Amber-Woody Scent: Alcohols with Divergent Structure Present Common Olfactory Characteristics and Sharp Enantiomer Differentiation

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Dedicated to Dr. *Günther Ohloff* on the occasion of his 80th birthday

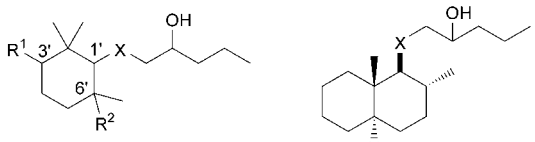
Only one out of the four possible *trans* isomers of the important perfumery alcohol *Norlimbanol*® (**1**) possesses a very strong amber-woody smell, the isomer **1A** with (1′*R*,3*S*,6′*S*) absolute configuration. Its enantiomer **1B** is almost odorless and devoid of amber-woody character, whereas the diastereoisomers **1C** and **1D** are considerably weaker and perceptible only by the most-sensitive persons. The same is true for a whole series of perceptual analogs of **1**, including β-alkoxy alcohols. These ethers belong to two structural classes: [(2,2,6-trimethylcyclohexyl)oxy]- (see **3**, **4**, and **16**) or {[2-(*tert*-butyl)cyclohexyl]oxy}alkan-2-ol derivatives (see **19** and **20**; *Table*). A superimposition model allowing for good overlap of the respective hydroxylated side chains offers a tentative explanation for the shared perceptual characteristics of the two classes (*Fig. 5*). The lipophilic cyclohexane moieties present only a minimal overlap in this model, suggesting that quite larger molecules might possess the same smell. (*S*)-Configured β-alkoxy alcohols can conveniently be obtained on a larger scale by enantioselective reduction of the corresponding ketones (*Scheme 9*).

1. Introduction. – Enantiomers may be discriminated by their smell [1]: this observation was essential in the elucidation of the molecular mechanisms of olfactory perception. It unambiguously suggested the involvement of chiral biological receptors in the recognition of odorous molecules.

The hunt for olfactory receptors culminated with the discovery of a huge multigene family encoding rhodopsin-like G-protein-coupled receptors [2]. Every animal species studied so far relies on these transmembrane proteins to detect odors, from nematodes to humans [3]. The olfactory receptor repertoire represents around 1–2% of the mammalian genome, with *ca.* 1000 expressed genes in rodents [4]. Humans seem to be provided with a somewhat reduced set of *ca.* 650 genes, half of which have mutated into nonfunctional pseudogenes [5]. The losses appear to be random across the genome. This still leaves the very impressive number of *ca.* 340 expressed odorant receptors within the human olfactory epithelium [4a][5]. Smell relies on the combinatorial encoding of airborne chemicals: every substance likely activates an array of olfactory receptors, and conversely, a receptor protein is activated by a range of molecules [6]. In rodents, it has been shown that the encoding of carvone enantiomers relies on the activation of partly overlapping sets of receptors [7]. The olfactory sensory neurons project their axons to the olfactory bulb, where the incoming signals are transformed into spatiotemporal patterns of activation [8]. Optical imaging techniques allow the visualization of odorant representations in the rodent olfactory bulb, and, in particular, the different spatial activation patterns elicited by a range of enantiomers [9].

Numerous examples of smell enantiodifferentiation have been reported in the literature[1]). The antipodes of a chiral molecule may differ in quality, perceived intensity, or both, although some pairs cannot be discriminated, like the camphors. The elucidation of the absolute configuration of chiral odorants is of considerable interest to perfumery, because a reduced amount of an optically active substance can help achieve superior quality or performance. Beyond this functional significance, configuration is the primary requisite for the correlation of smell with molecular attributes [11] ('structure–odor relationships').

Important perfumery ingredients derived from ionol caught our attention. Whereas tetrahydroionol (=4-(2,2,6-trimethylcyclohexyl)butan-2-ol) itself does not appear to be very remarkable, its ethyl-homologated side-chain derivatives **1** and **2** bear a characteristic smell (*Fig. 1*). The intensity of this smell is highly dependent on the molecular geometry: the OH-bearing side chain has to occupy an equatorial position [12]. Thus, the Me–C(6′) should be *trans* to the side chain, since *cis* ring substitution favors the axial position of the hydroxylated side chain. The 'irone-type' Me–C(3′) of **2** should also occupy the equatorial position, *i.e.*, reside *cis* to the hexanol chain. Compounds fulfilling these requirements possess an extremely strong smell, described as amber, woody, with distinct animal character. *Norlimbanol*® and *Limbanol*® are registered trade names for diastereoisomer mixtures of the racemic, all-equatorial alcohols **1** and **2**, respectively[2]) [12].



1 X = CH_2, R^1 = R^2 = H
2 X = CH_2, R^1 = Me, R^2 = H
3 X = O, R^1 = R^2 = H
4 X = O, R^1 = Me, R^2 = H
5 X = O, R^1 = H, R^2 = Me

6 X = CH_2
7 X = O

Fig. 1. *Chemicals with amber-woody* 'Limbanol®*-type' odor* [12]

Remarkably, the replacement of a CH_2 group by an ether linkage in the analogous cyclohexanol derivatives **3** and **4** does not change the odor profile. The 6′,6′-dimethyl homolog **5** also smells alike, although with reduced intensity. The additional axial Me group is, thus, not detrimental to the odor.

The *trans*-decalin analogs **6** and **7** of *Limbanol*® (**2**), designed by fusing the equatorial Me–C(2′) and Me–C(3′) substituents into a six-membered ring, were also found to possess the same strong characteristic odor of the parent material. The decalin structures were seen as *seco*-androstanes, and the animal undertones of their smells

[1]) For a comprehensive and recent review, see [10].
[2]) These two chemicals are produced by *Firmenich SA* for its own use.

reminded perfumers of the odors of certain steroid metabolites [13]. Although the alcohols **1**–**7** had only been synthesized as racemates, they were seen as partial structures of the hitherto unknown 18-nor-5α-androstan-13-ol (**8**), prompting the suggestion that 'the release of their particular scent could be correlated with a steroid-resembling receptor event' (*Fig. 2*) [12a].

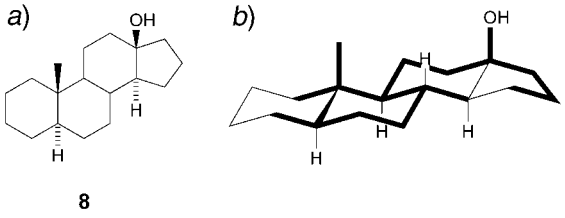


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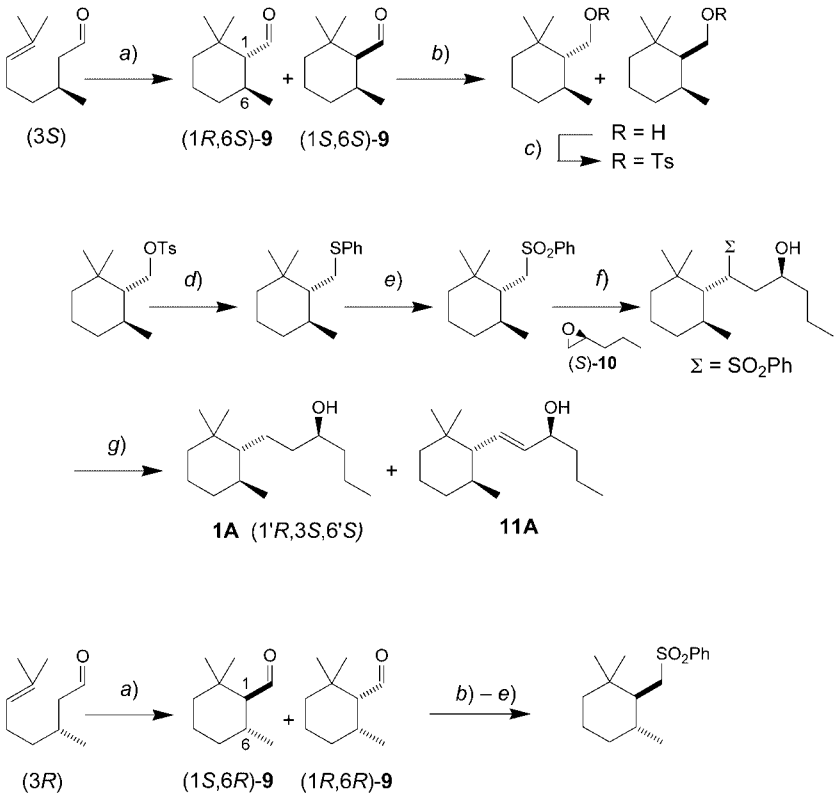
Fig. 2. a) *18-Nor-5α-androstan-13-ol* (**8**), *the proposed parent molecule of* Limbanol® (**2**); b) *superimposition of the two molecules* **2** and **8** *(Limbanol®* (**2**) is drawn with bold lines) [12]

The absolute configuration plays a major role in the odor of androstanes: *ent*-5α-androst-16-en-3-one is odorless and the corresponding 3α-alcohol barely perceptible [13]. We wanted to know whether the same is true for the ethyl-tetrahydro-ionols. The 18-nor-5α-androstan-13-ol (**8**) template predicts that the active enantiomer of *Norlimbanol®* (**1**) should have the (1′*S*,3*R*,6′*R*) absolute configuration. We felt that the link to the odorous androstanes was worthy of investigation, as this could lead to the targeted design of new odorous chemicals. We thus prepared the individual optical isomers of *Norlimbanol®* (**1**) and selected analogs, starting from optically active building blocks.

2. Syntheses and Odor Properties. – The acid-catalyzed cyclization of optically active citronellyl enol acetate to dihydrocyclocitral **9** [14] provides straightforward access to the trimethylcyclohexyl skeleton of *Norlimbanol®* (**1**; *Scheme 1*). The aldol condensation of aldehyde **9** with pentan-2-one followed by reduction would certainly be a practical route to **1**. However, this approach ultimately requires the hydrogenation of an allylic alcohol, a step during which we expect the intermediary appearance of a saturated ketone leading to the epimerization of the alcohol function. Further, we need end products with extremely high optical purity and known absolute configuration. We thus planned to couple the trimethylcyclohexyl moiety with 2-propyloxirane **10** of known absolute configuration [15]. Thus, dihydrocyclocitral (1*R*,6*S*)-**9** was reduced to dihydrocyclogeraniol with $NaBH_4$ and converted to the corresponding tosylate (*Scheme 1*). The tosylate could be transformed into the corresponding bromide or iodide by salt exchange, but the consecutive preparation of a magnesium or lithium organometallic reagent failed. Reaction of the tosylate with thiophenol afforded (1*R*,6*S*)-dihydrocyclogeranyl phenyl sulfide, which was oxidized to the crystalline sulfone. Repeated crystallization efficiently removed any traces of the *cis*-dihydrocyclogeranyl isomer. Deprotonation of the pure *trans*-sulfone with (*tert*-butyl)lithium (*t*BuLi) followed by addition of (2*S*)-propyloxirane ((*S*)-**10**) and treatment with naphthalenyllithium provided the (1′*R*,3*S*,6′*S*)-isomer **1A** of *Norlimbanol®* together

with 15% of allylic alcohol **11A**. The latter was identified by comparison with independently prepared (1′*R*,3*R*,6′*S*)/(1′*R*,3*S*,6′*S*)-allylic alcohol **11** [12b] and removed by ozonolysis of the corresponding acetate mixture. The smell of (1′*R*,3*R*,6′*S*)/(1′R,3*S*,6′*S*)-**11** is weak and only vaguely woody.

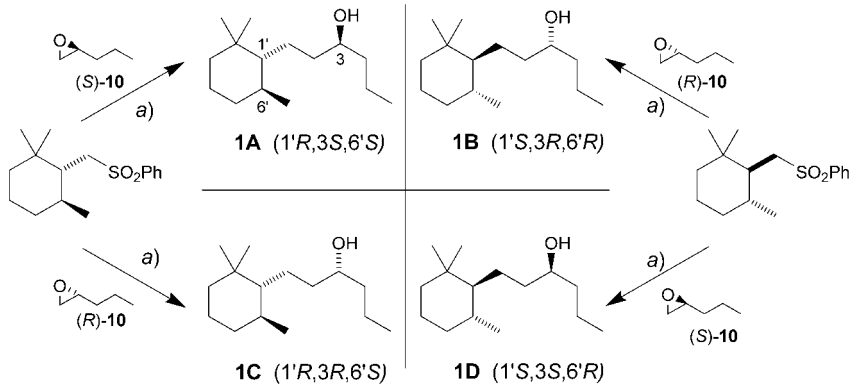
Scheme 1



a) See [14]. *b*) $NaBH_4$, EtOH, 0°. *c*) TsCl, pyridine, 25°. *d*) KSPh, EtOH, 0°; *b) – d)* 64%. *e*) *m*CPBA, CH_2Cl_2, 0°; 98%. *f*) 1. ᵗBuLi, THF/hexanes, –30°; 2. (*S*)-**10**/$BF_3 \cdot OEt_2$, –75° to 25°. *g*) Naphthalenyllithium, THF, –75°; *f)g)* 42%.

The same process was repeated for the coupling of the sulfone derived from dihydrocyclocitral (1*R*,6*S*)-**9** with (2*R*)-propyloxirane ((*R*)-**10**) to yield the diastereoisomer **1C**, and for the couplings of the sulfone derived from (1*S*,6*R*)-**9** with (2*R*)- and (2*S*)-2-propyloxirane **10** (*Scheme 2*). The isomers of **1** could be only partially resolved by GLC analysis on a chiral stationary phase, thus, the corresponding acetates (partially resolved by GLC) were also analyzed by ^{1}H-NMR in the presence of the shift reagent tris[(+)-3-(heptafluorobutanoyl)camphorato]europium ([Eu(hfbc)$_3$]). The enantiomer and diastereoisomer excesses of each isomer **1A** – **D** were above 99%. The olfactory evaluation of these isomers revealed dramatic differences (*Table*). The

Scheme 2



a) 1. ^{t}BuLi, THF/hexanes, $-30°$; 2. **10**, $BF_3 \cdot OEt_2$, $-75°$ to 25°. 3. Naphthalenyllithium, THF, $-75°$.

(1′*R*,3*S*,6′*S*)-isomer **1A** possesses an extremely powerful woody, ambery characteristic odor with animal undertones. Its enantiomer **1B** only carries a very faint woody smell that only persons with the highest sensitivity towards these materials can detect. The smells of the enantiomers **1C** and **1D** are also considerably weaker.

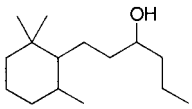
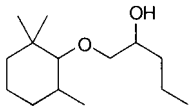
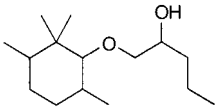
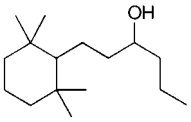
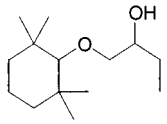
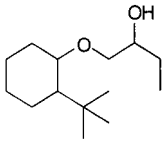
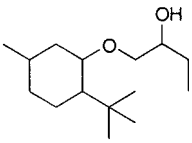
Since our initial patent on the use of **1A**–**D** with the report of their absolute configuration [16], a lipase-PS-catalyzed acetylation allowed the kinetic resolution of the four 1′,6′-*trans*-configured alcohols, affording the pure acetate of **1C**. Saponification, tosylation, and acetate displacement afforded pure **1A** [17].

Norlimbanol® (**1**) possesses three chiral centers: we wanted to know whether the environment of the polar function alone could influence the odor quality. Starting from 2,2,6,6-tetramethylcyclohexanecarboxaldehyde (**12**), conveniently obtained from citral after 1,4-methyl addition, enol acetate formation, and acidic cyclization [18], we prepared both antipodes of alcohol **13**. The same approach was used, opening of either (2*R*)- or (2*S*)-2-propyloxirane **10** by a lithiated achiral sulfone (*Scheme 3*). The enantiomer excesses of **13A** and **13B** exceed 99.5%, as determined by GLC analysis of the acetates. The odor difference of the enantiomers of **13** is spectacular: only the (*S*)-configured **13A** bears the strong *Norlimbanol*®-type odor (*Table*). The faint smell of the antipode **13B** is perceived by only the few most-sensitive persons.

We next turned our attention to the ether analog of *Norlimbanol*® (**1**), *Oxanorlimbanol* (**3**), as well as to *Oxalimbanol* (**4**). Although we anticipated a difficult reaction, we considered the opening of propyloxirane **10** by a suitable alcoholate as the reaction of choice to produce compounds with predictable configurations. The requested optically active *trans*-2,2,6-trimethylcyclohexanol **14** could be obtained in two steps from the corresponding dihydrocyclocitral: *Baeyer–Villiger* oxidation, then hydrolysis of the intermediate formic acid ester (*Scheme 4*).

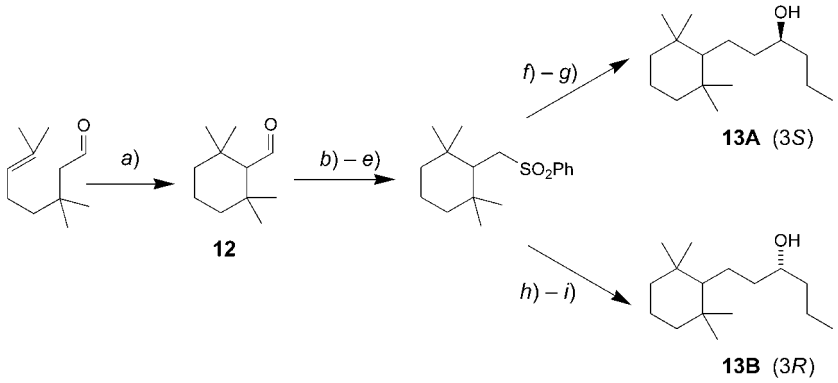
The preparation of the homologous 1,3-*cis*:1,6-*trans* enantiomers of 2,2,3,6-tetramethylcyclohexanol **15** required a longer, six-step synthesis starting from optically active citronellal [19]: intramolecular ene reaction to isopulegol (=5-methyl-2-(1-methylethenyl)cyclohexanol), oxidation to a mixture of pulegone (=5-methyl-2-(1-

Table. *Olfactory Characteristics of the Individual Isomers*

		Isomer			
		A	**B**	**C**	**D**
	**1**	amber, woody, dry, perspiration, very powerful	woody, camphor, vague, weak	woody, dry	woody, amber
	**3**	amber, costus, *Limbanol*®-type, dry, very powerful	woody, earthy, sesquiterpenes, lacks character	woody, amber, lacks character	woody, pencil, without character
	**4**	amber, woody, dry, exceedingly powerful	woody, cedar, very weak to odorless	woody, amber, somewhat powerful	woody, paper, slightly amber, weak
	**13**	amber, woody, *Limbanol*®-type, strong	woody, fairly weak, somewhat dirty		
	**16**	amber, woody, cedar, strong	celluloid, oil cloth		
	**19**	amber, woody, dry, nice and strong	woody, amber, very weak	without character	woody, amber, very weak
	**20**	amber, woody, not very powerful	chalk, dusty, vaguely woody, weak	floral, vague	floral, vague

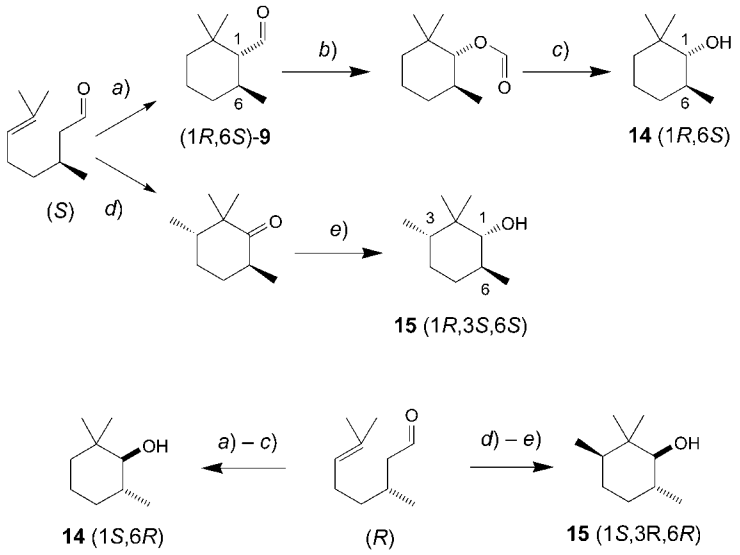
methylethylidene)cyclohexanone) and isopulegone, α-permethylation, ozonolysis, *retro*-aldolization and finally dissolving metal reduction (*Scheme 4*). Both alcohols **14** and **15** were crystallized to yield pure 1,6-*cis* isomers and 1,3-*cis*:1,6-*trans* isomers, respectively, with an enantiomer excess exceeding 99%, according to GLC. The four isomeric *oxanorlimbanols* **3A**–**D** and the four isomeric *oxalimbanols* **4A**–**D** were then obtained in individual coupling reactions of a potassium alcoholate with either enantiomer of 2-propyloxirane **10** (*Scheme 5*). As expected, the oxirane opening was difficult: the starting alcoholate is less reactive than the product alcoholate, and the reaction had to be interrupted at partial conversion. Finally, the optical isomers **3A**–**D**

Scheme 3



a) See [18]. *b*) $NaBH_4$, EtOH, 0°. *c*) TsCl, pyridine 25°. *d*) KSPh, EtOH, 0°; *b) – d)* 65%. *e*) *m*CPBA, CH_2Cl_2, 0°; 90%. *f*) 1. ^{t}BuLi, THF/hexanes, −30°; 2. (*S*)-**10**, $BF_3 \cdot OEt_2$, −75° to 25°. *g*) Naphthalenyllithium, THF, −75°; *f)g)* 20%. *h*) 1. ^{t}BuLi, THF/hexanes, −30°; 2. (*R*)-**10**, $BF_3 \cdot OEt_2$, −75° to 25°. *i*) Naphthalenyllithium, THF, −75°; *h) i)* 16%.

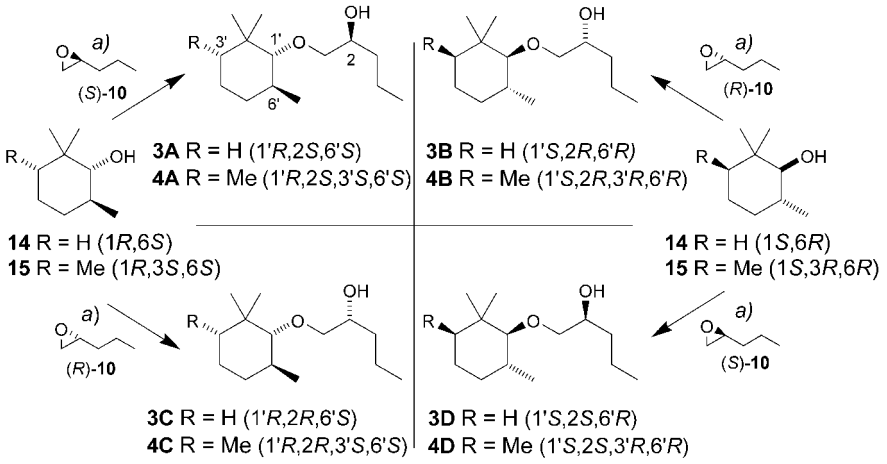
Scheme 4



a) See [14]. *b*) *m*CPBA, CH_2Cl_2, 25°; 82–85%. *c*) KOH, MeOH 25°; 92–95%. *d*) See [19]. *e*) Na, ^{i}PrOH/toluene, 0°; 70%.

and **4A – D** were all obtained with an isomer excess of 98–99% and an enantiomer excess exceeding 99%. Again, only the (2*S*)-alcohols **3A** and **4A** with (6′*S*) ring configuration bear the penetrating, extremely powerful amber-woody smell (see the *Table*). Their enantiomers **3B** and **4B** are almost odorless, whereas their diastereoisomers **3C** and **3D**, and **4C** and **4D** might still have some distinct woody smell,

Scheme 5

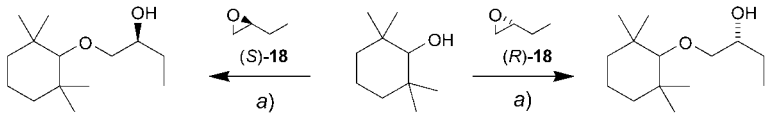


a) 1. KH, THF; 2. **10**, 80°; 15–41%.

although considerably weaker. Especially, a smelling strip impregnated with a small drop of **4A** will durably fill a room with a distinct and strong smell perceived by most persons.

The (2,2,6,6-tetramethylcyclohexyl)oxy counterpart **5** of the single-chiral-center alcohol **13** was also of interest to us. However, expert smellers consistently rated the racemic ethyl alcohol **16** as being stronger than the parent propyl alcohol **5**. We thus prepared the former by the coupling of 2,2,6,6-tetramethylcyclohexanol (**17**) with (2*R*)- and (2*S*)-2-ethyloxiranes **18** [20] (*Scheme 6*). The enantiomer excess of each enantiomer **16A** and **16B** was 97%. The enantiomer **16A** possesses the characteristic *Limbanol*®-type scent with a cedar note, its antipode **16B** has a weak, celluloid smell.

Scheme 6



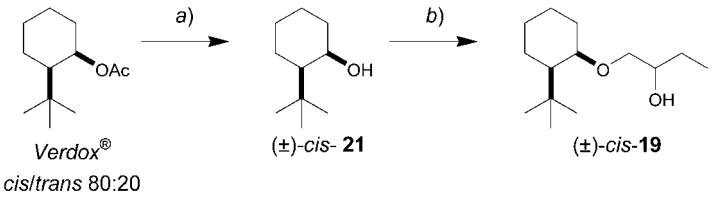
a) 1. KH, THF; 2. **18**, 80°; 18–20%.

The 1-alkoxy-butan-2-ol side chain is encountered in another fragrance chemical, **19**, named *Ambercore*®[3]) [21]. This alcohol is sold as a 60:40 mixture of *cis*- and *trans*-configured ring isomers that smells quite similar to *Limbanol*® (**2**): this is remarkable because their structural relationship is not obvious. We first prepared pure 1,2-*cis*- and 1,2-*trans*-2-(*tert*-butyl)cyclohexanol **21** by fractional distillation. Deprotonation of the

[3]) *Ambercore*® is a registered trade name of *Kao Corporation*, Japan.

alcohols with potassium hydride and treatment with racemic 2-ethyloxirane **18** provided *cis*- and *trans-Ambercore*® **19** (*Scheme 7*).

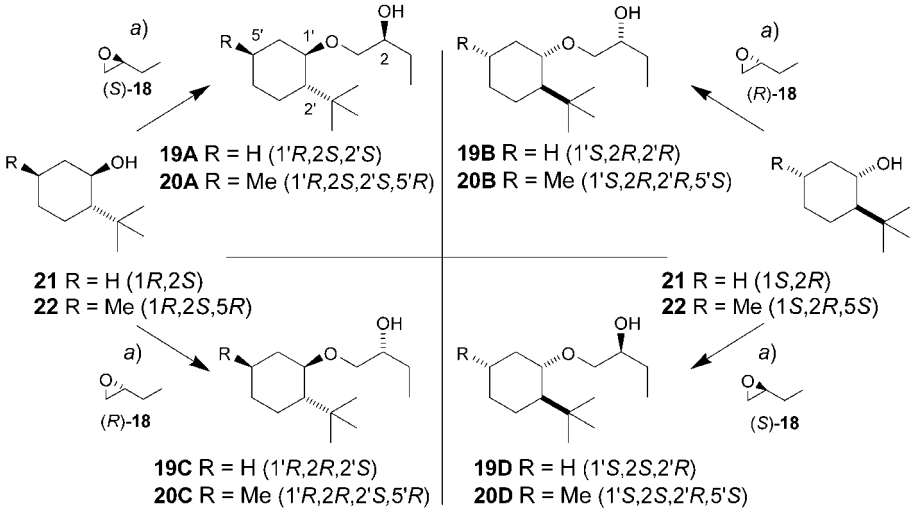
Scheme 7



a) KOH, MeOH 75°; 59%. *b*) 1. KH, THF; 2. (±)-**18**, 80°; 25%.

It became very clear that only the *trans* isomer possesses the *Limbanol*®-type smell, the *cis* isomer being perceived as extremely weak only by individuals with the highest sensitivity towards this kind of smell, whereas less-sensitive subjects rated it as odorless. We continued with the preparation of all 1,2-*trans*-configured isomers of *Ambercore*® (**19**; *Scheme 8*).

Scheme 8



a) 1. KH, THF; 2. **18**, 80°; 18–20%.

The racemic *trans*-2-(*tert*-butyl)cyclohexanol ((±)-*trans*-**21**) was resolved as a (−)-camphanic ester to provide the known (−)-(1*R*,2*S*)- and (+)-(1*S*,2*R*) alcohols **21** [22]. Amazingly, the crystals of the (−)-alcohol (−)-camphanate had cubic-like shapes, whereas the diastereoisomer crystallized as thin needles. This allowed efficient enrichment of the fractions by moderate blowing of air over the mixed crystals. Both pure enantiomeric alcohols **21** were then subjected to the usual transformation with each antipode of 2-ethyloxirane **18** (*Scheme 8*). The four isomers **19A**–**D** of *trans-Ambercore*® were obtained with enantiomer excesses of >99%, but with diaster-

eoisomer excesses of 97–98%. This series exhibits the same peculiar olfactory behavior that was observed in the previous examples: the smell of alcohol **19A** is strong, dry ambery and woody, its enantiomer **19B** is very weakly woody, and the diastereoisomers **19C** and **19D** are barely noticeable (see *Table*).

Finally, we also prepared the 5′-methylated cyclohexane-ring analogs of **19**, the '*methyl-Ambercore*®' **20**. Conjugated methyl addition to pulegone and dissolving metal reduction afforded the 1,2-*trans*:1,5-*cis* alcohols **22** [22]. The potassium alcoholates of **22** each reacted with (2*S*)- and (2*R*)-2-ethyloxirane **18** to yield the four isomers **20A–D** with enantiomer excesses above 99% and diastereoisomer excesses of 96–98% (*Scheme 8*). Only **20A** possesses the woody-ambery smell, albeit less powerful than the 5′-methyl-missing parent **19A**. No woody-ambery note is detected in the weak smell of the other isomers of **20** (see *Table*).

The (*S*) configuration of the alcohol group appears to be one of the essential features for the odor strength of all targeted molecules **1**, **3**, **4**, **13**, **16**, **19**, and **20**. Since the oxirane-opening syntheses have very little chance of being scaled up because of the low yield and unfavorable reaction conditions, we looked for alternative approaches to (*S*)-configured alcohols. The reduction of easily accessible enones leading to **1**, **2**, and **13** seems difficult as we mentioned above, because the intermediate allylic alcohol is likely to equilibrate with the alkanone during the following hydrogenation. On the other hand, α-alkoxy ketone precursors of **4**, **5**, **16**, **19**, and **20** have quite rigid side-chain geometries, imputable to stereoelectronic effects, and thus present two distinct faces that could be differentiated by a chiral reducing agent. We wanted to verify this idea, and thus we prepared the α-alkoxy ketones **25** and **28**. Etherification of the alcohols *r* **15** (racemic) and **17** to the allyl ethers **23** and **26**, respectively, was followed by peracid oxidation. The oxiranes **24** and **27** were opened with an ethyl and methyl metal reagent, respectively, to the secondary alcohols, which were then oxidized to the desired ketones **25** (racemic) and **28** (*Scheme 9*). We choose the oxazaborolidine-catalyzed hydroboration [23] as a proof of the stereoselective reduction concept. The diastereoisomer mixture **4A**/**4D** of (*S*)-configured alcohols and the (*S*)-alcohol **16A**, respectively, were obtained in the reductions with enrichments ranging from 90 to 93% by using only 4% loadings of the (*S*)-1,1-diphenylprolinol-based catalyst (*Scheme 9*).

The inspection of the putative chair transition state of the reduction (*Fig. 3*) [23] indicates that the alkoxycarbonyl group is the 'small' residue in the axial position, whereas the Et or Pr residues (R^L) are the 'large' ones! This counterintuitive finding

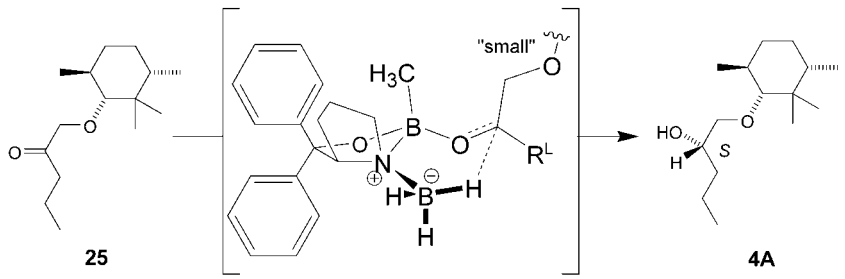
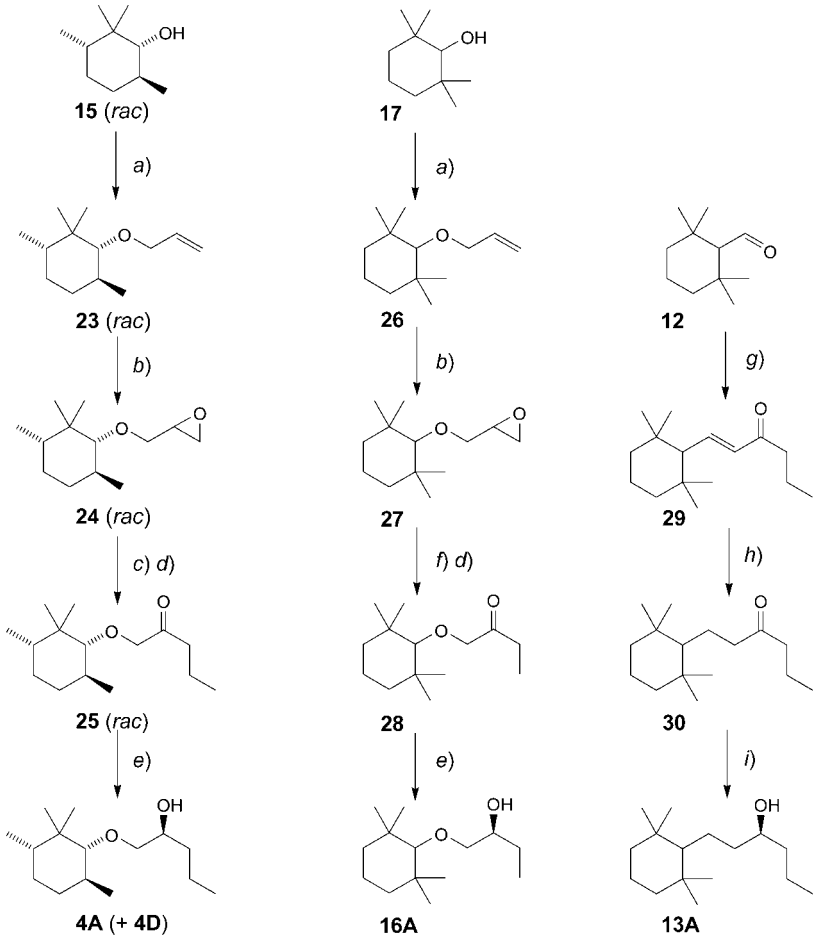


Fig. 3. *Stereoselective diphenyloxazaborolidine-catalyzed borane reduction: tentative transition state* [23]

Scheme 9



a) 1. KH, THF; 2. CH_2=$CHCH_2Br$, DMSO, 0°; 79–92%. *b*) *m*CPBA, CH_2Cl_2, 0–25°; 78–85%. *c*) EtMgBr, THF, 6% CuI, 0–25°; 72%. *d*) PCC, CH_2Cl_2, 25°; 88–89%. *e*) $BH_3 \cdot SMe_2$, THF, 4% (*S*)-diphenyloxazaborolidine catalyst, 0°; 76–94%. *f*) MeLi, THF, 6% CuI, 0–25°; 86%. *g*) NaOMe, MeOH, pentan-2-one, 80°; 79%. *h*) H_2, EtOH, cat. Pd/C, 25°; 78%. *i*) $BH_3 \cdot SMe_2$, THF, 10% (*S*)-diphenyloxazaborolidine catalyst, 0°; 72%.

might be explained by the strongly favored s-*anti* conformation of the two O-atoms leaving the vicinity of the carbonyl group quite accessible on the ether side. As anticipated, the oxazaborolidine reduction of the corresponding alkanone **30** (obtained from **12** *via* **29**) under similar conditions proved quite disappointing, since the (*S*)-alcohol **13A** was obtained with only 33% ee. Based on these preliminary results, we conclude that the specific α-alkoxy ketone substructure is a good candidate for stereospecific reductions or hydrogenations. This opens the way for the larger-scale stereoselective production of these extremely performing perfumery alcohols.

3. Results and Discussion. – The enantio- and diastereoselectivity of odor perception have been abundantly described [10]. This recognition selectivity is expected in a process involving chiral receptors, however, it is not always observed in olfaction[4]). The family of alcohols described here deserves a special interest. Rarely do the olfactory properties of optical isomers differ to such an extent. Although some remnant smell has been detected in most of the compounds, we might question how much of that odor is due to contamination by the strongest isomer. A threshold determination of *Norlimbanol*® (as a 1:1 mixture **1A**/**1C**) with 69 subjects [24] shows a very broad range of absolute sensitivities (*Fig. 4*). Four subjects have their threshold outside of the distribution (specific anosmia). The distribution appears bimodal, *i.e.*, the *Norlimbanol*® sensitivity criterion likely clusters the population into three groups: specific anosmics, moderately sensitive, and highly sensitive. Under such circumstances, the computation of an average detection threshold does not make sense, both from a behavioral and a statistical standpoint. The most-sensitive person could reliably detect the chemical at a liquid concentration 1000 times weaker than the least-sensitive one, and more than 50% of the subjects could detect the headspace above a concentration of 31 ppm (that is 31 mg/kg) in mineral oil. Since extremely sensitive people consistently evaluated our products, it is quite plausible that only the minor enantiomer or

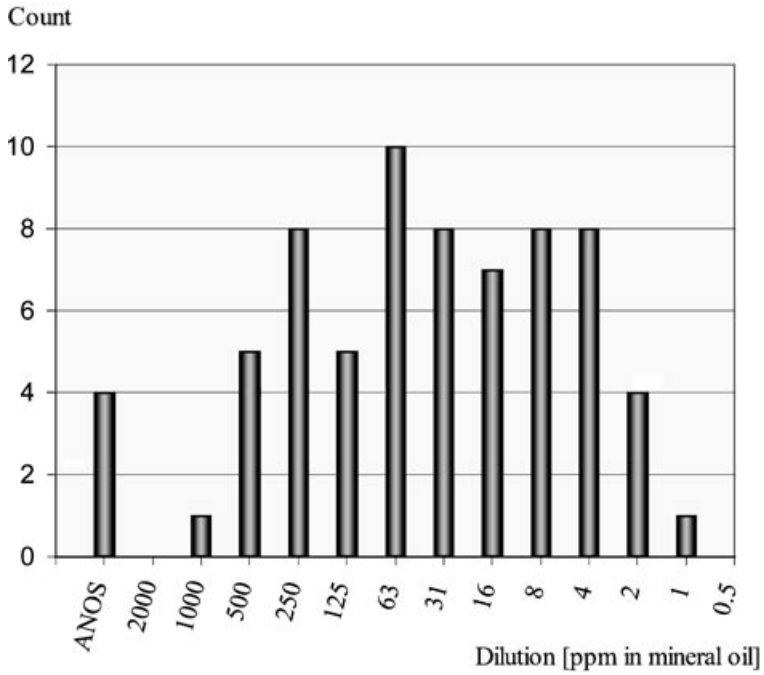


Fig. 4. *Detection-threshold distribution for a 1:1 mixture of* Norlimbanol® *isomers* **1A** *and* **1C**. The subject count is reported as a function of liquid concentration (w/w ppm *Norlimbanol*® in mineral oil). Anos = specific anosmics.

[4]) This subject is discussed in a recent article [11b].

diastereoisomer contamination by the odor-active isomer contributed to the odor impression.

The absolute configuration of the most-active *Norlimbanol*® **1A** isomer is just the opposite of that predicted by the androstanol **8** template, leading to the abandonment of this model. The smell divergence of the enantiomer pairs of alcohols **13** and **16** could induce the conclusion that the alcohol absolute configuration is the single most important determinant of activity, but a closer inspection of the *Table* convinces us that the configuration of the lipophilic cyclohexane moiety also plays an important role: the alcohols **1D**, **3D**, **4D**, **19D**, and **20D** with the required (*S*) alcohol configuration have only a very faint or absent smell. Alcohols **3C** and **4C** with the wrong alcohol configuration but correct ring configuration still possess a faint to medium woody ambery odor. Perhaps the most-intriguing question pertains to the common olfactory profile of these structurally diverse molecules. Obviously, the ability of the oxa analogs to adopt the active conformation(s) and activate the same receptors is not hindered by the presence of the ether linkage. But how can the *Norlimbanol*® **1A** and *Ambercore*® **19A** skeletons meet the apparently narrow requirements involved in the same molecular-recognition processes? Cross-adaptation experiments performed in our laboratory[5]) suggest that *Norlimbanol*® as a 1:1 mixture **1A**/**1C** and *Ambercore*® (**19**) really share perceptual channels, since the two molecules did mutually and selectively cross-adapt within a set of tested substances [26]. Both molecules may be superimposed in different manners; however, one superimposition mode appears especially attractive (*Fig. 5*). Both **1A** and **19A** possess a quaternary C-atom within their lipophilic part, with a Me substituent pointed axially. Superimposition of this axial Me–C bond of both molecules and across low-energy conformations led to the selection of two geometries allowing an easy overlap of the two OH functions. Small rotations along the side-chain bonds made this overlap quite convincing (*Fig. 5*).

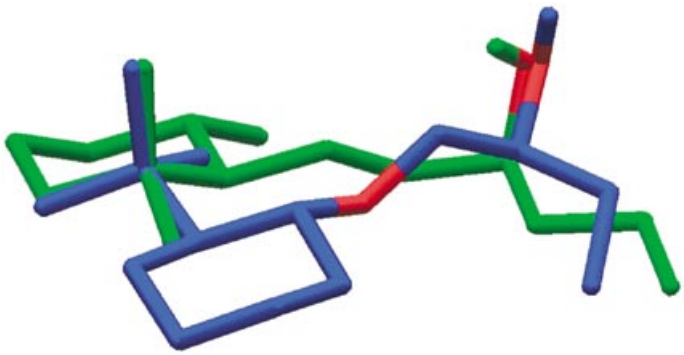


Fig. 5. *Superimposition of* **1A** (green skeleton) *and* **19A** (blue skeleton). O-Atoms are in red, H-atoms are omitted for clarity, except for the OH function.

[5]) Sensory adaptation is the selective reduction of sensitivity towards a stimulus following exposure to that stimulus. Cross-adaptation occurs when this decrease of sensitivity is induced upon exposure to another stimulus. For a short review on olfactory adaptation, see [25].

This model explains why the *Ambercore*® (**19**) side-chain should be one C-atom shorter than the *Norlimbanol*® (**1**) side-chain for maximal smell intensity, *i.e.*, because the tails of both the Et and Pr alcohol substituents end up in a similar area of space. This model could also explain why the allylic alcohol **11** has only a weak smell, because its more-rigid side-chain does not allow the torsions required for an optimum geometry. However, the most-striking feature of this superimposition model is the poor overlap of both cyclohexane rings. It suggests that only minimal structural requirements have to be satisfied to activate the receptors encoding this woody ambery smell. Further, these receptors might also recognize much larger ligands, and this prediction is also partly supported by the reported activity of alcohols **6** and **7** [12]. The activity of odorants specifically designed to verify the hypotheses of minimal structural requirements and to explore the largest active molecular shapes for the *Limbanol*®-type amber-woody smell are the subject of a future publication.

Beyond the structure/odor model, the question of olfactory coding arises. It is difficult to understand why a 340-receptors-based array could not better resolve such different molecules. A working hypothesis, the existence of nonlinear interactions within the olfactory coding organs, is an exciting lead to follow: a fraction of the olfactory receptors could be master switches, or could activate dominant processes that play a major role in imparting the odor quality [7]. Sets of chemicals with widely different structures but proven olfactory similarity appear very desirable to verify this hypothesis.

Finally, our work provides some extremely efficient perfumery materials and practical solutions for their preparation. Especially, the β-alkoxy alcohol analogs may be produced as diastereoisomer mixtures on a larger scale by the reduction of the corresponding ketones, owing to the structural characteristics of their side chain.

We are indebted to *Claude-Alain Richard* for skillful laboratory preparations, to Dr. *Charles Fehr* and Dr. *Christian Chapuis* who provided useful comments during the manuscript preparation, to Dr. *Pierre-Alain Blanc* and numerous colleagues at *Firmenich SA* for olfactory ratings and to the Research Management for continuous support of this work.

Experimental Part

1. *General*. All org. phases obtained from partition with aq. solns. were dried with Na_2SO_4. Column chromatography = CC. Gas chromatography (GLC): He carrier gas; capillary columns: low-polarity poly(dimethylsiloxane) *SPB-1* (30 m × 0.25 mm, *Supelco*) or higher-polarity *Carbowax 20M* '*Supelcowax*' (30 m × 0.25 mm, *Supelco*); for chiral compounds, modified cyclodextrins, either *CP-Chirasil-Dex CB* (15 m × 0.32 mm; *Chrompack*) or *Megadex 5* (25 m × 0.25 mm; *Megadex Capillary Columns Laboratory*). The purity of poorly resolved isomers was measured by ^{1}H-NMR in the presence of the shift reagent [Eu(hfbc)$_3$], hfbc = (+)-3-(heptafluorobutanoyl)camphorato. Optical rotations: *Perkin-Elmer 241* polarimeter; 1-ml cells. ^{1}H- and ^{13}C-NMR: *Bruker WH-360* spectrometer, $CDCl_3$ solns.; δ in ppm, J in Hz. MS: *Finnigan 1020* automated GC-MS instrument; 70 eV electron impact; in m/z (rel. %).

2. *Optically Active Building Blocks*. 2.1. *Cyclohexane Carboxaldehydes*. (+)-(1*R*,6*S*)-2,2,6-Trimethylcyclohexane-1-carboxaldehyde (1*R*,6*S*)-**9** and (−)-(1*S*,6*R*)-2,2,6-trimethylcyclohexane-1-carboxaldehyde (1*S*,6*R*)-**9** were prepared by cyclization of the enol acetate of the corresponding (3*S*)- and (3*R*)-citronellals, resp. (obtained from *Takasago Corp.* in ee > 99%) [14]. Both enantiomers of **9** contained 8–10% of the *cis* epimer. The achiral 2,2,6,6-tetramethylcyclohexane-1-carboxaldehyde (**12**) was analogously obtained by cyclization of the enol acetate of 3,3,7-trimethyloct-6-enal [18], and the latter was obtained by 1,4-addition of MeLi to (*E*/*Z*)-citral [27]. The 2,2,6,6-tetramethylcyclohexanol (**17**) was prepared according to a published procedure [28].

2.2. *Cyclohexanols. (+)-(1*R,6S*)-2,2,6-Trimethylcyclohexyl Formiate*. A soln. of (+)-(1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxaldehyde ((1*R*,6*S*)-**9**; 9.73 g, 63.0 mmol) was treated with 3-chloroperbenzoic acid

(70% pure; 23.5 g, 95 mmol) in CH_2Cl_2 (100 ml) at 25° during 4 days. Upon complete conversion, the mixture was poured onto H_2O (500 ml). Decantation, extraction with CH_2Cl_2, rinsing with brine, drying, evaporation at r.t., and bulb-to-bulb distillation afforded 9.0 g (82%) of 97% pure material. Integration of the ^{1}H-NMR signals showed the presence of 6–8% of the *cis* isomer. $[\alpha]_D^{20} = +37.4$ ($c = 4.0$, $CHCl_3$). IR: 2927*s*, 1719*s*, 1459*m*, 1388*w*, 1366*m*, 1186, 1167*s*, 945*s*. ^{1}H-NMR: 8.20 (*s*, 1 H); 4.50 (*d*, $J = 11$, 1 H); 1.7 (*m*, 2 H); 1.45 (*m*, 3 H); 1.3 (*m*, 1 H); 1.05 (*m*, 1 H); 0.95 (*s*, 3 H); 0.88 (*s*, 3 H); 0.84 (*d*, $J = 6$, 3 H). ^{13}C-NMR: 161.3 (*d*); 84.5 (*d*); 39.5 (*t*); 35.3 (*s*); 34.1 (*t*); 32.6 (*d*); 29.1 (*q*); 21.2 (*t*); 19.3 (*q*); 18.7 (*q*). MS: 170 (1, M^+), 124 (46), 109 (100), 95 (25), 82 (98), 69 (39).

*(−)-(1*S*,6*R*)-2,2,6-Trimethylcyclohexyl Formiate.* The reaction of (−)-(1*S*,6*R*)-2,2,6-trimethylcyclohexane-1-carboxaldehyde (1*S*,6*R*)-**9** with 3-chloroperbenzoic acid under the same conditions yielded 85% of (−)-(1*S*,6*R*)-2,2,6-trimethylcyclohexyl formiate. $[\alpha]_D^{20} = -37.0$ ($c = 4.0$, $CHCl_3$).

*(+)-(1*R*,6*S*)-2,2,6-Trimethylcyclohexanol* (**14** (1*R*,6*S*)). A soln. of (1*R*,6*S*)-2,2,6-trimethylcyclohexyl formiate (6.05 g, 35.6 mmol) in MeOH (50 ml) was heated under reflux in the presence of KOH (6.0 g, 106 mmol) in H_2O (18 ml) during 1 h to complete conversion. The mixture was cooled to 25°, partitioned with Et_2O (100 ml), and the aq. phase extracted twice with Et_2O (50 ml). The dried org. phase was evaporated and the concentrate filtered over silica gel (50 g, CH_2Cl_2): 4.90 g (95%) of pure (1*R*,6*S*)-**14**. Chemical purity > 99% (GC), *trans*/*cis ca.* 95:5 (^{1}H-NMR), ee 97% (*Megadex*). $[\alpha]_D^{20} = +28.1$ ($c = 4.0$, $CHCl_3$). IR: 3380, 2945, 1454, 1364, 1040, 952. ^{1}H-NMR: 2.82 (*d*, $J = 8.5$, 1 H); 1.69 (*ddq*, $J = 3.0$, 3.5, 13, 1 H); 1.4–1.5 (*m*, 5 H); 1.2 (*m*, 2 H); 0.98 (*s*, 3 H); 0.97 (*d*, $J = 8.0$, 3 H); 0.88 (*s*, 3 H). ^{13}C-NMR: 83.6 (*d*); 39.9 (*t*); 35.7 (*s*); 34.7 (*d*); 34.6 (*t*); 29.5 (*q*); 21.5 (*t*); 19.2 (*q*); 18.3 (*q*). MS: 142 (87, M^+), 124 (22), 109 (100), 95 (58), 82 (96), 81 (55), 71 (66).

*(−)-(1*S*,6*R*)-2,2,6-Trimethylcyclohexanol* (**14** (1*S*,6*R*)). As described above, **14** (1*S*,6*R*) was obtained in 92% yield and 99% chemical purity; *trans*/*cis ca.* 95:5 (^{1}H-NMR), ee 98% (*Megadex*). $[\alpha]_D^{20} = -28.5$ ($c = 4.0$, $CHCl_3$).

*(+)-(1*R*,3*S*,6*S*)-2,2,3,6-Tetramethylcyclohexanol* (**15** (1*R*,3*S*,6*S*)). Under Ar, a mixture of toluene (250 ml) and metallic Na (15 g, 0.65 mol) was heated under reflux for 15 min. Then the biphasic toluene/molten Na mixture was cooled down under vigorous mechanical stirring to solidify the Na as tiny spheres. At 0°, a soln. of (+)-(3*S*,6*S*)-2,2,3,6-tetramethylcyclohexanone [19] (33 g, 0.21 mol) in ^{i}PrOH (60 g, 1.0 mol) was added dropwise within 3 h to the Na preparation. The mixture was left under stirring at 0° overnight. The remaining Na was destroyed by the slow addition of EtOH, and the mixture was added to H_2O (500 ml). The crude mixture was decanted and the aq. phase extracted with toluene (2 × 100 ml). The combined org. phase was washed with brine (200 ml), dried and evaporated at 40 Torr: 38 g of concentrate. CC (silica gel (500 g), cyclohexane/AcOEt 95:5) followed by double crystallization provided 19.5 g (70%) of the pure, all-equatorial **15** (1*R*,3*S*,6*S*); ee > 98% (*Megadex*). $[\alpha]_D^{20} = +16.9$ ($c = 3.9$, $CHCl_3$). IR: 3384, 2955, 1454, 1095, 1011. ^{1}H-NMR: 2.77 (*dd*, $J = 10.5$, 5.5, 1 H); 1.65 (*dq*, $J = 12.5$, 3.5, 1 H); 1.54 (*d*, $J = 5$, 1 H); 1.5 (*m*, 1 H); 1.1–1.4 (*m*, 3 H); 1.0 (*m*, 1 H); 0.99 (*s*, 3 H); 0.97 (*d*, $J = 7.5$, 3 H); 0.85 (*d*, $J = 6.5$, 3 H); 0.71 (*s*, 3 H). ^{13}C-NMR: 84.0 (*d*); 40.8 (*d*); 39.0 (*s*); 34.3 (*d*); 33.5 (*t*); 30.2 (*t*); 25.8 (*q*); 19.4 (*q*); 15.8 (*q*);12.5 (*q*). MS: 156 (84, M^+), 138 (20), 123 (100), 113 (37), 109 (36), 95 (55).

*(−)-(1*S*,3*R*,6*R*)-2,2,3,6-Tetramethylcyclohexanol* (**15** (1*S*,3*R*,6*R*)). As described above, (−)-(3*R*,6*R*)-2,2,3,6-tetramethylcyclohexanone [19] was reduced to **15** (1*S*,3*R*,6*R*); ee > 98% (*Megadex*). $[\alpha]_D^{20} = -17.4$ ($c = 4.0$, $CHCl_3$).

*(±)-*cis*-2-(*tert*-Butyl)cyclohexanol* ((+)-*cis*-**21**) [29]. An 80:20 *cis*/*trans* mixture of 2-(*tert*-butyl)cyclohexyl acetate was fractionated over a 1-m *Sulzer* distillation column, and the first fractions containing the almost pure *cis* isomer were collected at 59.5–60°/1 mbar. A 96:4 *cis*/*trans* fraction was left to crystallize at r.t., and the solid was liberated from the remaining oil by washing with cold hexanes (0°) to produce > 99.5% *cis* acetate. *cis*-2-(*tert*-Butyl)cyclohexyl acetate (25.0 g, 0.126 mol) was dissolved in MeOH (100 ml), and 25% aq. KOH soln. (85 ml, 0.38 mol) was added under magnetic stirring. Heating to 75° (oil bath 100°) and keeping under reflux for 3 days converted 98% of the ester. The mixture was cooled down to 25°, diluted with Et_2O (100 ml), and poured onto 10% aq. sulfuric acid (250 ml). The org. phase was washed with H_2O, dried, and evaporated. Crystallization from hexanes afforded 11.5 g (59%) of crystalline (+)-*cis*-**21**; purity 99.6% (GLC). M.p. 53°.

*(±)-*trans*-2-(*tert*-Butyl)cyclohexanol* ((+)-*trans*-**21**) [30]. According to [30], 2-(*tert*-butyl)cyclohexanone was reduced with Na/^{i}PrOH in toluene to (±)-*trans*-**21**, which was crystallized from hexanes.

*(−)-(1*R*,2*S*)- and (+)-(1*S*,2*R*)-2-(*tert*-Butyl)cyclohexanol* (**21** (1*R*,2*S*) and (1*S*,2*R*), resp.). To a soln. of (±)-*trans*-**21** (18.0 g, 115 mmol) in pyridine (250 ml) and *N*,*N*-dimethylpyridin-4-amine (0.50 g) at r.t., (−)-camphanoyl chloride (ee 99%; 25.8 g, 119 mmol) was added and allowed to react for 1 day. The mixture was poured onto ice-water and the precipitate recovered by filtration. The precipitate was washed with ice-water, dried *in vacuo*, and crystallized from pentanes. On fractional crystallization, the (−)-(1*R*,2*S*)/(−)-camphanic

ester diastereoisomer crystallized as cubic-like crystals, whereas the other diastereoisomer crystallized as thin needles. Gentle blowing of N_2 gas with a pipette allowed an efficient enrichment of the fractions. The purified individual diastereoisomers were then hydrolyzed with the molar amount of KOH in refluxing MeOH.

Data of **21** (1*R*,2*S*): $[\alpha]_D^{20} = -42.6$ ($c = 1.1$, $CHCl_3$) ([22]: $[\alpha]_D^{28} = -44.4$); ee 99% (*Megadex*).

Data of **21** (1*S*,2*R*): $[\alpha]_D^{20} = +39.9$ ($c = 1.0$, $CHCl_3$) ([22]: $[\alpha]_D^{20} = +44.2$); ee 98% (*Megadex*).

*(−)-(1*R,2S,5R*)-2-(*tert*-Butyl)-5-methylcyclohexanol* (**22** (1*R*,2*S*,5*R*)). [22][31]. According to the published protocol [31], (+)-(5*R*)-pulegone was transformed in two steps (1,4-methyl addition, dissolving-metal reduction) to **22**. Crystallization afforded pure (1*R*,2*S*,5*R*)-**22**. $[\alpha]_D^{20} = -38.5$ ($c = 3.5$, $CHCl_3$) ([22]: $[\alpha]_D = -28$); ee 95% (*Megadex*).

*(+)-(1*S,2R,5S*)-2-(*tert*-Butyl)-5-methylcyclohexanol* (**22** (1*S*,2*R*,5*S*)). As described above, from (−)-(5*S*)-pulegone. Despite the crystallization, the obtained **22** (1*S*,2*R*,5*S*) remained contaminated by 5% of the (1*R*,2*S*,5*S*) diastereoisomer originating from the minor methyl 1,4-addition ketone. $[\alpha]_D^{20} = +29.0$ ($c = 3.5$, $CHCl_3$); ee 96% (*Megadex*).

2.3. *Oxiranes. (−)-(*2S*)-2-Propyloxirane* ((*S*)-**10**). Diazotization of (*R*)-norvaline to (2*R*)-2-chloropentanoic acid followed by $LiAlH_4$ reduction to (2*R*)-2-chloropentan-1-ol and ring closure with inversion under treatment with KOH was performed according to the published procedure [15a][32]. To a soln. of (*R*)-norvaline (48.5 g, 0.41 mol) in 6M HCl (700 ml) at −8°, $NaNO_2$ (46.4 g, 0.67 mol) was added under vigorous stirring maintaining the temp. between −8° and −5°. After stirring for 15 h at −5°, the mixture was extracted with Et_2O (2 × 200 ml). The combined Et_2O extract was washed with brine, dried (Na_2SO_4), and evaporated to yield 48.1 g of crude chloro acid. This acid was dissolved in Et_2O (50 ml) and added dropwise to a suspension of $LiAlH_4$ (12.5 g, 0.33 mol) in Et_2O (200 ml) at −10°. Excess hydride was destroyed with H_2O (30 ml), and 10% aq. H_2SO_4 soln. (250 ml) was added to dissolve the resulting aluminium salts. Decantation, extraction of the aq. phase with Et_2O (2 × 10 ml), drying, and evaporation at atmospheric pressure left an oil that was distilled through a 15-cm *Vigreux* column to afford 27.2 g of (2*R*)-2-chloropentan-1-ol, b.p. 88–90°/15 mbar. For purification, this intermediate was esterified with 2,4-dinitrobenzoyl chloride (57.5 g, 250 mmol) in pyridine (33 g, 0.42 mol) and toluene (500 ml) for 15 h at 25°. Then the mixture was poured onto ice-water (300 ml). Decantation, extraction with Et_2O (2 × 100 ml), drying, and evaporation left a crude solid ester, which crystallized five times from $^iPr_2O$/EtOH 2:1 to afford 26 g (39%) of the very pure dinitrobenzoate. M.p. 66–68° ([33]: 69.5–71°).

The alcohol was liberated upon treatment of the ester with 30% NaOMe in MeOH. Pure (2*R*)-2-chloropentan-1-ol (6.94 g, 56.5 mmol) was cooled to 0°, and freshly ground KOH (6.4 g, 110 mmol) was added in one portion. The mixture was stirred at 25° for 1 h and then bulb-to-bulb distilled at atmospheric pressure. A second distillation from CaH_2 afforded 4.7 g (96% from (2*R*)-2-chloropentan-1-ol) of (*S*)-**10**, b.p. 90°; ee > 99%, as shown by the absence of detectable signals of the antipode in the ^{1}H-NMR recorded in the presence of the shift reagent [Eu(hfbc)$_3$]. $[\alpha]_D^{25} = -15.8$ ($c = 1.0$, $CHCl_3$) ([15a]: $[\alpha]_D^{24} = -16.8$; [15b]: $[\alpha]_D^{21} = -12$).

*(+)-(*2R*)-2-Propyloxirane* ((*R*)-**10**). As described above, from (*S*)-norvaline in ee >99% (^{1}H-NMR with [Eu(hfbc)$_3$]). $[\alpha]_D^{25} + 16.0$ ($c = 1.0$, $CHCl_3$).

*(−)-(*2S*)-2-Ethyloxirane* ((*S*)-**18**). As described above, from (2*R*)-2-aminobutanoic acid in ee 96% (^{1}H-NMR with [Eu(hfbc)$_3$]). $[\alpha]_D^{25} = -4.3$ ($c = 8.6$, $CHCl_3$).

*(+)-(*2R*)-2-Ethyloxirane* ((*R*)-**18**). As described above, from (2*S*)-2-aminobutanoic acid in ee 97% (^{1}H-NMR with [Eu(hfbc)$_3$]). $[\alpha]_D^{25} = +4.4$ ($c = 8.3$, $CHCl_3$) ([20a]: $[\alpha]_D^{25} = +8.2$).

3. Norlimbanol® (**1**) *and Alcohol* **13**. *(−)-(1*R,6S*)-2,2,6-Trimethyl-1-[(phenylthio)methyl]cyclohexane (=(−)-2*R,3S*)-1,1,3-Trimethyl-2-[(phenylthio)methyl]cyclohexane)*. At 0°, (1*R*,6*S*)-**9** (=(3*S*)-dihydrocyclocitral) (purity 84%; 19.2 g, 0.10 mol) was added to a soln. of $NaBH_4$ (5.0 g, 0.13 mol) in EtOH (150 ml). After stirring for 3 h at 0°, the mixture was poured onto H_2O (500 ml) and extracted with pentanes. The combined org. phase was dried and evaporated. The crude oil (20.3 g) was dissolved in pyridine (200 ml), and TsCl (27.4 g, 0.14 mol) was added in five portions. After stirring for 15 h, the mixture was poured onto ice-water (500 ml) and extracted with pentanes. The combined extract was washed with ice-cold 10% aq. HCl soln., aq. $NaHCO_3$ soln., and brine, dried, and evaporated. The crude oil (29 g) was dissolved in EtOH (50 ml) and added dropwise to a soln. obtained by reacting thiophenol (21.5 g, 0.20 mol) with potassium (7.7 g, 0.20 mol) in EtOH (450 ml) at 0°. The mixture was stirred for 15 h at 25°, then poured onto H_2O (1 l), and extracted with pentanes. The combined extract was washed with 10% aq. NaOH, aq. NH_4Cl, and aq. $NaHCO_3$ solns., dried, and evaporated. Distillation of the concentrate through a 10-cm *Vigreux* column yielded 16.5 g (64% from dihydrocyclocitral) of (−)-(1*R*,6*S*)-2,2,6-trimethyl-1-[(phenylthio)methyl]cyclohexane. B.p. 117–119°/1 mbar. $[\alpha]_D^{20} = -11.1$ ($c = 4$, $CHCl_3$). IR (neat): 3010, 2900, 1580, 1475, 1360, 1167, 1018, 945. ^{1}H-NMR: 7.29 (*m*, 4 H); 7.16 (*m*, 1 H); 3.01 (*dd*, *J* = 11.0, 3.5, 1 H); 2.76 (*dd*, *J* = 11.0, 5.4, 1 H); 1.67 (*m*, 1 H); 1.3–1.6 (*m*, 5 H); 1.19 (*m*, 1 H); 1.0–1.1

(*m*, 1 H); 1.01 (*d*, *J* = 7.7, 3 H); 0.93 (*s*, 3 H); 0.88 (*s*, 3 H). MS: 248 (29, M^+), 138 (10), 123 (55), 109 (100), 95 (35), 83 (33), 69 (43), 55 (26), 41 (30).

*(+)-(1*S*,6*R*)-2,2,6-Trimethyl-1-[(phenylthio)methyl]cyclohexane* (*=(+)-(2*S*,3*R*)-1,1,3-Trimethyl-2-[(phenylthio)methyl]cyclohexane)*. As described above, in three steps and 62% overall yield from (1*S*,6*R*)-**9** (=(3*R*)-dihydrocyclocitral). $[\alpha]_D^{25}$ + 12.4 (*c* = 4, $CHCl_3$).

2,2,6,6-Tetramethyl-1-[(phenylthio)methyl]cyclohexane (*=1,1,3,3-Tetramethyl-2-[(phenylthio)methyl]cyclohexane)*. As described above, in three steps and 65% overall yield from 2,2,6,6-tetramethylcyclohexanecarboxaldehyde (**12**; 98 g, 0.58 mol). IR (CH_2Cl_2): 3073, 2920, 1580, 1480, 1435, 1384, 1091, 733. ^{1}H-NMR: 7.3 (*m*, 4 H); 7.14 (*dt*, *J* = 7.5, 1 H); 2.86 (*d*, *J* = 4.1, 2 H); 1.57 (*m*, 1 H); 1.43 (*m*, 3 H); 1.20 (*m*, 3 H); 0.96 (*s*, 6 H); 0.91 (*s*, 6 H). ^{13}C-NMR: 138.9 (*s*); 128.8 (*d*); 128.7 (*d*); 125.5 (*d*); 55.5 (*d*); 42.3 (*t*); 35.0 (*s*); 33.5 (*q*); 31.2 (*t*); 21.6 (*q*); 19.0 (*t*). MS: 262 (96, M^+), 137 (23), 123 (44), 109 (43), 97 (72), 83 (67), 69 (100), 57 (55), 41 (47).

*(+)-(1*R*,6*S*)-2,2,6-Trimethyl-1-[(phenylsulfonyl)methyl]cyclohexane* (*=(+)-(2*R*,3*S*)-1,1,3-Trimethyl-2-[(phenylsulfonyl)methyl]cyclohexane)*. At 0°, 3-chloroperbenzoic acid (28 g, 0.16 mol) was added in five portions over 15 min to a soln. of (1*R*,6*S*)-2,2,6-trimethyl-1-[(phenylthio)methyl]cyclohexane (16.5 g, 66.5 mmol) in CH_2Cl_2 (250 ml) at 0°. The ice bath was removed and the mixture stirred for 15 h. The mixture was poured onto H_2O (500 ml) and extracted with Et_2O (3 × 100 ml). The combined extract was washed twice with aq. $NaHCO_3$ soln. (100 ml), once with brine (100 ml), dried, and evaporated. The viscous oily concentrate crystallized on standing to yield 18.5 g (98%) of sulfone. Triple crystallization from warm EtOH yielded a very pure material; the ^{1}H-NMR in the presence of [Eu(hfbc)$_3$] did not show any signals from the antipode. M.p. 73°. $[\alpha]_D^{20}$ = +23.7 (*c* = 3.9, toluene). IR ($CHCl_3$): 3112, 2900, 1580, 1440, 1295, 1168, 1143, 975. ^{1}H-NMR: 7.93 (*d*, *J* = 7.0, 2 H); 7.64 (*t*, *J* = 7.0, 1 H); 7.56 (*t*, *J* = 7.0, 2 H); 3.11 (*dd*, *J* = 15, 3.5, 1 H); 2.94 (*dd*, *J* = 15, 4.0, 1 H); 1.70 (*m*, 1 H); 1.61 (*m*, 1 H); 1.52–2.0 (*m*, 5 H); 1.02 (*m*, 1 H); 0.94 (*d*, *J* = 7.0, 3 H); 0.83 (*s*, 3 H); 0.72 (*s*, 3 H). ^{13}C-NMR: 141.0 (*s*); 133.4 (*d*); 129.2 (*d*); 128.1 (*d*); 57.4 (*t*); 46.6 (*d*); 41.4 (*t*); 36.0 (*t*); 34.3 (*s*); 33.7 (*d*); 30.6 (*q*); 21.7 (*t*); 21.0 (*q*); 20.0 (*q*). MS: 280 (1, M^+), 169 (3), 138 (83), 123 (48), 109 (10), 95 (39), 83 (52), 77 (100), 69 (42), 55 (43), 51 (18), 41 (39).

*(−)-(1*S*,6*R*)-2,2,6-Trimethyl-1-[(phenylsulfonyl)methyl]cyclohexane* (*=(−)-(2*S*,3*R*)-1,1,3-Trimethyl-2-[(phenylthio)methyl]cyclohexane)*. As described above, by oxidation of (1*S*,6*R*)-2,2,6-trimethyl-1-[(phenylthio)methyl]cyclohexane in 98% yield. Crystallization afforded the sulfone as a single pure enantiomer with identical spectroscopic properties; the ^{1}H-NMR in the presence of [Eu(hfbc)$_3$] did not show any signals from the antipode. $[\alpha]_D^{25}$ = −24.5 (*c* = 3.5, toluene).

2,2,6,6-Tetramethyl-1-[(phenylsulfonyl)methyl]cyclohexane (*=1,1,3,3-Tetramethyl-2-[(phenylsulfonyl)methyl]cyclohexane)*. As described above by oxidation of 2,2,6,6-tetramethyl-1-[(phenylthio)methyl]cyclohexane (61 g, 0.23 mol) in 90% yield. Crystallization from warm EtOH provided a very pure material. M.p. 129°. IR (CH_2Cl_2): 3070, 2950, 1581, 1446, 1303, 1145, 1085, 735. ^{1}H-NMR: 7.93 (*d*, *J* = 8.0, 2 H); 7.5–7.7 (*m*, 3 H); 3.07 (*d*, *J* = 4.0, 2 H); 1.90 (*t*, *J* = 4.5, 1 H); 1.4–1.6 (*m*, 4 H); 1.26 (*td*, *J* = 4.0, 14, 2 H); 0.92 (*s*, 6 H); 0.80 (*s*, 6 H). ^{13}C-NMR: 141.4 (*s*); 133.4 (*d*); 129.2 (*d*); 127.8 (*d*); 56.0 (*t*); 48.5 (*d*); 41.7 (*t*); 34.5 (*s*); 33.4 (*q*); 21.9 (*q*); 18.8 (*t*). MS: 294 (1, M^+), 211 (5), 143 (44), 109 (25), 97 (46), 83 (37), 77 (33), 69 (100), 55 (6033), 69 (100), 55 (60), 41 (39).

*(1′*R*,3*S*,6′*S*)*-Norlimbanol® (**1A**). A soln. of (1*R*,6*S*)-2,2,6-trimethyl-1-[(phenylsulfonyl)methyl]cyclohexane (4.8 g, 17 mmol) in 100 ml THF was cooled to −30°, and 1.60M BuLi in hexanes (11.0 ml, 17.6 mmol) was added dropwise. The mixture was kept at −30° for 2.5 h before cooling to −78°. Then (*S*)-**10** (2.0 g, 23 mmol) in hexamethylphosphoric triamide (HMPA; 15 ml) was added, followed by dropwise addition of $BF_3 \cdot OEt_2$ (3.0 ml, 24 mmol). After stirring for 5 h at −78°, the mixture was allowed to slowly warm up to 25° overnight. The mixture was poured onto H_2O (200 ml), decanted, and extracted with Et_2O (3 × 50 ml). The combined org. phase was dried and evaporated and the residue subjected to CC (silica gel 2% → 6% AcOEt/toluene): *β*-hydroxy sulfone. The latter was dissolved in THF (100 ml) and cooled to −78°. Preformed 0.7M naphthalenyllithium/THF was added dropwise until a dark green color persisted (40 ml, 28 mmol). After 10 min at −78°, EtOH (20 ml) was added, and the mixture was allowed to warm up to 25°. The mixture was poured onto H_2O and extracted with hexanes (3 × 50 ml). The extracts were washed with 10% aq. NaOH soln., 10% HCl soln., and brine, dried, and evaporated. The crude material was filtered with hexane, then Et_2O over SiO_2 (50 g) to remove naphthalene, the filtrate evaporated, and the residue bulb-to-bulb distilled at 190°/0.5 mbar: 1.6 g (42% from the sulfone) of a 5.5 : 1 mixture **1A**/**11A**. The crude **1A**/**11A** was acetylated with Ac_2O (11 g, 0.11 mol) in Et_3N (3 ml) in the presence of *N*,*N*-dimethylpyridin-4-amine (50 mg) during 1 h at 0°. The acetylation mixture was poured onto ice and extracted with hexanes (3 × 50 ml). The extracts were washed with brine, dried, and evaporated. The residue was dissolved in hexane (25 ml) and the soln. cooled to −78° and saturated with ozone for 30 min until a blue color persisted. The soln. was degassed with N_2, warmed up to 0°,

and added over 10 min to a slurry of $LiAlH_4$ (1.0 g, 26 mmol) in Et_2O (20 ml). The temp. was allowed to rise to reflux temp., then the mixture was allowed to cool down over 1 h. The mixture was hydrolyzed with 3% aq. NaOH soln. (5 ml), then with H_2O (100 ml). Extraction with Et_2O (3×50 ml), drying, and evaporation left the almost pure **1A** which was subjected to CC (SiO_2, AcOEt/cyclohexane 3:97). Bulb-to-bulb distillation of the pure fractions' concentrate provided 0.85 g of pure **1A**.

(+)-(3S)-1-[(1R,6S)-2,2,6-trimethylcyclohexyl]hexan-3-ol (**1A** (1′*R*,3*S*,6′*S*)). $[\alpha]_D^{20} = +12.6$ ($c = 10.0$, EtOH); de 99%, ee >99% (acetate, *Chirasil*; ^{1}H-NMR in the presence of $[Eu(hfbc)_3]$). IR: 3310, 2860, 1450, 1362, 994. ^{1}H-NMR: 3.56 (*s*, 1 H); 1.2–1.7 (*m*, 14 H); 1.0–1.2 (*m*, 2 H); 0.93 (*t*, $J = 7.2$, 3 H); 0.89 (*s*, 3 H); 0.88 (*d*, $J = 6.6$, 3 H); 0.79 (*s*, 3 H); 0.54 (*ddd*, $J = 10.8, 4.4, 2.0$, 1 H). ^{13}C-NMR: 72.5 (*d*); 53.6 (*d*); 42.3 (*t*); 40.1 (*t*); 39.5 (*t*); 36.6 (*t*); 34.6 (*d*); 34.5 (*s*); 30.8 (*q*); 25.6 (*t*); 22.1 (*t*); 21.2 (*q*); 20.0 (*q*); 18.9 (*t*); 14.1 (*q*). MS: 226 (0, M^+), 208 (15), 193 (28), 183 (12), 165 (12), 152 (11), 138 (28), 124 (45), 109 (57), 95 (43), 82 (45), 69 (68), 55 (100), 41 (88).

The same conditions were used to prepare alcohols **1B**, **1C**, **1D**, **13A**, and **13B**.

(−)-(3R)-1-[(1S,6R)-2,2,6-Trimethylcyclohexyl]hexan-3-ol (**1B** (1′*S*,3*R*,6′*R*)). From (1*S*,6*R*)-2,2,6-trimethyl-1-[(phenylsulfonyl)methyl]cyclohexane and (*R*)-**10** in 14% yield; de 99%, ee >99% (acetate, *Chirasil*; ^{1}H-NMR in the presence of $[Eu(hfbc)_3]$). $[\alpha]_D^{20} = -11.1$ ($c = 9.9$, EtOH). Anal. data: identical to those of **1A**.

(+)-(3R)-1-[(1R,6S)-2,2,6-Trimethylcyclohexyl]hexan-3-ol (**1C** (1′*R*,3*R*,6′*S*)). From (+)-(1*R*,6*S*)-2,2,6-trimethyl-1-[(phenylsulfonyl)methyl]cyclohexane and (*R*)-**10** in 14% yield; de 99%, ee >99% (acetate, *Chirasil*; ^{1}H-NMR in the presence of $[Eu(hfbc)_3]$). $[\alpha]_D^{20} = +12.1$ ($c = 10.0$, EtOH). IR: 3310, 2860, 1450, 1360, 1120, 998. ^{1}H-NMR: 3.56 (*m*, 1 H); 1.61 (*d*, $J = 12.8$, 1 H); 1.3–1.6 (*m*, 13 H); 1.1–1.3 (*m*, 2 H); 0.93 (*t*, $J = 7.5$, 3 H); 0.90 (*d*, $J = 7.0$, 3 H); 0.89 (*s*, 3 H); 0.79 (*s*, 3 H); 0.53 (*ddd*, $J = 10.7, 5.1, 2.0$, 1 H). ^{13}C-NMR: 72.2 (*d*); 53.5 (*d*); 42.3 (*t*); 40.0 (*t*); 39.6 (*t*); 36.7 (*t*); 34.7 (*d*); 34.5 (*s*); 30.8 (*q*); 25.6 (*t*); 22.2 (*t*); 21.3 (*q*); 20.0 (*q*); 18.9 (*t*); 14.5 (*q*). MS: 226 (0, M^+); 208 (13), 193 (23), 183 (13), 165 (11), 152 (10), 138 (26), 123 (43), 109 (52), 95 (44), 82 (40), 69 (73), 55 (100), 41 (85).

(−)-(3S)-1-[(1S,6R)-2,2,6-Trimethylcyclohexyl]hexan-3-ol (**1D** (1′*S*,3*S*,6′*R*)). From (1*S*,6*R*)-2,2,6-trimethyl-1-[(phenylsulfonyl)methyl]cyclohexane and (*S*)-**10** in 21% yield; de 99%, ee >99% (acetate, *Chirasil*; ^{1}H-NMR in the presence of $[Eu(hfbc)_3]$). $[\alpha]_D^{20} = -11.6$ ($c = 10.1$, EtOH). Anal. data: identical to those of **1C**.

(+)-(3S)-1-(2,2,6,6-Tetramethylcyclohexyl)hexan-3-ol (**13A** (3*S*)). From 2,2,6,6-tetramethyl-1-[(phenylsulfonyl)methyl]cyclohexane and (*S*)-**10** in 20% yield; ee >99% (acetate, *Chirasil*; ^{1}H-NMR in the presence of $[Eu(hfbc)_3]$). $[\alpha]_D^{20} = +1.35$ ($c = 3.4$, $CHCl_3$). IR: 3350, 2900, 1480, 1380, 1360, 1125, 995. ^{1}H-NMR: 3.57 (*m*, 1 H); 1.3–1.6 (*m*, 12 H); 1.1–1.3 (*m*, 3 H); 0.94 (*t*, $J = 7.0$, 3 H); 0.85 (*s*, fine structure, 12 H); 0.75 (*t*, $J = 3.5$, 1 H). ^{13}C-NMR: 72.4 (*d*); 56.0 (*d*); 42.4 (*t*); 41.9 (*t*); 39.5 (*t*); 35.0 (*s*); 33.3 (*q*); 22.8 (*t*); 21.5 (*q*); 19.2 (*t*); 18.9 (*t*); 14.1 (*q*). MS: 240 (0, M^+), 222 (5), 152 (10), 137 (12), 123 (27), 109 (33), 99 (28), 95 (31), 83 (52), 69 (100), 55 (54), 41 (20).

(−)-(3R)-1-(2,2,6,6-Tetramethylcyclohexyl)hexan-3-ol (**13B** (3*R*)). From 2,2,6,6-tetramethyl-1-[(phenylsulfonyl)methyl]cyclohexane and (*R*)-**10** in 16% yield; ee >99% (acetate, *Chirasil*; ^{1}H-NMR in the presence of $[Eu(hfbc)_3]$). $[\alpha]_D^{20} = -1.4$ ($c = 4.0$, $CHCl_3$). Anal. data: identical to those of **13A**.

4. *Alkoxy Alcohol Isomers.* The procedure for the synthesis of alkoxy alcohol **3A** given below is representative of all the cyclohexanol coupling reactions with optically active oxiranes.

Under Ar, a 35% KH dispersion in mineral oil (2.7 g, 23 mmol) was washed twice with anh. pentane (20 ml), decanted, and then suspended in dry THF (30 ml). To this suspension was added dropwise over 10 min **14** (1*R*,6*S*) (2.20 g, 15.5 mmol) in (5 ml) THF. The mixture was stirred for 2 h before the addition of DMPU (2.0 ml). The mixture was then heated to reflux (bath 80°), and (*S*)-**10** (1.73 g, 20.1 mmol) was added in one portion. The mixture was kept at 80° overnight until *ca.* 90% of the starting **14** had disappeared. The mixture was poured onto ice-water (100 ml) and extracted twice with pentane (50 ml). The combined org. phase was washed twice with brine (100 ml), dried, and evaporated. The crude oil (4.2 g) was subjected to CC (silica gel (250 g), cyclohexane/AcOEt 9:1). The pure fractions were bulb-to-bulb distilled at 110° (oven)/0.1 Torr: 0.85 g (23% based on **14**) of *(+)-(2S)-1-{[(1R,6S)-2,2,6-Trimethylcyclohexyl]oxy}pentan-2-ol* (**3A** (1′*R*,2*S*,6′*S*)). Colorless liquid. $[\alpha]_D^{20} = +30.0$ ($c = 4$, $CHCl_3$); de 98%, ee 99% (*Megadex*). IR: 3444*w* (br.), 2922, 2865*s*, 1454*s*, 1380, 1364*m*, 1093*s*. ^{1}H-NMR: 3.8 (*m*, 1 H); 3.59 (*dd*, $J = 3.0, 9.0$, 1 H); 3.4 (*m*, 1 H); 2.48 (*d*, $J = 10$, 1 H); 2.45 (*d*, $J = 4.0$, 1 H); 1.3–1.7 (*m*, 10 H); 1.2 (*m*, 1 H); 0.99 (*s*, 3 H); 0.96 (*d*, $J = 6.0$, 3 H); 0.93 (*t*, $J = 7$, 3 H); 0.89 (*s*, 3 H). ^{13}C-NMR: 92.3 (*d*); 78.3 (*t*); 70.7 (*d*); 40.2 (*t*); 36.9 (*s*); 35.2 (*t*); 34.8 (*d* + *t*); 30.1 (*q*); 21.5 (*t*); 19.5 (*q*); 19.4 (*q*); 18.8 (*t*); 14.1 (*q*). MS: 228 (100, M^+), 213 (3), 157 (38), 142 (20), 125 (47), 109 (32), 82 (60), 69 (67).

(−)-(2R)-1-{[(1S,6R)-2,2,6-Ttrimethylcyclohexyl]oxy}pentan-2-ol (**3B** (1′*S*,2*R*,6′*R*)). From **14** (1*S*,6*R*) and (*R*)-**10** in 15% yield; de 98%, ee 99% (*Megadex*). $[\alpha]_D^{20} = -29.7$ ($c = 4$, $CHCl_3$). Anal. data: identical to those of **3A**.

*(+)-(2*R*)-1-{[(1*R*,6*S*)-2,2,6-Trimethylcyclohexyl]oxy}pentan-2-ol* (**3C** (1′*R*,2*R*,6′*S*)). From **14** (1*R*,6*S*) and (*R*)-**10** in 18% yield; de 98%, ee 99% (*Megadex*). $[\alpha]_D^{20} = +26.3$ ($c = 4.0$, $CHCl_3$). IR: 3426, 2923, 1454, 1380, 1093. ^{1}H-NMR: 3.8 (*m*, 1 H); 3.5 (*m*, 2 H); 2.54 (*d*, *J* = 3.0, 1 H); 2.47 (*d*, *J* = 10, 1 H); 1.3–1.7 (*m*, 10 H); 1.2 (*m*, 1 H); 0.97 (*d*, *J* = 6.0, 3 H); 0.96 (*s*, 3 H); 0.93 (*t*, *J* = 7.0, 3 H); 0.88 (*s*, 3 H). ^{13}C-NMR: 92.4 (*d*); 78.3 (*t*); 70.7 (*d*); 40.1 (*t*); 36.8 (*s*); 35.3 (*t*); 34.9 (*d* + *t*); 30.1 (*q*); 21.5 (*t*); 19.5 (*q*); 19.3 (*q*); 18.8 (*t*); 14.2 (*q*). MS: 228 (100, M^+), 213 (3), 157 (33), 142 (19), 125 (44), 109 (31), 95 (16), 87 (20), 82 (53), 69 (56).

*(−)-(2*S*)-1-{[(1*S*,6*R*)-2,2,6-Trimethylcyclohexyl]oxy}pentan-2-ol* (**3D** (1′*S*,2*S*,6′*R*)). From **14** (1*S*,6*R*) and (*S*)-**10** in 25% yield. $[\alpha]_D^{20} = -23.9$ ($c = 4$, $CHCl_3$); de 98%, ee 99% (*Megadex*). Anal. data: identical to those of **3C**.

*(+)-(2*S*)-1-{[(1*R*,3*S*,6*S*)-2,2,3,6-Tetramethylcyclohexyl]oxy}pentan-2-ol* (**4A** (1′*R*,2*S*,3′*S*,6′*S*)). From **15** (1*R*,3*S*,6*S*) and (*S*)-**10** in 41% yield; de 97% (^{1}H-NMR), ee 99% (*Megadex*). $[\alpha]_D^{20} = +25.5$ ($c = 4.1$, $CHCl_3$). IR: 3436, 2955, 1452, 1098. ^{1}H-NMR: 3.80 (*ddd*, *J* = 15.4, 7.5, 3.1, 1 H); 3.59 (*dd*, *J* = 8.0, 3.1, 1 H); 3.40 (*t*, *J* = 9.0, 1 H); 2.46 (*d*, *J* = 3.5, 1 H); 2.42 (*d*, *J* = 10.3, 1 H); 1.1–1.7 (*m*, 8 H); 1.0 (*m*, 2 H); 0.98 (*s*, 3 H); 0.95 (*d*, *J* = 6.0, 3 H); 0.94 (*t*, *J* = 7.1, 3 H); 0.82 (*d*, *J* = 6.3, 3 H); 0.75 (*s*, 3 H). ^{13}C-NMR: 92.7 (*d*); 78.3 (*t*); 70.6 (*d*); 40.9 (*d*); 40.2 (*s*); 35.1 (*d*); 34.7 (*d*); 33.7 (*t*); 30.2 (*t*); 26.2 (*q*); 15.6 (*q*); 18.8 (*t*); 15.6 (*q*); 14.1 (*q*); 13.6 (*q*). MS: 242 (60, M^+), 157 (25), 138 (100), 123 (42), 109 (22).

*(−)-(2*R*)-1-{[(1*S*,3*R*,6*R*)-2,2,3,6-Tetramethylcyclohexyl]oxy}pentan-2-ol* (**4B** (1′*S*,2*R*,3′*R*,6′*R*)). From **15** (1*S*,3*R*,6*R*) and (*R*)-**10** in 18% yield; de 96% (^{1}H-NMR), ee 99% (*Megadex*). $[\alpha]_D^{20} = -26.2$ ($c = 4.1$, $CHCl_3$). Anal. data: identical to those of **4A**.

*(+)-(2*R*)-1-{[(1*R*,3*S*,6*S*)-2,2,3,6-Tetramethylcyclohexyl]oxy}pentan-2-ol* (**4C** (1′*R*,2*R*,3′*S*,6′*S*)). From **15** (1*R*,3*S*,6*S*) and (*R*)-**10** in 39% yield; de 96% (^{1}H-NMR); ee 99% (*Megadex*). $[\alpha]_D^{20} = +22.7$ ($c = 3.9$, $CHCl_3$). IR: 3454, 2955, 1452, 1098. ^{1}H-NMR: 3.80 (*m*, 1 H); 3.5 (*m*, 2 H); 2.48 (*d*, *J* = 3.2, 1 H); 2.42 (*d*, *J* = 9.9, 1 H); 1.1–1.7 (*m*, 8 H); 0.96 (*d*, *J* = 6.0, 3 H); 0.95 (*s*, 3 H); 0.93 (*t*, *J* = 7.1, 3 H); 0.9–1.0 (*m*, 2 H); 0.82 (*d*, *J* = 6.0, 3 H); 0.73 (*s*, 3 H). ^{13}C-NMR: 92.9 (*d*); 78.3 (*t*); 70.6 (*d*); 40.9 (*d*); 40.1 (*s*); 35.2 (*t*); 34.7 (*d*); 33.8 (*t*); 30.2 (*t*); 26.1 (*q*); 19.7 (*q*); 18.8 (*t*); 15.6 (*q*); 14.1 (*q*); 13.5 (*q*). MS: 242 (55, M^+), 157 (25), 138 (100), 123 (42), 109 (21).

*(−)-(2*S*)-1-{[(1*S*,3*R*,6*R*)-2,2,3,6-Tetramethylcyclohexyl]oxy}pentan-2-ol* (**4D** (1′*S*,2*S*,3′*R*,6′*R*)). From **15** (1*S*,3*R*,6*R*) and (*S*)-**10** in 35% yield; de 95% (^{1}H-NMR), ee 99% (*Megadex*). $[\alpha]_D^{20} = -22.3$ ($c = 4.5$, $CHCl_3$). Anal. data: identical to those of **4C**.

*(+)-(2*S*)-1-[(2,2,6,6-Tetramethylcyclohexyl)oxy]butan-2-ol* (**16A** (2*S*)). *From* 2,2,6,6-tetramethylcyclohexanol (**17**) with (*S*)-**18** in 18% yield; ee 97% (*Megadex*). $[\alpha]_D^{20} = +5.4$ ($c = 3.4$, $CHCl_3$). IR: 3420, 2930, 1460, 1380, 1097. ^{1}H-NMR: 3.71 (*m*, 1 H); 3.61 (*dd*, *J* = 8.7, 3.5, 1 H); 3.49 (*dd*, *J* = 8.7, 7.5, 1 H); 2.64 (*s*, 1 H); 2.50 (*d*, *J* = 3.5, 1 H); 1.25–1.60 (*m*, 6 H); 1.15 (*dt*, *J* = 14, 4.0, 2 H); 0.97 (*t*, *J* = 7.5, 3 H); 0.97 (*s*, 3 H); 0.96 (*s*, 3 H); 0.92 (*s*, 3 H); 0.91 (*s*, 3 H). ^{13}C-NMR: 92.7 (*d*); 78.5 (*t*); 72.4 (*d*); 40.2 (*t*); 40.1 (*t*); 37.2 (*s*); 37.1 (*s*); 32.6 (*q*); 32.5 (*q*); 26.0 (*t*); 21.0 (*q*); 20.9 (*q*); 18.5 (*t*); 10.0 (*q*). MS: 228 (3, M^+), 138 (22), 123 (12), 109 (30), 82 (100), 69 (28), 55 (29), 41 (26).

*(−)-(2*R*)-1-[(2,2,6,6-Tetramethylcyclohexyl)oxy]butan-2-ol* (**16B** (2*R*)). From **17** with (*R*)-**18** in 20% yield; ee 97% (*Megadex*). $[\alpha]_D^{20} = -5.4$ ($c = 3.3$, $CHCl_3$). Anal. data: identical to those of **16A**.

*(±)-*cis*-1-[2-(*tert*-Butyl)cyclohexyl]oxy}butan-2-ol* ((±)-*cis*-**19**). From (±)-*cis*-**21** with (±)-2-ethyloxirane ((±)-**18**) as a 60 : 40 diastereoisomer mixture in 25% yield. ^{1}H-NMR: major diastereoisomer: 3.77 (*s*, 1 H); 3.67 (*m*, 1 H); 3.36 (*dd*, *J* = 8.7, 7.5, 1 H); 3.25 (*dd*, *J* = 8.9, 3.2, 1 H); 2.38 (*s*, 1 H); 2.03 (*d*, *J* = 13.9, 1 H); 1.77 (*m*, 1 H); 1.4–1.6 (*m*, 6 H); 1.0–1.3 (*m*, 3 H); 0.97 (*t*, *J* = 7.5, 3 H); 0.91 (*s*, 9 H); minor diastereoisomer: 3.77 (*s*, 1 H); 3.67 (*m*, 1 H); 3.54 (*dd*, *J* = 9.1, 3.5, 1 H); 3.08 (*dd*, *J* = 9.1, 7.5, 1 H); 2.33 (*s*, 1 H); 2.03 (*d*, *J* = 13.9, 1 H); 1.77 (*m*, 1 H); 1.4–1.6 (*m*, 6 H); 1.0–1.3 (*m*, 3 H); 0.98 (*t*, *J* = 7.5, 3 H); 0.92 (*s*, 9 H). ^{13}C-NMR: major diastereoisomer: 75.5 (*d*); 72.1 (*d*); 71.3 (*t*); 51.3 (*d*); 32.7 (*s*); 29.1 (*t*); 28.8 (*q*); 26.91 (*t*); 26.2 (*t*); 22.2 (*t*); 20.4 (*t*); 10.0 (*q*); minor diastereoisomer: 75.9 (*d*); 72.2 (*d*); 71.5 (*t*); 51.4 (*d*); 32.6 (*s*); 29.4 (*t*); 28.8 (*q*); 26.94 (*t*); 26.3 (*t*); 22.2 (*t*); 20.3 (*t*); 10.03 (*q*). MS: 228 (13, M^+), 213 (10), 138 (27), 123 (12), 95 (13), 83 (50), 73 (39), 67 (32), 57 (100), 55 (40), 41 (45).

*(−)-(2*S*)-1-{[(1*R*,2*S*)-2-(*tert*-Butyl)cyclohexyl]oxy}butan-2-ol* (**19A** (1′*R*,2*S*,2′*S*)). From **21** (1*R*,2*S*) and (*S*)-**18** in 25% yield; ee > 99%, de 97% (*Chirasil*). $[\alpha]_D^{20} = -57.6$ ($c = 4.3$, $CHCl_3$). IR: 3442, 2932, 1449, 1365, 1094. ^{1}H-NMR: 3.65 (*m*, 1 H); 3.62 (*dd*, *J* = 9.5, 3.5, 1 H); 3.12 (*m*, 2 H); 2.27 (*d*, *J* = 3.5, 1 H); 2.12 (*m*, 1 H); 1.81 (*dt*, *J* = 14, 3.0, 1 H); 1.70 (*m*, 3 H); 1.48 (*quint.*, *J* = 7.5, 2 H); 1.24 (*ddd*, *J* = 12.5, 9.3, 3.5, 1 H); 1.16 (*m*, 3 H); 0.97 (*t*, *J* = 7.5, 3 H); 0.96 (*s*, 9 H). ^{13}C-NMR: 81.7 (*d*); 72.4 (*d*); 71.8 (*t*); 51.6 (*d*); 33.0 (*s*); 31.8 (*t*); 29.4 (*q*); 27.0 (*t*); 26.4 (*t*); 26.2 (*t*); 24.7 (*t*); 10.0 (*q*). MS: 228 (11, M^+), 213 (10), 138 (27), 123 (15), 95 (16), 83 (58), 73 (46), 67 (38), 57 (100), 41 (53).

*(+)-(2*R*)-1-{[(1*S*,2*R*)-2-(*tert*-Butyl)cyclohexyl]oxy}butan-2-ol* (**19B** (1′*S*,2*R*,2′*R*)). From **21** (1*S*,2*R*) and (*R*)-**18** in 28% yield; ee > 99%, de 98%. $[\alpha]_D^{20} = +57.8$ ($c = 4.6$, $CHCl_3$). Anal. data: identical to those of **19A**.

*(−)-(2*R*)-1-{[(1*R*,2*S*)-2-(*tert*-Butyl)cyclohexyl]oxy}butan-2-ol* (**19C** (1′*R*,2*R*,2′*S*)). From **21** (1*R*,2*S*) and (*R*)-**18** in 28% yield; ee >99%, de 98% (*Chirasil*). $[\alpha]_D^{20} = -73.1$ ($c = 4.9$, $CHCl_3$). ^{1}H-NMR: 3.68 (*m*, 1 H); 3.41 (*t*, *J* = 8.0, 1 H); 3.30 (*dd*, *J* = 9.0, 3.5, 1 H); 3.11 (*dt*, *J* = 9.8, 4.0, 1 H); 2.32 (*d*, *J* = 3.2, 1 H); 2.12 (*m*, 1 H); 1.81 (*dt*, *J* = 14.0, 3.0, 1 H); 1.6–1.7 (*m*, 2 H); 1.47 (*quint.*, *J* = 7.5, 2 H); 1.1–1.3 (*m*, 5 H); 0.96 (*t*, *J* = 7.0, 3 H); 0.94 (*s*, 9 H). ^{13}C-NMR: 81.5 (*d*); 72.1 (*d*); 71.8 (*t*); 51.7 (*d*); 33.0 (*s*); 31.7 (*t*); 29.4 (*q*); 27.0 (*t*); 26.3 (*t*); 26.1 (*t*); 24.7 (*t*); 9.9 (*q*). MS: 228 (13, M^+), 213 (11), 138 (28), 123 (15), 95 (16), 83 (58), 73 (45), 67 (40), 57 (100), 41 (52).

*(+)-(2*S*)-1-{[(1*S*,2*R*)-2-(*tert*-Butyl)cyclohexyl]oxy}butan-2-ol* (**19D** (1′*S*,2*S*,2′*R*)). From **21** (1*S*,2*R*) and (*S*)-**18** in 24% yield; ee 97%, de 98% (*Chirasil*). $[\alpha]_D^{20} = +73.8$ ($c = 3.2$, $CHCl_3$). Anal. data: identical to those of **19C**.

*(−)-(2*S*)-1-{[(1*R*,2*S*,5*R*)-2-(*tert*-Butyl)-5-methylcyclohexyl]oxy}butan-2-ol* (**20A** (1′*R*,2*S*,2′*S*,5′*R*)). From **22** (1*R*,2*S*,5*R*) and (*S*)-**18** in 31% yield; de 95%, ee 92% (*Chirasil*). $[\alpha]_D^{20} = -68.1$ ($c = 3.5$, $CHCl_3$). IR: 3450, 2960, 1456, 1370, 1093. ^{1}H-NMR: 3.65 (*m*, 1 H); 3.62 (*dd*, *J* = 10, 3.2, 1 H); 3.14 (*m*, 2 H); 2.26 (*d*, *J* = 3.5, 1 H); 2.10 (*dq*, *J* = 12, 2.4, 1 H); 1.80 (*dq*, *J* = 13, 3.2, 1 H); 1.65 (*m*, 1 H); 1.48 (*quint.*, *J* = 7.5, 2 H); 1.33 (*m*, 1 H); 1.20 (*m*, 2 H); 0.97 (*t*, *J* = 7.5, 3 H); 0.96 (*s*, 9 H); 0.91 (*d*, *J* = 6.7, 3 H); 0.8–1.0 (*m*, 2 H). ^{13}C-NMR: 81.4 (*d*); 72.3 (*d*); 71.8 (*t*); 51.1 (*d*); 40.7 (*t*); 35.0 (*t*); 32.8 (*s*); 31.5 (*d*); 29.4 (*q*); 26.7 (*t*); 26.4 (*t*); 22.1 (*q*); 10.0 (*q*). MS: 242 (9, M^+), 227 (6), 152 (12), 143 (100), 137 (10), 97 (47), 81 (50), 71 (55), 57 (58), 41 (37).

*(+)-(2*R*)-1-{[(1*S*,2*R*,5*S*)-2-(*tert*-Butyl)-5-methylcyclohexyl]oxy}butan-2-ol* (**20B** (1′*S*,2*R*,2′*R*,5′*S*)). From **22** (1*S*,2*R*,5*S*) and (*R*)-**18** in 25% yield; de 95%, ee 93% (*Chirasil*). $[\alpha]_D^{20} = +67.1$ ($c = 3.9$, $CHCl_3$). Anal. data: identical to those of **20A**.

*(−)-(2*R*)-1-{[(1*R*,2*S*,5*R*)-2-(*tert*-Butyl)-5-methylcyclohexyl]oxy}butan-2-ol* (**20C** (1′*R*,2*R*,2′*S*,5′*R*)). From **22** (1*R*,2*S*,5*R*) and (*R*)-**18** in 25% yield; de 95%, ee 93% (*Chirasil*). $[\alpha]_D^{20} = -80.1$ ($c = 4.0$, $CHCl_3$); IR: 3460, 2930, 1456, 1370, 1108. ^{1}H-NMR: 3.68 (*m*, 1 H); 3.43 (*t*, *J* = 8.3, 1 H); 3.30 (*dd*, *J* = 9.1, 3.1, 1 H); 3.12 (*dt*, *J* = 10.3, 4.0, 1 H); 2.35 (*d*, *J* = 3.1, 1 H); 2.11 (*dq*, *J* = 12.3, 2.4, 1 H); 1.79 (*dq*, *J* = 12.5, 3.6, 1 H); 1.63 (*m*, 1 H); 1.47 (*m*, 2 H); 1.30 (*m*, 1 H); 1.17 (*ddd*, *J* = 12, 10.5, 3.5, 1 H); 0.96 (*t*, *J* = 7.5, 3 H); 0.95 (*s*, 9 H); 0.90 (*d*, *J* = 6.5, 3 H); 0.8–1.0 (*m*, 3 H). ^{13}C-NMR: 81.2 (*d*); 72.1 (*d*); 71.8 (*t*); 51.2 (*d*); 40.6 (*t*); 35.1 (*t*); 32.9 (*q*); 31.5 (*d*); 29.4 (*q*); 26.7 (*t*); 26.1 (*t*); 22.9 (*q*); 9.9 (*q*). MS: 242 (8, M^+), 227 (5), 152 (12), 143 (100), 137 (11), 97 (46), 81 (50), 71 (58), 57 (55), 41 (34).

*(+)-(2*S*)-1-{[(1*S*,2*R*,5*S*)-2-(*tert*-Butyl)-5-methylcyclohexyl]oxy}butan-2-ol* (**20D** (1′*S*,2*S*,2′*R*,5′*S*)). From **22** (1*S*,2*R*,5*S*) and (*S*)-**18** in 25% yield; de 95%, ee 92% (*Chirasil*). $[\alpha]_D^{20} = +78.4$ ($c = 4.0$, $CHCl_3$). Anal. data: identical to those of **20C**.

5. *Synthesis and Enantioselective Reduction of* **25**, **28**, *and* **30**. *(±)-*r*-2-(Allyloxy)-1,1,*t*-3,*c*-6-tetramethylcyclohexane* (=*(±)-(2*RS*,3*SR*,6*SR*)-1,1,3,6-Tetramethyl-2-(prop-2-enyloxy)cyclohexane*; **23**) [34]. A 20% KH dispersion in mineral oil (30 g, 0.15 mol) under Ar was washed twice with pentanes (50 ml) by stirring, decanting, and removing the liquid by pipette. Then, the residue was suspended in THF (100 ml), and (±)-2,2,*c*-3,*t*-6-tetramethylcyclohexan-*r*-1-ol (**15**) (20 g, 0.13 mol) in THF (10 ml) was added over 30 min. Stirring was continued for 1 h at 25°, before cooling to 0°. A soln. of allyl bromide (23 g, 0.19 mol) in DMSO (100 ml) was added within 1 h while keeping the temp. at 0°. The mixture was kept for 1 h at 0° after the addition, poured onto ice-water (500 ml), and partitioned with pentanes (3 × 100 ml). The combined org. phase was washed with 5% aq. ammonia (300 ml) and H_2O (2 × 200 ml), dried, and evaporated, and the crude oil (33 g) distilled through a 15-cm *Vigreux* column: 24 g (79%) of **23** purity 85% by GLC (*SP-2100*, 100–220°, 15°/min). Colorless liquid. B.p. 43–44°/0.1 Torr. A sample was bulb-to-bulb distilled to 96% purity. IR: 3080, 2921, 1648, 1456, 1387, 1098. ^{1}H-NMR: 5.96 (*dddd*, *J* = 17, 16, 10.5, 5.5, 1 H); 5.28 (*d*, *J* = 17, 1 H); 5.12 (*d*, *J* = 10.5, 1 H); 4.1 (*m*, 2 H); 2.42 (*d*, *J* = 10.4, 1 H); 1.6 (*m*, 2 H); 1.35–1.15 (*m*, 4 H); 0.97 (*s*, 3 H); 0.95 (*d*, *J* = 7, 3 H); 0.82 (*d*, *J* = 6, 3 H); 0.76 (*s*, 3 H). ^{13}C-NMR: 135.5 (*s*); 115.8 (*t*); 93.4 (*d*); 75.5 (*t*); 41.0 (*d*); 40.2 (*s*); 34.7 (*d*); 33.8 (*t*); 30.3 (*t*); 26.1 (*q*); 19.7 (*q*); 15.6 (*q*); 13.5 (*q*). MS: 196 (17, M^+), 138 (24), 123 (26), 111 (31), 109 (15), 97 (23), 96 (32), 95 (26), 83 (41), 81 (22), 69 (62), 41 (100).

*(±)-2-[(2,2,*c*-3,*t*-6-Tetramethylcyclohex*-r*-1-yloxy)methyl]oxirane* (**24**). A soln. of 70% pure 3-chloroperbenzoic acid (50 g, 0.2 mol) in CH_2Cl_2 (200 ml) was cooled to 0°, and a soln. of 85% **23** (19.5 g, 0.10 mol) in CH_2Cl_2 (200 ml) was added over 1.5 h at 0°. The mixture was allowed to reach 25° within 1 h, left overnight, and poured onto 10% aq. NaOH soln. (600 ml). After stirring for 30 min, the mixture was decanted, the separated org. phase washed with 10% aq. NaOH soln. (100 ml) and brine (200 ml), dried, and evaporated, and the crude oil (25 g) distilled through a 20-cm *Widmer* column: 19.0 g (85%) of **24** as a 6:4 diastereoisomer mixture (by ^{1}H-NMR) of 95% purity. Colorless liquid. IR: 3055, 2920, 1455, 1338, 1100. ^{1}H-NMR: 3.77 (*dd*, *J* = 21, 3.5, 1 H minor diastereoisomer); 3.74 (*dd*, *J* = 21, 4.0, 1 H major diastereoisomer); 3.6 (*m*, 1 H); 3.2 (*m*, 1 H); 2.80 (*t*, *J* = 5, 1 H); 2.60 (*dt*, *J* = 5.0, 2.5, 1 H); 2.42 (*d*, *J* = 10, 1 H); 1.6 (*m*, 2 H); 1.4–1.1 (*m*, 4 H); 1.0 (*m*, 6 H); 0.82

(*d*, *J* = 5.5, 3 H); 0.76 (*s*, 3 H major diastereoisomer); 0.75 (*s*, 3 H minor diastereoisomer). ^{13}C-NMR: 94.0, 93.9 (2*d*); 75.5, 75.2 (2*t*); 51.0, 50.9 (2*d*); 44.8, 44.6 (2*t*); 40.9, 40.8 (2*d*); 40.3 (*s*); 34.6 (*d*); 33.7 (*t*); 30.2 (*t*); 26.1, 26.0 (2*q*); 19.6, 19.5 (2*q*); 15.6 (*q*); 13.4 (*q*). MS: 212 (34, M^+), 138 (70), 127 (57), 123 (48), 109 (33), 96 (50), 83 (43), 69 (46), 57 (100).

*(±)-1-(2,2,*c*-3,*t*-6-Tetramethylcyclohex-*r*-1-yloxy)pentan-2-one* (**25**). A mixture of THF (60 ml), **24** (6.0 g, 26 mmol), and CuI (0.30 g, 1.5 mmol) under Ar was cooled to 0°, and 0.36M EtMgBr in THF (110 ml, 40 mmol) was added over 1.5 h while stirring. Stirring was continued for 30 min and the mixture allowed to warm to 25°. It was poured onto sat. aq. NH_4Cl soln. (400 ml), decanted with pentanes (3 × 100 ml) and washed with brine (100 ml). Drying, evaporation, and bulb-to-bulb distillation at 135° (oven temp.)/8 Torr provided 4.6 g (72%) of **4** as a 45 : 55 diastereoisomer mixture. Retention times and spectroscopic data: overlapping with those of the four single isomers **4A** – **D**.

A sample of **4** (4.0 g, 13 mmol) in CH_2Cl_2 (20 ml) was added to a suspension of pyridinium chlorochromate (14 g, 65 mmol) and *Celite* (15 g) in CH_2Cl_2 (300 ml) at 25°. The mixture was stirred for 30 min until conversion was complete and was filtered over SiO_2 (200 g). Bulb-to-bulb distillation of the concentrate at 85° (oven temp.)/0.1 Torr afforded 2.8 g (89%) of 98% pure racemic **25**. IR: 2964, 1720, 1458, 1372, 1108. ^{1}H-NMR: 4.20 (*d*, *J* = 16.2, 1 H); 4.08 (*d*, *J* = 16.2, 1 H); 2.54 (*t*, *J* = 7.5, 2 H); 2.42 (*d*, *J* = 10.3, 1 H); 1.6 (*m*, 4 H); 1.3 (*m*, 2 H); 1.2 (*m*, 2 H); 0.95 (*s*, 3 H); 0.94 (*t*, *J* = 7.5, 3 H); 0.93 (*d*, *J* = 6.3, 3 H); 0.83 (*d*, *J* = 6.0, 3 H); 0.80 (*s*, 3 H). ^{13}C-NMR: 209.6 (*s*); 94.4 (*d*); 80.2 (*t*); 41.2 (*t*); 40.1 (*d*); 40.2 (*s*); 34.6 (*d*); 33.7 (*t*); 30.1 (*t*); 26.1 (*q*); 19.6 (*q*); 16.7 (*t*); 15.6 (*q*); 13.8 (*q*); 13.5 (*q*). MS: 240 (4, M^+), 155 (22), 139 (39), 97 (14), 83 (100), 69 (41), 55 (39), 43 (41).

Enantioselective Reduction of **25**. A) *Catalyst Preparation*. To (*S*)-*α*,*α*-diphenylprolinol (= (2*S*)-*α*,*α*-diphenylpyrrolidine-2-methanol) (5.15 g, 20.0 mmol) in toluene (70 ml) under Ar, trimethylboroxin (1.70 g, 14.0 mmol) was introduced over 3 min. A white precipitate appeared, and toluene (35 ml) was added. After 30 min additional stirring, the mixture was heated to reflux (98°) and H_2O separated in a *Dean – Stark* trap. Toluene was occasionally added and the H_2O separation continued until no more H_2O distilled and all the precipitate had disappeared. The yellow soln. was cooled and transferred under Ar into a metered flask. The concentration of the diphenylprolinol-derived oxazaborolidine in the resulting 50 ml of soln. was 0.4M assuming a total and selective conversion.

B) *Reduction*. Anh. THF (25 ml) was cooled to 0° under Ar. The 0.4M oxazaborolidine catalyst soln. (0.7 ml, 0.3 mmol) was added, followed by 2M $BH_3 \cdot Me_2S$ in THF (2.4 ml, 4.8 mmol). With a syringe pump, racemic **25** (1.7 g, 7.1 mmol) was added over 6 h while the temp. was kept at 0°. Hydrolysis with 10% aq. NaOH soln. (300 ml), decantation, extraction with pentane (2 × 50 ml), rinsing with brine, drying, and evaporation left a residue that was bulb-to-bulb distilled at 125°/1 Torr: 1.6 g (94%) of **4A**/**4D** 55 : 45, both diastereoisomers with an optical purity of 90% (ee 80%; acetates, *Megadex*). Colorless liquid.

2-(Allyloxy)-1,1,3,3-tetramethylcyclohexane (**26**). As described for **23**, from **17** and allyl bromide in 92% yield. IR: 3080, 2930, 1460, 1380, 1136, 1090. ^{1}H-NMR: 5.94 (*ddt*, *J* = 17, 10.3, 5.2, 1 H); 5.31 (*dq*, *J* = 17, 2.0, 1 H); 5.11 (*dq*, *J* = 10.7, 1.5, 1 H); 4.14 (*d*, *J* = 5.0, 2 H); 4.14 (*d*, *J* = 5.0, 2 H); 2.62 (*s*, 1 H); 1.2 – 1.6 (*m*, 4 H); 1.14 (*dt*, *J* = 13.1, 3.2, 2 H); 0.95 (*s*, 6 H); 0.93 (*s*, 6 H). ^{13}C-NMR: 135.9 (*d*); 114.9 (*t*); 93.5 (*d*); 76.0 (*t*); 40.2 (*t*); 37.2 (*s*); 32.4 (*q*); 21.0 (*q*); 18.7 (*t*). MS: 196 (5, M^+), 181 (2), 123 (14), 109 (35), 95 (16), 82 (100), 69 (54), 55 (42), 41 (83).

(±)-2-{[(2,2,6,6-Tetramethylcyclohexyl)oxy]methyl}oxirane (**27**). From **26** by oxidation with 3-chloroperbenzoic acid in 78% yield. IR: 3040, 2930, 1470, 1380, 1096. ^{1}H-NMR: 3.83 (*dd*, *J* = 10.5, 3.5, 1 H); 3.64 (*dd*, *J* = 10.8, 4.8, 1 H); 3.17 (*m*, 1 H); 2.79 (*dd*, *J* = 4.6, 4.0, 1 H); 2.64 (*dd*, *J* = 5.2, 3.2, 1 H); 2.60 (*s*, 1 H); 1.25 – 1.55 (*m*, 4 H); 1.14 (*dt*, *J* = 12.8, 3.0, 2 H); 0.98 (*s*, 3 H); 0.96 (*s*, 3 H); 0.93 (*s*, 3 H); 0.92 (*s*, 3 H). ^{13}C-NMR: 94.0 (*d*); 75.7 (*t*); 51.3 (*d*); 44.6 (*t*); 40.1 (*t*); 37.2 (*s*); 32.4 (*q*); 20.9 (*q*); 18.6 (*t*). MS: 212 (1, M^+), 139 (18), 123 (14), 109 (35), 82 (100), 69 (39), 57 (31), 55 (36), 41 (41).

1-[(2,2,6,6-Tetramethylcyclohexyl)oxy]butan-2-one (**28**). As described for **25**, oxirane **27** was first opened by MeLi/CuI to give (±)-**5** in 86% yield. The latter was oxidized to **28** with PCC in 88% yield. IR: 2930, 1718, 1460, 1363, 1109. ^{1}H-NMR: 4.16 (*s*, 2 H); 2.69 (*q*, *J* = 7.3, 2 H); 2.64 (*s*, 1 H); 1.52 (*tq*, *J* = 13.4, 3.2, 1 H); 1.42 (*dt*, *J* = 13.5, 3.4, 2 H); 1.33 (*m*, 1 H); 1.16 (*dt*, *J* = 13.1, 3.6, 2 H); 1.09 (*t*, *J* = 7.0, 3 H); 0.97 (*s*, 6 H); 0.95 (*s*, 6 H). ^{13}C-NMR: 211.1 (*s*); 94.3 (*d*); 80.8 (*t*); 40.0 (*t*); 37.2 (*s*); 32.7 (*t*); 32.4 (*q*); 20.9 (*q*); 18.5 (*t*); 7.0 (*q*). MS: 226 (5, M^+), 155 (8), 139 (19), 123 (36), 109 (36), 95 (37), 82 (100), 69 (84), 57 (59), 41 (56).

Enantioselective Reduction of **28**. The diphenyloxazaborolidine-catalyzed BH_3 reduction of **28** was performed exactly as the reduction of **25** (see above). Alcohol **16A** was obtained in 76% yield and ee 87% (*Megadex*).

1-[(2,2,6,6-Tetramethylcyclohexyl)oxy]hex-1-en-3-one (**29**). Aldehyde **12** (9.0 g, 54 mmol) and pentan-2-one (9.0 g, 105 mmol) were added simultaneously to a 30% NaOMe soln. in MeOH (70 ml) at 80° over 2 h, and

the mixture was further heated to reflux during 20 h. The cooled mixture was poured onto 10% H_2SO_4 soln. (150 ml), extracted, and washed to neutrality. After drying and evaporation, the residue was submitted to CC (SiO_2 (200 g), hexanes, then hexanes/AcOEt 95:5). Unreacted **12** (2.7 g, 30%) eluted first. Bulb-to-bulb distillation at 125°/1 Torr) of the enone fractions provided 7.2 g (79% based on converted **12**) of colorless **29**. IR: 2954, 1694, 1671, 1620, 1454, 1385, 1370, 1250. ^{1}H-NMR: 6.83 (*dd*, *J* = 15.5, 10.9, 1 H); 6.05 (*d*, *J* = 15.7, 1 H); 2.55 (*t*, *J* = 7.3, 2 H); 1.4–1.7 (*m*, 7 H); 1.17 (*dt*, *J* = 13.5, 4.5, 2 H); 0.98 (*s*, 6 H); 0.96 (*t*, *J* = 7.4, 3 H); 0.78 (*s*, 6 H). ^{13}C-NMR: 200.5 (*s*); 146.6 (*d*); 133.6 (*d*); 60.0 (*d*); 42.1 (*t*); 41.6 (*t*); 33.9 (*s*); 33.7 (*q*); 22.3 (*q*); 19.0 (*t*); 18.0 (*t*); 13.9 (*q*). MS: 236 (5, M^+), 221 (7), 193 (36), 153 (100), 150 (32), 140 (36), 138 (15), 137 (27), 135 (18), 123 (29), 109 (58), 95 (28), 81 (33), 71 (47), 69 (59), 55 (34), 43 (46), 41 (50).

1-[(2,2,6,6-Tetramethylcyclohexyl)oxy]hexan-3-one (**30**). Enone **29** (3.3 g, 14 mmol) was diluted in EtOH (50 ml), and 10% Pd/C (0.4 g) was added. After absorption of 320 ml (*ca.* 14 mmol) of H_2, the mixture was filtered and the filtrate evaporated. Bulb-to-bulb distillation of the residue at 180°/10 Torr provided 2.6 g (78%) of **30**. IR: 2960, 1716, 1465, 1380, 1368, 1124. ^{1}H-NMR: 2.44 (*t*, *J* = 8.7, 2 H); 2.37 (*t*, *J* = 7.5, 2 H); 1.6 (*m*, 5 H); 1.4 (*m*, 3 H); 1.12 (*dt*, *J* = 13.1, 3.0, 2 H); 0.92 (*t*, *J* = 7.1, 3 H); 0.86 (*s*, 6 H); 0.74 (*t*, *J* = 4.0, 1 H). ^{13}C-NMR: 211.5 (*s*); 55.5 (*d*); 47.0 (*t*); 44.7 (*t*); 42.3 (*t*); 35.0 (*s*); 33.2 (*q*); 21.4 (*q*); 20.8 (*t*); 19.1(*t*); 17.4 (*t*); 13.8 (*q*). MS: 238 (13, M^+), 195 (13), 153 (18), 152 (18), 137 (41), 123 (18), 109 (46), 97 (55), 82 (54), 71 (90), 69 (78), 55 (64), 43 (100), 41 (98).

Enantioselective Reduction of **30**. The diphenyloxazaborolidine-catalyzed BH_3 reduction of **30** was performed as the reduction of **25** (see above), however, with 10% of the catalyst. Alcohol **13A** was obtained in 72% yield but only ee 33% (acetate, *Chirasil*).

6. *Molecular Modeling*. Geometry optimization was performed with the MM2 force-field implementation of the software MacroModel 5.5–7.0 [35], and Monte Carlo searches were performed to generate models of the low-energy conformations (arbitrary energy window 4 KJ above global minimum). Pairwise superimpositions of the low-energy conformers of **1A** and **19A** were tried by defining the axial/pseudoaxial Me–C bond and the OH function as superimposition anchors. The visually best fit was chosen and optimized by allowing small rotations of the side-chain bonds. The resulting geometries were both within an 8-KJ window above global minimum.

7. *Threshold Determination*. Basically, the ASTM method E1432 was used to determine the probability of detection of a volatile chemical by a human panel of observers [36]. Shortly, a 2.00-g sample of a 1:1 mixture **1A**/**1C**[6]) was diluted under vigorous stirring in 248.0 g of odorless mineral oil. Half of that 8.00 g/kg (8000 ppm) stock soln. was diluted with the same weight of mineral oil to a 4.00 g/kg (4000 ppm) soln. Binary dilution steps were continued to a final concentration of 0.5 ppm. For each concentration step, a triplet of 150-ml coded polypropylene squeeze bottles was prepared, with one bottle containing the odorized mineral oil and two bottles containing only mineral oil. The position of the odorized sample was randomized across concentrations. Subjects (70 *Firmenich SA* employees) had to determine the position of the odorized sample by scanning all triplets arranged in an ascending order of concentrations. The subjects had to provide one choice of a coded bottle, even when in doubt. Each subject provided six estimates on six different days within a month. The probability of correct response was reported as a function of dilution for each subject and the data subjected to a logistic fit. The concentration corresponding to 50% correct responses was defined as detection-threshold estimate. The results of one subject were dropped because of a general low sensitivity to odors. Individual data were reported as a histogram.

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