A cycloaddition approach to tricyclic taxoid skeletons

Yee-Fung Lu and Alex G. Fallis

Abstract: A cycloaddition approach to the functionalized tricyclo[9.3.1.$0^{3,8}$]pentadecene skeleton contained in Taxol® is described. The cyclohexenone **13** was converted as illustrated to the nitrile-aldehyde **24** to which the diene and acetylenic side chains were attached by sequential nucleophilic additions. Removal of the trimethylsilyl protecting group and Dess–Martin oxidation afforded the triene **35**. Microwave-assisted thermal cyclization stereoselectively generated the tricyclic ketone **36** whose structure was further established by conversion to the aromatic system **37** upon treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). An epoxidation sequence was developed to introduce the epimeric C13 alcohol **47** as required for this cycloaddition strategy. Alternatively, an allylic oxidation (CrO_3, 3,5-dimethylpyrazole) afforded the C13 ketone **49**.

Key words: Taxol®, Diels–Alder, synthesis, diterpene, alkaloid.

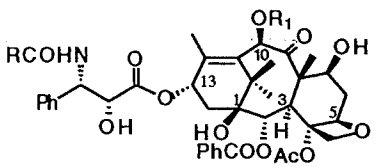
Résumé : On décrit une approche, impliquant une cycloaddition, au squelette du tricyclo[3.3.1.$0^{3,8}$]pentadécène fonctionnalisé contenu dans le Taxol®. Tel que représenté dans le diagramme 1, on transforme la cyclohexénone **13** en nitrile-aldéhyde **24** auquel on attache les chaînes latérales diénique et acétylénique par une séquence d'additions nucléophiles. Après enlèvement du groupe protecteur triméthylsilyle et oxydation de Dess–Martin, on a obtenu le triène **35**. Une cyclisation thermique sous l'effet de micro-ondes a fourni stéréosélectivement la cétone **36** dont la structure a été reconfirmée par conversion en système aromatique **37** par traitement avec de la 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). On a développé une séquence d'époxydations (diagramme 2) qui permet d'introduire l'alcool épimère en C_{13} (**47**) qui est requis par cette stratégie de cycloaddition. D'une manière alternative, une oxydation allylique (CrO_3, 3,5-diméthylpyrazole) a fourni la cétone en C_{13}, **49**.

Mots clés : Taxol®, Diels–Alder, synthèse, diterphène, alcaloïde.

[Traduit par la rédaction]

Introduction

The potent antitumor agent paclitaxel (Taxol,® **1**) was approved for the treatment of ovarian and breast cancer in 1993. This was more than 20 years after its structure was initially reported (1), and more than 30 years after its cytotoxicity was first detected. The medicinal potential for the taxoid family is further illustrated by the fact that a semi-synthetic analog, docetaxel (Taxotere,® **2**), is in final clinical trials and also



1 Taxol® R = Ph, R_1 = Ac
2 Taxotere® R = tBuO, R_1 = H

shows considerable therapeutic promise (2) (approved in Canada in September 1995). These compounds belong to a new class of antitumor drugs that interfere with the normal microtubule–tubulin cascade prior to cell division (3). This novel mode of action, plus the significant synthetic challenge presented by the sterically congested multicyclic structure, has stimulated worldwide interest in these molecules (4). Recently two groups reported total syntheses of taxol itself (5, 6). In spite of this success much remains to be investigated and over the next decade it is likely that simpler analogues with a better therapeutic profile will be synthesized and become useful pharmaceutical products. They will thus follow the path from natural products to medicine established earlier for penicillins, tetracyclines, etc., a path that depends upon improved knowledge of structure–activity relationships, the development of efficient synthetic and (or) semi-synthetic routes to the functionalized tricyclo[9.3.1.$0^{3,8}$]pentadecene nucleus, and the development of medicinally interesting analogs that possess a better therapeutic profile than paclitaxel itself.

Thus, synthetic interest int his area continues unabated and several recent reviews summarize the progress that is being achieved and the diversity of synthetic approaches that are under development (4). In this paper we describe an intramolecular Diels–Alder approach that proceeds in the left-to-right direction (ring A to BC). Commencing with a ring A cyclohexene building block, the sequence relies on a cycloaddition reaction to construct the B and C rings simultaneously. This strategy is hlghly convergent, and leads to the functionalized

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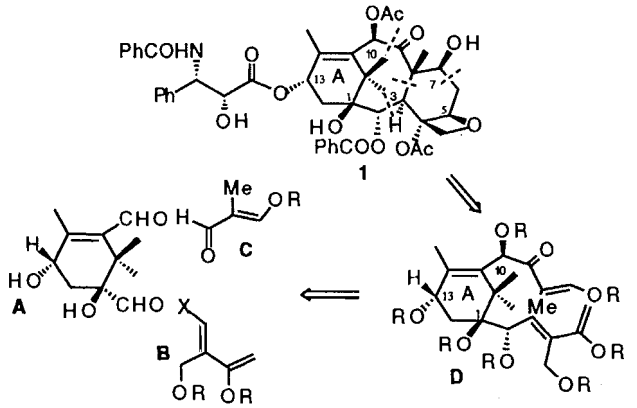
Y.-F. Lu and A.G. Fallis.[1] Ottawa–Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, ON K1N 6N5, Canada.

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

Scheme 1. Convergent ring C Diels–Alder approach.



tricyclo[9.3.1.$0^{3,8}$]pentadecene skeleton in which the C2 epimer controls the adduct stereochemistry.

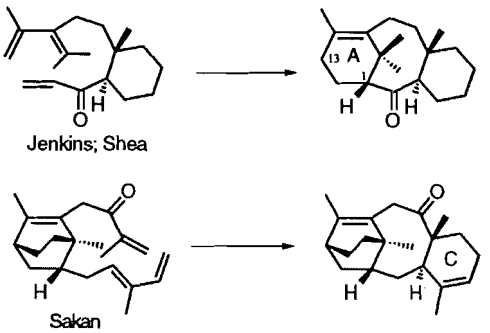
Synthetic strategy

In a retrosynthetic sense removal of the ring D oxetane followed by a double disconnection between C6—C7 and C3—C8 in ring C suggests a precursor related to the tetraene **D** (Scheme 1). In principle this intermediate could contain the majority of the Taxol® oxygen substituents, although in practice the use of less substituted systems may be more prudent. Construction of **D** may be envisaged in a direct manner from further disconnections between C2—C3 and C9—C10. In total, this leads to a highly convergent approach to the taxane nucleus from a suitably functionalized ring A synthon in the form of a masked dialdehyde synthon related to **A**, followed by attachment of the lower diene and upper dienophile units **B** and **C**, respectively. Subsequently, intramolecular Diels–Alder cycloaddition could afford the carbocyclic nucleus. However, several additional aspects must also be considered for this approach to have a reasonable chance of success.

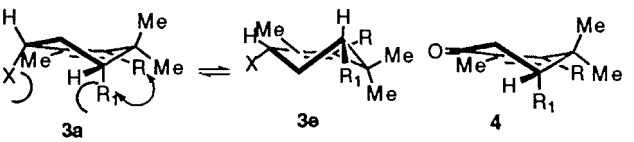
Other research groups have also examined the potential utility of an intramolecular [4+2] cycloaddition to generate the tricyclic skeleton. In independent studies, Bonnert and Jenkins (7) as well as Shea and co-workers (8) generated the A ring with the bridgehead double bond in place, as illustrated in general terms in Scheme 2. Unfortunately, a recent study reported that the *gem* dimethyl bridge in the adduct does not have the correct orientation in a more highly functionalized example (i.e., epimeric at C1) (9), and a related bis-normethyl system behaved similarly (10). The C ring had been constructed previously from a bicyclo[2.2.2]octene precursor by Sakan and Craven (11). It was assumed that the rigid geometry imparted by this bicyclic framework was required to hold the diene in an axial orientation. This allows the close proximity of the reactive components in order to achieve the proper alignment for the cyclization transition state and overcome the entropic difficulties associated with a conformationally mobile ring system such as a cyclohexene. In addition, the formation of sterically congested cyclooctanes via [4+2] cycloadditions is known to be difficult (12). However, it was not clear whether the one-carbon bridge between the C13 center and the C17 methyl group is essential for a successful intramolecular cyclization in this series.

The conformer population in cyclohexenes is known to vary with the substitution pattern (13). Thus, the potential 1,3-diax-

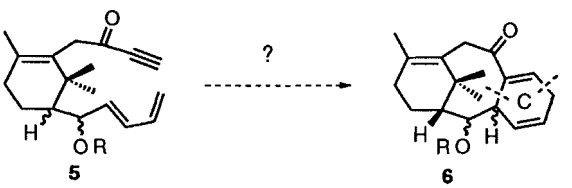
Scheme 2. Other representative Diels–Alder approaches.



Scheme 3. Conformational considerations.



Scheme 4. Ring C construction with acetylenic dienophile.

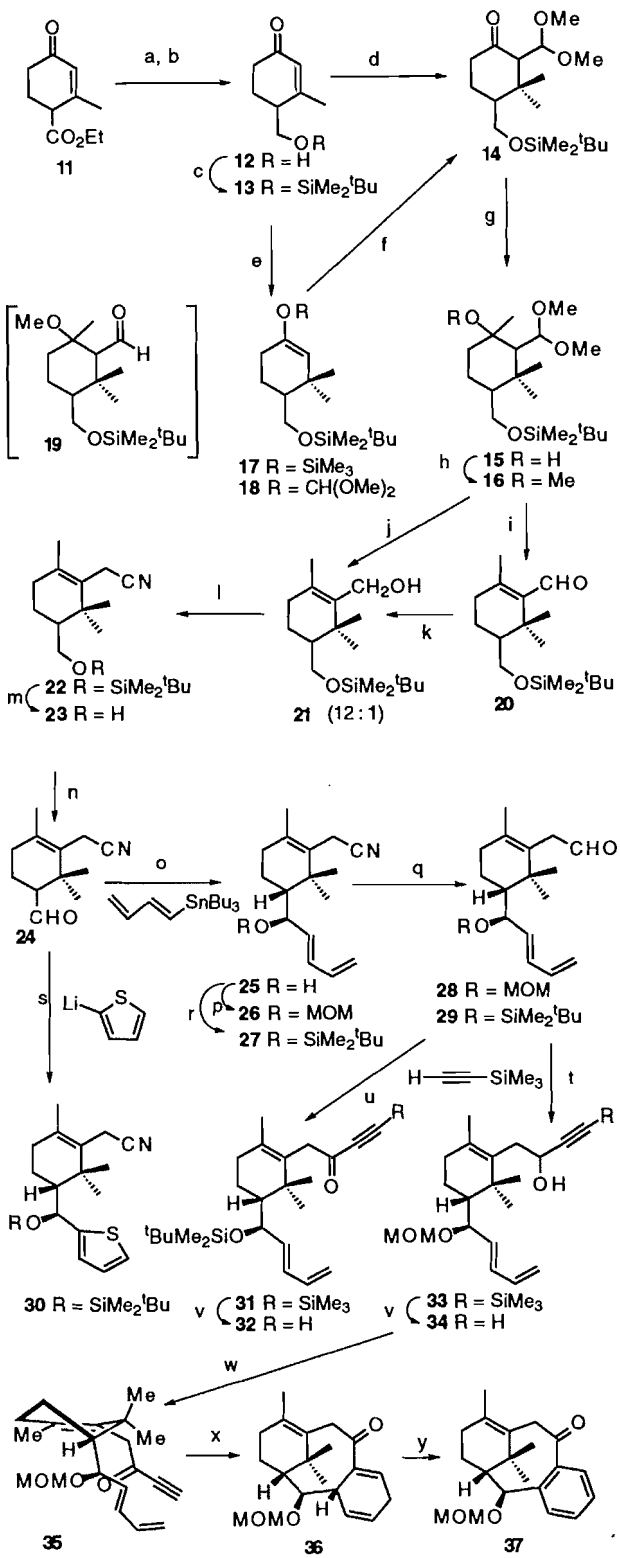


ial interaction (C—X versus C—R_1) in **3a** (Scheme 3) must be overcome if the reactive components represented by R and R_1 are to cyclize, since the equatorial conformer **3e** does not allow the two side chains to interact significantly. However, this limitation should not cause undue difficulty provided the reactive conformer makes up a reasonable percentage of the equilibrium mixture at the temperature selected. In addition, it will help if the cyclization step is sufficiently rapid that few collisions are required. When X = H the 1,3-interaction should be relatively minor and this will disappear entirely if a cyclohexenone such as **4** is employed. Nevertheless, there is a limitation to this approach for the total synthesis. The natural α orientation of the C13 ester side chain will increase the nonbonded interactions in the required conformer **3a** (X = OR). Thus for the Diels–Alder step to proceed, either the unnatural C13 epimer or the C13 ketone may have to be employed and the synthon **A** modified accordingly (Scheme 1). Consistent with this analysis, molecular mechanics calculations[2] indicated that 1,2,3,3,4-pentamethylcyclohexene preferred a conformation related to **3a** in which a slight twist minimized any 1,3-methyl-hydrogen interference. Therefore, additional ring constructions should not be required to access the transition state geometry for ring C directly when the diene and dienophile are attached to a cyclohexene. To further encourage the cycloaddition, the rotational parameters normally encountered with olefinic partners were minimized by selecting an acetylenic dienophile as illustrated in **5** (Scheme 4). Inherent in the transformation **5** to adduct **6** are several additional questions that require solution. These include the π-facial selectivity of

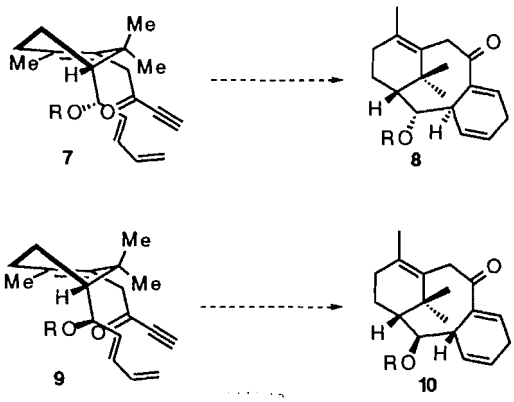
[2] Analysis by PCMODEL (Serena Software, Box 3076, Bloomington, IN 47402-3076, U.S.A.).

Chart 1. Synthetic sequence to **36** and **37**.

(a) DIBAL, C_6H_6, 0°C, 2 h, 21°C, 98%; (b) DDQ, dioxane, 25°C, 24 h, 92%; (c) TBSCI, imidazole, DMF, 24 h, 98%; (d) MeMgBr, CuI (cat), Et_2O, 0°C, 0.5 h; $CH(OMe)_3$, $BF_3{\cdot}OEt_2$, −78–0°C, 59%; (e) MeMgBr, CuI (cat), ether, Et_3N, TMSCl, 1 h 0°C, 4 h 21°C, 71%; (f) $(MeO)_3CH$, $TiCl_4$, CH_2Cl_2, −78–21°C, 1 h, 55%; (g) MeLi, Et_2O, 0°C, 0.5 h; or MeMgBr, toluene/Et_2O, 0–21°C, 30 min, 95%; (h) MeLi, Et_2O, HMPA, MeI, 0–21°C, 16 h, 94%; (i) $CH_2{=}CHCH_3$, TMSCl, NaI, CH_2Cl_2, 21°C, 5 min, CH_3ONa, CH_3OH, 65°C, 30 min, 70% or 15% aq. H_2SO_4, SiO_2, CH_2Cl_2, 2 min, 21°C, 96%; (j) $CH_2{=}CHCH_3$, TMSCl, NaI, CH_2Cl_2, 21°C, 5 min, CH_3ONa, CH_3OH, 65°C, 30 min, CH_3ONa, CH_3OH, 65°C, $NaBH_4$, $CeCl_3$, 21°C, 70%; (k) DIBAL, toluene, −78–21°C, 1.5 h, 21°C, 99%; (l) Ph_3PBr_2, Et_3N, CH_2Cl_2, −78°C, 1 h; then NaCN, methyl pyrrolidinone, 21°C, 1.5 h, 75%; (m) *n*-Bu_4NF, THF, 21°C, 4 h, 98%; (n) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78–21°C, 94%; (o) *n*-BuLi, THF, −78°C, 0.5 h, 96%; (p) $(i\text{-}Pr)_2EtN$, MOMCl, CH_2Cl_2, 90%; (q) DIBAL, CH_2Cl_2, −78–0°C; 1–2 h, H_3O^+, 70–91%; (r) TBSCl, DMF, DMAP, 21°C, 3 d, 81%; (s) *n*-BuLi, thiophene, THF, −78°C, 15 min, **24**, THF, −78°C, 30 min, 69%; TBSCl, $AgClO_4$, pyridine, CH_3CN, 21°C, 16 h, 72%; (t) HCCTMS, *n*-BuLi, THF, −78°C, 1 h, 95%; (u) HCCTMS, *n*-BuLi, THF, −78°C, 1 h, 0°C, 1 h, 93%; $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 15 min, Et_3N, 21°C, 30 min, 38%; (v) KOH, MeOH, CH_2Cl_2, 21°C, 99%; (w) Dess–Martin periodinane, CH_2Cl_2, 21°C, 55%; (x) microwave oven, sealed tube, toluene, 10 h, 34%; (y) DDQ, benzene, 80°C, 2 h, 69%; (z) *n*-BuLi, 2-bromopropene, THF, −78–21°C, 30 min, 72%; $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 15 min, Et_3N, 21°C, 30 min, 88%.



Scheme 5. Transition states for C_2 epimers.

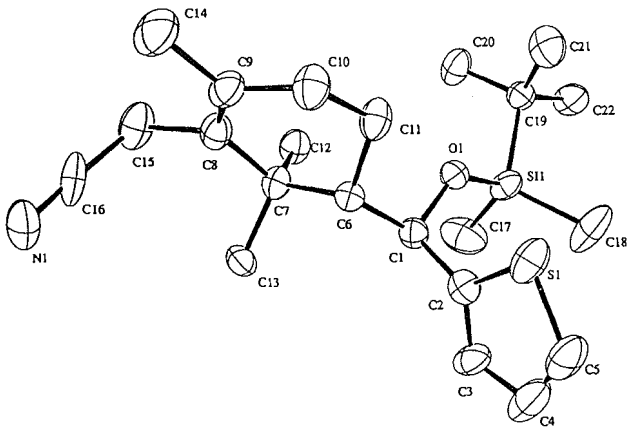


the cycloaddition and the influence of the C2 substituent on the transition states. These considerations are illustrated in Scheme 5 for the transition states of the C2 epimers **7** and **9**. This suggests that the orientation of this C2 group will determine the facial preference of the cycloaddition and hence the resultant stereochemistry of C3 in the adduct. The validity of these analyses have been demonstrated below by the synthesis of the tricyclic taxane nucleus **36** and the related aromatic system **37** (preliminary communication, ref. 14).

Results and discussion

To ascertain the practicality of this plan the carbonyl groups in Hagemann's ester (**11**) were reduced with DIBAL (diisobutylaluminum hydride) in benzene (Chart 1), the allylic alcohol oxidized with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), and the remaining primary alcohol protected as a *tert*-butyldimethylsilyl ether to afford the cyclohexenone **13** (15). Treatment of cyclohexenone **13** with methylmagnesium bromide in the presence of cuprous iodide, followed by the addition of methylorthoformate mediated by boron trifluoride etherate, afforded the keto-acetal **14** in 59% yield (Chart 1). Alternatively this compound was prepared in a two-step

Fig. 1. A view of 1-(2-thiophenyl)methyl-2-cyanomethyl-1,3,3-trimethylcyclohexene (**30**).

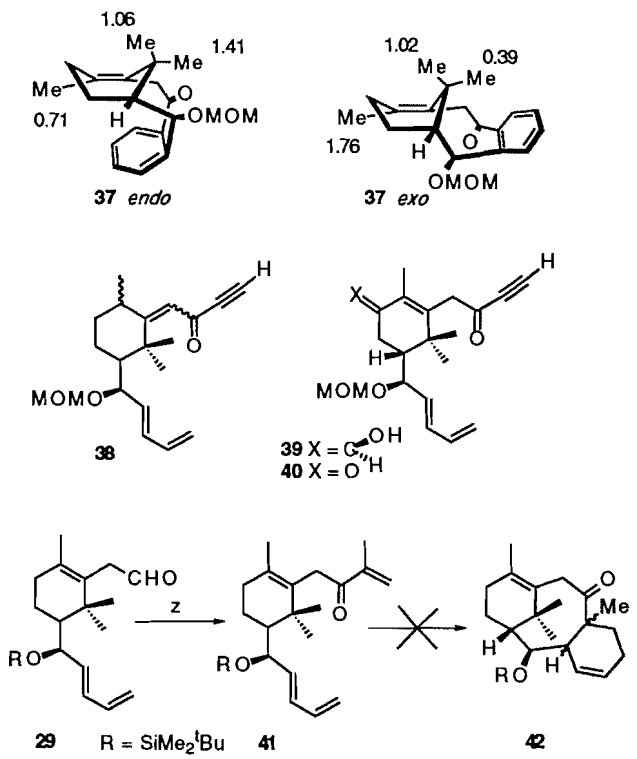


sequence via the intermediacy of the trimethylsilyl enol ether **17** and methylorthoformate in the presence of titanium tetrachloride. Addition of methyllithium to the carbonyl group in **14** allowed preparation of the tertiary alcohol **15**, or it could be alkylated directly in the presence of added HMPA (hexamethylphosphoramide) to give the trimethoxy ether **16**. Trimethylsilyliodide generated in situ (16) released the aldehyde function (i.e., **19**) so that direct treatment with base led to elimination of methoxide ion and the formation of the cyclohexene aldehyde **20** in 70% overall yield from **16**.

Reduction of aldehyde **20** ($NaBH_4$, $CeCl_3$, 70%) provided the alcohol **21** accompanied by a small amount of the less substituted endocyclic isomer (ratio 12:1). Alternatively, this alcohol could be prepared directly from **16** by sequential treatment with trimethylsilyl chloride, sodium iodide, sodium methoxide, and sodium borohydride – cerium trichloride. Chain extension to the nitrile **22** was accomplished by cyanide displacement (NaCN, methyl pyrrolidinone, 75%) of the primary bromide generated from the alcohol upon treatment with Ph_3PBr_2, Et_3N in CH_2Cl_2 at −78°C for 1 h. Removal of the silyl protecting group with fluoride ion (n-Bu_4NF, THF, 21°C, 3 h, 98%) followed by Swern oxidation (DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C, 94%) afforded the aldehyde **24**. The required nucleophilic diene unit was prepared by transmetallation of E-1,3-(1-tributylstannyl)butadiene (17) with n-BuLi and added to the aldehyde **24** (THF, −78°C, 0.5 h, 96%). From direct analysis of the resulting secondary alcohol (6:1 diastereomer ratio) it was not possible to determine which of the isomers corresponded to the Taxol® stereochemistry at C2. The stereochemistry was determined by condensation of 2-lithiothiophene with aldehyde **24**, followed by silylation with tert-butyldimethylsilyl chloride, to give the crystalline derivative **30**. X-ray determination showed the major isomer to have the opposite stereochemistry (C1—C2) to Taxol® as shown (Fig. 1). Alcohol **25** was assigned the same relative stereochemistry by analogy and comparison of spectral data and, as outlined, this isomer was used for subsequent experiments.

The secondary alcohol in **25** was protected as either a methoxymethyl ether (MOMCl, $(iPr)_2EtN$, CH_2Cl_2, 90%) or, alternatively a *tert*-butyldimethylsilyl ether to afford **26** and **27**, respectively. Diisobutylaluminum hydride reduction of the nitrile group in these compounds provided the corresponding aldehydes **28 and 29**. In a parallel, but independent, manner, these aldehydes were treated with lithium trimethylsilylacetylide (HCCTMS, n-BuLi, THF, −78°C, 95%) and then transformed into the desired ketones by oxidation either before or after removal of the trimethylsilyl group. These apparently straightforward operations were surprisingly challenging. Removal of the trimethylsilyl group from the acetylenic ketones proved very difficult in contrast to the ease with which this bond cleavage was affected on the acetylenic alcohol. Thus it was important to remove the trimethylsilyl group (KOH, MeOH, CH_2Cl_2, 21°C, 99%) at the alcohol stage on compound **33**. Only the Dass–Martin periodinane oxidation method (18), of several examined, generated the required ketone **35** in reasonable yield (55%). Attempted cycloadditions with ketones **31**, **32**, and the ketone derived from **33** all failed under the various conditions examined.

Fortunately, cyclization of ketone **35** could be affected by heating a 0.05 M toluene solution containing 1% mol-equiv. hydroquinone in a sealed glass tube in a modified microwave oven (19) for 10 h to afford the tricyclic system **36** stereoselectively in yields of 30–40%. This major adduct arose via the preferred transition state in which the nonbonded interactions were minimized due to the alignment of the dienophile under the triene remote from the MOM substituent as illustrated in **35**. This pattern of π-facial selectivity was consistent with related intermolecular cycloadditions involving acetylenes and acylic dienes (20) and implies that with the "natural" C2 stereochemistry the preferred geometry will resemble **7** and should provide the relative stereochemistry illustrated in **8** as required for Taxol® itself. The structural assignment of the adduct **36** was further established on the basis of its ^1H NMR spectrum, in which the C3 proton appeared at δ 2.95 as a doublet of doublets (J = 5.6, 9.6 Hz) due to coupling with the adjacent vinylic C4 and secondary C2 hydrogens.[3] Confirmation



[3] In addition to adduct **36**, the minor adduct epimeric at C3 was also formed (5–7%). This arose from the approach of the addends from the opposite face.

of the tricyclo[9.3.1.$0^{3,8}$]pentadecatriene skeleton was provided by the conversion of **36**, upon treatment with DDQ in refluxing benzene, to the aromatic ketone **37**. In keeping with related literature examples, this material existed as a mixture of exo and endo isomers (~1:1) (21) in which the vinyl methyl signal appeared at 0.71 (endo) or 1.76 (exo) depending upon the orientation of the benzene ring.

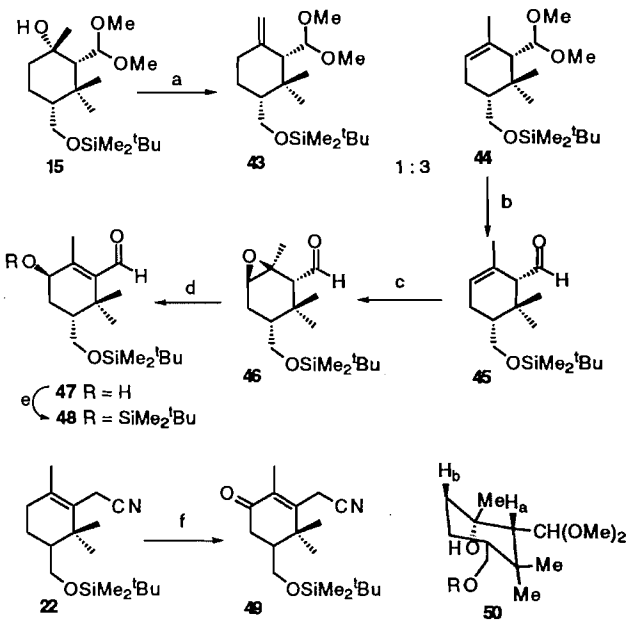
Unfortunately, it was not possible to catalyze the cycloaddition with Lewis acids, due to the ease with which the cyclohexene double bond migrated into conjugation with the acetylenic ketone and afforded the complex mixture of isomers represented by **38**. These components accounted for some of the uncyclized material in the thermal reaction. It is anticipated that, with the C13 ketone in place as in ketone **43** (Taxol® numbering), the cyclohexenone will help suppress this tendency for bond migration, flatten the ring, and reduce the axial interaction, and should lead to improved yields. Alternatively, the epi-C13 alcohol **39** is a potential Diels–Alder precursor, and a route to a suitable ring A building block is described below.

The direct introduction of the C8-methyl was also examined. Thus vinyl anion addition to aldehyde **29**, followed by Swern oxidation, afforded **41**. Unfortunately, this material could not be induced to undergo an intramolecular cycloaddition. The failure of the attempted cyclizations with **32** and **41** appears to be a consequence of the large protecting group attached to the C2 alcohol. Thus nonbonded interactions between this substituent and the germinal methyls inhibit attainment of the requisite geometry for cycloaddition. It remains to be established whether adducts of type **42** can be generated if different protecting groups and stereochemical combinations are employed.

An important feature of taxol itself is the C13 oxygen side chain. The requisite oxygen may be installed directly by allylic oxidation as illustrated by the **22** to **49** conversion (Chart 2). It is of interest that in spite of modest yields the reaction is clean and yields are 65–70% based on the recovered starting material. In addition, no oxygen was introduced at the position corresponding to C10 in Taxol® (6, 22, 23). A suitable synthon for the epimeric C13 alcohol (**47**) was prepared from the acetal **15**. Dehydration of this material was affected with thionyl chloride and pyridine to provide **43** and the major isomer **44** with the endocyclic double bond (1:3). This is a consequence of the relative stereochemistry in **15** and the favorable trans diaxial elimination that arises from the preferred conformation **50**. Thus the axial proton adjacent to the germinal methyl groups (H_a) is in a sterically encumbered environment and elimination from the other side (H_b) or the methyl group is more facile. The major isomer **44** was treated with acid to hydrolyze the acetal to give **45**, and oxidation of **45** with dioxirane provided the epoxide **46**, with the oxirane trans to the bulky silyl ether. Treatment with sodium methoxide in refluxing methanol installed the double bond and generated the secondary alcohol **47**, which was characterized as the silyl derivative **48**. This provided a direct route to epi-C13 precursors as required, based on the stereochemical analysis in the introduction. Stork and co-workers (24) have developed a different preparation of epimeric C13 ring A alcohol intermediates.

In conclusion, a carefully designed [4+2] cycloaddition strategy with an acetylenic dienophile can be employed to generate the substituted taxane nucleus directly, with good stereochemical control, in a convergent manner from a functionalized

Chart 2. Oxygen introduction at C13.
(a) $SOCl_2$, pyridine, CH_2Cl_2, 0–21°C, 0.5 h, 80%; (b) $(HOOC)_2$, H_2O, HOAc (cat), 100°C, 2 h, 85%; (c) Me_2CO_2, $Me_2C{=}O$, −4–21°C, 1 h, 77%; (d) NaOMe, MeOH, 65°C, 3 h, 66%; (e) TBSCl, imidazole, 21°C, 16 h, 91%; (f) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −4–21°C, 16 h, 31%.
Legend: DIBAL = diisobutylaluminium hydride; DDQ = 2,3-dichloro-5,6-dicyanoquinone; DMF = dimethylformamide; TBSCl = *tert*-butyldimethylsilylchloride



cyclohexene substrate. We are currently extending these results toward the total synthesis of Taxol® and the preparation of therapeutically promising analogs, using more highly oxygenated precursors, in which the C13 ketone and "natural" C2 epimer are expected to facilitate and control the cyclization.

Experimental section

Melting points were determined in capillary tubes with a Thomas–Hoover Unit-Melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 783 spectrometer or a Bomem MB 100 FTIR spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were measured at 60 MHz with a Varian spectrometer or at 200 MHz with a Varian Gemini spectrometer or at 300 MHz with a Varian XL-300 spectrometer in deuterochloroform unless otherwise stated. Carbon magnetic resonance spectra (^{13}C NMR) were measured at 50 MHz (Varian Gemini) or at 75 MHz (Varian XL-300). Chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). The multiplicity, number of protons, and coupling constants are indicated in parentheses. Mass spectra (MS) were determined on a VG micromass 7070 HS instrument using an ionization energy of 70 eV. Gas chromatograph – mass spectral (GC–MS) analyses were determined on a Hewlett–Packard 5890 Series II gas chromatograph – 5971A Mass Selective Detector equipped with a 12.5 m capillary column (0.2 mm i.d.) coated with cross-linked dimethylsilicone (0.33 μm). Elemental analyses were conducted by M-H-W Laboratories, Phoenix, Ariz. Analytical thin-layer chromatography (TLC) employed commer-

cial aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Flash column chromatography using E. Merck silica gel 60 (70–230 or 230–400 mesh) was employed for all column chromatography. 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.

Petroleum ether refers to a fraction with boiling range 30–60°C. Anhydrous diethyl ether (ether) and diisopropylamine were obtained by distillation from $LiAlH_4$ and anhydrous tetrahydrofuran (THF) from potassium–benzophenone. Absolute methanol and ethanol were dried by distillation from magnesium. Dry benzene, dimethylformamide (DMF), and carbon tetrachloride (CCl_4) were prepared by distillation from phosphorus pentoxide. Anhydrous hexamethylphosphoramide (HMPA) was obtained by distillation from calcium hydride, and acetone was dried by distillation from anhydrous K_2CO_3. Dioxane was distilled from $LiAlH_4$ and stored over Linde type 4A molecular sieves. CuI (99.99%, Aldrich) was purified by repeated Soxhlet extraction with THF and dried (80°C) under vacuum for 7 h. Solutions in organic solvents were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate and stripped of solvents with a Büchi rotatory evaporator connected to a water aspirator. Unless otherwise stated, all reactions were conducted under at atmosphere of dry nitrogen in flame-dried flasks equipped with a magnetic stirring bar and rubber septa.

X-ray measurements were made on a Rigaku diffractometer with Mo Kα radiation at −158°C using the ω–2θ technique to a maximum 2θ value of 46.9. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 25 reflections in the range $40 < 2\theta < 47$ corresponding to an orthorombic cell for compound **30** ($C_{22}H_{35}NOSSi$) with dimensions $a = 22.055$, $b = 9.031$, $c = 23.593$ Å. For $Z = 8$ and FW = 389.67, the calculated density is 1.102 g/cm^3. Based on the systematic absences, the space group was *Pbcn*. The data (3479 reflections) were collected for Lorentz and polarization effects (25). The structure was solved by direct methods all atoms refined except hydrogen. The hydrogen atoms were calculated by assuming a distance of 1.07 Å. The final cycle of full-matrix least-squares refinement was based on 1852 observed reflections ($I > 2.5\ \sigma(I)$) and 236 variable parameters using weights based on counting statistics. The maximum and minimum peaks on the final differences Fourier map were 0.55 and −0.47 e/Å^3, respectively. All calculations were performed using the NRCVAX crystallographic software package (26).[4]

4-Hydroxymethyl-3-methyl-2-cyclohexene-1-ol

Diisobutylaluminium hydride (1 M solution in toluene, Aldirch, 16.5 mL, 16.5 mmol) was added dropwise to a cold (0°C) solution of Hagemann's ester **11** (1.0 g, 5.5 mmol, Aldrich) in benzene (5 mL) and the mixture stirred at 0°C for 2 h, followed by a further hour at 21°C. The aluminum salts were decomposed at 0°C by dropwise addition of excess methanol (20 mL). The resulting white precipitate was removed by filtration and washed several times with hot methanol. The combined filtrate and washings were evaporated to give a thick oil plus a gel-like precipitate that was removed by a second filtration. The crude product was chromatographed (acetone/petroleum ether; 1:1) to afford the diol (770 mg, 98%). In subsequent experiments the initial product was used directly. IR (neat): 3350, 1660 cm^{-1}; ^{1}H NMR (200 MHz) δ: 5.65 (m, 1H), 4.16 (br s, 1H), 3.79 (m, 2H), 1.79 (s, 3H), 2.15 (m, 1H), 1.5–2 (m, 6H). ^{13}C NMR (50.3 MHz) δ: 136.8, 127.7, 65.3, 63.2, 41.4, 30.6, 29.3, 21.4. HRMS calcd. for $C_8H_{12}O$ ($M^+ - H_2O$): 124.0888; found: 124.0890.

4-Hydroxymethyl-3-methyl-2-cyclohexen-1-one (12)

The diol above (3.80 g, 26.8 mmol) was dissolved in dry dioxane (10 mL) and a dioxane solution of dichlorodicyanoquinone (7.92 g, 34.9 mmol, Aldrich) was added dropwise by syringe. The reaction was stirred at 21°C overnight (23 h, reaction complete by TLC). The reaction was concentrated, diluted with ether, filtered through Celite, and washed several times with ether until the washings were colourless. Concentration of the crude filtrate and chromatography (20% acetone – petroleum ether) on alumina (basic or neutral) gave the ketone **12** (3.5 g, 92%). IR (neat): 3300, 1665 cm^{-1}; ^{1}H NMR (200 MHz) δ: 5.92 (s, 1H), 3.79 (m, 2H), 1.98 (s, 3H); ^{13}C (50.3 MHz) δ: 199.5, 162.1, 128.5, 70.0, 42.1, 34.2, 24.9, 22.7. Anal. calcd. for $C_8H_{12}O_2$: C 68.54, H 8.62; found: C 67.91, H 8.70.

4-(*tert*-Butyldimethylsilyloxy)methyl-3-methyl-2-cyclohexen-1-one (13)

The alcohol **12** (0.97 g, 6.8 mmol) was dissolved in DMF (2 mL), imidazole (1.16 g, 17.0 mmol) and *tert*-butyldimethylsilyl chloride (1.23 g, 8.18 mmol, Aldrich) were added, and the mixture was stirred overnight (23 h) at 21°C. The reaction was diluted with ether and the combined organic extracts were washed with small portions of water (2 × 2 mL) and brine, dried, filtered, and concentrated. Chromatography (ethyl acetate/petroleum ether; 1:20) gave **13** (1.7 g, 98%). IR (neat): 1675 cm^{-1}; ^{1}H NMR (200 MHz) δ: 0.02 (s, 6H), 0.85 (s, 9H), 2.02 (m, 2H), 2.39 (m, 3H), 3.72 (d, 2H, $J = 5.5$ Hz), 5.87 (s, 1H); ^{13}C NMR (50.3 MHz) δ: −5,3 (2C), 17.8, 22.7, 25.1, 25.5 (3C), 34,3, 42.7, 63.3, 128.1, 162.5, 199.4. HRMS calcd. for $C_{10}H_{17}O_2Si$ ($M^+ - C_4H_9$): 197.0998; found: 197.1013. Anal. calcd. for $C_{14}H_{26}O_2Si$: C 66.08, H 10.3; found: C 65.91, H 9.51.

4-(*tert*-Butyldimethylsilyloxy)methyl-3,3-dimethyl-2-formyl(dimethylacetal)cyclohexanone (14)

A solution of methyl magnesium bromide (5.14 mL, 7.71 mmol, 1.5 M) in toluene – direthyl ether was added to a cold (0°C), stirred suspension of cuprous iodide (100 mg, 0.52 mmol) in dry diethyl ether (50 mL). After the reaction mixture had been stirred at 0°C for 10 min, a solution of the enone **13** (1.31 g, 5.14 mmol) in dry diethyl ether (2 mL) was added dropwise. The resulting light yellow mixture was stirred at 0°C for 30 min and then cooled to −78°C. Trimethyl orthoformate (5.62 mL, 51.4 mmol) and boron trifluoride etherate

[4] Tables of atomic parameters, anisotropic temperature factors, bond lengths and angles, and torsion angles have been deposited and can be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A 0R6. The tables of atomic parameters and bond lengths and angles have also been deposited with the Cambridge Crystallographic Data Centre, and can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(3.16 mL, 25.7 mmol) were syringed sequentially into the cold reaction mixture. After stirring for 5 min at −78°C, the solution was warmed to 0°C for 2 h. Saturated ammonium chloride solution was added and the mixture was extracted with diethyl ether. The combined ether extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 3:1) to afford 1.05 g (59%) of the ketal **14**. IR (neat): 2970, 1720, 1475, 1120, 880, 780 cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (s, 6H), 0.78 (s, 3H), 0.86 (s, 9H), 1.04 (s, 3H), 1.45–1.70 (m, 1H), 2.00–2.60 (m, 5H), 3.27 (s, 3H), 3.29 (s, 3H), 3.42 (t, 1H, J = 10 Hz), 3.85 (dd, 1H, J = 4, 10 Hz), 4.71 (d, 1H, J = 7 Hz); ^{13}C NMR (50.3 MHz) δ: −5.7 (2C), 17.9, 22.9, 25.6 (3C), 25.9, 26.0, 38.1, 40.0, 43.2, 52.6, 53.1, 63.3, 64.7, 101.9, 210.6; HRMS calcd. for $C_{14}H_{27}O_4Si$ ($M^+ - C_4H_9$): 287.1679; found: 287.1680. Anal. calcd. for $C_{18}H_{36}O_4Si$: C 62.75, H 10.53; found: C 62.83, H 10.43.

Minor products from this reaction were
*4-(*tert*-Butyldimethylsilyloxy)methyl-3,3-dimethylcyclohexanone*: IR (neat): 2960, 1720, 1475, 1260, 1105, 840, 780 cm^{-1}; ^1H NMR (200 MHz) δ: 0.03 (s, 6 H), 0.81 (s, 3H), 0.87 (s, 9H), 1.05 (s, 3H), 1.55–1.84 (m, 2H), 2.02–2.41 (m, 5H), 3.45 (dd, 1H. J = 7.8, 10 Hz), 3.82 (dd, 1H, J = 3.8, 10 Hz); ^{13}C NMR δ: 212.0, 63.3, 55.1, 47.0, 40.0, 37.2, 30.3, 25.6, 25.4, 22.0, 18.3, −5.7; HRMS calcd. for $C_{15}H_{30}O_2Si$ ($M^+ - C_4H_9$): 213.1310; found: 213.1266.
*4-(*tert*-Butyldimethylsilyloxy)methyl-1-(dimethoxy)oxy-3,3-dimethylcyclohex-1-ene* (**18**): IR (neat): 2960, 1600, 1480, 1100, 840, 780 cm^{-1}; ^1H NMR (200 MHx) δ: 0.03 (s, 6H), 0.82 (s, 3H), 0.88 (s, 9H), 1.06 (s, 3H), 1.35–1.50 (m, 2H), 1.80–1.95 (m, 1H), 2.05–2.15 (m, 2H), 3.34 (s and overlapping dd, 7H), 3.74 (dd, 1H, J = 4, 10 Hz), 4.62 (s, 1H), 5.35 (s, 1H).

Alternative preparation of 14 via 4-(*tert*-butyldimethylsilyloxy)methyl-3,3-dimethyl-1-trimethylsilyloxycyclohex-1-ene (17)

A solution of methyl magnesium bromide (0.48 mL, 0.072 mmol, 1.5 M) in toluene – diethyl ether was added to a cold (0°C), stirred suspension of cuprous iodide (0.01 g), in dry diethyl ether (4 mL). After stirring the reaction for 10 min at 0°C, a solution of enone **13** (0.122 g, 0.48 mmol) in dry diethyl ether (1 mL) was added dropwise. After 30 min at 0°C, triethyl amine (0.20 mL, 1.43 mmol) and trimethylsilyl chloride (0.12 mL, 0.95 mmol) were added sequentially. The reaction was stirred for 1 h at 0°C, warmed to 21°C, and stirring was continued for a further 4 h. A few drops of aqueous saturated ammonium chloride were added and the solution filtered through a short column of sand (1 g). The filtrate was concentrated, chromatographed on Florisil (petroleum ether/ether; 30:1), and the eluent concentrated to afford the enol silyl ether **17** (0.117 g, 71%). IR (neat): 2930, 1250 cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (s, 6H), 0.14 (s, 9H), 0.78 (s, 3H), 0.86 (s, 9H), 1.02 (s, 3H), 1.37–1.42 (m, 2H), 1.83–1.92 (m, 1H), 1.93–1.96 (m, 2H), 3.30 (dd, 1H, J = 8.7, 9.2 Hz), 3.72 (dd, 1H, J = 3.8, 9.9 Hz), 4.54 (br s, 1H); HRMS calcd. for $C_{18}H_{38}O_2Si_2$ (M^+ − Me): 327.2186; found: 327.2184.

Trimethyl orthoformate (0.78 mL, 7.10 mmol) and titanium tetrachloride (0.20 mL, 1.80 mmol) were syringed sequentially into a cold (−78°C), stirred solution of enolsilyl ether (0.229 g, 0.670 mmol) in dry dichloromethane (7 mL). The reaction mixture was stirred at 0°C for 1 h. Saturated ammonium chloride solution was added and the mixture was extracted thoroughly with diethyl ether. The combined ether extracts were washed (saturated $NaHCO_3$ solution, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 3:1) to afford 0.126 g (55%) of the ketal **14**.

1-Hydroxy-2-formyl(dimethylacetal)1,3,3-trimethyl-4-*tert*-butyldimethylsilyloxycyclohexane (15)

A 1.5 M solution of methylmagnesium bromide (2.0 mL, 3.0 mmol) in toluene – diethyl ether was added dropwise to a cold (0°C), stirred solution of the ketone **14** (0.713 g, 2.07 mmol) in dry diethyl ether (10 mL). The resulting mixture was stirred at 0°C for 10 min and then warmed to 21°C for 30 min. Saturated aqueous ammonium chloride solution was added and the mixture was extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine and dried. Removal of the solvent afforded 0.708 g (95%) of the alcohol **15**. IR (neat): 3560, 2960, 1090, 840, 780 cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (s, 6H), 0.86 (s, 9H), 1.00 (s, 3H), 1.15 (s, 3H), 1.29 (s, 3H), 1.30–1.65 (m, 4H), 1.90–2.10 (m, 2H), 3.34 (s, 3H), 3.47 (s, 3H), 3.55–3.75 (m, 2H), 3.98 (br s, 1H), 4.43 (s, 1H); ^{13}C NMR (50.3 MHz) δ: −5.8, −5.7, 17.9, 19.6, 25.7 (3C), 26.2, 28.4, 31.6, 34.6, 35.9, 47.4, 51.3, 55.8, 56.7, 62.2, 72.0, 109.6. Anal. calcd. for $C_{19}H_{40}O_4Si$: C 63.28, H 11.18; found: C 63.34, H 11.1.

1-Methoxy-2-formyl(dimethylacetal)-1,3,3-trimethyl-4-*tert*-butyldimethylsilyloxycyclohexane (16)

A solution of methyllithium (7.90 mL, 11.1 mmol, 1.4 M) in diethyl ether was added dropwise to a cold (0°C), stirred solution of the acetal **14** (2.50 g, 7.26 mmol) in dry diethyl ether (35 mL). After the reaction mixture has been stirred at 0°C for 30 min, hexamethylphosphoramide (2.52 mL, 14.5 mmol) and methyl iodide (1.80 mL, 28.9 mmol) were added sequentially. The resulting mixture was stirred at 0°C for 1 h and warmed to room temperature overnight (16 h). Water was added and the mixture was extracted thoroughly with diethyl ether. The combined ether extracts were washed (saturated sodium bicarbonate, water, and brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 2.07 g (76%) of the trimethoxy compound **16** and 0.418 g (16%) of the alcohol **15** (see below). IR (neat): 2950, 1470, 1260, 1200, 1080, 840, 780 cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (s, 6H), 0.85 (s, 9H), 1.00 (s, 3H), 1.18 (s, 3H), 1.19 (s, 3H), 1.30–1.80 (m, 6H), 3.10 (s, 3H), 3.32 (s, 3H), 3.36 (s, 3H), 3.54 (t, 1H, J = 10 Hz), 3.73 (dd, 1H, J = 10, 5 Hz), 4.65 (d, 1H, J = 4 Hz); ^{13}C NMR (50.3 MHz) δ: −5.7, −5.6, 18.0, 18.5, 25.0, 25.7 (3C), 26.4, 28.7, 28.9, 35.5, 47.8, 48.7, 54.7, 56.1, 61.2, 75.8, 108.4. Anal. calcd. for $C_{20}H_{42}O_4Si$: C 64.12, H 11.30; found: C 64.19, H 11.47.

Methyllithium (9.34 mL, 13.08 mmol) was added to a solution of **15** (3.0 g, 8.7 mmol) in ether (50 mL) at 0°C. HMPA (3.03 mL, 17.44 mmol) was added, followed by MeI (1.08 mL, 17.4 mmol), the reaction mixture was allowed to warm to 22°C, and stirring was continued overnight. The reaction was quenched with water and washed several times with saturated aqueous NH_4Cl solution, dried, and concentrated. Chromatography (5% Et_2O – petroleum ether) gave **16** in 94% yield.

2-Formyl-1,3,3-trimethyl-4-*tert*-butyldimethylsilyloxymethycyclohex-2-ene (20)

Method I

Propylene was bubbled through a solution of **16** (650 mg, 1.7 mmol) in CH_2Cl_2 (3 mL) at 21°C. NaI (279 mg, 1.86 mmol) was added, followed by trimethylsilyl chloride (0.24 mL, 1.86 mmol), and stirring was continued for 5 min. The reaction was quenched with water, and washed with water, aqueous 6% $Na_2S_2O_4$, and brine. The organic layer was concentrated to give the product **19**, which was directly dissolved in MeOH, and NaOMe (91.3 mg, 1.69 mmol) added. The reaction was heated under reflux for 30 min. The mixture was concentrated, ether added, the ether extracts washed with water, brine, and dried. Concentration followed by chromatography (5% Et_2O – petroleum ether) gave **20** (350 mg, 70% from **16**).

Method II

An aqueous 15% H_2SO_4 solution (1.2 mL) was added with continuous stirring to a suspension of silica gel (70–230 mesh, 12 g) in CH_2Cl_2 (15 mL). After 3 min, the aqueous phase disappeared, a solution of **16** (1.1 g, 2.9 mmol) in CH_2Cl_2 (2 mL) was added, and stirring continued at 21°C for 2 min during which time the reaction was completed. $NaHCO_3$ (0.1 g) was then added and stirring continued for 5 min, followed by filtration of the reaction mixture through a small plug of $MgSO_4$. Concentration gave the aldehyde **19**, which was used directly for the next step. NaOMe (140 mg, 2.6 mmol) was added to a solution of the aldehyde (876 mg, 2.6 mL) in MeOH (10 mL). The mixture was refluxed for 8 h, concentrated, ether added, and the ether extracts washed with water and brine, and dried. Concentration and chromatography (5% Et_2O – petroleum ether) gave the aldehyde **20** (846 mg) in 96% yield. IR (neat): 2921, 1698 cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (s, 6H), 0.85 (s, 9H), 1.01 (s, 3H), 1.30 (s, 3H), 1.36–1.20 (m, 2H), 1.84–1.87 (m, 1H), 2.02 (s, 3H), 2.10–2.20 (m, 2H), 3.33 (dd, 1H, J = 8.75, 10 Hz), 3.83 (dd, 1H, J = 3.65, 10 Hz), 10.62 (s, 1H); ^{13}C NMR δ: 192.3 (conjugated CHO), 156.3, 140.4, 62.9, 47.8, 35.3, 34.6, 26.3, 25.9, 21.4, 20.7, 19.4, 18.0, −5.3; HRMS calcd. for $C_{13}H_{23}O_2Si$ ($M^+ - C_4H_9$): 239.1467; found: 239.1466.

Method III

Hydrogen fluoride (1 mL, 50% solution) was added to a stirred solution of hydroxy-acetal **15** (0.40 g, 1.11 mmol) in acetonitrile (10 mL). The resulting mixture was refluxed for 15 min in a preheated oil bath. The solution was cooled and a saturated aqueous solution of sodium bicarbonate was added. Acetonitrile was removed under reduced pressure and the aqueous solution was extracted with dichloromethane. The combined organic extracts were washed (water, brine) and dried. Concentration afforded the aldehyde-alcohol. *tert*-Butyldimethylsilyl chloride (0.200 g, 1.33 mmol) was added to a stirred solution of the aldehyde-alcohol and imidazole (0.190 g, 2.79 mmol) in dry dichloromethane (10 mL). The resulting solution was stirred at 21°C for 16 h. Aqueous ammonium chloride solution (10%) was added and the mixture was extracted thoroughly with dichloromethane. The combined organic extracts were washed (water, brine), and dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 0.15 g (45%) of the aldehyde **20**.

2-Hydroxymethyl-1,3,3-trimethyl-4-*tert*-butyldimethylsilyloxymethyclohex-1-ene (21)

Treatment of the acetal **16** (1.34 g, 3.56 mmol) as described in Method I above; dry dichloromethane (35 mL), trimethylsilyl chloride (0.68 mL, 5.35 mmol), sodium iodide (0.80 g, 5.33 mmol), followed by sodium methoxide (0.19 g, 3.52 mmol) and methanol (10 mL) afforded the crude aldehyde **20**. Cerium(III) chloride heptahydrate (1.33 g, 3.57 mmol) and sodium borohydride (0.135 g, 3.56 mmol) were added slowly and the mixture was stirred at 21°C for 1 h. Water was added and the methanol was removed from the mixture under reduced pressure. Diethyl ether and 5% hydrochloric acid were added and the resulting solution extracted with diethyl ether. The combined ether extracts were washed (water, brine), dried, and concentrated. This material consisted of two alcohols (12:1 ratio), which were separated by chromatography (petroleum ether/diethyl ether; 9:1) to afford 0.745 g (70%) of alcohol **21** as a white solid and 0.070 g (6.5%) of the positional isomer (data below), as a colorless oil. **21**plainc: mp 53.5–55°C; IR ($CHCl_3$): 3620, 2960, 1260, 1090, 840 cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (s, 6H), 0.84 (s, 3H), 0.86 (s, 9H), 1.11 (s, 3H), 1.20–1.55 (m, 3H), 1.73 (s, 3H), 1.75–1.90 (m, 1H), 1.95–2.05 (m, 2H), 3.33 (dd, 1H, J = 10, 8.5 Hz), 3.75 (dd, 1H, J = 10, 3.9 Hz), 4.05 (d, 1H, J = 12 Hz), 4.13 (d, 1H, J = 12 Hz); ^{13}C NMR (75 MHz) δ: −5.3 (2C), 18.3, 19.7, 21.5, 22.3, 25.9 (3C), 27.1, 31.6, 36.3, 47.0, 58.8, 63.8, 133.9, 137.8. Anal. calcd. for $C_{17}H_{34}O_2Si$: C 68.39, H 11.48; found: C 68.50, H 11.26.

Alternatively, diisobutylaluminum hydride (1 M solution in toluene, 53.6 μL, 0.08 mmol) was added to a solution of the aldehyde **20** (20 mg, 0.07 mmol) in toluene (1.5 mL) at −78°C and the mixture stirred for 1.5 h at −78°C. The reaction was warmed to 0°C and MeOH was added until a white precipitate formed. The crude product was filtered through Celite and washed free of remaining product with hot MeOH. Concentration gave **21** (20 mg, 99%).

*1,5,5-Trimethyl-4-*tert*-butyldimethylsiloxy)methyl-6-hydroxymethylcyclohexene*: IR (neat): 3382, 2917, 1086, 843, 776 cm^{-1}; ^1H NMR (200 MHz) δ: 0.00 (s, 6H), 0.79 (s, 3H), 0.85 (s, 9H), 1.00–1.05 (m, 1H), 1.04 (s, 3H), 1.15–1.25 (m, 1H), 1.50–1.60 (m, 1H), 1.70 (s, 3H), 1.75–2.00 (m, 1H), 2.10–2.28 (m, 1H), 3.30–3.55 (m, 2H), 3.65–3.80 (m, 2H), 5.50–5.65 (m, 1H); HRMS calcd. for $C_{13}H_{23}OSi$($M^+ - C_4H_9$): 224.1463; found: 224.1463.

2-Cyanomethyl-2,3,3-trimethyl-4-*tert*-butyldimethylsilyloxymethylcyclohexene (22)

Bromine (0.011 mL, 0.218 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.57 g, 0.217 mmol) in dry methylene chloride (2 mL). Triethylamine (0.11 mL, 0.789 mmol) was added to the reaction mixture. After stirring at 21°C for 10 min, the resulting light yellow solution was cooled to −78°C. A solution of the alcohol **21** (59.3 mg, 0.198 mmol) in methylene chloride (1 mL) was added dropwise and the reaction mixture was allowed to stir for 1 h at −78°C. Petroleum ether was added and the precipitate was removed via filtration under reduced pressure. Concentration of the petroleum ether fractions precipitated additional triphenylphosphine oxide. Subsequent filtration and concentration provided a quantitative yield of the allylic bromide. IR (neat):

2917, 1466, 1253, 1093, 844, 776 cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (s, 6H), 0.85 (s, 9H), 0.91 (s, 3H), 1.19 (s, 3H), 1.19 (s, 3H), 1.30–1.50 (m, 2H), 1.73 (s, 3H), 1.75–1.85 (m, 1H), 2.00–2.10 (m, 2H), 3.33 (t, J = 8 Hz, 1H), 3.75 (dd, J = 8, 6 Hz, 1H), 4.01 (d, J = 10 Hz, 1H), 4.09 (d, J = 10 Hz, 1H). Sodium cyanide (19.0 mg, 0.397 mmol) was added to a solution of this allylic bromide in dry *N*-methyl pyrrolidinone (2 mL). The reaction mixture was stirred at 21°C for 1.5 h, pour into water, and extracted with diethyl ether. The combined ether extracts were washed (brine), dried, and concentrated. The crude product was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 45.0 mg (75%) of the nitrile **22** IR (neat): 2960, 2260, 1550, 1260, 1100, 840, 780 cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (s, 6H), 0.84 (s, 3H), 0.86 (s, 9H), 1.12 (s, 3H), 1.30–1.50 (m, 2H), 1.70 (s, 3H), 1.71–1.85 (m, 1H), 1.95–2.05 (m, 2H), 2.94 (br s, 2H), 3.35 (dd, 1H, J = 10, 8.2 Hz), 3.73 (dd, 1H, J = 10, 4.2 Hz); ^{13}C NMR (50.3 MHz) δ: −5.6 (2C), 15.8, 18.0, 20.0, 21.2, 21.3, 25.7 (3C), 26.4, 31.5, 37.0, 46.5, 63.5, 119.2, 127.5, 134.0; HRMS calcd. for $C_{14}H_{24}ONSi$ ($M^+ - C_4H_9$): 250.1627; found: 250.1654.

2-Cyanomethyl-1,3,3-trimethyl-4-hydroxycyclohexene (23)

A solution of compound **22** (1.00 g, 3.25 mmol) in dry THF (20 mL) was cooled to 0°C and a 1 M solution of tetra-*n*-butyl ammonium fluoride (6.50 mL, 6.50 mmol) and added dropwise. The mixture was warmed to 21°C for 4 h. Water was added and the resultant mixture was extracted with diethyl ether. The combined ether extracts were washed (brine, water), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 3:1) to afford 0.620 g (98%) of the alcohol **23**. IR (neat): 3405, 2924, 2246, 1465, 1030 cm^{-1}; ^1H NMR (200 MHz) δ: 0.85 (s, 3H), 1.13 (s, 3H), 1.30–1.55 (m, 3H), 1.71 (s, 3H), 1.80–1.92 (m, 1H), 2.00–2.10 (m, 2H), 2.95 (s, 2H), 3.39 (dd, 1H, J = 11, 8 Hz), 3.83 (dd, 1H, J = 11, 4 Hz); addition of D_2) simplified multiplet at δ 1.30–1.55; ^{13}C NMR (50.3 MHz) δ: 15.8, 19.9, 21.2 (2C), 26.3, 31.4, 36.9, 46.8, 63.3, 119.1, 127.4, 134.0; HRMS calcd. for $C_{12}H_{19}ON$: 193.1467; found: 193.1466. Anal. calcd. for $C_{12}H_{19}ON$: C 74.57, H 9.91; found: C 74.16, H 9.71.

2-Cyanomethyl-4-formyl-1,3,3-trimethylcyclohexene (24)

Oxalyl chloride (0.310 mL, 3.55 mmol) was added to a cold (−78°C), stirred solution of dry dimethyl sulfoxide (0.250 mL, 3.52 mmol) in dry dichloromethane (25 mL). The reaction mixture was stirred at −78°C for 15 min, a solution of **23** (620 mg, 3.21 mmol) in dry dichloromethane (2 mL) was added dropwise, and the resulting mixture stirred for 15 min. Dry triethylamine (1.78 mL, 12.7 mmol) was added and the solution stirred at −78°C for a further 5 min and then at 21°C for 30 min. Saturated aqueous ammonium chloride solution was added and the mixture was extracted with dichloromethane. The combined organic extract were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 1:1) to afford 579 mg (94%) of the aldehyde **24**. IR (neat): 2934, 2734, 2244, 1718, 1464 cm^{-1}; ^1H NMR (200 MHz) δ: 1.05 (s, 3H), 1.28 (s, 3H), 1.73 (s, 3H), 1.60–2.00 (m, 2H), 2.04–2.14 (m, 2H), 2.23 (dt, 1H, J = 11, 3 Hz), 3.00 (AB, 2H, J = 19 Hz), 9.83 (d, 1H, J = 5 Hz); ^{13}C NMR (50.3 MHz) δ: 15.7, 19.1, 20.0, 22.5, 26.7, 30.8, 36.9, 56.7, 118.6, 126.9, 133.8, 204.7; HRMS calcd. for $C_{12}H_{17}ON$: 191.1310; found: 191.1313.

2-Cyanomethyl-1,3,3-trimethyl-4-(1-hydroxy-2,4-pentadienyl)cyclohexene (25)

A solution of *n*-butyllithium (0.40 mL, 1.00 mmol, 2.5 M) in hexane was added dropwise to a cold (−78°C), stirred solution of (E)-1-tri-*n*-butylstannyl-1,3-butadiene (373 mg, 1.08 mmol) in dry THF (9 mL). After the reaction mixture had been stirred at −78°C for 10 min, a solution of aldehyde **24** (173 mg, 0.90 mmol) in dry THF (1 mL) was added dropwise. The resulting mixture was stirred at −78°C for 30 min. Water was added and the mixture warmed to 21°C and extracted with diethyl ether. The combined ether extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 1:1) to afford 213 mg (96%) of the alcohols as colorless oils (ratio 6:1). Further chromatography afforded the major isomer **25**. IR (neat): 3461, 2927, 2245, 1463, 1007 cm^{-1}; ^1H NMR (200 MHz) δ: 1.02 (s, 3H), 1.11 (s, 3H), 1.20–1.68 (m, 4H), 1.69 (s, 3H), 1.90–2.10 (m, 2H), 3.00 (AB, 2H, J = 19 Hz), 4.48 (t, 1H, J = 4 Hz), 5.06 (d, 1H, J = 8 Hz), 5.20 (d, 1H, J = 16 Hz), 5.74 (dd, 1H, J = 16, 4 Hz), 6.10–6.44 (m, 2H); ^{13}C NMR (50.3 MHz) δ: 16.1, 17.4, 19.9, 21.8, 26.3, 32.4, 38.3, 49.6, 70.4, 117.1, 119.1, 127.8, 130.1, 133.8, 136.3, 137.3; HRMS calcd. for $C_{16}H_{23}ON$: 245.1780; found: 245.1760.

2-Cyanomethyl-4-(1-methoxymethyloxy-2,4-pentadienyl)-1,3,3-trimethyl-2-cyanomethylcyclohexene (26)

Chloromethyl methyl ether (0.11 mL, 1.45 mmol) was added to a cold (0°C) solution of the alcohol **25** (301 mg, 1.23 mmol) and diisopropylethylamine (0.58 mL, 3.04 mmol) in dry dichloromethane (15 mL). The resulting solution was stirred at 0°C for 5 min and warmed to 21°C for 16 h. Aqueous ammonium chloride solution (10%) was added and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 4:1) to afford 321 mg (90%) of the nitrile **26**, as a slightly reddish oil. IR (neat): 2924, 2245, 1602, 1028, 914, 733 cm^{-1}; ^1H NMR (200 MHz) δ: 1.00 (s, 3H), 1.12 (s, 3H), 1.70 (s, 3H), 1.30–1.80 (m, 3H), 1.95–2.05 (m, 2H), 2.95 (AB, 2H, J = 19 Hz), 3.34 (s, 3H), 4.24 (br d, 1H, J = 10 Hz), 4.46 (d, 1H, J = 8 Hz), 4.65 (d, 1H, J = 8 Hz), 5.10 (br d, 1H, J = 18 Hz), 5.17 (dd, 1H J = 18, 2 Hz), 5.63 (dd, 1H, J = 18, 10 Hz), 6.05–6.42 (m, 2H); ^{13}C NMR (75 MHz) δ: 16.4, 18.8, 20.1, 21.5, 26.6, 32.9, 38.5, 50.1, 56.4, 76.0, 94.4, 117.5, 119.1, 127.9, 132.3, 133.7, 134.0, 136.2; HRMS calcd. for $C_{18}H_{27}O_2N$: 289.2042; found: 289.2032. Anal. calcd. for $C_{18}H_{27}O_2N$: C 74.70, H 9.40, O 11.06; found: C 74.62, H 8.92, O 11.56.

2-Cyanomethyl-1,3,3-trimethyl-4-(1-*tert*-butyldimethylsilyloxy-2,4-pentadienyl)-cyclohexene (27)

To a solution of alcohol **25** (213 mg, 8.70 mmol) in dry DMF (5 mL) was added sequentially *tert*-butyldimethylchlorosilane (170 mg, 1.13 mmol, Aldrich) and 4-(N,N-dimethylamino)pyridine (270 mg, 2.21 mmol). The resulting solution was stirred at 21°C for 3 days. Water was added, the mixture was extracted with diethyl ether, and the combined extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 19.1) to afford **27** (254 mg, 81%). IR (neat): 2925, 2245, 1603, 1114, 1068, 1006, 838, 774 cm^{-1}; ^1H NMR (200 MHz): δ −0.06 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 0.95 (s, 3H), 1.09 (s,

3H), 1.3–1.4 (m, 1H), 1.50–1.70 (m, 2H), 1.68 (s, 3H), 1.95–2.1 (m, 2H), 2.98 (AB, 2H, J = 19 Hz), 4.37 (d, 1H, J = 8 Hz), 5.07 (d, 1H, J = 10 Hz), 5.16 (d, 1H, J = 16 Hz), 5.75 (dd, 1H, J = 10, 16 Hz), 5.98–6.40 (m, 2H): ^{13}C NMR (75 MHz) δ: −4.8, −3.0, 16.3, 18.1, 18.7, 20.2, 22.2, 25.9 (3C), 26.6, 32.9, 38.5, 51.7, 72.6, 116.9, 119.2, 127.9, 129.9, 133.7, 136.5, 137.9; HRMS calcd. for $C_{18}H_{28}ONSi$ ($M^+ - C_4H_9$): 302.1940; found: 302.64. Anal. calcd. for $C_{22}H_{37}ONSi$: C 73.47, H 10.37, N 3.89; found: C 73.44, H 9.95, N 3.85.

2-Formylmethyl-1,3,3-trimethyl-4-(1-*tert*-methoxymethyloxy-2,4-pentadienyl)cyclohexene (28)

A solution of diisobutylaluminum hydride (1.5 M, 0.71 mL, 1.06 mmol) in toluene was added dropwise to a cold (−78°C), stirred solution of the nitrile **26** (207 mg, 0.715 mmol) in dry dichloromethane (10 mL). The resulting mixture was stirred at −78°C for 1 h and warmed to 0°C for another hour. Saturated ammonium chloride solution was added and the mixture was stirred at 21°C for 30 min. The resulting solution was extracted with dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 4:1) to afford 147 mg (70%) of the aldehyde **28**. IR (neat): 2915, 2717, 1721, 1029 cm^{-1}; ^{1}H NMR (200 MHz) δ: 0.97 (s, 3H), 1.00 (s, 3H), 1.54 (s, 3H), 1.40–1.85 (m, 3H), 1.90–2.10 (m, 2H), 3.07 (br s, 2H), 3.34 (s, 3H), 4.25 (br d, 1H, J = 8 Hz), 4.47 (d, 1H, J = 7 Hz), 4.65 (d, 1H, J = 7 Hz), 5.00–5.25 (m, 2H), 5.65 (dd, 1H, J = 14, 8 Hz), 6.00–6.44 (m, 2H), 9.48 (t, 1H, J = 2 Hz); ^{13}C NMR (75 MHz) δ: 18.9, 20.3, 21.7, 26.7, 33.0, 38.3, 43.8, 50.3, 56.4, 76.1, 94.4, 117.4, 129.1, 132.1, 132.5, 134.3, 136.2, 201.3; HRMS calcd. for $C_{18}H_{28}O_3$: 292.2038; found: 292.2052.

2-Formylmethyl-1,3,3-trimethyl-4-(1-*tert*-butyldimethylsilyloxy-2,4-pentadienyl)cyclohexene (29)

A solution of diisobutylaluminum hydride (1.0 M, 0.26 mL, 0.260 mmol) in toluene was added dropwise to a cold (−78°C), stirred solution of the nitrile **27** (72 mg, 0.201 mmol) in dry dichloromethane (5 mL). The reaction was stirred at −78°C for 2 h followed by 2 h at 0°C. Water was added and the mixture was stirred at 21°C for 30 min. The resulting solution was extracted with dichloromethane and the combined organic extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1) to give aldehyde **29** (66.3 mg, 91%). IR (neat): 2946, 2713, 1723, 1648, 1252, 1066, 1004, 838, 775 cm^{-1}; ^{1}H NMR (200 MHz) δ: −0.05 (s, 3H), 0.00 (s, 3H), 1.10–1.40 (m, 2H), 1.50)\(s, 3H), 1.60–1.75 (m, 1H), 1.80–2.10 (m, 3H), 3.08 (br s, 2H), 4.38 (d, 1H, J = 10 Hz), 5.05 (d, 1H, J = 10 Hz), 5.15 (d, 1H, J = 20 Hz), 5.78 (dd, 1H, J = 10, 20 Hz), 5.95–6.40 (m, 1H), 9.47 (t, 1H, J = 4 Hz); HRMS calcd. for $C_{18}H_{29}O_2Si$ ($M^+ - C_4H_9$): 305.1937; found: 305.1958.

1-(2-Thiophenyl)methyl-2-cyanomethyl-1,3,3-trimethylcyclohexene (30)

A solution of *n*-butyllithium (0.52 mL, 1.30 mmol, 2.5 M) in hexane was added dropwise to a cold (−78°C), stirred solution of thiophene (0.114 mL, 1.42 mmol) in of dry THF (10 mL). After the reaction mixture had been stirred at −78°C for 15 min, a solution of the aldehyde **24** (0.227 g, 1.19 mmol) in dry THF (1 mL) was added dropwise. The resulting orange mixture was stirred at −78°C for 30 min. Water was added and the mixture was extracted with diethyl ether. The combined ether extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed using radial chromatography (petroleum ether/diethyl ether; 2:1.5). Concentration of the appropriate fractions afforded 0.226 g (69%) of the major isomer and 0.0464 g (14%) of the minor isomer. Minor isomer, IR (neat): 3450, 2929, 2247, 1425, 1038 cm^{-1}; ^{1}H NMR (200 MHz) δ: 1.06 (s, 3H), 1.07–1.37 (m, 2H), 1.39 (s, 3H), 1.69 (s, 3H), 1.6–2.10 (m, 4H), 2.99 (br s, 2H), 4.87 (br d, 1H, J = 9 Hz), 6.9–7.0 (m, 2H), 7.2–7.28 (m, 1H); ^{13}C NMR (50.3 MHz) δ: 16.2, 20.0, 20.2, 22.5, 27.5, 32.1, 38.9, 51.0, 72.7, 119.3, 125.2, 125.3, 126.4, 128.6, 133.5, 149.0; HRMS calcd. for $C_{1621}ONS$: 275.1319; found: 275.1316.

Major isomer, IR (neat): 3458, 2918, 2247, 1376, 1110, 1045, 706 cm^{-1}; ^{1}H NMR (200 MHz) δ: 1.10 (s, 3H), 1.20 (s, 3H), 1.71 (s, 3H), 1.5–1.7 (m, 2H), 1.88 (d, 1H, J = 5.5 Hz), 1.95–2.10 (m, 2H), 2.99 (AB, 2H, J = 19 Hz), 5.28 (d, 1H, J = 5.5 Hz), 6.88–7.0 (m, 2H), 7.15–7.25 (m, 1H); ^{13}C NMR (50.3 MHz) δ: 16.1, 17.3, 20.0, 21.8, 26.3, 32.4, 38.5, 52.3, 69.2, 119.1, 122.7, 123.9, 126.8, 127.6, 134.1, 150.3; HRMS calcd. for $C_{16}H_{19}NS$ ($M^+ - H_2O$): 257.1238; found: 257.1238.

tert-Butyldimethylsilyl chloride (0.130 g, 0.862 mmol) was added to a stirred solution of silver perchlorate (0.160 g, 0.772 mmol) in dry acetonitrile (5 mL). The resultant white suspension was stirred at 21°C for 15 min. Pyridine (0.23 mL, 2.84 mmol) and a solution of the major alcohol (0.154 g, 0.561 mmol) were added sequentially and the mixture was stirred overnight at 21°C. Diethyl ether was added and the solids were removed by filtration. The ether filtrate was washed (5% aqueous sodium bicarbonate solution, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1 initially followed by petroleum ether/diethyl ether; 3:1) to afford 0.157 g (72%) of the silyl ether **30** and also 0.0154 g (10%) of the starting alcohol. The product **30** was recrystallized from petroleum ether/diethyl ether (1.1) to give colourless needles, mp 113–114°C. IR (KBr): 2945, 2244, 1109, 1072, 831, 744 cm^{-1}; ^{1}H NMR (200 MHz) δ: −0.36 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.01 (s, 3H), 1.12 (s, 3H), 1.45–1.70 (m, 1H), 1.68 (s, 3H), 1.90–2.10 (m, 1H), 2.95 (AB, 2H, J = 18 Hz), 5.18 (br s, 1H), 6.8–6.9 (m, 2H), 7.1–7.18 (m, 1H); ^{13}C NMR (75 MHz) δ: −4.87, −4.23, 16.5, 18.5, 20.0, 21.8, 25.9 (3C), 26.6, 30.6, 32.9, 38.8, 54.2, 69.7, 119.0, 123.1, 123.6, 125.7, 127.5, 133.8, 150.4; HRMS calcd. for $C_{18}H_{26}ONSSi$ ($M^+ - C_4H_9$): 332.1504; found: 332.1496.

4-(1-*tert*-butyldimethylsilyloxy-2,4-pentadienyl)-1,3,3-trimethyl-2-(2-oxo-4-trimethylsilyl-3-butynyl)cyclohexene (31)

A solution of *n*-butyllithium (1.50 mL, 3.75 mmol, 2.5 M) in hexane was added dropwise to a cold (−78°C), stirred, solution of (trimethylsilyl)acetylene (0.53 mL, 3.75 mmol) in dry THF (30 mL). After stirring at −78°C for 10 min, a solution of the aldehyde **29** (0.450 g, 1.24 mmol) in dry THF (5 mL) was added dropwise. The resulting mixture was stirred at −78°C for 1 h and at 0°C for a further hour. Water was added and the mixture was warmed to 21°C and extracted with diethyl ether. The combined ether extracts were washed with brine and dried. Concentration of the organic material afforded 186 mg (93%) of the acetylenic alcohol, which was used directly.

Oxalyl chloride (0.017 mL, 0.194 mmol) was added to a cold (−78°C), stirred, solution of dry dimethyl sulfoxide (0.014 mL, 0.197 mmol) in dry dichloromethane (5 mL). After the reaction mixture had been stirred at −78°C for 15 min, a solution of the acetylenic alcohol (0.0766 g, 0.166 mmol) in dry dichloromethane (1 mL) was added dropwise and the resulting mixture was stirred for 15 min. Dry trimethylamine (0.10 mL, 0.717 mmol) was added, the solution was stirred at −78°C for 5 min, and at 21°C for 30 min. Water was added and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 19:1) to afford 0.029 g (38%) of the ketone **31**. IR (neat): 2947, 2151, 1676, 1253, 1090, 851, 772 cm^{-1}; ^1H NMR (200 MHz) δ: −0.05 (s, 3H), 0.00 (s, 3H), 0.19 (s, 9H), 0.84 (s, 9H), 0.92 (s, 3H), 0.95 (s, 3H), 1.15 (s, 3H), 1–1.7 (m, 3H), 1.9–2.10 (m, 2H), 3.24 (br s, 2H), 4.37 (d, 1H, J = 7 Hz), 5.03 (br d, 1H, J = 8 Hz), 5.17 (br d, 1H, J = 18 Hz), 5.75 (dd, 1H, J = 10, 18 Hz), 6.03 (dd, 1H, J = 10, 18 Hz), 6.28 (dd, 1H, J = 10, 18 Hz); HRMS calcd. for $C_{23}H_{31}O_2Si_2$ ($M^+ - C_4H)_9$: 2332; found: 401.2340.

Alternative oxidation: pyridinium dichromate (0.080 g, 0.213 mmol) was added to a stirred solution of the acetylenic alcohol (0.036 g, 0.0793 mmol) in dry dichloromethane (5 mL). The resulting mixture was stirred at room temperature for 4 h. The solid was removed by filtration through a sintered glass funnel under aspirator pressure and was washed thoroughly with diethyl ether. The ether filtrates were concentrated to provided a tan oil. This residual oil was chromatographed (petroleum ether/diethyl ether; 40:1) to afford 0.010 g (26%) of the ketone **31**.

4-(1-*tert*-Butyldimethylsilyloxy-2,4-pentadienyl)-1,3,3-trimethyl-2-(2-oxo-3-butynyl)cyclohexene (32)

A solution of potassium hydroxide (0.200 g, 3.57 mmol) in methanol (5 mL) was added to a stirred solution of the acetylenic alcohol (0.531 mg, 1.15 mmol) (prepared as described above) in dichloromethane (5 mL). The resulting mixture was stirred for 3 h at 21°C. The organic solvent was removed under reduced pressure to provide yellow oil. A mixture of diethyl ether/water (1:1) was added and the solution was extracted thoroughly with diethyl ether. The combined ether extracts were washed with brine and dried. Concentration of the organic material afforded a quantitative yield of the deprotected acetylenic alcohol.

Dess–Martin periodinane (1.00 g, 1.71 mmol) was added to a solution of the deprotected acetylenic alcohol in dry dichloromethane (15 mL). The resulting bright yellow solution was stirred at 21°C for 2 h. Dilute aqueous sodium hydroxide solution (10 mL, 10%) was added and the mixture was stirred for a further 10 min. The solution was extracted with diethyl ether. The combined organic extracts were washed (10% sodium hydroxide solution, water, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 0.133 g (30%) of the ketone **32**. IR (neat): 3266, 2918, 2091, 1684, 839, 775 cm^{-1}; ^1H NMR (200 MHz) δ: −0.05 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 0.99 (s, 3H), 1.01 (s, 3H), 1.34–1.46 (m, 1H), 1.51 (s, 3H), 1.55–1.75 (m, 2H), 1.90–2.25 (m, 3H), 3.21 (s, 1H), 3.30 (d, 1H, J = 16 Hz), 3.42 (d, 1H, J = 16 Hz), 4.36 (br s, 1H), 5.05 (d, 1H, J = 10 Hz), 5.17 (d, 1H, J = 16 Hz), 5.72 (dd, 1H, J = 16.6 Hz); HRMS calcd. for $C_{29}H_{38}O_2Si$: 382.2641; found: 386.2649.

2-(2-Hydroxy-4-trimethylsilyl-3-butynyl)-4-(1-methoxymethyloxy-2,4-pentadienyl)-1,3,3-trimethylcyclohexene (33)

Addition of lithium trimethylacetylide to the aldehyde **29** (147 mg, 0.5.04 mmol) was conducted as described above to afford 186 mg (95%) of the alcohol **33**. IR (neat): 3415, 2918, 2170, 1648, 1045, 871 cm^{-1}; ^1H NMR (200 MHz) δ: 0.13 (s, 9H), 1.03 (br s, 3H), 1.07 (br s, 3H), 1.67 (br s, 3H), 1.00–1.80 (m, 5H), 1.90–2.10 (m, 2H), 2.48–2.60 (m, 1H), 3.34 (br s, 3H), 4.20–4.32 (m, 1H), 4.40–4.52 (m, 2H), 4.60–4.70 (m, 1H), 5.06 (br d, 1H, J = 20 Hz), 5.18 (br d, 1H, J = 20 Hz), 5.55–5.75 (m, 1H), 6.05–6.45 (m, 2H); MS (CI): 329 ($MH^+ - C_2H_6O_2$).

2-(2-Hydroxy-3-butynyl)-4-(1-methoxymethyloxy-2,4-pentadienyl)-1,3,3-trimethylcyclohexene (34)

A solution of potassium hydroxide (250 mg, 4.46 mmol) in methanol (5 mL) was added to a stirred solution of the alcohol **33** (471 mg, 1.21 mmol) in dichloromethane (5 mL). The resulting mixture was stirred for 3 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 a quantitative yield of alcohols **34**. IR (neat): 3431, 3300, 2926, 2112, 1647, 1027 cm^{-1}; ^1H NMR (200 MHz) δ: 1.03 (s, 3H), 1.06 (br s, 3H), 1.68 (br s, 3H), 0.8–1.8 (m, 7H), 1.90–2.05 (m, 2H), 2.44 (dd, 1H, J = 8, 2 Hz), 2.50–2.60 (m, 1H), 3.33 (br s, 3H), 4.26 (br d, 1H, J = 10 Hz), 4.46 (br d, 1H, J = 8 Hz), 4.62 (br d, 1H, J = 8 Hz), 4.62 (br d, 1H, J = 8 Hz), 5.09 (br d, 1H, J = 20 Hz), 5.15 (br d, 1H, J = 20 Hz), 5.63 (dd, 1H, J = 16, 8 Hz), 5.95–6.45 (m, 1H); ^{13}C NMR (50.3 MHz): ~3:2 diastereoisomer mixture, major isomer, most signals doubled, δ: 18.7, 21.1, 22.7, 27.3, 32.8, 36.8, 38.3, 50.3, 56.2, 62.1, 72.5, 76.1, 85.4, 94.2, 117.2, 131.9, 132.9, 134.2, 134.3, 136.1; MS (CI): 257 ($MH^+ - C_2H_6O_2$).

4-(1-Methoxymethyloxy-2,4-pentadienyl)-1,3,3-trimethyl-2-(2-oxo-3-butynyl)cyclohexene (35)

Dess–Martin periodinane (997 mg, 1.71 mmol) was added to a solution of the alcohol **34** (384 mg, 1.21 mmol) in dry dichloromethane (10 mL). The resulting bright yellow solution was stirred at 21°C for 1 h. Diethyl ether (20 mL) and aqueous sodium hydroxide solution (10 mL, 10%) were added and the mixture was stirred for a further 10 min. The solution was extracted with diethyl ether. The combined organic extracts were washed (10% sodium hydroxide solution, water, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 6:1) to afford 210 mg (55%) of the ketone **35**. IR (neat): 3252, 2918, 2089, 1681, 1074, 913 cm^{-1}; ^1H NMR (200 MHz) δ: 0.95 (s, 3H), 0.96 (s, 3H), 1.51 (s, 3H), 1.40–1.80 (m, 4H), 1.90–2.10 (m, 2H), 3.16 (s, 1H), 3.30 (br s, 2H), 3.34 (s, 3H), 4.23 (d, 1H, J = 8 Hz), 4.46 (d, 1H, J = 6.6 Hz), 4.64 (d, 1H, J = 6.6 Hz), 5.08 (d, 1H, J = 18 Hz), 5.15 (dd, 1H, J = 18, 2 Hz), 5.64 (dd, 1H, J = 15, 8 Hz), 6.05–6.40 (m, 1H); ^{13}C NMR (50.3 MHz) δ: 18.9, 20.8, 22.0, 26.6, 32.9, 38.2, 45.3, 50.1, 56.4, 76.2, 78.3, 81.7, 94.4, 117.3, 129.7, 132.8, 134.4, 136.3, 186.0; MS (CI): 317 (MH^+).

(1*R**,2*S**,3*S**)-2-Methoxymethyloxy-9-oxo-12,15,15-trimethyltricyclo[9.3.1.$0^{3,8}$]pentadeca-4,7,11-triene (36)

A solution of the acetylenic ketone **35** (0.121 g, 0.382 mmol)

in dry toluene (25 mL) containing hydroquinone (0.01 g, 0.09 mmol) 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 top of the microwave oven. Argon was bubbled through the solution for 10 min and the vessel sealed. The diameter of the even 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 12 × 0.5 h intervals, after which the tube was allowed to return to room temperature between each session and fresh moist vermiculite added to the beaker. The tube was cooled, solvent evaporated, and the residual oil chromatographed (petroleum ether/diethyl ether; 3:1) to afford the adduct **36** (0.041 g, 34%). (Unfortunately, the minor adduct, epimeric at C3, could not be fully characterized.) IR (neat): 2920, 1694, 1148, 1033, 919 cm^{-1}; ^1H NMR (200 MHz) δ: 1.04 (s, 3H), 1.50–2.30 (m, 4H), 2.50–2.60 (m, 1H), 2.60–2.70 (m, 1H), 2.71–2.85 (m, 1H), 2.95 (dd, 1H, J = 9.6, 5.6 Hz), 3.30 (br s, 2H), 3.32 (br s, 3H), 3.4–3.70 (m, 1H), 4.53 (br s, 2H), 5.5–6.1 (m, 3H); HRMS calcd. for $C_{20}H_{28}O_3$: 316.2040; found: 316.2061.

(1*R,2*S**)-3,4-Benzo-2-methoxymethyloxy-9-oxo-12,15,15-trimethyltricyclo[9.31.0^{3,8}]pentadec-11-ene (37) (*endo/exo* mixture, ~1:1)**

Dichlorodicyanoquinone (0.049 g, 0.216 mmol) was added to the diene (0.034 g, 0.108 mmol) dissolved in dry benzene (5 mL). The stirred reaction was refluxed for 2 h. The mixture was then cooled to 21°C and the solvent removed under aspirator pressure. The residual oil was chromatographed (petroleum ether/diethyl ether; 3:1) to afford 0.023 g (69%) of the mixture of aromatic products **37**. IR (neat): 2919, 1695, 1452, 1031, 923 cm^{-1}; ^1H NMR (200 MHz) δ: 0.39 (s, 3H), 0.71 (s, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.41 (s, 3H), 0.8–1.70 (m, 4H), 1.76 (s, 3H), 1.90–2.50 (m, 6H), 3.20 (br s, 3H), 3.35 (br s, 3H), 3.25–3.65 (m, 3H), 3.59 (d, 1H, J = 12 Hz), 4.02 (d, 1H, J = 9.6 Hz), 4.09 (d, 1H, J = 6 Hz), 4.27 (d, 1H, J = 6 Hz), 4.30 (d, 1H, J = 6 Hz), 4.40 (d, 1H, J = 6 Hz), 4.49 (d, 1H, J = 3 Hz), 7.00–7.60 (m, 8H); ^{13}C NMR (75 MHz) δ: 20.17, 20.58, 20.78, 21.58, 26.77, 27.78, 27.81, 28.81, 30.25, 30.47, 37.22, 38.72, 46.98, 47.45, 49.09, 53.78, 55.39, 56.46, 78.85, 86.32, 93.40, 95.02, 125.64, 126.18, 126.31, 127.29, 127.84, 127.92, 128.30, 129.24, 129.43, 129.58, 134.52, 135.85, 137.86, 138.50, 140.91, 143.38, 200.95, 209.43; HRMS calcd. for $C_{20}H_{26}O_3$: 314.1882; found: 314.1883.

4-(1-*tert*-Butyldimethylsilyloxy-2,4-pentadienyl)-1,3,3-trimethyl-2-(2-oxo-3-methyl-3-butenyl)cyclohexene (41)

A solution of *tert*-butyllithium (0.35 mL, 0.60 mmol, 1.7 M) in pentane was added dropwise to a cold (−78°C), stirred solution of 2-bromopropene (0.05 mL, 0.62 mmol) in of dry THF (2 mL). After the reaction was stirred at −78°C for 5 min, a solution of the aldehyde **29** (0.09 g, 0.25 mmol) in dry THF (1 mL) was added dropwise. The resulting mixture was stirred at −78°C for 30 min and warmed to 21°C. Ammonium chloride solution (saturated) was added and the mixture was extracted with diethyl ether. The combined ether extracts were washed (water, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 0.072 g (72%) of the alcohol, which was used directly.

Oxalyl chloride (0.014 mL, 0.160 mmol) was added to a cold (−78°C), stirred solution of dry dimethyl sulfoxide (0.0136 mL, 0.192 mmol) in dry dichloromethane (3 mL). After the reaction was stirred at −78°C for 15 min, a solution of the above alcohol (0.0519 g, 0.128 mmol) in dry dichloromethane (1 mL) was added dropwise and the resulting mixture stirred for a further 15 min. Dry triethylamine (0.070 mL, 0.502 mmol) was added and the solution was stirred at −78°C for 5 min and at 21°C for a further 30 min. Saturated aqueous ammonium chloride solution was added and the mixture was extracted with dichloromethane. The combined organic extracts were washed (water, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 15:1) to afford 0.045 g (88%) of the enone **41**. IR (neat): 2923, 1686, 1463, 1335, 1064, 1003, 837, 774 cm^{-1}; ^1H NMR (200 MHz) δ: −0.06 (s, 3H), −0.01 (s, 3H), 0.83 (s, 9H), 0.86 (s, 3H), 0.87 (s, 3H), 1–1.5 (m, 1H), 1.39 (s, 3H), 1.5–1.8 (m, 2H), 1.86 (s, 3H), 1.90–2.20 (m, 2H), 3.40 (AB, 2H, J = 20 Hz), 4.36 (d, 1H, J = 7.4 Hz), 5.02 (d, 1H, J = 10 Hz), 5.11 (d, 1H, J = 17 Hz), 5.71 (bs s, 1H), 5.99 (br s, 1H), 5.70–6.40 (m, 3H). HRMS calcd. for $C_{21}H_{33}O_2Si$ (M^+ − $C_4H)_9$: 345.2250; found: 345.2250.

5-(*tert*-Butyldimethylsilyloxy)methyl-3-formyl(dimethylacetal)-2,4,4-trimethylcyclohexene (44)

Thionyl chloride (0.070 mL, 0.960 mmol) was syringed into a cold (0°C), stirred solution of the alcohol **15** (0.174 g, 0.485 mmol) and dry pyridine (0.078 mL, 0.964 mmol) in dry dichloromethane (5 mL). The reaction was warmed to 0°C for 1 h and to 21°C for 30 min. Saturated sodium bicarbonate solution was added and the mixture was extracted with dichloromethane. The combined organic extracts were washed (water, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 0.132 g (80%) of a 3:1 mixture of the olefin acetals **44** and **43**. Compound **44**: IR (neat): 2914, 1090, 842, 775 cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (s, 6H), 0.79 (s, 3H), 0.85 (s, 9H), 1.00 (s, 3H), 1.00–1.50 (m, 1H), 1.77 (d, 3H, J = 1 Hz), 1.50–2.00 (m, 2H), 2.05–2.30 (m, 1H) 3.34 (s, 3H), 3.37 (s, 3.20–3.40 (m, 1H), 3.71 (dd, 1H, J = 5, 10 Hz), 4.29 (d, 1H, J = 4 Hz), 5.44–5.52 (br s, 1H); ^{13}C NMR (50.3 MHz) δ: −5.3 (2C), 18.2, 23.4, 25.9 (3C), 26.3, 27.5, 33.6, 39.9, 55.0, 55.2, 56.7, 64.2, 108.2, 123.0, 131.8; HRMS calcd. for $C_{19}H_{38}O_3Si$ (M^+ − MeOH): 310.2328; found: 310.2307.

5-(*tert*-Butyldimethylsilyloxy)methyl-3-formyl-2,4,4-trimethylcyclohexene (45)

Saturated oxalic acid solution (2 mL) and a drop of glacial acetic acid were added to a solution of **44** (0.056 g, 0.164 mmol) in diethyl ether (2 mL). The reaction was refluxed for 2 h, then cooled to 21°C. Water was added and the mixture was extracted with diethyl ether. The organic extracts were washed (water, brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 0.0411 g (85%) of the aldehyde **45**. IR (neat): 2940, 1724, 1200, 1080, 840, 780 cm^{-1}; ^1H NMR (200 MHz) δ: 0.01 (s, 3H), 0.86 (s, 9H), 1.04 (s, 3H), 1.58 (s, 3H), 1.70–2.00 (m,

2H), 2.10–2.40 (m, 2H) 3.30–3.50 (m, 1H) 3.78 (dd, 1H, $J = 4$, 10 Hz), 5.73 (br s, 1H), 9.54 (d, 1H, $J = 4$ Hz). HRMS calcd. for $C_{13}H_{23}O_2Si$ ($M^+ - C_4H_9$): 239.1468; found: 239.1469.

5-(*tert*-Butyldimethylsilyloxy)methyl-1,2-epoxy-3-formyl-2,4,4-trimethylcyclohexane (46)

A solution of freshly prepared dimethyloxirane (excess) in acetone (25 mL) was added dropwise to a cold (−4°C), stirred solution of aldehyde **45** (0.184 g, 0.622 mmol) in acetone (5 mL). After stirring at −4°C for 1 h, the reaction mixture was warmed to 21°C. Concentration of the mixture provided a residual oil that was chromatographed (petroleum ether/diethyl ether; 9:1) to afford 0.150 g (77%) of the epoxide **46**. IR (neat): 2946, 2742, 1720, 1467, 1100, 842, 778 cm^{-1}; ^1H NMR (200 MHz) δ: −0.00 (s, 6H), 0.85 (s, 9H), 0.89 (s, 3H), 0.93 (s, 3H), 1.32 (s, 3H), 1.70–1.90 (m, 2H), 1.98 (d, 1H, $J = 4.6$ Hz), 2.06–2.28 (m, 1H), 3.12 (t, 1H, $J = 1.6$ Hz), 3.51 (dd, 1H, $J = 10.4$, 5.6 Hz), 3.63 (dd, 1H, $J = 10.4$, 4 Hz), 9.66 (d, 1H, $J = 4.6$ Hz); ^{13}C NMR (50.3 MHz) δ: −5.5 (2C), 18.2, 23.4, 24.7, 24.8, 25.7, 25.8 (3C), 32.8, 37.2, 57.4, 58.5, 62.0, 63.1, 203.3. HRMS calcd. for $C_{13}H_{23}O_3Si$ ($M^+ - C_4H_9$): 255.1416; found: 255.1424.

5-(*tert*-Butyldimethylsilyloxy)methyl-3-formyl-2,4,4-trimethylclohex-2-en-1-ol (47)

Sodium methoxide (0.031 g, 0.574 mmol) was added to the epoxide **46** (0.15 g, 0.481 mmol) and methanol (10 mL). The reaction mixture was stirred under reflux for 3 h, then cooled to 21°C. Water was added and the solvent was removed. The residual oil was chromatographed (petroleum ether/diethyl ether; 3:1, then the petroleum ether/diethyl ether; 1:1). Concentration of the appropriate fractions afforded 0.0989 g (66%) of the alcohol **47**. IR (neat): 3402, 2942, 2761, 1673, 1254, 1094, 842, 777 cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (s, 6H), 0.86 (s, 9H), 1.02 (s, 3H), 1.27 (s, 3H), 1.5–1.80 (m, 3H), 1.80–2.0 (m, 1H), 2.17 (s, 3H), 3.39 (dd, 1H, $J = 10$, 8 Hz), 3.78 (dd, 1H, $J = 10$, 4 Hz), 3.95–4.10 (m, 1H), 10.11 (s, 1H); ^{13}C NMR (75 MHz) δ: −5.5, −5.4, 16.9, 18.2, 20.3, 35.92 (3C), 26.4, 30.3, 36.0, 42.3, 62.9, 69.7, 141.9, 151.1, 194.0. HRMS calcd. for $C_{17}H_{32}O_3Si$: 312.2120; found: 312.2110.

1-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldimethylsilyloxy)methyl-3-formyl-2,4,4-trimethylcyclohex-2-ene (48)

tert-Butyldimethylsilyl chloride (0.057 g, 0.378 mmol) was added to a stirred solution of the alcohol **47** (0.099 g, 0.317 mmol) and imidazole (0.53 g, 0.778 mmol) in dry dichloromethane (10 mL). The resultant solution was stirred at 21°C for 16 h. Water was added and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 19:1). Concentration of the appropriate fractions afforded 0.123 g (91%) of the silyl ether **48**. IR (neat): 2912, 2762, 1681, 1467, 1254, 1079, 841, 777 cm^{-1}; ^1H NMR (200 MHz) δ: 0.02 (s, 6H), 0.10 (s, 6H), 0.87 (s, 9H), 0.88 (s, 9H), 1.0 (s, 3H), 1.27 (s, 3H), 1.45–1.63 (m, 1H), 1.66–1.82 (m, 1H), 1.90 (dt, 1H, $J = 2$, 12 Hz), 2.08 (s, 3H), 3.33 (dd, 1H, $J = 10$, 12 Hz), 3.76 (dd, 1H, $J = 10$, 4 Hz), 4.02 (t, 1H, $J = 4$ Hz), 10.10 (s, 1H); ^1H NMR ($CDCl_3$, 50.3 MHz) δ: −5.39, −5.35, −4.67, −4.14, 16.82, 18.1, 18.4, 20.5, 25.8 (3C), 26.0 (3C), 26.5, 30.4, 35.7, 42.3, 63.1, 70.1, 141.0, 152.9, 194.1. HRMS calcd. for $C_{23}H_{46}O_3Si_2$: 426.2985; found: 426.2988.

5-(*tert*-Butyldimethylsilyloxy)methyl-2,4,4-trimethyl-3-cyanomethyl-2-cyclohexen-1-one (49)

3,5-Dimethylaminopyridine (0.33 g, 3.43 mmol) was added to a cold (−4°C) suspension of chromium trioxide (0.35 g, 3.50 mmol) in dry dichloromethane (4 mL). the reaction mixture was stirred at 0°C for 20 min and a solution of nitrile **22** (0.450 g, 0.146 mmol) was added. The resulting red-brown solution was stirred at −4°C for 1 h and warmed to 21°C for 16 h. Dilute sodium hydroxide (6 M, 1 mL) was added and the mixture was stirred at 21°C for 20 min. Water (5 mL) and dichloromethane (10 mL) were added and the resulting solution extracted thoroughly with dichloromethane. The combined organic extracts were washed (water, 10% HCl, and brine), dried, and concentrated. The residual oil was chromatographed (petroleum ether/diethyl ether; 1:1) to afford recovered **22** (40–50%) and 0.144 g (31%) of the enone **49**, mp 75–77°C. IR (neat): 2946, 2250, 1669, 1093, 846, 776 cm^{-1}; ^1H NMR (200 MHz) : 0.00 (s, 6H), 0.84 (s, 9H), 1.11 (s, 3H), 1.29 (s, 3H), 1.86 (s, 3H), 1.9–2.10 (m, 1H), 2.42 (dd, 1H, $J = 18$, 11 Hz), 2.65 (dd, 1H, $J = 18$, 5 Hz), 3.18 (br s, 2H), 3.57 (dd, 1H, $J = 10.2$, 6.4 Hz), 3.72 (dd, 1H, $J = 10.2$, 4.6 Hz); ^{13}C NMR (75 MHz) δ: −5.6, 11.8, 17.8, 18.2, 20.9, 25.8, 26.3, 37.1, 38.8, 45.8, 63.1, 116.4, 134.7, 150.6, 197.4. HRMS calcd. for $C_{17}H_{28}O_2Si$ (M^+ − Me): 306.1889; found: 306.1861.

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References

1. M.C. Wani, H.L. Taylor, M.E. Wall, P. Coggan, and A.T. McPhail. J. Am. Chem. Soc. **93**, 2325 (1971).
2. F. Lavelle, F. Guéritte-Voegelein, and D. Guénard. Bull. Cancer, **80**, 326 (1993).
3. M.L. Rothenberg. Curr. Opin. Invest. Drugs, **2**, 1269 (1993).
4. (*a*) A.N. Boa, P.R. Jenkins, and N.J. Lawrence. Contemp. Org. Synth. **1**, 47 (1994); (*b*) K.C. Nicolaou, W.-M. Dai, and R.K. Guy. Angew. Chem. Int. Ed. Engl. **33**, 15 (1994); (*c*) D.G.I. Kingston, A.A. Molinero, and J.M. Rimoldi. Prog. Chem. Org. Nat. Prod. **61**, 1 (1993); (*d*) C.S. Swindell. Org. Prep. Proced. Int. **23**, 465 (1991).
5. (*a*) R.A. Holton, C. Somoza, H.-B. Kim, F. Liang, R.J. Biediger, P.D. Boatman, M. Shindo, C.C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K.K. Murthi, L.N. Gentile, and J.H. Liu. J. Am. Chem. Soc. **116**, 1597 (1994); (*b*) R.A. Holton, H.-B. Kim, C. Somoza, F. Liang, R.J. Biediger, P.D. Boatmen, M. Shindo, C.C. Smith, S. Kim, H. Nadizadeh, Y. Suzudi, C. Tao, P. Vu, S. Tang, P. Zhang, K.K. Murthi, L.N. Gentile, and J.H. Liu. J. Am. Chem. Soc. **116**, 1599 (1994).
6. (*a*) K.C. Nicolaou, Z. Yang, J.J. Liu, H. Ueno, P.G. Nantermet, R.K. Guy, C.F. Claiborne, J. Renaud, E.A. Couladouros, K. Paulvannan, and E.J. Sorensen. Nature, **367**, 630 (1994); (*b*) K.C. Nicolaou, P.G. Nantermet, H. Ueno, R.K. Guy, E.A. Couladouros, and E.J. Sorensen. J. Am. Chem. Soc. **117**, 624 (1995); (*c*) K.C. Nicolaou, J.J. Liu, Z. Yang, H. Ueno, E.J. Sorensen, C.F. Claiborne, R.K. Guy, C.K. Hwang, M. Nakada, and P.G. Nantermet. J. Am. Chem. Soc. **117**, 634 (1995); (*d*) K.C. Nicolaou, Z. Yang, J.J. Liu, P.G. Nantermet, C.F.

Claiborne, J. Renaud, R.K. Guy, and K. Shibayama. J. Am. Chem. Soc. **117**, 645 (1995); (*e*) K.C. Nicolaou, H. Ueno, J.J. Liu, P.G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, and R. Chadha. J. Am. Chem. Soc. **117**, 653 (1995).
7. (*a*) R.V. Bonnert and P.R. Jenkins. J. Chem. Soc. Chem. Commun. 1540 (1987); (*b*) J. Chem. Soc. Chem. Soc. Perkin Trans. 1, 413 (1989).
8. R.W. Jackson, R.G. Highby, J.W. Gilman, and K.J. Shea. Tetrahedron, **48**, 7013 (1992).
9. R.W. Jackson and K.J. Shea. Tetrahedron Lett. **35**, 1317 (1994).
10. C.A. Alaimo, C.A. Coburn, and S.J. Danishefsky. Tetrahedron Lett. **35**, 6603 (1994).
11. (*a*) K. Sakan and B.M. Craven. J. Am. Chem. Soc. **105**, 3732 (1983); (*b*) K. Sakan, D.A. Smith, S.A. Babirad, F.R. Fronczek, and K.N. Houk. J. Org. Chem. **56**, 2311 (1991).
12. (*a*) A.G. Fallis. Can. J. Chem. **62**, 183 (1984); (*b*) E. Cignek. Org. React. **32**, 1 (1984); (*c*) D. Craig. Chem. Soc. Rev. **16**, 187 (1987).
13. (*a*) G.P. Kugatova-Shemyakina, G.M. Nikolaev, and V.M. Andreev. Tetrahedron, **23**, 2721 (1967); (*b*) N.M. Viktorova, S.P. Knyazen, N.S. Sefirov, Y.D. Gavrilov, G.M. Nilolaev, and V.F. Bystrov. Org. Magn. Reson. **6**, 236 (1974).
14. Y.-F. Lu and A.G. Fallis. Tetrahedron Lett. **34**, 3367 (1993).
15. M.T. Thomas and A.G. Fallis. J. Am. Chem. Soc. **98**, 1227 (1976).
16. (*a*) G.A. Olah, S.C. Narang, B.G.B. Gupta, and R. Malhotra. J. Org. Chem. **44**, 1247 (1979); (*b*) G.A. Olah, A. Husain, B.P. Singh, and A.K. Mehrotra. J. Org. Chem. **48**, 3667 (1983).
17. A.G. Angoh and D.L.J. Clive. Chem. Soc. Chem. Commun. 534 (1984).
18. D.B. Dess and J.C. Martin. J. Org. Chem. **48**, 4155 (1983).
19. (*a*) B. Lei and A.G. Fallis. J. Am. Chem. Soc. **112**, 4609 (1990); (*b*) Y.F. Lu, C.W. Harwig, and A.G. Fallis. J. Org. Chem. **58**, 4202 (1993).
20. A.G. Fallis and Y.-F. Lu. *In* Advances in cycloadditions. Vol. 3. *Edited by* D.P. Curran. JAI Press, Greenwich, Conn. 1993. pp. 1–66.
21. (*a*) K.J. Shea and J.W. Gilman. Tetrahedron Lett. **25**, 2451 (1984); (*b*) K.J. Shea, J.W. Gilman, C.D. Haffner, and T.K. Dougherty. J. Am. Chem. Soc. **108**, 4953 (1986).
22. A.S. Kende, S. Johnson, P. Sanfilippo, J.C. Hodges, and L.N. Jungheim. J. Am. Chem. Soc. **108**, 3512 (1986).
23. Y. Queneau, W.J. Krol, W.G. Bornmann, and A.S. Danishefshy. J. Org. Chem. **57**, 4043 (1992).
24. T. Doi, J. Robertson, G. Stork, and A. Yamashita. Tetrahedron Lett. **35**, 1481 (1994).
25. D.F. Grant and E.J. Gabe. J. Appl. Crystallogr. **11**, 114 (1978).
26. E.J. Gabe, F.L. Lee, and Y. Lepage. J. Appl. Crystallogr. **22**, 384 (1989).