Synthesis and Characterization of Nine-Membered Cyclic Enediynes, Models of C-1027 and Kedarcidin Chromophore: Equilibration with a *p*-Benzyne Biradical and Kinetic Stabilization†

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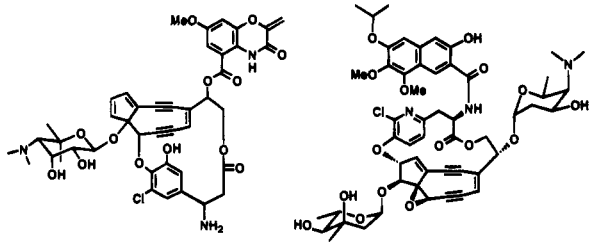
The recent discovery of nine-membered cyclic enediyne chromophores (**1** for the antitumor antibiotic C-1027; **2** for kedarcidin) stabilized by specific apoproteins[1] prompted us to synthesize a highly strained carbocyclic core structure to elucidate the specific mechanism which prevents their spontaneous aromatization.[2,3] Here, we report the successful synthesis of enediynes **4** and **8** as models of **1** and **2**, respectively, as well as the remarkable solvent dependence of the rate of cycloaromatization at ambient temperature.

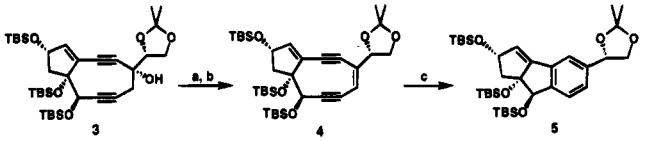


1 **2**

Nine-membered diynes **3** and **6**[3] were converted to enediynes **4** and **8** as shown in Schemes 1 and 2, respectively. The presence of an epoxide ring in the mesylate of **7** greatly facilitated the elimination reaction, which was completed within 30 min in the presence of DBU (~6 equiv) in CH_2Cl_2 at 25 °C. This is ~10 times faster than that of the mesylate of **3**. The enediyne **4** was too labile to be isolated as anticipated[4] and rapidly underwent spontaneous cycloaromatization ($t_{1/2} \approx 11$ min) in the presence of excess 1,4-cyclohexadiene at room temperature to afford **5** in a good yield (~87%). On the other hand, the epoxy enediyne **8** was more stable and could be purified by silica gel chromatography. Cycloaromatization of pure **8** was ~4 times slower than that of **4** in THF-d_8. Quantitative formation of unstable **9** in 1,4-cyclohexadiene–CH_2Cl_2 (1:1) was confirmed by NMR, but removal of the solvent or silica gel chromatography resulted in its complete decomposition. In this case, ketone **10** was isolated as a major product (~14%) by GPC column filtration. Bis-deuterated **9**-d_2 and **10**-d_2 were produced in the perdeuterated solvents.

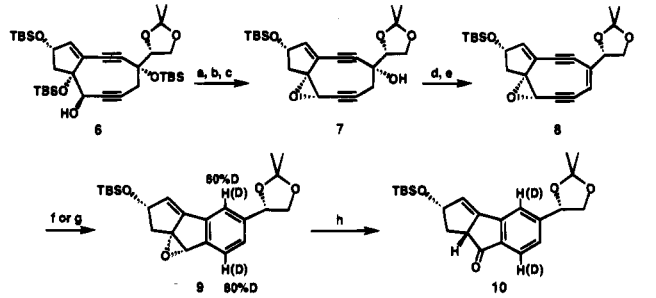
Yoshida and co-workers recently observed the unexpected solvent dependence of the rate of cycloaromatization of **1**.[2,5] Since a pure nine-membered enediyne (**8**) that is soluble in most organic solvents is now available, we examined more precisely

Scheme 1[a]



[a] (a) MsCl, Et_3N, CH_2Cl_2; (b) DBU (~6 equiv), CH_2Cl_2, 25 °C, 6 h; (c) 1,4-cyclohexadiene/CH_2Cl_2, 25 °C, 87% from **3**. TBS, *tert*-butyldimethylsily.

Scheme 2[a]



[a] (a) MsCl, Et_3N, DMPA, CH_2Cl_2; (b) TBAF, THF, 0 °C, 75% from **6**; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 91%; (d) MsCl, Et_3N, CH_2Cl_2; (e) DBU (~6 equiv), CH_2Cl_2, 25 °C, 0.5 h; (f) 1,4-cyclohexadiene/CH_2Cl_2, 25 °C, ~100% from **7**; (g) THF-d_8, 27 °C, 82%; (h) purification on GPC column, ~14%.

the cycloaromatization rate of **8** in various solvents. We were again surprised that the pseudo-first-order decay of **8** is highly dependent on the solvent as a hydrogen donor (Table 1). The data showed the relative rates of THF, benzene, and CH_3CN to be 1;0.2;0.1, which were only slightly lower than those reported for hydrogen abstraction by phenyl radical (1:0.1:0.02).[6a] A primary kinetic isotope effect was also noticed; its magnitude increased as the reaction became slow, as has been observed generally in hydrogen transfer reactions.[7] These results indicate that the hydrogen abstraction step by a *p*-benzyne biradical intermediate[8,9] (**11**) is kinetically significant in the cycloaromatization of **8** (Scheme 3), while the first cyclization step is known to be rate-limiting for acyclic enediynes.[8,10]

Thus, **8** may be virtually in equilibrium with **11** in CH_3CN and CD_2Cl_2, in which cycloaromatization is substantially retarded. If the hydrogen abstraction rate of **11** is slower than that of phenyl radical (CH_3CN, $k_H = 1.0 \times 10^5\ M^{-1}\ s^{-1}$)[6a] due to steric hindrance[11] by a factor of about 100,[12] the equilibrium

† Dedicated to Professor Shô Itô on the occation of his 70th birthday.

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(11) Through-bond interaction may somewhat stabilize the *p*-benzyne biradical.[9]

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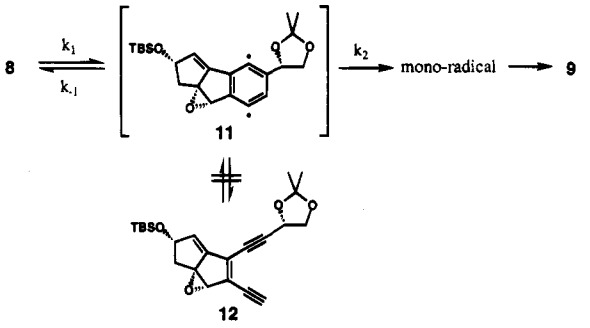
Table 1. Cycloaromatization Rate of **8** in Various Solvents at 28 °C[a]

entry	solvent	$t_{1/2}$ (min)[b]	$k(\times 10^{-5}\ s^{-1})$[b]	rel rate
1	CD_2Cl_2	680	1.7	0.035
2	CH_3CN	610	1.9	0.039
3	C_6H_6	330	3.5	0.071
4	1,4-dioxane-d_8	310	3.7	0.076
5	1,4-dioxane	110	11	0.22
6	THF-d_8[c]	220	5.4	0.11
7	THF	68	17	0.35
8	CD_3CD_2OD	130	8.8	0.18
9	CH_3CH_2OH	65	18	0.37
10	1,4-C_6D_8/CD_2Cl_2[d]	28	41	0.84
11	1,4-C_6H_8/CH_2Cl_2[e]	23	49	1.0

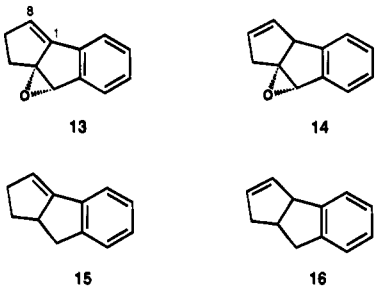
[a] Measured by HPLC except entry 6. [b] Deviation: ±1−6%. [c] Measured by ^{1}H-NMR. [d] 1,4-Cyclohexadiene-d_8−CD_2Cl_2 = 1:1 (v/v). [e] 1,4-Cyclohexadiene−CH_2Cl_2 = 1:1 (v/v).

Scheme 3



constant (K) in CH_3CN is estimated to be 2×10^{-9} (ΔG = ~12 kcal/mol) by steady state approximation to the concentration of **11** ($k_{obs} = k_1k_2/k_{-1} = Kk_2$) based on the assumption of the pseudo-first-order kinetic constant $k_2 = k_H[CH_3CN] \times 10^{-2} \approx k_H \times 10^{-1}\ s^{-1}$. This ΔG seems not unreasonable because the sum of this value and an E_a for hydrogen abstraction by phenyl radical (4−7 kcal/mol)[6b] and the increment due to steric hindrance, ~3 kcal/mol, is in good agreement with an apparent activation energy for the decay of **8** [E_a = 21.6 kcal/mol (ln A = 28.5, 20−32 °C in 1,4-C_6H_8−CH_2Cl_2); 18.5 kcal/mol (ln A = 21.9, 40−60 °C in EtOH)][13] obtained by the Arrhenius plot of the rate constants.

The ΔG (~12 kcal/mol) is similar to that reported for acyclic systems.[2,8,9a] It suggests that energy of **11** may also be raised to such an extent that **8** is destabilized by nine-membered ring strain. The destabilization should arise from the presence of a 1,8-double bond and an epoxide ring in the dehydrobenzopentalene core of **11**,[3] since MM2 calculations (MacroModel v. 4.5)[14] indicate that **13** and **15** are higher in total strain energy by 13.7 and 8.7 kcal/mol than **14** and **16**, respectively, while the nine-membered ring strain for cyclonon-3-ene-1,5-diyne is 14−15 kcal/mol. The barriers for cycloaromatization of acyclic



(*Z*)-3,4-dipropylhex-3-ene-1,5-diyne (**17**) to 2,3-dipropyl-1,4-dihydrobenzene (**18**), its back reaction, and an alternative ring opening of **18** to (*Z*)-dodec-6-ene-4,8-diyne (**19**) were reported to be 27.4, ~16, and ~10 kcal/mol, respectively.[8b] Therefore, the destabilization of both **8** and **11** should significantly decrease the barrier for their interconversion, and consequently the process became reversible at ambient temperature. The above Bergman's observation[8b] and our failure to detect even trace amounts of acyclic enediyne **12**[2] strongly suggests that cleavage of the less substituted bond of **11** leading to **12** has a considerably higher barrier. Nine-membered ring constraint may also contribute to lowering the barrier to **8** because the reaction of **11** to **8** requires less molecular deformation. Thus, the kinetic significance of the hydrogen abstraction step in the present system may be attributable to the large energy difference between **8** and **11**, i.e., the extremely low concentration of **11**, and the very low barrier for back reaction to **8**. This barrier must be lower than that for hydrogen abstraction.

These observations for **8** suggest a hypothesis that the chromophores (**1** and **2**) may also be equilibrated with their *p*-benzyne form and are stabilized kinetically by a specific apoprotein. Thus, **1** and **2** may exist indefinitely if they remain free of hydrogen donor(s) in the holoprotein complex. Aromatic amino acid residues, such as Tyr32, as well as the internal tyrosine and benzoxazine rings of **1**, seem to play an important role in this kinetic stabilization.[15] Attempts to detect a *p*-benzyne biradical intermediate in equilibrium by ESR spectroscopy are currently being investigated in our laboratory.[16]

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Supporting Information Available: Spectral and kinetic data (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) The apparent activation energy and the frequency factor for the decay of **8** calculated by the Arrhenius approximation are to be dependent on the temperature in the kinetic experiments. Measurement of the accurate E_a in CH_3CN has been unsuccessful.

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(16) Preliminary ESR measurements for a CD_2Cl_2 (or CH_3CN) solution of **8** and the powder C-1027 holoprotein exhibited broad spectra whose intensities varied reversibly with temperature. Identification and analysis of these spectra will be reported in due course.