in the yield of t-BuOH at high pH may find explanation in a change in mechanism of the O–O bond cleavage from homolysis to heterolysis. We attribute this change at high pH to the proton dissociation of the manganese(III)-coordinated ImH {i.e., (**1**)-Mn^{III}(OOR)(ImH) → [(**1**)Mn^{III}(OOR)(Im)]$^-$, pK_a = 11.5}. Additionally, the formation of $(Me)_2CO$ (34%) and t-BuOOMe indicates that some homolysis also occurs. The products from homolysis may be explained by the reactions with [(**1**)Mn^{III}-$(OH)]_2^-$. Since at high pH (**1**)$Mn^{III}(X)_2$ does not completely saturate in Im^- due to the competition between HO^- and Im^- ligands, the reaction mixture would be expected to contain some [(**1**)$Mn^{III}(OH)]_2^-$. The series of reactions that account for these observations are shown in Scheme VII.

When the reactions were carried out with ABTS present in the reaction mixture the major product was t-BuOH with small amounts of $(Me)_2CO$ (5%). The formation of small amounts of $(Me)_2CO$ may once again find explanation in the solvent caged reaction of eq 7. In the presence of ABTS the product distributions were the same regardless of the pH employed.

Comparison of ImH and Im^- as Axial Ligands. The reaction properties of many metalloporphyrins are significantly influenced by the nature of the ligand trans to the reactive site. A change in the properties of the axially ligated imidazole ring by proton dissociation represents a mechanism whereby the electronic environment of the metal center can be altered. These observations are supported by UV/visible studies with (**1**)$Mn^{III}X_2$ which display differences in the visible absorption bands when Im^- is an axial ligand rather than ImH {λ_{max} for (**1**)Mn^{III}(X)(ImH): 374, 398, 423 (shoulder), 471 (Soret), 572, 608 nm; and λ_{max} for [(**1**)-Mn^{III}(X)(Im)]$^-$: 373, 398, 468 (Soret), 573, 609 nm}. Similarly, the electronic absorption bands for the related mono-imidazolate complex, [(P)Fe^{II}(CO)(Im)]$^-$ (P = dianion of protoporphyrin dimethyl ester or dianion of *meso*-tetraphenylporphyrin), occur at lower energy than those for the corresponding imidazole complex (P)Fe^{II}(CO)(ImH), and the binding affinity and rate constants for CO binding to [(P)Fe^{II}(Im)]$^-$ have been shown to be lower than those of the protonated (P)Fe^{II}(ImH).[18] Thus, the electronic properties of the proximal ligand in many hemeproteins may well contribute significantly to defining the catalytic characteristics of the enzyme. Indeed several investigators have suggested that a number of hemeproteins which contain a histidine residue as a proximal ligand may possess an imidazolate, rather than an imidazole, as an axial ligand.[18a,19]

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

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Synthetic and Mechanistic Studies on the Antitumor Antibiotics Esperamicin A_1 and Calicheamicin γ_1: Synthesis of 2-Ketobicyclo[7.3.1] Enediyne and 13-Ketocyclo[7.3.1] Enediyne Cores Mediated by η^2 Dicobalt Hexacarbonyl Alkyne Complexes. Cycloaromatization Rate Studies

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Abstract: A general strategy for the construction of the bicyclo[7.3.1]tridecenediyne core structure of the antitumor antibiotics esperamicin and calicheamicin can be realized provided the 10,11-acetylenic bond is complexed as its derived η^2 $Co_2(CO)_6$ adduct. The 10,11-η^2-2-ketobicyclo[7.3.1] enediyne dicobalt hexacarbonyl adduct **38** was synthesized using η^2 dicobalt hexacarbonyl propargyl cation alkylation to form the crucial 10-membered ring. Oxidative decomplexation of **38** in 1,4-cyclohexadiene gave the cycloaromatized adduct **49**, presumably via the uncomplexed 2-ketobicyclo[7.3.1] enediyne **27**. The keto isomer 10,11-η^2-13-ketobicyclo[7.3.1] enediyne dicobalt hexacarbonyl adduct **39** was synthesized in a similar manner and its structure secured by single-crystal X-ray crystallography. Oxidative decomplexation of **39** gave the 13-ketobicyclo[7.3.1] enediyne **32** as a stable crystalline solid. The five-membered-ring analogue, 12-ketobicyclo[7.2.1] enediyne **94**, was readily made in the same way. The relative rates of cycloaromatization of **32** compared to the derived alcohol **86** and the five-membered-ring analogue **94** (and **97**) demonstrate that the distance (r) between the bonding acetylenes (leading to the 1,4-diyl) in the ground state does not control the rate of cycloaromatization. Strain release in the transition state predicts the relative rates of cycloaromatization.

Introduction

During the past 40 years or so, cancer chemotherapy has relied upon natural product chemistry to provide so-called lead compounds and continues to do so.[1] In 1975 Ferguson aptly stated, "What is sorely needed is a good guide or rationale for planning the structure of an effective cytotoxic agent. This stage will come when we have an understanding of the mechanisms of action of antitumor drugs which in turn is fostered by having a working hypothesis for a mode of action of a given type of drug. Organic

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(1) *Anticancer Agents Based on Natural Product Models*; Medicinal Chemistry 16; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980.

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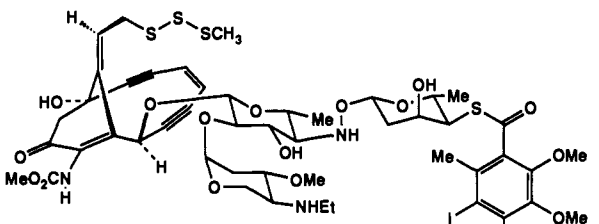
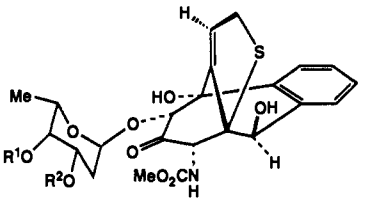
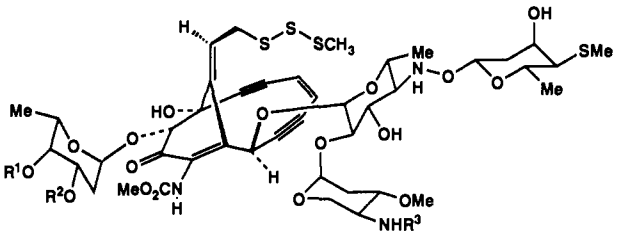
Chart I



1 Calicheamicin γ_1

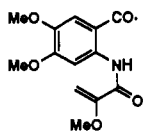


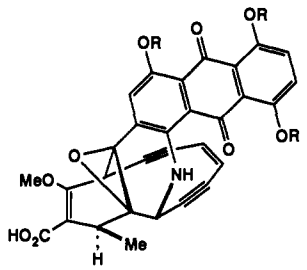
5 Esperamicin X



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.

AC =





6 Dynemicin, R = H and R = Ac.

chemists can play a leading role here. From their experiences in probing reaction mechanisms in vitro they can postulate likely intermediate metabolites and design experiments to follow the reaction sequences of drugs".[2]

The majority of antitumor antibiotics inhibit cell division by interfering with the synthesis or use of nucleic acids.[3] There is a constant need to discover new agents that interact with DNA in a mechanistically definable manner.[4]

In 1987 the Lederle[5] and Bristol-Myers[6] groups reported the unprecedented structures of calicheamicin γ_1 (**1**), esperamicin A_1 (**2**), A_{1b} (**3**), and A_2 (**4**), and the metabolite esperamicin X (**5**) (Chart I). They were isolated from fermentations of *Micromonospora echinospora* sp. calichensis and cultures of *Actinomadura verrucosospora* BBM 1675 and ATCC 39334, respectively. At present, 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.

While they contain a number of unusual structural features such as the allylic trisulfide, a hydroxylamino sugar, and a C_1–C_2 bridgehead double bond, it is the *Z*-enediyne that embues these molecules with a unique mechanism for cleaving DNA. It was proposed[5,6] that the trisulfide is cleaved by nucleophilic attack at the central sulfur atom to give the thiol (or thiolate) **7**, which can conjugatively add to C_1 to give the dihydrothiophene derivative **8**. Once the hybridization at C_1 is changed from trigonal (sp^2) to tetrahedral (sp^3), the transition state for the formation of the 1,4-diyl **9** is energetically feasible. The transition state in going from **8** to **9** must be substantially bicyclo[3.3.1]nonane-like in geometrical character and would be greatly elevated in energy if the C_1–C_2 double bond were still present (anti-Bredt). We will return to this point and the factors that permit access to the 1,4-diyl later.

The 1,4-diyl **9** can abstract a hydrogen atom in a highly exothermic process to give the cycloaromatized adduct **10**. It is interesting and historically instructive to note that Bergman's classical physical organic study of the thermal chemistry of the *Z*-enediyne prototype **11** preceded the reports of the structures of natural products containing this functionality by 25 years.[7] It is more than likely that the 1,4-diyl hypothesis described in Scheme I would not have been at all obvious in the absence of the basic physical organic chemical research. Studies on the interaction of **1** with DNA suggest that it binds into the minor groove and in the presence of thiols causes double- and single-strand scissions.[8] Molecular modeling indicates that the carbohydrate components are responsible for the molecular recognition and subsequent site-specificity at TCCT sites.[9]

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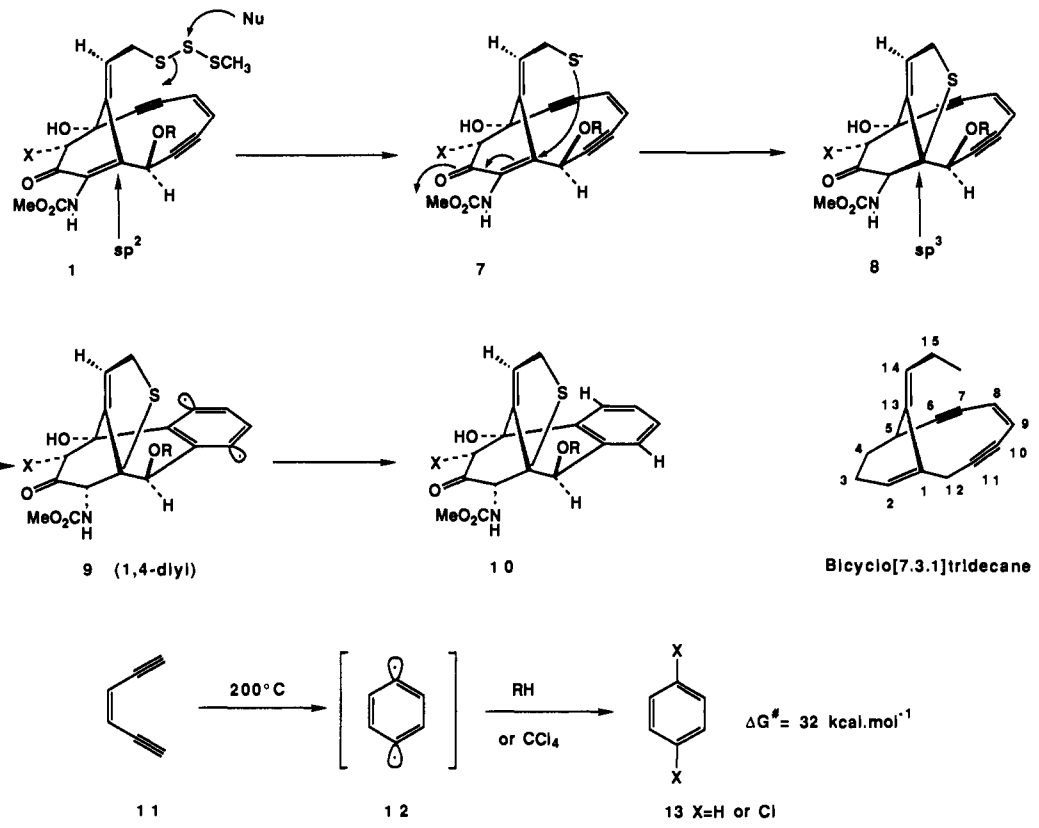
Scheme I



Related to the esperamicin/calicheamicin enediynes is the compound called neocarzinostatin chromophore A (**14**), which also cleaves DNA via the speculated sequence shown in Scheme II.[10] Most recently, the Bristol-Myers group have reported the structure of dynemicin (**6**), a potent antitumor antibiotic. Unlike the other enediyne antibiotics, dynemicin exhibited significant in vivo antibacterial activity and low toxicity.[11]

Because of the unique structures and beautifully designed[12] mechanism of DNA cleavage, the esperamicins and calicheamicins have immediately attracted a great deal of synthetic interest. Scheme III summarizes the overall strategies that have been adopted to date. Danishefsky has reported that the highly functionalized keto aldehyde **15** can be transformed into **16**, which undergoes intramolecular acetylide addition to give the bicyclo-[7.3.1] enediyne core **17**. This approach has culminated in the total synthesis of the aglycon of calicheamicin, namely, calicheamicinone.[13] Schreiber[14] reported that the α,β-unsaturated ester **18** undergoes a type 2 intramolecular Diels–Alder reaction[15] to give **19**. It was subsequently shown that the bicyclo[6.2.2] enediyne **20** was in fact the correct product, but this skeleton in the form of the more highly oxygenated derivative **21** can be rearranged to the desired bicyclo[7.3.1] enediyne **22** (Scheme III). Nicolaou has made a number of monocyclic enediynes **24**, using the Ramberg–Backlund reaction sequence from the α-chloro sulfones **23**, and examined their in vitro DNA cleaving properties.[16] The rates of cycloaromatization of **24** (n = 2, 3, 4, etc.) have been correlated with the distance r between the bonding acetylenic carbons.

The overall strategy we have adopted is based on the following premise.[17] Since the enediyne-containing natural products rep-

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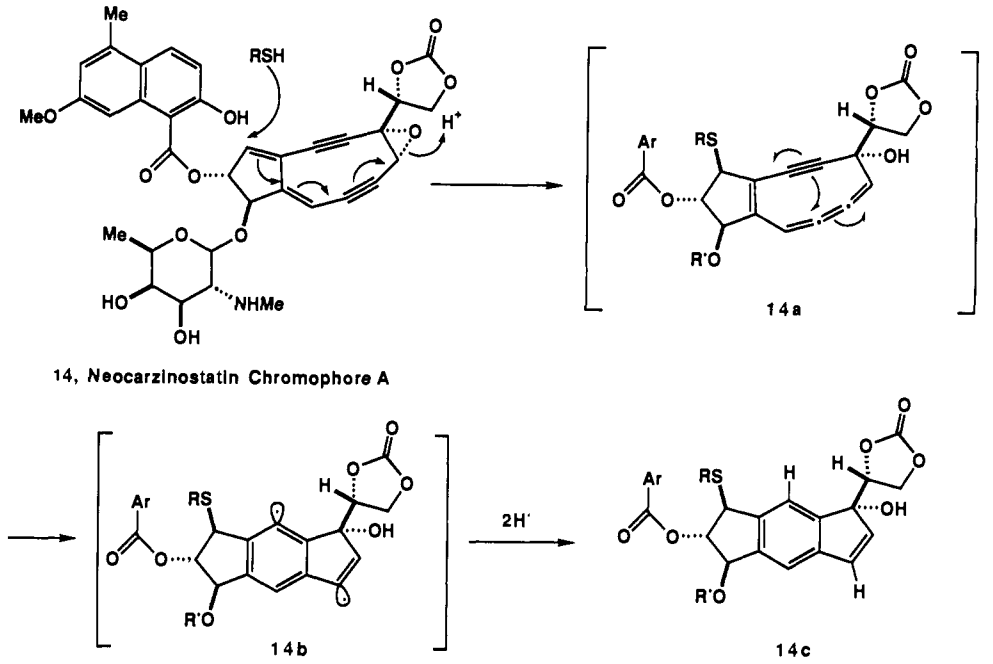
Scheme II



resent a new class of compounds whose chemistry had not yet been explored, a synthetic strategy that probes the reactivity of enediynes and the factors that control the rate of cycloaromatization was warranted. We have, at least initially, deliberately pursued a nonconvergent strategy in order to accrue a corpus of knowledge about the chemistry of the core bicyclo[7.3.1] enediyne system. The overall strategy is outlined in general terms in Scheme IV.

Addition of an acetylide **29** to the monoprotected 1,4-diketone **28** should lead to **26**, which upon ionization to the propargylic cation **26a** results in the 2-ketobicyclo[7.3.1]tridecenediyne **27**. Similarly, addition of **29** to the 1,2-diketone derivative **30** should provide **31**, which leads to the 13-ketobicyclo[7.3.1]tridecenediyne **32**, via **31a**. Some of the many questions to be addressed were whether the isomeric bicyclo[7.3.1] enediynes **27** and **32** were stable, isolable compounds with respect to their potential for cycloaromatization, and if so, what chemistry could be carried out on them.

A very convenient way to generate the propargylic cation-type intermediates **26a**/**31a** is to make use of the η^2 dicobalt hexacarbonyl alkyne complexes **33**, which have been shown by Nicholas[18] to ionize to the cation **34** when treated with Brønsted or Lewis acids. Trapping by a carbon nucleophile gives **35**.[19] A further benefit of the $Co_2(CO)_6$–η^2-alkyne complexes is that they bend the normally linear digonally hybridized acetylene triple bond to approximately 145° (see Figure 1, supplementary material). The propargylic cation is situated with near to axial alignment to the enol derivative **36**/**37** π-system.

Finally, if successful, the corresponding bicyclo[7.3.1]tridecenediynes **38**/**39** will be formed as their mono $Co_2(CO)_6$ complexes and therefore prevent cycloaromatization until the $Co_2(CO)_6$ cap is removed (Scheme V). This device should allow us to examine the release of the enediyne by oxidation and its subsequent cycloaromatization as separate steps. With this overall plan in mind, we initially examined the cyclohexane-1,4-dione system, which should allow us to look at the stability of **27**, and its potential for cycloaromatization.

2-Ketobicyclo[7.3.1]tridecenediyne System

Treatment of cyclohexane-1,4-dione monoketal **28** with lithium acetylide in tetrahydrofuran at 0 °C gave **40** (66%). Palladium(0)-catalyzed coupling of **40** to (*Z*)-dichloroethylene using literature procedures [$Pd(PPh_3)_4$/CuI/*n*-$BuNH_2$/PhH][20] gave **41** (64%). As a general comment, we have found these coupling reactions to be sensitive to dioxygen, particularly on a small scale (≤1 mmol). On a larger scale, where exclusion of dioxygen is less of a problem, the yields of the coupled product increase.

Protection of the tertiary hydroxyl group of **41** was achieved by treatment with *t*-$BuMe_2SiOTf/NEt_3/CH_2Cl_2$ to give **42** (88%). Acid hydrolysis of **42** with 35% trifluoroacetic acid/CH_2Cl_2 gave the ketone **43** (94%) without any detectable deprotection of the tertiary hydroxyl group. Coupling of **43** [$Pd(PPh_3)_4$/CuI/*n*-$BuNH_2$/PhH] with propargyl methyl ether gave **44** (81%), whereas similar coupling with propargyl alcohol gave **45** (56%) (Scheme VI).

When **44** was treated with $Co_2(CO)_8$ in heptane, the less sterically hindered acetylene was converted into the dicobalt hexacarbonyl adduct **46** (82%). Similarly, the propargylic alcohol **45** was converted into the crystalline adduct **47**, whose structure was confirmed by single-crystal X-ray crystallography (see Figure 1, supplementary material).[21] The η^2 $Co_2(CO)_6$ metallocycle bends

(17) Preliminary communications have been published. (a) Synthesis of 2-ketobicyclo[7.3.1]tridecenediyne: Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626. (b) Synthesis of 13-ketobicyclo[7.3.1]tridecenediyne: Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (c) Synthesis of the trisulfide functionality: Magnus, P.; Lewis, R. T.; Bennett, F. *J. Chem. Soc., Chem. Commun.* **1989**, 916. (d) Conjugation addition of thiol to initiate 1,4-diyl formation: Magnus, P.; Lewis, R. T. *Tetrahedron Lett.* **1989**, *30*, 1905. (e) Selenium dioxide oxidation of bridgehead trialkylsilyl enol ethers: Magnus, P.; Bennett, F. *Tetrahedron Lett.* **1989**, *30*, 3637. (f) Synthesis of the 12β-hydroxybicyclo[7.3.1]tridecenediyne core structure: Magnus, P.: Annoura, H.; Harling, J. *J. Org. Chem.* **1990**, *55*, 1709. (g) Molecular strain rather than π-bond proximity determines the cycloaromatization rates of bicyclo[7.3.1]tridecenediynes: Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986. For a recent extension of the $Co_2(CO)_6$–η^2-acetylene methodology, see: Maier, M. E.; Brandstetter, T. *Tetrahedron Lett.* **1991**, *32*, 3679.

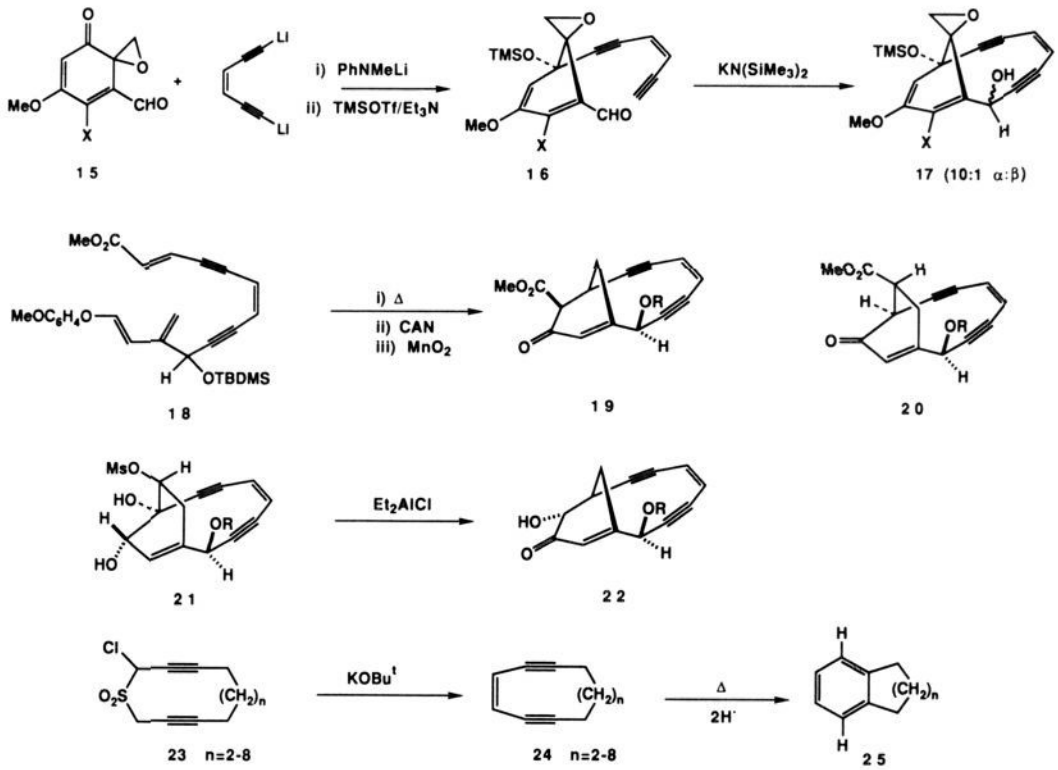
(18) Sly, W. G. *J. Am. Chem. Soc.* **1959**, *81*, 18. Howard, J. A. K. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1983**, *C39*, 1024. Nicholas, K. M.; Nestle, M. O.; Seyferth, D. *Transition Metal Organometallics in Organic Synthesis*; Alper, H., Ed.; Academic Press: New York, 1978; Vol. 2.

(19) The propargyl cation chemistry has recently been reviewed: Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. Nicholas, K. M.; Mulraney, M.; Bayer, M. *J. Am. Chem. Soc.* **1980**, *102*, 2508. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. Schreiber, S. L.; Klimas, M. Y.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749. Montana, A. M.; Nicholas, K. M.; Khan, M. A. *J. Org. Chem.* **1988**, *22*, 5193.

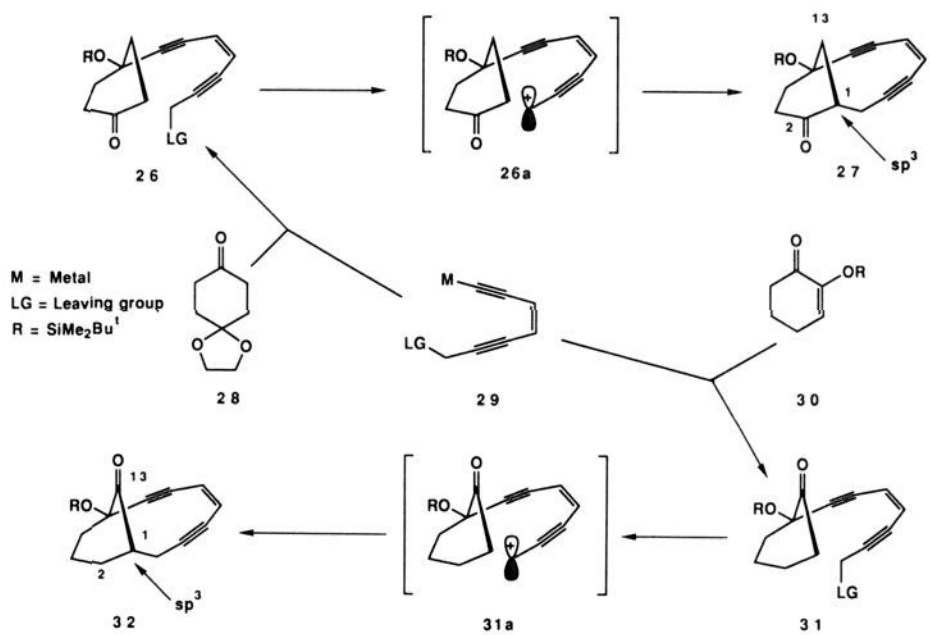
(20) Stephans, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001. Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1986**, *27*, 5857. Guillerm, D.; Linstumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811.

(21) Complete details of the X-ray crystallographic structure determination for **32**, **39**, **47**, **54**, **64**, and **95** are available as supplementary material.

Scheme III



Scheme IV

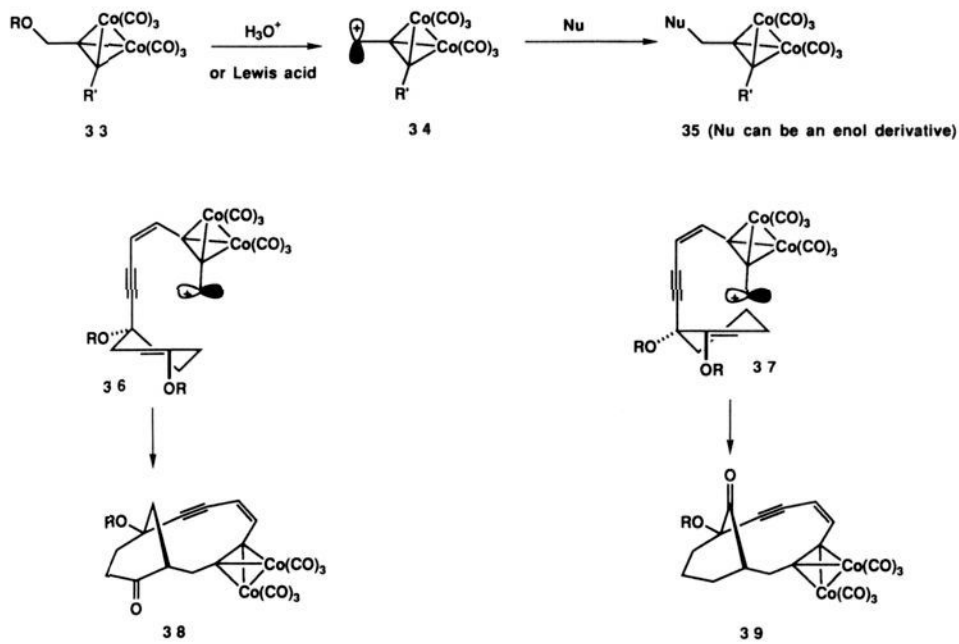


the normally linear (digonal) sp-hybridized acetylene from 180° to 143.5° and 145.6°. In the crystalline state **47** has the η^2-enediyne $Co_2(CO)_6$ appendage in an equatorial conformation, whereas in solution it must adopt an axial conformation for the propargylic carbon atom to allow axial alkylation of the derived enol(ate) form of either **46** or **47**.

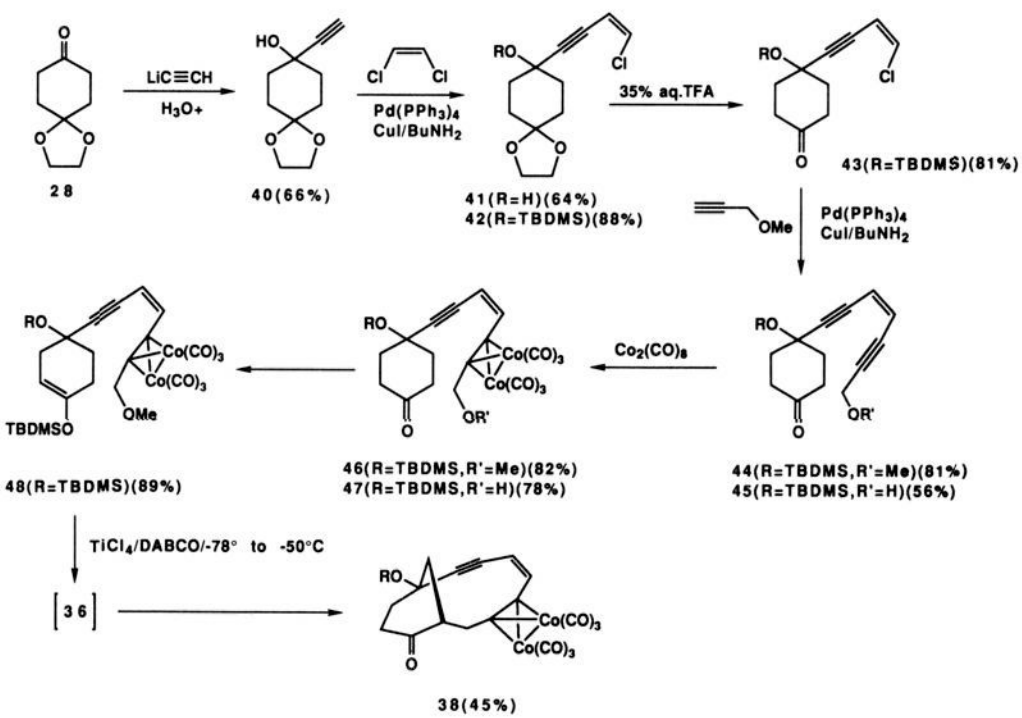
Treatment of **46** with *t*-$BuMe_2SiOTf/NEt_3/CH_2Cl_2$ gave the derived silyl enol ether **48** (89%). After considerable experimentation using a wide variety of Lewis acids [$BF_3{\cdot}OEt_2$, $SnCl_4$, $Ti(OPr^i)_4$, $NbCl_5$, etc.] and protic acids (CF_3CO_2H, HBF_4, and TsOH), it was eventually found that treatment of **48** in dichloromethane (−78 to −50 °C) with 1.0 M $TiCl_4$ and DABCO gave the required 2-ketobicyclo[7.3.1] enediyne dicobalt hexacarbonyl adduct **38** as a red oil in 45% yield. The choice of an amine that cannot be dehydrogenated (the iminium ion from DABCO would violate Bredt's rule) was arrived at by the following observation. If the above Lewis acid mediated ionization of **48** was carried out in the presence of triethylamine instead of DABCO, only small amounts of cyclization to **38** (<5%) were observed, and the major pathway was reduction of the intermediate cation **36** to a methyl group. This observation provides good evidence that the cation **36** is indeed the species undergoing cyclization to **38**. It is important that the temperature in the cyclization is kept below −45 to −50 °C, otherwise extensive decomposition occurs.

Oxidative decomplexation of **38** in 1,4-cyclohexadiene using

Scheme V



Scheme VI

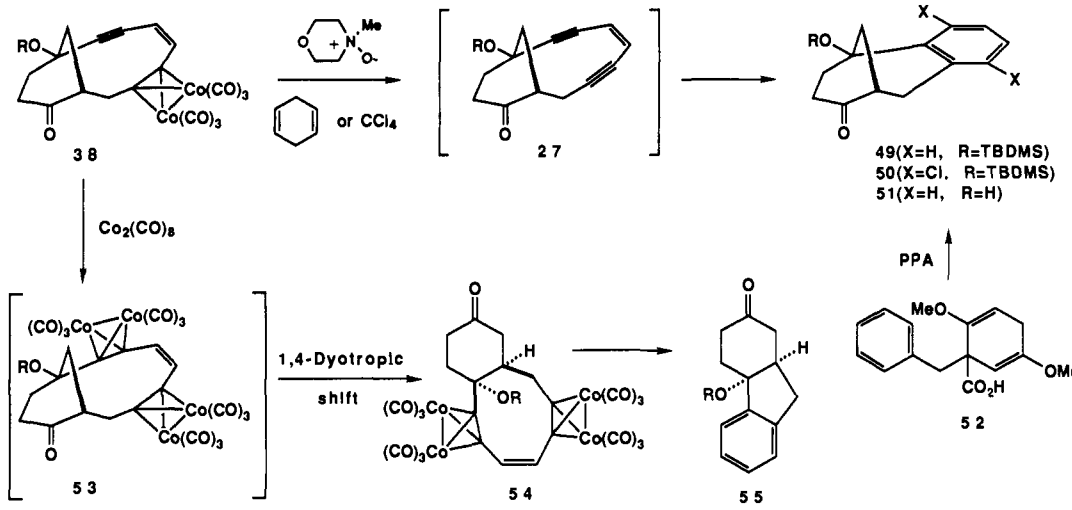


N-methylmorpholine *N*-oxide (NMMO)[22] at 20 °C rapidly gave **49** (42%), presumably via the uncomplexed 2-ketobicyclo[7.3.1] enediyne **27**. Even at lower temperatures (−20 °C), we could not isolate **27**, although a product was observed (^{1}H NMR and TLC) that decomposed to give **49** (Scheme VII).

The structure of **49** was evident from its ^{1}H NMR spectrum combined with decoupling experiments: δ 3.37 (dd) couples to δ 2.85/2.52; δ 2.85 couples to δ 3.37/2.67/2.52; δ 2.67 (dd) couples to δ 2.85/2.3; δ 2.59 couples to δ 2.1; δ 2.52 couples to δ 3.7/2.82. This shows the presence of two ABX spin systems where H_X is the bridgehead proton common to both ABX spin systems, and resonating at δ 2.85. While this is consistent with both the bridged ring structure **49** and the fused ring structure **55**, only **49** would have H_X at δ 2.85 (adjacent to the carbonyl group), whereas the corresponding methine H_X in **55** would be expected to appear at higher field. Further support for the structure of **38**, and therefore **49**, comes from the ^{13}C spectra [C_1 in **38** (57 ppm), **39** (50 ppm), and **64** (37 ppm). For the latter two compounds, see Figures 3

(22) Magnus, P.; Becker, D. P. *J. Chem. Soc., Chem. Commun.* **1985**, 640.
(23) Hook, J. M.; Mander, L. N. *J. Org. Chem.* **1980**, *45*, 1722. Treatment of the reductive benzylation product **52** with polyphosphoric acid is reported to give **51**. Although full experimental details were kindly supplied by Professor Mander, we were unable to make an authentic sample of **51**, and thence **49**.
(24) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969; *J. Org. Chem.* **1984**, *49*, 3912.

Scheme VII



and 5,[25] X-ray structures, in the supplementary material.

Decomplexation of **38** in carbon tetrachloride/NMMO gave the corresponding para dichloride **50** (29%). While we cannot exclude a cobalt-catalyzed process that results in the aromatized adducts **49**/**50**, the data obtained for the 13-ketobicyclo[7.3.1] enediyne **32** (see later) provide very strong evidence that removal of the $Co_2(CO)_6$–η^2-cap does not initiate a Co-catalyzed aromatization.

The hydroxy derivative **51** is a known compound made by Mander during the course of his studies on the synthesis of gibberellins.[23] Since an authentic sample of **51** was not available, and we were unable to reproduce the transformation of **52** into **51**, we attempted to make a crystalline derivative of **38**. Conversion of **38** into the dark green-black crystalline tetracobalt adduct, initially thought to be **53**, was readily achieved by treatment of **38** with dicobalt octacarbonyl. The ^1H NMR spectrum of the supposed **53** was very broad and diffuse and did not exhibit any definitive features. Fortunately the green-black crystals were of sufficient quality to give X-ray crystallographic data. Surprisingly, these data showed the structure to be the rearranged tetracobalt adduct **54** (Figure 2, supplementary material).[21] Apparently the adduct **53** has undergone a 1,4 acetylene shift accompanied by a 1,4 silyl shift to give the compound **54** (1,4 dyotropic shift),[25] a compound apparently resulting from β-alkylation! Decomplexation of **54** gave a complex mixture, and while we could not detect the bridged bicyclic system **49**, neither could we isolate the expected hexahydrofluorenyl adduct **55**. Consequently we were left with the question of whether the 1,4 dyotropic shift takes place before or after the second dicobalt hexacarbonyl complexation. As will be seen later, we have observed the 1,2-version of this rearrangement in the 13-keto series, and this series provides good evidence that the bicyclo[3.3.1]nonanes **49**/**50** are the correct structures and not hexahydrofluorenyl derivatives of **55**. Taken together with the NMR evidence, this strongly suggests that the 1,4 dyotropic rearrangement proceeds when **38** is converted into **53** and then to **54**. It is interesting to point out that **54** contains the 9-membered ring of neocarzinostatin CA (**14**); the rearrangement contracts the 10-membered esperamicin/calicheamicin ring system into the 9-membered neocarzinostatin core structure.

13-Ketobicyclo[7.3.1]tridecenediyne System

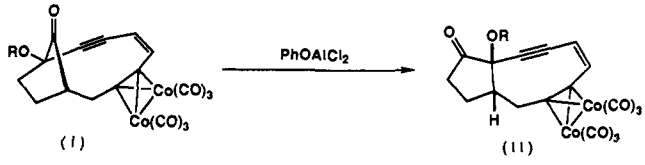
While the route used for the synthesis of the 2-ketobicyclo[7.3.1] enediyne system provides a practical method for the construction of the esperamicin core structure, the carbonyl group is not in a suitable position to examine bridgehead enol(ate) functionalization. However, starting with cyclohexane-1,2-dione should allow ready access to the potentially more useful 13-keto core structure **32**. Treatment of cyclohexane-1,2-dione with NaH/MEM-Cl/THF at −10 °C gave **56** (82%), which was exposed to lithium acetylide–ethylenediamine complex in dioxane to give **57** (74%). Coupling of **57** to (*Z*)-dichloroethylene to give **58** (77%) was accomplished with $Pd(PPh_3)_4$/CuI/*n*-$BuNH_2$. Protection of **58** (*t*-$BuMe_2SiOTf/NEt_3/CH_2Cl_2$) gave **59** (72%), which was coupled, as before, to methyl propargyl ether to give **60** (88%). Selective removal of the MEM enol ether in **60** using Me_2BBr[24] at −35 °C gave **61** (>95%), from which the derived *t*-$BuMe_2Si$ enol ether **62** (85%) was prepared. Treatment of **62** with $Co_2(CO)_8$/heptane at room temperature resulted in complexation predominately at the sterically less hindered acetylenic bond to give **63** (90%). Small amounts of the $Co_2(CO)_6$–acetylene regioisomer and its bis $Co_4(CO)_{12}$ complex are also formed; **63** is purified by chromatography prior to its conversion into **39**.

Treatment of **39** with $TiCl_4$/DABCO at −43 to −35 °C gave the required 10,11-η^2-bicyclo[7.3.1] enediyne dicobalt hexacarbonyl adduct **39** (55%) as a crimson crystalline solid, accompanied by a small amount (ca. 10%) of the α-ketol shift isomer **64** (Scheme VIII).

It is interesting to note that the rearranged product **64** contains the nine-membered-ring diyne system of the neocarzinostatin chromophore A (**14**) and, as such, establishes a structural relationship between the two classes of antitumor agents.[25]

Recently, Tomioka reported that the conversion of **63** into **39** did not proceed as we have reported, but gave instead the cationic allylic rearrangement product **65**.[26] They also reported that in order to make **39** it is necessary to use the corresponding trimethylsilyl enol ether derivative of **63**. Their conditions are identical to ours except the temperature was −60 °C. At −60 °C ($TiCl_4$/DABCO), **63** does indeed slowly rearrange to give **65**, but at −40 to −35 °C, **39** is rapidly formed. We and others[27] have also found the trimethylsilyl enol ether derivatives of **61** and **63** to be unstable with respect to hydrolysis to the corresponding ketones and as a consequence make purification difficult, resulting in inferior overall yields of **39**. The structure of **39** was secured

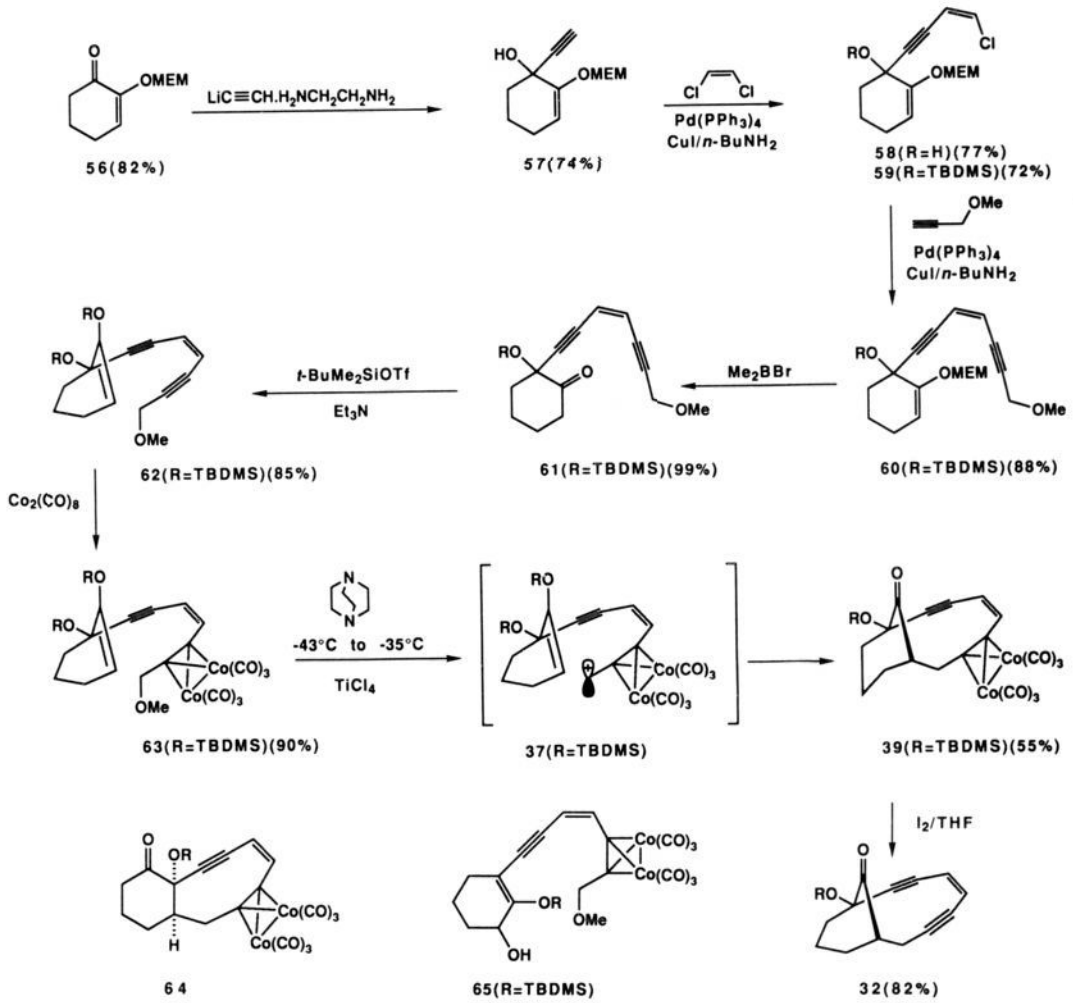
(25) See Figure 5, supplementary material. Dyotropic shifts of trialkylsilyl groups are well-known: Barnier, J. P.; Garnico, B.; Girard, C.; Denis, J. M.; Salaun, J.; Conia, J. M. *Tetrahedron Lett.* **1973**, *14*, 1747. We have used this rearrangement to construct the neocarzinostatin core structure. The adduct i rearranges to give ii when treated with $PhOAlCl_2$.



Magnus, P.; Fortt, S.; Pitterna, T., unpublished results. Magnus, P.; Pitterna, T. *J. Chem. Soc., Chem. Commun.* **1991**, 541.

(26) Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851.
(27) Kadow J., Bristol-Myers Squibb, private communication.

Scheme VIII

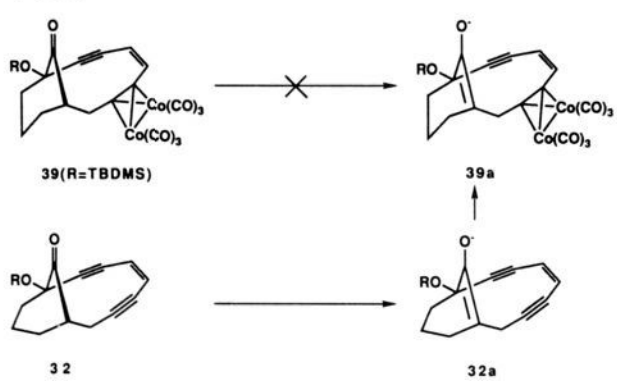


by single-crystal X-ray crystallography (Figure 3, supplementary material, shows an ORTEP representation. The newly formed carbon–carbon bond (C_1–C_{12}) is axial (with respect to the cyclohexanone ring) and consequently the hydrogen atom at C_1 is in an equatorial configuration. The C_1–H bond is orthogonal to the C_{13} carbonyl π-system and as a consequence should exhibit reduced kinetic acidity. In other words, there is a kinetic barrier to bridgehead enolization in **39** because of poor overlap in the developing enolate π-system. Not surprisingly, attempts to form the bridgehead enolate **39a** failed (see footnote 28). The uncomplexed acetylenic bond angles $C_{5,6,7}$ and $C_{6,7,8}$ in **39** have changed from 178° (using **47** as a reference) to 170.7° and 173.7°, respectively. There is relatively little change in the bond angles and bond lengths of the η^2 dicobalt hexacarbonyl group and the $C_{8,9}$ double bond. The axial C_1–C_{12} bond can only be accommodated in this configuration if the cyclohexanone ring is in a chair conformation, which is clearly shown in Figure 3, supplementary material.[21]

Oxidative decomplexation of **39** using iodine/THF at room temperature gave the 13-ketobicyclo[7.3.1] enediyne **32** (82%) as a stable crystalline solid (Figure 4, supplementary material, shows an ORTEP representation). When the 10,11-η^2 dicobalt hexacarbonyl group is removed, the $C_{9,10,11}$ and $C_{10,11,12}$ bond angles change from approximately 139° to 165.7° and 169.8°, respectively. This causes the previously axial $C_{1,12}$ bond to assume an equatorial configuration and thus forces the six-membered ring into a boat conformation. The bond angles and bond lengths of the $C_{8,9}$ double bond are normal, indicating that the strain in **32** is accommodated by the weak bending modes of the triple bonds.[29] The bridgehead C_1–H bond is axial and in the same plane as the C_{13} carbonyl π-system. Consequently, **32** should be capable of forming a bridgehead enol derivative because the developing π-character at C_1 can directly participate in enolate resonance stabilization.[28]

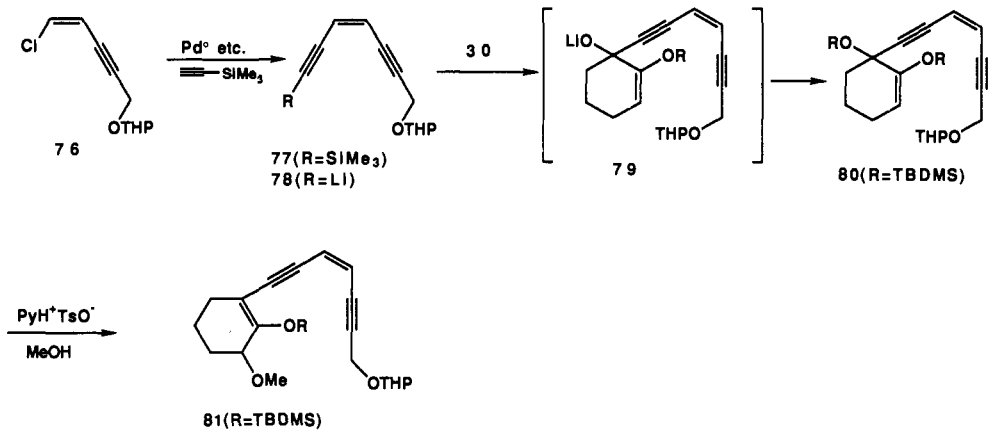
Before describing the rate of aromatization studies on **32** and related structures, we investigated more convergent routes to **32**, and improvements in the conversion of η^2 dicobalt hexacarbonyl adduct **63** into **39**. By use of the sequence of transformations

(28) While **39** could not be converted into **39a** the uncomplexed acetylene **32** readily formed **32a**, which could be isolated as its *t*-$BuMe_2$ silyl enol ether and then converted into the corresponding derivative of **39a**. See accompanying paper.

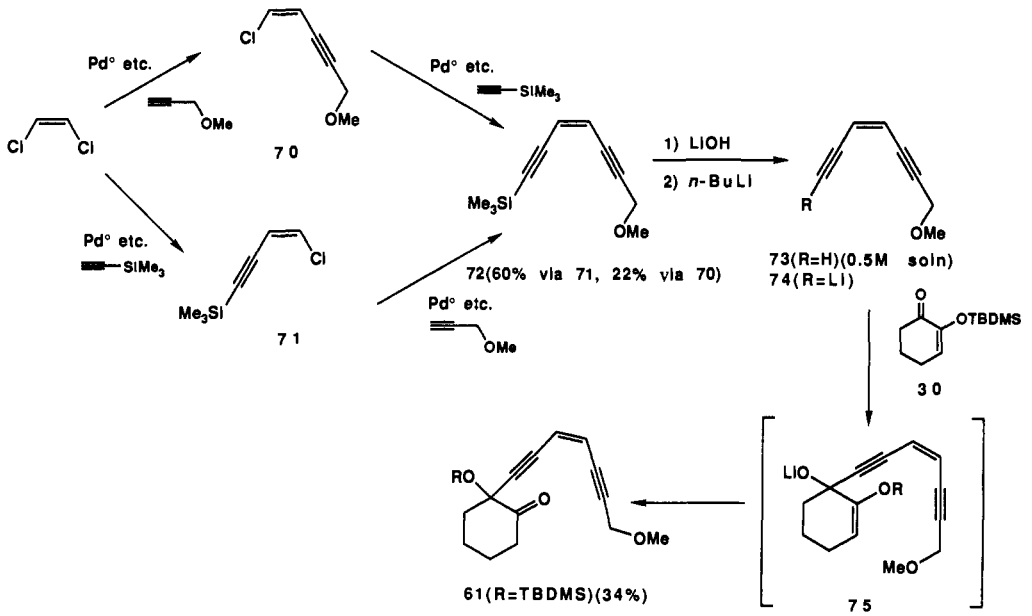


(29) *Chemistry of Acetylenes*; Viehe, G. M., Ed.; Marcel Dekker: New York, 1969. Behr, O. M.; Eglinton, G.; Galbraith, A. R.; Raphael, R. A. *J. Chem. Soc.* **1960**, 3614.

Scheme IX



Scheme X



outlined in Scheme IX, the vinyl chloride **59** was converted into the propargylic alcohol **68** via **66** and **67** in three steps, overall yield 62%.

Treatment of **68** with $Co_2(CO)_8$ gave selective complexation of the less hindered acetylene resulting in **69** (84%). When **69** was exposed to triflic anhydride in dichloromethane at −10 °C in the presence of 2,6-di-*tert*-butyl-4-methylpyridine, the η^2-13-ketobicyclo[7.3.1] enediyne dicobalt hexacarbonyl adduct **39** was isolated in 77% yield. The above route was made more convergent by utilizing the modification described by Kadow[30] in his adaptation of our original sequence. Treatment of **72** [best made from **71** in 60% overall yield from (*Z*)-dichloroethylene: the alternative route from **70** does not give a good yield in the first coupling reaction] with lithium hydroxide generated the unstable terminal acetylene **73**, which was used as a 0.5 M solution (pentane/Et_2O). The lithio species **74** (generated from **73**/*n*-BuLi/THF at −78 °C) was quenched with the enone **30** to give, initially, **75**, which on warming to 20 °C underwent 1,2 silyl migration to give **61**, albeit in only 34% yield (Scheme X). Enolization of **30** appears to be the source of the modest yield, since large amounts of **30** were recovered.

While the convergent route to the enediyne **61** in short (five steps, overall yield 20%, from (*Z*)-dichloroethylene), it does not capitalize on the improved closure of the propargylic alcohol **69** to **39** (77%) using triflic anhydride/2,6-di-*tert*-butyl-4-methylpyridine.

(*Z*)-Dichloroethylene was coupled to propargyl *O*-tetrahydropyranyl ether using $Pd(PPh_3)_4/CuI/n\text{-}BuNH_2$ to give **76** (58%). Further coupling in the same manner to (trimethylsilyl)acetylene gave **77** (58%), which was converted into the lithio reagent **78** by treatment with LiOH/THF, followed by *n*-BuLi/THF. Quenching of this acetylide anion with **30** and in situ silylation of **79** with *t*-$BuMe_2SiOTf/Et_3N$ gave **80** (>90%). Selective deprotection of the tetrahydropyranyl ether using the Grieco procedure[31] (pyridinium tosylate in methanol) unfortunately resulted in allylic rearrangement to give **81**, and none of the desired alcohol **68** (Scheme XI). Consequently, the route shown in Scheme IX provides the best overall yield of the η^2-13-ketobicyclo[7.3.1] enediyne dicobalt hexacarbonyl adduct **39** (10% from cyclohexane-1,2-dione) and makes use of the more efficient cyclization of **69** into **39**.

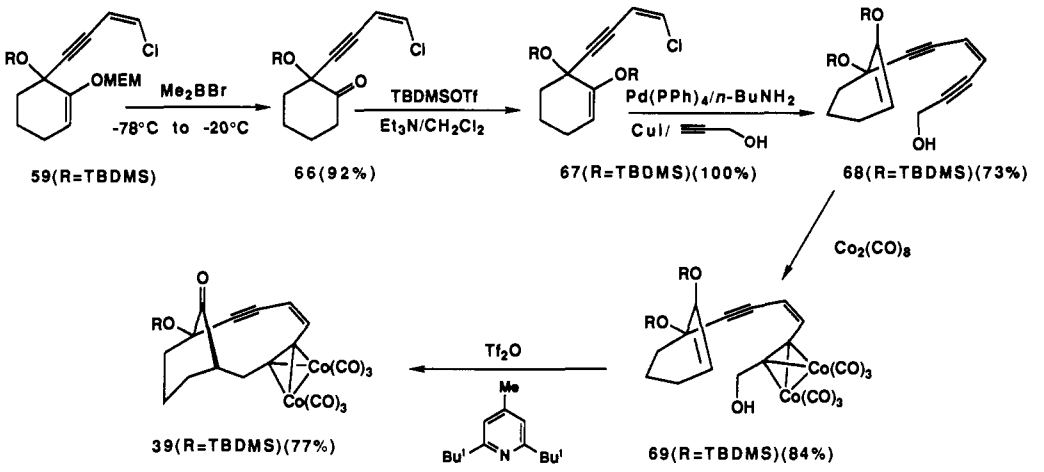
Rate of Cycloaromatization of the 13-Ketobicyclo[7.3.1]tridecenediyne System and Related Studies

Initial qualitative experiments readily showed that the 13-bicyclo[7.3.1] enediyne **32** is considerably more resistant to cycloaromatization than the 2-keto isomer **27**. While we could not isolate **27**, **32** is a stable crystalline compound below 80 °C. At

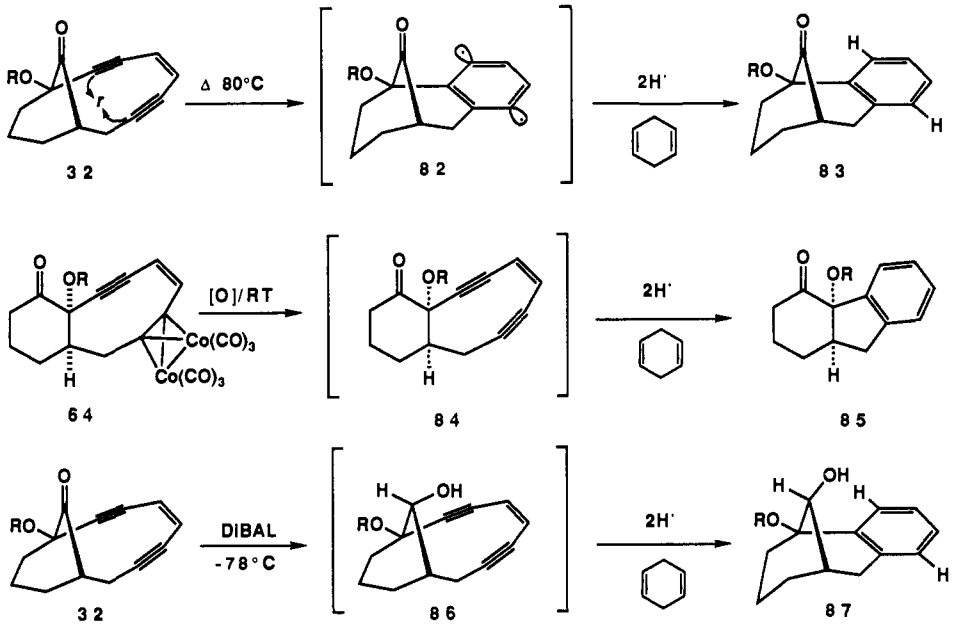
(30) Kadow, J. F.; Saulnier, M. G.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *Tetrahedron Lett.* **1989**, *30*, 3499.

(31) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

Scheme XI



Scheme XII[a]



[a] R = TBDMS.

80 °C, in 1,4-cyclohexadiene, **32** is converted into the aromatic adduct **83** (72%) via the 1,4-diyl **82** (Scheme XII). The Bergman prototype enediyne **11** (Scheme I), requires heating at 195 °C in the presence of a hydrogen atom donor in order to convert it into benzene. The $\Delta G^{\ddagger}$ for this conversion is approximately 32 kcal·mol^{-1}. It is clear that the esperamicins and calicheamicins **1–4** embody structural features that enable diyl formation to take place under physiological conditions (37 °C).

Recently Townsend[32] reported that treatment of calicheamicin **1** with n-Bu_3P at −67 °C in methanol-d_4 gave the dihydrothiophene **8** (X = H). At −11 °C, **8** (X = H) was transformed into the calicheamicin equivalent of esperamicin X **10** (X = H) at a convenient rate (VT ^{1}H NMR) that allowed useful first-order rate data to be measured; $k = 5 \pm 2 \times 10^{-4}$ s^{-1} and $\Delta G^{\ddagger} = 19.3 \pm 0.2$ kcal·mol^{-1}. Thus the half-life of the dihydrothiophene intermediate **8** (X = H) is 4.5 ± 1.5 s at 37 °C. The provocative and kinetically plausible conclusion is that the observed DNA sequence selectivity may well be the result of binding the dihydrothiophene **8** (X = H) to DNA, rather than calicheamicin itself.

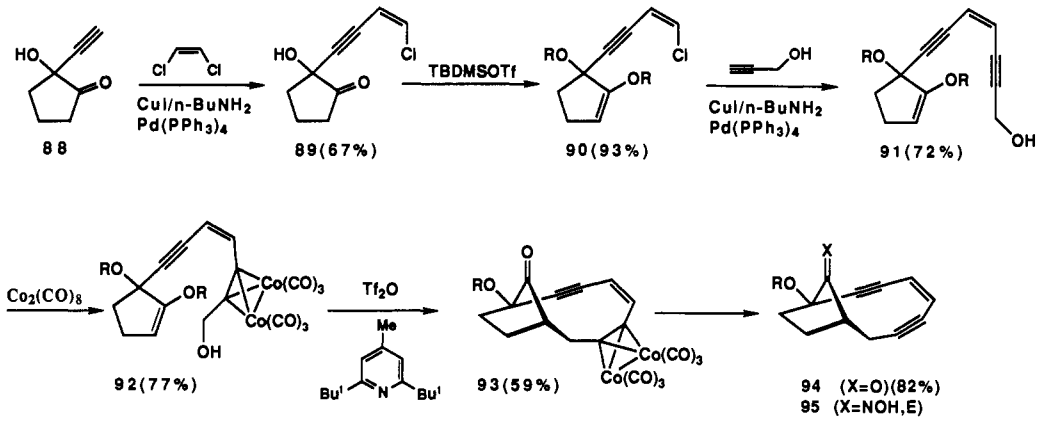
Nicolaou[16] examined a number of monocyclic enediynes **24** (n = 2–8) (Scheme III) and concluded from their relative stability, and several other similar previously reported enediynes,[7] that the ease of cycloaromatization can be correlated to the distance between the bonding acetylenic carbon atoms $r(C_{sp}–C_{sp})$. It should be noted as a reference point that the distance r between the two bonding acetylenes in **11** is 4.17 Å.[33] In the ground state a distance r of 3.16 Å is sufficient to cause spontaneous ambient cycloaromatization to the 1,4-diyl **9**. For the substrate **24** (n = 2, 10-membered-ring monocyclic analogue), $k = 6.4 \times 10^{-4}$ min^{-1} (1.07×10^{-5} s^{-1}) and E_{act} = 23.8 kcal·mol^{-1} ($\Delta G^{\ddagger}$ = 24.7 kcal·mol^{-1}). Snyder[34] has calculated (MM2, parameterized to reproduce the PRDDO-GVB-CI transition state) for **32** $\Delta G^{\ddagger}$ = 26.1 kcal·mol^{-1}, for **27** $\Delta G^{\ddagger}$ = 23.6 kcal·mol^{-1}, and for **86** $\Delta G^{\ddagger}$ = 20.6 kcal·mol^{-1}. The first value is in excellent agreement with the experimental value (see below), and the latter two values qualitatively parallel our observations. For the 2-ketobicyclo[7.3.1] enediyne **27**, the distance r is calculated to be 3.34 Å, for the isomeric 13-ketobicyclo[7.3.1] enediyne **32**, r is 3.41 Å, and for the alcohol **86**, r is 3.32 Å. Therefore, if the distance r between the bonding acetylenes in the ground state were the only factor governing the rate of cycloaromatization, the isomeric ketones **27** and **32** should be of comparable stability. Nevertheless, there

(32) De Voss, J. J.; Hangeland, J. J.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 4554.

(33) Adiwidjaja, G.; Groun-witte, G. *J. Organomet. Chem.* **1980**, *188*, 91.

(34) Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630. Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367. See also ref 17g.

Scheme XIII[a]



[a] R = TBDMS.

Scheme XIV

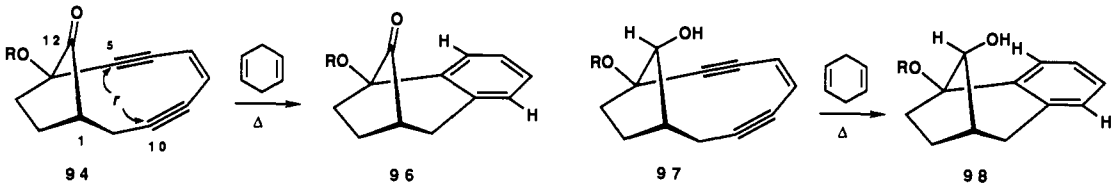


Table I. Kinetic Parameters for the Thermal Cyclization of Enediyne **32**

T, °C	k, s^{-1}	$t_{1/2}(\tau)$	T, °C	k, s^{-1}	$t_{1/2}(\tau)$
71	1.07×10^{-4}	2.10 h	95	1.16×10^{-3}	10 min
79	2.56×10^{-4}	45 min	104	2.58×10^{-3}	4.30 min
87	5.00×10^{-4}	23 min			

is a substantial rate difference in their respective first-order cycloaromatization. This points to factors other than simply the magnitude of r in the ground state controlling the rate of diyl formation. It is reasonable to assume that the rate of diyl hydrogen atom quenching is very fast compared with diyl formation, since it is a highly exothermic process.

The crystalline 13-ketobicyclo[7.3.1] enediyne **32** has been characterized by X-ray crystallography, r = 3.39 Å, in excellent agreement with calculation (3.41 Å). The cyclohexanone ring is in a boat conformation in the crystal and in solution. Heating a solution of **32** in 1,4-cyclohexadiene at temperatures ranging from 71 to 104 °C and monitoring both the rate of disappearance of **32** and the rate of formation of **83** (>70%) gave the *first-order* rate constants shown in Table I. Extrapolated to 37 °C, the thermodynamic parameters are $\Delta G^{\ddagger}$ = 26.3 kcal·mol^{-1} (calcd 26.1 kcal·mol^{-1}), $\Delta H^{\ddagger}$ = 24.0 kcal·mol^{-1}, $\Delta S^{\ddagger}$ = −7.33 eu, E_a = 24.6 kcal·mol^{-1}, and $k = 1.85 \times 10^{-6}$ s^{-1} (error ±2%).

The transition state for the conversion of **32** into **83** should be substantially bicyclo[3.3.1]nonane-like in geometrical character. If we replace the six-membered ring with a five-membered ring, the transition state for cycloaromatization will now be bicyclo-[3.2.1]octane-like in geometrical character (more strained), but with little or no change in the distance r between the bonding acetylenes.

The five-membered-ring analogue of **32**, namely, 12-ketobicyclo[7.2.1] enediyne **94**, was readily made in the same way (Scheme XIII) except the starting material was cyclopentane-1,2-dione. Scheme XIII parallels Scheme IX. The crucial transformation involved treatment of **92** with triflic anhydride/2,6-di-*tert*-butyl-4-methylpyridine/CH_2Cl_2 at −10 °C to give the η^2-12-ketobicyclo[7.2.1] enediyne dicobalt hexacarbonyl adduct **93** (59%). Decomplexation of **93** with I_2/THF at 0 °C gave the ketone **94** (82%) as a thick oil.

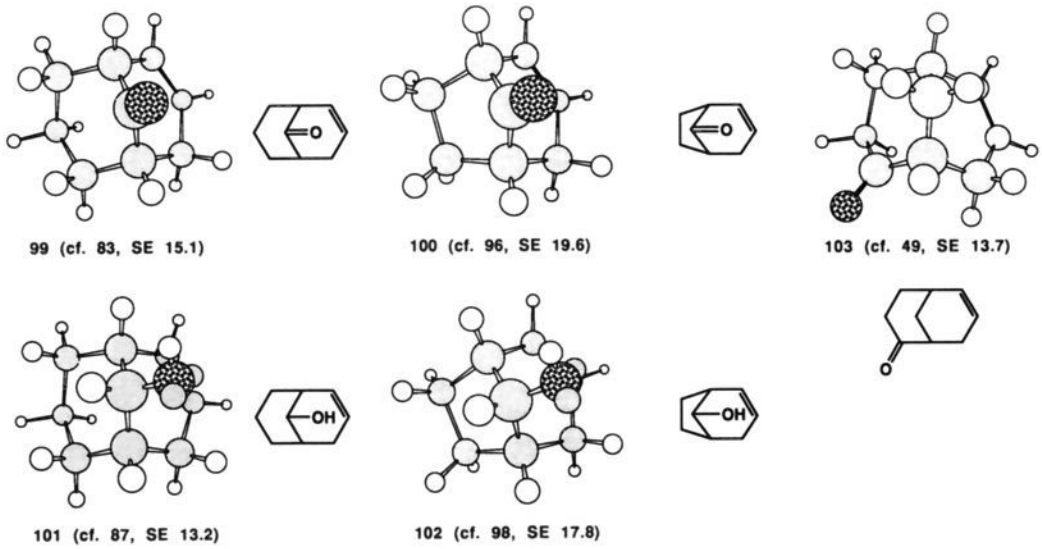
The *E*-oxime **95** gave suitable crystals for X-ray analysis (Figure 6, supplementary material).[21] The bond angles and bond lengths in the enediyne portions of **32** and **95** are very similar. The only significant differences in **95** are the increased bending of the C_5–C_6 acetylene (167.4°/166.8° vs 171.5°/168.7° for **32**) and the carbonyl bond angle (110.5° vs 118.3° in **32**) [ν_{max} 1764 (**94**) and 1734 cm^{-1} (**32**)].

The C_5/C_{10} separation is r = 3.37 Å (vs 3.39 Å for **32**). Although the distance between the two acetylenic carbons is almost within the range postulated for ambient cycloaromatization (<3.35 Å) and slightly below r in **32**, compound **94** is remarkably resistant to ring closure. At 124 °C (averaged over five runs), $k = 2.08 \times 10^{-5}$ s^{-1} for conversion of **94** into the bicyclo[3.2.1] system **96** (73%). This corresponds to a $\Delta G^{\ddagger}$ (124 °C) of 32.0 kcal·mol^{-1} and gives $\Delta\Delta G^{\ddagger}$ (**94** − **32**) = 5.1 ± 0.2 kcal·mol^{-1} at the same temperature.[34] In other words, even though r is less in **94** than in **32**, **94** *cycloaromatizes 650 times more slowly* at 124 °C. By contrast, the cycloaromatization rate of alcohol **97** to **98** at 85 °C ($k = 1.467 \times 10^{-4}$ s^{-1}) is *216 times faster* than **94** and *one-third* the rate of **32** ($\Delta G^{\ddagger}$ = 27.4 kcal·mol^{-1}). The alcohol derived from **32**, namely **86**, cycloaromatizes rapidly at 0 °C. These appreciable rate differences were predicted by Snyder prior to the rate measurements.[34]

A significant conformational difference between the five- and six-membered-ring analogues is that the boat cyclohexanone in **32** becomes a chair in **83** and provides approximately 6-kcal strain release in the transition state, whereas the five-membered-ring system **94** has no comparable driving force. The simple notion that the distance between the bonding acetylenic carbon atoms in the ground state determines the rate of diyl formation does not provide an adequate prediction of the ease of cycloaromatization for the bicyclic enediynes described above. The transition state model developed by Snyder is in good accord with the experimental results.

This model is product oriented. The transition state for the conversion of **32** into **83** should be substantially bicyclo[3.3.1]-nonane-like in geometrical character. If we accept this suggestion, there should be a correlation between the strain energy of the products and their relative rates of formation. The less strained product will be formed more rapidly. MM2 calculations carried out on the series of compounds **99**–**103** (Chart II) parallel the trends observed both experimentally and in the Snyder calculations: ΔSE (**100** − **99**) = 4.5 [exp$\Delta\Delta G^{\ddagger}$ (**94** − **32**) = 5.1 ± 0.2 kcal·mol^{-1}]; ΔSE (**102** − **99**) = 2.5 [exp$\Delta\Delta G^{\ddagger}$ (**97** − **32**) = 1.3 ± 0.2

Chart II[a]



[a] SE, strain energy.

kcal·mol^{-1}]; ΔSE (**99** − **103**) = 1.9 [calcd $\Delta\Delta G^{\ddagger}$ (**32** − **27**) = 1.5 kcal·mol^{-1}].

Summary

The overall general strategy for the construction of the bicyclo[7.3.1]tridecenediyne core structure of the antitumor antibiotics esperamicin and calicheamicin (Scheme IV) can be realized provided the 10,11-acetylenic bond is complexed as its derived η^2 $Co_2(CO)_6$ adduct (Scheme V). The advantages of the η^2 $Co_2(CO)_6$ propargylic cation cyclization are that the cation is aligned axially to the enol π-system in the cyclohexanone ring and the resulting products cannot undergo cycloaromatization. Attempts to cyclize **44**, **45**, **62**, and **68**, without the 10,11-η^2 $Co_2(CO)_6$ complexation resulted in decomposition with no evidence for either the formation of the bicyclo[7.3.1] enediyne core or the cycloaromatization products.

The route to the 13-ketobicyclo[7.3.1]tridecenediyne **32** (Scheme VIII) proceeds in 10 steps from cyclohexane-1,2-dione in an overall yield of 11.2%. The more convergent route to **32**, Scheme IX, proceeds in the same number of steps and a marginally improved overall yield of 12%. The $Co_2(CO)_6$–η^2 propargylic cation methodology is also applicable to the synthesis of the core structures of dynemicin (**6**) and neocarzinostatin (**14**).[10,11]

The rate of cycloaromatization of **32** compared to the derived alcohol **86** and the five-membered-ring analogue **94** (and **97**) dramatically demonstrates that the distance (r) between the bonding acetylenes (leading to the 1,4-diyl) in the ground state does not control the rate of cycloaromatization. Strain release in the transition state more adequately predicts the relative rates of cycloaromatization. This important conclusion, first suggested from qualitative experiments,[17b] then predicted by calculations,[34] and subsequently confirmed by quantitative first-order rate measurements,[17g] is a paramount consideration for designing analogue enediynes that cycloaromatize to a 1,4-diyl under physiological conditions.

The introduction of functionality into the 13-ketobicyclo[7.3.1] enediyne **32** via bridgehead enolate chemistry is the subject of the following article.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer either neat or in $CHCl_3$ as indicated. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3B UV/vis spectrophotometer in the indicated solvents. Proton NMR spectra were recorded on a Varian-90 MHz spectrometer in the indicated solvent and are reported in ppm downfield from TMS. Elemental analyses were performed by Midwest Microlab in Indianapolis, IN. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. Preparative-layer chromatography was performed using Merck 60H F_{254} silica gel, glass-supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel.

Air- and moisture-sensitive reactions were performed using the usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140 °C and then cooled under argon, and performed under a blanket of argon. Solvents and commercial reagents were dried and purified before use: Et_2O and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 and benzene were distilled from calcium hydride under argon.

4-Ethynyl-4-hydroxycyclohexan-1-one 1-Ethylene Ketal (40). To a stirred suspension of lithium acetylide–ethylenediamine complex (9.36 g, 0.102 mol) in dry THF (100 mL) at 0 °C was added dropwise a solution of cyclohexane-1,4-dione monoethylene ketal (**28**; 9.36 g, 0.06 mol) in dry THF (70 mL) over 0.5 h. The mixture was slowly warmed to 25 °C and allowed to stir for 16 h. Saturated aqueous ammonium chloride solution (120 mL) was added to the mixture and the resulting solution extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with water (3 × 50 mL), dried ($MgSO_4$), and evaporated in vacuo to give an orange oil (11.0 g). The oil was distilled under reduced pressure to give **40** (6.7 g 62%) as a clear colorless oil: bp 97–105 °C (0.03 mmHg). The yield of **40** over several runs averaged 66%: IR ($CHCl_3$) 3594, 3450, 3306, 2960, 1435, 1335, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (4 H, s), 2.45 (1 H, s), 2.2 (1 H, b), 1.6–2.0 (8 H, m). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 65.67; H, 7.73.

4-[(*Z*)-4-Chlorobut-3-en-1-ynyl]-4-hydroxycyclohexan-1-one 1-Ethylene Ketal (41) and Its *tert*-Butyldimethylsilyl Ether Derivative 42. A mixture of dry benzene (90 mL) and dry *n*-butylamine (8.88 mL, 90 mmol) was purged with dry argon for 5 min. To the above solution, at 0 °C, was added (*Z*)-dichloroethylene (4.54 mL, 60 mmol) followed by $Pd(PPh_3)_4$ (2.42 g, 2.10 mmol), the acetylene **40** (5.42 g, 29.8 mmol) in benzene (20 mL), and finally CuI (1.20 g, 6.39 mmol). The heterogeneous mixture was slowly warmed to 20 °C and stirred for 6 h. The mixture was poured into petroleum ether (100 mL), saturated aqueous ammonium chloride (90 mL), and water (20 mL). The aqueous phase was separated and extracted with petroleum ether (2 × 20 mL). The combined petroleum ether extracts were washed with water (15 mL) and brine (20 mL) and dried (Na_2SO_4). Evaporation of the petroleum ether solvent in vacuo gave crude **41** as a brown oil. Purification by chromatography over silica gel (60 g), eluting with petroleum ether/ethyl acetate (4:1), gave product fractions, which were concentrated to approximately 50 mL and the precipitated solids filtered through Celite, washing with ether. The filtrate was rechromatographed as above and concentrated in vacuo to give **41** (4.63 g, 64%) as a yellow-orange thixotropic liquid: IR ($CHCl_3$) 3608, 3450, 2970, 2260, 1599 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (1 H, d, J = 7.5 Hz), 5.85 (1 H, d, J = 7.5 Hz), 3.90 (4 H, s), 2.5 (1 H, b, OH), 1.7–2.1 (8 H, m); HRMS calcd for $C_{12}H_{15}ClO_3$ 207.1023, found m/e 207.1022.

The alcohol **41** (1.82 g, 7.5 mmol) in dichloromethane (25 mL) at 20 °C was treated with dry triethylamine (2.09 mL) and *tert*-butyldi-

methylsilyl triflate (2.58 mL, 11.3 mmol). After 3 h, the above solution was poured into aqueous $NaHCO_3$ solution (20 mL) and extracted with dichloromethane (2 × 5 mL). The dried (Na_2SO_4) extract was evaporated in vacuo and the residue chromatographed over silica gel, eluting with petroleum ether/ether (15:1) to give **42** (2.36 g, 88%) as white crystals: mp 50–51 °C (from aqueous ethanol); IR ($CHCl_3$) 2962, 2940, 2890, 2864, 1320, 1338, 1253, 1121, 1104, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (1 H, d, J = 7.4 Hz), 5.86 (1 H, d, J = 7.4 Hz), 3.92 (4 H, s), 1.66–2.03 (8 H, m), 0.86 (9 H, s), 0.16 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.18 (d), 111.55 (d), 108.05 (s), 101.16 (s), 78.82 (s), 68.46 (s), 64.25 (t), 38.31 (t), 31.14 (t), 25.87 (q), 18.22 (s), −2.90 (q). Anal. Calcd for $C_{18}H_{29}ClO_3Si$: C, 60.57; H, 8.19. Found: C, 60.87; H, 8.50.

4-[(*Z*)-4-Chlorobut-3-en-1-ynyl]-4-[(*tert*-butyldimethylsilyl)oxy]-cyclohexan-1-one (43). A mixture of the ketal **42** (5.28 g, 14.08 mmol), 35% aqueous trifluoroacetic acid (60 mL), and chloroform (60 mL) were vigorously stirred at 20 °C for 45 h. The aqueous phase was extracted with chloroform (3 × 10 mL), and the combined chloroform extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and water (5 mL) and dried ($MgSO_4$). Evaporation in vacuo gave a pale yellow oil, which was purified by chromatography over silica gel, eluting with petroleum ether/ether (15:1) to give **43** (3.75 g, 81%). Further chromatography of the mixed fractions gave a total yield of **43**: 4.36 g, 94%; IR ($CHCl_3$) 2940, 2860, 1712, 1600, 1465, 1334, 1253, 1110, 1046, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (1 H, d, J = 7.5 Hz), 5.89 (1 H, d, J = 7.4 Hz), 2.5–2.61 (2 H, m), 2.39–2.50 (2 H, m), 2.16 (4 H, t, J = 6.7 Hz), 0.88 (9 H, s), 0.21 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.73 (s), 129.04 (d), 111.12 (d), 99.45 (s), 79.68 (s), 67.63 (s), 40.12 (t), 37.33 (t), 25.82 (q), 18.21 (s), −3.01 (q); CIMS calcd for $C_{16}H_{25}ClO_2Si$ + 1 313.1390, found m/e + 1 313.1386.

(*Z*)-4-(7-Methoxyhept-3-ene-1,5-diynyl)-4-[(*tert*-butyldimethylsilyl)-oxy]cyclohexan-1-one (44). A solution of the vinyl chloride **43** (312.5 mg, 1 mmol) in dry benzene (10 mL) was purged with argon for several minutes and *n*-butylamine (593 μL, 6 mmol) followed by methyl propargyl ether (167 μL, 2 mmol, freshly distilled) was added. The above mixture was stirred at 20 °C for 3.5 h and then poured into saturated aqueous ammonium chloride (10 mL) and petroleum ether (20 mL). The petroleum ether layer was washed with aqueous ammonium chloride (10 mL) and aqueous ceric ammonium nitrate (ca. 500 mg/10 mL) and filtered through Celite. The aqueous phase was extracted with water (5 mL) and brine (5 mL) and dried ($MgSO_4$). The combined organic extracts were evaporated in vacuo and the residue was preadsorbed onto silica gel and chromatographed, eluting with petroleum ether/ether (4:1) to give **44**: 279 mg, 81% (average yield for four runs, 74%); IR ($CHCl_3$) 2940, 2860, 1711, 1464, 1358, 1250, 1100, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (2 H, m), 4.21 (2 H, d, J = 1.8 Hz), 3.36 (3 H, s), 2.50 (4 H, m), 2.14 (4 H, t, J = 6.9 Hz), 0.87 (9 H, s), 0.21 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.68 (s), 119.57 (d), 118.81 (d), 98.75 (s), 92.90 (s), 83.40 (s), 83.01 (s), 67.75 (s), 60.21 (t), 57.61 (q), 40.14 (t), 37.40 (t), 25.80 (q), 18.13 (s), −3.00 (q); HRMS calcd for $C_{20}H_{30}O_3Si$ 346.1964, found m/e 346.1972.

(*Z*)-(7-Hydroxyhept-3-ene-1,5-diynyl)-4-[(*tert*-butyldimethylsilyl)-oxy]cyclohexan-1-one (45). Similar coupling of **43** (1.56 g, 5 mmol) with propargyl alcohol (582 μL, 10.0 mmol) for 24 h gave **45** (931 mg, 56%): IR ($CHCl_3$) 3615, 3420, 2960, 2940, 2860, 1710, 1466, 1441, 1252, 1108, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (2 H, m), 4.39 (2 H, d, J = 2.4 Hz), 2.55 (4 H, t, J = 6.6 Hz), 2.20 (1 H, b, OH), 2.15 (4 H, t, J = 6.8 Hz), 0.88 (9 H, s), 0.22 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.97 (s), 119.64 (d), 118.59 (d), 98.48 (s), 95.59 (s) 83.32 (s), 82.35 (s), 67.81 (s), 51.18 (t), 39.89 (t), 37.46 (t), 25.75 (q), 18.10 (s), −3.02 (q); HRMS calcd for $C_{19}H_{28}O_3Si$ 332.1807, found m/e 332.1802.

[(*Z*)-4-[(5,6-η^2)-7-Methoxyhept-3-ene-1,5-diynyl]-4-[(*tert*-butyldimethylsilyl)oxy]cyclohexan-1-one]hexacarbonyldicobalt (46). To a carbon monoxide purged solution of the enediyne **44** (609 mg, 1.76 mmol) in heptane (10 mL) under a carbon monoxide atmosphere was added $Co_2(CO)_8$ (602 mg, 1.76 mmol). After 2 h the mixture was directly chromatographed over silica gel, eluting with petroleum ether/ether (20:1 to 15:1) to give **46** (909 mg, 82%) as a deep crimson oil: IR ($CHCl_3$) 2965, 2940, 2865, 2100, 2065, 2035, 1715, 1465, 1354, 12252, 1109, 1041, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (1 H, d, J = 10.8 Hz), 5.83 (1 H, d, J = 10.8 Hz), 4.73 (2 H, s), 3.49 (3 H, s), 2.70 (2 H, m), 2.30 (4 H, m), 2.1 (2 H, m), 0.92 (9 H, s), 0.21 (6 H, s); ^1H NMR (this spectrum is considerably better resolved in C_6D_6) δ 6.32 (1 H, d, J = 11.1 Hz), 5.50 (1 H, d, J = 11.1 Hz), 4.59 (2 H, s), 3.19 (3 H, s), 2.55 (2 H, ABXY, J = 15.2, 5.6, 1.6 Hz), 2.23 (2 H, ABXY, J = 15.2, 4.4 Hz), 1.8–2.1 (4 H, m), 0.95 (9 H, s), 0.22 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.77 (s), 136.82 (d), 109.84 (d), 102.22 (s), 94.18 (s), 83.39 (s), 81.76 (s), 73.38 (t), 67.44 (s), 58.99 (q), 39.74 (t), 37.18 (t), 25.95 (q), 18.40 (s), −2.94 (q). The compound did not give satisfactory mass spectral data (M^+ − 3COs) m/e 548, but was satisfactorily characterized as the alcohol **47**, made from **45** and $Co_2(CO)_8$ as above in 78% yield: mp 97–98 °C (from hexane); IR ($CHCl_3$) 3200–3600, 2960, 2940, 2860, 2100, 2060, 2035, 1710, 1464, 1391, 1254, 1230, 1108, 839 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.26 (1 H, d, J = 10.5 Hz), 5.44 (1 H, d, J = 11.0 Hz), 4.71 (2 H, d, J = 5.9 Hz), 2.54 (2 H, m), 2.21 (2 H, m), 1.84–2.08 (4 H, m), 1.80 (1 H, t, J = 5.9 Hz), 0.95 (9 H, s), 0.20 (6 H, s). Anal. Calcd for $C_{25}H_{28}Co_2O_9Si$: C, 48.55; H, 4.56. Found: C, 48.30; H, 4.46. Suitable crystals for single-crystal X-ray analysis were grown from hexane.

***tert*-Butyldimethylsilyl Enol Ether 48.** To a stirred solution of the ketone **46** (316 mg, 0.50 mmol) and triethylamine (139 μL, 1.0 mmol) in dichloromethane (8 mL) was added *tert*-butyldimethylsilyl triflate (172 μL, 0.75 mmol). After 2.5 h the mixture was diluted with dichloromethane (5 mL) and washed with saturated aqueous sodium bicarbonate solution (3 mL). The organic phase was dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed over silica gel, eluting with 2% ether in petroleum ether to give **48** (332 mg, 89%) as a red oil: IR ($CHCl_3$) 296, 2940, 2862, 2100, 2061, 2032, 1672, 1466, 1254, 1198, 1090, 839 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.30 (1 H, d, J = 11.1 Hz), 5.56 (1 H, d, J = 11.1 Hz), 4.77 (2 H, s), 4.75 (1 H, t, J = 3.0 Hz), 3.29 (3 H, s), 2.66 (1 H, d, ABX, J = 24 Hz), 2.50 (1 H, dd, ABX, J = 24, 3 Hz), 1.9–2.04 (4 H, m), 1.04 (9 H, s), 1.02 (9 H, s), 0.31 (3 H, s), 0.30 (3 H, s), 0.18 (6 H, s); ^{13}C NMR (75 MHz $CDCl_3$) δ 199.17 (m, 6COs), 149.74 (s), 135.95 (d), 110.37 (d), 104.15 (s), 99.60 (d), 94.33, 81.87 (s), 73.40 (t), 67.59 (s), 58.80 (q), 39.30 (t), 36.70 (t), 27.23 (t), 25.81 (q), 25.77 (q), 18.23 (s), 18.07 (s), −2.80 (q), 4.21 (q). This compound did not give satisfactory mass spectral data due to the loss of the CO ligands.

[(10,11-η^2)-2-Keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]tridec-8-ene-6,10-diyne]hexacarbonyldicobalt (38) (R = TBDMS). To a stirred solution of the enol ether **48** (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 (2 × 5 mL) and the combined organic phases were 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 **38** (86 mg, 45%) as a deep red oil: IR ($CHCl_3$) 2960, 2930, 2860, 2095, 2050, 2020, 1710, 1080, 1050, 835 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.88 (1 H, d, J = 9.4 Hz), 5.64 (1 H, d, J = 9.4 Hz), 3.20 (2 H, m), 2.7 (2 H, m), 2.3 (4 H, m), 0.92 (9 H, s), 0.26 (3 H, s), 0.18 (3 H, 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^+ − 2COs, base peak m/e 460, M^+ − 5COs. Running the above reaction of **48** (410 mg) gave **38** (186 mg, 56%).

1-[(*tert*-Butyldimethylsilyl)oxy]tricyclo[7.3.$10^{2,7}$]trideca-2,4,6-trien-10-one (49) and the Dichloro Analogue 50. To a stirred solution of the cobalt complex **38** (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 3 h a further quantity (15 mg, 128 mmol) of the *N*-oxide was added. The mixture was diluted with dichloromethane (2 × 5 mL) and the combined organic phases were 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 **49** (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 (4 H, m), 3.37 (1 H, dd, J = 9.0, 17.4 Hz), 2.82 (1 H, m), 2.67 (1 H, dd, J = 6.2, 15.7 Hz), 2.59 (1 H, m), 2.52 (1 H, dd, J = 5.2, 17.4 Hz), 2.31 (2 H, m), 2.16 (2 H, m), 0.87 (9 H, s), −0.06 (3 H, s), 0.19 (3 H, 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).

Similarly, the cobalt adduct **38** (17.8 mg, 29.7 μmol) in carbon tetrachloride (1 mL) and *t*-BuOH (300 μL) was treated with *N*-methylmorpholine *N*-oxide (22 mg). After 4.5 h at 20 °C the mixture was worked-up as above to give **50**: 3.3 mg 29%; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (1 H, d, J = 8.3 Hz), 7.17 (1 H, d, J = 8.3 Hz), 3.38 (1 H, dd, J = 9.3, 17.2 Hz), 2.84 (1 H, m), 2.73 (1 H, m), 2.65 (1 H, dd, J = 6.2, 15.6 Hz), 2.56 (2 H, m), 2.32 (2 H, m), 2.17 (1 H, m), 0.87 (9 H, s), −0.06 (3 H, s), −0.19 (3 H, s); HRMS calcd for $C_{19}H_{26}Cl_2O_2Si$: (−*t*-Bu) 327.0375, found m/e 327.0379 for $C_{15}H_{17}Cl_2O_2Si$ (M^+ − *t*-Bu).

Tetracobalt Adduct 54. Treatment of **38** (25 mg, 41.7 μmol) in heptane (2.5 mL) with $Co_2(CO)_8$ (142 mg, 417 μmol) under an atmosphere of carbon monoxide for 4 h followed by evaporation gave a dark green

residue. Purification by chromatography over silica gel, eluting with hexane/ether (5:1), gave **54** (27 mg, 73%) as greenish-black crystals with an undefined melting point. The NMR spectrum was too broad to be useful. Anal. Calcd for $C_{31}H_{26}Co_4O_{14}Si$: C, 41.99; H, 2.96. Found: C, 41.58; H, 2.80. Crystals suitable for X-ray crystallographic analysis were grown from ether/hexane.

Cyclohexane-1,2-dione Methoxyethoxymethyl Enol Ether 56. To a slurry of NaH (1.51 g, 1.05 equiv oil-free) in dry tetrahydrofuran at −10 °C was added a solution of cyclohexane-1,2-dione (6.72 g, 60 mmol) in tetrahydrofuran (40 mL) slowly over 5 min. The mixture was stirred at −5 °C until hydrogen evolution ceased. To the resulting yellow solution at 0 °C was added methoxyethoxymethyl chloride (6 mL) and the mixture allowed to warm slowly to 20 °C over 2 h, when the yellow color was discharged. The mixture was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with ether (3 × 100 mL). Evaporation of the combined dried (Na_2SO_4) extracts and chromatography of the residue over silica gel gave **56** (9.78 g, 82%) as a colorless oil: IR (neat) 2880, 1688, 1452, 1370, 1250, 1130, 990 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.40 (1 H, t, J = 4.4 Hz), 5.08 (2 H, s), 3.78 (2 H, m), 3.77 (2 H, m), 3.37 (3 H, s), 2.47 (4 H, m), 2.00 (2 H, m). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.97; H, 8.06. Found: C, 59.80; H, 7.84.

6-Ethynyl-6-hydroxy-1-[(methoxyethoxymethyl)oxy]cyclohex-1-ene (57). A solution of the ketone **56** (11.94 g, 55.47 mmol) in dioxane (20 mL) was added dropwise with stirring to a suspension of 40% lithium acetylide–ethylene diamine complex (7.11 g, 69.5 mmol, 1.25 equiv) in dioxane (100 mL) over 10 min. After 2 h at 20 °C saturated aqueous NH_4Cl (500 mL) was added and the mixture extracted with ether (3 × 100 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed over silica gel to give **57** (9.3 g, 74%) as a colorless oil: bp 150 °C (0.1 mmHg); IR (neat) 3430, 3270, 2935, 1665, 1365, 1235, 1155, 1060, 990 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.14 (1 H, t, J = 4.0 Hz), 5.08 (2 H, s), 3.82 (2 H, m), 3.58 (2 H, m), 3.37 (3 H, s), 2.48 (1 H, s), 1.7–2.2 (7 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.43, 101.91, 101.85, 93.28, 86.39, 71.29, 70.29, 70.71, 67.52, 66.10, 58.54, 58.50, 37.68, 23.45, 18.82. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.67; H, 8.21.

6-[(*Z*)-4-Chlorobut-3-en-1-ynyl]-6-hydroxy-1-[(methoxyethoxymethyl)oxy]cyclohex-1-ene (58) and Its Derived *tert*-Butyldimethylsilyl Ether Derivative 59. A solution of **57** (424 mg, 1.88 mmol) in dry benzene (6 mL) was added to CuI (76 mg, 0.4 mmol) under argon. To the frozen mixture (ice/acetone) were added *n*-$BuNH_2$ (560 μL, 5.67 mmol) and (*Z*)-dichloroethylene (290 μL, 3.83 mmol). To the above mixture at 0 °C was added a solution of $Pd(PPh_3)_4$ (29.4 mg, 0.013 equiv) in benzene (2 mL) and the resultant mixture was warmed to room temperature (ca. 20 °C). After 15 h the suspension was poured onto saturated aqueous NH_4Cl (50 mL), extracted with ether (2 × 10 mL), dried ($MgSO_4$), and evaporated in vacuo. Chromatography of the residue over silica gel, eluting with 50% petroleum ether/ether, gave **58** (415 mg, 77%) (On a larger scale, starting with 5.29 g of **57**, 4.92 g of **58** was obtained, corresponding to a yield of 73%): IR (neat) 3430, 2935, 1665, 1365, 1335, 1238, 1080, 990, 725 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.38 (1 H, d, J = 7.3 Hz), 5.90 (1 H, d, J = 5.73 Hz), 5.15 (1 H, t, J = 3.9 Hz), 5.10 (2 H, q, J = 6.2 Hz), 3.82 (2 H, m), 3.57 (2 H, t, J = 4.6 Hz), 3.49 (1 H, s, OH), 3.39 (3 H, s), 1.70–2.25 (6 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.42, 128.19, 111.50, 101.97, 100.09, 93.33, 71.53, 67.59, 66.89, 58.59, 37.68, 23.56, 19.01. The alcohol **58** was used directly in the next step.

A solution of **58** (1.323 g, 4.60 mmol) and Et_3N (930 mg, 9.2 mmol) in CH_2Cl_2 (15 mL) was treated with *tert*-butyldimethylsilyl triflate (1.34 g, 5.06 mmol). After 5 h at 20 °C the mixture was worked-up as for **42** to give **59** (1.324 g, 72%). A sample was purified for microanalysis by Kugelrohr distillation at ca. 150 °C (0.35 mmHg): IR (neat) 2922, 2846, 1660, 1452, 1360, 1336, 1240, 1090, 998, 848, 772, 718 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.34 (1 H, d, J = 7.6 Hz), 5.87 (1 H, d, J = 7.6 Hz), 5.07 (1 H, t, J = 4.3 Hz), 5.03 (2 H, q, J = 6.1 Hz), 3.79 (2 H, m), 3.55 (2 H, t, J = 9.1 Hz), 3.37 (3 H, s), 2.05 (4 H, m), 1.68 (2 H, m), 0.87 (9 H, s), 0.11 (3 H, s), 0.08 (3 H, s). Anal. Calcd for $C_{20}H_{33}ClO_4Si$: C, 59.90; H, 8.29; Cl, 8.84. Found: C, 60.13; H, 8.36; Cl, 8.92.

6-[(*Z*)-7-Methoxyhept-3-ene-1,5-diynyl]-6-[(*tert*-butyldimethylsilyl)oxy]-1-[(methoxyethoxymethyl)oxy]cyclohex-1-ene (60). To a solution of the vinyl chloride **59** (410 mg, 1.02 mmol) in benzene (8 mL) were added CuI (80 mg, 0.42 mmol) and *n*-$BuNH_2$ (600 μL), and the mixture was degassed at −10 °C. Methyl propargyl ether (500 μL) was added followed by a solution of $Pd(PPh_3)_4$ (162 mg, 0.14 mmol) in dry benzene (2 mL). The above mixture was stirred at 20 °C for 72 h and worked-up as for **58** to give **60**: 390 mg, 88%; IR (neat) 2930, 2880, 2850, 1662, 1455, 1355, 1242, 1090, 1000, 832, 774 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.77 (2 H, m), 5.02 (1 H, t, J = 4 Hz), 4.97 (2 H, s), 4.20 (2 H, s), 3.72 (2 H, m), 3.49 (2 H, t, J = 4.7 Hz), 3.34 (3 H, s), 3.32 (3 H, s), 2.0 (4 H, m), 1.65 (2 H, m), 0.15 (3 H, s), 0.12 (3 H, s), 0.81 (9 H, s); HRMS calcd for $C_{20}H_{29}O_5Si$ [M^+ − 57(*t*-Bu)] 377.1784, found m/e 377.1795.

(*Z*)-2-(7-Methoxyhept-3-ene-1,5-diynyl)-2-[(*tert*-butyldimethylsilyl)oxy]cyclohexan-1-one (61). To a solution of the enol ether **60** (960 mg, 2.2 mmol) in CH_2Cl_2 (18 mL) at −45 °C was added a solution of Me_2BBr in CH_2Cl_2 (3.0 mL, 1.5M soln). The above solution was stirred for 3 h and allowed to warm to −35 °C. The reaction was quenched by addition of THF (5 mL) followed by cannulation into 1:1 THF/saturated aqueous $NaHCO_3$ solution (40 mL). The mixture was extracted with Et_2O (100 mL), dried ($MgSO_4$), and evaporated in vacuo to give a residue. Chromatography of the residue over silica gel, eluting with 5:1 ether/petroleum ether, gave the ketone **61** (0.755 g, 99%) as a colorless oil: IR (neat) 2880, 1726, 1354, 1246, 1228, 1100, 922, 830, 776 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.88 (2 H, m), 4.25 (2 H, s), 3.38 (3 H, s), 2.72 (1 H, ddd, J = 13.5, 12.8, 5.0 Hz), 2.32 (1 H, m), 2.09 (1 H, m), 1.4–1.9 (5 H, m), 0.18 (3 H, s), 0.16 (3 H, s), 0.9 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.30, 119.88, 118.39, 96.31, 93.00, 86.02, 83.53, 60.29, 57.63, 44.07, 38.41, 27.54, 22.47, 25.87, 18.34, 3.29, 3.45; HRMS calcd for $C_{20}H_{30}O_3Si$ 346.1964, found m/e 346.1951.

***tert*-Butyldimethylsilyl Enol Ether 62.** To a solution of the ketone **61** (197.7 mg, 0.57 mmol) in dry CH_2Cl_2 (25 mL) and Et_3N (3 mL) was added at 20 °C *tert*-butyldimethylsilyl triflate (413 μL, 3.0 equiv) and the mixture stirred for 36 h. Work-up as described for **48** gave **62** (245 mg, 93.4%) as a colorless oil: bp 220 °C (0.05 mmHg). On a large scale the following quantities were used: **61** 5.22 g, CH_2Cl_2 100 mL, Et_3N 8 mL, *t*-$BuMe_2SiOTf$ 3.8 mL, yielding **62** (85%): IR (neat) 2930, 2885, 2855, 1658, 1462, 1354, 1248, 1180, 1095, 920, 840, 780 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.82 (2 H, m), 4.81 (1 H, t, J = 4.01 Hz), 4.26 (2 H, d, J = 1.54 Hz), 3.39 (3 H, s), 2.02 (4 H, s), 1.70 (2 H, m), 0.88 (9 H, s), 0.95 (9 H, s), 0.21 (3 H, s), 0.19 (3 H, s), 0.17 (3 H, s), 0.16 (3 H, s). Anal. Calcd for $C_{26}H_{44}O_3Si_2$: C, 67.77; H, 9.62. Found: C, 67.74; H, 9.60.

5,6-η^2-Dicobalt Hexacarbonyl Adduct 63. To a solution of the silyl enol ether **62** (245 mg, 0.53 mmol) in heptane (9 mL) under CO atmosphere was added $Co_2(CO)_8$ (200 mg, 1.1 equiv). After 2 h at 20 °C the mixture was preadsorbed onto silica gel and chromatographed, eluting with 10% ether/petroleum ether to give **63** (359 mg, 90.5%) as a red oil: IR (neat) 2935, 2858, 2082, 2010, 1656, 1460, 1245, 1088, 830, 772 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.64 (1 H, d, J = 10.5 Hz), 5.77 (1 H, d, J = 10.5 Hz), 4.90 (1 H, m), 4.76 (2 H, s), 3.52 (3 H, s), 2.2–1.5 (6 H, m), 0.94 (9 H, s), 0.88 (H, s), 0.17 (6 H, s), 0.16 (6 H, s); HRMS calcd for $C_{26}H_{44}O_3Co_2Si$ (M^+ − 6CO) 578.1492, found m/e 578.1481 (M^+ − 6CO).

[(10,11-η^2)-13-Keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]tridec-8-ene-6,10-diyne]hexacarbonyldicobalt (39). To a mixture the cobalt complex **63** (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 indicated 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 and filtered through Celite, and the dried (Na_2SO_4) organic layer was evaporated in vacuo. Chromatography of the residue over silica gel, eluting with 5% ether/petroleum ether, gave **39** (650 mg, 55.6%) as *black-red* crystals: mp 109–110 °C (sealed capillary); IR ($CDCl_3$) 2935, 2858, 2095, 2020, 1730, 1150, 940, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (1 H, d, J = 9.8 Hz), 5.75 (1 H, d, J = 9.8 Hz), 4.23 (1 H, m), 3.23 (1 H, m), 3.20 (1 H, m), 2.41 (1 H, m), 2.07 (1 H, m), 1.91 (2 H, m), 1.83 (1 H, ddd, J = 13.4, 13.4, 4.4 Hz), 1.72 (1 H, m), 0.86 (9 H, s), 0.14 (3 H, s), 0.06 (3 H, 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. A small amount (ca. 10%) of a byproduct was isolated from some experiments, in particular if the reaction mixture is allowed to remain at −35 °C for several hours. Its structure is assigned as **64** on the basis of single-crystal X-ray crystallography.

[(6,7-η^2)-13-Keto-1-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.4.0]tridec-4-ene-2,6-diyne]hexacarbonyldicobalt (64): IR ($CDCl_3$) 2950, 2925, 2855, 2080, 2020, 1730, 1258, 1075, 835 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.65, 1994 (m), 142.81, 110.10, 100.93, 99.34, 92.08, 83.23, 78.91, 38.96, 37.15, 28.46, 25.69, 22.90, 18.09, −3.35, −3.99. The ^1H NMR spectrum was too broadened to be useful. Anal. Calcd for $C_{25}H_{26}Co_2O_8Si$: C, 50.01; H, 4.36. Found: C, 49.78; H, 4.20.

13-Keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]tridec-8-ene-6,10-diyne (32). To a solution of **39** (5.9 g) in dry THF (700 mL) under argon was added a solution of iodine (50 g) in THF (500 mL) via can-

nula. 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) and saturated aqueous $NaHCO_3$ (200 mL) and extracted with ether (3 × 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 **32**: 2.53 g, 82%; mp 43–46 °C (from aqueous EtOH); IR (CCl_4) 2958, 2930, 2858, 1734, 1462, 1348, 1152, 1098, 952, 780 cm^{-1}; UV (MeOH) λ_{max} 201, 274 nm (ϵ 3600, 7600); ^1H NMR (500 MHz, C_6D_6) δ 5.398 (1 H, dd, J = 9.50, 0.9, 2.0 Hz), 5.348 (1 H, dd, J = 9.5, 1.1 Hz), 3.04 (1 H, ddd, J = 1.1, 0.9, 17.5, 3.8 Hz), 2.47 (1 H, m), 2.23 (1 H, ddd, J = 13.8, 8.4, 5.7 Hz), 2.06 (1 H, m), 1.89 (1 H, ddd, J = 2.0, 4.5, 17.5 Hz), 1.80 (1 H, ddd, J = 13.8, 8.7, 7.3 Hz), 1.65 (1 H, m), 1.17 (1 H, m), 1.12 (9 H, s), 0.43 (3 H, s), 0.49 (3 H, 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. Crystals suitable for single-crystal X-ray crystallography were grown by vapor diffusion of water into an ethanol solution of **32** at 20 °C.

6-[(*Z*)-4-Chlorobut-3-en-1-ynyl]-1,6-bis[(*tert*-butyldimethylsilyl)oxy]cyclohex-1-ene (67). To a solution of **66** (98 mg, 31 mmol) in dichloromethane (1 mL) were added triethylamine (500 μL) and *tert*-butyldimethylsilyl triflate (230 μL, 1 mmol). After being stirred at 20 °C overnight, the mixture was worked-up as for **42** to give **67**: 134 mg, 100%; IR (neat) 2944, 2919, 2850, 1655, 1470, 1250, 853, 776 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 6.33 (1 H, d, J = 7.4 Hz), 5.86 (1 H, d, J = 7.4 Hz), 4.82 (1 H, t, J = 4 Hz), 2.05 (4 H, m), 1.70 (2 H, m), 0.95 (9 H, s), 0.88 (9 H, s), 0.21 (3 H, s), 0.19 (3 H, s), 0.17 (3 H, s), 0.16 (3 H, s); HRMS calcd for $C_{22}H_{40}O_2Si_2Cl$ (M^+ − H) 427.2255, found m/e 427.2186.

6-[(*Z*)-7-Hydroxyhept-3-ene-1,5-diynyl]-1,6-bis[(*tert*-butyldimethylsilyl)oxy]cyclohex-1-ene (68). A solution of **67** (60 mg, 0.14 mmol) in dry benzene (5 mL) was added to CuI (11 mg, 0.06 mmol) under argon. To the frozen mixture (ice/acetone) were added *n*-$BuNH_2$ (85 μL, 0.84 mmol) and propargyl alcohol (50 μL, 0.84 mmol). To the above mixture at 0 °C was added a solution of $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) in benzene (1 mL) and the resultant mixture was warmed to room temperature. After 4 days the dark suspension was poured onto saturated aqueous NH_4Cl (30 mL), extracted with ether (2 × 10 mL), dried ($MgSO_4$), and evaporated in vacuo. Chromatography of the residue over silica gel, eluting with 30% ether/hexane, gave **68** (46 mg, 73%): IR (neat) 2953, 2930, 2858, 1659, 1472, 1249, 840, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (1 H, d, J = 11 Hz), 5.79 (1 H, d, J = 11 Hz), 4.81 (1 H, t, J = 3.8 Hz), 4.40 (2 H, s), 2.04 (4 H, m), 1.64 (3 H, m), 0.94 (9 H, s), 0.87 (9 H, s), 0.22 (3 H, s), 0.19 (3 H, s), 0.17 (3 H, s), 0.16 (3 H, s); HRMS calcd for $C_{25}H_{42}O_3Si_2$ 446.2672, found m/e 446.2665.

5,6-η^2 Dicobalthexacarbonyl Adduct 69. To a solution of the silyl enol ether **68** (40 mg, 0.9 mmol) in heptane (5 mL) under an argon atmosphere was added $Co_2(CO)_8$ (31 mg, 0.9 mmol). After 1 h at 20 °C the solvent was removed in vacuo and the residue chromatographed over silica gel, eluting with 20% ether/hexanes, to give **69** (55 mg, 84%) as a red oil: IR (neat) 2955, 2931, 2858, 2092, 2055, 2026, 1659, 1475, 1249, 838, 778 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.26 (1 H, d, J = 10.6 Hz), 5.53 (1 H, d, J = 10.6 Hz), 4.96 (2 H, m), 4.87 (1 H, t, J = 4 Hz), 2.28 (1 H, t, J = 6.6 Hz), 2.15 (1 H, m), 1.98 (1 H, m), 1.87 (2 H, m), 1.72 (1 H, m), 1.49 (1 H, m), 1.04 (9 H, s), 1.03 (9 H, s), 0.33 (3 H, s), 0.32 (3 H, s), 0.23 (3 H, s), 0.20 (3 H, s).

[(10,11-η^2)-13-Keto-5-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.3.1]tridec-8-ene-6,10-diyne]hexacarbonyldicobalt (39). To a solution of **69** (17 mg, 2.3 × 10^{-5} mol) and 2,6-di-*tert*-butyl-4-methylpyridine (100 mg) in dichloromethane (5 mL) under argon at −30 °C was added triflic anhydride (8 μL, 4.7 × 10^{-5} mmol). The reaction mixture was allowed to warm to −20 °C, where it was stirred for 30 min and 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 **39** (10.8 mg, 77%).

1-[(*tert*-Butyldimethylsilyl)oxy]tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-13-one (83) and the Isomer 85. A solution of the ketone **32** (27.7 mg, 88.2 μmol) in 1,4-cyclohexadiene (4.5 mL) under argon was heated at reflux (80–85 °C) for 42.5 h. The mixture was evaporated in vacuo and the residue purified by PLC, eluting with 10% ether/petroleum ether to give **83**: 20.2 mg, 72%; IR (neat) 2940, 2855, 1732, 1450, 1248, 1215, 1155, 1070, 928, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (1 H, dd, J = 7.9, 1.4 Hz), 7.27 (1 H, m), 7.21 (1 H, ddd, J = 7.9, 7.4, 1.5 Hz), 7.08 (1 H, bdd, J = 7.58, 1.0 Hz), 3.48 (1 H, ddd, J = 17.5, 7.2, 0.9 Hz), 3.10 (1 H, d, J = 17.5 Hz), 2.95 (1 H, m), 2.0 (4 H, m), 1.59 (1 H, m), 1.43 (1 H, m), 0.98 (9 H, s), 0.18 (3 H, s), 0.15 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.15, 142.69, 134.87, 127.19, 126.91, 126.27, 125.61, 81.11, 46.69, 46.50, 38.22, 36.40, 26.35, 20.41, 18.96, −2.15, −2.41; HRMS calcd for $C_{18}H_{25}O_2Si$ (M^+ − Me) 301.1624, found m/e 301.1623.

A degassed solution of the cobalt hexacarbonyl adduct **64** (41 mg, 54.8 μmol) in 1,4-cyclohexadiene (2 mL) was treated with a solution of *N*-methylmorpholine *N*-oxide (73 mg, 623 μmol) in dry dimethylformamide (1 mL). After 5 h at 25 °C the mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with ether. The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by PLC to give the aromatized adduct **85**: 7 mg, 40%; IR (neat) 2920, 2845, 1725, 1455, 1245, 1125, 950 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (2 H, m), 7.18 (1 H, t, J = 7.1 Hz), 7.04 (1 H, d, J = 7.5 Hz), 3.36 (1 H, dd, J = 15.5, 5.9 Hz), 2.72 (1 H, m), 2.52 (1 H, d, J = 15.5 Hz), 2.46 (1 H, ddt, J = 14.4, 3.8, 2.1 Hz), 2.24 (1 H, ddd, J = 14.4, 13.3, 5.4 Hz), 1.95 (1 H, m), 1.86 (1 H, m), 1.73 (1 H, m), 1.23 (1 H, m), 0.74 (9 H, s), 0.06 (3 H, s), −0.27 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.18, 144.65, 142.98, 129.03, 126.47, 125.96, 124.56, 90.92, 53.82, 39.32, 37.68, 30.16, 29.95, 26.03, 25.74, 24.54, 18.47, −2.91, −3.68; HRMS calcd for $C_{18}H_{25}O_2Si$ (M^+ − Me) 301.1624, found m/e 301.1604.

1-[(*tert*-Butyldimethylsilyl)oxy]tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-13-ol (87). A solution of the ketone **32** (61.5 mg) in Et_2O (6 mL) at −78 °C was treated with a solution of diisobutylaluminum hydride (600 μL, 3 portions/1.0 M soln in Et_2O). After 30 min methanol (1 mL) was added to the above solution and the mixture evaporated in vacuo at −30 °C. The residue was purified by PLC, eluting with 30% ether/petroleum ether. The least polar component was recovered by Et_2O extraction and the solvent evaporated at −30 °C. The initial ^{13}C NMR (10 min at 20 °C) showed the compound to be a mixture of the enediyne **86** and the aromatized material **87** (ca. 1:1). After 35 min at 20 °C this ratio changed to 1:9: ^{13}C NMR (75 MHz, $CDCl_3$) δ 124.85, 122.56, 106.53, 103.30, 87.81, 82.68, 79.81, 74.79, 40.06, 38.94, 30.11, 25.68, 21.01, 21.44, −2.71, −3.01 (The quaternary carbon in the t-Bu group was too weak to be seen.). Carrying out the above reduction and adding 1,4-cyclohexadiene (1.5 mL) during the work-up gave **87** (10 mg, from 35 mg of **32**): IR (CCl_4) 3595, 3065, 3022, 2935, 2860, 1465, 1454, 1360, 1250, 1110, 1085, 960, 940, 930, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (1 H, dd, J = 7.7, 1.5 Hz), 7.19 (1 H, t, J = 7.2 Hz), 7.15 (1 H, dt, J = 1.5, 7.4 Hz), 7.07 (1 H, dd, J = 7.4, 0.8 Hz), 3.85 (1 H, d, J = 4.1 Hz), 3.31 (1 H, dd, J = 17.6, 7.1 Hz), 2.52 (1 H, m), 2.52 (1 H, d, J = 17.6 Hz), 2.43 (1 H, s), 1.82 (1 H, dd, J = 12.1, 4.2 Hz), 1.72–1.8 (2 H, m), 1.66 (1 H, tt, J = 13.7, 4.4 Hz), 1.48 (1 H, m), 1.0 (1 H, m), 0.96 (9 H, s), 0.27 (3 H, s), 0.29 (3 H, s); NOEs between the C_{13}–H proton (δ 3.85) and the bridgehead and cyclcohexane protons allow the assignment of stereochemistry. No NOE was observed to the benzylic protons; ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.53, 137.04, 126.78, 126.46, 126.14, 125.85, 78.06, 75.63, 40.66, 32.33, 30.82, 25.93, 20.93, 20.86, 18.48, −1.58, −2.00; HRMS calcd for $C_{18}H_{27}O_2Si$ (M^+ − Me) 303.1773, found m/e 303.1788.

5-[(*Z*)-4-Chlorobut-3-en-1-ynyl]-1,5-bis[(*tert*-butyldimethylsilyl)oxy]cyclopent-1-ene (90). To a stirred suspension of CuI (82 mg, 0.43 mmol) in dry benzene (5 mL) under argon was added at 25 °C a solution of the acetylenic alcohol **88** (0.25 g, 2.0 mmol) in dry benzene (4 mL), followed by (*Z*)-dichloroethylene (0.6 mL, 8.0 mmol) and *n*-$BuNH_2$ (0.7 mL, 7.1 mmol). The resulting green solution was degassed via two freeze–thaw cycles and a solution of $Pd(PPh_3)_4$ (38 mg, 0.033 mmol) in dry benzene (3 mL) was added. The resulting yellow solution was stirred at 25 °C for 8 h. The resulting black solution was poured onto saturated aqueous NH_4Cl (25 mL) and extracted with ether (2 × 25 mL). The combined extracts were washed with saturated brine solution and dried ($MgSO_4$). Evaporation in vacuo gave **89** (0.57 g of a dark liquid), which was purified by chromatography over silica gel eluting with ether/petroleum ether (2:1) to give **89** (0.25 g, 67%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (2 H, q, J = 7.5 Hz), 3.21 (1 H, br s), 2.64–2.02 (6 H, m). This material was used directly in the next step.

To a solution of the keto alcohol **89** (2.0 g, 10.8 mmol) in dry CH_2Cl_2 (430 mL) and Et_3N (60 mL) was added at 20 °C *tert*-butyldimethylsilyl triflate (7.35 mL, 3.0 equiv) and the mixture stirred for 4 h. Work-up as described for **48** gave **90** (3.6 g, 93.0%) as a colorless oil: IR (neat) 3072, 2942, 2896, 2848, 2214, 1648, 1619, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (2 H, q, J = 7.5 Hz), 4.72 (1 H, t, J = 2.4 Hz), 2.48–2.06 (4 H, m), 0.95 (9 H, s), 0.85 (9 H, s), 0.20 (6 H, s), 0.18 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.41, 127.77, 111.90, 103.69, 100.25, 78.80, 41.56, 25.78, 25.67, 24.60, 18.19, 18.10, −3.13, −3.19, −4.71, −4.86; HRMS calcd for $C_{21}H_{37}ClO_2Si_2$ (M^+) 412.2008, found m/e 412.2021.

5-[(*Z*)-7-Hydroxyhept-3-ene-1,5-diynyl]-1,5-bis[(*tert*-butyldimethylsilyl)oxy]cyclopent-1-ene (91). To a stirred suspension of CuI (244 mg, 1.28 mmol) in dry benzene (28 mL) under argon was added at 25 °C a solution of the vinyl chloride **90** (1.0 g, 2.8 mmol) in benzene (6 mL)

followed by propargyl alcohol (1.8 mL, 31 mmol) and *n*-$BuNH_2$ (1.8 mL, 18 mmol). The resulting yellow suspension was degassed via a freeze–thaw cycle, and a solution of $Pd(PPh_3)_4$ (400 mg, 0.35 mmol) in benzene (5 mL) was added. The resulting green mixture was stirred at 25 °C for 3 days. Work-up as for **89** (see above) gave the enediyne **91** (0.87 g, 72%) as a pale yellow liquid: IR (neat) 3331, 3060, 2954, 2930, 2896, 2849, 1648, 1578, 1472, 1454, 1325, 1272, 1250, 1185, 837, 779 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.74 (2 H, m, J = 11.0, 1.6 Hz), 4.65 (1 H, t, J = 2.4 Hz), 4.33 (2 H, d, J = 4.1 Hz), 2.34–2.03 (4 H, m), 1.19 (1 H, t, J = 3.2 Hz), 0.88 (9 H, s), 0.80 (9 H, s), 0.14, 0.12, 0.11, and 0.10 (four 3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.47, 119.93, 118.04, 103.83, 99.94, 94.30, 83.20, 81.72, 77.33, 51.70, 41.75, 25.77, 25.65, 24.56, 18.18, 18.06, −3.11, −3.17, −4.72, −4.84; HRMS calcd for $C_{24}H_{40}ClO_3Si_2$ (M^+) 432.2516, found m/e 432.2505.

5,6-η^2 Dicobalt Hexacarbonyl Adduct 92. To a solution of the silyl enol ether **91** (180 mg, 0.42 mmol) in heptane (15 mL) under an argon atmosphere was added $Co_2(CO)_8$ (135 mg, 0.42 mmol). After 1 h at 20 °C the mixture was preadsorbed onto silica gel and chromatographed, eluting with 10% ether/petroleum ether, to give **92** (210 mg, 77%) and its regioisomer (0.03 g, 9%), both as red solids. For **92**: mp 89–90 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (2 H, q, J = 10.5 Hz), 4.97 (2 H, d, J = 6.9 Hz), 4.78 (1 H, t, J = 2.1 Hz), 2.42–2.11 (4 H, m), 0.94 (9 H, s), 0.87 (9 H, s), 0.18, 0.16, 0.17, and 0.13 (four 3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.41–199.03, 154.89, 136.19, 110.23, 104.63, 102.52, 97.27, 82.68, 82.25, 77.92, 64.33, 41.02, 25.77, 24.63, 25.68, 18.24, 18.13, −3.29, −3.20, −4.78, −4.84. Anal. Calcd for $C_{30}H_{40}Co_2O_9Si_2$: C, 50.14; H, 5.61. Found: C, 50.00; H, 6.10.

[(9,10-η^2)-12-Keto-4-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.2.1]dodec-7-ene-5,9-diyne]hexacarbonyldicobalt (93). To a stirred solution of the alcohol **92** (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-*tert*-butyl-4-methylpyridine (260 mg, in 0.5 mL of CH_2Cl_2) followed by trifluoromethylsulfonic 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/petroleum ether (1:20), to give the bicyclo[7.2.1] enediyne **93** (14.4 mg, 59%) as a red-brown solid: mp 99–101 °C dec; IR ($CHCl_3$) 2961, 2931, 2894, 2859, 2090, 2057, 2031, 1760, 1647, 1471, 1295, 1219, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (2 H, q, J = 10.4 Hz), 4.05 (1 H, dd, J = 17.2, 3.0 Hz), 3.66 (1 H, dd, J = 17.2, 7.4 Hz), 2.61–2.57 (1 H, m), 2.29 (1 H, dd, J = 10.9, 5.3 Hz), 2.14–1.92 (3 H, m), 0.90 (9 H, s), 0.21 (3 H, s), 0.19 (3 H, 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]dodec-7-ene-5,9-diyne (94) and Its Derived Oxime 95. The $Co_2(CO)_6$–η^2-adduct **93** (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/petroleum ether (1:20) to give **94** (11.8 mg, 82%) as a colorless oil: IR (neat) 2956, 2929, 2857, 2211, 1761, 1472, 1462, 1295, 1249, 1209 cm^{-1}; UV ($CHCl_3$) λ_{max} (ϵ) 274 (5580) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (2 H, q, J = 9.8 Hz), 3.08 (1 H, q, J = 4.4 Hz), 2.57–2.26 (4 H, m), 2.06–1.89 (2 H, m), 0.89 (9 H, s), 0.21 (3 H, s), 0.23 (3 H, 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.

The ketone **94** was converted into the oxime **95** by standard methods. Crystals suitable for X-ray analysis were obtained by vapor diffusion of water into a solution of the oxime in ethanol: mp 165 °C dec; IR ($CHCl_3$) 3264, 2941, 2917, 2860, 1733, 1647, 1462, 1457, 1358, 1290, 1283, 1249, 1145, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (2 H, q, J = 10 Hz), 3.58 (1 H, dd, J = 17.9, 3.7 Hz), 3.28–3.23 (1 H, m), 2.42–2.18 (3 H, m), 1.99–1.89 (2 H, m), 0.89 (9 H, s), 0.23 (3 H, s), 0.21 (3 H, s); HRMS calcd for $C_{18}H_{25}NO_2Si$ – Bu-*t* (M^+ – Bu-*t*) 258.0950, found m/e 258.0957.

12-Hydroxy-4-[(*tert*-butyldimethylsilyl)oxy]bicyclo[7.2.1]dodec-7-ene-5,9-diyne (97). The ketone **94** (10.2 mg, 0.034 mmol) in dry toluene (2 mL) was treated with diisobutylaluminum hydride (0.20 mL, 0.20 mmol) at −78 °C. After standard work-up and purification by PLC, the alcohol **97** (7.9 mg, 77%) was isolated as a white solid: mp 55–57 °C; IR (neat) 3529, 2942, 2919, 2896, 2840, 2184, 1465, 1403 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (2 H, q, J = 9.6 Hz), 4.05 (1 H, m), 2.81 (1 H, d, J = 12.9 Hz), 2.78 (1 H, dd, J = 14.8, 3.3 Hz), 2.62–2.48 (1 H, m), 2.34–2.26 (2 H, m), 2.03–1.99 (1 H, m), 1.86–1.79 (2 H, m), 0.87 (9 H, s), 0.18 (3 H, s), 0.17 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.80, 122.12, 102.89, 99.23, 90.57, 83.33, 83.23, 81.08, 37.93, 37.80, 29.70, 25.72, 20.52, 17.92, −3.16. HRMS calcd for $C_{18}H_{26}O_2Si$ (M^+) 302.1702. Found: m/e 302.1700.

1-[(*tert*-Butyldimethylsilyl)oxy]tricyclo[7.2.1.$0^{2,7}$]dodeca-2,4,6-trien-12-one (96) and Its Derived Alcohol 98. A solution of the enediyne **94** (7.5 mg, 0.025 mmol) in freshly distilled 1,4-cyclohexadiene (0.75 mL) under argon was heated in a sealed tube to 120 °C for 3.5 days. The mixture was evaporated and the residue purified by PLC, eluting with ether/petroleum ether (1:20) to give the aromatized adduct **96** (5.7 mg, 75%) as a colorless oil: IR (neat) 2956, 2931, 2856, 1763, 1472, 1459, 1451, 1314, 1256, 1214, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1 H, dd, J = 7.5, 1.7 Hz), 7.28–7.17 (2 H, m), 7.08 (1 H, dd, J = 7.1, 0.6 Hz), 3.49 (1 H, dd, J = 16.4, 3.7 Hz), 3.20 (1 H, dd, J = 16.4, 2.8 Hz), 2.62–2.57 (1 H, m), 2.24–2.12 (3 H, m), 1.79–1.72 (1 H, m), 0.98 (9 H, s), 0.16 (3 H, s), 0.15 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.36, 146.14, 131.38, 127.91, 127.48, 126.99, 123.98, 80.66, 43.35, 41.12, 37.34, 29.70, 26.13, 22.59, 18.72, −2.54, −2.62; MS (EI) 302 (<1%), 287, 284, 274, 259, 245 (100%); HRMS calcd for $C_{18}H_{26}O_2Si$ – *t*-Bu (M^+ – *t*-Bu) 245.0998, found m/e 245.0995.

Similarly, a solution of the alcohol **97** (5.5 mg, 0.018 mmol) was heated in 1,4-cyclohexadiene (0.50 mL) at 85 °C for 6 h. Work-up as above gave **98** (3.9 mg, 70%) as a white solid: mp 78–82 °C; IR ($CHCl_3$) 3471, 3021, 2975, 2906, 1474, 1416 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (1 H, dd, J = 7.0, 2.0 Hz), 7.22–7.07 (3 H, m), 4.15 (1 H, dd, J = 3.4, 2.0 Hz), 3.29 (1 H, dd, J = 13.2, 4.0 Hz), 2.55 (1 H, dd, J = 15.3, 1.7 Hz), 2.45–2.42 (1 H, m), 2.07–1.76 (4 H, m), 0.98 (H, s), 0.23 (3 H, s), 0.19 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.66, 133.88, 128.24, 126.69, 126.22, 125.15, 81.72, 38.12, 34.56, 33.88, 29.70, 29.36, 26.37, 25.97, 24.02, 18.44, −2.26, −2.39; HRMS calcd for $C_{18}H_{28}O_2Si$ – *t*-Bu (M^+ – *t*-Bu) 247.1154, found m/e 247.1145.

Rate of Aromatization of 32. The enediyne **32** (35 mg) and diphenyl ether (70 μL, internal standard) were dissolved in 1,4-cyclohexadiene (7 mL), and 100-μL samples of this solution were sealed in glass tubes under argon and heated in an oil bath (71, 79, 87, 95, and 104 °C, respectively). After the appropriate reaction time the sealed tube was cooled in a dry ice bath and opened, and the solution was diluted in hexane (1 mL). This solution was analyzed by HPLC [column Microsorb SiO_2, Si 80-125-C5; solvent hexane/dichloromethane (1:1); flow rate 1 mL/min; detector UV, λ = 274 nm; sample loop 5 μL]. The concentration of **32** and **83** was determined as the area ratio of the peaks corresponding to **32**/**83** and the internal standard. This system was also used for determining the rates of aromatization of **94** and **97**.

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Supplementary Material Available: Experimental descriptions for the synthesis of **70**, **72**, **61**, **76**, **77**, **80**, and **81**, details of the X-ray structure determinations of **32**, **39**, **47**, **54**, **64**, and **95**, and tables of fractional coordinates, isotropic thermal parameters, anisotropic thermal parameters, bond lengths, and bond angles (81 pages). Ordering information is given on any current masthead page.