PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Organometallic Chemistry can Simplify the Synthesis of Important Biologically Active Natural Products [and Discussion]

D. Becker, P. Carter, J. Elliott, R. Lewis, P. D. Magnus, L. Principe, M. Slater, B. T. Golding and A. B. Holmes

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Organometallic chemistry can simplify the synthesis of important biologically active natural products

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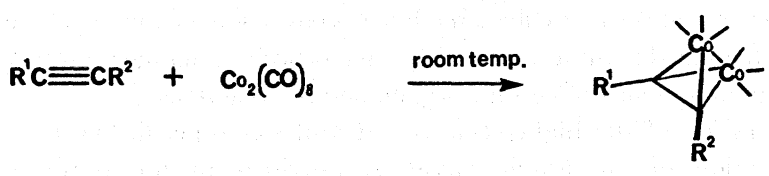
The stereoselectivity of the Pauson–Khand reaction used for the construction of a 6a-carboprostaglandin is described, and a mechanistic hypothesis is proposed to explain the experimentally observed results. A further illustration of the stereoselectivity of the dicobaltoctacarbonyl-mediated cyclization of 1,6-enynes to bicyclo[3.3.0]-octenones is provided by a sequence of transformations that depicts the route to the precursors of pentalenolactone G.

Further examples of the synthetic potential of the acetylene-$Co_2(CO)_6$ bimetalloclusters are shown by the synthesis of a vincristine model compound, and a sequence of transformations that provide strong evidence of the intermediacy of a 1,4-diyl (*p*-benzyne) in the collapse of a *Z*-diynene to an aromatic product.

Introduction

The major benefit that organometallic chemistry brings to organic synthesis is to dramatically increase the range of transformations available for planning a particular synthesis. Many chemical conversions that are controlled by organometallic reagents and/or organometallic intermediates, cannot be readily achieved, if at all, by so-called classical methodology. The synthesis of a complex organic structure is best accomplished in a simple, direct and uncontrived manner by using chemical transformations that offer new insights into the control of selectivity (reactivity) and stereochemistry. A major preoccupation of organic chemists, who conduct research into the use of organometallic mediated reactions, has been to attempt to define and understand how the above reaction parameters of selectivity and stereochemistry can be predictably controlled and used for efficient syntheses of natural products or variations thereof.

During the past few years we have been examining the use of dicobaltoctacarbonyl $Co_2(CO)_8$, and its complexes with acetylenes **1** (Sternberg *et al.* 1954) as suitable substrates for the synthesis of a range of biologically important natural products. More recently, we have extended this work to include molecules that we specifically designed to probe the biological mechanism of action of cytotoxic agents such as vinblastine **2**, vincristine **3** and esperamicin **4**, that are active at sufficiently high levels to be useful for the treatment of malignant tumours in the clinic.



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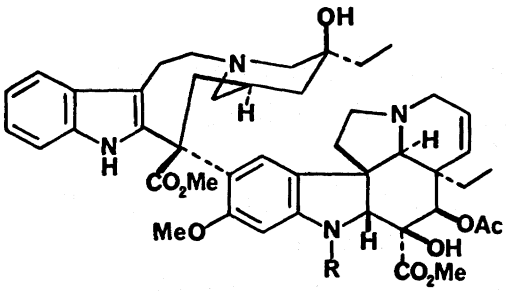
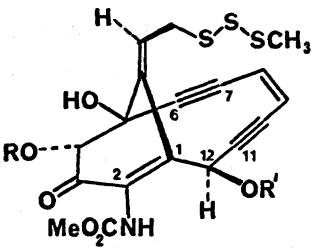


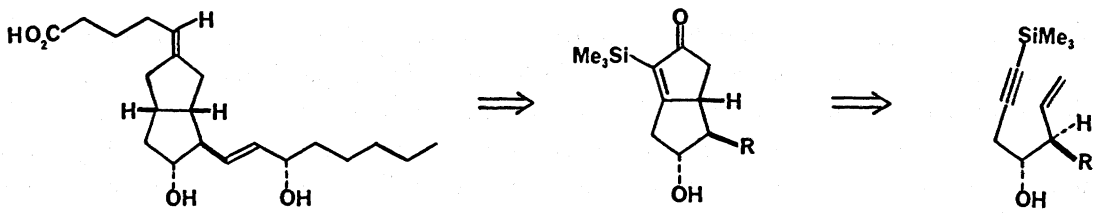
2 R=Me (vinblastine)
3 R=CHO (vincristine)



4 (esperamicin)

Stereoselectivity of the Pauson–Khand reaction

The Pauson–Khand reaction (Pauson *et al.* 1973) lends itself to an exceptionally concise retrosynthetic representation of the synthesis of 6a-carboprostaglandin **5**, and this is shown in scheme 1. The mechanistic hypothesis (Magnus & Principe 1985) that we have advanced in order to predict the stereochemical relation between allylic and propargylic substituents in the substrate **7** and the required product **6** predicts that the stereoisomer **6** should be the major product.

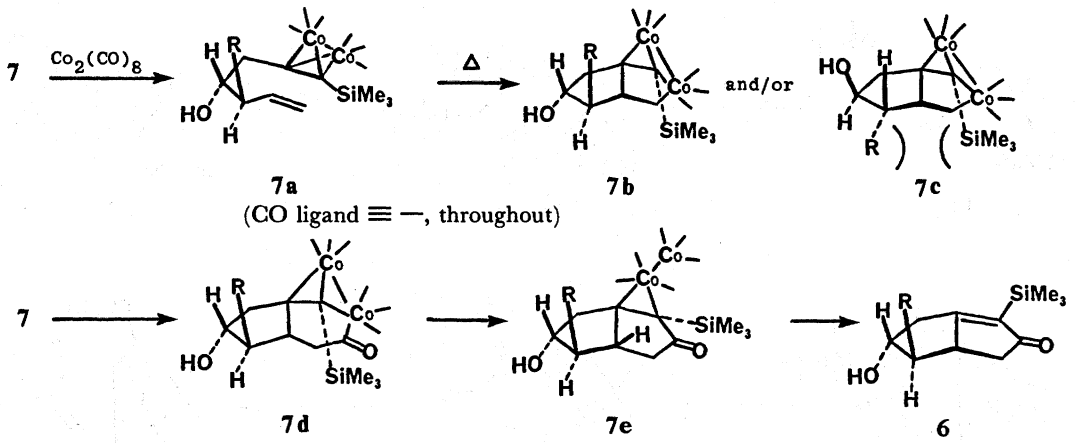


5 (carbocycline) 6 7

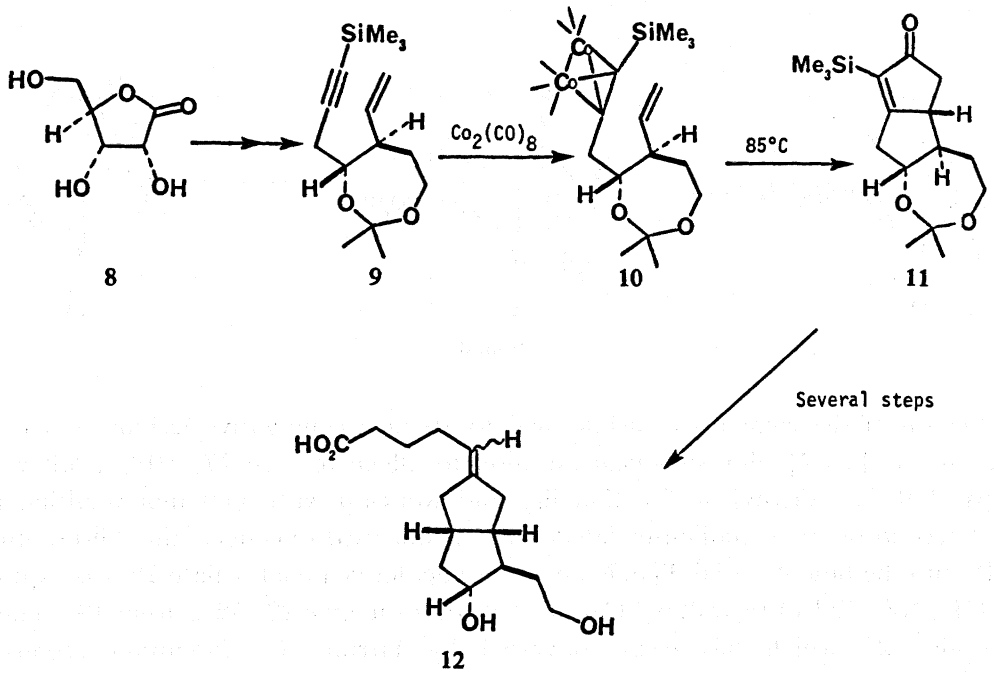
Scheme 1

As a generalization, this hypothesis predicts that allylic and propargylic substituents in the resulting bicyclo[3.3.0]octenone system appear on the *exo*-face, which corresponds to the more stable thermodynamic situation (scheme 2). In other words, if we compare **7b** with **7c**, **7b** is predicted to be the more stable metallocycle arising from **7a**. To test whether or not this is indeed the case, we converted D-(+)-ribonolactone **8** into the acetonide **9** through a sequence of conventional steps. Treatment of **9** with $Co_2(CO)_8$ gave the complex **10** (94%) as a red-brown oil, which on heating at 85 °C in the presence of tri-*n*-butylphosphine oxide (Pauson 1985) gave **11** (45%) as a single stereoisomer as judged by ^{1}H NMR and ^{13}C NMR. The enantiomeric purity was shown to be 99% or more. The bicyclo[3.3.0]octenone **11** was converted into the 6a-carbocycline analogue **12** using a series of standard transformations (Magnus & Becker 1987). The cobalt-mediated conversion of the acyclic enyne **9** into the bicyclo[3.3.0]octenone **11** in a completely stereospecific manner provides a convincing illustration of the uniqueness of certain organometallic reactions.

Another illustration of the highly convergent and stereospecific nature of the $Co_2(CO)_8$ mediated cyclization of an acyclic enyne is provided in the route to the antibiotic pentalenolactone G **13** described below (Seto *et al.* 1978) (scheme 3).



SCHEME 2



The cobalt-mediated cyclization precursor **14** is readily available in gram quantities through routine transformations. When a solution of **14** was treated with $Co_2(CO)_8$/2,6-di-*t*-butyl-4-methylpyridine (0.1 equivalent)/heptane (solvent), CO atmosphere, and heated at 85 °C in a sealed tube for 50 h, the enone **16** was isolated in 64% yield after oxidative decomplexation with *N*-methylmorpholine-*N*-oxide. Although both the ^{1}H NMR and ^{13}C NMR spectra of **16** indicated that a single stereoisomer had been formed, the specific stereochemical relation between the C(5)–C(6) hydrogen atoms was not conclusive because of the relatively small difference between *cis*- and *trans*-coupling constants associated with vicinal hydrogen atoms attached to carbon atoms in cyclopentane carbocyclic rings. The relative configuration shown in the structural depiction **16** was later confirmed by single crystal X-ray crystallography on a derivative of **16**.

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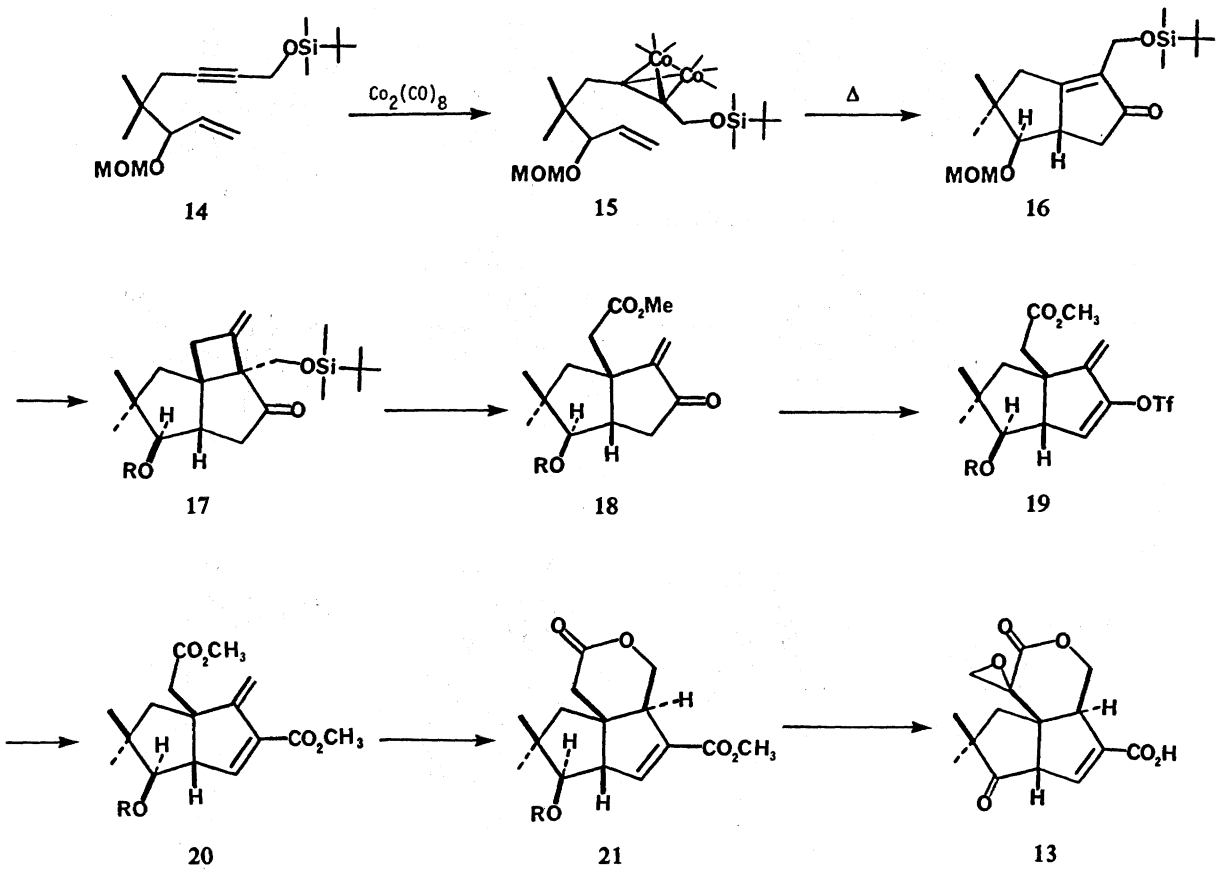


SCHEME 3

Introduction of the elements of acetic acid to **16** in a conjugative fashion at C(1) was achieved by the [2+2] photochemical addition to allene to give **17** (80%), followed by ozonolysis of the *exo*-methylene functionality and work-up with methanol resulting in **18** (62%). A second organometallic-mediated reaction was used to convert the α,β-unsaturated ketone **18** into the homologated dienoic ester **20**. The derived enol triflate **19** was exposed to $CO/MeOH/NEt_3/Pd(OAc)_2/PPh_3$ (Cacchi *et al.* 1985) to give **20** (52% from **18**). The final steps to give **21** which has been converted by Pirrung & Thompson (1988) into pentalenolactone G **13** proceeded with considerable difficulty, but, because no organometallic chemistry was involved, these steps will not be described.

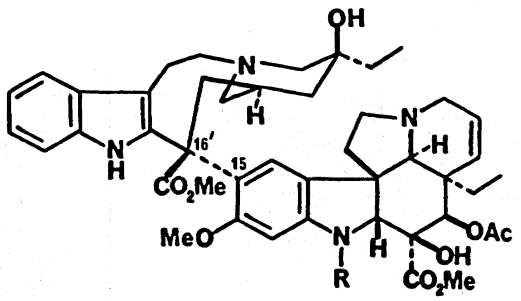
The important and central issue of the example of the Pauson–Khand reaction shown above is that the conversion of **14** to **16** proceeds in good yield, and is completely stereospecific. In general, the substituents in the resulting bicyclo[3.3.0]octenones appear on the *exo*-face, which usually corresponds to the thermodynamically more stable situation.

A VINCRISTINE MODEL

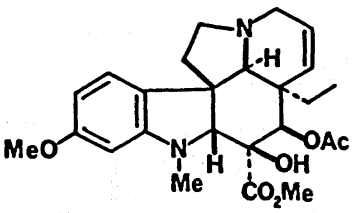
The clinically active antitumor agents vinblastine **22** and vincristine **23** have been the objects of considerable synthetic interest for the past twenty years (Lounasmaa & Nemes 1982). Two methods have been used to establish the crucial C-15/C-16[1] bond connecting vindoline

24 to carbomethoxyvelbanamine (upper half): the chloroindolenine route (Kutney *et al.* 1975) and the Potier adaptation of the Polonovski rearrangement (Potier *et al.* 1976). We have developed a different way of making the C-15/C-16′ bond that does not need a prior oxidative activation of precursors to the upper half. The example shown below illustrates the important features of this new method.

The tetracyclic amine **25** was treated with $PhOCOCl/CH_2Cl_2/3\text{-}MeOC_6H_4NMe_2$ to give the adduct **27** (92%). Presumably, this reaction proceeds via the intermediacy of the iminium ion **26**, which, in the presence of the aromatic nucleophile $3\text{-}MeOC_6H_4NMe_2$, is trapped to give, after proton loss, the adduct **27** (Magnus *et al.* 1987). The coupling reaction cannot be carried out with $3\text{-}MeOC_6H_4NHMe$, because it reacts with the chloroformate to give $3\text{-}MeOC_6H_4NMeCO_2Ph$, which is deactivated towards electrophilic aromatic substitution with the iminium ion **26**. Consequently, we required a nitrogen protecting group for $3\text{-}MeOC_6H_4$-NHMe that would not decrease the availability of the nitrogen lone pair to allow effective trapping of **26**, and be removed under sufficiently mild conditions that do not destroy the intact adduct. The usual range of nitrogen protecting groups such as amides and carbamates are obviously unsuitable, and *p*-methoxybenzyl did not allow the coupling process to take place efficiently. Given these somewhat rigorous and unusual chemical constraints, combined with



22 R=Me
23 R=CHO



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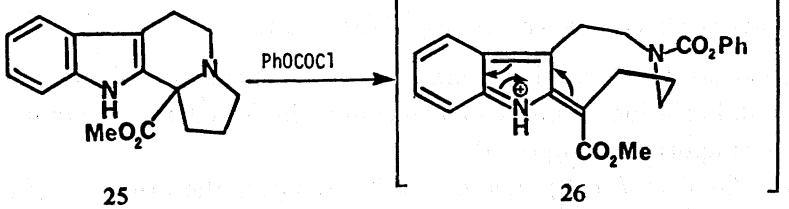
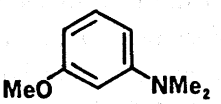
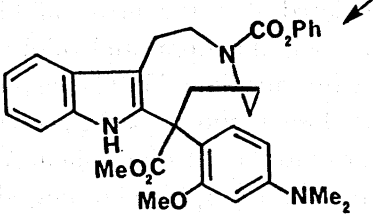


25 26

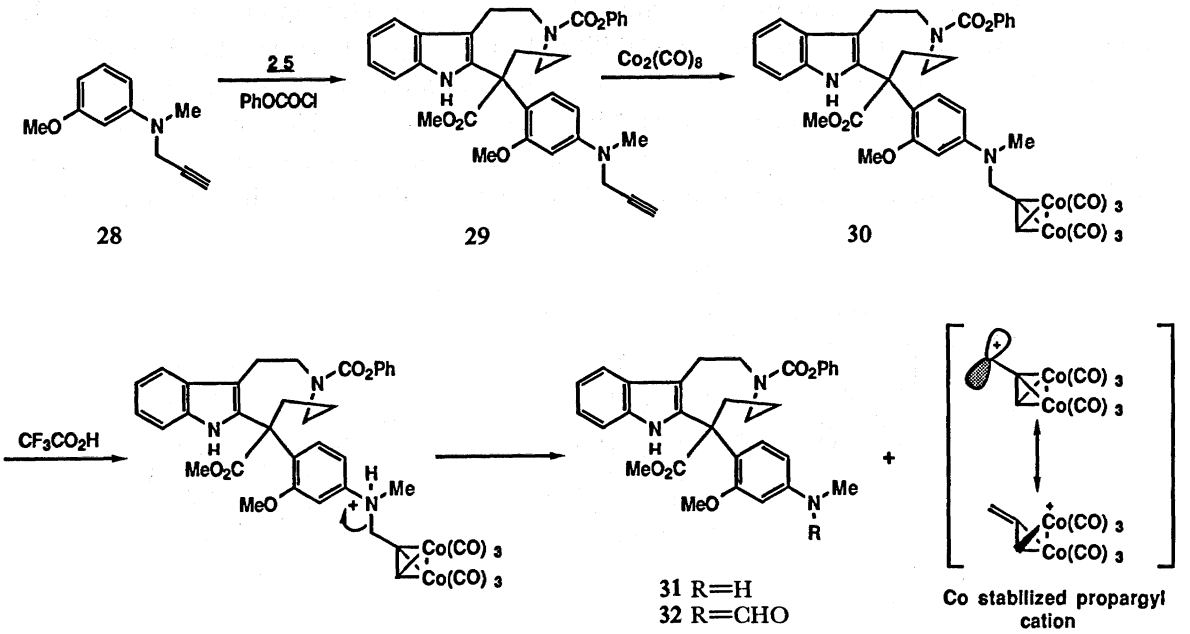




27

a lack of any literature precedent, a less than conventional solution was well worth exploring.

Treatment of 3-$MeOC_6H_4NHMe$ with $BrCH_2C{\equiv}CH/K_2CO_3/CH_3CN$ gave the *N*-propargyl derivative **28** (82%), which was coupled with **25** using $PhOCOCl/CH_2Cl_2$ to give **29** (78%). The adduct **29** was now treated with $Co_2(CO)_8$/EtOAc to give the tetrahedral dicobalt cluster **30** (93%). When **30** was exposed to trifluoroacetic acid at 25 °C the $Co_2(CO)_6$-propargyl cation was released to give the *sec*-amine **31** (85%) (Nicholas 1987). *N*-formylation of **31** with Ac_2O/HCO_2H gave the vincristine model **32** (55%). This particular illustration of the use of cobalt-stabilized cation chemistry vividly shows the compatibility of this protecting group with a reasonably complex array of functionality.



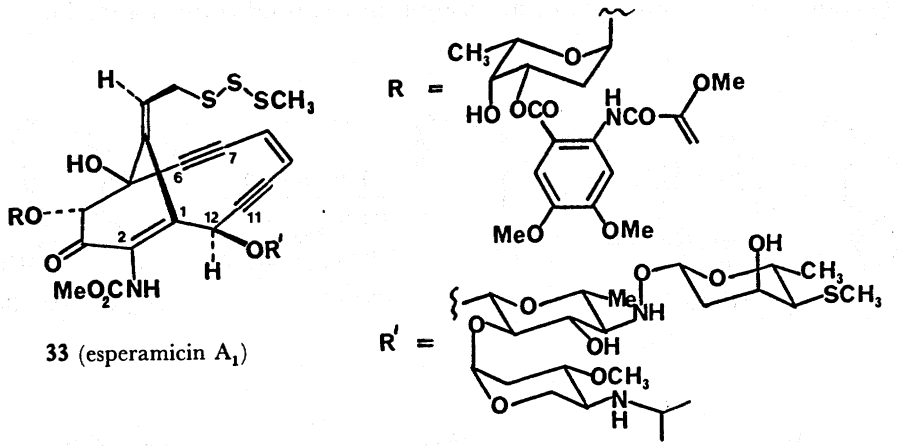
Stabilization of strained *Z*-diynenes

The last example of the extraordinary ability of organometallic chemistry to allow unique modes of reactivity, and the stabilization of otherwise inaccessible intermediates, is again taken from the field of biologically important compounds.

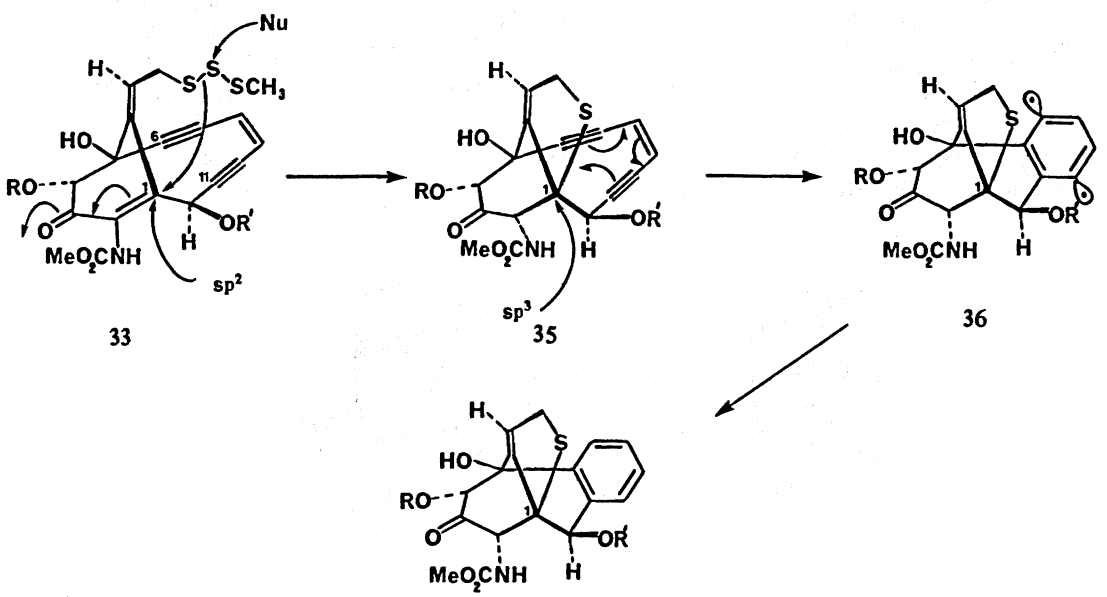
Very recently, two groups (Golik *et al.* 1987; Lee *et al.* 1987) reported the structures of a new class of extremely potent antitumor antibiotics of which esperamicin A_1 **33** has the aglycone bicyclo[7.3.1]diynene system. Co-occurring with these metabolites is an inactive compound, esperamicin X **34**. It was speculated that the mode of biological action of **33** involves nucleophilic attack on the central sulphur atom, and thiol addition to the α,β-unsaturated enone system to give the putative intermediate **35**. The change in hybridization at C-1 from sp^2 to sp^3, in conjunction with the close proximity of the acetylenes C-6/C-11, allows access to an energetically reasonable pathway to the 1,4-diyl (*p*-benzyne) **36**. The 1,4-diyl process has a parallel in the earlier work of Bergman (1973), who showed that the prototype diynene **37** could be converted into benzene and 1,4-dichlorobenzene when exposed to 2,6,10,14-

tetramethylpentadecane and CCl_4 respectively. The reported conditions (195 °C) hardly parallel the mild conditions (room temperature to 37 °C) speculated for the conversion of **33** into **34**.

We have constructed a model system that maintains C-1 as sp^3 hybridized, yet prevents cyclization into the diyl, because one of the triple bonds is complexed as its derived dicobalthexacarbonyl metallocycle. This device allows us to examine the release of the diynene

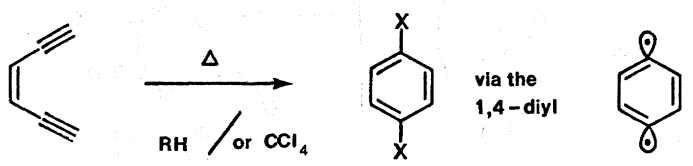


33 (esperamicin A_1)



33 **35** **36**

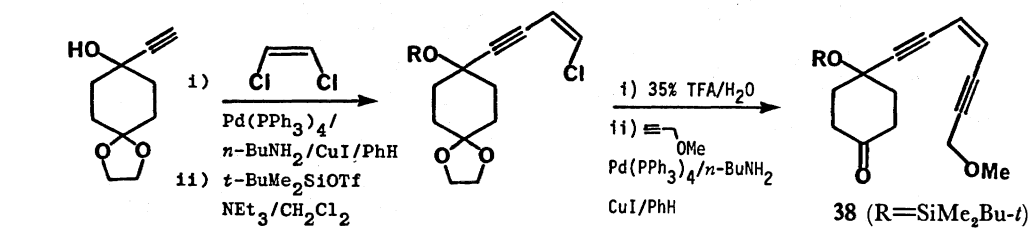
34 esperamicin X (R′=H)

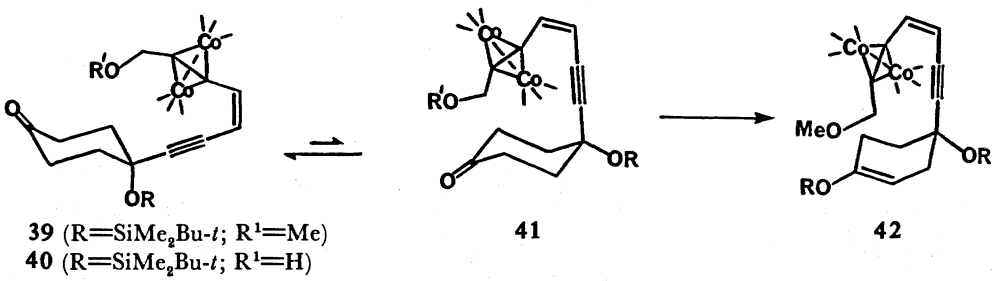


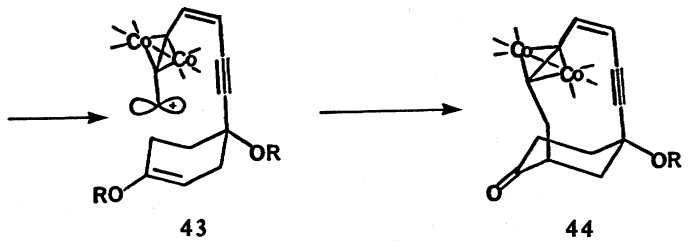
37

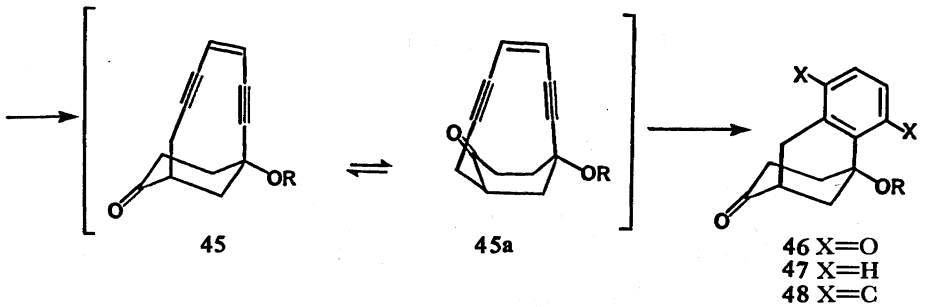
by oxidation, and the cyclization to a 1,4-diyl in the absence of the initiating thiol chemistry.

Cyclohexane-1,4-dione monoketal, as its acetylide adduct, was converted through the sequence of reactions shown below to give the diynene **38**. As expected, when **38** was treated with $Co_2(CO)_8$ (1.0 equivalent) in heptane, the least sterically hindered acetylene was converted into the dicobalthexacarbonyl cluster **39** (82%). The structure of **39** was confirmed by a single crystal X-ray structure of the corresponding alcohol **40**. This shows that the linear acetylene portions occupies an equatorial position in the solid state (figure 1).









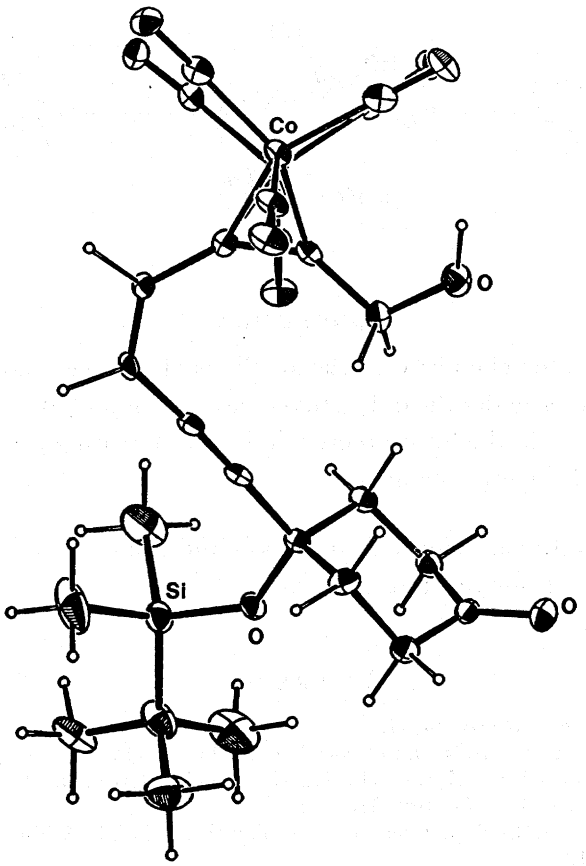
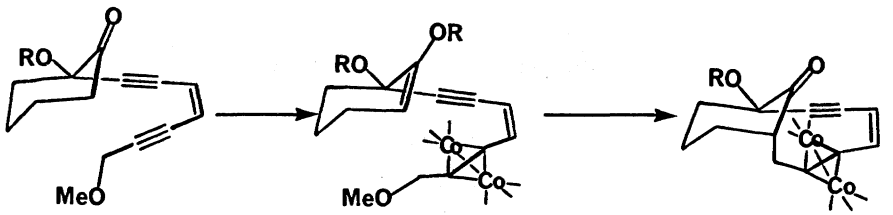


FIGURE 1. ORTEP drawing of **40**.

The compound **39** can only cyclize via the derived propargyl cation in the axial conformation **41**. Treatment of **39** with t-$BuMe_2SiOTf/NEt_3/CH_2Cl_2$ gave **42** (89%). When **42** was exposed to $TiCl_4$ (6 equivalents)/DABCO (1 equivalent) at −78 °C, followed by warming to −50 °C, the cyclized product **44** (56%) was obtained as a stable compound (Magnus & Carter 1988). Oxidative decomplexation of **44** in 1,4-cyclohexadiene with N-methyl morpholine N-oxide at 20 °C rapidly gave **47** (50%). Similarly, conducting the same decomplexation in CCl_4/t-BuOH gave **48** (29%). We could not detect the intermediate diynene **45**. It is important to note that the acyclic diynene dicobalthexacarbonyl adduct **39** can be oxidatively decomplexed to give the diynene **38** without aromatization. MMX calculations, which are parametrized to allow for the weak sp bending modes, suggest that the E_{act} for the conversion of **45a** into **47** is approximately 18.6 kcal mol^{-1}. It appears that the driving force for the conversion of the diynene **45/45a** into the diyl **46**, at room temperature, derives from the changes in strain energy for this transformation. Using a similar sequence of reactions, we have made the 1,3-carbonyl transposed isomer of **38**, which is **49**. We are currently examining the conversion of **49** into **51** using the dicobalthexacarbonyl metallocycle **50**. The substrate **51** should provide a useful system upon which to examine the introduction of the bridgehead double bond of esperamicin A_1.



49 50 51

Conclusions

The use of organometallic chemistry in the synthesis of complex biologically active natural products, in many cases, provides the only convenient way of making such molecules. One can confidently anticipate that in the future there will be an increasing reliance on organometallic chemistry in all areas of organic chemistry.

We thank both the National Science Foundation and the National Institutes of Health for their continued support of our research programs.

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Discussion

B. T. Golding (*Department of Organic Chemistry, University of Newcastle upon Tyne, U.K.*). Professor Magnus's *N*-protecting group could have the disadvantage that the carbocation released on deprotection might attack electron-rich moieties in the protected/deprotected molecule. Does he need to use the peptide chemist's trick of adding, for example, anisole as a scavenger (for *t*-butyl cation from *t*-butyloxycarbonyl)?

P. D. Magnus, F.R.S. This is a very reasonable concern. In the single example I have described we did not require a cation scavenger to achieve the yields mentioned. However, if

we intended to make this procedure a more general one for nitrogen protection, I am quite sure that the protocol of adding a cation scavenger such as anisole or 2-thionaphthol would be beneficial in the prevention of random and unproductive cationic reactions.

A. B. Holmes (*University Chemical Laboratory, University of Cambridge, U.K.*). Professor Magnus described some rather special conditions (6 equivalents $TiCl_4$, 2 equivalents DABCO, −78 °C) for generating the dicobalthexacarbonyl-complexed propargylic cation. The work reported in the literature suggests that such species should be readily available by treatment of the cobalt-complexed propargylic alcohol with acids such as trifluoroacetic acid. We have been unable to generate these cations by such procedures. In fact we have observed decomplexation of the metal. Could Professor Magnus describe how he arrived at the combination of $TiCl_4$/DABCO and why he thinks this reagent works where others apparently fail?

P. D. Magnus. Our experimental experiences with the literature (Nicholas 1987) methods of generating the cobalt-complexed propargylic cation using trifluoroacetic acid have also led to decomplexation of the metal, as you have described. We systematically examined a wide range of Lewis acids from BF_3OEt_2 to $TiCl_4$ (the strongest), and found that the latter to be the only one that accomplished conversion of **42** into **44**. The presence of base was also arrived at in a totally experimental way. It was reasoned that the liberation of HCl would be deleterious to the product **44**, and a tertiary amine should prevent this problem. The choice of DABCO was determined, because it cannot be dehydrogentated without the formation of a prohibitively high-energy bridgehead imminium ion. Consequently, we arrived at the reagent combination of $TiCl_4$/DABCO, which gave the best yields of **44**. More recently, we have found this system converts **50** into **51** where other Lewis acids fail.

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