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Synthesis and Reactivity of a New Designed Molecule, 6,7-Benzobicyclo[8.3.0]trideca-1,6,10-triene-3,8-diyn-5-one as a Pharmacophore of the Enediyne Antitumor Agents

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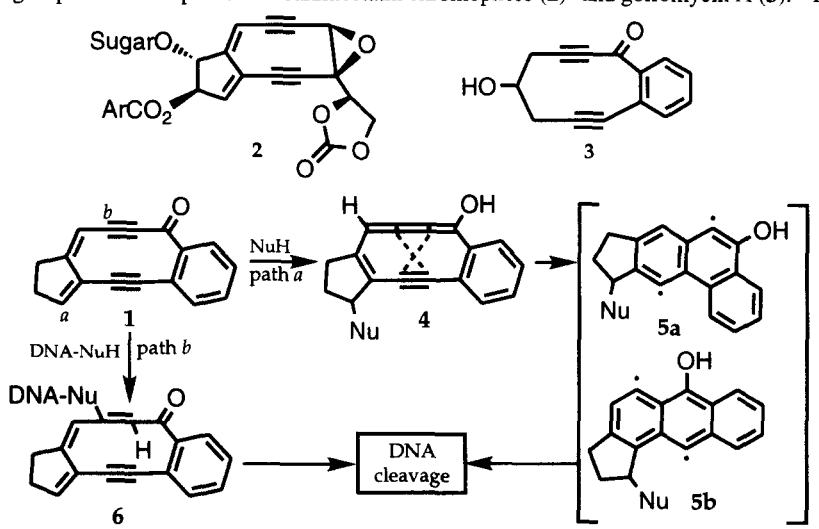
Abstract: A new designed tetradehydro[10]annulene quinomethide analogue **1**, which is a simplified analogue having combined structural features of neocarzinostatin chromophore and golfomycin A, was prepared. Cycloaromatization of **1** and Micheal-type addition of thiol to **16** which is a precursor of **1**, were also demonstrated.

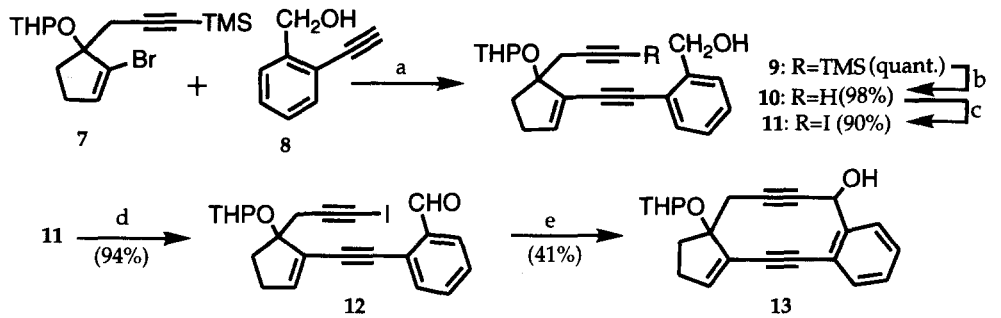
Synthetic and medicinal chemists have paid attention to the enediyne anticancer antibiotics which are rapidly emerging compounds derived from natural sources.[1] The family of compounds include neocarzinostatin, calicheamicins, esperamicins, and dynemicins. These antibiotics manifest their considerable biological activity in the form of DNA damage. The strand-scission is initiated by an arene diradical, the product of the thermally induced cyclization[2] of the enediyne functionality, which is present in each compound. From these biological and structural features, a great number of synthetic approaches for the construction of simpler compounds containing this pharmacophore have been published.[3] With the ultimate goal of developing functional analogues of these agents for potential use in chemotherapy, we have designed a new type tetradehydro[10]annulene quinomethide analogue, 6,7-benzobicyclo[8.3.0]trideca-1,6,10-triene-3,8-diyn-5-one (**1**) on the basis of overlapping of the acetylenic group of the core part of neocarzinostatin chromophore (**2**)[4] and golfomycin A (**3**).[5] The mechanistic



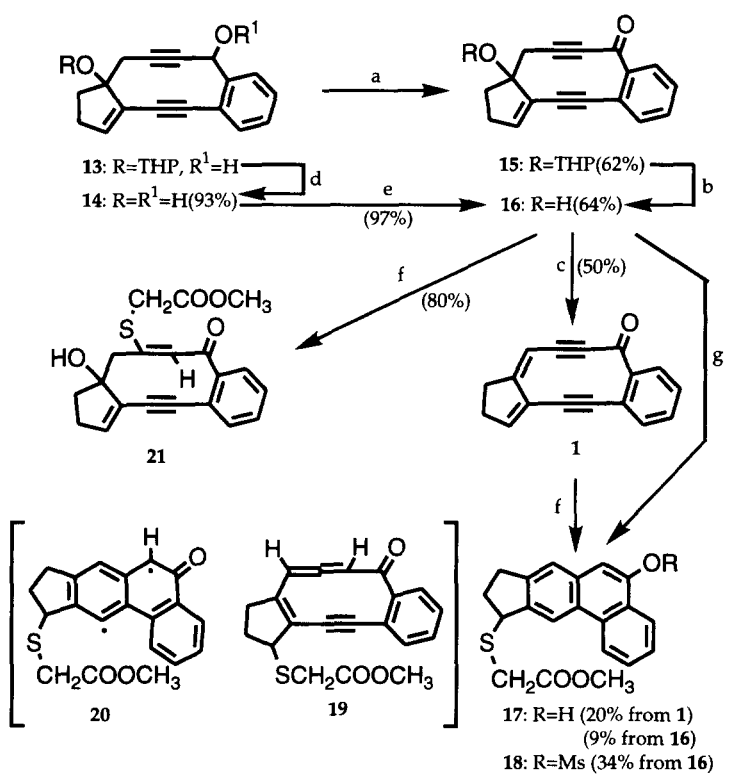
Scheme 1. Plausible mechanism of DNA cleaving action of **1**, path *a*: radical mechanism, path *b*: nucleophilic mechanism.

rationale that led to the design of **1** as a potential DNA-cleaving molecule is to be as follows: A nucleophilic attack at the position of *a* would lead to the cumulene-ene-yne structure (**4**), which is expected, on the basis of the reported results,[6] to undergo a facile cyclization to diradical (**5**). This radical is then expected to cleave DNA by a radical mechanism. Alternatively, nucleophilic addition by DNA-NuH at the position of *b* generates species (**6**)

which is projected to undergo chemistry leading to DNA cleavage via a nucleophilic mechanism in a manner similar to golfomycin A.



Scheme 2. Reagents and conditions: a: $PdCl_2(PhCN)_2$, CuI in piperidine, rt, 6 h. b: TBAF in THF, rt, 1 h. c: I_2, morpholine in benzene, 45 °C, 7 h. d: Dess-Martin periodinane in CH_2Cl_2, rt, 30 min. e: $CrCl_2/NiCl_2$ in THF, 0 °C, 5.5 h.



Scheme 3. Reagents and conditions: a: PDC in CH_2Cl_2, rt, 1 h. b: PPTS in MeOH, 55 °C, 3 h. c: MsCl, Et_3N, 1,4-cyclohexadiene in THF, 0 °C, 5 min. d: conc. HCl in THF, 0 °C, 2.5 h. e: Dess-Martin periodinane in CH_2Cl_2, rt, 45 min. f: $HSCH_2COOCH_3$, Et_3N, 1,4-cyclohexadiene in THF, 0 °C, 5 min. g: c, followed by f.

Reaction of **7**, prepared from 2-bromo-2-cyclopentenone[7] and $BrMgCH_2C{=}CTMS$[8], with **8** in the presence of $PdCl_2(PhCN)_2$ and CuI in piperidine gave **9** in quantitative yield. After removal of TMS group of **9** by treating with tetrabutylammonium fluoride (TBAF) in THF, **10** obtained was converted into iodo derivative **11** by a standard manner.[9] Compound **11** was subjected to Dess-Martin oxidation[10] to give aldehyde derivative **12**

in 94% yield. The key step conversion of **12** into the highly strained cyclic system was best effected by using a mixture of $CrCl_2$ and $NiCl_2$ in THF[11] at 0 °C for 5.5 h to give **13** in 41% yield. Dienediyne derivative **1** was prepared as follows: oxidation of **13** with pyridinium dichromate (PDC) gave **15** in 62% yield. Removal of tetrahydropyranyl (THP) group of **15** by treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol gave **16** in 64% yield. Compound **16** was also obtained in 93% yield by deprotection of THP group of **13**, followed by Dess-Martin oxidation. Compound **16** was treated with MsCl in the presence of triethylamine in THF to give the desired product **1**[12], which was purified in 50% yield by silicagel column chromatography at 0 °C with chloroform as an eluent. Compared with the high stability of **16**, **1** was found to be unstable at room temperature when kept neat. However, **1** in organic solvents such as chloroform, ether and benzene was considerably stable, compared with the neat.

The chemistry of **1** and **16** toward nucleophiles was then investigated using methyl thioglycolate as a model reagent.[13] Reaction of **1** with methyl thioglycolate in the presence of 1,4-cyclohexadiene and triethylamine gave **17** in 20% yield. On the other hand, **1**, prepared in situ from **16** and MsCl (3 equiv.), was allowed to react with methyl thioglycolate (2 equiv.) in the presence of triethylamine (8 equiv.) and 1,4-cyclohexadiene (34 equiv.) in THF at O °C for 5 min to give a mixture of **17** and **18**, which was to be methanesulfonylation product of **17**, in 9% and 34% yields, respectively. Compound **1** may be transformed upon treatment with methyl thioglycolate to intermediate **19** and then to diradical **20**.[14] Under similar conditions **16** furnished only Micheal-type addition product **21** in 80% yield.

In conclusion, this work shows the synthesis of a novel tetradehydro[10]annulene quinomethide system and its mode of action by a thiol addition. Our results demonstrate that this system has the ability to produce a phenanthrene derivative via the benzenoid diradical. The mechanism may be similar to that shown on the Hirama's product.[3a] Additionally, it has been shown that **16** gives a Micheal-type addition product suggesting the possibility of DNA cleavage via a nucleophilic mechanism.

Further studies toward the synthesis of more comlpex and more stable derivatives linked to a carrier with high affinity to DNA are in progress, although the evolution of the biological activity of **1**, **16**, and these analogues is under study.

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12. All new compounds in this paper gave IR, NMR, and mass spectral data consistent with the assigned structures and satisfactory elemental analyses and/or high-resolution mass spectroscopy except for **1** were obtained. Selected physical data. **1**: ^{1}H-NMR (270 MHz $CDCl_3$) δ (ppm) 2.77-2.72 (2H, m), 2.92-2.88 (2H, m), 5.81 (1H, m), 6.98 (1H, m), 7.66-7.46 (3H, m), and 8.35 (1H, m). **16**: colorless soild; IR ($CHCl_3$) 2200, 1625, and1585 cm^{-1}; UV ($CHCl_3$) λmax (log ε) 352 (3.79), 286 (4.24), and 262 (4.58) nm; HRMS (EI) Found: m/z 248.0837. Calcd for $C_{17}H_{12}O_2$: M^+, 248.0836; ^{1}H-NMR (270 MHz $CDCl_3$) δ (ppm) 1.98 (1H, ddd, J=14.0, 8.8, 5.4 Hz), 2.20 (1H, ddd, J =14.0, 8.8, 4.4 Hz), 2.51 (1H, dddd, J=18.8, 8.8, 4.4, 2.7 Hz), 2.65 (1H, dddd, J=18.8, 8.8, 5.4, 2.7 Hz), 2.84 (1H, bs), 2.94 (1H, d, J=17.7 Hz), 3.04 (1H, d, 17.7 Hz), 6.24 (1H, t, J=2.8 Hz), 7.43 (1H, m), 7.54-7.51 (2H, m), 8.18 (1H, td, J=7.9, 1.0 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ (ppm) 30.1, 33.2, 37.5, 80.9, 84.3, 92.8, 93.2, 94.8, 124.1, 128.6, 129.5, 129.6, 132.8, 133.1, 136.7, 138.6, and 175.6. **17**: colorless oil; IR (neat) 3400 and 1725 cm^{-1}; UV ($CHCl_3$) λmax (log ε) 361 (3.39), 343 (3.37), 306 (4.08), and 259 (4.79) nm; HRMS (EI) Found: m/z 338.0969. Calcd for $C_{20}H_{18}O_3S$: M^+, 338.0976; ^{1}H-NMR (270 MHz $CDCl_3$) δ (ppm) 2.27 (1H, m), 2.63 (1H, m), 3.04 (1H, m), 3.27 (1H, m), 3.32 (2H, s), 3.75 (3H, s), 4.69 (1H, dd, J=7.2, 4.0 Hz), 5.40 (1H, s), 6.96 (1H, s), 7.53 (1H, s) 7.63 (1H, ddd, J=7.5, 6.9, 1.3 Hz), 7.67 (1H, ddd, J=7.5, 6.9, 1.3 Hz), 8.28 (1H, dd, J=7.5, 1.3 Hz), 8.58 (1H, s), and 8.67 (1H, dd, J=7.5, 1.3 Hz); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ (ppm) 30.6, 32.9, 34.0, 49.1, 52.5, 106.2, 118.7, 122.2, 122.3, 122.8, 125.2, 125.8, 126.1, 127.2, 131.6, 132.9, 139.4, 143.1, 149.6, and 171.3. **21**: colorless prisms (from ether) mp 122-123 °C; IR ($CHCl_3$) 3575, 3475, 2250, 1735, 1640, 1595, and 1550 cm^{-1}; UV ($CHCl_3$) λmax (log ε) 330 (3.89), 291 (4.27), 272 (4.24), and 254 (4.26) nm; *Anal.* Found: C, 67.81; H, 5.09; S, 8.96%. Calcd for $C_{20}H_{18}O_4S$: C, 67.78; H, 5.12; S, 9.05%.; ^{1}H-NMR (270 MHz $CDCl_3$) δ (ppm) 2.01 (1H, m), 2.22 (1H, m), 2.47 (1H, m), 2.64 (1H, m), 3.00 (1H, s), 3.01 (1H, d, J=14.2 Hz), 3.31 (1H, d, J=14.2 Hz), 3.62 (1H, d, J=15.7 Hz), 3.67 (3H, s), 4.07 (1H, d, J=15.7 Hz), 6.29 (1H, t, J=2.8 Hz), 7.31 (1H, s) 7.52-7.39 (3H, m), and 7.99 (1H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ (ppm) 29.3, 34.8, 39.8, 47.6, 52.5, 81.4, 95.3, 95.7, 123.1, 128.6, 129.4, 129.7, 130.8, 131.5, 132.0, 140.3, 141.3, 142.9, 170.3, and 190.5.
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