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Total synthesis of 12(*R*)-HETE, 12(*S*)-HETE, $^2H_2$-12(*R*)-HETE and LTB_4 from racemic glycidol via hydrolytic kinetic resolution

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Abstract—The total synthesis of 12(*R*)-HETE, 12(*S*)-HETE (Samuelsson's HETE), [14,15-$^2H_2$]-12(*R*)-HETE and Leukotriene B_4 from racemic glycidol is described. The key steps are the hydrolytic kinetic resolution of racemic TES-glycidol with salen-Co catalyst and the selective oxidation of primary silyl ethers, in the presence of secondary ones, under Swern conditions to give a short entry to both enantiomers of 12-HETE and LTB_4. © 2000 Elsevier Science Ltd. All rights reserved.

The metabolism of arachidonic acid has attracted much attention over the years.[1] 12(*R*)-HETE (**1**) is formed via the cytochrome P-450 pathway and is present in high concentration in psoriasis lesions.[2] Its enantiomer, 12(*S*)-HETE (**2**), the major 12-lipoxygenase metabolite in platelets,[3] has been found to play a central role in various stages of metastatic process in tumors and is therefore a potential target for an anticancer treatment. 12(*S*)-HETE (**2**) inhibits tumor cell adhesion to endothelial cells.[4]

LTB_4 (**3**), a metabolite of arachidonic acid via the 5-lipoxygenase pathway, is a potent chemotactic agent for human eosinophils and neutrophils and a modulator of inflammatory responses.[5] Newer results demonstrated that LTB_4 (**3**) has high antiviral activity towards DNA viruses as well as retroviruses, including HIV-1 and HIV-2, comparable with antiviral drugs, such as Acylovir or Ganciclovir,[6] opening new perspectives for **3** and metabolically stable LTB_4 analogs.[7]

In the interest of evaluating the biological and pharmacological properties of these compounds it was necessary to obtain sufficient quantities by chemical synthesis. The first synthesis of 12(*S*)-HETE (**2**) was reported by Corey et al.[8] starting from *S*(−)-malic acid that was used later on as starting material by other groups.[9] D(+)-Mannitol and D(−)-arabinose were used in the synthesis of 12(*S*)-HETE (**2**) whereas L(+)-arabinose has been the chiral source of 12(*R*)-HETE (**1**) and LTB_4 (**3**).[10] Alpina-borane reduction[11] and the Sharpless kinetic resolution of racemic γ-iodoallylic alcohols (Sato's procedure)[12] were used in the synthesis of both enantiomers of 12-HETE and LTB_4. A recent report by Corey et al. described the synthesis of 12(*R*)-HETE and 12(*S*)-HETE utilizing the Sharpless asymmetric dihydroxylation.[13]

In this paper we report a short synthesis of the two enantiomers of 12-HETE, [14,15-$^2H_2$]-12(*R*)-HETE (**37**) and LTB_4 (**3**) (Fig. 1) from easily available starting materials. The synthesis of 12(*R*)-HETE (**1**) and LTB_4 (**3**) were based on the retrosynthetic analysis shown in Fig. 2.

The chiral TES glycidol (**7**),[14] a versatile C-3 building block, was obtained from racemic glycidol with >99% ee using Jacobsen's hydrolytic kinetic resolution with H_2O in the presence of 1% (*S*,*S*)-salen-Co catalyst (**14**) in Et_2O at room temperature,[15] as shown in Scheme 1. Simple bulb to bulb distillation gave **7** in 46% isolated yield (92% theoretical yield).

The nucleophilic opening of the epoxide **7** with 1-heptynyllithium in the presence of TMEDA, similar as described by Nicolaou,[16] was very slow. The protective group was cleaved under those conditions and large quantities of the dimerization product of 1-heptyne were isolated. Better results were achieved using the Yamaguchi method with $BF_3{\cdot}Et_2O$ at −78°C in THF.[17] The reaction was fast and only a small amount of deprotected material was observed. The optical purity was measured

Keywords: eicosanoids; hydrolytic kinetic resolution; selective Swern oxidation.

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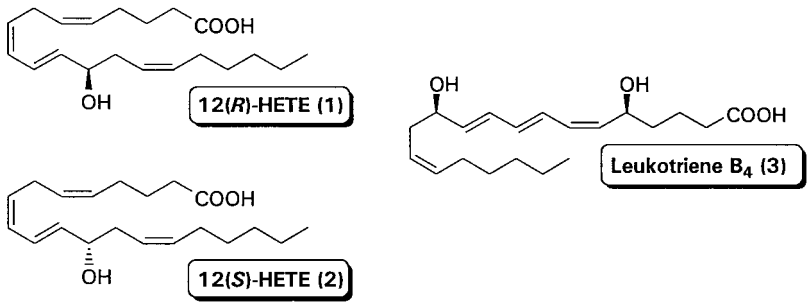


Figure 1.

by chiral HPLC [Column: OF-chiracel, mobile phase: hexane/*i*-PrOH (90:10), λ=265 nm, >99% ee] of the dibenzoate derivative obtained from compound **16** after cleavage of the TES ether. The secondary hydroxy group in **16** was protected with triethylsilylchloride to give **5**. Selective Swern oxidation of the primary TES ether in the presence of the secondary one produced directly the chiral key intermediate **4** (Scheme 2), required for the synthesis of 12(*R*)-HETE (**1**) and LTB_4 (**3**).[15]

The synthesis of 12(*R*)-HETE (**1**) (Scheme 2) was accomplished, similarly as described by Rokach et al.,[10f] by Wittig reaction of the aldehyde **4** with 3 equivalents of (triphenylphosphoranylidene)acetaldehyde (**8**)[18] in benzene at 60°C to produce the α,β-unsaturated aldehyde **20** in 87% isolated yield. Compound **20** was reacted with methyl 8-(triphenylphosphoranylidene)-5(*Z*)-octenoate (**9**), generated in situ from **22** with KHMDS, in THF/HMPA at −78°C to give the 12(*R*)-HETE precursor **23**. The critical step in the synthesis was the selective reduction of the triple bond in **23** to the *cis* double bond in **25** in the presence of the additional conjugated and isolated double bonds avoiding over-reduction.[19] Reaction conditions and solvents were very critical. Compound **25** was obtained from **23** by controlled hydrogenation (Lindlar catalyst, deactivated with pyridine, in hexane). 12(*R*)-HETE methyl ester (**27**)

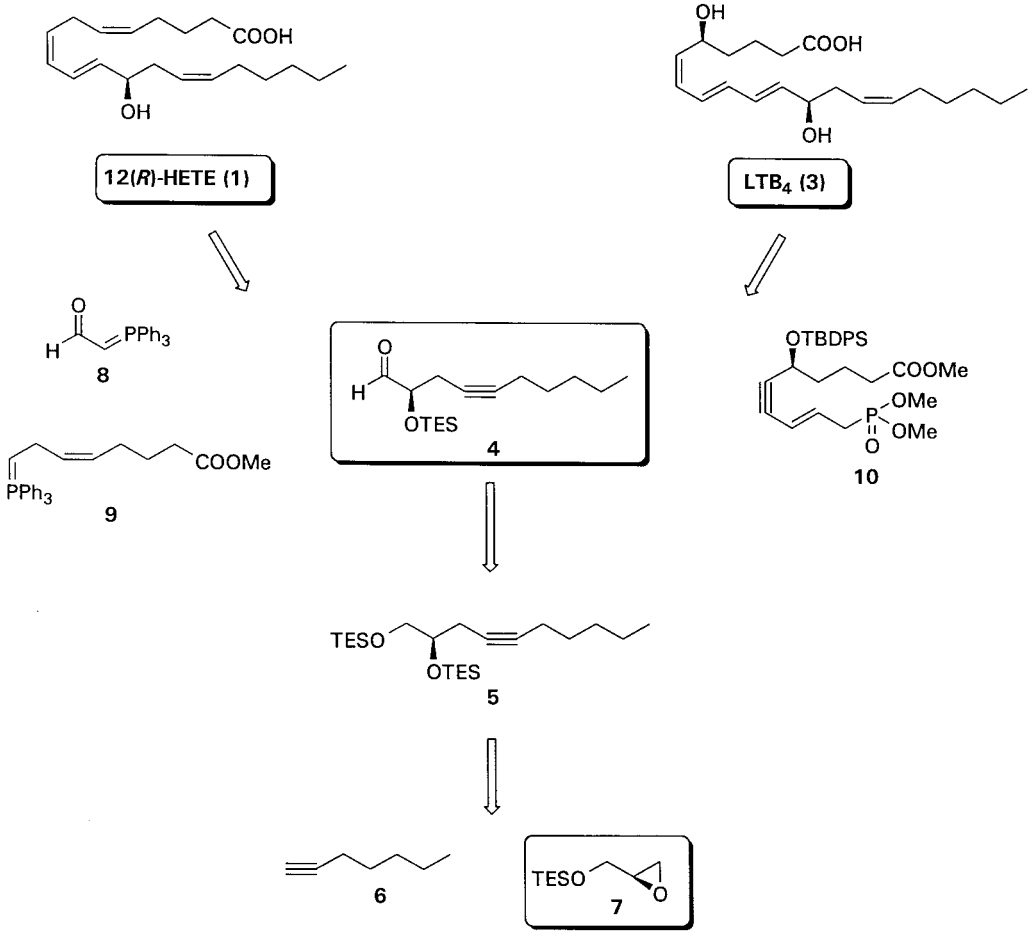
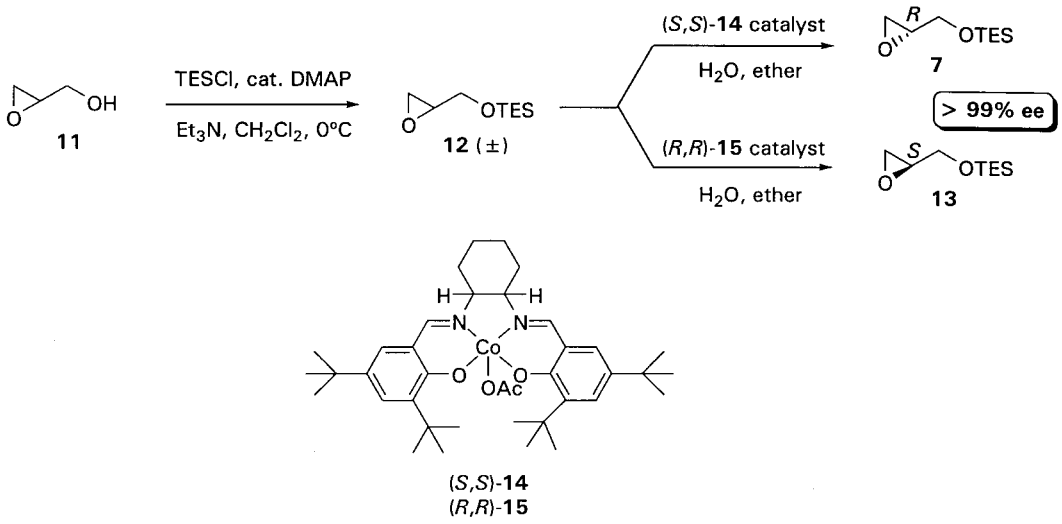
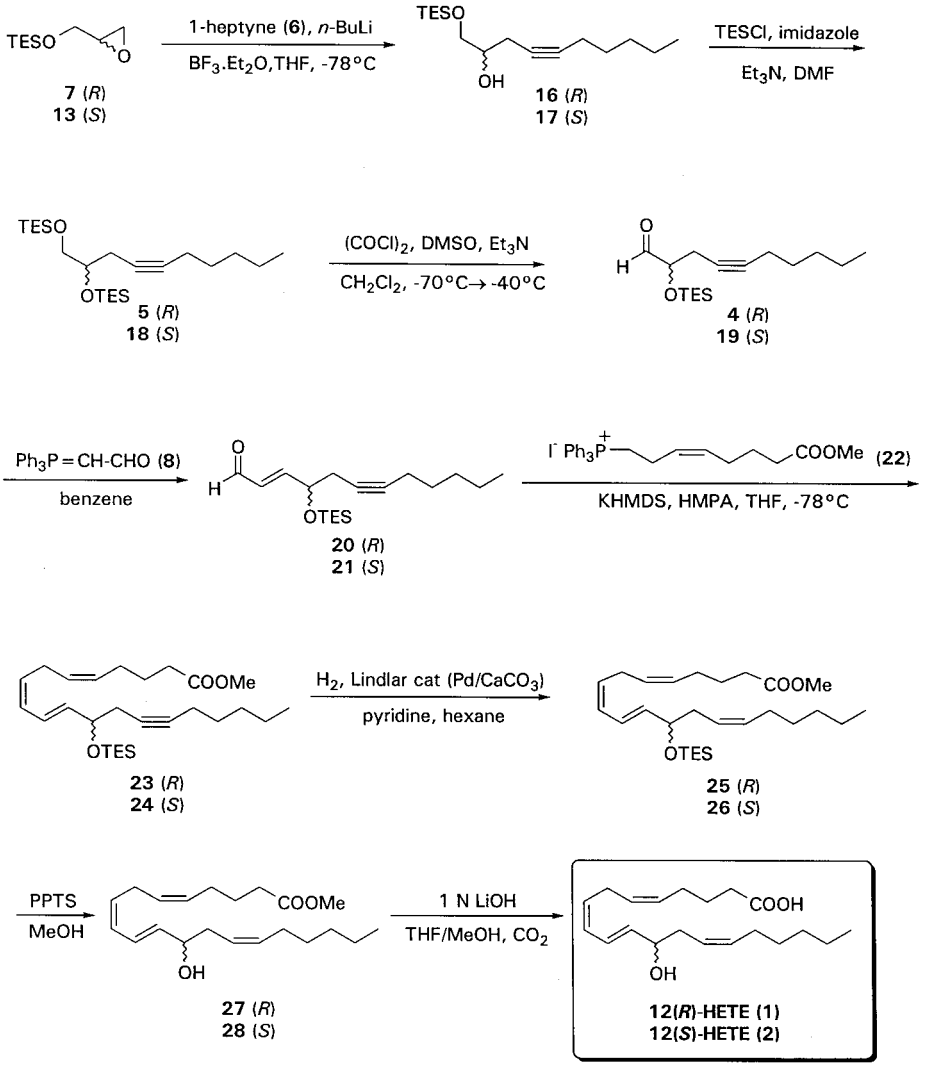


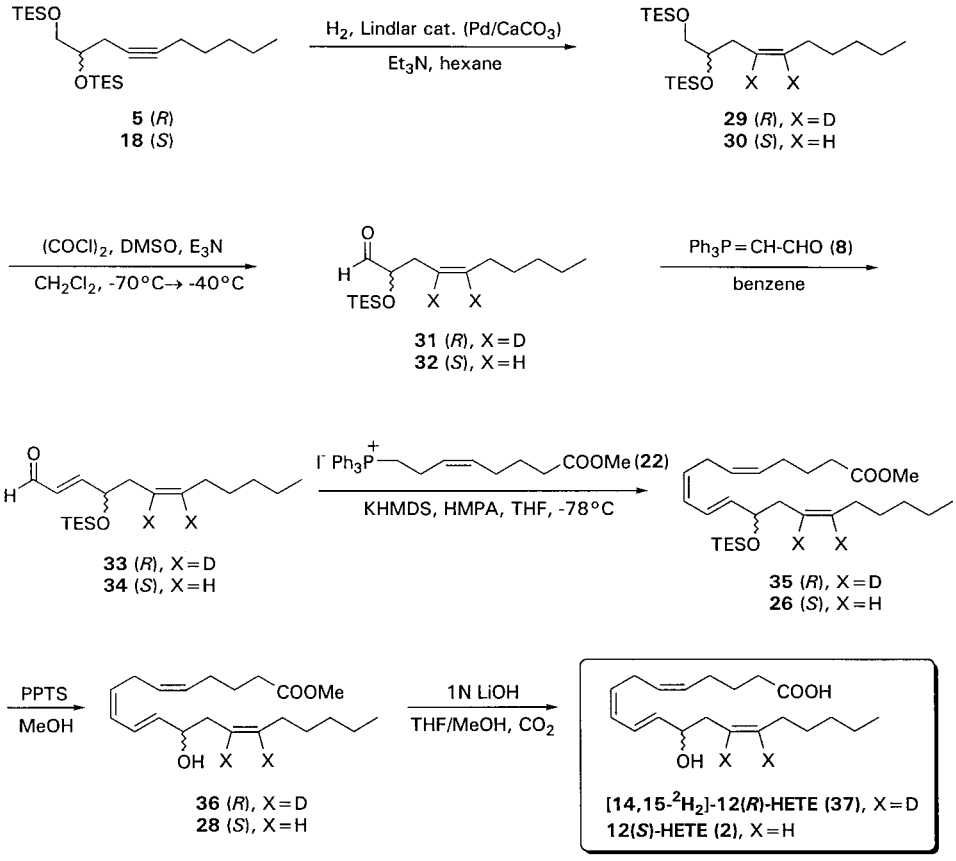
Figure 2.



Scheme 1.



Scheme 2.



Scheme 3.

was obtained in high yield by mild deprotection of the silyl ether in **25** with pyridinium *p*-toluenesulfonate in acetone/H_2O (2 h) or in MeOH (1.5 h). Compound **27** was characterized by ^{1}H NMR, ^{13}C NMR, APT, COSY, HETCOR and optical rotation. Final hydrolysis of **27** with a 1N aqueous solution of LiOH in THF/MeOH gave 12(*R*)-HETE (**1**) identical in all aspects with an authentic sample (Upjohn-Pharmacia).

The synthesis of the major platelet metabolite of arachidonic acid, 12(*S*)-HETE (**2**), was achieved using a similar route as described for its enantiomer 12(*R*)-HETE (**1**) (Scheme 2). The chiral TES-glycidol (**13**) was obtained with >99% ee using Jacobsen's hydrolytic kinetic resolution with 1% (*R*,*R*)-salen-Co catalyst (**15**) (Scheme 1). Compound **2** was characterized by ^{1}H NMR, ^{13}C NMR, APT, COSY, HETCOR and HPLC/API-ES/MS, and was identical in all aspects with an authentic sample (Upjohn-Pharmacia).

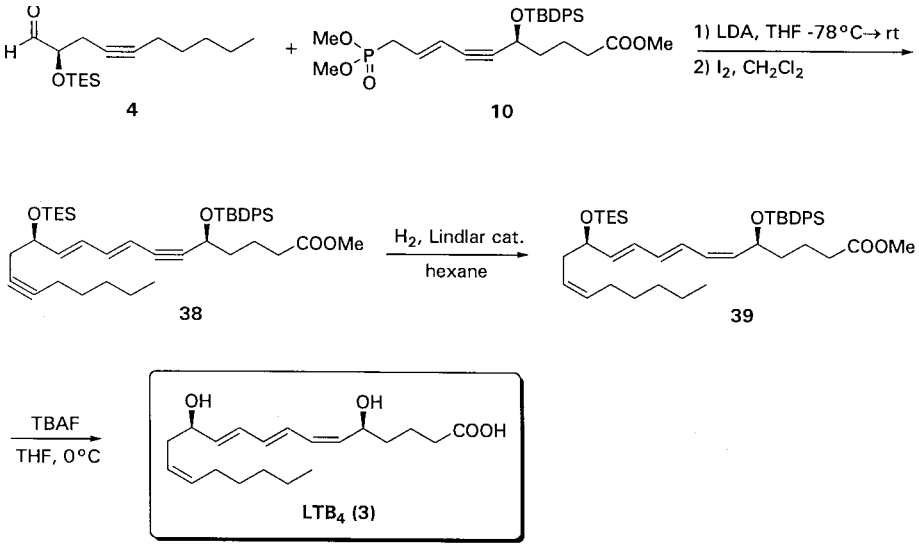
In order to avoid the difficulties encountered in the Lindlar reduction at a late stage we examined the reduction of the triple bond to the *cis* double bond at the first possible step. The synthesis of [14,15-$^2H_2$]-12(*R*)-HETE (**37**) and 12(*S*)-HETE (**2**) is outlined in Scheme 3. The di-TES ether **5** was cleanly reduced in hexane with deuterium, Lindlar catalyst and Et_3N affording **29** in quantitative yield. In a similar way intermediate **18** was reduced with hydrogen affording **30**.

Compound **29** was transformed to [14,15-$^2H_2$]-12(*R*)-HETE (**37**), as outlined in Scheme 3, through intermediates **31** and **33** to give [14,15-$^2H_2$]-12(*R*)-HETE methyl ester (**36**). Mild hydrolysis as previously described gave [14,15-$^2H_2$]-12(*R*)-HETE (**37**).

Compound **30** was transformed to **2** following the same steps as described for **37**, as outlined in Scheme 3. Compound **2** was identical with the material prepared by the method described in Scheme 2.

The synthesis of LTB_4 (**3**) was accomplished by Emmons–Horner reaction of aldehyde **4** with Nicolaou's chiral C_1–C_{10} phosphonate **10**.[16] (Scheme 4) The reaction of **4** with **10** produced unexpectedly the 8*E*,10*Z*-diene, however, the crude product could be easily isomerized with a catalytic amount of iodine in CH_2Cl_2 at room temperature to give **38** (>95% *E*,*E*). Lindlar hydrogenation of **38** followed by deprotection with TBAF gave LTB_4 (**3**) directly, identical in all aspects (^{1}H NMR, ^{13}C NMR, APT, COSY, HETCOR, UV, optical rotation, HPLC, HPLC/API-ES/MS and bioassay) with a sample prepared using Corey's route.[20]

In summary, a short and efficient total synthesis of 12(*S*)-HETE, 12(*R*)-HETE, [14,15-$^2H_2$]-12(*R*)-HETE and LTB_4 has been accomplished from racemic glycidol. The key steps are the Jacobsen hydrolytic kinetic resolution of racemic TES-glycidol and the selective oxidation of the primary TES ether in the presence of a secondary one. The application of this method towards other natural products will be reported in due course.



Scheme 4.

1. Experimental

1.1. General remarks

All reactions that were moisture and air-sensitive were carried out in flame-dried glassware and under an argon atmosphere. The progress of the reactions was checked by thin layer chromatography (TLC) using E. Merck silica gel 60F glass plates (0.25 mm). The spots were visualized with UV light, followed by heat staining with *p*-anisaldehyde in $EtOH/CH_3COOH/H_2SO_4$. Silica gel 60 from EM-Science was used for flash chromatography. HPLC analysis were performed on a Hewlett-Packard liquid chromatograph HP-1090 Series II with PV5 SDS (Solvent Delivery System) and DAD (Diode Array Detector) equipped with heated column compartment and automatic liquid injector, or on a Waters HPLC system (M-6000A pump, M-730 Data Module integrator, U6K Injector) and a Schoeffel SF-770 UV detector. For Chiral HPLC Chiracel OF, OD, OB columns (Daicel Chemical Ltd.) have been used. ^1H NMR and ^{13}C NMR data were recorded on a 300 MHz Varian Gemini 2000 Broadband High-Resolution NMR. IR spectra were measured on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. UV Spectra were obtained using a Hewlett Packard HP-8453 UV–Visible Spectrophotometer. Optical rotation was measured on a Perkin–Elmer Polarimeter 343. Mass Spectra were obtained using Hewlett Packard HP-59987A API-Electrospray (Atmospheric Pressure Ionization Electrospray) interface coupled to a Mass Spectrometer Hewlett Packard HP-5989B MS. High Resolution Mass Spectra (HRMS) were obtained at the University of Pennsylvania Mass Spectrometry Service Center on a VG Micromass using Electrospray Ionization Mode. Microanalysis were performed by Micro-Analysis, Inc., Wilmington, Delaware.

1.1.1. (Triethylsilyl)glycidyl ether (12). To a solution of glycidol (**11**) (7.4 g, 0.10 mol), Et_3N (15.9 ml, 0.11 mol) and 4-dimethylaminopyridine (50 mg, 0.41 mmol) in CH_2Cl_2 (50 ml) at 0°C was added dropwise chlorotriethylsilane (15.9 ml, 94.7 mmol). The reaction was allowed to reach room temperature and stirred until completion. The mixture was diluted with CH_2Cl_2 and poured in ice-cold H_2O. Separation of the organic phase, washing with a saturated solution of NaCl, drying over Na_2SO_4 and concentration under vacuo afforded crude **12** in quantitative yield. The product was purified by bulb to bulb distillation 60–80°C/1 mm affording **12** (15.7 g, 84%). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.8 (1H, ddd, J=11.8, 3.3, 0.4 Hz, ^1H of CH_2–OTES), 3.6 (1H, dd, J=11.8, 5.0 Hz, ^1H of CH_2–OTES), 3.1 (1H, m, CH–O), 2.7 (1H, ddd, J=5.1, 4.0, 0.4 Hz, ^1H of CH_2–O–CH), 2.6 (1H, dd, J=5.1, 2.8 Hz, ^1H of CH_2–O–CH), 0.9 (9H, t, J=7.8 Hz, CH_3–CH_2–Si), 0.6 (6H, q, J=7.8 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 63.6 (CH_2–OTES), 52.3 (CH–O), 44.5 (CH_2–O–CH), 6.5 (3C, CH_3–CH_2–Si), 4.2 (3C, CH_2–Si).

1.1.2. (*R*)-(Triethylsilyl)glycidyl ether (7). Compound **12** (12.2 g, 64.8 mmol) was dissolved in Et_2O (25 ml) and (*S*,*S*)-(salen)Co(III)(AcO) (**14**) (0.21 g, 0.32 mmol) was added. The mixture was cooled to 0°C and H_2O (0.64 ml, 35.6 mol) was added dropwise. The reaction was allowed to reach room temperature and stirred for 20 h. The Et_2O was evaporated and the residue was purified by bulb to bulb distillation 50–55°C/0.6 mm affording **7** (5.6 g, 46% yield). $[\alpha]_D^{25}$=1.9 (c=1.08, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.8 (1H, ddd, J=11.8, 3.3, 0.4 Hz, ^1H of CH_2–OTES), 3.6 (1H, dd, J=11.8, 5.0 Hz, ^1H of CH_2–OTES), 3.1 (1H, m, CH–O), 2.8 (1H, ddd, J=5.1, 4.0, 0.4 Hz, ^1H of CH_2–O–CH), 2.6 (1H, dd, J=5.1, 2.8 Hz, ^1H of CH_2–O–CH), 0.9 (9H, t, J=7.8 Hz, CH_3–CH_2–Si), 0.6 (6H, q, J=7.8 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 63.6 (CH_2–OTES), 52.3 (CH–O), 44.5 (CH_2–O–CH), 6.5 (3C, CH_3–CH_2–Si), 4.3 (3C, CH_2–Si).

1.1.3. (*R*)-1-[(Triethylsilyl)oxy]-4-decyn-2-ol (16). A solution of 1-heptyne (3.5 ml, 26.8 mmol) in THF (20 ml) at −78°C was treated with a 2.5 M solution of *n*-butyllithium in hexane (10.7 ml, 26.8 mmol). The solution was brought to 0°C and kept at that temperature for 15 min. The reaction was cooled again to −78°C and then the TES protected glycidol **7** (2.4 g, 12.7 mmol) in THF (5 ml) was added

followed by $BF_3{\cdot}Et_2O$ (3.4 ml, 26.8 mmol). After 30 min stirring the reaction was quenched by the addition of a saturated solution of NH_4Cl. The reaction was brought to room temperature and diluted with Et_2O. The phases were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuo. The crude product **16**, that contained small amount of the unprotected diol, was used without further purification for the next step. A small sample was purified by flash chromatography for analytical purpose. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.8–3.7 (2H, m, C*H*–OH, ^{1}H of CH_2–OTES), 3.7–3.5 (1H, m, ^{1}H of C*H*$_2$–OTES), 2.6–2.5 (1H, br. s, OH), 2.4–2.3 (2H, m, C*H*$_2$–CH–OH), 2.2–2.1 [2H, tt, J=7.0, 2.4 Hz, C*H*$_2$–$(CH_2)_3$–CH_3], 1.5–1.4 [2H, m, CH_2–$(CH_2)_2$–CH_3], 1.4–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.0–0.9 (9H, t, J=8.0 Hz, C*H*$_3$–CH_2–Si), 0.9–0.8 (3H, t, J=7.2 Hz, CH_3), 0.6 (6H, q, J=8.0 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 82.6 (≡C), 75.6 (≡C), 70.5 (CH–OH), 65.4 (CH_2–OTES), 31.0 (*C*H$_2$–CH_2–CH_3), 28.6 [*C*H$_2$–$(CH_2)_2$–CH_3], 23.3 (*C*H$_2$–CH–OH), 22.1 (*C*H$_2$–CH_3), 18.6 [*C*H$_2$–$(CH_2)_3$–CH_3], 13.8 (CH_3), 6.5 (3C, *C*H$_3$–CH_2Si), 4.2 (3C, CH_2–Si). Enantiomeric excess was determined to be >99% by chiral HPLC of the dibenzoate derivative obtained from compound **16** after cleavage of the TES ether [Column: OF-chiracel, mobile phase: hexane/*i*-PrOH (90:10), λ=265 nm].

1.1.4. (*R*)-1,2-Bis[(triethylsilyl)oxy]-4-decyne (5). To a solution of mono-protected compound **16** (3.6 g, 12.7 mmol) and imidazole (4.6 g, 67.6 mmol) in DMF (15 ml) at 0°C was added Et_3N (5.1 ml, 36.6 mmol) followed by chlorotriethylsilane (4.5 ml, 26.7 mmol). After 30 min stirring, the reaction was quenched over ice-cold H_2O layered with hexane/EtOAc (9:1). The organic layer was separated, washed four times with ice-cold H_2O and once with brine. After drying and concentrating under vacuo the crude was purified by flash chromatography with hexane/EtOAc (98:2) (0.5% Et_3N) and **5** (3.2 g, 64% two-steps) was obtained. $[\alpha]_D^{25}$=2.0 (c=1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.8 (1H, m, CH–OTES), 3.7–3.5 (2H, 2 dd AB system, J=9.9, 5.7 Hz, CH_2–OTES), 2.5–2.4 (1H, ddt AB system, J=16.5, 6.0, 2.4 Hz, ^{1}H of C*H*$_2$–CH–OTES), 2.3–2.2 (1H, ddt AB system, J=16.5, 5.7, 2.4 Hz, ^{1}H of C*H*$_2$–CH–OTES), 2.1 [2H, tt, J=6.9, 2.4 Hz, C*H*$_2$–$(CH_2)_3$–CH_3], 1.5–1.4 [2H, m, C*H*$_2$–$(CH_2)_2$–CH_3], 1.4–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.0–0.8 (21H, m, C*H*$_3$–CH_2–Si, CH_3), 0.7–0.5 (12H, m, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 81.6 (≡C), 77.0 (≡C), 72.5 (CH–OTES), 66.4 (CH_2–OTES), 31.1 (*C*H$_2$–CH_2–CH_3), 28.7 [*C*H$_2$–$(CH_2)_2$–CH_3], 24.6 (*C*H$_2$–CH–OTES), 22.2 (*C*H$_2$–CH_3), 18.7 [*C*H$_2$–$(CH_2)_3$–CH_3], 13.8 (CH_3), 6.7 (3C, *C*H$_3$–CH_2–Si), 6.6 (3C, *C*H$_3$–CH_2–Si), 4.9 (3C, CH_2–Si), 4.3 (3C, CH_2–Si). IR (film): 2955, 2935, 2912, 2875, 1459, 1415, 1239, 1123, 1081, 1005, 815, 743, 672 cm^{-1}.

1.1.5. (*R*)-2-[(Triethylsilyl)oxy]-4-decynal (4). To a −70°C solution of oxalyl chloride (0.19 ml, 2.2 mmol) in CH_2Cl_2 (2 ml) was added dropwise DMSO (0.31 ml, 4.4 mmol). After 15 min stirring the di-TES ether **5** (0.20 g, 0.5 mmol) in CH_2Cl_2 (2 ml) was added. The stirring was continued at −70°C for 20 min followed by 20 min at −40°C. The reaction was quenched at −70°C by the addition of Et_3N (1.05 ml, 7.5 mmol). The mixture was allowed to reach room temperature, diluted with CH_2Cl_2 and washed with ice-cold H_2O and brine. After drying and concentrating the crude was purified by flash chromatography affording aldehyde **4** (96 mg, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.6 (1H, d, J=1.8 Hz, CHO), 4.0 (1H, m, CH–OTES), 2.6–2.4 (2H, m, C*H*$_2$–CH–OTES), 2.2–2.0 [2H, m, C*H*$_2$–$(CH_2)_3$–CH_3], 1.5–1.4 [2H, m, C*H*$_2$–$(CH_2)_2$–CH_3], 1.4–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.0–0.8 (12H, m, CH_3, C*H*$_3$–CH_2–Si), 0.6 (6H, m, C*H*$_2$–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 202.2 (CHO), 83.0 (≡C), 76.0 (CH–OTES), 74.4 (≡C), 30.9 (*C*H$_2$–CH_2–CH_3), 28.3 [*C*H$_2$–$(CH_2)_2$–CH_3], 23.4 (*C*H$_2$–CH–OTES), 22.0 (*C*H$_2$–CH_3), 18.5 [*C*H$_2$–$(CH_2)_3$–CH_3], 13.7 (CH_3), 6.4 (3C, *C*H$_3$–CH_2–Si), 4.6 (3C, CH_2–Si). IR (film): 2955, 2933, 2875, 1741, 1459, 1239, 1122, 1077, 1007, 744, 730 cm^{-1}.

1.1.6. (*R*)-4-[(Triethylsilyl)oxy]-2(*E*)-dodecen-6-ynal (20). To the aldehyde **4** (96 mg, 0.34 mmol) in benzene (5 ml) was added (triphenylphosphoranylidene)acetaldehyde (**8**) (0.30 g, 1.0 mmol). The reaction mixture was brought to 60°C and stirred for 2 h. The solvent was evaporated under vacuo and the crude product was purified by flash chromatography [SiO_2, hexane/EtOAc (98:2) (1% Et_3N)] affording **20** (91 mg, 87%). $[\alpha]_D^{25}$=−45.3 (c=1.03, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.6 (1H, d, J=7.8 Hz, CHO), 6.9 (1H, dd, J=15.3, 4.2 Hz, =C*H*–CH–OTES), 6.3 (1H, ddd, J=15.3, 7.8, 1.5 Hz, =C*H*–CHO), 4.5 (1H, dddd, J=8.4, 5.7, 4.2, 1.5 Hz, CH–OTES), 2.6–2.5 (1H, ddt AB system, J=16.5, 5.7, 2.4 Hz, ^{1}H of C*H*$_2$–CH–OTES), 2.4–2.3 (1H, ddt AB system, J=16.5, 8.4, 2.4 Hz, ^{1}H of C*H*$_2$–CH–OTES), 2.1 [2H, tt, J=7.2, 2.4 Hz, C*H*$_2$–$(CH_2)_3$–CH_3], 1.5–1.4 [2H, m, C*H*$_2$–$(CH_2)_2$–CH_3], 1.4–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.0–0.8 (12H, m, CH_3, C*H*$_3$–CH_2–Si), 0.6 (6H, m, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.6 (CHO), 158.3 (=*C*H–CH–OTES), 131.2 (=*C*H–CHO), 83.4 (≡C), 75.1 (≡C), 70.8 (CH–OTES), 31.0 (*C*H$_2$–CH_2–CH_3), 28.4 [*C*H$_2$–$(CH_2)_2$–CH_3], 28.0 (*C*H$_2$–CH–OTES), 22.1 (*C*H$_2$–CH_3), 18.6 [*C*H$_2$–$(CH_2)_3$–CH_3], 13.8 (CH_3), 6.6 (3C, *C*H$_3$–CH_2–Si), 4.6 (3C, CH_2–Si). IR (film): 2956, 2934, 2915, 2876, 2808, 2719, 1696, 1459, 1107, 1006, 975, 744, 729 cm^{-1}.

1.1.7. (*R*)-12-[(Triethylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*)-eicosatrien-14-ynoic acid methyl ester (23). To a suspension of the phosphonium iodide salt **22** (0.20 g, 0.40 mmol) in THF (1.5 ml) at −78°C was added dropwise a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (0.84 ml, 0.42 mmol). The mixture was stirred for 30 min and aldehyde **20** (72.0 mg, 0.23 mmol) in THF (1.5 ml) followed by HMPA (0.25 ml) were added. After 30 min stirring at −78°C the mixture was brought to 0°C and added to a saturated solution of NH_4Cl layered with hexane/EtOAc (9:1). The phases were separated and the organic layer was washed with brine. After drying over Na_2SO_4 and concentrating under vacuo the crude was purified by flash chromatography affording **23** (88 mg, 86%). $[\alpha]_D^{25}$=−19.2 (c=0.83, acetone). ^{1}H NMR (d_6-benzene, 300 MHz): δ 6.9 (1H, ddt, J=15.2, 11.1, 1.2 Hz, C*H*=CH–CH–OTES), 6.2–6.1 (1H, br. t, J=11.1 Hz, =C*H*–CH=CH–CH–OTES), 6.0 (1H, dd, J=15.2, 6.0 Hz, =C*H*–CH–OTES), 5.6–5.3 [3H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO], 4.5 (1H, m, CH–OTES), 3.4 (3H, s, CH_3O), 3.0 [2H, br. t, J=7.4 Hz, CH_2–CH=CH–$(CH_2)_3$–COO], 2.7–2.6 (1H,

ddt AB system, J=16.2, 6.0, 2.4 Hz, ^{1}H of CH_2–CH–OTES), 2.6–2.5 (1H, ddt AB system, J=16.2, 7.0, 2.4 Hz, ^{1}H of CH_2–CH–OTES), 2.2 [4H, m, CH_2–$(CH_2)_3$–CH_3, CH_2–COO], 2.0 [2H, m, CH_2–$(CH_2)_2$–COO], 1.8–1.6 (2H, quint, J=7.2 Hz, CH_2–CH_2–COO), 1.6–1.5 [2H, m, CH_2–(CH_2)–COO], 1.5–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.1 (9H, t, J=8.0 Hz, CH_3–CH_2–Si), 0.9 (3H, t, J=7.9 Hz, CH_3), 0.7 (6H, q, J=7.9 Hz, CH_2–Si). ^{13}C NMR (d_6-benzene, 75.5 MHz): δ 173.2 (COO), 136.5 (=*C*H–CH–OTES), 130.1 (=CH), 129.6 [=*C*H–$(CH_2)_3$–COO], 128.7 (=CH), 128.6 (=*C*H–CH=CH–CH–OTES), 125.3 (*C*H=CH–CH–OTES), 82.3 (≡C), 77.1 (≡C), 72.6 (CH–OTES), 50.7 (CH_3–O), 33.2 (*C*H_2–COO), 31.2 (*C*H_2–CH_2–CH_3), 29.4 (*C*H_2–CH–OTES), 28.9 [*C*H_2–$(CH_2)_2$–CH_3], 26.6 [*C*H_2–$(CH_2)_2$–COO], 26.2 (=CH–*C*H_2–CH=), 24.9 (*C*H_2–CH_2–COO), 22.3 (*C*H_2–CH_3), 19.0 [*C*H_2–$(CH_2)_3$–CH_3], 13.9 (CH_3), 6.9 (3C, *C*H_3–CH_2–Si), 5.2 (3C, CH_2–Si). IR (film): 3011, 2953, 2933, 2875, 1741, 1458, 1435, 1240, 1155, 1107, 1073, 1005, 984, 951, 743, 727 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{46}O_3SiNa$ $(M+Na)^+$: 469.3114, found $(M+Na)^+$: 469.3106.

1.1.8. (*R*)-12-[(Triethylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid methyl ester (25). To a solution of alkyne **23** (88 mg, 0.20 mmol) in hexane (5 ml) under argon were added pyridine (92 μL) and Lindlar catalyst (130 mg). The argon atmosphere was exchanged by hydrogen and the mixture was stirred for 36 h. Filtration of the catalyst, evaporation of the solvent and purification by flash chromatography with hexane/EtOAc (95:5) (1% Et_3N) afforded **25** (75 mg, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.4 (1H, ddt, J=15.0, 11.1, 1.2 Hz, C*H*=CH–CH–OTES), 6.0 (1H, br. t, J=11.1 Hz, =C*H*–CH=CH–CH–OTES), 5.7–5.6 (1H, dd, J=15.0, 6.3 Hz, =C*H*–CH–OTES), 5.5–5.2 [5H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO, C*H*=C*H*–$(CH_2)_4$–CH_3], 4.2 (1H, m, CH–OTES), 3.6 (3H, s, CH_3O), 2.9 (2H, m, =CH–CH_2–CH=), 2.3 (2H, t, J=7.5 Hz, CH_2–COO), 2.3–2.2 (2H, m, CH_2–CH–OTES), 2.1 [2H, m, CH_2–$(CH_2)_2$–COO], 2.0 [2H, m, CH_2–$(CH_2)_3$–CH_3], 1.7 (2H, quint, J=7.5 Hz, CH_2–CH_2–COO), 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 1.0–0.9 (9H, m, CH_3–CH_2–Si), 0.9 (3H, t, J=6.9 Hz, CH_3), 0.6 (6H, m, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.1 (COO), 137.0 (=*C*H–CH–OTES), 132.1 [=*C*H–$(CH_2)_4$–CH_3], 129.5 (*C*H=CH–CH=CH–CH–OTES), 129.3 [=*C*H–$(CH_2)_3$–COO], 128.7 [*C*H=CH–$(CH_2)_3$–COO], 128.4 (=*C*H–CH=CH–CH–OTES), 125.2 [*C*H=CH–$(CH_2)_4$–CH_3], 124.5 (*C*H=CH–CH–OTES), 73.1 (CH–OTES), 51.3 (CH_3–O), 36.5 (*C*H_2–CH–OTES), 33.4 (*C*H_2–COO), 31.5 (*C*H_2–CH_2–CH_3), 29.2 [*C*H_2–$(CH_2)_2$–CH_3], 27.4 [*C*H_2–$(CH_2)_3$–CH_3], 26.5 [*C*H_2–$(CH_2)_2$–COO], 26.0 (=CH–*C*H_2–CH=), 24.8 (*C*H_2–CH_2–COO), 22.5 (*C*H_2–CH_3), 13.9 (CH_3), 6.7 (3C, *C*H_3–CH_2–Si), 5.0 (3C, CH_2–Si). IR (film): 3011, 2953, 2929, 2874, 1741, 1456, 1239, 1071, 1005, 743, 727 cm^{-1}. Anal. Calcd for $C_{27}H_{48}O_3Si$: C, 72.26; H, 10.78. Found: C, 72.69; H, 10.90.

1.1.9. 12(*R*)-HETE methyl ester (27). To compound **25** (75 mg, 0.17 mmol) in MeOH (10 ml) was added pyridinium *p*-toluenesulfonate (15 mg). The mixture was stirred for 1.5 h at room temperature and then quenched by the addition of Et_3N. The solvent was evaporated under vacuo and crude **27** was purified by flash chromatography with hexane/EtOAc (9:1) affording 12(*R*)-HETE methyl ester (47 mg, 84%). $[\alpha]_D^{25}$=−12 (c=0.9, acetone). {Ref.[12d] $[\alpha]_D^{20}$=−11.4 (c=1.0, acetone)}. UV (CH_3CN) λ_{max} 237 nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6–6.5 (1H, ddt, J=15.3, 11.1, 1.2 Hz, C*H*=CH–CH–OH), 6.0 (1H, br. t, J=11.1 Hz, =C*H*–CH=CH–CH–OH), 5.7 (1H, dd, J=15.3, 6.0 Hz, =C*H*–CH–OH), 5.6–5.5 [1H, m, =C*H*–$(CH_2)_4$–CH_3], 5.4–5.3 [4H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO, C*H*=CH–$(CH_2)_4$–CH_3], 4.2 (1H, m, C*H*–OH), 3.6 (3H, s, CH_3O), 2.9 (2H, m, =CH–CH_2–CH=), 2.4–2.2 (4H, t and m, J=7.5 Hz, CH_2–COO, CH_2–CH–OH), 2.2–2.0 [4H, m, CH_2–$(CH_2)_2$–COO, CH_2–$(CH_2)_3$–CH_3], 2.0–1.9 (1H, br. s, OH), 1.8–1.6 (2H, m, CH_2–CH_2–COO), 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 0.9 (3H, t, J=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.2 (COO), 136.0 (=*C*H–CH–OH), 133.7 [=*C*H–$(CH_2)_4$–CH_3], 130.3, 129.4, 128.5 [=*C*H–CH_2–*C*H=*C*H–$(CH_2)_3$–COO], 128.1 (=*C*H–CH=CH–CH–OH), 125.5 (*C*H=CH–CH–OH), 124.4 [*C*H=CH–$(CH_2)_4$–CH_3], 72.1 (*C*H–OH), 51.4 (CH_3–O), 35.4 (*C*H_2–CH–OH), 33.4 (*C*H_2–COO), 31.5 (*C*H_2–CH_2–CH_3), 29.2 [*C*H_2–$(CH_2)_2$–CH_3], 27.4 [*C*H_2–$(CH_2)_3$–CH_3], 26.6 [*C*H_2–$(CH_2)_2$–COO], 26.1 (=CH–*C*H_2–CH=), 24.7 (*C*H_2–CH_2–COO), 22.5 (*C*H_2–CH_3), 13.9 (CH_3).

1.1.10. 12(*R*)-HETE (1). To a solution of **27** (47 mg, 0.14 mmol) in THF (10 ml) at 0°C under an argon atmosphere was added 1N LiOH (2.8 ml, 2.8 mmol). MeOH (1.2 ml) was added to achieve a homogeneous solution. The mixture was stirred for 2.5 h and quenched by the addition of solid carbon dioxide. The mixture was concentrated under vacuo, diluted with EtOAc and layered with phosphate buffer pH 5.6. The phases were separated, the aqueous layer was re-extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated under vacuo affording 12(*R*)-HETE (**1**) (38 mg, 85%). $[\alpha]_D^{25}$=−11.7 (c=0.77, acetone). UV (CH_3CN) λ_{max} 237 nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6 (1H, ddt, J=15.3, 11.1, 1.2 Hz, C*H*=CH–CH–OH), 6.0 (1H, br. t, J=11.1 Hz, =C*H*–CH=CH–CH–OH), 5.7 (1H, dd, J=15.3, 6.3 Hz, =C*H*–CH–OH), 5.6–5.5 [1H, dtt, J=11.1, 7.2, 1.5 Hz, =C*H*–$(CH_2)_4$–CH_3], 5.5–5.3 [4H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO, C*H*=CH–$(CH_2)_4$–CH_3], 4.3–4.2 (1H, m, C*H*–OH), 3.0–2.8 (2H, m, =CH–CH_2–CH=), 2.4–2.3 (4H, m, CH_2–COO, CH_2–CH–OH), 2.1 [2H, m, CH_2–$(CH_2)_2$–COO], 2.1–2.0 [2H, m, CH_2–$(CH_2)_3$–CH_3], 1.7 (2H, m, CH_2–CH_2–COO), 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 0.9–0.8 (3H, t, J=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 178.1 (COO), 135.4 (=*C*H–CH–OH), 133.7 [=*C*H–$(CH_2)_4$–CH_3], 130.3, 129.4, 128.4 [=*C*H–CH_2–*C*H=*C*H–$(CH_2)_3$–COO], 127.8 (=*C*H–CH=CH–CH–OH), 125.6 (*C*H=CH–CH–OH), 124.3 [*C*H=CH–$(CH_2)_4$–CH_3], 72.1 (*C*H–OH), 35.3 (*C*H_2–CH–OH), 33.1 (*C*H_2–COO), 31.4 (*C*H_2–CH_2–CH_3), 29.2 [*C*H_2–$(CH_2)_2$–CH_3], 27.4 [*C*H_2–$(CH_2)_3$–CH_3], 26.4 [*C*H_2–$(CH_2)_2$–COO], 26.1 (=CH–*C*H_2–CH=), 24.5 (*C*H_2–CH_2–COO), 22.4 (*C*H_2–CH_3), 13.9 (CH_3). HPLC/API-ES/MS (m/z): 319 $[M_{12(R)\text{-HETE}}-H^+]^-$.

1.1.11. (*S*)-(Triethylsilyl)glycidyl ether (13). Compound **12** (6.0 g, 31.9 mol) was dissolved in Et_2O (5 ml) and (*R*,*R*)-(salen)Co(III)(AcO) (**15**) (0.10 g, 0.15 mmol) was added. The mixture was cooled to 0°C and H_2O (0.32 ml,

17.5 mmol) was added dropwise. The reaction was allowed to reach room temperature and then stirred for 20 h. The Et_2O was evaporated and the residue was purified by bulb to bulb distillation 50–55°C/0.6 mm affording **13** (2.7 g, 45% yield). $[\alpha]_D^{25}=-2.2$ (c=1.52, $CHCl_3$) {Ref.[13a] $[\alpha]_D^{20}=-2.20$ (c=0.64, $CHCl_3$)}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.8 (1H, ddd, J=11.8, 3.3, 0.4 Hz, ^1H of CH_2–OTES), 3.6 (1H, dd, J=11.8, 5.0 Hz, ^1H of CH_2–OTES), 3.1–3.0 (1H, m, CH–O), 2.8–2.7 (1H, ddd, J=5.1, 4.0, 0.4 Hz, ^1H of CH_2–O–CH), 2.6 (1H, dd, J=5.1, 2.8 Hz, ^1H of CH_2–O–CH), 0.9 (9H, t, J=7.8 Hz, CH_3–CH_2–Si), 0.6 (6H, q, J=7.8 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 63.6 (CH_2–OTES), 52.3 (CH–O), 44.4 (CH_2–O–CH), 6.4 (3C, CH_3–CH_2–Si), 4.2 (3C, CH_2–Si).

1.1.12. (*S*)-1-[(Triethylsilyl)oxy]-4-decyn-2-ol (17). The TES protected glycidol **13** (2.0 g, 10.6 mmol) was transformed in **17** following the same procedure as for the preparation of compound **16**. Crude **17** (2.9 g) was obtained and used for the next step without further purification. A small sample was purified by flash chromatography for analytical purpose. $[\alpha]_D^{25}=9.2$ (c=1.75, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.8–3.6 (2H, m, CH–OH, ^1H of CH_2–OTES), 3.6–3.5 (1H, m, ^1H of CH_2–OTES), 2.5 (1H, br. s, OH), 2.5–2.3 (2H, m, CH_2–CH–OH), 2.2–2.1 [2H, tt, J=7.0, 2.4 Hz, CH_2–$(CH_2)_3$–CH_3], 1.5–1.4 [2H, m, CH_2–$(CH_2)_2$–CH_3], 1.4–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.0–0.9 (9H, t, J=8.0 Hz, CH_3–CH_2–Si), 0.9–0.8 (3H, t, J=7.2 Hz, CH_3), 0.6 (6H, q, J=8.0 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 82.6 (≡C), 75.6 (≡C), 70.5 (CH–OH), 65.4 (CH_2–OTES), 31.0 (CH_2–CH_2–CH_3), 28.6 [CH_2–$(CH_2)_2$–CH_3], 23.3 (CH_2–CH–OH), 22.1 (CH_2–CH_3), 18.6 [CH_2–$(CH_2)_3$–CH_3], 13.8 (CH_3), 6.5 (3C, CH_3–CH_2–Si), 4.2 (3C, CH_2–Si). Enantiomeric excess was determined to be >99% by chiral HPLC of the dibenzoate derivative obtained from compound **17** after cleavage of the TES ether [Column: OF-chiracel, mobile phase: hexane/*i*-PrOH (90:10), λ=265 nm].

1.1.13. (*S*)-1,2-Bis[(triethylsilyl)oxy]-4-decyne (18). Following the same procedure that for the preparation of **5**, **17** (2.7 g, 9.5 mmol) was transformed in **18**. After drying and concentrating under vacuo the product was purified by flash chromatography with hexane/EtOAc (98:2) (0.5% Et_3N) affording **18** (2.8 g, 66% two-steps). $[\alpha]_D^{25}=-1.9$ (c=1.19, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.8 (1H, m, CH–OTES), 3.7–3.5 (2H, 2 dd AB system, J=9.9, 5.7 Hz, CH_2–OTES), 2.5–2.4 (1H, ddt AB system, J=16.5, 6.0, 2.4 Hz, ^1H of CH_2–CH–OTES), 2.3–2.2 (1H, ddt AB system, J=16.5, 5.7, 2.4 Hz, ^1H of CH_2–CH–OTES), 2.1 [2H, tt, J=6.9, 2.4 Hz, CH_2–$(CH_2)_3$–CH_3], 1.5–1.4 [2H, m, CH_2–$(CH_2)_2$–CH_3], 1.4–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.0–0.8 (21H, m, CH_3–CH_2–Si, CH_3), 0.7–0.5 (12H, m, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 81.6 (≡C), 77.0 (≡C), 72.5 (CH–OTES), 66.3 (CH_2–OTES), 31.1 (CH_2–CH_2–CH_3), 28.7 [CH_2–$(CH_2)_2$–CH_3], 24.6 (CH_2–CH–OTES), 22.2 (CH_2–CH_3), 18.8 [CH_2–$(CH_2)_3$–CH_3], 13.9 (CH_3), 6.7 (6C, CH_3–CH_2–Si), 4.9 (3C, CH_2–Si), 4.3 (3C, CH_2–Si). IR (film): 2955, 2935, 2912, 2876, 1459, 1415, 1239, 1123, 1081, 1005, 815, 743, 673 cm^{-1}. Anal. Calcd for $C_{22}H_{46}O_2Si_2$: C, 66.26; H, 11.63. Found: C, 66.53; H, 11.58.

1.1.14. (*S*)-2-[(Triethylsilyl)oxy]-4-decynal (19). Following the same procedure as described for the preparation of **4**, the di-TES **18** (0.30 g, 0.75 mmol) in CH_2Cl_2 (4 ml) was converted to **19**. Crude **19** was used without further purification for the next step.

1.1.15. (*S*)-4-[(Triethylsilyl)oxy]-2(*E*)-dodecen-6-ynal (21). To the crude aldehyde **19**, obtained in the previous reaction, in benzene (10 ml) was added (triphenylphosphoranylidene)acetaldehyde (**8**) (0.45 g, 1.5 mmol). The reaction mixture was brought to 60°C and stirred for 2 h. The solvent was evaporated under vacuo and the crude product was purified by flash chromatography [hexane/EtOAc (98:2) (1% Et_3N)] affording **21** (0.14 g, 61%). ^1H NMR ($CDCl_3$, 300 MHz): δ 9.6 (1H, d, J=7.8 Hz, CHO), 6.9 (1H, dd, J=15.3, 4.2 Hz, =CH–CH–OTES), 6.3 (1H, ddd, J=15.3, 7.8, 1.5 Hz, =CH–CHO), 4.5 (1H, dddd, J=8.4, 5.7, 4.2, 1.5 Hz, CH–OTES), 2.6–2.5 (1H, ddt AB system, J=16.5, 5.7, 2.4 Hz, ^1H of CH_2–CH–OTES), 2.4–2.3 (1H, ddt AB system, J=16.5, 8.4, 2.4 Hz, ^1H of CH_2–CH–OTES), 2.1 [2H, tt, J=7.2, 2.4 Hz, CH_2–$(CH_2)_3$–CH_3], 1.5–1.4 [2H, m, CH_2–$(CH_2)_2$–CH_3], 1.4–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.0–0.8 (12H, m, CH_3, CH_3–CH_2–Si), 0.6 (6H, m, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.3 (CHO), 158.0 (=C–CH–OTES), 131.2 (=C–CHO), 83.5 (≡C), 75.2 (≡C), 70.9 (CH–OTES), 31.0 (CH_2–CH_2–CH_3), 28.5 [CH_2–$(CH_2)_2$–CH_3], 28.1 (CH_2–CH–OTES), 22.1 (CH_2–CH_3), 18.7 [CH_2–$(CH_2)_3$–CH_3], 13.8 (CH_3), 6.6 (3C, CH_3–CH_2–Si), 4.8 (3C, CH_2–Si). IR (film): 2956, 2934, 2914, 2876, 2808, 2719, 1696, 1459, 1239, 1107, 1007, 975, 745, 730 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_2Si_2{\cdot}0.^2H_2O$: C, 69.26; H, 10.46. Found: C, 68.83; H, 9.96.

1.1.16. (*S*)-12-[(Triethylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*)-eicosatrien-14-ynoic acid methyl ester (24). Wittig reaction of aldehyde **21** (0.10 g, 0.32 mmol) with the phosphorane **9**, obtained in situ from the phosphonium iodide salt **22** (0.30 g, 0.56 mmol), under the same conditions as described for the preparation of compound **23**, afforded **24** (0.13 g, 87%) after flash chromatography purification. $[\alpha]_D^{25}=21.3$ (c=1, acetone). ^1H NMR (d_6-benzene, 300 MHz): δ 6.9 (1H, ddt, J=15.2, 11.1, 1.2 Hz, CH=CH–CH–OTES), 6.2–6.1 (1H, br. t, J=11.1 Hz, =CH–CH=CH–CH–OTES), 6.0 (1H, dd, J=15.2, 6.0 Hz, =CH–CH–OTES), 5.6–5.3 [3H, m, =CH–CH_2–CH=CH–$(CH_2)_3$–COO], 4.5 (1H, m, CH–OTES), 3.4 (3H, s, CH_3O), 3.0 [2H, br. t, J=7.4 Hz, CH_2–CH=CH–$(CH_2)_3$–COO], 2.7–2.6 (1H, ddt AB system, J=16.2, 6.0, 2.4 Hz, ^1H of CH_2–CH–OTES), 2.6–2.5 (1H, ddt AB system, J=16.2, 7.0, 2.4 Hz, ^1H of CH_2–CH–OTES), 2.2 [4H, m, CH_2–$(CH_2)_3$–CH_3, CH_2–COO], 2.0 [2H, m, CH_2–$(CH_2)_2$–COO], 1.8–1.6 (2H, quint, J=7.2 Hz, CH_2–CH_2–COO), 1.6–1.5 [2H, m, CH_2–(CH_2)–COO], 1.5–1.2 [4H, m, $(CH_2)_2$–CH_3], 1.1 (9H, t, J=8.0 Hz, CH_3–CH_2–Si), 0.9 (3H, t, J=7.9 Hz, CH_3), 0.7 (6H, q, J=7.9 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.1 (COO), 135.9 (=CH–CH–OTES), 129.8 (=CH), 129.3 [=CH–$(CH_2)_3$–COO], 128.6 (=CH), 128.2 (=CH–CH=CH–CH–OTES), 124.8 (CH=CH–CH–OTES), 82.2 (≡C), 76.6 (≡C), 72.1 (CH–OTES), 51.3 (CH_3–O), 33.3 (CH_2–COO), 31.0 (CH_2–CH_2–CH_3), 28.9 (CH_2–CH–OTES), 28.6 [CH_2–$(CH_2)_2$–CH_3], 26.4 [CH_2–$(CH_2)_2$–COO], 25.9 (=CH–CH_2–CH=), 24.7 (CH_2–CH_2–COO), 22.1 (CH_2–CH_3), 18.7 [CH_2–$(CH_2)_3$–CH_3], 13.8 (CH_3), 6.7

(3C, CH_3–CH_2–Si), 4.8 (3C, CH_2–Si). IR (film): 3011, 2953, 2933, 2875, 1741, 1457, 1435, 1239, 1155, 1107, 1072, 1005, 984, 951, 743, 727 cm^{-1}. Anal. Calcd for $C_{27}H_{46}O_3Si$: C, 72.59; H, 10.38. Found: C, 72.30; H, 10.76.

1.1.17. (*S*)-12-[(Triethylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid methyl ester (26). The alkyne **24** (67.0 mg, 0.15 mmol) was dissolved in hexane (4 ml) under argon and pyridine (70 μL) followed by Lindlar catalyst (100 mg) were added. The argon atmosphere was exchanged by hydrogen and the mixture was stirred for 36 h. Filtration of the catalyst, evaporation of the solvent and purification by flash chromatography with hexane/EtOAc (95:5) (1% Et_3N) afforded **26** (61 mg, 90%). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.4 (1H, ddt, *J*=15.3, 11.1, 1.2 Hz, C*H*=CH–CH–OTES), 6.0 (1H, br. t, *J*=11.1 Hz, =C*H*–CH=CH–CH–OTES), 5.7–5.6 (1H, dd, *J*=15.3, 6.3 Hz, =C*H*–CH–OTES), 5.5–5.2 [5H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO, C*H*=C*H*–$(CH_2)_4$–CH_3], 4.2 (1H, m, CH–OTES), 3.6 (3H, s, CH_3O), 2.9 (2H, m, =CH–CH_2–CH=), 2.3 (2H, t, *J*=7.5 Hz, CH_2–COO), 2.3–2.2 (2H, m, CH_2–CH–OTES), 2.1 [2H, m, CH_2–$(CH_2)_2$–COO], 2.0 [2H, m, CH_2–$(CH_2)_3$–CH_3], 1.7 (2H, quint, *J*=7.5 Hz, CH_2–CH_2–COO), 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 1.0–0.9 (9H, m, CH_3–CH_2–Si), 0.9 (3H, t, *J*=6.8 Hz, CH_3), 0.6 (6H, m, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.1 (COO), 137.0 (=*C*H–CH–OTES), 132.1 [=*C*H–$(CH_2)_4$–CH_3], 129.5 (*C*H=CH–CH=CH–CH–OTES), 129.3 [=*C*H–$(CH_2)_3$–COO], 128.7 [*C*H=CH–$(CH_2)_3$–COO], 128.3 (=*C*H–CH=CH–CH–OTES), 125.2 [*C*H=CH–$(CH_2)_4$–CH_3], 124.4 (*C*H=CH–CH–OTES), 73.0 (*C*H–OTES), 51.4 (CH_3–O), 36.4 (*C*H_2–CH–OTES), 33.4 (*C*H_2–COO), 31.5 (*C*H_2–CH_2–CH_3), 29.2 [*C*H_2–$(CH_2)_2$–CH_3], 27.4 [*C*H_2–$(CH_2)_3$–CH_3], 26.5 [*C*H_2–$(CH_2)_2$–COO], 26.0 (=CH–*C*H_2–CH=), 24.7 (*C*H_2–CH_2–COO), 22.5 (*C*H_2–CH_3), 13.9 (CH_3), 6.8 (3C, *C*H_3–CH_2–Si), 4.9 (3C, CH_2–Si). IR (film): 3011, 2953, 2931, 2875, 1743, 1457, 1239, 1073, 1005, 743, 727 cm^{-1}.

1.1.18. 12(*S*)-HETE methyl ester (28). To compound **26** (66 mg, 0.15 mmol) in MeOH (7 ml) was added pyridinium *p*-toluenesulfonate (10 mg). The mixture was stirred for 1.5 h at room temperature and then quenched by the addition of Et_3N. The solvent was evaporated under vacuo and the crude was purified by flash chromatography with hexane/EtOAc (9:1) affording 12(*S*)-HETE methyl ester (45 mg, 90%). $[\alpha]_D^{25}$=11.4 (*c*=1.1, acetone). {Ref.[10f] $[\alpha]_D^{20}$=13 (*c*=1.5, acetone)}. UV (CH_3CN) λ_{max} 237 nm. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.5 (1H, ddt, *J*=15.0, 11.1, 1.2 Hz, C*H*=CH–CH–OH), 6.0–5.9 (1H, br. t, *J*=11.1 Hz, =C*H*–CH=CH–CH–OH), 5.7 (1H, dd, *J*=15.0, 6.0 Hz, =C*H*–CH–OH), 5.6–5.5 [1H, m, =C*H*–$(CH_2)_4$–CH_3], 5.4–5.3 [4H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO, C*H*=CH–$(CH_2)_4$–CH_3], 4.2 (1H, m, C*H*–OH), 3.6 (3H, s, CH_3O), 2.9 (2H, m, =CH–CH_2–CH=), 2.4–2.2 (4H, t and m, *J*=7.5 Hz, CH_2–COO, CH_2–CH–OH), 2.2–2.0 [4H, m, CH_2–$(CH_2)_2$–COO, CH_2–$(CH_2)_3$–CH_3], 2.0–1.9 (1H, br. s, OH), 1.8–1.6 (2H, m, CH_2–CH_2–COO), 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 0.9 (3H, t, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.1 (COO), 136.0 (=*C*H–CH–OH), 133.6 [=*C*H–$(CH_2)_4$–CH_3], 130.2, 129.4, 128.5 [=*C*H–CH_2–*C*H=*C*H–$(CH_2)_3$–COO], 128.1 (=*C*H–CH=CH–CH–OH), 125.4 (*C*H=CH–CH–OH), 124.4 [*C*H=CH–$(CH_2)_4$–CH_3], 72.0 (CH–OH), 51.3 (CH_3–O), 35.4 (*C*H_2–CH–OH), 33.4 (*C*H_2–COO), 31.4 (*C*H_2–CH_2–CH_3), 29.2 [*C*H_2–$(CH_2)_2$–CH_3], 27.4 [*C*H_2–$(CH_2)_3$–CH_3], 26.6 [*C*H_2–$(CH_2)_2$–COO], 26.1 (=CH–*C*H_2–CH=), 24.7 (*C*H_2–CH_2–COO), 22.4 (*C*H_2–CH_3), 13.8 (CH_3).

1.1.19. 12(*S*)-HETE (2). Compound **28** (15.0 mg, 0.045 mmol) was converted to **2** using the same conditions as for the preparation of **1** affording 12(*S*)-HETE (13 mg, 90%). UV (CH_3CN) λ_{max} 237 nm. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.6 (1H, br. dd, *J*=15.3, 11.0 Hz, C*H*=CH–CH–OH), 6.0 (1H, br. t, *J*=11.0 Hz, =C*H*–CH=CH–CH–OH), 5.7 (1H, dd, *J*=15.3, 6.3 Hz, =C*H*–CH–OH), 5.6–5.5 [1H, dtt, *J*=11.1, 7.2, 1.5 Hz, =C*H*–$(CH_2)_4$–CH_3], 5.5–5.3 [4H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO, C*H*=CH–$(CH_2)_4$–CH_3], 4.3–4.2 (1H, m, C*H*–OH), 3.0–2.8 (2H, m, =CH–CH_2–CH=), 2.4–2.3 (4H, m, CH_2–COO, CH_2–CH–OH), 2.1 [2H, m, CH_2–$(CH_2)_2$–COO], 2.1–2.0 [2H, m, CH_2–$(CH_2)_3$–CH_3], 1.7 (2H, m, CH_2–CH_2–COO), 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 0.9–0.8 (3H, t, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 178.2 (COO), 135.4 (=*C*H–CH–OH), 133.7 [=*C*H–$(CH_2)_4$–CH_3], 130.3, 129.4, 128.4 [=*C*H–CH_2–*C*H=*C*H–$(CH_2)_3$–COO], 127.8 (=*C*H–CH=CH–CH–OH), 125.6 (*C*H=CH–CH–OH), 124.3 [*C*H=CH–$(CH_2)_4$–CH_3], 72.1 (*C*H–OH), 35.3 (*C*H_2–CH–OH), 33.5 (*C*H_2–COO), 31.4 (*C*H_2–CH_2–CH_3), 29.2 [*C*H_2–$(CH_2)_2$–CH_3], 27.4 [*C*H_2–$(CH_2)_3$–CH_3], 26.4 [*C*H_2–$(CH_2)_2$–COO], 26.2 (=CH–*C*H_2–CH=), 24.6 (*C*H_2–CH_2–COO), 22.4 (*C*H_2–CH_3), 13.9 (CH_3). HPLC/API-ES/MS (*m*/*z*): 319 $[M_{12(S)\text{-HETE}} - H^+]^-$.

1.1.20. (*S*)-1,2-Bis[(triethylsilyl)oxy]-4(*Z*)-decene (30). To a solution of alkyne **18** (0.30 g, 0.75 mmol) in hexane (10 ml) under argon was added Lindlar catalyst (50 mg) followed by Et_3N (50 μL). The atmosphere of argon was exchanged by hydrogen and the mixture was vigorously stirred for 1 h. The catalyst was filtered and the solvent evaporated under vacuo. The crude product **30** was used directly in the next step. $[\alpha]_D^{25}$=−2.3 (*c*=1 crude product, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.5–5.3 (2H, m, C*H*=C*H*), 3.7 (1H, m, CH–OTES), 3.6–3.4 (2H, m, CH_2–OTES), 2.4–2.3 (1H, br. dt, *J*=14.4, 5.7 Hz, ^1H of CH_2–CH–OTES), 2.3–2.1 (1H, br. dt, *J*=14.4, 6.0 Hz, ^1H of CH_2–CH–OTES), 2.0 [2H, m, CH_2–$(CH_2)_3$–CH_3], 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 1.0–0.8 (21H, br. t and t, *J*=7.8 Hz, *J*=6.9 Hz, CH_3–CH_2–Si, CH_3), 0.7–0.5 (12H, 2q, *J*=7.8 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 131.9 (=CH), 125.6 (=CH), 73.4 (CH–OTES), 66.8 (CH_2–OTES), 32.3 (*C*H_2–CH–OTES), 31.5 (*C*H_2–CH_2–CH_3), 29.3 [*C*H_2–$(CH_2)_2$–CH_3], 27.3 [CH_2–$(CH_2)_3$–CH_3], 22.5 (*C*H_2–CH_3), 13.9 (CH_3), 6.7 (3C, *C*H_3–CH_2–Si), 6.6 (3C, *C*H_3–CH_2–Si), 4.9 (3C, CH_2–Si), 4.3 (3C, CH_2–Si).

1.1.21. (*S*)-2-[(Triethylsilyl)oxy]-4(*Z*)-decenal (32). The di-TES **30** (0.20 g, 0.50 mmol) was oxidized following the same Swern conditions as described for the preparation of **4**. The crude product **32** was used without further purification for the next step.

1.1.22. (*S*)-4-[(Triethylsilyl)oxy]-2(*E*),6(*Z*)-dodecadienal (34). Wittig reaction of **32**, obtained in the previous

reaction, with **8** afforded aldehyde **34** using the conditions described for the preparation of **20**. The crude was purified by flash chromatography [hexane/EtOAc (98:2) (1% Et_3N)] affording **34** (91 mg, 59% two-steps). $[\alpha]_D^{25}$=21.7 (*c*=0.94, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 9.5 (1H, d, *J*=7.8 Hz, CHO), 6.8 (1H, dd, *J*=15.5, 4.5 Hz, =C*H*–CH–OTES), 6.4–6.2 (1H, ddd, *J*=15.5, 7.8, 1.6 Hz, =C*H*–CHO), 5.5 [1H, m, =C*H*–$(CH_2)_4$–CH_3], 5.3 [1H, m, C*H*=CH–$(CH_2)_4$–CH_3], 4.4 (1H, m, CH–OTES), 2.4–2.2 (2H, m, CH_2–CH–OTES), 2.0 [2H, m, CH_2–$(CH_2)_3$–CH_3], 1.4–1.2 [6H, m, (CH_2)$_3$–CH_3], 1.0–0.9 (9H, t, *J*=7.8 Hz, CH_3–CH_2–Si), 0.9–0.8 (3H, t, *J*=6.9 Hz, CH_3), 0.8 (6H, q, *J*=7.8 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.6 (CHO), 159.5 (=*C*H–CH–OTES), 133.4 [=*C*H–$(CH_2)_4$–CH_3], 130.8 (=*C*H–CHO), 123.6 [*C*H=CH–$(CH_2)_4$–CH_3], 71.5 (CH–OTES), 35.4 (*C*H_2–CH–OTES), 31.4 (*C*H_2–CH_2–CH_3), 29.1 [*C*H_2–$(CH_2)_2$–CH_3], 27.4 [*C*H_2–$(CH_2)_3$–CH_3], 22.4 (*C*H_2–CH_3), 13.9 (CH_3), 6.6 (3C, *C*H_3–CH_2–Si), 4.7 (3C, CH_2–Si). IR (film): 3011, 2956, 2929, 2876, 2858, 2808, 2719, 1695, 1459, 1414, 1239, 1141, 1102, 1006, 955, 743, 729 cm^{-1}. Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.03. Found: C, 68.95; H, 11.63.

1.1.23. (*S*)-12-[(Triethylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid methyl ester (26). Wittig reaction of aldehyde **34** (71.4 mg, 0.23 mmol) with the phosphorane **9**, obtained in situ from the phosphonium iodide salt **22** (0.20 g, 0.40 mmol), under the same conditions as described for the preparation of compound **23**, afforded **26** (85 mg, 82%) after flash chromatography. $[\alpha]_D^{25}$=13.4 (*c*=1.1, acetone).

1.1.24. 4,5-Dideuterio-1,2(*R*)-bis[(triethylsilyl)oxy]-4(*Z*)-decene (29). Following the same conditions used for the transformation of **18** to **30**, alkyne **5** (0.30 g, 0.75 mmol) was reduced with deuterium in the presence of Lindlar catalyst (100 mg) and Et_3N (80 μl). After 30 min the starting material was consumed, the reaction mixture was filtered and the solvent was evaporated affording **29** that was used without further purification in the next step. $[\alpha]_D^{25}$=−2.12 (*c*=2.1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.7 (1H, m, CH–OTES), 3.6–3.4 (2H, 2 dd AB system, *J*=9.9, 5.7 Hz, CH_2–OTES), 2.4–2.3 (1H, dd AB system, *J*=14.4, 5.7 Hz, ^1H of CH_2–CH–OTES), 2.2–2.1 (1H, dd AB system, *J*=14.4, 6.0 Hz, ^1H of CH_2–CH–OTES), 2.0 [2H, br. t, *J*=6.9 Hz, CH_2–$(CH_2)_3$–CH_3], 1.4–1.2 [6H, m, (CH_2)$_3$–CH_3], 1.0–0.9 [21H, br. t, *J*=7.8 Hz, t, *J*=6.9 Hz, (CH_3–CH_2)$_3$–Si, CH_3], 0.7–0.5 (12H, 2q, *J*=7.8 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 131.4 (t, *J*=23 Hz, =CD), 125.2 (t, *J*=23 Hz, =CD), 73.4 (CH–OTES), 66.8 (CH_2–OTES), 32.2 (*C*H_2–CH–OTES), 31.5 (*C*H_2–CH_2–CH_3), 29.3 [*C*H_2–$(CH_2)_2$–CH_3], 27.2 [CH_2–$(CH_2)_3$–CH_3], 22.5 (*C*H_2–CH_3), 13.9 (CH_3), 6.7 (3C, *C*H_3–CH_2–Si), 6.6 (3C, *C*H_3–CH_2–Si), 4.9 (3C, CH_2–Si), 4.3 (3C, CH_2–Si). IR (film): 2955, 2934, 2913, 2876, 2248, 1630, 1459, 1415, 1239, 1121, 1087, 1005, 811, 742, 728 cm^{-1}. Anal. Calcd for $C_{22}H_{46}D_2O_2Si_2$: C, 65.60; H, 12.51. Found: C, 64.83; H, 12.18.

1.1.25. 4,5-Dideuterio-2(*R*)-[(triethylsilyl)oxy]-4(*Z*)-decenal (31). The di-TES **29** (0.20 g, 0.50 mmol) was oxidized following the same Swern conditions as described for the preparation of **4**. The crude product **31** was used without further purification in the next step. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.6 (1H, d, *J*=1.8 Hz, CHO), 3.9 (1H, td, *J*=6.3, 1.8 Hz, CH–OTES), 2.4–2.3 (2H, d, *J*=6.3 Hz, CH_2–CH–OTES), 2.0–1.9 [2H, t, *J*=7.4 Hz, CH_2–$(CH_2)_3$–CH_3], 1.4–1.2 [6H, m, (CH_2)$_3$–CH_3], 1.0–0.8 (12H, m, CH_3, CH_3–CH_2–Si), 0.6–0.4 (6H, m, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 203.6 (CHO), 132.9 (t, *J*=23 Hz, =CD), 122.6 (t, *J*=23 Hz, =CD), 77.4 (CH–OTES), 31.4 (*C*H_2–CH_2–CH_3), 30.9 (*C*H_2–CH–OTES), 29.0 [*C*H_2–$(CH_2)_2$–CH_3], 27.1 [*C*H_2–$(CH_2)_3$–CH_3], 22.4 (*C*H_2–CH_3), 13.8 (CH_3), 6.4 (3C, *C*H_3–CH_2–Si), 4.8 (3C, CH_2–Si).

1.1.26. 6,7-Dideuterio-4(*R*)-[(triethylsilyl)oxy]-2(*E*),6(*Z*)-dodecadienal (33). Wittig reaction of **31**, obtained in the previous reaction, with **8** afforded aldehyde **33** using the conditions described for the preparation of **20**. The crude was purified by flash chromatography [SiO_2, hexane/EtOAc (98:2) (1% Et_3N)] affording **33** (90 mg, 59% two-steps). ^1H NMR ($CDCl_3$, 300 MHz): δ 9.6 (1H, d, *J*=7.8 Hz, CHO), 6.8 (1H, dd, *J*=15.6, 4.5 Hz, =C*H*–CH–OTES), 6.3 (1H, ddd, *J*=15.6, 7.8, 1.5 Hz, =C*H*–CHO), 4.4 (1H, dddd, *J*=6.9, 6.0, 4.5, 1.5 Hz, CH–OTES), 2.4 (2H, m, CH_2–CH–OTES), 2.0 [2H, m, CH_2–$(CH_2)_3$–CH_3], 1.4–1.2 [6H, m, (CH_2)$_3$–CH_3], 1.0–0.9 (9H, t, *J*=7.9 Hz, CH_3–CH_2–Si), 0.9–0.8 (3H, t, *J*=6.8 Hz, CH_3), 0.6 (6H, q, *J*=7.9 Hz, CH_2–Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.5 (CHO), 159.3 (=*C*H–CH–OTES), 133.0 [t, *J*=23 Hz, =*C*D–$(CH_2)_4$–CH_3], 131.0 (=*C*H–CHO), 123.2 [t, *J*=23 Hz, *C*D=CD–$(CH_2)_4$–CH_3], 71.7 (CH–OTES), 35.4 (*C*H_2–CH–OTES), 31.5 (*C*H_2–CH_2–CH_3), 29.1 [*C*H_2–$(CH_2)_2$–CH_3], 27.3 [*C*H_2–$(CH_2)_3$–CH_3], 22.4 (*C*H_2–CH_3), 13.8 (CH_3), 6.6 (3C, *C*H_3–CH_2–Si), 4.8 (3C, CH_2–Si). IR (film): 2956, 2928, 2876, 2856, 2807, 2718, 2249, 1695, 1459, 1239, 1139, 1104, 1005, 976, 744, 729 cm^{-1}. Anal. Calcd for $C_{18}H_{32}D_2O_2Si$: C, 69.17; H, 11.61. Found: C, 69.11; H, 11.59.

1.1.27. 14,15-Dideuterio-12(*R*)-[(triethylsilyl)oxy]-5(*Z*),8(*Z*),10(*E*),14(*Z*)-eicosatetraenoic acid methyl ester (35). Wittig reaction of aldehyde **33** (0.10 g, 0.32 mmol) with the phosphorane **9**, obtained in situ from the phosphonium iodide salt **22** (0.27 g, 0.5 mmol), under the same conditions as described for the preparation of compound **23**, afforded **35** (0.11 g, 84%) after flash chromatography purification. ^1H NMR (d_6-benzene, 300 MHz): δ 6.8 (1H, br. dd, *J*=15.3, 11.1 Hz, C*H*=CH–CH–OTES), 6.1 (1H, br. t, *J*=11.1 Hz, =C*H*–CH=CH–CH–OTES), 5.8 (1H, dd, *J*=15.3, 6.3 Hz, =C*H*–CH–OTES), 5.5–5.2 [3H, m, =C*H*–CH_2–C*H*=C*H*–$(CH_2)_3$–COO], 4.4–4.3 (1H, m, C*H*–OTES), 3.4 (3H, s, CH_3O), 3.0–2.9 (2H, m, =CH–CH_2–CH=), 2.6–2.4 (2H, 2 dd AB system, *J*=14.1, 6.6 Hz, CH_2–CH–OTES), 2.2–2.1 (2H, t, *J*=7.5 Hz, CH_2–COO), 2.1 [2H, m, CH_2–$(CH_2)_3$–CH_3], 2.1–1.9 [2H, m, CH_2–$(CH_2)_2$–COO], 1.7–1.6 (2H, m, CH_2–CH_2–COO), 1.5–1.2 [6H, m, (CH_2)$_3$–CH_3], 1.2–1.0 (9H, t, *J*=7.8 Hz, CH_3–CH_2–Si), 0.9 (3H, t, *J*=6.8 Hz, CH_3), 0.8–0.6 (6H, q, *J*=7.8 Hz, CH_2–Si). ^{13}C NMR (d_6-benzene, 75.5 MHz): δ 173.1 (COO), 137.5 (=*C*H–CH–OTES), 129.8, 129.6, 128.7 [=*C*H–CH_2–*C*H=*C*H–$(CH_2)_3$–COO], 127.9 (=*C*H–CH=CH–CH–OTES), 124.9 (*C*H=CH–CH–OTES), 73.5 (*C*H–OTES), 50.7 (CH_3–O), 36.8 (*C*H_2–CH–OTES), 33.3 (*C*H_2–COO), 31.7 (*C*H_2–CH_2–CH_3), 29.5 [*C*H_2–

(CH_2)$_2$–CH_3], 27.6 [*C*H_2–(CH_2)$_3$–CH_3], 26.7 [*C*H_2–(CH_2)$_2$–COO], 26.3 (=CH–*C*H_2–CH=), 24.9 (*C*H_2–CH_2–COO), 22.7 (*C*H_2–CH_3), 14.0 (CH_3), 6.9 (3C, *C*H_3–CH_2–Si), 5.4 (3C, CH_2–Si). The ^{13}C signals corresponding to the carbons *C*D=*C*D were not observed due to their low intensity. IR (film): 3011, 2953, 2929, 2875, 2247, 1742, 1456, 1435, 1239, 1071, 1005, 983, 950, 742, 726 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{46}D_2O_3SiNa$ $(M+Na)^+$: 473.3396, found $(M+Na)^+$: 473.3408.

1.1.28. 14,15-Dideuterio-12(*R*)-HETE methyl ester (36). To compound **35** (50 mg, 0.11 mmol) in MeOH (5 ml) was added pyridinium *p*-toluenesulfonate (10 mg). The mixture was stirred for 1.5 h at room temperature and then quenched by the addition of Et_3N. The solvent was evaporated under vacuo and the crude was purified by flash chromatography with hexane/EtOAc (9:1) affording **36** (34 mg, 92%). UV (CH_3CN) λ_{max} 237 nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.5 (1H, ddt, *J*=15.3, 11.1, 1.2 Hz, C*H*=CH–CH–OH), 6.0 (1H, br. t, *J*=11.1 Hz, =C*H*–CH=CH–CH–OH), 5.7 (1H, dd, *J*=15.3, 6.3 Hz, =C*H*–CH–OH), 5.4–5.3 [3H, m, =C*H*–CH_2–C*H*=C*H*–(CH_2)$_3$–COO], 4.2 (1H, m, C*H*–OH), 3.6 (3H, s, CH_3O), 2.9 (2H, m, =CH–C*H*$_2$–CH=), 2.4–2.2 (4H, m, CH_2–COO, C*H*$_2$–CH–OH), 2.2–2.0 [4H, m, C*H*$_2$–(CH_2)$_2$–COO, C*H*$_2$–(CH_2)$_3$–CH_3], 1.8–1.6 (2H, m, C*H*$_2$–CH_2–COO), 1.4–1.2 [6H, m, (CH_2)$_3$–CH_3], 0.9 (3H, t, *J*=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.2 (COO), 136.0 (=*C*H–CH–OH), 133.2 [t, *J*=23 Hz, =*C*D–(CH_2)$_4$–CH_3], 130.3, 129.3, 128.4 [=*C*H–CH_2–*C*H=*C*H–(CH_2)$_3$–COO], 128.0 (=*C*H–CH=CH–CH–OH), 125.4 (*C*H=CH–CH–OH), 123.9 [t, *J*=23 Hz, *C*D=CD–(CH_2)$_4$–CH_3], 72.0 (*C*H–OH), 51.4 (CH_3–O), 35.2 (*C*H_2–CH–OH), 33.4 (*C*H_2–COO), 31.4 (*C*H_2–CH_2–CH_3), 29.2 [*C*H_2–(CH_2)$_2$–CH_3], 27.2 [*C*H_2–(CH_2)$_3$–CH_3], 26.5 [*C*H_2–(CH_2)$_2$–COO], 26.0 (=CH–*C*H_2–CH=), 24.7 (*C*H_2–CH_2–COO), 22.5 (*C*H_2–CH_3), 13.9 (CH_3). IR (film): 3457 (br), 3009, 2953, 2927, 2856, 2248, 1739, 1437, 1156, 984, 950 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{32}D_2O_3Na$ $(M+Na)^+$: 359.2531, found $(M+Na)^+$: 359.2539.

1.1.29. [14,15-^{2}H$_2$]-12(*R*)-HETE (37). Compound **36** (1.6 mg, 4.8 μmol) was converted to **37** using the same conditions as for the preparation of **1** affording [14,15-^{2}H$_2$]-12(*R*)-HETE (1.4 mg, 91%). UV (CH_3CN) λ_{max} 237 nm. ^{1}H NMR (CD_3CN, 300 MHz): δ 6.6–6.5 (1H, br. dd, *J*=15.3, 11.1 Hz, C*H*=CH–CH–OH), 6.0 (1H, br. t, *J*=11.1 Hz, =C*H*–CH=CH–CH–OH), 5.7 (1H, dd, *J*=15.3, 6.3 Hz, =C*H*–CH–OH), 5.5–5.3 [3H, m, =C*H*–CH_2–C*H*=C*H*–(CH_2)$_3$–COO], 4.2–4.1 (1H, m, C*H*–OH), 2.9 (2H, m, =CH–C*H*$_2$–CH=), 2.4–2.0 (8H, m, C*H*$_2$–CH–OH, C*H*$_2$–CH_2–C*H*$_2$–COO, C*H*$_2$–(CH_2)$_3$–CH_3], 1.7–1.5 (2H, m, C*H*$_2$–CH_2–COO), 1.4–1.2 [6H, m, (CH_2)$_3$–CH_3], 0.9 (3H, t, *J*=6.8 Hz, CH_3). IR (film): 3369 (br), 3009, 2955, 2927, 2857, 2248, 1709, 1456, 1365, 1245, 1159, 1048, 983, 950 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{30}D_2O_3Na$ $(M+Na)^+$: 345.2375, found $(M+Na)^+$: 345.2390.

1.1.30. 5(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-12(*R*)-[(triethylsilyl)oxy]-8(*E*),10(*E*)-eicosadien-6,14-diynoic acid methyl ester (38). Phosphonate **10** (0.40 g, 0.74 mmol) was dissolved in THF (7 ml) and cooled to −78°C. A 1.5 M solution of LDA in cyclohexane (0.53 ml, 0.79 mmol) was added dropwise. After 2 min aldehyde **4** (0.19 g, 0.67 mmol) in THF (2 ml) was added. The reaction was stirred for 1 h at −78°C and then was allowed to reach room temperature before quenching with NH_4Cl aq/Et_2O. The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated under vacuo. The crude product was filtered through silica affording a mixture of *cis* and *trans* isomers at the C_{10}–C_{11} double bond.

The crude mixture was dissolved in CH_2Cl_2 (10 ml) and treated with a catalytic amount of I_2. After stirring at room temperature for 30 min the reaction was quenched by addition of a concentrated solution of $Na_2S_2O_3$ (1 ml). Separation of phases, drying over Na_2SO_4, concentrating and flash chromatography [hexane/EtOAc (98:2)] afforded **38** (0.23 g, 49%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8–7.6 (4H, m, Ar), 7.5–7.3 (6H, m, Ar), 6.4–6.1 (2H, m, =C*H*–C*H*=CH–CH–OTES), 5.8 (1H, dd, *J*=13.8, 5.7 Hz, =C*H*–CH–OTES), 5.4 (1H, m, =C*H*–C≡C–CH–OTBDPS), 4.5–4.4 (1H, m, CH–OTBDPS), 4.3–4.2 (1H, m, CH–OTES), 3.6 (3H, s, CH_3O), 2.5–2.2 (4H, m, CH_2–COO, C*H*$_2$–CH–OTES), 2.2–2.1 [2H, m, C*H*$_2$–(CH_2)$_3$–CH_3], 1.8–1.6 [4H, m, (C*H*$_2$)$_2$–CH_2–COO], 1.5–1.4 [2H, m, C*H*$_2$–(CH_2)$_2$–CH_3], 1.4–1.2 [4H, m, (C*H*$_2$)$_2$–CH_3], 1.1 [9H, s, (CH_3)$_3$C], 1.0–0.9 [9H, t, *J*=7.8 Hz, (C*H*$_3$–CH_2)$_3$Si], 0.9 (3H, t, *J*=6.9 Hz, CH_3), 0.6 [6H, q, *J*=7.8 Hz, (CH_3–C*H*$_2$)$_3$Si]. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.0 (COO), 141.1 (*C*H=CH–C≡), 138.1 (=*C*H–CH–OTES), 136.2, 136.0 (4C, ArCH), 133.9, 133.7 (2C, ArC), 129.8, 129.6 (2C, ArCH), 129.1 (*C*H=CH–CH–OTES), 127.7, 127.4 (4C, ArCH), 110.7 (=*C*H–C≡), 92.7 (C≡), 84.6 (C≡), 82.4 (C≡), 76.6 (C≡), 71.9 (CH–OTES), 64.0 (CH–OTBDPS), 51.4 (CH_3O), 37.6 [*C*H_2–(CH_2)$_2$–COO], 33.7 (*C*H_2–COO), 31.0 (*C*H_2–CH_2–CH_3), 28.8, 28.6 [*C*H_2–CH–OTES, *C*H_2–(CH_2)$_2$–CH_3], 26.9 [(*C*H_3)$_3$C], 22.1 (*C*H_2–CH_3), 20.4 (*C*H_2–CH_2–COO), 19.2 (C), 18.7 [*C*H_2–(CH_2)$_3$–CH_3], 13.9 (CH_3), 6.7 [(*C*H_3–CH_2)$_3$Si], 4.8 [(CH_3–*C*H_2)$_3$Si]. IR (film): 3070, 3047, 2954, 2931, 2874, 2858, 1741, 1460, 1428, 1361, 1241, 1171, 1149, 1111, 1080, 1005, 985, 822, 740, 701 cm^{-1}. HRMS (ESI) calcd for $C_{43}H_{62}O_4Si_2Na$ $(M+Na)^+$: 721.4084, found $(M+Na)^+$: 721.4115.

1.1.31. 5(*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-12(*R*)-[(triethylsilyl)oxy]-6(*Z*),8(*E*),10(*E*),14(*Z*)-eicosatetraenoic acid methyl ester (39). Compound **38** (30 mg, 0.043 mmol) was dissolved in hexane (10 ml) under an argon atmosphere and Lindlar catalyst (50 mg) was added. The argon atmosphere was exchanged by hydrogen and the mixture was stirred until TLC check showed completion. Dilution of the crude reaction with Et_2O, filtration of the catalyst, concentration and purification by flash chromatography [hexane/EtOAc (96:4)] afforded **39** (27 mg, 89%). ^{1}H NMR (d_6-benzene, 300 MHz): δ 7.8–7.7 (4H, m, Ar), 7.3–7.2 (6H, m, Ar), 6.1–6.0 (1H, m, C*H*=CH–CH–OTES), 5.8 (2H, m, C*H*=C*H*–CH=CH–CH–OTES), 5.8–5.7 (1H, m, C*H*=CH–CH–OTBDPS), 5.7–5.6 (1H, dd, *J*=14.9, 6.8 Hz, =C*H*–CH–OTES), 5.5 [2H, m, C*H*=C*H*–(CH_2)$_4$–CH_3], 5.5–5.4 (1H, dd, *J*=10.5, 9.3 Hz, =C*H*–CH–OTBDPS), 4.7–4.6 (1H, m, CH–OTBDPS), 4.2–4.1 (1H, m, CH–OTES), 3.2 (3H, s, CH_3O), 2.5–2.2 (2H, m, C*H*$_2$–CH–OTES), 2.1–1.9 [4H, m, CH_2–COO,

CH_2–$(CH_2)_3$–CH_3], 1.7–1.4 [4H, m, $(CH_2)_2$–CH_2–COO], 1.4–1.2 [6H, m, $(CH_2)_3$–CH_3], 1.2 [9H, s, $(CH_3)_3C$], 1.0 [9H, t, J=7.8 Hz, $(CH_3$–$CH_2)_3Si$], 0.9–0.8 (3H, t, J=6.9 Hz, CH_3), 0.6 [6H, q, J=7.8 Hz, $(CH_3$–$CH_2)_3Si$]. ^{13}C NMR (d_6-benzene, 75.5 MHz): δ 173.0 (COO), 137.8 (=*C*H–CH–OTES), 136.5, 136.4 (4C, ArCH), 134.7, 134.5 (2C, ArC), 134.2 (=*C*H–CH–OTBDPS), 133.8 (CH=), 132.2 [=*C*H–$(CH_2)_4$–CH_3], 129.9, 129.8 (2C, ArCH), 129.9 (*C*H=CH–CH–OTES), 128.9 (*C*H=CH–CH–OTBDPS), 127.8 (CH=), undefined (interference with d_6-benzene signal) (4C, ArCH), 125.5 [*C*H=CH–$(CH_2)_4$–CH_3], 73.5 (CH–OTES), 69.8 (CH–OTBDPS), 50.7 (CH_3O), 37.9 [CH_2–$(CH_2)_2$–COO], 36.9 (CH_2–CH–OTES), 33.7 (CH_2–COO), 31.7 (CH_2–CH_2–CH_3), 29.5 [CH_2–$(CH_2)_2$–CH_3], 27.7 [CH_2–$(CH_2)_3$–CH_3], 27.1 [$(CH_3)_3C$], 22.8 (CH_2–CH_3), 20.6 (CH_2–CH_2–COO), 19.4 (C), 14.1 (CH_3), 7.0 [$(CH_3$–$CH_2)_3Si$], 5.3 [CH_3–$CH_2)_3Si$]. IR (film): 3071, 3048, 2957, 2929, 2875, 2857, 1742, 1460, 1428, 1260, 1110, 1076, 821, 801, 740, 702 cm^{-1}. HRMS (ESI) calcd for $C_{43}H_{66}O_4Si_2Na$ $(M+Na)^+$: 725.4397, found $(M+Na)^+$: 725.4415.

1.1.32. Leukotriene B_4 (3). To a solution of **39** (15 mg, 0.021 mmol) in THF (2 ml) at 0°C was added a 1.0 M solution of TBAF in THF (0.4 ml, 0.40 mmol). After 15 h the reaction mixture was diluted with EtOAc (50 ml). Washing with brine, drying over Na_2SO_4 and concentrating afforded crude **3** that was purified by flash chromatography affording LTB_4 (**3**) (4.5 mg, 63%). $[\alpha]_D^{25}$=12.6 (c=0.1, $CHCl_3$) {Ref.[18b] $[\alpha]_D^{20}$=12.6 (c=0.46, $CDCl_3$)}. UV (MeOH) λ_{max} 260, 270, 281 nm. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.5 (1H, dd, J=13.5, 11.1 Hz, H-8), 6.4–6.2 (2H, m, H-9, H-10), 6.1 (1H, t, J=11.1 Hz, H-7), 5.8 (1H, dd, J=14.7, 6.3 Hz, H-11), 5.6–5.5 (1H, m, H-15), 5.5–5.3 (2H, m, H-14, H-6), 4.6 (1H, m, H-5), 4.2 (1H, m, H-12), 2.5–2.3 (4H, m, H-2, H-13), 2.1–2.0 (2H, m, H-16), 1.8–1.5 (4H, m, H-3, H-4), 1.4–1.2 (6H, m, H-17, H-18, H-19), 0.9 (3H, t, J=6.9 Hz, H-20). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.1 (C-1), 136.9 (C-11), 134.2, 134.0 (C-9, C-15), 133.7 (C-6), 130.3, 130.2 (C-7, C-10), 127.6 (C-8), 124.1 (C-14), 71.9 (C-12), 67.6 (C-5), 36.7 (C-4), 35.3 (C-13), 33.8 (C-2), 31.4 (C-18), 29.2 (C-17), 27.4 (C-16), 22.4 (C-19), 20.7 (C-3), 13.9 (C-20). HPLC/API-ES/MS (m/z): 335 $[M_{LTB4}-H^+]^-$.

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