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Synthetic approach to analogues of betulinic acid

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Abstract—2-Methylcyclohexane-1,3-dione **14** was converted via the Wieland–Miescher analogue **15** into the 6-silyloxy-2,5,5,8a-tetramethyldecalin-1-one **21** by an efficient process. Several routes were examined to transform this compound into the pentacyclic triterpene skeleton of betulinic acid and its structural analogues. For example, the iodide **39**, easily prepared from **21**, was converted via a Sonogashira-hydroboration–Suzuki process into the *E*-triene **45**. Photolysis of **45** using a benzanthrone sensitizer afforded the *Z*-triene **43**. However, all attempts at effecting the cyclization of this triene **43** to the cyclohexadiene **47** (electrocyclic via photochemical or thermal means, metal-catalyzed processes, oxidative and radical cyclizations) failed to produce the key pentacyclic material.

1. Introduction

Betulinic acid (**1**, Fig. 1) was first isolated in 1948 from the bark of the London plane tree (*Platanus acerifolia*) by Bruckner.[1] However, betulinic acid was a known derivative of betulin (**2**, Fig. 1), which was isolated by Löwitz[2] in 1788 from the bark of the white birch (*Betula alba*). The first structural assignment of betulin and its derivatives was made by Ruzicka in 1941.[3] Betulin is one of the most plentiful triterpenes, comprising up to 24% of the outer bark of the white birch and as much as 35% of the outer bark of the Manchurian white birch (*Betula platyphylla*).[4]

Derivatives of betulinic acid **1** and betulin **2** have shown promise as HIV therapeutics by inhibiting viral growth in a manner different from that of current HIV drugs.[5–9] Although betulinic acid and betulin themselves exhibited only weak activity against HIV replication in H9 lymphocytes (**1**, EC_{50} 1.4 μM, TI 9.3 and **2**, EC_{50} 23 μM, TI 1.9), their corresponding mono and diester derivatives **3** and **4**, respectively, have been shown to be very potent inhibitors (**3**, $EC_{50}<3.5\times10^{-4}$ μM, TI>20,000 and **4**, $EC_{50}<6.6\times10^{-4}$ μM, TI>21,515, Fig. 2).[7,8] Thus, **3** and **4** are more potent and less toxic than the well-known drug AZT (EC_{50} 1.5 μM, TI 12,000). The most current data suggest that the compounds are inhibitors of virion formation, disrupting a late step in Gag processing involving conversion of the capsid precursor (p25) to the mature capsid protein (p24).[10]

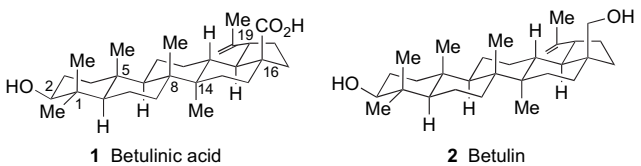

Figure 1.

In addition to the anti-HIV activity of betulinic acid and its derivatives, these compounds also exhibit anti-cancer activity in a wide variety of cell lines via selective cytotoxicity of tumor cells. Various C16 amino acid derivatives exhibit anti-melanoma/carcinoma activity with ED_{50}'s ranging from 1.5 to >20 μg/mL.[11]

Since all known derivatives have been made starting from natural materials, we chose to focus on the construction of the pentacyclic core with the two *anti*-quaternary methyl groups in the C ring. Due to the high steric demand of the β-face of the core structure in the environment around these methyl groups, their installation was seen to be quite challenging. Also, we wanted to develop a convergent synthesis where two highly functionalized portions of the ultimate core system could be joined late in the synthesis, with C ring formation as the key step. Such a strategy would allow for the facile synthesis of analogues by simply altering the construction of either of the components.

We envisioned the 11α-hydroxy betulinic acid derivative **5** to arise from dissolving metal reduction of the enone **6**,

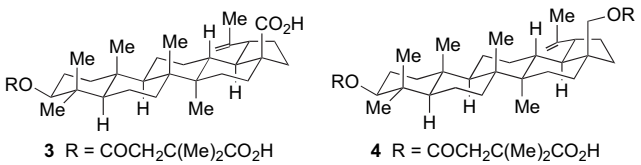

Figure 2.

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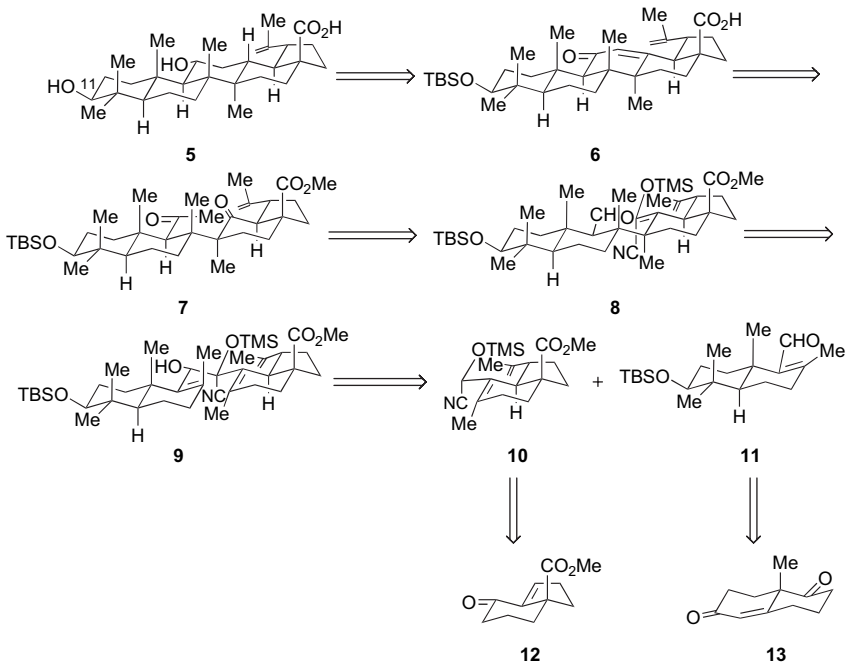


Scheme 1.

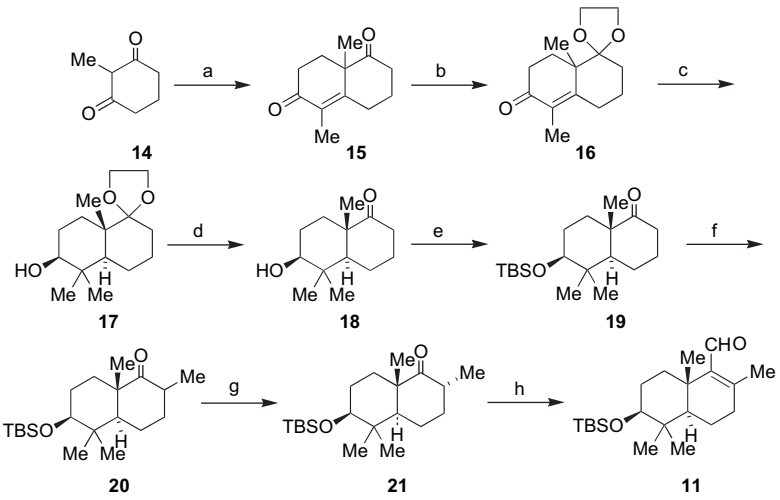
which in turn would be the product of an intramolecular aldol condensation of the diketone **7** (Scheme 1). The diketone **7** would be prepared from conversion of the aldehyde to the corresponding methyl ketone, dihydroxylation, and subsequent glycolytic cleavage of the silyl cyanohydrin of the aldehyde **8**. The aldehyde **8** would be formed via an anionic oxy-Cope rearrangement of the diene **9**, which would arise from nucleophilic addition of the acyl anion equivalent **10** to the α,β-unsaturated aldehyde **11**. The acyl anion equivalent **10** would be easily prepared from the known optically active enone ester **12**.[12] The α,β-unsaturated aldehyde **11** would be derived from the known Wieland–Miescher ketone **13**.[13] We report herein the full details of this approach, namely the facile synthesis of several advanced intermediates and our attempts to convert them into betulinic acid analogues.

2. Results and discussion

The synthesis of the DE ring system **12** was readily accomplished according to the literature method of Cossy.[12] We began synthesis of the AB ring system by converting 2-methyl-1,3-cyclohexanedione **14** into the 1-methyl analogue of the Wieland–Miescher ketone by treatment with ethyl vinyl ketone (EVK) in the presence of potassium hydroxide in methanol (Scheme 2). Subsequent reflux in benzene in the presence of catalytic pyrrolidine afforded the enone **15** in 61% yield. Selective protection of the ketone over the enone with ethylene glycol and *p*-toluenesulfonic acid in the presence of 4 Å molecular sieves provided the enone **16** in 98% yield. Reductive alkylation (Li/NH_3; MeI, THF) of the enone proceeded smoothly. The ketone was reduced in situ with additional lithium wire after the reductive alkylation was complete and then quenched with methanol to produce only the equatorial alcohol **17** in 54% yield. The ketal group of **17** was then hydrolyzed (TsOH, acetone/H_2O) to the ketone **18** and the alcohol protected (TBSOTf, pyridine, dichloromethane) as the TBS ether **19** in 83% yield. The TBS ether **19** was then treated with LDA followed by methyl iodide to furnish in 97% yield the methylated ketone **20**, as a mixture of diastereomers at the methyl stereocenter. The mixture of α-keto diastereomers was subjected to sodium methoxide in methanol to epimerize the mixture to give only the ketone **21** with the methyl group in the equatorial position in quantitative yield.

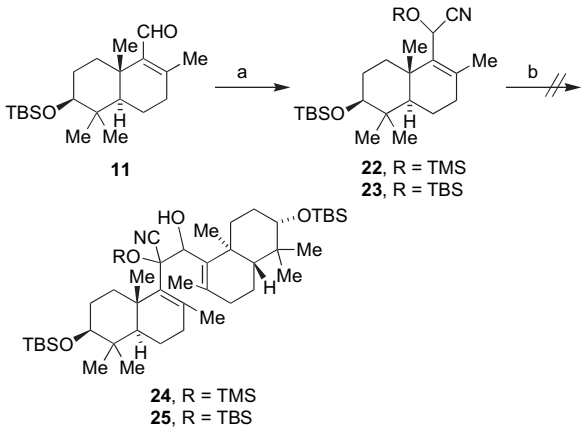
A method was then pursued that allowed direct conversion of the ketone **21** to the desired aldehyde **11**.[14] The procedure utilized dichloromethyllithium generated in situ from dichloromethane and LDA at −95 °C followed by warming to 23 °C and eventual reflux in THF. The solvents were removed and the newly generated α-chloro epoxide was then subjected to treatment with HMPA, lithium perchlorate, and calcium carbonate while being warmed to 130 °C, effecting conversion to the aldehyde **11** in 45% yield.

It was decided to work out the chemistry of the silyl cyanohydrin formation and the nucleophilic addition to the aldehyde **11** in a dimeric manner due the relative abundance of the aldehyde **11** over the enone **12**, which had not been converted to the corresponding aldehyde requisite for the synthesis. With the aldehyde **11** in hand, the trimethylsilyl cyanohydrin **22** of the aldehyde was prepared in 96% yield (TMSCN, ZnI_2, CH_2Cl_2) (Scheme 3) and the *tert*-butyl-dimethylsilyl (TBS) analogue **23** in 48% yield (TBSCN, ZnI_2, dichloromethane). In both cases, addition of the lithiate of the silyl cyanohydrin to the aldehyde **11** gave no reaction. A variety of temperatures ranging from −78 °C to reflux was used but no addition was ever seen. The addition of HMPA to the reaction mixture also had no effect on the reaction. Due to the stabilizing effect of the neighboring nitrile group as well as the sheer size of the nucleophile generated, it was believed that we would need a smaller and



Scheme 2. Reagents and conditions: (a) KOH, MeOH, EVK; pyrrol., PhH, reflux, 61%; (b) $HO(CH_2)_2OH$, TsOH, 4 Å MS, 98%; (c) Li/NH_3; MeI, THF; Li^0/NH_3; MeOH, 54%; (d) TsOH, acetone/H_2O, quant.; (e) TBSOTf, pyr., CH_2Cl_2, 0–23 °C, 83%; (f) LDA, THF, −78 °C; MeI, −78 to 23 °C, 97%; (g) NaOMe, MeOH, 23 °C, quant.; (h) LDA, −95 °C; CH_2Cl_2, **21**, −95 to −20 °C to reflux; HMPA, $LiClO_4$, $CaCO_3$, 130 °C, 45%.

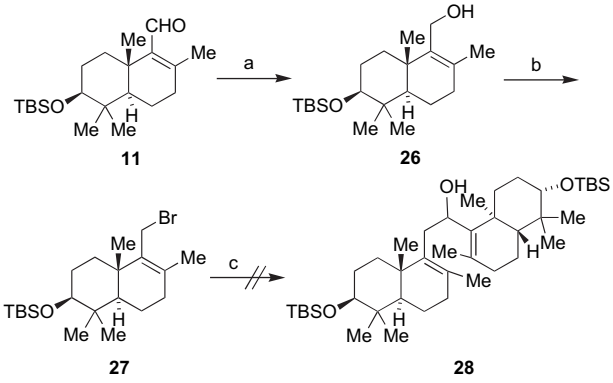
much more reactive nucleophile to be able to add to the very sterically hindered aldehyde **11**.



Scheme 3. Reagents and conditions: (a) TMSCN/TBSCN, ZnI_2, CH_2Cl_2, 0–23 °C, 96%/48% (**22**/**23**); (b) LDA, THF, −78 °C; **11**, −78 °C to reflux, 0%.

Despite reaching the requisite acyl anion equivalent of the silyl cyanohydrin and synthesizing the AB ring system as planned, the lack of reactivity of our nucleophile toward the aldehyde **11** would not allow us to prepare the substrate required to demonstrate our anionic oxy-Cope methodology for the construction of the *anti*-quaternary methyl groups in the C ring of betulinic acid **1**. Therefore, a smaller, stronger nucleophile was required to add to our very sterically hindered aldehyde in order to be able to test the validity of our anionic oxy-Cope methodology. Thus, we moved to other nucleophile sources for addition to the aldehyde **11** and the eventual construction of the ring system.

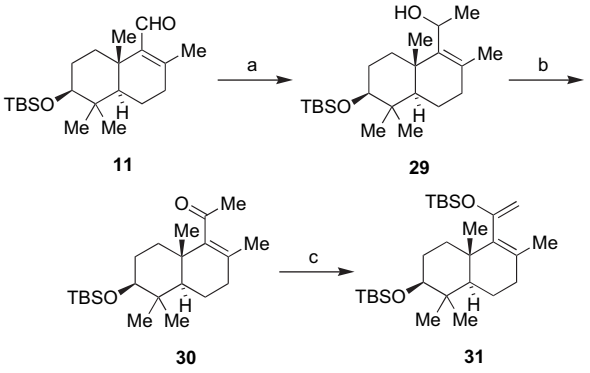
The aldehyde **11** was reduced in 98% yield to the corresponding alcohol **26** ($NaBH_4$, EtOH), which was readily converted into the bromide **27** in 48% yield (CBr_4, PPh_3, DCM) (Scheme 4). However, upon treatment of the bromide **27** with magnesium metal, even in the presence of iodine to activate the surface of the metal, and addition of the aldehyde **11**, there was no evidence of Grignard addition to form **28**.



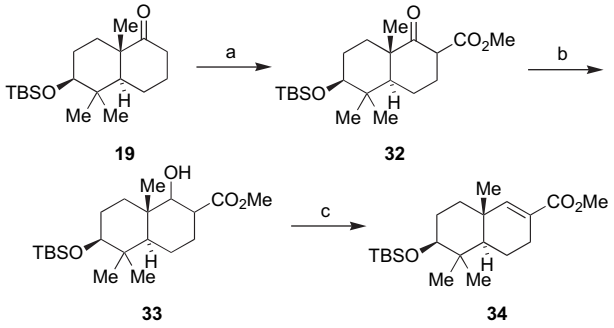
Scheme 4. Reagents and conditions: (a) $NaBH_4$, EtOH, 23 °C, 70%; (b) CBr_4, PPh_3, CH_2Cl_2, 0–23 °C, 48%; (c) Mg, Et_2O, reflux; **11**, 23 °C to reflux.

Since nucleophilic additions to the aldehyde **11** were unsuccessful, we concluded that using an anionic oxy-Cope as the key step to set the *anti*-quaternary methyl groups and ultimately close the C ring as originally designed was not viable. Starting from the aldehyde **11**, we devised a new synthetic strategy that would assemble the C ring with the *anti*-quaternary methyl groups through the use of a Diels–Alder reaction. The synthesis of the AB ring component began with methylation of the aldehyde **11** (MeLi, Et_2O) to give in 95% yield the allylic alcohol **29**, which was subsequently oxidized to the corresponding enone **30** in 80% yield (Dess–Martin periodinane, DMP, dichloromethane) (Scheme 5). The enone **30** was then converted into the kinetic silyl enol ether **31** in 99% yield (TBSOTf, TEA, dichloromethane). A possible dienophile **34** was synthesized by a three-step procedure starting from the ketone **19** by first forming the β-keto ester **32** with potassium hydride and dimethyl carbonate (Scheme 6). The ketone of **32** was then reduced to the alcohol **33** ($NaBH_4$, MeOH), and the alcohol eliminated ($POCl_3$, pyr., 80 °C) to form the α,β-unsaturated ester **34** in an overall unoptimized yield of 22%. The diene **31** and the dienophile **34** were reacted with a catalytic amount of a 5:1 mixture of aluminum tribromide and trimethylaluminum (Scheme 7), conditions proven to work in our laboratories[15] for highly hindered Diels–Alder reactions. However, these

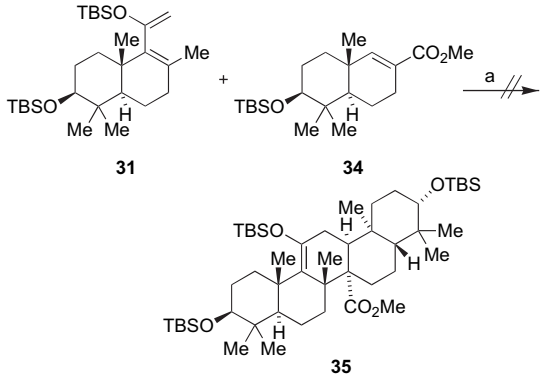
conditions failed to give the desired Diels–Alder adduct **35**. Despite the strength of the Lewis acid, only starting material was obtained. This outcome was undoubtedly due to the severe steric demand of both **31** and **34**.



Scheme 5. Reagents and conditions: (a) MeLi, Et_2O, 0–23 °C, 95%; (b) DMP, CH_2Cl_2, 23 °C, 80%; (c) TBSOTf, TEA, CH_2Cl_2, 0–23 °C, 99%.



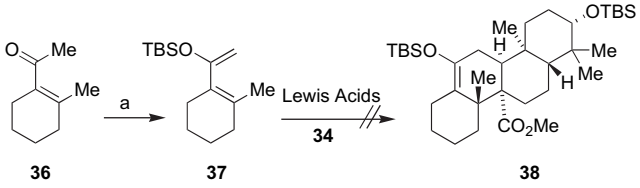
Scheme 6. Reagents and conditions: (a) KH/NaH, THF, Me_2CO_3, reflux; (b) $NaBH_4$, MeOH, 23 °C; (c) $POCl_3$, pyr., 80 °C, 22% (three steps).



Scheme 7. Reagents and conditions: (a) 5:1 $AlBr_3/AlMe_3$, $PhMe/CH_2Cl_2$, −9 to 23 °C.

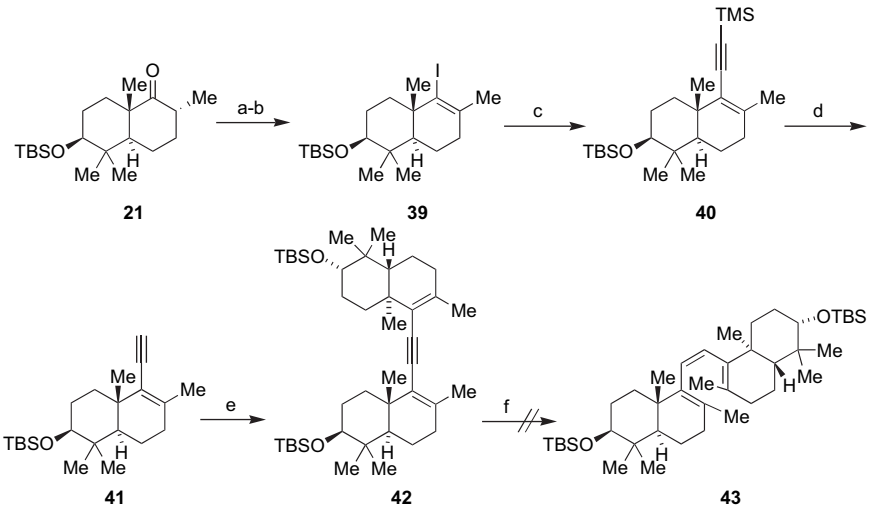
A variety of other Lewis acids were then screened in this system in hopes of finding a viable catalyst to furnish the Diels–Alder adduct **35**, but were ultimately unsuccessful. The reaction time and the variety and strength of Lewis acid catalysts should have been sufficient to see at least some formation of the Diels–Alder adduct **35**. At this point, we believed the diene was probably not cis-coplanar due to steric interaction between the silyloxy group and the adjacent quaternary center, thereby rendering the Diels–Alder reaction impossible due to poor orbital overlap. The high steric demand of the AB ring system in the environment of the silyl enol ether with its large TBS group could very easily twist the silyl enol ether out of planarity with the olefin in the B ring. Although we lacked evidence for this hypothesis other than a lack of reactivity of the diene and dienophile, we decided to test the hypothesis by eliminating the A ring and working with a smaller model system. Without the A ring present there would be no reason for the silyl enol ether to twist out of planarity.

With this hypothesis in mind, the known compound 2-methyl-1-acetyl-1-cyclohexene[16] **36** was converted into the corresponding TBS enol ether **37** (TBSOTf, TEA, dichloromethane, 0 °C) and reacted with the ester **34** using the same set of Lewis acids previously screened (Scheme 8). Once again only starting material or hydrolysis of the silyl enol ether was observed. Therefore, a rotation out of planarity was probably not the key issue since a substrate that could not even undergo this rotation also failed to produce a Diels–Alder adduct. Since the diene **37** has been successfully used in other hindered Diels–Alder reactions,[15a] the most likely explanation is that the ester **34** is just too poor a dienophile to participate. It is well known that esters are quite poor activators of alkenes as dienophiles.[15b]



Scheme 8. Reagents and conditions: (a) TBSOTf, TEA, CH_2Cl_2, 0–23 °C, quant.

Once again seeking a convergent strategy that would enable the mild coupling of two fully elaborated pieces followed by a key cyclization, we developed an organometallic coupling approach, namely a double Sonogashira sequence. Utilizing the advanced ketone **21**, we sought to install a vinyl iodide via the Barton vinyl iodide procedure (Scheme 9).[17] Following formation of the hydrazone of the ketone **21** in 75% yield (H_2NNH_2, AcOH, EtOH, reflux), nitrogen gas was eliminated by treatment with iodine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in diethyl ether followed by refluxing with DBU in benzene to afford the vinyl iodide **39** in 76% yield. Treatment of the vinyl iodide **39** with trimethylsilyl acetylene in the presence of palladium(II) [$PdCl_2(PPh_3)_2$], copper(I) iodide, and triethylamine at 23 °C effected a Sonogashira reaction to afford the silyl enyne **40**.[18] The first attempts at deprotection of the enyne under basic conditions (K_2CO_3 or KOH in MeOH) were unsuccessful. However, when fluoride ion (TBAF) was used, the enyne **41** was obtained. A second Sonogashira reaction mixture was then conducted using another equivalent of the vinyl iodide **39**, furnishing the dienyne **42** in 14% overall yield from **39** over three steps. With the dienyne in hand, several attempts were made at reduction of the alkyne to the *Z*-alkene **43**, including hydrogenation using Lindlar's catalyst as well as hydroboration ($BH_3\cdot DMS$; $BH_3\cdot THF$). Each of the reagents provided only starting material, even at extended reaction times of up to one week. We realized that if a molecule as small as borane was not reacting with

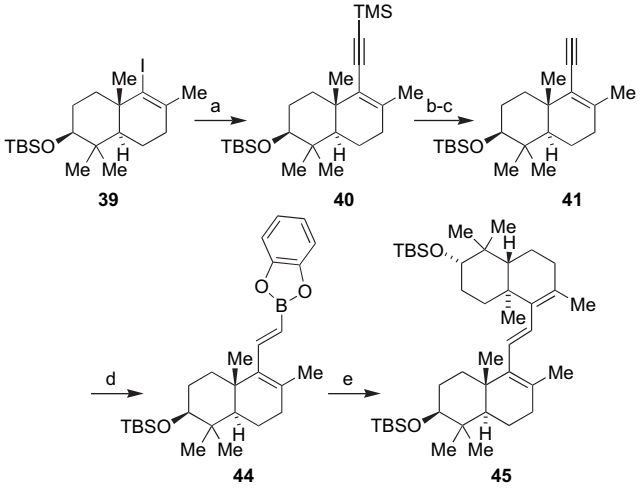


Scheme 9. Reagents and conditions: (a) NH_2NH_2, EtOH, AcOH, reflux, 75%; (b) I_2, DBU, Et_2O, 23 °C, then DBU, PhH, reflux, 76%; (c) TMS–acetylene, $PdCl_2(PPh_3)_2$, CuI, TEA, 23 °C; (d) TBAF, THF, 23 °C; (e) **39**, $PdCl_2(PPh_3)_2$, CuI, TEA, 23 °C, 14% (three steps); (f) H_2, Lindlar's cat. or BH_3.

the dienyne, it was not likely that anything else would either. Although the molecule seems not very sterically hindered, the lack of these reactions indicated that the steric environment surrounding the alkyne was heavily congested.

Even though we were unable to effect reduction to the requisite *Z*-alkene **43** for the cyclization to occur, we viewed this problem as a minor setback. All that was required to overcome this problem was a change in the type of coupling utilized. Therefore, we decided to investigate a new method of joining the two halves of the ring system that would avoid the sterically challenging alkyne reduction. By converting the enyne into a vinyl boron species, which could undergo a Suzuki reaction with another equivalent of the vinyl iodide, such as **39**, we would arrive at an *E*-triene intermediate suitable for cyclization.

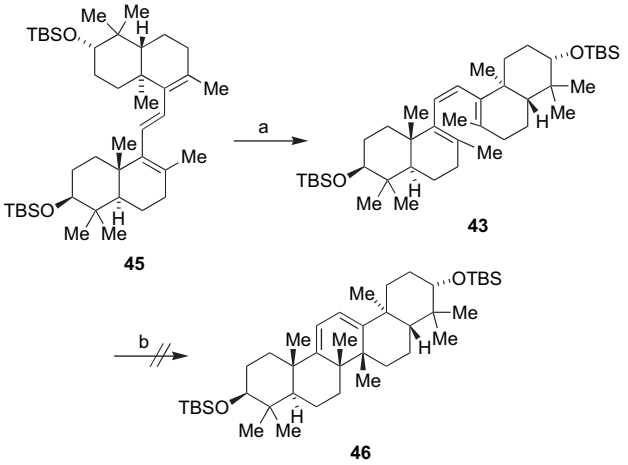
Before we subjected the enyne **41** to catecholborane, we decided to first optimize the synthesis of the enyne (Scheme 10).



Scheme 10. Reagents and conditions: (a) TMS–acetylene, $Pd(dba)_2$, CuI, PPh_3, TEA, 70 °C; (b) excess TBAF, THF, 23 °C; (c) TBSOTf, TEA, CH_2Cl_2, 0–23 °C, 75% (three steps); (d) $Cp_2Zr(H)Cl$, catecholborane, CH_2Cl_2, 96%; (e) **39**, $PdCl_2(dppf)$, 2 M NaOH, THF, 60 °C, 68%.

First, superior conditions for performing the Sonogashira reaction ($Pd(dba)_2$, CuI, PPh_3, triethylamine, 70 °C)[19] were discovered, resulting in a much better crude yield of the silyl enyne. A global desilylation was effected with excess TBAF. The resulting alcohol could then be reprotected with TBSOTf in the presence of triethylamine in dichloromethane at 0 °C to arrive at the enyne **41** in a much improved 75% yield for the three-step sequence. Treatment of the enyne **41** with bis-(cyclopentadienyl)-zirconium chloride hydride (Schwartz's reagent) to effect hydrozirconation followed by addition of catecholborane to transmetallate to the desired vinyl boronate **44** proceeded smoothly and in excellent yield. Suzuki coupling of the vinyl boronate **44** to the vinyl iodide **39** ($PdCl_2(dppf)$, 2 M NaOH, THF, 60 °C)[20] was carried out to afford the *E*-triene **45** in 68% yield.

With the *E*-triene **45** in hand, photoisomerization with a mercury lamp in the presence of a photosensitizer (benzanthrone) in a quartz tube was performed (Scheme 11). The *Z*-triene **43** was obtained in quantitative yield. Even though we ultimately wanted the *Z*-triene **43** to undergo a

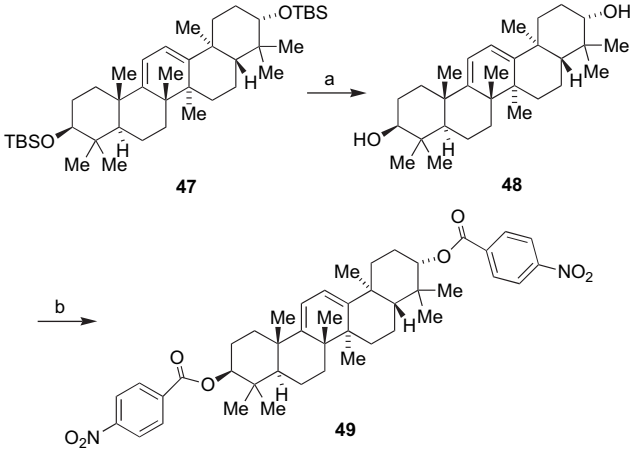


Scheme 11. Reagents and conditions: (a) hν (quartz), THF, benzanthrone, 84%; (b) DMF/1,2-$C_6H_4Cl_2$, sealed tube, 250 °C.

conrotatory six electron cyclization to achieve the desired *anti*-quaternary methyl groups in the C ring, we first tried thermal methods of disrotatory ring closure due to the reasonably similar precedent of Trost.[21] In his case, a less sterically hindered triene was able to cyclize under high heat. However, the initial attempt at heating **43** in *ortho*-dichlorobenzene and DMF (250 °C, sealed tube) gave a mixture of starting material and decomposition products arising from the HCl liberated in the breakdown of *ortho*-dichlorobenzene under the extreme heat instead of the desired diene **46**.

After this initial failure, a variety of other thermal experiments were conducted in an effort to prepare the diene **46** (Table 1). Microwave heating (entries 2–5) was investigated with solvents that had stable heating profiles, good solubility with the triene, and that facilitated monitoring the reaction by NMR. However, none of the runs furnished the diene **46**. Flash vacuum pyrolysis (FVP) was then utilized to try and effect triene cyclization (entries 6–10). Various vacuum strengths were explored at extreme temperatures to try to create as much intimate contact between the substrate and the hot tube as possible after injection of a solution of the triene **43** in diethyl ether. However, once again no cyclization was seen.

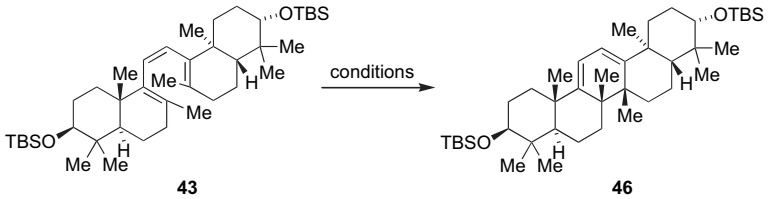
Since the thermal methods did not afford any of the cyclized substrate, we decided to switch to photochemical methods. A conrotatory photochemical cyclization was ultimately necessary to arrive at the *anti*-quaternary methyl groups, and it was thought that perhaps the excitation of the triene chromophore would more easily facilitate our sterically challenging cyclization where the thermal methods failed. Upon excitation of the triene **43**, a compound that appeared to be the desired C_2-symmetric pentacycle **47** by NMR and HRMS was isolated in 47% yield. However, the UV–vis spectrum of the isolated compound did not show absorbance typical of a *s*-cis diene in a ring, absorbing only up to about 245 nm. Therefore, it was necessary to obtain a crystal structure of the compound for structural verification. Deprotection of the TBS groups was effected with *p*-toluenesulfonic acid in 1:1 acetone/water, to afford what appeared to be the C_2-symmetric diol **48**. The corresponding bis-(*para*-nitrobenzoate) **49** (*p*-NO_2–C_6H_4COCl, pyr., DMAP, dichloromethane, 23 °C) was then prepared in good yield (Scheme 12). After much experimentation, very thin plate crystals of **49** were finally obtained from a 9:1 acetonitrile/hexanes solution. X-ray crystallographic analysis of the bis-(*p*-nitrobenzoate) **49** unambiguously showed that the triene **43** had cleaved by an unknown mechanism to give the simple olefin **50** (X-ray analysis performed on **51**) (Fig. 3).



Scheme 12. Reagents and conditions: (a) TsOH, 1:1 H_2O/acetone, 23 °C, 64%; (b) *p*-NO_2–C_6H_4COCl, pyr., DMAP, CH_2Cl_2, 23 °C, 93%.

At this point it was likely that enough energy was available to initiate photochemical transformations, but we wanted to temper the amount of energy to which the triene **43** was being exposed. Thus, a borosilicate NMR tube was used as the photolysis vessel as a thin filter against shorter wave UV and deuterobenzene (C_6D_6) was used as an internal filter as well (Table 2, entry 2). The consequence of this reaction was evidence of [1,5]-hydrogen shifts in a complex mixture of products. The identification of [1,5]-hydrogen shifts was confirmed by the similar findings of Parra[22] in his photochemical work toward the synthesis of oleanolic and maslinic acids. Looking more closely at the UV–vis spectrum of the triene, we decided to use filters to try and block out all wavelengths of light below the tail end of the absorbance

Table 1



Entry	Method	Conditions	Result
1	Sealed tube	DMF/1,2-$C_6H_4Cl_2$, 250 °C	SM+decomp.
2	μ-Wave	Hexanes, ~250 °C	SM+decomp.
3	μ-Wave	$CDCl_3$, ~250 °C	Complex mixture
4	μ-Wave	$CDCl_3$, ~200 °C	SM+decomp.
5	μ-Wave	C_7D_8, ~250 °C	SM
6	FVP (Et_2O carrier)	600 °C, <0.1 Torr	SM
7	FVP (Et_2O carrier)	600 °C, 30 Torr	SM
8	FVP (Et_2O carrier)	600 °C, 50 Torr	SM
9	FVP (Et_2O carrier)	600 °C, 100 Torr	SM
10	FVP (Et_2O carrier)	600 °C, 100 Torr, 6″ path of glass beads	SM

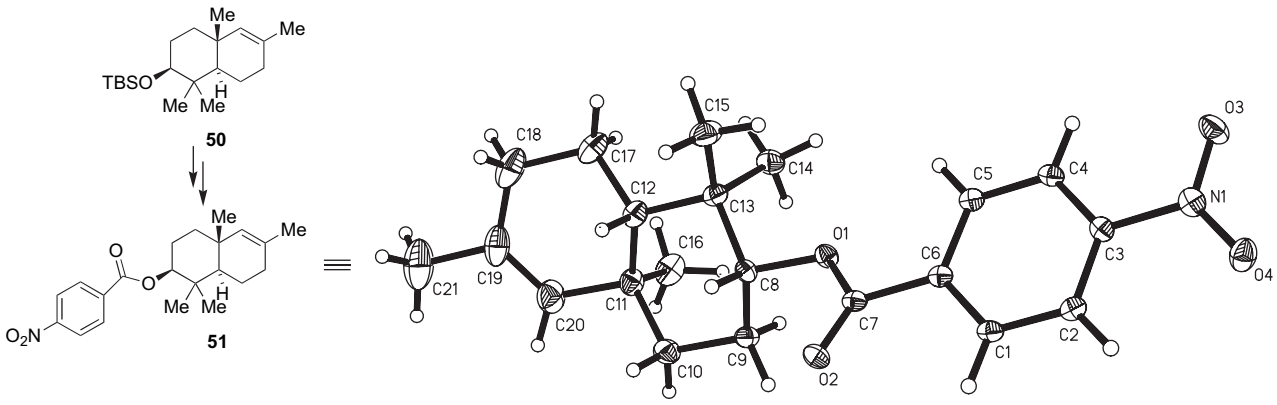
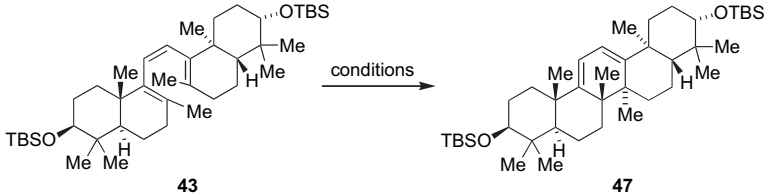


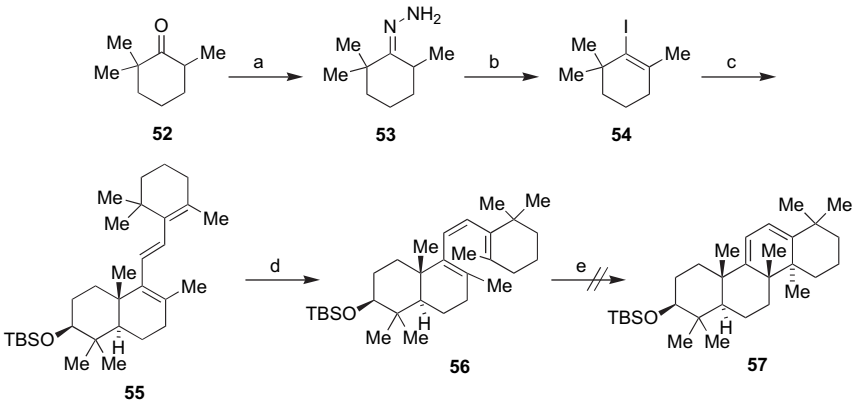
Figure 3.

Table 2



Entry	Method	Conditions	Result
1	Photolysis	THF, quartz tube	47% Cleavage product
2	Photolysis	C_6D_6, NMR tube, 3 h	[1,5]-Hydrogen shifts
3	Photolysis	C_6D_6, NMR tube, <330 nm filter, 4 h	SM
4	Photolysis	C_6D_6, NMR tube, <330 nm filter, 12 h	[1,5]-Hydrogen shifts
5	Photolysis	CD_3OD, NMR tube, <330 nm filter, 4 h	SM
6	Photolysis	CD_3OD, NMR tube, <330 nm filter, 12 h	SM
7	Photolysis	C_6D_6, 9,10-dicyanoanthracene, NMR tube, 12 h	SM
8	Reflux	PhSSPh, AIBN, PhH	SM
9	Reflux	DDQ, CH_2Cl_2	Complex mixture
10	70 °C	$Pd_2(dba)_3$, PPh_3, AcOH, PhH	SM
11	110 °C	$Pd(OAc)_2$, PhMe	SM
12	−78 to 23 °C	Cp_2ZrCl_2, *n*BuLi, THF	SM
13	60 °C	$Ni(COD)_2$, PPh_3, PhMe	SM

(entries 3–6). With the filters in place, no reaction was observed, except in the case of prolonged photolysis in C_6D_6, in which some [1,5]-hydrogen shifts had begun to take place. In hopes of activating the triene with a photooxidant, 9,10-dicyanoanthracene was employed (entry 7), but once again only starting material was obtained. Attempts were made to induce a radical cyclization through the use of diphenyl disulfide (entry 8) and a oxidative cyclization with DDQ (entry 9); however, both reactions failed. Several organometallic reagents were also employed that have been known



Scheme 13. Reagents and conditions: (a) H_2NNH_2, TEA, EtOH, reflux; (b) DBU, I_2, Et_2O, 23 °C; DBU, PhH, reflux, 76% (two steps); (c) **44**, $PdCl_2$(dppf), 2 M NaOH, THF, 60 °C, 72%; (d) hν, benzanthrone, THF, 82%; (e) hν, C_6D_6, 0%.

to promote metal-mediated oxidative cyclizations but all were unsuccessful.[23–26]

Although conditions to induce the desired cyclization were exhaustively attempted, we decided to perform the cyclization on a smaller analogue of the triene **43** to completely rule out steric complications from the larger analogue as the reason for the failure of the cyclization (Scheme 13). Repeating the same synthetic scheme as before, commercially available 2,2,6-trimethylcyclohexanone **52** was treated with hydrazine and triethylamine in refluxing ethanol to give the hydrazone **53**, which was then converted into the vinyl iodide **54** with DBU and iodine in 76% yield over the two steps. The vinyl iodide **54** was then coupled to the vinyl boronate **44** via a Suzuki reaction ($PdCl_2$(dppf), 2 M NaOH, THF, 60 °C) to give the *E*-triene **55** in 72% yield. This triene was then photolyzed in the presence of benzanthrone to effect isomerization to the *Z*-triene **56**. However, using the same photochemical conditions employed in Table 2 (entries 3–7), no cyclization of **56** to the diene **57** was observed. Consequently, we decided to abandon all work in this area, one step away from completing the synthesis of the pentacyclic core.

3. Conclusion

In conclusion, we have shown that the advanced bicyclic aldehyde **11**, the iodide **39**, and the silyl diene **31** can all be readily prepared in good overall yield and have proven to be very amenable to transformation into key compounds for a variety of synthetic pathways. Although Suzuki coupling of the advanced intermediates could be accomplished as well as photoisomerization to the potentially reactive *Z*-triene, final cyclization could not be achieved, despite extensive use of thermal, photochemical, and chemical means. The heavy steric interactions in the vicinity of the methyl groups on the olefins as well as the number of 1,3-diaxial interactions in the ring system all worked against the cyclization and formation of the *anti*-quaternary methyl groups.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether were both distilled from sodium benzophenone-ketyl. Dichloromethane, benzene, and toluene were all distilled from calcium hydride. Methanol was distilled from magnesium. Pyridine and triethylamine were both distilled from calcium hydride and diisopropylamine from NaOH. All reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise stated. Flash chromatography was performed using ACS certified solvents and Merck silica gel 60, mesh 230–400. Proton and carbon NMR spectra were obtained using a Brüker Avance 500 MHz, a Brüker ARX 400 MHz, or a Brüker ARX 500 MHz spectrometer. The signals are reported in parts per million relative to $CDCl_3$. The chemical shifts are reported in parts per million (ppm, δ). The coupling constants are reported in Hertz (Hz) using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. When the signals are broad, the designation 'b' is placed before the multiplicity. FT-IR spectra were obtained using either a Nicolet 510p or Nicolet Avatar 370 FT-IR spectrometer using liquid films (neat) on NaCl plates. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were recorded on a VG Analytical Autospec double focusing instrument using electron impact (EI) or chemical ionization (CI) techniques. The X-ray crystal structure was elucidated by Dr. Saeed Khan on a Brüker Smart 1000 CCD diffractometer equipped with a low temperature device from Oxford Cryosystems Model 600.

4.1.1. 3,4,8,8a-Tetrahydro-5,8a-dimethylnaphthalen-1(2*H*),6(7*H*)-dione (15). To a stirring solution of commercially available 2-methyl-1,3-cyclohexanedione **14** (5 g, 39.6 mmol), methanol (18 mL), and two pellets of KOH was added commercially available ethyl vinyl ketone (6.3 mL, 63.4 mmol) and the mixture heated to 40 °C. After 5 h, the solvent was removed in vacuo and excess water was removed azeotropically with three washings of benzene. To the crude residue was added benzene (21 mL) and pyrrolidine (0.37 mL, 4.4 mmol), and the mixture was heated to reflux overnight with a Dean–Stark trap. The solvent was removed in vacuo and the residue diluted with ether. The organic extract was washed once with a solution of 5% aqueous HCl, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo and the residue vacuum distilled (154–157 °C, <1 mmHg) to yield the diketone **15** as a pale yellow oil (4.6 g, 61%). The spectral data matched that of the compound reported in the literature.[13] IR (neat) 2953, 2872, 1711, 1686, 1611, 1455, 1421, 1356, 1308, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.80 (ddd, J=15.9, 4.9, 4.9 Hz, 1H), 2.61 (m, 1H), 1.91–2.52 (m, 8H), 1.73 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 197.7, 158.3, 130.7, 50.6, 33.7, 33.3, 29.4, 27.3, 23.4, 21.5, 11.3.

4.1.2. (±)-3′,4′,8′,8′a-Tetrahydro-5′,8′a-dimethylspiro-[1,3-dioxolane-2,1′-naphthalen]-6′(7′*H*)-one (16). A solution of the diketone **15** (1.67 g, 8.7 mmol), *p*-toluenesulfonic acid (1.7 g, 9 mmol), ethylene glycol (51 mL), and 4 Å MS was stirred at 23 °C overnight. The reaction mixture was poured into a solution of ice and saturated $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to afford the ketal **16** as a pale yellow oil (2.01 g, 98%). The spectral data matched that of the compound reported in the literature.[27] IR (neat) 2950, 2878, 1734, 1665, 1181, 1092, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87–3.98 (m, 4H), 2.70 (br d, J=19.6 Hz, 1H), 1.53–2.65 (m, 9H), 1.75 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 160.3, 130.1, 112.8, 65.3, 65.1, 45.3, 33.7, 29.7, 26.5, 26.4, 21.4, 20.9, 11.4; HRMS (EI) m/e (M^+) calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1420.

4.1.3. (±)-(4′a*S*,6′*S*,8′a*S*)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-5′,5′,8′′-trimethylspiro[1,3-dioxolane-2,1′-naphthalen]-6′-ol (17). A solution of the ketal **16** (7.6 g, 32.2 mmol) in THF (140 mL) was slowly added to a stirring solution of lithium metal (1.47 g, 209 mmol) in NH_3 (500 mL), and the resulting anion allowed to stir for 45 min. A solution of methyl iodide (30.1 mL, 483 mmol) in THF (60 mL) was added via syringe

to the reaction, and the resulting mixture allowed to stir for 45 min. To the white slurry was added lithium metal (6.3 g, 900 mmol) and the solution allowed to stir for 30 min. Methanol (50 mL) was added followed by 200 mL of ether, and the system was opened to the atmosphere overnight. A solution of 10% aqueous HCl was slowly added to the slurry before extracting three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Solvents were removed in vacuo and the resulting residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to yield the alcohol **17** as a clear, colorless oil (4.43 g, 54%). The spectral data matched that of the compound reported in the literature.[27] IR (neat) 3428 (br s), 2943, 2872, 1451, 1175, 1105, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79–3.94 (m, 4H), 3.24 (bdd, J=11.1, 4.3 Hz, 1H), 1.25–1.72 (m, 11H), 1.05 (s, 3H), 0.98 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 78.7, 65.3, 64.8, 48.2, 43.1, 38.8, 30.4, 28.7, 28.0, 27.1, 23.1, 20.6, 16.5, 15.4; HRMS (EI) *m/e* (M^+) calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1867.

4.1.4. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-hydroxy-5,5,8a-trimethylnaphthalen-1(2*H*)-one (18). A solution of the alcohol **17** (697 mg, 2.74 mmol), *p*-toluenesulfonic acid (521 mg, 2.74 mmol), and 1:1 acetone/water (14 mL) was stirred together at 23 °C overnight. The solution was poured into a solution of ice and saturated $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Solvents were removed in vacuo to yield the ketone **18** as a clear, colorless oil (576 mg, 100%). The spectral data matched that of the compound reported in the literature.[27] IR (neat) 3447 (br s), 2940, 2869, 1701, 1458, 1113, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (m, 1H), 2.54 (ddd, J=14.0, 14.0, 7.0 Hz, 1H), 2.17 (br d, J=14.0 Hz, 1H), 2.02–2.10 (m, 1H), 1.42–1.79 (m, 8H), 1.12 (s, 3H), 0.99 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 78.1, 52.6, 48.6, 37.4, 31.2, 30.9, 27.8, 26.9, 26.2, 20.7, 18.6, 15.8; HRMS (EI) *m/e* (M^+) calcd for $C_{13}H_{22}O_2$ 210.1612, found 210.1613.

4.1.5. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-5,5,8a-trimethylnaphthalen-1(2*H*)-one (19). To a stirring solution of the ketone **18** (3.3 g, 15.7 mmol), pyridine (5.08 mL, 62.8 mmol), and dichloromethane (27 mL) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.61 mL, 15.7 mmol). The solution was allowed to warm to 23 °C and stirred overnight. The solvent was removed in vacuo and the residue taken up in ether and a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed once with a solution of 10% aqueous $CuSO_4$, once with brine, and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to afford the TBS ether **19** as an oily, white solid (4.2 g, 83%). The spectral data matched that of the compound reported in the literature.[28] IR (neat) 2934, 2855, 1703, 1462, 1250, 1100, 1076, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.15 (m, 1H), 2.56 (ddd, J=14.0, 14.0, 7.0 Hz, 1H), 2.18 (br d, J=14.0 Hz, 1H), 2.03–2.09 (m, 1H), 1.47–1.80 (m, 8H), 1.14 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.86 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 78.7, 52.7, 48.6, 40.3, 37.5, 31.1, 28.4, 27.3, 26.4, 25.9, 21.0, 18.7, 18.1, 16.3, −3.8, −5.0; HRMS (EI) *m/e* (M^+) calcd for $C_{19}H_{36}O_2Si$ 324.2485, found 324.2493.

4.1.6. (±)-(2*R*,4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1(2*H*)-one (21). To a stirring solution of diisopropylamine (3.7 mL, 26.2 mmol) in THF (40 mL) cooled to 0 °C was added *n*-butyllithium (11.2 mL, 14.4 mmol, 1.28 M in hexanes). The solution was allowed to warm to 23 °C and stirred for 30 min before being cooled to −78 °C. A solution of the TBS ether **19** (4.25 g, 13.1 mmol) in THF (5 mL) was then added dropwise at −78 °C and the resulting solution allowed to warm to 23 °C and stirred for 45 min. The solution was then cooled to −78 °C and methyl iodide (8.2 mL, 131 mmol) was added and the solution allowed to warm to 23 °C and stirred for 3 h. The reaction was quenched with a saturated solution of $Na_2S_2O_3$ and extracted three times with ether. The combined organic extracts were washed once with a solution of 10% aqueous $CuSO_4$, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo to yield both diastereomers of the ketone **20** as a crude, orange-brown oil (4.43 g, 100%).

To a stirring solution of methanol (225 mL) and sodium metal (3 g, 131 mmol) at 23 °C was added a solution of the ketone **20** (4.43 g, 13.1 mmol) in methanol (25 mL) and the resulting mixture was allowed to stir overnight. The solvent was removed in vacuo and the crude residue diluted with ether and water and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to yield the ketone **21** as an oily, white solid (4.3 g, 97%). IR (neat) 2851, 1703, 1674, 1470, 1388, 1250, 1070, 1026, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.07 (dd, J=10.0, 5.1 Hz, 1H), 2.57 (ddq, J=13.0, 6.5, 6.5 Hz, 1H), 2.02 (m, 1H), 1.40–1.70 (m, 8H), 1.04 (s, 3H), 0.92 (d, J=6.5 Hz, 3H), 0.83 (s, 3H), 0.81 (s, 9H), 0.80 (s, 3H), −0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 78.6, 53.2, 48.1, 40.1, 39.6, 35.6, 31.1, 28.1, 27.2, 25.7, 21.1, 18.6, 17.9, 16.1, 14.8, −4.0, −5.2; HRMS (EI) *m/e* (M^+) calcd for $C_{20}H_{38}O_2Si$ 338.2641, found 338.2647.

4.1.7. (±)-(6*S*,4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-carboxaldehyde (11). To a stirring solution of diisopropylamine (2.5 mL, 17.9 mmol) and THF (9 mL) cooled to 0 °C was added *n*-butyllithium (5.6 mL, 8.9 mmol, 1.6 M in hexanes). The solution was allowed to stir for 30 min before being cooled to −95 °C. A solution of the ketone **21** in dichloromethane (9 mL) was added dropwise to the mixture and it was allowed to gradually warm to −20 °C over 2 h. The reaction mixture was then refluxed for 1 h, cooled to 0 °C, and the solvents removed in vacuo. To the crude residue was added hexamethylphosphoramide (17 mL), lithium perchlorate (951 mg, 8.9 mmol), calcium carbonate (1.12 g, 11.2 mmol), and the mixture was heated with stirring to 130 °C for 1.5 h. After the reaction mixture cooled, it was diluted with water and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was

removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to yield the aldehyde **11** as a brownish yellow oil (634 mg, 45%). IR (neat) 2945, 2856, 1676, 1472, 1389, 1253, 1105, 836, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.2 (s, 1H), 3.19 (dd, J=11.4, 4.7 Hz, 1H), 2.57 (ddd, J=13.4, 3.6, 3.6 Hz, 1H), 2.26 (m, 1H), 2.02 (s, 3H), 0.74–1.73 (m, 7H), 1.14 (s, 3H), 0.94 (s, 3H), 0.88 (s, 9H), 0.78 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 154.2, 143.4, 79.1, 51.0, 39.5, 37.3, 36.8, 34.2, 28.6, 28.0, 25.9, 20.1, 19.0, 18.3, 18.1, 16.0, −3.7, −5.0; HRMS (EI) *m/e* (M−H) calcd for $C_{21}H_{37}O_2Si$ 349.2563, found 349.2568.

4.1.8. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-α-(trimethylsilyloxy)-2,5,5,8a-tetramethylnaphthalene-1-acetonitrile (22). To a stirring solution of the aldehyde **11** (95.8 mg, 0.27 mmol), zinc iodide (4 mg, 0.016 mmol), and dichloromethane (0.5 mL) at 23 °C was added trimethylsilyl cyanide (43 μL, 0.32 mmol). The mixture was allowed to stir for 24 h. The reaction was quenched with pH 7 buffer and extracted three times with dichloromethane. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to yield the TMS cyanohydrin **22** as a light brown oil (118 mg, 96%). IR (neat) 2956, 2857, 2231, 1641, 1472, 1362, 1254, 1106, 842, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 3.21 (m, 1H), 2.10 (m, 1H), 1.85 (s, 3H), 1.49–1.80 (m, 8H), 1.01 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.76 (s, 3H), 0.26 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

4.1.9. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-α-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-acetonitrile (23). To a stirring solution of the aldehyde **11** (125 mg, 0.35 mmol), zinc iodide (4 mg, 0.016 mmol), and dichloromethane (0.6 mL) at 23 °C was added *tert*-butyldimethylsilyl cyanide (59 mg, 0.42 mmol). The mixture was allowed to stir for 24 h. The reaction was quenched with pH 7 buffer and extracted three times with dichloromethane. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to yield the TBS cyanohydrin **23** as a colorless oil (84 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 1H), 3.22 (m, 1H), 2.10 (m, 1H), 1.83 (s, 3H), 1.22–1.71 (m, 8H), 1.03 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 120.6, 79.0, 58.5, 50.9, 50.8, 39.4, 38.6, 34.8, 34.1, 32.4, 28.5, 27.9, 25.9, 22.5, 20.1, 19.2, 18.6, 18.1, 16.0, −2.9, −3.5, −5.0, −5.2.

4.1.10. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-methanol (26). A mixture of the aldehyde **11** (117 mg, 0.33 mmol), sodium borohydride (6.5 mg, 0.17 mmol), and ethanol (3.3 mL) was stirred together at 23 °C overnight. The reaction mixture was poured into water and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to afford the alcohol **26** as a colorless oil (80 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (d, J=11.4 Hz, 1H), 4.01 (d, J=11.4 Hz, 1H), 3.20 (dd, J=10.9, 5.1 Hz, 1H), 2.05 (m, 2H), 1.85 (dt, J=12.9, 3.3 Hz, 1H), 1.70 (s, 3H), 1.35–1.67 (m, 6H), 0.95 (s, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.76 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 132.5, 79.3, 58.2, 50.9, 39.3, 37.7, 34.9, 34.0, 28.5, 28.0, 25.9, 20.7, 19.2, 18.8, 18.1, 15.9, −3.8, −5.0. HRMS (EI) *m/e* (M+Na) calcd for $C_{21}H_{42}O_2SiNa$ 375.2690, found 375.2685.

4.1.11. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-1-Bromomethyl-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (27). To a stirring solution of the allylic alcohol **26** (193 mg, 0.55 mmol) and carbon tetrabromide (202 mg, 0.61 mmol) in dichloromethane (5.5 mL) cooled to 0 °C was added triphenylphosphine (160 mg, 0.61 mmol). The reaction was allowed to warm to 23 °C and stirred for 2.5 h. Celite was added to the reaction mixture and the solvent was removed in vacuo. The solid mixture was purified by flash chromatography on a very short column of silica gel (90% hexanes/ethyl acetate) to afford the bromide **27** as a colorless oil (109 mg, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (1H, d, J=10.0 Hz), 3.97 (1H, d, J=10.0 Hz), 3.20 (1H, m), 2.12 (2H, m), 1.39–1.90 (7H, m), 1.72 (3H, s), 1.00 (3H, s), 0.97 (3H, s), 0.90 (9H, s), 0.78 (3H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 126.7, 79.3, 50.7, 48.1, 39.8, 37.5, 36.9, 35.8, 28.1, 25.9, 24.1, 21.2, 20.8, 18.1, 15.9, −3.7, −4.9.

4.1.12. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-α,2,5,5,8a-pentamethylnaphthalene-1-methanol (29). To a stirring solution of the aldehyde **11** (141 mg, 0.40 mmol) in ether (1.4 mL) cooled to 0 °C was added methyllithium (0.57 mL, 0.80 mmol, 1.4 M in ether). The solution was allowed to warm to 23 °C and stirred for 1 h. The reaction was quenched with a solution of 15% aqueous NH_4Cl and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was removed in vacuo to yield a diastereomeric mixture of the two alcohols **29** as a colorless oil (139 mg, 95%). ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (q, J=6.7 Hz, 1H), 4.60 (q, J=6.8 Hz, 1H), 3.24 (m, 2H), 2.06 (m, 4H), 1.87 (s, 3H), 1.85 (s, 3H), 1.52–1.76 (m, 9H), 1.45 (d, J=6.8 Hz, 3H), 1.43 (d, J=6.7 Hz, 3H), 1.05–1.38 (m, 5H), 0.98 (s, 3H), 0.96 (s, 3H), 0.93 (s, 9H), 0.80 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 143.5, 130.7, 129.3, 79.1, 79.0, 66.1, 65.7, 51.5, 50.9, 39.3, 38.6, 35.4, 34.9, 28.6, 28.1, 25.8, 23.8, 20.5, 20.1, 18.7, 18.0, 16.0, −3.9, −5.1. HRMS (EI) *m/e* (M+Na) calcd for $C_{22}H_{42}O_2SiNa$ 389.2846, found 389.2840.

4.1.13. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene-1-ethanone (30). To a stirring solution of Dess–Martin periodinane (208 mg, 0.49 mmol) in dichloromethane (3 mL) at 23 °C was added the alcohol **29** (139 mg, 0.38 mmol) in dichloromethane (1 mL). The mixture was allowed to stir for 1 h, poured into a 1:1 mixture of a saturated solution of $NaHCO_3$ and a solution of 10%

aqueous $NaHSO_3$, and extracted three times with dichloromethane. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to afford the enone **30** as a colorless oil (110 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 (dd, J=11.3, 4.7 Hz, 1H), 2.23 (s, 3H), 2.04 (m, 2H), 1.52 (s, 3H), 1.50–1.74 (m, 5H), 1.45 (dd, J=13.0, 3.6, 3.6 Hz, 1H), 1.36 (dd, J=13.0, 13.0, 3.6 Hz, 1H), 1.20 (s, 3H), 0.91 (s, 3H), 0.86 (s, 9H), 0.76 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.4, 146.4, 127.4, 79.1, 49.8, 39.4, 36.8, 35.2, 33.7, 32.1, 28.3, 27.7, 25.8, 20.5, 20.1, 18.4, 18.0, 15.7, −3.9, −5.1. HRMS (EI) *m/e* (M+H) calcd for $C_{22}H_{41}O_2Si$ 365.2870, found 365.2879.

4.1.14. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-1-(1-[(1,1-dimethylethyl)dimethylsilyloxy]ethenyl)-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (31). To a stirring solution of the enone **30** (94 mg, 0.26 mmol), triethylamine (0.11 mL, 0.78 mmol), and dichloromethane (2.6 mL) cooled to 0 °C was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.09 mL, 0.39 mmol). The solution was allowed to warm to 23 °C and stirred for 2.5 h. The solvents were removed in vacuo and the residue taken up in ether and extracted three times from a saturated solution of $NaHCO_3$. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate with 2% triethylamine buffer) to afford the silyl enol ether **31** as a colorless oil (122 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (s, 1H), 3.91 (s, 1H), 3.26 (dd, J=11.2, 4.6 Hz, 1H), 2.10 (m, 2H), 1.70 (s, 3H), 1.32–1.74 (m, 5H), 1.10–1.15 (m, 2H), 0.98 (s, 3H), 0.97 (s, 9H), 0.95 (s, 3H), 0.93 (s, 9H), 0.84 (s, 3H), 0.25 (s, 3H), 0.23 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 141.7, 128.5, 125.0, 79.7, 50.3, 39.4, 35.5, 32.4, 31.5, 28.5, 28.2, 25.6 (2 C's), 22.5, 20.9, 18.6, 17.9, 15.8, 14.0, −3.1, −3.9, −4.7, −5.1.

4.1.15. Methyl (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-5,5,8a-trimethylnaphthalene-2-carboxylate (34). To a freshly washed slurry of NaH (1.4 g, 31.12 mmol, 55% w/w) and KH (five drops, 35% w/w) in THF (97 mL) was added dimethyl carbonate (2 mL, 23.3 mmol). A solution of the ketone **19** (2.5 g, 7.78 mmol) in THF (5 mL) was then added and the combined solution heated to reflux overnight. The solution was cooled to 0 °C and quenched with a solution of 15% aqueous ammonium chloride and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to afford the β-keto ester **32** as a crude, brown oil. The crude β-keto ester **32** was dissolved in methanol (78 mL), cooled to 0 °C, and sodium borohydride (194 mg, 5.13 mmol) was added. The reaction mixture was stirred at 0 °C for 6 h and quenched with a saturated solution of ammonium chloride and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo to furnish the β-hydroxy ester **33** as a crude, brown oil. The crude β-hydroxy ester **33** was dissolved in pyridine (78 mL) and stirred at 23 °C before phosphorus oxychloride (2.2 mL, 23.3 mmol) was added and the mixture heated to 80 °C for 4 h. The solvent was then removed in vacuo and the crude residue dissolved in ether and a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with a solution of 10% aqueous $CuSO_4$, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (95% hexanes/ethyl acetate) to afford the α,β-unsaturated ester **34** as a clear, colorless oil (610.7 mg, 22%, three steps). IR (neat) 2951, 2855, 1747, 1717, 1472, 1389, 1250, 1106, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 1H), 3.70 (s, 3H), 3.20 (dd, J=11.3, 6.6 Hz, 1H), 1.25–1.78 (m, 9H), 0.98 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.76 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 150.7, 126.6, 79.3, 51.5, 49.2, 39.2, 36.5, 35.6, 28.2, 27.9, 26.1, 25.9, 20.5, 18.3, 18.1, 15.9, −3.8, −5.0; HRMS (EI) *m/e* (M^+) calcd for $C_{21}H_{38}O_3Si$ 366.2590, found 366.2593.

4.1.16. 1-(1-[(1,1-Dimethylethyl)dimethylsilyloxy]-ethenyl)-2-methylcyclohexene (37). To a stirring solution of the enone **36** (424 mg, 3.07 mmol), prepared according to the literature,[16] and triethylamine (1.3 mL, 9.2 mmol) in dichloromethane (15 mL) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.06 mL, 4.6 mmol). The solution was allowed to warm to 23 °C and stirred for 2 h. The reaction mixture was diluted with ether and quenched with a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to afford the silyl enol ether **37** as a crude, pale yellow oil (774 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (d, J=2.9 Hz, 1H), 4.10 (d, J=2.9 Hz, 1H), 2.11 (m, 2H), 1.98 (m, 2H), 1.76 (s, 3H), 1.58–1.65 (m, 4H), 0.92 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 136.1, 128.5, 94.1, 31.8, 28.0, 25.7, 22.9, 21.4, 18.2, 18.1, −3.0. HRMS (EI) *m/e* (M+H) calcd for $C_{15}H_{29}OSi$ 253.1982, found 253.1982.

4.1.17. (±)-(2*S*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-5-iodo-2-[(1,1-dimethylethyl)dimethylsilyloxy]-1,1,4a,6-tetramethylnaphthalene (39). A stirring solution of the ketone **21** (474 mg, 1.4 mmol), hydrazine (2.2 mL, 70 mmol), acetic acid (0.4 mL, 7 mmol), and ethanol (5 mL) was refluxed overnight. The mixture was cooled to 23 °C, diluted with ether and water, and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to afford the hydrazone as an oily, white solid (377 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (br s, 2H), 3.16 (dd, J=10.0, 5.5 Hz, 1H), 3.00 (m, 1H), 1.85 (ddd, J=13.5, 3.3, 3.3 Hz, 1H), 1.37–1.69 (m, 8H), 1.16 (d, J=5.5 Hz, 3H), 1.12 (s, 3H), 0.91 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 79.2, 52.4, 42.1, 39.8, 34.8, 32.6, 28.5, 27.7, 25.9, 21.7, 18.4, 18.1, 17.6, 16.1, 14.1, −3.8, −4.9. To a stirring solution of the hydrazone (79.4 mg, 0.22 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.66 mL, 4.4 mmol) in ether (3 mL) at 23 °C was added iodine (122 mg,

0.48 mmol). The solution was allowed to stir for 30 min before being quenched with a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Solvents were removed in vacuo and the crude residue dissolved in toluene (3 mL) and DBU (0.16 mL, 1.1 mmol). The solution was then heated at 85–90 °C for 5 h before the solvent was removed in vacuo. The residue was dissolved in ether and washed once with a saturated solution of $Na_2S_2O_3$, once with brine, and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to afford the iodide **39** as an oily, white solid (76.3 mg, 76%). IR (neat): 2950, 2855, 2708, 2646, 1709, 1631, 1472, 1252, 1105, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.21 (m, 1H), 2.17–2.26 (m, 1H), 1.85 (s, 3H), 1.45–1.86 (m, 5H), 1.30 (dd, J=12.4, 1.8 Hz, 1H), 1.14–1.27 (m, 2H), 1.01 (s, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.77 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 120.7, 79.3, 51.3, 42.7, 42.1, 39.5, 35.1, 30.6, 28.6, 28.4, 26.0, 19.9, 18.9, 18.1, 15.9, −3.7, −4.9; HRMS (EI) *m/e* (M^+) calcd for $C_{20}H_{37}OISi$ 448.1658, found 448.1641.

4.1.18. (±)-(4a*S*,6*S*,8a*S*)-1-Ethynyl-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (41). To a stirring solution of the vinyl iodide **39** (1.96 g, 4.36 mmol), bis(dibenzylideneacetone)palladium(II) (50 mg, 0.087 mmol), copper(I) iodide (33 mg, 0.17 mmol), triphenylphosphine (114 mg, 0.44 mmol), and triethylamine (87 mL) was added (trimethylsilyl)acetylene (0.62 mL, 4.36 mmol). After the mixture was heated to 70 °C overnight, it was filtered through Celite with ether and the solvents removed in vacuo to afford the TMS enyne **40** as a crude, black oil. The crude TMS enyne **40** was dissolved in THF (44 mL) and tetrabutylammonium fluoride (5.2 mL, 5.2 mmol, 1 M in THF) was added with stirring at 23 °C. The reaction mixture was stirred overnight and the mixture was poured into a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford a crude, brown oil. The crude oil was dissolved in dichloromethane (15 mL) and triethylamine (1.8 mL, 13 mmol) and cooled to 0 °C before *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.99 mL, 4.33 mmol) was added. The reaction was allowed to warm to 23 °C and stirred for 3 h, diluted with ether and a saturated solution of sodium bicarbonate, and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford the enyne **41** as an oily, white solid (1.12 g, 75%, three steps). IR (neat) 3311, 2950, 2856, 2087, 1472, 1361, 1255, 1105, 1070, 883, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.26 (dd, J=10.8, 5.3 Hz, 1H), 3.07 (s, 1H), 2.09–2.22 (m, 2H), 2.05 (ddd, J=13.4, 3.5, 3.5 Hz, 1H), 1.89 (s, 3H), 1.59–1.79 (m, 4H), 1.51 (dddd, J=12.5, 11.4, 11.4, 6.7 Hz, 1H), 1.32 (ddd, J=13.4, 13.4, 4.6 Hz, 1H), 1.11 (s, 3H), 0.97 (s, 3H), 0.94 (s, 9H), 0.82 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 126.2, 81.7, 80.3, 79.2, 49.8, 39.3, 36.5, 36.1, 33.1, 28.3, 28.1, 25.8, 21.9, 20.4, 18.3, 18.0, 15.7, −3.9, −5.1; HRMS (EI) *m/e* (M^+) calcd for $C_{22}H_{38}OSi$ 346.2692, found 346.2702.

4.1.19. Bis-(±)-[(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1-yl]ethyne (42). To a stirring solution of the enyne **41** (61.5 mg, 0.14 mmol), copper(I) iodide (8 mg, 0.04 mmol), bis(triphenylphosphine)palladium(II) chloride (14 mg, 0.02 mmol), and triethylamine (4 mL) at 23 °C was added a solution of the vinyl iodide **39** (46 mg, 0.20 mmol) in triethylamine (1 mL). The resulting solution was allowed to stir overnight. The reaction mixture was filtered through a plug of silica gel with ethyl acetate and the solvents removed in vacuo. The crude residue was purified by flash chromatography on silica gel (100% hexanes) to afford the dienyne **42** as an oily, white solid (11 mg, 14%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.20 (m, 2H), 2.14 (m, 4H), 1.98 (ddd, J=13.4, 3.1, 3.1 Hz, 2H), 1.86 (s, 3H), 1.85 (s, 3H), 1.19–1.75 (m, 12H), 1.06 (s, 6H), 0.92 (s, 6H), 0.89 (s, 18H), 0.76 (s, 6H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 126.9, 79.9, 79.4, 77.6, 50.0, 39.4, 37.3, 36.4, 28.4, 28.2, 25.9, 22.4, 21.0, 18.1, 15.9, −3.8, −4.9; HRMS (EI) *m/e* (M^+) calcd for $C_{42}H_{74}O_2Si_2$ 666.5227, found 666.5231.

4.1.20. (±)-*E*-(4a*S*,6*S*,8a*S*)-1-[2-(1,3-Benzodioxaborolyl)-ethenyl]-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalene (44). To a stirring solution of the enyne **41** (268 mg, 0.77 mmol), Schwartz's reagent (119 mg, 0.46 mmol), and dichloromethane (8 mL) at 23 °C in the dark was added catecholborane (0.13 mL, 1.2 mmol) dropwise. The solution was allowed to stir overnight in the dark. The reaction mixture was diluted with ether and a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (70% hexanes/ethyl acetate) to furnish the boronate **44** as a clear, colorless oil (345 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=18.6 Hz, 1H), 7.22 (dd, J=5.9, 3.3 Hz, 2H), 7.07 (dd, J=5.9, 3.3 Hz, 2H), 5.71 (d, J=18.6 Hz, 1H), 3.22 (dd, J=11.2, 4.8 Hz, 1H), 2.14 (m, 2H), 1.77 (ddd, J=13.1, 3.4, 3.4 Hz, 1H), 1.72 (s, 3H), 1.20–1.65 (m, 5H), 1.15 (dd, J=12.5, 1.9 Hz, 1H), 1.10 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.3, 122.5, 121.2, 115.5, 112.2, 79.3, 50.4, 39.6, 37.6, 36.4, 34.0, 28.4, 28.1, 25.9, 21.2, 20.4, 18.7, 18.1, 15.9, −3.8, −4.9 (one downfield carbon not observed).

4.1.21. (±)-*E*-Bis-1,2-[(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1-yl]ethylene (45). A solution of the vinyl boronate **44** (247 mg, 0.53 mmol), the vinyl iodide **39** (260 mg, 0.58 mmol), dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) (22 mg, 0.027 mmol), 2 M NaOH (0.27 mL, 0.53 mmol), and THF (6 mL) was stirred together at 23 °C for 1 h before being heated to 60 °C overnight. The solution was diluted with a saturated solution of $NaHCO_3$ and extracted three times with ether. The combined

organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford the *E*-triene **45** as an oily, white solid (282 mg, 80%, two steps, tiny amount of *Z*-**43** present). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H) (*E*), 5.05 (s, 1H) (*Z*), 3.21 (m, 2H), 1.84 (s, 6H), 1.27–2.25 (m, 18H), 1.01 (s, 6H), 0.94 (s, 3H), 0.93 (s, 3H), 0.89 (s, 18H), 0.77 (s, 6H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (2 C's), 135.2 (2 C's), 126.6 (*E*), 120.7 (*Z*), 79.4, 79.3, 51.3 (2 C's), 42.7 (2 C's), 39.5, 35.1 (2 C's), 31.6 (2 C's), 30.6 (2 C's), 28.4 (2 C's), 25.9 (2 C's), 22.7 (2 C's), 21.8, 19.8 (2 C's), 18.1 (2 C's), 15.9 (2 C's), 14.1 (2 C's), −3.8 (2 C's), −4.9 (2 C's).

4.1.22. (±)-*Z*-Bis-1,2-[(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethylnaphthalen-1-yl]ethylene (43). A stirring solution of the *E*-triene **45** (282 mg, 0.42 mmol), benzanthrone (145 mg, 0.63 mmol), and THF (42 mL) was photolyzed with a medium pressure Hanovia mercury arc lamp in a Pyrex immersion well at ≥290 nm for 24 h. The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to furnish the *Z*-triene **43** as an oily, white solid (236 mg, 84%). IR (neat) 2936, 2855, 1472, 1462, 1389, 1253, 1105, 1071, 883, 885, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 2H), 3.21 (m, 2H), 1.94–2.23 (m, 3H), 1.84 (s, 6H), 1.21–1.72 (m, 15H), 1.06 (s, 6H), 0.94 (s, 6H), 0.89 (s, 18H), 0.78 (s, 6H), 0.05 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (all 2 C's) 136.6, 135.2, 120.7, 79.3, 51.3, 42.7, 42.1, 39.5, 35.1, 30.6, 28.6, 25.9, 21.6, 19.8, 18.9, 18.1, 15.9, −3.8, −4.9; HRMS (EI) *m*/*e* (M^+) calcd for $C_{42}H_{76}O_2Si_2$ 668.5384, found 668.5379.

4.1.23. (±)-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-6-(4-nitrobenzoyloxy)-naphthalene (51). A solution of the *Z*-triene **43** (42.8 mg, 0.064 mmol) in THF (6.4 mL) was degassed with Ar for 20 min and photolyzed in a quartz tube with a medium pressure Hanovia mercury arc lamp in a quartz immersion well at ≥200 nm for 24 h. The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to afford the silyl ether as an oily, white solid (20.1 mg, 47%). IR (neat) 2930, 2855, 1472, 1389, 1252, 1103, 1070, 882, 836, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (m, 1H), 3.21 (dd, *J*=11.3, 4.8 Hz, 1H), 1.95 (m, 2H), 1.58 (s, 3H), 1.37–1.71 (m, 5H), 1.18–1.26 (m, 2H), 0.91 (s, 6H), 0.89 (s, 9H), 0.76 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 130.1, 79.8, 50.1, 39.1, 37.9, 34.8, 31.9, 28.4 (2 C's), 25.9, 23.1, 21.6, 19.0, 18.1, 15.8, −3.7, −4.9. To a stirring solution of the silyl ether (85 mg, 0.13 mmol) in 1:1 acetone/water (1.5 mL) at 23 °C was added *p*-toluenesulfonic acid (72 mg, 0.38 mmol). The solution was stirred overnight, quenched with a saturated solution of sodium bicarbonate, and extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvents were removed in vacuo to afford a colorless residue. The residue (45.9 mg, 0.1 mmol) was dissolved in dichloromethane (1 mL) with 4-(*N*,*N*-dimethylamino)pyridine (6 mg, 0.05 mmol) and pyridine (40 μL, 0.5 mmol) at 23 °C. To the mixture was added 4-nitrobenzoyl chloride (56 mg, 0.3 mmol) and stirring was continued for 24 h. The reaction mixture was diluted with ether, quenched with a saturated solution of sodium bicarbonate, and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (90% hexanes/ethyl acetate) to furnish the ester **51** as colorless plates (71.4 mg, 93%). Crystals were obtained by slow evaporation of a solution in 9:1 acetonitrile/hexanes, which led to the determination of the X-ray crystal structure shown in Figure 3. IR (neat) 3405 (br s), 2961, 2912, 1711, 1609, 1531, 1351, 1291, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J*=10.8 Hz, 2H), 8.21 (d, *J*=10.8 Hz, 2H), 5.08 (s, 1H), 4.81 (dd, *J*=11.5, 5.0 Hz, 1H), 1.60 (s, 3H), 1.40–2.02 (m, 9H), 1.03 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 150.5, 136.3, 134.4, 130.6, 130.5, 123.5, 83.2, 50.2, 38.0, 37.4, 34.8, 31.7, 28.1, 24.3, 23.2, 23.1, 18.7, 16.7.

4.1.24. 1-Iodo-2,6,6-trimethylcyclohexene (54). A stirring solution of commercially available 2,2,6-trimethylcyclohexanone **52** (60 mg, 0.43 mmol), hydrazine (0.28 mL, 9.03 mmol), triethylamine (0.94 mL, 6.7 mmol), and ethyl alcohol (0.72 mL) was refluxed for 3 h. The solution was then diluted with water and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed in vacuo to furnish the hydrazone **53** as a white solid (66 mg, 100%). To a stirring solution of the hydrazone **53** (102.4 mg, 0.66 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 mL, 13.2 mmol) in ether (6 mL) at 23 °C was added iodine (381 mg, 1.5 mmol). The viscous orange-brown mixture was stirred for 30 min. The reaction was quenched with a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed twice with brine and dried (K_2CO_3). The solvents were removed in vacuo to afford a thick brown oil. The oil was then dissolved in benzene (8.3 mL) and DBU (0.49 mL, 3.3 mmol) was added before heating to reflux for 3 h. The solvents were removed in vacuo and the crude residue dissolved in ether and washed once with a saturated solution of sodium sulfite, twice with brine, and dried (K_2CO_3). The solvents were removed in vacuo and the crude residue purified by flash chromatography on silica gel (80% hexanes/ethyl acetate) to afford the known vinyl iodide **54** as an oily, white solid (126.7 mg, 76%).[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (t, *J*=6.0 Hz, 2H), 1.87 (s, 3H), 1.61–1.70 (m, 4H), 1.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 117.4, 39.6, 37.9, 33.7, 31.6, 31.1, 19.4.

4.1.25. (±)-*E*-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-1-[2-(2,6,6-trimethylcyclohexen-1-yl)ethenyl]-naphthalene (55). A stirring solution of the vinyl boronate **44** (829 mg, 1.78 mmol), the vinyl iodide **54** (423 mg, 1.69 mmol), dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) (73 mg, 0.09 mmol), and 2 M NaOH (1.1 mL, 2.1 mmol) in THF (18 mL) was heated to 60 °C overnight. The reaction was quenched with a saturated solution of sodium bicarbonate and extracted three times with ether. The combined organic extracts were washed once with brine and dried ($MgSO_4$). The solvents were removed

in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to yield the *E*-triene **55** as an oily, white solid (601.6 mg, 72%). IR (neat) 2933, 2856, 1667, 1472, 1361, 1253, 1106, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, J=17.1 Hz, 1H), 5.70 (d, J=17.1 Hz, 1H), 3.21 (dd, J=11.0, 4.8 Hz, 1H), 2.14 (m, 3H), 1.99 (m, 2H), 1.74 (s, 3H), 1.73 (s, 3H), 1.47–1.71 (m, 7H), 1.28 (m, 3H), 1.09 (s, 3H), 1.02 (s, 6H), 0.93 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 138.4, 132.3, 130.9, 127.8, 126.5, 79.4, 50.6, 39.6, 39.5, 38.0, 37.9, 34.1, 34.0, 33.0, 32.8, 31.6, 28.9, 28.5, 25.9, 22.0, 21.5, 20.2, 19.4, 18.5, 18.1, 15.9, −4.3, −4.9; HRMS (EI) *m/e* (M^+) calcd for $C_{31}H_{54}OSi$ 470.3944, found 470.3937.

4.1.26. (±)-*Z*-(4a*S*,6*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-6-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,5,8a-tetramethyl-1-[2-(2,6,6-trimethylcyclohexen-1-yl)ethenyl]-naphthalene (56). A stirring solution of the *E*-triene **55** (305.2 mg, 0.65 mmol), benzanthrone (255 mg, 0.98 mmol), and THF (65 mL) was photolyzed with a mercury lamp at 290 nm for 24 h. The solvent was removed in vacuo and the crude residue purified by flash chromatography on silica gel (99% hexanes/ethyl acetate) to furnish the *Z*-triene **56** as an oily, white solid (250.5 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J=11.0 Hz, 1H), 5.84 (d, J=11.0 Hz, 1H), 3.15 (dd, J=9.1, 3.6 Hz, 1H), 1.95–2.12 (m, 4H), 1.44–1.72 (m, 11H), 1.41 (s, 3H), 1.35 (s, 3H), 1.09 (s, 3H), 1.02 (s, 6H), 0.93 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.5, 132.1, 131.2, 130.1, 127.8, 79.3, 50.6, 40.0, 39.5, 37.5, 36.0, 35.7, 33.4, 33.3, 31.5, 29.3, 28.5, 28.0, 25.8, 23.0, 22.2, 20.9, 19.2, 18.7, 18.0, 15.8, −3.9, −5.0.

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Supplementary data

Proton and carbon NMR data for all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.023.

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