Tetrahedron Letters, Vol.31, No.51, pp 7437-7440, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF A NEW 10 -MEMBERED RING FUNCTIONALISED CYCLODIYNOL RELATED TO NEOCARZINOSTATIN CHROMOPHORE

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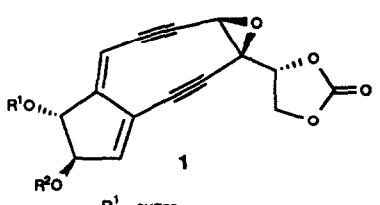
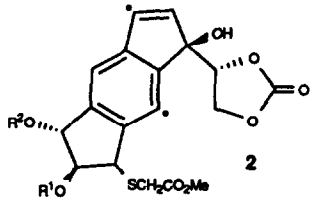
Summary: The diyne system **5** is synthesized from 2-bromobenzaldehyde in eight steps through an intramolecular allylsilane-terminated cyclisation .

The antitumor agent neocarzinostatin **1**[1] was discovered in 1965, but its structure was only unambigously assigned[2] in 1985. It consists of a protein subunit non-covalently complexed to a very labile non-protein chromophore **1** (so called NCS chrom). The unusual structure of this and related compounds calichemicin[3], esperamicin[4], dynemicin[5] as well as their very high activity as antitumor agents has generated interest in the synthesis of cyclic molecules containing an enediyne system[6].



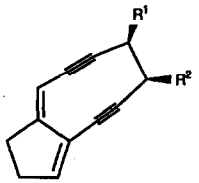


It was recently demonstrated that the bicyclic core plays an important role in the mechanism of action of NCS chrom **1**[7]. This highly strained unsaturated bicyclo[7,3,0]-dodecadienediyne nucleus is very unstable and is rapidly deactivated by UV light or by nucleophiles[8].

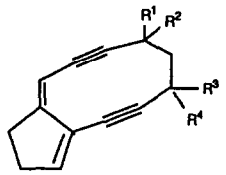
In the presence of a thiol under aerobic conditions, NCS chrom **1** binds to DNA by intercalation of the naphtoate ester, thus positioning the strained bicyclic system in the minor groove of DNA and selectively cleaving the desoxythymidine and deoxyadenosine residues[9] . Evidence to support that the active intermediate is the biradical **2**, which

abstracts hydrogen from DNA has been obtained[10]. Such a biradical has also been proposed for the action of calichemicin , esperamicin[11] and dynemicin[12].

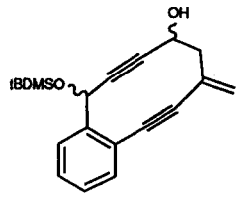
The design and synthesis of new molecules containing properly positioned triple bonds wich mimic the biological activity of NCS chrom 1 , but wich are more stable , are of interest as chemotherapeutic agents . We recently reported the first synthesis of the parent carbocyclic subunit **3a** of NCS chrom 1[13], and showed the instability of such a 9-membered ring (half-time life ≈ 48h at 20°C).Related compound **3b**[14] and the 10-membered ring analogue **4**[15] have been synthesized .



3a $R^1=R^2=H$
3b R^1=OAc , R^2= vinyl

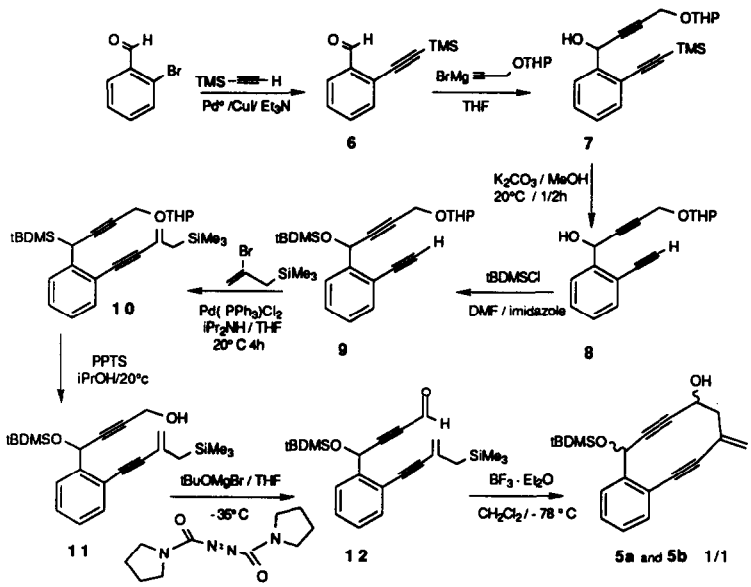


4a R^1,R^2 = O $R^3=R^4$= Me
4b R^1=OAc R^2=H $R^3=R^4$= Me
4c $R^1=R^2$=Me R^3,R^4=O



5

We present here the synthesis of the enediyne system **5**, which may undergo rapid cyclisation upon removal of the tBDMS group to provide a diradical species . Thus , reaction of (trimethylsilyl)acetylene with 2-bromobenzaldehyde using a modified Lau[16] procedure , ($Pd(PPh_3)_3Cl_2$/CuI ; THF/Et_3N 5/1 ; 25°C), gave the 2-[(trimethylsilyl)ethynyl]benzaldehyde **6** in 80% yield. Addition to **6** of the Grignard reagent prepared from THP-protected propargylic alcohol by treatment with EtMgBr , followed by deprotection of the TMS group by K_2CO_3 /MeOH[16] provided the secondary alcohol **8** (90% yield for the 2 steps) as a mixture of inseparable diastereomers[17]. This secondary alcohol was protected with tBDMSCl in the presence of imidazole in DMF[18] at 20°C to afford **9** in 85% yield .The coupling of the terminal alkyne **9** . with 2-bromoallyltrimethylsilane[19] in the presence of a catalytic amount of $Pd(PPh_3)_3Cl_2$/CuI in a mixture of THF/iPr_2NH 5/1 at 20°C for 4h led to the propargylic allylsilane **10** in 94% yield . The selective deprotection of the THP group of **10** in the presence of PPTS in EtOH or MeOH gave **11** respectively in only 53 % and 62% yields . However reaction of **10** with PPTS in iPrOH furnished the desired propargylic alcohol **11** in 81% yield . The next goal in this synthesis was the oxidation of alcohol **11** into the aldehyde **12** . Several classical oxidation procedures like PCC[20] , PCC/4Åsieves [21] , Swern oxidation[22] or MnO_2[23] only produced a low yield of **12** or degradation products . Eventually this oxidation was successfully achieved following the Saigo[24] procedure : reaction of **11** with tBuOMgBr in THF at -25°C followed by addition of 1,1-(azodicarbonyl)dipiperidide and slowly warming the solution to 20°C provided **12** , isolated in 90% yield as a clear yellow oil .



Intramolecular cyclisations using allylsilanes has been reported by several group[25]. The key reaction to induce the cyclisation of compound **11** was based on the property of allylsilanes to attack aldehydes or ketones in the presence of a Lewis acid or a fluoride anion[26,27]. Thus, when **12** was treated at -78°C in CH_2Cl_2 with 3 equivalents of $BF_3{\cdot}Et_2O$, **5** was isolated in 47% yield as a mixture of two separable diastereomers **5a** and **5b** in a ratio 1/1 . The structures of both diastereomers were confirmed by ^{1}H-NMR ,^{13}C-NMR , IR , and MS analysis[28] . Both diastereomers are crystalline compounds , stable at room temperature and can be stored at -40°C without degradation . Several other Lewis acids such $TiCl_4$, $SnCl_4$, Et_2AlCl ,Me_2AlCl or nBu_4NF gave lower yields or degradation products .

Experiments to improve this cyclisation and synthesis of other analogs of **5** , as well as preliminary biological tests on the ability of **5** to cleave DNA are in progress and will be reported in due course.

Acknowledgements: We thank the CNRS for financial support and Dr. A.Solladié-Cavallo for research facilities.

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28. Selected physical parameters of new compounds **12** , **5a** and **5b** :

12 IR(film) ν 2940,2850,2240,2180,1670,and 1250 cm^{-1} ;^{1}H-NMR 200MHz($CDCl_3$) δ 0.11(6H,s,$SiMe_2$), 0.13 (9H,s,$SiMe_3$), 0.93(9H,s,tBu), 1.79(2H,d,^{4}J=0.8Hz,CH_2SiMe_3) , 5.15(1H,d,^{2}J=1.8Hz,vinylic H) ,5.33 (1H,d,^{2}J=1.8Hz , vinylic H) , 6.03(1H, s, CHOtBDMS) , 7.26-7.70(4H, m, aro.), 9.22(1H, s, CHO); ^{13}C- NMR 50MHz($CDCl_3$) δ - 4.99, - 4.78 , -1.62, 0.52 , 18.23 , 25.67 , 28.00, 62.85 , 83.61 , 85.00 , 96.28 , 97.60, 119.71 , 120.91 , 126.38 , 128.20 , 128.56 , 128.79 ; 131.97, 141.00 ; 176.51;**5a** $C_{21}H_{26}O_2Si$ MS-CI(NH_3) $[M+NH_4]^+$ 356 ; IR($CHCl_3$) ν 3590, 2950, 2920, 2850 , 2235, 1620, 1460, 1375 , 1250, cm^{-1} ; ^{1}H-NMR 200MHz($CDCl_3$) δ 0.19 (3H,s,$SiCH_3$) , 0.20(3H , s ,$SiCH_3$) , 0.95(9H, s,tBu) , 2.03(1H , broad s , OH) 2.72(2H, AB part of an ABX system , J_{AB}=24Hz, J_{AX}=7.3Hz , J_{BX}=3.5Hz Δν =31Hz , allylic CH_2) , 4.55(1H , m, X part of ABX system, CHOH), 5.38 (1H , d, ^{2}J=1.6Hz , vinylic H) , 5.50(1H , d, ^{2}J=1.6Hz , vinylic H), 5.65(1H , s , CHOtBDMS) , 7.21-7.53(4H , m, aro.) ; ^{13}C-NMR 50MHz($CDCl_3$) δ = - 4.77 , -4.22 , 18.26 , 25.80 , 44.54 , 61.55 , 64.09 , 87.22 , 88.43 , 92.79 , 96.16 , 120.48 , 123.14 , 126.52 , 127.47 , 128.05 , 128.65 , 132.09 , 140.76 ; **5b** $C_{21}H_{26}O_2Si$ MS-CI(NH_3) $[M+NH_4]^+$ 356 ; IR($CHCl_3$) ν 3590, 2950, 2920, 2850 , 2235, 1620, 1460, 1375 , 1250, cm^{-1} ; ^{1}H-NMR 200MHz ($CDCl_3$) δ 0.20(6H , s, $Si(CH_3)_2$) , 0.96 (9H , s , tBu), 1.90(1H , broad s , OH), 2.73 (2H , AB part of ABX system , J_{AB}=25Hz , J_{AX}=7Hz , J_{BX}=3.3Hz , Δν 33Hz , allylic CH_2) , 4.58 (1H, X part of ABX system , ddd , J_{AX}=7Hz , J_{BX}=3.3Hz , ^{5}J=1.3Hz , CHOH) , 5.39(1H,d, ^{2}J=1.5Hz , vinylic H) , 5.51(1H , d, ^{2}J=1.5Hz , vinylic H) , 5.64 (1H , s , CHOtBDMS) , 7.22-7.54(4H ,m , aro); ^{13}C-NMR 50MHz ($CDCl_3$) δ = - 4.77 , - 4.21 , 18.28 , 25.83 , 44.08 , 61.42 , 63.95 , 87.27 , 88.63 , 92.90 , 96.17 , 120.46 , 123.56 , 126.45 , 127.46, 127.75 , 128.70 , 132.22 , 140.79 .

(Received in France 2 October 1990)