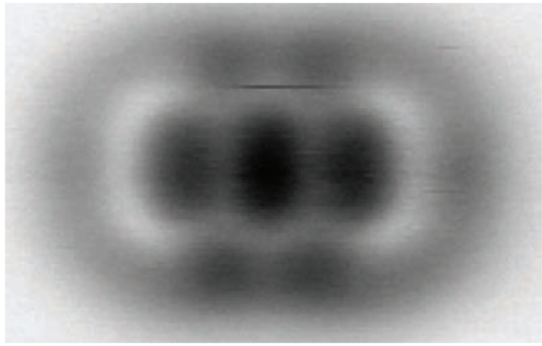
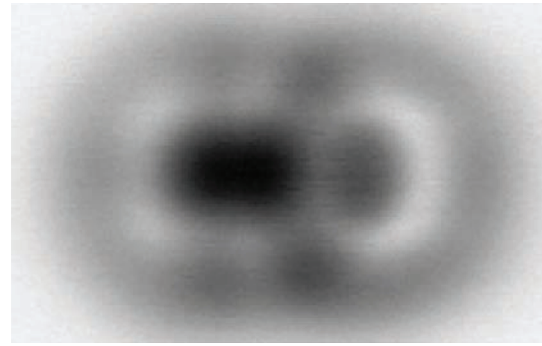
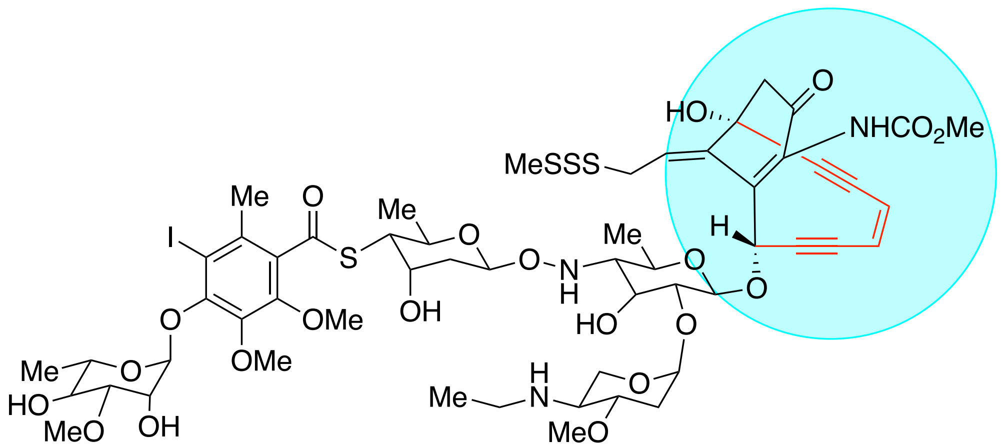
Bergman Cyclization and Enediyne Antibiotics

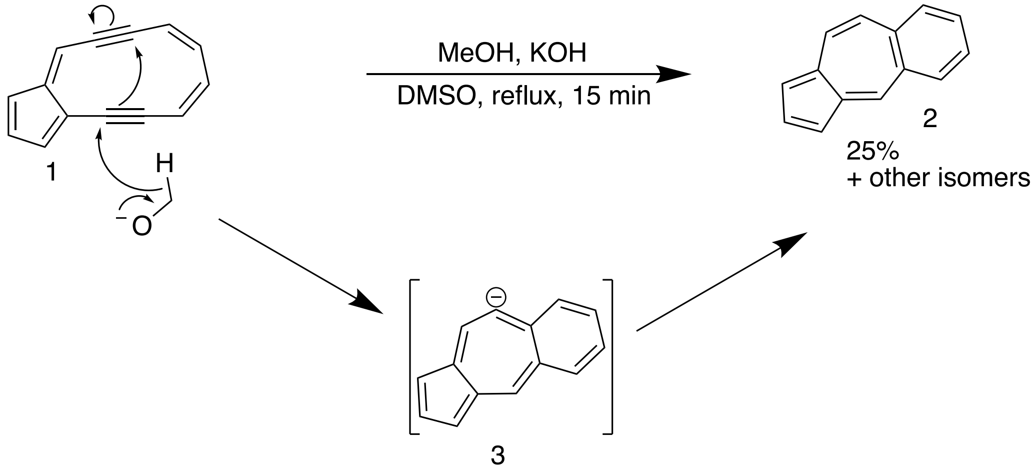




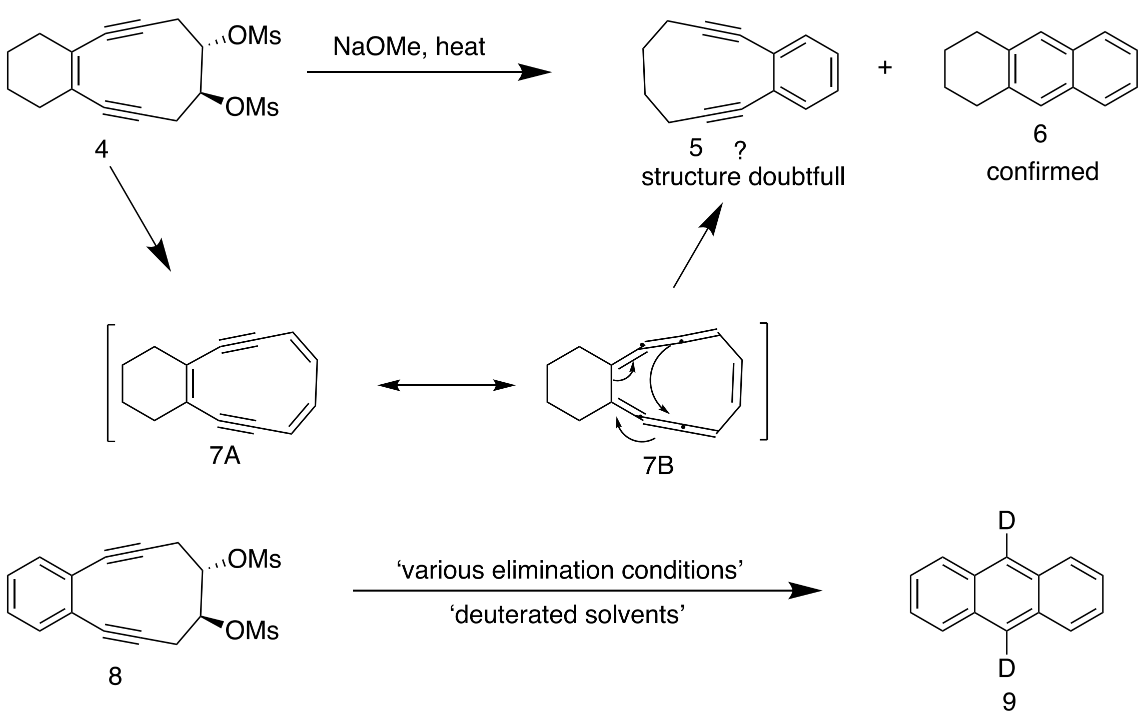


Soumitra Athavale
SED Group Meeting
20 June 2017

First reports of enediyne cyclizations



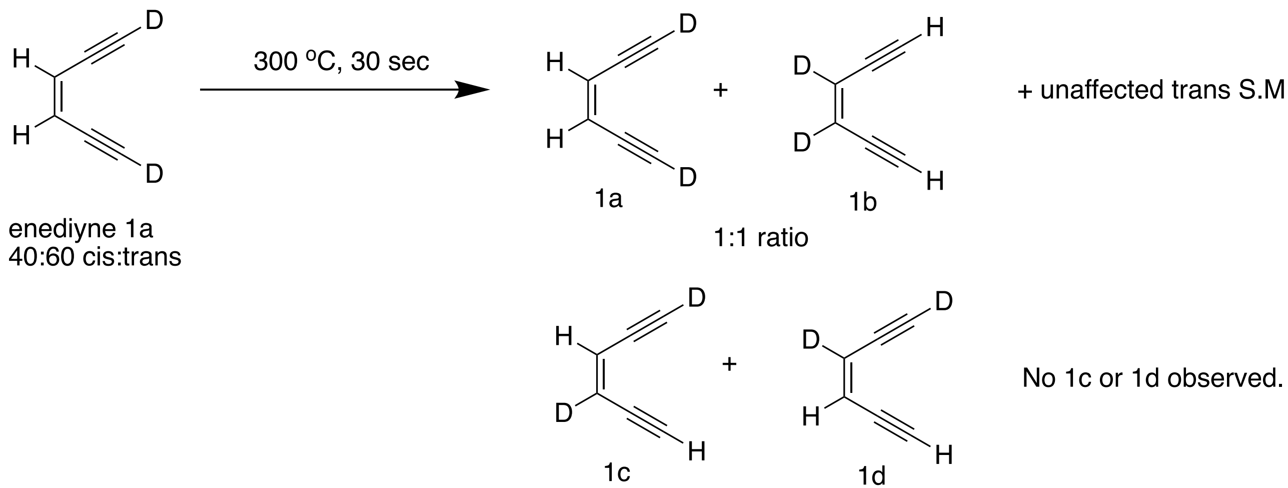
Sondheimer, 1966



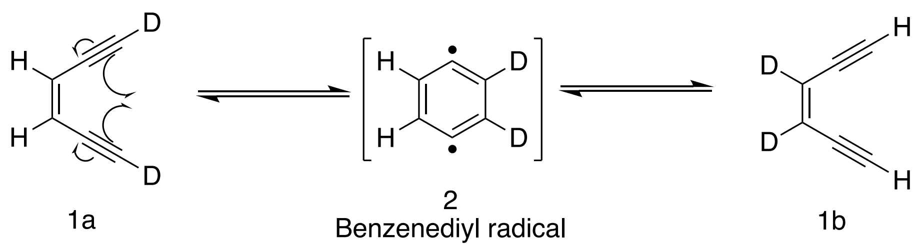
Masamune, 1971
Proposed mechanism

Sondheimer, F., Mayer, J., *J. Am. Chem. Soc.,* 1966, 88, 603.
Darby, N.; Kim, C. U; Salaiin, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *J. Chem. Soc., Chem. Commun D.* 1971, 1516.

Studies by Bergman



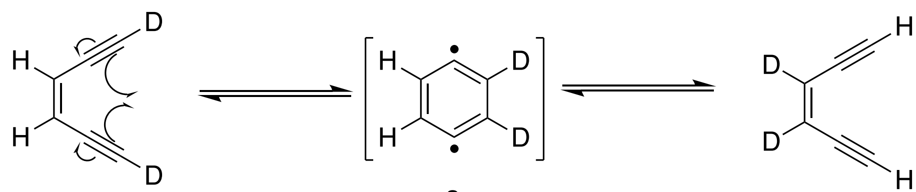
1a and 1b must be interconverting through a symmetrical intermediate



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

Studies by Bergman

2 is most well represented as a 1.4-diradical

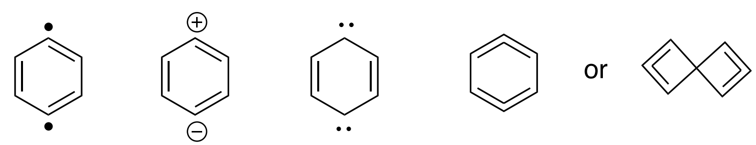


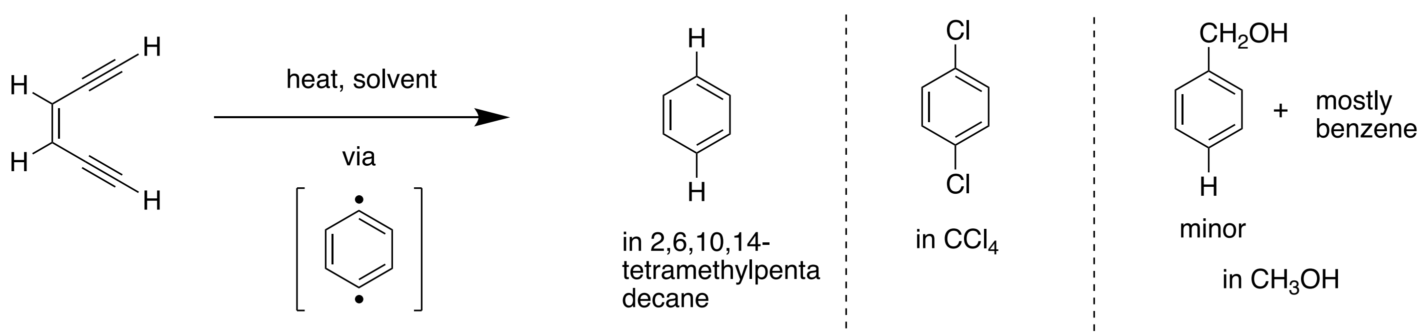
1a

2
Benzenediyl radical

1b

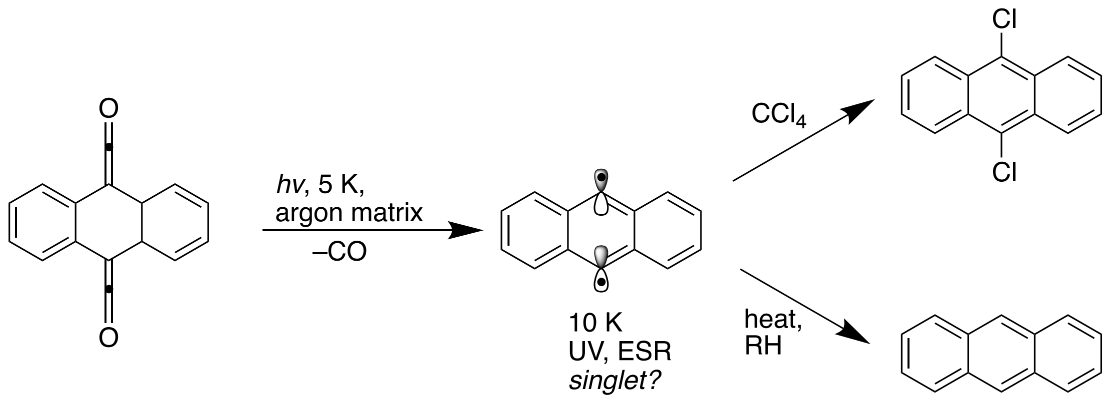
limiting structures





Jones, R., Bergman, R., *J. Am. Chem. Soc.,* 1972, 94, 660.
Bergman, R., *Acc. Chem. Res.,* 1973, 6, 25.

Other early studies



Chapman, 1976
Preliminary characterization attempts

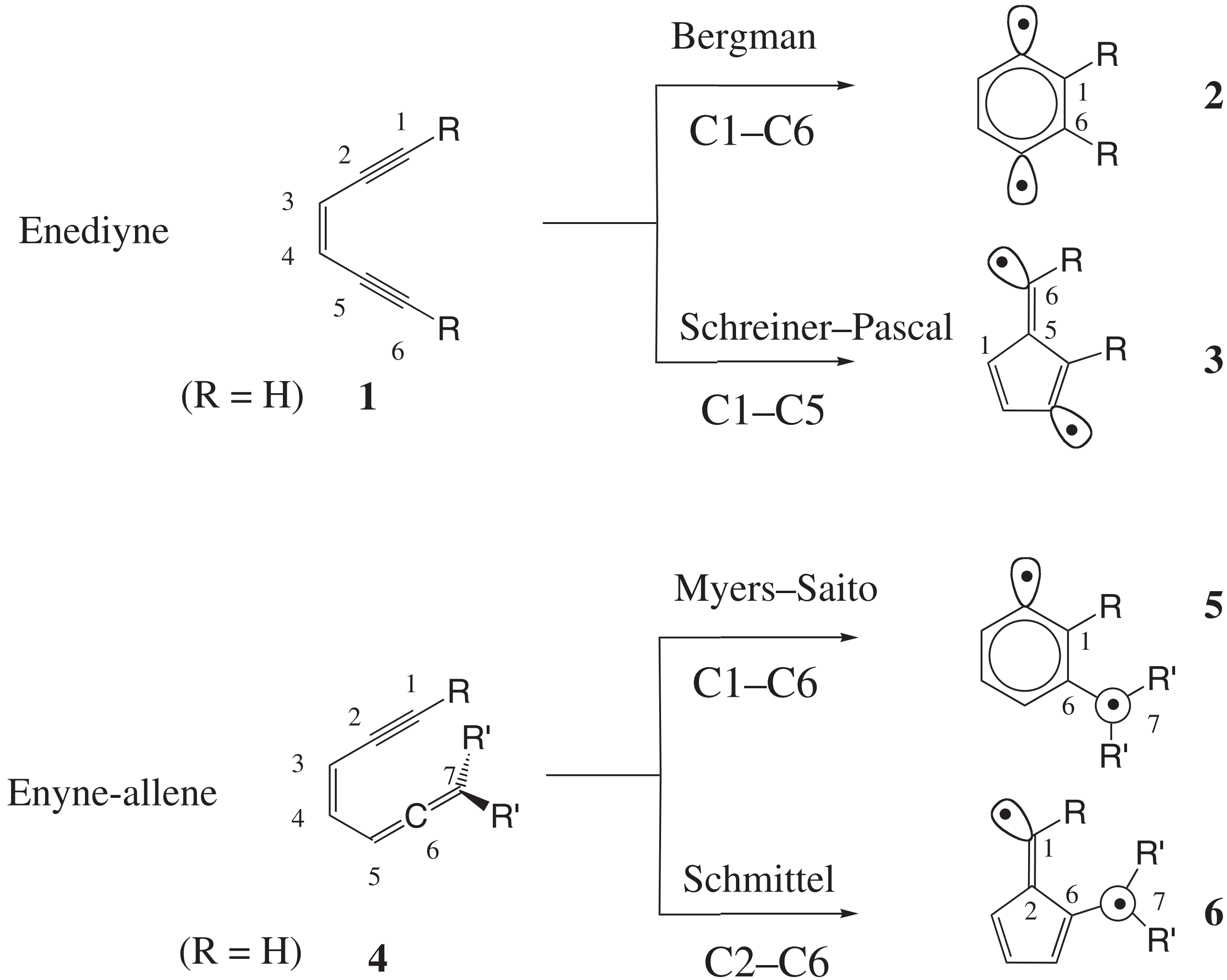
Table I. Calculated Energies of 1,4-Dehydrobenzene Structures

	relative energy of structures, kcal/mol		
	1		2
	triplet	singlet	singlet
Wilhite and Whitten (1971)[4] SCF–MO–CI	0	+3.45	
Dewar et al. (1974)[5] MINDO/3 (lim/CI)	+5	0 (ΔH_f = +117 kcal/mol)	+36
Washburn et al. (1979)[8] ab initio 4-31G (no CI)	0	(+82)	+94
Mueller (1973)[7] modified MINDO/2 (no CI)	0	(+24)	+18
Noell and Newton (1979)[6] ab initio GVB (4-31G)	+1.4	0	(~77)

Energy calculations were inconclusive

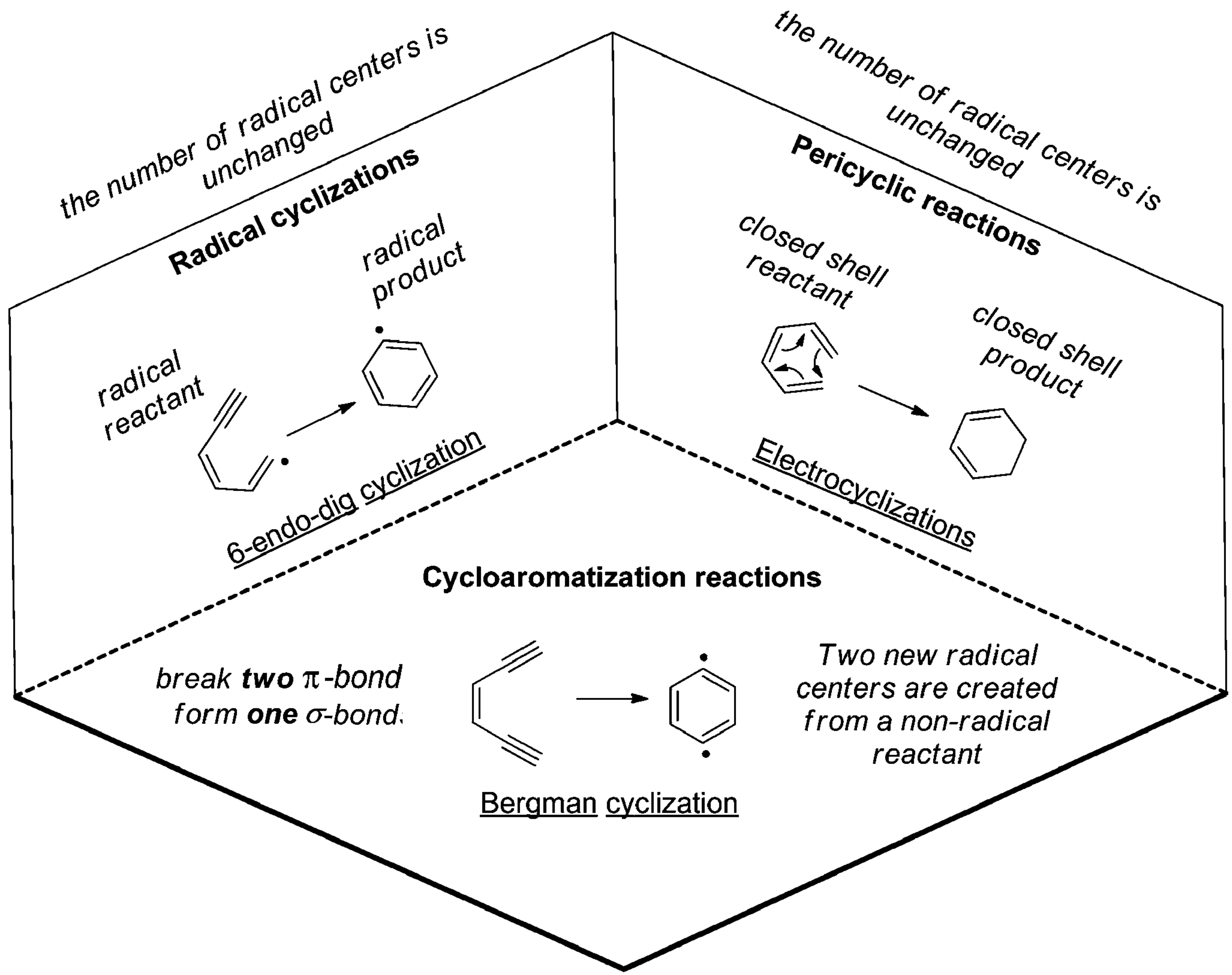
Chapman, O. L., et al., *J. Am. Chem. Soc.,* 1976, 98, 5703.
Lockhart, P and Bergman, R., *J. Am. Chem. Soc.,* 1981, 103, 4091.

Understanding Cycloaromatizations



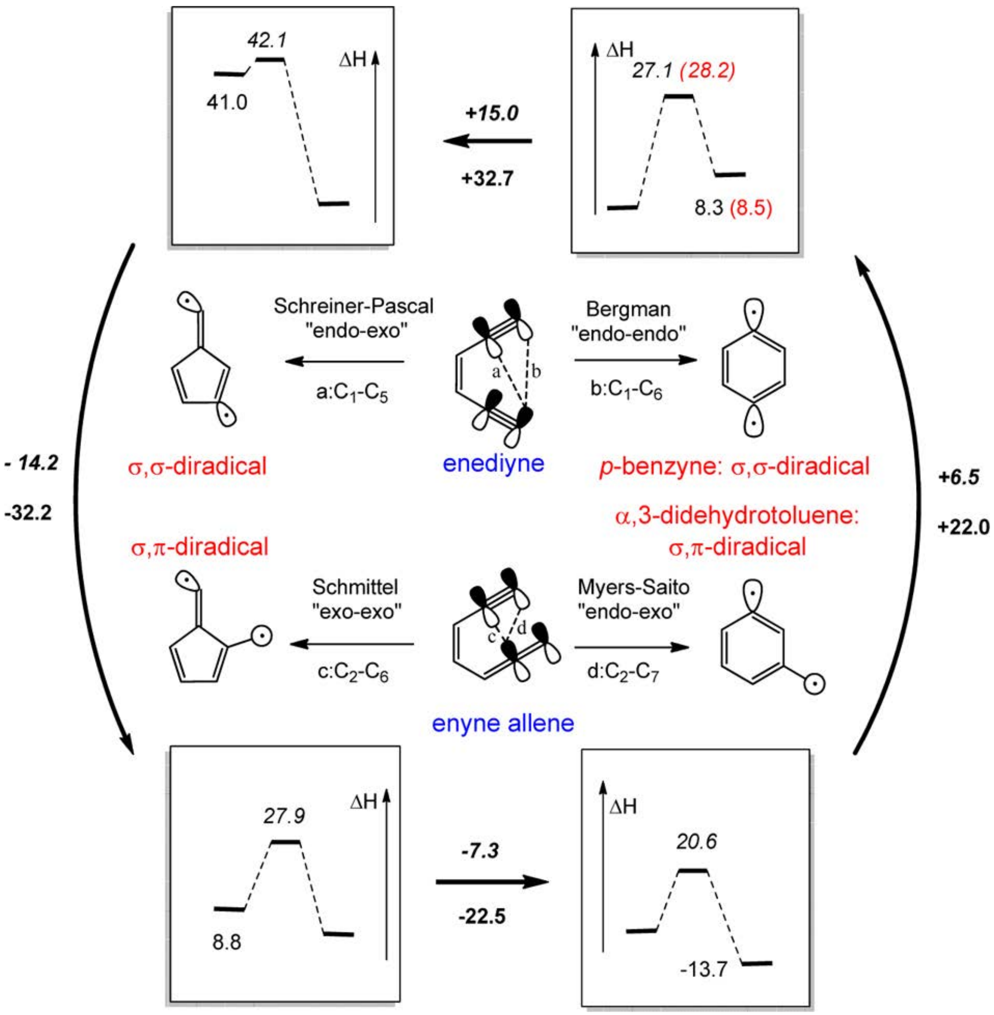
Kraka, E. and Cremer, D., *Comput. Mol. Sci.*, 2014, 4, 285.

Understanding Cycloaromatizations

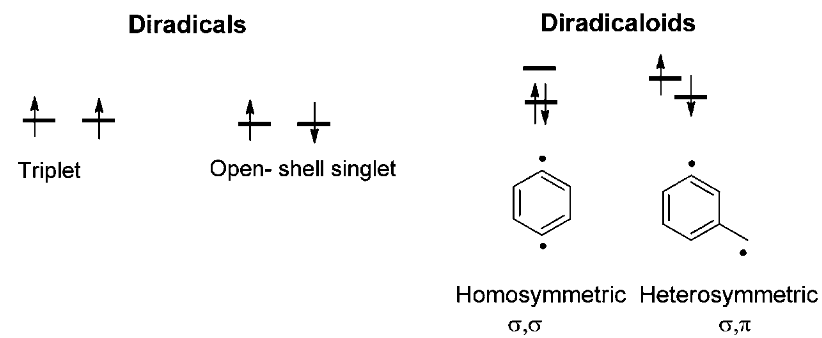


Mohamed, R., Peterson, P. and Alabugin, I., *Chem. Rev.,* 2013, 113, 7089.

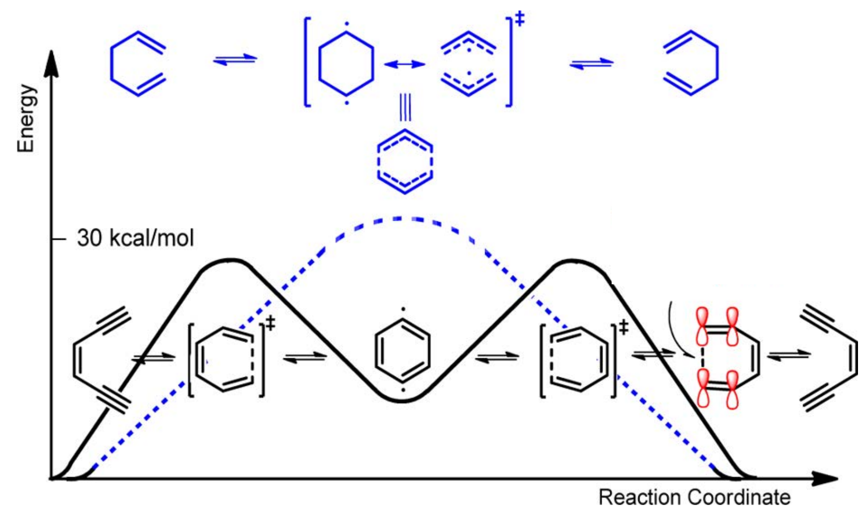
Understanding Cycloaromatizations



Bergman and M-S cyclizations are preferred



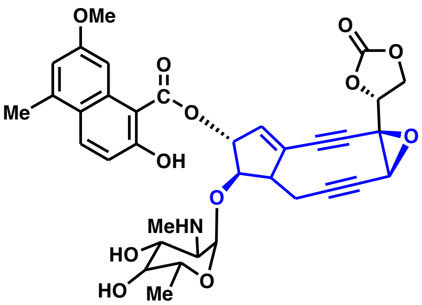
The intermediate diradicaloid with two coupled electrons



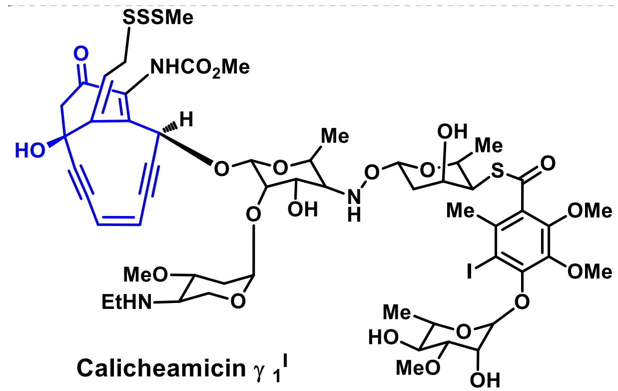
The BC can be thought of as a Cope rearrangement interrupted by aromatic stabilization

Mohamed, R., Peterson, P. and Alabugin, I., *Chem. Rev.,* 2013, 113, 7089.
Navarro-Vazquez, A, Prall, M.; Schreiner, P. R. *Org. Lett.,* 2004, 6, 2981.

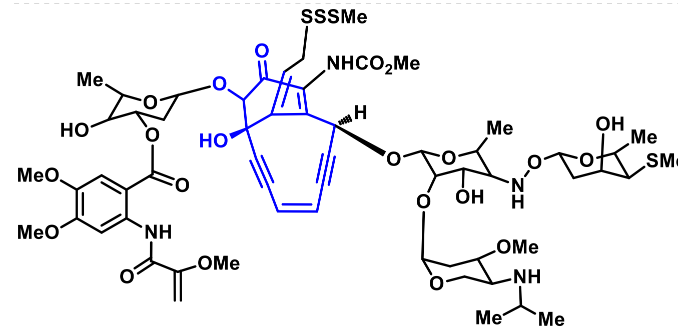
The enediyne antibiotics



Neocarzinostatin Chromophore



Calicheamicin γ_1^I



Esperamicin A1

Neocarzinostatin

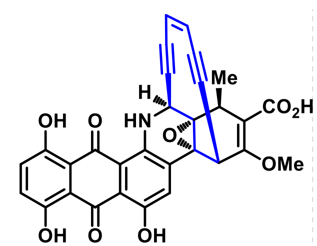
- First isolated in 1965 as a 1:1 protein complex
- Structure of the chromophore component was determined in 1985.
- Crystal structure of the complete protein-chromophore complex determined in 1993.

Calicheamicins

- First isolated in 1986 as a series of related compounds from microbial fermentation products
- Structure elucidation from 1987-1992.
- Active against both gram positive and gram negative bacteria. Extraordinary activity against murine tumours.

Esperamicins

- First isolated in 1985 from microbial fermentation products
- Structure elucidated by 1987.



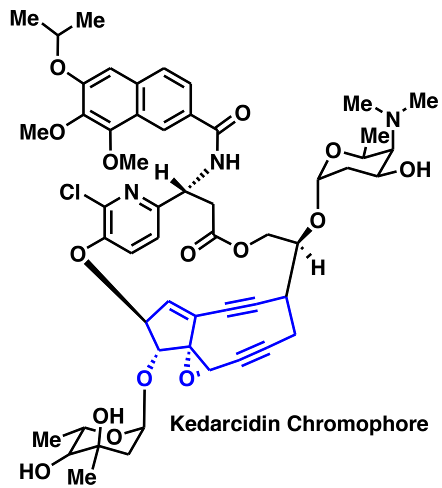
Dynemicin A

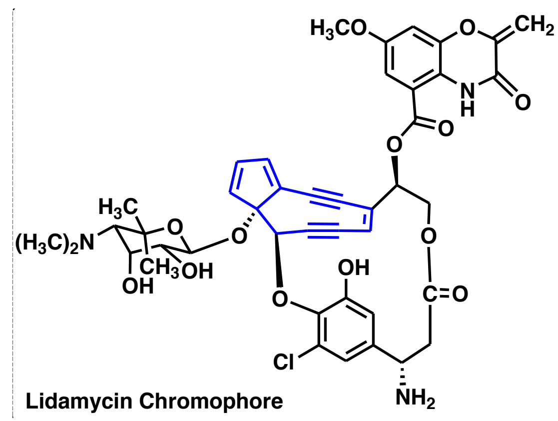
Dynemecins

- Isolated and characterized in 1989

Smith, A., Nicolaou, K. C., *J. Med. Chem.,* 1996, 39, 2103.

The enediyne antibiotics

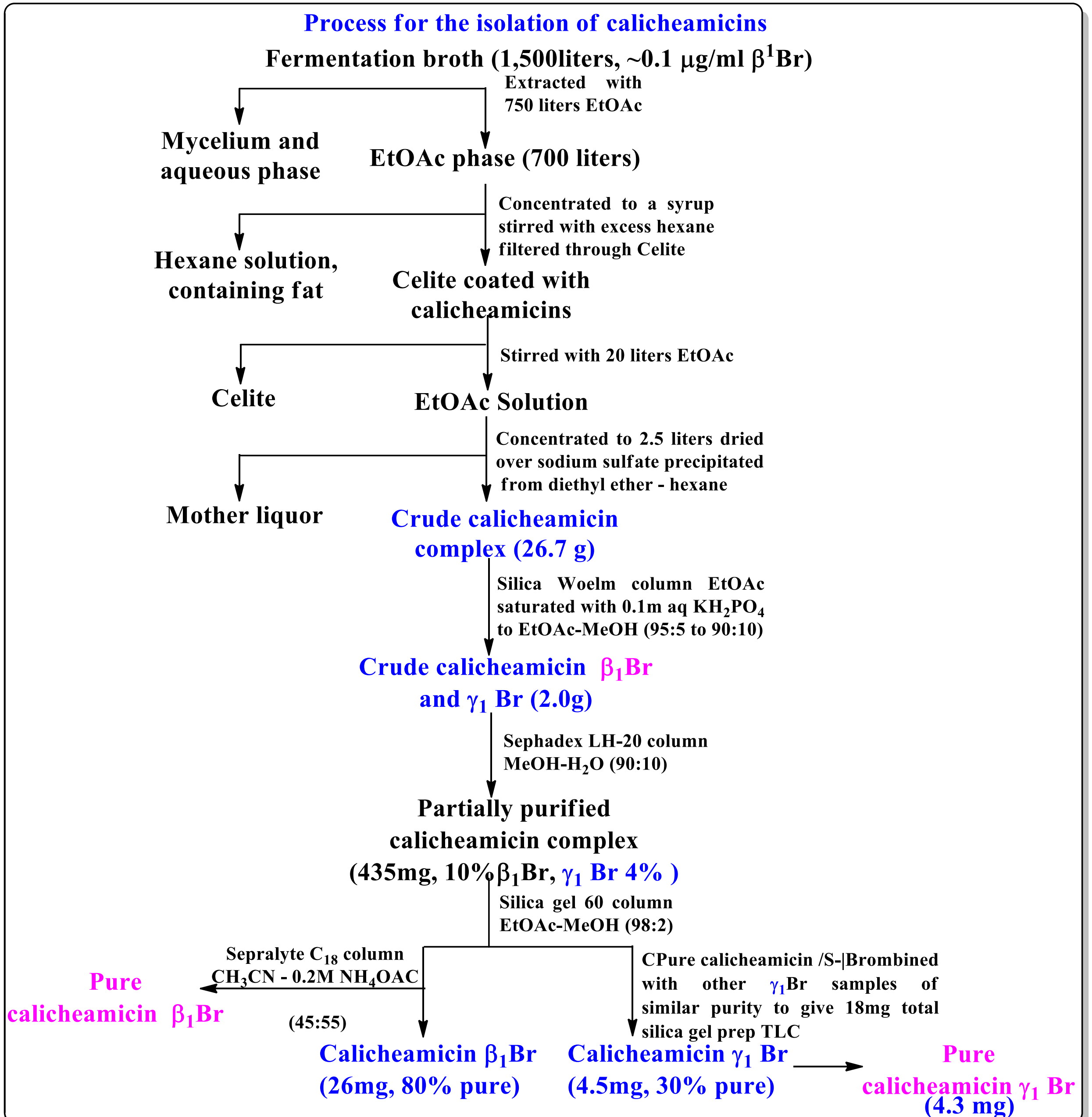




Agent	Producing Strain	*In Vitro* IC50 (nM)	*In Vivo* ID50 (μg/kg)
Neocarzinostatin	*Streptomyces carzinostaticus*	225～900	380
Lidamycin	*Streptomyces globisporus C-1027*	0.01～0.5	0.25～0.5
Kedarcidin	*Actinomycete strain L585-6*	1	2～3.3
Calicheamicins	*Micromonospora echinospora ssp*	6～9	0.5～1.5
Esperamicins	*Actinomadura verrucosospora*	0.3～8.3	0.1～0.2
Dynemicins	*Micromonospora chersina M956-1*	0.9～10	30～60

IC_{50}, half-inhibiting concentration; ID50, half-inhibiting dosage.

Shao, R., *Curr. Mol. Pharm.*, 2008, 1, 50.


Process for the isolation of calicheamicins
Fermentation broth (1,500liters, ~0.1 μg/ml β^1Br)
Extracted with 750 liters EtOAc
Mycelium and aqueous phase
EtOAc phase (700 liters)
Concentrated to a syrup stirred with excess hexane filtered through Celite
Hexane solution, containing fat
Celite coated with calicheamicins
Stirred with 20 liters EtOAc
Celite
EtOAc Solution
Concentrated to 2.5 liters dried over sodium sulfate precipitated from diethyl ether - hexane
Mother liquor
Crude calicheamicin complex (26.7 g)
Silica Woelm column EtOAc saturated with 0.1m aq KH_2PO_4 to EtOAc-MeOH (95:5 to 90:10)
Crude calicheamicin β_1Br and γ_1 Br (2.0g)
Sephadex LH-20 column MeOH-H_2O (90:10)
Partially purified calicheamicin complex (435mg, 10% β_1Br, γ_1 Br 4%)
Silica gel 60 column EtOAc-MeOH (98:2)
Sepralyte C_{18} column CH_3CN - 0.2M NH_4OAC (45:55)
Pure calicheamicin β_1Br
CPure calicheamicin /S-|Brombined with other γ_1Br samples of similar purity to give 18mg total silica gel prep TLC
Calicheamicin β_1Br (26mg, 80% pure)
Calicheamicin γ_1 Br (4.5mg, 30% pure)
Pure calicheamicin γ_1 Br (4.3 mg)

Challenges in Chemistry and Biochemistry

- Early 1970s: The Bergman cyclization is discovered as a radical cycloaromatization involving a 1,4-diyl intermediate.
- Remains a chemical curiosity upto the mid 1980's, and is underexplored in terms of reaction scope and synthetic utility
- Late 1980s: Characterization of unprecedented and highly potent enediyne antibiotics results in a massive renaissance in the chemistry of enediynes. Numerous avenues for research investigations are suddenly apparent and many researchers are now involved.

Enediynes as inspirations for mechanistic investigations into the BC.

Broadening synthetic utility

Biochemistry of enediynes

Mode of action

Synthesis of analogs and hybrids

Total synthesis challenge

Seminal Contributions

Robert Bergman (1942-)
Caltech and later Berkeley
Bergman Cyclization

Professor. Nakao Ishida (1923–2009)
Medical scientist, microbiologist, immunologist, entrepreneur, educator, and administrator

Tohuku University, Japan
NCS isolation, structure and mechanisms of action

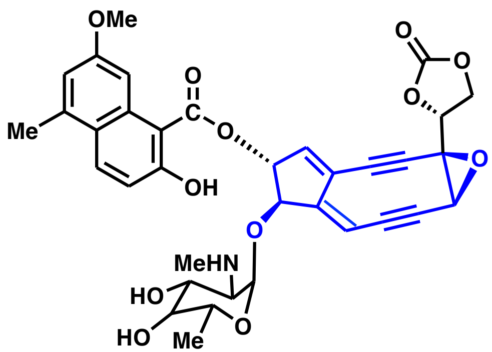
Bristol-Myers Squibb
American Cynamid

Isolation and structure elucidation of calicheamicin and esperamicin

K. C. Nicolaou (1946-)
UCSD, Scripps then Rice Univ.
Total Synthesis, structural studies, designed analogs

Andrew Myers
Caltech and now Harvard
Total Synthesis, mechanism of action

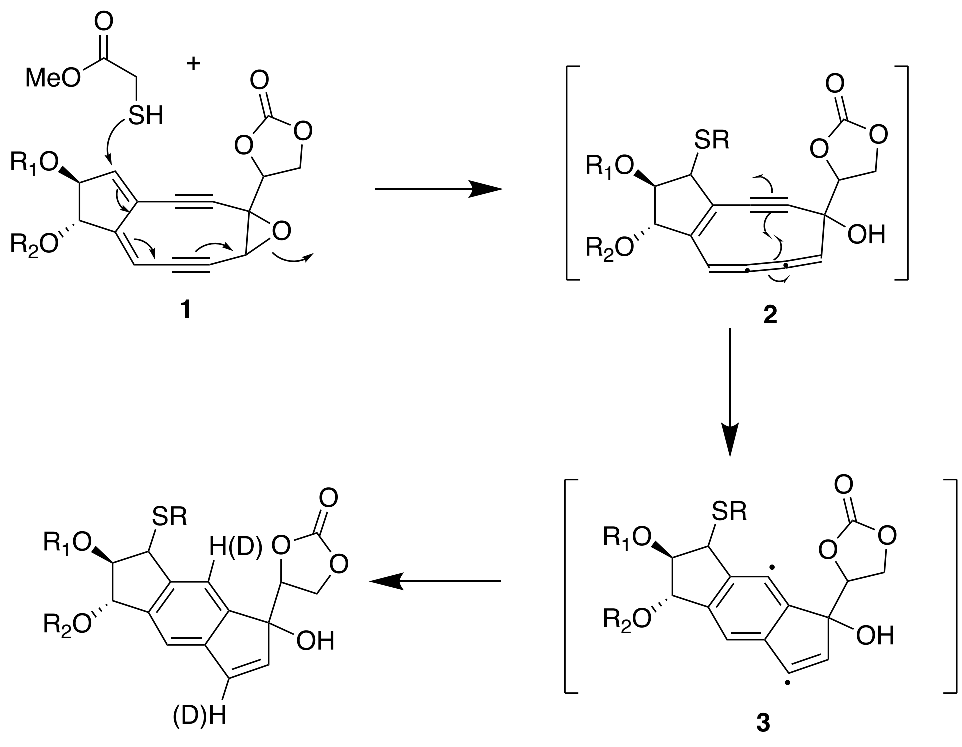
The enediyne antibiotics: mechanism of action



Neocarzinostatin Chromophore

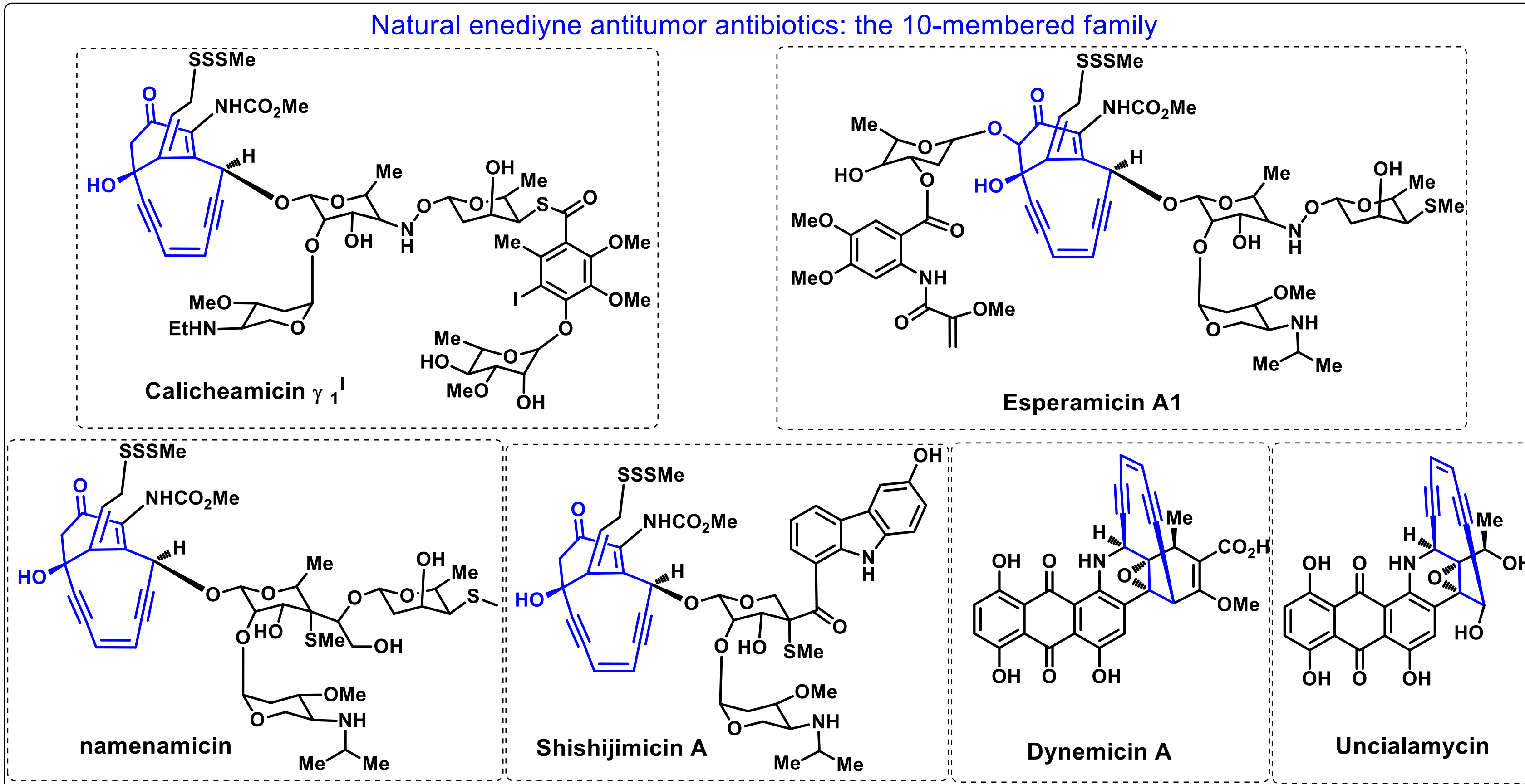
Pioneering work:

- 1978-1981: NCS binds to DNA and cleaves it. The transformation is accelerated drastically by added thiols and oxygen.
- 1983: (Goldberg et. al.) In absence of DNA, NCS reacts irreversibly with nucleophiles to form a covalent adduct which binds but does not cleave DNA. An epoxide ring is opened. Spectroscopic data for the adduct.
- 1987: (Myers) assignment of the adduct and cycloaromatization (Myers-Saito cyclization) proposal



Hensens, O.D. et. al., *Biochem. Biophys. Res. Comm.,* 1983, 113, 538.
Myers, A., *Tet. Lett.,* 1987, 28, 4493.

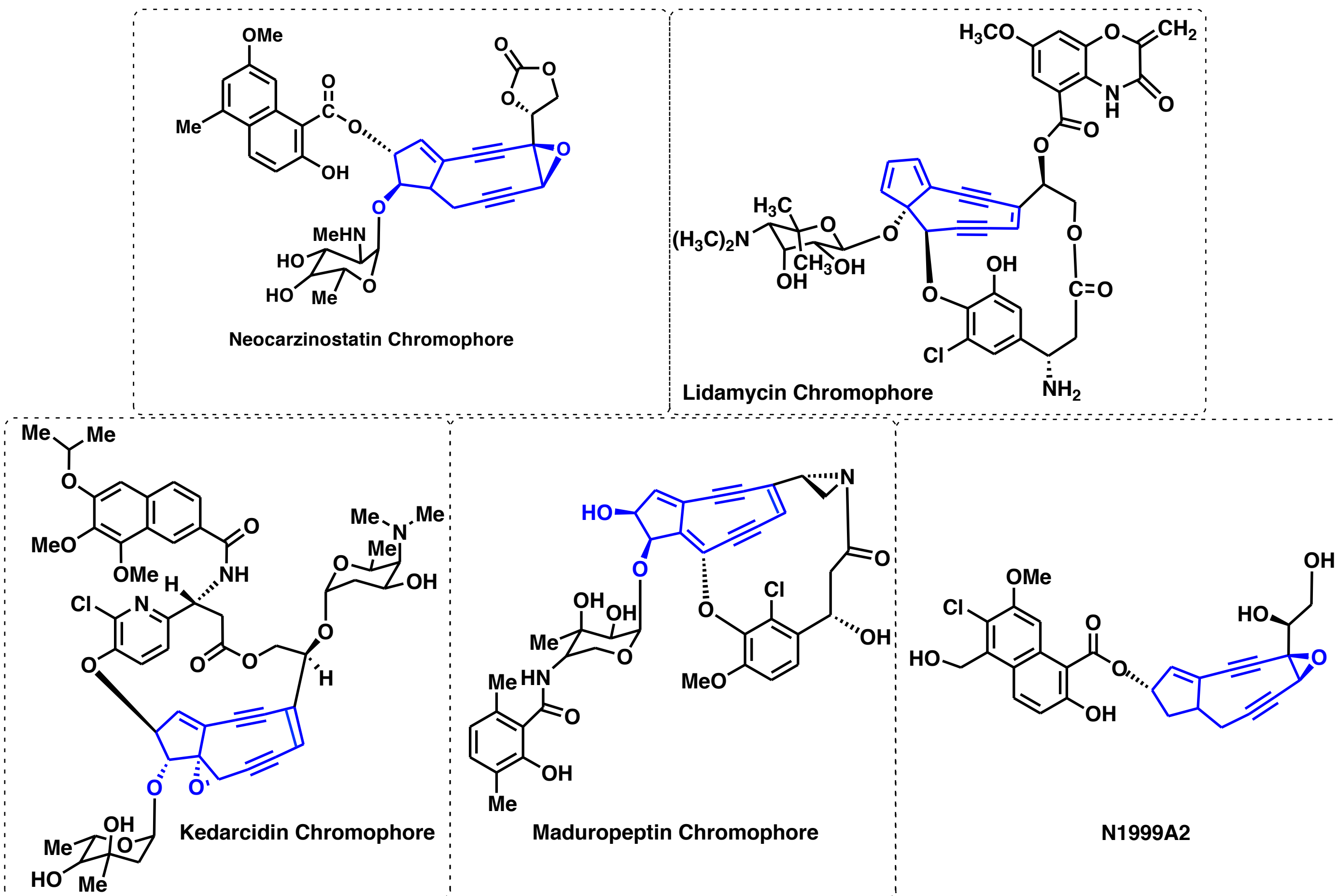
The enediyne antibiotics: mechanism of action



10-membered enediynes

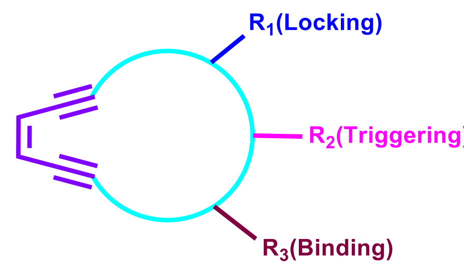
The enediyne antibiotics: mechanism of action

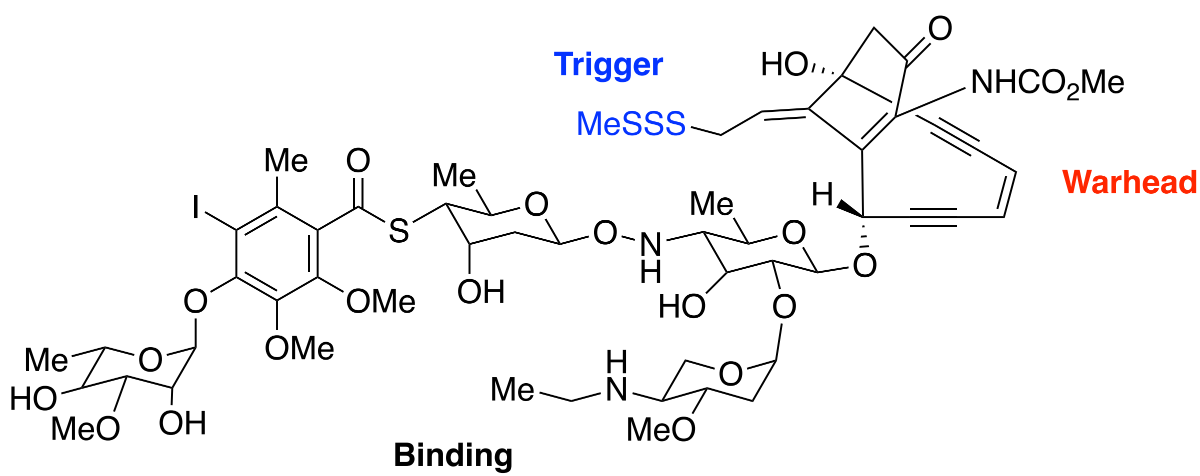
Natural enediyne antitumor antibiotics: the 9-membered family



- 9-membered enediynes as apoprotein complexes.
- N1999A2 is the only non-protein 9-membered cyclic enediyne found in nature.

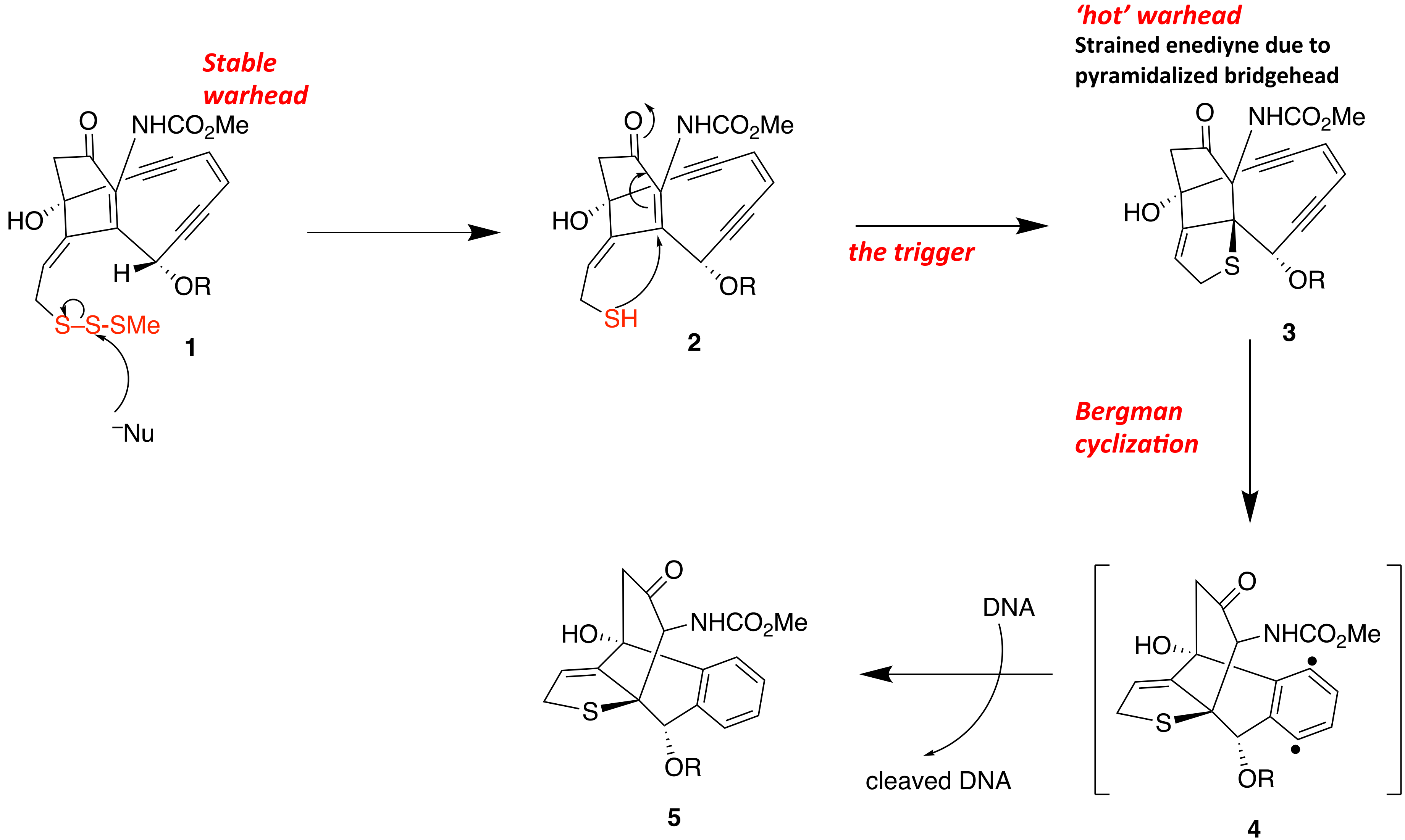
The enediyne antibiotics: mechanism of action

Structural Units	Structural Features/Functions	Pictorial presentation
Warhead	The Enediyne.	
Locking Device	Stabilizes the enediyne from undergoing rearrangement	
Triggering Device	It offers a mechanism by which locking is removed and enediynes become reactive	
Binding Device	Gives Specificity	



calicheamicin γ_1^I

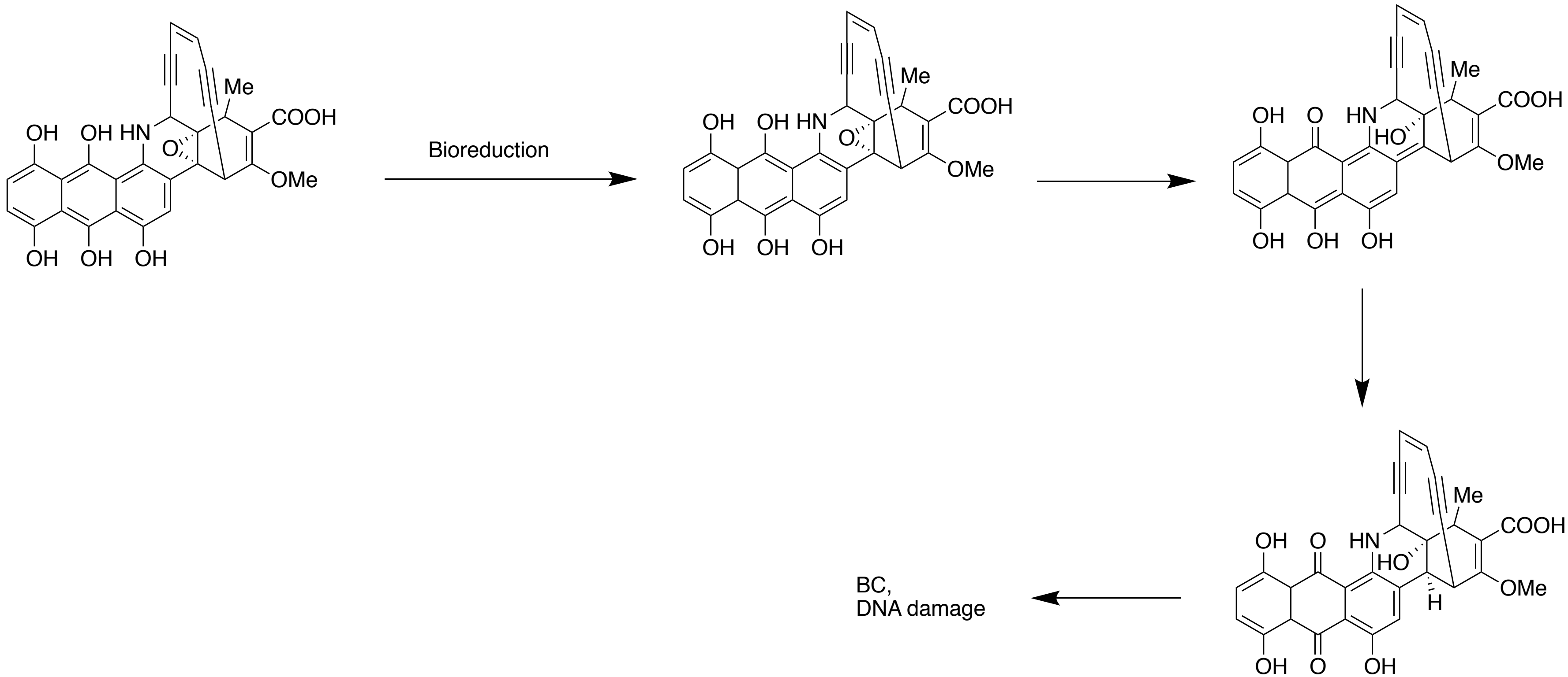
Calicheamicin: mechanism of action



These fundamental chain of events are more or less common to the mechanism of other enediyne antibiotics.

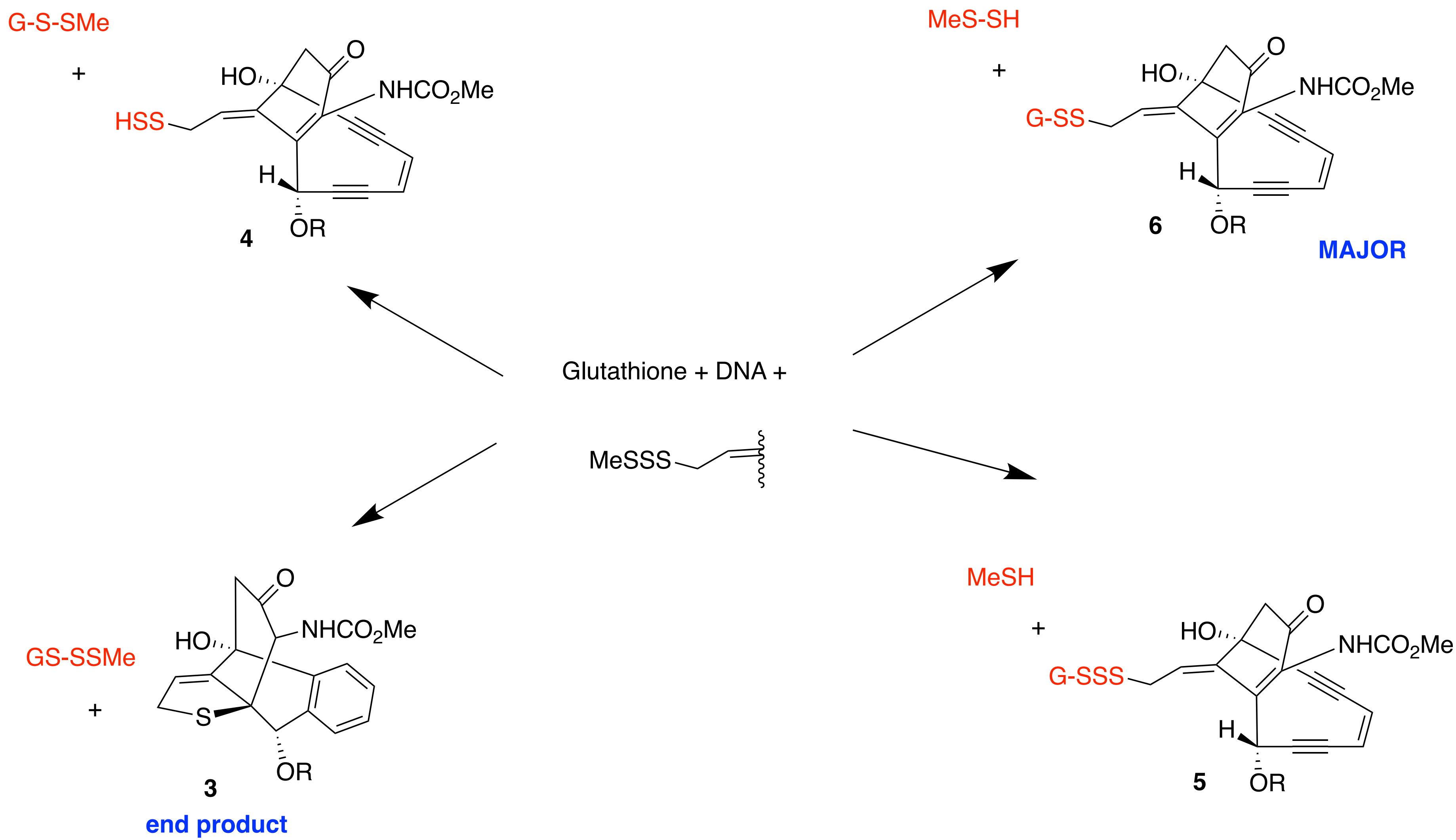
Smith, A., Nicolaou, K. C., *J. Med. Chem.,* 1996, 39, 2103.

Dynemicin: mechanism of action



Calicheamicin: Intricacies in the mechanism of action

1. Calicheamicin + Glutathione + DNA gives a mixture of products:



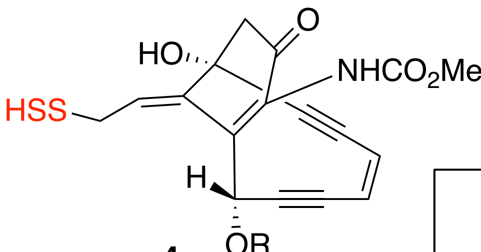
Myers, A. G. et al., *J. Am. Chem. Soc.*, 1994, 116, 1255.

Calicheamicin: Intricacies in the mechanism of action

1. Calicheamicin + Glutathione + DNA gives a mixture of products:

G-S-SMe

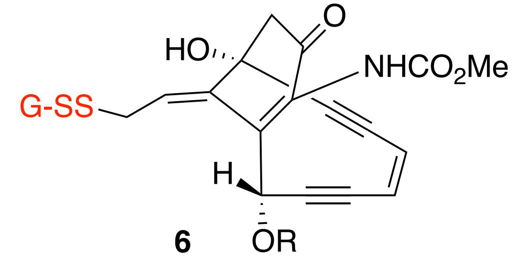
+



4

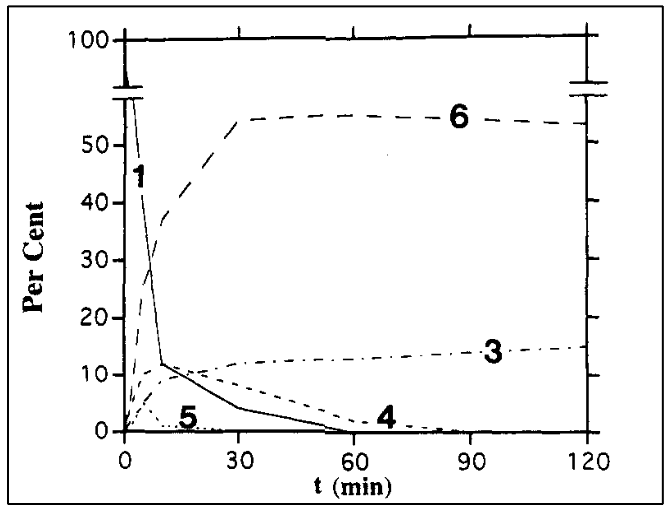
MeS-SH

+



6

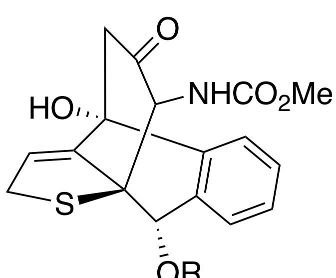
MAJOR



4-6 converge to 3.
4 and 5 disappear faster than 6

GS-SSMe

+

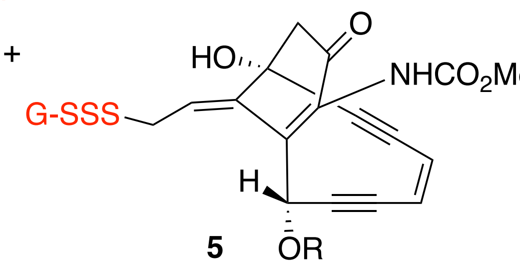


3

end product

MeSH

+

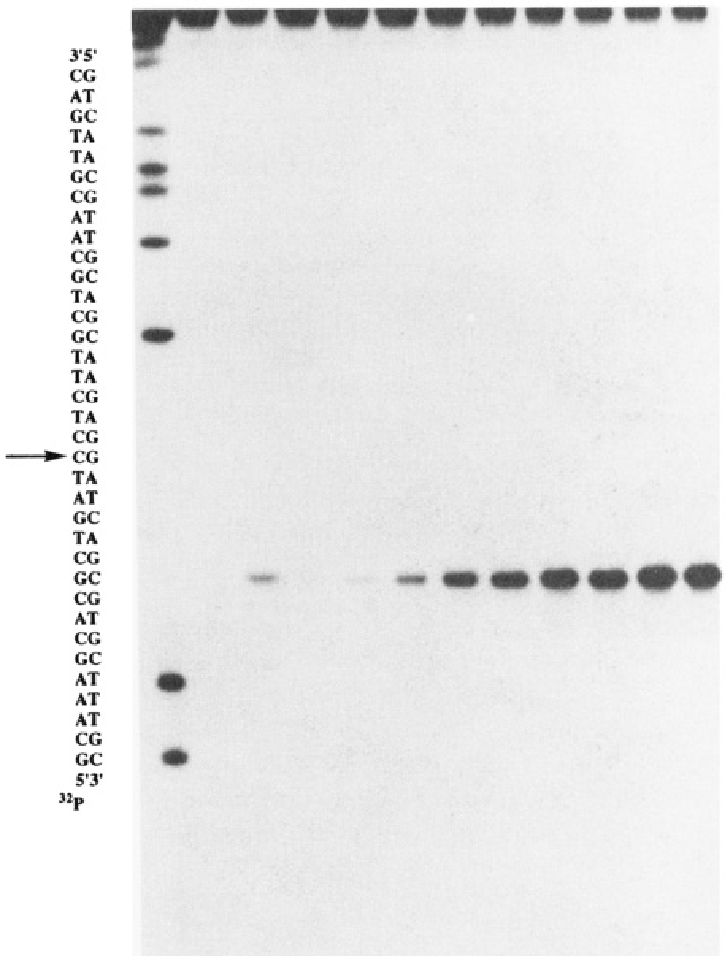


5

Myers, A. G. et al., *J. Am. Chem. Soc.*, 1994, 116, 1255.

Calicheamicin: Intricacies in the mechanism of action

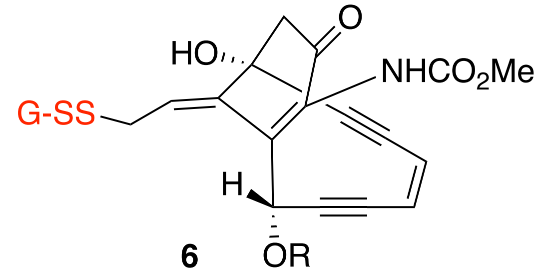
Substrate		6	1	6	6	6	6	6	6	6	6	6
[GSH] (mM)		0	1	1	10	10	10	10	10	10	10	10
t (hrs)			1	1	0.5	1	2	3	4	5	8	10
	1	2	3	4	5	6	7	8	9	10	11	12



Relative Cleavage	0	30	3	15	29	53	72	83	95	100	100

MeS-SH

+

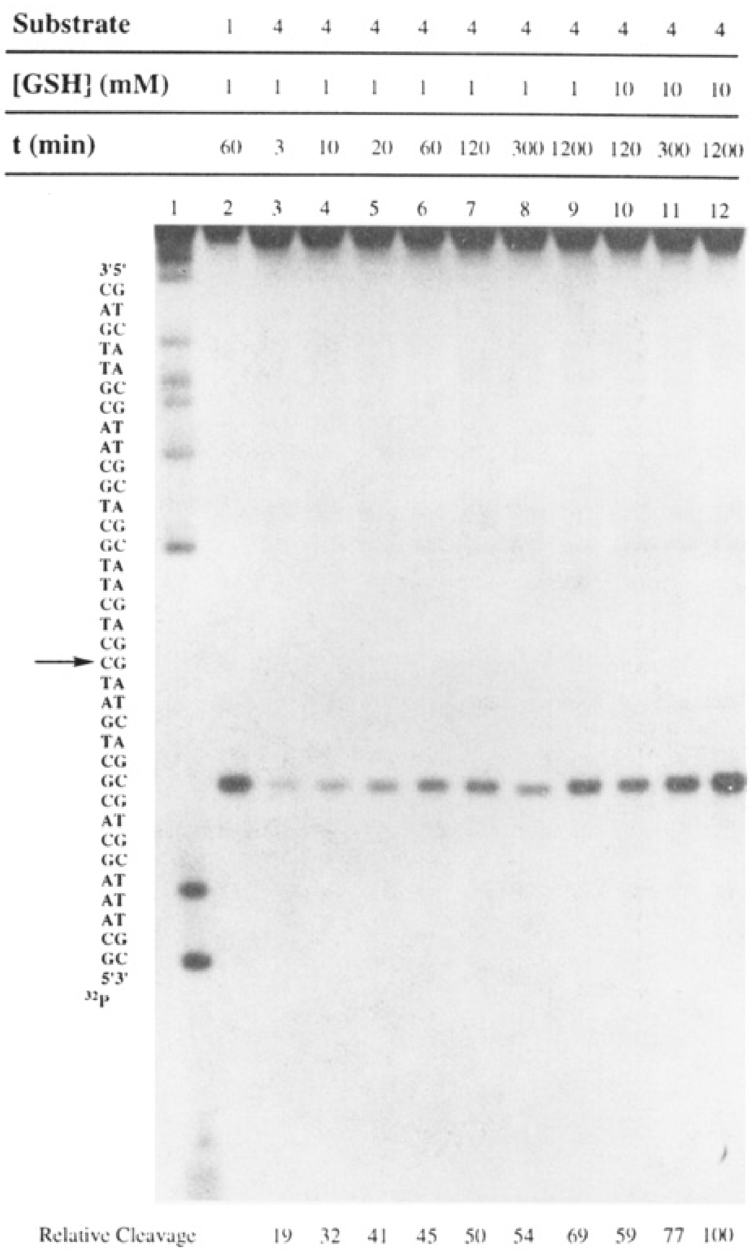


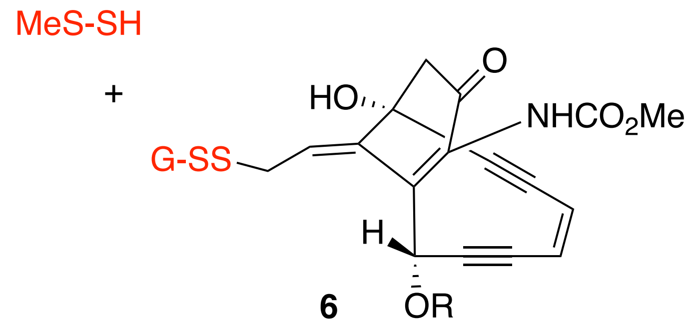
6

Rate of DNA cleavage by 6 is ~10 fold lower than that by 1 (chalecheamicin)

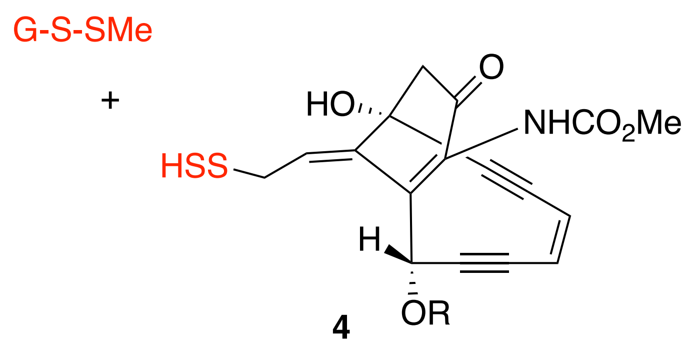
Myers, A. G. et al., *J. Am. Chem. Soc.*, 1994, 116, 1255.

Calicheamicin: Intricacies in the mechanism of action





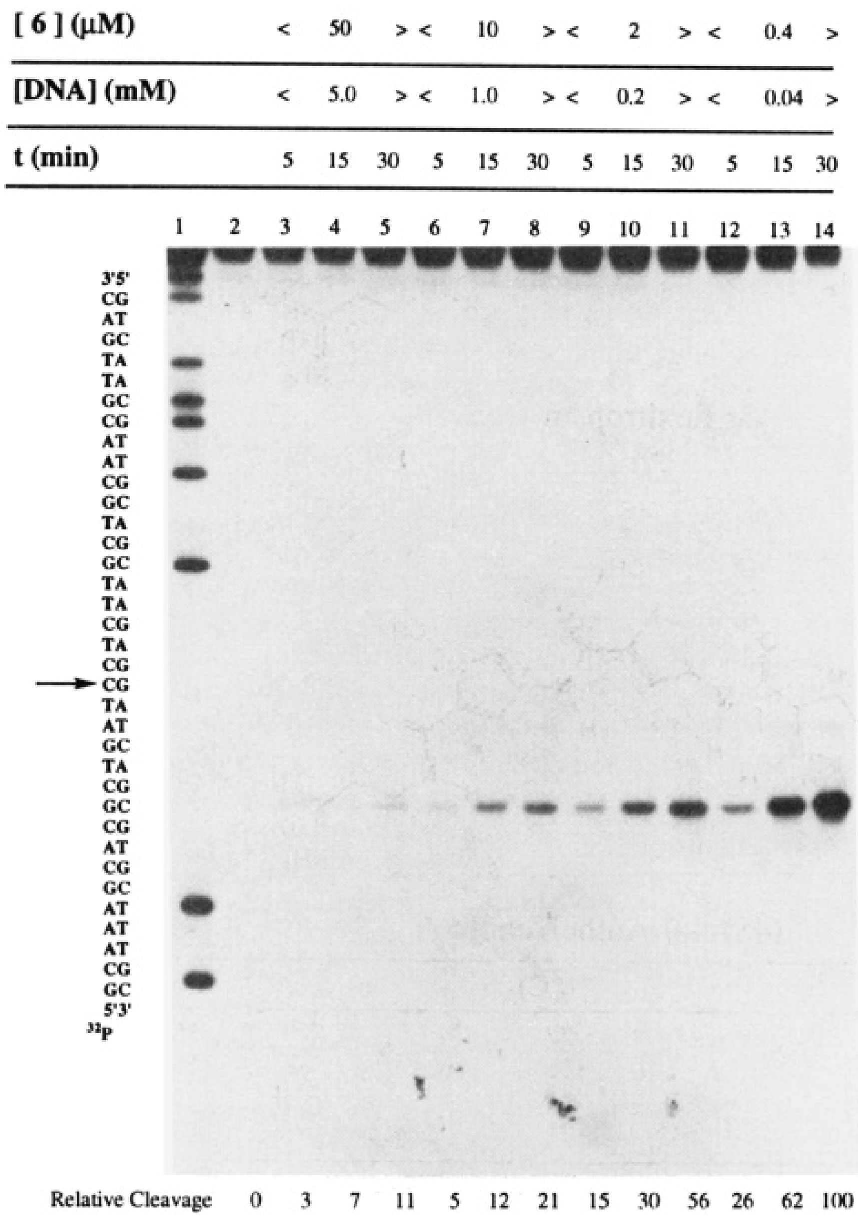
Rate of DNA cleavage by 6 is ~10 fold lower than that by 1 (chalecheamicin)



Rate of DNA cleavage by 4 lower than that by 1 but higher than 6.

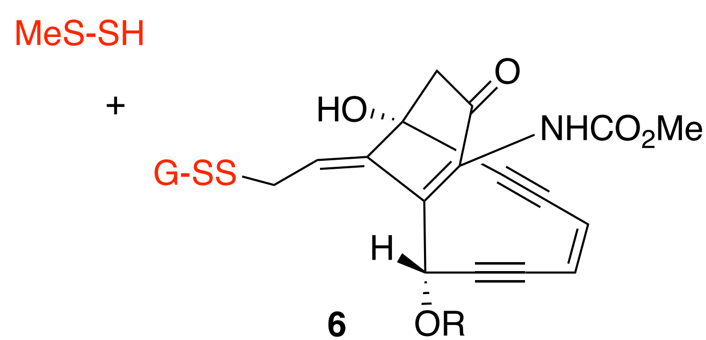
Myers, A. G. et al., *J. Am. Chem. Soc.*, 1994, 116, 1255.

Calicheamicin: Intricacies in the mechanism of action



- Does the reaction occur as a ternary complex of **1,** GSH, and **DNA,** or is **1** activated free in solution with subsequent binding of the reaction groduct(s) to **DNA?**

- What is the role of **DNA** in the primary and secondary activation steps?



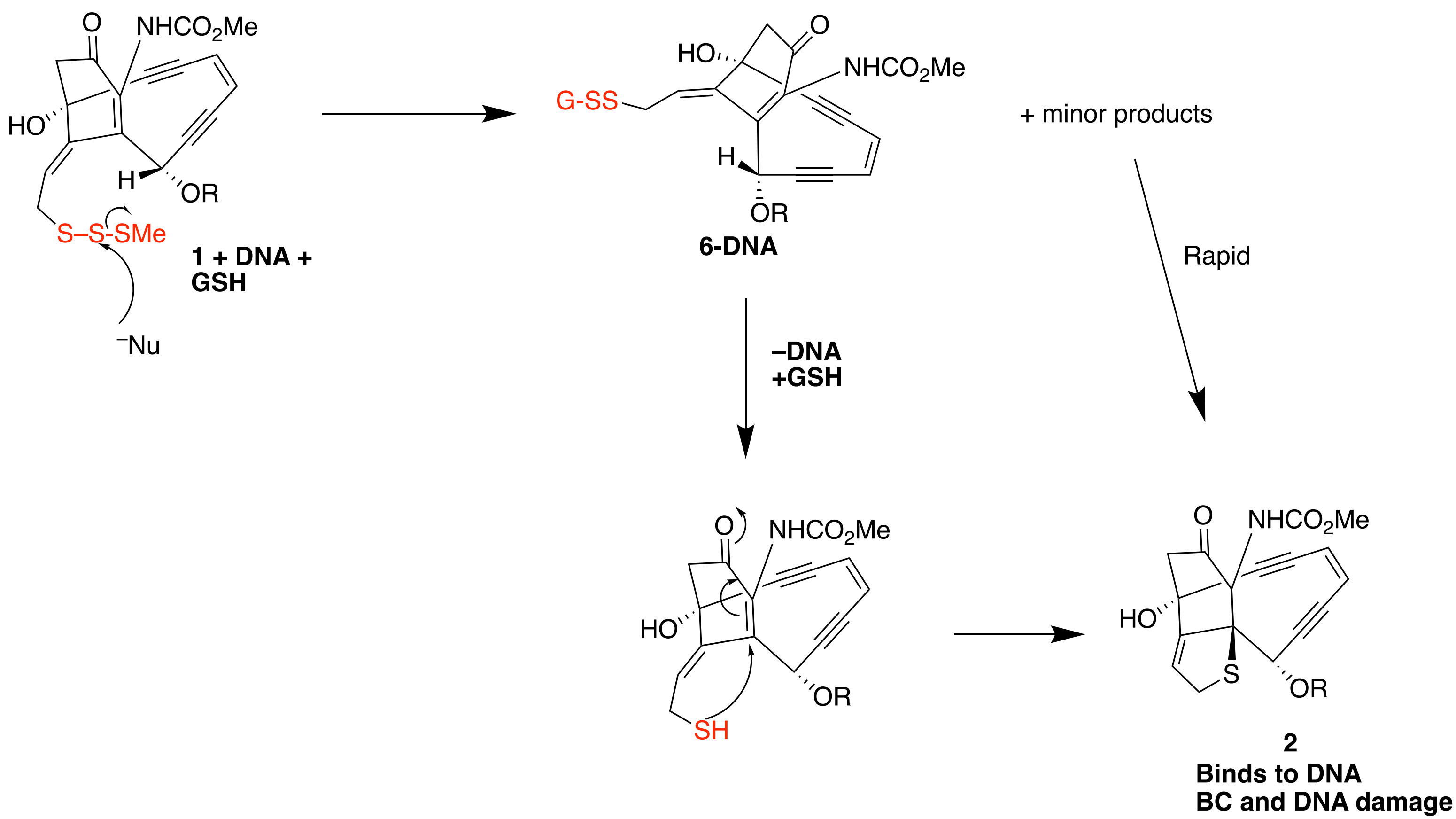
6

Excess DNA inhibits cleavage by 6.
The drug is partitioned between bound and free form where the latter reacts faster.

Myers, A. G. et al., *J. Am. Chem. Soc.*, 1994, 116, 1255.

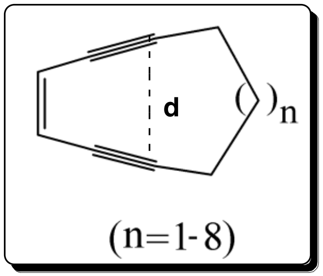
Calicheamicin: Intricacies in the mechanism of action

1. Reaction of 1 with GSH and DNA as a ternary complex produces **6** as the major product.
2. 6 must dissociate from the helix prior to reacting with GSH and produce **2.**
3. 2 binds to DNA followed by cycloaromatization and DNA cleavage.
4. DNA cleavage will follow a bimodal kinetic profile where the initial cleavage event will occur with a half-life on the order of a few minutes and the second, major stage of the cleavage will occur with a half-life of several hours, depending critically upon the exact concentration of nuclear DNA.



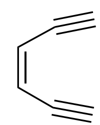
Myers, A. G. et al., *J. Am. Chem. Soc.,* 1994, 116, 1255.

Contributing factors: the distance theory

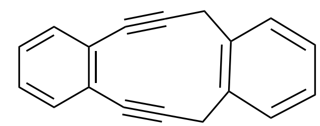


Entry	(n = x) Ring Size	**c,d-distance** (Å)	Stability
1	(n = 1) 9	2.84	Unknown
2	(n = 2) 10	3.25	Cyclization at 25 °C
3	(n = 3) 11	3.61	Stable at 25 °C
4	(n = 4) 12	3.90	Stable at 25 °C
5	(n = 5) 13	4.14	Stable at 25 °C
6	(n = 6) 14	4.15	Stable at 25 °C
7	(n = 7) 15	4.33	Stable at 25 °C
8	(n = 8) 16	4.20	Stable at 25 °C

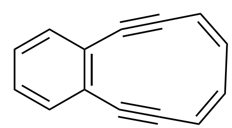
- Nicolaou: In the absence of other factors, distance *d* between the ends of the diyne system contributes to reactivity.
- Proposed that the critical range of *d* values between 3.20 and 3.31 would be necessary for biologically relevent activities.



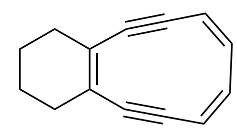
A
cd = 4.12 A
cyclizes at > 150 °C



B
cd = 3.03 A
cyclizes at 25 °C



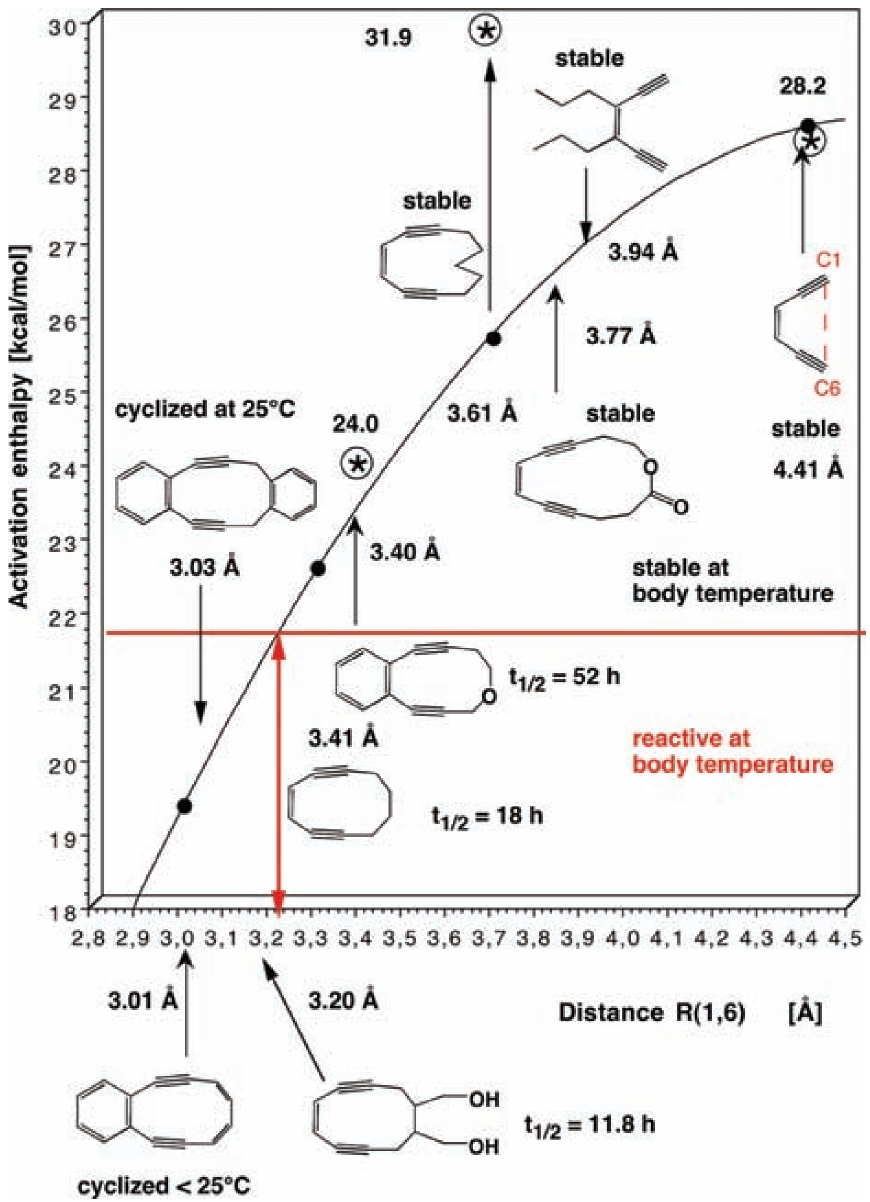
C
cd = 3.01 A
cyclizes at < 25 °C



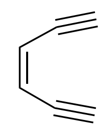
D
cd = 2.99 A
cyclizes at < 25 °C

Nicolaou. K. C. et al., *J. Am. Chem. Soc.*, 1992, 114, 7361.

Contributing factors: the distance theory

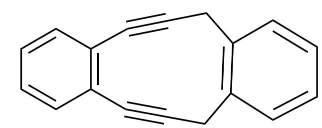


- Nicolaou: In the absence of other factors, distance *d* between the ends of the diyne system contributes to reactivity.
- Proposed that the critical range of *d* values between 3.20 and 3.31 would be necessary for biologically relevent activities.



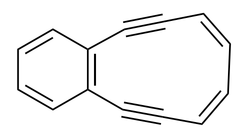
A

cd = 4.12 A
cyclizes at > 150 ^{o}C



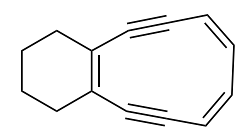
B

cd = 3.03 A
cyclizes at 25 ^{o}C



C

cd = 3.01 A
cyclizes at < 25 ^{o}C



D

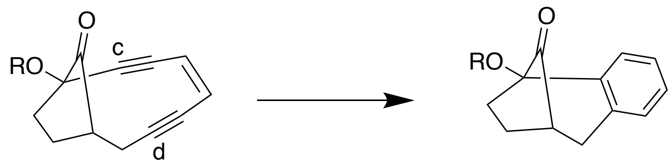
cd = 2.99 A
cyclizes at < 25 ^{o}C

Nicolaou. K. C. et al., *J. Am. Chem. Soc.*, 1992, 114, 7361.
Kraka, E. and Cremer, D., *Comput. Mol. Sci.*, 2014, 4, 285.

Attenuation of strain

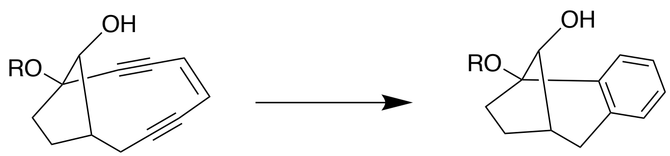
- Magnus, Snyder: the cyclization rates of bicyclic enediynes are best interpreted as governed by strain-energy modulation in the pseudocyclic transition state.

R = TBDMS

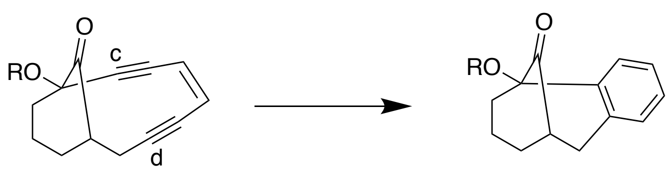


A → **B**

c,d = 3.368 Å

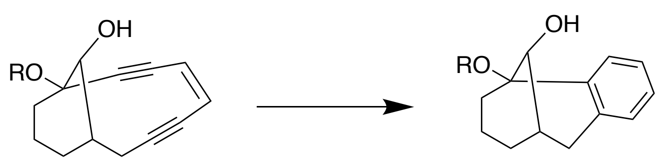


C → **D**



E → **F**

c,d = 3.391 Å



G → **H**

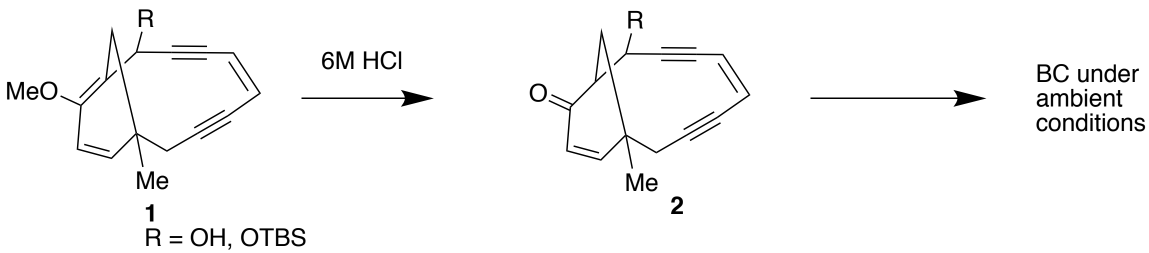
Reaction	k_{rel} at 85 ^oC	ΔE^*, kcal/mol (calculated, MM2)	ΔE^*_{ring}, kcal/mol (calculated, MM2)
A → B	1	31.2	1.5
C → D	216	27.5	-1.5
E → F	648	25.4	-6
G → H	N.D extremely rapid even at 0 ^oC	22	-6.1

- **A** has lower inter alkynyl distance but reacts slower.
- The cyclohexanone derivatives **E, G** enjoy a conformationally activated strain release mechanism from ground state to transition state.

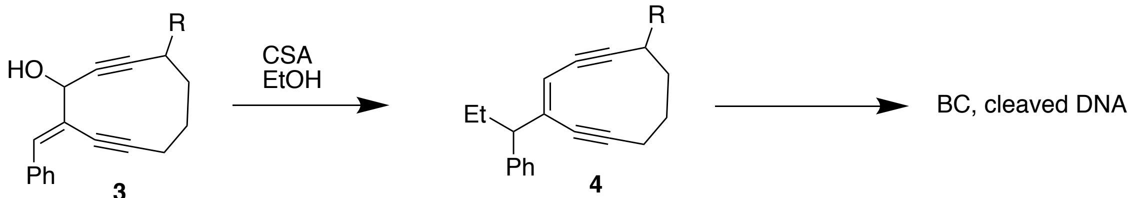
kcal (PRDDO). Secondly and more importantly, while the five-ring energy increases by 1.5 kcal as it moves from enediyne **10** to a biradicaloid transition state, the six-membered ring of **7** drops by 6.0 kcal (boat → chair) along the same route. At the

Magnus. P. et al., *J. Am. Chem. Soc.*, 1990, 112, 4986.

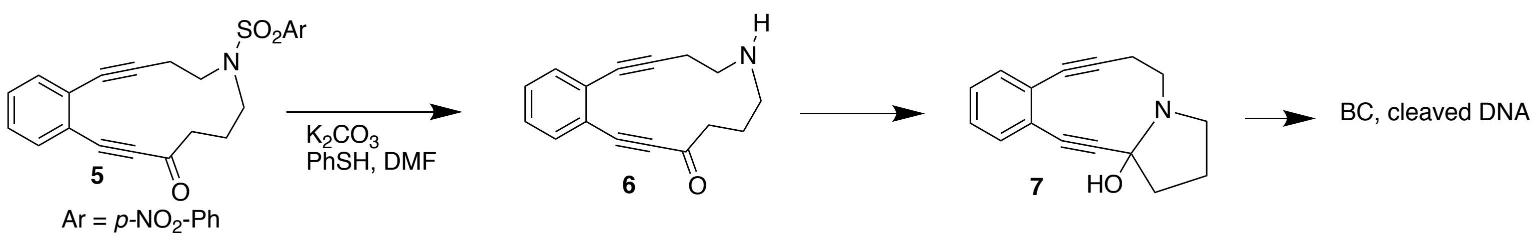
Activation and Triggers



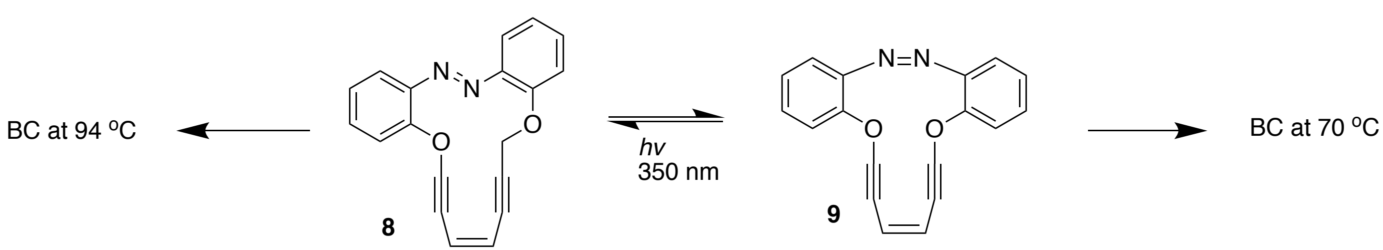
Semmelhack, M. F. et al., *J. Am. Chem. Soc.,* 1993, 115, 11618.



Dai, W. M. et al., *J. Org. Chem.,* 1999, 64, 682.

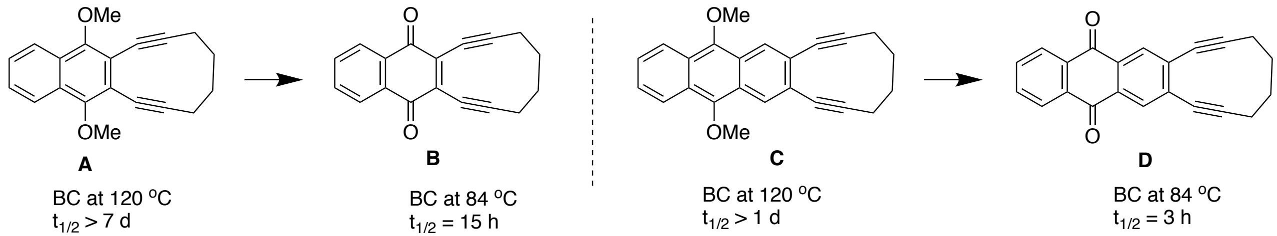


Basak, A. et al., *Angew. Chem. Int. Ed.,* 2005, 44, 132.

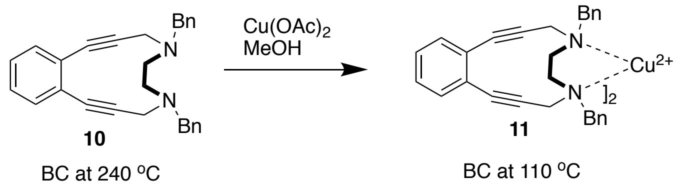


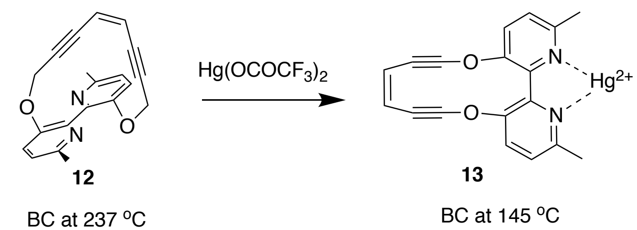
Basak, A. et al., *Bioorg. Med. Chem. Lett.,* 2005, 15, 5392.

Activation and Triggers



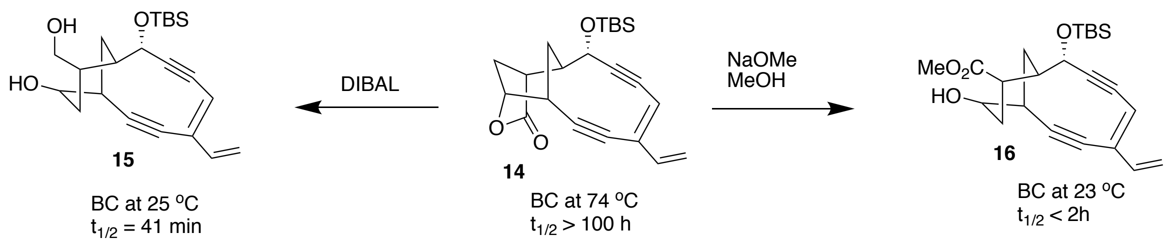
Semmelhack, M. F. et al., *J. Org. Chem.*, 1994, 59, 5038.



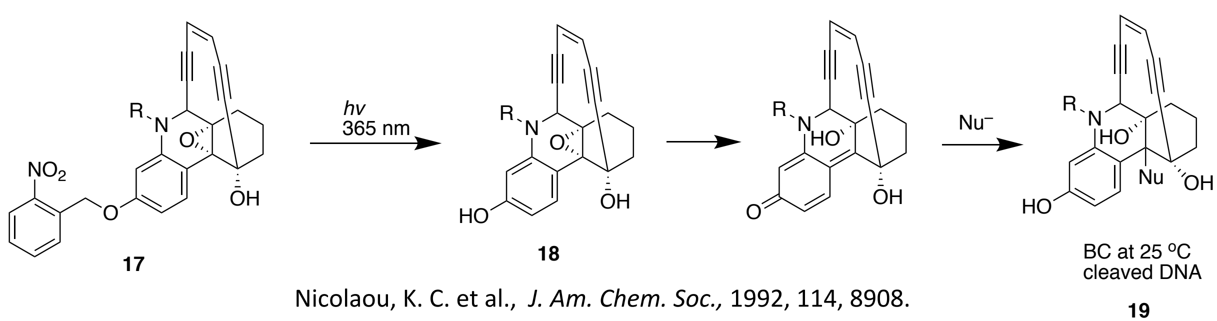


Konig, B. et al., *Angew. Chem. Int. Ed. Engl.,* 1995, 34, 2538.

Basak, A. et. al. *J. Chem. Soc. Perkin Trans.,* 2000, 1, 1955.



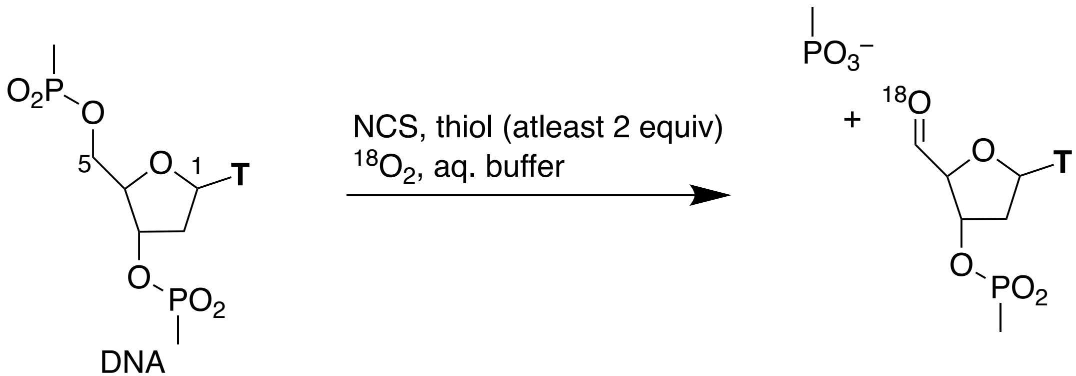
Semmelhack, M. F. et al., *J. Am. Chem. Soc.,* 2003, 125, 10496.



Nicolaou, K. C. et al., *J. Am. Chem. Soc.,* 1992, 114, 8908.

Group Problem: mechanisms of DNA cleavage

Investigations to reveal the mechanisms of DNA cleavage by NCS were pioneered by Irving Goldberg at Harvard in the late 1980's. Our understanding is primarily based on his series of elegant experiments. The major pathway involves single strand scission at thymine to produce a nucleoside aldehyde.

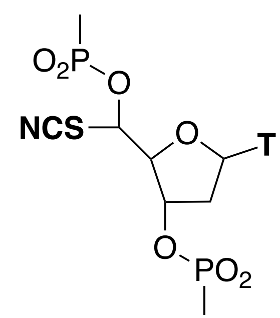


The initial NCS activation (diradical formation) is rapidly followed by uptake of 1 mol of O_2 per mole of chromophore. O_2 uptake is followed by the uptake of atleast an additional sulfhydryl group. Oxygen label is selectively incorporated into the product nucleoside aldehyde.

Tritium labelling demonstrates that the chromophore selectively abstracts tritium only from the 5'-position and incorporates it into a stable, non-exchangeable form of the chromophore.

In the absence of oxygen, strand cleavage is poor and NCS-DNA adducts are seen.

Provide a reasonable mechanism that is consistent with these experimental observations



NCS- DNA adduct

Goldberg, I., *Free Radical Biology and Medicine*, 1987, 3, 41.
Ohtsuki and Ono, *Neocarzinostatin*, Springer Japan, 1997.

Intermission

Total Synthesis highlights

Identified
Neocarzinostatin Chromophore
(Edo *et al.* 1985)

Total synthesis of
Dynemicin A
(Myers *et al.* 1995)
(Danishefsky *et al.* 1995)

Total synthesis of
N1999A2
(Kobayashi, Hirama *et al.* 2006)

Total synthesis of
Maduropeptin Chromophore
(Sato, Hirama *et al.* 2009)

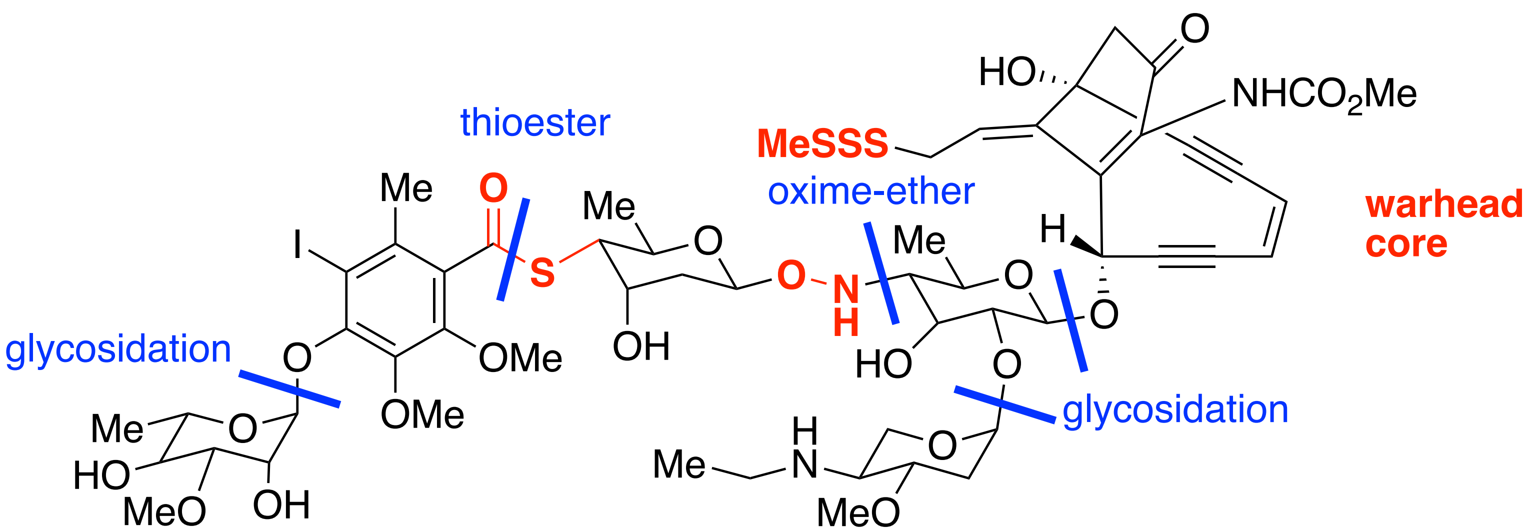
1985 1990 1995 2000 2005 2010 2011

Total synthesis of
Calicheamicin γ^{I}_{1}
(Nicolaou *et al.* 1992)
(Danishefsky *et al.* 1994)

Total synthesis of
Neocarzinostatin Chromophore
(Myers *et al.* 1998)

Total synthesis of
Kedarcidin Chromophore
(Myers *et al.* 2007)

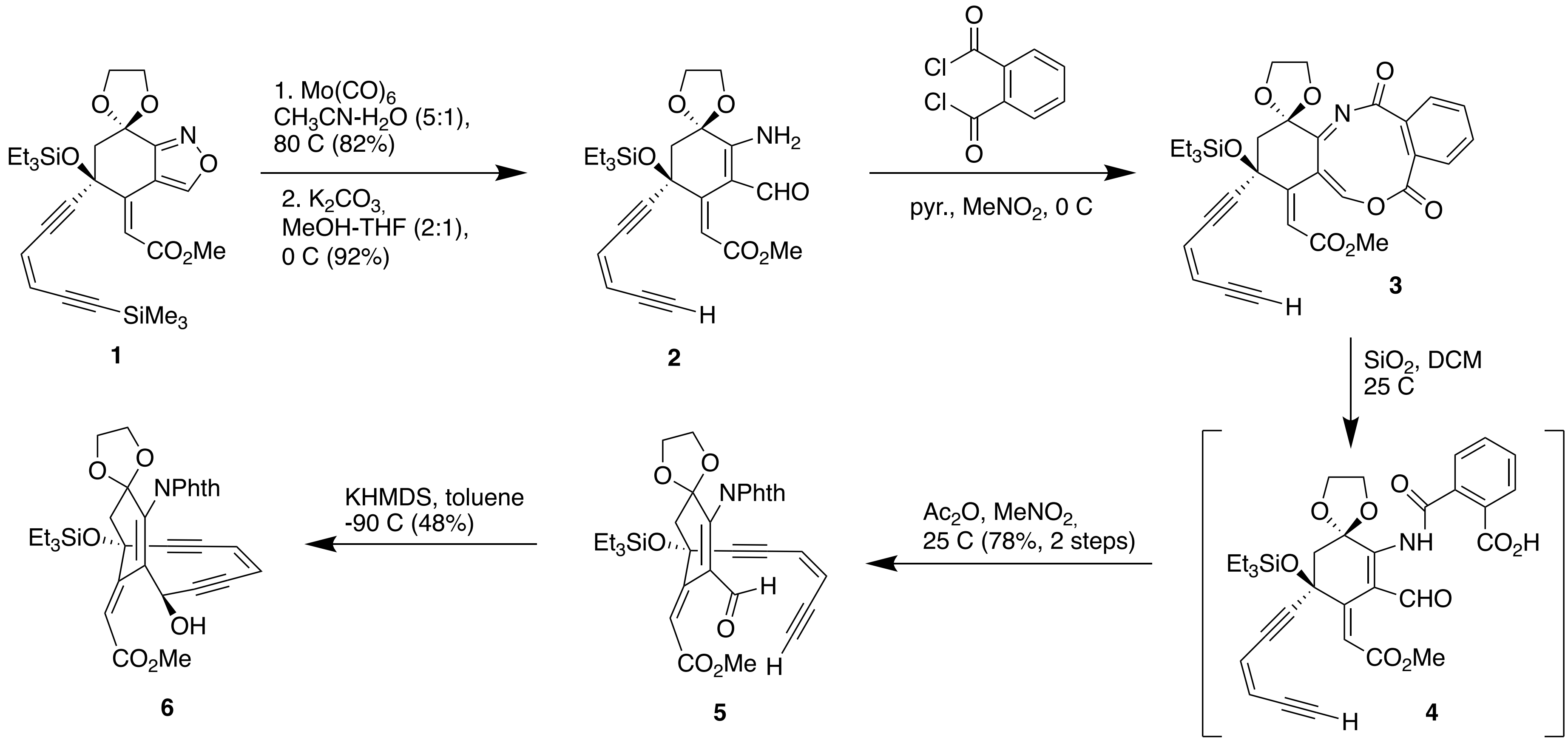
Nicolaou (1988-1992)



calicheamicin γ_1^{I}

Classics in Total Synthesis. Targets, Strategies, Methods. Von *K. C. Nicolaou und E. J. Sorensen*. VCH, Weinheim, 1996.

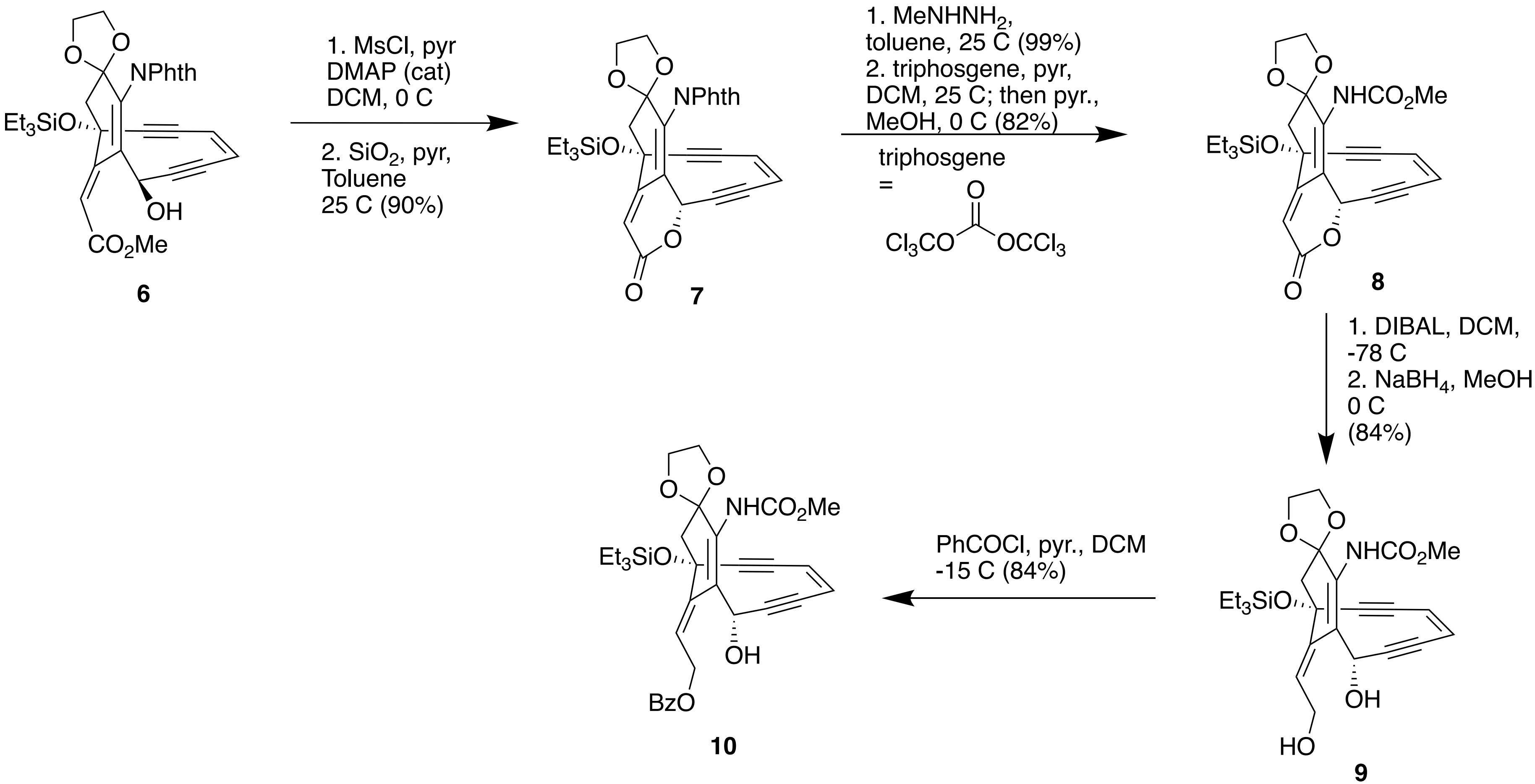
Nicolaou (1988-1992)



Why not a direct cyclization from **2** to **6?**

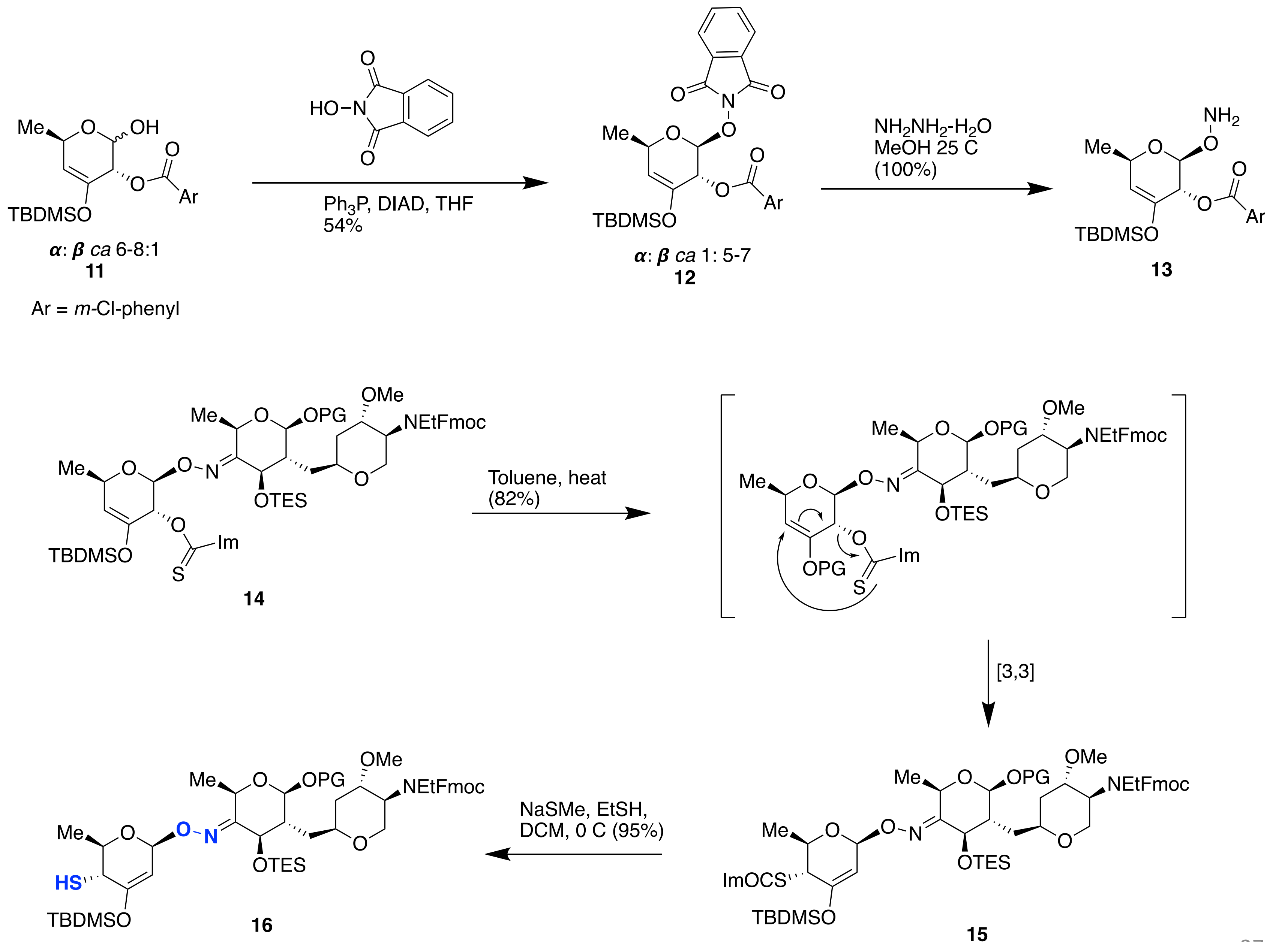
Classics in Total Synthesis. Targets, Strategies, Methods. Von *K. C. Nicolaou und E. J. Sorensen*. VCH, Weinheim, 1996.

Nicolaou (1988-1992)



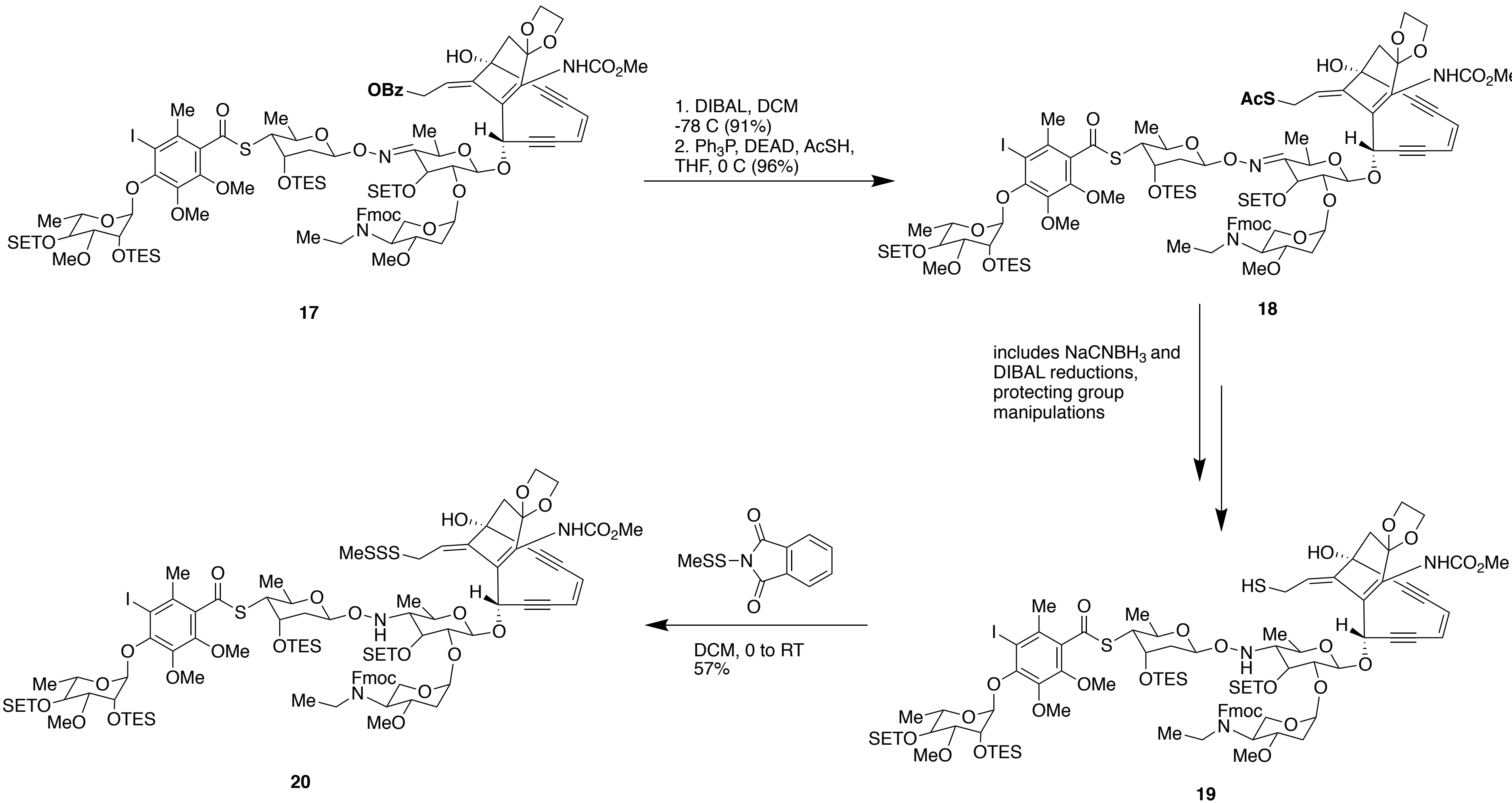
Classics in Total Synthesis. Targets, Strategies, Methods. Von *K. C. Nicolaou und E. J. Sorensen*. VCH, Weinheim, 1996.

Nicolaou (1988-1992)



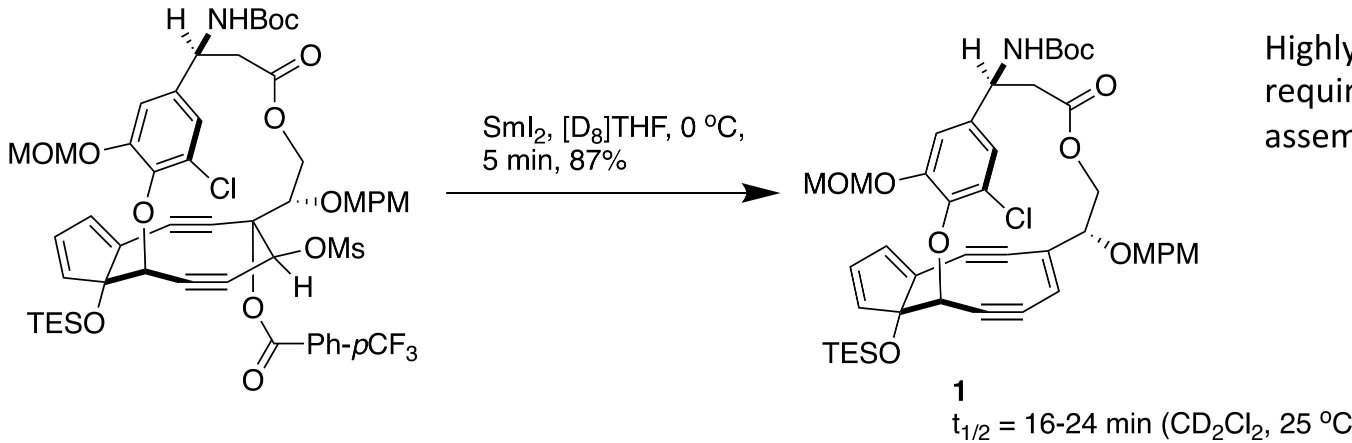
Classics in Total Synthesis. Targets, Strategies, Methods. Von *K. C. Nicolaou und E. J. Sorensen*. VCH, Weinheim, 1996.

Nicolaou (1988-1992)

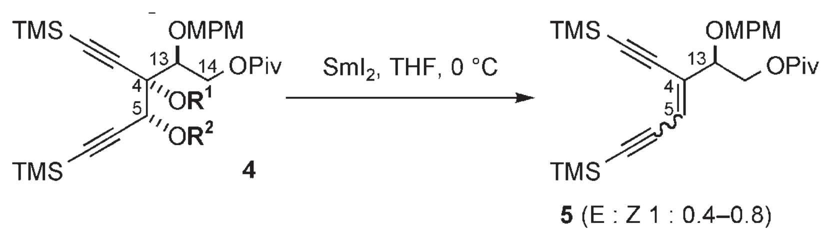


Classics in Total Synthesis. Targets, Strategies, Methods. Von *K. C. Nicolaou und E. J. Sorensen*. VCH, Weinheim, 1996.

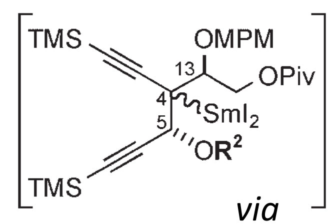
Synthesis of C-1027 core (Inoue, 2008)



Highly labile cores require novel assembly strategies

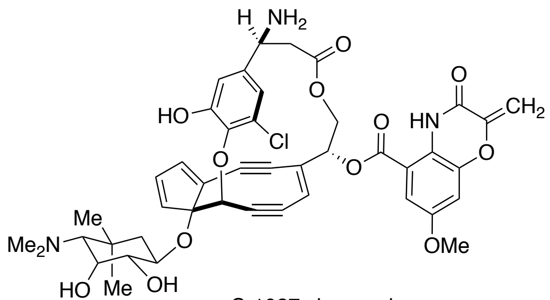


Entry	4	R^1	R^2	t	Yield [%]
1	**a**	Ms	Ms	2 h	94
2	**b**	O	O	0.7 h	80
3	**c**[a]	O OMe	O OMe	7 h	87
4	**d**	O F	O F	0.5 h	98
5	**e**	O CF_3	O CF_3	5 min	95
6	**f**	O CF_3	Ms	1 min	93



Inoue, M. et al., *Angew. Chem. Int. Ed.*, 2008, 47, 1777.

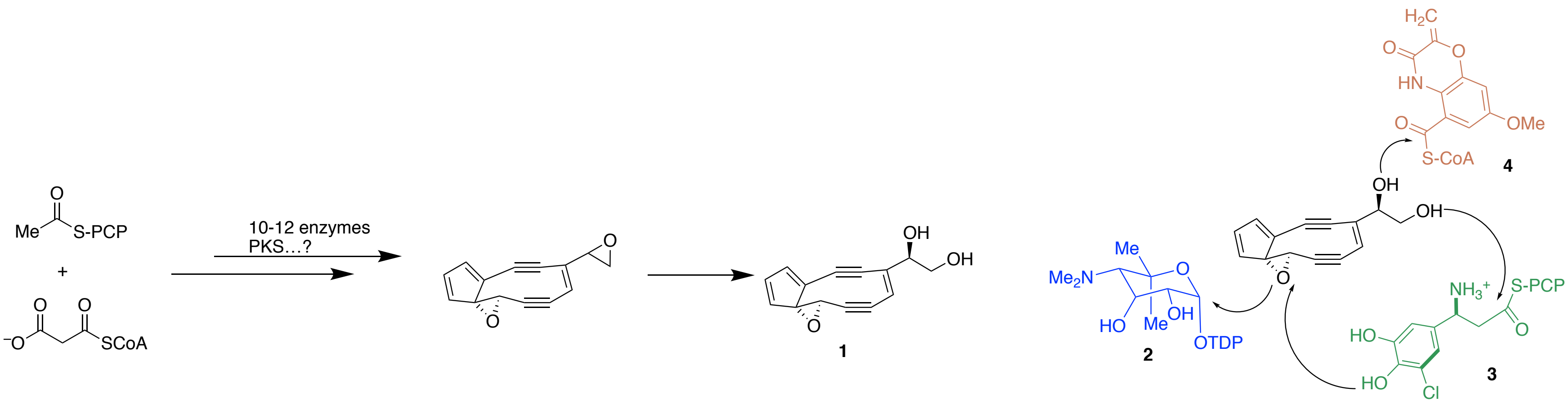
Biosynthesis of C-1027

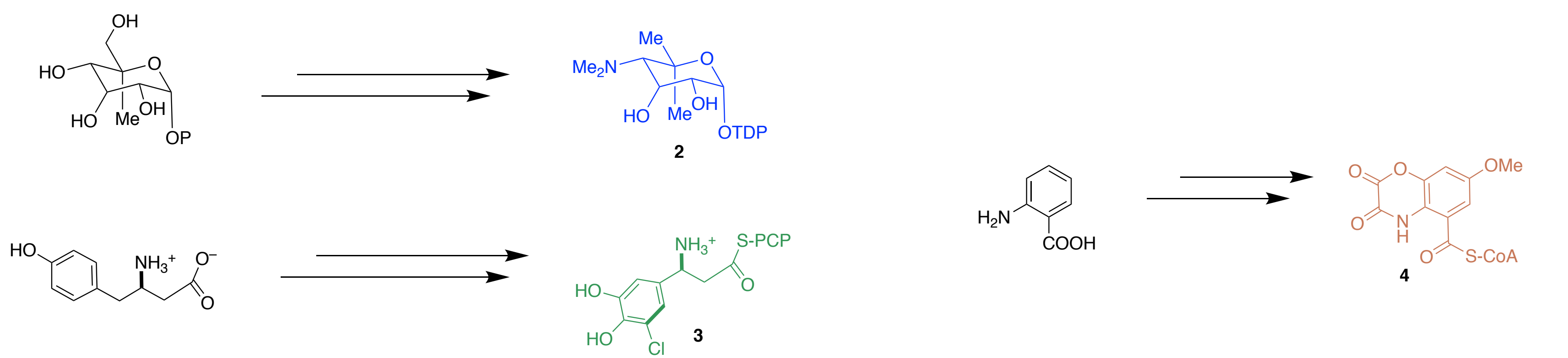


C-1027 chromophore

- Back to back reports in 2002 described the identification and cloning for the biosynthetic gene cluster of C-1027 and Calicheamicin.

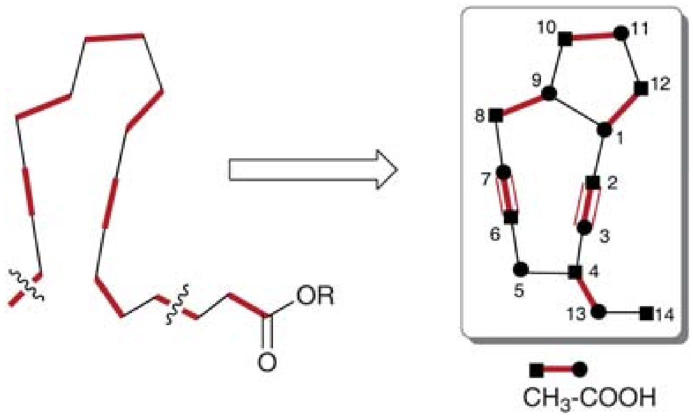
- The enediyne core is assembled by a highly conserved PKS complex in both cases and a modular convergent overall biosynthesis.





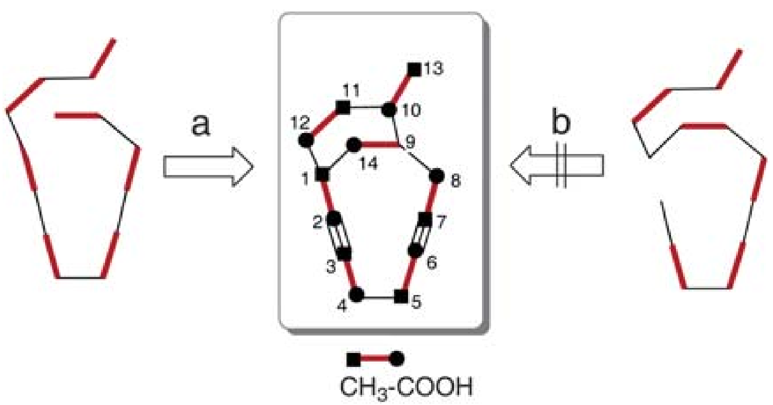
Liu, W., et al., *Science.,* 2002, 297, 1170.
Ahlert, J., et al., *Science.,* 2002, 297, 1173.

Core biosynthesis is not well understood

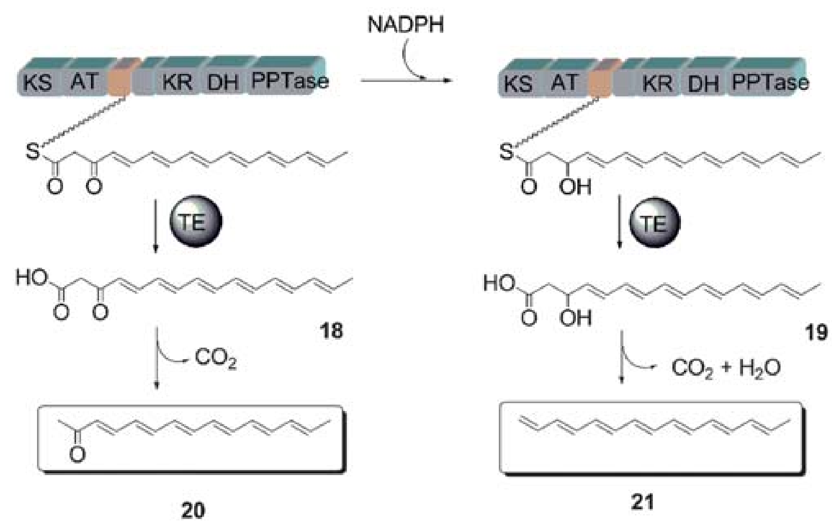


Folding pattern for the 9-membered enediyne of neocarzinostatin.

- Studies with ^{13}C labeled acetate, doubly labeled and mixed labeled.
- Core is likely derived from a linear precursor consisting of seven acetates assembled in a head to tail fashion
- In the 9-membered system, the alkyne carbons are derived from the same acetate unit. This is not the case for the 10-membered systems.
- The exact identity of the precursor and its subsequent transformations to the core remain ambiguous.

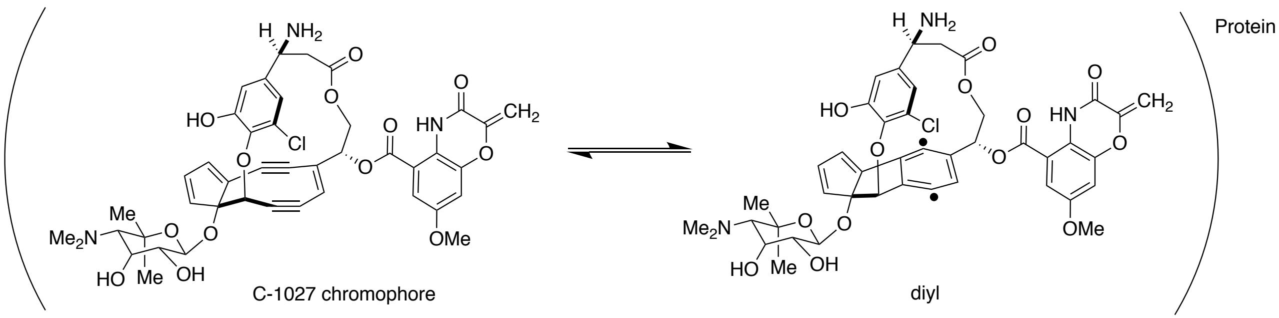


Folding patterns for the 10-membered enediyne of dynemicin A.



Liang, Z., *Nat. Prod. Rep.*, 2010, 27, 499.

C-1027 is protected by the apoprotein



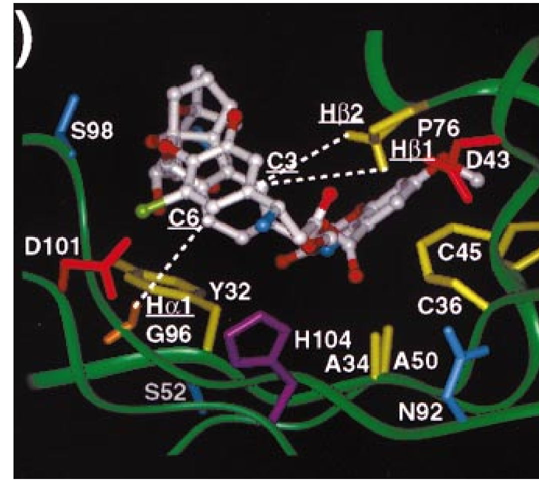


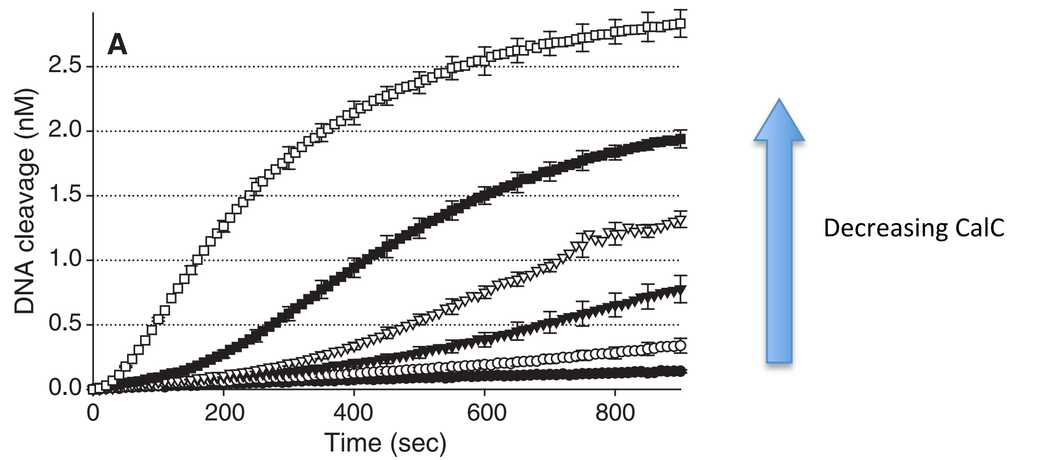
Table 4. Relationships in space between C6 or C3 of chromophore and hydrogens of the C-1027 apoprotein

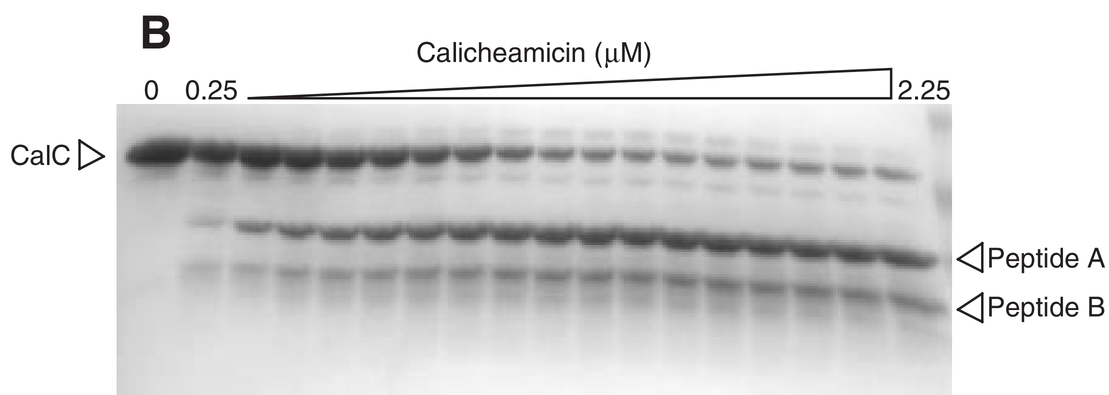
A. *C6*		Gly96 $H^{\alpha1}$	Asn97 H^{α}	
Distance (Å)	C6-H^{α}	4.59(±0.62)	4.21(±0.28)	
	C3-C^{α}	7.36(±0.45)	6.70(±0.27)	
Angle (deg.)	C3-C6-H^{α}	164.1(±6.1)	116.6(±6.6)	
	C6-H^{α}-C^{α}	93.5(±10.5)	109.2(±8.1)	
B. *C3*		Pro76 $H^{\beta1}$	Pro76 $H^{\beta2}$	Pro76 $H^{\gamma2}$
Distance (Å)	C3-H^{β} (or C3-H^{γ})	4.21(±0.43)	4.19(±0.75)	4.24(±0.47)
	C6-C^{β} (or C6-C^{γ})	7.15(±0.61)	7.15(±0.61)	7.11(±0.59)
Angle (deg.)	C6-C3-H^{β} (or C6-C3-H^{γ})	151.1(±9.6)	160.8(±10.6)	128.0(±11.6)
	C3-H^{β}-C^{β} (or C3-H^{γ}-C^{γ})	103.2(±14.2)	104.4(±15.6)	118.9(±15.5)

EPR studies reveal that the chromophore is in equilibrium with the diradical and is presumably stable due to lack of suitable hydrogen donors nearby.

Tanaka, T. et al., *J. Mol. Biol..*, 2001, 309, 267.

Sacrificial Proteins as instruments of self-preservation

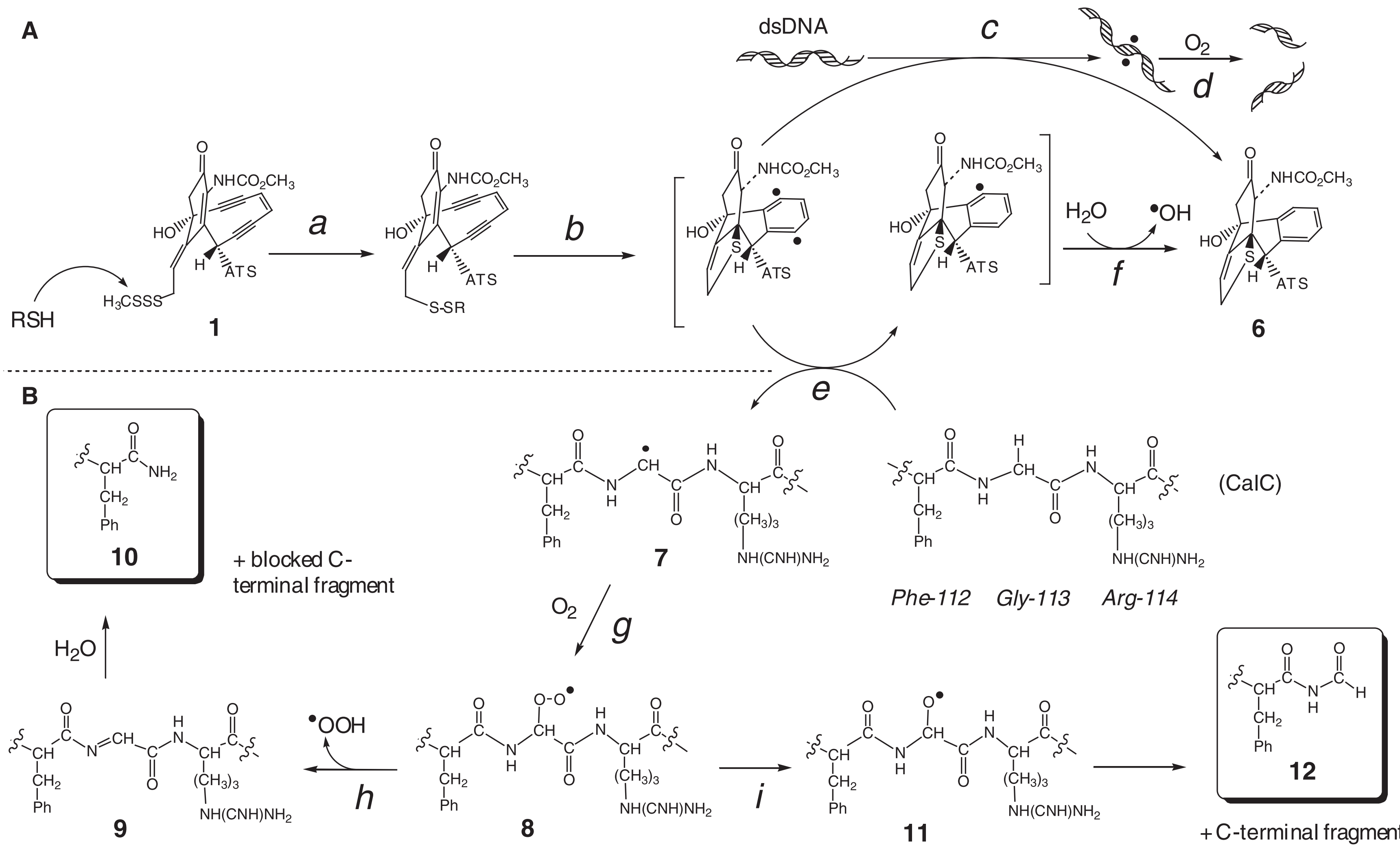




- CalC confers resistance by binding and undergoing cleavage at Gly-113 after trigger activation.

Biggins, J., et al., *Science.*, 2003, 301, 1537.

Sacrificial Proteins as instruments of self-preservation

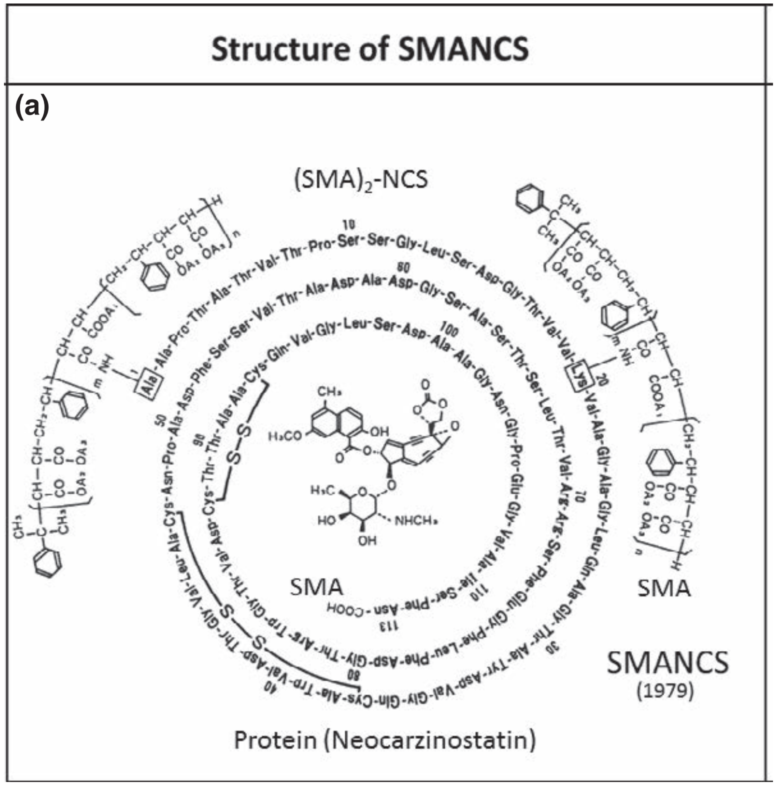


- CalC confers resistance by binding and undergoing cleavage at Gly-113 after trigger activation.

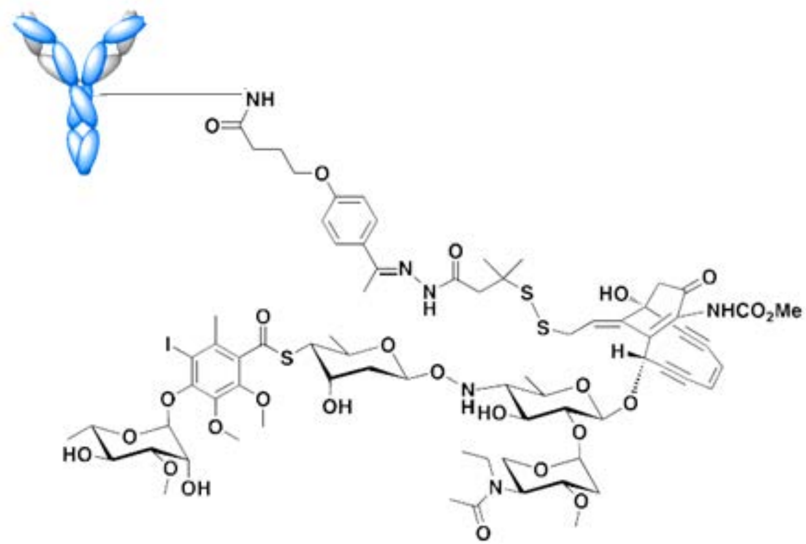
Biggins, J., et al., *Science.,* 2003, 301, 1537.

Therapeutic Prospects

- Without precise targeting, the extreme potency of enediyne antibiotics leads to undesired collateral damage.



Styrene-Maleic acid copolymer-NCS conjugate
Approved in 1993 and currently used in Japan

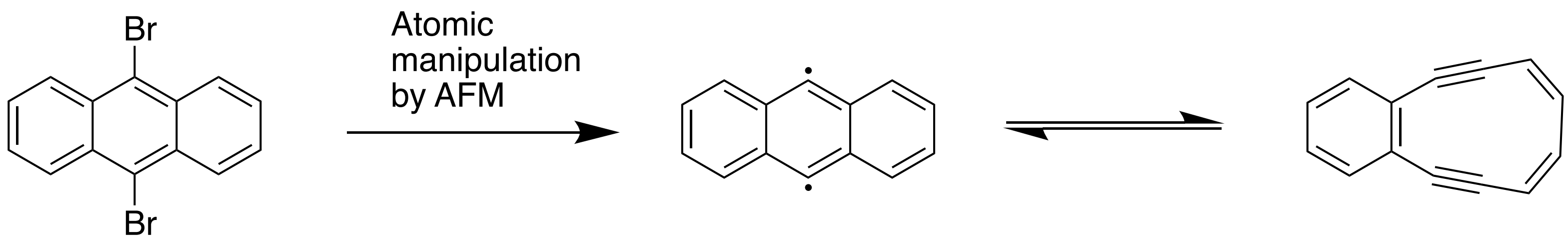


Mylotarg – Antibody conjugated Calicheamicin
FDA approved in 2000. Discontinued since 2010

A handful more antibody conjugates are undergoing clinical trials.

Maeda, H, et al., *Cancer Sci.,* 2013, 104, 779.

Single Molecule Visualization of Bergman Cyclization



9,10 - dibromoanthracene
(DBA)

Direct Observation of intermediates and products

Deposited on 2-
monolayer thick NaCl
island on a Cu-111
surface at 10K

Gross, L. et al., *Nat. Chem.,* 2016, 8, 220.

Single Molecule Visualization of Bergman Cyclization

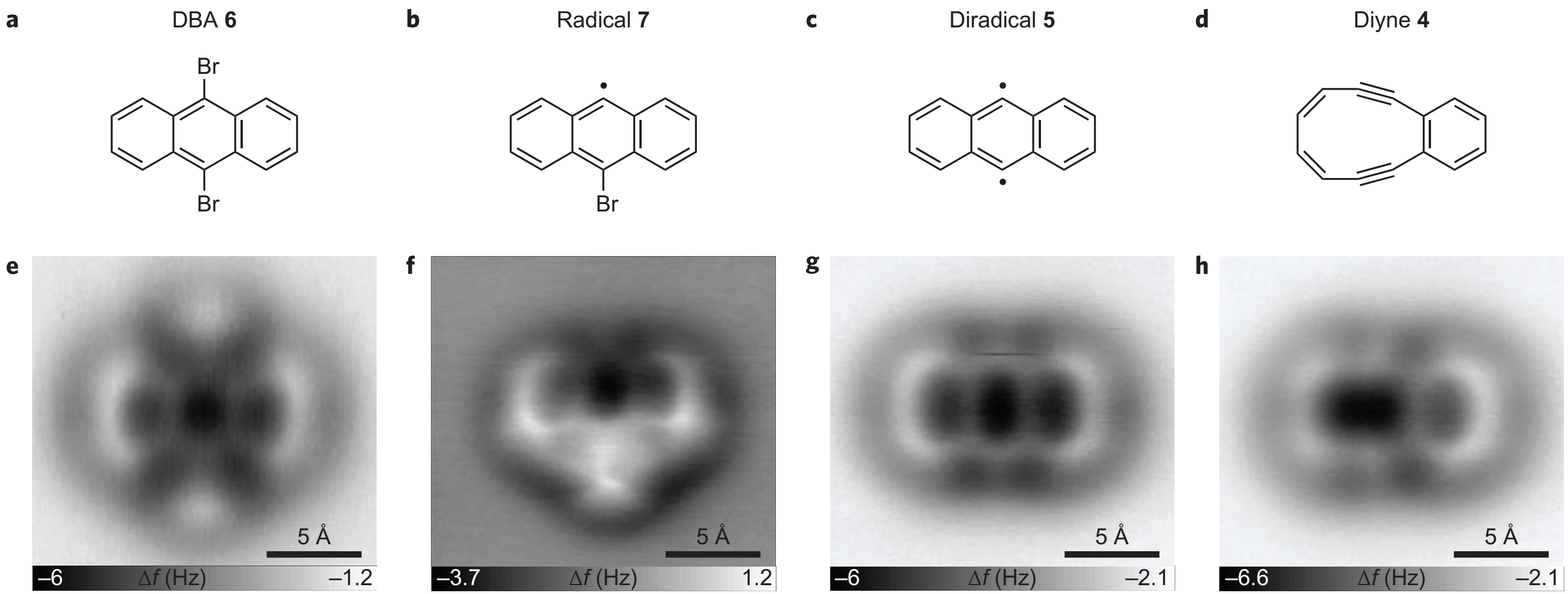


Figure 2 | Structures and AFM imaging of the starting material, reaction intermediates and product. a–d, Chemical structures of the reaction products formed by successive STM-induced debromination of DBA (6) (**a**) and subsequent retro-Bergman cyclization: DBA, 9-dehydro-10-bromoanthracene (radical 7) (**b**), 9,10-didehydroanthracene (diradical 5) (**c**) and 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne (diyne 4) (**d**). **e–h**, Corresponding constant-height AFM images of the molecules in **a–d**, respectively, on NaCl(2ML)/Cu(111) using a CO tip. Δ*f* corresponds to the frequency shift of the oscillating cantilever.

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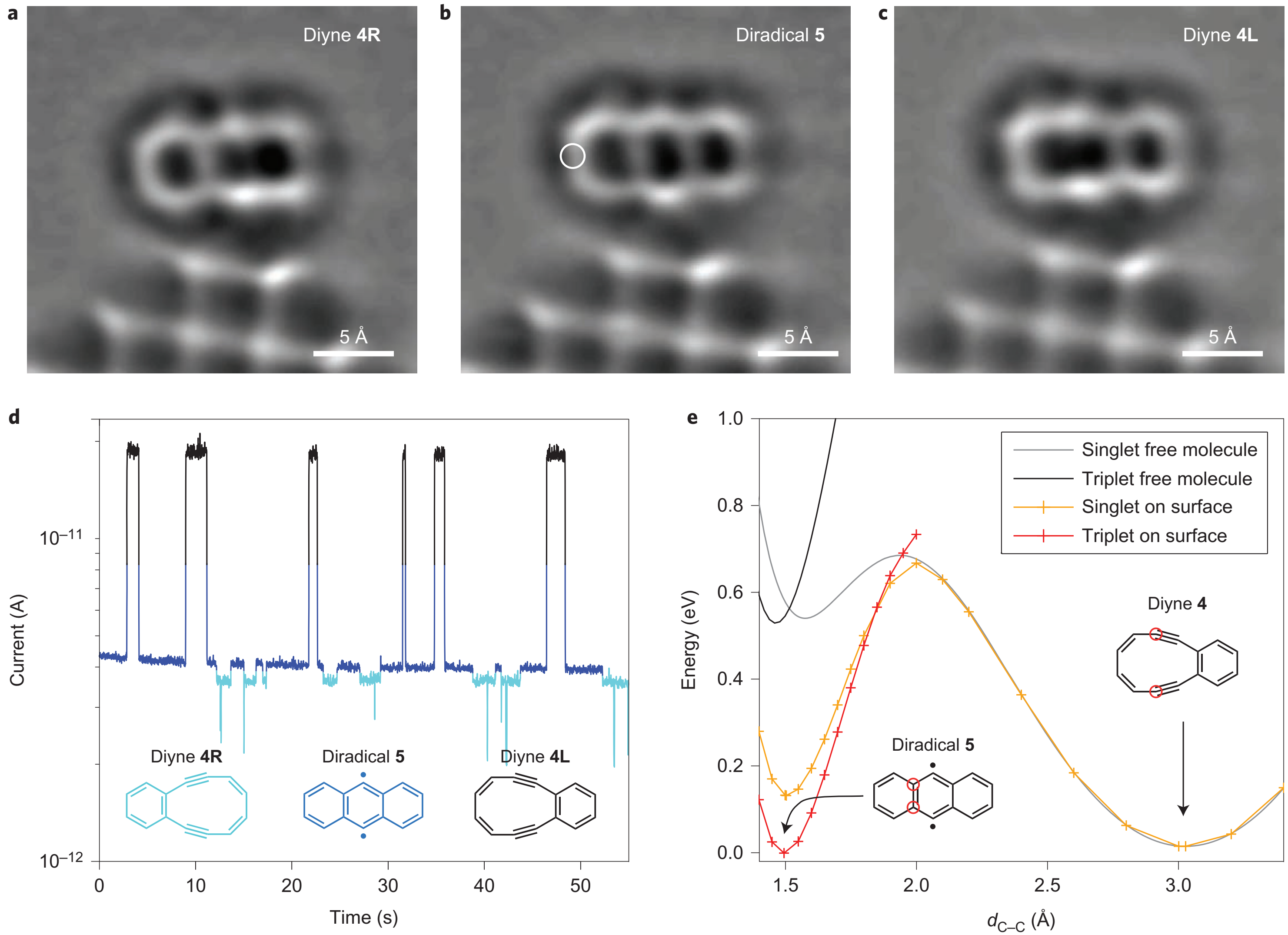

Figure 4 | Reversible Bergman cyclization. a–c, Laplace-filtered AFM images of diyne **4R** (**a**), diradical **5** (**b**) and diyne **4L** (**c**) on NaCl(2ML)/Cu(111). The molecule is adsorbed at a step edge of an NaCl(3ML)/Cu(111) island, seen in the lower part of the images. **d**, Current trace during a voltage pulse of $V = 1.64$ V at the position indicated by the white circle in **b**. The different current levels correspond to the molecular structures of the same colour shown in the inset. **e**, Calculated energies of the Bergman cyclization using the distance between the carbons indicated by red circles ($d_{C\text{-}C}$) as the reaction coordinate.

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