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Studies on the Synthesis of the Core Structures of the Antitumor Agents Neocarzinostatin, Kedarcidin, C-1027 and Maduropeptin

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Abstract: The bicyclo[7.3.0]dodecadiyne core structure of the antitumor agents neocarzinostatin, kedarcidin, C-1027 and maduropeptin can be readily constructed by an intramolecular aldol reaction to form the C-8/C-9 bond only if the C-6,7 triple bond is complexed as its $\eta^2Co_2(CO)_6$-acetylene adduct. Copyright © 1996 Elsevier Science Ltd

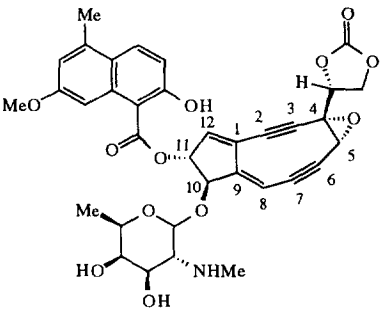
Introduction

The non-proteinoid component of neocarzinostatin contains the non-covalently bound highly unsaturated molecule called neocarzinostatin chromophore A, **1**, **Scheme 1**. While the protein bound complex of neocarzinostatin had been known for some thirty years, the structure of **1** was not known until 1985.[1] The extensive investigations of Goldberg[2] and Edo[3] established the structure of **1**, and later Myers[4] deduced its absolute configuration. Recently, other antitumor compounds have been isolated that contain the unusual bicyclo[7.3.0]dodecadiynetriene core structure. These compounds include kedarcidin **2**,[5] C-1027 **3** [6] and maduropeptin **4**.[7] There have been many reports of synthetic endeavors directed towards the core skeleton, and analogs that mimic the proposed *in vitro* mechanism of action.[8] These studies parallel contemporary investigations of calicheamicin, esperamicin and dynemicin that contain a bicyclo[7.3.1]tridecadiynene core structure.[9]

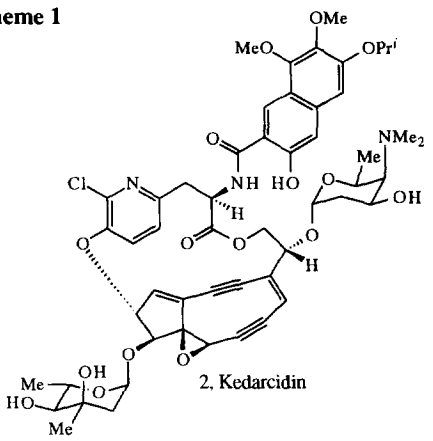
Myers suggested a plausible *in vitro* mechanism by which **1** interacts with thiols to trigger its collapse to a diradical (diyl) which can hydrogen abstract from the ribose backbone of DNA resulting in strand scission. It was proposed that thiol addition to C-12 leads to ring opening of the epoxide to give **1a** (pathway a, **Scheme 2**) The unstable cummulene **1a** undergoes cyclization to the diradical **1b**. Hydrogen atom abstraction from the proximal environment results in the cycloaromatized adduct **1c**.[10] Subsequently, Hensens and Goldberg[11] demonstrated that in the absence of thiol, under basic conditions, neocarzinostatin CA **1** can undergo intramolecular SN2'-type addition of the hydroxy-naphthoate (β-ketoacid) to give **1d** (pathway b). Once the epoxide ring has been opened the cycloaromatization reaction takes place to give the diradical **1e**, which after hydrogen abstraction results in **1f**. Fuchs has conducted some model studies that illustrate the C-alkylation of 2-hydroxynaphthoates.[12]

The *in vitro* mechanism of action of kedarcidin **2** proposed by the Bristol-Myers Squibb group is particularly interesting. While the distance between the bonding acetylenic carbon atoms (C-2/C-7) in **2** is 2.85Å (r), it does not undergo cycloaromatization since the epoxide causes the [3.3.0]-type transition state leading to cycloaromatization to be too strained. This is in agreement with our original proposal,[13] and

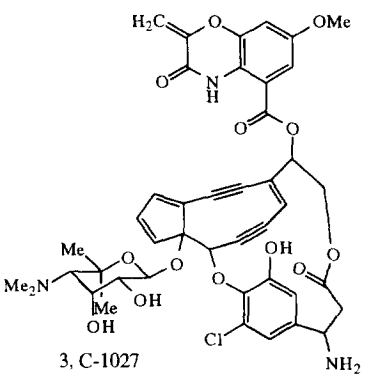
Scheme 1



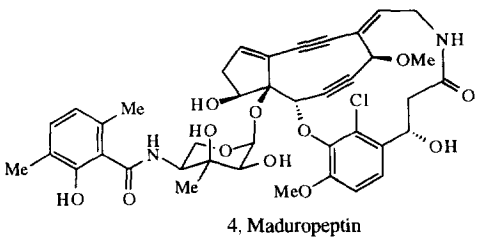
1, Neocarzinostatin CA



2, Kedarcidin



3, C-1027



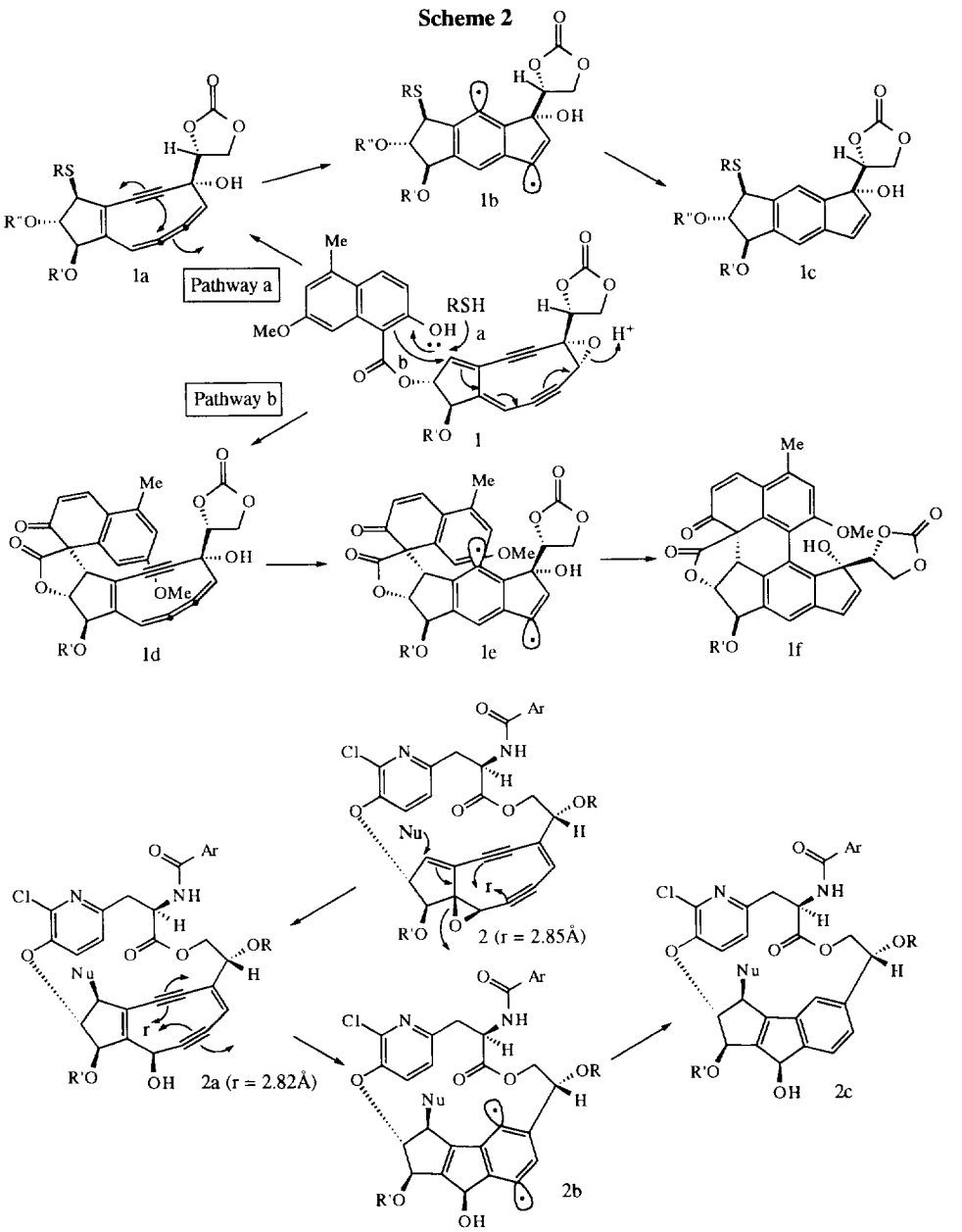
4, Maduropeptin

subsequent experimental verification, that transition state strain energy changes and not ground state distance between the two bonding acetylenes determines the ease (rate) of cycloaromatization.[14] Once the epoxide ring in **2** is opened by nucleophilic attack at C-12 to give **2a** (r = 2.82Å) the cycloaromatization reaction is energetically feasible and the diradical **2b** can be formed. Hydrogen atom abstraction results in **2c**. Presumably, the diradicals **1b** and **2b** are responsible for the DNA damage caused by these antitumor agents, and also may account for their extreme toxicity due to indiscriminate cell damage. This severe limitation may be alleviated by the technique of cell targeting.[15] These unusual structures, combined with their latent ability to form diradicals and potent antitumor activity, collectively make **1**, **2**, **3** and **4** important molecules for synthetic studies.[16]

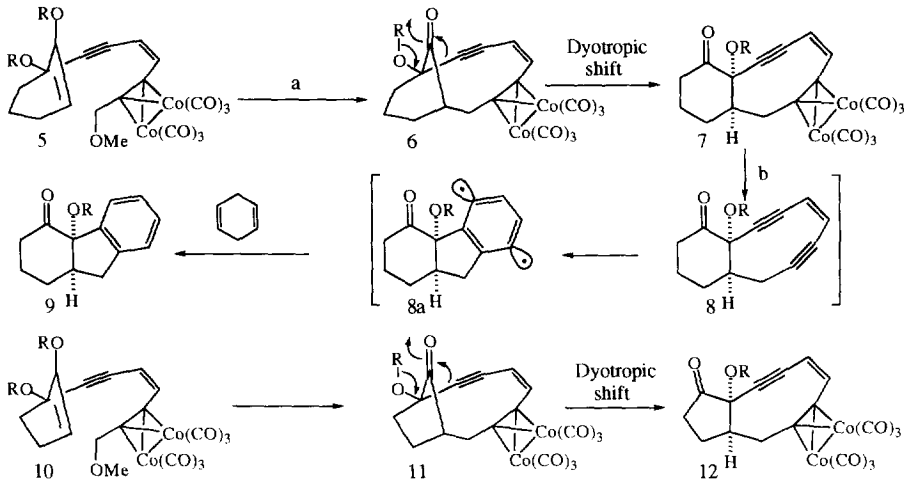
During the course of our studies on esperamicin and calicheamicin it was observed that treatment of **5** with $TiCl_4$/DABCO/-43° to -35°C gave the enediyne adduct **6**.[17] It was found that further exposure of **6** to these conditions gave the α-ketol shift (dyotropic isomerization) isomer **7**.[18] The structure of **7** was established by X-ray crystallography. Oxidative removal of the dicobalthexacarbonyl cluster with iodine in the presence of cyclohexa-1,4-diene produced the aromatized material **9**, via **8/8a**, **Scheme 3.** The α-ketol shift has the effect of ring contracting the 10-membered enediyne to the 9-membered ring of the neocarzinostatin core structure. In order to use this rearrangement to construct the neocarzinostatin skeleton, the five-membered ring analog of **5**, namely **10**, was synthesized.[19] When **10** was treated under the identical

conditions used to convert **5** into **7**, only traces of the unrearranged bicyclo[7.2.1]adduct **11** were formed along with the rearranged bicyclo[7.3.0]adduct **12** (10%). The structure of **12** was confirmed by single crystal X-ray crystallography. Unfortunately, all attempts to improve this transformation failed. In fact, for more substituted substrates with an appendage at C-4, none of the required rearrangement was observed. Consequently, it was decided to examine the retrosynthetic pathway shown in **Scheme 4**.

Scheme 2

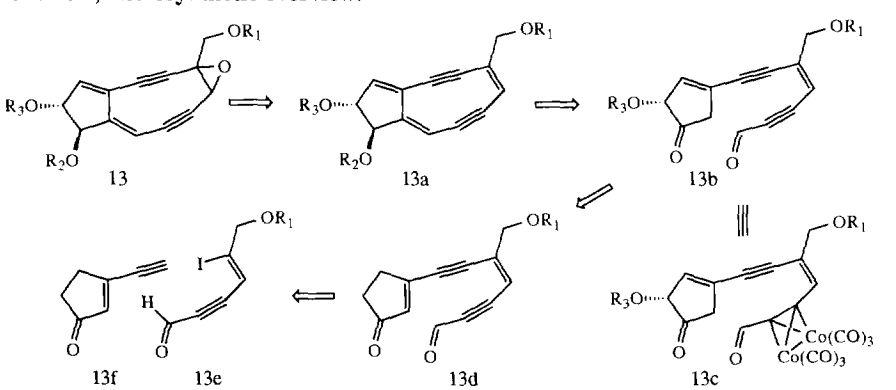


Scheme 3 (R = TBS)



The key reaction in the retrosynthesis is the intramolecular aldol reaction of **13b**, followed by dehydration, to form **13a**, **Scheme 4**. It was anticipated that the C-4 allylic alcohol would direct epoxidation resulting in **13**. Our previous experiences with a similar aldol reaction during studies on the synthesis of calicheamicin/esperamicin indicated that this reaction is readily reversible, and required the acetylene adjacent to the aldehyde to be complexed as its $\eta^2Co_2(CO)_6$-adduct in order to be successful.[20] Consequently, the $\eta^2Co_2(CO)_6$-acetylene adduct **13c** is equivalent to **13b**. The appropriately substituted cyclopentenone derivative **13d** should be available from standard palladium mediated coupling of **13f** with the vinyliodide **13e**.

Scheme 4, Retrosynthetic overview.

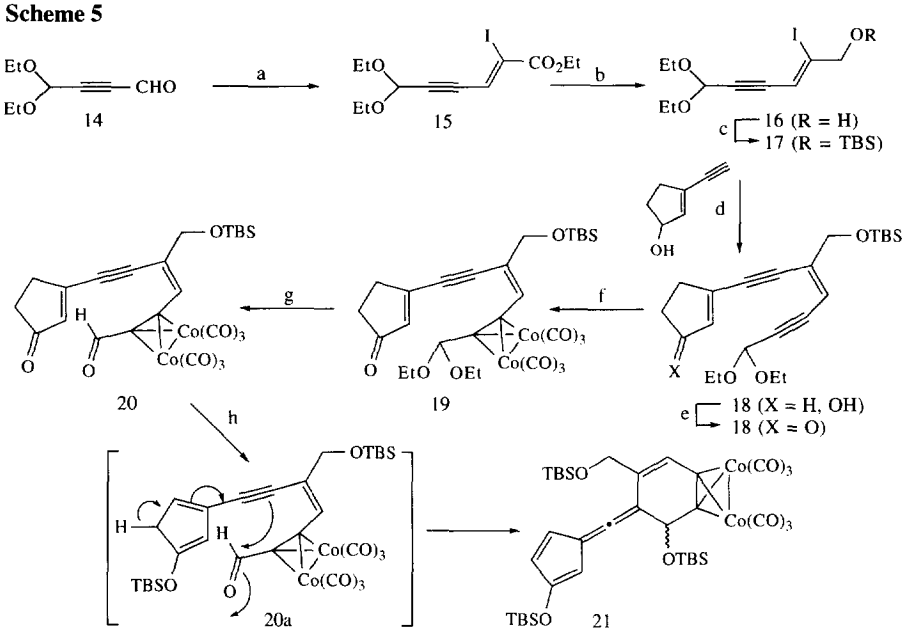


Results

The strategy depicted in **Scheme 4** was realized, although it was found that the substitution pattern and oxidation level of the cyclopentane portion needed to be altered from the one shown.[21] The known aldehyde-acetal **14**[22] was treated with the phosphorane **14a**[23] to give the Z-α,β-unsaturated ester **15** (85%), accompanied

by a small amount of the *E*-isomer (5%), **Scheme 5**. Diisobutylaluminum hydride reduction of **15** gave **16** (92%), which was protected as its *t*-butyldimethylsilyl ether **17** (99%), and coupled to cyclopentenol-3-yne[24] using the standard CuI/Pd(PPh$_3$)$_4$/*n*-BuNH$_2$ conditions[25] to provide the dienediyne **18** (X = OH, H) (78%). Oxidation to **18** (X = O) (58%) (pyridinium dichromate) and $Co_2(CO)_8$ complexation gave the adduct **19** (87%). Mild acid (30% aq. CF_3CO_2H/CH_2Cl_2) hydrolysis of **19** gave **20** (86%).

Scheme 5



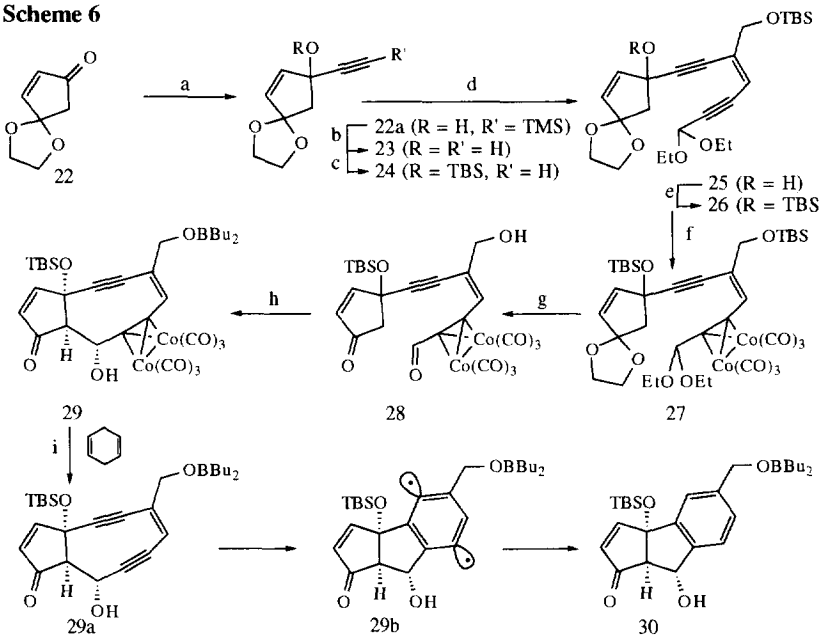
Conditions:- a) $Ph_3P{=}ClCO_2Et$ (**14a**)/CH_2Cl_2/-78° to 25°C (90%, *Z* : *E*, 85 : 5). b) DIBAL-H/THF/-78° to 25°C (92%). c) TBSOTf/CH_2Cl_2/Et_3N (99%). d) CuI/*n*-BuNH$_2$/Pd(PPh$_3$)$_4$/benzene25°C (78%). e) Pyridinium dichromate/CH_2Cl_2/25°C (58%). f) $Co_2(CO)_8$/*n*-heptane/25°C (87%). g) CF_3CO_2H/CH_2Cl_2/25°C for 5 mins (86%). h) TBSOTf/EtNPr$_2^i$/CH_2Cl_2/25°C for 10 mins (63%, 1:1 epimers).

When **20** was exposed to *t*-BuMe$_2$SiOTf/CH_2Cl_2/25°C a clean transformation took place to give not the expected aldol adduct [as its $\eta^2Co_2(CO)_6$ complex] but the unusual cyclopentadienylallene compound **21** (63%) as a 1:1 mixture of epimers. Presumably **20** is silylated to give **20a**, which undergoes proton loss to give **21**. If proton loss can be prevented this unanticipated pathway should be excluded.

The known monoketal of cyclopentene-1,3-dione **22**[26] was treated with lithium trimethyl silylacetylide in the presence of ceric trichloride to give **22a** (92%), which was exposed to TBAF/THF to give the terminal acetylene **23** (94%). Coupling to **17** to **23**, using the usual Pd° methodology providing **25** (71%), **Scheme 6**. The alcohol **25** was protected as its *t*-BuMe$_2$Si-ether **26** (77%), and the less hindered acetylene complexed with $Co_2(CO)_8$ to give the $\eta^2Co_2(CO)_6$-adduct **27** (83%). Mild acidic hydrolysis of **27** deprotected both ketal groups and removed the primary *t*-BuMe$_2$Si-ether to give **28** (82%). When the aldehyde **28** was exposed to *n*-Bu$_2$BOTf/Et_3N/CH_2Cl_2 a clean stereospecific aldol[27] reaction took place to close the crucial nine-membered ring resulting in **29** (82%), isolated as its -BBu$_2$ adduct. Interestingly, examination of the ^1H

NMR spectrum of the crude aldol product indicated that it was a 1:1 mixture of diastereomers, but after chromatography over silica gel only a single adduct was isolated. It appears that equilibration readily takes place since the yield of **29** is 82%. The relative stereochemistry of **29** is based upon the C-8/C-9 vicinal coupling [δ 5.68 (1H, d, J = 5.9 Hz) and 3.27 (1H, d, J = 5.9 Hz)]. Oxidative decomplexation of **29** using *N*-methylmorpholine *N*-oxide (NMMO) in 1,4-cyclohexadiene gave the cycloaromatized diquinane **30** (42%) *via* the enediyne **29a** and diyl **29b**.

Scheme 6



Conditions:- a) Trimethylsilylacetylene/*n*-BuLi/$CeCl_3$/THF/-78° to 25°C (92%) b) TBAF/THF/25°C (94%). c) i. TBSOTf/Et_3N/CH_2Cl_2. ii. LiOH.H_2O/THF/H_2O (78% from **22**). d) **17**/CuI/*n*-$BuNH_2$/$Pd(PPh_3)_4$/benzene25°C (71%). e) TBSOTf/CH_2Cl_2/Et_3N (77%). f) $Co_2(CO)_8$/*n*-heptane/25°C (83%). g) *p*-TsOH.H_2O/THF/H_2O (82%). h) *n*-Bu_2BOTf/Et_3N/CH_2Cl_2/25°C (82%). i) 1,4-cyclohexadiene/*i*-PrOH/NMNO/25°C (42%).

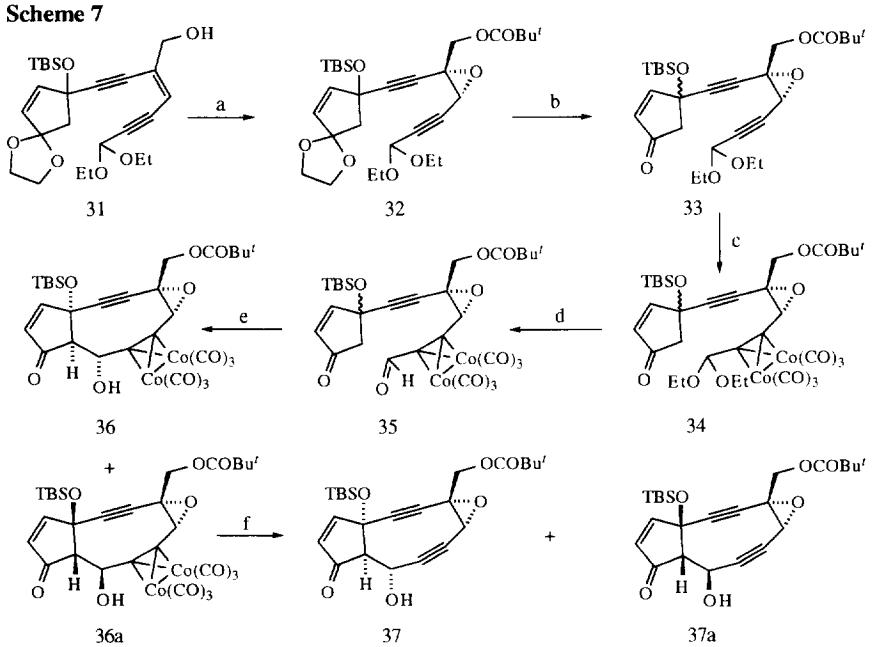
Removal of the BBu_2 group from **29** and attempted epoxidation of the allylic double-bond using a variety of standard allylic (Sharpless) oxidation reagents was unsuccessful, consequently the epoxide functionality must be introduced at an earlier stage in the synthesis. This poses an awkward reactivity problem. The 8,9-bond is made by a $\eta^2Co_2(CO)_6$-mediated aldol reaction under Lewis acid catalysis conditions. It would be surprising if the 4,5-epoxide **33** could survive these conditions and not open to a $\eta^2Co_2(CO)_6$-stabilized cation with concomitant release of ring-strain. Consequently we felt considerable reservation that the conversion of **33** to **36** would be successful, but there was no alternative since the epoxide cannot be introduced after the intramolecular aldol reaction, **Scheme 7**.

Coupling of **24** with the iodoalkene **16**, using $Pd(PPh_3)_4$ catalysis in the presence of CuI and *n*-$BuNH_2$ gave the diynene **31** (71%). At this stage the allylic double bond in **31** was epoxidized using the catalytic

Sharpless asymmetric epoxidation procedure with (-)-diethyl tartrate,[28] and the primary alcohol directly converted into the pivaloyl ester **32** (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. A pivaloyl ester derivative should 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 a cation. The epoxide **32** is a 1 : 1 mixture of inseparable diastereomers with an estimated enantiomeric excess of ca. 70%.[29]

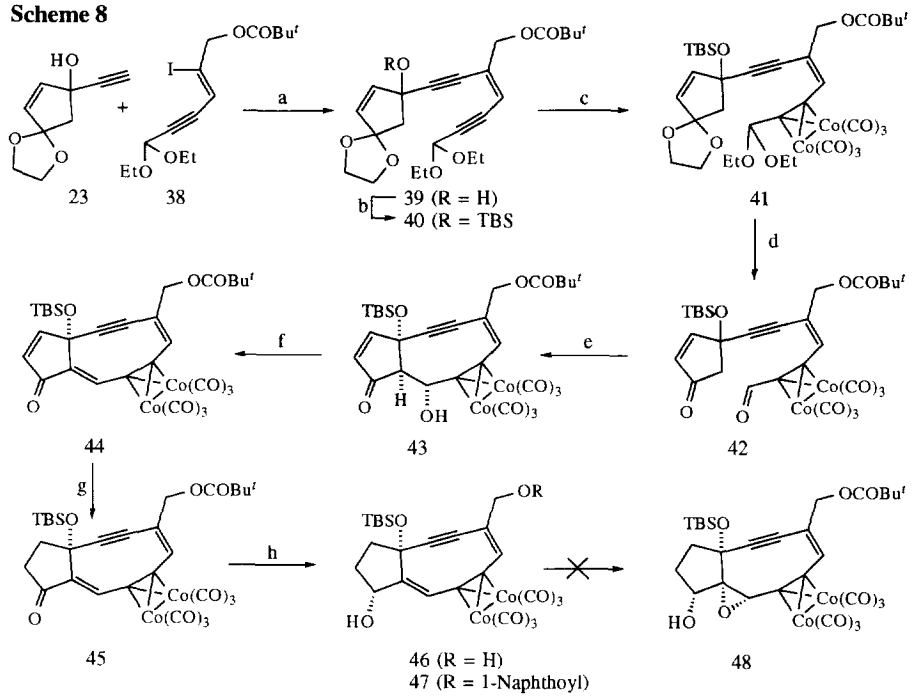
Treatment of **32** with aqueous trifluoroacetic acid in THF readily hydrolyzed the ethylene ketal to give **33** (99%). If more severe conditions are used with the intention of simultaneously hydrolyzing the diethyl acetal, the molecule was destroyed. Complexation of **33** with $Co_2(CO)_8$ gave the adduct **34** (80%) which allowed the now activated diethyl acetal to be hydrolyzed by treatment with aqueous trifluoroacetic acid in chloroform to give **35** (56%). Premixing *n*-$Bu_2BOTf/Et_3N/CH_2Cl_2$ at -78°C, warming to 0°C, followed by slow addition of **35** at 0°C, and warming to 25°C, resulted in conversion into the cyclized aldol adduct **36/36a** (57%). At this stage the diastereomers could be separated (plc), although we do not know which one has the stereochemistry represented in structure **36**. Oxidative decomplexation of **36/36a** with I_2/PhH gave **37/37a** (69-75%) as a stable compound both in solution and as a solid at room temperature. The compounds **37/37a** are the most highly functionalized bicyclo[7.3.0]dodecadiyne neocarzinostatin core structure synthesized to-date, and illustrates the surprising compatibility of the 4,5-epoxide to the cyclization conditions.

Scheme 7



Conditions:- a) i. (-)-DET/3Å MS/Ti(OPr^i)$_4$/*t*-BuOOH/CH_2Cl_2. ii. *t*-BuCOCl/Et_3N/DMAP/CH_2Cl_2 (67% overall, 1:1 distereoisomers). b) CF_3CO_2H/THF/H_2O/5°C (99%). c) $Co_2(CO)_8$/*n*-heptane/25°C (80%). d) CF_3CO_2H/$CHCl_3$/H_2O (56%). e) *n*-$Bu_2BOTf/Et_3N/CH_2Cl_2$/-78° to 0°C (57%, ca. 1:1 distereoisomers). f) I_2/PhH/25°C (69% and 75%, **37** and **37a** respectively).

Scheme 8



Conditions:- a) CuI/*n*-BuNH$_2$/Pd(PPh$_3$)$_4$/benzene25°C (50%). b) TBSOTf/Et$_3$N/CH$_2$Cl$_2$ (99%). c) Co$_2$(CO)$_8$/*n*-pentane/25°C (98%). d) *p*-TsOH.H$_2$O/THF/H$_2$O (96%). e) *n*-Bu$_2$BOTf/Et$_3$N/CH$_2$Cl$_2$/25°C (74%). f) MeSO$_2$Cl/Et$_3$N/DMAP/CH$_2$Cl$_2$/25°C (97%). g) NaCNBH$_3$/ZnCl$_2$/TMSCl, oxidative work-up with oxaziridine PhSO$_2$NOCHPh (36%). h) i. DIBAL-H in CH$_2$Cl$_2$/toluene/-78°C (57%). ii. 1-naphthoyl chloride/Et$_3$N/CH$_2$Cl$_2$/-5°C (77%).

The sequence of reactions shown in **Scheme 8** provided ready access to the aldol precursor **42** *via* **39**, **40** and **41**. Treatment of **42** with *n*-BuBOTf in the presence of triethylamine at 25°C gave the required aldol product **43** in 74% yield. After trying a number of low temperature procedures to dehydrate **43**, it was found that mesylation at 25°C under standard conditions gave **44** in excellent yield (97%). The 8,9-double bond proved to be unreactive towards nucleophilic addition and removal of the -Co$_2$(CO)$_6$ cluster only resulted in complete decomposition. The lack of reactivity of the 8,9-double bond can be attributed to the severe steric hindrance inflicted by the adjacent -Co$_2$(CO)$_6$-acetylene functionality. One reasonably clean transformation that could be conducted on **44** was the selective reduction of the 11,12-double bond with NaCNBH$_3$/ZnCl$_2$/TMSCl, followed by oxidative work-up with oxaziridine PhSO$_2$NOCHPh to give **45** (36%). Reduction of the C-10 carbonyl group in **45** with DIBAL-H was also accompanied by cleavage of the pivaloate ester, resulting in the diol **46**. The diol was selectively protected as the naphthoate ester **47**. All attempts to epoxidize the 8,9-double bond using standard directed epoxidation procedures did not give **48**. The only discernible reaction was oxidation of the alcohol to the corresponding C-10 ketone.

Summary

The intramolecular $\eta^2Co(CO)_6$-acetylene mediated aldol reaction to form the C-8/C-9 bond of the core structure of the antitumor agents neocarzinostatin CA, kedarcidin, C-1027 and maduropeptin provides an efficient route to the skeleton. In the three cases described the yields are 82%, 57% and 74% for compounds **29**, **36** and **43** respectively.

Experimental Section

Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen prior to use. *N*,*N*-Dimethylformamide (DMF), hexane and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide and stored over 3Å molecular sieves under argon. Triethylamine was distilled from calcium hydride and stored under argon. All reactions involving organometallic reagents or other moisture sensitive reactants were executed under an atmosphere of dry nitrogen or argon using oven dried and/or flame dried glassware.

^1H NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer as solutions in deuterochloroform ($CDCl_3$), unless otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (7.24 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are given in hertz (Hz). ^{13}C NMR spectra were recorded on General Electric QE-300 (75 MHz) instrument as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. IR spectra were recorded either neat on sodium chloride plates or as solutions in the solvent indicated using a Perkin-Elmer 1600 FT-IR spectrometer, and are reported in wave numbers (cm^{-1}). Low resolution chemical ionization (CI) mass spectra were obtained on a TSQ 70 instrument, and the exact mass determinations were obtained on a VG analytical ZAB2-E instrument.

Routine monitoring of reactions were performed using Merck Alufolien Kieselgel 60 F_{254} silica gel, aluminum-backed TLC plates. Flash chromatography was performed using silica gel Merck Kieselgel 60H F_{254} and Florisil 100-200 Mesh with the solvent indicated.

***Z*-Ethyl 6,6-diethoxy-2-iodo-hexa-4-yn-2-enoate 15**. 4,4-Diethoxy-2-butynal **14** (2.00 g, 12 mmol) was dissolved in dichloromethane (10 mL) and added to a solution of carboethoxy-iodotriphenylphosphonium methylide (5.70 g) in dichloromethane (30 mL) at -78°C under an atmosphere of argon. The mixture was stirred at -78°C for 15 min, and allowed to warm to room temperature over 45 min. The solvent was evaporated and the residue purified by flash chromatography over silica gel eluting with pentane/10% ether to give **15** (3.81 g, 90%) and its *E*-isomer (85 : 5). IR (CCl_4) 2981, 2932, 2898, 2888, 1715, 1581, 1477, 1445, 1393, 1368, 1353, 1326, 1300, 1250, 1157, 1090, 1055, 1019, 909, 877 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, J = 1.8 Hz), 5.47 (1H, d, J = 1.8 Hz), 4.27 (2H, m), 3.81 (2H, dd, J = 9.4, 7.1 Hz), 3.65 (2H, m, J = 9.4, 7.1 Hz), 1.32 (3H, t, J = 7.2 Hz), 1.24 (6H, t, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162, 131, 104, 99, 92, 84, 63, 61, 15, 14. MS (CI, m/e, rel.int.) 353 (38, $M^+ + 1$), 307 (100, M^+ -EtO), 103 (44). HRMS (CI) calcd. for $C_{12}H_{18}IO_4$ 353.0250. Found 353.0223.

***Z*-6,6-Diethoxy-2-iodo-hexa-4-yn-2-en-1-ol 16**. To a stirred solution of **15** (13.9 g, 0.0394 mol) in THF (300 mL) was added DIBAL-H (135 mL, 0.135 mol, 1M in hexanes) at -78°C under an argon atmosphere over 1.25 h. After 30 min at 0°C, the reaction mixture was recooled to -78°C and MeOH (22 mL) added dropwise. The cooling bath was removed and 10 % aqueous sodium tartrate (300 mL) was added, and stirred for 45 min. The mixture was filtered through celite and extracted with dichloromethane (4 x 300 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give a yellow liquid which was purified by chromatography over silica gel, eluting with 40% Et_2O/petroleum ether, to give the *Z*-vinyl iodide **16** (11.16 g, 0.036 mol, 92%). IR (CCl_4) 3640, 3460, 2979, 2930, 2898, 2222, 1732, 1443, 1393, 1370, 1354, 1326, 1263, 1172, 1087, 1054, 1009, 909, 831 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (1H, d, J = 1.3 Hz), 5.40 (1H, d, J = 1.3 Hz), 4.29 (2H, dd, J = 6.5, 1.3 Hz), 3.81 (2H, m, J = 9.5, 7.2 Hz), 3.63 (2H, m, J = 9.5, 7.2 Hz), 2.90 (1H, t, J = 6.5 Hz, -OH), 1.26 (6H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 119, 116, 92, 90, 84, 71, 61, 15. MS (CI, m/e, rel.int.) 293 (5.7, M^+ -OH), 265 (100, M^+ -EtO), 103 (32). HRMS (CI) calcd. for $C_{10}H_{15}IO_3$ 310.0066. Found 310.0042.

***Z*-6,6-Diethoxy-2-iodo-hexa-4-yn-2-en-1-*tert*-butyldimethylsilylether 17**. To a solution of **16** (5.66 g, 18 mmol) in dichloromethane (75 mL) was added, at room temperature under an atmosphere of argon, triethylamine (25 mL) and *t*-butyldimethylsilyltrifluoromethyl sulfonate (5.8 mL). After stirring for 2 h aqueous $NaHCO_3$ was added and the phases were separated. The organic phase was dried ($MgSO_4$), the solvent was evaporated *in vacuo*, and the residue purified by flash chromatography over silica gel eluting with pentane/5% ether to give **17** (7.64 g, 99%). IR (CCl_4) 2977, 2956, 2930, 2885, 2858, 1471, 1463, 1444, 1390, 1354, 1326, 1254, 1172, 1117, 1090, 1055, 1020, 939, 908, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (1H, m, J = 2.1, 1.8 Hz), 5.40 (1H, d, J = 1.8 Hz), 4.26 (2H, d, J = 2.1 Hz), 3.81 (2H, m, J = 9.4, 7.0 Hz), 3.61 (2H, m, J = 9.4 Hz, 7.0 Hz), 1.23 (6H, t, J = 7.0 Hz), 0.88 (9H, s), 0.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 118, 114, 92, 89, 85, 71, 61, 26, 18, 15, -5. MS (CI, m/e, rel.int.) 425 (5.9, M^+ + 1), 409 (16, M^+ -CH_3), 379 (100, M^+ -EtO). HRMS (CI) calcd. for $C_{16}H_{29}IO_3Si$ 424.0931. Found 424.0873.

***Z*-3-[3-*tert*-Butyldimethylsilyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]cyclopent-2-en-1-ol 18 (X = H, OH)**. To a stirred suspension of CuI (100 mg) in benzene (4 mL) was added *n*-butylamine (0.5 mL) at room temperature under an atmosphere of argon. A solution of **17** (310 mg, 0.73 mmol) in benzene (2 mL) was added, followed by a solution of *tetrakis*-(triphenylphosphine)palladium (370 mg) in benzene (15 mL), and a solution of 3-ethynyl-2-cyclopenten-1-ol (92 mg, 0.85 mmol) in benzene (2 mL). After 1 h the mixture was washed with saturated aqueous NH_4Cl, and the aqueous phase extracted with ether, dried ($MgSO_4$), and the solvent evaporated *in vacuo*. Flash chromatography of the residue over silica gel eluting with pentane/40% ether gave **18** (X = H, OH) (230 mg, 78%). IR (CCl_4) 3600, 3462, 2955, 2930, 2885, 2857, 2218, 1615, 1471, 1462, 1390, 1354, 1326, 1258, 1174, 1137, 1085, 1054, 1006, 938, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (1H, m, J = 7 Hz), 6.03 (1H, m, J = 1.7, 1.3 Hz), 5.42 (1H, d, J = 1.3 Hz), 4.87 (1H, bs), 4.19 (2H, d, J = 1.7 Hz), 3.76 (2H, m, J = 9.5, 7.0 Hz), 3.59 (2H, m, J = 9.5, 7.0 Hz), 2.61 (1H, m), 2.45-2.20 (3H, m), 1.69 (1H, m), 1.20 (6H, t, J = 7.0 Hz), 0.88 (9H, s), 0.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140, 136, 128, 112, 94, 92, 91, 89, 83, 77, 64, 61, 35, 33, 26, 18, 15, -6. MS (CI, m/e, rel.int.) 405 (9, M^+ +1), 387 (9, M^+ -EtO),

359 (100, M^+ -OH), 341 (58, M^+ -EtO-H_2O), 253 (25). HRMS (CI) calcd. for $C_{23}H_{37}O_4Si$ 405.2461. Found 405.2436.

***Z*-3-[3-*tert*-Butyldimethylsilyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]cyclopent-2-en-1-one 18 (X = O).** To a solution of **18** (X = H, OH) (3.34 g, 8.26 mmol) in dichloromethane (100 mL) was added pyridinium dichromate (4.7 g, 12.4 mmol), and the mixture stirred at room temperature for 2h. Ether was added, and the mixture was filtered through celite. The solvent was evaporated, and the residue purified by flash chromatography over silica gel eluting with pentane/30% ether, to give **18** (X = O) (1.94 g, 58%). IR (CCl_4) 2977, 2956, 2930, 2885, 2858, 2188, 1714, 1675, 1597, 1575, 1471, 1463, 1440, 1408, 1390, 1353, 1326, 1273, 1259, 1167, 1136, 1113, 1088, 1054, 1007, 930, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.31(1H, t, J = 1.8 Hz), 6.18 (1H, m, J = 2.2, 1.2 Hz), 5.42 (1H, d, J = 1.2 Hz), 4.24 (2H, d, J = 2.2 Hz), 3.74 (2H, m, J = 9.5 7.1 Hz), 3.59 (2H, m, J = 9.5, 7.1 Hz), 2.76 (2H, m), 2.43 (2H, m), 1.20 (6H, t, J = 7.1 Hz), 0.89 (9H, s), 0.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209, 156, 137, 135, 115, 100, 93, 92, 91, 82, 64, 61, 35, 32, 26, 18, 15, -6. MS (CI, m/e, rel.int.) 403 (3.5, M^+ +1), 357 (100, M^+ -EtO). HRMS (CI) calcd. for $C_{23}H_{35}O_4Si$ 403.2231. Found 403.2240.

***Z*-3-[3-*tert*-Butyldimethylsilyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-5,6-η²-dicobalthexacarbonyl-3-en]cyclopent-2-en-1-one 19.** To a solution of **18** (X = O) (75 mg, 0.19 mmol) in *n*-heptane (6 mL) was added dicobalt octacarbonyl (66 mg, 0.19 mmol), and the mixture was stirred under an atmosphere of argon at room temperature for 30 minutes. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography over silica gel eluting with pentane/15% ether to give **19** (111 mg, 87%). IR (CCl_4) 2955, 2930, 2857, 2093, 2058, 2033, 1714, 1626, 1585, 1471, 1463, 1441, 1389, 1330, 1308, 1260, 1166, 1133, 1112, 1063, 1005, 863, 838 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.35 (1H, bs), 6.43 (1H, bs), 5.52 (1H, s), 4.17 (2H, d, J = 1.2 Hz), 3.63 (2H, m, J = 9.0, 7.2 Hz), 3.48 (2H, m, J = 9.0, 7.2 Hz), 2.26 (2H, m), 1.90 (2H, m), 1.13 (6H, t, J = 7.2 Hz), 0.95 (9H, s), 0.01 (6H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 207, 200, 155, 137, 133, 126, 102, 101, 98, 97, 83, 66, 64, 34, 32, 26, 18, 15, -5. MS (CI, m/e, rel.int.) 689 (4.1, M^+ +1), 673 (1.5, M^+ -CH_3), 643 (100, M^+ -EtO). HRMS calcd for $C_{29}H_{34}Co_2O_{10}Si$ 688.0585. Found, 688.0590.

***Z*-3-[3-*tert*-Butyldimethylsilyl(oxy)methyl-7-oxa-hept-1,5-diyn-5,6-η²-dicobalthexacarbonyl-3-en] cyclopent-2-en-1-one 20.** To a solution of **19** (88 mg, 128 μmol) in dichloromethane (10 mL) was added 30% aqueous trifluoroacetic acid (1.0 mL), at room temperature under an atmosphere of argon. The mixture was stirred vigorously for 5 minutes, then aqueous $NaHCO_3$ was added. The aqueous phase was extracted with dichloromethane and the combined organic phases dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Flash chromatography over silica gel eluting with pentane/20% ether gave **20** (67 mg, 86%). IR (CCl_4) 2955, 2929, 2856, 2281, 2101, 2067, 2040, 1715, 1670, 1583, 1470, 1362, 1331, 1260, 1167, 1135, 1066, 864, 838 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 10.22 (1H, s), 7.10 (1H, t, J = 1.6 Hz), 6.43 (1H, t, J = 1.9 Hz), 4.05 (2H, d, J = 1.6 Hz), 2.24 (2H, m), 1.85 (2H, m), 0.92 (9H, s), -0.02 (6H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 207, 198, 189, 153, 138, 132, 126, 100, 97, 89, 84, 65, 34, 32, 26, 18, -5. MS (CI, m/e, rel.int.) 615 (92, M^+ +1), 587 (30, M^+ +1-CO), 559 (65, M^+ +1-2CO), 531 (18, M^+ +1-3CO), 483 (100). HRMS calcd for $C_{25}H_{24}Co_2O_9Si$ 613.9853. Found, 613.9850.

Adduct 21. To a solution of **20** (57.0 mg, 93 μmol) in dichloromethane (10 mL) under an atmosphere of argon was added ethyldiisopropylamine (200 μL) and *t*-butyldimethylsilyltrifluoromethane sulfonate (100 μL) at room temperature. After 10 minutes aqueous $NaHCO_3$ was added, and the mixture extracted with dichloromethane. After drying ($MgSO_4$) the solvent was evaporated *in vacuo*. Flash chromatography over silica gel eluting with pentane/2.5% ether gave **21** (49.2 mg, 63%) as a mixture of isomers (1:1). IR (CCl_4) 2958, 2930, 2895, 2886, 2858, 2094, 2058, 2034, 1916, 1579, 1260, 1107 cm^{-1}. UV (EtOH) λmax (ε) 324 (9,400), 268 (20,300), 203 (27,600) nm. ^1H NMR (300 MHz, C_6D_6) δ 7.10, 7.06 (1H, t, J = 1.8 Hz), 6.44 (1H, m, J = 5.4, 2.0 Hz), 6.23, 6.15 (1H, m, J = 5.4, 2.0 Hz), 5.94, 5.93 (1H, 2xs), 5.61 (1H, m, J = 2.0 Hz), 4.32 (2H, m, J = 15, 1.8 Hz), 1.1-0.8 (27H, m), 0.3-0.0 (18H, m). ^{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, -5 MS (FAB, m/e, 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), 154 (100). HRMS calcd for $C_{37}H_{52}Co_2O_9Si_3$ 842.1583. Found, 842.1580.

4-(Ethynyl-2-trimethylsilyl)-4-hydroxycyclopent-2-en-1-one ethylene acetal 22a. To a stirred solution of trimethylsilylacetylene (6.46 g, 9.3 mL, 0.066 mol) in THF (150 mL) was added *n*-BuLi (27.8 mL, 0.69 mol, 2.5M in hexanes) at -78°C under a nitrogen atmosphere. After 30 min at -78°C, freshly prepared $CeCl_3$ (17 g, 0.069 mol) was added and stirring continued for an additional 30 min. To the milky suspension, a precooled solution of **22** (4.27 g, 0.031 mol) in THF (50 mL) was added *via* cannula over 40 min. The orange solution was stirred at -78°C for 20 min then allowed to warm to 25°C and stirred for a total of 1.33 h. The reaction mixture was diluted in Et_2O (200 mL) and quenched with saturated aqueous NH_4Cl (300 mL). The solution was filtered through celite and extracted with Et_2O (3 x 300 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and the yellow liquid was purified by chromatography over silica gel, eluting with 80% Et_2O/petroleum ether to give **22a** (6.67 g, 92% yield). IR 3416, 2957, 2895, 2165, 1584, 1358, 1250, 1057, 948, 841, 759, 700, 629 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (1H, d, J = 5.4 Hz), 5.82 (1H, d, J = 5.4 Hz), 3.94 (4H, d, J = 2.1 Hz), 2.6 (1H, d, J = 14.4 Hz), 2.5 (1H, bs), 0.13 (9H, s). HRMS (CI) calcd for $C_{12}H_{19}O_3Si$ 239.1104. Found 239.1092.

4-Ethynyl-4-hydroxycyclopent-2-en-1-one ethylene acetal 23. To a stirred solution of **22a** (3.39 g, 0.014 mol) in THF (50 mL) was added TBAF (15 mL, 0.015 mol, 1M in THF). After 25 min, the red reaction mixture was diluted in Et_2O (50 mL), quenched with NH_4Cl (100 mL) and extracted with Et_2O (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*, and the yellow oil was purified by chromatography over silica gel, eluting with 80% Et_2O/petroleum ether, to give **23** (2.23 g, 94% yield). IR 3286, 2957, 2891, 2108, 1358, 1171, 1092, 1059, 1038, 948 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (1H, d, 5.4 Hz), 5.87 (1H, d, J = 5.4 Hz), 3.96 (4H, s), 2.65 (1H, d, J = 14.1 Hz), 2.59 (1H, s), 2.36 (1H, d, J = 14.1 Hz), 2.26 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139, 132, 117, 85, 73, 72, 65, 52. HRMS (CI) calcd for $C_9H_{11}O_3$ 167.0708. Found 167.0714.

4-Ethynyl-4-[*tert*-butyldimethylsilyl(oxy)]cyclopent-2-en-1-one ethylene acetal 24. To a solution of **22a** (9.74 g) in dichloromethane (100 mL) at 0°C under argon was added triethylamine (12.5 mL, 9.09 g, 0.09 mol) and *t*-butyldimethylsilyltrifluoromethyl sulfonate (18.8 mL, 21.6 g, 0.082 mol), and the solution allowed

to warm to 25°C. After stirring for a further 15 min, the mixture was diluted with more dichloromethane, poured into aqueous saturated $NaHCO_3$, washed with brine, dried ($MgSO_4$), and the solvent evaporated to give crude silyl ether. The product was dissolved in THF (250 mL)/water (50 mL), and lithium hydroxide monohydrate (12 g) added. The mixture was stirred overnight, poured onto water (300 ml), and extracted with Et_2O (4 x 200 mL). The ethereal extracts were washed with brine (200 mL), dried ($MgSO_4$), evaporated and the resulting oil purified by dry flash chromatography over silica gel eluting with hexane/ether (85/5) to give the **24** (10.5g, 78% from **22**) as a colorless oil. IR (CCl_4) 3309, 3072, 2956, 2084, 1472, 1360, 1136, 1101, 1069, 946 and 887 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (1H, d, J = 5.7 Hz), 5.76 (1H, d, J = 5.7 Hz), 3.93 (4H, m), 2 67 (1H, d, J = 13.8 Hz), 2.57 (1H, s), 2.30 (1H, d, J = 13.8 Hz), 0.84 (9H, s), 0.17 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140, 131, 117, 86, 75, 73, 65, 64, 54, 26, 18, -3. HRMS (CI) calcd for $C_{15}H_{25}O_3Si$ 281.1573. Found 281.1561.

***Z*-4-[3-*tert*-Butyldimethylsilyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]-4-hydroxycyclopent-2-en-1-one ethylene acetal 25**. To a suspension of copper (I) iodide (230 mg) in benzene (10 mL) was added *n*-butylamine (1.2 mL). To the resulting green solution was added the vinyl iodide **17** (710 mg, 1.57 mmol) in benzene (5 mL), followed by *tetrakis*-(triphenylphosphine)palladium (850 mg, 0.767 mmol) in benzene (35 mL). The mixture was subjected to three freeze-pump-thaw cycles, after which a solution of the alkyne **23** (320 mg, 1.80 mmol) in benzene (5 mL) was added rapidly. The solution was stirred at room temperature for 2 h, poured into saturated aqueous NH_4Cl and extracted into ether. The extracts were dried ($MgSO_4$), evaporated, and the residue purified by chromatography over Florisil (hexane-ether) to give **25** (552 mg, 71%) as a yellow oil. IR (CCl_4) 3603, 3469, 3067, 2978, 2956, 2930, 2884, 2858, 2221, 1472, 1463, 1444, 1425, 1390, 1356, 1327, 1259, 1171, 1114, 1086, 1056, 1009, 970, 946 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (1H, d, J = 5.5 Hz), 6.05 (1H, m), 5.84 (1H, d, J = 5.5 Hz), 5.43 (1H, d, J = 1.2 Hz), 4.17 (2H, d, J = 2.1 Hz), 3.95 (4H, bs), 3.76 (2H, m, J = 9.6, 7.1 Hz), 3.61 (2H, m, J = 9.6, 7.1 Hz), 3.04 (1H, bs), 2.65 (1H, d, J = 14.4 Hz), 2.40 (1H, d, J = 14.4 Hz), 1.22 (6H, t, J = 7.1 Hz), 0.88 (9H, s), 0.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139, 136, 133, 117, 112, 99, 92, 91, 83, 81, 74, 65, 64, 60.9, 60.8, 52, 26, 18, 15, -6. MS (CI, m/e, rel. int) 463 (2.3, M^+ +1), 447 (22), 446 (19), 445 (58), 419 (11), 417 (100), 418 (33), 405 (42). HRMS (CI) calcd. for $C_{25}H_{38}O_6Si$ 462.2438. Found 462.2441.

***Z*-4-[3-*tert*-Butyldimethylsilyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]-4-[*tert*-butyldimethyl silyl(oxy)]cyclopent-2-en-1-one ethylene acetal 26**. To a solution of **25** (682 mg, 1.47 mmol) in dichloromethane (7 mL) was added, at room temperature under an atmosphere of argon, triethylamine (7 mL) and *t*-butyldimethylsilyltrifluoromethyl sulfonate (880 μL). After stirring for 1 h aqueous $NaHCO_3$ was added and the phases were separated. The organic phase was dried ($MgSO_4$), the solvent was evaporated *in vacuo,* and the residue purified by flash chromatography over silica gel eluting with pentane/5% ether to give **26** (664 mg, 77%). IR (CCl_4) 2976, 2956, 2929, 2884, 2857, 1471, 1359, 1256, 1115, 1088, 1061, 1009, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (1H, q, J = 1.9 Hz), 5.99 (1H, d, J = 5.6 Hz), 5.74 (1H, d, J = 5.6 Hz), 5.40 (1H, d, J = 1.9 Hz), 4.14 (2H, d, J = 1.9 Hz), 3.91 (4H, m), 3.74 (2H, m, J = 9.4, 7.1 Hz), 3.58 (2H, m, J = 9.4, 7.1 Hz), 2.68 (1H, d, J = 14.0 Hz), 2.34 (1H, d, J = 14.0 Hz), 1.21 (6H, t, J = 7.1 Hz), 0.88 (9H, s), 0.83 (9H, s), 0.17 (3H, s), 0.16 (3H, s), 0.04 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140, 135, 131, 117, 112, 100, 92, 90,

83, 81, 75, 64.9, 64.8, 64.4, 60.7, 60.6, 54, 25.7, 25.5, 18.1, 17.8, 15, -3.1, -3.0, -6 MS (CI, m/e, rel. int): 576 (0.9, M^+), 534 (19), 533 (35), 532 (100), 519 (19), 446 (17). HRMS calcd. for $C_{31}H_{52}O_6Si_2$ 576.3302. Found 572.3298.

Z-4-[3-*tert*-Butyldimethylsilyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-5,6-η^2-dicobalthexacarbonyl-3-en]-4-[*tert*-butyldimethylsilyl(oxy)]cyclopent-2-en-1-one ethylene acetal 27. To a solution of **26** (664 mg, 1.15 mmol) in *n*-heptane (25 mL) was added dicobalt octacarbonyl (395 mg, 1.15 mmol), and the mixture was stirred under an atmosphere of argon at room temperature for 1 h. The solvent was evaporated *in vacuo* and the residue purified by flash chromatography over silica gel eluting with pentane/10% ether to give **27** (824 mg, 83%). IR (CCl_4) 2975, 2956, 2929, 2884, 2857, 2092, 2056, 2031, 1472, 1361, 1254, 1087, 1063, 839 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.28 (1H, t, J = 1.7 Hz), 6.10 (1H, d, J = 5.4 Hz), 5.72 (1H, d, J = 5.4 Hz), 5.72 (1H, s), 4.32 (2H, d, J = 1.7 Hz), 3.78 (2H, m), 3.62 (2H, m), 3.40 (4H, m), 3.00 (1H, d, J = 14.1 Hz), 2.70 (1H, d, J = 14.1 Hz), 1.21 (3H, t, J = 7.0 Hz), 1.19 (3H, t, J = 7.0 Hz), 1.00 (9H, s), 0.98 (9H, s), 0.28 (6H, s), 0.04 (6H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 200, 139, 133, 130, 125, 118, 104, 102, 97, 83.4, 82.6, 77, 66, 65.0, 64.7, 63.4, 63.3, 54, 25.9, 25.8, 18.5, 18.2, 15, -2.6, -2.7, -5. MS (CI, m/e, rel. int) 778 (M^+ -3CO), 750 (M^+ -4CO). HRMS calcd. for $C_{37}H_{52}Co_2O_{12}Si_2$ 862.1661. Found 862.1660.

Z-4-(3-Hydroxymethyl-7-oxa-hept-1,5-diyn-5,6-η^2-dicobalthexacarbonyl-3-en)-4-[*tert*-butyl dimethylsilyl(oxy)]cyclopent-2-en-1-one 28. To a solution of **27** (79 mg, 91 μmol) in THF (8 mL) was added *p*-toluenesulfonic acid monohydrate [100 mg, in water (4 mL)], at room temperature under an atmosphere of argon. The mixture was stirred vigorously for 3 h, then aqueous $NaHCO_3$ was added. The aqueous phase was extracted with dichloromethane and the combined organic phases dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Flash chromatography over silica gel eluting with pentane/40% ether gave **28** (47 mg, 82%). IR (CCl_4) 3633, 3490, 2957, 2930, 2896, 2886, 2859, 2102, 2067, 2039, 1731, 1670, 1254, 1073, 840 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 10.29 (1H, s), 7.18 (1H, d, J = 5.3 Hz), 6.79 (1H, bs), 5.90 (1H, d, J = 5.3 Hz), 3.70 (2H, bs), 2.94 (1H, d, J = 18.0 Hz), 2.66 (1H, d, J = 18.0 Hz), 1.35 (1H, bs), 0.88 (9H, s), 0.10 (6H, s). MS (FAB, m/e, rel. int) 631 (0.9, M^+ +1), 546 (6, M^+ -3CO), 518 (10, M^+ -4CO), 499 (10), 490 (16, M^+ -5CO), 462 (64, M^+ -6CO), 307 (100).

1α-*tert*-Butyldimethylsilyl(oxy)-4-di-*n*-butylboron(oxy)methyl-8α-hydroxy-9α-H-bicyclo[7.3.0] dodeca-2,6-diyn-6,7-η^2-dicobalthexacarbonyl-4,11-dien-10-one 29. To a solution of freshly distilled di-*n*-butylboron triflate (4.27 g) in dichloromethane (230 mL) and triethylamine (5.6 mL) at 25°C was added dropwise, a solution of **28** (371 mg, 0.59 mmol) in dichloromethane (90 mL) was added using a syringe pump (rate of addition: 1.1 mL/min). When the addition was complete the mixture was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography over silica gel eluting with hexane/30% ether to give the aldol product **29** (366 mg, 82%). IR (CCl_4) 3660, 2958, 2930, 2858, 2094, 2059, 2036, 2026, 1722, 1261, 1092, 839 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 7.53 (1H, d, J = 5.7 Hz), 7.08 (1H, bs), 6.24 (1H, d, J = 5.7 Hz), 5.68 (1H, d, J = 5.9 Hz), 4.12 (2H, d, J = 1.5 Hz), 3.54 (4H, t, J = 6.5 Hz), 3.27 (1H, d, J = 5.9 Hz), 1.50 (4H, m), 1.37 (4H, m), 0.93 (6H, t, J = 7.3 Hz), 0.89 (9H, s), 0.30 (3H, s), 0.28 (3H, s). ^{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, -2.7. MS data could not be obtained, see **30**.

Cycloaromatized adduct 30. To a solution of **29** (12.5 mg, 16.5 μmol) in isopropanol (0.5 mL) and 1,4-cyclohexadiene (1.0 mL) was added *N*-methylmorpholine *N*-oxide (20 mg, 10 eq) and the mixture stirred at 25 °C for 3 h. The mixture was filtered through celite and evaporated *in vacuo* to give an oil, which was chromatographed over silica gel eluting with hexanes/60% ether to give **30** (3.3 mg, 42%). IR (CCl_4) 3613, 3400, 2955, 2929, 2856, 1718, 1617, 1462, 1340, 1253, 1100, 1032, 908, 873, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, J = 5.6 Hz), 7.46 (1H, bs), 7.39 (2H, bs), 5.93 (1H, d, J = 5.6 Hz), 5.14 (1H, bs), 4.76 (2H, s), 3.48 (4H, m), 3.20 (1H, d, J = 2.0 Hz), 2.64 (1H, bs), 1.24 (14H, m), 0.88 (9H, s), 0.06 (3H, s), -0.08 (3H, s). ^{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, -3.1. HRMS (CI) calcd. for $C_{27}H_{43}BO_4Si$-$OBBu_2$ 329.1573. Found 329.1583.

***Z*-4-(3-Hydroxymethyl-7,7-diethoxy-hept-1,5-diyn-3-en)-4-[*tert*-butyldimethylsilyl(oxy)]cyclo pent-2-en-1-one ethylene acetal 31**. A 250 mL three-necked round-bottomed flask containing copper (I) iodide (1.026 g, 5.37 mmol) was evacuated and flushed with argon twice, benzene (36 mL) was added, followed by *n*-butylamine (8 mL). To the resulting green solution was added the vinyl iodide **16** (2.38 g, 7.67 mmol) in benzene (18 mL), then *tetrakis*-(triphenylphosphine)palladium (887 mg, 0.767 mmol) in benzene (40 mL). The mixture was subjected to three freeze-pump-thaw cycles, after which a solution of the alkyne **24** (2.36 g, 8.44 mmol) in benzene (30 mL) was added rapidly. The solution was stirred at room temperature for 2.5h, then poured into saturated aqueous NH_4Cl and extracted into ether. The extracts were dried ($MgSO_4$), evaporated, and the residue purified by chromatography over Florisil (hexane-ether) to give **31** (2.52g, 71%) as a yellow oil. IR (film) 3433, 2929, 1472, 1359, 1098, and 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (1H, d, J = 5.3 Hz), 5.92-5.95 (1H, m), 5.78 (1H, d, J = 5.3 Hz), 5.43 (1H, d, J = 1.5 Hz), 4.15 (2H, d, J = 1.6 Hz), 3.90-4.00 (4H, m), 3.46-3.62 and 3.64-3.81 (4H, m), 2.69 (1H, d, J = 14 Hz), 2.36 (1H, d, J = 14 Hz), 1.21 (6H, t, J = 14 Hz), 0.85 (9H, s), 0.20 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 135.2, 131.2, 117.0, 112.5, 93.0, 75.4, 65.0, 64.9, 64.8, 60.9, 60.2, 54.1, 25.6, 17.8, 15.1, -3.0. HRMS calcd. for $C_{25}H_{38}O_6Si$ 462.2437. Found 462.2443.

4-[3β-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3α,4α-oxido]-4-[*tert*-butyldimethylsilyl (oxy)]cyclopent-2-en-1-one ethylene acetal 32. To a suspension of powdered 3Å molecular sieves (1.5 g) in dichloromethane (42 mL) at -20°C under argon was added sequentially (-) - diethyl tartrate (0.223 mL, 271 mg, 1.33 mmol), titanium tetraisopropoxide (0.323 mL, 311 mg, 1.08 mmol) and *tert*-butyl hydroperoxide (7.2 mL, 21.6 mmol, 3M as a solution in isooctane). The mixture was stirred for 30 min, the allylic alcohol **31** (2.5g, 5.4 mmol) in dichloromethane (15 mL) was added, and the mixture warmed to -5°C and stirring continued for a further 22h at this temperature. Trimethyl phosphite (1.91 mL, 1.99g, 16 mmol) was slowly added, and the reaction mixture allowed to warm to 25°C, filtered through celite, and the celite washed with dichloromethane. The filtrate was washed with 10% aqueous tartaric acid, aqueous saturated $NaHCO_3$, brine, dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The crude product was dissolved in dichloromethane (75 mL) and cooled to 0°C. Triethylamine (1.13 mL, 820 mg, 8.11 mmol) and 4-dimethylaminopyridine (catalytic

amount) was added, followed by pivaloyl chloride (0.67 mL, 652 mg, 5.41 mmol). The solution was allowed to warm to 25°C, stirred for a further 45 min, diluted with dichloromethane (100 mL), washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The residue was purified by chromatography over silica (hexane-ether) to give the epoxide **32** (2.02 g, 67% over 2 steps) as a yellow oil (inseparable 1:1 mixture of diastereomers). IR (film) 2966, 2931, 2884, 1738, 1732, 1354, 1137, 1055, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (1H, d, J = 5.4 Hz), 5.74 and 5.75 (2H, 2d, J = 5.4 Hz; 1:1 mixture of diastereomers), 5.28 (1H, s), 4.37 and 4.38 (2H, 2d, J = 12.4 Hz; 1:1 mixture of diastereomers), 3.89-3.94 (4H, m), 3.67-3.78 (2H, m), 3.61 (1H, s), 3.53-3.62 (2H, m), 2.63 and 2.65 (2H, 2d, J = 18.2 Hz; 1:1 mixture of diastereomers), 2.29 and 2.30 (2H, 2d, J = 18.2 Hz; 1:1 mixture of diastereomers), 1.22 (9H, s), 1.20 (6H, t, J = 14 Hz), 0.88 (9H, s), 0.16 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 139.8, 139.7, 131.8, 131.7, 117.1, 117.1, 91.1, 89.5, 81.7, 77.8, 77.8, 75.0, 65.0, 64.8, 63.1, 61.1, -3.1, 78.9, 61.0, 60.9, 60.9, 53.5, 53.5, 49.1, 38.8, 27.1, 27.0, 26.4, 25.5, 25.4, 17.8, 15.0, -3.0. MS (CI) 563 (M^+ + H), 518, 431, 291, 182.

4-[3β-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3α,4α-oxido]-4-[*tert*-butyldimethylsilyl (oxy)]cyclopent-2-en-1-one 33. To a stirred solution of **32** (927 mg, 1.65 mmol) in THF (45 mL)/water (15 mL) at 0°C was added trifluoroacetic acid (45 mL), maintaining the temperature at 5°C. The solution was allowed to warm to 25°C, poured onto water (500 mL), extracted into ether, and the ethereal extracts washed repeatedly with saturated aqueous $NaHCO_3$ until neutral, then washed further with brine. The organic extracts were dried (Na_2SO_4) and evaporated to give essentially pure ketone **33** (852 mg, 99%) as a yellow oil (inseparable 1:1 mixture of diastereomers). IR (film) 2955, 2849, 1735, 1726, 1665, 1472, 1250, 1139, 836 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 and 7.38 (2H, 2d, J = 5.4 Hz; 1:1 mixture of diastereomers), 6.09 and 6.10 (2H, 2d, J = 5.4 Hz; 1:1 mixture of diastereomers), 5.24 (1H, s), 4.35 and 4.37 (2H, 2d, J = 12.4 Hz; 1:1 mixture of diastereomers), 4.10 and 4.11 (2H, 2d, J = 12.4 Hz; 1:1 mixture of diastereomers), 3.64-3.75 (2H, m), 3.63 (1H, s), 3.48-3.60 (2H, m), 2.90 and 2.92 (2H, 2d, J = 18.2 Hz; 1:1 mixture of diastereomers), 2.57 and 2.58 (2H, 2d, J = 18.2 Hz; 1:1 mixture of diastereomers), 1.22 (6H, t, J = 14 Hz), 1.20 (9H, s), 0.84 (9H, s), 0.20 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 177.2, 162.4, 162.3, 132.2, 132.1, 86.8, 86.8, 80.1, 78.5, 71.9, 65.8, 63.1, 63.0, 61.1, 61.0, 60.9, 54.9, 54.9, 52.3, 49.4, 49.3, 38.8, 27.0, 25.4, 17.7, 15.2, 15.0, -3.0, -3.1, -3.2. HRMS calcd. for $C_{28}H_{42}O_7Si$ 518.2699. Found 518.2693

4-[3β-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-5,6-η²-dicobalthexacarbonyl-3α,4α-oxido]-4-[*tert*-butyldimethylsilyl(oxy)]cyclopent-2-en-1-one 34. To a solution of **33** (850 mg, 1.64 mmol) in *n*-heptane (56 mL) at 25°C under argon was added portion wise dicobalt octacarbonyl (561 mg, 1.64 mmol). After stirring for a further 10 min, the heptane was removed under reduced pressure at 25°C, and the residue purified by passage through a short silica gel column (hexane-ether) to give the complexed alkyne **34** (1.05 g, 80%) as a viscous brown oil (inseparable 1:1 mixture of diastereomers). IR (film) 2958, 2932, 2097, 2059, 2033, 1738, 1731, 1472, 1255, 1139, 1062, 839 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 7.54 and 7.61 (2H, 2d, J = 5.4 Hz; 1:1 mixture of diastereomers), 6.23 and 6.26 (2H, 2d, J = 5.4 Hz; 1:1 mixture of diastereomers), 5.49 (1H, d, J = 1.9 Hz), 4.42 and 4.44 (2H, 2d, J = 11.7 Hz; 1:1 mixture of diastereomers), 4.38 (1H, s), 4.25 and 4.28 (2H, 2d, J = 11.7 Hz; 1:1 mixture of diastereomers), 3.74-3.89 (2H, 2m), 3.57-3.69 (2H, m), 2.87 and 2.96 (2H, 2d, J = 18.4 Hz; 1:1 mixture of diastereomers), 2.63 and 2.65 (2H, 2d, J = 18.4 Hz; 1:1 mixture of

diastereomers), 1.21 (15H, m), 0.88 (9H, s), 0.27 (6H, s). ^{13}C NMR (75 MHz, CD_3OD) δ 206.0, 200.2, 200.2, 178.6, 163.6, 163.5, 133.9, 133.8, 102.3, 102.3, 68.4, 64.4, 64.2, 64.1, 59.6, 59.5, 39.7, 27.5, 25.9, 18.6, 15.4, -2.6, -2.7. HRMS calcd. for $C_{34}H_{42}Co_2O_{13}Si$ 804.1058. Found 804.1052.

4-[3β-Pivaloyl(oxy)methyl-7-oxa-hept-1,5-diyn-5,6-η²-dicobalthexacarbonyl-3α,4α-oxido]-4-[*tert*-butyldimethylsilyl(oxy)]cyclopent-2-en-1-one 35. To a stirred solution of **34** (1.05 g, 1.3 mmol) in chloroform (36 mL)/water (12 mL) at 0°C was added trifluoroacetic acid (36 mL), maintaining the temperature at 5°C. The solution was allowed to warm to 25°C, stirred for a further 1h, poured onto water (300 mL) and extracted into ether. The ethereal extracts were washed repeatedly with saturated aqueous $NaHCO_3$ until neutral, then washed further with brine. The organic extracts were dried (Na_2SO_4), evaporated, and the residue purified by chromatography over Florisil (hexane-ether) to give the aldehyde **35** (538 mg, 56%) as an orange-brown oil (inseparable 1:1 mixture of diastereomers). LR or HR mass spec. unobtainable. IR (film) 2956, 2931, 2103, 2067, 2037, 1732, 1668, 1472, 1255, 1144, 1069, 839, 780 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 10.35 and 10.50 (2H, 2s; 1:1 mixture of diastereomers), 7.50 (1H, d, J = 5.4 Hz), 6.20 (1H, d, J = 5.4 Hz), 4.92, (1H, s), 4.21-4.39 (2H, m), 2.91 and 2.94 (2H, 2d, J = 18.4 Hz; 1:1 mixture of diastereomers), 2.56 and 2.57 (2H, 2d, J = 18.4 Hz; 1:1 mixture of diastereomers), 1.30 (9H, s), 0.90 (9H, s), 0.25 (6H, s). ^{13}C NMR (75 MHz, CD_3OD) δ 207.2, 192.9, 192.8, 192.5, 164.8, 164.5, 164.3, 164.2, 133.4, 133.2, 133.1, 87.7, 77.0, 73.7, 68.1, 67.2, 66.8, 53.2, 47.9, 40.2, 26.2, 26.1, 25.9, 18.6, 15.3, -2.7, -2.8.

1α-*tert*-Butyldimethylsilyl(oxy)-4β-pivaloyl(oxy)methyl-8α-hydroxy-9α-H-4α,5α-oxidobicyclo [7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalthexacarbonyl-11-en-10-one 36. A solution of freshly distilled di-*n*-butylboron triflate (0.381 mL, 474 mg, 1.72 mmol) in dichloromethane (10 mL) was cooled to -78°C under argon. Triethylamine (0.484 mL, 353 mg, 3.45 mmol) was added dropwise, maintaining the temperature at -70°C. The mixture was stirred for 10 min, brought to 0°C, and a solution of **35** (63 mg, 86 mmol) in dichloromethane (7.5 mL) was added using a syringe pump (rate of addition: 0.2 mL/min). When the addition was complete, the solution was warmed to 25°C, and stirred for a further 2h. A second identical experiment was run simultaneously with the above, using di-*n*-butylboron triflate (0.365 mL, 454 mg, 1.64 mmol) and triethylamine (0.464 mL, 338 mg, 3.28 mmol) in dichloromethane (10 mL), and ketoaldehyde **35** (60 mg, 82 mmol) in dichloromethane (7.5 mL). Each reaction mixture was diluted with dichloromethane (10 mL), washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The residue was purified by preparative thin layer chromatography over silica gel (hexane-ether) to give the diastereomeric aldol products **36** and **36a**. They were combined, affording 32 mg and 35 mg of the less polar and more polar diastereomers respectively (in order of elution); overall combined yield, 57%. *First diastereomer*: LR and HR mass spec. unobtainable. IR (film) 2960, 2931, 2063, 2042, 2030, 1735, 1716, 1576, 1370, 1121, 810 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 7.44 (1H, d, J = 5.4 Hz), 6.48 (1H, s), 6.23 (1H, d, J = 5.4 Hz), 5.82 (1H, d, J = 5.8 Hz), 3.60 (2H, m), 3.34 (1H, s), 1.30 (9H, s), 0.90, (9H, s), 0.30 and 0.35 (6H, 2s), -OH not observed. ^{13}C NMR (75 MHz, CD_3OD) δ 205.4, 163.4, 133.4, 89.1, 77.1, 76.2, 75.1, 74.8, 70.8, 66.5, 40.5, 27.7, 26.2, 18.8, -2.5, -2.7. *Second diastereomer*: ^1H NMR (300 MHz, CD_3OD) δ 6.25 and 7.52 (2H, 2d, J = 5.4 Hz), 6.19 (1H, s), 5.29 (1H, d, J = 7.1 Hz), 3.55 and 3.60 (2H, 2d, J = 6 Hz), 3.15 (1H, d, J = 7.1 Hz), 1.30 (9H, s), 0.86 (9H,

s), 0.25 and 0.30 (6H, 2s), -OH not observed. ^{13}C NMR (75 MHz, CD_3OD) δ 205.6, 162.5, 134.2, 77.8, 77.1, 76.1, 75.3, 74.6, 70.4, 64.9, 40.3, 27.2, 26.1, 18.8, 14.3, -2.4, -2.7.

1α-*tert*-Butyldimethylsilyl(oxy)-4β-pivaloyl(oxy)methyl-8α-hydroxy-9α-H-4α,5α-oxidobicyclo [7.3.0]dodeca-2,6-diyn-11-en-10-one 37. A solution of **36** (12 mg, 16.4 mmol; less polar diastereomer) in benzene (1 mL) at 25°C under argon was treated with iodine (21 mg, 82.2 mmol). After stirring for 1h, the reaction mixture was diluted with ether, washed with aqueous sodium thiosulphate, brine, dried (Na_2SO_4), the solvent evaporated *in vacuo*. The residue was purified by chromatography over silica gel (hexane-ether) to give the decomplexed product **37** (5 mg, 69%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, d, J = 5.4 Hz), 6.21 (1H, d, J = 5.4 Hz), 5.53 (1H, s), 5.07 (1H, d, J = 1.8 Hz), 4.16 (1H, d, J = 12 Hz), 3.65 (1H, d, J = 12 Hz), 3.44-3.52 (1H, m), 1.26 (9H, s), 0.95 (9H, s), 0.15 and 0.23 (6H, 2s), -OH not observed. HRMS (CI) calcd. for $C_{24}H_{33}O_6Si$ 445.2046 Found 445.2018.

A solution of **36a** (7.2 mg, 9.86 mmol; more polar diastereomer) in benzene (0.75 mL) at 25°C under argon was treated with iodine (12.5 mg, 49.3 mmol). After stirring for 1h, the reaction mixture was diluted with ether, washed with aqueous sodium thiosulphate, brine, dried (Na_2SO_4), and the solvent evaporated *in vacuo*. The residue was purified by column chromatography over silica gel (hexane-ether) to give the decomplexed product **37a** (3.3 mg, 75%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, d, J = 5.4 Hz), 6.17 (1H, d, J = 5.4 Hz), 5.44 (1H, s), 5.03 (1H, d, J = 12 Hz), 4.05 (1H, d, J = 12 Hz), 3.45-3.55 (2H, m), 1.30 (9H, s), 0.98 (9H, s), 0.18 and 0.22 (6H, 2s), -OH not observed.

***Z*-6,6-Diethoxy-2-iodo-hex-4-yn-2-en-1-pivaloate 38**. To a stirred solution of **16** (142 mg, 0.458 mmol) in dichloromethane (4 mL) was added Et_3N (250 μL) followed by 4-dimethylaminopyridine (10 mg, 0.082 mmol) and pivaloyl chloride (100 μL , 97.9 mg, 0.812 mmol) under an argon atmosphere. After 5 min the orange solution was diluted in dichloromethane (50 mL), quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with dichloromethane (3 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give a yellow liquid which was purified by chromatography over silica gel, eluting with 10% Et_2O/petroleum ether, to give **38** (175 mg, 0.444 mmol, 97%). IR 2976, 2932, 2883, 222, 1809, 1738, 1480, 1397, 1368, 1326, 1279, 1140, 1054, 1008 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (1H, d, J = 1.5 Hz), 5.41 (1H, d, J = 1.2 Hz), 4.76 (2H, d, J = 1.5 Hz), 3.5-3.8 (4H, m), 1.22 (15H, m). ^{13}C NMR ($CDCl_3$) δ 176.9, 118.6, 111.3, 91.5, 90.6, 84.0, 70.3, 61.0, 38.7, 27.0, 15.0. HRMS (CI) calcd for $C_{15}H_{23}O_4I$ 395.0719. Found 395.0705. MS 293 (10), 349 (100), 395 (5, M^+ +H).

***Z*-4-[3-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]-4-hydroxycyclopent-2-en-1-one ethylene acetal 39**. To a stirred solution of CuI (1.64 g, 0.86 mmol) in degassed benzene (150 mL) was added *n*-$BuNH_2$ (5.84 g, 7.9 mL, 0.080 mol) under an argon atmosphere, followed by a solution of the vinyl iodide **38** (4.5 g, 11.4 mmol) in degassed benzene (50 mL). Additional degassed benzene (200 mL) was added followed by freshly prepared *tetrakis*-(triphenylphosphine)palladium (5.80 g, 5.0 mmol), and the acetylene **23** (2.37 g, 14.3 mmol). Within 1 h, the solution had turned dark red. After 9.75 h, the dark reaction mixture was diluted with Et_2O (300 mL), poured onto saturated aqueous NH_4Cl (400 mL) and extracted with Et_2O (3 x 400 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give a crude slurry which was purified by

chromatography over silica gel, eluting with 50% Et_2O/petroleum ether, to give dark oil **39** (2.46 g, 5.7 mmol, 50%). IR 3435, 2976, 1732, 1480, 1354, 1146, 1091, 1056, 1008 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (1H, d, J = 5.7 Hz), 5.90 (1H, d, J = 1.5 Hz), 5.85 (1H, d, J = 5.4 Hz), 5.42 (1H, d, J = 1.2 Hz), 4.78 (2H, d, J = 1.5 Hz), 3.94 (4H, s), 3.54 (4H, m), 2.80 (1H, s), 2.63 (1H, d, J = 14.1 Hz), 2.39 (1H, d, J = 14.1 Hz), 1.2 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4., 139.0, 132. 8, 130.9, 117.2, 115.1, 99.3, 91.5, 82.1, 80.3, 74.0, 65.7, 64.9, 64.3, 64.3, 60.9, 51.7, 27.0, 14.9. MS 141 (16), 279 (20), 387 (96), 388 (32), 406 (32), 415 (100), 433 (7, M^+ +H). HRMS (CI) calcd for $C_{24}H_{32}O_7$ 432.2148. Found 432.2145.

***Z*-4-[3-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]-4-[*tert*-butyldimethylsilyl(oxy)] cyclopent-2-en-1-one ethylene acetal 40**. To a stirred solution of **39** (45 mg, 0.104 mmol) in dichloromethane (1 mL) and Et_3N (1 mL) was added *t*-butyldimethylsilyltrifluoromethyl sulfonate (57.5 mg, 50 μL, 0.218 mmol) under an argon atmosphere. After 1 h, an additional amount of *t*-butyldimethylsilyltrifluoromethyl sulfonate (57.5 mg, 50 μL, 0.218 mmol) was added and stirred for a total of 3 h. The reaction mixture was diluted in dichloromethane (20 mL), quenched with saturated aqueous $NaHCO_3$ (20 mL), extracted with dichloromethane (3 x 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give a crude slurry which was purified by chromatography over silica gel, eluting with 30% Et_2O/petroleum ether, to give a yellow oil **40** (57 mg, 0.104 mmol, 99%). IR 2974, 2930, 2285, 1734, 1358, 1139, 1099, 1057, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (1H, d, J = 5.4 Hz), 5.91 (1H, d, J = 1.5 Hz), 5.76 (1H, d, J = 5.7 Hz), 5.41 (1H, d, J = 0.9 Hz), 4.56 (2H, d, J = 1.2 Hz), 3.92 (4H, d, J = 2.4 Hz), 3.5-3.8 (4H, m), 2.68 (1H, d, J = 13.8 Hz), 2.34 (1H, d, J = 13.8 Hz), 1.2 (15H, m), 0.84 (9H, s), 0.18 (3H, s), 0.17 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 140.0, 131.4, 130.1, 118.9, 117.1, 115.0, 99.9, 91.7, 91.7, 81.9, 80.7, 75.4, 64.9, 64.8, 62.4, 61.0, 60.8, 53.7, 38.8, 27.1, 25.5, 17.8, 15.2, 15.0, -3.0. MS 415 (37), 489 (48), 501 (100), 502 (50), 531 (31), 547 (8, M^+ +H). HRMS (CI) calcd for $C_{36}H_{47}O_7Si$ 547.3091. Found 547.3082.

***Z*-4-[3-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-5,6-η²-dicobalthexacarbonyl-3-en]-4-[*tert*-butyldimethylsilyl(oxy)]cyclopent-2-en-1-one ethylene acetal 41**. To a stirred solution of **40** (224 mg, 0.410 mmol) in pentane (25 mL) was added $Co_2(CO)_8$ (140 mg, 0.410 mmol) under an argon atmosphere. After 1.5 h, the solution was concentrated *in vacuo* to give a crude oil which was purified by chromatography over silica gel, eluting with 30% Et_2O/petroleum ether, to give red oil **41** (333 mg, 0.40 mmol, 98%). IR 2930, 2055, 2027, 1732, 1138, 1098, 1064 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 6.09 (1H, d, J = 5.7 Hz), 5.71 (1H, d, J = 5.4 Hz), 5.68 (1H, s), 4.58 (2H, s), 3.5-3.9 (4H, m), 3.4 (4H, m), 2.98 (1H, d, J = 14.1 Hz), 2.68 (1H, d, J = 14.1 Hz), 1.19 (15H, m), 0.99 (9H, s), 0.28 (6H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 199.8, 176.9, 139.4, 135.2, 133.0, 120.8, 117.5, 104.0, 101.8, 98.2, 82.9, 81.8, 76.8, 67.0, 65.0, 64.7, 63.4, 63.3, 53.9, 38.9, 27.2, 26.2, 25.6, 22.8, 18.2, 15.4, 15.3, 10.5, -2.6. MS 133 (76), 645 (50), 647 (22), 703 (35), 731 (81), 787 (100), 833 (8, M^+ +H). HRMS (CI) calcd for $C_{36}H_{46}Co_2O_{13}Si$ 833.1450. Found 833.14552.

***Z*-4-[3-Pivaloyl(oxy)methyl-7-oxa-hept-1,5-diyn-5,6-η²-dicobalthexacarbonyl-3-en]-4-[*tert*-butyl dimethylsilyl(oxy)]cyclopent-2-en-1-one 42**. To a stirred solution of **41** (105 mg, 0.126 mmol) in THF (10 mL) and water (5 mL) was added *p*-toluenesulfonic acid (5.0 g, 0.026 mol). After 20 min, the reaction mixture was diluted with Et_2O (25 mL), quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with Et_2O

(3 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give a red oil which was purified by chromatography over silica gel, eluting with 30% Et_2O/petroleum ether, to give **42** (86 mg, 0.120 mmol, 96%). IR 2959, 2932, 2859, 2102, 2067, 2037, 1728, 1663, 1139, 1065, 839, 807, 780, 514 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 10.31 (1H, s), 6.65 (1H, s), 5.88 (1H, d, J = 5.4 Hz), 4.21 (2H, d, J = 3.6 Hz), 2.99 (1H, d, J = 18.3 Hz), 2.68 (1H, d, J = 18.3 Hz), 1.14 (9H, s), 0.88 (9H, s), 0.12 (3H, s), 0.12 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 202.9, 189.0, 177.0, 161.0, 134.4, 133.2, 129.8, 120.9, 102.1, 83.4, 82.5, 73.5, 65.4, 52.3, 38.8, 27.1, 25.9, 18.0, -2.8, -2.8. MS 527 (66), 583 (100), 584 (11), 613 (11), 715 (2, M^+ +H). HRMS (CI) calcd for $C_{30}H_{33}Co_2O_{11}Si$ 715.0518. Found 715.0456.

1α-*tert*-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methyl-8α-hydroxy-9α-H-bicyclo[7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalthexacarbonyl-4,11-dien-10-one 43. To a stirred solution of dichloromethane (125 mL) and Et_3N (2.47 g, 3.4 mL, 0.0244 mol) was added freshly prepared *n*-Bu_2BOTf (2.35g, 2.1 mL, 8.58 mmol) followed by a solution of **42** (204 mg, 0.286 mmol) in dichloromethane (50 mL) *via* syringe pump over 5.5 h under an argon atmosphere. After an additional 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (500 mL) and extracted with dichloromethane (4 x 500 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give a red oil which was purified by PLC, eluting with 30% Et_2O/petroleum ether, to give **43** (150 mg, 0.210 mmol, 74%). IR 3482, 3957, 2930, 2858, 2093, 2055, 2029, 1734, 1718, 1464, 1363, 1279, 1253, 1186, 840 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 6.81 (1H, d, J = 5.7 Hz), 6.78 (1H, s), 5.71 (1H, d, J = 5.7 Hz), 5.53 (1H, J = t, 7.5 Hz), 4.37 (1H, d, J = 12.9 Hz), 4.22 (1H, d, J = 12.9 Hz), 3.22 (1H, d, J = 6.9 Hz), 3.10 (1H, bd, J = 5.1 Hz), 1.16 (9H, s), 0.89 (9H, s), 0.22 (3H, s), 0.15 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 168.2, 160.9, 143.1, 132.4, 119.6, 100.8, 90.7, 84.5, 75.2, 74.8, 65.9, 63.1, 38.8, 27.2, 25.7, 18.1, 0.6, -2.6, -2.7. MS 153 (100), 546, 574, 602, 629, 713 (M -H). HRMS (FAB) calcd for $C_{30}H_{31}Co_2O_{11}Si$ 713.0299. Found 713.0298.

1α-*tert*-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalthexacarbonyl-4,8,11-trien-10-one 44. To a stirred solution of **43** (56.2 mg, 0.0787 mmol) in dichloromethane (6 mL) was added Et_3N (406 mg, 560 μL, 4.02 mmol) under an argon atmosphere, followed by 4-dimethylaminopyridine (39 mg, 0.32 mmol) and methanesulfonyl chloride (103.6 mg, 70 μL, 0.904 mmol). After 1.5 h, the reaction mixture was diluted with Et_2O (20 mL), extracted with 10% aqueous sodium tartrate (20 mL), saturated aqueous $NaHCO_3$ (20 mL), 1 M $CuSO_4$ (20 mL) and saturated aqueous NaCl (20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give a red oil **44** (53 mg, 0.0761 mmol, 97%). IR 2958, 2930, 2858, 2060, 2029, 1730, 1707, 1140 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.82 (1H, s), 6.80 (1H, d, J = 6 Hz), 6.69 (1H, s), 5.92 (1H, d, J = 6 Hz), 4.32 (2H, s), 0.87 (9H, s), 1.17 (9H, s), 0.08 (3H, s), 0.06 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 198.4, 192.1, 177.1, 155.2, 141.6, 140.5, 135.1, 133.2, 120.4, 103.1, 93.1, 85.0, 82.4, 70, 63.2, 38.8, 27.2, 25.9, 18.4, -2.3, -2.3. MS 154 (100), 269 (63), 392 (84), 697 (M^+ +H). HRMS (CI) calcd for $C_{30}H_{31}Co_2O_{10}Si$ 697.0351. Found 697.0360.

1α-*tert*-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalthexacarbonyl-4,8-dien-10-one 45. To a stirred (10 min) solution of $ZnCl_2$ (6.1 mg, 0.045 mmol) and $NaBH_3CN$ (4.7 mg, 0.075 mmol) in Et_2O (4 mL) at 0°C was added a solution of **44** (36.5 mg, 0.052 mmol) in

Et_2O (2 mL) followed by trimethylsilyl chloride (8 μL, 6.8 mg, 0.063 mmol, *via* cannula). After 1 h at 0°C and 2 h at 25°C, the mixture was recooled to 0°C and the oxaziridine $PhSO_2NOCHPh$ (65 mg, 0.249 mmol) was added over 15 min. After an additional 5 min at 0°C, the solution was warmed to 25°C and diluted with saturated aqueous. $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was purified by PLC, eluting with 30% Et_2O/petroleum ether, to give **45** (13 mg, 0.019 mmol, 36%). IR 2931, 2060, 2029, 1724, 1640, 1577, 1461, 1277, 1139, 1046, 988, 838 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.55 (1H, s), 6.67 (1H, s), 4.36 (2H, s), 2.4-2.6 (1H, m), 1.9-2.1 (2H, m), 1.6-1.8 (1H, m), 1.18 (9H, s), 0.87 (9H, s), 0.25 (3H, s), 0.22 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 202.2, 197.8, 177.1, 140.3, 139.7, 130.0, 120.3, 103.5, 89.3, 83.8, 81.0, 73.1, 63.4, 38.9, 35.6, 34.6, 27.2, 25.7, 18.2, -2.9. MS: 172 (50), 391 (100), 567 (11), 597 (23), 699 (M^+, 46). HRMS (FAB) calcd for $C_{30}H_{33}Co_2O_{10}Si$ 699.0510. Found 699.0500.

1α-*tert*-Butyldimethylsilyl(oxy)-4-hydroxymethylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalt hexacarbonyl-4,8-dien-10α-ol 46 (R = H). To a stirred solution of **45** (12 mg, 0.017 mmol) in toluene (3 mL) was added dropwise a solution of DIBAL-H (1.0 M in dichloromethane, 60 μL, 0.060 mmol) at -78°C under an atmosphere of argon. After 35 min at -78°C, methanol (50 μL) was added followed by saturated aqueous NH_4Cl (2 mL). The solution was allowed to warm to 25°C. The phases were separated and the aqueous phase extracted with Et_2O (4 x 5 mL). After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was purified by PLC, eluting with 30% Et_2O/petroleum ether, to give **46** (6 mg, 0.0097 mmol, 57%). IR 3417, 2929, 2857, 2089, 2054, 2023, 1254, 1162, 995, 838, 780 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 6.76 (1H, s), 6.71 (1H, s), 4.24 (1H, m), 3.6-3.7 (2H, m), 2.64 (1H, d, J = 10 Hz, -OH), 1.2-2.1 (4H, m), 0.90 (9H, s), 0.71 (1H, t, J = 6 Hz, -OH), 0.29 (3H, s), 0.27 (3H, s). MS 219 (21), 221 (38), 235 (50), 325 (42), 391 (38), 485 (100), 616 (M^+, 4). HRMS (CI) calcd for $C_{25}H_{26}Co_2O_9Si$ 616.001. Found 615.958.

1α-*tert*-Butyldimethylsilyl(oxy)-4-[1-naphthoyl(oxy)]methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalthexacarbonyl-4,8-dien-10α-ol 47 (R = 1-Naphthoyl). To a stirred solution of **46** (R = H) (5.7 mg, 0.0093 mmol) in dichloromethane (1 mL) was added Et_3N (30 μL, 22 mg, 0.22 mmol) followed by 1-naphthoyl chloride (1.4 μL, 1.8 mg, 0.0093 mmol) at -5°C. After 1.5 h at -5°C, saturated aqueous NH_4Cl (2 mL) was added and diluted with Et_2O (4 mL). The solution was allowed to warm to 25°C and the phases were separated. The aqueous phase was extracted with Et_2O (4 x 5 mL). After drying ($MgSO_4$) the solvent was evaporated *in vacuo* and the residue was purified by PLC, eluting with 30% Et_2O/petroleum ether, to give **47** (R = 1-Naphthoyl) (5.5 mg, 0.0071 mmol, 77%). IR 3550, 2930, 2361, 2055, 2023, 1720, 1241, 1129, 996, 780, 512 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 9.41 (1H, dd, J = 1.0, 8.4 Hz), 8.32 (1H, dd, J = 1.2, 7.5 Hz), 7.59 (1H, d, J = 8 Hz), 7.52 (1H, dd, J = 8.0, 0.6 Hz), 7.42 (1H, ddd, J = 1.8, 1.5, 8.0 Hz), 7.0-7.3 (3H, m), 6.76 (1H, s), 6.70 (1H, s), 4.65 (1H, d, J = 12.9 Hz), 4.59 (1H, d, J = 12.9 Hz), 2.62 (1H, d, J = 10.2 Hz, -OH), 1.4-2.1 (4H, m), 0.82 (3H, s), 0.16 (3H, s). MS 154 (90), 602 (100), 771 (M^+, 1). HRMS (CI) calcd for $C_{36}H_{32}Co_2O_{10}Si$ 770.4287. Found 770.0357.

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29. The enantiomeric purity of **32** was determined by derivatizing the epoxy alcohol, obtained directly from the Sharpless epoxidation, with R-(-)-1-(1-naphthyl)ethyl isocyanate.

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