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# A Novel Monocyclic Dienediyne System: Synthesis and Mode of Aromatization

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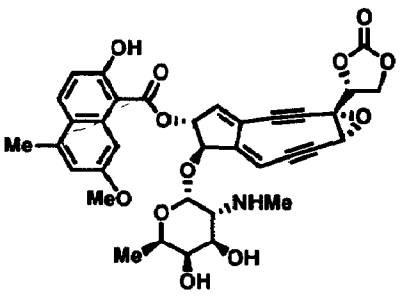
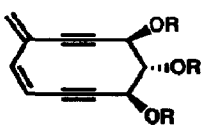
*Abstract:* The novel monocyclic dienediyne **2**, which is a simplified analogue of the neocarzinostatin chromophore (**1**), was synthesized from D-xylitol *via* conversion of the keto-aldehyde **13** into the highly strained 10-membered ring compound **14** by a simple intramolecular aldol condensation as the key step. The mode of cycloaromatization of **2** by a thiol addition, reminiscent of the chemistry of **1**, was also demonstrated.

The neocarzinostatin chromophore (**1**)[1,2] is the labile heart of neocarzinostatin, which is an antitumor antibiotic isolated from *Streptomyces carzinostaticus* by Ishida *et al.* in 1965[3], and plays a significant role in the biological activity of neocarzinostatin.[2,4] The bicyclic moiety of **1** containing the dienediyne system is now recognized to be responsible for the DNA damaging properties.[5,6] Because of the stimulant biological background and the unique structure of **1**, many groups have focused on the synthesis of the core units or the analogues of **1**.[7] From a synthetic standpoint, complex methods were generally required for construction of the highly strained medium membered ring structure. Furthermore, synthesis and mode of action of a monocyclic system containing a dienediyne function were rarely studied. In this communication, we wish to report the synthesis of a novel 10-membered monocyclic dienediyne compound **2**, which is a highly simplified analogue of the neocarzinostatin chromophore (**1**), by a simple intramolecular aldol condensation and its cycloaromatization profile by a thiol addition related to the mode of action of **1** in the DNA cleaving activity.

D-Xylitol **3** was selected as a cheap and readily available starting material for this synthesis. The primary alcohols of **3** were selectively protected with pivaloyl groups (2.5 equiv. PvCl, Py, 26°C, 15h) to give




**1**

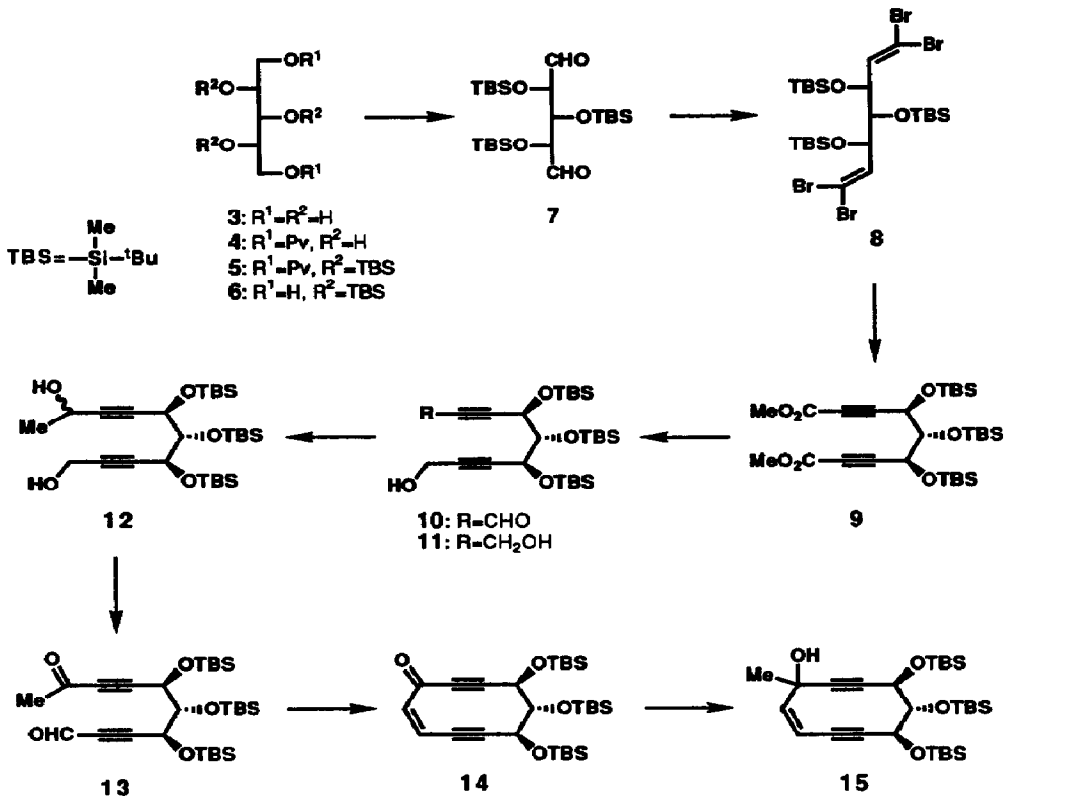


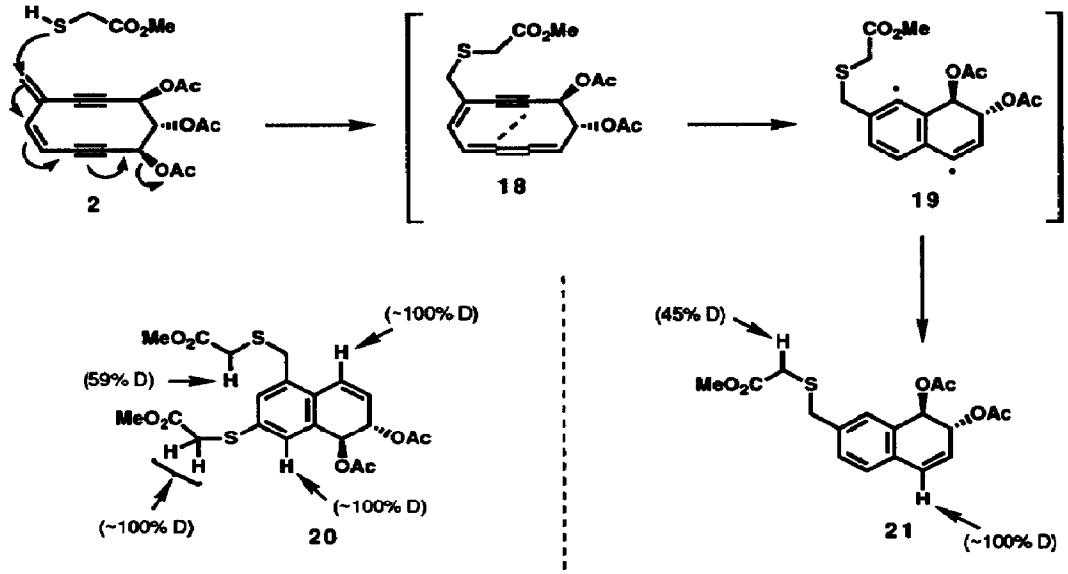

**2**: R=Ac
**16**: R=TBS
**17**: R=H

**4**[8] in 58% yield. The triol **4** was converted into the diol **6**[8] by standard manners in two steps (i. 4.5 equiv. TBSCl, 5.0 equiv. imidazole, DMF, 80°C, 12h, 95%; ii. 4.3 equiv. DIBAL, PhMe, -78°C, 40min, 96%) in 91% overall yield. Swern oxidation (3.0 equiv. $(COCl)_2$, 4.0 equiv. DMSO, 10 equiv. $Et_3N$, $CH_2Cl_2$, -78→0°C, 1.5h) of **6**, followed by bromo-olefination of the resulting crude dialdehyde **7** by Corey's method[9] (4.0 equiv. $CBr_4$, 8.0 equiv. $PPh_3$, $CH_2Cl_2$, 0°C, 0.5h) gave the tetrabromide **8**[8] in 97% overall yield. The tetrabromo compound **8** was treated with 6.0 equiv. of *n*-BuLi /hexane in THF at 0°C for 15min and then 10 equiv. of ClCOOMe at 0°C for 10min to give **9**[8] in 86% yield. Reduction of the methyl ester of **9** with 3.0 equiv. of DIBAL in toluene at -78→0°C for 0.5h afforded the desired mono-aldehyde **10**[8] (45%) and the diol **11**[8] (38%), the latter of which was selectively converted into **10** by the Dess-Martin oxidation[10] (0.8 equiv Dess-Martin periodinane, $CH_2Cl_2$, 0°C, 0.5h, 53%). The Grignard reaction (4.5 equiv. MeMgBr, ether, 25°C, 10min, 95%) of **10** afforded **12**[8] which was subjected to the Dess-Martin oxidation (3.2 equiv. Dess-Martin periodinane, $CH_2Cl_2$, 26°C, 45min, 99%) to give the keto-aldehyde **13**[8] in 94% overall yield from **10**. The key one-step conversion of **13** into the highly strained cyclic system was best effected by using 2.0 equiv. of 1.0M LiOH in EtOH (0.005 M for **13**) at 26°C for 3h to afford the monocyclic product **14**[8] [MS-CI m/z 535 $(M+H^+)$] and the dimer[8] [MS-CI m/z 1069 $(M+H^+)$] in 38% and 17% yields, respectively. Notably, the 10-membered ring keto-enediyne compound **14** was found to be stable in air or ambient light at room temperature. Although the Wittig reaction using $Ph_3P{=}CH_2$ and the Horner-Emmons reaction using $(MeO)_2P(O)Me$ and base were tried to introduce an olefinic function onto **14**, both attempts failed because of the low reactivity of the highly conjugated ketone of **14**. The desired dienediyne system of **16**[8] was obtained in two steps *via* dehydration of **15**[8] (i. 2.2 equiv. MeLi, ether, 0°C, 10min; ii. 4.0 equiv. MsCl, 8.0 equiv. $Et_3N$, $CH_2Cl_2$, 0°C, 20 min) in 57% overall yield. Finally, the dienediyne compound **2**[8] having good leaving groups, acetyl groups, at suitable position for the cyclization using a thiol was synthesized by standard desilylation following acetylation (3.3 equiv. TBAF, THF, 0°C, 30min and then 6.0 equiv. $Ac_2O$, 8.0 equiv. $Et_3N$, 0.1 equiv. 4-DMAP, 46%) without isolation of the extremely unstable triol **17**. Compared with the high stability of **14**, the 10-membered ring dienediyne compounds **2** and **16** were considerably unstable especially when kept neat.

Addition of methyl thioglycolate (3.0 equiv.) to **2** in the presence of triethylamine (1.0 equiv.) in MeOH at 26°C for 1h gave the benzenoid products **20**[8] and **21**[8] in 11.8% and 4.8% yields, respectively.[11] A similar experiment conducted in deuteriated solvent, MeOH-$d_4$, afforded **20** and **21** with the indicated levels of deuterium incorporation. Although the mechanism of the production of **20** is not definite,[12] the formation of **21** clearly suggest that the monocyclic dienediyne **2** undergoes an addition of thiol to produce the enyne-cumulene **18**, which proceeds the cycloaromatization leading to the diradical **19**. The intermediate **19** undergoes a particularly effective intramolecular hydrogen atom transfer from the methylene group of the methyl thioglycolate moiety.[13]

In conclusion, the present work shows not only the synthesis of a novel monocyclic dienediyne system related to the neocarzinostatin chromophore but also its mode of action by a thiol addition. Our results demonstrate that even such a simple monocyclic model containing a dienediyne system has the ability to produce the benzenoid product. Considering the proposed mechanism of DNA cleavage by the neocarzinostatin chromophore (1),[5,6] **2** has an indispensable structure and chemical property for this purpose. The evolution of the biological activity of **2** and its analogues is now in progress.


TBS=—Si(Me)(Me)—tBu
3: R1=R2=H
4: R1=Pv, R2=H
5: R1=Pv, R2=TBS
6: R1=H, R2=TBS
7
8
9
10: R=CHO
11: R=CH2OH
12
13
14
15


2
18
19
(~100% D)
(59% D)
(~100% D)
(~100% D)
20
(45% D)
21
(~100% D)

**Acknowledgement**

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8. All new compounds were purified by silica-gel column chromatography and were fully characterrized by spectoscopic means. Significant $^1$H-NMR spectra [270MHz, $CDCl_3$, δ (TMS), J(Hz)] are the following. **13**: 2.32 (3H, s, Me), 3.80 (1H, dd, J=4.4 and 4.4, H-5), 4.77 (2H, d, J=4.4, H-4 and 6), 9.21 (1H, s, CHO); **14**: 3.79 (1H, t, J=5.0, H-7), 4.5-4.6 (1H, m, H-6), 4.56 (1H, d, J=5.0, H-8), 6.33 (1H, dd, J=12.0 and 2.0, H-3), 6.41 (1H, d, J=12.0, H-2); **2**: 2.05 (3H, s, OAc), 2.07 (3H, s, OAc), 2.09 (3H, s, OAc), 5.46 (1H, t, J=9.0, H-7), 5.49 (1H, d, J=12.0, H-2 or 3), 5.51 (1H, s, =$CH_2$), 5.55 (1H, s, =$CH_2$), 5.67 (1H, d, J=9.0, H-6 or 8), 5.72 (1H, d, J=9.0, H-6 or 8), 6,34 (1H, d, J=12.0, H-2 or 3); **20**: 2.06 (3H, s, OAc), 2.09 (3H, s, OAc), 3.13 (2H, s, -SC$\underline{H}_2$COOMe), 3.67 (2H, s, -SC$\underline{H}_2$COOMe), 3.74 (3H, s, -COOMe), 3.76 (3H, s, -COOMe), 3.88 (2H, s, -C$\underline{H}_2$SCH$_2$COOMe), 5.58 (1H, ddd, J=7.2, 4.0 and 1.6, -C$\underline{H}$-OAc), 6.03 (1H, dd, J=10.0 and 4.0, -CH=C$\underline{H}$-), 6.13 (1H, d, J=7.2, -C$\underline{H}$-OAc), 6.88 (1H, br d, J=10.0, -C$\underline{H}$=CH-), 7.24 (1H, br s, aromatic), 7.27 (1H, br s, aromatic). **21** (acetone-$d_6$): 3.17 (2H, s, -SC$\underline{H}_2$COOMe), 3.67 (3H, s, -COOMe), 3.86 (2H, s, -C$\underline{H}_2$SCH$_2$COOMe), 5.54 (1H, ddd, J=6.4, 4.0 and 1.2, -C$\underline{H}$-OAc), 5.98 (1H, dd, J=10.0 and 4.0, -CH=C$\underline{H}$-), 6.11 (1H, d, J=6.4, -C$\underline{H}$-OAc), 6.71 (1H, br d, J=10.0, -C$\underline{H}$=CH-), 7.23 (1H, d, J=7.9, aromatic), 7.33 (1H, d, J=1.8, aromatic), 7.35 (1H, dd, J=7.9 and 1.8, aromatic).
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11. The structure of **20** was ascertained by the observation of NOE experiments. Thus irradiation at the olefinic proton at 6.88 ppm resonance frequency caused NOE of the protons (9.8%) at benzyl position.
12. When 0.3 equiv. of HSCH$_2$CO$_2$Me was used in the aromatization reaction, a significant decrease in the yield of **20** was observed, and **20** and **21** were obtained in 3.5% and 4.5% yields, respectively. The mechanism of the formation of **20** is now under investigation.
13. For related observation, see: (a) Refs. 7c and 7j. (b) Chin, D. -H.; Golgberg, I. H. *J. Am. Chem. Soc.* **1992**, 114, 1914.

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