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A General Strategy Using $\eta^2Co_2(CO)_6$ Acetylene Complexes for the Synthesis of the Enediyne Antitumor Agents Esperamicin, Calicheamicin, Dynemicin and Neocarzinostatin

Philip Magnus

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

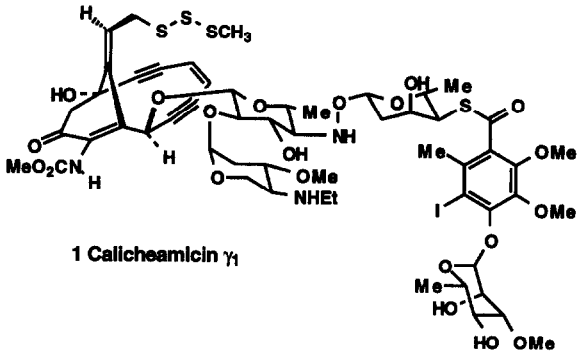
Abstract: A review of the use of $\eta^2Co_2(CO)_6$-acetylene complexes as stable intermediates for the construction of the core structures of the antitumor enediyne agents esperamicin, calicheamicin, dynemicin and neocarzinostatin from the authors laboratory is presented.

Introduction

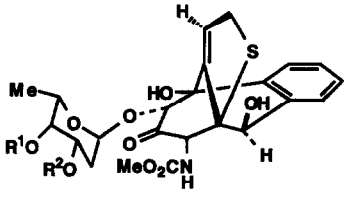
In the 1970's and 1980's it appeared that natural product chemistry and the synthesis of natural products was losing some of its previous momentum. The enormous structural diversity of secondary metabolites was confined to terpenoids, alkaloids and acetogenins, and very few dramatically different structural variations were evident. The degree of synthetic sophistication, particularly in the terpenoid area, had reached such a level that it was felt that any molecule could be synthesized, and moreover, the main reactions and strategies of organic synthesis had been discovered. If this were true, it suggests that the level of predictability of organic synthesis had reached a very reliable level and was in danger of becoming a routine tool. All pursuits of knowledge and discovery are destined to be subjected to periods of relative quietness, but provided we view science optimistically and are not prophets of doom, new challenges will arrive and new discoveries will be made.

It was in 1987 that the Lederle[1] and Bristol-Myers[2] groups reported the exciting and unprecedented structures of calicheamicin γ_1 **1**, esperamicin A_1 **2**, A_{1b} **3**, A_2 **4** and the metabolite esperamicin X **5**, **Scheme 1**. They were isolated from fermentations of *Micromonospora echinospora* sp. calichensis, and cultures of *Actinomadura verrucosospora* BBM 1675, ATCC 39334 respectively. Presently, these compounds are the most potent antitumor antibiotics known, being approximately 10^3 more active than adriamycin against murine tumors, and represent a new class of natural products based upon the Z-enediyne functionality. More recently the antitumor antibiotic dynemicin **6** can be added to the growing list of enediyne natural products.[3] It also exhibits extraordinarily potent antimicrobial and antitumor activity. Related to the esperamicin-calicheamicin enediynes is the compound called neocarzinostatin chromophore A **7**,[4] and very recently the neocarzinostatin-like compound kedarcidin **8** has been reported.[5]

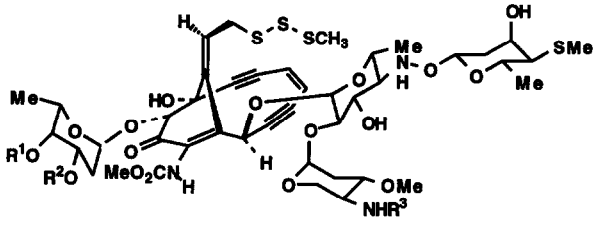
Scheme I



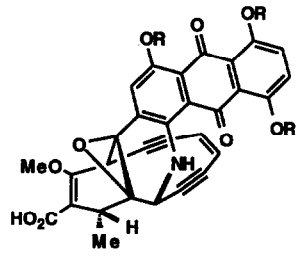
1 Calicheamicin γ_1



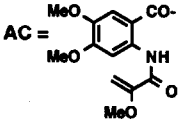
5 Esperamicin X

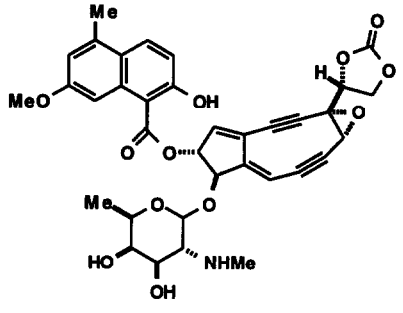


2 Esperamicin A_1, R^1= H, R^2 = AC, R^3 = *i*-Pr.
3 Esperamicin A_{1b}, R^1= AC, R^2 = H, R^3 = *i*-Pr.
4 Esperamicin A_2, R^1 = H, R^2 = AC, R^3 = Et.

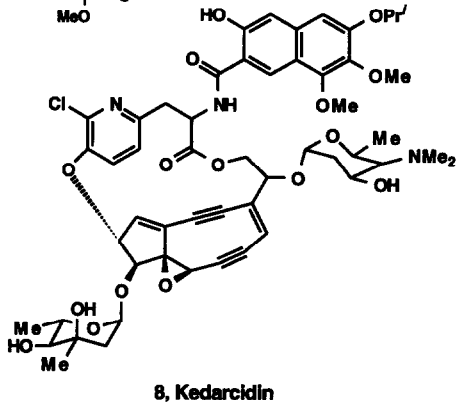


6 Dynemicin, R = H and R = Ac.





7, Neocarzinostatin Chromophore A

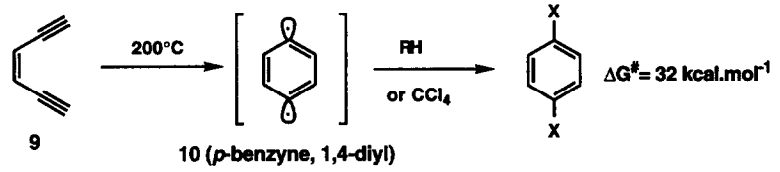


8, Kedarcidin

Because of their unique structures, and beautifully designed[1-6] mechanism of DNA cleavage, the esperamicins, calicheamicins, dynemicin and neocarzinostatin CA have immediately attracted a great deal of synthetic interest.[7] While the esperamicins-calicheamicins contain a number of unusual structural features, it is the Z-enediyne that embues these molecules with a unique mechanism for cleaving DNA. Without going into the details, since there has been extensive discussion of the *in vitro* mechanism of action of these compounds, the enediyne functionality in

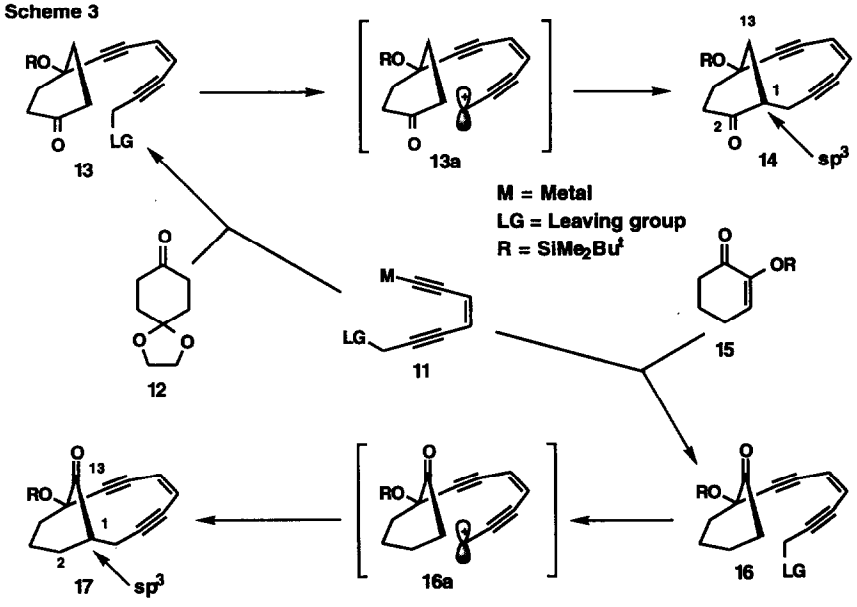
calicheamicin, esperamicin and dynemicin can, after an appropriate triggering event (bioreduction), undergo so-called Bergman cyclization (cycloaromatization) to the diradical **10** (*p*-benzyne or 1,4-diyl). It is this diradical that is the supposed culprit which causes damage to DNA. The prototype reaction is shown in **Scheme 2**.[8]

Scheme 2



When we first started this investigation nothing was known about the stability of the bicyclo[7.3.1]tridecaenediyne system with respect to cycloaromatization. Consequently, we adopted a strategy that would allow us to assess the relative stabilities of some simple bicyclic enediynes with respect to their potential for cycloaromatization. If they are stable, what chemistry can be carried out on them without causing cycloaromatization? The overall strategy is outlined in **Scheme 3**.

Scheme 3

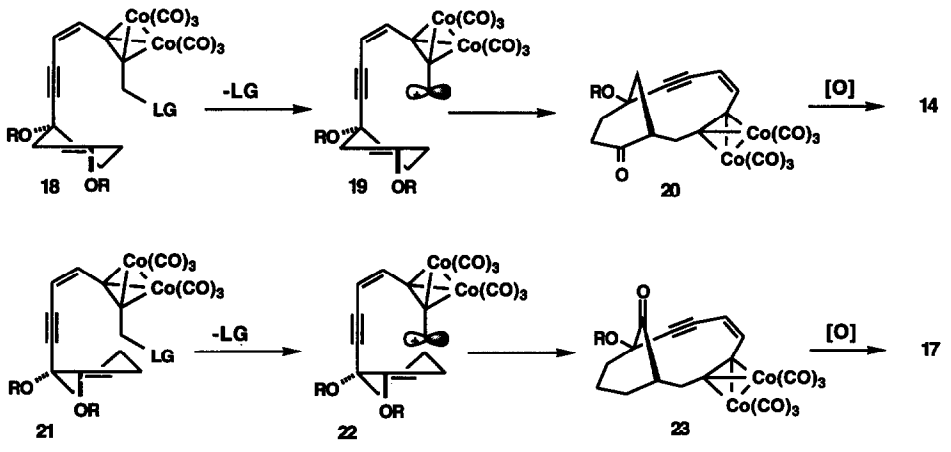


We envisioned that a preformed enediyne unit **11** could be added to the 1,4-dione derivative **12**, and in a single step to provide **13**. Ionization of **13** to the propargyl cation **13a** followed by enol(ate) trapping to give **14** should, in principle,

be a short route to the core bicyclo[7.3.1]enediyne system. Similarly, the 1,2-dione derivative **15** would allow access to the isomeric series of compounds **16** and **17**. At this stage we had no preconceived notion as to the stability of either **14** or **17**, and decided that it might be expedient to make them as their dicobalthexacarbonyl-acetylene complexes **20** and **23** respectively, which should be isolable adducts. In a separate step the oxidative decomplexation can be studied to assess the relative ease of cycloaromatization of the enediynes **14** and **17**. This strategy would allow us to take advantage of the dicobalthexacarbonyl-acetylene complexation chemistry.

A very convenient way to generate the propargylic cation-type intermediates **19/22** is to make use of the η^2-dicobalthexacarbonyl alkyne complexes **18/21**, which have been shown by Nicholas and Pettit to ionize to a stabilized cation when treated with Brönsted or Lewis acids.[9] A further possible benefit of the $\eta^2Co_2(CO)_6$-alkyne complexes is that they bend the normal linear diagonally hybridized acetylene triple-bond to approximately 145°. In an axial conformation the propargylic cation is situated with near to axial alignment to the enol derivative **19/22** π-system, **Scheme 4.**

Scheme 4

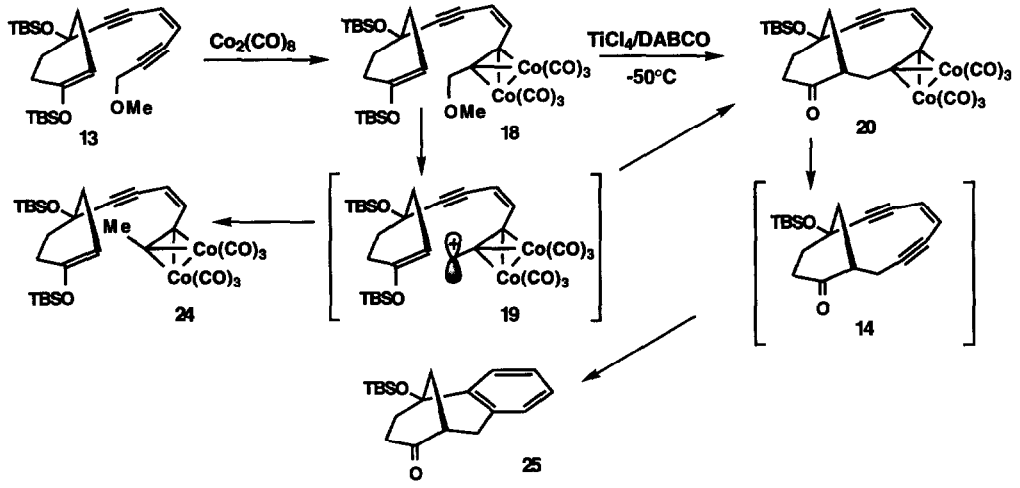


Finally, if successful, the corresponding bicyclo[7.3.1]tridecaenediynes **14/17** will be formed as their mono-$\eta^2Co_2(CO)_6$ complexes **20/23**, and therefore prevent cycloaromatization until the $Co_2(CO)_6$ cap is removed, **Scheme 4**. A major consideration in this strategy is the regiochemistry of the complexation of **13** and **16** with dicobalt octacarbonyl. Usually $Co_2(CO)_8$ forms more stable $\eta^2Co_2(CO)_6$-acetylene complexes with electron-deficient acetylenes. While there were no studies that described the complexation of separated diacetylenes with $Co_2(CO)_8$, we expected that the sterically less encumbered acetylene to be preferentially complexed. The first

substrate we studied was the 2-keto system **13**.

2-Ketobicyclo[7.3.1]tridecaenediyne System.

Scheme 5



Treatment of **13** with $Co_2(CO)_8$ in heptane at room temperature resulted in complexation predominately at the sterically less hindered acetylenic bond to give **18** (90%). Small amounts of the $Co_2(CO)_6$-acetylene regioisomer and its *bis*-$Co_4(CO)_{12}$ complex are also formed. Our initial attempts to ionize **18** to the cation **19** and intramolecular trapping to give **20** were not particularly encouraging. Using a variety of Lewis acids and reaction conditions completely destroyed **18**. Eventually, we found that $TiCl_4/CH_2Cl_2$ at -50°C gave a small amount of **20** (ca. 5%). At lower temperatures there is no reaction, and at higher temperatures **18** and **20** were destroyed. We thought that the formation of HCl under the above reaction conditions might be responsible for the low yield of **20**, consequently the treatment of **18** with $TiCl_4$ was carried out in the presence of triethylamine. These conditions resulted in a reasonably clean conversion into the adduct **24**. This provided good evidence that indeed the cation **19** is formed, and in the presence of triethylamine is reduced by hydride transfer to generate **24**. The obvious solution was to conduct the same reaction in the presence of a base that cannot donate hydride, such as 4-diazabicyclo [2.2.2]octane (DABCO). Treatment of **18** with $TiCl_4$/DABCO/-50°C gave the required bicyclo[7.3.1]enediyne-10,11-η^2-dicobalt-hexacarbonyl adduct **20** (45%), **Scheme 5**. It should be noted that attempts to ionize the uncomplexed enediyne **13** using the above reaction conditions resulted in decomposition and no evidence for the formation of **14** and/or the cycloaromatized product **25**.[10]

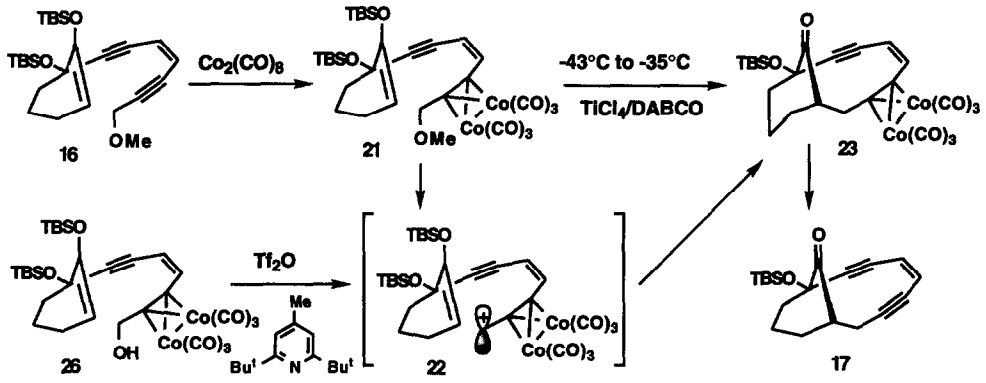
Oxidative decomplexation of **20** in 1,4-cyclohexadiene using N-methyl morpholine N-oxide at 20 °C rapidly gave **25** (42%), presumably *via* the uncomplexed 2-ketobicyclo[7.3.1]enediyne **14**. At lower temperatures (-20 °C) we could detect **14** (^{1}H NMR and tlc) but it could not be isolated.

While this initial investigation established the viability of the strategy, the ease of aromatization precluded further examination of the chemistry of the enediyne **14**. Consequently we decided to examine the isomeric 13-ketobicyclo[7.3.1]enediyne core **17**.

13-Ketobicyclo[7.3.1]tridecaenediyne System.

The substrate **16** was made in a similar sequence to **13** except the starting material is cyclohexane-1,2-dione. Treatment of **16** with $Co_2(CO)_8$/heptane at room temperature resulted in complexation predominately at the sterically less hindered acetylenic bond to give **21** (90%). Treatment of **21** with $TiCl_4$/DABCO/-43° to -35°C gave the required bicyclo[7.3.1]enediyne-10,11-η^2-dicobalt-hexacarbonyl adduct **23** (55%) as a crimson crystalline solid, **Scheme 6**.

Scheme 6

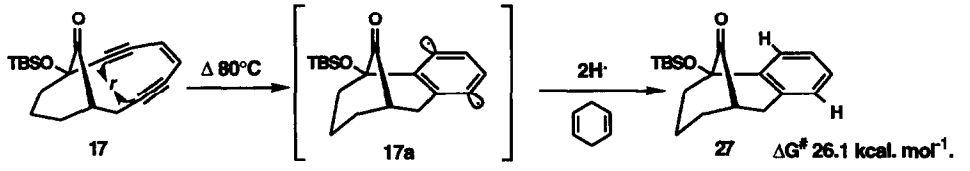


The structure of **23** was secured by single crystal X-ray crystallography. The newly formed carbon-carbon bond (C_1-C_{12}) is axial (with respect to the cyclohexanone ring) and consequently the hydrogen atom at C_1 is in an equatorial configuration. Oxidative decomplexation of **23** using iodine/THF at room temperature gave the 13-ketobicyclo[7.3.1]enediyne **17** (82%) as a stable crystalline solid. The best method we have found for cyclization is to treat the alcohol **26** with triflic anhydride in dichloromethane at -10°C in the presence of 2,6-di-*t*-butyl-4-methylpyridine, the 13-ketobicyclo[7.3.1]enediyne-η^2-dicobalthexacarbonyl adduct **23** was isolated in 77% yield. Consequently, the route shown in **Scheme 6** provides the best overall yield of the 13-ketobicyclo[7.3.1]enediyne-η^2-dicobalthexacarbonyl

adduct **23** (10% from cyclohexane-1,2-dione).[11]

Initial qualitative experiments readily showed that the 13-bicyclo[7.3.1] enediyne **17** is considerably more resistant to cycloaromatization than the 2-ketoisomer **14**. While we could not isolate **14**, **17** is a stable crystalline compound below 80°C. At 80°C, in 1,4-cyclohexadiene, **17** is converted into the aromatic adduct **27** (72%) via the 1,4-diyl **17a**, **Scheme 7.**

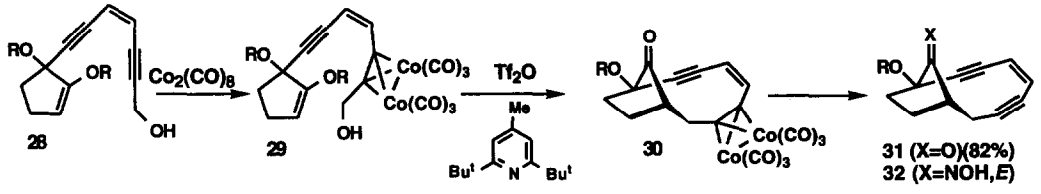
Scheme 7



The crystalline 13-ketobicyclo[7.3.1]enediyne **17** has been characterized by X-ray crystallography, r = 3.39Å, in excellent agreement with calculations (3.41Å, MM2).

The five-membered ring analogue of **17**, namely 12-ketobicyclo[7.2.1]enediyne **31**, was readily made in the same way except the starting material was cyclopentane-1,2-dione, **Scheme 8**. The oxime **32** was characterized by X-ray crystallography.[12]

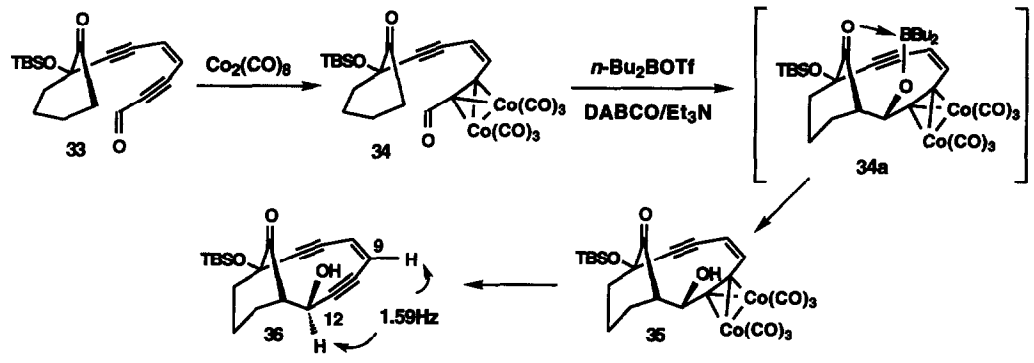
Scheme 8 (R = TBS)



η^2-$Co_2(CO)_6$-Alkyne Mediated Aldol Reaction: 12β-Hydroxyl Functionality.

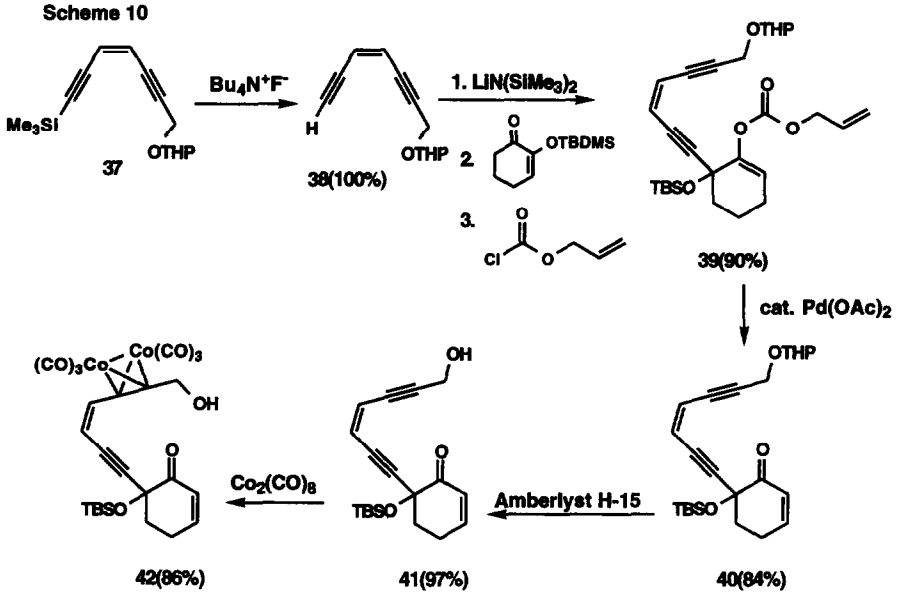
The aldehyde **33** was regiospecifically complexed with $Co_2(CO)_8$ to give **34** (>95%). When **34** was treated with n-Bu_2BOTf/DABCO/NEt_3/CH_2Cl_2-THF the aldol product **35** was isolated as a single stereoisomer (45%, via **34a**). When **35** was treated with N-methylmorpholine-N-oxide/THF/t-BuOH/RT the non-aromatized enediyne **36** was isolated in 76% yield. The 9-H to 12α-H proton-proton coupling is 1.59 Hz which corresponds very closely to that observed in the natural products **1** (1.8 Hz). The synclinal aldol $\eta^2Co_2(CO)_6$-acetylene mediated stereospecific synthesis of the 12β-hydroxybicyclo[7.3.1]enediyne system **36** is the only method for cyclization that gives entirely the correct 12β-configuration at the newly formed sec-hydroxyl group, **Scheme 9**.[13]

Scheme 9



Unfortunately, the above aldol reaction is difficult to reproduce in the same yield, most likely because of the reversibility of the aldol process. At this stage we needed to introduce the 12β-hydroxyl group and the 1,2-double bond, and make the introduction of the enediyne portion convergent. The sequence shown in **Scheme 10** represents an optimized route to the enone **42**. In a single step, the lithio-enediyne from **38** is added to the 1,2-diketone and the enolate (after TBDMS migration) is trapped with allyl chloroformate to give the allyl carbonate **39** in 90% yield on a large scale (>100g). Palladium diacetate catalyzed oxidation of **39** gave the enone **40**, which was deprotected to the alcohol **41**, **Scheme 10**.[14]

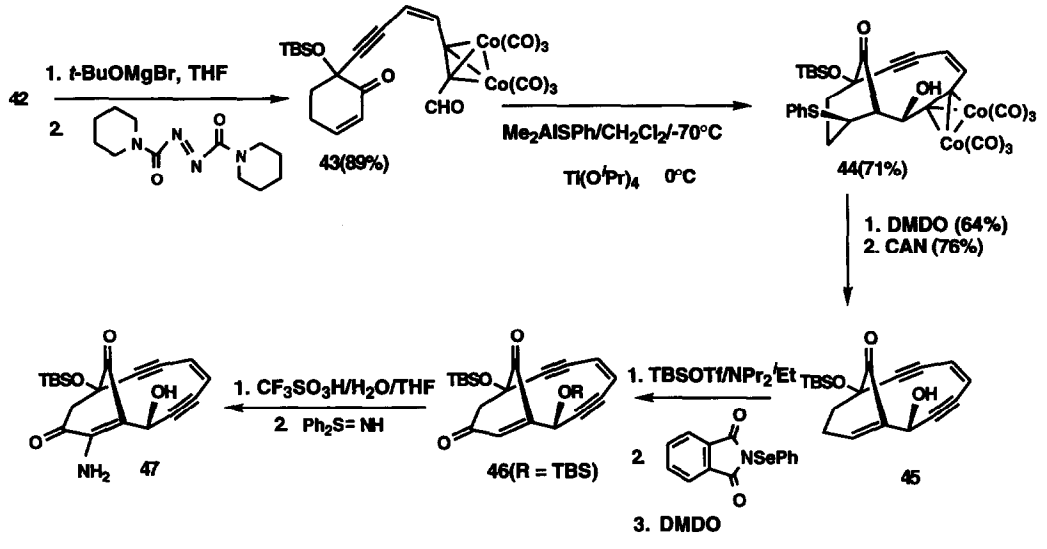
Scheme 10



Treatment of the enediyne **41** with dicobaltoctacarbonyl gave **42** (85%) and its regioisomer (14%). The incorrect regioisomer can be recycled by oxidation using ceric ammonium nitrate (CAN) to give **41**. Oxidation of the $\eta^2Co_2(CO)_6$-propargyl alcohol complex gave the aldehyde **43.** It should be noted that the aldehyde is more stable as the $\eta^2Co_2(CO)_6$-acetylene complex than as the free aldehyde. The $\eta^2Co_2(CO)_6$-acetylene complexes are air stable and can be chromatographed without significant decomposition, **Scheme 11.**

After considerable experimentation it was found that treatment of **43** with Me_2AlSPh at -70 °C followed by $Ti(O^iPr)_4$, and quenching the mixture with silica gel, resulted in the bicyclo[7.3.1]enediyne cobalt adduct **44** as a single stereoisomer. This ring closure gives exclusively the correct stereochemistry at the C-12 hydroxyl group. Oxidation of the sulfide **44** using dimethyldioxirane (DMDO) followed by decomplexation (CAN) gave the enone **45**. While the enediyne **45** might be viewed as a model compound, we have been able to oxidize it to the 1,4-dione **46** and convert this in a single step into the enamine **47**. This compound contains all of the core functionality, and only the allylic trisulfide group remains to be attached, **Scheme 11.**

Scheme 11

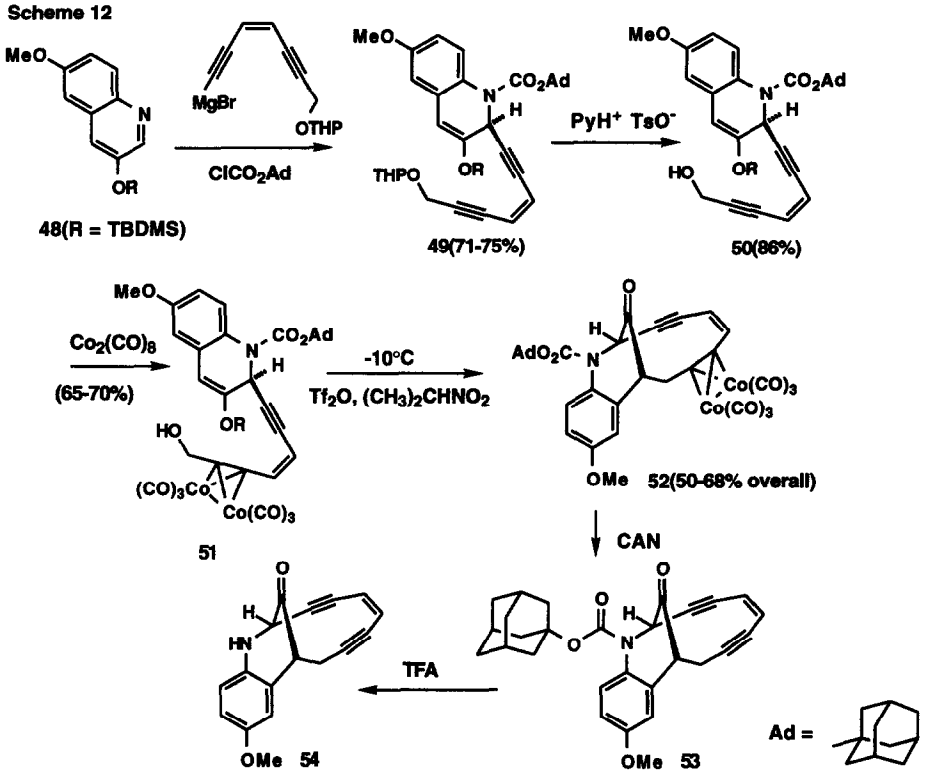


The $\eta^2Co_2(CO)_6$-Acetylene Complex Route to the Dynemicin Core Structure

We have extended the chemistry developed for the esperamicins and calicheamicins to the synthesis of the dynemicin core structure. Treatment of the *t*-butyldimethylsilyl ether of 6-methoxy-3-hydroxyquinoline **48** with the magnesio enediyne acetylide in the presence of adamantyl chloroformate gave, in a completely

regiospecific reaction, the dihydroquinoline **49** (71%), **Scheme 12**.[15] Selective deprotection of the THP ether to give **50** (86%) was accomplished using pyridinium tosylate/EtOH).[16] Complexation of **50** with $Co_2(CO)_8$ gave **51** (65%) along with some complexation at the other acetylene (ca. 15%) and *bis*-complexation. The incorrect regioisomer can be recycled. Treatment of **51** with triflic anhydride/(DBMP) in $(CH_3)_2CHNO_2$ at -10 °C gave the cyclized product **52** (50%). It is essential to use a nitroalkane solvent; dichloromethane alone gave a symmetrical ether derived from **51**. Oxidative decomplexation using ceric ammonium nitrate gave the core structure **53** (50-68% overall from **51**).[17]

Scheme 12

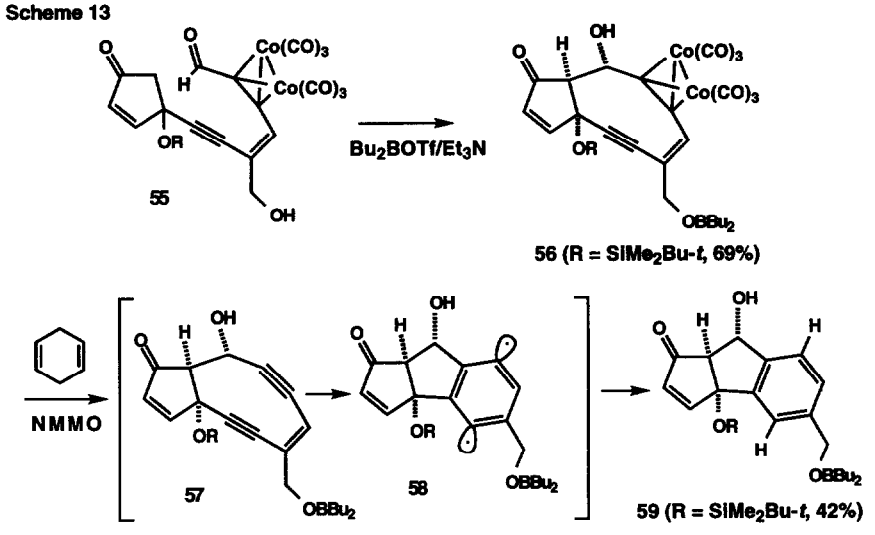


The adamantyl carbamate protecting group survives the above reaction conditions intact, and is readily removed by treatment of **53** with trifluoroacetic acid in dichloromethane to give the stable amine **54**. The amine **54** shows promising antitumor activity, and is available in gram quantities in six steps, **Scheme 12**.

The $\eta^2Co_2(CO)_6$-Acetylene Complex Route to the Neocarzinostatin Core Structure

The cobalt mediated aldol cyclization can also be used for the construction of the neocarzinostatin core structure. The aldehyde **55** was made by a short sequence similar to those described in for the other $\eta^2Co_2(CO)_6$-acetylene-complexes. Treatment of the aldehyde **55** with di-*n*-butylboron triflate/Et_3N gave the cyclized aldol product **56** (69%). As expected, when the cobalt metallocycle was oxidatively removed (N-methylmorpholine-N-oxide, NMMO) the enediyne **57** was too unstable to be isolated and immediately cycloaromatized to give the compound **59**, **Scheme 13**.[18]

Scheme 13

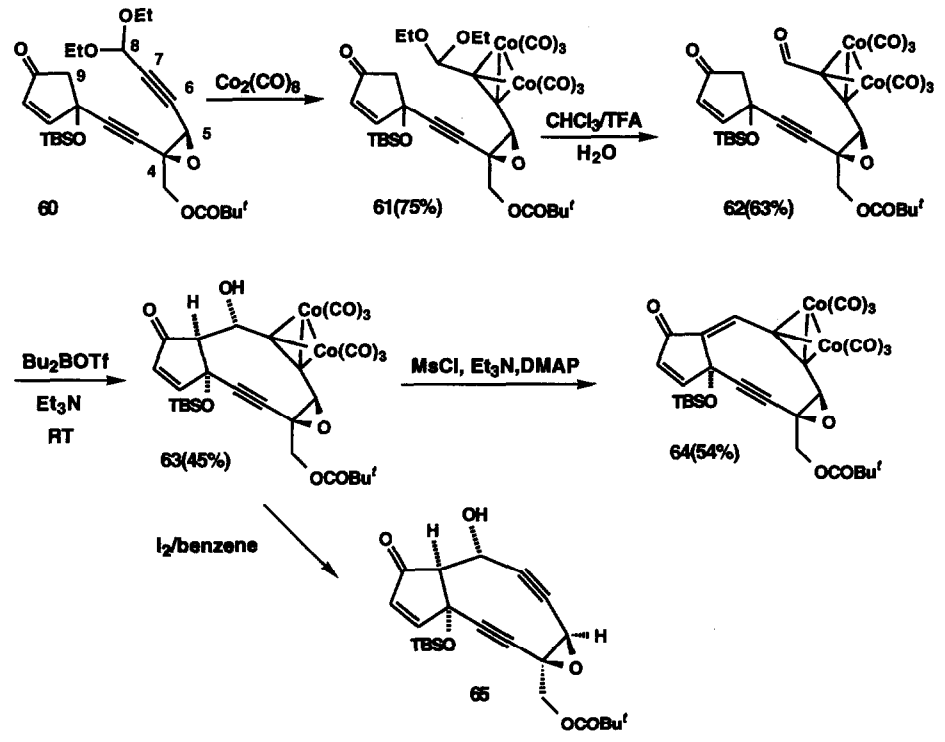


Removal of the BBu_2 group from **56** and attempted epoxidation of the allylic double-bond was unsuccessful. Consequently, the epoxide functionality must be introduced at an earlier stage in the synthesis, and this poses an awkward reactivity problem. The 8,9-bond is made by a $\eta^2Co_2(CO)_6$-mediated aldol reaction under Lewis acid catalysis conditions. It would be surprising if the 4,5-epoxide could survive these conditions and not open to the $\eta^2Co_2(CO)_6$-stabilized cation, with concomitant release of ring-strain.

Consequently, we were interested to see if an epoxide would be stable enough to be carried through the reaction sequence shown in **Scheme 14**. At the outset, it was decided not to conduct any model work to see if simpler compounds that contain an epoxide adjacent to the cobalt metallocycle would be stable. This proved to be a wise (in retrospect) decision, because the transformations shown in **Scheme 14** work for the real system, but so-called simple epoxyacetylenes do not form isolable

$\eta^2Co_2(CO)_6$-acetylene adducts such as **61**.[19]

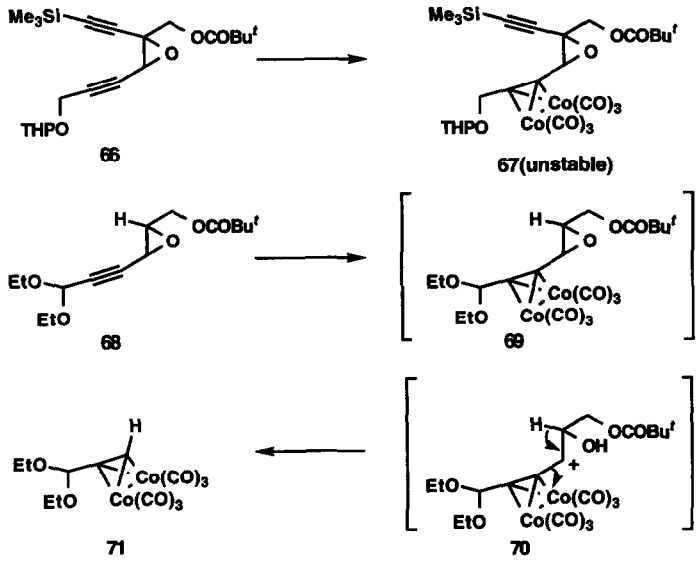
Scheme 14



The epoxide **60** is a 1:1 mixture of inseparable diastereomers with an estimated enantiomeric excess of ca. 70%. Complexation of **60** with $Co_2(CO)_8$ gave the adduct **61** (75%), which allowed the activated diethyl acetal to be hydrolyzed by treatment with aqueous trifluoroacetic acid in chloroform to give **62** (63%). Premixing *n*-$Bu_2BOTf/Et_3N/ CH_2Cl_2$ at -78°C, warming to 0°C, followed by slow addition of **62** at 0°C, and warming to 25°C, resulted in conversion into the cyclized aldol adduct **63** (45%). At this stage the diastereomers could be separated (plc), although we do not know which one has the stereochemistry represented in structure **63**. Oxidative decomplexation of **63** with I_2/PhH gave **65** (69-75%) as a stable compound both in solution and as a solid at room temperature. Treatment of **63** with mesyl chloride/Et_3N/DMAP dehydrated the aldol product to give the enone **64**, **Scheme 14**. The compound **65** is the most highly functionalized bicyclo[7.3.0]dodecadiyne neocarzinostatin core structure synthesized to-date, and illustrates the surprising compatibility of 4,5-epoxide to the cyclization conditions. This is more dramatically demonstrated by the following subsequent models.

Attempted complexation of **66** with $Co_2(CO)_8$ gave **67** which was extremely unstable towards acidic conditions, decomposing to polar material, presumably formed from opening of the epoxide ring. Interestingly, treatment of **68** with $Co_2(CO)_8$/heptane gave the fragmented adduct **71** as the only cobalt containing material. Its formation presumably arises from **69** *via* ring opening of the epoxide to give **70**, and elimination resulting in **71**.

Scheme 15



Summary

In all of the above $\eta^2Co_2(CO)_6$-acetylene mediated cyclizations the blank reaction without the cobalt metallocycle were unsuccessful. Either the substrate was completely destroyed or there was no reaction. The routes to the core enediynes are all quite short, and make available sufficient material for the more meaningful *in vivo* biological evaluations.

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Experimental Section

2-Keto-5-[*tert*-butyldimethylsilyl(oxy)]-bicyclo[7.3.1]tridec-6,10-diyn-(10,11-η^2-dicobalthexacarbonyl)-8-ene 20. To a stirred solution of the enol ether **18** (240 mg, 322 μmol) and DABCO (36.1 mg, 322 μmol, freshly distilled) in dichloromethane (24 mL) at -78 °C was added a 1.0 M solution of $TiCl_4$ in dichloromethane (1.93 mL). After 1.5 h the mixture was warmed over 0.5 h to -50 °C and recooled to -78°C. Triethylamine (5 mL) was added to quench the mixture (at -78 °C), and the solution warmed to room temperature. Saturated aqueous $NaHCO_3$ (15 mL) was added and the mixture filtered through celite washing with dichloromethane. The aqueous layer was separated and extracted with dichloromethane (2x5 mL) and the combined organic phases washed with brine (5 mL) and dried (Na_2SO_4). Evaporation *in vacuo* gave a residue that was preadsorbed onto silica gel and chromatographed eluting with petroleum ether/ether (4:1) to give **20** (86 mg, 45%) as a deep red oil. IR ($CHCl_3$) 2960, 2930, 2860, 2095, 2050, 2020, 1710, 1080, 1050 and 835 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 6.88 (1H, d, J = 9.4 Hz), 5.64 (1H, d, J = 9.4 Hz), 3.20 (2H, m), 2.7 (2H, m), 2.3 (4H, m), 0.92 (9H, s), 0.26 (3H, s), 0.18 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.52 (s), 198.74-199.00 (m), 142.69 (d), 109.50 (d), 102.70 (s), 99.28 (s), 88.63 (s), 83.11 (s), 69.78 (s), 56.64 (d), 45.42 (t), 41.09 (t), 36.81 (t), 35.36 (t), 25.84 (q), 18.28 (s), -3.10 (q). MS (CI, NH_3) m/e 544 corresponding to M+-2CO's, base peak m/e 460, M+-5CO's. Running the above reaction of **18** (410 mg) gave **20** (186 mg, 56%).

1-[*tert*-Butyldimethylsilyl(oxy)]tricyclo[7.3.$10^{2,7}$]trideca-2,4,6-trien-10-one 25. To a stirred solution of the cobalt complex **20** (23 mg, 38.3 μmol) in cyclohexa-1,4-diene (1 mL) at 20 °C was added N-methylmorpholine N-oxide (11.2 mg, 95.8 μmol). After 3h a further quantity (15 mg, 128 mmol) of the N-oxide was added. The mixture was diluted with dichloromethane (2 x 5 mL) and the combined organic phases washed with brine and dried (Na_2SO_4). Evaporation *in vacuo* and

chromatography of the residue over silica gel eluting with petroleum ether/ether (4:1) gave **25** (5.1 mg, 42%) as a colorless oil. IR ($CHCl_3$) 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (4H, m), 3.37 (1H, dd, J's = 9.0 and 17.4 Hz), 2.82 (1H, m), 2.67 (1H, dd, J's = 6.2 and 15.7 Hz), 2.59 (1H, m), 2.52 (1H, dd, J's = 5.2 and 17.4 Hz), 2.31 (2H, m), 2.16 (2H, m), 0.87 (9H, s), -0.06 (3H, s), 0.19 (3H, s). HRMS calcd for $C_{19}H_{28}O_2Si$(-*t*-Bu) 259.1155. Found m/e 259.1155 for $C_{15}H_{19}O_2Si$ (M+-*t*-Bu).

13-Keto-5-[*tert*-butyldimethylsilyl(oxy)]-bicyclo[7.3.1]tridec-6,10-diyn-(10,11-η^2-dicobalthexacarbonyl)-8-ene 23. To a mixture the cobalt complex **21** (1.455 g) and sublimed DABCO (220 mg, 1.0 equiv) was added *via* canula dry toluene (200 mL). The mixture was cooled to -45 °C (CH_3CN/solid CO_2) and a solution of $TiCl_4$ (freshly distilled, 650 μL, 3.0 equiv) in toluene (5 mL) was added dropwise as the temperature rose to -40 °C. The solution was stirred efficiently (bath and reaction) until the external thermometer indicates -35 °C. Triethylamine (7 mL) was added to the mixture followed by saturated aqueous $NaHCO_3$ (70 mL). The mixture was allowed to warm to 20 °C, filtered through celite, and the dried (Na_2SO_4) organic layer evaporated *in vacuo*. Chromatography of the residue over silica gel eluting with 5% ether/petroleum ether gave **23** (650 mg, 55.6%) as *black-red* crystals. M.p. 109-110 °C (sealed capillary). IR ($CDCl_3$) 2935, 2858, 2095, 2020, 1730, 1150, 940 and 780 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 9.8 Hz), 5.75 (1H, d, J = 9.8 Hz), 4.23 (1H, m), 3.23 (1H, m), 3.20 (1H, m), 2.41 (1H, m), 2.07 (1H, m), 1.91 (2H, m), 1.83 (1H, ddd, J's = 13.4, 13.4 and 4.4 Hz), 1.72 (1H, m), 0.86 (9H, s), 0.14 (3H, s), 0.06 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.50, 199-198 (m), 142.46, 109.75, 97.14, 95.10, 92.63, 82.40, 75.67, 49.83, 42.48, 39.61, 32.62, 25.65, 18.79, 18.18, -2.83, -3.23. HRMS calcd for $C_{23}H_{26}O_6SiCo_2$ (M+-2CO) 544.0162. Found: m/e 544.0191.

13-Keto-5-[*tert*-butyldimethylsilyl(oxy)]-bicyclo[7.3.1] tridec-6,10-diyn-8-ene 17. To a solution of **23** (5.9 g) in dry THF (700 mL) under argon was added a solution of iodine (50 g) in THF (500 mL) *via* canula. The resulting mixture was stirred for 2.5 h at 20 °C (protected from light). The solution was poured into aqueous sodium thiosulfate (200 mL, 1M), saturated aqueous $NaHCO_3$ (200 mL) and extracted with ether (3 x 200 mL). The organic layers were washed with saturated aqueous NH_4Cl (200 mL) to remove the pink coloration. The solvent was evaporated *in vacuo* at 20 °C and the residue dissolved in ether/pentane (1:4), dried ($MgSO_4$) and evaporated. Chromatography of the residue over silica gel eluting with 10% ether/pentane gave **17** (2.53 g, 82%). M.p. 43-46 °C (from aqueous EtOH). IR (CCl_4) 2958, 2930, 2858, 1734, 1462, 1348, 1152, 1098, 952 and 780 cm^{-1}. UV (MeOH) λ_{max} 201 and 274 nm (ε, 3600 and 7600). ^1H NMR (500 MHz, C_6D_6) δ 5.398 (1H, dd, J's = 9.50, 0.9 and 2.0 Hz), 5.348 (1H, dd, J's = 9.5 and 1.1 Hz), 3.04 (1H, ddd, J's = 1.1,

0.9, 17.5 and 3.8 Hz), 2.47 (1H, m), 2.23 (1H, ddd, J's = 13.8, 8.4 and 5.7 Hz), 2.06 (1H, m), 1.89 (1H, ddd, J's = 2.0, 4.5 and 17.5 Hz), 1.80 (1H, ddd, J's = 13.8, 8.7 and 7.3 Hz), 1.65 (1H, m), 1.17 (1H, m), 1.12 (9H, s), 0.43 (3H, s), 0.49 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 204.32, 124.49, 121.35, 100.25, 97.53, 91.57, 83.48, 74.33, 48.35, 36.85, 25.89, 24.50, 24.21, 18.79, 18.36, -2.98, -3.14. HRMS calcd for $C_{19}H_{26}O_2Si$ 314.1702. Found: m/e 314.1698.

13-Keto-5-[*tert*-butyldimethylsilyl(oxy)]-bicyclo[7.3.1]tridec-6,10-diyn-(10,11-η²-dicobalthexacarbonyl)-8-ene 23. To a solution of **26** (17 mg, 2.3 x 10^{-5} mol) and 2,6-di-*t*-butyl-4-methylpyridine (100 mg) in dichloromethane (5 mL) under argon at -30 °C was added triflic anhydride (8 μL, 4.7 x 10^{-5} mmol). The reaction mixture was allowed to warm up to -20 °C where it was stirred for 30 minutes then poured into cold aqueous $NaHCO_3$, extracted with dichloromethane, dried (Na_2SO_4) and evaporated *in vacuo* . Chromatography of the residue over silica gel eluting with 10% ether/hexanes afforded **23** (10.8 mg, 77%).

12-Keto-4-[*tert*-butyldimethylsilyl(oxy)]-bicyclo[7.2.1]didec-5,9-diyn-(9,10-η²-dicobalthexacarbonyl)-7-ene 30. To a stirred solution of the alcohol **29** (30 mg, 0.042 mmol) in dry dichloromethane (4 mL), under argon, at -15 °C, was added dropwise *via* syringe a solution of 2,6-di-*t*-butyl-4-methylpyridine (260 mg. in 0.5 mL of CH_2Cl_2) followed by trifluoromethyl sulfonic anhydride (0.10 mL, 0.59 mmol). The resulting red-brown solution was stirred at -10 °C for 20 min and quenched with saturated aqueous $NaHCO_3$ solution (4 mL). The dichloromethane layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography over silica gel eluting with ether/petrol (1:20) to give the bicyclo[7.2.1]diynene **30** (14.4 mg, 59%) as a red-brown solid. M.p. 99-101 °C (dec). IR ($CHCl_3$) 2961, 2931, 2894, 2859, 2090, 2057, 2031, 1760, 1647, 1471, 1295, 1219 and 1108 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (2H, q, J = 10.4 Hz), 4.05 (1H, dd, J's = 17.2 and 3.0 Hz), 3.66 (1H, dd, J's = 17.2 and 7.4 Hz), 2.61-2.57 (1H, m), 2.29 (1H, dd, J's = 10.9 and 5.3 Hz), 2.14-1.92 (3H, m), 0.90 (9H, s), 0.21 (3H, s), 0.19 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.88, 201-198, 140.50, 107.39, 95.65, 95.47, 90.29, 81.80, 76.83, 44.35, 39.87, 37.09, 25.71, 21.73, 18.08, -3.23, -3.28. Anal Calcd for $C_{24}H_{24}Co_2O_8Si$. C, 49.16; H, 4.13. Found: C, 49.17; H, 4.16%.

12-Keto-4-[*tert*-butyldimethylsilyl(oxy)]-bicyclo[7.2.1]didec-5,9-diyn-7-ene 31. The η2-$Co_2(CO)_6$-adduct **30** (28 mg, 0.048 mmol) in dry THF (3 mL) under argon at 0 °C was treated, *via* cannula, with a solution of iodine (184 mg, 0.72 mmol) in THF (2 mL). The resulting solution was warmed to 20°C. After 2 h the mixture was poured onto saturated aqueous $NaHCO_3$ solution (10 mL), aqueous sodium thiosulfate solution (10 mL, 1.0 M) and ether (20 mL). The organic phase

was washed with saturated brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with ether/petrol (1:20) to give **31** (11.8 mg, 82%) as a colorless oil. IR (neat) 2956, 2929, 2857, 2211, 1761, 1472, 1462, 1295, 1249 and 1209 cm^{-1}. UV ($CHCl_3$) λ_{max} (ε) 274 (5580) nm. ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (2H, q, J = 9.8 Hz), 3.08 (1H, q, J = 4.4 Hz), 2.57-2.26 (4H,m), 2.06-1.89 (2H, m), 0.89 (9H,s), 0.21 (3H,s), 0.23 (3H,s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.91, 123.57, 121.46, 99.04, 95.40, 94.01, 83.15, 76.45, 45.22, 37.59, 25.74, 21.46, 21.08, 18.09, -3.04, -3.13. HRMS calcd for $C_{18}H_{24}O_2Si$ (M^+) 300.1546. Found: m/e 300.1533.

13-Keto-5-[*tert*-butyldimethylsilyl(oxy)]-12β-hydroxy-2-β-thiophenylbicyclo[7.3.1]tridec-6,10-diyn-(10,11-η^2-dicobalthexacarbonyl)-8-ene 44. Redistilled thiophenol (1.06 mL, 10.4 mmol) was added slowly to a solution of trimethylaluminum (2 M in hexanes, 5.2 mL, 10.4 mmol) in anhydrous dichloromethane (21 mL) stirred at 0 °C under argon. The mixture was stirred at 0 °C for 20 minutes after which time anhydrous THF (845 μL, 10.4 mmol) was added. The mixture was then cooled to -78 °C and stirred for 10 minutes. The aldehyde **43** (3.19 g, 5.2 mmol) in anhydrous dichloromethane (10 mL; stirred over 4Å molecular sieves for 24 hours prior to cyclization) was added dropwise over 5 minutes and the mixture stirred for a further 10 minutes at -78 °C. Finally, titanium tetra-*iso*-propoxide (12.36 mL, 41.5 mmol, 8 eq.) was added dropwise over 15 minutes. The reaction mixture was stirred at -78 °C for 10 minutes, after which time the cold bath was replaced by an ice-water bath. The mixture was allowed to reach +10 °C over 2 hours and was stirred for a further 45 minutes at +10 °C after which time TLC showed almost all the starting material converted to product **44**. The reaction mixture was then recooled to -78 °C and silica gel (40 g) added slowly over 10 minutes *via* a solid addition funnel. The argon line was removed and the mixture stirred for a further 45 minutes in air. The mixture was then filtered through a plug of silica and the plug washed with diethyl ether. The filtrate was concentrated *in vacuo* and the residues purified by flash column chromatography (silica; hexanes-diethyl ether, 95:5, 90:10 then 80:20) to give the cyclized material **44** (2.66 g, 71 %). ^1H NMR (300 MHz, C_6D_6) δ 7.42 (2 H, d, J = 7.3 Hz), 6.98 (3 H, m), 6.34 (1 H, d, J = 10 Hz), 5.22 (1 H, d, J = 10 Hz), 5.17 (1 H, m), 4.20 (1 H, br. s), 3.11 (1 H, d, J = 9.2 Hz), 2.47 (1 H, m), 2.02 (2 H, m), 1.62 (1H, m), 1.25 (1 H, d, J = 7.4 Hz), 1.06 (9 H, s), 0.39 (3 H, s), 0.34 (3 H, s). IR ($CHCl_3$) 3500 (br s), 2929 (s), 2094 (vs), 2059 (vs), 2030 (vs), 1731 (s), 1471 (m), 1251 (m), 1155 (m), 1070 (m), 838 (s) cm^{-1}. Calculated for $C_{31}H_{30}O_9SSiCo_2$: C, 51.39; H, 4.17. Found C, 51.19; H, 4.26 %.

13-Keto-5-[*tert*-butyldimethylsilyl(oxy)]-12β-hydroxy-bicyclo [7.3.1]tridec-6,10-diyn-1.8-diene 45. The sulfide **44** (849 mg, 1.2 mmol) was

dissolved in dichloromethane (50 mL) and cooled to -78 °C under argon. *m*-Chloroperbenzoic acid (242 mg, 1.4 mmol) was added in one portion and the cooling bath removed. Stirring was continued at room temperature for 3 hours before TLC (hexanes-ethyl acetate, 80:20) showed no starting material remaining. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (50 mL) and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the residues purified by flash column chromatography (Florisil/hexanes-diethyl ether, 80:20) to afford the cobalt complexed enone (466 mg, 64%).

The cobalt complex (468 mg, 0.76 mmol) was dissolved in acetone (50 mL) and cooled to -10 °C. Ceric ammonium nitrate was added in small portions until the solution turned a light orange color. The reaction mixture was diluted with ether (150 mL), washed with saturated aqueous sodium bicarbonate solution (200 mL) and dried over anhydrous magnesium sulfate. Removal of the solvents under reduced pressure and purification of the residues by flash column chromatography (Florisil, hexanes-diethyl ether, 75:25) afforded the decomplexed enone **45** (190 mg, 76 %). M.p 123-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (1 H, m), 5.87 (1 H, d, J = 9.5 Hz), 5.84 (1H, d, J = 9.5 Hz), 5.24 (1 H, d, J = 10.5 Hz), 2.53 (2 H, m), 2.26 (1 H, m), 2.14 (1 H, m), 0.92 (9 H, s), 0.22 (3 H, s), 0.19 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197, 140, 137, 125, 123, 101, 96, 93, 88, 75, 69, 35, 26, 25, 18, -2.8, –3.1. IR ($CHCl_3$) 3457 (m br), 3024 (m), 2959 (m), 2856 (m), 1698 (s), 1257 (s), 1170 (s) cm^{-1}. Calculated for $C_{19}H_{24}O_3Si$: C, 69.47; H, 7.36. Found C, 69.56; H, 7.40 %.

***N*-(Carboadamantyloxy)-15-keto-13-methoxy-10-aza-14a,10a-benzo bicyclo[7.3.1]tridec-3,7-diyn-5-ene 53.** Trifluoromethanesulfonic anhydride (1.71 mL, 10.2 mmol) was added in a single portion to a stirred solution of the complex **51** (2.18 g, 2.54 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (3.13 g, 15.2 mmol) in 2-nitropropane (55 mL) at -10 °C. After stirring for 30 min at -10 °C the reaction was quenched by the addition of aqueous. saturated $NaHCO_3$ and the layers separated. Extraction of the aqueous layer with 2-nitropropane (1 x 15 mL), drying of the combined organic layers ($MgSO_4$), filtration and dilution with acetone (80 mL) gave an opaque red brown solution. After cooling to -10 °C, ceric ammonium nitrate (13.93 g, 25.4 mmol) was added portionwise over 3 to 4 min. After the initial gas evolution, the reaction mixture was stirred for 20 min at -10 °C, and diisopropylethylamine (8.85 mL, 50.8 mmol) was added. Elution of the reaction mixture through a short column of silica gel with 50:50-Et_2O:CH_2Cl_2 followed by evaporation gave a viscous brown oil. Flash chromatography (silica gel, neat CH_2Cl_2) afforded **53** (0.59 g 53% yield) as a white amorphous solid. Recrystallization from Et_2O/CH_2Cl_2 produced small white prisms. M.p 115-119 °C (dec.; rapid heating in

sealed capillary tube). R_f 0.42 (2x30:70-ether:pentane). IR ($CHCl_3$) 1733, 1696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8 Hz, 1H), 6.81 (dd, J = 8.9, 2.4 Hz, 1H), 6.76 (s, 1H), 5.77 (s, 1H), 5.75 (d, J = 9.5 Hz, 1H), 5.62 (d, J = 9.5 Hz, 1H), 3.79 (s, 3H), 3.68 (m, 1H), 3.47 (d, J = 15 Hz, 1H), 3.19 (m, 1H), 2.13 (m, 9H), 1.64 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5 (e), 157.1 (e), 151.8 (e), 129.5 (e), 129.3 (e), 126.8 (e), 126.3 (e), 121.1 (o), 112.3 (o), 111.6 (o), 99.1 (e), 91.5 (e), 90.0 (e), 83.3 (e), 82.3 (e), 55.4 (o), 54.2 (o), 49.2 (o), 41.4 (e), 36.0 (e), 30.9 (o), 21.5 (e). Mass spec. (FAB) *m/z* calcd for $C_{28}H_{28}NO_4$: 442.201, found 442.205; base peak 307, parent peak 442, 289, 154, 135.

Aldol Adduct 63. 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 below -70 °C. The mixture was stirred for 10 min, then brought to 0°C, and a solution of **62** (63 mg, 86 mmol) in dichloromethane (7.5 mL) was added using a syringe pump (rate of addition: 0.2ml/min). When addition was complete, the solution was brought to room temperature, 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 **62** (60 mg, 82 mmol) in dichloromethane (7.5 mL). Each reaction mixture was diluted with further dichloromethane, washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), the solvents removed and the residue purified by preparative thin layer chromatography on silica (hexane-ether) to give the diastereomeric aldol products **63**. These 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%. IR (CCl_4) 2960, 2931, 2063, 2042, 2030, 1735, 1716, 1576, 1370, 1121, 810 cm^{-1}. ^1H(300MHz; CD_3OD) δ 0.30 and 0.35 (6H, 2s), 0.90, (9H, s), 1.30 (9H, s), 3.34 (1H, s), 3.60 (2H, m), 5.82 (1H, d, J = 5.8Hz), 6.23 (1H, d, J = 5.4Hz), 6.48 (1H, s), 7.44 (1H, d, J = 5.4Hz). -OH not observed. ^{13}C (75MHz; CD_3OD) -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, 205.35.
Second diastereomer: ^1H (300MHz; CD_3OD) δ 0.25 and 0.30 (6H, 2s), 0.86 (9H, s), 1.30 (9H, s), 3.15 (1H, d, J = 7.1Hz), 3.55 and 3.60 (2H, 2d, J = 6Hz), 5.29 (1H, d, J = 7.1Hz), 6.19 (1H, s), 6.25 and 7.52 (2H, 2d, J = 5.4Hz).-OH not observed. ^{13}C (75MHz; CD_3OD) -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, 205.55.

Decomplexed Aldol Adduct 65. A solution of **63** (12 mg, 16.4 mmol, less polar diastereomer) in benzene (1 mL) at room temperature 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 thiosulfate, brine, dried (Na_2SO_4),

the solvents evaporated and the residue purified by column chromatography over silica (hexane-ether) to give the decomplexed product **65** (5 mg, 69%) as an off-white solid. ^1H (300MHz; $CDCl_3$) δ 0.15 and 0.23 (6H, 2s), 0.95 (9H, s), 1.26 (9H, s), 3.44-3.52 (1H, m), 3.65 (1H, d, J = 12Hz), 4.16 (1H, d, J = 12Hz), 5.07 (1H, d, J = 1.8Hz), 5.53 (1H, s), 6.21 (1H, d, J = 5.4Hz), 7.79 (1h, d, J = 5.4Hz). -OH not observed). Found: M^+, 445.2018. $C_{24}H_{32}O_6Si$ requires M, 445.2046.

A solution of **63** (7.2 mg, 9.86 mmol; more polar diastereomer) in benzene (0.75 mL) at room temperature 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 thiosulfate, brine, dried (Na_2SO_4), the solvents evaporated and the residue purified by column chromatography on silica (hexane-ether) to give the decomplexed product **65** (3.3 mg, 75%) as an off-white solid. ^1H (300MHz; $CDCl_3$) δ 0.18 and 0.22 (6H, 2s), 0.98 (9H,s), 1.30 (9H, s), 3.45-3.55 (2H, m), 4.05 (1H, d, J 12Hz), 5.03 (1H, d, J 12Hz), 5.44 (1H, s), 6.17 (1H, d, J 5.4Hz), 7.81 (1H, d, J 5.4Hz).-OH not observed.

References and Footnotes.

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