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Diastereoselective Synthesis of (1S,2S,3R,6S) 3-Chloro-3-methyl-6-isopropenyl-1,2-cyclohexanediol via Prins Reaction Induced by Zinc and Trimethylsilyl Chloride.

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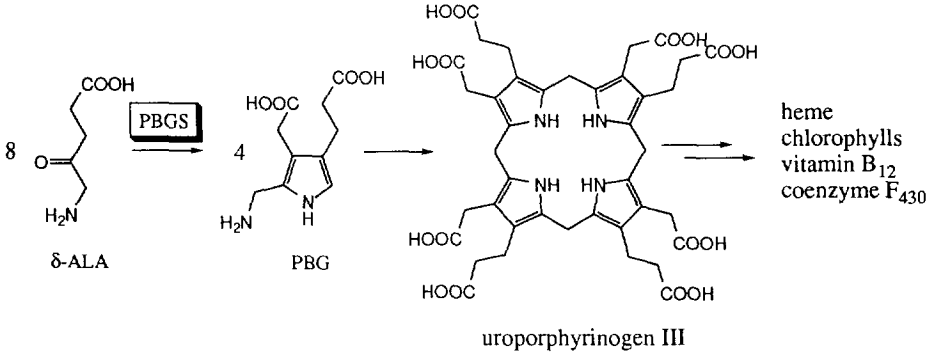
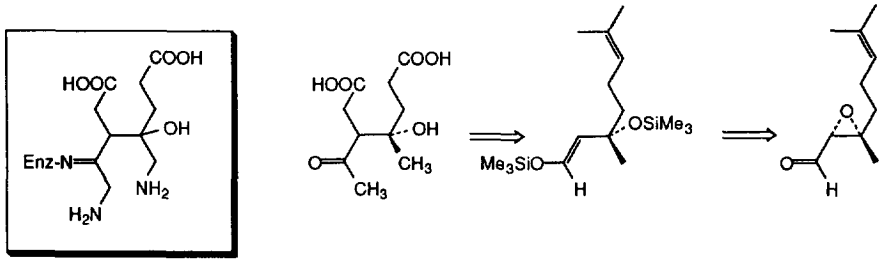
Abstract: While attempting to synthesize a potential inhibitor of the biosynthetic step of formation of PBG, a novel catalytic system inducing the Prins reaction was discovered. Treatment of epoxy geranial with Zn and trimethylsilyl chloride gave (1S,2S,3R,6S) 3-Chloro-3-methyl-6-isopropenyl-1,2-cyclohexanediol in high diastereoselectivity.

Introduction: Porphobilinogen (PBG) is obtained from two molecules of δ-aminolevulinic acid (δ-ALA) through the action of PBG-synthase (PBGS)[1]. Tetrameroidisation[2] of PBG gives uroporphyrinogen III, a tetrapyrrol which is the precursor of heme, chlorophylls, vitamin B_{12} or coenzyme F_{430} (see scheme 1). These tetrapyrrols have also been called the «pigments of life» [3,4] and are essential in many important biochemical transformations. Therefore, PBGS has been intensively studied. Despite this effort, the exact mechanism of formation of PBG is not clear yet and as far as we know, no x-ray structure of the enzyme have been published so far. This lack of knowledge on the structure of the active site lead to several mechanistic proposals for the PBG formation.



Scheme 1: Synthesis of the «pigments of life» from δ-ALA

Shemin postulated a C-C bond formation, *via* an aldol type reaction as the central step for the biosynthetic mechanism of formation of the intermediate **1** without indicating neither the relative nor the absolute configuration at the two chiral centres[5] (see scheme 2). This proposition is not consistent with the Knorr type synthesis of pyrrols, but has a lot of attractive features[6,7]. To obtain evidence of this mechanism we decided to test the inhibitor activity of analogues of this intermediate on PBGS e.g. the enantiomerically pure analogue **2**.



1 2 3 4

Scheme 2: Shemin's proposed intermediate **1** and an enantiomerically pure analogue **2**.

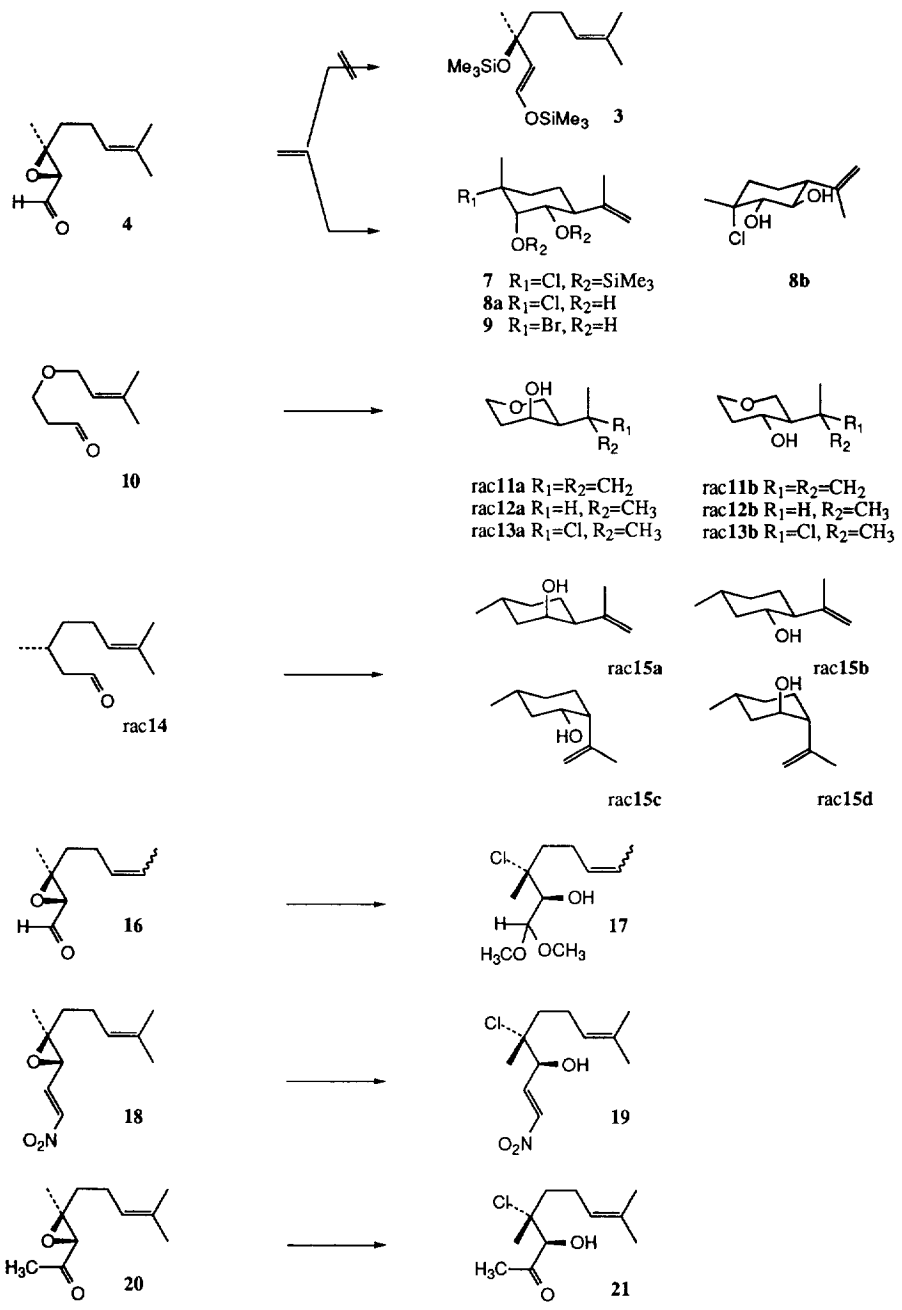
Results and discussion: The retrosynthetic analysis of analogue **2** is shown in scheme 2. Epoxide **4** should be readily available through a Sharpless epoxidation of geraniol[8], followed by an oxidation to the corresponding aldehyde. The acetate chain was to be introduced *via* the enolether **3**. Ozonolysis of the double bond and transformation of the aldehyde into the methyl ketone should give the desired analogue **2** (see scheme 2). Sharpless epoxidation of geraniol **5** gave the epoxialcohol **6** in an 88% yield and in a ee of 87% (analysis by chiral GC[9]). Oxidation of the primary alcohol to the epoxialdehyde **4** could achieved using PDC or MnO_2. The best yields (99%), however were obtained by the Swern oxidation at low temperature.

It was intended to form the silylenolether in a known fashion[10,11], however reduction of the aldehyde **4** with Zn in the presence of TMS-Cl with opening of the epoxide failed to give the expected enolether **3**. The only product isolated and characterised was the cyclised compound **7**, formed via an En- or so called Prins reaction (see scheme 3). The formation of the silylated halohydrine **27** obtained by ring opening of the epoxide (see also scheme 7), could be demonstrated to occur already after 15 min. It is known from literature, that the opening of epoxides by TMS-Cl leads to silylated halohydrines[12]. **27** could then be converted to the cyclised product **7** at room temperature over 5 hours in the presence of Zn and TMS-Cl.

Prins reactions with similar substrates have been reported in several publications using different Lewis acids as catalyst e.g. $SnCl_4$[13], Rh-complexes[14] or enantiomerically pure Zn-complex[15]. Direct transformation of **4** to **8a** and **8b** could be realised in 57% yield by removal of the silylgroups using acidified methanol. Careful separation of the reaction mixture made it possible to isolate the major diastereoisomer **8a** in 52% yield and the minor diastereoisomer **8b** in 5% yield. Compound **9** could be isolated in 44% yield using TMS-Br as catalyst.

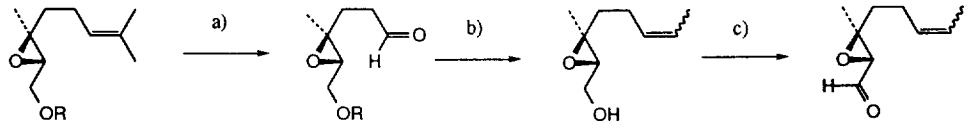
^{1}H-NMR analysis allowed to determine the relative configuration of three of the four chiral centres for both diastereoisomers **8a** and **8b**. However the relative configuration of the methyl and chloro group at C3 for **8a** and **8b** were unambiguously determined by X-ray analysis[16] (figure 1a an 1b). Selective esterification of the equatorial alcohol of **8a** was achieved in the presence of acetic anhydride (2 eq.) and triethylamine (4 eq.) to give 76% of the monoester and 16% of the diester[13].

In order to test the electronic requirement and the diastereoselectivity of the novel variant of the Prins reaction, it was decided to synthesize compound **16** and to observe its behaviour to our reaction conditions. Synthesis of the demethylated epoxy geranial **16** in a cis/trans ratio of 3.3:1 was achieved with a four step sequence, as shown in scheme 4[18]. We tried to obtain the demethylated epoxigeraniol first without protecting the primary alcohol. Submitting the unprotected aldehyde **23** to Wittig conditions leads to complete transformation of the starting material according to TLC, but the yield was quite low (17%). By protecting the primary alcohol as the acetate **22**, the yield of the Wittig reaction could be increased to 37% and the acetate



Scheme 3: Cyclisation experiments with different molecules using Zn and TMS-X (X=Cl, Br, I).

protecting group could be cleaved in situ with treatment of 1.2 eq. of NaOH. Oxidation of the alcohol **25** using a Swern procedure gave the desired product **16** in a 20% overall yield from **6**.



6 R=H
22 R=Ac

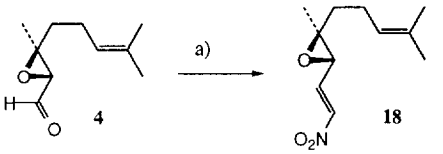
23 R=H
24 R=Ac

25

16

Scheme 4: Synthesis of demethylated **16**. a) Ac_2O, NEt_3, r.t. (99%). b) O_3, DMS, CH_2Cl_2, -78°C, (from **6** 95%, from **22**: 98%). c) BuLi, $[Ph_3PCH_2CH_3]^+Br^-$, THF, 0°C and then NaOH (from **23**: 17%, from **24**: 37%). d) DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, (60%).

Treatment of **16** under the conditions described above did not show any cyclised product on TLC by careful comparison with **7** and **8a** (see scheme 3). The only product detected after quenching of the reaction with methanol was the opened acetal **17** in 9% yield. In parallel, the corresponding methyl ketone[19], obtained by methylation of **4** with methyllitium followed by oxidation, or directly by methylation of **4** with diazomethane, did not show any cyclisation, although opening of the epoxide ring could be observed. The α,β-unsaturated nitroproduct **18**, obtained by addition of nitromethane to the aldehyde **4** (see scheme 5) and formation of the double bond by elimination of the *in situ* formed acetate, did not show any cyclised product either.



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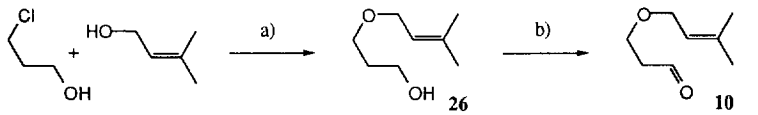
18

Scheme 5: Synthesis of the nitrocompound **18**. a) CH_3NO_2, KF, Isopropanol and then NEt_3, Ac_2O, (51%)



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10

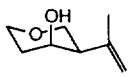
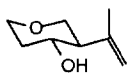
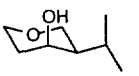
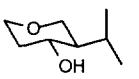
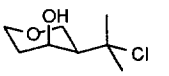
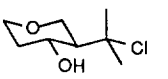
Scheme 6: Synthesis of ether **10**. a) $NaNH_2$, THF, 70°C (31%). b) DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, (87%).

To test if our reaction conditions were compatible with a heteroatom in the newly formed cycle, we synthesized the aldehyde **10**. This was accomplished by adding 1-chloro-3-propanol to a solution of 3-methyl-2-butenol and $NaNH_2$, followed by a Swern oxidation (see scheme 6). The overall yield of these 2 steps was 30%. Submission of the aldehyde **10** to various cyclisation conditions always gave a mixture of two diastereoisomers (see scheme 3). Table 1 shows the product distribution as analysed by GC.

Cyclisation of **10** with TMS-Cl and Zn as catalyst and isolation of the two diastereoisomers on silica gel yielded 21% of the crystalline tetrahydropyrane derivative **13a** and 9% of the oily derivative **13b**. The ^{13}C-NMR and the mass spectrum showed clearly, that we had obtained the addition product of HCl to the isopropenyl group. Furthermore the structure of **13a** was confirmed by X-ray crystallography of the pure sample (figure 1c). Thermal cyclisation of aldehyde **10** at 140°C for 30 min led to a mixture of the two

diastereoisomers **11a** and **11b** in a 43:57 ratio. Cyclisation of **10** with TMS-Br in presence of Zn did not afford any cyclised or halogenated product. However 11% of a mixture of **11a**:**12a**=54:46 and 4% of a mixture of **11b**:**12b**=69:31 could be isolated.

Table 1: Distribution of products obtained by the cyclisation of **10** by thermal reaction and using Zn and TMS-X (X=Cl, Br) as catalyst. a) Detected in GC due to elimination of HCl during the GC-separation from **13a** and **13b** respectively b) Isolated yields.

	11a  **11b** 	**12a**  **12b** 	**13a**  **13b** 
thermally	43 57	- -	
Zn/TMS-Cl in THF	66 a) 28 a)	4 2	21 b) 9 b)
Zn/TMS-Br in THF	40 18	34 8	

A well studied intramolecular Prins reaction is the cyclisation of citronellal (rac**14**). Quite drastic conditions are necessary for the thermal cyclisation (pyrolysis at 180°C for 30h), leading to a mixture of the four possible diastereoisomers of isopulegol (rac**15a** to **15d**). Much milder conditions (zinc halogenides as catalysts in toluene at 10°C) lead to isopulegol (rac**15b**) in 88% to 95% selectivity. We chose this cyclisation as standard and tried our conditions on this Prins reaction. Identification of the products was realised by GC-MS and comparison of the mass spectra with known data or analysis of the pure products by ^{1}H-NMR.

Table 2: Distribution of products obtained by the cyclisation of citronellal using Zn and TMS-X (X=Cl, Br, I). * GC-separation did not permit to distinguish between menthol and neomenthol.

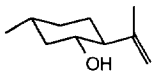
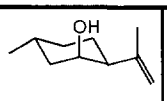
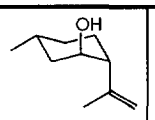
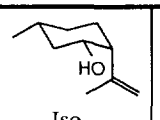
	 Isopulegol rac**15b**	 Neo-isopulegol rac**15a**	Neo-menthol + Menthol*	 Neoiso-isopulegol rac**15d**	 Iso-isopulegol rac**15c**	yield %
$ZnCl_2$ in benzene	88	12	-	-	-	
thermally	63	19	3	6	5	
Zn/TMS-Cl in THF	47	46	3	1	3	51
Zn/TMS-Br in THF	24	55	17	2	2	50
Zn/TMS-I in THF	22	32	39	4	3	38

Table 2 shows the product distribution determined by GC for the different reaction conditions. In accordance with the literature [20], thermal cyclisation yielded isopulegol (rac**15b**) as the major product and neo-isopulegol as the second product,. When the reaction was carried out using $ZnCl_2$ in toluene, isopulegol (rac**15b**) was obtained in 88% as the major diastereoisomer as reported by Nakatani et al[21]. Using the same salts in THF no Prins transformation could be observed. However, under our conditions (Zn, TMS-Cl in THF) 47% of the cyclised product could be isolated. Isopulegol and neoisopulegol are the main products formed in a

1:1 ratio. When the TMS halogenide was changed from TMS-Cl to TMS-Br to TMS-I the Prins reaction still took place but the distribution between the different isomers changed dramatically. Using TMS-I, the reduced products were the major component in the mixture; whereas using TMS-Br neoisopulegol (rac**15a**) was dominant (55%). The catalytic activity of our system in toluene was also tested. Using Zn and TMS-Cl the preference for neoisopulegol was reduced. Using Zn and TMS-Br a multitude of products which could not be characterised were formed. Leaving out the metallic zinc some cyclisation took place, but the formed products were quickly degraded.

The comparison of the effect of $ZnCl_2$ on the cyclisation of citronellal with the reaction of Zn and TMS-Cl clearly shows, that our system behaves differently. The fact that the zinc halogenides are unable to induce the cyclisation in THF, whereas metallic Zn and TMS-Cl only reacts sluggishly in toluene, clearly shows, that two different catalytic species are present, or that different reaction mechanisms are occurring. Changing TMS-Cl to TMS-I, the amount of reduced product drastically increases (3% to 39%). The preference for isopulegol compared to neoisopulegol (ratio 3 to 1) as obtained in the thermal reaction is changed in favour of the neoisopulegol using TMS-halogenides and metallic zinc. Using TMS-Br the ratio of isopulegol to neoisopulegol is almost inverted (1 to 2). That this preference for neoisopulegol is not reinforced when using TMS-I may be due to the reduction to the menthol diastereoisomers.

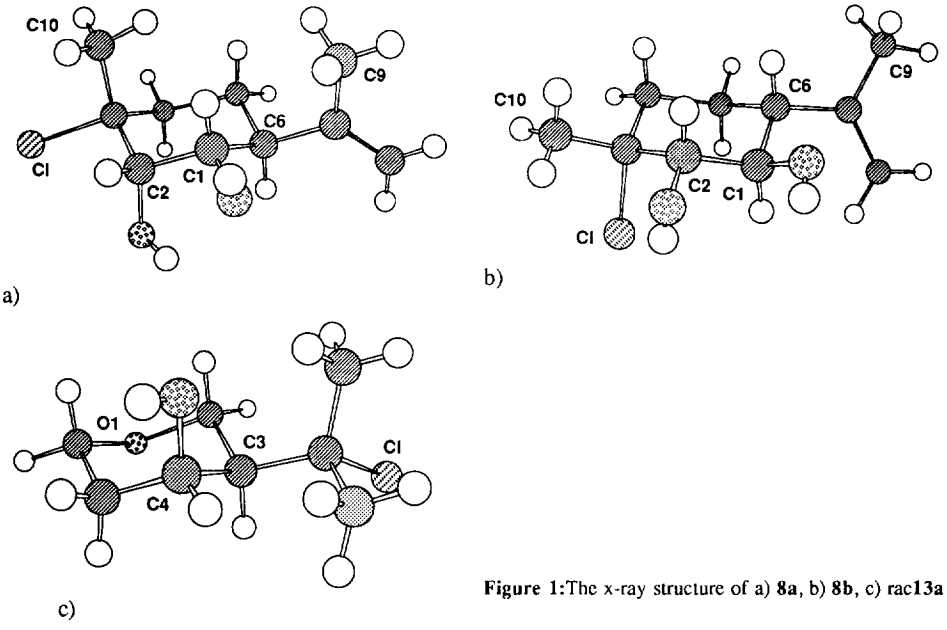


Figure 1: The x-ray structure of a) **8a**, b) **8b**, c) rac**13a**

Corey and co-workers reported cyclisations leading to five membered rings using 20 eq. of zinc and 6 eq. TMS-Cl in the presence of lutidine in THF[22] and proposed a radical mechanism. As the reaction conditions reported by Corey are rather similar to the ones used in our transformation, a radical mechanism could also be envisioned. Under Corey's reaction condition, cyclisation as well as reduction take place, whereas under our reaction condition reduction was only a minor side product at least when using TMS-Cl.

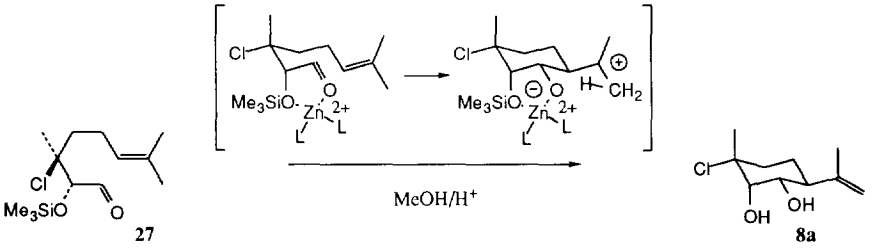
To explain the formation of the diastereoisomers of isopulegol *via* a radical mechanism one is forced to assume that the cyclised isopropyl radical is oxidised to the corresponding carbocation. The cation is then transformed by deprotonation to the olefin. In order to obtain 97% yield of the non reduced product the radical mechanism must be a radical chain and the oxidation process leading to the product must be highly efficient. The only reagent which could act as oxidant for the radical is the starting aldehyde. The redox potential of the

aldehyde and the radical clearly indicate that such an oxidation is not feasible. In order to check experimentally whether a radical chain is compatible with our reaction conditions, we added 1 eq. of BHT to our reaction mixture as a radical trap. No influence on the rate of reaction could be observed and also, the product distribution was identical to our standard conditions.

Therefore, we would favour a Lewis acid catalysed mechanism for the cyclisation similar to the one proposed by Snider et al[23]. Cyclisation goes over a carbenium ion with strong Lewis acids, when addition of the double bond to the carbonyl group is a fast process. Like Snider, we found, that Cl^- is added to the carbenium ion when cyclisation is a fast process as is the case for **10**. We also think that in the cyclisation of citronellal to the isopulegols, an addition of a halogen (especially in the case of TMS-Br and TMS-I) takes place. The so formed intermediate is then immediately reduced with Zn. Neomenthol and menthol are side products which appear using TMS-Br. The reduced products become the main products in the cyclisation with TMS-I (39%). No addition of a halogen can be seen in the cyclisation of **4** to **8a**. The reason for this could be that the rate of the cyclisation process is slower compared to the cyclisations previously described.

The diastereoselectivities observed for the thermal cyclisation of the aldehyde **10** and citronellal (see Table 1 and 2) might be the consequence of a concerted process, where a trans decaline like transition state is preferred. The catalyst in the reaction with $ZnCl_2$ in benzene stays largely undissolved, so that the nature of the catalytic species is difficult to postulate. For our catalytic system the amount of axial alcohol formed from the aldehyde increases when TMS-Cl is replaced by TMS-Br and TMS-I respectively. This observation is in accordance with the results reported by Keck et al[24]. This author could show that increasing the size of the Lewis acid leads to decreased amounts of equatorial alcohol. The reasons for this observation are not really clear, but the experimental results are unquestionable.

Based on these assumptions, the preferred transition state for the formation of the tetra substituted cyclohexane **8a** is shown in scheme 7. After opening of the epoxide, a chelated Zn^{2+}-species is produced in situ from Zn and TMS-Cl. The chelation control leads to a product like trans decaline transition state from which cyclisation occurs via a Prins-reaction.



Scheme 7: Proposed mechanism for the cyclisation of **27** in a trans decaline transition state complexed with Zn^{2+}

For the demethylated epoxy geranial **16** no cyclisation could be observed although the opening of the epoxide occurs smoothly as in the case of epoxy geranial **4**. This fact is probably due to the diminished electron density in the disubstituted double bond of **16** compared with the trisubstituted double bonds for **4**, **10** and citronellal (rac**14**).

EXPERIMENTAL SECTION:

General Procedure.

Reagents were purchased from Fluka. Tetrahydrofurane (THF) was freshly distilled over potassium and benzophenone. Dichloromethane (CH_2Cl_2) was distilled from CaH_2. Unless otherwise specified, all experiments were carried out under a nitrogen atmosphere using anhydrous solvents.

TLCs' were performed on Merck aluminium sheets coated with silica gel 60 F_{254}. Column chromatrographies were performed with silica gel 60 (230-400 mesh, Merck).

^1H NMR spectra and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on a Bruker AMX 400 n.m.r. spectrometer or at 200 MHz and 50 MHz respectively on a Varian Gemini 200 n.m.r. spectrometer. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 170 X (FT) spectrometer. Mass spectra (MS) were obtained using a Nermag R30-10; Chemical ionisation (CI) utilising NH_3 as reactant gas and electronic impact (EI) operated with 70 eV. GC-MS spectra were run on a Hewlett Packard 5890 series chromatograph linked to a HP 5971A mass selective detector. The results were analysed using the Wiley library.

Synthesis of 4 and cyclisation to 8a, 8b and 9.

(2R,3S) 3,7-Methyl-2,3-epoxi-6-octenal (4). Typical Swern - type oxidation procedure: In a three necked flask equipped with thermometer, septum 300 ml of dried CH_2Cl_2 are introduced under nitrogen and cooled to -60°C. Via a syringe oxalyl chloride (19.01g, 150 mmol, 1.5eq) is introduced and then DMSO (23.40g, 300 mmol, 3eq) is slowly added, causing vigorous gas formation. The mixture is stirred for 15 minutes and epoxy geraniol (**6**) (17g, 100 mmol, 1eq) is introduced. The clear solution turns opaque after 15 minutes. Triethylamine (30.31g, 299.56mmol, 3eq) is added and the reaction mixture is allowed to warm to r.t. 300 ml of water are added and the aqueous phase is extracted twice with CH_2Cl_2, the combined organic layers are washed with 200 ml of 0.5% HCl until the aqueous phase stays acid. After washing the organic phase with 200 ml of 1%$NaHCO_3$ it is dried over $MgSO_4$, the solvent is eliminated and the product is dried at high vacuum which leads to 16.66g (99%) of NMR pure **4**. R_f (hexane/EtOAc=3/1, $KMnO_4$) 0.44. n_D 1.464(8). **IR** (film) 2858s (ν CO-H); 2729w (ν CO-H); 1723 (ν C=O); 1678w (ν C=C); 1239w (oxiran). **^1H-NMR** (400 MHz, $CDCl_3$) 9.44 (d, $^3J(1,2)$=5.0, 1H, HC(1)); 5.05 (br.t, $^3J(6,5)$=7.1, 1H, HC(6)); 3.17 (d, $^3J(2,1)$=5.0, 1H, HC(2)); 2.09 (Ψq, J=7.6, 2H, HC(5)); 1.71 (dt, $^2J(4a,4b)$=14.1, $^3J(4a,5)$=7.6, 1H, HaC(4)); 1.68 (s, 3H, $H_3C(8)$); 1.59 (s, 3H, HC(8')); 1.54 (dt, $^2J(4b,4a)$=14.0, $^3J(4b,5)$=8.1, 1H, HbC(4)); 1.43 (s, 3H, CH_3). **^{13}C-NMR** (100 MHz, $CDCl_3$) 200.2 (C1); 133.4 (C7); 123.3 (C6); 64.8 (C3); 64.2 (C2); 39.0 (C4); 26.3 (C8); 24.1 (C5); 18.3 (C8'); 17.9 (CH_3). **CI-MS** 186 (59,M+NH_4^+); 169 (16, M^++1); 151 (16, M^++1-H_2O) 139 (38); 123 (30); 109 (100, $(CH_3)_2C{=}CHCH_2CH_2C^+{=}CH_2$); 69 (29, $(CH_3)_2C{=}CHCH_2^+$) 58 (17); 55 (7, $(CH_3)_2C{=}CH^+$).

(1S,2S,3R,6S) 3-Chloro-3-methyl-6-isopropenyl-1,2-cyclohexanediol (8a) and (1R,2S,3R,6R) 3-Chloro-3-methyl-6-isopropenyl-1,2-cyclohexanediol (8b): In a two necked dried flask equipped with a septum were introduced under nitrogen atmosphere Zn (0.389g, 5.9 mmol, 0.5eq) and 10 ml THF (dried over potassium). After the addition of TMS-Cl (2.58g, 23.8mmol, 2eq) the mixture was stirred for 15 min. During 2 min a solution of aldehyde **4** (2g, 11.9mmol, 1eq) in 1 ml THF is added dropwise to the stirred mixture at room temperature, and allowed to stir for 5 hours. To quench the reaction a solution of methanol/1M aqueous HCl (9:1) was added and the reaction mixture was stirred for another 10 hours. After addition of 50 ml of water, the aqueous phase was extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and the solvent evaporated, leaving 2.531g of crude product. The products were purified chromatographically (hexane/EtOAc = 2/1) yielding 1.255g (52%) of diastereoisomer **8a** and 0.119g (5%) of diastereoisomer **8b**.

Diastereoisomer **8a**: R_f (hexane/EtOAc=2/1, $KMnO_4$) 0.22. **mp.** 94-95°C. **IR** (KBr) 3458s (OH); 1645m (C=C);. **^1H-NMR** ($CDCl_3$, 200MHz) 4.92 (dq, $^2J(8b,8a)$=1.6, $^4J(8b,9)$=1.6, 1H, HbC(8)); 4.88-4-87 (m, 1H, HaC(8)); 3.93-3.91 (m, 1H, HC(2)); 3.69 (ddd,$^3J(1,6)$=11.0, $^3J(1,2)$=2.6, $^3J(1,OH)$=2.3, 1H, HC(1)); 2.67 (m, 1H, HOC(2))*; 2.48 (ddd, $^3J(6,5a)$=12.4, $^3J(6,1)$=10.8, $^3J(6,5b)$=4.5, 1H, HC(6)); 2.31 (ddd, $^2J(4a,4b)$=13.4, $^3J(4a,5a)$=13.4, $^3J(4a,5b)$=4.7, 1H, HaC(4)); 2.21 (d, $^3J(OH,1)$=7.7, 1H, HOC(1))*; 1.85 (dddd, $^2J(4b,4a)$=13.1, $^3J(4b,5a)$=4.0, $^3J(4b,5b)$=2.7, $^4J(4b,2)$=1.3, 1H, HbC(4)); 1.74 (d, $^4J(9,8b)$=1.4, 3H, HC(9)); 1.67 (s, 3H, HC(10)); 1.63 (dddd, $^2J(5b,5a)$=14.1, $^3J(5b,4a)$=4.5, $^3J(5b,6)$=4.5, $^3J(5b,4b)$=3.0, 1H, HbC(5)); 1.40 (dddd, $^2J(5a,5b)$=13.8, $^3J(5a,4a)$=13.8, $^3J(5a,6)$=12.5, $^3J(5a,4b)$=3.8, 1H, HaC(5)). **^{13}C-NMR** ($CDCl_3$, 200 MHz) 146.0 (C7); 113.9 (C8); 77.6 (C2); 75.2 (C3); 70.7 (C1); 46.4 (C6); 36.0 (C4); 27.4 (C5); 27.3 (C10); 19.9 (C9). **CI-MS** 204, 206 (2,1, M^+); 186, 188 (22,7, M+-

H_2O); 151 (70, M^+-H_2O-HCl); 109 (32); 95 (46); 84 (59); 67 (72); 55 (47); 43 (100). **Elemental analysis** calc: C 58.68, H 8.37, Cl 17.32; found: C 58.61, H 8.49, Cl 17.32. * exchange with D_2O

Diastereoisomer **8b**: R_f (hexane/EtOAc=2/1, $KMnO_4$) 0.10. **mp** 103.5°-104.6°C. **IR** (KBr) 3477s (OH); 1652m (C=C). **^{1}H-NMR** ($CDCl_3$, 400MHz) 4.92 (quint, J=1.6, 1H, HaC(8)); 4.88 (sept, J=0.8, 1H, HbC(8)); 3.66 (dd, ^{3}J(1,6)=10.3, ^{3}J(1,2)=8.8, 1H, HC(1)); 3.24 (d, ^{3}J(2,1)=8.8, 1H, HC(2)); 2.15-1.7 (br.s, 2H, OH); 2.14-2.08 (m, 2H, HaC(4), HC(6)); 1.89 (ddt, ^{2}J(5a,5b)=13.5, ^{3}J(5a,4b)=3.3, ^{3}J(5a,4a) = ^{3}J(5a,6)=12.7, 1H, HaC(5)); 1.77 (dd, ^{4}J(9,8a)=1.4, ^{4}J(9,8b)=0.8, 3H, H_3C(9)); 1.75 (ddd, ^{2}J(4b,4a)=14.5, ^{3}J(4b,5a)=3.8, ^{3}J(4b,5b)=1.6, 1H, HbC(4)); 1.69 (s, 3H, H_3C(10)); 1.57 (ddt, ^{2}J(5b,5a)=13.5, ^{3}J(5b,4b)=2.9, ^{3}J(5b,4a) = ^{3}J(5b,6)=3.8, 1H, HbC(5)). **^{13}C-NMR** (100MHz, $CDCl_3$, HETCOR) 145.9 (C7); 113.8 (C8); 80.9 (C2); 75.9 (C3); 73.4 (C1); 52.1 (C6); 40.2 (C4); 30.7 (C10); 26.4 (C5); 19.8 (C9). **CI-MS** 223, 225 (15, 7, M+NH_4^++1); 222, 224 (85, 41, M+NH_4^+); 187 (1); 170 (1); 151 (1); 133 (8); 91 (6); 82 (51); 68 (100).

(1S,2S,3R,6S) 3-Bromo-3-methyl-6-isopropenyl-1,2-cyclohexanediol (9): 1g (5.94mmol, 1eq) of aldehyde **4** is treated at r.t. during 5h with Zn (0.194g, 2.97mmol, 0.5eq) and TMS-Br (1.820g, 11.89mmol, 2eq) yielding after recrystallisation from hexane 0.653g (44%) of **9**. R_f (hexane/EtOAc=2/1, $KMnO_4$) 0.29 . **mp.** 97.5°-99°C (degradation 130°C). **IR** (KBr) 3560m; 3376s (OH) 3079w; 2946s; 2892m; 1645m (C=C); 1446m; 1403s; 1379s; 1108s; 1083m; 1042s; 888m; 653m. **^{1}H-NMR** (400MHz, $CDCl_3$). 4.91-4.90 (m, 1H, H_aC(8)); 4.86 (m, 1H, H_bC(8)); 4.01 (br. s, 1H, HC(2)); 3.74 (ddd, ^{3}J(1,6)=10.6, ^{3}J(1,OH)=7.6, ^{3}J(1,2)=2.8, 1H, HC(1)); 2.70 (m, 1H, HOC(2))*; 2.52 (dt, ^{3}J(4a,5b)=4.8, ^{2}J(4a,4b) = ^{3}J(4a,5a)=13.3, 1H, H_aC(4)); 2.49 (ddd, ^{3}J(6,5b)=4.6, ^{3}J(6,1) = 11.0, ^{3}J(6,5a)=12.3, 1H, HC(6)); 2.33 (d, ^{3}J(OH,1)=7.7, 1H, HOC(1))*; 2.01 (dddd, ^{2}J(4b,4a)=13.1, ^{3}J(4b,5a)=3.9, ^{3}J(4b,5b)=2.8, ^{4}J(4b,2)=1.2, 1H, H_bC(4)); 1.90 (s, 3H, H_3C(10)); 1.73 (dd, ^{4}J(9,8a)=1.3, ^{4}J(9,8b)=0.8, 3H, H_3C(9)); 1.54 (ddt, ^{2}J(5b,5a)=14.1, ^{3}J(5b,4b)=3.0, ^{3}J(5b,4a) = ^{3}J(5b,6)=4.7, 1H, H_bC(5)); 1.44 (dddd, ^{2}J(5a,5b)=14.0, ^{3}J(5a,4a)=13.4, ^{3}J(5a,6)=12.6, ^{3}J(5a,4b)=3.8, 1H, H_aC(5)). **^{13}C-NMR** (100MHz, $CDCl_3$, APT) 146.1 (C7); 114.0 (C8); 78.2 (C2); 73.4 (C3); 69.9 (C1); 46.5 (C6); 37.4 (C4); 28.6 (C10); 28.0 (C5); 19.9 (9). **EI-MS** 249, 251 (3, 3, M^++1); 248, 250 (2, 3, M^+); 231, 233 (5, 6, M^++1-H_2O); 230, 232 (4, 4, M^+-H_2O); 169 (7, M^+-Br); 151 (70); 123 (100); 107, 109 (52,53); 93, 95 (43, 43); 81 (87); 67 (41). *exchange with D_2O.

Synthesis of 10 and cyclisation to 11a, 11b, 13a and 13b.

1-(3-Methyl-2-buten)-3-hydroxypropanether (26): To a suspension of 13.6g $NaNH_2$ (343.48mmol, 1.5eq, stocked in toluene) in 150 ml THF 20g of 3-methyl-2-buten-1-ol (10g, 232.2mmol, 1eq) were carefully added. After the addition, the temperature was brought to 70°C and the suspension was stirred for 30 minutes. At this temperature 21.96g 3-chloro-1-propanol (232.2mmol, 1eq) were added. The reaction mixture was stirred for 1 hour, while NaCl was forming. After cooling to r.t., the reaction mixture was poured on to 400 ml of water and the aqueous phase was extracted three times with 100 ml EtOAc. The organic phase was dried over $MgSO_4$ and evaporated to give 28.83g (86%) of crude product. Fractionated distillation (12 mbar, 75-105°C) over a 10 cm vigreux column gave 10.36g (31%) of pure product. n_D 1.450(2). **IR** (film) 3392s (OH); 1676w (C=C);. **^{1}H-NMR** ($CDCl_3$, 200MHz) 5.33 (t septet ^{3}J(6,5)=6.9, ^{4}J(6,8)=^{4}J(6,8')=1.4, 1H, HC(6)); 3.96 (d, ^{3}J(5,6)=6.7, 2H, HC(5)); 3.77 (Ψq, ^{3}J(1,2) = ^{3}J(1,OH)=5.5, 2H, HC(1)); 3.60 (t, ^{3}J(3,2)=5.8, 2H, HC(3)); 2.44 (t, ^{3}J(OH,1)=5.1, 1H, OH)* 1.83 (quint., ^{3}J(2,1)=^{3}J(2,3)=5.7, 2H, HC(2)); 1.74 (s, 3H, CH_3(8)); 1.67 (s, 3H, CH_3(8')). **^{13}C-NMR** (100MHz, $CDCl_3$) 137.8 (C7); 121.6 (C6); 69.9 (C3); 68.3 (C5); 62.8 (C1); 32.8 (C2); 26.4 (C8); 18.7 (C8'). **EI-MS** 145 (7, M^++1); 144 (4, M^+); 143 (28); 129 (9); 85 (100); 84(65); 83 (75); 71 (50); 69 (37); 55 (64); 41 (65).* exchange with D_2O

1-(3-Methyl-2-buten)-3-propanalether (10): 19.10g (63.10mmol, 1eq) of alcohol **26** was subjected to a Swern-type oxidation yielding after washing the aqueous phase with 1M HCl, twice with 200 ml of 10% K_2CO_3 and finally with 100 ml of water 8.78g (98%) of NMR-pure aldehyde **10**. R_f (hexane/EtOAc=1/1, $KMnO_4$) 0.72. n_D 1.446(8). **IR** (film) 1728s (C=O); 1677w (C=C) **^{1}H-NMR** ($CDCl_3$, 400MHz) 9.78 (t, ^{3}J(1,2)=1.8, 1H, HC(1)); 5.32 (br.t, ^{3}J(6,5)=6.9, 1H, HC(6)); 3.97 (d, ^{3}J(5,6)=6.9, 2H, HC(5)); 3.74 (t, ^{3}J(3,2)=6.1, 2H, HC(3)); 2.66 (td, ^{3}J(2,3)=6.1, ^{3}J(2,1)=1.8, 2H, HC(2)); 1.73 (s, 3H, CH_3(8)); 1.66 (s, 3H, CH_3(8')). **^{13}C-NMR** ($CDCl_3$, 100MHz) 201.9 (C1); 138.1 (C7); 121.3 (C6); 68.2 (C5); 64.2 (C3); 44.6 (C2); 26.4 (C8); 18.7 (C8'). **EI-MS** 143 (2, M^++1); 142 (1, M^+); 141 (3); 127 (41); 85 (100); 71 (98); 69 (78); 67 (34); 57 (38); 55 (29); 41 (83).

Thermal cyclisation of 10: (3RS,4SR) 4-Hydroxy-3-isopropenyl-tetrahydropyrane (racl1a) and (3RS,4RS) 4-Hydroxy-3-isopropenyl-tetrahydropyrane (racl1b): In a sealed tube 1g of aldehyde **10** is heated for 1h at 140°C. The crude product is analysed by GC-MS. Column

chromatography first on silica gel and then on reversed phase (C18, MeOH/H_2O=2/1) lead to 0.004g of rac**11a** and 0.011g of rac**11b**.

Diastereoisomer rac**11a** R_f (silica gel, heptane/EtOAc=1/1, $KMnO_4$) 0.23. **IR** 3441s (OH); 1646m (C=C). **^{1}H-NMR** ($CDCl_3$, 400MHz, COSY) 4.99 (quint, ^2J(8a,8b) = ^4J(8a,9)=1.4, HaC(8)); 4.63 (m, 1H, HbC(8)); 4.10 (q, ^3J(4,3) = ^3J(4,5a) = ^3J((4,5b)=2.8, 1H, HC(4)); 3.77 (dt, ^3J(6a,5b)=3.2, ^2J(6a,5a) = ^2J(6a,6b)=11.5, 1H, HaC(6)); 3.76 (t, ^2J(2a,2b) = ^3J(2a,3)=11.3, 1H, HaC(2)); 3.74-3.69 (m, 1H, Hb(6)); 3.69 (dd, ^2J(2b,2a)=11.0, ^3J(2b,3)=4.4; 1H, HbC(2)); 2.36 (dt, ^3J(3,2a)=11.3, ^3J(3,2b) = ^3J(3,4)=2.1, 1H, HC(3)); 1.86 (dddd, ^2J(5a,5b)=14.1, ^3J(5a,6a)=11.3, ^3J(5a,6b)=5.6, ^3J(5a,4)=2.8, 1H, HC(5)); 1.83-1.78 (m, 1H, HbC(5)); 1.79 (s, 3H, H_3C(9)); 1.74 (s, 1H, OH). **^{13}C-NMR** ($CDCl_3$, 100MHz) 144.5 (C7); 112.9 (C8); 65.7 (C4); 64.0 (C2); 63.1 (C6); 47.8 (C3); 32.8 (C5); 23.6 (C9). **GC/CI-MS** 160 (100, M+NH_4^+); 143 (47, M^++1); 142 (16, M^+); 127 (2); 125 (9, M^++1-H_2O); 92 (3); 86 (19); 69 (11); 68 (71); 52 (14).

Diastereoisomer rac**11b** R_f (silica gel, heptane/EtOAc=1/1, $KMnO_4$) 0.29. **IR** 3408s (OH); 1646m (C=C). **^{1}H-NMR** ($CDCl_3$, 400MHz) 5.00 (dq, ^2J(8a,8b) = ^4J(8a,9)=1.5, 1H, HaC(8)); 4.92 (m, 1H, HbC(8)); 4.02 (ddt, ^2J(6b,6a)=11.7, ^3J(6b,5a)=4.8, ^3J(6b,5b)= ^4J(6b,2b)=1.5, 1H, HbC(6)); 3.88 (ddd, ^2J(2b,2a)=11.5, ^3J(2b,3)4.4, ^4J(2b,6b)=1.1, 1H, HbC(2)); 3.73 (dt, ^3J(4,5b)=4.6, ^3J(4,3)= ^3J(4,5a)=10.3, 1H, HC(4)); 3.43 (dt, ^3J(6a,5b)=2.2, ^2J(6a,6b)= ^3J(6a,5a)=12.2, 1H, HaC(6)); 3.21 (t, ^2J(2a,2b)= ^3J(2a,3)=11.3, 1H, HaC(2)); 2.23 (dt,^3J(3,2b)=4.4, ^3J(3,2a)= ^3J(3,4a)=10.6, 1H, HC(3)); 1.98 (ddt, ^2J(5b,5a)=12.8, ^3J(5b,4)=4.7, ^3J(5b,6a)= ^3J(5b,6b)=2.0, 1H, HbC(5)); 1.88 (br.s, 1H, OH); 1.75 (t, ^4J(9,8a)= ^4J(9,8b)=1.1, 3H, H_3C(9)); 1.63 (ddt, ^3J(5a,4)=10.7, ^3J(5a,6b)=4.9, ^2J(5a,5b)= ^3J(5a,6a)=12.7, 1H, HaC(5)). **^{13}C-NMR** ($CDCl_3$, 100MHz, HETCOR) 142.9 (C7); 114.8 (C8); 70.8 (C2); 69.9 (C4); 67.6 (C6); 54.2 (C3); 34.8 (C5); 21.6 (C9). **GC/CI-MS** 160 (63, M+NH_4^+); 143 (100, M^++1); 142 (7, M^+); 127 (15); 125 (4, M^++1-H_2O); 92 (14); 86 (100); 69 (18); 68 (2); 52 (8).

(3RS,4SR) 4-Hydroxy-3-(1-chloro-isopropyl)-tetrahydropyrane (rac13a) and (3RS,4RS) 4-Hydroxy-3-(1-chloro-isopropyl)-tetrahydropyrane (rac13b): 1.50g (10.55mmol, 1eq) of aldehyde **10** is placed at 0°C and during 30 min, under our cyclisation conditions using Zn (0.35g, 5.27mmol, 0.5eq) and TMS-Cl (3.44g, 31.65mmol, 3eq). Purification over column 0.35g (21%) of rac**13a** and 0.15g (9%) of rac**13b** were obtained.

Diastereoisomer rac**13a**: R_f (hexane/EtOAc=4/1, $KMnO_4$) 0.18. **mp.** 69°-71°C. **IR** (KBr) 3382s (OH). **^{1}H-NMR** ($CDCl_3$, 400MHz and COSY) 4.50 (br.s, 1H, HC(4)); 3.97 (dd, ^2J(2b,2a)=11.2, ^3J(2b,3)=4.1, 1H, HbC(2)); 3.87 (t, ^2J(2a,2b) = ^3J(2a,3)=11.0, 1H, HaC(2)); 3.82 (dt, ^3J(6a,5b)=2.3, ^2J(6a,6b) = ^3J(6a,5a)=12.5, 1H, HaC(6)); 3.73 (br.dd, ^2J(6b,6a)=11.5, ^3J(6b,5a)=5.2, 1H, HbC(6)); 2.08 (br.s, 1H, OH); 1.93(ddd, ^3J(3,2a)=10.9, ^3J(3,2b)=4.1, ^3J(3,4)=2.1, 1H, HC(3)); 1.84 (dddd, ^2J(5a,5b)=13.9, ^3J(5a,6a)=12.7, ^3J(5a,6b)=5.5, ^3J(5a,4)=2.6, 1H, HaC(5)); 1.7 (m, 1H, HbC(5)); 1.68 (s, 3H, CH_3); 1.66(s, 3H, CH_3). **^{13}C-NMR** ($CDCl_3$, 100MHz and HETCOR) 72.2 (C7); 65.7 (C4); 64.5 (C2); 62.9 (C6); 51.7 (C3); 35.3 (C5); 32.6 (CH_3); 32.2 (CH_3). **CI-MS** (NH_4^+) 197, 199 (11, 4); 196, 198 (100, 36, M+NH_4^+); 179, 181 (1, <1, M^++1); 160 (97, M+NH_4^+-HCl), 142 (12); 125 (2). **Elemental analysis** calc: C 53.78, H 8.46, Cl 19.84; found: C 53.86, H 8.43, Cl 19.45.

Diastereoisomer rac**13b**: R_f (hexane/EtOAc=4/1, $KMnO_4$) 0.13. **IR** (film) 3426s (OH). **^{1}H-NMR** ($CDCl_3$, 400MHz) 4.17 (dd, ^2J(2b,2a)=11.7, ^3J(2b,3)=4.3, 1H, HbC(2)); 3.97 (dt, ^3J(4,5b)=4.8, ^3J(4,3) = ^3J(4,5a)=10.0, 1H, HC(4)); 3.9 (m, 1H, HbC(6)); 3.38 (dt, ^3J(6a,5b)=2.4, ^2J(6a,6b) = ^3J(6a,5a)=11.8, 1H, HaC(6)); 3.20 (dd, ^2J(2a,2b)=11.1, ^3J(2a,3)=11.1, 1H, HaC(2)); 2.07 (br.s, 1H, OH); 1.98-1.92 (m, 2H, HbC(5), HC(3)); 1.92 (ddd, ^3J(3,4)=10.3, ^3J(3,2a)=10.3, ^3J(5,2b)=4.4, 1H, HC(3)); 1.72 (s, 3H, CH_3); 1.72-1.62 (m, 1H, HaC(5)); 1.69 (s, 3H, CH_3). **^{13}C-NMR** ($CDCl_3$, 100MHz and DEPT 135) 73.0 (C7); 70.6 (C4); 68.6 (C2); 67.2 (C6); 54.8 (C3); 36.5 (C5); 33.2 (CH_3); 32.9 (CH_3). **CI-MS** (NH_4^+) 196, 198 (29, 9 M+NH_4^+); 179, 181 (4, 2, M^++1); 160 (100, M+NH_4^+-HCl); 143 (17); 127 (21).

Cyclisation of Citronellal (rac14).

Thermal cyclisation of citronellal: In a round bottom flask (3g, 19.45mmol) of citronellal (rac**14**) are introduced and heated for 30h at 180°C. The crude product is analysed by GC-MS by doping with commercial product and comparison with the Wiley data base (see table 2). Purification over a silica gel column leads to 0.984g (47%) of the two main products isopulegol (**15b**) and neoisopulegol (**15a**).

Cyclisation of citronellal with Zn and TMS-X (X=Cl, Br, I): citronellal (rac**14**) (1.5g, 9.72mmol, 1eq) was placed at r.t. and for 1h, under our cyclisation condition with zinc (0.318g, 4.86mmol,

0.5eq) and TMS-X (TMS-Cl: 1.09g, 9.72mmol, 1eq; TMS-Br: 1.527g, 9.72mmol, 1eq; TMS-I: 1.984, 9.72mmol, 1eq) in 5 ml THF yielding a mixture of pulegols which were analysed by GC (see table 2).

Synthesis of 16 and transformation to 17.

(4S,5R) 6-Acetyl-4,5-epoxy-4-methylhexanal (24): 3.70g (17.4mmol, 1eq) of olefin **22** were dissolved in 70 ml of CH_2Cl_2 and ozonised at -78°C until the solution turned blue. 3.25g (52.3mmol, 3eq) of DMS were then added and the reaction mixture allowed to warm up to room temperature. The solution was poured onto 300 ml of water and the organic phase separated while the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated at the rotary evaporator. The crude product (3.30g 102%) was filtered over silica gel (hexane/EtOAc = 2:1) which afforded 3.18g (98%) of pure material. **IR** (film) 1741s (C=O); 1235s (C-O). **^{1}H-NMR** ($CDCl_3$, 400MHz) 9.75 (brs. 1H, CHO); 4.28 (dd, ^{2}J(6a,6b)=12.1, ^{3}J(6a,5)=4.4, 1H, HaC(6)); 4.03 (dd, ^{2}J(6b,6a)=12.1, ^{3}J((6b,5)=6.6, 1H, HbC(6)); 2.98 (dd, ^{2}J(5,6a)=4.4, ^{2}J((5,6b)=6.6, 1H, HC(5)); 2.52 (td, ^{3}J(2,3)=7.4, ^{3}J(2,1)=1.1, 2H, HC(2)); 2.09 (s, 3H, CH_3COO); 1.95 (td, ^{2}J(3a,3b)=14.5, ^{3}J(3a,2)=7.4, 1H, HaC(3)); 1.88 (td, ^{2}J(3b,3a)=14.5, ^{3}J(3b,2)=7.4, 1H, HbC(3)); 1.30 (s, 3H, CH_3). **^{13}C-NMR** ($CDCl_3$, 200MHz) 201.5 (C1); 171.5 (CO_2); 63.7 (C6); 60.3 (C4); 60.0 (C5); 39.5 (C2); 30.5 (C3); 21.4 (CH_3COO); 17.8 (CH_3). **CI-MS** (NH_4^+) 187 (89,M$^+$+1); 169 (15); 127 (44); 109 (100); 84 (49).

(2R,3S) 2,3-Epoxy-1-hydroxy-3-methyl-6-octene (25 cis and trans): 3.95g (10.63mmol, 1.2eq) of ethyltriphenylphosphonium-bromide were suspended in 70 ml of THF. Under a nitrogen atmosphere 9.4 ml (15.06mmol, 1.7eq) of a 1.6M buthyllithium solution in hexane were introduced, at 0°C, during 15 minutes. The solution was stirred for 15 minutes, then 1.65g (8.86mmol, 1eq) of aldehyde **24** were added via a syringe. The deep red solution became white and a precipitate was formed. After stirring for 17h at 0°C the reaction mixture was quenched by the addition of 30 ml of brine and 40 ml of water. The organic layer was separated and the aqueous phase extracted three times with EtOAc. The solvent of the combined organic layers was evaporated and the residue (3.04g) dissolved in 1 ml of methanol. 3.65 ml (10.63mmol, 1.2eq) of a NaOH solution (1.4g NaOH in 10 ml of methanol and 2 ml H_2O) were added and the reaction mixture was stirred at room temperature for 40 minutes. After adding 40 ml of brine the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated to afford 2.46g of product. Purification by column chromatography over silica gel (hexane/EtOAc = 2:1) gave 0.427g (31%) of pure **25**. The fraction R_f = 0.46 (silica gel, hexane/EtOAc=2/1, $KMnO_4$, 0.336g) was dissolved in 1 ml methanol and sapponified a second time with 1.2 ml of NaOH solution. After silica gel purification another 0.081g (6%) of pure **25** could be obtained (cis/trans=69/21). R_f (silica gel, hexane/EtOAc=2/1, $KMnO_4$) 0.16. **IR** (film) 3415s (OH); 1657w (C=C). **^{1}H-NMR** ($CDCl_3$, 400MHz) 5.47 (dqt, ^{3}J(7,6)=10.8, ^{3}J(7,8)=6.7, ^{4}J(7,5)=1.5, 1H, HC(7cis)); 5.35 (dtq, ^{3}J(6,7)=10.7, ^{3}J(6,5)=7.1, ^{4}J(6,8)=1.7, 1H, HC(6cis)); 3.86-3.78 (m, 1H, HaC(1cis), HaC(1trans)); 3.71-3.66 (m, 1H, HbC(1cis), HbC(1trans)); 2.99 (dd, ^{3}J(2.1b)=6.7, ^{3}J(2,1a)=4.3, 1H, HC(2cis)); 2.96 (dd, ^{3}J(2,1b)=6.7, ^{3}J(2,1a)=4.3, 1H, HC(2trans)); 2.15 (Ψq, J=7.6, 2H, HC(5cis)); 2.11-2.03 (m, 2H, HC(5trans)); 1.84 (brt, 1H, OH); 1.71 (dt, ^{2}J(4a,4b)=13.8, ^{3}J(4a,5)=7.6, 1H, HaC(4cis)); 1.64 (ddt, ^{3}J(8,7)=5.9, ^{4}J(8,6)=1.1, ^{5}J(8,5)=1.3, 3H, HC(8trans)); 1.61 (ddt, ^{3}J(8,7)=6.7, ^{4}J(8,6)=1.7, ^{5}J(8,5)=0.9, 3H, HC(8cis)); 1.51 (ddd, ^{2}J(4b,4a)=13.7, ^{3}J(4b,5a)=8.7, ^{3}J(4b,5b)=7.6, 1H, HbC(4cis)); 1.31 (s, 3H, HC(9cis)); 1.28 (s, 3H, HC(9trans)). **^{13}C-NMR** ($CDCl_3$, 200MHz) 130.9 (C6trans); 130.0 (C6cis); 126.2 (C7trans); 125.2 (C7cis); 63.6 (C2trans); 63.6 (C2cis); 62.1 (C1cis and trans); 61.7 (C3cis and trans); 39.1 (C4trans); 38.8 (C4cis); 28.9 (C5trans); 23.2 (C5cis); 18.5(C8trans); 17.4 (C9cis and trans); 13.4 (C8cis). **CI-MS** (NH_4^+) 174 (16, M+NH_4^+); 157 (22, M$^+$+1); 139 (65); 121 (39); 109 (25); 95 (96); 81 (100).

(2R,3S) 2,3-Epoxy-3-methyl-6-octenal (16 cis and trans): The Swern type oxidation procedure followed the procedure described for the synthesis of **4** from **6** yielding after purification over silica gel (hexane/EtOAc = 3:1) 0.177g (60%, cis/trans=67/23) of pure product starting from 0.300g of alcohol **25** ($(COCl)_2$: 0.366g, 2.88mmol, 1.5eq, DMSO: 0.630g, 8.07mmol, 4.2eq). R_f (silica gel, hexane/EtOAc=2/1, $KMnO_4$) 0.47. **IR** (film) 1723s (C=O); 1658w (C=C); **^{1}H-NMR** ($CDCl_3$, 400MHz) 9.46 (d, ^{3}J(1,2)=5.0, 1H, HC(1cis)); 9.45(d, ^{3}J(1,2)=4.9, 1H, HC(1trans)); 5.50 (dqt, ^{3}J(7,6)=10.7, ^{3}J(7.8)=6.8, ^{4}J(7.5)=1.6, 1H, HC(7cis)); 5.34 (dtq, ^{3}J((6,7)=10.7, ^{3}J(6,5)=7.2, ^{4}J(6,8)=1.8, 1H, HC(6cis)); 3.20 (d, ^{3}J(2,1)=5.0, 1H, HC(2cis)); 3.17 (d, ^{3}J(2,1)=5.0, 1H, HC(2trans)); 2.16(Ψq, J=7.8, 2H, HC(5cis)); 2.13-2.07 (m, 2H, HC(5trans)); 1.75 (dt, ^{2}J(4a,4b)=13.9, ^{3}J(4a,5)=7.7, 1H, HaC(4cis)); 1.65 (dq, ^{3}J(8,7)=6.1, ^{4}J(8,6) = ^{5}J(8.5)=1.3, 3H, Hc(8trans)); 1.61 (ddt, ^{3}J(8,7)=6.8, ^{4}J(8,6)=1.8, ^{5}J(7,5)=0.9, 3H, HC(8cis)); 1.6 (m, 1H, HbC(4cis)); 1.45 (s, 3H, CH_3cis); 1.43 (s, 3H, CH_3trans). **^{13}C-NMR** ($CDCl_3$, 200MHz) 200.2 (C1cis and trans); 130.0 (C6trans); 129.2 (C6cis); 126.8 (C7trans); 125.8 (C7cis); 64.7 (C3cis and trans); 64.2 (C2trans); 64.1 (C2cis); 38.8 (C4trans); 38.6 (C4cis); 28.5 (C5trans); 22.9 (C5cis); 18.5 (C8trans); 17.8 (C9cis and

trans); 13.4 (C8cis). **CI-MS** (NH_4^+) 173 (28, M+NH_4^++1); 172 (18, M+NH_4^+); 156 (4, M^++2); 155 (5, M^++1); 139 (3); 125 (7); 109 (16); 95 (100); 85 (89); 81 (20).

(2S,3R) 3-Chlor-1,1-dimethoxy-2-hydroxy-3-methyl-6-octen (17 cis and trans): 0.428g (2.78mmol, 1eq) of aldehyde **16** is subjected at r.t. during 22h to our cyclisation conditions (Zn: 0.181g, 2.78mmol, 1eq, TMS-Cl: 0.781g, 6.94mmol, 2.5eq) yielding after purification over silica gel 0.16g of product. Second purification gave 0.06g (9%) of pure halohydrine **17**. R_f (hexane/EtOAc=2/1, $KMnO_4$) 0.40. **IR** (film) 3533m (OH); 1658w (C=C). **^{1}H-NMR** ($CDCl_3$, 400MHz) 5.46 (dtq, ^{3}J(7,6)=10.7, ^{3}J(7,8)=6.6, ^{4}J(7,5)=1.4, 1H, HC(7cis)); 5.37 (dtq, ^{3}J((6,7)=10.7, ^{3}J(6,5)=7.0, ^{4}J(6,8)=1.6, 1H, HC(6cis)); 4.64 (d, ^{3}J(1,2)=2.8, 1H, HC(1cis)); 4.63 (d, ^{3}J(1,2)=2.8, 1H, HC(1trans)); 3.67 (br.s, 1H, HC(2cis)); 3.65 (br.s, 1H, HC(6trans)); 3.50 (s, 3H, CH_3Ocis), 3.49 (s, 3H, CH_3Otrans); 3.41 (s, 3H, CH_3Ocis); 3.40 (s, 3H, CH_3Otrans); 2.88 (br.s, 1H, OH); 2.31-2.17 (m, 2H, HC(5cis an trans)); 1.92 (ddd, ^{2}J(4a,4b)=14.3, ^{3}J(4a,5a)=11.0, ^{3}J(4a,5b)=5.6, 1H, HaC(4cis)); 1.78 (ddd, ^{2}J(4b,4a)=14.3, ^{3}J(4b,5a)=11.2, ^{3}J(4b,5b)=5.5, 1H, HbC(4cis)); 1.64 (m, 3H, HC(8trans)); 1.62 (ddt, ^{3}J(8,7)=6.6, ^{4}J(8,6)=1.5, ^{5}J(8,5)=0.9, 3H, HC(8cis)); 1.51 (s, 3H, CH_3cis); 1.48 (s, 3H, CH_3trans). **^{13}C-NMR** ($CDCl_3$, 200 MHz) 131.0, 130.1 (C6, cis, trans); 126.0, 125.2 (C7, trans, cis); 103.1, 103.1 (C1, cis, trans); 77.0, 77.0 (C2, trans, cis); 75.4, 75.3 (C3, cis, trans); 55.9 (CH_3O cis and trans), 54.5, 54.5 (CH_3O, cis, trans); 41.6 (C4trans); 41.4 (C4cis); 28.0 (C5trans); 25.7 (CH_3 cis and trans); 22.5 (C5cis); 18.6 (C8trans); 13.4 (C8cis). **CI-MS** (NH_3^+) 255, 257 (4, 1, M+NH_4^++1); 254, 256 (18, 7, M+NH_4^+); 237, 239 (<1, <1, M^++1); 222, 224 (29, 11, M+NH_4^+-MeOH); 205, 207 (6,2); 190, 192 (20, 7, M+NH_4^+-2MeOH); 169 (23); 109 (8); 98 (13); 75 (100).

Synthesis of 18 and transformation to 19.

(3S,4S) 4,8-Dimethyl-3,4-epoxi-1-nitro-1,7-nonadien (18): To 6 ml of isopropanol is added KF (0.035g, 0.59mmol, 0.1eq) nitromethane (0.435g, 7.13mmol, 1.2eq) and aldehyde **4** (1g, 5.94mmol, 1eq). After stirring at r.t. for 3h isopropanol is replaced with 10 ml of ether. After addition of triethylamine (1.804g, 17.83mmol, 3eq) and Ac_2O (1.213g, 11.89mmol, 2eq) the solution is stirred at r.t. for 12h. The reaction mixture is poured on 100 ml water and extracted 4 times with EtOAc. The crude product is purified over a column yielding 0.636g (51%) of NMR-pure nitrocompound **18**. R_f (hexane/EtOAc=2/1, UV, $KMnO_4$) 0.79. n_D 1.495(3). **IR** (KBr) 1651w (C=C); 1530s (NO_2). **^{1}H-NMR** (400MHz, $CDCl_3$) 7.20 (dd, ^{3}J(2,1)=13.3, ^{3}J(2,3)=5.3, 1H, HC(2)); 7.11 (d, ^{3}J(1,2)=13.5, 1H, HC (1)); 5.07 (br.t, ^{3}J(7,6)=7.1, 1H, HC(7)); 3.40 (d, ^{3}J(3,2)=5.3, 1H, HC(3)); 2.12 (Ψq, J=7.7, 2H, H_2C(6)); 1.77 (ddd, ^{2}J(5a,5b)=14.8, ^{3}J(5,6b)=8.1, ^{3}J(5,6a)=6.8, 1H, H_aC(5)); 1.70 (s, 3H, H_3C(9)); 1.61 (s, 3H, H_3C(9')); 1.63-1.56 (m, 1H, H_bC(5)); 1.29 (s, 3H, H_3C(10)). **^{13}C-NMR** (100MHz, $CDCl_3$, APT) 142.5 (C1); 138.1 (C2); 133.4 (C8); 123.5 (C7); 65.9 (C4); 58.9 (C3); 38.9 (C5); 26.4 (C9); 24.3 (C6); 18.4 (C9'); 17.1 (C10). **CI-MS** 229 (48, M+NH_4^+); 212 (13, M^++1); 199 (16); 186 (22); 127 (46); 109 (100, $(CH_3)_2C{=}CHCH_2CH{=}C^+CH_3$); 95 (41).

(3S,4R) 4,8-Dimethyl-4-chloro-3-hydroxy-1-nitro-1,7-nonadien (19): 0.492g (2.46mmol, 1eq) of nitrocompound **18** is treated at r.t. during 4h with Zn (0.080g, 1.23mmol, 0.5eq) and TMS-Cl (0.534g, 4.92mmol, 2eq) yielding after purification over column 0.245g (42%) of **19**. R_f (heptane/EtOAc=4/1, UV, $KMnO_4$) 0.20. **IR** (KBr) 3382s (OH); 1651w (C=C); 1623m (C=C); 1529s (NO_2). **^{1}H-NMR** (400MHz, $CDCl_3$) 7.38 (dd, ^{3}J(2,1)=13.2, ^{3}J(2,3)=4.1, 1H, HC(2)); 7.26 (dd, ^{3}J(1,2)=13.2, ^{4}J(1,3)=1.8, 1H, HC(1)); 5.11 (t sept, ^{3}J(7,6)=7.2, ^{4}J(7,9) = ^{4}J((7,9')=2.8, 1H, HC(7)); 4.49 (dd, ^{3}J(3,2)=4.1, ^{4}J(3,1)=1.8, 1H, HC(3)); 2.6 (br.s, 1H, OH); 2.30-2.21 (m, 1H, HaC(6)); 2.21-2.11 (m, 1H, HbC(6)); 1.92 (ddd, ^{2}J(5a,5b)=14.4, ^{3}J(5a,6a)=10.9, ^{3}J(5a,6b)=5.3, 1H, HaC(5)); 1.70 (d, ^{4}J(9,7)=0.9, 3H, H3C(9)); 1.66 (ddd, ^{2}J(5b,5a)=14.4, ^{3}J(5b,6a)=10.8, ^{3}J(5b,6b)=5.4, 1H, HbC(5)); 1.63 (s, 3H, H_3C(9')); 1.60 (s, 3H, H_3C(10)). **^{13}C-NMR** (100MHz, $CDCl_3$, DEPT 135, HETCOR) 142.6 (C2); 139.1 (C1); 134.0 (C8); 123.3 (C7); 76.6 (C4); 75.9 (C3); 40.2 (C5); 26.3 (C9 and C10); 23.6 (C6); 18.4 (C9'). **CI-MS** 265, 267 (7, 2, M+NH_4^+); 248, 250 (100, 42, M^++1); 232 (19); 217 (14); 212 (5, M^++1-HCl); 196 (24); 181 (7).

Transformation of 20 to 21.

(3S,4R) 4-Chloro-4,8-dimethyl-3-hydroxy-2-oxo-7-nonen (21): 0.50g (2.74mmol, 1eq) of ketone **20** in 20 ml THF is treated at 70°C. during 5h with Zn (0.090g, 1.37mmol, 0.5eq) and TMS-Cl (0.618g, 5.49mmol, 2eq) yielding after purification over column 0.184g (31%) of pure **21**. R_f (hexane/EtOAc=9/1, $KMnO_4$) 0.26. **IR** (KBr) 3451s (OH); 1713s (C=O). **^{1}H-NMR** (200MHz, $CDCl_3$) 5.13 (tsept, ^{3}J(7,6)=7.1, ^{4}J(7,9) = ^{4}J(7,9')=1.2, 1H, HC(7)); 4.29 (d, ^{3}J(3,OH)=6.2, 1H, HC(3)); 3.72 (d, ^{3}J(OH,3)=6.2, 1H, OH)* 2.47 (s, 3H, H_3C(1)); 2.25 (Ψq, J=7.9, 2H, H_2C(6)); 2.98 (dt, ^{2}J(5a,5b)=9.4, ^{3}J(5a,6)=7.0, 1H, HaC(5)); 1.84-1.72 (m, 1H, HbC(5)); 1.70 (d, ^{4}J(9,7)=1.1, 3H, H_3C(9)); 1.65 (s, 3H,

$H_3C(9')$); 1.39 (s, 3H, $H_3C(10)$). **^{13}C-NMR** (100MHz, $CDCl_3$, APT) 209.6 (C2); 133.2 (C8); 127.7 (C7); 81.7 (C3); 72.6 (C4); 42.5 (C5); 30.6 (C1); 26.4 (C9); 25.5 (10); 23.6 (C6); 18.3 (C9'). **CI-MS** 308 (24); 236, 238 (100, 45, $M+NH_4^+$); 200, 202 (19, 13, M^+-H_2O); 183 (19, M^++1-HCl); 165, 167 (31, 14); 123 (13). *exchange with D_2O.

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16. X-ray data for (**8a**), (**8b**), and (**13a**). Intensity data were collected on a Stoe AED2 4-circle diffractometer using MoKa graphite monochromated radiation (l = 0.71073 Å) with w/Q scans in the 2Q range 3 - 50°. For **8a** and **13a** data were collected at room temperature and the structures solved by direct methods using the programme system NRCVAX[25] which was also used for refinement and all further calculations. Hydrogen atoms were located from difference maps and refined isotropically. The non-H-atoms were refined anisotropically using weighted full-matrix least-squares refinement on F. For **8b** the data were collected at -60°C and the structure solved by direct methods using the programme SHELXS-86[26]. The hydroxyl H-atoms were located from difference maps and refined isotropically, the remainder were included in calculated positions. The non-hydrogen atoms were refined anisotropically using weighted full-matrix least-squares on F^2 using the programme SHELXL-93[27].
Crystal data for **8a**: $C_{10}H_{17}O_2Cl$, monoclinic, space group I2/a, a = 10.708(1), b = 10.880(1), c = 19.028(2) Å, b = 104.03(1) °, V = 2150.7 $Å^3$, Z = 8, 1407 observed reflections [I>2σ(I)], final R = 0.042, R_w = 0.078, residual density : max. 0.21, min. -0.18 e $Å^{-3}$.
Crystal data for **8b**: $C_{10}H_{17}O_2Cl$, trigonal, space group R3, a = 21.101(1), c = 6.215(1) Å, V = 2396.5 $Å^3$, Z = 9, 813 observed reflections [I>2σ(I)], final R1 = 0.030, wR2 = 0.057, residual density : max. 0.16, min. -0.13 e $Å^{-3}$.
Crystal data for **13a**: $C_8H_{15}O_2Cl$, monoclinic, space group $P2_1/n$, a = 8.190(1), b = 11.145(1), c = 11.112(1) Å, b = 109.98(1) °, V = 953.2 $Å^3$, Z = 4, 1147 observed reflections [I>2.5σ(I)], final R = 0.056, R_w = 0.110, residual density: max. 0.26, min. -0.22 e $Å^{-3}$.
Full tables of atomic parameters and bond lengths and angles may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ (U.K.) on quoting the full journal citation.
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