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A SHORT STEREOCONTROLLED SYNTHESIS OF LEUKOTRIENE B_4

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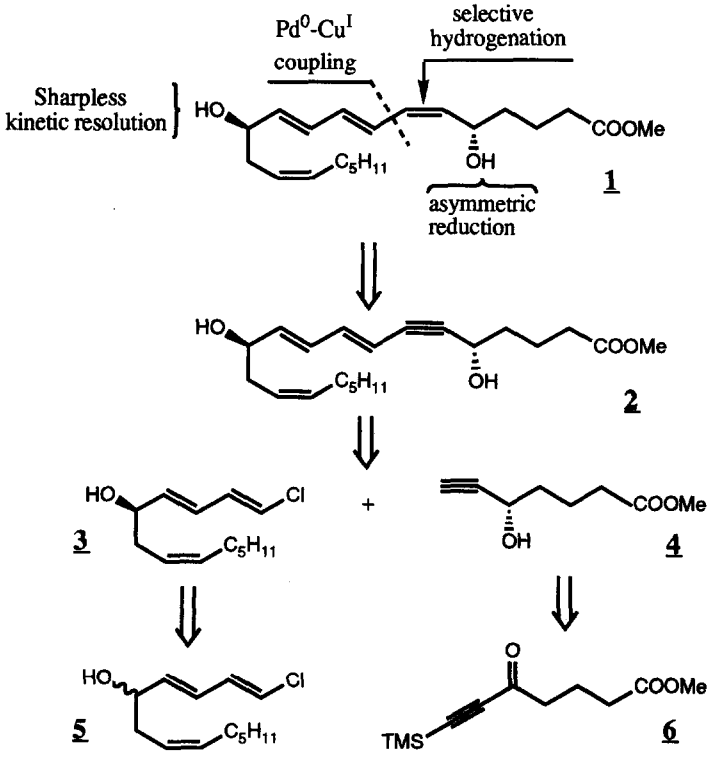
Abstract : A short convergent total synthesis of LTB_4 **1** is accomplished by an efficient palladium-catalyzed coupling reaction of two easily accessible chiral synthons **3** and **4**.

Leukotriene B_4 (LTB_4) is an important metabolite of the arachidonic acid formed via the 5-lipoxygenase pathway[1]. It has been shown to be one of the most potent inducers of chemotaxis, chemikinesis, aggregation and degranulation of leukocytes. In recent years, for further evaluation of its biological properties, several total syntheses have been reported[2]. We report herein a short synthesis of **1** from two easily prepared chiral synthons **3** and **4**. A retrosynthetic analysis is shown in scheme A.



Scheme A

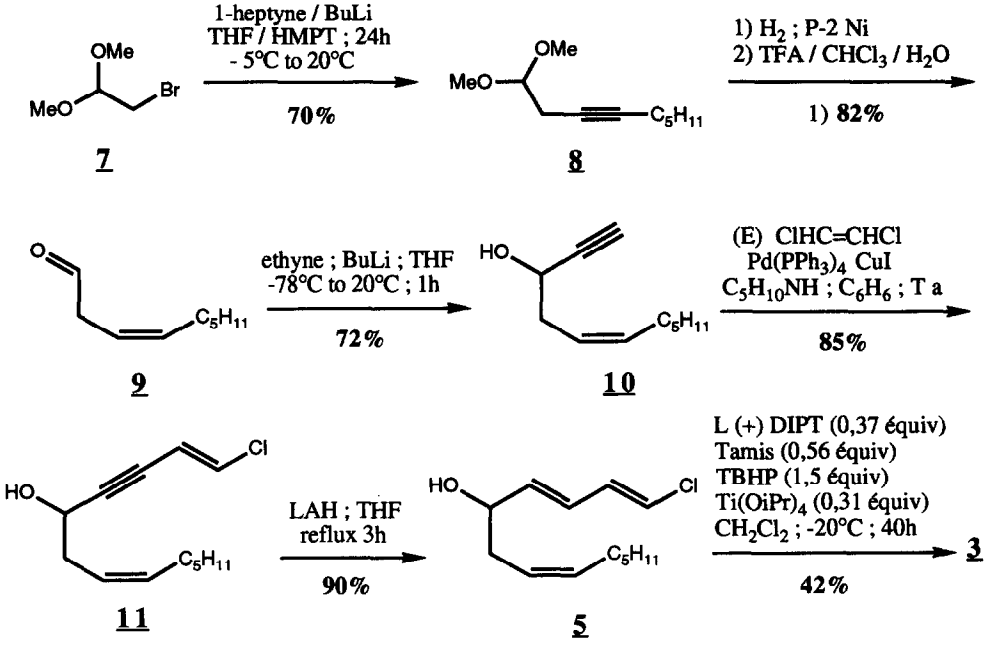
The most characteristic features of this strategy are :

i) the efficient stereospecific coupling reaction of the chlorodiene **3** with the propargyl alcohol **4**, followed by reduction of the triple bond which gives the (Z,E,E) conjugated triene system.

ii) the easy access to the chiral synthons **3** and **4** in high enantiomeric purity. A Sharpless kinetic resolution[3] of the racemic alcohol **5** gives **3**, an enantioselective reduction[4] of the propargyl ketone **6** gives **4**.

iii) the limited number of steps (eleven) of this synthesis which does not involve any protection-deprotection sequence of the alcohol functions.

The seven-step preparation of the chiral hydroxy chlorodiene **3** is presented in scheme B.

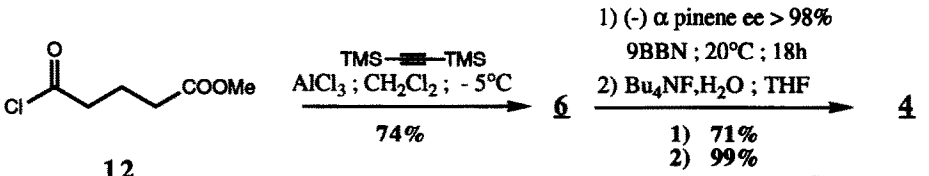


Scheme B

The reaction of hept-1-ynyl-lithium with bromoacetaldehyde dimethyl acetal **7** gave the acetal **8** in 70 % yield. Hydrogenation[5] in the presence of nickel P-2 afforded (3 Z) non-3-enal dimethylacetal in 82 % yield. Hydrolysis with trifluoroacetic acid (1 h) in chloroform-water (2:1) followed by ethynylation with lithium acetylide at -78°C (THF, 1h30) afforded (5 Z)-undec-5-en-1-yn-3-ol **10** in 68 % yield[6].

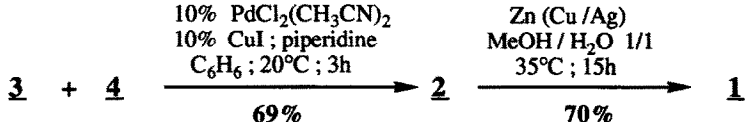
The propargyl alcohol **10** was coupled with (E)-1-2-dichloroethene in the presence of palladium tetrakis (triphenylphosphine) and copper iodide[7] to give (85 %) the enynol **11** which then was reduced by lithium aluminium hydride into the hydroxychlorodiene **5** in 90 % yield. Sharpless kinetic resolution of -dl- **5** using t-butylhydroperoxyde, titanium IV isopropoxide and L(+) diisopropyl tartrate afforded **3** (96 % ee) in 42 % yield.

The preparation[4] of the chiral synthon **4** is shown in scheme C.



Scheme C

Bis(trimethylsilyl) acetylene was reacted with **12** in the presence of aluminium chloride at -5°C to form the corresponding propargyl ketone **6** in 74 % yield. Asymetric reduction with Alpineborane, prepared from (-) α pinene (98 % ee) and 9-BBN, gave the corresponding alcohol in 71 % yield which was then desilylated to furnish the (S)-propargyl alcohol **4** (96 % ee) in 99 % yield.



Scheme D

Finally, coupling of the chiral hydroxy chlorodiene **3** with the propargyl alcohol **4** in piperidine in the presence of bis(acetonitrile) palladium chloride and copper iodide[8] gave the dienyne **2** which was reduced into leucotriene B_4 methyl ester **1** by activated zinc[9].(scheme D). The ester **1** was characterized by its spectroscopic properties[10] and by comparison with an authentic sample supplied by Dr J.Rokach [11].

In conclusion, a short synthesis of leukotriene B_4 has been realized by coupling two easily obtainable chiral synthons: a chlorovinyl alcohol **3** and a propargyl alcohol **4**. This strategy appears to be an efficient route to chiral trienols with a defined geometry.

EXPERIMENTAL

^1H NMR spectra were recorded on Brucker VM 250 instrument.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 599 spectrophotometer and are reported in wave numbers(cm^{-1}).
Analytical T.C.L.was performed on 0.25 mm precoated silica gel plates purchased from E.Merck.
Products were purified using the flash chromatography technique 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 dichloride,piperidine triethylamine, benzene and hexamethyl phosphoric triamide distilled over CaH_2; pentane over P_2O_5; ether and tetrahydrofuran over sodium-benzophenone ketyl.
Reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Non-3-ynal dimethyl acetal 8

To a stirred solution of hept-1-yne (11.73 g, 122 mmol) in THF (120 ml) at -5°C is added dropwise a solution of n-butyllithium (1.5 M in hexane, 90 ml, 134 mmol). After stirring for 1h, a solution of bromoacetaldehyde dimethyl acetal **7** (20g, 118 mmol) in HMPT (40 ml) is added to the mixture at -5°C. After 2h, the temperature is raised to 20°C and stirring is continued for 18h. After cooling to 5°C, water (200 ml) is added and the mixture is extracted with pentane. The organic phase is washed with water (2x50 ml), dried ($MgSO_4$) and concentrated. The crude product is distilled : bp 80°C (0.7 mm) ; yield, 15g, 69 %.
IR (neat) : ν = 2225, 1380, 1350, 1130, 1070 cm^{-1}.
^1H NMR ($CDCl_3$/TMS) : $\delta = H_1$ (4.50,t,J=6Hz) ; CH_3O (3.38,s) ; H_2 (2.50,dt,J=6Hz,J=2.5Hz), H_5 (2.22 to.2.08,m) ; H_6 to H_8 (1.62 to 1.22,m) ; H_9 (0.90,t,J=5Hz).
^{13}C NMR ($CDCl_3$) : δ = 102.7 (C_1) ; 81.8 ; 74.4 (C_3,C_4) ; 53.0 (CH_3O) ; 30.8 (C_7) ; 28.4 (C_6) ; 23.7 (C_2) ; 22.0 (C_8) ; 18.5 (C_5) ; 13.7 (C_9).
Anal. calcd. for $C_{11}H_{20}O_2$: C 71.69 ; H 10.94. Found : C 71.6 ; H 10.98.

(3Z) non-3-enal 9

- (3Z) non-3-enal dimethylacetal

Nickel acetate tetrahydrate (0.25 g, 1 mmol) is dissolved in 10 ml of 95 % ethanol under inert atmosphere in a closed system, connected to a gas burette. With vigorous stirring, sodium borohydride (0.038 g, 1 mmol) is rapidly added. The flask is purged with hydrogen and when the gas evolution ceased, the active catalyst is poisoned by 1-2-diamino ethane (0.12 g, 2 mmol) and the acetal **8** (1.47 g, 8 mmol) is injected. When the theorical volum of hydrogen has been adsorbed, the black mixture is filtered over a short plug of Celite and the Celite is rinsed with methylene dichloride. The organic layer is washed with brine, dried ($MgSO_4$), concentrated and subjected to flash column chromatography (silica gel, ether/pentane 10/90) furnishing (3Z) non-3-enal dimethylacetal (1.22 g, yield 82 %).
IR (neat) : ν = 2930, 2820, 1650, 1460, 1360, 1075, 730 cm^{-1}.
^1H NMR ($CDCl_3$/TMS) : $\delta = H_3$,H_4 (5.57 to 5.28, m) ; H_1 (4.37,t,J=5.8Hz) ; CH_3O (3.32,s) ; H_2 (2.37,td,J=5.8Hz,J=0.8Hz) ; H_5 (2.03,q,J=6.8Hz) ; H_6 to H_8 (1.40 to 1.23,m) ; H_9 (0.88,t,J=6.6Hz).
^{13}C NMR ($CDCl_3$) : δ = 132.5 (C_3) ; 123.2 (C_4) ; 104.2 (C_1) ; 52.8 (OCH_3) ; 31.5 (C_2) ; 30.9 (C_7) ; 29.2 (C_6) ; 27.4 (C_5) ; 22.5 (C_8) ; 14.0 (C_9).
Anal. calcd. for $C_{11}H_{22}O_2$: C 70.92 ; H 11.90 ; 0 17.17. Found : C 70.81 ; H 11.93.

- (3Z) non-3-enal **9**

To a stirred solution of nonenal dimethylacetal (5.58, 30 mmol) in methane trichloride (200 ml), is added a solution (50 % in water) of trifluoroacetic acid. The reaction is monitored by gas chromatography. After

disappearance of the acetal, the mixture is diluted in methylene dichloride (200 ml) and a saturated solution of $NaHCO_3$ is added. The organic phase is washed with water (3x50 ml), dried on MgSO4. Concentration afforded non-3-enal **9** which is used immediately without purification for the next step.

(5Z)-undec-5-en-1-yn-3-ol 10

In a dry 1 L flask equipped with a magnetic stirring bar and septum-capped under Argon, THF (300 ml) is added. The flask is cooled in a dry ice-acetone bath and acetylene is bubbled in the flask at -78°C during 2h. n-Butyllithium (1.5 M in hexane, 35 ml, 55 mmol) is added over a 15 min. period. After 30 min., crude non-3-enal **9** (5.48 g) in THF (20 ml) is added over a 15 min period. The solution is stirred for 20 min at -78°C and then warmed to room temperature. After 1h, ice is added and the product is extracted with ether. The organic layer is washed with brine (3x100 ml), dried ($MgSO_4$) and evaporated to dryness. The crude product is purified by flash column chromatography (silica gel, methylene dichloride/cyclohexane 80/20) to afford the propargyl alcohol[6] **10** 3.38 g (72 %).

IR (neat) : ν = 3350, 3300, 2950, 2110, 1650, 1460, 1375, 1050, 660 cm^{-1}.

^1H NMR ($CDCl_3$/TMS) : δ = H_5,H_6 (5.70 to 5.36, 2m) ; H_3 (4.38,td,J=6.20Hz,J=2.1Hz) ; H_4 (2.48,td,J=7Hz,J=0.5Hz) ; H_1 (2.45,d,J=2.1Hz) ; OH (2.17,sl) ; H_7 (2.05,q,J=7Hz) ; H_8 to H_{10} (1.465 to 1.20,m) ; H_{11} (0.87,t,J=6.7Hz).

^{13}C NMR ($CDCl_3$) : δ = 133.8 (C_5) ; 123.3 (C_6) ; 84.7 (C_2) ; 72.8 (C_1) ; 61.6 (C_3) ; 35.4 (C_4) ; 31.4 (C_9) ; 29.2 (C_8) ; 27.4 (C_7) ; 22.5 (C_{10}) ; 13.9 (C_{11}).

MS : (m/z) = 184 [$(M+18)^+$] ; 166 (M^+) ; 95.

(1E,7Z)-1-chloro trideca-1-7-dien-3-yn-5-ol 11

To a solution of (E)-1-2-dichloro-ethene (4.35g, 45 mmol) in benzene (15 ml) , $Pd(PPh_3)_4$ (0.52g, 0.45 mmol) piperidine (1.53g, 18 mmol) and propargyl alcohol **9** (1.5g, 9 mmol) are added. After 15 min, the flask is cooled in water-ice bath and cuprous iodide (0.171g, 0.9 mmol) is introduced into the stirred solution (exothermic reaction). After 3h, the mixture is poured into a saturated solution of NH_4Cl and extracted with ether, the organic phase is washed with water, dried ($MgSO_4$) and concentrated. Flash column chromatography (Silica gel, Et_2O/pentane 20/80) gives pure enynol **11** (1.61 g) in 85 % yield.

IR (neat) : ν = 3600 to 3100, 2940, 2920, 1580, 1225, 1165, 1050, 910 cm^{-1}.

^1H NMR ($CDCl_3$/TMS) : δ = H_1 (6.55,d,J=13.6Hz) ; H_2 (5.95,dd,J=13.6Hz,J=1.9Hz) ; H_7,H_8 (5.70 to 5.36,2m) ; H5 (4.50,td,J=6.6Hz,J=1.90Hz) ; H_6 (2.50,t,J=6.75Hz) ; H_9 (2.06,q,J=6.70Hz) ; OH (2.01,s) ; H_{10} to H_{12} (1.45 to 1.20,m) ; H_{13} (0.89,t,J=6.6Hz).

^{13}C NMR ($CDCl_3$) : δ = 134.2 (C_7) ; 130.6 (C_1) ; 122.9 (C_8) ; 113.0 (C_2) ; 92.4 (C_3) ; 79.7 (C_4) ; 62.2 (C_5) ; 35.3 (C_6) ; 31.3 (C_{11}) ; 29.1 (C_{10}) ; 27.3 (C_9) ; 22.4 (C_{12}) ; 13.9 (C_{13}) ppm.

MS : (m/z) = 246, 244, 228, 226, 209.

Anal Calcd for $C_{13}H_{19}OCl$: C 68.86 ; H 8.45 ; Found : C 68.77 ; H 8.50.

(1E,3E,7Z)-1-chloro trideca-1-3-7-trien-5-ol 5

To a suspension of lithium aluminium hydride (0.565 g, 14.13 mmol) in THF (40 ml), a solution of enynol **11**(2g, 8.83 mmol) in THF (5 ml) is added at room temperature. The suspension is refluxed for 3h. The reaction is worked up by cooling in a ice-bath, adding consecutively water (0.565 g), 15 % sodium hydroxide solution (0.565 g) and water (1.7g) in that order and stirring until the formation of the filterable granular precipitate of aluminium hydroxide is complete. The precipitate is washed by Et_2O (3x40 ml). Concentration followed by flash column chromatography (silica gel, Et_2O/pentane 30/70) affords the racemic diene **5** (1.82 g) 90 % yield.

IR (neat) : ν = 3600 to 3100 ; 3015 ; 2920 ; 2850 ; 1700 ; 1650 ; 1585 ; 1470 ; 1380 ; 980 ; 830 cm^{-1}.

^1H NMR ($CDCl_3$/TMS) : δ = H_2 (6.45,dd,J=13.15Hz,J=10.75Hz) ; H_1 (6.20,d,J=13.15Hz) ; H_3 (6.20,ddd,J=15.20Hz,J=10.75Hz;J=1.25Hz) ; H_4 (5.74,dd,J=15.30Hz,J=1.25Hz) ; H_7,H_8 (5.65 to 5.25,2m) ; H_5 (4.20,qd,J=6.00Hz,J=1.20Hz) ; H_6 (2.32,t,J=6.70Hz) ; H_9 (2.04,q,J=6.7Hz) ; OH (1.76,sl) ; H_{10} to H_{12} (1.29,m) ; H_{13} (0.89,t,J=6.60Hz) ppm.

^{13}C NMR ($CDCl_3$) : δ = 136.3 (C_4) ; 133.5 (C_7) ; 132.8 (C_2) ; 125.9 (C_3) ; 123.8 (C_8) ; 120.8 (C_1) ; 71.4 (C_5) ; 35.0 (C_6) ; 31.3 (C_{11}) ; 29.1 (C_{10}) ; 27.3 (C_9) ; 22.4 (C_{12}) ; 13.9 (C_{13}) ppm.

MS (m/z) : 230 ; 228 ; 193.

Anal. calcd. for $C_{13}H_{21}OCl$: C 68.26 ; H 9.25. Found : C 68.19 ; H 9.35.

(1E,3E,5R,7Z)-1-chloro trideca-1-3-7-trien-5-ol 3

To a solution of chlorodiene **5** (0.868 g, 3.8 mmol) in methylene dichloride (6 ml) stored on 3 Å molecular sieves during 30 mn, 3 Å molecular sieves (0.458 g, 0.56 equiv) are added. The solution is cooled to -15°C, L(+) diisopropyl tartrate (0.333g, 1.42 mmol) and titanium tetraisopropylate (0.339 g, 1.19 mmol) are added. After 30 min, ter-butyl hydroperoxide (1.9 ml, 3M in -2-2-4-trimethyl pentane) is slowly introduced into the stirred solution at -20°C.

After 40h at -20°C the solution is warmed to 0°C, hydrolyzed with water (2.5 ml) and aqueous sodium hydroxide solution 30 % (2 ml) saturated by sodium chloride. The resulting mixture is vigorously stirred for 1h and filtered through a pad of Celite. The organic layer is separated, dried ($MgSO_4$) and concentrated in vacuo. The crude product is chromatographed on silica gel (ether/pentane 80/20) to afford the (R) alcohol 3^{2n} (96% ee, 0.360 g) in 42 % yield.

$[\alpha]_D^{20}$ + 5.97° (c = 1.00, CCl_4) .

Methyl -5-oxo-7-trimethylsilyl hept-6-ynoate 6

To a stirred suspension of finely powdered aluminium chloride (22g, 165 mmol) in methylene dichloride (140 ml) at -5°C is added a solution of methyl -4-chloroformyl butanoate **12** (17.2g, 104 ml) in methylene dichloride (30 ml). After 30 min, the suspension is transferred by cannula into a dropwise funnel and added to a solution of bis(trimethylsilyl) acetylene (18g, 105 mmol) in methylene dichloride (50 ml) at -10°C. After stirring for 3h, the resulting mixture is shaken vigorously with ice-cold diluted hydrochloric acid (0.1 M) to dissolve the

aluminium salts. The organic phase is separated and the aqueous layer is extracted with ether, dried on $MgSO_4$ and the solvent is removed under reduced pressure. Flash column chromatography (silica gel, ethyl acetate/methylene dichloride 20/80) gives pure **6** [2f] (17.48g) in 74 % yield.

IR (neat) : ν = 2960, 2900, 2160, 1750, 1680 cm^{-1}.

^1H NMR ($CDCl_3$/TMS) : δ = OCH_3 (3.68,s) ; H_2 (2.63,t,J=7.3Hz) ; H_4 (2.34,t,J=7.3Hz) ; H_3 (1.95,q,J=7.3Hz) ; $Si(CH_3)_3$ (0.23,s) ppm.

^{13}C NMR ($CDCl_3$) : δ = 186.3 (C_5) ; 173.0 (C1) ; 101.6 (C_6) ; 97.6 (C_7) ; 51.3 (OCH_3) ; 43.9 (C_4) ; 32.9 (C2) ; 18.6 (C_3) ; -0.3 ($Si(CH_3)_3$) ppm.

MS (m/z) : 227 [$(M+1)^+$] ; 244 [$(M+18)^+$].

Methyl (5S)-5-hydroxy-hept-6-ynoate 4

-Methyl (5S)-5-hydroxy-7-trimethylsilyl-hept-6-ynoate

In a round-bottom flask equipped with a septum-capped magnetic stirring bar, reflux condenser, 9-BBN (5.4g, 44 mmol), (-) α-pinene ee 98 % (6.6g, 48.6 mmol) are charged and the flask is heated in an oil bath to 65°C for 5h. The flask is cooled to 0°C and the keto-ester **6** (5g, 22.1 mmol) is added. The mixture is then stirred at room temperature for 18h. After cooling to 0°C, acetaldehyde (2.21 ml) is injected to destroy the excess reagent. Liberated α-pinene is pumped off at 60°C (0.07 mm) and the residue dissolved in 25 ml ether. The solution is cooled to 0°C and ethanolamine (2.26g, 48.5 mmol) is added to remove the 9-BBN moiety. The white solid is separated by filtration on a pad of Celite and washed with cold Et_2O (3x20 ml). The organic layer is washed with brine (2x20 ml), dried on $MgSO_4$ and the solvent is evaporated with a rotary evaporator. Flash column chromatography (silica gel, methanol/methylene dichloride 2/98) furnishes methyl 5(S)-5-hydroxy-7-trimethylsilyl-hept-6-ynoate 3.6 g (71 %).

IR (neat) : ν = 3600 ; 3100 ; 2920 ; 2860 ; 2160 ; 1750 cm^{-1}.

^1H NMR ($CDCl_3$/TMS) : δ = H_5 (4.21,t,J=6.25Hz) ; OCH_3 (3.51,s) ; H_2 (2.22,t,J=7.5Hz) ; OH (2.10,sl) ; H_3,H_4 (1.50,m) ; $Si(CH_3)_3$ (0.2,s) ppm.

^{13}C NMR ($CDCl_3$) : δ = 174.0 (C_1) ; 106.5 (C_6) ; 89.0 (C_7) ; 61.9 (C_5) ; 51.4 (OCH_3) ; 36.7 (C_4) ; 33.4 (C_2) ; 20.4 (C_3) ; -0.3 $Si(CH_3)_3$ ppm.

MS (m/z) = 229 [$(M+1)^+$] ; 246 [$(M+18)^+$].

-Methyl (5S)-5-hydroxy-hept-6-ynoate **4**

To a solution of the preceding alcohol (3.60g 15.8 mmol) in THF (80 ml) at 0°C, a solution (1M) of tetrabutylammonium fluoride in THF (16 ml) is added. After 1h at room temperature, the solvent is evaporated, the suspension is filtered rapidly on a pad of silica gel (ethyl acetate/cyclohexane 40/60). Flash column chromatography (silica gel, ethyl acetate/cyclohexane 50/50) gives 2.45 g of alcohol **4** [2f] in 99 % yield (ee = 96 % determined by GPC of the carbamate isopropyl isocyanate of the alcohol (chiral column XE-60-S VALINE S.A., pea, chrompack 50m).

$[\alpha]_D^{20}$ -18.25° (c = 1.30, CCl_4).

IR (neat) : ν = 3420 ; 2095 ; 1730 cm^{-1}.

^1H NMR ($CDCl_3$/TMS) : δ = H_5 (4.40,td,J=6.15Hz,J=2Hz) ; H_8 (3.69,s) ; OH (2.76,s) ; H_7 (2.49,d,J=2.18Hz) ; H_2 (2.39,t,J=7.05Hz) ; H_3,H_4 (1.90 to 1.70,m) ppm.
^{13}C NMR ($CDCl_3$) : δ = 173.8 (C_1) ; 84.5 (C_6) ; 72.5 (C_7) ; 60.9 (C_5) ; 51.2 (C_8) ; 36.3 (C_4) ; 33.1 (C_2) ; 20.1 (C_3) ppm.
MS (m/s) = 174 [$(M+18)^+$] ; 157 [$(M+1)^+$] ; 139.

Methyl (5S,8E,10E,12R,14Z)-5-12-dihydroxy-eicosa-8-10-14-trien-6-ynoate 2

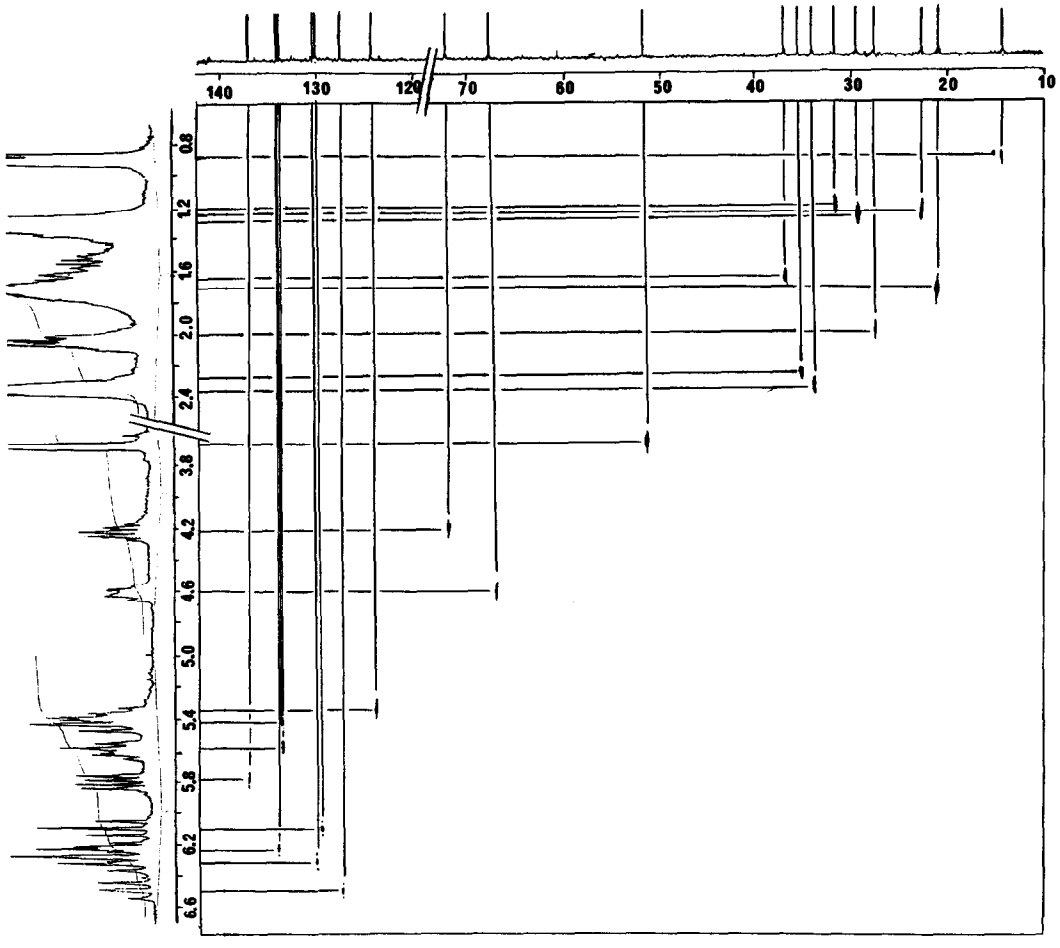
To a solution of chiral chlorodiene **3** (0.244 g, 1.07 mmol) in freshly distillated piperidine (10 ml) stirred at room temperature are added bis (acetonitrile) palladium chloride (0.26g, 0.107 mmol), the chiral alcohol ester **4** (0.300 g, 1.92 mmol) and cuprous iodide (0.020 g, 0.107 mmol). After 3h, the resulting mixture is hydrolyzed by a saturated ammonium chloride solution and aqueous solution hydrochloric acid (0.5M). The organic layer is diluted with ether, washed with water (3x20 ml) and dried on $MgSO_4$. The crude product, after concentration is purified by flash chromatography (ethyl acetate/cyclohexane 60/40) to afford compound **2** ^{2n} (0.257g, 69 %).
IR (neat) : ν = 3400 ; 3000 ; 2200 ; 1730 cm^{-1}.
^1H NMR ($CDCl_3$/TMS) : δ = H_9 (6.59,dd,J=15.50Hz,J=10.85Hz) ; H_{10} (6.21,dd,J=15Hz,J=10.85Hz) ; H_{11} (5.75,dd,J=15Hz,J=5.6Hz) ; H_8,H_{14} (5.60 to 5.43, m) ; H_{15} (5.38 to 5.21,m) ; H_5 (4.48 to 4.40,m) ; H_{12} (4.15,q,J=5.6Hz) ; OMe(3.60,s) ; H_2,H_{13} (2.37 to 2.20,m) ; H_{16} (1.97,q,J=6.70Hz) ; H_3,H_4 (1.70,m) ; H_{17},H_{18},H_{19} (1.23,m) ; H_{20} (0.82,t,J=6.5Hz) ppm.
^{13}C NMR ($CDCl_3$) : δ = 174.0 (C_1) ; 141.2 (C_9) ; 138.3 (C_{11}) ; 133.4 (C_{14}) ; 129.0 (C_{10}) ; 123.9 (C_{15}) ; 110.5 (C_8) ; 92.4 (C_7) ; 83.7 (C_6) ; 71.4 (C_{12}) ; 62.0 (C_5) ; 51.5 (OMe) ; 36.8 (C_4) ; 35.0 (C_{13}) ; 33.4 (C_2) ; 31.3 (C_{18}) ; 29.1 (C_{17}) ; 22.4 (C_{19}) ; 27.2 (C_{16}) ; 20.5 (C_3) ; 13.9 (C_{20}) ppm.
UV (EtOH) : λ_{max} = 265 ; 276 nm.

Methyl (5S,6Z,8E,10E,12R,14Z)-5-12-dihydroxy eicosa-6-8-10-14- tetraenoate 1

Activated zinc dust is prepared as previously described[9]. A solution of dienyne **2** (0.200 g, 0.5747 mmol) in 2 ml of MeOH is added to the suspension of activated Zn (2g) and stirred at 35°C. After 15h, the mixture is filtered on pad of Celite, washed with MeOH, and the combined solutions are concentrated to 1/3 of the original volume on Et_2O is added. The organic layer is washed with water, dried by $MgSO_4$, evaporated and flash column chromatography (silica gel, ethyl acetate/cyclohexane 40/60) furnishes the LTB_4 methyl ester **1** (0.102g, 70 %, 95 % purity by HPLC analysis[11]).
$[\alpha]_D^{20}$ + 6.47° (c = 1.8, CCl_4).

IR (neat) : ν = 3400, 3000, 1730, 1595 cm^{-1}.
^1H NMR ($CDCl_3$/TMS) : δ = H_8 (6.52,dd,J=14.5Hz,J=11.5Hz) ; H_{10} (6.34,dd,J=15Hz,J=11Hz) ; H_9 (6.27,dd,J=14Hz,J=11Hz) ; H_7 (6.12,t,J=11.5Hz) ; H_{11} (5.81,dd,J=15Hz,J=6.5Hz) ; H_{14} (5.66 to 5.57,m) ; H_6,H_{15} (5.50 to 5.36,m) ; H_5 (4.63,m) ; H_{12} (4.25,q,J=6.50Hz) ; OMe (3.70,s) ; H_2,H_{13} (2.45 to 2.32,m) ; H_{16} (2.09,m- ; H_4,H_3,2HO (1.90 to 1.65,m) ; H_{17},H_{18},H_{19} (1.40 to 1.28,m) ; H_{20} (0.90,t,J=6.5Hz).

^{13}C NMR ($CDCl_3$) : δ = 174.0 (C_1) ; 136.8 (C_{11}) ; 134.0 (C_9) ; 133.9 (C_6) ; 133.7 (C_{14}) ; 133.6 (C_{10}) ; 130.3 (C_7) ; 127.4 (C_8) ; 124.0 (C_{15}) ; 71.9 (C_{12}) ; 67.6 (C_5) ; 51.6 (OMe) ; 36.7 (C_4) ; 35.3 (C_{13}) ; 33.8 (C_2) ; 31.5 (C_{18}) ; 29.3 (C_{17}) ; 27.4 (C_{16}) ; 22.5 (C_{19}) ; 20.7 (C_3) ; 14.1 (C_{20}).
UV (EtOH) : λ_{max} = 259 ; 269 ; 280 nm.



Two dimensional $^1H,^{13}C$ heteronuclear shift correlated experiment at 250MHz of LTB_4 methyl ester.

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