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Two Distinct Epoxide Ring Opening Pathways in a Monocyclic Model System of the Kedarcidin Chromophore

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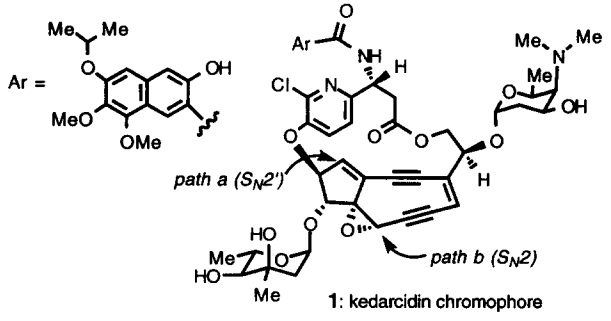
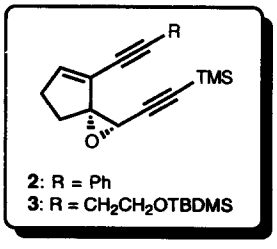
Abstract: Two monocyclic model compounds **2** and **3** were synthesized from (*Z*)-ketoeneyne **5** for studying the epoxide ring opening pathways related to activation of the kedarcidin chromophore (**1**). The solvent-derived S_N1 products **8a,b** and **9a,b** were formed from **2** and **3** in MeOH while the S_N2 products **10a,b** were produced from **2** and **3** with methyl thioglycolate in buffer (pH 7.0)-*i*PrOH; the latter reaction may provide a new scenario for bioreductive activation of the kedarcidin chromophore *via* an S_N2 attack of thiol at the propargylic carbon atom. © 1998 Elsevier Science Ltd. All rights reserved.

Kedarcidin is a chromoprotein antitumor antibiotic isolated from the fermentation broth of a novel actinomycete strain and its antitumor activity is due to the associated chromophore.[1,2] The isolated kedarcidin chromophore (**1**) is very unstable in solution and degrades under acidic conditions.[1] The chromophore is bioreductively activated and exhibits sequence selective single strand DNA cleavage.[2] The molecular structure and mechanism of action of **1** are similar to other naturally occurring enediyne antitumor antibiotics.[3] As in the cases of the neocarzinostatin chromophore[4] and dynemicin A,[5] it has been proposed that the kedarcidin chromophore is activated by reductive epoxide ring opening (*path a*) to initiate the radical-forming reaction cascade and then to cause DNA damage. This hypothesis is supported by the enhanced DNA cleavage potency of **1** in the presence of 2-mercaptoethanol[1,2] and by the isolation of $NaBH_4/NaBD_4$ reduction products of **1**.[1b] But the assumed thiol adduct of **1** was not isolated and characterized. Despite several recent reports on synthesis of the highly strained 9-membered ring enediyne sub-unit[6] the epoxide ring opening of **1** has not been fully addressed. We report here on the synthesis and two distinct epoxide ring opening reactions of the



1: kedarcidin chromophore



2: R = Ph
3: R = $CH_2CH_2OTBDMS$

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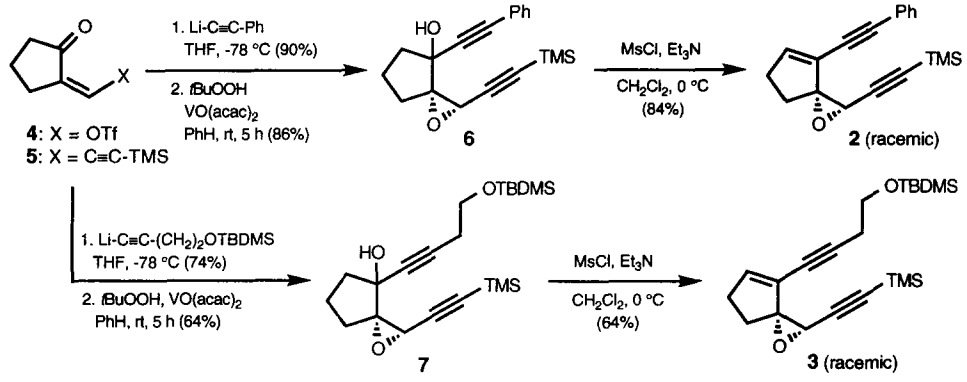
monocyclic model compounds **2** and **3**. Our new finding may provide an alternative scenario for an S_N2 thiol-assisted epoxide ring opening (*path b*) in the bioreductive activation of the kedarcidin chromophore (**1**).

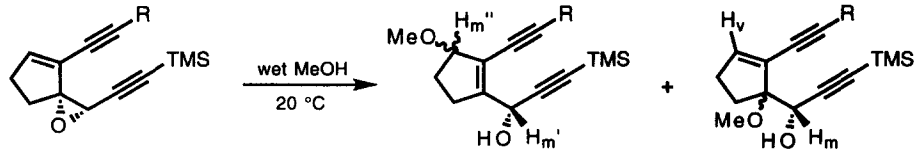
In order to avoid the implication associated with cycloaromatization of the very unstable 9-membered ring enediyne core, we used the monocyclic model compounds **2** and **3** to investigate the epoxide ring opening reactions. As shown in Scheme 1,[7] compounds **2** and **3** were synthesized from the known (*Z*)-ketoeneyne **5**[8] which was obtained *via* a stereoselective cross-coupling between (trimethylsilyl)acetylene and the labile (*Z*)-ketoenol triflate **4** [$Pd(PPh_3)_4$, CuI, Et_3N-CH_3CN (1:3), 0 °C, 10 min, 60%] recently developed by us.[9] Addition of lithium phenylacetylide to **5** gave the corresponding allylic alcohol (90%) which was oxidized to epoxide **6** by *t*BuOOH-$VO(acac)_2$ in 86% yield. Elimination of the tertiary hydroxyl group in **6** was effected by treating with MsCl (10 eq) and Et_3N (25 eq) in CH_2Cl_2 at 0 °C (3 min) to give **2** in 84% yield. Conversion of **6** into **2** could not be completed with less MsCl and Et_3N even after prolonged reaction at room temperature. Similarly, addition of $LiC{\equiv}C(CH_2)_2OTBDMS$ to **5** (74%) followed by epoxidation and dehydration afforded another model compound **3**. Epoxy-enediynes **2** and **3** are very unstable and they should be freshly prepared from the stable precursors **6** and **7** before use.

Scheme 1



We first attempted the reaction of EtSH with **2** in the presence of Et_3N in wet THF (Entry 1, Scheme 2).[7] After stirring for 5.5 h, only the substrate **2** was recovered. By performing the reaction in wet MeOH in the presence of EtSH or MeO_2CCH_2SH (Entries 2 and 3), the solvent adducts **8a** were formed as two separable diastereomers. A third product **9a**[10] was isolated from Entry 2. It was confirmed that the thiol is not required for the methanolysis of **2** and compounds **8a** and **9a** were obtained in 42% and 21% yield, respectively (Entry 4). Similarly, treatment of **3** in wet MeOH at 20 °C for 2.5 h afforded **8b** and **9b**[10] in ca. 2:1 ratio and in 52% combined yield (Entry 5), the silyl protecting group in **3** was also removed by MeOH. It is apparent that the methanolysis of epoxy-enediynes **2** and **3** takes place *via* an allylic cation intermediate which is trapped by the solvent molecules to afford **8** and **9** (an S_N1 reaction mechanism).[11] The structures of **8** and **9** are established spectroscopically. In the ^1H NMR spectra, two methine protons are found at 5.51 (d, J = 4.1 or 4.6 Hz, H_m') and 4.56 (m, H_m'') ppm for both diastereomers of **8a** or at 5.37 (d, J = 3.3 Hz or br s, H_m') and 4.44 (m, H_m'') ppm for both diastereomers of **8b**. Only one methine proton is observed at 4.75 (d, J = 1.2 Hz, H_m) ppm for **9a** or at 4.64 (d, J = 2.4 Hz, H_m) ppm for **9b**. The vinyl proton of **9a,b** appears at 6.46 (t, J = 2.6 Hz, H_v) and 6.32 (t, J = 2.3 Hz, H_v) ppm, respectively. The doublet splitting of H_m in **9a,b** indicates that the free hydroxyl group should be located at the propargylic position.

Scheme 2



2: R = Ph
3: R = $CH_2CH_2OTBDMS$

8a: R = Ph
8b: R = CH_2CH_2OH

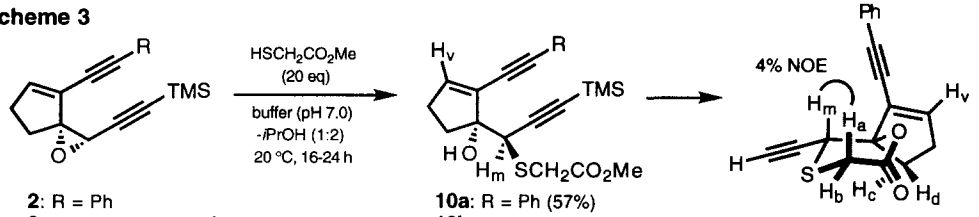
9a: R = Ph
9b: R = CH_2CH_2OH

Entry	Substrate	Reaction Conditions	Products (%)
1	**2**	EtSH (4.5 eq), Et_3N (2 eq), wet THF, 20 °C, 5.5 h	No reaction
2	**2**	EtSH (2 eq), wet MeOH, 20 °C, 6.5 h	**8a** (17^a+26^b); **9a** (23)
3	**2**	MeO_2CCH_2SH (15 eq), wet MeOH, 20 °C, 12 h	**8a** (26^a+16^b)
4	**2**	wet MeOH, 20 °C, 1.5 h	**8a** (20^a+22^b); **9a** (21)
5	**3**	wet MeOH, 20 °C, 2.5 h	**8b** ($18^{a,c}$+16^b); **9b** $(18)^c$

[a]The less polar diastereomer. [b]The more polar diastereomer. [c]Inseparable mixture of **9b** with the less polar diastereomer of **8b** in *ca.* 1:1 ratio.

Reactions of epoxides **2** and **3** with methyl thioglycolate were carried out in a different solvent system. Treatment of **2** with methyl thioglycolate (20 eq) in buffer (pH 7.0)-*i*PrOH (1:2) at 20 °C gave the thiol adduct **10a** in 57% yield. In addition, a minor solvolysis product related to **8a** (replacing MeO with *i*PrO) was isolated in 3% yield from a large scale reaction. A similar product **10b** was obtained from **3** in 47% yield (Scheme 3).[7] The ^1H NMR spectra confirmed that compounds **10a,b** possess a vinyl proton at 6.39 (t, J = 2.5 Hz, H_v) ppm for **10a** and at 6.15 (t, J = 2.3 Hz, H_v) ppm for **10b**. Since the methine proton H_m found at 4.27 ppm for **10a** or 4.17 ppm for **10b** is a singlet, the sulfur atom in **10a,b** should be attached to the propargylic carbon atom as shown. Furthermore, **10a** was converted into the unstable lactone **11** by saponification (aq KOH-MeOH, with

Scheme 3



2: R = Ph
3: R = $(CH_2)_2OTBDMS$

10a: R = Ph (57%)
10b: R = $(CH_2)_2OTBDMS$ (47%)

11 (from **10a**)

removal of the TMS group) and lactonization (DCC-DMAP, rt). In the ^1H NMR spectrum of **11**, H_d and H_c are found at 2.88 (ddd) and 2.26 (ddd) ppm, respectively. The large down-field shift of H_d is due to the deshielding effect of the carbonyl group and this supports the chair-like conformation of the spiro lactone in **11** as shown in Scheme 3. NOE experiments reveal that there is no enhancement in the H_c signal upon irradiation at H_m, suggesting that H_m is located at the axial position. Therefore, the relative stereochemistry of **10a,b** is confirmed and they are the S_N2 epoxide ring opening products.

In summary, we have examined the epoxide ring opening reaction related to the activation of the kedarcidin chromophore (**1**) using the monocyclic model compounds **2** and **3**. Two pathways were observed under the mild and neutral conditions, *i.e.* an S_N1 methanolysis and an S_N2 reaction with thiols. The proposed thiol-assisted S_N2' epoxide ring opening (*path a*)[1b] did not take place in our model compounds. Moreover, our

results described here point out a new scenario for activation of the kedarcidin chromophore *via* an S_N2 epoxide ring opening (*path b*) by thiol reducing agents. Attack of thiol at the propargylic position of **1** will form an intermediate structurally resembling another known 9-membered ring enediyne antitumor antibiotic, the C-1027 chromophore,[12] which readily undergoes cycloaromatization and causes DNA cleavage without a thiol-assisted bioreductive activation step.[13] Further studies are in progress in our laboratory.[14]

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10. Compound **9a** or **9b** could be a mixture of two diastereomers which are not distinguishable by ^1H NMR spectroscopy.
11. It is not clear why the thiol-adducts were not detected in Entries 2 and 3. One explanation may be that the epoxides **2** and **3** are solvated by MeOH through hydrogen bond which facilitates the epoxide ring opening. The resultant allylic cations are then trapped by the solvated MeOH molecules rather than the thiols.
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