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Dynamic Kinetic Resolution of 2,3-Dihydrobenzo[*b*]furans: Chemoenzymatic Synthesis of Analgesic Agent BRL 37959

Patrick Bongen, Jörg Pietruszka,* and Robert Christian Simon[a]

Abstract: An efficient asymmetric synthesis of (*S*)-2,3-dihydrobenzo[*b*]furan-3-carboxylic acid (**8a**) and (*S*)-5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylic acid (**8b**) was established. Key to the success was the highly stereoselective enzymatic kinetic resolution of the corresponding methyl or ethyl esters that was further developed into a dynamic process. As a reliable and fast tool for analysing the enantiomeric excess, HPLC coupled with a CD detector was utilized. The route was completed by a Friedel–Crafts acylation of ethyl (*S*)-5-chloro-2,3-dihydrobenzo[*b*]-furan-3-carboxylate (**7c**) followed by saponification leading to (*S*)-5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylic acid (**2**), an analgesic agent.

Keywords: chiral resolution · enantioselectivity · enzymes · hydrolases · dynamic kinetic resolution

Introduction

Catalytic processes are of major significance in current (organic) research because they enable production of the desired molecules in a most economical and environmental benign way. Nevertheless, the demand to create more efficient routes to fulfil the concept of sustainability increases steadily.[1] Biocatalysis, as such,[2] meets those requirements and has proven to be remarkably capable, especially in the pharmaceutical and chemical industries.[3] A vast number of different techniques have been elaborated to provide optically pure products, but kinetic resolution (KR)[4] still represents the most frequently used and powerful method developed so far.[5] Although the theoretical maximum overall yield is limited to only 50%, this method holds the advantage of open access to both stereoisomers, which can be important, for example, for enantiocomplementary biological evaluation studies. Nevertheless, because only one enantiomer is required in most synthetic applications, highly sophisticated methods have been established in which a racemisation of the undesired enantiomer is coupled with a chemical or enzymatic kinetic resolution process. The result, a dynamic kinetic resolution (DKR), allows the 50% barrier to be exceeded and can approach a theoretical yield of 100%.[2,6] Popular racemisation strategies include the use of transition-metal-based chemocatalysts, additional biocatalysts, reduction and oxidation processes, bases/acids, or ion-exchange resins.[7,8] Of course, certain issues are required to reach sufficient levels of efficiency in DKR: The resolution process needs to be highly selective ($E > 50$)[9] and the racemization constant (k_{rac}) must be higher than the resolution constant (k_A). Moreover, the final reaction must be irreversible and the product should be stable under certain reaction conditions and not undergo (unwanted) side reactions.[2,6,7]

Racemisation of esters can be especially challenging. Additional activation is often essential to increase the acidity of the substrate, for example, the use of thioesters instead of the required methyl ester was often found to be beneficial.[10] However, additional reaction steps are required to obtain the desired enantiomerically pure target compound. Although successful applications have been reported for unmodified esters, for example, for the synthesis of ibuprofen,[11] the rate for the overall transformation was usually low and hence prolonged reaction times were required. Herein, we present a detailed study on the synthesis of optically pure 3-substituted 2,3-dihydrobenzo[*b*]furan through enzymatic KR and enzymatic DKR that overcomes these restrictions.

The 2,3-dihydrobenzo[*b*]furan structural motif has been identified in an increasing number of natural products and used in (potential) pharmacological drugs exhibiting a broad range of biological activities (Figure 1). For example, imidazole derivative **1** serves as a novel gamma-secretase modulator developed by Pfizer in 2011. It relates to the treatment of Alzheimer's disease and other neurodegenerative disorders, and has IC_{50} values in the sub-micromolar range.[12] The racemic form of 5-chloro-substituted 2,3-dihydro-benzo[*b*]furan **2** (BRL 37959) combines potent analgesic activity with low gastric irritancy, likewise at low concentrations.[13] Novel prostaglandin (PG) D2 receptor antagonists, like compound **3**, were also synthesized and biologically evaluated recently.[14]

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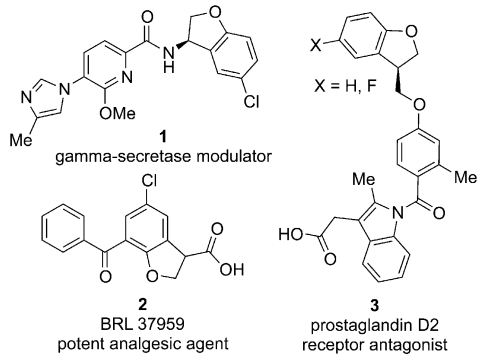


Figure 1. Bioactive substances containing the 2,3-dihydrobenzo[*b*]furan ring structure.

Numerous methods have been reported for the synthesis of 2,3-dihydrobenzo[*b*]furans, including dehydrative methods, cycloadditions, radical-, anionic- and electrochemical cyclisation or transition-metal-catalysed processes,[15] but stereoselective methods are rare. Although asymmetric catalytic hydrogenation of the corresponding benzofuran seems the most obvious route, to the best of our knowledge, only a few examples are known to date.[16] The reason for this paucity of successful outcomes is due to partial cleavage of the furan ring leading to the formation of 2-ethylcyclohexanol and other alcohols.[17]

Results and Discussion

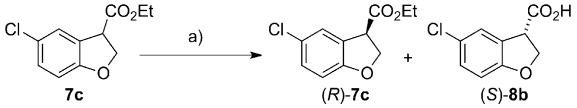
Substrate synthesis for the current study was straightforward (Scheme 1). According to a method described by Hossain and co-workers,[18] salicylaldehyde (**4a**) and its chloro-derivative **4b** were activated with $HBF_4{\cdot}Et_2O$ and treated with ethyl diazoacetate to give intermediates **5a** and **5b** after aryl migration; the semi-acetals were not isolated but directly converted. Subsequent water elimination upon treatment with concentrated H_2SO_4 afforded the corresponding benzofurans **6a** and **6b** in 90 and 75% yield, respectively (two steps). Reduction of the double bond under simultaneous transesterification was achieved with magnesium in MeOH[19] through a single electron transfer (SET) process. The resulting 2,3-dihydrobenzo[*b*]furans **7a** and **7b** were obtained in very good yield (90%). Because Boyle et al. reported a higher yield of the ethyl ester in comparison to the methyl ester **7b** in the late stage Friedel–Crafts aryolation (FCA) of analgesic agent BRL 37959 (**2**),[13] compound **7c** was also prepared by a common transesterification.

With the substrates in hand, we focused on the forthcoming biotransformations of esters **7**. Whereas in the case of methyl esters **7a** and **7b**, *Candida antarctica* Lipase B (CAL-B) and enantiocomplementary *Bacillus subtilis* esterase (BS3) were thought to be appropriate; both enzymes have already been shown to be superior in the enzymatic (D)KR of structurally related methyl 2,3-dihydro-1*H*-indene-3-carboxylate and methyl indoline-3-carboxylate in our previous studies[20] (see also the Supporting Information). To identify further potential hydrolytic enzymes that could be used with ethyl ester **7c**, a HPLC-CD selectivity assay, developed by Reetz and co-workers, was used.[21] The approach is based on HPLC analysis with an achiral stationary phase and a CD-detector, which allows direct determination of the enantiomeric composition (by using a circular dichroism CD-detector [$\Delta\varepsilon$]) of a defined sample at a fixed wavelength. Interestingly, although this ought to be a time-saving evaluation method for enzymes in general, it has only been recently applied in an ADH-screening for the first time after the initial report.[22] The main application still involves determination of the absolute configuration of compounds with unknown chirality.[23]

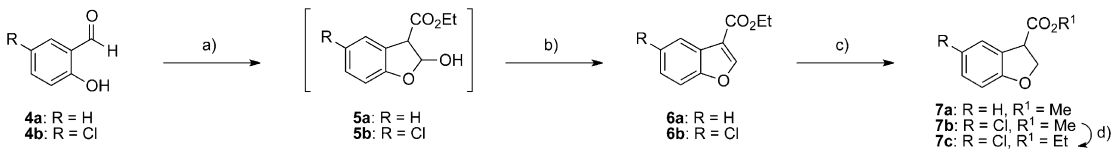
We examined the use of 22 hydrolases (for tested enzymes see the Supporting Information) in the reaction and the *ee* of the substrate was monitored by using HPLC-CD (for details on the method see the Supporting Information) to determine the enantioselectivity. As a result CAL-B and BS3 could be detected as stereoselective hydrolases (Table 1), with the former showing (*S*)-selectivity against the substrate, and the latter showing (*R*)-selectivity. These results were used for the following kinetic resolution studies.

The kinetic resolution of esters **7a–c** were finally performed on a preparative scale [*rac*-**7a**: 2.00 g (11.2 mmol); *rac*-**7b**: 2.00 g (9.4 mmol); *rac*-**7c**: 1.00 g (4.4 mmol)] using an immobilised form of the enzyme CAL-B (Novo 435) under the optimised conditions used for structurally related compounds (Table 2).[20] Due to the insolubility of the sub-

Table 1. Reagents and Conditions: a) CAL-B, 36°C, KPi buffer (100 mM, pH 8.5). ee_E = enantiomeric excess of the ester.

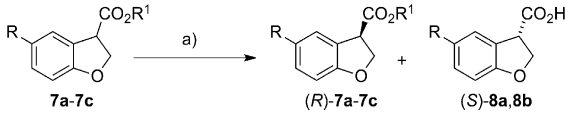


Entry	Enzyme	1 h ee_E [%]	5 h ee_E [%]	10 h ee_E [%]
1	CAL-B	33 (*R*)	66 (*R*)	81 (*R*)
2	BS3	36 (*S*)	50 (*S*)	78 (*S*)



Scheme 1. Synthesis of 2,3-dihydrobenzo[*b*]furans **7a–c**. a) $HBF_4{\cdot}Et_2O$, ethyl diazoacetate, CH_2Cl_2, RT; b) conc. H_2SO_4, CH_2Cl_2, RT (R = H: **6a** 90% over two steps; R = Cl: **6b** 73% over two steps); c) Mg turnings, MeOH (R = H: **7a** 90%; R = Cl: **7b** 90%); d) EtOH, conc. H_2SO_4, 30°C (94%).

Table 2. Kinetic resolution of esters **7a–c**. Reagents and conditions: a) CAL-B (Novo 435), RT, KPi buffer (100 mM, pH 8.5). ee_E = enantiomeric excess of the ester; ee_A = enantiomeric excess of the corresponding acid; c = conversion; t = reaction time.



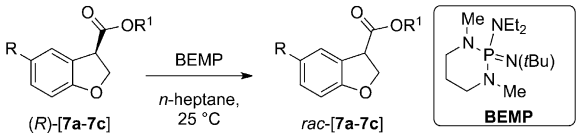
7a-7c (*R*)-**7a-7c** (*S*)-**8a**,**8b**

Entry	R	R^1	t [h]	c [%]	ee_E [%] (yield [%])	ee_A [%] (yield [%])	E value
1	H	Me	4	50	>99 (46)	≈97 (50)	>200
2	Cl	Me	6	50	>99 (49)	>99 (49)	>200
3	Cl	Et	6	50	>99 (47)	> 99 (48)	>200

strates in water, they were emulsified in pure buffer by vigorous stirring to generate a maximum surface and fast conversion. After the theoretical amount of base was consumed to maintain the pH at approximately 8.5 (4–6 h), the reactions were stopped by removing the enzyme by filtration. Subsequent purification afforded the (*R*)-configured esters **7a–c** and the corresponding (*S*)-configured acids **8a** and **8b** in remarkable optical purity (more than 97% *ee* in all cases) and excellent yields (greater than 46%) at 50% conversions (Table 2, entry 1–3). The enantioselectivity was therefore $E>200$ in all reactions. Moreover, considering the fact that only 2% of the net weight of Novo 435 is pure protein,[24] real catalytic ratios of 1:1000 (for *rac*-**7a** and *rac*-**7b**) and 1:2000 (*rac*-**7c**) for the hydrolysis may be calculated.

Regarding the enzymatic DKR, a reliable and efficient protocol for the racemisation was needed to overcome the yield limitation of 50%. Based on our experiences with base-catalysed racemisation and epimerisation,[20] enantiopure starting material (*R*)-[**7a–c**] was initially reacted with the sterically demanding, non-nucleophilic guanidine-base triazabicyclo-1,5,7[4.4.0]-dec-5-ene (TBD) in *n*-heptane. The loss of *ee* could be monitored by chiral HPLC, but TBD proved to be unsatisfactory for our intention; no racemisation could be detected, even at elevated temperatures of 80°C or when an excess of base was used (more than 10 equivalents). Upon seeking an alternative, the Schwesinger base *tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine (BEMP), which is a phosphorous-based organic "super base" with a pK_a of 27.5 (MeCN), was found to be convenient.[25] This base allowed the rate of racemisation to determine as a function of base concentration (Scheme 2).

From a practical point of view, the enantiopure esters (*R*)-[**7a–c**] were treated with different base concentrations and small samples were withdrawn after defined periods of



(*R*)-[**7a-7c**] *rac*-[**7a-7c**]

Scheme 2. Controlled racemisation of the esters (*R*)-[**7a–c**] in the presence of the Schwesinger base BEMP on an analytical scale.

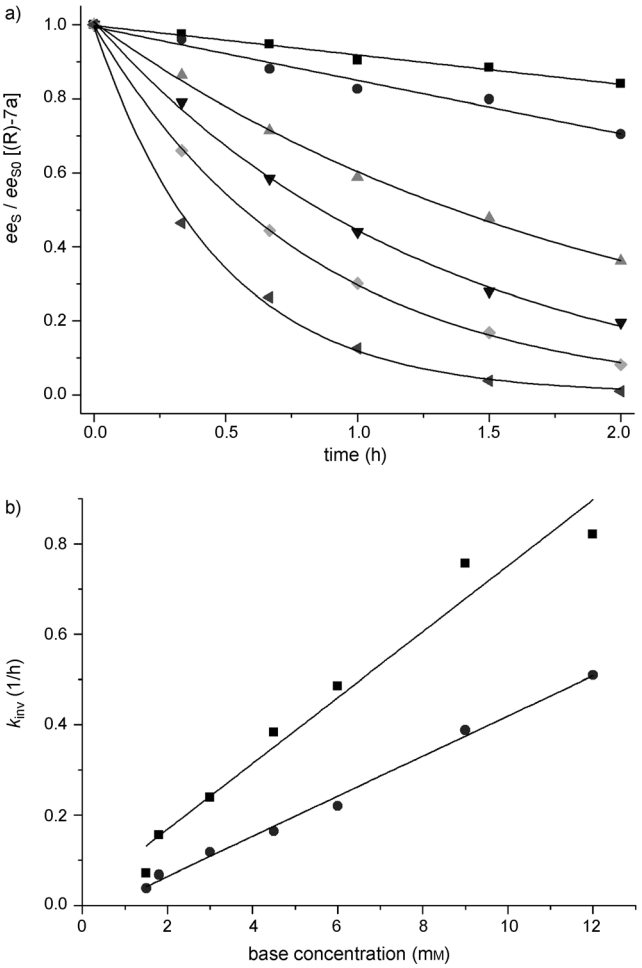
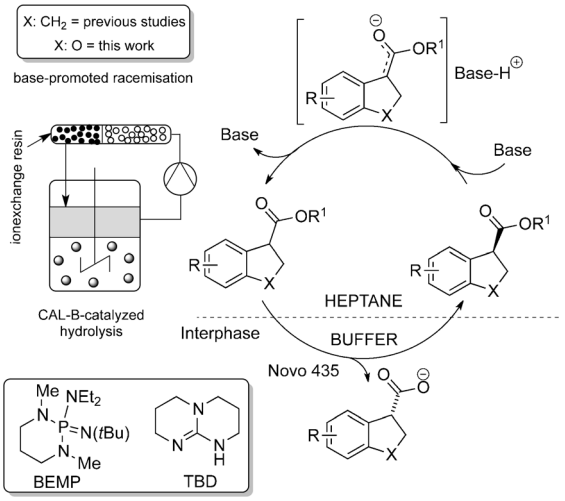


Figure 2. a) Controlled racemisation of methyl ester (*R*)-**7a** (11.2 mM) as a function of the amount of base amount (BEMP; analytical scale). Base concentrations: (■) 35 mM, (●) 68 mM, (▲) 133 mM, (▼) 196 mM, (◆) 256 mM, (◀) 342 mM; b) Linear dependency of the interconversion constants k_{inv} of esters **7b** (■) and **7c** (●) as a function of the amount of base. (——) Calculated values.

time and analysed by chiral HPLC. Figure 2a shows the time-dependent loss of optical purity for ester **7a** as a function of the amount of base (for racemisation curves of esters **7b** and **7c**, see the Supporting Information). As expected, increasing BEMP concentrations resulted in a faster decrease in the *ee* values and, hence, faster racemisation. Notably, all experimental findings are in quantitative agreement with the theoretical results, which are also reflected in the interconversion constants (k_{inv}) of esters **7b** and **7c** (Figure 2b). By using the data from Figure 2a and by considering the base concentration, the racemisation constant ($2k_{rac}=k_{inv}$) can be determined from the ratio of ee_S/ee_{S0} (ee_{S0} = initial *ee* value of the enantiomer, ee_S at a defined time).[26,27] For the nonhalogenated ester **7a**, a k_{rac}/c_{BEMP} value of 2.8×10^{-3} L mmol^{-1} h^{-1} and for the 5-chloro-substituted analogues **7b** and **7c**, 43.7×10^{-3} and 22.2×10^{-3} L mmol^{-1} h^{-1} were calculated, respectively. The reasons for the significant differences in the magnitude of the calcu-

lated values may lie in the stereoelectronic nature of the compounds themselves; the chlorine atom with its electron-withdrawing properties decreases the electron-density at C-3, resulting in faster racemisation. For comparison, it was found that, for complete racemisation of ester **7a** within two hours, approximately 30 equivalents of BEMP were needed, whereas for **7b** and **7c** only 3–4 equivalents were sufficient.

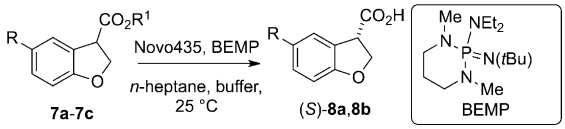
With respect to the enzyme-mediated dynamic kinetic resolution, a highly enantioselective enzyme (CAL-B) and a suitable base (BEMP) for a controlled racemisation were established. To combine both data sets, inactivation of the base through aqueous media needed to be considered. As such, an aqueous one-pot system was ineligible for our purposes. Alternatively, based on a two-compartment system described in 2005 by Bornscheuer and co-workers,[28] a simple reaction setup was designed in which a spatial separation of both processes is realized (Scheme 3).[20a] A standard reaction flask was connected with a peristaltic pump to a pre-packed column containing an immobilised form of BEMP. The application of a basic two-phase system (buffer and *n*-heptane as organic solvent) allows the enzyme and produced acid to be kept in the aqueous layer, whilst the ester (in the organic layer) was continuously pumped through the racemisation column. As a result, a constant racemisation of the ester can be obtained as the enantiomerically pure acid accumulates in the aqueous phase. To avoid unwanted side reactions or inactivation of the enzyme through base leaching, the racemisation column was equipped with a second layer of ion-exchange resin to trap the base.



Scheme 3. Process flow sheet of the reaction setup, and basic principles of the dynamic kinetic resolution for various substrates.

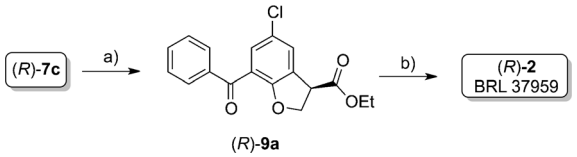
Initial results using methyl ester **7a** as substrate (preparative scale; 500 mg, 2.81 mmol) were promising; the corresponding acid (*S*)-**8a** was isolated after 26 h in 91 % yield with a high optical purity (84 % *ee*), thus already demonstrating dynamic kinetic resolution (Table 3, entry 1). To enhance the enantiomeric excess of the product, the amount of base was increased, keeping the other reaction parameters constant. As a result, the yield (95 %) and the *ee* (ca. 90 %) could be further increased (Table 3, entry 2). Further increasing the amount of base gave even better results; acid (*S*)-**8a** could be isolated after 24 h in a remarkable yield of 92 % with an *ee* value of more than 95 % (Table 3, entry 3). Transferring the reaction conditions to the chlorinated esters also proved to be convenient; in both cases, the acid (*S*)-**8b** was obtained in perfect optical purity (*ee* > 99 %) and in good yield (Table 2, entries 4 and 5). Hence, enzyme-mediated hydrolysis in combination with a chemical racemisation has been developed as a new approach to DKR. It should be noted that the influence of water content in *n*-heptane was not systematically investigated; however, when compared to the racemisation in anhydrous *n*-heptane, no change of the overall performance of the base was observed.

Table 3. Results of the dynamic kinetic resolution of the esters *rac*-**7a**–**c** on preparative scale (reaction setup is depicted in Scheme 3).



Entry	R	R^1	*t* [h]	BEMP [equiv]	ee_A [%]	Yield [%]
1	H	Me	26	0.88	> 84	91
2	H	Me	26	1.00	≈ 90	95
3	H	Me	24	1.50	> 95	92
4	Cl	Me	24	2.00	> 99	71
5	Cl	Et	24	1.00	> 99	82

Markwell and co-workers described in the mid 1980's the synthesis of various organic compounds that were evaluated for analgesic activity in the mouse phenyl-*p*-quinone-induced writhing test. Their studies revealed that racemic 7-benzoyl-5-chloro-2,3-dihydrobenzo[*b*]furan carboxylic acid (BRL 37959) combines potent analgesic activity with low gastric irritancy at low concentrations.[13] Interestingly, despite the promising biological feature, no enantioselective synthesis has yet been realized; therefore, enantiopure ethyl ester (*R*)-**7c** (either from the KR or the DKR after esterification) was treated with the Lewis acid $AlCl_3$ in CS_2 at room temperature, before benzoyl chloride was added. Purification afforded the *R*-configured ethyl ester (*R*)-**9a** in only moderate yield of 30 % after 72 h. Several attempts were made to increase the yield of this step (e.g., variation of ester functionality, the solvent, the reaction time, and amount of Lewis acid), but all failed (see the Supporting Information for optimization studies). Nevertheless, subsequent hydrolysis gave the desired bioactive compound BRL 37959 (*R*)-**2** in good yield (93 %) for the first time (Scheme 4).[29]



Scheme 4. Synthesis of enantiopure analgesic agent BRL 37959 (*R*)-**2**. a) CS_2, $AlCl_3$, 40 °C, 72 h (30 %); b) H_2O, conc. H_2SO_4, RT (93 %).

Conclusions

We have demonstrated that kinetic resolution is a powerful tool that can be used to synthesise enantiopure products with excellent *ee* and yields. Insights from kinetic resolution of methyl ester **7b** could be transferred to the ethyl ester **7c**. After enzyme screening by using HPLC-CD, a fast assay could also be established for the ethyl ester **7c**. Dynamic kinetic resolution can overcome disadvantages associated with kinetic resolution such as yield limitations. With the set-up described here, acids (*S*)-**8a** and (*S*)-**8b** could be obtained in 92 and 71 % yield, respectively, and the enantiomeric excess was determined to be more than 95 and 99 %. Acylation of ester (*R*)-**7c** and subsequent hydrolysis gave the active substance BRL 37959 (*R*)-**2**. Emerging difficulties encountered during the acylation of methyl ester **7b** were avoided by synthesising ethyl ester **7c**.

Experimental Section

All starting materials were obtained from commercial suppliers and used as received unless stated otherwise. Enzyme-catalysed reactions conducted on preparative scale were carried out with Novozyme 435 (*Candida antarctica* lipase B immobilized on acrylic resin from Sigma-Aldrich, activity according to specification: $\geq 10.000\ U\,g^{-1}$, EC: 3.1.1.3; no change of activity or selectivity was observed during the investigation). Synthetic transformations were performed by using standard Schlenk techniques under an Ar/N_2 atmosphere using oven-dried (120 °C) glassware. Solvents were dried and purified either by conventional methods prior to use or by using a Solvent Purification System (MBraun). Preparative chromatographic separations were performed by column chromatography on Merck silica gel 60 (0.063–0.200 μm). Solvents for flash chromatography (petroleum ether/ethyl acetate) were distilled before use. Petroleum ether refers to the fraction with a boiling point between 40–60 °C. TLC analysis was carried out with pre-coated plastic sheets (Polygram SIL G/UV, Macherey–Nagel) with detection by UV (254 nm) and/or by staining with cerium molybdenum solution [phosphomolybdic acid (25 g), Ce$(SO_4)_2 \cdot H_2O$ (10 g), conc. sulfuric acid (60 mL), H_2O (940 mL)]. Optical rotation was measured at 20 °C with a PerkinElmer Polarimeter 241 MC against sodium D-line. ^1H and ^{13}C NMR spectra were recorded at 20 °C with a Bruker Avance/DRX 600 spectrometer in $CDCl_3$ with TMS as internal standard. Chemical shifts are given in ppm relative to the Me_4Si (^1H: $Me_4Si = 0$ ppm) or relative to the resonance of the solvent (^{13}C: $CDCl_3 = 77.0$ ppm or ^{13}C: MeOD = 50.4 ppm).

Ethyl benzo[*b*]furan-3-carboxylate (6a): According to the literature,[18] aldehyde **4a** (2.00 g, 16.4 mmol) was diluted with anhydrous CH_2Cl_2 (4.0 mL) and $HBF_4 \cdot OEt_2$ (54 %, 224 μL, 1.64 mmol) was added at RT. The solution was cooled to 0 °C and ethyl diazoacetate (20 vol % in CH_2Cl_2, 3.00 g, 26.2 mmol) was added dropwise to the reaction within 1 h. When nitrogen formation had ceased, the remaining solvent was removed under reduced pressure. The residue was treated with conc. H_2SO_4 (0.8–1.0 mL) under vigorous stirring for 15 min, then the reaction was diluted with CH_2Cl_2 (15.0 mL) and neutralised with solid $NaHCO_3$. The residue was filtered and concentrated under reduced pressure. Subsequent flash column chromatography (petroleum ether/EtOAc) afforded the product **6a** (2.50 g, 13.1 mmol, 80 %) as a colourless liquid. Spectroscopic data are full in agreement with those reported previously.[18] ^1H NMR (600 MHz, $CDCl_3$) $\delta = 1.43$ (t, $^3J(2',1') = 7.2$ Hz, 3H; 2′-H), 4.41 (q, $^3J(1',2') = 7.2$ Hz, 2H; 1′-H), 7.36 (m_c, 2H; Ar-H), 7.53 (m_c, 1H; Ar-H), 8.07 (m_c, 1H; Ar-H), 8.26 ppm (s, 1H, 2-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 14.4$ (C-2′), 60.6 (C-1′), 111.7 (CH_{Ar}), 112.7 (C-9), 114.8 (CH_{Ar}), 122.1 (CH_{Ar}), 124.1 (CH_{Ar}),124.7 (CH_{Ar}), 125.3 (C_{ipso}), 150.9 (C-2), 155.6 (C_{ipso}), 163.5 ppm (*C*OOEt); GC-MS (EI, 70 eV): *m*/*z* (%): 190 (40) [M^+], 165 (26) [$C_9H_5O_3^+$], 145 (100) [$C_9H_5O_2^+$].

Ethyl 5-chlorobenzo[*b*]furan-3-carboxylate (6b): According to the literature,[18] aldehyde **4b** (3.00 g, 19.2 mmol) was diluted with anhydrous CH_2Cl_2 (15.0 mL) and $HBF_4 \cdot OEt_2$ (54 %, 270 μL, 1.71 mmol) was added at RT. The solution was cooled to 0 °C and ethyl diazoacetate (20 vol % in CH_2Cl_2, 3.00 g, 26.2 mmol) was added dropwise to the reaction within 1 h. When nitrogen formation had ceased, the remaining solvent was removed under reduced pressure. The residue was treated with conc. H_2SO_4 (0.5 mL) under vigorous stirring for 15 min, then the reaction was diluted with CH_2Cl_2 (15.0 mL) and neutralised with solid $NaHCO_3$. The residue was filtered and concentrated under reduced pressure. Subsequent flash column chromatography (petroleum ether/EtOAc) afforded the product **6b** (3.25 g, 14.5 mmol, 73 %) as a colourless solid. Spectroscopic data are full in agreement with those reported previously.[18] M.p. 58 °C; ^1H NMR (600 MHz, $CDCl_3$) $\delta = 1.43$ (t, $^3J(2',1') = 7.1$ Hz, 3H; 2′-H), 4.41 (q, $^3J(1',2') = 7.1$ Hz, 2H; 1′-H), 7.32 (dd, $^3J(6,7) = 8.8$ Hz, $^4J(6,4) = 2.0$ Hz, 1H; 6-H), 7.44 (d, $^3J(7,6) = 8.8$ Hz, 1H; 7-H), 8.03 (d, $^4J(4,6) = 2.1$ Hz, 1H; 4-H), 8.26 ppm (s, 1H; 2-H); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 14.2$ (C-2′), 60.8 (C-1′), 112.7 (CH_{Ar}), 114.6 (CH_{Ar}), 121.8 (CH_{Ar}), 125.6 (CH_{Ar}),125.8 (C_{ipso}), 130.0 (CCl_{Ar}), 152.0 (C-1′), 153.9 (C_{ipso}), 162.8 ppm (*C*OOEt); GC-MS (EI, 70 eV): *m*/*z* (%): 224 (41) [M^+], 196 (33) [$C_9H_4ClO_3^+$], 179 (100) [$C_9H_4ClO_2^+$], 123 (20) [$C_7H_4Cl^+$].

Methyl 2,3-dihydrobenzo[*b*]furan-3-carboxylate (7a): Mg turnings (1.38 g, 56.8 mmol) were added in small portions to a stirred solution of ester **6a** (2.20 g, 11.3 mmol) in anhydrous MeOH (80 mL). After all the Mg had reacted and no staring material could be detected by TLC, the mixture was concentrated under reduced pressure and the residue was extracted against saturated NH_4Cl (300 mL) with CH_2Cl_2 (4 × 20 mL) and EtOAc (50 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent flash column chromatography (petroleum ether/EtOAc acetate, 95:5) afforded the product **7a** (1.81 g, 10.2 mmol, 90 %) as a colourless oil. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 3.78$ (s, 3H; OMe), 4.34 (dd, $^3J(2a,2b) = 9.8$ Hz, $^3J(2a,3) = 6.6$ Hz, 1H; 2-H_a), 4.67 (dd, $^3J(2b,2a) = 9.8$ Hz, $^3J(2b,3) = 9.2$ Hz, 1H; 2-H_b), 4.93 (dd, $^3J(3,2b) = 9.2$ Hz, $^3J(3,2a) = 6.6$ Hz, 1H; 3-H), 6.82 (m_c, 1H; ArH), 6.89 (m_c, 1H; ArH), 7.18 (m_c, 1H; ArH), 7.37 ppm (m_c, 1H; ArH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 47.1$ (C-3), 52.6 ($COOCH_3$), 52.2 (C-2), 110.0, 120.7 (C_{ipso}), 124.1, 125.4, 129.5 (CH_{Ar}), 159.8 (C_{ipso}), 171.6 ppm (COOH); IR (ATR film): $\tilde{\nu} = 2954$, 1735 (C=O), 1596, 1482, 1460, 1435, 1330, 1233, 1204, 1172, 1016, 973, 749 cm^{-1}; GC-MS (EI, 70 eV): *m*/*z* (%): 178 (61) [M^+], 119 (100) [$C_8H_7O^+$], 91 (63) [$C_7H_7^+$]. Determination of the enantiomeric excess by chiral HPLC [column: 4.6 × 250 mm, Chiracel OD-H (Daicel); flow rate = 0.5 mLmin^{-1}; detection λ = 210 nm; solvent = *n*-hexane/2-PrOH (98:2)]: $R_t = 14.76$ [(*R*)-**7a**], 18.36 min [(*S*)-**7b**].

Methyl 5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (7b): Mg turnings (1.78 g, 73.4 mmol) were added in small portions to a stirred solution of ester **6b** (3.00 g, 13.4 mmol) in anhydrous MeOH (150 mL). After all the Mg had reacted and no staring material could be detected by TLC, the mixture was concentrated under reduced pressure and the residue was extracted against saturated NH_4Cl (300 mL) with CH_2Cl_2 (4 × 20 mL) and EtOAc (50 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Subsequent flash column chromatography (petroleum ether/ethyl acetate 90:10) afforded the methyl ester **7b** (2.55 g, 12.0 mmol, 90 %) a yellowish oil. ^1H NMR (600 MHz, $CDCl_3$): $\delta = 3.80$ (s, 3H; OCH_3), 4.32 (dd, $^3J(3,2a) = 6.8$ Hz, ^3J-

(3,2b) = 9.8 Hz, 1H; 3-H), 4.69 (dd, ^2J(2a,2b) = 9.3 Hz, ^3J(2a,3) = 10.2 Hz, 1H; 2-H$_a$), 4.95 (dd, ^3J(2b,3) = 6.8 Hz, ^2J(2b,2a) = 9.8 Hz, 1H; 2-H$_b$), 6.73 (d, J = 8.5 Hz, 1H; ArH), 7.14 (dd, J = 8.4 Hz, J = 2.0 Hz, 2H, ; ArH), 7.34 ppm (m$_c$, 1H; ArH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 47.0 (C-3), 52.8 (C-1′), 73.0 (C-2), 110.9 (CH_{Ar}), 125.4 (C_{ispo}), 125.5, 125.9, 129.4 (CH_{Ar}), 158.6 (C_{ipso}), 171.1 ppm (COOH); IR (ATR film) $\tilde{\nu}$ = 2954, 1736 (C=O), 1605, 1328, 1295, 1238, 1204, 1110, 710 cm^{-1}; GC-MS (EI, 70 eV): m/z (%): 212 (63) [M^+], 153 (100) [$C_8H_6ClO^+$], 125 (81) [$C_6H_3ClO^+$]; elemental analysis calcd (%) for $C_{10}H_{10}ClO_3$ (213): C 56.49, 4.27; found: C 56.32, H 4.32. Determination of the enantiomeric excess by chiral HPLC [column: 4.6×250 mm, Chiralpak IA (Daicel); flow rate = 0.5 mL min^{-1}; detection λ = 254 nm; solvent = *n*-heptane/2-PrOH (98:2)]: R_t = 14.70 [(*R*)-**7b**], 15.42 min [(*S*)-**7b**].

Ethyl 5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (7c): Conc. H_2SO_4 (0.5 mL) was added to a stirred solution of methyl ester **7b** (200 mg, 0.94 mmol) in ethanol (50 mL) and the reaction was stirred for 24 h at 30 °C. EtOH was removed and the H_2SO_4 was neutralised by addition of saturated $NaHCO_3$. The residue was extracted with CH_2Cl_2 (5× 5 mL) and the organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure and the product was purified by flash column chromatography (petroleum ether/EtOAc, 99:1). Ester **7c** (199 mg, 0.88 mmol, 94%) was obtained as a brownish oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.29 (t, ^3J(2′,1′) = 7.2 Hz, 3H; 2′-H), 4.22 (q, ^3J-(1′,2′) = 7.1 Hz, 2H; 1′-H), 4.27 (dd, 3 J(3,2a) = 9.6 Hz, ^2J(3,2b) = 7.0 Hz, 1H; 3-H), 4.65 (dd, ^2J(2a,2b) = 9.6 Hz, 1H; 2-H$_a$), 4.92 (dd, ^2J(2b,2a) = 9.2 Hz, ^3J(2b,3) = 6.9 Hz 1H; 2-H$_b$), 6.69 (d, ^3J(7,6) = 8.5 Hz, 1H; 7-H), 7.10 (dd, ^3J(6,7) = 8.5 Hz, ^4J(6,4) = 1.7 Hz, 1H; 6-H), 7.32 ppm (s, 1H; 4-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.2 (C-2′), 47.1 (C-3), 61.7 (C-1′), 73.0 (C-2), 110.8 (CH_{Ar}), 125.3 (C_{ipso}), 125.4 (CH_{Ar}), 126.2 (CCl_{Ar}), 129.3 (CH_{Ar}), 158.6 (C_{ipso}), 170.4 ppm (*C*OOEt); GC-MS (EI, 70 eV): m/z (%): 226 (63) [M^+], 153 (100) [$C_8H_6ClO^+$], 125 (51) [$C_6H_3ClO^+$]. Determination of the enantiomeric excess by chiral HPLC [column: 4.6×250 mm, Chiralpak IA (Daicel); flow rate = 0.5 mLmin^{-1}; detection λ = 300 nm; solvent = *n*-heptane/2-PrOH 99:1]: R_t = 13.1 [(*R*)-**7c**], 13.9 min [(*S*)-**7c**].

Enzymatic kinetic resolution of methyl 2,3-dihydrobenzo[*b*]furan-3-carboxylate (*rac*-7a): In a typical run, ester *rac*-**7a** (2.00 g, 11.3 mmol) was emulsified in potassium phosphate buffer (30 mL, 100 mM, pH 8.5) at 0 °C (magnetic stirring; >1000 rpm). The reaction was initiated by the addition of Novozyme 435 (100 mg) and the pH was monitored with a pH electrode. The pH was maintained at pH 8.5 during the reaction by the addition of small portions of NaOH solution (2 M) and was stopped after the consumption of 95% of the theoretical amount of base. The aqueous layer was filtered through a plug of cotton wool (to remove the enzyme beads), acidified with aqueous 2 M HCl to pH 2.0, and extracted with EtOAc (5×20 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Subsequent flash column chromatography (petroleum ether/ethyl acetate, 95:5 to 50:50) afforded the methyl ester (*R*)-**7a** (918 mg, 5.14 mmol, *ee* >99%, 46%) as a clear liquid, and the acid (*S*)-**8a** (915 mg, 5.15 mmol, *ee* <97%, 50%) as a colourless solid. Spectroscopic data of the ester **7a** are full in agreement with those reported for its racemate (see above). Optical rotation for (*R*)-**7a**: $[\alpha]_D^{20} = -85.5$ (*c* 0.81, $CHCl_3$, *ee* >99%) {Lit.:[30] $[\alpha]_D^{20} = -8.76$ (*c* 0.69, $CHCl_3$, *ee* 63%)}.

Spectroscopic data for acid (*S*)-8a: M.p. 94 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.37 (dd, ^3J(3,2b) = 9.7 Hz, ^3J(3,2a) = 6.4 Hz, 1H; 3H), 4.67 (dd, ^2J(2a,2b) = 9.4 Hz, ^3J(2a,3) = 9.7 Hz, 1H; 2-H$_a$), 4.92 (dd, ^2J(2b,2a) = 9.3 Hz, ^3J(2b,3) = 6.4 Hz, 1H; 2-H$_b$), 6.83 (dt, J = 8.1, 0.5 Hz, 1H; ArH), 6.90 (td, J = 7.5, 1.0 Hz, 1H; ArH), 7.20 (m$_c$, 1H; ArH), 7.41 ppm (m$_c$, 1H; ArH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 47.0 (C-3), 72.2 (C-2), 110.1, 120.8 (CH_{Ar}), 123.5 (C_{ipso}), 125.5, 129.8, 159.8 (C_{ipso}), 176.6 ppm (*C*OO); IR (ATR film): $\tilde{\nu}$ = 2898, 1720 (C=O), 1625, 1481, 1381, 1231, 970, 755 cm^{-1}; GC-MS (EI, 70 eV): m/z (%): 164 [M^+] (65), 119 [$C_8H_7O^+$] (100), 91 [$C_7H_7^+$] (88); elemental analysis calcd (%) for $C_9H_8O_3$: C 65.85, 4.91; found: C 66.17, H 5.13. Optical rotation for (*S*)-**8a**: $[\alpha]_D^{20} = +79.6$ (*c* 0.66, $CHCl_3$, *ee* <97%). Determination of the *ee* was performed after derivatisation with etherical diazomethane solution to the corresponding methyl ester (see above).

Enzymatic kinetic resolution of methyl 5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (*rac*-7b): In a two-necked reaction flask, ester *rac*-**7b** (2.00 g, 9.40 mmol) was emulsified in potassium phosphate buffer (60 mL, 100 mM, pH 8.0). The flask was equipped with a pH electrode and a magnetic stirring bar (stirring at >1000 rpm). After immobilized *Candida antarctica* (Novo 435) (100 mg) was added, the pH was maintained at pH 8.0 during the reaction by addition of small portions of NaOH (1 M). When an *ee* of more than 95% (determined by HPLC analysis, approx. 6 h) was reached for substrate (*R*)-**7b**, the mixture was filtered through a plug of cotton wool and the organic phase was separated. The remaining aqueous layer was acidified with 1 M HCl to pH 1.0 and extracted with EtOAc (4×40 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (petroleum ether/EtOAc 90:10 + 1 vol% AcOH) to give ester (*R*)-**7b** (995 mg, 4.68 mmol, *ee* >99%, 49%) as a colourless oil and the acid (*S*)-**8b** (921 mg, 4.70 mmol, *ee* >99%, 49%) as colourless solid. Spectroscopic data of the ester (*R*)-**7b** are full in agreement with those reported for its racemate (see above). Optical rotation for (*R*)-**7b** $[\alpha]_D^{20} = +29$ (*c* 0.91, $CHCl_3$, *ee* >99%).

Spectroscopic data for acid (*S*)-8b: M.p. 75 °C; $[\alpha]_D^{20} = -7$ (*c* 0.59, $CHCl_3$ *ee* >99%); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.36 (dd, ^3J(3,2a) = 9.4 Hz, ^3J-(3,2b) = 6.7 Hz, 1H; 3-H), 4.69 (dd, ^2J(2a,2b) = 9.5 Hz, ^2J(2a,3) = 9.5 Hz, 1H; 2-H$_a$), 4.93 (dd, ^2J(2b,2a) = 9.4 Hz, ^2J(2b,3) = 6.6 Hz, 1H; 2-H$_b$), 6.75 (d, ^3J(7,6) = 8.6 Hz, 1H; 7-H), 7.16 (dd, ^3J(6,7) = 8.6 Hz, ^4J(6,4) = 2.0 Hz, 1H; 6-H), 7.36–7.41 (m, 1H; 4-H), 11.36 ppm (s, 1H; COO*H*); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 46.9 (C-3), 72.7 (C-2), 111.0 (CH_{Ar}), 125.1 (C_{ipso}), 125.6 (CH_{Ar}), 125.6 (CCl_{Ar}), 129.8 (CH_{Ar}), 158.5 (C_{ipso}), 176.7 ppm (*C*OOH); MS (ESI): m/z (%): 198 (100) [M^+].

Enzymatic kinetic resolution of ethyl 5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (*rac*-7c): In a typical run, the ester *rac*-**7c** (1.00 g, 4.41 mmol) was emulsified in potassium phosphate buffer (100 mL, 100 mM, pH 8.5) at 0 °C. The flask was equipped with a pH electrode and a magnetic stirring bar (stirring at >1000 rpm). After immobilized *Candida antarctica* (Novo 435) (50 mg) was added, the pH was maintained at pH 8.5 during the reaction by addition of small portions of NaOH (1 M). When an *ee* of >95% (determined by HPLC analysis, approx. 6 h) was reached for substrate (*R*)-**7c**, the mixture was filtered through a plug of cotton wool and the organic phase was separated. The remaining aqueous layer was acidified with 1 N HCl to pH 1.0 and extracted with EtOAc (4×40 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (petroleum ether/EtOAc, 90:10 + 1 vol.% AcOH) to give the ester (*R*)-**7c** (412 mg, 2.07 mmol, *ee* >99%, 47%) as a colourless oil and the acid (*S*)-**8b** (480 mg, 2.11 mmol, *ee* >99%, 48%) as colourless solid. Spectroscopic data of ester (*R*)-**7c** are full in agreement with those reported for its racemate (see above). Optical rotation for (*R*)-**7c** $[\alpha]_D^{20} = +17.0$ (*c* 0.25, $CHCl_3$, *ee* >99%). Spectroscopic data of acid (*S*)-**8b** are in full agreement with those reported (see above).

Representative procedure for the determination of racemisation constant k_{rac} of [(*R*)-7a]: A stock solution (1 mL) of enantiopure (*R*)-**7a** (2 μL in 1 mL *n*-heptane) and BEMP (10, 20, 40, 60, 80 and 110 μL) were mixed in an Eppendorf vial. All reactions were shaken at 25 °C and 1400 rpm, and aliquots (50 μL) were removed after defined periods of time (20, 40, 60, 90 and 120 min). The removed samples were diluted with *n*-heptane (300 μL) and extracted against NH_4Cl (500 μL). The organic layer was dried over $MgSO_4$ and a sample (200 μL) of each was analysed by chiral HPLC (see above).

Enzymatic dynamic kinetic resolution of methyl 2,3-dihydrobenzo[*b*]furan-3-carboxylate (*rac*-7a): Before starting DKR, a 5 mL syringe was prepared as follows: cotton wool was placed on the bottom, overlaid with cation exchange resin (3.00 g; Merck, Amberlite, IRC-50, mesh 20–30). A second layer of cotton wool followed and the immobilised base BEMP on PS (2.00 g) was then added. The syringe was capped with a third layer of cotton. The ester *rac*-**7a** (500 mg, 2.81 mmol) was dissolved in *n*-heptane (20 mL) and placed in a three-necked flask with potassium phosphate buffer (65 mL, 100 mM, pH 8.5) and immobilized *Candida antarctica* lipase B (50 mg, Novo 435) was added. After 5 min, a Teflon tube con-

nected to a peristaltic pump (Pharmacia Bioscience P1, flow 0.5 mL min^{-1}) was dipped into the organic layer. The other side behind the peristaltic pump was connected to the syringe. The pump was run continuously until the end of the reaction. The pH value was monitored with a pH electrode and maintained at pH 8.8 by the addition of 1 M NaOH. When the theoretical amount of NaOH was consumed, the reaction was stopped (ca. 24 h). The mixture was filtered through cotton wool to remove the enzyme. The organic layer was separated and the aqueous layer was acidified with aqueous 2 M HCl to pH 2.0. The aqueous layer was extracted with EtOAc (5×20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/EtOAc 90:10+1 vol% AcOH) to give the acid (*S*)-**8a** (424 mg, 2.58 mmol, *ee*> 95%, 92%) as a colourless solid. Spectroscopic data are full in agreement with those reported in the kinetic resolution (see above).

Enzymatic dynamic kinetic resolution of methyl 5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (*rac*-7b): Before starting DKR, a 5 mL syringe was prepared as follows: cotton wool was placed on the bottom, overlaid with cation exchange resin (1.00 g; Merck, Amberlite, IRC-50, mesh 20–30). A second layer of cotton wool followed and the immobilised base BEMP on PS (1.00 g) was then added. The syringe was capped with a third layer of cotton. The ester *rac*-**7b** (500 mg, 2.35 mmol) was dissolved in *n*-heptane (40 mL) and placed with potassium phosphate buffer (60 mL, 100 mM, pH 8.0) in a three necked flask. Immobilised *Candida antarctica* Lipase B (25 mg, Novo 435) was then added. After 5 min, a Teflon tube connected to a peristaltic pump was dipped into the organic layer. The other side behind the peristaltic pump was connected to the syringe. The pump was run continuously at 0.5 mL min^{-1} until the end of the reaction. The pH value was monitored with a pH electrode and was maintained at pH 8.8 by the addition of 1 M NaOH. After the theoretical amount of NaOH was consumed, the reaction was stopped (ca. 35 h). The mixture was filtered through cotton wool to remove the enzyme. The organic layer was separated and the aqueous layer was acidified with 1 M HCl to pH 1.0. The aqueous layer was extracted with EtOAc (4× 40 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/EtOAc 90:10 + 1 vol% HOAc) to give the acid (*S*)-**8b** (329 mg, 1.66 mmol, *ee*>99%, 71%) as a colourless solid. Spectroscopic data are full in agreement with those reported in the kinetic resolution (see above).

Enzymatic dynamic kinetic resolution of ethyl 5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (*rac*-7c): Before starting DKR, a 5 mL syringe was prepared as follows: cotton wool was placed on the bottom, overlaid with cation exchange resin (2.00 g; Merck, Amberlite, IRC-50, mesh 20–30). A second layer of cotton wool followed and the immobilised base BEMP on PS (1.00 g) was then added. The syringe was capped with a third layer of cotton. The ester *rac*-**7c** (1.00 g, 4.41 mmol) was dissolved in *n*-heptane (20 mL) and placed with potassium phosphate buffer (40 mL, 100 mM, pH 8.0) in a three-necked flask. Immobilised *Candida antarctica* Lipase B (40 mg, Novo 435) was then added. After 5 min, a Teflon tube connected to a peristaltic pump was dipped into the organic layer. The other side behind the peristaltic pump was connected to the syringe. The pump was run continuously (0.5 mL min^{-1}) until the end of the reaction. The pH value was monitored with a pH electrode and was maintained at pH 8.5 by addition of 1 M NaOH. When the theoretical amount of NaOH was consumed, the reaction was stopped (ca. 24 h). The mixture was filtered through cotton wool to remove the enzyme. The organic layer was separated and the aqueous layer was acidified with 1 M HCl to pH 1.0. The aqueous layer was extracted with EtOAc (4× 40 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Subsequent flash column chromatography (petroleum ether/EtOAc 90:10 + 1 vol% AcOH) afforded the acid (*S*)-**8b** (720 mg, 3.62 mmol, *ee*>99%, 82%). Spectroscopic data are full in agreement with those reported in the kinetic resolution (see above).

Ethyl 7-benzoyl-5-chloro-2,3-dihydrobenzofuran-3-carboxylate [(*R*)-9a]: According to the literature,[13] $AlCl_3$ (1.60 g, 12.0 mmol) was suspended in CS_2 (10 mL) under an atmosphere of dry nitrogen. The mixture was cooled to 0 °C and benzoyl chloride (1.68 g, 12.00 mmol) was added. Ethyl ester (*R*)-**8c** (400 mg, 1.76 mmol) was diluted with CS_2 (2 mL) and transferred into the reaction vessel. The mixture was allowed to warm to ambient temperature and stirred for a further 72 h. The solution was poured onto ice with 5 M HCl and extracted with CH_2Cl_2 (3×40 mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remaining brown oil was purified by flash column chromatography (petroleum ether/EtOAc, 99:1) to afford the product (175 mg, 0.53 mmol, 30%) as a colourless oil. Spectroscopic data are full in agreement with those reported previously.[13] $[\alpha]_D^{20} = -43$ (*c* 0.32, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.34$ (t, $^3J(2',1') = 7.2$ Hz, 3H; 2′-H), 4.28 (q, $^3J(1',2') = 7.1$ Hz, 2H; 1′-H), 4.34 (dd, ^3J-(3,2a) = 9.4 Hz, $^2J(3,2b) = 7.9$ Hz, 1H; 3-H), 4.73 (dd, $^2J(2a,2b) = 13.0$ Hz, $^3J(2a,3) = 9.7$ Hz, 1H; 2-H_a), 4.95 (dd, $^2J(2b,2a) = 12.3$ Hz, $^2J(2b,3) =$ 7.4 Hz, 1H; 2-H_b), 7.41 (s, 1H; 6-H), 7.47 (m_c, 2H; ArH), 7.52 (s, 1H; 4-H), 7.59 (m_c, 1H, ArH), 7.76–7.84 ppm (m, 2H; ArH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 14.2$ (C-2′), 46.5 (C-3), 62.0 (C-1′), 73.8 (C-2), 122.3 (C-8), 125.5 (C_{ipso}), 128.1 (CCl_{Ar}), 128.3 (CH_{Ar}), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.9 (CH_{Ar}), 128.9 (CH_{Ar}), 129.6 (CH_{Ar}), 129.9 (CH_{Ar}), 137.1 (C-1‴), 157.2 (C_{ipso}), 169.9 (C-10), 192.9 ppm (*C*OOEt); GC-MS (EI, 70 eV): *m*/*z* (%): 330 (67) [M^+], 257 (63) [$C_{15}H_{10}ClO_2^+$], 179 (23) [$C_9H_5ClO_2^+$], 105 (100) [$C_7H_5O^+$], 77 (44) [$C_6H_5^+$].

7-Benzoyl-5-chloro-2,3-dihydrobenzofuran-3-carboxylic acid [(*R*)-2]: Ethyl ester (*R*)-**9a** (200 mg, 0.60 mmol) was dissolved in THF (5 mL) and conc. HCl (10 μL) was added to demineralised H_2O (1 mL). The aqueous solution was transferred to the reaction mixture that was stirred for 24 h at RT. THF was removed by rotary evaporation and the residue was quenched with NH_4Cl and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was dried over $MgSO_4$ and the solvent was removed by under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc, 90:10+1 vol.% AcOH) to afford the product (170 mg, 0.56 mmol, 93%) as a slightly yellow oil. Spectroscopic data are full in agreement with those reported in literature.[13] $[\alpha]_D^{20} = +40$ (*c* 0.58, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 4.41$ (dd, $^3J(3,2a) = 9.2$ Hz, $^3J(3,2b) = 7.3$, 1H; 3-H), 4.74 (dd, ^2J-(2a,2b) = 9.5 Hz, $^3J(2a,3) = 9.5$, 1H; 1-H_a), 4.96 (dd, $^2J(2b,2a) = 9.4$ Hz, ^3J-(2b,3) = 6.9 Hz, 1H; 2-H_b), 7.13–7.19 (m, 1H; ArH), 7.44–7.52 (m, 2H; ArH), 7.54–7.67 (m, 2H; ArH), 7.73–7.85 ppm (m, 2H; ArH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 21.4$ (C-3), 73.5 (C-2), 122.4 (C-7), 125.3 (C_{ipso}), 125.7 (CCl_{Ar}), 127.3 (CH_{Ar}), 128.3 (CH_{Ar}), 128.4 (CH_{Ar}),129.1 (CH_{Ar}), 129.1 (CH_{Ar}), 129.9 (CH_{Ar}), 130.6 (CH_{Ar}), 133.3 (C-1′), 137.0 (C-2′), 157.2 (C_{ipso}), 192.9 ppm (*C*OOH); MS (ESI, cation): *m*/*z* (%): 303 [M^+].

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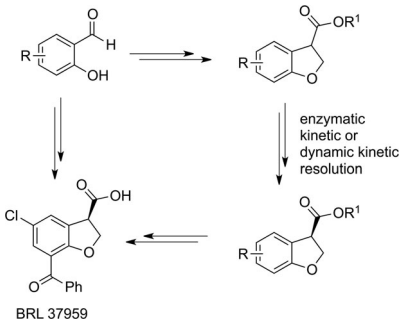
BRiLliant synthesis! With an enantioselectivity assay based on a HPLC-CD protocol as a starting point, first the kinetic and then the dynamic kinetic enzymatic resolution of the title compounds was performed (see scheme). For the first time, access to the enantiomerically pure active agent BRL 37959 was established in a short and concise manner.



Kinetic Resolution

*P. Bongen, J. Pietruszka,**
R. C. Simon ..... ▮▮▮▮–▮▮▮▮

Dynamic Kinetic Resolution of 2,3-Dihydrobenzo[*b*]furans: Chemoenzymatic Synthesis of Analgesic Agent BRL 37959