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SYNTHESIS OF A BICYCLIC OXACYCLOALKENEDIYNE SYSTEM RELATED TO NEOCARZINOSTATIN CHROMOPHORE A

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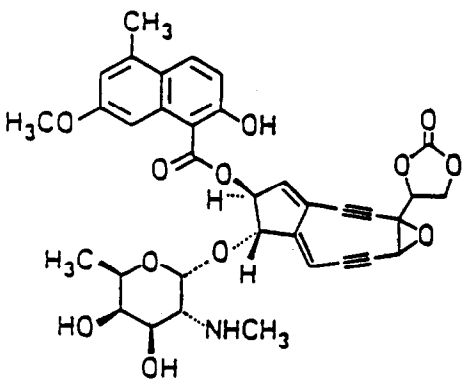
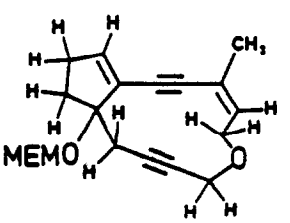
Abstract: The synthesis of a stable bicyclic 12-membered oxacycloalkenediyne 2 related to the neocarzinostatin chromophore A 1 is described.

Neocarzinostatin chromophore [1] (NCS-Chrom) is a member of a novel class of powerful antitumor antibiotics with a highly unusual cycloalkenediyne structure. Other examples are esperamicin,[2a] calicheamicin [2b] and dynemicin A.[3] Responsible for the biological activity of NCS-Chrom is a unprecedented, highly strained epoxybicyclo[7.3.0]dodecadienediyne system. The structure of NCS-Chrom was elucidated by Edo and coworkers.[4] The proposed mechanism for DNA damage involves activation of the chromophore by a thiol function. Generation of a very reactive biradical which abstracts a hydrogen from C-5' of the DNA backbone induces strand scission upon aerobic incubation.[5]

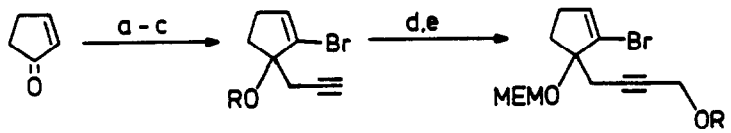


1



2

Not only due to the extraordinary potency toward diseased cells but also because of the unexpected structure of this natural product, it has been a great challenge to find a useful synthetic approach to the bicyclic core of NCS-Chrom. The first synthesis of the parent bicyclic subunit of NCS-Chrom has been published by Wender et al.[6] and recently Hirama and co-workers have synthesized stable 10-membered analogues.[7] Our synthetic effort is concentrated on the synthesis of a functionalized core of NCS-Chrom and related model systems. Here we describe the synthesis of a stable bicyclic oxaalkenediyne system, starting from cyclopentenone 3.



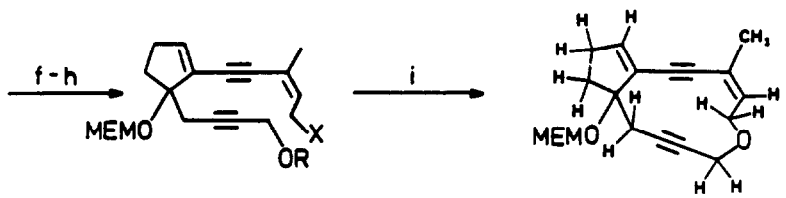
3

4 : R = H

5 : R = MEM

6 : R = H

7 : R = $SiMe_2tBu$



8 : R = $SiMe_2tBu$, X = OH

9 : R = -"- , X = Br

10 : R = H , X = Br

2

MEM = $CH_3OCH_2CH_2OCH_2$-

a) Br_2, Et_3N, CH_2Cl_2, 0°C ⟶ RT; b) $HCCCH_2MgBr$, Et_2O, RT; c) MEMCl, $(iPr)_2NEt$, CH_2Cl_2, 77%; d) LDA, -78°C; $[CH_2O]_n$, -78°C ⟶ RT, 75%; e) TBDMSiCl, imidazole, DMF, 96%; f) $HC{\equiv}C(CH_3)C{=}CCH_2OH$, $Pd(PPh_3)_4$, CuI, $PrNH_2$, 92%; g) SMe_2, NBS, CH_2Cl_2; 0°C, 61%; h) Bu_4NF, THF, 0°C, 54%; i) 50 %aq NaOH, TEBA-Cl, Et_2O, RT, 50%.

Bromination and dehydrobromination of the commercially available cyclopentenone 3 gave the bromocyclopentenone [8] which was exposed to propargylmagnesium bromide to give the acetylene 4.[6] Protection of the tertiary alcohol with methoxyethyloxymethyl chloride [9] (MEMCl) provided 5 in 77% yield. Transmetallation with lithium diisopropylamide (LDA) and condensation with paraformaldehyde afforded the alcohol 6 in 75% yield followed by silylation with tert.butyldimethylsilyl chloride which was achieved in 96% yield. Palladium catalyzed coupling of the vinyl bromide 7 with 1-hydroxy-3-methyl-2(Z)penten-4-yne gave the bisacetylenic alcohol 8 in excellent yield (92%). Cocatalysis with CuI is essential for this reaction.[10] Treatment of 8 with dimethyl sulfide, N-bromosuccinimide in methylene chloride [11] afforded the bromide 9 in 61% yield. Desilylation with tetrabutylammonium fluoride yielded the alcohol 10 (54%) as a potential precursor for the cyclisation. Slow addition of 10 to a vigorously stirred solution of aqueous NaOH (50%), diethyl ether and benzyltriethylammonium chloride as phase transfer catalyst gave 2 as a pale yellow oil in 50% yield.

The cycloalkenediyne 2 is characterized by spectroscopic data.[12] Most revealing was the detailed ^{1}H-NMR- and H,H-COSY-NMR-spectrum. It is interesting that one of the allylic protons appears at 4.05 ppm and the other at 4.57 ppm. This high field shift is in accord with the structure of 2 because one of the allylic protons is located in the anisotropic shielding cone of the two triple bonds.
Hitherto a novel route to the 9-membered core of the NCS-Chrom via a [2,3] sigmatropic Wittig-ring contraction has failed.
Further studies toward the synthesis of neocarzinostatin chromophore aglycone and model systems are in progress in our laboratories.

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12) All compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, CI-MS, IR spectroscopy and elemental analysis.

2: ^{1}H-NMR ($CDCl_3$, 250 MHz):

δ= 1.72-1.82 (m,1H,CH_2), 1.8 (d,^{4}J=1.59 Hz,3H,CH_3), 2.20-2.53 (m,3H,CH_2), 2.42 (dt,J_{AB}= 17.07Hz, J_{AX}=J_{BX}= 1.79 Hz,1H,C<u>H</u>-C≡C), 2.84 (dt,2H,J_{AB}= 17.07 Hz,J_{AZ}=J_{BZ}= 2.18 Hz,1H,C<u>H</u>-C≡C), 3.32 (s,3H,OCH_3), 3.50 (t,2H,$OCH_2C\underline{H}_2OCH_3$), 3.60-3.90 (m,2H,$OC\underline{H}_2CH_2OCH_3$), 4.01, 4.11 (mc,$J_{XZ}$=15.88 Hz,$J_{AX}$=$J_{BX}$= 1.79 Hz,$J_{AZ}$=$J_{BZ}$= 2.18 Hz,2H,C≡CC<u>H</u>$_2$O), 4.05 (m,1H,C=CC<u>H</u>O), 4.57 (dd,^{2}J= 10.72 Hz,^{3}J=8,54 Hz,1H,C=CC<u>H</u>O), 4.84 (AB,2H,OC<u>H</u>$_2$O), 5.75 (m,^{3}J= 8.54 Hz,^{4}J=8.59 Hz,1H,H_3CC=C<u>H</u>), 6.26 (t,^{3}J= 2.7 Hz,1H,olefin.H) ppm.

^{13}C-NMR ($CDCl_3$, 62.896 MHz):

δ = 22.59 (1C,CH_3), 30.05, 30.79 (each 1C,CH_2), 36.17 (1C,<u>C</u>H$_2$C≡C), 56.04 (1C,C≡C<u>C</u>H$_2$O), 58.97 (1C,OCH_3), 64.63 (1C,C=C<u>C</u>H$_2$O), 67.36, 71.78 (each 1C,OCH_2CH_2O), 78.54, 84.24, 89.06, 89.79, (each 1C, C≡C), 91.45 (1C,OCH_2O), 91.50 (1C,C_q), 126.96 (1C,C≡C-<u>C</u>=C), 127.89 (1C,HC=<u>C</u>R$_2$), 131.48 (1C,C≡C-C=<u>C</u>), 142.06 (1C,H<u>C</u>=CR$_2$) ppm.

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