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# Total Synthesis of Filipin III.

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***Abstract:*** Filipin III (**1**), a polyene macrolide antibiotic, has been synthesized for the first time. The polyol chain was assembled using a stereoselective carbon-carbon bond forming strategy previously developed in our lab: a cyanohydrin acetonide alkylation and reductive decyanation sequence. The polyene segment was prepared from L-ascorbic acid. These two components were coupled using Yamaguchi's esterification, and cyclized with an intramolecular Horner-Emmons reaction to form a trisubstituted alkene. Stereoselective reduction followed by deprotection gave filipin III. This highly convergent approach to filipin III represents the first total synthesis of a methylpentaene macrolide antibiotic. 

**Keywords**: synthesis, polyol, macrolides, antibiotics

Filipin belongs to a class of natural products known as the polyene macrolide antibiotics.[1] Although too toxic for therapeutic applications, Filipin has found widespread use as a histochemical stain for cholesterol and has even been used to quantitate cholesterol in cell membranes.[2] It was isolated in 1955 from the cell culture filtrates of *Streptomyces filipinensis*, found in the Philippine Islands[3] and was later shown to be a mixture of four components - filipin I (4%), II (25%), III (53%), and IV (18%).[4] The structure of filipin III, the major component of the filipin complex, was assigned in a series of degradation studies.[5] Recently, we completed the structure determination of filipin III by reporting its relative and absolute stereochemistry.[6] Reported herein is the first total synthesis of filipin III (**1**).[7]

Our retrosynthetic analysis of filipin III (Figure 1) took into account several limitations. The C16 methyl group confers increased acid lability when compared to other polyene macrolide antibiotics. Indeed, in the course of our stereochemical assignment work we discovered that the natural product decomposes upon exposure to strongly acidic conditions. Mild conditions gave a mixture of acetonides, with triacetonide **2** as the major product. Since this derivative, having the acetonide protecting groups at C3–C5, C7–C9, and C11–C13, was relatively stable, macrocycle **3**, which contains the same syn acetonides, was identified as a viable synthetic intermediate.

As shown in Figure 1, we envisioned that the macrocycle could be formed using a Horner-Emmons reaction. This approach was expected to be challenging for two reasons. First, closure at the C16–C17 double bond would require the formation of a trisubstituted alkene. And second, using a β-keto phosphonate for the Wittig reaction would require the stereoselective reduction of the obligatory ketone at a late stage of the synthesis. MM2 calculations indicated that the macrocyclic ring (Figure 2) blocks the top face of the ketone in **3**; thus reduction with a hydride reagent should give the desired configuration at C15. The lactone linkage could be formed using any one of a number of esterification reactions. This approach conveniently divides filipin III into a

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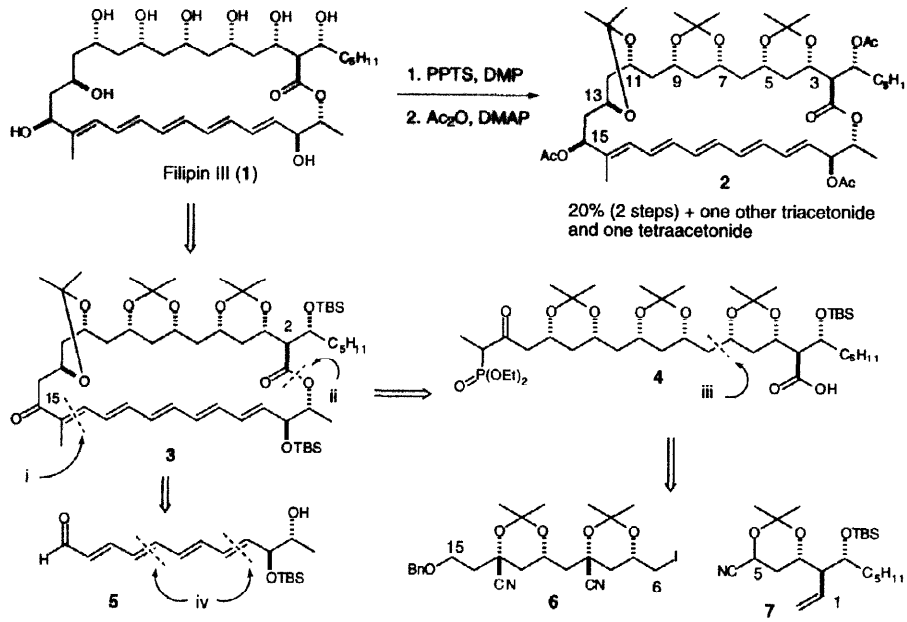



**Figure 1.** Retrosynthetic analysis of filipin III. (i) Horner-Emmons-Wittig, (ii) Yamaguchi esterification, (iii) Cyanohydrin acetonide alkylation, (iv) Wollenberg's reagent.

polyol segment **4** and a polyene segment **5**. The carboxylic acid functionality at C2 (filipin numbering) in the polyol segment can be masked as an alkene. The polyol segment **4** can be divided into two equally complex pieces, the C6–C15 piece **6** and the C1–C5 piece **7**, using the cyanohydrin acetonide alkylation methodology developed in this laboratory.[8] The polyene segment can be assembled by reacting a suitably functionalized aldehyde with Wollenberg's reagent.[9]

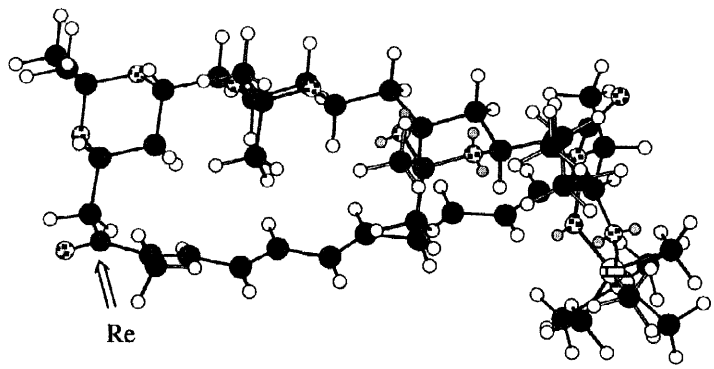
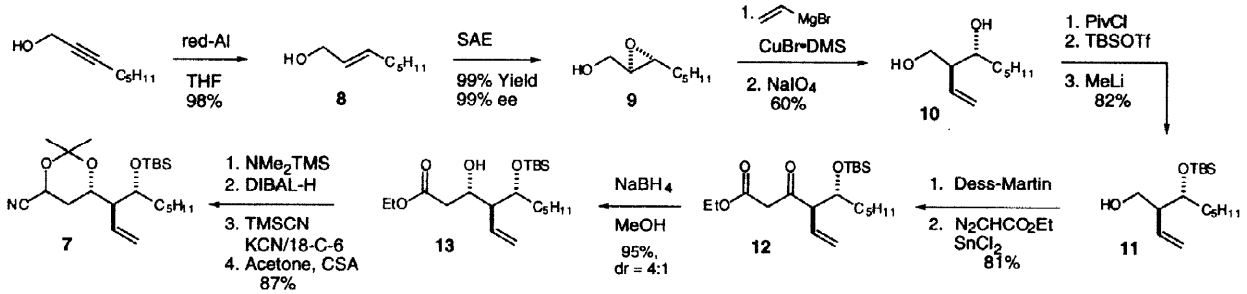



Figure 2. Stereoselective Re-face reduction of ketone **3** was predicted and observed. Ketone **3** was investigated with a 5000 step Monte Carlo search in Macromodel 5.5 using MM2 and $CHCl_3$ solvation.

The synthesis of the C1–C5 fragment **7** began with allylic alcohol **8** (Scheme 1) which was obtained in 98% yield by Red-Al reduction of 2-octyne-1-ol.[10] Sharpless asymmetric epoxidation[11] of allylic alcohol **8** provided oxirane **9** in near quantitative yield and 99% ee. Copper catalyzed nucleophilic opening of oxirane **9** with vinyl magnesium bromide gave a 2:1 mixture of regioisomers.[12] The minor, undesired 1,2-diol was oxidatively cleaved to the aldehyde so that the desired 1,3-diol **10** could be easily isolated by chromatography in 60% yield. A three step protection–deprotection sequence provided mono–TBS protected diol **11** in 82% overall yield from **10**. Oxidation of **11** to the aldehyde followed by reaction with ethyl diazoacetate catalyzed by $SnCl_2$[13] provided β-keto

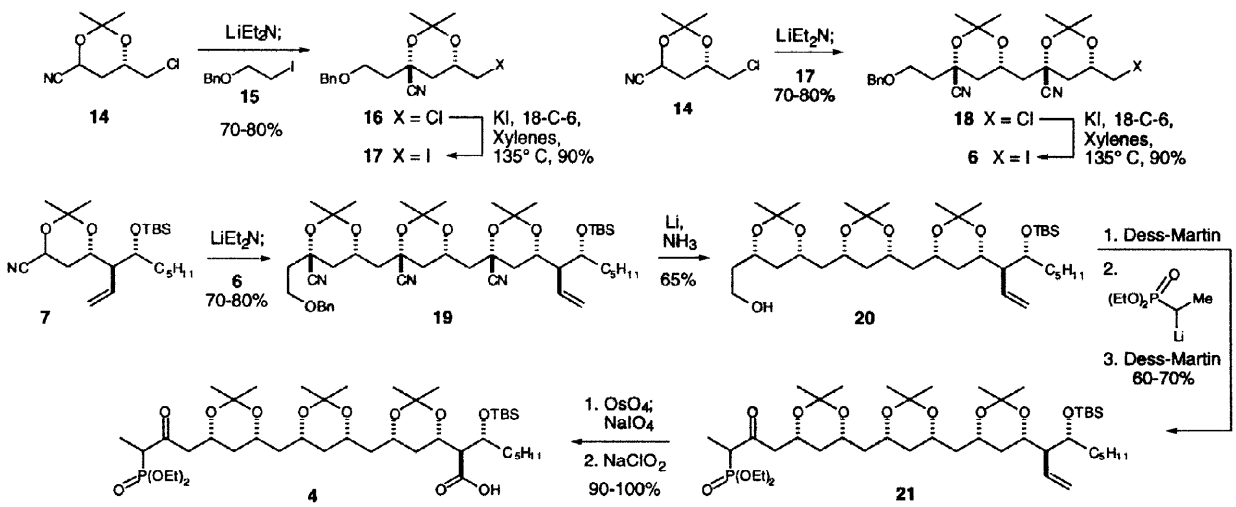
ester **12** in 81% yield. Reduction of β-keto ester **12** with $NaBH_4$ in MeOH provided the required β-hydroxy ester **13** in 95% yield with a diastereomeric ratio of 4:1. The diastereomers could be separated by silica gel MPLC and the minor undesired 1,3-*anti* diastereomer could be oxidized back to the β-keto ester and recycled. Silyl protection of the free alcohol of **13** followed by reduction of the ethyl ester to the aldehyde and cyanohydrin acetonide formation completed the synthesis of the C1–C5 piece **7**.

**Scheme 1**




The synthesis of the entire polyol chain of Filipin III is outlined in. Chlorocyanohydrin acetonide **14** was prepared from ethyl 4-chloroacetoacetate (65% overall yield, 94% ee).[8] Alkylation of iodide **15** with the anion of **14** gave the alkylated nitrile **16** in 70–80% yield. Conversion of **16** to iodide **17** was accomplished in high yield using forcing conditions. A second alkylation of **14**, this time with iodide **17**, provided dinitrile diacetonide **18** in 70–80% yield. Conversion of **18** to the iodide completed the synthesis of the C6–C15 piece **6**.

**Scheme 2**



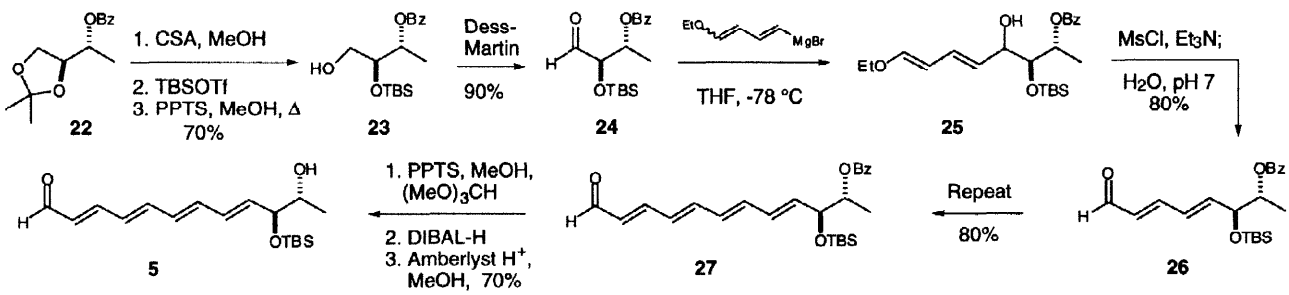

Cyanohydrin acetonide **7** was deprotonated with lithium diethyl amide and then alkylated with iodide **7** to give coupled product **19**. Addition of DMPU to this coupling reaction resulted in low yields due to facile degradation of the anion of **7**. The anion was stable in THF at –30 °C without DMPU and prolonged alkylation times (16 hrs) at this temperature resulted in consistently high yields of 70–80%. Reductive decyanation along with concurrent deprotection of the benzyl group afforded triacetonide **20** as a single diastereomer in 60–70% yield. The free hydroxyl of **20** was oxidized with Dess-Martin periodinane to the aldehyde that was then alkylated with the lithium anion of ethyl diethylphosphonate to give a secondary alcohol. The alcohol was immediately

oxidized to provide β-keto phosphonate **21** as a 1:1 mixture of diastereomers. This mixture is of no consequence as the methyl-bearing center is lost after the Wittig reaction to form the macrocyclic ring.

At this point it was necessary to oxidatively cleave the alkene to the acid. A one step oxidation catalyzed by $RuCl_3$[14] was effective but suffered from serious difficulties with regard to isolation and purification of the product. As a result, it was decided to rely on a three-step oxidation sequence. Initial attempts to dihydroxylate the alkene with $OsO_4$ were sluggish and unreliable. Fortunately, the reaction proceeded to completion in 16 hrs when carried out at 0.1 M concentration in substrate with 5 equivalents of NMO as the bulk oxidant and 10 mol percent of $OsO_4$. Addition of $NaIO_4$ to this reaction affected oxidative cleavage of the diol to the aldehyde, which could be isolated and characterized. Oxidation of the aldehyde to the acid using $KMnO_4$[15] was effective, but again, isolation and purification of the product was difficult. The much milder and cleaner oxidation with $NaClO_2$[16] turned out to be a practical alternative. After optimization, these conditions provided the completed polyol segment **4** in 90–100% yield.

The synthesis of the polyene segment is illustrated in Scheme 3. The appropriately protected triol **22** can be obtained conveniently on a large scale from L-ascorbic acid.[17] The acetonide protecting group was hydrolyzed with CSA and MeOH and the resulting 1,2-diol was protected as the bis-TBS ether. The primary TBS ether was then selectively cleaved with PPTS in MeOH to give **23** in 70% yield (starting material and fully deprotected diol could be separated and recycled). The free alcohol of **23** was oxidized with Dess-Martin periodinane to give aldehyde **24** in 90% yield. Aldehyde **24** was subjected to the Grignard reagent derived from Wollenberg's 1-(tributylstannyl)-4-ethoxybutadiene,[9] followed by mesylation and solvolysis[18] of the secondary alcohol **25** to provide dienal **26**. Repeating this sequence provided tetraenal **27** in 65% overall yield from **24**. The synthesis of the polyene segment **5** was completed by removing the benzoate protecting group of **27** in 70% yield using a three step procedure: protection of the aldehyde as the dimethyl acetal, cleavage of the benzoate with DIBAL-H, and then regeneration of the aldehyde with Amberlyst acid resin in MeOH. The same transformation could be accomplished in similar yield by reducing the benzoate and aldehyde concurrently with DIBAL and then selectively oxidizing the allylic alcohol with $MnO_2$.

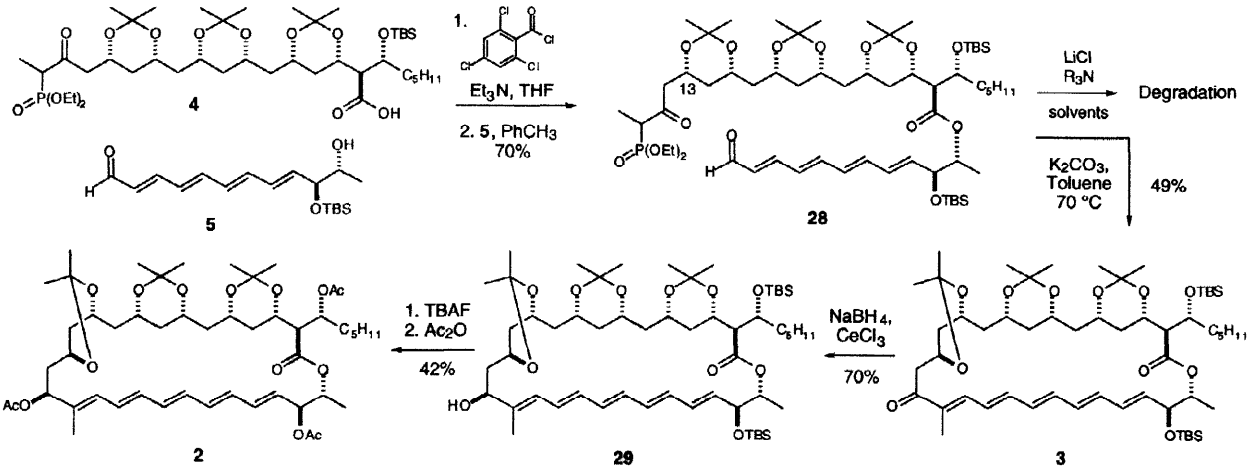
**Scheme 3**




The synthesis of macrocycle **3** is outlined in Scheme 4. Union of the polyol segment **4** and the polyene segment **5** proved difficult due to steric congestion about the ester linkage. A standard DCC/DMAP mediated esterification failed completely. Use of the BOP reagent[19] and DMAP also failed. The much more reactive PyBroP reagent[20] did result in successful coupling although in a disappointing 30% yield. Fortunately, it was found that this coupling could be accomplished efficiently using Yamaguchi's esterification protocol[21] to provide **28** in 70% yield. Formation of the macrocycle also proved to be challenging as mild methods to deprotonate the β-keto ester using amine bases and LiCl[22] resulted in elimination of the acetonide at C13, forming the α,β-

unsaturated ketone. Formation of the anion with $K_2CO_3$ in warm toluene[23] provided macrocycle **3** in an acceptable 49% yield. The ketone of **3** was reduced with $NaBH_4$ to provide a 3:1 mixture of C15 epimers,[24] which could be separated by flash chromatography to provide **29** as a single diastereomer in 70% yield.

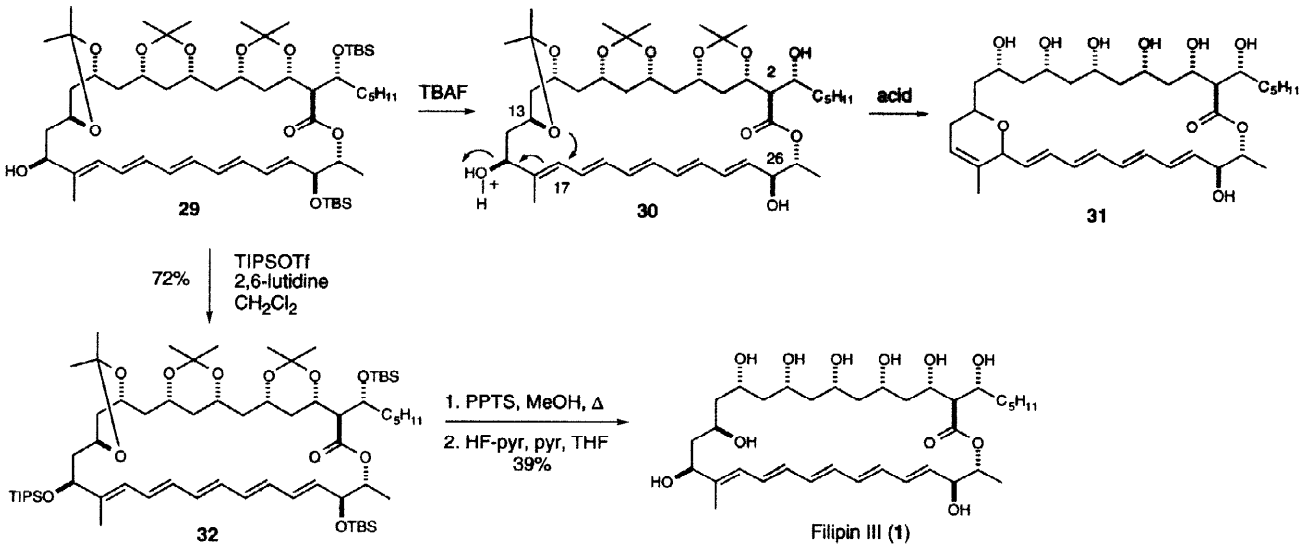
**Scheme 4**




Initial attempts to deprotect **29** with Dowex acid resin in methanol to give filipin III failed, giving a complex mixture of products similar to those obtained when the natural product is exposed to the same conditions. In order to insure we had made the correct diastereomer of the natural product, we decided to correlate the synthetic material to one of the acetonide derivatives that can be obtained directly from the natural product. The TBS protecting groups of **29** were removed and then the free hydroxyls acetylated to provide triacetonide **2** in 42% yield. This compound was compared to the major triacetonide of filipin III obtained during our stereochemical assignment work (figure 1). The two compounds were identical by TLC, $^1H$ NMR ($CDCl_3$ and $C_6D_6$) and optical rotation. These data insured that we had indeed synthesized filipin III, albeit in protected form. All that remained was the formidable challenge of deprotection.

The TBS groups of **29** can be removed with TBAF to give triacetonide **30** (Scheme 5). Complete deprotection of **30** is possible as judged by TLC using a variety of acidic conditions but failed to provide filipin III in good yield. The degradation products formed are less polar than filipin III. In addition, their UV-Vis spectra are blue shifted indicating that one of the alkenes is either gone or moved out of conjugation. Based on this limited information, we speculated that under acidic conditions, solvolysis of the alcohol at C15 occurs to give a cation conjugated throughout the polyene chain. The alcohols along the polyol chain can then attack the polyene to give a mixture of degradation products. For example, the alcohol at C13 could attack the polyene at C17 to form dihydropyran **31**. In order to reduce the propensity of the alcohol at C15 towards solvolysis, we decided to protect it with a TIPS group, which is stable to the acidic conditions necessary to deprotect the acetonides. Protection of **29** with TIPSOTf proceeded uneventfully to give **32** in 72% yield. The acetonides of **32** were removed with PPTS in warm methanol giving a mixture of products in which some of the TBS ethers have been removed as well. Exposure of this mixture to TBAF in THF gave a complex mixture of products that were more polar than filipin III. Although it seems unlikely, it might be possible these extremely basic conditions cause the lactone to hydrolyze. Deprotection of the silyl groups with HF•pyridine was successful giving filipin III in 39% overall yield from **32**. Synthetic and natural filipin III were identical by $^1H$ NMR, HRMS, and HPLC coinjection.

**Scheme 5**




Filipin III was prepared in a highly convergent route involving only 23 steps in the linear sequence from 2-octyne-1-ol. This synthesis demonstrates that our iterative strategy for the synthesis of *syn*-1,3-skipped polyol chains using synthon **14** is capable of building up the filipin III polyol chain quickly and easily. The deprotection of acetonides is particularly difficult when the natural product itself is acid sensitive. A solution to this problem was demonstrated in this synthesis. We identified an allylic alcohol that was a likely source of the difficulty and by reducing its propensity towards solvolysis we were able to deprotect the acetonides and produce the natural product. This highly convergent approach to filipin III represents the first synthesis of a methylpentaene macrolide antibiotic and should provide access to filipin III analogs by suitable modifications of the route.

## Experimental Section

**(2*R*,3*R*)-3-pentyloxirane-2-methanol (9).** The (*E*)-2-octene-1-ol, $Ti(OiPr)_4$, and *D*-(–)-diethyltartrate were freshly distilled. A 500 mL two neck flask was flame dried and flushed with Ar. Activated 4 Å sieves (1.5 g) and 200 mL of $CH_2Cl_2$ were added. The solution was cooled to –20 °C. A solution of *D*-(–)-diethyltartrate (1.54 g, 7.50 mmol) in 10 mL of $CH_2Cl_2$ and a solution of $Ti(OiPr)_4$ (1.86 mL, 6.2 mmol) in 10 mL of $CH_2Cl_2$ were each separately stirred with 4 Å sieves for 15 min and then transferred to the reaction flask via cannula. *Tert*-butyl hydroperoxide (13.5 mL of a 5.8 M solution in decane) was added to the solution via syringe. The reaction was stirred at –25 °C for 40 min. Then a solution of *E*-2-octene-1-ol (4.0 g, 31.2 mmol) in 10 mL of $CH_2Cl_2$ was stirred with 4 Å sieves for 15 min and then transferred to the reaction flask via cannula. The reaction was stirred at –25° C for 3 hr. The reaction was then warmed to 0 °C, 35 mL of water was added, and the reaction stirred for 1 hr. A 30% NaOH aqueous solution saturated with NaCl (6 mL) was added. After 20 min of stirring the solution had separated into two phases. The aqueous phase was extracted (2 x 100 mL) with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10–50% EtOAc/hexanes to yield 4.45 g (30.0 mmol, 99%) of a white solid: Analysis by chiral GC showed the product was 99% ee; mp = 34–36 °C; $[\alpha]_D^{27}$ =

+38.9 ($c$ = 1.11, $CHCl_3$); IR (neat) 3254, 3117, 2987, 2931, 2853 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.87 (ddd, $J$ = 2.4, 5.8, 12.5 Hz, 1 H), 3.57 (ddd, $J$ = 4.6, 6.9, 12.5 Hz, 1 H), 2.93–2.88 (m, 2 H), 2.43 (t, $J$ = 7.1 Hz, 1 H), 1.58–1.22 (m, 8 H), 0.863 (t, $J$ = 6.9 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H, 58.7, 56.1, *C*$H_2$, 61.8, 31.6, 31.5, 25.6, 22.5, *C*$H_3$, 14.0. Anal. calcd for $C_8H_{16}O_3$: C, 66.63; H, 11.18. Found: C, 66.40; H, 10.98.

**(3*S*,4*R*)-3-Hydroxymethyl-1-nonen-4-ol (10).** A 1000 mL flask was charged with freshly prepared CuBr•DMS (14.3 g, 69.6 mmol) and 200 mL of $Et_2O$. The solution was cooled to –25 °C. Methyl sulfide (10 mL, 136 mmol) and vinylmagnesium bromide (140 mL of a 1.0 M solution in THF, 140 mmol) were added and the reaction stirred for 15 min. A solution of oxirane **9** (4.0g, 27.7 mmol) in 10 mL of $Et_2O$ was added. The reaction was stirred at –20 °C for 16 hr and then allowed to warm to room temperature and stirred for 6 hr. The reaction was quenched with 200 mL of saturated $NH_4Cl$ which had been brought to pH 8 with $NH_4OH$. The aqueous layer was extracted (3 x 100 mL) with $Et_2O$. The combined organic layers were washed with brine, dried ($MgSO_4$), and then concentrated under reduced pressure. The crude mixture of diols was taken up in 150 mL of THF and 100 mL of water. $NaIO_4$ (12 g, 56 mmol) was added. The reaction was stirred for 1.5 hr and then diluted with 200 mL of brine. The aqueous phase was extracted (3 x 200 mL) with $Et_2O$. The combined organic layers were dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 30–50% EtOAc/hexanes to give 2.88 g (16.7 mmol, 60%) of a colorless oil: $[\alpha]_D^{27}$ = 22.5 ($c$ = 1.48, $CHCl_3$); IR (neat) 3348, 3078, 2955, 2930, 2865, 2860, 1640 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.64 (ddd, $J$ = 8.8, 11.1, 16.3 Hz, 1 H), 5.19–5.15 (m, 2 H), 3.82–3.67 (m, 3 H), 2.76 (t, $J$ = 5.0 Hz, 1 H), 2.56 (d, $J$ = 4.3 Hz, 1 H), 2.30 (m, 1 H), 1.59–1.23 (m, 8 H), 0.880 (t, $J$ = 7.0 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H, 136.2, 74.6, 51.4, *C*$H_2$, 117.8, 65.3, 35.4, 31.7, 24.9, 22.6, *C*$H_3$, 14.0. Anal. calcd for $C_{10}H_{20}O$: C, 69.72; H, 11.70. Found: C, 69.88; H, 11.36.

**(3*S*,4*R*)-3-*O*-(1,1-dimethylethyl)dimethylsilyl-3-hydroxymethyl-1-nonen-4-ol (11).** A 250 mL flask was charged with diol **10** (2.65 g, 15.4 mmol) and 150 mL of $CH_2Cl_2$. DMAP (94 mg, 0.77 mmol) and $Et_3N$ (2.15 mL, 15.4 mmol) were added and the solution was cooled to 0 °C. A solution of pivaloyl chloride (1.90 mL, 15.4 mmol) in 20 mL of $CH_2Cl_2$ was added dropwise via cannula. The reaction was stirred at room temperature for 4 hr. The reaction was quenched with 100 mL of saturated $NaHCO_3$. The aqueous layer was extracted (3 x 100 mL) with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 15–70% EtOAc/hexanes to give 3.32 g of a colorless oil.

The oil was dissolved in 130 mL of $CH_2Cl_2$ and transferred to a 250 mL flask. 2,6-Lutidine (2.0 mL, 17.2 mmol) was added and the solution was cooled to 0 °C. TBSOTf (3.27 mL, 14.2 mmol) was added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with 100 mL $NaHCO_3$. The aqueous layer was extracted (2 x 100 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 5% $Et_2O$/hexanes to give 4.56 g of a colorless oil.

The oil was dissolved in 120 mL THF and transferred to a 250 mL flask. The solution was cooled to 0 °C. Methyl lithium (20 mL of a 1.2 M solution in $Et_2O$, 24 mmol) was added. The reaction was stirred for 1 hr and then quenched with 100 mL of saturated $NH_4Cl$. The aqueous layer was extracted (3 x 100 mL) with EtOAc. The

combined organic layers were dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 15% EtOAc/hexanes to give 3.66 g (12.7 mmol, 82%) of a colorless oil: $[\alpha]_D^{27} = -13.1$ ($c$ = 1.45, $CHCl_3$); IR (neat) 3414, 3077, 2953, 2932, 2859, 1640 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, $J$ = 8.9, 9.7, 14.4 Hz, 1 H), 5.17–5.12 (m, 2 H), 3.77 (dt, $J$ = 5.6, 11.2 Hz, 1 H), 3.74–3.65 (m, 2 H), 2.48 (dd, $J$ = 4.5, 7.0 Hz, 1 H), 2.35 (dq, $J$ = 5.7, 8.9 Hz, 1 H), 1.52–1.48 (m, 2 H), 1.35–1.19 (m, 6 H), 0.882 (s, 9 H), 0.872 (t, $J$ = 6.9 Hz, 3 H), 0.064 (s, 3 H), 0.056 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 18.8 *C*H, 137.6, 75.2, 49.9, *C*$H_2$, 117.3, 63.5, 35.0, 32.0, 23.8, 22.6, *C*$H_3$, 25.8 (3), 14.0, –4.26, –4.69. Anal. calcd for $C_{16}H_{34}O_2Si$: C, 67.07; H, 11.96. Found: C, 67.13; H, 11.78.

**(4*S*, 5*R*)-5-(1,1-dimethylethyl)dimethylsiloxy-4-ethenyl-3-oxodecanoic acid, ethyl ester (12).** A 500 mL flask was charged with 100 mL of $CH_2Cl_2$, diol **11** (3.66 g, 12.7 mmol), and $NaHCO_3$ (3.63, 43.2 mmol). Dess-Martin periodinate (8.12 g, 21.6 mmol) was added and the reaction stirred for 1 hr. The reaction was quenched with 50 mL of saturated $NaHCO_3$ and 50 mL of 0.5 M $Na_2S_2O_3$ and stirred for 30 min. The aqueous layer was extracted (3 x 50 mL) with $CH_2Cl_2$. The combined organic layers were washed 2x with $NaHCO_3$, 2x with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude oil was purified by silica gel flash chromatography eluting with 10% EtOAc/hexanes to give 3.33 g of a colorless oil.

The oil was dissolved in 3 mL of $CH_2Cl_2$ and transferred via cannula into a 250 mL flask charged with 70 mL $CH_2Cl_2$, ethyl diazoacetate (1.48 mL, 14.1 mmol), and $SnCl_2$ (220 mg, 1.16 mmol). The reaction was stirred for 22 hr at room temperature. The solution was filtered through celite and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 5% EtOAc/hexanes to give 3.81 g (10.3 mmol, 81%) of a colorless oil: $[\alpha]_D^{24} = 57.1$ ($c$ = 1.20, $CHCl_3$); IR (neat) 3083, 2954, 2933, 2860, 1749, 1720, 1642 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.68 (dt, $J$ = 17.4, 9.7 Hz, 1 H), 5.20–5.15 (m, 2 H), 4.20–4.11 (m, 2 H), 4.08 (dt, $J$ = 8.4, 4.2 Hz, 1 H), 3.54 (d, $J$ = 15.8 Hz, 1 H), 3.46 (dd, $J$ = 9.1, 9.6 Hz, 1 H), 3.44 (d, $J$ = 15.8 Hz, 1 H), 1.48–1.38 (m, 2 H), 1.31–1.17 (m, 2 H), 1.24 (t, $J$ = 7.0 Hz, 3 H), 0.845 (s, 9 H), 0.845 (t, $J$ = 7.0 Hz, 3 H), 0.034 (s, 3 H), –0.009 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 202.3, 166.9, 18.0, *C*H, 133.0, 73.1, 62.4, *C*$H_2$, 119.5, 61.1, 50.7, 34.1, 32.0, 22.6, 22.4, *C*$H_3$, 25.8 (3), 14.3, 14.2, –4.53, –4.98. Anal. calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.33. Found: C, 64.92; H, 10.55.

**(3*S*,4*R*,5*R*)-5-(1,1-dimethylethyl)dimethylsiloxy-4-ethenyl-3-hydroxydecanoic acid, ethyl ester (13).** A 100 mL flask was charged with β-keto ester **12** (1.0 g, 2.7 mmol) and 25 mL of methanol. The solution was cooled to 0 °C and then $NaBH_4$ (520 mg, 13.7 mmol) was added. The reaction was stirred 10 min and then quenched with 5 mL of saturated $NH_4Cl$. The solution was partitioned between 20 mL of saturated $NH_4Cl$ and 25 mL of EtOAc. The aqueous layer was extracted (3 x 25 mL) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was filtered through a plug of silica gel eluting with $Et_2O$ and then the mixture of diastereomers was separated by MPLC on silica gel (4 x 30 cm) eluting with 5% EtOAc/hexanes to give 750 mg (2.0 mmol, 75%) of the major diastereomer and 200 mg (0.54 mmol, 20%) of the minor diastereomer.

major diastereomer: $[\alpha]_D^{25} = -19.1$ ($c$ = 1.05, $CHCl_3$); IR (neat) 3510, 3078, 2955, 2932, 2858, 1722, 1640 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.52 (dt, $J$ = 16.9, 10.1 Hz, 1 H), 5.13–5.07 (m, 2 H), 4.17–4.10 (m, 3 H), 3.91 (dt, $J$ = 11.3, 5.3 Hz, 1 H), 3.55 (d, $J$ = 3.5 Hz, 1 H), 2.56 (dd, $J$ = 3.3, 16.1 Hz, 1 H), 2.35 (ddd, $J$ = 6.5,

8.3, 10.1 Hz, 1 H), 2.31 (dd, $J$ = 9.1, 16.1 Hz, 1 H), 1.52–1.42 (m, 2 H), 1.38–1.20 (m, 6 H), 1.24 (t, $J$ = 7.1 Hz, 3 H), 0.886 (s, 9 H), 0.864 (t, $J$ = 7.2 Hz, 3 H), 0.095 (s, 3 H), 0.072 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 172.8, 18.1, *CH*, 135.4, 74.2, 68.9, 54.8, $CH_2$, 118.9, 60.5, 39.9, 34.1, 32.0, 23.7, 22.6, $CH_3$, 25.9 (3), 14.2, 14.1, –4.23, –4.59. Anal. calcd for $C_{20}H_{40}O_4Si$: C, 64.47; H, 10.82. Found: C, 64.13; H, 10.70.

minor diastereomer: $[\alpha]_D^{26}$ = 1.2 ($c$ = 1.24, $CH_2Cl_2$); IR (neat) 3503, 3075, 2956, 2931, 2858, 1721, 1639 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.99 (dt, $J$ = 17.3, 10.1 Hz, 1 H), 5.20–5.02 (m, 2 H), 4.51 (dddd, $J$ = 1.5, 1.7, 5.2, 8.3 Hz, 1 H), 4.12 (q, $J$ = 7.1 Hz, 2 H), 3.88 (dt, $J$ = 7.8, 4.6 Hz, 1 H), 3.71 (d, $J$ = 1.5 Hz, 1 H), 2.49 (dd, $J$ = 8.3, 15.9 Hz, 1 H), 2.29 (dd, $J$ = 5.2, 15.9 Hz, 1 H), 2.08 (ddd, $J$ = 1.7, 4.3, 9.8 Hz, 1 H), 1.78–1.20 (m, 8 H), 1.23 (t, $J$ = 7.1 Hz, 3 H), 0.867 (s, 9 H), 0.860 (t, $J$ = 6.9 Hz, 3 H), 0.059 (s, 3 H), 0.504 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 172.2, 18.0, *CH*, 135.8, 76.2, 66.4, 50.9, $CH_2$, 118.2, 60.4, 40.1, 35.0, 31.9, 24.2, 22.6, $CH_3$, 25.8 (3), 14.2, 14.0, –4.20, –4.77. Anal. calcd for $C_{20}H_{40}O_4Si$ : C, 64.47; H, 10.82. Found: C, 64.62; H, 10.60.

**(2*R*,4*S*,5*R*,6*R*) and (2*R*,4*S*,5*R*,6*R*)-2,4-dihydroxy-6-(1,1-dimethylethyl)dimethylsiloxy-5-ethenyl-2,4-*O*-(1-methylethylidine)-undecanenitrile (7).** A 50 mL flask equipped with an ice bath was charged with diol **13** (1.76 g, 4.72 mmol) and *N,N*-dimethyl trimethylsilyl amine (832 μL, 5.19 mmol). The reaction was allowed to warm to room temperature overnight. The thick oil was filtered through a plug of silica gel with $Et_2O$ and then concentrated under reduced pressure to a colorless oil.

The oil was dissolved in 50 mL of $Et_2O$, transferred to a 250 mL flask, and cooled to –78 °C. DIBAL-H (4.95 mL of a 1.0 M solution in cyclohexane, 4.95 mmol) was added dropwise. The reaction was stirred for 1 hr and then quenched with 150 μL of ethyl formate, warmed to 0 °C, and then 5 mL of 10% AcOH was added. The aqueous phase was extracted (3 x 30 mL) with $Et_2O$. The organic layers were washed with saturated $NaHCO_3$, water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure to a colorless oil.

The oil was transferred to a 250 mL flask equipped with an ice bath. Trimethylsilyl cyanide (860 mL, 7.09 mmol) was added followed by 1 mg of KCN/18-crown-6 complex. The reaction was stirred for 2 hr. A solution of 30 mL of acetone, 15 mL of 2,2-dimethoxypentane, and CSA (77 mg, 0.33 mmol) was added via cannula. The reaction was stirred for 14 hr. The reaction was quenched with 27 μL of $Et_3N$ and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 5% $Et_2O$/hexanes to give 1.62 g (4.09 mmol, 87%) of a colorless oil. A small amount of this mixture was further purified by silica gel chromatography to separate and characterize the two diastereomers.

Trans isomer: $[\alpha]_D^{26}$ = 36.4 ($c$ = 1.10, $CH_2Cl_2$); IR (neat) 3080, 2956, 2932, 2858, 1641, 1465 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.61 (dt, $J$ = 10.2, 16.9 Hz, 1 H), 5.16–5.04 (m, 2 H), 4.80 (t, $J$ = 4.1 Hz, 1 H), 4.18 (dt, $J$ = 6.0, 8.6 Hz, 1 H), 3.89 (dt, $J$ = 3.7, 7.5 Hz, 1 H), 4.57 (ddd, $J$ = 3.7, 8.6, 10.2 Hz, 1 H), 1.82–1.78 (m, 2 H), 1.63 (s, 3 H), 1.51–1.20 (m, 8 H), 1.34 (s, 3 H), 0.872 (s, 9 H), 0.866 (t, $J$ = 6.9 Hz, 3 H), 0.040 (s, 3 H), 0.027 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 119.9, 100.7, 18.1, *CH*, 134.1, 71.7, 64.8, 59.0, 54.9, $CH_2$, 119.1, 33.0, 32.3, 31.9, 25.4, 22.6, $CH_3$, 29.7, 25.9 (3), 21.7, 14.0, –4.34, –4.38. Anal. calcd for $C_{22}H_{41}NO_3Si$: C, 66.79; H, 10.44. Found: C, 67.00; H, 10.32.

Cis isomer: $[\alpha]_D^{26}$ = 29.9 ($c$ = 1.28, $CH_2Cl_2$); IR (neat) 3079, 2994, 2954, 2926, 2857, 1640, 1472, 1463 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 5.55 (dt, $J$ = 10.1, 16.8 Hz, 1 H), 5.16–5.05 (m, 2 H), 4.69 (dd, $J$ = 3.6, 11.3 Hz, 1 H), 3.92 (ddd, $J$ = 3.2, 8.4, 10.7 Hz, 1 H), 3.86 (m, 1 H), 2.29 (dt, $J$ = 3.9, 9.0 Hz, 1 H), 1.82–1.60 (m, 2 H),

1.40 (s, 3 H), 1.39 (s, 3 H), 1.31–1.16 (m, 8 H), 0.863 (s, 9 H), 0.873 (t, $J$ = 7.0 Hz, 3 H), 0.031 (s, 3 H), 0.024 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 117.9, 99.8, 18.1, *C*H, 134.0, 71.7, 67.1, 59.4, 54.7, *C*$H_2$, 119.3, 33.2 (2), 31.9, 25.2, 22.6, *C*$H_3$, 29.5, 25.9 (3), 19.0, 14.0, –4.36 (2). Anal. calcd for $C_{22}H_{41}NO_3Si$: C, 66.79; H, 10.44. Found: C, 66.65; H, 10.30.

**(2*S*,4*S*)-1-chloro-4-*C*-cyano-2:4-*O*-(1-methylethylidine)-6-*O*-phenylmethyl-hexane-2,4,6-triol (16).** A solution of chlorocyanohydrin acetonide **14** (1.50 g, 7.91 mmol) in 2 mL of THF was added via cannula to 9.29 mmol of $LiNEt_2$ in 20 mL of THF under Ar at –78 °C. The reaction was stirred for 2 hr. A solution of 2-(phenylmethoxy)-iodoethane (3.90 g, 14.9 mmol) in 2 mL of THF was then transferred to the reaction flask via cannula. DMPU (2.0 mL, 16.5 mmol) was added via syringe. The reaction was warmed to –30 °C with a MeOH/ice bath and then allowed to warm slowly to 15 °C over 15 hr. The reaction was quenched with 40 mL of saturated $NH_4Cl$ and then extracted (3 x 40 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10–15% EtOAc/hexanes to yield 1.64 g (6.26 mmol, 42%) of recovered iodide and 1.90 g (5.87 mmol, 74%) of the product as a colorless oil: $[\alpha]_D^{23}$ = 25.0 ($c$ = 1.10, $CHCl_3$); IR (neat) 3000, 2940, 2870, 2808, 1457, 1432 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H), 4.54 (d, $J$ = 11.8 Hz, 1 H), 4.51 (d, $J$ = 11.8 Hz, 1 H), 4.36 (dddd, $J$ = 2.1, 5.5, 7.6, 11.3 Hz, 1 H), 3.78–3.71 (m, 2 H), 3.56 (dd, $J$ = 5.3, 11.3 Hz, 1 H), 3.47 (dd, $J$ = 5.5, 11.3 Hz, 1 H), 2.19–2.12 (m, 2 H), 2.09 (dd, $J$ = 2.1, 13.6 Hz, 1 H), 1.72 (s, 3 H), 1.71 (dd, $J$ = 11.6, 13.6 Hz, 1 H), 1.41 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 137.8, 121.2, 101.5, 68.3, *C*H, 128.4 (2), 127.6 (3), 66.5, *C*$H_2$, 73.2, 64.8, 46.2, 41.9, 37.1, *C*$H_3$, 30.6, 21.4. Anal. calcd for $C_{17}H_{22}NO_3Cl$: C, 63.06; H, 6.85. Found: C, 62.86; H, 6.81.

**(2*S*,4*S*)-4-*C*-cyano-1-iodo-2:4-*O*-(1-methylethylidine)-6-*O*-phenylmethyl-hexane-2,4,6-triol (17).** A 100 mL Schlenk flask was charged with nitrile **16** (1.75 g, 5.40 mmol), 18-crown-6 (1.71 g, 6.47 mmol), and 40 mL of xylenes. The solution was purged with Ar and then powdered KI (22.4 g, 135 mmol) was added. The reaction was heated to reflux for 48 hr. After cooling to room temperature, 25 mL of saturated $Na_2SO_3$ and 10 mL of water were added. The aqueous layer was extracted (3 x 25 mL) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% EtOAc/hexanes to yield 2.0 g (4.8 mmol, 90%) of a colorless oil: $[\alpha]_D^{26}$ = 28.9 ($c$ = 1.70, $CHCl_3$); IR (neat) 3061, 2999, 2936, 2868, 2806, 1455 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5 H), 4.55 (d, $J$ = 11.8 Hz, 1 H), 4.52 (d, $J$ = 11.8 Hz, 1 H), 4.12 (dtd, $J$ = 2.0, 5.6, 11.5 Hz, 1 H), 3.77–3.69 (m, 2 H), 3.18–3.12 (m, 2 H), 2.20–2.05 (m, 3 H), 1.72 (s, 3 H), 1.63 (d, $J$ = 11.5, 13.6 Hz, 1 H), 1.42 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 137.9, 121.4, 101.8, 68.5, *C*H, 128.5 (2), 127.8 (3), 68.5, *C*$H_2$, 73.3, 64.9, 41.9, 37.2, 7.64, *C*$H_3$, 30.7, 21.5. Anal. calcd for $C_{17}H_{22}NO_3I$: C, 49.17; H, 5.34. Found: C, 49.30; H, 5.45.

**(2*S*,4*S*,6*S*,8*S*)-1-chloro-4,8-cyano-2:4,6:8-bis-*O*-(1-methylethylidine)-6-*O*-phenylmethyl-decane-2,4,6,8,10-pentol (18).** A solution of chlorocyanohydrin acetonide **14** (1.55 g, 8.17 mmol) in 2 mL of THF was added via cannula to 10.6 mmol of $LiNEt_2$ in 15 mL of THF under Ar at –78 °C. The reaction was stirred for 1.5 hr. A solution of iodide **17** (3.90 g, 14.9 mmol) in 2 mL of THF was then transferred to the reaction flask via

cannula. The reaction was warmed to –25 °C and stirred for 16 hr. The reaction was quenched with 50 mL of saturated $NH_4Cl$ and then extracted (3 x 50 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was filtered through silica gel eluting with 50% EtOAc/hexanes and then the mixture was separated by MPLC on silica gel (4 x 30 cm) eluting with 15% EtOAc/hexanes to give 262 mg (1.38 mmol, 17%) of recovered chlorocyanohydrin acetonide **15** and 1.50 g (3.14 mmol, 77%) of the product as a colorless oil: $[\alpha]_D^{24}$ = 48.5 (*c* = 1.26, $CHCl_3$); IR (neat) 2996, 2938, 2868, 1495, 1455 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5 H), 4.54 (d, *J* = 11.7 Hz, 1 H), 4.52 (m, 1 H), 4.50 (d, *J* = 11.7 Hz, 1 H), 4.37 (dtd, *J* = 2.0, 4.9, 11.8 Hz, 1 H), 3.76–3.69 (m, 2 H), 3.58 (dd, *J* = 4.9, 11.4 Hz, 1 H), 3.54 (dd, *J* = 5.0, 11.4 Hz, 1 H), 2.17–2.06 (m, 4 H), 2.01 (dd, *J* = 3.0, 14.6 Hz, 1 H), 1.91 (dd, *J* = 2.0, 13.6 Hz, 1 H), 1.87 (dd, *J* = 2.0, 13.6 Hz, 1 H), 1.70 (dd, *J* = 11.7, 13.6 Hz, 1 H), 1.73 (s, 6 H), 1.45 (s, 3 H), 1.37 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 137.8, 121.6, 121.4, 101.7, 101.1, 68.7, 67.6, *C*H, 128.5 (2), 127.7 (3), 66.4, $CH_2$, 73.3, 64.9, 46.6, 46.1, 41.9, 39.5, 35.0, $CH_3$, 30.8, 30.6, 21.5, 21.3. Anal. calcd for $C_{25}H_{33}N_2O_5Cl$: C, 62.95; H, 6.97. Found: C, 62.75; H, 6.95.

**(2*S*,4*S*,6*S*,8*S*)-bis-*C*-4,8-cyano-1-iodo-2:4,6:8-bis-*O*-(1-methylethylidine)-6-*O*-phenylmethyl-decane-2,4,6,8,10-pentol (6).** A 50 mL Schlenk flask was charged with dinitrile **18** (670 mg, 1.40 mmol), 18-crown-6 (370 mg, 1.40 mmol) and 14 mL of xylenes. The solution was purged with Ar and then powdered KI (22.4 g, 135 mmol) was added. The reaction was heated to reflux for 48 hr. After cooling to room temperature, 10 mL of saturated $Na_2SO_3$ and 5 mL of water were added. The aqueous layer was extracted (3 x 15 mL) with EtOAc. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% EtOAc/hexanes to yield 755 mg (1.33 mmol, 95%) of a colorless oil: $[\alpha]_D^{23}$ = 43.7 (*c* =1.74 , $CHCl_3$); IR (neat) 3062, 2994, 2935, 2866, 1494, 1455, 1431 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H), 4.54 (d, *J* = 11.8 Hz, 1 H), 4.52 (m, 1 H), 4.50 (d, *J* = 11.8 Hz, 1 H), 4.04 (dtd, *J* = 2.1, 5.2, 11.4 Hz, 1 H), 3.76–3.69 (m, 2 H), 3.24 (dd, *J* = 5.0, 10.5 Hz, 1 H), 3.21 (dd, *J* = 5.2, 10.5 Hz, 1 H), 2.16–1.99 (m, 5 H), 1.92–1.88 (m, 2 H), 1.75 (s, 3 H), 1.72 (s, 3 H), 1.70 (dd, *J* = 11.7, 13.6 Hz, 1 H), 1.45 (s, 3 H), 1.38 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 137.9, 121.8, 121.4, 101.9, 101.1, 68.7, 67.7, *C*H, 128.5 (2), 127.8 (3), 65.8, 61.7, $CH_2$, 73.3, 64.9, 46.0, 41.9, 39.5, 37.9, 8.7, $CH_3$, 30.8, 30.6, 21.7, 21.4. Anal. calcd for $C_{25}H_{33}N_2O_5I$: C, 52.82; H, 5.85. Found: C, 52.88; H, 6.04.

**(3*S*,5*S*,7*S*,9*S*,11*S*,13*S*,14*R*,15*R*)-1-*O*-phenylmethyl-3,7,11-tris-*C*-cyano-15-*O*-(1,1-dimethylethyl)dimethylsilyl-14-ethenyl-3:5,7:9,11:13-tris-*O*-(1-methylethylidine)-eicosane-1,3,5,7,9,11,13,15-octol (19).** A solution of nitrile **7** (835 mg, 2.11 mmol) in 1 mL of THF was added via cannula to 2.11 mmol of $LiNEt_2$ in 2 mL of THF under Ar at –78 °C. The reaction was stirred for 1 hr. A solution of iodide **6** (600 mg, 1.05 mmol) in 1 mL of THF was then transferred to the reaction flask via cannula. The reaction was stirred at –78 °C for 30 min and then warmed to –30 °C and stirred for 16 hr. The reaction was quenched with 25 mL of saturated $NH_4Cl$ and then extracted (3 x 25 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was filtered through silica gel eluting with 50% EtOAc/hexanes and then the mixture was separated by MPLC on silica gel (4 x 30 cm) eluting with 10% EtOAc/hexanes to give 230 mg (0.581 mmol, 28%) of recovered nitrile and 695 mg (0.831 mmol, 80%) of the product as a colorless oil: $[\alpha]_D^{26}$ = 50.7 (*c* =2.11, $CHCl_3$); IR (neat)

3076, 2994, 2929, 2857, 2255, 1640, 1462, 1433 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5 H), 5.62 (dt, *J* = 16.9, 9.8 Hz, 1 H), 5.17–5.05 (m, 2H), 4.52 (d, *J* = 11.9 Hz, 1 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.47 (m, 2 H), 4.19 (dt, *J* = 5.5, 8.3 Hz, 1 H), 3.91 (dddd, *J* = 3.9 Hz, 1 H), 3.72–3.69 (m, 2H), 2.28 (ddd, *J* = 3.9, 8.3, 9.8 Hz, 1 H), 2.13–1.68 (m, 12 H), 1.70 (s, 3 H), 1.69 (s, 3 H), 1.67 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.48–1.19 (m, 8 H), 0.881 (s, 9 H), 0.872 (t, *J* = 7.0 Hz, 3 H), 0.049 (s, 3 H), 0.037 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 137.8, 122.0, 121.6, 121.3, 101.2, 101.0, 100.9, 68.6, 67.9, 67.8, 18.1, *CH*, 134.1, 128.4 (2), 127.7, 127.6 (2), 71.4, 65.4, 61.9, 61.7, 55.0, *$CH_2$*, 119.1, 73.2, 64.8, 46.4, 46.2, 41.8, 39.5, 37.7, 36.5, 32.9, 31.8, 25.2, 22.5, *$CH_3$*, 30.7 (3), 25.9 (3), 21.3 (2), 21.2, 14.0, –4.39, –4.45. Anal. calcd for $C_{47}H_{73}N_3O_8Si$ : C, 67.51; H, 8.80. Found: C, 67.26; H, 8.55.

**(3*S*,5*S*,7*S*,9*S*,11*S*,13*S*,14*R*,15*R*)-15-*O*-(1,1-dimethylethyl)dimethylsilyl-14-ethenyl-3:5,7:9,11:13-tris-*O*-(1-methylethylidine)-eicosane-1,3,5,7,9,11,13,15-octol (20).** A 100 mL 2 neck flask, equipped with a cold finger, was cooled to –78 °C and charged with 20 mL $NH_3$ and Li (30 mg, 4.32 mmol). A solution of 0.5 mL of *tert*-butanol in 5 mL of THF was added and then a solution of trinitrile **19** (200 mg, 0.239) in 5 mL of THF was transferred to the reaction flask via cannula. The reaction was stirred for 1 hr and then quenched with 270 mg of $NH_4Cl$. The reaction was allowed to warm to room temperature and the $NH_3$ allowed to evaporate. Water was then added and the solution extracted (3 x 10 mL) with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 40–70% EtOAc/hexanes to yield 102 mg (0.152 mmol, 65%) of a colorless oil: $[\alpha]_D^{25}$ = 16.3 (*c* = 4.00, $CH_2Cl_2$); IR (neat) 3467, 3078, 2999, 2943, 2861, 1642, 1464 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.55 (dt, *J* = 10.0, 17.1 Hz, 1 H), 5.09–5.00 (m, 2 H), 4.08 (m, 1 H), 4.04–3.90 (m, 5 H), 3.83 (ddd, *J* = 1.9, 8.4, 10.8 Hz, 1 H), 3.76–3.69 (m, 2 H), 2.55 (dd, *J* = 4.3, 6.6 Hz, 1 H), 2.23 (dd, *J* = 4.3, 9.1 Hz, 1 H), 1.79–1.65 (m, 4 H), 1.46–0.890 (m, 16 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3H), 1.31 (s, 3 H), 0.847 (s, 9 H), 0.843 (t, *J* = 7.0 Hz, 3 H), 0.017 (s, 3 H), 0.005 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 98.5, 98.3, 98.1, 18.1, *CH*, 134.7, 71.3, 69.4, 68.1, 65.4, 65.1 (2), 65.0, 55.7, *$CH_2$*, 118.5, 60.9, 42.6, 42.5, 38.0, 36.4, 36.3, 35.0, 32.5, 31.8, 25.3, 22.6, *$CH_3$*, 30.2 (2), 30.1, 25.9 (3), 19.8 (2), 19.6, 14.1, –4.32, –4.42. Anal. calcd for $C_{37}H_{70}O_8Si$ : C, 66.23; H, 10.51. Found: C, 66.45; H, 10.36. HRMS(FAB) calcd for $C_{36}H_{67}O_8Si$: 655.4607. Found: 655.4638 (M–$CH_3$).

**(2*R*,5*R*,7*R*,9*R*,11*S*,13*S*,15*S*,16*R*,17*R*)- and (2*S*,5*R*,7*R*,9*R*,11*S*,13*S*,15*S*,16*R*,17*R*)-2-diethylphosphono-17-*O*-(1,1-dimethylethyl)dimethylsilyl-16-ethenyl-5:7,9:11,13:15-tris-*O*-(1-methylethylidine)-3-oxo-docosane-5,7,9,11,13,15,17-heptol (21).** A 25 mL flask was charged with 4 mL of triacetonide **20** (114 mg, 0.17 mmol), and $NaHCO_3$ (60 mg, 0.71 mmol). Dess-Martin periodinate (130 mg, 0.35 mmol) was added and the reaction stirred for 1 hr. The reaction was diluted with 10 mL of $Et_2O$, quenched with 5 mL of saturated $NaHCO_3$ and 5 mL of 0.5 M $Na_2S_2O_3$ and stirred for 30 min. The aqueous layer was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were washed 2x with $NaHCO_3$, 2x with water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20% EtOAc/hexanes to give 102 mg of the aldehyde as a colorless oil.

A 25 mL flask was charged with diethyl ethylphosphonate (133 mg, 0.782 mmol), 3 mL of THF, and cooled to –78 °C. *n*-BuLi (0.175 mL of a 2.65 M solution in hexane, 0.464 mmol) was added. The reaction was

stirred for 15 min. A solution of the aldehyde in 1 mL of THF was added to the reaction via cannula. The reaction was stirred for 1 hr and then quenched with 5 mL of saturated $NH_3Cl$. The solution was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were dried ($MgSO_4$) and then concentrated under reduced pressure to give a colorless oil.

The oil was dissolved in 3 mL $CH_2Cl_2$ and transferred to a 25 mL flask. $NaHCO_3$ (51 mg, 0.61 mmol) and Dess-Martin periodinate (114 mg, 0.30 mmol) were added and the reaction stirred for 1 hr. The reaction was diluted with 5 mL of $Et_2O$, quenched with 5 mL of saturated $NaHCO_3$ and 5 mL of 0.5 M $Na_2S_2O_3$, and then stirred for 30 min. The aqueous layer was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were washed with $NaHCO_3$, 2x with water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 70–90% EtOAc/hexanes to give 99 mg (0.12 mmol, 70%) of a colorless oil. The 1:1 mixture of diastereomers was not separated: IR (neat) 3077, 2988, 2938, 2857, 1715, 1640, 1462 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.55 (dt, $J$ = 10.1, 17.1 Hz, 1 H), 5.09–4.99 (m, 2 H), 4.36 (dtd, $J$ = 2.4, 6.1, 11.8 Hz, 1 H), 4.30 (dddd, $J$ = 2.3, 5.1, 7.5, 11.6 Hz, 1 H), 4.12–3.89 (m, 9 H), 3.82 (ddd, $J$ = 2.1, 8.6, 11.0 Hz, 1 H), 3.25 (m, 1 H), 2.82 (m, 1 H), 2.69 (m, 1 H), 2.22 (dt, $J$ = 4.2, 9.1 Hz, 1 H), 1.74 (m, 2 H), 1.55–1.01 (m, 43 H), 0.842 (s, 9 H), 0.838 (t, $J$ = 7.0 Hz, 3 H), 0.011 (s, 3 H), –0.001 (2, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 204.3, 134.7, 118.4, 98.5, 98.3, 98.1, 71.4, 68.1, 66.1, 65.5, 65.4, 65.1, 65.0, 62.5, 55.7, 49.9, 49.0, 48.5, 47.8, 46.8, 46.1, 42.6, 36.4, 36.1, 35.1, 32.6, 31.8, 30.1 (3), 25.9 (3), 25.3, 22.5, 19.7 (2), 19.6, 18.1, 16.4, 16.3, 14.0, 10.7, 10.5, –4.33, –4.44. HRMS(MALDI) calcd for $C_{43}H_{81}O_{11}PSiNa$: 855.5183. Found: 855.5183 (M+Na).

**[2(1*R*),2*R*,3*S*,5*S*,7*S*,9*R*,11*R*,13*R*,16*R*]- and [2(1*R*),2*R*,3*S*,5*S*,7*S*,9*R*,11*R*,13*R*,16*S*]-16-diethylphosphono-2-(1-(1,1-dimethylethyl)dimethylsiloxy-hexyl)-3,5,7,9,11,13-hexahydroxy-3:5,7:9,11:13-tris-*O*-(1-methylethylidine)-15-oxo-heptadecanoic acid (4)** A 5 mL flask was charged with β-keto phosphonate **21** (48 mg, 58 μmol), 500 μL of *t*-butanol, 100 μL of THF, and 50 μL of water. NMO (15 mg, 130 μmol) and $OsO_4$ (100 μL of a 2.5 wt. % solution in *t*-butanol, 8.4 μmol) were added. The reaction was stirred for 16 hr followed by the addition of 300 μL of water and $NaIO_4$ (75 mg, 350 μmol). The reaction was stirred for 1 hr and then quenched with 2 mL of saturated $Na_2SO_3$ and 2 mL of $NaHCO_3$. The solution was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure to give a colorless oil.

The oil was dissolved in 700 μL of *t*-butanol, 175 μL of THF and 450 μL of 2-methyl-2-butene. A 1 M solution of $KH_2PO_4$ (900 μL) and $NaClO_2$ (20 mg, 220 μmol) were added. The reaction was stirred for 1 hr and then diluted with 2 mL of 1 M $KH_2PO_4$. The solution was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were dried ($Na_2SO_4$) and then concentrated under reduced pressure. The product was filtered through silica gel eluting with 1:49:50 MeOH/THF/hexanes to give 49 mg (58 mmol, 100%) of a colorless oil.

The 1:1 mixture of diastereomers was not separated: IR (neat) 3700, 2989, 2938, 2857, 1718, 1462 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.2 (broad s, 1 H), 4.38–4.21 (m, 2 H), 4.13–3.91 (m, 9 H), 3.27 (m, 1 H), 2.83 (m, 1 H), 2.68 (m, 1 H), 2.58 (dd, $J$ = 5.1, 9.2 Hz, 1 H), 1.94 (d, $J$ = 12.5 Hz, 1 H), 1.75 (m, 2 H), 1.55–1.08 (m, 42 H), 0.881 (s, 9 H), 0.846 (t, $J$ = 7.0 Hz, 3 H), 0.106 (s, 3 H), 0.089 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ 204.4, 204.1, 172.6, 98.6 (2), 98.4, 69.9, 66.8, 66.2, 65.5, 65.1, 62.6, 55.9, 49.9, 49.1, 48.5, 47.7, 46.0, 42.5, 36.4,

36.1, 36.0, 32.3, 31.6, 30.1, 30.0, 25.7 (3), 25.1, 22.4, 19.7, 19.6, 17.9, 16.3, 13.9, 10.7, 10.5, –4.60, –4.72. HRMS(MALDI) calcd for $C_{42}H_{79}O_{13}PSiNa$: 873.4941. Found: 873.4925 (M+Na).

**(2*S*,3*R*)-3-*O*-benzoyl-2-*O*-(1,1-dimethylethyl)dimethylsilyl-butane-1,2,3-triol (23).** A 50 mL flask was charged with triol **22** (500 mg, 2.0 mmol) and 20 mL of MeOH. CSA (25 mg, 0.10 mmol) was added. The reaction was stirred for 16 hr, quenched with 25 μL $Et_3N$ and then concentrated under reduced pressure. The crude product was filtered through silica gel eluting with 70% EtOAc/hexanes to give 240 mg of a colorless oil.

The oil was dissolved in 20 mL of $CH_2Cl_2$, transferred to a 50 mL flask, and cooled to 0 °C. 2,6-Lutidine (630 μL, 5.4 mmol) and TBSOTf (1.0 mL, 4.4 mmol) were added. The reaction was stirred for 1 hr and then quenched with 10 mL of saturated $NaHCO_3$. The aqueous layer was extracted (3 x 10 mL) with $CH_2Cl_2$. The combined organic layers were washed 2x with water, brine, dried ($Na_2SO_4$), and then concentrated under reduced pressure. The crude product was filtered through silica gel eluting with 20% EtOAc/hexanes to give 870 mg of a colorless oil.

The oil was dissolved in 20 mL of MeOH and transferred to a 50 mL flask. PPTS (38 mg, 0.15 mmol) was added. The solution was warmed to 50 °C and stirred for 8 hr and then stirred at room temperature for 16 hr. The reaction was quenched with 25 μL of $Et_3N$ and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10–70% EtOAc/hexanes to give 450 mg (1.39 mmol, 69%) of a colorless oil: $[\alpha]_D^{25} = -10.5$ ($c$ = 1.18, $CHCl_3$); IR (neat) 3466, 2953, 2929, 2885, 2857, 1717, 1603, 1585 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.03–8.01 (m, 2 H), 7.55 (tt, $J$ = 1.2, 7.4 Hz, 1 H), 7.44–7.41 (m, 2 H), 5.22 (dq, $J$ = 4.6, 6.5 Hz, 1 H), 3.92 (q, $J$ = 4.6 Hz, 1 H), 3.65 (d, $J$ = 4.7 Hz, 1 H), 1.95 (s, 1 H), 1.36 (d, $J$ = 6.5 Hz, 1 H), 0.909 (s, 9 H), 0.097 (s, 3 H), 0.094 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 166.0, 130.4, 18.0, *C*H, 132.9, 129.6 (2), 128.3 (2), 74.6, 71.8, *C*$H_2$, 63.6, *C*$H_3$, 25.8 (3), 15.5, –4.50, –4.64. Anal. calcd for $C_{17}H_{28}O_4Si$: C, 62.93; H, 8.70. Found: C, 62.69; H, 8.57.

**(2*R*,3*R*)-3-benzoyloxy-2-(1,1-dimethylethyl)dimethylsiloxy-butanal (24).** A 25 mL flask was charged with triol **23** (150 mg, 0.46 mmol). $NaHCO_3$ (155 mg, 1.84 mmol) and Dess-Martin periodinate (348 mg, 0.93 mmol) were added and the reaction stirred for 1 hr. The reaction was diluted with 10 mL of $Et_2O$, quenched with 5 mL of saturated $NaHCO_3$ and 5 mL of 0.5 M $Na_2S_2O_3$, and then stirred for 30 min. The aqueous layer was extracted (3 x 10 mL) with $Et_2O$. The combined organic layers were washed with $NaHCO_3$, 2x with water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 50% $Et_2O$/hexanes to give 140 mg (0.434 mmol, 94%) of a colorless oil: $[\alpha]_D^{27}$ = 0.8 ($c$ = 1.54, $CH_2Cl_2$); IR (neat) 3064, 2955, 2931, 2887, 2858, 1738, 1721, 1603, 1585 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.66 (d, $J$ = 1.4 Hz, 1 H), 8.21–8.00 (m, 2 H), 7.56 (tt, $J$ = 1.2, 7.5 Hz, 1 H), 7.45–7.41 (m, 2 H), 5.43 (dq, $J$ = 3.8, 6.5 Hz, 1 H), 4.25 (dd, $J$ = 1.5, 3.8 Hz, 1 H), 1.35 (d, $J$ = 6.5 Hz, 1 H), 0.919 (s, 9 H), 0.068 (s, 3 H), 0.064 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 165.7, 130.0, 18.1, *C*H, 201.5, 133.1, 129.6 (2), 128.4 (2), 79.3, 71.5, *C*$H_3$, 25.6, 15.0, –4.75, –5.00. Anal. calcd for $C_{17}H_{26}O_4Si$: C, 63.32; H, 8.13. Found: C, 62.98; H, 7.89. HRMS(CI) calcd for $C_{17}H_{27}O_4Si$: 323.1678. Found: 323.1676 (M+H).

**(6*S*,7*R*)-7-benzoyloxy-6-(1,1-dimethylethyl)dimethylsiloxy-2,4-octadienal (26).** A 25 mL flask was charged with 1-(4-ethoxybutadienyl)tributylstannane (307 μL, 0.904 mmol) and 2 mL of THF. The solution was

cooled to –78 °C and then *n*-BuLi (273 μL of a 2.65 M solution in hexane, 0.723 mmol) was added. The reaction was stirred for 10 min and then $MgBr_2$ (3.07 mL of a 0.22 M solution in THF, 0.675 mmol) was added. The reaction was stirred for 10 min and then a solution of aldehyde **24** (145 mg, 0.453 mmol) in 1 mL of THF was added via cannula. The reaction was stirred for 1 hr. The reaction was quenched with 2 mL of pH 7 phosphate buffer and then warmed to room temperature. The solution was partitioned between 10 mL of $CH_2Cl_2$ and 10 mL of saturated $NH_4Cl$. The aqueous layer was extracted (2 x 10 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure to give a yellow oil.

The oil was dissolved in 10 mL of $CH_2Cl_2$ and cooled to –40 °C. $Et_3N$ (630 μL, 5.52 mmol) and MsCl (175 μL, 2.26 mmol) were added. The reaction was stirred for 45 min and then warmed to 0 °C followed by the addition of 10 mL of THF and 10 mL of pH 7 phosphate buffer. The reaction was stirred for 45 min and then partitioned between 10 mL $CH_2Cl_2$ and 10 mL of saturated $NH_4Cl$. The aqueous layer was extracted (2 x 10 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10–15% EtOAc/hexanes to give 135 mg (0.36 mmol, 80%) of a colorless oil: $[\alpha]_D^{27}$ = –31.4 (*c* = 1.54, $CH_2Cl_2$); IR (neat) 2955, 2932, 2888, 2858, 1717, 1686, 1645, 1602 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.54 (d, *J* = 8.0 Hz, 1 H), 8.02–7.98 (m, 2 H), 7.53 (tt, *J* = 1.3, 7.4 Hz, 1 H), 7.44–7.38 (m, 2 H), 7.09 (d, *J* = 10.9, 15.3 Hz, 1 H), 6.55 (dddd, *J* = 0.6, 1.4, 10.9, 15.3 Hz, 1 H), 6.26 (dd, *J* = 5.4, 15.3 Hz, 1 H), 6.11 (ddd, *J* = 0.6, 8.0, 15.3 Hz, 1 H), 5.12 (dq, *J* = 3.8, 6.5 Hz, 1 H), 4.51 (ddd, *J* = 1.4, 3.8, 5.4 Hz, 1 H), 1.29 (d, *J* = 6.5 Hz, 1 H), 0.890 (s, 9 H), 0.009 (s, 3 H), –0.021 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 166.0, 130.3, 18.2, *C*H, 193.6, 150.8, 143.8, 133.0, 132.0, 129.6 (2), 129.0, 128.4 (2), 74.2, 73.6, *C*$H_3$, 25.7 (3), 14.4, –4.56, –4.91. Anal. calcd for $C_{21}H_{30}O_4Si$: C, 67.34; H, 8.07. Found: C, 67.07; H, 8.16. HRMS(CI) calcd for $C_{21}H_{31}O_4Si$: 375.1992. Found: 375.1991 (M+H).

**(10*S*,11*R*)-11-benzoyloxy-10-(1,1-dimethylethyl)dimethylsiloxy-2,4,6,8-dodecatetraenal (27):** A 25 mL flask was charged with 1-(4-ethoxybutadienyl)-tributylstannane (236 μL, 0.695 mmol) and 2 mL of THF. The solution was cooled to –78 °C and then *n*-BuLi (210 μL of a 2.65 M solution in hexane, 0.557 mmol) was added. The reaction was stirred for 10 min and then $MgBr_2$ (2.37 mL of a 0.22 M solution in THF, 0.521 mmol) was added. The reaction was stirred for 10 min and then a solution of dienal **26** (130 mg, 0.347 mmol) in 1 mL of THF was added via cannula. The reaction was stirred for 5 min. The reaction was quenched with 2 mL of pH 7 phosphate buffer and then warmed to room temperature. The solution was partitioned between 10 mL of $CH_2Cl_2$ and 10 mL of saturated $NH_4Cl$. The aqueous layer was extracted (2 x 10 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure to a yellow oil.

The oil was dissolved in 5 mL of $CH_2Cl_2$ and cooled to –40 °C. $Et_3N$ (490 μL, 5.52 mmol) and MsCl (175 μL, 2.26 mmol) were added. The reaction was stirred for 10 min and then warmed to 0 °C followed by the addition of 10 mL of THF and 10 mL of pH 7 phosphate buffer. The reaction was stirred for 10 min and then partitioned between 10 mL of $CH_2Cl_2$ and 10 mL of saturated $NH_4Cl$. The aqueous layer was extracted (2 x 10 mL) with $CH_2Cl_2$. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10–15% EtOAc/hexanes to give 120 mg (0.28 mmol, 81%) of a yellow oil: $[\alpha]_D^{24}$ = –33.9 (*c* = 1.05,

$CH_2Cl_2$); IR (neat) 3024, 2952, 2929, 2856, 2712, 1717, 1674, 1640, 1594 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.54 (d, $J$ = 7.9 Hz, 1 H), 8.02–7.99 (m, 2 H), 7.53 (tt, $J$ = 1.4, 7.3 Hz, 1 H), 7.42–7.39 (m, 2 H), 7.10 (dd, $J$ = 11.3, 15.3 Hz, 1 H), 6.66 (dd, $J$ = 11.0, 14.8 Hz, 1 H), 6.48–6.40 (m, 2 H), 6.37 (ddd, $J$ = 1.4, 11.0, 15.1 Hz, 1 H), 6.29 (dd, $J$ = 11.0, 14.5 Hz, 1 H), 6.13 (dd, $J$ = 7.9, 15.1 Hz, 1 H), 5.87 (dd, $J$ = 6.0, 15.0 Hz, 1 H), 5.08 (dq, $J$ = 3.8, 6.5 Hz, 1 H), 4.44 (ddd, $J$ = 1.4, 3.8, 5.3 Hz, 1 H), 1.29 (d, $J$ = 6.5 Hz, 1 H), 0.891 (s, 9 H), 0.005 (s, 3 H), –0.019 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 165.9, 130.4, 18.1, *C*H, 193.4, 151.6, 142.3, 137.6, 136.6, 132.8, 131.6, 131.1, 130.9, 130.0, 129.5 (2), 128.2 (2), 74.5, 73.9, *C*$H_3$, 25.7 (3), 14.2, –4.51, –4.97. HRMS(CI) calcd for $C_{25}H_{35}O_4Si$: 427.2306. Found: 427.2317 (M+H).

**(10*S*,11*R*)-11-hydroxy-10-(1,1-dimethylethyl)dimethylsiloxy-2,4,6,8-dodecatetraenal (5).** A 25 mL flask was charged with tetraenal **27** (100 mg, 0.234 mmol), 2 mL of MeOH and 0.4 mL of trimethyl orthoformate. PPTS (5 mg, 20 μmol) was added. The reaction was stirred for 1 hr. The reaction was diluted with 10 mL of $Et_2O$ and then extracted with saturated $NaHCO_3$, water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure to give a yellow oil.

The oil was dissolved in 8 mL of $Et_2O$ and cooled to –78 °C. DIBAL-H (550 μL of a 1 M solution in cyclohexane, 0.55 mmol) was added. The reaction was stirred for 10 min and then quenched with 40 μL of ethylformate. The reaction was warmed to 0 °C and then 550 μL of AcOH was added. The solution was warmed to room temperature and then stirred until homogenous. The solution was diluted with 20 mL of $Et_2O$ and then extracted with saturated $NaHCO_3$, water, brine, dried ($MgSO_4$) and then concentrated under reduced pressure to a yellow oil.

The oil was dissolved in 5 mL of THF and 0.2 mL of water. Amberlyst-15 acidic ion exchange resin (40 mg) was added. The reaction was stirred for 2 hr. The solution was filtered and the resin washed with 25 mL of $Et_2O$. The combined filtrate was washed with $NaHCO_3$, water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20–30% EtOAc/hexanes to give 52 mg (0.16 mmol, 70%) of a yellow oil: $[\alpha]_D^{24}$ = 4.2° (*c* = 1.6, $CH_2Cl_2$); IR (neat) 3458, 2954, 2929, 2885, 2857, 1659, 1591 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.54 (d, $J$ = 7.9 Hz, 1 H), 7.11 (dd, $J$ = 11.3, 15.1 Hz, 1 H), 6.67 (dd, $J$ = 11.0, 14.8 Hz, 1 H), 6.48–6.41 (m, 2 H), 6.32–6.24 (m, 2 H), 6.13 (dd, $J$ = 7.9, 15.1 Hz, 1 H), 5.84 (dd, $J$ = 6.9, 15.0 Hz, 1 H), 4.07 (ddd, $J$ = 1.0, 3.8, 7.2 Hz, 1 H), 3.74 (tq, $J$ = 4.3, 6.5 Hz, 1 H), 2.18 (d, $J$ = 4.3 Hz, 1 H), 1.07 (d, $J$ = 6.5 Hz, 1 H), 0.883 (s, 9 H), 0.052 (s, 3 H), 0.016 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 18.2, *C*H, 193.5, 151.7, 142.3, 137.7, 136.1, 131.7, 131.6, 131.1, 130.1, 77.1, 70.9, *C*$H_3$, 25.8 (3), 17.6, –4.26, –4.85. HRMS(CI) calcd for $C_{18}H_{31}O_3Si$: 323.2043. Found: 323.2043 (M+H).

**[2(1*R*),2*R*,3*S*,5*S*,7*S*,9*R*,11*R*,13*R*,16*R*]- and [2(1*R*),2*R*,3*S*,5*S*,7*S*,9*R*,11*R*,13*R*,16*S*]-16-diethylphosphono-2-(1-((1,1-dimethylethyl)dimethylsiloxy)-hexyl)-3,5,7,9,11,13-hexahydroxy-3:5,7:9,11:13-tris-*O*-(1-methylethylidine)-15-oxo-heptadecanoic acid, (1*R*,2*S*)-1-methyl-2-(1,1-dimethylethyl)dimethylsiloxy-11-oxoundeca-3,5,7,9-tetraeneyl ester (28).** A 10 mL flask was charged with acid **4** (100 mg, 117 μmol), 2,4,6-trichlorobenzoyl chloride (20 μL, 128 μmol), and 1.0 mL of THF. $Et_3N$ (25 μL, 179 μmol) was added. The reaction was stirred for 16 hr. The solution was filtered through celite and the white precipitate washed with $Et_2O$. The combined organic washings were concentrated with a stream of $N_2$ and then under high vacuum for 10 min. A solution of alcohol **5** (42 mg, 130 μmol) and DMAP (30 mg, 246 μmol) in 1.0 mL of toluene was added. The

reaction was stirred for 2 hr and then quenched with 2 mL of water. The solution was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were washed with pH 7 phosphate buffer, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 50–80% EtOAc/hexanes with 1% MeOH to give 8 mg (25 μmol, 19%) of recovered alcohol and 95 mg (82 μmol, 70%) of coupled product as a yellow oil. The 1:1 mixture of diastereomers was not separated: IR (neat) 2991, 2953, 2930, 2857, 1720, 1678, 1594, 1463 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.54 (d, $J$ = 7.9 Hz, 1 H), 7.12 (dd, $J$ = 11.3, 15.1 Hz, 1 H), 6.66 (dd, $J$ = 11.0, 14.6 Hz, 1 H), 6.47–6.40 (m, 2 H), 6.32–6.26 (m, 2 H), 6.13 (dd, $J$ = 7.9, 15.1 Hz, 1 H), 5.81 (dd, $J$ = 5.9, 15.3 Hz, 1 H), 4.85 (dq, $J$ = 4.6, 6.4 Hz, 1 H), 4.38–4.23 (m, 2 H), 4.18–3.89 (m, 10 H), 3.27 (m, 1 H), 2.85 (m, 1 H), 2.74–2.65 (m, 2 H), 1.79–1.71 (m, 2 H), 1.58–1.05 (m, 46 H), 0.886 (s, 9 H), 0.861 (s, 9 H), 0.850 (t, $J$ = 7.0 Hz, 3 H), 0.050 (s, 3 H), 0.046 (s, 3 H), 0.020 (s, 3 H), –0.003 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$, DEPT) δ 204.5, 204.2, 193.4, 171.1, 151.6, 142.3, 137.6, 136.8, 131.7, 131.2, 130.9, 130.2, 129.5, 128.2, 98.6, 98.5, 98.3, 74.9, 73.4, 69.8, 67.7, 66.2, 65.5, 65.1 (3), 62.5 (2), 57.0, 49.9, 49.1, 48.6, 47.8, 46.9, 46.1, 42.9, 42.6 (2), 36.4, 36.1, 33.2, 31.8, 30.2 (2), 30.1, 25.9 (3), 25.8 (3), 24.8, 22.6, 19.8, 19.7, 19.6, 18.2, 18.0, 16.4, 16.3, 15.1, 14.0, 10.7, 10.5, –4.34, –4.39, –4.50, –4.74. HRMS(MALDI) calcd for $C_{60}H_{107}O_{15}PSi_2Na$: 1177.6783. Found: 1177.6778 (M+Na).

**1',26-bis-*O*-(1,1-dimethylethyl)dimethylsilyl-15-oxo-3,5:9,11:13,15-tris-*O*-(1-methylethylidine)filipin III (3).** A 250 mL flask was charged with coupled product **28** (95 mg, 82 μmol) and 85 mL of toluene. $K_2CO_3$ (700 mg, 5.06 mmol) and 18-crown-6 (700 mg, 2.65 mmol) were added. The reaction was heated to 60 °C for 20 hr. The reaction was quenched with 30 mL of pH 7 phosphate buffer and then extracted (2 x 25 mL) with EtOAc. The combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 20–30% EtOAc/hexanes to give 40 mg (40 μmol, 49%) of a yellow oil: $[\alpha]_D^{23}$ = –76.7° ($c$ = 1.0, $CH_2Cl_2$); IR (neat) 2992, 2942, 2858, 1729, 1651, 1615, 1572, 1461 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.11 (d, $J$ = 11.0 Hz, 1 H), 6.65 (dd, $J$ = 9.9, 14.6 Hz, 1 H), 6.55 (dd, $J$ = 11.0, 14.6 Hz, 1 H), 6.41–6.22 (m, 5 H), 5.98 (dd, $J$ = 5.0, 14.0 Hz, 1 H), 4.71 (dq, $J$ = 6.2, 7.6 Hz, 1 H), 4.18–3.92 (m, 6 H), 3.81–3.72 (m, 2 H), 3.15 (t, $J$ = 11.0 Hz, 1 H), 2.66 (t, $J$ = 7.0 Hz, 1 H), 2.61 (dd, $J$ = 3.8, 11.6 Hz, 1 H), 1.88 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.24 (d, $J$ = 6.3 Hz, 3 H), 1.20 (s, 3 H), 0.894 (s, 9 H), 0.875 (s, 9 H), 0.851 (t, $J$ = 7.0 Hz, 1 H), 0.053 (s, 3 H), 0.047 (s, 3 H), 0.041 (s, 3 H), 0.009 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 199.5, 170.6, 141.8, 141.0, 138.0, 136.3, 136.2, 131.2, 130.3, 129.7, 128.5, 127.5, 98.9, 98.6, 98.3, 74.3, 73.7, 69.7, 67.8, 67.7, 66.2, 65.5, 65.3, 65.1, 64.8, 57.3, 45.6, 44.4, 43.2, 42.5, 37.7, 37.5, 34.6, 33.2, 31.8, 30.2, 30.1, 30.0, 25.9 (3), 25.8 (3), 22.6, 19.8, 19.5 (2), 18.2, 18.1, 14.0, 11.7, –4.28, –4.31, –4.46, –4.99. HRMS(FAB) calcd for $C_{56}H_{96}O_{11}Si_2Na$: 1023.6388. Found: 1023.6350 (M+Na).

**1',26-bis-*O*-(1,1-dimethylethyl)dimethylsilyl-3,5:7,9:11,13-tris-*O*-(1-methylethylidine)filipin III (29).** A 10 mL flask was charged with macrocycle **3** (20 mg, 20 μmol), $CeCl_3 \cdot 7H_2O$ (25 mg, 67 μmol) and 2 mL of MeOH. The solution was cooled to –78 °C and then $NaBH_4$ (4 mg, 106 μmol) was added. The reaction was stirred for 20 min and then quenched with 2 mL pH 7 phosphate buffer. The solution was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 30–40%

EtOAc/hexanes to give 14 mg (14 μmol, 70%) of a colorless oil: $[\alpha]_D^{24} = -1.5°$ ($c$ = 1.6, $CH_2Cl_2$); IR (neat) 3466, 2991, 2953, 2933, 2858, 1731, 1471, 1463 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.41 (dd, $J$ = 11.4, 13.8 Hz, 1 H), 6.34–6.12 (m, 6 H), 6.07 (d, $J$ = 11.4 Hz, 1 H), 5.82 (dd, $J$ = 5.8, 14.5 Hz, 1 H), 4.68 (dq, $J$ = 8.6, 6.3 Hz, 1 H), 4.24 (m, 1 H), 4.13–4.84 (m, 6 H), 3.72 (m, 1 H), 3.62 (m, 1 H), 2.66 (t, $J$ = 7.1 Hz, 1 H), 2.16 (broad s, 1 H), 1.74 (s, 3 H), 1.51–1.08 (m, 20 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.23 (d, $J$ = 6.3 Hz, 1 H), 0.885 (s, 9 H), 0.870 (s, 9 H), 0.852 (t, $J$ = 7.0 Hz, 1 H), 0.039 (s, 6 H), 0.028 (s, 3 H), 0.001 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 170.6, 138.5, 134.8, 133.7, 133.6, 133.1, 132.5, 131.9, 130.7, 127.6, 126.5, 98.8, 98.6 (2), 77.2, 74.5, 73.8, 69.8, 68.0, 67.1, 66.3, 65.8, 65.7, 65.0, 56.2, 42.8, 42.5, 38.9, 37.4, 35.2, 33.8, 31.9, 30.4, 30.3, 30.1, 28.9, 25.9 (3), 25.8 (3), 23.9, 22.6, 20.0, 19.9, 19.6, 19.5, 18.1 (2), 14.0, 12.0, –4.15, –4.27, –4.49, –4.98. HRMS(MALDI) calcd for $C_{56}H_{98}O_{11}SiNa$: 1025.6548. Found: 1025.6553 (M+Na).

**1',15,26-tris-*O*-acetyl-3,5:7,9:11,13-tris-*O*-(1-methylethylidine)filipin III (2).** A 10 mL flask was charged with reduced macrocycle **29** (4 mg, 4 μmol) and 0.5 mL of THF. TBAF (50 μL of a 1 M solution in THF, 50 μmol) was added. The reaction was stirred for 30 min and then quenched with 2 mL pH 7 phosphate buffer. The solution was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give a colorless oil.

The oil was dissolved in 0.5 mL of THF and transferred to a 10 mL flask. $Ac_2O$ (5 μL, 53 μmol) and DMAP (7 mg, 57 μmol) were added. The reaction was stirred for 1 hr and then quenched with 2 mL of pH 7 phosphate buffer. The solution was extracted (3 x 5 mL) with $Et_2O$. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and the concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 25–30% EtOAc/hexanes to give 1.5 mg (1.7 μmol, 42%) of a colorless oil: $[\alpha]_D^{26} = -3.1°$ ($c$ = 0.8, $CH_2Cl_2$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.43–6.17 (m, 6 H), 6.13 (dd, $J$ = 10.8, 13.9 Hz, 1 H), 6.08 (d, $J$ = 10.5 Hz, 1 H), 5.73 (dd, $J$ = 6.1, 15.3 Hz, 1 H), 5.29 (dd, $J$ = 4.3, 10.1 Hz, 1 H), 5.21 (ddd, $J$ = 3.5, 6.0, 9.5 Hz, 1 H), 5.13 (dd, $J$ = 6.4, 8.7 Hz, 1 H), 5.01 (dq, $J$ = 9.6, 6.1 Hz, 1 H), 4.08 (ddd, $J$ = 2.3, 8.2, 11.0 Hz, 1 H), 3.95 (m, 1 H), 3.90–3.84 (m, 2 H), 3.78 (m, 1 H), 3.60 (m, 1 H), 2.77 (dd, $J$ = 6.1, 8.2 Hz, 1 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.82–1.08 (m, 20 H), 1.76 (s, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.23 (d, $J$ = 6.1 Hz, 1 H), 0.861 (t, $J$ = 7.0 Hz, 1 H); HRMS(FAB) calcd for $C_{50}H_{76}O_{14}$: 900.5235. Found: 900.5230 (M+).

**1',26-bis-*O*-(1,1-dimethylethyl)dimethylsilyl-3,5:7,9:11,13-tris-*O*-(1-methylethylidine)-15-*O*-triisopropylsiloxy-filipin III (32).** A 10 mL flask was charged with reduced macrocycle **29** (6.0 mg, 6.0 μmol) and 500 μL of $CH_2Cl_2$. The solution was cooled to 0 °C and then 2,6-lutidine (15.0 μL, 129 μmol) and TIPSOTf (16 μL, 60 μmol) were added. The reaction was allowed to warm to room temperature, stirred for 1 hr, and then quenched with 10 mL of saturated $NaHCO_3$. The aqueous layer was extracted 3 x with $Et_2O$. The combined organic layers were washed with water, brine, dried ($MgSO_4$), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10% EtOAc/hexanes to give 5.0 mg (4.8 μmol, 72%) of a colorless oil: $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.43–6.12 (m, 7 H), 5.99 (d, $J$ = 11.4 Hz, 1 H), 5.90 (dd, $J$ = 5.2, 15.6 Hz, 1 H), 4.76 (dq, $J$ = 8.8, 6.3 Hz, 1 H), 4.26 (dd, $J$ = 4.0, 9.8 Hz, 1 H), 4.14–3.84 (m, 6 H), 3.71 (m, 1 H), 3.58 (m, 1 H), 2.61 (t, $J$ = 6.9 Hz, 1 H), 1.74 (s, 3 H), 1.39 (s, 6 H), 1.37 (s, 3 H), 1.35 (s, 6 H), 1.33 (s, 3 H), 1.24 (d, $J$ = 6.3 Hz, 3 H), 1.95–1.18 (m, 23 H), 1.03 (s, 18 H), 0.891 (s, 9 H), 0.875 (s, 9 H), 0.870

(t, $J$ = 7.0 Hz, 3 H), 0.049 (s, 3 H), 0.040 (s, 3 H), 0.025 (s, 3 H), –0.002 (s, 3 H). HRMS(MALDI) calcd for $C_{65}H_{118}O_{11}Si_3Na$: 1181.7880. Found: 1181.7826 (M+Na).

**Filipin III (1).** A 10 mL flask was charged with TIPS ether **32** (5.0 mg, 4.8 μmol), 200 μL THF, 1.0 mL of MeOH, and 200 μL of ethylene glycol and then PPTS (3 mg, 11.9 μmol) was added. The reaction was warmed to 60 °C for 3 hrs. The reaction was quenched with 5 μL of $Et_3N$ and then diluted with 10 mL of EtOAc. The solution was washed with water, brine, dried ($Na_2SO_4$), and then concentrated under reduced pressure. The crude product was taken up in 300 μL of THF, 200 μL of pyridine, and cooled to 0 °C. A solution of HF•pyridine (100 μL) was added. The reaction was warmed to room temperature and stirred for 12 hrs. The reaction was quenched with 500 μL of TMSOEt and then filtered through silica gel eluting with 1:1 THF/hexanes with 5% MeOH. The crude product was dissolved in a minimum amount of MeOH and then injected onto a reversed-phase HPLC column and eluted with 65% MeOH / 35% $H_2O$ at 2.00 mL/min. The major peak eluting at 19 min was collected to give 1.1 mg (1.7 μmol, 39%) of a slightly yellow solid: $^1$H NMR (500 MHz, $CD_3OD$) δ 6.39 (dd, $J$ = 13.9, 11.2, 1 H), 6.33 (dd, $J$ = 8.9, 14.8 Hz, 1 H), 6.36–6.18 (m, 6 H), 5.94 (d, $J$ = 11.2, 1 H), 5.89 (dd, $J$ = 5.11, 14.8, 1 H), 4.72 (m, 1 H, obscured by MeOH), 4.08 (ddd, $J$ = 3.8, 7.4, 7.1, 1 H), 4.03 (dd, $J$ = 4.5, 10.8, 1 H), 3.97 (dd, $J$ = 6.3, 5.1, 1 H), 3.94–3.85 (m, 4 H), 3.75 (ddd, $J$ = 2.1, 8.4, 8.8, 1 H), 3.12 (m, 1 H, obscured by MeOH), 2.45 (dd, $J$ = 7.4, 8.8, 1 H), 1.79 (ddd, $J$ = 3.4, 9.4, 10.8, 1 H), 1.67 (s, 3 H), 1.66–1.58 (m, 3 H), 1.32–1.44 (m, 8 H), 1.16–1.30 (m, 8 H), 1.19 (d, $J$ = 6.3, 3 H), 0.816 (t, $J$ = 7.1, 3 H). HRMS(FAB) calcd for $C_{35}H_{59}O_{11}Na$: 677.3877. Found: 677.3867 (M + Na).

## References and Endnotes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