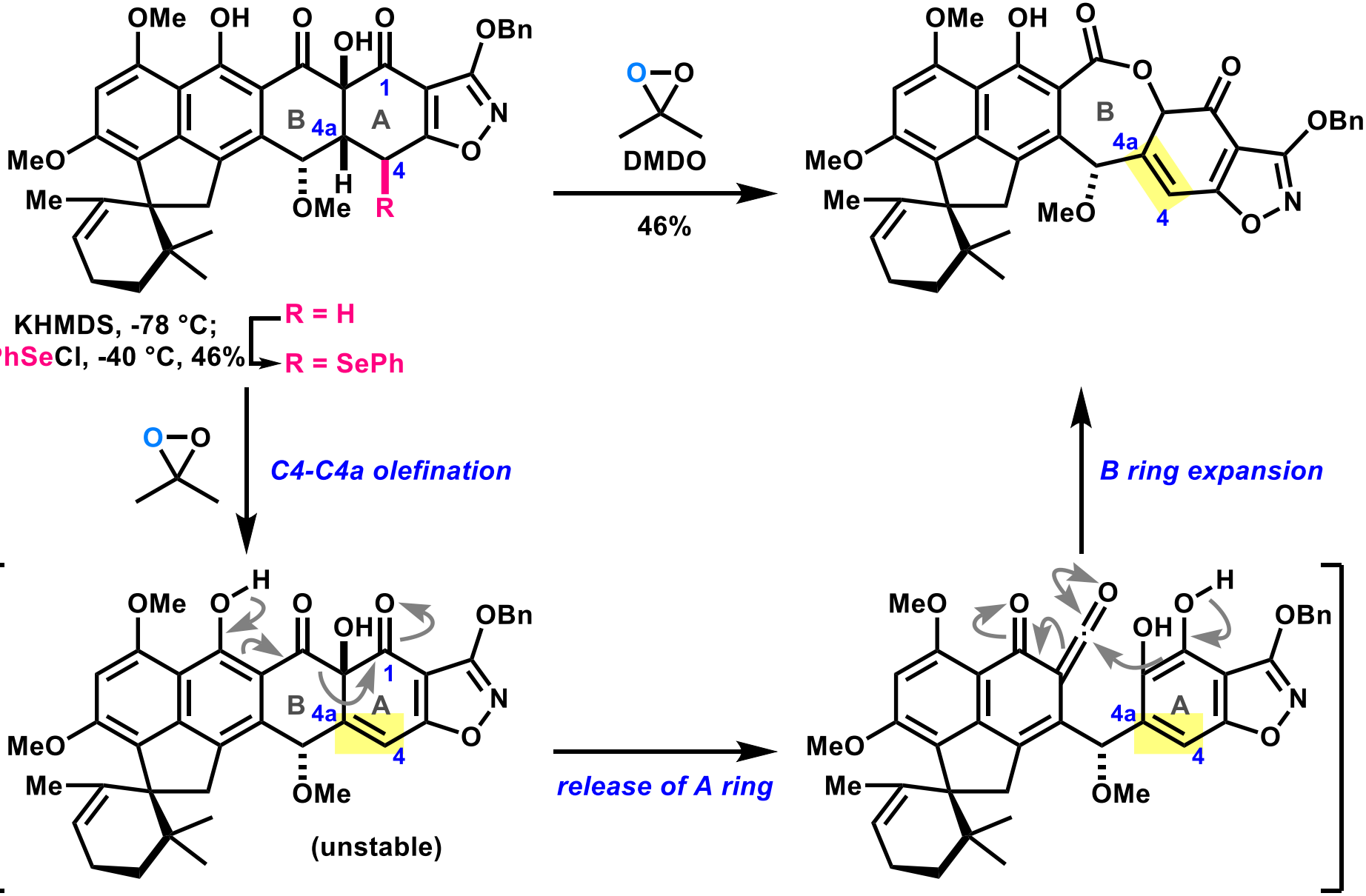
R = H

C4-C4a olefination



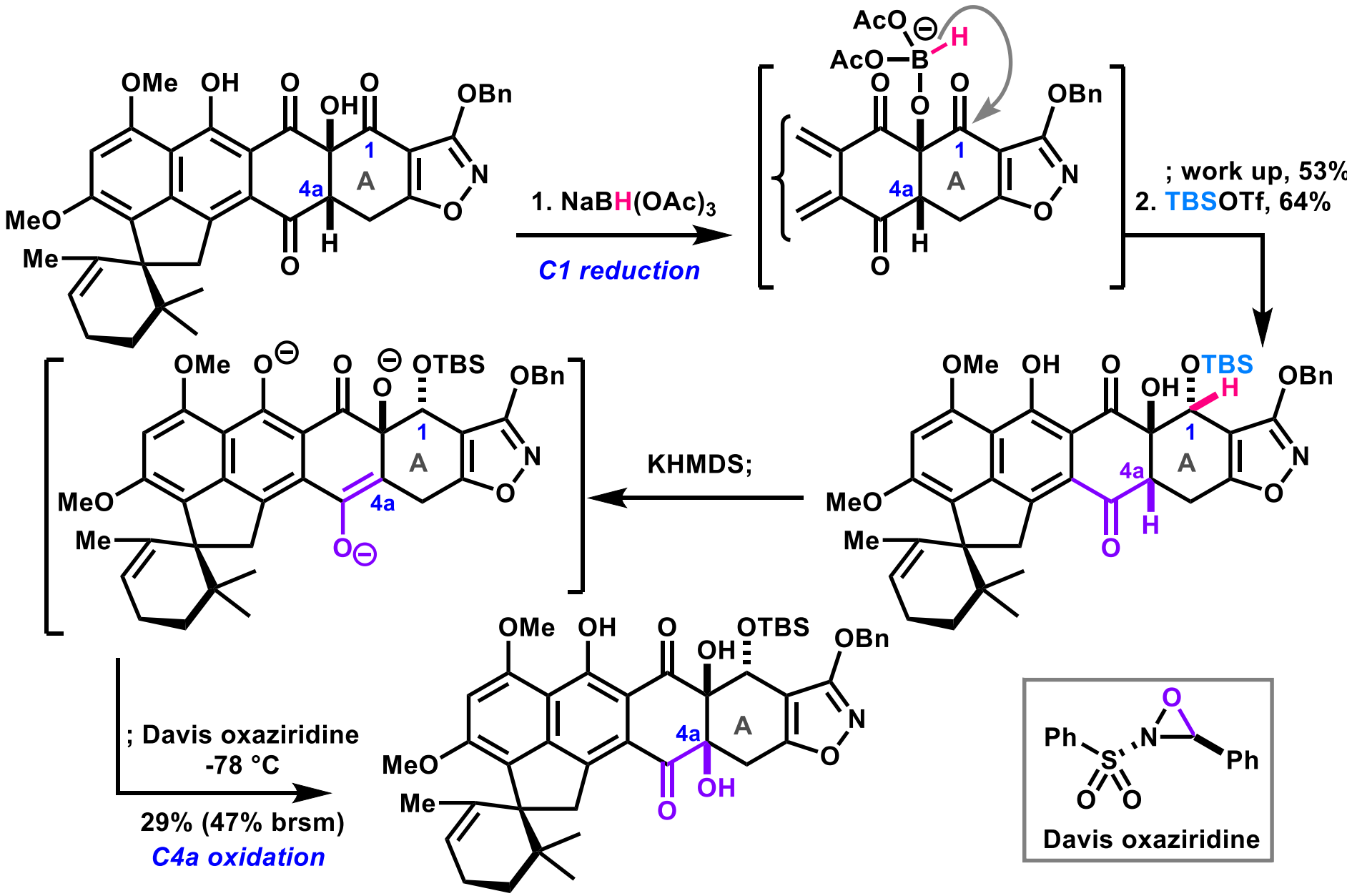
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Attempted C4-C4a Olefination[1)]



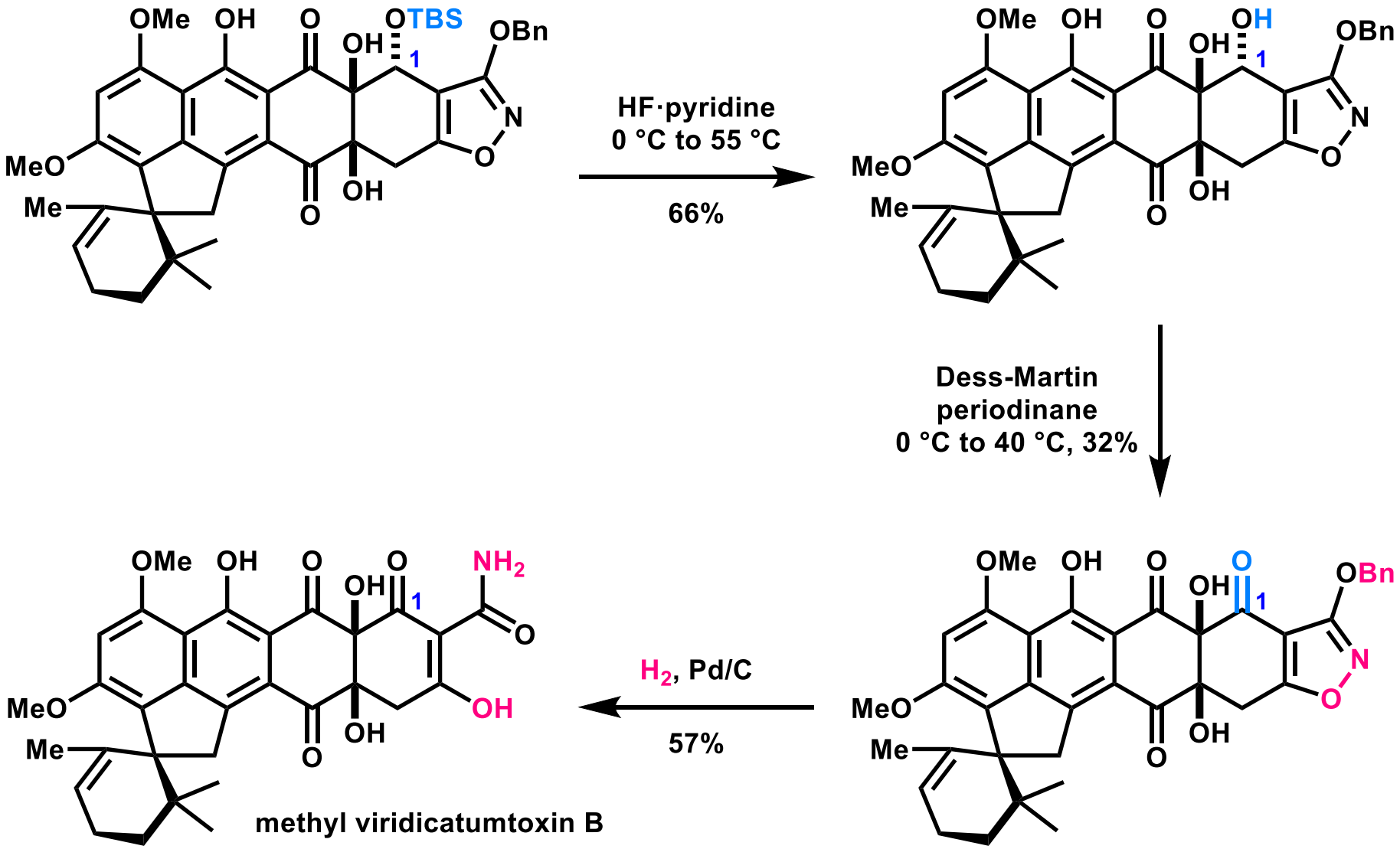
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Successful C4a Davis Oxidation [1)]



1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

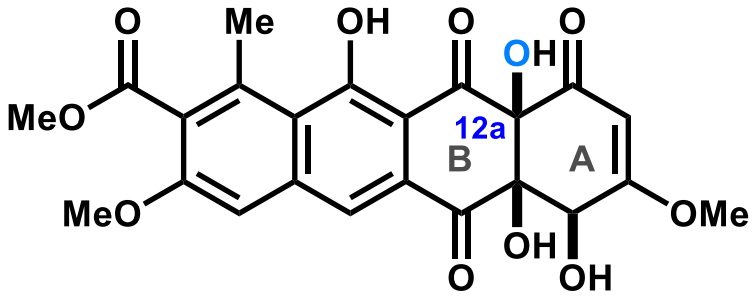
Synthesis of Methyl Viridicatumtoxin B [1)]



1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Contents

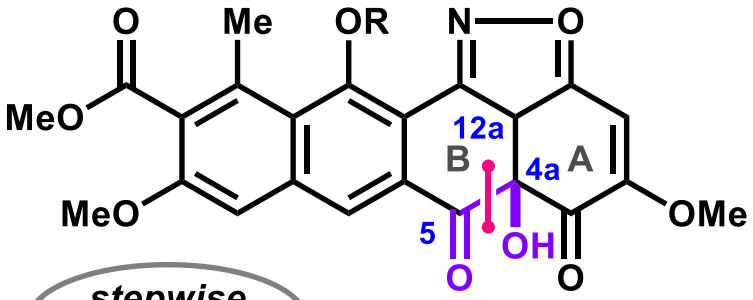
Suzuki's Retrosynthetic Analysis of Tetracenomycin[1)]



(+)-tetracenomycin C

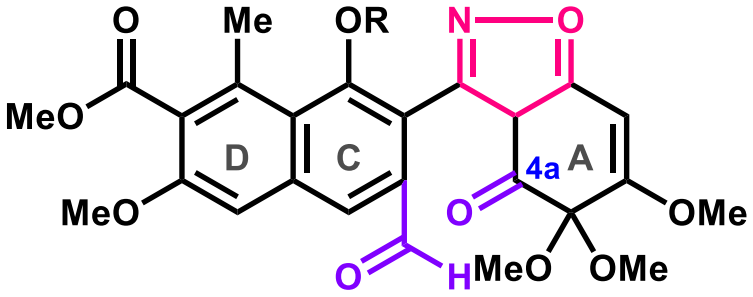
C12a [O]

isoxazole oxidation

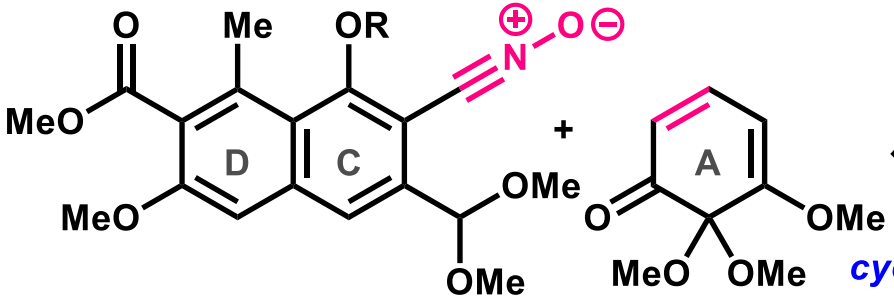


stepwise oxidation

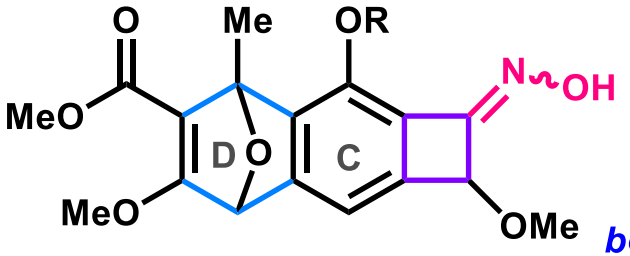
asymmmetric benzoin condensation



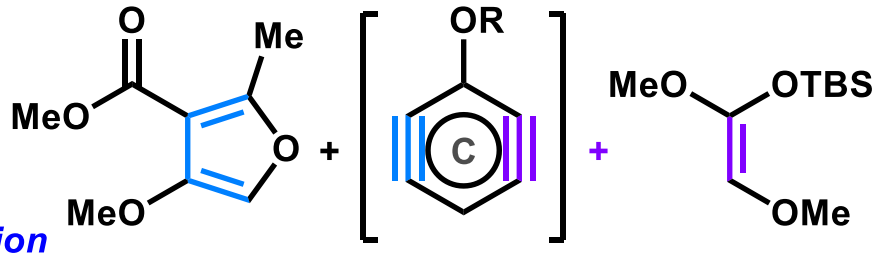
[3+2] cycloaddition



oxidative ring opening & *reductive aromatization*

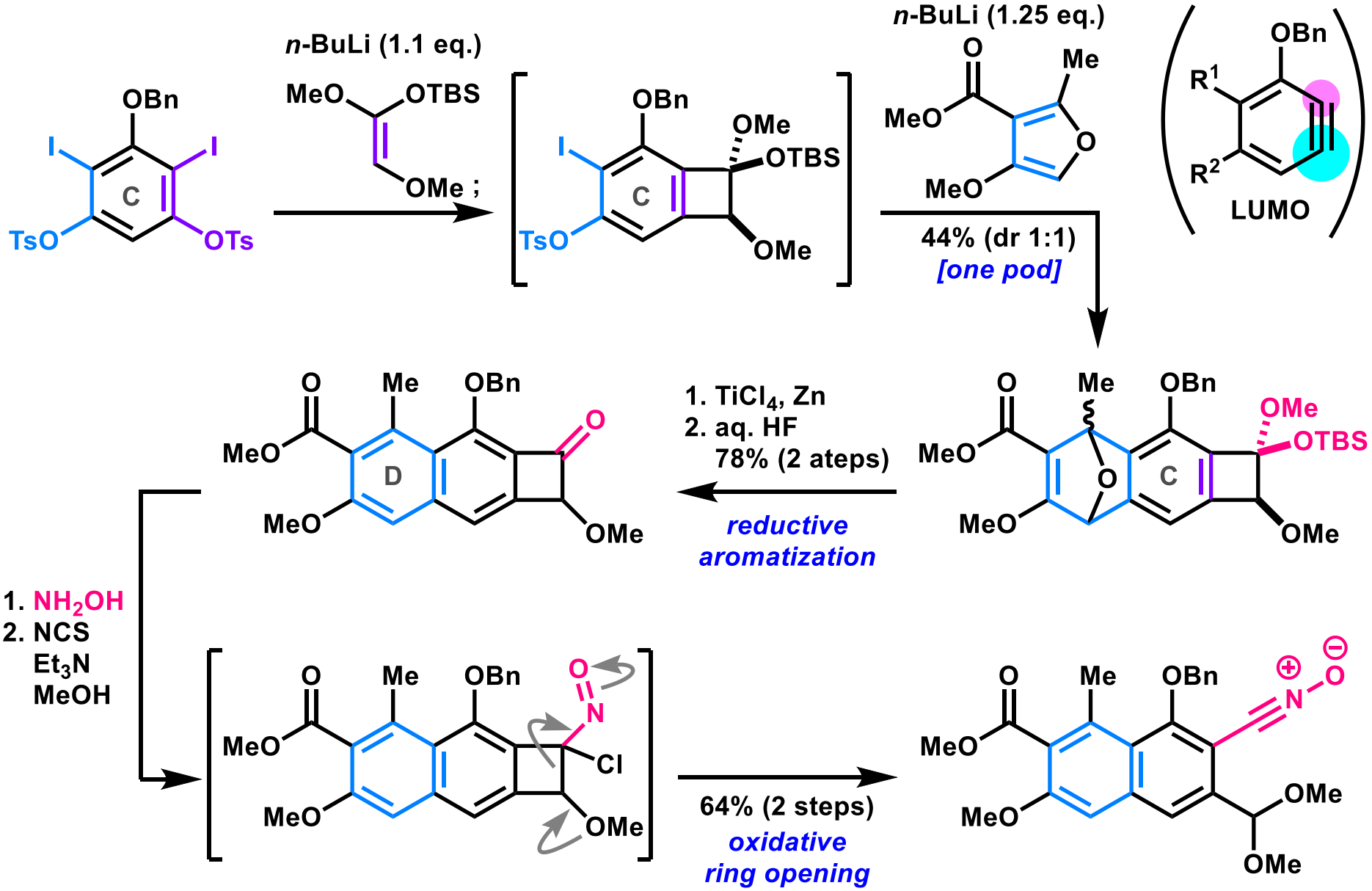


[4+2] & [3+2] benzyne cycloaddition



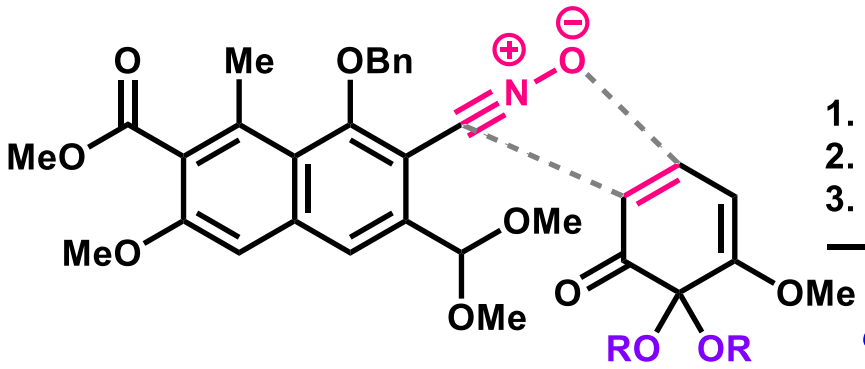
1) Suzuki, K.. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 12608.

Two Successive Benzyne Cycloaddition[1)]



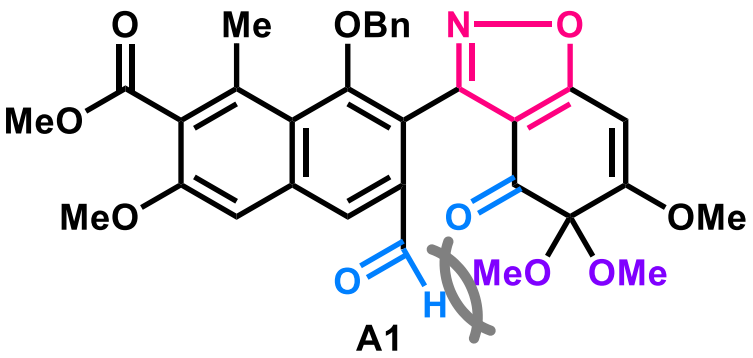
1) Suzuki, K.. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 12608.

Cycloaddition and Benzoin Condansation[1)]



1. PhCl, 79%
2. NiO_2, 0 °C, 82%
3. aq. H_2SO_4, 95%

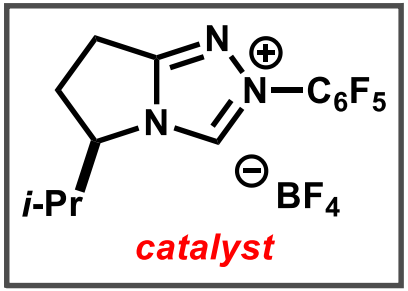
[3+2] cycloaddition



A1

1. PhCl, 50 °C, 76%
2. NiO_2, 0 °C, 82%
3. aq. H_2SO_4, 97%

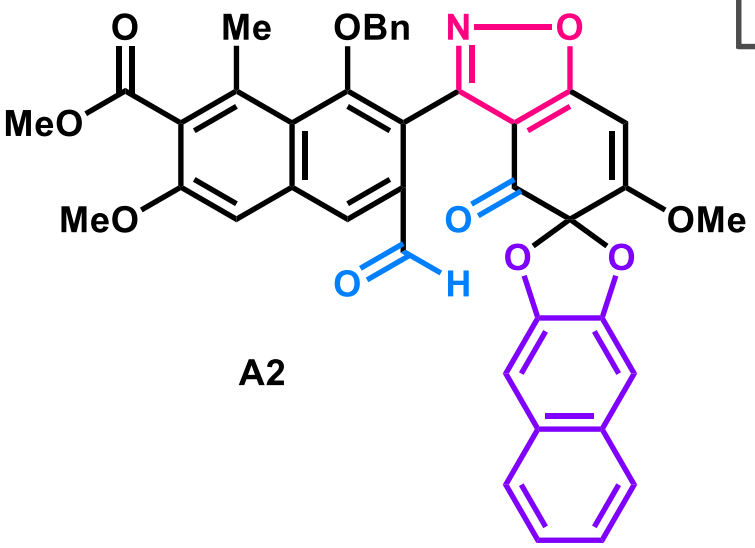
[3+2] cycloaddition



catalyst

catalyst
B1: 46%
recovery of A1: 20%

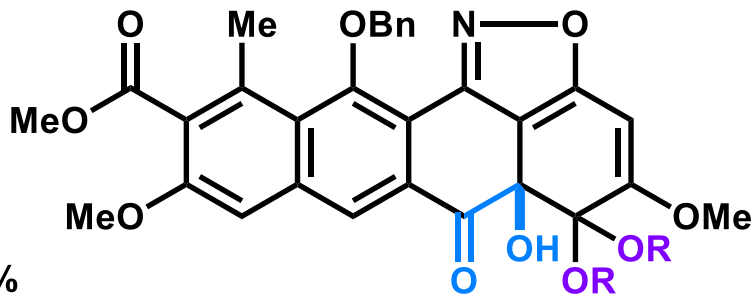
benzoin cdclization



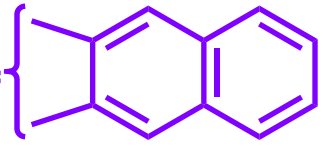
A2

catalyst
B2: 87%, >99% ee
recovery of A1: n/d%

benzoin cdclization

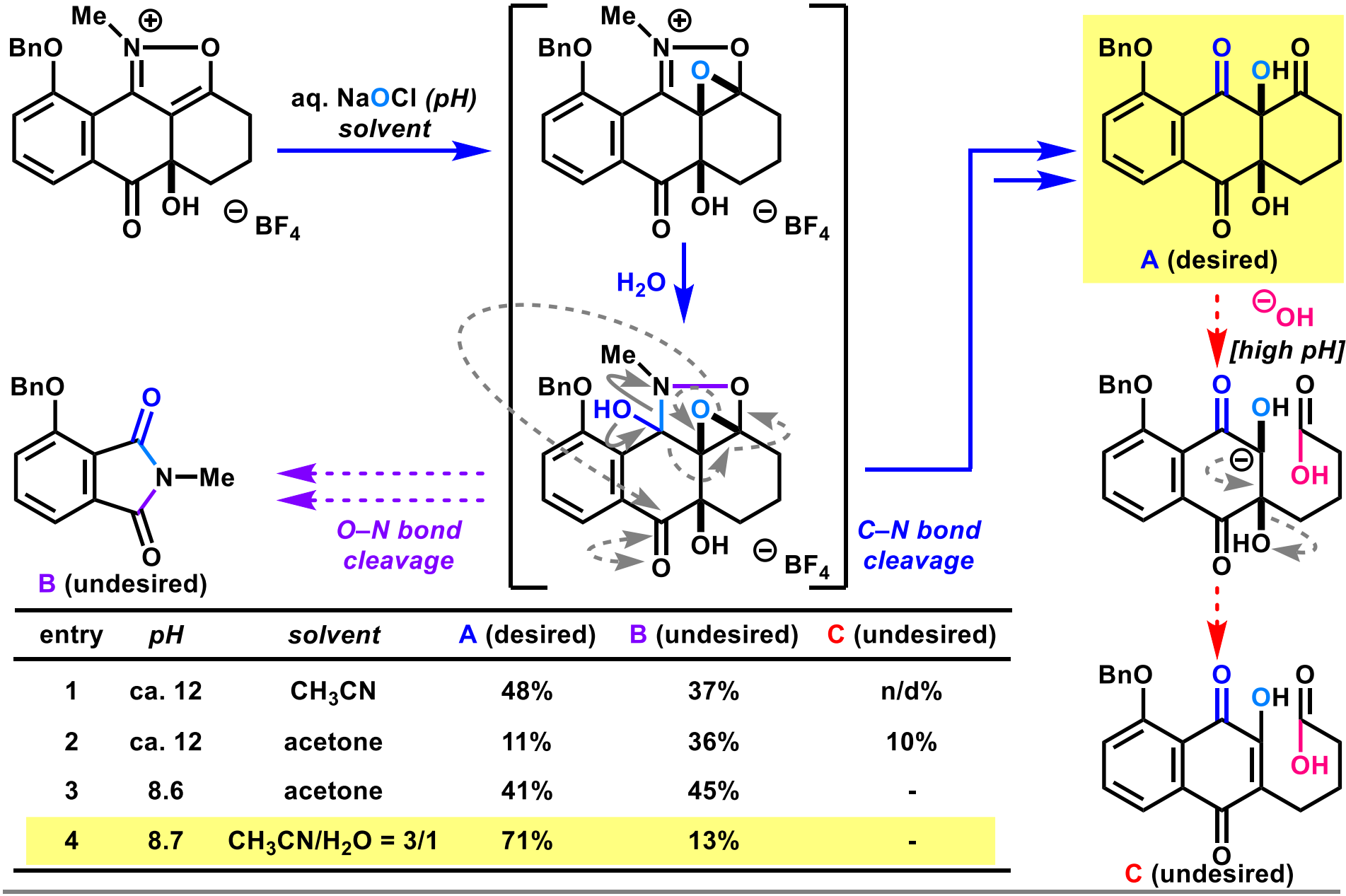


B1: R = Me

B2: R = 

1) Suzuki, K.. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 12608.

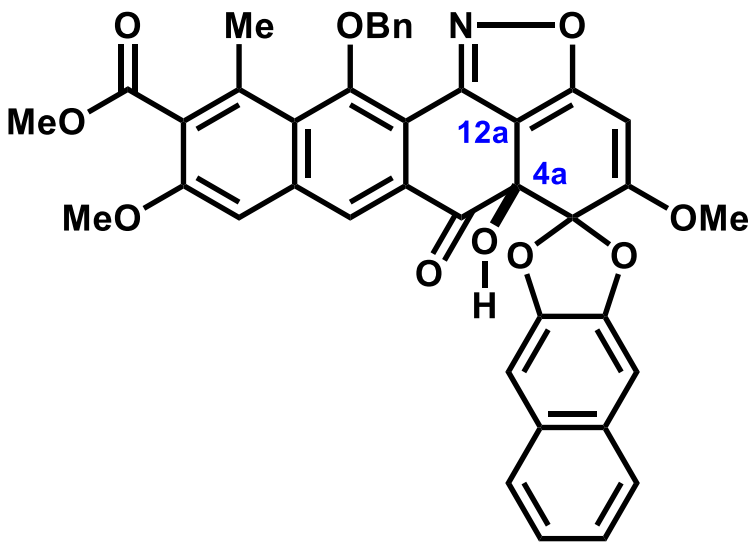
Optimization for Oxidation of Isoxazole Salt[1)]



entry	*pH*	*solvent*	A (desired)	B (undesired)	C (undesired)
1	ca. 12	CH_3CN	48%	37%	n/d%
2	ca. 12	acetone	11%	36%	10%
3	8.6	acetone	41%	45%	-
4	8.7	CH_3CN/H_2O = 3/1	71%	13%	-

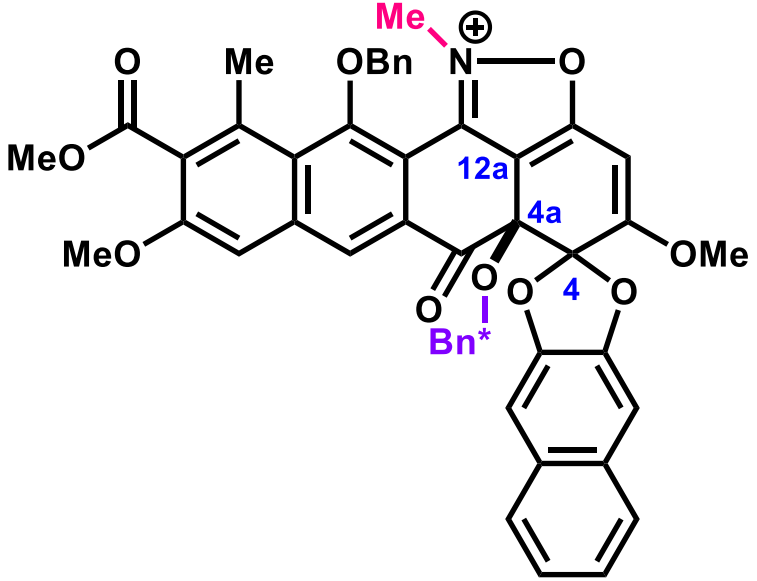
1) Suzuki, K.. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7446.

Total Synthesis of Tetracenomycin C [1)]



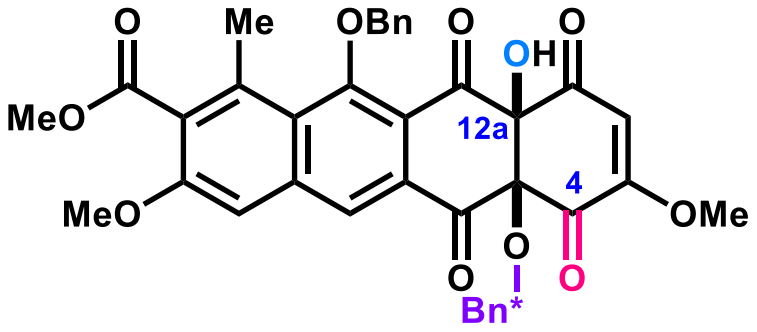
1. Bn*Br, 94%
2. $Me_3O \cdot BF_4$
   MS 4A, quant.

(Bn* = benzyl-d_7)

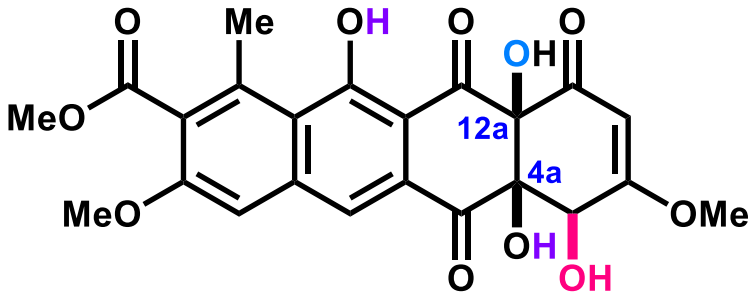


1. aq. NaOCl (pH 8.9)
   CH_3CN/H_2O, 66%
2. DDQ, 80 °C, 78%
   (cf. 35% for Bn, NOT Bn*)

C12a oxidation



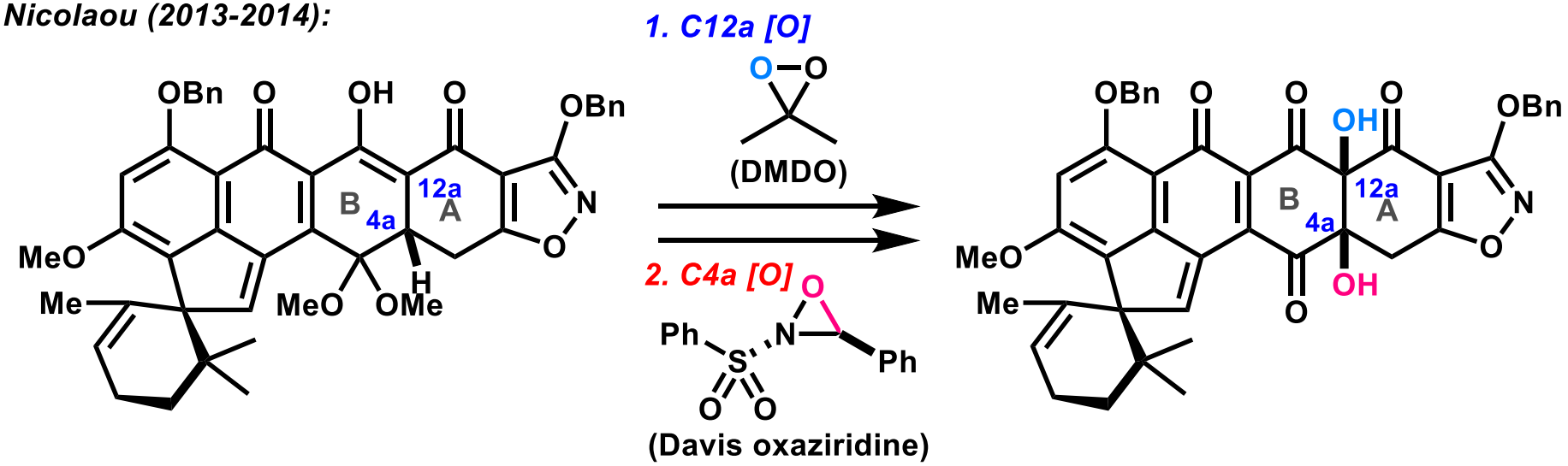
1. $NaBH_3CN$
   AcOH, 78%
2. H_2, Pd/C, 70%



1) Suzuki, K.. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 12608.

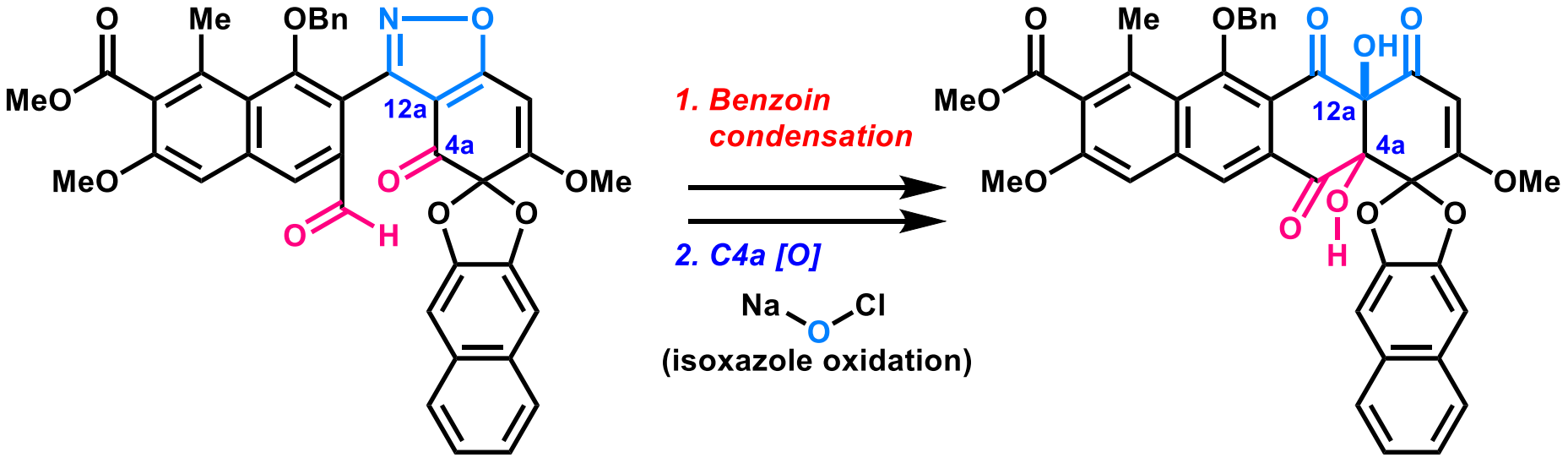
Short Summary

Nicolaou (2013-2014):



stepwise oxidation

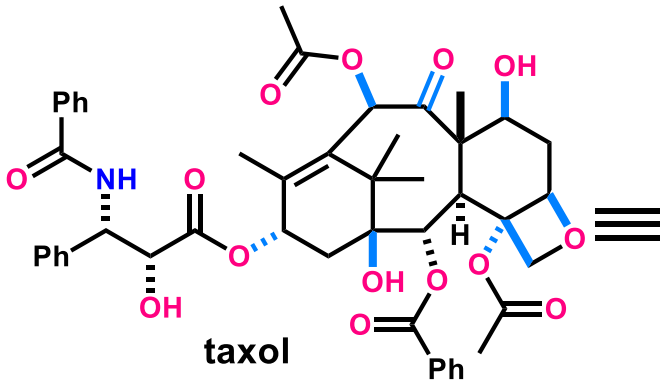
Suzuki (2017):

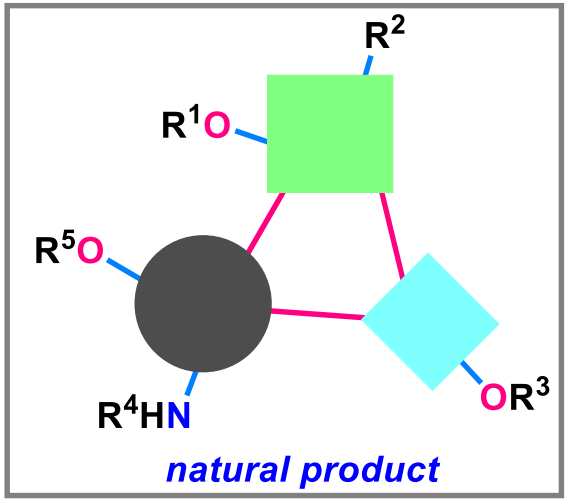


Contents

A New Strategy for Expeditious Biomimetic Synthesis

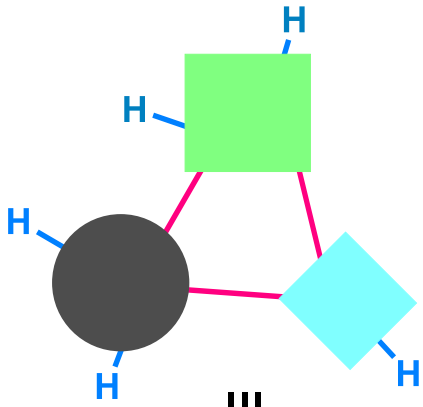
biomimetic two-phase synthesis





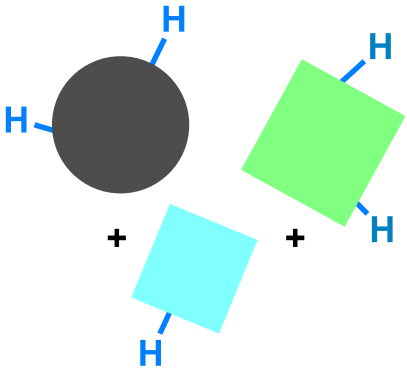
C–C bond formation

phase 1: framework construction

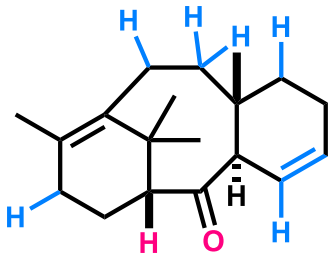


C–H bond activation

phase 2: C–H functinalization



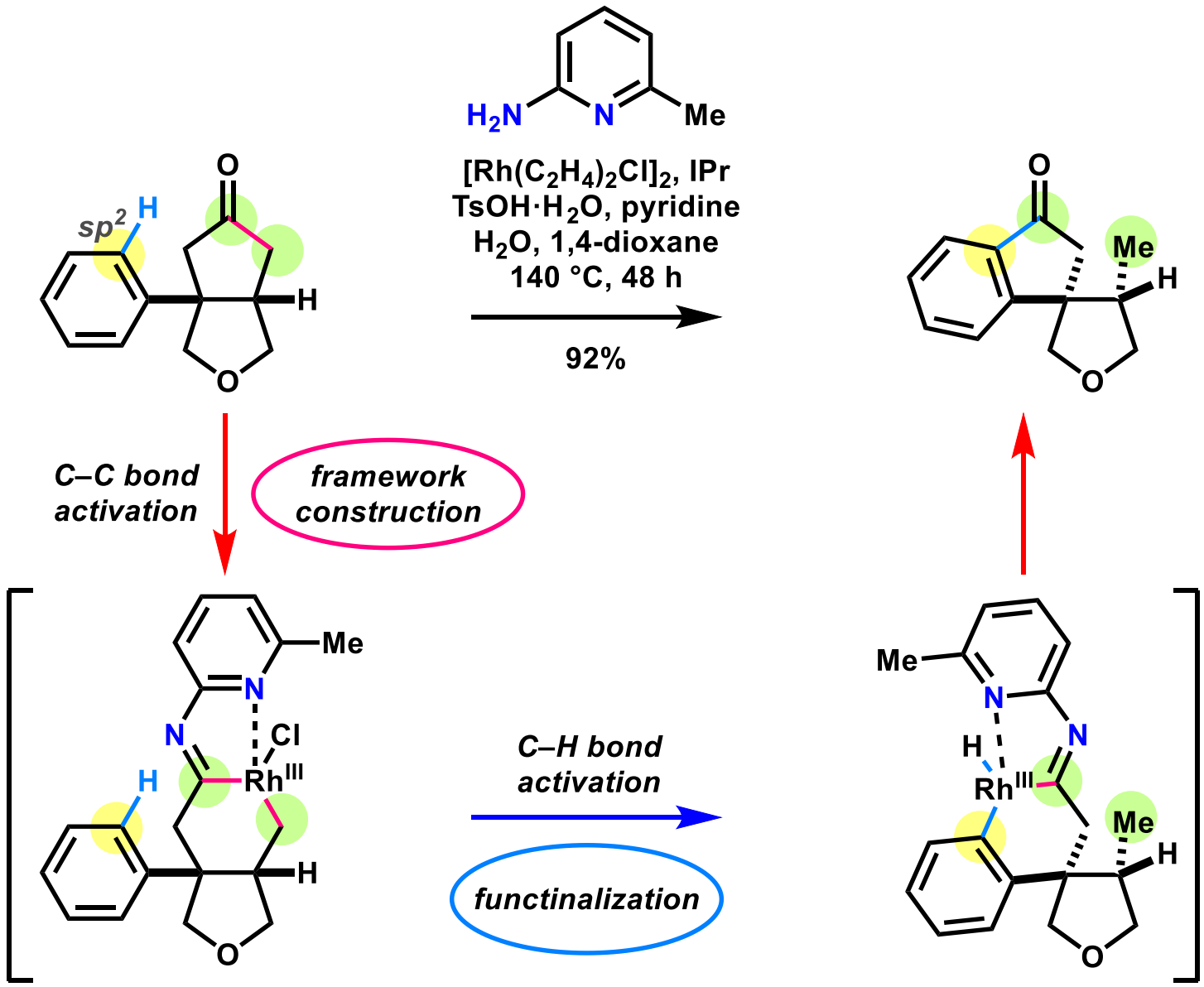
starting materials



taxadinenone (Baran, 2012)[1)]

1) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21.

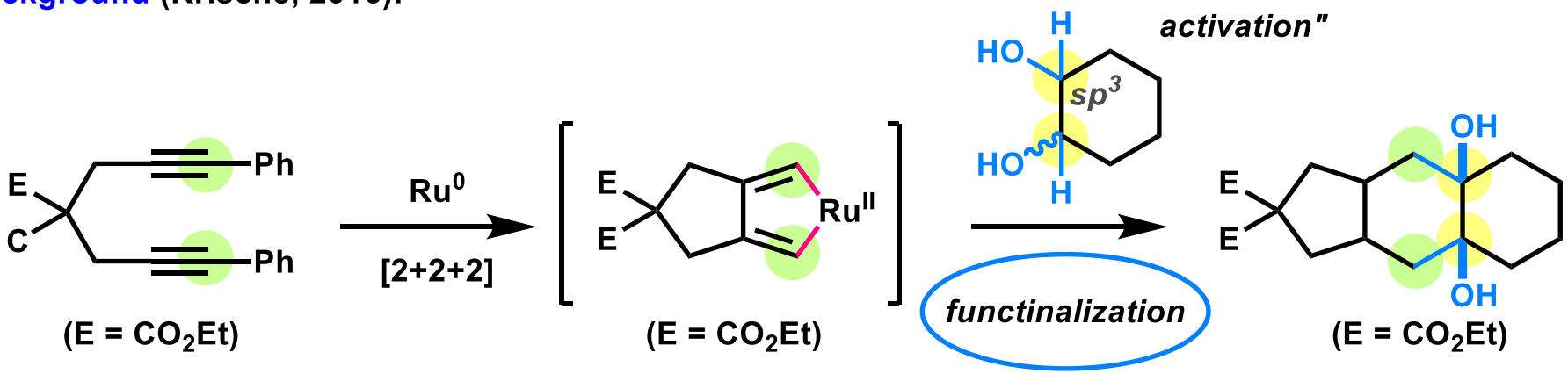
Successive C–C/C–H Bonds Activation in One-pod [1)]



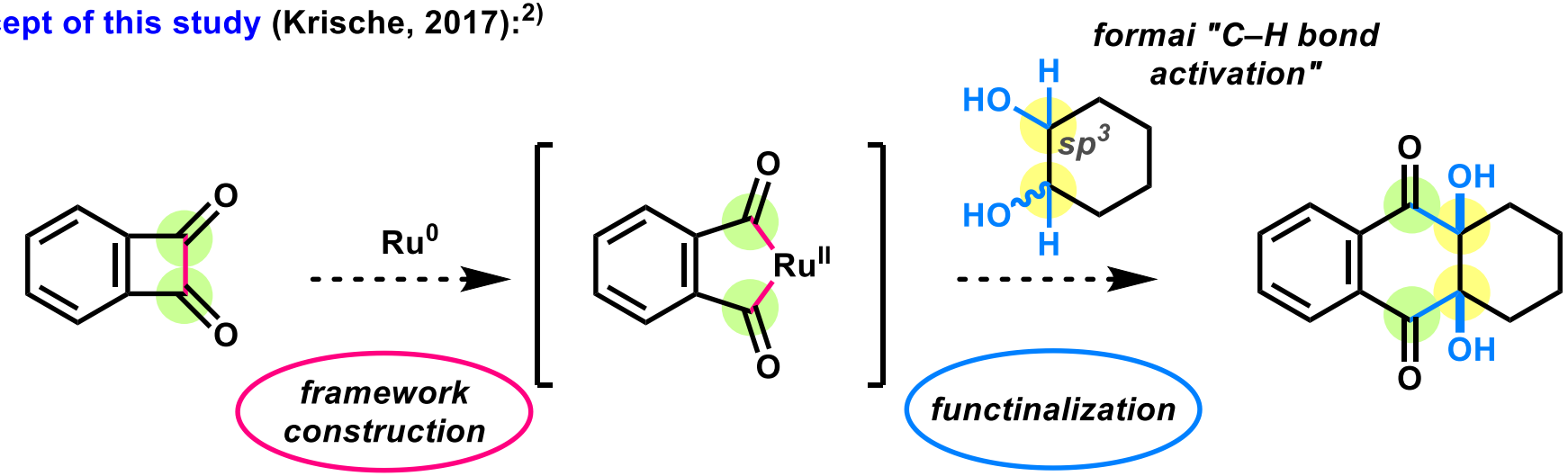
1) Xia, Y.; Wang, J.; Dong, G. *Angew. Chem. Int. Ed.* **2017**, *56*, 2376.
LS about successive C–C/C–H bonds activetion; 170121_LS_Tsukasa_Shimakawa.

Background and Concept [1)]

background (Krische, 2016):[1)]

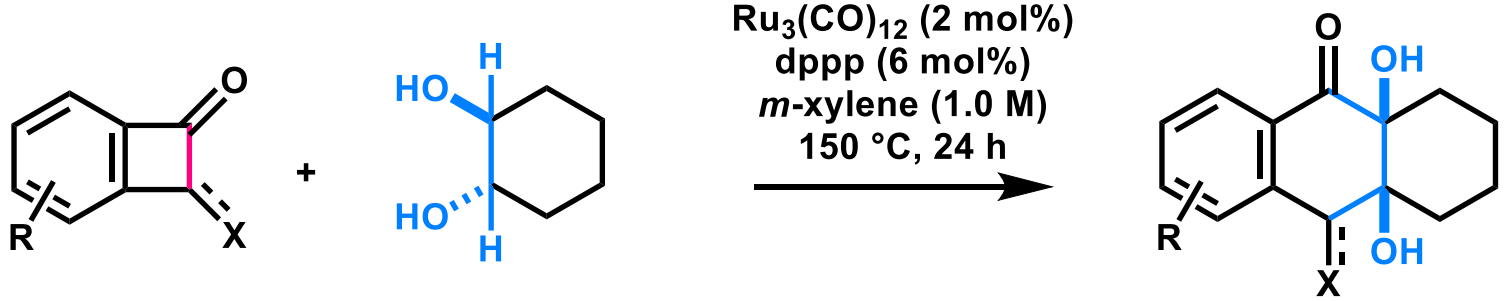


concept of this study (Krische, 2017):[2)]

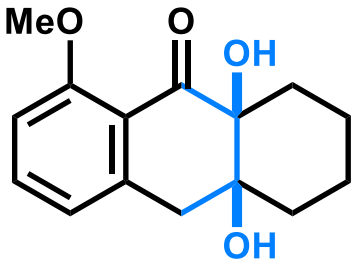


1) Sato, H.; Bender, M.; Chen, W.; Krische, M. *J. Am. Chem. Soc.* **2016**, *138*, 16244.
2) Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. *Science* **2017**, *357*, 779.

Substrate Scope (1)[1)]



(2.0 eq.) (*rac*, 1.0 eq.) (dr > 20:1)



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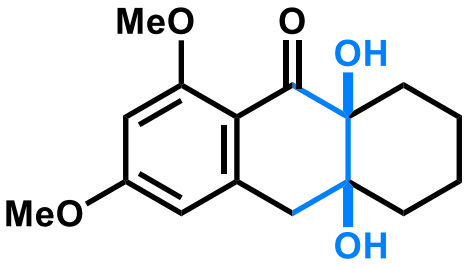

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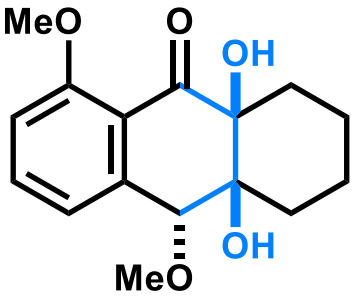

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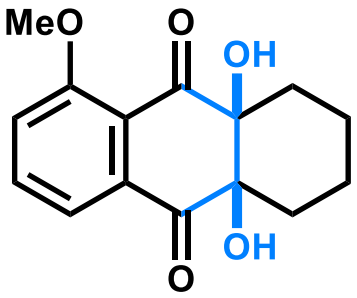

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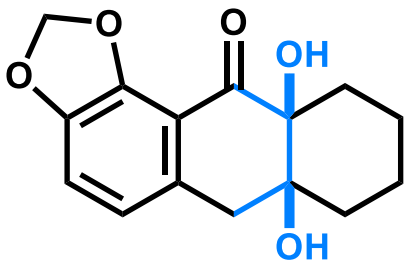

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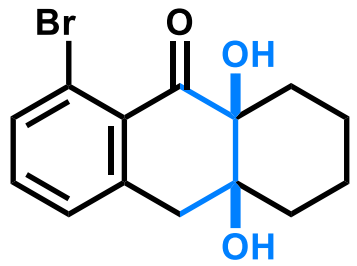
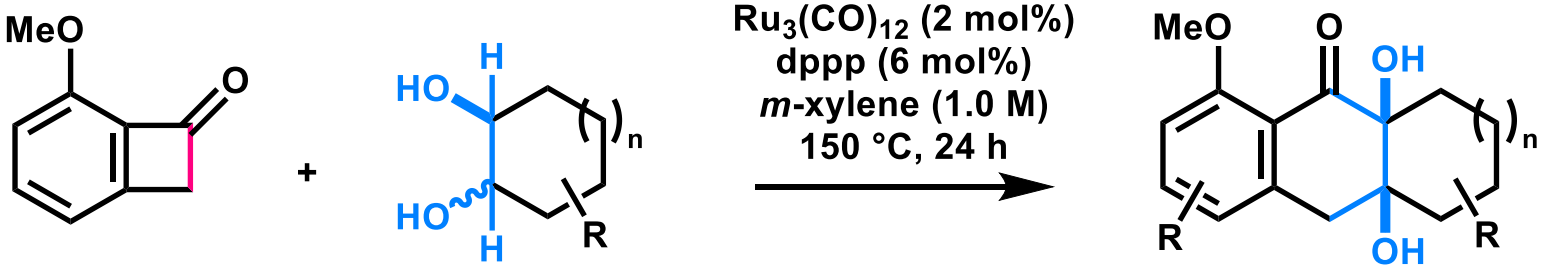


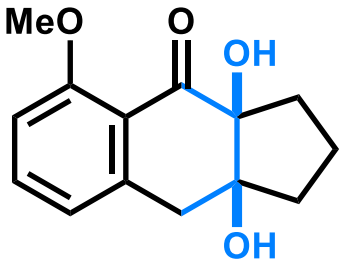
65%

1) Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. *Science* **2017**, *357*, 779.

Substrate Scope (2)[1)]



(2.0 eq.) (*rac*, 1.0 eq.) (dr > 20:1)



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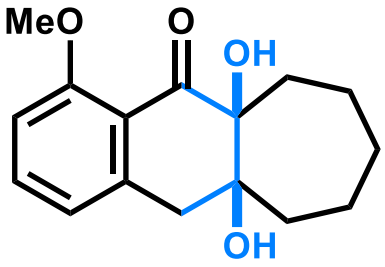

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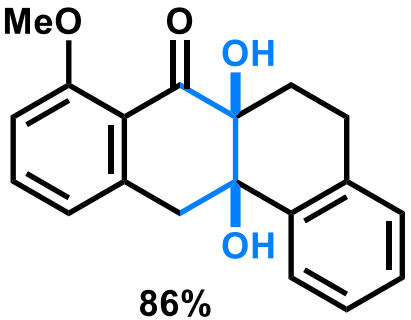

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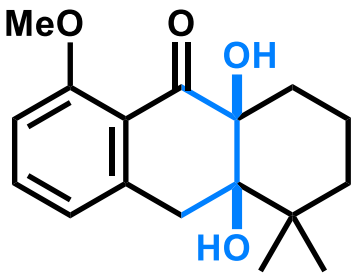
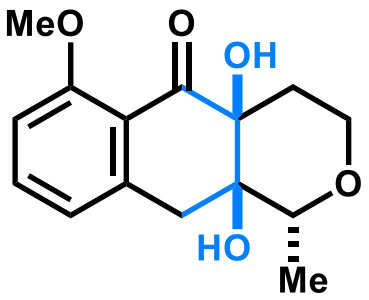
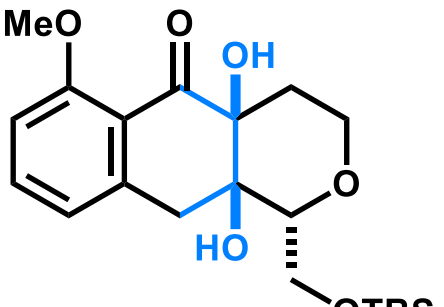


61%



69% (95% ee)*

* Chiral diol was used.

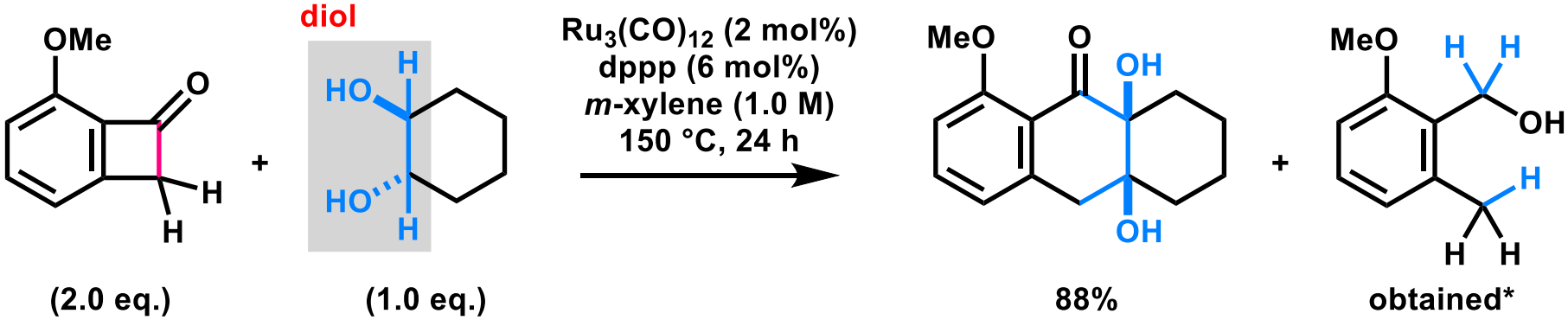


61% (>95% ee)*

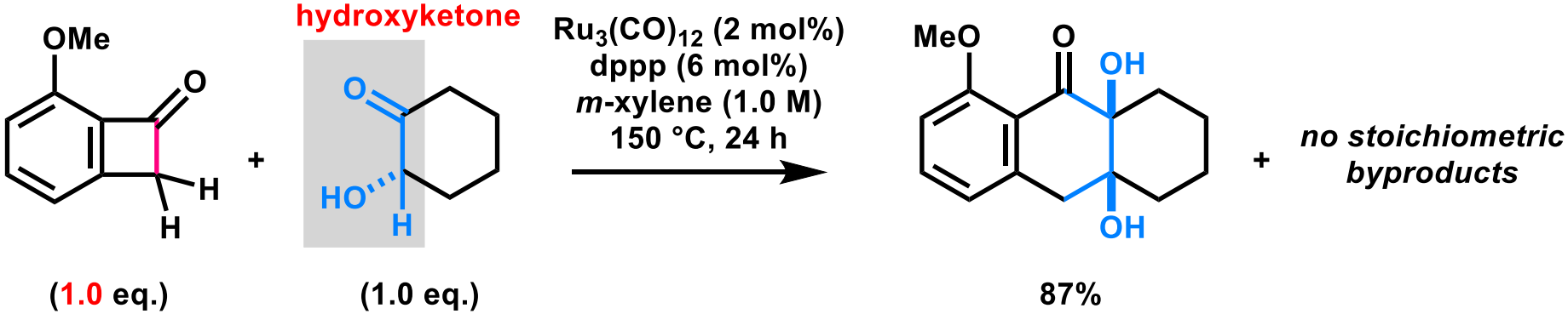
* Chiral diol was used.

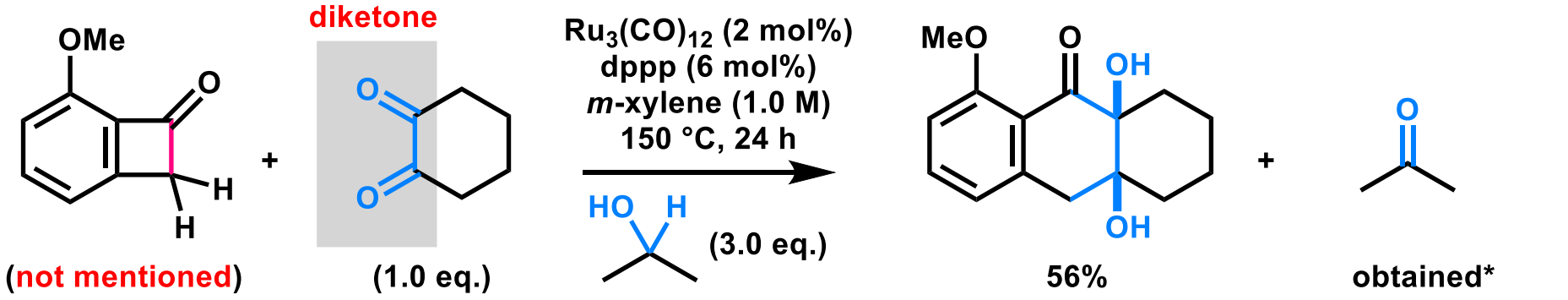
1) Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. *Science* **2017**, *357*, 779.

Redox-independent Cycloaddition [1)]



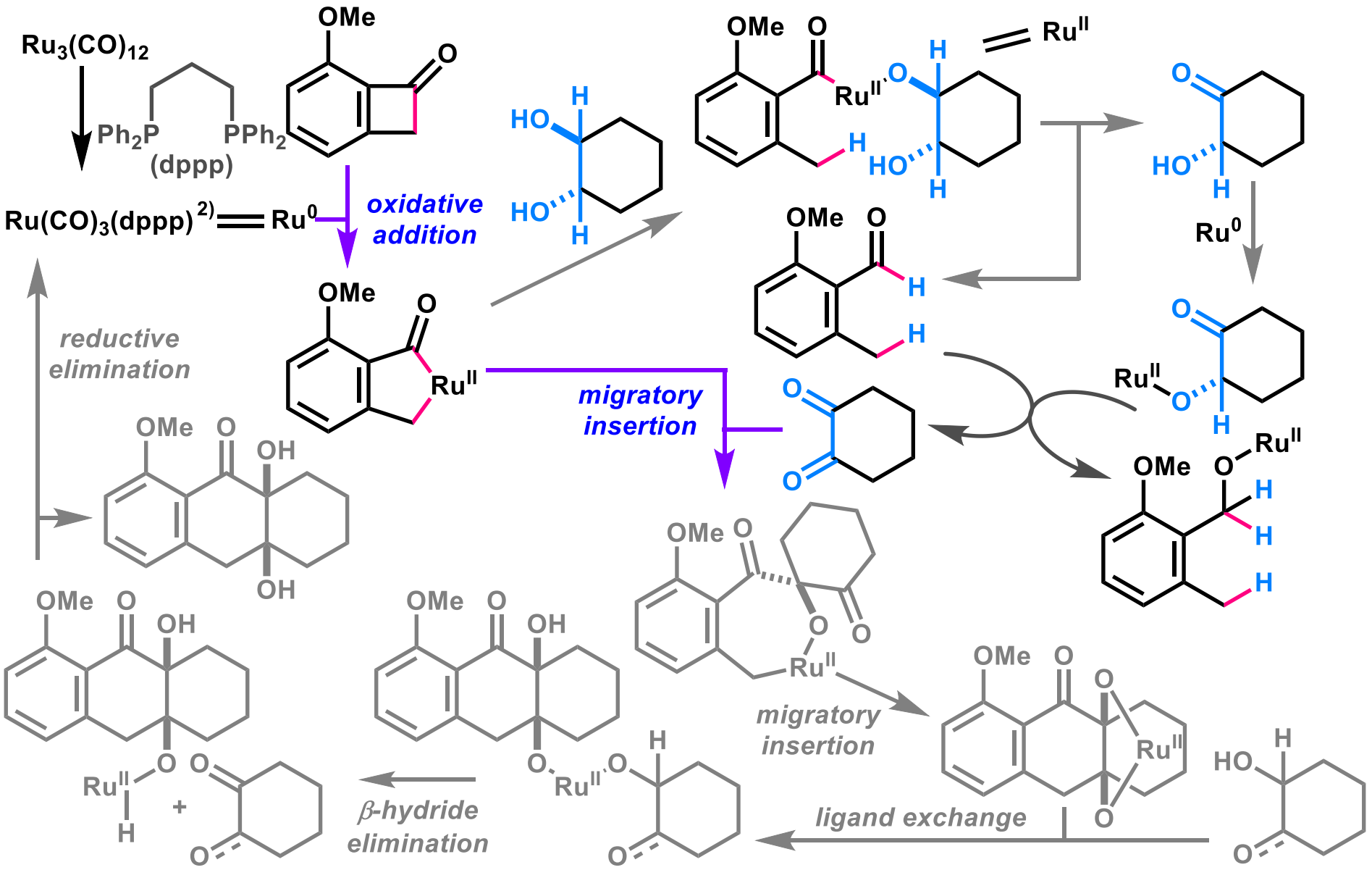
* Yield was not mentioned.





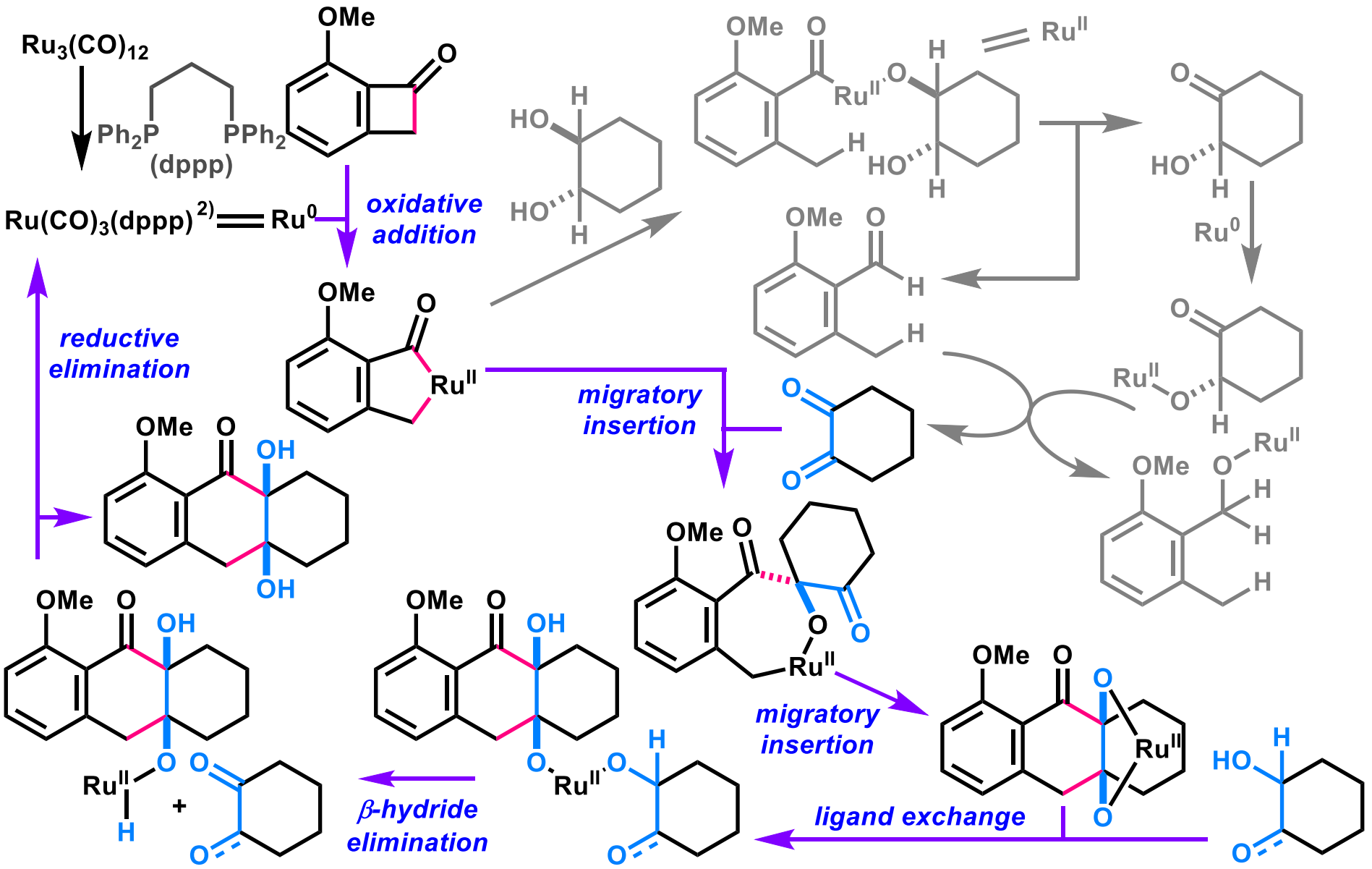
1) Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. *Science* **2017**, *357*, 779.

Proposed Reaction Mechanism [1)]



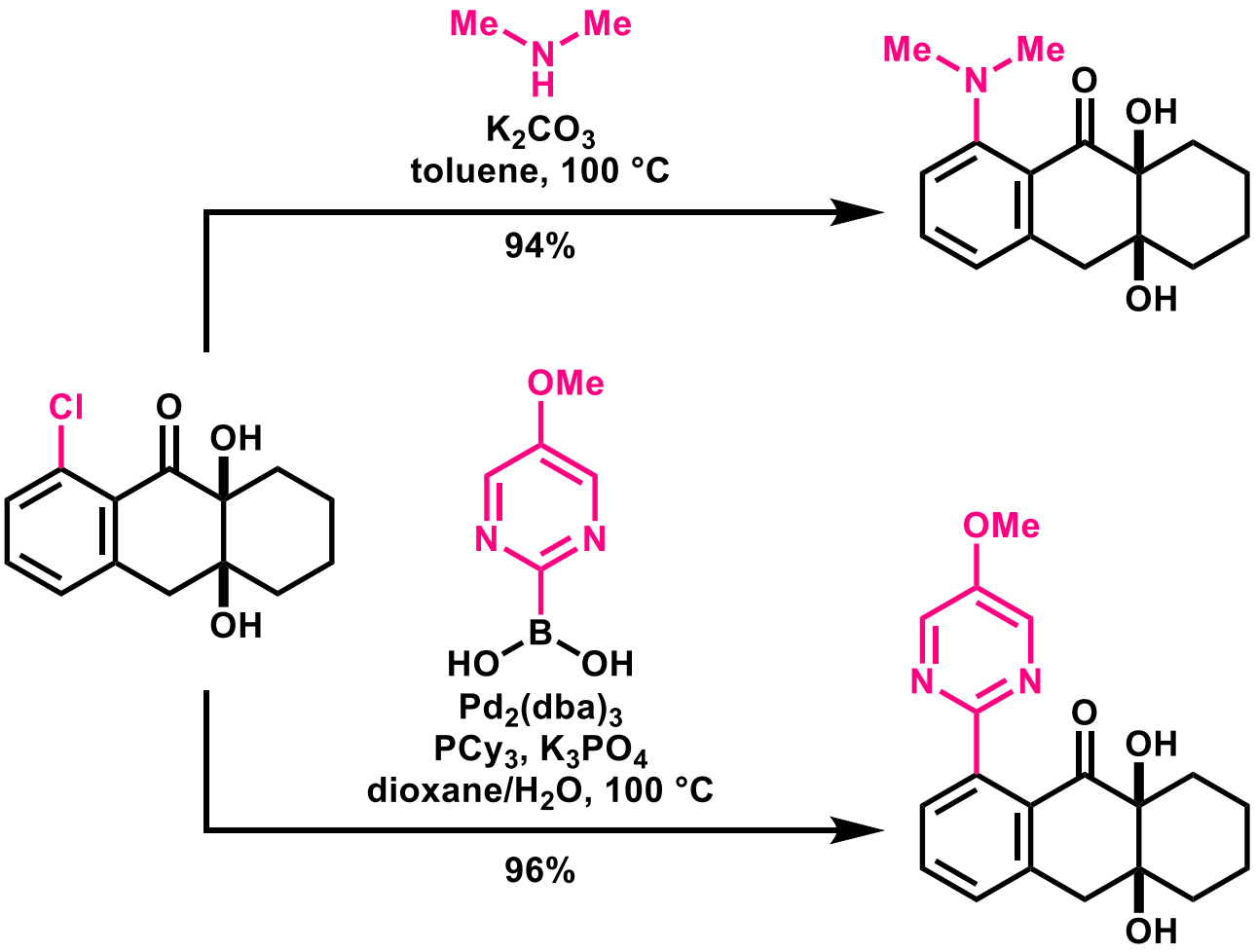
1) Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. *Science* **2017**, *357*, 779.
2) Sanchez-Delgado, R. A.; Bradley, J. S. Wilkinson,G. *J. Chem. Soc., Dalton Trans.* **1976**, 399.

Proposed Reaction Mechanism [1)]



1) Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. *Science* **2017**, *357*, 779.
2) Sanchez-Delgado, R. A.; Bradley, J. S. Wilkinson,G. *J. Chem. Soc., Dalton Trans.* **1976**, 399.

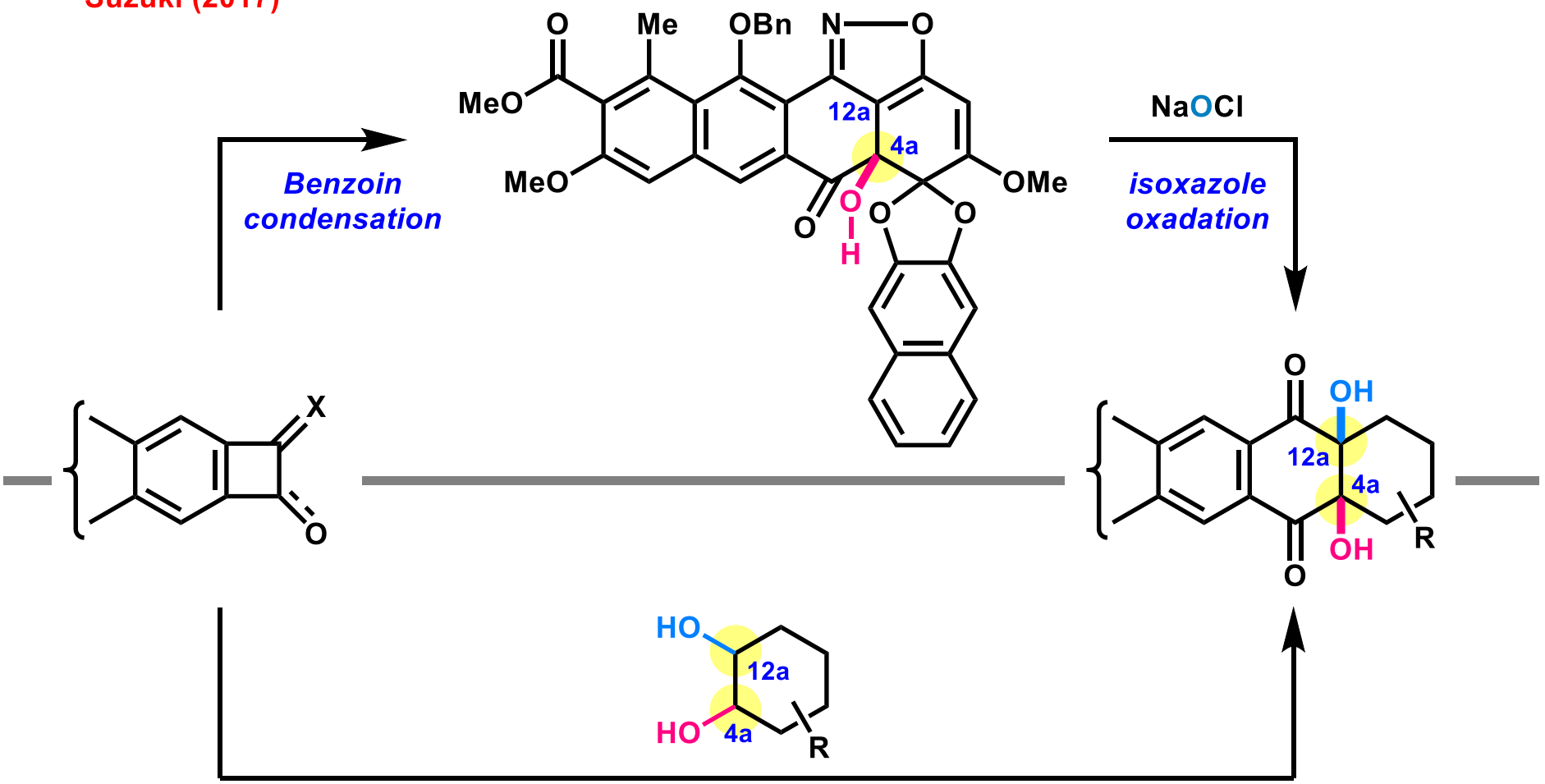
Elaboration of Cycloadduct [1)]



1) Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. *Science* **2017**, *357*, 779.

Summary

Suzuki (2017)

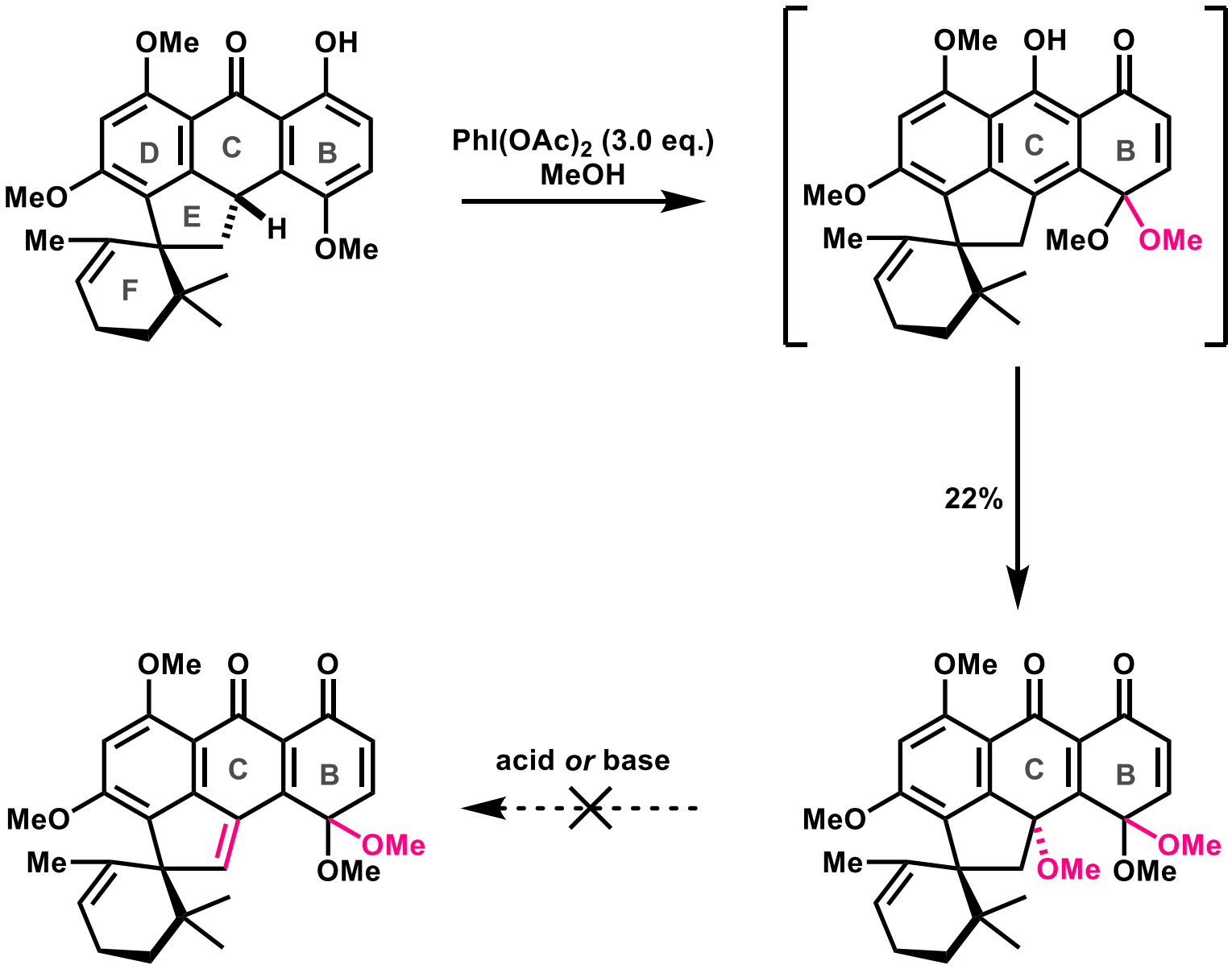


C–C & "formal" C–H bond activation

Krische (2017)

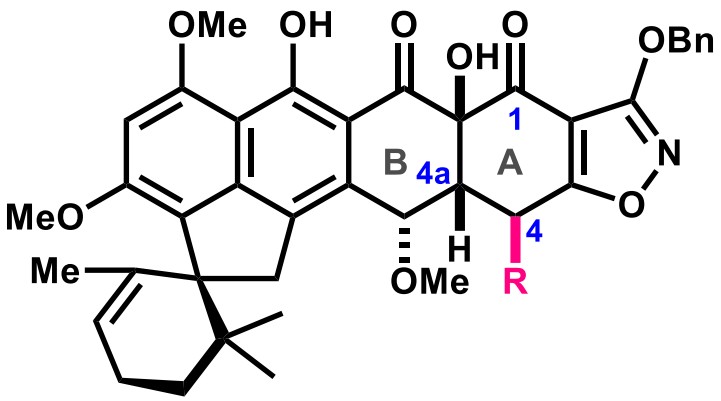
Appendix

Attempted Phenolic Oxidation at Once[1)]



1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

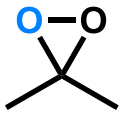
Another Possible Reaction Mechanism[1)]



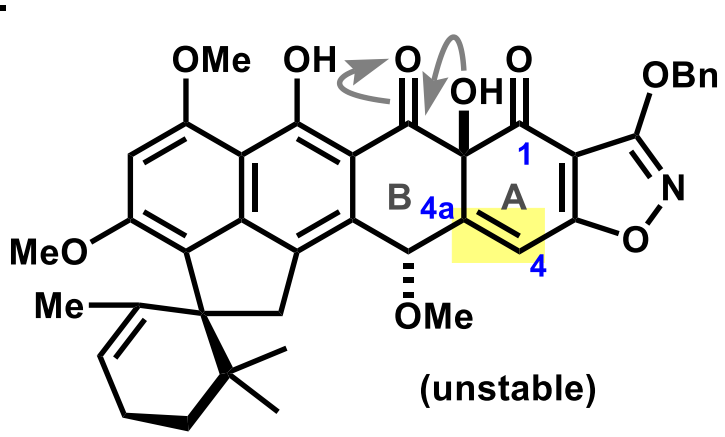
KHMDS, -78 °C;
PhSeCl, -40 °C, 46%

R = H

R = SePh

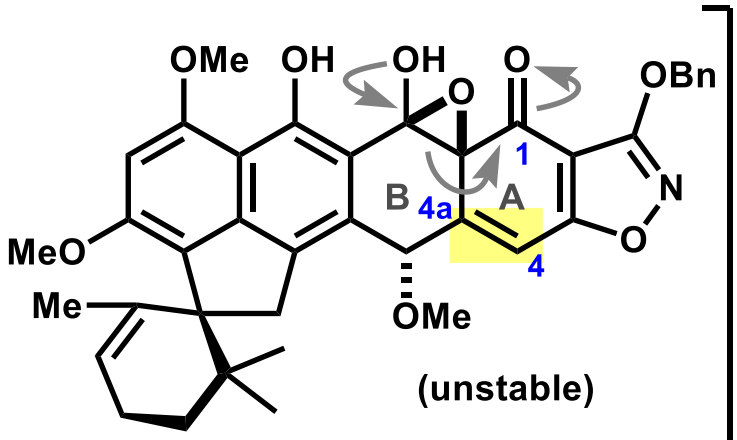


C4-C4a olefination



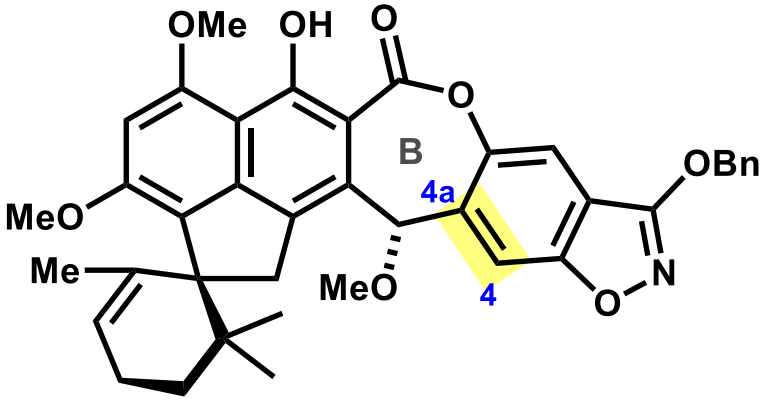
(unstable)

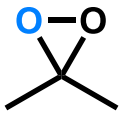
release of A ring



(unstable)

B ring expansion

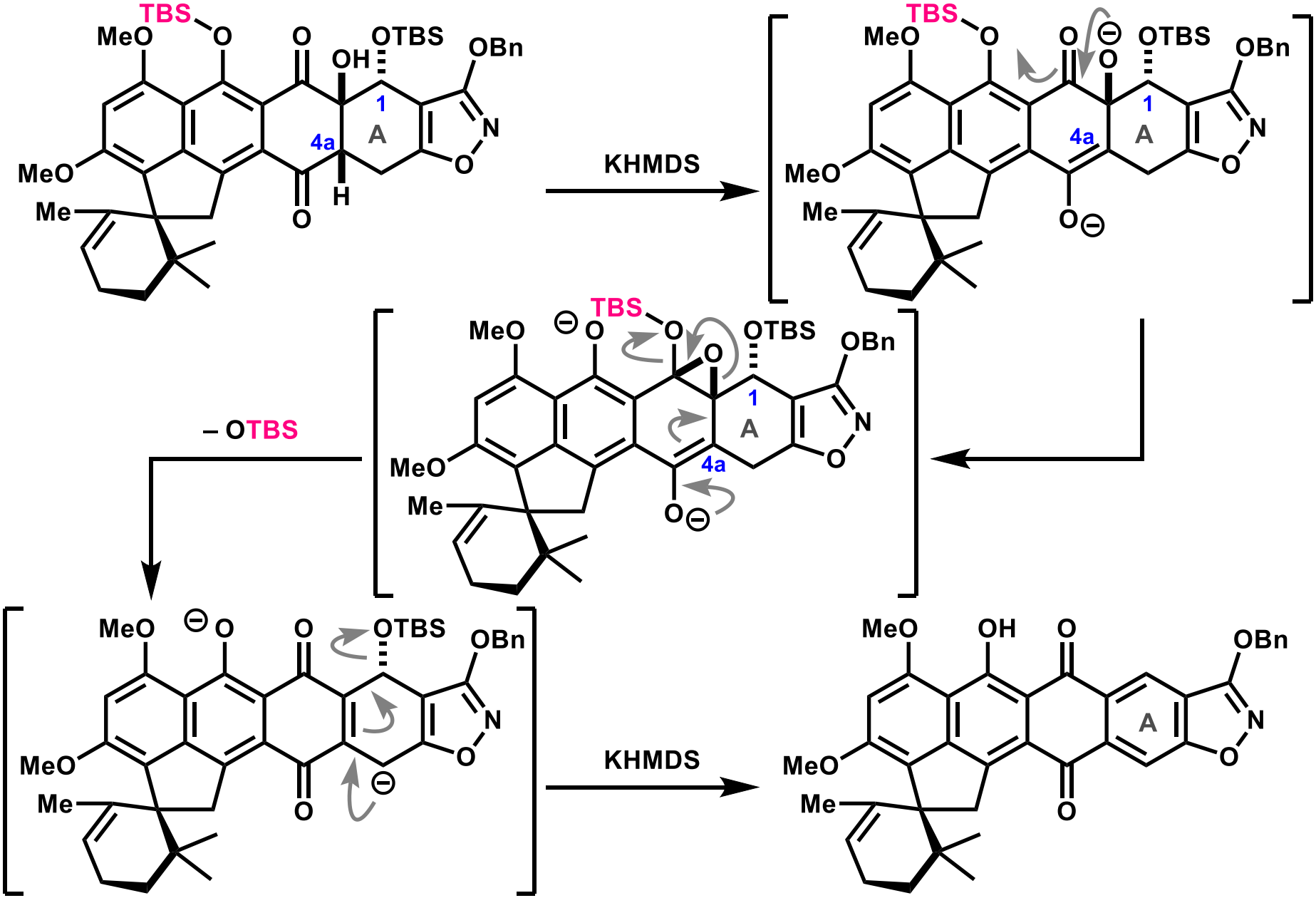




46%

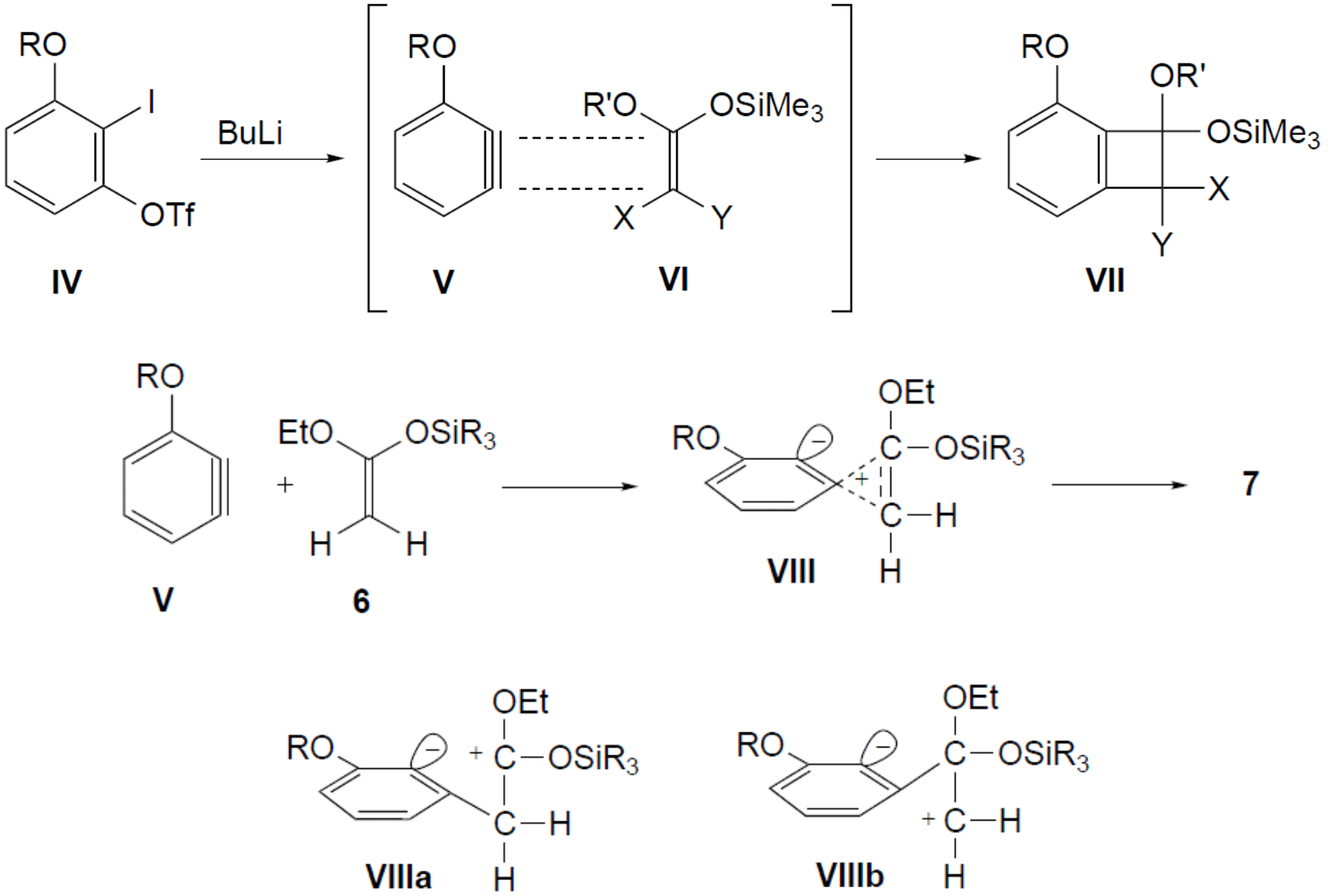
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

Attempted C4a Davis Oxidation by Dianion[1)]



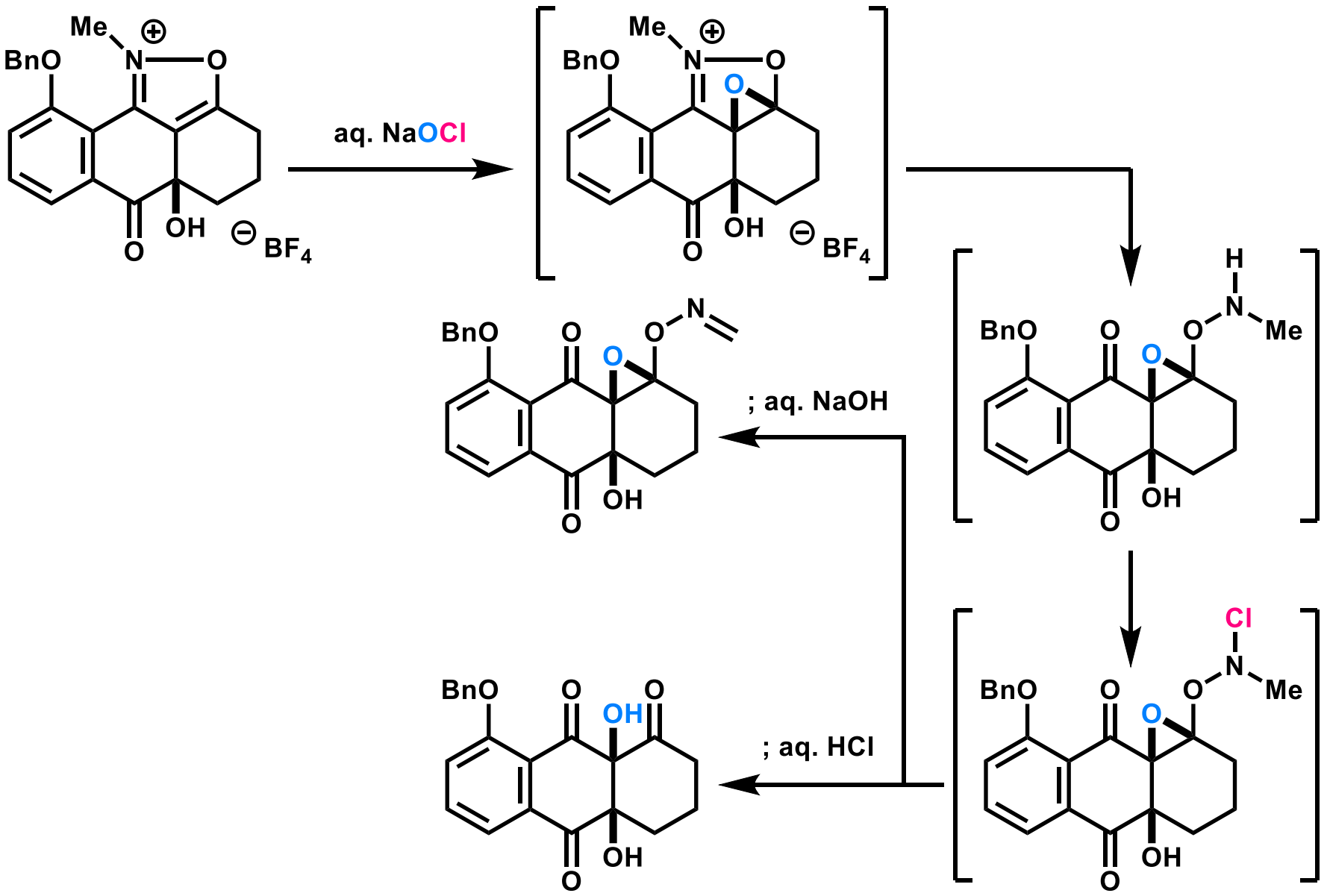
1) Nicalaou, K. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 12137.

[2+2] Cycloaddition of Benzoin and KSA[1)]



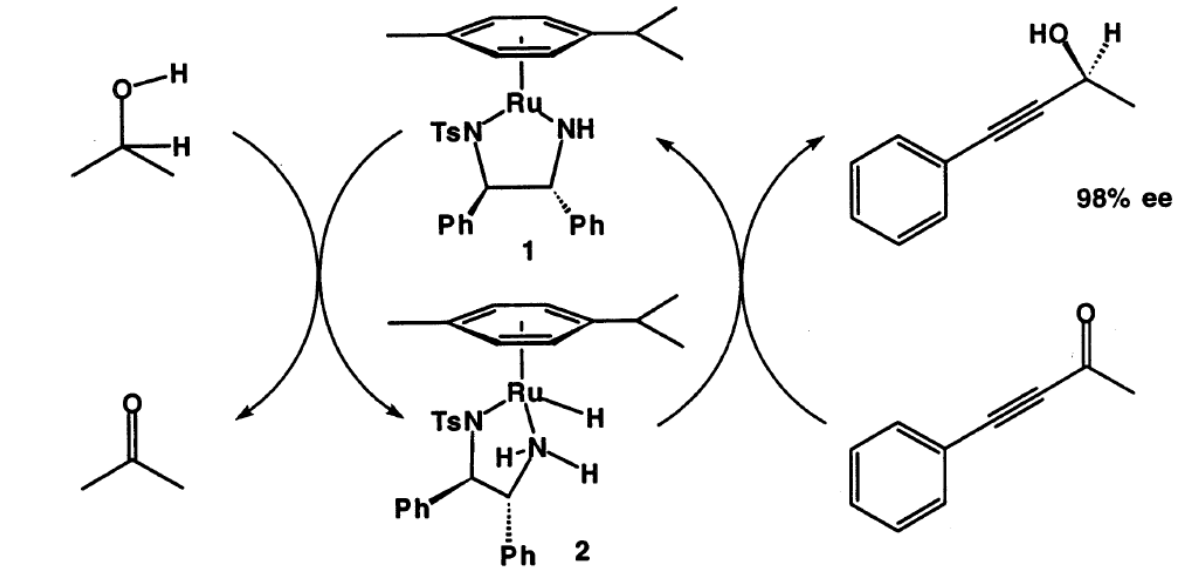
1) Suzuki, K.. *et al. Helv. Chim. Acta* **2002**, *85*, 3589.

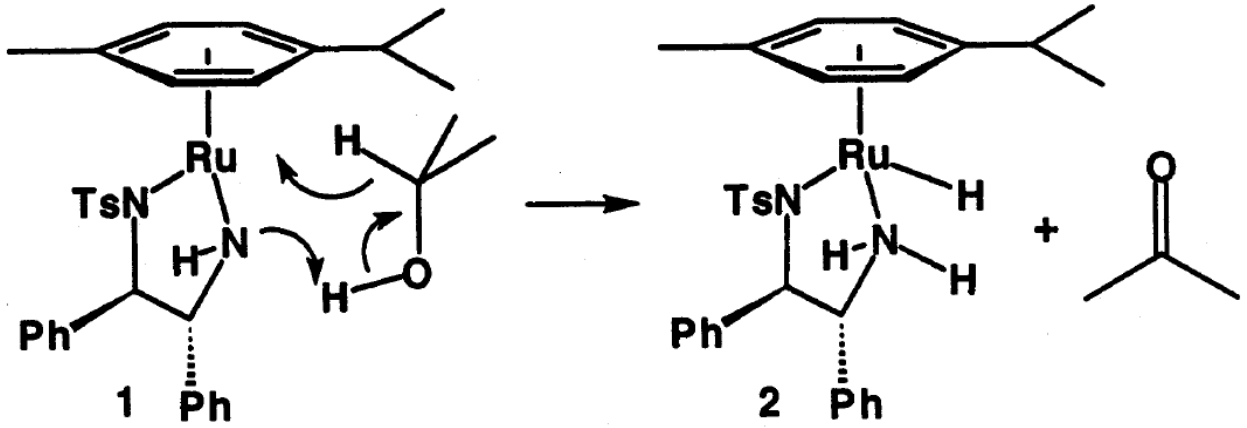
Trapping of the Intermediancy Epoxide [1)]



1) Takikawa, H.; Takada, A.; Hikita, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 7446.

Ligand-assisted Hydrogen Transfer [1)]





2) Casey, C. P.; Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998.