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An Efficient Stereocontrolled Synthesis of 12(R)-HETE and 12(S)-HETE

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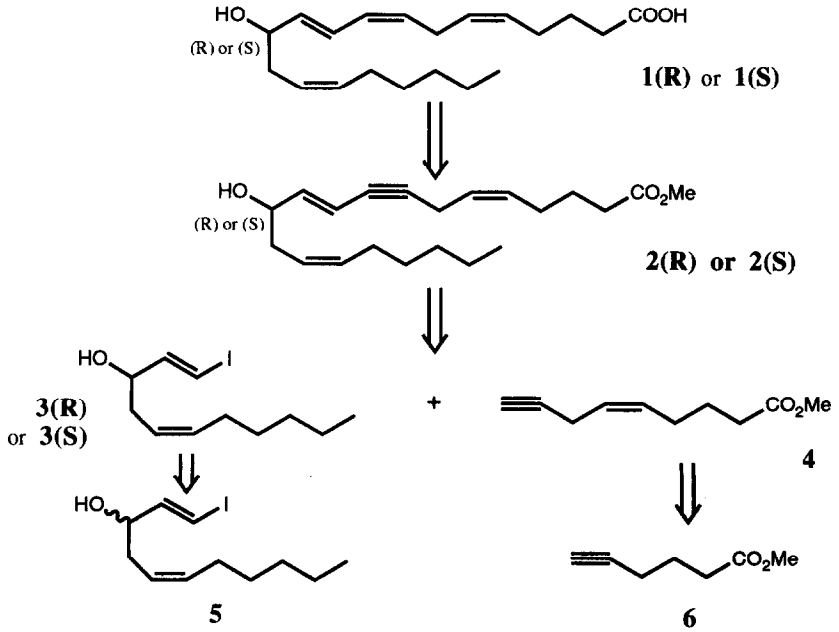
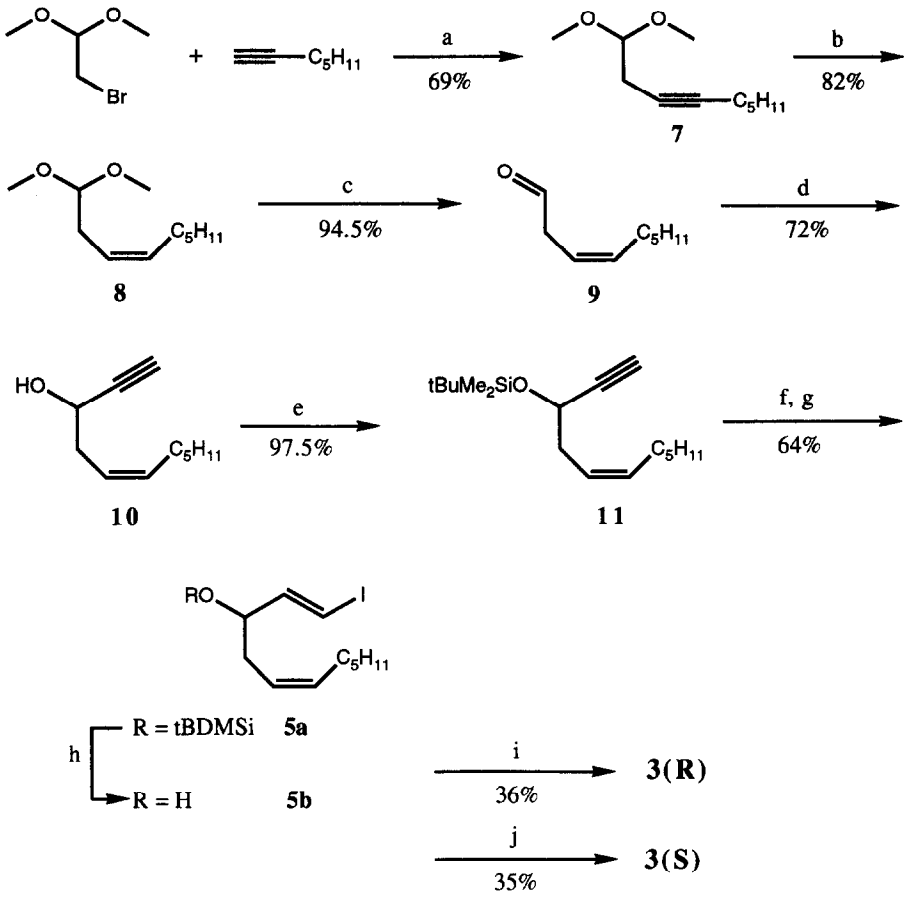
Abstract : An efficient synthesis of 12(R) and 12(S) HETEs was realized by assembly of the easily obtainable synthons: optically pure iodo-alcohols **3(R)** and **3(S)** with the ester **4**, followed by reduction with activated zinc.

12-HETE is an important and biologically active metabolite of arachidonic acid.[1] Both enantiomers have been found to occur naturally. 12(S) HETE **1(S)** is the major lipoxygenase product found in human platelets[2]. 12(R)-HETE **1(R)** is present in high concentrations in psoriatic lesions[3] and it has been postulated to have a regulatory role in ocular functions[4]. We report herein a short synthesis[5] of the two enantiomers of 12-HETE by assembly of the easily obtainable synthons **3(R** or **S)** with **4**: (i) both enantiomers **3(R)** and **3(S)** were prepared in high enantiomeric purity by the Sharpless kinetic resolution of the racemate **5** ; (ii) the enyne ester **4** was prepared by a three-step sequence from methyl hex-5-ynoate. A retrosynthetic analysis is shown in scheme A.



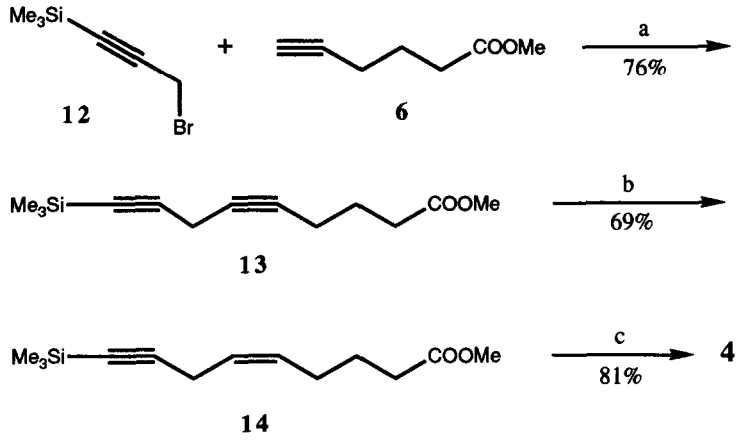
Scheme A

Both enantiomers of the iodo alcohol **5** were obtained as follows (scheme B): the reaction of heptynyllithium with the dimethyl acetal of bromoacetaldehyde gave the acetal **7** (69 % yield) which was reduced by P-2 nickel in 82 % yield[6]. Hydrolysis with trifluoroacetic acid followed by ethynylation with lithium acetylide at -78°C furnished the propargyl alcohol **10** in 68 % yield[7]. Protection of the alcohol function with a t-butyldimethyl silyl group, hydrozirconation with the Schwartz reagent,[8,9] iodolysis and deprotection furnished the iodo alcohol **5b** in 50 % overall yield. The Sharpless kinetic resolution[10] using t-butylhydroperoxide , titanium (IV) isopropoxide and L-(+)-diisopropyl tartrate gave the alcohol **3(R)** (ee = 97 %) in 36 % yield. In the same way, by using D-(-)-diisopropyl tartrate, the alcohol **3(S)** (ee = 96 %) was obtained in 35 % yield.



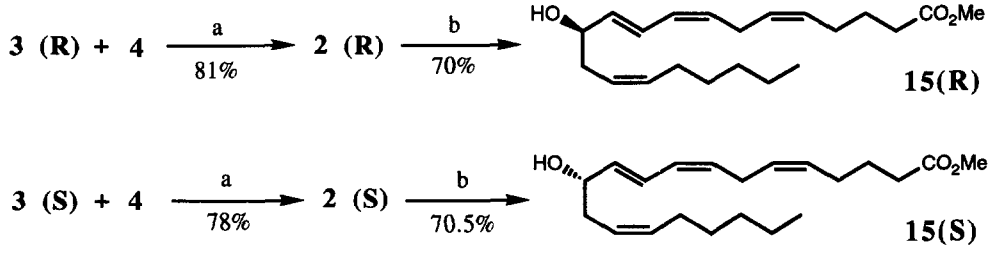
Scheme B : **(a)** BuLi, THF, HMPT, 24h, -5° to 20°C ; **(b)** H_2, P-2 Ni, EtOH ; **(c)** TFA, $CHCl_3$, H_2O,1h ; **(d)** ethyne, BuLi, THF, 1h, -78° to 20°C ; **(e)** $tBuMe_2SiCl$, DMF, imidazole, 20°C ; **(f)** $HZrCp_2Cl$ (2 equiv), C_6H_6, THF ; **(g)** I_2 ; **(h)** nBu_4NF, THF ; **(i)** L-(+)-DIPT (0.37 equiv), $Ti(OiPr)_4$ (0.31 equiv), TBHP (1.5 equiv),mol sieves (0.56 equiv), CH_2Cl_2, -20°C, 40h ; **(j)** D-(-)-DIPT (0.37 equiv), $Ti(OiPr)_4$ (0.31 equiv), TBHP (1.5 equiv), mol. sieves 4 Å (0.56 equiv),CH_2Cl_2, -20°C, 40h.

The synthon **4** was readily prepared by a three-step sequence as outlined in Scheme C. Phase-transfer reaction of 3-bromo-1-(trimethylsilyl) prop-1-yne[11] with methyl hex-5-ynoate in the presence of tetrabutyl ammonium chloride, cuprous iodide and sodium carbonate in DMF[12] gave the diyne **13** in 76 % yield. Selective hydrogenation in the presence of P-2 Nickel and desilylation furnished the synthon **4**[5d].



Scheme C : (a) nBu_4NCl, CuI, Na_2CO_3, DMF ; **(b)** H_2, P-2 Ni, EtOH ; **(c)** KF,$2H_2O$, DMF.

Finally, coupling of the chiral alcohol **3(R)** with the enyne **4** in the presence of tetrakis (triphenylphosphine) palladium, cuprous iodide and n-butylamine in benzene[13,5d] gave the enyne **2(R)** in 81 % yield. Selective reduction of the triple bond with activated zinc[14,15] led to pure 12 (R)-HETE methyl ester **15(R)** in 70 % yield $[\alpha]_D$ = -11.4° (C=1, acetone)[16]. The **15(R)** ester was characterized by its spectroscopic properties and by comparison with an authentic sample[17] (scheme D).



Scheme D : (a) 15% $Pd(PPh_3)_4$, 15% CuI, $nBuNH_2$ (5 equiv), C_6H_6, 20°C, 6h ; **(b)** Zn (Cu/Ag), MeOH/H_2O (1/1), 35°C, 15h.

Starting with the (S) enantiomer of the alcohol **5**, optically pure 12(S)-HETE methyl ester **15(S)** was prepared in the same way, $[\alpha]_D$ = + 12.6° (C=0.4, acetone)[17].

In conclusion, a short synthesis of 12(R) and 12(S) HETEs has been realized by coupling two easily obtainable synthons **3** and **4**. This strategy appears to be an efficient route to optically active conjugated dienols.

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, q=quadruplet 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 7

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 (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) ; 15g, yield, 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=5.0Hz).
^{13}C NMR ($CDCl_3$): δ = 102.7 (C_1) ; 81.8, 74.4 (C_3,C_4) ; 53.0 (2 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 71.56 ; H 11.1.

(3Z) non-3-enal dimethylacetal 8

Nickel acetate tetrahydrate (0.25 g, 1 mmol) is dissolved in 10 ml of 95 % ethanol under an 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 **7** (1.47 g, 8 mmol) is injected. When the theoretical volume 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): δ = 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.; Found : C 70.81 ; H 11.95.

(3Z) non-3-enal 9

To a stirred solution of nonenal dimethylacetal (5.58, 30 mmol) in chloroform (200 ml), is added a solution (50 % in water) of trifluoroacetic acid. The reaction is monitored by gas chromatography. After disappearance of the acetal (1.5h), 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 $MgSO_4$. 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 **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=6.2Hz, 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=7.0Hz) ; H_8 to H_{10} (1.46 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.

(5Z)-3-t Butyldimethylsilyloxy-undec-5-en-1-yne 11

To a stirred solution of **10** (2.50g, 15 mmol) in DMF (5 ml) at 0°C, t-butyldimethylsilyl chloride (2.80g, 18.58 mmol) and imidazole (2.86g, 42 mmol) are added. After 24h at room temperature, the mixture is hydrolyzed with water (20 ml) and extracted with pentane. The organic layer is washed with water (3x40 ml), dried over magnesium sulfate. The crude product is purified by flash chromatography (elution with pentane) to afford **11** (4.11 g, 97.5 % yield).

^{1}H NMR ($CDCl_3$/TMS): δ = H_5, H_6 (5.60 to 5.37, m) ; H_3 (4.34, td, J=6.6Hz, J=2.1Hz) ; H_4 (2.44, t, J=6.6Hz) ; H_1 (2.39, d, J=2.1Hz) ; H_7 (2.06, q, J=6.8Hz) ; H_8 to H_{10} (1.45 to 1.24, m) ; H_{11} and $(CH_3)_3C$ (0.98 to 0.80, m) ; $2CH_3$ (0.15 to 0.12, 2s).
^{13}C NMR ($CDCl_3$): δ = 132.5 (C_5) ; 124.0 (C_6) ; 85.1 (C_2) ; 71.8 (C_1) ; 62.6 (C_3) ; 36.4 (C_4) ; 31.3 (C_9) ; 29.1 (C_8) ; 27.2 (C_7) ; 25.5, 18.0 ($(CH_3)_3C$) ; 22.3 (C_{10}) ; 13.8 (C_{11}) ; -3.2, -4.9 ($2CH_3$).
Anal. calcd. for $C_{17}H_{32}OSi$: C 72.79, H 11.50 ; Found : C 72.5, H 11.65.

(1E,5Z)-1-Iodo-undeca-1,5-dien-3-ol
(1E,5Z)-1-Iodo-3-t-butyldimethylsilyoxy-undeca-1,5-diene 5a
To a stirred solution of **11** (2.10g, 7.49 mmol) in anhydrous benzene/THF (1/1, 60 ml), is added one equivalent of Schwartz's reagent (zirconocene chloride hydride)[18] (1.93g, 7.48 mmol). After stirring for 15 min, the resulting solution becomes clear, and a second equivalent of reagent is added. After 15 min., iodine is introduced until a violet persistence coloration. The mixture is diluted with pentane, filtered through a pad of celite, evaporated to dryness. The crude product is purified by flash chromatography (silica gel, pentane) to afford the compound (1.96g, 64 % in yield).

IR (neat): ν = 3080, 960, 840, 760 cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS): δ = H_2 (6.49, dd, J=14.3Hz, J=5.8Hz) ; H_1 (6.17, dd, J=14.3Hz,J=1.2Hz) ; H_5,H_6 (5.51 to 5.25, 2m) ; H_3 (4.05, qd, J=6.2Hz, J=1.1Hz) ; H_4 (2.20, t, J=7.2Hz) ; H_7 (1.77, q, J=6.5Hz) ; H_8 to H_{10} (1.34 to 1.18, m) ; H_{11},$3CH_3$ (0.85, m) ; $2CH_3$ (0.15 to 0.00, 2s).
Anal. calcd. for $C_{17}H_{33}OISi$: C 49.51, H 8.065 ; Found : C 49.39, H 8.24.

(1E,5Z)-1-Iodo-undeca-1,5-dien-3-ol 5b
To a solution of **5a** (1.90g, 4.65 mmol) in THF (50 ml) at 0°C is added tetrabutylammonium fluoride monohydrate (2.43g, 9.29 mmol). After stirring for 3h at room temperature, the mixture is hydrolyzed with water (30 ml) and extracted with ether. The organic phase is washed with water (3x30 ml), dried over magnesium sulfate. Flash column chromatography of the crude product (silica gel, methylene dichloride) gives pure iodo alcohol **5b** (1.06g, 78 % yield).

IR (neat): ν = 3350, 1920, 1600, 950 cm^{-1}.
^{1}H NMR ($CDCl_3$/TMS): δ = H_2 (6.60, dd, J=14.4Hz, J=5.6Hz) ; H_1 (6.37, dd, J=14.4Hz,J=1.25Hz) ; H_5,H_6 (5.68 to 5.28, 2m) ; H_3 (4.12, qd, J=6.0Hz, J=1.25Hz) ; H_4 (2.31, t, J=6.25Hz) ; H_7,OH (2.10 to 1.93, m) ; H_8 to H_{10} (1.45 to 1.20, m) ; H_{11} (0.89, t, J=6.5Hz).
^{13}C NMR ($CDCl_3$): δ = 147.8 (C_2) ; 134.5 (C_5) ; 123.2 (C_6) ; 77.3 (C_1) ; 73.9 (C_3) ; 34.6 (C_4) ; 31.5 (C_9) ;

29.2 (C_8) ; 27.4 (C_7) ; 22.5 (C_{10}) ; 14.0 (C_{11}).
MS (m/z): 312 [(M+18)$^+$] ; 294 (M^+) ; 277 [(m-17)$^+$].
Anal. calcd. for $C_{11}H_{19}OI$: C 44.91, H 6.51 ; Found: C 44.75, H 6.74.

(1E,3R,5Z)-1-Iodo-undeca-1,5-dien-3-ol 3(R)

To a solution of iodo-alcohol **5b** (0.50g, 1.7 mmol) in anhydrous methylene chloride (5 ml) stirred on 4 Å activated molecular sieves during 30 min is added 4 Å activated molecular sieves (0.29g, 0.56 equiv weight). The solution is cooled to -15°C, L-(+)-diisopropyl tartrate (0.15g, 0.638 mmol) and titanium tetraisopropoxide (n=0.151g, 0.634 mmol) are added. After 30 min, t-butyl hydroperoxide (0.85 ml, 3M in 2,2,4-trimethyl pentane) is slowly introduced into the stirred solution at -20°C. After 40h at this temperature, the solution is warmed to 0°C, hydrolyzed with water (20xn=20x0.151=3g) within 1h and a 30% aqueous sodium hydroxide solution (7 ml) saturated by sodium chloride, is added. The resulting suspension is filtered through a pad of celite and washed with ether. The organic layer is separated, dried over magnesium sulfate and concentrated in vacuo. The crude product is chromatographed on silica gel (ether / pentane 30/70) to furnish **3(R)** (0.18g, 36 % yield).$[\alpha]_D^{18}$ = +18.8° (C=1.2, $CHCl_3$). The enantiomeric excess is confirmed to be 97 %[15].

In the same way, (1E,3S,5Z)-1-iodo-undeca-1-5-dien-3-ol **3(S)** is prepared by using D-(-)-diisopropyl tartrate (35 %). The enantiomeric excess is 96 %, $[\alpha]_D^{18}$ = -22° (C=1.3, $CHCl_3$).

3-Bromo-1-(trimethylsilyl) prop-1-yne 12

To a solution of n-butyllithium (37.5 ml, 60 mmol, 1.6N in hexane) in anhydrous ether (45 ml), diisopropyl amine (6.06g, 60 mmol) is added at -5°C. Then, the solution is cooled to -80°C and 3-bromo prop-1-yne (5.95g, 50 mmol) in toluene (7.5 ml) is slowly added while keeping the temperature between -75 and -80°C (a cooling bath with liquid nitrogen is indispensable). After 5min. at -80°C, the solution is cooled to -90°C and trimethylchlorosilane (10.87g, 100 mmol) is slowly added. A solution of HMPT (8ml) in anhydrous ether (8ml) is then added dropwise between -80° and -90°C. The temperature is allowed to rise to -10°C over 1 hr. A white suspension is gradually formed. The reaction mixture is poured into aqueous hydrochloric acid 2M (125ml). The combined solutions are extracted with ether, washed with water, dried over magnesium sulfate. Distillation gives the bromide **12**, bp 65°C (20 mm), 6.2g (65 %)[11].

IR (neat): ν = 2960, 2900, 2180,n 1250, 1045, 850, 760 cm^{-1}.
^1H NMR ($CDCl_3$/TMS): δ = H_2 (3.87, s) ; $3CH_3$ (0.20, s)
^{13}C NMR ($CDCl_3$): δ = 100.0 (C_1) ; 92.1 (C_2) ; 14.52 (C_3) ; -0.4 ($3CH_3$).

Methyl 9-trimethylsilyl nona-5,8-diynoate 13

To a mixture of sodium carbonate (1.83g, 17.26 mmol), cuprous iodide (2.19g, 11.50 mmol) and tetrabutyl ammonium chloride (1.12g, 4 mmol) in 12 ml DMF at -20°C, is added methyl hexynoate **6** (1.45g, 11.5 mmol), followed by dropwise addition of **12** (2.75g, 14.74 mmol). After the end of the addition, the temperature is allowed to rise gradually to room temperature. After stirring overnight, the reaction mixture is diluted with ether (10 ml) and filtered through a pad of celite. The solution is hydrolyzed with water (50 ml),

extracted with ether. The organic layer is washed with a saturated solution of ammonium chloride and dried over magnesium sulfate. The solution is concentrated in vacuo and the crude product is purified by flash column chromatography (silica gel, ethyle acetate/pentane 10/90) to furnish **13** (2.07g, 76 %).

IR (neat): ν = 2960, 2900, 2180, 1740, 1250, 850, 760 cm^{-1}.
^1H NMR ($CDCl_3$/TMS): δ = OCH_3 (3.67, s) ; H_7 (3.17, t, J=2.4Hz) ; H_2 (2.43, t, J=7.3Hz) ; H_4 (2.23, tt, J=7.3Hz, J=2.4Hz) ; H_3 (1.81, q, J=7.3Hz) ; $3CH_3$ (0.15, s).
^{13}C NMR ($CDCl_3$): δ = 173.3 (C_1) ; 100.4 (C_9) ; 84.5 (C_8) ; 79.4 (C_5) ; 74.3 (C_6) ; 51.2 (OCH_3) ; 32.6 (C_2) ; 23.6 (C_3) ; 18.0 (C_4) ; 10.6 (C_7) ; -0.34 ($3CH_3$).
MS (m/z): 237 [$(M+1)^+$] ; 254 [$(M+18)^+$].

Methyl (5Z)-9-(trimethylsilyl) non-5-en-8-ynoate 14

Nickel acetate tetrahydrate (0.26g, 1.05 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 (0.040g, 1.05 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 (0.25g, 2.10 mmol) and the diyne **13** (2g, 8.47 mmol) is injected. When the theoretical volume of hydrogen has been absorbed, the black mixture is filtered over a short plug of celite and rinced with methylene dichloride. The organic layer is washed with brine, dried over $MgSO_4$ and subjected to flash column chromatography (silica gel, ethyle acetate/pentane 10/90) furnishing **14** (1.39g, yield 69 %).

IR (neat): ν = 3020, 2950, 2900, 2860, 2180, 1740, 1625, 1250, 850, 760 cm^{-1}.
^1H NMR ($CDCl_3$/TMS): δ = H_5,H_6 (5.54 to 5.36, m) ; CH_3O (3.67, s) ; H_7 (2.96, d, J=5.13Hz) ; H_2 (2.32, t, J=7.5Hz) ; H_4 (2.09, q, J=6.8Hz) ; H_3 (1.71, q, J=7.5Hz) ; $3CH_3$ (0.15, s).
^{13}C NMR ($CDCl_3$): δ = 173.6 (C_1) ; 130.3 (C_5) ; 124.9 (C_6) ; 104.9 (C_9) ; 83.9 (C_8) ; 51.2 (OCH_3) ; 33.1 (C_2) ; 26.3 (C_4) ; 24.2 (C_3) ; 18.1 (C_7) ; -0.17 ($3CH_3$).
MS (m/z): 239 [$(M+1)^+$] ; 256 [$(M+18)^+$].

Methyl (5Z)-non-5-en-8-ynoate 4

To a solution of **14** (1.30g, 5.46 mmol) in DMF (10 ml) is added potassium fluoride dihydrate (1.03g, 10.92 mmol). After stirring for 5h, the mixture is diluted with ether, washed with brine, dried over magnesium sulfate. The crude product is purified by flash chromatography (silica gel, ethyle acetate/pentane 10/90) to furnish **4** (0.732g, 81 %).

IR (neat): ν = 3300, 3020, 2950, 2860, 2120, 1730 cm^{-1}.
^1H NMR ($CDCl_3$/TMS): δ = H_5,H_6 (5.56 to 6.40, m) ; CH_3O (3.68, s) ; H_7 (2.94, dd, J=5.7Hz, J=2.7Hz) ; H_2 (2.33, t, J=7.45Hz) ; H_4 (2.10, q, J=6.8Hz) ; H_9 (1.98, t, J=2.7Hz) ; H_3 (1.72, q, J=7.3Hz).
^{13}C NMR ($CDCl_3$): δ = 173.4 (C_1) ; 130.4 (C_5) ; 124.5 (C_6) ; 82.2 (C_8) ; 67.9 (C_9) ; 51.0 (OCH3) ; 32.9 (C_2) ; 26.1 (C_4) ; 24.1 (C_3) ; 16.5 (C_7).
MS (m/z): 167 [$(M+1)^+$] ; 184 [$(M+18)^+$].

Methyl (5Z,10E,12R,14Z)-12-hydroxyeicosa-5,10,14-trien-8-ynoate 2(R)

To a stirred solution of chiral iodo-alcohol **3(R)** (0.294g, 1 mmol) in anhydrous benzene (5 ml) at room temperature, tetrakis (triphenylphosphine) palladium (0.173g, 0.15 mmol), n-butylamine (0.365g, 5 mmol), the ester **4** (0.250g, 1.5 mmol) and cuprous iodide (0.030g, 0.15 mmol) are added. After stirring for 6h, the reaction mixture is quenched by satured ammonium chloride solution. The organic layer is diluted with ether, washed with brine and dried over magnesium sulfate. The crude product is purified by flash column chromatography (silica gel, ether/pentane 40/60) to afford compound **2(R)** (0.269g, 81 %) $[\alpha]_D^{20}$ = +9.1° (C=1.1, $CHCl_3$).

The enantiomer **2(S)** is obtained by the same procedure in yield 78%, $[\alpha]_D^{20}$ = -9.8° (C=1.2, $CHCl_3$).

^1H NMR ($CDCl_3$/TMS): δ = H_{11} (6.08, dd, J=16Hz, J=5.85Hz) ; H_{10} (5.76 to 5.64, m) ; H_5,H_6,H_{14},H_{15} (5.64 to 5.29, m) ; H_{12} (4.17, q, J=6.1Hz) ; OCH_3 (3.66, s) ; H_7 (3.03, m) ; H_2,H_{13} (2.38 to 2.26, m) ; H_4,H_{16} (2.15 to 1.97, m) ; H_3 (1.71, q, J=7.3Hz) ; OH,H_{17} to H_{19} (1.36 to 1.23, m) ; H_{20} (0.88, t, J=6.7Hz).

^{13}C NMR ($CDCl_3$): δ = 174.0 (C_1) ; 143.8 (C_{11}) ; 134.1 (C_{14}) ; 130.5 (C_6) ; 125.1 (C_5) ; 123.8 (C15) ; 110.4 (C_{10}) ; 89.0 (C_8) ; 78.2 (C_9) ; 71.7 (C_{12}) ; 51.5 (OCH_3) ; 37.0 (C_4) ; 35.0 (C_{13}) ; 31.3 (C_{18}) ; 29.2 (C_{16}) ; 27.4 (C_{17}) ; 26.4 (C_2) ; 24.5 (C_3) ; 22.5 (C_{19}) ; 17.8 (C_7) ; 14.0 (C_{20}).

Methyl (5Z,8Z,10E,12R,14Z)-12-hydroxyeicosa-5,8,10,14-tetraenoate 15(R).

To a suspension of activated zinc dust (3g, prepared[14] from zinc Merck n° 8789) in 12 ml of MeOH/H_2O 1/1 (v/v), a solution of enyne **2(R)** (0.142g, 0.428 mmol) in 1 ml of methanol is added. The mixture is stirred at 35°C overnight and then diluted with methanol (2 ml). After filtration over Celite, the solution is concentrated (1/3) and a mixture pentane/ether (1/1) is added. The organic layer is washed with brine and dried over magnesium sulfate. Flash column chromatography (silica gel, ether/pentane 40/60) gives the 12(R)-HETE methyl ester (0.100g, 70 %).

$[\alpha]_D^{18}$ = -11.4° (C=1.0, acetone).

^1H NMR ($CDCl_3$/TMS): δ = H_{10} (6.48, ddt, J=15.2Hz, J=11.1Hz, J=1.15Hz) ; H_9 (5.92, t, J=11.0Hz) ; H_{11} (5.65, dd, J=15.15Hz, J=6.25Hz) ; H_{14} (5.57 to 5.42, m) ; H_5,H_6,H_8,H_{15} (5.41 to 5.24, m) ; H_{12} (4.16, q, J=6.2Hz) ; OCH_3 (3.60, s) ; H_7 (2.85, t, J=6.1Hz) ; H_2,H_{13} (2.34 to 2.20, m) ; H_4,H_{16} (2.10 to 1.90, m) ; H_3 (1.63, q, J=7.3Hz) ; OH,H_{17} to H_{19} (1.35 to 1.26, m) ; H_{20} (0.81, t, J=6.9Hz).

^{13}C NMR ($CDCl_3$): δ = 174.3 (C_1) ; 136.0 (C_{11}) ; 133.6 (C_{14}) ; 130.2, 129.3, 128.4 (C_5,C_6,C_8) ; 128.0 (C_9) ; 125.4 (C_{10}) ; 124.5 (C_{15}) ; 72.1 (C_{12}) ; 51.7 (OCH_3) ; 35.5, 33.5 (C_2,C_{13}) ; 31.6 (C_{18}) ; 29.4 (C_{17}) ; 27.5, 26.7 ($C_{4,16}$) ; 26.2 (C_7) ; 24.8 (C_3) ; 22.7 (C_{19}) ; 14.2 (C_{20}).

By using the same procedure, starting from the (S) enantiomer of **2**, 12(S)-HETE methyl ester **15(S)** is obtained (70.5 %). $[\alpha]_D^{18}$ = +12.6° (C=0.4, acetone).

REFERENCES

1. For a review, see Rokach, J.; Guindon, Y.; Yong, R.N.; Adams, J.; Atkinson, J.G. *The Total Synthesis of Natural Products*, Apsimon,J. Ed. Wiley: New-York, **1987**; *7*, p 141.
2. Hamberg, M.; Swensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA*, **1974**, *71*, 3824.
3. Wollard, P.M., *Biochem. Biophys. Res. Commun.*, **1986**, *136*, 169 ; Ruzika, T.; Burg, G. *J. Invest. Dermatol.*, **1987**, *88*, 120.
4. Gordon, J.A.; Figard, P.H.; Spector, A.A. *J. Lipid Res.*, **1989**, *21*, 731.
5. For total syntheses of 12-HETEs, see : (a) Corey, E.J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.*, **1978**, *100*, 1942 ; (b) Corey, E.J.; Marfat, A.; Falk, J.R.; Albright, J.O. *J. Am. Chem. Soc.*, **1980**, *102* , 1433 ; (c) Leblanc, Y.; Fitzsimmons, B.J.; Adams, J.; Perez, F. and Rokach, J. *J. Org. Chem.*, **1986**, *51*, 789 ; (d) Nicolaou, K.C.; Ladduwahetty, T.; Taffer, I.M.; Zipkin, R.E. *Synthesis*, 1986, 344 ; (e) Taffer, I.M. and Zipkin, R.E. *Tetrahedron Lett.*, **1987**, *28*, 6543 ; (f) Just, G.; Zhi Yuan Wang, *J. Org. Chem.*, **1986**, *51*, 4796 ; (g) Djuric, Z.W.; Miyashiro, J.M. and Pening, T.D. *Tetrahedron Lett.*, **1988**, *29*, 3459 ; (h) Nicolaou, K.C.; Ranphal, J.Y.; Abe, Y. *Synthesis*, **1989**, 898 ; (i) Mosset, P.; Pointeau, P.; Aubert, F.; Lellouche, J.P.; Beaucourt, J.P.; Gree, R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 298 ; (j) Lumin, S.; Falk, J.R. *Tetrahedron Lett.*, **1991**, *32*, 2315.
6. Brown, C.A.; Ajuha, V.K. *J. Org. Chem.*, **1973**, *38*, 2226.
7. Truboi, S.; Masuda, T.; Takeda, A. *Chemistry Letters*, **1983**, 1829.
8. Hart, D.W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.*, **1975**, *97*, 679 ; Carr, D.B.; Schwartz, J. *Ibid.*, **1979**, *101*, 3521.
9. Avignon-Tropis, M.; Treilhou, M.; Pougny, J.R.; Frechard-Ortuno, I.; Linstrumelle, G. *Tetrahedron*, **1991**, *47*, 7279-7286.
10. Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem.*, **1990**, *55*, 5324-5335.
11. Brandsma, L. *Preparative acetylenic chemistry* (2d edition), Elsevier: Amsterdam, 1988; p 122.
12. Gueugnot, S.; Jeffery, T.; Linstrumelle, G. *Tetrahedron Lett.*, **1992**, *33*, in press.
13. Ratovelomanana, V.; Linstrumelle, G. *Synthetic Comm.*, **1981**, *11*, 853 ; *Tetrahedron Lett.*, **1981**,*22*, 315 ; ibid., **1984**, *25*, 6001.
14. Boland, W.; Sieler, C.; Schroer, N.; Feigel, M. *Helvetica Chimica Acta*, **1987**, *70*, 1025-1040.
15. Avignon-Tropis, M.; Berjeaud, J.M.; Pougny, J.R.; Frechard-Ortuno, I.; Guillerm, D.; Linstrumelle, G. *J. Org. Chem.*, **1992**, *57* , 653 ; Chemin, D.; Linstrumelle, G. *Tetrahedron*, **1992**, *48*, 1943.
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18. Buchwald, S.L.; LaMaire, S.J.; Nielsen, R.B.; Watson, B.T.; King, S.M. *Tetrahedron Lett.*, **1987**, *28*, 3895.