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Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 4: Preparation of Fragment C_{7-24}

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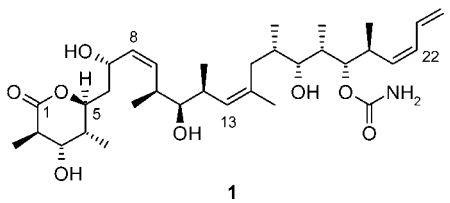
Abstract:

Coupling of C_{9-14} (4) and C_{15-21} (5a) fragments to produce the *cis*-trisubstituted olefin was achieved using Suzuki-type coupling conditions employed by Marshall (5a/*tert*-BuLi/B-OMe-9-BBN added to 4/Cs_2CO_3/Pd(dppf)$_2$). The terminal (*Z*)-diene moiety was attached to aldehyde 10 by using a sequential Nozaki−Hiyama allylation and Peterson olefination sequence; careful monitoring of the disappearance of both diastereomeric *β*-hydroxysilanes was found to be essential for achieving a high yield. In the oxidation of alcohols 12 and 16 to 13 and 7, respectively, using iodobenzene diacetate and TEMPO, addition of a trace of water was found to be crucial for complete conversion. The C_{8-9} (*Z*)-olefin functionality was introduced on to aldehyde 13 using a Still−Gennari HWE reaction. Subsequent carbamate installation at C-19 followed by a reduction/oxidation sequence gave the title fragment C_{7-24} (7) ready to be coupled with the C_{1-6} fragment, which is described in Part 2 of this series.

Introduction

In the preceding contributions of this five-part series, the large-scale preparations of the C_{1-6}, C_{9-14}, and C_{15-21} fragments that are required for the total synthesis of (+)-discodermolide (**1**) are discussed.



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In this contribution we present the results of coupling the key C_{9-14} (**4**) and C_{15-21} (**5**) fragments and further chain elaboration to afford an advanced intermediate C_{7-24} (**7**) that is needed for the final stage of the discodermolide synthesis. This required the construction of the synthetically challenging *Z*-trisubstituted double bond via sp^3-sp^2 cross coupling of an alkyl iodide and a vinyl iodide and subsequent elaboration of the product to the target aldehyde **7**. In the course of this synthetic sequence we smoothly make the transition from the Smith strategy[1] to the attractive end game approach of Paterson[2] (Scheme 1).

Results and Discussion

Coupling of Fragments C_{9-14} and C_{15-21}. The coupling of C_{9-14} (**4**) and C_{15-21} (**5a**) fragments to produce the (Z)-trisubstituted olefin **8** is shown in Scheme 2. We initially examined a variation of the Negishi coupling[3] as practiced by Smith.[1] This process produced several side products, as indicated by the NMR spectrum of the crude reaction mixture after workup, which were not separable from the desired product. Marshall described[4] an alternative Suzuki-type[5] cross-coupling step in his approach to discodermolide. Employing this protocol for our coupling reaction, [**5a**/*tert*-BuLi/9-methoxy-9-borabicyclo[3.3.1]nonane added to **4**/Cs_2CO_3/Pd(dppf)Cl_2, resulted in a much cleaner reaction mixture. The only byproduct generated was des-iodo compound **5b**. Some *trans* isomer of **8**, carried over from the *trans* impurity in **4**, was also observed. Pure **8** was easily obtained from the crude product in good yield (73%) by crystallization from acetonitrile. The structure and absolute configuration of **8**

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(1) Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654.
(2) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem, Int. Ed.* **2000**, *39*, 377.
(3) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.
(4) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.
(5) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

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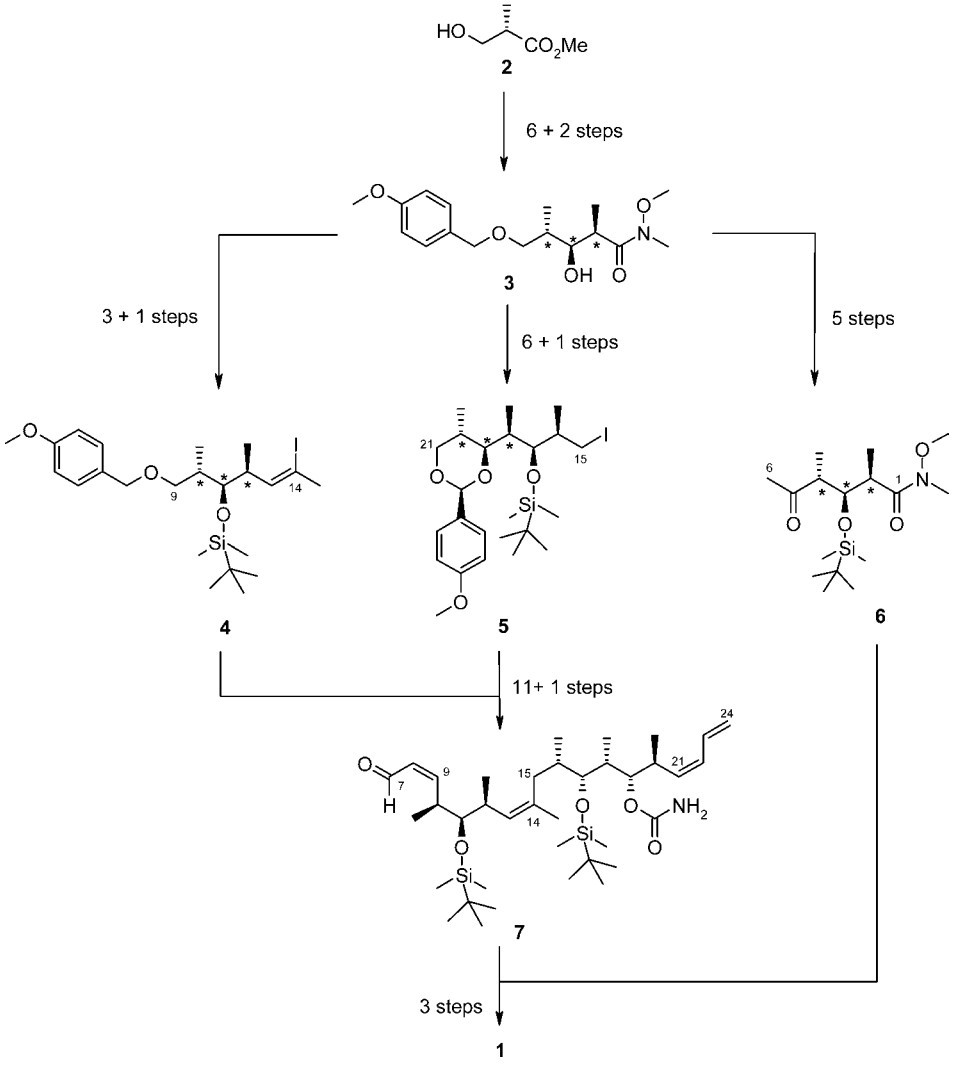
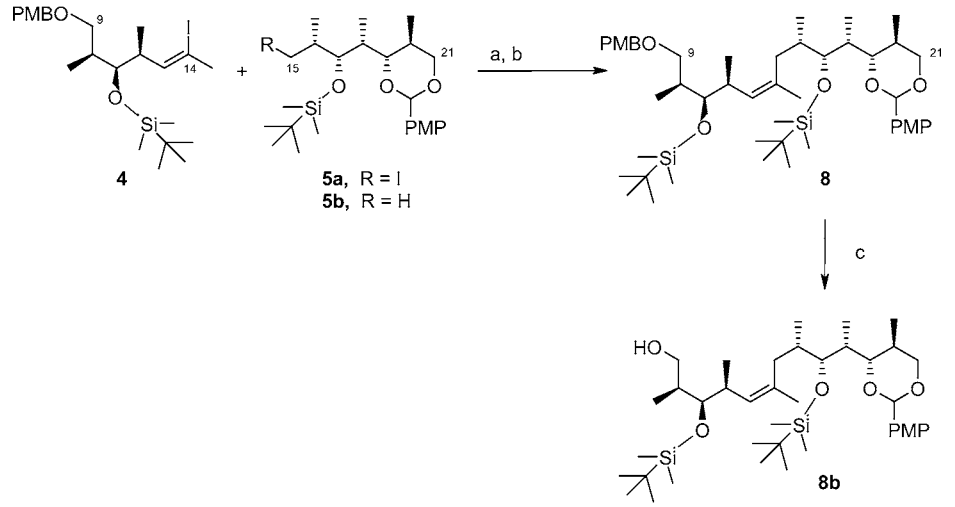
Scheme 1. **Synthetic strategy leading to the advanced fragment C_{7-24} (7) and (+)-discodermolide (1)**



Scheme 2. **Coupling of C_{9-14} and C_{15-21} fragments**[a]



[a] Reagents: a) *t*-BuLi. 9-MeOBBN, THF, −78 °C; b) Cs_2CO_3, DMF, $Pd(dppf)_2Cl_2$, 20 °C; c) DDQ.

was confirmed by single-crystal X-ray analysis of **8b** (Figure 1), obtained by removal of the *p*-methoxybenzyl protecting group of **8** with DDQ.

With the first fragment union successfully completed, the transition from the Smith approach to the Paterson route was now required to arrive at the final C_{7-24} coupling partner. This necessitates the elaboration of both termini to introduce the (*Z*)-enal and the terminal (*Z*)-diene unit and introduction of the pendant carbamate moiety as detailed in Scheme 3.

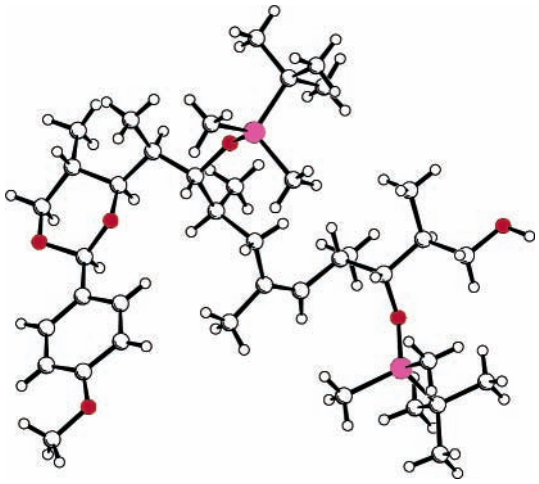
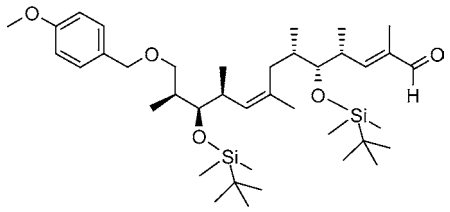


Figure 1. **Single-crystal X-ray structure of fragment 8b.**

Installation of the Terminal Diene. The elaboration of intermediate **8** to the advanced C_{7-24} fragment (**7**) is described in Scheme 3. Cleavage of the *p*-methoxyphenyl (PMP) acetal with DIBAL[6] afforded alcohol **9** in high yield (92%). Oxidation of **9** under Parikh−Doering conditions with SO_3/pyridine in DMSO gave aldehyde **10** in 93% yield. A cautious workup of the reaction mixture was critical for a high yield. If the reaction mixture was not rendered slightly basic, significant amounts (up to 20%) of the, β-unsaturated aldehyde **17** could be generated via elimination of *p*-methoxybenzyl alcohol.



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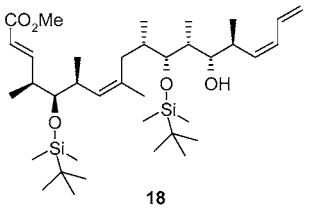
With the aldehyde **10** in hand, we departed from Smith's approach and turned our attention to the installation of the terminal diene. Numerous strategies have been employed for the introduction of this motif within the context of discodermolide syntheses. We chose to adopt the highly attractive Paterson two-step, one-pot protocol.[7] This was achieved by first employing Nozaki−Hiyama allylation conditions, whereby aldehyde **10** and allyl bromide **10b** were added to a suspension of $CrCl_2$ in dry THF to yield a β-hydroxysilane intermediate, which on treatment with KH underwent a Peterson *syn*-elimination to afford the required (*Z*)-diene. Reproducibility of this protocol was initially problematic after we had replaced KH with KOH as the base for reasons of safety and ease of operation. We observed that diene **11** was consistently contaminated with significant amounts of an impurity as shown by NMR. Further investigation suggested that a mixture of diastereomeric β-hydroxysilanes **11a** and **11b** was generated under our modified conditions (Scheme 4). Whether conversion of **11a** to **11** was completed could not be determined by TLC analysis since TLC could not separate these two compounds. This was overcome by developing an HPLC method to monitor the Peterson elimination reaction. Aided by HPLC, we observed that diastereomers **11a** and **11b** underwent *syn*-elimination at different rates. As a result, it was important to ensure that both β-hydroxysilanes were consumed before work up and isolation. This made the conversion of aldehyde **10** to diene **11** reproducible and afforded the latter as an oil in 81% yield after chromatography.

Conversion of C9 Alcohol to (*Z*)-Enal. Oxidative removal of the two *p*-methoxybenzyl protecting groups of diene **11** with DDQ/H_2O gave diol **12** as a foam in high yield (88%) after chromatography. Oxidation of diol **12** with iodobenzene diacetate and TEMPO produced aldehyde **13** as a red oil in 91% yield. Attempts to directly oxidize **11** to **13** were unsuccessful.[8] Aldehyde **13** thus generated was used without purification, since the iodobenzene generated from the reduction was judged not to interfere in the next step. It should be noted that traces of water have a dramatic effect on this reaction. This oxidation when performed on a 300-mg to 1-g scale with 2,2,6,6,-tetramethyl-1-piperidinyloxy (TEMPO, 0.1 equiv) and iodobenzene diacetate (DAIB, 1.2 equiv) gave a good yield of **13**. However, this reaction was not reproducible on scale-up, and the yield dropped to 10%. As the original report by Piancatelli[9] mentioned that the reaction "...can be performed in an open flask without any particular precautions, e.g., inert atmosphere or dry solvent...", we felt that these factors may be crucial for the progress of the reaction. This conclusion led to the addition of water (0.1 equiv) and resulted in a dramatic acceleration of the oxidation reaction.

Introduction of the *cis*-double bond C_{8-9} was accomplished utilizing the Still−Gennari variation of the Horner−Wadsworth−Emmons reaction.[10] Thus, generation of the anion of bis-2,2,2-trifluoroethylphosphonoacetic acid methyl ester with potassium hexamethyldisilazide in the presence of 18-crown-6 and reaction with crude aldehyde **13** gave *cis*-olefin **14** in 76% yield from **12**. About 2.5% of the *trans*-olefin **18** was formed under these conditions. The *trans*-isomer was separated by chromatography on silica gel, since we felt that purification at this stage was appropriate. Compound **18** was used to make the corresponding *trans*-isomers **19**−**21** for reference.



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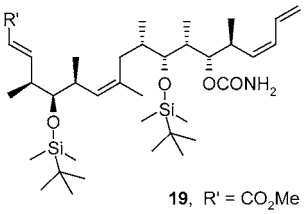


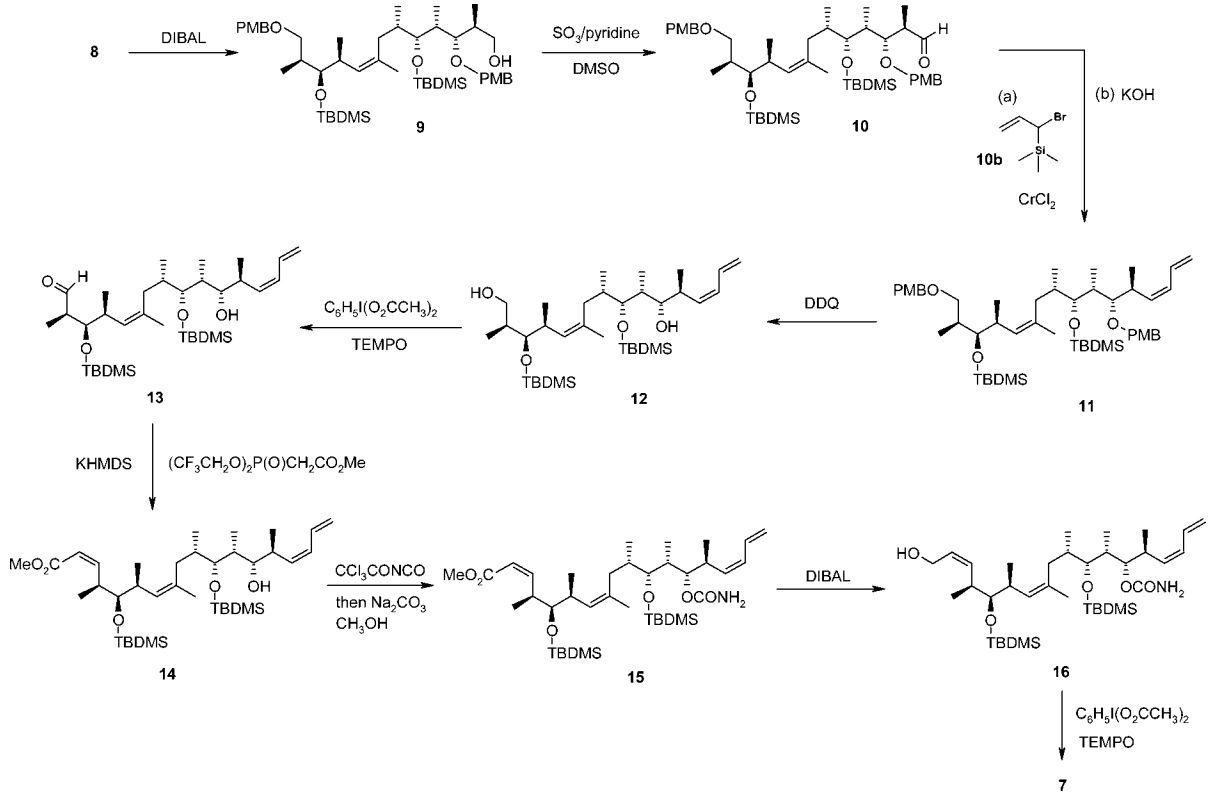
19, R' = CO_2Me
20, R' = CH_2OH
21, R' = CHO

Formation of carbamate **15** proceeded in quantitative yield by reaction of **14** with trichloroacetyl isocyanate followed

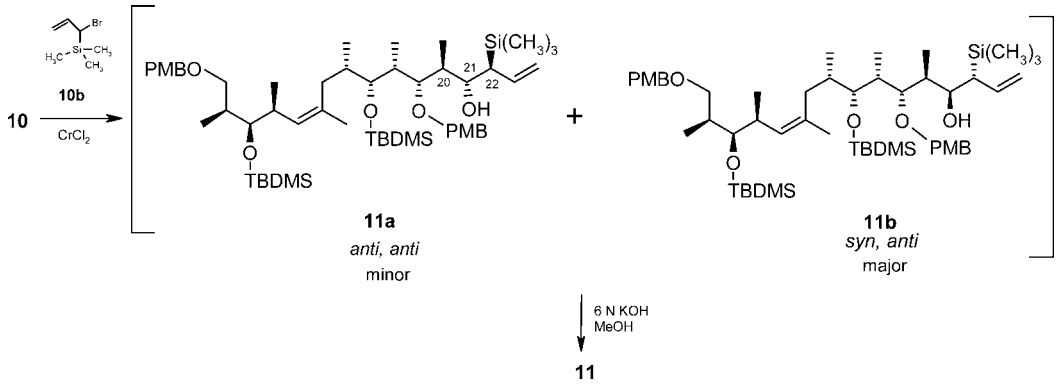
(6) (a) Takano, S.; Akiyama, M.; Sano, S.; Ogasawara, K. *Chem. Lett*. **1983**, 1593. (b) Evans, D. A.; Ng, H. P. *Tetrahedron Lett*. **1993**, *34*, 2229.
(7) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498.

(8) (a) Nakajima, N.; Uoto, K.; Yonemitsu, O. *Heterocycles* **1990**, *31*, 5. (b) McDonald, C. E.; Nice, L. E.; Kennedy, K. E. *Tetrahedron Lett*. **1994**, *35*, 57. (c) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem*. **2002**, *67*, 5176.

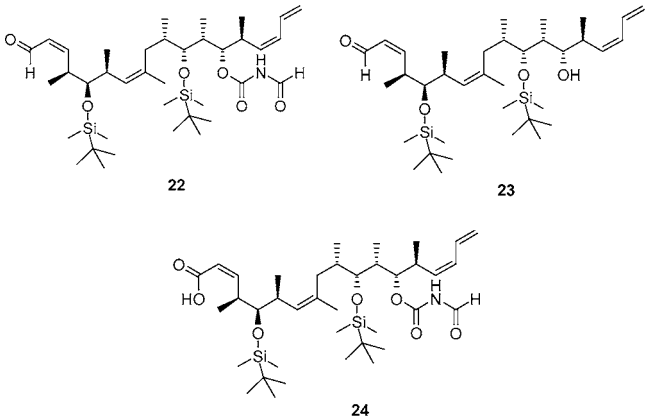
Scheme 3. **Synthesis of fragment C_{7-24} (7)**



Scheme 4. **Installation of the terminal diene unit**



by methanolysis as described by Paterson[2] in his modification of the Kocovsky procedure.[11] Reduction of the ester group **15** with DIBAL in dichloromethane at −78 °C yielded a mixture of alcohol **16** and aldehyde **7 (**10−20%, depending on the reaction time). Attempts to reduce ester **15** exclusively to aldehyde **7** were unsuccessful, since the latter was easily reduced to alcohol **16**. This mixture was used in the next step without further purification. Oxidation of **16** with iodobenzene diacetate and TEMPO in the presence of traces of water afforded **7** as a white foam in 80% yield (two steps from **15**) after chromatography. Three byproducts (**22, 23**, and **24**) were also isolated during the purification. Their origin could be attributed to byproducts present in the previous steps.



Having successfully assembled the pivotal fragment C_{7-24}, we were ready to address the most challenging phase of the entire campaign, the finale based on the C_6-C_7 coupling. The following contribution describes the chemistry involved

(9) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem*. **1997**, *62*, 6974.
(10) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(11) Kocovsky, P. *Tetrahedron Lett*. **1986**, *27*, 5521.

and the problems encountered in the large-scale synthesis of (+)-discodermolide.

Experimental Section

(4*S*,5*S*)-4-[(*Z*)-(1*R*,2*R*,3*S*,7*S*,8*R*,9*S*)-2,8-bis-(*tert*-butyldimethylsilanyloxy)-10-(4-methoxybenzyloxy)-1,3,5,7,9-pentamethyldec-5-enyl]-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxane (8). *(A) Suzuki Procedure.* A solution of *tert*-butyllithium (2.4 kg, 15%, 5.63 mol) in diethyl ether was diluted with 3 L of hexane and cooled to an internal temperature of −80 °C. To this solution was added a pre-cooled (−40 °C) solution of iodide **5a** (1.58 kg, 2.91 mol) in 16 L of tetrahydrofuran in 30 min, followed by the addition of a pre-cooled (−40 °C) solution of 9-methoxy-BBN (530 g, 3.49 mol) in tetrahydrofuran (5 L) in 15 min. A suspension formed after the addition. The cooling bath was removed, and this borane intermediate was added to a mixture of vinyl iodide **4** (1.1 kg, 2.12 mol) in DMF (19 L) containing $Pd(dppf)Cl_2$ (78 g, 0.10 mol) and cesium carbonate (2.4 kg, 7.37 mol, predissolved in 2 L of water) within 2.5 h. The resulting mixture was allowed to warm to 25 °C and stirred for an additional 20 h. The mixture was filtered through Cellflock (filter aid). The solid was rinsed with heptane, and the combined heptane filtrates were evaporated to a volume of about 12 L. Ethanolamine (235 g, 3.85 mol) was added, and the mixture was stirred for 15 min and filtered through Cellflock. The solids were rinsed with heptane (3 × 3 L). The combined heptane filtrates were evaporated to a volume of about 3 L. This concentrate was chromatographed on silica gel eluting with a mixture of heptane/*tert*-butyl methyl ether to give, after evaporation of the solvent, 2.07 kg of a light-orange oil. This oil was redissolved in a mixture of 8 L of acetonitrile and 2 L of heptane and warmed to 30 °C. About 2.5 L of the solvent was removed by distillation at 30 °C (mainly heptane), and the product began to crystallize. The suspension was cooled to room temperature, and the thick suspension was diluted with 3.5 L of acetonitrile. The suspension was cooled to 0 °C, stirred for 30 min, and filtered. The solid was rinsed with cold acetonitrile (1 L) and dried in a vacuum to give olefin **8** (1.26 kg, 73% based on **4**): $[\alpha]_D$ +27.7 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 7.22 (m, 2H), 6.85 (m, 4H), 5.37 (s, 1H), 4.99 (d, J = 9.97 Hz, 1H), 4.36 (ABq, J = 11.8 Hz, 2H), 4.09 (dd, J = 11.0 4.8 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.60 (dd, J = 7.0 & 1.9 Hz, 1H), 3.50−3.40 (m, 3H), 3.37 (dd, J = 6.3 4.8 Hz, 1H), 3.18 (pseudo t, J = 8.9 Hz, 1H), 2.50 (m, 1H), 2.31 (m, 1H), 2.11−1.82 (m, 4H), 1.65 (m, 1H), 1.54 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.7 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.72 (d, J = 6.2 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 9H). Note: The mother liquors were concentrated and chromatographed on silica gel to yield an additional 60−80 g of **8.** Further elution of the chromatography column led to the isolation of **5b**.

***tert*-Butyl-((*R*)-1-{(*R*)-1-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-[1,3]dioxan-4-yl]-ethyl}-2-methylpropoxy)-dimethylsilane (5b):** ^{1}H NMR (d_6-DMSO) δ 7.30 (m, 2H), 6.92 (m, 2H), 5.45 (s, 1H), 4.02 (dd, J = 11.9 5.5 Hz, 1H), 3.78 (s, 3H), 3.60−3.45 (m, 3H), 2.0−1.80 (m, 3H), 1.00−0.88 (m, 15H), 0.85 (d, J = 6.3 Hz, 3H), 0.62 (d, J = 6.5 Hz, 3H), 0.05 (s, 3H), 0.00 (s, 3H).

(B) Negishi Procedure. A solution of **5** (13.7 g, 25 mmol) in 400 mL of diethyl ether was treated with 26 mL of a 1.0 M solution of zinc chloride (1.0 M in diethyl ether), and the resulting thin suspension was cooled to an internal temperature of −75 °C. A solution of *tert*-butyllithium (40 mL, 1.7 M solution in pentane, 65 mmol) was added dropwise over 60 min. The solution was stirred for 30 min at −75 °C and slowly warmed to 20 °C within 60 min. The resulting white suspension was stirred for 60 min at 20 °C and treated with a solution of **4** (10.4 g, 20 mmol) in diethyl ether (140 mL). Tetrakis(triphenylphosphine)palladium(0) (1.0 g) was added, and the suspension was stirred for 3 h at 20 °C. The reaction mixture was treated with water (250 mL) and stirred for 30 min at 20 °C. The mixture was then filtered through Cellflock, and the solids were rinsed with 300 mL of *tert*-butyl methyl ether. The organic phase was separated and washed with brine (200 mL). The solvent was removed in vacuo at 30 °C to give 21.5 g of an oil. This oil was purified by silica gel chromatography eluting with hexane/ethyl acetate mixtures (1.5 L, 98/2 then 2 L, 94/6). The appropriate fractions were combined and evaporated to dryness to give 12.5 g, 76.8%, of **8** as a pink oil. This oil was dissolved in acetonitrile (200 mL) containing 10% hexane. The mixture was concentrated at 30 °C in vacuo (ca. 60 mL distilled) and cooled to 20 °C to induce crystallization. The suspension was stirred for 60 min at 25 °C and cooled to 0 °C, stirred for 60 min, and filtered. The solid was rinsed with 35 mL of cold acetonitrile, dried in vacuo at 20 °C to give **8** (10.0 g, 62% based on **4**): mp 79−80.5 °C; NMR identical to that above.

Alcohol 8b Crystal for X-ray. To a solution of olefin **8** (1.33 g, 1.6 mmol) in 16 mL of dichloromethane under a nitrogen atmosphere at 0 °C was added water (75 mg, 4.1 mmol). To this solution was added solid DDQ (387 mg, 1.7 mmol). The red-brown suspension was stirred at 0 °C for 4 h. The mixture was dried over $MgSO_4$, diluted with 20 mL of dichloromethane, and filtered. The filtrate was passed through a 1-in. thick pad of silica gel that was pre-wetted with ethyl acetate/hexane (1:1). The pad was rinsed with 25 mL of ethyl acetate/hexane (1:1). The filtrate was evaporated under vacuo to give an off-white solid (1.2 g). This solid was partially dissolved in 50 mL of ethanol at 23 °C. To the suspension was added solid sodium borohydride (250 mg, 6.7 mmol) at 23 °C. The resulting suspension was stirred for 20 min at 23 °C. The mixture was cooled to 0 °C, and quenched with saturated aqueous ammonium chloride (50 mL). The mixture was concentrated under vacuum to remove the ethanol. The residue was partitioned between dichloromethane (200 mL) and water (100 mL). The dichloromethane layer was separated, washed with water (100 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum to give a crude white solid (1.1 g, 100%). A single crystal of suitable size was grown for X-ray studies by dissolving 20 mg of this solid in 2-propanol and allowing the solvent to evaporate slowly under ambient conditions.

(*Z*)-(2*S*,3*S*,4*R*,5*R*,6*S*,10*S*,11*R*,12*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-3,13-bis-(4-methoxybenzyloxy)-2,4,6,8,10,12-hexamethyltridec-8-en-1-ol (9). A solution of olefin **8** (1.92 kg, 2.36 mol) in toluene (17 L) was cooled to an internal temperature of −15 to −20 °C. A solution of DIBAL in toluene (10.9 kg of a 1.0 M solution, 10.9 mol) was added dropwise within 60 min. The reaction mixture was warmed to 0−5 °C and stirred for 60 min. Ethyl acetate (15 L) was then added within 45 min, maintaining the temperature at 0 °C, followed by a solution of saturated sodium potassium tartrate (60 L). The mixture was warmed to 25 °C and stirred for an additional 60 min. The organic layer was separated. The aqueous phase was re-extracted with ethyl acetate (12 L). The combined organic phases were washed with 10 L of water. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo at 50 °C to give 1.91 kg of an oil. This oil was chromatographed on silica gel eluting with heptane/ethyl acetate, 3/1. The appropriate fractions were combined and concentrated to give **9** as an oil (1.78 kg, 92%): ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 4H), 6.85 (m, 4H), 5.01 (d, J = 10.5 Hz, 1H), 4.49 (ABq, J = 9.2 Hz, 2H), 4.36 (ABq, J = 11.7 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (dd, J = 11.3 & 2.9 Hz, 1H), 3.60−3.43 (m, 4H), 3.35 (m, 1H), 3.19 (pseudo t, J = 8.8 Hz, 1H), 2.80−2.67 (br s, exch D_2O, 1H), 2.49 (m, 1H), 2.22 (pseudo t, J = 12.0 Hz, 1H), 2.01−1.84 (m, 4H), 1.73 (m, 1H), 1.57 (s, 3H), 1.03 (m, 6H), 0.92 (m, 12H), 0.86 (m, 12H), 0.72 (d, J = 6 Hz, 3H), 0.06 (s, 6H), 0.00 (s, 6H).

(*Z*)-(2*R*,3*R*,4*R*,5*R*,6*S*,10*S*,11*R*,12*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-3,13-bis-(4-methoxybenzyloxy)-2,4,6,8,10,12-hexamethyltridec-8-enal (10). A solution of alcohol **9** (1.64 kg, 2.01 mol) in 10.5 L of dichloromethane containing 5.8 L of dimethyl sulfoxide was treated with 660 g, (6.52 mol) of triethylamine. The mixture was cooled to −5 °C, and a solution of sulfur trioxide/pyridine complex (768 g, 4.83 mol) in 9 L of dimethyl sulfoxide was added dropwise within 30 min. The mixture was stirred for 60 min at 0 °C, and heptane (30 L) was added followed by water (20 L). The organic phase was separated and washed sequentially with water (10 L), saturated sodium bicarbonate (10 L), and finally water (4 × 10 L). The organic phase was dried with $MgSO_4$ and filtered, and the solvent was removed to give an oil. This oil was purified by chromatography on silica gel to give **10** as an oil (1.53 kg, 93%): ^{1}H NMR ($CDCl_3$) δ 9.79 (d, J = 2.4 Hz, 1H), 7.21 (m, 4H), 6.84 (m, 4H), 5.01 (d, J = 10.2 Hz, 1H), 4.45 (ABq, J = 11.2 Hz, 2H), 4.35 (ABq, J = 11.9 Hz, 2H), 3.76 (s, 6H), 3.57−3.52 (m, 2H), 3.45 (dd, J = 9.2, 4.4 Hz, 1H), 3.36 (dd, J = 6.5, 4.8 Hz, 1H), 3.19 (pseudo t, J = 9.2 Hz, 1H), 2.73 (m, 1H), 2.49 (m, 1H), 2.23 (pseudo t, J = 12.3 Hz, 1H), 1.93 (m, 3H), 1.64 (m, 1H), 1.56 (s, 3H), 1.10 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.94−0.89 (m, 12H), 0.88−0.83 (m, 12H), 0.71 (d, J = 6.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 6H). The following compound (**17**) was also isolated from the chromatography.

(2*E*,8*Z*)-(4*R*,5*R*,6*S*,10*S*,11*R*,12*S*))-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-(4-methoxybenzyloxy)-2,4,6,8,10,12-hexamethyltrideca-2,8-dienal (17): ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1H), 7.22 (m, 2H), 6.84 (m, 2H), 6.36 (d, J = 9.5 Hz, 1H), 5.00 (d, J = 10.3 Hz), 4.36 (ABq, J = 12.7 Hz, 2H), 3.78 (s, 3H), 3.45 (m, 2H), 3.35 (dd, J = 4.83, 4.2 Hz, 1H), 3.19 (pseudo t, J = 7.8 Hz, 1H), 2.87 (m, 1H), 2.46 (m, 1H), 1.94 (m, 1H), 1.74 (s, 3H), 1.54 (s, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.91 (m, 12H), 0.86 (m, 12H), 0.72 (d, J = 6.6 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.00 (s, 6H).

***β*-Hydroxysilanes 11a and 11b.** A dried 5-L, four-necked, round-bottomed flask equipped with paddle stirrer, rubber septum, thermometer, and a glass stopper was filled with argon and placed in a dry bag under nitrogen purge. Chromium(II) chloride (23.1 g, 0.19 mol) was transferred to the flask in the dry bag under nitrogen purge. The flask was sealed and placed on a mechanical stirrer. Anhydrous, degassed THF (1.0 L, inhibited with 250 ppm of 2,6-di-*tert*-butyl-4-methylphenol) was added via cannula, and the green suspension was cooled to 0 °C under argon purge. A solution of aldehyde **10** (34.0 g, 0.04 mol) in anhydrous, degassed THF (2.2 L) was further degassed with argon for 30 min and transferred via cannula to the reaction flask. Allyl bromide **10b** (40.4 g, 0.21 mol) was added via syringe. With cooling bath in place and positive argon pressure applied, the reaction mixture was allowed to warm to 25 °C and stirred for an additional 16 h. Analytical samples for **11a** and **11b** were obtained by flash chromatography on SiO_2 (hexanes/ethyl acetate, 95/5, for **11a** and hexanes/ethyl acetate, 90/10, for **11b**).

***β*-Hydroxysilane 11a:** colorless oil; R_f 0.35 (toluene); $[\alpha]^{25}_D$ −3.3 (c = 0.5, $CHCl_3$); IR (KBr) 3496, 2957, 2930, 2856, 1613, 1514, 1463, 1360, 1302, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28−7.21 (m, 4H), 6.90−6.82 (m, 4H), 5.98 (ddd, J = 17.4, 10.4, 10.4 Hz, 1H), 5.03 (d, J = 10.2 Hz, 1H), 4.95 (dd, J = 10.2, 2.1 Hz, 1H), 4.83 (dd, J = 17.3, 2.1 Hz, 1H), 4.52 (ABq, J_{AB} = 10.8 Hz, $\Delta\delta_{AB}$ = 29.3 Hz, 2H), 4.38 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 19.4 Hz, 2H), 3.86 (b, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.76−3.71 (m, 1H), 3.52 (dd, J = 6.6, 2.0, 1H), 3.48 (dd, J = 9.2, 4.9 Hz, 1H), 3.39 (dd, J = 6.3, 4.7 Hz, 1H), 3.34 (dd, J = 6.4, 3.5 Hz, 1H), 3.21(dd, J = 8.7, 8.7 Hz, 1H), 2.57−2.44(m, 1H), 2.32 (dd, J = 12.4, 12.4, 1H), 2.01−1.79 (m, 4H), 1.73 (bd, J = 10.7, 1H), 1.68 (bd, J = 11.3, 1H), 1.59 (s, 3H), 0.97 (d, J = 7.0, 3H), 0.93 (d, J = 7.5, 3H), 0.92 (s, 9H), 0.89 (d, J = 7.5, 3H), 0.88 (s, 9H), 0.77 (d, J = 6.9, 3H), 0.74 (d, J = 6.7, 3H), 0.068 (s, 3H), 0.062 (s, 3H), 0.037 (s, 9H), 0.029 (s, 3H), 0.023 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.8, 159.4, 136.3, 132.0, 131.9, 131.4, 130.5, 129.9, 129.4, 114.3, 114.1, 113.8, 87.4, 78.8, 77.9, 75.3, 75.0, 73.1, 72.9, 55.7, 42.0, 41.3, 39.9, 39.2, 37.8, 36.1, 35.3, 32.0, 26.7, 26.5, 23.6, 23.0, 18.9, 18.8, 17.5, 16.2, 14.9, 14.5, 13.0, 12.2, −1.8, −2.8, −2.9, −3.4, −3.5. Anal. Calcd for $C_{53}H_{94}O_7Si_3$: C, 68.63; H, 10.21; Si, 9.08. Found: C, 68.74; H, 10.02; Si, 9.03.

***β*-Hydroxysilane 11b:** colorless oil; R_f 0.07 (toluene); $[\alpha]^{25}_D$ +3.2 (c = 0.8, $CHCl_3$); IR (KBr) 2957, 2931, 2856, 1613, 1513, 1463, 1376, 1312, 1249, 1080, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 5.65, 2 H), 7.24 (d, J = 5.8 Hz, 2H), 6.90−6.82 (m, 4H), 5.82 (ddd, J = 17.1, 10.4, 10.4 Hz, 1H), 5.04 (d, J = 10.2 Hz, 1H), 5.00 (dd, J = 10.4, 2.0

Hz, 1H), 4.91 (dd, J = 17.1, 1.8 Hz, 1H), 4.54 (ABq, J_{AB} = 10.8 Hz, $\Delta\delta_{AB}$ = 25.9 Hz, 2H), 4.38 (ABq, J_{AB} = 11.6 Hz, $\Delta\delta_{AB}$ = 17.9 Hz, 2H), 4.16−4.10 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.52 (dd, J = 5.6, 3.4 Hz, 1H), 3.48 (dd, J = 9.2, 4.9 Hz, 1H), 3.43 (dd, J = 5.6, 5.6 Hz, 1H), 3.40 (dd, J = 6.1, 4.7 Hz, 1H), 3.21 (dd, J = 8.8, 8.8 Hz, 1H), 2.62 (b, 1H), 2.56−2.46 (m, 1H), 2.28 (dd, J = 12.4, 12.4 Hz, 1H), 2.01−1.88 (m, 3H), 1.88−1.74 (m, 2H), 1.71 (bd, J = 12.1 Hz, 1H), 1.60 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.94 (s, 9H), 0.89 (s, 9H), 0.88 (d, J = 7.3 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H), 0.071 (s, 3H), 0.068 (s, 3H), 0.03 (s, 3H), 0.025 (s, 3H), 0.021 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.1, 159.0, 138.0, 131.54, 131.49, 131.0, 130.9, 129.0, 114.0, 113.77, 113.68, 85.0, 78.4, 77.6, 75.2, 72.7, 72.5, 69.7, 55.3, 42.1, 40.2, 39.3, 38.8, 36.8, 35.7, 35.1, 26.3, 26.1, 23.1, 22.7, 18.5, 18.4, 17.1, 14.1, 13.4, 11.7, 10.8, −1.9, −3.2, −3.8, −3.9. Anal. Calcd for $C_{53}H_{94}O_7Si_3$: C, 68.45; H, 9.84; Si, 9.13. Found: C, 68.57; H, 10.20; Si, 9.06.

1-[(5*Z*,13*Z*)-(2*S*,3*R*,4*S*,8*S*,9*R*,10*R*,11*S*,12*S*)-11-(4-Methoxybenzoxy)-3,9-bis-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,-10,12-hexamethylhexadeca-5,13,15-trienyloxymethyl]-4-methoxybenzene (11). A suspension of chromium(II) chloride (980 g, 7.97 mol) in tetrahydrofuran (90 L) was cooled to 0 °C and treated with a solution of aldehyde **10** (1.52 kg, 1.87 mol) in tetrahydrofuran (20 L). To the suspension was added a solution of 1-bromoallyltrimethylsilane (2.0 kg, 10.4 mol) in tetrahydrofuran (10 L). The mixture was stirred for 15 min at 0 °C and warmed to 15 °C, stirred for 60 min, and recooled to 0 °C. Methanol (7.5 L) was added followed by 15 L of a 6 M solution of potassium hydroxide. The mixture was warmed to 25 °C and stirred for 16 h. The organic phase was separated and the aqueous phase re-extracted with 30 L of tetrahydrofuran. The combined organic layers were washed with brine (10 L) and concentrated to give 1.71 kg of an oil. The oil was purified by chromatography on silica gel eluting with heptane/isopropyl alcohol mixtures to give *cis*-diene **11** as an oil (1.27 kg, 81%): ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 4H), 6.84 (m, 4H), 6.57 (dt, J = 16.5, 10.5 Hz, 1H), 5.99 (pseudo t, J = 10.6 Hz, 1H), 5.55 (pseudo t, J = 10.4 Hz, 1H), 5.18 (d, J = 16 Hz, 1H), 5.09 (d, J = 9.0 Hz, 1H), 4.94 (d, J = 10 Hz, 1H), 4.50 (ABq, J = 9.6 Hz, 2H), 4.35 (ABq, J = 11.2 Hz, 2H), 3.77 (s, 3H), 3.76 (2, 3H), 3.42 (m, 2H), 3.34 (m, 1H), 3.26−3.14 (m, 2H) 2.98 (m, 1H), 2.43 (m, 1H), 2.06−1.89 (m, 2H), 1.85−1.69 (m, 2H), 1.51 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.93 (m, 9H), 0.90 (d, J = 6.4 Hz, 3H), 0.86 (m, 9H), 0.84 (d, J = 6.9 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H), 0.08 (s, 6H), 0.00 (s, 6H).

(5*Z*,13*Z*)-(2*S*,3*R*,4*S*,8*S*,9*R*,10*R*,11*S*,12*S*)-3,9-Bis-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,10,12-hexamethylhexadeca-5,13,15-triene-1, 11-diol (12). To a solution of diene **11** (1.28 kg, 1.51 mol) in 20 L of dichloromethane was added solid DDQ (983 g, 4.33 mol). The red-brown suspension was stirred for 75 min at 25 °C and filtered through Cellflock. The solid was rinsed with 20 L of dichloromethane in two portions, and the solvent was concentrated to give 1.41 kg of a red oil. This was purified by chromatography over silica gel eluting with toluene/ethyl acetate mixtures (initially 97.5/2.5, finally 90/10). The fractions containing product were combined and concentrated to afford diol **12** as a foam (792 g, 88%): ^{1}H NMR ($CDCl_3$) δ 6.62 (dtd, J = 16.8, 11.7, 1.09 Hz, 1H), 6.13 (pseudo t, J = 10.9 Hz, 1H), 5.32 (pseudo t, J = 10.4 Hz, 1H), 5.22 (d, J = 16.7 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 3.66 (dd, J = 10.9, 4.5 Hz, 1H), 3.61 (dd, J = 5.8, 3.3 Hz, 1H), 3.39 (dd, J = 6.9, 3.8 Hz, 1H), 3.33 (dd, J = 8.1, 3.0 Hz, 1H), 2.80 (m, 1H), 2.57 (m, 1H), 2.17 (pseudo t, J = 11.7 Hz, 1H), 1.95−1.75 (m, 7H, becomes 5H on D_2O), 1.62 (s, 3H), 1.00−0.88 (m, 30H), 0.75 (d, J = 6.6 Hz, 3H), 0.09 (s, 6H), 0.08 (s, 6H).

(5*Z*,13*Z*)-(2*R*,3*R*,4*S*,8*S*,9*R*,10*R*,11*S*,12*S*)-3,9-Bis-(*tert*-butyldimethylsilanyloxy)-11-hydroxy-2,4,6,8,10,12-hexamethylhexadeca-5,13,15-trienal (13). To a solution of alcohol **12** (782 g, 1.31 mol) in dichloromethane (4 L) was added water (2.4 g). A mixture of iodobenzene diacetate (620 g, 1.92 mol) and TEMPO (40.1 g) was added in five portions over a period of 30 min with vigorous stirring. The orange reaction mixture was stirred for an additional 60 min at 25 °C and a 25% solution of sodium thiosulphate was added. The mixture was stirred for 15 min, and the organic phase was separated. The aqueous phase was re-extracted with dichloromethane (5 L), and the combined organic phases were treated with solid sodium bicarbonate (400 g). The suspension was filtered. The filtrate was washed with water (2 L) and evaporated in vacuo at 20 °C to give aldehyde **13** as a red oil (1.10 kg): ^{1}H NMR ($CDCl_3$) δ 9.63 (s, 1H), 6.64 (dt, J = 16.8, 11.7 Hz, 1H), 6.15 (pseudo t, J = 10.9 Hz, 1H), 5.35 (pseudo t, J = 10.2 Hz, 1H), 5.25 (d, J = 16.7 Hz, 1H), 5.17 (d, J = 9.8 Hz, 1H), 4.83 (d, J = 10.5 Hz, 1H), 3.76 (dd, J = 8, 3.6 Hz, 1H), 3.62 (dd, J = 5.8, 3.3 Hz, 1H), 3.36 (dd, J = 7.6, 3.3 Hz, 1H), 2.83 (m, 1H), 2.54 (m, 1H), 2.19 (pseudo t, J = 12.4 Hz, 1H), 1.96−1.72 (m, 4H), 1.60 (s, 3H), 1.08 (d, J = 7.1 Hz, 3H), 1.01−0.86 (m, 27H), 0.74 (d, J = 6.5 Hz, 3H), 0.10 (s, 9H), 0.07 (s, 3H). This oil was used without further purification.

(2*Z*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-hydroxy-4,6,8,10,12,14-hexamethyloctadeca-2,7,15,17-tetraenoic Acid Methyl Ester (14). A solution of 18-crown-6 (315 g), and bis-2,2,2-trifluoroethylphosphonoacetic acid methyl ester (570 g, 1.8 mol) in 10.3 L of toluene was cooled to 0 °C and treated with a solution of potassium hexamethyldisilazide in toluene (3 kg, 0.5 M solution, 1.72 mol). The red solution was stirred for 45 min at 0 °C and cooled to −20 °C. A solution of crude aldehyde **13** (1.05 kg, 1.76 mol) in toluene (3 L) was added within 15 min. The reaction mixture was stirred for 10 min, warmed to 0 °C, and stirred for an additional 90 min. The reaction was quenched with saturated aqueous ammonium chloride solution (10 L). The organic phase was separated, washed with brine (10 L), dried over $MgSO_4$, filtered, and concentrated to produce a yellow oil. Chromatography over silica gel eluting with hexane/ethyl acetate, 15/1, afforded ester **14** (622 g, 76% from **12**): $[\alpha]^{20}_D$ +53.7 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.64 (dtd, J = 16.9, 10.6, 1.0 Hz, 1H), 6.36 (dd, J = 11.9, 9.7 Hz, 1H), 6.12

(pseudo t, J = 11.1 Hz, 1H), 5.70 (d, J = 11.4 Hz, 1H), 5.33 (pseudo t, J = 10.6 Hz, 1H), 5.23 (dd, J = 16.8, 2.0 Hz, 1H), 5.14 (d, J = 9.8 Hz, 1H), 4.90 (d, J = 10.6 Hz, 1H), 3.71−3.61 (m, 4H), 3.57 (dd, J = 5.7, 3.5 Hz, 1H), 3.38−3.29 (m, 2H), 2.80 (m, 1H), 2.31 (m, 1H), 2.09 (pseudo t, J = 12.4 Hz, 1H), 1.89−1.73 (m, 2H), 1.64 (d, J = 11.6, 1H), 1.55 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.91−0.89 (m, 18H), 0.81 (d, J = 6.9 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 9H). Further elution of the chromatography column led to the isolation of **18**.

(2*E*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-hydroxy-4,6,8,10,12,14-hexamethyloctadeca-2,7,15,17-tetraenoic acid methyl ester (18): ^{1}H NMR ($CDCl_3$) δ 6.94 (dd, J = 15.3, 7.4 Hz, 1H), 6.59 (dtd, J = 16.8, 10.65, 1.1 Hz, 1H), 6.10 (pseudo t, J = 11.9 Hz, 1H), 5.64 (dd, J = 15.9, 1.7 Hz, 1H), 5.30 (pseudo t, J = 10.8 Hz, 1H), 5.20 (dd, J = 16.5, 2.3 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 4.88 (d, J = 10.3 Hz, 1H), 3.74−3.53 (m, 5H), 3.51−3.26 (m, 2H), 2.77 (m, 1H), 2.55−2.33 (m, 2H), 2.10 (pseudo t, J = 12.5 Hz, 1H), 1.90−1.77 (m, 4H), 1.54 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95−0.78 (m, 27H), 0.68 (d, J = 6.7 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

(2*Z*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-carbamoyloxy-4,6,8,10,-12,14-hexamethyloctadeca-2,7,15,17-tetraenoic Acid Methyl Ester (15). To a solution of ester **14** (739 g, 1.14 mol) in dichloromethane (5 L) was added dropwise trichloroacetyl isocyanate (332 g, 1.76 mol) over a period of 30 min. The reaction mixture was stirred for 90 min, and methanol (3 L) was added. The mixture was concentrated in vacuo at 20 °C until no more solvent distilled. Methanol (7.5 L) was added to the residue followed by solid sodium carbonate (365 g). The suspension was stirred at 25 °C for 2 h, and water (10 L) and *tert*-butyl methyl ether (10 L) were added. The organic phase was separated, and the aqueous phase was re-extracted with *tert*-butyl methyl ether (7.5 L). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give carbamate **15** (789 g, 100%) as a foam: $[\alpha]^{20}_D$ +76.3 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.58 (dtd, J = 17, 10.6, 1.0 Hz, 1H), 6.36 (dd, J = 11.6, 9.79 Hz, 1H), 6.01 (pseudo t, J = 11.4 Hz, 1H), 5.69 (dd, J = 11.6, 0.8 Hz, 1H), 5.37 (pseudo t, J = 10.8 Hz, 1H), 5.20 (dd, J = 17, 1.8 Hz, 1H), 5.12 (d, J = 10.1 Hz, 1H), 4.87 (d, J = 10.3 Hz, 1H), 4.71 (pseudo t, J = 5.9 Hz, 1H), 4.51 (s, 2H, NH_2), 3.71−3.61 (m, 4H), 3.39 (pseudo t, J = 4.5 Hz, 1H), 3.33 (dd, J = 7.2, 2.8 Hz, 1H), 2.97 (m, 1H), 2.27 (m, 1H), 1.99 (pseudo t, J = 12.8 Hz, 1H), 1.91−1.74 (m, 2H), 1.54 (s, 3H), 1.00 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.91 (m, 21H), 0.86 (d, J = 7.0 Hz, 3H), 0.67 (d, J = 6.9 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H). This was used without further purification.

(2*E*,7*Z*,15*Z*)-(4*S*,5*S*,6*S*,10*S*,11*R*,12*R*,13*S*,14*S*)-5,11-Bis-(*tert*-butyldimethylsilanyloxy)-13-carbamoyloxy-4,6,8,10,-12,14-hexamethyloctadeca-2,7,15,17-tetraenoic Acid Methyl Ester (19). Employing the same procedure for converting **14** to **15**, the *trans*-carbamate **19** can be obtained from the corresponding *trans*-ester **18** in a similar manner: ^{1}H NMR ($CDCl_3$) δ 6.93 (dd, J = 15.9, 7.2 Hz, 1H), 6.59 (dt, J = 16.9, 10.6 Hz, 1H), 5.99 (pseudo t, J = 11.1 Hz, 1H), 5.63 (dd, J = 15.5, 2.4 Hz, 1H), 5.33 (pseudo t, J = 10.2 Hz, 1H), 5.23−5.06 (m, 2H), 4.85 (d, J = 4.8 Hz, 1H), 4.69 (pseudo t, J = 6.3 Hz, 1H), 4.51 (s, 2H, NH_2), 3.74−3.53 (m, 5H), 3.51−3.26 (m, 2H), 2.77 (m, 1H), 2.55−2.33 (m, 2H), 2.10 (pseudo t, J = 12.5 Hz, 1H), 1.90−1.07 (m, 4H), 1.54 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95−0.78 (m, 27H), 0.68 (d, J = 6.7 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

Carbamic Acid (6*Z*,11*Z*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyl-dimethylsilanyloxy)-13-hydroxy-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-trideca-6,11-dienyl Ester (16). A solution of carbamate **15** (789 g, 1.14 mol) in dichloromethane (15 L) was cooled to −78 °C. A solution of DIBAL (5.6 L, 1.0 M solution in dichloromethane) was added dropwise over 60 min. The mixture was stirred for an additional 60 min at −78 °C and quenched with 12 L of a saturated aqueous solution of sodium potassium tartrate. Water (10 L) was added followed by *tert*-butyl methyl ether (10 L). The mixture was stirred vigorously for 15 min. The organic layer was separated and washed with water (2 × 7 L). The solvent was concentrated in vacuo at 20 °C to give crude alcohol **16** (810 g): $[\alpha]^{20}_D$ +76.3 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.56 (dtd, J = 16.8, 10.6, 1.1 Hz, 1H), 5.99 (pseudo t, J = 11.0 Hz, 1H), 5.59−5.67 (m, 2H), 5.32 (pseudo t, J = 10.6 Hz, 1H), 5.18 (dd, J = 16.8, 2 Hz, 1H), 5.09 (d, J = 10.3 Hz, 1H), 4.92 (d, J = 10.3 Hz, 1H), 4.67 (pseudo t, J = 6.1 Hz, 1H), 4.57−4.65 (s, 2H, NH_2), 4.04 (dd, J = 10.8, 3 Hz, 2H), 3.35 (dd, J = 5.7, 3.6 Hz, 1H), 3.21 (dd, J = 7.2, 3.4 Hz, 1H), 2.94 (m, 1H), 2.60 (m, 1H), 2.33 (m, 1H), 1.83 (m, 1H), 1.63−1.53 (m, 6H), 0.95 (d, J = 6.6 Hz, 3H), 0.92−0.86 (m, 24H), 0.84 (d, J = 6.6 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). This was used without further purification.

Carbamic Acid (6*Z*,11*E*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyl-dimethylsilanyloxy)-13-hydroxy-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-trideca-6,11-dienyl Ester (20). Employing the same procedure for converting **15** to **16**, the *trans*-allyl alcohol **20** can be obtained from the corresponding *trans*-ester **19** in a similar manner**:** ^{1}H NMR ($CDCl_3$) δ 6.57 (dt, J = 16.9, 0.5 Hz, 1H), 6.00 (pseudo t, J = 10.8 Hz, 1H), 5.65 (d, J = 7.4 Hz, 1H), 5.61 (d, J = 7.9 Hz, 1H), 5.52 (m, 1H), 5.34 (pseudo t, J = 10.5 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H), 5.10 (d, J = 10.1 Hz, 1H), 4.91 (d, J = 10.16 Hz, 1H), 4.69 (pseudo t, J = 6.1 Hz, 1H), 4.55−4.45 (s, 2H, NH_2), 4.05 (m, 1H), 3.31 (m, 2H), 3.24 (m, 1H), 2.90 (m, 1H), 2.55−2.33 (m, 2H), 2.10 (pseudo t, J = 12.5 Hz, 1H), 1.90−1.77 (m, 4H), 1.54 (s, 3H), 0.99 (d, J = 7 Hz, 3H), 0.95−0.78 (m, 27H), 0.68 (d, J = 6.7 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

Carbamic Acid (6*Z*,11*Z*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyl-dimethylsilanyloxy)-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-13-oxo-trideca-6,11-dienyl Ester (7). A solution of crude alcohol **16** (810 g, 1.22 mol) in dichloromethane (5 L) was charged with water (1.8 g). A mixture of iodobenzene diacetate (478 g, 1.5 mol) and TEMPO (31 g) was added in five portions over a period of

30 min with vigorous stirring. The orange reaction mixture was stirred for 60 min at 25°C, and a 25% solution of sodium thiosulphate was added. The mixture was stirred for 15 min, and the organic phase was separated. The aqueous phase was re-extracted with dichloromethane (5 L). The combined organic phases were treated with solid sodium bicarbonate (400 g). The suspension was filtered, and the filtrate was washed with water (2 L) and concentrated in a vacuum at 20 °C to give 1.04 kg of a red oil. This was purified by chromatography over silica gel eluting sequentially with mixtures of hexane/ethyl acetate, 12/1, 10/1, 8/1, and finally 4/1. The product fractions were combined, and the solvent was concentrated to give aldehyde **7** (647 g, 80%) as a white foam: $[\alpha]^{20}_{D}$ +84.9 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.78 (d, J = 8.1 Hz, 1H), 6.67 (pseudo t, J = 11.0 Hz, 1H), 6.54 (dtd, J = 17.0, 10.4 Hz, 0.95H, 1H), 5.94 (pseudo t, J = 10.7 Hz, 1H), 5.84 (dd, J = 11.3 & 8.5 Hz, 1H), 5.32 (pseudo t, J = 10.7 Hz, 1H), 5.16 (dd, J = 17.0, 2.0 Hz, 1H), 5.08 (d, J = 10.4 Hz, 1H), 4.87 (d, J = 10.4 Hz, 1H), 4.67 (pseudo t, J = 4.4 Hz, 1H), 4.56−4.41 (s, 2H, NH_2), 3.42−3.27 (m, 2H), 2.92 (m, 1H), 2.24 (m, 1H), 1.79 (m, 2H), 1.53 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.90−0.78 (m, 24H), 0.63 (d, J = 7.3 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H). The following byproducts (**22** and **23**) were also isolated by chromatography.

Formyl carbamate 22: ^{1}H NMR (d_6-DMSO) δ 10.91 (d, J = 9.2 Hz, 1H), 9.78 (d, J = 8.1 Hz, 1H), 8.87 (d, J = 8.5 Hz, 1H), 6.67−6.56 (m, 2H), 6.05 (pseudo t, J = 10.7 Hz, 1H), 5.83 (dd, J = 11.3, 8.5 Hz, 1H), 5.39 (pseudo t, J = 10.7 Hz, 1H), 5.25 (d, J = 17 Hz, 1H), 5.17 (d, J = 11.3 Hz, 1H), 5.00 (d, J = 10.4 Hz, 1H), 4.82 (pseudo t, J = 5.1 Hz, 1H), 3.55−3.20 (m, 4H [partially obscured by solvent]), 3.06 (m, 1H), 2.24 (m, 1H), 1.79 (m, 2H), 1.53 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.90−0.78 (m, 24H), 0.63 (d, J = 7.3 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H); MS (Na^+) 714.4.

Alcohol 23: ^{1}H NMR ($CDCl_3$) δ 9.75 (d, J = 7.9 Hz, 1H), 6.86 (pseudo t, J = 10.9 Hz, 1H), 6.54 (dt, J = 16.6, 10.3 Hz, 1H), 5.98 (pseudo t, J = 10.9 Hz, 1H), 5.84 (dd, J = 10.3, 8.0 Hz, 1H), 5.28−5.09 (m, 2H), 4.86 (m, 1H), 3.39−3.04 (m, 3H), 2.98 (m, 1H), 2.20 (m, 1H), 1.94−1.62 (m, 7H), 1.04 (d, J = 6.9 Hz, 3H), 0.965 (d, J = 6.9 Hz, 3H), 0.90−0.79 (m, 24H), 0.62 (d, J = 7.3 Hz, 3H), 0.04−0.00 (m, 12H).

Carbamic Acid (6*Z*,11*E*)-(1*S*,2*R*,3*R*,4*S*,8*S*,9*S*,10*S*)-3,9-Bis-(*tert*-butyldimethylsilanyloxy)-2,4,6,8,10-pentamethyl-1-((*Z*)-(*S*)-1-methylpenta-2,4-dienyl)-13-oxo-trideca-6,11-dienyl Ester (21). Employing the same procedure for converting **16** to **7**, *trans*-aldehyde **21** can be obtained from the corresponding *trans*-alcohol **20** in a similar manner: ^{1}H NMR ($CDCl_3$) δ 9.42 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 16.3, 7.0 Hz, 1H), 6.57 (dt, J = 16.7, 10.8 Hz, 1H), 6.01−5.89 (m, 2H), 5.31 (pseudo t, J = 10.8 Hz, 1H), 5.16 (d, J = 16.7 Hz, 1H), 5.08 (d, J = 10.1 Hz, 1H), 4.92 (d, J = 10.1 Hz, 1H), 4.66 (pseudo t, J = 5.9 Hz, 1H), 4.55−4.38 (s, 2H, NH_2), 3.42−3.29 (m, 2H), 2.93 (m, 1H), 2.61 (m, 1H), 2.35 (m, 1H), 1.81 (m, 2H), 1.57−1.49 (m, 5H), 1.03 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.89−0.78 (m, 24H), 0.64 (d, J = 7.3 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 9H).

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