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## Novel Synthesis of a Chiral Cyclic Dienediyne System Related to the Neocarzinostatin Chromophore

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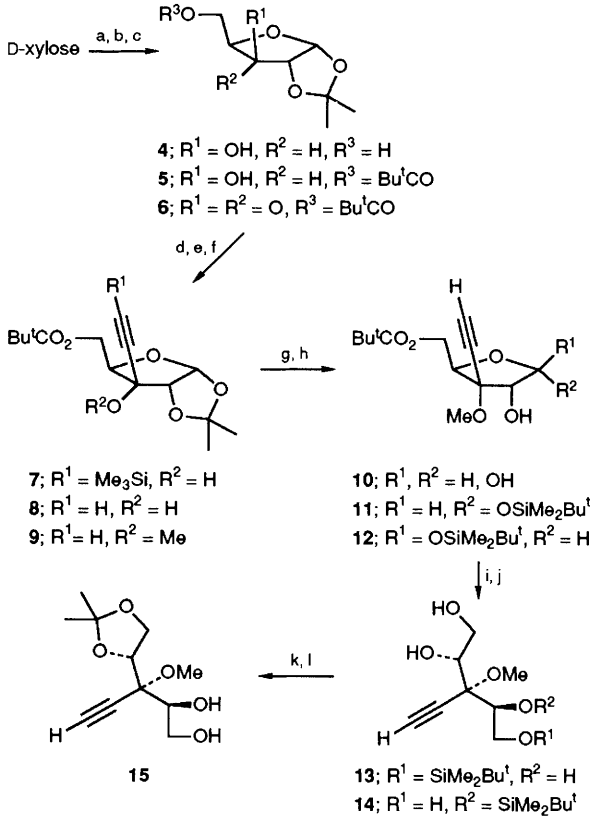
By successive treatment with lithium bistrimethylsilylamide and boron trifluoride–diethyl ether in tetrahydrofuran at −78 °C optically active (*Z*)-dienediyne epoxide **20** prepared from D-xylose and (*Z*)-enol triflate **16** is found to undergo smooth cyclization to afford the title compound.

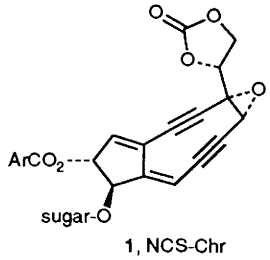
Neocarzinostatin chromophore **1** (NCS-Chr),[1,2] the active component of the antitumour antibiotic neocarzinostatin (NCS),[3] is a structurally novel DNA cleaving agent, and has attracted much attention recently because of its biological properties[4] and its interesting bicyclo[7.3.0]dodecadienediyne system.[5] Since it was discovered that **1** is extremely unstable upon separation from the peptide residue of NCS (apo-NCS), the synthesis of more stable analogues retaining the functions of **1** has become a challenging problem. While several groups have reported synthetic schemes directed towards cyclic analogues of **1**,[6] Wender's procedure ingeniously employing a cyclization–dehydration sequence[6a] has only been employed for final installation of the dienediyne system.[7]

From the viewpoint of the synthesis of various analogues of **1** and of **1** itself, a synthetic scheme featuring formation of the dienediyne system prior to ring construction was expected to be a candidate. In our previous report,[8] we demonstrated the synthesis of acyclic analogues of **1** with stereo-defined (*E*)- and (*Z*)-dienediyne systems.[9] We now report the first synthesis of the optically active 10-membered dienediyne compounds **2** and **3** from the (*Z*)-dienediyne epoxide **20** by a novel synthetic strategy. An attempt to obtain the corresponding 9-membered carbocyclic analogue is also reported.

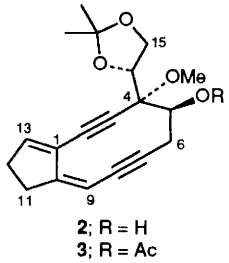
The key epoxide **20** was expected to be produced by Pd-catalysed coupling of the (*Z*)-enol triflate **16**[8a] and the acetylene **15** followed by epoxide formation and desilylation. Compound **13** bearing the required functional groups with correct stereochemistry[10] could be derived from D-xylose in optically active form. Thus, according to the literature,[11] D-xylose was converted to 1,2-*O*-isopropylidene-α-xylofuranose **4**, the primary alcohol of which was protected as its pivaloate to give alcohol **5**. Swern oxidation of **5** followed by addition of lithium trimethylsilylacetylide and desilylation with tetrabutylammonium fluoride (TBAF) cleanly afforded the highly crystalline acetylene **8**. The resulting tertiary alcohol of **8** was protected as its methyl ether to give the



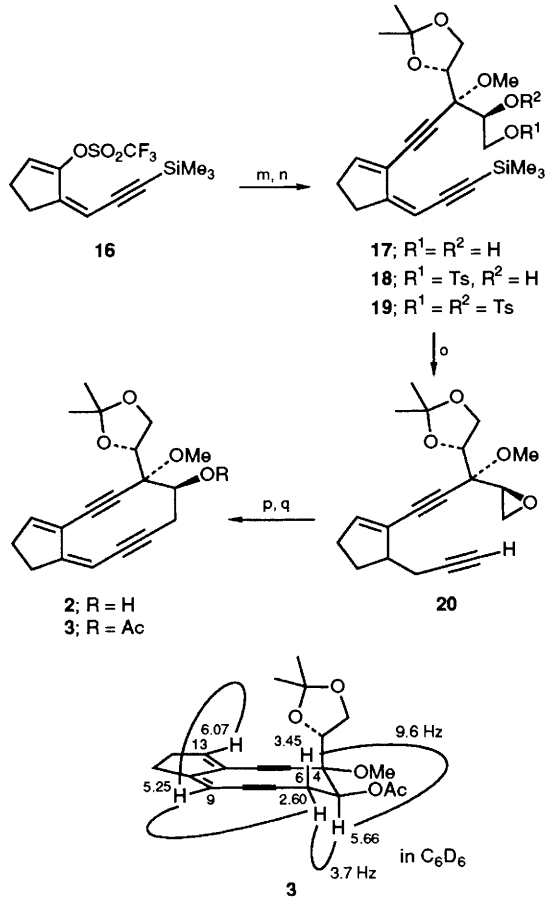

**Scheme 1** *Reagents and conditions*: a, acetone, cat. $H_2SO_4$; b, $Bu^tCOCl$, pyridine, room temp., 74% (2 steps); c, $(COCl)_2$, $Me_2SO$, $Et_3N$, $CH_2Cl_2$, −78 °C; d, LiC≡CSiMe$_3$, THF, −78 °C; e, TBAF, THF, 0 °C, 72%; (3 steps); f, MeI, $K_2CO_3$, acetone, sealed tube, 75 °C, 77%; g, $CF_3CO_2H$–$H_2O$ (5 : 1), room temp., 88%; h, $Bu^tMe_2SiO_3SCF_3$, 2,6-lutidine, $CH_2Cl_2$, −78 °C, **11** (62%), (11%); i, $NaBH_4$, THF–$H_2O$ (1 : 1), room temp.; j, NaOMe, MeOH, room temp., 82% (2 steps); k, acetone, $CuSO_4$, room temp.; l, TBAF, THF, room temp., 63% (2 steps)




**1**, NCS-Chr

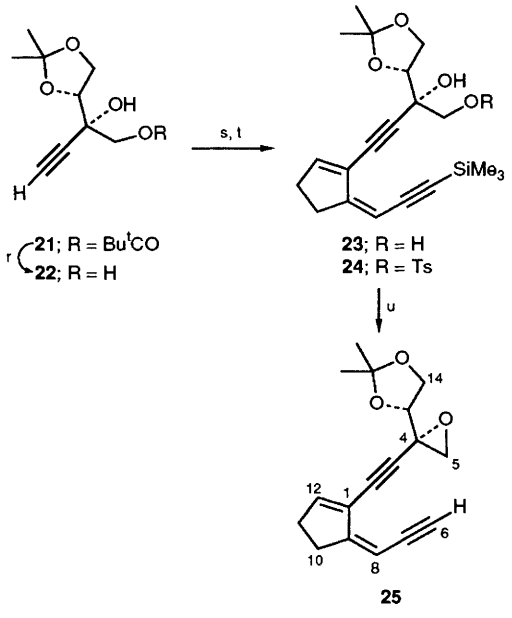



**2**; R = H
**3**; R = Ac




Ts = *p*-$MeC_6H_4SO_2$

**Scheme 2** *Reagents and conditions*: m, see text; n, TsCl, 4-dimethylaminopyridine (DMAP), $CH_2Cl_2$, **18** (55%), **19** (10%); o, TBAF, THF, room temp., 84%; p, $LiN(SiMe_3)_2$, THF, −78 °C, then $BF_3{\cdot}Et_2O$; q, $Ac_2O$, pyridine, DMAP




**Scheme 3** *Reagents and conditions*: r, NaOMe, MeOH, room temp., 89%; s, $Pd(PPh_3)_4$, CuI, $Et_2NH$, DMF, 75%; t, TsCl, pyridine, 94%; u, TBAF, THF, 61%

acetylene **9**, which was subsequently hydrolysed to the hemiacetal **10**. Treatment of **10** with *tert*-butyldimethylsilyl triflate gave rise to a mixture of two ethers, which upon separation provided the α- and β-glycosides **11** and **12**. The minor β-glycoside **12** could be recycled to **10** by desilylation with TBAF. Reduction of the desired α-glycoside **11** with sodium borohydride followed by deprotection of the pivaloate gave a mixture of triols **13** and **14** (*ca.* 4:1),† which were converted to acetylene **15** by sequential acetonide formation and desilylation (Scheme 1).

Next we focused on the coupling of **15** with the (*Z*)-enol triflate **16** and subsequent epoxide formation (Scheme 2). The coupling reaction of **15** and **16** was attempted in the presence of $Pd(PPh_3)_4$ (20 mol%), CuI (50 mol%)‡ and diethylamine (2 equiv.) in dimethylformamide (DMF) to give the (*Z*)-dienediyne diol **17** in 81% yield. Subsequent conversion of **17** to the (*Z*)-dienediyne epoxide **20** was accomplished in two steps. Thus, **17** was treated with an excess of tosyl chloride and 4-dimethylaminopyridine (DMAP) to afford a mixture of monotosylate **18** and ditosylate **19** with recovery of **17**. Subsequent desilylation of **18** separated from **19** and **17** with TBAF promoted epoxide formation to produce epoxide **20**.§ With the key epoxide **20** in hand, cyclization to the cyclic dienediyne system was next examined. Treatment of **20** with lithium bistrimethylsilylamide in tetrahydrofuran (THF) at −78 to 0 °C resulted in complete recovery of the starting material **20**. However, upon addition of $BF_3{\cdot}Et_2O$[12] after base treatment at −78 °C, a single product immediately appeared on TLC analysis. After usual work-up and silica gel column chromatography, compound **2** exhibiting a molecular ion mass spectral peak at *m/z* 314 could be obtained. Since the separation of the signals in the 400 MHz $^1H$ NMR spectrum of **2** measured in $C_6D_6$ was not sufficient for structure elucidation, **2** was acetylated to give the monoacetate **3** [*m/z* 356 ($M^+$)]. Decoupling and 2D NMR experiments firmly established the structure of **3** as a cyclic dienediyne from the

† The reduction of **11** presumably involves 1,2-silyl migration prior to reduction and a further migration back to give the major triol **13**. A similar silyl migration across the quaternary centre into the other side chain causing partial racemization was not observed however.

‡ Use of smaller proportions of $Pd(PPh_3)_4$ and CuI made the coupling reaction substantially slower and sometimes caused isomerization of the stereochemistry of the trisubstituted double bond.

§ Satisfactory spectroscopic data were obtained for all new compounds.

*Selected spectroscopic data*: **20**: $[\alpha]_D^{20}$ +68.0 (*c* 0.98, hexane); $^1H$ NMR ($C_6D_6$) δ 1.32, 1.56 (2 × s, 2 × 3H, $CMe_2$), 1.81 (m, 2H, 12-$CH_2$), 2.04 (m, 2H, 11-$CH_2$), 2.38 (dd, 1H, *J* 5.7, 3.9 Hz, 6α-CH), 2.98 (dd, 1H, *J* 5.7, 2.5 Hz, 6β-CH), 3.16 (d, 1H, *J* 2.7 Hz, 7-CH), 3.46 (dd, 1H, *J* 3.8, 2.5 Hz, 5-CH), 3.49 (s, 3H, OMe), 4.15 (dd, 1H, *J* 8.5, 6.8 Hz), 4.37 (t, 1H, *J* 6.7 Hz, 15-CH), 4.51 (dd, 1H, *J* 8.4, 6.7 Hz, 14-CH), 5.29 (m, 1H, 9-CH), and 6.25 (m, 1H, 13-CH); IR (neat) ν/$cm^{-1}$ 3300, 3000, 2950, 2230, 2100, 1615, 1450, 1370, 1215, 1090 and 855 $cm^{-1}$; *m/z* 299 [$(M-Me)^+$], 271, 213, 184, 153, 101 and 43.

**3**: $^1H$ NMR ($C_6D_6$) δ 1.29, 1.62 (2 × s, 2 × 3H, $CMe_2$), 1.65 (s, 3H, OAc), 1.90 (m, 2H, 12-$CH_2$), 2.13 (m, 2H, 11-$CH_2$), 2.60 (m, 1H, 6α-CH), 3.43 (s, 3H, OMe), 3.45 (m, 1H, 6β-CH, obscured by OMe), 4.13 (dd, 1H, *J* 8.5, 6.9 Hz, 15-CH), 4.42 (dd, 1H, *J* 8.5, 6.1 Hz, 15-CH), 4.59 (t, 1H, *J* 6.5 Hz), 5.25 (m, 1H, 9-CH), 5.66 (dd, 1H, *J* 9.6, 3.7 Hz, 5-CH) and 6.07 (m, 1H, 13-CH); IR ($CCl_4$) ν/$cm^{-1}$ 3000, 2950, 2280, 1750, 1370, 1090, 1030 and 850 $cm^{-1}$; *m/z* 356 $(M)^+$, 341 $[(M - Me)^+]$, 255, 239, 196, 152, 101 and 43.

**25**: $[\alpha]_D^{20}$ +63.8 (*c* 1.86, $CCl_4$); $^1H$ NMR ($C_6D_6$) δ 1.25, 1.46 (2 × s, 2 × 3H, $CMe_2$), 1.84 (m, 2H, 11-$CH_2$), 2.06 (m, 2H, 10-$CH_2$), 2.64, 2.88 (2 × d, 2 × 1H, *J* 6.0 Hz, 5-$CH_2$), 3.04 (d, 1H, *J* 2.4 Hz, 6-CH), 3.88 (br t, 1H, *J* 6.5 Hz, 14-CH), 3.98 (br dd, 1H, *J* 8.4, 6.7 Hz, 14-CH), 4.20 (pair of dd, total 1H, each *J* 8.5, 6.3 Hz, 13-CH), 5.26 (m, 1H, 8-CH) and 6.24 (m, 1H, 12-CH); IR ($CCl_4$) ν/$cm^{-1}$ 3340, 3010, 2950, 2240, 2110, 1370, 1215, 1070 and 850 $cm^{-1}$; *m/z* 270 $(M)^+$, 255 $[(M - Me)^+]$, 225, 212, 183, 153, 101 and 43.

observation of the long-range couplings between 6α-H and 9-H and 9-H and 13-H. While the preparation of stable 10-membered cyclic dienediynes had been reported by Hirama *et al.*,[6c,d] **2** and **3** were found to be extremely labile on concentration and could be handled only in solution.

With the successful synthesis of **2** and **3**, we next looked at preparation of the corresponding nine-membered cyclic analogue of **1** by employing the same epoxide opening strategy. The requisite (*Z*)-dienediyne epoxide **25** could be synthesized similarly to **20** (Scheme 3). Thus, diol **22** prepared from pivaloate **21**[8a] was coupled with (*Z*)-enol triflate **16** under the same conditions as employed for the preparation of **17** to afford diol **23**. Sequential tosylation of **23** and desilylative epoxide formation of the resulting tosylate **24** gave **25**. It was found, however, that **25** did not react in the same way as **20**. It is well known that epoxide opening involves $S_N2$ attack of the nucleophile colinear with the carbon–oxygen bond which is cleaved.[13] Studies using molecular models suggested that such alignment could be easily adopted in the case of **18**, but significant bending of the acetylenic bonds of **25** would be required for the backside attack of acetylide anion.

We have thus succeeded in the synthesis of **2** and **3**, the first examples of chiral cyclic dienediynes, by employing a novel dienediyne formation–cyclization strategy. The synthetic scheme explored might facilitate access to various types of cyclic compounds related to **1**.

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