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TOTAL SYNTHESIS OF (+)-LEUKOTRIENE B4 METHYL ESTER AND ITS 5-EPIMER FROM (R)-GLYCIDOL

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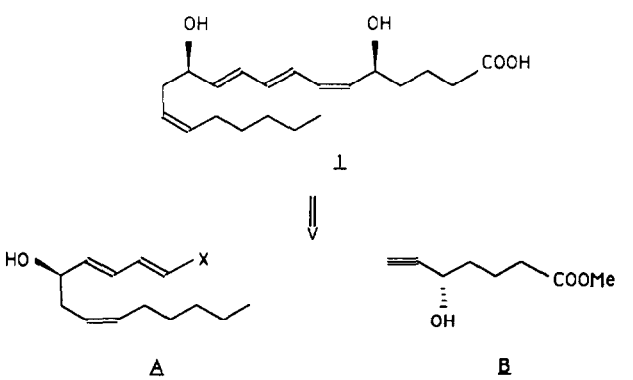
Abstract: The Pd-Cu coupling reaction of a chiral hydroxy-(E,E)-iododiene with a racemic acetylenic alcohol followed by reduction of the dienyne leads to the desired (Z,E,E) geometry and allows synthesis of LTB4 and its 5-epimer after separation of diastereomers

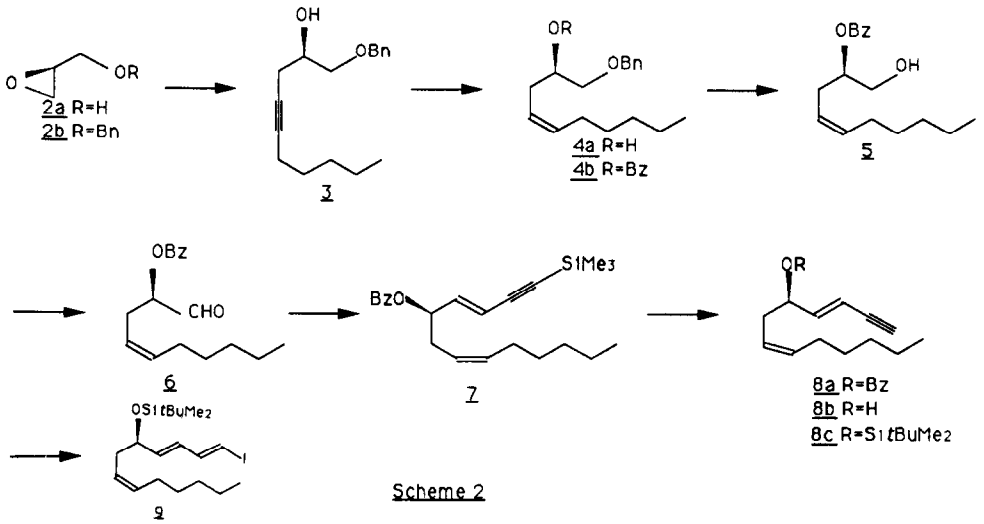
Leukotriene B4 (LTB4), a 5-lipoxygenase metabolite of arachidonic acid, is one of the most potent chemotactic agents produced by human polymorphonuclear leukocytes[1] Due to its physiological importance in inflammatory states and its low natural abundance, several syntheses of this compound have been realized[2] The Wittig reaction between two chiral fragments has often been utilized However, this reaction was not totally stereoselective and isolation of pure leukotriene B by H P L C was required In order to generate the trienic system with a stereodefined geometry, two new synthetic approaches have appeared one is based on the stereospecific coupling of a vinylmetal with a vinyl iodide[3,2(k)], the other is based on the stereospecific coupling of a vinyl halide with an acetylenic compound followed by reduction of the triple bond [2(f),4,5] Thus, retrosynthetic analysis (scheme 1) reveals that the hydroxy halogenodiene **A** and the acetylenic ester **B** are convenient building blocks for LTB4 construction[4]



Scheme 1

We describe herein a high yield coupling reaction of a chiral hydroxy (E,E)-iododiene with a racemic acetylenic alcohol, an efficient reduction of a dienyne into the desired (Z,E,E) system by using activated zinc and an easy separation of the thus formed diastereomers

Iododiene **9**, bearing the chiral C-12 of LTB4 was prepared from (R)-glycidol as illustrated in scheme 2

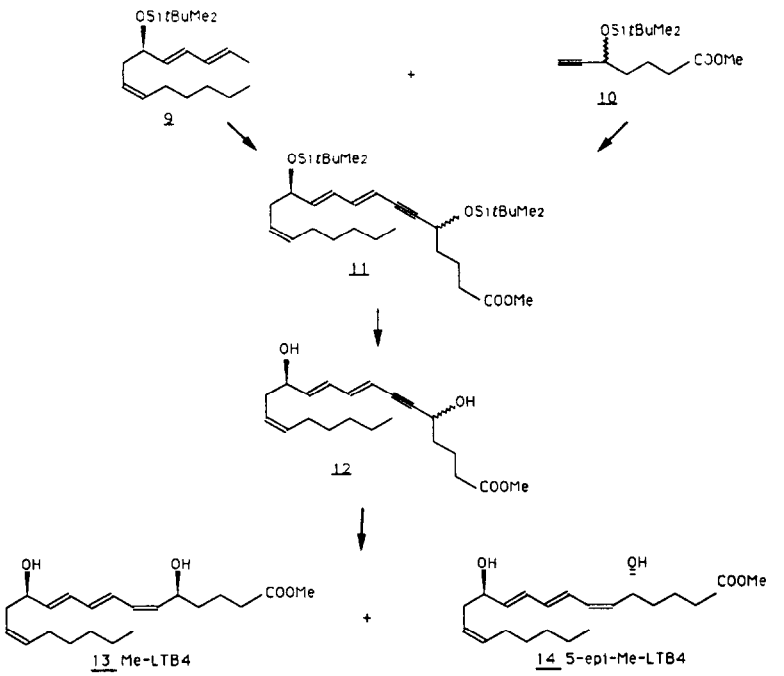


Scheme 2

The chiral epoxide **2b** was opened by heptyne anion in the presence of boron trifluoride etherate[6,2(f)] giving homopropargylic alcohol **3** which was then hydrogenated over Lindlar catalyst Benzoylation of the secondary alcohol **4a** and deprotection of the primary alcohol of compound **4b** with ethane thiol and aluminium chloride[7] gave compound **5** in 83% yield The classic method consisting of debenzoylation by hydrogenation on palladied charcoal was not possible because of the presence of the C4-C5 double bond

Swern oxidation[8] of alcohol **5** followed by reaction of **6** with (trimethylsilyl)propargylidene triphenyl phosphonium bromide[9] gave **7** (70%) as a mixture of E and Z isomers Desilylation gave the benzoates **8a** (E Z=73 27) in 80% yield, and the E and Z isomers were separated by H P L C

Saponification of **8a** (E) gave the enyne **8b**, and the secondary alcohol was protected by a tert-butyldimethylsilane group, in order to realize the hydrozirconation step The silylated enyne **8c** was hydrozirconated at +30°C with the Schwartz reagent (2 eq) under argon in darkness[10] The intermediate, not isolated, led by iodolysis to the unstable iododiene **9** (70%) which was immediately used



Scheme 3

Treatment of iododiene **9** with racemic methyl-5-(t-butyl)dimethylsilyloxy-6-heptynoate[2f] **10** (2 eq) under palladium-copper catalysis, gave the pure dienyne **11** in 73% yield

The iododiene **9** was more reactive than the corresponding chlorodiene which gave a 33% yield after coupling with the same propargyl alcohol[4]

Desilylation of the dienyne **11** with tetrabutylammonium fluoride (10 eq) in tetrahydrofuran, followed by re-esterification of the carboxylic acid formed with diazomethane, gave the dienyne **12** which was shown to be homogeneous on thin layer chromatography

Stereoselective reduction of dienyne **12** was performed in 70% yield by using Cu/Ag activated zinc dust in methanol-water[11] (1 1) The two (Z,E,E) diols **13** and **14** were easily separated by flash chromatography using methylene chloride/ethylacetate (6 4) as eluent (Scheme 3)

(+)-LTB4 methylester **13** was identical (H P L C, U V) with a sample supplied by Dr J Rokach[12] The compound **14** was the (5R, 12R)-LTB4 methylester

300 MHz proton NMR spectra of **13** and **14** were in good agreement with literature data[13] Coupling constants ($J_{6,7}$=11Hz, $J_{8,9}$=14 5Hz, $J_{10,11}$=15Hz) confirmed the trienic system geometry (E,E,Z) U V spectra showed charateristic bands at 259, 269 and 280 nm

The LTB4 methylester and the 5-epimer were differentiated by their αD values, respectively +4 6 (c 0 39, CCl_4) and -6 52 (c 0 46, CCl_4)

The strategy described enables leukotriene B4 and its 5-epimer to be synthesized from easily obtainable chiral source, (R)-glycidol

EXPERIMENTAL

^{1}-H-N M R spectra were recorded on Brucker AM 300 WB and Brucker VM 250 instruments The following abbreviations are used for spin multiplicity s= singlet, d= doublet, dd= doublet of doublets, t= triplet and m= multiplet

Mass spectra were determined on a Nermag R 10/10 instrument in the NH_3 chemical ionisation mode

Optical rotations were measured on a Perkin Elmer Model 241 polarimeter at room temperature

I R spectra were recorded on a Perkin Elmer Model 1600 FTIR spectrophotometer and are reported in wave numbers (cm^{-1})

Analytical T L C was performed on 0 25 mm pre-coated silica gel plates purchased from E Merck

Products were purified using the flash chromatography techrique on Kieselgel 60 (230-400 mesh ASTM, 0 040-0 063 mm) purchased from E.Merck

Commercial grade reagents and solvents were used as supplied with the following exceptions

Methylene chloride distilled over phosphorus pentoxide, toluene and hexane over calcium hydride, ether and tetrahydrofuran over sodium- benzophenone ketyl, dimethylsulfoxide, pyridine, triethylamine and hexamethyl phosphoric triamide over calcium hydride

Reactions sensitive to oxygen or moisture was conducted under an argon atmosphere

Elemental analyses were obtained from the "Service Central de Microanalyse du Centre National de la Recherche Scientifique" (Vernaison)

(2R)-1- benzyloxy dec-4- yn-2- ol **3**

To a 1-heptyne solution (2 2 ml, 16 5 mmol) in anhydrous tetrahydrofuran (40 ml) cooled to -78°C under inert atmosphere, were successively added dropwise i) n-butyllithium 1 6 M solution in hexane (10 ml, 16 5 mmol), ii) after 20 min, freshly distilled boron trifluoride etherate (2 ml, 16 5 mmol), iii) 20 min later, the chiral epoxide **2b** (1 7 g, 10 3 mmol) diluted in anhydrous tetrahydrofuran (5ml) Stirring was continued for 3 h at -78°C The reaction was then quenched by addition of a sodium bicarbonate aqueous solution After extraction with diethylether (3 times) the organic layer was dried over anhydrous magnesium sulfate and concentrated to give the crude alcohol **3**. Purification of **3** was achieved by flash chromatography, elution with hexane-ethylacetate 8 2 to give the pure compound **3** (2 19g, 82%)

$[\alpha]_D^{20}$=-12° (c 3 48, CCl_4), IR(NaCl) 3450(OH), 2150(C≡C) cm^{-1}, ^{1}H-NMR(250MHz, $CDCl_3$)(δ ppm) 7 32 (5H, m) C_6H_5, 4 57 (2H, s) CH_2Ph, 3 92 (1H, t, $J_{2,1}=J_{2,1'}$=4Hz) H_2, 3 6 (1H, dd, $J_{1,1'}$=10,3Hz, $J_{1,2}$=4Hz) H_1, 3 49 (1H, dd) $H_{1'}$, 2 42 (2H, m) H_3, 2 13 (2H, m) H_6, 1 65-1 21 (6H, m) aliphatics H, 0 89 (3H, t, $J_{10,9}$=7Hz) CH_3-10, Anal.Calc for $C_{17}H_{24}O_2$ C 78 42, H 9 29 Found C 78 59, H 9 50

(2R, 4Z)-1- benzyloxy dec-4-en-2- ol **4a**

Lindlar's catalyst, prepared according to the literature data[14], (500 mg) in anhydrous benzene (40 ml) was stirred under hydrogen until catalyst was entirely hydrogenated A solution of

compound **3** (2 1g, 8 mmol) in anhydrous benzene (10ml) was then added The reaction mixture was stirred vigorously at room temperature until one equivalent of hydrogen has been absorbed After dilution in diethylether, the catalyst was removed by filtration through magnesium sulfate The solvent was evaporated, filtration of the crude product through silica gel (elution with hexane-ethylacetate 8 2) gave the alcohol **4a** (2 11 g, 100%)
$[\alpha]_D^{20}$=-2° (c 3 46, CCl_4), IR(NaCl) 3450(OH), 3000(=CH) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 7 35 (5H, m) C_6H_5, 5 5 (1H, dt, $J_{4,5}$=11 3Hz, $J_{4,3}$=7 4Hz) H_4, 5 39 (1H, dt, $J_{5,6}$=6 5Hz) H_5, 4 55 (2H, m) CH_2-Ph, 3 85 (1H, m) H_2, 3 6 (1H, dd, $J_{1,1'}$=10 3Hz, $J_{1,2}$=4Hz) H_1, 3 39 (1H, dd, $J_{1',2}$=4Hz) $H_{1'}$, 2 52 (2H, m) CH_2-3, 2 01 (2H, m) CH_2-6, 1 42-1 21 (6H, m) aliphatics H, 0 89 (3H, t, $J_{10,9}$=7Hz) CH_3-10 ,Anal.Calc for $C_{17}H_{26}O_2$ C 77 65, H 9 99 Found C 77 74, H 9 97

(2R, 4Z)-1-benzyloxy-2-benzoyloxy dec-4-ene **4b**

Benzoyl chloride (1 2 ml, 10mmol) was added dropwise to a stirred solution of compound **4a** (2 2g, 8 4 mmol) in dry pyridine at 0°C After 2 h, ice was added and the mixture, dissolved in diethylether was successively extracted with 10% aqueous HCl, water and brine, dried through anhydrous magnesium sulfate Evaporation of the solvent and flash chromatography (elution with hexane-diethylether 9 1) gave **4b** (2 9 g, 94%)
$[\alpha]_D^{20}$=+1° (c 4 0, CCl_4), IR(NaCl) 1710(C=O), 1250(O-C=O) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 8 07 (2H, m) Ho benzoate, 7 62-7 15 (8H, m) C_6H_5, Hm,Hp of benzoate, 5 51 (1H, dt, $J_{5,4}$=11 3Hz, $J_{5,6}$=7 1Hz) H_5, 5 41 (1H, m) H_4, 5 31 (1H, q, $J_{2,1}$=$J_{2,3}$=5Hz) H_2, 4 55 (2H, m) CH_2-Ph, 3 65 (2H, m) CH_2-1, 2 52 (2H, t, $J_{3,4}$=$J_{3,2}$=7 5Hz) CH_2-3, 2 04 (2H, m) CH_2-6, 1 45-1 17 (6H, m) aliphatics H, 0 89 (3H, t, $J_{10,9}$=7Hz) CH_3-10

(2R, 4Z)-2- benzoyloxy dec-4-en-1-ol **5**

To a solution of **4b** (2 7 g, 7 4 mmol) in methylene chloride, ethane thiol (12 6 ml, 170 mmol) was added dropwise at -30°C and aluminium chloride (2 95 g, 22 mmol) was then introduced After stirring for 30 min, 125 ml of diethyl ether were added and the organic layer was washed with aqueous saturated sodium carbonate solution The organic layer was washed with aqueous saturated ammonium chloride solution, water, brine, dried through anhydrous magnesium sulfate and concentrated to give crude alcohol **5** , purification was achieved by flash chromatography (elution with hexane-ethylacetate 85 15) to give **5** (1 7 g, 83%)
$[\alpha]_D^{20}$=+4° (c 1 3, CCl_4), IR(NaCl) 3600-3400(OH), 1720(C=O), 1250(O-C=O) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 8 05-7 30 (5H, m) benzoate, 5 53 (1H, dt, $J_{5,4}$=11 3Hz, $J_{5,6}$=7 2Hz) H_5, 5 42 (1H, dt, $J_{4,3}$=7 2Hz) H_4, 5 17 (1H, qd, $J_{2,3'}$=3 6Hz, $J_{2,3}$=6 2Hz, $J_{2,1}$=$J_{2,1'}$=6 2Hz) H_2, 3 86 (1H, ddd, $J_{1,1'}$=12Hz, $J_{1,OH}$=6 6Hz) H_1, 3 79 (1H, ddd, $J_{1',OH}$=6 6Hz) $H_{1'}$, 2 51 (2H, m) CH_2-3, 2 07 (2H, dt, $J_{6,5}$=$J_{6,7}$=7 2 Hz) H_6, 2 01 (1H, dd) OH, 1 4-1 2 (6H, m) aliphatics H, 0 86 (3H, t, $J_{10,9}$=6 6Hz) CH_3-10

(2R,4Z)-2- benzoyloxy dec-4-en-1-al **6**

To a solution of dimethylsulfoxide (0 18 ml, 2 56 mmol) in dry methylene chloride (5ml) at -65°C, was added a solution of oxalyl chloride (0 17 ml, 1 9 mmol) in methylene chloride (0 7 ml) After 15 min , compound **5** (354 mg, 1 28 mmol) in dry methylene chloride (5 ml) was slowly introduced The resulting suspension was stirred for 30 min and then, triethylamine (0 5 ml, 3 7 mmol) was added dropwise The mixture was allowed to warm up to room temperature and diluted with diethylether The organic phase was washed with 1 N HCl, brine, and dried over anhydrous magnesium sulfate and concentrated to yield **6** which was used without purification
$[\alpha]_D^{20}$=+32° (c 1 50, CCl_4), IR(NaCl) 1720(C=O), 1260(O-C=O) cm^{-1}, ^{1}H NMR(300MHz, $CDCl_3$) (δ ppm) 8 58(1H, s) CHO, 8 03 (2H, m) H_o of benzoate, 7 62-7 09 (3H, m) H_m, H_p of benzoate, 5 55 (1H, dt, $J_{5,4}$=10Hz, $J_{5,6}$=$J_{5,6'}$=7 5Hz) H_5, 5 45 (1H, dt, $J_{4,3}$=$J_{4,3'}$=6 3Hz) H_4, 5 25 (1H, t, $J_{3,2}$=$J_{3',2}$=6 3Hz) H_2, 2 70 (2H, dd) H_3, 2 07 (2H, m) H_6, 1 93-1 22 (6H, m) aliphatics H, 0 86 (3H, t, $J_{10,9}$=7Hz) CH_3-10

(3E, 5R, 7Z)-5-benzoyloxy-1- trimethylsilyl trideca-3, 7-dien-1- yne **7**

To a stirred solution of ((trimethylsilyl) propargylidene) triphenyl phosphonium bromide (870 mg, 1 92 mmol) in dry tetrahydrofuran (6 ml) cooled to -78°C under argon, was added, dropwise a solution of a 1 6 M n-butyllithium in hexane (1 2 ml, 1 9 mmol) The resulting solution was stirred at -40°C for 30 min and was cooled to -78°C Aldehyde **6** (364 mg, 1 28 mmol) in dry tetrahydrofuran (2 ml) was added dropwise After 1 h at 0°C, the reaction was quenched by addition of an ammonium chloride aqueous solution The solution was then extracted with diethylether (3 times) and the organic layer dried over anhydrous magnesium sulfate The triphenyl phosphine oxide was precipitated in diethylether and removed by filtration The crude extract was chromatographied on silica gel (elution with methylene chloride) to afford compound **7** (330 mg, 70%)
IR(NaCl), 2150(C≡C), 840 and 760(Si-C) cm^{-1}

(3E, 5R, 7Z)-5-benzoyloxy trideca-3, 7-dien-1-yne **8a**

To a solution of the silylated enyne **7** (243 mg, 0 65 mmol) in dry tetrahydrofuran at 0°C, was added dropwise 1M tetrabutylammonium fluoride in tetrahydrofuran (0 85 ml, 0 85 mmol) After stirring at 0°C for 3 h, 2 ml of water were added and the reaction mixture was extracted with diethylether The organic phase was then washed with brine, dried over magnesium sulfate and concentrated to give crude enyne **8a**. Good separation of the E compound **8a** (130 mg, 67%) from its Z isomer (40 mg, 21%) was obtained by preparative liquid chromatography on silica gel (elution with hexane-ether 95 5) and U V detection

E-Isomer IR(NaCl), 3290(≡C-H), 2090(C≡C), 1725(C=O of benzoate), 965(C=C E) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 8 05-7 3 (5H of benzoate), 6 27 (1H, ddd, $J_{4,3}$=16Hz, $J_{4,5}$=5 5Hz, $J_{4,1}$=0 5Hz) H_4, 5 76 (1H, ddd, $J_{3,1}$=2 2Hz, $J_{3,5}$=1 4Hz) H_3, 5 55 (1H, m) H_5, 5 51 (1H, dt, $J_{8,7}$=11 3Hz, $J_{8,9}$=7 2Hz) H_8, 5 4 (1H, dt, $J_{7,6}$=7 2 Hz) H_7, 2 91 (1H, d) H_1, 2 53 (2H, m) H_6, 2 03(2H, dt, $J_{9,8}$=$J_{9,10}$=7 2Hz) CH_2-9, 1 34-1 22 (6H, m) aliphatics H, 0 86 (3H, t, $J_{13,12}$=6 6Hz) CH_3-13

Z-Isomer IR(NaCl) 3300(≡C-H), 2090(C≡C), 1725(C=O of benzoate), 760(C=C Z) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 8 05-7 3 (5H of benzoate), 6 06 (1H, ddd, $J_{4,3}$=10 73Hz, $J_{4,5}$=8 25Hz, $J_{4,1}$=0 85Hz) H_4, 5 98 (1H, m) H_5, 5 64 (1H, ddd, $J_{3,1}$=2 3Hz, $J_{3,5}$=0 5Hz) H_3, 5 51 (1H, dt, $J_{8,7}$=11 3Hz, $J_{8,9}$=7 2Hz) H_8, 5 45 (1H, dt, $J_{7,6}$=7Hz) H_7, 3 21 (1H, d) H_1, 2 58 (2H, m) H_6, 2 04 (2H, dt, $J_{9,8}$=$J_{9,10}$=7 2Hz) H_9, 1 4-1 2 (6H, m) aliphatics H, 0 86 (3H, t, $J_{13,12}$=6 6Hz) CH_3-13

(3E, 5R, 7Z) trideca-3, 7-dien-1-yn-5-ol **8b**

To a solution of compound **8a** (129 mg, 0 43 mmol) in dry methanol (0 5 ml) was added 1M sodium methanolate in methanol (0 1 ml) After stirring overnight at room temperature, Amberlite IR 120(H^+) was added until neutralisation After filtration, the crude deprotected product was purified by flash chromatography (elution with hexane-ethylacetate 9 1) to afford the compound **8b** (75 mg, 94%)

IR(NaCl), 3500-3300(OH), 3300(≡C-H), 2100(C≡C), 960(C=C E) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 6 26 (1H, ddd, $J_{4,3}$=16Hz, $J_{4,5}$=5 5Hz, $J_{4,1}$=0 5Hz) H_4, 5 72 (1H, ddd, $J_{3,1}$=2 2Hz, $J_{3,5}$=1 5Hz) H_3, 5 59 (1H, dt, $J_{8,7}$=11 3Hz, $J_{8,9}$=7 2Hz) H_8, 5 36 (1H, dt, $J_{7,6}$=7 2Hz) H_7, 4 21 (1H, m) H_5, 2 88 (1H, d) H_1, 2 32 (2H, dd, $J_{6,5}$=$J_{6,7}$=7Hz) H_6, 2 03 (2H, dt, $J_{9,8}$=$J_{9,10}$=7 2Hz) H_9, 1 65 (1H, m) OH, 1 37-1 17 (6H, m) aliphatics H, 0 88 (3H, t, $J_{13,12}$=6 6Hz) CH_3-13

(3E, 5R, 7Z)-5-tert-butyldimethylsilyloxy trideca-3,7-dien-1-yne **8c**

A mixture of the acetylenic alcohol **8b** (75 mg, 0 4 mmol) , tert-butyldimethylchlorosilane (74 mg, 0 5 mmol) and imidazole (75 mg, 1 1 mmol) in dry dimethylformamide (0 5 ml) was stirred at room temperature overnight, then diluted with hexane and extracted with water The aqueous phase was extracted 3 times with hexane The organic phase was dried over magnesium sulfate and evaporated to give, after filtration through silica gel, (elution with hexane-methylene chloride 8 2) the pure silylether **8c** (120 mg, 99%)

IR(NaCl) 3300(≡C-H), 2100(C≡C), 840 and 760(Si-C) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 6 24 (1H, ddd, $J_{4,3}$=16Hz, $J_{4,5}$=5 5Hz, $J_{4,1}$=0 5Hz) H_4, 5 65 (1H, ddd, $J_{3,1}$=2 2Hz, $J_{3,5}$=1 5Hz) H_3, 5 46 (1H, dt, $J_{8,7}$=11 3Hz, $J_{8,9}$=7 2Hz) H_8, 5 34 (1H, dt, $J_{7,6}$=7 2Hz) H_7, 4 17 (1H, m) H_5, 2 85 (1H, d) H_1, 2 25 (2H, m) H_6, 2 0 (2H, dt, $J_{9,8}$=$J_{9,10}$=7Hz) H_9, 1 35-1 2 (6H, m) aliphatics H, 0 88 (3H, t, $J_{13,12}$=6 6Hz) CH_3-13

(1E, 3E, 7Z)-5-tert-butyldimethylsilyloxy-1-iodo trideca- 1, 3, 7-triene **9** To a solution of **8c** (60 mg, 0 2 mmol) in 5 ml of anhydrous benzene-tetrahydrofuran (1 1) stirred at +35°C under inert atmosphere, was added one equivalent of Schwartz reagent (zirconocene chloride hydride) (38 mg, 0 2 mmol) After stirring for 15 min , the resulting solution became clear, and a second equivalent of reagent was then added (38 mg) After 15 min , cristallized iodine was added until a brown color persistence The reaction mixture was very quickly diluted with hexane and filtered over florisil The solvent was removed to give a crude product immediately purified by flash chromatography (elution with hexane) to afford **9** (60 mg, 70%)

IR(NaCl), 3080(=CH), 1595(C=C-C=C), 960(C=C E), 840 and 760(Si-C) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 7 00 (1H, dd, $J_{2,1}$=14 5Hz, $J_{2,3}$=10 5Hz) H_2, 6 26 (1H, d) H_1, 6 09 (1H, dd, $J_{3,4}$=15Hz) H_3, 5 7 (1H, dd, $J_{4,5}$=6Hz) H_4, 5 45 (1H, dtt, $J_{8,7}$=10 5Hz, $J_{8,9}$=7Hz, $J_{8,6}$=1 5Hz) H_8, 5 34 (1H, dtt, $J_{7,6}$=7Hz, $J_{7,9}$=1 5Hz) H_7, 4 12 (1H, m) H_5, 2 25 (2H, dt, $J_{6,5}$=$J_{6,7}$=7Hz) H_6, 1 98 (2H, dt, $J_{9,10}$=$J_{9,8}$=7Hz) H_9, 1 35-1 28 (6H, m) aliphatics H, 0 89 (12H, m, $J_{13,12}$=7Hz) CH_3-13 and $(CH_3)_3$-C, 0 04 (3H, s) CH_3-Si, 0 025 (3H, s) CH_3-Si

(8E, 10E, 12R, 14Z)-5, 12-tert-butyldimethylsilyloxy eicosa-8, 10, 14 -trien-6-methyl ynoate **11**

To a solution of iododiene **9** (60 mg, 0 19 mmol) in anhydrous benzene (1 5 ml) stirred under inert atmosphere at room temperature, was added tetrakis (triphenylphosphine) palladium (11 mg, 0 0095 mmol) After stirring for 30 min, n-butylamine (0 19 ml, 1 9 mmol), and copper iodide (4 mg, 0 019 mmol) were added Then, a solution of racemic compound **10** (103 mg, 0 38 mmol) in anhydrous benzene was added with a double-tipped needle over a period of 30 min The mixture was held at room temperature overnight, then diluted with diethylether, hydrolyzed with a saturated ammonium chloride aqueous solution (0 5 ml) The aqueous layer was extracted with diethylether and the combined organic layers were dried over anhydrous magnesium sulfate The crude extract obtained after concentration was purified by flash chromatography (elution with hexane-diethylether 95 5) to afford compound **11** (71 mg, 73%) which was immediately deprotected

(8E, 10E, 12R, 14Z)-5, 12-dihydroxy eicosa-8, 10, 14-trien-6-methyl ynoate **12**

1M tetrabutylammonium fluoride in tetrahydrofuran (1 2 ml, 1 2 mmol) was added to a solution of the t-butyldimethylsilyl ether of **11** (70 mg, 0 12 mmol) in anhydrous tetrahydrofuran (3 ml) After stirring for 2 h at room temperature, the mixture was hydrolyzed and extracted with diethylether An excess of diazomethane in diethylether was then added leading to the re-esterification of the carboxylic function After evaporation, the crude deprotected ester was purified by flash chromatography (elution with cyclohexane-ethylacetate 6 4) to give quantitatively the dienyne **12** (42 mg, 0 12 mmol)
IR(NaCl). 3400(OH), 3000(=CH), 2200(C≡C), 1730(C=O) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 6 56 (1H, dd, $J_{9,8}$=15 5Hz, $J_{9,10}$=10 5Hz) H_9, 6 27 (1H, dd, $J_{10,11}$=15 5Hz) H_{10}, 5 82 (1H, dd, $J_{11,12}$=6Hz) H_{11}, 5 6 (1H, dd, $J_{8,5}$=2Hz) H_8, 5 58 (1H, dtt, $J_{15,14}$=10 5Hz, $J_{15,16}$=7Hz, $J_{15,13}$=1 5Hz) H_{15}, 5 36 (1H, dtt, $J_{14,13}$=7Hz, $J_{14,16}$=1 5Hz) H_{14}, 4 52 (1H, m) H_5, 4 22 (1H, dt, $J_{12,13}$=$J_{12,11}$=6Hz) H_{12}, 3 67 (3H, s) -OCH_3, 2 34 (2H, m) H_{13}, 2 29 (2H, m) H_4, 2 03 (2H, dt, $J_{16,15}$=$J_{16,17}$=6Hz) H_{16}, 1 79-1 72 (5H, m) aliphatics H and OH, 1 4-1 26 (7H, m) aliphatics H and OH, 0 86 (3H, t, $J_{20,19}$=6 5Hz) CH_3-20

(5S, 6Z, 8E, 10E, 12R, 14Z)-5, 12-dihydroxy eicosa-6, 8, 10, 14-methyl tetraenoate **13**

Zinc dust was activated as previously described[11] The dienyne **12** (42 mg, 0 12 mmol) was reduced by zinc suspension in 1 ml of methanol-water (1 1) overnight at room temperature (25-30°C) After dilution with methanol, the residue was filtered on Celite 545 and coevaporated with toluene

The two diastereomers were separated by flash chromatography (elution methylene chloride-ethylacetate 65 35) The 5-epi-LTB4 methyl ester **14** (Rf 0 46) was first eluted (15 mg, 35%) followed by the LTB4 methyl ester **13** (Rf 0 37) (15 mg, 35%)
Compounds **13** and **14**
IR(NaCl) 3400(OH), 3000(C=H), 1730(C=O, 1595(C=C-C=C) cm^{-1}, ^{1}H-NMR(300MHz, $CDCl_3$) (δ ppm) 6 47 (1H, dd, $J_{8,9}$=14 5Hz, $J_{8,7}$=11Hz) H_8, 6 3 (1H, ddd, $J_{10,11}$=15Hz, $J_{10,9}$=10 5Hz, $J_{10,12}$=1Hz) H_{10}, 6 21 (1H, dd) H_9, 6 07 (1H, t, $J_{7,8}$=$J_{7,6}$=11Hz) H_7, 5 77 (1H, dd, $J_{11,12}$=6 3Hz) H_{11}, 5 55 (1H, dtt, $J_{15,14}$=10 5Hz, $J_{15,16}$=7Hz, $J_{15,13}$=1 5Hz) H_{15}, 5 54 (1H, dd, $J_{6,5}$=9 5Hz) H_6, 5 34 (1H, dtt, $J_{14,15}$=10 5Hz, $J_{14,13}$=7Hz, $J_{14,16}$=1 5Hz) H_{14}, 4 57 (1H, dt, $J_{5,6}$=9 5Hz, $J_{5,4}$=6 5Hz) H_5, 4 2 (1H, dt, $J_{12,13}$=$J_{12,11}$=6 3Hz) H_{12}, 3 65 (3H, s) O-CH_3, 2 33 (4H, m) H_4 and H_{13}, 2 02 (2H, dt, $J_{16,15}$=$J_{16,17}$=6Hz) H_{16}, 1 72-1 60 (5H, m) aliphatics H and OH, 1 36-1 21 (7H, m) aliphatics H and OH, 0 87 (3H, t, $J_{20,19}$=6 5Hz) CH_3-20
$[\alpha]_D^{20}$ of **13**= +4 6° (c 0 39, CCl_4)
$[\alpha]_D^{20}$ of **14**= -6 52° (c 0 46, CCl_4)

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