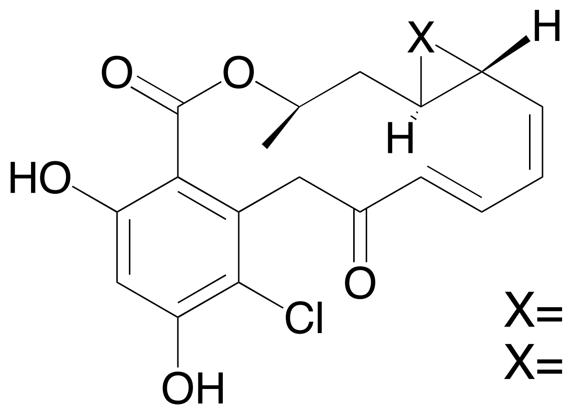
Synthesis of Resorcinylic Macrolides



X= O Radicicol (1)
X= CH2 Cycloproparadicicol (2)

Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP
Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413-416
Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602-9603
Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1280-1284
Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908
Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 773 and 777

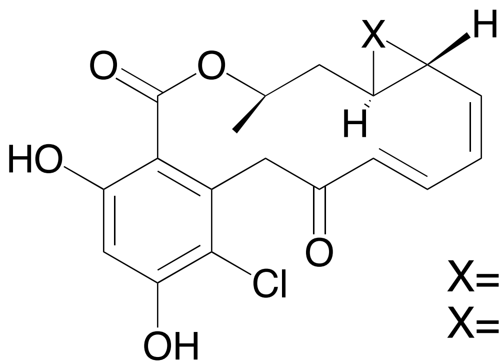
Bio-activity, Isolation and Total Synthesis of Radicicol

Bioactivity: 1) Antifungal and antibiotic

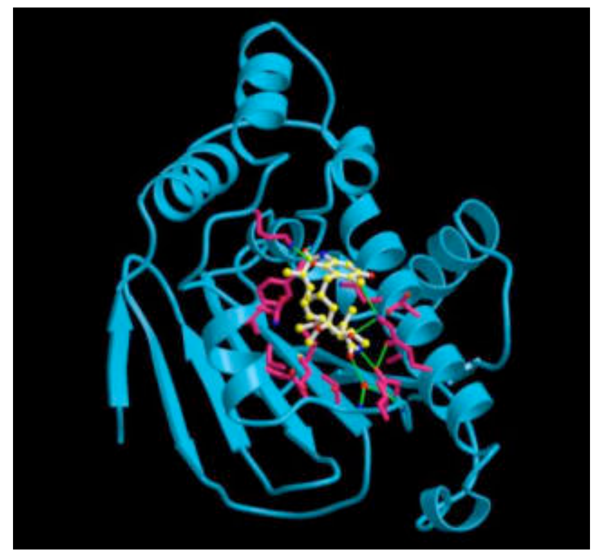
2) Antitumor properties —inhibitor of HSP90 (IC_{50}= 20nM)

Heat-Shock Proteins (hsps): The heat-shock or cell-stress response (changes in the expression of certain proteins),is essential strategy cell-survival.The stresses that can trigger this response vary widely, and include heat or cold, toxins, heavy metals. The proteins that are synthesized in response to such environmental stresses have been variously called: heat-shock proteins (hsps), or molecular chaperones.

Hsp90 — stablize and fold various oncogenic proteins



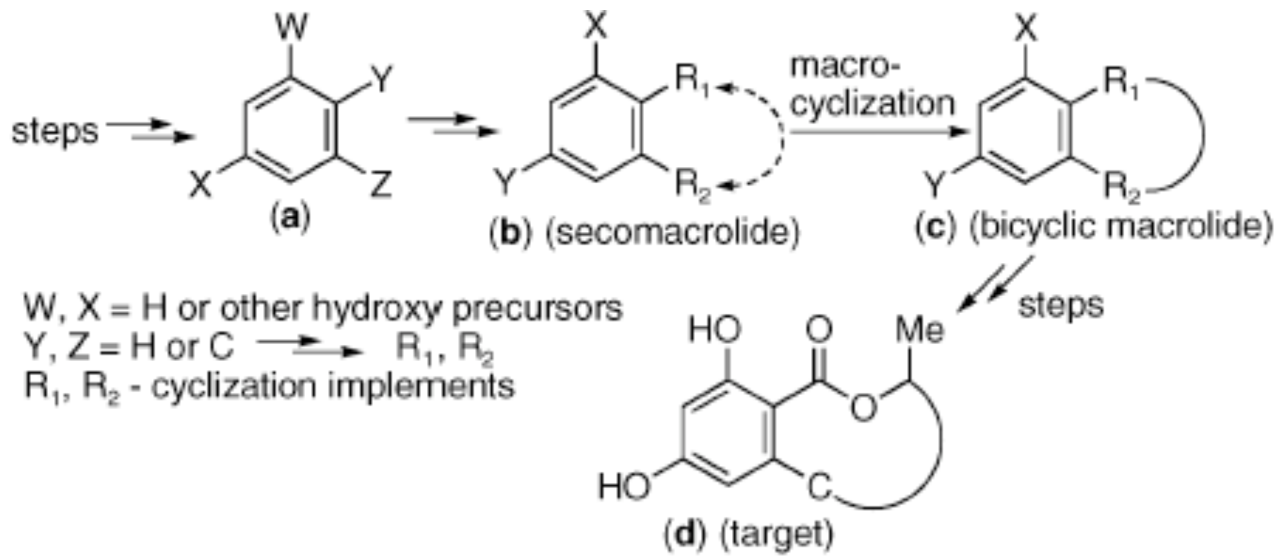
X= O   Radicicol (1)
X= CH2 Cycloproparadicicol (2)



Isolation: Isolated from *Monocillium nordinii*
Ayder, W. A.; Lee, S. P. *et al* *Can. J. Microbiol.* **1980**, *26*, 766.

Total synthesis: Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 773 and 777

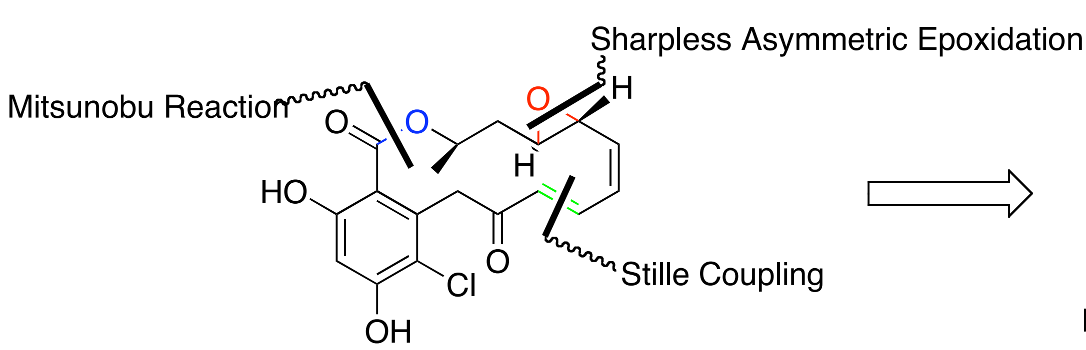
General Approaches toward Total Synthesis of Radicicol

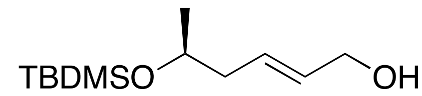


(**a**) Assembly of an aromatic core, with an actual or virtual resorcinylic functionality
(**b**) Chain extension of these implements to reach a macrocyclization candidate structure
(**c**) Macrocyclization
(**d**) Late stage deprotection and other functional group adjustments to reach the target

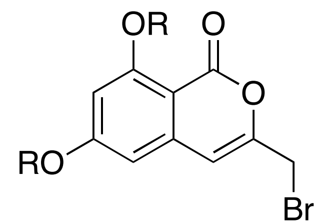
Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602-9603

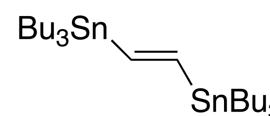
Strategies of Lett's Total Synthesis





4

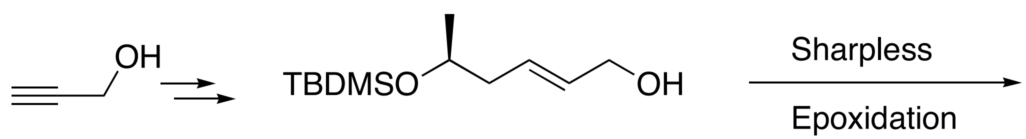




2

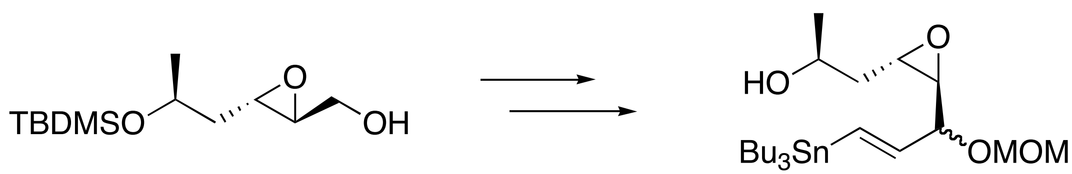
7

11



3

4

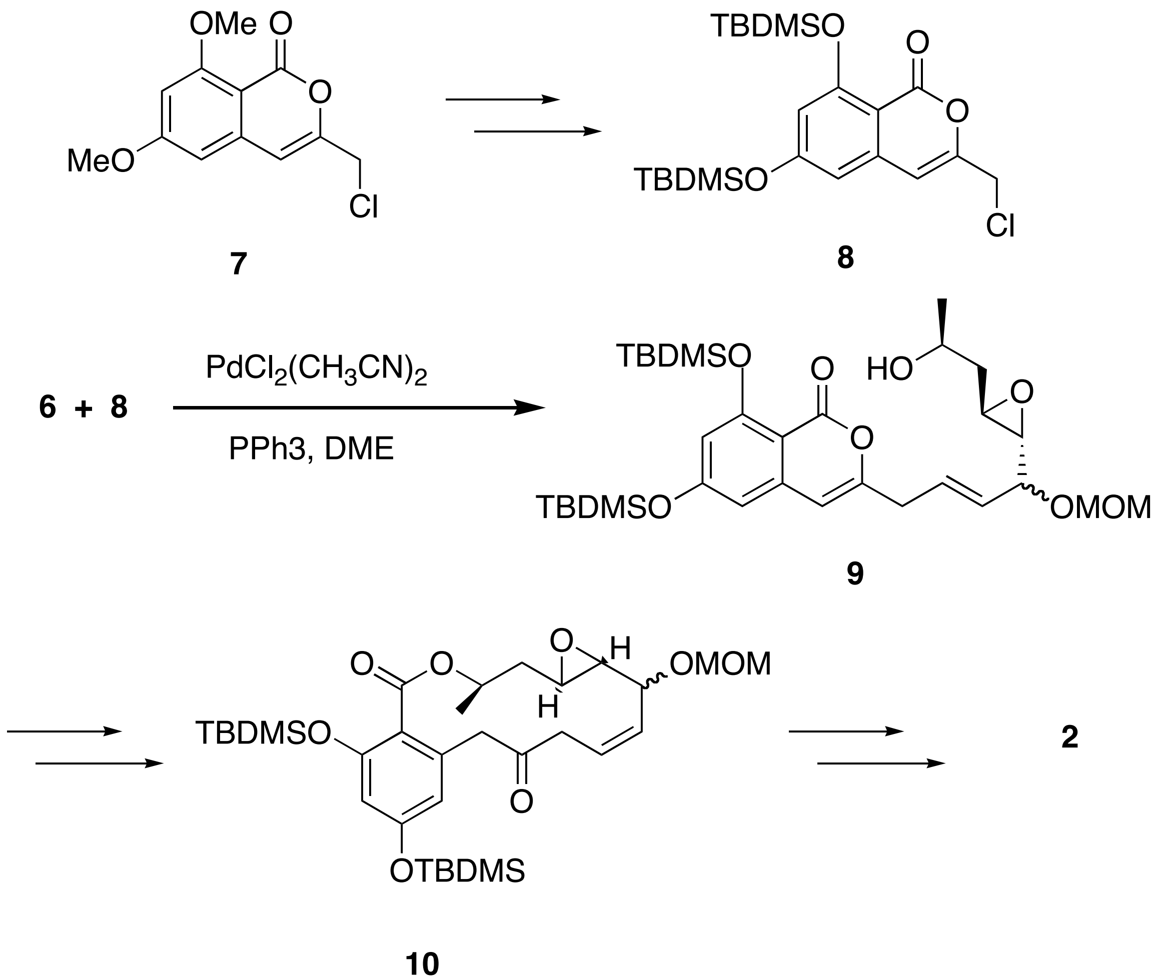


5

6

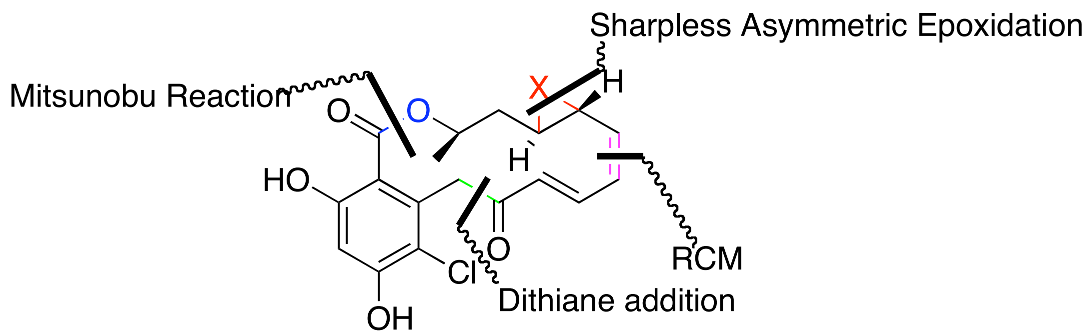
Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 773 and 777

Lett's Total Synthesis

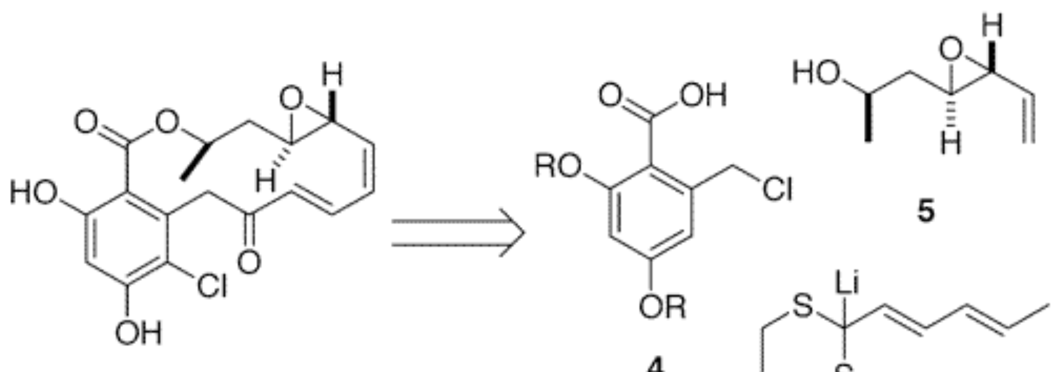


Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 773 and 777

Strategies of Danishefsky's First Total Synthesis



X= O Radicicol (**1**)
X= CH2 Cycloproparadicicol (**2**)

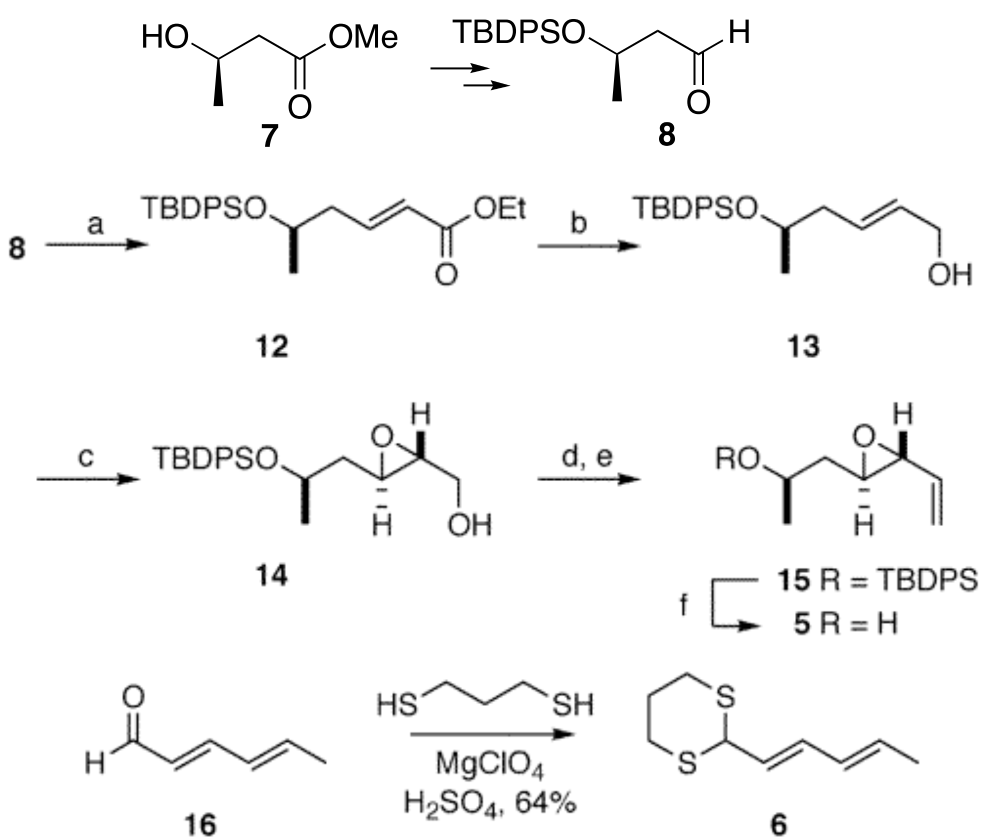


Radicicol (**1**) **4** **5** **6**

Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908

Resorcinylic Macrolides— Danishefsky's First Total Synthesis

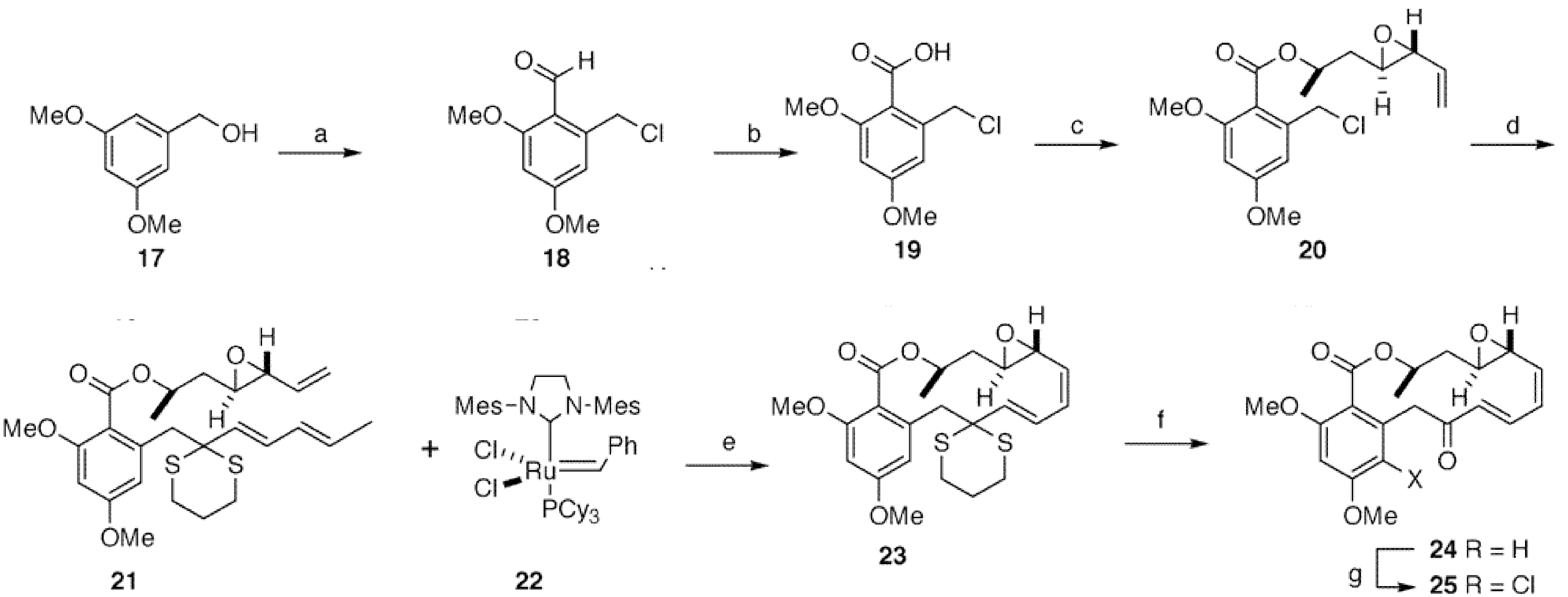
Synthesis of Fragment **5** and **6**



(a) LiCl, DIPEA $(EtO)_2P(O)CH_2CO_2Et$, 95%; (b) DIBALH, -20 ^{0}C, 96%;
(c) (+)-DET, $Ti(O\textit{i}Pr)_4$, TBHP, 90%, >95% ee;
(d) SO_3·pyridine, Et_3N, DMSO, 90%; (e) Ph_3PCH_3Br, NaHMDS, 0 ^{0}C, 82%; (f) TBAF, 89%.

Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908

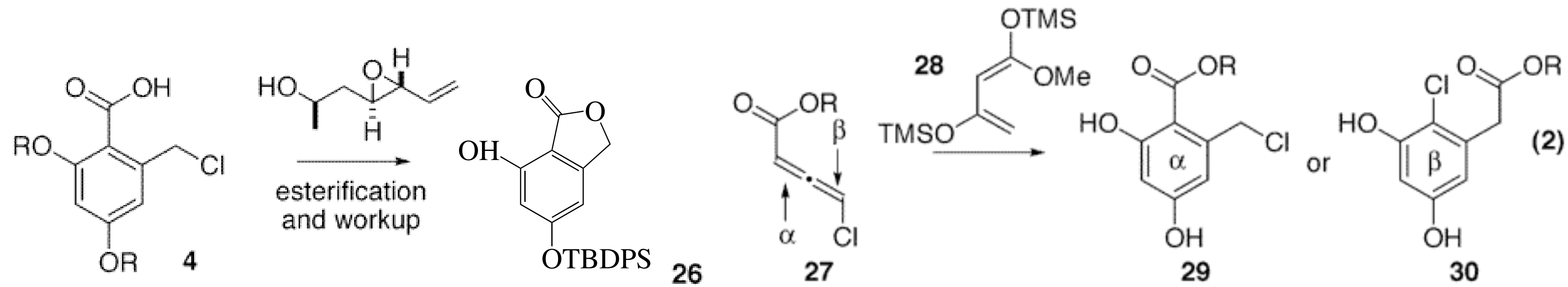
First Problem: Total Synthesis of Di-methyl Analogue **25**



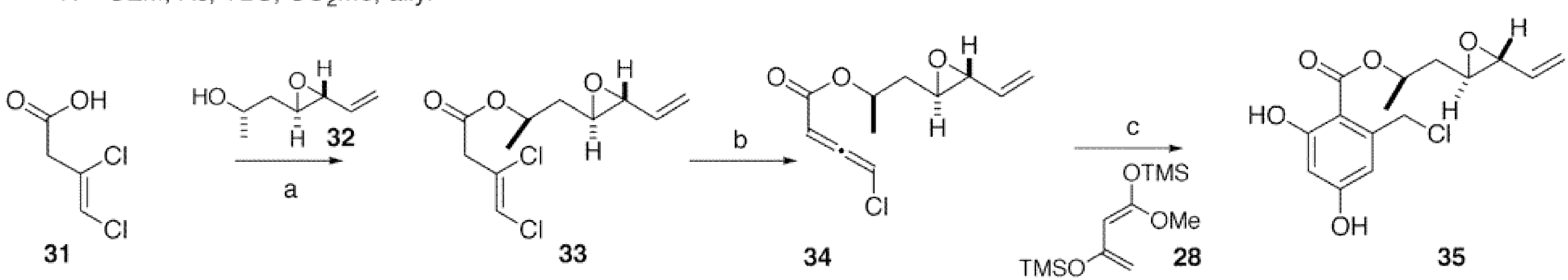
(a) $POCl_3$, DMF, 75 ^{0}C, 93%; (b) $NaClO_2$, 85%; (c) $(COCl)_2$, Et_3N, **5**, 80%;
(d) *n*-BuLi, **6**, 60%; (d) 45 ^{0}C, 55%; (f) mCPBA; Et_3N, Ac_2O, H_2O, 60 ^{0}C, 70%; (g) $Ca(OCl)_2$, 80%

Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908

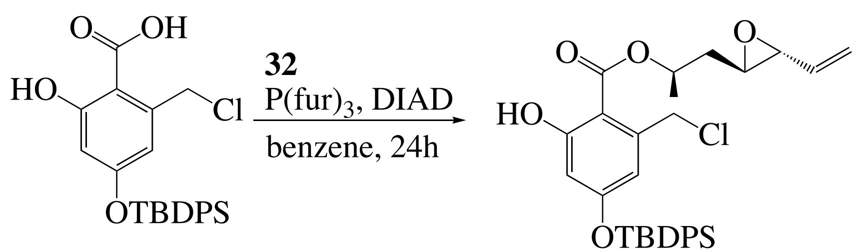
Second Problem: Phthalide Formation



R = SEM, Ac, TBS, CO_2Me, allyl

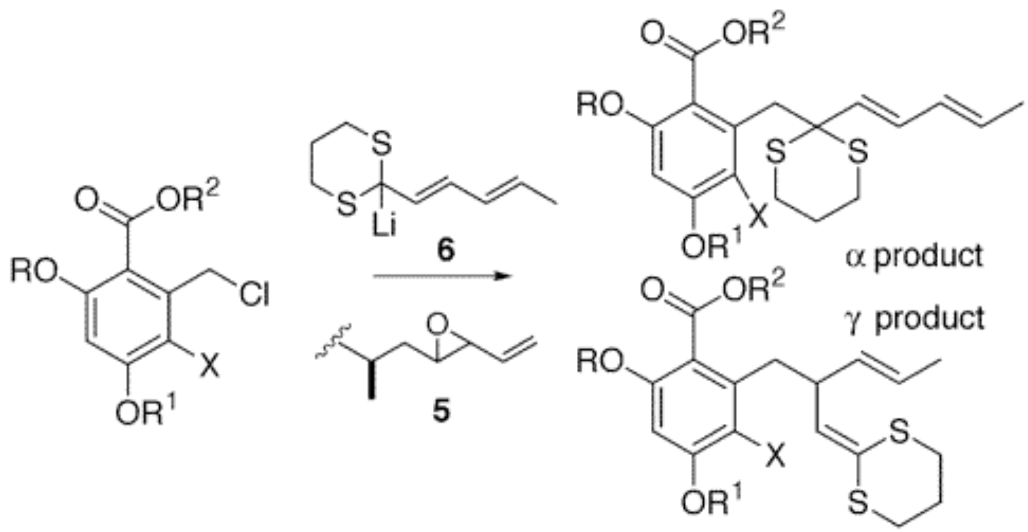


(a) DEAD, PPh_3, 70%; (b) i-Pr_2NEt, 70%; (c) 50% (4:1)



Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908

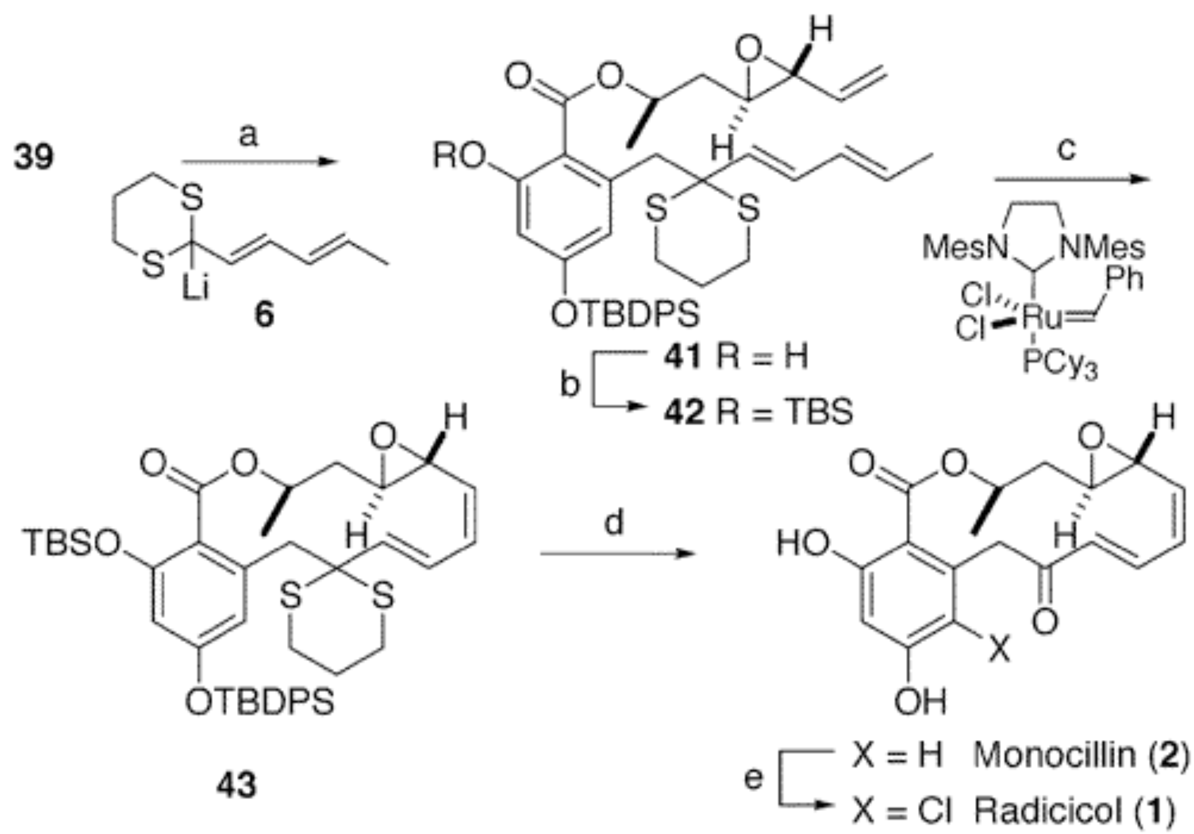
Third Problem: Competition of g-alkylation



	R	R^1	R^2	X	ratio [α : γ]	combined yield
6	H	TBDPS	**5**	H	6 : 1	50%

Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908

Final Steps: Completion of Total Synthesis



(a) *n*-BuLi, -78 ^{0}C, 50% (6:1); (b) TBSCl, 88%; (c) 42 ^{0}C, 60%; (d) (i) mCPBA, (ii) Ac_2O, Et_3N, H_2O, 60 ^{0}C, (iii) $NaHCO_3$, MeOH, 60%; (e) SO_2Cl_2, 58%.

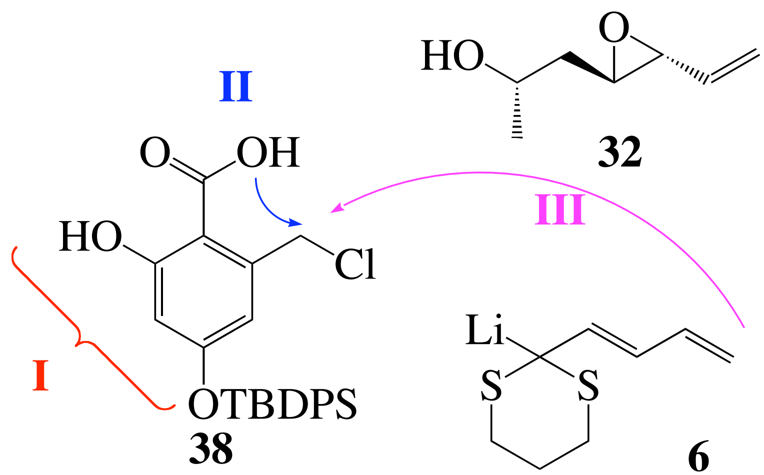
Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903-10908

Summaries of Danishefsky's First Total Synthesis

Advantage: highly convergent and concise— 6 steps from (**6**, **32** and **38**), 14 linear steps

Disadvantage: 1) suffered from several low yielding steps which did not improve following optimization.

2) the low yields sharply curtailed access to cycloproparadicicol for evaluation.



I Problems of functional groups deprotection

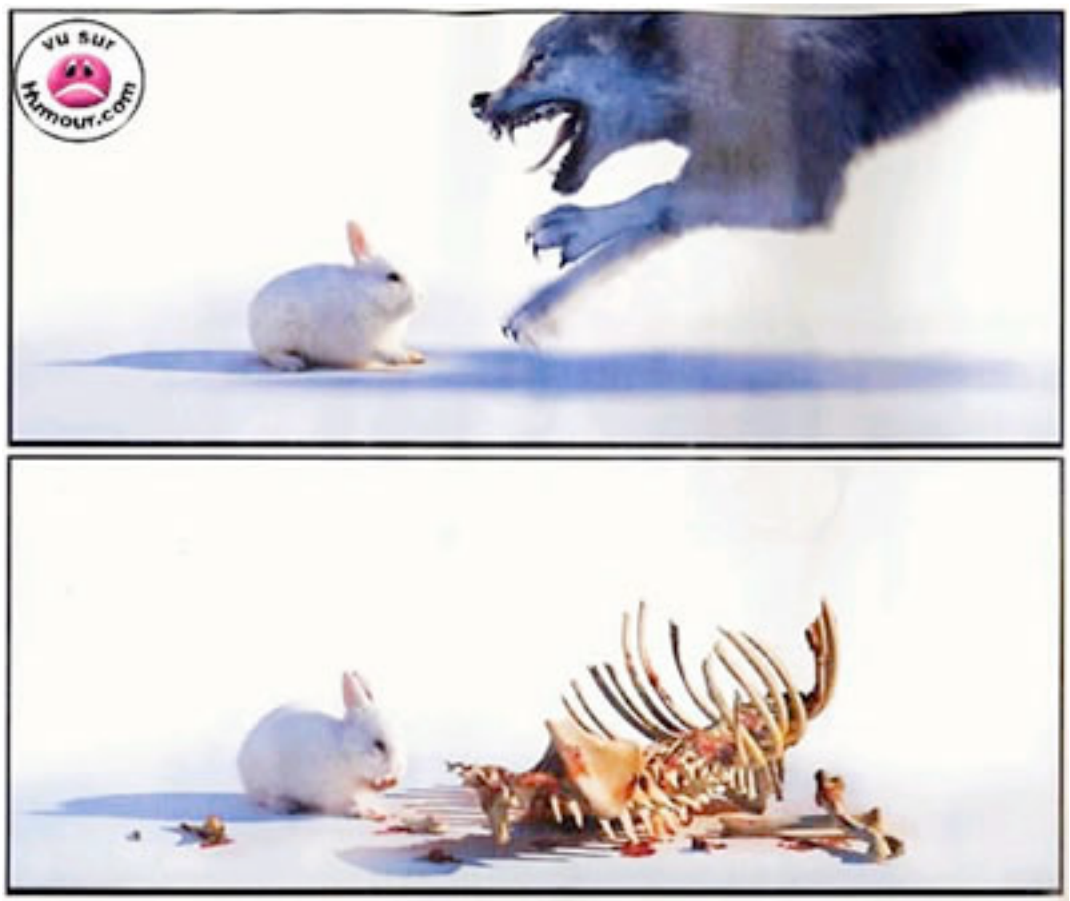
II Phthalide formation

III Regioselectivity

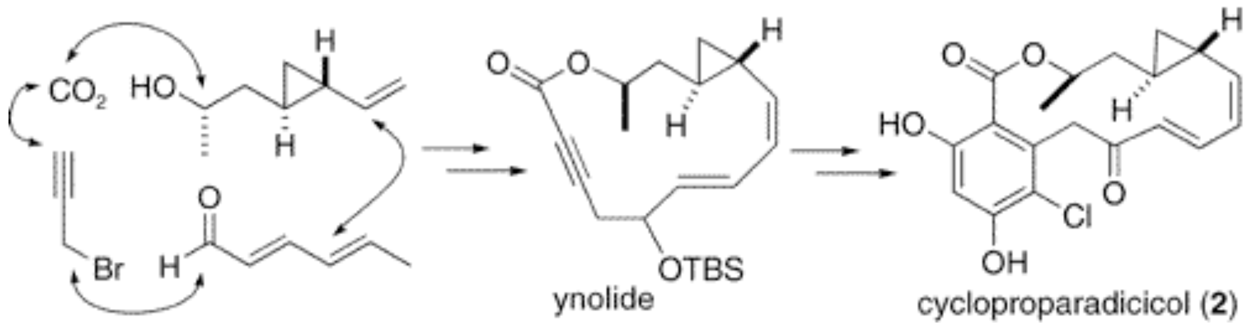
Solution: Furnish the aromatic core at late stage of the total synthesis

What We Can Learn…

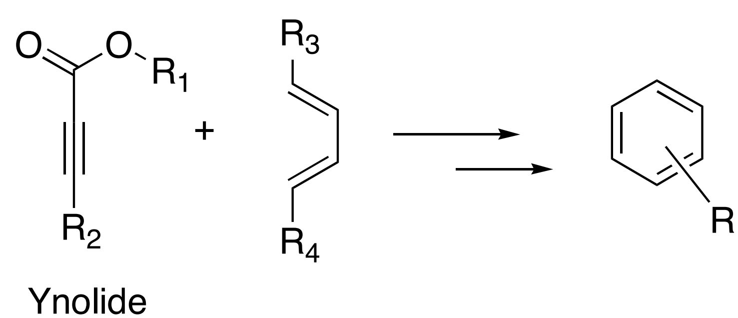
— Easy target could be deadly



Strategies of Danishefsky's Second Total Synthesis



Key Step: 1) Construction of the aromatic sector by Diels-Alder reaction of "ynolide"
2) Cobalt Complexation Promoted RCM Reaction

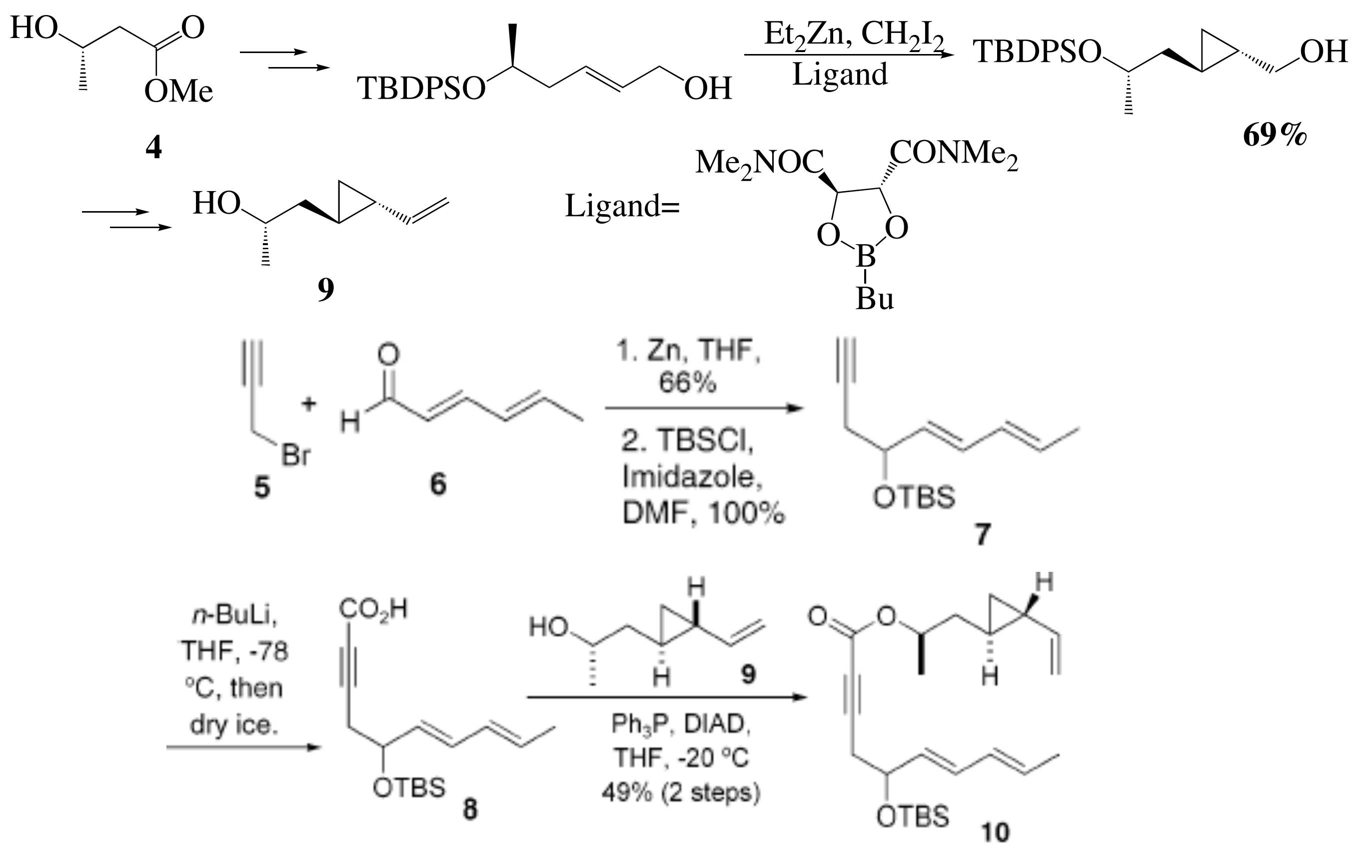


ynolide — a weak dienophile

Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP

Resorcinylic Macrolides— Danishefsky's Second Total Synthesis

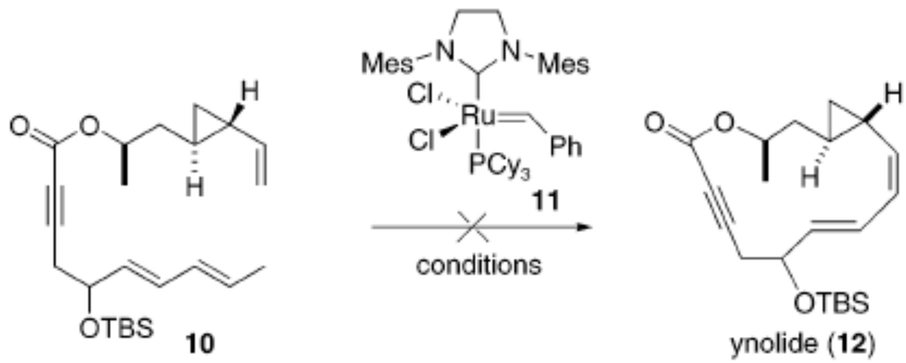
Synthesis of Acyclic Alkynoic Ester **10**



10 is ready for RCM reaction

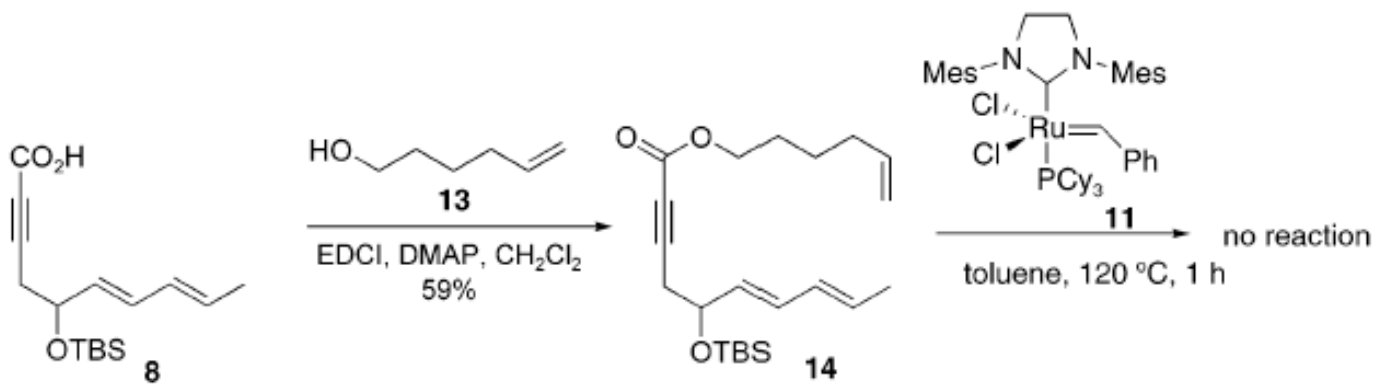
Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP
Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1280-1284

Attempted Ring-Closing Metathesis Reactions of **10**



Probable reason: 1) conformational rigidities associated with the trans-disubstituted cyclopropane and the linear acetylene "linker".

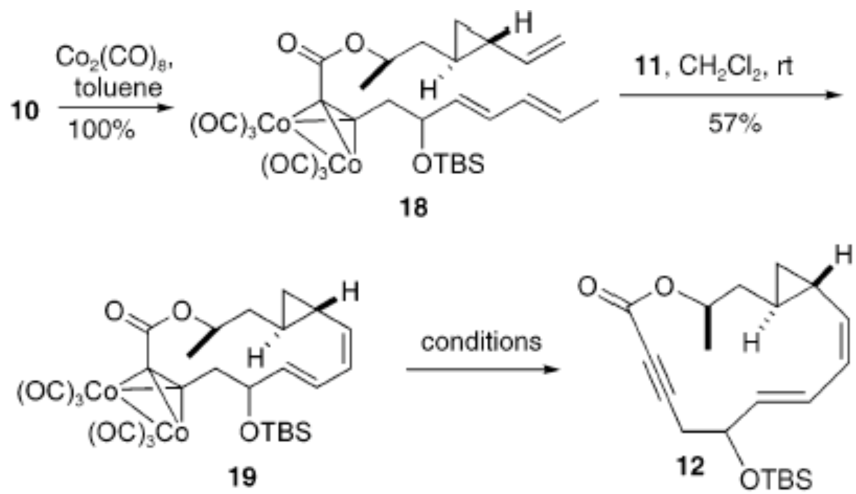
2) coordination of the acetylene to the RCM catalytic machinery.



Rule out the affect of conformational rigidities of the trans-disubstituted cyclopropane

Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP

Solution: Cobalt Complexation Promoted RCM Reaction of **10**

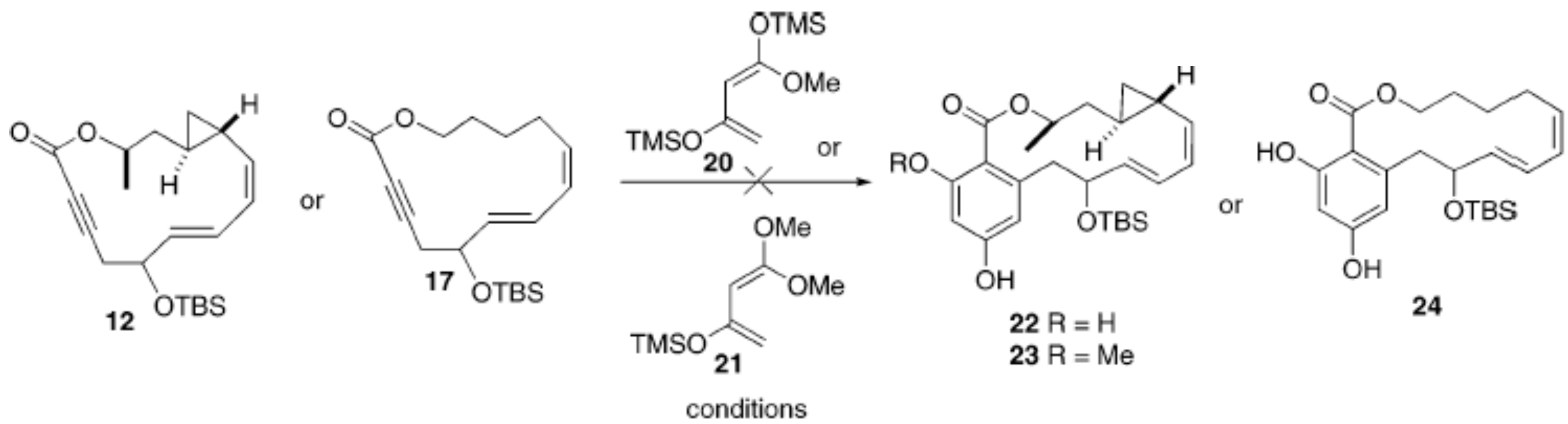


Entry	conditions	yields
1	CAN, acetone, -10 ºC	<10%
2	I_2, THF, 0 ºC	≤ 69%
3	Me_3NO, acetone/THF -78 ºC to rt	66%
4	CAN, DTBP, acetone, -10 ºC	50% from **18**

1) Geometry of cobalt-complexed alkyne is optimized
2) Alkyne function is protected

Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP

Attempted Diels-Alder Reactions with Ynolide



Entry	Conditions	Results
1	**12**, **20**, neat, 75 °C; then $Et_3N{\cdot}HF$, EtOH	recovered desilylated **12**
2	**12**, **21**, neat, 160 °C; then 0.1 N HCl	Decomposition
3	**17**, **20**, EuFOD, neat, 70 °C; then $Et_3N{\cdot}HF$, EtOH	recovered desilylated **17**
4	**17**, **20**, Ti(O*i*-Pr)$_4$, neat, 70 °C	recovered **17**

Probable reason: acetylenic dienophiles can be rather unreactive toward Diels-Alder Reactions

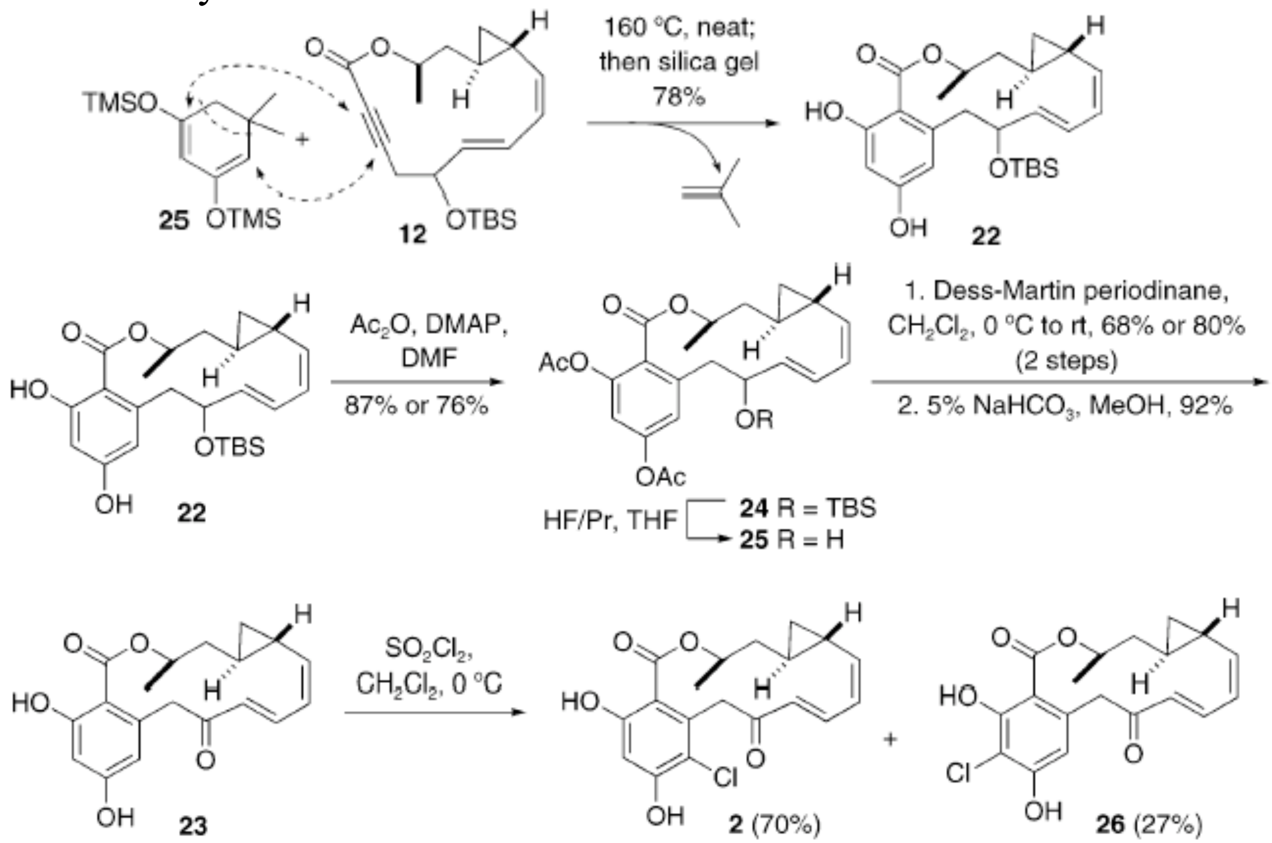
Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP

Solution: Using Cyclic Diene **25** in D-A Reaction with Ynolide **12**

Why?

1) more reactive (due to a locking in of the *s*-syn conformation by the six-member ring)

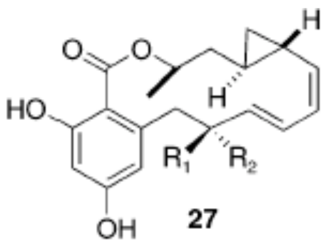
2) more thermally stable



6% yield following 13 steps

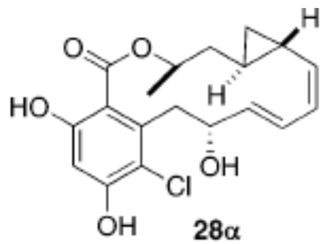
Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP

Synthesis of Analogues Cycloproparadicicol

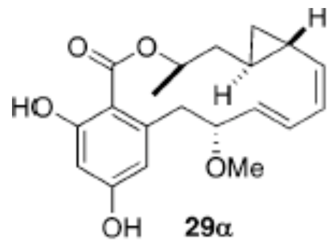


27

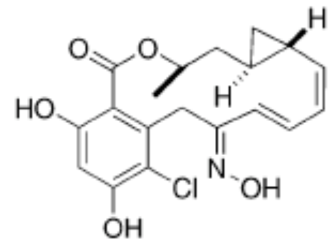
27α R_1 = H, R_2 = OH (74%)
27β R_1 = OH, R_2 = H (51%)



28α

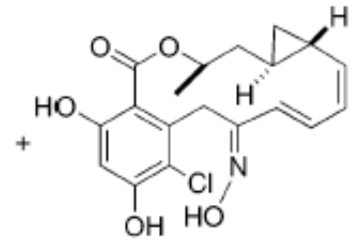


29α

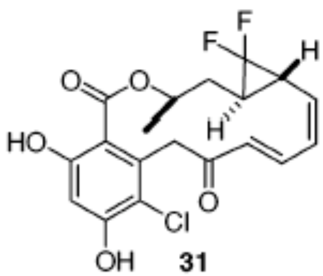


(*Z*)-**30** (42% based on consumed **2**)

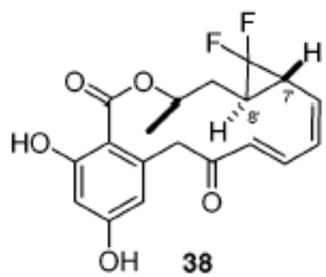
\+



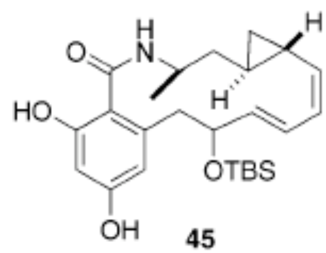
(*E*)-**30** (28% based on consumed **2**)



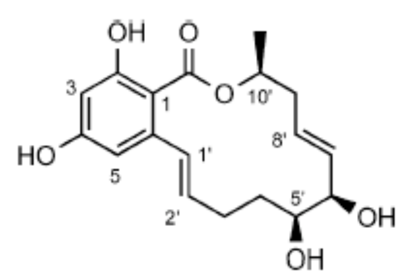
31



38



45



aigialomycin D (**46**)

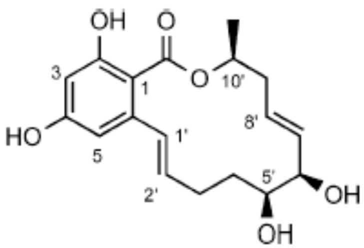
IC_{50} (nM) Values of Cycloproparadicicol Analogues and Aigialomycin D

compound	2	26	27α	27β	28α	29α	(*Z*)-30	(*E*)-30	31	38	46
IC_{50}	54	> 500	150	> 500	390	> 10 000	98	282	10 000	3000	> 10 000

Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP

Extension of the Ynolide Approach

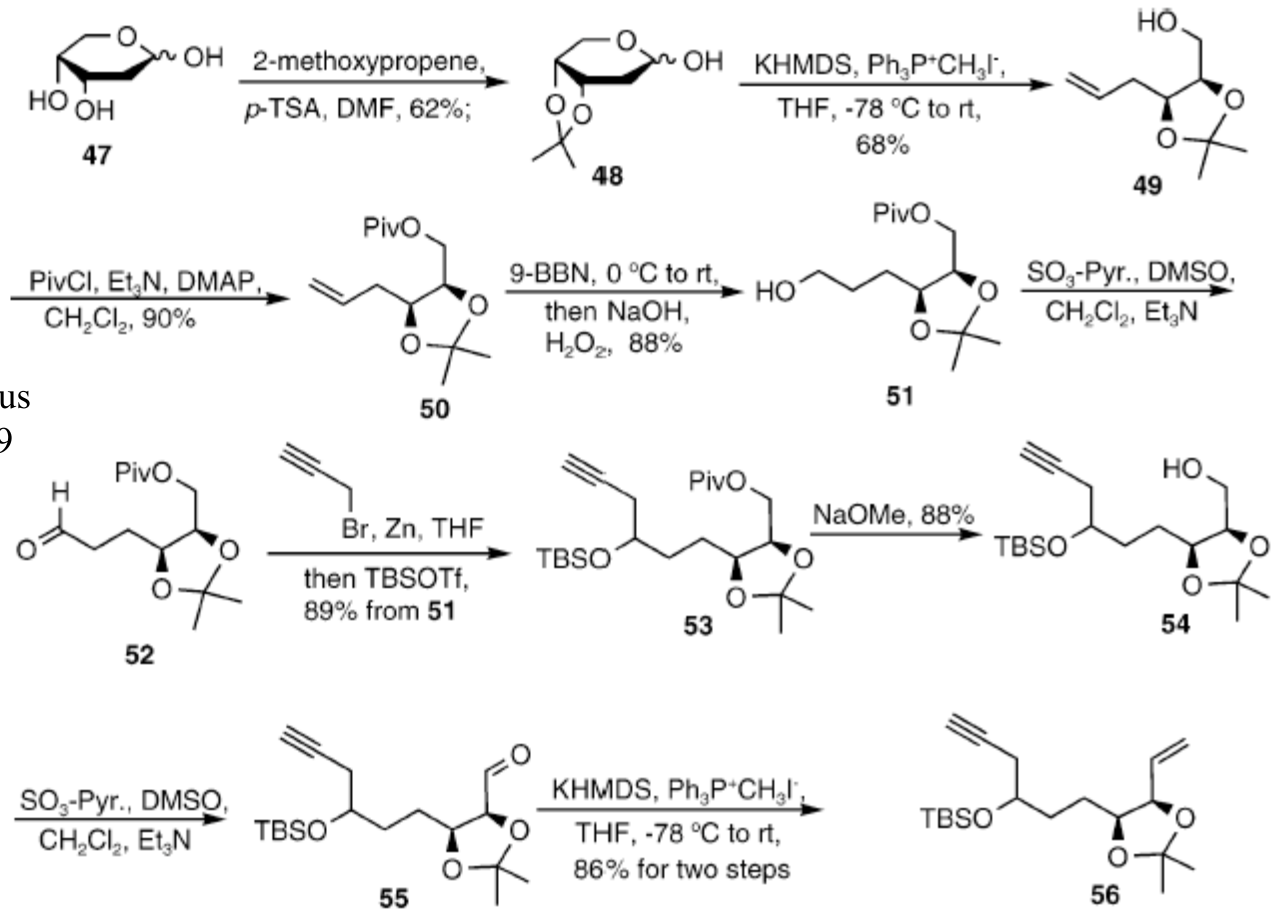
— The First Total Synthesis of Aigialomycin D



aigialomycin D (**46**)

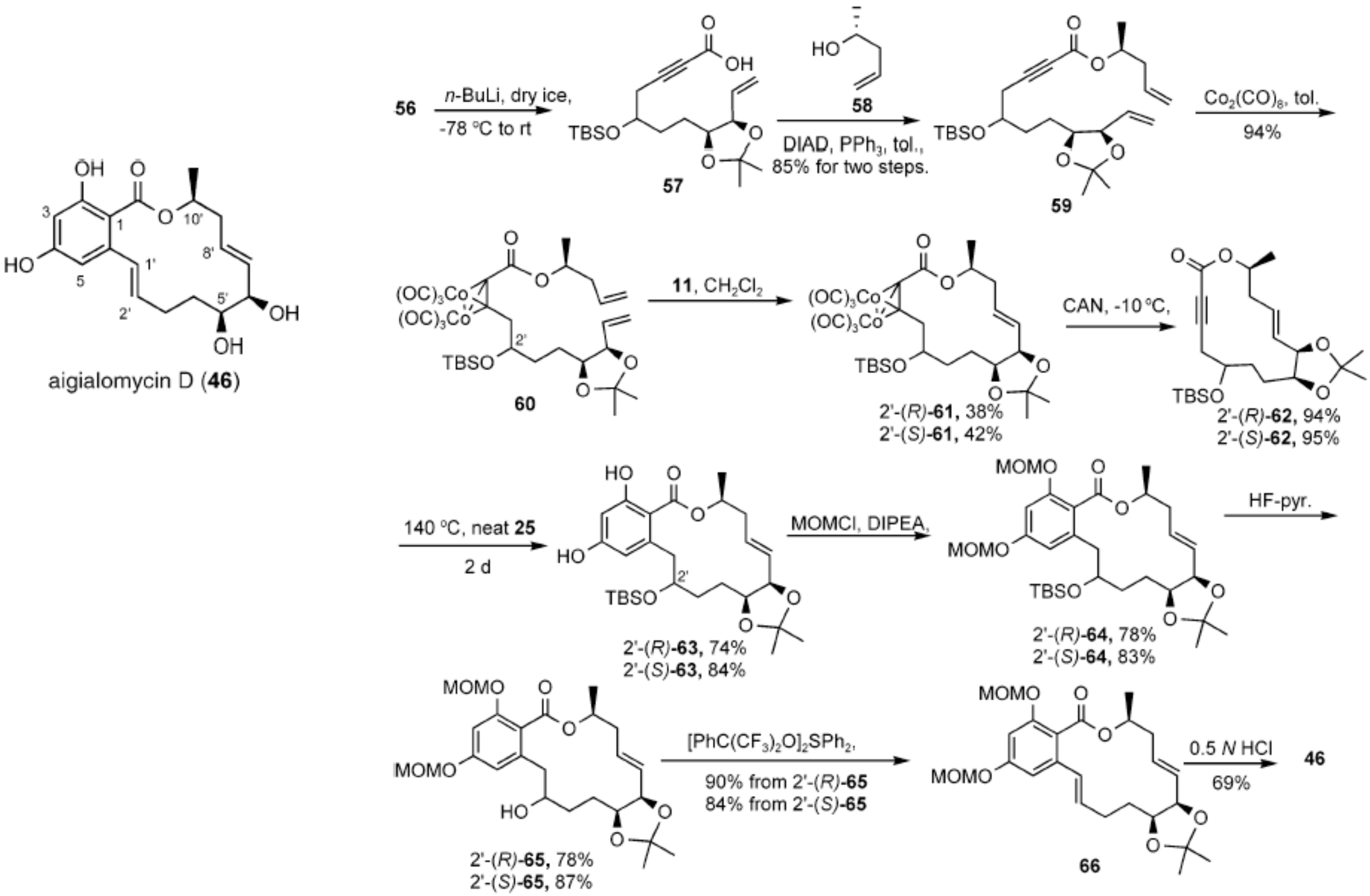
Isolatation: 2002, marine mangrove fungus *Aigialus parvus* BCC5311.59

Bioactivity: potent antimalarial activity and antitumor activity

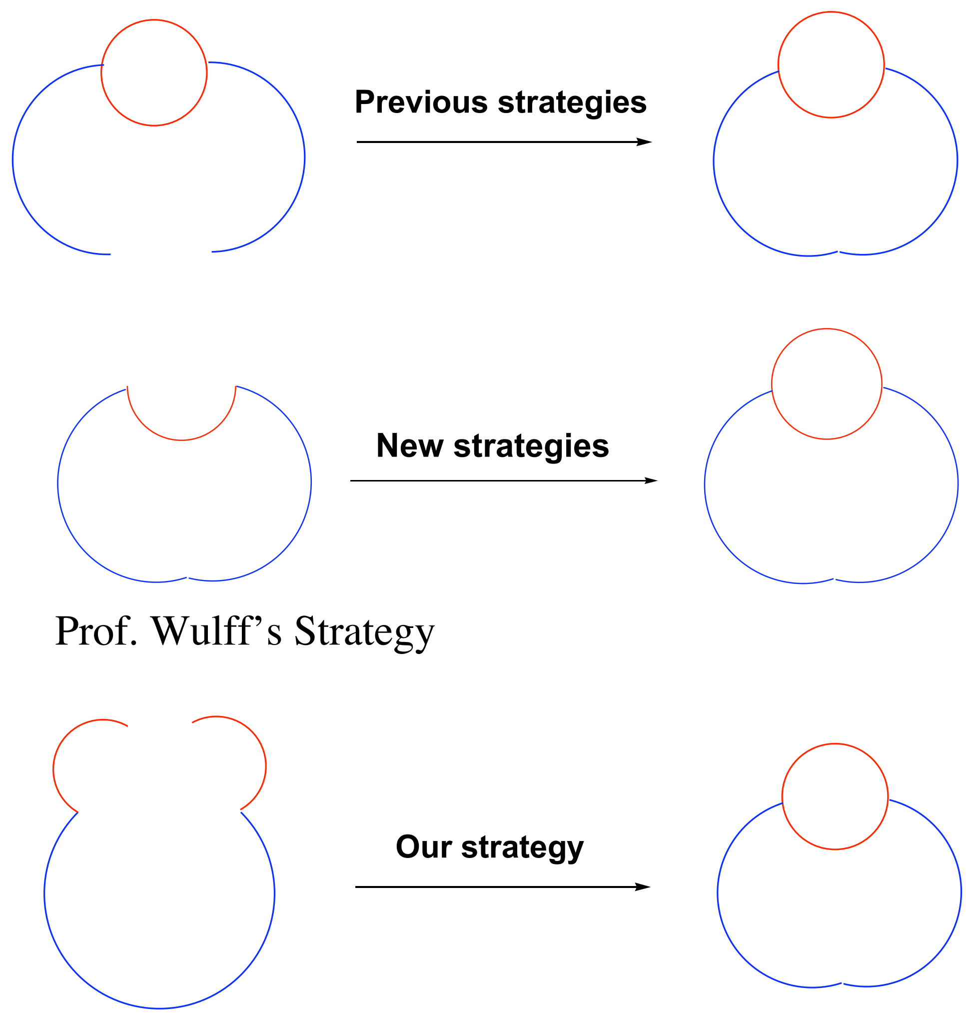


Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126,* ASAP

The First Total Synthesis of Aigialomycin D



Summary of Strategies toward Total Synthesis of Radicicol



Conclusions and What We Can Learn…

1) A new and efficient synthetic strategy have been developed to produce benzofused macrolides

2) A new method of cobalt-complexation-promoted RCM was established

3) Diels-Alder reaction of ynolides with dimedone-derived bis-siloxyl diene can fashion the desired resorcinylic macrolides and enable us to evaluate cycloproparadicicol as a feasible candidate for further advancement

4) The generality of the synthesis plan has been demonstrated by its application to the first total synthesis of aigialomycin D.

5) Some problems remained unresolved: the sluggish dienophilicity of monoactivated acetylenes make it hard to fully generalize the method. For instance, the yne lactam **44** and the ynolide **36**

6) The biological activities of cycloproparadicicol to inhibit Hsp90 at ca. 160 nM make it a possible target for this new group of anticancer agents

Extension of the Ynolide Approach to the First Total Synthesis of Aigialomycin D