Tetrahedron Vol. 42, No. 18, pp. 5003 to 5010, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00

ASYMMETRIC REDUCTION OF FARNESOL

Marc JULIA* and Pierre ROY

Laboratoire de Chimie, Ecole Normale Supérieure
24, Rue Lhomond, 75321, PARIS cedex 05 FRANCE

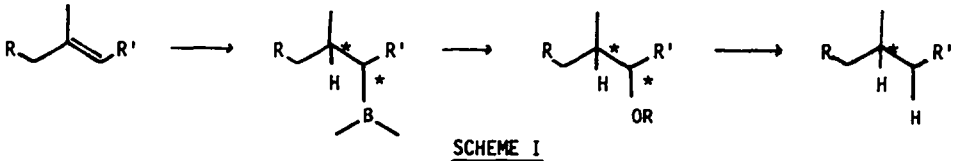
(*Received in France 4 July* 1986)

Abstract: Asymmetric hydroboration-oxidation followed by reductive deoxygenation has been used to bring about the asymmetric hydrogenation of simple trisubstituted olefins. This technique has been illustrated by the preparation of (R)-(-)-6,7,10,11-tetrahydrofarnesol.

The hydrogenation of non-proximal double bonds is an important aspect of the biosynthesis of some higher acyclic terpenes. Prominant examples are the incorporation of geranylgeraniol (GG) into tocopherols[1a] or chlorophyll[1b]. In a previous paper[2] advantage was taken of the different reactivities of the various double bonds in the geranyl, farnesyl and geranylgeranyl acetate (di-, tri- and tetra-prenol respectively) to carry out the selective hydrochlorination of the non -proximal double bond(s). Hydrogenolysis of the halogen led to the desired hydrogenated products. This route although practically convenient does not lead itself to an asymmetric hydrogenation. The synthesis of optically active compounds of this type has been actively pursued in recent years, particularly the side chain of vitamin E[3]. To the best of our knowledge, no partial hydrogenation of higher polyprenols has been described.

The asymmetric hydrogenation of carbon to carbon double bonds has been extensively investigated and considerable progress has been made[4]. Catalytic hydrogenation has proved extremely efficient when the double bonds carry some substituents such as NHR, COOR..., but this is not so with simple double bonds. Ionic hydrogenation[5] with trifluoroacetic acid (TFA) and optically active hydrogenosilane has led to a very small ee. Asymmetric epoxidation of double bonds has been efficiently achieved[6] with allylic alcohols. This would however be of no help in our problem. Asymmetric epoxidation of simple double bonds has been improving steadily[7]. However reduction of two sites including the sensitive one could be necessary.

Asymmetric hydroboration was potentially useful. When this work was started, it had led to fairly high induction. The ee was usually measured on the alcohol produced by oxidation of the borane[8], whereas we intended to use the ee induced on the other carbon atom of the original double bond which should be just as good.



SCHEME I

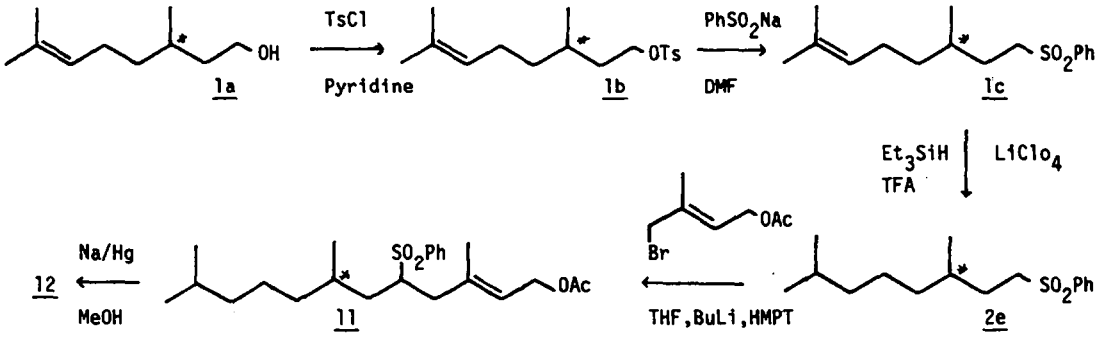
We did not expect to remove the boron from the intermediate borane by selective protonation[9] of the desired alkyl residue without affecting the allylic function. However, after the well exemplified hydroboration-oxidation of the double bond, reductive removal of the oxygen function should be possible without modifying the chirality of the adjacent saturated carbon atom. In polyprenols, the hydroboration was expected to take place on the non-proximal double bond[10]. Although cyclic hydroboration of 1,5-dienes can lead to interesting remote stereocontrol[3i], it is known to involve the proximal double bond in geranyl derivatives[10,11,12]. We therefore could not use monoisopinocampheyl borane ($IpcBH_2$[8c]) which had led to very high ee in the hydroboration of trisubstitued double bonds. Since diisopinocampheyl borane does not give good results with such olefins, we turned to the readily available limonyl borane 3 (limBH[8c]) to investigate the feasability of this approach. We selected as a first target tetrahydrofarnesol.

Whereas protonolysis of borane needs fairly severe conditions[9], the conversion into halides or alcohols is easy. We selected the well known hydrogen peroxide oxidation to obtain the alcohol.

Preliminary hydroboration-oxidation of citronellol 1a gave the expected diol 2a. The primary alcohol function was acetylated much more rapidly than the secondary one. The byproducts 2g and 2f are easily recycled. Monoacetate 2b was then treated with tosyl chloride in pyridine to give in high yield the acetate tosylate 2c. Lithium aluminium hydride (LAH) reduction of 2c gave tetrahydrogeraniol 2d in high yield. It proved essential to use a clear solution of LAH filtered through celite[13].

With geraniol 4b itself or its butyl ether 4a, the best conditions found involved addition of limBCl and Me_2S to a solution of olefin and LAH in ether. After the usual oxidation with hydrogen peroxide and sodium hydroxide, the mixture was separated by flash-chromatography. The desired diol 6a[14], and 5a respectively, was readily separated from the starting material. In some runs, small amounts of the isomeric glycol 8b[15] (8a respectively) or the diastereoisomeric triol 9b[12] (9a respectively) were isolated. The enantiomeric purity of the hydroboration-oxidation products 5a and 6a was determined by esterification with α-methoxy-α-trifluoromethyl phenyl acetyl chloride (MTPACl[16]) and HPLC analysis of the diastereoisomeric mixture formed. The values of the ee found were 52% for 5a and 50% for 6a.

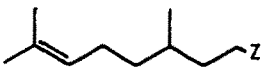
The next target was tetrahydrofarnesol 12; before embarking on the partial hydrogenation of farnesol, we needed an authentic sample of the optically active tetrahydrofarnesol of known enantiomeric purity for comparison purposes (Scheme II). (R)-(+)-citronellol was converted into the corresponding phenyl sulfone 1c via its tosylate[17] 2h. The reduction of the double bond was carried out with Et_3SiH-TFA-$LiClO_4$ as in the previous paper[2] to give (R)-tetrahydrogeranyl sulfone 2e. This was metalated with butyl lithium and condensed with 4-bromo-3-methyl-2-buten-1-yl acetate 10 (kindly provided by Dr Ferezou). Reductive desulfonylation of the sulfonyl acetate 11 was carried out with sodium amalgam in methanol to give tetrahydrofarnesol 12 which should have the same optical purity as the starting citronellol (ee 80%).



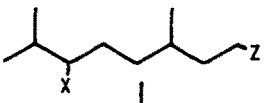
The farnesol 13 was then exposed to the hydroboration conditions. After oxidation, the desired diastereoisomeric triol 14 formed by double hydroboration was isolated in 31% yield together with the starting material (17%), a mixture of isomeric diols 18a and 18b (15%) formed by reaction at one of the non proximal double bonds and some (5%) of the triple hydroboration-oxidation product 17. Monoacetylation of to primary alcohol function of 14 to give 15a was less selective (45%) than in the geraniol series, but the side products 15b and 15c can be easily recycled. Ditosylation of 15a to 16a was carried out with a yield of 47%, with some byproducts: uncomplete tosylation (16b and 16c); elimination (19a and 19b). Hydrogenolysis of the two tosyloxy groups in 16a with lithium aluminium hydride in THF gave tetrahydrofarnesol 12 in a 50% yield. The optical purity was 53 + 12%. the absolute configuration was (R), as in the authentic sample prepared from (R)-citronellol.

It was thus possible to carry out asymmetric hydrogenation of the middle double bond of farnesol. The optical purity was about the same as that observed in the hydroboration of the distal double bond of geraniol. It is the best which could be expected with LimBH. While this work being completed, an extremely efficient chiral hydroboration reagent were described[18]; ee as high as 95% being obtained with trisubstituted olefins. This should allow the very efficient asymmetric reduction of internal double bond of farnesol and geranylgeraniol.

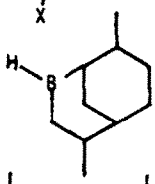
SCHEME III



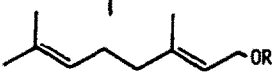
1 a Z=OH c Z=SO_2Ph
b Z=OTs



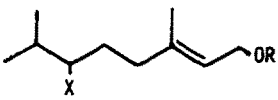
2 a X=Z=OH d X=H;Z=OH g X=OAc;Z=OH
b X=OH;Z=OAc e X=H;Z=SO_2Ph h X=OTs;Z=OH
c X=OTs;Z=OAc f X=Z=OAc



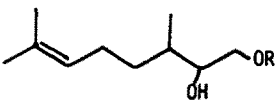
3



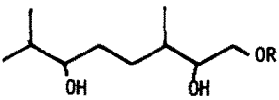
4 a R=nBu c R=Ac
b R=H



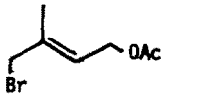
5 a R=nBu;X=OH 6 a R=H;X=OH 7 a R=Ac;X=OH
b R=nBu;X=OMTPA b R=H;X=H b R=Ac;X=OAc
c R=Ac;X=OMTPA



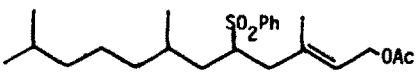
8 a R=nBu
b R=H



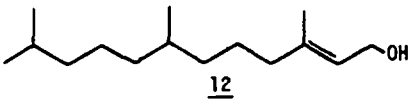
9 a R=nBu
b R=H



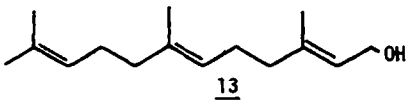
10



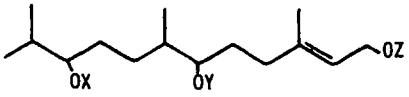
11



12



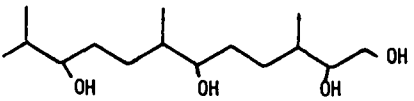
13



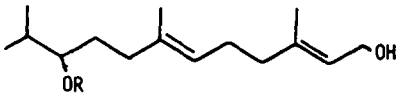
14 X=Y=Z=H

15 a X=Y=H; Z=Ac
b X=H; Y=Z=Ac
c Y=H; X=Z=Ac

16 a X=Y=Ts; Z=Ac
b X=H; Y=Ts; Z=Ac
c X=Ts; Y=H; Z=Ac

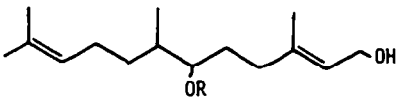


17



18 a R=H

19 a R=Ts



18 b R=H

19 b R=Ts

EXPERIMENTAL

The spectroscopic instrumentation included ^1H NMR (PMR) Brucker WH 80 (80 MHz) and Cameca 250 (250 MHz), in $CDCl_3$ solution . δ Value are given in PPM with respect to Me_4Si and coupling constant in Hertz (s: singlet; d: doublet; t: triplet; q: quadruplet; m: multiplet). IR: Perkin-Elmer 599, either neat or in $CHCl_3$. Values are given in cm^{-1}; S: strong; m: medium; w: weak. Mass spectra: Varian Mat CH 9,and for the GLC-Mass measurement: Ribermag with capillary column; CI: chemical ionisation; EI: electronic impact. GLC: Girdel 30, column: OV 101 10% (4m) or capillary column: SE 52, integrator intersmat minigrator and Hewlet packard HP 3380A respectively. TLC was carried out on Merck plates (5735, plastic sheet, silica gel 60F254, thickness 0.2 mm). Flash chromatography (FC)[19] was carried out with silica gel (Merck 7736), eluted with a mixture of pentane:ether:ethyl acetate. In several case, the amount of material available did not allowed the combustion analysis (microanalytical laboratories of the université Pierre et Marie Curie to whom our thanks are due).

Geraniol were purchased from Fluka. Butyl geranyl ether was kindly provided by Dr C. Schmitz. t,t-farnesol was isolated from the mixture (Fluka) of isomers by MPLC (LOBAR Merck) with a C(440-37) lichoprep Si60 column (4063 μm). (-)-LimBCl and (+)-LimBCl were prepared from (+) and (-)-limonene respectively[8b] and converted in situ into LimBH.

Hydroboration-oxidation-reduction of citronellol.

* 3,7-Dimethyl-1,6-octanediol 2a.

Prepared by hydroboration (B_2H_6) of citronellol and oxidation[12]. RN: 56067-10-0.

* 3,7-Dimethyl-1-acetoxy-6-octanol 2b.

Acetic anhydride (0.38 ml, 4 mmol) was slowly added to a solution of diol 2a (0.7 g, 4 mmol) in pyridine (3ml) and CH_2Cl_2 (10ml) at 0°C. After standing overnight at RT, the mixture was worked-up and the mono primary acetate 2b isolated by FC as a colourless oil (0.4 g, 46%). Small amounts of the other monoacetate 2g (3%) and diacetate 2f (6%) were isolated together with unchanged diol (32%). PMR(250): 0.90 (dd, J=1;7Hz,3H); 0.92 (dd, J=1;7Hz,6H); 1.1-1.7 (m,8H); 2.04 (s,3H); 3.31 (ddd, J=8.5;5;3Hz,1H); 4.03 (m,2H). IR: 3420 S; 2960-2860 S; 1720 S; 1650 w; 1450 w. MS CI(NH_3): 234 (M+18, 100); 217 (40); 199 (33). RN: 33730-43-7.

* 3,7-Dimethyl -1-acetoxy-6-p-toluenesulfonyloxy octane 2c.

The tosylate 2c was prepared by addition of tosyl chloride (380mg, 2 mmol) in pyridine (0.5ml) at 0°C to a solution of hydroxy acetate 2b (216 mg, 1 mmol) in pyridine (1ml). After 72 hr at 0°C the usual workup gave after FC 2c (302 mg, 82%) as a colourless oil. PMR(250): 0.84 (dd, J=7;1Hz,3H); 0.86 (d, J=7Hz,6H); 1-2 (m,8H); 2.03 (s,3H); 2.42 (s,3H); 4.00 (t, J=7Hz,2H); 4.38 (dt, J=7;5Hz,1H); 7.27 (d, J=8Hz,2H); 7.63 (d, J=8Hz,2H). IR: 2960-2880 S; 1735 S; 1595 m; 1460 m. MS CI(NH_3): 388 (M+18,100).

* 3,7-Dimethyl-1-octanol 2d (tetrahydrogeraniol).

A cooled solution of LAH in THF (0.83 M, filtered through celite, 2ml) was slowly added to a solution of the above tosylate 2c (112 mg, 0.3 mmol) in THF (0.5 ml) at -10°C, and the mixture was allowed to warm up to RT overnight. Workup gave a mixture of 2d (39 mg, 82% yield by GLC) identical with an authentic sample [2] and citronellol (6%).

Hydroboration-oxidation of geraniol.

* 3,7-Dimethyl-2E-octen-1,6-diol 6a.

A 20 ml flask was flame-dried and cooled under argon. Lithium aluminium hydride (57 mg, 1.5 mmol) and geraniol 4b (154 mg, 1 mmol) in dry ether (4ml) were cooled to -30°C. A solution of LimBCl (360 mg, 2 mmol) in Me_2S (0.243 ml, 4mmol) was then added. After 48 h standing at -30°C the temperature was allowed to rise 0°C and water (0.05 ml) and aqueous 3 M NaOH (1.5 ml) were added. 30% Hydrogen peroxide (2ml) was then slowly added and the mixture refluxed 2 h. After the usual work-up the mixture was fractionated by FC to give 32% of recovered geraniol 4b and 46% of the desired diol 6a[14]. PMR(250): 0.92 (dd, J=7;1Hz,6H); 1.4-1.7 (m,3H); 1.67 (s,3H); 2.1 (ddd, J=14;9.5;6.3Hz,1H); 2.2 (ddd, J=14;9.5;5.7Hz,1H); 3.34 (ddd,J=8.5;5;3Hz,1H); 4.12 (d, J=6.5Hz,2H); 5.43 (tq, J=6.5;1Hz,1H). IR: 3350 S; 2960-2860 S; 1710w; 1660 m; 1450 S. MS EI: M=172.

* 3,7-Dimethyl-2E-octene-1,6-diol acetate 7a.

The diol 6a was acetylated (Ac_2O, pyridine, CH_2Cl_2) as for 2b, to give 7a (66%) as a colourless oil. PMR(250): 0.91 (dd, J=7;1.5Hz,6H); 1.4-1.7 (m,3H); 1.72 (s,3H); 2.06(s,3H); 2-2.3 (m,2H); 3.35 (ddd, J=8.5,5;3Hz,1H); 4.59 (d, J=7Hz,2H); 5.39 (tq, J=7;1Hz,1H). IR: 3410 S; 2960-2860 S; 1710 S; 1660 w; 1450 S. MS CI (NH_3): 232 (M+18,14); 215 (1); 172 (75); 155 (100).

* Together with 11% of 3,7-dimethyl-2E-octene-1,6-diol diacetate 7b.

Colourless oil. PMR(250): 0.89 (d, J=6.7Hz,6H); 1.5-1.8 (m,3H); 1.68 (s,3H); 2.04 (s,6H); 2.05 (m,2H); 4.53 (d, J=7Hz,2H); 4.68 (t, J=6Hz,1H); 5.30 (tq, J=7;1Hz,1H).IR:2960-2860 S; 1735 S; 1650 w; 1465 m. MS CI(NH_3): 274 (M+18,100); 232 (10); 214 (50); 197 (25).

Hydroboration-oxidation of geranyl n-butyl ether.

Carried out as above with 5 mmol of 4a. FC gave in the order of elution: recovered 4a (5%); the unwanted isomer 8a (10%), the desired one 5a (22%) and the dihydroboration product 9a (33%).

* 3,7-dimethyl-1-butoxy-6-octen-2-ol 8a. Colourless oil. PMR(250): 0.88 (d, J=6.8Hz,3H); 0.91 (t, J=7.5Hz,3H); 1.16 (m,1H); 1.36 (m,2H); 1.54 (m,2H); 1.6 (m,2H); 1.60 (s,3H); 1.67 (s,3H); 2.0 (m,2H); 3.29 (dd, J=9.5;8.5Hz,1H); 3.44 (ddd, J=12.5;9.5;3Hz,1H); 3.45 (t, J=6.5Hz,2H); 3.58 (m,1H); 5.08 (t, J=7Hz,1H). IR: 3430 S; 2950-2850 S; 1630 w; 1450 S. MS EI: M=228. Anal.: calc. for $C_{14}H_{28}O_2$, C 73.63 H 12.36; found C 73.50 H 12.17.

* 3,7-Dimethyl-1-butoxy-2E-octen-6-ol 5a. Colourless oil. PMR(250): 0.89 (dd, J=6.8;1.5Hz,6H); 0.90 (t, J=7.5Hz,3H); 1.36 (m,2H); 1.54 (m,2H); 1.3-1.7 (m,3H); 1.66 (s,3H); 2.06 (ddd,J=14;9.5;5.7Hz,1H); 2.19 (ddd,J=14;9.5;6.3Hz,1H); 3.32 (ddd, J=8.5;5;3Hz,1H); 3.39 (t, J=6.5Hz,2H); 3.95 (d, J=6.5Hz,2H); 5.37 (tq, J=6.5;1Hz,1H).IR:3400 S, 2950-2860 S; 1650 w; 1450 m. MS EI: M=228. Anal.: calc. for $C_{14}H_{28}O_2$, C 73.63 H 12.36; found, C 73.75 H 12.43.

* 3,7-Dimethyl-1-butoxy-2,6-octene diol 9a. Colourless oil. PMR(250):0.9 (m,12H); 1.1-1.8 (m,10H); 3.2-3.6 (m,6H). IR: 3400 S; 2950-2870 S; 1460 S. MS CI(NH_3): 264 (M+18,23); 248 (60); 247 (42); 229 (100).

Preparation of diastereoisomeric esters.

* The MTPA ester 5b was prepared with 5a (15 mg, 0.065 mmol), NEt_3 (0.2 ml), 4-dimethyl amino pyridine (5mg) and MTPACl (18mg, 1eq). The mixture was worked up after 3 h at RT. Impurities were removed by filtration through a short column of silica gel. PMR(250): 0.90 (m,9H); 1.3-1.7 (m,7H); 1.59 + 1.63 (divided s,3H); 1.83-2.10 (m,2H); 3.40 + 3.42 (divided t, J=6.5Hz,2H); 3.55 (s,3H); 3.93 + 3.96 (divided d, J=6.5Hz,2H); 4.95 (m,1H); 5.27 + 5.34 (divided t, J=7Hz,1H); 7.40 (m,3H); 7.59 (m,2H).IR: 3060 w; 3000-2840 S; 1740-1720 S; 1650 m; 1490 w; 1460-1450 m. The analysis was performed by injecting the mixture, dissolved in pentane, into a Zorbax 5 , 25 cm HPLC column and eluting with ethyl acetate 1% in isooctane, flow rate 1.5 ml/min: ee 52%.

* The MTPA ester mixture 7c derived from 7a was prepared as above. PMR(250): 0.90 (d, J=6.7Hz,6H); 1.5-1.7 (m,3H); 1.6 + 1.66 (divided s,3H); 1.86-2.1 (m,2H); 2.02 + 2.04 (divided s,3H); 3.54 (s,3H); 4.53 + 4.55 (divided d, J=7Hz,2H); 4.91 (m,1H); 5.20 + 5.30 (divided tq, J=7;1Hz,2H); 4.91 (m,1H); 5.20 + 5.30 (divided tq, J=7;1Hz,1H); 7.34-7.50 (m,5H).IR: 3060 w; 3000-2840 S; 1740 S; 1650 m; 1490 w; 1460-1450 m. HPLC showed an ee of 50%.

Preparation of authentic (R)-tetrahydrofarnesol.

* (R)-(+)-Citronellol was tosylated[17]. The tosylate 1b (3 g, 9.7 mmol) and sodium benzene sulfinate in DMF were heated to 80°C overnight. The usual work-up gave unchanged tosylate (67%) and the desired sulfone 1c (0.8 g,27%). PMR(80): 0.84 (d, J=6Hz,3H); 1-1.7 (m,5H); 1.56 (s,3H); 1.66 (s,3H); 1.94 (m,2H); 3.10 (t,J=7Hz,2H); 5.02 (t, J=7Hz,1H); 7.2-8 (m,5H).IR: 3000-2860 S; 1640 w; 1590 m; 1460 m.

* (R)-3,7-Dimethyl-1-benzene sulfonyl octane 2e.

Crude sulfone 1c (0.8 g, 2.6 mmol), $LiClO_4$ (140 mg, 0.5 eq), Et_3SiH (1 ml, 2.5 eq) and TFA (0.54 ml) were heated for 3 h in 2-nitropropane at 80°C. After the usual work-up, FC gave crude tetrahydrogeranyl sulfone with an NMR spectrum identical to that of racemic component.

* 3,7,11-Trimethyl-5-benzenesulfonyl-2E-dodecen-1-yl acetate 11.

A solution of n-butyl lithium in hexane (1.52 M, 0.7 ml) was added at -78°C to a solution of sulfone 2e (297 mg, 1 mmol) in THF (5 ml). After standing for 30 min at RT, HMPT (0.3 ml) was added and after 30 more minutes, the mixture was cooled again to -78°C then bromo acetate 10 (300 mg, 1.57 eq) was added. After 1 h at -78°C and 2 h at RT the reaction was worked up to give after FC the sulfone 11 (136 mg, 35%). PMR(80): 0.84 (d, J=6Hz,9H); 1-1.7 (m,10H); 1.62 (s,3H); 2.02 (s,3H); 2.03 (m,2H); 3.11 (m,1H); 4.52 (d, J=7Hz,2H); 5.34 (t, J=7Hz,1H); 7.63-7.82 (m,5H).IR: 3000-2880 S; 1740 S; 1640 w; 1580 m; 1450 m; 1300 S; 1150 S.

* (R)-3,7,11-Trimethyl-2E-dodecen-1-ol 12.

To a solution of sulfone acetate 11 (100 mg, 0.25 mmol) in methanol (2ml) was added 6% sodium amalgam (580 mg, 6 eq) and the mixture was stirred 17 h at RT. The usual workup gave after FC, (R)-tetrahydrofarnesol 12 (30 mg, 54%), $[\alpha]_D^{25}$= -0.59° + 0.04° (c=2.54, $CHCl_3$). The NMR and mass spectra were identical with those of an authentic racemic sample[2].

From farnesol.

* All trans farnesol 13 (671 mg, 3 mmol) was introduced in a flame dried flask under argon. $LiAlH_4$ (51 mg, 1.34 mmol) and dry ether (2.5 ml) were then added at -30°C followed by (-)-IpcBCl (520 mg, 2.8 mmol) in Me_2S (0.4 ml). After 24 h at -30°C, (-)-IpcBCl (281 mg, 1.6 mmol) in Me_2S (0.2 ml) and LAH (30 mg, 0.8 mmol) in ether (2ml) were added and the addition repeated after 24 h. After standing another 24 h at -30°C, excess LAH was hydrolysed at 0°C; aqueous sodium hydroxide (3M, 4.4 ml) and 30% hydrogen peroxide (5.8 ml) were added and the mixture refluxed for 3 h. After the usual work-up the purification by FC gave some unchanged farnesol 13 (17%), a mixture of the isomeric diols 18a and 18b (15%), the desired triol 14 (31%) and some tetraol 17.

- The mixture 18a + 18b was identified by the NMR and Mass spectra. Colourless oil. PMR(250) partial: 5.36 (t, J=7Hz,1H); 5.12 (m,1H); 4.07 (m,2H); 3.33 (m,1H).IR: 3400 S; 2980-2880 S; 1710 m; 1670 m; 1460 m. MS CI(NH_3) (Me_3Si derivatives): 402 (M'+18, 22).

- 3,7,11-Trimethyl-2E-dodecen-1,6,10-triol 14. Colourless oil. PMR(250): 0.91 (d,

J=6Hz,9H); 1.2-1.7 (m,8H); 1.67 (s,3H); 2.0-2.3 (m,2H); 2.62 (s,3H); 3.28-3.42 (m,2H); 4.12 (d, J=7Hz,2H); 5.43 (t, J=7Hz,1H). IR: 3580-3410 S; 2960-2860 S; 1650 m; 1450 S. MS CI(NH_3) (Me_3Si derivative): 402 (M'+18,22).

- 3;7,11-Trimethyl-dodecane-1,2,6,10-tetraol 17. Colourless oil. PMR(250): 0.9 (m, 12H); 1.0-1.7 (m, 11H); 3.0-3.7 (m, 5).IR: 3400 S; 2980-2880 S; 1710 m; 1650 w; 1460 m. MS CI (NH_3) (Me_3Si derivative): 582 (M'+18, 31).

* Acetylation of 14. To a solution of triol 14 (241 mg, 241 mmol) in pyridine (2ml) at 0°C were added portionwise Ac_2O (0.087 ml, 1 eq) in pyridine (1ml). After 15 h at RT, the usual work-up and FC gave the dihydroxy acetate 15a as a colourless oil (45%). PMR (250): 0.91 (m,9H); 1-1.7 (m,12H); 1.71 (s,3H); 1.93 (s,2H); 2.04 (s,3H); 2.24 (m,2H); 3.33 (ddd, J=8.5;5;3.5Hz,1H); 3.41 (ddd, J=9;5.5;3Hz,1H); 4.57 (d,J=7Hz,2H); 5.38 (tq, J=7;1Hz,1H).IR: 3500 S; 2980-2880 S; 1740 S; 1680 w; 1460 m.

- Together with some triol 14 (12%), a mixture of the isomeric diacetates 15b + 15c (10%) were also isolated (Rf 0.59 in pentane/ether:30/70). PMR(250) partial: 5.32 (m,1H); 4.7 (m,1H); 4.54 (m,2H); 3.40 (m,1H); 2.04 (s,6H). IR: 3500 m; 2980-2880 S; 1740 S; 1680 w; 1460 m. MS CI(NH_3)(Me_3Si derivative): 432 (M'+18,97).

* 3,7,11-Trimethyl-6,10-di-p-tosyloxy-2E-dodecen-1-yl acetate 16a.

The tosylation of 15a was carried out as above to give the acetate ditosylate 16a (45%) as a middle fraction of a FC. PMR(250): 0.80 (m,9H); 1-1.7 (m,12H); 1.61 (s,3H); 1.78 (m,2H); 2.05 (s,3H); 2.42 (s,3H); 2.43 (s,3H); 4.37 (m,2H); 4.54 (d, J=7Hz,2H); 5.22 (t, J=7Hz,1H); 7.31 (m,2H); 7.75 (m,2H).IR: 2960-2880 S; 1735 S; 1735 S; 1670 w; 1590 m.

- The first fraction of the FC (Rf 0.46 in pentane/ether:70/30) showed vinylic protons indicating that elimination had taken place (10%). The last fraction contained the isomeric acetate monotosylate 16b and 16c (10%) (Rf 0.51 in pentane/ether: 30/70). PMR(250) partial: 7.74 (d, J=8Hz,2H); 7.28 (d, J=8Hz,2H); 5.37 (t, J=7Hz,1H); 4.57 (d, J=7Hz,2H); 4.42 (m,1H); 3.30 (m,1H); 2.42 (s,3H); 2.04 (s;3H).

* The ditosylate 16a (122 mg) was treated as above to give tetrahydrofarnesol (22 mg, 50%) $(\alpha)_{25}$= -0.31° + 0.05° (c=1.97, $CHCl_3$). The optical purity is therefore 53 + 12%.

Acknowledgements: Our thanks are due to the Ecole Polytechnique and to the DRET who financially supported this work and to the CNRS (LA 32) where this work was carried out.

REFERENCES

1 a) C.D. Poulter and H.C. Rilling, Biosynthesis of Isoprenoid Compounds, J.W. Porter and S.L. Surgeon Ed., vol. 1, p. 413, Wiley, New York (1983).b) Ibid., J.F. Pennock and D.R.Threlfall, vol. 2, p. 191. c) D.J. Creighton, J. Hadju, D.S. Sigman, J. Am. Chem. Soc., 98,4619 (1976).

2 M. Julia and P. Roy, preceding paper.

3 (a) J.W.K. Burell, R.F. Garwood, L.M. Jackman, E. Oskay, B.C.L. Weedon, J. Chem. Soc. (C), 2144 (1966).(b) K.K. Chan, A.C. Specian Jr, J.P. Denoble, N. Cohen, G. Saucy, J. Org; Chem., 41, 3497 (1976). K.K. Chan, A.C. Specian Jr, G. Saucy, ibid, 43, 3435 (1978).(c) L. Ahlquist, G. Bergström, C. Liljenberg, Prog. Chem. fats other Lipids, vol. 16, 231 (1978).(d) N. Cohen, C.G. Scott, C. Neukom, R.J. Lopresti, G. Weber, G. Saucy, Helv. Chim. Acta, 64, 1158 (1981).(e) N. Cohen, W.F. Eichel, R.J. Lopresti, C. Neukom, G. Saucy, J. Org. Chem., 41, 3505,3512 (1976). N. Cohen, R.J. Lopresti, C. Neukon, G. Saucy, ibid, 45, 582 (1980). C.T. Goodhue, J.R. Schaeffer, Biotechnol. Bioeng., 13, 203 (1971).(f) C. Fuganti, P. Grasselli, J. Chem. Soc. Chem. Comm., 995 (1979).(g) H.G.W. Leuenberger, W. Boguth, R. Barner, M. Schmid, R. Zell, Helv. Chim. Acta, 62, 455 (1979).(h) B.M. Trost and

T.P. Klun, J. Am. Chem. Soc., 101, 6756 (1979). B.M. Trost and T.P. Klun, J. Am. Chem. Soc., 103, 1864 (1981). B.M. Trost and J.P. Klun, J. Org. Chem., 45, 4256 (1980).(i) W.C. Still and K.P. Darst, J. Am. Chem. Soc., 102, 7385 (1980).(j) T. Fujisawa, T. Sato, T. Kawara, K. Ohashi, Tetrahedron Letters, 22, 4823 (1981).(k) C.H. Heathcock and E.T. Jarvi, Tetrahedron Letters, 23, 2825 (1982). D.A. Evans, J.V. Nelson, T.R. Taber, Topics in Stereochemistry, 13, 1 (1982), Interscience, New York.(l) M. Koreeda and L. Brown, J. Org. Chem., 48, 2122 (1983).(m) G. Helmchen and R. Schmierer, Tetrahedron Letters, 24, 1235 (1983).(n) G. Berubé and P. Deslongchamps, Can. J. Chem., 62, 1558 (1984).(o) J. Fujiwara, Y. Fukutani, M. Hasegawa,K. Maruoka, H. Yamamoto, J. Am. Chem. Soc., 106, 5004 (1984).(p) K. Takabe, J. Uchiyama, K. Okisaka, T. Yamada, T. Katagiri, T. Okazaki, Y. Oketa, H. Kumobayashi, S. Akutagawa, Tetrahedron Letters, 26, 5153 (1985) and ref. Cited therein.

4 H.B. Kagan in Asymmetric Synthesis, Vol. 5, J.D. Morrison, Academic Press N.Y. (1985)..

5 J.L. Fry and M.G. Adlington, J. Am. Chem. Soc., 100, 7641 (1978). J.D. Morrison and H.S. Mosher, Asymmetric Organic Reaction, Ed. Am. Chem. Soc. Whashington D.C., 266 (1976). J. Barluenga, J.M. Martinez Gallo, C. Najera, M. Yus, J. Chem Research, 266 (1985).

6 T. Katsuki and K.B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).

7 (a) W.H. Pirkle and P.L. Rinaldi, J. Org. Chem., 42, 2080 (1977).(b) R. Curci, M. Fiorentino, M.R. Serio, J. Chem. Soc. Chem. Comm., 155 (1984).(c) H.B. Kagan, H. Mimoun, C. Mark, V. Schurig, Angew. Chem. Int. Ed. Eng., 18, 485 (1979).(d) F.A. Davis, M.E. Haruka, S.B. Awad, J. Am. Chem. Soc., 105, 3123 (1983).(e) J.T. Groves and R.S. Myers, ibid , 105, 5791 (1983).(f) D. Mansuy, P. Battioni, J.P. Renaud, P. Guerin, ibid , 107, 155 (1985).(g) H. Ohta and H. Tetsukawa, J. Chem. Soc. Chem. Comm., 849 (1978).

8 (a) H.C. Brown, P.K. Jadhav, A.K. Mandal, Tetrahedron, 37, 3547 (1981).(b) P.K. Jadhav and S.U. Kulkani, Heterocycles, 18, 169 (1982).(c) H.C. Brown and B. Singaram, J. Am. Chem. Soc., 106, 1797 (1984).

9 (a) H.C. Brown, Boranes in Organic Chemistry, Cornell University Press, Ithaca N.Y. (1972).(b) H.C. Brown, Organic Synthesis with Boranes, Wiley Interscience, N.Y. (1975).(c) D.V. Banthorpe, H. Fitton, J. Lewis, J. Chem. Soc. Perkin Tr. I, 2051 (1973).

10 H.C. Brown and E. Negishi, Tetrahedron, 33, 2331 (1977).

11 R. Murphy and R.H. Prayer, Aust. J. Chem, 29, 617 (1976).

12 J. Wolinsky and R.H. Bedoukian, J. Org. Chem., 41, 278 (1976).

13 S. Krishnamurthy and H.C. Brown, ibid , 47, 276 (1982).

14 G. Ohloff, K.H. Schulte Elte, B. Willhalm, Helv. Chim. Acta, 47, 602 (1964).

15 S.M. Viti, Tetrahedron Letters, 23, 4541 (1982).

16 J.A. Dale, D.L. Dull; H.S. Mosher, J. Org. Chem., 34, 2543 (1969).

17 R.S. Atkinson, D.R.G. Brimage, R.S. Davidson, E. Gray, J. Chem. Soc.Perkin Tr. I, 960 (1973).

18 S. Masamune, B.M. Kim, J.S. Petersen, T. Sato, S.J. Veenstra, J. Am. Chem. Soc., 107, 4549 (1985).

19 W.C. Still, M. Kahn, A. Mitra, J. Org.Chem., 43, 2923 (1978).