Biocatalyzed preparation of the optically enriched stereoisomers of 4-methyl-2-phenyl-tetrahydro-2*H*-pyran (Doremox®)

Elisabetta Brenna, Claudio Fuganti, Sabrina Ronzani, and Stefano Serra

Abstract: The four stereoisomers of the rose oxide analogue Doremox® were prepared in enantiomerically enriched form by enantiospecific bakers' yeast reduction of suitable derivatives and by lipase-mediated kinetic resolution of diol precursors.

Key words: yeast, lipase, odorant, reduction, kinetic resolution.

Résumé : Faisant appel à une réduction énantiospécifique de dérivés appropriés à l'aide de levure de boulanger ou à une résolution cinétique de diols précurseurs à l'aide de lipase, on a préparé une forme énantiomériquement enrichie des quatre stéréoisomères du Doremox®, un analogue de l'oxyde de rose.

Mots clés : levure, lipase, odorant, réduction, résolution cinétique.

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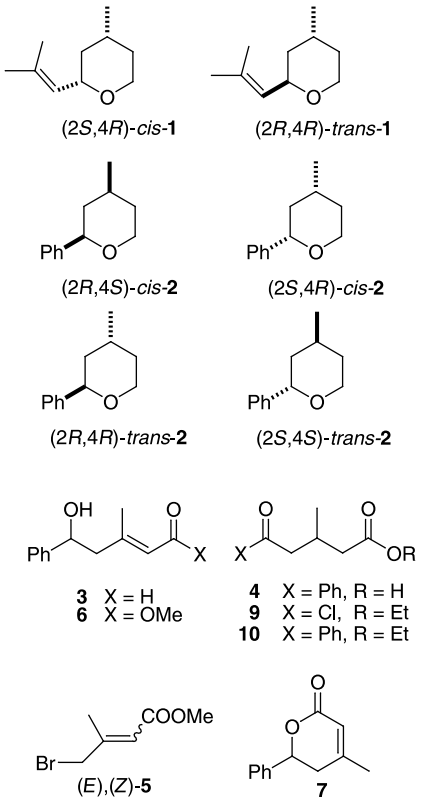
Introduction

The use of cyclic ethers as fragrant ingredients for the preparation of perfuming compositions and perfumed articles originated with the two diastereoisomeric rose oxides (2*S*,4*R*)-*cis*-**1** and (2*R*,4*R*)-*trans*-**1**, after their discovery in rose oil (1) and geranium oil (2) and their availability through efficient synthetic procedures (3).

In the aim of improving the olfactory properties of **1**, several structural modifications were realized. For example, the isobutenyl unit was elongated to produce sesquiterpenoid homologues showing a rather complex odour profile (4), or one carbon atom of the tetrahydropyrane ring was substituted with an oxygen atom, to afford chiral 3-oxa analogues (5).

In 1993, 4-methyl-2-phenyl-tetrahydro-2*H*-pyran (Doremox®, **2**) was obtained by Firmenich (6) as a mixture of the two racemic *cis*- and *trans*-diastereoisomers, by hydrogenation of 5,6-dihydro-4-methyl-2-phenyl-2*H*-pyran in the presence of Pd on charcoal. This preparation represented a further evolution in the structure–activity study of the olfactory properties of rose oxide. The isobutenyl fragment of **1** was substituted with a phenyl group, to increase the substantivity of rose scent, i.e the persistence of the perfume material on blotters, skin, or in the intended application (7). Substantivity is mainly determined by vapor pressure, which depends in turn on molecular weight. The phenyl group increases the mass, without a substantial change of the shape of the molecule, and thus without affecting the main odour characteristics (8).



The two isomers (*cis*-**2** and *trans*-**2**) were separated by preparative gas chromatography, and their odour properties

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This paper is dedicated to J. Bryan Jones on the occasion of his 65th birthday in recognition of his contributions to biocatalysis.

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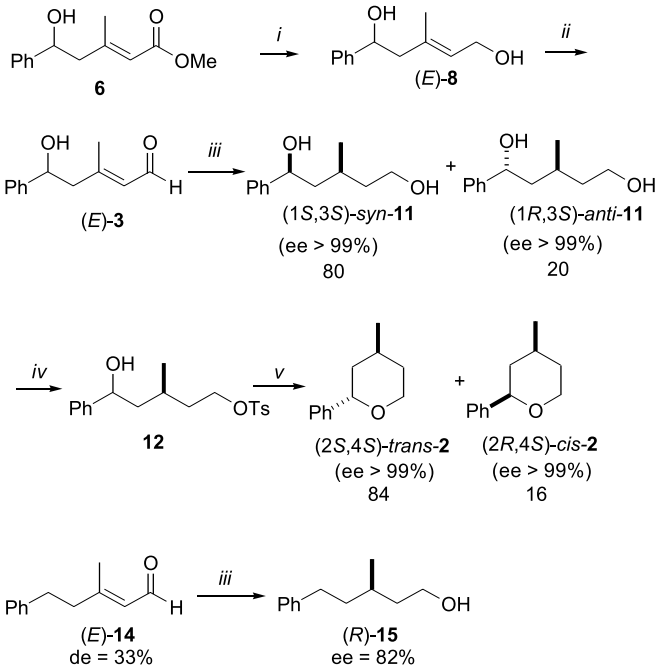
Scheme 1. (*i*) Diisobutylaluminum hydride in toluene; (*ii*) MnO_2 in hot DMF; (*iii*) baker's yeast; (*iv*) $CHCl_3$, TosCl, pyridine; (*v*) MeONa, MeOH.



were described (6). The racemic *cis*-diastereoisomer was found to be very powerful and to have a green, rose oxide – diphenyl oxide type note. The racemic *trans*-isomer had a much weaker odour, with a green, vegetable, slightly dirty and minty character and a floral undertone. Both of them were described to be useful in the preparation of perfumes and concentrated perfuming bases, as well as of a variety of articles, such as soaps, bath or cosmetic formulations, air and body deodorants, detergents, fabric softeners, and household products.

Neither enantioselective synthesis of the four stereoisomers of Doremox®, nor olfactory evaluation of each distinct isomer have been performed so far. The wide diffusion of this fragrant component in many commercial preparations induced us to investigate the possibility of obtaining the enantiomerically enriched isomers of *cis*-**2** and *trans*-**2**, to select those showing the most powerful and interesting odour properties. Now we wish to report on the outcome of this investigation, which is part of a research project aimed at the preparation of the olfactory active stereoisomers of commercial fragrances (9), via biocatalyzed methods.

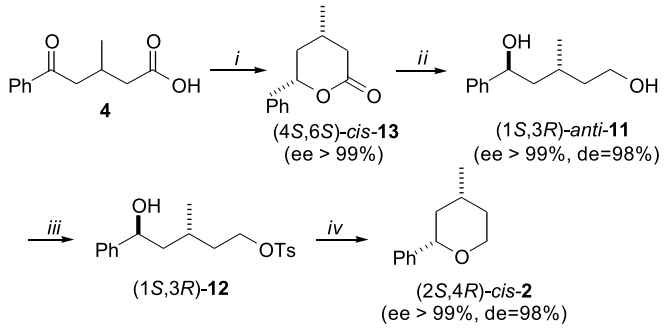
Results and discussion

Two different approaches to optically active Doremox® isomers were chosen on the basis of our past experience: (*i*) enantioselective synthesis based on bakers' yeast (BY) reduction; (*ii*) lipase-mediated kinetic resolution of suitable precursors.

Bakers' yeast approach

We had successfully developed synthetic methods for the preparation of enantiomerically enriched rose oxide (10) and Aerangis lactone (11), based on BY-enantiospecific and

Scheme 2. (*i*) Baker's yeast; (*ii*) $LiAlH_4$, THF; (*iii*) $CHCl_3$, TosCl, pyridine; (*iv*) MeONa, MeOH.



diastereoselective reduction of 1,5- and 1,4-difunctionalized synthons. Thus, as for the synthesis of **2**, we envisaged hydroxy aldehyde **3** and keto acid **4** as substrates for yeast fermentation.

Compound **3** was prepared according to this synthetic scheme. Reformatsky reaction of bromo derivative **5** (12) with benzaldehyde afforded a mixture of hydroxy ester **6** and lactone **7** (13) which were easily separated by column chromatography. DIBAL reduction of compound **6** in toluene solution gave unsaturated diol (*E*)-**8** (Scheme 1), which was straightforwardly oxidized to the desired aldehyde (*E*)-**3** (14) with MnO_2 in hot DMF; no oxidation of the benzylic hydroxylic group was observed in this reaction condition.

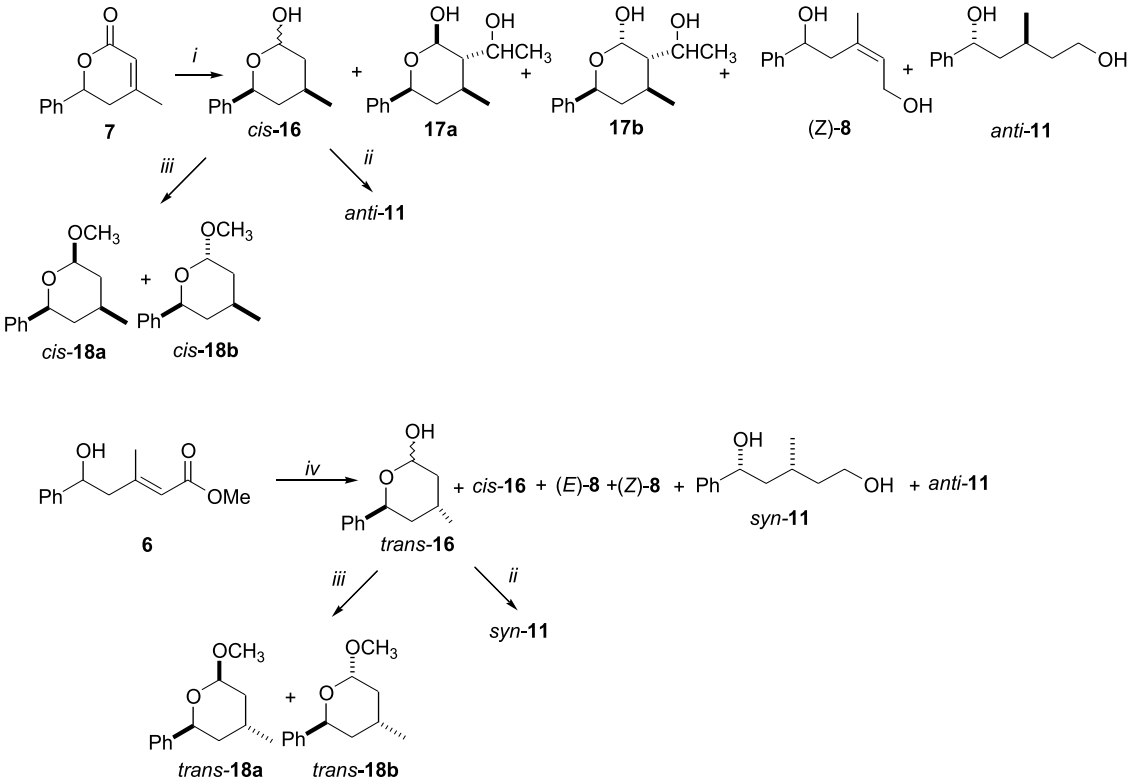
Keto acid **4** was prepared according to the following route. Friedel–Crafts acylation of benzene with the monochloride monomethyl ester of 3-methyl glutaric acid (**9**) (15) in the presence of aluminum(III) chloride gave mainly keto ester **10** (16), which was hydrolyzed with potassium hydroxide in methanol to afford keto acid **4** (17). Derivatives (*E*)-**3** and **4** were incubated with BY for 24 h, and, interestingly enough, the two reactions took different stereochemical courses.

Reduction of the double bond of derivative **3** (Scheme 1), in the presence of the benzylic stereocentre previously created without steric control, gave mainly (80%, GC–MS) diol (1*S*,3*S*)-*syn*-**11** (ee > 99%, chiral HPLC) and a minor quantity (20%, GC–MS) of diol (1*R*,3*S*)-*anti*-**11** (ee > 99%, chiral HPLC). The mixture of the two diastereoisomeric diols was converted into the corresponding monotosylate derivative **12** and, after treatment with sodium methylate in methanol, a sample of Doremox® with the following composition was obtained: (2*S*,4*S*)-*trans*-**2**, 86%, ee = 99% (chiral GC); (2*R*,4*S*)-*cis*-**2**, 14%, ee > 99%, $[\alpha]_D^{20}$ + 18.1 (*c* = 0.75, $CHCl_3$).

Reduction of the carbonyl function of racemic **4** (Scheme 2) gave lactone (4*S*,6*S*)-**13**, which was recovered in pure form after column chromatography, and reduced with $LiAlH_4$ to give diol (1*S*,3*R*)-*anti*-**11** (ee > 99%, de = 97%, chiral HPLC). This latter was then converted into (2*S*,4*R*)-*cis*-**2** (ee > 99%, de = 98%, $[\alpha]_D^{20}$ –54.1 (*c* = 1.05, $CHCl_3$)) according to the mentioned procedure, via the corresponding tosylate derivative (1*S*,3*R*)-*anti*-**12**.

In both cases the preferred isomer was produced enantiospecifically, but with different diastereoselection: *syn*-diastereoisomer prevailed when BY promoted the reduction of the double bond, while *anti*-diastereoisomer was obtained

Scheme 3. (*i*) $LiAlH_4$, THF, then AcOEt; (*ii*) $NaBH_4$, MeOH–CH_2Cl_2; (*iii*) MeOH–HCl; (*iv*) $LiAlH_4$, THF, then MeOH.



when the reduction of the carbonyl was involved. As for diol *anti*-**11**, opposite enantioselection was observed: (1*R*,3*S*)-*anti*-**11** was the product of BY reduction of hydroxy aldehyde **3**, while its enantiomer (1*S*,3*R*)-*anti*-**11** was the result of yeast fermentation of keto acid **6**.[2]

Lipase-mediated kinetic resolution

A second approach to optically active Doremox® was investigated, to prepare all the four possible stereoisomers in enantiomerically enriched form. For this purpose the preparation of the two racemic diols *anti*-**11** and *syn*-**11** was optimized.

Lactone **7** was treated with lithium aluminum hydride in THF (Scheme 3). When the reaction mixture was quenched with ethyl acetate, a complex mixture of products was obtained. The following compounds could be isolated and identified: tetrahydropyranol *cis*-**16** (1:1 mixture of the two possible epimers at C-2, 40%), substituted tetrahydropyranols **17a** (11%) and **17b** (10%),[3] unsaturated diol (*Z*)-**8** (8%) (20), and diol *anti*-**11** (12%). The structural assignment to *cis*-**16** was based on ^{1}H NMR and mass spectrometry data, and on its chemical reactivity; it afforded diol *anti*-**11** upon $NaBH_4$ reduction, and it was transformed into the mixture of the epimeric methyl glycosides *cis*-**18a** and *cis*-**18b** by treatment with MeOH–HCl.

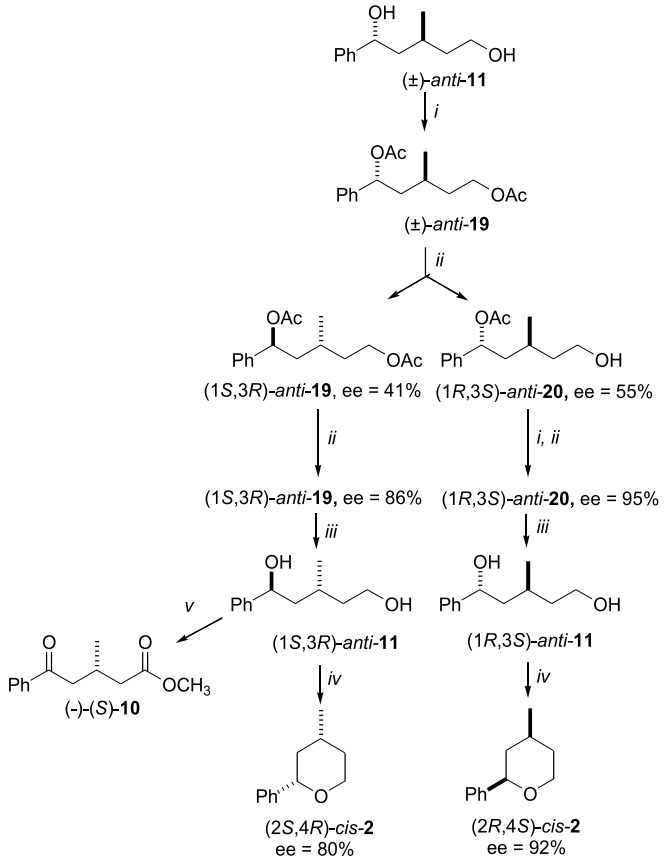
Low diastereoselection was obtained when hydroxy ester **6** was reduced (Scheme 3). GC–MS analysis of the reduction mixture allowed us to detect *cis*-**16** (25%) and *trans*-**16** (20%), *syn*-**11** (14%) and *anti*-**11** (10%), (*E*)-**8** (12%) and (*Z*)-**8** (6%) (20), and a complex system of compounds with retention times and mass spectra resembling those of **17a** and **17b** (12%). The reaction was then repeated using methanol to consume the excess of $LiAlH_4$ and the residue was chromatographed, to yield a nearly 1:1 mixture of *cis*-**16** and *trans*-**16** and a 2:1 mixture of *syn*-diol **11** and *anti*-diol **11**. The saturated diol fraction was enriched in the *syn*-diasteroisomer (de = 83%) by column chromatography. An analytical sample of *trans*-**16** was obtained by careful column chromatography and recrystallization from ether. This sample was reduced to *syn*-**11** with $NABH_4$ and converted into methyl glycosides *trans*-**18a** and *trans*-**18b** with MeOH–HCl.

Racemic diols *anti*-**11** (de > 99%) and *syn*-**11** (de = 83%) were acetylated with Ac_2O–Py, and the corresponding acetyl derivatives *anti*-**19** and *syn*-**19** were submitted separately to enzymic saponification, at pH 7.8 in the presence of lipase PS. As for diacetate *anti*-**19** (Scheme 4), the first enzymic saponification (monitored by chiral HPLC) afforded monoacetate (1*R*,3*S*)-*anti*-**20** showing 55% ee (chiral HPLC). This latter was acetylated and submitted again to lipase-mediated hydrolysis, to give (1*R*,3*S*)-*anti*-**20** with ee = 95% (chiral HPLC). Treatment with KOH in methanol gave (1*R*,3*S*)-*anti*-**11** (ee = 95%, chiral HPLC). Diacetate (1*S*,3*R*)-*anti*-**19** (ee = 41%), chiral HPLC of the corresponding diol), recovered

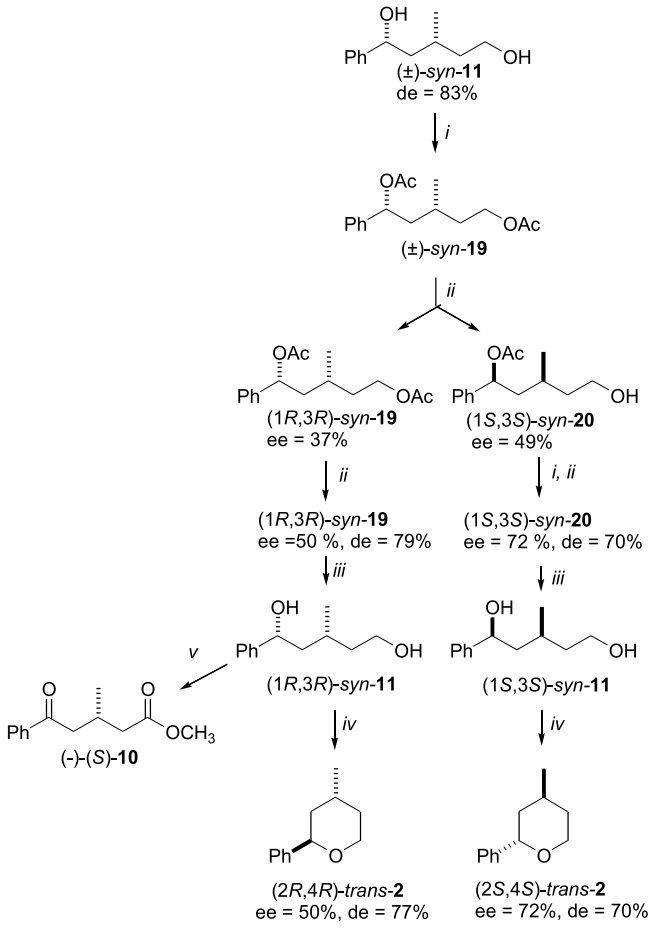
[2] When unsaturated aldehyde **14** (18*a*) (*E*:*Z*, 2:1) (Scheme 1) was submitted to yeast fermentation, saturated alcohol (+)-(*R*)-**15** (19) (ee 82%, chiral HPLC) was obtained. BY reduction of the conjugated double bond thus showed the same preferred enantioselectivity in structurally related compounds (CIP descriptors are different because the group priority changes from (*E*)-**3** to **14**).

[3] The formation of derivatives **17a** and **17b** was unexpected and unusual. ^{1}H NMR spectra showed that in both compounds the substituent $CH(OH)CH_3$ was located in the equatorial position (**17a** $J_{(H\text{-}3,H\text{-}4)}$ = 11.5 Hz, **17b** $J_{(H\text{-}2,H\text{-}3)}$ = 8.9 Hz).

Scheme 4. (*i*) Acetic anhydride, pyridine; (*ii*) lipase PS, THF–water, pH 7.8, 0.025 M NaOH; column chromatography; (*iii*) KOH, MeOH; (*iv*) TosCl, pyridine, then MeONa in methanol; (*v*) Jones' reactive acetone.



Scheme 5. (*i*) Acetic anhydride, pyridine; (*ii*) lipase PS, THF–water, pH 7.8, 0.025 M NaOH; column chromatography; (*iii*) KOH, MeOH; (*iv*) TosCl, pyridine, then MeONa in methanol; (*v*) Jones' reactive acetone.



unreacted from the first saponification, was depleted of the (1*R*,3*S*) enantiomer as much as possible by prolonged enzymic reaction. Finally, it afforded diol (1*S*,3*R*)-*anti*-**11** with ee = 86% (chiral HPLC) by reaction with KOH in methanol.

The same procedure was applied to diacetate *syn*-**19** (Scheme 5). (1*S*,3*S*)-*syn*-**11** (ee = 72%, de = 70%) and (1*R*,3*R*)-*syn*-**11** (ee = 50%, de = 79%) were obtained from monoacetate *syn*-**20** and survived diacetate *syn*-**19**, respectively.

The four enantiomerically enriched diols were treated with tosyl chloride and pyridine, then with sodium methylate in methanol, to promote ring closure. The following samples of Doremox® were obtained: (*i*) (2*R*,4*S*)-*cis*-**2** (from (1*R*,3*S*)-*anti*-**11**): ee = 92%, de > 99% (chiral GC), $[\alpha]_D^{20}$ +52 (*c* = 0.27, $CHCl_3$); (*ii*) (2*S*,4*R*)-*cis*-**2** (from (1*S*,3*R*)-*anti*-**11**): ee = 80%, de > 99% (chiral GC), $[\alpha]_D^{20}$ – 42 (*c* = 1.2, $CHCl_3$); (*iii*) (2*S*,4*S*)-*trans*-**2** (from (1*S*,3*S*)-*syn* -**11**): ee = 72%, de = 70% (chiral GC), $[\alpha]_D^{20}$ + 14.6 (*c* = 0.3, $CHCl_3$); this sample contained 15% of (+)-*cis*-**2** with ee = 73%; (*iv*) (2*R*,4*R*)-*trans*-**2** (from (1*R*,3*R*)-*syn*-**11**): ee = 50%, de = 77% (chiral GC), $[\alpha]_D^{20}$ – 9.8 (*c* = 1.15, $CHCl_3$); this sample contained 11.5% of (–)-*cis*-**2** with ee = 65%.

Configurational assignment

The absolute configurations of the two stereocentres of diols *anti*-**11** and *syn*-**11** and of *cis*-**2** and *trans*-**2** were assigned by chemical correlation on the basis of these data: (*i*) ^{1}H NMR spectra of *cis*-**2** and *trans*-**2** had been described, so the relative configurations of Doremox® isomers and those of the diol precursors could be defined; (*ii*) samples of (–)-*anti*-**11** (ee > 99%) and of (+)-*syn*-**11** (ee = 50%, de = 79%) were oxidized to the corresponding keto acids upon treatment with Jones' reactive in acetone solution. These latter derivatives were purified by column chromatography of the correponding methyl esters (diazomethane). In both cases, (–)-(*S*)-**10** (lit. value (21*a*) $[\alpha]_D^{20}$ – 5.65 (*c* = 1.24, benzene) for the (*S*)-isomer, ee = 90%; lit. value (21*b*) $[\alpha]_D^{20}$ +9.25 (neat) for the (*R*)-isomer, ee > 96%) was obtained showing optical rotation values of –5.02 (*c* = 0.85, benzene; prepared from *anti*-**11**) and –3.21 (*c* = 0.73, benzene; prepared from *syn*-**11**). (*R*)-Configuration was assigned to C-3 in (–)-*anti*-**11** and (+)-*syn*-**11** (the CIP descriptor of the stereogenic carbon atom changes because the order of group priority is different). The absolute configurations of all the derivatives involved in the synthetic scheme was then deduced.

Thus, it was possible to verify that lipase PS promoted the saponification of both the diol isomers showing (*S*)-configuration at the carbon atom nearer to the reactive site.

Olfactory descriptions

Olfactory evaluation of Doremox® samples gave the following results: (*i*) (2*R*,4*S*)-*cis*-**2**, ee = 92%, de > 99%: rose oxide, diphenyl oxide, metallic, slightly plastic; (*ii*) (2*S*,4*R*)-*cis*-**2**, ee = 80%, de > 99%: rose oxide, powerful, nice; (*iii*) (2*S*,4*S*)-*trans*-**2**, ee = 72%, de = 70%: weak, rosy, plastic, citronellol, a rose oxide note is also present; (*iv*) (2*R*,4*R*)-*trans*-**2**, ee = 50%, de = 77%: rosy, rose oxide, metallic, off-note.

Experimental

Lipase PS *Pseudomonas cepacia* (Amano Pharmaceuticals Co., Japan) was employed in this work. GC–MS analyses were performed on a HP 6890 gas chromatograph equipped with a 5973 mass detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 μm). The following temperature program was employed: 60°C (for 1 min)/6°/min to 150°C (for 1 min)/12°/min to 280°C (for 5 min). Chiral GC analyses of Doremox® stereoisomers were performed on a DeTBuSiBETA (086) 25 m × 0.25 mm column (Mega, Italy), installed on a DANI HT 86.10 gas chromatograph, with the following temperature program: 45°C (3′)/5°C/min to 75°C/0.5°C/min to 100°C/10°C/min to 180°C (5′): t_R (2*S*,4*R*)-**1a** = 45.4 min, t_R (2*R*,4*S*)-**1a** = 46.5 min, t_R (2*R*,4*R*)-**1b** = 49.2 min, t_R (2*S*,4*S*)-**1b** = 49.7 min. Chiral HPLC analyses were performed on a Chiralcel OD column (Daicel, Japan) installed on a Merck–Hitachi L-6200 apparatus: 0.6 mL min^{-1}, UV detector (254 nm), hexane:isopropanol (95:5). The following retention times were observed: (1*RS*,3*SR*)-*anti*-**19** (single peak) t_R = 11.4 min; (1*R*,3*S*)-*anti*-**20** t_R = 21.7 min; (1*S*,3*R*)-*anti*-**20** t_R = 28.9 min; (1*R*,3*S*)-*anti*-**11** t_R = 29.8 min; (1*S*,3*R*)-*anti*-**11** t_R = 30.6 min; (1*S*,3*S*)-*syn*-**19** t_R = 10.6 min; (1*R*,3*R*)-*syn*-**19** t_R = 11.1 min; (1*S*,3*S*)-*syn*-**20** t_R = 17.2 min; (1*R*,3*R*)-*syn*-**20** t_R = 23.9 min; (1*R*,3*R*)-*syn*-**11** t_R = 30.8 min; (1*S*,3*S*)-*syn*-**11** t_R = 41.9 min; (*R*)-**15** t_R = 14.9 min; (*S*)-**15** t_R = 17.2 min. ^{1}H NMR spectra were recorded at room temperature (r.t.) on a Bruker AC-250 spectrometer (250 MHz ^{1}H). The chemical shift scale was based on internal tetramethylsilane. Optical rotations were measured on a Dr. Kernchen Propol digital automatic polarimeter. Microanalyses were determined on a Carlo Erba 1106 analyzer. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns.

The mixture of (*E*)- and (*Z*)-methyl 4-bromo-3-methyl-2-butenoate (**5**) was prepared as described in ref. 12. The monochloride mono methyl ester of 3-methyl glutaric acid was prepared according to ref. 15. Aldehyde **14** was prepared according to ref. 18*a*, and the diasteroisomeric excess (33%) was determined on the basis of ^{1}H NMR spectra of (*E*)-**14** and (*Z*)-**14** in ref. 18*b*.

5-Hydroxy-3-methyl-5-phenyl-pent-2-enoic acid methyl ester (6) (13) and 4-methyl-6-phenyl-5,6-dihydropyran-2-one (7) (13)

A solution of bromo derivative **5** (38.4 g, 0.20 mol) and benzaldehyde (2.12 g, 0.20 mol) in 100 mL THF was added dropwise to a suspension of zinc (14.3 g, 0.22 mol) in 300 mL THF at 0°C. The reaction was refluxed for 2 h, poured into ice, and extracted with ethyl acetate. The organic layer was washed with a solution of ammonium chloride, dried (Na_2SO_4), and concentrated. Column chromatography (hexane–EtOAc, 9:1) provided hydroxy ester **6** (16.7 g, 38%) and lactone **7** (17.7 g, 47%).

6

GC–MS (t_R = 21.80 min) *m*/*z*: 186 (M^+ – 34) (50), 158 (100), 129 (40), 77 (25). ^{1}H NMR ($CDCl_3$, ppm): 7.32 (m, 5H, C_6H_5), 5.76 (q, *J* = 1.1 Hz, 1H, H-C_2), 4.89 (dd, *J* = 4.6, 8.1 Hz, 1H, H-C_5), 3.68 (s, 3H, $COOCH_3$), 2.53 (m, 2H, CH_2), 2.22 (d, *J* = 1.1 Hz, 3H, CH_3-C=C).

7

mp 60°C. GC–MS (t_R = 21.80 min) *m*/*z*: 188 (M^+) (10), 105 (8), 82 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.35 (m, 5H, C_6H_5), 5.87 (m, 1H, H-C_3), 5.37 (dd, *J* = 3.9, 11.8 Hz, 1H, H-C_6), 2.62 (ddm, *J* = 11.8, 18.0 Hz, 1H, H-C_5), 2.42 (dd, *J* = 3.9, 18.0 Hz, 1H, H-C_5), 1.99 (m, 3H, CH_3-C=C).

(*E*)-3-Methyl-5-phenyl-2-pentene-1,5-diol ((*E*)-8)

A 1.5 M solution of diisobutyl aluminum hydride in toluene (69 mL, 0.103 mol) was added dropwise to a solution of hydroxy ester **6** (10.0 g, 0.045 mol) in 100 mL toluene at –10°C. The reaction was allowed to warm to 25°C, treated with water, filtered through a Celite cake, and extracted with ethyl acetate. The residue was chromatographed (hexane:EtOAc, 6:4) to give unsaturated diol (*E*)-**8** (6.82 g, 79%). GC–MS (t_R = 20.89 min) *m*/*z*: 174 (M^+ – 18) (0.04), 107 (71), 105 (83), 68 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.25 (m, 5H, C_6H_5), 5.50 (tq, *J* = 6.7, 1.2 Hz, 1H, H-C_2), 4.76 (t, *J* = 6.7 Hz, 1H, H-C_5), 4.09 (m, 2H, CH_2OH), 2.35 (d, *J* = 6.7 Hz, 2H, CH_2), 1.71 (d, *J* = 1.2 Hz, 3H, CH_3-C=C). Anal. calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.75, H 8.53.

(*E*)-5-Hydroxy-3-methyl-5-phenyl-pent-2-enal ((*E*)-3) (14)

Manganese(IV) oxide (1.5 equiv) was added to a solution of unsaturated diol (*E*)-**8** (6.70 g, 0.035 mol) in 50 mL DMF. The suspension was heated at 80°C for 4 h, then filtered poured into water, and extracted with EtOAc. The organic phase was dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (hexane–EtOAc, 7:3) to afford (*E*)-**3** (6.05 g, 91%). GC–MS (t_R = 21.20 min) *m*/*z*: 190 (M^+) (0.01), 172 (6), 107 (92), 84 (100). ^{1}H NMR ($CDCl_3$, ppm): 9.99 (d, *J* = 7.9 Hz, 1H, CHO), 7.35 (m, 5H, C_6H_5), 5.95 (dt, *J* = 7.9, 1.1, 1H, H-C_2), 4.94 (dd, *J* = 4.9, 8.7 Hz, 1H, H-C_5), 2.68 (dd, *J* = 14.0, 8.7 Hz, 1H, H-C_4), 2.57 (dd, *J* = 14.0, 4.9 Hz, 1H, H-C_4), 2.22 (d, *J* = 1.1 Hz, 3H, CH_3-C=C).

Methyl 3-methyl-5-oxo-5-phenyl-pentanoate (10) (16)

Aluminum trichloride (15.9 g, 0.12 mol) was added to a solution of derivative **9** (17.8 g, 0.10 mol) in 300 mL benzene at 10°C. The reaction mixture was refluxed for 2 h, poured into ice and 10% HCl, and extracted with EtOAc. The organic phase was dried (Na_2SO_4), concentrated, and chromatographed (hexane–EtOAc, 95:5), to give keto ester **10** (14.1 g, 64%). GC–MS (t_R = 21.01 min) *m*/*z*: 220 (M^+) (1.4), 189 (7.1), 120 (75), 105 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.97 (m, 2H, aromatic hydrogens), 7.40 (m, 3H, aromatic hydrogens), 3.67 (s, 3H, COOMe), 3.11 (dd, *J* = 16.0, 5.8 Hz, 1H), 2.84 (dd, *J* = 16.0, 7.3 Hz, 1H), 2.66 (m, 1H,

H-C_3), 2.44 (dd, *J* = 15.4, 6.1 Hz, 1H), 2.31 (dd, *J* = 15.4, 7.3 Hz, 1H), 1.05 (d, *J* = 6.6 Hz, CH_3).

3-Methyl-5-oxo-5-phenyl-pentanoic acid (4) (17)

Keto ester **10** (14.0 g, 0.064 mol) was hydrolysed with KOH (5.38 g, 0.096 mol) in 70 mL MeOH to afford, after the usual work-up, keto acid **4** (12.4 g, 93%). ^{1}H NMR ($CDCl_3$, ppm): 7.95 (m, 2H, aromatic hydrogens), 7.40 (m, 3H, aromatic hydrogens), 2.98 (m, 2H), 2.67 (m, 1H), 2.45 (m, 2H), 1.09 (d, *J* = 6.3 Hz, CH_3).

$LiAlH_4$ reduction of lactone 7

Procedure A

A solution of lactone **7** (18.8 g, 0.10 mol), in 30 mL THF was added dropwise to a suspension of $LiAlH_4$ (7.6 g, 0.20 mol), in 250 mL THF. The reaction mixture was stirred at r.t. for 12 h, then EtOAc was added to consume the excess $LiAlH_4$. The reaction mixture was poured into ice, extracted with Et_2O, dried (Na_2SO_4), and chromatographed (from hexane–EtOAc (95:5) to hexane–EtOAc (1:1)). The following products, in order of progressive elution, were isolated.

*(2*RS*,4*RS*,6*RS*)-4-Methyl-6-phenyl-tetrahydro-2*H*-pyran-2-ol and (2*RS*,4*SR*,6*SR*)-4-methyl-6-phenyl-tetrahydro-2*H*-pyran2-ol (*cis*-**16**, 1:1 mixture of the two epimers at C-2)*

7.68 g (40%), mp 67°C (diethyl ether). GC–MS (t_R = 19.34 min, single peak) *m*/*z*: 192 (M^+) (1.7), 174 (13), 159 (17), 104 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.32 (m, 10H, $2C_6H_5$), 5.40 (m, 1H, H-C_2 of one epimer), 4.98 (dd, 1H, *J* = 11.8, 2.1 Hz, H-C_2 of one epimer), 4.74 (dd, 1H, *J* = 9.6, 2.1 Hz, H-C_6 of one epimer), 4.74 (dd, 1H, *J* = 11.3, 1.7 Hz, H-C_6 of one epimer), 2.16 (m, 1H), 1.78 (m, 5H), 1.39–0.97 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 3H, CH_3 of one epimer), 0.90 (d, *J* = 6.6 Hz, 3H, CH_3 of one epimer). Anal. calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 75.13, H 8.48.

A sample of *cis*-**16** was treated with MeOH–HCl to give the mixture of the corresponding *O*-methyl glycosides *cis*-**18a** and *cis*-**18b** (3:1 mixture of the two epimers at C-2). GC–MS major epimer (t_R = 17.61 min) *m*/*z*: 206 (M^+) (2), 174 (41), 104 (94), 58 (100); minor epimer (t_R = 18.17 min): 174 (M^+ – 32) (3), 146 (27), 104 (100), 58 (50). ^{1}H NMR ($CDCl_3$, ppm): 7.32 (m, $2C_6H_5$), 4.90 (m, 1H of the major epimer), 4.74 (dd, *J* = 11.8, 1.9 Hz, 1H of the major epimer), 4.48 (dd, *J* = 9.8, 1.9 Hz, 1H of the minor epimer), 4.43 (dd, *J* = 11.3, 1.4 Hz, 1H of the minor epimer), 3.52 (s, OCH_3 of the minor epimer), 3.39 (s, OCH_3 of the major epimer), 2.16 (m, 1H), 1.83 (m), 1.45–1.10 (m), 1.00 (d, *J* = 6.3 Hz, CH_3 of the minor epimer), 0.93 (d, *J* = 6.8 Hz, CH_3 of the major epimer).

*(2*RS*,3*SR*,4*SR*,6*SR*)-3-(1-Hydroxyethyl)-4-methyl-6-phenyl-tetrahydro-2*H*-pyran-2-ol (**17a**, stereochemistry undefined at the stereogenic carbon atom in the substituent group)*

2.59 g (11%). GC–MS (t_R = 24.12 min) *m*/*z*: 218 (M^+ – 18) (1.7), 200 (1), 174 (17), 159 (25), 104 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.28 (m, 5H, C_6H_5), 5.43 (d, *J* = 3.1 Hz, 1H, H-C_2), 5.02 (dd, 1H, *J* = 12.0, 2.9 Hz, H-C_6), 4.02 (dq, *J* = 3.1, 6.7 Hz, 1H, *CH*CH_3OH), 2.32 (m, 1H, H-C_4), 1.84 (dt, *J* = 12.0, 2.9 Hz, 1H, H-C_5), 1.36 (q, *J* = 12.0 Hz, 1H, H-C_5), 1.29 (dt, *J* = 11.5, 3.1 Hz, H-C_3), 1.12 (d, *J* = 6.7 Hz, 3H, *CH*$_3$CHOH), 0.94 (d, *J* = 6.7 Hz, 3H, CH_3-C_4). Anal. calcd. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 70.89, H 8.77.

An analytical sample of **17a** was treated with Ac_2O and pyridine to give the corresponding diacetyl derivative. GC–MS (t_R = 25.56 min) *m*/*z*: 200 (M^+ – 2 × 60) (47), 104 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.32 (m, 5H, C_6H_5), 6.52 (d, *J* = 3.1 Hz, 1H, H-C_2), 5.14 (dq, *J* = 3.1, 6.6 Hz, *CH*CH_3OAc), 4.89 (dd, 1H, *J* = 12.0, 2.9 Hz, H-C_6), 2.12 (m + s, 4H, H-C_4 + CH_3COO), 2.04 (s, 3H, CH_3COO), 1.95 (dt, *J* = 12.0, 2.9 Hz, 1H, H-C_5), 1.72 (dt, *J* = 11.5, 3.1 Hz, H-C_3), 1.40 (q, *J* = 12.0 Hz, 1H, H-C_5), 1.32 (d, *J* = 6.6 Hz, 3H, *CH*$_3$CHOAc), 1.01 (d, *J* = 6.6 Hz, 3H, CH_3-C_4).

*(2*RS*,3*RS*,4*RS*,6*RS*)-3-(1-Hydroxyethyl)-4-methyl-6-phenyl-tetrahydro-2*H*-pyran-2-ol (**17b**, stereochemistry undefined at the stereogenic carbon atom in the substituent group)*

2.35 g (10%). GC–MS (t_R = 24.15 min) *m*/*z*: 218 (M^+ – 18) (1.4), 200 (3.5), 174 (8.5), 159 (14), 104 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.30 (m, 5H, C_6H_5), 4.92 (d, *J* = 8.9 Hz, 1H, H-C_2), 4.50 (dd, 1H, *J* = 11.2, 2.2 Hz, H-C_6), 4.11 (dq, *J* = 2.9, 6.7 Hz, *CH*CH_3OH), 1.80 (dt, *J* = 12.6, 2.2 Hz, 1H, H-C_5), 1.66–1.25 (m, 3H, H-C_5, H-C_3, H-C_4), 1.19 (d, *J* = 6.7 Hz, *CH*$_3$CHOH), 0.98 (d, *J* = 6.7 Hz, 3H, CH_3-C_4). Anal. calcd. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 71.55, H 8.78.

An analytical sample of **17b** was treated with Ac_2O and pyridine to give the corresponding diacetyl derivative. GC–MS (t_R = 24.50 min) *m*/*z*: 200 (M^+ – 2 × 60) (50), 104 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.33 (m, 5H, C_6H_5), 5.94 (d, *J* = 8.5 Hz, 1H, H-C_2), 5.23 (dq, *J* = 2.0, 6.7 Hz, *CH*CH_3OAc), 4.61 (dd, *J* = 11.6, 2.0 Hz, 1H, H-C_6), 2.14–2.02 (m + 2s, 7H, 1H + 2CH_3COO), 1.94–1.4 (m, 3H), 1.29 (d, *J* = 6.9 Hz, 3H, *CH*$_3$CHOAc), 1.17 (d, *J* = 6.2 Hz, 3H, CH_3-C_4).

*(Z)-3-Methyl-5-phenyl-2-penten-1,5-diol ((Z)-**8**) (20)*

1.53 g (8%). GC–MS (t_R = 21.04 min) *m*/*z*: 174 (M^+ – 18) (2.8), 159 (3), 105 (86), 68 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.29 (m, 5H, C_6H_5), 5.72 (t, *J* = 7.2 Hz, 1H, H-C_2), 4.75 (dd, *J* = 3.4, 9.4 Hz, 1H, H-C_5), 4.09 (dd, *J* = 11.7, 7.2 Hz, 1H, H-C_1), 3.86 (dd, *J* = 11.7, 7.2 Hz, 1H, H-C_1), 2.74 (dd, *J* = 13.4, 9.4 Hz, 1H, H-C_4), 2.22 (dd, *J* = 13.4, 3.4 Hz, 1H, H-C_4), 1.81 (s, 3H, CH_3-C_3).

*(1*RS*,3*SR*)-3-Methyl-1-phenyl-pentane-1,5-diol (*anti-**11**)*

2.33 g (12%), mp 76°C. GC–MS (t_R = 20.89 min) *m*/*z*: 194 (M^+) (9), 176 (15), 107 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.33 (m, 5H, C_6H_5), 4.79 (m, 1H, H-C_1), 3.69 (m, 2H, CH_2OH), 1.87 (m, 2H), 1.55 (m, 2H), 1.42 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H, CH_3-C_3). Anal. calcd. for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 73.93, H 9.15.

Procedure B

A solution of lactone **7** (18.8 g, 0.10 mol), in 30 mL THF was added dropwise into a suspension of $LiAlH_4$ (7.60 g, 0.20 mol), in 250 mL THF. The reaction mixture was stirred at r.t. for 12 h, then MeOH was added to consume the excess $LiAlH_4$. The reaction mixture was poured into ice, extracted with Et_2O, dried (Na_2SO_4), and chromatographed (from hexane–EtOAc (95:5) to hexane:EtOAc (1:1)). The following products, in order of progressive elution, were isolated: *cis*-**16** (8.64 g, 45%), (*Z*)-**8** (1.15 g, 6%), *anti*-**11** (3.49 g, 18%).

cis-**16** (8.50 g, 0.045 mol) was treated with $NaBH_4$ (2.56 g, 0.067 mol) in 50 mL CH_2Cl_2–MeOH (2:1) solution, to afford, after the usual work-up, *anti*-**11** (7.59 g, 87%).

$LiAlH_4$ reduction of hydroxy ester 6

Procedure A

The reduction of **6** (22.0 g, 0.10 mol), followed by treatment with EtOAc, gave the following mixture of products (GC–MS identification only): *cis*-**16** (25%, t_R = 19.35 min), *trans*-**16** (20%, t_R = 19.59 min), *syn*-**11** (14%, t_R = 20.80 min), *anti*-**11** (10%, t_R = 20.89 min), (*Z*)-**8** (6%, t_R = 21.03 min), (*E*)-**8** (12.5%, t_R = 21.19 min), unidentified products 12%, 23.72–24.12 min.

Procedure B

The reduction of **6** (22.0 g, 0.10 mol), followed by treatment with MeOH, gave a residue which was chromatographed, to give (after column chromatography) a 1:1 mixture of *cis*- and *trans*-**16** (2.96 g, 15%), a 9:1 mixture of (*E*)- and (*Z*)-**8** (1.82 g, 9%), and a 2:1 mixture of *syn*- and *anti*-**11** (12.4 g, 64%).

*(2*RS,*4*RS,*6*SR*)-4-Methyl-6-phenyl-tetrahydro-2*H*-pyran-2-ol and (2*RS,*4*SR,*6*RS*)-4-methyl-6-phenyl-tetrahydro-2*H*-pyran-2-ol (*trans-***16***, mixture of two epimers)*

The 1:1 mixture of *cis*- and *trans*-**16** (2.96 g) was chromatographed (hexane–EtOAc, 9:1), to give, after crystallization from ether, *trans*-**16** (1.03 g), mp 72°C. GC–MS (t_R = 19.57 min (single peak)) *m*/*z*: 192 (M^+) (3.3), 174 (42), 159 (83), 104 (100). ^1H NMR ($CDCl_3$, ppm): 7.35 (m, $2C_6H_5$), 5.15 (m), 5.07 (dd, *J* = 9.1, 3 Hz, 1H), 4.74 (dd, *J* = 11.7, 2.3 Hz), 2.27 (m), 2.11–1.29 (m), 1.17 (d, *J* = 6.9 Hz, $2CH_3$). Anal. calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 75.26, H 8.11.

A sample of *trans*-**16** was treated with MeOH–HCl, to afford the mixture of the corresponding *O*-methyl glycosides *trans*-**18a** and *trans*-**18b** (2:1 mixture of the two epimers at C-2). GC–MS major epimer (t_R = 17.88 min) *m*/*z*: 174 ($M^+ - 32$) (23), 146 (25), 104 (100), 58 (85); minor epimer (t_R = 18.53 min) *m*/*z*: 174 ($M^+ - 32$) (4), 146 (21), 104 (100), 58 (50). ^1H NMR ($CDCl_3$, ppm): 7.35 (m, $2C_6H_5$), 4.96 (dd, *J* = 3.9, 9.3 Hz), 4.78 (t, *J* = 3.9 Hz), 4.71 (m), 3.50 (s, OCH_3 of the minor epimer), 3.39 (s, OCH_3 of the major epimer), 2.31 (m), 2.06–1.43 (m), 1.22 (d, *J* = 6.9 Hz, CH_3 of the major epimer), 1.21 (d, *J* = 6.7 Hz, CH_3 of the minor epimer).

*(*E*)-3-Methyl-5-phenyl-2-pentene-1,5-diol ((*E*)-8)*

Yield 1.82 g (9)%.

*(1*RS,*3*RS*)-3-Methyl-1-phenyl-pentane-1,5-diol (*syn-**11**)*

12.4 g (64%), de = 33%. The de was increased by column chromatography (hexane–EtOAc, 8:2), with *syn*-**11** eluting first. *syn*-**11** with de = 83% was obtained (8.71 g, 70%). GC–MS (t_R = 20.80 min) *m*/*z*: 194 (M^+) (7), 176 (9), 107 (100). ^1H NMR ($CDCl_3$, ppm): 7.29 (m, 5H, C_6H_5), 4.81 (t, *J* = 5.4 Hz, 1H, H-C_1), 3.66 (m, 2H, CH_2OH), 1.70 (m, 4H), 1.39 (m, 1H), 0.96 (d, *J* = 6.1 Hz, 3H, CH_3-C_3). Anal. calcd. for $C_{12}H_{18}O_2$: C 74.19, H 9.34; found: C 73.89, H 9.10.

Yeast reduction

A suspension of bakers' yeast (0.5 kg) and D-glucose (0.4 kg) in tap water (1.5 L) was stirred for 30 min at 32°C. A solution of the suitable substrate (0.03 mol) in ethanol (20 mL) was then added. After 48 h at r.t., Celite (200 g) was added, and the reaction mixture filtered, washing the Celite pad with ethyl acetate. The filtrate was adjusted to pH 4 with 2 N HCl, and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on a silica gel column. The following derivatives were obtained upon BY reduction.

*(1*S,*3*S*)-3-Methyl-1-phenyl-pentane-1,5-diol ((1*S,*3*S*)-syn-**11**)*

2.99 g (44%) (from (*E*)-**3** (6.60 g, 0.035 mol)), ee > 99% (chiral HPLC), de = 60% (GC–MS). The sample contained 20% of (1*R*,3*S*)-*anti*-**11** (ee > 99%, chiral HPLC). ^1H NMR and GC–MS spectra were in agreement with those of (±)-*syn*-**11**.

*(4*S,*6*S*)-4-Methyl-6-phenyl-tetrahydropyran-2-one (**13**) (23)*

4.27 g (31%) (from **4**). $[\alpha]_D^{20}$ –12.1 (*c* = 1.26, $CHCl_3$). GC–MS (t_R = 21.65 min) *m*/*z*: 190 (M^+) (28), 104 (100), 56 (95). ^1H NMR ($CDCl_3$, ppm): 7.37 (m, 5H, C_6H_5), 5.31 (dd, *J* = 3.7, 12.0 Hz, 1H, H-C_6), 2.81 (m, 1H), 2.30–2.10 (m, 3H), 1.53 (m, 1H), 1.08 (d, *J* = 6.0 Hz, 3H, CH_3-C_4). This derivative (4.20 g, 0.022 mol) was reduced with $LiAlH_4$ (0.841 g, 0.044 mol) in 50 mL THF, to afford, after the usual work-up, (1*S*,3*R*)-*anti*-**11** (3.03 g, 71%), ee = 99% (chiral HPLC), de = 99% (GC–MS). $[\alpha]_D^{20}$ –60.2 (*c* = 1.05, $CHCl_3$). ^1H NMR and GC–MS spectra were in agreement with those of (±)-*anti*-**11**.

*(*R*)-3-Methyl-5-phenyl-pentan-1-ol ((*R*)-**15**)*

2.99 g (29%) (from (*E*)-**14** (de = 33%, 10.1 g, 0.058 mol)), ee = 82% (chiral HPLC). $[\alpha]_D^{20}$ +11.2 (*c* = 11.4, $CHCl_3$) (lit. (19) $[\alpha]_D^{20}$ –2 (neat) for the (*S*)-isomer). GC–MS (t_R = 16.60 min) *m*/*z*: 178 (M^+) (30), 160 (35), 104 (91%), 91 (100). ^1H NMR ($CDCl_3$, ppm): 7.21 (m, 5H, C_6H_5), 3.68 (m, 2H, CH_2OH), 2.61 (m, 2H, CH_2Ph), 1.62 (m, 3H), 1.49 (m, 2H), 0.98 (d, *J* = 6.0 Hz, 3H, CH_3-C_3).

(1*RS,*3*SR*)-Acetic acid 5-acetoxy-3-methyl-1-phenyl-pentyl ester (*anti-**19**)

Diol *anti*-**11** (11.4 g, 0.056 mol) was treated with 6 mL Ac_2O and 6 mL pyridine, to afford, after the usual work-up, diacetate *anti*-**19** (14.5 g, 92%). GC–MS (t_R = 22.92 min) *m*/*z*: 278 (M^+) (1), 235 (31), 175 (92), 143 (75), 107 (100). ^1H NMR ($CDCl_3$, ppm): 7.30 (m, 5H, C_6H_5), 5.85 (dd, *J* = 4.6, 9.2 Hz, 1H, H-C_1), 4.10 (m, 2H, CH_2OAc), 2.06 (s, 3H, CH_3COO), 2.03 (s, 3H, CH_3COO), 1.98 (m, 1H), 1.81–1.44 (m, 4H), 0.97 (d, *J* = 6.2 Hz, 3H, CH_3-C_3). Anal. calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 69.27, H 7.81.

(1*RS,*3*RS*)-Acetic acid 5-acetoxy-3-methyl-1-phenyl-pentyl ester (*syn-**19**)

Diol *syn*-**11** (8.60 g, 0.044 mol) was treated with 5 mL Ac_2O and 5 mL pyridine, to afford, after the usual work-up, diacetate *syn*-**19** (11.1 g, 90%). GC–MS (t_R = 22.83 min) *m*/*z*: 235 ($M^+ - 43$) (33), 175 (94), 143 (73), 107 (100). ^1H NMR ($CDCl_3$, ppm): 7.30 (m, 5H, C_6H_5), 5.82 (t, *J* = 7.3 Hz, 1H, H-C_1), 4.06 (m, 2H, CH_2OAc), 2.05 (s, 3H, CH_3COO), 1.99

(s, 3H, CH_3COO), 1.86–1.38 (m, 5H), 0.98 (d, J = 6.2 Hz, 3H, CH_3-C_3). Anal. calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.85, H 8.21.

General procedure of lipase-mediated kinetic resolution

A solution of the suitable diacetate (10.0 g, 0.036 mol) in 2 mL THF was added to a suspension of lipase PS (5 g) in 100 mL water at pH 7.8 at room temperature. The pH was kept constant by means of a pH-Stat. The reaction was monitored by chiral HPLC. When the mono alcohol mono acetate formed upon saponification reached ee ~ 50%, the reaction was stopped. The mixture was filtered, extracted with EtOAc, and chromatographed (hexane–EtOAc, 9:1). The mono alcohol mono acetate was acetylated with Ac_2O and pyridine, and submitted again to enzymic saponification to enhance ee.

*(1*R,*3*S*)-Acetic acid 5-hydroxy-3-methyl-1-phenyl-pentyl ester ((1*R,*3*S*)*-anti-***20***) (from (±)-*anti-***19***)*

1.53 g (18%), ee = 95% (chiral HPLC), de > 99% (GC–MS). $[\alpha]_D^{20}$ +67 (c = 1.4, $CHCl_3$). GC–MS (t_R = 21.73 min) m/z: 193 (M^+ – 43) (67), 175 (11), 107 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.30 (m, 5H, C_6H_5), 5.86 (dd, J = 4.9, 9.4 Hz, 1H, H-C_1), 3.68 (m, 2H, CH_2OH), 2.04 (s + m, 4H, 1H + CH_3COO), 1.78–1.36 (m, 4H), 0.96 (d, J = 6.4 Hz, 3H, CH_3-C_3). Anal. calcd. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 71.33, H 8.32.

*(1*S,*3*S*)-Acetic acid 5-hydroxy-3-methyl-1-phenyl-pentyl ester ((1*S,*3*S*)*-syn-***20***) (from (±)-syn-***19***)*

1.36 g (16%), ee = 72% (chiral HPLC), de = 70% (GC–MS). $[\alpha]_D^{20}$ –19.2 (c = 0.92, $CHCl_3$). GC–MS (t_R = 21.65 min) m/z: 193 (M^+ – 43) (73), 175 (89), 107 (100). ^{1}H NMR ($CDCl_3$, ppm): 7.32 (m, 5H, C_6H_5), 5.86 (dd, J = 6.8, 7.9 Hz, 1H, H-C_1), 3.64 (m, 2H, CH_2OH), 2.05 (s, 3H, CH_3COO), 1.85–1.30 (m, 5H), 0.97 (d, J = 6.5 Hz, 3H, CH_3-C_3). Anal. calcd. for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found: C 70.91, H 8.37.

The diacetate (recovered unreacted) was submitted again to enzymic saponification to increase ee.

*(1*S,*3*R*)-Acetic acid 5-acetoxy-3-methyl-1-phenyl-pentyl ester ((1*S,*3*R*)*-anti-***19***) (from (±)-anti-***19***)*

2.30 g (23%), ee = 86% (chiral HPLC), de > 99% (GC–MS). $[\alpha]_D^{20}$ – 45 (c = 1.18, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of (±)-*anti*-**19**.

*(1*R,*3*R*)-Acetic acid 5-acetoxy-3-methyl-1-phenyl-pentyl ester ((1*R,*3*R*)*-syn-***19***) (from (±)-syn-***19***)*

2.38 g (28%), ee = 50%, de = 79%. $[\alpha]_D^{20}$ +13.5 (c = 1.51, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of (±)-*syn*-**19**.

(1*R,*3*S*)-3-Methyl-1-phenyl-pentane-1,5-diol ((1*R,*3*S*)*-anti-*11)

Mono alcohol mono acetate (1*R*,3*S*)-*anti*-**20** (1.50 g, 6.36 mmol) was hydrolysed with KOH (0.533 g, 9.54 mmol) in 10 mL MeOH, to afford diol (1*R*,3*S*)-*anti*-**11** (1.16 g, 94%), ee = 95% (chiral HPLC), de > 99% (GC–MS). $[\alpha]_D^{20}$ +54.8 (c = 0.5, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of (±)-*anti*-**11**.

(1*S,*3*R*)-3-Methyl-1-phenyl-pentane-1,5-diol ((1*S,*3*R*)*-anti-*11)

Diacetate (1*S*,3*R*)-*anti*-**19** (2.20 g, 7.91 mmol) was hydrolysed with KOH (0.644 g, 0.012 mol) in 10 mL MeOH, to afford diol (1*S*,3*R*)-*anti*-**11** (1.39 g, 91%), ee = 86% (chiral HPLC), de > 99% (GC–MS). $[\alpha]_D^{20}$ –53.4 (c = 0.55, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of (±)-*anti*-**11**.

(1*S,*3*S*)-3-Methyl-1-phenyl-pentane-1,5-diol ((1*S,*3*S*)*-syn-*11)

Mono alcohol mono acetate (1*S*,3*S*)-*syn*-**20** (1.30 g, 5.51 mmol) was hydrolysed with KOH (0.464 g, 8.26 mmol) in 10 mL MeOH, to afford diol (1*S*,3*S*)-*syn*-**11** (1.01 g, 95%), ee = 70% (chiral HPLC), de = 72% (GC–MS). $[\alpha]_D^{20}$ –15.5 (c = 1.05, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of ((±)-*syn*-**11**.

(1*R,*3*R*)-3-Methyl-1-phenyl-pentane-1,5-diol ((1*R,*3*R*)*-syn-*11)

Diacetate (1*R*,3*R*)-*syn*-**19** (2.30 g, 8.27 mmol) was hydrolysed with KOH (0.694 g, 0.012 mol) in 10 mL MeOH, to afford diol (1*R*,3*R*)-*syn*-**11** (1.41 g, 88%), ee = 50% (chiral HPLC), de = 77% (GC–MS). $[\alpha]_D^{20}$ +11.05 (c = 1.05, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of (±)-*syn*-**11**.

General procedure for the preparation of Doremox®

p-Toluene-sulfonyl chloride (1.47 g, 7.73 mmol) was added to a solution of the suitable diol (1.00 g, 5.15 mmol), in 10 mL CH_2Cl_2 and 2 mL pyridine at 0°C. The reaction mixture was stirred at room temperature for 3 h, then poured into water and extracted with CH_2Cl_2. The residue, obtained upon concentration, was dissolved in 10 mL MeOH, and treated with MeONa in MeOH (1 M, 8 mL). The reaction mixture was stirred at r.t. for 2 h, poured into water, and extracted with EtOAc. The organic phase was dried (Na_2SO_4), concentrated, and chromatographed (hexane–EtOAc, 95:5), to afford *cis* or *trans*-**2**.

*(2*R,*4*S*)-*cis-***2** *(from (1*R,*3*S*)-*anti-***11** *(1.1 g, 5.67 mmol))*

0.668 g (67%), ee = 92%, de > 99% (chiral GC). $[\alpha]_D^{20}$ +52 (c = 0.27, $CHCl_3$). GC–MS (t_R = 15.59 min) m/z: 176 (M^+) (100), 175 (90), 105 (73). ^{1}H NMR ($CDCl_3$, ppm): 7.31 (m, 5H, C_6H_5), 4.31 (dd, J = 1.9, 11.2 Hz, 1H, H-C_2), 4.15 (ddd, J = 1.5, 4.2, 11.2, 1H, C-H_6), 3.60 (m, 1H, H-C_6), 1.82 (m, 2H), 1.58 (m, 1H), 1.26 (m, 2H), 0.98 (d, J = 6.2 Hz, 3H, CH_3-C_4).

*(2S,4R)-cis-***2** *(from (1S,3R)-anti-***11** *(1.30 g, 6.70 mmol))*

0.778 g (66%), ee = 80%, de > 99% (chiral GC). $[\alpha]_D^{20}$ – 42 (c = 1.2, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of (+)-*cis*-**2**.

*(2*S,*4*S*)-*trans-***2** *(from (1*S,*3*S*)-*syn-***11** *(0.981 g, 5.05 mmol))*

0.577 g (65%), ee = 72%, de = 70% (chiral GC). $[\alpha]_D^{20}$ +14.6 (c = 0.3, $CHCl_3$); this sample contained 13% of (+)-*cis*-**2** and 2% of (–)-*cis*-**2**. GC–MS (t_R = 16.05 min) m/z: 176 (M^+) (100), 175 (89), 105 (80). ^{1}H NMR ($CDCl_3$, ppm): 7.31 (m, 5H, C_6H_5), 4.67 (dd, J = 3.1, 9.6 Hz, 1H, H-C_2), 3.83 (m, 2H, CH_2-O), 2.10 (m, 1H), 1.92 (m, 2H), 1.61 (m, 1H), 1.34 (m, 1H), 1.17 (d, J = 7.1 Hz, 3H, CH_3-C_4).

*(2*R*,4*R*)*-trans-***2** *(from (1*R*,3*R*)*-syn-***11** *(1.30 g, 6.70 mmol))*

0.743 g (63%), ee = 50%, de = 77% (chiral GC). $[\alpha]_D^{20}$ –9.8 (*c* = 1.15, $CHCl_3$); this sample contained 9.5% of (–)-*cis*-**2** and 2% of (+)-*cis*-**2**. ^{1}H NMR and GC–MS spectra were in agreement with those of (+)-*trans*-**2**.

*(2*S*,4*R*)*-cis-***2** *(from (1*S*,3*R*)*-anti-***11** *(1.50 g, 7.73 mmol, obtained by reduction of (4*S*,6*S*)-***13***))*

0.925 g (68%), ee = 98%, de > 99% (chiral GC). $[\alpha]_D^{20}$ –54.1 (*c* = 1.05, $CHCl_3$). ^{1}H NMR and GC–MS spectra were in agreement with those of (+)-*cis*-**2**.

*(2*S*,4*S*)*-trans-***2** *(from (1*S*,3*S*)*-syn-***11** *(obtained by BY reduction of (*E*)-***3***))*

ee = 99%, de = 72% (chiral GC). $[\alpha]_D^{20}$ +18.1 (*c* = 0.75, $CHCl_3$); this sample contained 14% of (+)-*cis*-**2** with ee > 99%. ^{1}H NMR and GC–MS spectra were in agreement with those of (+)-*trans*-**2**.

Configurational assignment

Two samples of (–)-*anti*-**11** (ee = 86%, de > 99%) and (+)-*syn*-**11** (ee = 50%, de = 79%) were oxidized with Jones' reagent in acetone. The corresponding keto acids were treated with diazomethane in Et_2O, and the corresponding methyl ester derivatives were purified by column chromatography (hexane). The following samples of keto ester **10** were obtained: (*i*) (–)-**10** (from (–)-*anti*-**11**): chemical purity (GC–MS) = 98%. $[\alpha]_D^{20}$ –5.02 (*c* = 0.85, benzene) lit. value (21*a*) $[\alpha]_D^{20}$ –5.65 (*c* = 1.24, benzene) for (*S*)-isomer ee = 90%; lit. value (21*b*) $[\alpha]_D^{20}$ +9.25 (neat) for (*R*)-isomer ee > 96%; (*ii*) (–)-**10** (from (+)-*syn*-**11**): chemical purity (GC–MS) = 97%. $[\alpha]_D^{20}$ –3.21 (*c* = 0.73, benzene).

Conclusion

The preparation of the four stereoisomers of Doremox® in enantiomerically enriched form was accomplished. BY reduction of suitable precursors **3** and **4** resulted in enantiospecific and highly diastereoselective compounds. Diol precursors of (–)-*cis*-**2** (ee > 99%, de = 98%) or of (+)-*trans*-**2** (ee > 99%, de = 72%) were obtained when a carbonyl or a carbon–carbon double bond was reduced by yeast, under the influence of a preexisting stereocentre in position β. Thus, an interesting, unpredictable stereochemical feature of BY reduction was highlighted.

Lipase PS-mediated kinetic resolution of diol *anti*-**11** and *syn*-**11** was less efficient, but it allowed us to obtain both the enantiomers of the *cis* and *trans* series. The high reactivity of primary acetate groups towards saponification prevented the accomplishment of higher enantiomeric excesses. However, the enzymic reaction of diacetate derivatives enriched in the most reactive enantiomer allowed us to reach quite satisfactory enantiomeric excesses. Biocatalyzed reactions are once again the most effective in the optical activation of such scarcely functionalised substrates as diols *anti*-**11** and *syn*-**11**.

The whole work put into evidence the supremacy of yeast reduction with respect to lipase-mediated hydrolysis. Once the substrate has been accepted by yeast, the whole-cell reductive system always assures enantiospecific transformations, which greatly compensate for the troublesome workup. Lipases are of much wider application, showing less demanding requisites on the substrate acceptance, but their stereochemical course is sometimes less satisfactory, and strongly dependent on structural factors.

The unusual behaviour of hydroxy ester **6** and lactone **7** under hydride reduction was fully described. Lactols were isolated, as well as products of a diastereoselective addition of some intermediates on EtOAc, followed by reduction.

Olfactory evaluation of optically enriched Doremox samples clearly showed that (2*S*,4*R*)-*cis*-**2** is the nicest and the most powerful isomer of the series. This stereoisomer, incidentally, has the same absolute configuration of the most appreciated of rose oxide isomers (22) (i.e., (2*S*,4*R*)-*cis*-**1**).

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