The Enol–Keto Trigger in Initiating Arene Diradical Formation in Calicheamicin/Esperamicin Analogs

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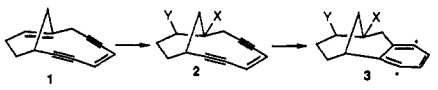
According to substantial *in vitro* information, the cytotoxic activity of the calicheamicin/esperamicin group of natural toxins[1] is due to a series of chemical steps occurring in the [7.3.1] bicyclic "warhead": (a) reductive cleavage of a tri- or disulfide, (b) conversion of an sp^2 bridgehead carbon to an sp^3 center by conjugate addition of the thiol, (c) rearrangement of the enediyne unit to an arene-1,4-diyl, and (d) cleavage of DNA by hydrogen atom abstraction from a ribose unit and ensuing degradation.[2] A significant message from these studies is that removal of the bridgehead double bond from a simple framework such as **1** can allow rapid formation of the high-energy intermediate **2** and that **2**, if delivered and positioned properly, can be an effective DNA cleavage agent via rapid formation of the diradical **3**.[3] It allows for the possibility of a general triggering mechanism which might be initiated by a variety of chemical forces, such as pH control, light activation, redox control, etc.[3,4]



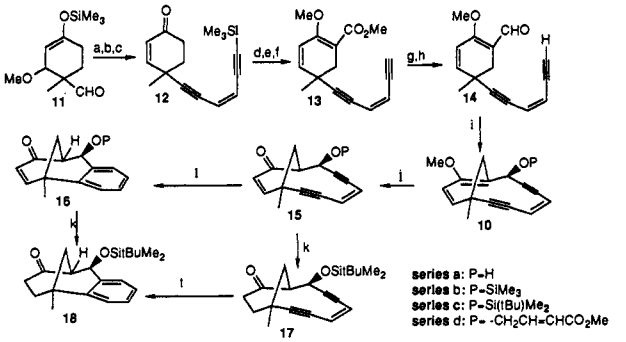
We report here the demonstration of examples of an enol–keto trigger. Our initial goal was based on the enol ether **4a** related to Magnus's model **5a** of the calicheamicin warhead.[5] Ketone **5a** was inferred to have a short lifetime at 25 °C; it has not been characterized, but the arene derivative **6a** was obtained in 50% yield. Compounds **4b–d** bear a propargylic hydroxyl group, expected to be useful in attaching appendages which can interact with the minor groove of DNA and position the diradical (i.e., an analog of **3**) for optimal DNA cleavage effectiveness. Both **4c** and **4d** were prepared in about 10 steps and 10% overall yields from the monoethyleneketal of 1,4-cyclohexadione.[6] Acid hydrolysis provided ketones (**5c,d**) which were surprisingly stable toward the Bergman rearrangement (Table I).

Table I. Thermal Rearrangement of Ketones **5a**, **5c**, **5d**, **15a**, **15b**, and **17**

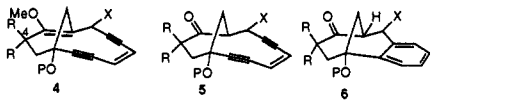
keto-enediyne	concn in C_6D_6 (M)	$t_{1/2}$/temp (°C)	arene product (yield)
[**5a**]		<1 h/<25	**6a** (50%; ref 5)
5c	*a*	>24 h/50	*c*
5d	*a*	20–25 h/25	**6d** (43%)[d,e]
15a	0.04[b]	35 min/38	**16a** (42%)[e]
15a	0.008[b]	5 h/16–18	**16a** (major)[e]
15c	0.025[b]	53 min/37	**16c** (72%)[e]
17	0.007[b]	9.0 h/37	**18** (40%)[e]

[a] In neat CHD. [b] 5 mol equiv of 1,4-cyclohexadiene (CHD); under argon. [c] Decomposition was rapid at 85 °C, but the arene product (**6c**) was not isolated. [d] Based on 25% recovered **5b**. [e] The yield is based on ^1H NMR integration using an internal standard.

Scheme I.[a] Synthesis and Rearrangement of the Enones **15** and Ketone **17** $OSiMe_3$



[a] (a) 1.04 mol equiv $(MeO)_2POCHN_2$, 1.04 mol equiv tBuOK, THF, -78 °C → -9 °C, 16.5 h; (b) 0.3 mol equiv camphorsulfonic acid, ether, 20 °C, dark, 72 h; (c) 20 mol % CuI, 5 mol % $Pd(PPh_3)_4$, 3.5 mol equiv Et_2NH, 1.8 mol equiv (*Z*)-ClCHCHCCTMS, 25 °C, 15 min; 50% yield from **11**; (d) (i) 1.4 mol equiv LiHMDS, THF, -78 °C, 20 min, (ii) 1.2 mol equiv HMPA, (iii) 1.4 mol equiv CH_3OCOCN, -78 °C, 20 min; (e) 1.7 mol equiv NaH, 3:1 THF/HMPA, 2 mol equiv CH_3OSO_2F, -78 °C → -10 °C, 50 min; (f) 1 mol equiv $(nBu)_4NF\cdot(H_2O)_x$ 1.2 mol equiv K_2CO_3, THF, 0 °C, 5 min; 57% yield from **12**; (g) 2.1 mol equiv DIBAL, toluene, -16 °C, 40 min; (h) 7 mol % $RuCl_2(PPh_3)_3$, 2.4 mol equiv *N*-methylmorpholine *N*-oxide, acetone, 20 °C, 20 min; 78% yield from **13**; (i) (i) 2 mol equiv LiHMDS, THF, -78 °C, 12 min, (ii) see text; (j) 6 M HCl, 0 °C, 35 min; (k) 5:1 THF:HMPA, 10 mol % CuI, 8 mol equiv DIBAL, -55 °C, 1 h (acid quench); (l) see text for each series.



An alternative target is **10**, which is available via a short synthesis (Scheme I) in 14% yield from Danishefsky's diene[7] and methacrolein. The known[8] Diels–Alder adduct **11** was converted to the enediyne **12** by aldehyde-to-alkyne conversion[9] followed by conventional Pd-catalyzed coupling with 1-chloro-4-(trime-

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(5) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626–1628. Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921-6923. Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986–4987.

(6) The preparation of **4c** and **4d** follows a general strategy of ring closure (as employed in Scheme I, step i). The full characterization data are presented in the supplementary material. Compound **4b** could not be prepared by a parallel ring closure, apparently due to enolization and proton transfer during base-promoted ring closure. The details of these synthesis efforts will be reported in the full paper describing this work.

(7) Danishefsky, S.; Kitahara. T.; Schuda, P. F. *Org. Synth.* **1983**, *61*, 147–151.

(8) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996–6700.

(9) Gilbert, J.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997–4998.

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thylsilyl)-(*Z*)-but-1-en-3-yne (50% overall).[10] Generation of the enolate, quenching with methyl cyanoformate,[11] conversion to the methyl enol ether, and cleavage of the trimethylsilyl group produced **13** (57% overall). Reduction and reoxidation gave the aldehyde **14** (78%),[12] and ring closure using 2 mol equiv of LiN(SiMe$_3$)$_2$ and quenching with trimethylsilyl triflate gave **10b** (59% yield).[12] The free alcohol **10a** was obtained in 55% yield under the same ring closure conditions but with use of an aqueous quench; however, it is more prone to decomposition during isolation at 25 °C.[12] Ring closure of **14** and *in situ* acid hydrolysis gave the ketone **15a** (55%), which was stabilized as the *tert*-butyldimethylsilyl derivative **15c**.[12] Reduction of **15c** to the saturated ketone **17c** was carried out with use of CuH (22% overall for silylation and reduction).[12,13] The crotonate derivative **10d** was prepared (by addition of the triflate ester of methyl 4-hydroxy-(*E*)-but-2-enonate immediately after base-promoted cyclization; 33% yield) and is expected to be useful for tethering an enediyne system to agents which associate with the minor groove of DNA.[14]

In the case of **10d**, the minimum acidity necessary for a reasonable rate of hydrolysis of the enol ether unit (half life of 12 h at 37 °C) was determined to be pH 2.0 (1:3:3 KCl–HCl buffer/THF/EtOH). The reactivity of the ketones **5a**, **5c**, **5d**, **15a**, **15c**, and **17** toward Bergman rearrangment is summarized in the Table I.

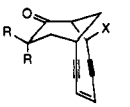

Figure 1. Pseudochair conformation of **5**.

It is noteworthy that the stability of ketone **5c** is much higher than that inferred for **5a**.[5] The *gem*-dimethyl group might have the effect of reducing the internal bond angles of the bicyclic skeleton and increasing the strain involved in proceeding to the transition state for the Bergman rearrangement. The α-spirocyclopropyl group in **5d** should have the opposite effect, and, indeed, the rate of rearrangement of **5d** is much higher than that for **5c**. However, **5d** is not nearly as reactive as estimated for **5a**. Another possible explanation for the retarding effect of an alkyl substitution adjacent to the keto unit is based on an analysis reported previously:[5] while the pseudoboat form is the lowest energy conformation, the pseudochair form (Figure 1) leads to the best transition state for the Bergman rearrangement, and the energy of that transition state is raised due to a 1,3-diaxial interaction between a methyl and methylene units.[6] Finally, while we have been unable to prepare and study **5b**, the ketone **17** also does not suffer from alkyl substitution adjacent to the keto unit and yet is quite slow to rearrange to the arenediyl. The enones **15a** and **15c** differ in several structural features compared to the series of structures **5** and **17**, and the origin of the increased reactivity of **15a** and **15c** compared to **17** is not obvious. The subtle effects of substituents and structure on the rate of the enediyne rearrangement are important in tuning the reactivity and are not yet subject to generalization. The reactivity of ketones **15** is in the useful range for effective DNA cleavage under physiological conditions, and we are proceeding with the design of more delicate triggering processes for the enol–ketone conversion.

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Supplementary Material Available: Experimental procedures and full characterization data for all new compounds reported here as well as NMR spectra (^{1}H and ^{13}C) for compounds **5c**, **5d**, **10b**, **14**, **15a**, and **17c** (21 pages). Ordering information is given on any masthead page.

(10) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811–3812; Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217–4220.

(11) Mander, L.; Sethi, S. P. *Tetrahedron. Lett.* **1983**, *24*, 5425–5428.

(12) Compound **14**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.1 (s, 1H), 6.40 (d, J = 10 Hz, 1H), 6.23 (d, J = 10 Hz, 1H), 5.86 (d, J = 10.9 Hz, 1H), 5.75 (dd, J = 10.9, 2.3 Hz, 1H), 3.82 (s, 3H), 3.29 (d, J = 2.3, 1H), 2.82 (d, J = 16 Hz, 1H), 2.57 (d, J = 16 Hz, 1H); ^{13}C NMR (67.5 Hz, $CDCl_3$) δ 188.3, 163.8, 146.0, 121.6, 118.3, 117.8, 112.4, 101.6, 84.4, 80.5, 78.3, 56.7, 32.2, 31.9, 26.0; IR (oil on salt plate) 3287, 3250, 2972, 2945, 2845, 2214, 1091, 1644, 1568, 1411, 1216 cm^{-1}; MS *m/e* (relative intensity) 226 (M$^+$, 7.5), 211 (9.9), 197 (86.6), 182 (100), 165 (78.4), 153 (63.8), 152 (76.7), 139 (70.5), 128(43.7), 115 (40.8). Compound **10b**: ^{1}H NMR (270 MHz, C_6D_6) δ 6.29 (d, J = 1.7 Hz, 1H), 5.80 (d, J = 9.6 Hz, 1H), 5.59 (d, J = 9.2 Hz, 1H), 5.51 (d [with fine structure], J = 9.6 Hz, 1H), 5.49 (d, J = 9.2 Hz, 1H), 3.20 (s, 1H), 2.97 (dd, J = 15, 1.8 Hz, 1H), 2.37 (d, J = 15 Hz, 1H), 1.16 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (67.5 Hz, C_6D_6) δ 144.2, 135.9, 126.2, 123.4, 123.0, 118.1, 105.1, 102.6, 87.0, 84.2, 60.9, 56.9, 39.8, 33.2, 26.5, 0.065; IR (oil on salt plate) 2957, 2931, 2900, 2872, 2205, 2179, 1658, 1251, 1077, 1034, 887, 843, cm^{-1}; MS *m/e* found 298.1410, calcd 298.1389. Compound **10a** is stable in dilute solution at –20 °C but polymerizes to a dark yellow tar slowly in solution at 25 °C and rapidly when concentrated: ^{1}H NMR (270 MHz, C_6D_6) δ 5.97 (dd, J = 9.2, 1.3 Hz, 1H), 5.78 (d, J = 9.6 Hz, 1H), 5.59 (d, J = 9.2 Hz, 1H), 5.48 (dd, J = 9.2, 1.7, 1H), 5.49 (ddd, J = 9.6, 1.7, 1.0 Hz, 1H) 3.16 (s, 3H), 2.67 (dd, J = 15, 1.8 Hz, 1H)), 2.22 (d, J = 15 Hz, 1H), 1.14 (s, 3H); IR (oil on salt plate) 3250–3600 (broad), 2190 cm^{-1}. Compound **15c**: ^{1}H NMR (270 MHz, C_6D_6) δ 6.05 (dd, J = 10, 1.8 Hz, 1H), 5.80 (d, J = 10 Hz, 1H), 5.56 (d, J = 4.3 Hz, 1H), 5.39 (s, 2H), 3.09 (d, J = 14.8 Hz, 1H), 2.76 (ddd, J = 14.8, 4.3, 1.0 Hz, 1H),1.76 (d, J = 15 Hz, 1H), 1.72 (d, J = 15 Hz, 1H), 1.00 (s, 3H), 0.95 (s, 9H), 0.19 (s, 3H), 0.11 (s, 3H). Compound **17c**: ^{1}H NMR (270 MHz, C_6D_6) δ 5.46 (d [with fine structure], J = 5 Hz, 1H), 5.43 (m, 2H), 2.89 (dt, J = 14.5, 2.5 Hz, 1H), 2.68 (ddd, J = 7 Hz [overlap prevents extraction of the other two coupling constants], 1H), 2.64 (dd, J = 13, 6.0 Hz, 1H), 2.09 (dd [with fine structure] J = 19, 4.8 Hz, 1H), 1.60 (dd, J = 14.7, 11.4 Hz, 1H), 1.17 (dd, J = 14, 5 Hz,1H), 1.05 (s, 3H), 0.96 (s, 9H), 0.18 (s, 3H), 0.099 (s, 3H); ^{13}C NMR (67.5 Hz, C_6D_6) δ 208, 125.0, 123.6, 108.2, 101.5, 86.0, 85.0, 64.9, 53.7, 39.3, 37.2, 33.4, 32.0, 29.2, 25.9, 18.4, –4.5, –5.1; IR (oil on salt plate) 2954, 2930, 2897, 2858, 2190, 1703, 1462, 1349, 1257, 1075, 839, 779 cm^{-1}.

(13) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T and Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540.

(14) Tethering of a simple monocyclic enediyne to a netropsin derivative through a crotonate tether gives strongly enhanced DNA cleaving potency: Semmelhack, M. F.; Gallagher, J. J., manuscript submitted for publication.