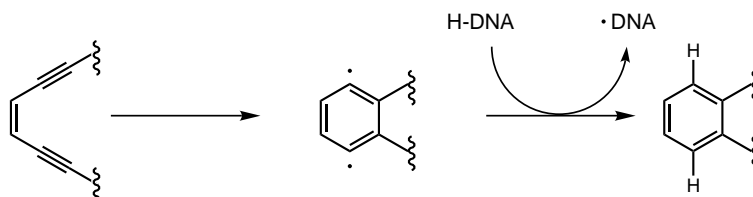


Highlights in the Total Synthesis of Eneidyne Containing Natural Products

Travis Dunn

Evans Group Evening Seminar

Friday, November 10, 2000



Reviews:

Percy Carter. Evans Group Evening Seminar, May 1993.

Nicolaou, K. C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1387.

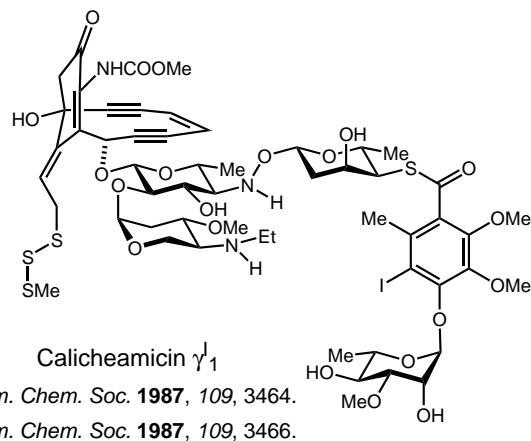
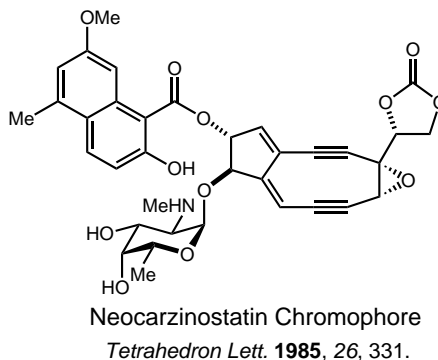
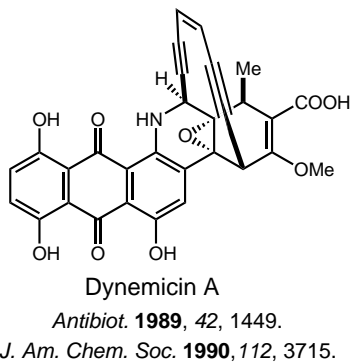
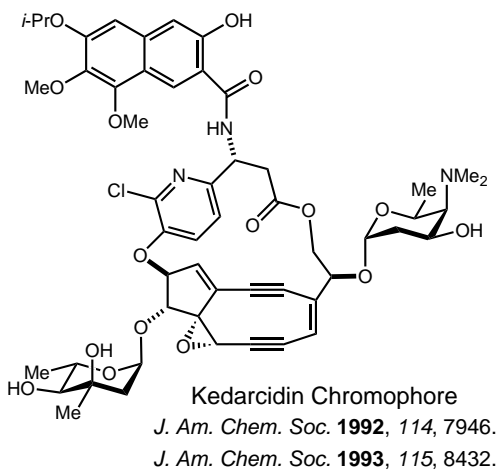
Lhermitte, H.; Grierson, D. S. *Contemporary Organic Synthesis* **1996**, 3, 41.

Lhermitte, H.; Grierson, D. S. *Contemporary Organic Synthesis* **1996**, 3, 93.

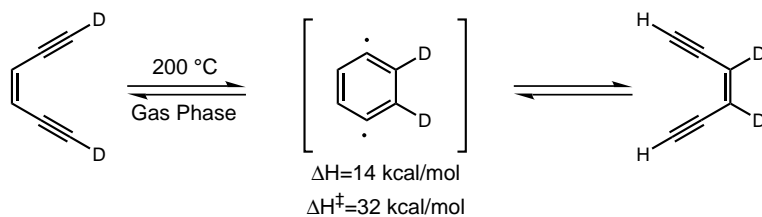
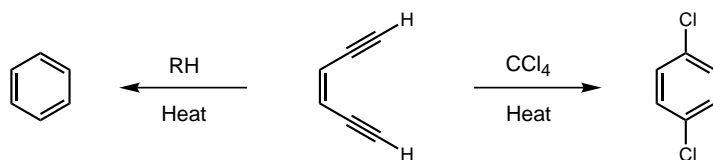
Grissom, J. W. *et al. Tetrahedron* **1996**, 52, 6453.

Caddick, S. *et al.* Synthesis of eneidyne and dieneidyne. In *The Chemical Synthesis of Natural Products*, Hale, K. J., Ed.; CRC Press: Boca Raton, 2000; 229.

Eneidyne Natural Products



Bergman Cyclization

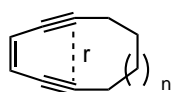


Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.

Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

Cyclic Ene diyne Stability

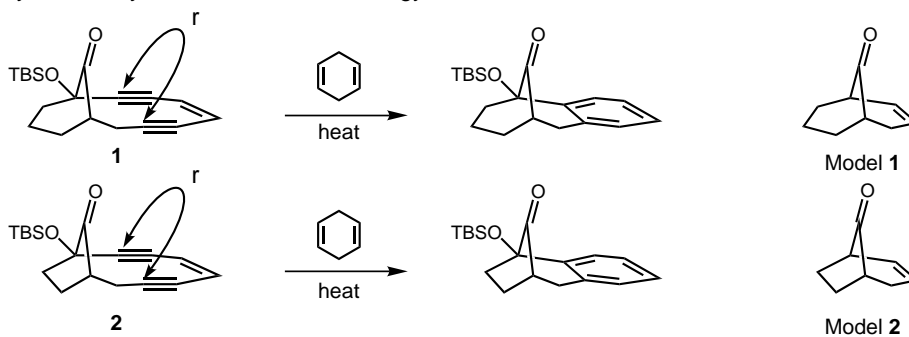
Ene diyne stability a function of internuclear distance



n	ring size	r (Å, calc.)	stability at 25 °C
1	10	3.25	half life=18 hrs
2	11	3.61	stable
3	12	3.90	stable

Nicolaou, K. C. *et al. Acc. Chem. Res.* **1992**, *25*, 497.

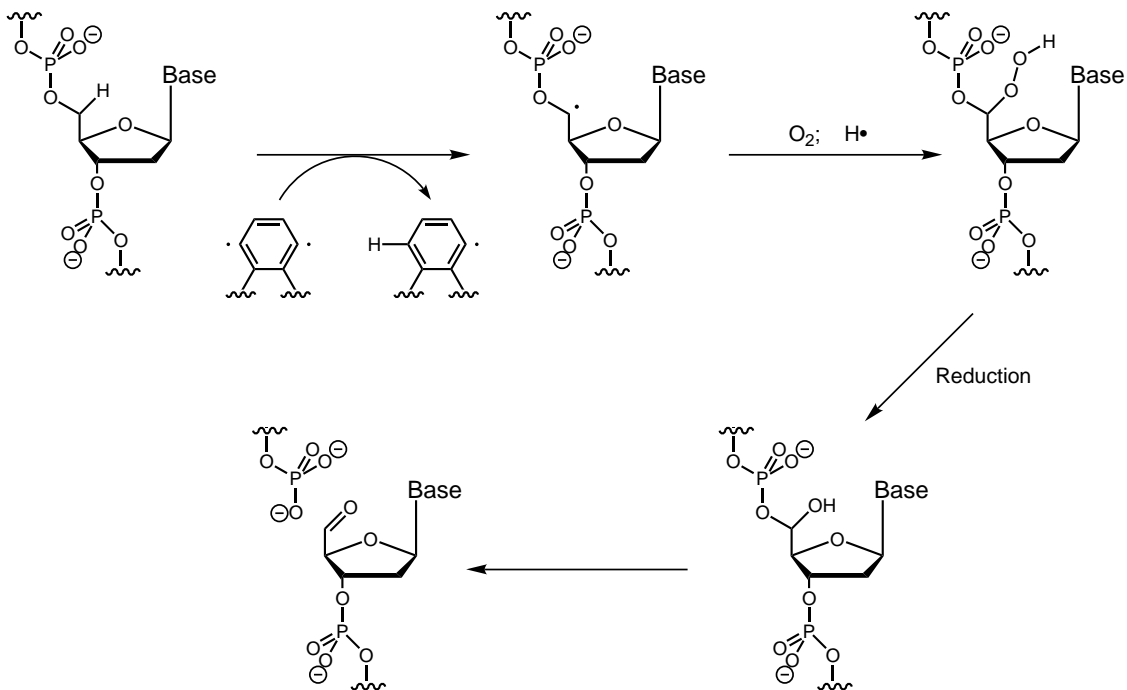
Ene diyne stability a function of strain energy



Cpd	r (Å)	Strain _{Model}	$\Delta G^\ddagger(124\text{ }^\circ\text{C})$
1	3.39	15.1 kcal/mol	26.9 kcal/mol
2	3.37	19.6 kcal/mol	32.0 kcal/mol

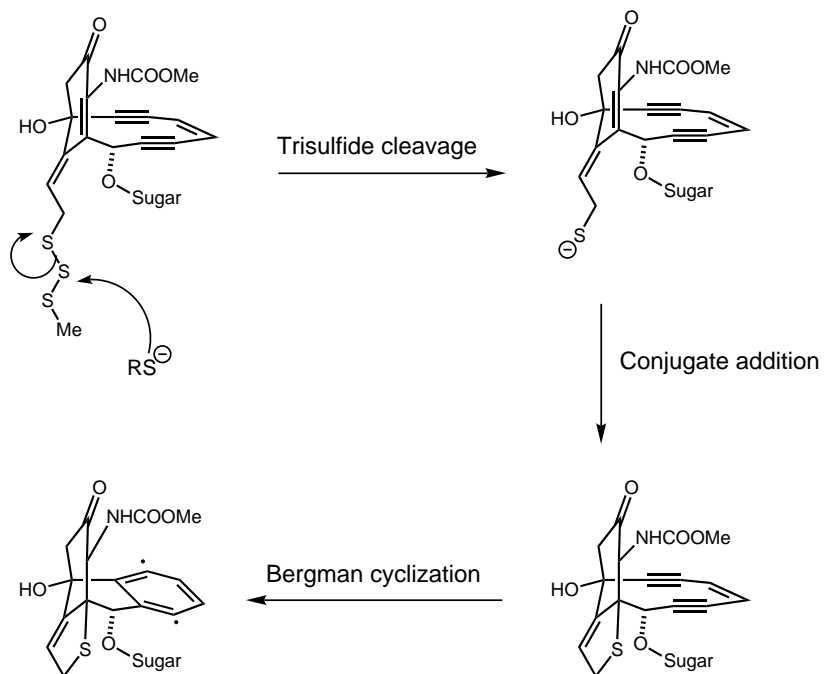
Magnus, P. *et al. J. Am. Chem. Soc.* **1992**, *114*, 2544.

Mechanism of DNA Damage

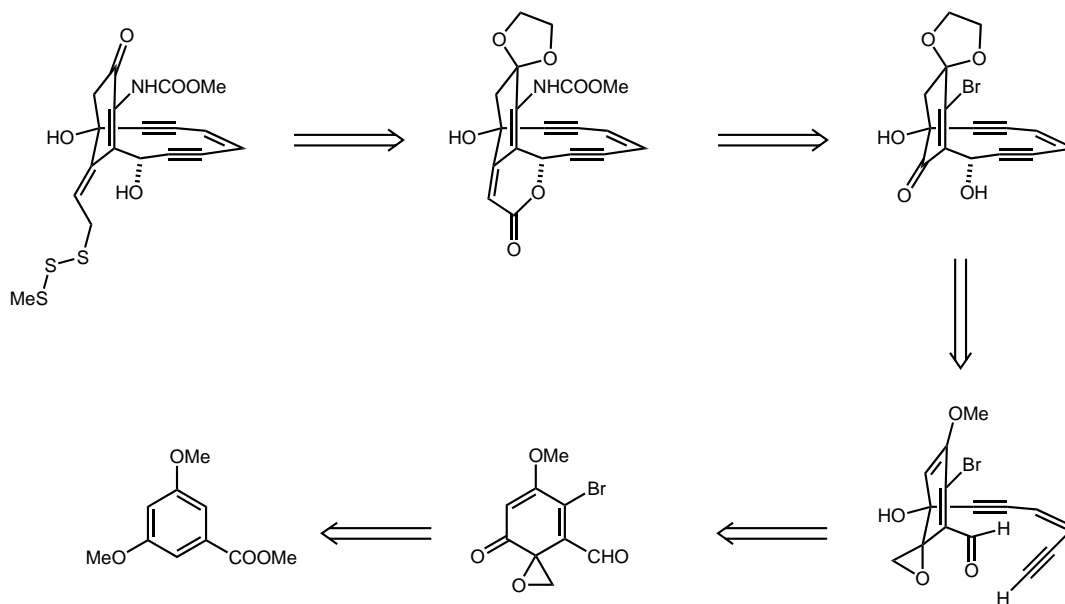


Nicolaou, K. C. et al. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1387.

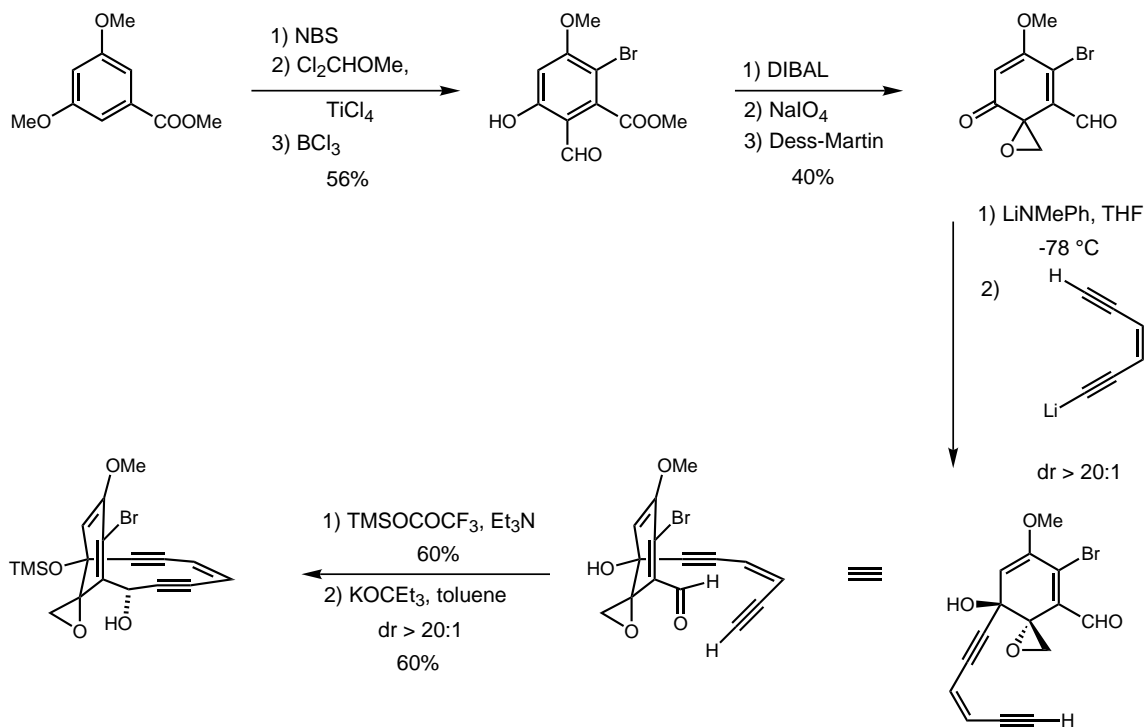
Calicheamicin Mechanism of Action



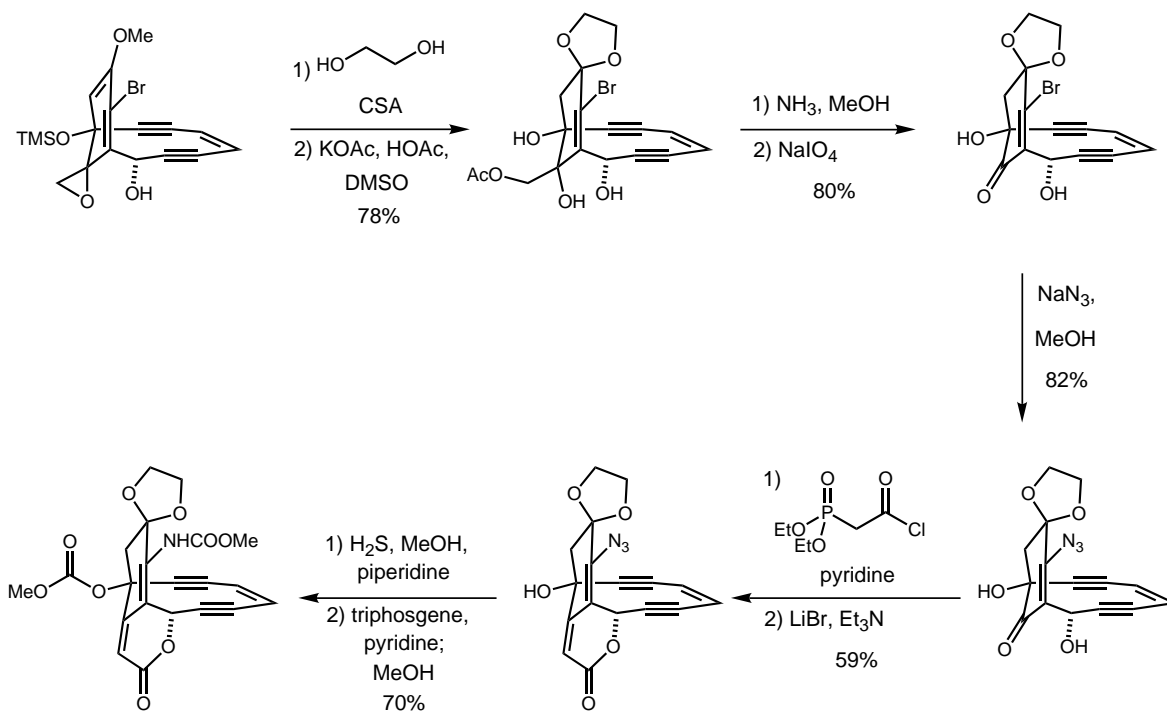
(±)-Calicheamicin Retrosynthesis: Danishefsky



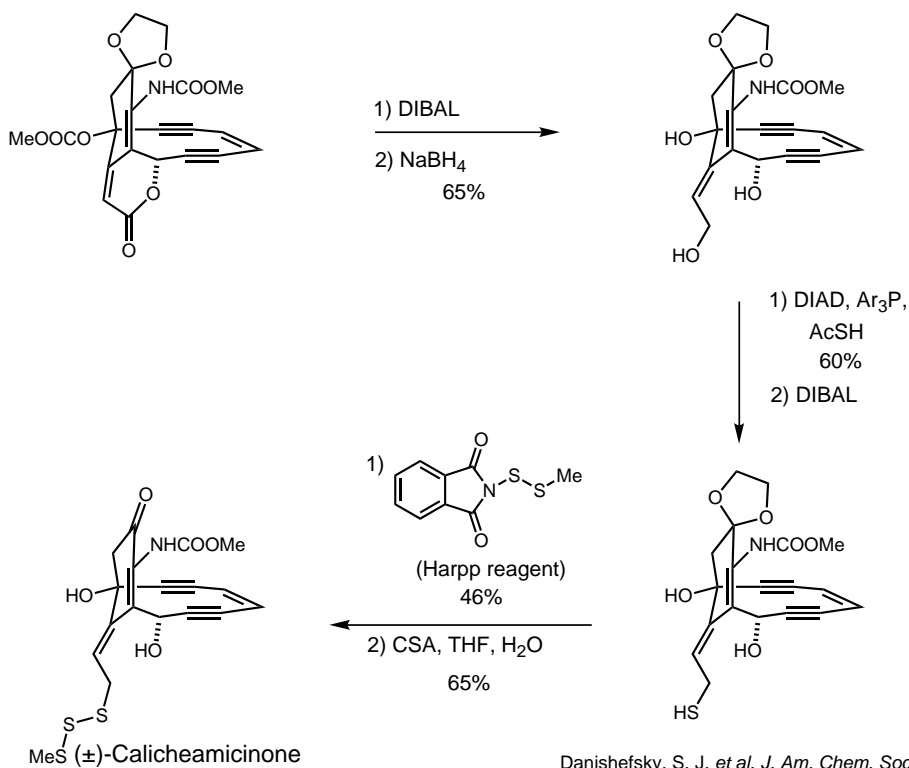
(±)-Calicheamicin: Core Construction



(±)-Calicheamicin: Carbamate Installation



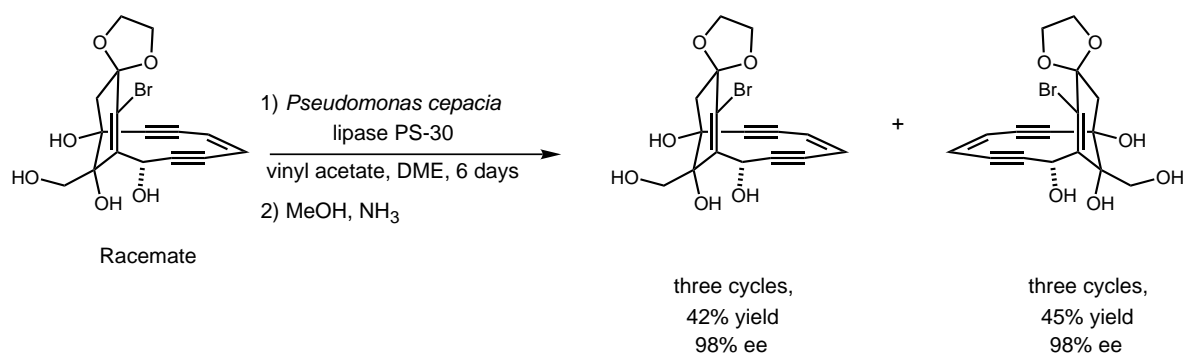
(±)-Calicheamicin: Aglycone Completion



Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1990**, *112*, 3253.

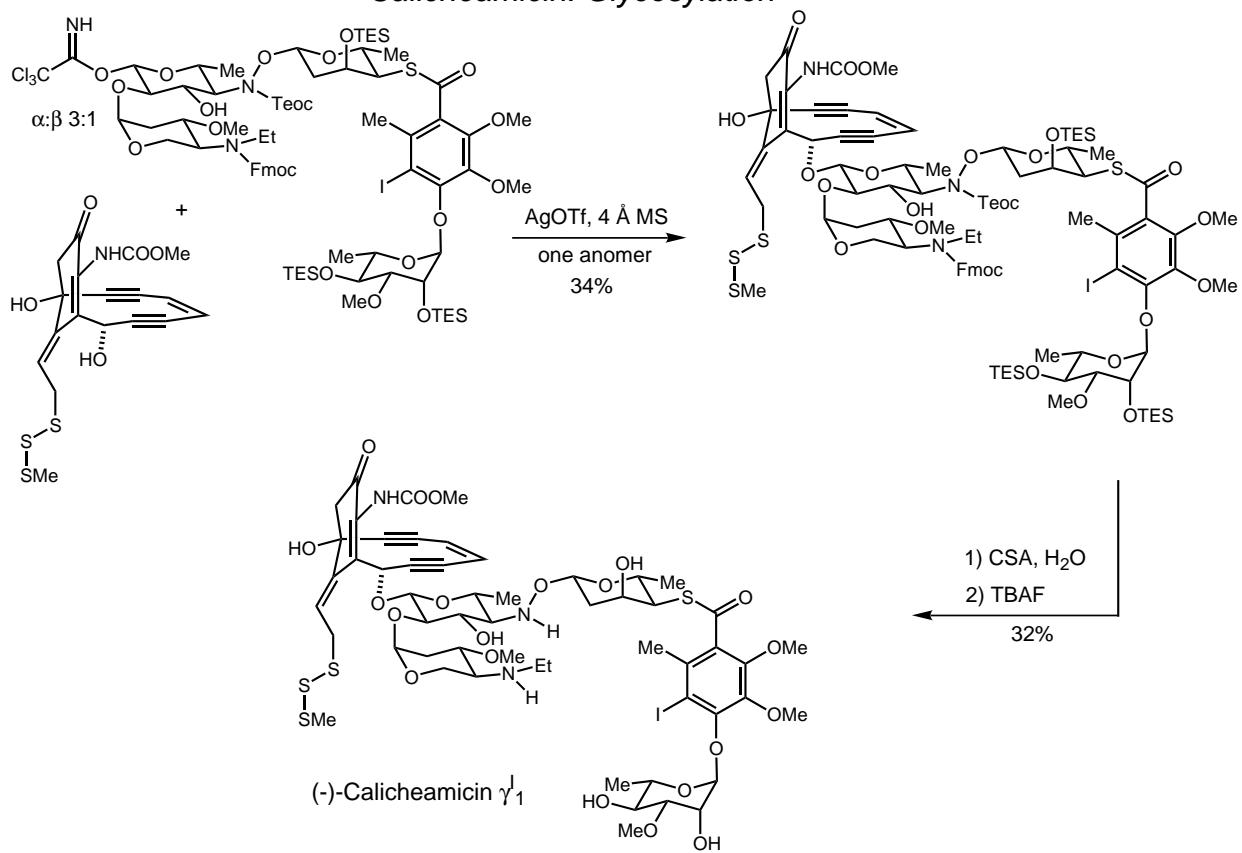
Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1991**, *113*, 3850.

Calicheamicin: Enzymatic Resolution of an Intermediate



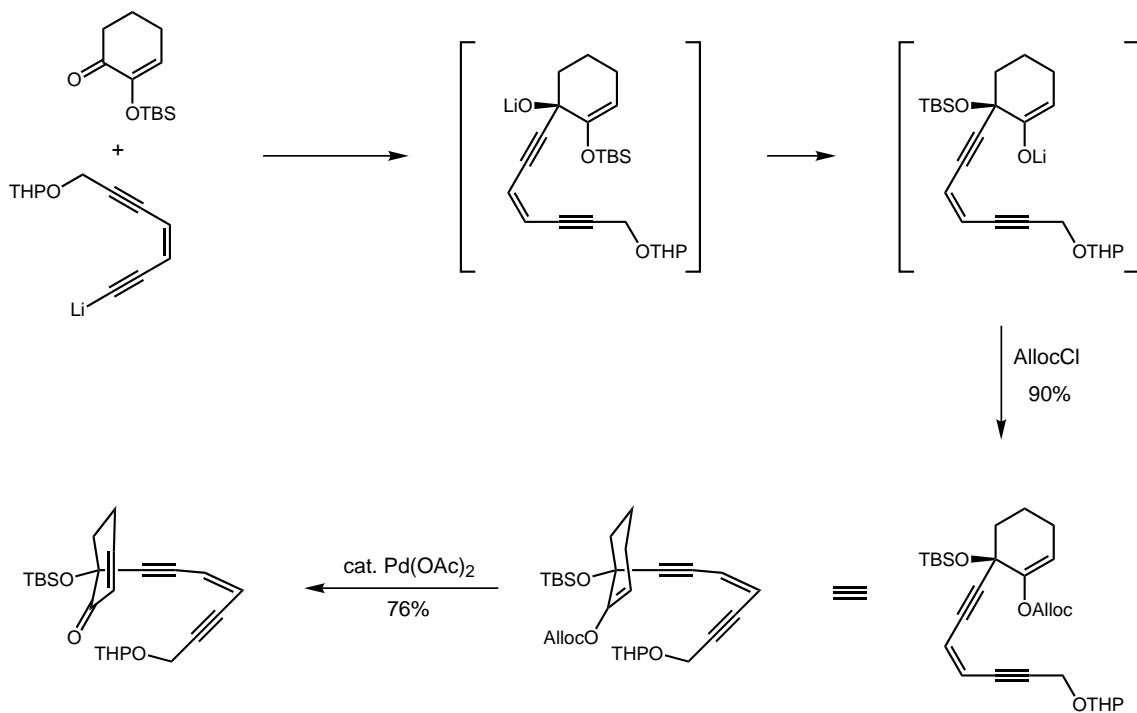
Danishefsky, S. J. *et al. Tetrahedron Lett.* **1991**, 32, 6671.

Calicheamicin: Glycosylation



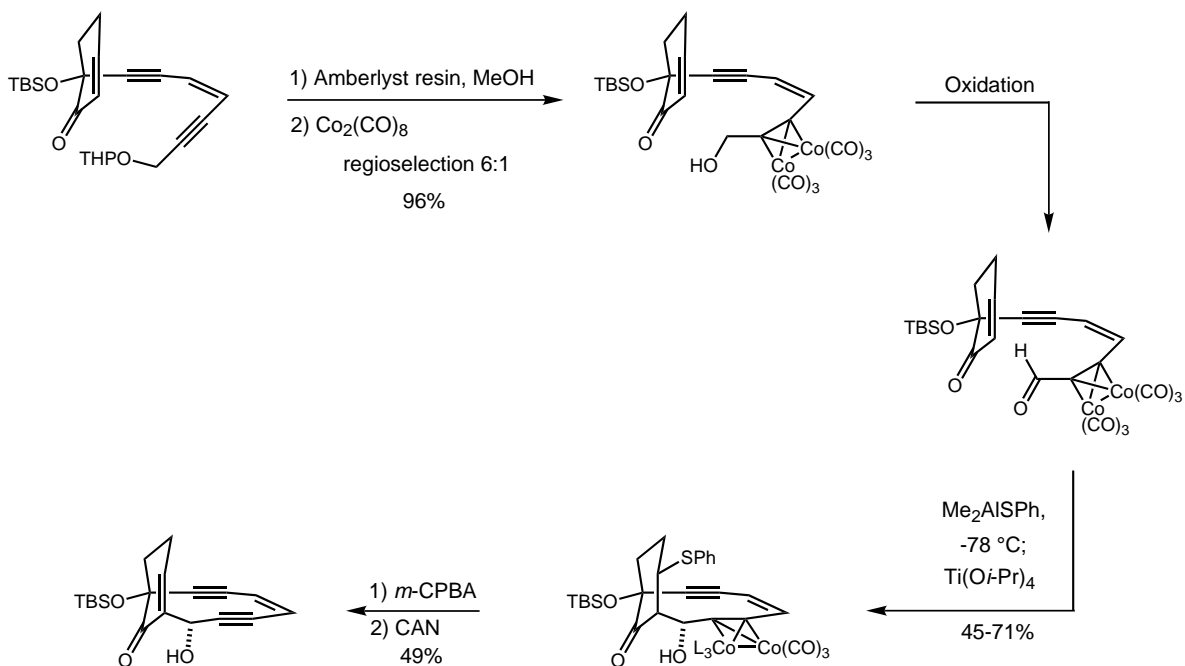
Danishefsky, S. J. *et al. Angew. Chem. Int. Ed. Engl.* **1994**, 33, 858.
Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1995**, 117, 5750.

Calicheamicin Approach: Magnus



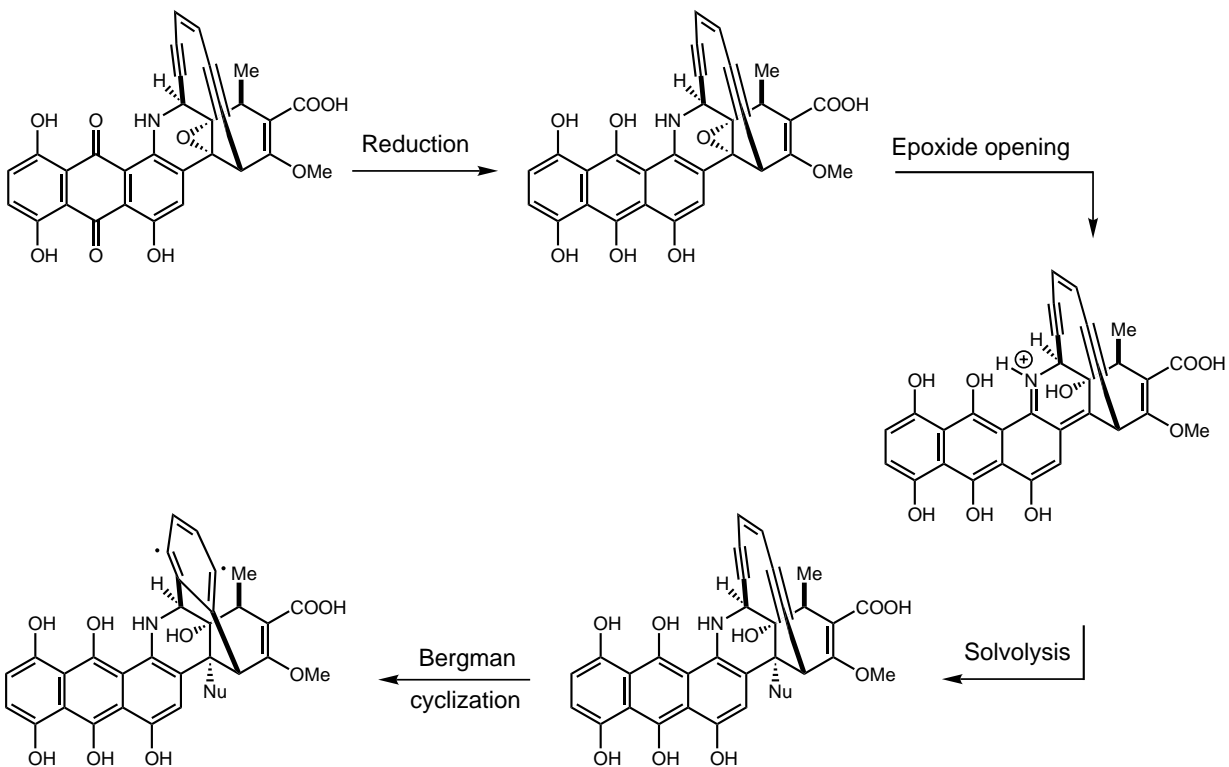
Magnus, P. et al. *J. Am. Chem. Soc.* **1997**, 119, 6739.

Calicheamicin Approach: Magnus

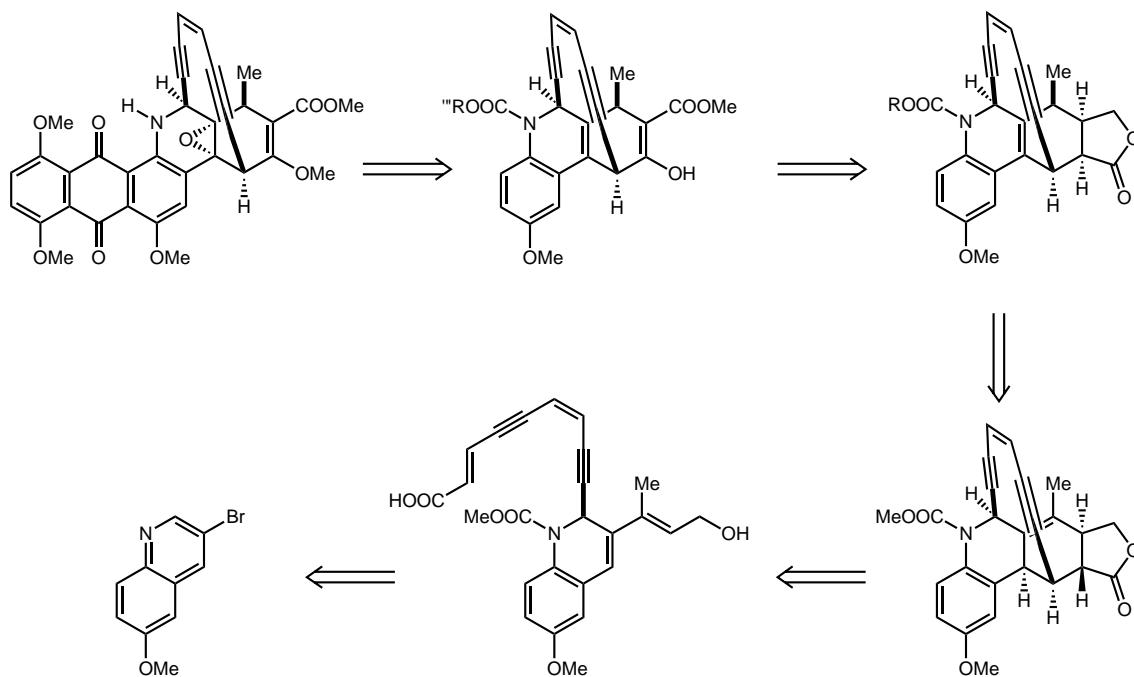


Magnus, P. et al. *J. Am. Chem. Soc.* **1997**, 119, 6739.

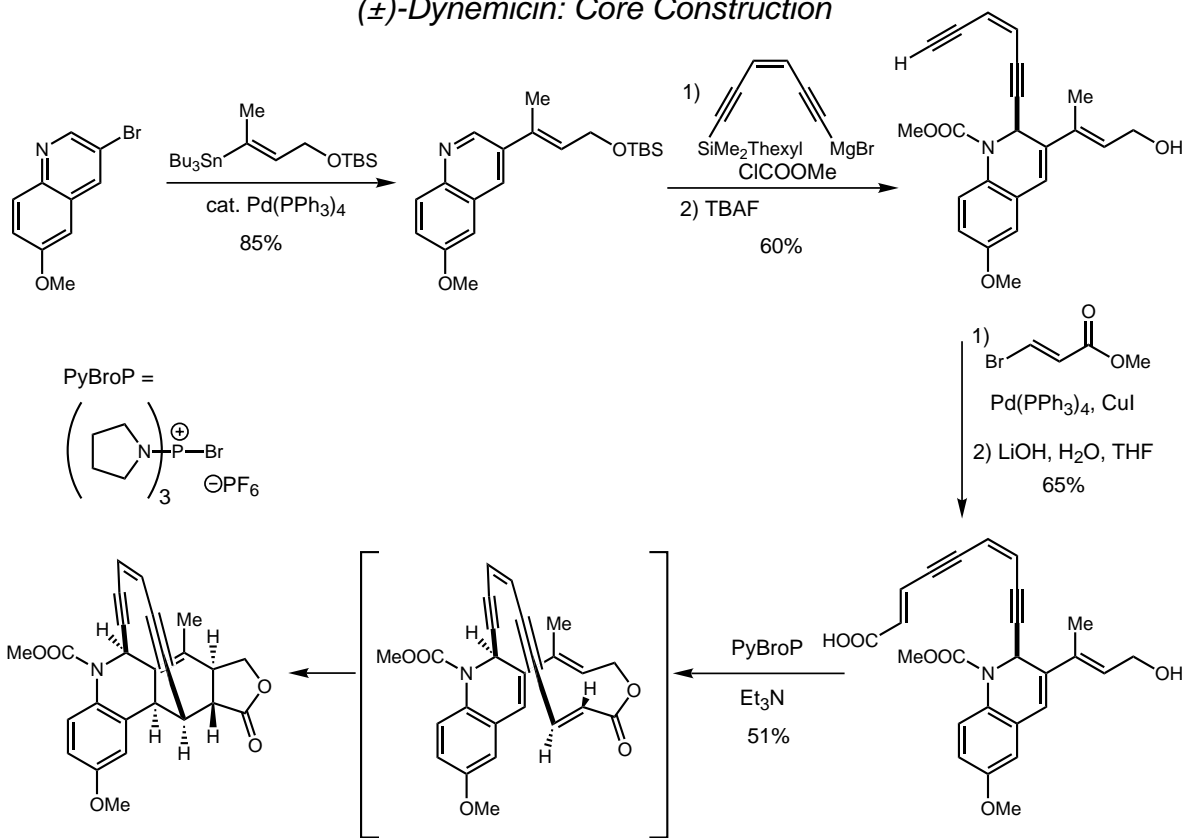
Dynemicin Mechanism of Action



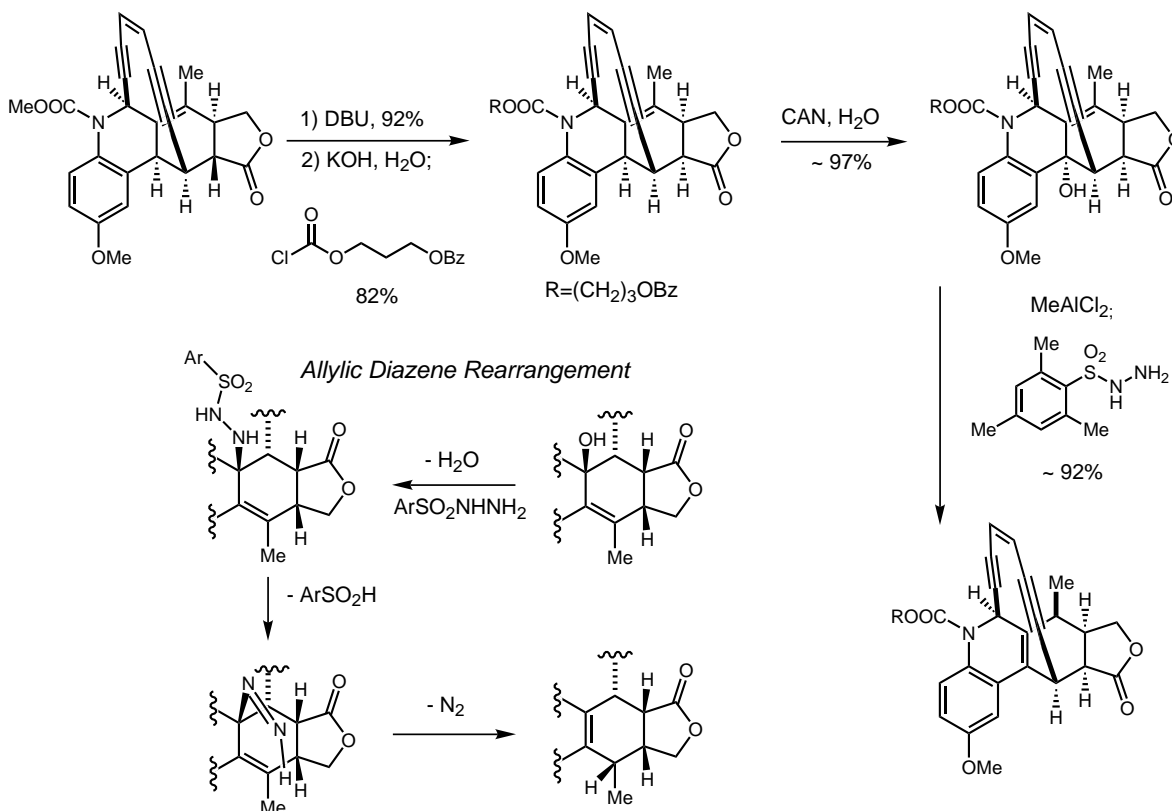
(±)-Dynemicin Retrosynthesis: Schreiber



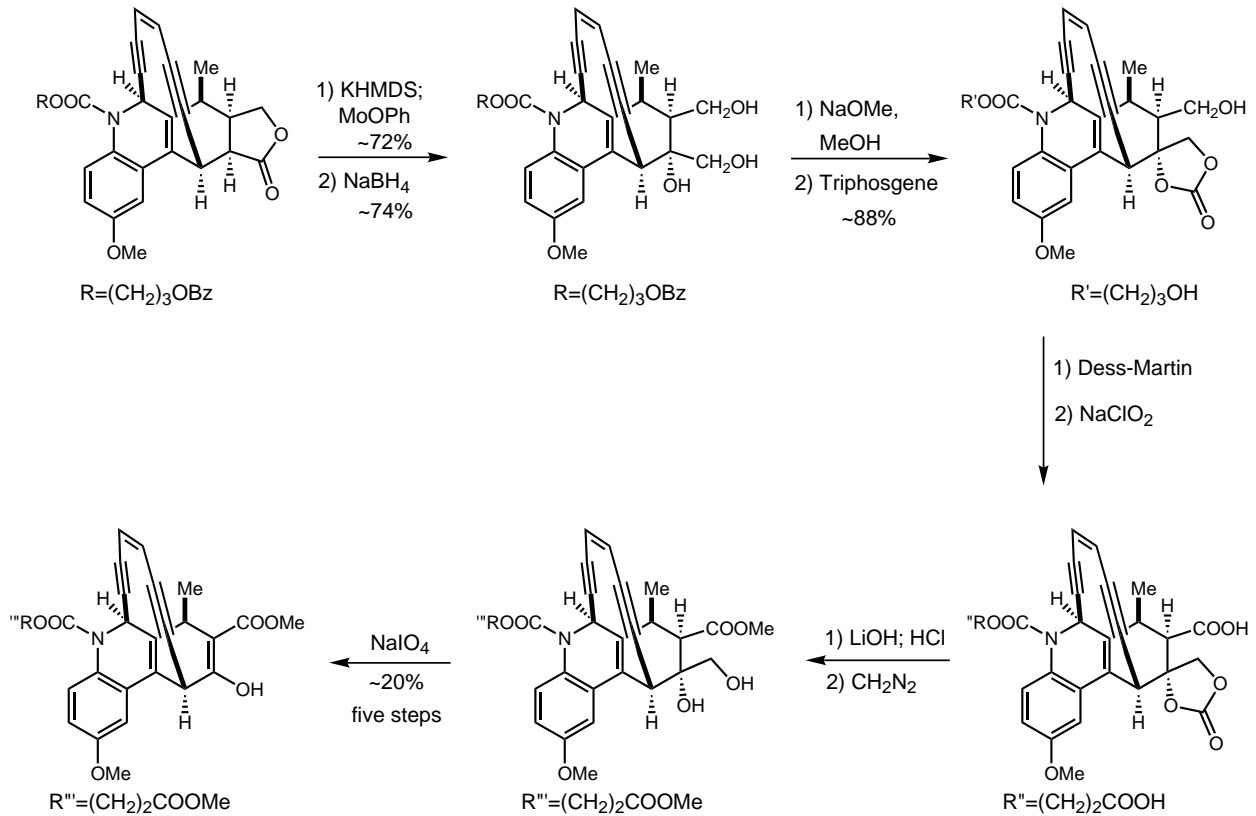
(±)-Dynemicin: Core Construction



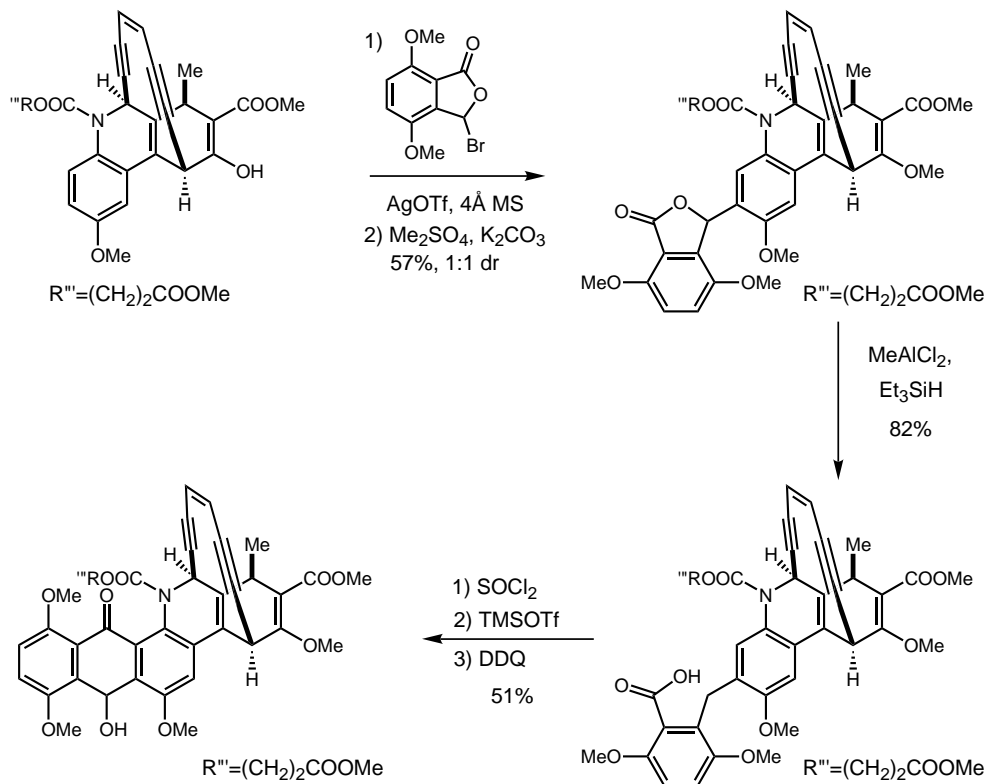
(±)-Dynemicin: Allylic Transposition



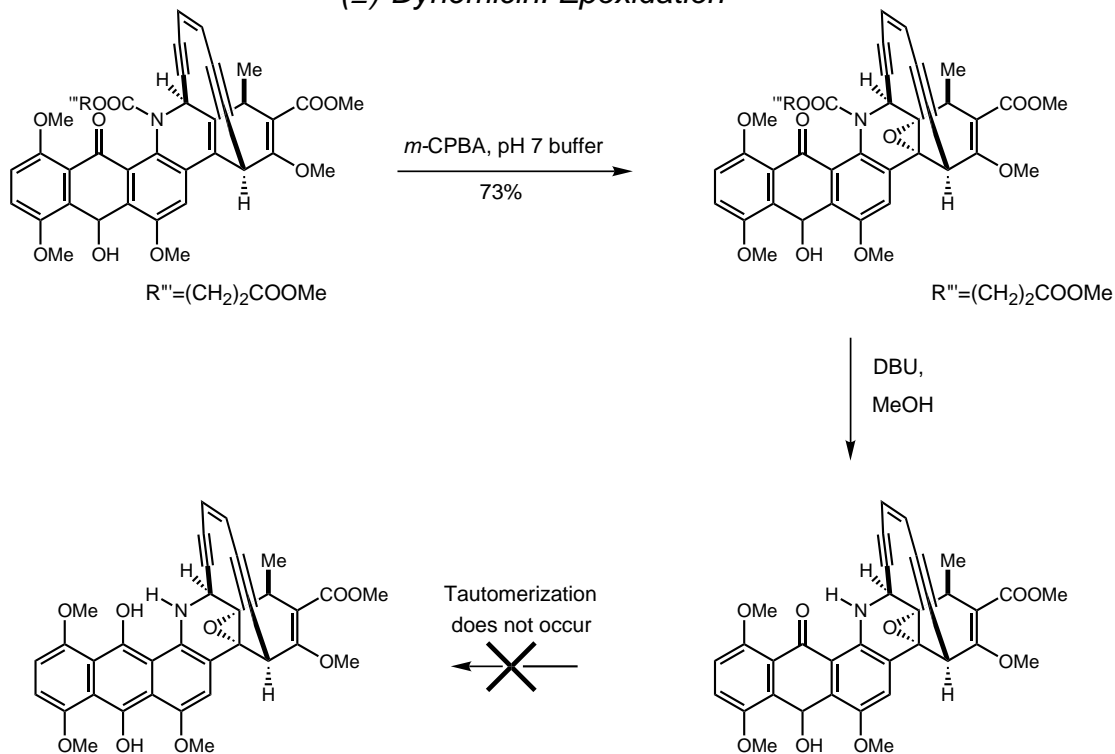
(±)-Dynemicin: A Ring Functionalization



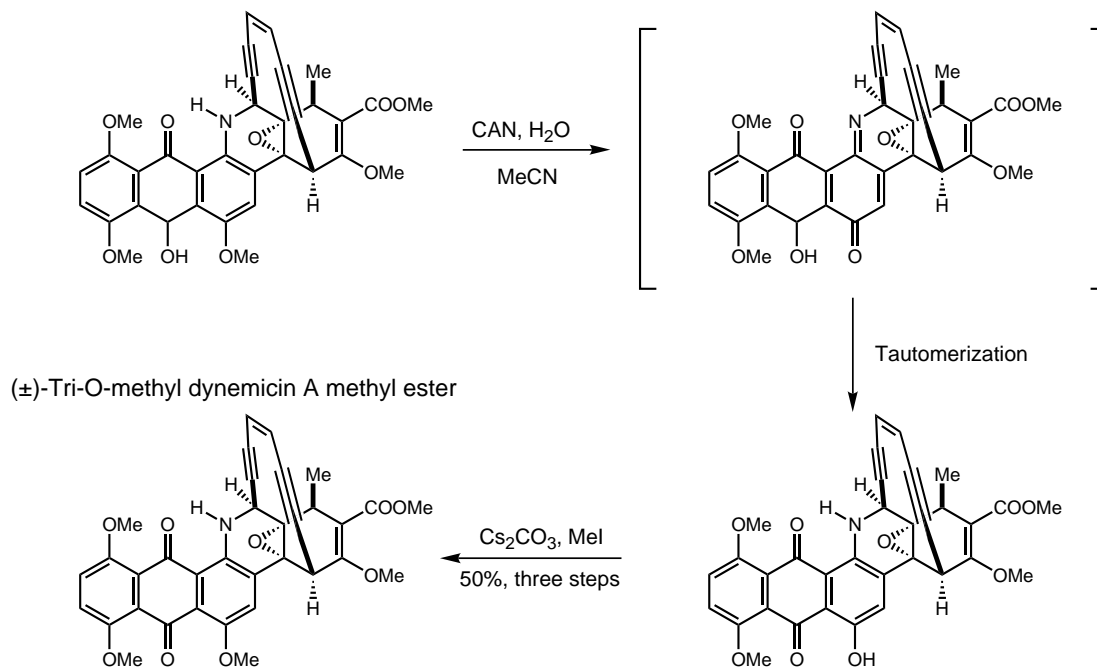
(±)-Dynemicin: DE Ring Appendage



(±)-Dynemicin: Epoxidation



(±)-Dynemicin: Endgame

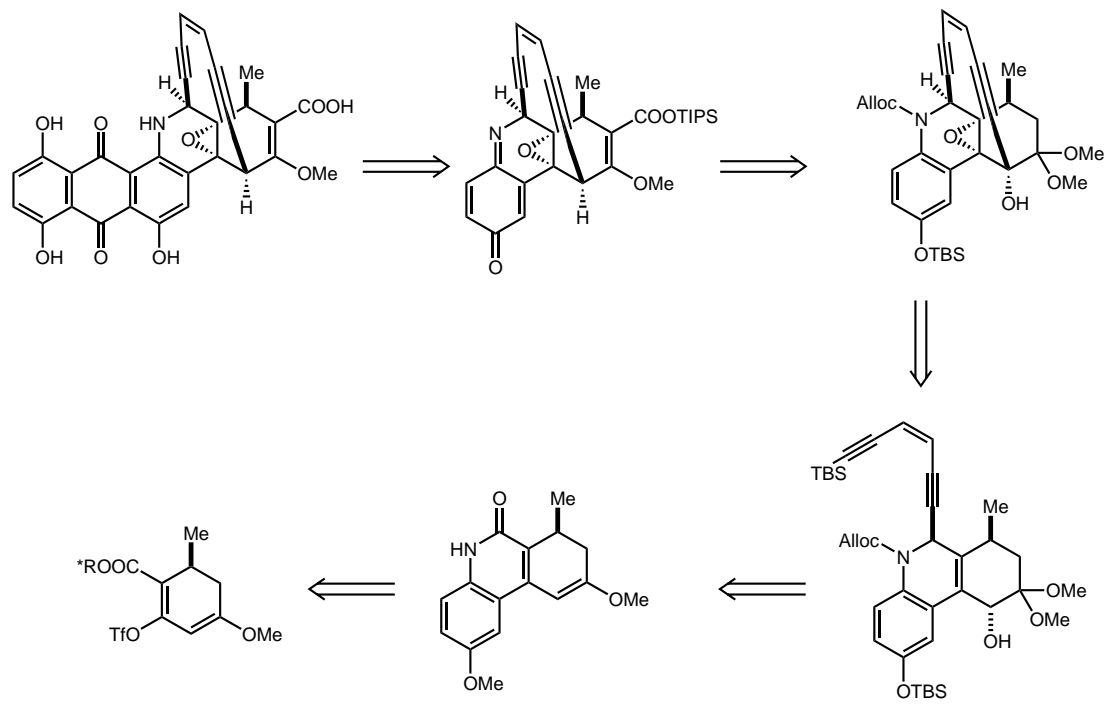


Schreiber, S. L. *et al. J. Am. Chem. Soc.* **1990**, 112, 7410.

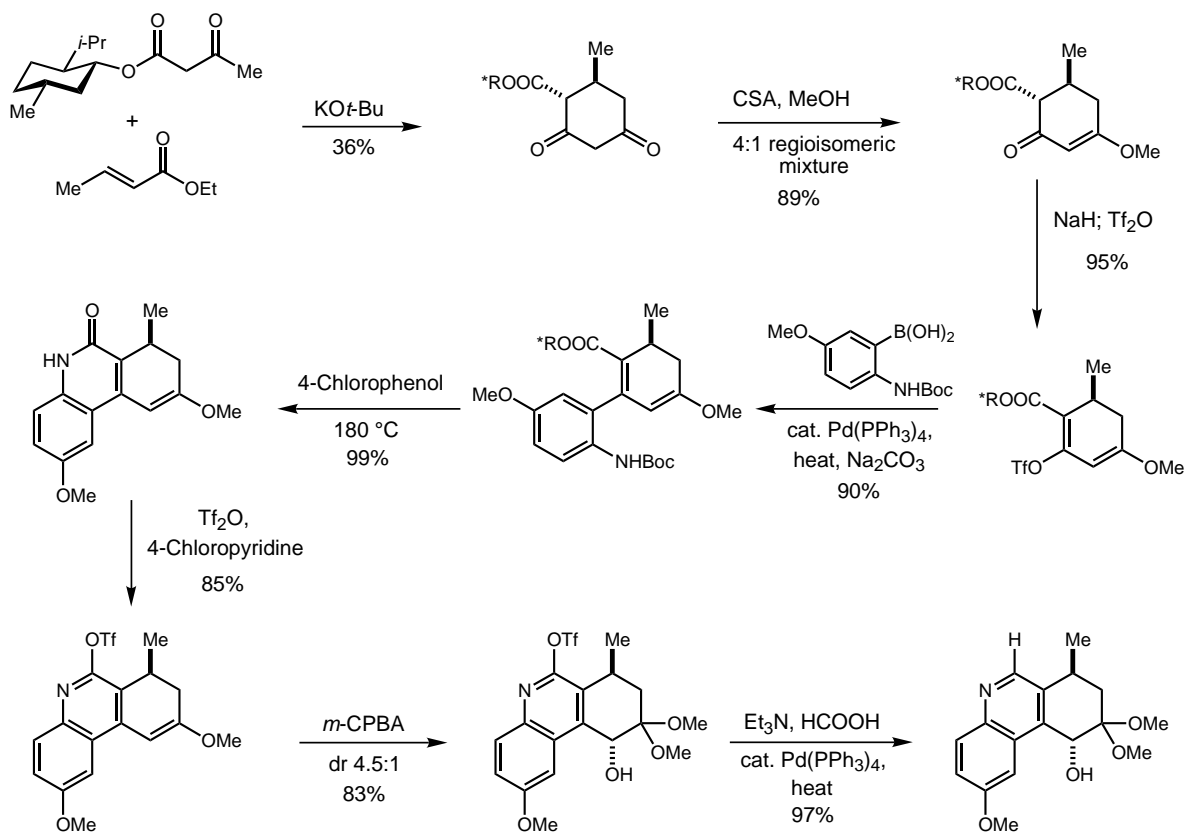
Schreiber, S. L. *et al. J. Am. Chem. Soc.* **1992**, 114, 5898.

Schreiber, S. L.; *et al. J. Am. Chem. Soc.* **1993**, 115, 10378.

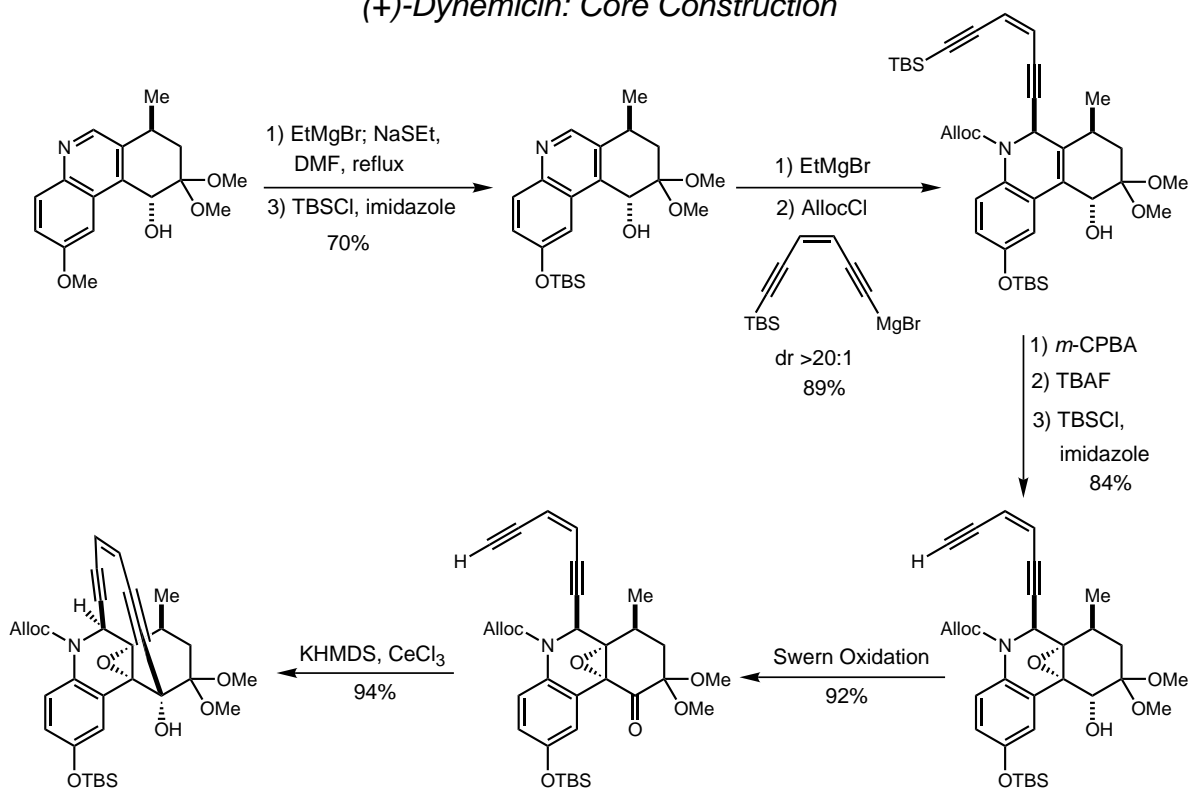
(+)-*Dynemicin* Retrosynthesis: Myers



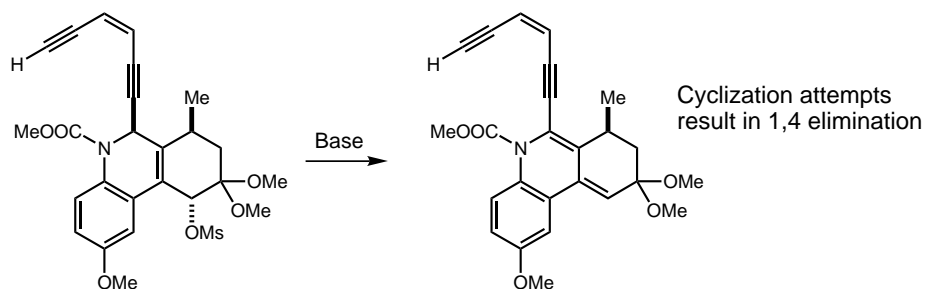
(+)-*Dynemicin*: Quinoline Construction



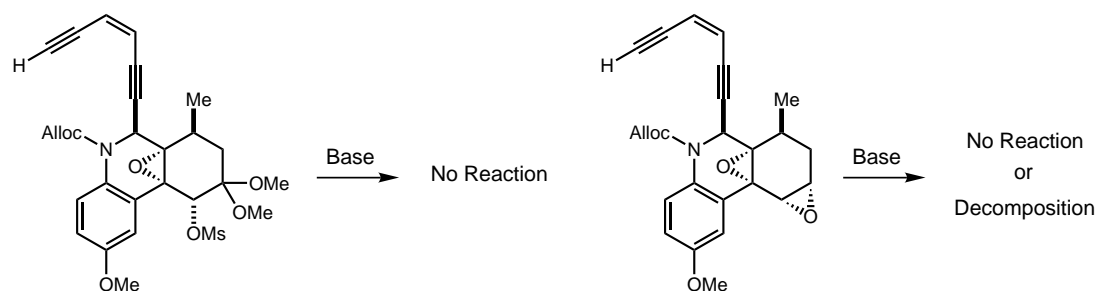
(+)-Dynemicin: Core Construction



(+)-Dynemicin: Alternate Coupling Strategies



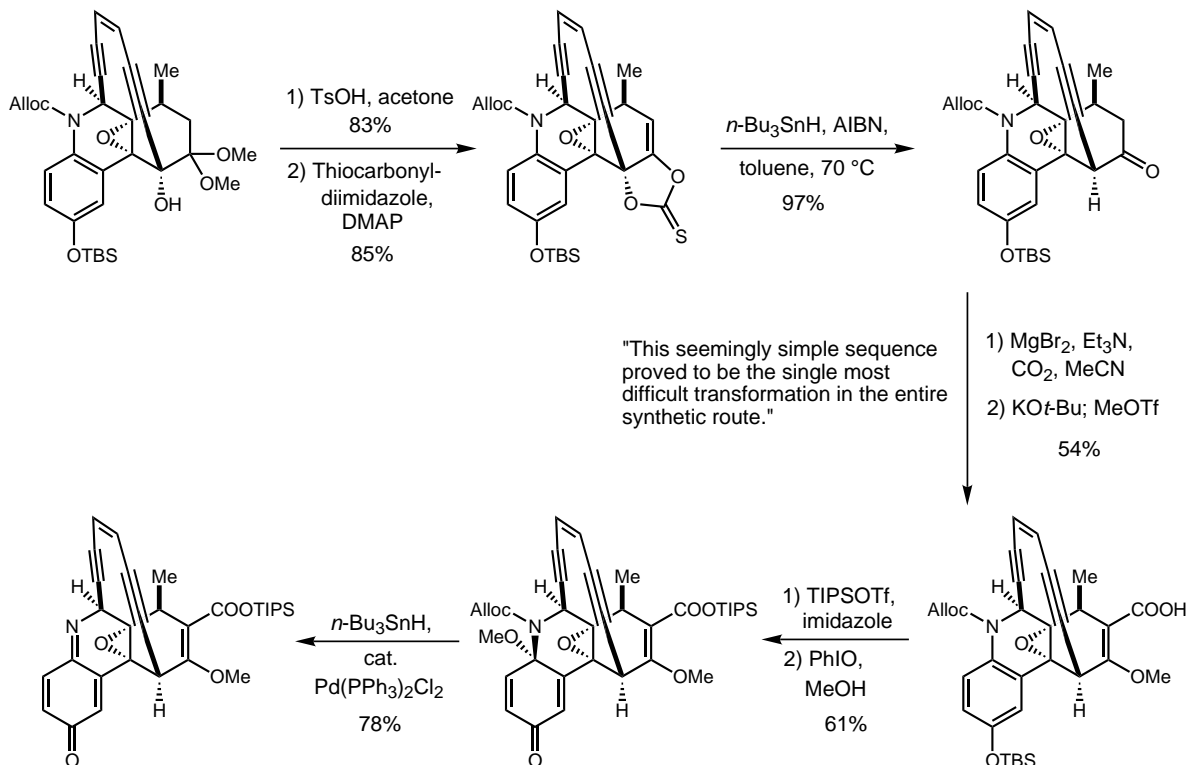
Installation of the epoxide could solve this problem...



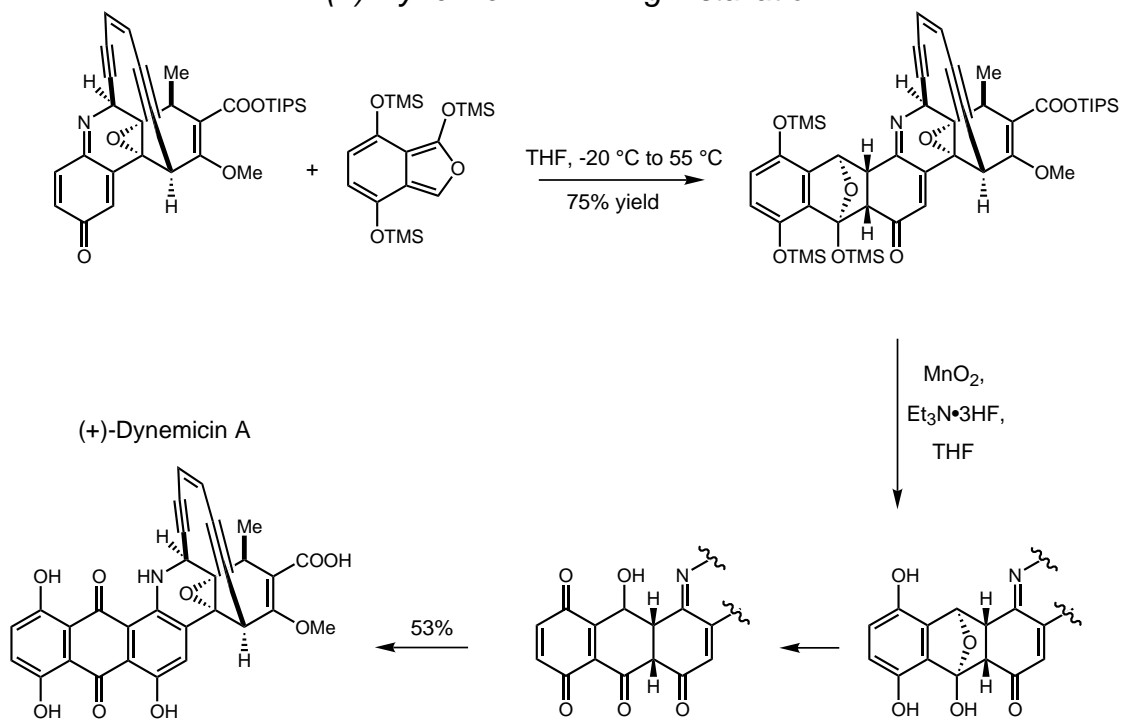
The corresponding triflate could not be prepared.

...but a suitable electrophilic coupling partner could not be accessed.

(+)-Dynemicin: A Ring Functionalization



(+)-Dynemicin: DE Ring Installation

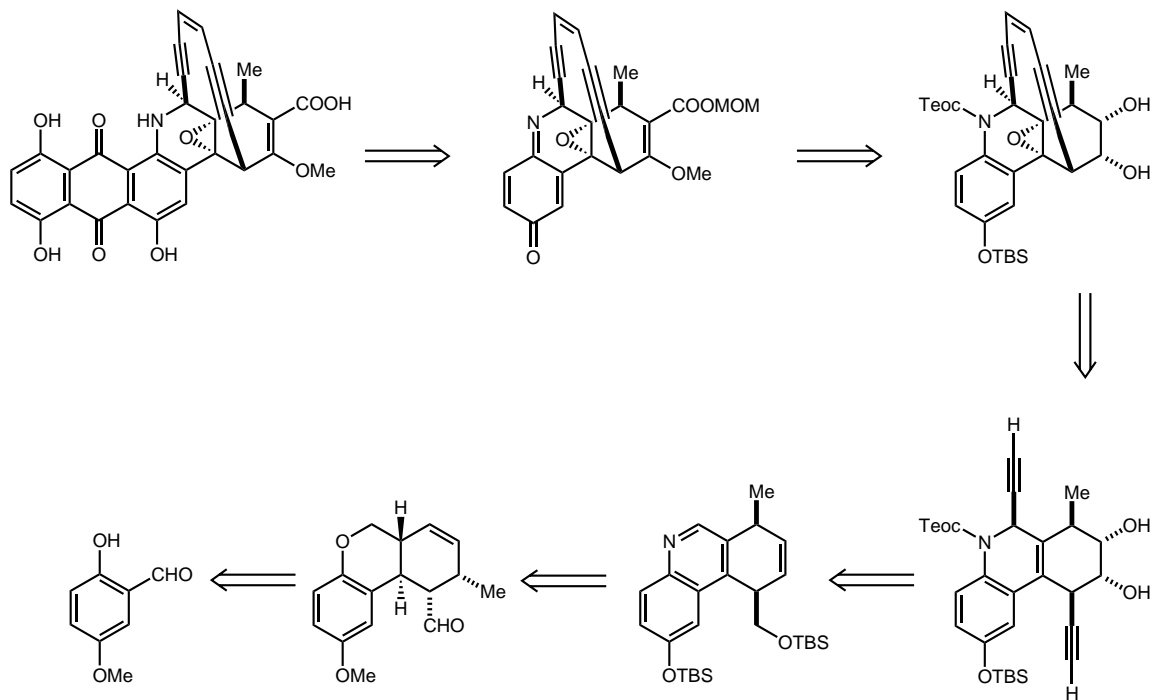


Myers, A. G. *et al.* *J. Am. Chem. Soc.* **1994**, *116*, 11556.

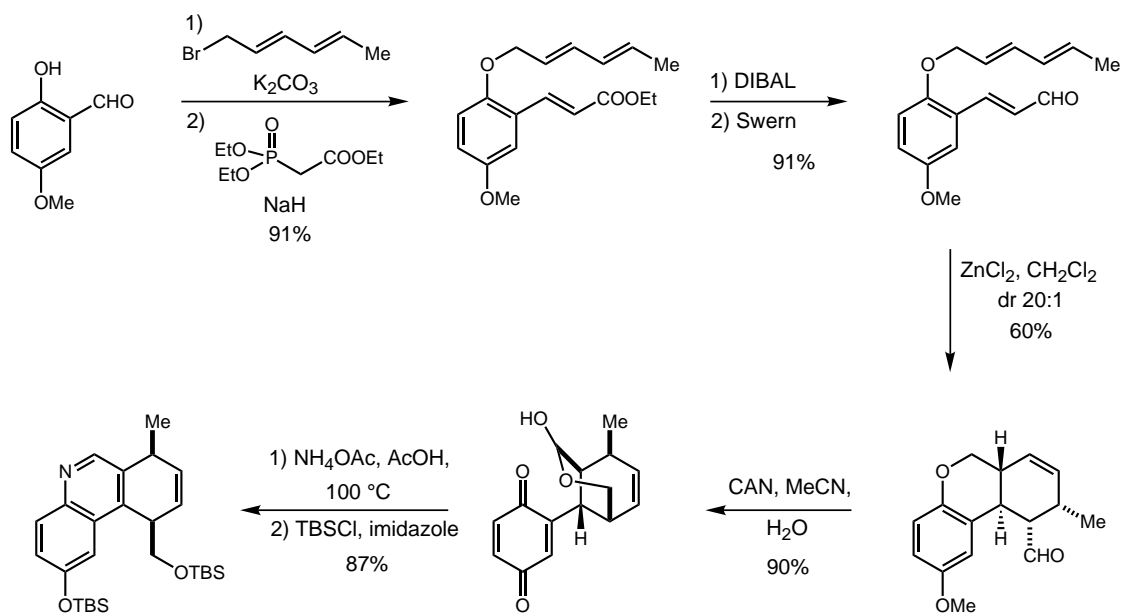
Myers, A. G. *et al.* *Chem. Biol.* **1995**, *2*, 33.

Myers, A. G. *et al.* *J. Am. Chem. Soc.* **1997**, *119*, 6072.

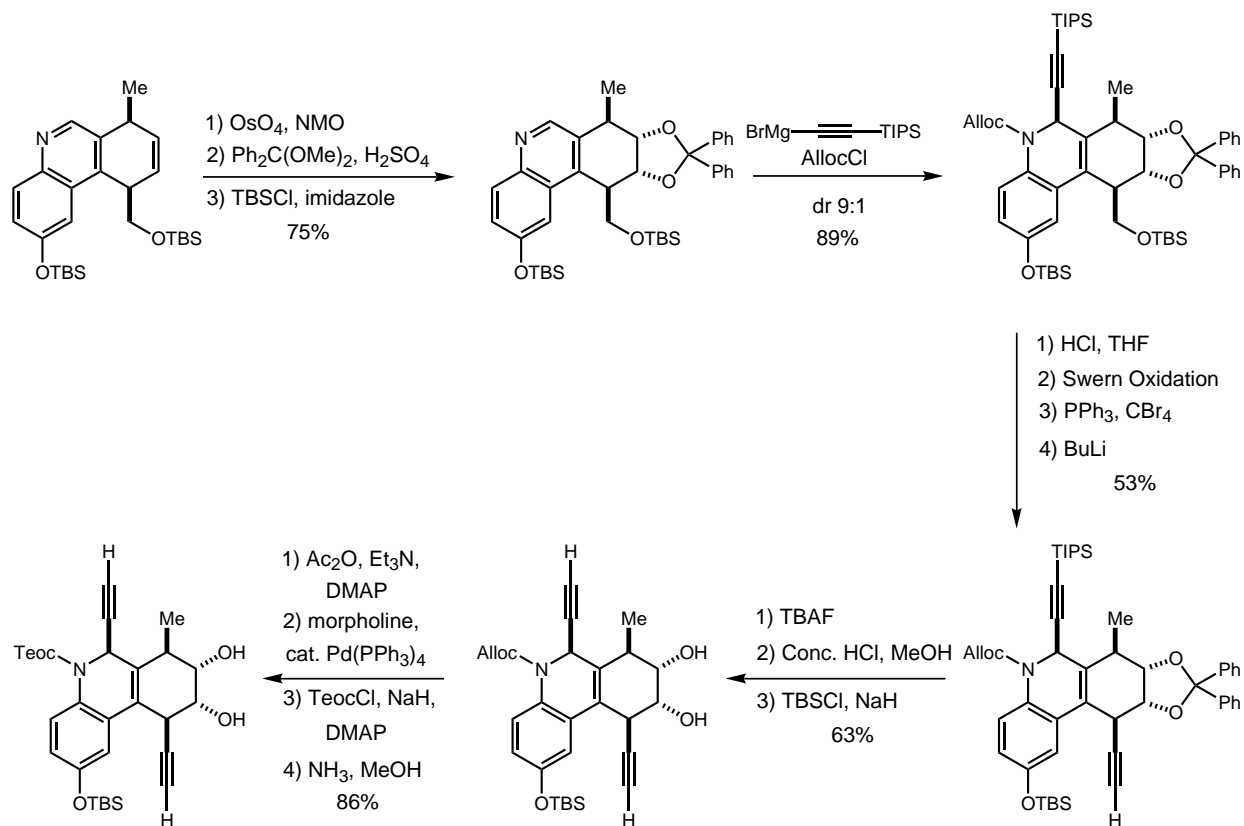
(±)-Dynemicin Retrosynthesis: Danishefsky



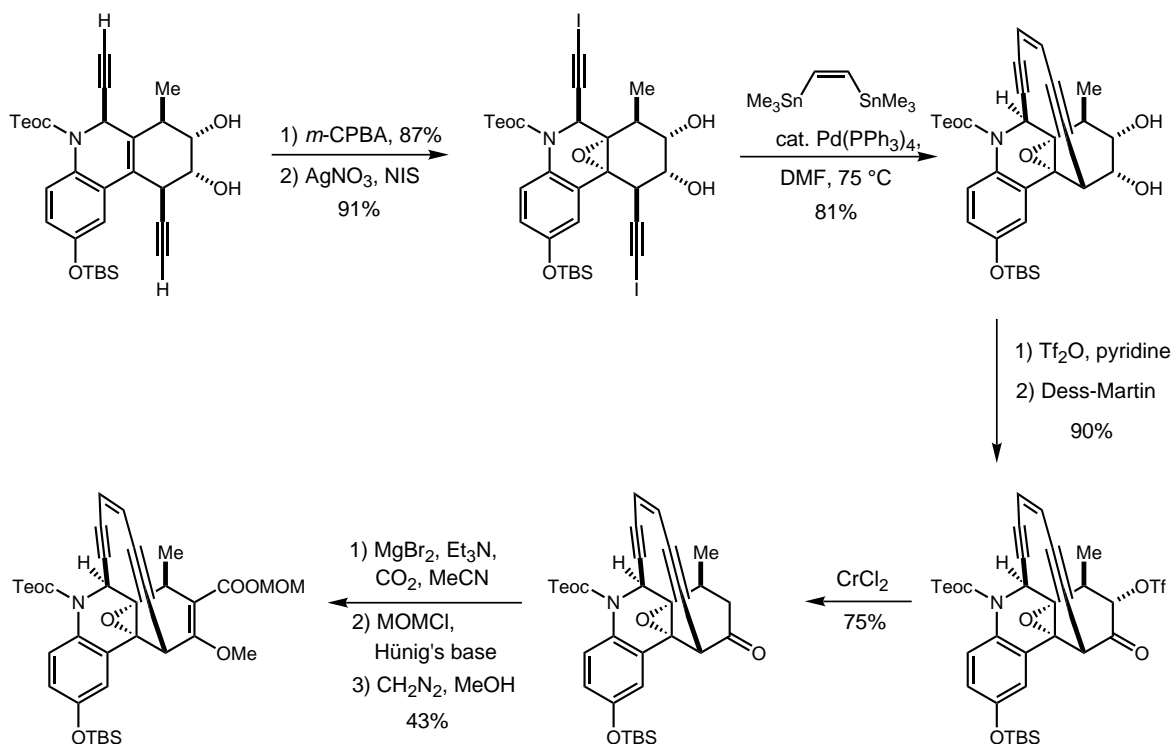
(±)-Dynemicin: Intramolecular Diels-Alder



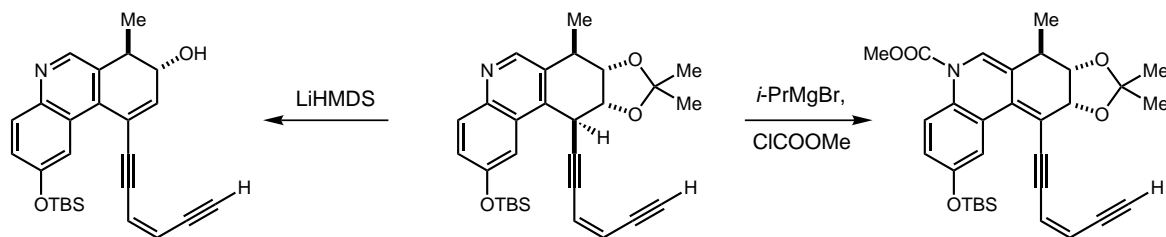
(±)-Dynemicin: Diyne Construction



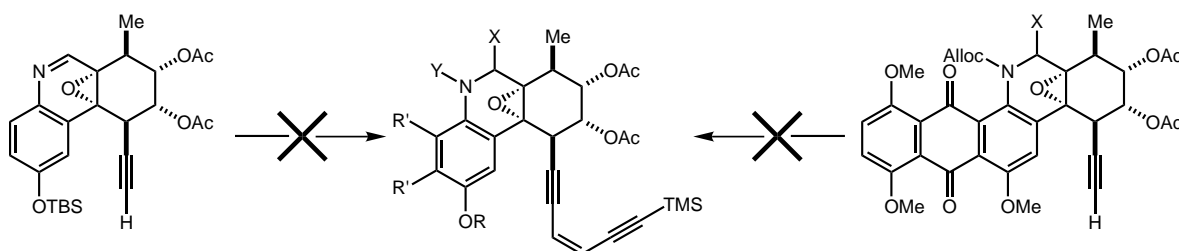
(±)-Dynemicin: Core Construction



(±)-Dynemicin: Alternate Coupling Strategies

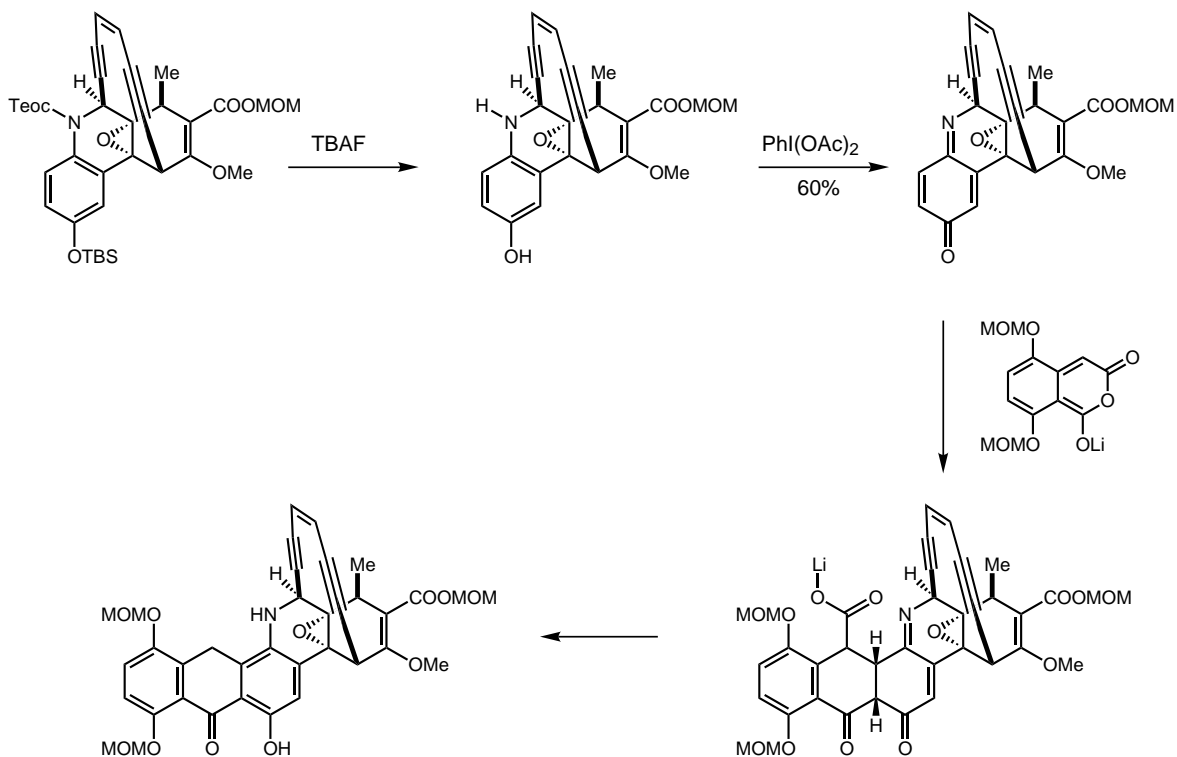


Once again (c.f. Myers) kinetic acidity of the propargylic proton proved to be problematic.

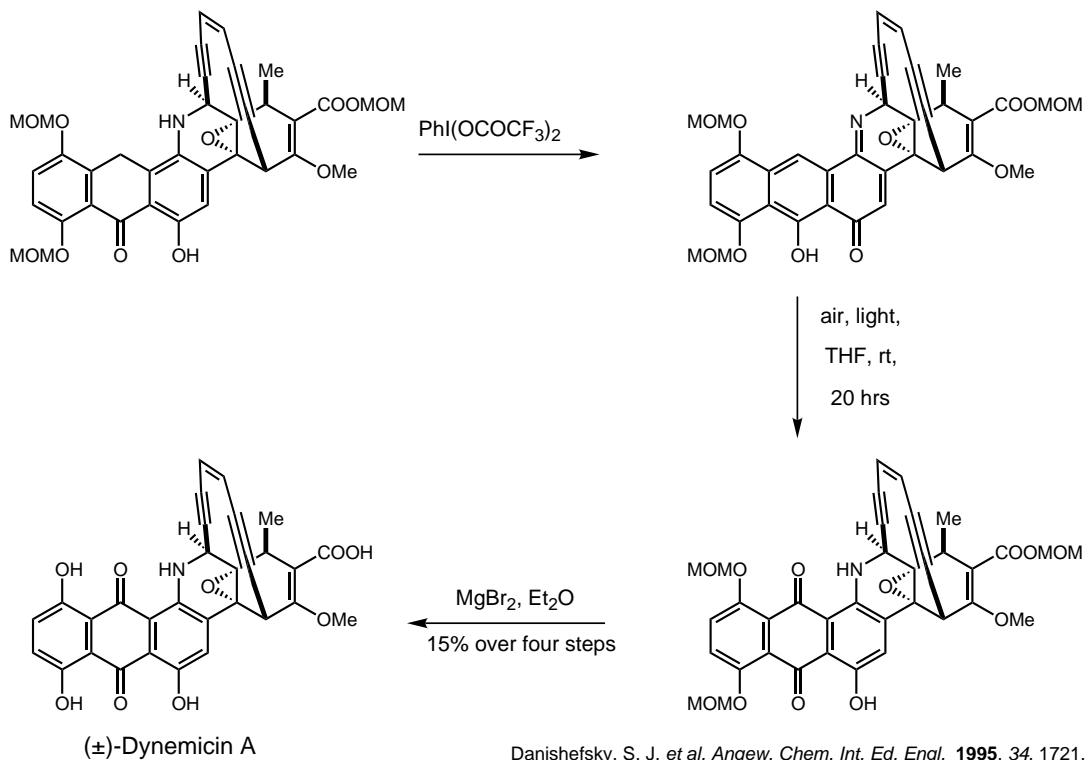


Epoxidation of the olefin was again investigated as a solution, but elaboration to the enediyne cyclization precursor was not possible from these intermediates.

(±)-Dynemicin: DE Ring Installation



(±)-Dynemicin: Endgame

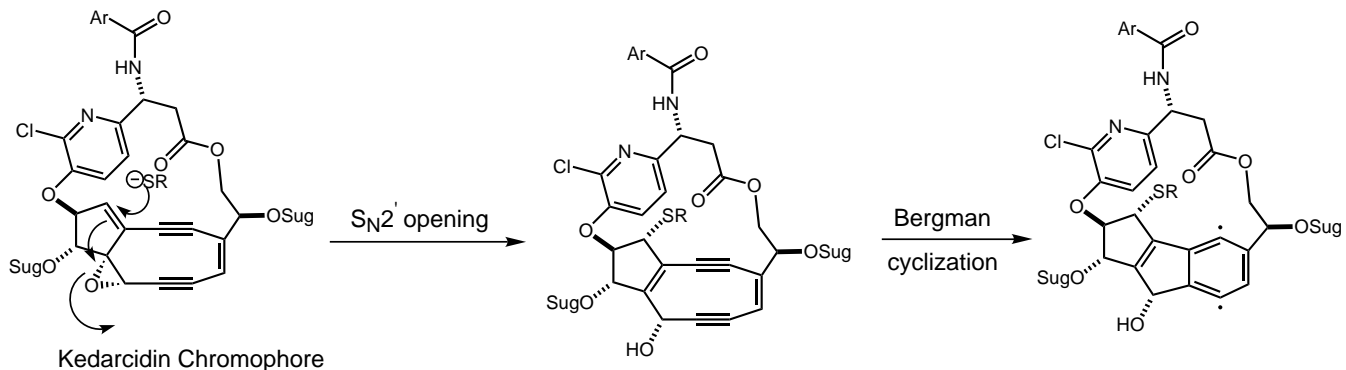
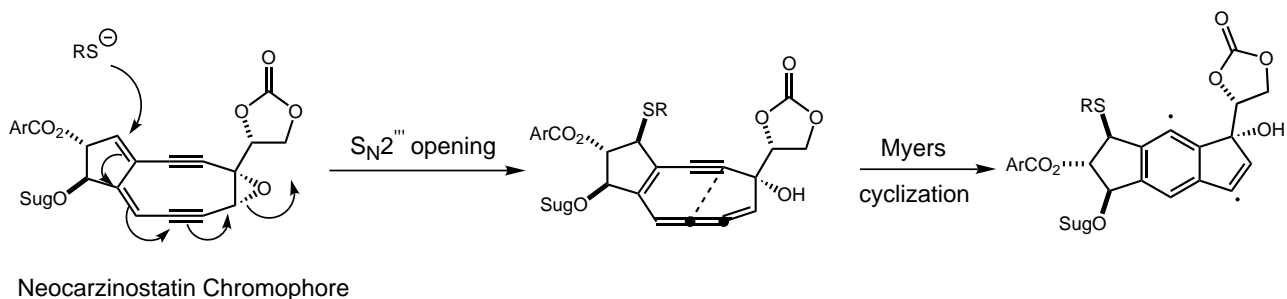


Danishefsky, S. J. *et al. Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1721.

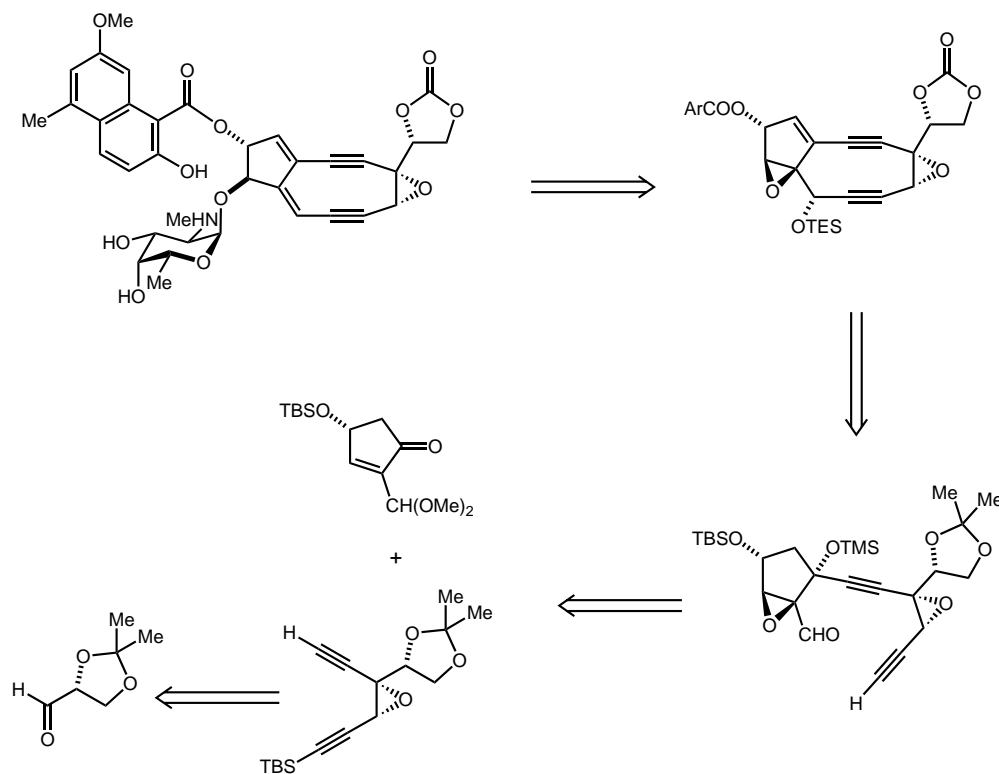
Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1996**, 118, 9509.

Danishefsky, S. J. *et al. J. Org. Chem.* **1996**, 61, 16.

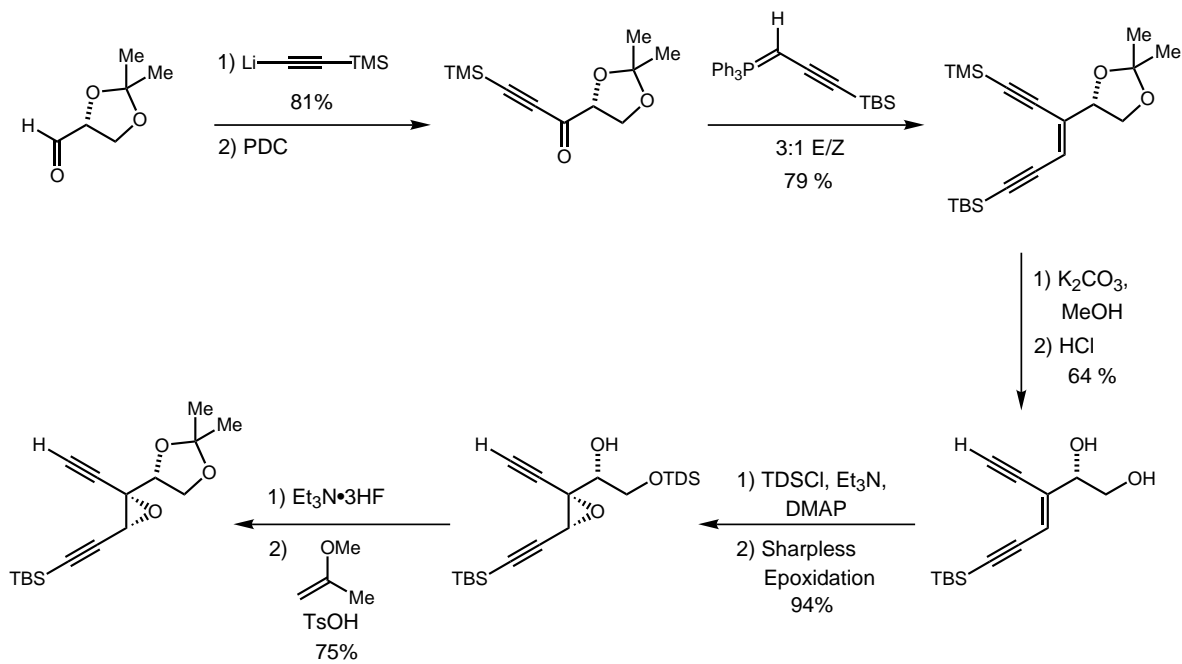
Neocarzinostatin/Kedarcidin Mechanism of Action



(+)-Neocarzinostatin Chromophore Retrosynthesis

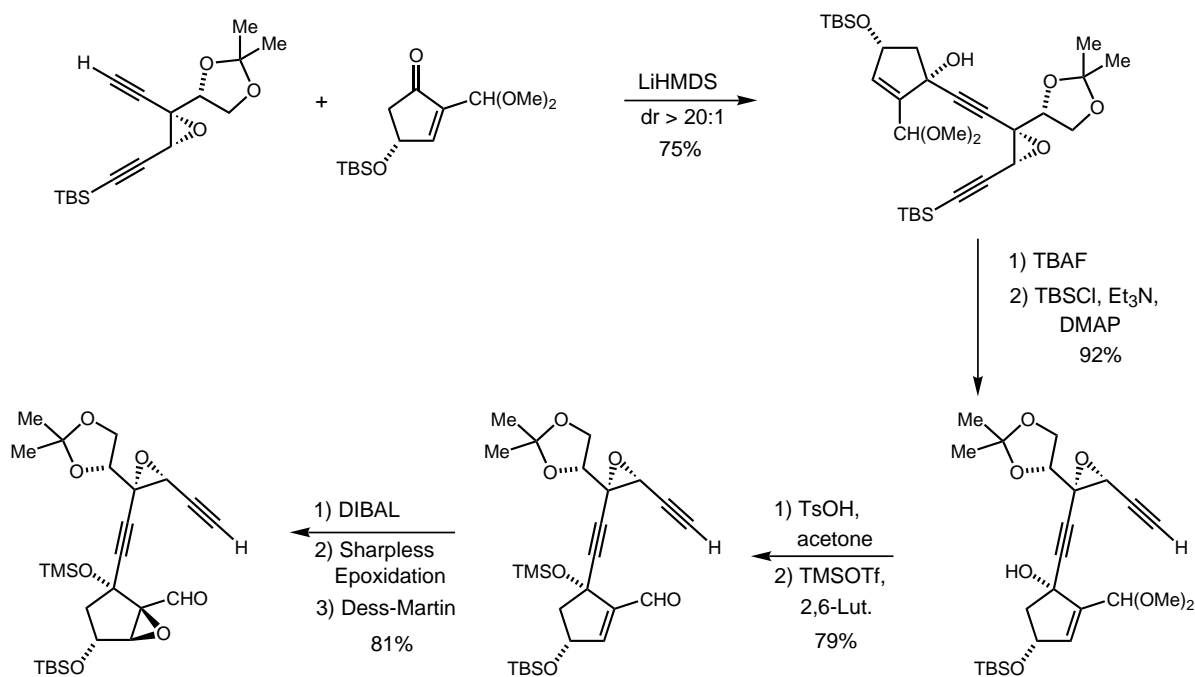


(+)-Neocarzinostatin: Epoxy Diyne



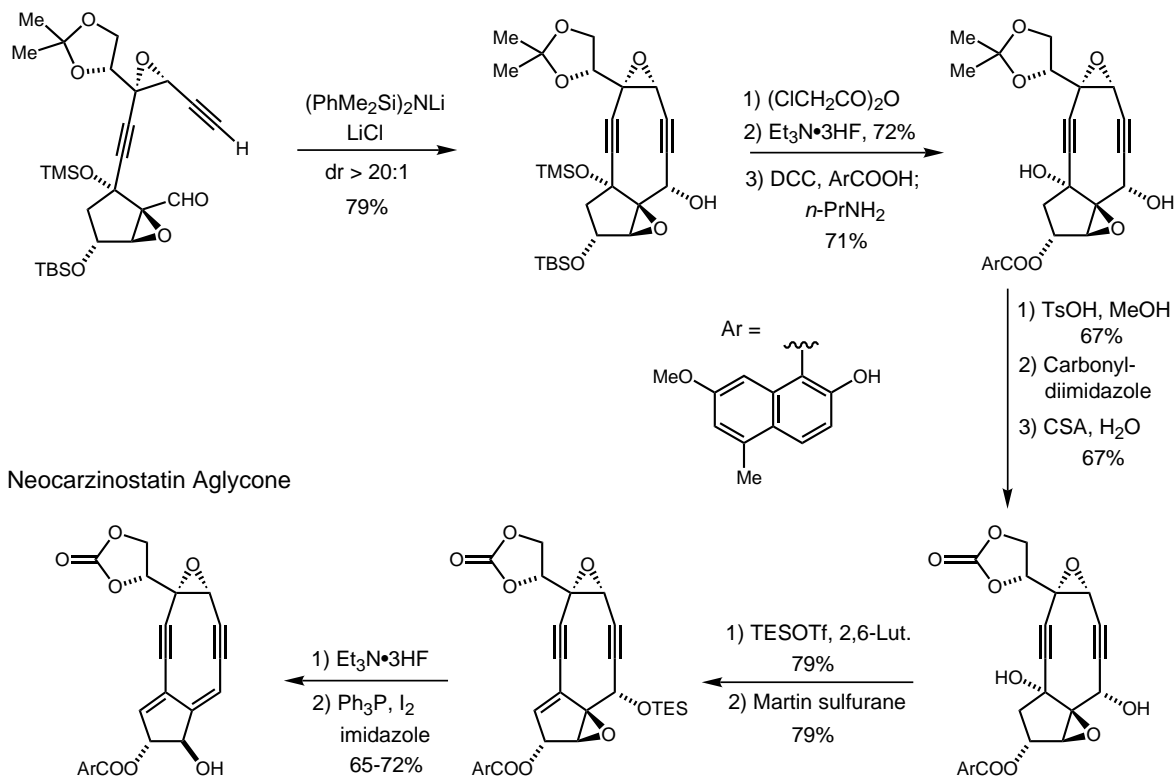
Myers, A. G. *et al.* *J. Am. Chem. Soc.* **1996**, *118*, 10006.

(+)-Neocarzinostatin: Cyclization Precursor



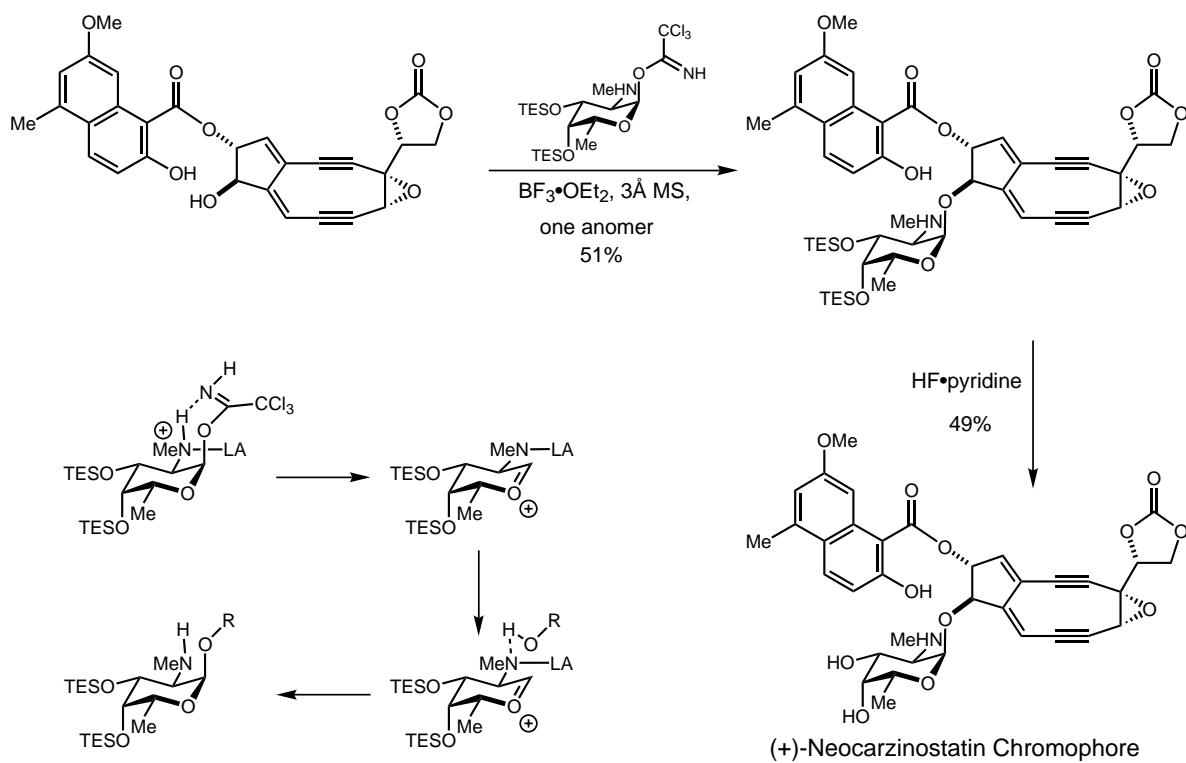
Myers, A. G. *et al. J. Am. Chem. Soc.* **1996**, *118*, 10006.

(+)-Neocarzinostatin Chromophore Aglycone



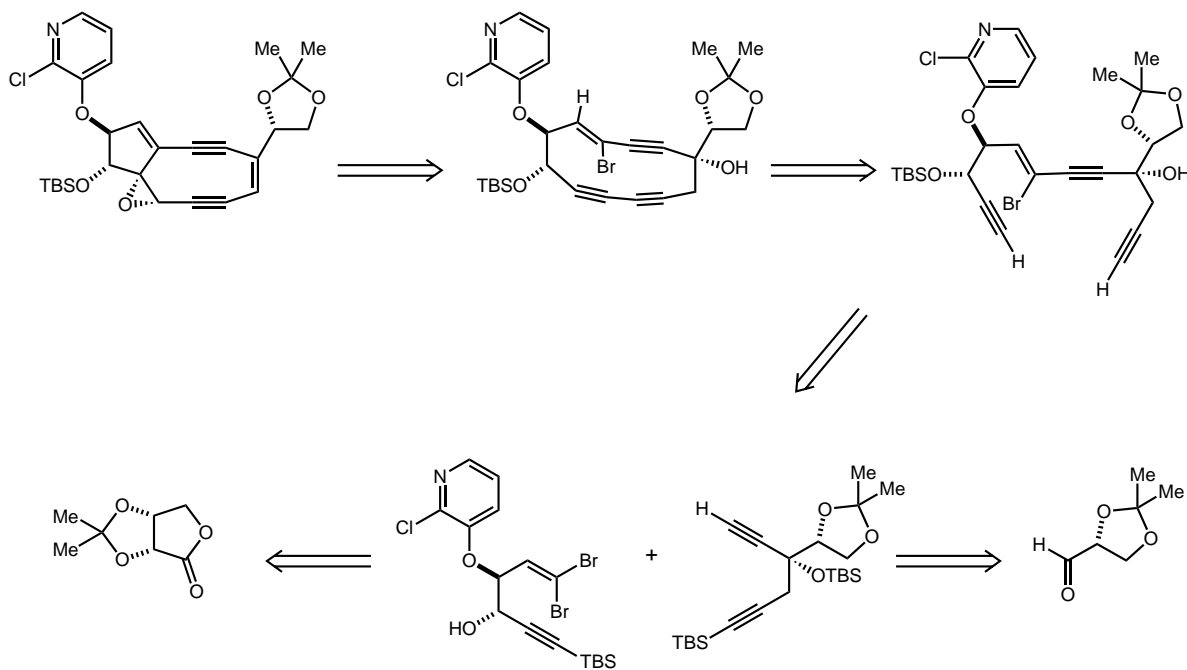
Myers, A. G. *et al. J. Am. Chem. Soc.* **1996**, *118*, 10006.

(+)-Neocarzinostatin Chromophore: Glycosylation



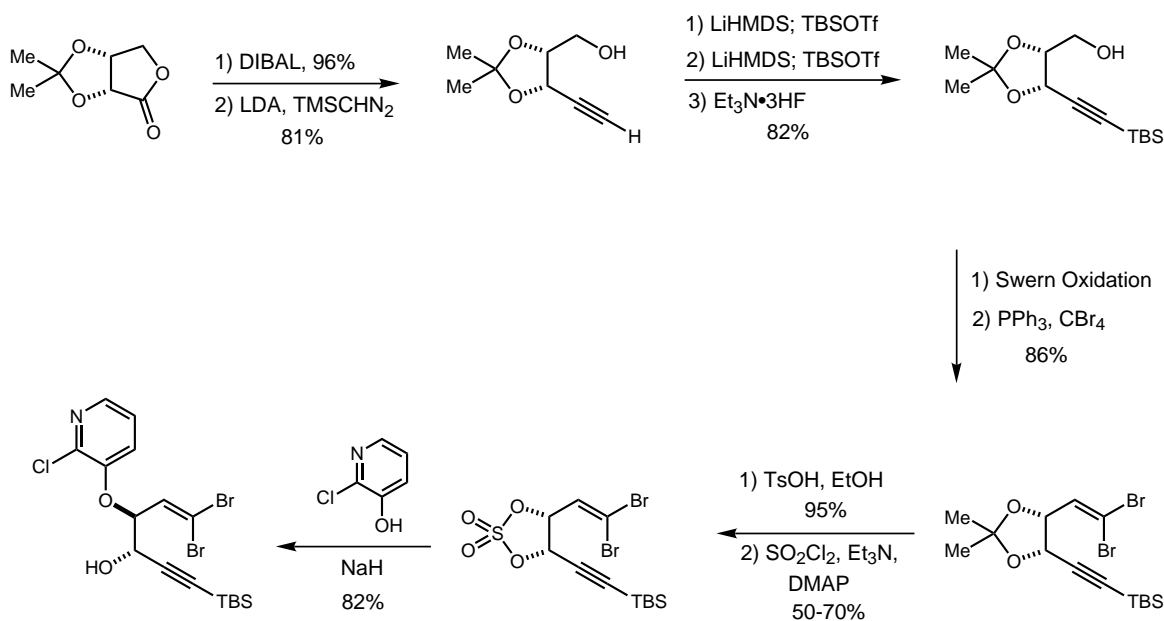
Myers, A. G. *et al.* *J. Am. Chem. Soc.* **1998**, 120, 5319.

Kedarcidin Core Retrosynthesis: Myers

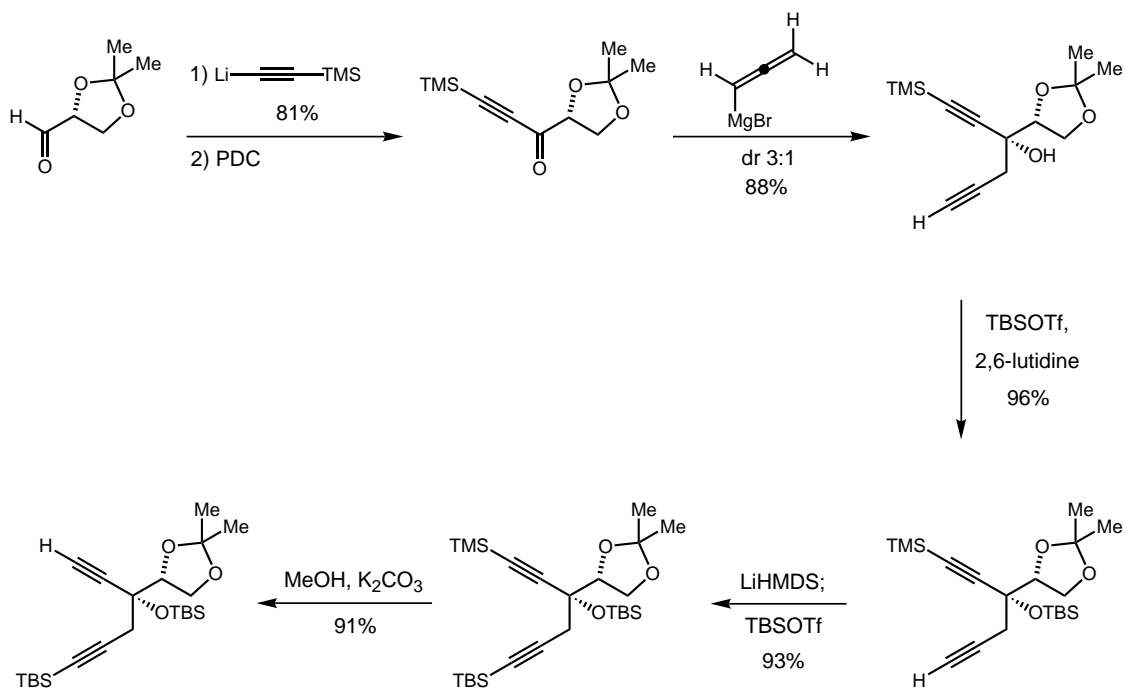


Myers, A. G. Goldberg, S. D. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 2732.

Kedarcidin: Vinyl Dibromide

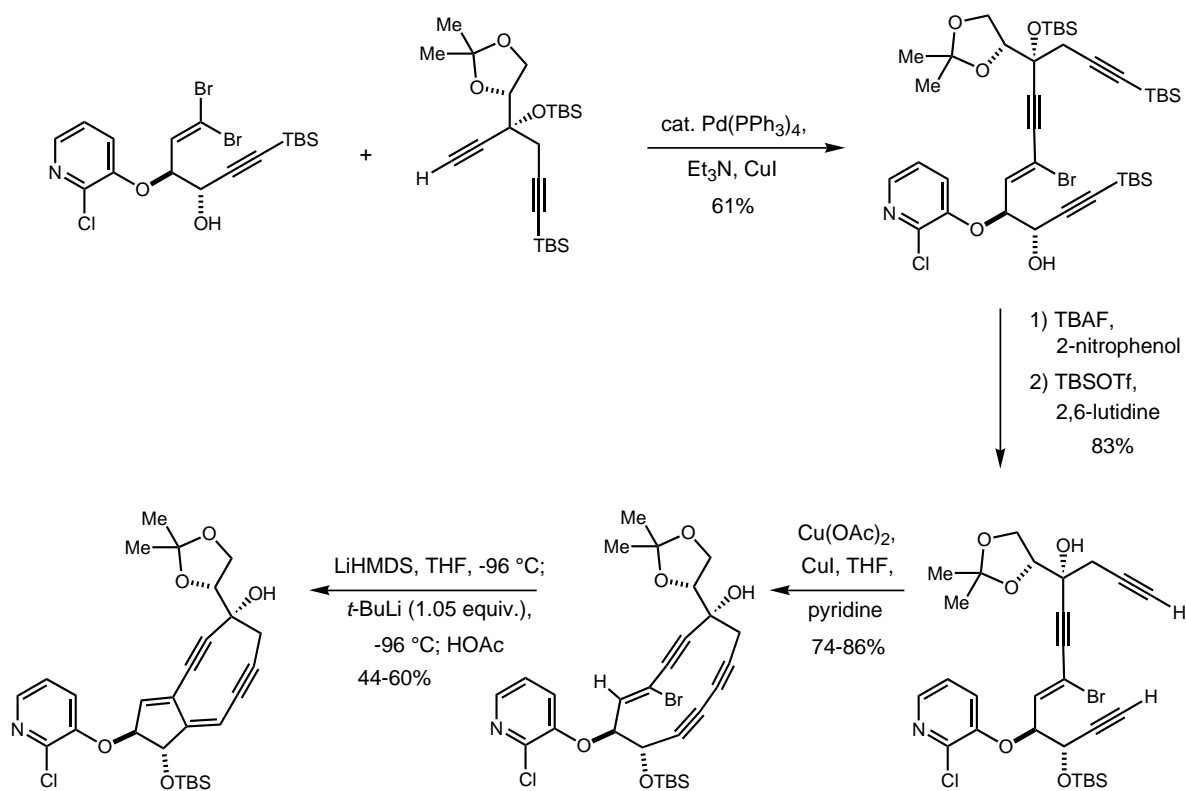


Kedarcidin: Diyne Construction



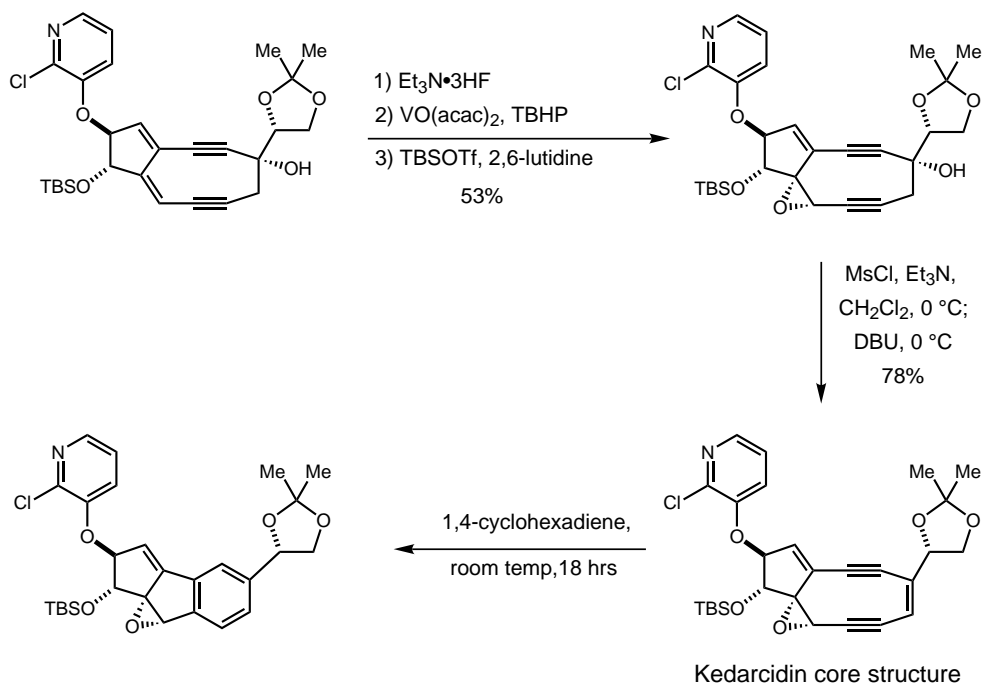
Goldberg, S. D. Synthesis of the Kedarcidin Core Structure by a Transannular Cyclization Pathway. Ph. D. thesis, Harvard University, Cambridge, MA, May 2000.

Kedarcidin: Transannular Cyclization



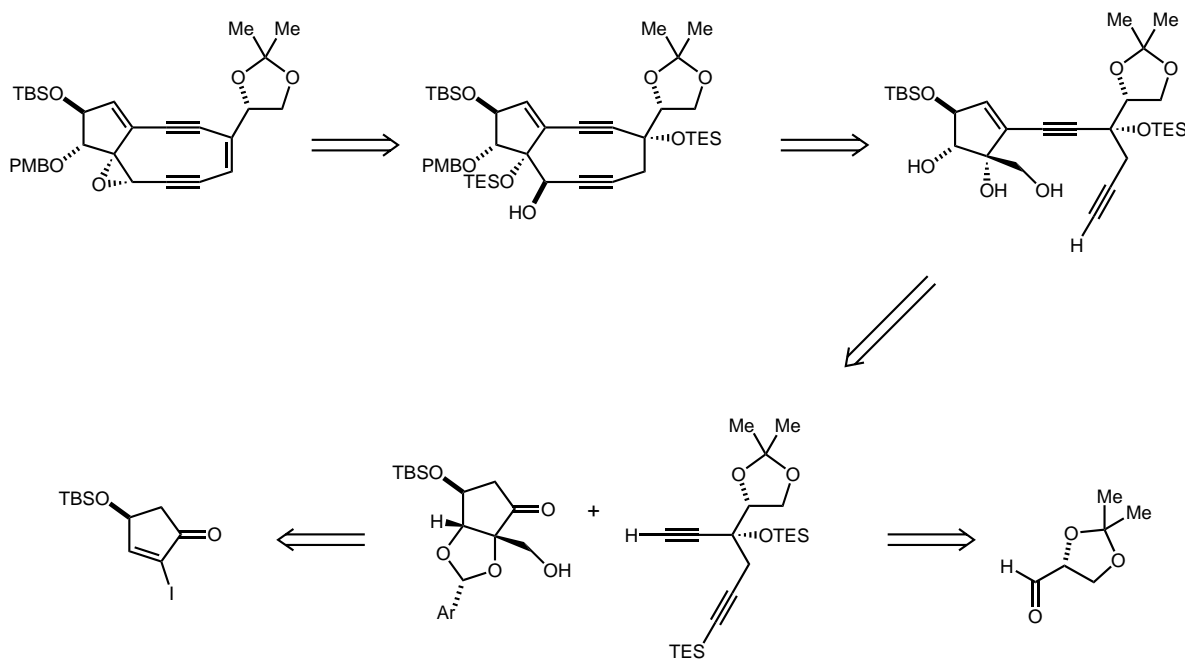
Myers, A. G. Goldberg, S. D. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2732.

Kedarcidin Core: Endgame

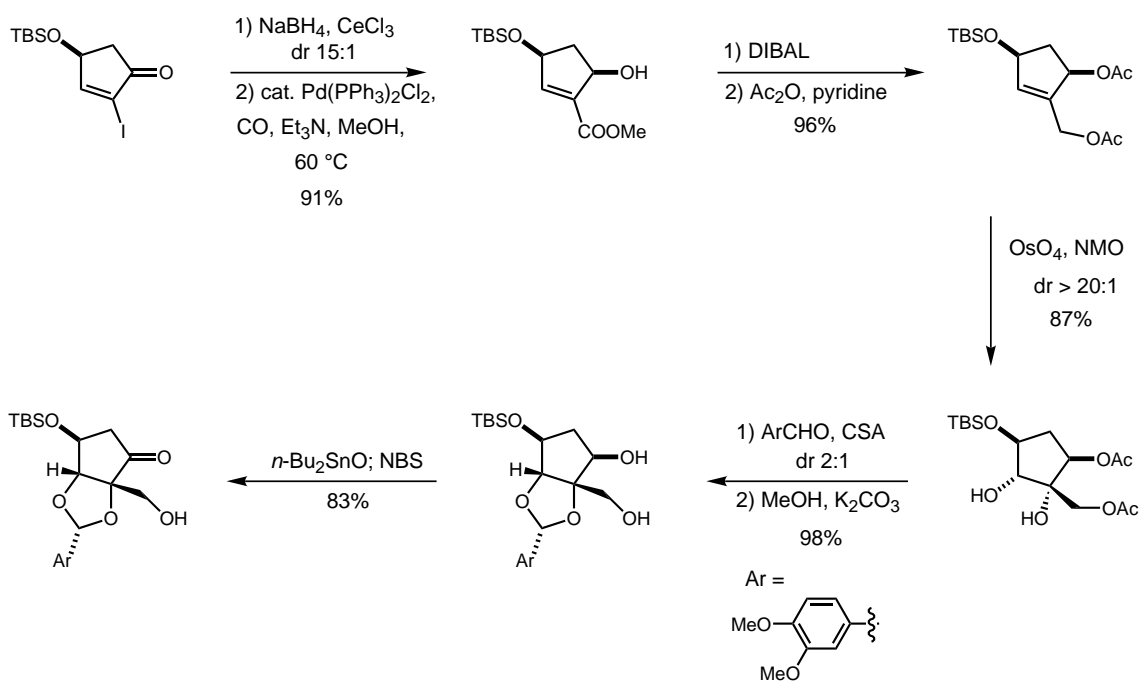


Myers, A. G. Goldberg, S. D. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2732.

Kedarcidin Core Retrosynthesis: Hirama

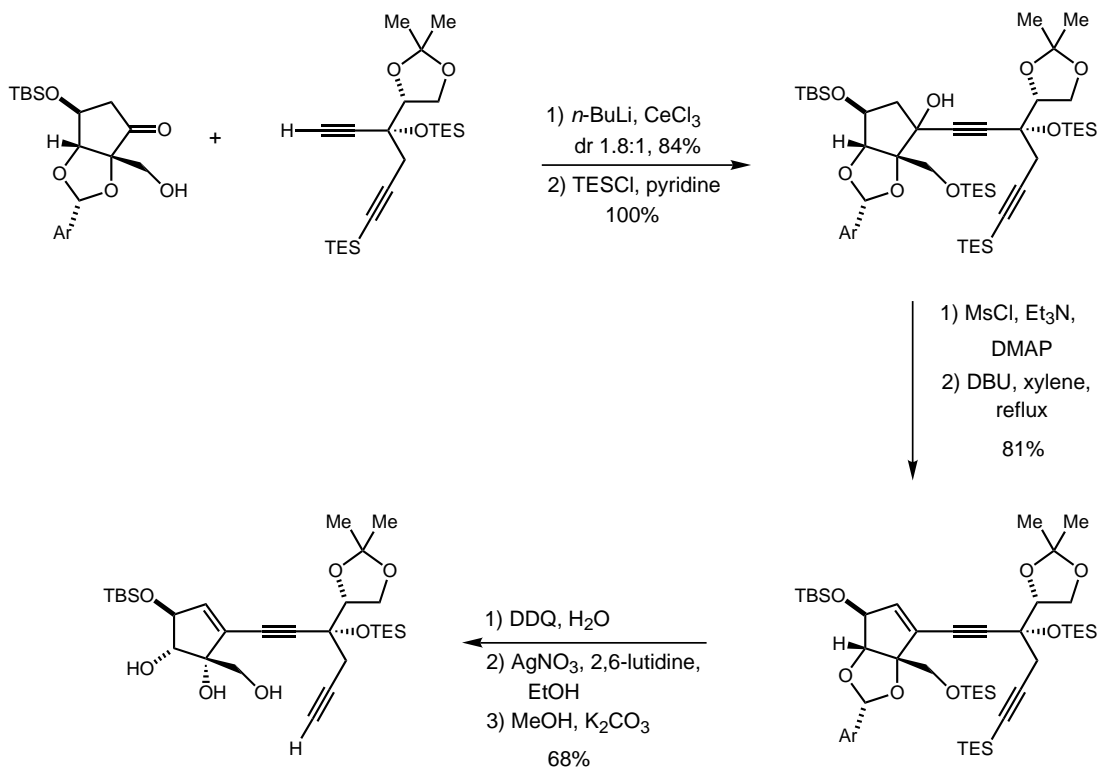


Kedarcidin: Cyclopentanone Construction



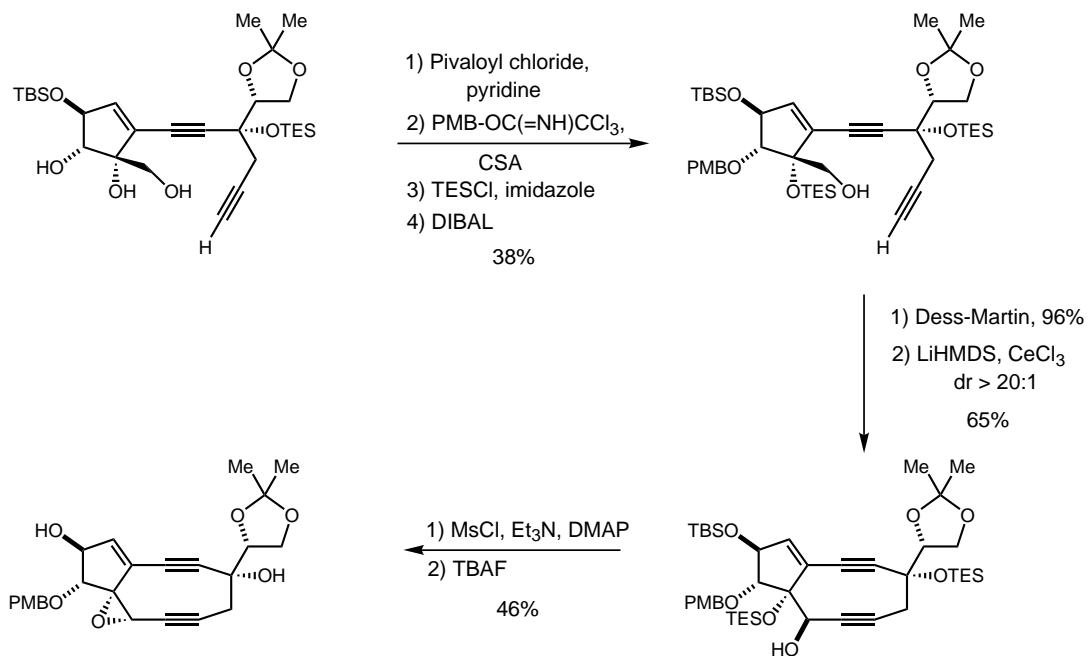
Hirama, M. *et al.* *J. Am. Chem. Soc.* **1995**, 117, 8875.
 Hirama, M. *et al.* *Synlett* **1997**, 250.

Kedarcidin: Fragment Coupling



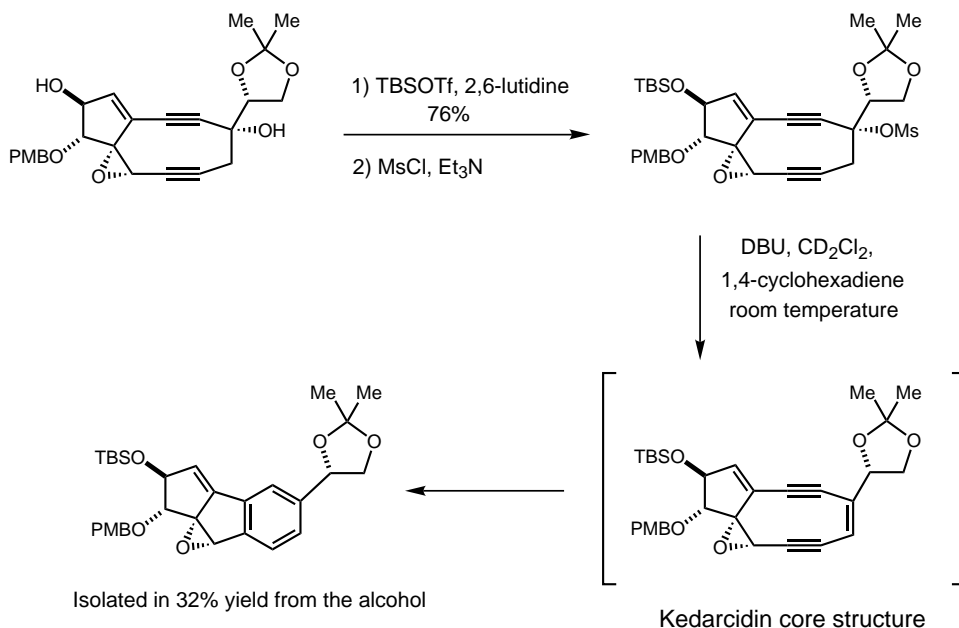
Hirama, M. *et al.* *J. Am. Chem. Soc.* **1995**, 117, 8875.
Hirama, M. *et al.* *Synlett* **1997**, 250.

Kedarcidin: Cyclization



Hirama, M. *et al.* *J. Am. Chem. Soc.* **1995**, 117, 8875.
Hirama, M. *et al.* *Synlett* **1997**, 250.

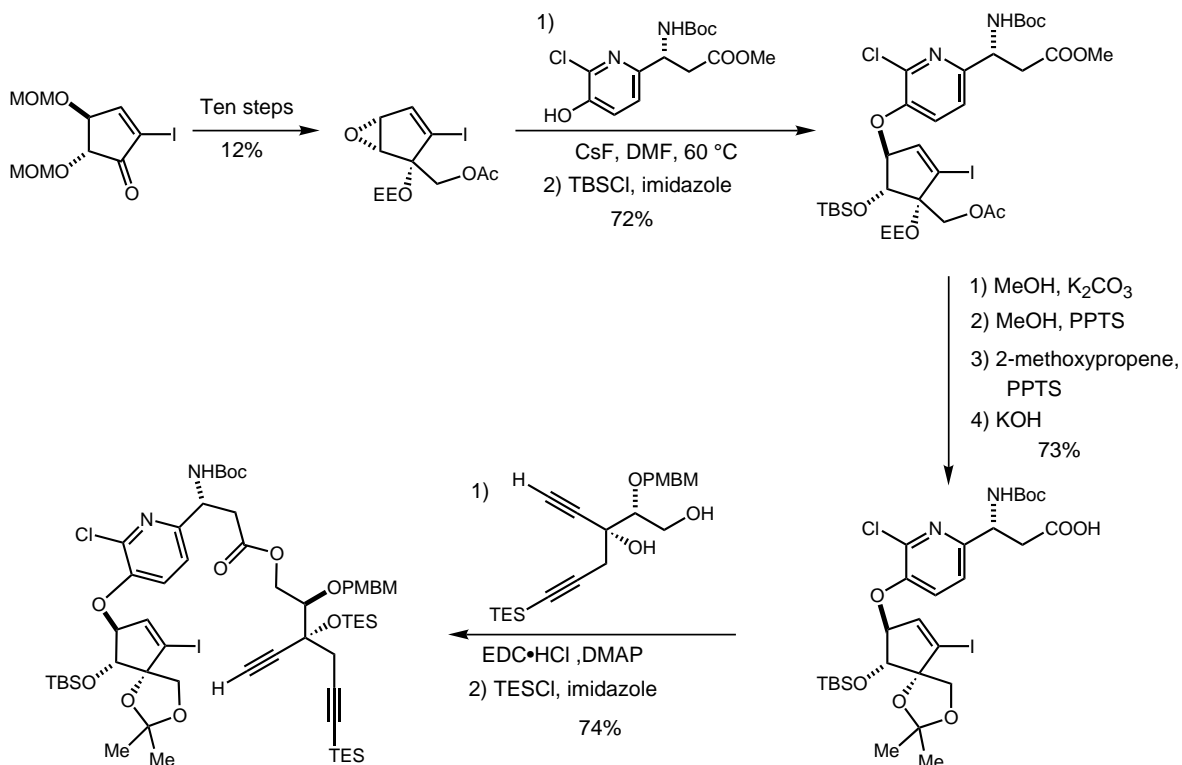
Kedarcidin Core: Endgame



This molecule has a half life of approximately 30 minutes in dichloromethane at room temperature.

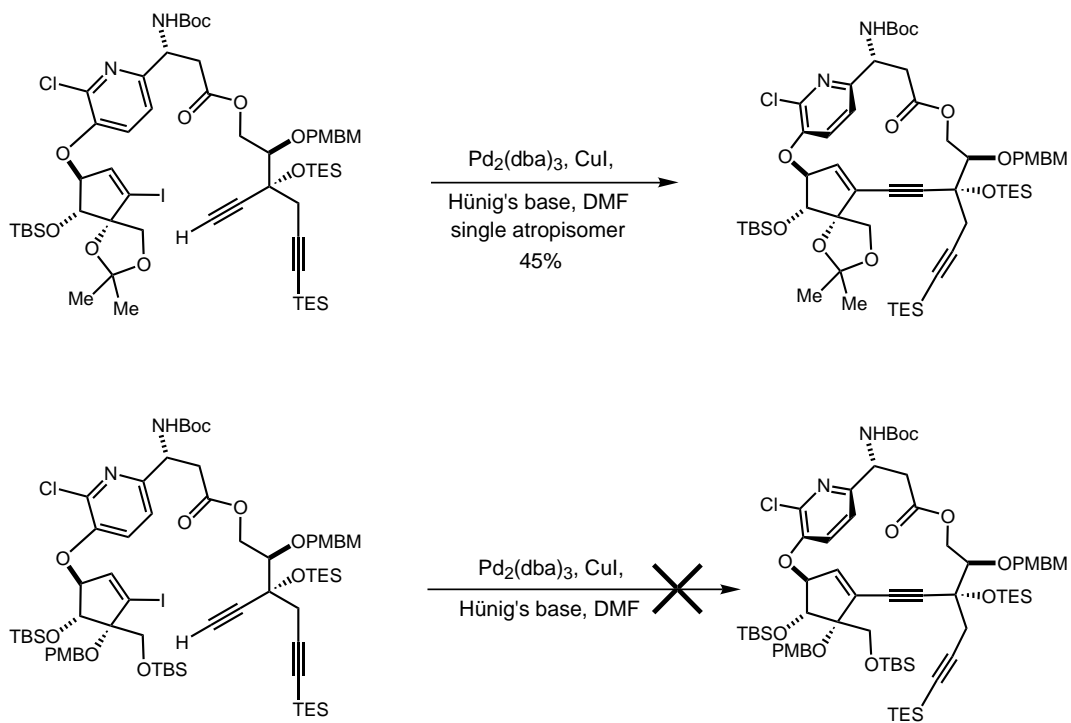
Hirama, M. *et al.* *J. Am. Chem. Soc.* **1995**, *117*, 8875.
Hirama, M. *et al.* *Synlett* **1997**, 250.

Kedarcidin Core: Macrocycle Precursor



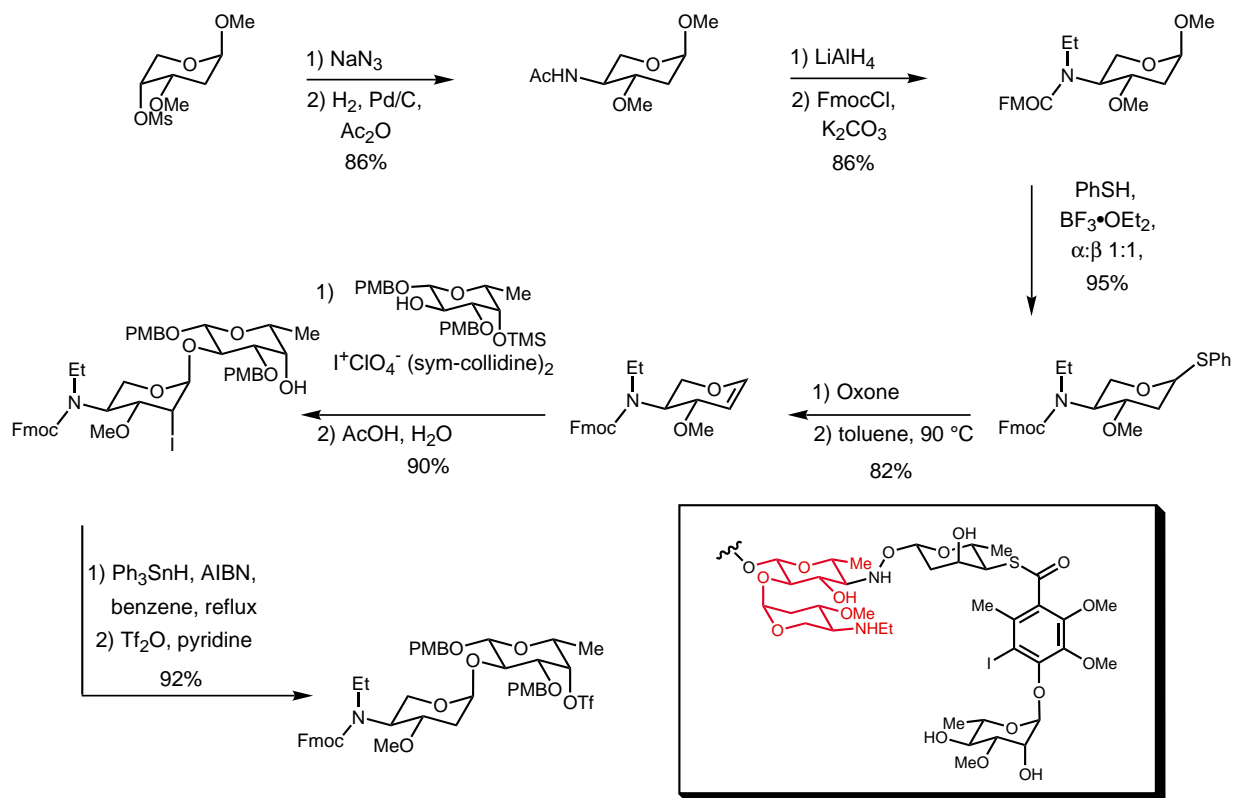
Hirama, M. *et al.* *Tetrahedron Lett.* **1999**, *40*, 8281.

Kedarcidin Core: Atropselective Macrocyclization



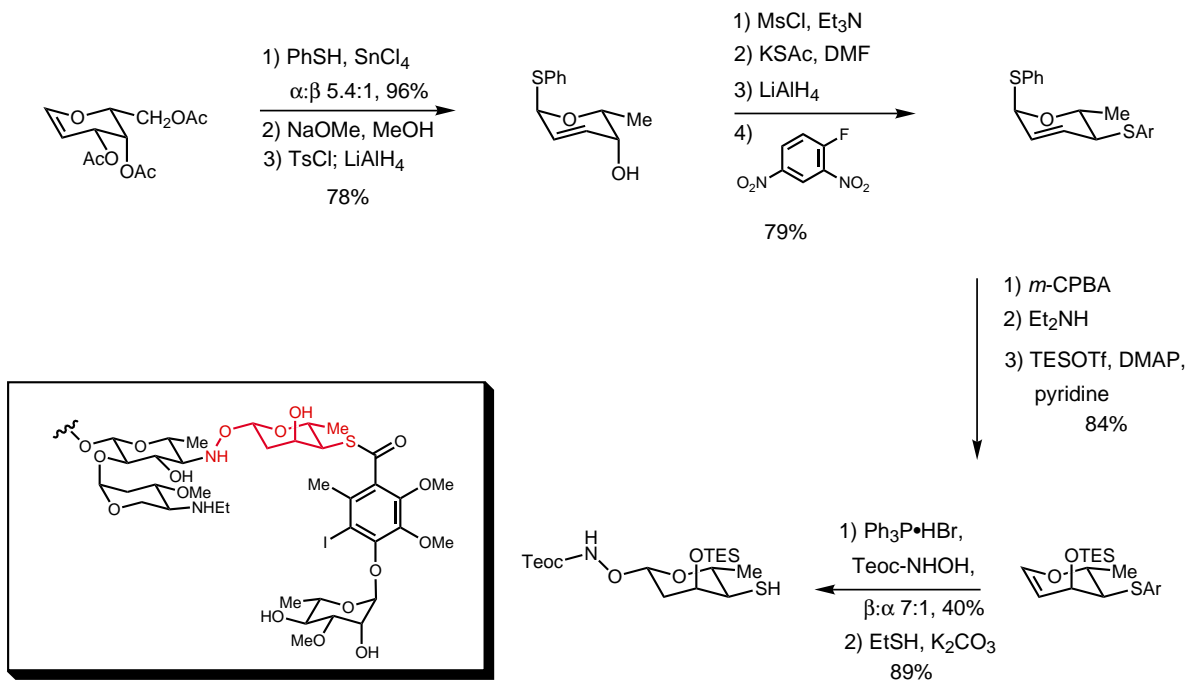
Hirama, M. *et al. Tetrahedron Lett.* **1999**, *40*, 8281.

Calicheamicin: Danishefsky



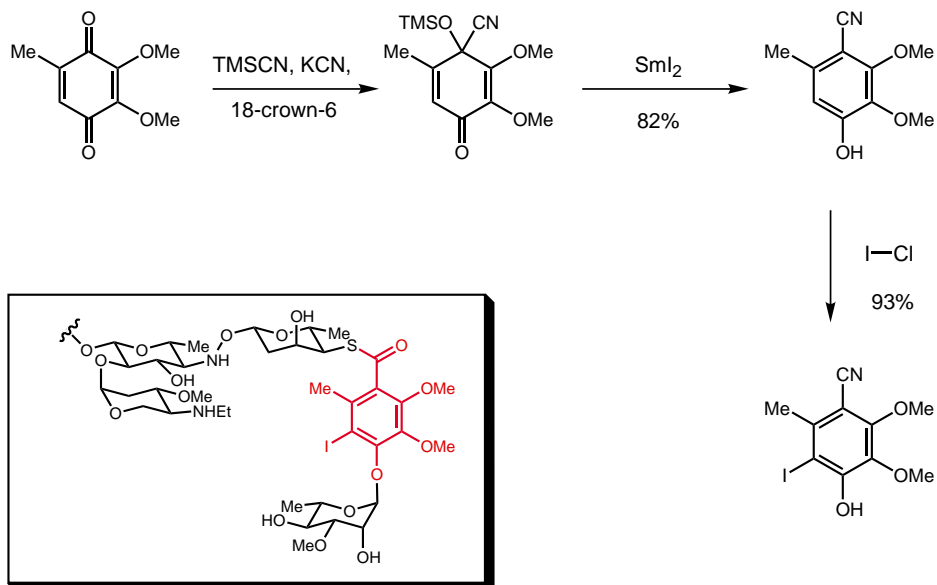
Danishefsky, S. J. et al. *J. Am. Chem. Soc.* **1995**, 117, 5720.

Calicheamicin: Danishefsky



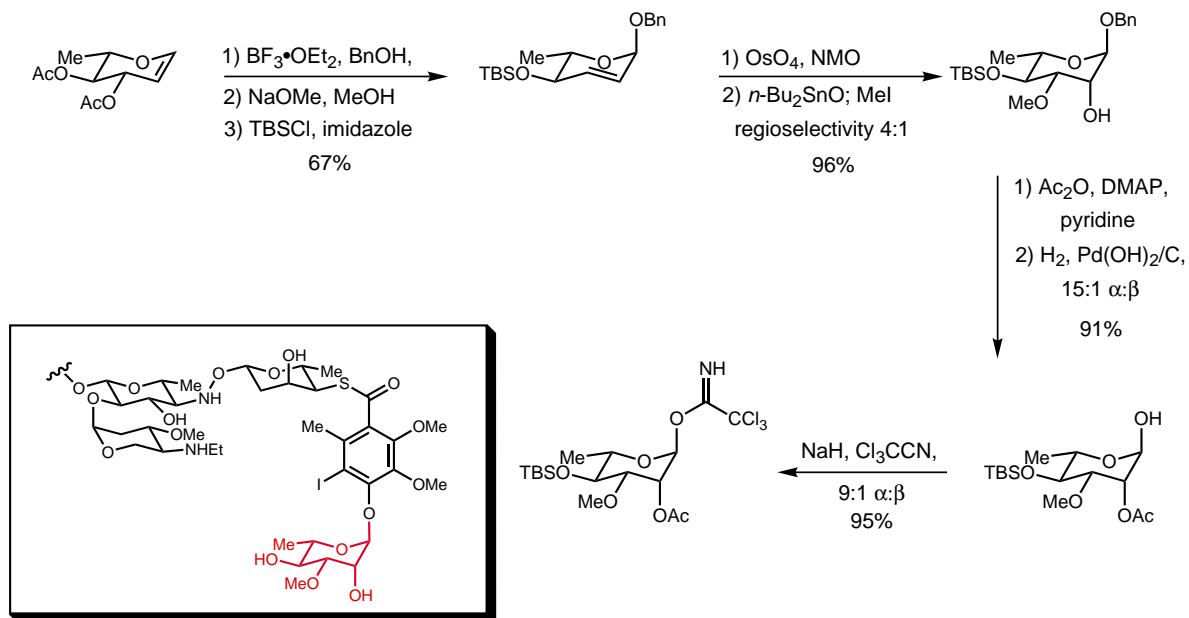
Danishefsky, S. J. et al. *J. Am. Chem. Soc.* **1995**, 117, 5720.

Calicheamicin: Danishefsky



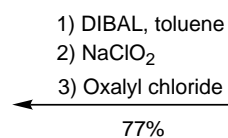
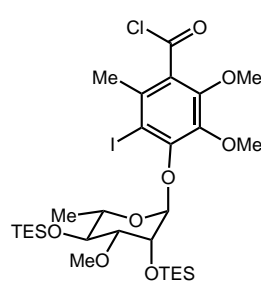
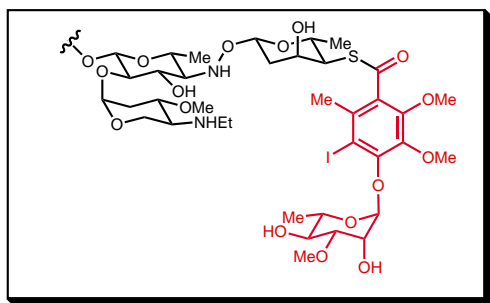
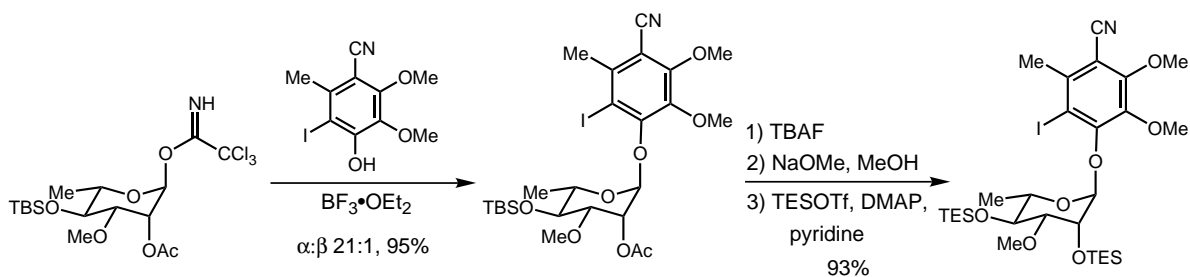
Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **1995**, *117*, 5720.

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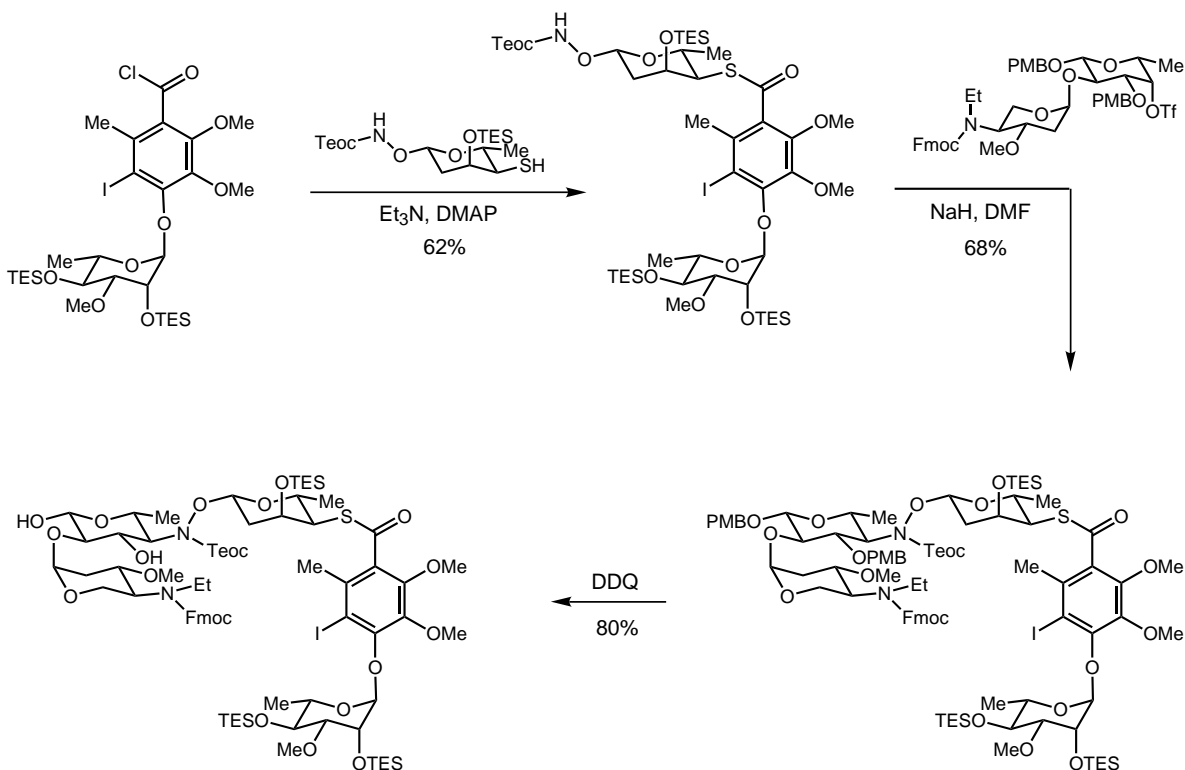
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