Lipase-mediated synthesis of the enantiomeric forms of 4,5-epoxy-4,5-dihydro-α-ionone and 5,6-epoxy-5,6-dihydro-β-ionone. A new direct access to enantiopure (*R*)- and (*S*)-α-ionone

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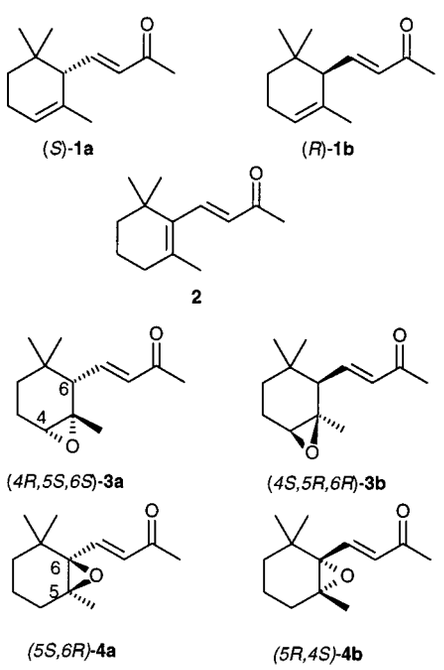
Stereoselective lipase-mediated esterifications of epoxy-α-ionol **5** and epoxy-β-ionol **9** afforded suitable precursors of the enantiomers of the corresponding oxidised derivatives epoxy-α-ionone **3** and epoxy-β-ionone **4**. An interesting development of this work is the easy conversion of enantiopure **3a** and **3b** into highly valuable enantiopure (*S*)- and (*R*)-ionone (**1a** and **1b**) *via* a mild deoxygenation reaction.

Amongst the naturally occurring and synthetic polyoxygenated compounds possessing the C_{13} ionone skeleton reported in recent years,[1] epoxy ionones **3** and **4**, directly accessible from α- and β-ionone **1** and **2**, respectively, upon peracid treatment,[2]



are particularly important. Whereas epoxy-β-ionone **4** has been identified as a flavour component in many foods, including, among others, carrots[3] and black tea,[4] epoxy-α-ionone **3** was used as a starting material for one of the first syntheses of γ-ionone.[5] Subsequently, enantiomerically pure **3a** and **3b** were used by Eugster *et al.* as starting materials in the synthesis of a variety of naturally occurring hydroxylated derivatives of **1** and **2** and of oxidised carotenoids such as isozeaxanthine and diepoxy-β,β-carotene.[6–11] The enantiomers of **3** needed for this synthesis were prepared by peracid treatment of (*S*)- and (*R*)-α-ionone **1**.[12] Enantiomerically pure (−)-**4b** was obtained from (−)-**3a** in a lengthy five step sequence.[8] The aforementioned methods to enantiomerically pure **3a**,**b** and **4b** suffered from the major drawback of the twenty crystallisations of the (−)-menthyl hydrazone needed to obtain optically pure (*R*)-α-ionone, and the ten crystallisations to prepare the (*S*)-enantiomer.[13] Since the work of Eugster, apparently no improvements in the methods of synthesis of enantiomerically pure **3** and **4** have been reported, apart from the preparation of enantiomerically enriched (+)-**4a** and (−)-**4b** through a solid state kinetic resolution of the racemic material,[14] and the preparation of the precursors of (*R*)- and (*S*)-α-ionone from the enantiomers of α-damascone.[15]

Recently, we described a new access to the enantiomeric forms of α-ionone based on the preparation of the enantiopure diastereoisomers of α-ionol *via* lipase-mediated selective acylation of the racemic mixture, followed by MnO_2 oxidation.[16] The relative simplicity of this procedure prompted us to study an extension of this method to the preparation of enantiomerically pure **3a**,**b** and **4a**,**b** starting from the racemic materials. We report herein on the stereoselective enzyme-mediated esterification of *cis*-epoxy-α-ionol **5** and epoxy-β-ionol **9**, affording suitable precursors of the enantiomers of the corresponding oxidised derivatives **3** and **4**. A further development of this work is the easy conversion of **3a** and **3b** into highly valuable enantiopure (*S*)- and (*R*)-ionone (**1a** and **1b**) *via* a mild deoxygenation reaction.[17]

Results and discussion

4,5-Epoxy-4,5-dihydro-α-ionone

It was known in the literature[11] that peracid epoxidation of α-ionone afforded predominantly the *cis*-epoxide. Both ^{1}H NMR and GC data showed that the mixture we obtained upon *m*-chloroperbenzoic acid treatment of α-ionone at 0 °C contained racemic *cis*-epoxy-α-ionone and racemic *trans*-epoxy-α-ionone in a 5 : 1 ratio.

Preliminary studies of lipase-mediated acetylation in *tert*-butyl methyl ether in the presence of vinyl acetate as an acyl donor were performed on the 1 : 1 mixture of the two racemic diastereoisomers of *cis*-4,5-epoxy-α-ionol **5a**,**c** and **5b**,**d** obtained upon reduction of the epoxidation mixture with sodium borohydride. The *trans*-stereoisomers made up an estimated 17% of the total content, on the basis of the ^{1}H NMR spectra (δ_H 3.07 C(4)H_{cis}, 2.98 C(4)H_{trans}). The enzyme-catalysed experiments were followed by means of chiral GC analysis, as under suitable conditions the acetate derivatives **6a**–**d** of the four stereoisomers **5a**–**d** gave rise to four baseline-separated peaks on a permethylated β-cyclodextrin column. In order to

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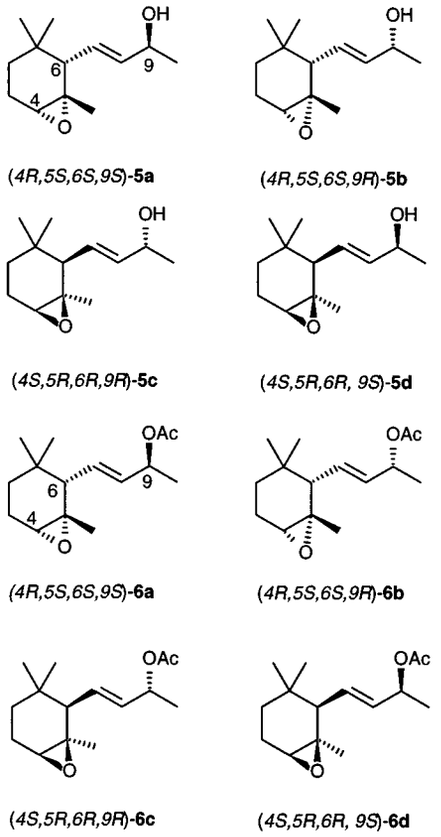


assign the correct stereochemistry to **6a**–**d** a sample of optically pure (*S*)-α-ionone **1a**[16] was treated with *m*-chloroperbenzoic acid, reduced with sodium borohydride, and acetylated in acetic anhydride and pyridine: the first two peaks of the chiral GC chromatogram were thus found to be the two *cis*-stereoisomers having the (*S*)-configuration at C6. We then assumed that the two diastereoisomers preferentially acetylated by the lipase (second and third peak) had the (*R*)-configuration at C9, as we had already verified this by means of chemical correlation for the enzyme-mediated esterification of α-ionol in some previous work.[16] As we shall see later on in this work, this assumption was subsequently confirmed at the end of the synthetic sequence.

The results of the bio-catalysed esterifications of **5a**–**d** are reported in Table 1. PPL mediated acetylation afforded enantiomerically enriched acetate derivatives **6b** (second GC peak, ee 86%) and **6c** (third GC peak, ee 79%) in a 1.6:1 ratio, the overall content of the *trans* stereoisomers of the starting material being maintained. Lower enantiomeric excesses were shown by the same two diastereoisomers produced in CCL-catalysed reactions, with a slight preference for diastereoisomer **6c**. The use of Lipase PS (from *Pseudomonas cepacia*) as a catalyst assured enantiospecific acetylation of substrates **5b** and **5c**, with very low diastereoselectivity. These results clearly showed that an efficient method for the separation of the two diastereoisomers of epoxy α-ionol **5a**,**c** and **5b**,**d** was to be found, in order to prepare suitable precursors of enantiopure *cis*-epoxy-α-ionone taking advantage of the enantiospecificity shown by Lipase PS.

Fortunately, the two racemic diastereoisomers of *cis*-epoxy-α-ionol could be separated by column chromatography and submitted to Lipase PS-mediated esterification separately (Scheme 1 and Table 2).

The first eluted racemic stereoisomer **5a**,**c** (first and third peak in the GC analysis of the corresponding acetate derivatives) was found to contain 6% of racemic *trans*-epoxy-α-ionol (de[18] = 88%, GC and ^{1}H NMR). Enzyme-mediated acetylation gave enantiopure (GC) acetate derivative **6c** {third peak, GC; de = 84%, GC and ^{1}H NMR; $[a]_D^{20}$ = 179 (*c* 1.00, $CHCl_3$)}, and

Table 1 Results of enzyme-mediated acetylation of (i) 4,5-epoxy-4,5-dihydro-α-ionol **5** (5:1 mixture of racemic *cis*- and racemic *trans*-epoxides), (ii) racemic 5,6-epoxy-5,6-dihydro-β-ionol **9**, (iii) α-ionol (1:1 mixture of two racemic diastereoisomers)[16].

(i) Epoxy-α-ionol **5**

		Products		
Enzyme	*cis*:*trans* (GC)	**6b**:**6c** (GC)	**6b** ee (%) (GC)	**6c** ee (%) (GC)
PPL	4.4:1	1.6:1	86	79
CCL	3.4:1	1 :1.8	64	78
Lipase PS	4.4:1	1 :1.4	99	99

(ii) Epoxy-β-ionol **9**

Enzyme	**10c**:**10d** (GC)	**10c** ee (%) (GC)	**10d** ee (%) (GC)
PPL	1:3.7	99	99
CCL	1:1	99	99
Lipase PS	1:2.3	99	99

(iii) α-Ionol

Enzyme	(6*S*,9*R*):(6*R*,9*R*) (GC)	(6*S*,9*R*) ee (%) (GC)	(6*R*,9*R*) ee (%) (GC)
PPL	3:1	90	64
CCL	1:1.15	72	79
Lipase PS	1:1	99	99

Table 2 Results of Lipase PS mediated acetylations of the two separate diastereoisomers **5a**,**c** and **5b**,**d**

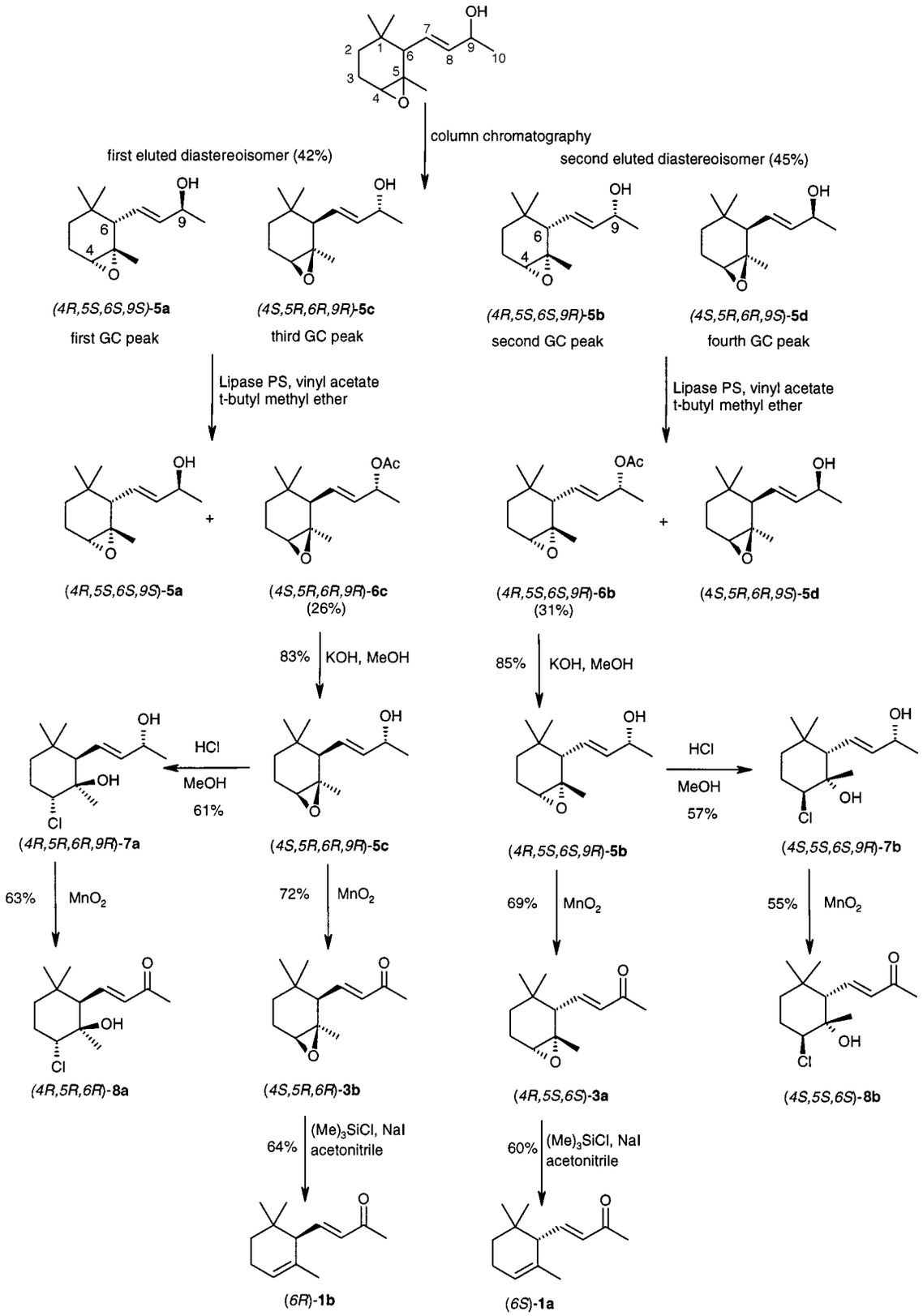
Substrate	Recovered alcohol: ee (%), de (%)[a]	Acetylated product: ee (%), de (%)[a]	E[b,c] (%)
5a,**c**	**5a**: 47, 84	**6c**: 99, 84	316, 32
5b,**d**	**5d**: 91, 65	**6b**: 99, 67	635, 48

[a] Ees and des were measured by GC. [b] Enantiomeric ratio. [c] Conversion.

unreacted alcohol **5a**, having ee = 47% (GC) and de = 84% (GC) (E = 316, c = 32).[19] Saponification of substrate **6c** with methanolic potassium hydroxide afforded enantiopure derivative **5c** {de = 84%, ^{1}H NMR; $[a]_D^{20}$ = 141 (*c* 0.49, $CHCl_3$)}, which was oxidised with MnO_2 to give (+)-4,5-epoxy-α-ionone **3b** {ee > 99%, GC; de = 64%, GC and ^{1}H NMR; $[a]_D^{20}$ = 141 (*c* 1.3, EtOH); lit.,[11] $[a]_D^{20}$ = 210 (*c* 1, EtOH)}, thus confirming the assumption of the (*R*)-configuration at C9 made at the beginning of the work. (+)-4,5-Epoxy-α-ionone **3b** was brought to diastereoisomeric purity {$[a]_D^{20}$ = 207 (*c* 1.2, EtOH)} by means of a careful chromatographic purification on a silica gel column.

Treatment of enantiopure **5c** (de = 84%) with a saturated solution of HCl in methanol[20] (Scheme 1) allowed us to isolate for the first time an enantiomerically pure sample of chlorohydrin derivative **7a** (de = 98%, ^{1}H NMR) showing $[a]_D^{20}$ = −30, (*c* 0.51, $CHCl_3$), which was soon converted into the corresponding oxidised product **8a** {ee > 99%, GC; de > 99%, GC; $[a]_D^{20}$ = −23 (*c* 0.66, $CHCl_3$)}. To the best of our knowledge, no previous resolution of racemic chlorohydrin **8** has ever been reported in the literature.

A useful development of the work was then the conversion of the optically active dextrorotatory isomer of *cis*-epoxy-α-ionone ($[a]_D^{20}$ = 141) into (*R*)-α-ionone by means of reaction with trimethylchlorosilane and sodium iodide in acetonitrile[17] (Scheme 1). The sample of (*R*)-**1b** was found to be enantiomerically pure by chiral GC analysis, thus showing that the



Scheme 1

trans-epoxide by-product lowering the diastereoisomeric purity of **3b** had the same configuration at C6.

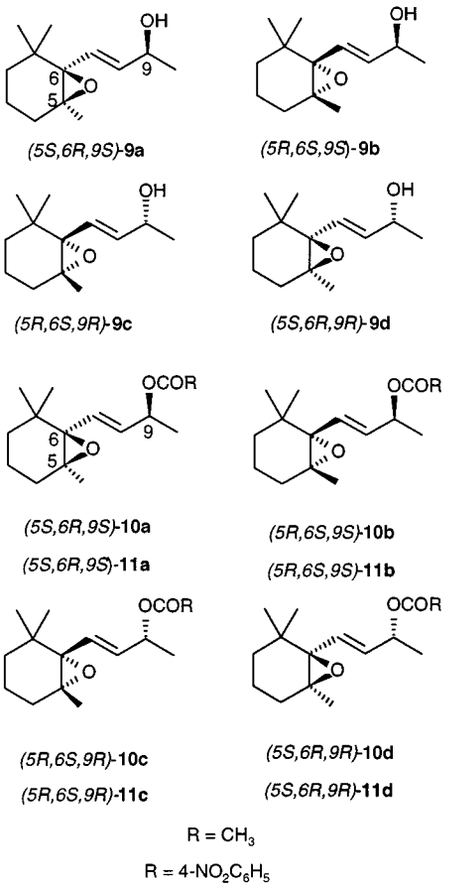
The second eluted diastereoisomer **5b**,**d** (second and fourth peaks in the GC analysis of the corresponding acetate derivatives) was found to contain the corresponding *trans*-epoxide stereoisomer (de = 66%, GC and ^{1}H NMR). Lipase PS-mediated acetylation of **5b**,**d** allowed us to obtain enantiopure acetate derivative **6b** (second peak, GC) showing de = 67% (GC and ^{1}H NMR) and $[\alpha]_D^{20} = -56$ (*c* 1.04, $CHCl_3$), and enantiomerically enriched alcohol **5d** (ee = 91%, GC, de = 65%, GC; E = 635, c = 48). Treatment of substrate **6b** with potassium hydroxide in methanol afforded *cis*-epoxy-α-ionol **5b** {ee > 99%, GC; de = 88%, ^{1}H NMR; $[\alpha]_D^{20} = -142$ (*c* 0.57, $CHCl_3$)}, which was converted into enantiopure **3a** (de = 89%, GC and ^{1}H NMR) showing $[\alpha]_D^{20} = -199$ (*c* 0.61, $CHCl_3$) {lit.,[6] $[\alpha]_D^{20} = -210$ (*c* 0.59, $CHCl_3$)}, upon oxidation with MnO_2 in methylene chloride. The oxirane ring of derivative **5b** (ee > 99%, de > 88%) was opened by means of gaseous HCl in methanol to

give enantiopure chlorohydrin **7b** {ee > 99%, GC; de = 98%, ^{1}H NMR; $[\alpha]_D^{20} = 46$ (*c* 0.72, $CHCl_3$)} which was oxidised to **8b** by reaction with MnO_2 in methylene chloride. The other enantiomer of chlorohydrin **8** was thus obtained in enantiopure form {ee > 99%, GC; de > 99%; $[\alpha]_D^{20} = 24$ (*c* 0.52, $CHCl_3$)}.

An enantiopure sample of (*S*)-ionone **1a** was prepared by treatment of laevorotatory **3a** ($[\alpha]_D^{20} = -199$) with trimethylchlorosilane and sodium iodide in acetonitrile, thus showing the efficiency of this resolution procedure for the synthesis of both the enantiomers of the precious fragrance α-ionone.

5,6-Epoxy-5,6-dihydro-β-ionone

For the sake of completeness the same preliminary studies (Table 1) of enzyme-mediated acetylation in *tert*-butyl methyl ether solution, in the presence of vinyl acetate, were performed on the 1 : 1 mixture of the two racemic diastereoisomers of 5,6-epoxy-5,6-dihydro-β-ionol **9a**–**d**, prepared upon reaction of

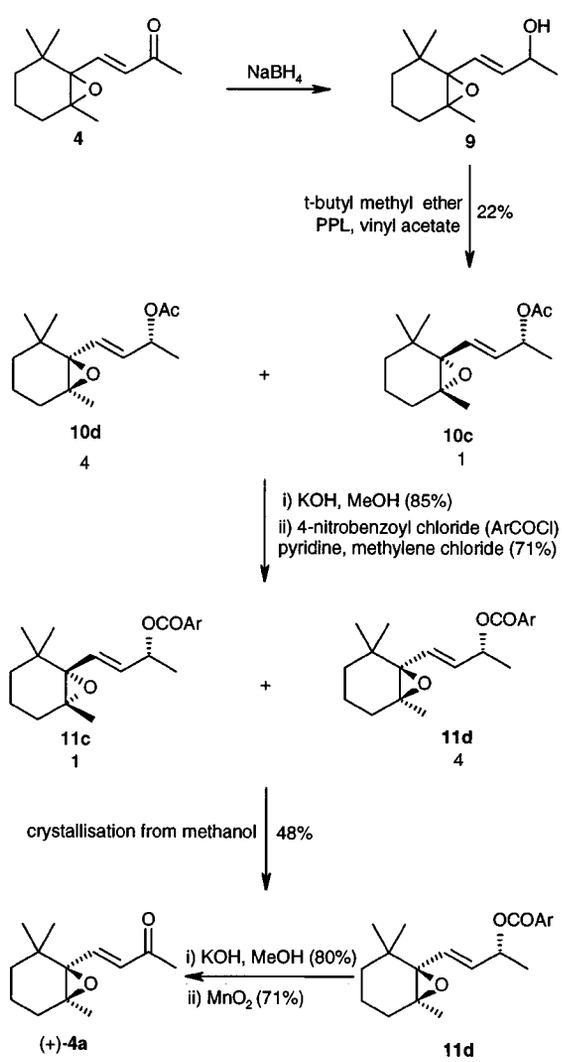


racemic epoxy-β-ionone **4** with sodium borohydride. These enzymic reactions were followed by means of chiral GC analysis, in spite of the fact that it was not possible to find suitable conditions for a complete gas chromatographic separation of the corresponding four acetate derivatives **10a**–**d**: a partial overlapping of the two central peaks was observed. The assignment of the right configuration to the GC peaks was performed on the basis of these considerations: (i) the enantiopure acetate derivative **10d** (fourth GC peak), prepared by enzyme-mediated esterification, afforded at the end of the synthetic sequence (+)-(5*S*,6*R*)-**4a**; (ii) the diastereoisomers preferentially acetylated by lipases (third and fourth GC peaks) were assumed to have the (*R*) configuration at C9; (iii) **9a** and **9c** are the two enantiomers of epoxy-β-ionol (first and third peaks in the GC analysis of the corresponding acetate derivatives) affording the 4-nitrobenzoate derivative which was found to be less soluble in hexane.

PPL-Mediated acetylation afforded enantiomerically pure diastereoisomers **10c** and **10d** in a nearly 1 : 4 ratio (GC and ^{1}H NMR) in 22% yield. Higher conversion and worse diastereoselection were observed in Lipase PS-catalysed acetylation: the acetate derivative was found to be a 2.3 : 1 mixture of enantiopure **10d** and **10c** (45% yield). On the contrary, the use of CCL led to a complete loss of diastereoselectivity, as a 1 : 1 mixture of enantiopure **10c** and **10d** was obtained.

As the diastereoselectivity of these enzymic reactions was poor, the preparation of the enantiomers of epoxy-β-ionone required the complete separation of the two diastereoisomers of epoxy-β-ionol. No separation could be achieved by column chromatography, so we decided to rely upon the fractional crystallisation of some crystalline derivatives. As a matter of fact, in some previous work[16] the crystallisation of 4-nitrobenzoate esters of α-ionol had allowed us to obtain diastereoisomeric enrichment.

Enantiopure acetate derivative **10d**, prepared by PPL-mediated acetylation of **9a**–**d** and containing 20% of diastereoisomer **10b**, was hydrolysed in methanolic potassium hydroxide and transformed into the corresponding 4-nitrobenzoate ester (de = 60%, ^{1}H NMR: $\delta_H = 0.93$ C(1)Me in **11d**, $\delta_H = 0.90$ C(1)-Me in **11b**) (Scheme 2). This latter derivative was brought to



Scheme 2

diastereoisomeric purity (^{1}H NMR) by crystallisation from methanol, converted into the corresponding alcohol derivative **9d** by saponification, and oxidised with MnO_2 to afford a sample of enantiopure dextrorotatory epoxy-β-ionone **4a** {$[\alpha]_D^{20} = 99$ (*c* 0.66, $CHCl_3$); lit.,[21] $[\alpha]_D^{20} = 104$ (*c* 0.70, $CHCl_3$)}.

In order to devise a convenient access to a suitable precursor of laevorotatory epoxy-β-ionone **4b**, the 1 : 1 mixture of the two

racemic diastereoisomers of epoxy-β-ionol **9a–d** was treated with 4-nitrobenzoyl chloride and pyridine in methylene chloride, to give the corresponding ester derivatives **11a–d**. Five crystallisations from hexane afforded racemic diastereoisomer **11a**,**c** (first and third peaks of the GC analysis of the corresponding acetate derivatives) in 19% yield from epoxy-β-ionol. It is very likely that PPL-mediated acetylation of alcohol derivative **9a**,**c**, recovered from 4-nitrobenzoate ester **11a**,**c**, affords enantiopure acetate **10c** as a single diastereoisomer, to be used as a precursor of laevorotatory epoxy-β-ionone **4b**.

Conclusions

The experimental work described in this paper can fulfil two different purposes: the study of the effect of substrate structure on the steric course of lipase-mediated acetylations within a certain class of compounds and the application of these enzymic techniques to the preparation of enantiopure derivatives, showing intrinsic interest or as precursors to relevant chiral products.

The data for the diastereoselectivity and enantioselectivity of lipase-mediated acetylations of epoxy derivatives of α- and β-ionol can be usefully compared with those of α-ionol collected during previous work[16] and repeated in Table 1 for the sake of clarity. The steric course of the biocatalysed acetylation of these substrates clearly appears to be unpredictable; however, some general conclusions can be made.

The three kinds of lipase we employed on α-ionol, epoxy-α-ionol and epoxy-β-ionol always showed a clear preference for the acetylation of (9*R*)-alcohol diastereoisomers. The highest enantiomeric excesses were always obtained using Lipase PS (from *Pseudomonas cepacia*), while PPL generally assured the best diastereoselection. The presence of the oxirane ring at C4 and C5 in epoxy-α-ionol was found to be deleterious to the diastereoselectivity.

However, the combination of physical (column chromatography) or chemical (fractional crystallisation of 4-nitrobenzoate esters) methods for diastereoisomer separation with enantioselective lipase-catalysed acetylation reactions allowed us to obtain enantiopure epoxy derivatives of α- and β-ionone. We thus devised a synthetic access to these substrates which did not suffer from the drawbacks of the known routes, starting from enantiopure α-ionone. Indeed, we have shown that (*S*)- and (*R*)-α-ionone can be prepared from enantiopure **3a** and **3b** through a mild deoxygenation reaction. The great improvement is that because the two racemic diastereoisomers of epoxy-α-ionol are separable by column chromatography, laborious crystallisations of (−)-menthyl hydrazone derivatives[13] or 4-nitrobenzoate esters[16] are readily avoided.

The search for new and efficient synthetic methods affording enantiopure (*R*)- and (*S*)-α-ionone is of much current interest. As a matter of fact, α-ionone is itself a well known floral odorant[22] and careful studies have shown that the (*R*)-enantiomer shows the finest and most powerful organoleptic properties.[23] Moreover, α-ionone has been used as a precursor of new synthetic woody odorants, such as dehydro-nor-Ambrox,[24] displaying an ambergris aspect with a wood-tobacco tonality, and the derivative responsible for the intense woody odour of ISO E Super.[25] Work is now in progress to exploit this synthetic sequence to enantiopure α-ionone, *via* enzymatic acetylation of epoxy-α-ionol derivatives, in order to prepare optically active γ-ionone.

Experimental

The following enzymes were employed in this work: *Candida Cylindracea Lipase* (CCL) (Sigma, Type VII, 900 U mg^{-1}), *Porcine Pancreas Lipase* (PPL) (Sigma, Type II), and *Lipase PS Pseudomonas cepacia* (Amano Pharmaceuticals Co., Japan). Enantiomeric and diastereoisomeric excesses were determined by chiral GC analysis on a Chirasil DEX CB, 25 m × 0.25 mm (Chrompack), column using a DANI HT 86.10 gas chromatograph; 70 °C (1 min)—3.5 °C min^{-1}—140 °C (6 min)—8 °C min^{-1} 180 °C (1 min): t_R/min; **1a**, 19.08; **1b**, 19.63; **3a**, 23.25; **3b**, 23.98; **6a**, 24.15; **6b**, 24.66; **6c**, 24.92; **6d**, 25.08; **10a**, 23.18; **10b**, 23.27; **10c**, 23.32; **8d**, 23.61; **8a**, 24.55; **8b**, 23.81. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz). The chemical shift scale was based on internal tetramethylsilane. *J* Values are in Hz. Optical rotations were measured on a JASCO DIP 181 digital polarimeter, and are given in 10^{-1} deg cm^2 g^{-1}. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns.

4,5-Epoxy-4,5-dihydro-α-ionone 3

m-Chloroperbenzoic acid (67 g, 0.39 mol) was added to a solution of racemic α-ionone **1** (50 g, 0.26 mol) in methylene chloride (450 cm^3) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then poured into water. The organic phase was washed with a saturated solution of sodium hydrogen carbonate, dried on sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on a silica gel column eluting with hexane→hexane–ethyl acetate 8:2. The first eluted fractions gave 4,5-epoxy-4,5-dihydro-α-ionone (38 g, 71%), which was found to be (^{1}H NMR) a 5:1 mixture of *cis* (δ_H 3.11 C(4)H) and *trans* (δ_H 3.02 C(4)H) diastereoisomeric epoxides (Found: C, 74.91; H, 9.62; $C_{13}H_{20}O_2$ requires: C, 74.96; H, 9.68%); ν_{max}/cm^{-1} (neat) 1700, 1680, 1620, 1250; δ_H major diastereoisomer (*cis*-4,5-epoxy-4,5-dihydro-α-ionone) 6.73 (1H, dd, *J* 10 and 16, C(7)H), 6.09 (1H, d, *J* 16, C(8)H), 3.11 (1H, m, C(4)H), 2.30 (3H, s, *Me*CO), 2.09 (1H, d, *J* 10, C(6)H), 2.00–1.80 (2H, m, $C(3)H_2$), 1.40 (1H, m, C(2)H), 1.26 (3H, s, C(5)Me), 1.01 (1H, m, C(2)H), 0.94 (3H, s, C(1)Me), 0.76 C(1)Me); *m*/*z* 208 (M^+, 5%), 165 (30), 109 (62), 95 (48).

4,5-Epoxy-4,5-dihydro-α-ionol 5

Reduction of 4,5-epoxy-4,5-dihydro-α-ionone **3** (38 g, 0.18 mol) with sodium borohydride (9.0 g, 0.24 mol) in methylene chloride–methanol 2:1 (350 cm^3) at 0 °C gave 4,5-epoxy-4,5-dihydro-α-ionol **5** (33 g, 91%) (Found: C, 74.31; H, 10.49; $C_{13}H_{22}O_2$ requires: C, 74.24; H, 10.54%); ν_{max}/cm^{-1} (neat) 3423, 1601, 1451, 1365; *m*/*z* 210 (M^+, 1%), 195 (10), 165 (15), 123 (21), 109 (17), 95 (32), 43 (100). This reduction mixture was chromatographed on a silica gel column eluting with hexane→hexane–ethyl acetate 7:3. The first eluted fractions gave racemic *cis*-epoxy-α-ionol **5a**,**c** (14.4 g, 42%) which was found to contain 6% of the corresponding racemic *trans*-epoxy-α-ionol diastereoisomer (δ_H 2.98 C(4)H); de = 88% (from ^{1}H NMR and GC analysis of the corresponding acetate derivatives); δ_H: 5.61 (2H, m, vinylic H), 4.36 (1H, m, C(9)H), 3.06 (1H, m, C(4)H), 2.0–1.7 (3H, m, $C(3)H_2$ + C(6)H), 1.5–1.2 (7H, m + d + s, *J* 6, C(2)H + CH_3CHOH + C(5)Me), 0.95 (1H, m, C(2)H), 0.88 (3H, s, C(1)Me), 0.75 (3H, s, C(1)Me). The last eluted fractions gave racemic *cis*-epoxy-α-ionol **5b**,**d** (15.4 g, 45%) which was found to contain 17% of the corresponding racemic *trans*-epoxy-α-ionol diastereoisomer (δ_H 3.00 C(4)H); de = 66% (by ^{1}H NMR and GC analysis of the corresponding acetate derivatives); δ_H 5.61 (2H, m, vinylic H), 4.36 (1H, m, C(9)H), 3.09 (1H, m, C(4)H), 2.0–1.6 (3H, m, C(6)H + $C(3)H_2$), 1.4–1.1 (7H, m + d + s, *J* 6, C(2)H + CH_3CHOH + C(5)Me), 0.95 (1H, m, C(2)H), 0.88 (3H, s, C(1)Me), 0.71 (3H, s, C(1)Me).

General procedure for enzyme-mediated acetylations of 4,5-epoxy-4,5-dihydro-α-ionol 5

A mixture of 4,5-epoxy-4,5-dihydro-α-ionol **5** (10 g, 0.04 mol), lipase (10 g), and vinyl acetate (40 cm^3) in *tert*-butyl methyl ether

(150 cm^3) was stirred at room temperature for 24 h. The residue obtained upon evaporation of the filtered reaction mixture was chromatographed on a silica gel column, eluting with hexane→hexane–ethyl acetate 1:1. The first eluted fractions provided the acetate derivative to be analysed on a chiral GC column. The last eluted fractions afforded the unreacted starting material, a sample of which was acetylated by treatment with acetic anhydride and pyridine to perform chiral GC analysis. This procedure was employed both for the preliminary studies performed on the 1:1 mixture of the two diastereoisomeric *cis*-epoxides, containing the corresponding *trans*-stereoisomers, and for Lipase PS mediated acetylation of the two separate diastereoisomers **5a**,**c** and **5b**,**d**. Detailed results of the enzyme-mediated acetylations are reported in Tables 1 and 2.

(+)-(4*S*,5*R*,6*R*,9*R*)-4,5-Epoxy-4,5-dihydro-α-ionol *O*-acetate 6c. Lipase PS-mediated acetylation of racemic *cis*-epoxy-α-ionol **5a**,**c** (first and third peaks in the GC analysis of the corresponding acetate derivatives) (10 g, 0.048 mol) gave, after purification on a silica gel column eluting with hexane and bulb to bulb distillation (bp 130 °C, 0.2 mmHg), enantiopure acetate derivative (4*S*,5*R*,6*R*,9*R*)-**6c** (3.1 g, 26%) (third GC peak; ee > 99%, GC; de = 84%, GC; $[\alpha]_D^{20} = 179$ (*c* 1.00, $CHCl_3$) (Found: C, 71.31; H, 9.52; $C_{15}H_{24}O_3$ requires: C, 71.39; H, 9.59%); ν_{max}/cm^{-1} (neat) 1736, 1458, 1369; *m*/*z* 252 (M^+, 1%), 210 (5), 192 (10), 165 (15), 123 (18), 95 (54), 43 (100); δ_H 5.69 (1H, dd, *J* 15 and 10, C(7)H), 5.50 (1H, dd, *J* 15 and 6, C(8)H), 5.36 (1H, quintet, *J* 6, C(9)H), 3.06 (1H, m, C(4)H), 2.03 (3H, s, CH_3OCO), 2.0–1.75 (3H, m + d, *J* 10, C(3)H_2 + C(6)H), 1.5–1.3 (4H, m + d, *J* 6, C(2)H + C(9)Me), 1.23 (3H, s, C(5)Me), 0.92 (1H, m, C(2)H), 0.87 (3H, s, C(1)Me), 0.72 (3H, s, C(1)-Me). This compound was found to contain 8% of a single (ee > 99%, GC) *trans*-epoxy diastereoisomer ($\delta_H = 2.98$ C(4)H). The recovered unreacted alcohol derivative **5a** (5.9 g, 58%) showed ee = 47% and de = 84% (by GC of the corresponding acetate derivative) (E = 316, c = 32).

(+)-(4*S*,5*R*,6*R*,9*R*)-4,5-Epoxy-4,5-dihydro-α-ionol 5c

Treatment of acetate derivative **6c** (3.1 g, 0.012 mol) with potassium hydroxide (0.90 g, 0.016 mol) in methanol solution (35 cm^3) at room temperature afforded, after bulb to bulb distillation (bp 120 °C, 0.8 mmHg), enantiopure alcohol derivative (4*S*,5*R*,6*R*,9*R*)-**5c** (2.9 g, 83%) showing $[\alpha]_D^{20} = 141$ (*c* 0.49, $CHCl_3$). This product was found to contain 8% of a *trans*-epoxy diastereoisomer ($\delta_H = 2.98$ C(4)H). The ^1H NMR of this enantiopure stereoisomer was in accordance with that of the racemic mixture **5a**,**c**.

(+)-(4*S*,5*R*,6*R*)-4,5-Epoxy-4,5-dihydro-α-ionone 3b

Oxidation of enantiopure ionol derivative **5c** (2.10 g, 10 mmol) with manganese(IV) oxide (1.5 equiv.) in methylene chloride (20 cm^3) at room temperature afforded, after purification on a silica gel column eluting with hexane and bulb to bulb distillation (bp 130 °C, 0.2 mmHg) *cis*-epoxy-α-ionone (4*S*,5*R*,6*R*)-**3b** (1.49 g, 72%) showing ee > 99% (GC), de = 84% (GC) and $[\alpha]_D^{20} = 141$ [*c* 1.3, EtOH; lit.,[11] $[\alpha]_D^{20} = 210$ (*c* 1, EtOH)]. This derivative was found to contain 8% of a single (ee > 99%, GC) *trans*-epoxy diastereoisomer ($\delta_H = 3.02$ C(4)H). Careful chromatographic purification on a silica gel column, using hexane→hexane–ethyl acetate 9:1 as eluents, afforded a sample of (4*S*,5*R*,6*R*)-**3b** showing both enantiomeric and diastereoisomeric purity (GC) ($[\alpha]_D^{20} = 207$, *c* 1.2, EtOH). The ^1H NMR spectrum of enantiopure **3b** was in accordance with that of racemic *cis*-epoxy-α-ionone **3**.

(+)-(6*R*)-α-Ionone 1b

Trimethylchlorosilane (2.39 g, 22 mmol) was added dropwise to a solution of sodium iodide (1.62 g, 11 mmol) in dry acetonitrile under nitrogen. After a few minutes, a solution of (4*S*,5*R*,6*R*)-4,5-epoxy-4,5-dihydro-α-ionone **3b** {$[\alpha]_D^{20} = 141$ (*c* 1.3, EtOH)} (1.5 g, 7.2 mmol) in acetonitrile was added. After stirring at room temperature for 30 minutes, the reaction mixture was poured into a 4 M solution of sodium thiosulfate, and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated under reduced pressure, to give a residue which was chromatographed on a silica gel column, eluting with hexane. The first eluted fractions gave (*R*)-α-ionone (0.88 g, 64%, ee 98% GC) showing, after bulb to bulb distillation, $[\alpha]_D^{20} = 418$ [*c* 1, $CHCl_3$; lit.,[15] $[\alpha]_D^{20} = 407$ (*c* 0.04, $CHCl_3$)].

(−)-(4*R*,5*R*,6*R*,9*R*)-4-Chloro-5-hydroxy-1,1,5-trimethyl-6-(3-hydroxybut-1-en-1-yl)cyclohexane 7a

Treatment of (4*S*,5*R*,6*R*,9*R*)-4,5-epoxy-4,5-dihydro-α-ionol **5c** {$[\alpha]_D^{20} = 141$ (*c* 0.57, $CHCl_3$)} (1.5 g, 7.1 mmol) with a saturated solution of hydrogen chloride in methylene chloride afforded, after purification on a silica gel column eluting with hexane→hexane–ethyl acetate 7:3 and crystallisation from hexane, enantiopure chlorohydrin **7a** {1.06 g, 61%, de > 99% by ^1H NMR, $[\alpha]_D^{20} = -30$ (*c* 0.51, $CHCl_3$)} (Found: C, 63.17; H, 9.29; $C_{13}H_{23}ClO_2$ requires: C, 63.27; H, 9.39%); mp 85 °C; ν_{max}/cm^{-1} (Nujol) 3310, 1142, 737; δ_H 5.66 (2H, m, 2 vinylic H), 4.37 (1H, quintet, *J* 6, C*H*OH), 3.98 (1H, m, C*H*Cl), 2.42 (1H, m, C(3)H), 2.07 (1H, d, *J* 10, C(6)H), 1.78 (2H, m, C(3)H and C(2)H), 1.4–1.2 (m + d + s, *J* 6, C(2)H + CH_3CHOH + C(5)Me), 1.02 (3H, s, C(1)Me), 0.87 (3H, s, C(1)Me); *m*/*z* 248 (M^+ + 2, 1%), 246 (M^+, 4), 195 (15), 123 (30).

(−)-(4*R*,5*R*,6*R*)-4-Chloro-5-hydroxy-1,1,5-trimethyl-6-(3-oxobut-1-en-1-yl)cyclohexane 8a

Oxidation of chlorohydrin **7a** {1.0 g, 4.1 mmol, $[\alpha]_D^{20} = -30$ (*c* 0.51, $CHCl_3$)} with manganese(IV) oxide (1.5 equiv.) in methylene chloride (20 cm^3) gave, after purification on a silica gel column eluting with hexane and bulb to bulb distillation (bp 200 °C, 0.6 mmHg), enantiopure derivative **8a** (0.63 g, 63%; ee > 99%, GC; de > 99%, GC) showing $[\alpha]_D^{20} = -23$ (*c* 0.66, $CHCl_3$) (Found: C, 63.72; H, 8.70; Cl, 14.53; $C_{13}H_{21}ClO_2$ requires: C, 63.79; H, 8.65; Cl, 14.48%); ν_{max}/cm^{-1} (CCl_4) 3470, 1660, 1640; δ_H 6.93 (1H, dd, *J* 16 and 10, C(7)H), 6.11 (1H, d, *J* 16, C(8)H), 3.98 (1H, m, C*H*Cl), 2.48 (1H, m, C(3)H), 2.30 (3H, s, C*H*$_3$CO), 2.24 (1H, d, *J* 10, C(6)H), 1.82 (2H, m, C(2)H + C(3)H), 1.35–1.2 (4H, m + s, C(2)H + C(5)Me), 1.06 (3H, s, C(1)H), 0.86 (3H, s, C(1)H); *m*/*z* 246 (M + 2, 1%), 244 (M, 5), 193 (30), 125 (100).

(−)-(4*R*,5*S*,6*S*,9*R*)-4,5-Epoxy-4,5-dihydro-α-ionol *O*-acetate 6b

Lipase PS-mediated acetylation of racemic *cis*-epoxy-α-ionol **5b**,**d** (second and fourth peaks in the GC analysis of the corresponding acetate derivatives) (10 g, 0.048 mol) gave, after purification on a silica gel column eluting with hexane and bulb to bulb distillation (bp 130 °C, 0.2 mmHg), enantiopure acetate derivative (4*R*,5*S*,6*S*,9*R*)-**6b** (3.7 g, 31%) {second GC peak; ee > 99%, GC; de = 67%, GC; $[\alpha]_D^{20} = -56$ (*c* 1.04, $CHCl_3$)}. This compound was found to contain 17% of a single (ee > 99%, GC) *trans*-epoxy diastereoisomer ($\delta_H = 2.98$ C(4)H): δ_H 5.61 (2H, m, vinylic H), 5.37 (1H, m, C(9)H), 3.06 (1H, m, C(4)H), 2.05 (3H, s, CH_3OCO), 2.0–1.75 (3H, m, C(3)H_2 + C(6)H), 1.4–1.3 (4H, m + d, *J* 6, C(2)H + C(9)Me), 1.24 (3H, s, C(5)-Me), 0.95 (1H, m, C(2)H), 0.87 (3H, s, C(1)Me), 0.71 (3H, s, C(1)Me). The recovered unreacted alcohol (3.9 g, 39%) showed ee = 91% and de = 65% (GC of the corresponding acetate derivative) (E = 635, c = 48).

(−)-(4*R*,5*S*,6*S*,9*R*)-4,5-Epoxy-4,5-dihydro-α-ionol 5b

Treatment of acetate derivative **6b** (3.7 g, 0.015 mol) with potassium hydroxide (1.06 g, 0.019 mol) in methanol (30 cm^3) at room temperature afforded, after bulb to bulb distillation (bp

115 °C, 0.8 mmHg), enantiopure alcohol derivative (4*R*,5*S*,6*S*,9*R*)-**5b** (2.68 g, 85%) showing $[\alpha]_D^{20} = -142$ (*c* 0.57, $CHCl_3$). This substrate was found to contain 6% of a *trans*-epoxy diastereoisomer ($\delta_H = 3.00$ C(4)H). The ^{1}H NMR of this enantiopure stereoisomer was in accordance with that of the racemic mixture **5b**,**d**.

(−)-(4*R*,5*S*,6*S*)-4,5-Epoxy-4,5-dihydro-α-ionone 3a

Oxidation of enantiopure ionol derivative **5c** (2.60 g, 0.02 mol) with manganese(IV) oxide (1.5 equiv.) in methylene chloride (20 cm^3) at room temperature afforded, after purification on a silica gel column eluting with hexane and bulb to bulb distillation (bp 130 °C, 0.2 mmHg), *cis*-epoxy-α-ionone (4*R*,5*S*,6*S*)-**3a** (1.72 g, 69%) showing ee > 99% (GC), de = 89% (GC), and $[\alpha]_D^{20} = -199$ {*c* 0.61, $CHCl_3$; lit.,[6] $[\alpha]_D^{20} = -210$ (*c* 0.59, $CHCl_3$)}. This derivative was found to contain 5% of a single (ee > 99%, GC) *trans*-epoxy diastereoisomer ($\delta_H = 2.98$ C(4)H). The ^{1}H NMR spectrum of enantiopure **3a** was in accordance with that of racemic *cis*-epoxy-α-ionone **3**.

(−)-(6*S*)-α-Ionone 1a

Trimethylchlorosilane (2.39 g, 22 mmol) was added dropwise to a solution of sodium iodide (1.62 g, 11 mmol) in dry acetonitrile (20 cm^3) under nitrogen. After a few minutes, a solution of (4*R*,5*S*,6*S*)-4,5-epoxy-4,5-dihydro-α-ionone **3a**, $[\alpha]_D^{20} = -199$ (*c* 0.59, $CHCl_3$) (1.50 g, 7.2 mmol) in acetonitrile (5 cm^3) was added. After stirring at room temperature for 30 minutes, the reaction mixture was poured into a 4 M solution of sodium thiosulfate, and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated under reduced pressure, to give a residue which was chromatographed on a silica gel column, eluting with hexane. The first eluted fractions gave (*S*)-α-ionone (0.83 g, 60%, ee 97%, GC) showing, after bulb to bulb distillation, $[\alpha]_D^{20} = -418$ {*c* 1, $CHCl_3$; lit.,[15] $[\alpha]_D^{20} = -431$ (*c* 0.035, $CHCl_3$)}.

(+)-(4*S*,5*S*,6*S*,9*R*)-4-Chloro-5-hydroxy-1,1,5-trimethyl-6-(3-hydroxybut-1-en-1-yl)cyclohexane 7b

Treatment of (4*R*,5*S*,6*S*,9*R*)-4,5-epoxy-4,5-dihydro-α-ionol **5b** {$[\alpha]_D^{20} = -142$ (*c* 0.57, $CHCl_3$)} (1.5 g, 7.1 mmol) with a saturated solution of hydrogen chloride in methylene chloride afforded, after purification on a silica gel column eluting with hexane→hexane–ethyl acetate 7:3 and crystallisation from hexane, enantiopure chlorohydrin **7b** (0.99 g, 57 %) {de > 99%, ^{1}H NMR, $[\alpha]_D^{20} = 46$ (*c* 0.72, $CHCl_3$)} (Found: C, 63.18; H, 9.32; Cl, 14.29; $C_{13}H_{23}ClO_2$ requires: C, 63.27; H, 9.39; Cl, 14.37%); mp 85 °C; ν_{max}/cm^{-1} (Nujol) 3315, 1140, 730; δ_H 5.70 (1H, dd, *J* 15.5 and 9, C(7)H), 5.57 (1H, dd, *J* 15.5 and 6, C(8)H), 4.36 (1H, quintet, *J* 6, C*H*OH), 3.98 (1H, m, C*H*Cl), 2.43 (1H, m, C(3)H), 2.06 (1H, d, *J* 9, C(6)H), 1.78 (2H, m, C(3)H and C(2)H), 1.4–1.2 (7H, m + d + s, *J* 6, C(2)H + CH_3CHOH + C(5)Me), 1.00 (3H, s, C(1)Me), 0.84 (3H, s, C(1)Me); *m*/*z* 248 (M^+ + 2, 2%), 246 (M^+, 7), 195 (18), 123 (35).

(+)-(4*S*,5*S*,6*S*)-4-Chloro-5-hydroxy-1,1,5-trimethyl-6-(3-oxobut-1-en-1-yl)cyclohexane 8b

Oxidation of chlorohydrin **7b** {0.90 g, 3.68 mol, $[\alpha]_D^{20} = 46$ (*c* 0.72, $CHCl_3$)} with manganese(IV) oxide (1.5 equiv.) in methylene chloride (20 cm^3) gave, after purification on a silica gel column eluting with hexane and bulb to bulb distillation (bp 180 °C, 0.2 mmHg), enantiopure derivative **10b** (0.494 g, 55%; ee > 99%, GC; de > 99%, GC) showing $[\alpha]_D^{20} = 23$ (*c* 0.66, $CHCl_3$). The ^{1}H NMR was in accordance with that of the corresponding enantiomer **8a**.

(±)-5,6-Epoxy-5,6-dihydro-β-ionone 4

m-Chloroperbenzoic acid (67 g, 0.39 mol) was added to a solution of β-ionone **2** (50 g, 0.26 mol) in methylene chloride (450 cm^3) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then poured into water. The organic phase was washed with a saturated solution of sodium hydrogen carbonate, dried on sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on a silica gel column eluting with hexane→hexane–ethyl acetate 8:2, to give racemic 5,6-epoxy-5,6-dihydro-β-ionone (40 g, 74%) (Found: C, 74.91; H, 9.61; $C_{13}H_{20}O_2$ requires: C, 74.96; H, 9.68%); ν_{max}/cm^{-1} (neat) 1700, 1680, 1630; δ_H 7.03 (1H, d, *J* 16, C(7)H), 6.09 (1H, d, *J* 16, C(8)H), 2.28 (3H, s, *Me*CO), 2.0–1.3 (6H, 2 m, C(2)H_2 + C(3)H_2 + C(4)H_2), 1.17 (6H, s, C(5)Me + C(1)Me), 0.96 (3H, s, C(1)Me); *m*/*z* 193 (M^+ − 15, 1%), 135 (10), 123 (100), 95 (8), 43 (34).

5,6-Epoxy-5,6-dihydro-β-ionol 9

Reduction of (±)-5,6-epoxy-5,6-dihydro-β-ionone **4** (40 g, 0.19 mol) with sodium borohydride (9.4 g, 0.25 mol) in methylene chloride–methanol 2:1 (350 cm^3) at 0 °C gave, after purification on a silica gel column eluting with hexane→hexane–ethyl acetate 7:3, 5,6-epoxy-5,6-dihydro-β-ionol **7** (34.7 g, 87%) (Found: C, 74.29; H, 10.61; $C_{13}H_{22}O_2$ requires: C, 74.24; H, 10.54%) as a 1:1 mixture of the two racemic diastereoisomers **9a**,**c** and **9b**,**d**; ν_{max}/cm^{-1} (neat) 3422, 1458, 1363; δ_H 5.89 (1H, d, *J* 15.5, C(7)H), 5.73 (1H, dd, *J* 15.5 and 5.5, C(8)H), 4.38 (1H, m, C*H*OH), 2.0–1.3 (6H, m, C(2)H_2 + C(3)H_2 + C(4)H_2), 1.28 (3H, d, *J* 6, C(9)Me), 1.17 and 1.15 (3H, 2 s, C(5)Me of the two diastereoisomers), 1.07 and 1.05 (3H, 2 s, C(1)Me of the two diastereoisomers), 0.94 and 0.92 (3H, 2 s, C(1)Me of the two diastereoisomers); *m*/*z* 195 (M^+ − 15, 3%), 123 (100), 95 (14).

4-Nitrobenzoate ester derivatives of epoxy-β-ionol (1:1 mixture of two racemic diastereoisomers) 11a–d

A solution of epoxy-β-ionol **9** (40 g, 0.19 mol), 4-nitrobenzoyl chloride (46 g, 0.25 mol) and pyridine (40 cm^3) in methylene chloride (300 cm^3) was stirred at room temperature for 2 h. The reaction mixture was poured into ice, and treated with 10% aqueous HCl; the organic layer was separated, washed first with a saturated solution of sodium hydrogen carbonate, then with water, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography eluting with hexane. The first eluted fractions gave a 1:1 mixture of 4-nitrobenzoate esters (50.4 g, 74%) **11a**,**c** and **11b**,**d** (Found: C, 66.92; H, 7.08; N, 3.96; $C_{20}H_{25}NO_5$ requires: C, 66.84; H, 7.01; N, 3.90%); ν_{max}/cm^{-1} (Nujol) 1721, 1523; δ_H 8.26 (4H, m, aromatic H), 6.05 (1H, d, *J* 15, C(7)H), 5.8–5.6 (2H, m, C(8)H + C(9)H), 1.6–1.2 (2H, m, cyclohexane H), 1.48 and 1.49 (3H, 2 overlapping d, *J* 6, C(9)Me of the two diastereoisomers), 1.40 (4H, m, cyclohexane H), 1.16 and 1.12 (3H, 2 s, C(5)Me of the two diastereoisomers), 1.08 and 1.05 (3H, 2 s, C(1)Me of the two diastereoisomers), 0.93 and 0.90 (3H, 2 s, C(1)Me of the two diastereoisomers). Six crystallisations from hexane afforded diastereoisomer **11a**,**b** (12.9 g, 26%; de > 99%, ^{1}H NMR): mp 72 °C; δ_H 8.26 (4H, m, aromatic H), 6.05 (1H, d, *J* 15, C(7)H), 5.77 (1H, dd, *J* 15 and 6, C(8)H), 5.66 (1H, quintet, *J* 6, C(9)H), 1.6–1.2 (3H, m, cyclohexane H), 1.48 (3H, d, *J* 6, C(9)Me), 1.40 (3H, m, cyclohexane H), 1.16 (3H, s, C(5)Me), 1.08 (3H, s, C(1)Me), 0.90 (3H, s, C(1)Me).

General procedure for enzyme-mediated acetylations of 5,6-epoxy-5,6-dihydro-β-ionol 9

A mixture of 5,6-epoxy-5,6-dihydro-β-ionol **9** (10 g, 0.048 mol), lipase (10 g), and vinyl acetate (40 cm^3) in *tert*-butyl methyl ether (150 cm^3) was stirred at room temperature for 24 h. The residue obtained upon evaporation of the filtered reaction mixture was chromatographed on a silica gel column, eluting with hexane→hexane–ethyl acetate 1:1. The first eluted fractions provided the acetate derivative to be analysed on a chiral GC column. The last eluted fractions afforded the unreacted

starting material, a sample of which was acetylated by treatment with acetic anhydride and pyridine to perform chiral GC analysis. Detailed results of the enzyme-mediated acetylations are reported in Table 1.

(5*S*,6*R*,9*R*)-5,6-Epoxy-5,6-dihydro-β-ionol *O*-acetate 10d

Lipase PS-mediated acetylation of epoxy-β-ionol **9** (1 : 1 mixture of two racemic diastereoisomers) (10 g, 0.048 mol) gave, after purification on a silica gel column eluting with hexane, enantiopure acetate derivative **10d** (fourth GC peak, 2.66 g, 22%; de = 60%, GC and ^{1}H NMR) (Found: C, 71.43; H, 9.52; $C_{15}H_{24}O_3$ requires: C, 71.39; H, 9.59%) contaminated with enantiopure (third GC peak) diastereoisomer **10c** (δ_H = 2.09 OAc); ν_{max}/cm^{-1} (neat) 1730, 1450, 1371; δ_H (major diastereoisomer) 5.90 (1H, d, *J* 15.5, C(7)H), 5.64 (1H, dd, *J* 15.5 and 6.5, C(8)H), 5.38 (1H, quintet, *J* 6.5, C(9)H), 2.03 (3H, s, OAc), 1.4–2.2 (9H, m + d, *J* 6.5, cyclohexane H + C(9)Me), 1.13 (3H, s, C(5)Me), 1.05 (3H, s, C(1)Me), 0.91 (3H, s, C(1)Me); *m*/*z* 237 (M^+ − 15%), 192 (15), 123 (20).

(5*S*,6*R*,9*R*)-5,6-Epoxy-5,6-dihydro-β-ionol *O*-*p*-nitrobenzoate 11d

Epoxy-β-ionol *O*-acetate **10d** (3.0 g, 0.012 mol), prepared by lipase-mediated acetylation of **9**, was hydrolysed with potassium hydroxide in methanol (85%) and converted into the corresponding 4-nitrobenzoate ester derivative **11d** (de = 60%, ^{1}H NMR; 2.60 g, 71%) by reaction with 4-nitrobenzoyl chloride and pyridine in methylene chloride. The ester was crystallised thrice from methanol to give **11d** as a single diastereoisomer (^{1}H NMR) {1.25 g, 48%; $[a]_D^{20}$ = 11 (*c* 0.42, $CHCl_3$)}: mp 79 °C; δ_H 8.26 (4H, m, aromatic H), 6.05 (1H, d, *J* 15, C(7)H), 5.77 (1H, dd, *J* 15 and 6, C(8)H), 5.66 (1H, quintet, *J* 6, C(9)H), 1.6–1.2 (2H, m, cyclohexane H), 1.50 (3H, d, *J* 6, C(9)Me), 1.40 (4H, m, cyclohexane H), 1.12 (3H, s, C(5)Me), 1.05 (3H, s, C(1)Me), 0.93 (3H, s, C(1)Me).

(5*S*,6*R*,9*R*)-5,6-Epoxy-5,6-dihydro-β-ionol 9d

4-Nitrobenzoate derivative **11d** (1.25 g, 3.48 mmol) was hydrolysed by treatment with potassium hydroxide (0.253 g, 4.52 mmol) in methanol (15 cm^3) to afford, after bulb to bulb distillation (145 °C, 2 mmHg), enantiopure epoxy-β-ionol **9d** (0.585 g, 80%), showing $[a]_D^{20}$ = 47 (*c* 0.50, $CHCl_3$); δ_H 5.88 (1H, d, *J* 15.5, C(7)H), 5.73 (1H, dd, *J* 15.5 and 6.5, C(8)H), 4.38 (1H, quintet, *J* 6.5, C(9)H), 1.3–2.0 (6H, m, cyclohexane H), 1.29 (3H, d, *J* 6, C(9)Me), 1.17 (3H, s, C(5)Me), 1.07 (3H, s, C(1)Me), 0.92 (3H, s, C(1)Me).

(5*S*,6*R*)-5,6-Epoxy-5,6-dihydro-β-ionone 4a

Enantiopure epoxy-β-ionol **9d** (0.585 g, 2.78 mmol) was oxidised by treatment with manganese(IV) oxide (1.5 equiv.) in methylene chloride (15 cm^3), to afford, after bulb to bulb distillation, enantiomerically pure (+)-epoxy-β-ionone **4a** (0.411 g, 71%) showing $[a]_D^{20}$ = 99° (*c* 0.66, $CHCl_3$). The ^{1}H NMR spectrum was in accordance with that of the racemic mixture.

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