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An efficient enantioselective synthesis of (*R,R*)-formoterol, a potent bronchodilator, using lipases

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Abstract

The potent β_2-adrenergic receptor agonist formoterol (*R,R*)-**1** has been obtained in enantiomerically pure form by a convenient chemoenzymatic approach by coupling of epoxide (*R*)-**6** with the unprotected primary amine (*R*)-**9**. Both chiral precursors have been prepared by enantiodifferentiation processes involving *Pseudomonas cepacia* (lipase PS) and *Candida antarctica* lipase (CALB), respectively. For the resolution of amine **9**, we have found that utilization of triethylamine as non-reactive base enhances the reaction rate and the enantioselectivity of the process. The key coupling reaction of (*R*)-**6** and (*R*)-**9** has been conducted through derivatization of the amine with the labile trimethylsilyl group, which liberates the amino group of the resulting amino alcohol (*R,R*)-**11** upon column chromatography purification. In this way, the overall approach is shorter than others previously described.

1. Introduction

It is well known that β_2-adrenergic receptor agonists are efficient bronchodilators in the therapy of asthma and chronic bronchitis. A variety of β_2-adrenoceptor agonists are currently available, although some of them are not selective and produce important side effects, such as isoproterenol (A),[1] or display a short effect (seldom over 4–6 h), such as salbutamol (B) and terbutaline (C).[2] Formoterol (*R,R*)-**1** (Fig. 1) is a new, long-lasting, β_2-adrenoceptor agonist which offers high selectivity for β_2-adrenoceptors, a fast onset of action and an excellent safety and tolerance profile.[3] These compounds and other receptor agonists have in common a substituted arylethanolamine functionality, an important feature in the structure of β_3-adrenoceptor agents which are being assayed in clinical trials for the treatment of obesity.[4,5] Formoterol **1** is commercialized in the racemic form, but the different stereoisomers, corresponding to the two stereogenic centers of the molecule, have different pharmacological potencies, the order being *R,R* > *R,S* > > *S,R* > *S,S*.[6] In spite of its interesting properties, very few syntheses of the most

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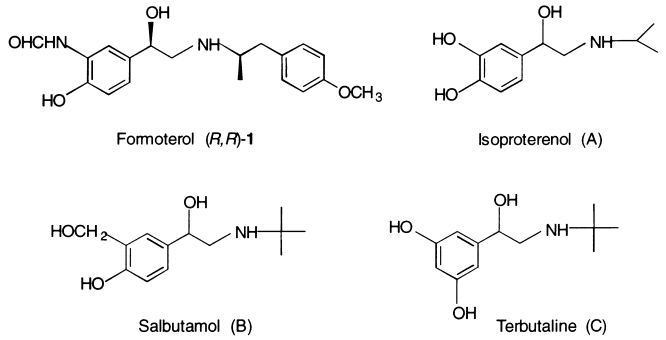

Figure 1.

active *R*,*R* enantiomer of formoterol have been described employing a resolution process of one pair of enantiomers,[6] a HPLC-semipreparative separation of diastereomers,[7] with low overall yields in both cases, and an asymmetric borane reduction using a chiral oxazaborolidine as reducing agent.[8]

Enzyme-catalyzed reactions have great potential for the synthesis of enantiomerically pure products through kinetic resolution of the racemic precursors or by asymmetrization of prochiral substrates.[9] Continuing our efforts directed to the synthesis of biologically active compounds through lipases,[10] we report herein an enantioselective synthesis of formoterol (*R*,*R*)-**1** in which the required chiral synthons (*R*)-**6** and (*R*)-**9** are generated from convenient enantiomeric resolutions through lipases.

2. Results and discussion

Epoxide (*R*)-**6**, the first chiral synthon needed, had been previously prepared through enantioselective borane reduction of the corresponding ketone catalyzed by chiral *cis*-1-amino-2-indanol.[8] This process required expensive starting reagents, so a more simple and lower-cost procedure was envisioned. Bromination of methyl ketone **2**[11] was carried out by bubbling a stream of nitrogen onto the reaction mixture to remove HBr and thus minimizing formation of the dibrominated product. The reaction furnished the corresponding mono-bromoketone **3**,[1] which was subjected to a conventional borane reduction to obtain bromoalcohol (*RS*)-**4** in 71.3% overall yield. A number of reports have been found in the literature to obtain optically active halohydrins. They comprise enantioselective oxazaborolidine,[12] borane[13] or microbial reduction[14] of α-haloketones, enantioselective hydrolysis of α-halo acetates,[15] and resolution of halohydrins by acetylation.[16] In our case, bromoalcohol (*RS*)-**4** was subjected to an enzyme-directed enantiodifferentiation process by treatment with some commercially available lipases. Although porcine pancreatic lipase (PPL, Sigma) has been reported to be useful for resolution of benzylic alcohols,[17] in our case the enzyme did not recognize compound **4** as a good substrate for the esterification and no acetate was detected after 22 h reaction (Table 1). However, *Pseudomonas cepacia* (lipase PS, Amano), either as commercially received or immobilized on Celite, efficiently resolved the racemic compound to provide alcohol (*R*)-**4** and acetate (*S*)-**5** in good yield and ee. The resolution was carried out on a thermostated bath at 37°C in *tert*-butyl methyl ether as solvent and vinyl acetate as acylating agent. The lipase:alcohol ratio was 2:1 in weight when the crude enzyme was used, and 0.2:1 for the immobilized enzyme. The amount of vinyl acetate was

10 equiv. with respect to the substrate and the reaction was stopped when ca. 50% conversion was achieved (Table 1). The mixture was filtered and the non-reactive alcohol (*R*)-**4** separated from the acetate (*S*)-**5** by column chromatography. (*R*)-**4** was obtained in 48% yield and 96% ee as determined by integration of the CF_3 signals of the ^{19}F NMR spectrum of the corresponding Mosher ester with (*S*)-(+)-MTPA chloride (*S*,*R* diastereomer at δ –71.70; *R*,*R* diastereomer at δ –71.92 ppm). Acetate (*S*)-**5** was hydrolyzed to the expected alcohol (*S*)-**4** but this spontaneously cyclized to epoxide (*S*)-**6** under the basic conditions used (K_2CO_3/MeOH) in 84% overall yield. The enantiomeric purity of the latter compound (77% ee) was calculated in base to its specific rotation[8] and the enantiomeric ratio of the enzymatic process ($E=65$) determined from the ee of the residual substrate and the extent of conversion.[18] Celite-immobilized lipase PS also resulted in an excellent resolving agent with the additional advantage of requiring lower amounts of lipase, ca. one order of magnitude, than that used for the non-immobilized enzyme ($E=111$) (Table 1). Cyclization of unreacted alcohol (*R*)-**4**, under identical conditions to those used for hydrolysis/cyclization of (*S*)-**5**, afforded the required intermediate epoxide (*R*)-**6** in 89% yield and 94% ee (Fig. 2).

Table 1
Resolution of (*RS*)-**4** through lipases

LIPASE	LIPASE: ALCOHOL	TIME	CONV. (%)	YIELD (*R*)-**4** (%)[a]	$[\alpha]_D^{20}$ (*R*)-**4**	ee (*R*) (%)	YIELD (*S*)-**5** (%)[a]	$[\alpha]_D^{20}$ (*S*)-**5**	ee (*S*) %	E[b]
PPL	2	22 h	--	--	--	--	--	--	--	--
PS	2	72 h	52	48	-33.6	96	50	+42.9	77	65
PS immob	0.1	263 h	54	43	-33.1	95	49	+41.0	74	35
PS immob	0.2	99 h	50	46	-33.6	96	48	+47.0	86	111

[a]Yields refer to pure isolated products after column chromatography purification.

[b]Enantiomeric ratio (E) values were determined from the ee of the residual substrate and the extent of conversion[18].

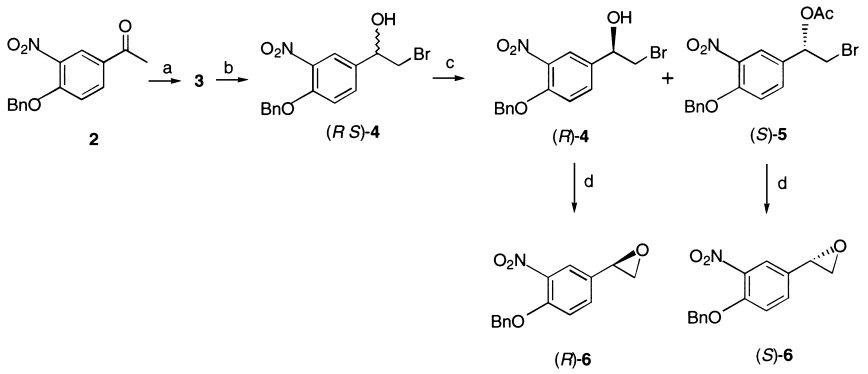

Figure 2. (a) Br_2, $CHCl_3$, N_2 bubbling, 25°C, 82%; (b) BH_3·THF (1.2 equiv.), THF, –20°C, 87%; (c) lipase, *t*-BuOMe, vinyl acetate, 37°C; (d) anh. K_2CO_3, MeOH, 25°C, 2.5 h, 89% for (*R*)-**6**, 84% for (*S*)-**6**

Synthesis of racemic amine (*RS*)-**9**, a well-known amphetamine derivative,[19] is outlined in Fig. 3. Nitrostyrene **8** was efficiently prepared by Henry reaction of anisaldehyde with nitroethane in the presence of ammonium acetate[20] at reflux for a short time (35 min, 81% yield). Reduction

of nitroderivative **8** with lithium aluminum hydride in ether directly provided amine (*RS*)-**9** in 78% yield. This yield resulted as being superior to others involving the intermediate formation of a ketoxime[19] or the catalytic reduction with Pd/C at high pressure.[21] Other procedures, such as utilization of RED-AL [sodium bis-(2-methoxyethoxy)aluminum dihydride] in benzene,[20] in our hands gave inferior results (only 54% isolated yield), due to the rather difficult separation of the salts formed during the work-up of the reaction.

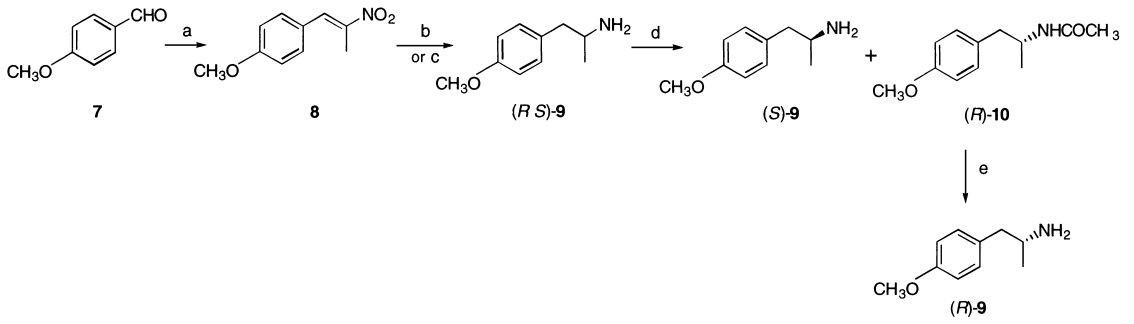

Figure 3. (a) $EtNO_2$, NH_4AcO (1.25 equiv.), reflux 35 min, 81%; (b) $LiAlH_4$, Et_2O, reflux 2 h, 78%; (c) RED-AL, benzene, reflux 2.5 h, 54%; (d) CALB, AcOEt, Et_3N cat., 30°C; (e) KOH 3 M, reflux, 3 h, 68%

Unlike the enzymatic resolution of alcohols, which has become a very useful strategy to obtain both enantiomers simultaneously,[9] selective enzymatic acylation of amines is less appealing since two drawbacks arise. First, amines are much more nucleophilic than alcohols and may react in a conventional way with the acyl donor (normally esters) used in the enzymatic process, and second, after acylation of the amine the deacylation process very often requires harsh conditions to liberate the free amine. This precludes utilization of enzymatic deacylation of amides and also restricts further reaction of the chiral amide after the enzymatic acylation. Therefore, and to circumvent these drawbacks, several approaches for the enzymatic resolution of amines have been developed.[22] In our case we decided to initially test those enzymes (subtilisin Carlsberg, subtilisin BPN′, etc.) which preferentially recognize the *S*-enantiomer leaving the required *R*-enantiomer unreacted. However, subtilisin Carlsberg protease failed to esterify racemic (*RS*)-**9** with trifluoroethyl butyrate in anh. 3-methyl-3-pentanol[22a] after 12 days of incubation at 30°C (only 7% of conversion). Better results were obtained with subtilisin BPN′ and diallyl carbonate in phosphate buffer 0.1M (pH 8.0)[22b] for 15 h at room temperature (50% conversion), but the enantioselectivity was poor (22% ee for the unreactive (*R*)-**9** by ^{19}F NMR spectra of the diastereomeric Mosher amide) (Table 2). We then turned our attention to the utilization of lipases, which, in contrast to proteases, show preference to acylate the *R*-enantiomer. Incubation of our substrate with *Candida antarctica* lipase B (CALB) in the presence of ethyl butyrate as transesterification reagent yielded the desired butylated amide, which resulted in being extremely resistent to hydrolysis even under acid (no reaction after 24 h reflux in the presence of trifluoroacetic acid or conc. HCl) or enzymatic conditions (no reaction with CALB in phosphate buffer pH = 7.5). Use of ethyl acetate as acyl donor and solvent was more encouraging, since the obtained amide (*R*)-**10** could be successfully hydrolyzed by refluxing overnight with a 3 M KOH soln. The resolution was performed at 30°C for 15 h to give unreactive (*S*)-**9** (47% yield, 68% ee) and amide (*R*)-**10**, which was hydrolyzed as described to furnish (*R*)-**9** in 32% overall yield and 84% ee. Determination of the enantiomeric excess was based on the ^{19}F NMR spectra of the

diastereomeric Mosher amides (*R,R* diastereomer at δ –69.21; *S,R* diastereomer at δ –69.51 ppm). In order to enhance the enantioselectivity of the resolution we followed two different approaches: sequential kinetic resolution, and use of a non-reactive organic base. Utilization of an appropriate sequential kinetic resolution is an useful tool to increase the enantiomeric purity of a specific enantiomer.[10a,23] In our case, a batch of racemic amine (*RS*)-**9** was treated with CALB in ethyl acetate for 18 h. After this time a 48% conversion was achieved, and the resulting amide was purified and hydrolyzed to the corresponding amine (*R*)-**9** (26% overall yield, 74% ee). This latter amine was subjected to a new enzymatic resolution for 19 h at 69% conversion, and the new amide hydrolyzed to provide chiral amine (*R*)-**9** in 11% overall yield from the racemic material with a good enantioselectivity (96% ee) (Table 2).

Table 2
Resolution of amine (*RS*)-**9** through lipases

LIPASE	LIPASE: AMINE	TIME	CONV. (%)	UNREACTIVE AMINE		REACTIVE AMINE		E[d]
				Yield[a]	ee[b] (%)	Yield[a,c]	ee[b] (%)	
Subt. Carlsberg	0.3	12 d	7	--	--	--	--	--
Subt. BPN'	0.3	15 h	50	36	22	32	n.d.	--
CALB	0.25	15 h	45	47	68	32	84	24
CALB[e]	0.25	18+19 h	48+69	n.d.	n.d.	11[f]	96	--
CALB (Et_3N)	0.25	4 h	42	58	56	21	94	66

[a]Yields refer to pure isolated products after column chromatography purification.

[b]Ee based on the ^{19}F NMR analysis of the corresponding Mosher amide or specific rotation.

[c]Overall yield of chiral amine after hydrolysis of the initially formed chiral amide *(R)*-**10**.

[d]Enantiomeric ratio (E) values were determined as reported[18].

[e]Sequential kinetic resolution.

[f]Overall yield.

The ability of bases to increase the enantioselectivity in enzymatic resolutions has been previously documented. Thus, in transesterification reactions of alcohols the base was added to neutralize any acetic acid liberated by hydrolysis of the acylating agent, particularly vinyl acetate,[24] or the carboxylic acid formed when acid anhydrides are used as acyl donors.[25] Rakels et al.,[26] on the other hand, utilized non-reactive amines in water-saturated organic solvents to enhance the ee and yield of enzyme-mediated ester hydrolysis, while Turner et al. used triethylamine in CALB-promoted alcoholysis of (±)-2-phenyl-4-benzyloxal-5(4*H*)-one[27a] and to catalyze resolution of other 4-substituted oxazolones with *Mucor miehei*.[27b] With these precedents in mind, we decided to test triethylamine as catalyst to enhance the enantioselectivity of the resolution. To our satisfaction, the presence of 0.15 equiv. of this amine with regard to the substrate provided, after only 4 h reaction, a 42% conversion of racemic amine (*RS*)-**9** into the corresponding amide (*R*)-**10**. Hydrolysis of the latter under the same conditions cited above led to the required amine (*R*)-**9** in 21% overall yield and 94% ee ($E=66$) (Table 2). To our knowledge, this is the first time that a non-reactive amine is described to catalyze the reaction rate and enantioselectivity of an enzyme-mediated resolution of amines.

As cited above, the β-amino alcohol function is a common structural unit of a variety of bioactive natural products, in particular in the pharmaceutical field, and therefore a variety of methods have been developed for their synthesis.[28] The classical procedure, reaction of an epoxide with an excess of amine in a protic solvent, presents a number of limitations, such as the requirement of an excess of amine, elevated temperatures and poor yields when non-nucleophilic (e.g. aromatic amines) or bulky amines are used.[29] When a primary amine is used, another drawback arises: the lack of regioselectivity. Thus, while nucleophilic attack at the less substituted carbon to give the desired β-amino alcohols usually predominates, significant amounts of the α products as well as bis-alkylation adducts are also obtained.[30] To overcome these drawbacks, Overman protected primary amines as dialkylaluminum amides[31] and Weigel as *N*-(trimethylsilyl)amines.[30] More recently, these authors almost suppressed bis-alkylation products by using 1 equiv. of bis-(trimethylsilyl)acetamide (BSA) and an amine:epoxide ratio of 1:1.2.[32] In our case, a mixture of amine (*R*)-**9** and BSA (1.1 equiv.) in anh. DMSO was stirred for 30 min under nitrogen. Then epoxide (*R*)-**6** (1 equiv.) in DMSO was added and the mixture stirred for 87 h at 75–80°C. After work-up, the crude was purified by column chromatography on neutral alumina, which promoted concomitant hydrolysis of the silylated intermediate (Fig. 4) to provide amino alcohol **11** in 80% overall yield from (*R*)-**9**. Compound **11** was a mixture of only two (*R*,*R* and *R*,*S*), out of the four possible diastereomers, in 75:25 ratio by integration of the ^{1}H and ^{13}C NMR signals of the benzylic protons next to the hydroxyl group. (*R*,*R*)-**11** presented a doublet of doublets at δ 4.53 ppm (J = 9.0, J′ = 3.6 Hz) while the same signal in (*R*,*S*)-**11** appeared at δ 4.61 ppm. In the ^{13}C NMR the aliphatic carbons at δ 70.3, 54.4, 54.0, 42.8 and 20.3 ppm appeared duplicated accounting for the presence of two diastereomers.

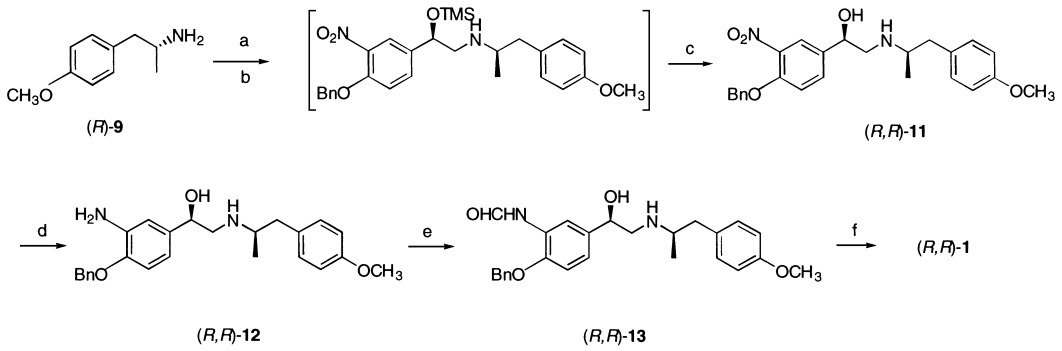

Figure 4. (a) BSA, anh. DMSO, 25°C, 30 min; (b) (*R*)-**6**, DMSO, 80°C, 87 h; (c) neutral Al_2O_3 III, 80% overall from (*R*)-**9**; (d) Fe, 1 M HCl, MeOH reflux 45 min, 67%; (e) anh. HCOOH, py, 60°C, 6.5 h, 69%; (f) H_2, Pd/C, EtOH, 3 kg/cm^2, rt overnight, 73%

Although the present approach is not highly diastereoselective, it is convenient since it does not need to protect/deprotect amine (*R*)-**9** as described[8,33] and provides good yields of the new amino alcohol (*R*,*R*)-**11** in one step. At this stage this compound could not be separated from the *R*,*S* diastereomer, so we decided to proceed forward and free the active material from the undesired diastereomer in the next step. Reduction of the nitro group of (*R*,*R*)-**11** was easily achieved by treatment with iron turnings (4 equiv.) and 1 M HCl in MeOH. Careful column chromatographic purification on neutral alumina (activ. IV) afforded diastereomerically pure amine (*R*,*R*)-**12** in

67% yield. Selective *N*-formylation of the primary amino group (*R*,*R*)-**12** was accomplished by reaction of the amine with an excess of anh. formic acid in pyridine at 60°C for 6.5 h to provide (*R*,*R*)-**13** in 69% yield after purification on column chromatography. The progress of the reaction was followed by HPLC using a Spherisorb ODS 25 μm column. It should be noted that under the more classical conditions, such as treatment with a mixture of formic acid and acetic anhydride (3:2) in $CHCl_3$,[33] a mixture of the corresponding mono *N*- and *O*-formyl compounds along with the bis-formylated derivative was obtained. Formyl amine (*R*,*R*)-**13** was obtained as a 70:30 mixture of the *syn* and *anti* conformers as deduced from its spectroscopic features. Thus, in the ^{13}C NMR spectrum signals at δ 158.7 and 161.2 ppm were assigned to the carbonyl groups of the *syn* and *anti* conformers, respectively. In the ^1H NMR spectrum the NH signals, which disappeared upon treatment with D_2O, appeared as broad singlets at δ 8.75 and 7.82 ppm and were attributed to the *anti* and *syn* conformers, respectively. Particularly noteworthy is the highly deshielding effect promoted by the carbonyl on the vicinal aromatic proton of the *syn* conformer (δ 8.39) while the corresponding proton of the *anti* conformer resonates at δ 7.22 ppm. Finally, deprotection of the benzyl group of (*R*,*R*)-**13** with Pd/C in EtOH at moderate pressure afforded (*R*,*R*)-**1** as a yellow amorphous solid in 73% isolated yield, after purification on a reverse-phase Isolute SPE C18 column. The (L)-(+)-tartrate salt of (*R*,*R*)-**1** showed an enantiomeric purity ≥99% based on its specific rotation $[\alpha]_D^{20} = -29.4$ (H_2O, *c* 0.61) in comparison to the reported value.[34]

3. Conclusion

In summary, a convenient new synthesis of enantiomerically pure formoterol (*R*,*R*)-**1** was achieved through the enzyme-directed preparation of the chiral precursors epoxide (*R*)-**6** and amine (*R*)-**9**. For this amine we found that use of triethylamine effectively catalyzes the reaction rate and enantioselectivity of the process. This effect has been noticed in other processes but, to our knowledge, not for resolution of primary amines. The synthetic approach is shorter than others previously reported since in situ derivatization of amine (*R*)-**9** with the labile trimethylsilyl group avoids the generally assumed protection/deprotection of the primary amine. Further work to study the scope of the use of non-reactive amines as catalyst in the enzymatic resolution of amines is in progress in our laboratory and the results will be reported in due course.

4. Experimental

Melting points were determined on a Koffler apparatus and are uncorrected. Elemental analyses were carried out on Carlo Erba models 1106, 1107 and 1500. IR spectra were recorded on a Bomem MB-120 instrument with Fourier transform. [^1H] and [^{13}C] NMR spectra were obtained in $CDCl_3$ solutions on a Varian XL-200 and Unity 300 spectrometers, operating at 200 and 300 MHz for [^1H] and 50 and 75 MHz for [^{13}C]. The values are expressed in δ scale relative to internal Me_4Si. [^{19}F] NMR spectra were recorded on a Varian Unity 300 instrument operating at 282 MHz and the values are reported in δ scale relative to trichlorofluoromethane as internal standard. GC analyses were performed on Carlo Erba model 4130, equipped with a FID detector, using a BPX 35 (SGE) 25m×0.25 μm ID fused silica capillary column and hydrogen as carrier

gas. Optical rotations were measured on Perkin–Elmer 141 and 341 polarimeters operating at 589 nm. Analytical-grade reagents were obtained from commercial suppliers and were used directly without further purification. Anhydrous tetrahydrofuran, benzene and diethyl ether were prepared by drying with solid KOH followed by distillation from Na/benzophenone under N_2, *n*-hexane, dimethylsulfoxide and methylene chloride by distillation from CaH_2, triethylamine and pyridine by distillation from KOH, and formic acid by reflux and distillation from phthalic anhydride.

4.1. Acylation of 1-(4′-benzyloxy-3′-nitro)phenyl-2-bromoethanol (RS)-4 with Pseudomonas cepacia lipase. Preparation of (R)-(–)-4 and (S)-(+)-5

In a 10 ml Erlenmeyer flask was placed a mixture of 101 mg (0.29 mmol) of (*RS*)-**4** in 6.3 mL of *tert*-butyl methyl ether, 202 mg of *Pseudomonas cepacia* lipase (lipase PS) and 0.247 g (2.87 mmol) of vinyl acetate. The Erlenmeyer-flask was capped, placed in a thermostated bath at 37°C and shaken at 80 U/min. The reaction was monitored by TLC and when the transformation was 52% (72 h reaction), the mixture was filtered off and the enzyme washed with diethyl ether. The solvent was stripped off and the resulting crude purified by column chromatography on silica gel eluting with a hexane–CH_2Cl_2 mixture to furnish 56.8 mg (50%) of acetate (*S*)-(+)-**5**; 77% ee, $[\alpha]_D^{20}$ = +42.9 ($CHCl_3$, *c* 2.84) and 48.4 mg (48%) of unreactive alcohol (*R*)-(–)-**4**, 96% ee, $[\alpha]_D^{20}$ = –33.6 ($CHCl_3$, *c* 2.42). (*R*)-(–)-**4**: R_f: 0.09 (SiO_2, hexane:CH_2Cl_2, 1:3). Elem. anal. calcd for $C_{15}H_{14}NO_4Br$: C, 51.16; H, 4.01; N, 3.98; Br, 22.69. Found: C, 51.27; H, 4.03; N, 3.96; Br, 22.64. IR, *ν*: 3531, 3066, 3033, 1622, 1575, 1531, 1353, 1280, 1265, 1018, 1000, 908, 736, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), *δ*: 7.90 (d, J = 2.1 Hz, 1H), 7.52 (dd, J = 8.7 Hz, J′ = 2.4 Hz, 1H), 7.47–7.26 (c, 5H), 7.12 (d, J = 8.7 Hz, 1H), 5.24 (s, 2H), 4.92 (dt, J = 8.7 Hz, J′ = 3.3 Hz, 1H), 3.62 (dd, J = 10.5 Hz, J′ = 3.6 Hz, 1H), 3.49 (dd, J = 10.5 Hz, J′ = 8.4 Hz, 1H), 2.75 (d, J = 3.6 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 151.6, 139.8, 135.2, 133.1, 131.5, 128.6, 128.2, 126.9, 123.3, 115.2, 72.1, 71.1, 39.3 ppm. (*S*)-(+)-(**5**): R_f: 0.09 (SiO_2, hexane:CH_2Cl_2, 1:3). IR, *ν*: 3066, 3033, 1747, 1622, 1533, 1454, 1371, 1355, 1286, 1263, 1236, 1022, 912, 819, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), *δ*: 7.88 (d, J = 2.4 Hz, 1H), 7.50 (dd, J = 8.6 Hz, J′ = 2.4 Hz, 1H), 7.47–7.31 (c, 5H), 7.12 (d, J = 8.7 Hz, 1H), 5.93 (dd, J = 7.2 Hz, J′ = 5.7 Hz, 1H), 5.25 (s, 2H), 3.63 (dd, J = 10.8 Hz, J′ = 7.2 Hz, 1H), 3.56 (dd, J = 10.8 Hz, J′ = 5.4 Hz, 1H), 2.15 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 169.6, 152.1, 140.0, 135.2, 132.6, 130.4, 128.8, 128.4, 126.9, 124.0, 115.1, 73.2, 71.2, 33.5, 20.9 ppm.

4.2. Enantiomeric excess of alcohol (R)-(–)-4 and acetate (S)-(+)-5

(*R*)-(+)-α-Methoxy(trifluoromethyl)phenylacetic acid was converted into the acid chloride as previously described.[35] A sample of the alcohol (*R*)-(–)-**4** (2.3 mg) was mixed with 134 μl of a 9.6×10^{-2} M soln. of (*S*)-(+)-MTPA chloride in anh. CH_2Cl_2, 6 μl of Et_3N and two crystals of DMAP. The mixture was stirred for 2 h at room temperature under nitrogen, after which time no starting material was detected on TLC. After evaporation of the solvent, direct ^{19}F NMR (282 MHz, $CDCl_3$) spectrum of the crude diastereomeric esters allowed calculation of the ee by integration of the CF_3 signals (*S*,*R* diastereomer, *δ*: –71.70 (s); *R*,*R* diastereomer, *δ*: –71.92 (s)). The calculated enantiomeric purity of the alcohol (*R*)-(–)-**4** was 96%. The ee of acetate (*S*)-(+)-**5** was determined by hydrolysis and cyclization into the corresponding epoxide (*S*)-**6** and calculation of the enantiomeric excess of the latter (see below).

4.3. Acylation of 1-(4′-benzyloxy-3′-nitro)phenyl-2-bromoethanol (RS)-**4** with Pseudomonas cepacia *lipase immobilized on Celite*

When immobilized lipase PS was used, starting from 4.30 g (12.2 mmol) of alcohol (*RS*)-**4**, 0.87 g of immobilized lipase and 11.4 mL of vinyl acetate dissolved in 18 mL of *tert*-butyl methyl ether were obtained, after 99 h reaction at 37°C and purification as above, 2.30 g (48%) of acetate (*S*)-(+)-**5**, $[\alpha]_D^{20} = +47.0$ ($CHCl_3$, *c* 2.23) (ee = 86%) and 1.96 g (46%) of unreactive alcohol (*R*)-(–)-**4**, $[\alpha]_D^{20} = -33.6$ ($CHCl_3$, *c* 2.81) (ee = 96%).

4.4. (R)-4-Benzyloxy-3-nitrostyrene oxide (R)-(–)-**6**

A mixture of 1.81 g (5.14 mmol) of alcohol (*R*)-(–)-**4** and 1.07 g (7.71 mmol) of anh. K_2CO_3 in 49 mL of MeOH was stirred for 2.5 h at room temperature, at which time there was no starting material left by TLC. The mixture was diluted with water and thoroughly extracted with CH_2Cl_2. The combined organic phases were washed with water, dried ($MgSO_4$) and the solvent removed under vacuum. The crude was purified by column chromatography on neutral alumina (act. III) eluting with hexane–CH_2Cl_2 mixtures to leave 1.24 g (89%) of epoxide (*R*)-(–)-**6**, $[\alpha]_D^{20} = -12.1$ ($CHCl_3$, *c* 1.05) (ee = 94%). M.p.: 86.0–87.5°C. R_f: 0.46 (SiO_2, CH_2Cl_2). Elem. anal. calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.37; H, 4.82; N, 5.20. IR, *ν*: 3056, 3037, 1625, 1575, 1531, 1498, 1355, 1278, 862, 736, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), *δ*: 7.79 (d, J = 2.2 Hz, 1H), 7.48–7.26 (c, 6H), 7.10 (d, J = 8.6 Hz, 1H), 5.24 (s, 2H), 3.85 (dd, J = 3.8 Hz, J′ = 2.6 Hz, 1H), 3.15 (dd, J = 5.1 Hz, J′ = 4.2 Hz, 1H), 2.76 (dd, J = 5.3 Hz, J′ = 2.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 151.7, 140.5, 135.4, 130.9, 130.6, 128.7, 128.3, 127.0, 123.0, 115.4, 71.3, 51.1 ppm.

4.5. (S)-4-Benzyloxy-3-nitrostyrene oxide (S)-(+)-**6**

Following a similar procedure as described for the preparation of epoxide (*R*)-**6**, hydrolysis of bromoacetate (*S*)-(+)-**5** (56.8 mg, 0.15 mmol) with K_2CO_3 in MeOH produced the expected bromoalcohol (*S*)-(+)-**4**, which concomitantly cyclized to give 33.1 mg (84%) of (*S*)-(+)-**6**, $[\alpha]_D^{20} = +9.9$ ($CHCl_3$, *c* 1.66) (ee = 77% by comparison with the literature value).[34]

4.6. Resolution of amine (RS)-**9** with Candida antarctica *lipase catalyzed by triethylamine*

In a 10 mL Erlenmeyer-flask were placed a solution of 111.2 mg (0.67 mmol) of (*RS*)-**9** in 2.0 mL of anh. ethyl acetate, 27.8 mg of *Candida antarctica* lipase and 13 μL of triethylamine. The Erlenmeyer-flask was capped, placed in a thermostated bath and shaken at 30°C and 80 U/min. The reaction was monitored by TLC and when the transformation was ca. 50% (4 h, 42% conversion), the mixture was filtered off and the enzyme washed with ethyl acetate, CH_2Cl_2 and MeOH. The solvent was stripped off and the resulting crude dissolved in 15 mL of CH_2Cl_2, acidified with 1 M HCl and repeatedly extracted with CH_2Cl_2. The organic phases were washed with water, dried ($MgSO_4$), filtered and freed from solvent. The residue was purified by column chromatography on silica gel eluting with hexane–ethyl acetate mixtures to give acyl amine (*R*)-**10** (43.9 mg, 31%). M.p.: 88.0–91.0°C. R_f: 0.42 (SiO_2, AcOEt:MeOH, 10:1). IR, *ν*: 3327, 1635, 1610, 1537, 1512, 1242, 1033, 813 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), *δ*: 7.09 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.78 (bd, J = 7.8 Hz, 1H), 4.19 (m, 1H), 3.78 (s, 3H), 2.78 (dd, J = 13.5 Hz, J′ = 5.7 Hz, 1H), 2.63 (dd, J = 13.6 Hz, J′ = 7.2 Hz, 1H), 1.92 (s, 3H), 1.09 (d, J = 6.8 Hz, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$), δ: 169.3, 158.0, 130.2, 129.9, 113.6, 55.1, 46.1, 41.3, 23.3, 19.7 ppm. The aqueous layer, containing unreactive amine (*S*)-**9** as the hydrochloride, was made basic with 2 M NaOH, extracted with CH_2Cl_2, washed with water and dried ($MgSO_4$). After filtration, evaporation of the solvent left chiral amine (*S*)-**9** as an oil (64.3 mg, 58%).

4.7. *Hydrolysis of acetamide (*R*)-**10**. Amine (*R*)-**9***

A mixture of amide (*R*)-**10** (43.9 mg) and 11 mL of a 3 M KOH aq. soln. was refluxed overnight. Completion of reaction was assessed by TLC analysis. The mixture was then diluted with water, extracted with CH_2Cl_2 and washed with water. After drying ($MgSO_4$), the solvent was removed to obtain 23.8 mg (68%) of amine (*R*)-**9** (94% ee, see below). R_f: 0.08 (SiO_2, CH_2Cl_2:MeOH, 5:1). IR, ν: 3361, 3284, 2958, 1612, 1583, 1514, 1247, 1035, 804 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.11 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.10 (m, 1H), 2.66 (dd, J = 13.3 Hz, J′ = 5.3 Hz, 1H), 2.44 (dd, J = 13.4 Hz, J′ = 8.0 Hz, 1H), 1.10 (d, J = 6.4 Hz, 3H), 1.22 (b, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), δ: 158.1, 131.8, 130.1, 113.8, 55.2, 48.6, 45.8, 23.5 ppm.

4.8. *Enantiomeric excess of amines (*S*)-**9** and (*R*)-**9***

Following a similar procedure as for alcohol (*R*)-**4**, formation of the diastereomeric Mosher amides of (*S*)-**9** and (*R*)-**9** allowed determination of the ee of the latter compounds by their ^{19}F NMR spectra (282 MHz, $CDCl_3$) (*R*,*R*-diastereomer, δ: –69.21 (s). *S*,*R*-diastereomer, δ: –69.51 ppm). The enantiomeric purities of (*R*)-**9** and (*S*)-**9** were 94 and 56%, respectively.

4.9. *Coupling reaction of amine (*R*)-**9** with epoxide (*R*)-**6**. Preparation of (*R*,*R*)-**11***

A mixture of 0.75 g (4.5 mmol) of amine (*R*)-**9**, 22.5 mL of anh. DMSO and 640 μL of N,O-bis-(trimethylsilyl)acetamide was stirred under nitrogen for 30 min at room temperature. Then 1.23 g (4.5 mmol) of epoxide (*R*)-**6** dissolved in 22.5 mL of anh. DMSO were added and the resulting mixture heated at 80°C for 87 h. The mixture was cooled, the solvent distilled off (0.1 mm) and the resulting crude purified by column chromatography in neutral alumina (activity III) eluting with hexane–ethyl acetate mixtures. Compound **11** was obtained as an orange gum (1.35 g, 80% overall yield from (*R*)-**9**) as a mixture of diastereomers *R*,*R* and *R*,*S* in 75:25 ratio. R_f: 0.40 (SiO_2, AcOEt:MeOH, 3:1). $[\alpha]_D^{20} = -39.8$ ($CHCl_3$, *c* 1.21). Elem. anal. calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.95; H, 6.46; N, 6.58. IR, ν: 3282, 3068, 2933, 2835, 1620, 1531, 1512, 1454, 1352, 1276, 1245, 1035, 910, 817, 732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.83 (d, J = 2.1 Hz, 1H), 7.47–7.29 (c, 6H), 7.07 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 5.21 (s, 2H), 4.53 (dd, J = 9.0 Hz, J′ = 3.6 Hz, 1H), 3.78 (s, 3H), 2.90–2.84 (c, 2H), 2.7 (b, 2H) 2.64–2.57 (c, 3H), 1.08 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), δ: 158.1, 151.1, 140.0, 135.6, 135.4, 131.3, 130.9, 130.1, 128.7, 128.2, 127.0, 123.1, 115.1, 113.9, 71.2, 70.3, 55.2, 54.4, 54.0, 42.8, 20.3 ppm.

4.10. *Amine (*R*,*R*)-**12***

To a solution of 406 mg (0.93 mmol) of (*R*,*R*)-**11** in 3.5 mL of methanol were added 208 mg (3.72 mmol) of iron turnings and 1.2 mL of 1 M HCl. The mixture was brought to reflux for

45 min, after which time no starting material was detected by TLC. After cooling, the mixture was diluted with 5 mL of MeOH and the precipitate filtered under vacuum. The filtrate was made basic with 1 M NaOH and filtered again. The filtrate was concentrated, diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water and dried ($MgSO_4$). After filtration and evaporation of the solvent, the residue was purified by careful column chromatography on neutral alumina (activity IV) eluting with hexane–ethyl acetate mixtures to provide amine (*R*,*R*)-**12** as a yellow gum (253 mg, 67%). R_f: 0.24 (SiO_2, AcOEt:MeOH, 2:1). $[\alpha]_D^{20} = -28.2$ ($CHCl_3$, *c* 1.01). IR, *ν*: 3468, 3369, 3197, 3031, 2931, 1614, 1512, 1247, 1220, 1035, 808, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), *δ*: 7.46–7.29 (c, 5H), 7.07 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 2.1 Hz, 1H), 6.64 (dd, J = 8.3 Hz, J′ = 2.0 Hz, 1H), 5.06 (s, 2H), 4.47 (dd, J = 8.7 Hz, J′ = 3.9 Hz, 1H), 3.83 (b, 2H), 3.78 (s, 3H), 2.88 (dd, J = 6.5 Hz, J′ = 6.5 Hz, 1H), 2.83 (dd, J = 11.9 Hz, J′ = 4.1 Hz, 1H), 2.68 (dd, J = 11.9 Hz, J′ = 8.9 Hz, 1H), 2.65 (dd, J = 13.4 Hz, J′ = 6.9 Hz, 1H), 2.55 (dd, J = 13.5 Hz, J′ = 6.6 Hz, 1H), 1.05 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 158.0, 145.8, 137.1, 136.4, 135.7, 131.3, 130.2, 128.5, 128.0, 127.5, 115.7, 113.7, 112.6, 111.8, 71.7, 70.5, 55.2, 54.4, 54.3, 42.8, 20.3 ppm. HRMS: calcd mass for $C_{25}H_{30}N_2O_3$: 406.225643; Found: 406.224823.

4.11. Formylation of amine (R,R)-12

To a solution of 243 mg (0.60 mmol) of amine (*R*,*R*)-**12** in 15 mL of anh. pyridine were added 3.6 mL of anh. formic acid and the mixture heated at 60°C for 6.5 h under an inert atmosphere. Progress of the reaction was followed by HPLC on a Spherisorb ODS column 25 μm 12.5×0.46 cm, isocratic CH_3CN:buffer soln. 65:35. The buffer soln. contained Et_3N–AcOH (40 mM) for pH = 6.8 (R_t of (*R*,*R*)-**12**: 4.9 min, (*R*,*R*)-**13**: 3.9 min). The solvent was evaporated off and the residue diluted with 1 M Na_2CO_3 soln. and extracted with CH_2Cl_2. The organic phases were washed with water, dried ($MgSO_4$), filtered and the solvent removed. The residue was purified by column chromatography on neutral alumina (activity IV), eluting with hexane–ethyl acetate mixtures, to afford 180 mg (69%) of formyl amine (*R*,*R*)-**13** as a mixture of *syn* and *anti* (70:30) conformers. R_f: 0.24 (SiO_2, AcOEt:MeOH, 2:1). $[\alpha]_D^{20} = -37.4$ ($CHCl_3$, *c* 1.68). IR, *ν*: 3398, 3327, 3064, 3033, 2960, 2931, 1693, 1610, 1598, 1531, 1512, 1247, 1035, 788, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), *δ*: 8.75 (b, 1H *anti* conformer), 8.39 (d, J = 1.8 Hz, 1H *syn* conformer), 8.33 (d, J = 2.1 Hz, 1H *syn* conformer), 7.82 (b, 1H *syn* conformer), 7.44–7.34 (c, 5H), 7.22 (d, J = 1.8 Hz, 1H, *anti* conformer), 7.12 (d, J = 2.1 Hz, 1H, *anti* conformer), 7.08 (dm, J = 8.7 Hz, 3H), 6.93 (dd, J = 8,4 Hz, J′ = 1.5 Hz, 1H), 6.83 (dm, J = 8.7 Hz, 2H), 5.08 (s, 2H), 4.53 (dd, J = 9.0 Hz, J′ = 3.6 Hz, 1H *syn*), 4.50 (dd, J = 9.0 Hz, J′ = 3.6 Hz, 1H *anti*), 3.78 (s, 3H), 2.91–2.80 (c, 2H), 2.72–2.52 (c, 3H), 1.08 (d, J = 6.0 Hz, 1H *anti*), 1.05 (d, J = 6.3 Hz, 1H *syn*). ^{13}C NMR (75 MHz, $CDCl_3$), *δ*: 161.2, 158.7, 158.0, 146.9, 146.3, 136.1, 135.8, 135.7, 131.2, 131.0, 130.14, 130.10, 128.7, 128.5, 128.4, 127.9, 127.6, 126.7, 126.4, 122.3, 121.4, 118.2, 113.8, 112.4, 111.3, 71.4, 71.1, 70.94, 70.86, 55.2, 54.4, 54.3, 54.2, 42.8, 20.4, 20.3 ppm.

4.12. Formoterol (R,R)-1

A mixture of 89 mg (0.20 mmol) of (*R*,*R*)-**13** dissolved in 3.4 mL of abs. ethanol and 76 mg (0.072 mmol) of 10% Pd/C was hydrogenated at 3 kg/cm^2 and room temperature overnight. The mixture was filtered under vacuum and the catalyst thoroughly washed with ether, ethanol and methylene chloride. Removal of the solvent left a residue which was chromatographed on a

reverse-phase column (1 g, Isolute SPE C_{18}) using mixtures of MeOH–H_2O as eluent. The solvent was evaporated off and the aqueous solution lyophilized (–35°C, 0.6 bar) overnight to obtain 51.5 mg (73%) of formoterol (*R*,*R*)-**1** as amorphous solid. R_f: 0.27 (SiO_2, AcOEt:MeOH, 1:1). $[\alpha]_D^{20} = -41.5$ ($CHCl_3$, *c* 0.53). IR, *v*: 3383, 2967, 2923, 1674, 1668, 1610, 1514, 1442, 1247, 1033, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ: 8.11 (b, 1H), 7.46 (b, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.9–6.7 (c, 4H), 4.46 (m, 1H), 4.34 (b, 3H interchangeable), 3.74 (s, 3H), 2.90–2.45 (c, 5H), 1.02 (d, J = 5.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), δ: 160.2, 158.3, 147.7, 133.4, 130.6, 130.2 (2C), 125.7, 123.7, 119.5, 117.8, 114.0 (2C), 71.3, 55.3, 54.7, 53.6, 42.0, 19.4 ppm. CI (positive, LC-MS) (*m*/*z*, %) 435 (M+1, 100). The tartrate salt was prepared by dissolving 13.8 mg (0.04 mmol) of (*R*,*R*)-**1** and 6.0 mg (0.04 mmol) of (L)-(+)-tartaric acid in 150 μL of 85% aqueous isopropanol. The solution was left standing overnight and the resulting crystalline solid (7.6 mg) purified on a reverse-phase column (1 g, Isolute SPE C_{18}) using mixtures of MeOH–H_2O as eluent. The solvent was removed under vacuum and the aqueous solution lyophilized (–35°C, 0.6 bar) overnight. The (L)-(+)-tartrate salt of (*R*,*R*)-**1** showed an $[\alpha]_D^{20} = -29.4$ (H_2O, *c* 0.61) (> 99% ee based on the reported value [34]).

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