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SYNTHESES OF ENANTIOMERICALLY PURE 9(S)- AND 9(R)-HETE FROM D-MANNITOL. USE OF A MALIC DIALDEHYDE EQUIVALENT.

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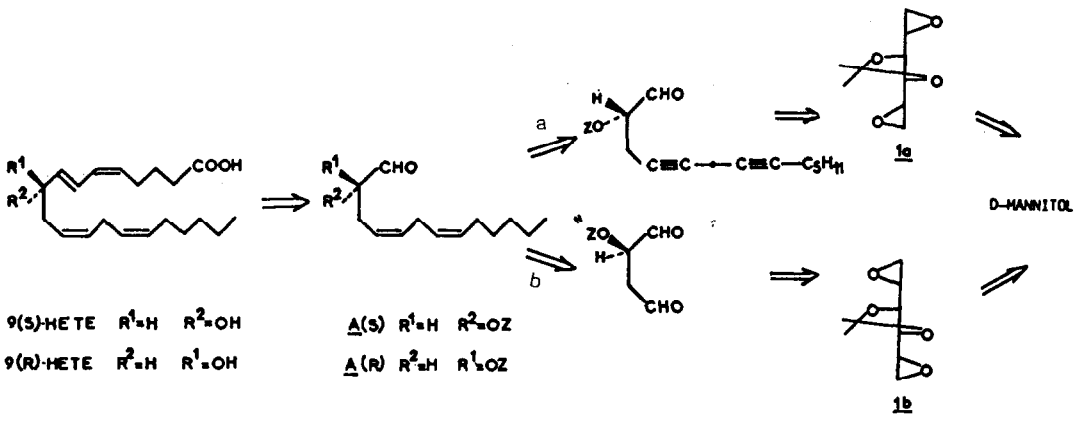
Summary : Starting from D-mannitol, the total syntheses of methyl 9(S)- and 9(R)-hydroxy 5(Z), 7(E), 11(Z), 14(Z) eicosatetraenoate are described by two different ways. One route uses a diepoxide opening by an acetylide while the second one involves the transformation of a diepoxide into an equivalent of malic aldehyde, an important intermediate in the synthesis of other oxidation products of arachidonic acid. Both methods are available for the synthesis of each enantiomer .

In the last few years a considerable amount of interest has been given to hydroxylated eicosatetraenoic acids derived from arachidonic acid by lipoxygenase metabolic pathways (5-HETE, leukotriene A_4, B_4, C_4, D_4 and E_4)[1]. These metabolites have generated a large involvement in the search for new drugs that may offer new therapeutic intervention in disease states such as asthma, allergic diseases, inflammation, etc... Recently, LTB4 and various monohydroxyeicosatetraenoic acids (5-HETE, 9-HETE, 11-HETE, 12-HETE and 15-HETE) have been isolated and identified from incubation of chopped rat brain tissue with ionophore A 23187.[2] The isolation of 9-HETE suggested the presence of lipoxygenase activity in the brain. Formation of this compound has not been reported to occur in mammalian tissues.

As part of an ongoing research project concerning the synthesis of lipoxygenase derived metabolite of arachidonic acid, we turned our interest toward 9-hydroxyeicosatetraenoic acid (9-HETE). Previously, this compound has not been the subject of many investigations (it has been shown to possess chemotactic activity[3]) and only two syntheses ((±)9-HETE[4] and 9(S)-HETE[5]) have been published. In the interest of fully evaluating the biological properties of 9-HETE it was desirable to obtain adequate supplies of both enantiomers. It was our plan to produce 9(R)-HETE and 9(S)-HETE starting from D-mannitol derivatives, specifically from 1,2:5,6-dianhydro-3,4-O-methylethylidene D-mannitol **1b**[6] or L-iditol **1a**[6]. This, in fact, was a viable approach and our results have already been disclosed in a preliminary form[7]. We detail herein our synthetic routes and the structure of the related compounds.

Examining the structure **A**, it was recognized that this compound could be obtained in a straightforward manner by the coupling of an acetylenic anion with the diepoxide (route a) or by transformation of the diepoxide into malic dialdehyde equivalent[5,7,8] followed by a Wittig reaction (route b).



Synthesis of 9(S)-HETE (route a)

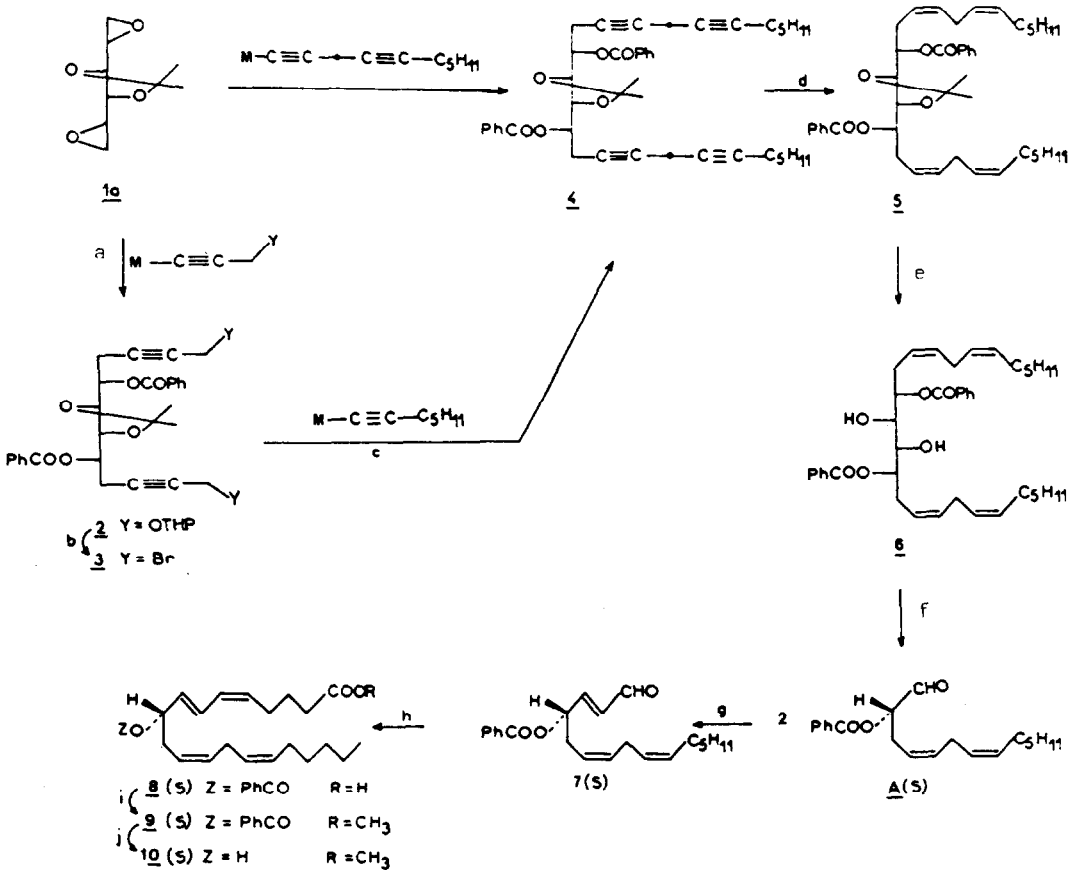
The synthesis, described in Scheme I, is related to the chemistry we developed for (+)-LTB4[9] and 19-hydroxy LTB4[10]. The α-hydroxyaldehyde **A**(S) is obtained by regiospecific nucleophilic opening of diepoxide **1a** with an acetylenic organometallic followed by protection of alcohol functions, controlled hydrogenation of the triple bonds, removal of the acetonide group and oxidative cleavage of the 3,4-diol.

In this case, introduction of the decadiyne unit can be made by nucleophilic opening of the diepoxide **1a** by an organometallic of 1,4-decadiyne (10C method) or by a functionalized propargylic entity (3C) followed by lengthening of the carbon chain with heptynide (3C+7C method).

10C Method : Many attemps to introduce 1,4-decadiyne[11] in one step failed. For example, with the lithio derivative of 1,4-decadiyne in THF in the presence of boron trifluoride-etherate at -78°C, compound **4** is obtained in very poor yield and formation of an allenic compound is observed. In toluene, with alane[12] or lithio derivative of 1,4-decadiyne at -78°C, the allenic compound is not observed, but the yield in **4** is low (15 %, no starting materials were recovered). Therefore, an alternative method was necessary to introduce the decadiyne unit.

3C+7C Method : Nucleophilic opening of the diepoxide **1a** by the lithium salt of propargyl O-THP ether followed by benzoylation in situ led to **2** in 80 % yield. Direct conversion of the THP ethers into the dibromide[13] **3** (70 %), followed by the coupling of **3** at low temperature with an excess of the heterocuprate of 1-heptyne gave the tetrayne **4** in 90 % yield[14]. Thus , "L-iditol diepoxide" was converted in three steps into **4** in 50 % overall yield.

Triple bond selective hydrogenation of the compound **4** catalyzed with palladium on barium sulfate in the presence of quinoline led to tetraene **5** in 60 % yield. Other hydrogenation conditions : $Pd/BaSO_4$ without quinoline or Lindlar catalyst converted **4** into **5** in very poor yield.



Scheme I

a) -5°C, $LiC{\equiv}C\text{-}CH_2OTHP$ (4eq.), THF/HMPA 10/1, reflux 20h, then 0°C, PhCOCl (5eq.), 80 % ; b) DIPHOS-$2Br_2$ (4eq.), CH_2Cl_2, 1h30, 25°C, 70 % ; c) $C_5H_{11}\text{-}C{\equiv}CH$ (4eq.), CuBr Me_2S (2eq.), THF, 30 min, -10°C ; then -78°C, BuLi (2eq.), -78°C → -40°C, 20 min ; then **3**, -78°C → 0°C ; then HMPA 0°C → RT, overnight, 90 % ; d) H_2, $Pd/BaSO_4$ 5 %, quinoline (1 %), ethyl acetate, 60 % ; e) TFA/H_2O 9/1, -5°C, 30 min, 100 % ; f) $Pb(OAc)_4$ (1.2eq.), CH_2Cl_2, -10°C, 1h, 75 % ; g) $Ph_3P^+\text{-}CH_2\text{-}CHO\ Br^-$ (1.1eq.), NEt_3 (1.4eq.), C_6H_6, 25°C, 24h, 70 % ; h) $Ph_3P^+\text{-}(CH_2)_4\text{-}COOH\ Br^-$ (2.8eq.), LiHMDS (5.3eq.), THF/HMPA 4/1, 0°C ; then -78°C, **7**(S), 75 % ; i) CH_2N_2, Et_2O ; j) K_2CO_3, methanol.

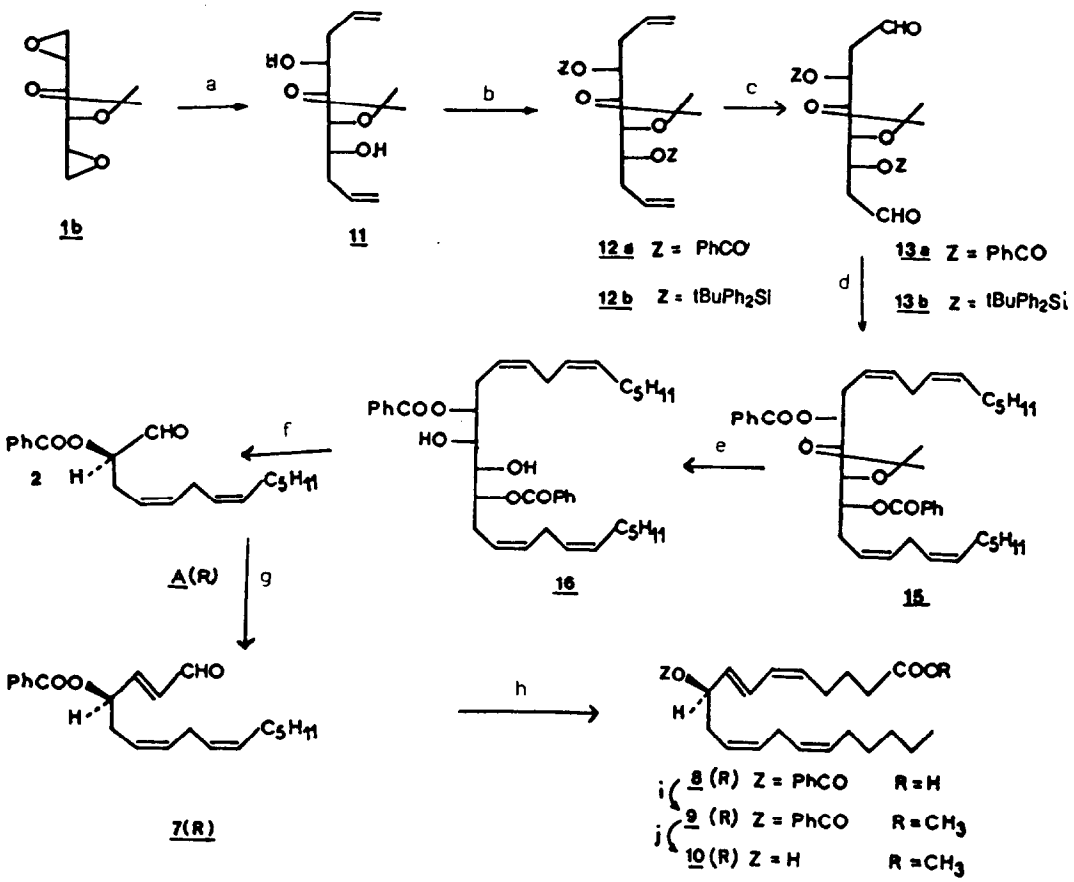
Removal of the acetonide group with aqueous trifluoroacetic acid and lead tetracetate cleavage of the 3,4-diol gave the chiral α-hydroxyaldehyde **A** (S) $[\alpha]_D$ -11° (c 1.2, CH_2Cl_2). Reaction of **A** (S) with formylmethylene triphenylphosphorane in dry benzene resulted in the unsaturated aldehyde **7** (S) (70 %) $[\alpha]_D$ +67° (c 1.3, CH_2Cl_2). Condensation of **7** (S), under cis olefination conditions with the ylide derived from the 4-carboxybutyltriphenylphosphonium bromide provided **8** (S) (75 % $[\alpha]_D$+51° (c 1.6, CH_2Cl_2).[15] **8** (S) was esterified with diazomethane and after treatment with K_2CO_3 in methanol the 9 (S)-HETE methyl ester was obtained.

Synthesis of 9(R)-HETE (route b)

For the synthesis of 9(R)-HETE (Scheme II) via the α-hydroxyaldehyde **A** (R), from the "D-mannitol diepoxide" **1b**, the same transformation as above can be applied, however we prefered to study a new approach using an equivalent of malic dialdehyde, a useful synthon for the access to various HETE.[8a]

Introduction of the formyl unit can be carried out by nucleophilic opening of the diepoxide with a vinylic organometallic compound followed by ozonolysis of the double bond. The malic dialdehyde equivalent **13** contains a free aldehyde function, with the other one being masked inside the glycol.

In order to introduce the vinyl group, we tried different organometallic compounds. For example, nucleophilic opening of the "D-mannitol diepoxide" **1b** by vinyllithium (from vinylbromide and tert-butyllithium) in presence of BF_3-OEt_2 or by divinyllithium cuprate (from vinyllithium and CuI) failed to give the desired product ; in this case we obtained a mixture of halohydrins which result from a competitive action of halide ion (Br^- and I^-)[16]. However, lithium divinylcyanocuprate at low temperature, a more reactive organometallic towards epoxides, led regiospecifically to the divinyl compound **11**, with 80 % yield, which was benzoylated or silylated[17] to give respectively **12a** or **12b**. Ozonolysis of **12a** afforded the crude dialdehyde **13a**. This unstable dialdehyde **13a** (highly prone to elimination of benzoic acid) was not purified but condensed immediately with the ylide derived from the triphenyl (Z)-non-3-en-1-yl phosphonium bromide **14**[18] to give **15** (overall yield from divinyl **11** was 50 %). By a three-step procedure the decadiene unit was introduced on the diepoxide **1b** in a 40 % overall yield whereas in the precedent methodology this was accomplished by a four-step procedure in 30 % overall yield. In contrast to aldehyde **13a**, **13b** was quite stable and could be purified by silica gel chromatography, but all attempts to couple **13b** with the ylide **14** proved futile, probably due to the steric hindrance in the molecule. Treatment of the acetonide **15** with aqueous trifluoroacetic acid generated the corresponding diol and lead tetraacetate cleavage of this diol gave the aldehyde **A** (R) $[\alpha]_D$ +11° (c 1.14, CH_2Cl_2). Completion of the synthesis of 9(R)-HETE methyl ester was then carried out, as above, after homologation by treatment with formylmethylene triphenylphosphorane to give the α,β-unsaturated aldehyde **7** (R) ($[\alpha]_D$ -69° (c 1.55, CH_2Cl_2)), Wittig condensation with the ylide derived from the 4-carboxybutyltriphenylphosphonium bromide, esterification with diazomethane and treatment with K_2CO_3 in methanol.



Scheme II

a) $(CH_2{=}CH)_2CuCNLi_2$ (3eq.), THF, -78°C, -78°C → RT, 2h, 80 % ; b) -40°C, PhCOCl (6eq.), -40°C → RT, 40 min, 90 % ; or $tBuPh_2SiCl$ (2.5eq.), imidazol (5.2eq.), 50°C 24h, 82 % ; c) O_3, CH_2Cl_2, -78°C, then Ph_3P (2eq.), -78°C → RT, 24h ; d) **14** $Br^-\ Ph_3\overset{+}{P}CH_2.CH_2\text{-}CH{=}CH\text{-}C_5H_{11}$ (4eq.), THF, BuLi (3.9eq.), -78°C, 1h, then **13a,** -78°C → RT, 2h, 50 % from **11** ; e) TFA/H_2O 9/1, -5°C, 30 min, 100 % ; f) $Pb(OAc)_4$ (1.2eq.), CH_2Cl_2, -10°C, 30 min, 76 %. g) $Ph_3\overset{+}{P}\text{-}CH_2\text{-}CHO\ Br^-$ (1.1eq.), NEt_3 (1.4eq.), C_6H_6, 25°C, 24h, 70 %; h) $Ph_3\overset{+}{P}\text{-}(CH_2)_4\text{-}COOH\ Br^-$ (2.8eq.), LiHMDS (5.3eq.) THF/HMPA 4/1, 0°C ; then -78°C, **7**(R), 75 %; i) CH_2N_2, Et_2O ; j) K_2CO_3, methanol.

Analysis of the 9(S) and 9(R)-HETE methyl esters using a Baker dinitrobenzoylphenylglycine (covalent) chiral phase HPLC column revealed in each case the presence of a single enantiomer.

In summary from D-mannitol, an inexpensive chiral compound, the above sequences for the preparation of both enantiomers of 9-HETE are simple, efficient and allows access to these biologically important molecules in substantial quantities.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian EM 390 (90 MHz) or a Bruker AM 250 (250 MHz). All signals were expressed as ppm downfield from tetramethylsilane used as an internal standard (δ-value). ^{13}C NMR spectra were obtained on a Bruker AM 250. Infrared spectra were obtained with a Perkin-Elmer 783 spectrophotometer. Optical rotations were obtained at 20°C with the indicated solvent and concentration by using a Perkin-Elmer 241-C polarimeter. Mass spectrometry (MS, 70eV) was performed on a Riber 10-10 instrument. All reactions were carried out under inert atmosphere of nitrogen or argon and were monitored by thin layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography[19] was performed with Merck Kieselgel 60 (230-400 mesh ASTM) silica.

To the 9(S)-HETE methyl ester
5 (S), 8 (S)-dibenzoyloxy-1,12-ditetrahydropyranyloxy-6 (R), 7 (R)-O-methylethylidene-2,10 dodeca-diyn-6,7 diol (2) : To a stirred solution of 3-tetrahydropyranyloxypropyne (1.176g 8.4 mmol) in THF (15 mL) at -5°C n-butyllithium (1.6M in hexanes 5 mL - 8 mmol) was added dropwise. After stirring for one hour at 0°C, the diepoxide **1a**[6] (372 mg, 2 mmol) in THF (15 mL) and HMPA (1.6 mL) were successively added and the mixture was refluxed for 20h. The resulting alcoholate functions were protected in situ at 0°C by dropwise addition of benzoylchloride (1.16 mL - 10 mmol) ; after stirring one hour at room temperature, the reaction mixture was poured into water-ether (10 mL - 30 mL) and extracted with ether (3x20 mL). The combined ether layer was washed with brine and dried over $MgSO_4$ and the solvent was removed at reduced pressure. Flash chromatography of the residue (95:5 CH_2Cl_2-Et_2O, Rf 0.22) afforded 896 mg (80 % yield) of **2** : $[\alpha]_D$ -6° (c 0.9, CH_2Cl_2) ; ^1H NMR[20] (250MHz) δ 8.20-7.30 (m,10H,Ph), 5.35 (t,2H,H-5,$J_{5,6}$=6Hz,$J_{4,5}$=7Hz), 4,56 (m,2H,H-a), 4.24 (s,2H,H-6), 4.00 (m,4H,H-1), 3.35-3.64 (m,4H,H-b), 2.72 (m,4H,H-4), 1.30-1.70 (m,18H,C(CH_3)$_2$,H-c,d,e) ; ^{13}C NMR[20] δ 165.7 (Ph-COO-), 133.2, 129.8, 128.5 (Ph), 110.1 (C(CH_3)$_2$), 96.6 (C-a), 80.9 (C-2), 78.8 (C-3), 76.7 (C-5), 70.2 (C-6), 62.0, 54.2 (C-1,b), 30.2 (C-4), 27.1 (C(CH_3)$_2$), 25.3, 22.0, 19.1 (C-c,d,e) ; MS [m/e (70eV, %)] 659 ((M-CH_3)$^{\cdot+}$,2), 287 (7), 122 (10), 105 (100), 77 (50). NH_3 chemical ionization : 692 $(M+18)^+$.

5(S), 8(S)-dibenzoyloxy-1,12-dibromo-6(R), 7(R)-O-methylethylidene-2,10-dodecadiyn-6,7 diol (3) : A solution of bromine (500 mg - 3.17 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a stirred solution of 1,2-bis(diphenylphosphino) ethane (DIPHOS) (625 mg - 1.57 mmol) in CH_2Cl_2 (2 mL) at 0°C.To this mixture was added a solution of **2** (285 mg - 0.42 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was then stirred at 25°C for 1.30h Then ether (20 mL) and pentane (40 mL) were added to precipitate the undesired by-products. Filtration on a thin pad of silica gel and flash chromatography (Rf 0.6, CH_2Cl_2) afforded 187 mg (70 %) of **3** : $[\alpha]_D$ -10° (c 1.0, CH_2Cl_2) ; ^1H NMR[20] (250 MHz) δ 8.05-7.30 (m,10H,Ph), 5.38 (t,2H,$J_{4,5}$=7Hz), 4.28 (s,2H,H-6), 3.69 (m,4H,H-1), 2.78 (m,4H, H-4), 1.50 (s,6H,C(CH_3)$_2$). ^{13}C NMR[20] δ 165.8 (PhCOO), 133.3, 129.8, 128.5 (Ph), 110.1 (C(CH_3)$_2$), 82.2, 78.0 (C-2,3), 69.8, 76.5 (C-5,6), 27.2 (C(CH_3)$_2$), 22.0 (C-1), 14.5 (C-4). Anal. $C_{29}H_{28}O_6Br_2$ Calcd : C, 55.08 ; H, 4.46. Found : C, 55.29; H, 4.56.

12(S), 15(S)-dibenzoyloxy-13(R), 14(R)-O-methylethylidene-6,9,17,20-hexaeicosatetrayn-13,14-diol (4) : To a stirred solution of CuBr-Me_2S (276 mg - 1.33 mmol) in THF (4 ml) at -10°C was added dropwise heptyne (356 µL, 2.67 mmol). After stirring for 20 min at room temperature the resulting mixture was cooled to -78°C and butyllithium (1.6M in hexanes, 836 µL - 1.33 mmol) was added slowly. The mixture was warmed to -40°C and stirred 20 min. Then the mixture was added dropwise at -78°C to a solution of **3** (272 mg - 0.43 mmol) in THF (3 mL), then HMPA (6mL) was added at O°C. The mixture was allowed to warm to room temperature for overnight and poured into a mixture of NH_4Cl-NH_3 solution (pH=8, 30 mL) and pentane (30 mL) then

filtered through Celite and extracted with pentane (3x20 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and the solvent was removed at reduced pressure. Filtration through a pad of silica gel afforded 245 mg (90 %) of **4** : $[\alpha]_D$ +3° (c 1.35, CH_2Cl_2) ; ^1H NMR[20] (250 MHz) δ 8.05-7.30 (m,10H,Ph), 5.34 (m, 2H, H-12), 4.30 (m, 2H, H-13), 2.95 (quint., 4H, H-8, $J_{5,8}=J_{8,11}=3Hz$), 2.70 (m,4H,H-8), 2.04 (t t , 4H, H-5, $J_{5,4}=6.5Hz$, $J_{5,8}=3Hz$), 1.45 (s,6H,C(CH_3)$_2$), 1.25 (m,12H,H-2,3,4), 0.90 (t,6H,H-1, J=7Hz). IR (cm^{-1}) 2210 (C≡C).

12(S),15(S)-dibenzoyloxy-13(R),14(R)-O-methylethylidene-6(Z),9(Z),17(Z),20(Z)hexaeicosatetraene-13,14 diol (5) : A mixture of 5 % $Pd/BaSO_4$ (330 mg) in ethyl acetate (30 mL) was treated with hydrogen at room temperature for 2h followed by the addition of quinoline (322 µL) and **4** (585 mg, 0.88 mmol) in ethyl acetate (20 mL). After the uptake of the theoretical amount of hydrogen was observed (6h), the ethyl acetate was removed in vacuo after filtration and the crude residue was chromatographied (90:10 cyclohexane:ethylacetate, Rf 0.4) to give **5** (344mg, 60%) : $[\alpha]_D$ +8° (c 0.9, CH_2Cl_2). ^1H NMR[20] (250 MHz) δ 8.05-7.30 (m,10H,Ph), 5.35 (m,2H,H-12), 5.27 (m,8H,H-6,7,9,10), 4.05 (m,2H,H-13), 2.57 (m,4H,H-11), 2.76-2.67 (m,4H,H-8), 1.95 (m,4H,H-5), 1.40 (s,6H,C(CH_3)$_2$), 1.25 (m,12H,H-2,3,4), 0.85 (t,6H,H-1). ^{13}C NMR[20] δ 165.7 (Ph-CO); 132.8, 131.8, 130.3, 129.9, 129.5, 128.1, 127.0, 123.6 (Ph,C-6,7,9,10) ; 109.3 (C(CH_3)$_2$) ; 76.3, 71.1 (C-12,13) ; 28.7 (C(CH_3)$_2$) ; 31.3, 29.4, 29.1 (C-5,8,11) ; 26.9, 25.4, 22.2 (C-2,3,4) ; 13.8 (C-1). MS NH_3 chemical ionization : 671 $(M+1)^{\cdot+}$, 688 $(M+18)^{\cdot+}$

12 (S), 15 (S) dibenzoyloxy-6 (Z), 9 (Z), 17 (Z), 20 (Z) hexaeicosatetraene 13, 14-diol (6) : The acetonide **5** (340 mg, 0.5 mmol) in 90 % aqueous trifluoroacetic acid (4.28 mL) was stirred for 30 min at -5°C. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and water (10 mL) and extracted with ether (3x20 mL). The combined organic extracts were washed with $NaHCO_3$ aqueous solution (3 %) until pH 7 and dried over $MgSO_4$. Evaporation gave the diol **6** as an oil in 100 % yield. **6** was used without further purification. ^1H NMR[20] (250 MHz) δ 8.10-7.35 (m,10H,Ph), 5.35-5.27 (m,10H,H-6,7,9,10,12), 4.03 (m,2H,H-13), 2.80-2.57 (m,8H,H-8,11), 1.95 (m,4H,H-5), 1.25 (m,12H,H-2,3,4), 0.85 (t,6H,H-1, J=7Hz). ^{13}C NMR[20] δ 131.9, 130.8, 130.5, 129.9, 129.8, 128.4, 127.2, 123.7 (Ph,C-6,7,9,10) ; 77.5, 71.3 (C-12,13) ; 31.4, 29.7, 29.1 (C-5,8,11) ; 27.2, 25.7, 22.5 (C-2,3,4) ; 14.0 (C-1).

2 (S)-benzoyloxy-4 (Z), 7 (Z)-tridecadienal (A(S)) : To a solution of the crude diol **6** (315 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added lead tetracetate (280 mg, 0.63 mmol) at -10°C. After one hour at -10°C, filtration and evaporation of the solvent in vacuo and flash chromatography of the residue (95:5 CH_2Cl_2, ethyl acetate Rf,0.6) afforded aldehyde **A**(S) (70 % from acetonide **5**). $[\alpha]_D$ -11° (c 1.2, CH_2Cl_2). ^1H NMR[20] (250 MHz) : δ 9.64 (s,1H,H-8) ; 8.10-7.50 (m,5H,Ph), 5.60-5.20 (m,5H,H-9,11,12,14,15), 2.81 (t,2H,H-13,J=7Hz), 2.72 (t,2H,H-10, J=7Hz), 2.01 (q,2H,H-16, J=7Hz), 1.27 (m,6H,H-17,18,19), 0.86 (t,3H,H-20,J=7Hz).

4 (S)-benzoyloxy-2 (E), 6 (Z), 9 (Z)-pentadecatrienal (7 (S)) : To a benzene solution (1 mL) of formylmethyltriphenylphosphonium chloride (140 mg, 0.4 mmol) at room temperature was added triethylamine (85 µL, 0.51 mmol). After stirring for one hour, the freshly prepared aldehyde **A**(S) (110 mg, 0.35 mmol) in benzene (1mL) was added and the mixture was stirred for 24 h at room temperature ; benzene was removed under reduced pressure. The product was extracted with ether and solid triphenylphosphine oxide was removed by filtration ; the organic extracts were concentrated in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2, Rf : 0.4) giving aldehyde **7** (80 % yield) : $[\alpha]_D$ +67° (c 1.3, CH_2Cl_2). ^1H NMR[20] (250 MHz) ; δ 9.55 (d,1H,H-6, J=7.5Hz); 7.90-7.30 (m,5H,Ph); 6.85 (dd,1H,H-8, J=4.5, 16Hz); 6.30 (ddd, 1H, H-7, J=1.5,7.5,16Hz); 5.80 (m,1H,H-9); 5.54-5.28 (m,4H,H-11,12,14,15), 2.85 (m,2H,H-13); 2.60 (m,2H,H-10,), 2.00 (m,2H,H-16), 1.30 (m,6H, H-17,18,19), 0.86 (t,3H,H-20,J=7Hz). ^{13}C NMR[20] δ 172.6 (C-1); 165.5 (Ph-CO); 153.2 (C-3); 133.5, 131.8, 131.0, 129.8, 128.5, 126.7, 122.5 (C-2, 6,7,9,10,Ph); 72.3 (C-4); 31.8, 31.5, 29.4 (C-5,8,11); 27.3, 25.9, 22.5 (C-12,13,14); 14.0 (C-15). MS NH_3 chemical ionization : 341 $(M+1)^+$, 358 $(M+18)^+$.

9 (S)-benzoyloxy-5 (Z), 7 (E), 11 (Z), 14 (Z)-eicosatetraenoic acid 8 (S) : To a stirred solution 4-carboxybutyltriphenylphosphonium bromide (dried under vacuum over 2 hours) (75 mg, 0.17 mmol) in THF (250 µL) and HMPA (75 µL) at 0°C was added dropwise a solution of lithium bis(trimethylsilyl)amide (LiHMDS : 1M in THF, 312 µL). After stirring for 30 min at room temperature the deep red ylide was formed, it was then dropwise added to a solution at -78°C of the aldehyde **7** (S) (20 mg, 0.059 mmol) in THF (250 µL). Stirring was continued at -78° for one hour then 40 min at room temperature. The reaction mixture was diluted with water (4 mL) and CH_2Cl_2 (1.5 mL). The resulting mixture was acidified with aqueous hydrogen chloride (1N) to pH 3. After extraction with CH_2Cl_2 (3x2 mL), the combined organic extracts were washed with brine and dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography, 60:40 (cyclohexane-ethylacetate, Rf : 0.23) afforded 9(S)-benzoyl-HETE with 75 % yield. $[\alpha]_D$ +51° (c 1.6, CH_2Cl_2) ; ^1H NMR[20] (250 MHz): δ 8.1-7.5 (m,5H,Ph); 6.58 (dd,1H,H-7, J=11,15Hz); 6.01 (t,1H,H-6,J=11Hz); 5.66 (dd,1H,H-8,J=7.5, 16Hz); 5.60-5.20 (m,6H,H-5,9,11,12,14,15); 2.79-1.90 (m,10H,H-2,4,10,13,16); 1.70 (m,2H, H-3); 1.23 (m,6H,H-17,18,19); 0.86 (t,3H,H-20,J=7Hz). ^{13}C NMR[20] δ 177.9 (C-1), 165.5 (Ph-CO-), 132.9, 132.1, 131.3, 131.0, 130.7, 129.6, 128.2, 128.1, 127.3, 123.8 (C-5,6,7,8,11,12,14,15), 74.8 (C-9), 32.8, 32.6, 31.5, 29.4 (C-4,10,13,16), 26.9, 25.8, 22.5 (C-17,18,19), 14.1 (C-20). MS NH_3 chemical ionization : 442 $(M+18)^+$, 425 $(M+1)^+$.

Methyl 9 (S)-benzoyloxy-5 (Z), 7 (E), 11 (Z), 14 (Z) eicosatetraenoate (9 (S)) : To a solution of compound **8**(S) in CH_2Cl_2 at room temperature was added diazomethane 0.5M in ether, and the solution was stirred for 30 min. ; removal of solvent at reduced pressure gave the crude product. After purification by flash chromatography, the pure methyl ester was obtained (CH_2Cl_2 Rf 0.4). ^1H NMR[20] (250 MHz) δ 8.05-7.30 (m,5H,Ph); 6.56 (dd,1H,H-7,$J_{7,8}$=16Hz, $J_{6,7}$= 11Hz); 5.98 (t,1H,H-6,$J_{6,7}$=11Hz); 5.69 (dd,1H,H-8, $J_{7,8}$=16Hz, $J_{8,9}$=7.5Hz); 5.50-5.20 (m,6H,H-5,9,11,12,14,15); 3.62 (s,3H,OCH_3); 2.8-1.8 (m,10H,H-2,4,10,13,16); 1.73 (m,1H,H-3); 1.25 (m,6H,H-17,18,19); 0.9 (t,3H,H-20,J=7Hz). MS NH_3 chemical ionization : 456 (M^++18,15), 317 (M^++1-PhCOOH, 100). HMRS (m/z) for $C_{28}H_{38}O_4$ M^+, calcd 438.2770, found 438.2767.

Methyl 9 (S)-hydroxy-5 (Z), 7 (E), 11 (Z), 14 (Z)-eicosatetraenoate (10 (S)) : In a suspension of K_2CO_3 (dried under vacuum) in methanol was added **9** (S), the mixture was stirred for 30 min at room temperature, then one hour at 40°C ; then a solution of acetic acid 5 % in methanol was added until pH=5 ; removal of solvent at reduced pressure and purification by flash chromatography gave crude product (95:5 CH_2Cl_2-Et_2O Rf=0.3). UV (hexane) λ_{max} 228 nm, 232 nm. Analysis of the 9(R) and 9(S)-HETE methyl ester using a Baker dinitrobenzoylphenylglycine (covalent) chiral phase HPLC column : eluent 2-propanol 0.5 % in hexane ; flow rate of 1.6 mL/min, λ=239 nm, t=45min for 9 (S) HETE and t=46.5 min for 9 (R) HETE methyl ester. ^1H NMR[20] (250 MHz) : δ 6.48 (ddt, 1H, H-7, $J_{7,8}$=16Hz, $J_{6,7}$=11Hz); 6.02 (t,1H,H-6,$J_{6,7}$=$J_{6,5}$=11Hz); 5.70 (dd,1H,H-8, $J_{7,8}$=16Hz,$J_{8,9}$=6Hz); 5.60 - 5.30 (m,5H,H-5,11,12,14,15); 4.2 (m,H-9); 3.62 (s,3H,OCH_3), 2.80 (m,2H,H-13); 2.40-1.70 (m,10H,H-2,3,4,10,16); 1.25 (m,6H,H-17,18,19); 0.9 (t,3H,H-20, J=7Hz).

To the 9 (R) HETE methyl ester :

5 (R), 6 (R)-O-methylethylydene-1,9 decadiene-4 (R), 5,6,7 (R) tetrol (11) : To a suspension of CuCN (538 mg, 6 mmol) dried under high vacuum and conservated under argon, in THF (6 mL) at -78°C was added dropwise vinyllithium in pentane (prepared from 12 mmol of vinyl bromide, 24 mmol of terbutyllithium in pentane and 2 mL of ether)[21]. The heterogenous mixture was stirred for 1h30 and warmed gradually until room temperature and recooled to -78°C. The diepoxide **1b** (372 mg, 2 mmol) in THF solution was then introduced and stirred for 2 hours ; the reaction was quenched with a mixture of NH_4Cl-NH_3 solution (pH=8), filtered through celite and extracted with ether (3x50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed at reduced pressure. Flash chromatography of the residue (80:20 CH_2Cl_2-Et_2O , Rf 0.3) afforded 387 mg (80 % yield) of **11** : ^1H NMR[20] (250 MHz) δ 5.85 (m, 2H, H-2), 5.12 (m, 4H, H-1), 3.67 (m, 4H, H-4,5), 2.57-2.20 (m, 4H, H-3), 1.34 (s, 6H,

$C(CH_3)_2$). MS [m/e (70 eV, %)] 243 ($(M+1)\cdot^+$,25), 227 ($(M-CH_3)\cdot^+$, 11), 59 (100). NH_3 chemical ionization : 260 $(M+18)^+$, 243 $(M+1)^+$.

4 (R), 7 (R)-dibenzoyloxy-5 (R), 6 (R)-O-methylethylidene-1,9-decadiene-5,6 diol (12a) : To the lithium divinylcyanocuprate solution (6 mmol) in THF (5 mL), prepared as above, was added the diepoxide (**1b**) (372 mg, 2 mmol) at -78°C. The mixture was stirred for 2h at -78°C and the resulting alcoholate functions were protected in situ by addition of benzoylchloride (1.39 mL, 12 mmol) at -40°C. After stirring for 30 min at room temperature, the reaction was quenched with a mixture of NH_4Cl-NH_3 solution (pH=8), filtered through celite and extracted with ether (3x50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed at reduced pressure. Flash chromatography of the residue (70:30 CH_2Cl_2, cyclohexane, Rf=0.30) afforded 850 mg (90 % yield) of **12a** : $[\alpha]_D$ +31.3° (c 1.0, CH_2Cl_2). ^1H NMR[20] (250 MHz) δ 7.94-7.34 (m,10H,Ph), 5.78 (m,2H,H-2), 5.34 (m,2H,H-4), 5.10-4.98 (m,4H,H-1), 4.27 (m,2H,H-5), 2.55 (m,4H,H-3), 1.40 (s,6H,$C(CH_3)_2$). ^{13}C NMR[20] δ 165.8 (Ph-CO), 133.0, 130.0, 129.7, 128.3 (Ph), 132.9 (C-1), 118.2 (C-2), 110.8 ($C(CH_3)_2$), 79.3, 73.6 (C-4,5), 35.1 (C-3), 27.7 ($C(CH3)2$). MS [m/e (70 eV, %)] 435 ($(M-CH_3)\cdot^+$,3), 217 (14), 105 (100), 77 (35). NH_3 chemical ionization : 468 $(M+18)^+$. Anal. $C_{27}H_{30}O_6$ calcd : C, 71.98 ; H, 6.71 ; found : C, 71.4 ; H, 6.7.

4 (R), 7 (R)-ditertiobutyldiphenylsilyloxy-5 (S), 6 (S)-O-methylethylidene-1,9-decadiene-5,6-diol (12b) : Tertiobutyldiphenylsilyl chloride (650 µl, 2.5 eq) was added to a solution of **11** (242 mg, 1 mmol) in DMF (1.5 mL) in presence of imidazol (354 mg, 5.2 eq). The mixture was refluxed for 24h at 50°C then hydrolyzed with brine (30 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$; the solvent was removed at reduced pressure. Flash chromatography of the residue (50:50 CH_2Cl_2-hexane, Rf : 0.35) afforded 588 mg of **12b** (82 % yield). ^1H NMR[20] (250 MHz) δ 7.70-7.40 (m,20H,Ph), 5.63 (m,2H,H-2), 4.85 (m,4H,H-1), 3.97 (d,2H,H-5, $J_{4,5}$=2Hz), 3.62 (td,2H,H-4, $J_{3,4}$=7Hz, $J_{4,5}$=2Hz), 2.21-1.72 (m,4H,H-3), 1.33 (s,6H,$C(CH_3)_2$), 1.04 (s,18H,$C(CH_3)_3$). NH_3 chemical ionization : 737 (M+18).

3 (R), 6 (R)-dibenzoyloxy-4 (R), 5 (R)-dihydroxy-4,5-O-methylethylidene-1,8-octanediol (13a) : The diene **12a** (360 mg, 0.8 mmol) in CH_2Cl_2 (20 mL) was cooled to -78°C and ozone was bubbled into the solution through a glass tube until the blue color appeared. The reaction mixture was swept with N_2 for 35 min and then a solution of triphenylphosphine (420 mg, 1.6 mmol) in CH_2Cl_2 (4 mL) was added at -78°C. The mixture was allowed to warm up to room temperature and stirred 24h. The solvent was removed at reduced pressure and the crude dialdehyde was used without further purification for Wittig reaction. ^1H NMR[20] (250 MHz) δ 9.7 (t, 2H, H-1, $J_{1,2}$=2Hz), 5.7 (m, 2H, H-3), 4.3 (dd, 2H, H-4, $J_{3,4}$=1.75Hz, $J_{4,5}$=4.0Hz), 2.9 (dt, 4H, H-2, $J_{2,3}$=5.5Hz, $J_{1,2}$=2.0Hz), 1.4 (s, 6H, $C(CH_3)_2$).

3 (R), 6 (R)-ditertiobutyldiphenylsilyloxy)-4 (S), 5 (S)-dihydroxy-4,5-O-methylethylidene-1,8-octanedial (13b) : Ozonolysis of **12b** was carried out under identical conditions as for **12a** described beforehand. However trimethylphosphite (9 eq) instead of triphenylphosphine reductor was used for the destruction of the ozonid. **13b** was purified by flash chromatography (90:10 cyclohexane-ethyl acetate , Rf 0.3) with 71 % yield.^1H RMN[20] (90 MHz) δ 9.4 (m,2H,H-1), 7.7 (m,20H,Ph), 3.4 (m,4H,H-3,4), 2.0 (m,4H,H-2), 1.2 (s,6H, $C(CH_3)_2$), 1.0 (m,18H,$C(CH_3)_3$).

To the 3 (Z)-nonenetriphenylphosphonium bromide (14) :

3 (Z)-nonenol : A mixture of Lindlar catalyst (600 mg) in hexane (60 mL) was treated with hydrogen at 1 atm and room temperature for 2 hours. Then the 3-nonynol (5.6 g, 0.04 mmol) in hexane (5 mL) was added and the progress of hydrogenation was monitored by the volume of hydrogen absorbed. Filtration and evaporation of the filtrate in vacuo afforded 5.3g of 3(Z)-nonenol (95 %) as an oil. ^1H NMR [20] (250 MHz) δ 5.5 (dtt,1H,H-3, $J_{2,3}$=6.5Hz, $J_{3,4}$=11.0Hz), 5.35 (dtt,1H,H-4, $J_{3,4}$=11Hz, $J_{4,5}$=6Hz), 3.60 (t,2H,H-1, $J_{1,2}$=6Hz), 2.30 (td,2H,H-2,$J_{2,3}$=6.5Hz, $J_{1,2}$=6.0Hz), 2.03 (td,2H,H-5, $J_{4,5}$=6Hz), 1.27 (m,6H,H-6,7,8), 0.85 (t,3H,H-9, $J_{8,9}$=7Hz).

1-bromo-3 (Z)-nonene : At 0°C to a solution of 3(Z)-nonenol (1.28 g, 9 mmol) in CH_2Cl_2 (13.5 mL) was added carbon tetrabromide (3.8 g, 12 mmol) then triphenylphosphine (3.5 g, 12 mmol). The mixture was stirred for 10 min at 0°C and concentrated under reduced pressure. Pentane (10 mL) was added and precipitated triphenylphosphine oxide was removed by filtration and filtrate evaporation afforded 1.84 g of quantitative crude bromide. ^1H NMR[20] (90 MHz) : δ 5.6-5.2 (m, ,2H, H-3, H-4), 3.3 (t,2H,H-1, $J_{1,2}$=10.5Hz), 2.6 (m,2H,H-2), 2.0 (m,2H,H-5), 1.3 (m,6H,H-6,7,8), 0.9 (m,3H,H-9).

3 (Z)-nonene triphenylphosphonium bromide (14) : To a solution of 1-bromo-3(Z) nonene (1.84 g, 9 mmol) in acetonitrile (67.5 mL) was added triphenylphosphine (2.6 g) and the mixture was refluxed during 6 days. Then ether was added and the crude phosphonium bromide precipitate (4.29 g, quantitative). ^1H NMR[20] (250 MHz) : δ 7.75 (m,15H,Ph), 5.47 (m,1H,H-3), 5.35 (m,1H,H-4), 3.75 (m,2H, H-1), 2.40 (m, 2H, H-2), 1.75 (m,2H,H-5), 1.15 (m,6H,H-6,7,8,9), 0.75 (t,3H,H-9, J=7Hz).

12(R), 15(R)dibenzoyloxy-13(R), 14(R)-O-methylethylidene-6(Z), 9(Z), 17(Z), 20(Z)-hexaeicosatetraene-13, 14 diol (15) : To a solution of 3(Z)-nonene triphenylphosphonium bromide **14** (1.5 g, 3.2 mmol, previously dried under vacuum) in THF (30 mL) was added dropwise at -78°C butyllithium (1.6 M in hexanes, 1.95 mL, 3.12 mmol). The resulting mixture was stirred one hour at -78°C. Then the crude dialdehyde **13a** (0.8 mmol) was added at -78°C and the temperature was slowly raised to RT. Then, the mixture was poured into an aqueous ammonium chloride solution and extracted with ether (4x50 mL). After drying over $MgSO_4$, removal of the solvent and flash chromatography (CH_2Cl_2, Rf 0.4) 246 mg (46 % yield from **12a**) was obtained as an oil : $[\alpha]_D$ +9.8° (c 1.58, CH_2Cl_2) ; ^1H NMR[20] (250 MHz) : δ 7.94-7.34 (m,10H,Ph), 5.5-5.1 (m,10H, H-6,7,9,10,12), 4.28 (m,2H,H-13), 2.72 (m,4H,H-11), 2.55 (m,4H,H-8), 1.96 (m,4H,H-5), 1.40 (s,6H,C(CH_3)$_2$), 1.23 (m,12H,H-2,3,4), 0.85 (m,6H,H-1,J=7Hz).

12 (R), 15 (R) dibenzoyloxy-6 (Z), 9 (Z), 17 (Z), 20 (Z)-hexaeicosatetraene-13 (S), 14 (S) diol (16) : Desacetylation reaction on **15** was carried out under identical conditions as for **5**, described beforehand. ^1H NMR[20] (90 MHz) : δ 7.9-7.3 (m,10H, Ph), 5.4-5.0 (m,10H, H-6,7,9,10,12), 3.6 (m, 2H, H-13), 2.6 (m, 8H, H-8,11), 1.9 (m,4H,H-5), 1.2 (m,12H,H-2,3,4), 0.8 (t,6H,H-1,J=7Hz).

2 (R)-benzoyloxy-4 (Z), 7 (Z)-tridecadienal (A(R)) : Oxidative cleavage reaction on **16** was carried out under identical conditions as for **6**, described beforehand. Flash chromatography (95:5 CH_2Cl_2-ethylacetate, Rf 0.55 afforded aldehyde **A**(R)(70 % from alkene acetonide **15**). $[\alpha]_D$ +11° (c 1.14, CH_2Cl_2). The ^1H NMR[20] (250 MHz), ^{13}C NMR[20] (22.93 MHz), S.M. spectra for this compound are almost superposable to those obtained for the enantiomer (**A**(S)).

4 (R)-benzoyloxy-2 (E), 6 (Z), 9 (Z)-pentadecatrienal (7 (R)) : Wittig reaction on **A** (R) was carried out under identical conditions as for **A**(S), described beforehand. Flash chromatography (CH_2Cl_2, Rf 0.4) afforded aldehyde **7** (R) (75 % yield) : $[\alpha]_D$ -69° (c 1.55, CH_2Cl_2). The ^1H NMR (250 MHz), ^{13}C NMR[20] (22.93 MHz), S.M. spectra for this compound are almost superposable to those obtained for the enantiomer **7** (S).

(R)-benzoyloxy-5 (Z), 7 (E), 11 (Z), 14 (Z)-eicosatetraenoic acid (8 (R)) : Wittig reaction on **7**(R)) was carried out under identical conditions as for **7**(S), described beforehand. According to assay up to 10 % of E isomer were occasionally obtained ; in this case, pure **8**(R) is easily obtained after HPLC separation microporasil column (eluent hexane/AcOEt/NEt_3 98/2/0.1), λ = 284 nm, flow rate 10 mL/min, retention time of Z isomer : 16,7 min, E isomer : 15,3 min.

Methyl 9 (R)-benzoyloxy-5 (Z), 7 (E), 11 (Z), 14 (Z)-eicosatetraenoate (9 (R))
Methylation on **8**(R) was carried out under identical conditions as for **8**(S) described beforehand. The ^1H NMR[20] (250 MHz), S.M. spectra, HMRS for this compound are almost superposable to those obtained for the enantiomer **9** (S).

Methyl 9 (R)-hydroxy-5 (Z), 7 (E), 11 (Z), 14 (Z)-eicosatetraenoate (10(R))
Debenzoylation of **9**(R) was carried out under identical conditions as for **9**(S) described beforehand. The UV (hexane), ^1H NMR[20] (250 MHz) spectra for this compound are almost superposable to those obtained for the enantiomer **10** (S).
Analysis of **10**(R) and **10**(S) using a chiral phase HPLC column revealed in each case the presence of a single enantiomer.

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(14) In this reaction when HMPA was added before the dibromide **3**, yield of adduct **4** decreases considerably.
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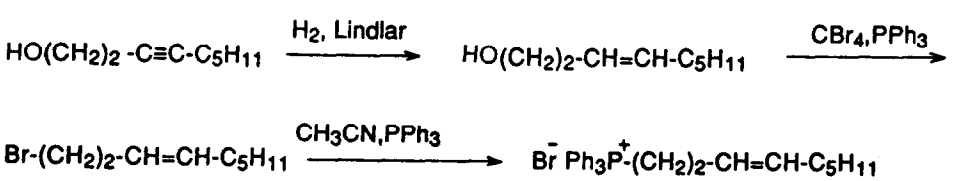
(18) Prepared in three steps as follows :



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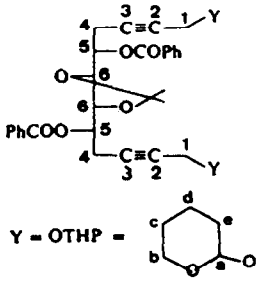
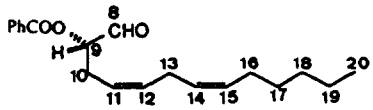
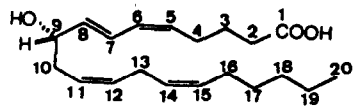
(20) To facilitate the notation of ^{1}H and ^{13}C NMR,data in the Experimental Section, only half of each symmetrical molecule is numbered ; for the compounds **A**, **7**, **8**, **9** and **10**, the numbering of carbons has been the same as in 9-HETE and the notation of tetrahydropyranyl group is the following :







(21) Lipshutz,B.H.; Wilhelm,R.S.; Kozlowski,J.A.; Parker,D.; J. Org. Chem., 1984, **49**, 3937.