Taxamycins: a new enediyne family with synthetic and biological potential

Yee-Fung Lu, Curtis W. Harwig, and Alex G. Fallis

Abstract: The Pd(0) based synthesis of two disilyl synthons (Z-1-trimethylsilyl-6-*tert*-butyldiphenylsilylhex-3-ene-1,5-diyne (**18**) and Z-1-trimethylsilyl-6-triisopropylsilylhex-3-ene-1,5-diyne (**19**)) and the selective removal of the trimethylsilyl group (K_2CO_3, MeOH) to afford **24** and **25** is described. These building blocks are employed in the construction of the taxamycin-12 compound **38** (16,17,18-trimethyl-2-methyloxymethoxy-9-hydroxybicyclo[9.3.1]pentadec-5-ene-3,7-diyne). The final ring closure to the 12-membered ring utilizes an intramolecular Cr–Ni mediated condensation of the iodoalkyne **37** (1,3,3-trimethyl-2-(2-oxoethyl)-4-(Z-1-methyloxymethoxy-7-iodohept-4-ene-2,6-diynyl)cyclohexene).

Key words: cancer, enediynes, synthesis, Pd(0) coupling.

Résumé : On décrit la synthèse, basée sur l'utilisation du Pd(0), de deux synthons disilyés (Z-1-triméthylsilyl-6-*tert*-butyldiphénylsilylhex-3-ène-1,5-diyne (**18**) et Z-1-triméthylsilyl-6-triisopropylsilylhex-3-ène-1,5-diyne (**19**)) et l'enlèvement sélectif du groupe triméthylsilyle (K_2CO_3, MeOH) pour conduire aux composés **24** et **25**. On a utilisé ces blocs pour la préparation du composé **38** (16,17,18-triméthyl-2-méthyloxyméthoxy-9-hydroxybicyclo[9.3.1]pentadéc-5-ène-3,5-diyne), un dérive de la taxamycine-12. La cyclisation finale du cycle à 12 chaînons fait appel à une condensation de l'iodoalcyne **37** (1,3,3-triméthyl-2-(2-oxoéthyl)-4-(Z-1-méthyloxyméthoxy-7-iodohept-4-ène-2,6-diynyl)cyclohexène) aidée par du Cr–Ni.

Mots clés : cancer, ènediynes, synthèse, couplage Pd(0).

[Traduit par la rédaction]

Introduction

Historically, medicinal leads have arisen from novel structures provided by nature. Frequently, it is not the natural products themselves that become drugs but modified forms of the original structure so that the actual therapeutic agents have improved biological activity. These changes minimize side effects, improve efficacy, and simplify the synthetic and manufacturing steps. The penicillins and tetracyclines provide well-known examples. In the antitumor cancer chemotherapy field, two quite different classes of natural products, the enediynes and taxoids, are receiving intense worldwide attention. The enediyne family forms an important new class of antitumor antibiotics that destroy cells by DNA cleavage. Compounds such as esperamicin A (**1**) (1) and calicheamicin γ_1 (**2**) (2) have generated widespread interest due to their novel mechanism of DNA cleavage (3) and the synthetic challenge these structures represent. Consequently, considerable effort is being devoted both to the synthesis of the natural products themselves (4) and a variety of structural analogues (5). (Esperamicin A_1 is currently in clinical trials in North America and Europe.)

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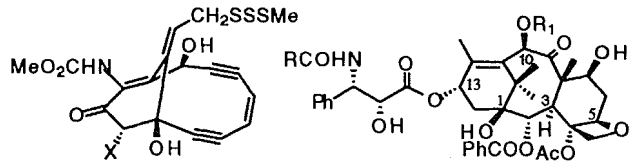
Y.-F. Lu, C.W. Harwig, and A.G. Fallis.[1] The Ottawa–Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa, ON K1N 6N5, Canada.

[1] Author to whom correspondence may be addressed. Telephone: (613) 562-5728. Fax: (613) 562-5170. E-mail: afallis@oreo.chem.uottawa.ca

In a similar manner, the potent antitumor agent paclitaxel (Taxol,® **1**) (6) and the related analog, docetaxel (Taxotere,® **2**) (7) have proven therapeutic utility as summarized in the preceding paper. These structures have also stimulated significant research interest due to their complex structure and novel mode of action with tubulin (8). The number of new biologically active analogues is growing rapidly and a better understanding of the key structure–activity relationships is slowly emerging (9). It has been established that in certain cases the paclitaxel side chain may be attached to modified nuclei with retention of respectable tubulin activity (10). Consequently, we have designed a new family of potentially biologically active agents called taxamycins and wish to report the synthesis of the parent nucleus **38** (preliminary communication, ref. 11).

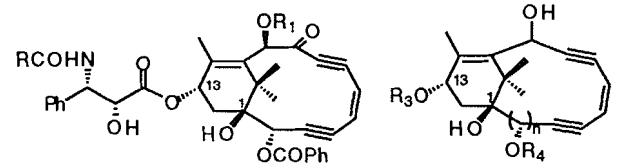
Structures **5** and **6** are representative of the parent taxamycin-12 ring system (where the number represents the size of the ring containing the enediyne unit). Structure **7** summarizes some other members of this new family but many variations are possible depending upon the ring sizes and substitution patterns. It is anticipated that with suitable functionality in place these compounds will associate with tubulin in the cell. Equipped with an appropriate cycloaromatization trigger, they should aromatize and result in DNA or related damage by hydrogen abstraction. This will depend in part on the ring size, strain, and separation of the acetylenic termini.

The sequence by which DNA cleavage occurs in the esperamicin–calicheamicin duet involves nucleophilic attack on the trisulfide followed by conjugate addition. This reaction brings the two acetylene termini into bonding distance and



1 Esperamicin aglycon X = OH
2 Calicheamicin aglycon X = H

3 Taxol®, R = Ph, R_1 = Ac
4 Taxotere®, R = tBuO, R_1 = H



5 Taxol mimic, R = Ph, R_1 = Ac
6 Taxotere mimic, R = tBuO, R_1 = H

n = 0, 1, 2
7 Taxamycins-10, 11,12

Taxamycin-12 examples

Bergman cyclization (12) ensues to form a *para*-benzyne intermediate. Preferential abstraction of the C5′ hydrogen from the deoxyribose followed by oxygenation and reduction generates a hemi-acetal, which collapses to the aldehyde causing the strand to break. Related analogs have been shown recently to exert similar effects and for some systems the aromatization sequence may be initiated by thiolate (13). These dynemicin models displayed considerable in vivo potency and activity. Similarly, a synthetic calicheamicin displayed good potency against several cancers including breast and ovarian cancers, areas where taxoids are also most effective (14). This emphasizes the medicinal potential of the molecules we intend to synthesize. They may be viewed as doubly armed warheads in the fight for control and destruction of cancerous cells.

The taxamycins are also of interest for their synthetic versatility both for the construction of aromatic systems in a direct fashion and for the capture of the *para*-benzyne intermediate to functionalize the benzenoid system under neutral conditions (15). This potential is summarized in Scheme 1 by the implicit conversion of **8** to **9**. In the cell, DNA damage should occur, while in the laboratory *para* functionalization may generate **10** for taxoid synthesis. Several approaches for the total synthesis of taxol utilize benzenoid intermediates for the preparation of the C ring (16) and some recent ring C aromatic systems have displayed interesting biological activity (10*c*). The synthesis of the taxamycin-12 **38** has been examined in order to investigate these various possibilities, including the synthetic utility of the Bergman cycloaromatization in these large rings and the factors responsible for biradical formation in this series.

Results and discussion

The initial synthetic approach envisaged the use of the protected diol acetylene **14**, which was prepared from the ring A synthon, aldehyde **11**, described in the preceding paper (Chart 1). This aldehyde **11** was condensed with the lithium trimethylsilylacetylide to afford **12** as a mixture of diastereomers (1:1). The trimethylsilyl group was removed with KOH at room temperature (21°C) and the secondary alcohol protected as its MOM ether. Unfortunately, under various conditions the

Scheme 1. Taxamycin-12 cyclization potential.

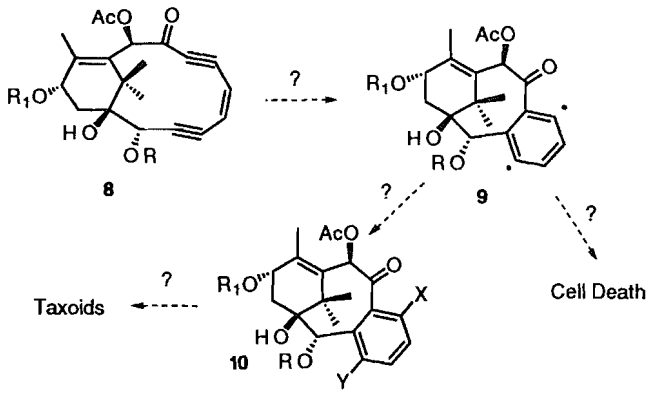
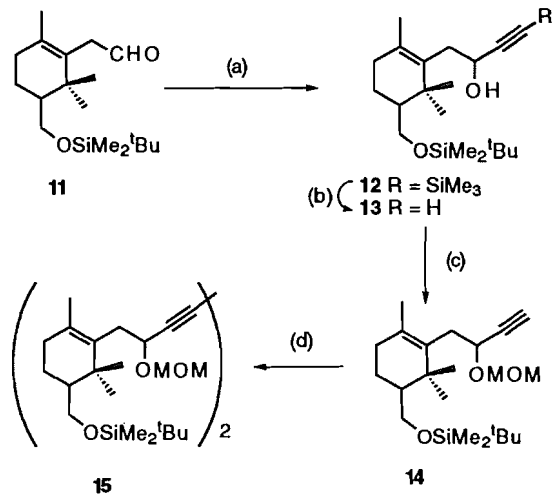


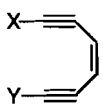
Chart 1. Initial clockwise approach to a taxamycin.



(a) HCCTMS, ^{n}BuLi, THF, −78–21°C, 1.5 h, 93%; (b) KOH, MeOH/CH_2Cl_2 (1:1), 21°C, 4 h, 90%; (c) MOMCl, $EtN^i(Pr)_2$, CH_2Cl_2, 21°C, 16 h, 70%; (d) ClCH=CHCCTMS, $Pd(Ph_3P)_4$, ^{n}BuNH$_2$, CuI, Et_2O, 21°C, 16 h, 95%.

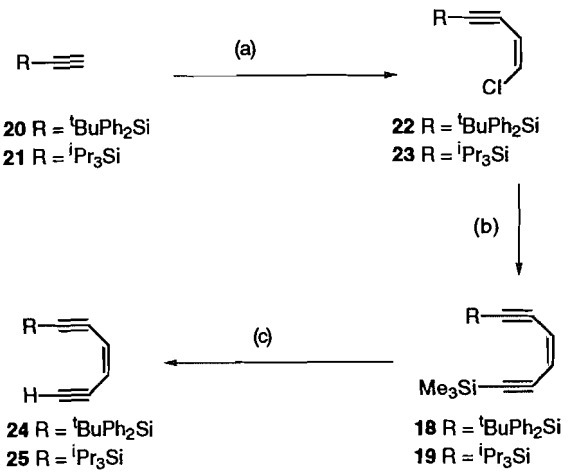
Pd(0)–CuI mediated coupling failed to give the desired enediyne and afforded the dimer **15** (95%) instead. Competitive dimerizations have also interfered with other enediyne syntheses (17). To circumvent this problem a versatile approach based on preconstructed enediyne building blocks was selected. These compounds **17**–**19** should suffice for a variety of objectives.

The use of the dilithio salts derived from **16** to insert the enediyne chromophore was examined previously with variable results and requires the handling of a very volatile precursor (18). Our initial attempts to prepare systems such as **17** with different elements, for example silicon and tin, at the terminal acetylenes were disappointing. It is well established that



16 X = Y = H
17 X = Me_3Si, Y = Me_3Sn
18 X = Me_3Si, Y = ^{t}BuPh$_2$Si
19 X = Me_3Si, Y = ^{i}Pr$_3$Si

Chart 2. Synthesis of enediyne synthons.

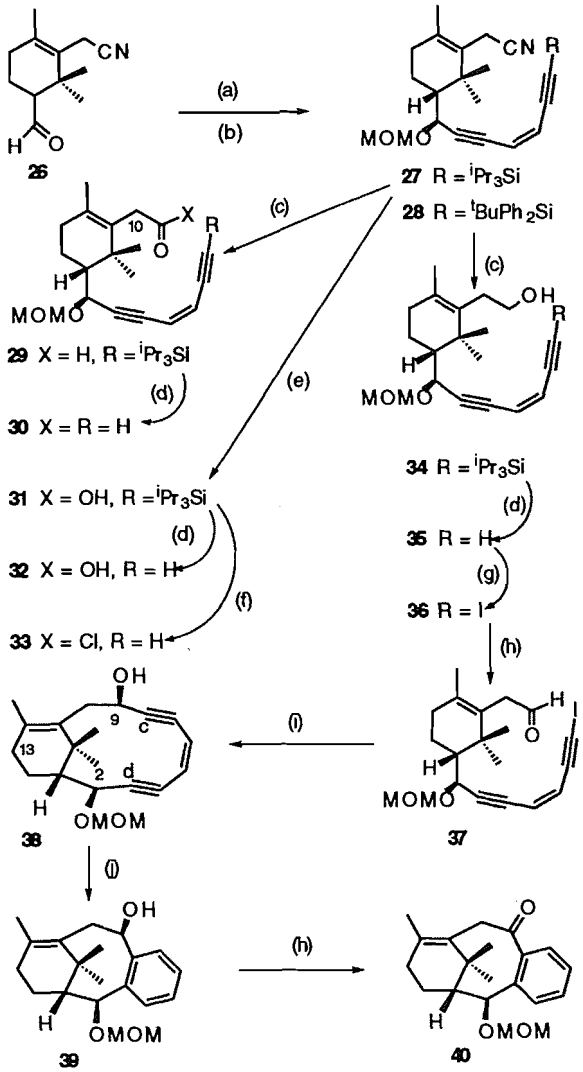


(a) ClCH=CHCl, $Pd(Ph_3P)_4$, $^nBuNH_2$, CuI, Et_2O, 21°C, 15 h, 83–95%; (b) HCCTMS, $Pd(Ph_3P)_4$, $^nBuNH_2$, CuI, Et_2O, 21°C, 16 h, 64–78%; (c) K_2CO_3, MeOH, C_6H_6, 21°C, 2 h, 90–95%.

the rates of base-induced cleavage of silylalkynes depend upon the relative steric bulk of the groups involved. (Relative rates: Et_3Si (1), Ph_3Si (12), $EtMe_2Si$ (49), Me_3Si (277) (ref. 19).) This should allow selective protection and release of the appropriate silyl group at the terminus of interest. Thus the synthesis of two suitable building blocks, Z-1-trimethylsilyl-6-*tert*-butyldiphenylsilyhex-3-ene-1,5-diyne (**18**) and Z-1-trimethylsilyl-6-triisopropylsilylhex-3-ene-1,5-diyne (**19**) was examined. As outlined in Chart 2, these compounds were prepared by repetitive Pd(0) based coupling followed by removal of the trimethylsilyl group in K_2CO_3–methanol. The triisopropyl system **25** has proven more useful than **24**. This is a consequence of the bulk and polarity of *tert*-butyldiphenylsilyl fluoride and the difficulty encountered upon chromatographic separation (silica gel) of this material from the enediyne-alcohol product in some cases. Schreiber and co-workers (20) have used a related compound, 1-*tert*-hexyldimethylsilylhex-1,5-diyne-3-ene, to introduce the enediyne unit.

For the synthesis of the model taxamycin system, the cyanoaldehyde **26** was prepared from Hagemann's ester as described in the preceding paper for the synthesis of the taxane nucleus by an intramolecular Diels–Alder approach (21). The lithium acetylide derived from **25** was condensed with **26** (Chart 3) to afford a 4:1 mixture of alcohol diastereomers. Protection of the secondary hydroxyl of the major diastereomer as its monomethyl ether proceeded slowly but smoothly to give **27** (98%). Diisobutylaluminum hydride reduction of the nitrile function in **27** could be terminated at the aldehyde stage to generate **29** directly or could be reduced further with additional reagent to generate the primary alcohol **34**. A variety of methods have been examined for the intramolecular ring closure of medium-sized cyclic enediynes, particularly for 10-membered rings that mimic calicheamicin and esperamicin. These include ring contraction of a cyclic ether by [2,3]-Wittig rearrangement (5*e*), Nicholas-type cyclization of η^2-dicobalthexacarbonyl complexed propargylic cations with Lewis acid (5*d*), direct condensation of the acetylenic anion with an aldehyde (18*a*, 22), fluoride-induced desilylation–condensation (17*a*, 23), and chromium(II)-mediated coupling of an iodoacetylene and an aldehyde (24).

Chart 3. Synthesis of the taxamycin-12 compound **40**.



(a) **24** or **25**, ^{n}BuLI, THF, −78–0°C, 1 h, 94%; (b) MOMCl, $EtN^i(Pr)_2$, CH_2Cl_2, 21°C, 16 h, 98%; (c) DIBAL-H, CH_2Cl_2, −78–0°C, 2 h, 66%; (d) $^nBu_4NF$, THF, −78°C, 2 h, 86%; (e) DIBAL-H, CH_2Cl_2, −78°C, 1 h, aq NH_4Cl; ^{t}BuOH/CH_2Cl_2 (2:1), $NaClO_2$, NaH_2PO_4, 30% H_2O_2, 21°C, 16 h, 74%; (f) $(COCl_2)$, THF, 21°C, 2 h; (d); (g) morpholine, I_2, C_6H_6, 40°C, 2 h, 86%; (h) PDC, CH_2Cl_2, 21°C, 16 h, 82%; (i) $CrCl_2$, $NiCl_2$ (cat.), THF, 21°C, 4 h, 60%; (j) sealed tube, microwave, 4 h; (h) PDC, CH_2Cl_2, 21°C, 6 h.

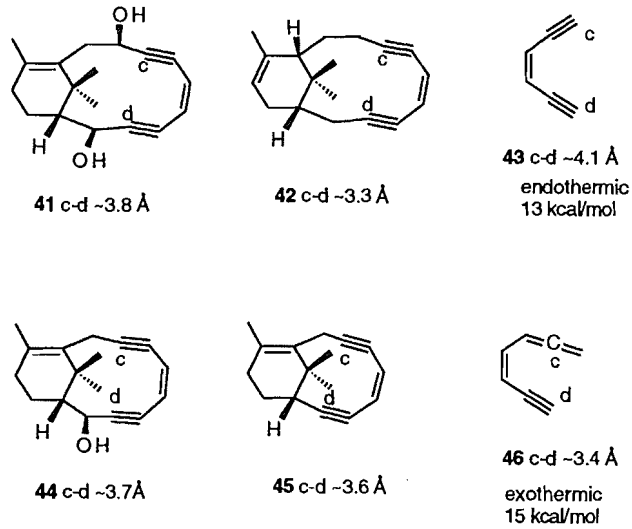
In spite of the success of fluoride-mediated desilylation – intramolecular condensation of silyl acetylenes with aldehydes in other systems, this direct, concurrent desilylation–cyclization with **29** to **38** did not occur under a variety of conditions. Completely anhydrous fluoride sources such as tretrabutylammonium difluorotriphenylstannate (25) also suppressed desilylation. Thus it proved most efficient to prepare **30** directly with tetrabutylammonium fluoride CsF in THF. Similarly the direct anionic condensation was unsatisfactory,

including the use of $Sn(OTf)_2$ and 1,8-bis(dimethylamino)naphthalene (26). A complication in the present example is the fact that the ring size is larger (12-membered) than any of the reported cases. In addition, the C10 hydrogens (Taxol® numbering) are both allylic and adjacent to the aldehyde so their acidity is higher than that of the acetylene proton. In an attempt to overcome these difficulties the acid chloride **33** was prepared from the corresponding carboxylic acid **31**. This was obtained from the nitrile **27** by diisobutylaluminum hydride reduction followed by sodium chloride – hydrogen peroxide oxidation (27). Unfortunately, treatment of the acid chloride under various conditions, including Pd(0) or base, was unsuccessful. In the latter case it was anticipated that ketene formation would be competitive with acetylene anion formation and the corresponding flattening of the reactive components would bring them closer together to encourage addition. In simple systems we have developed a procedure to add lithium acetylides to dimethoxy acetals in the presence of zinc chloride and boron trifluoride etherate.[2] Unfortunately, except for model aldehydes, the yields with these silyl-substituted enediynes have been poor (10–15%). In the case of aldehyde **30** attempts to form the dimethoxy acetal with cerium trichloride or other catalysts failed.

In view of the success of the $CrCl_2$–$NiCl_2$ based coupling of iodoacetylenes with aldehydes to form smaller enediyne ring systems, this approach was examined next. Desilylation of **34** with tretrabutylammonium fluoride in THF and conversion of the resulting alkyne **35** into the alkynyliodide **36** was accomplished with morpholine and iodine (86%). The primary alcohol was oxidized to the aldehyde **37** with pyridinium dichromate (82%). The desired ring closure was effected smoothly with the nickel-catalyzed chromium-based procedure to provide the bicyclo[9.3.1]pentadecadienediyne system **38** in 60% isolated yield. Recent studies (28) have used THF as the solvent and found that the yields for 10-membered rings were almost as high in the absence of $NiCl_2$. A single diastereomer of **38** was formed. Based on molecular models, preferential attack from the bottom (si face) was anticipated and thus it seems likely the new secondary alcohol at C9 is *syn* relative to the C2 MOM group. This stereochemical result is consistent with related intramolecular cases in which the same stereochemical preference was observed for closure to 10-membered rings (22*c*).

The cycloaromatization of **38** was examined to ascertain the potential for direct entry to aromatic taxanes without triggering devices or saturation of the cyclohexene double bond. Thus **38** was heated for 4 h in a sealed tube in toluene in a microwave oven. The crude alcohol **39** was oxidized directly with pyridinium dichromate to provide the aromatic ketone **40** (5% from **38**) prepared previously by a Diels–Alder-aromatization route (preceding paper). Clearly this is not a viable synthetic route to aromatic taxanes at present. Molecular mechanics calculations indicated that the c–d distance in **41** is ~3.8 Å and thus this separation is significantly larger than the separation of ~3.1 Å required for spontaneous cyclization. This separation is less than the simplest enediyne system **43** (*cis*-3-hexene-1,5-diyne) with a separation of approximately 4.1 Å, which underwent cycloaromatization – ring opening above 200°C with low efficiency. Recent calculations have determined that this reaction is endothermic by 13 kcal/mol. In contrast, the related allene system **46**, with a c–d separation of ~3.4 Å in the most favorable conformation for cyclization, closes much more readily and is exothermic by 15 kcal/mol (29). Literature examples display this same relative ease of cyclization (17*b*). As summarized in Chart 4, the lower taxamycin homologues **44** and **45** reduce the c–d separation by approximately 0.1 Å. Isomerization of the double bond away from the bridgehead as in **42** results in a 0.5 Å improvement. These features suggest that synthetic modifications to this family will in the future yield useful synthons that cycloaromatize more easily.

Chart 4. Calculation summary of c–d separations.



In conclusion, the directness of this approach to enediyne systems, using the disilyl-enediyne unit **19** followed by an intramolecular Ni–Cr mediated coupling, should prove beneficial for a variety of synthetic objectives. These include the cycloaromatization of more highly functionalized skeletons to aromatic taxoids and the synthesis of ring-contracted taxamycin-10 nuclei that should mimic their esperamicin and calicheamicin relatives.

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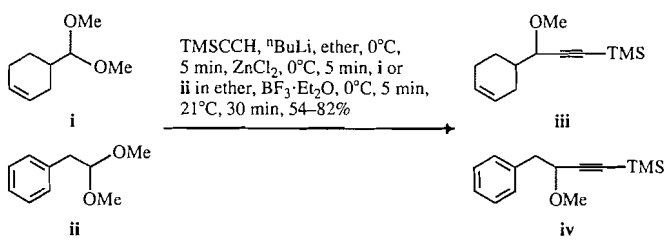

Experimental

For general experimental see preceding paper.

4-*tert*-Butyldimethylsilyloxymethyl-1,3,3-trimethyl-2-(2-hydroxy-4-trimethylsilyl-3-butynyl)cyclohexene (12)

A solution of *n*-butyllithium (0.27 mL, 0.675 mmol, 2.5 M) in hexane was added dropwise to a cold (−78°C), stirred, solution of trimethylsilylacetylene (0.095 mL, 0.672 mmol) in dry THF (5 mL). After 30 min at −78°C, a solution of the alde-

hyde **11** (140 mg, 0.451 mmol) in dry THF (2 mL) was added dropwise and the resulting mixture was stirred at −78°C for 1 h. Saturated aqueous ammonium chloride solution was added and the mixture was warmed to 21°C (room temperature) and extracted with diethyl ether. The combined ether extracts were washed with brine and dried. Concentration of the organic material afforded 171 mg (93%) of the alcohol **12** (1:1 ratio). IR (neat): 3384, 2921, 2171, 1462, 1253, 844 cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (br s, 6H), 0.15 (br s, 9H), 0.86 (br s, 12H), 1.08 (br s, 3H), 1.10–1.60 (m, 1H), 1.69 (br s, 3H), 1.70–1.89 (m, 2H), 1.90–2.05 (m, 2H), 2.52 (br d, 2H, J = 6 Hz), 3.34 (br s, 1H, J = 10 Hz), 3.75 (br dd, 1H, J = 10, 3 Hz), 4.40–4.55 (m, 1H); MS (CI): 409 (MH^+, $C_{23}H_{44}O_2Si_2$).

4-*tert*-Butyldimethylsilyloxymethyl-1,3,3-trimethyl-2-(2-hydroxy-3-butynyl)cyclohexene (13)

A solution of potassium hydroxide (200 mg, 3.57 mmol) in methanol (5 mL) was added to a stirred solution of the alcohol **12** (171 mg, 0.419 mmol) in dichloromethane (5 mL). The resulting mixture was stirred for 4 h at 21°C. The organic solvent was removed under reduced pressure to provide a yellow oil. A mixture of diethyl ether/water (1:1) was added and the solution was extracted with diethyl ether. The combined ether extracts were washed with brine and dried. Concentration afforded alcohol **13**, 126 mg (90%, 1:1 ratio). IR (neat): 3400, 3307, 2917, 1466, 1254, 1069, 843, 776 cm^{-1}; ^1H NMR (200 MHz) δ: 0.016 (br s, 12H), 0.86 (br s, 18H), 0.88 (br s, 6H), 1.07 (br s, 6H), 1.69 (br s, 6H), 0.9–2.0 (m, 13H), 2.4–2.6 (m, 4H), 3.34 (br t, 2H, J = 10 Hz), 3.69–3.80 (m, 2H), 4.49 (br t, 2H, J = 8 Hz); MS (CI): 337 (MH^+, $C_{20}H_{36}O_2Si$).

4-*tert*-Butyldimethylsilyloxymethyl-1,3,3-trimethyl-2-(2-methoxymethylether-3-butynyl)cyclohexene (14)

Chloromethyl methyl ether (0.043 mL, 0.566 mmol, Aldrich) was added to a cold (0°C) solution of the alcohol **13** (0.126 g, 0.376 mmol) and diisopropylethylamine (0.100 mL, 0.574 mmol) in dry dichloromethane (5 mL) and the solution stirred at 21°C for 16 h. Additional chloromethyl methyl ether (0.0285 mL, 0.376 mmol) and diisopropylethylamine (0.065 mL, 0.375 mmol) were added and the mixture was stirred for another 16 h. Water was added and the mixture was extracted thoroughly with dichloromethane. The combined organic extracts were washed with brine, dried, and concentrated. Chromatography of the residual oil (20:1; petroleum ether/diethyl ether) afforded 0.099 g (70%) of the ether **14** (1:1 ratio). IR (neat): 3301, 2925, 2113, 1465, 1090 cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (br s, 12H), 0.87 (br s, 18H), 1.07 (br s, 6H), 1.53 (br s, 6H), 1.67 (br s, 6H), 1.2–2.0 (m, 12H), 2.3–2.4 (m, 2H), 2.52 (br d, 4H, J = 8 Hz), 3.29 (s, 3H), 3.32 (s, 3H), 3.3–3.4 (m, 2H), 3.7–3.8 (m, 2H), 4.38–4.55 (m, 4H), 4.86 (d, 1H, J = 6 Hz), 4.89 (d, 1H, J = 6 Hz); MS (CI): 381 (MH^+, $C_{22}H_{40}O_3Si$). Anal. calcd. for $C_{22}H_{40}O_3Si$: C 69.42, H 10.59; found: C 69.48, H 10.59.

Bis-4-*tert*-butyldimethylsilyloxymethyl-1,3,3-trimethyl-2-(2-methoxymethylether-3-butynyl)cyclohexene (15)

An anhydrous ether solution (50 mL) containing the chloride **22** (0.082 g, 0.517 mmol), acetylene **14** (0.666 g, 0.174 mmol), *n*-butylamine (0.034 mL, 0.343 mmol), tetrakistriphenylphosphine palladium (0.010 g, 0.009 mmol, Aldrich), and cuprous iodide (0.002 g, 0.010 mmol) was stirred at 21°C for 16 h. Concentration followed by chromatography (9:1; petroleum ether/diethyl ether) afforded the dimer **15**, 0.061 g (69%, 1:1 ratio. IR (neat): 2919, 2157, 1467, 1253, 1095, 1028, 848 cm^{-1}; ^1H NMR (200 MHz) δ: 0.17 (br s, 24H), 0.20 (br s, 36H), 0.86 (br s, 24H), 1.05–1.98 (m, 8H), 1.53 (s, 24H), 2.52 (br d, 8H, J ~ 8 Hz), 3.28 (s, 12H), 3.31 (s, 12H), 3.41 (m, 4H), 3.75 (d m, 4H), 4.48 (m, 8H), 4.85 (m, 4H).

***Z*-1-Chloro-4-triisopropylsilylbutene-3-yne (23)**

An anhydrous diethyl ether solution (50 mL) containing triisopropyl acetylene (1.98 g, 10.8 mmol, Aldrich), 1,2-*cis*-dichloroethylene (1.63 mL, 21.0 mmol, Aldrich), *n*-butylamine (2.10 mL, 21.6 mmol), tetrakistriphenylphosphine palladium (0.376 g, 0.30 mmol, Aldrich), and cuprous iodide (0.061 g, 0.30 mmol) were stirred at 21°C for 15 h. The reaction mixture was concentrated and chromatographed (silica gel, petroleum ether) to provide the eneyne **23** (2.17 g, 83%). IR (neat): 2945, 2154, 1463, 882, 671 cm^{-1}; ^1H NMR (200 MHz) δ: 1.06 (s, 3H), 1.08 (s, 18H), 5.88 (d, 1H, J = 7.4 Hz), 6.37 (d, 1H, J = 7.4 Hz); ^{13}C NMR (50 MHz) δ: 11.2 (3C), 18.6 (6C), 100.1, 100.7, 112.3, 129.2; HRMS (EI) calcd. for $C_{13}H_{23}SiCl$: 242.1257; found: 242.1285.

***Z*-1-Trimethylsilyl-6-triisopropylsilylhex-3-ene-1,5-diyne (19)**

An anhydrous ether solution (50 mL), containing the chloride **23** (1.96 g, 8.07 mmol), trimethylsilyl acetylene (2.27 mL, 223 mmol), *n*-butylamine (1.60 mL, 16.2 mmol), tetrakistriphenylphosphine palladium (0.280 g, 0.242 mmol, Aldrich), and cuprous iodide (0.046 g, 0.241 mmol) was stirred at 21°C for 16 h. The brown residue obtained upon concentration under reduced pressure was chromatographed (petroleum ether) to afford enediyne **19** (1.91 g, 78%). IR (neat): 2948, 2153, 2121, 1250, 1069, 848 cm^{-1}; ^1H NMR (200 MHz) δ: 0.17 (s, 9H), 1.04–1.10 (br s, 21H), 5.83 (s, 2H); ^{13}C NMR δ: 0.22 (3C), 11.2 (3C), 18.7 (6C), 99.8, 101.9, 102.9, 103.8, 120.0, 120.4; HRMS (EI) calcd. for $C_{18}H_{32}Si_2$: 304.2042; found: 304.2032.

***Z*-1-Triisopropylsilylhex-3-ene-1,5-diyne (25)**

Potassium carbonate (0.11 g, 0.80 mmol) was added to a benzene/methanol solution (1:1, 10 mL) containing **19** (0.217 g, 0.713 mmol) and the resulting mixture stirred at 21°C for 2 h. The solvent was removed, water added, and the mixture extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine, dried, filtered, and concentrated to give **25** (0.157 g, 95%). IR (neat): 3303, 2945, 2149, 1463, 1049, 882, 746 cm^{-1}; ^1H NMR (200 MHz) δ: 1.0–1.1 (br s, 21H), 3.29 (dd, 1H, J = 0.8, 2.2 Hz), 5.79 (dd, 1H, J = 2.2, 11 Hz), 5.93 (dd, 1H, J = 0.8, 11 Hz); ^{13}C NMR (50 MHz) δ: 11.2 (3C), 18.6 (3C), 80.8, 84.8, 100.1, 103.3, 119.3, 121.9; HRMS (EI) calcd. for $C_{15}H_{24}Si$: 189.1099; found: 189.1100.

***tert*-Butyldiphenylsilylacetylene (20)**

tert-Butyldiphenylsilyl chloride (1.45 mL, 5.57 mmol, Aldrich) was added to a cold (0°C), stirred solution of lithium acetylide – ethylene diamine complex (0.618 g, 6.70 mmol) in anhydrous THF (30 mL). The resultant solution was stirred at 0°C for 1 h and warmed to 21°C for 16 h. Water was added slowly and the mixture was extracted thoroughly with diethyl ether. The combined organic extracts were washed with brine,

dried ($MgSO_4$), and concentrated. The residual oil was recrystallized from petroleum ether/diethyl ether (1:1), to provide **20** (1.15 g, 65%): IR (KBr): 3266, 2943, 2034 cm^{-1}; ^1H NMR (200 MHz) δ: 1.08 (s, 9H), 2.69 (s, 1H), 7.30–7.40 (m, 6H), 7.70–7.80 (m, 4H); ^{13}C NMR δ: 18.4, 27.0 (3C), 85.4, 97.3, 127.8 (4C), 129.7 (2C), 132.7 (2C), 135.6 (4C); HRMS (EI) calcd. for $C_{18}H_{20}Si$: 264.1334; found: 264.1343.

Z-1-Trimethylsilyl-6-*tert*-butyldiphenylsilylhex-3-ene-1,5-diyne (18)

Copper(I) iodide (0.017 g, 0.089 mmol) was added to a stirred anhydrous diethyl ether solution (20 mL) containing the acetylene **20** (0.776 g, 2.94 mmol), *n*-butylamine (0.58 mL, 5.86 mmol), *cis*-1,2-dichloroethylene (0.44 mL, 5.83 mmol), and $Pd(Ph_3P)_4$ (0.10 g, 0.0865 mmol, Aldrich). The greenish reaction mixture was stirred at 21°C for 16 h and the resultant brownish mixture concentrated. The residual oil was chromatographed (3:1, petroleum ether/diethyl ether) to afford 0.871 g of the vinyl chloride **22** as a yellowish oil that was used directly in the next reaction. ^1H NMR (200 MHz) δ: 1.10 (s, 9H), 6.02 (d, 1H, J = 8 Hz), 6.50 (d, 1H, J = 8 Hz), 7.30–7.40 (m, 6H), 7.70–7.90 (m, 4H).

Copper(I) iodide (0.007 mmol) was added to a stirred, anhydrous, diethyl ether solution (20 mL) containing trimethylsilylacetylene (0.750 mL, 5.31 mmol), *n*-butylamine (0.53 mL, 5.36 mmol), $Pd(Ph_3P)_4$ (0.07 g, 0.060 mmol), and the vinyl chloride **22**. The reaction mixture was stirred at 21°C for 16 h and then concentrated. The black residual oil was chromatographed (petroleum ether) to afford 0.665 g (64%) of the enediyne **18**. IR (neat): 2948, 2154, 2122, 1428, 1109, 1070, 843, 700 cm^{-1}; ^1H NMR (200 MHz) δ: 0.13 (s, 9H), 1.10 (s, 9H), 5.94 (s, 2H) 7.30–7.40 (m, 6H), 7.70–7.80 (m, 4H); HRMS (EI) calcd. for $C_{21}H_{21}Si_2$ (M^+ − *tert*-butyl): 329.1181; found: 329.1163.

Z-1-*tert*-Butyldiphenylsilylhex-3-ene-1,5-diyne (24)

A benzene solution (5 mL) of **18** (0.662 g, 1.71 mmol) was added to a stirred solution of potassium bicarbonate (0.260 g, 1.88 mmol) in methanol (10 mL). The reaction mixture was stirred at 21°C for 3 h and then concentrated. Water was added and the mixture was extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 0.508 g (94%) of the enediyne **24**. IR (neat): 3293, 2944, 2152, 1428, 1187, 1051 cm^{-1}; ^1H NMR (200 MHz) δ: 1.10 (s, 9H), 3.38 (d, 1H, J = 4 Hz), 5.92 (dd, 1H, J = 4, 10 Hz), 6.05 (d, 1H, J = 10 Hz), 7.30–7.45 (m, 6H), 7.75–7.90 (m, 4H); HRMS (EI) calcd. for $C_{18}H_{13}Si$(M^+ − *tert*-butyl): 257.0787; found: 257.0792.

1,3,3-Trimethyl-2-cyanomethyl-4-(*Z*-1-methyloxymethoxy-7-triisopropylsilylhept-4-ene-2,6-diynyl)cyclohexene (27)

A solution of *n*-butyllithium (1.45 mL, 3.62 mmol, 2.5 M) in hexane was added dropwise to a cold (−78°C), stirred solution of the enediyne **25** (0.837 g, 3.61 mmol) in dry THF (30 mL). After stirring at −78°C for 15 min, a solution of (1,3,3-trimethyl-2-cyanomethyl-4-formyl)cyclohexene (**26**) (0.541 g, 2.83 mmol) in dry THF (5 mL) was added dropwise. The reaction was stirred at −78°C for further 1 h, warmed to 0°C for an additional hour, and water added. The mixture was warmed to room temperature and extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed (5:1, petroleum ether/diethyl ether) to afford 1.13 g (94%) of the alcohol (4:1 epimeric ratio). Major diastereomer, IR (neat): 3450, 2914, 2247, 2140, 1462, 1018, 883, 669 cm^{-1}; ^1H NMR (300 MHz) δ: 1.02 (s, 3H), 1.06 (br s, 3H), 1.08 (br s, 18H), 1.15 (s, 3H), 1.59 (d, 1H, J = 4 Hz), 1.62–1.69 (m, 2H), 1.72 (s, 3H), 1.84–1.94 (m, 1H), 2.01–2.15 (m, 2H), 2.97 (AB, 2H, J = 12 Hz), 4.82 (br d, 1H, J = 4 Hz), 5.83 (br s, 2H); ^{13}C NMR (75 MHz) δ: 11.21 (3C), 16.25, 18.64 (3C), 18.83, 20.17, 21.17, 26.67, 32.42, 38.27, 50.89, 62.92, 82.19, 98.55, 99.70, 103.6, 118.9, 119.4, 120.0, 127.6, 133.8; HRMS (EI) calcd. for $C_{24}H_{34}ONSi$ (M^+ − isopropyl): 280.2410; found: 280.2424.

Chloromethyl methyl ether (0.23 mL, 3.03 mmol, Aldrich) was added to a cold (0°C) dichloromethane solution (25 mL) of the alcohol (0.863 g, 2.04 mmol) and diisopropylethylamine (0.71 mL, 4.07 mmol). The resultant solution was stirred at 0°C for 10 min and warmed to 21°C for 16 h. Water was added and the mixture was extracted thoroughly with diethyl ether. The combined organic extracts were washed sequentially with aqueous 10% HCl, water, brine, dried, filtered, and concentrated to provide the ether **27** (0.934 g, 98%). IR (neat): 2913, 2247, 2140, 1455, 1066, 883, 667 cm^{-1}; ^1H NMR (200 MHz) δ: 1.02 (s, 3H), 1.06 (s, 21H), 1.16 (s, 3H), 1.71 (s, 3H), 1.59 (d, 1H, J = 4 Hz), 1.60–1.80 (m, 2H), 1.85–2.00 (m, 1H), 2.00–2.15 (m, 2H), 2.96 (br s, 2H), 3.36 (s, 3H), 4.52 (d, 1H, J = 6.6 Hz), 4.73 (br s, 1H), 4.95 (d, 1H, J = 6.6 Hz), 5.83 (s, 2H); ^{13}C NMR (50 MHz) δ: 11.2 (3C), 16.3, 18.6 (6C), 19.8, 20.2, 22.1, 26.8, 32.7, 38.3, 50.3, 56.6, 66.7, 83.0, 94.7, 96.4, 99.5, 103.6, 119.0, 119.4, 119.6, 129.5, 133.8; HRMS (EI) calcd. for $C_{26}H_{38}O_2NSi$ (M^+ − isopropyl): 424.2671; found: 424.2655. Anal. calcd. for $C_{29}H_{45}O_2NSi$: C 74.46, H 9.70; found: C 74.43, H 9.88.

1,3,3-Trimethyl-2-cyanomethyl)-4-(*Z*-1-methyloxymethoxy-7-*tert*-butyldiphenylsilylhept-4-ene-2,6-diynyl)cyclohexene (28)

A solution of *n*-butyllithium (0.21 mL, 0.53 mmol, 2.5 M) in hexane was added dropwise to a cold (−78°C), stirred solution of the enediyne **24** (0.162 g, 0.517 mmol) in dry THF (8 mL). The black solution was stirred at −78°C for 15 min and a solution of (1,3,3-trimethy-2-cyanomethyl-4-formyl)cyclohexene (**26**) (0.090 g, 0.471 mmol) in dry THF (2 mL) was added dropwise. The reaction was stirred at −78°C for 1 h further, warmed to 0°C for an additional hour, and water added. The mixture was warmed to 21°C and extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine, dried, and concentrated. The residual black oil was chromatographed (3:1, petroleum ether/diethyl ether) to afford 0.205 g (85%) of the alcohol (3:1 epimeric ratio). Major diastereomer, IR (neat): 3454, 2918, 2247, 2144, 1026 cm^{-1}; ^1H NMR (200 MHz) δ: 0.90 (s, 3H), 1.02 (s, 3H), 1.06 (s, 9H), 1.62 (s, 3H), 0.8–2.10 (m, 5H), 2.7–3.05 (m, 2H), 3.30 (s, 3H), 4.40 (d, 1H, J = 6.7 Hz), 4.75 (br d, 1H, J = 8 Hz), 4.93 (d, 1H, J = 6.7 Hz), 5.96 (br s, 2H), 7.3–7.4 (m, 6H), 7.7–7.85 (m, 4H).

Chloromethyl methyl ether (0.072 mL, 0.948 mmol, Aldrich) was added to a cold (0°C) dichloromethane solution (6 mL) of the alcohol (0.321 g, 0.636 mmol) and diisopropylethylamine (0.27 mL, 1.55 mmol). The resultant solution was

stirred at 0°C for 10 min and warmed to 21°C for 16 h. Water was added and the mixture was extracted thoroughly with dichloromethane. The combined organic extracts were washed sequentially with aqueous 10% HCl, water, brine, dried, filtered, concentrated, and chromatographed (3:1, petroleum ether/diethyl ether) to provide the ether **28** (0.271 g, 78%). IR (neat): 2913, 2247, 2140, 1455, 1066, 883, 667 cm^{-1}; ^1H NMR (200 MHz) δ: 0.95 (s, 3H), 1.07 (s, 3H), 1.08 (s, 9H), 1.54 (s, 3H), 1.5–1.9 (m, 5H), 2.89 (AB, 2H, $J \sim 18$ Hz), 3.30 (s, 3H), 4.40 (d, 1H, $J = 6.7$ Hz), 4.70 (br s, 1H), 4.91 (d, 1H, $J = 6.7$ Hz), 5.96 (br s, 2H), 7.3–7.42 (m, 6H), 7.75–7.82 (m, 4H); ^{13}C NMR (50 MHz) δ: 16.3, 18.7, 19.9, 20.2, 22.1, 26.8, 27.1 (3C), 32.5, 38.2, 50.2, 56.6, 66.7, 83.0, 94.7, 97.8, 97.9, 105.6, 119.0, 119.3, 120.6, 120.7, 127.3, 127.8 (4C), 129.6 (2C), 132.9, 133.8; HRMS (EI) calcd. for $C_{32}H_{34}O_2NSi$: 492.2358; found: 492.2349.

1,3,3-Trimethyl-2-(2-oxoethyl)-4-(*Z*-1-methyloxymethoxy-7-triisopropylsilylhept-4-ene-2,6-diynyl)cyclohexene (29)

A toluene solution of diisobutylaluminum hydride (1 M, 0.58 mL, 0.58 mmol, Aldrich) was added dropwise to a cold (−78°C), stirred solution of the nitrile **27** (0.136 g, 0.291 mmol) in dry dichloromethane (5 mL). The reaction was stirred at −78°C for 1 h and warmed to 0°C for an additional hour. Dilute HCl (aqueous 5%) was added, the mixture was stirred at 21°C for 30 min, and the solution was extracted thoroughly with diethyl ether. The combined organic extracts were washed with water, brine, dried, filtered, and concentrated and the residual oil was chromatographed (3:1, petroleum ether/diethyl ether) to afford 0.091 g (66%) of the aldehyde **29**. IR (neat): 2914, 2718, 2141, 1723, 1463, 1029, 883 cm^{-1}; ^1H NMR (200 MHz) δ: 0.98 (s, 3H), 1.06 (s, 24H), 1.55 (s, 3H), 1.60–1.84 (m, 2H), 1.85–2.00 (m, 1H), 2.00–2.20 (m, 2H), 3.07 (br s, 1H), 3.35 (br s, 1H), 3.36 (br s, 3H), 4.53 (d, 1H, $J =$ 8 Hz), 4.73 (br s, 1H), 4.95 (d, 1H, $J = 8$ Hz), 5.82 (br s, 2H), 9.47 (t, 1H, $J = 1.5$ Hz); ^{13}C NMR (75 MHz) δ: 11.3 (3C), 18.7 (6C), 20.1, 22.3, 27.1, 32.9, 43.8, 50.7, 56.6, 66.9, 82.8, 93.7, 94.7, 96.7, 99.4, 103.5, 119.4, 128.7, 132.5, 201.0; HRMS (EI) calcd. for $C_{27}H_{41}O_2Si$ (M^+ − isopropyl): 425.2876; found: 425.2877.

1,3,3-Trimethyl-2-(2-oxoethyl)-4-(*Z*-1-methyloxymethoxyhept-4-ene-2,6-diynyl)cyclohexene (30)

A dry THF solution (6 mL) of the silyl acetylene **29** (0.038 g, 0.107 mmol) was cooled to −78°C and then a 1 M solution of *n*-tetrabutyl ammonium fluoride (0.11 mL, 0.11 mmol) added dropwise. The reaction was stirred at −78°C for 2 h, water was added, and the resultant solution was extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated and the residual oil was chromatographed (3:1, petroleum ether/diethyl ether) to give 0.027 g (86%) of the acetylene **30**. IR (neat): 3275, 2918, 2720, 2094, 1720, 1462, 1150, 1000 cm^{-1}; ^1H NMR (200 MHz) δ: 0.99 (s, 3H), 1.07 (s, 3H), 1.55 (s, 3H), 1.0–2.2 (m, 5H), 3.07 (br s, 2H), 3.28 (br s, 1H), 3.38 (s, 3H), 4.57 (d, 1H, $J = 6.5$ Hz), 4.73 (br s, 1H), 5.02 (d, 1H, $J = 6.5$ Hz), 5.76 (br d, 1H, $J = 10$ Hz), 5.90 (d, 1H, $J = 10$ Hz), 5.90 (d, 1H, $J = 10$ Hz), 9.49 (t, 1H, $J = 2$ Hz); HRMS (EI) calcd. for $C_{18}H_{21}I_2$ ($M^+ - CH_3OCH_2$): 269.1541; found: 269.1530.

1,3,3-Trimethyl-2-(2-carboxyethyl)-4-(*Z*-1-methyloxymethoxy-7-triisopropylsilylhept-4-ene-2,6-diynyl)cyclohexene (31)

Diisobutylaluminum hydride (0.350 mL, 0.525 mmol, 1 M in toluene) was added dropwise to a cold (−78°C), stirred solution of the nitrile **27** (0.171 g, 0.366 mmol) in dry dichloromethane (10 mL). The resulting mixture was stirred at −78°C for 1 h. Saturated aqueous ammonium chloride was added; the mixture was stirred at room temperature for 30 min and extracted thoroughly with dichloromethane. The combined organic extracts were washed (water, brine), dried, and concentrated. Sodium chlorite (0.060 g, 0.663 mmol) was added to a solution (2:1, *tert*-butanol/dichloromethane, 15 mL) of the aldehyde **29**, aqueous NaH_2PO_4 (0.10 g in 2 mL), and 30% H_2O_2 (0.12 mL, 1.06 mmol). The mixture was stirred at 21°C for 16 h and concentrated. 10% HCl was added and the resulting mixture was extracted thoroughly with diethyl ether. The combined ether extracts were washed (water, 6% sodium thiosulphate solution, and brine), dried, and concentrated. Flash chromatography (1:1, petroleum ether/diethyl ether; then 2:1, petroleum ether/diethyl ether) afforded 0.140 g (74%) of the acid **31**. IR (neat): 2924, 2703, 2141, 2103, 1711, 1463, 1028 cm^{-1}; ^1H NMR (200 MHz) δ: 1.01 (s, 3H), 1.06 (s, 3H), 1.07 (br s, 20H), 1.59 (s, 3H), 1.5–2.15 (m, 6H), 3.10 (s, 2H), 3.37 (s, 3H), 4.52 (d, 1H, $J = 6.7$ Hz), 4.78 (br s, 1H), 4.97 (d, 1H, $J = 6.7$ Hz), 5.83 (br s, 2H), 10.0 (br s, 1H); ^{13}C NMR (75 MHz) δ: 11.3 (3C), 18.5, 18.6 (6C), 19.9, 20.5, 22.6, 27.1, 32.4, 33.7, 37.9, 50.1, 56.7, 67.1, 83.2, 94.8, 96.5, 99.5, 103.6, 119.5, 119.5, 130.1, 132.9, 176.0.

1,3,3-Trimethyl-2-(2-carboxyethyl)-4-(*Z*-1-methyloxymethoxyhept-4-ene-2,6-diynyl)cyclohexene (32)

A solution of the silyl acetylene **27** (0.084 g, 0.162 mmol) in dry THF (5 mL) was cooled to −78°C and *n*-tetrabutyl ammonium fluoride (0.32 mL, 0.32 mmol, 1 M THF) was added dropwise. The mixture was stirred at −78°C for 5 h, quenched with water, and extracted thoroughly with diethyl ether. The combined ether extracts were washed (10% HCl, brine), dried, concentrated, and chromatographed (3:1 petroleum ether/diethyl ether, then 1:1 petroleum ether/diethyl ether) to provide **32**, 0.0410 g (77%). IR (neat): 3281, 2929, 2094, 1714, 1464, 1151, 1029 cm^{-1}; ^1H NMR (200 MHz) δ: 0.87 (s, 3H), 1.08 (s, 3H), 1.59 (s, 3H), 1.5–2.30 (m, 5H), 1.58 (s, 3H), 3.08 (br s, 2H), 3.28 (d, 1H, $J = 2.2$ Hz), 3.37 (s, 3H), 4.55 (d, 1H, $J = 6.7$ Hz), 4.74 (br s, 1H), 5.01 (d, 1H, $J = 6.7$ Hz), 5.76 (dd, 1H, $J = 10.9$, 2.2 Hz), 5.88 (d, 1H, $J = 10.9$ Hz), 10.50 (br s, 1H).

1,3,3-Trimethyl-2-(2-hydroxymethyl)-4-(*Z*-1-methyloxymethoxy-7-triisopropylsilylhept-4-ene-2,6-diynyl)cyclohexene (34)

A toluene solution of diisobutylaluminum hydride (1.5 M, 0.55 mL, 0.825 mmol, Aldrich) was added dropwise to a cold (−78°C), stirred solution of the nitrile **27** (0.351 g, 0.752 mmol) in dry dichloromethane (10 mL). The resulting mixture was stirred at −78°C for 1 h and warmed to 0°C for an additional hour. Dilute HCl (aqueous 5%) was added and the mixture was stirred at 21°C for 30 min. The solution was extracted thoroughly with dichloromethane. The combined organic

extracts were washed with water, brine, dried ($MgSO_4$), filtered, and concentrated and the residual oil was filtered through a short column of neutral alumina to afford the aldehyde **29**. This material was dissolved in dry dichloromethane (10 mL) and the reduction procedure repeated (diisobutylaluminum hydride, 1.5 M, 0.55 mL, 0.825 mmol). Chromatography (silica gel; 3:1, petroleum ether/diethyl ether) of the resulting oil provided the alcohol **34** (0.180 g, 51%). IR (neat): 3348, 2913, 2141, 1461, 1028 cm^{-1}; ^1H NMR (200 MHz) δ: 1.00 (s, 3H), 1.06 (br s, 24H), 1.1–1.4 (m, 2H), 1.62 (s, 3H), 1.5–2.1 (m, 4H), 2.32 (br t, 2H, $J = 8$ Hz), 3.36 (s, 3H), 3.58 (br q, 2H, $J = 8$ Hz), 4.52 (d, 1H, $J = 6.6$ Hz), 4.77 (br s, 1H), 4.94 (d, 1H, $J = 6.6$ Hz), 5.81 (br s, 2H); ^{13}C NMR (50 MHz) δ: 11.2 (3C), 18.6 (6C), 19.9, 20.3, 22.9, 27.3, 32.2, 32.6, 38.1, 50.8, 56.5, 62.4, 66.9, 82.7, 94.7, 97.0, 99.3, 103.6, 119.4, 119.5, 129.6, 132.8, 201.0; HRMS (EI) calcd. for $C_{29}H_{48}O_3Si$: 472.3373; found: 472.3426.

1,3,3-Trimethyl-2-(2-hydroxymethyl)-4-(*Z*-1-methyloxymethoxyhept-4-ene-2,6-diynyl)cyclohexene (35)

A dry THF solution (10 mL) of the silyl acetylenic alcohol **34** (0.130 g, 0.275 mmol) was cooled to −78°C and then a 1 M solution of *n*-tetrabutyl ammonium fluoride (0.55 mL, 0.540 mmol) was added dropwise. The reaction was stirred at −78°C for 1 h, warmed to 0°C, water was added, and the resultant solution was extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated and the residual oil was chromatographed (1:1, petroleum ether/diethyl ether) to give 0.079 g (91%) of the acetylene **35**. IR (neat): 3366, 3286, 2921, 2094, 1459, 1150, 1029 cm^{-1}; ^1H NMR (200 MHz) δ: 0.99 (s, 3H), 1.09 (s, 3H), 1.60 (s, 3H), 1.5–2.0 (m, 6H), 2.30 (br t, 2H, $J = 8$ Hz), 3.27 (d, 1H, $J = 1$ Hz), 3.36 (s, 3H), 3.55 (t, 2H, $J = 8$ Hz), 4.54 (d, 1H, $J = 6.8$ Hz), 4.71 (br s, 1H), 4.99 (d, 1H, $J = 6.8$ Hz), 5.75 (dd, 1H, $J = 11$, 2.2 Hz), 5.88 (dt, 1H, $J = 11$. 0.5 Hz); HRMS (EI) calcd. for $C_{18}H_{21}O_2$ ($M^+ - CH_3OCH_2$): 269.1541; found: 269.1530.

1,3,3-Trimethyl-2-(2-hydroxymethyl)-4-(*Z*-1-methyloxymethoxy-7-iodohept-4-ene-2,6-diynyl)cyclohexene (36)

Freshly dried morpholine (0.29 g, 3.31 mmol) and iodine (0.11 g, 0.433 mmol) were added sequentially to the acetylene **35** (0.070 g, 0.222 mmol) dissolved in dry benzene (10 mL) in a round-bottom flask (25 mL) equipped with a condenser. The reaction mixture was heated and stirred at ~40°C for 3 h. The mixture was then cooled to 21°C and aqueous sodium thiosulphate solution (6%) added. The resulting mixture was extracted thoroughly with diethyl ether. The combined organic extracts were washed with brine, dried, filtered, concentrated, and chromatographed (1:1, petroleum ether/diethyl ether) to afford the iodoalcohol **36** (0.084 g, 86%). IR (neat): 3376, 2927, 2247, 2153, 1029, 914 cm^{-1}; ^1H NMR (200 MHz) δ: 1.02 (s, 3H), 1.13 (s, 3H), 1.1–2.1 (m, 6H), 1.63 (s, 3H), 2.34 (br t, 2H, $J = 8$ Hz), 3.38 (s, 3H), 3.60 (br t, 2H, $J = 8$ Hz), 4.58 (d, 1H, $J = 6.3$ Hz), 4.73 (br s, 1H), 5.00 (d, 1H, $J = 6.3$ Hz), 5.78 (dd, 1H, $J = 10$, 1 Hz), 5.89 (d, 1H, $J = 10$ Hz); ^{13}C NMR (50 MHz) δ: 20.2, 20.4, 22.8, 27.5, 32.3, 32.8, 38.2, 50.9, 56.6, 62.5, 67.0, 82.5, 91.7, 94.7, 97.4, 119.6, 119.8, 121.7, 129.7, 132.8.

1,3,3-Trimethyl-2-(2-oxoethyl)-4-(*Z*-1-methyloxymethoxy-7-iodohept-4-ene-3,6-diynyl)cyclohexene (37)

Pyridinium dichromate (0.136 g, 0.359 mmol) was added to a stirred solution of the alcohol **36** (0.080 g, 0.181 mmol) in dry dichloromethane (10 mL). The resulting mixture was stirred at 21°C for 16 h. The reaction mixture was filtered through a sintered glass funnel under aspirator pressure and the collected precipitate washed thoroughly with diethyl ether. The ether filtrates were concentrated to provide a brownish oil that was purified by chromatography (3:1, petroleum ether/diethyl ether) to afford the aldehyde **37** (0.065 g, 82%). IR (neat): 2924, 2721, 2251, 2154, 1718, 1042, 1021 cm^{-1}; ^1H NMR (200 MHz) δ: 1.00 (s, 3H), 1.08 (s, 3H), 1.0–2.2 (m, 5H), 1.55 (s, 3H), 3.08 (br s, 2H), 3.39 (s, 3H), 4.58 (d, 1H, $J = 7$ Hz), 4.73 (br s, 1H), 5.00 (d, 1H, $J = 7$ Hz), 5.77 (dd, 1H, $J = 9$, 1.5 Hz), 5.91 (d, 1H, $J = 9$ Hz), 9.48 (t, 1H, $J = 2.3$ Hz); ^{13}C NMR (50 MHz) δ: 20.4, 22.3, 27.1, 29.7, 33.0, 38.1, 43.8, 50.7, 56.6, 66.9, 82.7, 91.7, 94.7, 97.2, 119.9, 121.7, 128.8, 131.6, 132.7, 201.2; HRMS (EI) calcd. for $C_{18}H_{20}O_2$ ($M^+ - CH_3OCH_2$): 395.0467; found: 395.0501.

16,17,18-Trimethyl-2-methyloxymethoxy-9-hydroxybicyclo[9.3.1]pentadec-5-ene-3,7-diyne (38)

Nickel(II) chloride (0.012 g, 0.096 mmol) and chromium(II) chloride (0.170 g, 1.38 mmol) were added to a stirred solution of the aldehyde **37** (0.061 g, 0.138 mmol) in dry THF (20 mL). The resulting mixture was stirred at 21°C for 4 h, water was added, and the mixture was extracted thoroughly with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed (3:1, petroleum ether/diethyl ether, then 1:1, petroleum ether/diethyl ether) to the cyclic enediyne **38** (0.026 g, 60%). IR (neat): 3380, 2924, 2204, 1029 cm^{-1}; ^1H NMR (200 MHz) δ: 1.10 (s, 3H), 1.29 (s, 3H), 1.5–2.1 (m, 5H), 1.64 (s, 3H), 2.3–2.7 (m, 3H), 3.35 (s, 3H), 4.50 (d, 1H, $J = 6.8$ Hz), 4.59 (br s, 1H), 4.89 (d, 1H, $J = 6.8$ Hz), 5.02–5.18 (m, 1H), 5.78 (br s, 2H); ^{13}C NMR (50 MHz) δ: 21.0, 25.1, 25.3, 29.4, 32.0, 36.7, 37.2, 49.1, 55.6, 63.5, 70.1, 82.8, 84.9, 93.3, 95.4, 98.4, 120.7, 121.2, 131.1, 132.5; HRMS (EI) calcd. for $C_{18}H_{21}O_2$ ($M^+ - CH_3OCH_2$): 269.1542; found: 269.1541.

3,4,5,6,7,8-Hexadehydro-2*a*-methoxymethyl-9-oxo-12,15,15-trimethyltricyclo[9.3.1.$0^{3,8}$]pentadec-11-ene (40)

The alcohol **38** (0.015 g, 0.05 mmol) in dry toluene (10 mL) containing 1,4-cyclohexadiene (0.5 mL) was placed in a thick-walled Pyrex pressure tube equipped with a threaded plastic cap. The top of the tube extended through a small hole in the tope of the microwave oven. Argon was bubbled through the solution for 10 min and the vessel sealed. The diameter of the oven opening is less than 3 cm and is shielded to minimize microwave leakage. The base of the tube inside the microwave oven was surrounded by a beaker of damp (H_2O) vermiculite to facilitate heat transfer. A commercial oven was used (Toshiba model ERF-6630C (720 W)) at a power setting of 500 W in which the magnetron was tuned to the water frequency (2450 MHz). The reaction was conducted behind a shield in a fume hood. The reaction was heated for eight 0.5 h intervals in which the tube was allowed to return to room temperature between each session and fresh moist vermiculite was

added to the beaker. The tube was cooled, solvent was evaporated, and the residual oil chromatographed (petroleum ether/diethyl ether, 3:1) to generate the alcohol, which was used directly. Alcohol **39** was dissolved in CH_2Cl_2, pyridinium dichromate (0.10 g) was added, and the reaction was stirred at 21°C for 6 h. After filtration through a sintered glass funnel under reduced pressure (water aspirator) the solution was concentrated and chromatographed (petroleum ether/diethyl ether, 3:1) to afford 0.001 g (6%) of ketone **40**. Identified by spectral comparison (NMR, IR, MS) with an authentic sample (preceding paper).

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