Synthesis of the 4,5-Epoxybicyclo[7.3.0]dodecadiyne Neocarzinostatin Core Structure. Surprising Compatibility of the 4,5-Epoxide with a η^2-Hexacarbonyldicobalt Mediated Aldol Reaction

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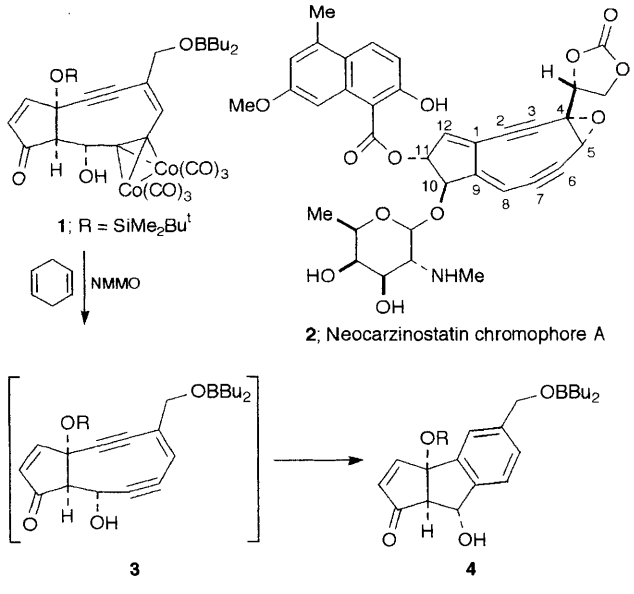
The highly functionalized neocarzinostatin core structure **16** has been synthesized from the enynone **9** in a hexacarbonyldicobalt mediated aldol reaction in which the epoxide ring is unexpectedly not opened.

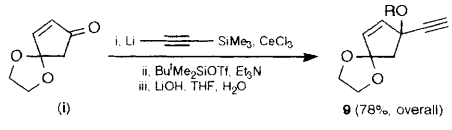
Recently we reported the synthesis of the η^2-$Co_2(CO)_6$-neocarzinostatin core diynene **1**,[1] which lacks the important 4,5-epoxide functionality present in neocarzinostatin chromophore A, **2**.[2] When the η^2-hexacarbonyldicobalt acetylene cap in **1** is oxidatively removed by treatment with *N*-methylmorpholine *N*-oxide (NMMO) in cyclohexa-1,4-diene the intermediate diynene **3** was not observed but immediately cycloaromatized to the diquinane **4** (Scheme 1). Removal of the BBu_2 group from **1** and attempted epoxidation of the allylic double bond was unsuccessful; consequently the epoxide functionality must be introduced at an earlier stage in the synthesis. This poses an awkward reactivity problem. The 8,9-bond is made by a η-$^2Co_2(CO)_6$-mediated aldol reaction under Lewis acid catalysis conditions. It would be surprising if the 4,5-epoxide **5** could survive these conditions and not open to the η-$^2Co_2(CO)_6$-stabilized cation **6**, with concomitant release of ring strain. On the other hand if the epoxide opening to the cation **6** is reversible the required aldol adduct **8** should be formed, although this compound can ionise to the cation **7**, among many potentially destructive pathways (Scheme 2). Consequently we felt considerable reservation that the conversion of **5** to **8** would be successful, but there is no alternative since the epoxide cannot be introduced after the intramolecular aldol reaction.

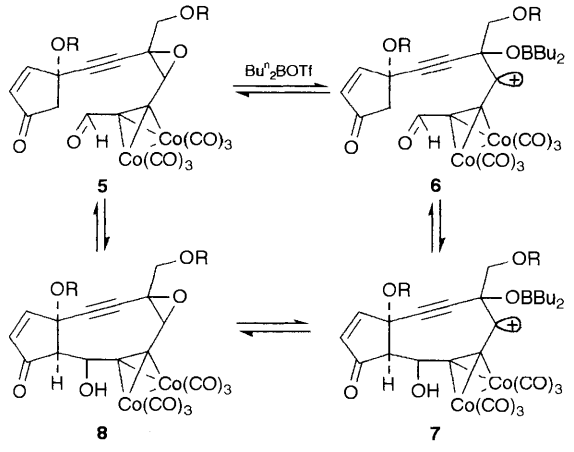


Scheme 1

Coupling of **9**† with the iodoalkene **9a**, using $Pd(PPh_3)_4$ catalysis in the presence of CuI and Bu^nNH_2 gave the diynene **10** (75%).[4] At this stage the allylic double bond in **10** was

† The known enone (**i**) was converted into **9** as shown below.[3]

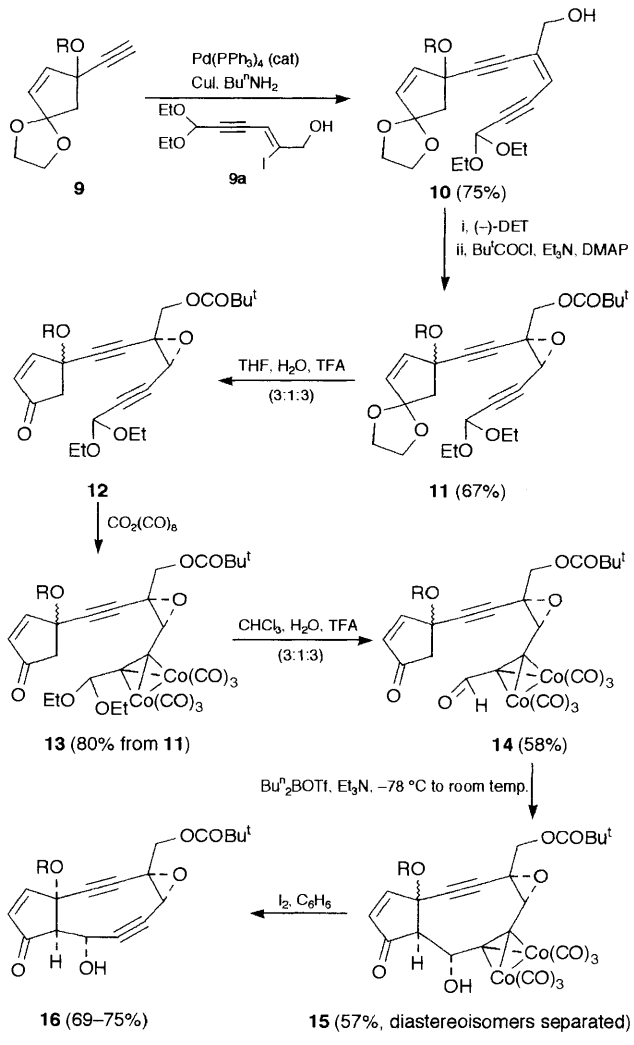




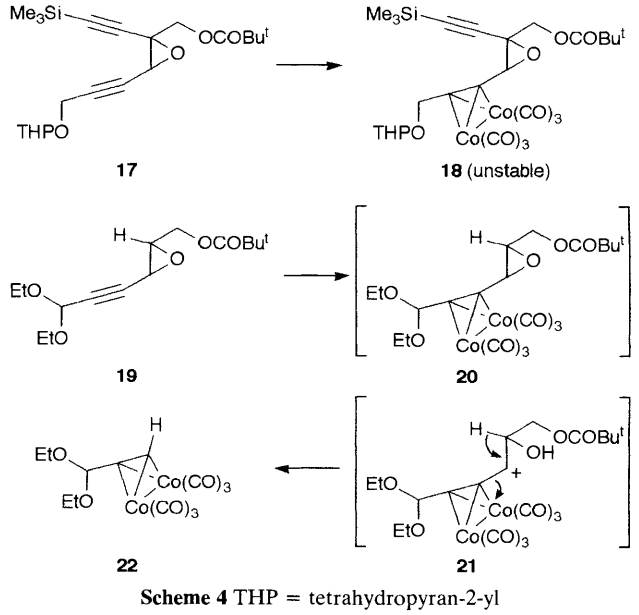
Scheme 2 Tf = CF_3SO_2

epoxidised using the catalytic Sharpless asymmetric epoxidation procedure with (−)-diethyl tartrate,[5] and the primary alcohol directly converted into the pivaloyl ester **11** (67% overall). Initially we protected the primary alcohol as its methyl carbonate derivative and found that many of the subsequent steps, especially the crucial aldol cyclization (28%), did not proceed in acceptable yields. We reasoned that the pivaloyl ester derivative would be more stable, and in particular would be less likely to participate in reactions that open the epoxide ring. Furthermore an electron-withdrawing group adjacent to the epoxide ring should retard ionization to the cation **6**. The epoxide **11** is a 1 : 1 mixture of inseparable diastereoisomers with an estimated enantiomeric excess of *ca.* 70%.‡

Treatment of **11** with aqueous trifluoroacetic acid in tetrahydrofuran (THF) readily hydrolysed the ethylene ketal to give **12** (100%). If more severe conditions are used with the intention of simultaneously hydrolysing the diethyl acetal, the molecule is destroyed. Complexation of **12** with $Co_2(CO)_8$ gave the adduct **13** (80%) which allowed the activated diethyl acetal to be hydrolysed by treatment with aqueous trifluoroacetic acid in chloroform to give **14** (58%). Premixing Bu^n_2BOTf–Et_3N–CH_2Cl_2 at −78 °C and warming to 0 °C, followed by slow addition of **14** at 0 °C, and warming to 25 °C, resulted in conversion into the cyclised aldol adduct **15** (57%). At this stage the diastereoisomers could be separated (PLC), although we do not know which one has the stereochemistry represented in structure **15**.§ Oxidative decomplexation of **15**



Scheme 3 (−)-DET = (−)-diethyl tartrate; DMAP = 4-dimethylaminopyridine; THF = tetrahydrofuran; TFA = trifluoroacetic acid; R = Bu^tMe_2Si



Scheme 4 THP = tetrahydropyran-2-yl

with I_2–C_6H_6 gave **16** (69–75%) as a stable compound both in solution and as a solid at room temperature (Scheme 3).§ The compound **16** is the most highly functionalized bicyclo[7.3.0]dodecadiyne neocarzinostatin core structure synthe-

‡ The enantiomeric purity of **11** was determined by derivatizing the epoxy alochol, obtained directly from the Sharpless epoxidation, with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate.

§ *Spectral data* for the diastereoisomers **15**: ^{1}H NMR (300 MHz, CD_3OD) δ 0.30 (3H, s), 0.35 (3H, s), 0.90 (9H, s), 1.30 (9H, s), 3.34 (1H, s), 3.60 (2H, m), 5.82 (1H, d, *J* = 5.8 Hz), 6.23 (1H, d, *J* = 5.4 Hz), 6.48 (1H, s) and 7.44 (1H, d, *J* = 5.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ −2.70, −2.49, 18.84, 26.15, 27.72, 40.53, 66.54, 70.75, 74.81, 75.06, 76.15, 77.10, 89.07, 133.40, 163.41 and 205.35.

^{1}H NMR (300 MHz, CD_3OD) δ 0.25 (3H, s), 0.30 (3H, s), 0.86, (9H, s), 1.30 (9H, s), 3.15 (1H, d, *J* = 7.1 HZ), 3.55–3.60 (2H, 2d, *J* = 6 Hz), 5.29 (1H, d, *J* = 7.1 Hz), 6.19 (1H, s) and 6.25–7.52 (2H, 2d, *J* = 5.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ −2.70, −2.42, 14.28, 18.80, 26.06, 27.20, 40.32, 64.92, 70.42, 74.56, 75.30, 76.09, 77.08, 77.76, 134.17, 162.49 and 205.55

Spectral data for the diastereoisomers **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (3H, s), 0.23 (3H, s), 0.95 (9H, s), 1.26 (9H, s), 3.44–3.52 (1H, m), 3.65 (1H, d, *J* = 12 Hz), 4.16 (1H, d, *J* = 12 Hz), 5.07 (1H, d, *J* = 1.8 Hz), 5.53 (1H, s), 6.21 (1H, d, *J* = 5.8 Hz) and 7.79 (1H, d, *J* = 5.8 Hz).

^{1}H NMR (300 MHz, CD_3OD) δ 0.18 (3H, s), 0.22 (3H, s), 0.98 (9H, s), 1.26 (9H, s), 3.45–3.55 (2H, m), 4.05 (1H, d, *J* = 12 Hz), 5.03 (1H, d, *J* = 1.8 Hz), 5.44 (1H, s), 6.17 (1H, d, *J* = 5.8 Hz) and 7.81 (1H, d, *J* = 5.8 Hz).

sized to date, and illustrates the surprising compatibility of the 4,5-epoxide to the cyclisation conditions. This is more dramatically demonstrated by the following subsequent models (Scheme 4).

Attempted complexation of **17** with $Co_2(CO)_8$ gave **18** which was extremely unstable towards acidic conditions, decomposing to polar material, presumably formed from opening of the epoxide ring. Interestingly, treatment of **19** with $Co_2(CO)_8$–heptane gave the fragmented adduct **22** as the only cobalt-containing material. Its formation presumably arises from **20** *via* ring opening of the epoxide to give **21**, and elimination resulting in **22**.[9]

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