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THE USE OF METHYL SUBSTITUTED CHIRAL SYNTHONS IN THE SYNTHESIS OF PINE SAWFLIES PHEROMONES

Marc LARCHEVEQUE and Caroline SANNER
ER 12 du CNRS, Laboratoire de Chimie, Ecole Normale Supérieure
24 Rue Lhomond, 75231 PARIS Cedex 05, France

Robert AZERAD and Didier BUISSON
Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques associé au CNRS,
Université R. Descartes, 45 Rue des Saints Pères, 75270 PARIS Cedex 06, France

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Abstract : *The preparation of methyl-substituted synthons of high enantiomerical purities by Claisen transposition, cuprate substitution of secondary optically active alcohols and microbial reduction of β-ketoesters was investigated and applied to the synthesis of (2S,3S,7S) and (2S,3R,7R)-3,7-dimethylpentadecan-2-ol, the pheromones of diprionid species of pine sawflies.*

A large number of mono or polyhydroxylated chiral compounds is available for the synthesis of biologically active substances. In contrast, simple optically active methyl substituted starting materials are rare enough, and it would be of unquestionable interest to develop methods allowing to prepare such synthons in high enantiomerical purities.

In the course of our work on the pine sawflies pheromones, the synthesis of several methylated synthons was required. Pine sawflies are small hymenopters which cause severe damage to pine forests. The major sex pheromone of various diprionid sawflies are either acetate or propionate of (2S,3S,7S)-3,7-dimethyl pentadecan-2-ol 1 and it was recently recognized that the male response is enhanced by a small amount of the (2S,3R,7R)-isomer 2 (1).

Several syntheses of optically active diastereomers have been reported : Mori has described a synthesis of all the four possible isomers having 2,3-*erythro* configuration (2) ; besides, the preparation of enantiomerically enriched (2S,3S,7S)-isomer was also reported (3). A recent paper has described the obtention of both (2S,3S,7S)-*erythro* and (2S,3R,7R or 7S)-*threo* isomers (4). However, all these previously reported methods suffered from poor yields inherent to multistep syntheses and /or poor diastereoselectivity in creating the desired asymmetry at the new optical centers. Although it is theoretically possible to realize such synthesis by using 1-5 relative inductions (5), efficient methods for such inductions are rare enough (6). The most reliable procedure to prepare compounds such as 1 or 2 is to assemble optically pure building blocks by a method which avoids racemisation of the chiral centers. This method is especially interesting because it possibly allows to enhance the enantiomerical purity of the final product ; for instance, starting from two enantiomers of 90 % ee it is possible to obtain the main diastereomer with a 99.4 % ee* provided that the diastereomers may be separated (7).

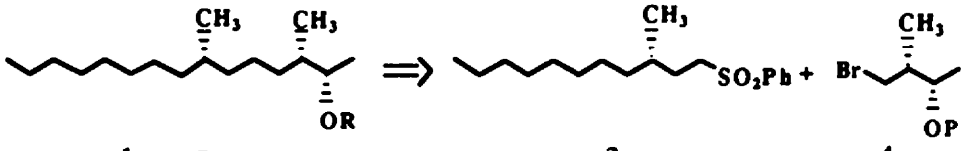
In this paper we describe a method for preparing four enantiomerically pure synthons : the sulfones 3 and ent-3, and the bromides 4 and 5, the coupling of which allowed us to prepare the essential isomers of the pine sawflies pheromones (2S,3S,7S)-1a and (2S,3R,7R)-2 with the correct stereochemistry.

Our approach centers about the formation and the condensation of a carbanion in the α position to a sulfonyl

* $ee = \frac{RR-SS}{RR+SS} = \frac{(95\times95)-(5\times5)}{(95\times95)+(5\times5)} = 99.4\ \%$

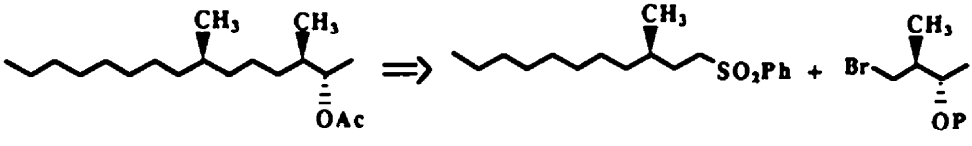
group to effect the coupling reaction. The use of sulfones presents some advantages : they are often crystallized, a fact which allows, if necessary, to enhance the enantiomeric purity. Moreover it was thought that the presence of the sulfo-

Scheme I



1 a R = Ac
b R = Pr

3 4



2 ent-3 5

6 7

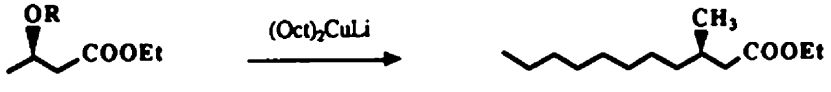
nyl function would perhaps afford a better separation of the diastereoisomers obtained after the coupling reaction. The required synthons **4** and **5** were readily prepared *via* transformation of the two diastereomeric *syn* and *anti* β-hydroxyesters **6** and **7**.

Synthesis of the sulfones 3 and ent-3

Apart from asymmetric synthesis, the most frequently used methodology to prepare methylated synthons is the modification of a substrate derived from the "chiral pool" such as (+) citronellol (8), or (+)-pulegone which allows an access to enantiomerically pure (+)-citronellic acid (4,9). However, their use is restricted to one enantiomer only. Other chiral synthons of microbiological origin such as R or S-methyl 3-hydroxy-2-methyl propionates (10) are now commercially available.

We desired to develop an approach which would allow to prepare both optically pure enantiomers 3 without the necessity of changing the reactional scheme. Two methods were investigated: one based on the substitution of a β-hydroxy ester derived tosylate, and the second based on a Claisen transposition.

Ethyl β-hydroxy butanoates **8a** or **ent-8a** may be prepared in high enantiomerical purity in both R and S forms. The R compound is obtained by depolymerisation of a polyhydroxybutyrate biopolymer (11a) while the S com-



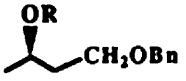
8 a R = H
b R = Ts

9

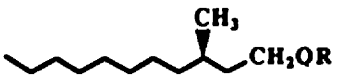
pound is prepared by baker's yeast reduction of ethyl β-keto butanoate (11b).

The direct substitution of the tosylate **8b** offers an interesting route to the β-methyl ester **9**. However, this reaction is known to give a high amount of elimination product (12). Indeed the reaction of **8b** with magnesium dioctylcuprate at -50°C afforded the ester **9** in 25 % yield.

As the ester group probably favours this unwanted elimination reaction, we then investigated the substitution reaction of the tosylate **10b** derived from the monoprotected diol **10a**.



10 a R = H
b R = Ts



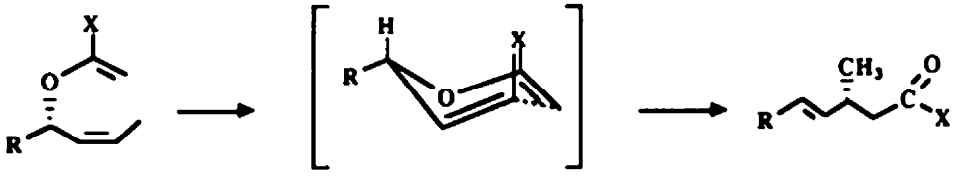
11 a R = H
b R = Bn

This compound has been previously used to synthesize S-(-)-citronellol by substitution with lithium homocuprates (13) ; more recently, it was also successfully reacted with magnesium dioctylcuprate (eight days at -25°C) (14). We were unable to repeat this latter reaction ; in contrast, the reaction of lithium diooctylcuprate with **10b** at -50°C afforded the protected alcohol **11b** in 73 % yield.

The optical purity of **11b** was determined after reductive removal of the benzyl protection and oxidation into 3-methyl undecanoic acid. This acid was converted into the corresponding (R)-(+)-1-(1-naphthyl)-ethylamide and analyzed by HPLC. The optical purity was checked to be 71 %. The ee of the starting material being > 99 %, this value was not in agreement with previous works which reported a nearly complete inversion of configuration with lithium cuprates (12,13).

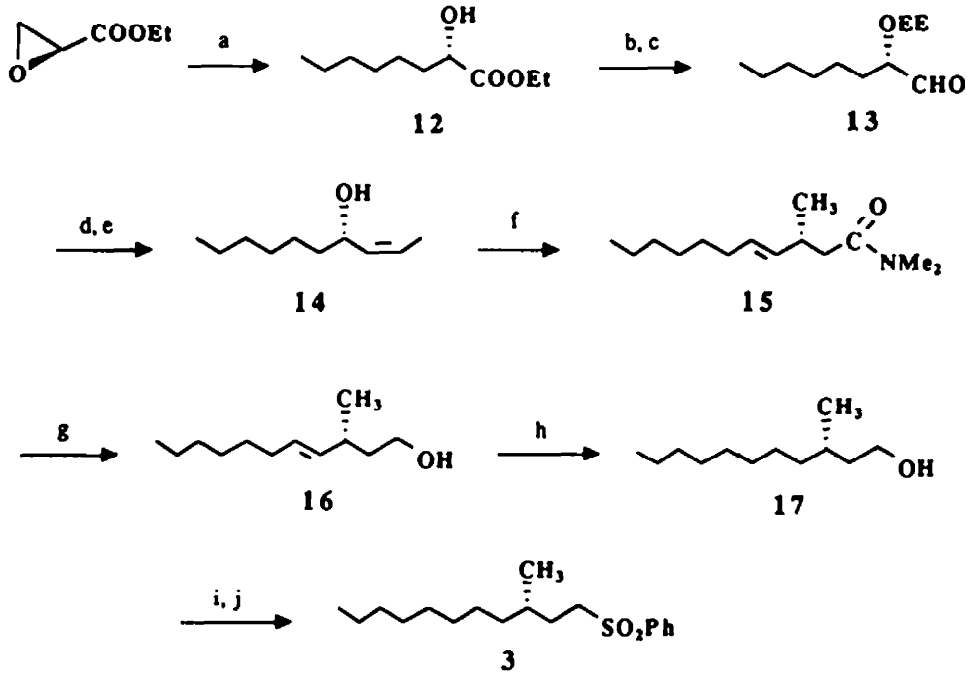
This result led us to investigate an alternative method using a Claisen rearrangement. One of the most powerful methods developed during the recent decades for creating a new asymmetric center in a predictable configuration involves the use of sigmatropic rearrangements like Claisen rearrangement or its variations (15). Due to the strong preference for a chair transition state, it is possible to transfer the chirality of an allylic alcohol to a chiral center by creating a new carbon-carbon bond.

However, the efficiency of such a procedure depends on the enantiomerical purity of the starting compound and on the stereochemical purity of the double bond in the allylic system.



We have previously developed a synthesis of α-hydroxy esters from optically active glycidic esters derived from serine (16). These esters could be transformed into protected aldehydes without racemisation in nearly quantitative yields. We applied this sequence to the preparation of the allylic alcohols required for the Claisen transposition (scheme II).After protection as 1-ethoxyethyl ether, the ester **12** was reduced into aldehyde **13** and reacted with a phosphorus ylide. After acidic hydrolysis, the *cis* alcohol **14** was obtained from **12** in 60 % yield (Z/E : 96/4). A chromatography on a silver nitrate coated silica gel column gave a pure (Z) compound **14** (ee > 99 %, measured by chiral gas chromatography) which was submitted to a Claisen rearrangement. The best results were obtained with the amide acetal Eschenmoser variation which afforded the rearranged amide **15** in 90 % yield. The enantiomeric excess of this amide was 96 % as measured by HPLC after hydrolysis and transformation into naphthylethylamide as reported previously. The amide **15** was then reduced with retention of the initial optical purity into the corresponding alcohol **16** using superhydride (yield: 91 %) (17). Several methods were tried to obtain optically pure alcohols **17** ; reduction with lithium aluminium hydride in the presence of cobalt chloride, which was claimed to reduce without racemisation (18) was rather inefficient (yield: 80 %; ee: 86 %).

Scheme II



a) $(C_5H_{11})_2CuMgBr$, -60°C ; b) ethylvinylether ; c) DIBAH ; d) $Ph_3P{=}CH\text{-}CH_3$; e) H_3O^+ ; f) $CH_3\text{-}C(OMe)NMe_2$, Δ ; g) $LiBHEt_3$; h) Reduction ; i) Ph_2S_2, nBu_3P ; j) *m*-CPBA.

It is known that catalytic hydrogenation of α–methyl substituted unsaturated compounds leads to a certain amount of racemisation (6a). Table I shows that the hydrogenation of **16** in various conditions always results in some racemisation of the methyl group. This problem could be circumvented through the use of diimide in ethanol as reductant which gives the desired alcohol **17** without any loss in optical purity. The enantiomeric alcohols **17** or **11a** were then submitted to the same sequence : reaction with diphenyldisulfide in the presence of tri *n*-butyl phosphine (20) to give a sulfide which was oxidized into the sulfones **3** or **ent-3** with *m*-chloroperbenzoic acid.

Table 1. Reduction of alcohol **16**.

Reactif	Solvent	Rdt (%)	Racemisation rate (%)*
$LiAlH_4/CoCl_2$	THF	80	6
NH=NH	EtOH	80	0
H_2-Pd/C 10 %	EtOH	80	3
H_2-PtO_2	AcOEt	90	19
H_2-$(Ph_3P)_3RhCl$	Benzene	0	-
H_2-Rh/alumina 5 %	EtOH	80	8.5

* Racemisation rate: $\left(1 - \frac{\text{ee for 17}}{\text{ee for 16}}\right) \times 100$

Synthesis of *syn* and *anti* ethyl 2-methyl-3-hydroxy butanoates 6 and 7

2-Methyl-3-hydroxy esters are important building blocks in organic synthesis. Theoretically *syn* compounds could be obtained by a diastereoselective aldolisation (21). However, this method was not, until now, applied to small molecules such as 2-methyl-3-hydroxybutanoic esters. *Anti* compounds may be prepared by α–alkylation of β–hydroxyesters (22), a method which is dependent on the availability of these β–hydroxyesters in optically pure form and which suffers in some cases from poor diastereoselectivity.

Because of their easy enolization, the microbiological reduction of α–substituted β–ketoesters could offer an attractive high yield alternative route to optically active diastereoisomers. However, its use for the preparation of 2-methyl compounds is generally of poor synthetic value, most of the reductions being achieved with baker's yeast to give a mixture of *syn* and *anti* isomers of variable enantiomeric purity, which are generally difficult to separate.

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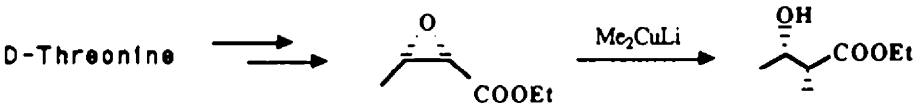
We found that by using the mould *Geotrichum candidum* in particularly defined conditions, it was possible to obtain the *anti* isomer in nearly pure form with > 98 % ee (23). The chemical yield was very satisfactory (70 %), and this method which may be used on an extended scale allows very simple access to the *anti* ester 7. Although the use of other microorganisms has been shown to produce the *syn* isomer 6, but only as a major product of the reaction (23), this compound was not optically pure enough for a synthetic use.

To prepare this compound, we thus utilized the regiospecific opening of the glycidic ester derived from threonine that we have recently published (24).



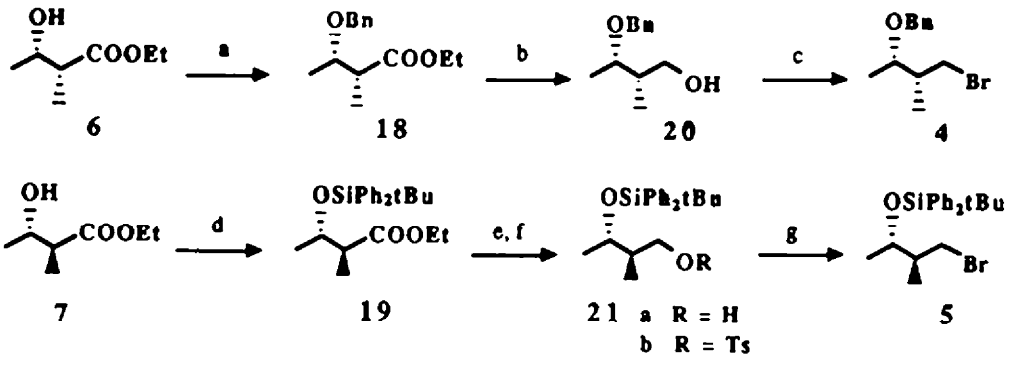
6

Synthesis of (2S,3S,7S) and (2S,3R,7R)-pheromones.

With these four synthons in our hands, we completed the pheromone synthesis by the following way (Scheme III and IV) : the esters 6 and 7 were protected as benzyl ether **18** or *t*-butyldiphenylsilylether **19** respectively . The benzyl ether **18** was prepared by reaction with benzyl-2,2,2-trichloroacetimidate (85 % yield) (25). After reduction and tosylation, the alcohols **20** and **21a** were transformed into bromides **4** and **5** and condensed with the sulfones **3** and **ent-3**. These condensations were difficult enough to realize; due to the low stability of the sulfone carbanion at room temperature, it was necessary to use more than two equivalents of base, and the best results were obtained by inverse addition of lithium diisopropylamide on the mixture of halide and sulfone in the presence of HMPT at -60°C. A mixture of stereoisomers was obtained (75 % yield) from which it was possible to separate by column chromatography the main diastereomers (48/48/2/2), either (2S,3S,5RS,7S)-**22** or (2S,3R,5RS,7R)-**23** (96/4). Reductive elimination of the phenylsulfonyl groups was performed with sodium amalgam in methanol (26) to afford the protected 3,7-dimethyl pentadecan-2-ol **24a** or **25a** . Debenzylation or desilylation were effected in the usual conditions to give (2S,3S,7S) or (2S,3R,7R)- alcohols **24b** or **25b** which were acetylated into the desired pheromones **1** and **2**.

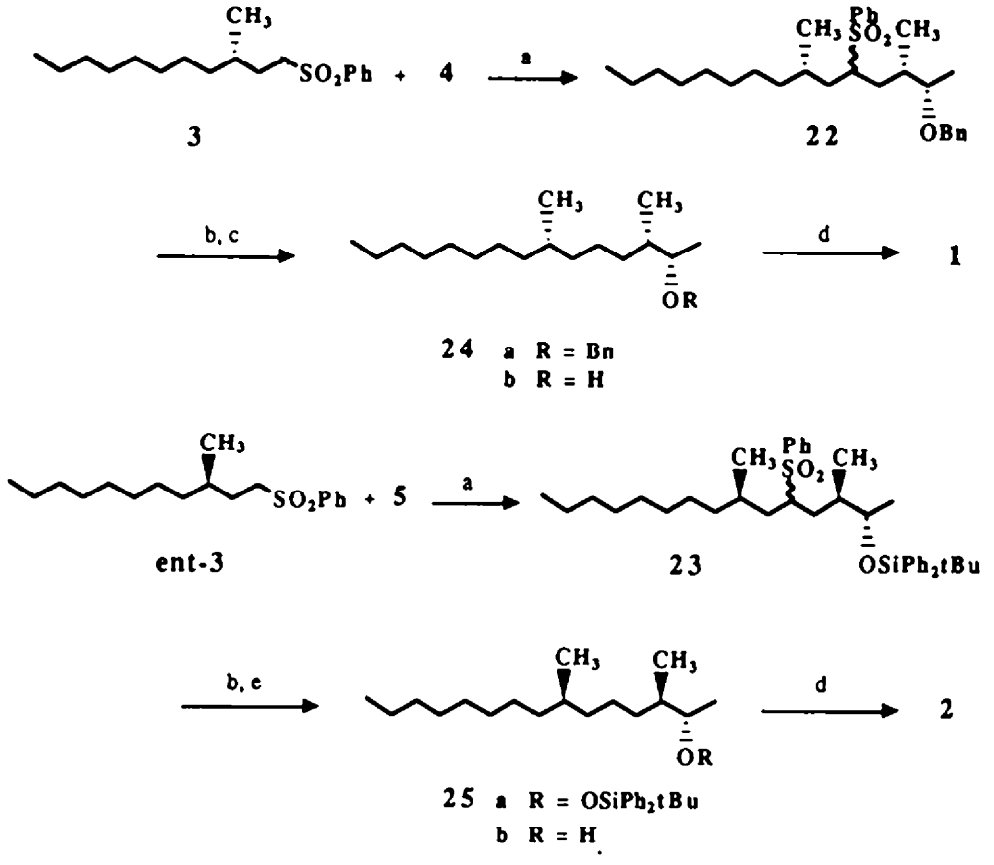
The optical rotations ($[\alpha]_D^{20}$ = -6.3° (c=2.03, hexane) for **1** and $[\alpha]_D^{20}$ = +6.3° (c=4.1, hexane) for **2**) were in good agreement with literature values (3,4b). Furthermore, capillary VPC analysis indicated that each material contained > 99 % of the desired isomer.

Scheme III



a) $Cl_3CC(=NH)OCH_2Ph$, CF_3SO_3H ; b) Reduction ; c) Ph_3P, DEAD, LiBr ; d) $ClSiPh_2tBu$;
e) DIBAH ; f) TsCl; g) LiBr

Scheme IV



a) LDA,HMPT ; b) Hg/Na ; c) H_2, Pd/C ; d) Ac_2O, Pyr. ; e) HF.

Experimental

Products were purified by distillation or by medium pressure liquid chromatography on a Jobin-Yvon Modulprep (Kieselgel 60H Merck) or by flash chromatography (Kieselgel 60 Merck: 230-400 Mesh ASTM), (solvent : cyclohexane/ ethyl acetate) and analyzed by gas chromatography (10% SE30, 3m column or 10% SE52, 3m column) or by thin layer chromatography (silicagel 60F 254). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^{1}H-NMR spectra were recorded on a Bruker WP 80 or on a Bruker AM at 400.13 MHz for ^{1}H and 100.56 MHz for ^{13}C. Deuterochloroform was used as solvent with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 599. Mass spectra were recorded on a Nermag R 10-10 (fitted with a VPC-mass coupling; column: CP Sil 5.40m).

(R)-(-)-Ethyl-3-tosyloxybutanoate 8b.

p.Toluenesulfonylchloride (4.28g, 22.5mmol) was added to a stirred and ice-cooled solution of (R)-(-)-ethyl-3-hydroxybutanoate **8a** (2g, 15mmol) in dry pyridine (2.5ml) and dry CH_2Cl_2 (4ml). After 12 h at 0°C, the mixture was hydrolyzed with water, extracted with ether and washed with a saturated solution of $NaHCO_3$. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. After purification (cyclohexane/ EtOAc: 8/2) 4.13g of pure **8b** (yield: 95%) were obtained.

$[\alpha]D^{20}$=-0.6° (c= 7.31; CH_2Cl_2). ^{1}H NMR (250MHz): δ 1.22 (t, 3H, J= 7.0 Hz) $COOCH_2$-CH_3 ; 1.36 (d, 3H, J= 6.5 Hz) CH_3-CH(OTs) ; 2.48 (s, 3H) CH_3-C_6H_5 ; 2.54 (q, 1H, J=7.0 Hz and J'=16.0 Hz) CH_2COOEt ; 2.76 (q, 1H, J=7.0 Hz and J'=16.0 Hz) CH_2-COOEt ; 4.10 (m, 2H) COO-CH_2-CH_3; 5.03 (m, 1H) CH(OTs) ; 7.42 and 7.88 (2d, 4H,) SO_2-C_6H_4-CH_3.

(R)-Ethyl-3-methylundecanoate 9.

To a slurry of CuBr-Me_2S (1.07g; 5.7mmol) in THF(13ml) and ether (3ml) was added octyl magnesium bromide (10.5 mmol, 1M ether solution) at -65°C. After 45min at -35°C, tosylate **8b** (1g, 3.5mmol) diluted with THF (9ml) and ether (9ml) was added to the solution at -78°C. The reaction was quickly warmed up to -40°C. After 2h, the reaction mixture was hydrolyzed with a solution of NH_4Cl/ conc.NH_4OH (1/1:v/v;12ml). After evaporation and extraction with ether; the organic layer was dried over $MgSO_4$ and reduced *in vacuo* to obtain the crude product. After chromatography (cyclohexane/CH_2Cl_2: 3/1) 0.2g of 9 was obtained (Yield: 25%).

^{1}H NMR (250MHz): δ 0.90 (m, 9H) 3 CH_3 ; 1.28 (s, 14H) 7 CH_2 ; 2.10 (q, 2H, J=8.0 Hz and J'=14.5 Hz) $CH(CH_3)$ and CH_2-CO ; 2.32 (q, 1H, J=6.0 Hz and J'=14.5 Hz) CH_2CO ; 4.16 (q, 2H, J=7.0 Hz and J'=14.5 Hz) O-CH_2. Mass spectrum m/z: 247 (m+NH_4^+) ; 246 (m+NH_3) ; 230 (m+1) ; 229 (m).

(R)-(+)-3-Methylundecan-1-ol 11a from (R)-3-hydroxybutanoate 8a.

(R)-(+)-1,3-Butanediol 1-benzylether 10a.

Pyridinium *p*-toluenesulfonate (950mg, 3.79 mmol) was added to a solution of ester **8a** (5g, 38mmol) and ethyl vinyl ether (7.25ml, 75mmol) in CH_2Cl_2 (150ml) at 0°C. After 1 h at room temperature, the solution was hydrolyzed with a saturated solution of $NaHCO_3$ and extracted with ether; 7.61g of crude ethyl-3-(1-ethoxyethoxy) butanoate were obtained (yield: 99%). The crude ester (37mmol) dissolved in ether was added to $LiAlH_4$ (1.44g; 38mmol) in ether at -78°C. After 2 h, the reaction was hydrolyzed with a saturated solution of KH_2PO_4 (14ml). After filtration, drying over $MgSO_4$ and reducing *in vacuo*, the solution was chromatographed (hexane/ EtOAc: 6/4) to give 5.2g of 3-(1-ethoxyethoxy) butanol (yield: 85% from ester **8a**) .

^{1}H NMR (250 MHz): δ 1.24 (m,6H) CH_3-CH(OEE) and O-CH_2-CH_3; 1.34 (d, 3H, J=7.0 Hz) O-CH(CH_3)-OEt ; 1.66 (m, 2H) CH(OEE)-CH_2-CH_2OH ; 2.22 (s, 1H) OH ; 3.74 (q, 4H, J=7.0 Hz and J'=14.0 Hz) CH_2OH and O-CH_2-CH_3 ; 4.12 (dq, 1H, J=1.0 Hz, J'=5.0 Hz and J"=10.0 Hz) CH(OEE) ; 4.75 (q, 1H, J=5.0 Hz and J'= 10.0 Hz) O-CH(CH_3)-OEt. Mass spectrum (m/z):162 (m).

The crude product (5.1g, 31mmol) diluted in THF (20ml) was added slowly into a solution of NaH (50% in oil, 2.4g) in THF (30ml). After 1.5 h at reflux, benzyl bromide (8g, 47mmol) was added and the reaction was refluxed for 3 h. The solution was cooled to room temperature and was hydrolyzed with water. After extraction with ether, the organic layer was washed with a saturated solution of $NaHCO_3$ and with a saturated solution of NaCl, then dried over $MgSO_4$ and reduced *in vacuo*. The crude product was chromatographed (cyclohexane/ EtOAc: 97/3) to give 6.28g of 3-(1-ethoxyethoxy)-butanol benzyl ether (yield: 80%).

^{1}H NMR (80 MHz): δ 1.17 (m, 9H) 3 CH_3; 1.75 (m, 2H) CH(OEE)-CH_2 ; 3.47 (m, 4H) CH_2-OBn and O-CH_2-CH_3 ; 3.80 (m, 1H) CH(OEE) ; 4.42 (s, 2H) O-CH_2-C_6H_5 ; 4.62 (q, 1H, J=5.0 Hz and J'=10.0 Hz) O-CH(CH_3)-O ; 7.20 (s, 5H) C_6H_5.

The crude product (6g, 24mmol) was deprotected with 1N HCl (15ml) in THF (40ml). After 1 h, the solution was concentrated *in vacuo* and after extraction with ether, washing with a saturated solution of $NaHCO_3$ and concentrating *in vacuo*; the crude product (4.22g) was chromatographed (cyclohexane/ EtOAc: 7/3) to give 4g of **10a** (quantitative yield).

$[\alpha]D^{20}$=+2.6° (c= 5.39; $CHCl_3$); Lit:$[\alpha]D^{24}$=-2.12° (c= 1.13; $CHCl_3$)(27). ^{1}H NMR (250 MHz): δ 1.19 (d, 3H, J= 6.5 Hz) CH_3-CHOH ; 1.74 (m, 2H) CHOH-CH_2 ; 3.05 (s,1H) OH ; 3.70 (m, 2H) CH_2OBn ; 4.03 (m, 1H) CHOH ; 4.54 (s, 2H) O-CH_2-C_6H_5 ; 7.40 (s, 5H) C_6H_5. ^{13}C NMR : δ 23.21; 38.01; 67.07; 68.81; 73.07; 127.49; 127.56;

128.28; 137.82. Mass Spectrum m/z:198 ($m+NH_4^+$) and 181 (m+1). Anal. cald. for $C_{11}H_{16}O_2$ C: 73.39, H: 8.96; found C: 72.80, H: 9.35.

(R)-(-)-3-Tosyloxybutan-1-ol benzylether 10b .

p. Toluenesulfonylchloride (6.4g, 33.6mmol) was added to a stirred and iced-cooled solution of **10a** (4g, 22mmol) in dry pyridine (3.6ml) and dry CH_2Cl_2 (5ml). After 12 h at 0°C, the mixture was hydrolyzed with water, extracted with ether and washed with a saturated solution of $NaHCO_3$. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. After purification (cyclohexane/ EtOAc: 85/15) 6.63g of pure **10b** (yield: 90%) were obtained. $[\alpha]D^{20}$=-18.1° (c= 5.56; $CHCl_3$); Lit: $[\alpha]D^{23}$=+15.0° (c= 1.11; $CHCl_3$) (14). ^1H NMR (250 MHz): δ 1.30 (d, 3H, J=6.0 Hz) CH_3-OTs ;1.86 (m, 2H) CHOTs-CH_2 ; 2.42 (s, 3H) CH_3-C_6H_5 ; 3.42 (m, 2H) CH_2-OBn ; 4.34 (s, 2H) O-CH_2-C_6H_5 ; 4.86 (m, 1H) CHOTs ; 7.34 (m, 7H) O-CH_2-C_6H_5 and SO_2-C_6H_5-CH_3 ; 7.86 (d, 2H, J=8.0 Hz) SO_2-C_6H_5-CH_3. Mass spectrum m/z:352 ($m+NH_4^+$); 335 (m+1). Anal.cald for $C_{18}H_{22}O_4S$ C: 64.72, H: 6.64; found C: 64.79, H: 6.73.

(R)-(+)-3-Methylundecan-1-ol benzylether 11b.

To a slurry of CuI (3.88g, 20mmol) in ether was added octyl lithium (40mmol, 0.49M ether solution) at -60°C; the solution was warmed up to -30°C in 45min and stirred for 1 h. Tosylate **10b** (3.4g, 10mmol) in ether (40ml) was added at -73°C and the reaction warmed up quickly at - 45°C. After 2 h, the reaction was hydrolyzed with a solution of NH_4Cl/ conc. NH_4OH (1/1: v/v; 80ml). After extraction with ether and washing with NH_4Cl, ether solution was dried over $MgSO_4$ and reduced *in vacuo*. After chromatography 2g of product **11b** were obtained (yield : 73%). $[\alpha]D^{20}$=+2.1° (c= 6.08; $CHCl_3$); Lit: $[\alpha]D^{24}$=-2.62° (c= 3.92; $CHCl_3$) (14). ^1H NMR (80 MHz): δ 0.85 (overlapped s+d, 6H) $2CH_3$; 1.25 (s, 14H) $7CH_2$; 1.52 (m, 3H) CH_2-CH_2OBn and $CH(CH_3)$; 3.45 (t, 2H, J=6.0 Hz) CH_2OBn ; 4.44 (s, 2H) O-CH_2-C_6H_5 ; 7.22 (s, 5H) C_6H_5. Anal. Cald. for $C_{19}H_{32}O$ C:82.68, H:11.69; found C:82.34, H:11.99.

(R)-(+)-3-Methylundecan-1-ol 11a.

Compound **11b** (3g, 11mmol) was hydrogenated on 10% Pd/C (664mg) in EtOH (45ml) for one day. After filtration on celite and evaporation of EtOH; the crude product was dried over $MgSO_4$ and concentrated *in vacuo*. After chromatography, 2g of **11a** (quantative yield) were obtained.
$[\alpha]D^{20}$=+4.5° (c= 5.03; hexane); Lit: $[\alpha]D^{20}$=+4.80° (c= 5.10; hexane) (4c). ^1H NMR (80MHz): δ 0.88 (overlapped t+d, 6H, J=4.0 Hz) $2CH_3$; 1.26 (s,16H) $7CH_2$ and CH_2-CH_2OH ;1.40 (s, 1H) OH ; 3.62 (t, 2H, J=6.0 Hz) CH_2OH. ^{13}C NMR : δ 14.05 ; 19.57 ; 22.63 ; 26.96 ; 29.31 ; 29.46 ; 29.69 ; 29.91 ; 31.88 ; 37.12 ; 39.89 ; 81.10. I.R (neat): ν = 3 340 cm^{-1} (OH). Mass spectrum m/z: 204 ($m+NH_4^+$) and 187 (m+1). Anal. cald. for $C_{12}H_{26}O$ C:77.35, H:14.07 ; found C:77.42, H:14.04.

Determination of optical purity of 11a and 17.

Alcohol **11a** (10mg, 5.10^{-2}mmol) was oxidized with PDC (80mg, 0.21mmol) in DMF (160 µl) for 12 h. 3N HCl (1.6ml) was added and after 20 min, the solution was extracted with a solution of ether/ petroleum ether (1/1: v/v). After treatment with charcoal, the solution was filtered on celite, then evaporated and refluxed with oxalyl chloride (14µl) in benzene (2ml) for 3 h. After evaporating *in vacuo*, the acid chloride was reacted with (R)-(+) -1-naphthylethylamine (17 µl) (> 99.5% optical purity; Janssen Chimica) to give the amide. Diastereomers were separated by HPLC (Zorbax Sil column: 4.6mm x 250mm): 2,2,4-dimethyl pentane- EtOAc: 85/15, flow rate, 1.5ml/min, Rt=8.2min (amide derived from (+) **11a**), 10.8min (amide derived from (-) **17**). Measured optical purity: 71% for (+) **11a** , 96% for (-) **17**.

(S)-(-)-3-Methylundecan-1-ol 17 from glycidic ester.

(S)-(-)-(Z)-2-Decen-4-ol 14.

α-Hydroxyester **12** (16) was protected as previously described: 8.2g of protected compound (quantitative yield) were obtained from **12** (6g, 32mmol).

^1H NMR (80 MHz): δ 0.85 (s, 3H) CH_3-$(CH_2)5$; 1.15 (d, 3H, J=0.1 Hz) O-CH(CH_3)-O ; 1.30 (m; 14H) CH_3-$(CH_2)_4$-CH_2 and 2(O-CH_2-CH_3) ; 1.65 (s, 2H) CH_2-CH(OEE) ; 3.52 (m, 2H) O-CH_2-CH_3 ; 4.15 (m, 3H) O-CH_2-CH_3 and CH(OEE) ; 4.67 (q, 1H, J=4.0 Hz and J'=10.0 Hz) O-CH(CH_3)-O. I.R (neat): ν =3 540 cm^{-1} (OH).

DIBAH (33ml, 1M solution in hexane) was added dropwise at -78°C to a solution of ester (8.2g, 31mmol) in pentane (300ml). After 4 h, the reaction mixture was hydrolyzed with a saturated solution of NH_4Cl. After stirring for 1 h, the solution was filtered, dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde was diluted in ether (80ml) and added at -78°C on a THF solution of the ylide prepared from ethyl triphenylphosphonium bromide (17.55g, 47mmol) and *n*BuLi (21ml, 2.3M solution in hexane) at low temperature. The reaction was warmed up slowly to room temperature and after 12 h, solvents were evaporated. The residue was diluted with ether, hydrolyzed with a saturated solution of NH_4Cl, and extracted with ether. After drying over $MgSO_4$ and concentrating *in vacuo*, the product was chromatographed on a small Florisil column (to eliminate the triphenylphosphine oxide). Then, it was treated with a 1N solution of HCl (50ml) in THF (200ml). After 2 h, the solvent was evaporated *in vacuo*; and the residue was diluted with ether. After extraction with ether and neutralizing with a saturated solution of $NaHCO_3$, the crude compound was analyzed on a capillary VPC to obtain a 96/4 Z/E ratio. The product was purified by chromatography on 10% $AgNO_3$ containing silica gel (cyclohexane/ EtOAc: 8/2). From ethyl-2-(1-ethoxyethoxy) octanoate (8.2g, 31.5 mmol), 2.5g of alcohol were obtained (yield: 60%; Z/E> 99/1). The enantiomeric excess of the isopropyl carbamate measured by chiral VPC (XE60,S-valine-α-phenylethylamide: Chrompack: 50mx0.23mm with He carrier gas) (28) was better than 99%.
$[\alpha]D^{20}$=-27.1° (c: 0.15; CH_2Cl_2). ^1H NMR (250 MHz): δ 0.90 (s, 3H) CH_3-$(CH_2)5$; 1.30 (s, 8H) CH_3-$(CH_2)_4$-CH_2 ; 1.52 (m, 2H) CH_2-CHOH ; 1.66 (s, 1H) OH ; 1.72 (q, 3H, J=2.0 Hz and J'=6.0 Hz) CH=CH-CH_3 ; 4.06 (m, 1H) CHOH ; 5.53 (m, 1H) CH=CH-CH_3 ; 5.71 (m, 1H) CH=CH-CH_3. ^{13}C NMR : δ 13.92 ; 17.48 ; 22.54 ; 25.35 ; 29.20 ; 31.78 ; 37.39 ; 73.01 ; 126.30 ; 134.59.

(S)-(-)-3-Methyl-4-undecenoic acid N,N-Dimethylamide 15.

The alcohol **14** (2.5g, 16mmol) was stirred with N,N-dimethyl acetamide dimethylacetal (4.7ml, 32mmol) in xylene at 150°C for 36 h. After evaporating the solvent, the residue was chromatographed (cyclohexane/ EtOAc: 6/4) to give 3.24g of amide **15** (yield: 90%).

$[\alpha]_D^{25}$=-14.4° (c= 4.63; CH_2Cl_2). ^1H NMR (80 MHz): δ 0.85 (s, 3H) CH_3-$(CH_2)_5$; 1.02 (d, 3H, J=6.0 Hz) $CH(CH_3)$-CH_2; 1.27 (s, 8H) CH_3-$(CH_2)_4$-CH_2 ; 1.97 (m, 2H) CH_2 ; 2.22 (m, 2H) CH_2-$CON(CH_3)_2$; 2.65 (m 1H) $CH(CH_3)$-CH_2 ; 2.90 (s, 3H) $N(CH_3)_2$; 2.96 (s, 3H) $N(CH_3)_2$; 5.32 (m, 2H) CH=CH. ^{13}C NMR : δ 13.97 ; 20.33 ; 22.51 ; 28.68 ; 31.62 ; 32.42 ; 33.52 ; 37.27 ; 37.44 ; 40.47 ; 129.01 ; 134.56 ; 172.12. I.R (neat): ν = 1 650 cm^{-1} (C=O amide). Mass Spectrum m/z: 226 (m+1). Anal. cald. for $C_{14}H_{27}NO$ C: 74.61, H: 12.08, N: 6.22; found C: 73.93, H: 11.93, N: 5.97.

(S)-(-)-3-Methyl-4-undecen-1-ol 16.

Superhydride (LiBHEt3, 29ml, 1M solution in hexane) was added at -78°C to amide **15** (3.24g, 14.4mmol) diluted in THF (130ml). After 5 h, the reaction was hydrolyzed with water (29ml) and solvents were evaporated *in vacuo*. After extraction with ether and drying over $MgSO_4$, the product was purified by chromatography (cyclohexane/ EtOAc: 8/2) to give 2.49g of **16** (yield: 90%). The optical purity (96%) was determined as described for **17**.

$[\alpha]_D^{20}$=-30.4° (c= 5.99; CH_2Cl_2). ^1H NMR (250 MHz): δ 0.90 (s, 3H) CH_3-$(CH_2)_5$; 1.00 (d, 3H, J=7.0 Hz) $CH(CH_3)$; 1.30 (s, 8H) CH_3-$(CH_2)_4$-CH_2 ; 1.56 (m, 2H) CH_2-CH_2OH ; 2.00 (q, 2H, J=6.0 Hz and J'=14.0 Hz) CH_3-$(CH_2)_4$-CH_2 ; 2.20 (s, 1H) OH ; 2.27 (m, 1H) $CH(CH_3)$; 3.69 (t, 2H, J=6.0 Hz) CH_2OH ; 5.33 (q, 1H, J=7.0 Hz and J'=15.0 Hz) CH=CH-$CH(CH_3)$; 5.47 (q, 1H, J=6.0 Hz and J'=15.0 Hz) CH_2-CH=CH. ^{13}C NMR : δ 14.03 ; 21.15 ; 22.57 ; 28.78 ; 29.50 ; 31.66 ; 32.46 ; 33.88 ; 39.73 ; 61.27; 129.36 ; 135.59. I.R (neat): ν = 3 270 cm^{-1} (OH) and 970 cm^{-1} (CH=CH trans). Mass Spectrum m/z: 202 (m+NH_4^+).

(S)-(-)-3-Methylundecan-2-ol 17.

To a suspension of dry $CoCl_2$ (3.52, 27mmol) in dry THF at -78°C was added $LiAlH_4$ (1g, 27mmol). Alcohol **16** (2.49g, 13.5mmol) was then added and the mixture was warmed up slowly to room temperature. After 6 h, the solution was hydrolyzed with 1N HCl, extracted with ether, dried over $MgSO_4$ and evaporated *in vacuo*. The same procedure was effected twice again. The product was chromatographed (cyclohexane/ EtOAc: 9/1) to give 2g of **17** (yield: 80%). Alternatively, **16** was reduced by H_2 at room temperature with a catalyst (10% Pd/C, PtO_2, Rh on alumina 5% or Wilkinson's catalyst). The solvents used were respectively: EtOH, EtOAc, EtOH and benzene. The reaction was filtered on celite and the solvent evaporated *in vacuo*; the product was then chromatographed.

For reduction with diimide, acetic acid (2ml, 35mmol) was added to a solution of **16** (2.49g, 13.5mmol) and potassium azodicarboxylate (PADA) (2.73g, 17.6mmol) in EtOH (150ml) at room temperature. After 6 h, an other portion of PADA (2.73g, 17.6mmol) and acetic acid (2ml, 35 mmol) was added. The operation was repeated until the reaction was completed; the mixture was then filtered and EtOH was evaporated *in vacuo*. The residue was hydrolyzed with a saturated solution of NH_4Cl, extracted with ether, dried over $MgSO_4$ and solvent was evaporated *in vacuo*. After chromatography 2g were obtained (yield: 80%). The optical purity was determined as described.

$[\alpha]_D^{20}$=-4.8° (c=3.0; hexane); Lit:$[\alpha]_D^{20}$=+4.8° (c= 5.10, hexane) (4c). ^1H NMR (80 MHz): δ 0.88 (overlapped t + d, 6H) $2CH_3$; 1.26 (s, 16H) $8CH_2$; 1.40 (s, 1H) $CH(CH_3)$; 3.62 (t, 2H, J=6.0 Hz) CH_2OH. ^{13}C NMR : δ 14.05 ; 19.57 ; 22.63 ; 26.92 ; 29.31 ; 29.46 ; 29.62 ; 29.91 ; 31.88 ; 37.12 ; 39.89 ; 81.06. I.R (neat): 3 340 cm^{-1} (OH). Mass spectrum m/z: 204 (m+NH_4^+).

1-Phenylsulfonyl-3-methylundecane.

(S)-(+)-1-Phenylsulfonyl-3-methylundecane 3.

To a solution of alcohol **17** (2g, 11mmol) and diphenyl disulfide (2.8g, 13mmol) in CH_2Cl_2 (70ml) was added tri-*n*-butylphosphine (3.7ml, 14.5mmol) at room temperature, and the mixture was stirred for 12 h. Then the reaction was hydrolyzed with a saturated solution of NH_4Cl. After extraction with ether and washing with a saturated solution of $NaHCO_3$, the crude product was purified by chromatography (hexane) to eliminate the diphenyl disulfide. (S) -1-phenylsulfide-3-methylundecane (3g, 11mmol) was oxidized with *m*-CPBA (3.5g, 27mmol) in CH_2Cl_2 (100ml) at -15°C for 4 h. After hydrolysis with a saturated solution of $KHCO_3$ and extraction with ether, the product was purified by chromatography (cyclohexane/ EtOAc: 9/1) to give 3.2g of sulfone **3** (yield: 96%).

$[\alpha]_D^{25}$=+4.5° (c= 5.42; CH_2Cl_2). ^1H NMR (250 MHz): δ 0.88 (s, 3H) CH_3-$(CH_2)_7$; 0.90 (d, 3H, J=6.0 Hz) $CH(CH_3)$; 1.24 (s, 14H) CH_3-$(CH_2)_7$; 1.50 (m, 2H) CH_2-CH_2-SO_2-C_6H_5 ; 1.72 (m, 1H) $CH(CH_3)$; 3.10 (m, 2H) CH_2-SO_2-C_6H_5 ; 7.61 (t, 2H, J=7.0 Hz) C_6H_5 ; 7.68 (d, 1H, J=7.0 Hz) C_6H_5 ; 7.95 (d, 2H, J=7.0 Hz) C_6H_5. ^{13}C NMR : δ 14.06 ; 19.13 ; 22.62 ; 26.70 ; 29.10 ; 29.23 ; 29.50 ; 29.72 ; 31.82 ; 31.84 ; 36.29 ; 54.40 ; 128.00 ; 133.55 ; 139.21. Anal. cald. for $C_{18}H_{30}O_2S$ C: 69.74, H: 9.75; found C: 69.55, H: 9.62.

(R)-(-)-1-Phenylsulfonyl-3-methylundecane ent-3.

Prepared from **11a** as described for **3**.

$[\alpha]_D^{20}$=-5.1° (c= 6.10; CH_2Cl_2). ^1H NMR (250MHz): identical to (S)-(+) **3**. ^{13}C NMR: identical to (S)-(+) **3**.

(2R,3S)-(+)-Ethyl-2-methyl-3-hydroxybutanoate benzylether 18.

Trifluoromethane sulfonic acid (205 µl, 2.30mmol) was added slowly to a solution containing (2R,3S) -ethyl-3-hydroxy-2-methyl butanoate **6** (2g, 13.60 mmol) (24) and benzyl-2,2,2-trichloroacetimidate (3.10ml, 16.2mmol) in cyclohexane (20ml) and CH_2Cl_2 (10ml). The reaction is slightly exothermic and the temperature raised up to 35°c. After 3 h, the reaction was filtered on celite and washed with a saturated solution of $NaHCO_3$ (50ml); water (50ml) and with a saturated solution of NaCl (20ml). After medium pressure chromatography (cyclohexane/ EtOAc: 95/5) , 2.44g of compound **18** were obtained (yield: 94%).

$[\alpha]_D^{22}$=+16.2° (c= 2.90, MeOH). ^1H NMR (80 MHz): δ 1.20 (overlapped t+2d, 9H) $3CH_3$; 2.50 (t, 1H, J=6.0 Hz)

$CH(CH_3)$-CO ; 3.72 (m, 1H) CHOBn ; 4.05 (q, 2H, J=6.0 Hz) O-CH_2-CH_3 ; 4.42 (d, 2H, J=2.0 Hz) O-CH_2-C_6H_5 ; 7.42 (s, 5H) O-C_6H_5 .

(2S,3S)-(+)-2-Methyl-1,3-butanediol 3-benzylether 20.

DIBAH (23ml of a 1M solution in hexane) was added at -78°c to a solution of ester **18** (2.44g, 10mmol). After 1 h, the solution was warmed up to 0°C for 5h. It was hydrolyzed with NH_4Cl (1.5ml) and HCl 1N (3ml) for 1 h, the solution was filtered, dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by chromatograghy (cyclohexane/ EtOAc: 75/25) to give 1.2g of **20** (yield: 60%).

Reduction of ester **18** with $LiAlH_4$ in ether at -78°C led to **20** with identical yield.

$[\alpha]D^{22}$=+40.5° (c= 3.0, MeOH). ^1H NMR (250MHz): δ 0.86 (d, 3H, J=7.0 Hz) $CH(CH_3)$-CH_2OH ; 1.18 (d, 3H, J=6.0 Hz) CH_3-CHOBn ; 2.00 (m, 1H) $CH(CH_3)$-CH_2OH ; 2.37 (s, 1H) OH ; 3.56 (q, 1H, J=4.5 Hz and J'=11.0 Hz) CH_2OH ; 3.71 (m, 2H) CH_2OH and CHOBn ; 4.46 (d, 1H, J=12.0 Hz) O-CH_2-C_6H_5 ; 4.62 (d, 1H, J=12.0 Hz) O-CH_2-C_6H_5 ; 7.36 (s, 5H) C_6H_5.

(2R,3S)-(+)-1-Bromo-2-methylbutan-3-ol benzylether 4.

Diethyl azodicarboxylate (2.6g, 15mmol) was added at 0°C to a solution of triphenylphosphine (3.93g, 15mmol) in anhydrous THF (60ml). After 20mn, LiBr (2.6g, 30mmol) was added to the stirred solution followed by a solution of alcohol **20** (1.17g, 6mmol) in THF (10ml). After 6 h at 0°C, THF was evaporated *in vacuo* and the remaining mixture was hydrolyzed with water. After extraction, the organic layer was dried and evaporated to give after chromatography (cyclohexane/ EtOAc: 98/2) 1.23g of **4** (yield: 80%).

$[\alpha]D^{25}$=+43.3° (c= 4.31; MeOH). ^1H NMR (250 MHz): δ 1.07 (d, 3H, J=7.0 Hz) $CH(CH_3)$-CH_2Br ; 1.18 (d, 3H, J=7.0 Hz) CH_3-CHOBn ; 1.96 (m, 1H) $CH(CH_3)$-CH_2Br ; 3.34 (q, 1H, J=6.0 Hz and J'=10.0 Hz) CH_2Br ; 3.58 (q, 1H, J=6.0 Hz and J'=10.0 Hz) CH_2Br ; 3.70 (m, 1H) CHOBn ; 4.44 (d, 1H, J=12.0 Hz) O-CH_2-C_6H_5 ; 4.61 (d,1H, J=12.0 Hz) O-CH_2-C_6H_5 ; 7.36 (s, 5H) C_6H_5. ^{13}C NMR : δ 13.77 ; 16.33 ; 37.65 ; 41.24 ; 70.84 ; 75.73 ; 127.38 ; 127.47 ; 128.22 ; 128.29 ; 128.88 ; 129.63 ; 138.70. Mass Spectrum m/z: 274 (m+NH_3); 257 (m). Anal. cald. for $C_{12}H_{17}OBr$ C: 56.08, H: 6.67; found C:57.02, H: 6.92.

(2S,3S)-(+)-Ethyl-2-methyl-3-hydroxybutanoate 7.

The cells obtained from a 48 h-grown culture of *Geotrichum candidum* in the following medium: KH_2PO_4 (0.5g), corn steep liquor (5g), $NaNO_3$ (1g), KCl (0.25g), $MgSO_4,7H_2O$ (0.25g), $FeSO_4,7H2O$ (0.01g), glucose (15g) in distilled water (500ml), were filtered, washed, then preincubated in water at 27°C during 24h. The filtered cells were resuspended in 2% NaCl (250ml) and stirred at 27°C during 3 days with ethyl 2-methyl-3-oxobutanoate (3g, 21mmol). The filtrate and the cell cake were extracted with EtOAc. The combined extracts were dried and evaporated to give 2.4g of crude **7** (yield: 80%). b.p: 84°/15torr. This product contained <1.5% of *syn* isomer; ee (mesured by MTPA ester)(29): 97%.

$[\alpha]D^{20}$=+26.8° (c= 4.9; MeOH). ^1H NMR (250 MHz): δ 1.12 (d, 3H, J=6.9 Hz) $CH(CH_3)$-CO ; 1.25 (t, 3H, J=7.0 Hz) CH_2-CH_3 ; 1.70 (d, 3H, J=6.9 Hz) CH_3-CHOH ; 2.45 (q, 1H, J=6.9 Hz and J'=14.0 Hz) $CH(CH_3)$-CO ; 3.85 (q, 1H, J=6.9 Hz and J'=14.0 Hz) CHOH ; 4.05 (q, 2H, J=7 Hz and J'=14.0 Hz) O-CH_2-CH_3. ^{13}C NMR : δ 13.56 ; 13.93 ; 20.32 ; 46.82 ; 60.29 ; 69.05 ; 175.66.

(2S,3S)-(+)-Ethyl-2-methyl-3-hydroxybutanoate *t*-butyldiphenylsilylether 19.

(2S,3S)-Ethyl-3-hydroxy-2-methylbutanoate **7** (2.2g, 15mmol) was stirred at room temperature with *t*-butyldiphenylsilyl chloride (5ml, 18mmol) and imidazole (5.12g, 75mmol) in DMF for 3 days. Then the reaction was warmed for 5 h. After adding water and extraction with ether, the ether solution was washed with 2N HCl, saturated solutions of $NaHCO_3$ and NaCl to give a product which was chromatographed (cyclohexane/ EtOAc: 98/2). 4.74g of compound **19** were obtained (yield: 82%).

$[\alpha]D^{20}$=+20.3° (c= 5.38; CH_2Cl_2). ^1H NMR (250 MHz): δ 1.02 (d,3H, J=6.0 Hz) $CH(CH_3)$; 1.04 (s, 3H) $C(CH_3)_3$; 1.12 (d, 3H, J=6.0 Hz) CH_3-CHOTBDPS ; 1.22 (t, 3H, J=7.0 Hz) O-CH_2-CH_3 ; 2.62 (m, 1H) $CH(CH_3)$; 4.11(q, 2H, J=7.0 Hz and J'=14.0 Hz) O-CH_2-CH_3 ; 4.19 (m, 1H) CHOTBDPS ; 7.45 (m, 6H) $(C_6H_5)_2$; 7.77 (2d, 4H, J=7.0 Hz) $(C_6H_5)_2$. Mass Spectrum m/z: 402 (m+NH_4^+) ; 385 (m+1).

(2R,3S)-(+)-2-Methyl-1,3-butanediol-3 *t*-butyldiphenylsilylether 21a.

At -78°C, ester **19** (4.74g, 12mmol) was reduced with DIBAH (25ml, 1M solution in hexane) in ether (220ml). After 1 h, the reaction was warmed up to -55°C for 3 h. After 2 h, the reaction was hydrolyzed with 0.1N HCl. After extraction with ether and drying over $MgSO_4$, the product was chromatographed (cyclohexane/ EtOAc: 85/15) to give 3.17g of alcohol **21a** (yield: 75%).

$[\alpha]D^{20}$=+10.0° (c= 5.08; CH_2Cl_2). ^1H NMR (250 MHz): δ 0.87 (d, 3H, J=7.0 Hz) $CH(CH_3)$; 1.04 (d, 3H, J=6.0 Hz) CH_3-CHOTBDPS ; 1.06 (s, 9H) $C(CH_3)_3$; 1.71 (m, 1H) $CH(CH_3)$; 2.20 (s, 1H) OH ; 3.62 (q, 1H, J=6.0 Hz and J'=11.0 Hz) CH_2OH ; 3.78 (q, 1H, J=4.5 Hz and J'=11.0 Hz) CH_2OH ; 3.92 (m, 1H) CHOTBDPS ; 7.48 and 7.78 (m, 10H) C_6H_5.

(2S,3S)-(+)-1-Tosyloxy-2-methylbutan-3-ol *t*-butyldiphenylsilylether 21b.

p.toluenesulfonyl chloride (2.7g, 14mmol) was added to a stirred and ice-cooled solution of (+) alcohol **21a** (3.17g, 9mmol) in dry pyridine (1.5ml, 18.5mmol) and dry CH_2Cl_2 (1.5ml) . After 12 h at 0°C, the mixture was hydrolyzed with water, extracted with ether and washed with a saturated solution of $NaHCO_3$. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. After purification (cyclohexane/ EtOAc: 95/5) 3.90g of compound **21b** were obtained (yield: 85%).

$[\alpha]D^{20}$=+9.7° (c= 5.69; CH_2Cl_2). ^1H NMR (250 MHz): δ 0.90 (d, 3H, J=7.0 Hz) $CH(CH_3)$; 0.91 (d, 3H, J=6.0 Hz) CH_3-CHOTBDPS ; 0.98 (s, 9H) $C(CH_3)_3$; 1.94 (m, 1H) $CH(CH_3)$; 2.46 (s, 3H) C_6H_5-CH_3 ; 3.78 (m, 1H) CHOTBDPS ; 3.92 (q, 1H, J=7.0 Hz and J'=9.5 Hz) CH_2OTs ; 4.12 (q, 1H, J=5.5 Hz and J'=9.5 Hz) CH_2OTs ; 7.44 (m, 8H) C_6H_5 ; 7.69 (m,4H) C_6H_5 ; 7.81 (d, 2H, J=1.7 Hz) C_6H_5. Anal. cald. for $C_{28}H_{36}O_4SSi$ C: 67.80, H: 7.32; found C: 67.27, H: 7.51.

(2R,3S)-(+)-1-Bromo-2-methylbutan-3-ol *t*-butyldiphenylsilylether 5.

The silyl ether **21b** (3.90g, 7.80mmol) was stirred at room temperature for 12 h with LiBr (3.42g, 39mmol) in THF (10ml). After evaporating the solvent and treating the reaction as usual, the same procedure was effected twice again to obtain a crude product which was chromatographed to give 3.12g of compound **5** (quantitative yield).

$[\alpha]_D^{20}$=+3.2° (c= 3.05; CH_2Cl_2). ^1H NMR (250 MHz): δ 0.98 (d, 3H, J=6.0 Hz) CH(CH_3) ; 1.01 (d, 3H, J=6.0 Hz) CH_3-CHOTBDPS ; 1.06 (s, 9H) C(CH_3)3 ; 1.96 (m, 1H) CH(CH_3) ; 3.50 (d, 2H, J=6.0 Hz) CH_2Br ; 3.90 (m, 1H) CHOTBDPS ; 7.48 (m, 10H) C_6H_5. ^{13}C NMR : δ 14.66 ; 19.32 ; 19.72 ; 27.00 ; 37.91 ; 42.78 ; 71.28 ; 127.38 ; 127.59 ; 129.45 ; 129.66 ; 133.53 ;134.57; 135.83 ; 135.84. Anal. cald. for $C_{21}H_{29}BrOSi$ C: 62.27, H: 7.22; found C: 62.24, H:7.33.

(2S,3S,5RS,7S)-5-Phenylsulfonyl-3,7-dimethylpentadecan-2 benzylether 22.

LDA in ether (2.9 equivalents) was added at -78°C to a solution containing 1-phenylsulfonyl-3-methylundecan **3** (0.412g, 1.33mmol) , 1-bromo-2-methylbutan-3-ol benzyl ether **4** (2.55g, 6.3mmol) and HMPT (2ml) in THF (25ml). The mixture was warmed up quickly to -52°C. After 4 h, the reaction was hydrolyzed with a saturated of NH_4Cl and THF was evaporated *in vacuo*. The residue was extracted with ether. The product was chromatographed (cyclohexane/ EtOAc: 95/5) to give 452mg of product **22** as a mixture of diastereoisomers (yield: 70%).

^1H NMR (250 MHz): δ 0.84 (d, 3H, J=7.0 Hz) CH(CH_3)-CH_2-CH(SO_2-C_6H_5) ; 0.90 (t, 3H, J=7.0 Hz) CH_3-(CH_2)7 ; 0.92 (d, 3H, J=7.0 Hz) CH(CH_3)-CHOBn ; 1.06 (d, 3H, J=6.5 Hz) CHOBn-CH_3 ; 1.26 (s, 14H) CH_3-(CH_2)7 ; 1.82 (m, 1H) CH(CH_3)-CHOBn ; 2.08 (m, 2H) CH(SO_2-C_6H_5)-CH_2 ; 3.24 (m, 1H) CH(SO_2-C_6H_5) ; 3.45 (dq, 1H, J=6.5 Hz) CHOBn ; 4.43 (d, 1H, J=17.0 Hz) CH_2-CH(SO_2-C_6H_5) ; 4.56 (d, 1H, J=17.0 Hz) CH_2-CH(SO_2-C_6H_5) ; 7.40 (s, 5H) O-CH_2-C_6H_5 ; 7.52,7.64 and 7.91 (3t, 5H) SO_2-C_6H_5.

(2S,3S,7S)-(-)-3,7-Dimethylpentadecan-2-ol 24b.

Sulfone **22** (0.247g, 0.5mmol) was reduced with an excess of Na(Hg) 6% (2.26g, 20 equivalents in powder) with Na_2HPO_4 (0.86g, 12 equivalents) in MeOH (20ml) at room temperature. After filtration, addition of a saturated solution of NH_4Cl and extraction with ether, the solution was dried over $MgSO_4$ and evaporated *in vacuo* to obtain 106mg of crude **24a** (yield: 60%).Compound **24a** (0.106g, 0.6mmol) was reduced with H_2 on Pd/C 10% (0.23g) to obtain after a flash chromatography (cyclohexane/ EtOAc: 8/2) 68mg of pure **24b** (yield: 86%).

$[\alpha]_D^{20}$=-11.5° (c= 0.79; hexane); Lit: $[\alpha]_D^{20}$=-10.4° (c= 3.70; hexane) (4c).^1H NMR (250 MHz): δ 0.86 (overlapped t + 2d, 9H) 3CH3 ; 1.16 (d, 3H, J=6.0 Hz) CHOH-CH_3 ; 1.27 (s, 22H) CH_2 and CH(CH_3) ; 3.74 (m, 1H) CHOH. ^{13}C NMR : δ 14.05 ; 14.16 ; 19.70 ; 20.20 ; 22.64 ; 24.73 ; 27.03 ; 29.33 ; 29.65 ; 29.99 ; 31.89 ; 32.72 ; 32.94 ; 36.97 ; 37.35 ; 39.77 ; 71.26. I.R(neat): ν = 3 380 cm^{-1} (OH). Mass Spectrum m/z: 274 (m + NH_4^+) ; 257 (m + 1). Anal. cald. for $C_{17}H_{36}O$ C: 79.61, H: 14.15; found C: 79.25, H: 14.04 .

(2S,3S,7S)-(-)-3,7-Dimethylpentadecan-2-yl acetate 1.

Alcohol **24b** (0.6g, 0.23mmol) was stirred with acetic anhydride (33µl, 0.35mmol) , Et_3N (49µl, 0.35mmol) and DMAP (2mg, $1.9.10^{-2}$mmol) in CH_2Cl_2 at room temperature for 12 h. The reaction was hydrolyzed with 2N HCl, extracted with ether and washed twice with a saturated solution of $NaHCO_3$. After drying over $MgSO_4$ and evaporating *in vacuo*, 69mg of pure compound **1** were obtained after flash chromatography (cyclohexane/ EtOAc: 95/5) (quantitative yield).

$[\alpha]_D^{20}$=-6.3° (c= 2.03; hexane); Lit: $[\alpha]_D^{23}$=-6.6° (neat) (3). ^1H NMR (250 MHz): δ 0.90 (m, 9H) 3CH_3; 1.18 (d, 3H, J=6.0 Hz) CH_3-CHOAc ; 1.28 (s, 21H) CH_2 and CH(CH_3) ; 1.60 (m, 1H) CH(CH_3)-CHOAc; 2.05 (s, 3H) CH_3-CO ; 4.88 (m, 1H) CHOAc. ^{13}C NMR : δ 14.05 ; 14.75 ; 16.87 ; 19.65 ; 21.23 ; 22.65; 24.46 ; 27.02 ; 29.33 ; 29.65 ; 29.99 ; 31.89 ; 32.67 ; 32.71 ; 36.97 ; 37.26 ; 37.55 ; 73.97 ; 170.68. Mass Spectrum m/z: 316 (m + NH_4^+). Anal. cald. for $C_{19}H_{38}O_2$ C: 76.45, H: 12.83; found C: 76.33, H:12.74.

(2S,3R,5RS,7R)-5-Phenylsulphonyl-3,7-dimethylpentadecan-2-ol *t*-butyldiphenylsilylether 23.

LDA in ether (2.9 equivalents) was added at -78°C to a solution containing 1-phenylsulfonyl-3-methylundecan **ent-3** (1.77g, 5.7mmol), 1-bromo-2-methylbutan-3-ol *t*-butyldiphenylsilyl ether **5** (2.55g, 6.3mmol) and HMPT (11ml) in THF (70ml). The mixture was warmed up quickly to -52°C. After 4 h, the reaction was hydrolyzed with a saturated solution of NH_4Cl and THF was evaporated *in vacuo*. The residue was extracted with ether. The product was chromatographed (cyclohexane/ EtOAc: 95/5) to give 2.65g of product **23** as a mixture of diastereoisomers (yield: 74%).

^1H NMR (80 MHz): δ 0.87 (m, 12H) 4CH_3 ; 1.22 (s, 15H) CH_3-(CH_2)7-CH(CH_3) ; 1.41 (s, 9H) C(CH_3)3 ; 1.57 (m, 5H) CH_2-CH($OSO_2C_6H_5$)-CH_2-CH(CH_3) ; 2.87 (m, 1H) CH($OSO_2C_6H_5$) ; 3.57 (m, 1H) CHOTBDPS ; 7.27, 7.47 and 7.70 (3m, 15H) C_6H_5.

(2S,3R,7R)-(+)-3,7-Dimethylpentadecan-2-ol 25b.

23 (2.5g, 3.9mmol) was treated with Na(Hg) 6% (in powder) (17.6g, 20 equivalents) in MeOH (80ml), Na_2HPO_4 (6.7g,12 equivalents) and THF (1ml) at room temperature. After filtration, addition of a saturated solution of NH_4Cl and extraction with ether, the solution was dried over $MgSO_4$, evaporated *in vacuo* to give 1.22g of **25a** (yield: 63%). Crude product **25a** (1.22g, 2.5mmol) was deprotected with a concentrated solution of HF (1.5ml) in CH_3CN/ THF (v/v: 1/1) to obtain after chromatography (cyclohexane/ EtOAc: 95/5) 340mg of **25b** (yield: 62%).

$[\alpha]_D^{20}$=+14.9° (c= 3.33; hexane); Lit: $[\alpha]_D^{20}$=+16.03 (c= 5.20; hexane) (4c). ^1H NMR (250 MHz): δ 0.86 (overlapped t + 2d, 9H, J=6.0 Hz) CH_3 ; 1.14 (d, 3H, J=6.5 Hz) CH_3-CHOH ; 1.28 (s, 21H) CH_2 and CH(CH_3)-CH_2 ; 1.52 (m, 1H) CH(CH_3)-CHOH ; 3.70 (m, 1H) CHOH. ^{13}C NMR : δ 14.08 ;14.51;19.26; 19.73 ; 22.66 ; 24.67 ; 27.04 ; 29.34 ; 29.67 ; 30.01 ; 31.91 ; 32.73 ; 32.90 ; 36.99 ; 37.38 ; 40.05 ; 71.70. I.R (neat): ν =3 380 cm^{-1} (OH). Mass spectrum m/z: 274 (m+NH_4^+) ; 255 (m-1). Anal. cald. for $C_{17}H_{36}O$ C: 79.61, H: 14.15 ; found C: 79.46, H: 14.21.

(2S,3R,7R)-(+)-3,7-Dimethylpentadecan-2-yl acetate 2.

Alcohol **25b** (0.19g, 0.74mmol) was stirred with acetic anhydride (105µl, 1.11mmol), Et_3N (155µl, 1.11mmol) and DMAP (70 mg, 6.10^{-2}mmol) in CH_2Cl_2 at room temperature for 12 h. The reaction was hydrolyzed with 2N HCl and extracted with ether and washed twice with a saturated solution of $NaHCO_3$. After drying over $MgSO_4$ and evaporating *in vacuo*, 210mg of pure compound was obtained after flash chromatography (cyclohexane/EtOAc: 95/5) (quantitative yield).

$[\alpha]D^{20}=+6.3°$ (c= 4.10; hexane); Lit: $[\alpha]D^{20}=+6.9°$ (c= 1.17; hexane) (4b). ^1H NMR (250 MHz): δ 0.88 (m, 9H) $3CH_3$; 1.15 (d, 3H, J=6.3 Hz) $CHOAc-CH_3$; 1.28 (s, 21H) $10CH_2$ and $CH(CH_3)$; 1.70 (m, 1H) $CH(CH_3)$-CHOAc ; 2.06 (s, 3H) $COCH_3$; 4.86 (m, 1H) CHOAc. ^{13}C NMR : δ 14.07 ; 14.51 ; 15.70 ; 19.67 ; 21.31 ; 22.65 ; 24.48 ; 27.02 ; 29.33 ; 29.63 ; 29.98 ; 31.89 ; 32.67; 39.92 ; 36.83 ; 37.18 ; 74.23; 170.86. Mass spectrum m/z: 316 ($m+NH_4^+$). Anal. cald. for $C_{19}H_{38}O_2$ C: 76.45, H: 12.83; found C: 76.39, H: 12.98.

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