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Lipase-mediated resolution of substituted 2-aryl-propanols: application to the enantioselective synthesis of phenolic sesquiterpenes

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ABSTRACT

A comprehensive study of the lipase-mediated resolution of substituted 2-aryl-propanols is reported. The latter alcohols were submitted to the irreversible acetylation catalyzed either by PPL, CRL, or lipase PS. The enantioselectivity of these transformations was dependent on the type of lipase used. The type of substituents and particularly their position on the aromatic ring strongly affected the selectivity of the reaction. The experiments described prove that PPL is the more versatile lipase catalyzing the acetylation with an enantiomeric ratio (*E*) value that ranges from 1 up to 144, depending on the substrate used. Conversely, the same transformations were catalyzed by CRL and lipase PS with an enantiomeric ratio value, which is always less than 5. The remarkable behavior of PPL was exploited in the large scale resolution of some substituted 2-aryl-propanols whose enantiomeric forms are relevant building blocks in the enantioselective synthesis of phenolic sesquiterpenes. By these means, the synthesis of (*S*)-turmeronol B and the formal syntheses of (*R*)-curcumene, (*R*)-curcuphenol, (*R*)-xanthorrhizol, and (*R*)-curcuhydroquinone were accomplished.

1. Introduction

Enantiomerically pure substituted 2-aryl-propanols of type **1** (Fig. 1) are important intermediates in the synthesis of different biologically active compounds. The first and direct application of these compounds involved their oxidation to give optically active 2-arylpropionic acids **2**,[1] which are well known non-steroidal anti-inflammatory drugs. In addition, a second application concerns their use as chiral building blocks in bisabolane sesquiterpenes synthesis. The latter compounds have been isolated from many different natural sources[2] and show a wide range of biological activities. These properties are strongly dependent on the absolute configuration, thus justifying the scientific interest in their enantioselective preparation. Aromatic derivatives such as curcumene **3**[2a,2c] and turmerone **4**[2b] are the olfactorally active components of a large number of essential oils whereas the odorless phenolic sesquiterpenes **5–9**[2c–h] exhibit different pharmacological properties. All of these compounds are characterized by a benzylic stereogenic center with a methyl group at this position. Despite their rather simple structure, their asymmetric synthesis is particularly demanding. This is due to the difficulty of introducing a defined absolute stereochemistry at the non-functionalized benzylic position.

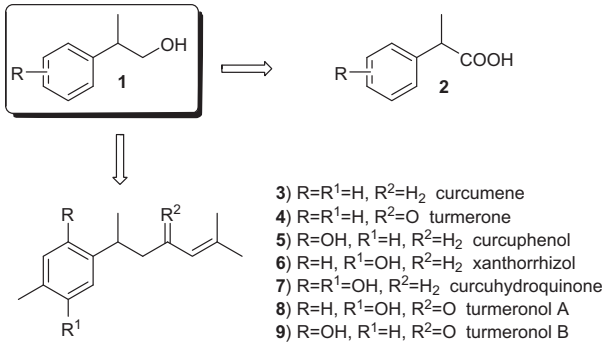

Figure 1. General structure of the substituted 2-aryl-propan-1-ols **1** of the substituted arylpropanoic acids **2** and of the relevant bisabolane sesquiterpenes **3–9**.

Hence, their preparation starting from enantioenriched 2-aryl-propanols, in turn obtainable by racemate separation, is a more suitable approach. This gives access to both enantiomeric forms of a given substrate and it is based on the use of inexpensive and easily available starting materials. In this context the enzyme-mediated kinetic resolution protocol of compounds of type **1** has received increasing attention. While lipases can accept a wide range of substrates, the enantioselectivity of the lipase-catalyzed

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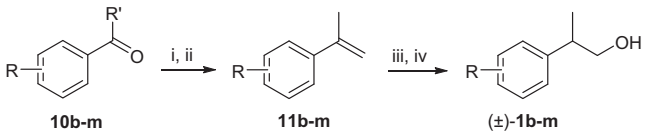
acylation of 2-methyl-branched primary alcohols[3] is usually very low (enantiomeric ratio <10) so that the resolution processes may lose their synthetic relevance. Therefore, much effort has been devoted to increasing the selectivity.[4–7] The influence of the type of enzyme, solvent, and acyl donor on the stereochemical course of the reaction have been greatly studied. Some successful approaches resulted. These are based mainly on the use of bulky acyl moiety[5] or on the use of a chiral acyl donor[6] either in lipase-mediated acylation or hydrolysis processes. However, a comprehensive investigation on the influence of the aromatic structure on the enantioselectivity is still lacking. On this subject, the data reported in the literature are contrasting. For instance, PPL catalyses both the acetylation of 2-(3-isopropylphenyl)-propanol[8] and the hydrolysis of 2-(4-methoxy)-propanol acetate,[9] with low and very high enantiomeric ratios, respectively. We envisaged that the substituents on the aromatic ring could strongly affect the stereochemical course of the resolution process. Herein we report the results of this study and some relevant applications in the field of natural products synthesis.

2. Results and discussion

2.1. Preparation of racemic 2-aryl-propan-1-ol derivatives

As mentioned earlier, this study concerns the influence of the aromatic moiety structure on the stereochemical trend of the lipase-mediated acetylation reaction of substituted 2-aryl-propanols. Thus, our work first involved the preparation of a valuable amount of racemic starting materials. We selected alcohols **1a–m** as substrates to be tested (Table 1). Since only 2-phenylpropanol **1a** is commercially available, the remaining compounds **1b–m** had to be prepared. The most direct precursors of alcohols **1b–m** are the acetophenones or methylbenzoate esters **10b–m** (Scheme 1).



Scheme 1. Synthesis of racemic 2-aryl-propan-1-ol **1b–m**. Reagents and conditions: (i) MeMgI, Et_2O; (ii) PTSA cat., benzene, reflux; (iii) $BH_3{\cdot}Me_2S$, THF; (iv) NaOH/H_2O then H_2O_2.

Indeed, these compounds are either commercially available or obtainable by chemical synthesis (see Section 4). The treatment of **10b–m** with methylmagnesium iodide afforded the corresponding dimethylcarbinols which were heated in benzene in the presence of catalytic PTSA. The dehydration reaction afforded the substituted styrenes with a rate that was noticeably dependent on the electronic properties of the substituents. Compounds with electron-donating substituents **10b**, **10g–m** reacted completely within a few minutes whereas compounds bearing electron-withdrawing groups **10c–f** needed up to two hours to reach a good conversion. Since PTSA also catalyzes the polymerization of the products, it was mandatory to stop the reactions as soon as they were completed. The styrenes obtained were then hydroborated by reaction with the diborane–dimethylsulfide complex. The

Table 1
Results of the enzyme-mediated acetylation of 2-arylpropan-1-ols (±)-**1a–m**

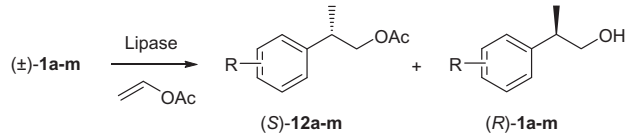
Entry	Substituents	Enzyme	Acetylated derivatives			Enantiomeric ratio[c] (E)
			Configuration	Conversion (%)	ee (%)	
1a	H	PPL	(*S*)	41	78	13.8
		CRL	(*R*)	36	10	1.3
		PS	(*S*)	47	28	2.2
1b	2-OMe, 4-Me	PPL	(*S*)	48	88	39.2
		CRL	(*R*)	50	1	<1.1
		PS	(*S*)	32	32	2.2
1c	2,4-Dichloro	PPL	(*S*)	40	83	18.7
		CRL	(*R*)	50	4	1.1
		PS	(*S*)	56	43	4.2
1d	2-Br	PPL	(*S*)	18	11	1.3
		CRL	(*R*)	44	31	2.4
		PS	(*S*)	46	25	2.0
1e	2-I	PPL	(*S*)	28	26	1.9
		CRL	(*R*)	49	43	3.7
		PS	(*R*)	47	11	1.4
1f	2-NO_2	PPL	(*S*)	34	3	<1.1
		CRL	(*R*)	42	49	4.1
		PS	(*R*)	62	5	1.2
1g	2-Me	PPL	(*S*)	18	11	1.3
		CRL	(*R*)	35	25	1.9
		PS	(*R*)	23	43	2.8
1h	2-Et	PPL	(*S*)	13	19	1.5
		CRL	(*R*)	32	20	1.6
		PS	(*R*)	27	54	4.0
1i	2,6-OMe, 4-Me	PPL	a	a	a	a
		CRL	b	51	21	1.9
		PS	b	8	5	1.1
1j	4-OMe	PPL	(*S*)	43	97	144
		CRL	(*S*)	38	3	<1.1
		PS	(*S*)	51	6	1.2
1k	4-Me	PPL	(*S*)	53	82	33.3
1l	3-OMe, 4-Me	PPL	(*S*)	40	85	21.8
1m	2,5-OMe, 4-Me	PPL	(*S*)	25	88	20.8

(a) The substrate was not acetylated; (b) data not determined; (c) $E = \ln[1 - c \times (1 + ee_p)]/\ln[1 - c \times (1 - ee_p)]$.

organoborane intermediates were then oxidized in situ with H_2O_2 in the presence of NaOH to give alcohols **1b**–**m** in very good yield and with almost complete regioselectivity.

2.2. Lipase-mediated acetylation of the racemic 2-aryl-propan-1-ol derivatives

The reactivity of each substrate toward irreversible acetylation was tested by the employment of three different lipases (PPL, CRL, and lipase PS). The latter enzymes were chosen since they are commercially available and were previously employed by us in a different resolution of primary alcohol derivatives.[10,11] Moreover, in the cases of 2-methyl-branched alcohols with a *p*-menthane structure,[11] they displayed different enantioselectivity. PPL and lipase PS acetylated the (*S*) isomers whereas CRL acetylated the (*R*)-isomers. Thus, in the experiments described herein, each alcohol was treated with vinyl acetate in *t*-butyl-methyl ether in the presence of the aforementioned enzymes. The reactions were interrupted at the desired conversion and the acetates **12a**–**m** and the unreacted alcohol **1a**–**m** were separated and characterized (Scheme 2).



Scheme 2. Lipases-mediated acetylation of racemic 2-aryl-propan-1-ol **1a**–**m**.

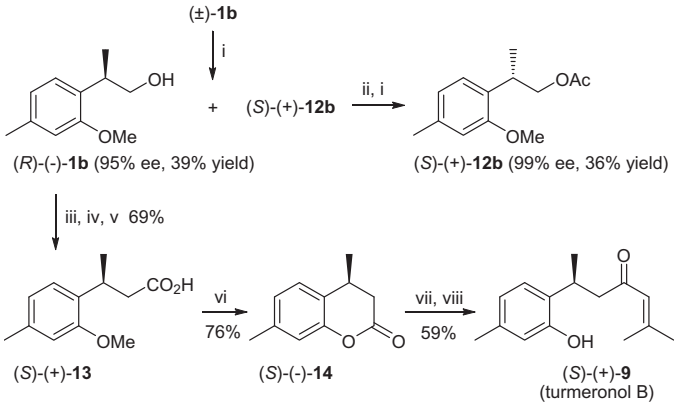
The results are collected in the Table 1 and show some interesting considerations. All the lipases used mediated the acetylation of the alcohols with the exception of substrate **1i**, which was not transformed by PPL catalysis. The enantioselectivity of the transformations was affected by the lipase used. In addition, the type of substituent and particularly its position on the aromatic ring greatly influenced the stereochemical course of the reaction. Unsubstituted compound **1a** was transformed in (*S*)-acetate **12a** by PPL and lipase PS with high and low enantiomeric ratios, respectively. Conversely, CRL afforded (*R*)-acetate **12a** with very low enantioselectivity. The same trend was observed when compound **1b** was used. In this case PPL catalyzed the transformation with high enantiomeric ratio (E = 39). Since the presence of the methoxy group near to the benzylic stereocentre could influence the enantioselectivity due to the steric effect, further *ortho*-substituted substrates were tested. The 2,4-dichloro-substituted alcohol **1c** showed a steric hindrance around the aromatic ring that was very similar to that of **1b**. In spite of this fact, the transformation catalyzed by PPL displayed 18.7 as a value of enantiomer ratio which is about half that measured for **1b**. Thus, the specific presence of the methoxy group increased the PPL enantioselectivity. Conversely, the removal of the *para*-substituent and the use of either electron withdrawing or electron donating *ortho*-substituents **1d**–**h** dramatically decreased the PPL enantioselectivity (E <2) independent of the steric hindrance at this position. In addition, for compounds **1e**–**h**, lipase PS inverted its enantioselectivity to afford (*R*)-acetates **12e**–**h** whereas PPL and CRL gave (*S*)- and (*R*)-acetate, respectively. Thus, the presence of an *ortho*-substituent seemed to be detrimental for the PPL enantioselectivity while the presence of a *para*-substituent had opposite effect.

This hypothesis was confirmed by testing the same transformation on substrate **1j**. In this case the activating methoxy group is placed at the *para*-position and the enantiomeric ratio reached the value of 144. When the *para*-methoxy group was switched with a *para*-methyl group, the enantiomeric ratio decreased to a value of 33, which is inferior but comparable to that described for the transformation of **1b** (E = 39). Concerning the effect of the *meta*-substituents, we have previously reported the PPL-mediated resolution of 2-(3-isopropylphenyl)-propanol[8] which displayed a low value of enantiomeric ratio (E = 6.8). Two further experiments confirmed that substituents in *meta*-positions decreased the enantioselectivity. Alcohols **1l** and **1m**, in addition to having a *para*-methyl activating group, have either at the *meta*-methoxy substituent or the *ortho*, *meta* dimethoxy substituents, respectively. The PPL-mediated acetylation reactions of the latter compounds exhibited an enantiomeric ratio value of 21.8 and 20.8, respectively. These data indicated a definite decrease in the enantioselectivity when compared with compounds **1k** and **1b**.

Overall, these results are difficult to interpret since there is no unambiguous explanation for the unique selectivity of PPL. Of course the steric effect of the substituents plays a relevant role but, if considered alone, it is not sufficient to give a rational justification. A multi-pocket model of the catalytic domain of the lipases is generally accepted. One possibility is that the large aromatic moiety could fit with one of the latter pockets with a specific affinity not due exclusively to steric factors. The interaction of the substituents, e.g. the formation of hydrogen bonding inside the hydrophobic pocket, may change the enzyme-substrate affinity, thus modifying the overall reaction rate and selectivity

2.3. Enantioselective synthesis of the phenolic sesquiterpene (*S*)-turmeronol B and formal syntheses of (*R*)-curcumene, (*R*)-curcuphenol, (*R*)-xanthorrhizol and (*R*)-curcuhydroquinone

As described in the introduction paragraph, the enantiomerically pure substituted 2-aryl-propanols are suitable chiral building blocks for bisabolane sesquiterpenes synthesis. The latter natural products have an aromatic ring bearing both a methyl group and a C-8 aliphatic chain, placed in a *para*-orientation. Concerning the phenolic sesquiterpenes, these are characterized by the presence of further hydroxyl groups which are linked to the aromatic ring as shown in Figure 1 (compounds **3–9**). Alcohols **1b**, **1k**, **1l,** and **1m** display aromatic rings with the aforementioned substitution frameworks and are good substrates for the PPL-mediated resolution process (E >20). Thus they are the ideal starting materials to be employed in the enantioselective synthesis of compounds **3–9**. For these reasons, we devised a large scale resolution protocol of the selected alcohols. The procedure is fully described for the resolution of **1b** (Scheme 3) and was generally applied for the other alcohols. Accordingly, racemic **1b** was treated with vinyl acetate in *t*-butyl-methyl ether in the presence of PPL. When the acetylation



Scheme 3. PPL-mediated resolution of 2-(2-methoxy-4-methyl-phenyl)-propan-1-ol **1b** and synthesis of (*S*)-turmeronol B. Reagents and conditions: (i) PPL, *t*-BuOMe, vinyl acetate then chromatography; (ii) NaOH, MeOH, reflux; (iii) TsCl, Py, CH_2Cl_2, rt; (iv) NaCN, DMSO, 80 °C; (v) NaOH, diethylene glycol/H_2O reflux; (vi) BBr_3, CH_2Cl_2; (vii) *N*,*O*-dimethyl-hydroxylamine chloride, Et_3N, DMF, 80 °C; (viii) 2-methyl-1-propenylmagnesium bromide, THF.

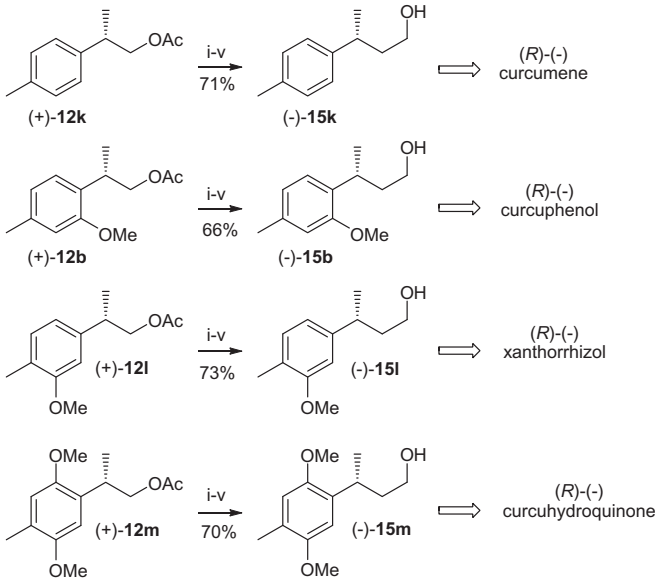
reached about 60% conversion the reaction was stopped and the unreacted alcohol (*R*)-**1b** (95% ee, 39% yield) was separated by chromatography. The acetate (*S*)-**12b** was hydrolyzed and submitted again to the PPL-mediated acetylation process until about 60% of the alcohol was transformed. The chromatographic separation afforded (*S*)-**12b** (99% ee, 36% yield). Using this protocol, we obtained both isomeric forms of **1b** in good yield and in high enantiomeric purity. Next, alcohol (*R*)-**1b** was used as the starting material for the synthesis of (*S*)-turmeronol B **9**.

This natural product is a phenolic sesquiterpene which can be isolated from turmeric spice (*Curcuma Longa*, L.).[2h] It exhibits important biological activities since it is both a strong antioxidant and a lipoxygenase inhibitor. To the best of our knowledge, only one enantioselective synthesis of (*S*)-turmeronol B has been described so far.[12] The latter approach is based on the asymmetric synthesis of the benzylic stereocentre by means of the diastereoselective Michael addition of a dialkylcuprate. Despite its elegance, the process requires the stoichiometric employment of a chiral auxiliary, thus limiting use when scaling up. Conversely, the presented resolution approach gave (*R*)-**1b** in a scalable way. The latter alcohol was then homologated to the acid (*S*)-**13** via a three step process. The alcoholic group was converted into the corresponding tosylate which was heated with NaCN in DMSO. The nucleophilic substitution reaction afforded the cyano-derivate, which was not isolated but hydrolyzed with NaOH in diethylene glycol/water at reflux. The obtained acid **13** was treated with boron tribromide in dichloromethane to afford lactone (*S*)-**14** in good yield. The latter compound reacted with *N*,*O*-dimethyl-hydroxylamine and underwent ring opening to give the corresponding Weinreb amide. This intermediate was treated with an excess of 2-methyl-1-propenylmagnesium bromide to afford (*S*)-turmeronol B, whose spectroscopic data were in good agreement with those reported for the natural product.

The enantioenriched alcohols **1b**, **1k**, **1l,** and **1m** may be used as starting compounds for the synthesis of further different bisabolane sesquiterpenes. We next turned our attention to compounds **3–7**, whose asymmetric synthesis of their (*S*)-enantiomeric form has been previously reported.[13] In these earlier works, we introduced the benzylic stereocentre by Baker's yeast-mediated enantioselective reduction of substituted (*E*)-β-methylcinnamaldehydes.[14] The obtained (*S*)-3-arylbutanols were thus used as chiral building blocks in the straightforward preparation of compounds **3–7**. It is noteworthy that only the (*S*)-isomers were preparable by this method while the (*R*)-isomers of curcumene **3**,[2c] curcuphenol **5**,[2c] xanthorrhizol **6**[2e] and curcuhydroquinone **7**[2c] occur in nature.

Both enantiomeric forms of the 2-aryl-propanols are available by resolution and the simple C1 homologation of the (*S*)-alcohols **1k**, **1b**, **1l,** and **1m** allows their transformation into the corresponding (*R*)-3-arylbutanols **15k**, **15b**, **15l,** and **15m**, respectively (Scheme 4). The latter compounds can in turn be converted into the (*R*)-isomers of sesquiterpenes **3**, **5**, **6,** and **7**, respectively, by mean of our former synthetic path. Therefore, we applied the large scale resolution protocol used for the alcohols **1b** to the resolution of alcohols **1k**, **1l,** and **1m**. The enantiopure acetates obtained were converted into the corresponding alcohols, which were homologated to the (*R*)-**15** derivatives via a four step process which did not require purification of the intermediates.

Accordingly, the alcoholic groups were transformed into the corresponding tosylate esters, which were treated with NaCN in DMSO. The cyanoderivates were not isolated but hydrolyzed with NaOH in diethylene glycol/water at reflux. The crude acids were reduced with $LiAlH_4$ in refluxing ether to give the suitable (*R*)-3-arylbutanols **15k**, **15b**, **15l,** and **15m** with good overall yields (66–73%). The analytical data of the latter compounds were in good agreement with those previously reported by us with the exception of the specific rotation value, which showed a negative sign. By this



Scheme 4. Formal synthesis of the (*R*)-enantiomeric forms of the bisabolane sesquiterpenes curcumene, curcuphenol, xanthorrhizol and curcuhydroquinone. Reagents and conditions: (i) NaOH, MeOH, reflux; (ii) TsCl, Py, CH_2Cl_2, rt; (iii) NaCN, DMSO, 80 °C; (iv) NaOH, diethylene glycol/H_2O reflux; (v) $LiAlH_4$, ether, reflux.

method, the formal syntheses of (*R*)-(−)-isomers of curcumene, curcuphenol, xanthorrhizol, and curcuhydroquinone were accomplished.

3. Conclusion

The presented study on the lipase-mediated resolution of substituted 2-aryl-propanols has afforded some relevant results. The enantioselectivity of the transformations was affected by the lipase used. PPL invariably acetylated the (*S*)-isomers whereas CRL and lipase PS showed a preference for the (*R*)- and (*S*)-isomers, respectively with some exceptions. The described experiments prove that PPL is the more versatile lipase catalyzing the acetylation with enantiomeric ratios ranging from 1 up to 144, depending on the substrate used. Conversely, the same transformations were catalyzed by CRL and lipase PS with an enantiomeric ratio value which is always less than 5. In addition, the type of substituents and particularly their position on the aromatic ring strongly affected the selectivity of the reaction. Concerning the remarkable behavior of PPL, substituents situated at the *para*-position to the aliphatic chain greatly increased the enantioselectivity whereas those placed at either the *meta*- or *ortho*-position displayed the opposite effect. Amongst the type of the substituents investigated, the methoxy group mostly increased the enantioselectivity. These results were exploited by the large scale resolution of substituted 2-aryl-propanols **1b**, **1k**, **1l,** and **1m** whose enantiomeric forms are relevant building blocks in the enantioselective synthesis of different phenolic sesquiterpenes. The combination of the aforementioned resolution processes with a few straightforward chemical transformations allowed the synthesis of (*S*)-turmeronol B and the formal syntheses of (*R*)-curcumene, (*R*)-curcuphenol, (*R*)-xanthorrhizol, and (*R*)-curcuhydroquinone, all in high enantiomeric purity.

4. Experimental

4.1. General

All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality.

Lipase from *Porcine pancreas* (PPL) type II, *Sigma*, 147 units/mg; lipase from *Candida rugosa* (CRL) type VII, *Sigma*, 1150 units/mg and Lipase from *Pseudomonas cepacia* (PS), *Amano Pharmaceuticals* Co., Japan, 30 units/mg were employed in this work. TLC: *Merk* Silica Gel 60 F_{254} plates. Column chromatography (CC): silica gel. GC–MS analyses: *HP-6890* gas chromatograph equipped with a 5973 mass detector, using a *HP-5MS* column (30 m × 0.25 mm, 0.25 μm firm thickness; Hewlett–Packard) with the following temp. program: 60° (1 min)–6°/min–150° (1 min)–12°/min–280° (5 min); carrier gas, He; constant flow 1 ml/min; split ratio, 1/30; t_R given in min: t_R(**1a**) 10.55, t_R(**1b**) 17.74, t_R(**1c**) 18.68, t_R(**1d**) 16.48, t_R(**1e**) 18.72, t_R(**1f**) 18.52, t_R(**1g**) 13.04, t_R(**1h**) 14.48, t_R(**1i**) 20.66, t_R(**1j**) 16.17, t_R(**1k**) 12.82, t_R(**1l**) 17.85, t_R(**1m**) 20.62, t_R(**9**) 22.96, t_R(**11b**) 12.53, t_R(**11c**) 12.30, t_R(**11d**) 10.19, t_R(**11e**) 12.38, t_R(**11g**) 6.73, t_R(**11h**) 8.55 t_R(**11i**) 16.30, t_R(**11j**) 12.04, t_R(**11l**) 13.34, t_R(**11m**) 16.71, t_R(**12b**) 19.64, t_R(**12c**) 20.08, t_R(**12d**) 18.72, t_R(**12e**) 20.23, t_R(**12f**) 20.11, t_R(**12g**) 15.56, t_R(**12h**) 16.94, t_R(**12i**) 21.46, t_R(**12j**) 18.71, t_R(**12k**) 15.73, t_R(**12l**) 19.52, t_R(**12m**) 21.70, t_R(**13**) 20.60, t_R(**14**) 18.36, t_R(**15b**) 18.93, t_R(**15k**) 16.12, t_R(**15l**) 19.23, t_R(**15m**) 22.50; mass spectra: *m*/*z* (rel.%). Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomer excesses determined on a CHIRASIL DEX CB-Column with the following temp. program: compound **12c**: 80° (0 min)–2°/min–110° (0 min)–0.5°/min–115° (0 min)–30°/min–180° (0 min); t_R given in min: t_R((+)-**12c**) 22.5, t_R((−)-**12c**) 22.2. Chiral HPLC analyses: Merck-Hitachi l–7100 equipped with a Merck-Hitachi L-4250 UV–vis detector, constant flow, detector 210 nm, t_R given in min; with the following elution conditions: compound **12b**: flow 0.6 mL/min, eluent Hexane/*i*PrOH 99.5:0.5 t_R((**+**)-**12b**) 13.4, t_R((−)-**12b**) 14.4; compound **12d**: flow 1.0 mL/min, eluent Hexane/*i*PrOH 98:2 t_R((**+**)-**12d**) 5.8, t_R((−)-**12d**) 7.1; compound **12e**: flow 1.0 mL/min, eluent Hexane/*i*PrOH 99:1 t_R((**+**)-**12e**) 6.9, t_R((−)-**12e**) 8.8; compound **12f**: flow 1.0 mL/min, eluent Hexane/*i*PrOH 98:2 t_R((**+**)-**12f**) 9.4, t_R((−)-**12f**) 11.1; compound **1g**: flow 1.0 mL/min, eluent Hexane/*i*PrOH 98:2 t_R((**+**)-**1g**) 16.1, t_R((−)-**1g**) 14.4; compound **1h**: flow 1.0 mL/min, eluent Hexane/*i*PrOH 98:2 t_R((**+**)-**1h**) 16.2, t_R((−)-**1h**) 13.0; compound **12i**: flow 1.0 mL/min, eluent Hexane/*i*PrOH 98:2 t_R((**+**)-**12i**) 6.0, t_R((−)-**1g**) 7.4; compound **1j**: flow 1.0 mL/min, eluent Hexane/*i*PrOH 98:2 t_R((**+**)-**1j**) 24.2, t_R((−)-**1j**) 21.1; compound **12m**: flow 0.6 mL/min, eluent Hexane/*i*PrOH 99.5:0.5 t_R((**+**)-**12m**) 17.0, t_R((−)-**12m**) 14.8. Enantiomer excesses of compounds **1a**, **1k** and **1l** were determined by measurement of their specific rotation value and comparison with that of enantiopure **1a**, **1k** and **1l**, respectively. Optical rotations: *Jasco-DIP-181* digital polarimeter. ^{1}H and ^{13}C Spectra: $CDCl_3$ solns. at rt; *Bruker-AC-400* spectrometer at 400 and 100 MHz, respectively; chemical shifts in ppm rel to internal $SiMe_4$ (=0 ppm), *J* values in Hertz. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected.

4.2. Synthesis of the racemic 2-aryl-propan-1-ol 1a–m

Compound **1a** was purchased from Fluka and was used without further purification. The remaining compounds **1b**–**m** were prepared from the corresponding acetophenones (or benzoate esters) **10b**–**m** as described below. Compound **1f** was prepared both from 2-nitroacetophenone (as described in Scheme 1) and by reaction of 2-ethyl-nitrobenzene and paraformaldehyde.[15] The latter procedure was employed in the following experimental section. Acetophenones **10c**, **10d**, **10j,** and **10k** are commercially available. Acetophenones **10b**, **10l,** and **10m** are known compounds and were prepared as previously described.[13b] Acetophenone **10i** was prepared by methylation of 2,6-dihydroxy-4-methylacetophenone[16] with Me_2SO_4 and Na_2CO_3 in refluxing acetone. Methyl esters **10e**, **10g,** and **10h** were prepared by esterification (MeOH/H_2SO_4) of the corresponding benzoic acids. 2-Iodo-benzoic acid and 2-methyl-benzoic acid are commercially available. 2-Ethyl-benzoic acid was obtained by the reaction of an ether solution of (2-ethylphenyl)-magnesium iodide with carbon dioxide. The latter Grignard reagent was prepared starting from 2-ethyl-iodobenzene which was obtained from 2-ethyl-aniline.[17]

4.2.1. Preparation of substituted styrenes 11b–e and 11g–m

To a 3 M solution of methylmagnesium iodide in dry ether (150 mL, 0.45 mol), a solution of the appropriate acetophenone derivative 0.35 mol or methyl benzoate derivative (0.2 mol) in 150 mL of dry ether was added dropwise during 30 min at 0 °C. The mixture was stirred for 3 h at rt and then poured into a mixture of ice and satd aq NH_4Cl solution (250 mL). The aqueous layer was extracted three times with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained crude carbinol was used in the following dehydration step without purification. A solution of the above mentioned carbinol in benzene was treated with a catalytic amount of *p*-toluenesulfonic acid (100 mg, 0.5 mmol) and hydroquinone (100 mg, 0.9 mmol). The mixture was heated at reflux and the liberated water was separated by mean of a Dean Stark apparatus. The formation of the elimination product was monitored by TLC analysis. The reaction was stopped as soon as the starting carbinol was disappeared (from few minutes to 2 h, depending on the substrate used) and the mixture was washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography eluting with hexane/ether (95:5–4:1) as eluent. The obtained alkene was further purified by distillation or crystallisation. The yields and properties of the styrenes are given below.

4.2.1.1. 1-Isopropenyl-2-methoxy-4-methyl-benzene 11b. Colorless oil, 76% yield, 94% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.26 (s, 3H), 3.73 (s, 3H), 4.95–4.99 (m, 1H), 5.02–5.05 (m, 1H), 6.61 (s, 1H), 6,64 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz) δ 21.4, 23.2, 55.4, 111.9, 114.6, 121.1, 129.1, 129.9, 138.3, 144.0, 156.6. GC–MS *m*/*z* (rel intensity) 162 (M^+, 68), 147 (100), 131 (14), 119 (84), 103 (10), 91 (29), 77 (13), 65 (6), 51 (5).

4.2.1.2. 1-Isopropenyl-2,4-dichloro-benzene 11c. Colorless oil, 85% yield, 97% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 4.94–4.97 (m, 1H), 5.21–5.25 (m, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.17 (dd, J = 8.2, 2.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz) δ 23.1, 116.8, 126.9, 129.4, 130.5, 132.7, 133.2, 141.3, 143.2. GC–MS *m*/*z* (rel intensity) 190 (M^++4, 13), 188 (M^++2, 69), 186 (M^+, 100), 173 (24), 171 (35), 159 (8), 151 (49), 136 (25), 115 (64), 99 (13), 89 (7), 75 (14), 63 (7).

4.2.1.3. 1-Bromo-2-isopropenyl-benzene 11d. Colorless oil, 77% yield, 98% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (dd, J = 1.5, 1.0 Hz, 3H), 4.92–4.94 (m, 1H), 5.20–5.22 (m, 1H), 7.05–7.11 (m, 1H), 7.15–7.26 (m, 2H), 7.53 (dd, J = 7.9, 1.0 Hz, 1H). ^{13}C NMR (100 MHz) δ 23.5, 116.0, 121.5, 127.2, 128.3, 129.7, 132.8, 144.9, 145.8. GC–MS *m*/*z* (rel intensity) 198 (M^++1, 100), 196 (M^+−1, 96), 183 (10), 181 (10), 171 (2), 169 (2), 158 (2), 156 (2), 117 (70), 115 (86), 102 (28), 91 (20), 75 (9), 63 (8), 51 (7), 39 (5).

4.2.1.4. 1-Iodo-2-isopropenyl-benzene 11e. Colorless oil, 61% yield, 98% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (dd, J = 1.6, 0.9 Hz, 3H), 4.86–4.90 (m, 1H), 5.19–5.22 (m, 1H), 6.87–6.93 (m, 1H), 7.15 (dm, J = 7.6 Hz, 1H), 7.24–7.30 (m, 1H), 7.81 (dm, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz) δ 23.8, 96.9, 116.0, 128.0, 128.3, 128.4, 139.2, 148.3, 148.8. GC–MS *m*/*z* (rel

intensity) 244 (M^+, 100), 229 (2), 127 (2), 117 (17), 115 (47), 102 (8), 91 (16), 75 (3), 63 (4), 51 (4), 39 (3).

4.2.1.5. 1-Isopropenyl-2-methyl-benzene 11g. Colorless oil, 64% yield, 95% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (dd, J = 1.4, 0.8 Hz, 3H), 2.30 (s, 3H), 4.81–4.85 (m, 1H), 5.15–5.19 (m, 1H), 7.06–7.17 (m, 4H). ^{13}C NMR (100 MHz) δ 19.7, 24.3, 114.6, 125.5, 126.8, 127.8, 130.1, 134.4, 143.9, 145.9. GC–MS m/z (rel intensity) 132 (M^+, 100), 128 (8), 117 (93), 103 (3), 91 (32), 77 (6), 65 (9), 51 (5), 39 (5).

4.2.1.6. 1-Ethyl-2-isopropenyl-benzene 11h. Colorless oil, 60% yield, 94% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.6 Hz, 3H), 2.03 (dd, J = 1.4, 0.8 Hz, 3H), 2.65 (q, J = 7.6 Hz, 2H), 4.81–4.84 (m, 1H), 5.13–5.17 (m, 1H), 7.03–7.25 (m, 4H). ^{13}C NMR (100 MHz) δ 15.9, 25.1, 25.9, 114.6, 125.4, 127.0, 128.1, 128.4, 140.7, 143.5, 145.8. GC–MS m/z (rel intensity) 146 (M^+, 44), 131 (100), 129 (18), 115 (24), 103 (5), 91 (33), 77 (7), 65 (4), 51 (4) 39 (3).

4.2.1.7. 1,3-Dimethoxy-2-isopropenyl-5-methyl-benzene 11i. Colorless needles (hexane), mp 65–66 °C, 52% yield, 99% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.35 (s, 3H), 3.79 (s, 6H), 4.84–4.87 (m, 1H), 5.29–5.33 (m, 1H), 6.40 (s, 2H). ^{13}C NMR (100 MHz) δ 22.0, 23.5, 55.9, 105.0, 115.7, 118.7, 138.0, 139.2, 157.1. GC–MS m/z (rel intensity) 192 (M^+, 60), 177 (100), 162 (14), 149 (49), 134 (8), 119 (23), 105 (6), 91 (21), 77 (8), 65 (5), 51 (3), 39 (3).

4.2.1.8. 1-Isopropenyl-4-methoxy-benzene 11j. Colorless oil which crystallized on standing, mp 31–33 °C, 55% yield, 99% chemical purity by GC;^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.80 (s, 3H), 4.96–5.00 (m, 1H), 5.25–5.29 (m, 1H), 6.85 (dm, J = 8.7 Hz, 2H), 7.40 (dm, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz) δ 21.8, 55.2, 110.6, 113.6, 126.6, 133.9, 142.6, 159.1. GC–MS m/z (rel intensity) 148 (M^+, 100), 133 (68), 115 (6), 105 (12), 89 (8), 77 (13), 63 (5), 51 (4).

4.2.1.9. 1-Isopropenyl-4-methyl-benzene 11k. The crude compound (77% yield) was obtained as an unstable oil which polymerized both on standing and during distillation. Thus, the latter styrene derivative was used in the next step without further purification.

4.2.1.10. 1-Methyl-2-methoxy-4-isopropenyl-benzene 11l. Colorless oil, 66% yield, 98% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (dd, J = 1.2, 0.7 Hz, 3H), 2.20 (s, 3H), 3.83 (s, 3H), 5.01–5.05 (m, 1H), 5.30–5.34 (m, 1H), 6.92 (d, J = 1.7 Hz, 1H), 6.95 (dd, J = 7.7, 1.7 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H). ^{13}C NMR (100 MHz) δ 15.8, 21.9, 55.2, 107.4, 111.6, 117.6, 126.1, 130.3, 140.4, 143.5, 157.6. GC–MS m/z (rel intensity) 162 (M^+, 100), 147 (36), 131 (14), 122 (15), 115 (16), 103 (6), 91 (21), 77 (9), 65 (4), 51 (5).

4.2.1.11. 1-Isopropenyl-2,5-dimethoxy-4-methyl-benzene 11m. Colorless oil, 71% yield, 98% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.21 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 5.05–5.08 (m, 1H), 5.11–5.14 (m, 1H), 6.69 (s, 1H), 6.70 (s, 1H). ^{13}C NMR (100 MHz) δ 16.1, 23.2, 56.0, 56.3, 112.0, 114.7, 114.7, 126.2, 130.6, 144.3, 150.3, 151.6. GC–MS m/z (rel intensity) 192 (M^+, 100), 177 (71), 162 (19), 149 (32), 134 (9), 119 (13), 105 (6), 91 (21), 77 (9), 65 (5), 51 (3), 39 (4).

4.2.2. Preparation of 2-aryl-propan-1-ol 1b–e and 1g–m

The borane–methyl sulfide complex (3 mL, 31.6 mmol) was added dropwise to a cooled (0 °C) solution of the appropriate styrene derivative (60 mmol) in dry THF (50 mL) under nitrogen. The resulting clear solution was warmed to rt and stirred at this temperature for 2 h. Sodium hydroxide (25 mL of aqueous 4 N solution) was added slowly and the resulting mixture was then warmed to 40 °C for 1 h. After this time, hydrogen peroxide (35% solution in water, 20 mL, 206 mmol) was added dropwise keeping the reaction temperature below 30 °C by external cooling (ice bath). When the addition was complete, the reaction mixture was stirred at rt overnight. The main part of the THF was removed under reduced pressure and the aqueous mixture was extracted with Et_2O (3 × 60 mL). The organic phase was successively washed with 5% aq $Na_2S_2O_5$ (100 ml) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ether (9:1–2:1) as eluent to afford pure 2-aryl-propan-1-ol derivative. Yields and properties of the latter compounds are given below.

4.2.2.1. 2-(2-Methoxy-4-methyl-phenyl)-propan-1-ol 1b. Colorless oil, 87% yield, 99% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 7.1 Hz, 3H), 1.61 (br s, 1H), 2.35 (s, 3H), 3.34–3.45 (m, 1H), 3.62–3.77 (m, 2H), 3.83 (s, 3H), 6.72 (s, 1H), 6.78 (d, J = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz) δ 16.6, 21.3, 35.0, 55.3, 67.8, 111.7, 121.3, 127.1, 128.8, 137.2, 157.2. GC–MS m/z (rel intensity) 180 (M^+, 23), 149 (100), 134 (7), 119 (13), 105 (5), 91 (18), 77 (5), 65 (2).

4.2.2.2. 2-(2,4-Dichloro-phenyl)-propan-1-ol 1c. Colorless oil, 89% yield, 98% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 7.0 Hz, 3H), 1.54 (br s, 1H), 3.41–3.52 (m, 1H), 3.63–3.72 (m, 1H), 3.72–3.81 (m, 1H), 7.16–7.25 (m, 2H), 7.38 (s, 1H). ^{13}C NMR (100 MHz) δ 16.7, 37.7, 66.9, 127.3, 128.5, 129.4, 132.6, 134.8, 139.7. GC–MS m/z (rel intensity) 208 (M^++4, 2), 206 (M^++2, 16), 204 (M^+, 24), 175 (75), 173 (100), 159 (6), 137 (26), 125 (4), 114 (4), 102 (30), 75 (7), 63 (2).

4.2.2.3. 2-(2-Bromo-phenyl)-propan-1-ol 1d. Colorless oil, 85% yield, 96% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 7.0 Hz, 3H), 1.48 (br t, J = 5.8 Hz, 1H), 3.45–3.55 (m, 1H), 3.64–3.73 (m, 1H), 3.74–3.83 (m, 1H), 7.04–7.10 (m, 1H), 7.23–7.31 (m, 2H), 7.53–7.59 (m, 1H). ^{13}C NMR (100 MHz) δ 17.0, 40.7, 67.3, 125.2, 127.6, 127.6, 127.9, 133.1, 142.6. GC–MS m/z (rel intensity) 216 (M^++1, 10), 214 (M^+−1, 10), 185 (99), 183 (98), 171 (6), 169 (6), 135 (47), 117 (24), 104 (100), 91 (8), 77 (39), 63 (6), 51 (9), 39 (4).

4.2.2.4. 2-(2-Iodo-phenyl)-propan-1-ol 1e. Colorless oil, 92% yield, 94% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 7.0 Hz, 3H), 1.78 (br s, 1H), 3.25–3.38 (m, 1H), 3.58–3.68 (m, 1H), 3.70–3.80 (m, 1H), 6.86–6.93 (m, 1H), 7.20 (dd, J = 7.9, 1.6 Hz, 1H), 7.27–7.34 (m, 1H), 7.84 (dd, J = 7.9, 1.3 Hz, 1H). ^{13}C NMR (100 MHz) δ 17.3, 45.7, 67.3, 102.2, 126.9, 128.2, 128.5, 139.7, 145.7. GC–MS m/z (rel intensity) 262 (M^+, 32), 231 (100), 217 (4), 135 (39), 117 (10), 104 (63), 91 (6), 77 (18), 63 (3), 51 (5).

4.2.2.5. 2-(2-Nitro-phenyl)-propan-1-ol 1f. Obtained by reaction of 1-ethyl-2-nitrobenzene with paraformaldehyde,[15] colorless oil, 95% yield, 97% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.9 Hz, 3H), 2.06 (br s, 1H), 3.44–3.55 (m, 1H), 3.71–3.81 (m, 2H), 7.31–7.38 (m, 1H), 7.48 (dd, J = 8.0, 1.3 Hz, 1H), 7.53–7.60 (m, 1H), 7.73 (dd, J = 8.0, 1.3 Hz, 1H). ^{13}C NMR (100 MHz) δ 17.5, 36.3, 67.7, 124.0, 127.1, 128.2, 132.5, 138.1, 150.7. GC–MS m/z (rel intensity) 151 (38), 146 (1), 134 (100), 117 (5), 103 (22), 92 (19), 77 (45), 65 (13), 51 (10).

4.2.2.6. 2-(2-Methyl-phenyl)-propan-1-ol 1g. Colorless oil, 90% yield, 97% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ

1.22 (d, J = 6.9 Hz, 3H), 1.72 (br t, J = 5.8 Hz, 1H), 2.34 (s, 3H), 3.16–3.26 (m, 1H), 3.57–3.73 (m, 2H), 7.05–7.22 (m, 4H). ^{13}C NMR (100 MHz) δ 17.4, 19.5, 37.2, 67.9, 125.4, 126.1, 126.2, 130.4, 136.2, 141.8. GC–MS m/z (rel intensity) 150 (M^+, 33), 132 (1), 119 (100), 105 (9), 91 (26), 77 (8), 65 (5), 51 (2), 39 (2).

4.2.2.7. 2-(2-Ethyl-phenyl)-propan-1-ol 1h. Colorless oil, 89% yield, 96% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.6 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.64 (br s, 1H), 2.59–2.80 (m, 2H), 3.20–3.30 (m, 1H), 3.63 (dd, J = 10.7, 6.8 Hz, 1H), 3.69 (dd, J = 10.7, 7.3 Hz, 1H), 7.09–7.21 (m, 4H). ^{13}C NMR (100 MHz) δ 15.8, 18.1, 25.8, 36.5, 68.3, 125.6, 126.2, 126.3, 128.9, 141.3, 142.4. GC–MS m/z (rel intensity) 164 (M^+, 24), 146 (2), 133 (100), 117 (10), 105 (48), 91 (16), 77 (7), 65 (3), 51 (2).

4.2.2.8. 2-(2,6-Dimethoxy-4-methyl-phenyl)-propan-1-ol 1i. Colorless oil, 80% yield, 99% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 7.1 Hz, 3H), 1.74 (br s, 1H), 2.32 (s, 3H), 3.58–3.70 (m, 1H), 3.78 (s, 6H), 3.78 (dd, J = 10.1, 6.5 Hz, 1H), 3.88 (dd, J = 10.1, 7.6 Hz, 1H), 6.38 (s, 2H). ^{13}C NMR (100 MHz) δ 15.4, 21.8, 32.5, 55.7, 66.7, 105.4, 116.8, 137.5, 158.7. GC–MS m/z (rel intensity) 210 (M^+, 15), 192 (1), 179 (100), 164 (3), 149 (7), 134 (4), 119 (7), 105 (3), 91 (10), 77 (5), 65 (2).

4.2.2.9. 2-(4-Methoxy-phenyl)-propan-1-ol 1j. Colorless oil, 90% yield, 99% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, J = 7.0 Hz, 3H), 1.65 (br s, 1H), 2.81–2.92 (m, 1H), 3.62 (d, J = 6.9 Hz, 2H), 3.77 (s, 3H), 6.85 (dm, J = 8.7 Hz, 2H), 7.13 (dm, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz) δ 17.6, 41.5, 55.1, 68.7, 114.0, 128.3, 135.7, 158.3. GC–MS m/z (rel intensity) 166 (M^+, 19), 135 (100), 120 (6), 105 (15), 91 (10), 77 (7), 65 (3).

4.2.2.10. 2-(4-Methyl-phenyl)-propan-1-ol 1k. Colorless oil, 63% yield from **10k**, 97% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 7.0 Hz, 3H), 1.56 (br s, 1H), 2.31 (s, 3H), 2.82–2.93 (m, 1H), 3.63 (d, J = 6.9 Hz, 2H), 7.11 (s, 4H). ^{13}C NMR (100 MHz) δ 17.6, 20.9, 42.0, 68.6, 127.3, 129.2, 136.1, 140.6. GC–MS m/z (rel intensity) 150 (M^+, 18), 119 (100), 103 (4), 91 (17), 77 (5), 65 (4).

4.2.2.11. 2-(3-Methoxy-4-methyl-phenyl)-propan-1-ol 1l. Colorless oil, 85% yield, 98% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 3H), 1.50 (br s, 1H), 2.18 (s, 3H), 2.84–2.95 (m, 1H), 3.62–3.70 (m, 2H), 3.82 (s, 3H), 6.69 (s, 1H), 6.72 (dm, J = 7.5 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H). ^{13}C NMR (100 MHz) δ 15.7, 17.6, 42.5, 55.2, 68.7, 109.4, 118.9, 124.9, 130.7, 142.6, 157.9. GC–MS m/z (rel intensity) 180 (M^+, 31), 162 (1), 149 (100), 134 (8), 119 (8), 117 (9), 103 (3), 91 (15), 77 (5), 65 (2).

4.2.2.12. 2-(2,5-Dimethoxy-4-methyl-phenyl)-propan-1-ol 1m. Colorless needles (hexane), mp 76–77 °C, 90% yield, 99% chemical purity by GC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 7.1 Hz, 3H), 1.64 (br s, 1H), 2.20 (s, 3H), 3.32–3.43 (m, 1H), 3.61–3.75 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 6.69 (s, 1H), 6.70 (s, 1H). ^{13}C NMR (100 MHz) δ 16.0, 16.6, 35.5, 56.1, 56.3, 68.0, 110.4, 114.4, 125.3, 129.7, 151.1, 152.0. GC–MS m/z (rel intensity) 210 (M^+, 32), 192 (2), 179 (100), 164 (28), 149 (10), 134 (3), 117 (4), 103 (3), 91 (9), 77 (5), 65 (2), 53 (2).

4.3. Lipase-mediated resolution of racemic 2-aryl-propan-1-ol. *General procedure*. A solution of the suitable 2-aryl-propan-1-ol derivative (30 mmol), lipase (5 g), vinyl acetate (15 mL) and *t*-BuOMe (60 mL) was stirred at rt and the formation of the acetylated compounds was monitored by TLC analysis. The reaction was stopped at the reported conversion (see Table 1) by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was then purified by chromatography using hexane–diethyl ether (95:5–3:1) as eluent.

The general procedure afforded:

(Using PPL as catalyst): acetate (*S*)-(−)-**12a** as a colorless oil, $[\alpha]_D^{20} = -1.4$ (c 3.5, $CHCl_3$), 98% chemical purity by GC, 78% ee, Ref. 18 $[\alpha]_D$: −2.8 (c 10.09, $CHCl_3$). Alcohol (*R*)-(+)-**1a** as a colorless oil, $[\alpha]_D^{20} = +8.7$ (c 3.2, $CHCl_3$), 98% chemical purity by GC, 66% ee, Ref. 19 (for *S*-isomer) $[\alpha]_D^{28} = -11.7$ (c 1.2, $CHCl_3$).

(Using PPL as catalyst): acetate (*S*)-(+)-**12b** as a colorless oil, $[\alpha]_D^{20} = +24.1$ (c 2, $CHCl_3$), 98% chemical purity by GC, 88% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.9 Hz, 3H), 2.02 (s, 3H), 2.35 (s, 3H), 3.43–3.55 (m, 1H), 3.82 (s, 3H), 4.14 (dd, J = 10.6, 7.4 Hz, 1H), 4.21 (dd, J = 10.6, 6.1 Hz, 1H), 6.70 (s, 1H), 6.75 (d, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz) δ 16.9, 20.9, 21.3, 31.9, 55.2, 68.5, 111.5, 121.1, 127.1, 128.2, 137.3, 157.0, 171.0. GC–MS m/z (rel intensity) 222 (M^+, 4), 162 (38), 149 (100), 134 (6), 119 (20), 105 (7), 91 (17), 77 (5), 65 (3). According to Scheme 3, the procedure was repeated on a larger scale (0.1 mol) allowing the acetylation reaction to reach a conversion of about 60%. The alcohol obtained (*R*)-(−)-**1b** (7 g, 39 mmol) showed the following analytical data: 97% chemical purity by GC, 95% ee by chiral HPLC; $[\alpha]_D^{20} = -2.8$ (c 2.5, $CHCl_3$). The acetate obtained (+)-**12b** was treated with NaOH (6 g, 0.25 mol) in MeOH (80 mL) at reflux for 1 h. After a work-up procedure, the alcohol obtained was again submitted to the resolution procedure allowing the acetylation reaction reached a conversion of about 60%. The obtained acetate (+)-**12b** (8.1 g, 36.5 mmol) showed the following analytical data: 99% chemical purity by GC, 99% ee by chiral HPLC; $[\alpha]_D^{20} = +27.2$ (c 2.5, $CHCl_3$).

(Using PPL as catalyst): acetate (*S*)-(+)-**12c** as a colorless oil, $[\alpha]_D^{20} = +13.3$ (c 3, $CHCl_3$), 98% chemical purity by GC, 83% ee by chiral GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 7.0 Hz, 3H), 2.00 (s, 3H), 3.57–3.68 (m, 1H), 4.12–4.23 (m, 2H), 7.17–7.25 (m, 2H), 7.38 (d, J = 2.0 Hz, 1H). ^{13}C NMR (100 MHz) δ 17.1, 20.7, 34.5, 67.6, 127.3, 128.4, 129.4, 132.8, 134.7, 139.1, 170.7. GC–MS m/z (rel intensity) 246 (M^+, <1), 188 (72), 186 (100), 175 (37), 173 (56), 159 (8), 151 (7), 137 (16), 115 (9), 102 (19), 73 (10). Alcohol (*R*)-(−)-**1c** as a colorless oil, $[\alpha]_D^{20} = -1.4$ (c 3, $CHCl_3$), 97% chemical purity by GC, 52% ee by chiral GC.

(Using lipase PS as catalyst): acetate (*S*)-(+)-**12d** as a colorless oil, $[\alpha]_D^{20} = +8.6$ (c 8, $CHCl_3$), 98% chemical purity by GC, 25% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 7.0 Hz, 3H), 2.01 (s, 3H), 3.59–3.70 (m, 1H), 4.19 (d, J = 6.9 Hz, 2H), 7.05–7.10 (m, 1H), 7.22–7.31 (m, 2H), 7.53–7.57 (m, 1H). ^{13}C NMR (100 MHz) δ 17.4, 20.8, 37.5, 68.0, 124.8, 127.6, 127.6, 128.1, 133.0, 142.1, 170.9. GC–MS m/z (rel intensity) 258 (M^++1, <1), 256 ((M^+−1, <1), 198 (100), 196 (98), 185 (48), 183 (49), 171 (5), 169 (5), 147 (30), 117 (13), 115 (12), 104 (37), 91 (5), 77 (21), 63 (3), 51 (4). Alcohol (*R*)-(−)-**1d** as a colorless oil, $[\alpha]_D^{20} = -2.5$ (c 3.5, $CHCl_3$), 97% chemical purity by GC, 22% ee by chiral HPLC.

(Using PPL as catalyst): acetate (*S*)-(+)-**12e** as a colorless oil, $[\alpha]_D^{20} = +9.6$ (c 3, $CHCl_3$), 97% chemical purity by GC, 26% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 7.0 Hz, 3H), 2.01 (s, 3H), 3.42–3.53 (m, 1H), 4.17 (d, J = 6.9 Hz, 2H), 6.87–6.94 (m, 1H), 7.20 (dd, J = 7.8, 1.6 Hz, 1H), 7.27–7.34 (m, 1H), 7.84 (dd, J = 7.8, 1.2 Hz, 1H). ^{13}C NMR (100 MHz) δ 17.7, 20.8, 42.5, 68.1, 101.5, 126.8, 128.3, 128.4, 139.7, 145.2, 170.7. GC–MS m/z (rel intensity) 304 (M^+, 3), 244 (100), 231 (38), 217 (3), 177 (2), 147 (9), 135 (3), 115 (7), 104 (21), 91 (4), 77 (7). Alcohol (*R*)-(−)-**1e** as a colorless oil, $[\alpha]_D^{20} = -1.8$ (c 5, $CHCl_3$), 97% chemical purity by GC, 10% ee by chiral HPLC.

(Using CRL as catalyst): acetate (*R*)-(−)-**12f** as a colorless oil, $[\alpha]_D^{20} = -82.8$ (c 6, $CHCl_3$), 97% chemical purity by GC, 49% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 6.9 Hz, 3H), 1.98 (s, 3H), 3.66–3.77 (m, 1H), 4.16 (dd, J = 10.8, 7.6 Hz, 1H),

4.25 (dd, J = 10.8, 6.3 Hz, 1H), 7.34–7.40 (m, 1H), 7.47 (dd, J = 8.0, 1.3 Hz, 1H), 7.53–7.60 (m, 1H), 7.75 (dd, J = 8.0, 1.3 Hz, 1H). ^{13}C NMR (100 MHz) δ 17.6, 20.6, 32.9, 68.2, 124.0, 127.3, 128.0, 132.5, 137.2, 150.4, 170.6. GC–MS m/z (rel intensity) 177 (4), 163 (5), 151 (57), 146 (12), 134 (100), 121 (21), 115 (9), 104 (21), 92 (15), 77 (25), 65 (8), 51 (6). Alcohol (*S*)-(+)-**1f** as a colorless oil, $[\alpha]_D^{20} = +2.1$ (c 6, $CHCl_3$), 96% chemical purity by GC, 38% ee by chiral HPLC.

(Using lipase PS as catalyst): acetate (*R*)-(−)-**12g** as a colorless oil, $[\alpha]_D^{20} = -9.2$ (c 6, $CHCl_3$), 97% chemical purity by GC, 43% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.9 Hz, 3H), 1.99 (s, 3H), 2.34 (s, 3H), 3.30–3.41 (m, 1H), 4.08 (dd, J = 10.8, 7.9 Hz, 1H), 4.19 (dd, J = 10.8, 6.3 Hz, 1H), 7.06–7.22 (m, 4H). ^{13}C NMR (100 MHz) δ 17.7, 19.3, 20.7, 33.9, 68.9, 125.5, 126.1, 126.2, 130.3, 135.7, 141.2, 170.8. GC–MS m/z (rel intensity) 192 (M^+, 1), 149 (1), 132 (96), 119 (100), 105 (7), 91 (20), 77 (6), 65 (4), 51 (2), 43 (17). Hydrolysis of the above described (−)-**12g** (NaOH/MeOH) gave alcohol (*R*)-(+)-**1g** as a colorless oil, $[\alpha]_D^{20} = +2.4$ (c 3, $CHCl_3$), 98% chemical purity by GC, Ref. 20 [for the (*S*)-isomer] $[\alpha]_D^{23} = -5.3$ (c 1.5, $CHCl_3$).

(Using lipase PS as catalyst): acetate (*R*)-(−)-**12h** as a colorless oil, $[\alpha]_D^{20} = -11.7$ (c 3, $CHCl_3$), 97% chemical purity by GC, 54% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.6 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.99 (s, 3H), 2.60–2.78 (m, 2H), 3.34–3.45 (m, 1H), 4.11 (dd, J = 10.8, 7.9 Hz, 1H), 4.19 (dd, J = 10.8, 6.5 Hz, 1H), 7.11–7.23 (m, 4H). ^{13}C NMR (100 MHz) δ 15.7, 18.4, 20.7, 25.8, 33.3, 69.3, 125.8, 126.1, 126.5, 128.8, 140.7, 141.9, 170.8. GC–MS m/z (rel intensity) 206 (M^+, 1), 163 (1), 146 (54), 133 (83), 131 (100), 117 (17), 105 (41), 91 (19), 77 (7), 43 (18). Alcohol (*S*)-(−)-**1h** as a colorless oil, $[\alpha]_D^{20} = -1.0$ (c 4, $CHCl_3$), 96% chemical purity by GC, 18% ee by chiral HPLC, Ref. 21 [for the (*R*)-isomer] $[\alpha]_D$ = +5.6 (c 7.15, $CHCl_3$).

(Using CRL as catalyst): acetate (+)-**12i** as a colorless oil, $[\alpha]_D^{20} = +2.1$ (c 2, $CHCl_3$), 96% chemical purity by GC, 21% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 7.1 Hz, 3H), 1.99 (s, 3H), 2.31 (s, 3H), 3.64–3.76 (m, 1H), 3.77 (s, 6H), 4.24 (dd, J = 10.4, 6.4 Hz, 1H), 4.42 (dd, J = 10.4, 8.5 Hz, 1H), 6.35 (s, 2H). ^{13}C NMR (100 MHz) δ 15.9, 21.0, 21.8, 29.1, 55.6, 68.1, 105.2, 116.3, 137.5, 158.6, 171.2. GC–MS m/z (rel intensity) 252 (M^+, 6), 192 (20), 179 (100), 165 (3), 149 (10), 134 (4), 119 (8), 105 (4), 91 (9), 77 (4), 65 (2). Alcohol (+)-**1i** as a colorless oil, $[\alpha]_D^{20} = +5.0$ (c 2, $CHCl_3$), 95% chemical purity by GC, 30% ee by chiral HPLC.

(Using PPL as catalyst): acetate (*S*)-(−)-**12j** as a colorless oil, $[\alpha]_D^{20} = -9.5$ (c 3, $CHCl_3$), 98% chemical purity by GC, 97% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 7.0 Hz, 3H), 1.99 (s, 3H), 2.98–3.09 (m, 1H), 3.77 (s, 3H), 4.08 (dd, J = 10.8, 7.4 Hz, 1H), 4.15 (dd, J = 10.8, 6.8 Hz, 1H), 6.84 (dm, J = 8.7 Hz, 2H), 7.13 (dm, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz) δ 18.1, 20.7, 38.0, 55.1, 69.5, 113.9, 128.1, 135.2, 158.3, 170.8. GC–MS m/z (rel intensity) 208 (M^+, 1), 148 (100), 135 (78), 120 (5), 105 (13), 91 (9), 77 (6), 65 (2). Alcohol (*R*)-(+)-**1j** as a colorless oil, $[\alpha]_D^{20} = +16.6$ (c 3, $CHCl_3$), 97% chemical purity by GC, 89% ee by chiral HPLC, Ref. 9 $[\alpha]_D^{25} = +16.8$ (c 1.37, $CHCl_3$).

(Using PPL as catalyst): acetate (*S*)-(−)-**12k** as a colorless oil, $[\alpha]_D^{20} = -6.7$ (c 3.5, $CHCl_3$), 98% chemical purity by GC, 82% ee, Ref. 22 [for (*R*)-isomer] $[\alpha]_D^{20} = +8.0$ (c 10.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 7.0 Hz, 3H), 2.00 (s, 3H), 2.32 (s, 3H), 2.99–3.10 (m, 1H), 4.10 (dd, J = 10.8, 7.4 Hz, 1H), 4.17 (dd, J = 10.8, 6.8 Hz, 1H), 7.11 (s, 4H). ^{13}C NMR (100 MHz) δ 18.1, 20.8, 20.9, 38.5, 69.4, 127.1, 129.1, 136.1, 140.2, 170.9. GC–MS m/z (rel intensity) 192 (M^+, <1), 132 (100), 119 (76), 105 (5), 91 (15), 77 (5), 65 (3), 43 (15). The procedure was repeated on a larger scale (0.2 mol) allowing the acetylation reaction reached a conversion of about 60%. The alcohol obtained (*R*)-(+)-**1k** (11.5 g, 76.7 mmol) showed the following analytical data: 96% chemical purity by GC, 96% ee; $[\alpha]_D^{20} = +18.0$ (c 3.5, $CHCl_3$), Ref. 22 $[\alpha]_D^{20} = +15.7$ (c 9, $CHCl_3$). The obtained acetate (−)-**12k** was treated with NaOH (12 g, 0.5 mol) in MeOH (150 mL) at reflux for 1 h. After work-up procedure, the obtained alcohol was submitted again to the resolution procedure allowing the acetylation reaction to reach a conversion of about 60%. The acetate obtained (−)-**12k** (13.6 g, 70.8 mmol) showed the following analytical data: 99% chemical purity by GC, 98% ee; $[\alpha]_D^{20} = -8.0$ (c 3.5, $CHCl_3$).

(Using PPL as catalyst): acetate (*S*)-(−)-**12l** as a colorless oil, $[\alpha]_D^{20} = -4.1$ (c 3.3, $CHCl_3$), 98% chemical purity by GC, 85% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 7.0 Hz, 3H), 2.02 (s, 3H), 2.19 (s, 3H), 3.00–3.12 (m, 1H), 3.82 (s, 3H), 4.11 (dd, J = 10.8, 7.5 Hz, 1H), 4.19 (dd, J = 10.8, 6.9 Hz, 1H), 6.68 (s, 1H), 6.72 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz) δ 15.8, 18.2, 20.9, 38.8, 55.1, 69.4, 109.0, 118.7, 124.8, 130.5, 142.0, 157.6, 171.0. GC–MS m/z (rel intensity) 222 (M^+, 8), 162 (100), 149 (45), 134 (7), 117 (9), 105 (3), 91 (13), 77 (4), 65 (2). The procedure was repeated on a larger scale (0.1 mol) allowing the acetylation reaction to reach a conversion of about 65%. The alcohol obtained (*R*)-(+)-**1l**[†] (6.25 g, 34.7 mmol) showed the following analytical data: 96% chemical purity by GC, 96% ee; $[\alpha]_D^{20} = +15.7$ (c 3.5, $CHCl_3$). The acetate obtained (−)-**12k** was treated with NaOH (6 g, 0.15 mol) in MeOH (80 mL) at reflux for 1 h. After work-up procedure, the obtained alcohol was submitted again to the resolution procedure allowing the acetylation reaction to reach a conversion of about 60%. The acetate obtained (−)-**12l** (7.8 g, 35.1 mmol) showed the following analytical data: 99% chemical purity by GC, 95% ee; $[\alpha]_D^{20} = -4.6$ (c 3.5, $CHCl_3$).

(Using PPL as catalyst): acetate (*S*)-(+)-**12m** as a colorless oil, $[\alpha]_D^{20} = +4.0$ (c 2, $CHCl_3$), 98% chemical purity by GC, 88% ee by chiral HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 7.0 Hz, 3H), 2.02 (s, 3H), 2.20 (s, 3H), 3.43–3.54 (m, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 4.14 (dd, J = 10.5, 7.5 Hz, 1H), 4.20 (dd, J = 10.5, 6.2 Hz, 1H), 6.67 (s, 1H), 6.68 (s, 1H). ^{13}C NMR (100 MHz) δ 16.0, 17.1, 20.9, 32.2, 56.2, 56.2, 68.5, 110.4, 114.2, 125.4, 129.1, 151.0, 151.8, 171.1. GC–MS m/z (rel intensity) 252 (M^+, 46), 209 (1), 192 (84), 179 (100), 164 (41), 149 (19), 134 (5), 119 (7), 105 (5), 91 (14), 77 (8), 65 (2), 53 (2). Hydrolysis of the above described (+)-**12m** (NaOH/MeOH) gave alcohol (*S*)-(−)-**1m**[‡], $[\alpha]_D^{20} = -12.9$ (c 2.5, $CHCl_3$), that was recrystallized from hexane to give (−)-**1m**, mp 98–99 °C, $[\alpha]_D^{20} = -13.9$ (c 2, $CHCl_3$), 99% chemical purity by GC, 99% ee by chiral HPLC. The procedure was repeated on a larger scale (0.1 mol) allowing the acetylation reaction reached a conversion of about 65%. The obtained alcohol (+)-**1m** (7.2 g, 34.3 mmol) showed the following analytical data: 96% chemical purity by GC, 95% ee; $[\alpha]_D^{20} = +13.0$ (c 3, $CHCl_3$). The acetate obtained (+)-**12m** was treated with NaOH (6 g, 0.15 mol) in MeOH (80 mL) at reflux for 1 h. After work-up procedure, the obtained alcohol was submitted again to the resolution procedure allowing the acetylation reaction reached a conversion of about 50%. The acetate obtained (+)-**12m** (8 g, 31.7 mmol) showed the following analytical data: 99% chemical purity by GC, 93% ee; $[\alpha]_D^{20} = +4.2$ (c 3, $CHCl_3$).

4.4. Determination of the absolute configuration of the enantioenriched 2-arylpropan-1-ols 1a–m

The absolute configuration and the specific rotations of compounds **1a**,[19] **1g**,[20] **1h**,[21] **1j**[9] and **1k**[22] were previously assigned and measured, respectively. Compound **1i** is new. Since lipases acetylated the latter compound with very low enantioselectivity and a straightforward path to chemical correlate **1i** with a known chiral compound was not found, its absolute configuration was left

[†] This compound was previously prepared (Ref. 23) but its specific rotation value was not reported.

[‡] This compound was previously prepared (Ref. 24) but its specific rotation value was not reported.

unassigned. The absolute configuration of compounds **1b**, **1l,** and **1m** was assigned by chemical correlation with the known[13b] (−)-(*R*)-3-aryl-butan-1-ol derivatives **15b**, **15l,** and **15m**, respectively as described below. Compounds **1c**, **1d,** and **1e** were chemically correlated with compound **1a** via reductive cleavage of the halogen atoms. Compound **1f** was converted into compound **1e** thus allowing chemical correlation with **1a**.

4.4.1. Correlation of compounds 1c–e with the alcohol 1a

The enantioenriched compounds **1c**–**e** or their acetylated derivatives **12c**–**e** (20 mmol) were treated with NaOH (50 mL of a 2 M solution in methanol) and were hydrogenated at atmospheric pressure using 10% Pd/C (100 mg) as catalyst. When 1 equiv of hydrogen (2 equiv for compound **1c**) was adsorbed the catalyst was removed by filtration and the solutions were partitioned between water (100 mL) and ether (100 mL). The aqueous phases were extracted again with ether (50 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residues were purified by chromatography and bulb to bulb distillation to afford enantioenriched 2-phenylpropan-1-ol. Yields and properties of the latter compound are given below.

The hydrogenation of (+)-**12c** (83% ee) afforded (*S*)-(−)-**1a**: yield 85%, $[\alpha]_D^{20} = -10.9$ (*c* 3, $CHCl_3$), 98% chemical purity by GC.

The hydrogenation of (−)-**1d** (22% ee) afforded (*R*)-(+)-**1a**: yield 79%, $[\alpha]_D^{20} = +3.4$ (*c* 3, $CHCl_3$), 97% chemical purity by GC.

The hydrogenation of (+)-**12e** (26% ee) afforded (*S*)-(−)-**1a**: yield 93%, $[\alpha]_D^{20} = -3.3$ (*c* 3, $CHCl_3$), 98% chemical purity by GC.

4.4.2. Correlation of compound (−)-12f with the acetate (−)-12e

A sample of compound (−)-**12f** {$[\alpha]_D^{20} = -82.8$ (*c* 6, $CHCl_3$), 49% ee, 0.94 g, 4.2 mmol} was dissolved in methanol (20 ml) and then hydrogenated at atmospheric pressure using Raney Ni (100 mg) as catalyst. After complete reduction of the nitro group (6 h, TLC analysis) the catalyst was removed by filtration and the solution was diluted with a 1 M aq HCl solution (20 mL). The mixture was cooled to 0 °C and a solution of $NaNO_2$ (0.35 g, 5 mmol) in water (10 mL) was added dropwise under vigorous stirring. After 10 min. a solution of KI (0.9 g, 5.4 mmol) in water (10 mL) was added and the reaction was stirred at room temperature for 4 h. The mixture was then extracted with ether and the organic phase washed with a satd aq $NaSO_3$ solution and then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography using hexane/ether (95:5–8:2) as eluent to afford pure (*R*)-(−)-2-(2-iodo-phenyl)-propan-1-ol acetate **12e** (0.42 g, 33% yield), $[\alpha]_D^{20} = -14.9$ (*c* 3, $CHCl_3$), 94% chemical purity by GC.

4.5. Synthesis of (+)-(*S*)-turmeronol B

4.5.1. (*S*)-3-(2-Methoxy-4-methyl-phenyl)-butyric acid 13

A solution of *p*-toluenesulphonyl chloride (2.85 g, 15 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of alcohol (−)-**1b** {$[\alpha]_D^{20} = -2.8$ (*c* 2.5, $CHCl_3$), 95% ee, 2 g, 11.1 mmol} in pyridine (5 mL). After 4 h, the mixture was diluted with ether (100 mL) and washed in turn with a 1 M aq HCl solution (100 mL), saturated $NaHCO_3$ solution (50 mL) and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in dry DMSO (30 mL) and treated with NaCN (2.5 g, 51 mmol) stirring at 80 °C until the starting tosylate could no longer be detected by TLC analysis (3 h). The mixture was diluted with ether (100 mL) and washed in turn with water and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was then refluxed with NaOH (4 g, 0.1 mol) in ethylene glycol/water 2:1 (50 mL) for 2 h. After cooling the reaction was diluted with water and extracted with ether. The organic phase was discharged and the aqueous phase was acidified with 5 M aq HCl solution and extracted with CH_2Cl_2. Removal of the solvent in vacuo left a thick oil which was purified by chromatography and crystalization from hexane to afford pure (*S*)-3-(2-methoxy-4-methyl-phenyl)-butyric acid **13** (1.61 g, 69% yield), mp 41–43 °C, $[\alpha]_D^{20} = +16.6$ (*c* 2, $CHCl_3$), 97% chemical purity by GC, ee >95%, Ref. 25 $[\alpha]_D^{25} = +16.2$ (*c* 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 7.0 Hz, 3H), 2.32 (s, 3H), 2.51 (dd, *J* = 15.4, 8.8 Hz, 1H), 2.71 (dd, *J* = 15.4, 5.9 Hz, 1H), 3.53–3.64 (m, 1H), 3.80 (s, 3H), 6.67 (s, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz) δ 20.0, 21.3, 29.7, 41.1, 55.2, 111.6, 121.1, 126.7, 130.5, 137.2, 156.8, 179.1. GC–MS *m*/*z* (rel intensity) 208 (M^+, 28), 193 (1), 175 (3), 149 (100), 134 (4). 119 (10), 105 (6), 91 (12), 77 (5), 65 (2).

4.5.2. (*S*)-4,7-Dimethyl-chroman-2-one 14

To a solution of the aforementioned acid (+)-**13** (1.2 g, 5.8 mmol) in dry methylene chloride (30 mL) at 0 °C was added BBr_3 (1.7 mL, 17.6 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 3 h, and then water (10 mL) was added. The resulting mixture was allowed to warm to ambient temperature and neutralized by saturated $NaHCO_3$. The aqueous layer was extracted with ether (2 × 60 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by bulb to bulb distillation to give pure (*S*)-4,7-dimethyl-chroman-2-one (−)-**14**[§] (0.78 g, 76% yield), $[\alpha]_D^{20} = -16.9$ (*c* 2, $CHCl_3$), 98% chemical purity by GC, ee >95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, *J* = 7.0 Hz, 3H), 2.33 (s, 3H), 2.53 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.81 (dd, *J* = 15.6, 5.5 Hz, 1H), 3.13 (m, 1H), 6.85 (s, 1H), 6.93 (dm, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz) δ 19.8, 20.9, 29.0, 36.9, 117.3, 124.7, 125.2, 126.1, 138.4, 151.1, 168.4. GC–MS *m*/*z* (rel intensity) 176 (M^+, 94), 161 (100), 148 (7), 134 (51), 117 (17), 115 (18), 105 (25), 91 (26), 77 (15), 65 (6), 51 (7).

4.5.3. (*S*)-6-(2-Hydroxy-4-methyl-phenyl)-2-methyl-hept-2-en-4-one (turmeronol B) 9

Triethylamine (2 mL, 14.3 mmol) was added dropwise to a stirred mixture of the lactone (−)-**14** (0.6 g, 3.4 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.2 g, 12.3 mmol) in dry DMF (20 mL) under a static atmosphere of nitrogen. The resulting mixture was warmed at 80–90 °C and stirring was prolonged for 24 h. After cooling the reaction was partitioned between satd aq NH_4Cl solution (60 mL) and ethyl acetate (100 mL). The aqueous phase was extracted with further ethyl acetate (50 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in dry THF (20 mL) and the obtained solution was added dropwise to a stirred and cooled (0 °C) solution of 2-methyl-1-propenylmagnesium bromide (30 mL of 1.5 M THF solution, 45 mmol) under nitrogen. After 2 h, the reaction was partitioned between satd aq NH_4Cl solution (100 mL) and ether (100 mL). The aqueous phase was extracted with ether (80 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (9:1–2:1) as eluent to afford pure turmeronol B **9**, as a pale yellow oil which solidified on standing (0.47 g, 59% yield), mp 52–55 °C, $[\alpha]_D^{20} = +80.5$ (*c* 2, $CHCl_3$), 97% chemical purity by GC, ee >95%, Ref. 2g $[\alpha]_D^{20} = +73$ (*c* 0.1, $CHCl_3$), Ref. 2h $[\alpha]_D^{23} = +79$ (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 7.1 Hz, 3H), 1.85 (d, *J* = 0.9 Hz, 3H), 2.11 (d, *J* = 0.9 Hz, 3H), 2.25 (s, 3H), 2.72–2.85 (m, 2H), 3.51–3.62 (m, 1H), 5.98–6.02 (m, 1H), 6.67–6.74 (m, 2H), 7.01 (d, *J* = 7.8 Hz, 1H), 7.93 (s, 1H). ^{13}C NMR (100 MHz) δ 20.9, 21.1, 21.3, 25.8, 27.8, 54.0,

[§] This compound was previously prepared (Ref. 12) but its specific rotation value was not reported.

118.4, 121.6, 123.1, 126.1, 130.2, 137.1, 153.7, 157.7, 201.9. GC–MS *m*/*z* (rel intensity) 232 (M^+, 31), 214 (7), 199 (100), 176 (11), 161 (7), 148 (6), 135 (85), 121 (8), 115 (12), 105 (4), 91 (14), 83 (65), 77 (5), 55 (10).

4.6. Synthesis of (−)-(*R*)-3-aryl-butan-1-ol derivatives 15k, 15b, 15l and 15m

Four samples of the enantioenriched (*S*)-(+)-acetates **12k**, **12b**, **12l,** and **12m** (98%, 99%, 95% and 99% ee, respectively, 5 mmol each) were treated with NaOH (1 g, 25 mmol) in MeOH (20 mL) at reflux for 1 h. After work-up, the alcohols obtained were homologated to their corresponding (*R*)-3-aryl-butyric acid using the procedure described for the synthesis of (*S*)-(+)-**13**. The crude acids obtained were dissolved in dry ether (20 mL) and the solutions were added dropwise to a stirred suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in dry ether (50 mL) under a static atmosphere of nitrogen. The reactions were heated at reflux for 1 h, then cooled to 0 °C and quenched with a 1 M aq HCl solution. The aqueous layers were extracted with ether (100 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residues were purified by chromatography using hexane/ether (9:1–2:1) as eluent to afford pure (*R*)-3-aryl-butan-1-ol derivatives. Yields and properties of the latter compounds are given below.

4.6.1. (*R*)-3-(4-Methyl-phenyl)-butan-1-ol (−)-15k

Colorless oil, 71% yield, $[\alpha]_D^{20} = -32.1$ (*c* 3, $CHCl_3$), 98% chemical purity by GC, Ref. 13a [for the (*S*)-isomer] $[\alpha]_D^{20} = +31.6$ (*c* 1, $CHCl_3$); ^{13}C NMR (100 MHz) δ 20.9, 22.4, 36.1, 41.0, 61.2, 126.8, 129.1, 135.5, 143.8. ^1H NMR and EI-MS superimposable to those previously reported for the (+)-(*S*)-isomer.

4.6.2. (*R*)-3-(2-Methoxy-4-methyl-phenyl)-butan-1-ol (−)-15b

Colorless oil, 66% yield, $[\alpha]_D^{20} = -22.9$ (*c* 2, $CHCl_3$), 97% chemical purity by GC, Ref. 13b [for the (*S*)-isomer] $[\alpha]_D^{20} = +22.8$ (*c* 4, $CHCl_3$); ^{13}C NMR (100 MHz) δ 21.1, 21.3, 27.5, 40.9, 55.5, 61.1, 111.5, 121.7, 126.6, 131.4, 136.7, 156.7. ^1H NMR and EI-MS superimposable to those previously reported for the (+)-(*S*) isomer.

4.6.3. (*R*)-3-(3-Methoxy-4-methyl-phenyl)-butan-1-ol (−)-15l

Colorless oil, 73% yield, $[\alpha]_D^{20} = -25.6$ (*c* 3, $CHCl_3$), 97% chemical purity by GC, Ref. 13b [for the (*S*)-isomer] $[\alpha]_D^{20} = +26.9$ (*c* 2, $CHCl_3$); ^{13}C NMR (100 MHz) δ 15.7, 22.4, 36.6, 41.1, 55.2, 61.3, 108.9, 118.6, 124.3, 130.5, 145.8, 157.8. ^1H NMR and EI-MS superimposable to those previously reported for the (+)-(*S*)-isomer.

4.6.4. (*R*)-3-(2,5-Dimethoxy-4-methyl-phenyl)-butan-1-ol (−)-15m

Colorless oil, 70% yield, $[\alpha]_D^{20} = -41.9$ (*c* 2, $CHCl_3$), 98% chemical purity by GC, Ref. 13b [for the (*S*)-isomer] $[\alpha]_D^{20} = +40.7$ (*c* 4, $CHCl_3$); ^{13}C NMR (100 MHz) δ 16.0, 21.2, 28.0, 41.0, 56.1, 56.5, 61.1, 109.7, 114.4, 124.9, 132.6, 150.7, 152.4. ^1H NMR and EI-MS superimposable to those previously reported for the (+)-(*S*)-isomer.

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