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# An Efficient Total Synthesis of 5-(*S*)-HETE

**Sylvie Gueugnot[a], Mouâd Alami[a], Gérard Linstrumelle[a], Lengo Mambu[b], Yves Petit[b] and Marc Larchevêque[b]**

a: Département de Chimie, Ecole Normale Supérieure, URA 1679, 24 rue Lhomond 75231 Paris Cedex 05, France
Fax: (+33) 1 47 07 68 56.

b: Laboratoire de Synthèse Organique, ENSCP, URA 1381, 11 rue P. et M. Curie 75231 Paris Cedex 05, France
Fax: (+33) 1 43 25 79 75.

**Abstract**: A short and convergent synthesis of (5*S*)-HETE **1a** was accomplished by coupling of two easily accessible synthons **2** and **3a**. 

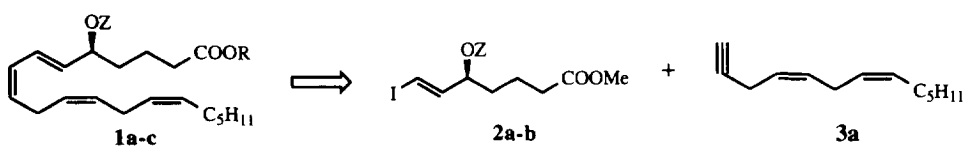
The metabolism of arachidonic acid by the lipoxygenase pathway leads to a wide variety of oxygenated compounds which possess a chiral oxygen functionality adjacent to a conjugated *E,Z*-diene. Among them, (5*S*)-hydroxy-(6*E*,8Z,11Z,14Z)-eicosatetraenoic acid namely 5-HETE **1a** is an important biological mediator which has been shown to be implicated as a chemotactic factor for human eosinophils and neutrophils.[1] During the last decade, for further biological investigations, many syntheses have been described.[2]

As part of our studies on the total synthesis of biologically active polyene compounds,[3] we report herein a convergent and stereoselective synthesis of (5*S*)-HETE based:

- on the short and efficient synthesis of the chiral synthon **2** in high enantiomeric excess (ee ≥ 98%) according two different approaches (i) by the Sharpless kinetic resolution of the racemic derivative **6** and (ii) by the opening of a chiral acetal to synthetise an optically pure propargylic alcohol precursor of the protected iodide **2b**.

- on the easy preparation of the skipped dienyne **3a**, by the recently reported approach[4] to skipped (Z,Z,Z)-trienes involving the reaction of propargylic halides with 1-alkynes in the presence of CuI, $Na_2CO_3$ and $Bu_4NCl$.

- on the stereospecific palladium-copper-catalyzed coupling reaction of the two easily prepared synthons **2** and **3a** followed by the stereoselective reduction of the enyne **15** so obtained.




**1a-c** **2a-b** **3a**

**a** R = H Z = H
**b** R = Me Z = H
**c** R = Me Z = $SiPh_2t$-Bu

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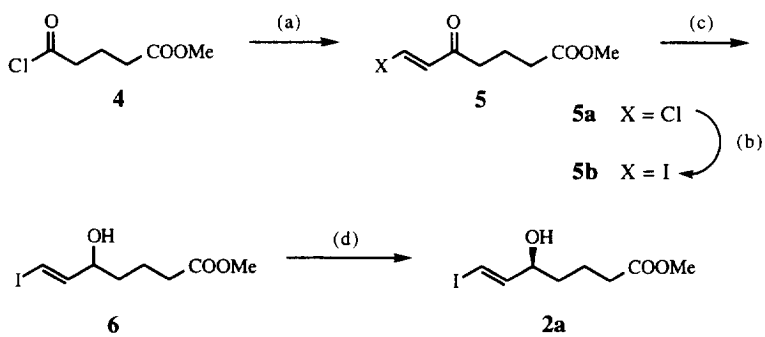
**b** Z = $SiPh_2t$-Bu

**A.** Synthesis of the vinylic iodides **2**

In order to study the possibilities offered by the direct coupling of dienyne **3a** with the free alcohol **2a**, two strategies were developed in order to obtain the synthons **2**: the first one was based on a kinetic resolution of the racemic alcohol **6**, and the second used the opening of a chiral acetal to prepare an optically pure propargylic alcohol precursor of the protected vinylic iodide **2b**.

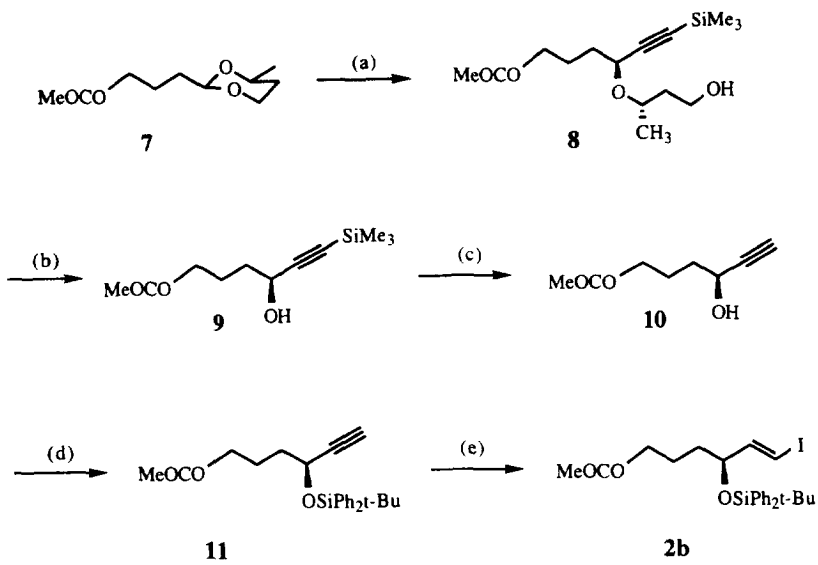
The chiral iodo vinyl alcohol **2a** was readily obtained in 42% yield (ee ≥ 98%) by kinetic resolution[5] of the racemic alcohol **6**[3b,c] which was prepared by a three-step sequence as followed: chlorovinylation[6] of methyl-4-(chloroformyl)-butyrate **4**, halogen exchange[6] to the iodo vinyl ketone **5b** and selective reduction[7] to the iodo alcohol **6** (scheme 1).




**Scheme 1:** (a) HC≡CH, 4 equiv. $AlCl_3$, $CCl_4/CH_2Cl_2$, -40° to 20°C, 3h, 80%; (b) NaI, $AlCl_3$, acetone, 79%; (c) $NaBH_4$, $CeCl_3,7H_2O$, MeOH, 92%; (d) 0.37 equiv. D (-) DIPT, 0.31 equiv. Ti(O*i*-Pr)4, 1.5 equiv. *t*-BuOOH, 4 Å mol. sieves, $CH_2Cl_2$, -20°C, 48h, 42%.

A second approach makes use of the Lewis acid promoted opening of acetals with silicon-containing nucleophiles, a method which has proven to be a powerful method for carbon-carbon bond formation.[8] Based on Johnson's landmark studies of acetal-initiated, cationic polyolefin cyclisations, both Kishi[9] and Johnson and Bartlett[10] reported remarkable levels of stereoselection in the Lewis acid promoted, nucleophilic opening of chiral dioxolane and dioxane acetals derived from optically active 2,3-butanediol and 2,4-pentanediol. Using bis-trimethylsilyl acetylene as nucleophile, propargylic alcohols were thus synthesized in high enantiomerical purities.[11] However, the application of such a methodology to functionnalized substrates was rare enough; moreover, the required 2,4-pentanediol was rather difficult to obtain in an optically pure form. We decided then to use the acetals derived from 2,4-butanediol which is easily obtained in bulk quantities by reduction of 3-hydroxy propanoates derived from microbial reduction of β-ketoesters,[12] depolymerisation of polyhydroxybutyrate[13] or nitrous deamination of threonine.[14] Due to disymmetry of the diol, these acetals may exist as two diastereomers; however, it was previously shown that, under thermodynamic control, a single diastereomer in which the two substituents are in equatorial position was obtained.[15]

The regioselectivity of the opening of such acetals was also questionable. Indeed, although it has been reported that the acetals derived from 2,4-butanediol form a single complex with $BF_3$ on the less hindered oxygen,[16] the opening of these acetals with nucleophiles does not give always the primary alcohol resulting from the regioselective cleavage of this less hindered C-O bond.[17]

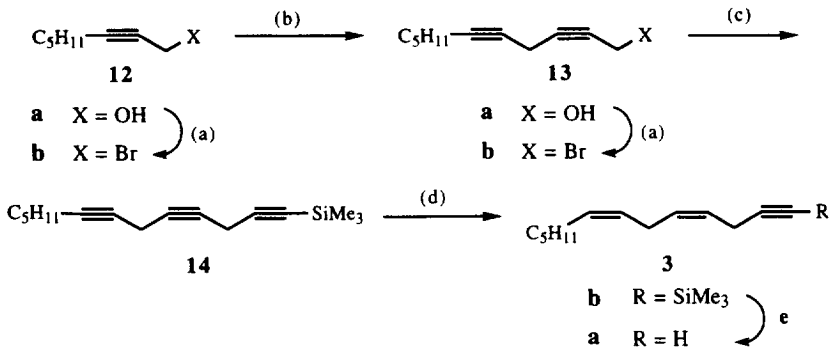



**Scheme 2**: (a) $Me_3SiC{\equiv}CSiMe_3$, $TiCl_4$, $CH_2Cl_2$, -78°C, 71%; (b) DMSO, $(COCl)_2$, -60°C, $Et_3N$ -60° to 20°C then $Bn_2NH_2^+$ $CF_3COO^-$, $C_6H_6$, 2h, 84%; (c) $Bu_4N^+F^-$, THF, 0°C, 1.5h, 78%; (d) *t*-$BuPh_2SiCl$, imidazole, DMF, 48h, 74%; (e) $Bu_3SnH$, 130°C, 2h then $I_2$, $CH_2Cl_2$, 0°C, 63%.

When the acetal **7** was reacted with bis-trimethylsilyl acetylene by slow addition at low temperature of a $TiCl_4$ solution in methylene chloride (4.5 M), the primary alcohol **8** resulting from the cleavage of the less hindered C-O bond was isolated in 71% yield as a pure diastereoisomer (scheme 2). Small quantities (7%) of the regioisomeric secondary alcohols easily separable by flash-chromatography were also observed.[18] The pure alcohol **8** was then oxidized by Swern oxidation and transformed into the free secondary alcohol **9** after β-elimination with dibenzylammonium trifluoroacetate in 84 % combined yield.[19] After deprotection of the triple bond, the resulting propargylic alcohol **10** was protected as a *t*-butyldiphenylsilyl ether to give **11** and transformed into the vinylic iodide **2b** by addition of tributyltin hydride followed by iodolysis according the reported procedures.[20]

**B.** Synthesis of the dienyne **3a**

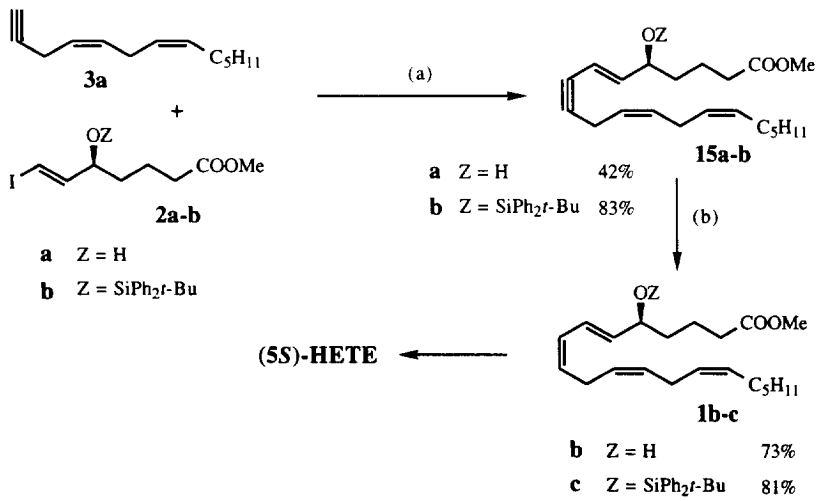
On the other hand, the skipped (*Z*,*Z*)-dienyne **3a** was obtained according to the following sequence (scheme 3). Treatment of alcohol **12a** with $PPh_3$ and $CBr_4$[21] followed by direct propargylic substitution of bromine by reaction of propargylic alcohol in the presence of copper iodide, sodium carbonate and tetra-*n*-butyl ammonium chloride in DMF[4] leads to the skipped diyne **13a** in 68% yield. The skipped triyne **14** was obtained under the same conditions as described above in 64% yield. Semi reduction of triyne **14** with P-2 Ni[22] and desilylation with $AgNO_3$-KCN[23] gave dienyne **3a** in 61% yield.




**Scheme 3:** (a) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0°C, 85-95%; (b) 1.1 equiv. HC≡C-$CH_2OH$, $Na_2CO_3$, CuI, $Bu_4NCl$, DMF, -15° à 20°C, 22h, 68%; (c) 1.2 equiv. $Me_3SiC{\equiv}CH$, $Na_2CO_3$, CuI, $Bu_4NCl$, DMF, -20° à 20°C, 19h, 75%; (d) P-2 Ni, $H_2$, EtOH, 68%; (e) $AgNO_3$,KCN, $H_2O$, MeOH, 89%.

## C. Synthesis of 5-HETE

In order to synthetise 5-HETE, the coupling reaction was achieved in a first time between the dienyne **3a** and the protected vinylic iodide **2b**. Using a catalytical amount of tetrakis-(triphenylphosphine)palladium and cuprous iodide in the presence of piperidine,[24] the trienyne **15b** was obtained in 83 % yield (scheme 4). The stereoselective reduction of the triple bond was achieved with activated zinc according to Boland and coll.[25] to give exclusively the pure 6*E*,8*Z*,11*Z*,14*Z* tetraene **1c**. The coupling with the unprotected vinylic iodide **2a** was also attempted and gave the conjugated enyne **15a** together with the corresponding δ-lactone (2:1 ratio, 42% yield). Stereoselective reduction by activated zinc[25] provided the conjugated diene **1b** in 73% yield. The ester **1b** was caracterized by its spectroscopic properties and is in accordance with literature.[26]




**Scheme 4:** (a) 10% CuI, 5% $Pd(PPh_3)_4$, $C_6H_6$, 2 equiv. piperidine 20°C, 6h; (b) Zn (Cu/Ag), MeOH/$H_2O$ 1/1, 30°C, 15h.

In conclusion, the described synthesis of (5*S*)-HETE has been realized by the coupling of two easily obtainable synthons **2** and **3a**. This strategy based on the efficient palladium-copper coupling reaction demonstrate further the generality and scope to make polyene compounds. Furthermore, the synthon **2** is also a useful precursor to (5*S*,12*S*)-di-HETE and to lipoxine B.

## Experimental

Products were purified by distillation or by flash chromatography (Kieselgel 60 Merck: 230-400 Mesh) and analyzed by VPC (BP5, 25 m capillary column ) or by TLC (silica gel 60F 254). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on a Bruker AC at 250 MHz for $^1$H and 100.56 MHz for $^{13}$C-NMR. $CDCl_3$ was used as solvent with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 599. Mass spectra were recorded on a Nermag R 10-10 (fitted with a VPC-mass coupling; column: CP Sil 5, 40 m).

(6*E*)-7-Chloro-5-oxo-hept-6-enoic acid, methyl ester **5a**

To a 500 mL flask fitted with a mechanical stirrer were added, at -40°C, 200 mL of $CCl_4$, 100 mL of $CH_2Cl_2$ and acetylene was bubbled through at a saturation rate for 30 min. Aluminium chloride (0.16 mol, 21.4 g) was added and acetylene was bubbled continuously through the mixture with stirring. The acid chloride **4** (0.04 mol, 6.58 g) dissolved in 10 mL of $CCl_4$ was added, at -40°C, via seringue pump (time addition 2.5 h) to the reaction mixture. After stirring at room temperature for 3 h, the black reaction mixture was poured into an ice-salt mixture and extracted with ether (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography ($CH_2Cl_2$) afforded the product **5a** in 80% yield (6.1 g). $C_8H_{11}O_3Cl$ calc. C 50.41 H 5.82, found C 50.35, H 5.95; I.R. (neat) cm$^{-1}$: 1730, 1680, 1095, 1585; $^1$H-NMR: δ 7.35 (d, 1H, J = 13.7Hz), 6.53 (d, 1H, J = 13.7Hz), 3.68 (s, 3H), 2.63 (t, 2H, J = 7.1Hz), 2.38 (t, 2H, J = 7.1Hz), 1.95 (quint, 2H, J = 7.1Hz); $^{13}$C-NMR: δ 196.55, 173.60, 136.40, 132.30, 51.65, 32.90, 32.85, 18.80; MS: m/z (%) 193 ((M+1), $^{37}$Cl), 192 (M, $^{37}$Cl), 191 (100, (M+H), $^{35}$Cl), 190 (M, $^{35}$Cl).

(6*E*)-7-Iodo-5-oxo-hept-6-enoic acid, methyl ester **5b**

To a solution of NaI (0.06 mol, 9.0 g) in acetone (40 mL) was added successively chloro enone **5a** (0.03 mol, 5.72 g) and $AlCl_3$ (6.6 mmol, 0.89 g) at room temperature. The stirred solution was kept at room temperature for 16 h before hydrolysis with water (20 mL). The aqueous layer was extracted with ether (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography ($CH_2Cl_2$) afforded the compound **5b** in 79% yield (6.7 g). I.R. (neat) cm$^{-1}$: 1730, 1670, 1565; $^1$H-NMR: δ 7.86 (d, 1H, J = 15.0Hz), 7.16 (d, 1H, J = 15.0Hz), 3.68 (s, 3H), 2.62 (t, 2H J = 7.1Hz), 2.38 (t, 2H J = 7.1Hz), 1.95 (quint, 2H J = 7.1Hz); $^{13}$C-NMR: δ 196.40, 173.40, 144.40, 99.25, 51.55, 39.00, 32.75, 18.70; MS: m/z (%) 300 (M+18), 283 (100, (M+1)), 268 (M-15).

(6*E*)-5-Hydroxy-7-iodo-6-enoic acid, methyl ester **6**

To a solution of iodo enone **5b** (9.6 mmol, 2.7 g) and $CeCl_3$ ; $7H_2O$ (10.56 mmol, 3.95 g) in MeOH (30 mL) was added slowly $NaBH_4$ (10.85 mmol, 410 mg) at room temperature. After complete addition, the reaction was stirred for 15 min. and was hydrolysed with brine (10 mL). The aqueous layer was extracted

with AcOEt (3 x 10 mL) and ether (3 x 10 mL). The combined organic layers were washed with water (15 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (cyclohexane:AcOEt 7:3) afforded the alcohol **6** in 92% yield (2.5 g). $C_8H_{13}O_3I$: calc. C 33.82 H 4.61, found C 33.70 H 4.75; I.R. (neat) $cm^{-1}$ : 3420, 1730, 1600, 1020; $^1$H-NMR: δ 6.58 (dd, 1H, J = 14.5 and 6.1Hz), 6.37 (dd, 1H, J = 14.2 and 0.8Hz), 4.10 (q, 1H, J = 6.1Hz), 3.68 (s, 3H), 2.36 (t, 2H, J = 7.1Hz), 2.00 (s, 1H), 1.82-1.64 (m, 2H), 1.58 (qd, 2H, J = 7.2 and 1.7Hz); $^{13}$C-NMR: δ 174.05, 148.30, 77.40, 74.00, 51.65, 35.75, 33.60, 20.45; MS (m/z): 253 (M-31), 267 (100, (M-17)), 285 (M+1), 302 (M+18).

(6*E*)-(5*S*)-Hydroxy-7-iodo-6-enoic acid, methyl ester **2a**

To a mixture of molecular sieves (4Å, 720 mg), D (-) DIPT (1.72 mmol, 410 mg) and Ti(O*i*-Pr)$_4$ (1.44 mmol, 410 mg) in 5 mL of $CH_2Cl_2$, at -20°C, was added the iodo alcohol **6** (4.58 mmol, 1.3 g) dissolved in 3 mL of $CH_2Cl_2$. After 15 min at -20°C, *t*-BuOOH (6.87 mmol, 2.3 mL, 3M in isooctane) was added dropwise and stirring was continued for 48 h at -20°C. The reaction mixture was hydrolysed, at -20°C, with a saturated aqueous solution of $Na_2SO_4$ for 1 h and then treated at room temperature with aqueous sodium hydroxide solution 30% (1 mL). The resulting mixture was vigorously stirred for 15 min. and filtered through a pad of celite. The aqueous layer was extracted with $Et_2O$ (2 x 15 mL), and the combined organic layers were washed successively with water (2 x10 mL), with brine (1 x 10 mL), dried over $MgSO_4$ and the solvant was removed *in vacuo*. Purification by flash chromatography ($CH_2Cl_2$:AcOEt 9:1) through silica gel afforded the iodo alcohol **2a** in 42% yield (547 mg). The enantiomeric excess of (*S*)-**2a** was confirmed to be ≥ 98% by capillary gas chromatographic columns on the derived (*S*)-α-acetoxypropanoic ester.[27] (*S*)-**2a**: $[\alpha]_D^{20}$ - 6 (c = 1.1, acetone).

(2*R*,4*S*)-2-(3'-carbomethoxypropyl)-4-methyl-1,3-dioxane **7**

A solution of methyl 4-formylbutanoate (2.86 g, 22 mmol)[28], (S)-1,3-butanediol (1.80 g, 20 mmol)[14] and *p*-toluenesulfonic acid monohydrate (0.19 g, 1 mmol) in anhydrous benzene was refluxed in a Dean-Stark. After refluxing for 6 hours, the solution was neutralized with a saturated solution of aqueous sodium hydrogenocarbonate and extracted with ether (3 x 20 mL). The organic phase was washed with a saturated solution of sodium chloride, dried on $MgSO_4$ and concentrated *in vacuo*. After chromatography on silica gel (cyclohexane:AcOEt 8:2), 3.14 g of pure acetal were isolated (yield: 82%). $C_{10}H_{18}O_4$ : calc. C 59.39 H 8.97, found C 59.25 H 8.75; $[\alpha]_D^{20}$ + 1.8 (c = 3.31, $CH_2Cl_2$); IR (neat) $cm^{-1}$ 1735 (C=O); $^1$H-NMR: δ 1.19 (t, 3H, J = 6.3Hz), 1.38 (m, 1H), 1.57 (m, 5H), 2.30 (t, 2H, J = 6.9Hz), 3.65 (s, 3H), 3.69 (dt, 2H, J = 2.5 and 6.2Hz), 4.03 (dq, 1H, J = 4.8 and 1.1Hz), 4.50 (t, 1H, J = 4.8Hz); $^{13}$C-NMR: δ 19.45, 21.55, 32.85, 33.60, 34.20, 51.25, 66.35, 72.50, 101.30, 173.70; MS: m/z (%) 220 (100, M+18), 203 (23, M+1), 147 (10).

(5*S*,1'*R*)-5-(3'-hydroxy-1'-methylpropoxy)-7-trimethylsilyl-hept-6-ynoic acid, methyl ester **8**

A freshly prepared solution of $TiCl_4$ (5.69 g, 30 mmol) in methylene chloride (6 mL) was slowly added (1 hour) to a cold (- 78 °C) solution of acetal **7** (2.73 g, 15 mmol) and bis-trimethylsilyl acetylene (10.22 g, 60 mmol) in methylene chloride (200 mL). After stirring for an additional period of 30 min., the solution was quenched by addition of a saturated solution of aqueous sodium hydrogenocarbonate and the aqueous phase was extracted with ether (3 x 30 mL). After drying on $MgSO_4$ and concentration, the residual oil was

chromatographed on silicagel (cyclohexane:AcOEt 7:3) to give the secondary alcohol (0.305 g, 7%) and the alcohol **8** (3.20 g; 71%). $C_{15}H_{28}O_4Si$: calc. C 59.96 H 9.39, found C 60.05 H 9.35; $[\alpha]_D^{20}$ - 26.6 (c = 1.75, $CH_2Cl_2$); IR (neat) $cm^{-1}$ 3400-3200 (OH), 1735 (C=O); $^1$H-NMR: δ 0.05 (s, 9H), 1.11 (d, 3H, J = 6.2Hz), 1.5-1.6 (m, 6H), 2.13 (s, 1H), 2.16 (t, 2H, J = 7.0Hz), 3.50, (s, 3H), 3.53 (t, 2H, J = 5.6Hz), 3.72 (q, 1H, J = 5.8Hz), 3.92 (t, 1H, J = 6.1Hz); $^{13}$C-NMR: δ -0.20, 20.65, 21.20, 33.50, 34.75, 37.25, 51.35, 63.80, 69.80, 90.70, 104.10, 173.65; MS: m/z (%) 314 (15, M+18), 301 (5, M+1), 283 (100).

(5*S*)-5-Hydroxy-7-trimethylsilyl-hept-6-ynoic acid, methyl ester **9**

DMSO (1.25 g, 16 mmol) was added at - 60°C to a solution of oxalyl chloride (1.02 g, 8 mmol) in $CH_2Cl_2$ (25 mL). After stirring for ten minutes, a solution of the alcohol **8** (2.20 g, 7 mmol) was added and stirred for 15 min. $Et_3N$ (3.53 g, 35 mmol) was then added and the mixture was warmed up to room temperature for 30 min. before hydrolysis. After extraction with $CH_2Cl_2$ (3 x 20 mL), the organic phase was washed with HCl 1N, dried on $MgSO_4$ and concentrated. The crude aldehyde is directly added to a solution of dibenzylammonium trifluoroacetate[29] in benzene (130 mL) and stirred at 0-5°C for two hours. After hydrolysis and extraction with ether (3 x 20 mL), the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give after flash-chromatography (cyclohexane:AcOEt 7:3) the pure propargylic alcohol **9** (1.35 g, 84%). $C_{11}H_{20}O_3Si$: calc. C 57.86 H 8.83, found C 58.35 H 8.90. $[\alpha]_D^{20}$ - 6.4 (c = 1.40, $CH_2Cl_2$); IR (neat) $cm^{-1}$ 3400 and 3300 (OH), 2540 (C=C), 1730 (C=O); $^1$H-NMR: δ 0.02 (s, 9H), 1.6-1.9 (m, 4H), 2.39 (t, 2H, J = 7.0Hz), 2.75 (br s, 1H), 3.65 (s, 3H), 4.25 (t, 1H, J = 6.2Hz). $^{13}$C-NMR: δ - 0.20, 19.85, 33.55, 36.70, 51.80, 61.50, 73.00, 83.20, 174.00.

(5*S*)-5-Hydroxy-hept-6-ynoic acid, methyl ester **10**

A solution of the alcohol **9** (1.35 g, 5.9 mmol) in THF (10 mL) was slowly added at 0°C to tetrabuylammonium fluoride 1M in THF (11.8 mL, 11.8 mmol). After stirring for 1.5 hour, the reaction was hydrolyzed with saturated aqueous ammonium chloride and extracted with ether (4 x 15 mL). The organic phase was dried on $MgSO_4$ and concentrated *in vacuo* without heating. Flash-chromatography on silica gel (cyclohexane:AcOEt 7:3) afforded the pure alcohol **10** (720 mg, 78%). $C_8H_{12}O_3$: calc. C 61.52 H 7.74, found C 61.35 H 7.90; $[\alpha]_D^{20}$ - 20.2 (c = 2.2, $CCl_4$)- (Lit[3a]: $[\alpha]_D^{20}$ - 18.2 (c = 1.3, $CCl_4$); IR (neat) $cm^{-1}$ 3400 and 3300 (OH), 2540 (C=C), 1730 (C=O); $^1$H-NMR: δ 1.6-1.9 (m, 4H), 2.39 (t, 2H, J = 7.0Hz), 2.48 (d, 1H, J = 1.9Hz), 2.75 (Br s, 1H), 3.70 (s, 3H), 4.39 (dt, 1H, J = 1.9 and 6.2Hz); $^{13}$C-NMR: δ 19.80, 33.50, 36.75, 51.80, 61.25, 73.50, 83.90, 174.00; MS: m/z (%) 174 (15, M+18), 157 (5, M+1), 142 (100).

(5*S*)-5-*t*-butyl diphenyl silyloxy-hept-6-ynoic acid, methyl ester **11**

*t*-Butyldiphenylchlorosilane (1.10 g, 4 mmol) was added at 0°C to a solution of the alcohol **10** (468 mg, 3 mmol) and imidazole (1 g, 15 mmol) in DMF (7 mL). After stirring for two days at room temperature, the mixture was hydrolyzed with HCl 1N, extracted with ether, dried and concentrated. The crude product was chromatographed on silica gel column (cyclohexane:AcOEt 93:7). Yield: 74% (874 mg); $[\alpha]_D^{20}$ - 38.5 (c = 1.35, $CH_2Cl_2$); $^1$H-NMR: δ 1.12 (s, 9H), 1.6-1.9 (m, 4H), 2.25 (t, 2H, J = 7.0Hz), 2.32 (d, 1H, J = 2.2Hz), 3.65 (s, 3H), 4.35 (m, 1H), 7.35 (m, 6H), 7.70 (m, 4H); MS: m/z (%) 412 (100, M+18), 395 (10, M+1), 337 (25).

(5*S*)-(6*E*)-5-*t*-butyl diphenyl silyloxy-7-iodo-hept-6-enoic acid, methyl ester **2b**

A mixture of the silylated alcohol **11** (788 mg, 2 mmol), tributyltin hydride (786 mg, 2.7 mmol) and azobisisobutyronitrile (8 mg, 0.05 mmol) was heated at 130°C for 2 hours. After cooling to 0°C, a solution of iodine (685 mg, 2.7 mmol) in anhydrous $CH_2Cl_2$ was slowly added. The solution was then hydrolyzed, extracted with ether and washed with a solution of sodium thiosulfate. After drying on $MgSO_4$, the organic phase was concentrated *in vacuo* and chromatographed on a silica gel column (cyclohexane:AcOEt 97:3). Yield: 63% (658 mg). $C_{24}H_{31}IO_3Si$: calc. C 55.17 H 5.98, found C 54.98 H 5.80. $[\alpha]_D^{20}$ - 48.8 (c = 1.91, $CH_2Cl_2$); IR (neat) $cm^{-1}$ 1735 (C=O), 900 and 750 (C=C); $^1$H-NMR: δ 1.05 (s, 9H), 1.4-1.7 (m, 4H), 2.20 (t, 2H, J = 7.0Hz), 3.65 (s, 3H), 4.30 (m, 1H), 5.95 (dd, 1H, J = 1.0 and 14.4Hz), 6.45 (dd, 1H, J = 6.8 and 14.4Hz), 7.35 (m, 6H), 7.72 (m, 4H); $^{13}$C-NMR: δ 19.30, 28.95, 33.60, 38.25, 51.45, 75.45, 77.30, 127.50, 128.15, 129.75, 135.75, 135.80, 147.85, 173.90; MS: m/z (%) 540 (17, M+18), 465 (35), 267 (100).

1-Bromo-oct-2-yne **12b**

To a solution of propargyl alcohol **12a** (20 mmol, 2.52 g) and carbon tetrabromide (26 mmol, 8.63 g) in 40 mL of $CH_2Cl_2$ was added dropwise, at 0°C, triphenylphosphine (28 mmol, 7.33 g) dissolved in 10 mL of $CH_2Cl_2$. After 45 min., the stirred reaction was treated with 80 mL of ether-pentane (1:4) and a precipitate of phosphine oxide was formed. The mixture was then filtered on silica gel (pentane) and the organic layers were concentrated under vacuum. Purification by distillation afforded propargyl bromide **12b** in 95% yield (3.59 g) bp 62°C (6 mmHg); I.R. (neat) $cm^{-1}$ : 2950, 2920, 2850, 2300, 2200, 1460, 1420, 1200, 760; $^1$H-NMR: δ 3.93 (t, 2H, J = 2.4Hz), 2.33 (tt, 2H, J = 7.1 and 2.4 Hz), 1.58 to 1.46 (m, 2H), 0.90 (t, 3H, J = 7.1Hz); $^{13}$C-NMR: δ 88.05, 75.15, 30.90, 27.95, 22.05, 18.80, 15.60, 13.80.

Undeca-2,5-diyn-1-ol **13a**

To a suspension of sodium carbonate (18 mmol, 1.91 g), copper iodide (12 mmol, 2.29 g) and tetrabutylammonium chloride (12 mmol, 3.34 g) in 10 mL of DMF were added successively, at -15°C, propargyl alcohol (13.2 mmol, 0.74 g) and propargyl bromide **12b** (12 mmol, 2.27 g) dissolved in 4 mL of DMF. After stirring at -5°C for 2 h and at room temperature for 20 h, the reaction mixture was treated with saturated solution of $NH_4Cl$ (20 mL). The aqueous layer was extracted with ether (3 x 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography ($CH_2Cl_2$:AcOEt 96:4) afforded the propargyl alcohol **13a** in 68% yield (1.33 g); I.R. (neat) $cm^{-1}$ : 3350, 2960, 2920, 2860, 2260, 2220, 1460, 1310, 1020; $^1$H-NMR: δ 4.28 (t, 2H, J = 2.2Hz), 3.20 (quin, 2H, J = 2.3Hz), 2.16 (tt, 2H + OH, J = 7.0 and 2.4Hz), 1.50 (quin, 2H, J = 7.0Hz), 1.43 to 1.24 (m, 4H), 0.9 (t, 3H, J = 7.0Hz); $^{13}$C-NMR: δ 80.95, 80.35, 78.20, 73.15, 50.75, 30.85, 28.15, 21.95, 18.40, 13.70, 9.55; MS: m/z (%) 182 (100, M+18), 164 (M). The spectral properties of **13a** were in good agreement with those reported in the literature.[30]

1-Bromo-undeca-2,5-diyne **13b**

To a solution of propargyl alcohol **13a** (7.07 mmol, 1.16 g) and carbon tetrabromide (9.2 mmol, 3.05 g) in 18 mL of $CH_2Cl_2$ was added dropwise, at 0°C, triphenylphosphine (9.87 mmol, 2.59 g) dissolved in 4 mL of $CH_2Cl_2$. After 45 min., the stirred reaction was treated with 40 mL of ether-pentane (1:4) and a

precipitate of phosphine oxide was formed. The mixture was then filtered on silica gel (pentane) and the organic layers were concentrated under vacuum. Purification by flash chromatography (pentane) afforded the propargyl bromide **13b** in 85% yield (1.37 g); I.R. (neat) $cm^{-1}$: 2950, 2920, 2850, 2260, 2220, 1460, 1310, 1210, 610; $^1$H-NMR: δ 3.92 (t, 2H, J = 2.4Hz), 3.22 (quin, 2H, J = 2.4Hz), 2.15 (tt, 2H, J = 7.0 and 2.4Hz), 1.50 (quin, 2H, J = 7.0Hz), 1.42 to 1.24 (m, 4H), 0.9 (t, 3H, J = 7.0Hz); $^{13}$C-NMR: δ 81.85, 81.15, 74.95, 72.50, 30.80, 28.10, 21.95, 18.40, 14.61, 13.70, 9.85. The spectral properties of **13b** were in good agreement with those reported in the literature.[31]

1-Trimethyl silyl-trideca-1,4,7-triyne **14**

To a suspension of sodium carbonate (20 mmol, 2.12 g), copper iodide (13.37 mmol, 2.54 g) and tetrabutylammonium chloride (13.37 mmol, 3.72 g) in 13 mL of DMF were added successively, at -20°C, trimethylsilyl acetylene (16.32 mmol, 1.60 g) and propargyl bromide **13b** (13.37 mmol, 3.035 g) dissolved in 3 mL of DMF. After stirring at -5°C for 2 h and at room temperature for 20 h, the reaction mixture was treated with saturated solution of $NH_4Cl$ (20 mL). The aqueous layer was extracted with ether (3 x 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (cyclohexane:AcOEt 98:2) afforded the skipped triyne **14** in 75% yield (2.44 g); $C_{16}H_{24}Si$: calc. C 78.61 H 9.9, found C 78.45 H 10.02; I.R. (neat) $cm^{-1}$: 2960, 2920, 2860, 2180, 1250, 850, 760; $^1$H-NMR: δ 3.20 (t, 2H, J = 2.4Hz), 3.13 (quin, 2H, J = 2.4Hz), 2.14 (tt, 2H, J = 7.0 and 2.4Hz), 1.42 to 1.54 (m, 2H), 1.38 to 1.23 (m, 4H), 0.87 (t, 3H, J = 7.0Hz), 0.14 (s, 9H); $^{13}$C-NMR: δ 99.90, 85.05, 80.95, 75.40, 73.65, 73.60, 31.05, 28.40, 22.20, 18.65, 13.95, 10.90, 9.75, -0.15; MS: m/z (%) 262 (100, (M+18)).

(4*Z*,7*Z*)-1-Trimethyl silyl-trideca-4,7-dien-1-yne **3b**

To a vigorously stirring solution of nickel acetate tetrahydrate (1.46 mmol, 0.365 g) in 95% ethanol (25 mL) under a hydrogen atmosphere was added a solution of sodium borohydride (1.46 mmol, 0.055 g) in ethanol (2.5 mL). After 30 min. ethylenediamine (2.93 mmol, 0.176 g) was added followed by a solution of triyne **14** (9.13 mmol, 2.229 g) in ethanol (4 mL). When hydrogen uptake was quantitative in 2.5 h and then virtually ceased, the black mixture was filtered over a short column of silca gel and the silica gel was rinsed several times with ether-pentane (1:1). The organic layers were concentrated under vacuum and purification by flash chromatography (pentane) afforded the skipped dienyne **3b** in 68% yield (1.54 g); Z stereoisomeric purity = 97% determined by gas chromatographic analyses performed on a model Girdel equipped with capillary column (SGE 50 QC 2 / BP5 0.25). $C_{16}H_{28}Si$: calc. C 77.34 H 11.36, found C 77.05 H 11.52; I.R. (neat) $cm^{-1}$: 3010, 2960, 2920, 2860, 2180, 1650, 1450, 1250, 850, 760; $^1$H-NMR: δ 5.53 to 5.24 (m, 4H), 3.02 (d, 2H, J = 4.8Hz), 2.80 (t, 2H, J = 5.6Hz), 2.05 (q, 2H, J = 6.7Hz), 1.46 to 1.17 (m, 6H), 0.88 (t, 3H, J = 6.8Hz), 0.15 (s, 9H); $^{13}$C-NMR: δ 130.85, 130.10, 126.85, 124.05, 105.10, 84.20, 31.50, 29.25, 27.20, 25.55, 22.55, 18.35, 14.05, 0.05; MS: m/z (%) 267 (M+19), 266 (M+18), 249 (M+1), 175 (M-73).

(4*Z*,7*Z*)-trideca-4,7dien-1-yne **3a**

To a silylated skipped dienyne **3b** (5.56 mmol, 1.38 g) dissolved in 15 mL of ethanol was added, in 5 min. at room temperature, silver nitrate (14.83 mmol, 2.52 g) dissolved in 5 mL of water and 20 mL of

ethanol. The temperature rose to 30 °C and a precipitate of the silver acetylide was formed. After 20 min., the stirred reaction was treated with a solution of potassium cyanide (70.30 mmol, 4.64 g) in 6.5 mL of water. Stirring was continued until the precipitate had dissolved and the reaction mixture was then concentrated. Ether was added (20 mL) and the organic layer washed with $H_2O$ (2 x 10 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (pentane) afforded the skipped dienyne **3a** in 89% yield (0.87 g); I.R. (neat) $cm^{-1}$: 3300, 3000, 2960, 2920, 2840, 2120, 1640, 1450; $^1$H-NMR: δ 5.53 to 5.24 (m, 4H), 2.99 (dd, 2H, J = 5.4 and 2.7Hz), 2.82 (t, 2H, J = 6.0Hz), 2.06 (q, 2H, J = 6.7Hz), 2.00 (t, 1H, J = 2.7Hz), 1.45 to 1.18 (m, 6H), 0.91 (t, 3H, J = 6.8Hz); $^{13}$C-NMR: δ 130.85, 130.35, 126.70, 123.75, 82.60, 68.00, 31.45, 29.25, 27.15, 25.45, 22.55, 16.80, 14.00; MS: m/z (%) 177 (100, (M+1)). The spectral properties of **3a** were in good agreement with those reported in the literature.[32]

(5*S*)-(6*E*,11*Z*,14*Z*)-5-hydroxy-eicosa-6,11,14-trien-8-ynoic acid, methyl ester **15a**

Piperidine (43 mg, 0.5 mmol) and cuprous iodide (5 mg, 0.026 mmol) were added at room temperature to a solution of vinyl iodide **2a** (71 mg, 0.25 mmol) and tetrakis(triphenylphosphine)palladium (15 mg, 0.013 mmol). Then, dienyne **3a** (90 mg, 0.51 mmol) in benzene (2 mL) was slowly added (time addition 2h). The mixture was stirred for 6 hours, diluted in ether (10 mL) and washed with a saturated solution of ammonium chloride. After drying, the organic phase was concentrated in vacuo and chromatographed on silica gel. (cyclohexane:AcOEt 7:3); Yield: 42% (35 mg); IR (neat) $cm^{-1}$ 1735 (C=O); 740 and 700 (C=C); $^1$H-NMR: δ 0.85 (t, 3H, J = 6.7Hz), 1.10-1.75 (m, 11H), 1.97 (m, 2H), 2.27 (t, 2H, J = 7.2Hz), 2.73, (t, 2H, J = 5.9Hz), 3.02 (m, 2H), 3.60 (s, 3H), 4.07 (m, 1H), 5.18-5.48 (m, 4H), 5.65 (m, 1H), 5.94 (dd, 1H, J = 6.2 and 15.8Hz); $^{13}$C-NMR: δ 173.95, 144.05, 130.85, 130.15, 126.80, 124.00, 110.60, 89.15, 78.05, 71.85, 51.55, 36.15, 33.70, 31.45, 29.25, 27.20, 25.50, 22.50, 22.60, 17.20, 14.05.

(5*S*)-(6*E*,11*Z*,14*Z*)-5-*t*-butyl diphenyl silyloxy-eicosa-6,11,14-trien-8-ynoic acid, methyl ester **15b**

Piperidine (34 mg, 0.4 mmol) and cuprous iodide (4 mg, 0.02 mmol) were added at room temperature to a solution of vinyl iodide **2b** (105 mg, 0.2 mmol) and tetrakis(triphenylphosphine)palladium (12 mg, 0.01 mmol). Then, dienyne **3a** (68 mg, 0.38 mmol) in benzene (2 mL) was slowly added (time addition 2 h). The mixture was stirred for 6 hours, diluted in ether (10 mL) and washed with a saturated solution of ammonium chloride. After drying, the organic phase was concentrated in vacuo and chromatographed on silica gel. (cyclohexane:AcOEt 95:5); Yield: 83% (91 mg); $[\alpha]_D^{20}$ - 68 (c = 1.39, acetone); IR (neat) $cm^{-1}$ 1740 (C=O); 740 and 700 (C=C); $^1$H-NMR: δ 0.89 (t, 3H, J = 6.7Hz), 1.06 (s, 9H), 1.20-1.64 (m, 10H), 2.03 (m, 2H), 2.12 (t, 2H, J = 7.3Hz), 2.80, (t, 2H, J = 5.8Hz), 3.12 (m, 2H), 3.61 (s, 3H), 4.12-4.27 (m, 1H), 5.27-5.57 (m, 5H), 5.99 (dd, 1H, J = 6.0 and 15.8Hz), 7.23-7.40 (m, 6H), 7.50-7.60 (m, 4H); $^{13}$C-NMR: δ 13.70, 17.70, 19.15, 19.50, 22.35, 25.35, 26.85, 27.05, 29.10, 31.30, 33.70, 36.45, 51.15, 72.80, 78.25, 88.35, 109.95, 124. 05, 126.75, 127.30, 129.50, 129.50, 129.80, 133.90, 135.65, 135.70, 143.70, 173.50; MS: m/z (%) 588 (25, M+18), 571 (5, M+1), 315 (100).

(5*S*)-(6*E*,8*Z*,11*Z*,14*Z*)-5-hydroxy-eicosa-6,8,11,14-tetraenoic acid, methyl ester **1b**

To a solution of compound **15a** (22 mg, 0.066 mmol) in water-methanol 1:1 (20 mL) was added activated zinc powder (1 g)[25]. After stirring and warming to 40°C for 12 hours, the mixture was filtered on a pad of celite. The organic phase was concentrated *in vacuo*, diluted in ether (5 mL) and washed with water.

After drying on $MgSO_4$, the compound was purified by chromatography on silica gel (cyclohexane:AcOEt 7:3). Yield: 73% (16.2 mg); $[\alpha]_D^{20}$ 13 (c = 1.3, $C_6H_6$)-(Lit[2d]: ; $[\alpha]_D^{23}$ 14 (c = 2.0, $C_6H_6$)); $^1$H-NMR: δ 6.53 (dd, 1H, J = 15.0 and 11.0Hz), 5.99 (t, 1H, J = 11.0Hz), 5.69 (dd, 1H, J = 15.0 and 6.7Hz), 5.50 to 5.29 (m, 5H), 4.18 (m, 1H), 3.67 (s, 3H), 2.96 (t, 2H, J = 6.5Hz), 2.81 (t, 2H, J = 6.0Hz), 2.36 (t, 2H, J = 7.3Hz), 2.17 (s, 1H), 2.05 (q, 2H, J = 7.0Hz), 1.80 to 1.51 (m, 4H), 1.46 to 1.20 (m, 6H), 0.90 (t, 3H, J = 6.7Hz); $^{13}$C-NMR: δ 174.00, 135.95, 130.70, 130.65, 129.05, 127.90, 127.45, 127.35, 125.75, 72.35, 51.55, 36.60, 33.85, 31.55, 29.35, 27.25, 26.10, 25.70, 22.60, 20.85, 14.05. The spectral properties of **1b** were in good agreement with those reported in the literature.[26]

(5*S*)-(6*E*,8*Z*,11*Z*,14*Z*)-5-*t*-butyl diphenyl silyloxy-eicosa-6,8,11,14-tetraenoic acid, methyl ester **1c**

To a solution of compound **15b** (76 mg, 0.133 mmol) in water-methanol 1:1 (20 mL) was added activated zinc powder (1 g)[25]. After stirring and warming to 40°C for 14 hours, the mixture was filtered on celite. The organic phase was concentrated *in vacuo*, diluted in ether (5 mL) and washed with water. After drying on $MgSO_4$, the compound was purified by chromatography on silica gel (cyclohexane:AcOEt 95:5). Yield: 81% (62 mg); $[\alpha]_D^{20}$ - 21 (c = 1.11, acetone); IR (neat) cm$^{-1}$ 1740 (C=O); 1680 (C=C) 740 and 700 (C=C); $^1$H-NMR: δ 0.89 (t, 3H, J = 6.7Hz), 1.07 (s, 9H), 1.24-1.43 (m, 6H), 1.47-1.70 (m, 4H), 2.05 (m, 2H), 2.20 (t, 2H, J = 7.1Hz), 2.79, (m, 4H), 3.63 (s, 3H), 4.22 (m, 1H), 5.24-5.50 (m, 5H), 5.59 (dd, 1H, J = 6.8 and 15.1Hz), 5.88 (t, 1H, J = 10.9Hz) 6.17 (dd, 1H, J = 11.0 and 15.2Hz), 7.38 (m, 6H), 7.66 (m, 4H); $^{13}$C-NMR: δ 14.05, 19.30, 20.10, 22.55, 25.60, 25.95, 27.00, 27.15, 29.30, 31.45, 33.95, 37.20, 51.35, 73.70, 125.45, 127.45, 127.50, 128.05, 128.75, 129.45, 129.55, 130.50, 134.05, 134.65, 135.85, 135.95, 173.90; MS: m/z (%) 590 (17, M+18), 573 (5, M+1), 317 (100).

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