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Synthesis of Optically Active Diastereomers of a Nonproteic Neurotrophic Mimetic

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Abstract : The four diastereomers **3**, elongated analogues of perhydroretinol, are synthesized starting from both optically pure 3-bromo-2-methyl-1-propanol enantiomers. All exhibit neurotrophic activity on cultured neuronal cells derived from fetal rat cerebral hemispheres.

Introduction

Neurotrophic factors such as NGF (Nerve Growth Factor), BDNF (Brain-Derived Neurotrophic Factor) and FGFs[1] (Fibroblast Growth Factors) are involved in the survival of developing neurons and in the maintenance of mature neurons throughout life. Such discoveries have raised the hope that these factors may potentially lead to a viable therapy to alter the pathogenesis of neurodegenerative diseases. However, bioavailability and stability are among the key difficulties to overcome with these high molecular weight neurotrophic proteins. Additionally, the blood-brain barrier effectively excludes the entry of these biological macromolecules into the brain. Thus, several strategies are suggested to overcome these difficulties by looking for small lipid components that are able to mimick the biological effect of the natural neurotrophic factors, to stimulate their production, or to enhance their activity.[2]

We had shown earlier that *Hygrophila erecta* (Acanthaceae), a tropical plant reported to be used to cure wounds in traditional medicine, contained substances which were able to promote the survival and differentiation of rat central nervous neurons in culture. This finding led to the isolation of the active principle : the fatty C_{26} primary alcohol, n-hexacosanol, containing 26 carbon atoms.[3] The length of the hydrocarbon chain seems to be a determining factor for the biological activity, as n-tetracosanol (C_{24}) and n-triacontanol (C_{30}) are devoid of neurological activity, while n-octacosanol (C_{28}) is only slightly active. To understand the structure-activity relationships, many other fatty alcohols have been synthesized. Several of these compounds are also able to improve, in primary cultures, survival and differentiation of neurons from different fetal brain areas and to restore the memory deficit in lesioned rats.[4] One of these active compounds is **2**, an elongated analogue of perhydroretinol (scheme 1). This compound promotes the survival and differentiation of rat neurons at concentrations of 10^{-7}-10^{-8}M. Additionally, it is capable of crossing the intestinal barriers as well as the blood-brain barrier[5].

Recently, several other examples of low-molecular compounds exhibiting neurotrophic properties have been reported : catecholamines,[6] benzoquinones,[7] hericenone[8] and fellutamide[9] are NGF-inducers ; sesquiterpene-neolignans,[10] phosphatidylinositol,[11] SR57746A[12] and 1,1,3-tricyano-2-amino-1-propene[13] promote neurite outgrowth.

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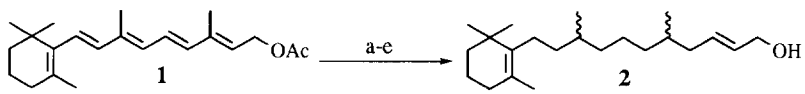
2 was obtained from retinol acetate **1** (scheme 1) by catalytic hydrogenation, acetate hydrolysis, oxidation with pyridinium chlorochromate,[14] Wittig reaction with carbomethoxymethylene triphenylphosphorane and finally reduction with diisobutylaluminium hydride.[15] Catalytic hydrogenation of **1** should lead to four diastereomers of **2**. As the racemic mixture **2** has been shown to possess neurotrophic activity on several types of neurons in culture, as well as in living animals, it was tempting to go further in chemical investigations by synthesizing the four different stereomers.

In this paper, we report the synthesis of each diastereomer and preliminary results of their neurotrophic activities.

Scheme 1



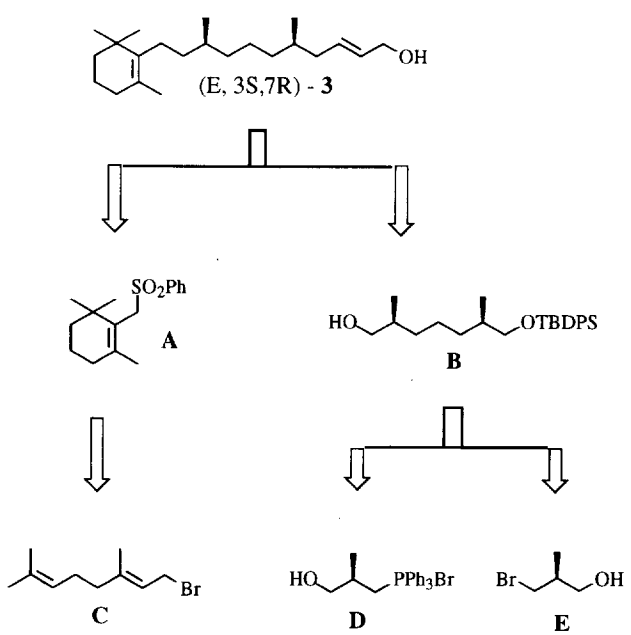
Reagents : a) H_2/Pd, MeOH, r.t., 20 h (70%) ; b) NaOH, Bu_4NBr, THF, reflux (90%) ; c) PCC, CH_2Cl_2, r.t. (80%) d) $Ph_3P{=}CHCO_2Me$, THF (80%) ; e) DIBAH, toluene, -78°C (90%).

Results and discussion

Synthesis of the four diastereomers

Scheme 2 shows the retrosynthetic analysis of (E,3S,7R)-**3**, one of the four stereomers of **2**. **3** can be broken up to give the components sulfone **A** and a chiral building block **B**.

Scheme 2

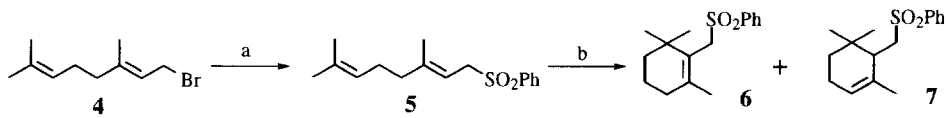


Several syntheses of **B**, or analogous asymmetric molecules, have already been reported, mainly for the purpose of the total synthesis of vitamin E,[16] or of archaeal lipids.[17] For the critical carbon-carbon bond step, different chemical reactions can be used : sulfone alkylation, Grignard or Wittig reactions, *etc.* We have chosen

the Wittig reaction : thus, **B** is prepared from two commercially-available reagents[18] **D** (R)-(3-hydroxy-2-methylpropyl)-triphenylphosphonium bromide and **E** (S)-3-bromo-2-methyl-1-propanol. The present synthetic scheme enables us to synthesize the four stereomers of **2**, by using the Wittig reaction with different enantiomers of **D** and **E** as substrates.

For the synthesis of **A**, geranyl bromide **4** was transformed into the corresponding geranyl phenylsulfone **5** which was cyclised as described by Krishna[19] and Torii[20] to afford a mixture of **6** and **7** (85 : 15) in 90% yield (Scheme 3). The two isomers were separated by successive recrystallizations in hexane, the desired **6** thus obtained in 74% yield, with a purity >99%.

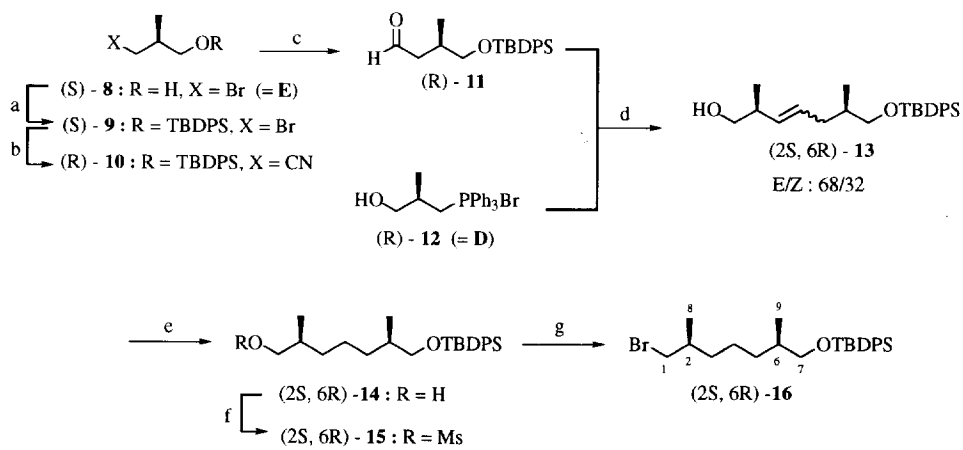
Scheme 3



Reagents : a) $PhSO_2Na$, MeOH, 0°C, 1 h (80%) ; b) H_2SO_4 32 eq., AcOH, 12°C, 30 min (90%).

The preparation of the side chains is outlined in scheme 4. The primary alcohol **8** was protected with a t-butyldiphenylsilyl group,[21] and bromide **9** was substituted by sodium cyanide. The resulting nitrile **10** was reduced with diisobutylaluminium hydride[15] and hydrolysed to aldehyde **11**. Optically active salt **12** was treated with two equivalents of lithium diisopropylamide,[22] and aldehyde **11** was added to the reaction medium at -78°C. The resulting mixture of cis-trans olefins **13** was submitted to catalytic hydrogenation to yield **14**, which was then transformed into the corresponding mesylate **15**. Displacement of mesylate with tetra-n-butylammonium bromide in DMF afforded the bromide **16**.

Scheme 4



Reagents : a) TBDPSCl, DMF, Imidazole, r.t., 4 h (98%) ; b) NaCN, DMSO, 120°C, 2 h (99%)
c) DIBAL-H, toluene, 0°C then HCl 1N (90%) ; d) 1) **12**, LDA, THF, 1 h, 2) **11**, 90 min (65%)
e) H_2, Pd/C, MeOH, r.t., 12 h (80%) ; f) MsCl, py., 0°C to r.t., 20 min (98%) ; g) Bu_4NBr, DMF, 60°C, 5 h (94%).

By adding (R)-**11** to (R)-**12** we have obtained (2S,6R)-**16**. Similarly the following stereomers of **16** were also obtained in the same manner and with the same yield.

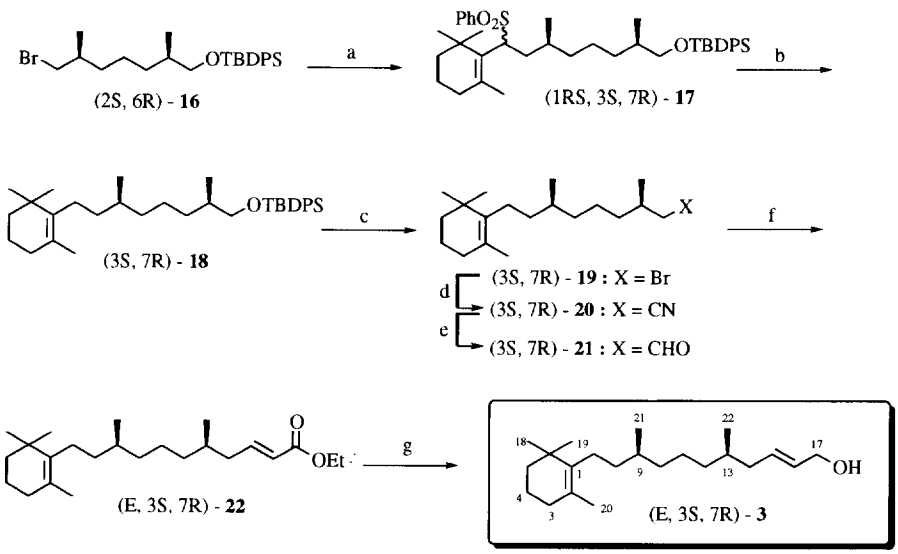
(S) - **11** + (S) - **12** → (2R, 6S) -**16**

(R) - **11** + (S) - **12** → (2R, 6R) -**16**

(S) - **11** + (R) - **12** → (2S, 6S) -**16**

As shown in Scheme 5, sulfone **6** and bromide **16** were coupled to give **17**. A 70% yield was obtained if the reaction was undertaken at low temperature (-78°C), and in a mixture of THF and HMPA, to avoid elimination of the bromide. **17** was then submitted to desulfonylation by means of Na/Hg amalgam.[23] The resulting ether **18** was transformed in one step into bromide **19** using triphenylphosphine dibromide.[24] **19** was treated by sodium cyanide to afford nitrile **20** which was reduced to aldehyde **21**. Wadsworth-Emmons reaction between this aldehyde and triethyl phosphonoacetate,[25] followed by reduction with diisobutylaluminium hydride afforded asymmetric **3** with an overall yield of 13% (in 14 steps).

Scheme 5



reagents : a) 1) **6**, nBuLi, THF, HMPA, -78°C to r.t., 1h, 2) **16**, -78°C, 4 h (70%) ; b) Na-Hg, MeOH, 12 h, 0°C to r.t. (94%) ; c) PPh_3Br_2, CH_2Cl_2, r.t., 12 h (70%) ; d) NaCN, DMSO, 120°C, 1 h (94%) ; e) DIBAL-H, toluene, 0°C, 30 min then HCl 1N (97%) ; f) $(EtO)_2POCHCO_2EtNa$, DMSO, r.t., 1 h (77%) ; g) DIBAL-H, toluene, -78°C, 30 min (95%).

Similarly the following stereomers of **16** were transformed to the corresponding stereomers of **3**.

6 + (2R, 6S) - **16** → (E, 3R, 7S) - **3**

6 + (2R, 6R) - **16** → (E, 3R, 7R) - **3**

6 + (2S, 6S) - **16** → (E, 3S, 7S) - **3**

Effect of different diastereomers 3 on primary neuronal cultures

The neurotrophic activities of different diastereomers **3** were investigated using neurons in primary culture derived from fetal rat cerebral hemispheres (13 day-old). Cultures were performed as described by Borg et al.[26] with modifications. The dissociated cells were seeded at a density of $1.5x10^5$ cells per 35-mm polylysine-coated Petri dish containing 3 ml of a chemically defined culture medium (DMEM, supplemented with insulin, transferrin, progesterone, sodium selenite and putrescine). Each compound was dissolved in ethanol and added immediately after seeding at different concentrations (from 10^{-5} to 10^{-9} M). Cells were cultured without medium change for two days, cultures were, then, fixed with 2% glutaraldehyde (in PBS) and neurons were observed and photographed under a phase-contrast microscope. Control cultures were treated with ethanol only. Morphological evaluations and measurements of neurite outgrowth (shown in figures 1 and 2) indicated that each diastereomer (at a concentration of 5.10^{-7} M) enhanced neurite formation, and even seemed to be a little more active than the mixture **2** of the four diastereomers. Compared to the neurotrophic effect of basic FGF (bFGF) the mixture **2** is less active, the compounds (E, 3R, 7R)-**3**, (E, 3R, 7S)-**3** and (E, 3S, 7R)-**3** similarly active and the compound (E, 3S, 7S)-**3** more active. Our compounds exhibited stimulating activities at concentrations ranging between 10^{-6} and 5.10^{-8} M. They were found to be toxic at concentrations of 10^{-5} and 5.10^{-6} M.

An alternative measurement of neurite outgrowth involves the quantification of the amount of neurofilament protein produced by a given number of neurons by immunocytochemical and ELISA methods which are underway. Further biochemical studies have to be done, such as measurements of choline acetyltransferase activity, protein kinase activity, *etc.*, and detailed results of this work will be reported in a separate paper.

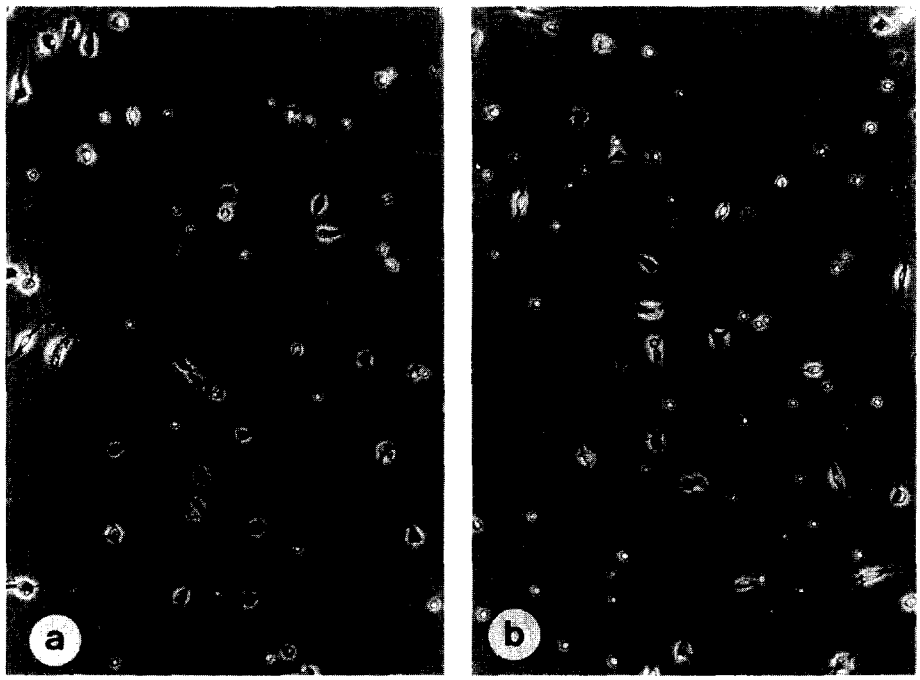


Figure 1 : Phase-contrast microscopy of a 2-day-old neuronal culture after treatment with the diastereomer (E,3S,7S)-**3** (b) compared to control (a). The cultures were obtained from cerebral hemispheres of 13-day-old rat embryos. Stronger neurite outgrowth in treated cultures can be clearly seen. The photograph (b) represents the best of the three data we have obtained (239 %). Bar = 50 μm.

	Control	A	B	C	D	2	bFGF
Fiber length (μm)	65 ± 5	90 ± 14	104 ± 0.2	95 ± 15	120 ± 14	84 ± 11	104 ± 0.2
%	100	139	160	146	185	129	160

Figure 2 : Quantitation of the neurite outgrowth in 2-day-old-neuronal cultures. Cells were cultured either in the presence of : one diastereomer **3** (5.10^{-7}M in EtOH, **A** : (E,3R,7R)-**3** ; **B** : (E,3R,7S)-**3** ; **C** : (E,3S,7R)-**3** ; **D** : (E,3S,7S)-**3**), the mixture **2** of the four diastereomers (5.10^{-7}M in EtOH), bFGF (10 ng/ml), or in the absence of any compound (Control). Measurements were taken with a curvometer and mean values (± SD) were calculated from measuring 30-40 neurons on 3 different microphotographs.

Experimental section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone under argon prior to use. *N,N*-Dimethylformamide (DMF), dichloromethane, methanol and toluene were distilled from calcium hydride. Pyridine was distilled from potassium hydroxide. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over 3Å molecular sieves under argon. All reactions involving moisture sensitive reactants were executed under an atmosphere of dry argon using oven dried and/or flame dried glassware.

^{1}H NMR spectra were recorded on Bruker SY 200 (200 MHz) and AM 400 (400 MHz) spectrometers as solutions in deuterochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet ; d, doublet ; t, triplet ; q, quartet ; m, multiplet ; br, broad. Coupling constants are given in hertz (Hz). ^{13}C NMR spectra were recorded on Bruker SY 200 (50 MHz) and AM 400 (100 MHz) spectrometers as solutions in $CDCl_3$. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard (*, ° : interchangeable assignments). The attribution of the different carbons (C, CH, CH_2, CH_3) was determined by ^{13}C to ^{1}H polarisation transfer (DEPT). IR spectra were recorded on sodium chloride using Perkin-Elmer 881 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). UV spectra were obtained in acetonitrile solution using a Kontron-Uvikon 810 UV-Vis spectrometer. Mass spectra (MS) were measured on a TRIO 2000 apparatus by direct introduction (an ionisation potential of 70 eV was used, m/z relative intensities (in %) are noted in round brackets) or coupled to a GC DB5 column (J.W). GC chromatograms were obtained by dissolving the sample in ethyl acetate, using a Carlo-Erba apparatus and an SE 30 column. Various programs were used : A : 50-190 °C (15 °C/min), 190-250 °C (5 °C/min), 250-280 °C (15 °C/min) ; B : 30-220 °C (15 °C/min), 220-270 °C (5 °C/min) ; C : 40-150 °C (15 °C/min), 150-180 °C (5 °C/min), 180-280 °C (20 °C/min) ; D : 50-170 °C (20 °C/min), 170-200 °C (2 °C/min), 200-280°C (20 °C/min) ; E : 50-220 °C (20 °C/min), 220-250 °C (5 °C/min), 250-280 °C (15 °C/min). Optical rotations ([α]) were measured on a Perkin-Elmer 241 polarimeter in $CHCl_3$ at different wavelengths. Microanalyses were performed by the Service Central de Microanalyse du CNRS (Strasbourg). Routine monitoring of reactions were performed using 60 F_{254} silica gel TLC plates (Merck), which were dipped in a solution of vanillin (1 g) in EtOH/H_2SO_4 (95/5, 1 l) and heated on a hot plate. Flash chromatography was conducted using 60 F_{254} silica gel (Merck) with the solvent indicated.

(S)-3-Bromo-1-(t-butyldiphenylsilyloxy)-2-methylpropane [(S)-9]

(S)-3-bromo-2-methyl-1-propanol **8** (5 g, 32.7 mmol, 1 eq.) was dissolved in dry DMF (30 ml), imidazole (4.6 g, 68 mmol, 2.1 eq.) and t-butyldiphenylsilyl chloride (8.8 ml, 1.1 eq.) were added. After stirring at room temperature for 4h, the mixture was then acidified to pH 2 with 1N HCl, extracted with ether (3 times), washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow liquid which was purified by chromatography over silica gel, eluting with hexane-ether (9.5-0.5 then 9-1), to give **9** (colorless oil, 12.5 g, 98%). **TLC** : (hexane-AcOEt : 8-2) Rf = 0.7 ; **^{1}H NMR** (200 MHz), δ : 1 (d, J = 6.8 Hz, 3H, H-4) ; 1.06 (s, 9H, $SiCMe_3$) ; 2 (m, 1H, H-2) ; 3.48-3.68 (m, 4H, H-1, 3) ; 7.34-7.48 (m, 6H, H ar-3',4') ; 7.64-7.71 (m, 4H, H ar-2') ; **MS** : 335 (M-CMe_3, 27) ; 333 (M-CMe_3, 27) ; 280 (81) ; 263 (59) ; 261(59) ; 201 (30) ; 203 (29) ; 78 (100) ; 63 (100) ; 45 (31) ; $[\alpha]_D^{23}$ = + 5 ($CHCl_3$, c = 2).

(R)-3-Bromo-1-(t-butyldiphenylsilyloxy)-2-methylpropane [(R)-9]

prepared in the same manner as described above. TLC, NMR, MS were identical with those of (S)-**9**. $[\alpha]_D^{23}$ = - 5 ($CHCl_3$, c = 2).

(R)-4-(t-Butyldiphenylsilyloxy)-3-methylbutanenitrile [(R)-10]

To a solution of ether (S)-**9** (12.36 g, 31.6 mmol, 1 eq.) in dry DMSO (*Aldrich 99+%*, 25 ml) was added sodium cyanide (4.6 g, 94 mmol, 3 eq.), and the mixture stirred at 120°C for 2h. Water was added and the aqueous phase was extracted with ether (3 times), the combined organic phases were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Flash chromatography over silica gel, eluting

with hexane-AcOEt (9.5-0.5 then 9-1), gave **10** as a colorless oil (10.6 g, 99%). **TLC** : (hexane-AcOEt : 8-2) Rf = 0.6 ; **^{1}H NMR** (200 MHz), δ : 1.03 (d, J = 6.8 Hz, 3H, H-5) ; 1.06 (s, 9H; SiCMe$_3$) ; 2.06 (m, 1H, H-3) ; 2.37 (dd, J_{gem} = 16.6 Hz, J_{2-3} = 5.1 Hz, 1H, H-2) ; 2.57 (dd, J_{gem} = 16.6 Hz, J_{2-3} = 5.4 Hz, 1H, H-2) ; 3.47 (dd, J_{gem} = 10.3 Hz, J_{4-3} = 7.4 Hz, 1H, H-4) ; 3.64 (dd, J_{gem} = 10.3 Hz, J_{4-3} = 4.7 Hz, 1H; H-4) ; 7.35-7.48 (m, 6H, H ar-3',4') ; 7.62-7.66 (m, 4H, H ar-2') ; **^{13}C NMR** (50 MHz), δ : 16.0 (C-5) ; 19.4 (-Si<u>C</u>Me$_3$) ; 21.2 (C-2) ; 26.9 (-SiC(<u>C</u>H$_3$)$_3$) ; 33.4 (C-3) ; 66.9 (C-4) ; 118.9 (-CN) ; 127.9 (C ar-3') ; 129.9 (C ar-4') ; 133.3 (C ar-1') ; 135.6 (C ar-2') ; **IR** : 3071, 3050 (w, C-H ar.) ; 2960, 2931, 2858 (s, C-H) ; 2246 (w, CN) ; 1589 (w, C=C ar.) ; 1472 ; 1428 (s) ; 1112 (s, C-O) ; 1034 ; 824 ; 703 (s, ar. monosubst.) ; **UV** λ_{max} : 218.5 nm (ε 39880) ; MS : 280 (M-CMe$_3$, 100) ; 199 (5) ; 78 (48) ; 63 (26) ; 61 (5) ; $[\alpha]_D^{23}$ = + 14 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{21}H_{27}ONSi$ (337.5) C : 74.73, H : 8.06, N : 4.15 ; found C : 74.8, H : 8.2, N : 4.3.

(S)-4-(t-Butyldiphenylsilyloxy)-3-methylbutanenitrile [(S)-10]

prepared in the same manner as described above. TLC, NMR, MS, IR, UV were identical with those of (R)-**10**. $[\alpha]_D^{23}$ = - 15 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{21}H_{27}ONSi$ (337.5) C : 74.73, H : 8.06, N : 4.15 ; found C : 74.60, H : 8.04, N : 4.13.

(R)-4-(t-Butyldiphenylsilyloxy)-3-methylbutanal [(R)-11]

To a solution of nitrile (R)-**10** (4.84 g, 14.3 mmmol, 1 eq.) in dry toluene (10 ml) was added diisobutylaluminium hydride (*Aldrich 1M in toluene*, 15.8 ml, 16 mmol, 1.1 eq.) dropwise at 0°C under argon. After stirring for 30 min, iced water was added slowly followed by HCl 1N (50 ml) and aqueous saturated potassium tartrate. Stirring was continued for 15 min at 0°C and the aqueous layer was extracted with dichloromethane (3 times), the combined organic phases were washed with aqueous $NaHCO_3$ and brine then dried with $MgSO_4$. The extract was concentrated *in vacuo* and the slightly yellow oil obtained was used without purification for the next step (4.4 g, 90%). An analytical sample was purified by flash chromatography over silica gel, eluting with hexane-ether (9.5-0.5). **TLC** : (CH_2Cl_2) Rf = 0.55 ; **^{1}H NMR** (200 MHz), δ : 0.95 (d, J = 6.6 Hz, 3H, H-5) ; 1.05 (s, 9H, SiCMe$_3$) ; 2.3 (m, 2H, H-2) ; 2.61 (m, 1H, H-3) ; 3.43 (dd, J_{gem} = 9.9 Hz ; J_{4-3} = 6.9 Hz,1 H, H-4) ; 3.59 (dd, J_{gem} = 9.9 Hz, J_{4-3} = 5 Hz,1H, H-4) ; 7.33-7.47 (m, 6H, H ar-3',4') ; 7.62-7.68 (m, 4H, H ar-2') ; 9.79 (t, J = 2 Hz, 1H, CHO) ; **^{13}C NMR** (50 MHz), δ : 16.8 (C-5) ; 19.3 (Si<u>C</u>Me$_3$) ; 26.9 (SiC(<u>C</u>H$_3$)$_3$) ; 31.3 (C-3) ; 48.2 (C-2) ; 68.4 (C-4) ; 127.7 (C ar-3') ; 129.7 (C ar-4') ; 133.6 (C ar-1') ; 135.6 (C ar-2') ; 202.6 (CHO) ; **IR**, ν : 3071, 3050 (w, C-H ar.) ; 2958, 2931, 2858 (s, C–H) ; 2718 (w, C-H ald.) ; 1726 (s, C=O) ; 1589 (w, C=C ar) ; 1472, 1428 (m) ; 1112 (s, C-O) ; 824 (m) ; 702 (s, ar. monosubst.) ; $[\alpha]_D^{23}$ = + 4 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{21}H_{28}O_2Si$ (340.5) C : 74.07, H : 8.29 ; found C : 74.3, H : 8.5.

(S)-4-(t-Butyldiphenylsilyloxy)-3-methylbutanal [(S)-11]

prepared in the same manner as described above. TLC, NMR, IR, were identical with those of (R)-**11**. $[\alpha]_D^{23}$ = - 5 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{21}H_{28}O_2Si$ (340.5) C : 74.07, H : 8.29 ; found C : 74.2, H : 8.1.

(E/Z,2S,6R)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethyl-3-hepten-1-ol [(2S,6R)-13]

Optically pure (R)-phosphonium salt **12** (dried overnight at 60°C *in vacuo* , 2.7 g, 6.5 mmol, 1.1 eq.) and triphenylmethane (5 mg) were dissolved in dry THF (15 ml) under argon. At -78°C, LDA (1.4 M, 10 ml, 2.4 eq.) was added slowly and the mixture stirred at this temperature for 30 min, then at room temperature for 30 min too. The reaction mixture was recooled to -78°C and aldehyde (R)-**11** (2 g, 5.9 mmol, 1 eq.) added dropwise. Stirring was continued at -78°C for 30 min, then at 0°C for 1h. The mixture was poured into saturated aqueous NH_4Cl (50 ml), the aqueous layer extracted with ether, the combined organic layers washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane-CH_2Cl_2 (6-4) until pure CH_2Cl_2 to obtain a yellow oil (1.3 g, 55%, 65% after recovering unreacted **11**). **TLC** (CH_2Cl_2-Et_2O : 9-1) Rf (*cis* isomer) = 0.5 ; Rf (*trans* isomer) = 0.55 ; **GC** (A) *cis* isomer : 16.6 min (32 %) ; *trans* isomer : 16.8 min (68 %) ; **^{1}H NMR** (200 MHz), δ : ***trans*** : 0.9 (d, J = 6.9 Hz, 3H, H-9) ; 0.97 (d, J = 6.9 Hz, 3H, H-8) ; 1.06 (s, 9H, SiC<u>Me</u>$_3$) ; 1.64-1.8 (m, 1H, H-6) ; 1.82-2 (m, 1H, H-5) ; 2.17-2.36 (m, 2H, H-2, 5) ; 3.43-3.57 (m, 4H, H-1, 7) ; 5.25 (ddt, J_{3-4} = 15.5 Hz, J_{3-2} = 7.6 Hz, ^{4}J = 1 Hz, 1H, H-3) ; 5.48 (dt, J_{4-3} = 15.3 Hz, J_{4-5} = 7 Hz, 1H, H-4) ; 7.33-7.47 (m, 6H, H ar-3',4') ; 7.61-7.74 (m, 4H, H ar-2'), ***cis*** : 0.9 (d, J = 6.7 Hz, 3H, H-9) ; 0.92 (d, J = 6.7 Hz, 3H, H-8) ; 1.06 (s, 9H, SiC<u>Me</u>$_3$) ; 1.64-1.8 (m, 1H, H-6) ; 1.82-2 (m, 1H, H-5) ; 2.17-2.36 (m, 1H, H-5) ; 2.63-2.74 (m, 1H, H-2) ; 3.28-3.43 (m, 4H, H-1, 7) ; 5.16 (ddt, J_{3-4} = 11.1 Hz, J_{3-2} = 9.6 Hz, ^{4}J = 1.5 Hz, 1H, H-3) ; 5.53 (dt, J_{4-3} = 11.1 Hz, J_{4-5} = 3.7 Hz, 1H, H-4) ; 7.33-7.47 (m, 6H, H ar-3',4') ; 7.61-7.74 (m, 4H,

H ar-2') ; **^{13}C NMR** (50 MHz), δ : ***trans*** : 16.5 (C-8) ; 17 (C-9) ; 19.3 (Si<u>C</u>Me$_3$) ; 26.9 (SiC(<u>C</u>H$_3$)$_3$) ; 31.1 (C-5) ; 34.8 (C-6) ; 36.4 (C-2) ; 67.4 (C-7) ; 68.3 (C-1) ; 127.6 (C ar-3') ; 129.5 (C ar-4') ; 133.1 (C-4) ; 133.8 (C-3) ; 134 (C ar-1') ; 135.6 (C ar-2'), ***cis*** : 16.7 (C-8, C-9) ; 19.3 (Si<u>C</u>Me$_3$) ; 26.9 (SiC(<u>C</u>H$_3$)$_3$) ; 36.3 (C-5) ; 36 (C-6) ; 39.8 (C-2) ; 67.7 (C-7) ; 68.4 (C-1) ; 127.6 (C ar-3') ; 130.3 (C ar-4') ; 133.1 (C-4) ; 133.8 (C-3) ; 134 (C ar-1') ; 135.6 (C ar-2') ; **IR** ν : 3355 (broad, O-H) ; 3071, 3049 (w, C-H arom., olefin) ; 2958, 2930, 2858 (s, C-H aliphat.) ; 1590 (w, C=C) ; 1472, 1428 (m) ; 1112 (s, C-O) ; 1035 (m) ; 972 (w) ; 824 (m) ; 739 (m) ; 702 (s, ar. monosubst.) ; $[\alpha]_D^{23}$ = - 5 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{25}H_{36}O_2Si$ (396.6) C : 75.70, H : 9.15 ; found C : 75.6, H : 9.2.

(E/Z,2R,6S)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethyl-3-hepten-1-ol [(2R,6S)-13]

prepared in the same manner as described above. TLC, GC, NMR, IR, were identical with those of (2S,6R)-**13**. $[\alpha]_D^{23}$ = +5 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{25}H_{36}O_2Si$ (396.6) C : 75.70, H : 9.15 ; found C : 75.6, H : 9.0.

(E/Z,2R,6R)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethyl-3-hepten-1-ol [(2R,6R)-13]

prepared in the same manner as described above. TLC, GC, NMR, IR, were identical with those of (2S,6R)-**13**. $[\alpha]_D^{23}$ = + 13 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{25}H_{36}O_2Si$ (396.6) C : 75.70, H : 9.15 ; found C : 75.8, H : 9.1.

(E/Z,2S,6S)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethyl-3-hepten-1-ol [(2S,6S)-13]

prepared in the same manner as described above. TLC, GC, NMR, IR, were identical with those of (2S,6R)-**13**. $[\alpha]_D^{23}$ = - 12 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{25}H_{36}O_2Si$ (396.6) C : 75.70, H : 9.15 ; found C : 75.9, H : 9.4.

(2S,6R)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethylheptan-1-ol [(2S,6R)-14]

To a solution of olefins (E/Z,2S,6R)-**13** (0.9 g, 2.27 mmol, 1 eq.) in methanol (40 ml) were added sodium nitrite (391 mg, 2.5 eq.) and palladium on activated carbon (Pd content 10%, 400 mg). The mixture was stirred at room temperature under an atmosphere of H_2 for 12h and filtered through a pad of Celite®. The filtrate was evaporated *in vacuo* and the residue purified by chromatography over silica gel, eluting with 85% CH_2Cl_2-hexane until 100% CH_2Cl_2 to give a colorless oil (724 mg, 80%). **TLC** : (CH_2Cl_2-Et_2O : 9-1) Rf = 0.43 ; **GC** (A) : 17.14 min, 99% ; **^{1}H NMR** (200 MHz), δ : 0.9 (d, J = 6.7 Hz, 3H, H-8) ; 0.92 (d, J = 6.7 Hz, 3H, H-9) ; 1.06 (s, 9H, SiC(<u>C</u>H$_3$)$_3$) ; 1.15-1.4 (m, 6H, H-3, 4, 5) ; 1.57-1.67 (m, 2H, H-2 et 6) ; 3.36-3.56 (m, 4H, H-1 et 7) ; 7.33-7.47 (m, 6H, H ar-3',4') ; 7.64-7.74 (m, 4H, H ar-2') ; **^{13}C NMR** (50 MHz), δ : 16.6 (C-9*) ; 17 (C-8*) ; 19.4 (Si<u>C</u>Me$_3$) ; 24.4 (C-4) ; 26.9 (SiC(<u>C</u>H$_3$)$_3$) ; 33.5 (C-3 et 5) ; 35.8 (C-2 et 6) ; 68.4 (C-7) ; 68.9 (C-1) ; 127.6 (C ar-3') ; 129.5 (C ar-4') ; 134.2 (C ar-1') ; 135.7 (C ar-2') ; **IR** ν : 3344 (broad, O-H) ; 3071, 3049 (w, C-H arom.) ; 2956, 2930, 2857 (s, C-H) ; 1590 (w, C=C ar.) ; 1472, 1428 (m) ; 1112 (s, C-O) ; 939 (w) ; 824 (m) ; 702 (s, C-H ar.. monosubst.) ; $[\alpha]_D^{23}$ = - 2 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{25}H_{38}O_2Si$ (398.7) C : 75.32, H : 9.61 ; found C : 75.6, H : 9.5.

(2R,6S)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethylheptan-1-ol [(2R,6S)-14]

prepared in the same manner as described above. TLC, GC, NMR, IR, were identical with those of (2S,6R)-**14**. $[\alpha]_D^{23}$ = + 2 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{25}H_{38}O_2Si$ (398.7) C : 75.32, H : 9.61 ; found C : 75.5, H : 9.7.

(2R,6R)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethylheptan-1-ol [(2R,6R)-14]

prepared in the same manner as described above. TLC, GC, NMR, IR, were identical with those of (2S,6R)-**14**. $[\alpha]_D^{23}$ = + 5 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{25}H_{38}O_2Si$ (398.7) C : 75.32, H : 9.61 ; found C : 75.5, H : 9.8.

(2S,6S)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethylheptan-1-ol [(2S,6S)-14]

prepared in the same manner as described above. TLC, GC, NMR, IR, were identical with those of (2S,6R)-**14**. $[\alpha]_D^{23}$ = - 4 ($CHCl_3$, c = 2) ; **microanalysis** (%) : calcd for $C_{25}H_{38}O_2Si$ (398.7) C : 75.32, H : 9.61 ; found C : 75.5, H : 9.6.

(2S,6R)-7-(t-Butyldiphenylsilyloxy)-2,6-dimethylheptyl methanesulfonate [(2S,6R)-15]

To a solution of alcohol (2S,6R)-**14** (0.7 g, 1.8 mmol, 1 eq.) in dry pyridine (20 ml) was added dropwise distilled mesyl chloride (0.3 ml, 2 eq.) at 0°C under argon. The mixture was stirred at room temperature for 20 min and poured into aqueous HCl (1N, 100 ml) slowly. The aqueous layer was extracted with dichloromethane (3 times), the combined organic layers were washed with saturated aqueous $NaHCO_3$, with brine, dried ($MgSO_4$) and concentrated *in vacuo* to obtain a slightly yellow oil (0.82 g, 98%). An analytical sample was purified by flash chromatography over silica gel (hexane-AcOEt : 9-1 as eluent). **TLC** : (hexane-AcOEt : 7-

3) Rf = 0.4 ; GC (B) : 21.2 min, 97% ; **^{1}H NMR** (200 MHz), δ : 0.91 (d, J = 6.7 Hz, 3H, H-9) ; 0.97 (d, J = 6.7 Hz, 3H, H-8) ; 1.05 (s, 9H, SiC(C$\underline{H}_3$)$_3$) ; 1.13-1.43 (m, 6H, H-3, 4, 5) ; 1.56-1.72 (m, 1H, H-6) ; 1.8-1.98 (m, 1H, H-2) ; 2.99 (s, 3H, CH_3-SO_2) ; 3.4 (dd, J_{gem} = 9.8 Hz, J_{7-6} = 6.1 Hz, 1H, H-7); 3.5 (dd, J_{gem} = 9.8 Hz, J_{7-6} = 5.8 Hz, 1H, H-7) ; 3.98 (dd, J_{gem} = 9.4 Hz, J_{1-2} = 6.6 Hz, 1H, H-1) ; 4.08 (dd, J_{gem} = 9.4 Hz, J_{1-2} = 5.8 Hz, 1H, H-1) ; 7.33-7.47 (m, 6H, H ar-3',4') ; 7.64-7.74 (m, 4H, H ar-2') ; **microanalysis** (%) : calcd for $C_{26}H_{40}O_4SSi$ (476.8) C : 65.50, H : 8.47 ; found C : 65.4, H : 8.4.

3 other diastereomers [(2R,6S)-15] ; [(2R,6R)-15] ; [(2S,6S)-15]

prepared in the same manner as described above. TLC, GC, NMR, were identical with those of (2S,6R)-**15**.

(2S,6R)-7-(t-Butyldiphenylsilyloxy)-1-bromo-2,6-dimethylheptane [(2S,6R)-16]

To a solution of mesylate (2S,6R)-**15** (1.4 g, 2.9 mmol, 1 eq.) in dry DMF (40 ml) was added tetrabutylammonium bromide (5.7 g, 6 eq.), the reaction mixture was stirred at 60°C for 5h under argon then quenched with water, extracted with ether (3 times). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (hexane and then 10% AcOEt as eluent) gave a slightly yellow oil (1.26 g, 94%). **TLC** : (hexane-AcOEt : 7-3) Rf = 0.7 ; GC (B) : 17.2 min, >99% ; **^{1}H NMR** (200 MHz), δ : 0.92 (d, J = 6.7 Hz, 3H, H-9) ; 1 (d, J = 6.6 Hz, 3H, H-8) ; 1.06 (s, 9H, SiC(C$\underline{H}_3$)$_3$) ; 1.15-1.44 (m, 6H, H-3, 4, 5) ; 1.6-1.78 (m, 2H, H-2 et 6) ; 3.3 (dd, J_{gem} = 9.8 Hz, J_{1-2} = 6.1 Hz, 1H, H-1) ; 3.39 (dd, J_{gem} = 9.8 Hz, J_{1-2} = 5 Hz, 1H, H-1) ; 3.44 (dd, J_{gem} = 9.8 Hz, J_{7-6} = 6.1 Hz, 1H, H-7) ; 3.51 (dd, J_{gem} = 9.8 Hz, J_{7-6} = 5.8 Hz, 1H, H-7) ; 7.33-7.47 (m, 6H, H ar-3',4') ; 7.64-7.74 (m, 4H, H ar-2') ; **^{13}C NMR** (50 MHz), δ : 17 (C-9) ; 18.8 (C-8) ; 19.3 (Si$\underline{C}$Me$_3$) ; 24.2 (C-4) ; 26.9 (SiC(C$\underline{H}_3$)$_3$) ; 33.2 (C-5) ; 35.1 (C-3) ; 35.6 (C-2, 6) ; 41.5 (C-1) ; 68.8 (C-7) ; 127.6 (C ar-3') ; 129.5 (C ar-4') ; 134.1 (C ar-1') ; 135.6 (C ar-2') ; $[\alpha]_D^{25}$ = + 2 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{25}H_{37}OBrSi$ (461.6) C : 65.06, H : 8.08 ; found C : 65.2, H : 8.1.

(2R,6S)-7-(t-Butyldiphenylsilyloxy)-1-bromo-2,6-dimethylheptane [(2R,6S)-16]

prepared in the same manner as described above. TLC, GC, NMR, were identical with those of (2S,6R)-**16**. $[\alpha]_D^{25}$ = - 2 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{25}H_{37}OBrSi$ (461.6) C : 65.06, H : 8.08 ; found C : 65.3, H : 8.3.

(2R,6R)-7-(t-Butyldiphenylsilyloxy)-1-bromo-2,6-dimethylheptane [(2R,6R)-16]

prepared in the same manner as described above. TLC, GC, NMR, were identical with those of (2S,6R)-**16**. $[\alpha]_D^{25}$ = + 2.5 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{25}H_{37}OBrSi$ (461.6) C : 65.06, H : 8.08 ; found C : 65.2, H : 8.0.

(2S,6S)-7-(t-Butyldiphenylsilyloxy)-1-bromo-2,6-dimethylheptane [(2S,6S)-16]

prepared in the same manner as described above. TLC, GC, NMR, were identical with those of (2S,6R)-**16**. $[\alpha]_D^{25}$ = - 2.5 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{25}H_{37}OBrSi$ (461.6) C : 65.06, H : 8.08 ; found C : 65.1, H : 8.2.

(3S,7R)-1-(8-(t-Butyldiphenylsilyloxy)-3,7-dimethyl-1-phenylsulfonyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7R)-17]

To a solution of sulfone **6** (813 mg, 2.9 mmol, 2 eq.) in dry THF (8 ml) and dry HMPA (2 ml) was added n-butyllithium (1.4 M in hexane, 2 ml, 1.9 eq.) at -78°C under argon. After stirring for 10 min, the mixture was stirred at room temperature for 1h, then was recooled at -78°C and bromide (2S,6R)-**16** (0.68 g, 1.5 mmol, 1 eq.) was added dropwise. After 4h at this temperature, the mixture was poured cautiously into a saturated aqueous NH_4Cl solution (50 ml), extracted with ether, washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane-AcOEt (9.5-0.5) to give **17** as a colorless oil (676 mg, 70%). **TLC** : (hexane-AcOEt : 7-3) Rf = 0.7 ; **^{1}H NMR** (200 MHz), δ : 0.58 (d, J = 6.5 Hz, 3H, H-18*) ; 0.7 (d, J = 6.4 Hz, 3H, H-19*) ; 0.89 (s, 3H, H-15) ; 0.90 (s, 3H, H-16) ; 1-1.25 (m, 6H, H-10, 11, 12) ; 1.06 (s, 9H, SiC(C$\underline{H}_3$)$_3$) ; 1.3-1.65 (m, 6H, H-4, 5 et 8) ; 1.56 (s, 3H, H-17) ; 1.98 (m, 5H, H-3, 9 et 13) ; 3.37 (dd, J_{gem} = 9.8 Hz, J_{14-13} = 6.4 Hz, 1H, H-14) ; 3.51 (dd, J_{gem} = 9.8 Hz, J_{14-13} = 5.7 Hz, 1H, H-14) ; 3.8-3.97 (m, 1H, H-7) ; 7.37-7.43 (m, 6H, H-3', 4' SiPh) ; 7.46-7.56 (m, 3H, H-3', 4' SO_2Ph) ; 7.63-7.7 (m, 4H, H-2' SiPh) ; 7.88-7.94 (m, 2H, H-2' SO_2Ph) ; **IR**, ν : 3070 (w, C-H ar.) ; 2930, 2857 (s, C-H) ; 1589 (w, C=C) ; 1472, 1447, 1428 (m) ; 1304, 1144 (s, SO_2) ; 1112 (s, C-O) ; 1084 (s) ; 824 (m) ; 703 (s, ar. monosubst.).

3 other diastereomers [(3R,7S)-17] ; [(3R,7R)-17] ; [(3S,7S)-17]
prepared in the same manner as described above. TLC, NMR and IR were identical with those of (3S,7R)-**17**.

(3S,7R)-1-(8-(t-Butyldiphenylsilyloxy)-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7R)-18]
To a solution of sulfone (3S,7R)-**17** (1 g, 15.2 mmol, 1 eq.) in dry methanol (30 ml) were added sodium phosphate, dibasic Na_2HPO_4 (857 mg, 4 eq.) and mercury-sodium amalgam (6% Na, 4.5 g) at 0°C under argon. The heterogeneous mixture was stirred at room temperature for 12h, then quenched with water, extracted with dichloromethane (3 times), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane-AcOEt (99-1) to give **18** as a colorless oil (745 mg, 94%). **TLC** : (hexane) Rf = 0.35 ; **^{1}H NMR** (200 MHz), δ : 0.89 (d, J = 6.7 Hz, 3H, H-19*) ; 0.92 (d, J = 6.8 Hz, 3H, H-18*) ; 0.98 (s, 6H, H-15, 16) ; 1.06 (s, 9H, $SiC(CH_3)_3$) ; 1.12-1.45 (m, 12H, H-4, 5, 8, 10, 11 et 12) ; 1.5-1.75 (m, 2H, H-9 et 13) ; 1.57 (s, 3H, H-17) ; 1.87-2 (m, 4H, H-3 et 7) ; 3.43 (dd, J_{gem} = 9.8 Hz, J_{14-13} = 6.4 Hz, 1H, H-14) ; 3.52 (dd, J_{gem} = 9.8 Hz, J_{14-13} = 5.8 Hz, 1H, H-14) ; 7.3-7.46 (m, 6H, H ar-3',4') ; 7.6-7.71 (m, 4H, H ar-2') ; **^{13}C NMR** (50 MHz), δ : 17 (C-19) ; 19.3 ($SiCMe_3$) ; 19.8 (C-18, 17) ; 24.5 (C-11) ; 26.4 (C-4) ; 26.9 ($SiC(CH_3)_3$) ; 28.7 (C-15, 16) ; 32.8 (C-7) ; 33.5 (C-12) ; 33.9 (C-9) ; 35 (C-6) ; 35.8 (C-13) ; 37.2 (C-3*) ; 37.4 (C-8*, 10*) ; 39.9 (C-5) ; 68.9 (C-14) ; 126.3 (C-2) ; 127.6 (C ar-3') ; 129.4 (C ar-4') ; 134.2 (C ar-1') ; 135.6 (C ar-2') ; 137.8 (C-1) ; **GC-MS** : 518 (M^+, 0.09) ; 461 (29) ; 199 (100) ; 183 (20) ; 137 (34) ; 123 (87) ; 95 (48), 98% purity ; $[\alpha]_D^{23}$ = + 5 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{35}H_{54}OSi$ (518.9) C : 81.01, H : 10.49 ; found C : 81.3, H : 10.2.

(3R,7S)-1-(8-(t-Butyldiphenylsilyloxy)-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3R,7S)-18]
prepared in the same manner as described above. TLC, GC, NMR and MS were identical with those of (3S,7R)-**18**. $[\alpha]_D^{23}$ = - 4 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{35}H_{54}OSi$ (518.9) C : 81.01, H : 10.49 ; found C : 80.9, H : 10.3.

(3R,7R)-1-(8-(t-Butyldiphenylsilyloxy)-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3R,7R)-18]
prepared in the same manner as described above. TLC, GC, NMR and MS were identical with those of (3S,7R)-**18**. $[\alpha]_D^{23}$ = - 2 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{35}H_{54}OSi$ (518.9) C : 81.01, H : 10.49 ; found C : 81.2, H : 10.3.

(3S,7S)-1-(8-(t-Butyldiphenylsilyloxy)-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7S)-18]
prepared in the same manner as described above. TLC, GC, NMR and MS were identical with those of (3S,7R)-**18**.
$[\alpha]_D^{23}$ = + 1.5 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{35}H_{54}OSi$ (518.9) C : 81.01, H : 10.49 ; found C : 80.9, H : 10.6.

(3S,7R)-1-(8-Bromo-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7R)-19]
To a solution of ether (3S,7R)-**18** (0.9 g, 1.7 mmol, 1 eq.) in dry dichloromethane (15 ml) was added triphenylphosphine dibromide (3.6 g, 8.5 mmol, 5 eq.) and the mixture was stirred at room temperature for 12h under argon, then quenched with water, extracted with dichloromethane (3 times). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane to give bromide **19** as a colorless oil (420 mg, 70%). **TLC** : (hexane) Rf = 0.55 ; **GC** (C) 15.2 min ; **^{1}H NMR** (200 MHz), δ : 0.91 (d, J = 6.2 Hz, 3H, H-18) ; 0.98 (s, 6H, H-15, 16) ; 1.02 (d, J = 6.6 Hz, 3H, H-19) ; 1.1-1.45 (m, 12H, H-4, 5, 8, 10, 11, 12) ; 1.5-1.63 (m, 1H, H-9) ; 1.58 (s, 3H, H-17) ; 1.74-1.84 (m, 1H, H-13) ; 1.87-2 (m, 4H, H-3, 7) ; 3.33 (dd, J_{gem} = 9.8 Hz, J_{14-13} = 6.1 Hz, 1H, H-14); 3.41 (dd, J_{gem} = 9.8 Hz, J_{14-13} = 5 Hz, 1H, H-14) ; **^{13}C NMR** (50 MHz), δ : 18.8 (C-19) ; 19.6 (C-17*) ; 19.8 (C-18*) ; 24.3 (C-11) ; 26.3 (C-4) ; 28.7 (C-15, 16) ; 32.8 (C-7) ; 33.8 (C-9, 13) ; 34.9 (C-6) ; 35.2 (C-12) ; 36.9 (C-8°, 10°) ; 37.4 (C-3°) ; 39.9 (C-5) ; 41.5 (C-14) ; 126.3 (C-2) ; 137.7 (C-1) ; **MS** : 344 (M^+, 2) ; 342 (M^+, 2) ; 329 (M-15, 5) ; 327 (M-15, 5) ; 123 (C_9H_{15}, 100) ; 95 (23) ; 81 (29) ; $[\alpha]_D^{23}$ = + 7 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{19}H_{35}Br$ (343.4) C : 66.46, H : 10.27 ; found C : 66.3, H : 10.4.

(3R,7S)-1-(8-Bromo-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3R,7S)-19]
prepared in the same manner as described above. TLC, NMR and GC-MS were identical with those of (3S,7R)-**19**. $[\alpha]_D^{23}$ = - 6.4 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{19}H_{35}Br$ (343.4) C : 66.46, H : 10.27 ; found C : 66.6, H : 10.1.

(3R,7R)-1-(8-Bromo-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3R,7R)-19]
prepared in the same manner as described above. TLC, NMR and GC-MS were identical with those of (3S,7R)-**19**. $[\alpha]_D^{23}$ = - 4 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{19}H_{35}Br$ (343.4) C : 66.46, H : 10.27 ; found C : 66.6, H : 10.1.

(3S,7S)-1-(8-Bromo-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7S)-19]
prepared in the same manner as described above. TLC, NMR and GC-MS were identical with those of (3S,7R)-**19**. $[\alpha]_D^{23}$ = + 3 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{19}H_{35}Br$ (343.4) C : 66.46, H : 10.27 ; found C : 66.7, H : 10.5.

(3S,7R)-1-(8-Cyano-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7R)-20]
To a solution of bromide (3S,7R)-**19** (420 mg, 1.2 mmol, 1 eq.) in dry DMSO (20 ml) was added sodium cyanide (460 mg, 8 eq.) and the mixture was stirred at 120°C for 1h under argon, then quenched with water, extracted with ether, washed with HCl 1N, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (hexane-AcOEt : 98-2 as eluent) gave a colorless oil (330 mg, 94%). **TLC** : (hexane-AcOEt : 9-1) Rf = 0.5 ; **GC** (D) 12.3 min ; **^{1}H NMR** (200 MHz), δ : 0.90 (d, J = 6 Hz, 3H, H-18) ; 0.98 (s, 6H, H-15, 16) ; 1.07 (d, J = 6.6 Hz, 3H, H-19) ; 1.15-1.45 (m, 12H, H-4, 5, 8, 10, 11, 12) ; 1.5-1.67 (m, 2H, H-9, 13) ; 1.58 (s, 3H, H-17) ; 1.75-2.05 (m, 4H, H-3, 7) ; 3.33 (dd, J_{gem} = 9.8 Hz, $J_{14\text{-}13}$ = 6.1 Hz, 1H, H-14); 3.41 (dd, J_{gem} = 9.8 Hz, $J_{14\text{-}13}$ = 5 Hz, 1H, H-14) ; **^{13}C NMR** (50 MHz), δ : 19.6 (C-17, 19) ; 19.8 (C-18) ; 24.4 (C-11*) ; 24.5 (C-14*) ; 26.3 (C-4) ; 28.7 (C-15, 16) ; 30.5 (C-13) ; 32.8 (C-7) ; 33.8 (C-9) ; 35 (C-6) ; 36.2 (C-12) ; 36.8 (C-8°, 10°) 37.4 (C-3°) ; 39.9 (C-5) ; 118.9 (CN) ; 126.4 (C-2) ; 137.7 (C-1) ; **GC-MS** : 289 (M^+, 4) ; 274 (M-Me, 10) ; 233 (3) ; 123 (C_9H_{15}, 100) ; 95 (18) ; 81 (19) ; $[\alpha]_D^{23}$ = + 4 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{20}H_{35}N$ (289.5) C : 82.98, H : 12.19 ; found C : 83.1, H : 12.1.

(3R,7S)-1-(8-Cyano-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3R,7S)-20]
prepared in the same manner as described above. TLC, NMR and GC-MS were identical with those of (3S,7R)-**20**. $[\alpha]_D^{23}$ = - 4.4 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{20}H_{35}N$ (289.5) C : 82.98, H : 12.19 ; found C : 82.8, H : 12.0.

(3R,7R)-1-(8-Cyano-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3R,7R)-20]
prepared in the same manner as described above. TLC, NMR and GC-MS were identical with those of (3S,7R)-**20**. $[\alpha]_D^{23}$ = - 7 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{20}H_{35}N$ (289.5) C : 82.98, H : 12.19 ; found C : 82.8, H : 12.0.

(3S,7S)-1-(8-Cyano-3,7-dimethyloctyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7S)-20]
prepared in the same manner as described above. TLC, NMR and GC-MS were identical with those of (3S,7R)-**20**. $[\alpha]_D^{23}$ = + 7 ($CHCl_3$, c = 4) ; **microanalysis** (%) : calcd for $C_{20}H_{35}N$ (289.5) C : 82.98, H : 12.19 ; found C : 82.9, H : 12.1.

(3S,7R)-1-(3,7-Dimethyl-8-formyl-octyl)-2,6,6-trimethyl-1-cyclohexene [(3S,7R)-21]
To a solution of nitrile (3S,7R)-**20** (310 mg, 1.1 mmol, 1 eq.) in dry toluene (10 ml) was added DIBAL-H (1M in toluene, 1.8 ml, 1.8 eq.) at 0°C under argon. After 30 min at 0°C, the reaction mixture was slowly poured into iced water and stirred further 15 min. HCl 1N (30 ml) and saturated aqueous potassium tartrate (50 ml) were added and the medium was extracted with dichloromethane (4 times), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* (without heating) to give a slightly yellow oil (303 mg, 97%). **TLC** : (complexed with $AgNO_3$, CH_2Cl_2) Rf = 0.7 ; **GC** (D) 11.9 min ; **^{1}H NMR** (200 MHz), δ : 0.87 (d, J = 5.5 Hz, 3H, H-19) ; 0.93 (d, J = 6.9 Hz, 3H, H-18) ; 0.98 (s, 6H, H-15, 16) ; 1.06-1.43 (m, 12H, H-4, 5, 8, 10, 11, 12) ; 1.49-1.70 (m, 2H, H-9, 13) ; 1.57 (s, 3H, H-17) ; 1.86-2.07 (m, 4H, H-3, 7) ; 2.2 (ddd, J_{gem} = 15.7 Hz, $J_{14\text{-}13}$ = 7.5 Hz, $J_{14\text{-}HCO}$ = 2.5 Hz, 1H, H-14); 2.4 (ddd, J_{gem} = 15.7 Hz, $J_{14\text{-}13}$ = 5.7 Hz, $J_{14\text{-}HCO}$ = 2.1 Hz, 1H, H-14) ; 9.76 (t, J = 2.3 Hz, 1H, HC=O) ; **GC-MS** : 292 (M^+, 4) ; 277 (M-Me, 5) ; 124 (11) ; 123 (C_9H_{15}, 100) ; 109 (7) ; 95 (17) ; 81 (21) ; $[\alpha]_D^{23}$ = + 5 ($CHCl_3$, c = 4).

3 other diastereomers [(3R,7S)-21] ; [(3R,7R)-21] ; [(3S,7S)-21]
prepared in the same manner as described above. TLC, NMR and GC-MS were identical with those of (3S,7R)-**21**.

(E,3S,7R)-1-(10-(Ethoxycarbonyl)-3,7-dimethyl-9-decenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3S,7R)-22]
A suspension of sodium hydride (80% in mineral oil : washed quickly with hexane, 70 mg, 2.3 mmol, 2.3 eq.) in dry DMSO (4 ml) was stirred at 80°C for 1h under argon. After cooling at room temperature, triethyl phosphonoacetate (0.45 ml, 2.3 mmol, 2.3 eq.) was added and stirring was continued for 30 min. Then this mixture was added to a solution of aldehyde (3S,7R)-**21** (300 mg, 1 mmol, 1 eq.) in DMSO (5 ml). After stirring for 1h, the medium was quenched with water and saturated aqueous NH_4Cl, extracted with ether (3 times), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography over silica gel (complexed with $AgNO_3$), eluting with hexane-CH_2Cl_2 (9-1 until 6-4) to give ester **22** as a colorless oil (280 mg, 77%). **TLC** : (complexed with $AgNO_3$, hexane-AcOEt : 9.5-0.5) Rf = 0.61 ; **GC** (E) : 11.2 min, >99% ; **^{1}H NMR** (200 MHz), δ : 0.90 (d, J = 6.4 Hz, 6H, H-20, 21) ; 0.98 (s, 6H, H-17, 18) ; 1.07-1.44 (m, 12H, H-4, 5, 8, 10, 11, 12) ; 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3) ; 1.49-1.70 (m, 2H, H-9, 13) ; 1.58 (s, 3H, H-19) ; 1.85-1.96 (m, 4H, H-3, 7) ; 2.02 (dt, J_{gem} = 13.9 Hz, J = 7.1 Hz, 1H, H-14); 2.2 (dt, J_{gem} = 13.9 Hz, J = 7 Hz, 1H, H-14) ; 4.19 (qa, J = 7.1 Hz, 2H, OCH_2) ; 5.8 (d, J_{16-15} = 15.7 Hz, 1H, H-16) ; 6.9 (dt, J_{15-16} = 15.7 Hz, J_{15-14} = 7.5 Hz, 1H, H-15) ; **^{13}C NMR** (50 MHz), δ : 14.3 ($\underline{C}H_3CH_2O$) ; 19.6 (C-19, 21) ; 19.8 (C-20) ; 24.5 (C-11) ; 26.3 (C-4) ; 28.7 (C-17, 18) ; 32.6 (C-13) ; 32.8 (C-7) ; 33.9 (C-9) ; 34.9 (C-6) ; 37 (C-8°, 10°) 37.4 (C-3°) ; 39.7 (C-12) ; 39.9 (C-5, 14) ; 60.1 (CH_2O) ; 122.3 (C-16) ; 126.3 (C-2) ; 137.7 (C-1) ; 148.2 (C-15) ; 166.6 (CO_2Et) ; **MS** : 362 (M^+, 2) ; 347 (M-Me, 5) ; 317 (2) ; 163 (6) ; 151 (5) ; 123 (C_9H_{15}, 100) ; 109 (14) ; 95 (35) ; 81 (33) ; 69 (12) ; 67 (13) ; 55 (17) ; **IR** : 3051 (w, H-C=) ; 2927, 2867 (s, C-H) ; 1724 (s, C=O) ; 1654 (m, C=C) ; 1461 (m, C-H) ; 1367 (w) ; 1317 (w) ; 1264 (m, C-O) ; 1177 (m, C-O) ; 1045 (w) ; 983 (w) ; **UV** λ_{max} : 208.5 nm (ε 20170) ; $[\alpha]_D$ = + 8.7, $[\alpha]_{578}$ = + 9.1, $[\alpha]_{546}$ = + 10.3, $[\alpha]_{436}$ = + 18, $[\alpha]_{365}$ = + 29.3, ($CHCl_3$, c = 2), 23°C ; **microanalysis** (%) : calcd for $C_{24}H_{42}O_2$ (362.6) C : 79.50, H : 11.68 ; found C : 79.6, H : 11.8.

(E,3R,7S)-1-(10-(Ethoxycarbonyl)-3,7-dimethyl-9-decenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3R,7S)-22]
prepared in the same manner as described above. TLC, GC, NMR, MS, IR and UV were identical with those of (E,3S,7R)-**22**. $[\alpha]_D$ = - 8.8, $[\alpha]_{578}$ = - 9, $[\alpha]_{546}$ = - 10.5, $[\alpha]_{436}$ = - 18.1, $[\alpha]_{365}$ = - 30, ($CHCl_3$, c = 2), 23°C ; **microanalysis** (%) : calcd for $C_{24}H_{42}O_2$ (362.6) C : 79.50, H : 11.68 ; found C : 79.4, H : 11.6.

(E,3R,7R)-1-(10-(Ethoxycarbonyl)-3,7-dimethyl-9-decenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3R,7R)-22]
prepared in the same manner as described above. TLC, GC, NMR, MS, IR and UV were identical with those of (E,3S,7R)-**22**. $[\alpha]_D^{21}$ = - 5 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{24}H_{42}O_2$ (362.6) C : 79.50, H : 11.68 ; found C : 79.3, H : 11.8.

(E,3S,7S)-1-(10-(Ethoxycarbonyl)-3,7-dimethyl-9-decenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3S,7S)-22]
prepared in the same manner as described above. TLC, GC, NMR, MS, IR and UV were identical with those of (E,3S,7R)-**22**. $[\alpha]_D^{21}$ = + 5 ($CHCl_3$, c = 3) ; **microanalysis** (%) : calcd for $C_{24}H_{42}O_2$ (362.6) C : 79.50, H : 11.68 ; found C : 79.4, H : 11.8.

(E,3S,7R)-1-(3,7-Dimethyl-11-hydroxy-9-undecenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3S,7R)-3]
To a solution of ester (E,3S,7R)-**22** (150 mg, 0.4 mmol, 1 eq.) in dry toluene (10 ml) was added DIBAL-H (1M in toluene, 1 ml, 2.5 eq.) at -78°C under argon. After 30 min at -78°C, the reaction mixture was slowly poured into iced water, saturated aqueous NH_4Cl (20 ml) and potassium tartrate (20 ml) were added, then the medium was extracted with dichloromethane (4 times), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with hexane-AcOEt (95-5 then 9-1) to give alcohol **3** as a colorless oil (126 mg, 95%). **TLC** : (hexane-AcOEt : 9-1) Rf = 0.2 ; **GC** (E) : 10 min, >99% ; **^{1}H NMR** (400 MHz), δ : 0.87 (d, J = 6.7 Hz, 3H, H-22) ; 0.90 (d, J = 6.4 Hz, 3H, H-21) ; 0.98 (s, 6H, H-18, 19) ; 1.07-1.42 (m, 12H, H-4, 5, 8, 10, 11, 12) ; 1.47-1.60 (m, 2H, H-9, 13) ; 1.58 (s, 3H, H-20) ; 1.83-1.92 (m, 4H, H-3, 7) ; 1.94-2.04 (m, 1H, H-14); 2.06 (dt, J_{gem} = 12.8 Hz, J = 5.7 Hz, 1H, H-14) ; 4.09 (t, J = 5.1 Hz, 2H, H-17) ; 5.62 (dt, J_{16-15} = 15.3 Hz, J_{16-17} = 5 Hz, 1H, H-16) ; 5.68 (dt, J_{15-16} = 15.3 Hz, J_{15-14} = 5.7 Hz, 1H, H-15) ; **^{13}C NMR** (100 MHz), δ : 19.5 (C-20*) ; 19.6 (C-22*) ; 19.8 (C-21*) ; 24.5 (C-11) ; 26.3 (C-4) ; 28.7 (C-18, 19) ; 32.8 (C-7) ; 33 (C-13) ; 33.9 (C-9) ; 34.9 (C-6) ; 36.9 (C-14°) ; 37.1 (C-8°, 10°) ; 37.4 (C-3) ; 39.7 (C-12) ; 39.9 (C-5) ; 63.8 (C-17) ; 126.3 (C-2) ; 130.1 (C-16) ; 132 (C-15) ; 137.8 (C-1) ; **MS** : 392 ($MTMS^+$, 2) ; 302 (5) ; 177 (3) ; 169 (3) ; 163 (3) ; 161 (3) ; 150 (2) ; 123 (C_9H_{15}, 77) ; 121 (100) ; 95 (38) ; 81 (38) ; 73 (37) ; **IR** (film) : 3315 (m broad, O-H) ; 2926, 2866 (s, C-H) ; 1660 (w, C=C) ; 1459 (m, C-H) ; 1377 (m) ;

1089 (w) ; 1003 (w) ; 970 (m) ; $[\alpha]_D$ = + 10.4, $[\alpha]_{578}$ = + 10.9, $[\alpha]_{546}$ = + 12.3, $[\alpha]_{436}$ = + 21.2, $[\alpha]_{365}$ = + 34.1, ($CHCl_3$, c = 2), 23°C ; **microanalysis** (%) : calcd for $C_{22}H_{40}O$ (320.6) C : 82.43 H : 12.58 ; found C : 82.3, H : 12.7.

(E,3R,7S)-1-(3,7-Dimethyl-11-hydroxy-9-undecenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3R,7S)-3]
prepared in the same manner as described above. TLC, GC, NMR, MS and IR were identical with those of (E,3S,7R)-**3**.
$[\alpha]_D$ = - 10.1, $[\alpha]_{578}$ = - 10.7, $[\alpha]_{546}$ = - 12.1, $[\alpha]_{436}$ = - 21, $[\alpha]_{365}$ = - 34, ($CHCl_3$, c = 2), 23°C ; **microanalysis** (%) : calcd for $C_{22}H_{40}O$ (320.6) C : 82.43 H : 12.58 ; found C : 82.2, H : 12.7.

(E,3R,7R)-1-(3,7-Dimethyl-11-hydroxy-9-undecenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3R,7R)-3]
prepared in the same manner as described above. TLC, GC, NMR, MS and IR were identical with those of (E,3S,7R)-**3**.
$[\alpha]_D$ = - 4.7, $[\alpha]_{578}$ = - 4.8, $[\alpha]_{546}$ = -5.6, $[\alpha]_{436}$ = -10.3, $[\alpha]_{365}$ = - 18.1, ($CHCl_3$, c = 2), 23°C ; **microanalysis** (%) : calcd for $C_{22}H_{40}O$ (320.6) C : 82.43 H : 12.58 ; found C : 82.5, H : 12.6.

(E,3S,7S)-1-(3,7-Dimethyl-11-hydroxy-9-undecenyl)-2,6,6-trimethyl-1-cyclohexene [(E,3S,7S)-3]
prepared in the same manner as described above. TLC, GC, NMR, MS and IR were identical with those of (E,3S,7R)-**3**.
$[\alpha]_D$ = + 5, $[\alpha]_{578}$ = + 5.1, $[\alpha]_{546}$ = +5.7, $[\alpha]_{436}$ = + 10.2, $[\alpha]_{365}$ = + 18, ($CHCl_3$, c = 2), 23°C ; **microanalysis** (%) : calcd for $C_{22}H_{40}O$ (320.6) C : 82.43 H : 12.58 ; found C : 82.3, H : 12.6.

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