Pergamon

Tetrahedron Vol. 50, No. 5, pp. 1469-1502, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0212-X

Application and Mechanistic Studies of the [2,3]-Wittig Rearrangement: An Approach to the Bicyclic Core Structure of the "Enediyne" Antitumor Antibiotics Calicheamicin γ_1^I and Esperamicin-A_1

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Abstract: Starting from readily available β,γ-unsaturated cyclohexenone precursors the 13-membered bicyclic enediyne **8** was prepared as well as the corresponding "dihydro" analogs **11** and **42** lacking the C4-C5 double bond. [2,3]-Wittig ring contraction of **8** to **9**, possessing the bicyclo [7.3.1] tridecadiynene system, characteristic of the enediyne antibiotics calicheamicin and esperamicin, was obstructed by competing electron transfer reactions involving the planar enediyne system. However, [2,3]-Wittig rearrangement of the 1,5-diynes **11** and **42** proved efficient. Under mild base conditions (DBU, 20°C) the 10-membered bicyclic 1,5-diyne **57**, bearing a OMs group at C_4, was converted to enediyne **9**. This product underwent spontaneous Bergman cyclization giving a series of products, several of which lacked the O-Me substituent which was introduced at C_8. These results, confirmed by deuterium labeling studies, brought to light the occurence of an internal quenching process involving 1,5-radical translocation.

INTRODUCTION

In 1987 researchers from Lederle and Bristol-Myers simultaneously announced the structural elucidation of two unique but related complex glycosides of bacterial origin, calicheamicin γ_1^I (**1**) and esperamicin A_1 (**2**) (Figure 1).[1,2] These antibiotics are amongst the most potent antitumoral agents known, displaying *in vitro* and *in vivo* activities at ng/ml levels (IC_{50}'s) against a number of tumor systems (B16 melanoma, Moser human carcinoma, HCT-116 carcinoma, and a normal and vincristine resistant leukemia).[3] This is attributed to their capacity to cleave double strand DNA by a totally unprecedented and very efficient mechanism, involving initial site selective complexation with DNA and subsequent activation through nucleophilic attack on the novel trisulfide moiety. The thiolate anion which is liberated then reacts at C_9 (calicheamicin numbering) of the conjugated enone system (Michael addition) giving **3**. This structural change favors ambiant temperature Bergman-type cycloaromatization of **3** to a highly reactive 1,4-benzenoid diradical **4**, which abstracts hydrogen from the ribosyl backbone of duplex DNA causing single and/or double strand breaks.[1c,4]

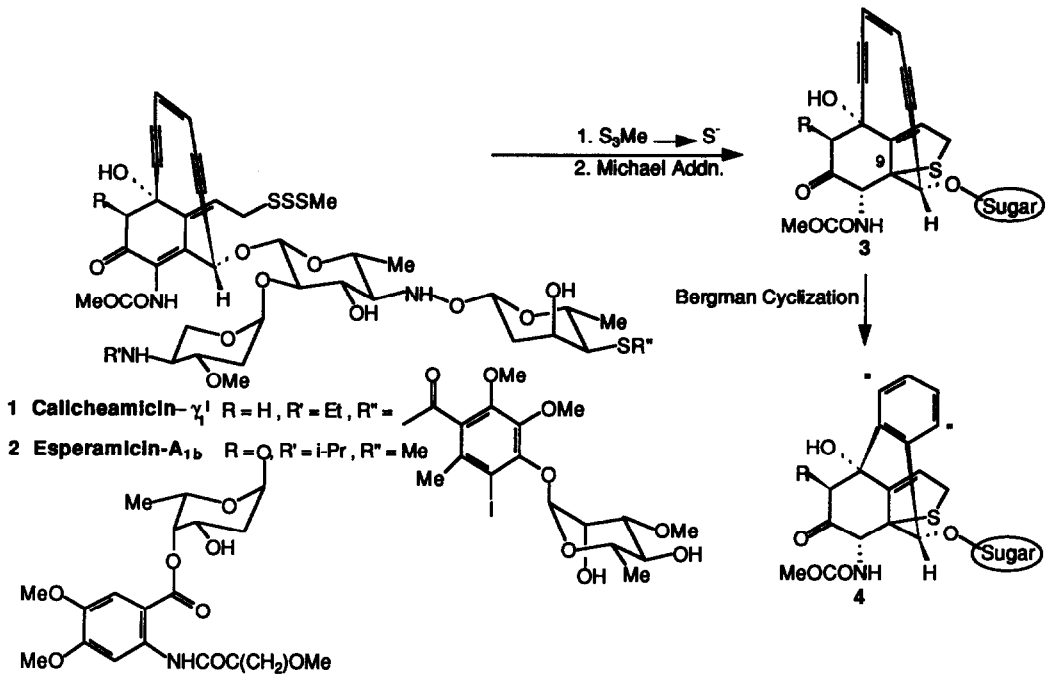


Figure 1

In view of the novel structure and biological properties of these molecules intense efforts have been made to achieve both their total synthesis, and the synthesis of mechanism based analogs with improved anti-cancer profiles.[5,6] To date two syntheses of the aglycone of **1**[7-9] and the oligosaccharide portion[10-13] of both antibiotics have been described. Very recently Nicolaou and co-workers also reported the total synthesis of (-)-calicheamicin γ_1^I.[14]

An important concern to early synthetic work in this domain was the development of methodology permitting efficient formation of the crucial C-C bond that completes assembly of the highly strained enediyne bridge (Figure 2). This transformation is rendered difficult by the often large distance between reacting centers in acyclic precursors and by the fact that on bond formation considerable distortion of the enediyne system is incurred. Magnus *et al.* showed that these problems can be circumvented via Nicholas-type ring closure of cation **5** in which the bond angles of the propargyl acetylene unit are contracted to 145° through formation of a η^2 $Co_2(CO)_6$ metallocycle.[9a] On the other hand, Danishefsky[7], Nicolaou[8] and Kende[9f] have shown that condensation of the acetylenyl anion and aldehyde carbonyl components in such highly functionalized intermediates as **6** and **7** is feasible.

Attacking the problem from a different angle, we considered the possibility that strained bicyclo [7.3.1] tridecandiynenes such as **9** could be constructed by [2,3]-Wittig ring contraction of a larger unstrained

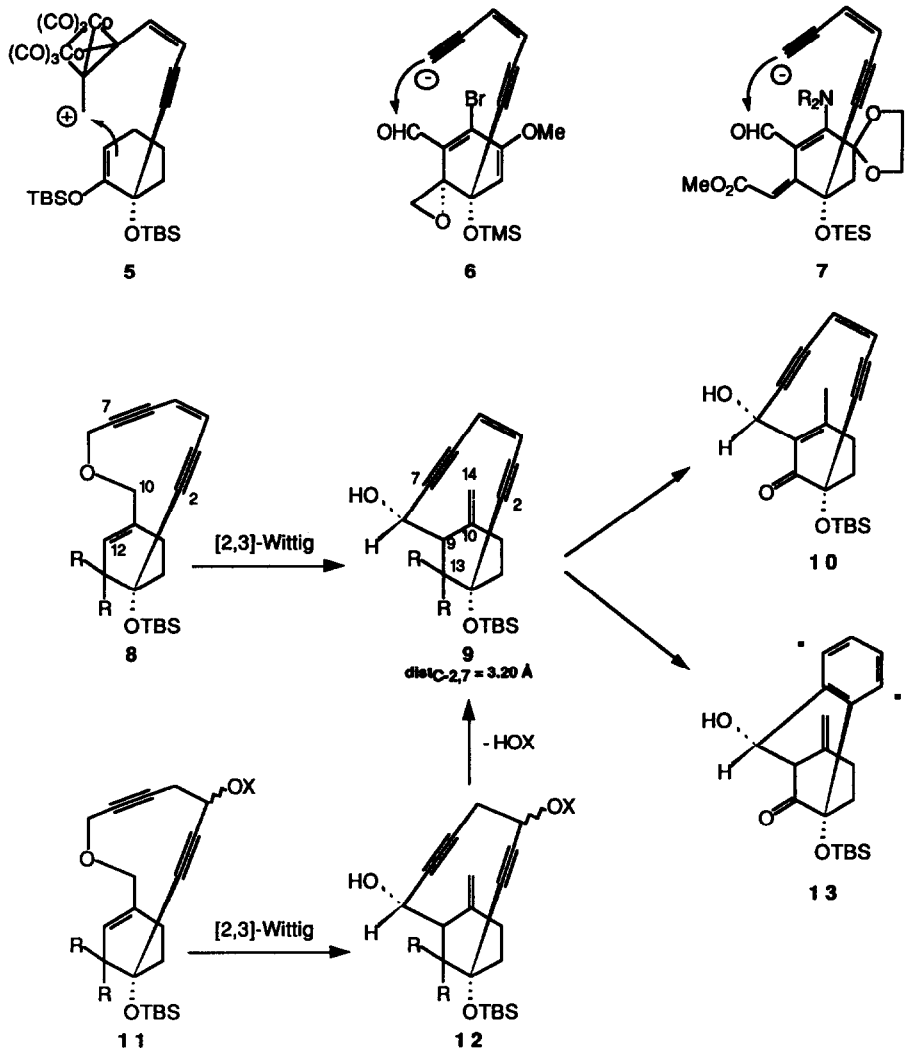


Figure 2

13-membered cyclic precursor **8**. Hydrolysis of the ketal function in **9** (R = OCH_3) accompanied by double bond migration would then provide the stable enone **10**, an advanced intermediate in our projected synthesis of a series of calicheamicin-esperamicin aglycone analogs. Work by Marshall and co-workers on the synthesis of cembrane diterpenes demonstrates that [2,3]-Wittig rearrangement of 13- and 17-membered propargylic ethers to their respective 10- and 14-membered carbocycles is efficient, and that a high level of stereocontrol can be achieved during the creation of the new hydroxyl bearing center due to the concerted nature of these reactions.[15,16] In our case molecular modeling further suggested that macrocycle **8** can adopt a favorable conformation for rearrangement to occur. However, it was more difficult to access the influence of ring strain on the mechanism ([1,2] versus [2,3]-Wittig) of the reaction and its activation energy relative to alternate reaction pathways involving the planar enediyne system.

To evaluate the feasibility of the [2,3]-Wittig approach to the synthesis of bicyclic 10-membered enediynes we have investigated the rearrangement of the simplified macrocyle **8** (R = H) and its "dihydro" derivative **11**.[17,18] The study of the ring contraction of **8** was of added interest in view of the propensity of the derived enediyne product **9** (R = H) to undergo Bergman cycloaromatization. Indeed, on the basis of molecular mechanics calculations (MMX) ($2\text{-}7_{dist}$ = 3.20 Å)[19] and the structural similarity of enediyne **9** to model compounds prepared by Magnus *et al.* [9a,b] there was every reason to believe that it would spontaneously cycloaromatize at ambient temperature to 1,4-diyl **13**. In contrast, [2,3]-Wittig ring contraction of compound **11** would lead to a stable product **12** from which **9** could be generated through acid, base or photochemically induced elimination of the elements of HOX. This transformation represents a new and potentially interesting "triggering" device for the generation of highly reactive enediynes.[20]

RESULTS AND DISCUSSION

Two plausible routes were considered for the synthesis of the oxabicyclo intermediate **8** which differ in the manner in which the enediyne bridge is built onto a β,γ-unsaturated ketone "platform" structure (Figures 3 and 4). To access compound **20** bearing an *O* -penteneyne moiety (Figure 3), the Diels-Alder adduct derived from the reaction of 2-trimethylsilyloxy-1,3-butadiene (**14**) with methyl propiolate (**15**) (toluene, reflux, 36 h) was converted to its corresponding ketal **16** (ethylene glycol, TsOH, 60% overall yield).[21] The derived ketal was then treated with lithium aluminium hydride in THF (0°C; 75%) in order to reduce the ester functionality. Small quantities of the regioisomeric cycloaddition adduct (10-15%) also carried through these steps was separated from **17** at this stage. Alkylation of the sodium alkoxide of **17** with propargyl bromide in DMF was uneventful, affording the ether **18** (R = propargyl) in 74% yield. Subsequent coupling of **18** with *cis* -1,2-dichloroethylene under Sonogashira's conditions ($Pd(OAc)_2$, Ph_3P, CuI, *n* -$BuNH_2$) furnished the vinyl chloride **19** (79% yield).[22] Mindful that hydrolysis of the ketal function in **19** could be problematic, we were fortunate to observe that on treatment with mild aqueous acid (35% aq. TFA, $CHCl_3$, 24 h) the required β,γ-unsaturated ketone **20** was obtained in high yield.

Introduction of an acetylene unit at C_1 in **20** was readily achieved using the non-basic cerium reagent prepared from trimethylsilylethynyllithium (THF, -78°C, 1 h).[23] Subsequent C-TMS deprotection was carried out by reaction of **21** with precisely one equivalent of TBAF. In this way, fluoride ion promoted elimination to give the triyne **24** (diagram) was effectively avoided.[24] With the O-TBS protected precursor **22** in hand we were then in a position to test the Pd(0) catalyzed macrocyclization to enediyne **8** (R = H). The preferred axial orientation of the less bulky ethynyl group in **22** was expected to favor this ring closure. However, a report by Beau *et al.*, which appeared at that time, describing an unsuccessful attempt to generate a 10-membered enediyne carbocycle via this same approach dampened our hopes to some extent.[25] In the experiment, reaction of **22** under standard Sonogashira Pd(0) coupling conditions and high dilution, afforded a whole series of products, from which the major component was identified as dimer **23** (ca. 10% yield). It may be that formation of the required bicyclic palladocycle intermediate in this process is disfavored due to ring strain. However, recent

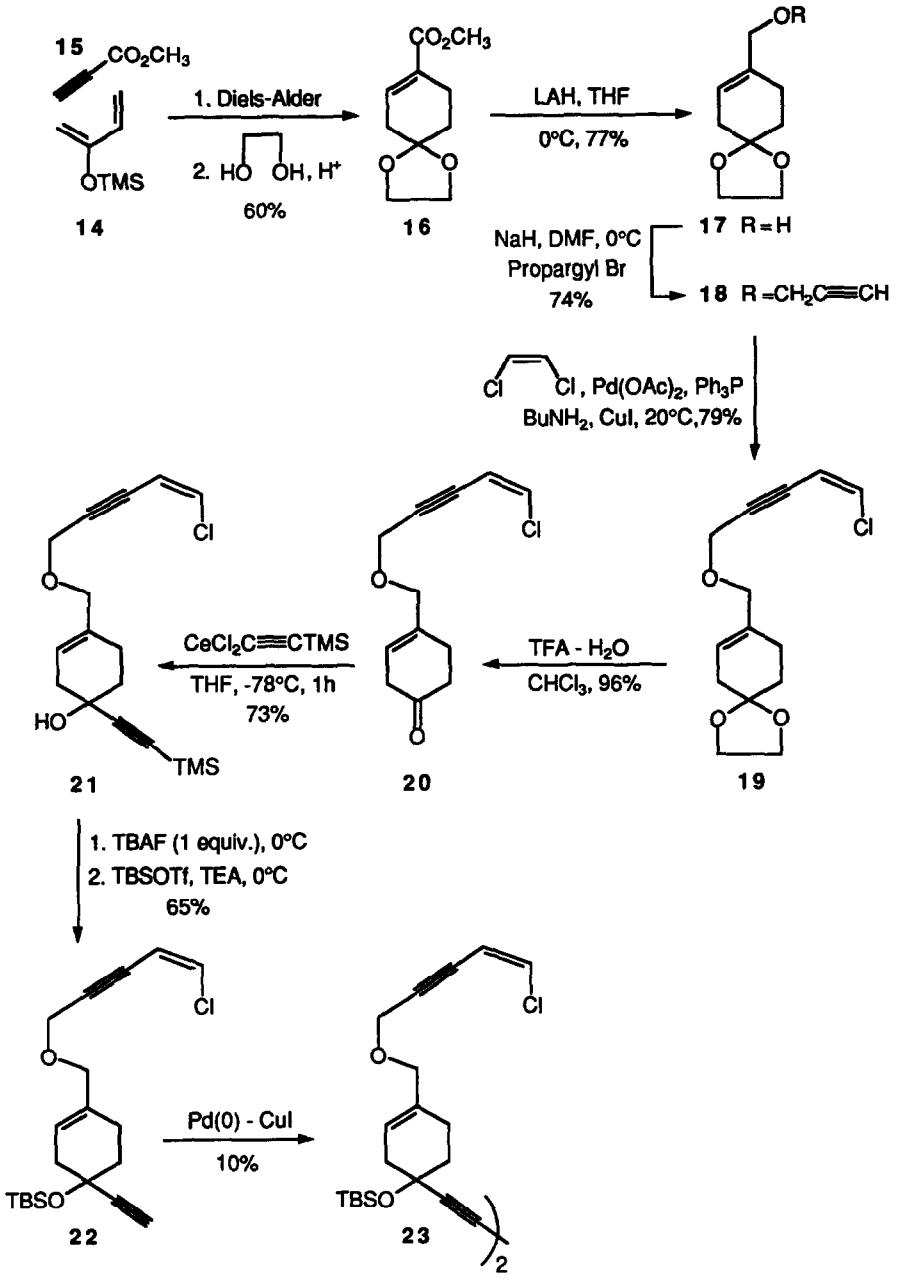
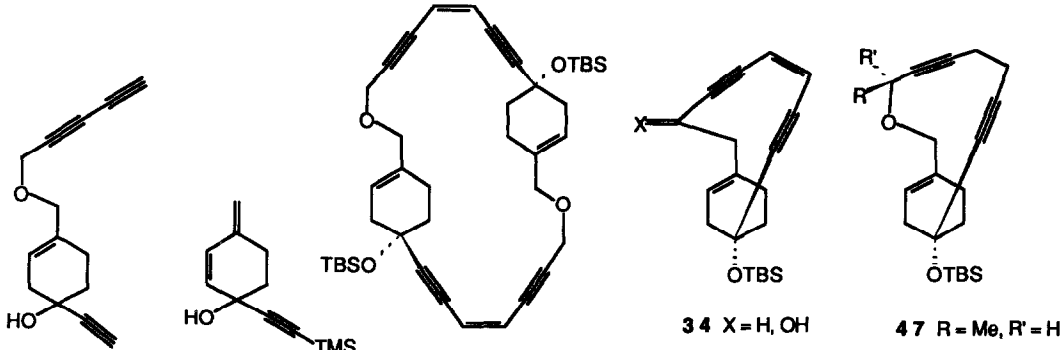

15
CO2CH3
OTMS
14
1. Diels-Alder
2. HO OH, H+
60%
CO2CH3
16
LAH, THF
0°C, 77%
OR
17 R=H
NaH, DMF, 0°C
Propargyl Br
74%
18 R=CH2C≡CH
Cl Cl, Pd(OAc)2, Ph3P
BuNH2, CuI, 20°C,79%
19
TFA - H2O
CHCl3, 96%
20
CeCl2C≡CTMS
THF, -78°C, 1h
73%
HO
TMS
21
1. TBAF (1 equiv.), 0°C
2. TBSOTf, TEA, 0°C
65%
Pd(0) - CuI
10%
TBSO
22
TBSO
23
2

Figure 3

results from Schinzer's group on the preparation of a *trans* -fused 11-membered enediyne demonstrates that this type of ring closure is possible.[26]

In view of the problems encountered in the palladium mediated ring closure approach, our efforts were directed to constructing the macrocycle **8** according to Figure 4. Once again, hydrolysis of the *O* -benzoyl substituted ketal **18** (R = COPh) was successful employing TFA-H_2O in $CHCl_3$. However, closer study of this hydrolysis reaction revealed that its outcome was highly dependant upon the nature of the allylic alcohol substituent. To illustrate this point, whereas hydrolysis of **18** where R = benzoyl leads to the desired β,γ-unsaturated ketone **27**, the reaction of the corresponding acetate and *n* -propyl derivatives under the same conditions leads to essentially *quantitative formation of trifluoroacetate 26* [δ 7.12 and 6.00 (CH=CH), 5.35 (CH_2OCOCF_3); MS(EI) m/z 222 M^+]. Apparently these subtile changes in the oxygen substituent strongly influences the rate formation of enol **25**. In keeping with this hypothesis it was found that prolonged exposure of the β,γ-unsaturated ketone **18** (R = benzoyl) to aqueous trifluoroacetic acid in $CHCl_3$ results in slow build-up of ketone **26**.

In the two step preparation of acetylene derivative **28** from ketone **27** it was also necessary to use $TMSC{\equiv}CCeCl_2$ (THF, -78°C, 1 h), as the corresponding condensation step using an ethynyllithium reagent resulted in formation of the elimination-addition product **29** (diagram). Subsequent protection of the tertiary alcohol using TBSOTf/TEA/CH_2Cl_2, and liberation of the allylic alcohol by hydride reduction (DIBAL-H, CH_2Cl_2, -78°C) gave **30**. The timing of the latter deprotection step was important in order to avoid competing π-allyl palladium reactions during enediyne construction. Elaboration of intermediate **30** to the acyclic enediyne **31** involved successive Pd(0) couplings with *cis* -1,2-dichloroethylene and the *O* -TBS derivative of propargyl alcohol (59% overall yield). It was also possible to attach the entire enediyne chain to intermediate **27** in a single step through reaction with the cerium reagent prepared from *O* -THP protected 6-hydroxymethylhexa-3-ene-1,5-diyne. However, the yield of this reaction is low (25%), and it offers no advantage in terms of the total number of steps required. At this stage allylic alcohol function in **31** was transformed to its corresponding bromide under standard conditions (MsCl, TEA, CH_2Cl_2 followed by LiBr, acetone) and the primary propargyl *O* -TBS group was cleaved using TBAF at -20°C. This afforded the bromoalcohol **32** in high yield.



24 **29** **33** **34** X = H, OH; **35** X = O; **47** R = Me, R' = H; **48** R = H, R' = Me

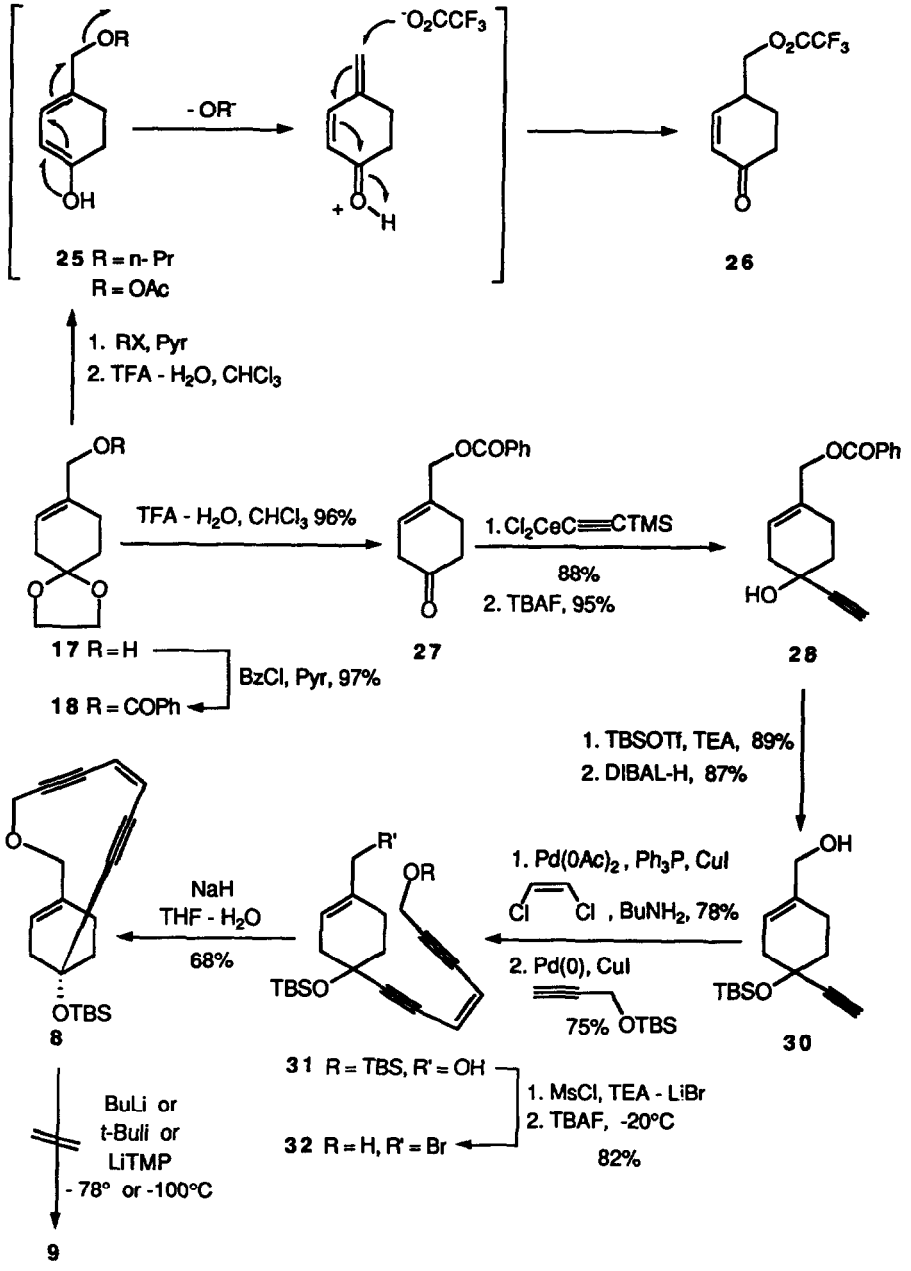

OR
- OR⁻
OH
⁻O₂CCF₃
+ O H
O₂CCF₃
O
25 R = n-Pr
R = OAc
26
1. RX, Pyr
2. TFA - H₂O, CHCl₃
OR
O O
17 R = H
18 R = COPh
BzCl, Pyr, 97%
TFA - H₂O, CHCl₃ 96%
OCOPh
O
27
1. Cl₂CeC≡CTMS
88%
2. TBAF, 95%
OCOPh
HO
28
1. TBSOTf, TEA, 89%
2. DIBAL-H, 87%
OH
TBSO
30
1. Pd(0Ac)₂, Ph₃P, CuI
Cl Cl , BuNH₂, 78%
2. Pd(0), CuI
75% OTBS
R'
OR
TBSO
31 R = TBS, R' = OH
32 R = H, R' = Br
1. MsCl, TEA - LiBr
2. TBAF, -20°C
82%
NaH
THF - H₂O
68%
O
OTBS
8
BuLi or
t-BuLi or
LiTMP
- 78° or -100°C
9

Figure 4

In initial macrocyclization experiments, addition of excess NaH to highly diluted solutions (0.9 mM) of **32** in dry THF, with or without DMPU[27], did not result in formation of the 13-membered bicycle **8**. However, the addition of a small quantity of water (giving approx. a $[H_2O] = 0.03\text{-}0.05$ M) was observed to "catalyze" this ring closure; the reaction going to completion in ca. 48 h, affording the desired bicycle **8** in 68% yield along with its corresponding 26-membered macrocyclic dimer **33** (9%) (diagram). It is not exactly clear why the presence of water assists macrocyclization, but one can logically assume that a dilute solution of sodium hydroxide in wet THF is produced which acts as the base. Under other conditions, including the use of 5N NaOH/Bu_4NHSO_4/benzene or NaH/18-crown-6/benzene, compound **8** was obtained only as a minor product.

The structure of macrocycle **8** was readily deduced from the spectral data, and in particular from its ^1H NMR spectrum. Compared to **32** where the signals for the propargylic and allylic methylenes appear as two singlets at δ 4.44 and δ 3.96, respectively, the absorptions for protons C_8 and C_{10} in **8** were clearly separated [H_{8a} δ 4.63 (dd), H_{8b} δ 4.04 (d), H_{10a} δ 4.34 (dd), H_{10b} δ 3.76 (d)]. Their multiplicity results from small coupling to the vinylic protons H_5 and H_{12}. NOe's observed between H_{8b} and H_{10b}, and H_{10b} and H_{12} also revealed that **8** prefers the conformation where the C_8 and C_{12} centers involved in the [2,3]-Wittig rearrangement are on the same side of the molecule. The calculated (MMX) C_2-C_7 distance of 4.11 Å further suggests that, like acyclic enediynes[28], compound **8** is relatively unstrained.

Having gone to all the trouble to prepare this 13-membered bicyclic enediyne, it was disconcerting to observe the rapidity with which it totally decomposed when reacted under typical [2,3]-Wittig rearrangement conditions (*n* -BuLi, -78°C; LDA, -78°C, *n* -BuLi; -100°C, *t* -BuLi, -100°C). Indeed, in less than 10 min after addition of base to a cold THF solution of **8**, the reaction changed colour from red-brown to blue to green (on work-up), and the formation of a multitude of products was confirmed by TLC. The absence of any peaks in the aromatic region of the NMR spectrum of the crude product mixture further revealed that the diradical that would be formed on spontaneous cycloaromatization of the [2,3]-Wittig product was not involved in its decomposition. Remarkable also was the finding that on conducting the experiment at higher temperature (-25°C) using the non-nucleophilic base, lithium 2,2,6,6-tetramethylpiperidide (LiTMP), the alternate [1,2]-Wittig rearrangement product **34** was produced as a mixture of epimers in a 40% yield. No cycloaromatized products were produced under these conditions. Compound **34** was oxidized to the corresponding ketone derivative **35** for characterization purposes using Dess-Martin periodinane.[29]

Rapid single electron transfer from the alkyllithium or amide base to the planar enediyne system was evidently predominating in the reactions at low temperature, blocking access to the [2,3]-Wittig reaction manifold. To determine whether failure to obtain the desired [2,3]-Wittig ring contraction was not also due to excessive ring strain in attaining the transition state for rearrangement, the corresponding reaction of the dihydro analog **42** in which electron transfer reactions were not expected to participate was examined.

Preparation of **42**, facilitated by the fact that 1,5-hexadiyne is commercially available, was achieved as illustrated in Figure 5. Treatment of ketone **27** with three equivalents of the dicerium reagent of 1,5-hexadiyne, followed by protecting group manipulations, furnished compound **38** in 37% overall yield. Transformation of this alcohol to chloride **39** was achieved using standard protocol (MsCl/2,6-lutidine/LiCl/DMF). One carbon

homologation (BuLi, $(CH_2O)_n$, THF) then provided propargyl alcohol **40** in 76% yield. As attempts to cyclize chloride **40** under conditions described by Marshall et al.[16a] were unsuccessful, it was converted to the corresponding bromide **41** (LiBr, acetone, 96%) and cyclized using our method involving reaction with NaH in wet THF. In this manner, crystalline bicycle **42** (m.p. 87-88°C) was obtained in 61% yield along with minor amounts (10%) of a dimer analogous to **33**.

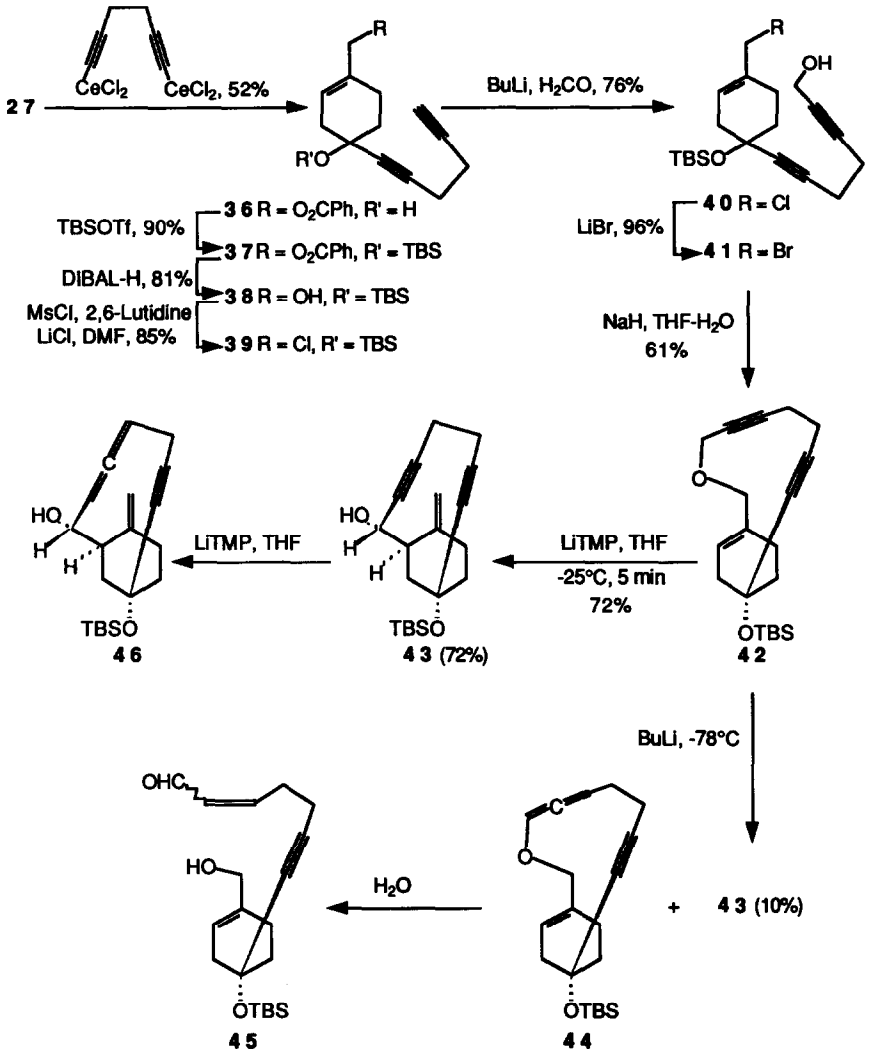


Figure 5

Extensive decomposition was again observed on treatment of a THF solution of **42** with *n* -BuLi at -78°C. However, the rearranged product **43** was isolated from this mixture, albeit in low yield (10%). Indicative of the formation of **43** was the presence of two resonances for the geminal C_{14} exocyclic methylene

protons at δ 5.04 (s) and δ 4.84 (s), a signal for the C_8 methine at δ 4.30, and the distinct absence of peaks corresponding to the methylene protons at C_8 and C_{10} in the starting material. The *cis* -α,β-unsaturated aldehyde **45** was also isolated, undergoing slow isomerization to its corresponding *trans* -isomer in $CDCl_3$. Formation of this aldehyde probably involves a base-promoted rearrangement of **42** to the allenyl ether **44** and subsequent hydrolytic cleavage of the strained ring on contact with silica gel. In marked contrast, the reaction of **42** with 1.8 equivalents of LiTMP in THF at -25°C for 5 min (conditions used to effect [1,2]-rearrangement of **8**) was highly chemoselective, furnishing the [2,3]-Wittig product **43** in a 72% isolated yield.[30] The presence of greater quantities of base in this reaction promoted formation of allene **46** (undefined stereochemistry), whereas longer reaction times led to decomposition.

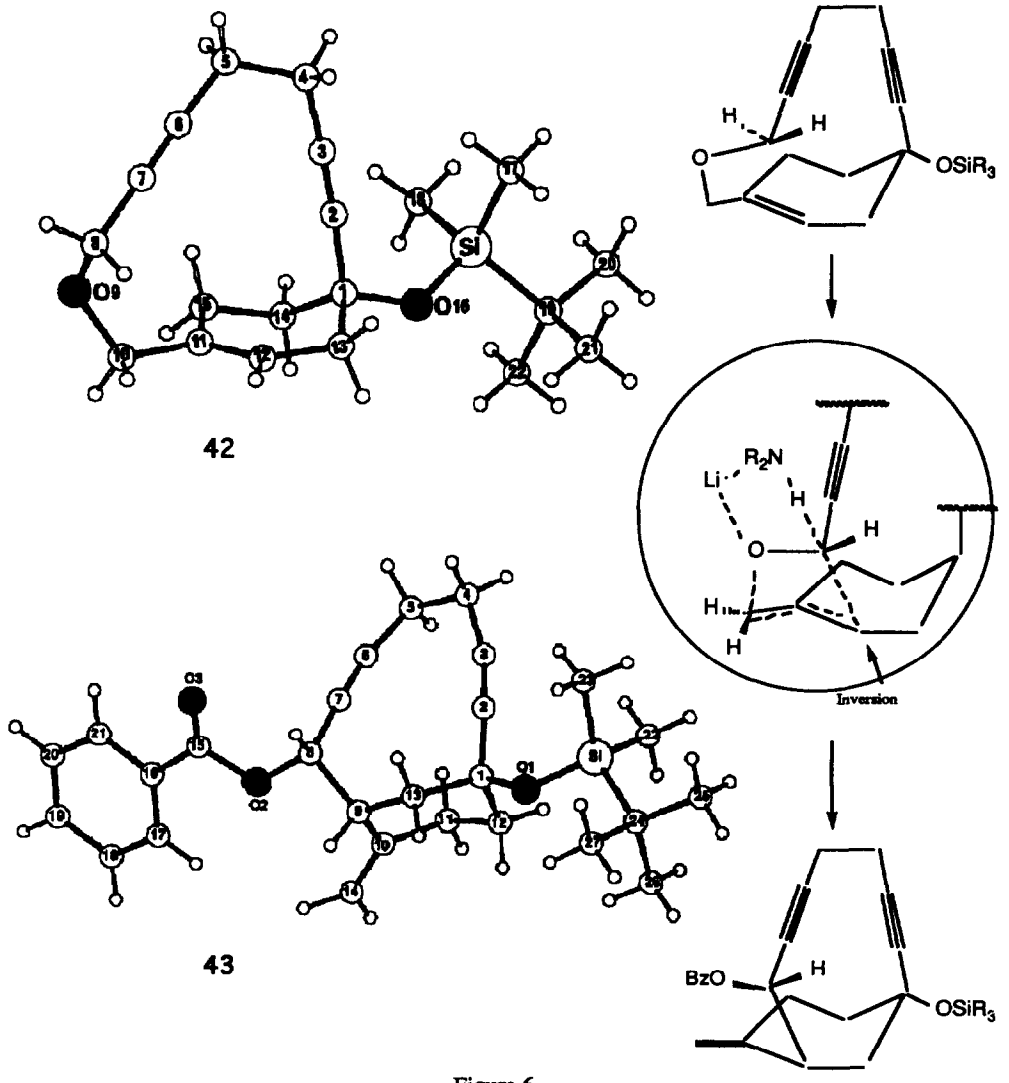


Figure 6

Pertinent information concerning the facility of this rearrangement was obtained from the X-ray crystal structures of **42** and **43** (Figure 6). Immediately evident is that, in the solid state, compound **42** already adopts the required conformation for ring contraction with a C_8-C_{12} distance of 3.721 (5) Å. This same conformation, in which the C_8 methylene group sits preferentially above C_{12} of the double bond, was also predicted from n.O.e. experiments. Both molecular mechanics calculations and the X-ray data reveal that the acetylene bond angles in this relatively strain free molecule are normal, and that the C_2-C_7 distance is: 3.954 (5) Å (X-ray); 3.60-Å (MMX).

Particularly noteworthy in the crystal structure of the benzoate derivative of **43** is the approx. 0.8 Å decrease in the interatomic C_2-C_7 distance (3.15 (2) Å) relative to the separation of the same carbons in **42**, and the distortion of the acetylene bond angles to 166°-176° (see Table 1). The C_4-C_5 bond length as well as the $C_{3,4,5}$, and $C_{4,5,6}$ bond angles do not deviate significantly from the theoretical values, indicating that, similar to a number of related enediyne models, the ring strain in **43** is almost entirely confined to the weak bending modes of the acetylenic bonds.[7,9a,c] In addition, the two linear acetylene units diverge from coplanarity by approx. 32°. This probably plays a large role in rendering bicycle **43** less strained than its enediyne counterpart. Important also is the observation that the cyclohexane ring prefers the quasi-chairlike conformation to avoid 1,3-allylic interactions involving the exocyclic methylene group rather than the boat-like conformation favoured in related bicyclic ketones prepared by Magnus.[9a]

In view of the ground state geometry of **42** and the only minor structural deformation in compound **43** induced by ring strain, it is possible to speculate that on treatment of macrocycle **42** with strong base the transition state for ring contraction should be readily accessible . The efficient formation of bicyclic diyne **43** by this route is consistent with this picture, as are the results of *ab initio* calculations carried out by Houk and Marshall[31] which predict that the [2,3]-Wittig rearrangement is highly exothermic occurring via an early transition state. Furthermore, in terms of their transition state model it would be the *pro-R* hydrogen in **42** which interacts with the base. In a concerted, but non synchronous fashion, removal of this proton would be accompanied by simultaneous formation of the C_8-C_9 bond. This results in inversion of configuration at C_8 and stereospecific formation of compound **43** as is observed.

To test this mechanism we synthesized compounds **47** and **48** (diagram), in which either the *pro-R* or *pro-S* hydrogen has been replaced by a methyl group, by a procedure similar to that used to prepare **42**.[32] On treatment of the mixture of these compounds with base only **47** underwent [2,3]-Wittig rearrangement.[33] Similarily, starting material was isolated upon reaction of pure **48** under the same conditions. Although these results concord with the Houk-Marshall mechanism, a stepwise mechanism involving anion formation and inversion through an allenyl anion followed by rearrangement remains a possibility.

Having shown that the dihydro enediyne analog **43** could be prepared by [2,3]-Wittig rearrangement of the 13-membered macrocycle **42** it remained for us to modify the synthetic route to this "dihydro" system such that a suitable oxygen containing functionality would be present at C_4 in anticipation of a subsequent step in which the enediyne double bond is created. This strategy to complete formation of the enediyne system in the last step of the synthesis through elimination of the elements of HOX from **12** (see Figure 2) was of interest for

several reasons. First, it liberates us from the problem of having to fine tune reactions that might otherwise have to be conducted in the presence of the fragile enediyne system. Second, it limits the risk of handling potentially dangerous intermediates, and finally, it provides a novel triggering device for the generation of highly reactive enediynes which may find its place in the conception of new anticancer agents.

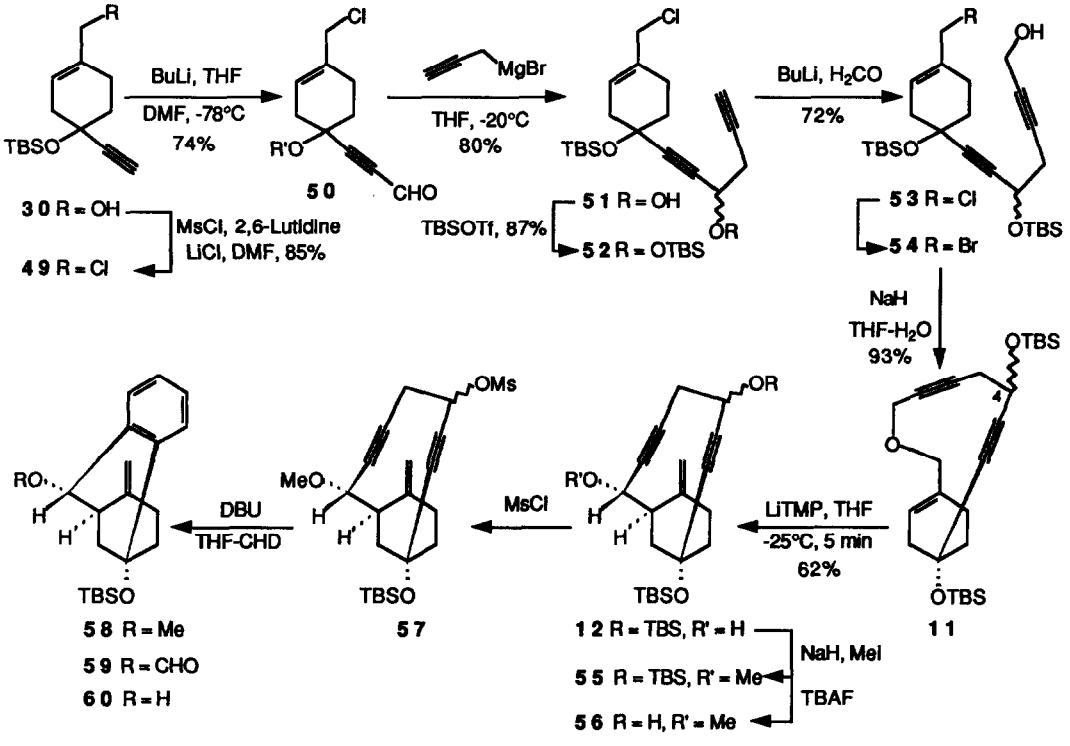


Figure 7

To access compound **12** (X = TBS) (Figure 7) alcohol **30** was converted to the corresponding chloride **49** as described above (cf. **39**). Treatment of **49** with *n* -BuLi at -78°C, followed by addition of DMF gave the aldehyde **50** which was reacted with propargyl magnesium bromide[16f] at -20°C in THF. This furnished diyne **51** in 60% overall yield. Silylation of the derived secondary alcohol with TBSOTf/TEA/CH_2Cl_2 giving **52** was followed by introduction of the hydroxymethyl unit (BuLi/$(CH_2O)_n$/THF). Macrocyclization of bromide **54** proceeded extremely well (NaH in wet THF) providing **11** (X = TBS) as a 1:1 mixture of diastereomers (93% yield). Wittig rearrangement of **11** with 1.8 equivalents of LiTMP for 5 min at -25°C was also efficient producing the [7.3.1] bicyclic product **12** in 62% yield.

To study the elimination-cycloaromatization steps, the C_8 hydroxyl in **12** was methylated (NaH/MeI/THF) so as to permit chemoselective activation of the C_4-OH. The derived *O* -methyl ether **55** was then desilylated using TBAF and mesylated on treatment with MsCl/DMAP/CH_2Cl_2. Compound **57** was obtained in 76% overall yield for the three steps. Although the two diastereomeric mesylates **57** were separable, the mixture was treated with four equivalents of DBU in THF/1,4-cyclohexadiene (CHD) without precaution to

exclude oxygen. This resulted in the slow disappearance of both compounds and the appearance of a complex mixture of products (TLC analysis). Upon complete consumption of **57** (approx. 7-8 h) the crude product mixture was examined by NMR. That cycloaromatization had occurred was evident from the signals in the δ 8.5-7.1 range. In contrast, no peaks were observed for the parent enediyne system. Isolation of the major reaction components by silica gel column chromatography gave, in the faster running fractions, the expected cyclized product **58** as an admixture with formate **59** (**58/59** 3:1 mixture; 17% overall yield). Quite surprisingly, the more polar alcohol **60**, in which the *O* -methyl group is lost, was also isolated in 8% yield. The numerous minor components of the reaction were not characterized owing to difficulties in the isolation of such minute amounts of material.

Although the origin of **58** could be explained by quenching of the intermediate 1,4-diyl with CHD, radical translocation by a 1,5-hydrogen atom transfer from the *O* -methyl group to C_6 was apparently involved in the formation of the two unexpected products **59** and **60**. Such 1,5-hydrogen transfers involving highly reactive phenyl radicals have observed by Bergman *et al.* in their studies of simple 1,6-dialkyl substituted hexa-3-en-1,5-diynes, and have been exploited in synthesis.[34,35]

To confirm this hypothesis, the *O* -mesylate elimination was studied using the deuterium labelled compound **61**. Reacting **61** in CHD-THF (8 h) led to formation of three major components, identified as the benzoate **65**, alcohol **66** and the ketone **67** (Figure 8). As anticipated deuterium incorporation at C_6 of the phenyl ring was observed in all three cases. With these results in hand, several pathways leading to the observed products from diyl **62** are proposed. According to pathway 1, radical translocation gives intermediate **63** which reacts with dioxygen forming the hydroxyperoxide **64**. Base-induced fragmentation of **64** then produces compounds **65** (via **a**) and **67** (via **c**), whereas its reduction by DBU[36] (**b**) gives a hemiacetal which on work-up hydrolyses to **66**.[37]

Alternatively (pathway 2), if intermediate **63** undergoes β-fragmentation to benzyl radical **68**, hydroperoxide **69** could accumulate on reaction with dioxygen. Its subsequent reduction (**d**) or base-promoted fragmentation (**e**) would give **66** or **67**, respectively. However, examination of Dreiding models reveals that there would be no steric preference for the introduction of dioxygen from either side of the planar radical **68**. This strongly suggests that a mixture of epimeric alcohols would be formed. Since the ^{13}C NMR of the crude reaction mixture shows the presence of only one alcohol product, whose structure **66** was ultimately assigned from the observed n.O.e between H_8 and H_{13}, it was concluded that formation of **66** follows only **Path 1**.

Compared to calicheamicin and esperamicin, compound **61** possesses the opposite stereochemistry at C_8. Molecular modelling studies suggest, however, that this may be irrelevant as in both this product and its stereoisomer the *O* -methyl hydrogens can approach to within 1.4-1.6 Å of the C_6 carbon center. Therefore, essentially the same propensity for radical translocation should be displayed by these C_8 epimers. Recent experiments described by Wender and Goldberg[38,39] demonstrate that internal 1,5-hydrogen atom transfer in activated neocarzinostatin systems does occur. The same authors have suggested that this may account, in part, for the low ratio of double to single strand DNA cleavage observed for the natural product.[36,40] From our results it is clear that simple analogues of the enediyne antibiotics can also undergo these events, implying that the

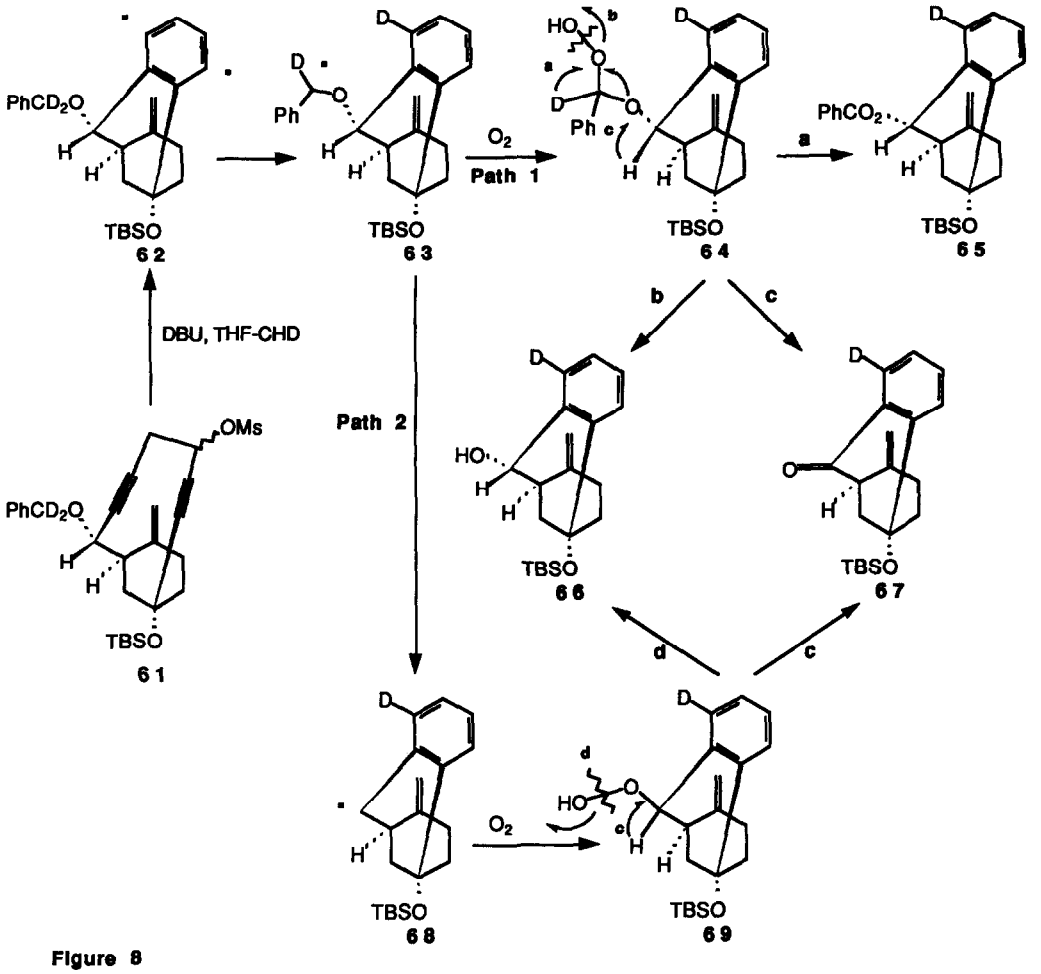


Figure 8

proper choice of the C_8-OH substituent is important to the generation of a fully effective 1,4-aryl diradical. As to whether, calicheamicin and esperamicin display these same characteristics remains to be seen, but it has been suggested that similar events involving the C_{12} substituent of the latter may explain its single strand DNA cleavage behaviour.[41]

In conclusion, having demonstrated that highly reactive enediynes can be generated under mild conditions from suitably activated dihydro precursors, the adaptation of this strategy to the conception of novel bicyclic 1,5-diyne prodrugs for the selective targeting of cancer tumors is in progress.

ACKNOWLEDGEMENTS:

This work has been generously supported by Servier Laboratories (ADIR), and by a grant from the Ministère de la Recherche et Technologie.

Experimental Section

General. Melting points (mp) were determined using a Reichert Thermovar apparatus and are uncorrected. NMR Spectra were recorded on Brucker WP-200,WP-250 or WP-400 instruments at 200, 250 at 400 MHz for ^{1}H and at 50.13 or 62.89 MHz for ^{13}C using deuterated solvents. Chemical shift data is reported in parts per million (δ in ppm) where s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet respectively. Infrared (IR) spectra were recorded on a Nicolet 205 FT IR spectrophotometer. Thin layer chromatography (TLC) was performed using Merck 60 F_{254} (0.2 mm thickness) silica gel plates. Standard flash column chromatography was done using Merck silica gel 60 (Art. 9385). Mass spectra (MS) were recorded on a MS-9 AEI spectrometer for chemical ionisation (CI) (isobutane as carreir gas unless otherwise stated), and on a Kratos MS80RF spectrometer for fast atom bombardment (FAB) (4kv, pos, thioglycerol). Elemental analyses were performed by the microanalysis laboratory at the ICSN.

4-Methoxycarbonylcyclohex-3-ene-1-one 1-Ethylene Ketal (16). A solution of 2-trimethylsilyloxy-1,3-butadiene (5.5 g, 37.9 mmol),[21] and methyl propiolate (5.4 ml, 60 mmol) in toluene (50 ml) was refluxed under argon for 36 h, and then concentrated under vacuum. The residual oil was dissolved in benzene (40 ml), containing *p*-TsOH (400 mg) and ethylene glycol (4.0 g, 64.5 mmol), and the resulting mixture was refluxed (Dean-Stark) for 6 h. After cooling, the reaction mixture was partitioned between ether and aqueous $NaHCO_3$ (sat^{d}). The organic phase was washed with aqueous $NaHCO_3$ (sat^{d}), water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 3:1) afforded methyl ester **16** as a colourless oil (5.61 g, 60%), in admixture with its regioisomer (15%): ^{1}H NMR (200 MHz, $CDCl_3$) d 6.78 (m, 1H, C=CH), 3.92 (s, 4H, OCH_2CH_2O), 3.66 (s, 3H, CH_3), 2.45 (m, 2H, CH_2), 2.36 (m, 2H, CH_2), 1.52 (t, 2H, CH_2) and for the regioisomer d 7.02 (m, 1H, C=CH) .

4-Hydroxymethylcyclohex-3-ene-1-one 1-Ethylene Ketal (17). A solution of ester **16** (1.0 g, 5.05 mmol), contaminated with the regioisomeric cycloaddition product, in THF (10 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (200 mg, 5.26 mmol) in THF (60 ml) at 0°C, under argon. After 1 h, water (0.2 ml), 15% aqueous NaOH (0.2 ml) and water (0.6 ml) were added successively, and stirring was continued for 20 min. The mixture was then filtered through celite and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 1:2) provided alcohol **17** as a colourless syrup (642 mg, 77%): IR (neat) 3425, 2931, 2894, 1119, 1062, 950, 856 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) d 5.60 (bs, 1H, C=CH), 4.06 (s, 2H, CH_2OH), 4.00 (s, 4H, OCH_2CH_2O), 2.29 (m, 5H, $2CH_2$ and OH), 1.75 (t, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) d 137.2, 119.5, 108.1, 66.2, 64.2, 35.3, 30.7, 24.7; MS (CI, isobutene) *m/z* 171 (M+1), 153 (M+1-H_2O); Analysis calc'd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.48; H, 8.34.

4-Benzoyloxymethylcyclohex-3-ene-1-one 1-Ethylene Ketal (R = COPh, 18). Benzoyl chloride (1.0 ml, 8.6 mmol) was added with stirring to a solution of alcohol **17** (1.0 g, 5.9 mmol) in pyridine (20 ml) at 0°C. After continued stirring for 1 h, the solution was left overnight at 4°C. Aqueous $NaHCO_3$ (sat^{d}) was then added followed by stirring for 1 h., and extraction with ether. The organic phase was washed with 1N AcOH, water and aqueous $NaHCO_3$ (sat^{d}), dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash

chromatography (Heptane: EtOAc, 3:1) afforded benzoate **18** as a colourless syrup (1.56 g, 97%): IR (neat) 2953, 2934, 2881, 1723, 1448, 1310, 1278, 1115, 1062, 1016, 859 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 8.09 (d, 2H, Ph), 7.60 (t, 1H, Ph), 7.44 (t, 2H, Ph), 5.70 (bs, 1H, C=CH), 4.75 (s, 2H, CH_2OBz), 4.00 (s, 4H, OCH_2CH_2O), 2.35 (m, 4H, $2CH_2$), 1.85 (t, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) d 167.3, 133.9, 133.6, 131.3, 130.7, 129.3, 124.1, 108.8, 69.0, 65.4; 39.5, 31.8, 26.2; MS (CI, isobutene) *m/z* 275 (M+1), 229 (M+1-CH_3CH_2OH), 153 (M+1-PhCOOH); Analysis calc'd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.68; H, 6.71.

4-Benzoyloxymethylcyclohex-3-ene-1-one (27). Aqueous trifluoroacetic acid (35%; 37 ml) was added to a solution of ketal **18** (1.50 g, 5.47 mmol) in $CHCl_3$ (50 ml) and the two phase mixture was vigorously stirred until the starting material was consumed (approx. 36 h). The organic phase was then washed several times with water, dried (Na_2SO_4) and evaporated *in vacuo* affording crude ketone **27** (1.21g, 96%): IR (neat) 1718, 1924, 1112 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 8.02 (d, 2H, Ph), 7.57 (t, 1H, Ph), 7.42 (t, 2H, Ph), 5.87 (bs, 1H, C=CH), 4.79 (s, 2H, CH_2OBz), 2.92 (bs, 2H, CH_2), 2.54 (bs, 4H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) d 209.3, 166.2, 133.6, 133.2, 130.0, 129.6, 128.5, 122.6, 67.39, 39.31, 38.14, 26.13; MS (CI, isobutene) *m/z* 231 (M+1), 109 (M+1-PhCOOH). Ketone **27** decomposed slowly on standing and hence was immediately used in the subsequent reactions.

1-Benzoyloxymethyl-4-ethynyl-4-hydroxycyclohex-1-ene (28). *n*-BuLi (21.0 ml, 27.0 mmol) in hexanes was added to a stirred solution of TMS acetylene (3.80 ml, 26.6 mmol) in THF (60 ml) at -78°C under Ar. After stirring for 5 min, the solution was transferred to a precooled suspension of $CeCl_3$ (29.2 mmol)[23] in THF (75 ml) at -78°C. The resulting orange suspension was stirred for 30 min, afterwhich a solution of ketone **27** (4.53 g, 19.7 mmol) in THF (30 ml) was injected. Stirring was continued for 3 h, then aqueous NH_4Cl (sat^d) and ether were added. The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane: EtOAc, 3:1) afforded 5.60 g (88% yield) of the TMS alkyne as a colourless oil: ^1H NMR (250 MHz, $CDCl_3$) d 8.06 (d, 2H, Ph), 7.61-7.32 (m, 3H, Ph), 5.74 (bs, 1H, C=CH), 4.75 (s, 2H, CH_2OBz), 2.70-2.13 (m, 5H, $2CH_2$, OH), 2.07-1.80 (m, 2H, CH_2), 0.17 (s, 9H, Me_3Si).

A solution of the derived alkyne (1.11 g, 3.39 mmol) in THF (60 ml) containing TBAF:$3H_2O$ (1.18 g, 3.75 mmol) was stirred at 0°C for 2 h. Ether and water were then added and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 2:1) afforded **28** as a colourless syrup (823 mg, 95% yield): IR (neat) 3450, 3284, 2926, 1718, 1448, 1306, 1266, 1172, 1104, 1077, 1037, 713 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) d 8.04 (d, 2H, Ph), 7.66-7.28 (m, 3H, Ph), 5.70 (bs, 1H, C=CH), 4.72 (s, 2H, CH_2OBz), 2.76-1.72 (m, 8H, $3CH_2$, OH, CCH); ^{13}C NMR (50 MHz, $CDCl_3$) d 166.5, 133.1, 132.7, 129.7, 128.5, 121.7, 87.3, 71.5, 68.1, 66.0, 39.6, 35.3, 24.1; MS (CI, isobutene) *m/z* 257 (M+1), 239 (M+1-H_2O), 135 (M+1-BzOH), 117 (M+1-BzOH-H_2O); Anal. Calc'd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.93; H, 6.07.

4-(*t*-Butyldimethylsilyloxy)-4-ethynyl-1-hydroxymethylcyclohex-1-ene (30). A solution of alcohol **28** (1.90 g, 7.42 mmol), TBSOTf (2.6 ml, 11.1 mmol) and TEA (2.0 ml, 14.8 mmol) in CH_2Cl_2 (60 ml) was stirred at 0°C for 2 h. Water was added, and the organic phase was washed with water several times, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 15:1)

afforded the TBS ether (2.49 g, 89%) as a colourless oil: ^{1}H NMR (250 MHz, CDCl3) d 8.05 (d, 2H, J = 8.2 Hz, Ph), 7.57 (t, 1H, J = 7.3 Hz, Ph), 7.46 (t, 2H, J = 7.1 Hz, Ph), 5.70 (bs, 1H, C=CH), 4.76 (s, 2H, CH_2OBz), 2.66-2.17 (m, 4H), 2.45 (s, 1H, CC-H), 1.98 (m, 2H), 0.88 (s, 9H, *t*-Bu), 0.22 (s, 6H, Me_2Si); HRMS (EI) calc'd for $C_{20}H_{30}O_3Si$ 313.1260, found 313.1211.

The residue was redissolved in CH_2Cl_2 (100 ml), cooled to -78°C with stirring, and treated with DIBAL-H (14 ml, 14.0 mmol) in hexanes. After stirring for 20 min, water was added and the organic phase was washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 3:1) afforded **30** (1.42 g; 77% overall yield) as a colourless syrup: IR (neat) 3350, 3310, 2956, 2929, 2897, 2867, 1473, 1252, 1102, 1091, 1030, 1006, 837, 777 cm^{-1}; ^{1}H NMR (250 MHz, CDCl3) d 5.53 (bs, 1H, C=CH), 4.02 (s, 2H, CH_2O), 2.49-2.14 (m, 4H, $2CH_2$), 2.43 (s, 1H, CCH), 1.89 (m, 2H, CH_2), 1.50 (s, 1H, OH), 0.86 (s, 9H, *t*-Bu), 0.19 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, CDCl3) d 137.1, 121.9, 118.8, 87.9, 72.0, 67.3, 66.7, 41.0, 36.7, 25.8, 23.9, 18.1, -2.9; MS (CI, isobutene) *m/z* 267 (M+1), 249 (M+1-H_2O) 173 (M+1-TBSOH-H_2O+isobutene), 135 (M+1-TBSOH), 117 (M+1-TBSOH-H_2O): Analysis calc'd for $C_{15}H_{26}O_2$: C, 67.61; H, 9.83. Found: C, 67.64; H, 9.90.

4-(*t*-Butyldimethylsilyloxy)-4-[(Z)-7-(*t*-butyldimethylsilyloxy)hept-3-ene-1,5-diynyl]-1-hydroxymethylcyclohex-1-ene (31). $Pd(OAc)_2$ (48 mg, 0.22 mmol) and PPh_3 (282 mg, 1.08 mmol) were quickly added to a stirred degassed solution of *cis*-1,2-dichloroethylene (1.5 ml, 19.9 mmol) in benzene (10 ml) under Ar. After stirring for 30 min, alkyne **30** (1.12 g, 4.21 mmol)) in degassed benzene (3 ml) was injected followed by addition of *n*-butylamine (1.2 ml, 12.3 mmol) and CuI (165 mg, 0.87 mmol). After stirring for 12 h, the dark coloured reaction was quenched with aqueous NH_4Cl (sat^d) and stirring was continued for an additional 10 min. Ether was then added, and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 3:1) afforded the vinyl chloride as a light yellow oil (1.08 g, 78% yield): ^{1}H NMR (250 MHz, CDCl3) d 6.29 (d, 1H, HC=CH), 5.83 (d, 1H, HC=CH), 5.47 (bs, 1H, C=CH), 3.95 (s, 2H, $C{=}CCH_2O$), 2.58-2.07 (m, 5H, $2CH_2$, OH), 1.98-1.74 (m, 2H), 0.83 (s, 9H, *t*-Bu), 0.15 (s, 6H, Me_2Si).

The second coupling reaction was carried out in an identical manner: vinyl chloride (1.08 g, 3.31 mmol) in benzene (12 ml), TBS protected propargylic alcohol (2.81 g, 12.8 mmol), $Pd(OAc)_2$ (58 mg, 0.25 mmol), PPh_3 (327 mg, 1.27 mmol), *n*-butylamine (1.4 ml, 14.3 mmol) and CuI (192 mg, 1.01 mmol). Flash chromatography (Heptane:EtOAc, 4:1) afforded **31** as a colourless oil (1.13 g, 75% yield): IR (neat) 2956, 2929, 2896, 2858, 1473, 1463, 1361, 1254, 1147, 1088, 1030, 1006, 837, 814, 778 cm^{-1}; ^{1}H NMR (200 MHz, CDCl3) d 5.78 (s, 2H, HC=CH), 5.48 (bs, 1H, C=CH), 4.46 (s, 2H, $CCCH_2O$), 3.97 (s, 2H, $C{=}CCH_2O$), 2.62-2.07 (m, 4H, $2CH_2$), 1.91 (m, 2H, CH_2), 1.72 (bs, 1H, OH), 0.92 (s, 9H, *t*-Bu), 0.86 (s, 9H, *t*-Bu), 0.31 (s, 6H, Me_2Si), 0.24 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, CDCl3) d 137.2, 119.4, 119.0, 118.9, 101.0, 95.2, 82.3, 81.4, 68.0, 67.0, 52.4, 41.1, 36.8, 26.0, 25.9, 24.1, 18.4, 18.2, -2.8, -5.0; MS (EI) *m/z* 403 (M-*t*-Bu), 346 (M-2*t*-Bu); HRMS (EI) calc'd for $C_{20}H_{28}O_2Si$ 460.2829, found 460.2851.

1-Bromomethyl-4-(*t*-butyldimethylsilyloxy)-4-[(Z)-7-hydroxyhept-3-ene-1,5-diynyl]cyclohex-1-ene (32). Mesyl chloride (0.13 ml, 4.0 mmol) was added to a stirred solution of alcohol **31** (1.23 g, 2.60 mmol) in CH_2Cl_2 (20 ml) and TEA (0.58 ml, 4.0 mmol) at -40°C. Over a period of 1 h the reaction was warmed to 0°C, then stopped by addition of water. The organic phase was washed with water,

dried (Na_2SO_4) and evaporated to dryness. The crude mesylate was immediately dissolved in acetone (50 ml), and reacted with dry LiBr (900 mg) with stirring at 20°C for 45 min. Pentane and water were then added and the organic phase was washed several times with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 15:1) afforded the bromide product as a colourless oil (1.28 g, 92% yield); ^1H NMR (200 MHz, $CDCl_3$) d 5.82 (s, 2H, HC=CH), 5.71 (bs, 1H, C=CH), 4.49 (s, 2H, CH_2O), 3.96 (s, 2H, CH_2Br), 2.64-2.17 (m, 4H), 2.06-1.84 (m, 2H), 0.95 (s, 9H, *t*-Bu), 0.85 (s, 9H, *t*-Bu), 0.27 (s, 6H, Me_2Si), 0.17 (s, 6H, Me_2Si).

To a solution of he bromide (1.06 g, 2.03 mmol) in THF (120 ml) at -78°C was added 1M TBAF (2.10 ml, 2.10 mmol) in THF. The temperature of the solution was raised over a period of 1 h to -20°C and stirring was continued for an additional 10 min. Water and ether were added, and the organic phase was washed several times with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Hexane:EtOAc, 3:1) afforded 735 mg (89% yield) of the bromoalcohol **32** as a colourless syrup: IR (neat) 3450, 2954, 2929, 2897, 2856, 1472, 1251, 1091, 1023, 1007, 838, 778 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.84 (s, 2H, HC=CH), 5.72 (bs, 1H, C=CH), 4.44 (s, 2H, $CCCH_2O$), 3.96 (s, 2H, CH_2Br), 2.62-2.24 (m, 4H, $2CH_2$), 1.95 (m, 2H, CH_2), 1.78 (bs, 1H, OH), 0.86 (s, 9H, *t*-Bu), 0.21 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 134.2, 124.2, 119.7, 118.8, 100.9, 94.7, 83.1, 81.4, 67.4, 51.7, 41.4, 38.3, 36.7, 25.8, 24.7, 18.1, -2.9; MS (CI, isobutene) *m/z* 409, 411 (M+1), 391, 393 (M+1-H_2O), 329 (M+1-HBr), 277, 279 (M+1-TBSOH), 259, 261 (M+1-TBSOH-H_2O), 197 (M+1-TBSOH-HBr), 179 (M+1-TBSOH-HBr-H_2O), 133 ($TBSOH_2$); HRMS (EI) calc'd for $C_{20}H_{28}O_2Si$ 351.0416, found 351.0383.

1-(*t*-Butyldimethylsilyloxy)-9-oxabicyclo[9.2.2]pentadeca-4,11-diene-2,6-diyne (8) and Dimer 33. NaH (100 mg, 2.1 mmol, 50% dispersion in oil) was added to a stirred solution of bromoalcohol **32** (201 mg, 0.49 mmol) in THF (600 ml) containing approx. 0.05 M H_2O at 20°C. After 16 h, an additional portion of NaH (60 mg, 1.3 mmol) was added and stirring was continued for 6 h. Hexane and water were then added and the organic phase was washed exhaustively with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Hexane:EtOAc, 30:1) afforded cyclic ether **8** (109 mg, 68% yield) as a colourless syrup: IR (neat) 2956, 2930, 2857, 1252, 1105, 838, 777, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.83 (d, 1H, J = 10.5 Hz, HC=CH), 5.78 (dd, 1H, J = 10.5, 2.1 Hz, HC=CH), 5.55 (m, 1H, C=CH), 4.63 (dd, 1H, J = 17.3, 2.1 Hz, $CCCH_2O$), 4.34 (dd, 1H, J = 13.0, 2.0 Hz, $C{=}CCH_2O$), 4.04 (d, 1H, J = 17.3 Hz, $CCCH_2O$), 3.76 (d, 1H, J = 13.0 Hz, $C{=}CCH_2O$), 2.85 (m, 1H), 2.60 (bd, 1H, J = 16.8 Hz), 2.31 (bd, 1H, J = 16.8 Hz), 2.12 (dd, 1H, J = 17.7, 5.4 Hz), 1.98 (dd, 1H, J = 12.1, 5.9 Hz), 1.75 (ddd, 1H, J = 12.3, 12.1, 5.4 Hz), 0.87 (s, 9H, *t*-Bu), 0.19 (6H, s, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 135.6, 122.0, 120.3, 119.8, 100.4, 94.8, 83.2, 79.4, 68.6, 59.9, 42.5, 36.1, 27.0, 25.9, 18.1, -2.6, -2.7; MS (EI) *m/z* 328 (M), 271 (M-*t*-Bu); HRMS (EI) calc'd for $C_{20}H_{28}O_2Si$ 328.1859, found 328.1877.

Further elution of the column gave dimer **33** as a colourless solid (16 mg, 10% yield): IR (KBr) 2957, 2928, 2857, 1252, 1105, 1076, 1012 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) d 5.82 (s, 4H, 2HC=CH), 5.56 (bs, 2H, 2C=CH), 4.26 (s, 4H, $2CCCH_2O$), 3.98 (s, 4H, $2C{=}CCH_2O$), 2.64-2.11 (m, 8H), 1.91 (m, 4H), 0.85 (s, 18H, 2-Bu), 0.17 (s, 12H, $2Me_2Si$); ^{13}C NMR (50 MHz, $CDCl_3$) d 133.8, 133.6, 122.1, 121.8, 120.0, 119.9, 119.2, 101.5, 93.0, 83.3, 81.5, 73.5, 67.8, 57.3, 57.1, 41.2, 36.8, 25.9, 24.0, 18.2, -2.9; MS (CI, isobutene) *m/z* 657 (M+1), 625 (M+1-TBSOH), 393 (M+1-2TBSOH); HRMS (EI) calc'd for $C_{40}H_{56}O_4Si_2$ 656.3717, found 656.3680, calc'd for $C_{40}H_{56}O_4Si_2$ - *t*-Bu 599.3013, found 599.3025.

[1,2] Wittig Product 34 and Ketone 35. To a stirred solution of ether **8** (50 mg, 0.15 mmol) in THF (2 ml) at -25°C under Ar, was added 0.65 ml of a 0.5 M solution of LiTMP (0.33 mmol) in THF/Hexanes. Stirring was continued for 1 min, afterwhich aqueous NH_4Cl (sat^d) and ether were added. The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 6:1) afforded a 1.5:1 epimeric mixture of **34** (20 mg, 40% yield, colourless oil) based on the integration of the C_{11}-protons at d 5.33 and 5.48 ppm, resp., of the ^1H NMR (400 MHz) spectrum: IR (neat) 3352, 2953, 2934, 2894, 2855, 1474, 1278, 1252, 1141, 1108, 1043, 886, 840, 774 cm^{-1}; MS (CI, isobutene) *m/z* 329 (M+1), 311 (M+1-H_2O), 197 (M+1-TBSOH), 179 (M+1-TBSOH-H_2O), 133 ($TBSOH_2$). The [1,2]-Wittig rearrangement product **34** was characterized as its corresponding ketone **35**.

Dess-Martin periodinane (26 mg, 0.061 mmol)[29] was added to a stirred solution of the epimers **34** (9 mg, 0.027 mmol) in CH_2Cl_2 (1.0 ml), and stirring was continued for 20 min. Ether and aqueous $NaHCO_3$ containing $Na_2S_2O_3$ was added, and after stirring vigorously for 10 min the organic phase was separated and then washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Hexane:EtOAc, 30:1) afforded ketone **35** as colourless solid (7 mg, 78%): IR (KBr) 2960, 2927, 2901, 2855, 2175, 1658, 1251, 1239, 1108, 840, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 6.21 (d, 1H, *J* = 10.2 Hz, HC=CH), 5.97 (d, 1H, *J* = 10.2 Hz, HC=CH), 5.54 (bd, 1H, *J* = 5.6 Hz, C=CH), 3.24 (d, 1H, *J* = 17.5 Hz, CH_2CO), 3.05 (dd, 1H, *J* = 17.5, 2.6 Hz, CH_2CO), 2.84 (m, 1H), 2.54 (bd, 1H, *J* = 16.6 Hz), 2.42 (bd, 1H, *J* = 16.6 Hz), 2.10 (dd, 1H, *J* = 18.0, 6.0 Hz), 1.93 (ddd, 1H, *J* = 11.7, 6.6, 2.4 Hz), 1.83 (ddd, 1H, *J* = 11.7, 11.7, 6.0 Hz), 0.88 (s, 9H, *t*-Bu), 0.21 (6H, s, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 187.9, 131.7, 128.4, 125.2, 118.2, 104.3, 93.6, 90.0, 83.4; 68.9, 52.6, 41.8, 35.7, 29.6, 25.8, 18.1, -2.6; MS (CI, isobutene) *m/z* 327 (M+1), 195 (M+1-TBSOH), 133 ($TBSOH_2$); HRMS (EI) calc'd for $C_{20}H_{26}O_2Si$ 326.1703, found 326.1697.

1-Benzoyloxymethyl-4-(hexa-1,5-diynyl)-4-hydroxycyclohex-1-ene (36). *n*-BuLi (20.5 ml, 32.9 mmol) in hexanes was added to a stirred solution of 1,5-hexadiyne (1.07 g, 13.7 mmol) in THF (75 ml) at -78°C under Ar. After stirring for 10 min, the solution was transferred to a precooled suspension of $CeCl_3$ (28.0 mmol)[23] in THF (400 ml) at -78°C and stirring was continued for 30 min. Ketone **27** (1.04 g, 4.56 mmol) in THF (75 ml) was then injected, and after an additional 1.5 h, ether and aqueous NH_4Cl (sat^d) were added, and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Hexane:EtOAc, 3:1) afforded alcohol **36** (729 mg, 52% yield) as a colourless oil: IR (neat) 3450, 3293, 2927, 1717, 1455, 1272, 1108, 1075, 715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) d 8.04 (d, 2H, Ph), 7.55 (t, 1H, Ph), 7.43 (t, 2H, Ph), 5.70 (bs, 1H, C=CH), 4.73 (s, 2H, CH_2O), 2.64-2.17 (m, 8H, $4CH_2$), 2.01 (t, 1H, CCH), 1.95 (m, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) d 166.5, 133.0, 132.6, 129.7, 128.5, 122.1, 84.7, 82.8, 82.0, 69.4, 68.3, 66.4, 39.9, 35.7, 24.4, 18.8; MS (CI, isobutene) *m/z* 309 (M+1), 291 (M+1-H_2O), 187 (M+1-BzOH), 169 (M+1-BzOH-H_2O), 123 ($BzOH_2$); Anal. Calc'd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.57; H, 6.31.

1-Benzoyloxymethyl-4-(*t*-butyldimethylsilyloxy)-4-(hexa-1,5-diynyl)cyclo-hex-1-ene (37). A solution of the alcohol **36** (1.53 g, 4.97 mmol), TBSOTf (1.74 ml, 7.44 mmol) and TEA (1.34 ml, 9.92 mmol) in CH_2Cl_2 (40 ml) was stirred at 0°C for 2 h. Water was then added, and the organic phase was

washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 20:1) afforded TBS ether **37** (1.88 g, 90% yield) as a colourless oil: IR (neat) 3306, 2960, 2927, 2855, 1723, 1265, 1102, 833 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) d 8.06 (d, 2H, Ph), 7.58 (t, 1H, Ph), 7.44 (t, 2H, Ph), 5.66 (bs, 1H, C=CH), 4.71 (s, 2H, CH_2O), 2.56-2.15 (m, 8H, $4CH_2$), 2.02 (t, 1H, CCH), 1.88 (m, 2H, CH_2) 0.85 (s, 9H, *t*-Bu), 0.19 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 167.2, 133.0, 132.6, 129.8, 129.4, 122.9, 85.4, 82.8, 82.3, 69.4, 68.8, 67.0, 41.3, 36.9, 25.9, 24.5, 19.0, 18.9, 18.8, 18.2, -2.8; MS (CI, isobutene) *m/z* 423 (M+1), 301 (M+1-BzOH), 291 (M+1-TBSOH), 169 (M+1-TBSOH-BzOH), 133 ($TBSOH_2$), 123 ($BzOH_2$); Anal. Calc'd for $C_{26}H_{34}O_3Si$: C, 73.89; H, 8.11. Found: C, 74.03; H, 8.06.

4-(*t*-Butyldimethylsilyloxy)-4-(hexa-1,5-diynyl)-1-hydroxymethylcyclohex-1-ene (38). DIBAL-H (9.2 ml, 9.2 mmol) in hexanes was injected into a stirred solution of the benzoate **37** (1.82 g, 4.31 mmol) in CH_2Cl_2 (70 ml) at -78°C. After 20 min, water was added and the organic phase was washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 3:1) afforded **38** (1.11 g; 81% yield) as a colourless syrup: IR (neat) 3450, 3306, 2960, 2934, 2901, 2855, 1474, 1252, 1095, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) d 5.48 (bs, 1H, C=CH), 3.98 (s, 2H, CH_2O), 2.52-2.26 (m, 6H, $3CH_2$), 2.18 (m, 2H, CH_2), 2.00 (t, 1H, CCH), 1.83 (m, 2H, CH_2), 1.57 (s, 1H, OH), 0.84 (s, 9H, *t*-Bu), 0.16 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 137.1, 119.4, 85.5, 82.9, 82.0, 69.4, 67.4, 67.0, 41.4, 37.0, 25.9, 24.2, 19.0, 18.8, 18.2, -2.8; MS (CI, isobutene) *m/z* 319 (M+1), 301 (M+1-H_2O), 187 (M+1-TBSOH), 169 (M+1-TBSOH-H_2O); Anal. Calc'd for $C_{19}H_{30}O_2Si$: C, 71.64; H, 9.49. Found: C, 71.95; H, 9.50.

4-(*t*-Butyldimethylsilyloxy)-1-chloromethyl-4-(hexa-1,5-diynyl)cyclohex-1-ene (39). A solution of allylic alcohol **38** (895 mg, 2.81 mmol) in 2,6-lutidine (0.86 ml, 7.4 mmol) was added to a stirred precooled solution of LiCl (250 mg, 5.90 mmol) in DMF (9 ml) at 0°C. After 45 min, mesyl chloride (0.40 ml, 4.87 mmol) was added and stirring was continued for 2 1/2 h. Pentane and water were then added, and the organic phase was washed several times with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 40:1) afforded chloride **39** (803 mg; 85% yield) as a colourless oil: IR (neat) 3311, 2954, 2929, 2898, 2856, 1473, 1251, 1091, 1027, 838, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.63 (bs, 1H, C=CH), 4.01 (s, 2H, CH_2Cl), 2.57-2.14 (m, 8H, $4CH_2$), 2.01 (t, 1H, CCH), 1.87 (m, 2H, CH_2), 0.86 (s, 9H, *t*-Bu), 0.18 (6H, s, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 133.9, 123.9, 85.2, 82.8, 82.3, 69.6, 69.2, 66.9, 49.8, 41.4, 36.9, 25.9, 24.6, 18.9, 18.8, 18.2, -2.8; MS (CI, isobutene) *m/z* 337, 339 (M+1), 301 (M+1-HCl), 205, 207 (M+1-TBSOH), 169 (M+1-TBSOH-HCl); Anal. Calc'd for $C_{19}H_{29}OSiCl$: C, 67.72; H, 6.67; Cl, 10.52. Found: C, 67.64; H, 8.70; Cl, 10.32.

4-(*t*-Butyldimethylsilyloxy)-1-chloromethyl-4-(7-hydroxyhepta-1,5-diynyl)-cyclohex-1-ene (40). *n*-BuLi (4.2 ml, 6.24 mmol) in hexanes was added to a stirred solution of alkyne **39** (1.77 g, 5.27 mmol) in THF (50 ml) at -78°C under Ar. After 30 min, solid paraformaldehyde (400 mg, 13.3 mmol) was added directly to the solution. The cooling bath was removed and stirring was continued for 2 h. Ether and aqueous NH_4Cl (sat^d) were added, and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 3:1) afforded chloroalcohol **40** as a

colourless syrup (1.47 g, 76% yield): IR (neat) 3346, 2960, 2927, 2898, 2855, 1468, 1252, 1095, 1023, 833, 774 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) d 5.63 (bs, 1H, C=CH), 4.25 (s, 2H, CH_2O), 4.01 (s, 2H, CH_2Cl), 2.56-2.13 (m, 8H, $4CH_2$), 1.85 (m, 2H, CH_2), 1.64 (s, 1H, OH), 0.84 (s, 9H, *t*-Bu), 0.16 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 133.9, 123.9, 85.2, 64.8, 82.5, 79.5, 66.9, 51.4, 49.7, 41.5, 36.9, 25.8, 24.4, 19.1, 19.0, 18.2, -2.8; MS (CI, isobutene) *m/z* 367, 369 (M+1), 349, 351 (M+1-H_2O), 331 (M+1-HCl), 235, 237 (M+1-TBSOH), 217, 219 (M+1-TBSOH-H_2O), 199 (M+1-TBSOH-HCl), 181 (M+1-TBSOH-HCl-H_2O); Anal. Calc'd for $C_{20}H_{31}O_2SiCl$: C, 65.45; H, 8.51; Cl, 9.66. Found: C, 65.52; H, 8.32; Cl, 9.63.

1-Bromomethyl-4-(*t*-butyldimethylsilyloxy)-4-(7-hydroxyhepta-1,5-diynyl)-cyclohex-1-ene (41). A solution of the chloroalcohol **40** (1.45 g, 3.96 mmol) and dried LiBr (12.6 g) in acetone (150 ml) was allowed to stir for 48 h at 30°C. Pentane and water were added, and the organic phase was washed several times with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*, affording **41** as a colourless syrup (1.57 g, 96%): IR (neat) 3339, 2953, 2927, 2901, 2855, 1474, 1435, 1252, 1213, 1095, 1023, 840, 774 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.68 (bs, 1H, C=CH), 4.23 (s, 2H, CH_2O), 3.95 (s, 2H, CH_2Br), 2.52-2.14 (m, 8H, $4CH_2$), 1.86 (m, 2H, CH_2), 1.56 (s, 1H, OH), 0.84 (s, 9H, *t*-Bu), 0.17 (6H, s, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 134.1, 124.5, 85.0, 84.8, 82.5, 79.5, 66.8, 51.4, 41.6, 38.6, 36.8, 25.8, 24.8, 19.1, 19.0, 18.1, -2.9; MS (CI, isobutene) *m/z* 411, 413 (M+1), 393, 395 (M+1-H_2O), 331 (M+1-HBr), 313 (M+1-HBr-H_2O), 279, 281 (M+1-TBSOH), 199 (M+1-TBSOH-HBr), 181 (M+1-TBSOH-HBr-H_2O), 133 ($TBSOH_2$).

1-(*t*-Butyldimethylsilyloxy)-9-oxabicyclo[9.2.2]pentadec-11-en-2,6-diyne (42). NaH (600 mg, 12.5 mmol, 50% dispersion in oil) was added to a stirred solution of bromoalcohol **41** (771 mg, 1.88 mmol) in THF (2 l) containing approx. 0.05 M H_2O at 20°C. After 24 h, hexane and water were added, and the organic phase was exhaustively washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Hexane:EtOAc, 30:1) afforded cyclic ether **42** (379 mg, 61% yield) as colourless crystals: m.p. 87-88°C (Hexane); IR (neat) 2953, 2934, 2898, 2855, 1474, 1434, 1252, 1102, 840, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.55 (bs, 1H, C=CH), 4.41 (dd, 1H, *J* = 16.4, 2.0 Hz, $CCCH_2O$), 4.26 (dd, 1H, *J* = 13.2, 2.0 Hz, $C{=}CCH_2O$), 3.82 (d, 1H, *J* = 16.4 Hz, $CCCH_2O$), 3.74 (d, 1H, *J* = 13.2 Hz, $C{=}CCH_2O$), 2.82 (m, 1H), 2.54 (bd, 1H, *J* = 17.0 Hz), 2.49-2.31 (m, 4H), 2.24 (bd, 1H, *J* = 17.0 Hz), 2.07 (dd, 1H, *J* = 17.4, 5.2 Hz), 1.97 (dd, 1H, *J* = 12.4, 6.2 Hz), 1.72 (ddd, 1H, *J* = 12.4, 12.4, 5.8 Hz), 0.87 (s, 9H, *t*-Bu), 0.19 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 136.1, 122.7, 85.2, 84.4, 83.1, 79.7, 79.2, 68.2, 59.2, 42.3, 37.8, 26.9, 25.9, 19.3, 18.5, 18.0, -2.6; MS (EI) *m/z* 330 (M), 315 (M-CH_3), 273 (M-*t*-Bu), 215 (M-TBS); HRMS (EI) calc'd for $C_{20}H_{30}O_2Si$ 330.2016, found 326.2008.

Further elution of the column gave the corresponding dimer as a colourless solid (16 mg, 10% yield): IR (KBr) 2956, 2931, 2856, 1256, 1106, 887, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.53 (bs, 2H, 2C=CH), 4.12 (d, 1H, *J* = 14.3 Hz), 4.11 (d, 1H, *J* = 15.8 Hz), 4.03 (d, 2H, *J* = 12.0 Hz), 3.96 (d, 1H, *J* = 15.8 Hz), 3.91 (d, 1H, *J* = 14.6 Hz), 3.83 (d, 1H, *J* = 14.3 Hz), 3.80 (d, 1H, *J* = 14.6 Hz), 2.51-2.22 (m, 14H), 2.12 (m, 2H), 1.88 (m, 2H), 1.77 (m, 2H), 0.88 (s, 18H, 2-*t*-Bu), 0.18 (s, 12H, $2Me_2Si$); ^{13}C NMR (50 MHz, $CDCl_3$) d 133.7, 133.6, 123.5, 123.3, 85.1, 84.8, 82.6, 77.4, 74.0, 73.7, 67.9, 67.8, 56.4, 56.2, 41.7, 37.2, 25.4, 25.2, 19.3, 19.0, 18.1, -2.7; MS (CI, isobutene) *m/z* 661 (M+1), 529 (M+1-TBSOH), 397 (M+1-2TBSOH); HRMS (EI) calc'd for $C_{40}H_{60}O_4Si_2$ 660.4030, found 660.4053; calc'd for $C_{40}H_{60}O_4Si_2$ - *t*-Bu 603.3326, found 603.3320.

1-(*t*-Butyldimethylsilyloxy)-10-ethylidene-8-hydroxybicyclo[7.3.1]trideca-2,6-diyne (43). *n*-BuLi (3.33 ml, 5.0 mmol) in hexanes was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.85 ml, 5.0 mmol) in THF (6.7 ml) at 0°C, and stirring was continued for 30 min. To a stirred solution of ether **42** (120 mg, 0.36 mmol) in THF (4 ml) at -25°C under Ar, was added 1.3 ml of the 0.5 M solution of LiTMP (0.65 mmol). Stirring was continued for 5 min, afterwhich aqueous NH_4Cl (sat[d]) and ether were added. The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 10:1) afforded **43** (86 mg, 72% yield) as a colourless syrup: IR (neat) 3450, 3100, 2957, 2927, 2898, 2855, 1645, 1463, 1252, 1091, 839, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.04 (bs, 1H, C=CH_2), 4.84 (bs, 1H, C=CH_2), 4.37 (m, 1H, CHOH), 2.83 (dd, 1H, *J* = 10.0, 4.7 Hz), 2.76 (bt, 1H, *J* = 12.8 Hz), 2.55-2.31 (m, 5H), 2.30-2.21 (m, 2H), 2.08 (dd, 1H, *J* = 14.5, 9.8 Hz), 2.06 (m, 1H), 1.60 (ddd, 1H, *J* = 14.5, 12.2, 3.0 Hz), 0.87 (s, 9H, *t*-Bu), 0.19 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 145.3, 114.4, 91.3, 86.6, 85.8, 83.9, 67.9, 64.4, 48.5, 43.7, 42.7, 31.5, 25.9, 19.3, 18.9, 18.0, -2.6; MS (EI) *m/z* 330 (M), 315 (M-CH_3), 273 (M-*t*-Bu); HRMS (EI) calc'd for $C_{20}H_{30}O_2Si$ 330.2016, found 326.2014.

Treatment of 42 with Excess Lithium 2,2,6,6-Tetramethylpiperidide: Formation on Allene 46. Treatment of **42** with a five fold excess of LiTMP furnished a 1.5:1 mixture of **43** and **46** in 42% yield. Benzoylation (BzCl/pyridine, 0°C), the two products permitted their separation by flash chromatography (Hexane:EtOAc, 30:1). The less polar fraction contained benzoylated **46**: IR (KBr) 2953, 2927, 2855, 1703, 1278, 1252, 1108, 833, 774, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 8.05 (d, 2H, Ph), 7.57 (t, 1H, Ph), 7.45 (t, 2H, Ph), 5.54 (m, 1H, CHOBz), 5.34 (m, 2H, HC=C=CH), 5.02 (bs, 1H, C=CH_2), 4.96 (bs, 1H, C=CH_2), 3.01 (bd, 1H, *J* = 8.6 Hz), 2.96 (dd, 1H, *J* = 4.5, 3.5 Hz), 2.94 (dd, 1H, *J* = 4.4, 3.5 Hz), 2.66 (bt, 1H, *J* = 14.3 Hz), 2.33 (bd, 1H, *J* = 14.1 Hz), 2.06 (dd, 1H, *J* = 14.3, 8.6 Hz), 2.05 (m, 1H), 1.55 (ddd, 1H, *J* = 14.4, 12.2, 3.5 Hz), 0.87 (s, 9H, *t*-Bu), 0.18 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 205.4, 165.5, 145.0, 133.0, 130.9, 129.7, 128.5, 113.9, 94.8, 89.3, 89.0, 84.1, 80.4, 67.9, 48.4, 46.7, 41.5, 32.2, 25.9, 19.9, 18.1, -2.6; MS (CI, isobutene) *m/z* 435 (M+1), 313 (M+1-BzOH), 303 (M+1-TBSOH), 181 (M+1-TBSOH-BzOH), 133 ($TBSOH_2$), 123 ($BzOH_2$); HRMS (EI) calc'd for $C_{27}H_{34}O_3Si$ 434.2277, found 434.2290.

Further elution of the column (Hexane:EtOAc, 20:1) afforded benzoylated **43** as a colourless syrup which crystallized from hexane: m.p. 95-97°C; IR (neat) 3071, 2953, 2927, 2894, 2855, 1723, 1645, 1455, 1304, 1265, 1088, 840, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 8.07 (d, 2H, *J* = 8.0 Hz, Ph), 7.57 (t, 1H, *J* = 8.0 Hz, Ph), 7.44 (t, 2H, *J* = 8.0 Hz, Ph), 5.72 (bs, 1H, CHOBz), 5.08 (bs, 1H, C=CH_2), 4.87 (bs, 1H, C=CH_2), 3.05 (dd, 1H, *J* = 9.8, 3.9 Hz), 2.89 (bt, 1H, *J* = 14.0 Hz), 2.61-2.44 (m, 2H), 2.43-2.27 (m, 4H), 2.11 (dd, 1H, *J* = 14.6, 10.1 Hz), 2.08 (m, 1H), 1.61 (ddd, 1H, *J* = 14.9, 12.3, 3.0 Hz), 0.87 (s, 9H, *t*-Bu), 0.23 (s, 3H, MeSi), 0.21 (s, 3H, MeSi); ^{13}C NMR (50 MHz, $CDCl_3$) d 165.5, 144.4, 133.2, 130.3, 130.0, 128.5, 114.7, 91.2, 86.0, 85.8, 83.1, 68.0, 67.8, 45.7, 43.9, 42.9, 31.6, 25.9, 19.5, 18.9, 18.2, -2.6; MS (CI, isobutene) *m/z* 435 (M+1), 313 (M+1-BzOH), 303 (M+1-TBSOH), 181 (M+1-TBSOH-BzOH), 133 ($TBSOH_2$), 123 ($BzOH_2$); HRMS (EI) calc'd for $C_{27}H_{34}O_3Si$ 434.2277, found 434.2286.

Treatment of 42 with *n*-BuLi. *n*-BuLi (0.20 ml, 0.26 mmol) in hexanes was added to a stirred solution of **42** (39 mg, 0.12 mmol) in heptane (1.4 ml) and THF (0.2 ml) at -78°C under Ar. After stirring for 2 h, aqueous NH_4Cl (sat^d) and ether were added, and the organic phase was washed several times with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Hexane:EtOAc, 10:1) afforded unreacted cyclic ether **42** (10 mg), and the more polar [2,3]-Wittig rearrangement product **43** (4 mg, 10% yield), both as colourless syrups . Further elution (Hexane:EtOAc, 3:1) afforded aldehyde **45** as a colourless oil (6 mg, 15% yield): IR (neat) 3450, 2957, 2931, 2898, 2864, 1696, 1636, 1463, 1257, 1091, 839; 779 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 9.50 (d, 1H, *J* = 8.0 Hz, CHO), 6.87 (ddd, 1H, *J* = 15.9, 6.0, 6.0 Hz, HC=CCHO), 6.18 (ddd, 1H, *J* = 15.9, 8.0, 1.1 Hz, C=CHCHO), 5.49 (bs, 1H, C=CH), 2.62-2.36 (m, 6H, $3CH_2$), 2.34 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 1.82 (m, 2H, CH_2), 1.72 (bs, 1H, OH), 0.84 (s, 9H, *t*-Bu), 0.17 (s, 6H, Me_2Si); ^{13}C NMR (50 MHz, $CDCl_3$) d 194.1, 156.2, 137.1, 133.9, 119.1, 86.0, 81.8, 67.6, 66.9, 41.4, 37.0, 31.7, 25.8, 24.3, 18.2, 17.6, -2.6; MS (CI, isobutene) *m/z* 349 (M+1), 331 (M+1-H_2O), 217 (M-*t*-Bu), 215 (M+1-TBSOH), 199 (M+1-TBSOH-H_2O); HRMS (EI) calc'd for $C_{20}H_{32}O_3Si$ - *t*-Bu 291.1416, found 291.1399.

4-*t*-Butyldimethylsilyloxy-1-chloromethyl-4-ethynylcyclohex-1-ene (49). Allylic alcohol **30** (1.0 g, 3.76 mmol) in 2,6-lutidine (1.15 ml, 9.87 mmol) was added to a stirred precooled (0°C) solution of LiCl (334 mg, 7.90 mmol) in DMF (12 ml). After 45 min, mesyl chloride (0.50 ml, 6.02 mmol) was added and the mixture was stirred for 2.5 h. Pentane and water were then added and the organic phase was washed several times with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 50:1) afforded chloride **49** as a colorless oil (818 mg; 79%): IR (neat) 3306, 2953, 2933, 2855, 1474, 1258, 1094, 837, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.62 (s, 1H, C=CH), 4.00 (s, 2H, CH_2Cl), 2.45 (s, 1H, CC-H), 2.39 (m, 4H, 2 CH_2), 1.90 (t, 2H, CH_2), 0.84 (s, 9H, *t*-Bu), 0.20 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) d 134.00, 123.48, 87.69, 72.28, 66.76, 49.48, 41.12, 36.57, 25.81, 24.19, 18.18, -2.87; MS (CI, isobutene) *m/z* 249 (M+1-HCl), 153-155 (M+1-TBDMSOH), 133 ($TBDMSOH_2^+$), 117 (M+1-HCl-TBDMSOH); Analysis calc'd for $C_{15}H_{25}OSiCl$: C, 63.24; H, 8.84; Cl, 12.44. Found: C, 63.54; H, 8.90; Cl, 12.42.

4-*t*-Butyldimethylsilyloxy-1-chloromethyl-4-(3-hydroxy-1,5-hexadiynyl)-cyclohex-1-ene (51). *n*-Butyl lithium (0.44 ml, 0.70 mmol) in hexane was added to a stirred solution of alkyne **49** (200 mg, 0.70 mmol) in THF (4 ml) at -78°C under Ar. After stirring for 15 min, DMF (0.54 ml, 7.03 mmol) was and stirring was continued for 3 h at -78°C. The reaction was quenched with aq. NH_4Cl (sat^d) and extracted with ether. The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 20:1) afforded propargylic aldehyde **50** (818 mg; 74%) plus starting material (27 mg). Aldehyde **50** was directly used in the subsequent step: IR (neat) 2954, 2930, 2900, 2857, 1676, 1257, 1104, 839, 779, 686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 9.24 (s, 1H, CHO), 5.66 (s, 1H, C=CH), 4.01 (s, 2H, CH_2Cl), 2.50 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.02 (t, 2H, CH_2), 0.86 (s, 9H, *t*-Bu), 0.20 (s, 6H, $Si(CH_3)_2$); MS (CI, isobutene) *m/z* 313-315 (M+1), 277 (M+1-HCl), 181-183 (M+1-TBDMSOH).

A solution of propargylic bromide (1.3 ml, 11.4 mmol, 80% in toluene) in ether (10 ml) was added dropwise to a stirred suspension of magnesium (1.0 g, 41.1mmol) in ether (23 ml) at 22°C. After heating had

ceased, 10 ml of the etheral solution was transferred to another flask and cooled to -20°C. A solution of the aldehyde **50** (527 mg, 1.68 mmol) in ether (10 ml) was added dropwise to the Grignard reagent, and stirring was continued for 30 min. Ether and aqueous NH_4Cl (sat^d) were then added and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness in vacuo. Flash chromatography (Heptane:EtOAc, 4:1) afforded alcohol **51** (476 mg; 80%): IR (neat) 3391, 3313, 2959, 2933, 2855, 1252, 1095, 838, 779 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.65 (s, 1H, HC=C), 4.57 (s, 1H, OH), 4.01 (s, 2H, CH_2Cl), 2.64 (dt, J = 6, 2 Hz, 2H, CH_2-CC), 2.31 (m, 4H, 2 CH_2), 2.12 (t, J = 2 Hz, 1H, H-CC), 1.90 (t, 2H, CH_2), 0.87 (s, 9H, t-Bu), 0.20 (s, 6H, $(Me)_2Si$); MS (CI, isobutene) *m/z* 335-337 (M+1-H_2O), 317 (M+1-HCl), 221-223 (M+1-TBDMSOH), 203-205 (M+1-TBDMSOH-H_2O), 185 (M+1-TBDMSOH-HCl); Analysis calc'd for: C, 64.65; H, 8.28; Cl, 10.04. Found: C, 64.43; H, 8.34; Cl, 9.94.

4-*t*-Butyldimethylsilyloxy-4-(3-*t*-butyldimethylsilyloxy-1,5-hexadiynyl)-1-chloromethylcyclohex-1-ene (52). TEA (0.37 ml, 2.7 mmol) and *t*-butyldimethylsilyl triflate (0.46 ml, 2.0 mmol) was added to a stirred solution of alcohol **51** (476 mg, 1.35 mmol) in CH_2Cl_2 (12 ml) at 0°C. After stirring for 1h, CH_2Cl_2 was added and the organic phase was washed several times with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 50:1) afforded TBS ether **52** (546 mg, 87% yield): IR (neat) 3312, 2956, 2931, 2897, 2858, 1463, 1257, 1091, 839, 779 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.62 (s, 1H, HC=C), 4.52 (t, J = 6.8 Hz, 1H, HCOTBDMS), 4.00 (s, 2H, CH_2Cl), 2.58 (dd, J = 6.8, 2 Hz, 2H, CH_2-CC), 2.36 (m, 4H, 2 CH_2), 2.10 (t, J = 2 Hz, 1H, CC-H), 1.89 (t, J = 3.5 Hz, 2H, CH_2), 0.91 (s, 9H, t-Bu), 0.85 (s, 9H,t-Bu), 0.20 (s, 6H, $2SiCH_3$), 0.12 (s, 6H, $2SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) d 133.89, 123.72, 80.63, 70.47, 66.82, 62.15, 49.64, 41.15, 36.60, 29.38, 25.85, 24.24, 18.33, 18.19, -2.73, -4.46; MS (CI, isobutene) *m/z* 431 (M+1-HCl), 335 (M+1-TBDMSOH-HCl), 213 (M+1-254), 167 (M+1-HCl-2 TBDMSOH); HRMS (EI) calc'd for $C_{25}H_{43}O_2Si_2Cl$-*t*-Bu 409.1787, found 409.1760.

4-*t*-Butyldimethylsilyloxy-4-(3-*t*-butyldimethylsilyloxy-7-hydroxy-1,5-hepta-diynyl)-1-chloromethylcyclohex-1-ene (53). To a stirred solution of alkyne **52** (546 mg, 1.17 mmol) in THF (9 ml) at -78°C was added dropwise *n*-BuLi (0.80 ml, 1.29 mmol). After stirring for 15 min solid paraformaldehyde (81 mg, 2.70 mmol) was added, and the cooling bath was removed. After an additional 3h stirring, aqueous NH_4Cl (sat^d) and ether were added. The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAC, 4:1) afforded alcohol **53** as a colourless syrup (420 mg, 72% yield): IR (neat) 3369, 2956, 2931, 2894, 2856, 1473, 1463, 1361, 1253, 1094, 837, 781 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.62 (s, 1H, HC=C), 4.50 (t, J = 7.0 Hz, 1H, HCOTBDMS), 4.24 (d, J = 2.0 Hz, 2H, CH_2OH), 4.02 (s, 2H, CH_2Cl), 2.69 (dt, J = 7.0, 2.0 Hz, 2H, CH_2-CC), 2.35 (m, 4H, 2 CH_2), 1.89 (t, J = 6.4 Hz, 2H, CH_2), 1.56 (s, 1H, OH), 0.90 (s, 9H,t-Bu), 0.85 (s, 9H,t-BuSi), 0.20 (s, 6H, $2SiCH_3$), 0.12 (s, 6H, $2SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) d 133.86, 123.61, 88.12, 84.38, 82.57, 80.56, 66.77, 62.19, 51.36, 49.53, 41.12, 36.58, 29.60, 25.79, 24.22, 18.28, 18.11, -1.39, -1.83, -1.94, -2.81; MS (CI, isobutene) *m/z* 497-499 (M+1), 461 (M+1-HCl), 365-367 (M+1-TBDMSOH), 329 (M+1-HCl-TBDMSOH), 233 (M+1-2 TBDMSOH), 197 (M+1-HCl-2 TBDMSOH); Analysis calc'd for $C_{26}H_{45}O_3Si_2Cl$: C, 62.80; H, 9.11; Cl, 7.12. Found: C, 62.86; H, 9.36; Cl, 7.08.

Di-1,4-(*t*-butyldimethylsilyloxy)-9-oxabicyclo[9.2.2]pentadec-11-en-2,6-diyne (11). A solution of chloride **53** (2.09 g, 4.21 mmol) and LiBr (7.31 g, 84.2 mmol) in acetone (200 ml) was stirred for 48h at 30°C. The reaction mixture was partitioned between pentane and water, and the organic phase was washed with water several times, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give the crude bromide **54** (2.11 g, 93% yield). Without purification **54** was immediately used in the next step: ^1H NMR (200 MHz, $CDCl_3$) d 5.70 (s, 1H, HC=C), 4.51 (t, J=6.8 Hz, 1H, HCOTBDMS), 4.27 (d, J=2.0 Hz, 2H, CH_2OH), 3.95 (s, 2H, CH_2Br), 2.60 (dt, J=6.8, 2.0 Hz, 2H, CH_2-CC), 2.32 (m, 4H, 2 CH_2), 1.91 (t, J=6.0 Hz, 2H, CH_2), 1.54 (s, 1H, OH), 0.92 (s, 9H, *t*-BuSi), 0.86 (s, 9H, *t*-BuSi), 0.20 (s, 6H, 2 $SiCH_3$), 0.12 (s, 6H, 2 $SiCH_3$).

Sodium hydride (221 mg, 4.60 mmol, 50% dispersion in oil) was added to a solution of bromoalcohol **54** (162 mg, 0.30 mmol) in THF (430 ml) containing approximately 0.05 M H_2O. The mixture was stirred for 2.5 days after which the reaction mixture was partitioned between water and pentane. The organic phase was exhaustively washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 30:1) afforded **11** as a colourless syrup (128 mg, 93%): IR (neat) 2960, 2933, 2900, 2855, 1468, 1363, 1252, 1108, 839, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.5 (bs, 2H, 2 C=CH), 4.56 (dd, J = 7.0, 5.1 Hz, 1H, CHOTBS), 4.54 (dd, J = 9.7, 5.1 Hz, 1H, CHOTBS), 4.41 (ddd, J = 16.5, 2.4, 2.4 Hz, 1H, CC-CH_2O), 4.40 (dd, J = 16.5, 1.7 Hz, 1H, CC-CH_2O), 4.25 (bd, J = 12.7 Hz, 2H, 2 C=C-CH_2O), 3.86 (ddd, J = 16.5, 2.0, 2.0 Hz, 1H, CC-CH_2O), 3.75 (bd, J = 16.5 Hz, 1H, CC-CH_2O), 3.73 (d, J = 12.7 Hz, 1H, C=C-CH_2O), 3.71 (d, J = 12.7 Hz, 1H, C=C-CH_2O), 2.84 (m, 1H), 2.70 (m, 1H), 2.69-2.44 (m, 6H), 2.29-2.20 (m, 2H), 2.11-1.95 (m, 4H), 1.71 (ddd, J = 12.5, 12.5, 5.6 Hz, 2H), 0.89 (s, 18H, 2*t*-Bu), 0.87 (s, 18H, 2*t*-Bu), 0.22 (s, 3H, $SiCH_3$), 0.21 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) d 136.20, 136.07, 122.64, 122.05, 87.70, 84.64, 84.49, 81.78, 81.48, 80.75, 80.14, 78.98, 68.28, 68.15, 62.53, 62.25, 59.62, 58.95, 42.25, 42.09, 37.75, 37.60, 30.30, 30.09, 27.00, 26.78, 25.89, 18.23, 18.08, -1.18, -1.41, -1.56, -2.47; MS (EI) *m/z* 460 (M), 403 (M-*t*-Bu), 345 (M-*t*-BuSi), 329 (403-$(Me)_2Si0$), 271, 147; HRMS (EI) calc'd for $C_{26}H_{44}O_3Si_2$ - *t*-Bu 403.2124, found 403.2129.

Di-1,4-(*t*-butyldimethylsilyloxy)-10-ethylidene-8-hydroxybicyclo[7.3.1]tri-deca-2,6-diyne (12). To a stirred solution of **11** (465 mg, 1.01 mmol) in THF (16 ml) at -25°C was added 3.23 ml of a preformed 0.5 M solution of LiTMP (1.62 mmol) in THF/Hexanes. Stirring was continued for 5 min afterwhich the reaction was quenched with aqueous NH_4Cl (sat^d) and extracted with ether. The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 8:1) afforded **12** as a colourless syrup (290 mg; 62%): IR (neat) 3293, 2950, 2929, 2857, 1468, 1253, 1125, 1086, 869, 837, 777, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 5.06 (bs, 1H, C=CH), 5.04 (bs, 1H, C=CH), 4.85 (bs, 2H, 2 C=CH), 4.83 (dd, J = 9.2, 7.0 Hz, 1H, CHOTBS), 4.62 (dd, J = 5.4, 2.5 Hz, 1H, CHOTBS), 4.44 (m, 1H, CHOH), 4.30 (m, 1H, CHOH), 2.87- 2.78 (m, 4H), 2.71-2.63 (m, 2H), 2.55 (ddd, J = 15.7, 6.6, 2.0 Hz, 1H), 2.46 (ddd, J = 8.7, 8.7, 3.4 Hz, 1H), 2.43-2.03 (m, 10H), 1.67-1.55 (m, 2H), 0.90 (s, 18H, 2*t*-Bu), 0.86 (s, 9H, *t*-Bu), 0.85 (s, 9H, *t*-Bu), 0.22 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$); ^{13}C NMR (63 MHz, C_6D_6) d 144.69, 114.54, 94.87, 93.50, 87.84, 87.57, 87.48, 86.98, 83.58, 82.62, 68.38, 64.85, 64.67, 64.55, 64.16, 49.06, 48.66, 43.74, 43.66, 43.01, 42.65, 31.98, 31.80, 31.68, 30.82, 26.07, 25.97, 25.93, 18.35, 18.25, -2.22, -2.36, -4.32, -4.57, -4.80, -4.93; MS

(CI, isobutene) *m/z* 461 (M+1), 443 (M+1-H_2O), 329 (M+1-TBDMSOH), 197 (M+1-2 TBDMSOH), 133 ($TBDMSOH_2^+$); HRMS (EI) calc'd for $C_{26}H_{44}O_3Si_2$ 460.2828, found 460.2835.

Di-1,4-(*t*-butyldimethylsilyloxy)-10-ethylidene-8-methoxybicyclo[7.3.1]tri-deca-2,6-diyne (55). Sodium hydride (5 mg, 0.087 mmol, 50% dispersion in oil) and methyl iodide (11 ml, 0.17 mmol) was added to a stirred solution of alcohol **12** (20.0 mg, 0.044 mmol) in THF (1 ml). After stirring for 2 h the THF was removed and the residue was partitioned between pentane and water. The organic phase was washed with water, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAC, 30:1) provided methyl ether **55** as a colourless syrup (20.6 mg, 99% yield): IR (neat) 2956, 2931, 2894, 2856, 1718, 1462, 1362, 1256, 1094, 837 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.0 (bs, 2H, 2 C=CH), 4.85 (dd, *J* = 10.0 Hz, 1H, CHOTBS), 4.83 (bs, 2H, 2 C=CH), 4.63 (dd, *J* = 5.2, 2.6 Hz, 1H, CHOTBS), 4.06 (m, 1H, CHOMe), 3.93 (m, 1H, CHOMe), 3.42 (s, 3H, OMe), 3.38 (s, 3H, OMe), 3.02-1.98 (m, 16H), 1.68-1.48 (m, 2H), 0.91 (s, 18H, 2*t*-Bu), 0.86 (s, 18H, 2*t*-Bu), 0.22 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.19 (s, 6H, $2SiCH_3$), 0.15 (s, 6H, $2SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$); MS (EI) *m/z* 474 (M), 417 (M-*t*-Bu), 343 (417-$(Me)_2SiO$); HRMS (EI) calc'd for $C_{27}H_{46}O_3Si_2$ 474.2985, found 474.2976.

1-(*t*-Butyldimethylsilyloxy)-10-ethylidene-4-hydroxy-8-methoxybicyclo-[7.3.1]trideca-2,6-diyne (56). TBAF:$3H_2O$ (18 mg, 0.057 mmol) was added to a stirred solution of silylether **55** (25.0 mg, 0.052 mmol) in THF (3 ml). After stirring for 20 min at 20°C, ether and water were added, and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Hexane:EtOAc, 3:1) provided **56** as a colourless syrup (16.6 mg, 89% yield): IR (neat) 3409, 2951, 2931, 2898, 2864, 1251, 1125, 1091, 1025, 945, 885, 839, 779 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.02 (bs, 2H, 2C=CH), 4.86 (bs, 2H, 2C=CH), 4.82 (dd, *J* = 8.5, 7.0 Hz, 1H, CHOH), 4.53 (dd, *J* = 4.3, 2.2 Hz, 1H, CHOH), 4.03 (m, 1H, CHOMe), 3.95 (m, 1H, CHOMe), 3.42 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.04-1.83 (m, 18H), 1.68 -1.49 (m, 2H), 0.87 (s, 18H, 2*t*-Bu), 0.20 (s, 12H, $2Si(CH_3)_2$); MS (CI, isobutene) *m/z* 361 (M+1), 343 (M+1-H_2O), 329 (M+1-MeOH), 229 (M+1-TBDMSOH), 133 ($TBDMSOH_2^+$); HRMS (EI) calc'd for $C_{21}H_{32}O_3Si$ 360.2122, found 360.2108.

1-(*t*-Butyldimethylsilyloxy)-10-ethylidene-4-mesyloxy-8-methoxybicyclo-[7.3.1]trideca-2,6-diyne (57). To a stirred solution of alcohol **56** (59 mg, 0.164 mmol) and DMAP (80 mg, 0.66 mmol) in CH_2Cl_2 (6 ml) at -20°C was added mesyl chloride (26 ml, 0.33 mmol). The solution was warmed to 0°C and stirring was continued for 2 h. Ether and water were added, and the organic phase was washed with 1N AcOH, aqueous $NaHCO_3$ (sat^d) and brine, dried (Na_2SO_4) and evaporated to dryness, affording crude mesylate **57** (68 mg): IR (neat) 2953, 2933, 2855, 1370, 1252, 1180, 1088, 951, 901, 840 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 5.54 (dd, *J* = 8.6, 7.2 Hz, 1H, CHOMs), 5.34 (dd, *J* = 4.5, 2.2 Hz, 1H, CHOMs), 5.03 (bs, 2H, 2C=CH), 4.86 (bs, 2H, 2C=CH), 4.05 (bs, 1H, CHOMe), 3.94 (bs, 1H, CHOMe), 3.42 (s, 3H, OMe), 3.38 (s, 3H, OMe), 3.13 (s, 6H, $2SO_2CH_3$), 3.05-2.54 (m, 8H), 2.38-2.01 (m, 8H), 1.71-1.53 (m, 2H), 0.86 (s, 18H, 2*t*-Bu), 0.21 (s, 6H, $2SiCH_3$), 0.20 (s, 6H, $2SiCH_3$).

Elimination and Cycloaromatization of Mesylate 57. Mesylate **57** was dissolved in THF (6 ml) and 1,4-cyclohexadiene (2 ml), and DBU (92 ml, 0.62 mmol) was added. After stirring for one night, complete consumption of the mesylate was observed (TLC analysis). Ether and water were added, and the organic phase was washed with 1N AcOH, aqueous $NaHCO_3$ (sat^d) and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 40:1 and Heptane:EtOAc, 5:1) afforded two fractions. The faster moving fraction was rechromatographed (Heptane:EtOAc, 80:1) giving an inseparable 3:1 mixture of **58** and **59** (9 mg, 17% total yield): IR (neat) 2952, 2934, 2856, 1260, 1182, 1135, 1123, 1099, 1063, 986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.50 (dd, *J* = 7, 2 Hz, 1H), 7.45 (dd, *J* = 7, 1.5 Hz, 1H), 7.22 (m, 2H), 4.85 (s, 1H, HC=C), 4.82 (s, 1H, HC=C), 4.49 (d, *J* = 6.2 Hz, 1H, CHOMe), 3.54 (s, 3H, OMe), 3.28 (m, 1H), 2.19 (m, 2H), 2.15 (m, 1H), 1.87-1.63 (m, 3H), 0.92 (s, 9H, *t*-Bu), 0.12 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) d 144.80, 142.57, 138.76, 127.58, 127.20, 126.20, 124.92, 114.95, 73.82, 69.96, 47.69, 43.04, 41.17, 30.97, 26.07, 18.39, -1.53, -1.93; MS (IC, NH_3) *m/z* 362 ($M+NH_4^+$), 345 (M+1), 330 ($M+NH_4^+$ -MeOH), 313 (M+1-MeOH), 230 ($M+NH_4^+$ -TBSOH), 213 (M+1 -TBSOH); HRMS (EI) calc'd for $C_{21}H_{32}O_2Si$-*t*-Bu 287.1467, found 287.1444. The presence of formate **59** was apparent by an IR stretch at 1718 cm^{-1}, and from signals at d 8.21 (s, HCO), 6.18 (d, J = 6.1 Hz, CHCO) in the ^1H NMR spectrum (400 MHz, $CDCl_3$) and the absorption at d 160.9 in the ^{13}C NMR spectrum (50 MHz, $CDCl_3$).

The slower moving fraction was rechromatographed (Heptane:EtOAc, 8:1) affording alcohol **60** as a colourless syrup (4 mg, 8% yield): IR (neat) 3416, 2957, 2928, 2856, 1462, 1254, 1135, 1111, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.52 (m, 2H), 7.25 (m, 2H), 4.97 (dd, *J* = 2.0, 2.0 Hz, 1H, HC=C), 4.95 (dd, *J* = 2.0, 2.0 Hz, 1H, HC=C), 4.86 (d, *J* = 6 Hz, 1H, CHOH), 3.07 (bs, 1H), 2.22 (m, 2H), 2.09 (dd, *J* = 11.9, 4.5 Hz, 1H), 1.85 (m, 1H), 1.73-1.50 (m, 3H), 0.93 (s, 9H, *t*-Bu), 0.12 (s, 3H, MeSi), 0.01 (s, 3H, MeSi); ^{13}C NMR (63 MHz, $CDCl_3$) d 144.80, 142.57, 138.76, 127.58, 127.20, 126.20, 124.92, 114.95, 73.82, 69.96, 47.69, 43.04, 41.17, 30.97, 26.07, 18.39, -1.53, -1.93; MS (CI, isobutene) *m/z* 313 (M+1-H_2O); HRMS (EI) calc'd for $C_{20}H_{30}O_2Si$-*t*-Bu 273.1310, found 273.1309.

1-(*t*-Butyldimethylsilyloxy)-10-ethylidene-4-mesyloxy-8-(^{2}H-phenylmethyloxy)bicyclo[7.3.1]trideca-2,6-diyne (61). Sodium hydride (20 mg, 0.40 mmol, 50% dispersion in oil) was added to a stirred solution of alcohol **12** (93 mg, 0.20 mmol) and ^{2}H-benzyl bromide (100 ml, 0.81 mmol) in THF (5 ml) containing 0.2 M H_2O, and the mixture was stirred overnight. Pentane and water were added, and the organic phase was washed with water several times, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography (Heptane:EtOAc, 50:1) to give 81 mg (0.15 mmol) of the protected alcohol, which was immediately dissolved in THF (20 ml). TBAF:3H_2O (51 mg, 0.16 mmol) was added and the solution was stirred at 20°C for 20 min. Ether and water were added, and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 4:1) gave 49 mg of the corresponding propargylic alcohol (55% overall yield) as a colourless syrup: ^1H NMR (250 MHz, $CDCl_3$) d 7.40-7.26 (m, 10H), 5.05 (bs, 2H, 2C=CH), 4.99 (bs, 1H, C=CH), 4.96 (bs, 1H, C=CH), 4.82 (dd, *J* = 8.3, 7.0 Hz, 1H, CHOH), 4.54 (dd, *J* = 4.7, 2.5 Hz, 1H, CHOH), 4.18 (m, 1H, $HCOCD_2Ph$), 4.09 (m, 1H, $HCOCD_2Ph$), 3.06-2.94 (m, 2H), 2.93-1.98 (m, 14H), 1.68 (bs, 2H, 2 OH), 1.67-1.53 (m, 2H), 0.86 (s, 18H, 2*t*-Bu), 0.21 (s, 6H, 2$SiCH_3$), 0.20 (s, 6H, 2$SiCH_3$); MS (IC, isobutene)

m/z 439 (M+1), 421 (M+1-H_2O), 329 (M+1-$PhCD_2OH$), 307 (M+1-TBSOH); HRMS (EI) calc'd for $C_{27}H_{34}D_2O_3Si$ 438.2560, found 438.2523.

Mesyl chloride (16 ml, 0.21 mmol) was added to a stirred solution of the propargylic alcohol (46 mg, 0.10 mmol) and DMAP (51 mg, 0.42 mmol) in CH_2Cl_2 (4 ml) at -20°C. The solution was warmed to 0°C and stirring was continued for 2 h. Ether and water were added and the organic phase was washed with 1N AcOH, aqueous $NaHCO_3$ (sat^d) and brine, and then dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 4:1) provided mesylate **61** as a colourless syrup (39 mg, 73% yield): ^1H NMR (250 MHz, $CDCl_3$) d 7.39-7.24 (m, 10H), 5.54 (dd, *J* = 8.7, 7.0 Hz, 1H, HCOMs), 5.36 (dd, *J* = 4.7, 2.3 Hz, 1H, HCOMs), 5.07 (bs, 2H, 2C=CH), 4.98 (bs, 2H, 2C=CH), 4.20 (m, 1H, $HCOCD_2Ph$), 4.07 (m, 1H, $HCOCD_2Ph$), 3.12 (s, 6H, $2SO_2CH_3$), 3.07-2.58 (m, 8H), 2.40-2.00 (m, 8H), 1.71-1.55 (m, 2H), 0.86 (s, 18H, 2*t*-Bu), 0.20 (s, 3H, $SiCH_3$), 0.19 (s, 9H, $3SiCH_3$); MS (IC, isobutene) *m/z* 573 (M+57), 517 (M+1), 407 (M+1-$PhCD_2OH$); HRMS (EI) calc'd for $C_{28}H_{36}D_2O_5SSi$ 516.2336, found 516.2338.

Cycloaromatization and Deuterium Transfer Studies of 61. DBU (45 ml, 0.30 mmol) was added to a stirred solution of **61** (39 mg, 0.076 mmol) in THF (3 ml) and 1,4-cyclohexadiene (1 ml) at 20°C. After stirring overnight TLC analysis revealed complete consumption of starting material. Ether and water were added, and the organic phase was washed with 1N AcOH, aqueous $NaHCO_3$ (sat^d) and brine, and then dried (Na_2SO_4) and evaporated to dryness *in vacuo*. Flash chromatography (Heptane:EtOAc, 10:1) afforded two fractions. The slower moving fraction gave **66** as a colourless syrup (2.4 mg, 10% yield): IR (neat) 3416, 2957, 2928, 2856, 1462, 1254, 1135, 1111, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.52 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.27 (m, 2H), 4.99 (bs, 1H, C=CH), 4.96 (bs, 1H, C=CH), 4.87 (dd, *J* = 9.5, 6.0 Hz, 1H, CHOH), 3.85 (bs, 1H), 2.24 (m, 2H), 2.10 (dd, *J* = 12.0, 4.2 Hz, 1H), 1.84 (m, 2H), 1.71 (m, 1H), 0.97 (s, 9H, *t*-Bu), 0.16 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) d 144.86, 142.58, 138.74, 127.60, 127.11, 124.94, 114.93, 73.87, 69.98, 47.74, 43.09, 41.23, 31.00, 26.09, 18.41, -1.52, -1.91; MS (CI, isobutene) *m/z* 314 (M+1-H_2O); HRMS (EI) calc'd for $C_{20}H_{29}DO_2Si$ -*t*-Bu 274.1373, found 274.1379.

The faster moving fraction was rechromatographed (Heptane:EtOAc, 80:1) to give two other fractions. The more polar fraction afforded **67** (3.3 mg, 13% yield): IR (neat) 2956, 2932, 2859, 1688, 1685, 1271, 1259, 1139, 1111, 987 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.72 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 5.02 (s, 1H, C=CH), 4.83 (s, 1H, C=CH), 3.55 (bs, 1H, HCCO), 2.58 (ddd, *J* = 12.0, 2.8, 2.5 Hz, 1H), 2.28 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.20 (dd, *J* = 11.8, 3.0 Hz, 1H), 2.07-1.93 (m, 1H), 1.93-1.76 (m, 2H), 0.97 (s, 9H, *t*-Bu), 0.19 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); MS (IC, isobutene) *m/z* 330 (M+1); HRMS (EI) calc'd for $C_{20}H_{27}DO_2Si$ 329.1921, found 329.1913.

The less polar fraction was rechromatographed (Heptane:Toluene, 2:1) to give **65** as a colourless syrup (1 mg, 3% yield): IR (neat) 2956, 2951, 2945, 2931, 2858, 1712, 1702, 1336, 1269, 1136, 1112, 986 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 8.04 (dd, *J* = 8.5, 1.0 Hz, 2H, benzoate), 7.63 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.57 (t, *J* = 7.5, Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.34 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.25 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.32 (d, *J* = 6.5 Hz, 1H, HCCOOPh), 4.72 (s, 1H, C=CH), 4.67 (s, 1H, C=CH), 3.48 (bs, 1H), 2.35 (ddd, *J* = 12.0, 2.5, 2.5 Hz, 1H), 2.24 (d, *J* = 9.0 Hz, 1H), 2.09 (dd, *J* = 12.0, 4.0 Hz, 1H), 1.94-1.76 (m, 3H), 0.96 (s, 9H, *t*-Bu), 0.19 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$); MS (CI, isobutene) *m/z* 391 (M+1-45), 314 (M+1-PhCOOH); HRMS (EI) calc'd for $C_{27}H_{33}DO_3Si$ - *t*-Bu 378.1635, found 378.1685.

Table 1. Fractional Atomic Coordinates ($x10^4$) for the Non-H Atoms and the Equivalent Isotropic Thermal Factor ($Å^2 x10^3$) for Compound **42**.

	x	y	z	Ueq
Si	1663 (1)	2586 (1)	3947 (1)	49 (1)
C1	3032 (3)	959 (2)	3495 (2)	46 (2)
C2	2561 (3)	271 (2)	4123 (2)	50 (3)
C3	2233 (3)	-335 (2)	4627 (3)	66 (4)
C4	1935 (4)	-1120 (3)	5282 (4)	94 (5)
C5	1772 (4)	-2159 (3)	4849 (4)	90 (5)
C6	2669 (4)	-2475 (3)	4358 (3)	67 (4)
C7	3361 (3)	-2680 (2)	3918 (3)	66 (4)
C8	4232 (4)	-2958 (3)	3386 (3)	84 (5)
O9	3887 (2)	-2581 (2)	2386 (2)	73 (2)
C10	4519 (3)	-1661 (2)	2268 (3)	70 (4)
C11	4067 (3)	-705 (2)	2649 (2)	53 (3)
C12	4807 (3)	-126 (2)	3371 (3)	55 (3)
C13	4431 (3)	846 (2)	3775 (2)	49 (3)
C14	2467 (3)	682 (2)	2394 (2)	55 (3)
C15	2739 (3)	-433 (2)	2190 (3)	58 (3)
O16	2792 (2)	2031 (1)	3647 (2)	56 (2)
C17	1746 (4)	2281 (3)	5265 (3)	70 (4)
C18	138 (3)	2168 (3)	3105 (3)	76 (4)
C19	1933 (3)	4010 (2)	3813 (3)	56 (3)
C20	974 (4)	4642 (3)	4121 (3)	83 (5)
C21	3220 (3)	4312 (3)	4493 (3)	75 (4)
C22	1856 (4)	4269 (3)	2732 (3)	88 (5)

Crystal data for compound 42. $C_{20}H_{30}O_2Si$, molecular weight 330.54, crystals obtained from slow evaporation of hexane; monoclinic system, space group P $2_1/c$, Z = 4, a = 11.434 (7), b = 12.930 (8), c = 14.018 (9) Å, β= 107.82 (2) °, V = 1973 (2) $Å^3$, d_c = 1.11 g cm^{-3}, F(000) = 720, λ (Cu Kα) = 1.5418 Å, μ = 1.08 mm^{-1}; 3931 measured intensities, 2971 observed.

Crystal data for compound 43 (C8-*O*-benzoate). $C_{27}H_{34}O_3Si$, molecular weight 434.65, crystals obtained from slow evaporation of hexane; triclinic system, space group P -1, Z = 2, a = 7.364 (6), b = 8.031 (6), c = 23.362 (16) Å, α = 85.66 (5), β = 90.58 (5), γ = 111.81 (4) °, V = 1278 (2) $Å^3$, d_c = 1.13 g cm^{-3}, F(000) = 468, λ (Cu Kα) = 1.5418 Å, μ = 0.97 mm^{-1} ; 4732 measured intensities, only 1782 observed due to the poor quality of the crystal, explaining the high values of the R factors for this structure.

For both compounds, intensity data were measured on a Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation and the (θ-2θ) scan technique up to θ = 68° . Only intensities with I > 3.0 σ(I) for compound 1, 2.5 σ(I) for 2 were considered as observed and kept in refinement calculations, σ(I) being derived from counting statistics. Cell parameters were obtained from the refinement of 25 well-centered reflections.

The structures were solved by direct methods using *SHELXS86* and refined by full matrix least-squares, minimizing the function $\Sigma w(Fo - |Fc|)^2$, with the program *SHELX76*. The hydrogen atoms, located for most of them in difference Fourier maps, were introduced in the refinement at theoretical positions (C-H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was

reached at R = 0.072 and R_w = 0.086 for 1 ; R = 0.111, R_w = 0.150 for 2 (with $R_w = \{\Sigma w(Fo- |Fc|)^2 / \Sigma wFo^2\}^{1/2}$ and $w = 1/[\sigma^2(Fo)+kFo^2]$ (k = 0.0 for 1, - 0.04361 for 2). No residual was higher than 0.60 e $Å^{-3}$ for 1, 0.72 for 2 near the Si atom, in the final difference map. Atomic scattering factors taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). Final atomic coordinates and bond distances and angles are given in Tables 1 and 2 for compound 1, Tables 3 and 4 for compound 2.

Table 2. Bond Distances (Å), Bond and Torsion Angles (°) for Compound **42**.

Si - O16	1.641 (2)	C6 - C7	1.172 (6)
Si - C17	1.863 (4)	C7 - C8	1.460 (6)
Si - C18	1.862 (4)	C8 - O9	1.422 (5)
Si - C19	1.886 (3)	O9 - C10	1.428 (4)
C1 - C2	1.465 (4)	C10 - C11	1.500 (5)
C1 - C13	1.533 (4)	C11 - C12	1.332 (4)
C1 - C14	1.522 (4)	C11 - C15	1.499 (5)
C1 - O16	1.441 (3)	C12 - C13	1.495 (4)
C2 - C3	1.191 (5)	C14 - C15	1.520 (4)
C3 - C4	1.476 (6)	C19 - C20	1.531 (5)
C4 - C5	1.463 (5)	C19 - C21	1.539 (5)
C5 - C6	1.458 (6)	C19 - C22	1.528 (5)

O16 - Si - C17	110.9 (1)	C7 - C8 - O9	113.1 (3)
O16 - Si - C18	111.6 (1)	C8 - O9 - C10	113.7 (3)
O16 - Si - C19	103.7 (1)	O9 - C10 - C11	113.8 (3)
C17 - Si - C18	108.7 (2)	C10 - C11 - C12	121.7 (3)
C17 - Si - C19	110.2 (2)	C10 - C11 - C15	117.0 (3)
C18 - Si - C19	111.7 (2)	C12 - C11 - C15	121.2 (3)
C2 - C1 - C13	109.5 (2)	C11 - C12 - C13	124.8 (3)
C2 - C1 - C14	110.2 (3)	C1 - C13 - C12	112.5 (2)
C2 - C1 - O16	111.9 (2)	C1 - C14 - C15	111.5 (3)
C13 - C1 - C14	108.9 (2)	C11 - C15 - C14	112.4 (3)
C13 - C1 - O16	106.6 (2)	Si - O16 - C1	131.2 (2)
C14 - C1 - O16	109.6 (2)	Si - C19 - C20	109.9 (2)
C1 - C2 - C3	175.7 (3)	Si - C19 - C21	109.9 (2)
C2 - C3 - C4	175.1 (4)	Si - C19 - C22	110.6 (3)
C3 - C4 - C5	113.4 (4)	C20 - C19 - C21	108.8 (3)
C4 - C5 - C6	115.8 (4)	C20 - C19 - C22	109.5 (3)
C5 - C6 - C7	175.7 (4)	C21 - C19 - C22	108.2 (3)
C6 - C7 - C8	178.6 (4)		

C13	C1	C2	C3	-38.5 (4)	O9	C10	C11	C12	120.4 (4)
C14	C1	C2	C3	81.2 (4)	O9	C10	C11	C15	-58.9 (3)
C1	C2	C3	C4	31.1 (5)	C11	C12	C13	C1	16.1 (3)
C2	C3	C4	C5	-79.2 (6)	C12	C13	C1	C14	-44.5 (3)
C3	C4	C5	C6	43.1 (4)	C13	C1	C14	C15	61.6 (3)
C4	C5	C6	C7	-64.5 (6)	C1	C14	C15	C11	-47.6 (3)
C5	C6	C7	C8	-170.5 (8)	C14	C15	C11	C12	17.5 (3)
C6	C7	C8	O9	151.1 (6)	C15	C11	C12	C13	-1.9 (3)
C7	C8	O9	C10	99.9 (4)	C2	C1	O16	Si	-31.1 (2)
C8	O9	C10	C11	-75.5 (3)					

Table 3. Fractional Atomic Coordinates ($x10^4$) for the Non-H Atoms and the Equivalent Isotropic Thermal Factor ($Å^2x10^3$) for Compound **43** (C_8-*O*-benzoate).

	x	y	z	Ueq
Si	2843 (4)	-247 (4)	6238 (1)	58 (3)
O1	1850 (10)	-525 (8)	6872 (3)	62 (8)
O2	1127 (9)	1890 (10)	9240 (3)	59 (8)
O3	3848 (9)	2513 (11)	9762 (3)	80 (11)
C1	1726 (13)	800 (12)	7262 (4)	50 (11)
C2	3533 (14)	2404 (13)	7213 (4)	50 (11)
C3	4850 (15)	3831 (14)	7195 (5)	63 (13)
C4	6289 (15)	5555 (14)	7324 (5)	66 (13)
C5	5508 (17)	6286 (15)	7824 (5)	73 (15)
C6	4417 (15)	4835 (15)	8238 (5)	60 (12)
C7	3425 (14)	3422 (14)	8486 (5)	54 (12)
C8	2234 (13)	1663 (14)	8758 (4)	53 (11)
C9	662 (12)	454 (14)	8359 (5)	55 (11)
C10	-864 (13)	1226 (12)	8164 (5)	51 (11)
C11	-477 (14)	2272 (15)	7598 (6)	71 (14)
C12	-100 (15)	1183 (15)	7131 (5)	63 (13)
C13	1513 (13)	-234 (12)	7862 (4)	43 (10)
C14	-2459 (14)	856 (16)	8469 (6)	76 (15)
C15	2215 (14)	2361 (13)	9732 (4)	50 (11)
C16	1028 (14)	2809 (12)	10159 (4)	49 (11)
C17	-978 (15)	2343 (15)	10139 (5)	60 (13)
C18	-1945 (18)	2813 (17)	10560 (5)	80 (16)
C19	-896 (23)	3781 (17)	11007 (5)	86 (19)
C20	1083 (19)	4281 (15)	11020 (5)	70 (15)
C21	2060 (16)	3811 (13)	10606 (5)	64 (13)
C22	2769 (24)	1727 (22)	5780 (6)	113 (23)
C23	5458 (18)	182 (24)	6301 (7)	119 (24)
C24	1468 (20)	-2350 (16)	5903 (5)	79 (16)
C25	2370 (27)	-2421 (26)	5318 (7)	149 (30)
C26	-677 (20)	-2533 (25)	5804 (7)	124 (25)
C27	1406 (32)	-3982 (24)	6291 (9)	165 (35)

Table 4. Bond Distances (Å), Bond and Torsion Angles (°) for Compound **43** (C_8-*O*-benzoate).

Si - O1	1.62 (1)	C8 - C9	1.56 (1)
Si - C22	1.86 (2)	C9 - C10	1.52 (1)
Si - C23	1.83 (2)	C9 - C13	1.55 (1)
Si - C24	1.85 (1)	C10 - C11	1.48 (2)
O1 - C1	1.48 (1)	C10 - C14	1.30 (2)
O2 - C8	1.46 (1)	C11 - C12	1.54 (2)
O2 - C15	1.39 (1)	C15 - C16	1.48 (1)
O3 - C15	1.16 (1)	C16 - C17	1.38 (2)
C1 - C2	1.47 (1)	C16 - C21	1.40 (1)
C1 - C12	1.51 (2)	C17 - C18	1.38 (2)
C1 - C13	1.55 (1)	C18 - C19	1.40 (2)
C2 - C3	1.19 (1)	C19 - C20	1.36 (2)
C3 - C4	1.45 (2)	C20 - C21	1.37 (2)
C4 - C5	1.55 (2)	C24 - C25	1.54 (2)
C5 - C6	1.45 (2)	C24 - C26	1.55 (2)
C6 - C7	1.20 (2)	C24 - C27	1.52 (2)

O1	- Si	- C22	115.2 (6)	C10	- C9	- C13	113.3 (8)
O1	- Si	- C23	109.8 (6)	C9	- C10	- C11	115.9 (9)
O1	- Si	- C24	104.5 (5)	C9	- C10	- C14	120.4 (10)
C22	- Si	- C23	104.2 (7)	C11	- C10	- C14	123.6 (10)
C22	- Si	- C24	110.3 (7)	C10	- C11	- C12	111.1 (9)
C23	- Si	- C24	113.2 (7)	C1	- C12	- C11	110.0 (9)
SI	- O1	- C1	130.9 (6)	C1	- C13	- C9	117.2 (8)
C8	- O2	- C15	113.9 (8)	O2	- C15	- O3	123.0 (10)
O1	- C1	- C2	109.6 (8)	O2	- C15	- C16	108.7 (8)
O1	- C1	- C12	108.8 (8)	O3	- C15	- C16	128.0 (10)
O1	- C1	- C13	102.6 (7)	C15	- C16	- C17	124.8 (9)
C2	- C1	- C12	113.9 (9)	C15	- C16	- C21	116.1 (9)
C2	- C1	- C13	111.4 (8)	C17	- C16	- C21	119.0 (9)
C12	- C1	- C13	110.0 (8)	C16	- C17	- C18	120.2 (11)
C1	- C2	- C3	171.1 (11)	C17	- C18	- C19	119.8 (12)
C2	- C3	- C4	165.2 (12)	C18	- C19	- C20	120.1 (13)
C3	- C4	- C5	109.4 (10)	C19	- C20	- C21	120.6 (12)
C4	- C5	- C6	110.6 (10)	C16	- C21	- C20	120.2 (10)
C5	- C6	- C7	166.5 (12)	Si	- C24	- C25	111.9 (10)
C6	- C7	- C8	176.9 (12)	Si	- C24	- C26	110.6 (10)
O2	- C8	- C7	109.5 (8)	Si	- C24	- C27	110.9 (11)
O2	- C8	- C9	105.0 (8)	C25	- C24	- C26	107.7 (12)
C7	- C8	- C9	114.0 (9)	C25	- C24	- C27	108.6 (13)
C8	- C9	- C10	113.8 (8)	C26	- C24	- C27	107.0 (13)
C8	- C9	- C13	114.3 (8)				

C12	C1	C2	C3	30.6 (13)	C7	C8	C9	C13	69.7 (10)
C13	C1	C2	C3	-94.4 (14)	C8	C9	C10	C11	95.1 (11)
O1	C1	C2	C3	152.7 (15)	C8	C9	C13	C1	-98.9 (10)
C1	C2	C3	C4	55.7 (19)	C9	C10	C11	C12	53.0 (10)
C2	C3	C4	C5	-23.8 (13)	C10	C11	C12	C1	-63.5 (10)
C3	C4	C5	C6	36.9 (11)	C11	C12	C1	C13	57.8 (10)
C4	C5	C6	C7	-29.6 (14)	C12	C1	C13	C9	-44.6 (9)
C5	C6	C7	C8	13.9 (17)	C1	C13	C9	C10	33.7 (9)
C6	C7	C8	C9	-44.2 (14)	C13	C9	C10	C11	-37.8 (9)
C7	C8	C9	C10	-62.7 (10)	C2	C1	O1	Si	-36.0 (7)

REFERENCES AND FOOTNOTES

1. (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. (c) Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res.* **1991**, *24*, 235.
2. (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.
3. (a) Maiese, W. M.; Lechevalier, M. P.; Lechevalier, H. A.; Korshalla, J.; Kuck, N.; Fantini, A.; Wildey, M. J.; Thomas, J.; Greenstein, M. *J. Antibiotics* **1989**, *42*, 558. (b) Lee, M. D.; Manning, J. K.; Williams, D. R.; Kuck, N. A.; Testa, R. T.; Borders, D. B. *J. Antibiotics* **1989**, *42*, 1070. (c) Konishi, M.; Ohkuma, H.; Saitoh, K.-I.; Kawaguchi, H.; Golik, J.; Dubay, G.; Groenewold, G.; Krishnan, B.; Doyle, T. W. *J. Antibiotics* **1985**, *38*, 1605.
4. (a) Hangeland, J. J.; De Voss, J. J.; Heath, J. A.; Townsend, C. A.; Ding, W.-d.; Ashcroft, J. S.; Ellestad, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 9200. (b) Christner, D. F.; Frank, B. L.; Kozarich, J. W.; Stubbe, J.; Golik, J.; Doyle, T. W.; Rosenberg, I. E.; Krishnan, B. *J. Am. Chem. Soc.* **1992**, *114*, 8763. (c) Walker, S.; Landovitz, R.; Ding, W. D.; Ellestad, G. A.; Kahne, D. *Proc. Natl. Acad. Sci.*

USA **1992**, *89*, 4608. (d) Drak, J.; Iwasawa, N.; Danishefsky, S.; Crothers, D. M. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 7464. (e) Kishikawa, H.; Jiang, Y.; Goodisman, J.; Dabrowiak, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 5434. (f) De Voss, J. J.; Hangeland, J. J.;Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 4554. (g) De Voss, J. J.; Townsend, C. A.; Ding, W.-D.; Morton, G. O.; Ellestad, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9669. (h) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697. (i) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888. (j) Sugiura, Y.; Uesawa, Y.; Takahashi, Y.; Kuwahara, J.; Golik, J.; Doyle, T. W. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 7672. (k) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 2. (l) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198.

5. Nicolaou, K. C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.
6. Skrydstrup, T.; Audrain, H.; Ulíbarri, G.; Grierson, D. S. In *Recent Progress in the Chemical Synthesis of Antibiotics*.; G. Lukacs Ed.; Springer-Verlag: 1993; Vol. *II*; pp. 213-292.
7. Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253.
8. Nicolaou, K. C.; Smith, A. L.; Hwang, C.-K.; Pitsinos, E.; Scarlato, G. R. *J. Am. Chem. Soc.* **1992**, *114*, 3134.
9. For other synthetic studies on the aglycone see: (a) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544. (b) Magnus, P.; Lewis, R.; Bennett, F. *J. Am. Chem. Soc.* **1992**, *114*, 2560. (c) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631. (d) Schreiber, S. L.; Kiessling, L. L. *Tetrahedron Lett.* **1989**, *30*, 433. (e) Schreiber, S. L.; Schoenen, F. J.; Porco, J. A., Jr.; VanDuyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765. (f) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. (g) Kadow, J.F.; Tun, M.M.; Vyas, D.M.; Wittman, M.D.; Doyle, T.W. *Tetrahedron Lett.* **1992**, *33*, 1423.
10. Nicolaou, K. C.; Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schulze, T. J.; Stahl, W. *J. Am. Chem. Soc.* **1990**, *112*, 8193.
11. Danishefsky, S. J.; Halcomb, R. L.; Wittman, M. D.; Olson, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 5080.
12. Danishefsky, S. J.; Halcomb, R. L.; Boyer, S. H. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 338.
13. Nicolaou, K. C.; Clark, D. *Angew. Chem. Int. Ed. Ingl.* **1992**, *31*, 855.
14. Nicolaou, K. C.; Hummel, C. W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082.
15. (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. (b) Nakai, T.; Mikami, K. *Synthesis* **1991**, 594. (c) Marshall, J. A. *Comprehensive Organic Synthesis*; Pergamon Press, Oxford: 1991; Vol. 3, pp 975.
16. (a) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3860. (b) Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883. (c) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925. (d) Marshall, J. A.; Lebreton, J. *J. Org; Chem.* **1988**, *53*, 4108. (e) Marshall, J. A.; Nelson, D. J. *Tetrahedron Lett.* **1988**, *29*, 741. (f) Marshall, J. A.; Robinson, E. D.; Lebreton, J. *J. Org. Chem.* **1990**, *55*, 227. (g) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450.
17. For preliminary communications of part of this work see: (a) Skrydstrup, T.; Audrain, H.; Ulibarri, G.; Grierson, D. S. *Tetrahedron Lett.* **1992**, *33*, 4563. (b) Skrydstrup, T.; Audrain, H.; Ulibarri, G.; Grierson, D. S. *Synlett* **1992**, 20.
18. (a) Takahashi, T.; Doi, T. *J. Org. Chem.* **1991**, *56*, 3465-3467. (b) Wender, P. A.; McKinney, J. A.; Mukai, C. *J. Am. Chem. Soc.* **1990**, *112*, 5369-5370. (c) Wender, P. A.; Grissom, J. W.; Hoffmann, U.; Mah, R. *Tetrahedron Lett.* **1990**, *31*, 6605.
19. PCMODEL version 2.0, (c) 1989 Serena Software, Bloomington, In.
20. Recently the installment of the complete 3-ene-1,5-diyne from a 1,5-diyne precursor has been achieved under oxidative and reductive conditions: (a) Maier, M. E.; Brandstetter, T. *Tetrahedron Lett.* **1991**, *32*, 3679. (b) Maier, M. E.; Greiner, B. *Liebigs Ann. Chem.* **1992**, 855. (c) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1992**, *114*, 5859.
21. Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677.
22. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811.
23. Imamoto, T.; Sugiura, Y.; Takiyama, N.; *Tetrahedron Lett.* **1984**, *25*, 4233.

24. Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655.
25. Beau, J.-M.; Crévisy, C. *Tetrahedron Lett.* **1991**, *32*, 3171.
26. Schinzer, D.; Kabbara, J. *Synlett* **1992**, 766.
27. (a) Seebach, D.; Mukhopadhyay, T. *Helv. Chim. Acta*, **65**, 385 (1982). (b) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705.
28. Adiwidjaja, G.; Groun-witte, G. J. *J. Organomet. Chem.* **1980**, *188*, 91.
29. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
30. Wender *et al.* have shown that highly strained enediyne systems related to neocarzinostatin can be constructed through cyclization of an intermediate bromoaldehyde under $CrCl_2$ conditions (Nozaki-Hiyama reaction)[18b,c] Oxidation of bromoalcohol **41** (Dess-Martin Periodinane; 80%) and reaction of the derived aldehyde with $CrCl_2$ was thus studied as an alternate route to diyne **43**. In the experiment, treatment of a 1.0 mM solution of bromoaldehyde in degassed THF with 5 equivalents of commercial (Aldrich) $CrCl_2$ over 1 h resulted in partial consumption of the starting aldehyde and formation of compound **43**. However, to drive the reaction to completion required use of *50 equivalents of* $CrCl_2$. Although **43** was essentially the only product formed (TLC) in this reaction, it was isolated in only 35% yield.
31. Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421.
32. By modifying the sequence of reactions in Figure **5**, such that formaldehyde is replaced by acetaldehyde, the macrocyclic ethers **47** and **48** were prepared in three steps from the acyclic diyne **39**. In this case the cyclization step required heating at 45°C for 5 days to go to completion, and although compounds **47** and **48** could not be separated by column chromatography each epimer was positively identified by NMR (e.g. C_{12} vinylic proton: δ 5.33 for **47**, and δ 5.85 for **48**).
33. (a) Cohen, T.; Verner, E. J. *J. Am. Chem. Soc.* **1992**, *114*, 375. (b) Hoffmann, R.; Bruckner, R. *Angew. Chem. Int. Ed. Ingl.* **1992**, *31*, 647. (c) Tomooka, K.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795.
34. (a) Snieckus,V.; Cuevas, J.-C.; Sloan, C.P.; Liu, H; Curran, D. *J. Am. Chem Soc* **1990**, *112*, 896. (b) Curran, D.P.; Abraham, A.C.; Liu, H.T. *J. Org. Chem.* **1991**, *56*, 4335. (c) Curran, D.P.; Yu, H. *Synthesis* **1992**, 123. (d) Griffiths, J.; Murphy, J.A. *J. Chem. Soc., Chem. Commun.* **1991**, 1422.
35. Lochart, T.P.; Comita, P.B.; Bergman, R.G. *J. Am. Chem. Soc.* **1981**, *103*, 4082.
36. In the activation of calicheamicin γ_1^I with Ph_3P Ellestad *et al.* isolated Ph_3PO along with Ph_3PS. This was suggested to arise from reaction of the benzenoid diradical (or a carbon centered radical derived from it) with oxygen to give a peroxide which is subsequently reduced by Ph_3P. Ellestad, G.A.; Hamann, P.R.; Zein, N.; Morton, G.O.; Siegel, M.M.; Pastel, M.; Borders, D.B.; McGahren, W.J. *Tetrahedron Lett.* **1989**, *30*, 3033.
37. A Wieland-type rearrangement involving migration of the phenyl group to the oxygen atom in **64** could also subsequently give **66**. (a) Wilt, J.W. *Free Radicals*, Ed. Kochi, J.K., Vol. 1, p. 353, John Wiley & Sons, New York 1973. (b) Nahavandi, F.; Razamara, F.; Stevens, M.P. *Tetrahedron Lett.* **1973**, 301.
38. Wender, P.A., Tebbe, M.J.*Tetrahedron Lett.* **1991**, *32*, 4863.
39. Chin, D.-H.; Goldberg, I.H. *J. Am. Chem. Soc.* **1992**, *114*, 1914.
40. An internal hydrogen atom transfer involving the aryl C3 carbon radical has also been proposed to account for the low double to single DNA strand scission observed for esperamicin A_1.[4e]
41. In theory, radical transposition to the anomeric center of the A-ring sugar could also participate for the calicheamicin antibiotics, but a recent analysis of the solution conformation of calicheamicin ϵ[42] makes us suggest that a large conformational change would be required for such a process to occur.
42. Walker, S.; Valentine, K.G.; Kahne, D. *J. Am. Chem. Soc.* **1990**, *112*, 6428.

(*Received* 30 *July* 1993; *accepted* 24 *November* 1993)