

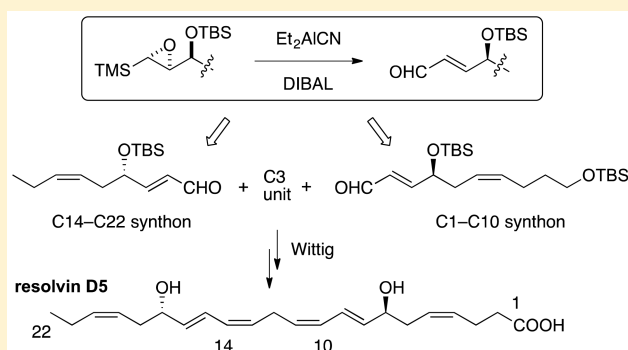
Total Synthesis of Resolvin D5

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S Supporting Information

ABSTRACT: Resolvin D5 (RvD5) is a metabolite of docosahexanoic acid with anti-inflammatory activity that has not yet been thoroughly investigated because of its low biological availability. A synthetic route to optically active RvD5 was developed by assembling the C1–C10 aldehyde, C11–C13 phosphonium salt, and C14–C22 aldehyde building blocks. The aldehyde fragments were prepared by Sharpless asymmetric epoxidation of corresponding racemic (*E*)-1-TMS-1-alken-3-ols followed by reaction of the TBS ethers of the resulting epoxy alcohols with Et₂AlCN and DIBAL reduction of the (*E*)-1-cyano-1-alken-3-ol derivatives. The C14–C22 aldehyde was connected with the C11–C13 fragment, i.e., [TBSO(CH₂)₃PPh₃]⁺ Br[−], by Wittig reaction. The resulting C11–C22 intermediate was converted to the phosphonium salt, which was attached to the C1–C10 aldehyde by Wittig reaction to yield the structure of RvD5.



INTRODUCTION

Lipoxygenase metabolites of docosahexaenoic acid (DHA) are potent inflammation-resolving chemical mediators.¹ Among them, protectin D1 (**1**) and maresin 1 (**2**) (Figure 1) have been

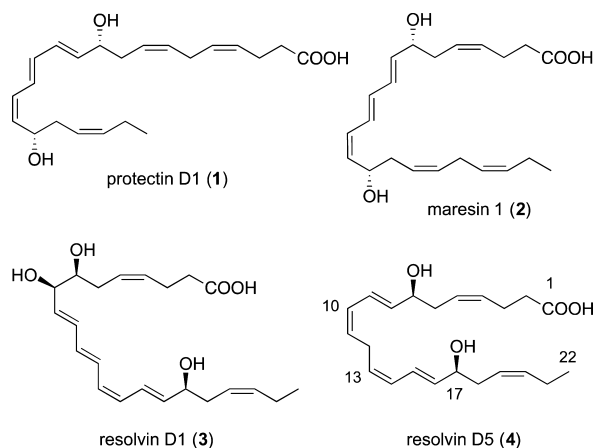


Figure 1. Metabolites of DHA.

widely studied with their supply by organic synthesis, whereas others, including resolvins D1–D6, are still in the early stages of investigation. Resolvin D5 (RvD5) (**4**) is a particularly attractive synthetic target. It was originally detected in leukocytes, brain, and glial cells,² and later, its presence was also demonstrated in patient models.³ Its ability to activate the host defense system in mice during bacterial infection has been disclosed.⁴ In addition, **4** was reported to be produced from DHA by plant lipoxygenases.⁵ However, biological and

biochemical studies of **4** are hampered by the limited biological availability of this compound. To our knowledge, only one synthetic route to **4** was reported by Spur,⁶ which involves a Sonogashira coupling of 1,4-pentadiyne with vinyl iodides corresponding to the C1–C9 and C15–C22 moieties, which were in turn obtained from a glycidol derivative through NHK-Takai iodoolefination. The olefination reaction was convenient but suffered from somewhat low stereoselectivity; moreover, it involved the undesirable use of highly toxic chromium reagents. Thus, an alternative approach to **4** with high stereoselective formation of the stereogenic centers and the *E,Z*-diene was sought.

Previously, we reported the TMS-specific reaction of epoxy alcohol derivatives **A** with Et₂AlCN followed by hydride reduction of the resulting nitriles **B** to afford aldehydes **C** stereoselectively as shown in Scheme 1.⁷ With this transformation in mind and in view of the ready availability of epoxy alcohol derivatives **A** by Sharpless asymmetric epoxidation,⁸ we envisaged the synthesis of RvD5 (**4**) by connecting aldehydes **E** and **F** to the central fragment **D** by Wittig reaction (Scheme 1). This method, which is complementary to the synthesis reported by Spur, would provide an additional opportunity for biological investigations using **4**.

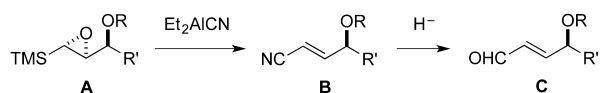
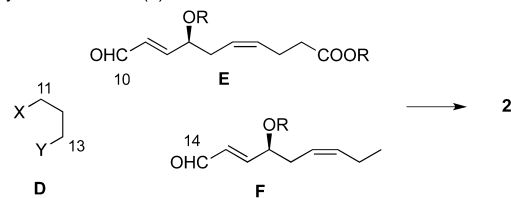
RESULTS AND DISCUSSION

Aldehyde **11** corresponding to key intermediate **F** was synthesized by a sequence of reactions delineated in Scheme 2. Alcohol **5** was synthesized from 3-(trimethylsilyl)propargyl alcohol in 69% yield in three steps involving (1) LiAlH₄

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Scheme 1. Access to RvD5

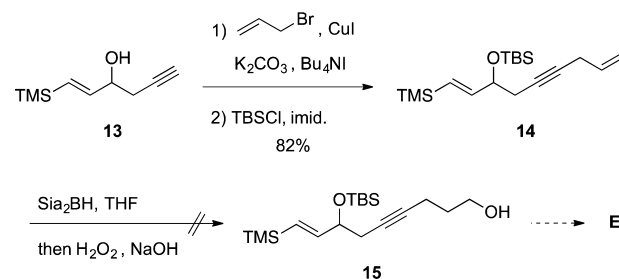
transformation of TMS-epoxides **A** to aldehydes **C**synthesis of RvD5 (**2**)X, Y = Ph₃P⁺

reduction, (2) PCC oxidation, and (3) aldol reaction with MeCOO-*n*-Bu/LDA according to the reported procedure⁹ and converted to TBS ether **6** in 89% yield. DIBAL reduction of **6** afforded aldehyde **7**, which upon Wittig reaction with the ylide derived from [PrPPh₃]⁺ Br⁻ and NaN(TMS)₂ (NaHMDS) followed by desilylation with TBAF afforded racemic allylic alcohol *rac*-**8** in 74% yield from ester **6** with high *cis* olefin purity (>98%) as confirmed by ¹³C NMR spectroscopy. Sharpless asymmetric epoxidation of *rac*-**8** using L-(+)-diisopropyl tartrate (DIPT) and Ti(O-*i*-Pr)₄ was regio- and stereoselective, producing epoxy alcohol **9** and allylic alcohol (*R*)-**8** in 47 and 48% yields, respectively, after silica gel chromatography. High enantiomeric excess (ee) given in the scheme was determined by ¹H NMR spectroscopy of the derived MTPA esters. The hydroxyl group in **9** was protected with TBSOTf,¹⁰ and the resulting TBS ether was subjected to reaction with Et₂AlCN to afford nitrile **10** in 79% yield from **9** via epoxide ring opening followed by Peterson elimination. Nitrile **10** was also obtained from (*R*)-**8** in five steps. Briefly, epoxidation of (*R*)-**8** (96.5% ee) using D-(-)-DIPT/Ti(O-*i*-Pr)₄ produced epoxide *ent*-**9** with >99% ee. The increased ee

was the result of the slow epoxidation of the (*S*)-enantiomer, which was contaminated (in ~2%) in 96.5% ee of (*R*)-**8**. The Mitsunobu inversion, silylation of the resulting epoxy alcohol **12**, and subsequent reaction with Et₂AlCN proceeded smoothly affording nitrile **10** in 70% yield from (*R*)-**8**. Finally, reduction of **10** with DIBAL gave aldehyde **11** in 73% yield. The total yield of **11** from *rac*-**8** through **9** and (*R*)-**8** was calculated to be 52%.

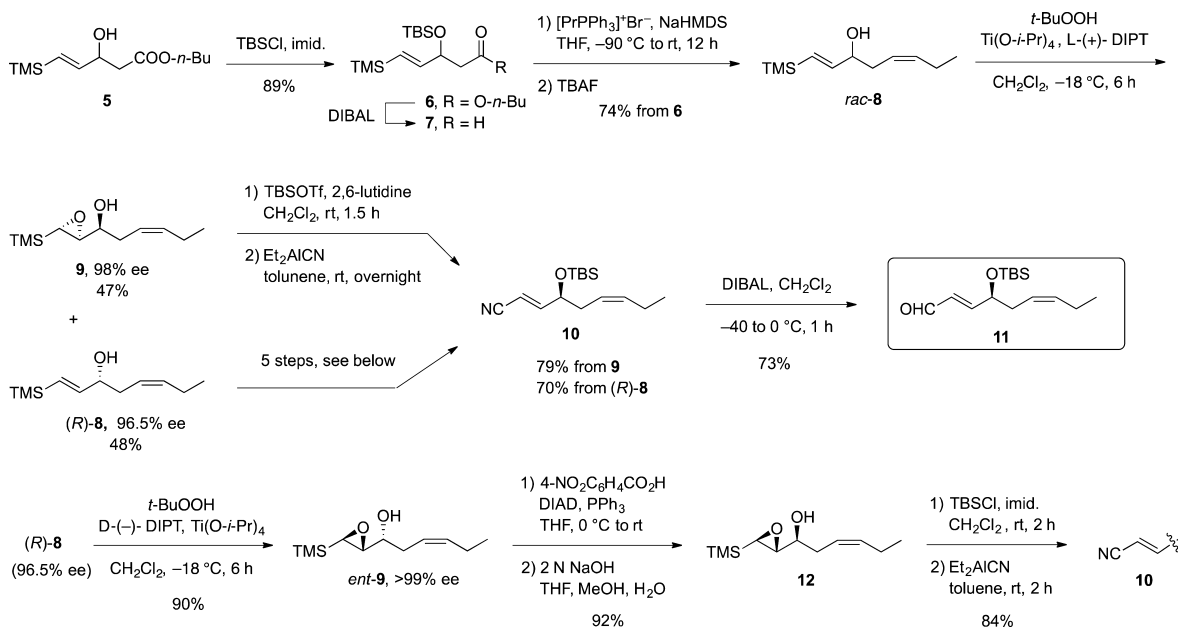
Several reaction sequences were attempted to obtain an intermediate corresponding to aldehyde **E** in Scheme 1. Alkylation of **13** with allyl bromide under literature conditions¹¹ followed by silylation proceeded to completion to afford **14** in 82% yield (Scheme 3). However, hydroboration of **14** with

Scheme 3. Attempted Construction of Intermediate E

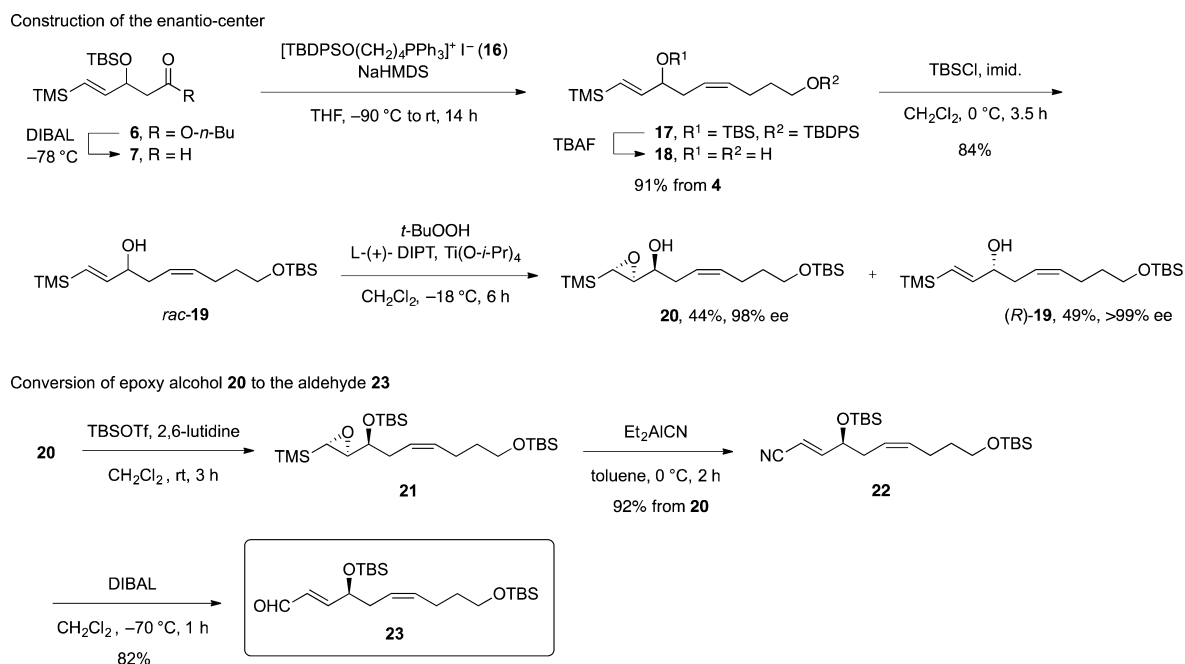


Sia₂BH gave a complex mixture of products (TLC, ¹H NMR).¹² Moreover, alkylation of the ethoxyethyl (EE) ether of **13** with I(CH₂)₃OTBS (LiNH₂, NH₃/THF; BuLi, HMPA/THF) gave the product in low yield (<22%).¹³

Alternatively, Wittig reaction of aldehyde **7** synthesized again from ester **6** with the ylide derived from **16** and NaHMDS yielded olefin **17**, which was converted to racemic alcohol *rac*-**19** in good yield by deprotection with TBAF followed by regioselective silylation with TBSCl and imidazole (Scheme 4). The ¹³C NMR spectrum of *rac*-**19** revealed the high purity of the *cis* olefin (>98%). Asymmetric epoxidation of *rac*-**19** with L-(+)-DIPT/Ti(O-*i*-Pr)₄ provided a mixture of **20** and (*R*)-**19**,

Scheme 2. Synthesis of Aldehyde **11** Corresponding to Intermediate F

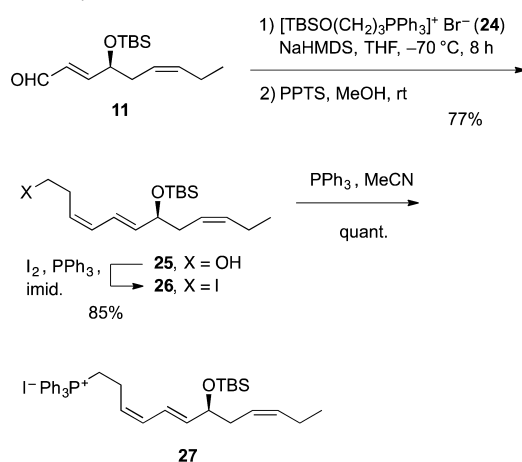
Scheme 4. Synthesis of C1–C10 Intermediate 23



which were separated by silica gel chromatography in 44 and 49% yields, respectively. The ee was determined by Mosher analysis to be 98 and >99%, respectively. Similar to the transformation of 9 to nitrile 10 (Scheme 2), epoxy alcohol 20 was converted to nitrile 22 in 92% yield.¹⁴ Finally, reduction of 22 with DIBAL provided aldehyde 23.

Among the two possible pathways for connecting aldehydes 23 and 11 to the C11–C13 unit, a sequence first connecting 11 and the C11–C13 unit was examined because the reverse order of the connection was expected to be unsuccessful in regioselective deprotection of the TBS group at C13 in the 1,13-bis-TBS ether intermediate. As delineated in Scheme 5,

Scheme 5. Synthesis of C11–C22 Intermediate 27



Wittig reaction of 11 with phosphonium salt 24 and subsequent regioselective desilylation at the primary position afforded alcohol 25, which was subjected to iodination and subsequent reaction with PPh₃ to provide phosphonium salt 27 in 85% yield from 25.

The last stage of the synthesis commenced with the Wittig reaction of aldehyde 23 with the ylide derived from 27 and

NaHMDS to afford 28, which upon regioselective desilylation using PPTS in MeOH afforded primary alcohol 29 in 53% yield from 23 (Scheme 6). The high chemical purity (>95%) of 29, confirmed by ¹³C NMR spectroscopy, indicated the high stereoselectivity of the Wittig reaction. Alcohol 29 was then converted to carboxylic acid 30 in 81% yield by PCC oxidation followed by Pinnick oxidation. Desilylation with TBAF afforded a mixture of RvD5 (4) and TBAF residue(s), which could be only partially separated by silica gel chromatography. Thus, acid 30 was first converted to the methyl ester, and subsequent desilylation with TBAF afforded diol ester 31, which was easily purified. Finally, hydrolysis of 31 with LiOH afforded RvD5 (4) in 45% yield. The ¹H NMR spectrum in CD₃CN was consistent with that reported in the literature.⁶ The structure of 4 was also confirmed by the ¹H and ¹³C-attached proton test (APT) NMR spectra in CDCl₃.

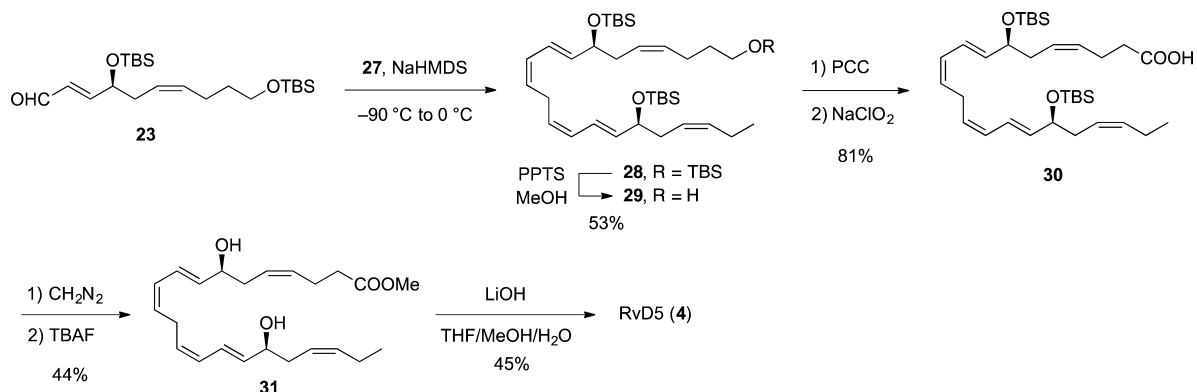
CONCLUSIONS

In summary, RvD5 (4) was constructed by assembling three building blocks, i.e., C11–C13 phosphonium salts 24, C1–C10 aldehyde 23, and C14–C22 aldehyde 11, which correspond to fragments D–F in Scheme 1. Remarkably, the *E,Z*-diene and the C7 and C17 stereogenic centers were constructed in a highly stereoselective manner. This synthetic methodology providing readily access to RvD5 could facilitate future biological investigations. Furthermore, we think that, based on the structural similarity, C1–C10 aldehyde 23 and C14–C22 aldehyde 11 would be key intermediates for the syntheses of RvD2 and other RvD1,2,4, respectively.

EXPERIMENTAL SECTION

General Remarks. The ¹H (300 or 400 MHz) and ¹³C NMR (75 or 100 MHz) spectroscopic data were recorded in CDCl₃ using Me₄Si ($\delta = 0$ ppm) and the centerline of the triplet ($\delta = 77.1$ ppm), respectively, as internal standards. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (*J*) are given in hertz (Hz). Chemical shifts of carbons are accompanied by negative (for C and CH₂) and

Scheme 6. Last Stage of the Synthesis of RvD5



positive (for CH and CH₃) signs of the attached proton test (APT) experiments. High-resolution mass spectroscopy (HRMS) was performed with a double-focusing mass spectrometer. The solvents that were distilled prior to use are THF (from Na/benzophenone), Et₂O (from Na/benzophenone), and CH₂Cl₂ (from CaH₂). After extraction of the products, the extracts were concentrated by using an evaporator, and then the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60N).

Butyl (E)-3-[(tert-Butyldimethylsilyloxy)-5-(trimethylsilyl)pent-4-enoate (6). A solution of aldol **5**⁹ (6.41 g, 26.2 mmol), imidazole (3.68 g, 54.1 mmol), and TBSCl (5.93 g, 39.3 mmol) in CH₂Cl₂ (150 mL) was stirred at rt overnight and diluted with saturated NaHCO₃. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give silyl ester **6** (8.36 g, 89%) as a liquid; *R*_f = 0.67 (5:1 hexane/EtOAc); IR (neat) 1740, 1250, 838 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.05 (s, 9 H), 0.86 (s, 9 H), 0.92 (t, *J* = 7.4 Hz, 3 H), 1.32–1.43 (m, 2 H), 1.56–1.64 (m, 2 H), 2.42 (dd, *J* = 14.5, 5.0 Hz, 1 H), 2.49 (dd, *J* = 14.5, 8.2 Hz, 1 H), 3.99–4.11 (m, 2 H), 4.54 (dt, *J* = 8.2, 5.5 Hz, 1 H), 5.84 (dd, *J* = 18.8, 1.0 Hz, 1 H), 5.97 (dd, *J* = 18.8, 5.5 Hz, 1 H); ¹³C-APT NMR (100 MHz, CDCl₃) δ -5.0 (+), -4.2 (+), -1.4 (+), 13.8 (+), 18.2 (-), 19.2 (-), 25.8 (+), 30.7 (-), 43.5 (-), 64.3 (-), 72.8 (+), 129.8 (+), 147.5 (+), 171.3 (-); HRMS (EI⁺) calcd for C₁₈H₃₈O₃Si₂ [M⁺] 358.2360, found 358.2360.

(1E,5Z)-1-(Trimethylsilyloxy)octa-1,5-dien-3-ol (rac-8). To a solution of ester **6** (3.04 g, 8.48 mmol) in CH₂Cl₂ (100 mL) was added DIBAL (1.03 M in hexane, 8.2 mL, 8.5 mmol) at -78 °C. After 1 h of stirring at -78 °C, the mixture was poured into H₂O (0.50 mL, 28 mmol), NaF (7.11 g, 169 mmol), and Celite (8.1 g). The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give aldehyde **7** as a liquid; *R*_f = 0.30 (10:1 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.06 (s, 9 H), 0.87 (s, 9 H), 2.49 (ddd, *J* = 15.6, 4.8, 2.3 Hz, 1 H), 2.59 (ddd, *J* = 15.6, 7.2, 3.0 Hz, 1 H), 4.61 (dt, *J* = 7.2, 5.1 Hz, 1 H), 5.88 (d, *J* = 18.6 Hz, 1 H), 6.00 (dd, *J* = 18.6, 5.1 Hz, 1 H), 9.76 (t, *J* = 2.4 Hz, 1 H). This aldehyde was used for the next reaction without further purification.

To an ice-cold suspension of [PrPPh₃]⁺ Br⁻ (7.24 g, 18.8 mmol) in THF (60 mL) was added NaHMDS (1.0 M in THF, 14.1 mL, 14.1 mmol). The resulting yellow mixture was stirred at 0 °C for 1 h and cooled to -90 °C (liquid N₂ + hexane). A solution of the above aldehyde in THF (20 mL) was added to the mixture dropwise, and then the reaction temperature was allowed to raise to rt gradually over 12 h before addition of saturated NaHCO₃. The mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO₄ and concentrated to afford a residue, which was semipurified by chromatography on silica gel (hexane/EtOAc) to give the corresponding olefin, which was used for the next reaction without further purification: *R*_f = 0.46 (10:1 hexane/EtOAc).

To an ice-cold solution of the above olefin in THF (80 mL) was added TBAF (1.0 M in THF, 9.50 mL, 9.50 mmol). The solution was stirred at rt for 3 h and diluted with saturated NH₄Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO₄ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol *rac*-**8** (1.24 g, 74% from ester **6**) as a liquid; *R*_f = 0.33 (2:1 hexane/EtOAc); IR (neat) 3341, 1248, 989, 867; ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 9 H), 0.97 (t, *J* = 7.6 Hz, 3 H), 1.67 (d, *J* = 4.4 Hz, 1 H), 2.02–2.12 (m, 2 H), 2.31 (t, *J* = 6.8 Hz, 2 H), 4.09–4.17 (m, 1 H), 5.33 (dt, *J* = 10.6, 7.6, 1.5 Hz, 1 H), 5.57 (dt, *J* = 10.6, 7.6, 1.5 Hz, 1 H), 5.88 (dd, *J* = 18.8, 1.2 Hz, 1 H), 6.07 (dd, *J* = 18.8, 5.2 Hz, 1 H); ¹³C-APT NMR (100 MHz, CDCl₃) δ -1.2 (+), 14.3 (+), 20.8 (-), 35.0 (-), 73.8 (+), 123.9 (+), 129.4 (+), 135.3 (+), 147.8 (+); HRMS (FAB⁺) calcd for C₁₁H₂₁OSi [(M - H)⁺] 197.1359.

(S,Z)-1-((2S,3S)-3-(Trimethylsilyloxy)iran-2-yl)hex-3-en-1-ol (9) and (R,1E,5Z)-1-(Trimethylsilyloxy)octa-1,5-dien-3-ol [(R)-8]. To an ice-cold solution of Ti(O-*i*-Pr)₄ (1.90 mL, 6.41 mmol) in CH₂Cl₂ (15 mL) was added L-(+)-DIPT (2.2 mL, 7.59 mmol). The solution was stirred at 0 °C for 20 min and cooled to -20 °C. A solution of the allylic alcohol *rac*-**8** (1.24 g, 6.26 mmol) in CH₂Cl₂ (9 mL) was added to the solution. After 30 min of stirring at -20 °C, the solution was cooled to -40 °C, and *t*-BuOOH (2.1 mL, 3.07 M in CH₂Cl₂, 6.4 mmol) was added dropwise. The reaction mixture was stirred at -18 °C for 6 h, and Me₂S (1.4 mL, 19 mmol) was added. Stirring was continued at -18 °C overnight, and aqueous 10% tartaric acid (0.5 mL), NaF (5.3 g, 126 mmol), and Celite (5.3 g) were added successively. The mixture was vigorously stirred at 0 °C for 1 h and filtered through a pad of Celite. The filtrate was concentrated, and the residue was diluted in MeOH (15 mL) and aqueous 10% NaOH (2.7 mL) at 0 °C. The mixture was vigorously stirred at 0 °C for 1 h and extracted with CH₂Cl₂ three times. The combined extracts were dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford epoxy alcohol **9** (640 mg, 47%) and allylic alcohol (R)-**8** (597 mg, 48%). The enantiomeric excesses of the epoxy alcohol and the allylic alcohol were determined to be 98 and 96.5%, respectively, by ¹H NMR spectroscopy of the derived MTPA ester. Epoxy alcohol **9** was obtained as a liquid; *R*_f = 0.32 (10:1 hexane/EtOAc); [α]_D²¹ +3 (c 0.77, CHCl₃); IR (neat) 3443, 1250, 1045, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 9 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 1.92 (d, *J* = 2.0 Hz, 1 H), 2.08 (quint, *J* = 7.4 Hz, 2 H), 2.34 (t, *J* = 7.0 Hz, 1 H), 2.37 (d, *J* = 3.8 Hz, 1H), 2.90 (t, *J* = 3.8 Hz, 1 H), 3.81–3.88 (m, 1 H), 5.42 (dt, *J* = 10.8, 7.4, 1.5 Hz, 1 H), 5.55 (dt, *J* = 10.8, 7.0, 1.5 Hz, 1 H); ¹³C-APT NMR (100 MHz, CDCl₃) δ -3.6 (+), 14.3 (+), 20.8 (-), 31.7 (-), 47.9 (+), 58.8 (+), 69.4 (+), 123.3 (+), 135.0 (+); HRMS (FAB⁺) calcd for C₁₁H₂₂O₂SiNa [(M+Na)⁺] 237.1287, found 237.1290. Allylic alcohol (R)-**8**: [α]_D²¹ +12 (c 1.05, CHCl₃).

(S,2E,6Z)-4-[(tert-Butyldimethylsilyloxy]nona-2,6-dienal (11). A solution of epoxy alcohol **9** (511 mg, 2.38 mmol), 2,6-lutidine (0.55 mL, 4.8 mmol), and TBSOTf (0.82 mL, 3.57 mmol) in CH₂Cl₂

(30 mL) was stirred at 0 °C for 1.5 h and diluted with saturated NaHCO₃. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO₄ and concentrated. The residue was semipurified by chromatography on silica gel (hexane/EtOAc) to give the corresponding silyl ether, which was used for the next reaction without further purification as a liquid; *R_f* = 0.65 (10:1 hexane/EtOAc); IR (neat) 1471, 1250, 1092, 837 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.06 (s, 9 H), 0.88 (s, 9 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 2.06 (quint, *J* = 7.4 Hz, 2 H), 2.19 (d, *J* = 3.5 Hz, 1 H), 2.35 (t, *J* = 5.8 Hz, 2 H), 2.76 (dd, *J* = 5.8, 3.5 Hz, 2 H), 3.49 (q, *J* = 5.8 Hz, 1 H), 5.38–5.53 (m, 2 H); ¹³C-APT NMR (100 MHz, CDCl₃) δ -4.6 (+), -4.3 (+), -3.5 (+), 14.3 (+), 18.2 (-), 20.8 (-), 25.9 (+), 33.8 (-), 50.0 (+), 58.5 (+), 73.5 (+), 124.2 (+), 133.8 (+).

To an ice-cold solution of the above epoxide in toluene (20 mL) was added Et₂AlCN (0.70 M in toluene, 6.8 mL, 4.8 mmol). The solution was stirred overnight with gradual warming to rt before addition of H₂O (0.50 mL, 28 mmol), NaF (1.99 g, 47.6 mmol), and Celite (4 g). The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford nitrile **10** (505 mg, 79% from **9**) as a liquid, which was used for the next reaction without further purification; *R_f* = 0.60 (10:1 hexane/EtOAc); IR (neat) 2226, 1252, 1107, 838, 777 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.90 (s, 9 H), 0.96 (t, *J* = 7.6 Hz, 3 H), 2.01 (quint, *J* = 7.5 Hz, 2 H), 2.21–2.38 (m, 2 H), 4.27–4.34 (m, 1 H), 5.28 (dt, *J* = 10.8, 7.5, 3.2 Hz, 1 H), 5.52 (dt, *J* = 10.8, 7.5, 1.2 Hz, 1 H), 5.61 (dd, *J* = 16.0, 2.4 Hz, 1 H), 6.76 (dd, *J* = 16.0, 3.6 Hz, 1 H); ¹³C-APT NMR (100 MHz, CDCl₃) δ -4.85 (+), -4.77 (+), 14.1 (+), 18.2 (-), 20.8 (-), 25.8 (+), 35.1 (-), 71.5 (+), 98.6 (+), 117.7 (-), 122.6 (+), 135.2 (+), 157.0 (+).

To a solution of nitrile **10** (505 mg, 1.90 mmol) in CH₂Cl₂ (30 mL) was added DIBAL (1.03 M in hexane, 2.80 mL, 2.88 mmol) at -40 °C. The solution was warmed to 0 °C over 1 h, and 1 N HCl (5 mL) was added dropwise. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated NaHCO₃, dried over MgSO₄, and concentrated to give aldehyde **11** (371 mg, 73%) as a liquid; *R_f* = 0.55 (10:1 hexane/EtOAc); [α]_D²¹ +31 (c 0.99, CHCl₃); IR (neat) 1696, 1100, 837 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.91 (s, 9 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 2.03 (quint, *J* = 7.5 Hz, 2 H), 2.28–2.43 (m, 2 H), 4.40–4.46 (m, 1 H), 5.33 (dt, *J* = 10.8, 7.5, 1.2 Hz, 1 H), 5.52 (dt, *J* = 10.8, 7.5, 1.0 Hz, 1 H), 6.28 (ddd, *J* = 15.3, 8.0, 2.4 Hz, 1 H), 6.81 (dd, *J* = 15.3, 4.4 Hz, 1 H), 9.56 (d, *J* = 8.0 Hz, 1 H); ¹³C-APT NMR (100 MHz, CDCl₃) δ -4.78 (+), -4.70 (+), 14.2 (+), 18.3 (-), 20.8 (-), 25.8 (+), 35.3 (-), 71.7 (+), 123.1 (+), 130.8 (-), 134.8 (+), 159.8 (+), 193.7 (+); HRMS (FAB⁺) calcd for C₁₅H₂₉O₂Si [(M+H)⁺] 269.1937, found 269.1941.

(R,Z)-1-[(2R,3R)-3-(Trimethylsilyloxy)oxiran-2-yl]hex-3-en-1-ol (ent-9). According to the epoxidation of *rac-8* to epoxide **9**, allylic alcohol (*R*)-**8** (340 mg, 1.71 mmol) was converted to epoxide *ent-9* using Ti(O-*i*-Pr)₄ (0.50 mL, 1.71 mmol), D-(-)-DIPT (0.43 mL, 2.06 mmol), and *t*-BuOOH (3.51 M in CH₂Cl₂, 0.73 mL, 2.56 mmol) in CH₂Cl₂ (11 mL) at -18 °C for 6 h. The reaction was quenched by adding Me₂S (0.38 mL, 5.14 mmol), 10% tartaric acid (0.5 mL), NaF (1.6 g, 38 mmol), and Celite (3.2 g). The resulting mixture was filtered through a pad of Celite with CH₂Cl₂. The filtrate was mixed with 10% NaOH (25 mL), and the mixture was vigorously stirred at rt for 30 min. The phases were separated, and the aqueous layer was extracted with CH₂Cl₂ twice. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford epoxide *ent-9* (331 mg, 90%, >99% ee by ¹H NMR spectroscopy of the derived MTPA ester). The ¹H NMR spectrum of the product was consistent with that of *rac-9*: [α]_D¹⁹ -5 (c 0.94, CHCl₃).

(S,2E,6Z)-4-[(tert-Butyldimethylsilyloxy]nona-2,6-dienetriole (10). To an ice-cold solution of *ent-9* (302 mg, 1.41 mmol), 4-(NO₂)₂C₆H₄CO₂H (306 mg, 1.83 mmol), and PPh₃ (473 mg, 1.80 mmol) in THF (5 mL) was added DIAD (0.35 mL, 1.80 mmol). The solution was stirred at rt for 11 h and diluted with saturated NaHCO₃.

The mixture was extracted with EtOAc twice. The combined extracts were dried over MgSO₄ and concentrated to leave the corresponding ester, which was passed through a short column of silica gel for the next reaction as a liquid; *R_f* = 0.59 (7:1 hexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 0.09 (s, 9 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 2.09 (quint, *J* = 7.5 Hz, 2 H), 2.23 (d, *J* = 3.4 Hz, 1 H), 2.49–2.72 (m, 2 H), 3.09 (dd, *J* = 6.9, 3.4 Hz, 1 H), 4.88 (q, *J* = 6.9 Hz, 1 H), 5.30–5.42 (m, 1 H), 5.48–5.61 (m, 1 H), 8.40 (d, *J* = 9.0 Hz, 2 H), 8.30 (d, *J* = 9.0 Hz, 2 H).

To a solution of the above ester in THF (2 mL) and MeOH (2 mL) was added 2 N NaOH (2.0 mL, 4.0 mmol). The mixture was stirred at rt for 1 h and diluted with saturated NH₄Cl. The product was extracted with EtOAc twice, and the combined extracts were dried over MgSO₄. Evaporation and column chromatography of the residue on silica gel (hexane/EtOAc) afforded alcohol **12** (279 mg, 92% from *ent-9*) as a liquid; *R_f* = 0.35 (7:1 hexane/EtOAc); [α]_D²⁰ +7 (c 0.98, CHCl₃); IR (neat) 3421, 1250, 1065, 842 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.07 (s, 9 H), 0.98 (t, *J* = 7.5 Hz, 3 H), 2.08 (quint, *J* = 7.5 Hz, 2 H), 2.20–2.30 (m, 2 H), 2.30–2.48 (m, 2 H), 2.86 (t, *J* = 4.2 Hz, 1 H), 3.46 (quint, *J* = 5.4 Hz, 1 H), 5.33 (dt, *J* = 10.2, 7.5 Hz, 1 H), 5.54 (dt, *J* = 10.2, 7.5 Hz, 1 H); ¹³C-APT NMR (75 MHz, CDCl₃) δ -3.6 (+), 14.3 (+), 20.7 (-), 32.5 (-), 49.5 (+), 58.9 (+), 72.8 (+), 123.4 (+), 134.9 (+).

According to the silylation of **5**, a solution of alcohol **12** (269 mg, 1.25 mmol), TBSCl (226 mg, 1.50 mmol), and imidazole (171 mg, 2.51 mmol) in CH₂Cl₂ (5 mL) was stirred at rt for 2 h and diluted with saturated NaHCO₃. The product was extracted with CH₂Cl₂ and purified by chromatography on silica gel to afford the corresponding TBS ether (399 mg, 97%) as a liquid; *R_f* = 0.79 (8:1 hexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 0.06 (s, 9 H), 0.07 (s, 3 H), 0.11 (s, 3 H), 0.91 (s, 9 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 1.97–2.13 (m, 3 H), 2.20–2.39 (m, 2 H), 2.79 (dd, *J* = 6.3, 3.6 Hz, 1 H), 3.27 (q, *J* = 6.3 Hz, 1 H), 5.32 (dt, *J* = 10.5, 7.2 Hz, 1 H), 5.42 (dt, *J* = 10.5, 7.2 Hz, 1 H).

According to the conversion of the TBS ether of **9** to nitrile **10**, a solution of Et₂AlCN (0.70 M in toluene, 2.60 mL, 1.82 mmol) was added to a solution of the above epoxide (399 mg, 1.21 mmol) in toluene (12 mL) at 0 °C. After 2 h at rt, H₂O (0.30 mL, 17 mmol) was added dropwise. The resulting mixture was stirred for 30 min, and NaF (0.80 g, 19 mmol) was added to the mixture, which was further stirred at rt for 30 min. The resulting mixture was filtered through a pad of Celite, and the product was purified by chromatography on silica gel (hexane/EtOAc) to give cyanide **10** (270 mg, 84%). The ¹H NMR spectrum and *R_f* value on TLC were consistent with those obtained from epoxide **9**.

(1E,5Z)-9-[(tert-Butyldimethylsilyloxy]-1-(trimethylsilyl)nona-1,5-dien-3-ol (rac-19). Reduction of ester **6** (2.18 g, 6.08 mmol) with DIBAL (1.03 M in hexane, 6.5 mL, 6.7 mmol) in CH₂Cl₂ (75 mL) was carried out under similar conditions to those mentioned above (-78 °C, 1.5 h to give aldehyde **7** (1.56 g); *R_f* = 0.33 (15:1 hexane/EtOAc). This aldehyde was used for the next reaction without further purification.

To an ice-cold suspension of phosphonium salt **16** (8.22 g, 11.7 mmol) in THF (80 mL) was added NaHMDS (1.0 M in THF, 8.7 mL, 8.7 mmol). The resulting yellow mixture was stirred at 0 °C for 1 h and cooled to -90 °C. A solution of the above aldehyde in THF (20 mL) was added to the mixture dropwise, and then the reaction temperature was allowed to raise to 0 °C gradually over 14 h before addition of saturated NaHCO₃. The product was extracted with EtOAc and semipurified by chromatography on silica gel (hexane/EtOAc) for the next reaction as a liquid; *R_f* = 0.74 (20:1 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.04 (s, 9 H), 0.88 (s, 9 H), 1.04 (s, 9 H), 1.59 (quint, *J* = 7.2 Hz, 2 H), 2.12 (dt, *J* = 8.0, 7.6 Hz, 2 H), 2.21 (t, *J* = 6.4 Hz, 2 H), 3.65 (t, *J* = 6.4 Hz, 2 H), 4.05 (q, *J* = 6.0 Hz, 1 H), 5.30–5.46 (m, 2 H), 5.76 (d, *J* = 18.8 Hz, 1 H), 5.97 (dd, *J* = 18.8, 6.0 Hz, 1 H), 7.26–7.44 (m, 6 H), 7.66 (d, *J* = 6.4 Hz, 4 H).

An ice-cold solution of the above olefin in THF (50 mL) was mixed with TBAF (1.0 M in THF, 11.6 mL, 11.6 mmol). The solution was stirred at rt for 4 h and diluted with saturated NH₄Cl. The product was extracted with EtOAc and purified by chromatography on silica gel

(hexane/EtOAc) to afford diol **18** (1.26 g, 91% from ester **6**) as a liquid; $R_f = 0.17$ (2:1 hexane/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.07 (s, 9 H), 1.56–1.73 (m, 2 H), 1.87 (br s, 2 H), 2.10–2.40 (m, 4 H), 3.66 (t, $J = 6.2$ Hz, 2 H), 4.13–4.20 (m, 1 H), 5.45 (dt, $J = 10.8$, 7.6 Hz, 1 H), 5.56 (dt, $J = 10.8$, 7.4 Hz, 1 H), 5.89 (dd, $J = 18.7$, 1.4 Hz, 1 H), 6.08 (dd, $J = 18.7$, 5.0 Hz, 1 H); $^{13}\text{C-APT NMR}$ (100 MHz, CDCl_3) δ -1.3 (+), 23.5 (-), 31.9 (-), 34.8 (-), 61.5 (-), 73.7 (+), 125.7 (+), 129.3 (+), 132.2 (+), 147.9 (+).

A solution of diol **18** (1.26 g, 5.52 mmol), imidazole (471 mg, 6.92 mmol), and TBSCl (915 mg, 6.07 mmol) in CH_2Cl_2 (80 mL) was stirred at 0 °C for 3.5 h and diluted with saturated NaHCO_3 . The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give silyl ether *rac*-**19** (1.58 g, 84%) as a liquid; $R_f = 0.60$ (10:1 hexane/EtOAc); IR (neat) 3351, 1620, 1249, 1101, 775 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.05 (s, 6 H), 0.07 (s, 9 H), 0.89 (s, 9 H), 1.57 (t, $J = 7.7$ Hz, 2 H), 1.77 (d, $J = 4.4$ Hz, 1 H), 2.13 (q, $J = 7.7$ Hz, 1 H), 2.31 (t, $J = 7.1$ Hz, 2 H), 3.62 (t, $J = 6.4$ Hz, 2 H), 4.09–4.17 (m, 1 H), 5.42 (dt, $J = 11.0$, 7.1 Hz, 1 H), 5.57 (dt, $J = 11.0$, 7.1 Hz, 1 H), 5.88 (dd, $J = 18.8$, 1.6 Hz, 1 H), 6.07 (dd, $J = 18.8$, 4.8 Hz, 1 H); $^{13}\text{C-APT NMR}$ (100 MHz, CDCl_3) δ -5.2 (+), -1.2 (+), 18.4 (-), 23.7 (-), 26.0 (+), 32.6 (-), 35.0 (-), 62.4 (-), 73.8 (+), 125.2 (+), 129.2 (+), 132.6 (+), 148.0 (+); HRMS (FAB⁺) calcd for $\text{C}_{18}\text{H}_{39}\text{O}_2\text{Si}_2$ [(M+H)⁺] 343.2489, found 343.2484.

(*S,Z*)-7-[(*tert*-Butyldimethylsilyloxy)-1-[(2*S,3S*)-3-(trimethylsilyloxiran-2-yl)hept-3-en-1-ol (**20**) and (*R,1E,5Z*)-9-[(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilyl)nona-1,5-dien-3-ol [(*R*)-**19**]]. According to the epoxidation of *rac*-**8** to epoxide **9**, allylic alcohol *rac*-**19** (1.58 g, 4.61 mmol) was subjected to asymmetric epoxidation using $\text{Ti}(\text{O-}i\text{-Pr})_4$ (1.40 mL, 4.73 mmol), *L*-(+)-DIPT (1.20 mL, 5.73 mmol), and *t*-BuOOH (1.24 mL, 3.07 M, 4.59 mmol) in CH_2Cl_2 (16 mL) at -18 °C for 6 h. The reaction was quenched by adding Me_2S (1.0 mL, 17 mmol), and the solution was stirred at -18 °C overnight. To this solution were added successively H_2O (1.0 mL, 56 mmol), NaF (3.8 g, 90 mmol), and Celite (5.0 g). The resulting mixture was vigorously stirred at rt for 1 h and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (hexane/EtOAc) to afford epoxy alcohol **20** (719 mg, 44%) and allylic alcohol (*R*)-**19** (777 mg, 49%). The enantiomeric excesses of epoxy alcohol **20** and allylic alcohol (*R*)-**19** were determined to be 98 and >99% by $^1\text{H NMR}$ spectroscopy of the derived MTPA esters. Epoxy alcohol **20** was obtained as a liquid; $R_f = 0.43$ (4:1 hexane/EtOAc); $[\alpha]_{\text{D}}^{21} +24$ (c 1.01, CHCl_3); IR (neat) 3447, 1251, 1102, 839 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.04 (s, 6 H), δ 0.06 (s, 9 H), 0.88 (s, 9 H), 1.57 (quint, $J = 6.8$ Hz, 2 H), 2.07 (d, $J = 2.0$ Hz, 1 H), 2.08–2.20 (m, 2 H), 2.31–2.40 (m, 2 H), 2.36 (d, $J = 3.6$ Hz, 1 H), 2.88 (t, $J = 3.6$ Hz, 1 H), 3.61 (t, $J = 6.7$ Hz, 2 H), 3.77–3.85 (m, 1 H), 5.46 (dt, $J = 10.6$, 7.0 Hz, 1 H), 5.54 (dt, $J = 10.6$, 7.4 Hz, 1 H); $^{13}\text{C-APT NMR}$ (100 MHz, CDCl_3) δ -5.2 (+), -3.6 (+), 18.4 (-), 23.7 (-), 26.0 (+), 31.8 (-), 32.6 (-), 47.8 (+), 58.1 (+), 62.5 (-), 69.5 (+), 124.6 (+), 132.5 (+); HRMS (FAB⁺) calcd for $\text{C}_{18}\text{H}_{39}\text{O}_3\text{Si}_2$ [(M+H)⁺] 359.2438, found 359.2438. Allylic alcohol (*R*)-**19**: $[\alpha]_{\text{D}}^{20} +8$ (c 1.00, CHCl_3).

(*S,2E,6Z*)-4,10-Bis[(*tert*-butyldimethylsilyloxy)deca-2,6-dien-enitrile (**22**). A solution of epoxy alcohol **20** (719 mg, 2.01 mmol), 2,6-lutidine (0.64 mL, 5.5 mmol), and TBSOTf (1.05 mL, 4.48 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 3 h and diluted with saturated NaHCO_3 . The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO_4 and concentrated. The residue was semipurified by chromatography on silica gel (hexane/EtOAc) to give silyl ether **21**, which was used for the next reaction without further purification as a liquid; $R_f = 0.61$ (20:1 hexane/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 6 H), 0.07 (s, 9 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.58 (quint, $J = 7.5$ Hz, 2 H), 2.06–2.16 (m, 2 H), 2.19 (d, $J = 3.6$ Hz, 1 H), 2.36 (t, $J = 6.1$ Hz, 2 H), 2.75 (dd, $J = 5.5$, 3.6 Hz, 1 H), 3.51 (q, $J = 5.5$ Hz, 1 H), 3.61 (t, $J = 6.1$ Hz, 2 H), 5.44–5.54 (m, 2 H); $^{13}\text{C-APT NMR}$ (100 MHz, CDCl_3) δ -5.2 (+), -4.6 (+), -4.3 (+), -3.5

(+), 18.2 (-), 18.4 (-), 23.8 (-), 25.9 (+), 26.1 (+), 32.8 (-), 33.9 (-), 49.8 (+), 58.5 (+), 62.7 (-), 73.3 (+), 125.3 (+), 131.5 (+).

According to the conversion of the TBS ether of **9** to nitrile **10**, a solution of Et_2AlCN (0.70 M in toluene, 7.2 mL, 5.0 mmol) was added to a solution of the above epoxide in toluene (20 mL) at 0 °C. After 2 h at 0 °C, H_2O (0.40 mL, 22 mmol), NaF (840 mg, 20 mmol), and Celite (1.0 g) were added to the solution. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give nitrile **22** (754 mg, 92% from epoxy alcohol **20**) as a liquid; $R_f = 0.52$ (10:1 hexane/EtOAc); $[\alpha]_{\text{D}}^{21} +21$ (c 1.12, CHCl_3); IR (neat) 2226, 1255, 1100, 837, 777 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.03 (s, 9 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.54 (quint, $J = 6.6$ Hz, 2 H), 2.01–2.10 (m, 2 H), 2.18–2.37 (m, 2 H), 3.59 (t, $J = 6.6$ Hz, 2 H), 4.26–4.33 (m, 1 H), 5.32 (dt, $J = 11.0$, 7.4 Hz, 1 H), 5.52 (dt, $J = 11.0$, 7.4 Hz, 1 H), 5.60 (dd, $J = 16.2$, 1.8 Hz, 1 H), 6.75 (dd, $J = 16.2$, 3.6 Hz, 1 H); $^{13}\text{C-APT NMR}$ (100 MHz, CDCl_3) δ -5.3 (+), -4.93 (+), -4.85 (+), 18.1 (-), 18.3 (-), 23.7 (-), 25.7 (+), 25.9 (-), 32.5 (-), 35.0 (+), 62.2 (-), 71.4 (+), 98.5 (+), 117.4 (-), 123.6 (+), 132.8 (+), 156.8 (+); HRMS (FAB⁺) calcd for $\text{C}_{22}\text{H}_{42}\text{NO}_2\text{Si}_2$ [(M-H)⁺] 408.2754, found 408.2766.

(*S,2E,6Z*)-4,10-Bis[(*tert*-butyldimethylsilyloxy)deca-2,6-dien-al (**23**). According to the reduction of nitrile **10** to aldehyde **11**, DIBAL (1.02 M in hexane, 0.20 mL, 0.204 mmol) was added to a solution of nitrile **22** (63 mg, 0.154 mmol) in CH_2Cl_2 (10 mL) at -70 °C dropwise. The solution was stirred at -70 °C for 1 h, and excess hydride was quenched by adding *i*-PrOH (0.10 mL, 1.30 mmol). The solution was warmed to 0 °C, and 1 N HCl was added until the mixture became slightly acidic. The mixture was extracted with CH_2Cl_2 twice. The combined extracts were washed with saturated NaHCO_3 and then with brine, dried over MgSO_4 , and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give aldehyde **23** (52 mg, 82%) as a liquid; $R_f = 0.50$ (10:1 hexane/EtOAc); $[\alpha]_{\text{D}}^{21} +31$ (c 1.06, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.04 (s, 9 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 0.91 (s, 9 H), 1.55 (quint, $J = 6.9$ Hz, 2 H), 2.08 (q, $J = 6.9$ Hz, 2 H), 2.28–2.43 (m, 2 H), 3.60 (t, $J = 6.9$ Hz, 2 H), 4.43 (ddt, $J = 6.9$, 1.6, 4.4 Hz, 1 H), 5.39 (dt, $J = 10.8$, 6.9 Hz, 1 H), 5.52 (dt, $J = 10.8$, 6.9 Hz, 1 H), 6.28 (ddd, $J = 15.4$, 8.0, 1.6 Hz, 1 H), 6.85 (dd, $J = 15.4$, 4.4 Hz, 1 H), 9.56 (d, $J = 8.0$ Hz, 1 H); $^{13}\text{C-APT NMR}$ (100 MHz, CDCl_3) δ -5.2 (+), -4.8 (+), -4.7 (+), 18.2 (-), 18.4 (-), 23.9 (-), 25.8 (+), 26.0 (+), 32.7 (-), 35.3 (-), 62.5 (-), 71.7 (+), 124.2 (+), 130.9 (+), 132.6 (+), 159.7 (+), 193.7 (+); HRMS (FAB⁺) calcd for $\text{C}_{22}\text{H}_{45}\text{O}_3\text{Si}_2$ [(M+H)⁺] 413.2907, found 413.2903.

(*S,3Z,5E,9Z*)-7-[(*tert*-butyldimethylsilyloxy)dodeca-3,5,9-trien-1-ol (**25**). To an ice-cold suspension of phosphonium salt **24** (1.05 g, 2.04 mmol) in THF (5 mL) was added NaHMDS (1.0 M in THF, 1.50 mL, 1.50 mmol). The resulting yellow mixture was stirred at 0 °C for 1 h and cooled to -70 °C. A solution of aldehyde **11** (364 mg, 1.36 mmol) in THF (1 mL) was added to the mixture. The solution was stirred at -70 °C for 8 h and poured into saturated NH_4Cl with vigorous stirring. The product was extracted with hexane three times and semipurified by chromatography on silica gel (hexane/EtOAc) as a liquid; $R_f = 0.77$ (10:1 hexane/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 0.04 (s, 3 H), 0.05 (s, 9 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 0.95 (t, $J = 7.5$ Hz, 3 H), 2.03 (quint, $J = 7.5$ Hz, 2 H), 2.14–2.35 (m, 2 H), 2.40 (q, $J = 7.0$ Hz, 2 H), 3.62 (dt, $J = 8.7$, 7.0 Hz, 2 H), 4.16 (quint, $J = 6.2$ Hz, 1 H), 5.26–5.53 (m, 3 H), 5.66 (dd, $J = 15.0$, 5.8 Hz, 1 H), 6.03 (t, $J = 11.0$ Hz, 1 H), 6.43 (dd, $J = 15.0$, 11.0 Hz, 1 H).

A solution of the above olefin and PPTS (376 mg, 1.50 mmol) in MeOH (5 mL) was stirred at rt for 3 h and diluted with saturated NaHCO_3 . The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over MgSO_4 and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol **25** (325 mg, 77% from aldehyde **11**) as a liquid; $R_f = 0.28$ (10:1 hexane/EtOAc); $[\alpha]_{\text{D}}^{20} +17$ (c 0.70, CHCl_3); IR (neat) 3343, 1255, 836, 776 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.90 (s, 9 H), 0.95 (t, $J = 7.4$ Hz, 3 H), 1.33 (t, $J = 6.0$ Hz, 1 H), 2.03 (quint, $J = 7.4$ Hz, 2 H), 2.15–2.39 (m, 2 H), 2.43–2.50 (m, 2 H), 3.68 (q, $J = 6.0$ Hz, 2 H),

4.18 (q, $J = 6.2$ Hz, 1 H), 5.30–5.50 (m, 3 H), 5.70 (dd, $J = 15.2, 6.2$ Hz, 1 H), 6.13 (t, $J = 11.1$ Hz, 1 H), 6.46 (dd, $J = 15.2, 11.1$ Hz, 1 H); ^{13}C -APT NMR (100 MHz, CDCl_3) δ -4.7 (+), -4.4 (+), 14.3 (+), 18.3 (-), 20.8 (-), 25.9 (+), 31.3 (-), 36.3 (-), 62.3 (-), 73.1 (+), 124.2 (+), 124.6 (+), 126.8 (+), 131.0 (+), 133.6 (+), 137.6 (+); HRMS (FAB⁺) calcd for $\text{C}_{18}\text{H}_{34}\text{O}_2\text{SiNa}[(\text{M}+\text{Na})^+]$ 333.2226, found 333.2231.

tert-Butyl[[(S,3Z,7E,9Z)-12-iodododeca-3,7,9-trien-6-yl]oxy]dimethylsilane (26). To a solution of alcohol 25 (219 mg, 0.705 mmol) in CH_2Cl_2 (15 mL) were added PPh_3 (271 mg, 1.03 mmol), imidazole (96 mg, 1.4 mmol), and I_2 (272 mg, 1.07 mmol). The mixture was stirred at rt for 18 h and diluted with aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO_4 , and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give iodide 26 (253 mg, 85%) as a liquid; $R_f = 0.83$ (10:3 hexane/EtOAc); $[\alpha]_{\text{D}}^{20} +22$ (c 0.46, CHCl_3); IR (neat) 1254, 1169, 836, 776 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3 H), 0.06 (s, 3 H), 0.91 (s, 9 H), 0.95 (t, $J = 7.4$ Hz, 3 H), 2.03 (quint, $J = 7.4$ Hz, 2 H), 2.15–2.34 (m, 2 H), 2.75 (q, $J = 7.4$ Hz, 2 H), 3.15 (t, $J = 7.4$ Hz, 2 H), 4.18 (q, $J = 6.0$ Hz, 1 H), 5.33 (dt, $J = 11.1, 7.4$ Hz, 2 H), 5.45 (dt, $J = 11.1, 7.4$ Hz, 1 H), 5.73 (dd, $J = 15.1, 5.6$ Hz, 1 H), 6.10 (t, $J = 11.1$ Hz, 1 H), 6.40 (dd, $J = 15.1, 11.1$ Hz, 1 H); ^{13}C -APT NMR (100 MHz, CDCl_3) δ -4.6 (+), -4.4 (+), 5.0 (-), 14.3 (+), 18.4 (-), 20.8 (-), 26.0 (+), 32.0 (-), 36.3 (-), 72.9 (+), 123.9 (+), 124.6 (+), 129.0 (+), 130.3 (+), 133.7 (+), 138.2 (+); HRMS (EI⁺) calcd for $\text{C}_{18}\text{H}_{33}\text{OSi}[\text{M}^+]$ 420.1345, found 420.1352.

(4Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,17-Bis[tert-butyl(dimethylsilyl)oxy]docosa-4,8,10,13,15,19-hexaen-1-ol (29). A mixture of iodide 26 (253 mg, 0.602 mmol) and PPh_3 (235 mg, 0.896 mmol) in MeCN (15 mL) was heated under reflux for 18 h, cooled to rt, and concentrated. The residue was washed with hexane to give phosphonium salt 27 as a liquid; ^1H NMR (300 MHz, CDCl_3) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.01 (t, $J = 7.5$ Hz, 3 H), 2.01–2.16 (m, 2 H), 2.19–2.37 (m, 2 H), 2.60–2.76 (m, 2 H), 3.83–4.22 (m, 3 H), 5.36 (dt, $J = 11.0, 7.2$ Hz, 1 H), 5.50 (dt, $J = 11.0, 7.2$ Hz, 1 H), 5.66–5.81 (m, 2 H), 6.02 (t, $J = 11.0$ Hz, 1 H), 6.16 (dd, $J = 14.4, 11.0$ Hz, 1 H), 7.74–7.83 (m, 6 H), 7.84–7.98 (m, 6 H). This product was used for the next reaction without further purification.

In addition, phosphonium salt 27 was synthesized again from alcohol 25 to estimate the yield of 27. Thus, iodide 26 derived from alcohol 25 (151 mg, 0.486 mmol) with I_2 (149 mg, 0.587 mmol), PPh_3 (154 mg, 0.587 mmol), and imidazole (40 mg, 0.588 mmol) in CH_2Cl_2 (5 mL) was mixed with PPh_3 (167 mg, 0.637 mmol) in MeCN (5 mL) to afford 27 (302 mg) in 91% yield from alcohol 25.

According to the Wittig reaction of aldehyde 7 with 16, a solution of aldehyde 23 (142 mg, 0.344 mmol) in THF (1 mL) was added at -90°C to the ylide in THF (4 mL) generated from the above phosphonium salt and NaHMDS (1.0 M in THF, 0.45 mL, 0.45 mmol) at 0°C for 1 h. The mixture was warmed to 0°C over 8 h and diluted with saturated NH_4Cl . The product was extracted with EtOAc and semipurified by passing through a silica gel column (hexane/EtOAc) for the next reaction without further purification as a liquid; $R_f = 0.80$ (10:1 hexane/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 0.04 (s, 12 H), 0.06 (s, 6 H), 0.89 (s, 9 H), 0.90 (s, 18 H), 0.97 (t, $J = 7.6$ Hz, 3 H), 1.95–2.12 (m, 4 H), 2.16–2.36 (m, 4 H), 2.90–3.09 (m, 2 H), 3.59 (t, $J = 6.3$ Hz, 2 H), 4.12–4.25 (m, 2 H), 5.26–5.51 (m, 6 H), 5.61–5.73 (m, 2 H), 6.00 (t, $J = 10.8$ Hz, 2 H), 6.45 (dd, $J = 15.0, 11.2$ Hz, 2 H).

To an ice-cold solution of the above olefin in MeOH (5 mL) and CH_2Cl_2 (5 mL) was added PPTS (87 mg, 0.35 mmol) at 0°C . The solution was stirred at rt for 8 h and diluted with saturated NaHCO_3 . The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO_4 and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol 29 (104 mg, 53% from aldehyde 23) as a liquid; $R_f = 0.33$ (3:1 hexane/EtOAc); $[\alpha]_{\text{D}}^{21} +25$ (c 0.94, CHCl_3); IR (neat) 3352, 1255, 1070, 836, 776 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.04 (s, 6 H), 0.06 (s, 6 H), 0.90 (s, 18 H), 0.95 (t, $J = 7.2$ Hz, 3 H), 1.62 (quint, $J = 7.2$ Hz, 2 H), 1.96–2.18 (m, 5 H), 2.18–2.40 (m, 4

H), 3.05 (t, $J = 7.3$ Hz, 2 H), 3.58–3.72 (m, 2 H), 4.20 (quint, $J = 6.3$ Hz, 2 H), 5.28–5.54 (m, 6 H), 5.63–5.74 (m, 2 H), 6.00 (t, $J = 11.0$ Hz, 2 H), 6.46 (dd, $J = 15.3, 11.0$ Hz, 2 H); ^{13}C -APT NMR (75 MHz, CDCl_3) δ -4.6 (+), -4.3 (+), 14.3 (+), 18.4 (-), 20.8 (-), 23.8 (-), 26.0 (+), 26.5 (-), 32.5 (-), 36.4 (-), 36.5 (-), 62.5 (-), 73.07 (+), 73.13 (+), 124.2 (+), 124.3 (+), 124.7 (+), 126.3 (+), 128.5 (+), 128.6 (+), 129.0 (+), 129.2 (+), 130.9 (+), 133.6 (+), 137.1 (+), 137.2 (+).

(4Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,17-Bis[tert-butyl(dimethylsilyl)oxy]docosa-4,8,10,13,15,19-hexaenoic Acid (30). A solution of alcohol 29 (46 mg, 0.080 mmol), PCC (26 mg, 0.12 mmol), and Celite (50 mg) was stirred at rt for 2 h and diluted with Et_2O . The resulting mixture was filtered through a pad of silica gel. The filtrate was concentrated to give the corresponding aldehyde, which was used for the next reaction without further purification as a liquid; $R_f = 0.51$ (10:3 hexane/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 0.036 (s, 3 H), 0.040 (s, 3 H), 0.051 (s, 3 H), 0.057 (s, 3 H), 0.896 (s, 9 H), 0.901 (s, 9 H), 0.95 (t, $J = 7.3$ Hz, 3 H), 2.03 (quint, $J = 7.3$ Hz, 2 H), 2.20–2.40 (m, 6 H), 2.48 (t, $J = 6.9$ Hz, 2 H), 3.05 (t, $J = 7.5$ Hz, 2 H), 4.20 (quint, $J = 6.6$ Hz, 2 H), 5.28–5.52 (m, 6 H), 5.67 (dt, $J = 15.1, 6.6$ Hz, 2 H), 5.99 (t, $J = 10.8$ Hz, 2 H), 6.45 (dd, $J = 15.1, 10.8$ Hz, 2 H), 9.76 (t, $J = 1.8$ Hz, 1 H).

A mixture of the above aldehyde, 2-methyl-2-butene (0.34 mL, 3.2 mmol), NaClO_2 (79% purity, 14 mg, 0.12 mmol) in McIlvaine's phosphate buffer (pH 5.0, 1.4 mL), and *t*-BuOH (1.4 mL) was stirred at rt for 1 h and diluted with H_2O (5 mL). The mixture was extracted with Et_2O three times. The combined extracts were washed with brine and dried over MgSO_4 . The resulting mixture was filtered through a pad of silica gel to give acid 30 (39 mg, 81% from alcohol 29) as a liquid; $R_f = 0.17$ (10:3 hexane/EtOAc); $[\alpha]_{\text{D}}^{21} +21$ (c 0.89, CHCl_3); IR (neat) 1713, 1255, 1072, 836 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.036 (s, 3 H), 0.042 (s, 3 H), 0.052 (s, 3 H), 0.059 (s, 3 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 0.95 (t, $J = 7.3$ Hz, 3 H), 2.03 (quint, $J = 7.3$ Hz, 2 H), 2.16–2.44 (m, 8 H), 3.05 (t, $J = 7.5$ Hz, 2 H), 4.19 (quint, $J = 5.9$ Hz, 2 H), 5.28–5.54 (m, 6 H), 5.67 (dt, $J = 15.1, 5.9$ Hz, 2 H), 5.99 (t, $J = 11.0$ Hz, 2 H), 6.46 (dd, $J = 15.1, 11.0$ Hz, 2 H); ^{13}C -APT NMR (75 MHz, CDCl_3) δ -4.6 (+), -4.3 (+), 14.3 (+), 18.3 (-), 20.8 (-), 22.8 (-), 26.0 (+), 26.5 (-), 33.8 (-), 36.4 (-), 72.9 (+), 73.1 (+), 124.2 (+), 124.4 (+), 124.7 (+), 127.3 (+), 128.5 (+), 128.6 (+), 129.0 (+), 129.3 (+), 133.6 (+), 136.9 (+), 137.2 (+), 177.7 (-); HRMS (FAB⁻) calcd for $\text{C}_{34}\text{H}_{59}\text{O}_4\text{Si}_2[(\text{M}-\text{H})^-]$ 587.3952, found 587.3976.

Methyl (4Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,17-Dihydroxydocosa-4,8,10,13,15,19-hexaenoate (31). To an ice-cold solution of acid 30 (39 mg, 0.066 mmol) in Et_2O (1 mL) was added an ethereal solution of CH_2N_2 (3 mL). After 5 min of stirring at 0°C , the mixture was concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to give the corresponding methyl ester, which was used for the next reaction without further purification as a liquid; $R_f = 0.67$ (10:3 hexane/EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 0.036 (s, 3 H), 0.040 (s, 3 H), 0.052 (s, 3 H), 0.057 (s, 3 H), 0.897 (s, 9 H), 0.901 (s, 9 H), 0.95 (t, $J = 7.3$ Hz, 3 H), 2.03 (quint, $J = 7.3$ Hz, 2 H), 2.17–2.38 (m, 8 H), 3.05 (t, $J = 7.6$ Hz, 2 H), 3.66 (s, 3 H), 4.19 (quint, $J = 5.5$ Hz, 2 H), 5.27–5.52 (m, 6 H), 5.67 (dt, $J = 15.3, 5.5$ Hz, 2 H), 5.99 (t, $J = 11.1$ Hz, 2 H), 6.45 (dd, $J = 15.3, 11.1$ Hz, 2 H); ^{13}C -APT NMR (75 MHz, CDCl_3) δ -4.6 (+), -4.3 (+), 14.3 (+), 18.3 (-), 20.8 (-), 23.1 (-), 26.0 (+), 26.5 (-), 29.8 (-), 34.1 (-), 36.4 (-), 51.6 (+), 72.9 (+), 73.1 (+), 124.2 (+), 124.4 (+), 124.7 (+), 127.1 (+), 128.5 (+), 128.6 (+), 129.0 (+), 129.2 (+), 129.3 (+), 133.6 (+), 136.9 (+), 137.2 (+), 173.7 (-); HRMS (FAB⁺) calcd for $\text{C}_{35}\text{H}_{62}\text{O}_4\text{Si}_2\text{Na}[(\text{M}+\text{Na})^+]$ 625.4084, found 625.4076.

A mixture of the above methyl ester and TBAF (1.0 M in THF, 0.81 mL, 0.81 mmol) in THF (0.5 mL) was stirred at rt for 1.5 h and diluted with McIlvaine's phosphate buffer (pH 5.0, 5 mL). The resulting mixture was extracted with Et_2O three times. The combined extracts were dried over MgSO_4 and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give diol 31 (11 mg, 44% from acid 30) as a liquid; $R_f = 0.10$ (2:1 hexane/EtOAc); $[\alpha]_{\text{D}}^{19} +6$ (c 0.53, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.96 (t, $J = 7.4$ Hz, 3 H), 2.03 (quint, $J = 7.4$ Hz, 2 H), 2.26–2.48 (m, 8 H), 1.8–2.5 (br s, 2 H), 3.09 (t, $J = 7.6$ Hz, 2 H), 3.67 (s, 3 H), 4.24 (quint, $J = 6.0$ Hz, 2 H), 5.28–5.62 (m, 6 H), 5.73

(dt, $J = 15.1, 6.0$ Hz, 2 H), 6.01 (t, $J = 11.0$ Hz, 2 H), 6.59 (dd, $J = 15.1, 11.0$ Hz, 2 H); ^{13}C -APT NMR (75 MHz, CDCl_3) δ 14.3 (+), 20.8 (-), 22.9 (-), 26.7 (-), 33.8 (-), 35.3 (-), 35.4 (-), 51.8 (+), 71.7 (+), 71.9 (+), 123.7 (+), 125.3 (+), 126.4 (+), 128.29 (+), 128.32 (+), 129.6 (+), 131.0 (+), 135.4 (+), 136.00 (+), 136.03 (+), 173.8 (-).

Resolvin D5 (4). To a solution of alcohol **31** (10 mg, 0.029 mmol) in MeOH (0.5 mL) and THF (0.5 mL) was added 1 N LiOH (0.30 mL, 0.30 mmol). The mixture was stirred at rt for 1.5 h and diluted with McIlvaine's phosphate buffer (pH 5.0, 10 mL). The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica gel (*i*-PrOH/Et₂O to give resolvin D5 (**4**) (4.3 mg, 45%) as a liquid; $R_f = 0.08$ (1:1 hexane/EtOAc); $[\alpha]_D^{20} +18$ (c 0.22, CHCl_3); IR (neat) 3366, 1715, 1261, 1036 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.96 (t, $J = 7.4$ Hz, 3 H), 2.06 (quint, $J = 7.4$ Hz, 2 H), 2.28–2.48 (m, 8 H), 1.8–2.6 (br s, 3 H), 2.92–3.24 (m, 2 H), 4.22–4.34 (m, 2 H), 5.28–5.62 (m, 6 H), 5.74 (dm, $J = 15.1$ Hz, 2 H), 5.95–6.08 (m, 2 H), 6.54–6.74 (m, 2 H); ^1H NMR (300 MHz, CD_3CN) δ 0.94 (t, $J = 7.4$ Hz, 3 H), 2.04 (quint, $J = 7.4$ Hz, 2 H), 2.21–2.36 (m, 8 H), 1.9–2.4 (br s, 3 H), 3.07 (t, $J = 7.6$ Hz, 2 H), 4.12 (q, $J = 6.2$ Hz, 2 H), 5.28–5.53 (m, 6 H), 5.72 (dd, $J = 15.0, 6.2$ Hz, 2 H), 6.01 (t, $J = 11.0$ Hz, 2 H), 6.55 (dd, $J = 15.0, 11.0$ Hz, 2 H); ^{13}C -APT NMR (75 MHz, CDCl_3) δ 14.3 (+), 20.8 (-), 22.8 (-), 26.7 (-), 33.5 (-), 35.1 (-), 35.3 (-), 71.6 (+), 72.0 (+), 123.7 (+), 125.0 (+), 125.5 (+), 126.6 (+), 127.9 (+), 128.5 (+), 129.2 (+), 129.7 (+), 130.9 (+), 135.4 (+), 135.6 (+), 136.0 (+), 177.0 (-); HRMS (FAB⁻) calcd for $\text{C}_{22}\text{H}_{31}\text{O}_4$ [(M-H)⁻] 359.2222, found 359.2217. The ^1H NMR (300 MHz, CD_3CN) spectrum was consistent with that previously reported.⁶

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02870.

^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Colas, R. A.; Shinohara, M.; Dalli, J.; Chiang, N.; Serhan, C. N. *Am. J. Physiol. Cell Physiol.* **2014**, *307*, C39–C54. (b) Serhan, C. N. *Nature* **2014**, *510*, 92–101. (c) Serhan, C. N.; Chiang, N. *Curr. Opin. Pharmacol.* **2013**, *13*, 632–640. (d) Serhan, C. N.; Arita, M.; Hong, S.; Gotlinger, K. *Lipids* **2004**, *39*, 1125–1132.
- (2) Hong, S.; Gronert, K.; Devchand, P. R.; Moussignac, R.-L.; Serhan, C. N. *J. Biol. Chem.* **2003**, *278*, 14677–14687.
- (3) (a) Hong, S.; Tjonahen, E.; Morgan, E. L.; Lu, Y.; Serhan, C. N.; Rowley, A. F. *Prostaglandins Other Lipid Mediators* **2005**, *78*, 107–116. (b) Giera, M.; Ioan-Facsinay, A.; Toes, R.; Gao, F.; Dalli, J.; Deelder, A. M.; Serhan, C. N.; Mayboroda, O. A. *Biochim. Biophys. Acta, Mol. Cell Biol. Lipids* **2012**, *1821*, 1415–1424. (c) Miyahara, T.; Runge, S.; Chatterjee, A.; Chen, M.; Mottola, G.; Fitzgerald, J. M.; Serhan, C. N.; Conte, M. S. *FASEB J.* **2013**, *27*, 2220–2232. (d) Dalli, J.; Kraft, B. D.; Colas, R. A.; Shinohara, M.; Fredenburgh, L. E.; Hess, D. R.; Chiang,

N.; Welty-Wolf, K.; Choi, A. M.; Piantadosi, A. A.; Serhan, C. N. *Am. J. Respir. Cell Mol. Biol.* **2015**, *53*, 314–325.

(4) Chiang, N.; Fredman, G.; Bäckhed, F.; Oh, S. F.; Vickery, T.; Schmidt, B. A.; Serhan, C. N. *Nature* **2012**, *484*, 524–529.

(5) (a) Butovich, I. A.; Lukyanova, S. M.; Bachmann, C. J. *Lipid Res.* **2006**, *47*, 2462–2474. (b) Butovich, I. A.; Hamberg, M.; Rådmark, O. *Lipids* **2005**, *40*, 249–257.

(6) Rodríguez, A. R.; Spur, B. W. *Tetrahedron Lett.* **2005**, *46*, 3623–3627.

(7) Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* **2009**, *50*, 6079–6082.

(8) (a) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780. (b) Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* **1988**, *44*, 4073–4086.

(9) Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem.* **2001**, *2001*, 1873–1881.

(10) Silylation with TBSCl and imidazole suffered from the formation of the corresponding chorohydrin in varying yields.

(11) (a) Jeffery, T.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett.* **1992**, *33*, 5757–5760. (b) Caruso, T.; Spinella, A. *Tetrahedron* **2003**, *59*, 7787–7790.

(12) The propargylic CH_2 signals at δ 2.3–2.9 ppm were less than expected 4 H.

(13) Alkylation of the EE ether of **13** with EtBr under similar conditions (BuLi, HMPA/THF, -70 °C to rt, overnight) followed by hydrolysis of the EE moiety by aqueous HCl gave the alkylation product in 74–78% yields. In addition, hydrogenation gave *rac*-**8** as well.

(14) Because a high enough quantity of **22** was obtained from **20**, (*R*)-**19** was not converted to **22**.