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New chiral building blocks from acetovanillone using lipase A and B from *Candida antarctica*

Erik Fuglseth, Thorleif Anthonsen and Bård Helge Hoff*

Department of Chemistry, Norwegian University of Science and Technology, N-7491, Norway

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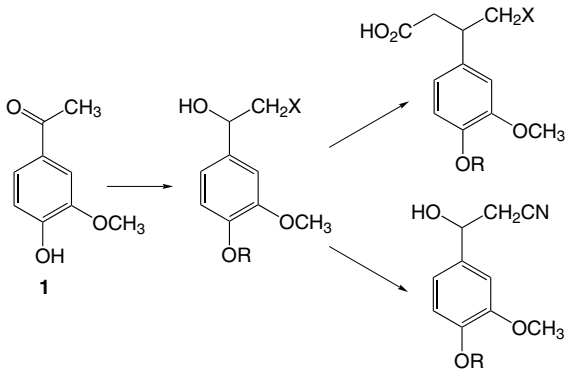
Abstract—Acetovanillone has been used as the starting material for the synthesis of a series of secondary alcohols, which were resolved by lipase catalyzed esterification. 1-(4-Benzyloxy-3-methoxyphenyl)ethanol was efficiently resolved using immobilized lipase B from *Candida antarctica* (Novozym 435, CAL-B), whereas immobilized lipase A from *C. antarctica* (Novozym 735, CAL-A) was the lipase of choice for the resolution of the corresponding 2-bromo- and 2-chloro-derivatives. The enantioenriched alcohols are new building blocks for potential use in the synthesis of bioactive compounds.

1. Introduction

Nature is the primary source for new drug candidates. For instance, extraction of plants and herbs used in folk medicine revealed a number of bioactive molecules containing the 3,4-dihydroxyphenyl-fragment. Examples include flavones with hapatoprotective properties in *Anastatica hierochuntica*,[1] the antihepatoxic flavonolignan Silychristin,[2,3] components in *Salvia miltiorrhiza* with activity against myocardiac infarct and angina pectoris,[4] potential anticancer agents from *Aglaia silvestris*[5] and alkaloids from the Indian medical plant *Alangium lamarckii*.[6] Furthermore, a number of drugs on the market contain the 3,4-dihydroxyphenyl-motif including DOPA, isoprenaline, formoterol and salbutamol. Most of the above mentioned drug and drug candidates contain stereogenic centres, meaning that methods for providing enantiopure starting materials are required, for the synthesis of the target molecules and potentially new analogues. Acetovanillone is a potential starting material in synthetic routes to such compounds. The molecule offers several sites for modification, including halogenation of the α-carbonyl position, reaction at the keto-function, protection of the free phenolic group and substitution of the aromatic ring. The possibility of having two different protecting groups in the aromatic part of the molecule, adds flexibility in the design of a total synthesis. The methoxy group can be removed by the use of $AlCl_3$ and ethanethiol,[7,8] while the benzyl group is most conveniently removed by hydrogenolysis.

Chain elongation of the alkyl part is also possible (Scheme 1). Reaction of the alcohol functionality with triethyl orthoformate yields a new carboxylic acid,[9] whereas cyanation of halohydrins give access to the corresponding nitriles.



Scheme 1. Chain elongation of the alkyl part of acetovanillone **1**.

There are several strategies available for obtaining enantioenriched secondary alcohols, lipase catalyzed kinetic resolution is one option.

Although resolution has the disadvantage of giving a maximum of only 50% yield of each enantiomer, other factors

* Corresponding author. Tel.: +47 73 593 973; fax: +47 73 550 877; e-mail: Bard.Helge.Hoff@chem.ntnu.no

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might favour enzymatic resolution over asymmetric reduction in a commercial setting, such as clean reactions, the possibility of recycling the unwanted enantiomer, and ease of catalyst recycling. In enzyme kinetic resolution, the enantiomeric excesses of the products depend on the degree of conversion. This makes it possible to obtain high ee's provided that lower yield can be accepted. Moreover, in most cases enzymatic resolutions, can be performed in multi-purpose equipment, whereas a more advanced set-up is required for asymmetric reductions.

In enzyme catalyzed resolutions of secondary alcohols, the latter usually have one bulky and one small substituent at the stereogenic centre. Thus provided that steric effects are the primary selection factor, high values are expected. Replacement of a hydrogen at the smaller substituent with a halogen, gives valuable information about the substrate–enzyme interaction. In such cases, electronic effects play a crucial role.

Some structurally related compounds have been resolved using lipases. These include 1-(4-benzyloxy-3-nitrophenyl)-2-bromoethanol,[10] 1-(4-hydroxy-3-methoxyphenyl)-2,2,2-trifluoroethanol,[11] 2,3-dihydro-α-methyl-1,4-benzodioxine-6-methanol[12] and 1-(4-hydroxy-3-methoxyphenyl)-2,2,2-trifluoroethanol.[13]

2. Results and discussion

2.1. Synthesis of racemic starting materials

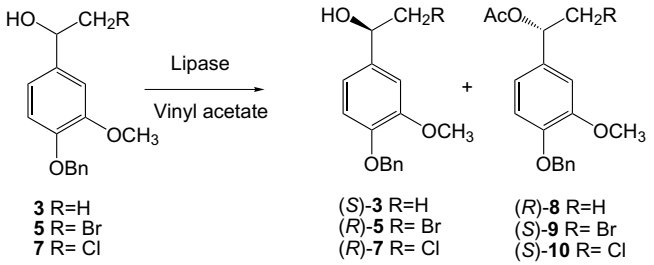
The racemic alcohols were synthesized as shown in Scheme 2. Acetovanillone **1** was benzylated using benzyl chloride and potassium carbonate giving 1-(4-benzyloxy-3-methoxyphenyl)ethanone **2** in good yield. Reduction, using sodium borohydride, gave the racemic alcohol **3**.

Bromination of 1-(4-(benzyloxy)-3-methoxyphenyl) ethanone was troublesome and several reaction systems were investigated. The best was to slowly add bromine into a highly dilute solution of ketone **2**. Product **4** was isolated as a crystalline material. The major by-product was 2,2-dibromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanone. Reduction of α-bromoketone **4** gave racemic alcohol **5**.

The corresponding chloroalcohol **7** was obtained from **5** by transformation to epoxide **6** followed by hydrochlorination aided by β-cyclodextrin.[14] Low yields were experienced in this reaction.

2.2. Kinetic resolution

Racemic alcohols **3**, **5** and **7** (Scheme 3) were resolved with various lipases using dichloromethane and dichloromethane/hexane 1:1 as solvent systems. A fivefold excess of vinyl acetate was used as the acyldonor.



3 R=H
5 R= Br
7 R= Cl

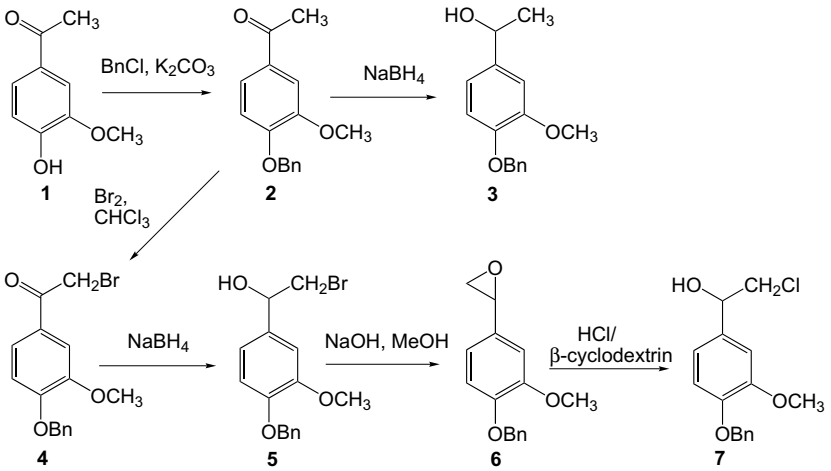
(*S*)-**3** R=H
(*R*)-**5** R= Br
(*R*)-**7** R= Cl

(*R*)-**8** R=H
(*S*)-**9** R= Br
(*S*)-**10** R= Cl

Scheme 3. Lipase catalyzed resolution of the secondary alcohols **3**, **5** and **7**.

Alcohol **3** was the only substrate, which could be resolved with a reasonable reaction rate in pure dichloromethane. Table 1 gives a summary of the selectivity and the relative rate of reaction in the two solvent systems.

The *E*-value of the reaction depended on the enzyme preparation and the solvent used. High *E*-values were obtained using Novozym 435 (CAL-B), *Humicola lanuginosa* (HLL) and Lipozyme TL IM as catalysts. CAL-B has successfully been employed in the resolution of secondary alcohols having a methyl substituent and a very bulky substituent connected to the stereogenic centre.[15–17]



Scheme 2. Synthesis of racemic starting materials.

Table 1. Resolution of **3**

Catalyst	*E*-value Solvent **1**	*E*-value Solvent **2**	Relative rate Solvent **2**/solvent **1**
Novozym 435	94	108	28
Novozym 735	28	24	6
HLL	81	125	11
RML	58	152	7
Lipozyme TL IM	34	97	2

E-values for different catalysts and solvent systems. Solvent **1**; CH_2Cl_2, solvent **2**; CH_2Cl_2/hexane 1:1.

Whereas the enantiomeric ratios in the resolution of **3**, **5** and **7** catalyzed by the *Candida antarctica* lipases were only moderately affected by solvent, a significant effect was observed for the other lipases. Higher *E*-values were obtained using dichloromethane/hexane as the solvent system.

As expected, the rate of reaction was largely affected by the solvent. Lipase B from *C. antarctica* was more sensitive to the choice of solvent than the other lipases. For all lipases, CH_2Cl_2/hexane 1:1 gave the highest rate of reaction.

As both rate and enantiomeric ratio were favoured by the use of dichlormethane/hexane as solvent, **5** and **7** were resolved in this system. The *E*-values in resolutions performed in this solvent system for the secondary alcohols **3**, **5** and **7** are summarized in Table 2.

Table 2. *E*-values obtained in lipase catalyzed resolution of **3**, **5** and **7** in dicloromethane/hexane

Catalyst	*E*-value		
	3	**5**	**7**
Novozym 435	108	No conversion	Slow conversion
Novozym 735	24	>200	89
HLL	125	133	49
RML	152	24	No conversion
Lipozyme TL IM	97	85	25

Novozym 435 was unable to convert **5** to the corresponding esters and reaction of **7** proceeded very slowly with a low *E*-value. This can be explained by the electronic environment at the active site of the enzyme.[18,19] Unfavourable interactions between the halides (at the small sized substituent of the substrate) with the active site of the enzyme, slow down the conversion for the faster reacting enantiomer. This has been observed for a number of substrate classes, including alkyl 4-chloro-3-hydroxybutanoates,[20] 1-aryloxy-3-halo-2-propanols[21–23] and 1-halo-2-alkanols. Resolution of 1-(1,3-dithiane-2-yl)-3-chloro-2-propanol was resolved with a high *E*-value, however the low rate of reaction indicates the same effect.[24] When the small sized substituent contains a chloro-, bromo- or iodo-substituent, CAL-B is not the ideal choice of catalyst. Switching to hydrolytic media seems to be favourable for such substrates.[23]

CAL-A has some unique catalytic properties.[25] Among others, this lipase catalyzes the esterification of tertiary alcohols.[26] The active site of this lipase appears to be rather wide, resulting in low discrimination between enantiomers in many cases. However, high *E*-values have been observed when a bulky group is located in close vicinity to the stereogenic centre.[27] For Novozym 735 catalyzed resolution, the *E*-value is increased when the substrate is changed from **3** to **7**, whereas an *E*-value of 89 was observed for the resolution of **5**. The rate of reaction was not significantly different for the resolution of **3**, **5** and **7**. CAL-A is the enzyme of choice for the resolution **5** and **7**.

H. lanuginosa catalyzed resolution of **3** and **7** with high *E*-values, whereas **5** was resolved with a moderate *E*-value of 49. The rate of reaction was low compared to the other lipases.

The use of Lipozyme TL IM also gave good *E*-values in the cases of **3** and **7**. However, the rate of reaction was extremely low. It is interesting to note that HLL in all cases gave a higher selectivity than Lipozyme TL IM. This might be due to physical changes caused by the immobilization or trace impurities of other lipolytic enzymes.

Rhizomucor lipase (RML) catalyzed the conversion of **3** with a high *E*-value. The introduction of the halides seems to slow down the conversion considerably, probably by decreasing the reaction rate for the faster reacting enantiomer. Other substrates containing $-CH_2Cl$ as the medium sized substituent have been resolved with a high *E*-value using this lipase.[20,28]

The substrates were preparatively resolved in order to characterize the specific rotation properties of these new pairs of enantiomers. Novozym 435 was used for the resolution of **3**, whereas Novozym 735 was used for the resolution of **5** and **7**. The specific rotation data and ee-values are summarized in Table 3.

Table 3. Enantiomeric excesses and specific rotation data for alcohols **3**, **5** and **7** and esters **8**, **9** and **10**

Catalysts	Alcohol	%ee	$[\alpha]_D^{20}$	Acetate ester	%ee	$[\alpha]_D^{20}$
Novozym 435	**3**	99 (*S*)	−27.9	**8**	92 (*R*)	+78.6
Novozym 735	**5**	94 (*R*)	+5.8	**9**	98 (*S*)	+43.1
Novozym 735	**7**	97 (*R*)	−12.1	**10**	95 (*S*)	+39.4

The solvent used for **3**, **5**, **8**, **9** and **10** was chloroform. Methanol was used for compound **7**.

3. Conclusions

Methods have been found for the resolution of a new class of chiral building blocks, which are potentially useful for the preparation of new bioactive molecules. As expected, CAL-B (Novozym 435) displayed high selectivity towards **3**, whereas low activity was observed in the resolution of other substrates. The opposite was true for CAL-A (Novozym 735), giving moderate *E*-value in the case of **3** and preparatively useful *E*-values in resolution of the bromohydrin **5** and chlorohydrin **7**. What this means, in terms of enzyme-substrate interactions, remains to be understood.

For this substrate class, the *Candida antarctica* lipases are complementary in terms of selectivity. The methods

developed could also be useful for resolving structural analogues.

4. Experimental

4.1. General

All enzyme preparations were gifts from Novozymes, Bagsværd, Denmark. Acetovanillone was provided by Borregaard Synthesis, Sarpsborg, Norway. Other chemicals were purchased from Fluka. Column and flash chromatographies were performed using silica gel 60A from Fluka, pore size 40–63 μm.

4.2. Analyses

Optical rotations were determined using a Perkin–Elmer 243 B instrument, concentrations are given in g/100 mL. NMR was recorded with Bruker Avance DPX 300 and Bruker Avance DPX 400 operating at 300 MHz and 400 for ^{1}H and 75 and 100 MHz for ^{13}C. Chemical shifts are in parts per million relative to TMS while coupling constants are in hertz. The mass spectra were recorded using a MAT 95 XL (ThermoQuest Finnigan) with EI probe (DIP) as ionization source. Melting points were determined using a Sanyo Gallenkamp melting point instrument. Enantiomeric ratios, *E*, were calculated based on ping-pong bi-bi kinetics using the computer program *E & K Calculator 2.1b.*[29]

Chiral analyses were performed with a Varian HPLC coupled to a Varian 2550 UV detector. The HPLC column used was a Diacel Chiracel OD-H (i.d. 4.6 mm, length 25 cm, particle size 5 μm). Hexane and isopropanol were used as eluents. Conditions: alcohol **3**: hexane/isopropanol (90:10), flow rate: 1 mL/min, retention times: 16.4 min (*S*)-**3**, 19.7 min (*R*)-**3**, $R_S = 2.1$, alcohol **5**: hexane/isopropanol (95:5), flow rate: 1 mL/min, retention times: 58.1 min (*R*)-**5**, 70.3 min (*S*)-**5**, $R_S = 1.7$, alcohol **7**: hexane/isopropanol (90:10), flow rate: 1 mL/min, retention times: 33.8 min (*R*)-**7**, 42.5 min (*S*)-**7**, $R_S = 2.5$. Acetate **8**: hexane/isopropanol (98:2), flow rate: 1 mL/min, retention times: 24.4 min (*S*)-**8**, 28.9 min (*R*)-**8**, $R_S = 1.9$. Acetate **9**: hexane/isopropanol (95:5), flow rate: 1 mL/min, retention times: 48.1 min (*S*)-**9**, 54.5 min (*R*)-**9**, $R_S = 1.5$. Acetate **10**: hexane/isopropanol (95:5), flow rate: 1 mL/min, retention times: 20.2 min (*S*)-**10**, 22.7 min (*R*)-**10**, $R_S = 1.5$.

4.3. Determination of absolute configurations

The absolute configuration of the faster reacting enantiomer in lipase catalyzed resolution was determined by the known enatiopreference of CAL-B. All enzyme preparations showed the same enatiopreference. Moreover, the elution orders on Diacel Chiracel OD-H of the faster reacting enantiomers were the same.

4.4. Enzymatic reactions

Test reactions were performed in a Minitron Incubator Shaker at 30 °C agitating at 200 rpm. Racemic alcohol (0.12 mmol) and vinyl acetate (50 mg, 0.60 mmol) were mixed in the solvent (3 mL) and the reactions started by the addition of lipase (20 mg). Chiral HPLC analyses gave ee_s- and ee_p-values, from which the degree of conversion was determined according to $c = ee_s/(ee_s + ee_p)$. In controlled experiments under the reaction conditions without enzyme, no acylation was observed. Larger scale reactions were performed as described below.

4.5. Syntheses

1-(4-(Benzyloxy)-3-methoxyphenyl)ethanone **2**: Acetovanillone **1** (11.05 g, 66.5 mmol), potassium carbonate (6.50 g, 0.47 mmol) and benzyl chloride (11.00 g, 86.0 mmol) were mixed in DMF (50 mL) and reacted at 100 °C for 1 h. The solution was then cooled to 50 °C and water (50 mL) was added over 30 min. The crystalline product was isolated by filtration, washed with water (600 mL), dried and re-crystallized from MeOH to give 16.5 g (97%) of **2**, mp: 86–88 °C. MS (*m*/*z*): 256.1 ($M^{\cdot+}$), 92.2, 91.1, 65.1. ^{1}H NMR ($CDCl_3$) δ: 2.52 (3H, s), 3.91 (3H, s), 5.20 (2H, s), 6.87 (1H, d, $J = 8.4$ Hz), 7.29–7.53 (7H, m). ^{13}C NMR ($CDCl_3$) δ: 26.25, 56.06, 70.78, 110.52, 112.13, 123.14, 127.26 (2C), 128.16, 128.73 (2C), 130.73, 136.33, 149.50, 152.41, 196.80.

1-(4-(Benzyloxy)-3-methoxyphenyl)ethanol **3**: 1-(4-(Benzyloxy)-3-methoxyphenyl)ethanone **2** (3.84 g, 15 mmol) was dissolved in MeOH (15 mL) and reduced using sodium borohydride (0.76 g, 20 mmol). Excess sodium borohydride was quenched with dilute HCl. Crystallization from di-isopropyl ether gave 3.50 g (90%) of white crystalline **3**, mp: 47–50 °C. MS (*m*/*z*): 258.0 ($M^{\cdot+}$), 240.0, 167.0 150.0, 92.0, 91.0, 65.0. ^{1}H NMR ($CDCl_3$) δ: 1.48 (3H, d, $J = 6.4$ Hz), 1.84 (1H, s), 3.90 (3H, s), 4.82 (1H, q, $J = 6.4$ Hz), 5.14 (2H, s), 6.82–6.96 (3H, m), 7.28–7.45 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 25.47, 56.41, 70.63, 71.50, 109.60, 114.29, 117.93, 127.68 (2C), 128.21, 128.94 (2C), 137.62, 139.53, 147.90, 150.16.

2-Bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanone **4**: Under an N_2 atmosphere, 1-(4-(benzyloxy)-3-methoxyphenyl)ethanone **2** (5.00 g, 19.5 mmol) was dissolved in dry $CHCl_3$ (100 mL) and bromine (19.7 mmol) dissolved in dry $CHCl_3$ (200 mL) was added during 3 h. The reaction was continued for 12 h more. The $CHCl_3$ solution was washed with $NaHCO_3$ solution (3×100 mL) and water (3×100 mL) and dried over $MgSO_4$. The crude product was crystallized from EtOH yielding 2.45 g (38%), mp: 106–108 °C. MS (*m*/*z*): 336.2/334.2 ($M^{\cdot+}$), 256.3, 92.1, 91.1, 85.0, 83.0, 65.1. ^{1}H NMR ($CDCl_3$) δ: 3.96 (3H, s), 4.40 (2H, s), 5.26 (2H, s), 6.92 (1H, d, $J = 8.4$ Hz), 7.38–7.54 (7H, m). ^{13}C NMR ($CDCl_3$) δ: 30.41, 56.13, 70.87, 99.99, 111.27, 112.12, 123.67, 127.21, 127.27, 128.23, 128.76 (2C), 136.04, 149.78, 153.18 and 190.08.

2-Bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **5**: 2-Bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanone **4** (1.68 g, 5.0 mmol) was dissolved in MeOH (50 mL) at 0 °C and $NaBH_4$ (0.19 g, 5.0 mmol) was added over 5 min. The reduction was continued for 1 h. The reaction mixture was quenched with water and dilute HCl and the

water fraction extracted with CH_2Cl_2 (2×40 mL). The organic fraction was washed with dilute HCl and brine, dried over $MgSO_4$ and concentrated in vacuum yielding an oil. Upon addition of di-isopropyl ether, orange crystals formed. They were isolated by filtration yielding 1.30 g (77%), mp: 61–64 °C. MS (*m*/*z*): 338.2/336.2 ($M^{\cdot+}$), 243.2, 240.3, 149.2, 92.1 and 91.1. ^{1}H NMR ($CDCl_3$) δ: 2.04 (1H, s), 3.54 (1H, dd, $J = 9.2$ and 10.4 Hz), 3.61 (1H, dd, $J = 3.3$ and 10.4 Hz), 3.92 (3H, s), 4.86 (1H, dd, $J = 3.3$ and 9.2 Hz), 5.17 (2H, s), 6.85–6.97 (3H, m), 7.31–7.35 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 40.29, 56.05, 71.02, 73.68 109.45, 113.88, 118.38, 127.25 (2C), 127.90, 128.58 (2C), 133.37, 136.98, 148.23, 149.85.

2-(4-(Benzyloxy)-3-methoxyphenyl)oxirane **6**: To a solution of 2-bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **5** (950 mg, 2.8 mmol) in MeOH (20 mL) was added NaOH (120 mg, 3.0 mmol) while keeping the temperature at 20 °C. The reaction was agitated for 2 h prior to dilution with water (30 mL) and extraction with dichloromethane (2×20 mL). The organic fraction was washed further with water (40 mL) and brine (40 mL). The crude product was purified by column chromatography (EtOAc/pentane, 4:1) giving 415 mg (58%) of the epoxide **6**. MS (*m*/*z*): 256.1 ($M^{\cdot+}$), 165.0, 137.0, 91.0. ^{1}H NMR ($CDCl_3$) δ: 2.78 (1H, dd, $J = 2.6$ and 5.5 Hz), 3.11 (1H, dd, $J = 4.1$ and 5.2 Hz), 3.80 (1H, dd, $J = 2.6$ and 4.1 Hz), 3.90 (3H, s), 5.29 (2H, s), 6.77–6.86 (3H, m), 7.26–7.34 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 51.07, 52.93, 56.02, 71.12, 108.54, 114.04, 118.35, 127.29 (2C), 127.86, 128.56 (2C), 130.62, 137.06, 148.21, 150.04.

2-Chloro-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **7**: β-Cyclodextrin (1135 mg, 1.0 mmol) was dissolved in water (25 mL), shaken at 60 °C, and 2-(4-(benzyloxy)-3-methoxyphenyl)oxirane (**6**) (256 mg, 1.0 mmol) dissolved in MeOH (2 mL) was added. The solution was cooled to 20 °C and HCl (1.5 mL, 1 M, 1.5 mmol) was added. The reaction mixture was left stirring for 2 days, before work up by extraction with EtOAc (3×25 mL). After washing with water, the organic fraction was dried over $MgSO_4$ and concentrated in vacuum. The crude product was crystallized from $CHCl_3$, yield 60 mg (21%), mp: 67–69.5 °C. MS (*m*/*z*): 292/294 ($M^{\cdot+}$, not observed), 274.1, 256.1, 243.1, 91.0. ^{1}H NMR ($CHCl_3$) δ: 3.62 (1H, dd, $J = 8.3$ and 11.1 Hz), 3.66 (1H, dd, $J = 3.5$ and 11.2 Hz), 3.89 (3H, s), 4.26 (1H, br), 4.70 (1H, dd, $J = 3.3$ and 8.3 Hz), 5.12 (2H, s), 6.83–6.98 (3H, m), 7.29–7.35 (5H, m). ^{13}C NMR ($CHCl_3$) δ: 56.00, 68.02, 71.06, 74.41, 109.77, 113.95, 118.31, 127.21 (2C), 127.82, 128.51 (2C), 133.69, 137.05, 147.89, 149.78.

Resolution of 1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **3**: 1-(4-(Benzyloxy)-3-methoxyphenyl)ethanol **3** (903 mg, 3.5 mmol) and vinyl acetate (1507 mg, 17.5 mmol) were dissolved in CH_2Cl_2/hexane (1:1, v/v, 20 mL) and Novozym 435 (100 mg) were added. While keeping the temperature at 30 °C, the mixture was agitated at 200 rpm using a shaker incubator. The reaction was stopped after 24 h by removal of the catalysts by filtration. Ester **8** and alcohol **3** were separated by column chromatography using $CHCl_3$ as mobile phase. Results: (*S*)-1-(4-(Benzyloxy)-3-methoxyphenyl)ethanol (*S*)-**3**: Yield 428 mg (47%) ee (HPLC) 99%, $[\alpha]_D^{20} = -27.9$ (*c* 1.00 $CHCl_3$), mp: 47–50 °C. (*R*)-1-Acetoxy-1-(4-(benzyloxy)-3-methoxyphenyl)ethane (*R*)-**8**: Yield 454 mg (43%), ee (HPLC) 92%, $[\alpha]_D^{20} = +78.6$ (*c* 1.00 $CHCl_3$), mp: 54–56 °C.

(*R*)-1-(4-(Benzyloxy)-3-methoxyphenyl)ethanol (*R*)-**3**: Acetate (*R*)-**8** (454 mg, 1.51 mmol) was hydrolyzed to the corresponding alcohol (*R*)-**8** by standard methods. Yield 280 mg (65%), ee (HPLC) 92%, $[\alpha]_D^{20} = +26.8$ (*c* 1.00 $CHCl_3$), mp: 47–50 °C.

(*S*)-1-Acetoxy-1-(4-(benzyloxy)-3-methoxyphenyl)ethane (*S*)-**8**: Alcohol (*S*)-**3** (428 mg, 1.66 mmol) was acetylated under standard conditions. Yield 337 mg (68%), ee (HPLC) 99%, $[\alpha]_D^{20} = -92.2$ (*c* 1.00 $CHCl_3$), mp: 54–56 °C.

Resolution of 2-bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **5**: 2-Bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **5** (450 mg, 1.3 mmol) and vinyl acetate (575 mg, 6.7 mmol) were dissolved in CH_2Cl_2/hexane (1:1 v/v, 20 mL). Novozym 735 (100 mg) was added and the reaction agitated for 8 h at 30 °C. The catalyst was filtered off and the solvent removed. The product ester and the remaining alcohol were separated by column chromatography ($CHCl_3$/EtOAc, 4:1). Results: (*R*)-2-Bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol (*R*)-**5**: yield 198 mg (44%), ee (HPLC): 94%, $[\alpha]_D^{20} = +5.8$ (*c* 1.00 $CHCl_3$), mp: 47–50 °C. (*S*)-1-Acetoxy-2-bromo-1-(4-(benzyloxy)-3-methoxyphenyl)ethane (*S*)-**9**: yield 231 mg (46%), ee (HPLC): 98%, $[\alpha]_D^{20} = +43.1$ (*c* 1.00 $CHCl_3$), mp: 54–56 °C. MS (*m*/*z*): 379.8/377.8 ($M^{\cdot+}$), 319.8, 297.9, 239.0 206.9, 164.9, 148.9, 92.0, 91.0. ^{1}H NMR ($CDCl_3$) δ: 2.11 (3H, s), 3.56 (1H, dd, $J = 4.6$ and 10.8 Hz), 3.63 (1H, dd, $J = 8.5$ and 10.8 Hz), 3.88 (3H, s), 5.13 (2H, s), 5.88 (1H, dd, $J = 4.6$ and 8.5 Hz), 6.82–6.89 (3H, m) 7.27–7.45 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 21.46, 34.68, 56.49, 71.34, 75.19, 110.67, 114.04, 119.48, 127.62 (2C), 128.33, 128.98 (2C), 131.02, 137.29, 149.00, 150.07, 170.30.

Resolution of 2-chloro-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **7**: 2-Chloro-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol **7** (92 mg, 0.32 mmol) and vinyl acetate (138 mg, 1.6 mmol) were dissolved in CH_2Cl_2/hexane (1:1 v/v, 10 mL). Novozym 735 (55 mg) was added and the reaction was shaken at 30 °C with an agitation rate of 200 rpm. The reaction stopped after 8 h by filtering off the enzyme. The solvent was removed and ester **10** and alcohol **7** were separated by column chromatography (EtOAc/pentane, 4:1). Results: (*R*)-2-Chloro-1-(4-(benzyloxy)-3-methoxyphenyl)ethanol (*R*)-**7**: yield 35 mg (38%), ee (HPLC): 97%, $[\alpha]_D^{20} = -12.1$ (*c* 1.00 MeOH), mp: 67–69.5 °C. (*S*)-1-Acetoxy-2-chloro-1-(4-(benzyloxy)-3-methoxyphenyl)ethane (*S*)-**10**: yield 27 mg (25%), ee (HPLC): 95%, $[\alpha]_D^{20} = +39.4$ (*c* 1.00, $CHCl_3$) MS (*m*/*z*): 334/336 ($M^{\cdot+}$, not observed), 298.1, 256.1, 243.1, 207.1, 91.0. ^{1}H NMR ($CDCl_3$) δ: 2.10 (3H, s), 3.88 (3H, s), 4.29 (2H, m), 5.14 (2H, s), 5.95 (1H, dd, $J = 5.0$ and 7.2 Hz), 6.85–6.89 (3H, m) 7.26–7.36 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 21.10, 56.05, 66.02, 70.95, 73.11, 110.53, 113.76, 119.24, 127.18 (2C), 127.85, 128.54 (2C), 129.42, 136.92, 148.44, 149.66, 170.00.

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