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Enhanced diastereoselectivity in the addition of ester enolate to optically active α,β-epoxyaldehydes obtained from nerol and geraniol.

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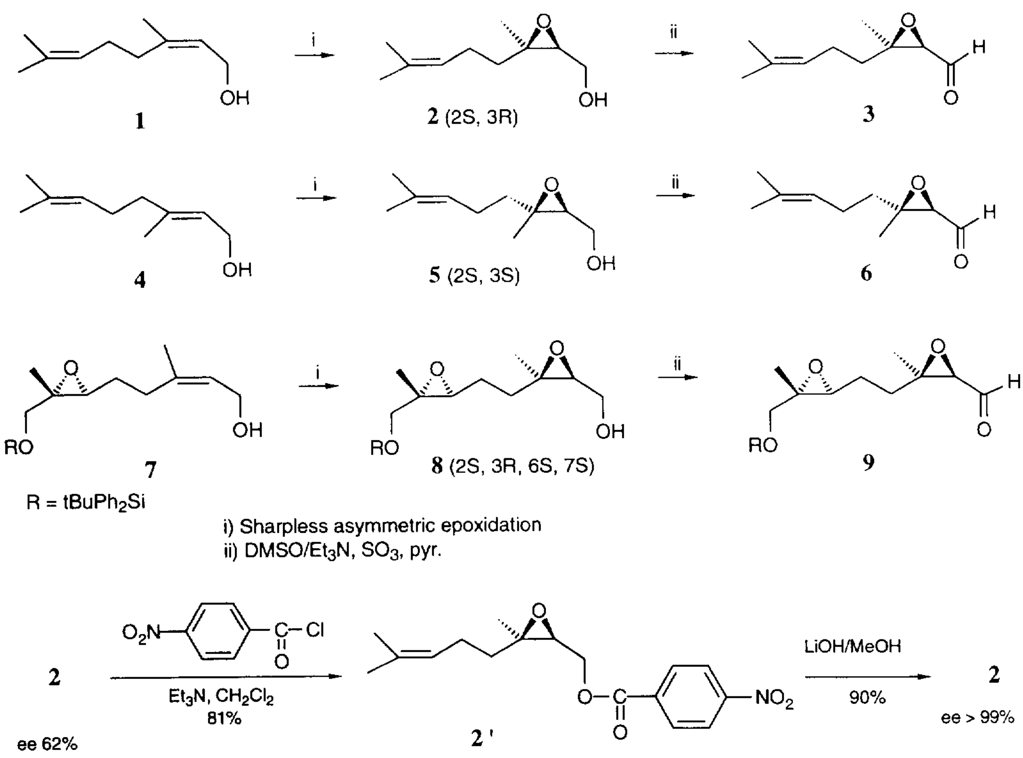
Abstract: Optically active α,β-epoxyaldehydes obtained from nerol and geraniol were allowed to react with lithium tert-butylacetate. The diastereofacial preference of the aldolisation reaction was always *anti* ("Si"face attack of the carbonyl). The best diastereoselectivity ever observed in these series (>99 : <1 *anti* : *syn*) was obtained for the α,β-epoxyneral aldolisation. Copyright © 1996 Elsevier Science Ltd

The synthesis of optically active functionalized 1,3 or 1,2,3 polyhydroxylated systems has received considerable attention during the last decades because many biologically active compounds contain this frame[1]. Their synthesis has led to the development of a great number of methods[2]. In the course of our studies towards the synthesis of this kind of chiral synthons, we developed[3] a method based on two key reactions: a) Sharpless asymmetric epoxidation of an allylic alcohol and b) stereocontrolled addition of a tert-butyl lithioester to an optically active α,β-epoxyaldehyde. We achieved a facial discrimination for the aldolisation reaction in favour of the "Si" face nucleophilic attack of the carbonyl that varies from 4 : 1 to 13 : 1 for the *cis* α,β-epoxyaldehydes while it is invariable for the α,β-*trans* epoxyaldehydes (3 : 1). In addition we have extended the scope of this reaction, by their clean transformation to optically active γ-hydroxy butyrolactones when reacted with Zn°/$SiMe_3Cl$.[4]

We now describe the synthesis of optically active γ,δ-epoxy-β-hydroxyesters obtained from terpenic allylic alcohols nerol and geraniol and the stereochemistry of the addition of lithium tert-butyl acetate to the corresponding aldehydes. These compounds can be considered as useful chiral synthons for the synthesis of analogues of polyether ionophore systems bearing the nerol and/or geraniol functionality and known as antibiotics.[5] They can also be used as synthons for the synthesis of optically active lactones, modified furanosides, pyranosides and nucleosides.

Sharpless asymmetric epoxidation of nerol and geraniol was retained to synthesize the optically active mono epoxyalcohols **2**, **5** in high yields (scheme 1, table 1). The enantiomeric purity, although not important for the diastereoselectivity studies, can be useful for further experiments and was tested on benzoylated compounds **2'**,which were isolated in ~80% yield; the enantiomeric excess was determined by analytical HPLC chromatography with a chiral stationary phase.

The enantiomeric excess for epoxynerol was essentially due to a longer reaction time than in the original Sharpless procedure;[6] we have verified that the (2S,3R)-epoxynerol **2** can also be obtained optically pure by repeated recrystallization of the 4-nitro benzoylated compound **2'**;[7] unfortunately we were enable to crystallize the benzoylated (2S,3S)-epoxygeraniol in the same conditions.



Scheme 1

Table 1. Yields and optical purities of the α,β-epoxyalcohols and α,β-epoxyaldehydes

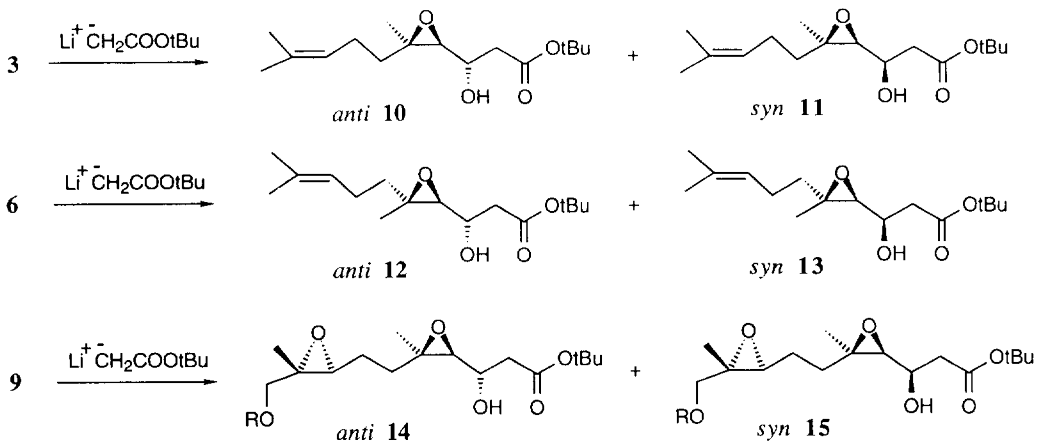
epoxyalcohol	Yield [a] (%)	$[\alpha]_D^{25}$	ee (%)	epoxyaldehyde	Yield (%)	$[\alpha]_D^{25}$
2 [b]	93	- 15.2	62	**3**	90	+ 79.4
2	(39)*	(-23.4)	(>99)	**3**	(100)	(+ 137.6)
5 [c]	96	- 4.7	81	**6**	78	+ 115.8
8	88	- 22.9	>97	**9**	76	+ 34.2

a) time reaction ~3 h, -20 °C; b) lit.[6] time reaction for **2** ~1 h, -20 °C, 79%, ee : 94%; c) lit.[6] time reaction for **5** ~45 mn, -20 °C, 95%, ee : 91%;

* Values in brackets are for compound **2** after recrystallization; the theoretical yield corresponding to optically pure **2** after Sharpless epoxidation reaction is 59% .

Diepoxy alcohol **8** was synthesized through a variant of a known synthetic procedure used by Sharpless[5a] and Paterson[5b]. Allylic oxidation by SeO_2 of the neryl acetate followed by Sharpless asymmetric epoxidation (95% ee) of the allylic alcohol formed, silylation of the primary alcohol and deprotection of the acetate group, gave the allylic alcohol precursor **7** which was then epoxidised leading to **8** in 69% overall yield. The epoxyalcohol thus obtained was oxidised to the corresponding aldehyde **9** by the optimized Doering procedure[8, 3] (pyridine/SO_3, DMSO, Et_3N) in good to excellent yields (table 1).

The α,β-epoxyaldehydes were subjected to the aldolisation reaction with lithium-tert-butylacetate under various experimental conditions (scheme 2, table 2). Acidic hydrolysis of the reaction medium and usual work-up lead to a mixture of the two adducts which is used to determine the diastereoisomeric ratio measured by G.C. column chromatography (entries 1-9), or by HPLC (entry 10).



Scheme 2

Table 2. Diastereoselectivity of the reaction of lithium tert-butylacetate with the α,β-epoxyaldehydes

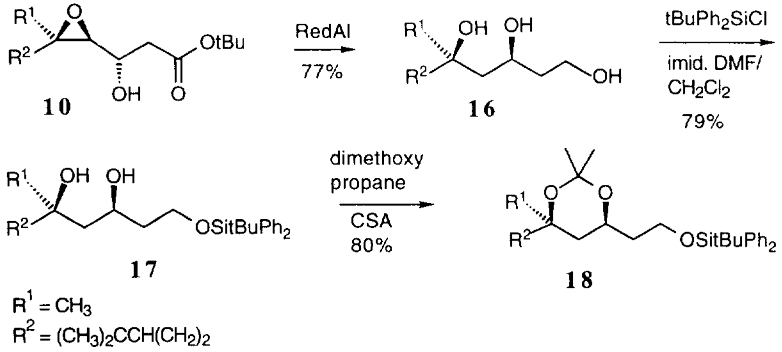
entry	aldehyde	enolate/ald	T °C	Yield %	*anti* : *syn*	epoxyester
1	**3***	1	-78	89	92 : 8	**10 : 11**
2	**3**	2	-78	61	93 : 7	**10 : 11**
3	**3**	1	-78 +25	92	92 : 8	**10 : 11**
4	**3**	2	-78 +25	71	>99 : <1	**10 : 11**
5	**3**	2	+25	85	>99 : <1	**10 : 11**
6	**6***	1	-78	61	86 : 14	**12 : 13**
7	**6**	2	-78	84	94 : 6	**12 : 13**
8	**6**	1	-78 +25	65	86 : 14	**12 : 13**
9	**6**	2	-78 +25	83	87 : 13	**12 : 13**
10	**9**	2	-78	81	86 : 14	**14 : 15**

* The lithium tert-butylacetate addition was also conducted on the enantiomeric aldehydes and led to the same results.

At -78 °C, a very good *anti* diastereoselectivity was obtained with epoxyneral **3** (*anti/syn* : 92:8) while in the same conditions the diepoxyneral **9** gave only a 86:14 *anti* preference. Variations of the reaction temperature or time reaction did not provide any significant changes in the selectivity when the aldehyde and the enolate are in a stoichiometric amount. The selectivity with **3** can be improved to 99:1 when using two enolate equivalents and increasing the temperature.

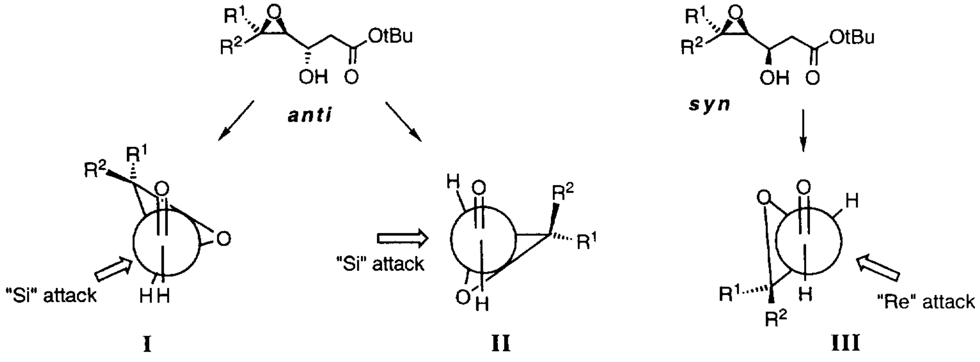
The aldolisation reaction of epoxygeranial **6** gave the best *anti* diastereoselectivity when carried out at -78 °C in presence of 2 eq of enolate (*anti* /*syn* : 94:6) while under all other experimental conditions the diastereoselectivity found was only in a ratio *anti* /*syn* ≈ 86:14. The role of the second enolate molecule when increasing the temperature of the aldolisation reaction is not well understood.

The stereochemical assignment of the aldol products was established for compound **10** by conversion to the six membered acetonide according to a known procedure[9] (scheme 3). The ^{13}C NMR shifts of the acetal carbons were in agreement with our previous results[3] and those reported in the literature[10] attributing a *cis* configuration to the two hydroxy functions of compound **17** and thus an *anti* configuration for the major diastereoisomer **10**.



Scheme 3

The *anti* diastereofacial preference observed under kinetic control conditions can be explained according to the Felkin-Anh or Cornforth [11] type models **I** or **II**. For the first model (**I**) a non perpendicular nucleophilic attack on the carbonyl takes place antiperiplanar to the epoxide C-O bond, while for **II** the carbonyl group is antiperiplanar to the epoxide C-O bond and the attack will occur from the less hindered "Si" face. The "Re" attack on the gauche conformer **III** will lead to the minor *syn* diastereoisomer.



Another way to analyze the results is to consider the hypothesis that the diastereoselectivity in the reaction of chiral aldehydes with achiral enolates can successfully be predicted using ground state energies and geometries.[12] In the aldol reaction, where it is assumed that the transition states are rather "reactant like", their relative energies, leading to the two different diastereoisomers, would be strongly determined by the rotational profile of the aldehyde.

The energetically more favoured conformers have been calculated from MMX programme[13] for the epoxyneral **3** and epoxygeranial **6** compounds and their rotational profile have two discrete energy minima.[14] The most favoured conformer is a Cornforth model type **II** for epoxyneral while it is the Felkin-Anh **I** for the epoxygeranial; the difference is probably due to a change in the steric constraints between R^2 and the carbonyle.

The theoretically predicted ratio *anti* : *syn* for the two diastereoisomers, according to the differences between the two described energy minima, are very close to the experimental values. Even if this agreement has to be examined with caution since we do not consider any solvent effects and other reaction conditions, the calculations show the right trend and it may mean that these models correctly predicts the results obtained.

In conclusion the aldolisation reaction of lithium tert-butylacetate with α,β-epoxyaldehyde proceeded with good to excellent *anti* diastereoface preference; the best diastereoselectivity being observed (>99/<1) for the aldolisation of α,β-epoxyneral.

EXPERIMENTAL

Commercially available reagents were used as supplied. n-Butyllithium was purchased from Aldrich in 100 mL bottles as 1.6 M solution in hexane. All solvents were distilled prior to use. THF on sodium was freshly distilled before use. HPLC chromatography was carried out on a Jobin-Yvon apparatus using Merck 15 μm or Amicon silica (6-35 μm). The analytical HPLC apparatus used was composed by Kratos Spectroflow 400 pump, an UV abI 759A detector and either a Chiralcel OD (L = 25 cm, Ø = 0.46 cm) column for determination of enantiomeric excess (% ee) or a Waters Novapack silica column (L = 15 cm, Ø = 0.39 cm) for determination of diastereoisomeric excess of compounds **11**, **12**. Diastereoisomeric ratio determination of other aldol adducts was carried out on a Hewlett-Packard 5890A G.C. apparatus having a flame ionization detector, (T° oven = 190 °C, T° inj = 230 °C, T° det = 220 °C by using SE 30 (L = 10 and 12 m, Ø = 0.53 and 0.33 μm) and Carbowax (L = 12 m, Ø = 0.53 μm) columns. Infrared spectra were recorded in a Perkin-Elmer 883 spectrophotometer. ^{1}H, ^{13}C NMR spectra were recorded using Bruker AC 250 instrument with TMS as internal reference. Mass spectra were obtained on a Nermag R10-10 mass spectrometer. Optical rotations were measured on a Perkin Elmer 141 polarimeter.

Preparation of (2S,3R) and (2S,3S), 3,7-dimethyl-2,3-epoxy 6-octene-1-ol, (2,3-epoxynerol **2**, 2,3-epoxygeraniol **5**). They were prepared according to the procedure described by Sharpless for 2,3-epoxygeraniol[6] but the reaction was allowed to continue 3 h at -20 °C.
For compound **2**. HPLC silica-gel purification, eluent petroleum ether/ether (2:3). IR (film), ν cm^{-1}: 3428 (OH), 2971- 2929 (C-H), 1590 (C=C). NMR ^{1}H (250 MHz, $CDCl_3$) δ ppm: 5.07 (t hept; 1H, J = 7.5, 1.5 Hz, CH=), 3.70 and 3.63 (ddd, 2H, J = 12.5, 7.5, 5, 4.5 Hz, $-CH_2O$), 2.95 (dd, 1H, J = 7.5, 4.5 Hz, CHOep), 2.29 (dd, 1H, J = 7.5, 5 Hz, OH), 2.07 (m, 2H, $CH_2CH=$), 1.71 and 1.61 (2s, 6H, $(CH_3)_2C=$), 1.65 and 1.47 (m, 2H, $CH_2Cep(Me)$), 1.32 (s, 3H, CH_3Cep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 133.9, 123.2, 64.3, 61.5, 61.2, 33.1, 25.6-17.6, 24.1, 22.1. **2**, $[\alpha]_D^{25}$ = -15.2° (c = 2.6, $CHCl_3$), ee: 62%. Analysis (calculated/found): %C 70.55 (70.10), %H 10.66 (10.62).

Improvement of the optical purity of 2. (2S,3R)-1-(p nitrobenzyloxy) 2,3- dimethyl-2,3-epoxy 6-octene **2'**. To a solution of (2S,3R)-epoxynerol (12.49 g, 73.45 mmol) in anhydrous methylene chloride (210 mL) at 0 °C was added triethylamine (12.3 mL, 88.1 mmol) and the p-nitrobenzoyl chloride (15 g, 80.8 mmol). After 1.5 h the reaction was quenched by addition of tartric acid 10 % aqueous solution (75 mL). The organic layer was washed two times with this solution (2 fold 75 mL), twice with sat. $NaHCO_3$ (2 fold 50 mL) and twice with sat. NaCl (2 fold 50 mL), then dried over $MgSO_4$ and concentrated. Recristallization in cold petroleum ether/ether

mixture (70/30, 75/25, 0/100) gave 10.11 g of **2'** (ee >99%), 6.31 g (ee = 36%). The remaining filtrate was purified over silica gel eluting with petroleum ether/ether (4:1) to afford 2.65 g of a racemic mixture of **2'**. Paranitrobenzoylation over all yield is 81% (19.07 g, 59.78 mmol).
IR (KBr), ν cm^{-1}: 3114-2971 (C-H), 1726 (C=O), 1103 (C-O). NMR ^{1}H (250 MHz, $CDCl_3$) δ ppm: 8.25 (m, 4H, phenyl), 5.10 (t hept, 1H, J = 7, 1 Hz, CH=), 4.66 and 4.28 (AB part of an ABX syst, 2H, J = 12.1, 3.8, 7.4 Hz, CH_2O), 3.13 (dd, 1H, J = 7.4, 3.8 Hz, CHOep), 2.12 (m, 2H, CH_2CH=), 1.68-1.61 (2s, 6H, $(CH_3)_2C$=), 1.65 (m, 2H, $CH_2Cep(Me)$), 1.37 (s, 3H, CH_3Cep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 164.6, 150.7-135.1), 132.7, 130.9-123.6, 123.0, 64.8, 61.0, 60.7, 33.3-24.2, 25.7-17.7, 22.0. Analysis (calculated/found): %C 63.94 (63.60), %H 6.63 (6.64), %N 4.39 (4.31). $[\alpha]_D^{25}$ = - 33.6° (c = 0.94, $CHCl_3$).
To a solution of **2'** (9 g, 28.21 mmol) in methanol (100 mL) at 0 °C was added lithium hydroxide monohydrate (1.12 g, 26.69 mmol). After 20 min the solvent was evaporated and the crude product was allowed to crystallize in diethylether (100 mL). Lithium p-nitrobenzoate was filtered off, the filtrate washed with sat. $NaHCO_3$, dried over $MgSO_4$ and solvent evaporated. Purification over silica gel eluting with petroleum ether/ether (2 : 3) gave **2** (4.34 g, 25.52 mmol, 90%). $[\alpha]_D^{25}$ = -23.4° (c = 1.7, $CHCl_3$), % ee >99.

Synthesis of (2S,3R,6S,7S)-8-(tert-butyldiphenylsilyloxy)-3,7-dimethyl 2,3,6,7-bisepoxyoctanol. **8**
i) Synthesis of (2S,3S)-8-acetoxy-2,6-dimethyl-2,3-epoxy-6Z-octene 1-ol. To a solution of nerol (10 g, 64.83 mmol) in methylene chloride (120 mL) was added under N_2 and stirring, pyridine (14.7 mL, 181.5 mmol) and acetyl chloride (8 mL, 112.5 mmol). After 40 min the reaction was quenched with H_2O (60 mL) and diluted with diethylether (200 mL). The organic layer was washed with H_2O, sat. aqueous NaCl dried over $MgSO_4$ and evaporated to give quantitatively acetyl nerol. To a solution of selenium dioxide (3.46 g, 31.15 mmol) in anhydrous methylene chloride was added tert-butylhydroperoxide (29.47 mL of a 3M solution, 88.4 mmol). After 1 h a solution of acetyl nerol (12.2 g, 62.24 mmol) in CH_2Cl_2 (42 mL) was added slowly. After 3 h of stirring the mixture was diluted with ethanol (253 mL) and sodium borohydride (5.6 g, 147.4 mmol) was added at -35 °C. After 1.5 h the reaction was quenched with sat. NH_4Cl (35 mL) ; the solvents were evaporated and the crude product dissolved in ether (100 mL) was extracted with H_2O sat. NaCl and dried over $MgSO_4$. Silica gel purification eluent petroleum ether/ether (1:1) gave the corresponding 1-hydroxyl neryl acetate. To a suspension of molecular sieves (4 Å) in CH_2Cl_2 at -20 °C under N_2 and stirring was added titanium tetraisopropoxide (724 mL, 2.43 mmol), (+) diethyl tartrate (595 mg, 2.83 mmol) and tert butylhydroperoxide (15.7 mL of 3M solution, 47.1 mmol). After 30 min 1-hydroxynerylacetate (5 g, 23.58 mmol) in CH_2Cl_2 (10 mL) was added. After 4.5 h the reaction mixture was stopped by addition of 6 mL of NaOH 30% brine. The mixture was allowed to reach the r.t. (1 h) and then was diluted with ether (100 mL) dried over $MgSO_4$ filtrated over a pad of celite and the solvents evaporated. The crude product was purified on silica gel chromatography eluent petroleum ether/ether (1 : 1) to give the corresponding 2,3-epoxy-1-hydroxy neryl acetate (4.66 g, 87%).
IR (film), ν cm^{-1}: 3449 (O-H), 2936 (C-H), 1737 (C=O), 1668 (C=C), 1030 (C-O). NMR ^{1}H (250 MHz, $CDCl_3$) δ ppm: 5.39 (td, 1H, J = 7.1, 1 Hz, CH=), 4.56 (d, 2H, J = 7.1 Hz, CH_2OAc), 3.64 and 3.56 (AB part of an ABX syst, 2H, J = 12, 4.2, 7.9 Hz, CH_2OH), 3.01 (t, 1H, J = 6 Hz, CHOep), 2.25 (dd, 2H, J = 7.5; 7.1 Hz, CH_2), 2.08 (m, 1H, OH), 2.03 (s, 3H, CH_3CO), 1.73 (s, 3H, CH_3C=), 1.67 (m, 2H, CH_2), 1.27 (s, 3H, CH_3Cep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 171.1, 141.3, 120.0, 65.3, 61.1, 60.9, 59.5, 28.7-26.7, 23.4, 21.1, 14.2. $[\alpha]_D^{25}$ = - 11.0° (c = 4.7, $CHCl_3$). Analysis (calculated/found): %C 63.14 (63.69), %H 8.83 (9.08).

ii) Synthesis of (6S, 7S)-8-(tert-butyldiphenylsilyloxy)-3,7-dimethyl-6,7-epoxy-2Z-octene-1-ol **7.** To a solution of 2,3-epoxy-1-hydroxynerylacetate (1.5 g, 6.58 mmol) and imidazole (1.34 g, 19.68 mmol) in anhydrous DMF (26.3 mL) under N_2 and at r.t. was added tert-butyldiphenylsilane chloride (2.6 mL, 15.08 mmol). After 13 h of stirring the reaction mixture was hydrolized with sat. aqueous NH_4Cl (10 mL) and ether was added (50 mL). The organic phase was extracted and washed with H_2O (3 fold 15 mL) dried over $MgSO_4$ and concentrated. The crude product was diluted in H_2O/MeOH (26 mL, 1 : 4) and K_2CO_3 was added (1 g, 7.24 mmol). After 2.5 h ether (30 mL) was added and then aqueous sat. NH_4Cl (10 mL). The organic phase obtained was dried over $MgSO_4$ and solvent evaporated. The crude product was purified over silica gel eluting with petroleum ether/ether (1 : 1) to give 2.52 g (90%) of allylic alcohol **7**. IR (film), ν cm^{-1}: 3440 (O-H), 3073-2933 (C-H), 1110 (C-O). NMR ^{1}H (250 MHz, $CDCl_3$) δ ppm: 7.67-7.41 (m, 10H, phenyl), 5.51 (td, 1H, J = 6.5, 1 Hz, CH=), 4.10 (m, 2H, CH_2OH), 3.64-3.60 (AB syst, 2H, J = 11.2 Hz, CH_2OSi), 2.83 (dd, 1H, J = 7.5, 5.7 Hz, CHOep), 2.24 (m, 2H, CH_2), 1.77 (d, 3H, J = 1 Hz, CH_3C=), 1.31 (s, 3H, CH_3Cep), 1.08 (s, 9H, tBu). NMR

^{13}C (63 MHz, $CDCl_3$) δ ppm: 138.6, 135.7, 129.8, 123.7, 133.3, 125.3, 88.1, 61.4, 60.5, 58.8, 28.5-26.4, 26.8, 23.3, 19.3, 14.5. $[\alpha]_D^{25}$ = - 12.9° (c = 4.2, $CHCl_3$). Analysis (calculated/found): %C 73.54 (73.48), %H 8.54 (8.59).

iii) To a suspension of molecular sieves (4 Å) in 40 mL CH_2Cl_2 at -20 °C under N_2 and stirring was added titanium tetraisopropoxide (434 µl, 1.41 mmol), (+) diethyl tartrate (357 mg, 1.73 mmol) and tert butyl hydroperoxide 3 M (3.14 mL, 9.42 mmol). After 30 min compound **7** (2 g, 4.72 mmol) in CH_2Cl_2 (5 mL) was added. After 1.2 h the temperature of the reaction mixture was allowed to warm from -22 °C to 0 °C. After dilution with ether (50 mL) and the addition of 2 mL of NaOH 30% brine, the mixture was allowed to reach the r.t. (1 h) and then was dried over $MgSO_4$ filtrated over a pad of celite and the solvents evaporated. The crude product was purified on silica gel chromatography eluent petroleum ether/ether (2 : 3) to give pure **8** (1.82 g, 4.14 mmol, 88%). IR (film), ν cm^{-1}: 3441 (O-H), 3073-2934 (C-H), 1111 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 7.87-7.40 (m, 10H, phenyl), 3.74 (t, 2H, J = 6 Hz, CH_2OH), 3.65-3.59 (2d, 2H, J = 11 Hz, AB syst., CH_2OSi), 3.00 (t, 1H, J = 5.7 Hz, C_2HOep), 2.80 (dd, 1H, J = 8, 3.5 Hz, C_6Hep), 2.45 (t, 1H, J = 6 Hz, OH), 1.70 (m, 4H, $2CH_2$), 1.33-1.32 (2s, 6H, $2CH_3Cep$), 1.06 (s, 9H, tBu). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 135.6-129.8-127.8, 133.2, 67.9, 63.9, 61.5-61.3 61.0 60.7, 30.0, 26.8, 24.4, 22.1, 19.3, 14.3. $[\alpha]_D^{25}$ = - 22.9° (c = 3.4, $CHCl_3$), ee > 97%. Analysis (calculated/found): %C 70.87 (69.78), %H 8.23 (8.18).

Synthesis of 2,3-epoxyaldehydes **3**, **6**, **9**, general procedure: To a solution of the corresponding α,β-epoxyalcohol in anhydrous CH_2Cl_2 (1.6 mL/mmol) at r.t. and under N_2, was added under stirring, DMSO (2 mL/mmol), triethylamine (5 eq), and portion wise the SO_3.pyridinium complex (5 eq). After 1 h of stirring the reaction was stopped by adding ether (7 times the CH_2Cl_2 volume). The organic phase was washed with H_2O (3 times 1/3 CH_2Cl_2 volume) dried over $MgSO_4$ and solvent evaporated. The crude product was purified over silica gel.

(2R, 3R)-3,7-dimethyl-2,3-epoxy-6-octene-1-al **3** . Starting from epoxyalcohol **2** (4.34g, 23.53 mmol) we obtained after purification (eluent petroleum ether/ether 4 : 1) epoxyaldehyde **3** (3.56 g, 90%). IR (film), ν cm^{-1}: 2972-2929 (C-H), 1721 (C=O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 9.39 (d, 1H, J = 5 Hz, HC=O), 5.02 (t hept, 1H, J = 7; 1.7 Hz, CH=), 3.12 (d, 1H, J = 5 Hz, CHOep), 2.20 (m, 2H, CH_2), 1.67 and 1.63 (m, 2H, CH_2), 1.77 and 1.54 (2s, 6H, $(CH_3)_2C=$), 1.39 (s, 3H, CH_3ep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 196.7 (C_1), 133.3, 122.4 , 64.6, 64.6, 33.4 , 25.9 - 22.1, 24.2, 17.6.
3 : $[\alpha]_D^{25}$ = + 137.6° (c = 2.4, $CHCl_3$, ee >99%), $[\alpha]_D^{25}$ = + 79.4° (c = 2.4, $CHCl_3$, ee = 62%).

(2R, 3S)-3,7-dimethyl-2,3-epoxy-6-octene-1-al, **6**. Starting from epoxyalcohol **5** (5.9 g, 34.71 mmol) we obtained after purification (eluent petroleum ether/ether 7 : 3) epoxyaldehyde **6** (4.56 g, 78%). IR (film), ν cm^{-1}: 3430-2973-2924 (C-H), 1723 (C=O), 1110 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 9.44 (d, 1H, J = 5 Hz, HC=O), 5.05 (t hept, 1H, J = 7; 1.5 Hz, CH=), 3.17 (d, 1H, J = 5 Hz, CHOep), 2.05 (broad q, 2H, J = 7.5 Hz, CH_2), 1.77 and 1.53 (m, 2H, CH_2), 1.67 and 1.56 (2s, 6H, $(CH_3)_2C=$), 1.42 (s, 3H, CH_3ep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 199.6, 132.8, 122.6, 64.1, 63.5, 38.3, 25.7, 23.5, 17.7,17.2. **6**: $[\alpha]_D^{25}$ = +115.8° (c = 2.1, $CHCl_3$).

(2R, 3R, 6S, 7S)-8-(tert-butyldiphenylsilyloxy)-3,7-dimethyl-2, 3-6, 7-bisepoxy octanal **9**. Starting from epoxyalcohol **8** (1.8 g, 4.11 mmol) we obtained after purification (eluent petroleum ether/ether 7 : 3), epoxyaldehyde **9** (1.37 g, 76%). IR (film), ν cm^{-1}: 3073-2934-2860 (C-H), 1722 (C=O), 1111 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 9.51 (d, 1H, J = 4.5 Hz, HC=O), 7.66-7.40 (m, 10H, phenyl), 3.65-3.58 (AB syst, 2H, J = 11.2 Hz, CH_2OSi), 3.24 (d, 1H, J = 4.5 Hz, C_2HOep), 2.75 (m, 1H, C_6Hep), 1.80-1.61 (m, 4H, $2CH_2$), 1.42-1.31 (2s, 6H, $2CH_3Cep$), 1.05 (s, 9H, tBu). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 198.8, 135.6, 129.8, 127.7, 133.3, 68.1, 64.7, 64.4, 61.1, 60.1, 30.2, 24.6, 26.8, 22.1, 14.3, 19.3. $[\alpha]_D^{25}$ = + 34.2° (c = 1.6, $CHCl_3$).

Aldolisation reaction: General procedure

To a solution of lithium diisopropylamide (LDA) (0.5 M or 1 M in diethylether) at -78 °C under N_2 and stirring was added slowly tert-butyl acetate (1 eq). After 1 h the lithiated adduct was transferred to a solution of α,β-epoxyaldehyde (0.5 M in ether) at -78 °C or at r.t. (table 2 entry 5). The reaction mixture was stirred for 2 h at

-78 °C or allowed to reach the r.t.. The reaction was stopped by addition of an aqueous solution of sat. NH_4Cl. The organic phase was extracted and the aqueous phase was washed three times with diethylether. The combined organic phases were dried over $MgSO_4$ and solvent evaporated. The crude product was purified on silica gel. The diastereoselectivity of the aldolisation reaction is measured on the crude product by GC or HPLC. The diastereoisomer ratio obtained after purification and the one measured on the crude product can be different; HPLC fractions of the major diastereoisomer (*anti*) when contaminated by residual aldehyde were not considered in the yield calculations.

(3S, 4S, 5R) and (3R, 4S, 5R)-tert-butyl-5,9-dimethyl-4,5-epoxy-3-hydroxy-8-ene decanoate **10** and **11**
Starting from epoxyaldehyde **3** (1 g, 5.95 mmol) we obtained after purification eluent petroleum ether/ethylacetate/methylene chloride (5 : 1 : 4) compounds **10** (1.4 g, 4.93 mmol) and **11** (0.06 g, 0.21 mmol) 85% overall yield. (table 2, entry 5).

Compound 10. IR (film), ν cm^{-1}: 3455 (O-H), 2976 (C-H), 1728 (C=O), 1155 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 5.11 (t hept , 1H, J = 7, 1.5 Hz, CH=), 3.76 (tdd, 1H, J = 9, 9, 4, 3 Hz, CHOH), 3.37 (d, 1H, J = 4 Hz, OH), 2.63 and 2.49 (AB part of an ABXY syst, 2H, J = 17, 9, 3 Hz, CH_2CO), 2.60 (d, 1H, J = 9 Hz, CHOep), 2 15 (m, 2H, CH_2), 1.67 and 1.61 (2s, 6H, $(CH_3)_2C=$), 1.65 and 1.47 (m, 2H, CH_2), 1.45 (s, 9H, tBu), 1.32 (s, 3H, CH_3Cep).
NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 172.3, 132.3, 123.6, 81.65, 66.4, 65.3, 62.0, 39.7, 32.9, 28.1, 25.6 and 17.7, 24.1 (C_6), 22.1. $[\alpha]_D^{25}$ = - 39.4° (c = 1.6, $CHCl_3$) ee > 99%. MS (DCI, NH_3), 285 (M+1, 6.6%), 302 (M+18, 13.1%). Analysis (calculated/found): %C 67.42 (67.60), %H 9.91 (9.86).

Compound 11. IR: as **10**. NMR ^1H (200 MHz, $CDCl_3$) δ ppm: 5.10 (t hept, 1H, J = 7, 1.5 Hz, CH=), 3.90 (m, 1H, CHOH), 2.89 (d, 1H, J = 3.6 Hz, OH), 2.75 (d, 1H, J = 7.4 Hz, CHOep), 2.55 and 2.40 (AB part of an ABXY syst, 2H, J = 15, 6, 3 Hz, CH_2CO), 2.13 (broad q, 2H, J = 8 Hz, CH_2), 1.67 and 1.60 (2s, 6H, $(CH_3)_2C=$), 1.57 (m, 2H, CH_2), 1.45 (s, 9H, tBu), 1.30 (s, 3H, CH_3Cep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 170.6, 132.3, 123.4, 81.5, 66.8 and 66.9, 61.7, 40.0, 33.0, 28.1, 25.7 and 17.8, 24.0, 22.1. $[\alpha]_D^{25}$ = + 3.6° (c = 2.2, $CHCl_3$). MS (DCI, NH_3): 285 (M+1, 13.5%), 302 (M+18, 21.4%). Analysis (calculated/found): %C 67.68 (67.60), %H 9.80 (9.86).

(3S, 4S, 5S) and (3R, 4S, 5S)-tert-butyl-5,9-dimethyl-4,5-epoxy-3-hydroxy-8-ene decanoates **12** and **13**. Starting from epoxyaldehyde **6** (0.5 g, 2.98 mmol) we obtained after purification (eluent petroleum ether/ethylacetate/methylene chloride 5 : 1 : 4) compounds **12** (0.64 g, 2.24 mmol) and **13** (0.06 g, 0.21 mmol) 84% overall yield. (table 2, entry 7).

Compound 12. IR (film), ν cm^{-1}: 3451 (O-H), 2977-2933 (C-H), 1728 (C=O), 1154 (C-OH). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 5.1 (t hept, 1H, J = 7, 1.5 Hz, CH=), 3.67 (tdd, 1H, J = 8.5, 8.5, 4.3, 3 Hz, CHOH), 3.32 (d, 1H, J = 4.3 Hz, OH), 2.70 (d, 1H, J = 8.50 Hz, CHOep), 2.63 and 2.5 (AB part of an ABX syst, 2H, J = 16.7, 8.5, 3 Hz, CH_2CO), 2.09 (broad q, 2H, J = 7.5 Hz, CH_2), 1.67 and 1.63 (2s, 6H, $(CH_3)_2C=$), 1.53 (m, 2H, CH_2), 1.47 (s, 9H, tBu), 1.34 (s, 3H, CH_3Cep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 172.2, 132.1, 123.4, 81.7, 66.7, 64.0, 61.86, 39.68, 38.4, 28.1, 25.7, 23.7, 17.6 and 16.6. $[\alpha]_D^{25}$ = - 21.0° (c = 2.4, $CHCl_3$). Analysis (calculated/found): %C 67.57 (67.60), %H 9.92 (9.93).

Compound 13. IR: as **12**. NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 5.06 (t hept, 1H, J = 7: 1.5 Hz, CH=), 3.88 (m, 1H, CHOH), 2.94 (d, 1H, J = 3.5 Hz, OH), 2.75 (d, 1H, J = 7.7 Hz, CHOep), 2.48 and 2.38 (ddd, 2H, J = 16.5, 8.5, 4.3 Hz, CH_2CO), 2.04 (q broad, 2H, J = 7.5 Hz, CH_2), 1.68 and 1.58 (2s, 6H, $(CH_3)_2C=$), 1.45 (s, 9H, tBu), 1.35 (m, 2H, CH_2), 1.30 (s, 3H, CH_3Cep). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 170.6, 132.2, 123.3, 81.5, 66.1, 65.6, 61.2, 39.7, 36.6, 28.0, 25.7, 23.8, 17.1 and 15.3. $[\alpha]_D^{25}$ = - 4.4° (c = 1.1 $CHCl_3$).

(3S, 4S, 5R, 8S, 9S) and (3R, 4S, 5R, 8S, 9S)-tert-butyl-10-(tert-butyldiphenylsilyloxy)-(5,9-(dimethyl)-8,9-4,5-bisepoxy-3-hydroxydecanoates **14** and **15** starting from **9** (1.3 g, 2.97 mmol, 0.5 M in Et_2O) were obtained after purification (eluent petroleum ether/ethylacetate/methylene chloride 5 : 1 : 4), **14**: 1.14 g (2.06 mmol) **15**: 191 mg (0.34 mmol), 81% overall yield (table 2, entry 10).

Compound 14. IR (film), ν cm^{-1}: 3462 (O-H), 2974-2934 (C-H), 1730 (C=O), 1155-1111 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 7.67-7.40 (m, 10H, phenyl), 3.80 (m, 1H, CHOH), 3.65 (d, 1H, J = 3.5 Hz, OH), 3.64 and 3.59 (AB syst, 2H, J = 11 Hz, CH_2OSi), 2.80 (m, 1H, C_8HOep), 2.74 (d, 1H, J = 8.5 Hz, C_4HOep), 2.63 and 2.50 (AB part of an ABX syst, 2H, J = 16, 3.5, 8.5 Hz, CH_2CO), 1.76-1.64 (m, 4H, $2CH_2$), 1.47 (s, 9H, OtBu), 1.34 (s, 6H, $2CH_3$), 1.05 (s, 9H, SitBu). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 171.9, 135.6, 135.6, 129.8, 127.7, 133.3, 81.5, 68.1, 66.4, 65.5, 61.8, 61.5, 61.0, 39.9, 29.9, 28.1, 26.8, 24.3, 22.1, 19.3, 14.3. $[\alpha]_D^{25}$ = - 27.5° (c = 1.5, $CHCl_3$). Analysis (calculated/found): %C 69.28 (69.21), %H 8.36 (8.53).

Compound 15. IR (film), ν cm^{-1}: 3442 (O-H), 2973-2934 (C-H), 1729 (C=O), 1112 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 7.67-7.40 (m, 10H, phenyl), 3.93 (m, 1H, CHOH), 3.63-3.59 (dd, 2H, J = 11 Hz, CH_2OSi), 2.90 (d, 1H, J = 3.5 Hz, OH), 2.80 (d, 1H, J = 7.5 Hz, C_4HOep), 2.78 (m, 1H, C_8HOep), 2.54 (dd, 1H, J = 16, 8 Hz, CH_2CO), 2.47 (dd, 1H, J = 16, 4.5 Hz, CH_2CO), 1.67 (m, 4H, $2CH_2$), 1.46 (s, 9H, OtBu), 1.34-1.31 (2s, 6H, $2CH_3$), 1.05 (s, 9H, SitBu). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 170.6, 135.7, 135.6, 129.8, 133.4, 87.6, 68.4, 66.9, 61.3, 61.3, 60.6, 40.0, 29.8, 28.1, 26.9, 24.4, 22.1, 19.3, 14.4. $[\alpha]_D^{25}$ = - 2.8° (c = 4.7, $CHCl_3$).

(3S, 5R)-5,9-dimethyl-3,5-dihydroxy-8-decen-1-ol **16**. To a solution of **10** (0.81 g, 286 mmol) in THF (12 mL) at r.t. was added Red Al (1.74 mL, 5.72 mmol). After 1 h under stirring two other equivalents of Red Al (1.74 mL, 5.72 mmol) were added. After 13 h of reaction the mixture was diluted with ether (22 mL) then H_2O was added dropwise (12 mL), and acidified (pH = 3) with an HCl 10% solution. The organic phase extracted was washed with aqueous sat. $NaHCO_3$ (4.4 mL). The aqueous phases were continuously extracted with ether (reflux for 24 h). The combined organic phases were dried over $MgSO_4$, solvents evaporated and the crude product was purified on silica gel eluting with ethylacetate/methylene chloride (9/1) to give pure triol **16** (476 mg, 77%). IR (film) ν cm^{-1}: 3349 (O-H), 2923 (C-H), 1118-1054 (C-H). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 5.08 (hept t, 1H, J = 7, 1.5 Hz, CH=), 4.64 (broad s, 1H, OH), 3.83 (m, 1H, C_3HOH), 3.81 (m, 2H, CH_2OH), 3.51 (broad s, 2H, OH), 2.06 (m, 2H, CH_2CH=), 1.72 (m, 2H, $C\underline{H}_2CH_2OH$), 1.67-1.61 (2s, 6H, $(CH_3)_2C$=), 1.60-1.45 (m, 4H, $2CH_2$), 1.28 (s, 3H, CH_3C-OH). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 132.0, 124.1, 73.9, 69.2, 61.0, 45.9, 44.4, 39.1, 25.7, 25.5, 22.3, 17.9. $[\alpha]_D^{25}$ = + 0.4° (c = 1.9, $CHCl_3$).

(3S, 5R)-5,9-dimethyl-1-(tert-butyldiphenylsilyloxy)-3,5-dihydroxy-8-decene, **17**. To a solution of triol **16** (104 mg, 0.48 mmol) in methylene chloride (1.5 mL) at r.t. was added imidazole (0.08 g, 2.3 eq). After 1 h of stirring tertbutyldiphenylchlorosilane (138.5 µl, 0.53 mmol, 1.2 eq) was added along with a mixture of DMF/CH_2Cl_2 (1 : 1, 1.5 mL). After 13h of reaction the mixture was diluted with ether, solvents evaporated and the crude product was purified on reverse phase silica gel C_{18} eluting with $EtOH/H_2O$ (7 : 1) to obtain compound **17** (172 mg, 0.38 mmol, 79%). IR (film) ν cm^{-1}: 3497 (O-H), 3004-2935 (C-H), 1202-1111 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 7.70-7.43 (m, 10H, phenyl), 5.13 (t hept, 1H, J = 7; 1.5 Hz, CH=), 4.34 (m, 1H, CHOH), 3.87 (dd, 2H, J = 7; 6 Hz, CH_2OSi), 3.85 (m, 1H, OH), 2.06 (m, 2H, CH_2CH=), 1.80-1.50 (m, 6H, $3CH_2$), 1.69;1.52 (s, 6H, $(CH_3)_2C$=), 1.31 (s, 3H, CH_3), 1.06 (s, 9H, tBu). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 135.6, 129.8, 124.6, 133.0, 131.6, 124.6, 72.9, 69.4, 63.0, 46.0, 44.2, 39.4, 26.8, 25.9, 25.7, 22.4, 19.0, 17.7. $[\alpha]_D^{25}$ = + 4.5° (c = 0.7, $CHCl_3$). Analysis (calculated/found): %C 66.30 (66.60), %H 11.0 (11.1).

(4R,6S),-4-[4'-methyl-pent-3'-enyl]-6-[tert-butyldiphenylsilyloxyethyl]-4-methyl-2,2-[dimethyl]-1,3-dioxacyclohexane **18**. To a solution of compound **17** (0.10 g, 0.23 mmol) in dimethoxypropane (2 mL) at r.t. and under N_2, was added camphorsulfonique acid (cat 2%). After 45 min of stirring the reaction was stopped by adding an aqueous solution of sat. $NaHCO_3$ (2 mL). The solvents were evaporated and the crude product purified on silica gel eluting with petroleum ether/ether (9.6 : 0.4) to obtain acetonide **18** (0.09 g, 0.18 mmol, 80 %). IR (film), ν cm^{-1}: (film) ν cm^{-1}:3008-2936 (C-H), 1202-1121 (C-O). NMR ^1H (250 MHz, $CDCl_3$) δ ppm: 7.7-7.41 (m, 10H, phenyl), 5.1 (t hept, 1H, J = 7.5; 1.5 Hz, CH=), 4.3 (m, 1H, CHO), 3.86 and 3.73 (AB part of an ABXY syst, 2H, J = 10.5, 8; 5.5; 5 Hz, CH_2OSi), 2.03 (broad q, 2H, 8 Hz, =$CHCH_2$), 1.76-1.70 (m, 2H, J = 13, 7.5, 5.5, 5, 4, 3 Hz, CH_2), 1.68-1.62 (2s, 6H, $(CH_3)_2C$=), 1.47-1.39 (2s, 6H, $C(CH_3)_2$), 1.44 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 1.33 (s, 3H, CH_3CO), 1.06 (s, 9H, tBu). NMR ^{13}C (63 MHz, $CDCl_3$) δ ppm: 135.6-129.6-127.6, 133.9, 131.3, 124.7, 98.3, 72.7, 62.3, 59.8, 45.5-39.3, 39.4, 31.8, 26.9, 26.4, 25.7, 25.1, 21.9, 19.2, 17.7. $[\alpha]_D^{25}$ = - 4.5° (c = 0.2, $CHCl_3$). MS (DCI/NH_3): 495 (M+1, 100%), 512 (M+18, 6%). Analysis (calculated/found): %C 75.10 (75.30), %H 9.42 (9.30).

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14 Epoxyneral **3**: two discrete minima

E (Kcal/mol):	1.02	dihedral angles	$OC^1{\frown}C^2C^3$: 92°	$OC1{\frown}C^2Oep$: 159°	~conf. **II**
	2.54		$OC^1{\frown}C^2C^3$: -125°	$OC1{\frown}C^2Oep$: -58°	~conf. **III**

Epoxygeranial **6** two discrete minima

E (Kcal/mol):	1.36	dihedral angles	$OC^1{\frown}C^2C^3$: 53°	$OC1{\frown}C^2Oep$: 120°	~conf. **I**
	2.74		$OC^1{\frown}C^2C^3$: -130°	$OC1{\frown}C^2Oep$: -63°	~conf. **III**

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