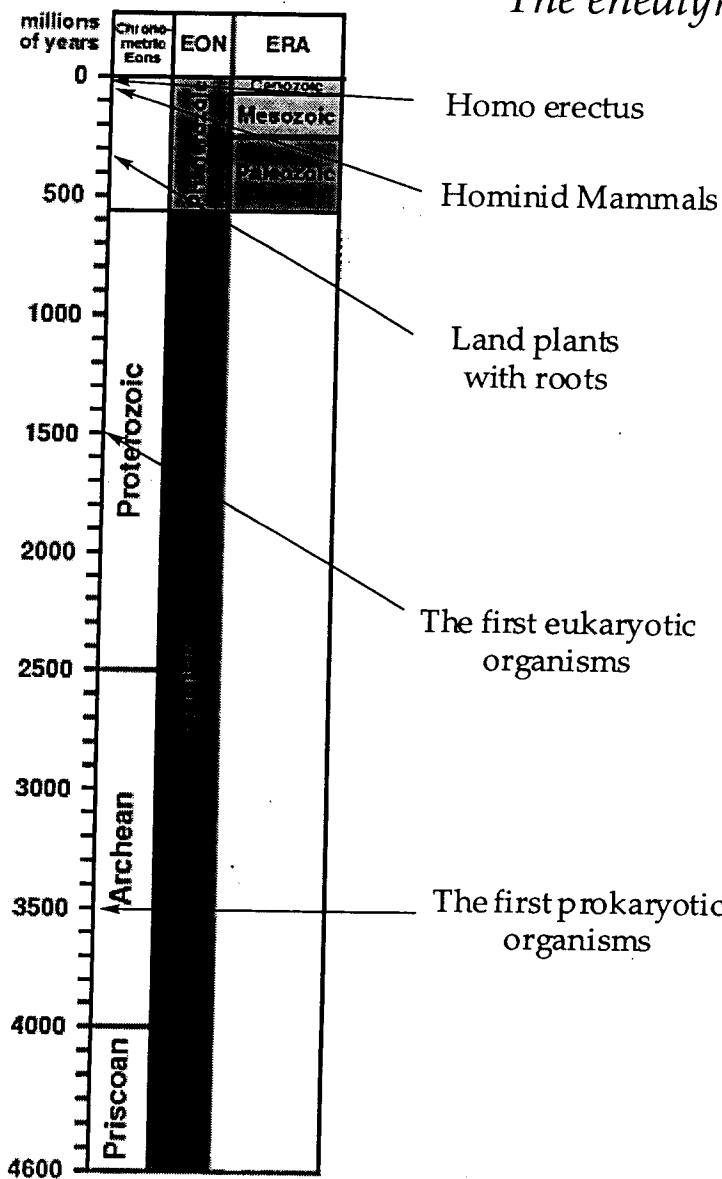


The Synthesis of 'Warhead' Anticancer Antibiotics.

The enediyne natural product Kedarcidin



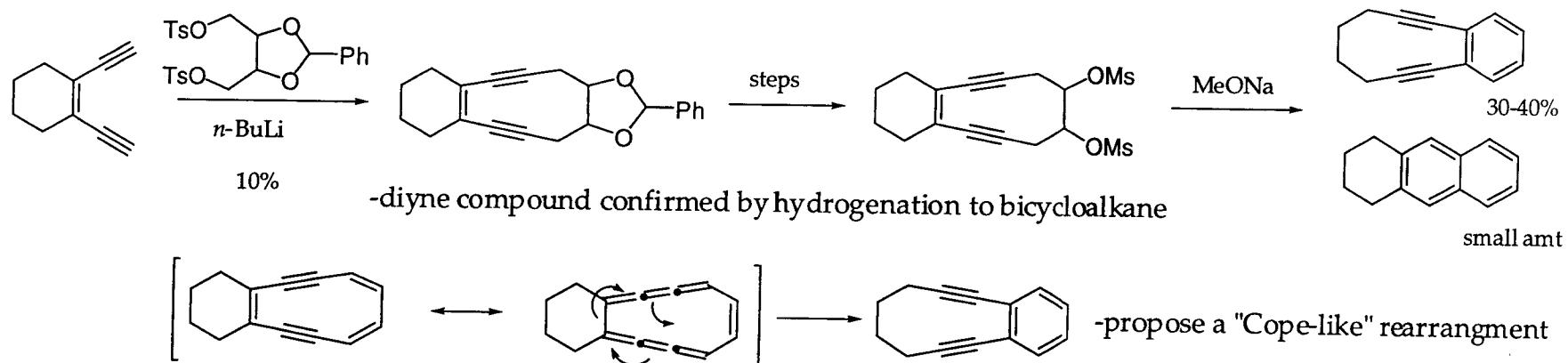
"Microorganisms and human beings have one thing in common: Both are attacked by toxic bacteria and viruses. However, microorganisms have been on the earth at least 2 billion years longer than human beings, and therefore, they know much better how to protect themselves against bacteria and viruses."

Elfi Kraka and Dieter Cremer JACS, 2000, 122, 8245

Jeromy Cottell
June 25, 2002

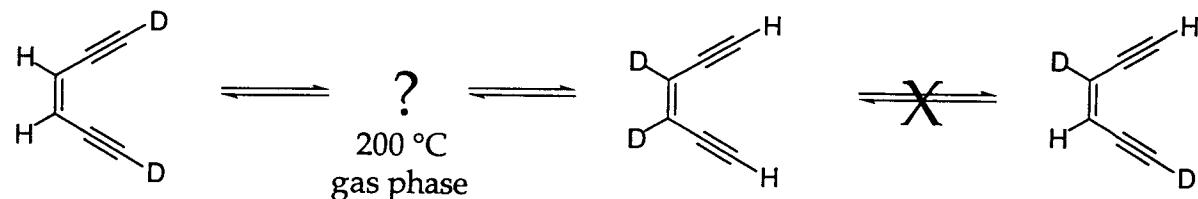
Bergman Cyclization

Masamune:



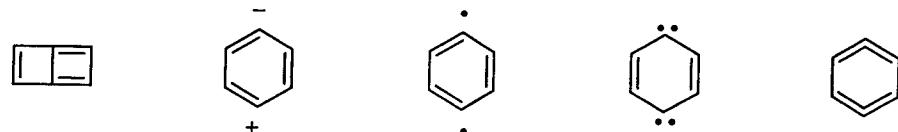
Chem. Comm. 1971, 1516

Bergman:



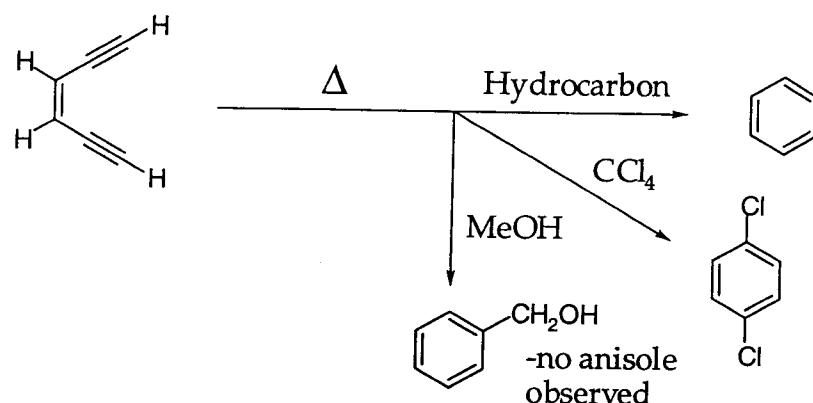
The *trans* isomer does NOT show deuterium scramble.

Proposed a symmetrical intermediate:



JACS 1972, 94, 660

Cyclization studies



Trapping agents suggest a radical intermediate

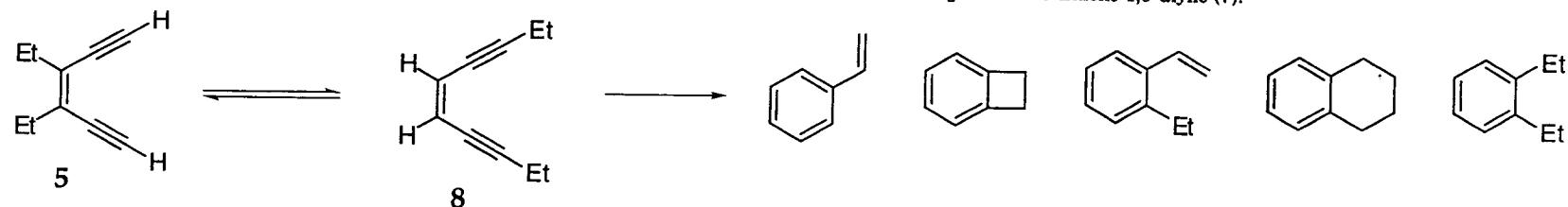


Table II. Product Yields in the Reaction of 5

run	phase	$T, ^\circ\text{C}$	absolute yield, ^a %				
			8 cis + trans	styrene	benzo-cyclobutene	σ -ethyl-styrene	tetralin
1	gas ^b	400	100	0	0	0	0
2	gas ^b	500	76.8	1.3	7.8	8.8	1.6
3	benzene solution ^c	195	51	0	0	0	0
4	benzene + 1,4-cyclohexadiene (1.1 M) ^c	195	6	0	0	0	75

^a Yields determined by digital integration of FID VPC trace and reference to internal standard. ^b N₂ flow. ^c [5] = 0.01 M.

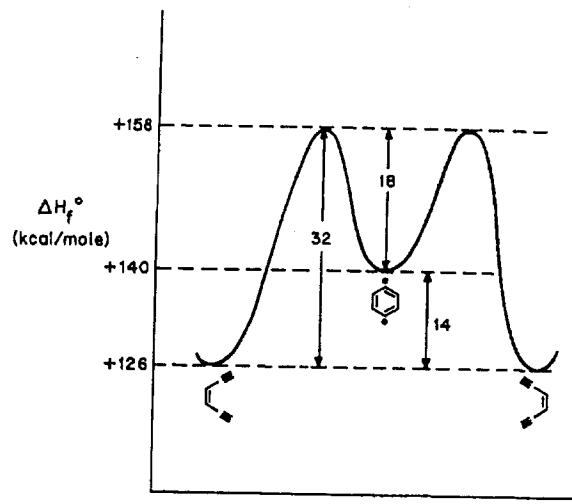
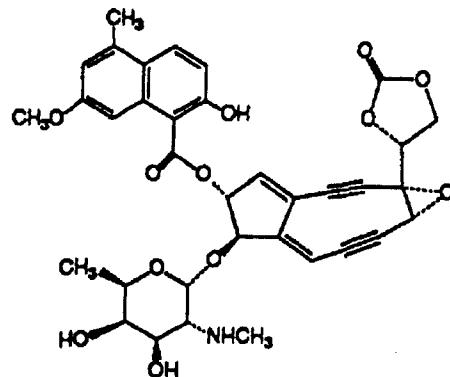


Figure 1. Reaction coordinate diagram for the degenerate rearrangement of 3-hexene-1,5-diyne (7).

Similar products were observed starting from 8

Meanwhile... Deep Undergroud...

Neocarzinostatin:



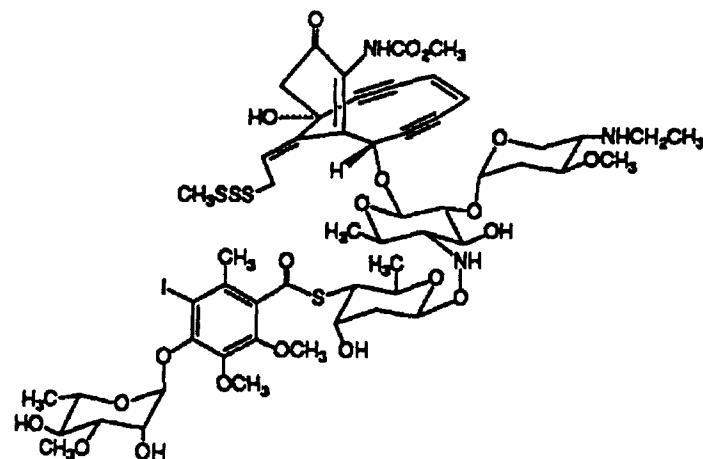
Isolated - Ishida *J. Antibiot.* 1965, 18, 68

Compound is extracted bound to a protein (NCS apoprotein)
NCS showed very high antitumor and antibiotic actions

Mode of action was through DNA cleavage

Structure - Edo *TL* 1985, 26, 331

Calicheamicin γ_1^I



Isolation and Structure - Lee *JACS*, 1987, 109, 3464

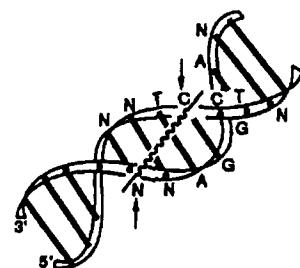
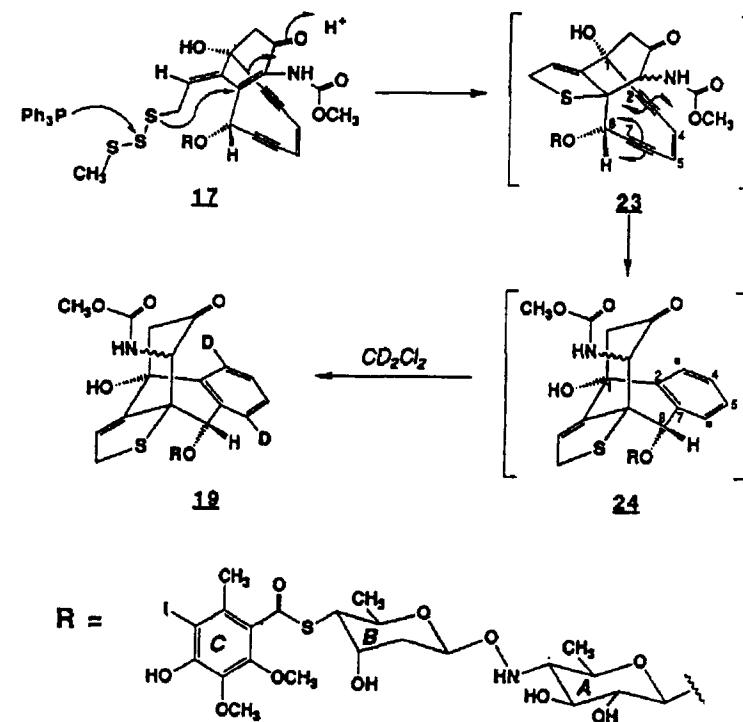
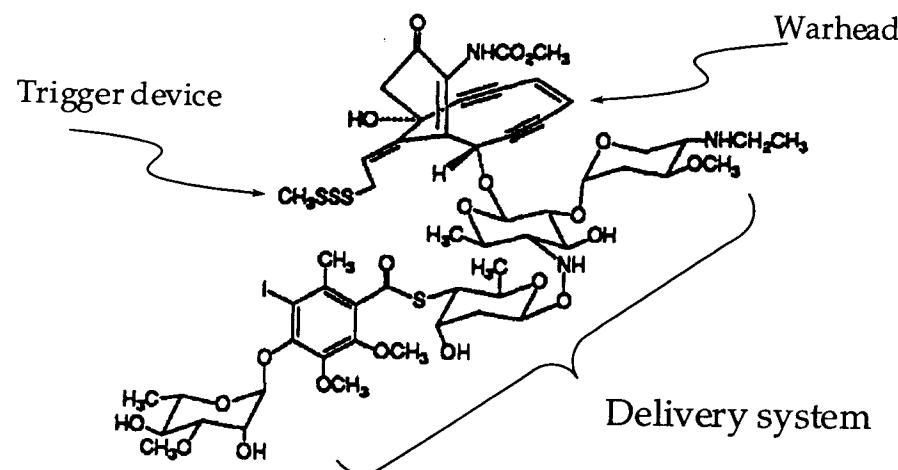
Compound was NOT isolated with a bound protein
Showed very high antitumor activity

Was also shown to cleave DNA

Mechanism of Action

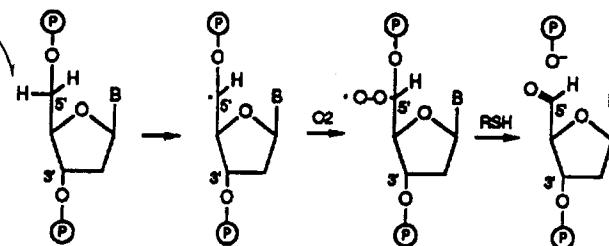
Calicheamicin γ_1^I

The cycloaromatization was observed upon addition of phosphine to the natural product (reduction of the trisulfide group)



Drug •

Probable Mechanism of DNA Cleavage at the 5'-Carbon of the Preferred Deoxyribose

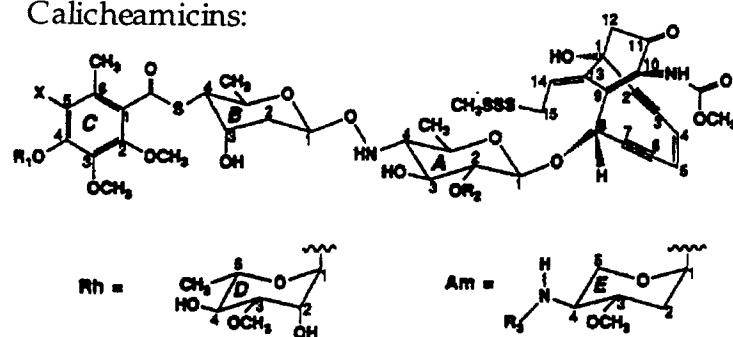


Does NOT show high sequence selectivity

Figure 1. Depiction of minor groove DNA cleavage by calicheamicin. Arrows denote the positions of hydrogen abstraction by the diradical intermediate.

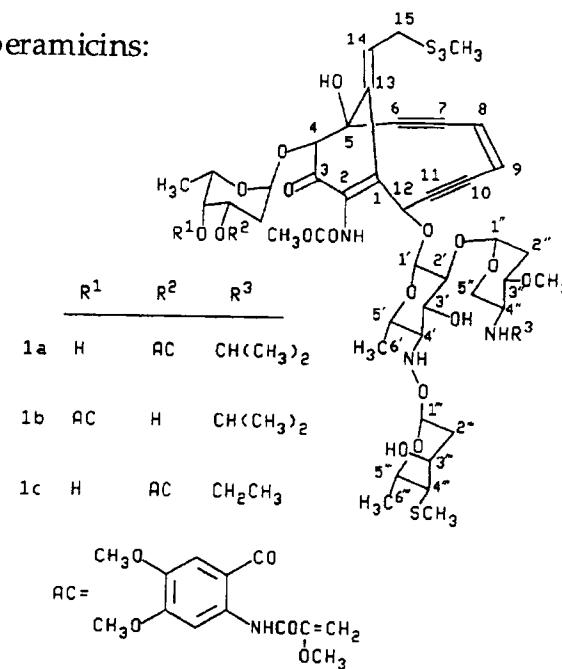
10-Membered Enediyne Compounds

Calicheamicins:

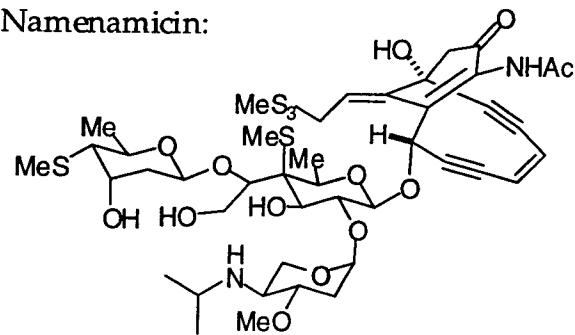


calicheamicin	X	R ₁	R ₂	R ₃
β_1^{Br} (5)	Br	Rh	Am	(CH ₂) ₂ CH
γ_1^{Br} (6)	Br	Rh	Am	CH ₂ CH ₃
α_1^{I} (7)	I	H	Am	CH ₂ CH ₂
α_1^{I} (8)	I	Rh	H	
β_1^{I} (9)	I	Rh	Am	(CH ₂) ₂ CH
γ_1^{I} (1)	I	Rh	Am	CH ₂ CH ₂
δ_1^{I} (10)	I	Rh	Am	CH ₃

Esperamicins:



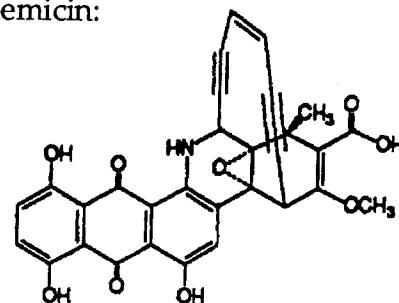
Namenamycin:



Ireland JACS, 1996, 118, 10898

Golik JACS, 1987, 109, 3462

Dynemicin:

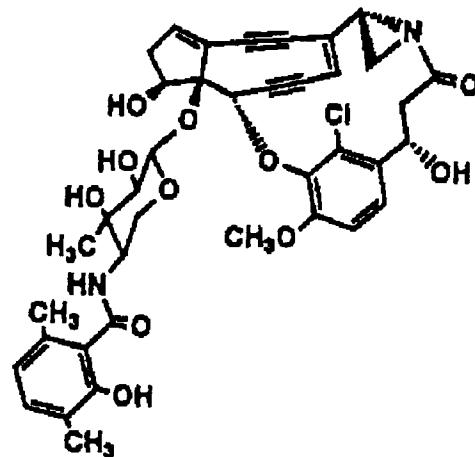


Konishi J. Antibiot. 1989, 42, 1449
6

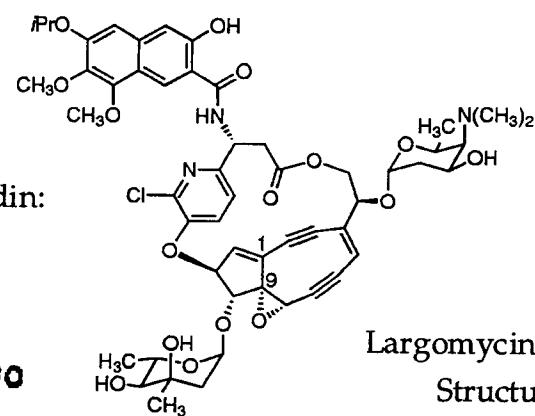
9-Membered Enediyne Compounds

Neocarzinostatin:

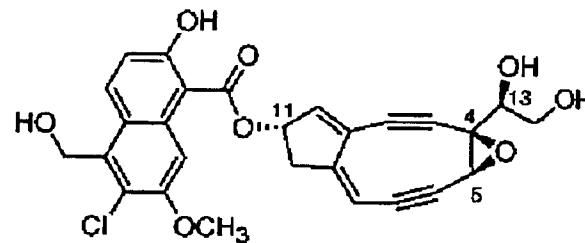
Meduropeptin:



Kedarcidin:



N1999-A2:



Largomycin:

Structure not determined

Sporamycin:

Structure not determined

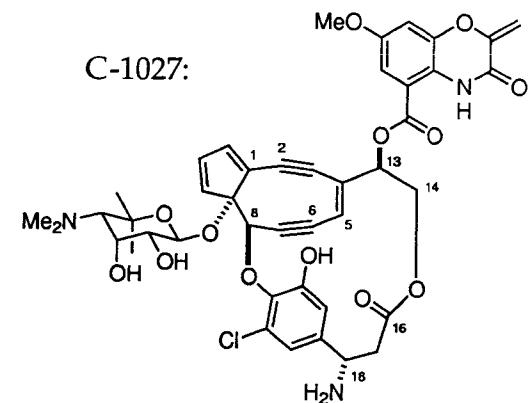
Ando *TL*, 1998, 39, 6495

Yoshida *TL*, 1993, 34, 2637

Schroeder *JACS*, 1992, 114, 7946

Schroeder *JACS*, 1994, 116, 9351

C-1027:



Macromomycin (Auromomycin):
Structure not determined

Actinoxanthin:

Structure not determined

All compounds isolated as
peptide complex except
N1999-A2!!!

Umezawa *J. Antibiot.* 1979, 32, 330

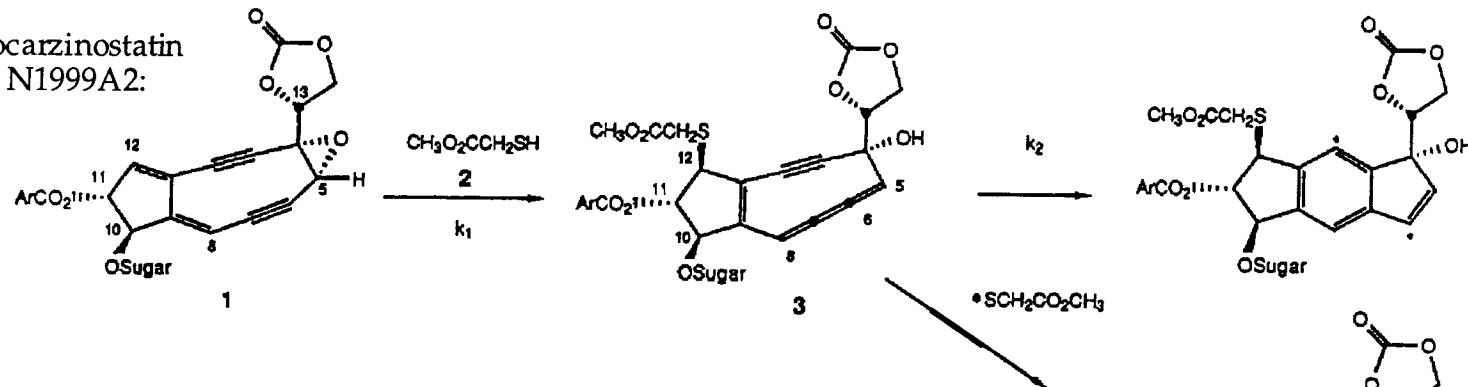
Khokhlov *J. Antibiot.* 1969, 22, 541

Yamaguchi *J. Antibiot.* 1970, 23, 369

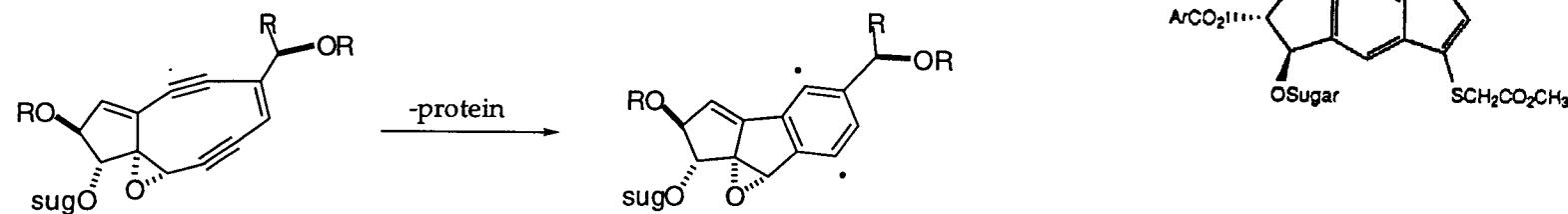
Umezawa *J. Antibiot.* 1977, 30, 202

Mechanism of Cyclization

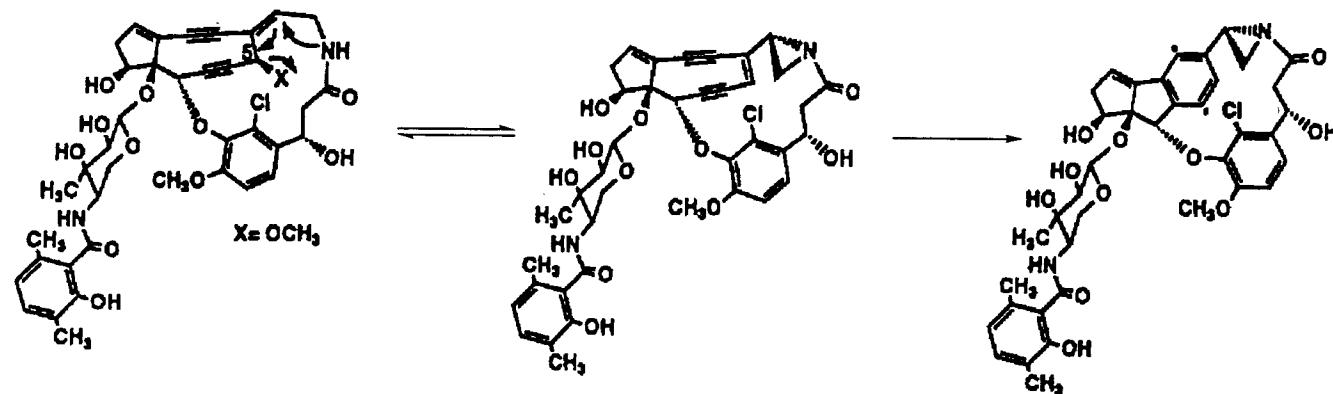
Neocarzinostatin
and N1999A2:



Kedarcidin and C-1027:

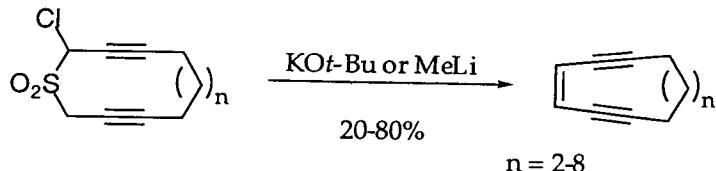


Meduropeptin:



Cyclic Enediynes

When do cyclic enediynes rearrange?



Simple cyclic enediynes suggest a correlation between stability (E_a) and the distance between the triple bonds.

Calc. distances of 3.31-3.20 Å show moderate reactivity.

Nucleophilic attack (in Calicheamicin) changes hybridization to decrease distance (3.35 → 3.16 Å).

Only side products were isolated for the Ramberg-Bäcklund reaction of n=1

Table I. Acetylene Proximity and MM2//PRDDO Cycloaromatization Barriers for a Series of Nine-Membered-Ring Enediynes

X	R ₁	R ₂	R ₃	R ₄	r(C _{sp} -C _{sp}), Å	ΔE*, kcal
CH ₂	H	H	H	H	2.99	17.9
CH ₂	CH ₃	CH ₃	CH ₃	CH ₃	2.95	12.5
CH ₂	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	2.94	16.3
C(CH ₃) ₂	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	2.90	7.0
C=CH ₂	H	H	H	H	3.00	17.4
C=CH ₂	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	2.96	17.0
C=CH(tBu)	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	2.98	22.3
C=C(CH ₃) ₂	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	cyclopropyl ^a	3.00	26.0
C=C(CH ₃) ₂	▷.....F	▷.....F	▷.....F	▷.....F	3.01	30.9

^aSpirocyclopropyl. ^bThe symmetrical F's are syn to the X flap and pointing inward. Four inward-directed F's are needed to guarantee that the high barrier is effectively probed.

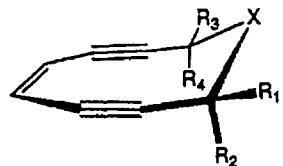
Table I. Calculated^a Strain Energies and Distances Between Acetylenic Carbons in Cyclic Conjugated Enediynes.

Entry	Compound	Ring Size	Strain Energy (kcal/mole)	a b (Å)	c d (Å)	Stability	Ref
1	5 (n = 1)	9	14.80	2.51	2.84	should cyclize	unknown
2	5 (n = 2)	10	11.40	2.60	3.25	cyclization at 25 °C	this work
3	5 (n = 3)	11	8.96	2.72	3.61	stable at 25 °C	this work
4	5 (n = 4)	12	7.60	2.80	3.90	stable at 25 °C	this work
5	5 (n = 5)	13	7.37	2.87	4.14	stable at 25 °C	this work
6	5 (n = 6)	14	8.21	2.87	4.15	stable at 25 °C	this work
7	5 (n = 7)	15	8.39	2.93	4.33	stable at 25 °C	this work
8	5 (n = 8)	16	11.35 ^b	2.88 ^b	4.20 ^b	stable at 25 °C	this work

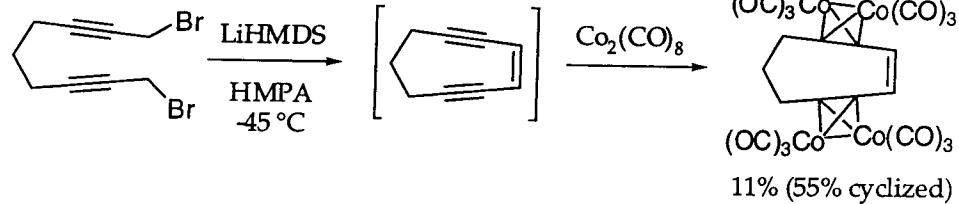
^aMM2 calculations were performed by using MacroModel.⁶ ^bThe origin of this seemingly anomalous result is unknown at present.

Nicolaou JACS 1988, 110, 4866

Additional factors such as sunstitution and additional rings complicate the analysis



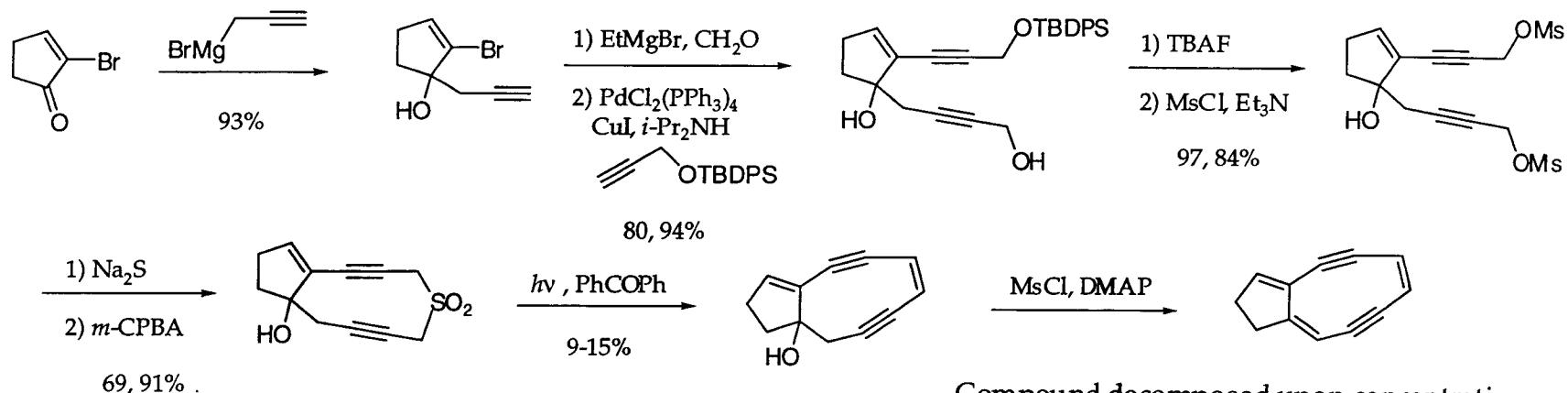
Snyder JACS 1990, 112, 5367



Jones JACS 2000, 122, 1943

Preparation of 9-Mem. Rings

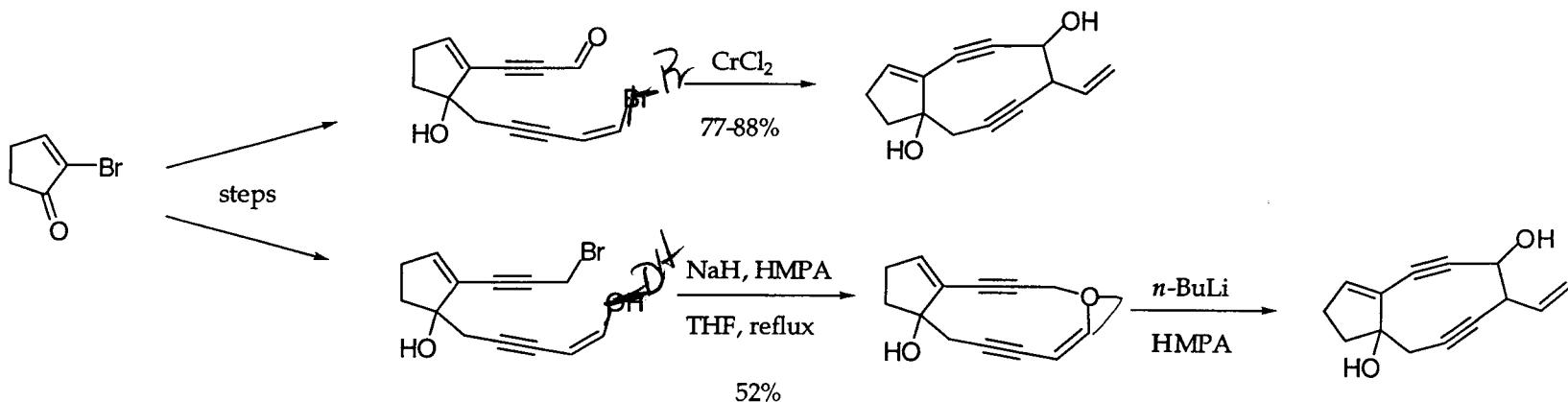
Wender:



Compound decomposed upon concentration

$- t_{1/2} = 48 \text{ h at rt, in solution}$

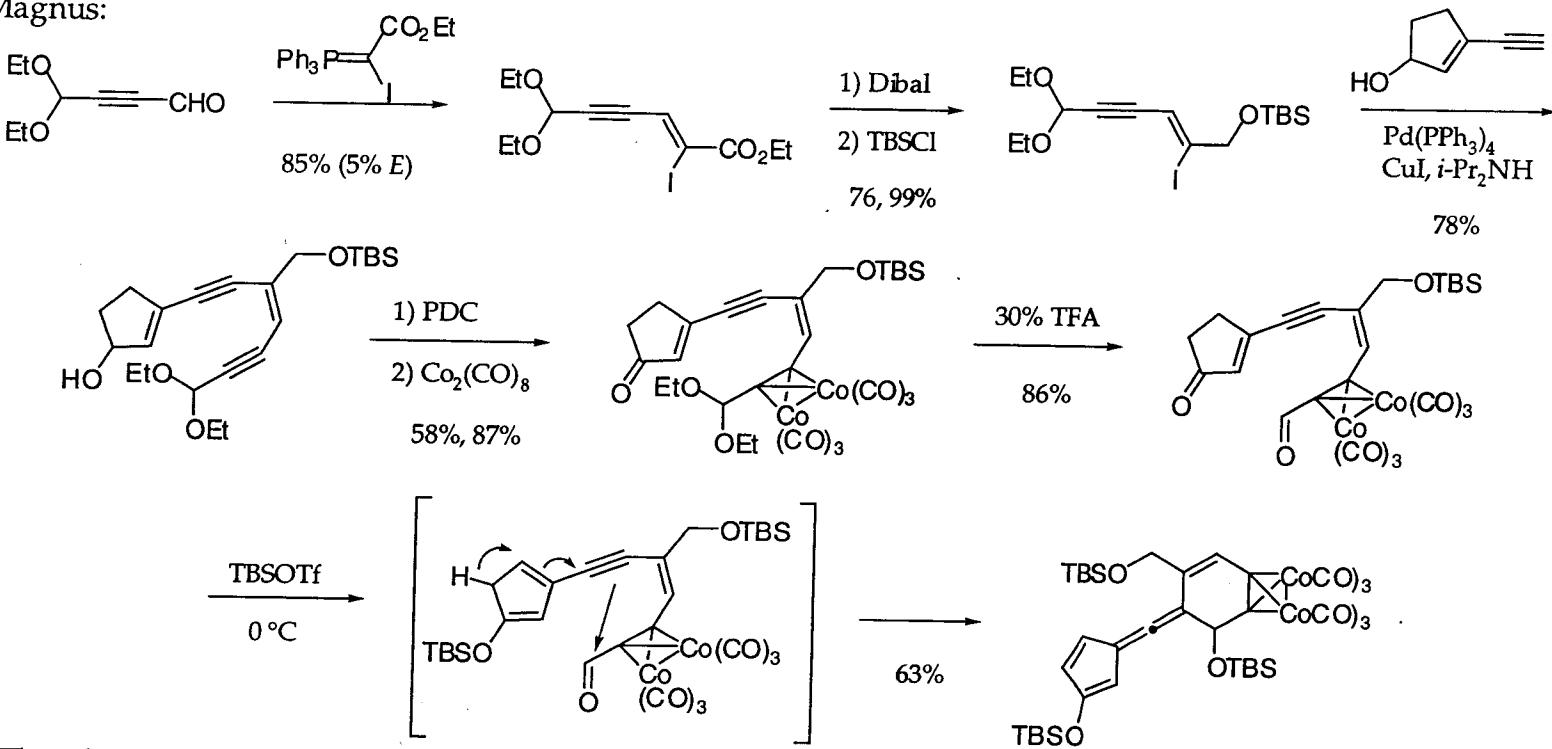
Wender *TL*, 1988, 29, 909



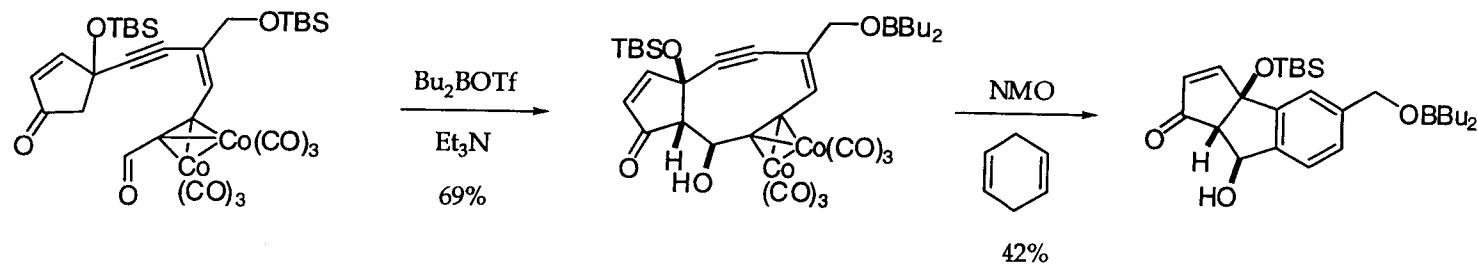
Wender *JACS*, 1990, 112, 5369

With a Bit of Substitution

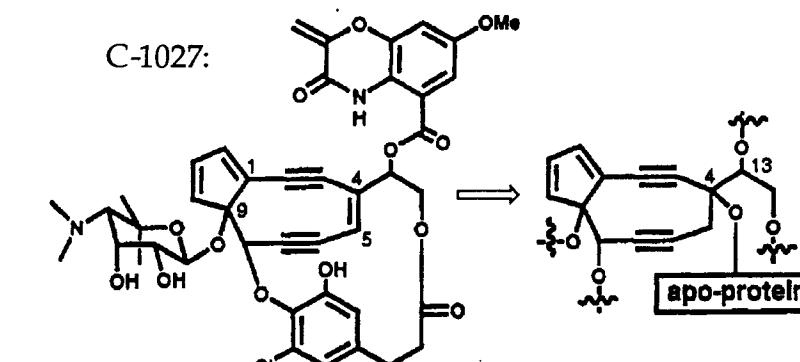
Magnus:



Therefore prepared:



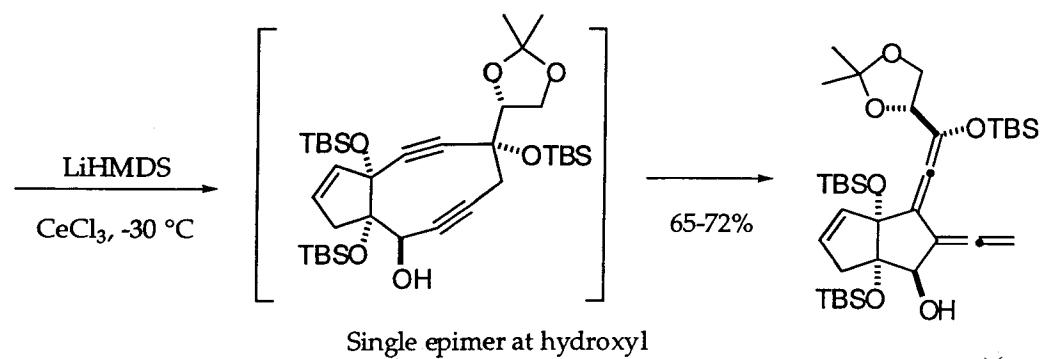
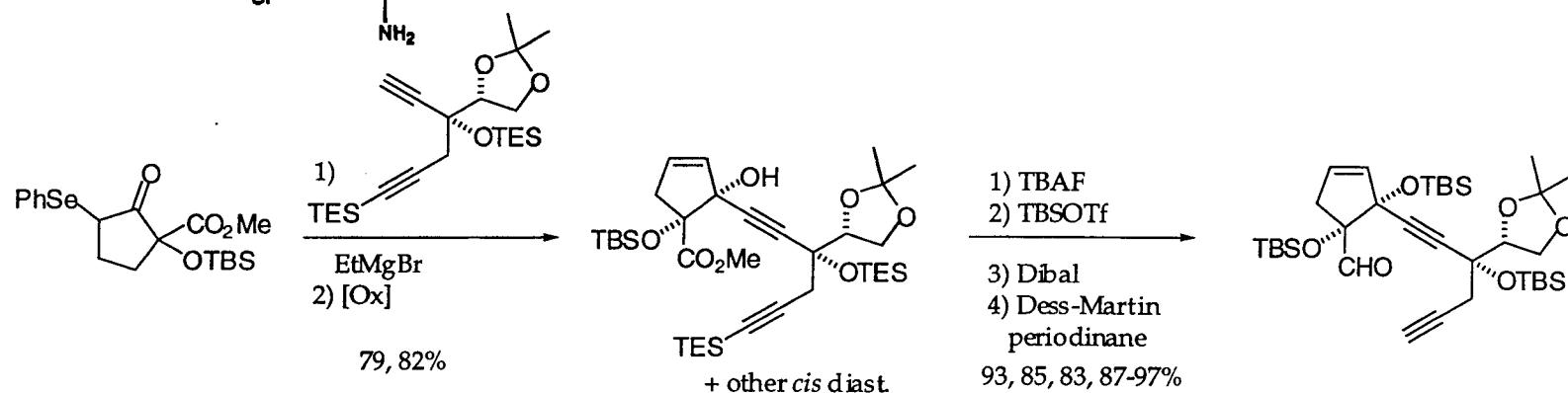
Total Synthesis Attempts



Hirama proposed that the enediyne is covalently stabilized in the apo-protein binding site.

-An approach to the substituted diyne may provide access to the desired enediyne.

Hirama JACS 1994, 116, 10310



Concluded that the multiple sp³ centers allowed for the Cope cyclization to occur

Towards a Stable Enediyne

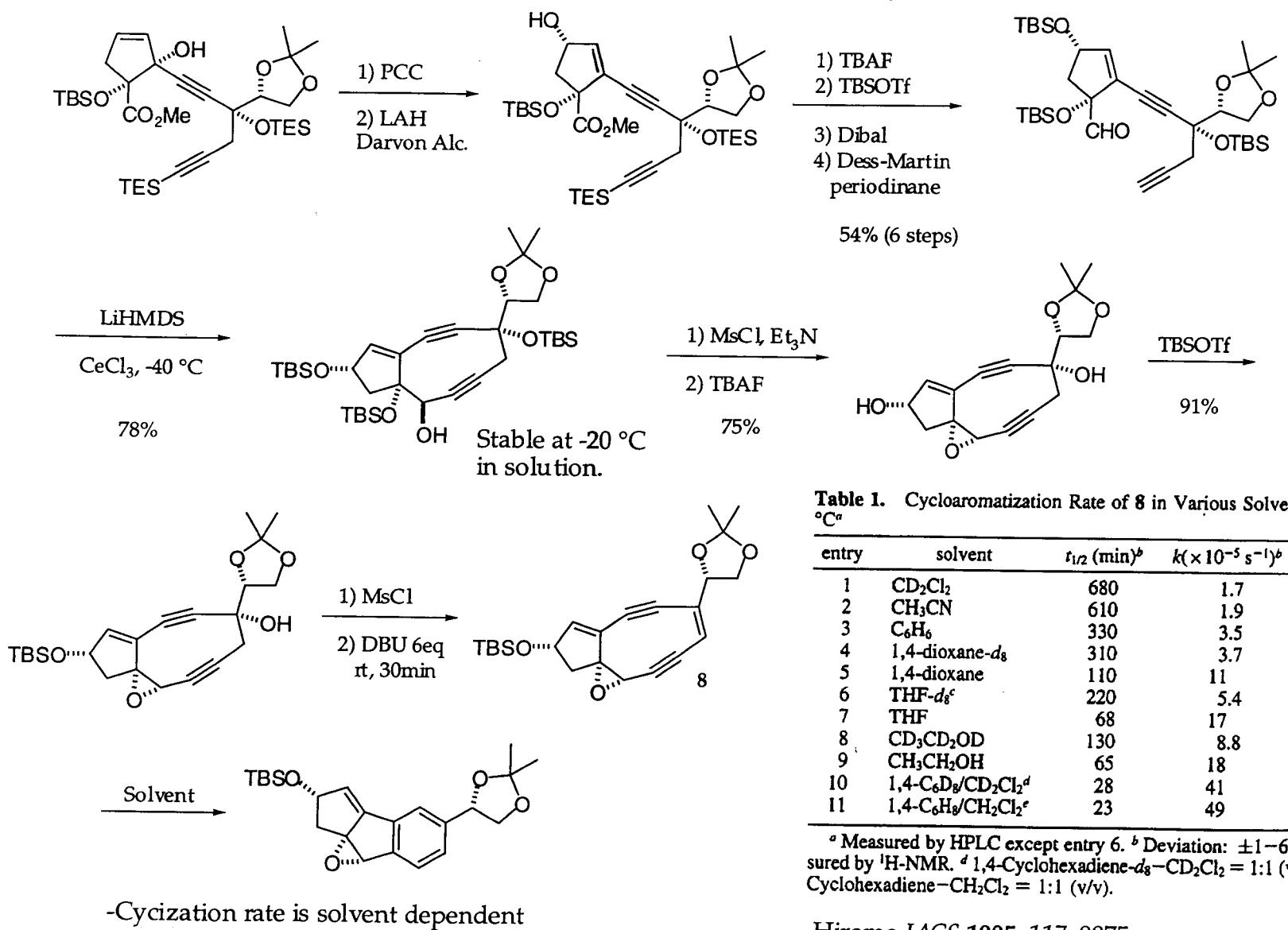
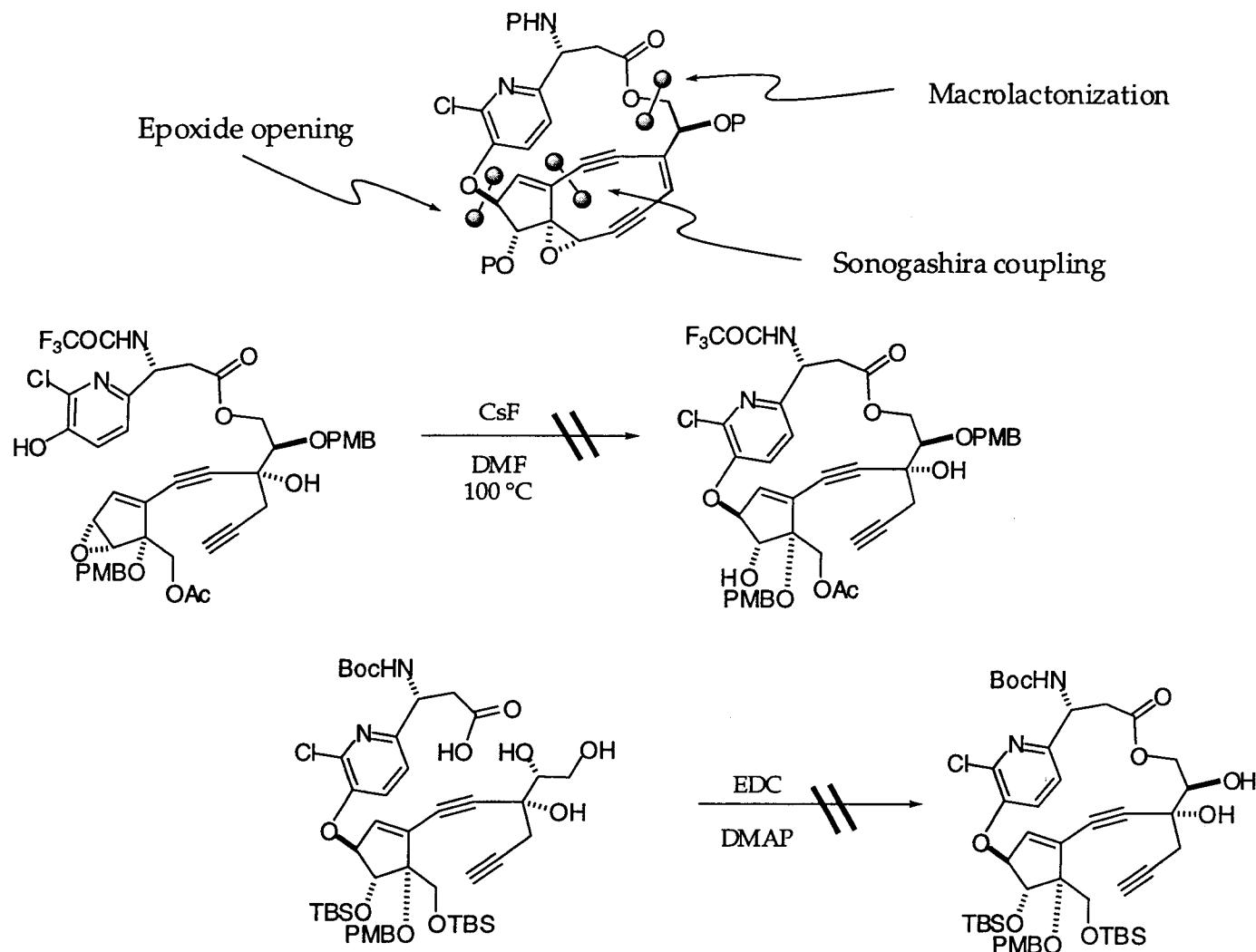


Table 1. Cycloaromatization Rate of **8** in Various Solvents at 28 °C^a

entry	solvent	<i>t</i> _{1/2} (min) ^b	<i>k</i> ($\times 10^{-5}$ s ⁻¹) ^b	rel rate
1	CD ₂ Cl ₂	680	1.7	0.035
2	CH ₃ CN	610	1.9	0.039
3	C ₆ H ₆	330	3.5	0.071
4	1,4-dioxane- <i>d</i> ₈	310	3.7	0.076
5	1,4-dioxane	110	11	0.22
6	THF- <i>d</i> ₆ ^c	220	5.4	0.11
7	THF	68	17	0.35
8	CD ₃ CD ₂ OD	130	8.8	0.18
9	CH ₃ CH ₂ OH	65	18	0.37
10	1,4-C ₆ D ₈ /CD ₂ Cl ₂ ^d	28	41	0.84
11	1,4-C ₆ H ₈ /CH ₂ Cl ₂ ^e	23	49	1.0

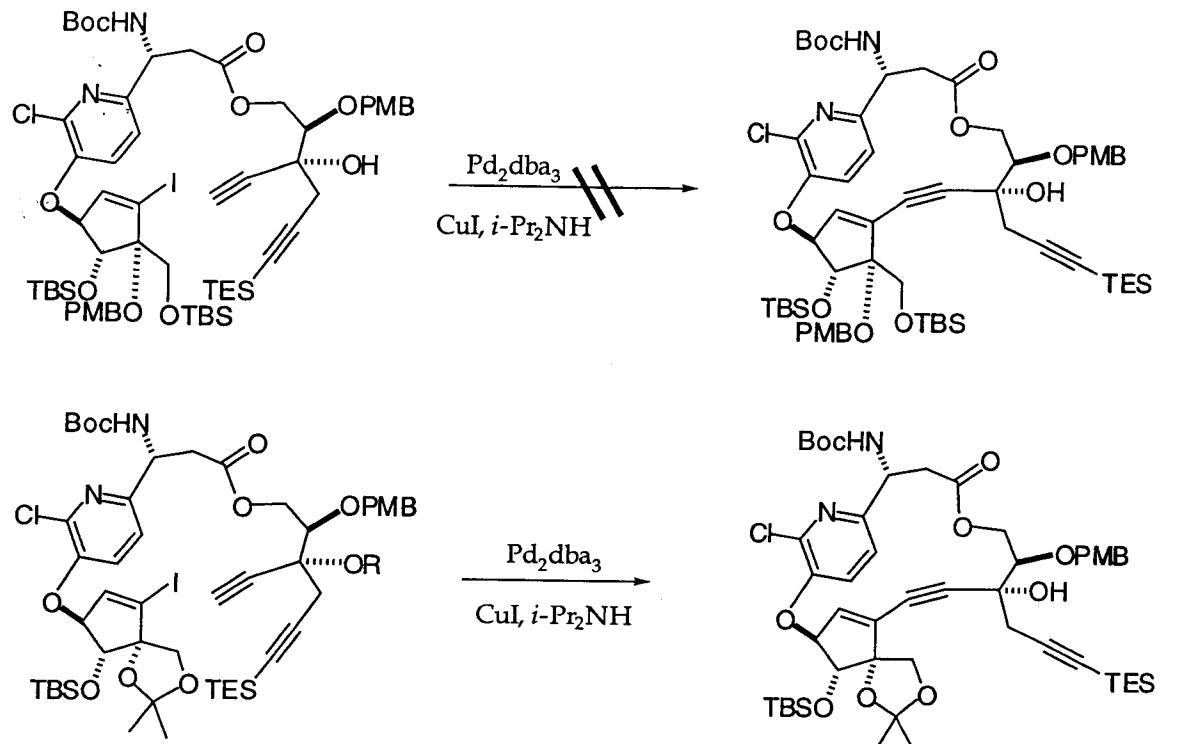
^a Measured by HPLC except entry 6. ^b Deviation: ±1–6%. ^c Measured by ¹H-NMR. ^d 1,4-Cyclohexadiene-*d*₈-CD₂Cl₂ = 1:1 (v/v). ^e 1,4-Cyclohexadiene-CH₂Cl₂ = 1:1 (v/v).

Ansa Bridge



Hirama *TL*, 1999, 40, 8281

Ansa Bridge

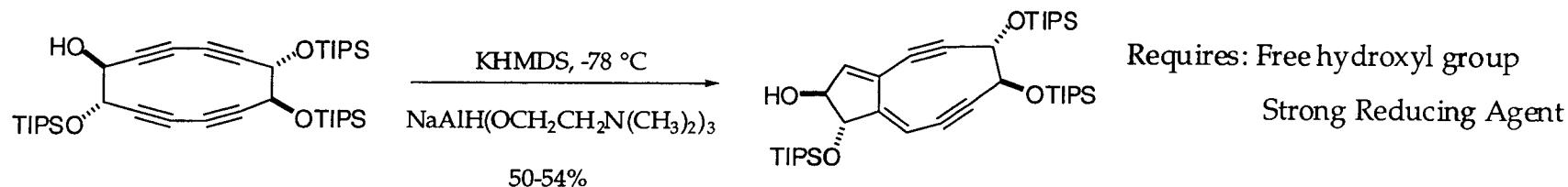


Acetonide group helps orient reactive groups towards each other

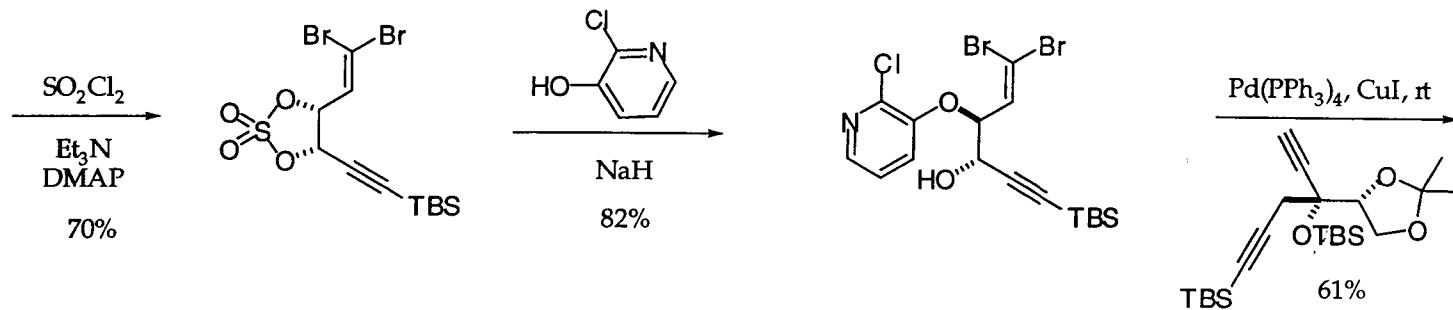
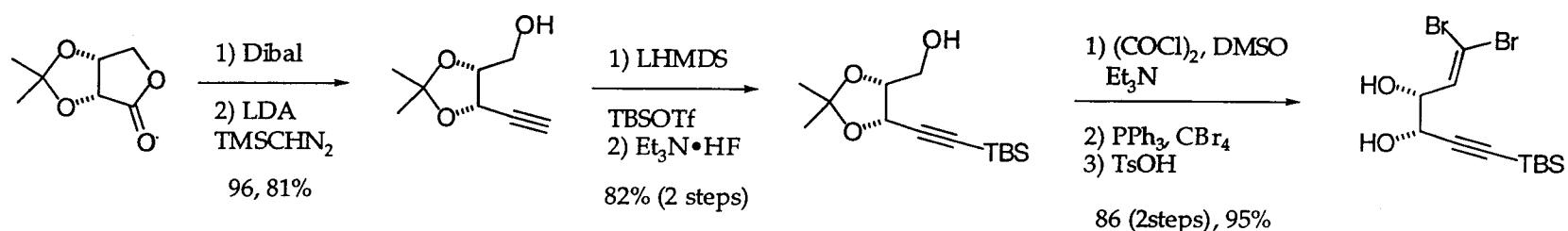
Macrolactone isolated as a single, desired, atropisomer

Hirama *TL*, 1999, 40, 8281

Transannular Cyclization

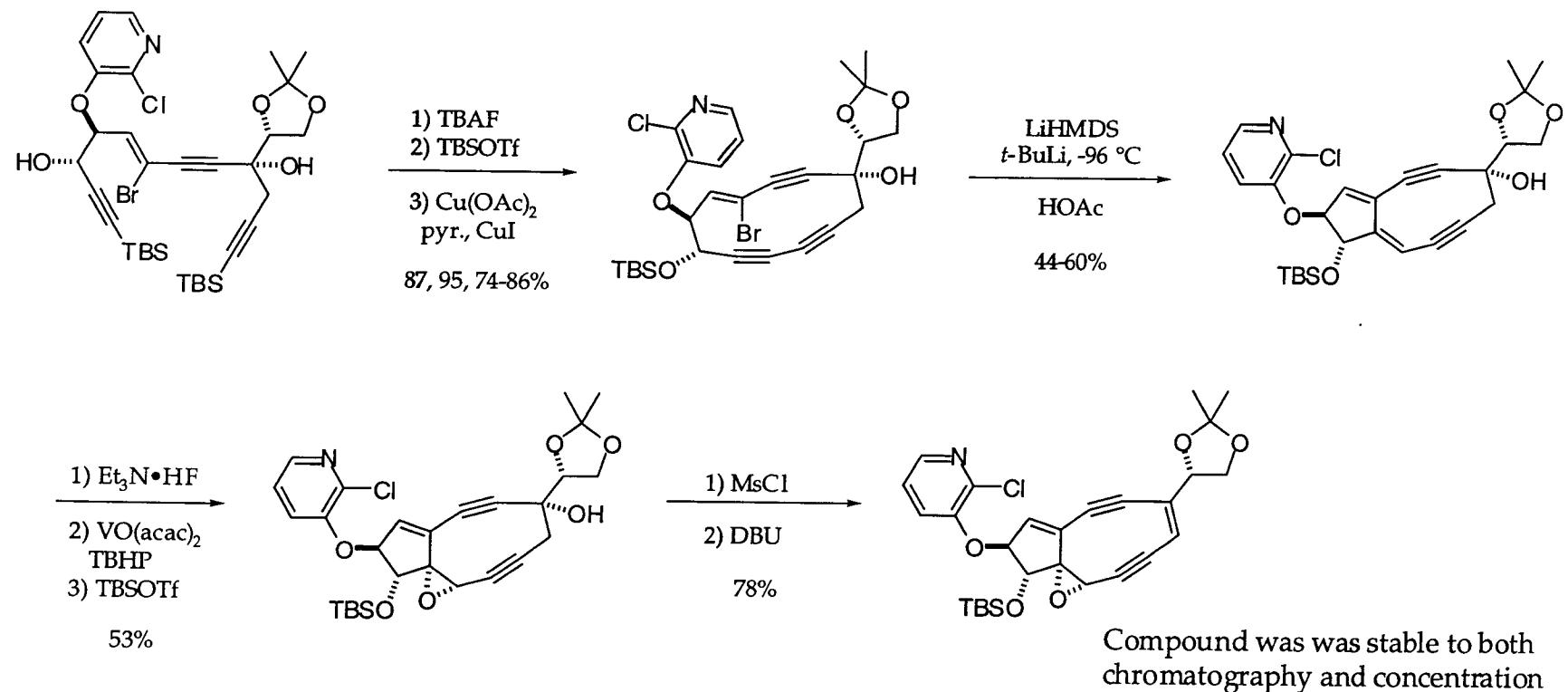


Try to access same intermediate:

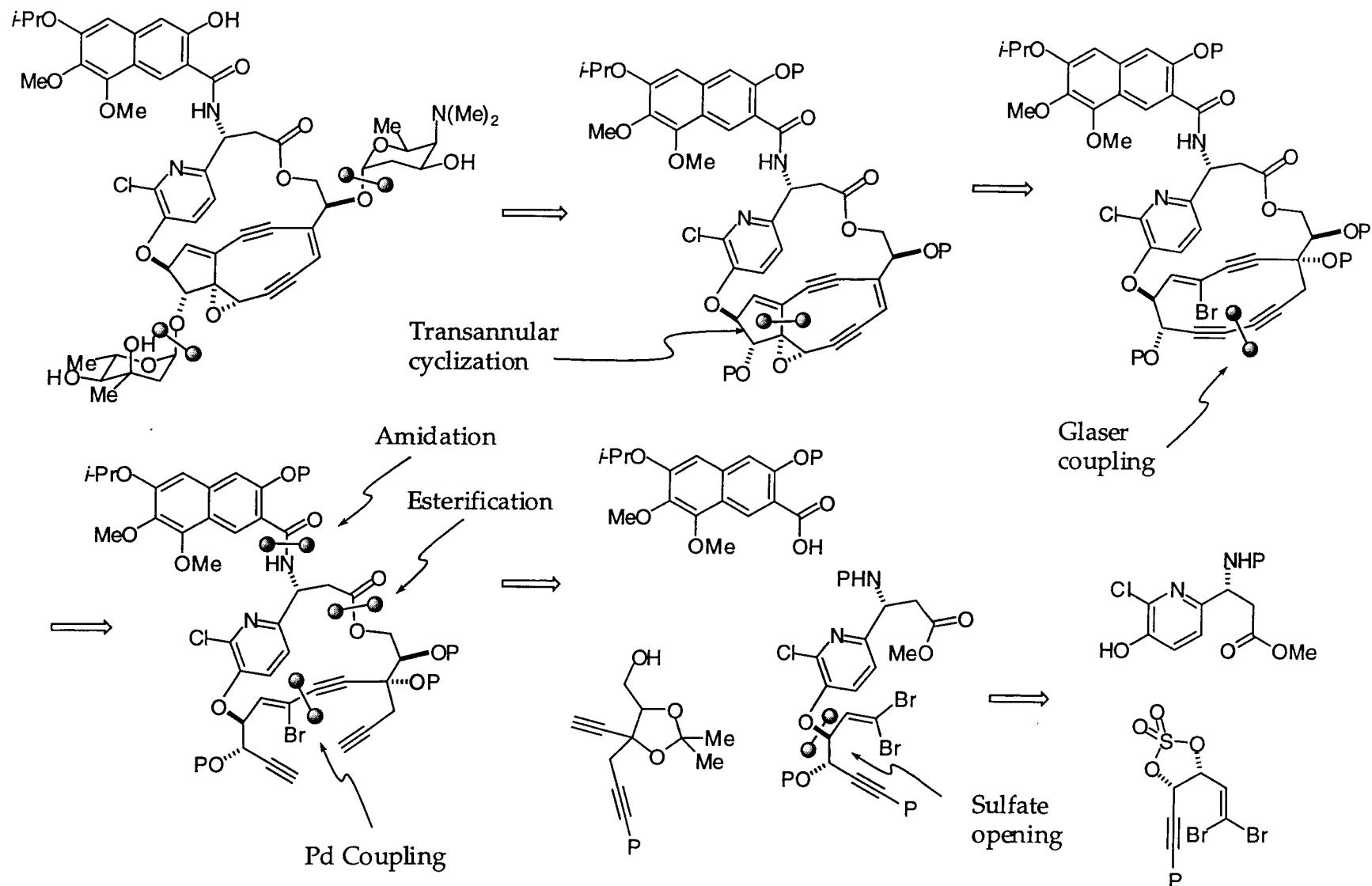


Myers Angew. Chem. Int. 2000, 39, 2732

Advanced Model System

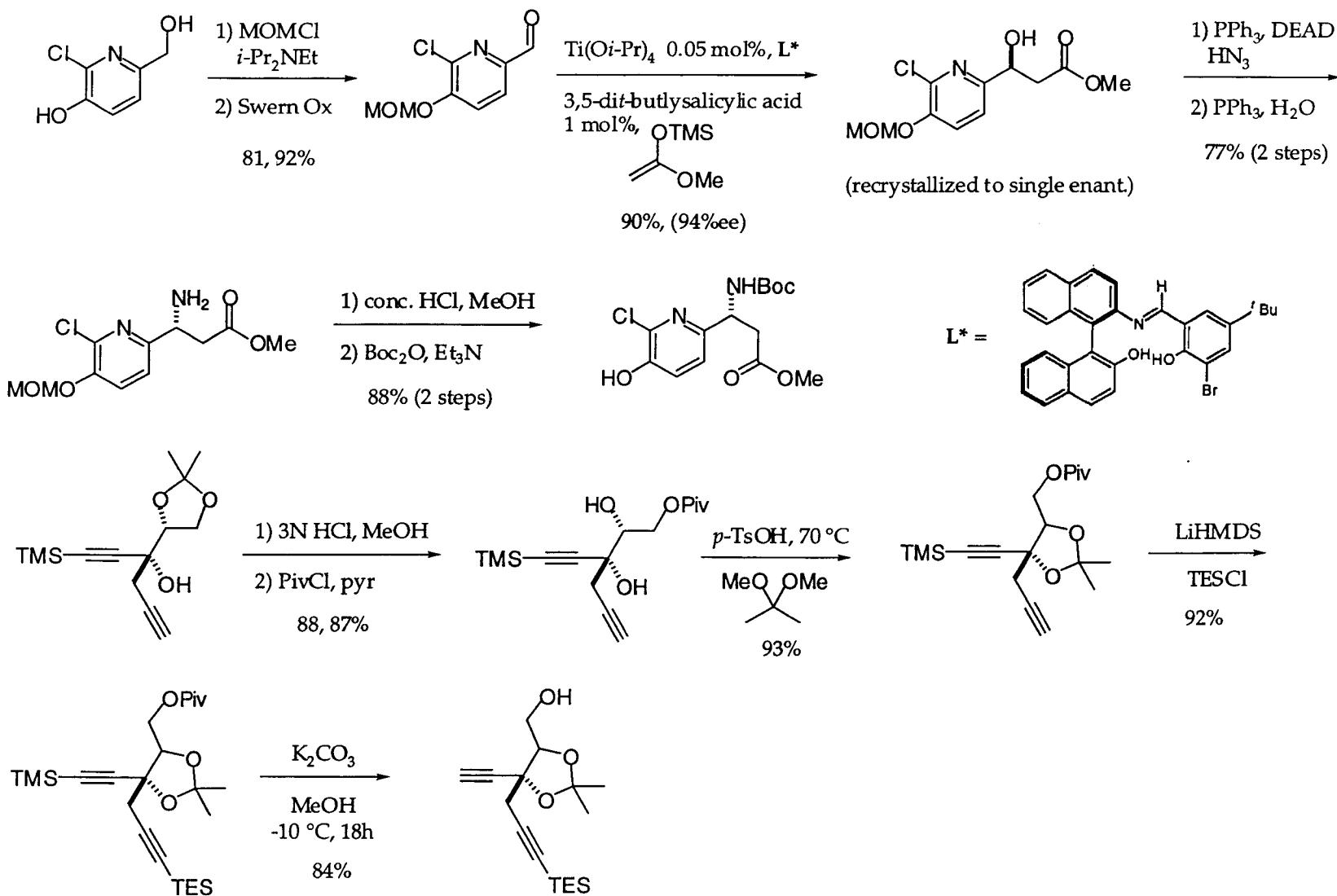


Kedarcidin Retro-Synthesis

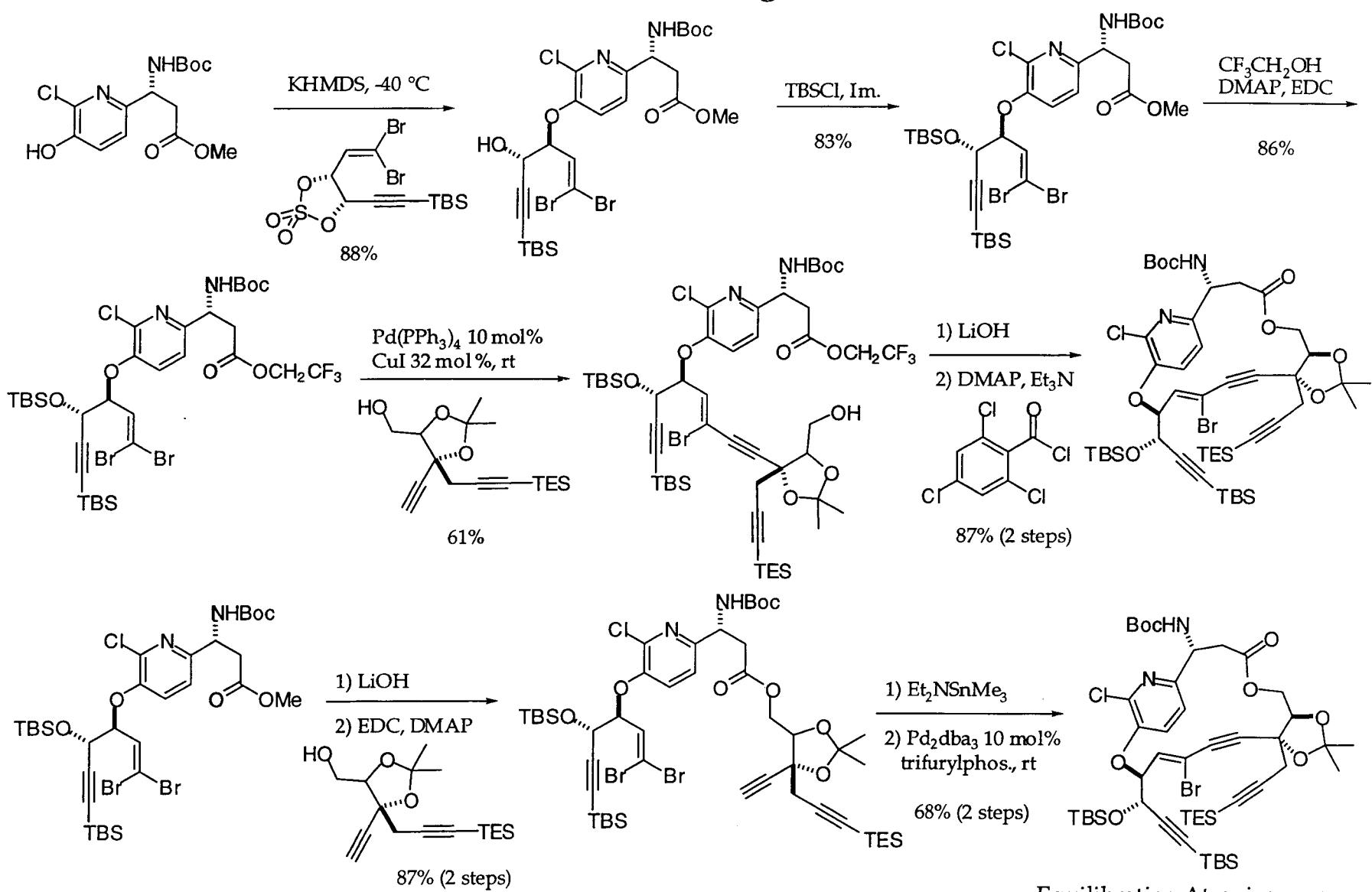


Myers *Angew. Chem. Int.*, 2002, 41, 1062. *JACS*, 2002, 124, 4583

Starting Materials



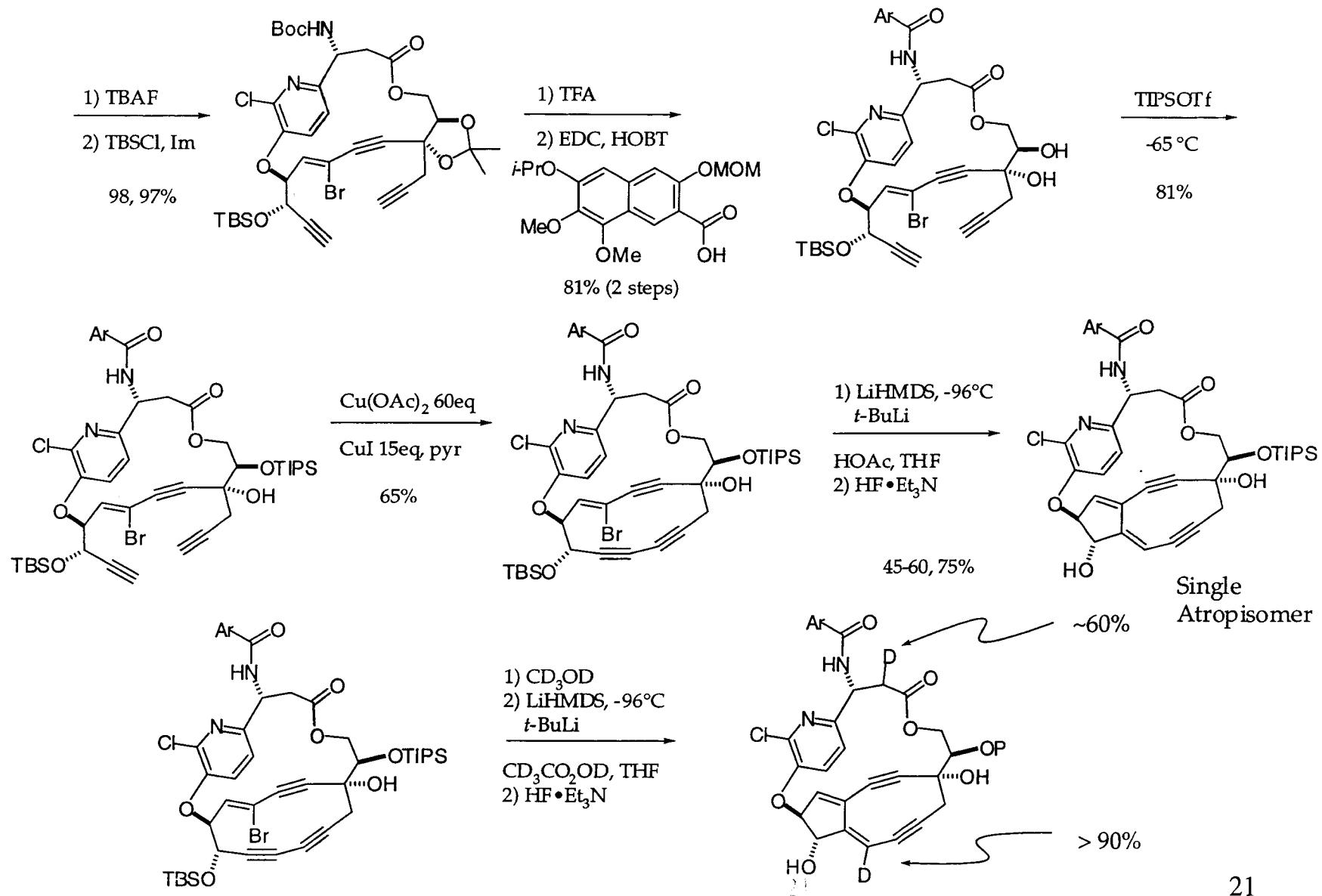
Ansa Bridge



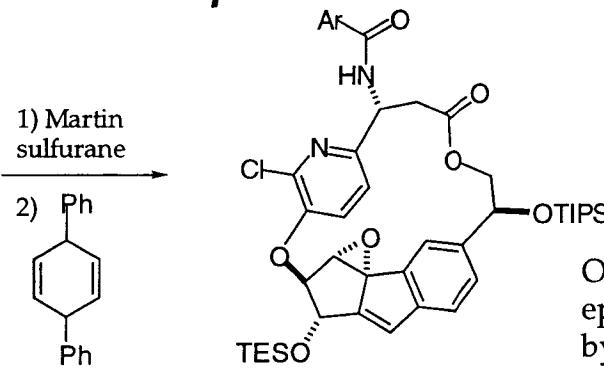
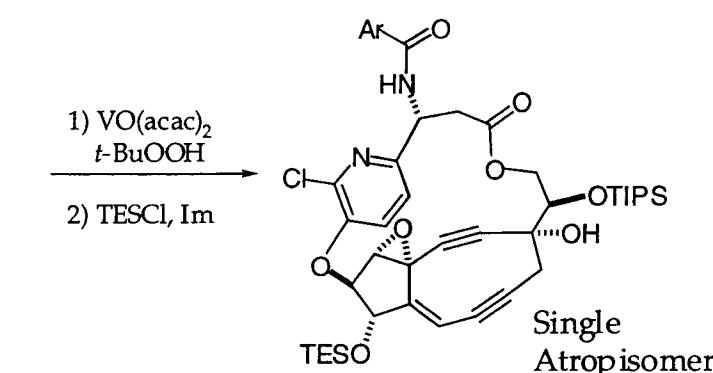
Equilibrating Atropisomers

20

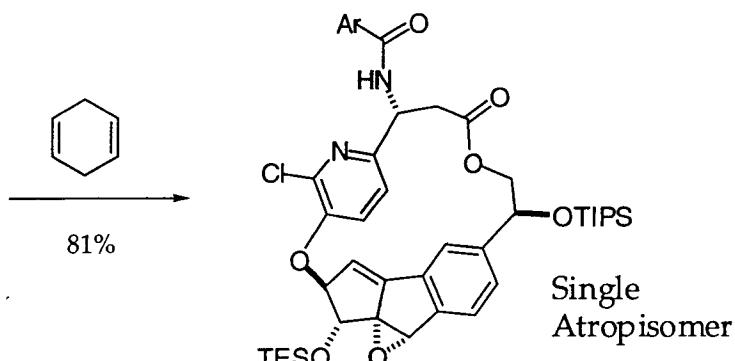
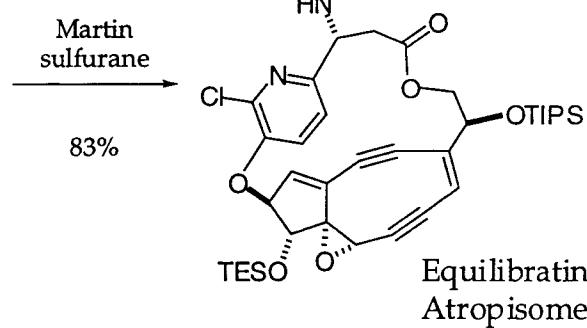
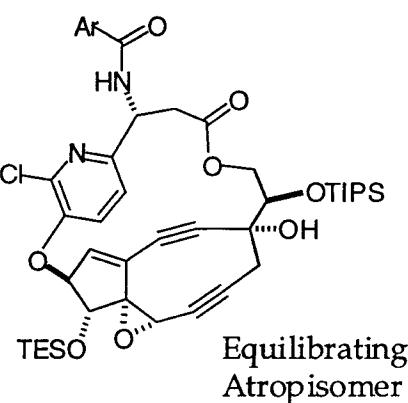
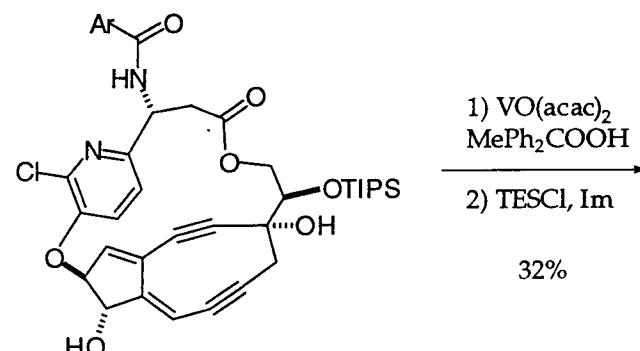
Transannular Cyclization



Final Steps

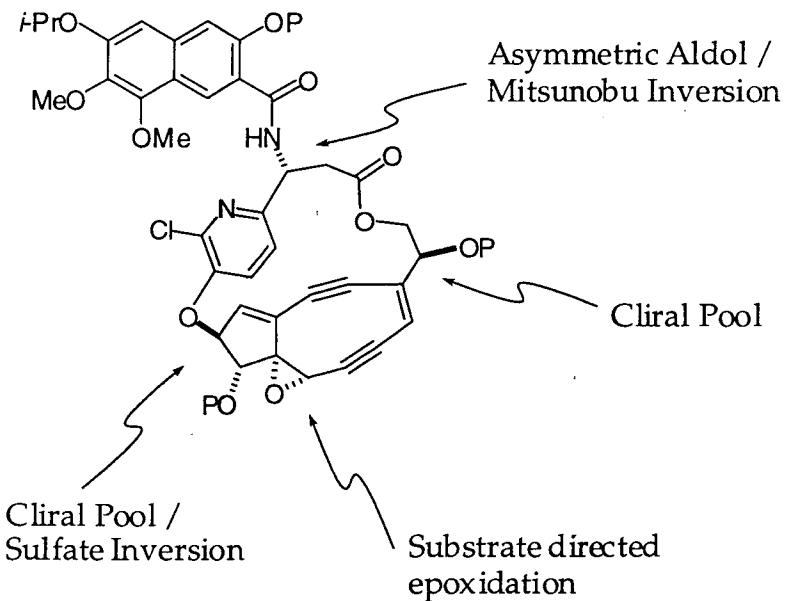


Oxidation gave the wrong epoxide (NOT predicted by model)



Rate of Cyclization is solvent dependent.

Conclusions



Longest Linear route (from known SM's): 25 steps

Overall Yield: 1%

Average Yield: 82%

- Enediyne natural products provide a completely novel family of antitumor antibiotics.
- Several attempts have been made at the synthesis of 9 and 10-mem enediyne macrocycles
- Only a few groups have successfully synthesized these natural products.

Reviews:

- Bergman *Accounts* 1973, 6, 25
Nicolaou *Angew. Chem. Int.* 1991, 30, 1387
Grierson *Contemp. Org. Syn.* 1996, 3, 41
Grierson *Contemp. Org. Syn.* 1996, 3, 93
Borders *Accounts*, 1991, 24, 235
Nicolaou *Accounts* 1992, 25, 497
Nicolaou *J. Med. Chem.* 1996, 39, 2103
Nicolaou *Proc. Natl. Acad. Sci. USA* 1993, 90, 5881