Bergman Reactivities of Imidazole-fused Enediynes

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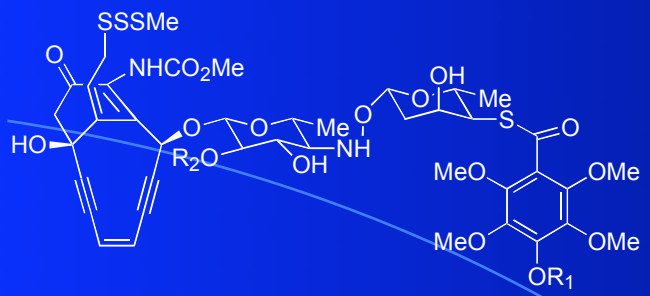
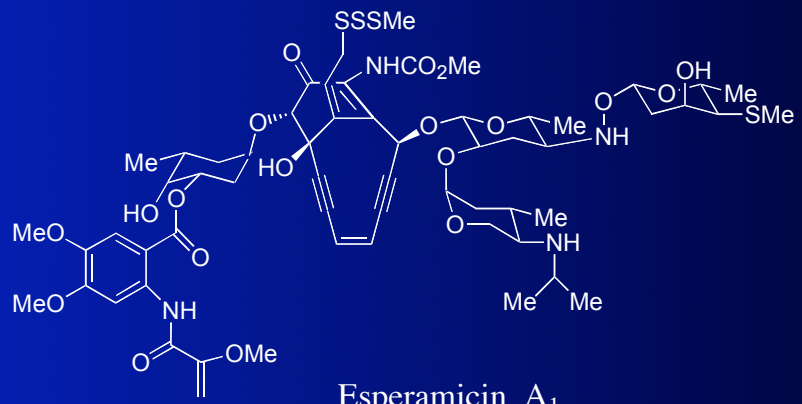
Background

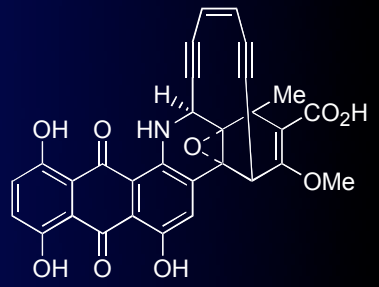
- Enediynes are an important class of naturally occurring compounds with potent antitumor activities (Figure 1).
- Enediynes exert their antitumor effects by generating benzenoid diradicals which react with DNA, RNA, or proteins (Figures 2–3).
- Unfortunately, naturally occurring enediynes do not target tumor cells selectively, and their general cytotoxicities prohibit their use as clinically useful antitumor agents.



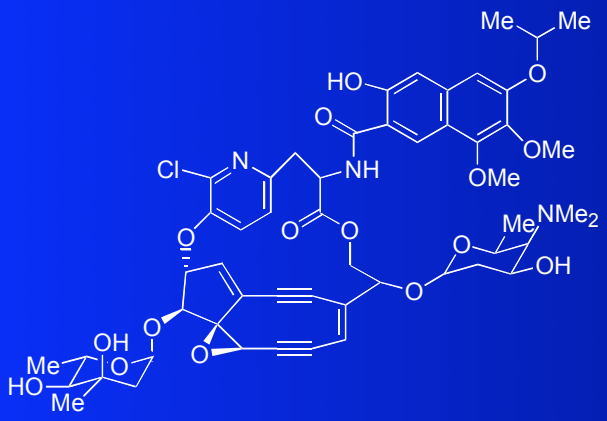
Calicheamicins



Esperamicin A_1

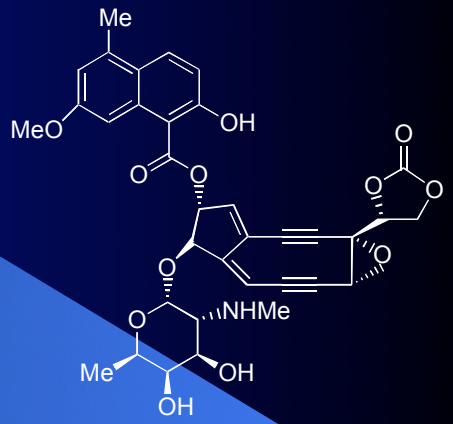


Dynemicin A



Kedarcidin Chromophore

C-1027 Chromophore



Neocarzinostatin Chromophore

Figure 1

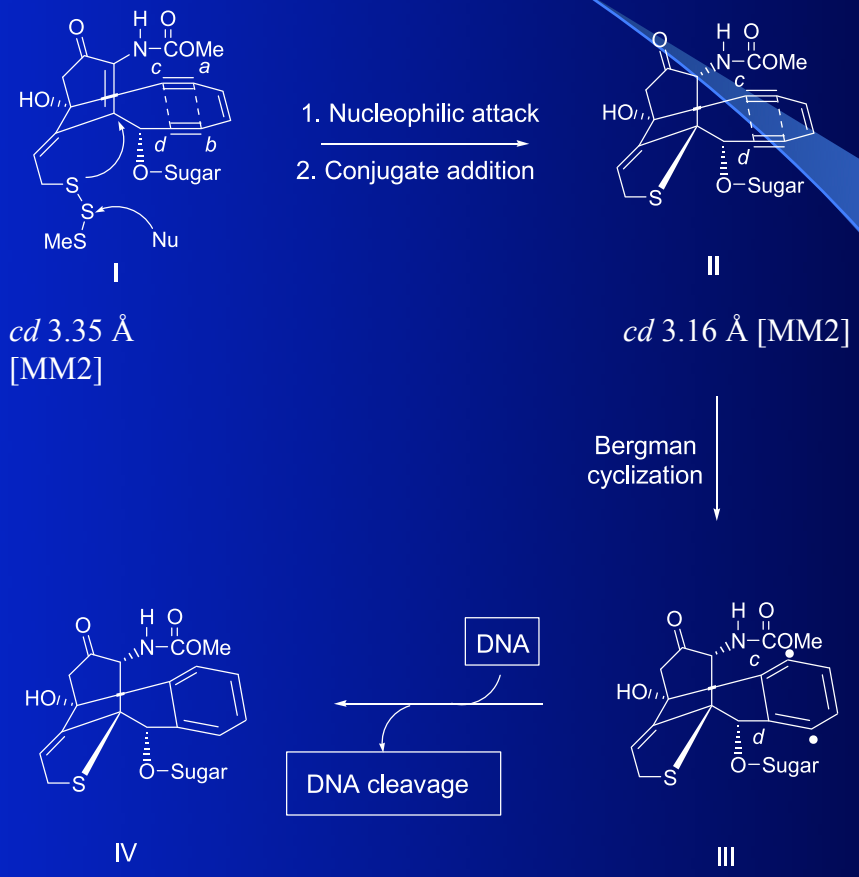
Bergman Cycloaromatization Reaction

cd 4.12 Å [MM2]

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

Figure 2

Mechanism of DNA-Cleaving Action of Calicheamicin



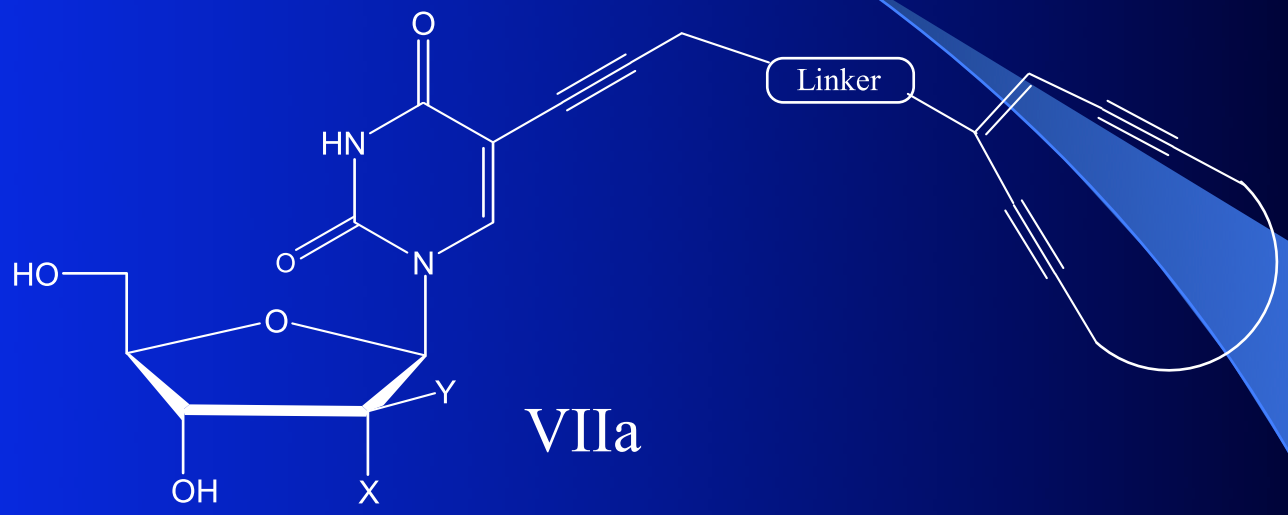
Nicolaou, K. C.; Zuccarello, G.; Riemer, C.; Estevez, V. A.; Dai, W. M. *J. Am. Chem. Soc.;* **1992**; *114*(19); 7360-7371.

Figure 3

Hypotheses

- We reasoned that nucleoside linked enediynes (e.g., VIIa) might selectively target rapidly dividing tumor cells due to their enhanced need for building blocks for DNA or RNA (Figure 4a).
- Imidazolium-fused enediynes such as VIIb might provide a useful prodrug approach, as N3-substituted enediynes react sluggishly in Bergman cycloaromatization (Figure 4b).
- Beta-elimination of the imidazole-fused enediyne from the glutarate moiety of VIIb could serve as a trigger for in situ generation of a more reactive enediyne species.

Targeted Enediynes

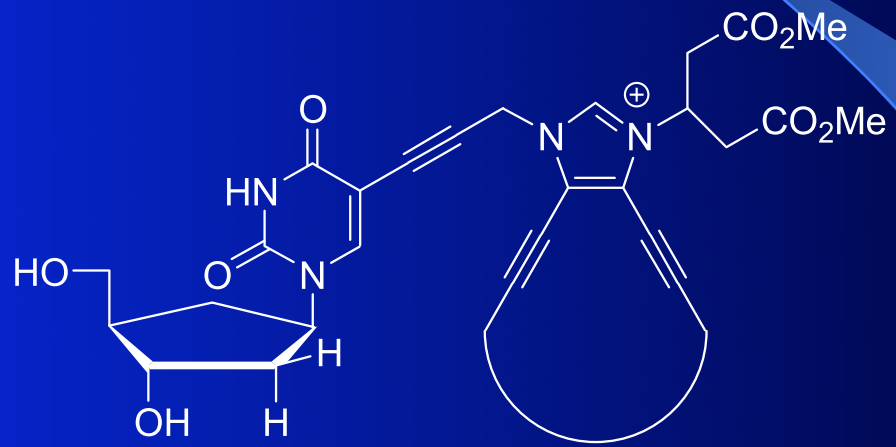


VIIa

Targeted enediynes: enediynes that are covalently linked to biologically relevant delivery molecules such as substrates for receptor proteins, enzymes, etc.

Figure 4a

Beta-elimination of imidazole-fused enediyne could serve as an effective trigger



VIIb

Figure 4b

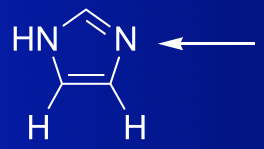
Results

- In order to lay a groundwork for accomplishing our long range goals (see hypotheses), we investigated the Bergman cycloaromatization of imidazole-fused enediynes.
- Imidazole is a versatile scaffold whose eletronic properties can be modulated via modification at N1, N3, and C2 (Figure 4c).
- Imidazole-fused enediynes were synthesized as shown in Figure 4d.

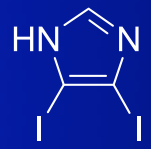
Versatility of the Imidazole Ring System

C2: Substitution at this site could alter the electronics of the imidazole ring and thus allow fine-tunning of the Bergman cycloaromatization reactivity.

N1: May be used to link the endiyne to a suitably functionalized nucleoside



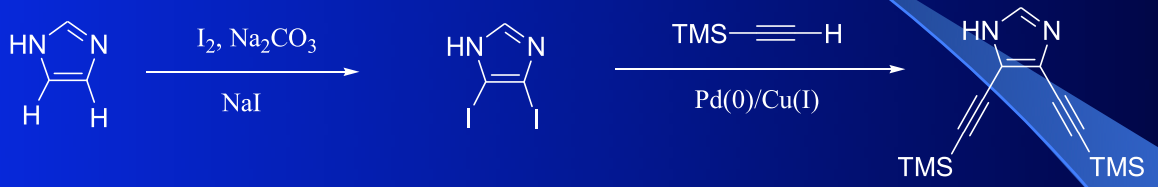
N3: Alkylation at this site should reduce Bergman cycloaromatization reactivity. Beta-elimination of the heterocycle could serve as a triggering mechanism for release of a more reactive enediyne.



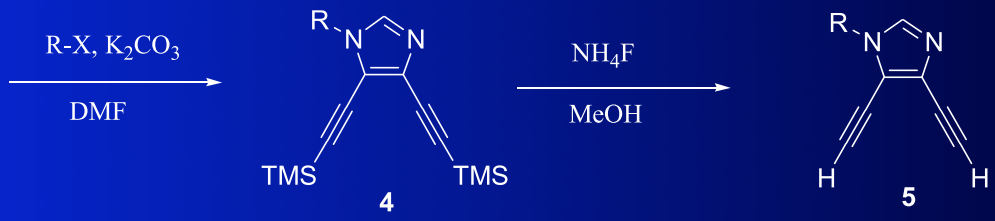
4,5-Diiodoimidazole is an inexpensive precursor to novel enediynes.

Figure 4c

N^1-Alkyl Derivatives



1 **2** (79%) **3** (85%)



4 **5**

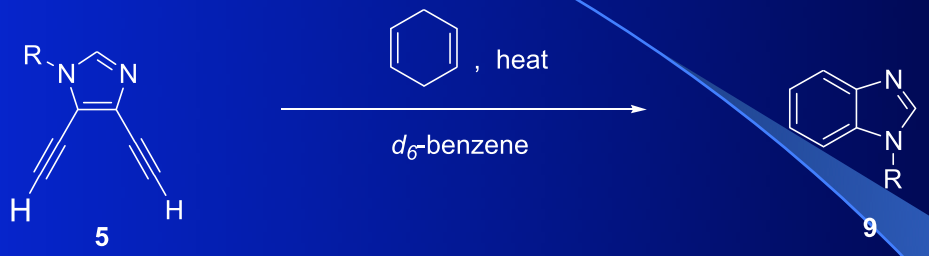
4a R = Butyl (92%)
4b R = Benzyl (46%)
4c R = *p*-MeObenzyl (90%)
4d R = *p*-Nitrobenzyl (60%)

5a R = Butyl (95%)
5b R = Benzyl (88%)
5c R = *p*-MeObenzyl (95%)
5d R = *p*-Nitrobenzyl (78%)

Figure 4d

- Bergman cycloaromatization rates of N^1-alkyl (**5a–d**) and N^1-aryl (**7a–c**) substituted imidazole-fused enediynes were compared (Figures 5a–d).
- Rates for the N^1-aryl substituted derivatives were from four to sevenfold greater than the N^1-alkyl substituted series. (Figures 5c and 6c).

Half-lives of N^1-Alkyl Derivatives



5

5a R = Butyl
5b R = Benzyl
5c R = *p*-MeObenzyl
5d R = *p*-Nitrobenzyl

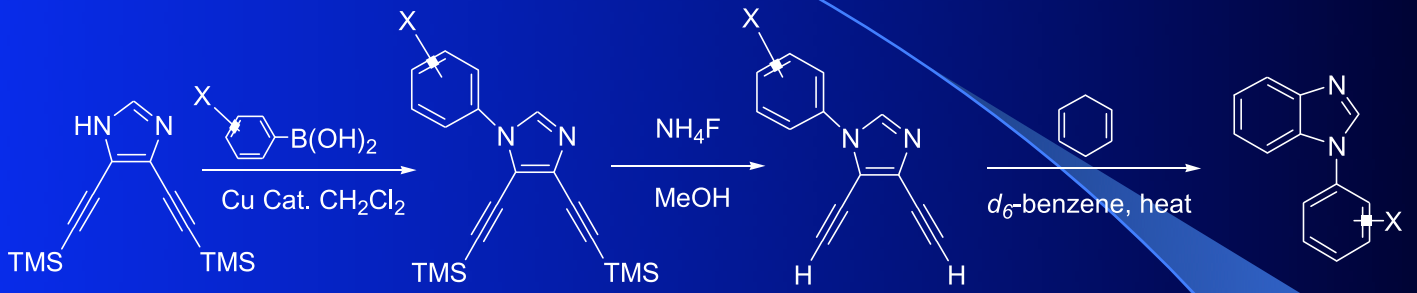
9

9a R = Butyl
9b R = Benzyl
9c R = *p*-MeObenzyl
9d R = *p*-Nitrobenzyl

Compounds	R =	125 °C (hrs)	R	145 °C (hrs)	R	165 °C (hrs)	R
5a	Butyl	38.2	0.9937	8.8	0.9877	1.8	0.9958
5b	Benzyl	47.2	0.9907	9.8	0.9942	2.0	0.9892
5c	*p*-MeObenzyl	54.8	0.9947	14.7	0.9907	2.6	0.9941
5d	*p*-Nitrobenzyl	54.2	0.9949	11.9	0.9917	2.2	0.9836

Figure 5a

N^1-Phenyl Derivatives **I** and Their Cycloaromatization Rate



3 **6** **7** **8**

6a x = H (67%)
6b x = 4-OMe (62%)
6c x = 3-NO_2 (65%)

7a x = H (80%)
7b x = 4-OMe (62%)
7c x = 3-NO_2 (65%)

8a x = H
8b x = 4-OMe
8c x = 3-NO_2

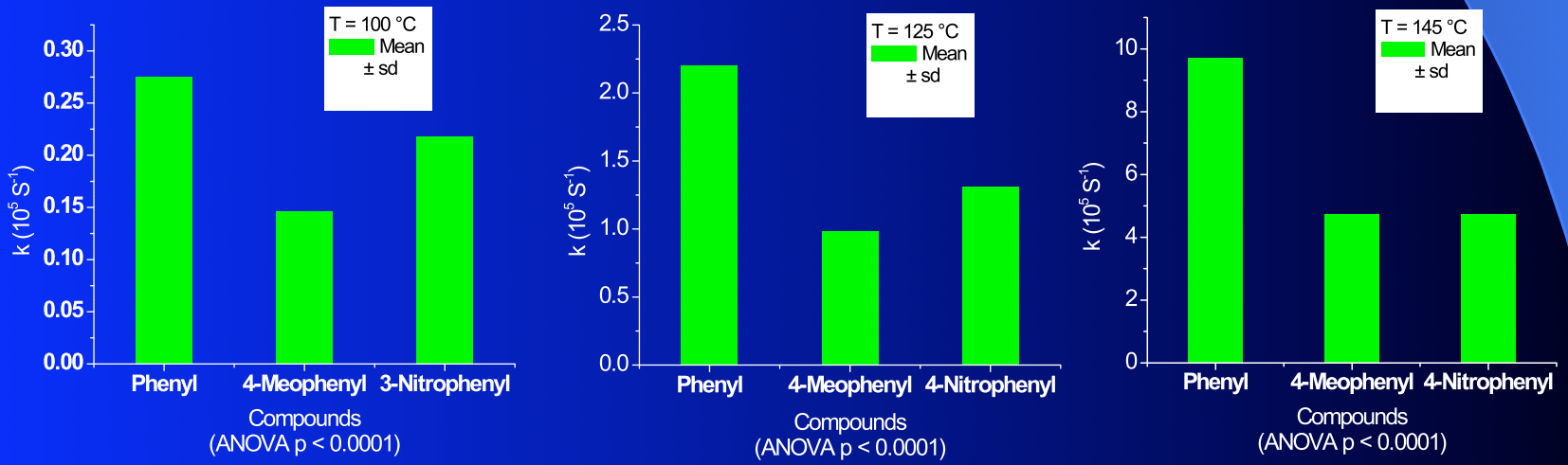
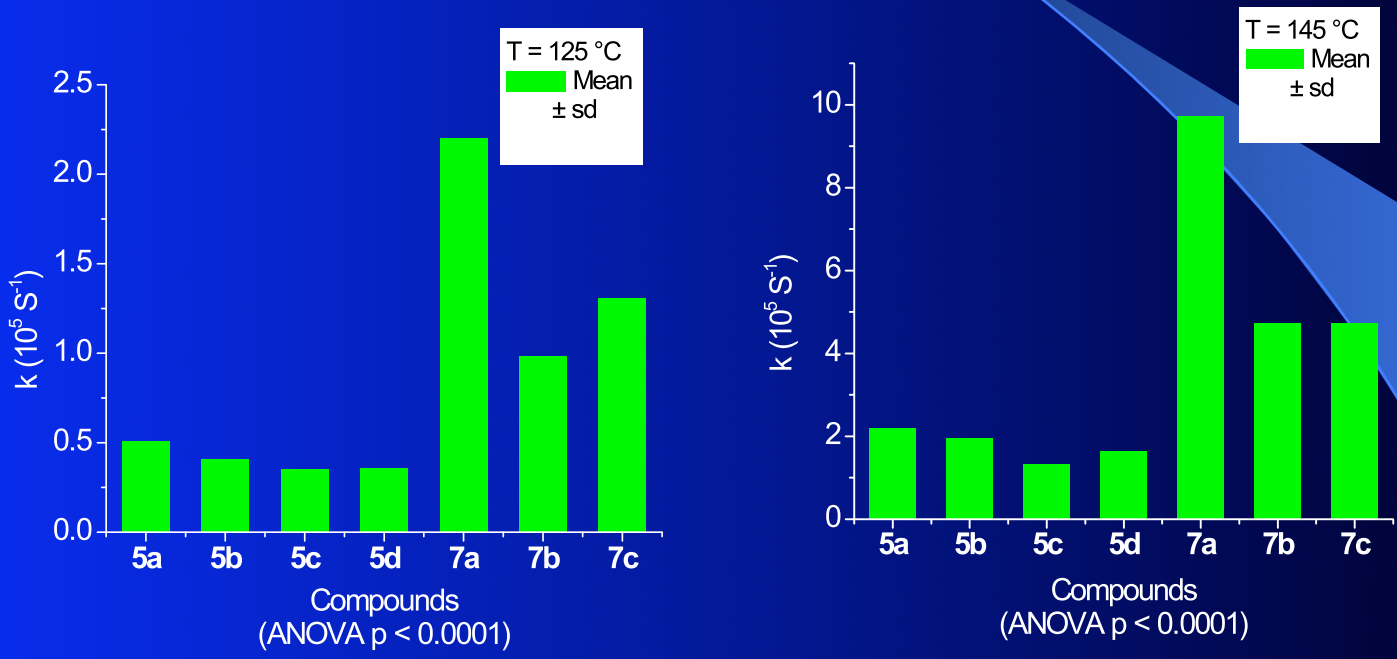


Figure 5b

Comparison of N^1-Alkyl Derivatives and N^1-Phenyl Derivatives **I**



5a R = Butyl; **5b** R = Benzyl; **5c** R = *p*-MeObenzyl; **5d** R = *p*-Nitrobenzyl;
7a R = Phenyl; **7b** R = 4-MeOphenyl; **7c** R = 3-Nitrophenyl

Figure 5c

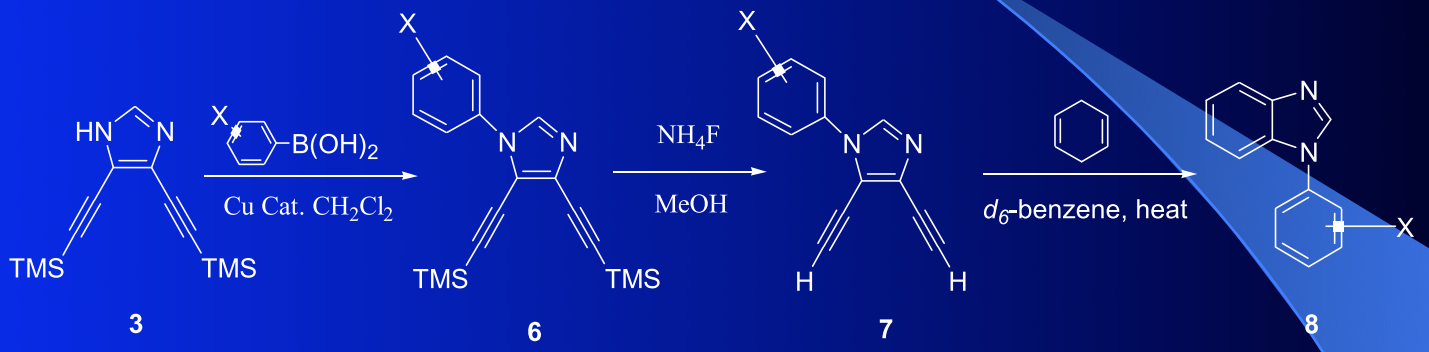
Comparison of N^1-Alkyl Derivatives and N^1-Phenyl Derivatives I

Compounds	R =	125 °C (hrs)	R	145 °C (hrs)	R	165 °C (hrs)	R
5a	Butyl	38.2	0.9937	8.8	0.9877	1.8	0.9958
5b	Benzyl	47.2	0.9907	9.8	0.9942	2.0	0.9892
5c	*p*-MeObenzyl	54.8	0.9947	14.7	0.9907	2.6	0.9941
5d	*p*-Nitrobenzyl	54.2	0.9949	11.9	0.9917	2.2	0.9836

Compounds	R =	100 °C (hrs)	R	125 °C (hrs)	R	145 °C (hrs)	R
7a	Phenyl	70.5	0.9931	8.7	0.9943	2.2	0.9873
7b	4-Meophenyl	131.7	0.9937	19.7	0.9989	4.1	0.9928
7c	3-Nitrophenyl	88.8	0.9939	14.8	0.9934	4.0	0.9928

Figure 5d

Synthesis of N^1-Phenyl Derivatives **II**



3 6 7 8

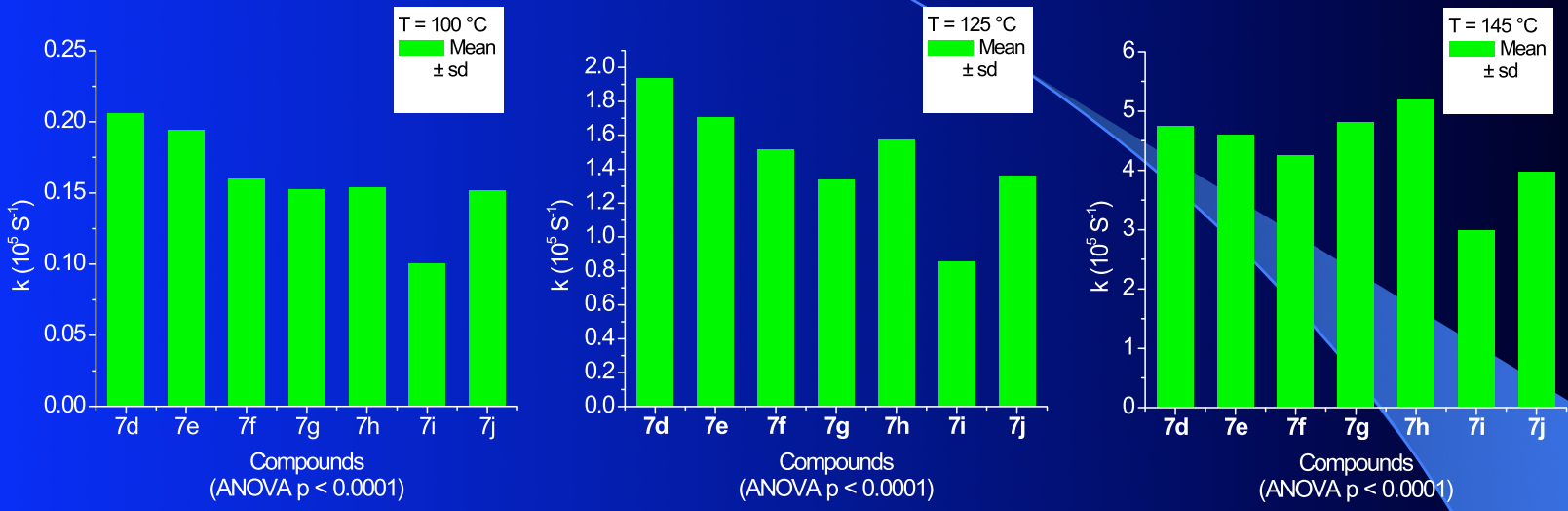
6d x = 4-I (79%)
6e x = 4-Br (57%)
6f x = 4-Cl (55%)
6g x = 4-F (55%)
6h x = 4-MeO_2C (80%)
6i x = t-butyl (78%)
6j x = ethyl (64%)

7d x = 4-I (85%)
7e x = 4-Br (88%)
7f x = 4-Cl (84%)
7g x = 4-F (86%)
7h x = 4-MeO_2C (67%)
7i x = t-butyl (84%)
7j x = ethyl (63%)

8d x = 4-I
8e x = 4-Br
8f x = 4-Cl
8g x = 4-F
8h x = 4-MeO_2C
8i x = t-butyl
8j x = ethyl

Figure 6a

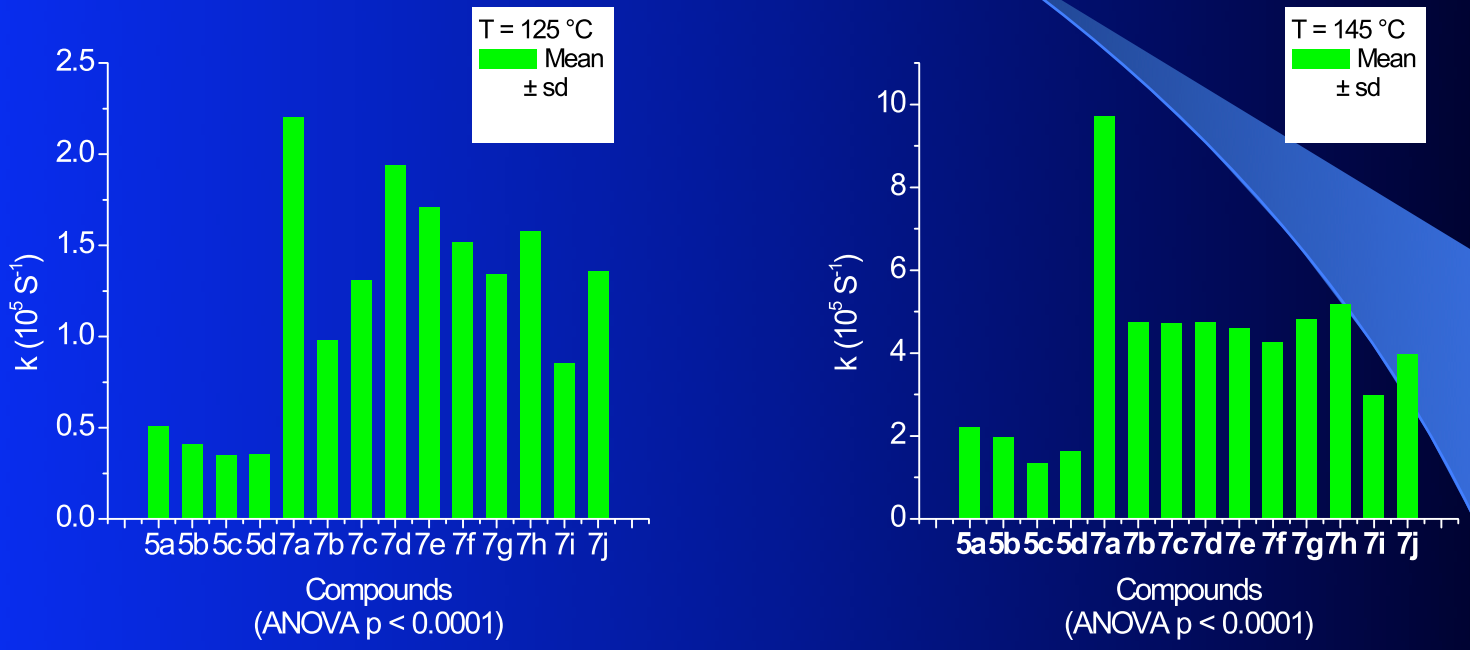
Cycloaromatization Rate and Half-lives of N^1-Phenyl Derivatives **II**



Compounds	R =	100 °C (hrs)	R	125 °C (hrs)	R	145 °C (hrs)	R
7d	4-Iodophenyl	95.1	0.9900	9.9	0.9963	4.1	0.9915
7e	4-Bromophenyl	99.4	0.9901	11.4	0.9962	4.2	0.9967
7f	4-Chlorophenyl	120.6	0.9954	12.7	0.9930	4.5	0.9929
7g	4-Fluorophenyl	127.7	0.9972	14.4	0.9896	4.0	0.9958
7h	4-Methoxycarbonylphenyl	125.9	0.9926	12.2	0.9976	3.8	0.9987
7i	4-*t*-Buphenyl	191.3	0.9920	22.8	0.9983	6.5	0.9991
7j	4-Ethylphenyl	128.6	0.9895	14.3	0.9839	4.9	0.9932

Figure 6b

Comparison of N^1-Alkyl Derivatives and N^1-Phenyl Derivatives



5a R = Butyl; **5b** R = Benzyl; **5c** R = *p*-MeObenzyl; **5d** R = *p*-Nitrobenzyl;

7a R = Phenyl; **7b** R = 4-MeOphenyl; **7c** R = *3*-Nitrophenyl; **7d** R = 4-Iodophenyl;
7e R = 4-Bromophenyl; **7f** R = 4-Chlorophenyl; **7g** R = 4-Fluorophenyl;
7h R = 4-Methoxycarbonylphenyl; **7i** R = 4-*t*ert-Butylphenyl; **7d** R = 4-Ethylphenyl;

Figure 6c

- Attempts to prepare more reactive cyclic imidazole-fused enediyne **4** were not successful (Figure 7).
- 11- and 12-membered cyclic enediynes **12** and **13** were prepared in low yield. An unusually long c,d-distance (4.62 Å) and bond angles of 129 ° may make ring closure energetically unfavorable (Figure 8).
- 11-Membered cyclic enediyne **13** reacted 10–15 fold slower than the acyclic analogue **11** (Figure 9).
- This difference in reactivity may be attributed to enhanced olefin strain for **13** relative to **11** (Figure 10).

The Synthesis of Cyclic Enediyne

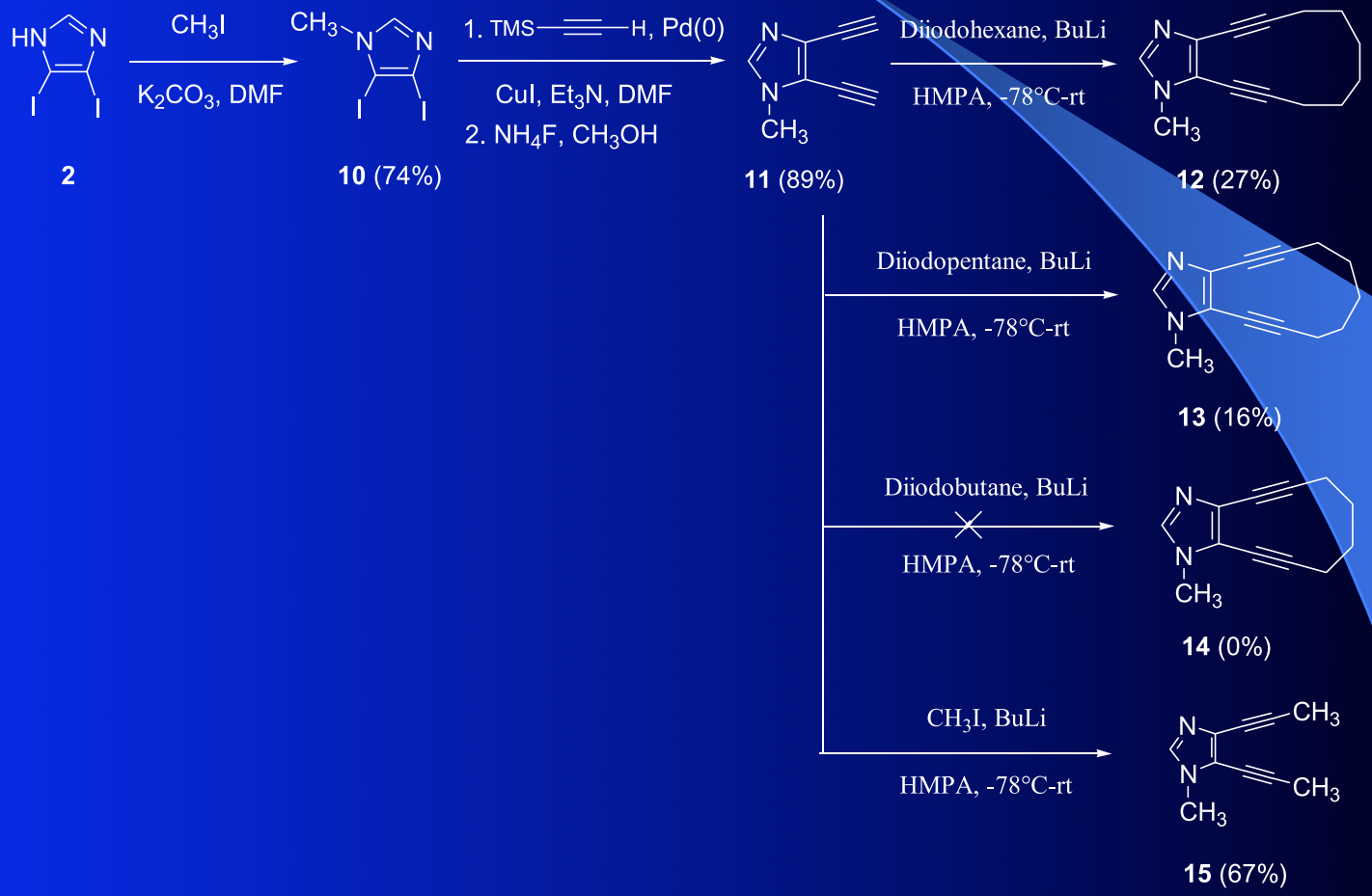
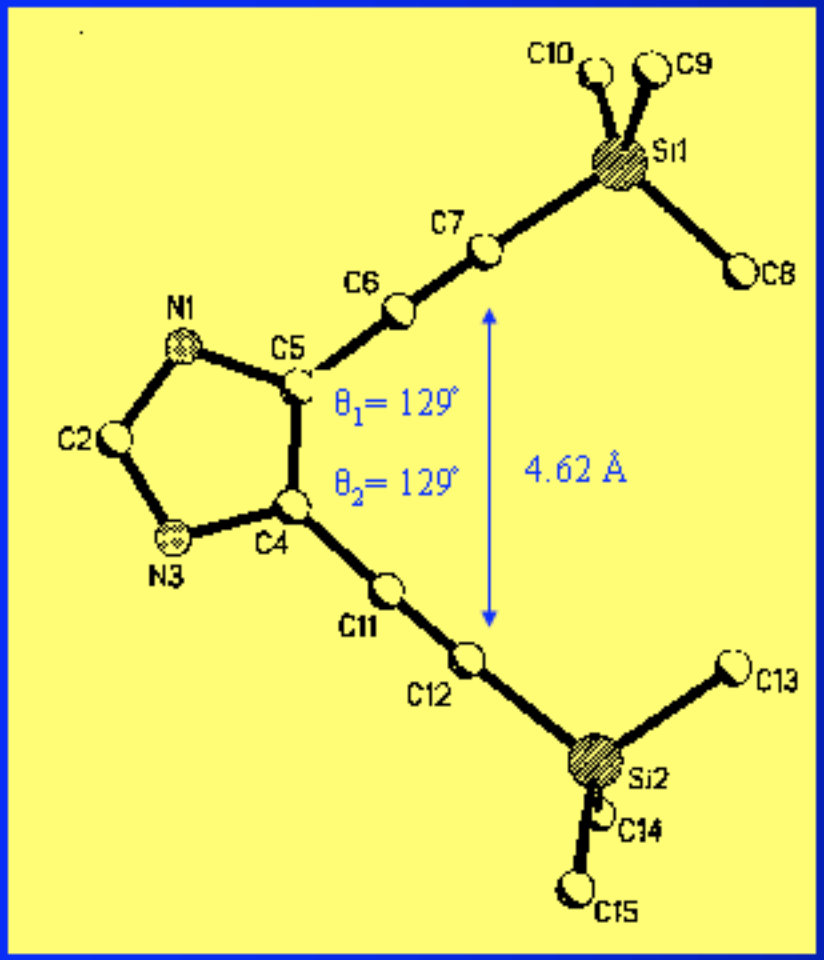
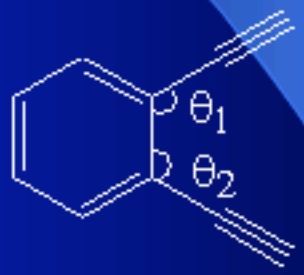


Figure 7

Bond Angles/cd Distance for compound **3** and 1,2-Diethynylbenzene



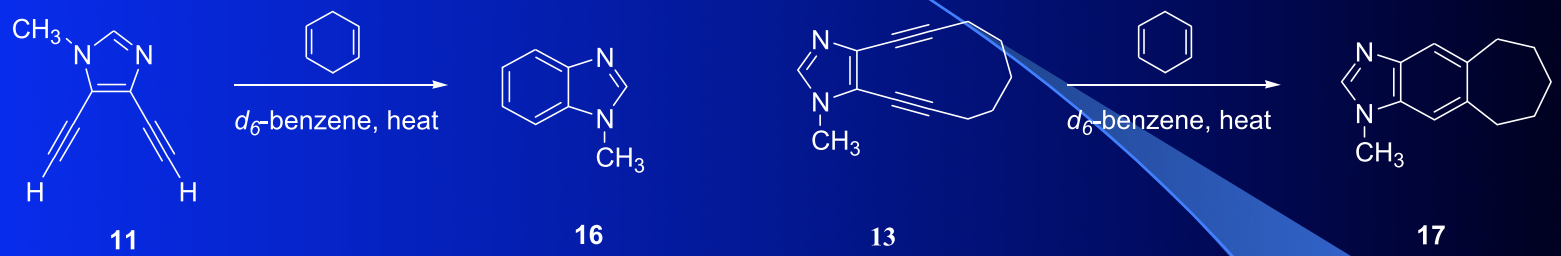


$\theta_1 = \theta_2 = 121.3^{\circ}$

cd distance = 4.13 Å

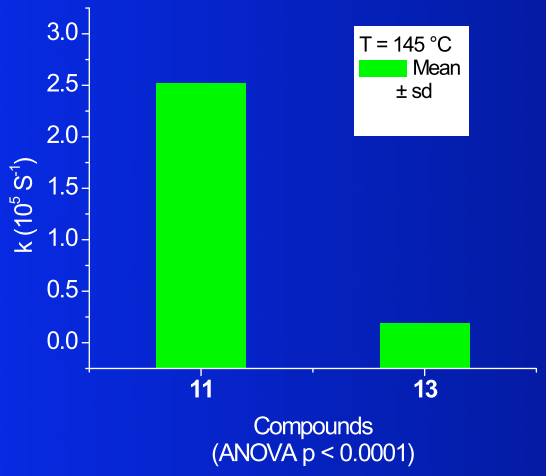
Figure 8

Thermally Promoted Cycloaromatization of **13**



11 **16** **13** **17**

Compounds	125 °C (hrs)	R	145 °C (hrs)	R	155 °C (hrs)	R	165 °C (hrs)	R
11	45.9	0.9958	7.7	0.9926	–	–	3.7	0.9962
13	–	–	100.9	0.9947	57.7	0.9974	35.3	0.9975



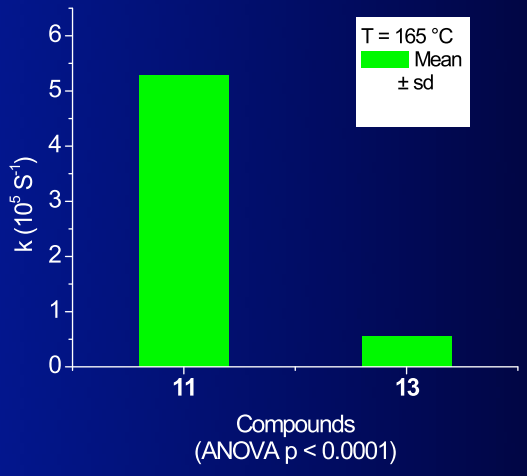
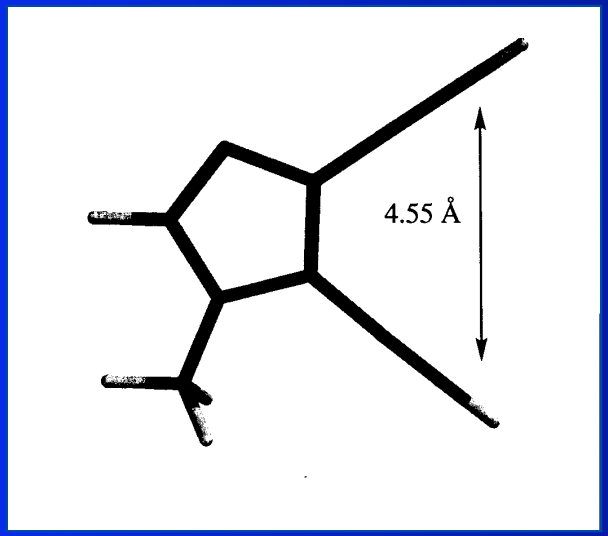
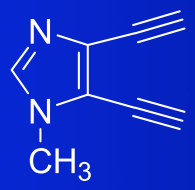


Figure 9

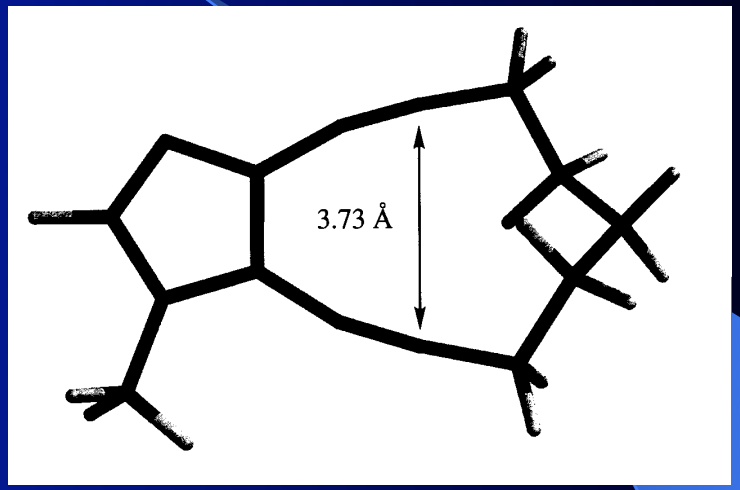
Molecular Models of Enediynes **11** and **13**



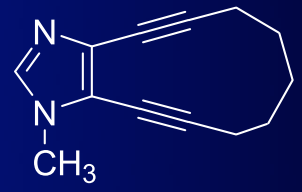
cd 4.55 Å [AM1]



11



cd 3.73 Å [AM1]

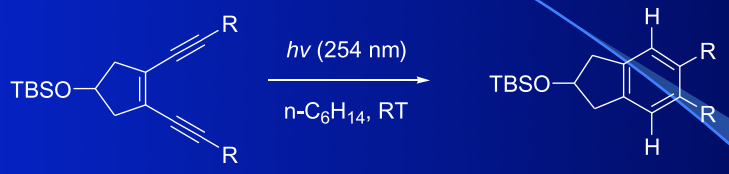


13

Figure 10

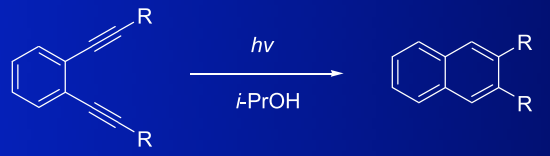
•Imidazole-fused enediynes underwent photopromoted Bergman cycloaromatization and were shown to cleave supercoiled plasmid DNA (Figures 12–14).

Photochemical Cycloaromatization of Enediynes



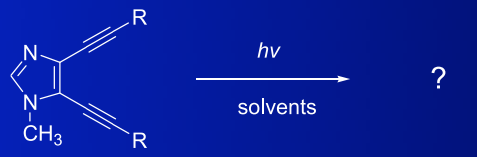
R = Me
R = Ph

R = Me (80%)
R = Ph (0)



R = Ph
R = n-Pr

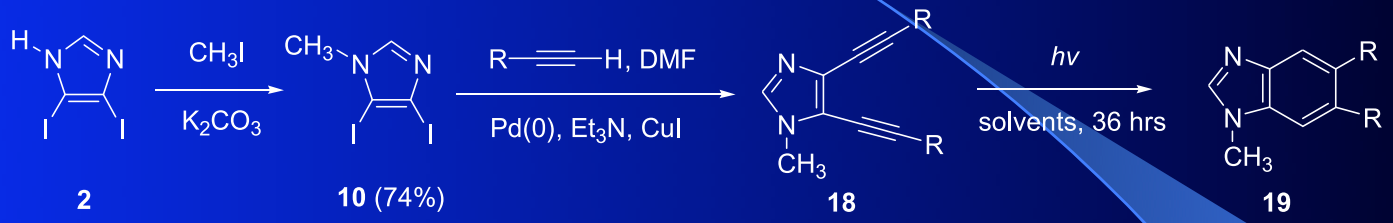
R = Ph (75%)
R = n-Pr (24%, no triplet sensitizer)
(2%, with xanthone sensitizer)
(3%, with acetophenone sensitizer)



Kaneko T.; Takahashi, M.; Hirama M. *Angew. Chem. Int. Ed.* **1999,** *38*, 1267-1268
Evenzahav A.; Turro N. J. *J. Am. Chem. Soc.* **1998,** *120,* 1835-1841.

Figure 11

Photochemical Cycloaromatization of Imidazole-fused Enediynes



2 **10** (74%) **18** **19**

18a R = CH_3 (83%)
18b R = C_4H_9 (85%)
18c R = Ph (86%)

19a R = CH_3
19b R = C_4H_9
19c R = Ph

Solvents	**19a**	**19b**	**19c**
THF	6%	31%	64%
*i*PrOH	Trace	24%	58%
Hexane	7%	22%	47%
Cyclohenane	6%	16%	51%
CH_3CN	6.5%	Trace	46%
n-hexane/1,4-cyclohexadiene	6%	15%	44%
CH_2Cl_2	Trace	Trace	40%
tert-Butanol	Trace	Trace	26%

[a] Yield is the conversion yield.

Figure 12

Photochemical Cycloaromatization of Bicyclic Enediyne **13**

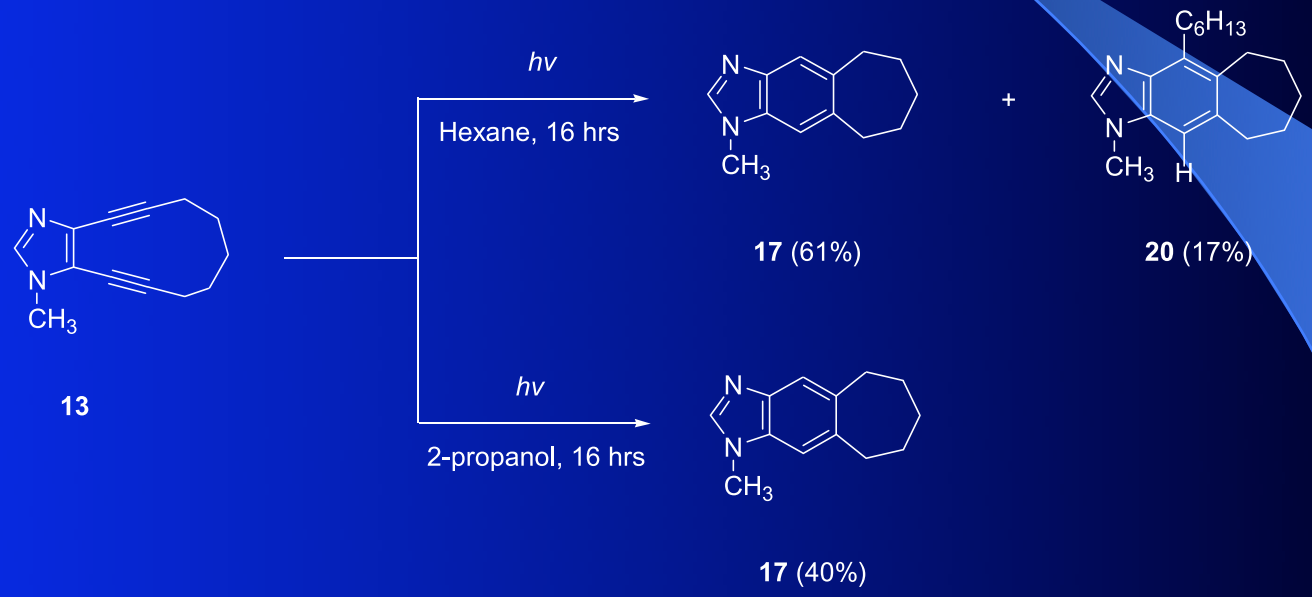


Figure 13

DNA Cleavage with Bicyclic Enediyne **13**

1. DNA base pairladder
2. Dark DNA control
3. 1500 μM of **13** in 30 min
4. 1500 μM of **13** in 60 min
5. 150 μM of **13** in 60 min
6. 15 μM of **13** in 60 min
7. 1.5 μM of **13** in 60 min
8. Light DNA control

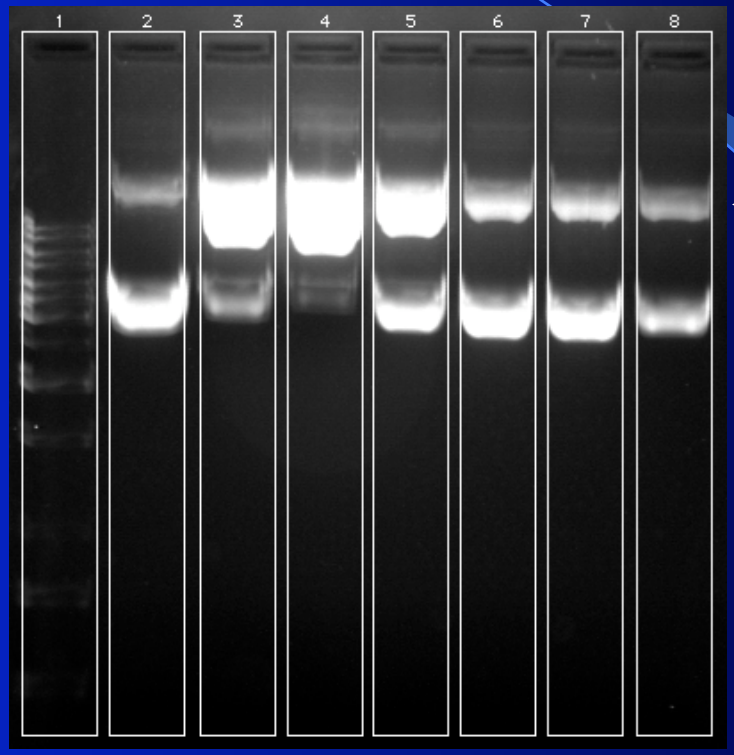


Figure 14

Conclusions

• Rate constants for Bergman cycloaromatization of N^1-phenyl derivative are from four–seven times greater than the average rate constant for the corresponding N^1-alkyl derivatives, depending on the temperature.

• A statistically significant reactivity trend for N^1-phenyl derivatives is observed:
X= H > X = F, Cl, Br, NO_2, CH_3O, CO_2Me > X = *tert*-Bu, Et

• Bicyclic enediyne **13** reacts 10 to 15 times slower than the monocyclic analogue, depending on the temperature.

• Imidazole-fused enediynes undergo photochemical cycloaromatization

• Imidazole-fused enediynes promote photoinduced cleavage of double–stranded DNA.