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Activation of a Dienediyne Model of Neocarzinostatin Chromophore through an Acid Mediated Solvolysis. Evidence for a New Cyclization Mode of Enyne[3]cumulenes

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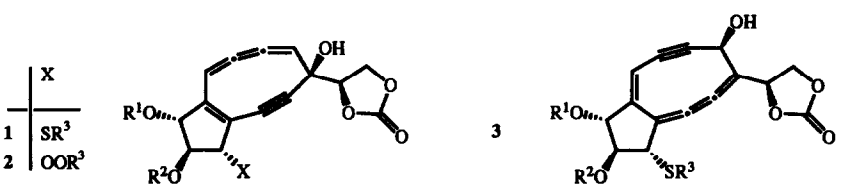
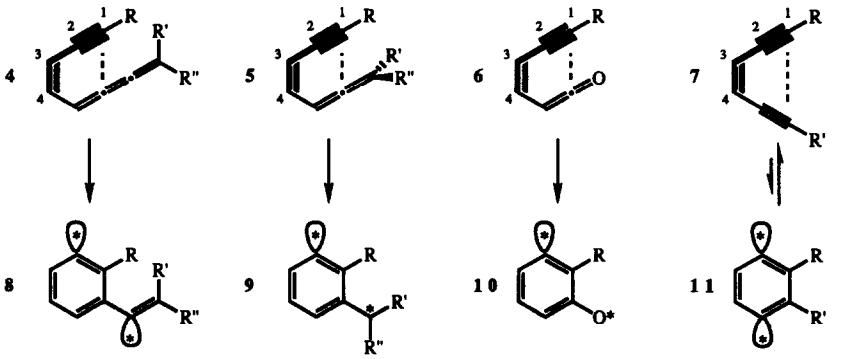
Abstract: When treated with 0.1 equiv. of triflic acid, a solution of the *Z*-configurated dienediyne **19** in a 2:3 mixture of *tert*-BuSH and CH_2Cl_2 furnished the brightly yellow enyne[3]cumulene **20** through a S_N''-reaction. **20** reacted at room temperature through a Saito-Myers cyclization to the substituted styrenes **31** and **24** and through an unprecedented cycloisomerization to the anthracene **25**.

Neocarzinostatin chromophore ("NCS") [1] is a bicyclic dienediyne which cleaves DNA [2] upon activation as one of the enyne[3]cumulenes **1** [3], **2** [4], or **3** [5]. These species contain nine-membered rings which are enyne[3]cumulenes. This makes them so strained that they undergo a so-called cycloaromatization of type **4**→**8** at physiological temperature or even below: A benzenoid biradical is formed [4]. It saturates its half-empty orbitals rapidly through uptake of H atoms from DNA in vivo or from 1,4-cyclohexadiene added during almost all laboratory cycloaromatizations of that kind [3b-c, 6].

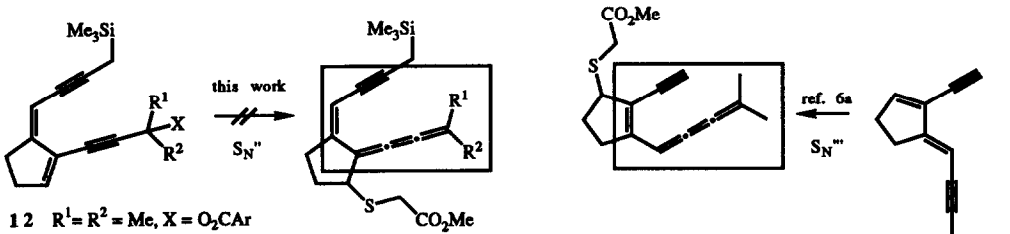


Cycloaromatizations with bond formation between the terminal carbon atom C-1 of a conjugated enyne C=C-C≡C and an sp-hybridized C-6 are known not only for the NCS-type **4**→**8**. Related processes are the Saito[7]-Myers [8] cyclization of enyne allenes **5** leading to σ,π-biradicals **9** [9-11]; the Moore cyclizations of enyne ketenes **6** providing the oxa analogs **10** of **9** [12]; and the Bergman cyclization of enynes **7** giving the biradicals **11** [2a, 13]. The Bergman reaction is favored in the cyclization mode to the *localized* σ,σ-biradical **11** only if its inherent endothermicity [9, 14] is overcompensated by the concomitant loss of ring strain. Since the NCS type cycloaromatization **4**→**8** gives a *localized* σ,σ-biradical, too, it might also be inherently endothermic unless additionally strain energy is released. Nonetheless, Hirama *et al.* were able to cycloaromatize the unstrained enyne[3]cumulene **16** in refluxing 1,4-cyclohexadiene by the NCS type process **4**→**8** [6a]. **16** constitutes a *monocyclic analog of forms 1/2 of activated NCS*. It was derived from the 3,5-dinitrobenzoate **17** by an S_N''' substitution with methyl thioglycolate in the presence of NEt_3.

We wanted to prepare a *monocyclic analog of form 3 of activated NCS*. First, we tested Hirama's conditions in an attempted S_N'' reaction between the 3,5-dinitrobenzoate **12** and methyl thioglycolate. But in-

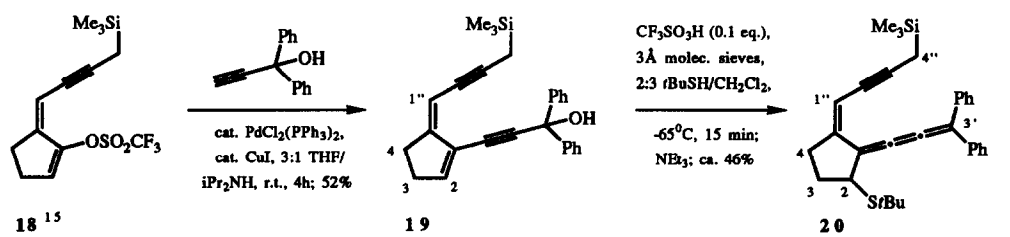


stead of enyne[3]cumulene **15** ($R^1 = R^2$ = Me) we found unreacted starting material or observed decomposition. Mesylate **13** did react with HS-CH_2-CO_2Me/NEt_3 but provided the dienediyne **14** by a direct S_N reaction rather than the desired S_N'' product.



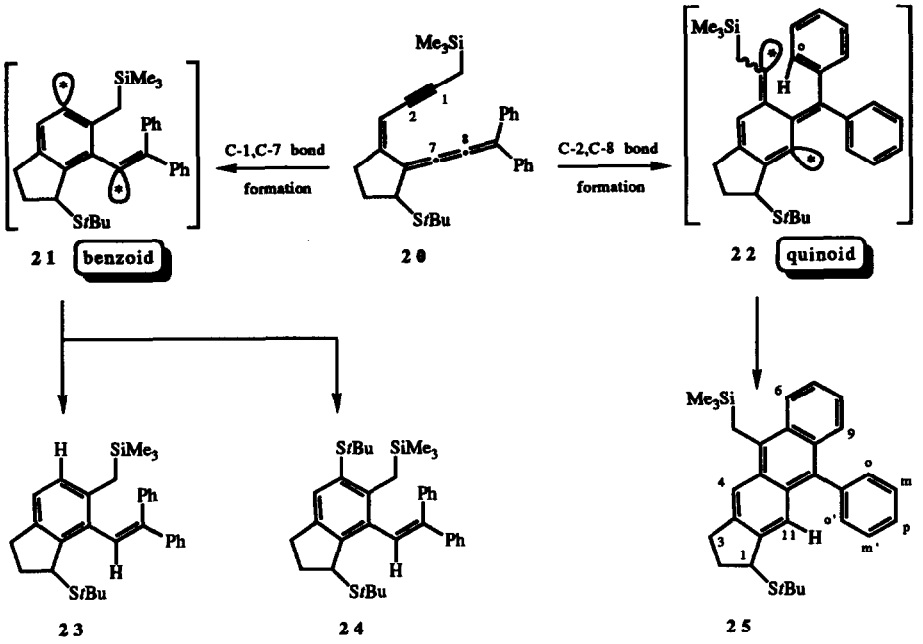
12 $R^1 = R^2$ = Me, X = O_2CAr
13 R^1 = Ph, R^2 = H, X = OMs
14 R^1 = Ph, R^2 = H, X = SCH_2CO_2Me

Success came after a Pd(0)/CuI mediated coupling of the earlier described enoltriflate **18** [15] with 1,1-diphenylpropargyl alcohol giving the *Z*-configurated dienediyne **19** [16]. When **19** was dissolved in 2:3 *tert*-BuSH/CH_2Cl_2 and treated at -65°C with 0.1 equiv. of triflic acid in the presence of 3Å molecular sieves, we obtained a brightly yellow solution. After addition of NEt_3, aqueous workup, and flash chromatography, we isolated a dark-red foam. We believe that it was a slightly contaminated sample of cumulene **20**. Indicative for structure **20** are (1) the single olefinic ^{1}H-NMR signal at δ 5.56 (m_c, 1''-H) vs. δ_{19} 5.50 (m_c, 1''-H) and 6.59 (m_c, 2-H); (2) the appearance of a triplet at δ_{20} 4.04 ($J_{2,3}$ = 6.1 Hz, 2-H) instead of the singlet at δ_{19} 2.97 (OH); and (3) that 4''-H_2 appears as an AB part of an ABX spectrum rather than an A_2 part of an A_2X spectrum (δ_A = 0.88, δ_B = 0.97, J_{AB} = 16.4 Hz, $^5J_{A,1'}$ = 3.1 Hz, $^5J_{B,1'}$ = 3.3 Hz): The anisochrony of these protons cannot be due to the remote stereocenter at C-2; it must reflect a distortion out of the cumulene plane of the otherwise too proximate phenyl group at C-3' including its quatenary center.

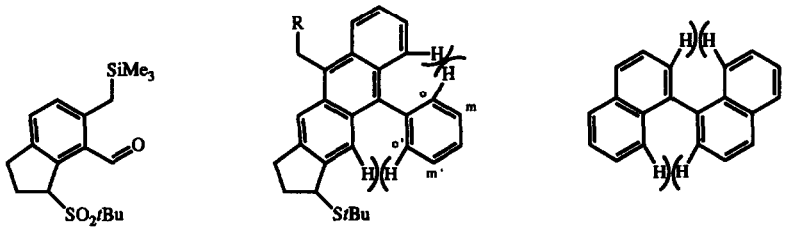


18 [15] **19** **20**

Our failure to obtain cumulene **20** entirely pure was at least partly due to its reactivity. When, for example, **20** was kept in the *tert*-BuSH/CH_2Cl_2/NEt_3 mixture in which it was formed for 4 d at room temperature, it disappeared completely (HPLC monitoring). Two new compounds were detected by their UV absorptions. They were isolated by preparative HPLC and assigned the styrene structures **23** (4% yield) and **24** (2% yield) on the basis of their high resolution mass, ^{1}H-NMR, and ^{13}C-NMR spectra. Ozonolyses of **23** and **24** gave benzophenone (69% and 68%, respectively) in accordance with the proposed structures; in addition, we obtained the sulfonyl aldehyde **26** (42%) starting from **23**.



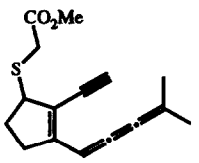
Also, we tried to purify by HPLC (RP-18 silica, MeOH/H_2O 97.5:2.5) cumulene **20** which when obtained by flash chromatography was still contaminated. We were surprised to isolate - guided by a strong UV absorption - in 10% yield an *isomer* $C_{31}H_{36}SSi$ according to the high resolution mass spectrum. It constitutes a cyclopenta[b]anthracene as deduced from 1D (^1H, ^{13}C) [17] and 2D NMR experiments (H,H-COSY, delayed H,H-COSY, C,H correlation). This assignment was corroborated by desilylation with excess Bu_4NF in THF (room temp., 3h) giving **27** (39% after preparative HPLC). The ^1H-NMR spectrum of **27** showed a singlet at δ 3.13 for Ar-CH_3 instead of the singlet at δ 3.17 for Ar-CH_2-$SiMe_3$. Interestingly, the phenyl substituent in the anthracenes **25** and **27** cannot rotate freely on the time scale of the ^1H-NMR experiment since *ortho*- and *ortho'*-H possess different chemical shifts as do *meta*- and *meta'*-H. The rotational barrier is caused by two interactions which are also present - although differently arranged with respect to each other - in 1,1'-binaphthyl (**28**) and cause a rotational barrier of 21-23 kcal/mol there [18].



The molecular formula of styrene **23** (**24**) differs from that of **20** by an uptake of $H_2(C_4H_{10}S)$. Their formation would therefore be explicable with the assumption that cumulene **20** undergoes a NCS-type cycloaromatization through bond formation *between C-1 and C-7* delivering the *benzenoid* biradical **21**. **21** would give the isolated products by H atom transfer from *tert*-BuSH (2 x →**23**) or by one such H transfer plus a radical recombination reaction with the by-product *tert*-BuS· thereof (→**24**).

Quite differently, anthracene **25** has the same molecular formula as cumulene **20**. The transformation **20**→**25** is novel and includes no cyclo*aromatization*. **20**→**25** seems to begin with bond formation *between C-2 and C-8* which would give *quinoid* σ,σ-biradical **22**. A subsequent radical cyclization - also interpretable as a 1,6-electrocyclization - would lead to a cyclopenta[b]anthracene derived σ,π-biradical as an immediate pre-

cursor of the final product **25**.- In view of this rational Hirama's spontaneous conversion of enyne[3]cumulene **16** into benzocyclobutene **29** via the σ,π-biradical **36** might have to be supplemented by a previously unconsidered [6a] intermediate, namely the *quinoid* σ,σ-biradical **31**: **16**→**31** would be completely analogous to **20**→**22**.



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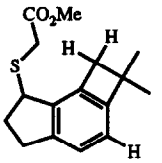

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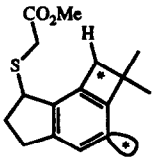

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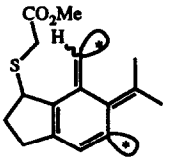

31

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17. ^{1}H NMR (500 MHz, $CDCl_3$; *J* in Hz): δ = 0.03 [s, $Si(CH_3)_3$], 1.33 (s, tBu), 2.14 (dddd, J_{gem} = 12.5, $J_{2\text{-}H(1),1}$ = $J_{2\text{-}H(1),3\text{-}H(1)}$ = $J_{2\text{-}H(1),3\text{-}H(2)}$ = 8.0, 2-H^1), 2.61 (dddd, J_{gem} = 12.4, $J_{2\text{-}H(2),1}$ = $J_{2\text{-}H(2),3\text{-}H(1)}$ = 7.6, $J_{2\text{-}H(2),3\text{-}H(2)}$ = 4.8, 2-H^2), 3.03 (dddd, J_{gem} = 15.9, $J_{3\text{-}H(1),2\text{-}H(1)}$ = $J_{3\text{-}H(1),2\text{-}H(2)}$ = 7.9, $J_{3\text{-}H(1),1}$ = 1.3, 3-H^1), 3.17 (s, CH_2SiMe_3), 3.21 (dddm$_c$, J_{gem} ≈ 16, $J_{3\text{-}H(2),2\text{-}H(1)}$ ≈ 8.5, $J_{3\text{-}H(2),2\text{-}H(2)}$ ≈ 5, 3-H^2), 4.25 (ddd, $J_{1,2\text{-}H(1)}$ = $J_{1,2\text{-}H(2)}$ = 7.5, $J_{1,3\text{-}H(1)}$ = 1.5, 1-H), 7.26 (ddd, $J_{8,9}$ = 8.8, $J_{8,7}$ = 6.3, $J_{8,6}$ = 1.1, 8-H), 7.37 (dm$_c$, $J_{o,m}$ ≈ 7.0, *o*-H), 7.40 (ddd, $J_{7,6}$ = 8.9, $J_{7,8}$ = 6.4, $J_{7,9}$ = 1.3, 7-H), 7.45 (dm$_c$, $J_{o',m'}$ ≈ 7.6, *o'*-H), 7.49 (dddd, $J_{p,m}$ = $J_{p,m'}$ = 7.3, $J_{p,o}$ = $J_{p,o'}$ = 1.5, *p*-H), 7.52 (dddd, $J_{m,o}$ = $J_{m,p}$ = 7.3, $J_{m,m'}$ = 1.6, $J_{m,o'}$ = 0.5, *m*-H), 7.57 (dddm$_c$, $J_{m',o'}$ = $J_{m',p}$ = 7.2, $J_{m',m}$ = 1.7, *m'*-H), 7.61 (m$_c$, 11-H), superimposes the high-field branch of 7.62 (dm$_c$, $J_{9,8}$ ≈ 10, 9-H), 8.00 (br. s, 4-H), 8.18 (br. d, $J_{6,7}$ = 8.9, 6-H); assignments of o-/o'-H and m-/m'-H interchangeable.
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