Synthesis of the Neocarzinostatin Chromophore A Core Diynene Structure Using an η^2-Hexacarbonyldicobalt mediated Aldol Reaction

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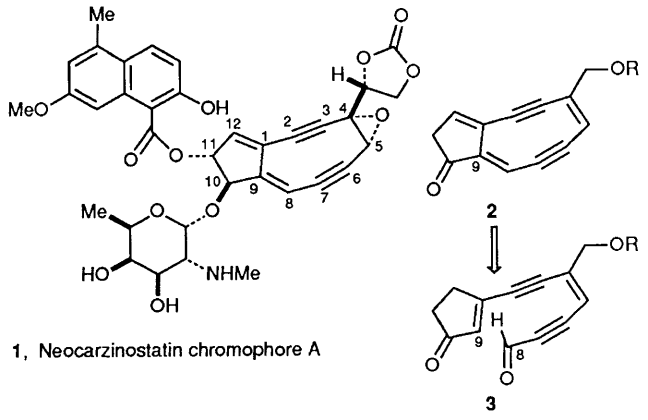
The monoketal of cyclopentene-1,3-dione was converted into the η^2-$Co_2(CO)_6$ neocarzinostatin core **19** in six steps; oxidative decomplexation in the presence of cyclohexa-1,4-diene gave the cycloaromatized adduct **22**.

The non-proteinoid component of neocarzinostatin contains the non-covalently bound highly unsaturated molecule called neocarzinostatin chromophore A, **1**. The extensive investigations of Goldberg *et al.*[1] and Edo *et al.*[2] established the structure of **1**, and more recently Myers *et al.*[3] deduced its absolute configuration. Myers has also suggested a plausible mechanism by which **1** interacts with thiols to trigger its collapse to a diradical (diyl) which can hydrogen abstract from the ribose backbone of DNA resulting in strand scission.[4] The unusual structure, instability, potent antitumour activity and possible mechanism of action, collectively conspire to make **1** an important molecule for synthetic studies.[5]

The approach we have adopted to construct the core bicyclo[7.3.0]dodecadiynetriene **2** is to examine the intramolecular aldol reaction of the cyclopentenone derivatives such as **3** to form the crucial C(9)–C(8) bond. The known



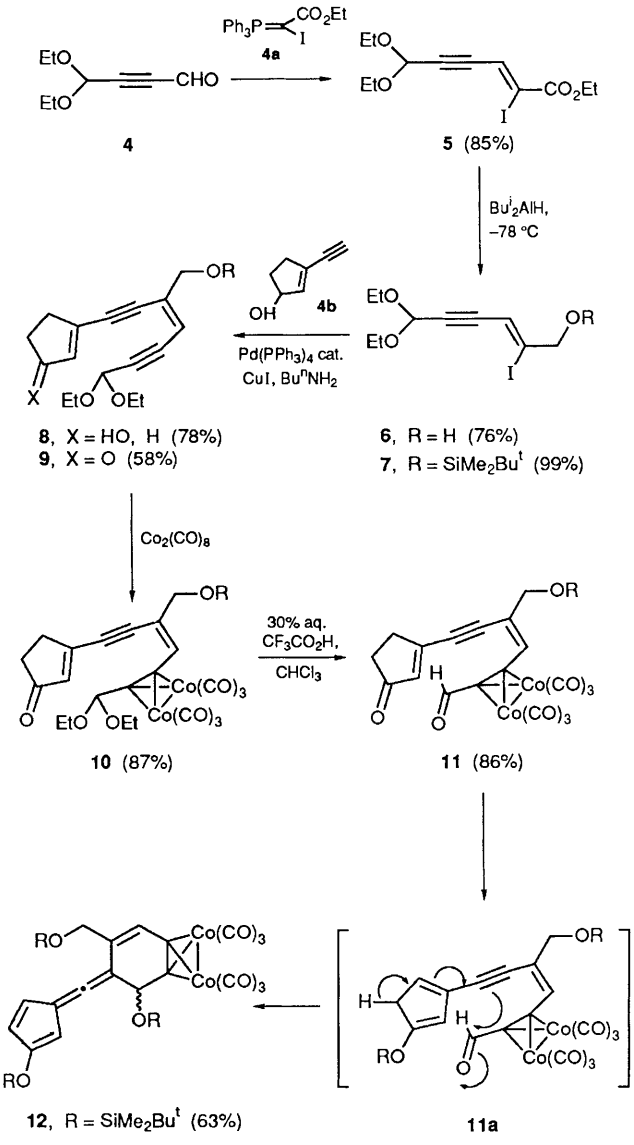
1, Neocarzinostatin chromophore A

Scheme 1

aldehyde–acetal **4**[6] was treated with the phosphorane[7] **4a** to give the *Z*-α,β-unsaturated ester **5**† (85%), accompanied by a small amount of the *E*-isomer (5%). Diisobutylaluminium hydride reduction of **5** gave **6** (76%), which was protected as its *tert*-butyldimethylsilyl ether **7** (99%), and coupled to 3-ethynylcyclopent-2-enol **4b**[8] using the standard $Pd(PPh_3)_4$–CuI–Bu^nNH_2 conditions[9] to provide the diynediene **8** (78%). Oxidation to **9** (58%) (pyridinium dichromate) and $Co_2(CO)_8$ complexation gave the adduct **10** (87%). Mild acid (30% aq. $CF_3(CO_2H$–$CHCl_3)$ hydrolysis of **10** gave **11** (86%).

When **11** was exposed to $Bu^tMe_2SiOSO_2CF_3$–CH_2Cl_2 at 0 °C a clean transformation took place to give not the expected aldol adduct [as its η^2-$Co_2(CO)_6$ complex] as indicated in Scheme 1, but the unusual cyclopentadienylallene compound **12** (63%) as a 1:1 mixture of epimers. Presumably **11** is silylated to give **11a**, which undergoes proton loss to give **12**.† If proton loss can be prevented this unexpected pathway should be excluded.

The known monoketal of cyclopentene-1,3-dione **13**[10] was treated with lithium acetylide to give **14** (39%), which was coupled to **7** using the usual Pd^0 methodology providing **15**



Scheme 2 Tf = CF_3SO_2

(71%). The tertiary alcohol was protected as its Bu^tMe_2Si ether **16** (77%), and the less hindered acetylene was complexed with $Co_2(CO)_8$ to give the η^2-$Co_2(CO)_6$ adduct **17** (90%). Mild acidic hydrolysis of **17** deprotected both ketal groups and the primary Bu^tMe_2Si ether to give **18** (82%). When the aldehyde **18** was exposed to $Bu^n_2BOSO_2CF_3Et_3N$–CH_2Cl_2 a clean stereospecific aldol[11] reaction took place to close the crucial nine-membered ring resulting in **19**† (69%), isolated as its BBu_2 adduct. Oxidative decomplexation of **19** using *N*-methylmorpholine *N*-oxide (NMMO) in cyclohexa-1,4-diene gave the cycloaromatized diquinane **22**† (42%) *via* the diynene **20** and diyl **21**.[12]‡ The relative stereochemistry of

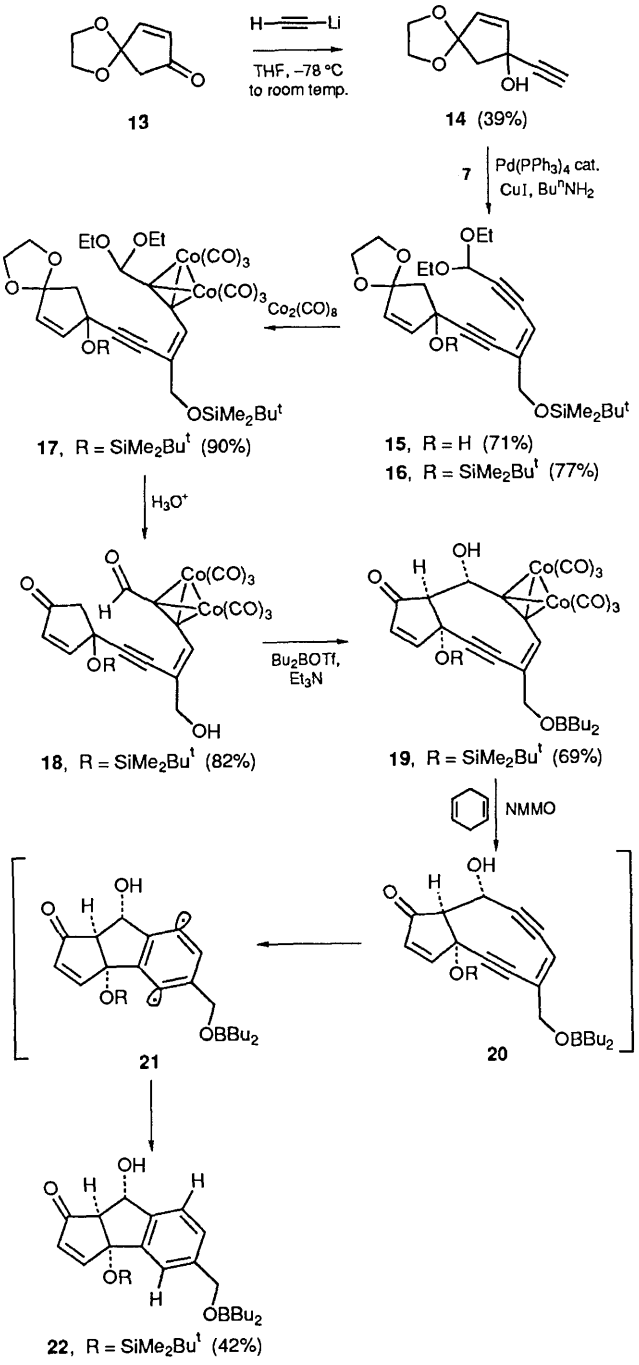
† Satisfactory spectroscopic data were obtained for all new compounds, and high-resolution mass spectra were consistent with the molecular formulae for **5**, **6**, **7**, **8**, **9**, **14**, **15** and **22**.

Selected spectroscopic data: **12**: IR (CCl_4) ν_{max}/cm^{-1} 2958, 2930, 2895, 2886, 2858, 2094, 2058, 2034, 1916, 1579, 1260 and 1107; UV (EtOH, λ_{max}/nm, ε/l mol^{-1} cm^{-1}) 324 (9400), 268 (20300) and 203 (27600); ^{1}H NMR (300 MHz, C_6D_6) δ 7.10, 7.06 (2 × t, 1H, *J* 1.8 Hz), 6.44 (m, 1H, *J* 5.4 and 2.0 Hz), 6.23, 615 (2 × m, 1H, *J* 5.4 and 2.0 Hz), 5.94, 5.93 (2 × s, 1H), 5.61 (m, 1H, *J* 2.0 Hz), 4.32 (m, 2H, *J*. 15 and 1.8 Hz), 1.1 to 0.8 (m, 27H) and 0.3–0.0 (m, 18H); ^{13}C NMR (75 MHz, C_6D_6) δ 208, 199, 159, 158, 139, 138, 130, 129, 127, 126, 124, 116, 115, 113, 112, 99, 98, 87, 76, 64, 26, 25.9, 25.8, 18 and −5; mass spectra (FAB) *m/z* (rel. int): 843 (0.2, M^+ + 1), 787 (0.2, M^+ + 1 − 2CO), 731 (4, M^+ + 1 −4CO), 730 (7, M^+ −4CO), 702 (1, M^+ −5CO), 674 (2, M^+ −6CO) and 154 (100).

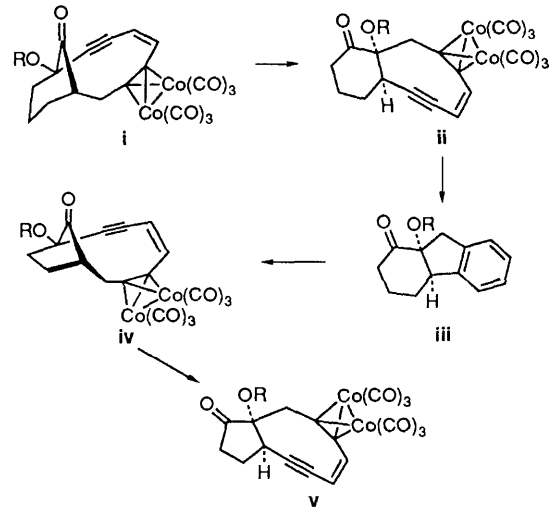
19: IR (CCl_4) ν_{max}/cm^{-1} 3660, 2958, 2930, 2858, 2094, 2059, 2036, 2026, 1722, 1261, 1092 and 839; ^{1}H NMR (300 MHz, CD_3OD) δ 7.53 (d, 1H, *J* 5.7 Hz), 7.08 (brs, 1H), 6.24 (d, 1H, *J* 5.7 Hz), 5.68 (d, 1H, *J* 5.9 Hz), 4.12 (d, 2H, *J* 1.5 Hz), 3.54 (t, 4H, *J* 6.5 Hz), 3.27 (d, 1H, *J* 5.9 Hz), 1.50 (m, 4H), 1.37 (m, 4H), 0.93 (t, 6H, 7.3 Hz), 0.89 (s, 9H), 0.30 (s, 3H) and 0.28 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 206, 201, 164, 139, 133, 127, 102, 100, 92, 88, 76.1, 76.0, 68, 62.7, 62.6, 36, 27.2, 26.5, 26.1, 20, 19, 14.3, 14.2, −2.5 and −2.7.

22: IR (CCl_4) ν_{max}/cm^{-1} 3613, 3400, 2955, 2929, 2856, 1718, 1617, 1462, 1340, 1253, 1100, 1032, 908, 873 and 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J*.5.6 Hz), 7.46 (br.s, 1H), 7.39 (br.s, 2H), 5.93 (d, 1H, *J*. 5.6 Hz), 5.14 (br.s, 1H), 4.76 (s, 2H), 3.48 (m, 4H), 3.20 (d, 1H, *J*.2.0 Hz), 2.64 (br.s, 1H), 1.24 (m, 14H), 0.88 (s, 9H), 0.06 (s, 3H) and −0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207, 165, 144, 143, 142, 130, 129, 126, 123, 89, 75, 68, 66, 65, 30, 26, 22, 18, 15, −2.7 and −3.1; HRMS (CI): calc. for $C_{27}H_{43}BO_4Si$ − $OBBu_2$ 329.1573; found, *m/z* 329.1583.

‡ In conjunction with our studies on esperamicin we have observed that **i** rearranges to **ii**, albeit in low yield (*ca.* 10%), when exposed to Lewis acids. Decomplexation of **ii**, at 20 °C in the presence of cyclohexa-1,4-diene, gave the cycloaromatized adduct **iii**. Similarly the analogue **iv** rearranged to **v** (*ca.* 10%) but since we had only extremely small amounts it was not decomplexed. However, in view of the conversion of **ii** into **iii** it would be expected that cycloaromatization would be equally facile. While **v** has the neocarzinostatin core structure and was characterized by single crystal X-ray analysis, the low yield and lack of applicability to a 4-CH_2OR substituted analogue militated against pursuing this strategy. Dr S. Fortt is thanked for the synthesis of **v**.



Scheme 3



22 and hence **19** was assigned, as shown, on the basis of the vicinal coupling of 2.0 Hz. This short route (6 steps) to the neocarzinostatin core should be capable of modifications that allow either the isolation of stable diynenes or their 4,5-epoxy derivatives. We are studying such possibilities.

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