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Enzyme-catalysed approach to the preparation of triazole antifungals: synthesis of (−)-genaconazole

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ABSTRACT

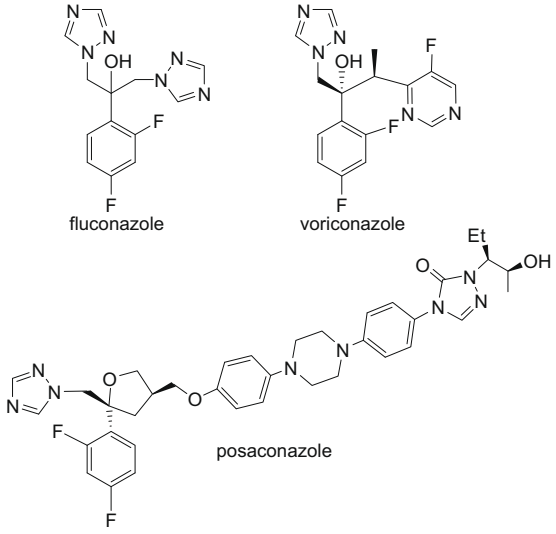
The work describes a new enzyme-mediated approach to optically active epoxide (2*R*,3*S*)-**6**, which is an important key intermediate in the preparation of single enantiomers of chiral azole antifungals. The conversion of (2*R*,3*S*)-**6** into (−)-genaconazole is reported as an example of its synthetic relevance.

1. Introduction

The need for effective treatments for fungal infections has become more urgent over the last decade by the growing increase of immuno-compromised patients, suffering from AIDS, or subjected to transplantations or anti-cancer therapy. Although a major breakthrough has been brought about by the licensing of potent azoles, that is, fluconazole,[1] voriconazole[2] and posaconazole[3] (Scheme 1), some therapeutic problems still remain, particularly related to the appearance of new pathogenic fungal species, and to the development of significant drug resistance.[4]

Several azole agents have been investigated, most of which show the core structure **I** (Scheme 2), such as (−)-**1**,[5] the active enantiomer of racemic genaconazole, albaconazole **2**, ravuconazole **3**,[6] and many new structures **4**[7] and **5**[8] that are currently being introduced.

The key structural motif **I** can be obtained in the correct absolute configuration by ring opening of epoxide (2*R*,3*S*)-**6** by means of a suitable nucleophilic reagent (Scheme 3). We have developed a lipase-mediated preparation of (2*R*,3*S*)-**6**, and employed it to prepare the azole antifungal (−)-**1**, that is, the eutomer of genaconazole, as a demonstration of its synthetic utility.



Scheme 1.

2. Results and discussion

The preparation of epoxide (2*R*,3*S*)-**6** reported in the literature employed compound (*R*)-**7** as a key intermediate (Scheme 3). This latter was obtained either from (*R*)-[9,10] or (*S*)-lactic acid,[11] or by enantioselective hydroxylation of the corresponding ketone[12] with camphorsulfonyl oxaziridines, or by enzymatic resolution of the hydroxy ketone mediated by lipases.[13] The second stereogenic centre was created by conversion of (*R*)-**7** into either diol (2*R*,3*R*)-**8**,[9,10,12] triol (2*R*,3*R*)-**9**,[11a,14] or epoxy alcohol (2*R*,3*S*)-**10**.[11b] Diastereoisomeric purity was achieved by crystallisation of diol (2*R*,3*R*)-**8**,[9,12] and by means of diastereoselective reactions for triol (2*R*,3*R*)-**9**,[14] and epoxy alcohol (2*R*,3*S*)-**10**.[11b] In a completely different approach, a Sharpless–Katsuki epoxydation was employed to prepare epoxy alcohol (2*R*,3*S*)-**10** with moderate enantiomeric purity.[15]

Slightly different procedures were then exploited to convert (2*R*,3*R*)-**8**, (2*R*,3*R*)-**9** and (2*R*,3*S*)-**10** into the desired epoxide.

We devised an alternative synthetic sequence to (2*R*,3*S*)-**6**: the key step being the lipase-mediated acetylation of racemic triol (2*RS*,3*RS*)-**9a**, which was obtained according to a new synthetic procedure as reported in Scheme 4, from commercial 2,4-difluoro-

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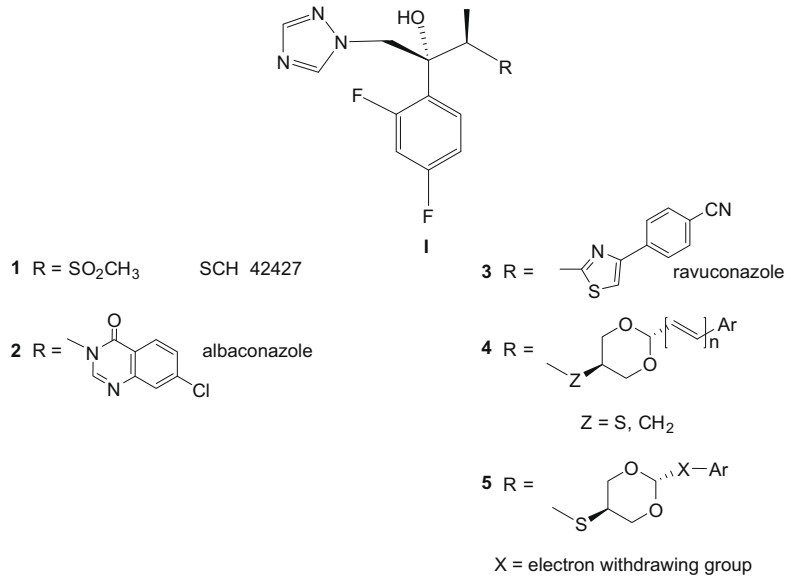
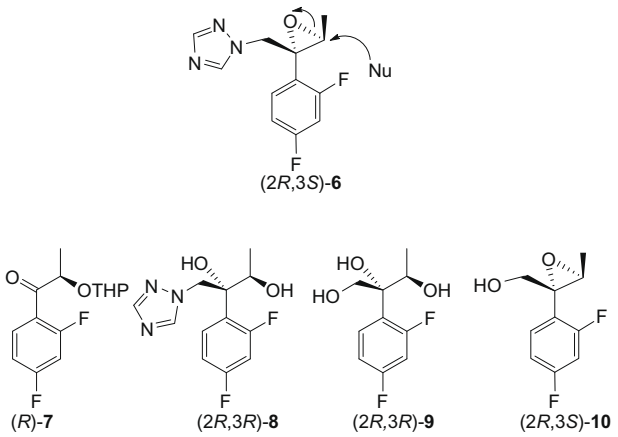
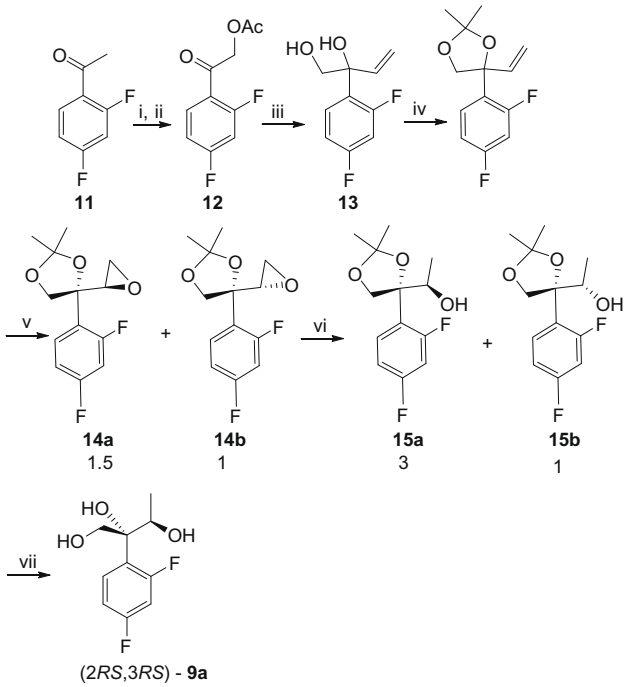


Scheme 2.



Scheme 3.



Scheme 4. i. Br_2, AcOH; ii. AcONa, DMF; iii. vinylmagnesium bromide, THF; iv. 2,2-dimethoxypropane, acetone, PPTS; v. *m*-chloroperbenzoic acid, CH_2Cl_2; column chromatography; vi. $LiAlH_4$, THF; column chromatography; vii. HCl, AcOH, THF; crystallisation from hexane-diethylether.

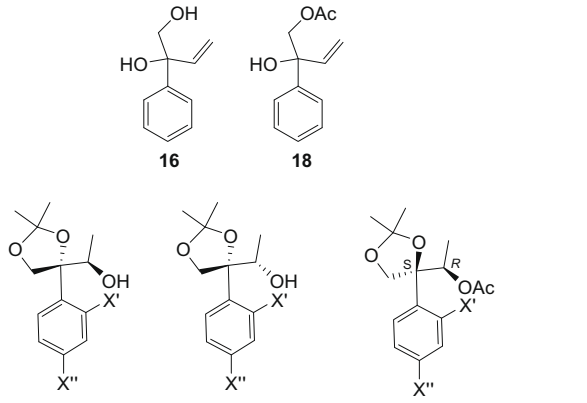
acetophenone **11**, and brought to diastereoisomeric purity by fractional crystallisation.

Compound **11** was carefully brominated and then reacted with sodium acetate in DMF, to afford acetoxy ketone **12**. The latter was treated with vinyl magnesium bromide in THF to give diol **13**, which was protected as an acetonide and submitted to epoxidation with *m*-chloroperbenzoic acid, to afford a 1:1.3 mixture of epoxides **14a** and **14b**. Column chromatography allowed us to enrich this mixture into the desired diastereoisomer **14a** (**14a**/**14b** 1.5/1). Lithium aluminium hydride reduction and a further enrichment by column chromatography afforded compound **15** as a 3/1 mixture of diastereoisomers **15a** and **15b**. These latter derivatives were deprotected to give triols **9a** and **9b**; the desired isomer, (2*RS*,3*RS*)-**9a**, could be obtained with de = 99% (^{1}H NMR) by crystallisation from hexane/diethyl ether 8/2.

The choice of triol **9a** as the best intermediate for this sequence to be submitted to biocatalytic kinetic resolution was the result of an investigation which was developed as follows; we first studied the behaviour under the conditions of lipase-mediated transesterification of model compounds **16** and **17a,b** (Scheme 5) with no fluorine atoms on the aromatic ring, which could be easily prepared from the largely available acetophenone.

The lipase-mediated acetylation of the primary OH moiety of compound **16** was characterised by very modest enantioselectivity, and by a different stereochemical course according to the lipase, which was employed as a catalyst. Lipase PS gave (*S*)-**18** (ee = 15%, of the corresponding alcohol), while either PPL (*Porcine pancreatic* lipase) or CRL (*Candida rugosa* lipase) afforded (*R*)-**18** (ee = 37% and 23% of the corresponding alcohol, respectively).

The biocatalytic transesterification of the 1:1 mixture of diastereoisomers **17a** and **17b** was found to be characterised by high values of enantio- and diastereoselectivity, when lipase PS was employed as a catalyst: acetate (+)-**19b**[16] was obtained with



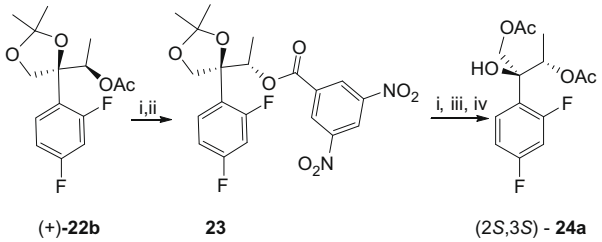
X' = X'' = H **17a** X' = X'' = H **17b** X' = X'' = H (+)-**19b**
X' = H, X'' = F **20a** X' = H, X'' = F **20b** X' = H, X'' = F (+)-**21b**
X' = X'' = F **15a** X' = X'' = F **15b** X' = X'' = F (*R*,*S*)-(+)-**22b**

Scheme 5.

ee = 99%, and de = 91% (Table 1). The diastereoselectivity was slightly lower when *C. rugosa* lipase was used, and acetate (+)-**19b** was obtained with ee = 97% and de = 69%. No acetylation was observed with PPL as a catalyst. We also investigated the course of the lipase-mediated acetylation of racemic diastereoisomers **20a** and **20b**, which showed one fluorine atom on the aromatic ring.

When the 1:1 mixture of the two racemic diastereoisomers **20a** and **20b** (Table 1) was submitted to lipase PS-catalysed transesterification, only acetate (+)-**21b**[16] was obtained, showing ee = 99% and de = 87%. When CRL was employed, diastereoisomeric acetate (+)-**21b** was produced with ee = 94% and de = 33%. PPL gave modest values of stereoselectivity, with a slight preference for the other diastereoisomer: acetate **21a** was obtained with de = 59% (the ee could not be determined).

As for the kinetic resolution of **15a** and **15b** (Table 1), only lipase PS proved to be successful in the production of an acetate derivative: acetate (+)-**22b** was obtained as a single enantiomerically pure diastereoisomer. Unfortunately **22b** was the wrong diastereoisomer for our synthetic sequence: after saponification and acetal hydrolysis, diol **9b** was recovered. The absolute configuration of acetate (+)-**22b** was determined to be (*R*,*S*) by chemical correlation, according to the procedure shown in Scheme 6. A sample of (+)-**22b** was submitted to saponification and a Mitsunobu esterification with 3,5-dinitrobenzoic acid, to give ester **23**. Compound **23** was hydrolysed and acetylated to afford diacetate (2*S*,3*S*)-**24a**, thus confirming the preference of Lipase PS for the acetylation of (*R*)-stereogenic centres.[16]



(+)-**22b** **23** (2*S*,3*S*) - **24a**

Scheme 6. i. KOH, MeOH; ii. DIAD, PPh_3, 3,5-dinitrobenzoic acid, THF; iii. HCl, AcOH, THF; iv. Ac_2O, pyridine.

The results of the kinetic resolution of **15a,b** prompted us to move the enzymatic resolution step further along the synthetic procedure. The only other possible candidate to be resolved by enzyme-catalysed acetylation was triol **9** (Scheme 7).

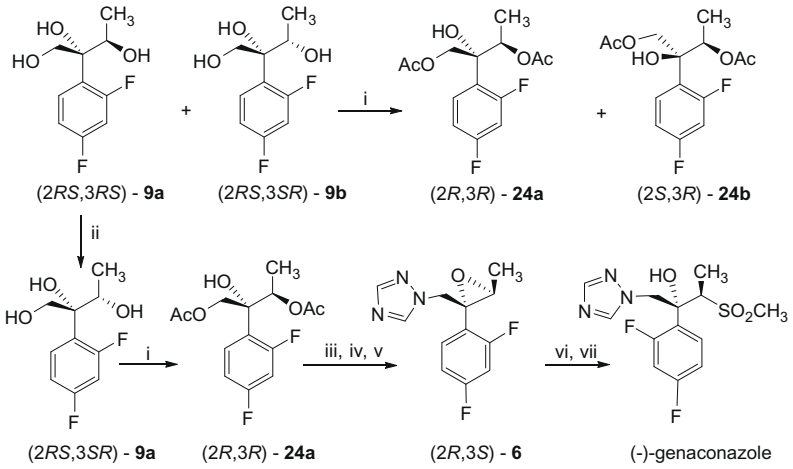
When a 1:1 mixture of the diastereoisomeric diols **9a** and **9b** was treated either with CRL or Lipase PS for 96 h in *t*-butylmethyl ether in the presence of vinyl acetate, a 1:1 mixture of the two enantiomerically pure diacetates **24a** and **24b** was recovered, in 17% and 34% isolated yields, respectively. When PPL was employed as the catalyst a complex mixture of regioisomeric and stereoisomeric monoacetates was obtained, in addition to the unreacted starting triols **9a** and **9b**.

The kinetic resolution of triol **9** showed no diastereoselectivity, thus diastereoisomer separation had to be performed by means of fractional crystallisation of the mixture **9a**–**b** from 8:2 hexane/diethyl ether (Scheme 7). Diacetate (2*R*,3*R*)-**24a** was then obtained from racemic (*RS*,*RS*)-**9a** by Lipase PS mediated acetylation with ee = 99% and de = 99%, and then hydrolysed to known (2*R*,3*R*)-**9a**.

A known procedure was then employed to convert triol (2*R*,3*R*)-**9a** into epoxide (2*R*,3*S*)-**6**, which involved the treatment with mesyl chloride in pyridine, and subsequent reaction with the sodium salt of 1,2,4-triazole and NaH in DMF solution. Ring opening promoted by sodium thiomethylate gave a sulfide intermediate, which was oxidised to (−)-**1**, the most active enantiomer of genaconazole.

Table 1
Lipase-mediated acetylation of the mixtures of **17a**–**b**, **20a**–**b**, and **15a**–**b**

	Acetate derivative	Unreacted alcohol
17a–b		
Lipase PS	**19b**: ee = 99%, de = 91% (first eluting enantiomer in GC)	**17b**: ee = 31% (second eluting enantiomer in GC as acetate derivative); **17b**/**17a** = 2.9/7.1
CRL	**19b**: ee = 97%, de = 69% (first eluting enantiomer in GC)	**17b**: ee = 17%, (second eluting enantiomer in GC as acetate derivative); **17b**/**17a** = 4.3/5.7
PPL	—	—
20a–b		
Lipase PS	**21b**: ee = 99%, de = 87% (first eluting enantiomer in GC)	**20b**: ee = 99% (second eluting enantiomer in GC as acetate derivative; **20b/20a** = 3.3/6.6
CRL	**21b**: ee = 94%, de = 33% (first eluting enantiomer in GC)	**20b**: ee = 3.7% (second eluting enantiomer in GC as acetate derivative); **20b/20a** = 4.5/5.5
PPL	**21a**: ee = not determined, de = 59% **21b**: ee = 40% (first eluting enantiomer in GC)	**20a**: ee = not determined; **20b**: ee = 1.8% (second eluting enantiomer in GC as acetate derivative); **20b/20a** = 5.4/4.6
15a–b		
Lipase PS	**22b**: ee = 99%, de = 99% (first eluting enantiomer in GC)	**15b**: ee = 10%; **15b/15a** = 0.9/1.0
CRL	—	—
PPL	—	—



Scheme 7. i. Lipase PS, *t*-butylmethylether, vinyl acetate; ii. crystallisation from hexane-diethyl ether; iii. KOH, MeOH; iv. mesyl chloride, pyridine; v. 1,2,4-triazole, NaH, DMF; vi. CH_3SNa, CH_3OH; vii. *m*.-chloroperbenzoic acid, CH_2Cl_2.

3. Conclusions

The work highlights the great versatility of lipases in the catalysis of transesterification reactions. The best results were achieved by using lipase PS: the kinetic resolution of secondary alcohols **17a**–**b**, **20a**–**b**, and **15a**–**b** proved to be enantiospecific and totally diastereoselective; the acetylation of triols **9a**–**b** was enantiospecific, but not diastereoselective. The synthetic route we have devised for optically active epoxide (2*R*,3*S*)-**6** is characterised by interesting key intermediates that can be enriched in the desired diastereoisomer either by column chromatography (i.e., epoxides **14** and alcohols **15**) or by crystallisation (triols **9**). The procedure is well suited for investigating the possibility of integrating the physical methods of diastereoisomer separation with chemical techniques of optical activation, in order to enhance the production yield of the desired stereoisomer. The synthetic target, epoxide (2*R*,3*S*)-**6,** is a valuable chiral structural moiety, whose synthesis is worth being optimised, as it plays a central role in the preparation of relevant antifungal drugs.

4. Experimental

The enantiomeric excess values were determined either by GC or HPLC analysis: (a) GC analysis was performed using a Chirasil DEX CB, 25 m × 0.25 mm (Chrompack) column, installed on a DANI HT 86.10 gas chromatograph; (b) HPLC analyses were performed using a Chiralcel OD column, installed on a Merck-Hitachi l-7100 instrument with a Merck-Hitachi L-4250 UV–vis detector. The GC and HPLC analyses conditions and the observed retention times are hereafter reported:

(a) Compound **19b**: GC temperature programme 60 °C (3 min)—1.5 °C min^{-1}—180 °C; t_R = 36.5 min, 36.8 min.
(b) Compound **21b**: GC temperature programme 60 °C (3 min)—1.5 °C min^{-1}—180 °C; t_R = 37.5 min, 38.0 min.
(c) Compound **22b**: GC temperature programme 60 °C (3 min)—1.5 °C min^{-1}—180 °C; t_R = 33.9 min, 34.9 min.
(d) Compound **24a**: HPLC, 1.0 ml/min, 254 nm, 99:1 hexane/isopropanol, t_R = 16.3 min, 20.8 min.
(e) Compound **24b**: HPLC, 1.0 ml/min, 254 nm, 99:1 hexane/isopropanol, t_R = 24.7 min, 29.7 min.

4.1. 2-(2,4-Difluorophenyl)-2-oxoethyl acetate 12

To a solution of 2,4-difluoroacetophenone (40.0 g, 0.256 mol) in acetic acid (500 mL), bromine (41.0 g, 0.256 mol) was added: an exothermic reaction took place with concomitant decolouration. After 30 min, sodium acetate (42.0 g, 0.512 mol) was added and the reaction mixture was concentrated under reduced pressure. Next, DMF (300 mL) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with diethyl ether. The combined organic phases were washed with water, dried on sodium sulfate and concentrated under reduced pressure to give a solid residue, from which compound **12** was recovered by crystallisation from hexane: (35.1 g, 64%); δ_H (400 MHz; $CDCl_3$): 2.21 (3H, s, CO*CH*$_3$), 5.19 (2H, d, *J* 3.8 Hz, *CH*$_2$), 6.91 (1H, m, aromatic H), 7.01 (1H, m, aromatic H), 8.02 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 20.4, 68.8 (d), 104.7 (ddt), 112.7 (dd), 119.2 (dd), 132.8 (dd), 163.3 (dd), 166.6 (dd), 170.2, 189.0 (d); GC/MS t_R 14.91 min, *m*/*z* 214 (M^+, 1), 172 (1), 154 (3), 141 (100).

4.2. 2-(2,4-Difluorophenyl)but-3-ene-1,2-diol 13

To a solution of vinyl magnesium bromide in THF, obtained by the addition of vinyl bromide (78.8 g, 0.736 mol) to a suspension of magnesium turnings (25.4 g, 1.10 mol) in THF (500 mL), compound **12** (35.0 g, 0.164 mol) was added dropwise. After 30 min, the reaction mixture was poured into a saturated NH_4Cl water solution, and extracted with diethyl ether. The organic phase was dried and concentrated under reduced pressure, to obtain a residue which was chromatographed on silica gel with hexane–ethyl acetate 9:1, affording derivative **13** (23.3 g, 71%): δ_H (400 MHz; $CDCl_3$): 3.85 (2H, s, *CH*$_2$), 5.24 (1H, d, *J* 10.5 Hz, =C*H*H), 5.35 (1H, d, *J* 17.3 Hz, =CH*H*), 6.22 (1H, ddd, *J* = 2.2, 10.8, 17.3 Hz, C*H*=), 6.77 (1H, m, aromatic H), 6.87 (1H, m, aromatic H), 7.62 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 67.8 (d), 76.3 (d), 104.2 (t), 111.1 (dd), 115.8, 125.5 (dd), 129.1 (dd), 138.9 (d), 159.5 (dd), 162.5 (dd); GC/MS t_R 14.19 min, *m*/*z* 200 (M^+, 2), 182 (1), 169 (100), 151 (17), 141 (26).

4.3. 4-(2,4-Difluorophenyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane

Compound **13** (23.0 g, 0.115 mol) was treated with dimethoxypropane (10 ml), in acetone solution (200 mL), in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate, to afford the corresponding acetonide derivative (24.0 g, 87%): δ_H (400 MHz; $CDCl_3$): 1.38 (3H, s, C*CH*$_3$), 1.55 (3H, s, C*CH*$_3$), 4.20 (1H, dd, *J* 1.2, 8.9 Hz, C*H*H), 4.35 (1H, dd, *J* 2.8, 8.9 Hz, CH*H*), 5.09 (1H, dd, *J* 0.6, 10.6 Hz, =C*H*H), 5.17 (1H, d, *J* 17.0 Hz, =CH*H*), 6.12 (1H, ddd *J* 1.2, 10.6, 17.0 Hz, C*H*=), 6.77 (1H, m, aromatic H), 6.86 (1H, m, aromatic H), 7.61 (1H, m, aromatic H); δ_C (100.61 MHz,

$CDCl_3$): 25.8, 26.7, 74.5 (d), 82.5 (d), 103.8 (t), 110.3, 111.0 (dd), 114.0, 126.9 (dd), 128.5 (dd), 139.9, 159.0 (dd), 162.7 (dd); GC/MS t_R 13.63 min, *m*/*z* 240 (M^+, 4), 225 (68), 210 (52), 182 (33), 165 (59), 151 (100).

4.4. 4-(2,4-Difluorophenyl)-2,2-dimethyl-4-(oxiran-2-yl)-1,3-dioxolane 14a and 4-(2,4-difluorophenyl)-2,2-dimethyl-4-(oxiran-2-yl)-1,3-dioxolane 14b

m-Chloroperbenzoic acid (20.5 g, 0.119 mol) was added at 0 °C to a solution of the acetonide derivative of compound **13** (23.8 g, 0.0991 mol) in methylene chloride (300 mL) under stirring. After 2 h at room temperature, the reaction mixture was poured into water, and extracted with methylene chloride. The organic phase was washed with a saturated sodium pyrosulfite solution, dried on sodium sulfate and concentrated under reduced pressure, to give a residue, which was chromatographed on a silica gel column, eluting with hexane and increasing amount of ethyl acetate. The main fraction (19.8 g, 78%) consisted of a 1.5:1 mixture of epoxide derivatives **14a** and **14b**. The following data were obtained for enriched samples of the two diastereoisomers.

*Data of **14a***: δ_H (400 MHz; $CDCl_3$): 1.34 (3H, s, CCH_3), 1.51 (3H, s, CCH_3), 2.60 (1H, dd, *J* 3.9, 5.4 Hz, OC*H*H oxirane ring), 2.74 (1H, dd, *J* 2.5, 5.7 Hz, OCH*H* oxirane ring), 3.24 (1H, m, C*H*O oxirane ring), 4.22 (1H, dd, *J* 1.7, 9.1 Hz, C*H*H), 4.56 (1H, dd, *J* 2.5, 9.1 Hz, CH*H*), 6.82 (1H, m, aromatic H), 6.89 (1H, m, aromatic H), 7.59 (m, 1H, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 25.8, 25.9, 43.5, 54.5 (d), 72.3 (d), 80.3 (d), 103.9 (t), 110.6, 111.3 (dd), 124.9 (dd), 129.2 (dd), 158.9 (dd), 162.7 (dd); GC/MS t_R 17.43 min, *m*/*z* 256 (M^+, 1), 241 (16), 213 (100), 181 (14), 155 (53).*Data of **14b***: δ_H (400 MHz; $CDCl_3$): 1.33 (3H, s, CCH_3), 1.56 (3H, s, CCH_3), 2.64 (1H, m, OC*H*H oxirane ring), 2.75 (1H, m, OCH*H* oxirane ring), 3.25 (m, 1H, CHO oxirane ring), 4.16 (1H, dd, *J* 1.7, 9.1 Hz, C*H*H), 4.41 (1H, dd, *J* 2.8, 9.1 Hz, CH*H*), 6.79 (1H, m, aromatic H), 6.89 (1H, m, aromatic H), 7.61 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 25.4, 26.4, 44.3 (d), 55.2, 71.1 (d), 81.2 (d), 103.9 (t), 110.3, 111.1 (dd), 124.4 (dd), 129.3 (dd), 159.0 (dd), 162.6 (dd); GC/MS t_R 17.79 min, *m*/*z* 256 (M^+, 1), 241 (17), 213 (100), 181 (15), 155 (66).

4.5. 1-(4-(2,4-Difluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 15a and 1-(4-(2,4-difluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 15b

The 1.5:1 mixture of epoxides **14a**–**14b** (19.7 g, 0.077 mol) was reduced with $LiAlH_4$ (1.46 g, 0.038 mol) in refluxing THF solution (200 mL). After the usual work-up, column chromatography eluting with hexane and with increasing amounts of ethyl acetate allowed the isolation of a fraction (13.9 g, 70%) consisting of a 3:1 mixture of derivatives **15a** and **15b**. The following data were obtained for the enriched samples of the two diastereoisomers.*Data of **15a***: δ_H (400 MHz; $CDCl_3$): 0.94 (3H, dd, *J* 1.1, 6.2 Hz, CHCH_3), 1.31 (3H, s, CCH_3), 1.57 (3H, s, CCH_3), 3.95 (1H, m, C*H*OH), 4.16 (1H, dd, *J* 2.2, 8.8 Hz, C*H*H), 4.58 (1H, dd, *J* 2.5, 9.1 Hz, CH*H*), 6.78 (1H, m, aromatic H), 6.88 (1H, m, aromatic H), 7.58 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 17.9, 25.2, 26.6, 70.5, 72.1 (d), 85.5 (d), 103.8 (t), 110.1, 111.1 (dd), 125.7 (dd), 130.1 (dd), 159.4 (dd), 162.3 (dd); GC/MS t_R 16.91 min, *m*/*z* 243 (M^+−15, 10), 213 (100), 183 (13), 155 (91), 141 (14).*Data of **15b***: δ_H (400 MHz; $CDCl_3$): 1.16 (3H, dd, *J* 1.1, 6.2 Hz, CHCH_3), 1.22 (3H, s, CCH_3), 1.55 (3H, s, CCH_3), 3.88 (1H, dq, *J* 1.1, 6.2 Hz, C*H*OH), 4.18 (1H, dd, *J* 1.9, 9.4 Hz, C*H*H), 4.42 (1H, dd, *J* 2.8, 9.4 Hz, CH*H*), 6.78 (1H, m, aromatic H), 6.87 (1H, m, aromatic H), 7.58 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 16.9, 24.8, 26.1, 70.4 (d), 71.7, 85.5 (d), 103.9 (t), 109.8, 110.9 (dd), 124.1 (dd), 129.1 (dd), 158.9 (dd), 162.3 (dd); GC/MS t_R 17.45 min, *m*/*z* 243 (M^+−15, 9), 213 (100), 183 (11), 155 (90), 141 (13).

4.6. (2*RS*,3*RS*)-2-(2,4-Difluorophenyl)butane-1,2,3-triol (2*RS*,3*RS*)-9a and (2*RS*,3*SR*)-2-(2,4-difluorophenyl)butane-1,2,3-triol (2*RS*,3*SR*)–9b

The 3:1 mixture of derivatives **15a** and **15b** (13.8 g, 0.053 mol) was dissolved in THF (100 mL), then a few drops of acetic acid and of HCl 37% were added. The mixture was heated at 40 °C for 3 h, then concentrated under reduced pressure, poured into a saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was chromatographed on silica gel. From the first eluted fraction, two crystallisations from hexane/ethyl ether 8:2 allowed the isolation of triol **9a** as a pure crystalline solid (4.62 g, 40%). From the last eluted fractions, diol **9b** (2.31 g, 20%) was recovered.*Data of **9a***: δ_H (400 MHz; acetone-d_6): 0.88 (3H, d, *J* 6.2 Hz, CH_3CH), 3.81 (1H, d, *J* 11.1 Hz, C*H*H), 4.11 (1H, dd, *J* 1.7, 11.1 Hz, CH*H*), 4.33 (1H, m, C*H*OH), 6.91 (1H, m, aromatic H), 6.98 (1H, m, aromatic H), 7.78 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 19.2, 69.6 (d), 71.7 (d), 79.5 (d), 105.4 (m), 112.6 (m), 128.0 (d), 132.6 (m), 161.1 (dd), 163.9 (dd).*Data of **9b***: δ_H (400 MHz; $CDCl_3$): 1.12 (3H, d, *J* 6.4 Hz, CH_3CH), 3.94 (1H, d, *J* 11.4, *CH*H), 4.01 (1H, q, *J* 6.4 Hz, C*H*CH_3), 4.06 (1H, dd, *J* = 2.2, 11.4 Hz, CH*H*), 6.7586 (1H, m, aromatic H), 6.86 (1H, m, aromatic H), 7.56 (1H, m, aromatic H); ^{13}C NMR (100.61 MHz,$CDCl_3$): 17.0, 64.4 (d), 71.9 (d), 78.5 (d), 104.1 (dd), 111.1 (dd), 124.5 (dd), 130.6 (dd), 159.3 (dd), 162.4 (dd).

4.7. (2*R*,3*R*)-2-(2,4-Difluorophenyl)-2-hydroxybutane-1,3-diyl diacetate (−)-24a

From triol **9a** (4.5 g, 0.0206 mol) with lipase PS after 96 h, diacetate (−)-**24a** was recovered (1.92 g, 31%): $[\alpha]_D = -22.6$ (*c* 0.93, $CHCl_3$); ee = 99% (HPLC on a chiral column, t_R = 16.3 min); δ_H (400 MHz; $CDCl_3$): 1.04 (3H, d, *J* 6.4 Hz, CH_3CH), 1.93 (3H, s, COCH_3), 2.12 (3H, s, COCH_3), 4.47 (1H, dd, *J* = 1.2, 11.5 Hz, C*H*H), 4.56 (1H, dd, *J* 1.2, 11.8 Hz, CH*H*), 5.47 (1H, dq, *J* 1.6, 6.4 Hz, *CH*OAc), 6.80 (1H, m, aromatic H), 6.91 (1H, m, aromatic H), 7.69 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 14.4, 20.4, 21.0, 67.9 (d), 72.4 (d), 77.05, 104.0 (t), 111.3 (dd), 122.9 (dd), 130.2 (dd), 159.0 (dd), 162.8 (dd), 169.9, 171.6; GC/MS t_R 20.61 min, *m*/*z* 242 (M^+−60, 1), 229 (40), 215 (71), 187 (45), 173 (100).

4.8. (2*R*,3*R*)-2-(2,4-Difluorophenyl)butane-1,2,3-triol (+)-9a

Saponification of diacetate (−)-**24a** (1.85 g, 6.13 mmol) with KOH (0.411 g, 7.35 mmol) in methanol (20 mL) gave (+)-**9a** (1.19 g, 89%): $[\alpha]_D$ = +5.74 (*c* 0.88, acetone), lit. Ref. 11a $[\alpha]_D$ = +11.4 (*c* 1.11, $CHCl_3$); ^1H and ^{13}C NMR spectra were in accordance with those of the racemic compound.

4.9. (2*R*,3*R*)-2-(2,4-Difluorophenyl)-2-hydroxybutane-1,3-diyl dimethanesulfonate

Triol **9a** (1.10 g, 5.04 mmol) was dissolved in pyridine (10 mL) and mesyl chloride (12.1 mmol, 1.29 g) was added at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was poured into water, and extracted with ethyl acetate. The organic phase was washed with HCl 1%, and dried over Na_2SO_4, to afford a residue (1.71 g, 91%), which was submitted without any further purification to the following reaction step: δ_H (400 MHz; $CDCl_3$): 1.26 (3H, d, *J* 6.4 Hz, CHCH_3), 2.97 (3H, s, SO_2CH_3), 3.11 (3H, s, SO_2CH_3), 4.65 (1H, d, *J* 11 Hz, CH*H*OMs), 4.70 (1H, d, *J* 11 Hz, C*H*HOMs), 5.26 (1H, q, *J* 6.4 Hz, *CH*OMs), 6.82 (1H, m, aromatic H), 6.94 (1H, m, aromatic H), 7.75 (1H, m, aromatic H). GC/MS t_R 20.61 min, *m*/*z* 278 (M^+−96, 3), 251 (36), 169 (32), 155 (42), 141 (100).

4.10. 1-(((2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methyloxiran-2-yl)-methyl)-1*H*-1,2,4-triazole (2*R*,3*S*)–6

A solution of triazole (2.03 g, 29.4 mmol) in DMF (5 mL) was dropped into a suspension of sodium hydride (60% dispersion in mineral oil, 1.03 g, 25.7 mmol) in DMF (20 mL) at 0 °C. When hydrogen evolution was ceased, a solution of the dimesyl derivative of triol (+)-**9a** (1.60 g, 7.34 mmol) in DMF (5 mL) was added. The reaction mixture was stirred at 70 °C for 2 h, then cooled and poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford a residue, which was purified by column chromatography to afford oxirane (−)-**6** (0.719 g, 67%): $[\alpha]_D = -12.2$ (*c* 0.96, $CHCl_3$), lit. Ref. 11a $[\alpha]_D = -7.55$ (*c* 1.06, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 1.64 (3H, d, *J* 5.4 Hz, $CHCH_3$), 3.19 (1H, q, *J* 5.4 Hz, *CH*O oxirane ring), 4.44 (1H, d, *J* 14.7 Hz, *CH*H), 4.87 (1H, d, *J* 14.4 Hz, CH*H*), 6.68–6.81 (2H, m, aromatic H), 7.02 (1H, m, aromatic H), 7.80 (1H, s, triazole H), 7.96 (1H, s, triazole H); δ_C (100.61 MHz, $CDCl_3$): 13.9, 51.6, 59.7, 60.4, 103.8 (t), 111.6 (dd), 121.0 (dd), 129.4 (dd), 143.6, 151.9, 162.7 (dd), 163.2 (dd); GC/MS t_R 20.59 min, *m*/*z* 236 (M^+−15, 6), 220 (1), 206 (1), 153 (12), 141 (40), 96 (100).

4.11. (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(methylthio)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol

A solution of compound (−)-**6** (0.600 g, 2.39 mmol) in DMSO (5 mL) was added to a solution of sodium thiomethylate (0.250 g, 3.58 mmol) in DMSO (5 mL). After stirring at 25 °C for 2 h, the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford a residue which was purified by column chromatography to afford the title compound (0.493 g, 69%): $[\alpha]_D = -125.2$ (*c* 0.87, MeOH), lit. Ref. 17 $[\alpha]_D = -126.7$ (*c* 0.5, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 1.16 (3H, d, *J* 7.1 Hz, $CHCH_3$), 2.26 (3H, s, SCH_3), 3.21 (1H, q, *J* 7.1 Hz, *CH*SCH_3), 4.87 (1H, d, *J* 14.1 Hz, *CH*H-triazole), 5.06 (1H, d, *J* 14.1 Hz, CH*H*-triazole), 6.69–6.77 (2H, m, aromatic H), 7.37 (1H, m, aromatic H), 7.76 (1H, s, triazole H), 7.81 (1H, s, triazole H); δ_C (100.61 MHz, $CDCl_3$): 14.3, 16.2, 47.5 (d), 56.7 (d), 79.3 (d), 103.9 (dd), 111.5 (dd), 124.3 (dd), 130.5 (dd), 143.8, 151.8, 157.8 (dd), 162.7 (dd); GC/MS t_R 23.91 min, *m*/*z* 234 (M^+−65, 3), 224 (100), 155 (3), 141 (15), 127 (17).

4.12. (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(methylsulfonyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

m-Chloroperbenzoic acid (0.575 g, 3.34 mmol) was added at 0 °C to a solution of the (−)-methylthioderivative (0.400 g, 1.34 mmol) in CH_2Cl_2 (10 mL). After stirring at room temperature for 2 h, the reaction mixture was poured into a saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford (−)-**1** (0.256 g, 58%); $[\alpha]_D = -36.9$ (*c* 0.98, MeOH); lit. Ref. 17 $[\alpha]_D = -38.5$ (*c* 1, MeOH); δ_H (400 MHz; $CDCl_3$): 1.27 (3H, d, *J* 7.3 Hz, $CHCH_3$), 3.11 (3H, s, SO_2CH_3), 3.61 (1H, q, *J* 7.3 Hz, CH), 5.01 (1H, d, *J* 14.4 Hz, *CH*H), 5.43 (1H, d, *J* 14.4 Hz, CH*H*), 6.71–6.82 (2H, m, aromatic H), 7.29 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 12.5, 40.1, 55.7 (d), 64.7, 76.7, 104.3 (t), 111.9 (dd), 123.1 (dd), 129.6 (dd), 143.9, 151.5, 157.6 (dd), 163.1 (dd); GC/MS t_R 26.20 min, *m*/*z* 331 (M^+, 1), 252 (27), 249 (44), 224 (14), 141 (67), 83 (100).

4.13. 2-Oxo-2-phenylethyl acetate[18]

This was prepared (20.5 g, 69%) from acetophenone (20.0 g, 0.167 mol) according to the same procedure described for obtaining compound **12** from 2,4-difluoroacetophenone: δ_H (400 MHz; $CDCl_3$): 2.22 (3H, s, $COCH_3$), 5.32 (s, 2H), 7.49 (2H, m, aromatic H), 7.61 (1H, m, aromatic H), 7.92 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 20.8, 66.3, 128.0, 129.21, 134.1, 134.54, 170.6, 192.1.

4.14. 2-(4-Fluorophenyl)-2-oxoethyl acetate[19]

This was prepared (16.8 g, 59%) from 4-fluoroacetophenone (20.0 g, 0.145 mol) according to the same procedure described for obtaining compound **12** from 2,4-difluoroacetophenone: δ_H (400 MHz; $CDCl_3$): 2.21 (3H, s, $COCH_3$), 5.29 (2H, s, CH_2OAc), 7.15 (2H, m, aromatic H), 7.94 (2H, m, aromatic H); GC/MS t_R 16.30 min, *m*/*z* 196 (M^+, 1), 154 (1), 136 (2), 123 (100), 95 (18).

4.15. 2-Phenylbut-3-ene-1,2-diol 16[20]

This was prepared (13.8 g, 74%) from 2-oxo-2-phenylethyl acetate (20.3 g, 0.114 mol), according to the same procedure described for obtaining compound **13** from **12**; δ_H (400 MHz; $CDCl_3$): 3.71 (2H, s, CH_2OH), 5.22 (1H, d, *J* 10.8 Hz, =*CH*H), 5.32 (1H, d, *J* 17.1 Hz, =CH*H*), 6.09 (1H, dd, *J* 10.8, 17.1 Hz, C*H*=), 7.23 (1H, m, aromatic H), 7.31 (2H, m, aromatic H), 7.41 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 69.2, 77.3, 115.3, 125.6, 127.2, 128.2, 140.5, 142.4; GC/MS t_R 15.38 min, *m*/*z* 164 (M^+, 1), 133 (100), 115 (8).

4.16. 2-(4-Fluorophenyl)but-3-ene-1,2-diol

This was prepared (11.6 g, 75%) from 2-(4-fluorophenyl)-2-oxoethyl acetate (16.7 g, 0.0852 mol), according to the same procedure described for obtaining compound **13** from **12**: δ_H (400 MHz; $CDCl_3$): 3.75 (2H, s, CH_2OH), 5.29 (1H, d, *J* 10.8 Hz, =*CH*H), 5.36 (1H, d, *J* 17.4 Hz, =CH*H*), 6.12 (1H, dd, *J* 10.8, 17.4 Hz, C*H*=), 7.03 (2H, m, aromatic H), 7.42 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 69.3, 77.0, 115.2 (d), 115.7, 127.5 (d), 138.2 (d), 140.5, 162.2 (d); GC/MS t_R 15.54 min, *m*/*z* 182 (M^+, 2), 164 (1), 151 (100), 133 (16).

4.17. 2,2-Dimethyl-4-phenyl-4-vinyl-1,3-dioxolane

This was prepared (14.5 g, 85%) from **16** (13.7 g, 0.0835 mol) according to the same procedure described for obtaining 4-(2,4-difluorophenyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane from **13**; δ_H (400 MHz; $CDCl_3$): 1.41 (3H, s, CCH_3), 1.54 (3H, s, CCH_3), 4.16 (1H, d, *J* 8.5 Hz, *CH*H), 4.26 (1H, d, *J* 8.5 Hz, CH*H*), 5.15 (1H, dd, *J* 1.1, 10.8 Hz, =*CH*H), 5.21 (1H, dd, *J* 10.5, 17.1 Hz, =CH*H*), 6.11 (1H, dd, *J* 1.1, 17.1 Hz, CH=), 7.21–7.41 (m, 5H, Ar); GC/MS t_R 14.86 min, *m*/*z* 204 (M^+, 4), 189 (12), 146 (50), 129 (100).

4.18. 4-(4-Fluorophenyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane

This was prepared (11.4 g, 81%) from 2-(4-fluorophenyl)but-3-ene-1,2-diol (16.5 g, 0.0632 mol) according to the same procedure described for obtaining 4-(2,4-difluorophenyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane from **13**: δ_H (400 MHz; $CDCl_3$): 1.40 (3H, s, CCH_3), 1.52 (3H, s, CCH_3), 4.13 (1H, d, *J* 8.5 Hz, *CH*H), 4.24 (1H, d, *J* 8.5 Hz, CH*H*), 5.16 (1H, d, *J* 10.8 Hz, =*CH*H), 5.18 (1H, d, *J* 17.1 Hz, =CH*H*), 6.08 (1H, dd, *J* = 10.8, 17.1 Hz, C*H*=), 7.01 (2H, m, aromatic H), 7.35 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 26.3, 26.7, 74.4, 84.4, 110.6, 114.5, 114.9 (d), 127.3 (d), 138.9 (d), 141.4, 161.9; GC/MS t_R 14.73 min, *m*/*z* 222 (M^+, 4), 207 (12), 192 (13), 164 (51), 147(95), 72 (100).

4.19. (*RS*)-2,2-Dimethyl-4-((*RS*)-oxiran-2-yl)-4-phenyl-1,3-dioxolane and (*RS*)-2,2-dimethyl-4-((*SR*)-oxiran-2-yl)-4-phenyl-1,3-dioxolane

These compounds were prepared (10.7 g, 70%) from 2,2-dimethyl-4-phenyl-4-vinyl-1,3-dioxolane (14.3 g, 0.0701 mol)

according to the same procedure described for obtaining **14a** and **14b** from 4-(2,4-difluorophenyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane. The following spectral data were obtained for enriched samples of the two diastereoisomers:*Data of the first eluted diastereoisomer*: δ_H (400 MHz; $CDCl_3$): 1.37 (3H, s, CCH_3), 1.51 (3H, s, CCH_3), 2.69 (1H, dd, *J* 3.9, 5.4 Hz, *CH*O oxirane ring), 2.86 (1H, dd, *J* 2.5, 5.4 Hz, OC*H*H oxirane ring), 3.12 (1H, dd, *J* 2.5, 3.9 Hz, OCH*H* oxirane ring), 4.04 (1H, d, *J* 8.8 Hz, *CH*H), 4.32 (1H, d, *J* 8.8 Hz, CH*H*), 7.25–7.40 (5H, m, aromatic H); GC/MS t_R 18.49 min, *m*/*z* 220 (M^+, 1), 205 (17), 177 (100), 119 (62).*Data of the second eluted diastereoisomer*: δ_H (400 MHz; $CDCl_3$): 1.37 (3H, s, CCH_3), 1.58 (3H, s, CCH_3), 2.37 (1H, dd, *J* 2.5, 4.8 Hz, OC*H*H oxirane ring), 2.73 (1H, dd, *J* 3.9, 4.8 Hz, *CH*O oxirane ring), 3.25 (1H, dd, *J* 2.5, 3.9 Hz, OCH*H* oxirane ring), 4.08 (1H, d, *J* 8.5 Hz, C*H*H), 4.33 (1H, d, *J* = 8.5 Hz, CH*H*), 7.24–7.40 (5H, m, aromatic H); GC/MS t_R 18.55 min, *m*/*z* 220 (M^+, 1), 205 (18), 177 (100), 119 (65).

4.20. (*RS*)-4-(4-Fluorophenyl)-2,2-dimethyl-4-((*RS*)-oxiran-2-yl)-1,3-dioxolane and (*RS*)-4-(4-fluorophenyl)-2,2-dimethyl-4-((*SR*)-oxiran-2-yl)-1,3-dioxolane

These compounds were prepared (8.84 g, 73%) from 4-(4-fluorophenyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane (11.3 g, 0.0509 mol) according to the same procedure described for obtaining **14a** and **14b** from 4-(2,4-difluorophenyl)-2,2-dimethyl-4-vinyl-1,3-dioxolane. The following spectral data were obtained for enriched samples of the two diastereoisomers:*Data of the first eluted diastereoisomer*: δ_H (400 MHz; $CDCl_3$): 1.36 (3H, s, CCH_3), 1.50 (s, 3H, CCH_3), 2.71 (1H, dd, O*CH* oxirane ring), 2.83 (1H, dd, *J* 2.5, 5.4 Hz, OCH*H* oxirane ring), 3.08 (1H, dd, *J* 2.8, 3.8 Hz, OCH*H* oxirane ring), 3.98 (1H, d, *J* 8.9 Hz, *CH*H), 4.27 (1H, d, *J* 8.9 Hz, CH*H*), 7.04 (2H, m, aromatic H), 7.41 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 26.0, 26.7, 44.2, 55.2, 71.0, 82.2, 110.8, 115.2 (d), 127.0 (d), 138.0 (d), 162.5; GC/MS t_R 18.32 min, *m*/*z* 238 (M^+, 1), 223 (11), 195 (100), 163 (11), 137 (61).*Data of the last eluted diastereoisomer*: δ_H (400 MHz; $CDCl_3$): 1.36 (3H, s, CCH_3), 1.57 (3H, s, CCH_3), 2.30 (1H, dd, *J* 2.5, 4.7 Hz, OC*H*H oxirane ring), 2.72 (1H, dd, *J* 3.8, 4.7 Hz, O*CH* oxirane ring), 3.22 (1H, dd, *J* 2.5, 3.8 Hz, OCH*H* oxirane ring), 4.05 (1H, d, *J* 8.5 Hz, *CH*H), 4.34 (1H, d, *J* 8.5 Hz, CH*H*), 7.02 (2H, m, aromatic H), 7.33 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 25.8, 26.7, 44.4, 55.6, 72.2, 82.9, 110.7, 114.9 (d), 127.4 (d), 136.2 (d), 162.5; GC/MS t_R 18.34 min, *m*/*z* 238 (M^+, 1), 223 (11), 195 (100), 163 (11), 137 (57).

4.21. (*RS*)-1-((*RS*)-2,2-Dimethyl-4-phenyl-1,3-dioxolan-4-yl)-ethanol 17a and (*RS*)-1-((*SR*)-2,2-dimethyl-4-phenyl-1,3-dioxolan-4-yl)ethanol 17b

These compounds were prepared (4.11 g, 68%) from (*RS*)-2,2-dimethyl-4-((*RS*)-oxiran-2-yl)-4-phenyl-1,3-dioxolane and (*RS*)-2,2-dimethyl-4-((*SR*)-oxiran-2-yl)-4-phenyl-1,3-dioxolane (6.0 g, 0.0273 mol) according to the same procedure described for obtaining **15a** and **15b** from **14a** and **14b**. The following spectral data were obtained for enriched samples of the two diastereoisomers.*Data of the first eluted diastereoisomer*: δ_H (400 MHz, $CDCl_3$): 0.95 (3H, d, *J* 6.5 Hz, CHCH_3), 1.30 (3H, s, CCH_3), 1.57 (3H, s, CCH_3), 3.84 (1H, m, C*H*OH), 4.15 (1H, d, *J* 8.2 Hz, C*H*H), 4.50 (1H, d, *J* 8.2 Hz, CH*H*), 7.22–7.42 (5H, m, aromatic H).*Data of the last eluted diastereoisomer*: δ_H (400 MHz, $CDCl_3$): 1.04 (3H, d, *J* 6.2 Hz, CHCH_3), 1.21 (3H, s, CCH_3), 1.52 (3H, s, CCH_3), 3.86 (1H, m, C*H*OH), 4.26 (1H, d, *J* 8.5 Hz, C*H*H), 4.43 (1H, d, *J* 8.5 Hz, CH*H*), 7.25–7.42 (5H, m, aromatic H).

4.22. (*RS*)-1-((*RS*)-4-(4-Fluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 20a and (*RS*)-1-((*SR*)-4-(4-fluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 20b

These compounds were prepared (4.48 g, 74%) from (*RS*)-4-(4-fluorophenyl)-2,2-dimethyl-4-((*RS*)-oxiran-2-yl)-1,3-dioxolane and (*RS*)-4-(4-fluorophenyl)-2,2-dimethyl-4-((*SR*)-oxiran-2-yl)-1,3-dioxolane (6.0 g, 0.0252 mol) according to the same procedure described for obtaining **15a** and **15b** from **14a** and **14b**. The following spectral data were obtained for enriched samples of the two diastereoisomers.*Data of the first eluted diastereoisomer*: δ_H (400 MHz; $CDCl_3$): 1.01 (3H, d, *J* 6.4 Hz, CHCH_3), 1.21 (3H, s, CCH_3), 1.51 (3H, s, CCH_3), 3.84 (1H, m, C*H*OH), 4.20 (1H, d, *J* 8.6 Hz, C*H*H), 4.42 (1H, d, *J* 8.6 Hz, CH*H*), 7.03 (2H, m, aromatic H), 7.37 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 17.2, 25.9, 26.7, 70.1, 71.9, 86.9, 110.1, 114.8 (d), 128.1 (d), 137.6 (d), 162.2 (d); GC/MS t_R 17.97 min, *m*/*z* 225 (M^+−15, 4), 195 (95), 137 (100), 109 (100).*Data of the last eluted diastereoisomer*: δ_H (400 MHz; $CDCl_3$): 0.95 (3H, d, *J* 6.4 Hz, CHCH_3), 1.29 (3H, s, CCH_3), 1.55 (3H,s, CCH_3), 3.81 (m, 1H, C*H*OH), 4.12 (1H, d, *J* 8.0 Hz, C*H*H), 4.47 (1H, d, *J* 8.0 Hz, CH*H*), 7.02 (2H, m, aromatic H), 7.28 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 17.8, 25.6, 26.7, 72.2, 72.3, 86.8, 110.3, 114.7 (d), 127.3 (d), 138.6 (d), 162.2 (d); GC/MS t_R 18.13 min, *m*/*z* 225 (M^+−15, 6), 195 (100), 137 (94), 109 (95).

4.23. General procedure for lipase-mediated acetylations

In a typical experiment, a solution of the suitable alcohol derivative (1.0 g) in vinyl acetate/*tert*-butyl methyl ether (1:2, 15 mL), was stirred with the chosen lipase (1.0 g) at room temperature. The filtered solution was concentrated, and the residue was chromatographed with increasing amounts of ethyl acetate in hexane. Under these conditions, the following results were obtained.

4.24. (−)-(*S*)-2-Hydroxy-2-phenylbut-3-enyl acetate (−)-18

From racemic **16** (20.0 g, mol), with Lipase PS after 24 h, (−)-**18** (10.3 g, 41%) was obtained: $[\alpha]_D$ = −6.0 (*c* 2.5, EtOH); δ_H (400 MHz; $CDCl_3$): 4.30 (1H, d, *J* 11.4 Hz, C*H*HOAc), 4.42 (1H, d, *J* 11.4 Hz, C*H*HOAc), 5.25 (1H, dd, *J* 0.8, 10.7 Hz, =C*H*H), 5.38 (1H, d, *J* 0.8, 17.3 Hz, =CH*H*), 6.14 (1H, dd, *J* 10.7, 17.3 Hz, C*H*=), 7.27 (1H, m, aromatic H), 7.34 (2H, m, aromatic H), 7.46 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 20.7, 70.0, 76.1, 115.1, 125.5, 127.5, 128.3, 140.2, 141.9, 170.9; GC/MS t_R 17.68 min, *m*/*z* 146 (M^+−60, 22), 133 (100), 115 (10).

Saponification of (−)-**18** ($[\alpha]_D$ = −6.0 (*c* 2.5, EtOH)) with KOH in MeOH gave (−)-(*S*)-**16:** $[\alpha]_D$ = −7.1 (*c* 1.1, EtOH), ee = 15%, lit. Ref. 20 $[\alpha]_D$ = +47.3 (*c* 1.2, EtOH) for (*R*)-**16** and Ref. 21 $[\alpha]_D$ = −43.4 (*c* 0.20, EtOH) for (*S*)-**16**; spectral data were in accordance with those of the racemic compound.

4.25. (+)-(*R*)-1-((*S*)-4-(2,4-Difluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate (+)-22b

From a 1:1 mixture of alcohols **15a** and **15b** (5.0 g, 0.019 mol), with Lipase PS after 48 h, (+)-**22b** (0.46 g, 8%) was obtained: $[\alpha]_D$ = +54.3 (*c* 0.6, $CHCl_3$); ee = 99%, de = 99% (GC on a chiral column); δ_H (400 MHz; $CDCl_3$): 1.22 (3H, d, *J* 6.54 Hz, CHCH_3), 1.24 (3H, s, CCH_3), 1.58 (3H, s, CCH_3), 1.84 (3H, s, COCH_3), 4.16 (dd, 1H, *J* 1.2, 9.6 Hz, C*H*H), 4.39 (1H, dd, *J* 3.2, 9.6 Hz, CH*H*), 5.22 (1H, q, *J* = 6.51 Hz, *CH*OAc), 6.77 (1H, m, aromatic H), 6.86 (1H, m, aromatic H), 7.58 (1H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 14.3, 20.8, 24.9, 26.3, 71.8 (d), 72.8, 83.7 (d), 103.8 (t), 110.5 (dd), 110.6 (d), 125.1 (dd), 130.0 (dd), 158.9 (dd), 162.7 (dd), 170.5;

GC/MS t_R 19.22 min, *m*/*z* 285 (M^+−15, 11), 213 (100), 183 (33), 155 (89), 141 (11).

4.26. (+)-1-(2,2-Dimethyl-4-phenyl-1,3-dioxolan-4-yl)ethyl acetate (+)-19b

From a 1:1 mixture of alcohols **17a** and **17b** (5.0 g, 0.022 mol), with lipase PS after 48 h, (+)-**19b** (1.12 g, 19%) was obtained: $[\alpha]_D$ = +34.4 (*c* 1.20, $CHCl_3$); ee = 99%, de = 91% (GC on a chiral column); δ_H (400 MHz, $CDCl_3$): 1.12 (3H, d, *J* 6.2 Hz, CHC*H*$_3$), 1.27 (3H, s, C*CH*$_3$), 1.54 (3H, s, C*CH*$_3$), 1.93 (3H, s, OAc), 4.17 (1H, d, *J* 8.8 Hz, C*H*H), 4.31 (1H, d, *J* 8.8 Hz, CH*H*), 5.12 (1H, q, *J* 6.2 Hz, *CH*OAc), 7.23–7.41 (5H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 14.8, 20.9, 25.6, 26.6, 71.9, 73.9, 85.4, 110.6, 126.2, 127.2, 127.7, 141.7, 169.7.

4.27. (+)-1-(4-(4-Fluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate (+)-21b

From a 1:1 mixture of alcohols **20a** and **20b** (5.0 g, 0.021 mol), with lipase PS after 48 h, (+)-**21b** (2.05 g, 35%) was obtained: $[\alpha]_D$ = +29.7 (*c* 1.16, $CHCl_3$); ee = 99%, de = 87% (GC on a chiral column); δ_H (400 MHz; $CDCl_3$): 1.10 (3H, d, *J* 6.1 Hz, CHC*H*$_3$), 1.27 (3H, s, C*CH*$_3$), 1.53 (3H, s, C*CH*$_3$), 1.96 (3H, s, CO*CH*$_3$), 4.13 (1H, d, *J* 8.6 Hz, C*H*H), 4.29 (1H, d, *J* 8.6 Hz, CH*H*), 5.08 (1H, q, *J* 6.1 Hz, *CH*OAc), 7.02 (2H, m, aromatic H), 7.36 (2H, m, aromatic H); δ_C (100.61 MHz, $CDCl_3$): 14.8, 20.9, 25.7, 26.6, 72.2, 73.9, 85.1, 110.8, 114.6 (d), 127.9 (d), 137.5 (d), 162.0 (d), 169.8; GC/MS t_R 19.87 min, *m*/*z* 267 (M^+−15, 6), 195 (100), 165 (28), 137 (91), 109 (71).

4.28. Determination of the absolute configuration of acetate (+)-22b

4.28.1. (+)-1-(4-(2,4-Difluorophenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (+)-15b

A sample of acetate (+)-**22b** (0.200 g, 0.67 mmol) was treated with KOH (0.056 g, 1.1 mmol) in MeOH (10 mL), to afford, after the usual work-up, alcohol (+)-**15b** (0.140 g, 81%): $[\alpha]_D$ = +1.08 (*c* 6.1, $CHCl_3$). Spectroscopic and GC/MS data were in accordance with those of racemic **15b**.

4.29. (2*S*,3*S*)-2-(2,4-Difluorophenyl)-2-hydroxybutane-1,3-diyl diacetate (+)-(2*S*,3*S*)-24

Alcohol (+)-**15b** (0.120 g, 0.46 mmol) was submitted to a Mitsunobu esterification with 3,5-dinitrobenzoic acid (0.475 g, 2.24 mmol) in THF (10 mL), in the presence of diisopropylazodicarboxylate (0.452 g, 2.24 mmol) and triphenylphosphine (0.586 g, 2.24 mmol). The nitro ester **23** was thus recovered (0.101 g, 49%), after column chromatography eluting with hexane/ethyl acetate 97/3: δ_H (400 MHz; $CDCl_3$): 1.25–1.30 (9H, m, CHC*H*$_3$ + 2CC*H*$_3$), 4.14 (1H, dd, *J* 8.6, 1.6 Hz, C*H*H), 4.53 (1H, dd, *J* 8.6, 3.8 Hz, CH*H*), 5.45 (1H, m, *CH*OAr), 6.84 (1H, m, aromatic H), 6.98 (1H, m, aromatic H), 7.70 (1H, m, aromatic H), 9.23 (1H, t, *J* 1.9 Hz, aromatic H), 9.28 (2H, d, *J* 1.9 Hz, aromatic H); GC/MS t_R 29.92 min, *m*/*z* 437 (M^+−15, 5), 213 (100), 155 (56), 127 (44). Compound **23** was treated first with KOH (0.019 g, 0.34 mmol) in MeOH (10 mL), then with acetic anhydride (2 mL) in pyridine (2 mL). The usual work afforded compound (+)-(2*S*,3*S*)-**24** (0.031 g, 46%): $[\alpha]_D$ = +20.7 (*c* 0.75, $CHCl_3$); ee = 99% (HPLC on a chiral column, t_R = 20.8 min); NMR and GC/MS data were in accordance with those of the enantiomer.

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References

1. Richardson, K. GB 2099818, 1982.; Richardson, K. U.S. 4404216, 1983.
2. Ray, S. J.; Richardson, K. EP 440372, 1991.; Ray, S. J.; Richardson, K. U.S. 5278175, 1994.
3. Saksena, A. K.; Girijavallabhan, V.; Lovey, R. G.; Pike, R. E.; Wang, H.; Liu, Y.; Ganguly, A. K.; Bennett, F. WO 9517407, 1995.; Saksena, A. K.; Girijavallabhan, V.; Lovey, R. G.; Pike, R. E.; Wang, H.; Liu, Y.; Ganguly, A. K.; Bennett, F. U.S. 566115, 1997.
4. Pasqualotto, A. C.; Denning, D. W. *J. Antimicrob. Chemother.* **2008**, *61*, i19–i30.
5. Ohashi, N.; Miyauchi, H.; Shimago, K. EP 405502, 1991.; Fujimoto, K.; Shimako, K.; Ohashi, N. JP 5230039, 1993.
6. Naito, T.; Hata, K.; Kaku, Y.; Akihiko, A.; Tsukada, I.; Yanagisawa, M.; Toyosawa, T.; Nara, K. EP 667346, 1995.; Naito, T.; Hata, K.; Kaku, Y.; Akihiko, A.; Tsukada, I.; Yanagisawa, M.; Toyosawa, T.; Nara, K. U.S. 5648372, 1997.; Tsuruoka, A.; Kaku, Y.; Kakinuma, H.; Tsukada, I.; Yanagisawa, M.; Nara, K.; Naito, T. *Chem. Pharm. Bull.* **1998**, *46*, 623–630; Tsuruoka, A.; Kaku, Y.; Kakinuma, H.; Tsukada, I.; Yanagisawa, M.; Nara, K.; Naito, T. *Chem. Pharm. Bull.* **1998**, *46*, 1125–1129.
7. Uchida, T.; Somada, A.; Kagoshima, Y.; Konosu, T.; Oida, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6538–6541.
8. Uchida, T.; Kagoshima, Y.; Konosu, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2013–2017.
9. Tasaka, A.; Tamura, N.; Matsushita, Y.; Teranishi, K.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **1993**, *41*, 1035–1042.
10. Park, J. S.; Yu, K. A.; Kang, T. H.; Kim, S.; Suh, Y.-G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3486–3490.
11. (a) Konosu, T.; Miyaoka, T.; Tajima, Y.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2241–2246; (b) Konosu, T.; Miyaoka, T.; Tajima, Y.; Oida, S. *Chem. Pharm. Bull.* **1992**, *40*, 562–564.
12. Gala, D.; Di Benedetto, D. J.; Mergelsberg, I.; Kugelman, M. *Tetrahedron Lett.* **1996**, *37*, 8117–8120.
13. Gala, D.; Di Benedetto, D. J.; Clark, J. E.; Murphy, B. L.; Schumacher, D. P.; Steinman, M. *Tetrahedron Lett.* **1996**, *37*, 611–614.
14. Konosu, T.; Tajima, Y.; Takeda, N.; Miyaoka, T.; Kasahara, M.; Yasuda, H.; Oida, S. *Chem. Pharm. Bull.* **1990**, *38*, 2476–2486.
15. Bennett, F.; Ganguly, A. K.; Girijaavallabhan, V. M.; Pinto, P. A. *Synlett* **1995**, 1110–1111.
16. The absolute configurations depicted in Scheme 5 for (+)-**19b** and (+)-**21b** were attributed by analogy to that of (+)-**22b** which was established by chemical correlation (see text).
17. Miyauchi, H.; Ohashi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3591–3598.
18. Sabot, C.; Kumar, K. A.; Antheaume, C.; Mioskowski, C. *J. Org. Chem.* **2007**, *72*, 5001–5004.
19. Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244–12245.
20. Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron* **1995**, *51*, 4043–4056.
21. Vargas-Díaz, M. E.; Chacón-García, L.; Velázquez, P.; Tamariz, J.; Joseph-Nathan, P.; Zepeda, L. G. *Tetrahedron: Asymmetry* **2003**, *14*, 3225–3232.