Preparation of the Enantiomerically Enriched Isomers of the Odorous Cyclic Ethers *Clarycet*®, *Florol*®, and *Rhubafuran*® by Enzymatic Catalysis

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To the memory of *Enrica Zardoni*

All the enantiomerically enriched stereoisomers of *Clarycet*® (**1**), *Florol*® (**2**), and *Rhubafuran*® (**3**) were prepared by biocatalysis routes. Their absolute configurations were established, and their olfactory properties were fully evaluated.

Introduction. – One of the main goals of fragrance industry is to find more-intense and more long-lasting odorous molecules to be used as alternatives to known products. The target is to obtain powerful compounds that can satisfy the global demand in reduced quantities. Lower volumes imply less impact on health and the environment and simpler registration [1]. Possible approaches to molecules with enhanced odor potency are the discovery of new compounds, may be upon Nature inspiration, or the investigation of the odor properties of all the possible isomers of known chiral odorants. For the last few years, we have been preparing the enantiomerically pure isomers of commercial chiral fragrances to establish the real odor vectors. This systematic work gave us the chance to highlight examples of the different odor thresholds shown by enantiomers: (+)-*Florhydral*® is 25 times more potent than its enantiomer [2]; (+)-γ-ionone is much stronger than (−)-γ-ionone, with an odor threshold of 0.07 ng/l *vs.* 11 ng/l [3].

We now wish to report the preparation of all enantiomerically pure isomers of the floral odorants *Clarycet*® (**1**), *Florol*® (**2**), and *Rhubafuran*® (**3**)[2]) prepared by biocatalysis routes. These fragrances are commercialized as mixtures of two racemic diastereoisomers. *Clarycet*® (*IFF*) is described to have a 'herbal floral, rosy odor with a dried fruitiness and a suggestion of clary sage'. *Florol*® (*Firmenich*) is 'fresh, soft, with a natural floral note; it can be used in almost all perfume types where it gives elegant floral diffusion without changing the character of the fragrance'. *Rhubafuran*® (*Quest International*) is a 'grapefruit fragrance with rhubarb undertones'.

Results and Discussion. – *Syntheses.* As for the synthesis of the two tetrahydropyranyl ethers, we envisaged hydroxy ketones **4** and **5** as starting materials to be prepared

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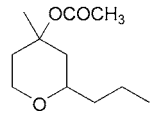
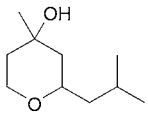
[1]) 21st May 1976 – 28th February 2003

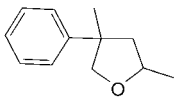
[2]) For previously reported syntheses of mixture of the two racemic diastereoisomers of tetrahydro-4-methyl-2-(2-methylethyl)-2*H*-pyran-4-ol, and tetrahydro-4-methyl-2-propyl-2*H*-pyran-4-ol, see [4]; for the two racemic diastereoisomers of tetrahydro-2,4-dimethyl-4-phenyl-furan, see [5].



1 *Clarycet*®

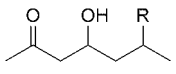


2 *Florol*®

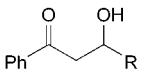


3 *Rhubafuran*®

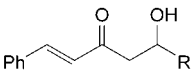
in enantiomerically pure form. Aldol reaction is a powerful tool in synthetic chemistry, and great effort is devoted to find new efficient chiral catalysts to optimize useful enantioselective modifications [6]. Biochemical methods have also been developed to prepare enantiomerically enriched aldols [7]. We have recently exploited the lipase-mediated transesterification of racemic hydroxy ketone **6** to prepare a suitable building block for the synthesis of the enantiomerically pure isomers of the odorant *Floropal*® [8]. We used the same strategy to synthezise enantiomerically enriched 1,3-dioxane odorants related to *Floropal*® and, thus, submitted hydroxy ketones **7**–**11** to lipase-catalyzed acetylation (*Table*) [9].



4 R = H
5 R = Me



6 R = Me
7 R = Et
8 R = Pr



9 R = Me
10 R = Me_2CH
11 R = Pr

Table. *Lipase-Mediated Transesterification for the Synthesis of Enantiomerically Enriched Odorants*

Substrate	Enzyme[a])	Acetate (ee [%]), Chemical yield [%]	Alcohol (ee [%]), Chemical yield [%]
4	CCL	(*S*)(60), 18	Racemic
5	lipase PS	(*S*)(95), 30	(*R*)(91), 35
6	lipase PS	(*R*)(97), 33	(*S*)(93), 37
7	lipase PS	(*R*)(96), 41	(*S*)(94), 37
8	lipase PS	(*R*)(86), 28	(*S*)(50), 55
9	lipase PS	(*R*)(46)	(*S*)(82)
	PPL	(*R*)(98), 39	(*S*)(76), 33
10	PPL	Racemic	Racemic
11	PPL	Racemic	Racemic

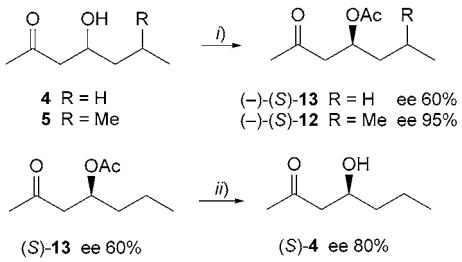
[a]) CCL = *Candida cylindracea*[3]) lipase; lipase PS = *Pseudomonas cepacia* lipase; PPL = porcine pancreas lipase.

On the basis of our previous experience, we investigated the lipase-mediated acetylation of **4** and **5** in ^{t}BuOMe solution, using vinyl acetate as an acyl donor. Lipase PS catalyzed the enantioselective acetylation of derivative **5** to afford the corresponding acetate (*S*)-**12** (30% yield) with an ee of 95% (*Scheme 1*). A rather slow enrichment of the starting alcohol led us to recover hydroxy ketone (*R*)-**5** showing an ee of 91% (35% yield). Different results were obtained with racemic **4**. Only CCL (*Candida cylindracea*[3]) lipase) promoted the acetylation of **4** with low enantioselectivity. Acetate (*S*)-**13** (18% yield) showed an ee of 60%. Further enrichment was

[3]) A more-common recent name for *Candida cylindracea* is *Candida rugosa*.

obtained by submitting (*S*)-**13** (60% ee) to biocatalyzed hydrolysis in H_2O/THF solution at pH 7.8 in the presence of CCL. Alcohol (*S*)-**4** (67% yield) was recovered with an ee of 80%. A striking influence of the structure on the steric course of lipase acetylation was thus observed. The branched chain of hydroxy ketone **5** seems to be a favorable structural feature, and acetylation proceeds with high enantioselectivity. (*S*)-**4** and (*S*)-**5** had been previously prepared by enantioselective aldol reaction with an ee of 58–89% [10–12] and 73–84% [12][13], respectively.

Scheme 1

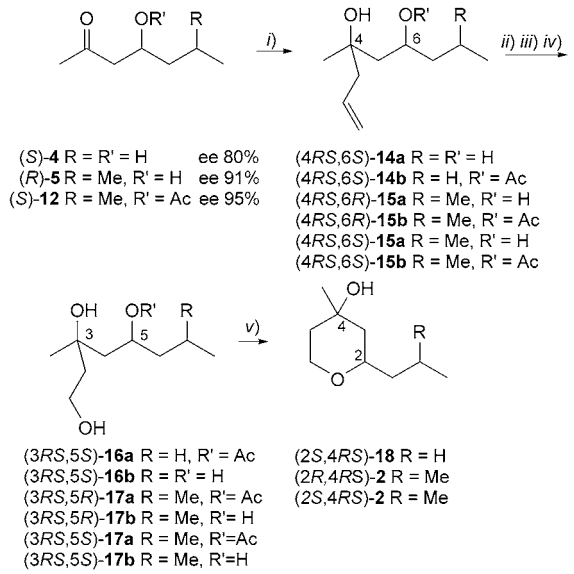


i) ^{t}BuOMe, vinyl acetate, lipase; column chromatography. *ii*) THF/H_2O, pH 7.8, CCL.

The *Table* shows that rather high ee values can be achieved with this procedure of biocatalytic resolution of hydroxy ketones, characterized by the easy handling of largely available lipases. While we were preparing the manuscript of this work, a paper appeared describing the enzymatic kinetic resolution of some other β-hydroxy ketones [14], completing a previous investigation of a few aromatic aldols [15]. These data, combined with our results, highlight the synthetic potentiality of lipase resolution of racemic hydroxy ketones, which can be employed as an alternative to enantioselective aldol reactions catalyzed by chiral catalysts.

Enantiomerically enriched hydroxy ketones (*S*)-**4** (80% ee), (*R*)-**5** (91% ee), and acetate (*S*)-**12** (95% ee) were treated with allylmagnesium bromide in THF to afford diols (4*RS*,6*S*)-**14a** (72% yield), (4*RS*,6*R*)-**15a** (76% yield), and (4*RS*,6*S*)-**15a** (71% yield), respectively, all as mixtures of two diastereoisomers (*Scheme 2*). These latter derivatives were acetylated and submitted to ozonolysis in CH_2Cl_2/MeOH. After quenching with $NaBH_4$ and saponification, triols (3*RS*,5*S*)-**16b** (65% yield from (4*RS*,6*S*)-**14a**), (3*RS*,5*R*)-**17b** (63% yield from (4*RS*,6*R*)-**15a**), and (3*RS*,5*S*)-**17b** (70% yield from (4*RS*,6*S*)-**15a**) were obtained. Reaction with TsCl in pyridine allowed us to isolate the following cyclized compounds directly, each one as a mixture of two diastereoisomers: (2*S*,4*RS*)-**18**, (2*R*,4*RS*)-**2**, and (2*S*,4*RS*)-**2** (*Scheme 2*). The diastereoisomers of each mixture could be separated by column chromatography to afford the following products: (2*S*,4*R*)-**18** (> 99% de, 80% ee, 39% yield), (2*S*,4*S*)-**18** (> 99% de, 80% ee, 31% yield), (2*R*,4*R*)-**2** (> 99% de, 91% ee, 30% yield), (2*R*,4*S*)-**2** (96% de, 91% ee, 37% yield), (2*S*,4*R*)-**2** (> 99% de, 95% ee, 35% yield), and (2*S*,4*S*)-**2** (> 99% de, 95% ee, 29% yield). Treatment of (2*S*,4*R*)-**18** and (2*S*,4*S*)-**18** in refluxing Ac_2O in the presence of NaOAc gave (2*S*,4*R*)-**1** (76% yield) and (2*S*,4*S*)-**1** (74% yield), respectively (*Fig. 1*).

Scheme 2



i) Allyl magnesium bromide, THF. *ii*) Ac_2O, pyridine. *iii*) O_3, CH_2Cl_2/MeOH; then $NaBH_4$. *iv*) KOH, MeOH. *v*) TsCl, pyridine.

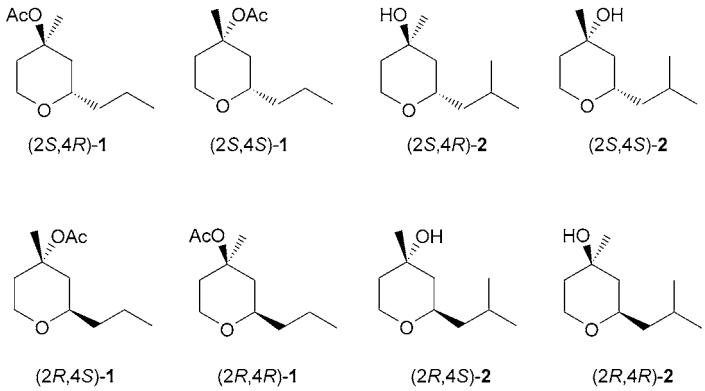
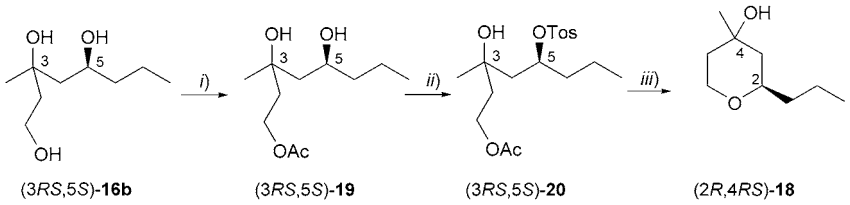


Fig. 1. *Synthesized odorants* **1** *and* **2**

The CCL-mediated acetylation of (±)-**4** was too slow to allow recovery of the enantiomerically enriched isomer (*R*)-**4**, thus a different route to the (2*R*)-configured *Clarycet*® diastereoisomers was devised (*Scheme 3*). The mixture of the two diastereoisomeric triols (3*RS*,5*S*)-**16b** was treated with lipase PS in ^{t}BuOMe and vinyl acetate to afford the two diastereoisomeric monoacetates (3*RS*,5*S*)-**19** (78% yield). These latter derivatives were treated with TsCl in pyridine to give (3*RS*,5*S*)-**20**, which was then submitted to saponification with 10% NaOH solution in EtOH. Ring closure occurred with inversion of configuration at C(2), and a mixture of the two

Scheme 3

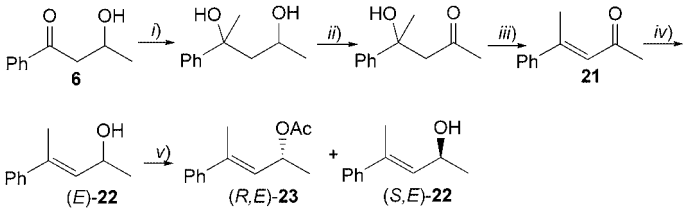


i) Lipase PS, ^{t}BuOMe, vinyl acetate. *ii*) TsCl, pyridine. *iii*) 10% NaOH soln., EtOH.

diastereoisomers (2*R*,4*RS*)-**18** was obtained. The two diasteroisomers were separated by column chromatography (30% and 38% yield) and submitted separately to acetylation in refluxing Ac_2O in the presence of NaOAc to give the two enantiomerically enriched *Clarycet*® isomers (2*R*,4*S*)-**1** (69% yield) and (2*R*,4*R*)-**1** (64% yield) (*Fig. 1*).

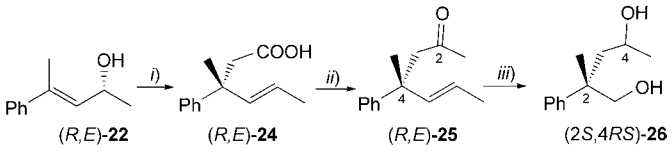
As for the synthesis of the four *Rhubafuran*® stereoisomers, we employed hydroxy ketone **6** as a starting material. Addition of methylmagnesium bromide, CrO_3 oxidation, and subsequent dehydration afforded ketone **21** which was reduced to allylic alcohol (*E*)-**22** [16] (*Scheme 4*). This latter was submitted to lipase-PS acetylation, and after 72 h, acetate (*R*,*E*)-**23** (> 99% ee, 36% yield) and alcohol (*S*,*E*)-**22** (> 99% ee, 37% yield) were isolated after column chromatography. (*R*,*E*)- and (*S*,*E*)-**22** were treated with triethyl orthoacetate in the presence of a catalytic amount of propanoic acid (*Scheme 5*). Distillation *in vacuo* of the reaction mixture, followed by saponification, allowed us to isolate the two enantiomeric acids (*R*,*E*)- and

Scheme 4



i) MeMgBr, THF. *ii*) CrO_3, acetone. *iii*) 10% HCl soln., THF. *iv*) $NaBH_4$, CH_2Cl_2/MeOH. *v*) Lipase PS, ^{t}BuOMe, vinyl acetate; column chromatography.

Scheme 5

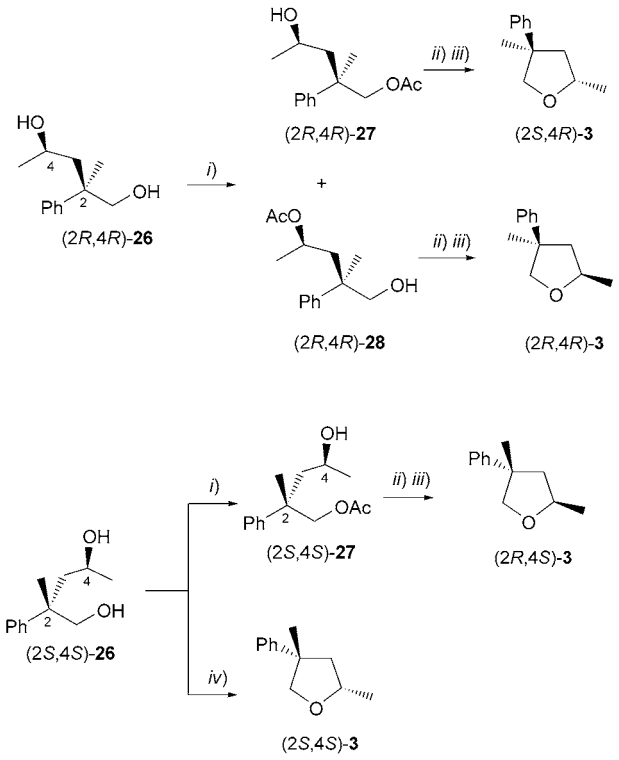


i) Triethyl orthoacetate, propanoic acid; NaOH, H_2O/EtOH. *ii*) Et_3N, ClCOOEt; then MeMgCl, THF, $-20°$. *iii*) O_3, CH_2Cl_2/MeOH.

(*S*,*E*)-**24** (64% and 60% yield). Treatment with ethyl carbonochloridate in THF solution in the presence of Et_3N gave a mixed anhydride, which was converted into ketones (*R*,*E*)- and (*S*,*E*)-**25** (69% and 67% yield) by addition of methylmagnesium chloride at $-20°$. Ozonolysis, followed by $NaBH_4$ quenching, afforded diols (2*S*,4*RS*)- and (2*R*,4*RS*)-**26**, respectively. Each mixture of diastereoisomers was submitted to column chromatography, and the four isomers of diol **26** were obtained as pure compounds (28–35% yield). Unfortunately, when the diastereoisomerically pure diols **26** were treated with triphenylphosphine and *N*-bromosuccinimide (NBS), or reacted with TsCl and pyridine, mixtures of *Rhubafuran*® diastereoisomers were obtained. The steric hindrance of the stereogenic C-atom next to the primary OH group seems to make its reaction with NBS or TsCl quite difficult, and the reaction of the secondary OH group becomes competitive.

As in the case of the *Clarycet*® isomers, we tried to selectively convert the primary OH group to an acetate ester by submitting the four enantiomerically pure stereoisomers of diol **26** to enzyme-mediated acetylation in the presence of lipase PS in separate experiments. The following results were obtained (*Scheme 6*): diols (2*R*,4*S*)-**26** and (2*S*,4*R*)-**26** gave, after 8 days, a 1:1 mixture of the two possible monoacetates,

Scheme 6



i) Lipase PS, ^{t}BuOMe, vinyl acetate. *ii*) TsCl, pyridine. *iii*) KOH, MeOH. *iv*) PPh_3, NBS, CH_2Cl_2.

which could not be separated by column chromatography. Diols (2*R*,4*R*)-**26** and (2*S*,4*S*)-**26** gave, after 5 days, a 1:1 mixture of the two monoacetates (2*R*,4*R*)-**27**/(2*R*,4*R*)-**28** (which could be separated by column chromatography, 35% and 32% yield) and the single monoacetate (2*S*,4*S*)-**27** (44% yield), respectively. Even enzymes did not show a definite preference for the hindered primary OH group of this kind of substrates. Reaction with TsCl in pyridine, followed by saponification with 10% NaOH solution in EtOH, afforded the following samples of *Rhubafuran*®: (2*R*,4*R*)-**3** (84% de, >99% ee, 50% yield from (2*R*,4*R*)-**28**), (2*S*,4*R*)-**3** (66% de, >99% ee, 56% yield from (2*R*,4*R*)-**27**), (2*R*,4*S*)-**3** (78% de, >99% ee, 49% yield from (2*S*,4*S*)-**27**). The preparation of the fourth isomer was accomplished by reaction of (2*S*,4*S*)-**26** with NBS and Ph_3P (60% de, >99% ee, 67% yield).

Configuration Assignment. – The absolute configuration (*S*) of dextrorotatory hydroxy ketone **4** is known from the literature [10][12][17] (see also *Exper. Part*). Alcohol **4** (80% ee), obtained by enzyme-mediated hydrolysis of acetate **13**, prepared in turn by CCL acetylation of (±)-**4**, showed a positive $[\alpha]_D$; thus, (*S*) configuration could be assigned to the enantiomer of **4** converted by CCL to the acetate derivative. The relative configurations of the two stereogenic C-atoms in *Clarycet*® isomers were established by NOE experiments. When the Me group at C(4) in (2*R*,4*R*)-**1** was irradiated, NOE effects were observed on $H_{ax}-C(2)$ (4%) and $H_{ax}-C(6)$ (8%), thus showing a *trans* arrangement of Me–C(4) and Pr–C(2). The *cis* relationship between the Me group and the aliphatic chain in the corresponding diastereoisomer was confirmed by submitting (2*R*,4*S*)-**1** to NOESY experiments in C_6D_6 solution; no NOE effects were observed between Me–C(4) and $H_{ax}-C(2)$ and $H_{ax}-C(6)$, respectively.

As for dextrorotatory hydroxy ketone **5**, the (*S*) configuration had been assigned in the literature by analogy to **4** [12] (see also *Exper. Part*). The alcohol **5** left unreacted by lipase PS in the enzyme-mediated acetylation of (±)-**5** was found to be levorotatory. Thus, (*S*)-configuration was assigned to the enantiomer of **5** converted by lipase PS into the acetate derivative. The *trans* arrangement of the Me–C(4) and $Me_2CHCH_2-C(2)$ in (2*R*,4*R*)-**2** was shown by NOESY experiments (NOEs Me–C(4)/$H_{ax}-C(2)$ and $H_{ax}-C(6)$. No NOE effects were observed between Me–C(4) and $H_{ax}-C(2)$ and $H_{ax}-C(6)$ in the case of (2*R*,4*S*)-**2**, thus confirming this assignment.

The absolute configuration (*S*) of levorotatory allylic alcohol **22** had been established by chemical correlation [16]. Thus (*R*) configuration was assigned to the enantiomer of **22** converted by lipase PS into the acetate derivative. The relative configuration of the two stereogenic C-atoms in *Rhubafuran*® samples was established by NOE experiments. When Me–C(4) of (2*R*,4*R*)-**3** was irradiated, NOE effects were observed on H–C(2) (5.9%) and both H–C(3) (3.1 and 4.4%), thus showing a *trans* arrangement of Me–C(4) and Me–C(2). The *cis* relationship between the two Me groups in the corresponding diastereoisomer was confirmed by submitting (2*R*,4*S*)-**3** to NOE experiments (no NOE Me–C(4)/H–C(2)).

Olfactory Evaluation. – All the samples were submitted to olfactory evaluation (*Givaudan* perfumers) with the following results:

(2*S*,4*S*)-**1**: Green, fresh, earthy, fruity (sage), dry down odorless.

(2*S*,4*R*)-**1**: Floral, agrestic, fruity, touch acetic-green-tobacco, dry down slightly fruity, but very weak.

(2*R*,4*R*)-**1**: Pine, pine oil, terpenic, woody, dry down dusty dirty.

(2*R*,4*S*)-**1**: Fruity, rosy, rose ketone, good, touch earthy, dry, sweet, woody, sage, dry down floral-sage.

(2*R*,4*R*)-**2**: Most pronounced and most intense *Florol*® stereoisomer (odor threshold 1.21 ng/l air). Fresh, soft, sweet, and natural floral odor reminiscent of muguet with some rose oxide side note and earthy nuances.

(2*S*,4*S*)-**2**: Second intense *Florol*® stereoisomer (odor threshold 26 ng/l air), but already much weaker. Similar fresh-floral note as the enantiomer, but less sweet and also more linalool-type, more herbaceous, and more earthy in tonality.

(2*R*,4*S*)-**2**: The second weakest in the series of *Florol*® stereoisomers (odor threshold 520 ng/l air). Relatively weak, mainly fruity, grape-like, but also reminiscent of linalyl acetate and clary sage oil, with some nuances of dry herbs.

(2*S*,4*R*)-**2**: Odorless on GC olfactometry (odor threshold > 600 ng/l air). The weakest of all *Florol*® stereoisomers. Very weak in odor, mainly linalool and coumarine like, with some citric and hesperidic nuances.

(2*R*,4*R*)-**3**: Nuts, acidic, animalic, slightly rhubarb.

(2*S*,4*R*)-**3**: Citric, rhubarb, slightly green, slightly animalic.

(2*S*,4*S*)-**3**: Grapefruit-like, bitter, cassis, slightly oxane-like and reminiscent of dimethyloctenone. Dry down (24 h) bitter, grapefruit, oxane.

(2*R*,4*S*)-**3**: The most pleasant one, floral, linalool-like, rhubarb and citrus, green, slightly eucalyptus.

(2*R*,4*S*)-**3**, followed by its enantiomer, are the closest to the commercial *Rhubafuran*®.

Conclusions. – The olfactory evaluations reported in this study highlight the effect of configuration both on odor quality and odor thresholds.

As for *Clarycet*®, the single enantiomer (2*R*,4*S*)-**1** has a nice floral odor, which makes it distinguished from the other stereoisomers. This latter can be related to the best isomers of other tetrahydropyran fragrances, such as (2*S*,4*R*)-rose oxide and (2*S*,4*R*)-*Doremox*® [18] (*Fig. 2*), which have a *cis* diequatorial arrangement of the Me–C(4) and the substituent at C(2), just as in (2*R*,4*S*)-**1**.

A gradual variation of odor intensity was noticed in the four *Florol*® isomers, from 1.21 ng/l of (2*R*,4*R*)-**2** to more than 600 ng/l of (2*S*,4*R*)-**2**. The two enantiomers of the diastereoisomer bearing the OH group and the isobutyl chain in equatorial positions are decidedly the most intense, and are responsible for the odor of commercial *Florol*®.

The same is true also for *Rhubafuran*®: the two enantiomers of just one diastereoisomer, in particular the one bearing the Me groups on the same side, are the real vectors of *Rhubafuran*® fragrance. This latter can be structurally correlated to the odorant *Floropal*® by removing the acetal Me–CH moiety and replacing the O-atom by a CH_2 unit (*Fig. 2*). The same relative configuration is shown by the best diastereoisomer of both the odorants.

The observed stereoselective bioaccumulation of certain chiral odorants [19], the increasing need to control and limit fragrances considered to be allergens [20], the necessity to reduce the global volume of chemicals employed in fine and functional

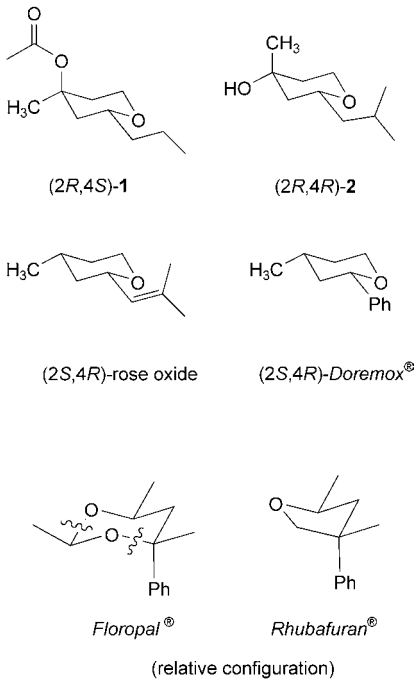


Fig. 2. *Comparison of the structures of some odorants*

perfumery make the investigation of the odor properties of chiral commercial odorants highly necessary. The preparation of enantiomerically pure single isomers and the establishment of their absolute configuration help to determine the effective odor vector and to implement the study of structure – odor relationship. For this purpose, both enantiomers of every single stereoisomer are to be prepared. Biocatalyzed kinetic resolutions are particularly useful as they provide both enantiomers of a chiral molecule within a single step, unlike most of the methods of asymmetric synthesis that require the optimization of both enantiomers of the chiral auxiliary. Classical methods of resolution are difficult to apply to fragrance molecules, which are usually poorly functionalized. The work we have been doing in recent years shows the wide applicability and synthetic versatility of enzymatic procedures in the field of fragrance chemistry. Lipase-mediated resolutions are characterized by easy and rapid applications and allow the preparation of good quantities of enantiomerically pure isomers.

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Experimental Part

General. Hydroxy ketones **4** [21], **5** [22], and **6** [23] were prepared according to the literature by aldol condensation. 2-Phenylpentane-2,4-diol was prepared according to [8], and was then oxidized with CrO_3 in acetone at r.t. The resulting ketone was dehydrated to compound **21** according to [24]. Reduction of **21** to **22**[4]) was performed according to [26]. Lipase PS from *Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan) and *Candida rugosa*[3]) lipase (*Sigma*) were employed in this work. Chiral GC: *Chirasil DEX-CB* column (25 × 0.25 mm; *Chrompack*), *DANI HT-86.10* gas chromatograph; t_R in min; acetate **13**: temp. program 60° (3 min) – 5°/min – 180° (2 min); t_R 9.02 ((*R*)-**13**), 9.32 ((*S*)-**13**), acetate **12**: temp. program 50° (3 min) – 8°/min – 100° (30 min) – 8°/min – 180° (1 min); t_R 10.58 ((*R*)-**12**), 10.68 ((*S*)-**12**); **23**: temp. program 50° (3 min) – 4°/min – 160° – 8°/min – 180° (5 min); t_R 21.70 ((*S*)-**23**), 22.17 ((*R*)-**23**). TLC: *Merck* silica gel *60* F_{254} plates. Column chromatography (CC): silica gel. Optical rotations: *Dr. Kernchen-Propol* digital automatic polarimeter. Microanalyses: Analyzer *1106 Carlo-Erba*. ^{1}H- and ^{13}C-NMR: *Bruker AC-250* spectrometer (250 MHz ^{1}H); $CDCl_3$ solns. at r.t. unless otherwise stated, chemical shifts δ in ppm rel. to internal $SiMe_4$, *J* values in Hz. GC-MS: *HP-6890* gas-chromatograph, *5973* mass detector, *HP-5MS* column (30 m × 0.25 mm × 0.25 μm), temp. program 60°(1 min) – 6°/min – 150° (1 min) – 12°/min – 280° (5 min); t_R in min.

1. Lipase-Mediated Acetylation. 1.1. *General Procedure 1* (*GP1*). A mixture of the suitable substrate (10 g), lipase (7 g), and vinyl acetate (10 ml) in ^{t}BuOMe (80 ml) was stirred at r.t. for 24 h. The residue obtained upon evaporation of the filtered mixture was submitted to CC.

1.2. *(4*S*)-4-Acetoxyheptan-2-one* ((*S*)-**13**). According to *GP1* (5 day reaction time), with racemic **4** (130 g, 1 mol) and CCL. CC (hexane/AcOEt 9:1) gave (*S*)-**13** (30.9 g, 18%). Chemical purity 96% by GC/MS (t_R 10.41); 60% ee (chiral GC). $[\alpha]_D^{20} = -0.71$ (*c* = 1.12, $CHCl_3$). ^{1}H-NMR: 5.25 (*quint.*, *J* = 6.7, H–C(4)); 2.6–2.9 (*m,* 2 H–C(3)); 2.13 (*s,* Me(1)); 2.0 (*s,* MeCOO); 1.20–1.55 (*m*, CH_2CH_2); 0.88 (*t*, *J* = 7.1, $MeCH_2$). ^{13}C-NMR: 205.6; 170.4; 70.1; 50.3; 46.8; 30.1; 23.1; 21.5; 20.8. GC/MS: 129 (7, $[M-43]^+$), 112 (17), 97 (21), 43 (100). Anal. calc. for $C_9H_{16}O_3$: C 62.77, H 9.36; found: C 62.38, H 9.58.

1.3. *(4*S*)-4-Acetoxy-6-methylheptan-2-one* ((*S*)-**12**) and *(4*R*)-4-Hydroxy-6-methylheptan-2-one* ((*R*)-**5**). According to *GP1* (5 day reaction time), with racemic **5** (60.0 g, 0.42 mol) and lipase PS. CC (hexane/AcOEt 9:1) gave (*S*)-**12** (23.3 g, 30%). Chemical purity 97% by GC/MS (t_R 11.36); 95% ee (chiral GC). $[\alpha]_D^{20} = -21.8$ (*c* = 1.02, $CHCl_3$). ^{1}H-NMR [27]: 5.10–5.40 (*m*, H–C(4)); 2.72 (*dd*, *J* = 7.3, 16.2, H–C(3)); 2.59 (*dd*, *J* = 5.6, 16.2, 1 H–C(3)); 2.16 (*s,* Me(1)); 2.02 (*s,* MeCOO); 1.72–1.24 (*m*, CH_2CH); 0.93–0.92 (2*d*, *J* = 6.7, Me_2CH). ^{13}C-NMR: 208.1; 170.8; 68.7; 50.4; 45.7; 31.0; 24.2; 23.2; 21.8; 20.8. GC/MS: 171 (0.5, $[M-15]^+$), 143 (6), 126 (7), 108 (20), 43 (100).

The unreacted **5**, recovered by CC, was enantiomerically enriched by prolonged (15 days) lipase-PS treatment, according to *GP1*. CC (hexane/AcOEt 95:5) gave (*R*)-**5** (21.2 g, 35%). Chemical purity 97% by GC/MS (t_R 8.11); 91% ee (chiral GC of the corresponding acetate). $[\alpha]_D^{20} = -46.6$ (*c* = 0.97, $CHCl_3$) ([12]: (*S*)-**5** $[\alpha]_D = +47.04$ (*c* = 0.7, $CHCl_3$; 84% ee). ^{1}H-NMR [12]: 4.20–4.05 (*m*, H–C(4)); 2.70–2.40 (*m,* 2 H–C(3)); 2.18 (*s,* Me(1)); 1.80–1.70 (*m*, H–C(6)); 1.55–1.40 (*m*, 1 H–C(5)); 1.20–1.05 (*m*, H–C(5)); 0.92 (*d*, *J* = 6.4, 2 Me_2CH). ^{13}C-NMR: 210.0; 65.6; 50.3; 45.4; 30.8; 24.3; 23.2; 21.9. GC/MS: 143 (0.5 $[M-1]^+$), 126 (3), 108 (18), 43 (100).

1.4. *(2*R*,3*E*)-4-Phenylpent-3-en-2-ol Acetate* ((*R*,*E*)-**23**) *and (2*S*,3*E*)-4-Phenylpent-3-en-2-ol* ((*S*,*E*)-**22**). According to *GP1* (48 h reaction time), with racemic (*E*)-**22** (60.0 g, 0.37 mol) and lipase PS. CC (hexane/AcOEt 9:1) gave (*R*,*E*)-**23** (27.2 g, 36%) and (*S*,*E*)-**22** (22.1 g, 37%).

*Data of (*R,E*)-***23***:* Chemical purity 98% by GC/MS (t_R 17.51); > 99% ee (chiral GC). $[\alpha]_D^{20} = +68.5$ (*c* = 1.01, $CHCl_3$). ^{1}H-NMR [28]: 7.50–7.20 (*m*, 5 arom. H); 5.80–5.60 (*m*, H–C(3), H–C(2)); 2.1 (*s*, Me(5)); 2.03 (*s,* MeCOO); 1.41 (*d*, *J* = 6.2, Me(1)). ^{13}C-NMR: 170.5; 142.5; 137.9; 133.1; 128.2; 127.4; 125.8; 68.3; 21.3; 20.8; 16.2. GC/MS: 204 (11, M^+), 161 (33), 129 (100).

*Data of (*S,E*)-***22***.* Chemical purity 96% by GC/MS (t_R 15.06); > 99% ee (chiral GC of the corresponding acetate). $[\alpha]_D^{20} = -44.3$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR [16]: 7.49–7.21 (*m*, 5 arom. H); 5.80 (*dq*, *J* = 8.5, 1.5, H–C(3)); 4.76 (*dq*, *J* = 8.5, 6.2, H–C(2)); 2.1 (*s*, Me(5)); 1.35 (*d*, *J* = 6.2, Me(1)). ^{13}C-NMR: 142.9; 136.0; 131.8; 128.1; 127.2; 125.5; 65.0; 23.5; 16.0. GC/MS: 162 (27, M^+), 147 (100), 129 (73).

1.5. *(3*RS,5S*)-3-Methyloctane-1,3,5-triol 1-Acetate* ((3*RS,5S*)-**19**). According to *GP1* (24 h reaction time), with (3*RS*,5*S*)-**16b** (5.70 g, 0.032 mol; 1.8:1 diastereoisomer mixture) and lipase PS. CC (hexane/AcOEt 9:1) gave (3*RS*,5*S*)-**19** (5.44 g, 78%; 2:1 diastereoisomer mixture): ^{1}H-NMR: 4.24 (*m*, CH_2OAc of both diast.); 3.90–4.10 (*m, CH*OH of both diast.); 2.10–1.32 (*m*, 8 H of both diast.); 1.26 (*s*, Me–C(3) of one diast.); 1.25 (*s*,

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[4]) For other approaches to racemic **22**, see [25].

Me–C(3) of the other diast.); 0.81–0.98 (*m*, 2 *Me*CH of both diast.). GC/MS: diast. I (t_R 18.72): 175 (1, $[M-43]^+$), 157 (11), 131 (36), 97 (40), 71 (100); diast. II (t_R 18.88) 175 (1, $[M-43]^+$), 157 (15), 131 (38), 97 (42), 71 (100). Anal. calc. for $C_{11}H_{22}O_4$: C 60.52, H 10.16; found: C 60.74, H 10.55.

1.6. *(2*R*,4*R*)-2-Methyl-2-phenylpentan-1,4-diol 4-Acetate* ((2*R*,4*R*)-**28**) *and (2*R*,4*R*)-2-Methyl-2-phenylpentan-1,4-diol 1-Acetate* ((2*R*,4*R*)-**27**). According to *GP1* (5 day reaction time), with (2*R*,4*R*)-**26** (2.70 g, 0.014 mol) and lipase PS. CC (hexane/AcOEt 9:1) gave (2*R*,4*R*)-**28** (1.06 g, 32%) and (2*R*,4*R*)-**27** (1.15 g, 35%).

*Data of (2*R*,4*R*)-***28***: Chemical purity 92% by GC/MS (t_R 20.89 min) with 8% of (2*R*,4*R*)-**27** by GC/MS (t_R 20.65 min). $[\alpha]_D^{20} = -8.97$ ($c = 0.86$, $CHCl_3$). ^{1}H-NMR: 7.49–7.11 (*m*, 5 arom. H); 4.90–5.00 (*m*, C*H*OAc); 3.72 (*d*, *J* = 11.2, 1 H, *CH*$_2$OH); 3.59 (*d*, *J* = 11.2, 1 H, *CH*$_2$OH); 1.93 (*s*, MeCOO); 1.96–1.83 (*m*, 2 H–C(3)); 1.38 (*s*, Me(5)); 1.07 (*d*, *J* = 7.0, *Me*CH). ^{13}C-NMR: 148.3; 128.7; 126.5; 126.4; 125.7; 72.1; 65.1; 48.9; 42.6: 25.6; 21.5; 20.7. GC/MS: 175 (1, $[M-61]^+$), 161 (2), 145 (100). Anal. calc. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 71.39, H 8.88.

*Data of (2*R*,4*R*)-***27***: Chemical purity 83% by GC/MS (t_R 20.65 min) with 17% of (2*R*,4*R*)-**28** by GC/MS (t_R 20.89 min). $[\alpha]_D^{20} = -5.94$ ($c = 0.98$, $CHCl_3$). ^{1}H-NMR: 7.39–7.18 (*m*, 5 arom. H); 4.27 (*d*, *J* = 11.2, 1 H, *CH*$_2$OAc); 4.19 (*d*, *J* = 11.2, 1 H, *CH*$_2$OAc); 3.80–3.75 (*m*, *CH*OH); 2.01 (*s*, MeCOO); 1.95–1.85 (*m*, 2 H–C(3)); 1.49 (*s*, Me(5)); 1.07 (*d*, *J* = 7.0, *Me*CH). ^{13}C-NMR: 148.2; 128.5; 126.4; 126.0; 125.8; 70.7; 66.2; 48.8; 42.5; 25.6; 21.5; 20.7. GC/MS: 176 (1, $[M-60]^+$), 163 (6), 119 (100). Anal. calc. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 70.87, H 8.21.

1.7. *(2*S*,4*S*)-2-Methyl-2-phenylpentan-1,4-diol 1-Acetate* ((2*S*,4*S*)-**27**). According to *GP1* (5 day reaction time), with (2*S*,4*S*)-**26** (2.70 g, 0.014 mol) and lipase PS. CC (hexane/AcOEt 9:1) gave (2*S*,4*S*)-**27** (1.44 g, 44%). Chemical purity 92% by GC/MS (t_R 20.65 min) with 8% of (2*S*,4*S*)-**28** by GC/MS (t_R = 20.89 min). $[\alpha]_D^{20} = +21.3$ ($c = 0.77$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer. Anal. calc. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 71.47, H 8.76.

1.8. *(4*S*)-4-Hydroxyheptan-2-one* ((*S*)-**4**). Saponification of (*S*)-**13** (30.9 g, 0.18 mol) in H_2O/THF 9:1 at pH 7.8 (pH-stat) in the presence of CCL gave, after CC (hexane/AcOEt 8:2), (*S*)-**4** (15.7 g, 67%). Chemical purity 95% by GC/MS (t_R 6.82); 80% ee (chiral GC of the corresponding acetate). $[\alpha]_D^{20} = +45.2$ ($c = 0.965$, $CHCl_3$) ([10]: $[\alpha]_D = +35.1$ ($c = 2.1$ $CHCl_3$; 58% ee); [12]: $[\alpha]_D = +42.3$ ($c = 5$, $CHCl_3$; 84% ee); [17]: $[\alpha]_D = +44$ ($c = 0.18$, $CHCl_3$; 73% ee)). ^{1}H-NMR [29]: 4.00 (*m*, H–C(4)); 2.55 (*m*, 2 H–C(3)); 2.13 (*s*, MeCO); 1.20–1.55 (*m*, CH_2CH_2); 0.90 (*t*, *J* = 7.1, *Me*CH_2). 1.36 (*d*, *J* = 6.4, Me). ^{13}C-NMR: 205.7; 67.4; 50.2; 46.9; 30.2; 23.3; 21.7. GC/MS: 129 (1, $[M-1]^+$), 112 (12), 97 (18), 87 (62), 43 (100).

2. Addition of Allylmagnesium Bromide to Hydroxy or Acetoxy Ketone Derivatives. 2.1. *General Procedure 2 (GP2).* The suitable hydroxy or acetoxy derivative (0.10 mol) was dropped into a soln. of allylmagnesium bromide (from 0.3 or 0.4 mol of allyl bromide and 0.33 or 0.44 mol of Mg) in Et_2O (500 ml) at 10°. The mixture was refluxed for 1 h, poured into ice, quenched with sat. NH_4Cl soln., and extracted with Et_2O. The org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to CC (hexane/AcOEt 7:3).

2.2. *(4*RS*,6*S*)-4-Methylnon-1-ene-4,6-diol* ((4*RS*,6*S*)-**14a**). According to *GP2*, with (*S*)-**4** (80% ee; 15.5 g, 0.12 mol): (4*RS*,6*S*)-**14a** (14.8 g, 72%; 1.8:1 diastereoisomer mixture (GC/MS)). ^{1}H-NMR: 6.01 (*dd*, *J* = 11.0, 17.3, H–C(2)); 5.32 (*dd*, *J* = 17.3, 1.4, 1 H–C(1)); 5.05 (*dd*, *J* = 11.0, 1.4, 1 H–C(1)); 4.10–3.90 (*m*, H–C(6)); 1.90 (*d*, *J* = 14.7, 1 H–C(3)); 1.74 (*d*, *J* = 14.7, H–C(3)); 1.54–1.16 (*m*, 3 CH_2, Me); 0.93 (*t*, *J* = 7.1, Me(9)). GC/MS: diast. I (t_R 12.16): 157 (5, $[M-15]^+$), 131 (44), 113 (100), 93 (66); diast. II (t_R 12.27) 157 (5, $[M-15]^+$), 131 (45), 113 (100), 93 (55). Anal. calc. for $C_{10}H_{20}O_2$: C 69.72, H 11.70; found: C 69.41, H 11.57.

2.3. *(4*RS*,6*R*)-4,8-Dimethylnon-1-ene-4,6-diol* ((4*RS*,6*R*)-**15a**). According to *GP2*, with (*R*)-**5** (91% ee; 21.0 g, 0.15 mol): (4*RS*,6*R*)-**15a** 1.9:1 diastereoisomer mixture (GC/MS). ^{1}H-NMR: 5.72–6.00 (*m*, H–C(2) of both diast.); 5.21–5.05 (*m*, 2 H–C(1) of both diast.); 4.15–4.0 (*m*, H–C(6) of both diast.); 2.49–2.20 (*m*, 2 H–C(3) of both diast.); 1.90–1.65 (*m*, H–C(8) of both diast.); 1.61–1.1 (*m*, 2 H–C(5), 2 H–C(7) of both diast.); 1.29 (*s*, Me–C(4) of one diast.); 1.21 (*s*, Me–C(4) of the other diast.); 0.99–0.87 (*m*, 2 *Me*CH of both diast.). GC/MS: diast. I (t_R 13.11) 171 (2, $[M-15]^+$), 145 (20), 109 (65), 43 (100); diast. II (t_R 13.26); 171 (2, $[M-15]^+$), 145 (17), 109 (73), 43 (100). Anal. calc. for $C_{11}H_{22}O_2$: C 70.92, H 11.90; found: C 70.38, H 11.57.

2.4. *(4*RS*,6*S*)-4,8-Dimethylnon-1-ene-4,6-diol* ((4*RS*,6*S*)-**15a**). According to *GP2*, with (*S*)-**12** (95% ee; 23.0 g, 0.12 mol): (4*RS*,6*S*)-**15a** (16.3 g, 71%; 1.9:1 diastereoisomer mixture (GC/MS)). ^{1}H-NMR and GC/MS: in accordance with those of (4*RS*,6*R*)-**15a**. Anal. calc. for $C_{11}H_{22}O_2$: C 70.92, H 11.90; found: C 71.13, H 12.21.

3. *Ozonolysis of Diols* **14a** *and* **15a**. 3.1. *General Procedure 3* (*GP3*). The suitable diol derivative (0.12 mol) was acetylated with Ac_2O (20 ml) in pyridine (20 ml). The resulting monoacetate was treated with O_3 at −78° in CH_2Cl_2/MeOH 1:1 (400 ml). The mixture was quenched with $NaBH_4$ (0.24 mol, 9.12 g). After the usual workup, the residue was submitted to CC (hexane/AcOEt 8:2).

3.2. *(3*RS,*5*S*)-3-Methyloctane-1,3,5-triol 5-Acetate* ((3*RS*,5*S*)-**16a**). According to *GP3*, with (4*RS*,6*S*)-**14a** (14.5 g, 0.084 mol): (3*RS*,5*S*)-**16a** (13.4 g, 73%; 1:2 diastereoisomer mixture (GC/MS)). ^{1}H-NMR: 5.30–5.10 (*m*, C*H*OAc); 3.90–3.70 (*m*, CH_2OH); 2.05 (*s*, MeCOO); 1.8–1.3 (*m*, 8 H); 1.25 (*s*, Me–C(4)); 0.95 (*t*, *J* = 7.0, *Me*CH$_2$). GC/MS: diast. I (t_R 18.57) 173 (1, [*M* – 45]$^+$), 143 (13), 113 (58), 89 (76), 43 (100); diast. II (t_R 18.75) 173 (4, [*M* – 45]$^+$), 143 (11), 113 (59), 89 (78), 43 (100). Anal. calc. for $C_{11}H_{22}O_4$: C 60.52, H 10.16; found: C 60.38, H 10.42.

3.3. *(3*RS,*5*R*)-3,7-Dimethyloctane-1,3,5-triol 5-Acetate* ((3*RS*,5*R*)-**17a**). According to *GP3*, with (4*RS*,6*R*)-**15a** (20.3 g, 0.11 mol): (3*RS*,5*R*)-**17a** (17.4 g, 69%; 1:1.8 diastereoisomer mixture (GC/MS)). ^{1}H-NMR: 5.23–5.05 (*m*, *CH*OAc of one diast.); 4.28–4.18 (*m*, *CH*$_2$OH of one diast.); 4.17–4.02 (*m*, *CH*OAc of one diast.); 3.75–3.95 (*m*, *CH*$_2$OH of one diast.); 2.06 (*s*, AcO of one diast.); 2.04 (*s*, AcO of one diast.); 2.00–1.12 (*m*, 10 H of both diast.); 0.97–0.88 (*m*, 2 *Me*CH of both diast.). GC/MS: diast. I (t_R 19.10) 187 (5, [*M* – 45]$^+$), 157 (13), 127 (35), 89 (95), 43 (100); diast. II (t_R 19.28) 187 (5, [*M* – 45]$^+$), 157 (11), 127 (33), 89 (100), 43 (95). Anal. calc. for $C_{12}H_{24}O_4$: C 62.04, H 10.41; found: C 62.35, H 10.73.

3.4. *(3*RS,*5*S*)-3,7-Dimethyloctane-1,3,5-triol 5-Acetate* ((3*RS*,5*S*)-**17a**). According to *GP3*, with (4*RS*,6*S*)-**15a** (16.0 g, 0.086 mol): (3*RS*,5*S*)-**17a** (14.9 g, 75%; 1:1.8 diastereoisomer mixture (GC/MS)). ^{1}H-NMR and GC/MS: in accordance with those described for (3*RS*,5*R*)-**17a**. Anal. calc. for $C_{12}H_{24}O_4$: C 62.04, H 10.41; found: C 61.89, H 10.11.

4. *Saponifications:* **16b** *and* **17b**. 4.1. *(3*RS,*5*S*)-3-Methyloctane-1,3,5-triol* ((3*RS*,5*S*)-**16b**). Saponification of (3*RS*,5*S*)-**16a** (13.4 g, 0.061 mol) with KOH (4.47 g, 0.080 mol) in MeOH (100 ml) gave (3*RS*,5*S*)-**16b** (9.56 g, 89%; 1.8:1 diastereoisomers mixture). ^{1}H-NMR: 4.10–4.00 (*m*, C*H*OH); 3.90–3.80 (*m*, CH_2OH); 1.7–1.3 (*m*, 8 H); 1.27 (*s*, Me–C(3)); 0.95 (*t*, *J* = 7.0, *Me*CH$_2$). GC/MS: diast. I (t_R 17.19): 161 (1, [*M* – 15]$^+$), 131 (24), 113 (39), 89 (67), 43 (100); diast. II (t_R 17.27) 161 (4, [*M* – 45]$^+$), 131 (20), 113 (40), 89 (70), 43 (100). Anal. calc. for $C_9H_{20}O_3$: C 61.33, H 11.44; found: C 61.75., H 11.69.

4.2. *(3*RS,*5*R*)-3,7-Dimethyloctane-1,3,5-triol* ((3*RS*,5*R*)-**17b**). Saponification of (3*RS*,5*R*)-**17a** (17.1 g, 0.074 mol) with KOH (5.39 g, 0.096 mol) in MeOH (100 ml) gave (3*RS*,5*R*)-**17b** (12.7 g, 91%; diastereoisomer mixture). ^{1}H-NMR: 4.24–3.80 (*m*, CH_2OH, C*H*OH of both diast.); 2.22 (*ddd*, *J* = 5.0, 10.8, 15.1, 1 H of one diast.); 1.88–1.09 (*m*, 6 H of both diast., and 1 H of one diast.; 1.35 (*s*, Me–C(3) of one diast.); 1.31 (*s*, Me–C(3) of the other diast.); 0.86–0.99 (*m*, 2 *Me*CH of both diast.). GC/MS: br. single peak (t_R 18.25): 145 (23, [*M* – 45]$^+$), 115 (31), 109 (51), 89 (86), 43 (100). Anal. calc. for $C_{10}H_{22}O_3$: C 63.12, H 11.65; found: C 63.44., H 11.32.

4.3. *(3*RS,*5*S*)-3,7-Dimethyloctane-1,3,5-triol* ((3*RS*,5*S*)-**17b**). Saponification of (3*RS*,5*S*)-**17a** (14.9 g, 0.064 mol) with KOH (4.67 g, 0.083 mol) in MeOH (100 ml) gave (3*RS*,5*S*)-**17b** (11.4 g, 94%; diasteroisomer mixture). ^{1}H-NMR and GC/MS: in accordance with those of (3*RS*,5*R*)-**17b**. Anal. calc. for $C_{10}H_{22}O_3$: C 63.12, H 11.65; found: C 63.44, H 11.32.

5. *Pyranols* **18** *and* **2**. 5.1. *(2*S,*4*R*)- and (2*S,*4*S*)-Tetrahydro-4-methyl-2-propyl-2*H*-pyran-4-ol* ((2*S*,4*R*)- and (2*S*,4*S*)-**18**) [30]. Treatment of (3*RS*,5*S*)-**16b** (3.7 g, 0.021 mol) with TsCl (5.99 g, 0.031 mol) in pyridine (20 ml) gave, after CC (hexane/AcOEt 95:5), (2*S*,4*R*)-**18** (1.29 g, 39%) and (2*S*,4*S*)-**18** (1.03 g, 31%).

*Data of (2*S,*4*R*)-***18***: Chemical purity 96% by GC/MS (t_R 9.27); >99% de (GC/MS). $[\alpha]_D^{20} = +0.83$ (*c* = 0.97, $CHCl_3$). ^{1}H-NMR: 3.90–3.80 (*m*, 1 H); 3.79–3.65 (*m*, 1 H); 3.65–3.45 (*m*,1 H); 1.75–1.18 (*m*, 8 H); 1.26 (*s*, Me–C(4)); 0.92 (*t*, *J* = 7.0, *Me*CH$_2$). GC/MS: 157 (1, [*M* – 1]$^+$), 140 (37), 115 (44), 71 (100), 43 (90).

*Data of (2*S,*4*S*)-***18***: Chemical purity 97% by GC/MS (t_R 9.71); >99% de. $[\alpha]_D^{20} = +5.32$ (*c* = 1.01, $CHCl_3$). ^{1}H-NMR: 3.96 (*ddd, J* = 12.0, 5.2, 1.8, H_{eq}–C(6)); 3.43 (*dt, J* = 2.6, 12.0, H_{ax}–C(6)); 3.40–3.20 (*m*, H_{ax}–C(2)); 1.83–1.14 (*m*, 8 H); 1.33 (*s*, Me–C(4)); 0.91 (*t*, *J* = 7.1, *Me*CH$_2$). GC/MS: 157 (1, [*M* – 1]$^+$), 140 (8), 115 (69), 71 (100), 43 (91).

5.2. *(2*R,*4*S*)- and (2*R,*4*R*)-Tetrahydro-4-methyl-2-(2-methylpropyl)-2*H*-pyran-4-ol* ((2*R*,4*S*)- and (2*R*,4*R*)-**2**, resp. As described in *5.1*, with (3*RS*,5*R*)-**17b** (12.6 g, 0.066 mol), TsCl (18.81 g, 0.099 mol), and pyridine (20 ml): (2*R*,4*S*)-**2** (4.2 g, 37%) and (2*R*,4*R*)-**2** (3.4 g, 30%).

*Data of (2*R,*4*S*)-***2***: Chemical purity 98% by GC/MS (t_R 10.47); 96% de (GC/MS); 91% ee (from (*R*)-**5**). $[\alpha]_D^{20} = -0.98$ (*c* = 1.27, $CHCl_3$). ^{1}H-NMR (400 MHz): 3.80 (*ddd, J* = 11.5, 5.5, 1.8, H_{eq}–C(6)); 3.73 (*ddd*, *J* = 12.5, 11.5, 2.4, H_{ax}–C(6)); 3.66 (*dddd*, *J* = 11.1, 8.4, 4.4, 2.2, H–C(2)); 1.82–1.70 (*m*, Me$_2$C*H*); 1.63 (*ddd*, *J* = 13.6, 12.5, 5.5, H_{ax}–C(5)); 1.50 (*dt*, *J* = 13.6, 2.4, H_{eq}–C(3)); 1.44–1.38 (*m*, H_{eq}–C(5), 1 H Me$_2$CHCH_2); 1.27 (*dd*, *J* = 13.6, 11.1, H_{ax}–C(3)); 1.23 (*s*, Me–C(4)); 1.11 (*ddd*, *J* = 13.3, 8.3, 4.5, 1 H Me$_2$CHCH_2); 0.88 (*d*, *J* = 6.6, *Me*$_2$CH). ^{13}C-NMR: 71.1; 67.9; 63.5; 45.3; 45.1; 38.7; 31.7; 24.2; 23.2; 22.2. GC/MS: 172 (1, *M*$^+$), 154 (25), 139 (20), 115 (58), 69 (100), 43 (75).

*Data of (2*R,*4*R*)-***2***: Chemical purity 97% by GC/MS (t_R 10.81); >99% de (GC/MS); 91% ee (from (*R*)-**5**). $[\alpha]_D^{20} = -4.5$ (*c* = 1.83, $CHCl_3$). ^{1}H-NMR (400 MHz): 3.95 (*ddd*, *J* = 12.0, 5.4, 2.0, H_{eq}–C(6)); 3.41 (*ddd*, *J* = 12.5,

11.9, 2.4, H_{ax}–C(6)); 3.34 (*ddd*, *J* = 11.2, 8.2, 4.4, 2.3, H_{ax}–C(2)); 1.82–1.72 (*m*, Me_2CH); 1.69 (*dddq*, *J* = 12.7, 12.5, 5.4, 0.8, H_{ax}–C(5)); 1.62 (*dt*, *J* = 12.5, 2.4, H_{eq}–C(3)); 1.58 (*dddd*, *J* = 12.6, 2.4, 2.3, 2.0, H_{eq}–C(5)); 1.49 (*ddd*, *J* = 13.9, 8.3, 5.9, 1 H, Me_2CHCH_2); 1.35 (*ddq*, *J* = 12.5, 11.5, 0.8, H_{ax}–C(3)); 1.32 (*t*, *J* = 0.8, Me–C(4)); 1.17 (*ddd*, *J* = 13.9, 8.3, 4.5, 1 H, Me_2CHCH_2), 0.88 (*d*, *J* = 6.6, 2 Me_2CH). ^{13}C-NMR: 73.5; 68.7; 65.3; 46.9; 45.3; 40.6; 25.3; 24.2; 23.1; 22.3. GC/MS: 154 (10, $[M-18]^+$), 139 (8), 115 (85), 71 (100), 43 (80).

5.3. *(2S,4R)- and (2S,4S)-Tetrahydro-4-methyl-2-(2-methylpropyl)-2*H*-pyran-4-ol* ((2*S*,4*R*)- and (2*S*,4*S*)-**2**, resp.). As described in *5.1*, with (3*RS*,5*S*)-**17b** (11.2 g, 0.059 mol), TsCl (16.72 g, 0.088 mol), and pyridine (20 ml): (2*S*,4*R*)-**2** (3.55 g, 35%) and (2*S*,4*S*)-**2** (2.94 g, 29%).

Data of (2S,4R)-**2**: Chemical purity 98% by GC/MS (t_R 10.47); > 99% de (GC/MS); 95% ee (from (*S*)-**12**). $[\alpha]_D^{20} = +1.22$ (*c* = 1.63, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

Data of (2S,4S)-**2**: Chemical purity 97% by GC/MS (t_R 10.81); > 99% de (GC/MS); 95% ee (from (*S*)-**12**). $[\alpha]_D^{20} = +4.9$ (*c* = 1.14, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

5.4. *(2R,4S)- and (2R,4R)-Tetrahydro-4-methyl-2-propyl-2*H*-pyran-4-ol* ((2*R*,4*S*)- and (2*R*,4*R*)-**18**, resp.). The mixture (3*RS*,5*S*)-**19** (5.30 g, 0.024 mol) was treated with TsCl (6.93 g, 0.036 mol) in pyridine (30 ml). After the usual workup, saponification with 10% NaOH soln. (10 ml) in EtOH (50 ml) gave, after CC (hexane/AcOEt 95:5), (2*R*,4*R*)-**18** (1.29 g, 34%) and (2*R*,4*S*)-**18** (1.14 g, 30%).

Data of (2R,4S)-**18**: Chemical purity 95% by GC/MS (t_R 9.27); > 99% de (GC/MS). $[\alpha]_D^{20} = -0.63$ (*c* = 0.96, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

Data of (2R,4R)-**18**: Chemical purity 96% by GC/MS (t_R 9.71); > 99% de. $[\alpha]_D^{20} = -4.40$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

6. *Pyranol Acetates* **1**. 6.1. *(2S,4R)-Tetrahydro-4-methyl-2-propyl-2*H*-pyran-4-ol Acetate* ((2*S*,4*R*)-**1**). Treatment of (2*S*,4*R*)-**18** (1.10 g, 6.96 mmol) in refluxing Ac_2O (10 ml) in the presence of NaOAc (0.856 g, 10.4 mmol) gave, after the usual workup, (2*S*,4*R*)-**1** (1.06 g, 76%): Chemical purity 95% by GC/MS (t_R 12.06); > 99% de (GC/MS); 80% ee (from (*S*)-**4**). $[\alpha]_D^{20} = -3.11$ (*c* = 0.94, $CHCl_3$). ^{1}H-NMR (400 MHz, C_6D_6): 3.71 (*ddd*, *J* = 11.6, 5.3, 1.6, H_{eq}–C(6)); 3.57 (*ddd*, *J* = 12.6, 11.6, 2.1, H_{ax}–C(6)); 3.52 (*dddd*, *J* = 11.4, 7.4, 4.6, 2.3, H_{ax}–C(2)); 2.20 (*dt*, *J* = 13.8, 2.3, H_{eq}–C(3)); 2.05 (*dddd*, *J* = 14.1, 2.3, 2.1, 1.6, H_{eq}–C(5)); 1.68 (*s*, MeCOO), 1.40 (*s*, Me–C(4)); 1.60–1.25 (*m*, CH_2CH_2); 1.28 (*ddd*, *J* = 14.1, 12.6, 5.3, H_{ax}–C(5)); 1.02 (*dd*, *J* = 13.8, 11.3, H_{ax}–C(3)); 0.89 (*t*, *J* = 7.2, *Me*CH_2). GC/MS: 157 (0.5, $[M-43]^+$), 140 (20), 125 (30), 97 (100).

6.2. *(2S,4S)-Tetrahydro-4-methyl-2-propyl-2*H*-pyran-4-ol Aacetate* ((2*S*,4*S*)-**1**). As described in *6.1*, with (2*S*,4*S*)-**18** (0.95 g, 6.01 mmol), Ac_2O (10 ml), and NaOAc (0.739 g, 9.02 mmol): (2*S*,4*S*)-**1** (0.889 g, 74%). Chemical purity 95% by GC/MS (t_R 13.24); > 99% de (GC/MS); 80% ee (from (*S*)-**4**). $[\alpha]_D^{20} = -1.67$ (*c* = 0.94, $CHCl_3$). ^{1}H-NMR (400 MHz): 3.93 (*ddd*, *J* = 12.1, 5.3, 1.9, H_{eq}–C(6)); 3.46 (*ddd*, *J* = 12.6, 12.1, 2.3, H_{ax}–C(6)); 3.33 (*m*, H_{ax}–C(2)); 2.10 (*dt*, *J* = 12.6, 2.2, H_{eq}–C(3)); 2.03 (*dddd*, *J* = 12.8, 2.3, 2.2, 1.9, H_{eq}–C(5)); 1.97 (*s*, MeCOO), 1.86 (*dddq*, *J* = 12.8, 12.6, 5.3, 0.9, H_{ax}–C(5)); 1.62 (*t*, *J* = 0.9, Me–C(4)); 1.55–1.30 (*m*, CH_2CH_2); 1.54 (*ddq*, *J* = 12.6, 11.5, 0.9, H_{ax}–C(3)); 0.91 (*t*, *J* = 7.2, *Me*CH_2). GC/MS: 157 (0.5, $[M-43]^+$), 140 (20), 125 (30), 97 (100).

6.3. *(2R,4S)-Tetrahydro-4-methyl-2-propyl-2*H*-pyran-4-ol Acetate* ((2*R*,4*S*)-**1**).

As described in *6.1*, with (2*R*,4*S*)-**18** (1.00 g, 6.32 mmol), Ac_2O (10 ml), and NaOAc (0.777 g, 9.48 mmol): (2*R*,4*S*)-**1** (0.872 g, 69%). Chemical purity 97% by GC/MS (t_R 12.06); > 99% de (GC/MS). $[\alpha]_D^{20} = +3.8$ (*c* = 0.94, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

6.4. *(2R,4R)-Tetrahydro-4-methyl-2-propyl-2*H*-pyran-4-ol Acetate* ((2*R*,4*R*)-**1**). As described in *6.1*, with (2*R*,4*R*)-**18** (1.00 g, 6.32 mmol), Ac_2O (10 ml), and NaOAc (0.777 g, 9.48 mmol): (2*R*,4*R*)-**1** (0.808 g, 64%). Chemical purity 94% by GC/MS (t_R 13.24); > 99% de (GC/MS). $[\alpha]_D^{20} = +1.88$ (*c* = 0.96, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

7. *Rhubafurans* **3**. 7.1. *Precursors* **22**–**26**. *(2R,3E)-4-Phenylpent-3-en-2-ol* ((*R*,*E*)-**22**). Saponification of (*R*,*E*)-**23** (27.0 g, 0.132 mol) with KOH (9.63 g, 0.172 mol) in MeOH (300 ml) gave, after the usual workup, (*R*)-**22** (19.7 g, 92%). $[\alpha]_D^{20} = +45.8$ (*c* = 1.1, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

(3R,4E)-3-Methyl-3-phenylhex-4-enoic Acid ((*R*,*E*)-**24**). A soln. of (*R*,*E*)-**22** (19.4 g, 0.12 mol) in triethyl orthoacetate (500 ml), in the presence of propanoic acid (0.5 ml) was heated at 140°, removing EtOH by distillation. After evaporation, the residue was treated with 10% NaOH soln. (50 ml) in refluxing EtOH (200 ml). The mixture was poured into H_2O, acidified with 10% HCl soln., and extracted with Et_2O. The org. phase was dried (Na_2SO_4) and evaporated: (*R*,*E*)-**24** (15.6 g, 64%): $[\alpha]_D^{20} = +2.88$ (*c* = 1.04, $CHCl_3$); ^{1}H-NMR: 7.36–7.13 (*m*, 5 arom. H); 5.76 (*dq*, *J* = 15.7, 1.7, H–C(4)); 5.47 (*dq*, *J* = 15.7, 6.1, H–C(5)); 2.81 (*d*, *J* = 14.5, 1 H–C(2)); 2.75 (*d*, *J* = 14.5, 1 H–C(2)); 1.72 (*dd*, *J* = 1.7, 6.1, Me(6)); 1.53 (*s*, Me–C(3)). ^{13}C-NMR: 177.4; 146.4;

138.1; 128.1; 126.2; 126.0; 123.1; 45.8; 42.4; 26.1; 18.1. Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.73, H 7.58.

*(3S,4*E*)-3-Methyl-3-phenylhex-4-enoic Acid* ((*S,E*)-**24**). As described for (*R,E*)-**24**, with (*S,E*)-**22** (22.0 g, 0.13 mol): (*S,E*)-**24** (16.62 g, 60%). $[\alpha]_D^{20} = -2.67$ ($c = 0.94$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer. Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.12, H 7.08.

*(4*R,5E*)-4-Methyl-4-phenylhept-5-en-2-one* ((*R,E*)-**25**). A soln. of (*R,E*)-**24** (15.5 g, 0.076 mol) in THF (100 ml) was treated with ethyl carbonochloridate (9.82 g, 0.091 mol) and Et_3N (9.19 g, 0.091 mol) at 0°. The mixture was poured into H_2O and extracted with Et_2O, the org. phase dried (Na_2SO_4) and evaporated, and the residue dissolved in THF (150 ml). To this soln., 3M MeMgCl (33 ml, 0.099 mol) was quickly added at −20°. The mixture was poured into sat. NH_4Cl soln. and extracted with Et_2O, the org. phase evaporated, and the residue submitted to CC (hexane): (*R,E*)-**25** (10.59 g, 69%). Chemical purity 97% by GC/MS (t_R 17.52). $[\alpha]_D^{20} = -11.06$ ($c = 0.95$, $CHCl_3$). ^{1}H-NMR: 7.36–7.15 (*m*, 5 arom. H); 5.76 (*dq*, $J = 15.7, 1.5$, H−C(5)); 5.47 (*dq*, $J = 15.7, 6.6$, H−C(6)); 2.92 (*d*, $J = 14.3$, 1 H−C(3)); 2.82 (*d*, $J = 14.3$, 1 H−C(3)); 1.87 (*s*, MeCO); 1.73 (*dd*, $J = 1.5, 6.6$, Me(7)); 1.48 (*s*, Me−C(4)). ^{13}C-NMR: 208.1; 146.9; 138.8; 138.1; 128.1; 126.3; 122.7; 29.7; 26.11; 18.1; GC/MS: 187 (3, $[M-15]^+$), 159 (12), 145 (100), 117 (42). Anal. calc. for $C_{14}H_{18}O$: C 83.12, H 8.97; found: C 83.47, H 9.32.

*(4*S,5E*)-4-Methyl-4-phenylhept-5-en-2-one* ((*S,E*)-**25**). As described for (*R,E*)-**25**, with (*S,E*)-**24** (16.5 g, 0.081 mol): (*S,E*)-**25** (10.96 g, 67%). Chemical purity 96% by GC/MS (t_R 17.52). $[\alpha]_D^{20} = +10.7$ ($c = 1.05$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer. Anal. calc. for $C_{14}H_{18}O$: C 83.12, H 8.97; found: C 82.88, H 9.24.

*(2*S,4R*)- and (2*S,4S*)-2-Methyl-2-phenylpentane-1,4-diol* ((2*S*,4*R*)- and (2*S*,4*S*)-**26**, resp.). Ketone (*R,E*)-**25** (10.4 g, 0.051 mol) was treated with O_3 at −78° in CH_2Cl_2/MeOH (200 ml). The mixture was quenched with $NaBH_4$ (3.88 g, 0.102 mol). After the usual workup, the residue was separated by CC (hexane/ethyl acetate 7:3): (2*S*,4*R*)-**26** (3.46 g, 35%) and (2*S*,4*S*)-**26** (2.87 g, 29%).

Data of (2*S*,4*R*)-**26**: Chemical purity 97% by GC/MS (t_R 19.07); >99% de; >99% ee (from (*R*)-**23**). $[\alpha]_D^{20} = -8.54$ ($c = 0.96$, $CHCl_3$). ^{1}H-NMR: 7.50–7.12 (*m*, 5 arom. H); 4.00 (*d*, $J = 11.2$, H−C(1)); 3.90–3.77 (*m*, H−C(4)); 3.74 (*d*, $J = 11.2$, 1 H−C(1)); 2.0–1.85 (*m*, 2 H−C(3)); 1.28 (*s*, Me−C(2)); 1.19 (*d*, $J = 6.2$, Me(5)). ^{13}C-NMR: 145.2; 128.4; 128.1; 126.4; 126.1; 69.81; 65.14; 58.2; 48.3; 42.73; 27.4; 25.0; GC/MS: 176 (1, $[M-18]^+$), 164 (12), 146 (38), 131 (42), 119 (100). Anal. calc. for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.35, H 9.01.

Data of (2*S*,4*S*)-**26**: Chemical purity 96% by GC/MS (t_R 19.46); >99% de; >99% ee (from (*R*)-**23**). $[\alpha]_D^{20} = +13.1$ ($c = 0.89$, $CHCl_3$). ^{1}H-NMR: 7.50–7.16 (*m*, 5 arom. H); 4.1–3.95 (*m*, H−C(4)); 3.80 (*d*, $J = 11.2$, 1 H−C(1)); 3.66 (*d*, $J = 11.2$, 1 H−C(1)); 2.01 (*dd*, $J = 9.2, 15.1$, 1 H−C(3)); 1.73 (*dd*, $J = 1.9, 15.1$, 1 H−C(3)); 1.41 (*s*, Me−C(2)); 1.19 (*d*, $J = 6.2$, Me(5)). ^{13}C-NMR: 147.1; 128.3; 126.5; 126.2; 125.8; 70.9; 64.7; 48.9; 42.3; 25.5; 21.5. GC/MS: 176 (1, $[M-18]^+$), 164 (8), 146 (46), 131 (58), 119 (100). Anal. calc. for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 73.87, H 9.77.

*(2*R,4S*)- and (2*R,4R*)-2-Methyl-2-phenylpentane-1,4-diol* ((2*R*,4*S*)- and (2*R*,4*R*)-**26**, resp.). As described for (2*S*,4*R*)- and (2*S*,4*S*)-**26**, with (*S,E*)-**25** (10.80 g, 0.053 mol), O_3, CH_2Cl_2/MeOH (200 ml), and $NaBH_4$ (4.03 g, 0.106 mol): (2*R*,4*S*)-**26** (3.19 g, 31%) and (2*R*,4*R*)-**26** (2.87 g, 28%).

*Data of (2*R,4S*)-***26**: Chemical purity 96% by GC/MS (t_R 19.07); >99% de; >99% ee (from (*S*)-**22**). $[\alpha]_D^{20} = +8.34$ ($c = 1.53$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer. Anal. calc. for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.42., H 9.77.

*Data of (2*R,4R*)-***26**: Chemical purity 97% by GC/MS (t_R 19.46); >99% de; >99% ee (from (*S*)-**22**). $[\alpha]_D^{20} = -11.7$ ($c = 0.87$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer. Anal. Calc. For $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 74.54, H 8.99.

7.2. *Ring Closure of Derivatives* **27** *and* **28**. 7.2.1. *General Procedure 3* (*GP3*). The suitable monoacetate derivative (4.7 mmol) was treated with TsCl (1.34 g, 7.05 mmol) in pyridine (5 ml). After the usual workup, saponification with 10% NaOH soln. (2 ml) in ethanol (10 ml) gave *Rhubafuran*® samples which were purified by CC (hexane/AcOEt 95:5).

7.2.2. *(2*S,4R*)-Tetrahydro-2,4-dimethyl-4-phenylfuran* ((2*S*,4*R*)-**3**). According to *GP3*, with (2*R*,4*R*)-**27** (1.0 g, 4.23 mmol): (2*S*,4*R*)-**3** (0.417 g, 56%). Chemical purity 97% by GC/MS (t_R 13.78); 66% de; >99% ee (from (*S*)-**22**). $[\alpha]_D^{20} = +12.5$ ($c = 0.97$, $CHCl_3$). ^{1}H-NMR (400 MHz): 7.34–7.18 (*m*, 5 arom. H); 4.12 (*ddq*, $J =$ 7.7, 7.5, 6.2, H−C(2)); 3.99 (*d*, $J = 12.4$, 1 H−C(5)); 3.91 (*d*, $J = 12.4$, 1 H−C(5)); 2.43 (*dd*, $J = 12.4, 7.5$, 1 H−C(3)); 1.66 (*dd*, $J = 12.4, 7.7$, 1 H−C(3)); 1.45 (*s*, Me−C(4)); 1.34 (*d*, $J = 6.2$, Me−C(2)). ^{13}C-NMR: 147.6; 128.3; 125.9; 125.7; 78.9; 75.5; 47.7; 29.1; 28.1; 21.8. GC/MS : 176 (2, M^+); 145 (12); 131 (100).

7.2.3. *(2*R,4R*)-Tetrahydro-2,4-dimethyl-4-phenylfuran* ((2*R*,4*R*)-**3**). According to *GP3*, with (2*R*,4*R*)-**28** (1.0 g, 4.23 mmol): (2*R*,4*R*)-**3** (0.372 g, 50%). Chemical purity 97% by GC/MS (t_R 13.86); 84% de; >99% ee

(from (*S*)-**22**). $[\alpha]_D^{20} = +2.66$ ($c = 0.67$, $CHCl_3$). ^{1}H-NMR: 7.34–7.18 (*m*, 5 arom. H); 4.32 (*quint. d*, $J = 5.9$, 9.5, H–C(2)); 4.02 (*d*, $J = 8.2$, 1 H–C(5)); 3.90 (*d*, $J = 8.2$, 1 H–C(5)); 2.22 (*dd*, $J = 12.1$, 5.9, 1 H–C(3)); 1.85 (*dd*, $J = 12.1$, 9.5, 1 H–C(3)); 1.43 (*s*, Me–C(4)); 1.29 (*d*, $J = 5.9$, Me–C(2)). ^{13}C-NMR: 147.8; 128.3; 126.0; 125.9; 125.7; 78.5; 74.9; 47.9; 28.1; 21.4. GC/MS: 176 (12, M^+); 146 (23), 131 (100).

7.2.4. *(2*R*,4*S*)-Tetrahydro-2,4-dimethyl-4-phenylfuran* ((2*R*,4*S*)-**3**). According to *GP3*, with (2*S*,4*S*)-**27** (1.1 g, 4.7 mol): (2*R*,4*S*)-**3** (0.401 g, 49%). Chemical purity 97% by GC/MS (t_R 13.78); 78% de; >99% ee (from (*R*)-**23**). $[\alpha]_D^{20} = -39.5$ ($c = 0.4$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

7.2.5. *(2*S*,4*S*)-Tetrahydro-2,4-dimethyl-4-phenylfuran* ((2*S*,4*S*)-**3**). NBS (1.19 g, 6.69 mmol) was added to a soln. of (2*S*,4*S*)-**26** (1.0 g, 5.15 mmol) and PPh_3 (1.75 g, 6.69 mmol) in CH_2Cl_2 (20 ml). After 30 min at r.t., the mixture was poured into H_2O and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to CC (hexane): (2*S*,4*S*)-**3** (0.607 g, 67%); 60% de, >99% ee. $[\alpha]_D^{20} = -10.2$ ($c = 0.84$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

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