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Synthesis of a *trans*,*syn*,*trans*-Dodecahydrophenanthrene via a Bicyclic Transannular Diels−Alder Reaction: Intermediate for the Synthesis of Fusidic Acid

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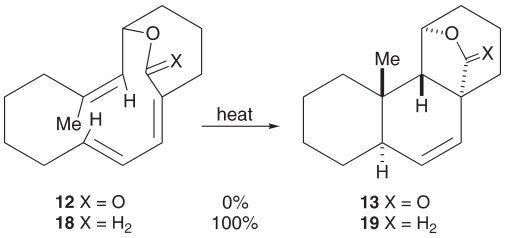

While thermolysis of the macrobicyclic triene lactone **12** did not produce the expected bicyclic transannular Diels−Alder (BTADA) product **13**, heating the corresponding ether **18** to 110 °C for 4 h afforded a quantitative yield of the desired cycloadduct **19**, which could be easily reduced to the perhydrophenanthrene, an ABC ring analogue of fusidic acid **1**. Theoretical calculations with hybrid density functional theory (B3LYP/6-31G(d)) help rationalize why the lactone does not cyclize whereas the ether does.

Introduction

Fusidic acid (**1**, Scheme 1) is a potent antibiotic used in a variety of medical applications.[1] Given its biological activity and complex structure, several groups pursued its total synthesis, with formal total syntheses being achieved by Dauben and Tanabe years ago.[2] Deslongchamps[3] likewise constructed a model ABC ring system using a *monocyclic* transannular Diels−Alder (TADA)[4] reaction of the trienone diester **2**, which gave **3** (Scheme 2), with the entire ABC ring juncture stereochemistry correct, but with the C3-stereochemistry inverted, in excellent yield and selectivity. We wondered if a related *bicyclic* triene lacking the ketone function could be induced to undergo a *bicyclic* transannular Diels−Alder reaction (BTADA) to produce a similar *trans*,*syn*,*trans*-dodecahydrophenanthrene system, which potentially could be used for the preparation of fusidic acid and its analogues. We report here the results of those exploratory studies.

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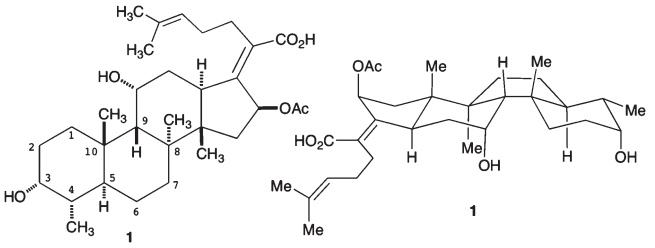
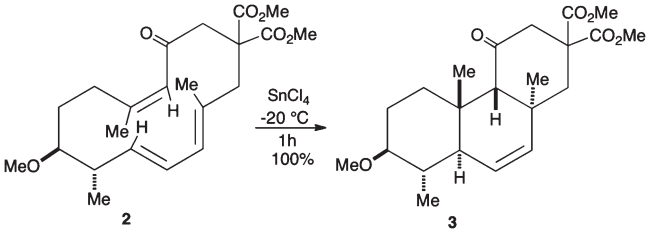
SCHEME 1. Structure of Fusidic Acid 1



SCHEME 2. TADA for the Synthesis of *trans*,*syn*,*trans*-Dodecahydrophenanthrene



Results and Discussion

The synthesis of the bicyclic triene lactone **12**, with the carbon precursor to the methyl group at C-8 and the required alcohol at C-11 (Scheme 3), was straightforward and generally high-yielding. The known *E*-enoate[5] **4**, readily available from 5-bromo-1-pentanol via oxidation to the aldehyde and Wittig reaction, was reduced with DIBAL to give in 94% yield the primary alcohol that was then protected to produce the TBS ether **5** in quantitative yield. S_N2 displacement of the bromide with the commercially available lithium acetylide ethylenediamine (EDA) complex gave, in 94% yield, the terminal alkyne, the anion of which underwent carboalkoxylation to afford the acetylenic ester **6**. Addition of lithium dimethylcuprate to **6** provided, in 94% yield, the desired *Z* stereoisomer of the β-methylacrylate, thereby setting the required stereochemistry of the olefin that is destined to be the syn related proton and methyl groups at C9−C10. DIBAL reduction of this ester gave the *Z*-allylic alcohol **7** in quantitative yield. The aldehyde formed by Dess−Martin periodinane (DMP) oxidation of this alcohol (91% yield) was reacted with the 3-alkoxypropyl Grignard reagent to give the expected alcohol in 87% yield. Final protection of the hydroxyl function, which will become the 11-hydroxy group of fusidic acid, with TBDPS chloride furnished the triether **8** in 94% yield. The *p*-methoxybenzyl (PMB) protecting group was removed in 80% yield with DDQ and the alcohol was converted to the bromide **9** in 90% yield. Alkylation of **9** with the anion of methyl bis(trifluoroethyl-)phosphonoacetate (sodium hydride in DMF) furnished the desired phosphono ester in 70% yield. Removal of the TBS ether with aqueous acid (96% yield) and oxidation with Dess−Martin periodinane furnished the aldehyde **10**, which was not purified but immediately subjected to an intramolecular Horner Wadsworth Emmons reaction to give the desired macrocyclic enoate **8** in 90% yield for the two steps. The stereochemistry of the new alkene was shown to be mainly the desired *Z*-isomer by several NMR experiments, especially NOESY. We elected to carry out the BTADA of the lactone **12** rather than that of the silyloxytriene ester **11** for two reasons: (a) the lactone would have fewer steric interactions than the silyl ether ester because the ester and hydroxyl group would be connected and (b) the lactone **12** would hold the triene system in the specific conformation **12A** (Scheme 4) so that only the *trans*,*syn*,*trans* Diels−Alder adduct **12B** could be formed. Although Deslongchamps had shown in his monocyclic system that this was the preferred mode of cyclization,[3] closer examination of molecular models revealed that this might well not be the case here. In fact, it seemed likely that the monocyclic silyloxy triene ester would prefer to cyclize via the conformation **11A**, which would give the *cis*,*syn*,*cis* Diels−Alder adduct **11B**. Thus the TBDPS ether of **11** was removed with TBAF (65% yield) and the ester was hydrolyzed by using lithium hydroxide in methanol to give the hydroxy acid in 70% yield. Cyclization of this hydroxy acid was carried out with the Yamaguchi reagent to give the bicyclic lactone **12** in 61% yield. Thus the triene ester **11** was available in 14 steps and 20% overall yield from **4** with the lactone **12** being available in three more steps and overall 5.5% yield from **4**.

With the triene lactone **12** in hand, we attempted its BTADA reaction. Heating **12** at different temperatures and in various solvents gave no products with the desired dodecahydrophenanthrene skeleton (Scheme 5). Starting material was consumed but many products were formed, none of which had the characteristics of the desired Diels−Alder product. Examination of molecular models indicated that the triene lactone could adopt an appropriate conformation favorable for the BTADA and therefore it was disappointing that the desired cycloaddition did not occur. However, manipulation of the molecular models indicated that there was also another readily accessible conformation that was not in position to give the cycloadduct. For this reason, we decided to look at two alternate strategies: (a) preparation and cyclization of an alternate substrate and (b) theoretical calculations[6] to better understand the conformational energy landscape of these substrates with the aim of carrying out the desired BTADA.

Of the many possible analogues of the lactone **12** which might have a more favorable equilibrium for the conformation leading to cyclization, we first chose compounds with more atoms in the connecting chain. This was in the hope that the higher conformational flexibility would allow the molecule to attain the required transition state conformation for the cycloaddition. The ester **11** was reduced with DIBAL and the silyl ether cleaved to give, in 78% yield for the two steps, the diol **14**, which was converted into the cyclic bis-(silyl) ether **15** in 68% yield (Scheme 6). Heating **15** in a microwave at 125 °C for 10 h afforded a 75% yield of the product of a [1,5]-hydride shift,[7] namely the silyl enol ether **16** instead of the desired cycloadduct **17**. Therefore the bis-(silyl) ether **15** preferred a conformation such as **E** in which the [1,5]-hydride shift was more favorable than the desired Diels−Alder cycloaddition.

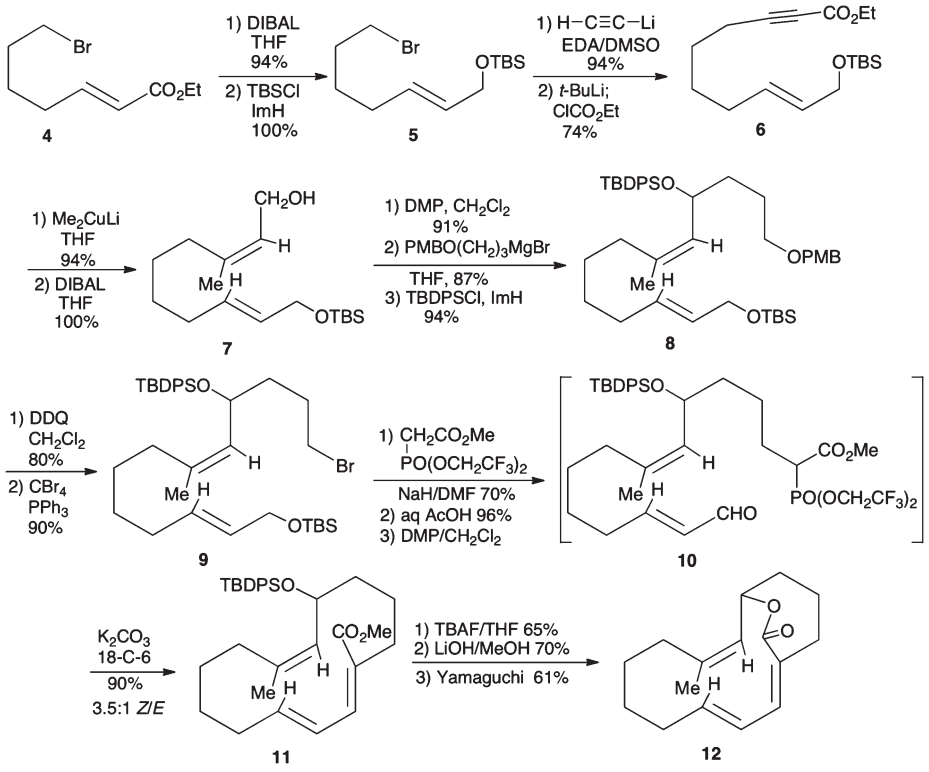
Theoretical calculations were carried out which showed that although the conformation **A′** did indeed place the diene

(5) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472–1473.

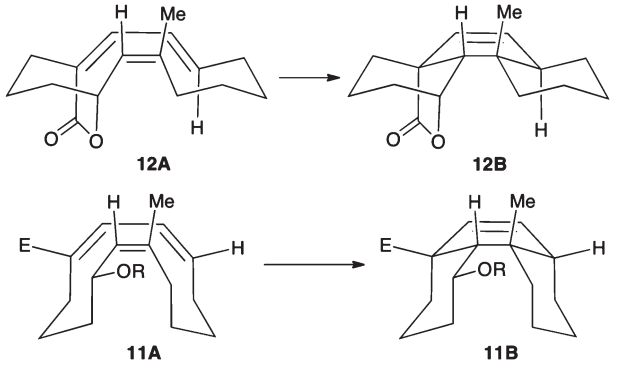
(6) All calculations were carried out with B3LYP-6-31G(d) as implemented in Gaussian 03. Frisch, M. J. et al. *Gaussian03*, Revision C.02; Gaussian, Inc., Wallingford, CT, 2004.

(7) Miller, B. *Advanced Organic Chemistry*, 2nd ed.; Prentice Hall: Upper Saddle River, NJ, 2004. Garciá-Granados, A.; Lopez, P. E.; Melguizo, E.; Parra, A.; Simeo, Y. *Tetrahedron* **2004**, *60*, 1491.

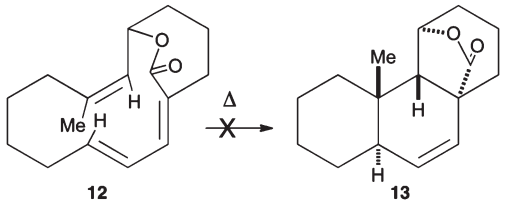
SCHEME 3. Synthesis of Bicyclic Triene Lactone 12, BTADA Substrate



SCHEME 4. Conformational Analysis of the Silyloxy Ester 11 and the Lactone 12

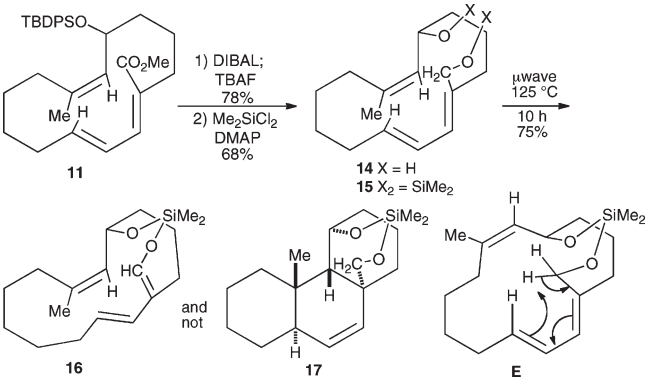


SCHEME 5. Attempted BTADA Reaction of the Bicyclic Triene Lactone 12



and dienophile in the proper orientation for the cycloaddition to **13**, this was not the most stable conformation (Figure 1). Conformation **A′** was 7.4 kcal/mol higher in energy than **A**; the calculated barrier for their interconversion via **A-TS-1** is 51.3 kcal/mol. The high barrier for interconversion is attributed to a combination of factors including the

SCHEME 6. Attempted BTADA Reaction of the Bicyclic Bis-(silyl) Ether 15



energy needed for the diene to rotate out of conjugation as well as the increase in transannular strain as the C═O bond is inverting. Thus it was obvious that the lactone was too strained to easily convert the most stable conformation **A** into the conformer **A′** that could undergo the cycloaddition. Significant changes in the macrobicyclic skeleton are required for this conformational change, compounded by the necessity to rotate about the ester linkage. As a result, several analogues were studied computationally, the most promising of which appeared to be the simple ether, where the lactone CO is replaced by a CH_2 group. Conformation **B′** was 10.3 kcal/mol higher in energy than **B** but the calculated barrier for their interconversion via **B-TS-1** is only 15.1 kcal/mol. This molecule **B** is predicted to have an activation free energy for cyclization of only 26.2 kcal/mol, with a ready interconversion of conformers, and thus cyclization to **B″** (**19**) is quite favorable.

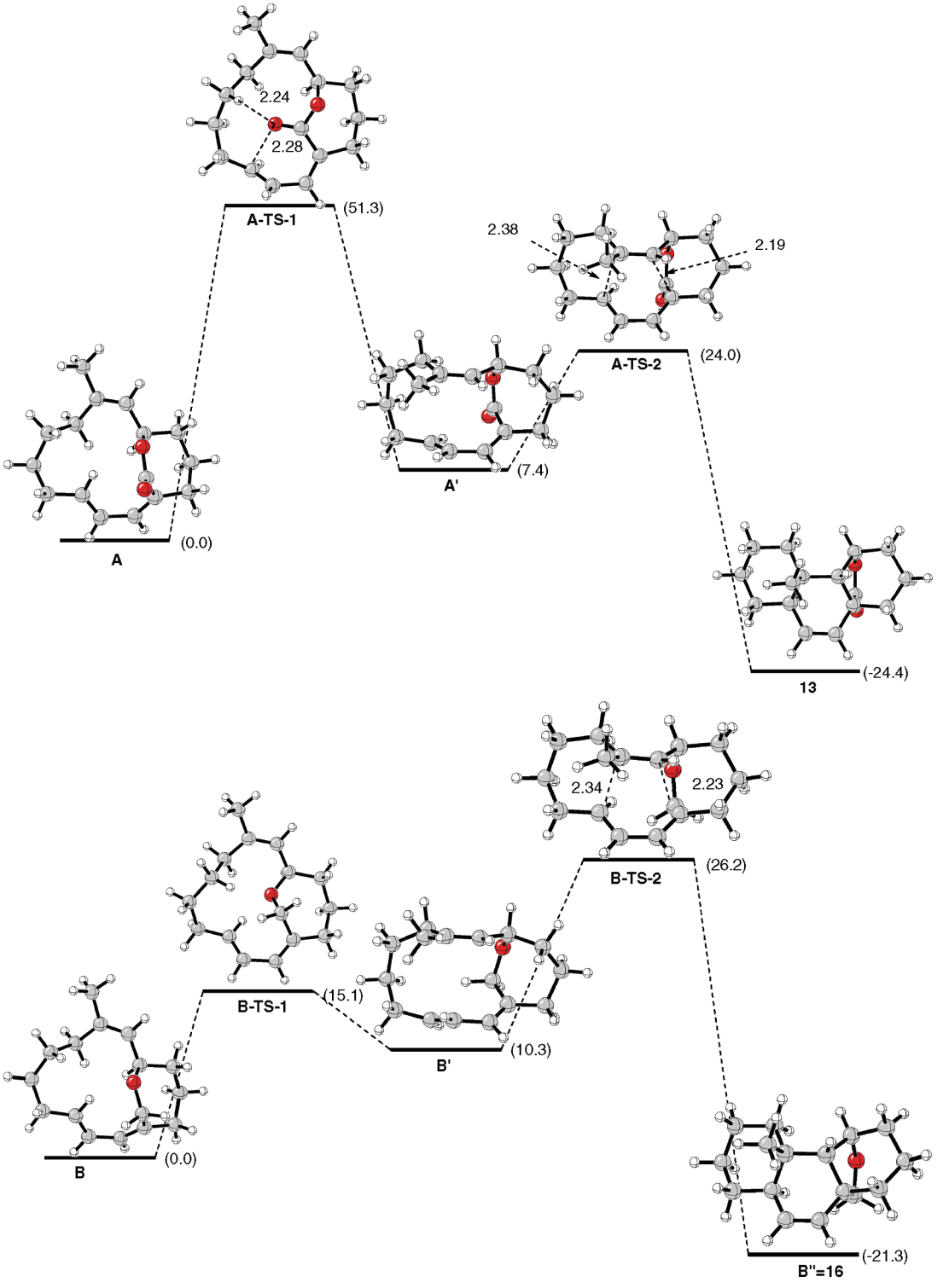


FIGURE 1. Theoretical calculations of the BTADA transitions states. All structures were computed with B3LYP/6-31G(d). Gibbs free energies are in kcal/mol. Selected distances are in angstroms.

Thus when the diol **14** was treated with triphosgene, instead of the carbonate, the cyclic ether **18** was formed in 65% yield (Scheme 7). Presumably the primary allylic alcohol is converted to the allylic chloride, which cyclizes with the secondary alcohol. This same ether could also be formed by treatment of the diol **14** with thionyl chloride although in somewhat lower yield. Heating **18** for 4 h at 110 °C afforded the cycloadduct **19** as the sole product isolated in quantitative yield. In fact, during the formation of **18** from **14** at 25 °C, we had already isolated about 20% of the cycloadduct **19**, thus demonstrating the ease of this BTADA reaction. The structure of **19** was assigned based on the proton and carbon NMR data, which indicated that the desired cycloaddition had indeed occurred. However the stereochemistry of

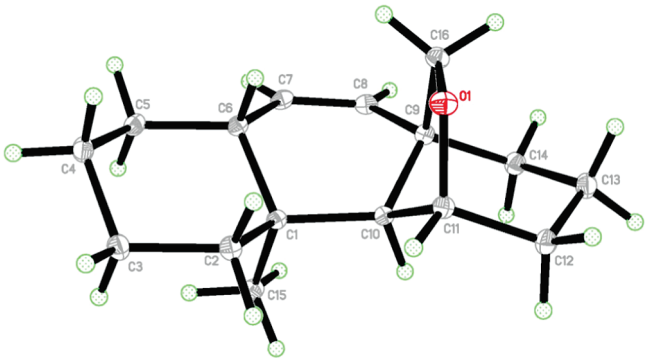
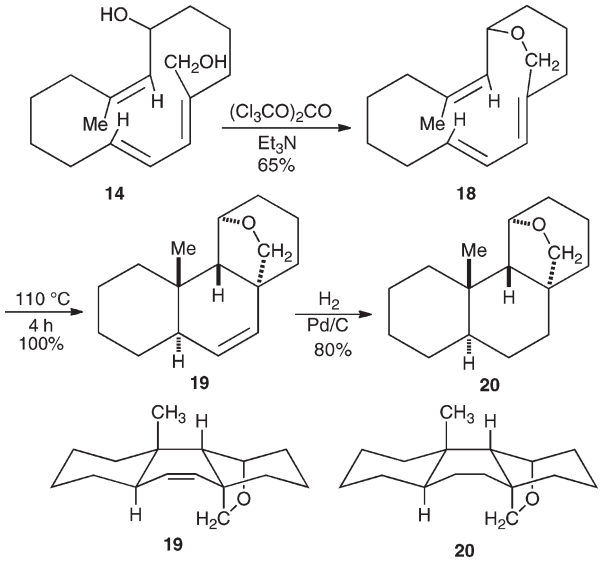


FIGURE 2. Structure of **19**.

SCHEME 7. BTADA Reaction of the Bicyclic Triene Ether 18



the structure was established by a single-crystal X-ray structure (Figure 2), which unambiguously shows the *trans*,*syn*, *trans* nature of the dodecahydrophenanthrene system. As expected, this ring structure requires that ring B be held in a boat conformation. The Diels−Alder adduct **19** could be easily converted into an analogue of the ABC ring system of fusidic acid by catalytic hydrogenation to give **20**. Furthermore, the compound has the correct stereochemistry and convertible functional groups at all ring junctions of the ABC ring subunit of fusidic acid.

In summary, we have demonstrated that the *trans*,*syn*, *trans*-perhydrophenanthrene ring system can be prepared easily by a bicyclic transannular Diels−Alder (BTADA) reaction of the properly arranged bicyclic triene ether **18** to produce, after processing, the desired system **20**. The use of such a process for the synthesis of fusidic acid and other natural terpenoids having ring B locked in the boat conformation is currently under study in our laboratories.

Experimental Section

General. All reactions were carried out under an argon atmosphere unless otherwise specified. Tetrahydrofuran (THF) and diethyl ether were distilled from benzoquinone ketyl radical under an argon atmosphere. Dichloromethane, toluene, benzene, pyridine, triethylamine, and diisopropylethylamine (DIPEA) were distilled from calcium hydride under an argon atmosphere. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride and stored over 4 Å molecular sieves. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR and ^{13}C NMR spectra were obtained at 400 and 500 MHz for proton and 100 and 125 MHz for carbon. The chemical shifts are reported in parts per million (ppm, δ). The coupling constants are reported in Hertz (Hz) and the multiplicities are reported as follows: br (broad), s (singlet), d (double), t (triplet), q (quartet), and m (multiplet). Thin-layer chromatography (TLC) was carried out with precoated silica gel sheets. Visual detection was performed with ultraviolet light, *p*-anisaldehyde stain, potassium permanganate stain, or iodine. Flash chromatography was performed with flash grade silica gel with compressed air.

(*E*)-7-Bromohept-2-en-1-ol. To a stirred solution of 2.35 g (10 mmol) of (*E*)-ethyl 7-bromohept-2-enoate[5] (**4**) in 25 mL of THF was added 25 mL of DIBAL-H (1.0 M in hexane) at −78 °C under Ar. The solution was stirred at −78 °C for 1 h and then was gradually warmed to −30 °C. TLC showed the reaction completed. A saturated K−Na tartrate solution (3.0 mL) was added slowly to the solution until no hydrogen was generated. The solution was warmed to 21 °C and 20.0 mL of a satd K−Na tartrate solution and 30.0 mL of ether were added. The solution was stirred at 21 °C until it became clear. The aqueous phase was extracted twice with ether and the combined organic phase was washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded 1.74 g (91%) of the known crude alcohol,[8] which was pure enough for the next reaction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 2H), 4.18 (d, J = 5.5 Hz, 2H), 3.47 (t, J = 6.5 Hz, 2H), 2.13 (m, 2H), 1.93 (m, 2H), 1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.2, 129.5, 63.5, 33.5, 32.0, 31.1, 27.5.

(*E*)-7-Bromo-1-[(1,1-dimethylethyl)dimethylsilyloxy]hept-2-ene, 5. To a stirred solution of 3.5 g (18.2 mmol) of the above alcohol in 30 mL of THF was added 3.06 g (45.5 mmol, 2.5 equiv) of imidazole and 4.10 g (27.0 mmol, 1.5 equiv) of TBSCl. The solution was stirred at 21 °C for 3 h. The solution was cooled to 0 °C and quenched with satd $NaHCO_3$ (20.0 mL) and the mixture was allowed to warm to 21 °C. After the mixture had stirred for 30 min at 21 °C, 40 mL of ether was added and the phases were separated. The aqueous phase was extracted twice with 10 mL of ether and the combined organic layer was washed with water and brine and dried over $MgSO_4$. Removal of the solvent provided a crude oil that was evacuated under high vacuum overnight to give 5.8 g (100%) of the bromo silyl ether. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (m, 2H), 4.12 (dd, J = 6.0, 1.3 Hz, 2H), 3.40 (t, J = 8.5 Hz, 2H), 2.06 (td, J = 8.5, 8.5 Hz, 2H), 1.85 (m, 2H), 1.52 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3, 129.9, 63.9, 33.8, 32.2, 31.3, 27.7, 26.0, 18.5, −5.1.

(*E*)-9-[(1,1-Dimethylethyl)dimethylsilyloxy]non-7-en-1-yne. To a stirred solution of 600 mg of lithium acetylide ethlyenediamine (6.5 mmol, 2 equiv) in 8.0 mL of dry DMSO in a 20 mL vial under Ar was added slowly 1.0 g (3.25 mmol) of the bromide, **5**. The solution was stirred at 21 °C for 40 min and was then poured into a solution of 20 mL of ether and 10 mL of water. The aqueous layer was extracted twice with 10 mL of ether and the combined organic layer was washed with water and brine and dried over $MgSO_4$. Removal of the solvent and purification by flash column chromatography on silica gel with hexane:ethyl acetate (6:1) afforded 770 mg (94%) of the alkyne. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (m, 2H), 4.17 (d, J = 5.5 Hz, 2H), 2.23 (m, 2H), 2.09 (m, 2H), 1.98 (t, J = 2.7 Hz, 1H), 1.56 (m, 4H), 0.96 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.7, 129.4, 84.5, 68.0, 62.9, 32.1, 28.2, 25.9, 24.9, 18.3, 18.2, −5.4. HRMS calcd for $C_{15}H_{32}NOSi$

(8) Fernandez-Garcia, C.; McKervey, M. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2905–2906.

$[M + NH_4]^+$ 270.2253, found (GCMS) m/z 270.2249, error 0.4 ppm.

(*E*)-Ethyl 10-[(1,1-Dimethylethyl)dimethylsilyloxy]dec-8-en-2-ynoate, 6. To a stirred solution of 900 mg (3.57 mmol) of the above terminal alkyne in 10 mL of THF at −78 °C was added dropwise 2.45 mL of *tert*-butyllithium (1.6 M in hexane, 3.92 mmol, 1.1 equiv). The solution was stirred at −78 °C for 10 min and then was warmed to −10 °C. The reaction mixture was cooled again to −78 °C and 407 μL (4.28 mmol, 1.2 equiv) of ethyl chloroformate was added. The resulting solution was stirred at −78 °C for 1 h and was then warmed slowly to 0 °C. After being stirring for 1 h, the reaction mixture was quenched with 5 mL of saturated NH_4Cl, followed by the addition of 30 mL of ether. The organic phase was washed with water and brine and dried over $MgSO_4$. Purification by flash column chromatography on silica gel with hexane:ethyl acetate (5:1) afforded 855 mg (74%) of the ester **6**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (m, 2H), 4.21 (q, J = 7.0 Hz, 2H), 4.12 (dd, J = 5.0, 1.0 Hz, 2H), 2.33 (t, J = 7.0 Hz, 2H), 2.04 (m, 2H), 1.59 (m, 2H), 1.49 (m, 2H), 1.30 (t, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 130.3, 129.7, 89.1, 73.1, 63.8, 61.7, 31.4, 28.2, 26.9, 25.9, 18.4, 18.3, 13.9, −5.2.

(2*Z*,8*E*)-Ethyl 3-Methyl-10-[(1,1-dimethylethyl)dimethylsilyloxy]-deca-2,8-dienoate. To a stirred suspension of 402 mg (2.11 mmol, 1.2 equiv) of CuI in 20 mL of THF at −10 °C was added 2.64 mL of methyllithium (1.6 M in hexane, 4.22 mmol). The solution was allowed to stir at 0 °C. When the solution became clear, it was cooled to −78 °C and then a solution of 570 mg (1.76 mmol) of the ynoate **6** in 4 mL of THF was added. The reaction mixture was stirred at −78 °C for 30 min and then warmed to −40 °C. After being stirred for 30 min, the solution was poured into a solution of 30 mL of ether and 10 mL of satd NH_4Cl. The organic layer was washed with satd NH_4Cl, water, and brine and dried over $MgSO_4$. Removal of the solvent gave 560 mg (94%) of the *Z*-acrylate, which was used directly in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (s, 1H), 5.66 (m, 1H), 5.59 (m, 1H), 4.17 (m, 4H), 2.67 (t, J = 7.5 Hz, 2H), 2.09 (m, 2H), 1.91 (d, J = 1.5 Hz, 3H), 1.50 (m, 4H), 1.31 (t, J = 7.0 Hz, 3H), 0.95 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 160.4, 131.0, 129.2, 116.0, 63.9, 59.3, 33.0, 31.9, 29.1, 27.6, 25.9, 25.0, 18.3, 14.2, −5.2.

(2*Z*,8*E*)-3-Methyl-10-[(1,1-dimethylethyl)dimethylsilyloxy]-deca-2,8-dien-1-ol, 7. To a stirred solution of 2.2 g (6.47 mmol) of the above ester in 20 mL of THF was added 16.5 mL of DIBAL-H (1.0 M in hexane, 2.5 equiv). The solution was stirred at −78 °C for 1 h and then was warmed slowly to −40 °C. After being stirred at −40 °C for 30 min, the reaction was quenched with satd K−Na tartrate (10 mL). After the addition of 40 mL of ether, the solution was allowed to stir at 21 °C until it became clear. The organic layer was washed with water and brine and dried over $MgSO_4$. Removal of the solvent gave 2.01 g (100%) of the crude allylic alcohol **7**, which was pure enough for the next reaction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.54 (m, 1H), 5.41 (t, J = 8.5 Hz, 1H), 4.12 (d, J = 5.5 Hz, 2H), 4.11 (d, J = 5.0 Hz, 2H), 2.06 (m, 4H), 1.72 (d, J = 1.0 Hz, 3H), 1.37 (m, 4H), 0.89 (s. 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 131.0, 129.3, 123.9, 63.9, 59.0, 31.9, 31.6, 28.8, 27.6, 25.9, 23.3, 18.3, −5.2. HRMS calcd for $C_{17}H_{34}O_2Si$ 321.2226, found (ESI) m/z 321.2232, error 0.6 ppm.

(2*Z*,8*E*)-3-Methyl-10-[(1,1-dimethylethyl)dimethylsilyloxy]deca-2,8-dienal. To a solution of 600 mg (2.01 mmol) of the above allylic alcohol in 10 mL of dichloromethane was added sequentially 320 mg (3.81 mmol, 1.9 equiv) of $NaHCO_3$ and then 1.5 g (3.6 mmol, 1.8 equiv) of Dess−Martin periodinane (DMP). The solution was stirred at 21 °C for 2 h. When TLC indicated no allylic alcohol remaining, 10 mL of satd $NaHCO_3$ was added, which was then followed by the addition of 10 mL of satd $Na_2S_2O_3$. The resulting solution was stirred for 20 min and then the phases were separated by the addition of 30 mL of ether. The organic phase was washed with 10 mL of satd $Na_2S_2O_3$ twice and brine and dried over $MgSO_4$. Purification by flash column chromatography on silica gel with hexane:ethyl acetate (3:1) afforded 544 mg (91%) of the pure enal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (d, J = 8.0 Hz, 1H), 5.91 (d, J = 8.2 Hz, 1H), 5.60 (m, 2H), 4.16 (dd, J = 6.2, 1.2 Hz, 2H), 2.57 (t, J = 9.5 Hz, 2H), 2.06 (m, 2H), 1.96 (d, J = 1.5 Hz, 3H), 1.55 (m, 2H), 1.43 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 164.4, 130.2, 129.7, 128.3, 63.8, 32.3, 31.7, 28.8, 28.1, 25.8, 24.9, 18.3, −5.2.

(2*Z*,8*E*)-13-(4-Methoxyphenylmethoxy)-8-methyl-1-[(1,1-dimethylethyl)dimethylsilyloxy]deca-2,8-dien-10-ol. A solution of 2.9 g (11.0 mmol, 2.5 equiv) of 1-bromo-3-(4-methoxyphenylmethoxy)-propane in 25 mL of THF was added to 5.0 g of Mg and I_2 was used as the initiator. After the solution refluxed for 2 h, it was cooled to 21 °C. The above solution was transferred by syringe to a solution of 1.3 g (4.4 mmol) of the above enal in 15 mL of THF at −78 °C. The resulting solution was allowed to stir for 1 h and was then warmed to 21 °C. After being stirred for 1 h at 21 °C, the reaction was quenched with satd NH_4Cl. The organic phase was washed twice with 10 mL of satd NH_4Cl, water, and brine. After drying over $MgSO_4$, the solvent was removed to afford 1.80 g (87%) of the allylic alcohol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.61 (m, 1H), 5.55 (m, 1H), 5.17 (d, J = 9.5 Hz, 1H), 4.44 (s, 2H), 4.35 (m, 1H), 4.11 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.47 (t, J = 6.0 Hz, 2H), 2.03 (m, 4H), 1.68 (s, 3H), 1.7−1.3 (m, 8H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 138.9, 131.0, 130.3, 129.3, 129.2, 128.3, 113.7, 72.6, 70.1, 67.9, 63.9, 55.2, 34.9, 32.0, 31.9, 29.0, 27.7, 26.0, 25.9, 23.3, 18.3, −5.2.

(2*E*,8*Z*)-13-(4-Methoxyphenylmethoxy)-8-methyl-1-[(1,1-dimethylethyl)dimethylsilyloxy]-10-[(1,1-dimethylethyl)diphenylsilyloxy]-trideca-2,8-diene, 8. To a stirred solution of 600 mg (1.26 mmol) of the above allylic alcohol in 15 mL of dry DMF was added 300 mg (4.41 mmol, 3.5 equiv) of imidazole and 518 μL (1.89 mmol, 1.5 equiv) of TBDPSCl. The solution was allowed to stir at 21 °C overnight and then was quenched with 5% $NaHCO_3$. After addition of 30 mL of ether, the solution was stirred at 21 °C for 30 min. After extraction and washing, the solution was dried over $MgSO_4$. Purification by flash column chromatography on silica gel with hexane:ethyl acetate (6:1) gave 847 mg (94%) of the silyl ether. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.35 (m, 6H), 7.22 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.48 (m, 2H), 5.13 (d, J = 8.5 Hz, 1H), 4.36 (s, 2H), 4.35 (m, 1H), 4.09 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.34 (t, J = 6.5 Hz, 2H), 1.82 (m, 2H), 1.70−1.30 (m, 9H), 1.03 (m, 4H), 1.02 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 136.0, 135.9, 135.8, 134.7, 134.5, 134.4, 131.1, 130.7, 129.3, 129.11, 129.06, 129.04, 128.6, 127.3, 127.1, 113.6, 72.3, 70.2, 69.7, 63.9, 55.2, 35.2, 31.8, 31.7, 29.1, 27.2, 26.9, 25.9, 25.2, 22.9, 19.2, 18.3, −5.2.

(5*Z*,11*E*)-6-Methyl-13-[(1,1-dimethylethyl)dimethylsilyloxy]-4-[(1,1-dimethylethyl)diphenylsilyloxy]trideca-5,11-dien-1-ol. To a stirred solution of 550 mg (0.77 mmol) of the PMB ether **8** in 16 mL of dichloromethane and 4 mL of a pH 7 buffer solution was added 262 mg (1.16 mmol, 1.5 equiv) of DDQ in five portions. After the addition, the solution was stirred at 0 °C for 1 h and then was warmed to 21 °C. The solution was kept at 21 °C until TLC indicated no starting material remaining. The reaction was then quenched with satd $NaHCO_3$ and was extracted twice with 20 mL of ether. The organic phase was washed with water and brine and dried over $MgSO_4$. Removal of the solvent gave a crude yellow oil that was then dissolved again in 15 mL of methanol. To this solution was added 73.0 mg (1.92 mmol, 2.5 equiv) of $NaBH_4$ at 0 °C. After being stirred at 21 °C for 1 h, the solution was added to 20 mL of brine and 40 mL of ether. The layers were separated and the organic phase was washed with brine and dried over $MgSO_4$. The residue after removal of the solvent was purified by flash column chromatography on silica gel with hexane:ethyl acetate (3:1) as eluent to give 366 mg (80%) of the primary alcohol. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.66 (t, J = 6.5 Hz, 4H), 7.40 (m, 6H), 5.50 (m, 2H), 5.20 (d, J = 9.0 Hz, 1H), 4.40 (m, 1H), 4.08 (d, J = 5.0 Hz, 2H), 3.54 (m, 2H), 1.84 (m, 2H), 1.50 (s, 3H), 1.70−1.00 (m, 10H), 1.03 (s, 9H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.9, 135.8, 134.7, 134.3, 134.2, 131.1, 129.5, 129.4, 129.2, 129.0, 128.3, 127.6, 127.4, 127.1, 69.7, 63.9, 63.0, 34.9, 31.8, 29.0, 28.2, 27.1, 26.9, 26.4, 25.9, 22.9, 19.2, 18.4, −5.2.

(2*E*,8*E*)-13-Bromo-8-methyl-1-[(1,1-dimethylethyl)dimethylsilyloxy]-10-[(1,1-dimethylethyl)diphenylsilyloxy]deca-2,8-diene, 9. To a stirred solution of the above primary alcohol (500 mg, 0.84 mmol) in dichloromethane (20 mL) was added triethylamine (1.16 mL, 8.4 mmol, 10 equiv), followed by triphenylphosphine (650 mg, 2.47 mmol, 3 equiv) and carbon tetrabromide (824 mg, 2.47 mmol, 3 equiv). After being stirred for 1 h, the reaction was quenched with satd $NaHCO_3$ and extracted twice with dichloromethane. The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography with hexane:ethyl acetate (10:1) as eluent afforded 497 mg (90%) of the bromide **9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, J = 8.0 Hz, 4H), 7.39 (m, 6H), 5.56 (m, 2H), 5.20 (d, J = 3.5 Hz, 1H), 4.41 (m, 1H), 4.15 (dd, J = 5.5, 1.0 Hz, 2H), 3.29 (dt, J = 7.0, 1.0 Hz, 2H), 1.85 (m, 4H), 1.52 (d, J = 1.5 Hz, 3H), 1.70−1.00 (m, 8H), 1.08 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 135.9, 135.7, 134.3, 134.2, 131.0, 129.4, 129.2, 129.1, 128.3, 127.4, 127.1, 69.0, 63.9, 37.1, 34.0, 31.8, 31.7, 29.1, 28.4, 27.2, 26.9, 25.9, 22.9, 19.2, 18.3, −5.2; HRMS calcd for $C_{36}H_{57}Br^{79}O_2Si_2$ 679.2978, found (ESI) m/z 679.2978, error 0.3 ppm, calcd for $C_{36}H_{57}Br^{79}O_2Si_2$ 681.2965, found (ESI) m/z 681.2968, error 0.3 ppm.

(7*Z*,13*E*)-Methyl 2-Bis(2,2,2-trifluoroethoxy)phosphoryl-8-methyl-15-[(1,1-dimethylethyl)dimethylsilyloxy]-6-[(1,1-dimethylethyl)diphenylsilyloxy]pentadeca-7,13-dienoate. To a stirred suspension of NaH (60%, 84.0 mg, 2.1 mmol, 2.5 equiv) in anhydrous DMF (2.5 mL) was added methyl 2-(bis(2,2,2-trifluoroethoxy)-phosphoryl)acetate (670 mg, 2.1 mmol, 2.5 equiv). The resulting solution was stirred at 21 °C for 1.5 h and a solution of the bromide **9** (540 mg, 0.82 mmol) was added. The solution was heated to 60 °C overnight and then was partitioned between ether (20 mL) and water (10 mL). The reaction mixture was extracted with ethyl acetate and the organic phase was washed with water and brine and dried over $MgSO_4$. Removal of the solvent gave a residue that was purified by flash column chromatography on silica gel (hexane:ethyl acetate 2:1) to afford 513 mg (70%) of the phosphono ester. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.40 (m, 6H), 5.56 (m, 2H), 5.17 (t, J = 8.0 Hz, 1H), 4.41 (m, 5H), 4.14 (d, J = 5.0 Hz, 2H), 3.78 (d, J = 9.5 Hz, 3H), 3.10 (m, 1H), 1.98 (m, 1H), 1.88 (t, J = 6.5 Hz, 2H), 1.70−1.10 (m, 14H), 1.06 (s, 9H), 0.95 (s, 1H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 136.3, 136.2, 135.88, 135.86, 135.7, 134.3, 134.2, 131.0, 129.3, 129.2, 129.1, 128.2, 127.3, 127.1, 69.4, 69.3, 63.9, 52.7, 45.9, 44.8, 37.9, 31.8, 31.7, 29.1, 27.2, 27.0, 26.8, 25.8, 22.9, 19.2, 18.3, −5.2; HRMS calcd for $C_{43}H_{65}F_6O_7PSi_2Na$ 917.3809 $[M + Na]^+$, found (ESI) m/z 917.3806, error 0.3 ppm.

(7*Z*,13*E*)-Methyl 2-[Bis(2,2,2-trifluoroethoxy)phosphoryl]-15-hydroxy-8-methyl-6-[(1,1-dimethylethyl)diphenylsilyloxy]pentadeca-7,13-dienoate. The above phosphono ester (350 mg, 0.39 mmol) was dissolved in 9 mL of acetic acid, 6 mL of THF, and 3 mL of water. The resulting solution was stirred for 5 h and then was extracted with 30 mL of ether. The organic phase was washed with water and brine and dried over $MgSO_4$. Removal of the solvent followed by flash column chromatography on silica gel (hexane:ethyl acetate 1:1) gave 292 mg (96%) of the allylic alcohol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.37 (m, 6H), 5.62 (m, 2H), 5.12 (t, J = 7.5 Hz, 1H), 4.38 (m, 5H), 4.07 (d, J = 4.5 Hz, 2H), 3.72 (d, J = 7.0 Hz, 3H), 3.04 (m, 1H), 2.00 (m, 2H), 1.90−1.30 (m, 12H), 1.10 (d, J = 1.0 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 135.9, 135.81, 135.79, 135.73, 134.4, 134.3, 132.9, 129.4, 129.2, 129.0, 128.9, 127.73, 127.69, 127.4, 127.1, 69.79, 69.76, 63.6, 52.7, 45.9, 44.8, 39.0, 37.6, 31.94, 31.92, 28.6, 26.9, 26.8, 19.1, 16.0.

(1*Z*,3*E*,9*Z*)-Methyl 11-[(1,1-Dimethylethyl)diphenylsilyloxy]-9-methylcyclotetradeca-1,3,9-trienecarboxylate, 11. To a stirred solution of the above allylic alcohol (250 mg, 0.32 mmol) in dichloromethane (10 mL) was added $NaHCO_3$ (52.0 mg, 0.64 mmol, 2.0 equiv) followed by DMP (240.0 mg, 0.57 mmol, 1.8 equiv). The solution was stirred at 21 °C for 2 h until TLC indicate no starting material remaining. The reaction mixture was treated with 20 mL of ether and 10 mL of a solution of satd $NaHCO_3$ (5 mL) and satd $Na_2S_2O_3$ (5 mL). The organic phase was washed again with satd $Na_2S_2O_3$ (3 × 5 mL) and dried over $MgSO_4$. Removal of the solvent afforded 250 mg of the crude aldehyde **10**. This aldehyde was dissolved in 100 mL of dry toluene followed by addition of 1.0 g of freshly crystallized 18-Crown-6. The resulting solution was transferred to a 250 mL flask that contained 270 mg of flame-dried K_2CO_3. The solution was allowed to stir at 21 °C overnight and then 20 mL of water was added. The organic phase was washed with brine and dried over $MgSO_4$. Removal of the solvent and purification by flash column chromatography on silica gel with hexane:ethyl acetate (6:1) provided 150 mg (90% over 2 steps) of the cyclic triene ester **11** as a 3.5:1 mixture of Z/E isomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, J = 8.0, 1.5 Hz, 2H), 7.65 (dd, J = 8.0, 1.5 Hz, 2H), 7.38 (m, 6H), 6.92 (dd, J = 15.0, 8.0 Hz, 1H), 5.89 (d, J = 11.0 Hz, 1H), 5.47 (dt, J = 13.0, 5.0 Hz, 1H), 4.95 (d, J = 9.5 Hz, 1H), 4.20 (dt, J = 10.0, 2.0 Hz, 1H), 3.69 (s, 3H), 2.46 (m, 1H), 2.29 (m, 1H), 1.93 (m, 3H), 1.80−1.40 (m, 6H), 1.37 (s, 3H), 1.02 (s, 9H), 0.85 (m, 2H), 0.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 143.8, 143.2, 136.2, 134.7, 134.62, 134.58, 129.9, 129.4, 129.0, 128.2, 127.5, 126.7, 125.4, 67.1, 51.0, 35.1, 33.8, 33.61, 32.57, 27.1, 27.0, 24.6, 22.5, 21.4, 19.4 (one low-field carbon not resolved).

(1*Z*,3*E*,9*Z*)-Methyl 11-Hydroxy-9-methylcyclotetradeca-1,3,9-trienecarboxylate. To a stirred solution of the silyl ether **11** (150 mg, 0.29 mmol) in 1.5 mL of THF was added TBAF (1.5 mL, 1 M in THF, 5.0 equiv). The resulting solution was heated at 45−50 °C for 48 h. The solution was allowed to cool to 21 °C and 10 mL of ether was added followed by addition of 2.0 mL of a pH 7 buffer solution. The aqueous phase was extracted twice with 5.0 mL of ether. After drying over $MgSO_4$, the ether was removed in vacuo. The residue was purified by flash column chromatography on silica gel with hexane:ethyl acetate (3:1) to give 52.4 mg (65%) of the secondary alcohol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, J = 15.0, 8.0 Hz, 1H), 6.55 (d, J = 11.0 Hz, 1H), 5.89 (dt, J = 13.0, 5.0 Hz, 1H), 4.95 (d, J = 8.5 Hz, 1H), 4.30 (dt, J = 10.0, 2.0 Hz, 1H), 3.76 (s, 3H), 2.62 (m, 1H), 2.30 (m, 3H), 1.95 (m, 3H), 1.70 (s, 3H), 1.70−1.40 (m, 5H), 1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.30, 143.2, 141.8, 137.1, 129.2, 128.6, 127.1, 65.8, 51.3, 35.2, 33.3, 27.0, 25.7, 23.1, 21.0 (two high-field carbons not resolved); HRMS calcd for $C_{17}H_{26}O_3Na$ 301.1780 $[M + Na]^+$, found (ESI) m/z 301.1772, error 0.8 ppm. During this reaction, some of the acid (due to hydrolysis) was isolated as well.

(1*Z*,3*E*,9*Z*)-11-Hydroxy-9-methylcyclotetradeca-1,3,9-trienecarboxylic Acid. To a stirred solution of the above hydroxy ester (100 mg, 0.36 mmol) in 9.0 mL of methanol was added 3.0 mL of 1 M LiOH slowly. The solution was allowed to stir at 21 °C for 10 d until TLC indicated only a trace of starting material remaining. The reaction mixture was extracted with 20.0 mL of ethyl acetate and the organic phase was washed and dried over $MgSO_4$. The residue was purified by flash column chromatography on silica gel with ethyl acetate as eluent to afford 66.4 mg (70%) of the hydroxy acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (dd, J = 15.0, 11.5 Hz, 1H), 6.64 (d, J = 11.0 Hz, 1H), 5.94 (br d, J = 7.5 Hz, 1H), 4.97 (d, J = 8.5 Hz, 1H), 4.35 (dt, J = 10.0, 2.5 Hz, 1H), 2.61 (m, 1H), 2.30 (m, 3H), 2.00 (m, 2H), 1.63 (d, J = 1.0 Hz, 3H), 1.70−1.10 (m, 8H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.2, 142.8, 142.2, 135.7, 129.4, 128.7, 126.8, 65.0, 34.4, 33.1, 33.0, 26.8, 25.1, 21.9, 20.8 (one high-field carbon not resolved); HRMS calcd for $C_{16}H_{24}O_3Na$ 287.1623 $[M + Na]^+$, found (ESI) m/z 287.1625, error 0.2 ppm.

(2*Z*,8*E*,10*E*)-3-Methyl-15-oxabicyclo[9.3.2]hexadeca-2,8,10-trien-16-one, 12. To a solution of the above hydroxy acid (8.0 mg, 0.03 mmol) in THF (300 μL) at 0 °C were added triethylamine (8.4 μL, 0.06 mmol) and 2,4,6-trichlorobenzoyl chloride (9.0 μL, 0.054 mmol), and the resulting mixture was stirred at 21 °C for 2 h before dilution with toluene (3.5 mL). This solution was added dropwise over a period of 10 min to a solution of DMAP (7.5 mg, 0.06 mmol) in toluene (10 mL). This solution was stirred at 21 °C for 3 h and then 5.0 mL of water was added. The organic phase was washed with 1 M HCl, satd $NaHCO_3$, and brine and dried over $MgSO_4$. It was then filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel afforded 4.5 mg (61%) of the bicyclic lactone **12**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (m, 2H), 5.63 (dt, J = 13.0, 5.0 Hz, 1H), 5.21 (d, J = 9.5 Hz, 1H), 5.05 (dt, J = 9.0, 3.0 Hz, 1H), 2.30 (m, 3H), 2.01 (m, 1H), 1.91 (m, 3H), 1.80−1.60 (m, 4H), 1.72 (s, 3H), 1.19 (m, 2H), 0.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 145.1, 135.0, 133.2, 128.6, 127.6, 122.5, 75.9, 33.0, 32.7, 32.5, 29.5, 26.9, 25.7, 25.2, 23.9.

(2*Z*,8*E*,10*Z*)-11-(Hydroxymethyl)-3-methylcyclotetradeca-2,8,10-trienol, 14. To a stirred solution of the ester silyl ether **11** (100 mg, 0.193 mmol) containing a 3.5:1 mixture of *Z*/*E* isomers in 3.0 mL of THF was added DIBAL-H (3.0 mL, 1.0 M in hexane, 15.0 equiv) at −78 °C. The solution was allowed to warm to −50 °C and was then quenched with satd K−Na tartrate (4.0 mL) followed by the addition of 20 mL of ether. The solution was stirred until it became clear. The organic phase was washed with water and brine and dried over $MgSO_4$. It was then filtered and concentrated under reduced pressure. The residue, which contained an inseparable mixture of *Z*/*E* isomers, was dissolved in 3.0 mL of THF and TBAF (4.0 mL, 1.0 M in THF, 20.0 equiv) was added. After being stirred at 21 °C overnight, the reaction was quenched with a pH 7 buffer solution and was extracted with 30 mL of ether. After removal of the solvent, the residue was purified by flash column chromatography on silica gel with hexane:ethyl acetate (2:1) to afford 30.0 mg (78% over 2 steps) of the diol **14**, which was only the *Z* isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (dd, J = 15.0, 11.5 Hz, 1H), 6.10 (d, J = 11.5 Hz, 1H), 5.58 (dt, J = 12.5, 4.5 Hz, 1H), 4.95 (d, J = 9.0 Hz, 1H), 4.56 (m, 2H), 4.10 (d, J = 12.5 Hz, 1H), 2.48 (m, 1H), 2.38 (m, 1H), 2.3−1.9 (m, 4H), 1.65 (s, 3H), 1.8−1.5 (m, 4H), 1.5−1.1 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 137.7, 135.7, 131.0, 128.6, 126.9, 65.6, 62.0, 36.1, 33.6, 33.2, 27.0, 26.2, 23.4, 21.4 (one high-field carbon not resolved); HRMS calcd for $C_{16}H_{26}O_2Na$ 273.1830 $[M + Na]^+$, found (ESI) m/z 273.1828, error 0.2 ppm.

(1*Z*,3*E*,9*Z*)-9,13,13-Trimethyl-12,14-dioxa-13-silabicyclo[9.4.3]-octadeca-1,3,9-triene, 15. To a stirred solution of the diol **14** (18 mg, 0.072 mmol) in dichloromethane (6.0 mL) was added triethylamine (25.0 μL, 0.18 mmol, 2.5 equiv) and DMAP (2.0 mg, 0.014 mmol, 0.2 equiv). To this cooled solution (0 °C) was added slowly a solution of dichloromethane (2.0 mL) containing dichlorodimethylsilane (10.0 mg, 0.079 mmol, 1.1 equiv). The solution was allowed to stir for 20 min and then was quenched with satd $NaHCO_3$ and extracted with ether (10.0 mL). The organic phase was washed with water and brine and dried over $MgSO_4$. It was then filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with hexane:ethyl acetate (6:1) and afforded 15.0 mg (68%) of the silyl ether **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, J = 12.0, 10.0 Hz, 1H), 5.95 (d, J = 11.0 Hz, 1H), 5.58 (dt, J = 12.0, 3.6 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.73 (m, 1H), 4.12 (d, J = 12.0 Hz, 1H), 2.44 (m, 3H), 2.08 (m, 3H), 1.80 (m, 1H), 1.62 (d, J = 1.0 Hz, 3H), 1.60−1.00 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 136.2, 135.2, 130.4, 129.4, 127.0, 67.2, 62.6, 38.8, 35.5, 33.8, 33.7, 27.2, 26.3, 23.2, 21.7, −2.7, −3.4.

(1*Z*,2*E*,9*Z*)-9,13,13-Trimethyl-12,14-dioxa-13-silabicyclo[9.4.3]-octadeca-1(15),2,9-triene, 16. A degassed solution of the silyl ether **15** (10 mg, 0.032 mmol) in 5.0 mL of toluene was heated in a microwave to 125 °C overnight. The residue was purified by preparative TLC to afford 7.5 mg (75%) of the silyl enol ether **16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.64 (d, J = 11.0 Hz, 1H), 5.52 (dt, J = 11.0, 3.5 Hz, 1H), 5.11 (d, J = 7.5 Hz, 1H), 5.00 (t, J = 7.5 Hz, 1H), 2.90 (m, 1H), 2.71 (m, 1H), 2.15 (m, 1H), 2.12 (m, 1H), 1.85 (m, 4H), 1.66 (d, J = 1.0 Hz, 3H), 1.60−1.10 (m, 7H), 0.87 (m, 1H), 0.25 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 134.6, 131.5, 130.1, 128.4, 124.3, 69.7, 40.3, 30.0, 29.0, 26.6, 26.2, 25.6, 24.6, 23.5, 22.8, −2.4, −3.2.

(2*Z*,8*E*,10*Z*)-3-Methyl-15-oxabicyclo[9.3.2]hexadeca-2,8,10-triene, 18. To a stirred solution of the diol **14** (15.0 mg, 0.06 mmol) and triethylamine (50 μL, 0.36 mmol, 6.0 equiv) in dichloromethane (15.0 mL) was added a solution of triphosgene (27.0 mg, 0.09 mmol, 1.5 equiv) in 2.0 mL of dichloromethane. The solution was allowed to stir for 20 min at 0 °C and then satd $NaHCO_3$ was added. The solution was diluted with 20 mL of ether. After the phases were separated, the organic phase was washed with water and brine and dried over $MgSO_4$. Removal of the solvent and purification of residue by flash column chromatography on silica gel afforded 10.8 mg (65%) of the cyclic ether **18**, which had already cyclized to the tetracyclic ether **19** in about 20% yield by NMR. ^{1}H NMR (500 MHz, benzene-d_6) of **18**: δ 6.46 (dd, J = 15.0, 11.0 Hz, 1H), 6.15 (d, J = 10.0 Hz, 1H), 5.35 (d, J = 15.0 Hz, 1H), 5.32 (dt, J = 11.0, 4.5 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.25 (t, J = 10.5 Hz, 1H), 3.66 (d, J = 11.5 Hz, 1H), 2.2 (m, 2H), 2.0 (m, 1H), 1.85 (m, 3H), 1.70−0.9 (m, 11H); ^{13}C NMR (125 MHz, benzene-d_6) δ 150.3, 139.8, 135.4, 130.8, 130.0, 129.8, 128.1, 69.8, 66.4, 36.9, 33.8, 32.82, 32.79, 28.6, 26.2, 25.5, 23.6.

(±)-(4*R*,4a*S*,4b*S*,8a*R*,10a*R*)-4,10a-(Epoxymethylene)-4b-methyl-1,2,3,4,4a,4b,5,6,7,8, 8a,10a-dodecahydrophenanthrene, 19. A degassed solution of the cyclic ether **18** (10.0 mg, 0.036 mmol) in 5.0 mL of toluene was heated to reflux in a sealed tube for 4 h. Removal of the solvent under reduced pressure afforded 10.0 mg (100%) of the pure tetracyclic ether **19**. ^{1}H NMR (500 MHz, benzene-d_6) δ 5.55 (dd, J = 9.0, 2.5 Hz, 1H), 5.50 (dd, J = 9.0, 2.5 Hz, 1H), 4.48 (d, J = 3.5 Hz, 1H), 3.83 (d, J = 8.0 Hz, 1H), 3.67 (d, J = 8.0 Hz, 1H), 2.0 (m, 1H), 1.84 (m, 2H), 1.70−0.70 (m, 16H); ^{13}C NMR (125 MHz, benzene-d_6) δ 150.3, 134.8, 131.6, 78.0, 77.0, 64.1, 47.0, 41.7, 38.6, 36.9, 34.7, 34.4, 27.2, 26.1, 22.9, 21.7, 18.9; HRMS calcd for $C_{16}H_{24}ONH_4$ 250.2171 $[M + NH_4]^+$, found (ESI) m/z 250.2165, error 0.6 ppm.

(±)-(4*R*,4a*S*,4b*S*,8a*R*,10a*R*)-4,10a-(Epoxymethylene)-4b-methylperhydrophenanthrene, 20. To a stirred solution of cyclic ether **19** (3.4 mg, 15 μmol) in 0.6 mL of ethyl acetate was added 10% Pd/C (1.6 mg, 1.5 μmol). The heterogeneous mixture was stirred at 21 °C under a balloon of hydrogen for 1 h and then filtered through a plug of silica gel. The eluent was concentrated in vacuo. Further purification by flash chromatography on silica gel (hexanes:ethyl acetate 20:1) afforded 2.7 mg (12 μmol, 80%) of the saturated ether **20**. ^{1}H NMR (500 MHz, benzene-d_6) δ 4.46 (d, 1H, J = 4 Hz), 3.77 (d, 1H, J = 8.5 Hz), 3.61 (d, 1H, J = 8 Hz), 1.84 (m, 2H), 1.60 (m, 3H), 1.50−0.70 (m, 14H); ^{13}C NMR (125 MHz, benzene-d_6) δ 77.4, 75.1, 61.4, 44.3, 41.3, 36.2, 35.7, 34.6, 33.2, 30.0, 29.6, 26.4, 24.9, 24.4, 22.2, 21.9.

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Supporting Information Available: Proton and carbon NMR data for all compounds, X-ray crystallographic data (ORTEP and CIF file) for compound **19**, and Cartesian coordinates and energies for calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.