

Kinamycins and Lomaiviticins

Zijing Chen

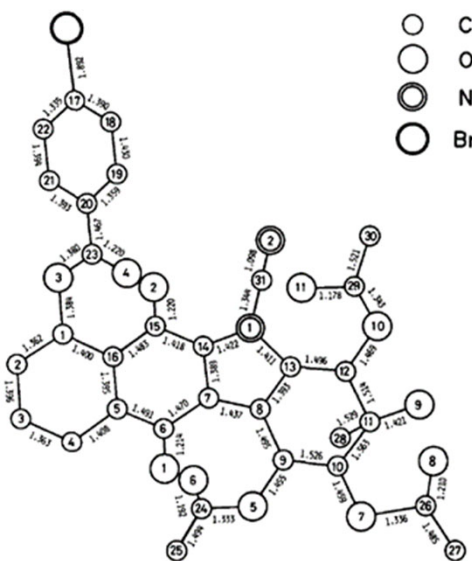
College of Chemistry and Molecular Engineering

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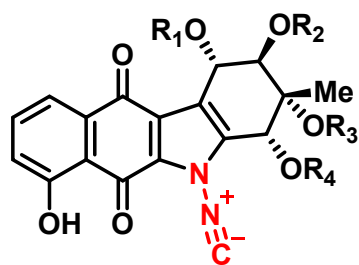
- Isolation & Characterization
- Biological Activities
- Biosynthesis
- Synthetic Studies & Total Syntheses
- Structure Revision
- Summary & Acknowledgements

Isolation & Structure Correction



Streptomyces murayamaensis (链霉菌)

alp: gene cluster to produce kinamycin D



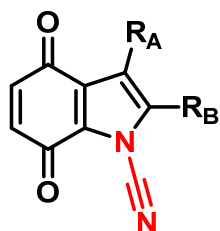
Isocyanamide assignment:

Vetoed by a positive Nessler's reagent test and a negative chromotropic acid test for its hydrolysate

Scaffold prepared by Dmitrienko

IR: 2237 – 2245 cm^{-1}

^{13}C NMR: δ 105 – 108 ppm

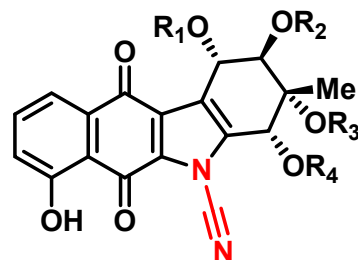


Original assignment:

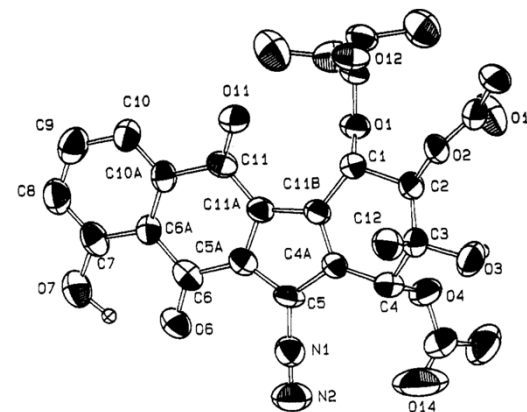
Cyanobenzocarbazole

IR: 2119 – 2170 cm^{-1}

^{13}C NMR: δ 78.5 – 83.7 ppm



Revised structure by Gould & Dmitrienko



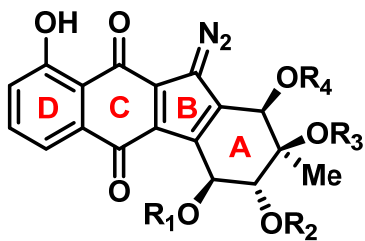
Ito, S.; Matsuya, T.; Omura, S.; Otani, M.; Nakagawa, A.; Iwai, Y.; Ohtani, M.; Hata, T. *J. Antibiot.* **1970**, *23*, 315-317.

Furusaki, A.; Matsui, M.; Watanabe, T.; Omura, S.; Nakagawa, A.; Hata, T. *Isr. J. Chem.* **1972**, *10*, 173-187.

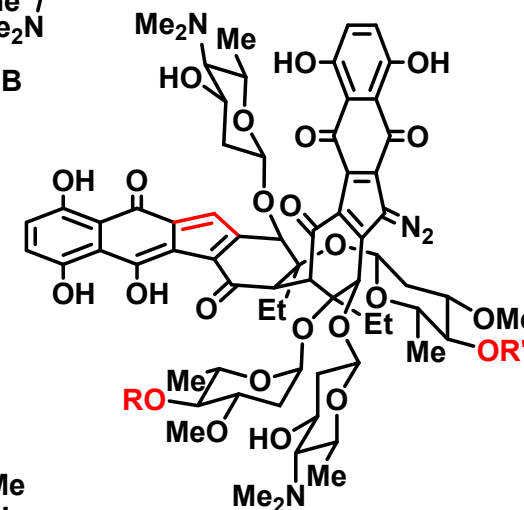
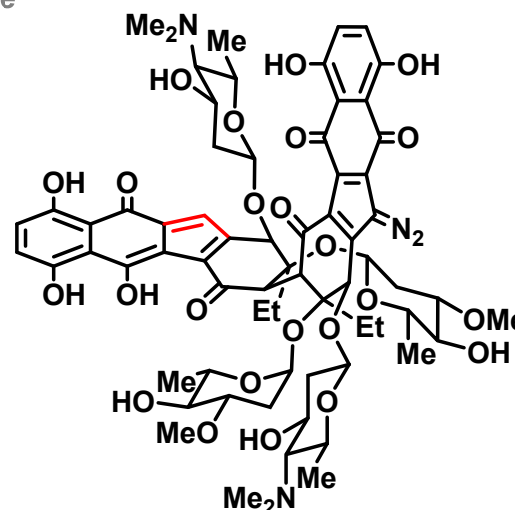
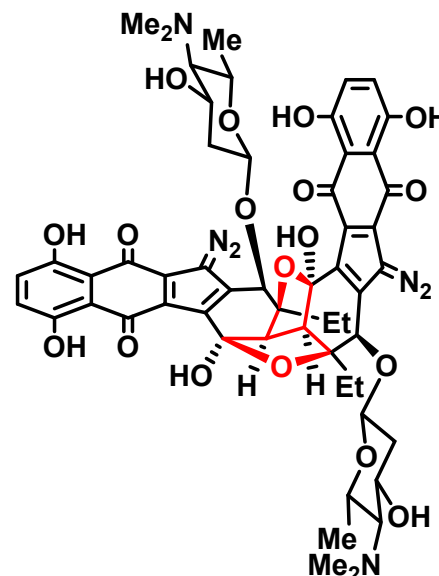
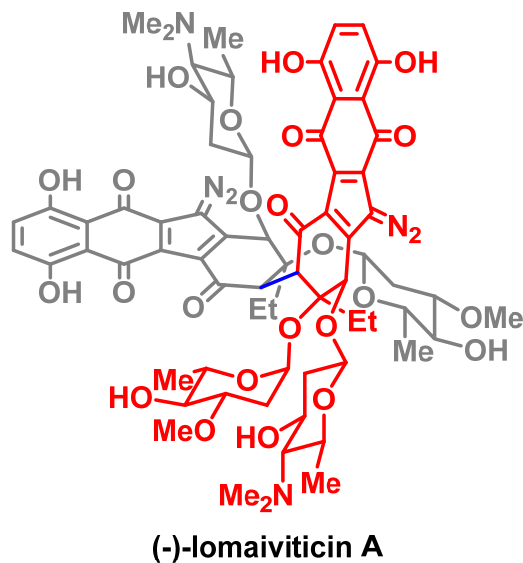
Gould, S.; Tamayo, N.; Melville, C.; Cone, M. *J. Am. Chem. Soc.* **1994**, *116*, 2207-2208.

Mithani, S.; Weeratunga, G.; Taylor, N.; Dmitrienko, G. *J. Am. Chem. Soc.* **1994**, *116*, 2209-2210.

Discovery of Lomaiviticins



kinamycin A: $R_1 = H, R_2 = Ac, R_3 = Ac, R_4 = Ac$
 kinamycin B: $R_1 = H, R_2 = Ac, R_3 = H, R_4 = Ac$
 kinamycin C: $R_1 = Ac, R_2 = Ac, R_3 = H, R_4 = Ac$
 kinamycin D: $R_1 = Ac, R_2 = H, R_3 = Ac, R_4 = Ac$
 kinamycin E: $R_1 = H, R_2 = H, R_3 = H, R_4 = Ac$
 kinamycin F: $R_1 = H, R_2 = H, R_3 = H, R_4 = H$
 kinamycin J: $R_1 = Ac, R_2 = Ac, R_3 = Ac, R_4 = Ac$



(-)-lomaiviticin E: $R = R' = Me$

Micromonospora lomaiviticins (小单孢菌)
 from *Polysyncraton lithostrotum* (斐济海鞘)
lom: lomaiviticin biosynthetic gene cluster

Luo Group Meeting (CCME@PKU)

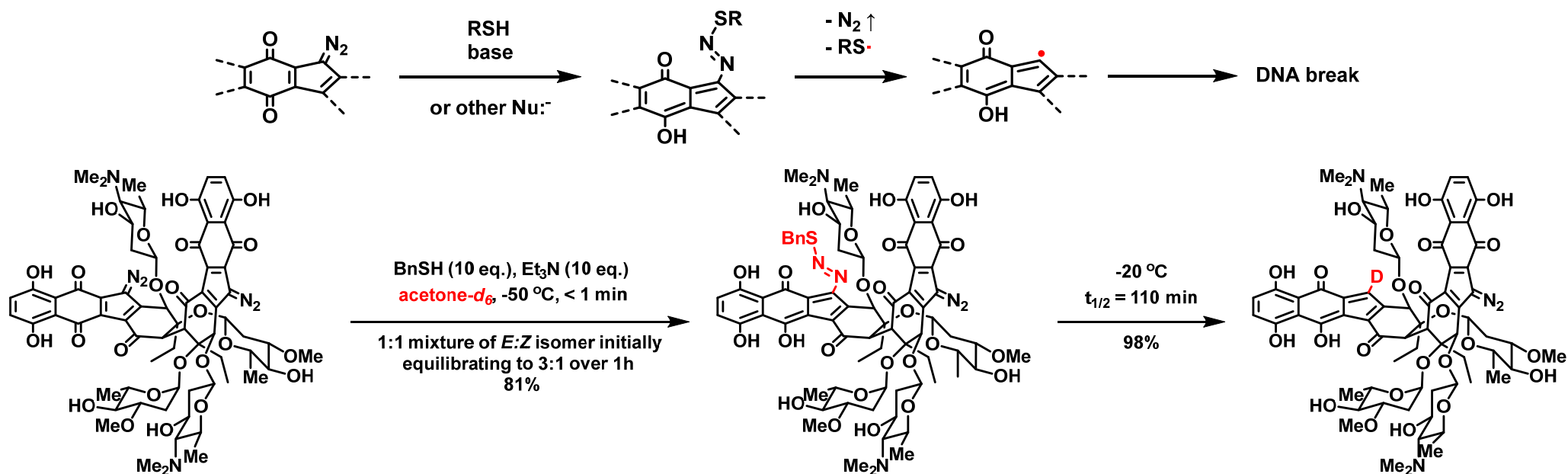
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Biological Activities

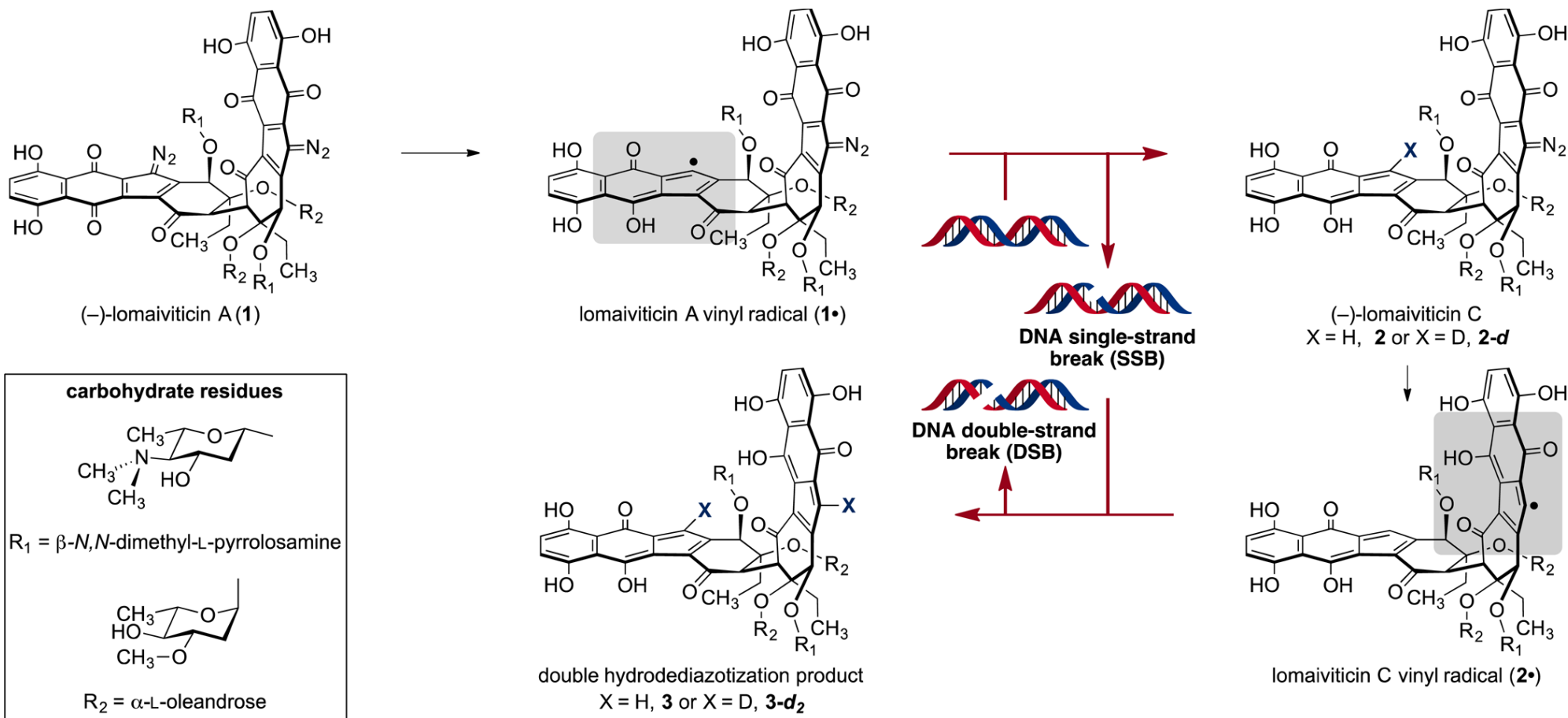
IC_{50} Values (nM) of (-)-Kinamycin C and (-)-Lomaiviticins A, C, D, E

Compound	K562	LNCap	HCT-116	HeLa
Kinamycin C	72	116	274	517
Lomaiviticin A	11	2	2	7
Lomaiviticin C	472	332	223	589
Lomaiviticin D	197	196	167	161
Lomaiviticin E	469	964	255	292



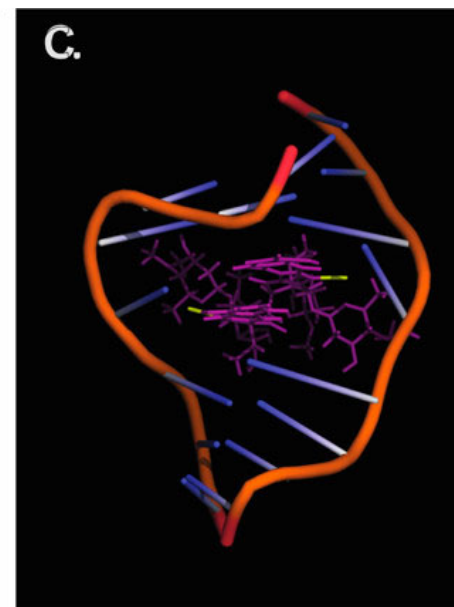
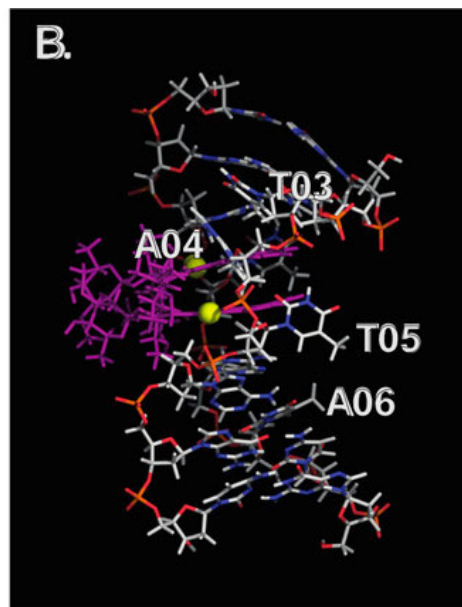
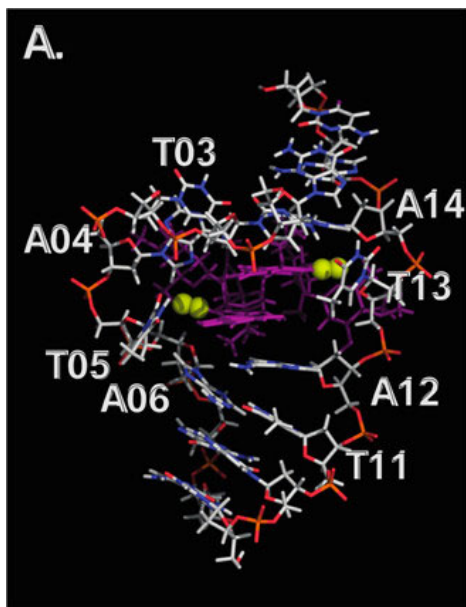
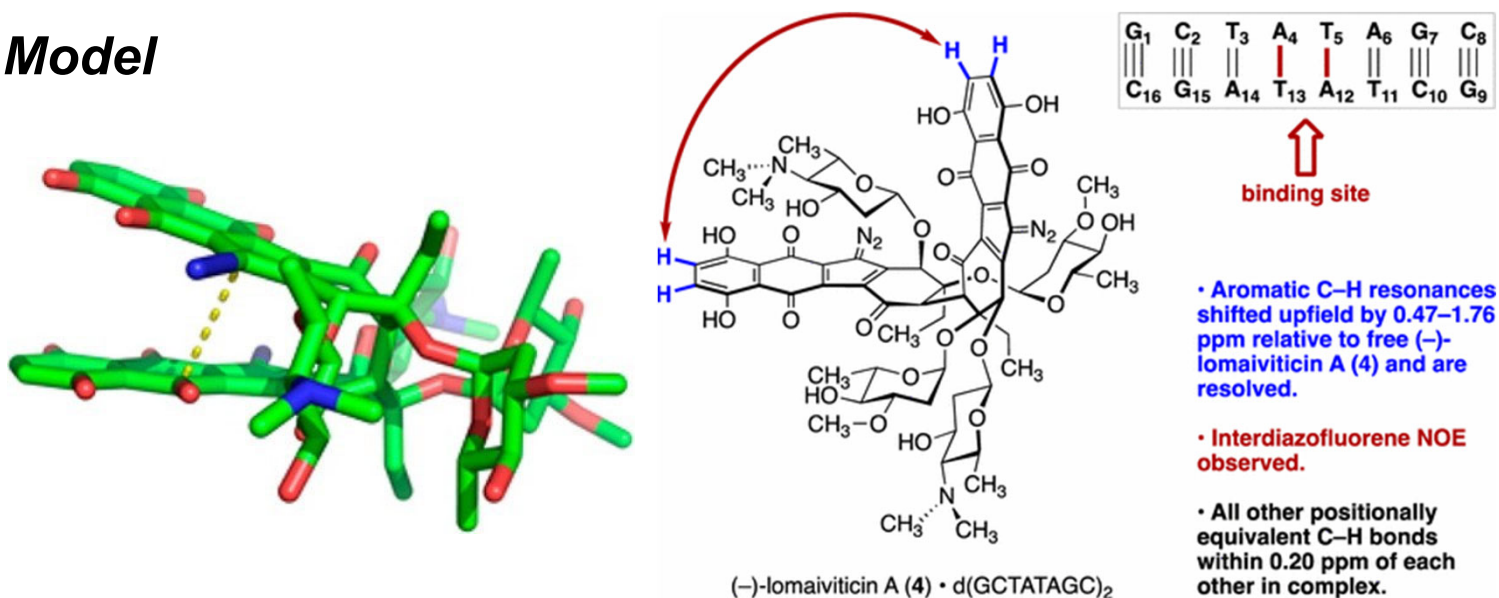
Mechanism of Action

- DNA strand break**



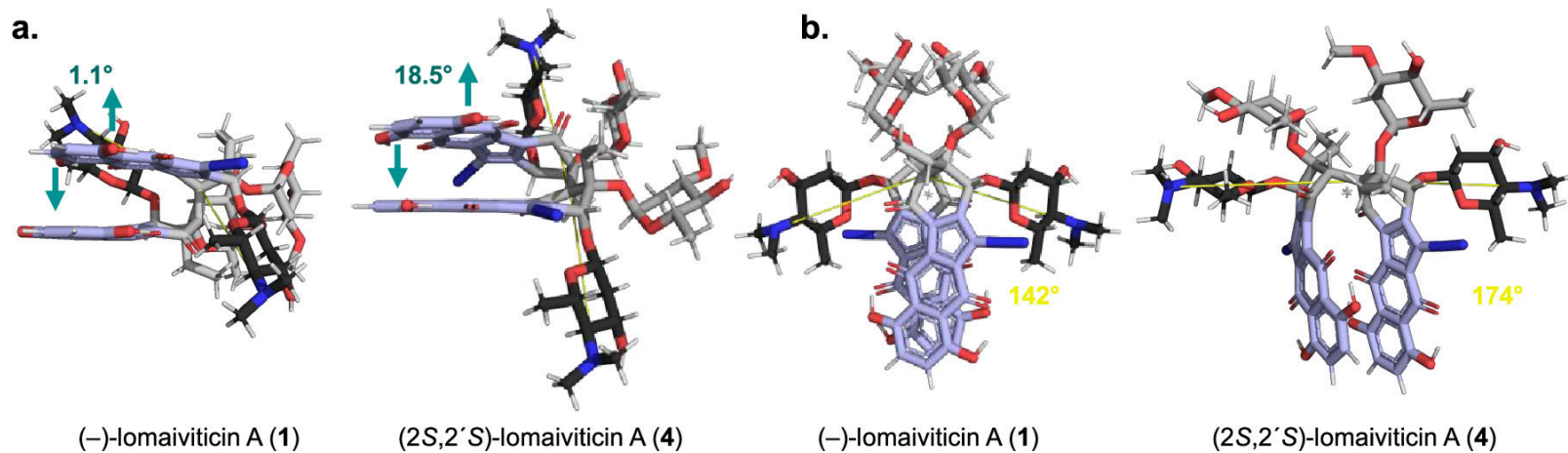
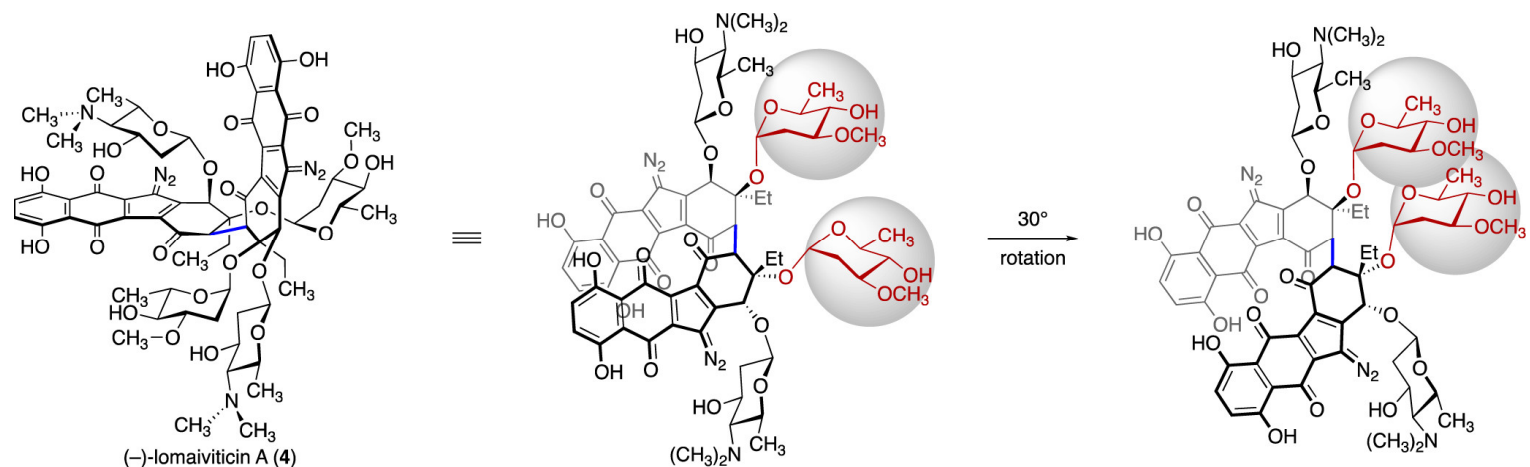
Mechanism of Action

- Binding Model**



Mechanism of Action

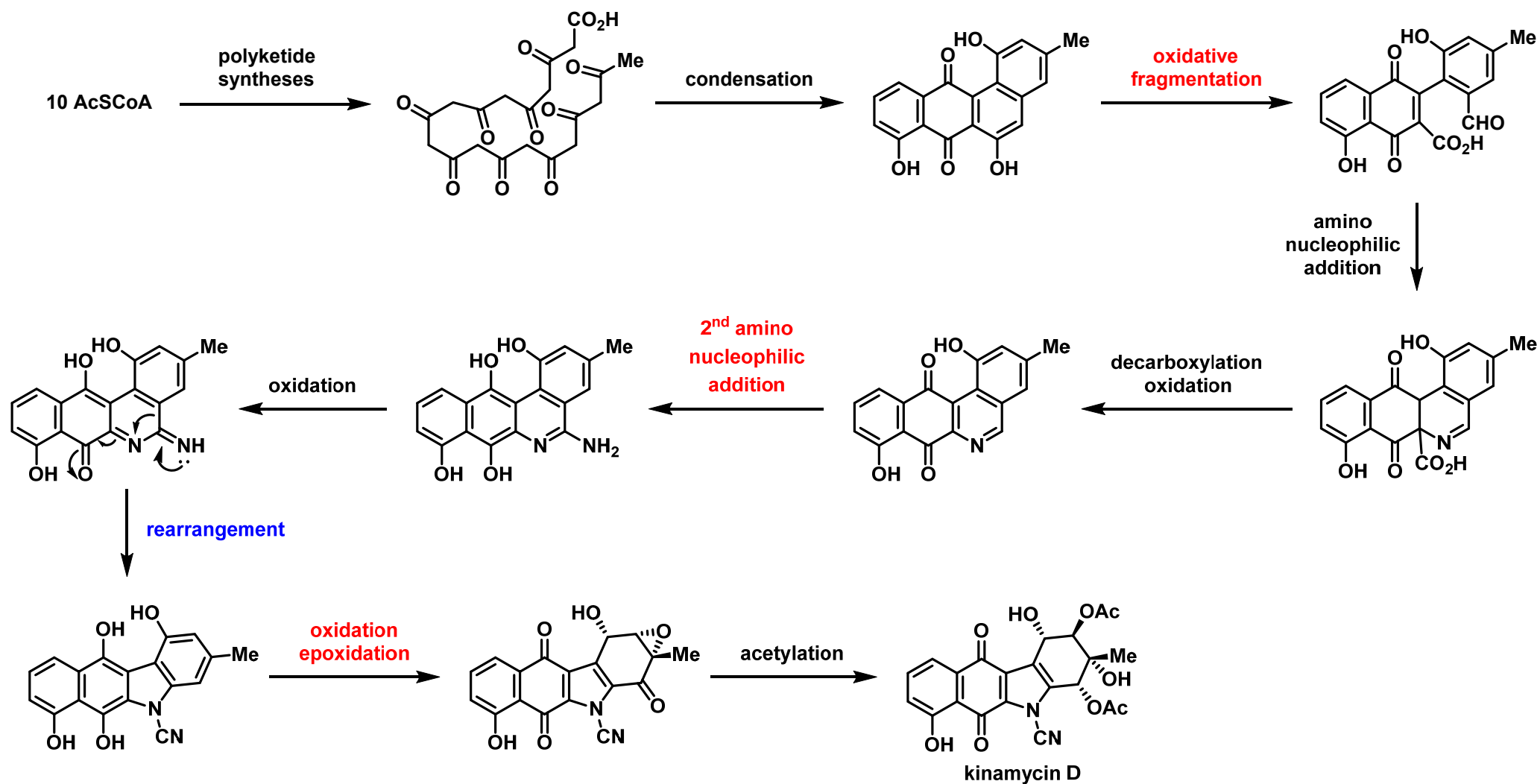
- *The role of carbohydrate residues*



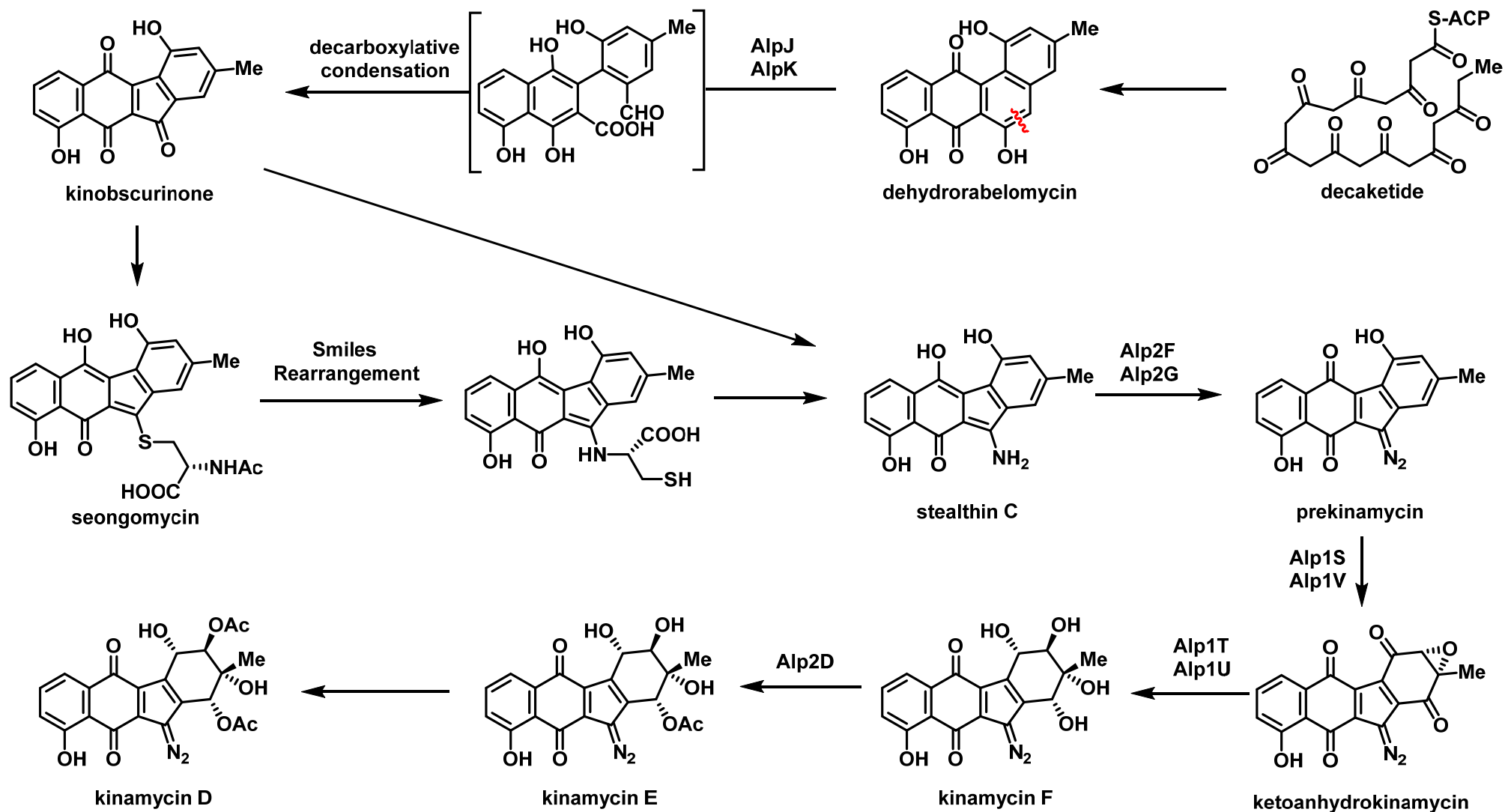
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Proposed Biosynthesis Pathway



Proposed Biosynthesis Pathway



Wang, B.; Guo, F.; Ren, J.; Ai, G.; Aigle, B.; Fan, B.; Yang, K. *Nat. Commun.* **2015**, *6*, 7674.

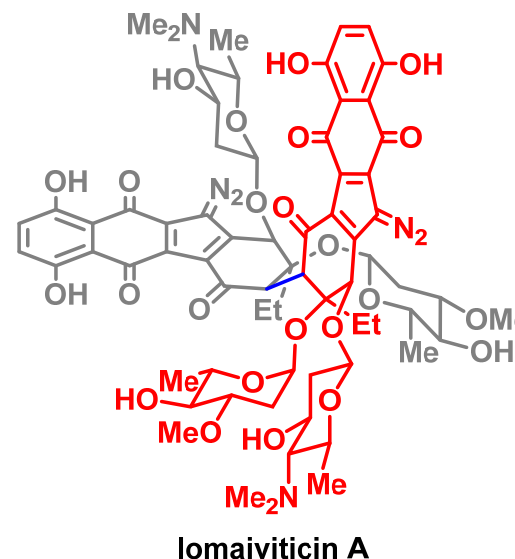
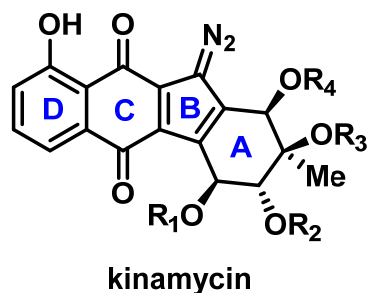
Liu, X.; Liu, D.; Xu, M.; Tao, M.; Bai, L.; Peng, Z.; Pfeifer, B.; Wang, M. *J. Nat. Prod.* **2018**, *81*, 72-77.

Wang, P.; Hong, G.; Wilson, M.; Balskus, M. *J. Am. Chem. Soc.* **2017**, *139*, 2864-2867.

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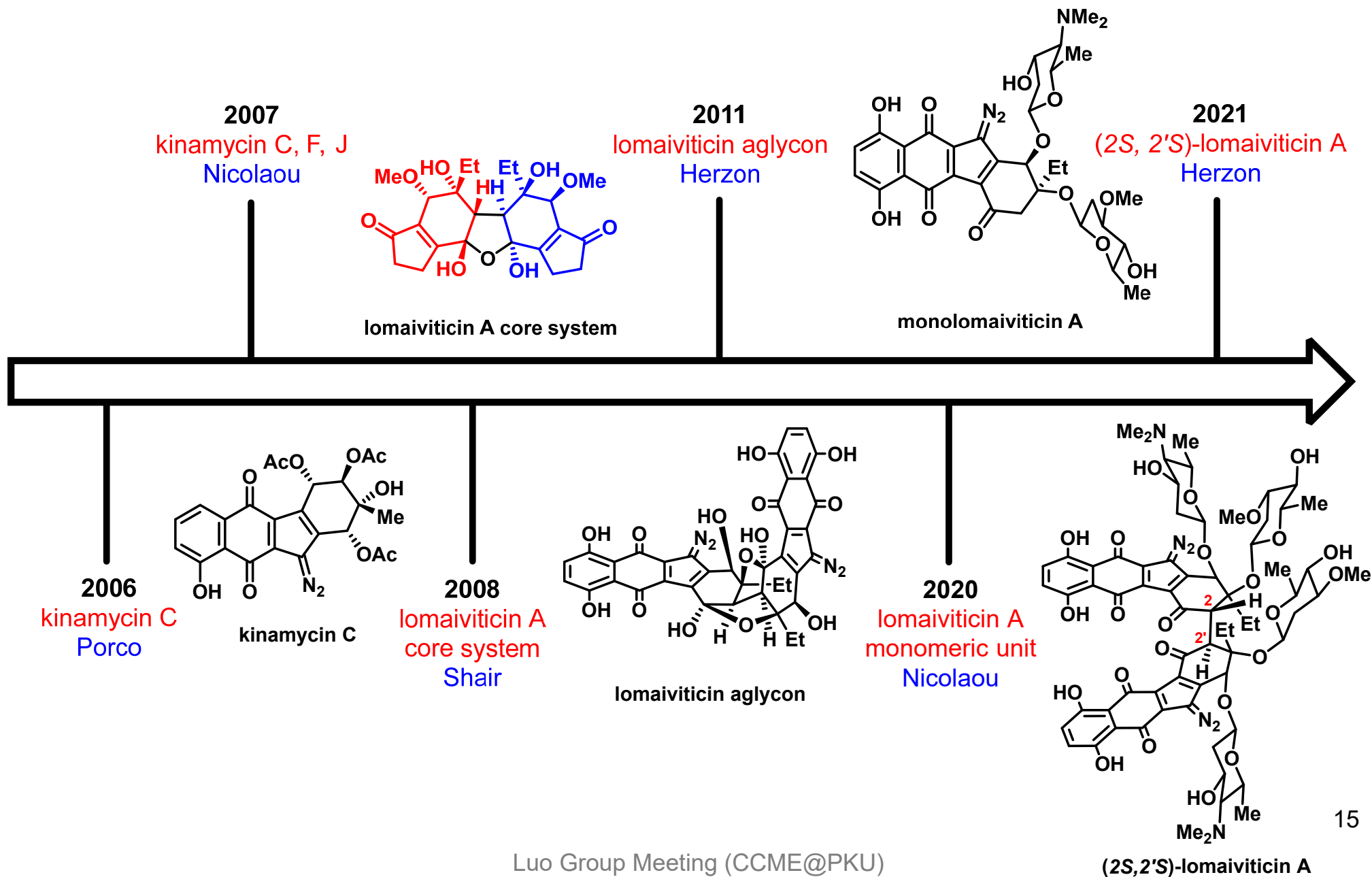
Synthetic Studies & Total Syntheses



Challenges

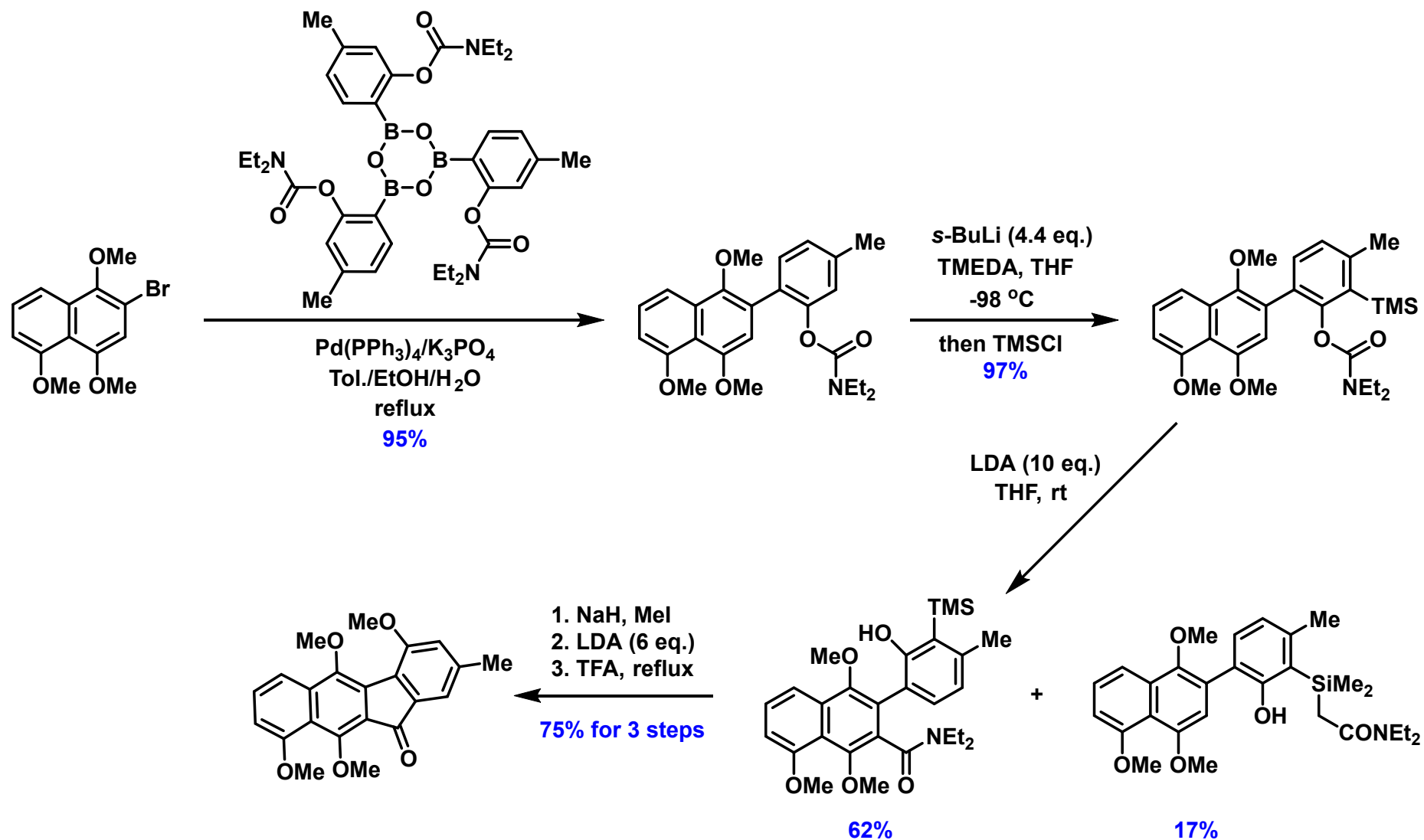
- Densely oxygenated A ring with correct configuration
- Diazo-containing B ring
- Selective oxidation of C ring (rather than D ring) to quinone
- Oxidative dimerization to furnish Lomaiviticins

Synthetic Studies & Total Syntheses



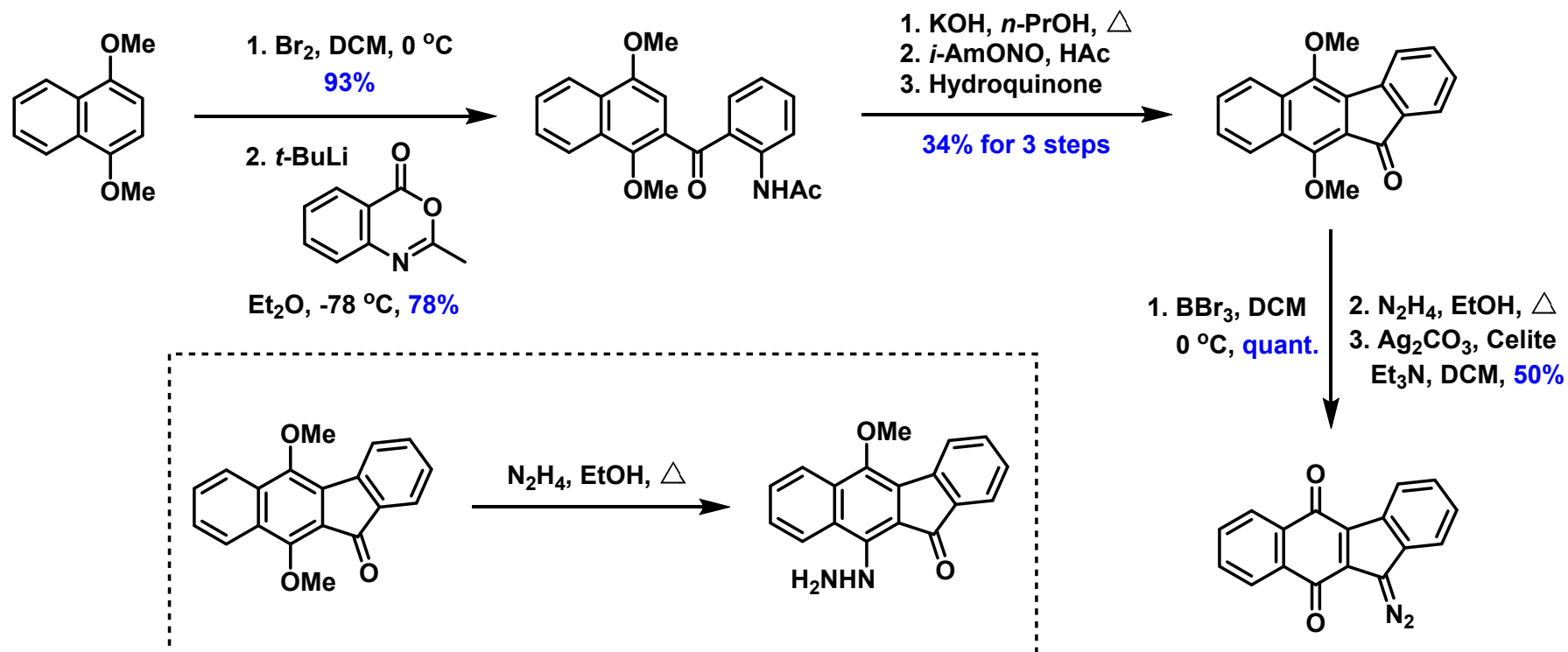
Early Studies

- 1997, Snieckus group, acylamide condensation



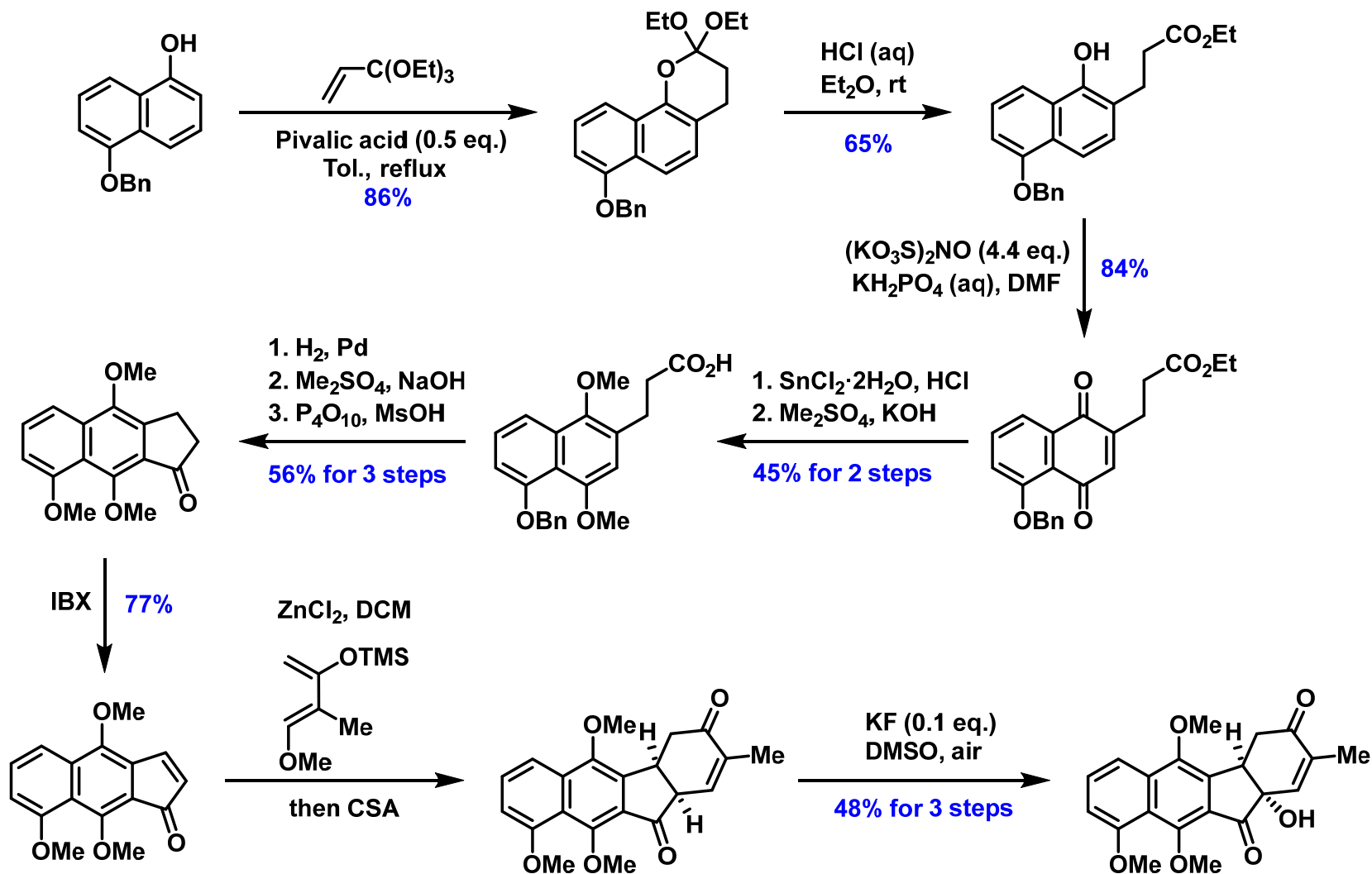
Early Studies

- 1997, Jebaratnam group, diazotization strategy



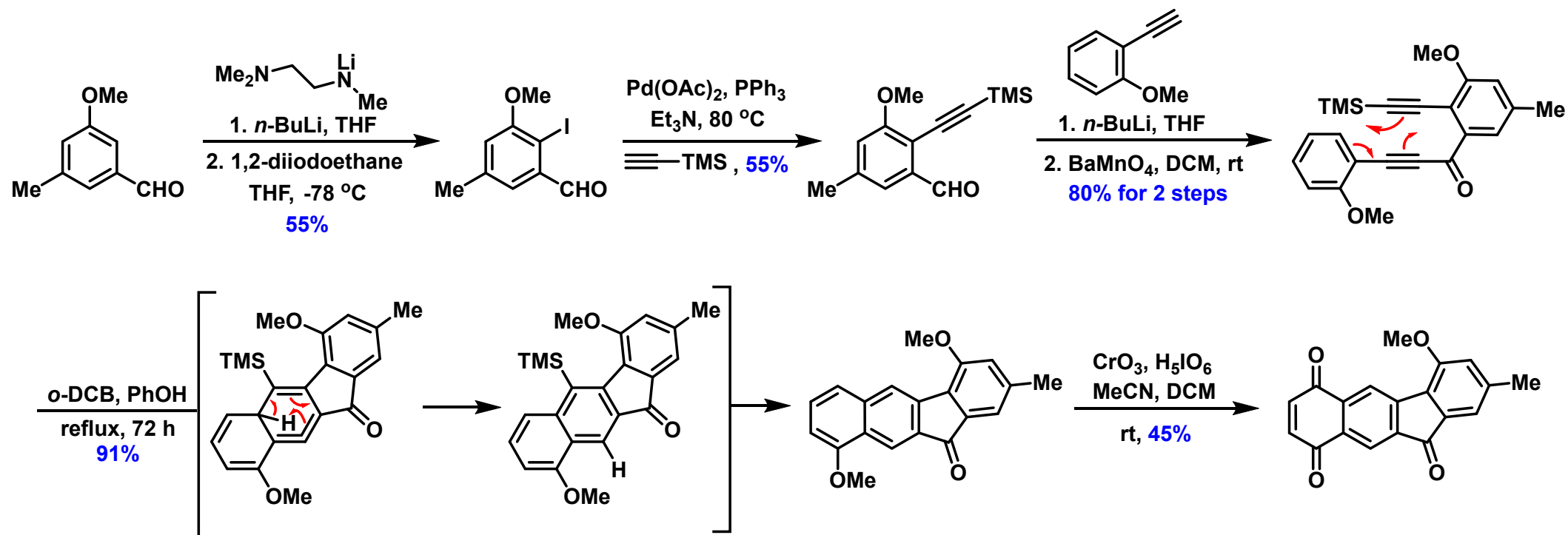
Early Studies

- 2000, Ishikawa group, intramolecular FC acylation / DA cyclization

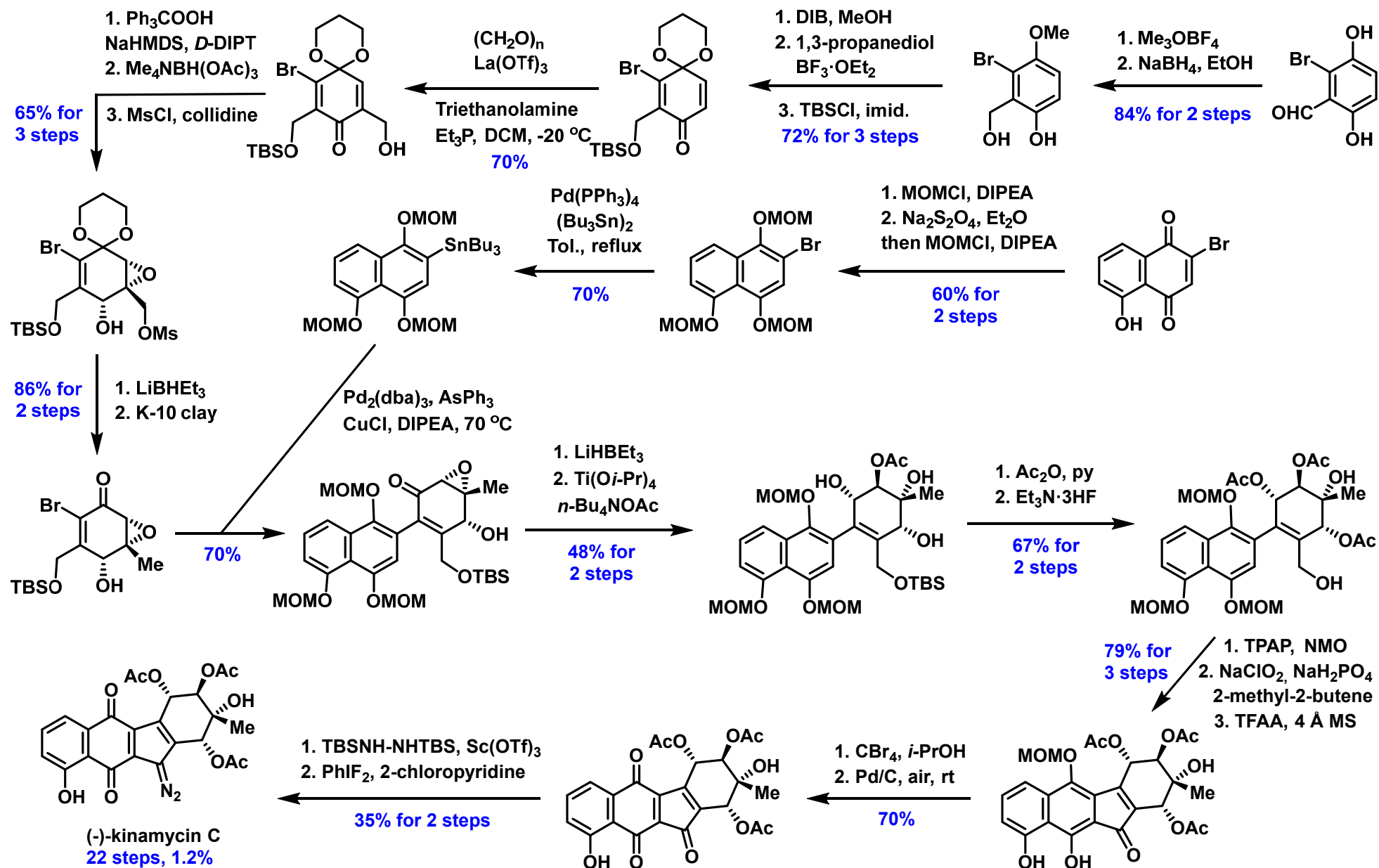


Early Studies

- 2006, Echavarren group, failed to give prekinamycin (pericyclic strategy)

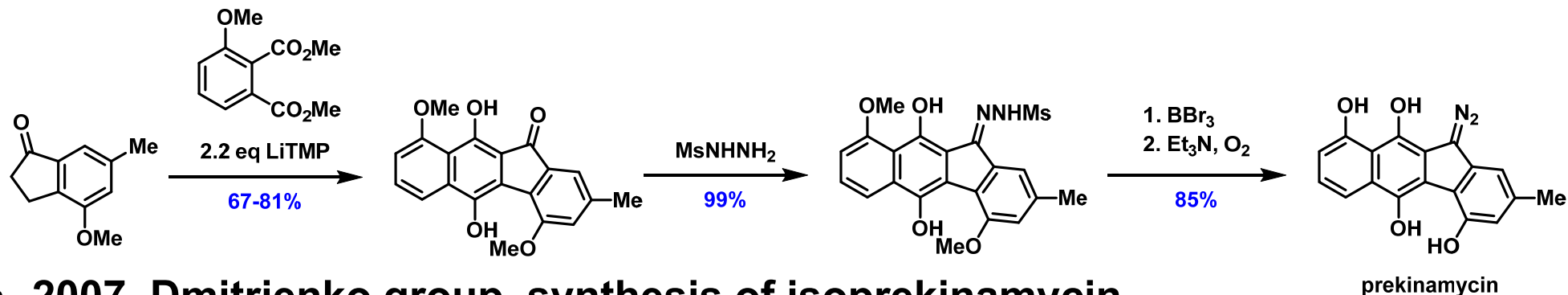


1st Total Synthesis of Kinamycin (2006 Porco)

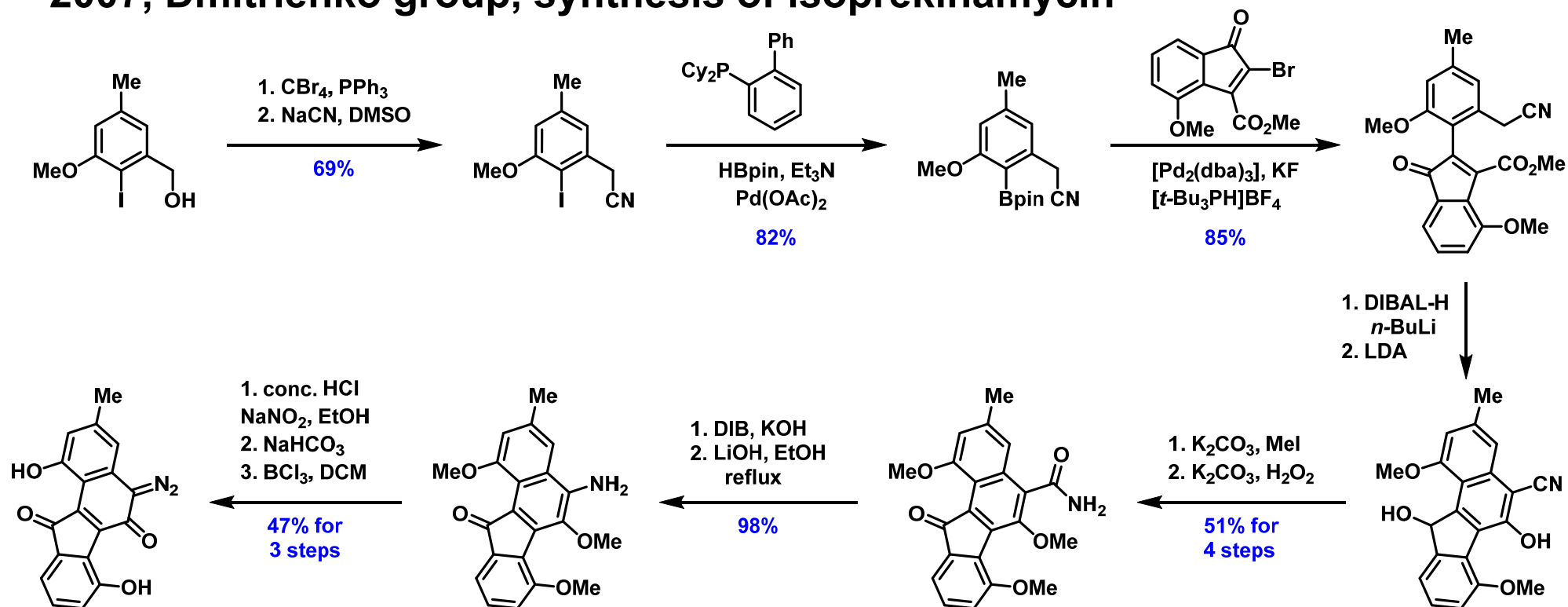


Prekinamycin and Isoprekinamycin

- 2007, Birman group, synthesis of prekinamycin



- 2007, Dmitrienko group, synthesis of isoprekinamycin



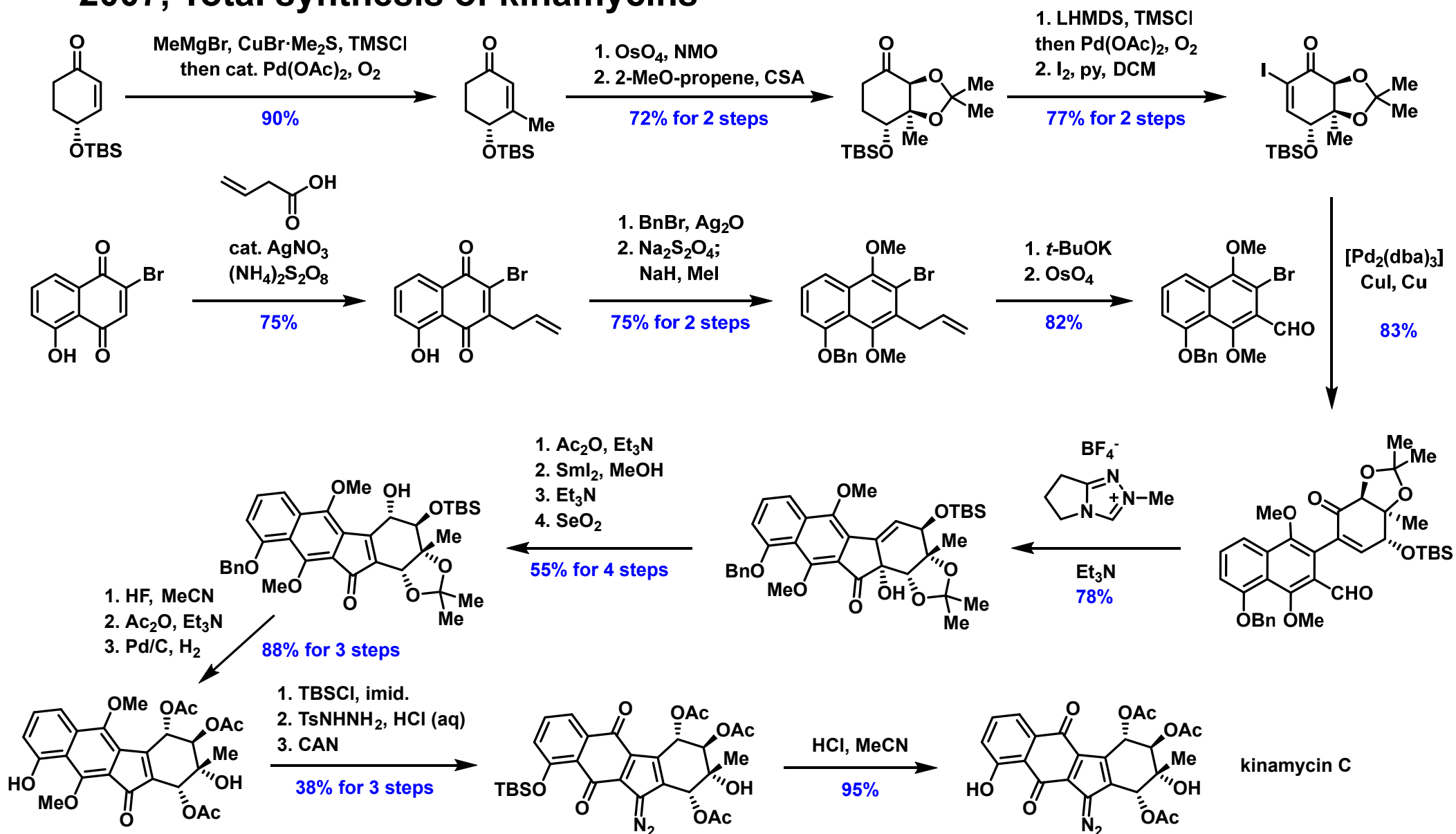
isoprekinamycin

Birman, B.; Zhao, Z.; Guo, L. *Org. Lett.* 2007, 9, 1223-1225.

Liu, W.; Buck, M.; Chen, N.; Shang, M.; Taylor, N.; Asoud, J.; Wu, X.; Hasinoff, B.; Dmitrienko, G. *Org. Lett.* 2007, 9, 2915-2918.

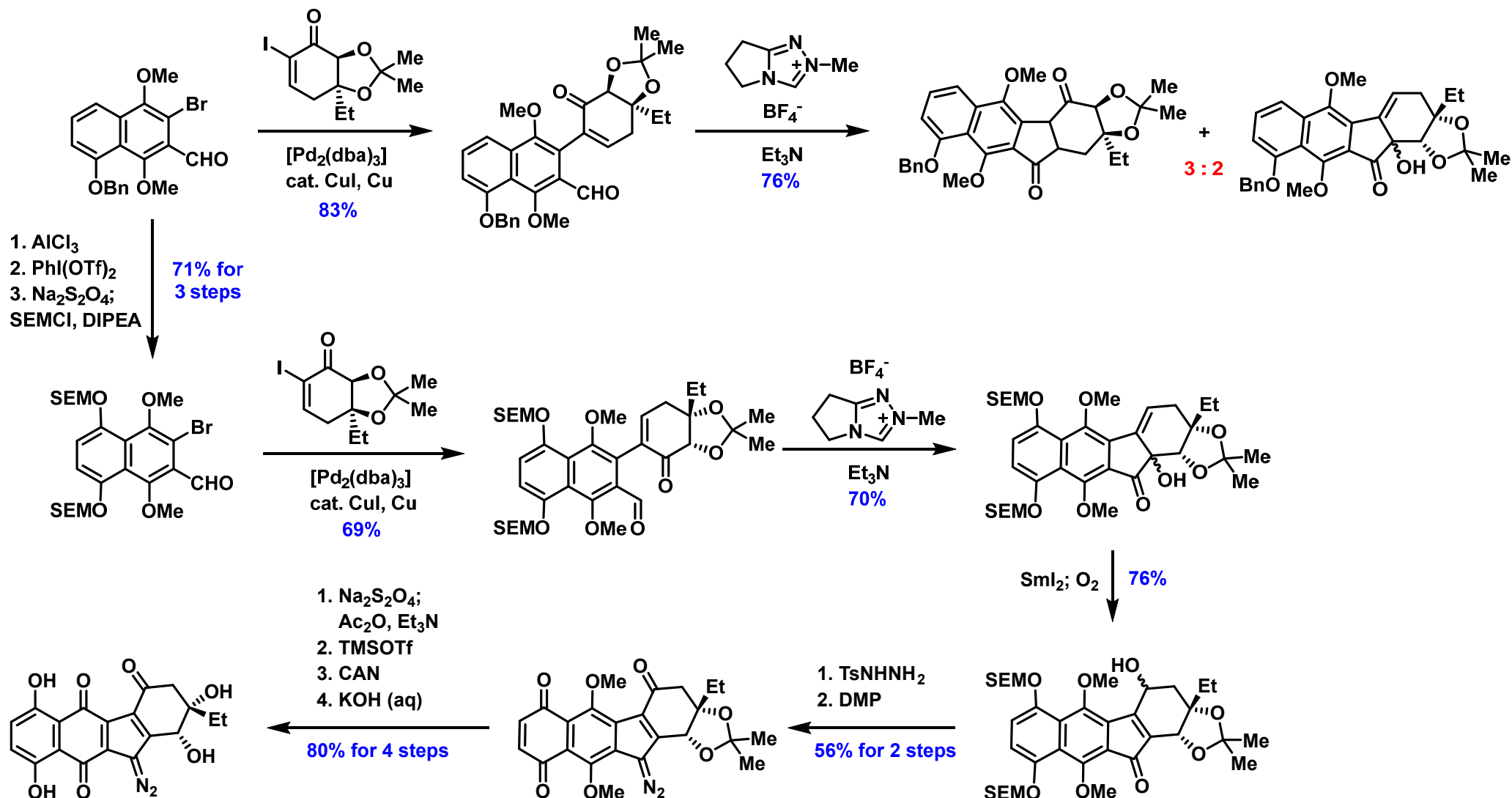
Nicolaou's Ullman & Benzoin Strategy

• 2007, Total synthesis of kinamycins



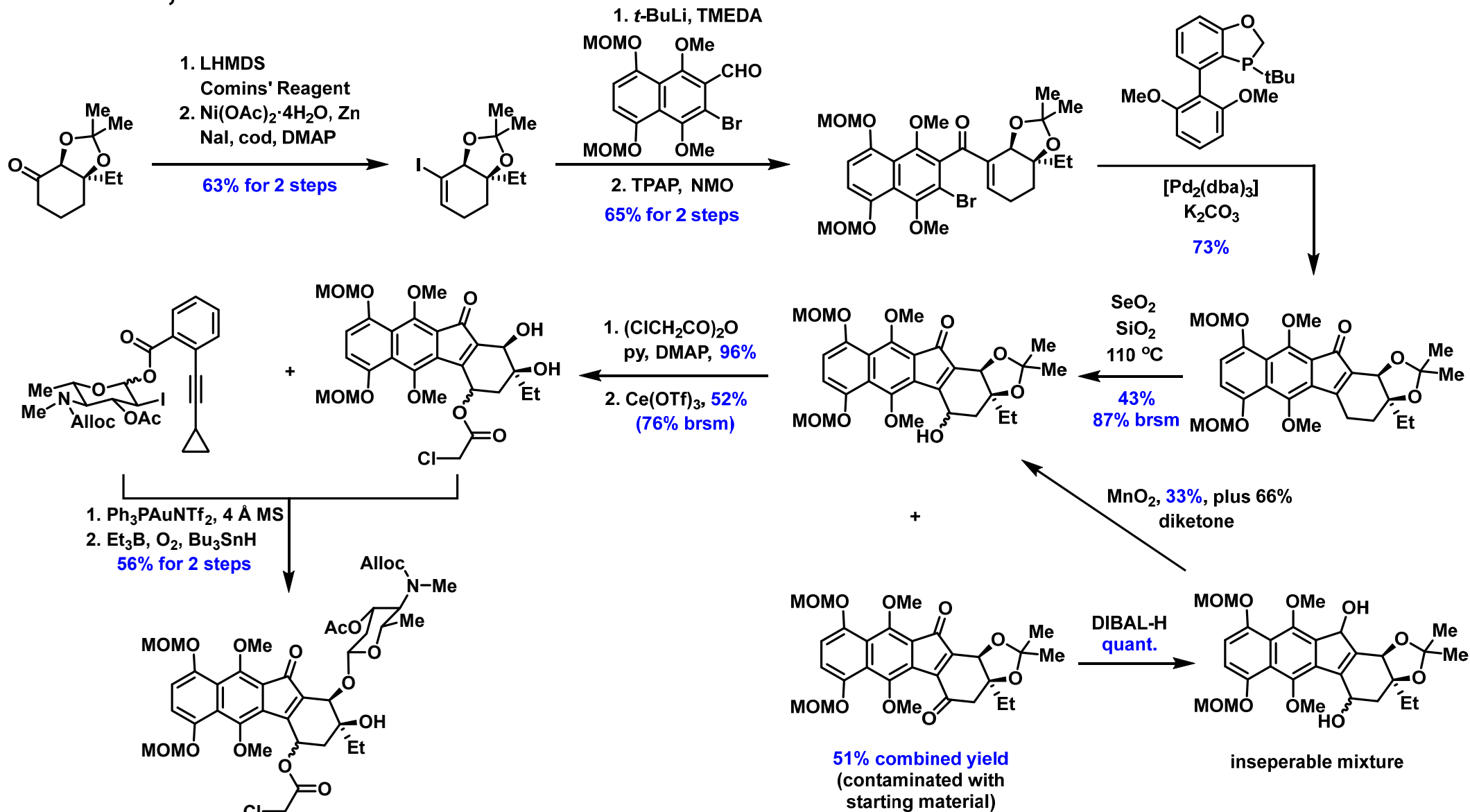
Nicolaou's Ullman & Benzoin Strategy

- 2009, Lomaiviticin aglycon monomeric unit

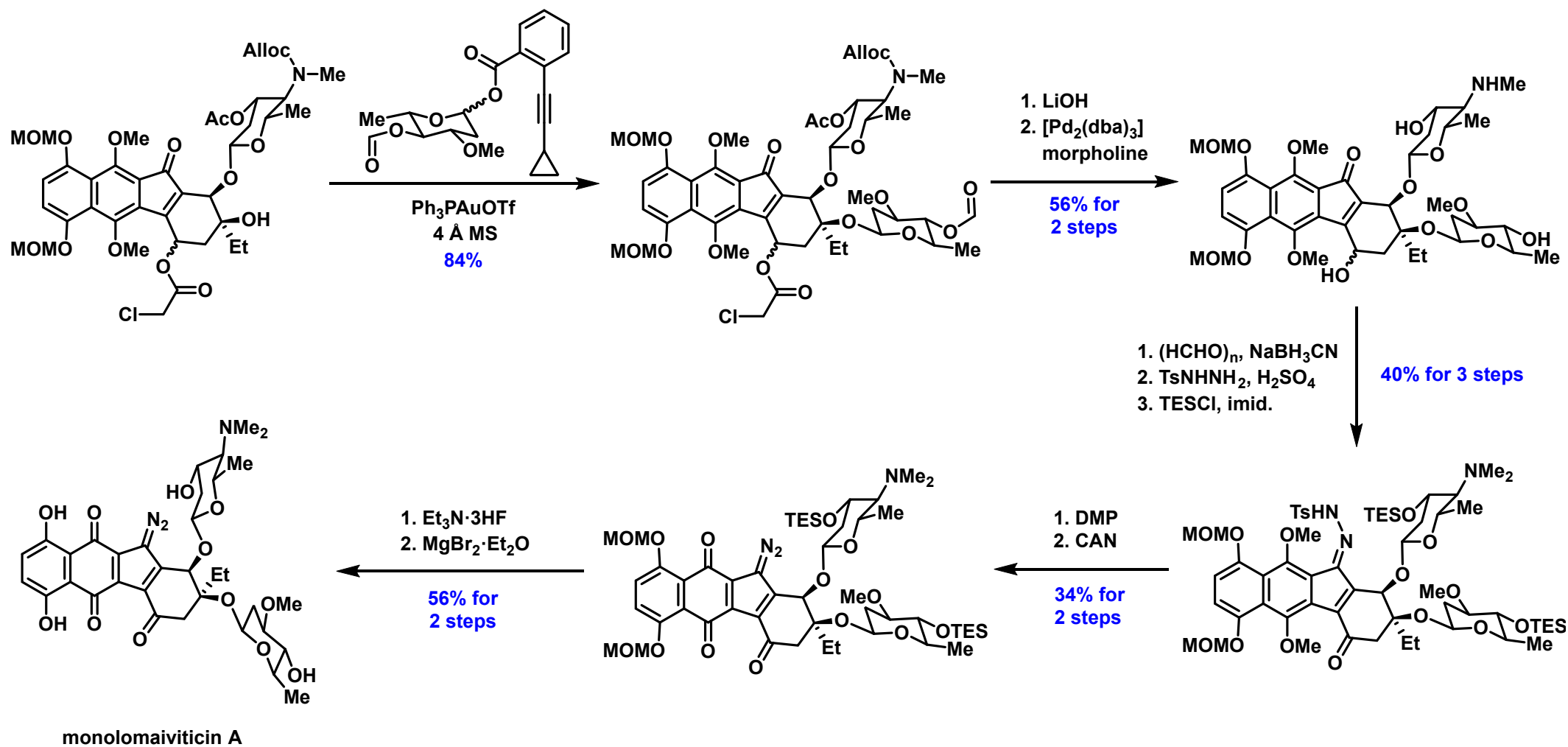


Nicolaou's Ullman & Benzoin Strategy

• 2020, Lomaiviticin A monomeric unit

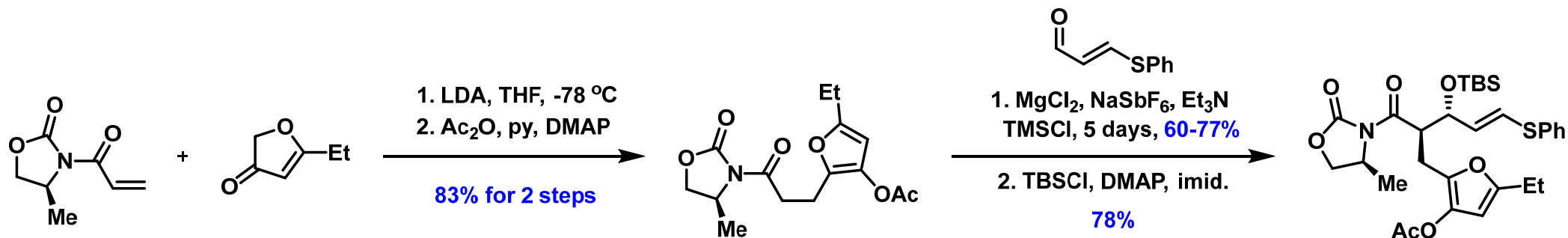
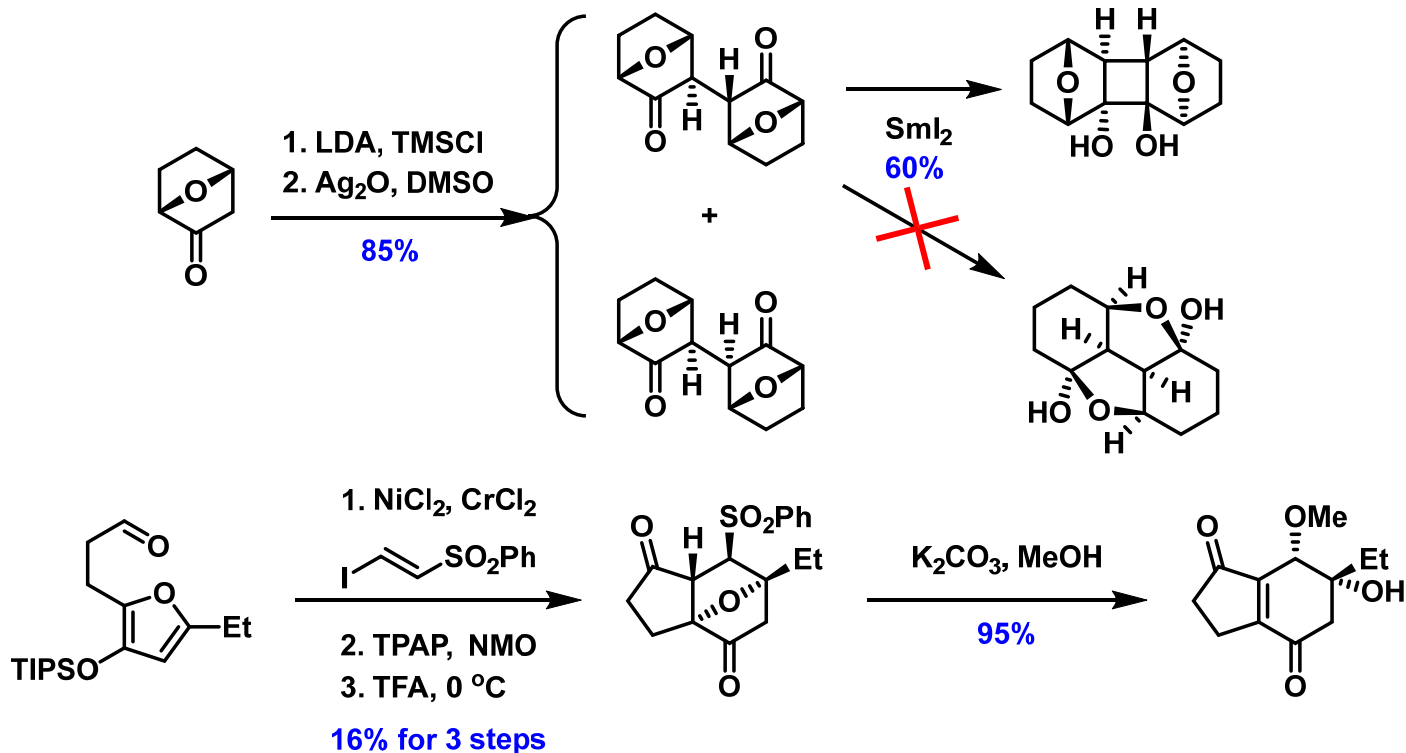


Nicolaou's Ullman & Benzoin Strategy

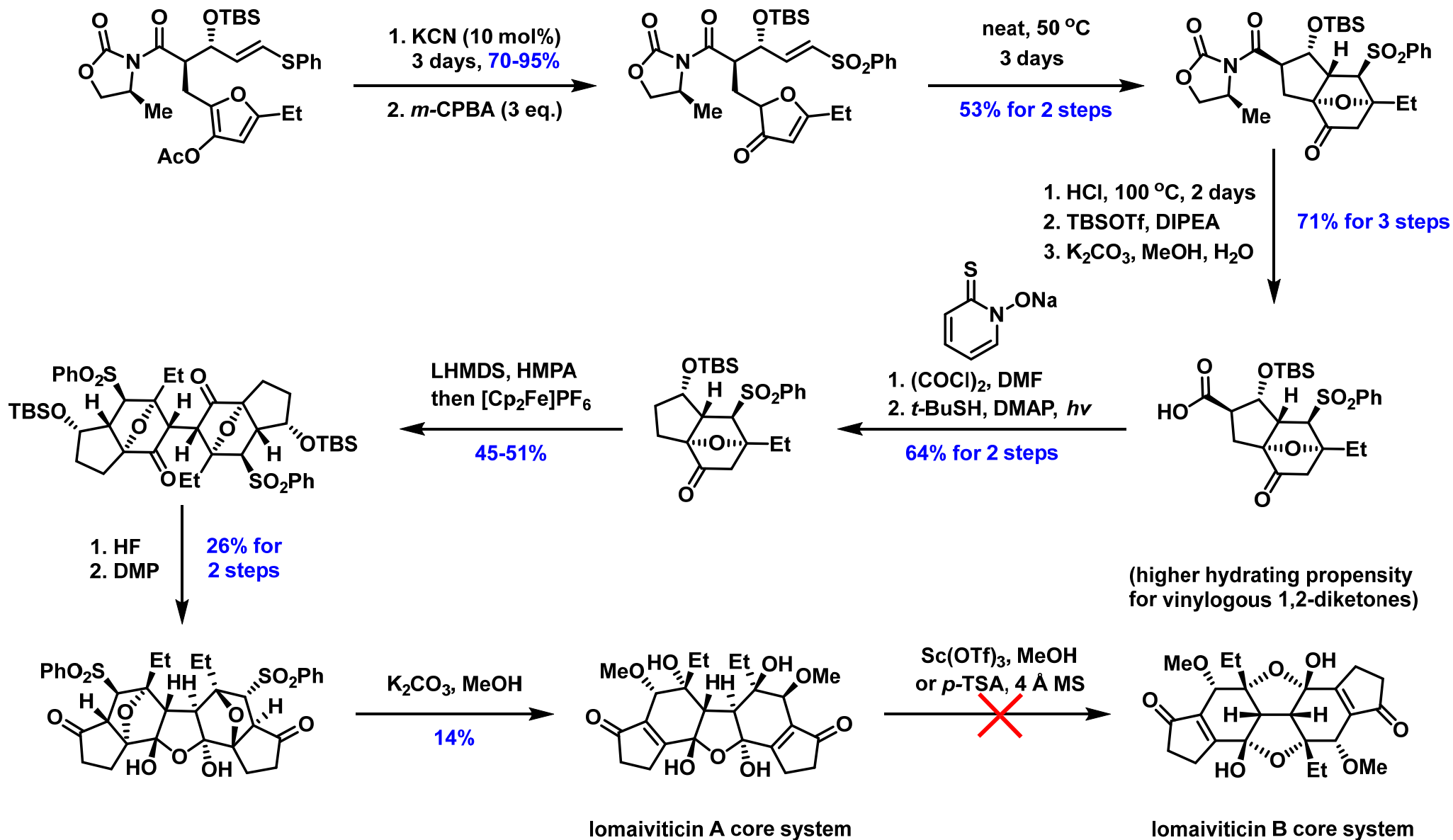


Shair's Diels-Alder Strategy

- 2008, Lomaiviticin A central ring system

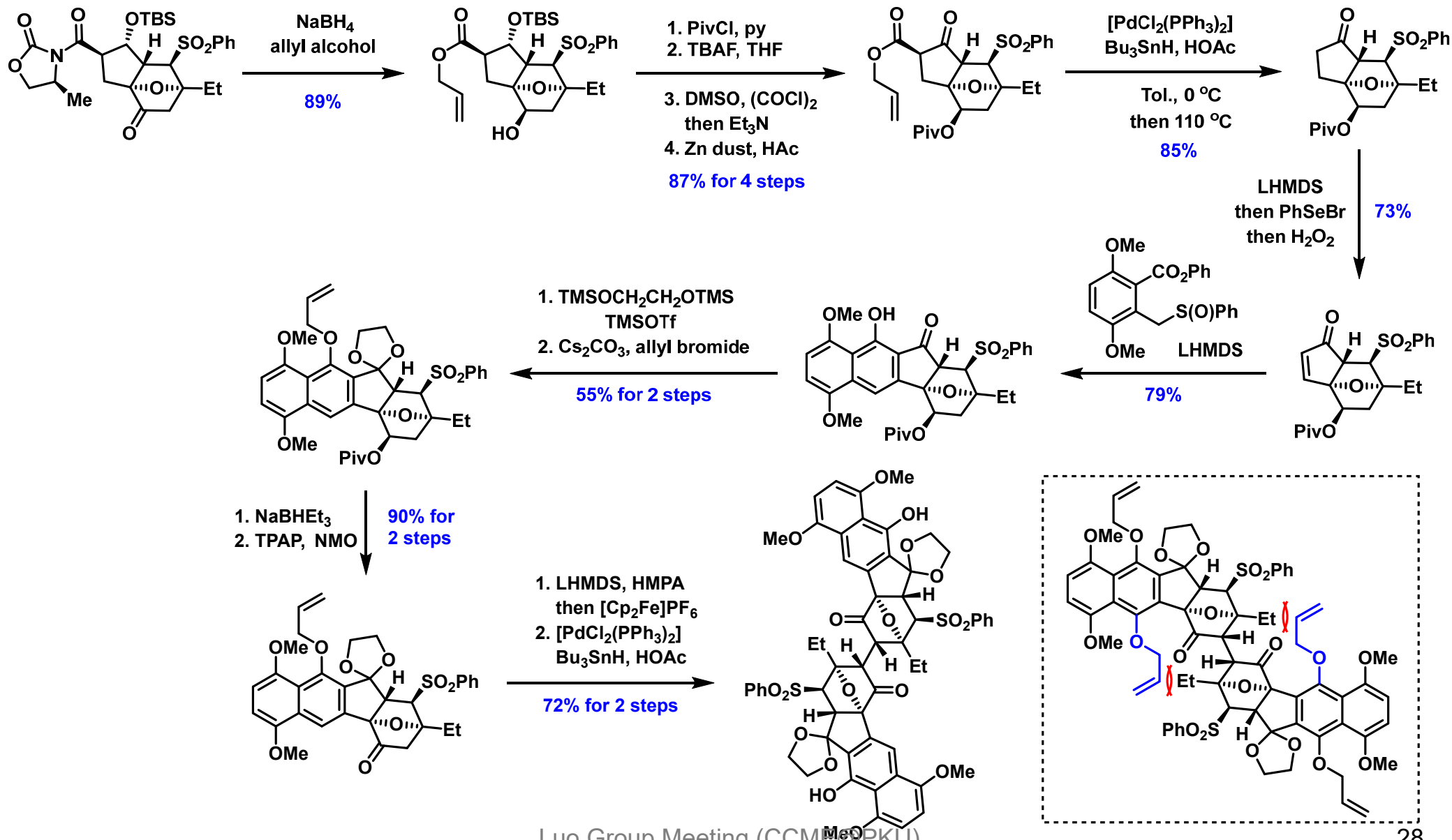


Shair's Diels-Alder Strategy



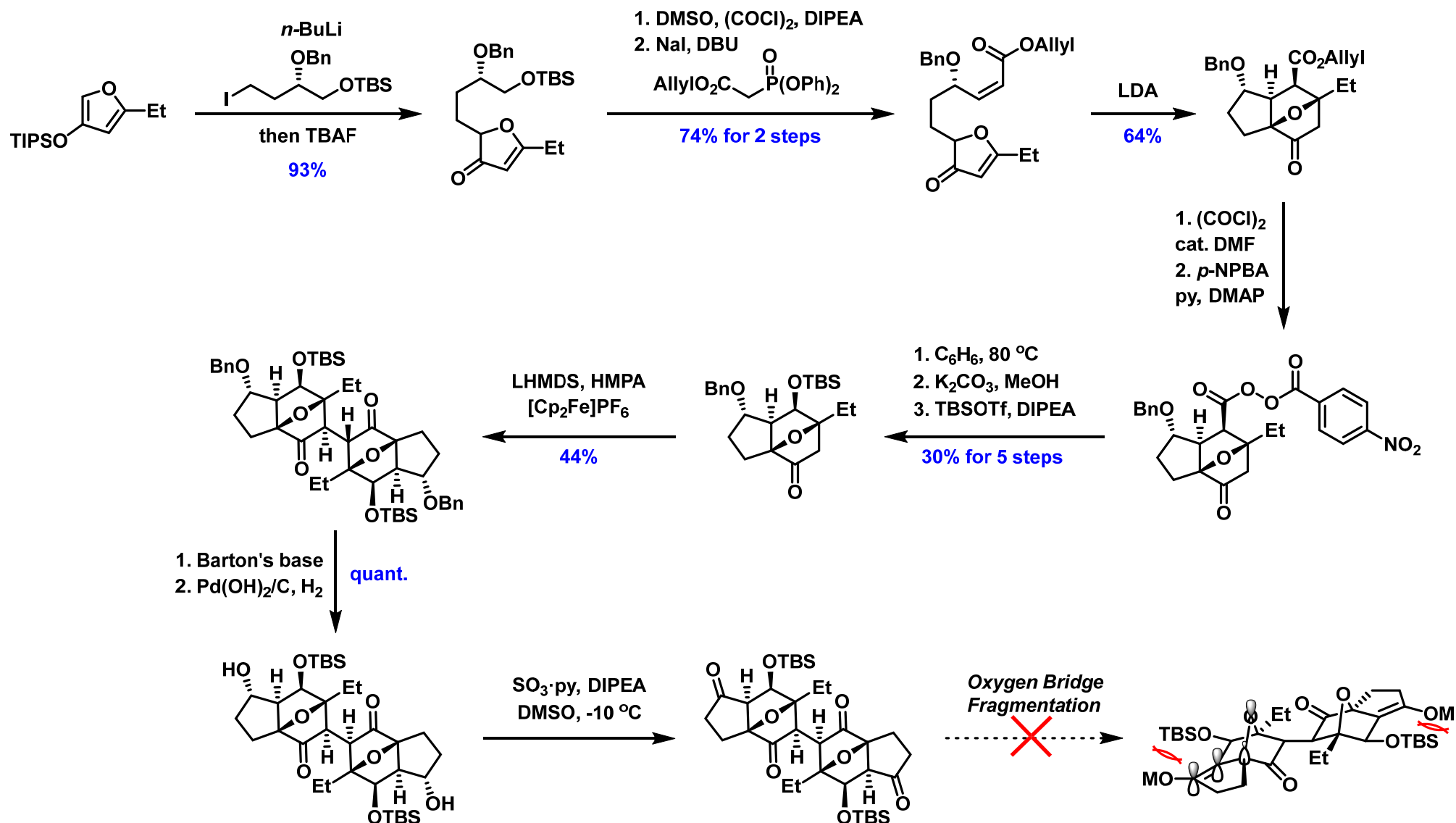
Shair's Diels-Alder Strategy

- 2010, Lomaiviticin aglycon skeleton

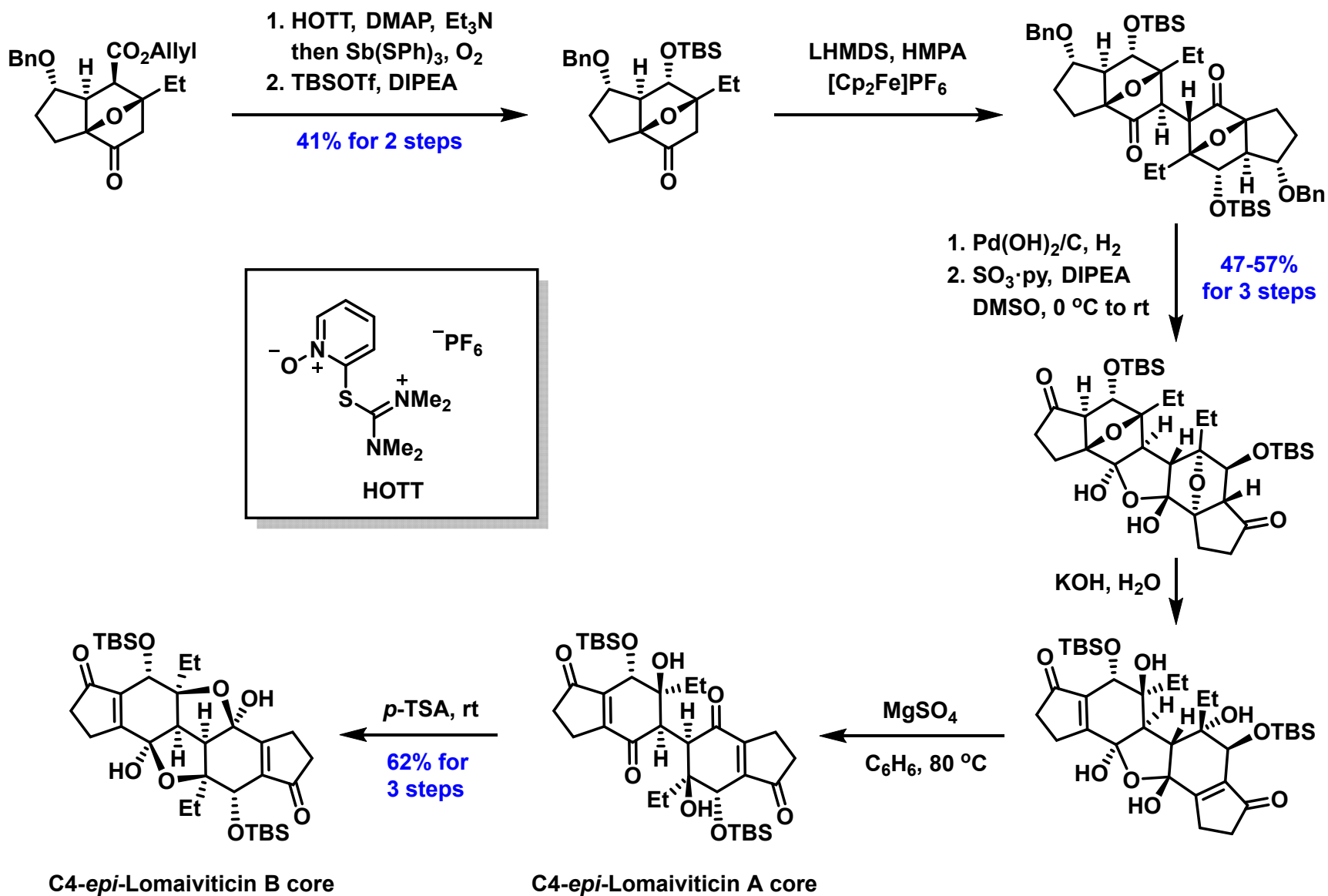


Shair's Diels-Alder Strategy

• 2013, C4-Epi-Lomaiviticin B

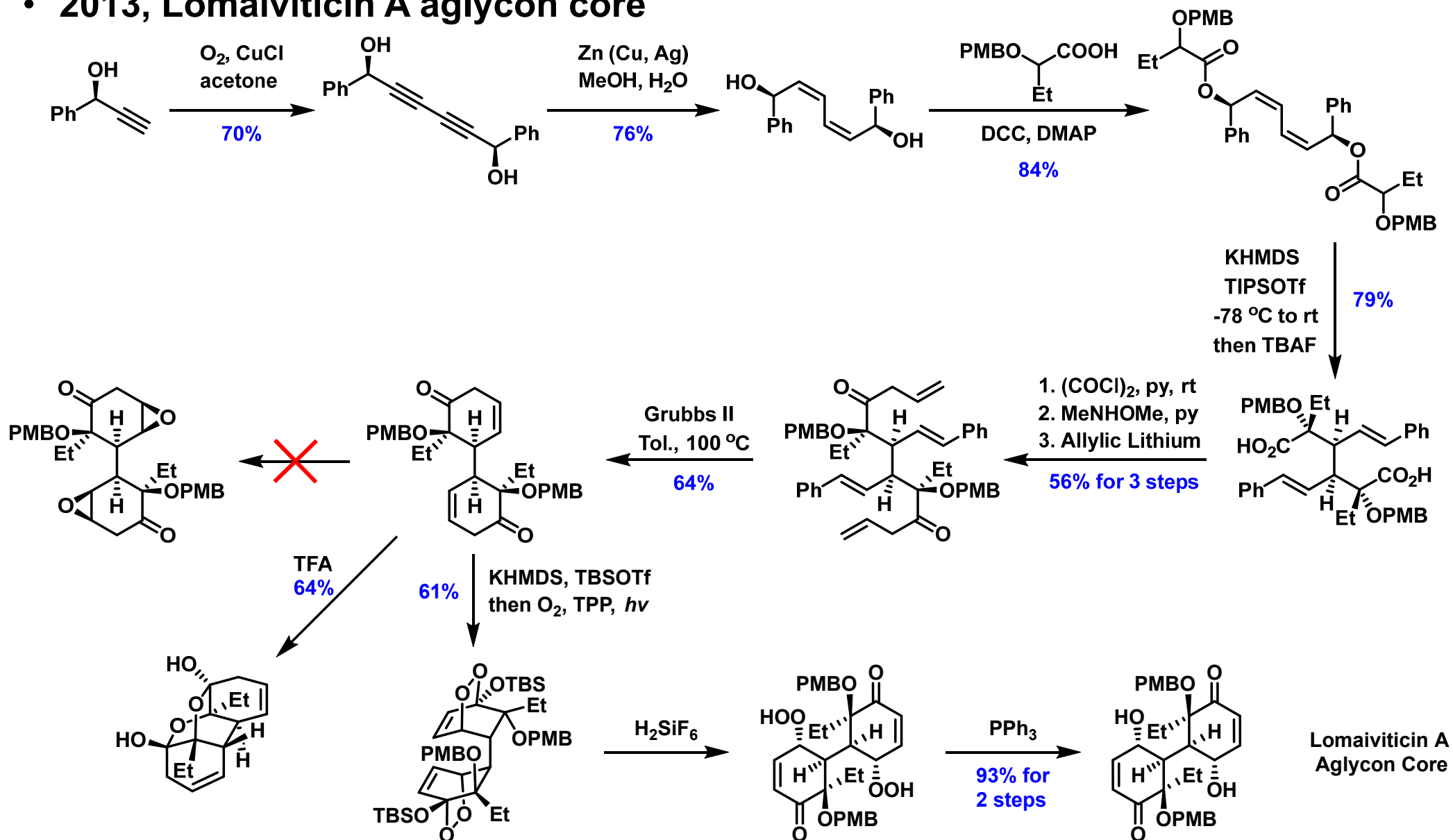


Shair's Diels-Alder Strategy



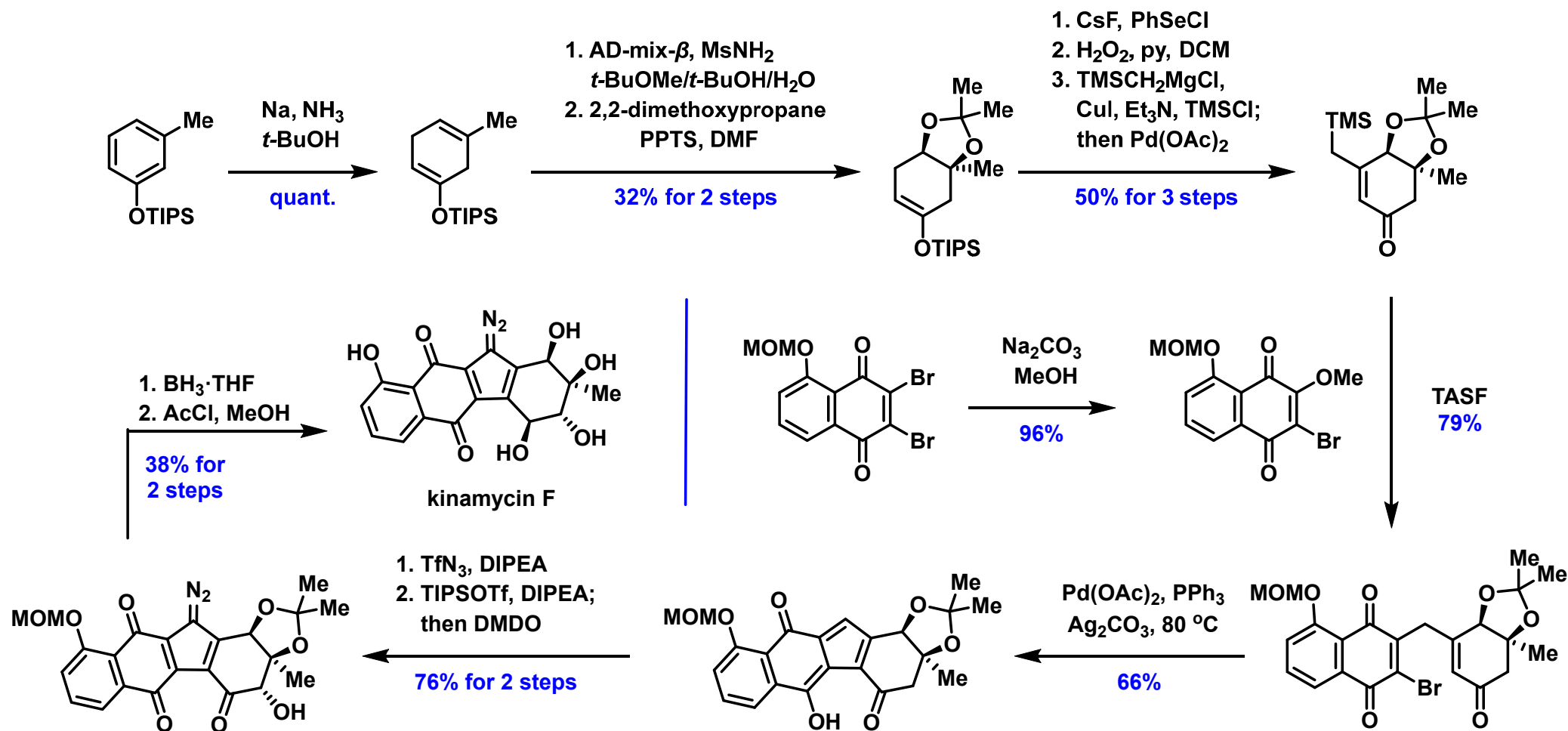
Feldman's Double Claisen & OM Strategy

• 2013, Lomaiviticin A aglycon core



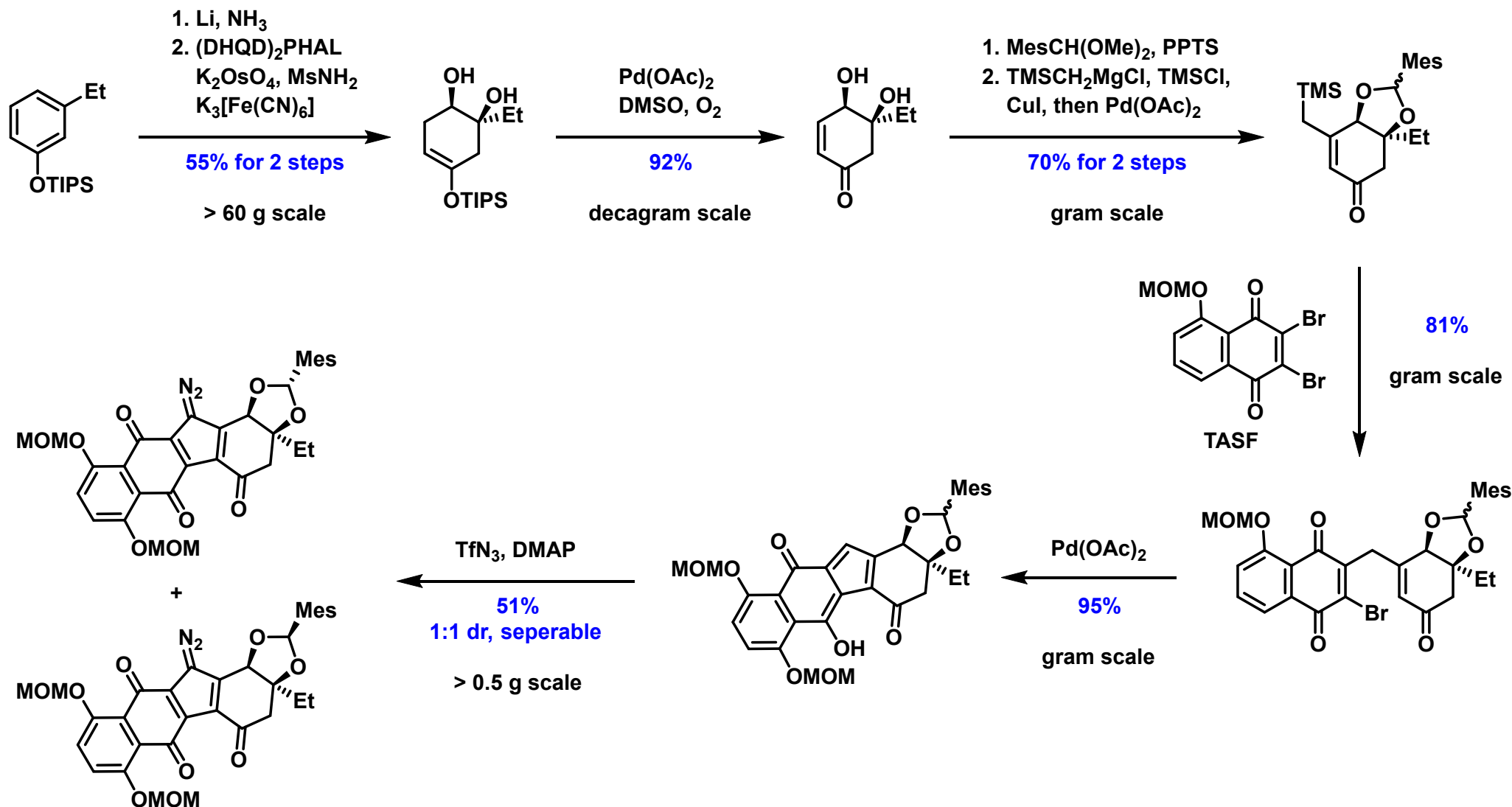
Herzon's Heck Strategy

- 2010, Kinamycin F

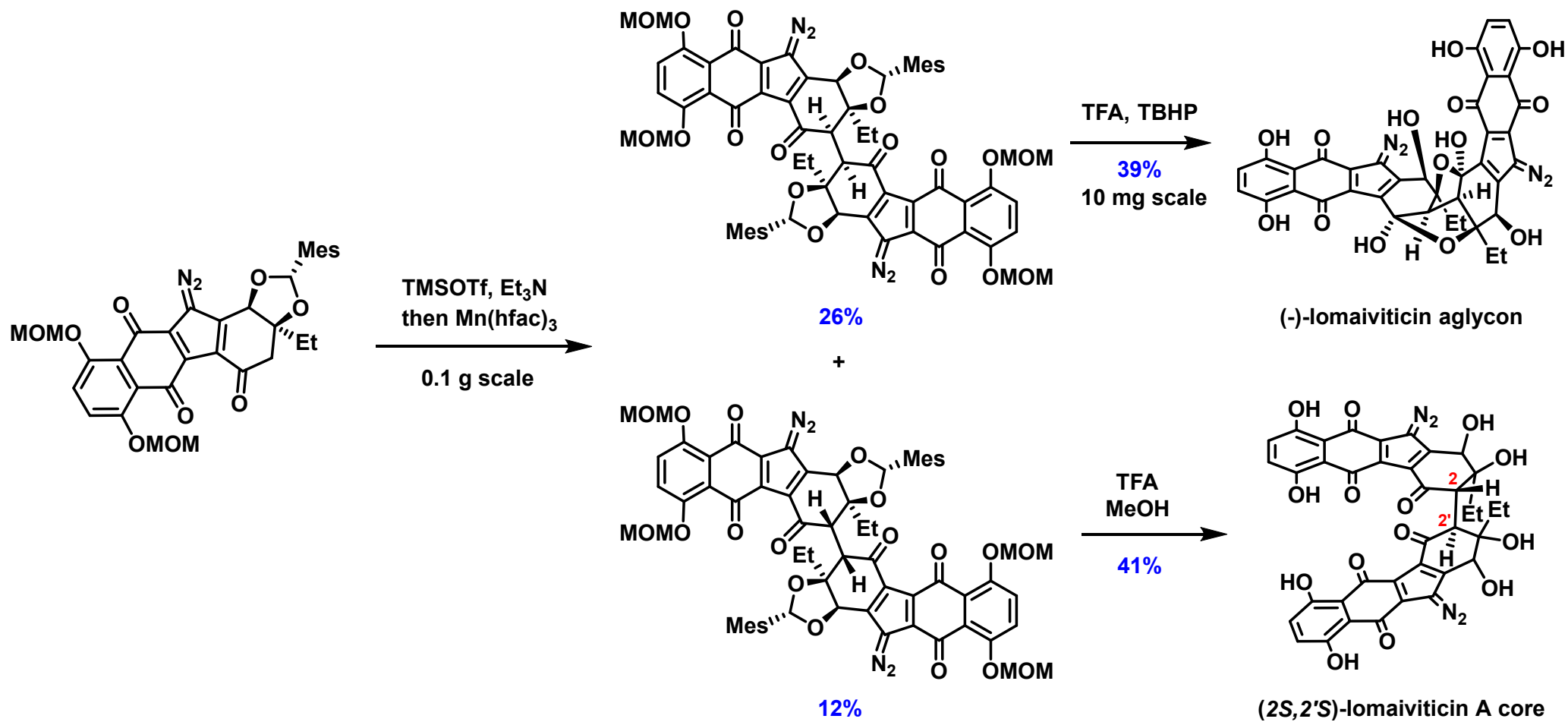


Herzon's Heck Strategy

- 2011, Lomaiviticin aglycon

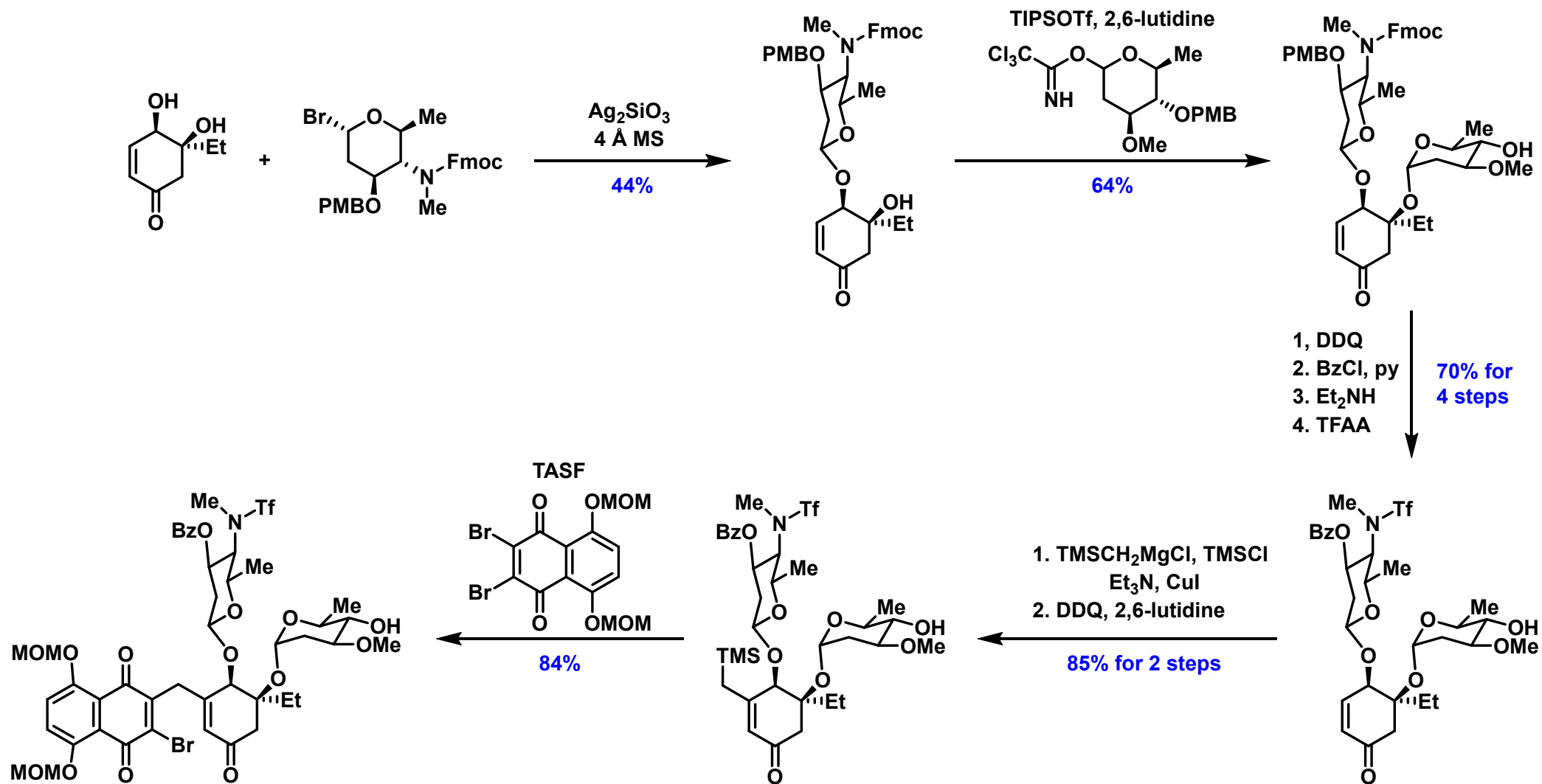


Herzon's Heck Strategy

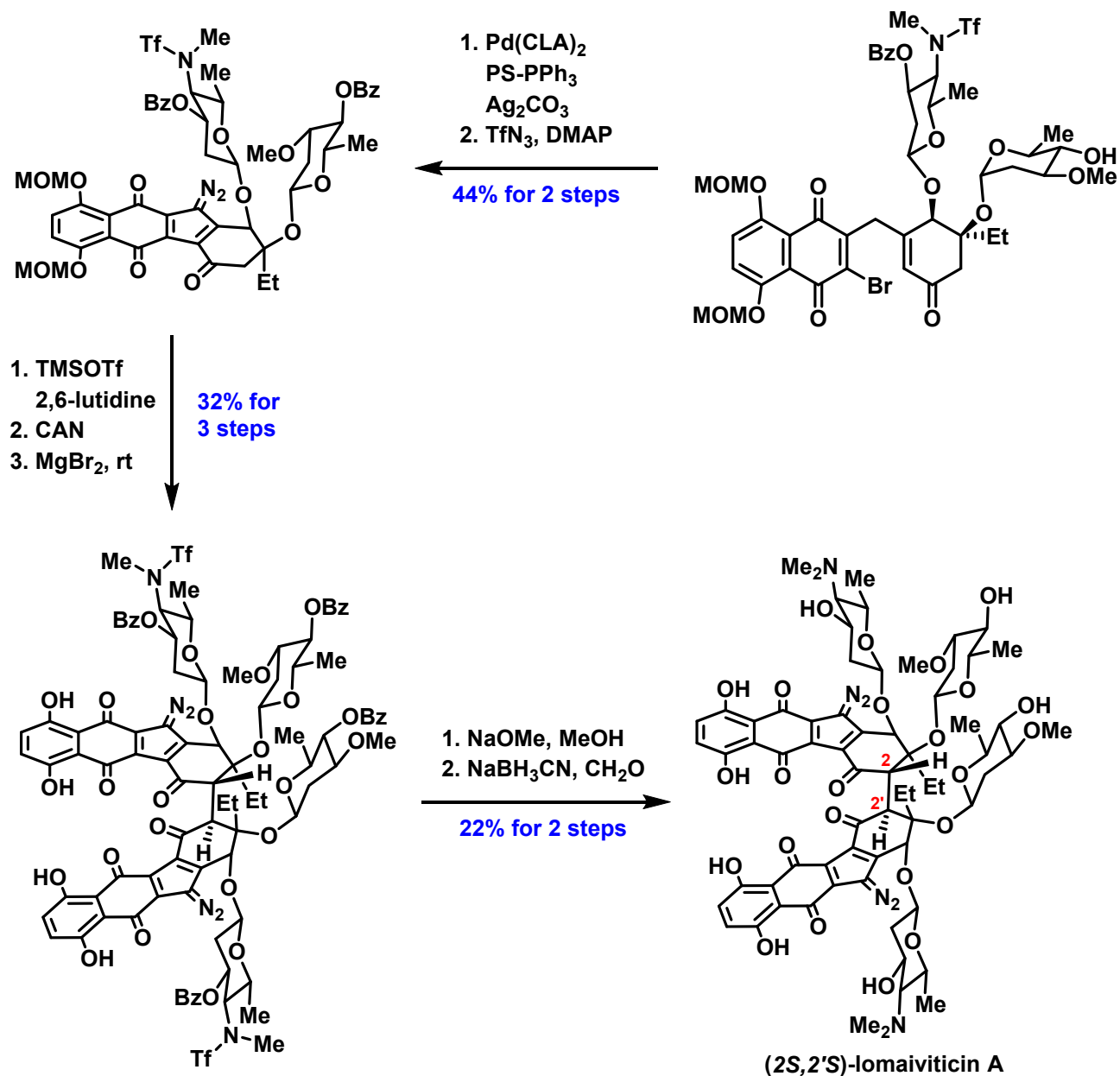


Herzon's Heck Strategy

- 2021, (2S,2'S)-Lomaiviticin A

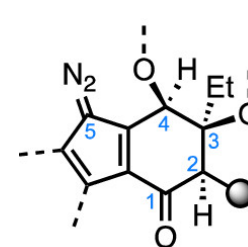
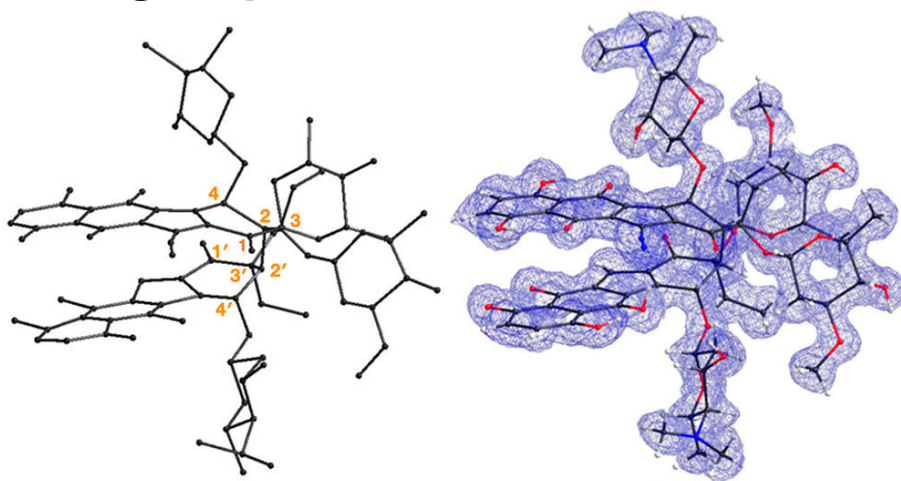


Herzon's Heck Strategy

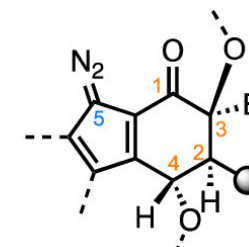


Structure Revision of the Lomaiviticins

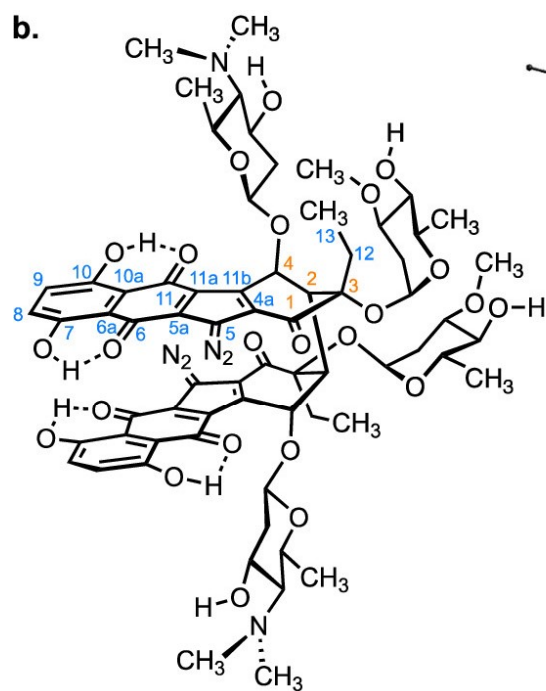
- 2021, Herzon group, microED



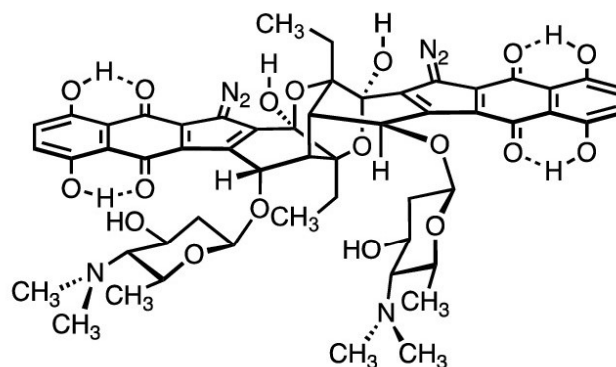
original assignment



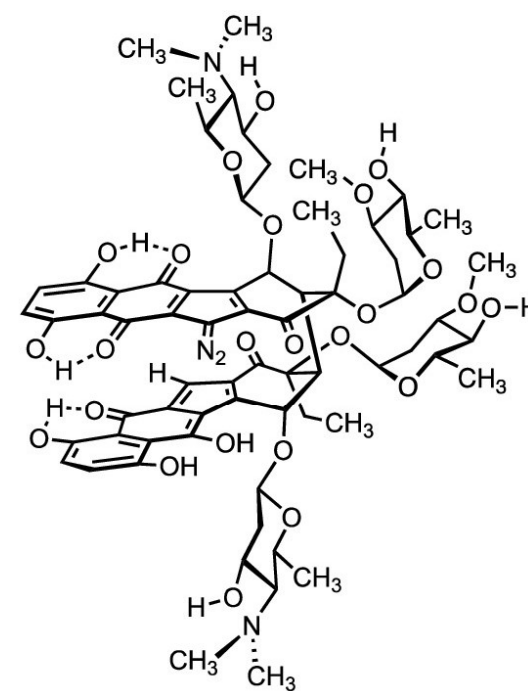
revised assignment



(-)-lomaiviticin A
(2021 structure assignment, **1b**)



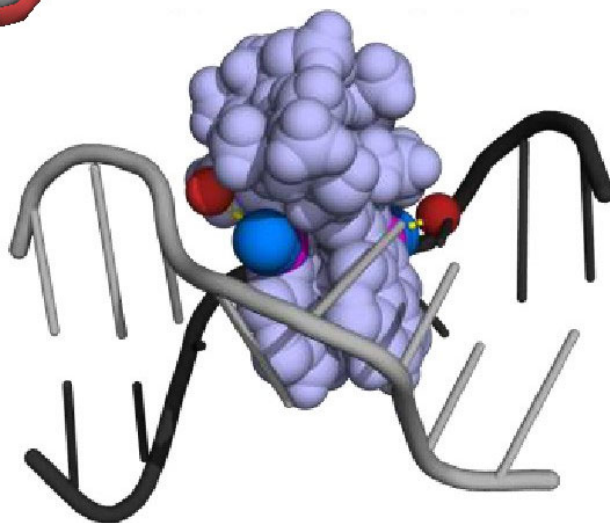
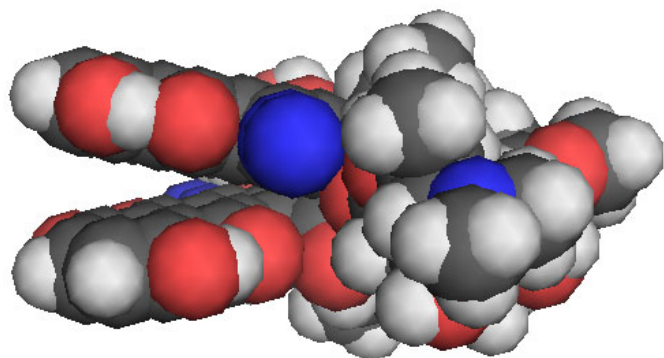
(-)-lomaiviticin B
(2021 structure assignment, **2b**)



(-)-lomaiviticin C
(2021 structure assignment, **3b**)

Summary

- Intriguing diazo
- DNA strand breaking mechanism
- Anti – cancer and anti – leukemia potential
- Synthetic challenges
- Structure revision



B Ring
Friedel-Crafts, Porco
Benzoin, Nicolaou
Heck, Herzon

C Ring
Claisen, Birman

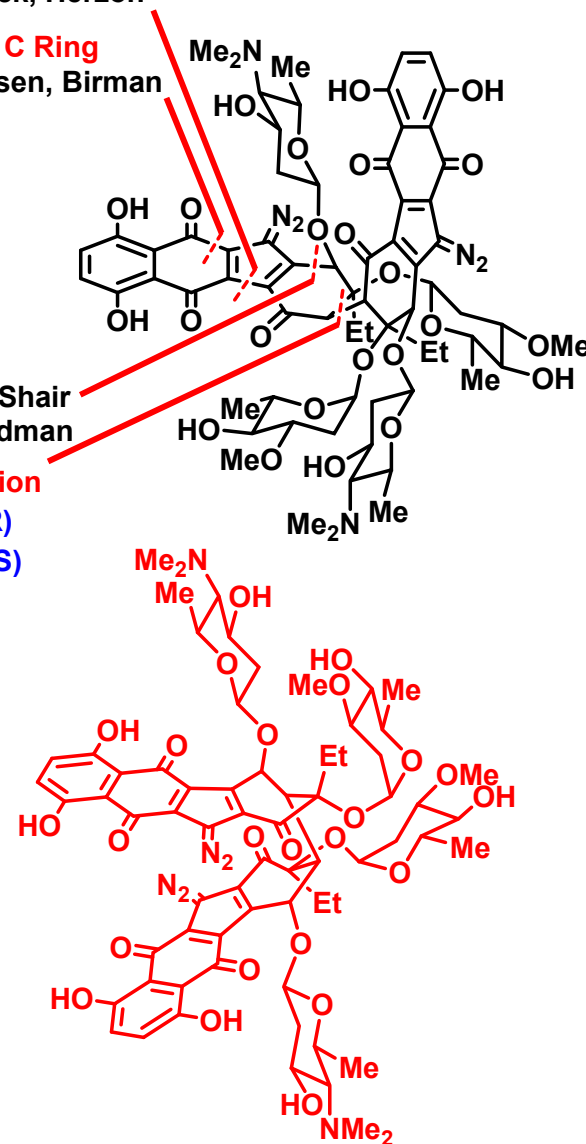
A Ring
Diels-Alder, Ishikawa/Shair
Olefin Metathesis, Feldman

Oxidative Dimerization

$\text{Mn}(\text{hfac})_3 \rightarrow (\text{R}, \text{R})$

$[\text{Cp}_2\text{Fe}]\text{PF}_6 \rightarrow (\text{R}, \text{S})$

$\text{CAN} \rightarrow (\text{S}, \text{S})$



Lomaiviticin A