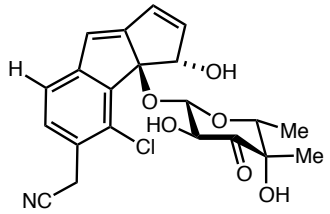
The Chemistry of Nine-Membered Enediyne Natural Products

Zhang Wang

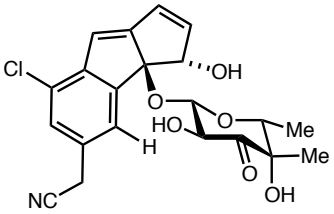
MacMillan Group Meeting

April 17, 2013

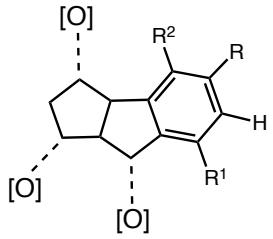
Natural Products Sharing a Unique Structure



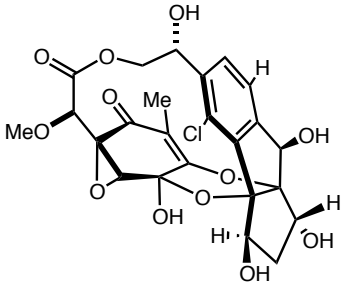
cyanosporaside A



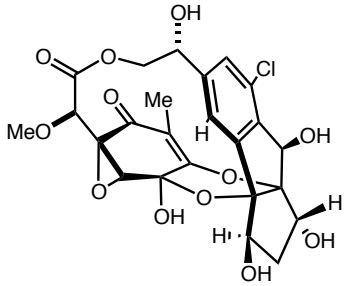
cyanosporaside B



R^1 = H, R^2 = Cl
or R^1 = Cl, R^2 = H



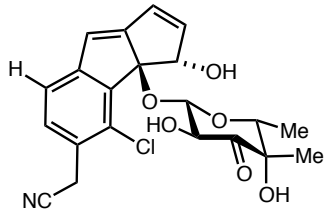
sporolide A



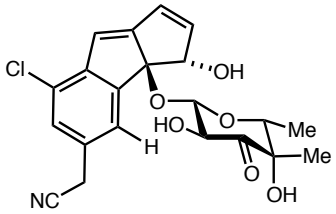
sporolide B

Oh, D.-C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 1021-1024.
Buchanan, G. O.; Williams, P. G.; Feling R. H.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2005**, *7*, 2731-2734.

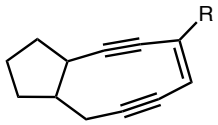
Natural Products Sharing a Unique Structure



cyanosporaside A

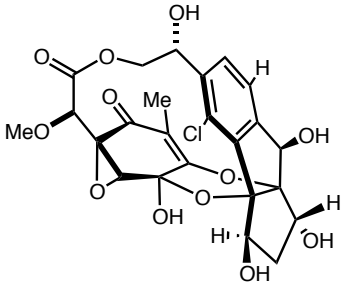


cyanosporaside B

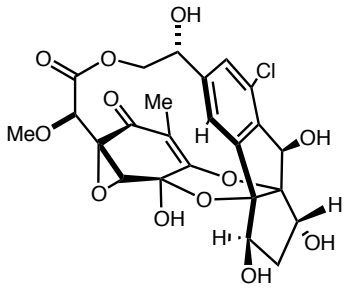


+ "magic"

+ "HCl"



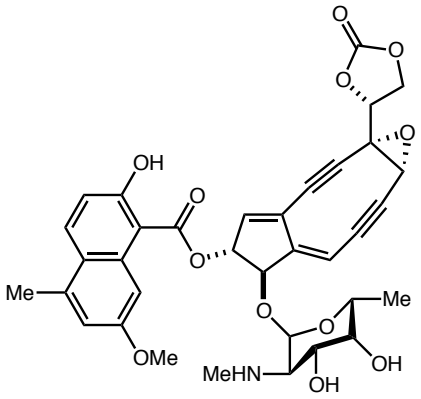
sporolide A



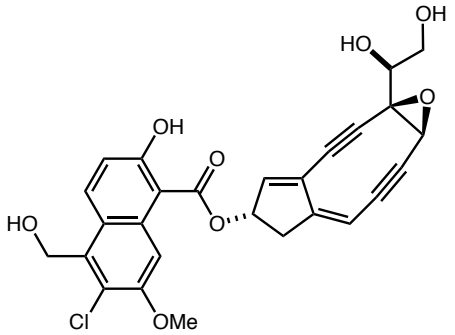
sporolide B

Oh, D.-C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 1021-1024.
Buchanan, G. O.; Williams, P. G.; Feling R. H.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2005**, *7*, 2731-2734.

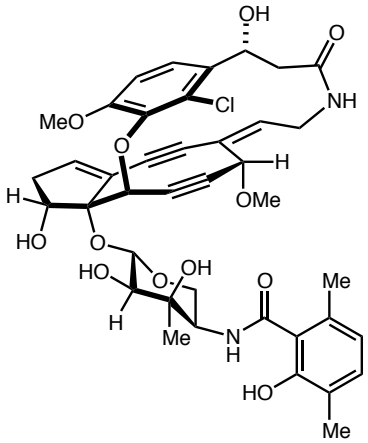
Examples of Nine-Membered Enediynes



neocarzinostatin chromophore

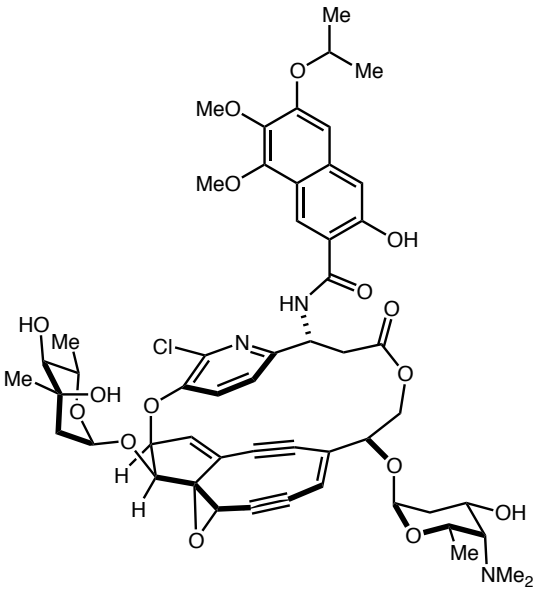


N1999A2

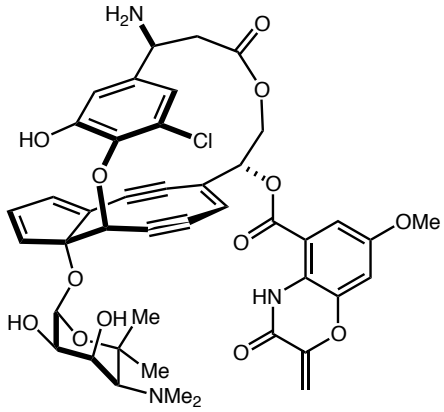


maduropeptin
chromophore

Examples of Nine-Membered Enediynes

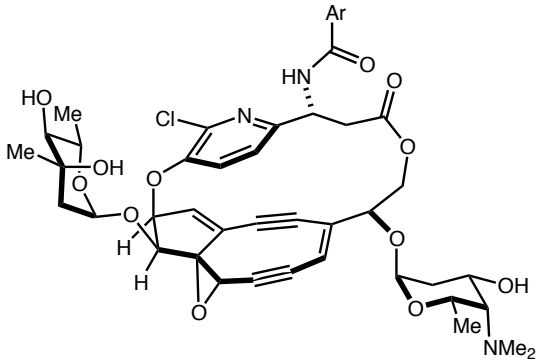


proposed kedarcidin chromophore

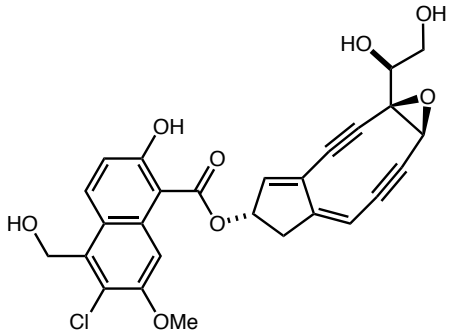


C-1027 chromophore

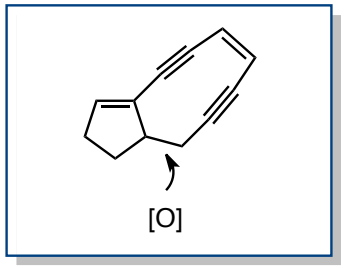
Two Types of Nine-Membered Enediynes



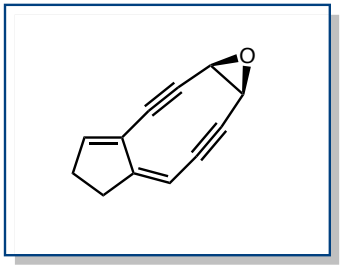
proposed kedarcidin chromophore



N1999A2

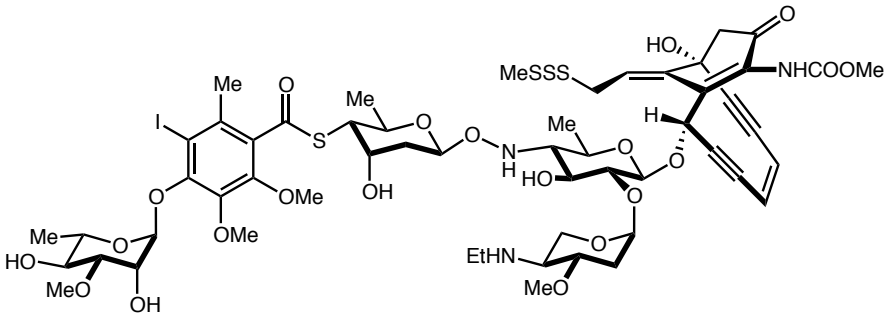


Bergman cyclization

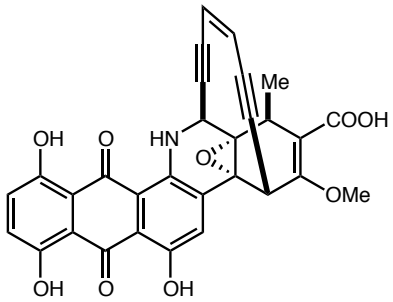


Myers cyclization

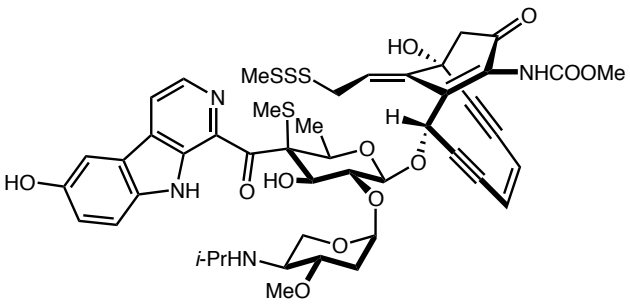
Ten-Membered Enediyne Natural Products



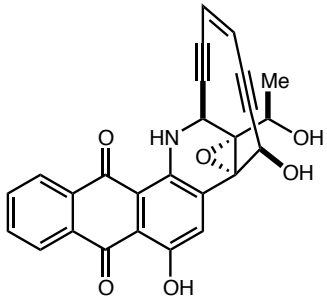
calicheamicin γ_1^I



dynemicin A

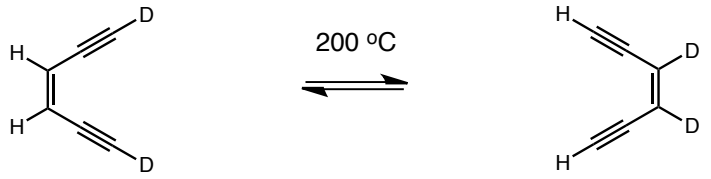


shishijimicin A

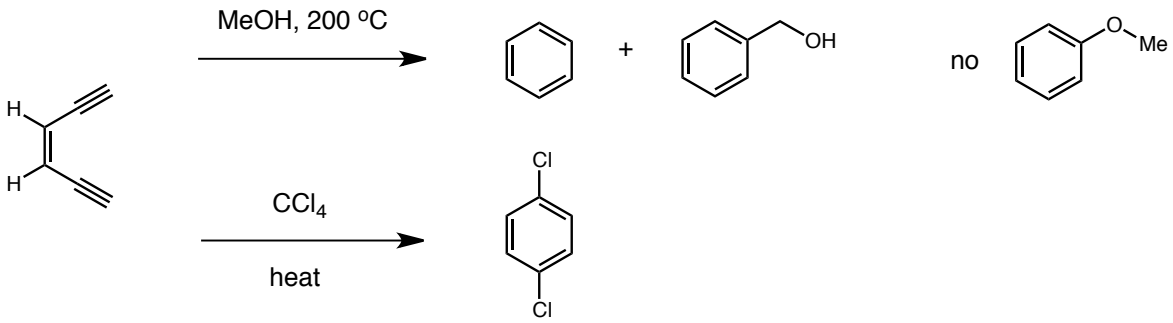


uncialamycin

Bergman Cyclization



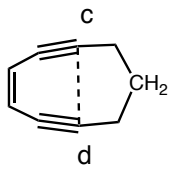
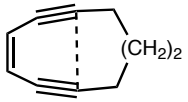
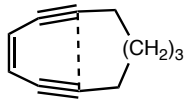
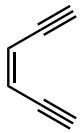
- *p*-Benzyne diradical intermediate



Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660-661.

Bergman Cyclization

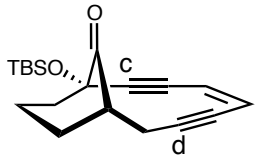
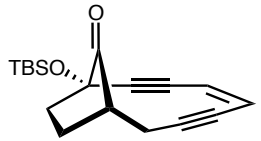
- Nicolaou's distance theory based on calculation and experiments

Compound	Ring size	c…d distance Å	stability
	9	2.84	unknown, should cyclize
	10	3.25	cyclize at 25 °C
	11	3.61	stable at 25 °C
		4.12	stable at 25 °C $t_{1/2}$ = 30 s at 200 °C

Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866-4868.

Bergman Cyclization

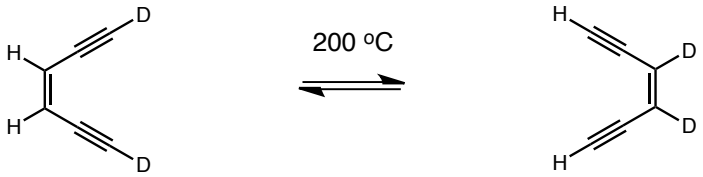
- Magnus-Snyder least motion/strain energy theory

	c...d distance Å	relative rate of Bergman cyclization at 124 °C	strain energy release after cyclization kcal
	3.391	650	6.0 (cyclohexanone adopts a chair conformer in product)
	3.368 (oxime)	1	-1.5

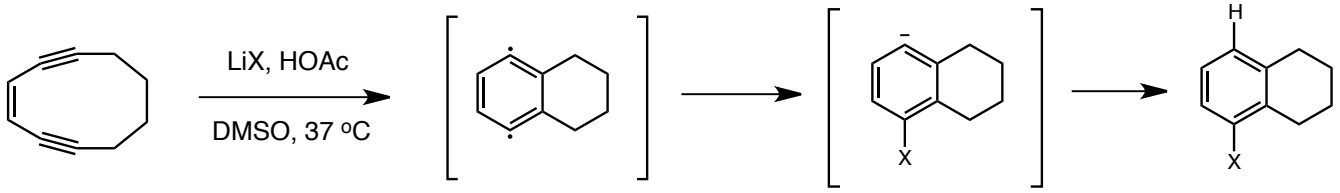
Global strain energy of starting material and product should be considered for complex molecules

Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630-7632.
Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986-4987.

Bergman Cyclization



- Nucleophiles can react with *p*-benzyne diradical, producing phenyl anion



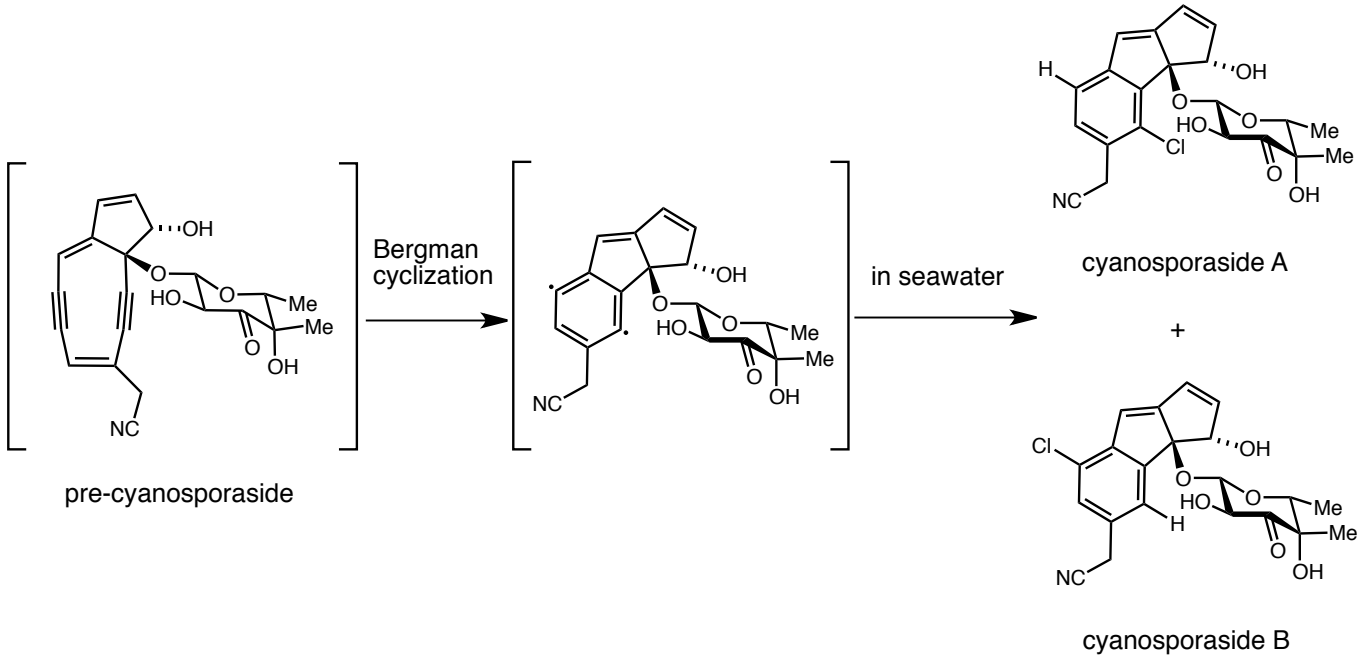
ΔG = -80 to -100 kJ/mol

can be treated as  towards halides

Perrin, C. L.; Rodgers, B. L.; O'Connor, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4795-4799.

Bergman Cyclization

- Cyanosporasides from enediyne precursor



pre-cyanosporaside

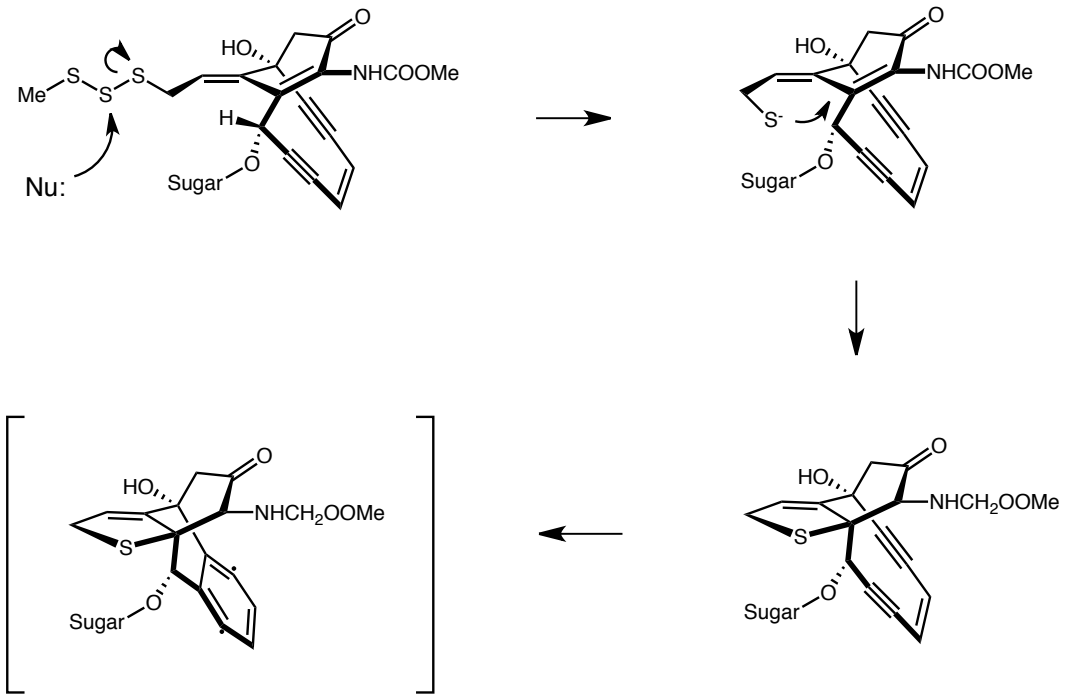
cyanosporaside A

cyanosporaside B

Oh, D.-C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 1021-1024.

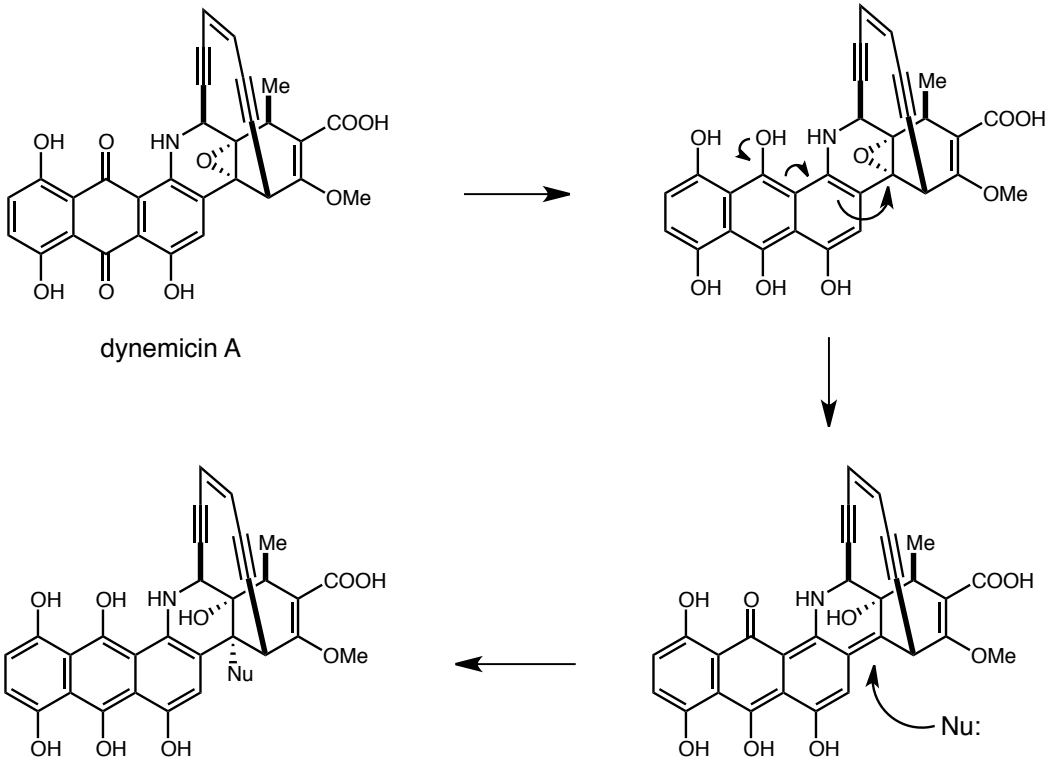
Bergman Cyclization

- Bergman cyclization of calicheamicin



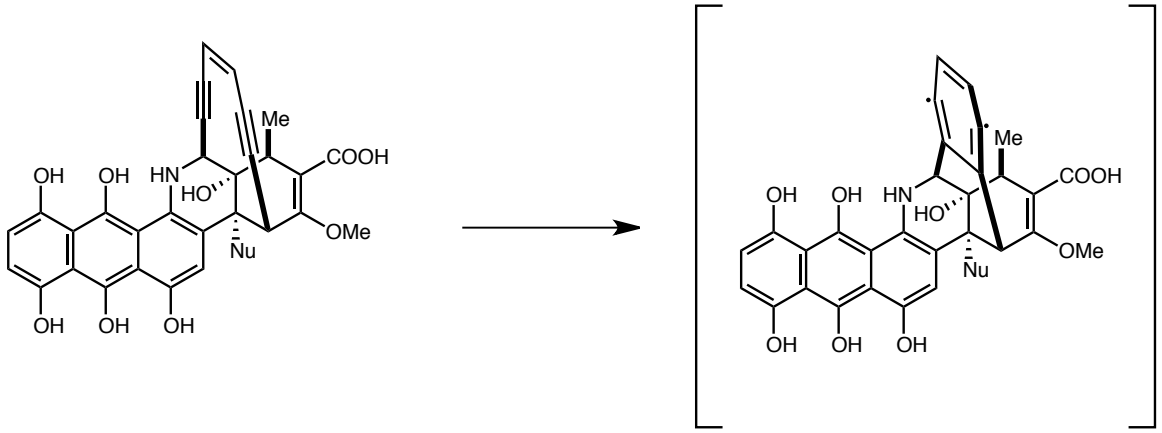
Bergman Cyclization

- Bergman cyclization of dynemicin

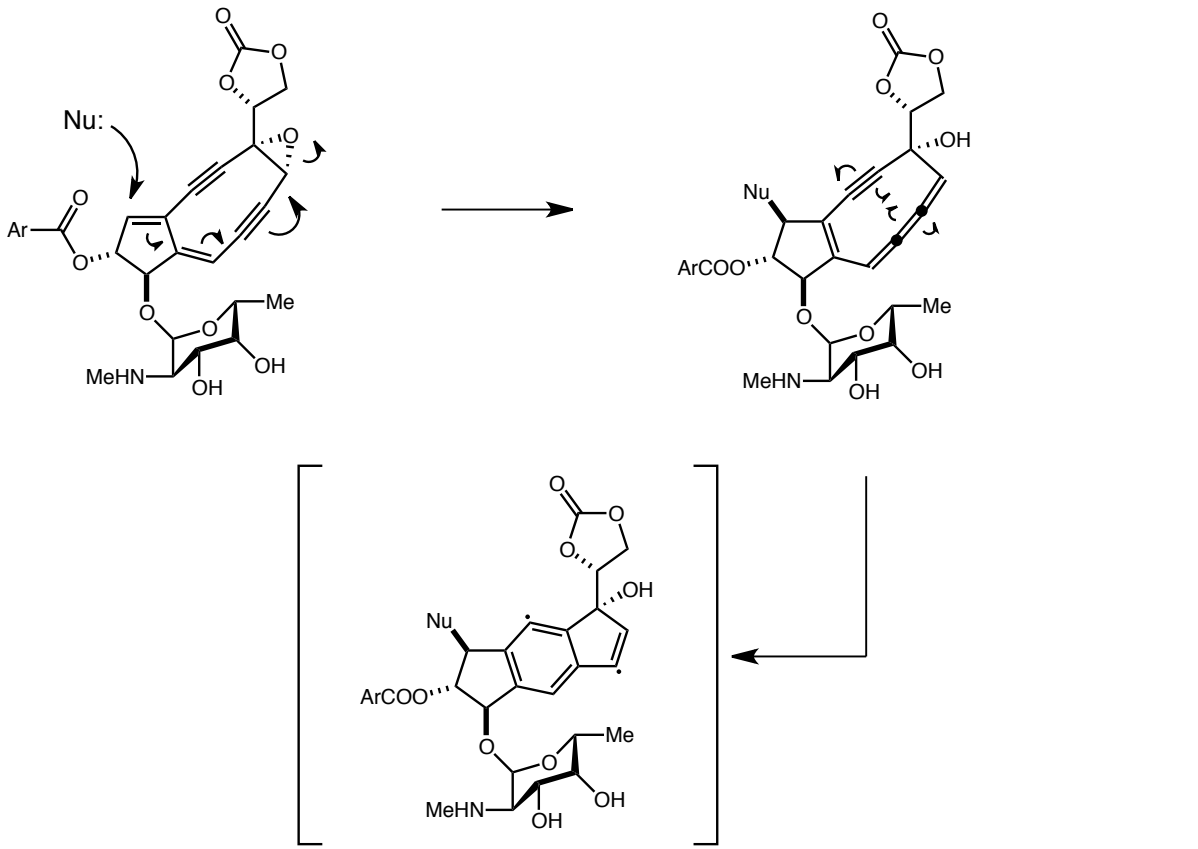


Bergman Cyclization

- Bergman cyclization of dynemicin

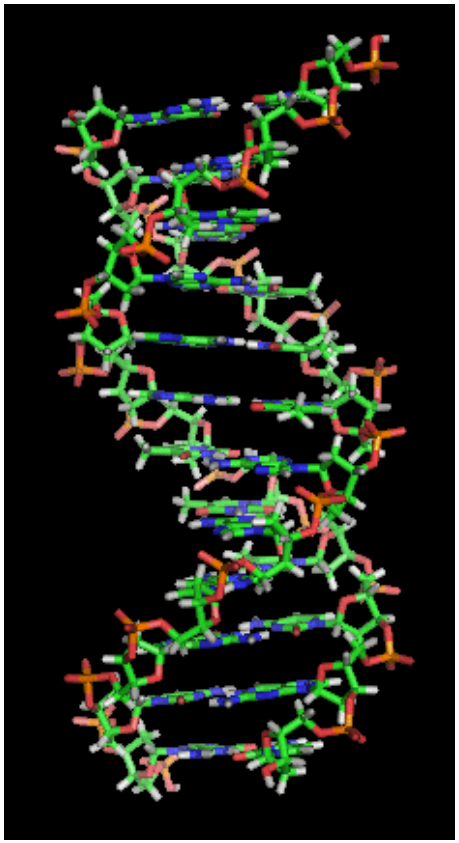


Myers Cyclization



Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493-4496.

DNA Cleavage with Diradical

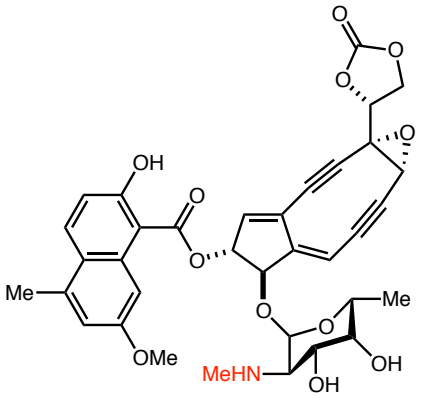


favors T, A rich sequences

Naphthoate parallels DNA base pairs

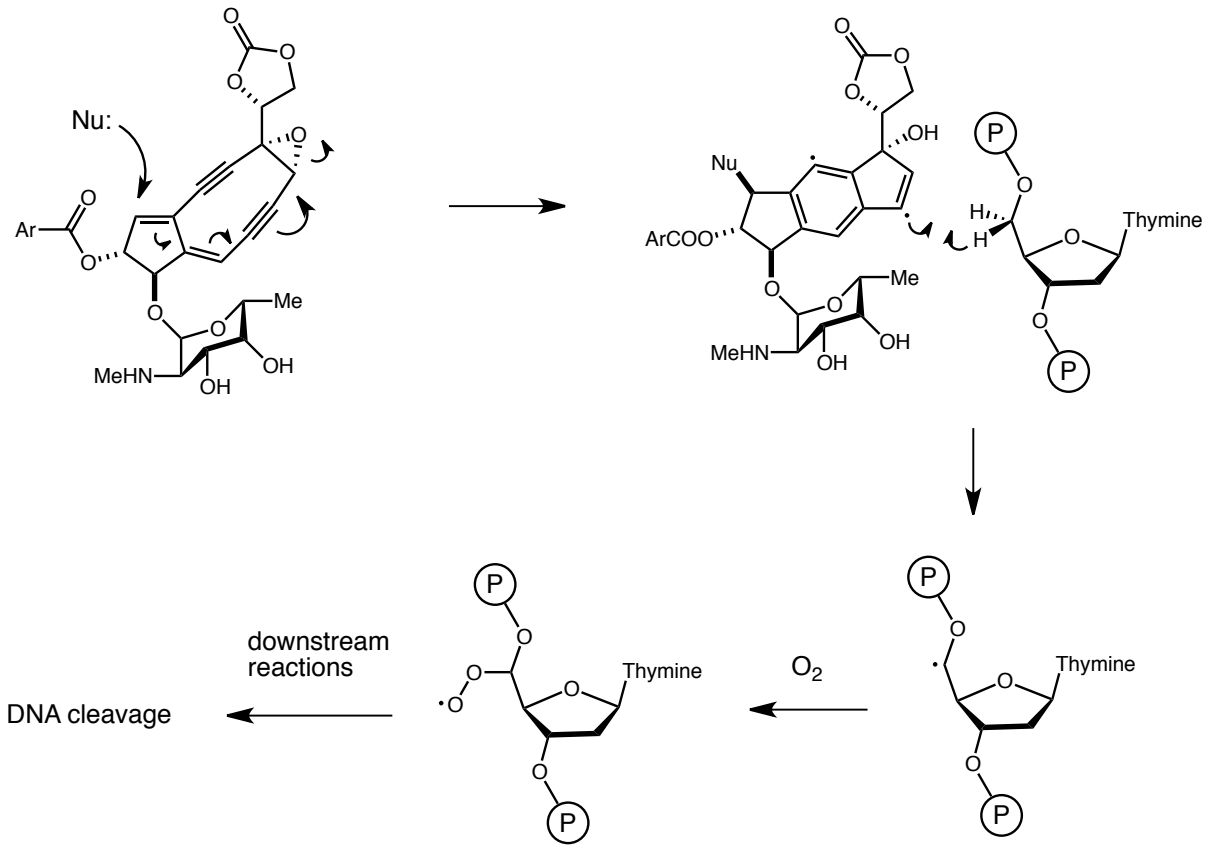
positively charged amino sugar interacts with phosphate

binds DNA
minor groove



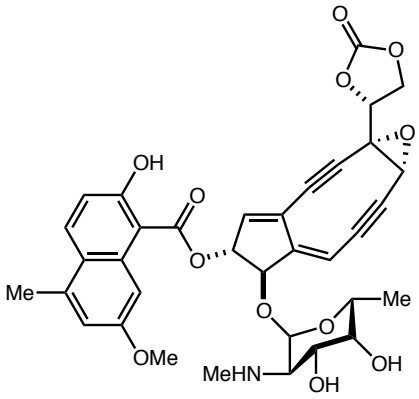
neocarzinostatin chromophore

DNA Cleavage with Diradical

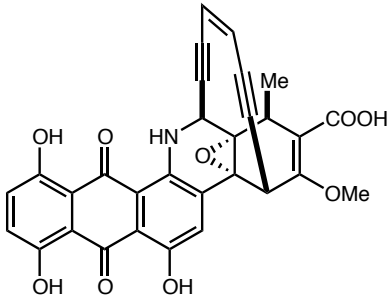


Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191-198.

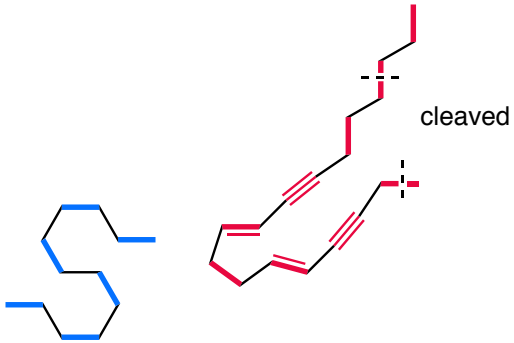
Enediyne Natural Products Are Polyketides

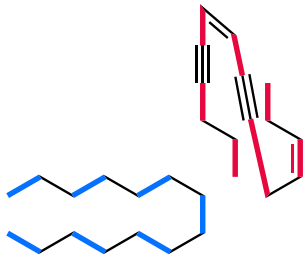


neocarzinostatin chromophore



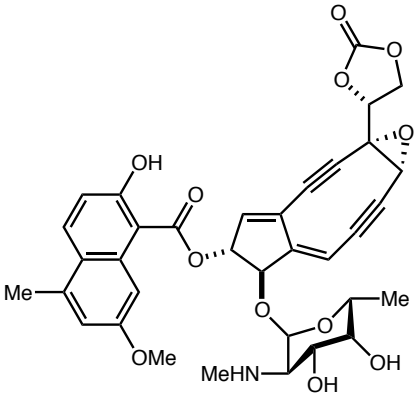
dynemicin A



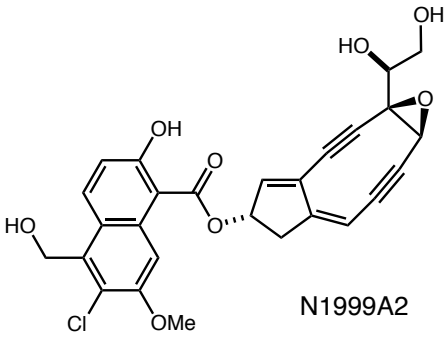


Liang, Z.-X. *Nat. Prod. Rep.* **2010**, *27*, 499-528.

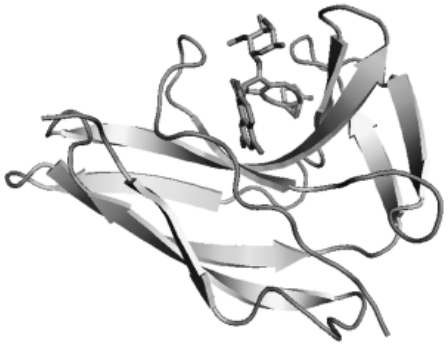
Apoprotein of Nine-Membered Enediynes



neocarzinostatin chromophore



N1999A2

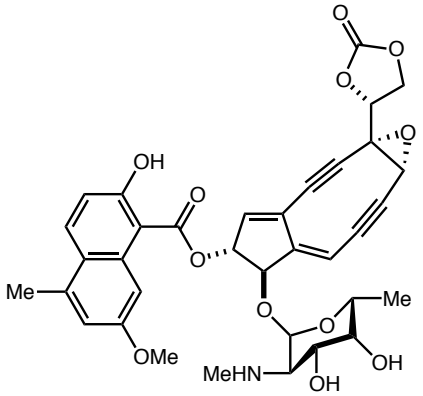


neocarzinostatin

- Nine-membered enediynes isolated with apoproteins except N1999A2
- Apoproteins protect and transport enediynes
- Apoproteins have about 110 amino acids
- Structural features of apoproteins avoid:
  external nucleophile attack,
  electrophile activation of epoxides,
  H-abstraction of diradical intermediates

Baker, J. R.; Woolfson, D. N.; Muskett, F. W.; Stoneman, R. G.; Urbaniak, M. D.; Caddick, S. *ChemBioChem* **2007**, *8*, 704-717.

Neocarzinostatin Chromophore

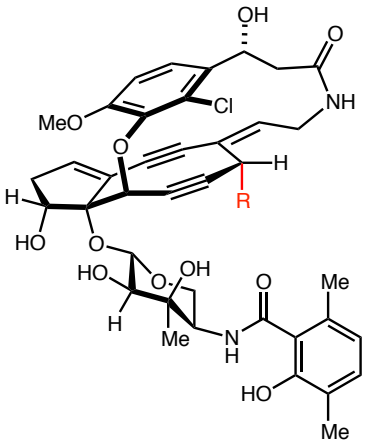


neocarzinostatin chromophore

1957	isolation of carzinostatin
1965	isolation of neocarzinostatin
1972	Bergman cyclization
1979	1:1 noncovalent complex of a protein and chromophore was identified
1985	gross structure of neocarzinostatin chromophore was identified
1987	ten-membered enediynes were found Myers cyclization proposed
1988	relative and absolute stereochemistry of neocarzinostatin chromophore was determined
1996	the aglycon was synthesized
1998	neocarzinostatin chromophore synthesized

Nan Ji, PhD thesis, Harvard University **2006**.

Maduropeptin Chromophore



isolation condition	product composition
Tris•HCl and MeOH	R = OMe, Cl, OH
without Cl^-, and MeOH	R = OMe, OH
use EtOH instead of MeOH	R = OEt

DNA cleaving ability

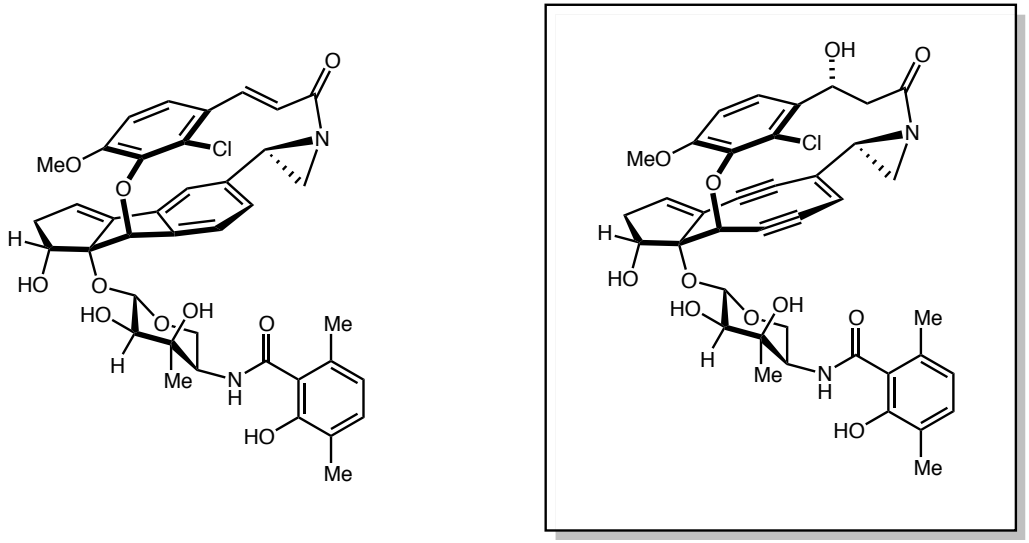
R = Cl > R = OMe

enhanced ability in basic media

no DNA scission upon adding thiol

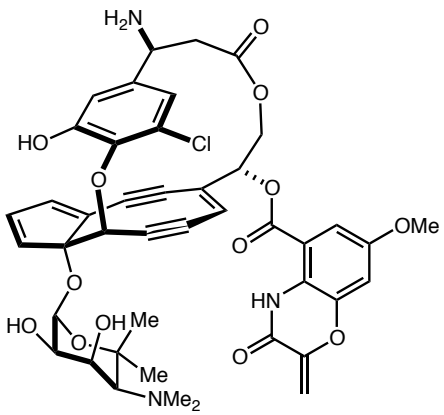
Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Zein, N.; Langley, D. R.; Lee, M. S.; Matson, J. A.; Doyle, T. W. *J. Am. Chem. Soc.* **1994**, *116*, 9351-9352.

Maduropeptin Chromophore

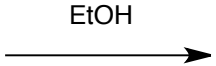


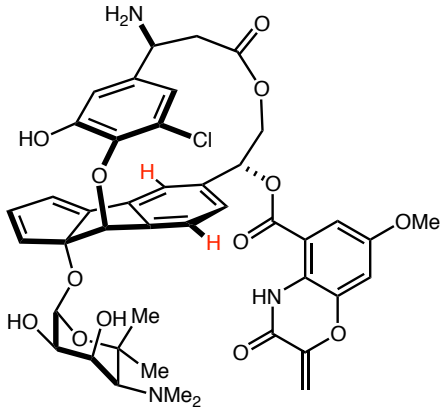
Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Zein, N.; Langley, D. R.; Lee, M. S.; Matson, J. A.; Doyle, T. W. *J. Am. Chem. Soc.* **1994**, *116*, 9351-9352.

C-1027 Chromophore



in apoprotein

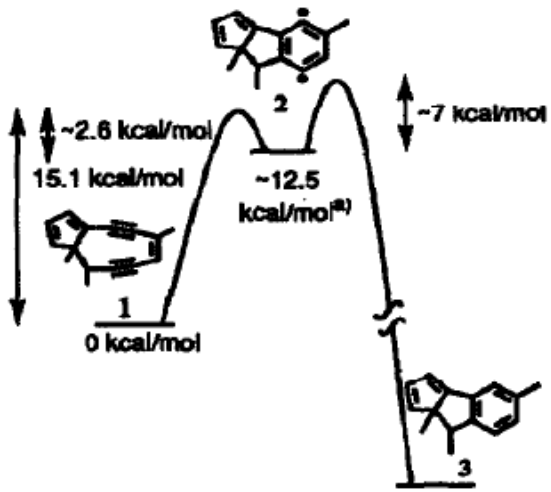


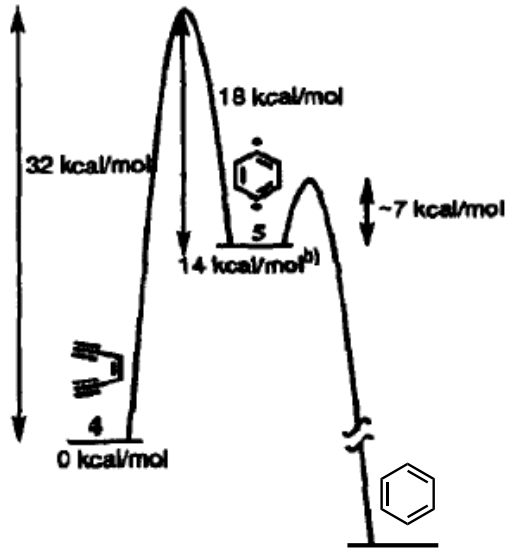


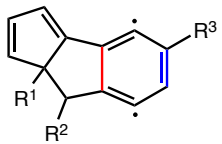
$k_H/k_D = 3.8$

Yoshida, K.-i.; Minami, Y.; Otani, T.; Tada, Y.; Hirama, M. *Tetrohedron Lett.* **1994**, *35*, 5253-5256.

C-1027 Chromophore





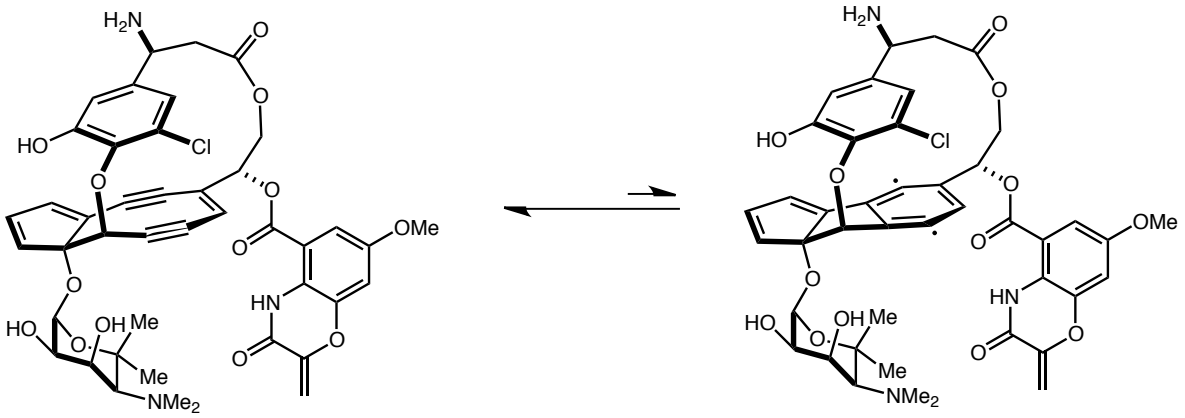


bond order: 1.21, 1.44 Å

bond order: 1.35, 1.41 Å

Yoshida, K.-i.; Minami, Y.; Otani, T.; Tada, Y.; Hirama, M. *Tetrohedron Lett.* **1994**, *35*, 5253-5256.

C-1027 Chromophore



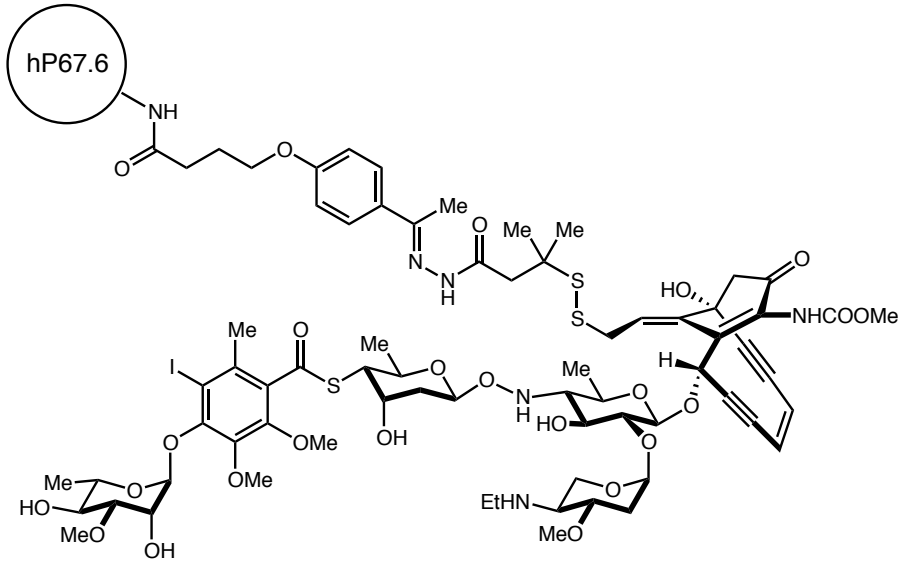
in apoprotein

slow

H-abstraction pdt.

Hirama, M. et. al. *J. Am. Chem. Soc.* **2000**, *122*, 720-721.

Drugs from Enediynes ---- Mylotarg



MYLOTARG

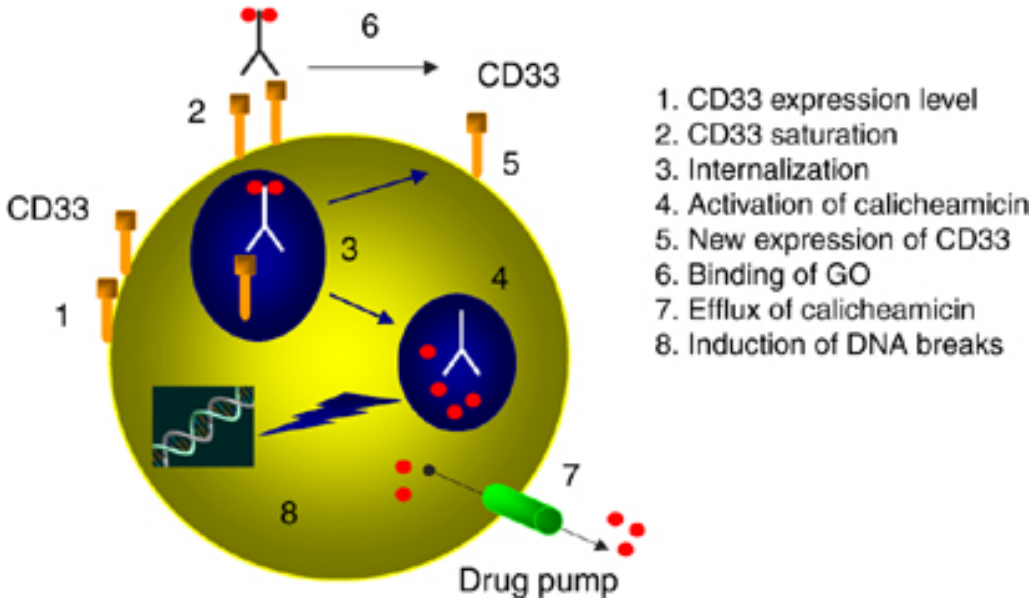
By Wyeth, and later Pfizer

For treatment of acute myeloid leukemia

2000 to 2010

Withdrawn by Pfizer in 2010 due to side effects

Drugs from Enediynes ---- Mylotarg



http://www.biology.iupui.edu/biocourses/Biol540/6secondwavequestionCSS.html

Drugs from Enediynes ---- SMANCS

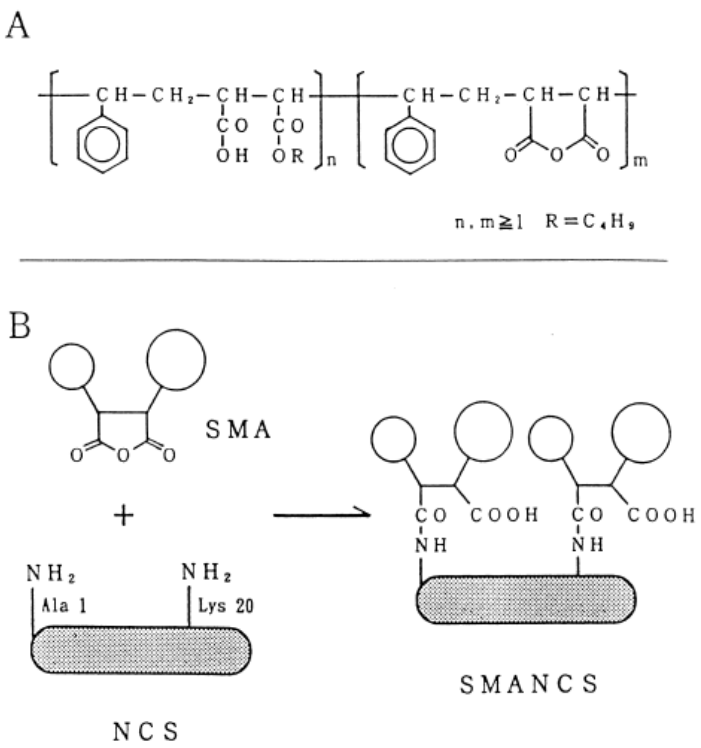
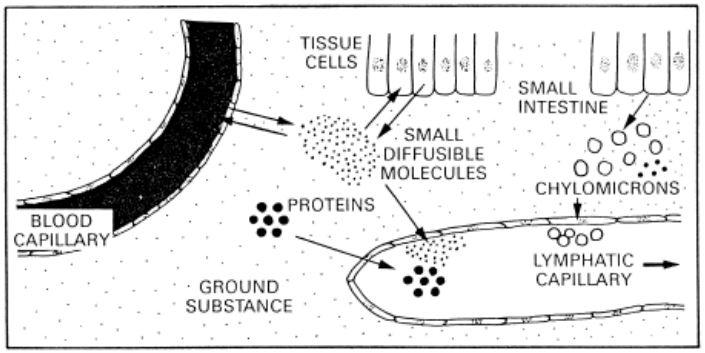


Fig. 1. (A) Structure of SMA, poly(styrene-co-maleic acid/anhydride) half butyl ester and (B) diagrammatic representation of the reaction with NCS to produce the conjugate SMANCS.

Maeda, H. *Advanced Drug Delivery Reviews* **2001**, *46*, 169-185.

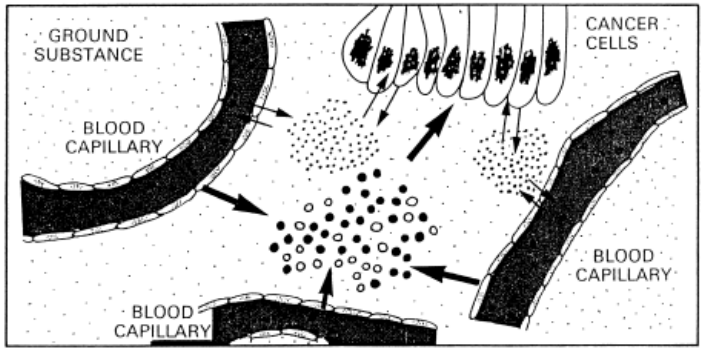
Drugs from Enediynes ---- SMANCS

A Normal Tissues



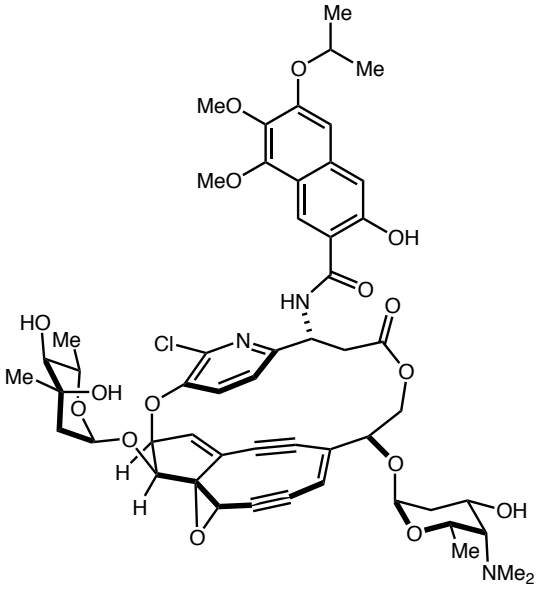
B Tumor Tissues

(Hypervascularity, no lymphatic capillary)

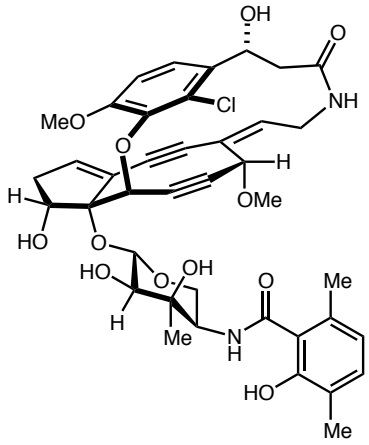


Maeda, H. *Advanced Drug Delivery Reviews* **2001**, *46,* 169-185.

Total Synthesis of Nine-Membered Enediynes



proposed kedarcidin chromophore



maduropeptin chromophore

Fast synthesis of fragments

Correct sequence to assemble

Mild reaction conditions in late stage

Courage, prudence and persistance

Total Synthesis of Nine-Membered Enediynes

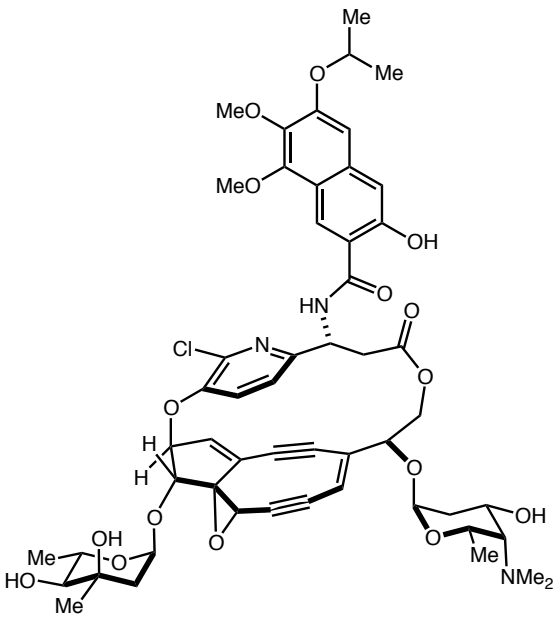
Professor Andrew G. Myers

Harvard University

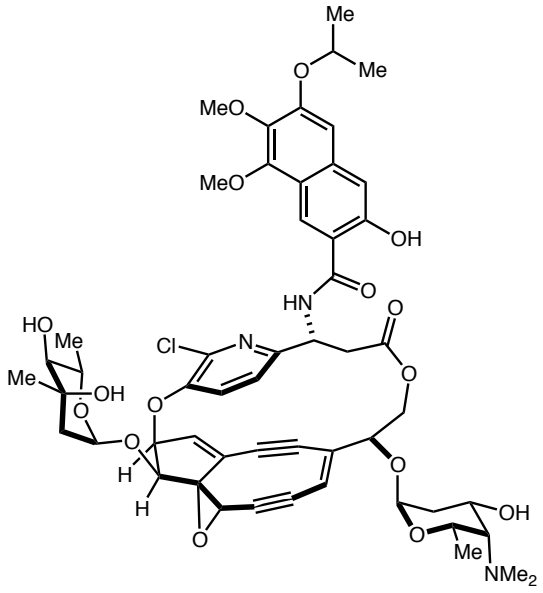
Professor Masahiro Hirama

Tohoku University

Total Synthesis of Proposed Kedarcidin Chromophore



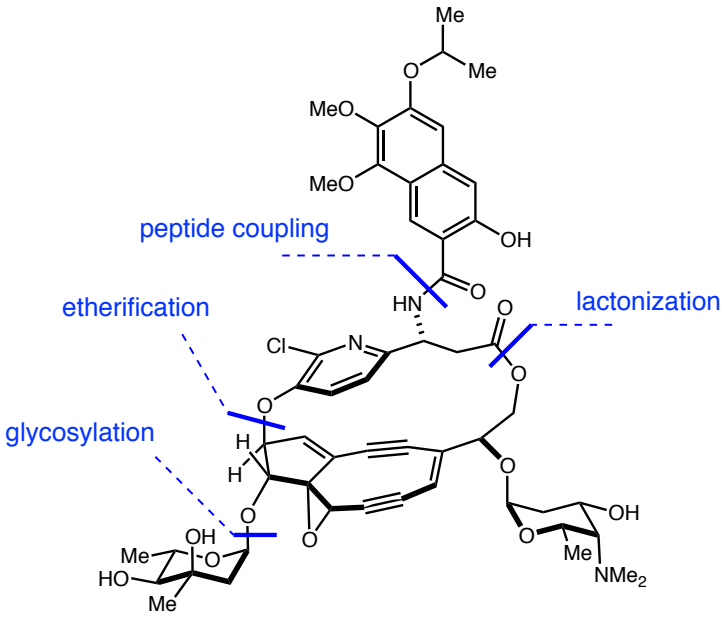
proposed kedarcidin chromophore (1997)



proposed kedarcidin chromophore (2007)

Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007***, 129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore



proposed kedarcidin chromophore (1997)

Enediyne core should be synthetized at a relatively late stage

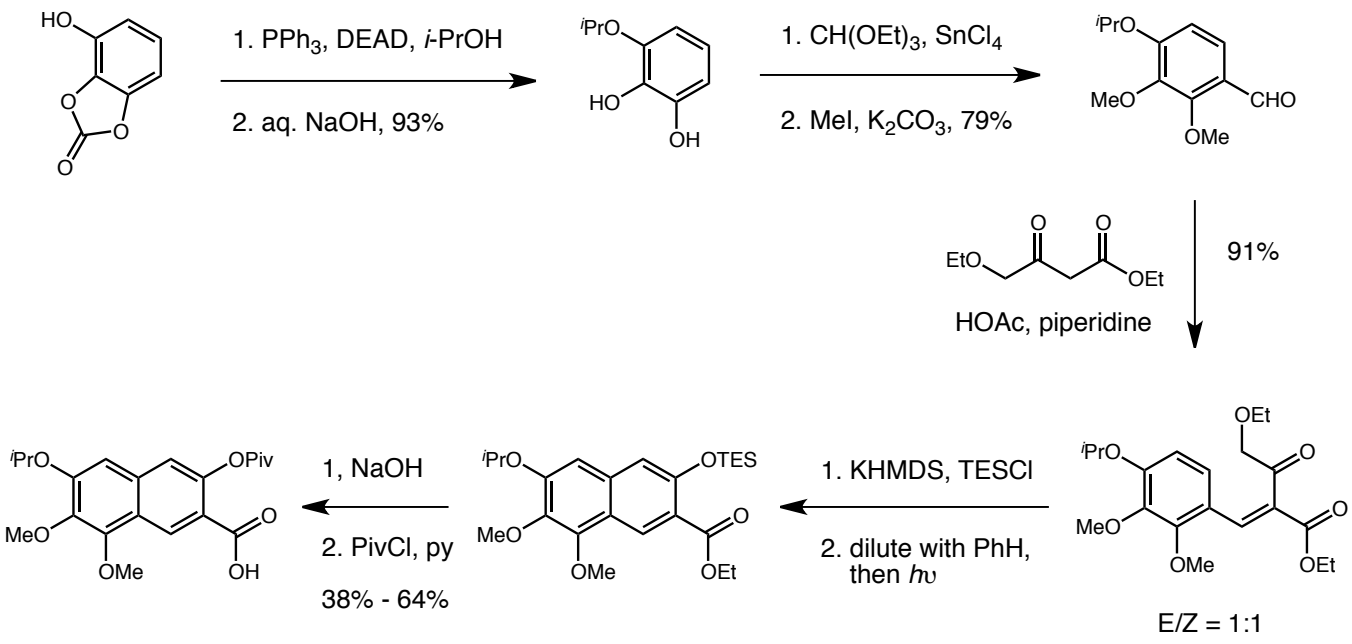
Correct protecting groups

Powerful while mild conditions

Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

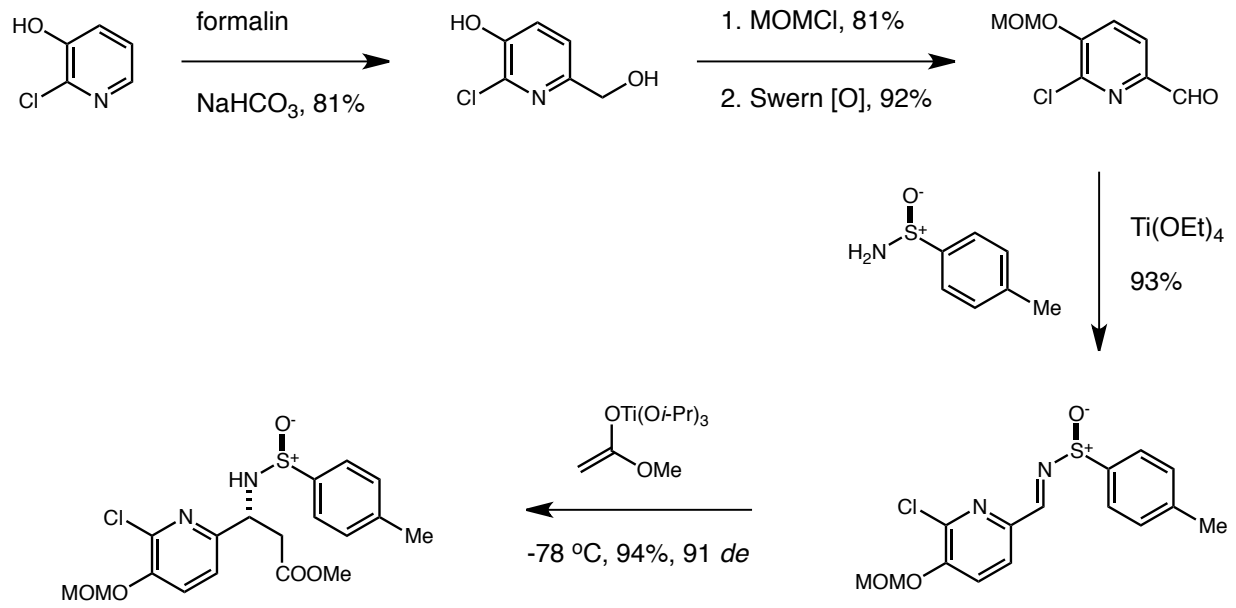
- Naphthoate synthesis



Myers, A. G.; Horiguchi, Y. *Tetrahedron Lett.* **1997**, *38*, 4363-4366.

Total Synthesis of Proposed Kedarcidin Chromophore

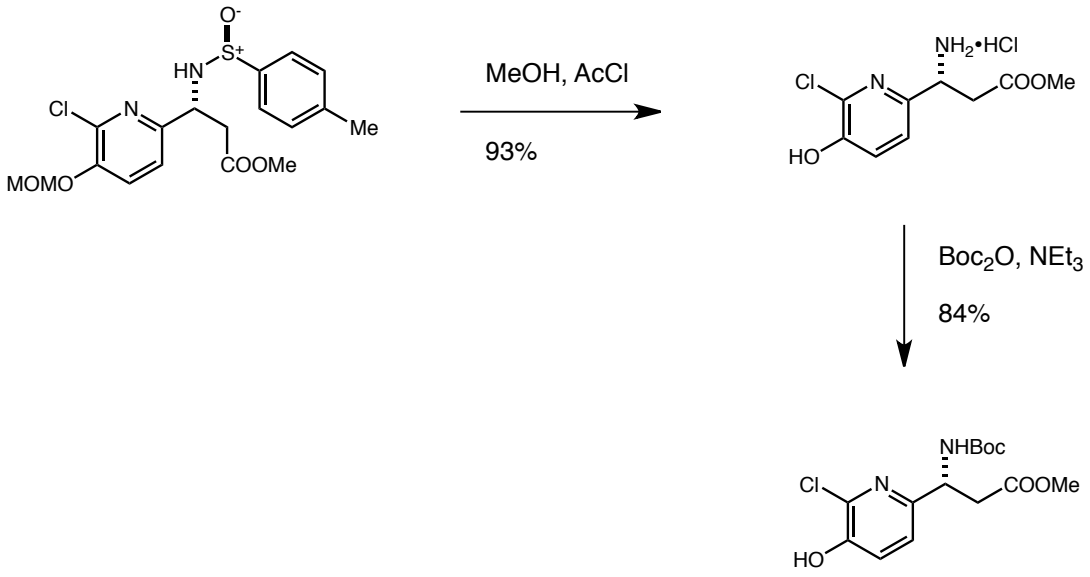
- Chloropyridine synthesis



Myers, A. G.; Hogan, P. C.; Hurd, A. R.; Goldberg, S. D. *Angew. Chem. Int. Ed.* **2002**, *41*, 1062-1067.
Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

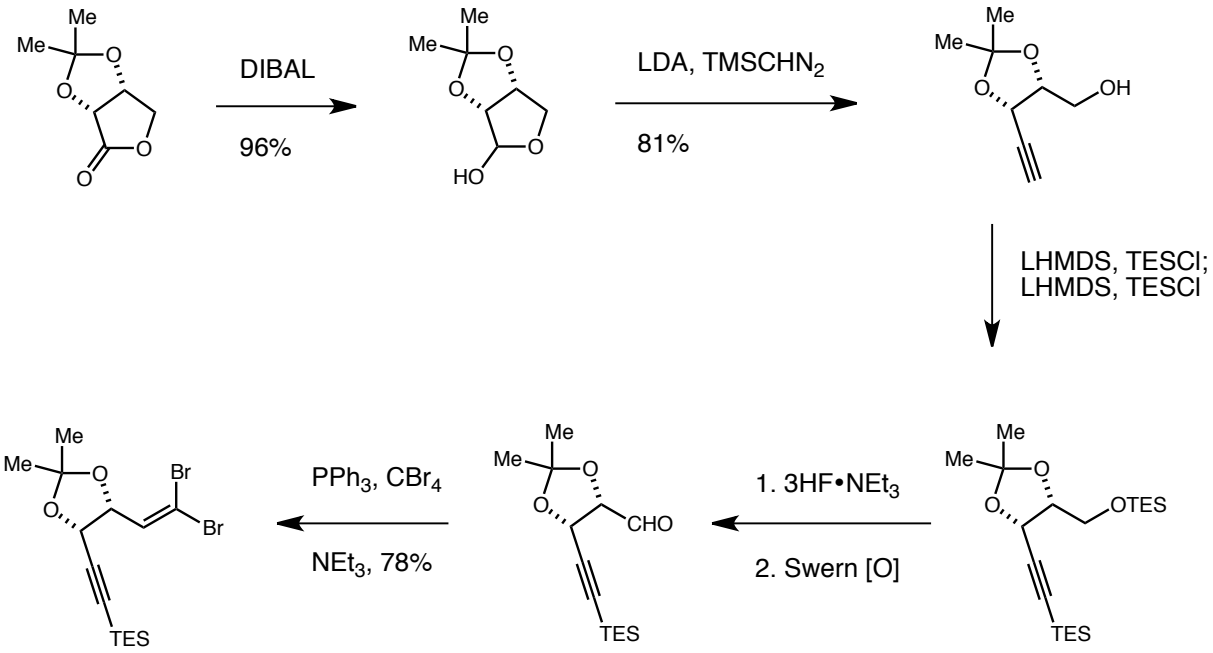
- Chloropyridine synthesis



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

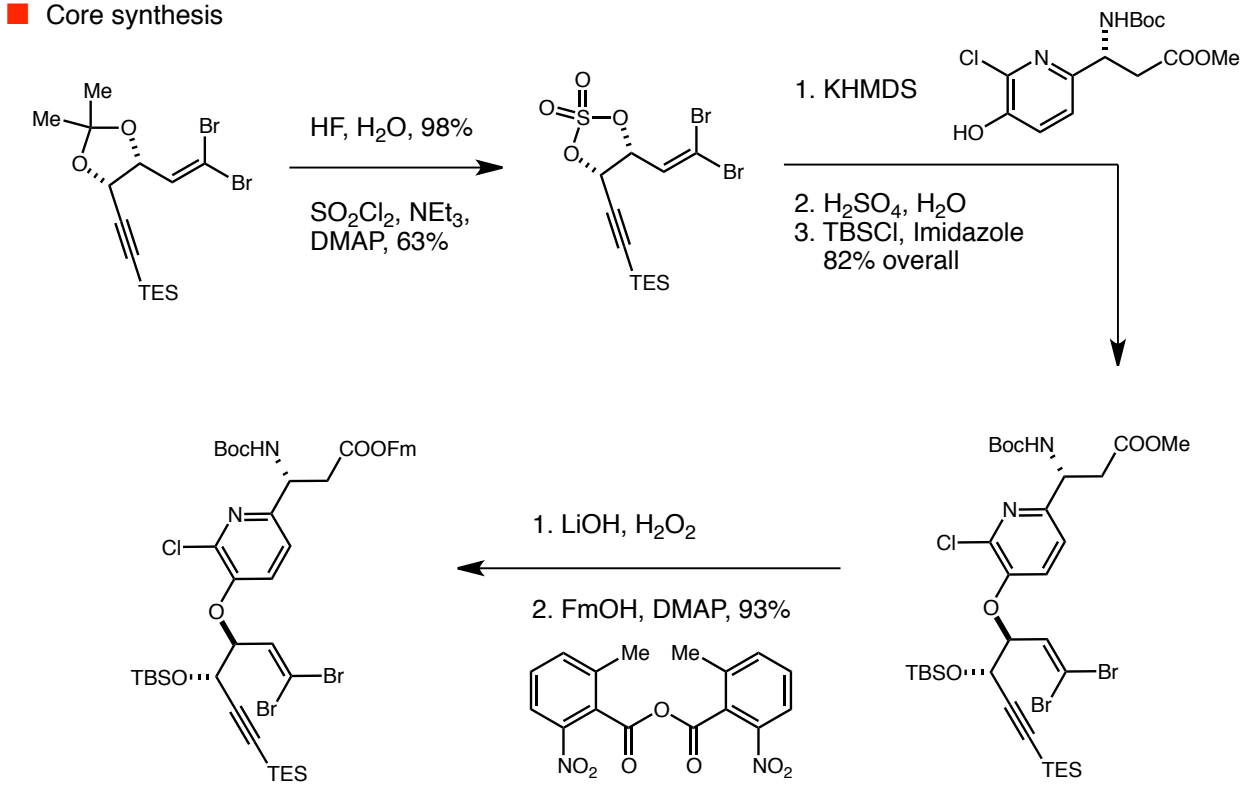
- Core synthesis



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

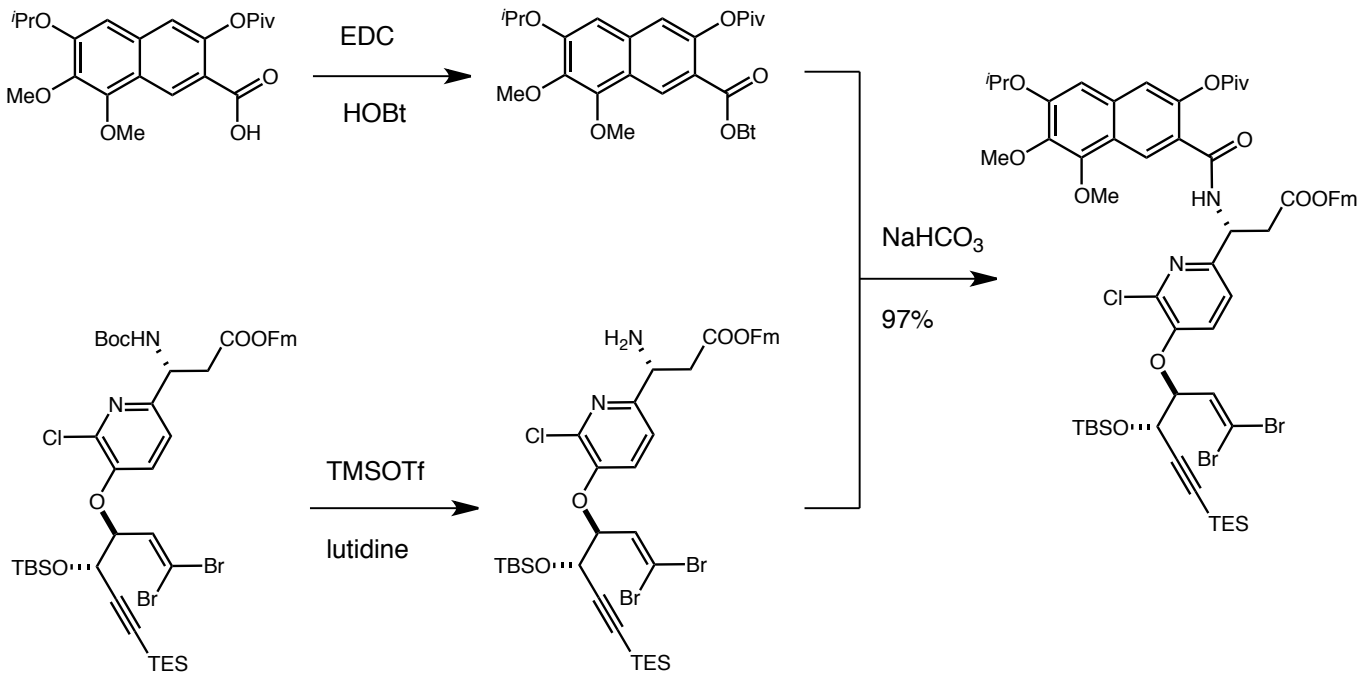
■ Core synthesis



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

■ Core synthesis



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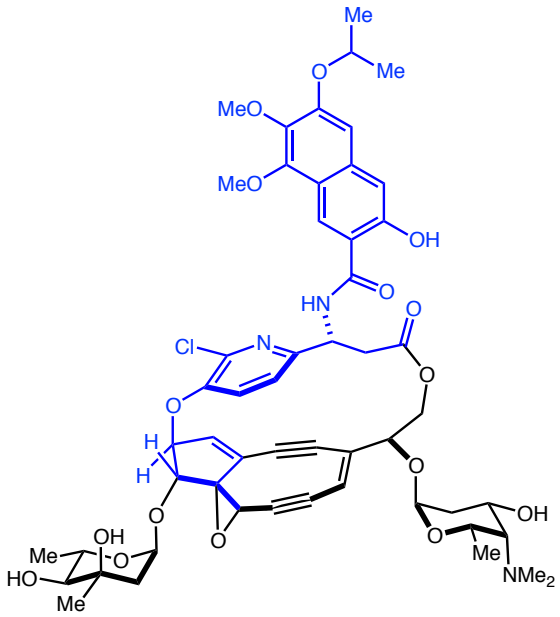
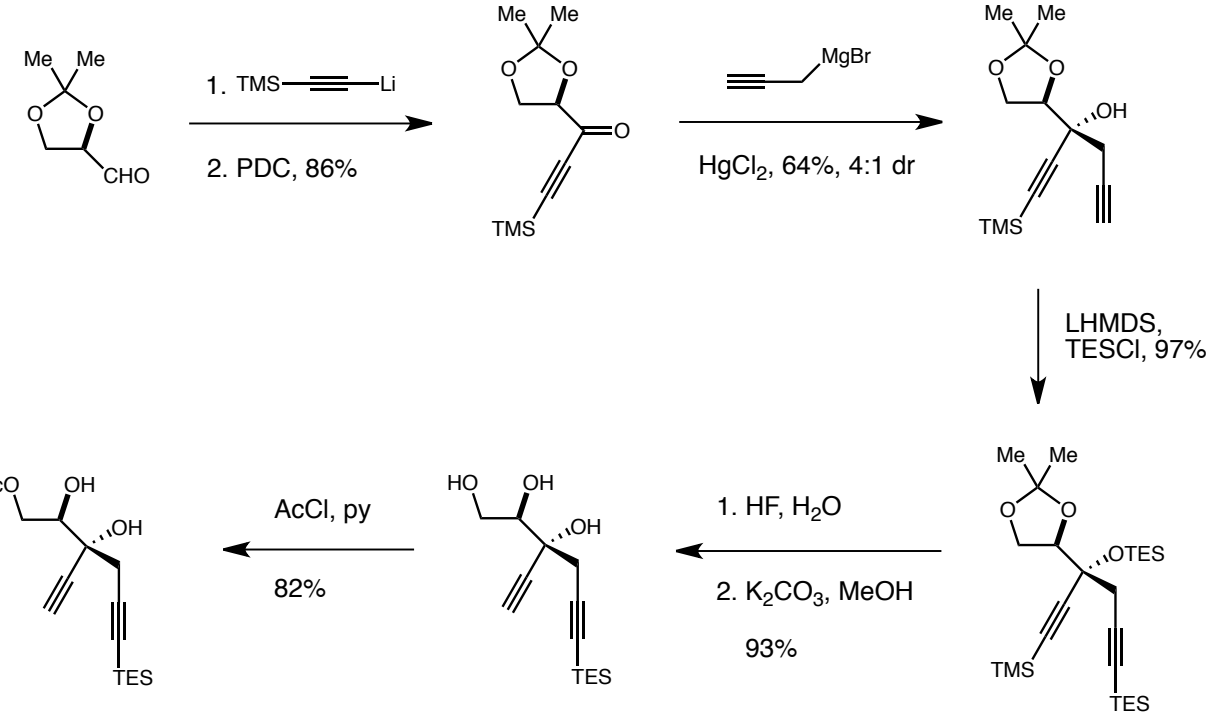
Total Synthesis of Proposed Kedarcidin Chromophore



proposed kedarcidin chromophore (1997)

Total Synthesis of Proposed Kedarcidin Chromophore

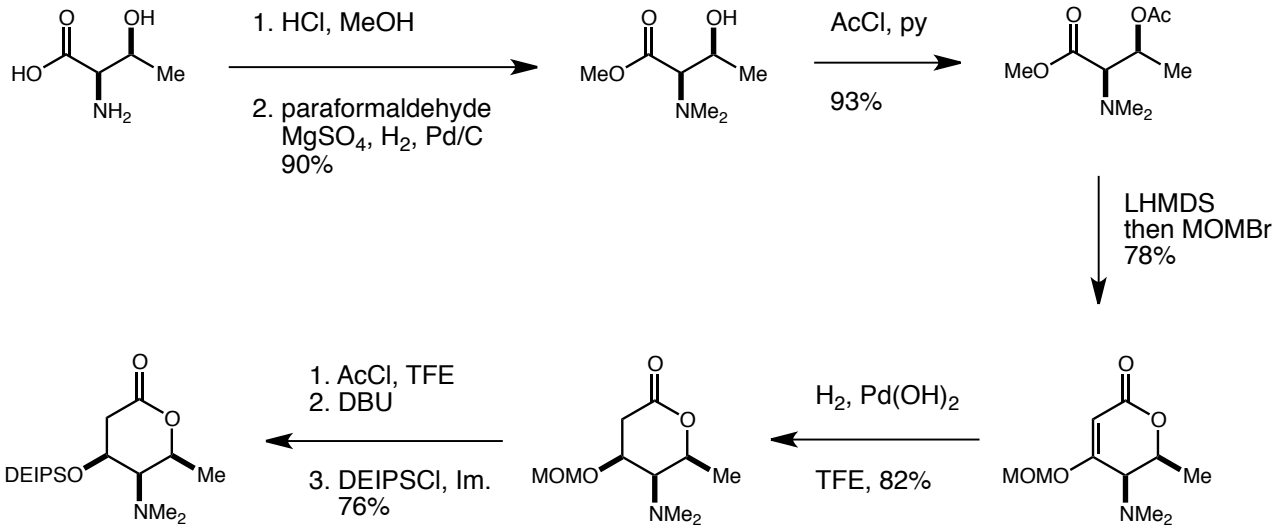
- Core synthesis



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

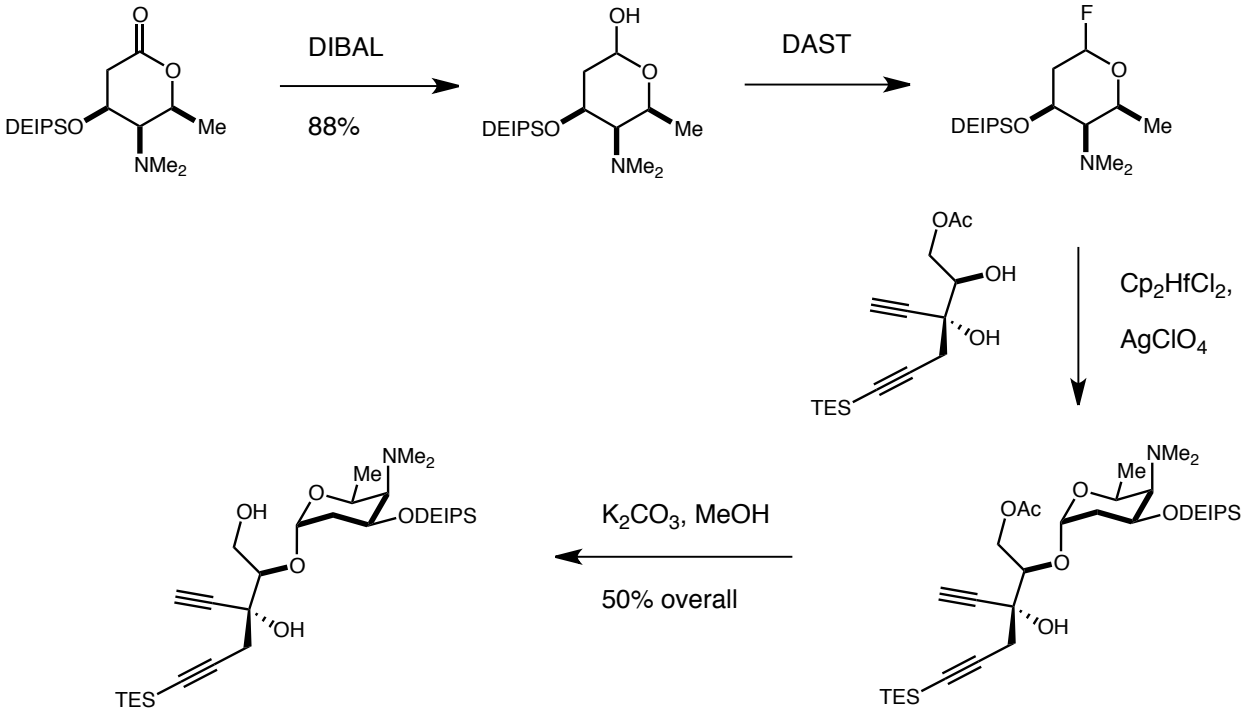
- Suger synthesis



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *Org. Lett.* **2007**, *9*, 1923-1925.

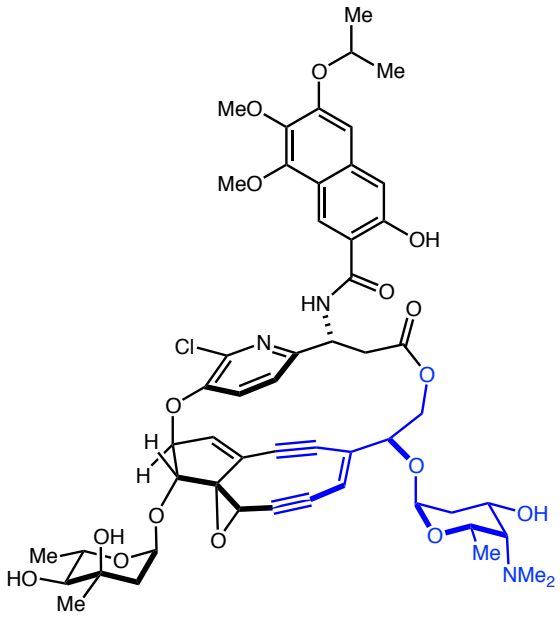
Total Synthesis of Proposed Kedarcidin Chromophore

- Core synthesis



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *Org. Lett.* **2007**, *9*, 1923-1925.

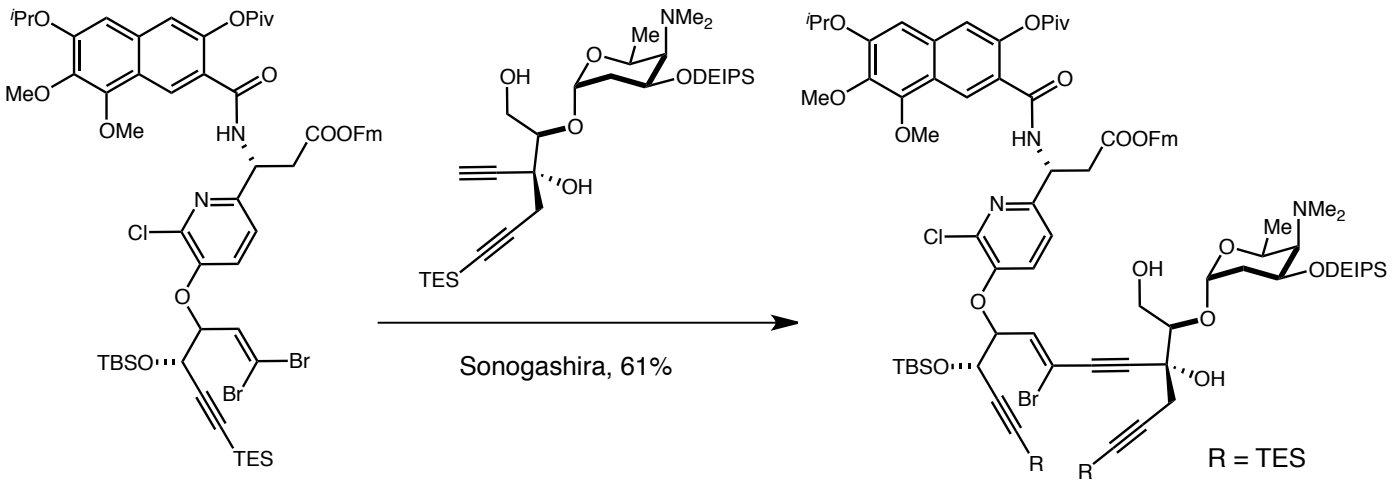
Total Synthesis of Proposed Kedarcidin Chromophore



proposed kedarcidin chromophore (1997)

Total Synthesis of Proposed Kedarcidin Chromophore

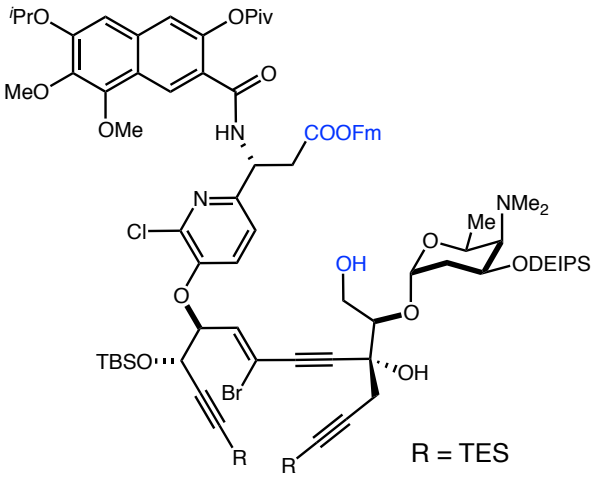
- Core synthesis



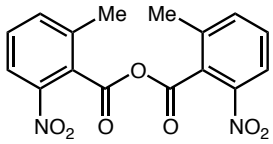
Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

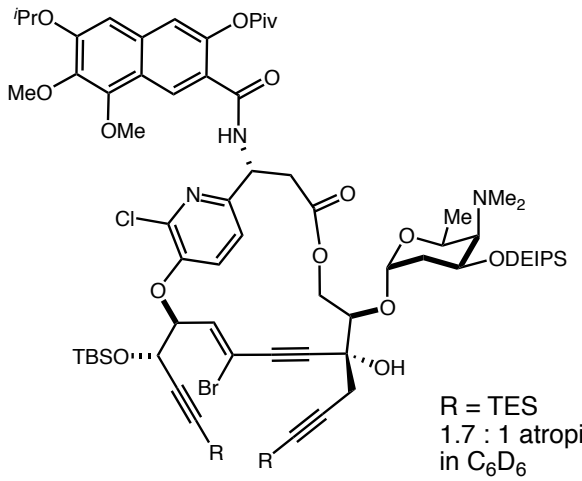
■ Core synthesis



1. NEt_3, 2. DMAP



66%

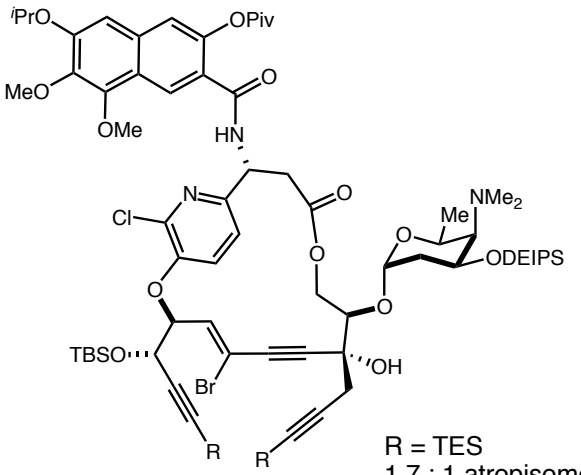


R = TES
1.7 : 1 atropisomers
in C_6D_6

Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

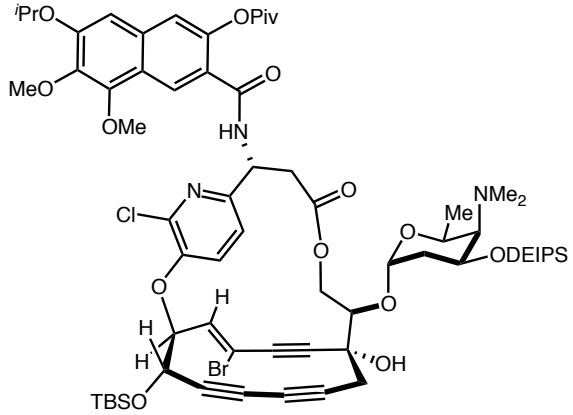
Total Synthesis of Proposed Kedarcidin Chromophore

- Glaser coupling



R = TES
1.7 : 1 atropisomers
in C_6D_6

1. $AgNO_3$, 73%
2. $Cu(OAc)_2$, CuI, py, 59%

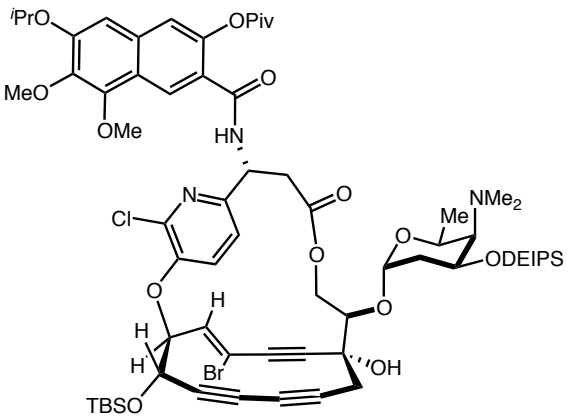


9 : 1 atropisomers in C_6D_6

Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

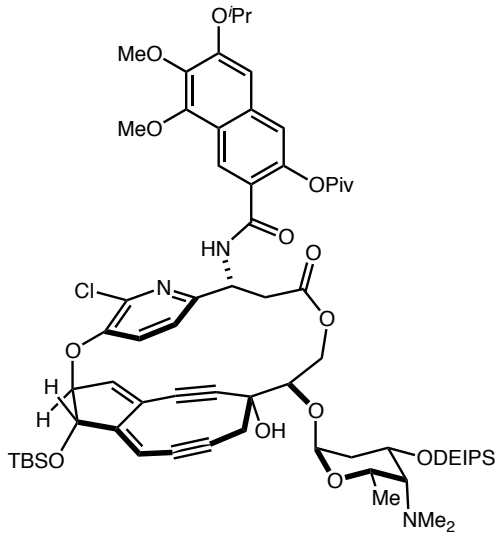
- Transannular cyclization



9 : 1 atropisomers
in C_6D_6

LHMDS, then *t*-BuLi,
quenched with HOAc immediately (< 3 s)

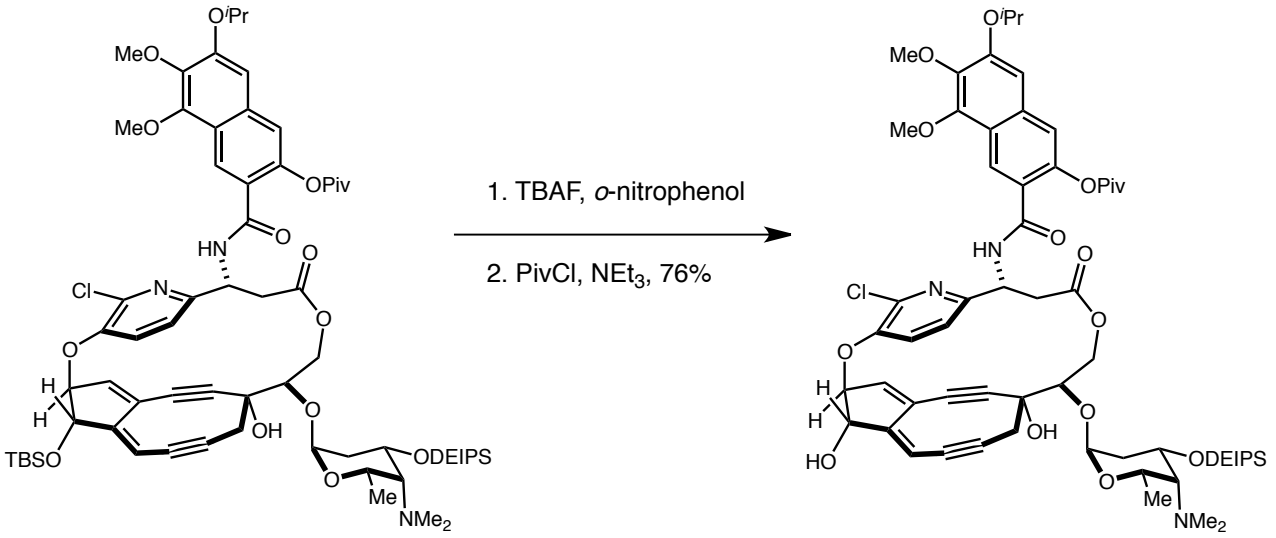
52%



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

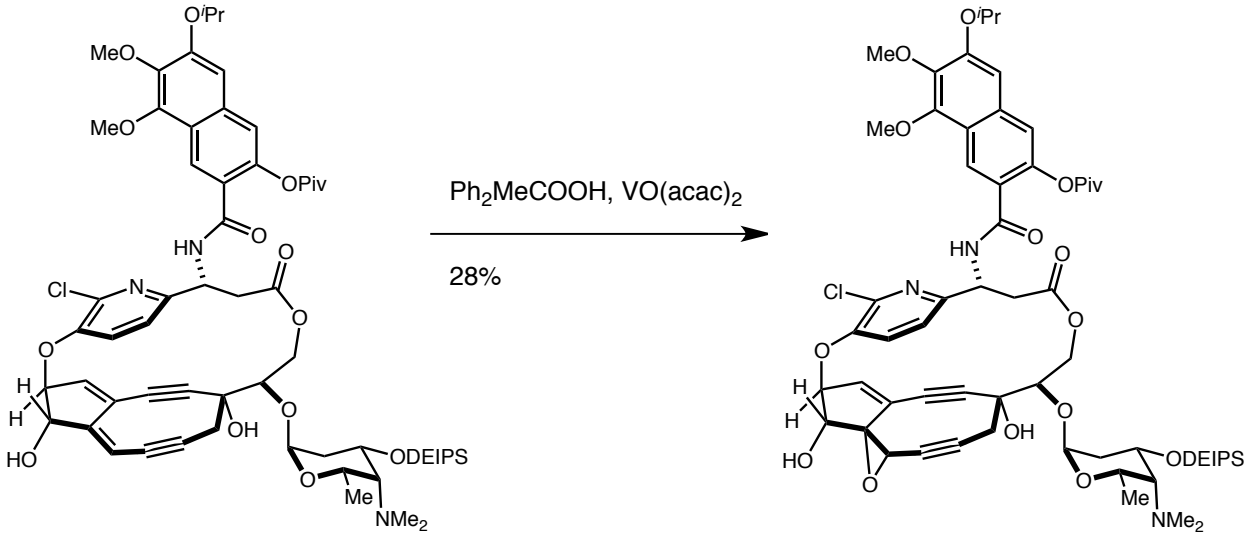
- Advanced stage



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

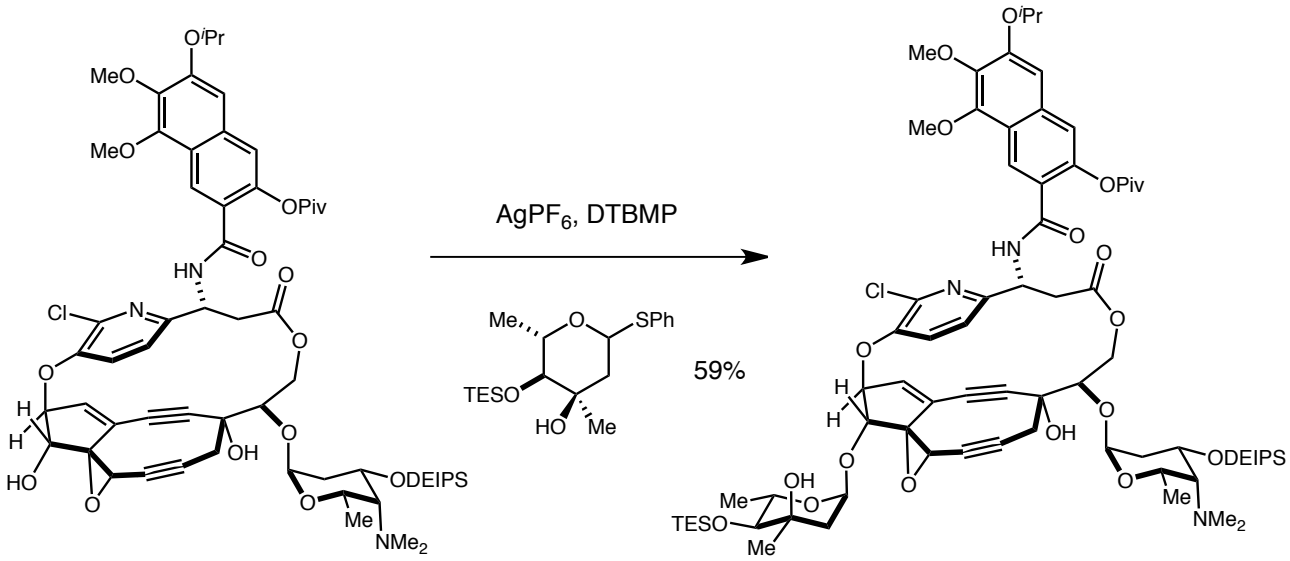
- Advanced stage



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

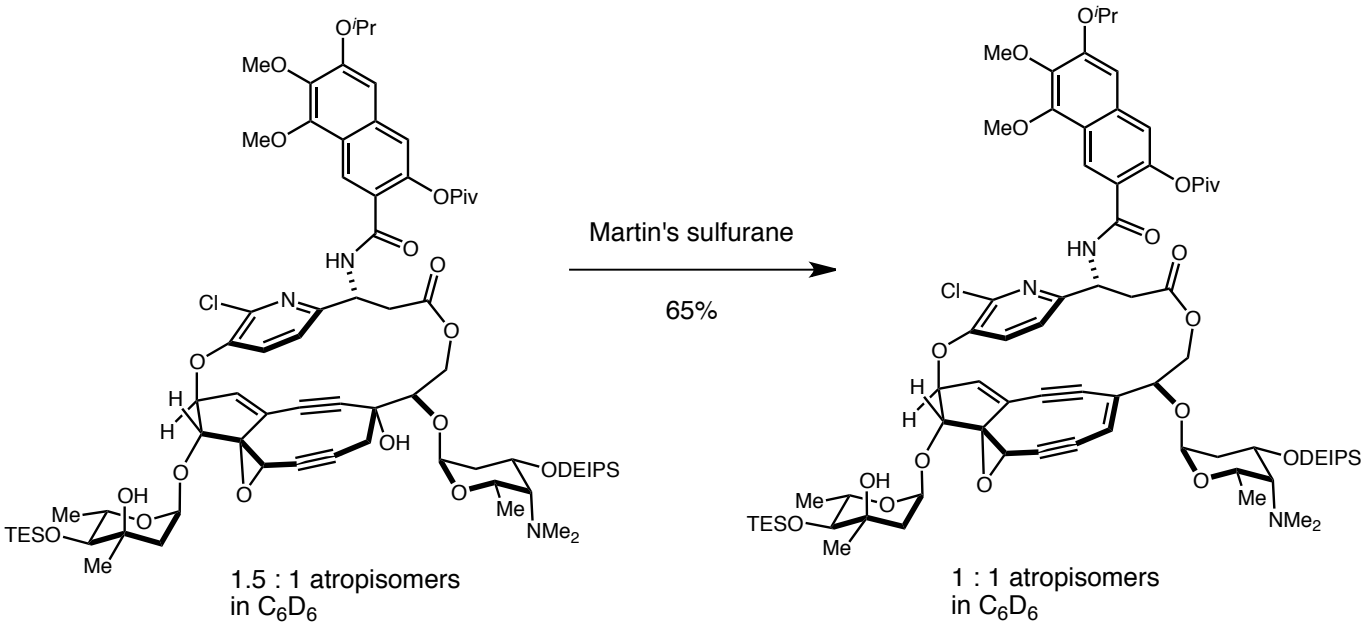
- Advanced stage



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore

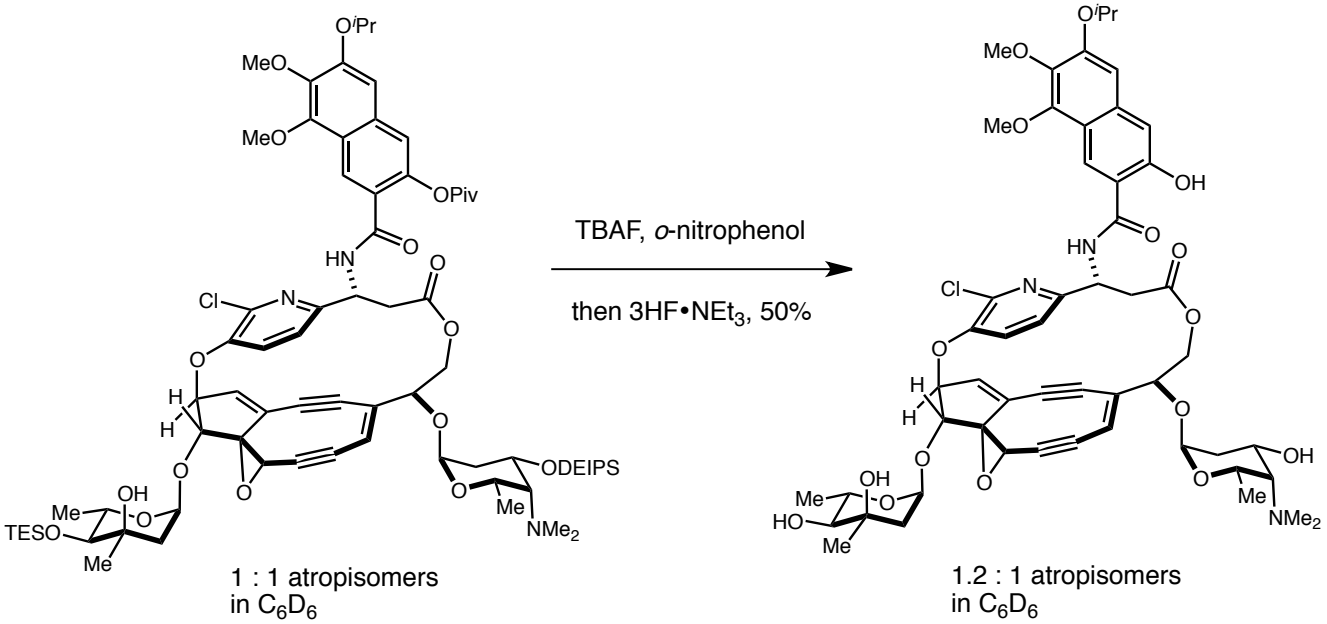
- Advanced stage



Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

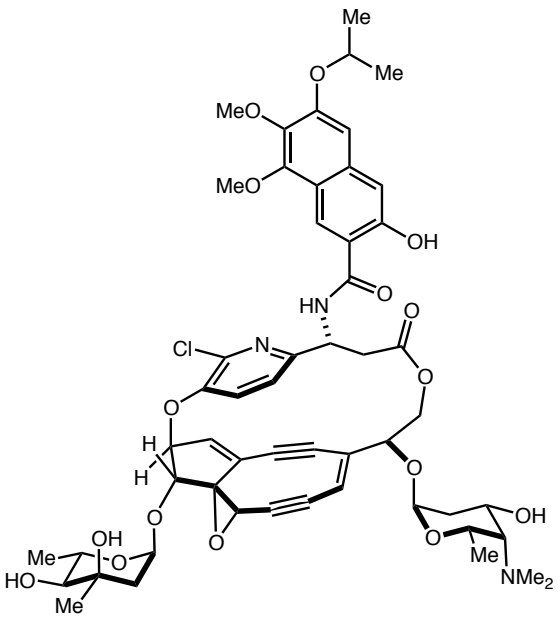
Total Synthesis of Proposed Kedarcidin Chromophore

- End game

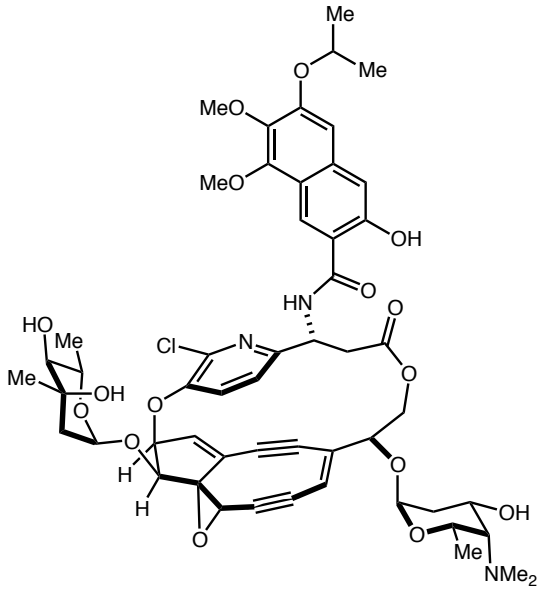


Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383.

Total Synthesis of Proposed Kedarcidin Chromophore



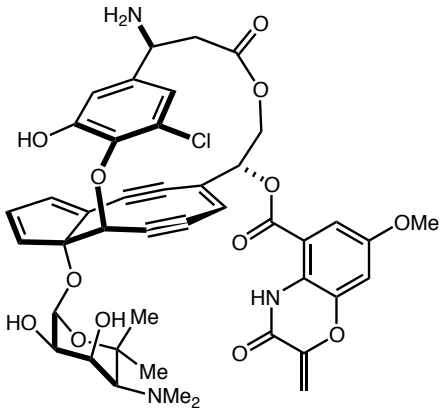
proposed kedarcidin chromophore (1997)



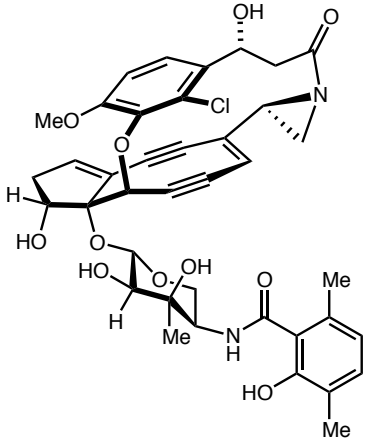
proposed kedarcidin chromophore (2007)

Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007***, 129*, 5381-5383.

Unfinishable Mission?



C-1027 chromophore



real maduropeptin chromophore?