

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

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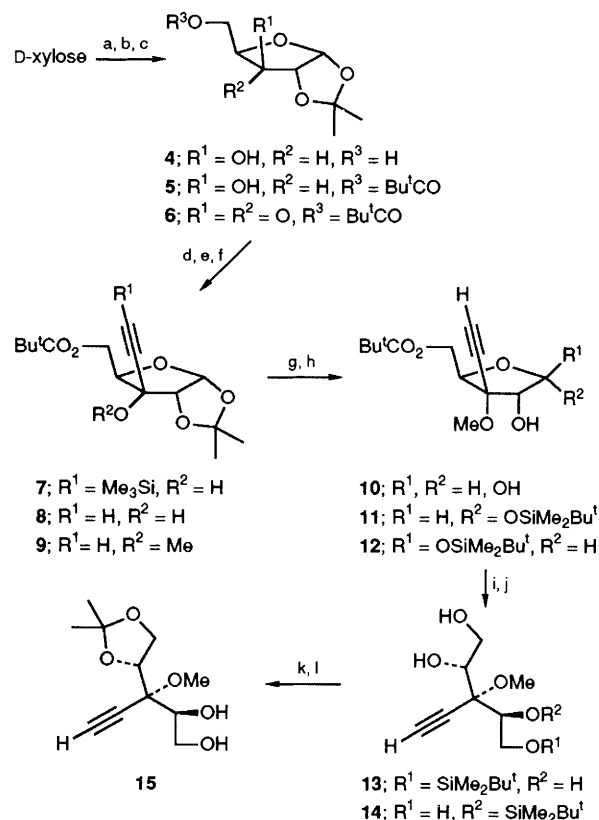
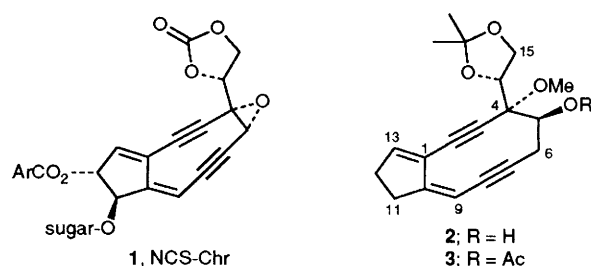
By successive treatment with lithium trimethylsilylamide and boron trifluoride–diethyl ether in tetrahydrofuran at -78°C optically active (*Z*)-dienediynes epoxide **20** prepared from *D*-xylose and (*Z*)-enol triflate **16** is found to undergo smooth cyclization to afford the title compound.

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 properties⁴ and its interesting bicyclo[7.3.0]dodecadienediynes 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 dienediynes system.⁷

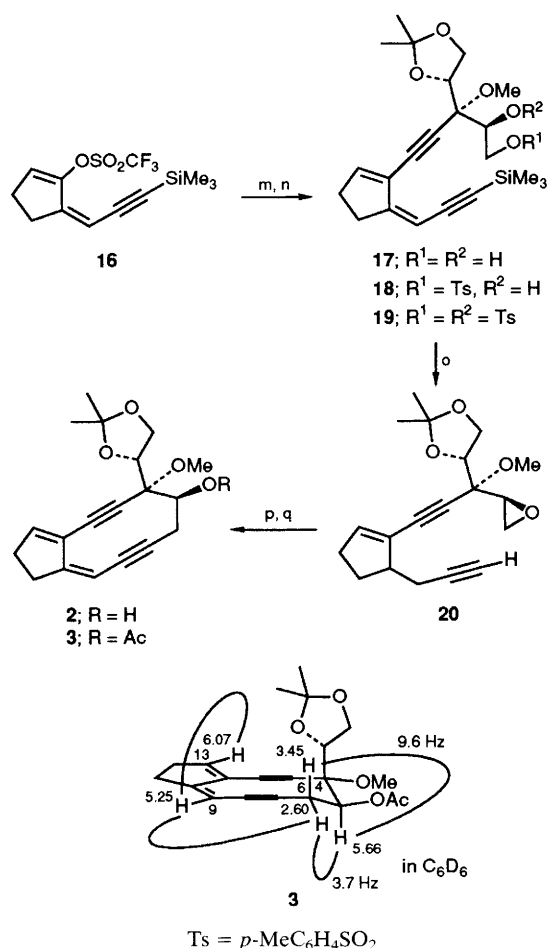
From the viewpoint of the synthesis of various analogues of **1** and of **1** itself, a synthetic scheme featuring formation of the dienediynes system prior to ring construction was expected to be a candidate. In our previous report,⁸ we demonstrated the synthesis of acyclic analogues of **1** with stereo-defined (*E*)- and (*Z*)-dienediynes systems.⁹ We now report the first synthesis of the optically active 10-membered dienediynes compounds **2** and **3** from the (*Z*)-dienediynes 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 stereochemistry¹⁰ 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 pivalate 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. H₂SO₄; b, Bu^tCOCl, pyridine, room temp., 74% (2 steps); c, (COCl)₂, Me₂SO, Et₃N, CH₂Cl₂, -78°C ; d, LiC $\equiv$ CSiMe₃, THF, -78°C ; e, TBAF, THF, 0°C , 72%; f, MeI, K₂CO₃, acetone, sealed tube, 75°C , 77%; g, CF₃CO₂H–H₂O (5 : 1), room temp., 88%; h, Bu^tMe₂–SiO₃SCF₃, 2,6-lutidine, CH₂Cl₂, -78°C , **11** (62%), (11%); i, NaBH₄, THF–H₂O (1 : 1), room temp.; j, NaOMe, MeOH, room temp., 82% (2 steps); k, acetone, CuSO₄, room temp.; l, TBAF, THF, room temp., 63% (2 steps)



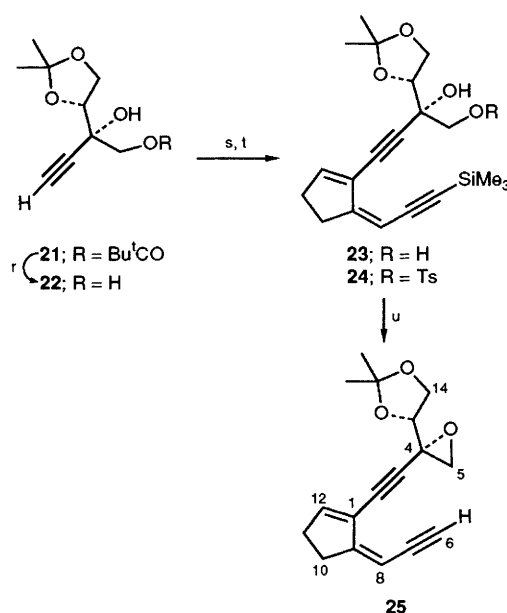
Scheme 2 Reagents and conditions: m, see text; n, TsCl, 4-dimethylaminopyridine (DMAP), CH₂Cl₂, **18** (55%), **19** (10%); o, TBAF, THF, room temp., 84%; p, LiN(SiMe₃)₂, THF, -78°C, then BF₃·Et₂O; q, Ac₂O, pyridine, DMAP

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 pivalate 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(PPh₃)₄ (20 mol%), CuI (50 mol%)[‡] and diethylamine (2 equiv.) in dimethylformamide (DMF) to give the (*Z*)-dienediynes **17** in 81% yield. Subsequent conversion of **17** to the (*Z*)-dienediynes 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**.

[†] 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(PPh₃)₄ and CuI made the coupling reaction substantially slower and sometimes caused isomerization of the stereochemistry of the trisubstituted double bond.



Scheme 3 Reagents and conditions: r, NaOMe, MeOH, room temp., 89%; s, Pd(PPh₃)₄, CuI, Et₂NH, DMF, 75%; t, TsCl, pyridine, 94%; u, TBAF, THF, 61%

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 dienediynes 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 BF₃·Et₂O¹² 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 C₆D₆ 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 dienediynes from the

[§] Satisfactory spectroscopic data were obtained for all new compounds.

Selected spectroscopic data: **20**: [α]_D²⁰ +68.0 (c 0.98, hexane); ¹H NMR (C₆D₆) δ 1.32, 1.56 (2 $\times$ s, 2 $\times$ 3H, CMe₂), 1.81 (m, 2H, 12-CH₂), 2.04 (m, 2H, 11-CH₂), 2.38 (dd, 1H, *J* 5.7, 3.9 Hz, 6 α -CH), 2.98 (dd, 1H, *J* 5.7, 2.5 Hz, 6 β -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 (C₆D₆) δ 1.29, 1.62 (2 $\times$ s, 2 $\times$ 3H, CMe₂), 1.65 (s, 3H, OAc), 1.90 (m, 2H, 12-CH₂), 2.13 (m, 2H, 11-CH₂), 2.60 (m, 1H, 6 α -CH), 3.43 (s, 3H, OMe), 3.45 (m, 1H, 6 β -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 (CCl₄) 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: [α]_D²⁰ +63.8 (c 1.86, CCl₄); ¹H NMR (C₆D₆) δ 1.25, 1.46 (2 $\times$ s, 2 $\times$ 3H, CMe₂), 1.84 (m, 2H, 11-CH₂), 2.06 (m, 2H, 10-CH₂), 2.88 (2 $\times$ d, 2 $\times$ 1H, *J* 6.0 Hz, 5-CH₂), 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 (CCl₄) 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 6 α -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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