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Total Synthesis of Resolvin D5

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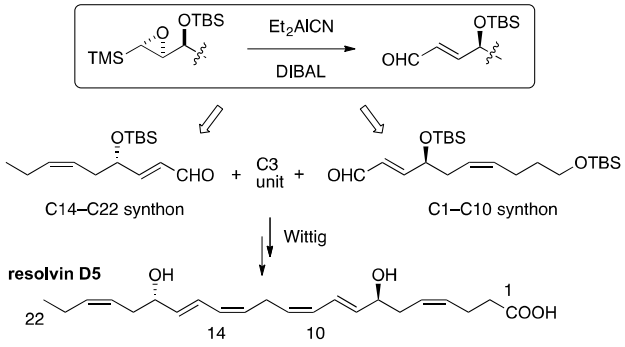


ABSTRACT:

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 Et_2AlCN, 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., $[TBSO(CH_2)_3PPh_3]^+ Br^-$, 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 widely studied with their supply by organic synthesis, whereas others, including resolvins D1–D6, are still at 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] and its ability to activate the host defense system in mice during bacterial infection was 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] involving 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 highly stereoselective formation of the stereogenic centers and the *E*,*Z*-diene was sought.

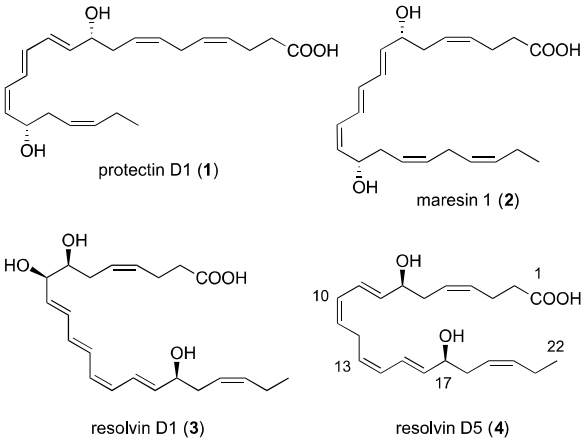
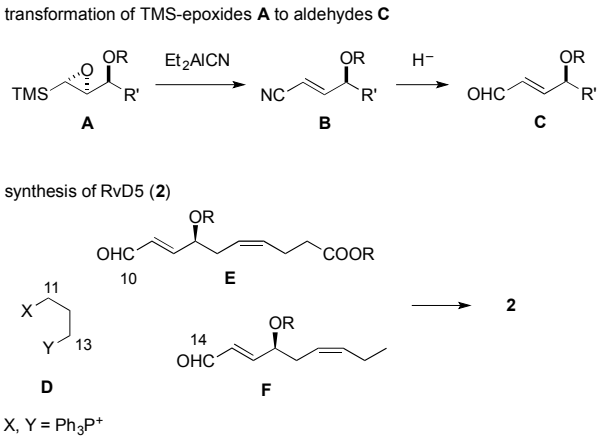


Figure 1. Metabolites of DHA.

Previously, we reported the TMS-specific reaction of epoxy alcohol derivatives **A** with Et_2AlCN 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**.

Scheme 1. An Access to RvD5

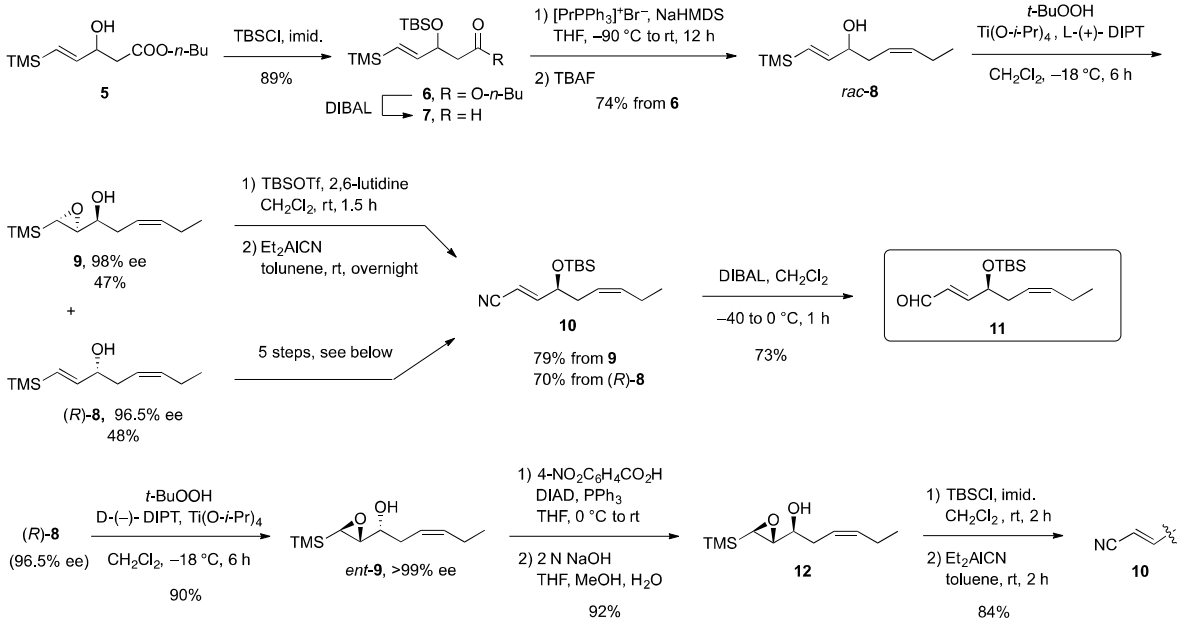


RESULTS AND DISCUSSION

Aldehyde **11** corresponding to the 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) $LiAlH_4$ reduction; (2) PCC oxidation; and (3) aldol reaction with MeCOO-*n*-Bu/LDA according to the reported procedure,[9] and converted to the TBS ether **6** in 89% yield. DIBAL reduction of **6** afforded aldehyde **7**, which upon Wittig reaction with the ylide derived from $[PrPPh_3]^+ Br^-$ and $NaN(TMS)_2$ (NaHMDS) followed by desilylation with TBAF afforded racemic allylic alcohol *rac*-**8** in 74 % yield from ester **6** and with high cis olefin purity (>98%) as confirmed by ^{13}C NMR spectroscopy. Sharpless asymmetric epoxidation of *rac*-**8** using L-(+)-diisopropyl tartrate (DIPT) and $Ti(O\text{-}i\text{-}Pr)_4$ 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 Et_2AlCN 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 ca. 2%) in 96.5% ee of (*R*)-**8**. The Mitsunobu inversion, silylation of the resulting epoxy alcohol **12**, and subsequent reaction with Et_2AlCN 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%.

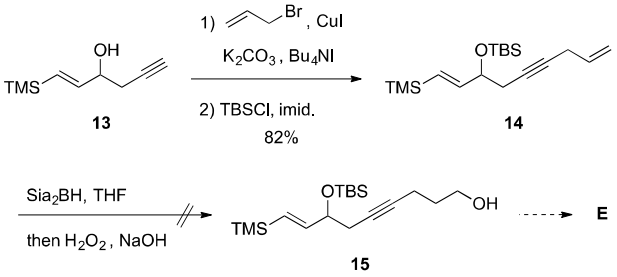
Scheme 2. Synthesis of Aldehyde 11 Corresponding to the Intermediate F



Several reaction sequences were attempted to obtain an intermediate corresponding to aldehyde **E** in Scheme 1. Allylation of **13** with allyl bromide under literature conditions[11] followed by silylation proceeded to completion to afford **14** in 82% yield (Scheme 3).

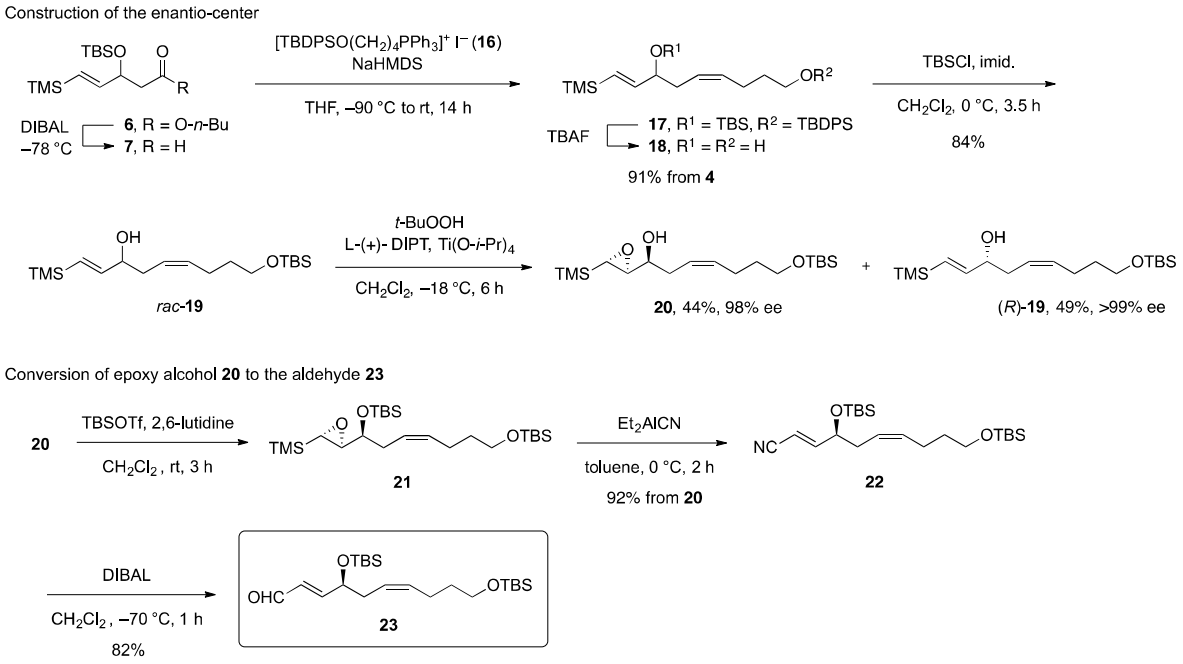
However, hydroboration of **14** with Sia_2BH gave a complex mixture of products (TLC, ^1H NMR).[12] Moreover, alkylation of the ethoxyethyl (EE) ether of **13** with $I(CH_2)_3OTBS$ ($LiNH_2$, NH_3/THF; BuLi, HMPA/THF) gave the product in low yield (<22%).[13]

Scheme 3. Attempted Construction of Intermediate E



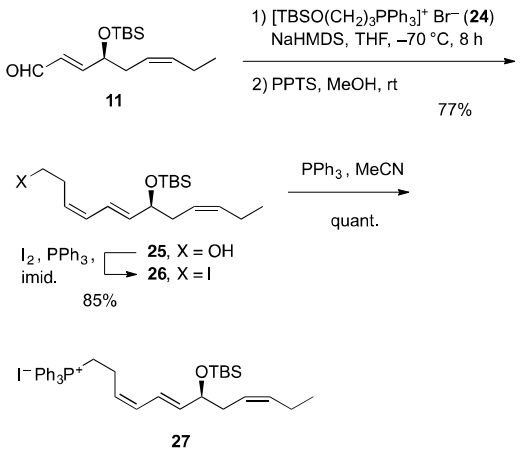
Alternatively, Wittig reaction of aldehyde **7** synthesized again from ester **6** with the ylide derived from **16** and NaHMDS yielded olefin **17**, which was converted to racemic alcohol *rac*-**19** in good yield by deprotection with TBAF followed by regioselective silylation with TBSCl and imidazole (Scheme 4). The ^{13}C 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**, 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 into nitrile **22** in 92% yield.[14] Finally, reduction of **22** with DIBAL provided aldehyde **23**.

Scheme 4. Synthesis of the C1–C10 Intermediate 23



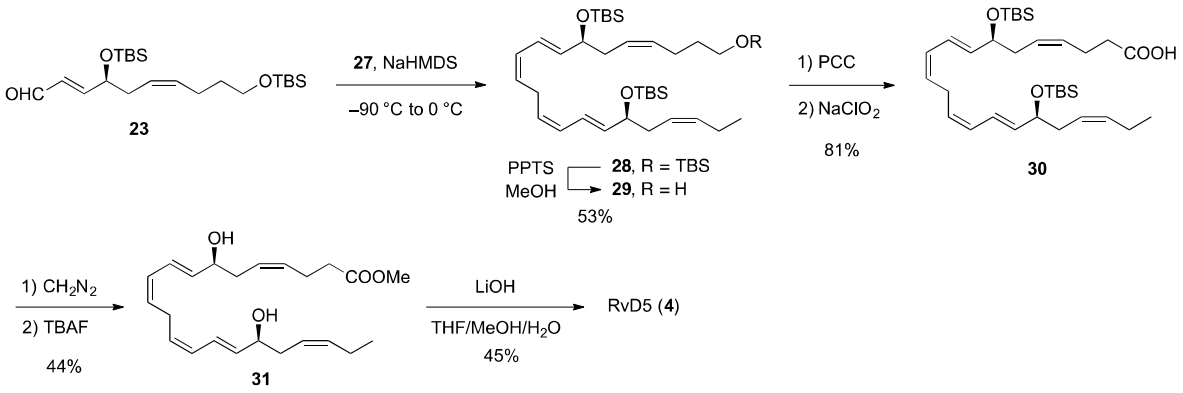
Among the two possible pathways for connecting the two aldehydes **23** and **11** to the C11–C13 unit, a sequence first connecting **11** and the C11–C13 unit was examined, because the reverse order of the connection was expected to be unsuccessful in regioselective deprotection of the TBS group at C13 in the 1,13-bis-TBS ether intermediate. As delineated in Scheme 5, 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 PPh_3 to provide phosphonium salt **27** in 85% yield from **25**.

Scheme 5. Synthesis of the C11–C22 Intermediate 27



The last stage of the synthesis was 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 ^{13}C 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 ^{1}H NMR spectrum in CD_3CN was consistent with that reported in the literature.[6] The structure of **4** was also confirmed by the ^{1}H and ^{13}C–APT NMR spectra in $CDCl_3$ (APT: attached proton test).

Scheme 6. The Last Stage of the Synthesis of RvD5



CONCLUSION

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 synthesis of RvD2 and other RvD1,2,4, respectively.

EXPERIMENTAL SECTION

General Remarks. The ^{1}H (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectroscopic data were recorded in $CDCl_3$ using Me_4Si ($\delta = 0$ 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 CH_2) and positive (for CH and CH_3) 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), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). 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*-butyldimethylsilyl)oxy]-5-(trimethylsilyl)pent-4-enoate (6). A solution of the 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 CH_2Cl_2 (150 mL) was stirred at rt overnight 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 ester **6** (8.36 g, 89%): liquid; R_f 0.67 (hexane/EtOAc 5:1); IR (neat) 1740, 1250, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C–APT NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{38}O_3Si_2$ [M^+] 358.2360, found 358.2360.

(1*E*,5*Z*)-1-(Trimethylsilyl)octa-1,5-dien-3-ol (*rac*-8). To a solution of ester **6** (3.04 g, 8.48 mmol) in CH_2Cl_2 (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 H_2O (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**: liquid; R_f 0.30 (hexane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) 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 $[PrPPh_3]^+$ 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 N_2 + 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 $NaHCO_3$. The mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was semi-purified 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 (hexane/EtOAc 10:1).

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 NH_4Cl. 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 afford alcohol *rac*-**8** (1.24 g, 74% from ester **6**): liquid; R_f 0.33 (hexane/EtOAc 2:1); IR (neat) 3341, 1248, 989, 867; ^{1}H NMR (400 MHz, $CDCl_3$) 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 (dtt, J = 10.6, 7.6, 1.5 Hz, 1 H), 5.57 (dtt, 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); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ –1.2 (+), 14.3 (+), 20.8 (–), 35.0 (–), 73.8 (+), 123.9 (+), 129.4 (+), 135.3 (+), 147.8 (+); HRMS (FAB$^+$) calcd for $C_{11}H_{21}OSi$ [(M–H)$^+$] 197.1362, found 197.1359.

(*S*,*Z*)-1-((2*S*,3*S*)-3-(Trimethylsilyl)oxiran-2-yl)hex-3-en-1-ol (9) and (*R*,1*E*,5*Z*)-1-(trimethylsilyl)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 CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2, 6.4 mmol) was added dropwise. The reaction mixture was stirred at –18 °C for 6 h, and Me_2S (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), 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 CH_2Cl_2 three times. The combined extracts were dried over $MgSO_4$ 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%). Enantiomeric excess of the epoxy alcohol and the allylic alcohol was determined to be 98% and 96.5% by ^{1}H NMR spectroscopy of the derived MTPA ester. Epoxy alcohol **9**: liquid; R_f 0.32 (hexane/EtOAc 10:1); $[\alpha]_D^{21}$ +3 (*c* 0.77, $CHCl_3$); IR (neat) 3443, 1250, 1045, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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 (dtt, J = 10.8, 7.4, 1.5 Hz, 1 H), 5.55 (dtt, J = 10.8, 7.0, 1.5 Hz, 1 H); ^{13}C–APT NMR (100 MHz, $CDCl_3$) δ –3.6 (+), 14.3 (+), 20.8 (–), 31.7 (–), 47.9 (+), 58.8 (+), 69.4 (+), 123.3 (+), 135.0 (+); HRMS (FAB^+) calcd for $C_{11}H_{22}O_2SiNa$ [$(M+Na)^+$] 237.1287, found 237.1290. Allylic alcohol (*R*)-**8**: $[\alpha]_D^{21}$ +12 (*c* 1.05, $CHCl_3$).

(*S*,2*E*,6*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]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 CH_2Cl_2 (30 mL) was stirred at 0 °C for 1.5 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 semi-purified by chromatography on silica gel (hexane/EtOAc) to give the corresponding silyl ether, which was used for the next reaction without further purification: liquid; R_f 0.65 (hexane/EtOAc 10:1); IR (neat) 1471, 1250, 1092, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C–APT NMR (100 MHz, $CDCl_3$) 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 Et_2AlCN (0.70 M in toluene, 6.8 mL, 4.8 mmol). The solution was stirred overnight with gradual warm to rt before addition of H_2O (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**), which was used for the next reaction without further purification: liquid; R_f 0.60 (hexane/EtOAc 10:1); IR (neat) 2226, 1252, 1107, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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 (dtt, *J* = 10.8, 7.5, 3.2 Hz, 1 H), 5.52 (dtt, *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); ^{13}C–APT NMR (100 MHz, $CDCl_3$) 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 CH_2Cl_2 (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 $NaHCO_3$, dried over $MgSO_4$, and concentrated to give aldehyde **11** (371 mg, 73%): liquid; R_f 0.55 (hexane/EtOAc 10:1); $[\alpha]_D^{21}$ +31 (*c* 0.99, $CHCl_3$); IR (neat) 1696, 1100, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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 (dtt, *J* = 10.8, 7.5, 1.2 Hz, 1 H), 5.52 (dtt, *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); ^{13}C–APT NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{29}O_2Si$ $[(M+H)^+]$ 269.1937, found 269.1941.

(*R*,*Z*)-1-[(2*R*,3*R*)-3-(Trimethylsilyl)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 $Ti(O\text{-}i\text{-}Pr)_4$ (0.50 mL, 1.71 mmol), D-(–)-DIPT (0.43 mL,

2.06 mmol), and *t*-BuOOH (3.51 M in CH_2Cl_2, 0.73 mL, 2.56 mmol) in CH_2Cl_2 (11 mL) at –18 °C for 6 h. The reaction was quenched by adding Me_2S (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 CH_2Cl_2. The filtrate was mixed with 10% NaOH (25 mL) and the mixture was stirred at rt for 30 min vigorously. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford epoxide *ent*-**9** (331 mg, 90%, >99% ee by ^{1}H NMR spectroscopy of the derived MTPA ester). The ^{1}H NMR spectrum of the product was consistent with that of *rac*-**9**: $[\alpha]_D^{19}$ –5 (*c* 0.94, $CHCl_3$).

(*S*,2*E*,6*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]nona-2,6-dienenitrile (10). To an ice-cold solution of *ent*-**9** (302 mg, 1.41 mmol), 4-$(NO_2)C_6H_4CO_2H$ (306 mg, 1.83 mmol), and PPh_3 (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 $NaHCO_3$. The mixture was extracted with EtOAc twice. The combined extracts were dried over $MgSO_4$ and concentrated to leave the corresponding ester, which was passed through a short column of silica gel for the next reaction: liquid; R_f 0.59 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) 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 NH_4Cl. The product was extracted with EtOAc twice and the combined extracts were dried over $MgSO_4$. Evaporation and column chromatography of the residue on silica gel

(hexane/EtOAc) afforded alcohol **12** (279 mg, 92% from *ent*-**9**): liquid; R_f 0.35 (hexane/EtOAc 7:1); $[\alpha]_D^{20}$ +7 (*c* 0.98, $CHCl_3$); IR (neat) 3421, 1250, 1065, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C–APT NMR (75 MHz, $CDCl_3$) 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 CH_2Cl_2 (5 mL) was stirred at rt for 2 h and diluted with saturated $NaHCO_3$. The product was extracted with CH_2Cl_2 and purified by chromatography on silica gel to afford the corresponding TBS ether (399 mg, 97%): liquid; R_f 0.79 (hexane/EtOAc 8:1); ^1H NMR (300 MHz, $CDCl_3$) 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 Et_2AlCN (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, H_2O (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**.

(1*E*,5*Z*)-9-[(*tert*-Butyldimethylsilyl)oxy]-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 CH_2Cl_2 (75 mL) was carried out under similar conditions mentioned above (–78 °C, 1.5 h to give aldehyde **7** (1.56 g): R_f 0.33 (hexane/EtOAc 15:1). This aldehyde was used for the next reaction without further purification.

To an ice-cold suspension of the 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 $NaHCO_3$. The product was extracted with EtOAc and semi-purified by chromatography on silica gel (hexane/EtOAc) for the next reaction: liquid; R_f 0.74 (hexane/EtOAc 20:1); ^{1}H NMR (400 MHz, $CDCl_3$) 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 NH_4Cl. 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**): liquid; R_f 0.17 (hexane/EtOAc 2:1); ^{1}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}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%): liquid; R_f 0.60 (hexane/EtOAc 10:1); IR (neat) 3351, 1620, 1249, 1101, 775 cm^{-1}; ^1H 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}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 $C_{18}H_{39}O_2Si_2$ [$(M+H)^+$] 343.2489, found 343.2484.

(*S*,*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*S*,3*S*)-3-(trimethylsilyl)oxiran-2-yl]hept-3-en-1-ol (20) and (*R*,1*E*,5*Z*)-9-[(*tert*-butyldimethylsilyl)oxy]-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 $Ti(O\text{-}i\text{-}Pr)_4$ (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%). Enantiomeric excess of the epoxy alcohol **20** and the allylic alcohol (*R*)-**19** was determined to be 98% and >99% by ^{1}H NMR spectroscopy of the derived MTPA esters. Epoxy alcohol **20**: liquid; R_f 0.43 (hexane/EtOAc 4:1); $[\alpha]_D^{21}$ +24 (*c* 1.01, $CHCl_3$); IR (neat) 3447, 1251, 1102, 839 cm^{-1}; ^{1}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}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 $C_{18}H_{39}O_3Si_2$ [(M+H)$^+$] 359.2438, found 359.2438. Allylic alcohol (*R*)-**19**: $[\alpha]_D^{20}$ +8 (*c* 1.00, $CHCl_3$).

(*S*,2*E*,6*Z*)-4,10-Bis[(*tert*-butyldimethylsilyl)oxy]deca-2,6-dienenitrile (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 semi-purified by chromatography on silica gel (hexane/EtOAc) to give silyl ether **21**, which was used for the next reaction without further purification: liquid; R_f 0.61 (hexane/EtOAc 20:1); ^{1}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}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**): liquid; R_f 0.52 (hexane/EtOAc 10:1); $[\alpha]_D^{21}$ +21 (*c* 1.12, $CHCl_3$); IR (neat) 2226, 1255, 1100, 837, 777 cm^{-1}; ^1H 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}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 $C_{22}H_{42}NO_2Si_2$ [$(M–H)^+$] 408.2754, found 408.2766.

(*S*,2*E*,6*Z*)-4,10-Bis[(*tert*-butyldimethylsilyl)oxy]deca-2,6-dienal (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%): liquid; R_f 0.50

(hexane/EtOAc 10:1); $[\alpha]_D^{21}$ +31 (*c* 1.06, $CHCl_3$); ^{1}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}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 $C_{22}H_{45}O_3Si_2$ [$(M+H)^+$] 413.2907, found 413.2903.

(*S*,3*Z*,5*E*,9*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]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 semi-purified by chromatography on silica gel (hexane/EtOAc): liquid; R_f 0.77 (hexane/EtOAc 10:1); ^{1}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**): liquid; R_f 0.28 (hexane/EtOAc 10:1); $[\alpha]_D^{20}$ +17 (*c* 0.70, $CHCl_3$); IR (neat) 3343, 1255, 836, 776 cm^{-1}; ^1H 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 $C_{18}H_{34}O_2SiNa$ $[(M+Na)^+]$ 333.2226, found 333.2231.

***tert*-Butyl[{(*S*,3*Z*,7*E*,9*Z*)-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 $Na_2S_2O_3$. 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%): liquid; R_f 0.83 (hexane/EtOAc 10:3); $[\alpha]_D^{20}$ +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 $C_{18}H_{33}OSiI$ $[M^+]$ 420.1345, found 420.1352.

(4*Z*,7*S*,8*E*,10*Z*,13*Z*,15*E*,17*S*,19*Z*)-7,17-Bis[(*tert*-butyldimethylsilyl)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**: liquid; ^{1}H 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 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 semi-purified by passing through a silica gel column (hexane/EtOAc) for the next reaction without further purification: liquid; R_f 0.80 (hexane/EtOAc 10:1); ^{1}H 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 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**): liquid; R_f 0.33 (hexane/EtOAc 3:1); $[\alpha]_D^{21}$ +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 (+).

(4*Z*,7*S*,8*E*,10*Z*,13*Z*,15*E*,17*S*,19*Z*)-7,17-Bis[(*tert*-butyldimethylsilyl)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) were 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: liquid; R_f 0.51 (hexane/EtOAc 10:3); ^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, 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**): liquid; R_f 0.17 (hexane/EtOAc 10:3); $[\alpha]_D^{21}$ +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 $C_{34}H_{59}O_4Si_2$ [$(M–H)^-$] 587.3952, found 587.3976.

Methyl (4*Z*,7*S*,8*E*,10*Z*,13*Z*,15*E*,17*S*,19*Z*)-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: liquid; R_f 0.67 (hexane/EtOAc 10:3); ^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 $C_{35}H_{62}O_4Si_2Na$ [$(M+Na)^+$] 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**): liquid; R_f 0.10 (hexane/EtOAc 2:1); $[\alpha]_D^{19}$ +6 (*c* 0.53, $CHCl_3$); ^{1}H 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/Et_2O to give resolvin D5 (**4**) (4.3 mg, 45%): liquid; R_f 0.08 (hexane/EtOAc 1:1); $[\alpha]_D^{20}$ +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 $C_{22}H_{31}O_4$ [$(M–H)^-$] 359.2222, found 359.2217. The ^1H NMR (300 MHz, CD_3CN) spectrum was consistent with that reported.[6]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxx.

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

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Notes

The authors declare no competing fi nancial interest.

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(12) The propargylic CH_2 signals at δ 2.3–2.9 ppm was 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 addiiton, hydrogenation gave *rac*-**8** as well.

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