A Mild Route to α-Alkoxyacetylenes Mediated by Lewis Acids and Synthetic Routes to 10-, 11-, and 12-Membered Ring Enediyne Carbocycles

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Abstract. The condensation of silyl substituted acetylenes with dimethoxy acetals via a modified "Mukaiyama-type reaction" to afford α-alkoxyacetylenes is described. These propargylic ethers **17**–**21** were synthesized from the reaction of aluminum or zinc acetylides with acetals mediated by Lewis acids. In appropriate cases, when a second acetal was present in the initial acyclic product (**24**), a subsequent intramolecular acetal-ene (Prins) cyclization ensued to afford the silylalkylidenealkoxycyclopentane (**25**). Enediyne species were unreactive under these conditions, even in an intramolecular case. Routes to 11- and 12-membered carbocyclic enediyne compounds (**43**, **44**) were developed via an intramolecular pinacol coupling of the dialdehydes **39** with sammarium diodide/HMPA. The requisite double bond was introduced using the thiocarbonate expulsion method with trimethyl phosphite. A route to the highly substituted 10-membered ring enediyne **50** is also described based on the use of an isopropylidene acetal tether control group to facilitate an intramolecular chromium (II)/nickel (II)-mediated coupling of the iodoacetylene aldehyde **49**.

INTRODUCTION

Acetylenes represent a well-studied functional group recognized for their synthetic versatility due to the cross section of reactions in which they participate.[1] The current interest in natural products, such as calicheamicin and esperamicin[2] (Fig. 1), has generated considerable synthetic activity. Similarily, in related areas, the construction of acetylenic bridged annulenes, cyclophanes, and carbon networks has provided novel molecular arrays.[3] In particular, cobalt trimerizations,[4] the use of tin- and palladium-based coupling methods, and enediyne syntheses has stimulated the development of methods to introduce triple bonds under mild conditions, particularly for carbocyclic systems that contain enediyne units.[5] Historically, the most direct route for the preparation of propargyl alcohols has been the direct condensation of metal acetylides (usually Li and MgX) with carbonyl systems. However, for mutifunctionalized compounds these methods are often not appropriate.

In part, this study was motivated by our interest in constructing bicyclic enediyne systems (taxcamycins) that would combine aspects of the important pharmacophores found in the enediyne and taxoid natural product families. It was anticipated that suitable functionality should facilitate tubulin binding, and cycloaromatization would induce cell damage. We have previously synthesized various 10-, 11-, and 12-membered ring systems related to **1** and **2** (Fig. 1).[6] Unfortunately, the bicyclo[7.3.1]trideca-4,9-dien-2,6-diyne compound **2** with the docetaxel (Taxotere) side chain attached lacked the desired biological activity.[6d] Consequently, we sought a mild, direct route to acetylene building blocks and simple cyclic enediynes in which the secondary alcohols could be differentiated.

A variety of milder metal acetylides have been examined and compared to alkoxides for use in sensitive systems to avoid the undesirable side reactions that may accompany strongly basic conditions. Among an exten-

This paper is dedicated to Professor Raymond U. Lemieux on the occassion of his 80th birthday and the receipt of the Wolf Prize. Presented with respect and gratitude for his contributions to organic chemistry and our friendship.

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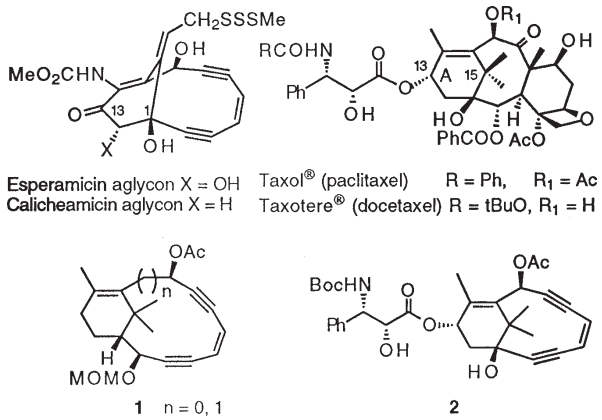
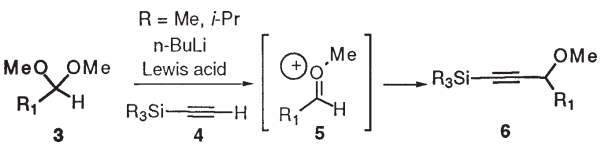


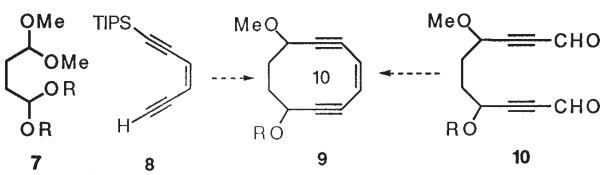
Fig. 1. Taxamycins (taxoid-enediyne hybrids).

sive list aluminum-,[7] boron-,[8] cerium-,[9] chromium-,[10] manganese-,[11] tin-,[12] and vanadium-based[13] protocols are representative. Often these methods require a large excess of the acetylide and enolization can be a significant problem, particularly when enediyne anions are added to aldehydes. In these cases, the addition of cerium trichloride to form the cerium acetylide in situ is beneficial.[9b] The synthetic utility and mild conditions of Mukaiyama-type reactions involving silyl enol ethers or allylsilanes with acetals under Lewis acid condition are well established.[14] This implied that the condensation of zinc or aluminum silyl acetylides with methoxy acetals could be mediated with Lewis acids, as outlined in Scheme 1. Thus the condensation of **3** with **4** was expected to provide **6** via the intermediacy of **5**. This is the case, and we have developed a simple procedure to afford α-propargylmethyl ethers directly under mild conditions.

Unfortunately, this protocol failed with combinations related to **7** and **8**. However, both the 11- and 12-membered ring systems related to **9** have been prepared via a pinacol coupling sequence as described below. The



Scheme 1. General route to α-propargyl ethers.



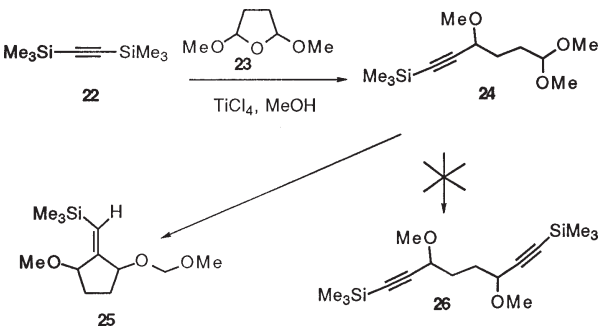
Scheme 2. Possible routes to carbocyclic enediynes.

knowledge gained from this investigation has been employed in a direct synthesis of an analogue of **9** based on an acetal "tether control" strategy.

LEWIS ACID-MEDIATED ADDITIONS OF SILYLACETYLENES TO ACETALS

Table 1 summarizes the results for several experiments. The standard procedure involved treatment of the silyl acetylenes (**11** or **12**) with *n*-butyllithium at 0 °C, followed by the addition of either zinc chloride or aluminum trichloride to generate the metal complexes. Subsequently, the acetal (**13** to **16**) was added, and, in the case of the zinc chloride reaction, this was followed by one equivalent of boron trifluoride etherate. In the absence of additional Lewis acid, no product was formed. In the case of dimethoxy acetals derived from stable aldehydes (Entries a,b), the yields were 81% and 53%, respectively. 1,3-Propandial (malonaldehyde) is difficult to manipulate, especially in the presence of base. However, as Entries c–f indicate, the (bis)dimethyl acetal **15** reacted under various conditions to give modest yields of the methoxy ethers **19** or **20.** The greater steric bulk of the ethoxy group in **16** had minimal effect on the yield and the triethyl ether **21** was isolated in 27% yield. In the case of Entry f**,** two equivalents of acetylide were added, but only mono addition to give **20** was observed. Thus acid-sensitive molecules can be prepared under these conditions and retain functionality for further synthetic manipulation.

In principle, it should be possible to conduct double addition to these bis-acetal systems under appropriate conditions, although as noted with the substrates above, this was not observed. In order to investigate this potential, excess bis-trimethylacetylene **22** was combined with the masked 1,4-butanedial (2,5-dimethoxytetrahydrofuran **23**) in the presence of titanium tetrachloride in the expectation that the product would be the disilyldiyne **26** (Scheme 3). However **26** was not detected, but instead the initially formed mono adduct **24** was isolated, accompanied by a small amount of a sec-



Scheme 3. Preparation of **24** and cyclopentane **25**.

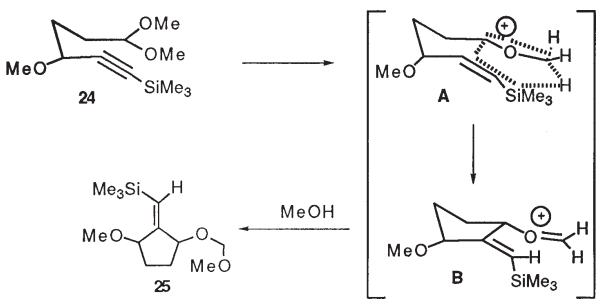
Table 1. Results of Lewis acid-mediated silylacetylide addition to acetals

entry	acetylene	substrate	method	product	yield
a	Me_3Si— ≡ **11**	$PhCH_2CH(OMe)_2$ **13**	A	Me_3Si— ≡ —C(OMe)(CH_2Ph) **17**	81%
b	i-Pr_3Si— ≡ **12**	—CH(OMe)$_2$ **14**	A	i-Pr_3Si— ≡ —C(OMe)(cyclohexenyl) **18**	53%
c	Me_3Si— ≡ **11**	$(MeO)_2CHCH_2CH(OMe)_2$ **15**	A	Me_3Si— ≡ —C(OMe)($CH(OMe)_2$) **19**	23%
d	i-Pr_3Si— ≡ **12**	$(MeO)_2CHCH_2CH(OMe)_2$ **15**	A	i-Pr_3Si— ≡ —C(OMe)($CH(OMe)_2$) **20**	18%
e	i-Pr_3Si— ≡ **12**	$(MeO)_2CHCH_2CH(OMe)_2$ **15**	B	i-Pr_3Si— ≡ —C(OMe)($CH(OMe)_2$) **20**	37%
f	i-Pr_3Si— ≡ **12**	$(MeO)_2CHCH_2CH(OMe)_2$ **15**	C	i-Pr_3Si— ≡ —C(OMe)($CH(OMe)_2$) **20**	33%
g	i-Pr_3Si— ≡ **12**	$(EtO)_2CHCH_2CH(OEt)_2$ **16**	B	i-Pr_3Si— ≡ —C(OEt)($CH(OEt)_2$) **21**	27%

A = 1 equiv *n*-BuLi, 0 °C, ether, 1 equiv $ZnCl_2$, 1 eq. $BF_3(EtO)_2$, 30 min.
B = 1 equiv *n*-BuLi, 0 °C, hexanes, 1 equiv $AlCl_3$, CH_2Cl_2, 30 min.
C = 2 equiv *n*-BuLi, 0 °C, hexanes, 2 equiv $AlCl_3$, CH_2Ci_2, 30 min.

ond product. Further experimentation established that exposure of **24** to additional titanium chloride induced an intramolecular reaction which afforded a cyclic product in 82% yield. This material lacked triple bonds and its spectroscopic features satisfied the cyclopentene-ether structure **25**. Consistent with this assignment, the ^{1}H NMR spectrum contained a broad singlet at d 5.90 ppm for the vinyl hydrogen and the ^{13}C NMR spectrum displayed a signal for an sp^2 hybridized carbon at d 158.3 ppm, typical of an exocyclic double bond.

A likely mechanism for this cyclization is illustrated in Scheme 4. Cyclization to **25** may arise from the initial loss of methanol from acetal **24** to form the oxonium ion **A.** This sets the stage for rearrangement via an intramolecular acetal-ene reaction pathway to **B.** Subsequent addition of methanol afforded the methyloxymethyl ether **25**. Thus this cyclization belongs to the family of intramolecular acetal-ene or Prins reactions (when free carbonyl is involved). Previous examples with acetals and alkenes have been shown to involve methoxycarbonyl cations[15] and Overman and coworkers[16] have utilized related cyclizations for the synthesis of



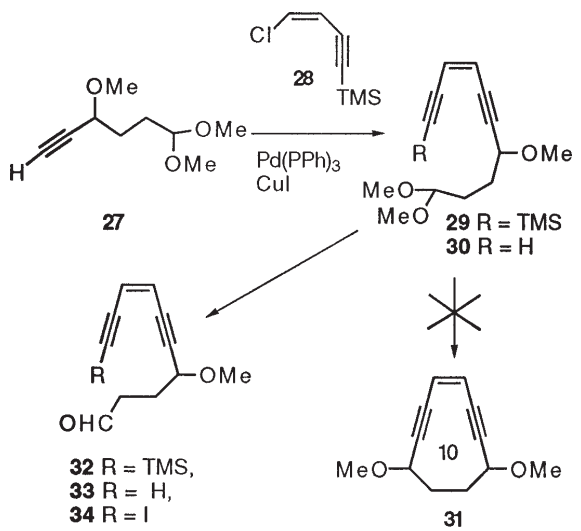
Scheme 4. Oxonium ion-ene reaction to **25**.

oxocycles from vinylsilane acetals by a related intramolecular acetal-ene reactions initiated by $SnCl_4$ at –15 °C.

Irrespective of the experimental method, these silylacetylide condensations are synthetically equivalent although the nature of the zinc and aluminum acetylide complexes may differ. The zinc acetylide is less nucleophilic and behaves more like a tightly held organozinc anion. Thus additional Lewis acid, such as borontrifluoride etherate, is required for the reaction to proceed.

APPROACHES TO 10-MEMBERED RINGS

Several attempts to extend these zinc and aluminum condensation protocols, described in Table 1, to the tri-*i*-propylsilyl-3-ene-1,5-diyne building block **8** with acetals failed. This is probably a consequence of the reduced nucleophilicity present in these extended π-systems. However, given the planar nature of the enediyne chromophore, it seemed possible that an intramolecular reaction to form a 10-membered ring was feasible. We suspected the cyclodecene system should form more easily due to the limited conformational mobility of the alkyl component compared to the larger ring homologues. These experiments are outlined in Scheme 5. The silyl acetylene **24** prepared above was treated with base to remove the trimethylsilyl group to afford the acetylene-acetal **27**. This was coupled with vinyl chloride **28** using the palladium/copper-mediated conditions we have employed previously.[6] The silyl-substituted enediyne **29** was reacted with titanium tetrachloride as described earlier, but neither this method nor related reactions with the free acetylene system **30** gave any of the desired carbocycle **31**. Further modification of **29** afforded the two aldehydes **32** and **33**, but these molecules also failed to undergo intramolecular condensation under fluoride ion or basic conditions with lithium diisopropyl amide, for which there is literature precedent.[17] A referee has kindly suggested that the back reaction, retrocyclization to afford starting material, may be favored in these systems and account for these observations. In previous research we have established that the chromium(II)/nickel(II)-mediated intramolecular reaction often succeeds where other methods fail.[6] Unfortunately in this series, we were unable to synthesize the iodo-aldehyde **34** to examine this alternative.



Scheme 5. Attempted intramolecular acetal coupling.

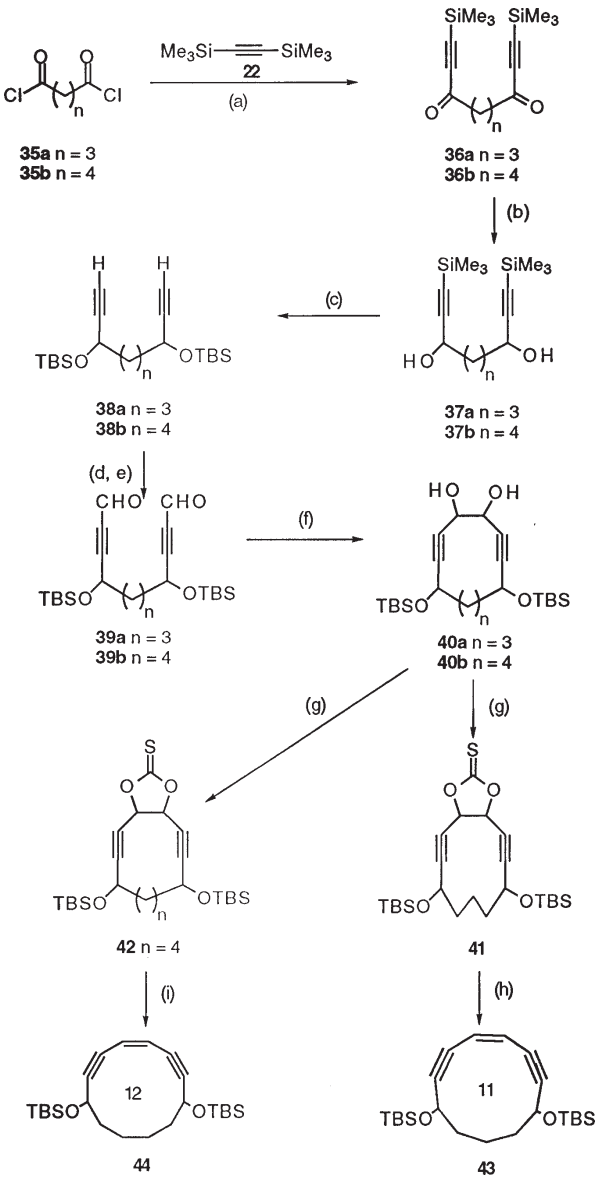
PINACOL-BASED ROUTE TO 11- AND 12-MEMBERED RINGS

The investigations above imply that for effective intramolecular reactions to these ring systems, the precursor must possess a more rigid geometry, in which restricted rotation will facilitate the interaction of the reactive centers. Pinacol coupling of dialdehydes, similar to structure **9** in Scheme 2, has been used by Myers and Dragovich[18] to prepare an unsubstituted 10-membered ring in which the coupling step afforded the expected α-hydroxycyclodecendiyne ketone in 32% yield with VCl_3·3THF/Zn. Nicolaou and coworkers[19] have also synthesized 10-membered carbocyclic enediyne rings which contained dimethyl functionality adjacent to the aldehydes. However, we are not aware of any syntheses of the high homologues related to 11- and 12-membered rings by this procedure.

This approach is outlined in Scheme 6 and requires the synthesis of the acetylenic aldehydes **39**, in which the rigid linear orientation of the triple bonds should assist the cyclization reaction. Small conjugated alkynals are not ideal intermediates as they have a tendency to be unstable, are often difficult to manipulate, and are sometimes explosive. However, with these higher molecular weight compounds, this was not the case.

In a parallel series of reactions, the appropriate acyl chloride was coupled with bis-trimethysilyl acetylene (**22**) in the presence of aluminum trichloride to provide the diketones **36**. Reduction of the ketones to the corresponding alcohols **37** was readily accomplished with sodium borohydride and cerium trichloride in methanol. The trimethylsilyl groups were removed under phase transfer conditions with sodium hydroxide and the protection of the secondary alcohols as their *t*-butyldimethylsilyl ethers was effected with the silyl chloride and imidazole in yields of 90% or better.

In order to introduce the aldehyde functionality, direct condensation of the dilithioacetylides, derived from **38**, were reacted with paraformaldehyde, followed by Dess–Martin periodinane oxidation to the aldehydes **39**. The direct condensation with dimethylformamide followed by hydrolysis was also investigated, but this was less satisfactory than the two-step procedure. A series of pinacol coupling conditions were examined and in each case samarium iodide/HMPA was the best reagent, as summarized in Table 2. Under these conditions (Entries a and b), the cyclizations proceeded smoothly to provide **40a** and **40b** in yields of 84% and 74%, respectively. The use of vanadium trichloride tris(tetrahydrofuran) complex in dichloromethane at 21 °C for 3 h gave a diminished yield of 35% for **40b**, and the vanadium reagents also failed completely in the case of the 11-membered ring (Entry e). Titanium reagents have a



Scheme 6. Pinacol route to 11- and 12-membered rings.

Table 2. Pinacol couplings

entry	reagent	ring size	compound	yield
a	SmI_2/HMPA	11	**40a**	84%
b	SmI_2/HMPA	12	**40b**	74%
c	SmI_2	11	**40a**	21%
d	SmI_2	12	**40b**	52%
e	VCl^3·3THF/Zn	11	**40a**	0
f	VCl^3·3THF/Zn	12	**40b**	35%

(a) CS_2, $AlCl_3$, 0 °C, 30 min, 66%, 90%; (b) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 57%, 88%; (c) NaOH, $BnEt_3NCl$, CH_3CN, 0 °C, 0.5 h; t-$BuMe_2SiCl$, Imidazole, THF, 21 °C, 15 h, 90%, 95%; (d) *n*-BuLi, THF, $(CHO)_2$, –78–21 °C, 15 h, 82%, 84%; (e) Dess-Martin peiodinane CH_2Cl_2, 21 °C, 15 min, 87%, 93%; (f) SmI_2, THF, HMPA, –78–21 °C, 84%, 74%; (g) DMAP, ClC = SCl, CH_2Cl_2, –10 °C, 30 min, 66%, 71%; (h) $(MeO)_3P$, 55 °C, 5 d, 9%; (i) $(MeO)_3P$, 45 °C, 24 h, 75%.

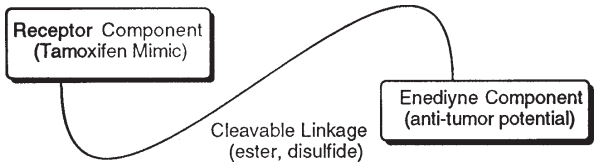
Unsuccessful titanium reagents: $TiCl_3$/K, $TiCl_4$/Zn, $TiCl_4$/Mg(Hg), $CpTiCl_3$/$LiAlH_4$, $TiCl_3$/$LiAlH_4$, $TiCl_3$/Zn-Cu.

reputation for being particularly useful for this type of transformation,[20] but as the list at the bottom of the table indicates, none of the reaction combinations listed gave any of the desired product.

The successful synthesis of the diols, which were a 1:1 cis/trans mixture in each case, set the stage for introduction of the double bonds using the thiocarbonate procedure of Corey and Winter.[21] Treatment of the diols **40** independently with thiophosgene provided the thiocarbonates **41** and **42**, respectively. Elimination to form **43** proved particularly troublesome, as at 40 °C only starting material was recovered and complete decomposition occurred at 70 °C in the presence of trimethylphosphite. The best procedure was to conduct the reaction for 4 h at 55 °C to produce a 9% yield of **43**. The yield was reduced to 2% upon direct thermolysis. In contrast, the 12-membered ring system **44** was formed in 75% yield when the reaction was conducted at 45 °C for 24 h. The low yield encountered in the case of the 11-membered ring is likely a consequence of the unfavorable geometry and increased ring strain that results from introduction of further unsaturation into the enediyne ring. An attempt to modify the nature of the acetylene geometry was examined, through the preparation of the bis-hexacarbonyl cobalt derivative of **41**, but the desired introduction of the double bond was not observed. Nevertheless, this route has provided the desired compounds **43** and **44**.

ACETAL-CONTROLLED ROUTE TO A 10-MEMBERED RING

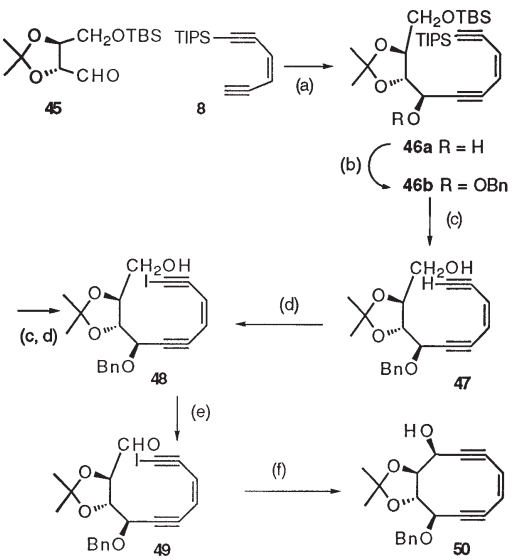
The knowledge gained above has been extended to the synthesis of functionalized 10-member rings. It is anticipated that appropriate combinations of a biological recognition agent and an endiyne will afford compounds with medicinal potential. We have designed antiestrogen-enediyne hybrid species that will possess both an anti-estrogenic and cytotoxic component. They will be linked together by a chain that would be hydrolyzed after administration, as illustrated in the general concept outlined in Scheme 7. For the enediyne component, a stable molecule is required during the synthesis, but the cyclodecenediyne should contain a trigger device in order to induce cycloaromatization in the range of 35–40 °C. A model to explore the potential of this concept has been developed based on a route that em-



Scheme 7. Antiestrogen-enediyne hybrids.

ploys an isopropylidene acetal tether control group. This principle has proved very useful in our intramolecular Diels–Alder studies directed toward paclitaxel and related natural products.[22]

This basic strategy for the synthesis of the enediyne **50** is outlined in Scheme 8. The known acetal **46** was derived from diethyl tartrate.[23] The acetal will act as a control group to facilitate the 10-membered ring cyclization. In addition, upon deprotection, the useful functionality is restored. In addition, the strain inherent in the trans isopropylidene moiety should inhibit Bergman cyclization initially, but allow the required close acetylene contact required upon hydrolysis to the diol. Eventually the enediyne will be linked to a steroidal or a tamoxifen mimic, which is known to interact with the breast cancer receptor. As illustrated, the enediyne component **8** was condensed with the aldehyde **45** and the resulting secondary alcohol **46a** (3:1 ratio) protected as its benzyl ether. The silyl groups were removed with tetrabutylammonium fluoride in THF to provide the acetylene-alcohol **47** in 96% yield.



(a) *n*-BuLi, **8**, THF, -78 °C, 86%; (b) NaH, BnBr, THF, 0-21 °C,16 h, 88%; (c) TBAF, THF, -78 - 0 °C, 0.5 h, 96%; (d) LDA, I_2, -78 -21 °C, 2.5 h, 93%; (e) Dess-Martin periodinane CH_2Cl_2, $NaHCO_3$, 45 min, 91%; (f) $NiCl_2$ (0.3 equiv.), $CrCl_2$, (9 equiv.) THF, 21 °C, 1.5 h, 35-71%.

Scheme 8. Acetal-controlled route to cyclodecaenediyne **50**.

Introduction of the iodine substituent by quenching the lithium acetylide with iodine provided **48** and set the stage for the preparation of the iodo-aldehyde **49** by Dess–Martin periodinane oxidation in 91% yield. Consistent with our previous experience,[6] the chromium mediated condensation produced variable yields, and in the best case the reaction was conducted at room temperature (21 °C), with excess chromium dichloride and a catalytic amount of nickel dichloride to afford the desired compound **50** in 71% yield (average 57%).

CONCLUSIONS

In summary, these investigations provide a direct route to simple alkoxypropargylic systems, from sensitive substrates, under mild Lewis acid conditions without excess reactant. Selection of the appropriate substitution pattern provides direct access to trisubstituted cyclopentene systems. A pinacol-based coupling route has been developed to 11- and 12-membered enediyne carbocycles, and this has been extended to a highly substituted 10-membered ring based on an acetal tether control strategy employing chromium/nickel-mediated cyclization.

EXPERIMENTAL

General

Melting points were determined in capillary tubes with a Thomas–Hoover unit-melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bomem Michelson 100 FTIR spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were measured at 200 MHz with a Varian Gemini spectrometer, at 300 MHz with a Varian XL-300 spectrometer, or at 500 MHz with a Brüker AMX500 spectrometer in deuterochloroform, unless otherwise stated. Carbon magnetic resonance spectra (^{13}C NMR) were measured at 50 MHz (Varian Gemini), at 75 MHz (Varian XL-300), or at 125 MHz (Brüker). The residual $CHCl_3$ signal was used as an internal reference, $CDCl_3$ ^{1}H; δ 7.24 ppm; ^{13}C; δ 77.0 ppm. Chemical shifts are reported in ppm downfield from trimethylsilane (δ scale). The multiplicity, coupling constants (Hz), and number of protons are indicated in parentheses. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instrument using an ionization energy of 70 eV. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, AZ, USA. The purity of all title compounds was judged to be >95% as determined by a combination of GC-MS, ^{1}H NMR, and ^{13}C NMR analyses.

Unless otherwise stated, all nonaqueous reactions were performed under an atmosphere of nitrogen in flame-dried glassware equipped with a magnetic stirring bar and a rubber septum. Standard inert atmosphere techniques were used in handling all air- and moisture-sensitive reagents. Reactions were monitored by analytical thin layer chromatography (TLC) using commercial aluminum sheets precoated (0.2 mm

layer thickness) with silica gel 60 F_{254} (E. Merck). Product purification employed flash column chromatography using E. Merck silica gel 60 (230–400 mesh). Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvents with a Büchi rotatory evaporator connected to a water aspirator. Trace solvents were removed on a vacuum pump. All compounds were stored at –15 °C in vials flushed with nitrogen.

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30–60 °C. Anhydrous diethyl ether (ether) and anhydrous tetrahydrofuran (THF) were distilled from benzophenone/sodium. Dry benzene, toluene, dichloromethane (CH_2Cl_2), and triethylamine were distilled from calcium hydride, and ethanol was distilled from lithium aluminum hydride. Commercial starting materials were purchased from Aldrich Chemical Company unless otherwise indicated.

*1-Trimethylsilyl-4-phenyl-3-methoxy-1-butyne **(17)***

Trimethysilylacetylene (**11**) (0.7 mL, 5 mmol) was dissolved in ether (12.5 mL) cooled to 0 °C, *n*-butyllithium (2.25 mL, 5.6 mmol, 2.5 M solution of in hexanes) was added, followed in 15 min by zinc dichloride (5.5 mL, 5.5 mmol, 1M solution in ether). The reaction was stirred for 30 min, and phenylacetaldehyde dimethylacetal (**13**) (0.9 g, 5.4 mmol) was added, followed immediately by boron trifluoride etherate (0.93 mL, 6.2 mmol). The reaction was quenched after 4 h with methanol, washed with saturated aqueous sodium bicarbonate, brine, and dried ($MgSO_4$). The mixture was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:5) to afford **17** (81%, 0.96 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2 (m, 5H), 4.1 (t, *J* = 6.7 Hz, 1H), 3.4 (s, 3H), 3.0 (m, 2H), 0.1 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.1, 42.0, 56.5, 72.6, 91.5, 103.8, 126.5, 128.1, 128.2, 129.4, 129.7, 137.2; IR (NaCl, neat) 3061, 3028, 2954, 2865, 2169, 1694, 1601; MS 232 (M^+, 0.6), 217 (M^+-Me 16), 141 (100); HRMS (EI): calcd for $C_{13}H_{17}OSi$ (M^+-Me) 217.1048, found 217.1038.

General Methods for Silylacetylene Addition

5-Triisopropylsilyl-3-methoxy-4-pentyn-1-al dimethyl acetal **(20).** *Method A*. Triisopropylsilylacetylene (**12**) (0.515 mL, 2.3 mmol) was dissolved in ether (4 mL), cooled to 0 °C, *n*-butyllithium (1.012 mL, 2.5 mmol, 2.5 M solution in hexane) was added, followed 15 min later by zinc dichloride (2.5 mL, 2.5 mmol, 1 M solution in ether). The reaction was stirred for 30 min, malondialdehyde tetramethylacetal (**15**) (0.46 g, 2.5 mmol) was added, followed by borontrifluoride etherate (0.31 mL, 2.5 mmol). The reaction was quenched after 16 h with methanol, washed with saturated aqueous sodium bicarbonate, brine, and dried ($MgSO_4$). The mixture was filtered concentrated and chromatographed (ether/petroleum ether, 1:5) to afford **20** (18%, 0.128 g).

Method B. Triisopropylsilylacetylene (**12**) (0.9 mL, 4 mmol) was dissolved in hexane (8 mL), cooled to 0 °C, and *n*-butyllithium (1.78 mL, 4.4 mmol, 2.5 M solution in hexanes) was added. After stirring for 15 min, the solution was transferred via cannula into aluminum trichloride (0.49 g, 3.7 mmol) and stirred for an additional 30 min. The solvent was evaporated under a stream of nitrogen and the solvent replaced with methylene dichloride (10 mL). Malondialdehyde tetramethylacetal (**15**) (0.6 mL, 3.6 mmol) was added and the reaction was stirred for 16 h at 0 °C. The reaction was quenched with water, extracted with ether, and washed with 10% aqueous potassium sodium tartrate solution until the organic phase was clear. The organic phase was dried ($MgSO_4$). The mixture was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:5) to afford **20** (37%, 0.4 g).

Method C. Triisopropylsilylacetylene (**12**) (0.26 mL, 1.2 mmol) was dissolved in hexane (2 mL), cooled to 0 °C, and *n*-butyllithium (0.47 mL, 4.4 mmol, 2.5 M solution in hexanes) was added. After stirring for 15 min, the solution was transferred via cannula into aluminum trichloride (0.072 g, 0.54 mmol) and stirred for an additional 30 min. The solvent was evaporated under a stream of nitrogen and the solvent replaced with methylene dichloride (3 mL). Malondialdehyde tetramethylacetal (**15**) (0.09 mL, 0.54 mmol) was added and the reaction was stirred for 16 h at 0 °C, followed by further stirring for 24 h at 21 °C. The reaction was quenched with water, extracted with ether, and washed with 10% aqueous potassium sodium tartrate solution until the organic phase was clear. The organic phase was dried ($MgSO_4$). The mixture was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:5) to afford **20** (33%, 0.06 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.6 (t, *J* = 5.9 Hz, 1H), 4.0 (t, *J* = 6.7 Hz, 1H), 3.4 (s, 3H), 3.3 (s, 6H), 1.7-2.1 (m, 2H), 1.0 (s, 21H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.1, 18.5, 39.1, 53.1, 53.6, 56.2, 68.2, 87.1, 102.0, 105.7; IR (NaCl, neat) 2908, 2167, 1731, 1457, 1378, 1071 cm^{-1}; MS 283 (M^+-OMe· 1.9), 271 (M^+-iPr, 16), 213 (92), 105 (100); HRMS (EI): calcd for $C_{14}H_{27}O_3Si$ (M^+-*i*-Pr) 271.1729, found 271.1718.

*1-Triisopropylsilyl-3-methoxy-3-(3′-cyclohexenyl)-1-propyne **(18)**. Method A*. **18** (54%, 0.29 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.6 (bs, 2H), 3.84 and 3.82 (2d, *J* = 4 .0 Hz, *J* = 4.4 Hz, 1H), 3.4 (s, 3H), 1.8–2.2 (7H), 1.1 (bs, 21H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.2, 18.6, 22.7, 24.4, 24.8, 24.9, 27.2, 27.6, 38.7, 56.5, 75.8, 76.0, 87.4, 105.2, 105.3, 125.9, 126.1, 126.8, 127.0; IR (NaCl, neat) 3023, 2946, 2858, 2165, 1457, cm^{-1}; MS 305 (M^+-H, 0.3), 291 (M^+-Me, 12), 263 (M^+-iPr, 23), 75 (100); HRMS (EI): calcd for $C_{18}H_{31}OSi$ (M^+-Me) 291.2144, found 291.2178.

*5-Trimethylsilyl-3-methoxy-4-pentyne-1-al dimethyl acetal **(19)**. Method A*. **19** (23%, 0.128 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.54 (t, *J* = 5.9 Hz, 1H), 4.0 (t, *J* = 6.4 Hz, 1H), 3.4 (s, 3H), 3.3 (s, 6H), 1.8–2.1 (m, 2H), 0.1 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.1, 38.7, 52.9, 53.3, 56.3, 68.1, 90.9, 101.6, 103.7; IR (NaCl, neat) 2940, 2828, 2170, 1455, 1380 cm^{-1}; MS 215 (M^+-Me, 0.6), 200 (M^+-2Me, 1), 199 (M^+-OMe, 3), 141 (19), 75 (100); HRMS (EI): calcd for $C_{10}H_{19}O_3Si$ (M^+-Me) 215.1103, found 215.1115.

*5-Triisopropylsilyl-3-ethoxy-4-pentyne-1-al diethyl acetal **(21)**. Method B*. **21** (27%, 0.063 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.7 (t, ^{3}*J* =5.9Hz, 1H), 4.1(t, *J* = 6.5 Hz, 1H), 3.4 (m, 6H), 1.7–2.1 (m, 2H), 1.2 (t, *J* = 7 Hz, 9H), 1.0 (s, 21H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 11.1, 15.1, 15.3, 18.6, 40.3, 61.5,

62.1, 64.0, 66.5, 100.3, 106.6; IR (NaCl, neat) 2913, 2166, 1458, 1367, 1078 cm^{-1}; MS 313 (M^+-*i*-Pr, 19), 241 (100); HRMS (EI): calcd for $C_{17}H_{33}O_3Si$ (M^+-*i*-Pr) 313.2199, found 313.2204.

4-Methoxy-6-trimethylsilyl-5-hexynal dimethylacetal ***(24)***. 2,5-Dimethoxytetrahyrofuran (**23**) (0.330 mL, 2.5 mmol) was dissolved in methylene chloride (10 mL), bis-(trimethylsilyl) acetylene (**22**) (0.56 mL, 2.5 mmol) was added, the reaction cooled to –78 °C, and treated with titanium tetrachloride (0.375 mL, 1M solution in methylene chloride). The reaction was stirred for 30 min, quenched with excess methanol, and warmed to room temperature (21 °C). The solution was washed with aqueous 10% HCl, water, and dried ($MgSO_4$). The organic phase was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:4) to afford **24** (51%, 0.310 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3–4.4 (m, 1H), 3.9–4.0 (m, 1H), 3.3 (s, 3H), 3.2 (s. 6H), 1.6–1.8 (m, 4H), 0.1 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.1. 27.9, 30.4, 52.5, 56.3, 71.1, 90.6, 104.0, ; IR (NaCl) 2950, 2856, 2169, 1727, 1453, 1250 cm^{-1}; MS 244 (0.1), 229 (0.3), 198(3.6), 182 (5.4), 154 (12.7), 141 (20.2), 75(100); HRMS (EI): calcd for (M^+-) $C_{11}H_{21}O_3Si$ (M^+-Me) 229.1260, found 229.1250.

1-Trimethysilyl-3-methoxymethyloxy-6-methoxy-1-cyclohexene ***(25)***. Acetal (**24**) (0.110 g, 0.45 mmol) was dissolved in methylene chloride, (10 mL) bis-(trimethylsilyl) acetylene (**22**) (0.3 mL, 1.3 mmol, 1.3 equiv), was added, the reaction cooled to –78 °C, and treated with titanium tetrachloride (0.7 mL, 1M solution in methylene chloride). The reaction was stirred for 30 min, quenched with excess methanol, and warmed to 21 °C. The solution was washed with aqueous 10% HCl, water, and dried ($MgSO_4$). The organic phase was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:6) to afford **25** (82%, 0.091 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9 (bs, 1H), 4.71 and 4.64 (AB, J = 6.5 Hz, 2H), 4.1–4.2 (m, 1H), 4.0–4.1 (m, 1H), 3.3 (s, 3H), 3.2 (s, 3H), 1.6–1.9 (m, 4H), 0.9 (s, 9H);^{13}C NMR (200 MHz, $CDCl_3$) δ –0.4, 27.5, 29.4, 55.2, 55.3, 79.57, 79.63, 94.6, 130.4, 158.3; IR (NaCl) 2952, 2820, 1727, 1637, 1452, 1355, 1247, 1149 cm^{-1}; MS 229 (0.5), 199 (7.1), 182 (14.3), 167 (24.9), 89 (100); MS-FAB 555 (0.1), 497(0.2), 459 (1.5), 73.1 (100); HRMS (EI): calcd for $C_{11}H_{21}O_3Si$ 229.1260, found 229.1252.

4-Methoxy-5-hexyne-1-al dimethyl acetal ***(27)***. 2,5-Dimethoxytetrahydrofuran (**23**) (0.990 mL, 7.5 mmol) and *bis*-trimethylsilylacetylene (**22**) (1.68 mL, mmol) were dissolved in methylene chloride (30 mL), cooled to –78 °C, and titanium tetrachloride (11.25 mL 1M solution in methylene chloride) was added. The reaction was stirred for 30 min, quenched with excess methanol, and warmed to 21 °C. The solution was washed with aqueous 10% HCl, water, dried ($MgSO_4$), filtered, and concentrated to afford **25** (1.85 g). This material was dissolved in acetonitrile (10 mL), TEBA (0.35 mmol) was added, followed by 12 M sodium hydroxide solution (2 mL), and stirred at 0 °C for 45 min. The reaction was quenched with a 1:1 mixture of water and ether (60 mL), the organic phase was washed with water, brine, and dried ($MgSO_4$). The organic phase was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:19) to afford **27** (54%, 0.7 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3 (m, 1H), 3.9 (m, 1H), 3.3 (s, 3H), 3.2 (s, 6H), 2.4 (d, J = 2.0 Hz, 1H), 1.7 (m, 4H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 27.9, 30.4, 52.6, 56.3, 70.5, 73.9, 82.2, 104.0; IR (NaCl, neat) 3273, 2935, 2828, 2109, 1453, 1092 cm^{-1}; MS-EI 172 (0.03), 171 (0.3), 141 (2.2), 109 (24.7), 75 (100); HRMS (EI): calcd for $C_8H_{13}O_2$, (M^+-MeO) found 141.09344.

(Z)-4-Methoxy-10-trimethylsilyl-7-decene-5,9-diyne-1-al dimethyl acetal ***(29)***. Trimethylsilylacetylene (**11**) (3 mL, 21 mmol), *cis*-dichloroethylene (3 mL, 42 mmol), and *n*-butylamine (10 mL, 100 mmol) were dissolved in ether (50 mL). Tetrakis(triphenylphosphine)palladium (1.16 g, 1 mmol) and copper iodide (0.4 g, 2.2 mmol) were added and the reaction was stirred under nitrogen for 15 h. The reaction mixture was concentrated, petroleum ether added (50 mL), filtered through a plug of Celite®, reconcentrated, and chromatographed (ether/petroleum ether, 1:9) to afford the pure enyne (**28**) (57%, 2.0 g). The alkyne (**27**) (0.172 g, 1 mmol), eneyne (**28**) (0.16 g, 1 mmol), and *n*-butylamine (1 mL, 10 mmol) were dissolved in ether (10 mL). Tetrakis(triphenylphosphine)palladium (0.05 g, 0.05 mmol) and copper iodide (0.04 g, 0.21 mmol) were added and stirring continued for 15 h. Ether (50 mL) was added to the reaction mixture, filtered through a plug of Celite®, concentrated and chromatographed (ether/petroleum ether, 1:4) to afford enediyne **29** (40%, 0.120 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8 (m, 2H), 4.4 (m, 1H), 4.1 (m, 1H), 3.4 (s, 3H), 3.3 (s, 6H), 1.7 (m, 4H), 0.1 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.3, 28.0, 30.4, 30.5, 52.6, 56.5, 71.2, 83.3, 95.8, 101.8, 102.9, 104.1, 119.8, 110.0; IR (NaCl, neat) 2954, 2858, 2827, 2145, 1453, 1251, 1093 cm^{-1}; MS-EI 293 (0.04), 279 (0.17), 263 (5.22), 191 (26.8), 159 (17.2), 89 (27.3), 75 (100); HRMS (EI): calcd for $C_{15}H_{23}O_2Si$ (M^+-MeO) 263.1467, found 263.1467.

(Z)-4-Methoxy-7-decene-5,9-diyne-1-al dimethyl acetal ***(30)***. The enediyne (**29**) (1.4 g, 4.7 mmol) was dissolved in THF (4 mL) and added to THF/methanol (10 mL:28 mL) solution containing potassium carbonate (1 g). The reaction was stirred for 2.5 h and ether (25 mL) and water (5 mL) added. The organic phase was dried ($MgSO_4$), filtered, concentrated, and chromatographed (ether/petroleum ether, 1:4) to afford acetal **30** (87%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.9 (dd, J = 11 Hz, J = 0.75 Hz, 1H), 5.75 (dd, J = 11 Hz, J = 2.2 Hz, 1H), 4.3 (m, 1H), 4.1 (m, 1H), 3.4 (s, 3H), 3.2 (s, 6H), 1.7 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 27.9, 30.3, 52.5, 56.3, 71.1, 80.5, 82.8, 84.8, 95.3, 103.9, 118.8, 121.0; IR (NaCl, neat) 3271, 2937, 2828, 1453, 1387, 1336 cm^{-1}; MS-EI 191 (4.6), 161 (3.9), 159 (13.8),128 (20), 75 (100); HRMS (EI): calcd for $C_{13}H_{18}O_3$ 191.1072, found 191.1061.

(Z)-4-Methoxy-10-trimethylsilyl-7-decene-5,9-diyne-1-al (32). Dimethylacetal (**29**) (0.080 g, 0.27 mmol) was dissolved in dry acetone (3 mL) and *p*-toluenesulphonic acid (3 mg). The reaction was stirred for 15 h and chloroform added (25 mL). The organic phase was washed with water, brine, and dried ($MgSO_4$). The organic phase was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:9) to afford aldehyde **32** (63%, 0.042 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.8 (bs,

1H), 5.8 (s, 2H), 4.2 (t, 1H), 3.4 (s, 3H), 2.6 (t, 2H), 2.1 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.2, 28.1, 39.5, 56.6, 70.4, 83.8, 94.9, 101.7, 103.1, 119.6, 120.2, 201.5; IR (NaCl, neat) 2950.5, 2825, 2144, 1725, 1446, 1390, 1251, 1098 cm^{-1}; MS-EI 248 (0.9), 220 (1.2), 191 (11.5)159.0 (10.9), 115.1 (11.8)84.0 (100); HRMS (EI): calcd for $C_{14}H_{20}O_2Si$, 248.1232, found 248. 1219.

(Z)-4-Methoxy-7-decene-5,9-diyne-1-al ***(33)***. Enediyne (**32**) (0.11 g, 0.44 mmol) and acetic anhydride (0.084 mL, 0.88 mmol) were dissolved in acetonitrile (2 mL), cesium fluoride (0.23 g, 1.54 mmol) and sodium bicarbonate (0.037 g) were added and the reaction was stirred for 3 h. The reaction mixture was filtered through silica gel, concentrated, and chromatographed (ether/petroleum ether, 1:7) to afford the endiyne **33** (89%, 0.069 g). Note: For consistent results, the CsF should be dried under vacuum for 2 h at 100 °C, acetonitrile refluxed over calcium hydride and distilled, and acetic anhydride refluxed with quinoline and distilled. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.8 (bs, 1H), 5.9 (d, J = 11 Hz, 1H), 5.75(d, J = 11 Hz, 1H), 4.1 (m, 1H), 3.4 (s, 3H), 2.6 (t, 2H), 2.1 (m, 2H), 1.8 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 28.4, 39.3, 56.4, 71.1, 80.3, 82.6, 84.9, 95.7 118.5, 121.4, 201.2; IR (NaCl, neat) 3275, 2938, 2825, 1724, 1097 cm^{-1}.

3,7-Dioxo-1,9-ditrimethylsilyl-1,8-nonadiyne ***(36a)***. A solution of glutaryl chloride (**35a**) (2.94 mL, 23 mmol) and *bis*-trimethylsilylacetylene (**22**) (10.39 mL, 46 mmol) in carbon disulfide (10 mL) was added via syringe pump (30 minutes) to a stirred suspension of aluminum trichloride (6.14 g, 46 mmol) in carbon disulfide (50 mL) at 0 °C. The reaction was stirred for 30 min and the resulting brown suspension was poured over crushed ice, and the organic phase was washed (4×) with 10% hydrochloric acid, followed by brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (ether/petroleum ether, 1:4) to afford **36a** (66%, 4.4 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.5 (t, J = 7.1 Hz, 4H), 1.8 (qv, J = 7.1 Hz, 2H), 0.08 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.08, 17.6, 43.8, 43.9, 98.14, 101.7, 186.5; IR (NaCl) 2919, 2900.8, 2150.2, 1677.3, 1253. 1108, 860.9 cm^{-1}; MS 277.1 (16.2), 167.1 (18.6), 125 (100), 97 (41.1), 73 (59); HRMS (EI): calcd for $C_{14}H_{21}O_2Si_2$ 277.1080, found 277.1091; Anal. Calcd for $C_{12}H_{24}O_2Si_2$: C, 61.58; H, 8.26. Found: C, 61.42; H, 8.25.

3,8-Dioxo-1,10-ditrimethylsilyl-1,9-decadiyne ***(36b)***. A parallel reaction with adipoyl chloride (**35b**) (3.36 mL, 23 mmol) gave **36b** as a yellow liquid (90%, 6.3 g) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (m, 4H), 1.55 (m, 4H), 0.1 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.8, 22.9, 44.7, 97.8, 101.8, 187; IR (NaCl) cm^{-1} 2943, 2150, 2092, 1676, 1407, 1357, 1252, 1109, 1045, 859, 762 cm^{-1}; MS 291 (13), 263 (2.6), 193(2.4), 173 (4.2), 155(8.7), 140 (15.7), 125 (93.7), 97 (41,6), 73 (100); HRMS (EI): calcd for $C_{15}H_{23}O_2Si_2$ 291.1236, found 291.1219.

1,9-Ditrimethylsilyl-1,8-nonadiyne-3,7-diol ***(37a)***. The diketone **36a** (4.4 g, 14.95 mmol) was dissolved in methanol (500 mL), cerium trichloride heptahydrate (51 g, 138 mmol) was added and the reaction stirred for 10 min. The solution was cooled to 0 °C, sodium borohydride (6.96 g, 184 mmol) was added in portions portionwise, and the reaction was monitored by TLC and quenched with 10% hydrochloric acid. The reaction was concentrated under vacuum, extracted with ethyl acetate (3 × 50 mL), the organic phase was extracted with brine. The organic phase was dried ($MgSO_4$), filtered, concentrated, and chromatographed (ether/petroleum ether, 1:2) to afford **37a** (57%, 3.9 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.26 (m, 2H), 2.5 (bs, 2H), 1.4–1.7 (m, 6H), 0.02 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.1, 20.7, 37.0, 62.4, 89.22, 106.8; IR (NaCl) 3359, 2943, 2172, 1397, 1326, 1251 cm^{-1}.

1,10-Ditrimethylsilyl-1,9-decadiyne-3,8-diol ***(37b)***. The parallel reaction with diketone **36b** (6.3 g, 20.7 mmol) afforded **37b** (88%, 6.2 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.23 (t, J = 6.4 Hz, 2H), 2.1 (bs, 2H), 1.55 (m, 4H), 1.37 (m, 4H), 0.04 (s, 18H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –0.12, 24.7, 37.4, 62.6, 89.3, 106.8; IR (NaCl) 3350, 2919, 2171, 1411, 1251, 1036, 855 cm^{-1}.

*3,7-Di(*t*-butyldimethylsilyloxy)-1,9-ditrimethylsilyl-1,8-nonadiyne* ***(38a)***. A sodium hydroxide solution (12 M, 36% W/W, d = 1.39 g/mL, 24 mL, 288 mmol) was added dropwise to a cold (0 °C), stirred solution containing 1,9-ditrimethylsilyl-1,8-decadiyne-3,7-diol (**37a**) (8.27 g, 28.3 mmol), benzyltriethylammonium chloride (0.3 g) in acetonitrile (25 mL) for 30 min. The reaction mixture was diluted with ether, washed with water, brine, dried ($MgSO_4$), filtered, concentrated, to give the diacetylene (4 g, 26.7 mmol). This material and imidazole (9.5 g, 140.4 mmole) were dissolved in tetrahydrofuran (20 mL), a THF solution (20 mL) containing tert-butyldimethylsilylchloride (9.75 g, 65 mmol) was added. The reaction stirred for 15 h, petroleum ether and 1M hydrochloric acid added, and the organic phase was washed with aqueous saturated sodium bicarbonate and brine. The organic extracts were filtered, concentrated, and chromatographed (ether/petroleum ether, 1:30) to afford **38a** (90%, 9.1 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3 (m, 2H), 2.3 (d, J = 2.1 Hz, 2H), 1.4-1.8 6H), 0.9 (s, 18H), 0.09 (d, 12H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.0, –4.5, 18.1, 21.0, 25.8, 38.2, 62.6, 72.1, 85.5; IR (NaCl) 3303, 2910, 1467 cm^{-1}; MS 380 (0.05), 323 (17.4), 147 (79.6), 73 (100); HRMS (EI): calcd for $C_{17}H_{31}O_2Si_2$ (M^+-*t*-Bu) 323.1862, found 323.1858.

*3,8-Di(*t*-butyldimethylsilyloxy)-1,10-ditrimethylsilyl-1,9-decadiyne* ***(38b)***. A parallel reaction with 1,10-ditrimethylsilyl-1,9-decadiyne-3,8-diol (**37b**) (4.8 g, 15.5 mmol) gave **38b** (95%, 5.8 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.23 (dt, J = 6 Hz, J = 2 Hz, 2H), 2.26 (d, J = 2 Hz, 2H), 1.6 (m, 4H), 1.3 (m, 4H), 0.8 (s, 18 H), 0.0 (2s, 12 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.1, –4.5, 18.2, 24.7, 25.7, 38.5, 62.6, 71.9, 85.6; IR (NaCl) 3307, 2943, 2859, 1467, 1361, 1254, 1081, 841, 779 cm^{-1}; MS 337 (11), 263 (7.5), 243 (8.1), 189 (12.2), 169 (11.3), 147 (100), 131 (14.6), 91 (14.3), 73 (83); HRMS (EI): calcd for $C_{18}H_{33}O_2Si_2$ 337.2019, found 337.2052; Anal. Calcd for $C_{22}H_{42}O_2Si_2$: C, 66.94; H, 10.72. Found: C, 66.79; H, 10.84.

*4,8-Di(*t*-butyldimethylsilyloxy)-2,9-diyne-1,11-undecadiol*. The diyne (**38a**) (5.5 g, 14.5 mmol) was dissolved in tetrahydrofuran (100 mL), cooled to –78 °C and *n*-butyllithium (13 mL, 33 mmol, 2.5 M solution in hexanes)was added

dropwise. After 15 min, paraformaldehyde (4.3 g, 145 mmol) (previously dried under water aspirator vacuum for two hours at 80°C) was added, the bath removed, the reaction mixture stirred for 15 h at 21 °C. Saturated ammonium chloride solution was added followed by ether and the extracts washed with brine. The organic extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed (ether/petroleum ether, 1:5) to afford the diol (82%, 5.2 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3 (m, 2H), 4.2 (s, 4H), 2.7–2.9 (bs, 2H), 1.5-1.8 (m, 6H), 0.8 (s, 18H), 0.06 (d, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.0, –4.5, 18.1, 20.7, 20.9, 25.7, 38.0, 50.8, 62.9, 82.5, 86.9; IR (NaCl) 3344, 2942, 2858, 1466 cm^{-1}; MS 422.8 (M^+-H_2O, 2.5), 382.9 (M^+-*t*-Bu, 1.7), 364.9 (4.1), 291 (100).

*4,9-Di(*t-*butyldimethylsilyloxy)-2,10-diyne-1,12-dodecadiol*. A parallel reaction with diyne (**38b**) (1.8 g, 4.5 mmol) afforded the corresponding diol (84%, 1.7 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.25–4.4 (m, 2H), 4.2 (s, 4H), 2.3–2.5 (bs, 2H), 1.5–1.7 (m, 4H), 1.3–1.5 (m, 4H), 0.8 (s, 18H), 0.07 (d, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.0, –4.5, 18.2, 24.7, 25.8, 38.4, 50.9, 62.8, 82.2, 87.3; IR (NaCl) 3355, 2909, 1468.9 cm^{-1}.

*4,8-Di(*t-*butyldimethylsilyloxy)-2,9-diyne-1,11-undecadial* ***(39a)***. Dess-Martin reagent (3.7 g, 8.8 mmol) was added to the diol (1.8 g, 4 mmol) in methylene chloride (200 mL) and after 15 min, ether (200 mL) was added. The reaction was concentrated to ~20 mL and additional ether (300 mL) added followed by a 1:1 mixture of 1 M sodium thiosulphate and 1 M sodium bicarbonate aqueous solution The reaction was stirred until two clear phases separated. The organic phase was washed with brine, back extracted with ether, and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:20) to yield **39a** (87%, 1.5 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.2 (s, 2 H), 4.5 (t, *J* = 6.1 Hz, 2 H), 1.5–1.7 (m, 6H), 0.8 (s, 18 H), 0.07 (d, 12 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.2, –4.7, 18.0, 20.6, 25.6, 37.1, 62.4, 83.6, 97.2, 176.4; IR (NaCl) 2943, 2858, 2215, 1671, 1467 cm^{-1}; MS-CI $(M-1)^+$, 421; MS-EI 421, 407, 379.

*4,9-Di(*t-*butyldimethylsilyloxy)-2,10-diyne-1,12-dodecadial* ***(39b)***. A parallel reaction with the **b** diol (2.3 g, 5 mmol) gave **39b** (93%, 2.1 g)**.** ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.2 (s, 2H), 4.5 (t, *J* = 6.4 Hz, 2H), 1.6–1.8 (m, 4H), 1.3–1.5 (m, 4H), 0.9 (s, 9H), 0.09 (d, *J* = 6 Hz, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.2, –4.7, 18.1, 24.5, 25.6, 37.5, 62.5, 83.5, 97.5, 176.5; IR (NaCl) 2909, 2215, 1671.6, 1467, 1388 cm^{-1}.

*5,9-Di(*t-*butyldimethylsilyloxy)-3,10-cycloundecadiyne-1,2-diol* ***(40a)***. Dialdehyde (**39a**) (0.1 g, 0.22 mmol) was dissolved in tetrahydrofuran (3 mL) in a nitrogen atmosphere and frozen in liquid nitrogen. Three freeze–thaw cycles were conducted. In a separate flask, dry HMPA (1 mL) and tetrahydrofuran (4 mL) were degassed by the same freeze–thaw procedure. Samarium diiodide (8.8 mL, 0.88 mmol, 0.1M solution in tetrahydrofuran was added to the HMPA solution to give a dark purple solution which was cooled to –78 °C. The degassed dialdehyde solution was injected by syringe pump over 1 h and the reaction was quenched with 1 M hydrochloric acid. Ether and aqueous 10% sodium thiosulfate solution were added. The organic phase was washed with brine and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:2.5) to yield **40a** (84%, 0.081 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.3–4.5 (bs, 4H), 2.7–2.9 (bs, 1H), 2.5–2.7 (bs, 1H), 1.5–2.0 (m, 6H), 0.8 (s, 18H), 0.08 (d. 12H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.0, –4.9, –4.6, –4.3, 18.2, 19.7, 20.1, 25.8, 37.0, 63.4, 63.5, 68.0, 68.1, 82.8, 89.6; IR (NaCl) 3363, 2910, 1466 cm^{-1}; Anal. Calcd for $C_{23}H_{42}O_4Si_2$: C, 62.96; H 9.64. Found: C 63.32; H 9.75.

*5,10-Di(*t-*butyldimethylsilyloxy)-3,11-cyclododecadiyne-1,2-diol* ***(40b)***. The parallel method with dialdehyde **39b** (0.1 g, 0.22 mmol) afforded the diol **40b** (74%, 0.074 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.4–4.7 (m, 4H), 2.5–2.8 (m, 2H), 1.6–1.9 (m, 8H), .95 (bs, 18H), 0.15 (bs, 12 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.0, –4.9, –4.5, 18.21, 23.1, 23.3, 23.6 23.7, 25.8, 36.3, 36.4, 36.7, 62.7, 62.8, 63.04, 63.2, 67.1, 67.2, 81.7, 81.8, 89.0, 89.1; IR (NaCl) 3373, 2942, 2858, 1254, 1075.7, 842.2 cm^{-1}; Anal. Calcd for $C_{24}H_{44}O_4Si_2$: C, 63.66; H 9.79. Found: C 63.80; H 9.81.

Alternative method: Vanadium trichloride tris(tetrahydrofuran) complex (0.144 g, 0.38 mmol) and zinc (0.014 g, 0.21 mmol) were suspended in methylene chloride (5 mL) and stirred for 15 min until the solution turned dark green color. Dialdehyde (**39b**) (0.05 g, 0.11 mmol) in methylene chloride (1 mL) was added dropwise and stirred for 3 h. Aqueous sodium tartrate 10% w/v was added and the reaction mixture extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium bicarbonate, and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:2) to yield **41b** (35%, 0.018 g).

*Bicyclo[9.3.0]-3,8-di(*t-*butyldimethylsilyloxy)-13-thiono-12,14-dioxa-2,9-tetradecadiyne* ***(41)***. A methylene dichloride solution (2 mL) containing the diol (**40a**) (0.1 g, 0.22 mmol) and 4-dimethylaminopyridine (0.064 g, 0.53 mmol) was cooled to –10 °C and thiophosgene (0.02mL, 0.26 mmol) added dropwise. After 30 min, silica gel (0.4 g) was added, the reaction was concentrated and chromatographed (ether/petroleum ether, 1:20) to afford **43** (66%, 0.074 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.39 (*J* = 11.3, *J* = 2.24, 1H), 5.31–5.36 (m, 2H), 5.26 (*J* = 11.3, *J* = 1.3, 1H), 1.6–2.0 (m, 6H), 0.9 (d, 18H), 0.07 (d, 12 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.1, –5.0, –4.8, –4.7, 18.1, 18.6, 18.9, 19.2, 25.7, 38.4, 38.6, 38.9, 63.3, 63.5, 75.0, 75.1, 75.9, 76.0, 100.0, 100.2, 189.3; IR (NaCl) 2910, 2222, 1842, 1465 cm^{-1}; MS 423, (9.4), 363.2 (3.5), 231 (13.5), 147 (25.9), 73 (100); HRMS (EI): calcd for $C_{20}H_{31}O_4Si_2S$ 423.1498, found 423.1472.

*Bicyclo[10.3.0]-3,10-di(*t-*butyldimethylsilyloxy)-14-thiono-13,15-dioxa-2,10-tetradecadiyne* ***(42)***. A parallel reaction with diol **40b** (0.170 g, 0.37 mmol) afforded **42** (71%, 0.129 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.2–5.4 (2H), (5.35 (dd, *J* = 11.4Hz, *J* = 2.4Hz, 1H), 5.29 (bs, 2H), 5.24 (dd, *J* = 11.4Hz, *J* = 1.1Hz, 1H), 4.5 (m, 1H), 4.4 (m, 1H), 1.4–1.8 (m, 8H), 0.87 (bs, 18 H), 0.09 and 0.07(s, 12H); ^{13}C NMR (500 MHz, $CDCl_3$) δ –5.1, –4.7, 18.1, 23.7, 23.8, 23.9, 24.2, 25.7, 25.8, 37.0, 37.4, 37.6, 62.6, 62.7, 62.9, 63.0, 74.0, 74.1, 74.3,

74.5, 75.5, 75.6, 97.9, 98.0, 189.5; IR (NaCl) 2911, 2234, 1843, 1465 cm^{-1}; MS 437 (4.5), 73 (100); HRMS (EI): calcd for $C_{21}H_{33}O_4Si_2S$ 437.1655, found 437.1622.

*7,11-Di(*t*-butyldimethylsilyloxy)-3-ene-1,5-cycloundecadiyne* ***(43)***. Thionocarbonate (**41**) (0.120 g, 0.25 mmol) was heated in trimethylphosphite at 55 °C for 3 days. The reaction mixture was concentrated, petroleum ether and aqueous saturated sodium bicarbonate were added. The organic phase was dried($MgSO_4$), filtered, concentrated, and chromatographed (ether/petroleum ether, 1:20) to yield enediyne **43** (9%, 0.009 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8 (s, 2H), 4.6–4.8 (m, 2H), 1.6–1.9 (m, 6H), 0.8 (s, 18H), 0.1 (s, 12H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –5.0, –4.6, 18.4, 20.1, 25.8, 37.2, 63.4, 82.1, 98.2, 120.3; IR (NaCl) 2950, 2850, 1468, 1339 cm^{-1}; MS 347.1 (12.6), 271 (7.9), 215 (25), 141 (41), 73 (100); HRMS (EI): calcd for $C_{19}H_{31}O_2Si_2$, 347.1862, found 347.1858.

*7,12-Di(*t*-butyldimethylsilyloxy)-3-ene-1,5-cyclododecadiyne* ***(44)***. Thionocarbonate (**42**) (1 g, 2 mmol) was dissolved in trimethylphosphite (20 mL) and heated at 45 °C for 24 h. The reaction mixture was concentrated, petroleum ether and aqueous saturated sodium bicarbonate were added. The organic phase was dried($MgSO_4$), filtered, concentrated, and chromatographed (ether/petroleum ether, 1:20) to yield enediyne **44** (75%, 0.62 g). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.8 (s, 2H), 4.6 (m, 2H), 1.6–1.9 (m, 8H), 0.9 (s, 18 H), 0.08 and 0.1 (2s, 12H); ^{13}C NMR (200 MHz, $CDCl_3$) δ –4.9, –4.5, 18.3, 23.8, 24.3, 25.8, 36.7, 36.8, 63.6, 64.0, 82.9, 98.5, 98.7, 120.6; IR (NaCl) 2810, 2234, 1468, 1337 cm^{-1}; MS 361 (12.6), 229 (28), 155 (30.6), 73 (100); HRMS (EI): calcd for $C_{20}H_{33}O_2Si_2$ 361.2019, found 361.2038.

(2S, 3S, 7Z)-4-Hydroxy-1-tert-butyldimethylsilyloxy-2,3-O-isopropylidenedec-7-en-(9-tri-isopropylsilyl)-5-9-diyne-2,3-diol ***(46a)***. *n*-Butyllithium (2.56 M in THF, 11.47 mL, 29.36 mmol) was added slowly to a cold (–78 °C) solution of 1-(triisopropylsilyl)-3-hexen-1,5-diyne (**8**) (6.500g, 27.96 mmol) in THF (100 mL). The initial yellow solution turned dark brown. The reaction was stirred for 20 min and a solution of freshly distilled **45** (3.837 g, 13.98 mmol) in THF (15 mL) was added dropwise. The reaction was stirred at –78 °C for an additional 30 min and warmed to 0 °C. Water (50 mL) and ether (50 mL) were added and the phases were separated. The aqueous fraction was extracted with ether (3 × 50 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:10 to 1:5) to afford **46a** (86%, 6.1 g) as an orange oil. IR (neat) 3435, 2942, 2864, 2361, 2339, 1464, 1379, 1252, 1142, 1083, 1018, 882, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.05 (s, 3H), 0.93 (s, 9H), 1.05–1.14 (m, 3H), 1.17 (d, 18H, *J* = 6.4 Hz), 1.39 (s, 3H), 1.41 (s, 3H), 2.47 (d, 1H, *J* = 5.2 Hz), 3.80 (dd, 1H, *J* = 10.8, 4.3 Hz), 3.83 (dd, 1H, *J* = 10.8, 4.3 Hz), 4.14–4.25 (m, 2H), 4.70 (ddd, 1H, *J* = 5.0, 5.0, 1.7 Hz), 5.47 (d, 1H, *J* = 11.1 Hz), 5.51 (d, 1H, *J* = 11.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.4, –5.3, 11.6, 18.9, 26.1, 27.2, 27.5, 64.1, 64.4, 75.0, 80.5, 83.9, 95.8, 99.9, 104.4, 109.9, 120.0, 120.5; HRMS (EI): calcd for $C_{27}H_{47}O_4Si_2$ (M^+-Me) 491.3015, found 491.3001.

(2S, 3S, 7Z)-4-Benzyloxy-1-hydroxy-2,3-O-isopropylidenedec-7-en-5,9-diyne-(9-tri-isopropylsilyl)-2,3-diol ***(46b)***. Alcohol **46a** (9.342 g, 18.4 mmol) was transfered via canula to an ice cold (0 °C) solution of NaH (60% suspension in mineral oil, 25 mg, 0.62 mmol) which was previously washed with pentane (3 × 45 mL) prior to the addition of THF (10 mL). The resulting brown solution was stirred for 20 min at 0 °C followed by the dropwise addition (syringe) of benzyl bromide (3.462 g, 20.24 mmol). The reaction was allowed to warm to 21 °C and stirred for 17 h. Water (50 mL) and ether (50 mL) were added to the orange-brown solution and the mixture stirred for further 2 h. The aqueous and organic phases were separated. The aqueous fraction was extracted with ether (3 × 20 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:20) to afford **46b** (88%, 7.90 g) as a colorless oil and recovered starting material, **46a** (1.7 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.97 (s, 9H), 1.05–1.11 (m, 3H), 1.15 (d, 18H, *J* = 6.5 Hz), 1.46 (s, 6H), 3.83-3.86 (m, 1H), 3.99-4.02 (m, 1H), 4.40 (d, 1H, *J* = 3.2 Hz), 4.40–4.50 (m, 1H), 4.53 (d, 1H, *J* = 11.7 Hz), 4.59 (d, 1H, *J* = 2.9 Hz), 4.93 (d, 1H, *J* = 11.7 Hz), 4.89–5.55 (m, 2H), 7.06–7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.2, –5.1, 11.6, 18.9, 26.1, 27.3, 27.7, 64.5, 71.2, 71.4, 78.9, 79.6, 85.1, 94.3, 100.1, 104.4, 110.0, 119.7, 120.6, 127.9, 128.0, 128.2, 128.5, 138.2.

(2S, 3S, 7Z)-4-Benzyloxy-1-hydroxy-2,3-O-isopropylidenedec-7-en-5,9-diyne-2,3-diol ***(47)***. *t*-Butyl ammonium fluoride (1M in THF, 3.59 mL, 3.59 mmol) was added to THF (15 mL) at –78 °C containing **46b** (1.023 g, 1.171 mmol). The reaction was stirred at –78 °C for 2 h, for a further 2 h at 0 °C, water was added, and stirring was continued for a further 20 min. Ether (2 mL) was added, the aqueous fraction which was extracted with ether (3 × 15 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:1) to afford **47** (93%, 519 mg) as a colorless oil. IR (neat) 3459, 3285, 3033, 2987, 2910, 2096, 1496, 1455, 1377, 1248, 1215, 1165, 1060, 906, 854 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 1.34 (s, 3H), 1.37 (s, 3H), 1.88 (br s, 1H), 2.97 (s, 1H), 3.70–3.81 (m, 2H), 4.16–4.28 (m, 2H), 4.40–4.43 (m, 1H), 4.48 (d, 1H, *J* = 11.8 Hz), 4.84 (d, 1H, *J* = 11.8 Hz), 5.35 (d, 1H, *J* = 11.0 Hz), 5.44 (d, 1H, *J* = 11.0 Hz), 7.05–7.32 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ 27.0, 27.4, 63.2, 70.4, 71.2, 79.1, 79.6, 81.0, 84.9, 85.7, 93.8, 109.8, 119.8, 120.9, 127.8, 128.0, 128.2, 128.8, 137.8; HRMS (EI): calcd for $C_{19}H_{19}O_4$ (M^+-Me) 311.1283, found 311.1271.

(2S, 3S, 7Z)-4-Benzyloxy-1-hydroxy-2,3-O-isopropylidenedec-7-en-5,9-diyne-9-iodo-2,3-diol ***(48)***. *n*-Butyllithium (2.56 M in hexanes, 0.29 mL, 0.74 mmol) was added via syringe to a –78 °C solution of diisopropylamine (78 mg, 0.77 mmol) in THF (10 mL). The reaction was stirred for 5 min at –78 °C, warmed to 0 °C for 20 min and the solution recooled to –78 °C. A solution of **47** (115 mg, 0.35 mmol) in THF (1 mL) was added and stirring was continued for 1 h. Iodine (89.5 mg, 0.35 mmol) addition produced an orange-

brown solution The reaction was stirred at –78 °C for a further 6.5 h, 1 h at 0 °C, and saturated aqueous Na_2SO_3 (5 mL) was added. After stirring for 20 min, ether (5 mL) was added and the organic and aqueous phases were separated. The aqueous fraction was extracted with ether (3 × 3 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 3:10) to afford **48** (93%, 147 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.37 (s, 3H), 2.20 (br s, 1H), 3.69–3.87 (m, 2H), 4.17–4.24 (m, 2H), 4.40 (d, 1H, *J* = 3.7 Hz), 4.51 (d, 1H, *J* = 11.7 Hz), 4.87 (d, 1H, *J* = 11.7 Hz), 5.37 (d, 1H, *J* = 10.9 Hz), 5.47 (d, 1H, *J* = 10.9 Hz), 7.07–7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 27.5, 63.2, 70.5, 71.2, 79.0, 79.8, 85.0, 92.0, 94.0, 109.9, 120.6, 121.3, 127.8, 128.0, 128.2, 128.6, 128.7, 137.8.

(2S, 3S, 7Z)-4-Benzyloxy-1-formyl-2,3-O-isopropylidenedec-7-en-5,9-diyne-2,3-diol ***(49)***. Sodium bicarbonate (2.2115g, 26.3 mmol) and Dess-Martin periodinane (2.3524g, 5.55 mmol) were added to a solution of **48** (2.3847g, 5.27 mmol) in CH_2Cl_2 (100 mL) and stirred at 21 °C for 1 h. A 1:1 mixture of $NaCO_3$ (aqueous, saturated)/NaS_2O_3 (aqueous saturated) (60 mL) was added and stirring continued for 20 min. Ether (40 mL) was added and the phases were separated. The aqueous fraction was extracted with ether (3 × 30 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 3:2) to afford **49** (91%, 2.165 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.38 (s, 3H), 4.32–4.46 (m, 3H), 4.49 (d, 1H, *J* = 11.8 Hz), 4.86 (d, 1H, *J* = 11.8 Hz), 5.34 (d, 1H, *J* = 10.8 Hz), 5.44 (d, 1H, *J* = 10.9 Hz), 7.07–7.40 (m, 5H), 9.50 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) d 26.6, 27.0, 70.3, 71.1, 78.8, 82.5, 82.7, 85.4, 92.0, 93.2, 112.3, 121.0, 121.1, 128.0, 128.3, 128.4, 128.5, 128.6, 137.8, 198.6.

(2S, 3S, 7Z)-4-Benzyloxy-1-hydroxy-2,3-O-isopropylidenecyclodec-7-en-5,9-diyne-9-iodo-2,3-diol ***(50)***. A solution of aldehyde **49** (40.0 mg, 0.09 mmol) in THF (2 mL) was added to a suspension of $NiCl_2$ (3.6 mg, 0.03 mmol) and $CrCl_2$ (102.5 mg, 0.79 mmol) in THF (5 mL) via syringe and stirred at 21 °C for 1 h. Ammonium chloride (aq, sat. 3 mL) was added and stirring continued for 20 min. Ether (5 ≤mL) was added, the aqueous fraction was extrated with ether (3 × 10 mL). The organic extracts were washed with brine and dried ($MgSO_4$). The solution was filtered, concentrated, and chromatographed (ether/petroleum ether, 1:4) to afford **50** (57%, 12.5 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.53 (s, 3H), 1.94 (br d, 1H, *J* = 3.0 Hz), 4.38 (d, 1H, *J* = 11.7 Hz), 4.52 (dd, 1H, *J* = 1.8, 1.8 Hz), 4.65 (br s, 1H), 4.73 (d, 1H, *J* = 11.7 Hz), 4.89 (dd, 1H, *J* = 5.6, 2.0 Hz), 4.95 (dd, 1H, *J* = 5.6, 2.2 Hz), 5.44 (d, 1H, *J* = 2.5 Hz), 5.45 (d, 1H, 2.5 Hz), 7.04–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 28.1, 63.4, 70.8, 72.0, 80.6, 80.8, 86.7, 87.8, 98.7, 99.6, 111.2, 124.7, 125.2, 127.8, 128.0, 128.2, 128.3, 128.6, 137.9. HRMS (EI): calcd for $C_{19}H_{17}O_4$ (M^+-Me 309.1127, found 309.1119.

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