Tetrahedron: Asymmetry Vol. 2, No. 6, pp. 457-469, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Asymmetric Synthesis of the C-1-C-8 Fragment of Leukotriene B_4 and C-11-C-20 Fragments of Leukotriene B_4 and 12(S)-Hydroxy-5,8,14(Z), 10(E) Eicosatetraenoic Acid

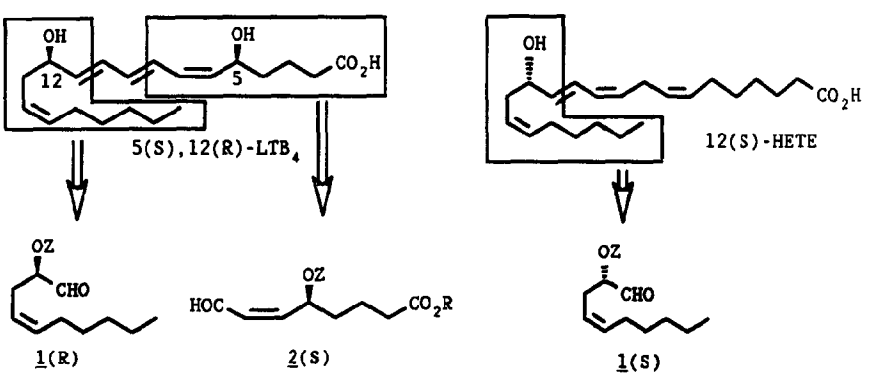
Guy Solladié*, Chafiq Hamdouchi, Chewki Ziani-Chérif

Ecole Européenne des Hautes Etudes des Industries Chimiques (URA 466), 67008-Strasbourg, France.

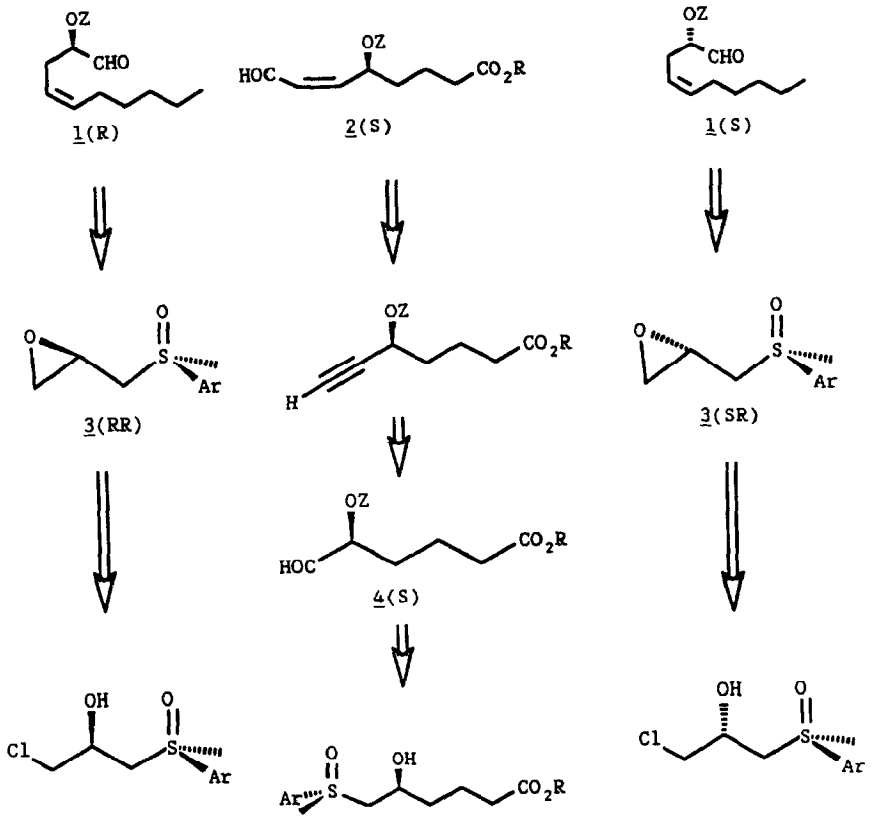
(*Received* 9 *May* 1991)

Abstract : *An asymmetric synthesis of the C-1-C-8 fragment of LTB_4 based on the reduction of optically active β-ketosulfoxides is described as well as the asymmetric synthesis of the C-11-C-20 fragments of LTB_4 and 12(S)-hydroxy-5,8,14(Z), 10(E) eicosatetraenoic acid (12-HETE) from optically active α-sulfinyl epoxides.*

Leukotrienes and hydroxyeicosatetraenoic acids (HETE'S) are a class of biologically important arachidonic acid metabolites, some of which have been implicated in inflammation and a number of health problems. Their extremely low availability from natural sources coupled with the demand for these compounds for biological investigations prompted us to investigate possible strategies for their constructions. In this paper we report the asymmetric synthesis of the chiral parts (R)-1, (S)-2 of 5(S), 12(R) LTB_4 as well as that of a precursor of the chiral moiety (S)-1 of 12(S).

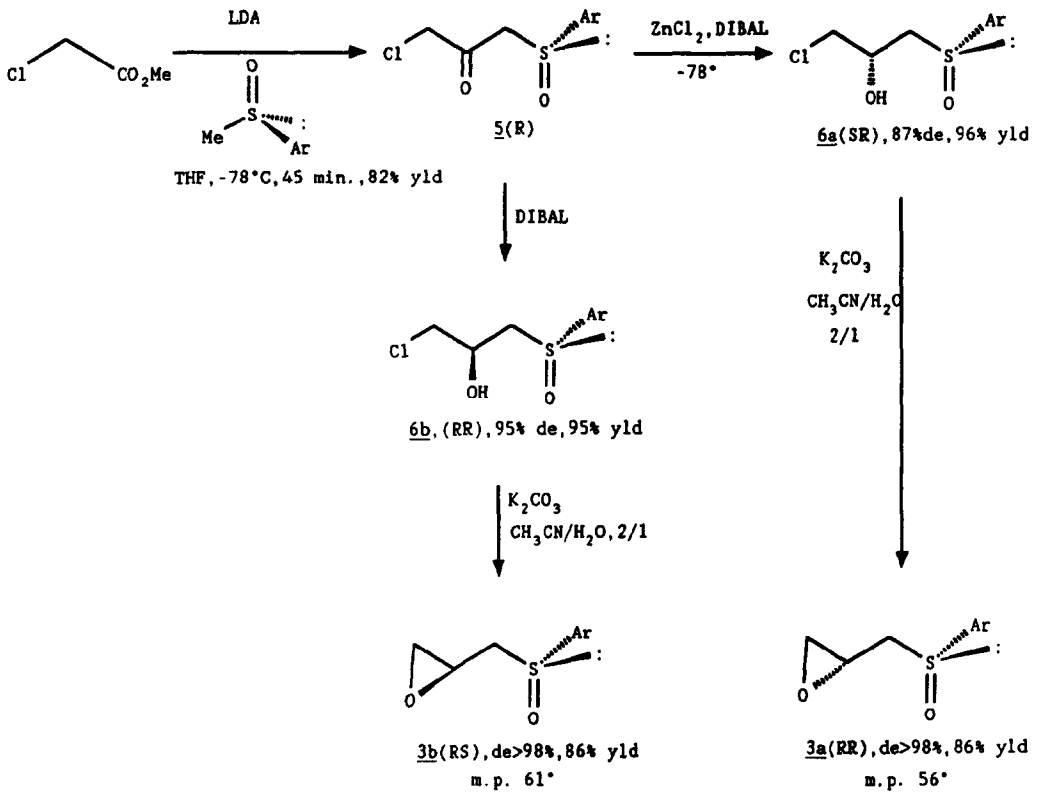


The homoallylic hydroxy-aldehydes enantiomers (R)-1 and (S)-1 were readily prepared from the α-sulfinyl epoxides (RR)-3 and (RS)-3 easily obtained from the corresponding γ-chloro β-hydroxysulfoxides[1]. The hydroxyaldehyde (S)-2 vinylogue of compound 4 was synthesized from the corresponding β-hydroxysulfoxide via a Pummerer rearrangement.



I. Synthesis of the α-sulfinyl epoxides (RR)-3 and (RS)-3

The γ-chloro β-ketosulfoxide, (R)-5 was obtained in 82% yield from the reaction of methyl chloroacetate and (+)(R) methyl p-tolylsulfoxide. From the numerous examples reported from our laboratory[2], the reduction with DIBAL in presence of zinc chloride afforded the γ-chloro β-hydroxysulfoxide 6 in the RS configuration (87% de) while the reduction with DIBAL alone gave the RR diastereoisomer (95% de). The diastereoisomeric excess was determined by ^1H NMR[2] from the signals corresponding to the methylene protons α to sulfur.

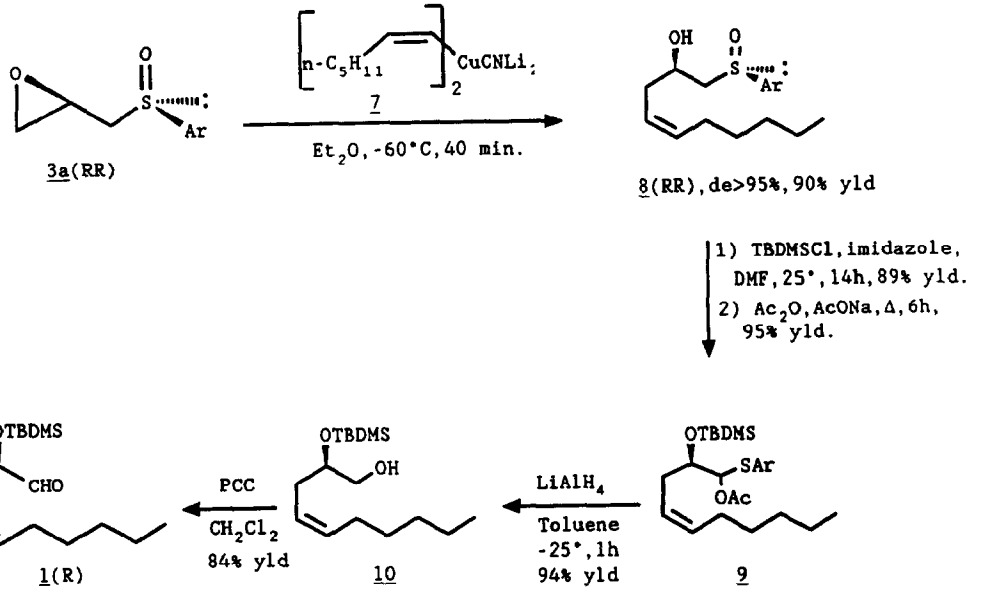


Finally the epoxides (RS)-3 and (RR)-3 were obtained in 86% yield by treatment with potassium carbonate in an acetonitrile-water mixture. These epoxides which are white solids can be purified by crystallization, the diastereoisomeric excess was shown to be higher than 98% by ^1H NMR from the ABC pattern of the epoxydic protons.

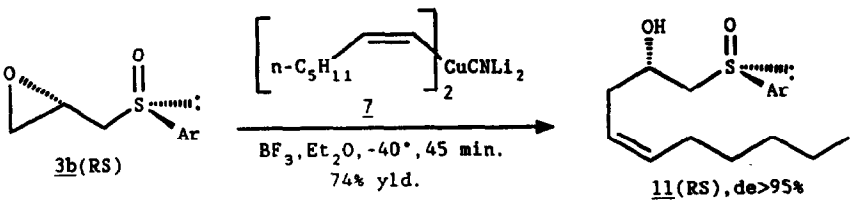
II. Synthesis of the homoallylic hydroxyaldehyde (R)-1 and of the precursor (RS)-11 of (S)-1

The epoxide (RR)-3 was reacted with the (E) cyanocuprate 7 in the conditions described by Normant[3] to give the homoallylic ß-hydroxysulfoxide (RR)-8 in 90% yield. The diastereoisomeric excess was checked by ^1H NMR from the AB pattern of the protons α to the sulfoxide group. The absolute configuration was also confirmed by the value of the non-equivalence between these 2 protons : $\Delta\nu$ = 33Hz in the RR configuration and $\Delta\nu$ = 86Hz in the RS configuration (compound 11). Finally the E configuration of the double bond was also attested by the coupling constant (J=10.3Hz). After protecting the OH group with a TBDMS, the molecule was submitted to a Pummerer rearrangment in acetic anhydride and the resulting

acetate 9 reduced with $LiAlH_4$ in toluene. Finally oxidation of the primary alcohol gave the homoallylic hydroxyaldehyde (R)-1 in 84% yield.

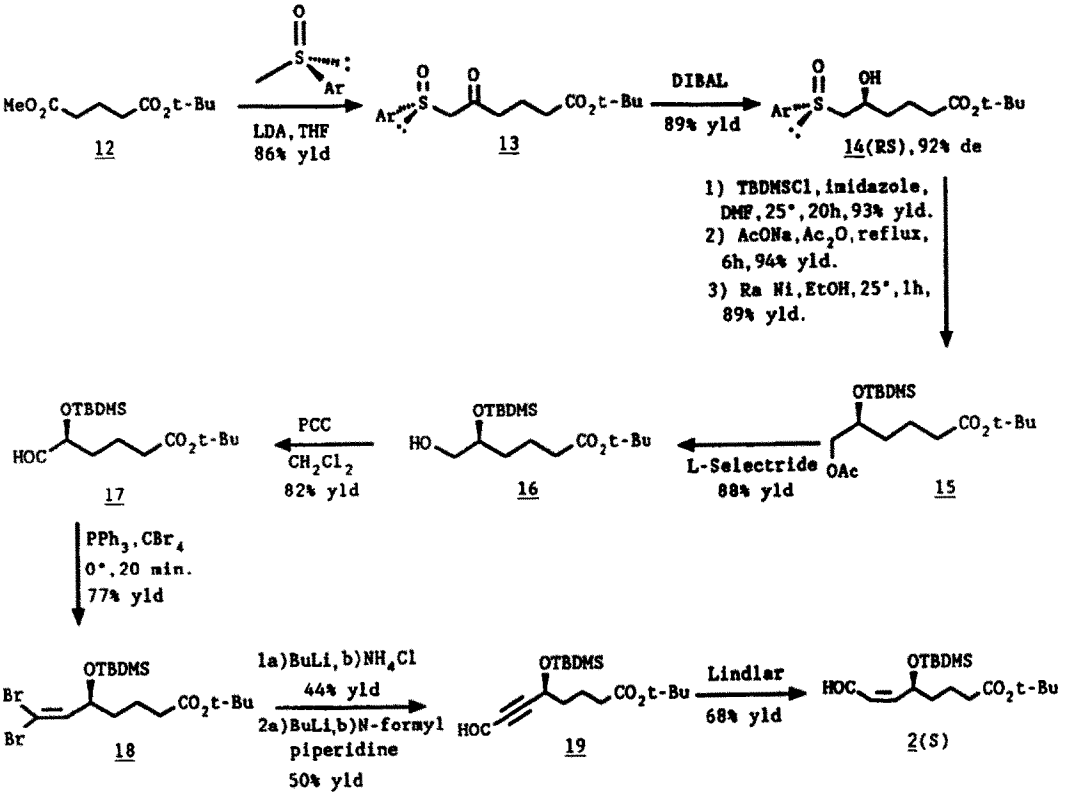


Similarly the epoxide (RS)-3 was reacted with the same cyanocuprate 7 in presence of boron trifluoride to give in 74% the allylic β-hydroxysulfoxide (RS)-11 with a diastereoisomeric excess higher than 95%. The same strategy will allow to obtain the enantiomeric homoallylic hydroxyaldehyde (S)-1.



III. Synthesis of the fragment (S)-2 of LTB_4

The β-ketosulfoxide 13 was obtained from the ester 12 in 86% yield in using two equivalents of (+)(R)-methyl p-tolylsulfoxide. Reduction with DIBAL gave the (RS) diastereoisomer 14 in 89%



yield and 92% de. Protection of the hydroxyl, Pummerer rearrangement and desulfurization with Raney Nickel afforded the acetate **15** which was reduced with L-selectride (saponification of this acetate gave mainly the transfer of the protecting group to the primary OH). Finally oxidation to the aldehyde with PCC followed by a Wittig type reaction with carbon tetrabromide, halogen elimination and formylation gave the propargylic aldehyde **19** which was reduced with Lindlar catalyst to the target molecule (S)-**2**.

The described synthesis of these molecules demonstrated further the generality and scope of the asymmetric synthesis mediated by a chiral sulfoxide group. The total synthesis of LTB_4 and analogues from the intermediates (R)-**1** and (S)-**2** will be reported in the near future.

Experimental part

(R)3-chloro 1-p-tolylsulfinyl 2-propanone, 5

(+)(R) methyl p-tolylsulfoxide (26g, 0.17 mmol) in THF solution (100 ml) was dropwise added at -40°C to a THF LDA solution (2.2 equiv. prepared from 52.4 ml, 0.374 mmol of

diisopropylamine 200 ml of THF and 263 ml, 0.374 mmol of a 1.42M butyl lithium solution in hexane). After stirring at -40°C for 30 min., the reaction mixture was cooled at -78°C and a solution of methyl chloroacetate (22g, 0.20 mmol) in THF (100 ml) was dropwise added. After stirring at -78°C for 30 min., the reaction mixture was hydrolyzed with a 5% sulfuric acid solution till acidic pH. After separation the aqueous phase was extracted with ether (2x200 ml), the organic layers dried and evaporated to yield a white solid crystallized from a dichloromethane-ether solution. The mother liquors were concentrated and chromatographed (eluent : Et_2O/CH_2Cl_2 : 25/75, Rf = 0.42). Yield : 32g (0.14 mmol), 82% m.p. 119°-120° ; $[\alpha]_D$ + 260 (acetone, c=2).
IR ($CHCl_3$) : 1720 cm^{-1}
^1H NMR (200MHz, $CDCl_3$) : δ : 2.43 (s, 3H, CH_3) ; 3.96 [AB, 2H, J_{AB}=13.2Hz, $\Delta\nu$=27Hz, $CH_2S(O)$] ; 4.15 (s, 2H, $ClCH_2$) ; 7.44 (AA'BB', 4H, J_{AB}=7.9Hz, $\Delta\nu$=29Hz, aromatic).

[2(S),S(R)] 3-chloro 1-p-tolylsulfinyl 2-propanol, 6a

A THF solution (200 ml) of chloroketosulfoxide 5 (14g, 61 mmol) was added to zinc chloride (10g, 73 mmol, 1.2 equiv.), stirred at room temperature for 30 min. and dropwise added to a 1M DIBAL solution in toluene (110 ml, 110 mmol, 1.8 equiv.) at -78°C. The reduction monitored by TLC was finished after 30 min. Methanol (10 ml) was then added at -78°C, ethyl acetate (300 ml) and finally saturated sodium tartrate (300 ml). After stirring at room temperature for 10 to 15 min., the layers were separated and the aqueous layer extracted with ethyl acetate (2x100 ml). The organic phases were washed with saturated sodium chloride (200 ml), dried and concentrated. The resulting white solid is recrystallized in an ether-acetone mixture and the mother liquors chromatographed (AcOEt-hexane : 60/40).
Yield : 13.6g (58.4 mmol, 96%) ; Rf = 0.22 (Et_2O/CH_2Cl_2 : 25/75). m.p. 95-7°C ; $[\alpha]_D$ + 151 (acetone, c=1).
IR ($CHCl_3$) : 3680, 3360 cm^{-1}.
^1H NMR ($CDCl_3$, 200MHz) : δ : 2.43 (s, 3H, CH_3) ; 3.04 (AB part of ABX, 2H, J_{AX}=J_{BX}=6Hz, CH_2S) ; 3.64 (AB part of ABX, 2H, J_{AB}=11.8Hz, J_{AX}=5Hz, J_{BX}=5.6Hz, $\Delta\nu$=19Hz, CH_2Cl) ; 4.16 (d, 1H, J=3.3Hz, OH), 4.41 (m, 1H) ; 7.47 (AA'BB', 4H, J=8.4Hz, $\Delta\nu$=38.8Hz, aromatic).

[2(R),S(R)] 3-chloro 1-p-tolylsulfinyl 2-propanol, 6b

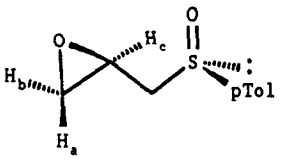
The γ-chloro β-ketosulfoxide 5 (8g, 34.7 mmol) in THF solution (100 ml) was treated at -78°C by a 1M DIBAL solution in toluene (70ml, 70 mmol, 2 equiv.) which was dropwise added. The reduction, monitored by TLC, was finished after 15 min. at -78°C. The hydrolysis was conducted as before with methanol, ethyl acetate and sodium tartrate, as well as the reaction work-up. The product was recrystallized in ether.
Yield : 7.7g (33 mmol, 95%), Rf = 0.22 (Et_2O/CH_2Cl_2 : 25/75) ; m.p. 128°-9°C ; $[\alpha]_D$ + 225 (c=2, acetone).
IR ($CHCl_3$) : 3680, 3360 cm^{-1}.
^1H NMR ($CDCl_3$, 200MHz) : δ : 2.44 (s, 3H, CH_3) ; 2.9 (AB part of ABX, 2H, J_{AB}=13.6Hz, J_{AX}=10Hz, J_{BX}=2.1Hz, $\Delta\nu$=71Hz, CH_2S) ; 3.56 (AB part of ABX, 2H, J_{AB}=10Hz,

J_{AX}=J_{BX}=5.1Hz, $\Delta\nu$=12.1Hz, CH_2Cl) ; 4.22 (d, 1H, J=3Hz, OH) ; 4.37 (m, 1H, CHOH) ; 7.46 (AA'BB', 4H, J_{AB}=8.3Hz, $\Delta\nu$=32Hz, aromatic).

[2(R),S(R)] 2-(p-tolylsulfinyl)methyl oxirane, 3a

A 20% aqueous solution of K_2CO_3 (475 ml) was added to a solution of the preceeding 2(S)S(R) chlorohydroxysulfoxide 6 (11g, 47 mmol) in acetonitrile (1 l). After stirring at room temperature for 9 h, one added water (500 ml) and extracted with ethylacetate (3x250 ml). The organic phases were washed with saturated NaCl (500 ml), dried and evaporated. The resulting solid was recrystallized in ether.

Yield : 85% ; m.p. 61-2°, $[\alpha]_D$ + 180 (c=1, acetone).



^1H NMR ($CDCl_3$, 200MHz) : δ : 2.4 (s, 3H, CH_3) ; 2.67 (dd, 1H, J_{ab}=4.5Hz, J_{ac}=2Hz, H_a) ; 2.83 (dd, 1H, J_{ba}=4.5Hz, J_{bc}=41Hz, H_b) ; 3.05 (m, ABX, 3H, H_c and CH_2S) ; 7.4 (AA'BB', J=8Hz, $\Delta\nu$=42Hz, aromatic).

Microanalysis : calc. for $C_{10}H_{12}O_2S$: C 61.2, H 6.16 ; found C 61.1, H 6.2.

[2(S)S(R)] 2-(p-tolylsulfinyl) methyl oxirane, 3b

The preceeding 2(R)S(R) chlorohydroxysulfoxide **6b** lead in the same conditions to the α-sulfinyl epoxide **3b**.

Yield : 86% ; m.p. 55-6° ; $[\alpha]_D$ + 239 (c=2, acetone).

^1H NMR ($CDCl_3$, 200MHz) : δ : 2.4 (s, 3H, CH_3) ; 2.6 (dd, 1H, $J_{b\text{-}a}$=4.5Hz, $J_{b\text{-}c}$=2.5Hz, H_b) ; 2.9 (dd, 1H, $J_{a\text{-}b}$=4.5Hz, $J_{a\text{-}c}$=4Hz, H_a) ; 2.95 (AB part of ABX, 2H, J_{AB}=13Hz, J_{AX}=5Hz, J_{BX}=7Hz, =21Hz, CH_2S) ; 3-4 (m, 1H, H_c) ; 7.4 (AA'BB', 4H, J_{AB}=8Hz, $\Delta\nu$=40Hz, aromatic).

Microanalysis : calc. for $C_{10}H_{12}O_2S$: C 61.2, H 6.16 ; found C 61.08, H 6.09.

[2(R),4(Z),S(R)] 1-p-tolylsulfinyl 4-decen-2-ol, 8

The cyanocuprate 7 was prepared from Z 1-iodoheptene (21g, 94 mmol) in ether solution (150 ml) which was treated at -78°C by a 1.53M BuLi solution in hexane (61.4ml, 94 mmol). After stirring at -78° for 45 min., cuprous cyanide (4.63g, 51.7 mmol) was added in one time and the temperature allowed to reach -25°C. The resulting green solution was stirred at this temperature for 30 min. then cooled at -60°C before adding an ether solution of the sulfinyl epoxide 3a (4.61g, 23.5 mmol, 50ml of ether). After stirring for 40 min. at -60°C, the reaction mixture was hydrolyzed with a mixture of a 10% ammonia solution and a saturated ammonium chloride (600 ml) and stirred for 30 min. The layers were separated and the aqueous phase extracted with ether (3x100 ml). The organic phases were finally washed with saturated NaCl, dried and evaporated. The crude product was purified by column chromatography (Et_2O/hexane : 80/20).

Yield : 6.2g (21 mmol, 90%) ; Rf = 0.43 (Et_2O) ; m.p. = $[\alpha]_D$ + 99 (c=2.3, acetone).

^1H NMR ($CDCl_3$, 200MHz) : δ : 0.85 (t, 3H, J=7.5Hz, H_{10}) ; 1.25 (m, 6H, H_7, H_8, H_9) ; 2 (m, 2H, H_6) ; 2.38 (m, 2H, H_3) ; 2.43 (s, 3H, CH_3) ; 2.9 (AB part of ABX, J_{AB}=13Hz,

J_{AX}=9Hz, J_{BX}=2.6Hz, $\Delta\nu$=26.4Hz, 2H, H_1) ; 3.76 (d, 1H, J=1.8Hz, OH) ; 4.33 (X part of ABX, H_2) ; 5.4 and 5.6 (2H, J_{cis}=10.8Hz, H_4 and H_5) ; 7.45 (AA'BB', 4H, J_{AB}=7.5Hz, $\Delta\nu$=40Hz, aromatic).
Microanalysis : calc. for $C_{17}H_{26}O_2S$: C 69.34, H 8.90 ; found : C 69.17, H 8.94.

[2(S),4(Z),S(R)] 1-p-tolylsulfinyl 4-nonen-2-ol, 11

The β-hydroxysulfoxide **11** was obtained from the sulfinyl epoxide **3b** and the cyanocuprate **7** by the method described for compound **8**.
Yield : 74% ; Rf : 0.47 (Et_2O), m.p. 54-5°, $[\alpha]_D$ + 179 (c=2.8, acetone).
^1H NMR ($CDCl_3$, 200MHz) : δ : 0.9 (t, 3H, H_9) ; 1.26 (m, 4H, H_7 and H_8) ; 2 (m, 2H, H_6) ; 2.25 (m, 2H, H_3) ; 2.41 (s, 3H, CH_3) ; 2.68 (B part of ABX, 1H, J_{AB}=13.6Hz, J_{BX}=2Hz, $\Delta\nu$=86Hz, H_1) ; 3.06 (A part of ABX, 1H, H_2) ; 5.25 and 5.6 (2H, vinylic H, H_4 and H_5, J_{cis}=10.3Hz) ; 7.4 (AA'BB', 4H, aromatic).

[2(R),4(Z),S(R)] 2-t-butyldimethylsililoxy-1 p-tolylsulfinyl 4-decene

A mixture of the hydroxysulfoxide **8** (6 g, 20.4 mmol) imidazole (5.6 g, 81.6 mmol, 4 equiv.), t-butyldimethylsilyl chloride (6.76 g, 44.9 mmol, 2.2 equiv.) in freshly distilled DMF (100 ml) was stirred at room temperature for 14 h and then hydrolyzed with saturated NH_4Cl (500 ml), ether extracted (3x200 ml). The organic phases were washed with saturated NaCl, dried and evaporated. The crude product was purified by chromatography (eluent : Et_2O/hexane : 30/70, Rf : 0.27).
Yield : 7.4 g (18.1 mmol, 89%) ; $[\alpha]_D$ + 101 (c=0.7, acetone).
^1H NMR ($CDCl_3$, 200MHz) : the same spectrum as compound **8** with in addition a signal at 0.08 ppm (s, 6H, $(CH_3)_2Si$) and at 0.9 (m, 12H, $(CH_3)_3CSi$ and H_{10}).

[2(R),4(Z)] 1-acetoxy 2-t-butyldimethylsilyloxy 1-p-tolylsulfinyl 4-decene, 9

The preceeding sulfoxide (6.2 g, 13 mmol) was treated under reflux in acetic anhydride (150 ml) in presence of sodium acetate (12 g) for 6 h. Then toluene (3x200 ml) was added to evaporate acetic anhydride excess by azeotropic mixture. The resulting white solid was finally purified by chromatography (Et_2O/hexane : 2/98, Rf : 0.18).
Yield : 5.93 g (13.16 mmol, 95%)
IR (CCl_4) : 3000, 1770 cm^{-1}.
^1H NMR (200MHz, $CDCl_3$) : two diastereoisomers in equal amount ; δ : 0.09 (4s, 6H, $(CH_3)_2Si$) ; 0.9 (2s and 1m, 12H, $(CH_3)_3CSi$, $\Delta\nu$=10Hz and H_{10}) ; 1.3 (m, 6H, H_7, H_8 and H_9) ; 2 (m, 2H, H_6) ; 2.05 (s, 3H, CH_3CO) ; 2.32 (2s, 3H, CH_3, $\Delta\nu$=4Hz) ; 2.45 (m, 2H, H_3) ; 3.9 (m, 1H, H_2) ; 5.45 (m, 2H, H_4 and H_5) ; 6 and 6.17 (2d, 1H, J=7Hz and J=3Hz, H_1) ; 7.25 (4H, aromatic).

[2(R),4(Z)]-2-t-butyldimethylsilyloxy 4-decenol, 10

Compound **9** (5.43 g, 12 mmol) in toluene (50 ml) isoled at -25°C was treated with a 1.15M $LiAlH_4$ ether solution (10.5 ml, 12 mmol). After stirring at -25°C for 45 mn, the reaction mixture was hydrolyzed with water (1 ml), a 15% NaOH solution (1 ml) and water (3 ml). After

filtration the solvant was evaporated and the crude product purified by chromatography (Et_2O/hexane : 10/90).
Yield : 3.22 g (11.2 mmol, 94%) ; $[\alpha]_D$ - 16 (c=0.5, $CHCl_3$)
IR ($CHCl_3$) : 3680, 3600 cm^{-1}.
^1H NMR (200MHz, $CDCl_3$) : δ : 0.08 (s, 6H, $(CH_3)_2Si$) ; 0.9, 0.92 (1t and 1s, 12H, H_{10} and $(CH_3)_3CSi$) ; 1.3 (m, 6H, H_7, H_8 and H_9) ; 1.60 (m, 1H, OH) ; 2.05 (m, 2H, H_6) ; 2.25 (m, 2H, H_3) ; 3.5 (m, 2H, H_1) ; 3.75 (m, 1H, H_2) ; 5.45 and 5.58 (2m, 2H, H_4 and H_5).

2(R), 4(Z)-2-t-butyldimethylsilyloxy-4-decenal, 1

Compound **10** (0.6 g, 2.1 mmol) in dichloromethane (freshly distilled on CaH_2, 30 ml) containing molecular sieves (4A, 2.6 g) was treated by freshly prepared PCC (1.13 g, 2.5 equiv) at room temperature for 3 h. The visquous reaction mixture was extracted with ether (3x50 ml) and filtered on florisil (ϕ=30, h=100 mm) with ether as eluent. The visquous residue of the extraction was treated by florisil (30 g) and ether (100 ml). After evaporating the solvant, the product supported on florisil (yellow powder) was added to a chromatogrphy column containing florisil (ϕ=30, h=50 mm) and eluted with ether. The combined ether fractions were evaporated yielding aldehyde **1** as a yellow liquid (this aldehyde decomposed by purification on silica gel).
Yield : 0.5 g (1.75 mmol, 84%) ; $[\alpha]_D$=+7.9 (c=1, $CHCl_3$)
IR ($CHCl_3$)=1700 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) : δ : 0.09 (s, 6H, $(CH_3)_2Si$) ; 0.9-0.92 (1t and 1s, 12H, H_{10} and $(CH_3)_2CSi$) ; 1.3 (m, 6H, H_7, H_8, H_9) ; 2.05 (m, 2H, H_6) ; 2.4 (m, 2H, H_3) ; 4 (m, 1H, H_2) ; 5.45-5.58 (m, 2H, H_4 and H_5) ; 9.6 (d, J=2Hz, CHO).
Microanalysis : calc. for $C_{16}H_{32}O_2Si$: C 67.54, H 11.34 ; found C 67.65, H 11.42.

(R) t-butyl-5-oxo-6-p-tolylsulfinyle hexanoate, 13.

To a solution of diisopropylamine (7.3 ml, 52 mmol) in THF (25 ml) was added at -40°C n-BuLi (1.52 M in hexane, 34.2 ml, 52 mmol). After stirring for 15 min, (R) methyl-p-tolylsulfoxide (7.6 g, 49.4 mmol) in THF (30 ml) was dropwise added. After stirring the reaction mixture at -40°C for 30 min, t-butyl methyl pentanedioate (5 g, 24.7 mmol) in THF (15 ml) was dropwise added and then the reaction mixture was allowed to reach room temperature under stirring for 2 h. Hydrolysis with a saturated ammonium chloride solution (100 ml) followed by addition of a 5% H_2SO_4 solution till pH=3, ether extraction (3x50 ml), evaporation of the solvant and chromatography (silica gel, ether) gave the ß-ketosulfoxide **13** as a yellow oil.
Yield : 6.9 g (21.2 mmol, 86%) ; $[\alpha]_D$=+152 (c=0.5, acetone)
IR (CCl_4)=1720, 1750 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) : δ : 1.39 (s, 9H, $(CH_3)_3C$) ; 1.75 (m, 2H, H_3) ; 2.2 (t, 2H, J=7Hz, H2) ; 2.38 (s, 3H, p-tolyl) ; 2.52 (td, J=9Hz and J=2Hz, H_4) ; 3.8 (AB, 2H, J_{AB}=14Hz, $\Delta\nu$=18Hz, H_6) ; 7.4 (AA'BB', 4H, J_{AB}=8Hz, $\Delta\nu$=35.4Hz, aromatic H).

[5(S),S(R)] t-butyl-5-hydroxy-6-p-tolylsulfinyl hexanoate, 14.

DIBAL (1 M toluene solution, 44 ml, 44 mmol) was added at -78°C to a solution of the ß-ketosulfoxide **13** (11 g, 33.9 mmol) in THF (100 ml). After 1 h, hydrolysis at -78°C with methanol (3 ml), ethyl acetate (200 ml) and a saturated sodium tartrate solution (200 ml), stirring for 15 min at room temperature, the two phases are separated, the aqueous layer extracted with ethyl acetate (2x200 ml). The combined organic phases are washed with saturated sodium chloride solution (300 ml), dried and concentrated. A chromatographic purification (silica gel, ether) gave a white solid.

Yield : 9.83 g (30.1 mmol, 89%)

m.p.=82°C, $[\alpha]_D$=+145 (c=2, acetone), d.e. 92%

IR (CCl_4) : 3600, 3300, 1760 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz) : δ : 1.41 (s, 9H, t-Bu) ; 1.55 (m, 4H, H_3 and H_4) ; 2.2 (t, 2H, H_2) ; 2.43 (s, 3H, CH_3) ; 2.8 (ABX, 2H, J_{AB}=13.5Hz ; J_{AX}=9.7Hz, J_{BX}=1.8Hz, $\Delta\nu$=87Hz, H_6) ; 3.97 (d, J=3.33Hz, 1H, OH) ; 4.15 (X from ABX, 1H, H_5) ; 7.42 (AA'BB', J_{AB}=8.2Hz, $\Delta\nu$=32.3Hz, 4H, arom. H).

(S) t-butyl 6-acetoxy 5-t-butyldimethylsilyloxy heptanoate, 15.

a) Hydroxyle protection

The ß-hydroxysulfoxide **14** (8.3 g, 25.4 mmol) in DMF (100 ml) was treated by TBDMSCl (8.42 g, 55.9 mmol, 2.2 equiv) in presence of imidazole (6.92 g, 101.6 mmol, 4 equiv), at room temperature for 20 h. Hydrolysis with saturated NH_4Cl (500 ml), ether extraction (3x200 ml). The organic phase was then washed with saturated ClNa and evaporated. Purification by chromatography (silica gel, ether/hexane : 50/50) giving an oily product.

Yield : 10.35 g (23.5 mmol, 93%).

^1H NMR (200 MHz, $CDCl_3$) : δ : 0.13 and 0.22 (2s, 6H, $(CH_3)_2Si$) ; 0.94 (s, 9H, tBuSi) ; 1.42 (s, 9H, tBuO) ; 1.56 (m, 4H, H_3, H_4) ; 2.19 (m, 2H, H_2) ; 2.42 (s, 3H, CH_3) ; 2.77 (AB part from ABX, 2H, J_{AB}=13Hz, J_{AX}=3.2Hz, J_{BX}=9.2Hz, $\Delta\nu$=25Hz, H_6) ; 4.3 (m, X from ABX, 1H, H_5) ; 7.4 (AA'BB', 4H, J_{AB}=8Hz, $\Delta\nu$=36.7Hz, 4H, arom. H).

b) Pummerer rearrangement

The protected hydroxysulfoxide (3.8 g, 8.62 mmol) in solution in acetic anhydride (60 ml) was refluxed for 6 h in presence of sodium acetate (6 g). Toluene (3x100 ml) was then added and evaporate the solvent to eliminate the acetic anhydride excess. The product was finally purified by chromatography (silica gel, Et_2O/hexane : 10/90).

Yield : 3.91 g (8.1 mmol, 94%), liquid.

^1H NMR (200 MHz, $CDCl_3$), 2 diastereoisomers in similar proportions : δ : 0.05-0.1 (4s, 6H, $(CH_3)_2Si$) ; 0.88 and 0.92 (2s, 9H, tBuSi) ; 1.45 (s, 9H, tBuO) ; 1.69 (m, 4H, H_3 and H_4) ; 2.044 and 2.047 (2s, 3H, CH_3COO) ; 2.2 (m, 2H, H_2) ; 2.41 and 2.47 (2s, 3H, CH_3) ; 3.8 and 3.9 (2m, 1H, H_5) ; 6.0 and 6.08 (2d, 1H, J=6Hz and J=3Hz, H_6) ; 7.3 (2AA'BB'parts, 4H, arom. H).

c) Acetylation

The acetoxysulfide obtained in the preceeding step (4 g, 11.1 mmol) in ethanol (200 ml) was desulfurized with Raney Nickel. After 1 h, the reaction mixture was filtered, the solvent evaporated and the crude product purified by chromatography (Et_2O/hexane : 10/90) yielding the acetate **15** as an oily compound.
Yield : 3.55 g (9.85 mmol, 89%) ; Rf=0.39 (Et_2O/hexane : 20/80) ; $[\alpha]_D$=+0.8 (c=2.5, $CHCl_3$) ; $[\alpha]_{450}$=+8° ; $[\alpha]_{350}$=+15.
IR ($CHCl_3$) : 1720 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) : δ : 0.12 (s, 6H, Me_2Si) ; 0.91 (s, 9H, tBuSi) ; 1.43 (s, 9H, tBuO) ; 1.64 (m, 4H, H_3 and H_4) ; 2.05 (s, 3H, MeCO) ; 2.26 (t, 2H, H_2) ; 3.9-4 (m, 3H, H_5 and H_6).

(S) t-butyl 6-Hydroxy-5-t-butyldimethylsilyloxy hexanoate, 16.

The acetate **15** (70 mg, 0.194 mmol) in THF (3 ml) was treated, under argon at -78°C, with a 1 M solution of L-Selectride in THF (0.3 ml). The reaction was monitored by TLC (ether/hexane : 40/60) and completed by adding an excess of L-Selectride (0.1 ml) and stirring for 1 h. Then, the mixture was hydrolyzed at room temperature with 0.5 M NaOH (0.5 ml) and 30% H_2O_2 (0.15 ml), stirred for 30 min and extracted with ether. The crude product was finally purified by TLC (ether/hexane = 35/65).
Yield : 55 mg (0.17 mmol, 88%), Rf = 0.32, $[\alpha]_D$ + 5 (c=1, $CHCl_3$).
^1H NMR (200 MHz, $CDCl_3$) : δ : 0.15 (s, 6H, Me_2Si) ; 0.92 (s, 9H, tBuSi) ; 1.45 (s, 9H, tBuOC) ; 1.66 (m, 4H, H_3 and H_4) ; 1.9 (t, 1H, OH) ; 2.22 (t, 2H, H_2) ; 3.50 (m, 2H, H_6) ; 3.75 (m, 1H, H_5).
Microanalysis : calc. for $C_{16}H_{34}O_4Si$: C 60.33, H 10.76 ; found : C 60.52, H 10.84.

(S) t-butyl 5-formyl-5-t-butyldimethylsilyloxyhexanoate, 17.

The alcohol **16** (1.13 g, 3.55 mmol) in CH_2Cl_2 (40 ml) was oxidized with PCC (1.6 g, 7.46 mmol, 2.1 equiv) in the conditions described for compound **10** and the product **17** purified by the same procedure.
Yield : 0.92 g (2.9 mmol, 82% yield), Rf=0.5 (Et_2O/hexane : 30/70)
IR ($CHCl_3$) = 1700 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$) : δ : 0.15 (s, 6H, Me_2Si) ; 0.9 (s, 9H, tBuSi) ; 1.44 (s, 9H, tBuO) ; 1.65 (m, 4H, H_3 and H_4) ; 2.22 (m, 2H, H_2) ; 3.97 (m, 1H, H_5) ; 9.6 (d, 1H, J=1.6Hz, aldehydic H).

(S) t-butyl 7,7-dibromo-5-t-butyldimethylsilyloxy-6-heptenoate, 18.

The aldehyde **17** (0.8 g, 2.57 mmol) in CH_2Cl_2 (5 ml) was treated by a mixture of triphenylphosphine (2.7 g, 10.28 mmol, 4 equiv), carbon tetrabromide (1.7 g, 5.14 mmol, 2 equiv.) in CH_2Cl_2 (30 ml) at 0°C. After stirring at 0°C for 20 min, hexane (100 ml) was added and the mixture filtered on celite. After evaporation of the solvent, the crude product was purified by chromatography (Et_2O/hexane : 5/95).
Yield : 0.93 g (1.97 mmol, 77%), oil, Rf=0.4 (Et_2O/hexane : 5/95).

^{1}H NMR (200 MHz, $CDCl_3$) : δ : 0.11 and 0.12 (2s, 6H, Me_2Si) ; 0.89 (s, 9H, tBuSi) ; 1.45 (s, 9H, tBuO) ; 1.5-1.7 (m, 4H, H_3 and H_4) ; 2.23 (t, 2H, H_2) ; 4.3 (m, 1H, H_5) ; 6.36 (d, 1H, J=8Hz, H_6).

(S) t-butyl 5-t-butyldimethylsilyloxy-7-formyl-6-heptynoate, 19.

a) The dibromide **18** (732 mg, 1.55 mmol) in THF (6 ml) was treated at -78°C with n-BuLi (1.64 M in hexane, 2.1 ml, 3.4 mmol, 2.2 equiv). After stirring at -60°C for 1 h, the reaction mixture was hydrolyzed with a saturated ammonium chloride solution (0.5 ml), extracted with ether (50 ml) and purified by chromatography (Et_2O/hexane : 5/95).
Yield : 215 mg (0.69 mmol, 44%), Rf=0.39, $[\alpha]_D$=-28 (c=1, $CHCl_3$).
IR (CCl_4) = 3310, 1730 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz) : δ : 0.12 and 0.13 (2s, 6H, Me_2Si) ; 0.92 (s, 9H, tBuSi) ; 1.43 (s, 9H, tBuO) ; 1.7 (m, 4H, H_3 and H_4) ; 2.3 (t, 2H, H_2) ; 2.4 (d, 1H, J=2Hz, acetylenic H) ; 4.4 (m, 1H, H_5).

b) Formylation

The preceeding compound (200 mg, 0.64 mmol) in THF (5 ml) was treated at -78°C with n-BuLi (1.64 M in hexane, 0.39 ml, 0.64 mmol). After stirring for 1 h at -40°C, N-formylpiperidine (87 mg, 0.77 mmol, 1.2 equiv) in THF (2 ml) was added. After stirring for 1 h at 0°C, the reaction mixture was hydrolyzed at 0° with 3N HCl (0.5 ml), extracted with ether and purified by thin-layer chromatography (Et_2O/hexane : 30/70).
Yield : 110 mg (0.32 mmol, 50%), oil, Rf=0.68.
^{1}H NMR (200 MHz, $CDCl_3$) : δ : 0.11 and 0.13 (2s, 6H, Me_2Si) ; 0.92 (s, 9H, tBuSi) ; 1.43 (s, 9H, tBuO) ; 1.7 (m, 4H, H_3 and H_4) ; 2.2 (m, 2H, H_2) ; 4.52 (m, 1H, H_5) ; 9.22 (s, 1H, aldehydic H).

(5S,6Z) t-butyl 5-t-butyldimethylsilyloxy-7-formyl-6-hexenoate, 2.

The propargylic aldehyde **19** (82 mg, 0.24 mmol) in THF (10 ml) was reduced with Lindlar catalyst (50 mg) and hydrogen at room temperature for 3 h. The crude product was purified by thin layer chromatography (Et_2O/hexane : 30/70).
Yield : 56 mg (0.16 mmol, 68%), oil, Rf=0.57, $[\alpha]_D$ +26 (c=1, $CHCl_3$).
^{1}H NMR (200 MHz, $CDCl_3$) : δ : 0.12 (s, 6H, Me_2Si) ; 0.91 (s, 9H, tBuSi) ; 1.42 (s, 9H, tBuO) ; 1.70 (m, 4H, H_3 and H_4) ; 2.25 (m, 2H, H_2) ; 5.9 (ddd, 1H, J_{7-6}=11Hz, J_{7-8}=7Hz, J_{7-5}=2Hz, H_7) ; 6.5 (dd, 1H, J_{7-6}=11Hz, J_{6-5}=7.5Hz, H_6) ; 10.1 (d, 1H, J_{7-8}=7Hz, aldehydric H).
Microanalysis : calc. for $C_{18}H_{34}O_4Si$: C 63.11, H 10.00 ; found : C 63.25, H 10.12.

Acknowledgments : Financial support from L'OREAL is gratefully acknowledged.

References

1) Solladié G., Hamdouchi C., Vicente M., *Tetrahedron Lett.* 1988, **29**, 5929, for a preliminary report.

2) a) Solladié G., Demailly G., Greck C., *Tetrahedron Lett.* 1985, **26**, 435 ; b) Solladié G., Demailly G., Greck C., *J. Org. Chem.* 1985, **50**, 1552 ; c) Solladié G., Frechou C., Demailly G., Greck C., *J. Org. Chem.* 1986, **51**, 1912 ; d) Carreño M.C., Garcia-Ruano J.L., Martin A., Pedregal C., Rodriguez J.H., Rubio A., Sanchez J., Solladié G., *J. Org. Chem.* 1990, **55**, 2120 ; e) Solladié G., Rubio A., Carreño M.C., Garcia Ruano J.L., *Tetrahedron Asymmetry* 1990, **1**, 187 ; f) Solladié-Cavallo A., Suffert J., Adib A., Solladié G., *Tetrahedron Lett.* 1990, **31**, 6649.

3) a) Normant J.F., *Synthesis* 1972, 63 ; b) Alexakis A., Cahiez G., Normant J.F., *J. Organometal. Chem.* 1979, 177, 293 ; c) Alexakis A., Jachiet D., Normant J.F., *Tetrahedron* 1986, **42**, 5607.