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Direct resolution of α-monoalkyl-α-aryloxyacetic acids via ester or imide derivatives

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Abstract

This paper describes a simple procedure for the resolution of racemic α-monoalkyl α-aryloxyacetic acids, using the chromatographic separation of their covalent derivatives. (*R*)-Ethyl mandelate, (*R*)-pantolactone and (*S*)-4-(1-methylethyl)-2-oxazolidinone are the resolving agents involved in the formation of equimolecular diastereomeric mixtures of esters or imides. Chromatographic resolutions were performed by means of gas chromatography (GC), thin-layer chromatography (TLC) and flash chromatography. Successive hydrolysis of separated diastereomers provided optically pure aryloxyacetic acids.

Keywords: α-Monoalkyl α-aryloxyacetic acids; Direct resolution; Ester derivatives; Imide derivatives; (*R*)-Ethyl mandelate; (*R*)-Pantolactone; (*S*)-4-(1-Methylethyl)-2-oxazolidinone

1. Introduction

Clofibrate, a halogenated phenoxypropanoic acid derivative, is clinically used for the management of hyperlipidemia. In vivo the drug is rapidly hydrolyzed by plasma esterases into clofibric acid [2-(4-chlorophenoxy)-2-methylpropanoic acid], its active metabolite. As a result of the adverse effects reported in patients treated with the drug, therapy with clofibrate should be limited to substantial hyperlipidemia with high risk of associated morbidity and mortality. In order to improve the pharmacological activity of clofibrate, several chiral α-substituted α-aryloxyacetic acids analogs of clofibric acid have been synthesized [1] and resolved into their optical antipodes. In particular, the two enantiomers of α-*p*-chlorophenoxypropanoic and butanoic acids show different and in some cases opposite biological responses. The (*R*)-(+) isomers have a significant hypolipidemic effect and inhibit platelet metabolism [2,3]. Unlike (*S*)-(−) isomers, these compounds cause less myotonic effects [4] and proliferation of peroxisomes involved in hepatocarcinogenicity [5]. The resolution of α-monoalkyl α-aryloxyacetic acids was performed by fractional crystallization of their brucine salts [4], direct HPLC separation [1] and enzymatic hydrolysis of methyl esters [6].

In the current investigation, several chiral clofibrate analogues were separated by chromatography of their covalent diastereomers prepared by coupling with derivatizing chiral agents. This procedure offers various advantages over the conventional resolution methods such as a cheaper access to both pure enantiomers, and their preparation on a multigram scale.

2. Results and discussion

In the literature the number of resolutions via the formation of two covalent diastereomers from a racemate [7] is quite large. In particular, the separation of enantiomers of chiral carboxylic acids can be carried out by performing chromatography of their diastereomeric esters [8] or amides [9].

Taking advantage of this separation method, the racemic **1a–e** α-substituted α-aryloxy acids (Fig. 1) were resolved by conversion into ester and imide derivatives with enantiopure (*R*)-ethyl mandelate (***R*-2**), (*R*)-pantolactone (***R*-3**), (*S*)-4-(1-methylethyl)-2-oxazolidinone (***S*-4**) (Fig. 2), and subsequent chromatographic separation.

The racemic acids **1a–e** were prepared by condensation of the corresponding ethyl 2-bromo alkanoates with a substituted phenol and successive hydrolysis under basic conditions [1].

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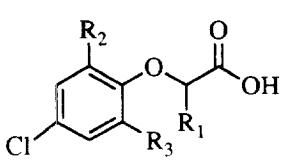


1a R_1= Me, R_2=R_3= H

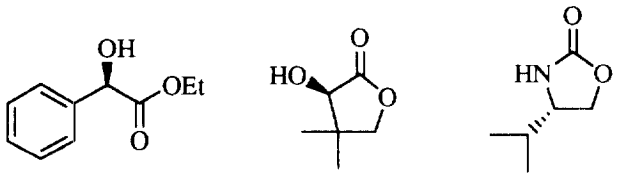
1b R_1= Et, R_2=R_3=H

1c R_1= Pro, R_2=R_3=H

1d R_1=Et, R_2=R_3=Me

1e R_1=Hex, R_2= R_3=H

Fig. 1. Chiral α-monoalkyl derivatives of *p*-chlorophenoxyacetic acid.



***R*-2** ***R*-3** ***S*-4**

Fig. 2. Chiral auxiliaries for the resolution of acids **1a–e**.

The reaction with (*R*)-ethyl mandelate and (*R*)-pantolactone was performed by adding ***R*-2** or ***R*-3** to a cooled (0°C) CH_2Cl_2 solution of acid **1** containing 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) [10]. The expected diastereomeric pairs of α-aryloxy esters **5a–e** and **6a–e** were obtained in good chemical yield (Scheme 1).

Analyses of the reaction mixtures by ^{1}H NMR spectroscopy showed differences between the chemical shifts of the protons H-2′ of esters with (*R*)-ethyl mandelate and H-3′ of esters with (*R*)-pantolactone, such as to determine the equimolecular formation of diastereomeric pairs.

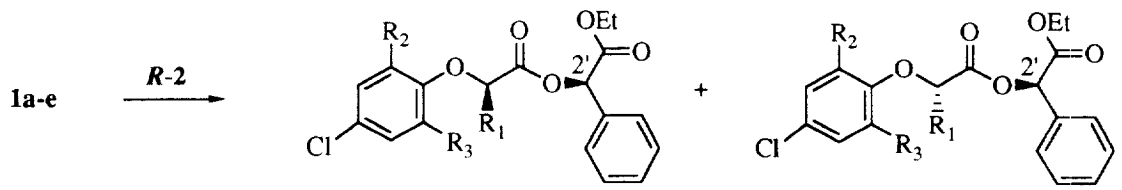
The chiral oxazolidinone ***S*-4** was easily prepared by reaction of (*S*)-valinol with diethyl carbonate [11], and N-acylated [12] (Scheme 2) via deprotonation with n-butyl lithium followed by quenching at −78°C with acid chlorides **7a–e**. The diastereomeric mixtures of chiral imides **8a–e** were obtained in good chemical yield.

The diastereomeric 1:1 ratio in the N-acylation reaction was deduced from GC data, by assuming the ratio of areas to be equivalent to the molar ratio of imides.

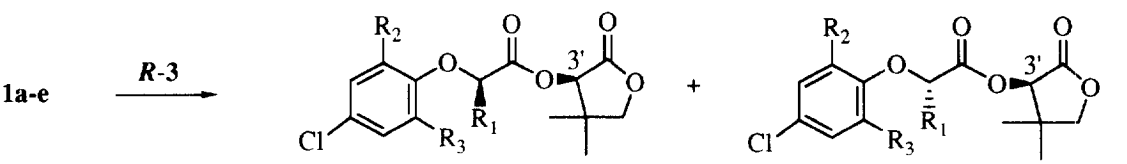
The chromatographic resolution of diastereomeric pairs derived from racemic acids **1a–e** has been developed using GC, TLC and flash chromatography. Table 1 shows the chromatographic results.

(*R*)-Ethyl mandelate allowed the separation of racemic acids **1a–d** only by GC.

Among the (*R*)-pantolactone esters, only the diastereomers **6d** were resolved on GC and silica, using petroleum ether/ethyl acetate 9:1 as eluent. After chromatography, the

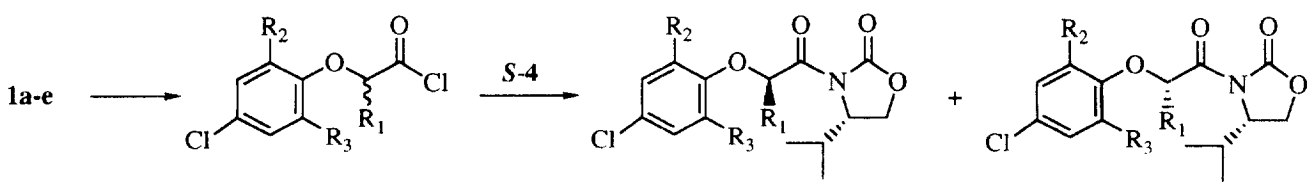


***2R,2′R*-5a-e** ***2S,2′R*-5a-e**



***2R,3′R*-6a-e** ***2S,3′R*-6a-e**

Scheme 1. Synthesis of ester derivatives of acids **1a–e**.



7a-e ***2R,4′S*-8a-e** ***2S,4′S*-8a-e**

Scheme 2. Synthesis of imide derivatives of acids **1a–e**.

Table 1
Chromatographic resolution of ester and imide derivatives of **1a–e**

Racemate	Resolving agent		
	***R*-2**	***R*-3**	***S*-4**
1a	GC	no separation	GC, TLC, flash
1b	GC	no separation	GC, TLC, flash
1c	GC	no separation	GC, TLC, flash
1d	GC	GC, TLC, flash	GC, TLC, flash
1e	no separation	no separation	GC

more polar diastereomer was contaminated by small amounts of the less polar diastereomer. Their cleavage under basic conditions led to the optically active 2-(*o,o'*-dimethyl-*p*-chlorophenoxy)-butanoic acid (**1d**), whose absolute configuration was not reported in the literature. Complete resolution was well achieved with chiral auxiliary ***S*-4** by separation of *N*-acyloxazolidinone pairs **8a–d** with GC and flash silica gel chromatography (cyclohexane/ethyl acetate 9:1). The derivatives **8e** were resolved only by means of GC. Hydrolysis of the separated imides **8a–d** with lithium hydroperoxide [13] gave the expected enantiopure α-monoalkyl α-aryloxyacetic acids **1a–d** in high yield, with concomitant recovery of auxiliary ***S*-4** in stereochemical purity (Scheme 3).

The measurement of the optical rotations, in comparison with the known literature values, showed that the **1a–c** acids were obtained as pure enantiomers. Using the same optical data, it was possible to assign the absolute configuration of the imides **8a–c**, and to determine that the less polar diastereomers are always formed by the ***R*-1a–c** acids.

As illustrated above, the absolute configuration of the acid **1d** is unknown. Therefore, it is impossible to determine the stereochemistry of imides **8d** by optical rotation measurement.

However, the 2*R*,4′*S* stereochemical assignment for the less polar diastereomer of the **8d** pair could be supposed because of the similar behavior with compounds **8a–c**.

In conclusion, this work describes a simple and general method for the covalent resolution of α-monoalkyl α-aryloxyacetic acids. It represents significant improvements with regard to the ease of chromatographic separations and absence of racemization, allowing the efficient preparation of pure enantiomers on a multigram scale.

The resolving ability is different for the chiral auxiliaries ***R*-2**, ***R*-3** and ***S*-4**. Furthermore, the (*R*)-ethyl mandelate was found to be efficient for analytical resolutions (GC), and the (*R*)-pantolactone seems to have a high resolving ability only for the *o,o',p*-substituted compound. Thanks to the well established possibilities to resolve via silica gel column and to hydrolyze the N-acylated heterocycles under mild conditions, the chiral oxazolidinone was found to be very efficient as chiral auxiliary in the optical resolution of the aryloxyacetic acids.

Further studies are in progress using both conformational analysis and ^{1}H NMR spectroscopy to rationalize the different activity of the resolving agents that have been used and to increase the application range of our separation method.

3. Experimental

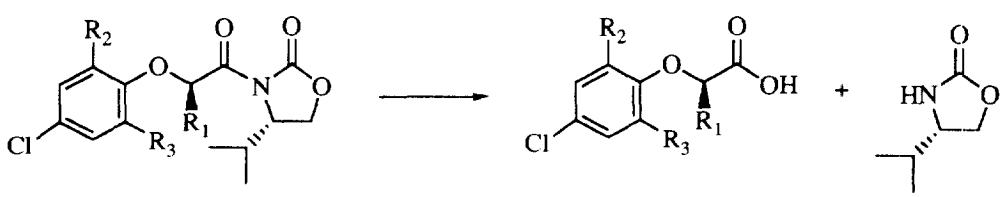
Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Melting points were determined on a Electrothermal IA 9100 digital apparatus and are uncorrected. 300 MHz ^{1}H NMR experiments were performed on a Bruker 300 MHz spectrometer. Chemical schifts (δ) are reported in ppm. GC analyses were performed on a Autosystem GC Perkin-Elmer apparatus using a fused silica capillary column (30 m, 0.53 mm ID), SPB-5 SUPELCO. The IR spectra were recorded on a FT-IR 1600 Perkin-Elmer spectrometer. Mass spectra were measured on a Kratos MS 80 spectrometer. Dry CH_2Cl_2 was purchased from Aldrich. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Silica gel 60 Fluka (230–400 mesh ASTM) was used for column chromatography. Microanalyses were carried out with an HP model 185 CHN analyzer (the analytical results are within 0.4% of the theoretical values).

*3.1. General procedure for the preparation of rac-α-substituted-α-aryloxy acids **1a–e***

Racemic **1a–e** were prepared following the literature procedure [1].

*3.2. General procedure for the reaction of rac-α-substituted-α-aryloxyacetic acids **1a–e** with (R)-ethyl mandelate (**R-2**)*

A mixture of **1** (1.0 equiv.), ***R*-2** (1.2 equiv.), DCC (1.0 equiv.) and DMAP (0.08 equiv.) in dry CH_2Cl_2 (12 ml/mmol) was stirred at 0°C for 5 min and at room temperature for 3 h. After filtration, the solution was washed with 0.5 N HCl and saturated aqueous solutions of $NaHCO_3$ and NaCl.



***2R,4'S*-8a-d** **1a-d** ***S*-4**

Scheme 3. Hydrolysis of imides **2*R*,4′*S*-8a–d**. The same scheme can be applied to imides **2*S*,4′*S*-8a–d**.

The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue containing the equimolecular pairs of the esters **5a–e** was purified on silica gel (petroleum ether/ethyl acetate 9:1).

(2R,2'R)- and (2S,2'R)-2-(p-Chlorophenoxy)-propanoic acid, ethyl mandelate esters ***2R,2'R-5a*** *and* ***2S,2'R-5a***. Mixture, 89% yield. IR (KBr): 1132, 1238, 1481, 1747 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15–1.24 (m, 3H, CH_3CH_2), 1.64 and 1.73 (both d, $J=6.5$ Hz, $J=6.7$ Hz, 3H, CH_3CH), 4.05–4.30 (m, 2H, CH_3CH_2), 4.80–4.88 (m, 1H, CH_3CH), 5.93 and 5.95 (both s, 1H, C_6H_5CH), 6.77–7.28 (m, 4H, aromatic), 7.30–7.45 (m, 5H, aromatic).

(2R,2'R) and (2S,2'R)-2-(p-Chlorophenoxy)-butanoic acid, ethyl mandelate esters ***2R,2'R-5b*** *and* ***2S,2'R-5b***. Mixture, 95% yield. IR (KBr): 1170, 1231, 1481, 1747 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.05 and 1.14 (both t, $J=7.2$ Hz, $J=7.2$ Hz, 3H, CH_3CH_2CH), 1.17 (t, $J=6.9$ Hz, 3H, $CH_3CH_2OC=O$), 1.96–2.19 (m, 2H, CH_3CH_2CH), 4.04–4.24 (m, 2H, $CH_3CH_2OC=O$), 4.62–4.67 (m, 1H, CH_2CH), 5.92 and 5.95 (both s, 1H, C_6H_5CH), 6.78–7.26 (m, 4H, aromatic), 7.34–7.41 (m, 5H, aromatic).

(2R,2'R)- and (2S,2'R)-2-(p-Chlorophenoxy)-pentanoic acid, ethyl mandelate esters ***2R,2'R-5c*** *and* ***2S,2'R-5c***. Mixture, 70% yield. IR (KBr): 1170, 1231, 1489, 1747 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.93 and 0.98 (both t, $J=7.3$ Hz, $J=7.3$ Hz, 3H, $CH_3CH_2CH_2$), 1.17 (t, $J=6.9$ Hz, 3H, $CH_3CH_2OC=O$), 1.48–1.68 (m, 2H, $CH_3CH_2CH_2$), 1.89–2.09 (m, 2H, $CH_3CH_2CH_2$), 4.04–4.25 (m, 2H, $CH_3CH_2OC=O$), 4.66–4.72 (m, 1H, CH_2CH), 5.91 and 5.94 (both s, 1H, C_6H_5CH), 6.77–7.24 (m, 4H, aromatic), 7.33–7.41 (m, 5H' aromatic).

(2R,2'R)- and (2S,2'R)-2-(o,o'-Dimethyl-p-chlorophenoxy)-butanoic acid, ethyl mandelate esters ***2R,2'R-5d*** *and* ***2S,2'R-5d***. Mixture, 84% yield. IR (KBr): 1201, 1474, 1747 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.02 and 1.06–1.23 (t and m, $J=7.3$ Hz, 6H, $CH_3CH_2OC=O$ and CH_3CH_2CH), 1.94–2.12 (m, 2H, CH_3CH_2CH), 2.21 (s, 6H, $ArCH_3$), 4.05–4.25 (m, 2H, $CH_3CH_2OC=O$), 4.51–4.55 (m, 1H, CH_2CH), 5.88 and 5.92 (both s, 1H, C_6H_5CH), 6.89 and 6.92 (both s, 2H, aromatic), 7.32–7.43 (m, 5H' aromatic).

(2R,2'R)- and (2S,2'R)-2-(p-Chlorophenoxy)-octanoic acid, ethyl mandelate esters ***2R,2'R-5e*** *and* ***2S,2'R-5e***. Mixture, 90% yield. IR (KBr): 1481, 1762, 2111, 2854, 2922 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.81–0.89 (m, 3H, $CH_3(CH_2)_5$), 1.17 (t, $J=6.9$ Hz, 3H, $CH_3CH_2OC=O$), 1.21–1.78 (m, 8H, $CH_3(CH_2)_4CH_2$), 1.90–2.10 (m, 2H, $CH_3(CH_2)_4CH_2$), 4.04–4.25 (m, 2H, $CH_3CH_2OC=O$), 4.64–4.70 (m, 1H, CH_2CH), 5.91 and 5.94 (both s, 1H, C_6H_5CH), 6.77–7.24 (m, 4H, aromatic), 7.33–7.46 (m, 5H' aromatic).

3.3. General procedure for the reaction of rac-α-substituted-α-aryloxyacetic acids ***1a–e*** *with (R)-pantolactone (****R-3****)*

A mixture of **1** (1.0 equiv.), ***R-3*** (3.0 equiv.), DCC (1.0 equiv.) and DMAP (0.08 equiv.) in dry CH_2Cl_2 (12 ml/mmol) was stirred at 0°C for 5 min, and at room temperature for 3 h. After filtration, the solution was washed with 0.5 N HCl, saturated aqueous solution of $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue containing the equimolecular pairs of the esters **6a–e** was purified on silica gel (petroleum ether/ethyl acetate 9:1).

(2R,3'R)- and (2S,3'R)-2-(p-Chlorophenoxy)-propanoic acid, pantolactone esters ***2R,3'R-6a*** *and* ***2S,3'R-6a***. Mixture: 75% yield. IR (nujol): 1080, 1237, 1748, 1786 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94, 1.05 and 1.16 (each s, 6H, CH_3CCH_3), 1.60–1.69 (m, 3H, CH_3CH), 3.96–4.04 (m, 2H, $(CH_3)_2CCH_2O$), 4.81–4.89 (m, 1H, CH_3CH), 5.34 and 5.35 (both s, 1H, $(CH_3)_2CCHOC=O$), 6.79–7.25 (m, 4H, aromatic).

*(2R,3'R)- and (2S,3'R)-2-(p-Chlorophenoxy)-butanoic acid, pantolactone esters (****2R,3'R-6b*** *and* ***2S,3'R-6b***. Mixture: 78% yield. IR (nujol): 1244, 1490, 1754, 1792 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.93, 1.03, 1.06 and 1.16 (each s, 6H, CH_3CCH_3), 1.08–1.15 (m, 3H, CH_3CH_2), 1.98–2.13 (m, 2H, CH_3CH_2), 3.95–4.04 (m, 2H, $(CH_3)_2CCHH$), 4.63–4.69 (m, 1H, CH_2CH), 5.36 and 5.37 (both s, 1H, $(CH_3)_2CCHOC=O$), 6.81–7.25 (m, 4H, aromatic).

(2R,3'R)- and (2S,3'R)-2-(p-Chlorophenoxy)-pentanoic acid, pantolactone esters ***2R,3'R-6c*** *and* ***2S,3'R-6c***. Mixture: 67% yield. IR (KBr): 1132, 1246, 1481, 1748, 1789 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.93, 1.03, 1.06 and 1.15 (each s, 6H, CH_3CCH_3), 0.94–0.99 (m, 3H, $CH_3CH_2CH_2$), 1.50–1.66 (m, 2H, $CH_3CH_2CH_2$), 1.92–2.03 (m, 2H, $CH_3CH_2CH_2$), 3.95–4.04 (m, 2H, $(CH_3)_2CCHH$), 4.67–4.74 (m, 1H, CH_2CH), 5.35 and 5.36 (both s, 1H, $(CH_3)_2CCHOC=O$), 6.79–7.24 (m, 4H, aromatic).

(2R,3'R)- and (2S,3'R)-2-(o,o'-Dimethyl-p-chlorophenoxy)-butanoic acid, pantolactone esters ***2R,3'R-6d*** *and* ***2S,3'R-6d***. Mixture: 88% yield. IR (nujol): 1140, 1201, 1754, 1792 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.91–1.18 (m, 9H, CH_3CCH_3 and CH_3CH_2), 1.91–2.09 (m, 2H, CH_3CH_2), 2.25 (s, 6H, $ArCH_3$), 3.97–4.04 (m, 2H, $(CH_3)_2CCHH$), 4.50–4.57 (m, 1H, CH_2CH), 5.33 and 5.39 (both s, 1H, $(CH_3)_2CCHOC=O$), 6.94 (s, 2H, aromatic).

Less polar diastereomer: $[\alpha]_D^{25}$ +29 (*c* 0.6, $CHCl_3$). IR (nujol): 1140, 1201, 1754, 1792 cm^{-1}. M.p. 71–73°C. ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H, CH_3CCH_3), 1.04 (s, 3H, CH_3CCH_3), 1.09 (t, 3H, CH_3CH_2), 2.02 (quintet, $J=5.9$ Hz, $J=7.2$ Hz, 2H, CH_3CH_2), 2.25 (s, 6H, $ArCH_3$), 3.98 (ab, 2H, $(CH_3)_2CCHH$), 4.52 (t, 1H, CH_2CH), 5.33 (s, 1H, $(CH_3)_2CCHOC=O$), 6.94 (s, 2H, aromatic). MS: *m/z* 354.10 (M^+), 41.05, 43.05, 69.10, 91.10, 155.05, 156.05, 157.05, 158.05.

(2R,3'R)- and (2S,3'R)-2-(p-Chlorophenoxy)-octanoic acid, pantolactone esters ***2R,3'R-6e*** *and* ***2S,3'R-6e***. Mixture: 89% yield. IR: 1079, 1163, 1238, 1489, 1762, 1792 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.84–0.88 (m, 3H, $CH_3(CH_2)_5$), 0.93, 1.03, 1.05 and 1.15 (each s, 6H, CH_3CCH_3), 1.21–1.37 (m, 6H, $CH_3(CH_2)_3CH_2CH_2$), 1.49–1.54 (m, 2H, $CH_3(CH_2)_3CH_2CH_2$), 1.95–2.04 (m, 2H, $CH_3(CH_2)_4CH_2$),

3.96–4.04 (m, 2H, $(CH_3)_2CCHH$), 4.66–4.73 (m, 1H, CH_2CH), 5.34 and 5.36 (both s, 1H, $(CH_3)_2CCHOC{=}O$), 6.79–7.24 (m, 4H, aromatic).

3.4. General procedure for the preparation of rac-α-substituted-α-aryloxyacetyl chlorides 7a–e

A mixture of **1** (1.0 equiv.) and $SOCl_2$ (6.0 equiv.) in dry CH_2Cl_2 (12 ml/mmol) was stirred at 40°C for 2 h. Evaporation of the volatile products gave the corresponding **7**, that was used as such in the following steps.

*(S)-4-(1-methylethyl)-2-oxazolidinone (**S-4**)* was prepared according to the literature procedure [11] (75% yield).

*3.5. General procedure for the reaction of rac-α-substituted-α-aryloxyacetyl chorides 7a–e with (S)-4-(1-methylethyl)-2-oxazolidinone (**S-4**)*

BuLi (1.6 M in hexane, 1.0 equiv.) was added to a solution of ***S*-4** (1.0 equiv.) in dry THF (0.3 ml/mmol), under N_2 atmosphere, at −78°C. After 15 min, **7** (1.1 equiv.) in dry THF (0.3 ml/mmol) was added dropwise, and the mixture was stirred for 1 h at −78°C. After quenching with saturated aqueous NH_4Cl, the THF was evaporated, and the mixture extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4 and concentrated in vacuo. The residue containing the equimolecular pairs of the imides **8a–e** was purified on silica gel (cyclohexane/ethyl acetate 9:1).

*(2R,4'S)- and (2S,4'S)-2-(p-Chlorophenoxy)-propanoic acid, 4-(1-methylethyl)-2-oxazolidinone imides **2R,4'S-8a** and **2S,4'S-8a***. Yield: 81%. After silica gel chromatography, the product **2S,4'S-8a** is the more polar one.

2*R*,4'*S*-8a: $[\alpha]_D^{25}$ +69.7 (*c* 0.7, $CHCl_3$). IR (nujol): 1489, 1709, 1784 cm^{-1}. M.p. 95–98°C. ^1H NMR ($CDCl_3$): δ 0.87 (d, *J* = 5.4 Hz, 3H, CH_3CHCH_3), 0.89 (d, *J* = 5.7 Hz, 3H, CH_3CHCH_3), 1.65 (d, *J* = 6.5 Hz, 3H, $CH_3CHC{=}O$), 2.28–2.38 (m, 1H, CH_3CHCH_3), 4.25 (dd, *J* = 3.7 Hz, *J* = 8.8 Hz, 1H, OCHH), 4.36 (t, *J* = 8.5 Hz, 1H, OCHH), 4.47 (ddd, *J* = 3.7 Hz, *J* = 3.7 Hz, *J* = 8.5 Hz, 1H, OCH_2CH), 5.91 (q, *J* = 6.5 Hz, 1H, $CH_3CHC{=}O$), 6.76–7.24 (m, 4H, aromatic). MS: *m/z* 311.05 (M^+), 41.10, 43.10, 55.05, 69.15, 110.95, 116.05, 155.10, 184.10.

2*S*,4'*S*-8a: $[\alpha]_D^{25}$ +5.8 (*c* 1.2, $CHCl_3$). IR (nujol): 1489, 1709, 1784 cm^{-1}. M.p. 110–113°C. ^1H NMR ($CDCl_3$): δ 0.85 (d, *J* = 5.3 Hz, 3H, CH_3CHCH_3), 0.87 (d, *J* = 5.4 Hz, 3H, CH_3CHCH_3), 1.58 (d, *J* = 6.4 Hz, 3H, $CH_3CHC{=}O$), 2.27–2.35 (m, 1H, CH_3CHCH_3), 4.26 (dd, *J* = 3.3 Hz, *J* = 8.7 Hz, 1H, OCHH), 4.33 (t, *J* = 8.7 Hz, 1H, OCHH), 4.42 (ddd, *J* = 3.3 Hz, *J* = 3.3 Hz, *J* = 8.0 Hz, 1H, OCH_2CH), 5.96 (q, *J* = 6.4 Hz, 1H, $CH_3CHC{=}O$), 6.77–7.29 (m, 4H, aromatic). MS: *m/z* 311.05 (M^+), 41.10, 43.10 55.05, 56.05, 69.15, 70.15, 75.05, 110.95, 116.05, 155.00, 184.10.

*(2R,4'S)- and (2S,4'S)-2-(p-Chlorophenoxy)-butanoic acid, 4-(1-methylethyl)-2-oxazolidinone imides **2R,4'S-8b** and **2S,4'S-8b***. Yield: 73%. After silica gel chromatography, the product **2S,4'S-8b** is the more polar one.

2*R*,4'*S*-8b: $[\alpha]_D^{25}$ +84.4 (*c* 0.8, $CHCl_3$). IR (nujol): 1488, 1580, 1701, 1777, 1791 cm^{-1}. M.p. 51°C. ^1H NMR ($CDCl_3$): δ 0.87 (d, *J* = 4.9 Hz, 3H, CH_3CHCH_3), 0.89 (d, *J* = 5.2 Hz, 3H, CH_3CHCH_3), 1.12 (t, *J* = 7.1 Hz, 3H, CH_3CH_2), 1.85–2.00 (m, 1H, CH_3CHH), 2.01–2.09 (m, 1H, CH_3CHH), 2.26–2.37 (m, 1H, CH_3CHCH_3), 4.25 (dd, *J* = 3.7 Hz, *J* = 8.9 Hz, 1H, OCHH), 4.35 (t, *J* = 8.9 Hz, 1H, OCHH), 4.47 (ddd, *J* = 3.7 Hz, *J* = 3.7 Hz, *J* = 8.5 Hz, 1H, OCH_2CH), 5.75 (dd, *J* = 3.4 Hz, *J* = 7.6 Hz, 1H, $CH_2CHC{=}O$), 6.76–7.24 (m, 4H, aromatic). MS: *m/z* 325.05 (M^+), 41.00, 43.10, 55.05, 69.05, 70.15, 130.15, 169.10, 198.10.

2*S*,4'*S*-8b: $[\alpha]_D^{25}$ +22.5 (*c* 1.0, $CHCl_3$). IR (nujol): 1488, 1580, 1701, 1777, 1791 cm^{-1}. M.p. 106–107°C. ^1H NMR ($CDCl_3$): δ 0.85 (t, *J* = 6.4 Hz, 6H, CH_3CHCH_3), 1.09 (t, *J* = 7.3 Hz, 3H, CH_3CH_2), 1.81–2.00 (m, 2H, CH_3CH_2), 2.27–2.38 (m, 1H, CH_3CHCH_3), 4.26 (dd, *J* = 3.1 Hz, *J* = 8.7 Hz, 1H, OCHH), 4.32 (t, *J* = 8.7 Hz, 1H, OCHH), 4.41 (ddd, *J* = 3.1 Hz, *J* = 3.1 Hz, *J* = 7.8 Hz, 1H, OCH_2CH), 5.80 (dd, *J* = 3.9 Hz, *J* = 7.3 Hz, 1H, $CH_2CHC{=}O$), 6.77–7.24 (m, 4H, aromatic). MS: *m/z* 325.05 (M^+), 41.00, 43.10, 55.05, 69.05, 70.15, 130.15, 169.10, 198.10.

*(2R,4'S)- and (2S,4'S)-2-(p-Chlorophenoxy)-pentanoic acid, 4-(1-methylethyl)-2-oxazolidinone imides **2R,4'S-8c** and **2S,4'S-8c***. Yield: 78%. After silica gel chromatography, the product **2S,4'S-8c** is the more polar one.

2*R*,4'*S*-8c (oil): $[\alpha]_D^{25}$ +67.4 (*c* 1.0, $CHCl_3$). IR (nujol): 1390, 1466, 1572, 1709, 1777 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.86 (d, *J* = 4.3 Hz, 3H, CH_3CHCH_3), 0.88 (d, *J* = 4.3 Hz, 3H, CH_3CHCH_3), 0.96 (t, *J* = 7.2 Hz, 3H, $CH_3CH_2CH_2$), 1.54–1.67 (m, 2H, $CH_3CH_2CH_2$), 1.81–1.95 (m, 2H, $CH_3CH_2CH_2$), 2.26–2.37 (m, 1H, CH_3CHCH_3), 4.25 (dd, *J* = 3.5 Hz, *J* = 8.8 Hz, 1H, OCHH), 4.36 (t, *J* = 8.8 Hz, 1H, OCHH), 4.47 (ddd, *J* = 3.5 Hz, *J* = 3.5 Hz, *J* = 8.8 Hz, 1H, OCH_2CH), 5.80 (dd, *J* = 3.9 Hz, *J* = 7.5 Hz, 1H, $CH_2CHC{=}O$), 6.72–7.24 (m, 4H, aromatic). MS: *m/z* 339.10 (M^+), 41.00, 43.10, 55.05, 83.05, 130.05, 141.00, 183.10, 169.10, 212.10.

2*S*,4'*S*-8c: $[\alpha]_D^{25}$ +18.2 (*c* 1.0, $CHCl_3$). IR (nujol) 1390, 1466, 1572, 1709, 1777 cm^{-1}. M.p. 147–149°C. ^1H NMR ($CDCl_3$): δ 0.84 (d, *J* = 5.9 Hz, 3H, CH_3CHCH_3), 0.86 (d, *J* = 5.7 Hz, 3H, CH_3CHCH_3), 0.95 (t, *J* = 7.1 Hz, 3H, $CH_3CH_2CH_2$), 1.47–1.69 (m, 2H, $CH_3CH_2CH_2$), 1.78–1.88 (m, 2H, $CH_3CH_2CH_2$), 2.15–2.37 (m, 1H, CH_3CHCH_3), 4.26 (dd, *J* = 3.2 Hz, *J* = 8.8 Hz, 1H, OCHH), 4.32 (t, *J* = 8.8 Hz, 1H, OCHH), 4.40 (ddd, *J* = 3.2 Hz, *J* = 3.2 Hz, *J* = 7.7 Hz, 1H, OCH_2CH), 5.86 (dd, *J* = 4.3 Hz, *J* = 7.6 Hz, 1H, $CH_2CHC{=}O$), 6.77–7.24 (m, 4H, aromatic). MS: *m/z* 339.10 (M^+), 41.00, 43.10, 55.05, 83.05, 130.05, 141.00, 183.10, 212.10.

*(2R,4'S)- and (2S,4'S)-2-(o,o'-Dimethyl-p-chlorophenoxy)-butanoic acid, 4-(1-methylethyl)-2-oxazolidinone imides **2R,4'S-8d** and **2S,4'S-8d***. Yield: 75%.

Less polar diastereomer (oil): $[\alpha]_D^{25}$ +60.8 (*c* 1.4, $CHCl_3$). IR (KBr): 1198, 1386, 1475, 1713, 1770, 2966 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.85 (d, *J* = 6.7 Hz, 3H, CH_3CHCH_3), 0.90 (d, *J* = 6.8 Hz, 3H, CH_3CHCH_3), 1.09 (t, *J* = 7.3 Hz, 3H, CH_3CH_2), 1.92–2.09 (m, 2H, CH_3CH_2), 2.19–2.39 and 2.27 (m and s, 7H, CH_3CHCH_3 and $ArCH_3$), 4.18 (dd, *J* = 3.6 Hz, *J* = 8.8 Hz, 1H, OCHH), 4.24 (t, *J* = 8.8 Hz, 1H, OCHH), 4.44 (ddd, *J* = 3.6 Hz, *J* = 3.6 Hz, *J* = 7.2 Hz, 1H, OCH_2CH), 5.83 (t, *J* = 5.3 Hz, 1H, $CH_2CHC{=}O$), 6.92 (s, 2H, aromatic). MS: *m/z* 353.20 (M^+), 41.10, 43.10, 69.05, 91.05, 130.05, 156.10, 198.10.

More polar diastereomer (oil): $[\alpha]_D^{25}$ +20.0 (*c* 1.5, $CHCl_3$). IR (KBr): 1198, 1386, 1475, 1713, 1770, 2966 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.64 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3), 0.84 (d, *J* = 6.9 Hz, 3H, CH_3CHCH_3), 1.05 (t, *J* = 7.4 Hz, 3H, CH_3CH_2), 1.86–1.99 (m, 2H, CH_3CH_2), 2.01–2.31 and 2.26 (m and s, 7H, CH_3CHCH_3 and $ArCH_3$), 4.17 (dd, *J* = 3.2 Hz, *J* = 9.0 Hz, 1H, OCHH), 4.25 (t, *J* = 9.0 Hz, 1H, OCHH), 4.40 (ddd, *J* = 3.2 Hz, *J* = 3.2 Hz, *J* = 7.9 Hz, 1H, OCH_2CH), 5.85 (t, *J* = 5.6 Hz, 1H, $CH_2CHC{=}O$), 6.92 (s, 2H, aromatic). MS: *m/z* 353.20 (M^+), 41.10, 43.10, 69.05, 91.05, 130.05, 156.10, 198.10.

(2R,4'S)- and (2S,4'S)-2-(p-Chlorophenoxy)-octanoic acid, 4-(1-methylethyl)-2-oxazolidinone imides ***2R,4'S-8e*** *and* ***2S,4'S-8e***. Mixture: 60% yield. IR (KBr): 1239, 1489, 1709, 1779, 2926, 2959 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.82–0.90 (m, 9H, CH_3CHCH_3 and $CH_3(CH_2)_5$), 1.27–1.35 (m, 6H, $CH_3(CH_2)_3CH_2CH_2$), 1.49–1.58 (m, 2H, $CH_3(CH_2)_3CH_2CH_2$), 1.82–1.98 (m, 2H, $CH_3(CH_2)_3CH_2CH_2$), 2.26–3.44 (m, 1H, CH_3CHCH_3), 4.20–4.49 (m, 3H, OCHH and OCH_2CH), 5.78–5.86 (m, 1H, $CH_2CHC{=}O$), 6.75–7.21 (m, 4H, aromatic).

3.6. GC data of the diastereomeric ester or imide pairs

Mixture of **2*R*,2'*R*-5a** and **2*S*,2'*R*-5a**: r.t. 16.35 and 16.77 min (220°C). Mixture of **2*R*,2'*R*-5b** and **2*S*,2'*R*-5b**: r.t. 20.00 and 20.51 min (220°C). Mixture of **2*R*,2'*R*-5c** and **2*S*,2'*R*-5c**: r.t. 24.30 and 24.92 min (220°C). Mixture of **2*R*,2'*R*-5d** and **2*S*,2'*R*-5c**: r.t. 7.97 and 8.48 min (260°C). **6d** (more polar diastereomer): r.t. 5.24 min; **6d** (less polar diastereomer): r.t. 5.73 min (260°C). **2*R*,4'*S*-8a**: r.t. 4.35 min (260°C); **2*S*,4'*S*-8a**: r.t. 4.00 min (260°C). **2*R*,4'*S*-8b**: r.t. 4.82 min (260°C); **2*S*,4'*S*-8b**: r.t. 4.39 min (260°C). **2*R*,4'*S*-8c**: r.t. 5.51 min (260°C); **2*S*,4'*S*-8c:** r.t. 5.08 min (260°C). **8d** (more polar diastereomer): r.t. 11.54 min; **8d** (less polar diastereomer): r.t. 11.87 min (230°C). Mixture of **2*R*,4'*S*-8e** and **2*S*,4'*S*-8e**: r.t. 7.22 and 7.79 min (270°C).

3.7. General procedure for the hydrolysis of esters 6d

To a stirred solution of **6d** (more polar or less polar diastereomer) (1.0 equiv.) in 1:1 THF/H_2O (3 ml/mmol) was added NaOH (2.2 equiv.). The mixture was stirred for 5 h at room temperature. The THF was evaporated, and the mixture was extracted twice with $CHCl_3$. The organic extracts were concentrated in vacuo to give a residue consisting of the chiral auxiliary ***R*-3**. 2 N HCl was added to the aqueous layer until pH = 1, and the precipitate was extracted twice with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give the optically active acids **1a–d**.

*Optically active 2-(o,o'-dimethyl-p-chlorophenoxy)-butanoic acid (**1d**)* (from less polar **6d**). Yield: 97% (oil). $[\alpha]_D^{20}$ +21.6 (*c* 1.2, MeOH). IR (KBr): 1180, 1450, 1710, 3100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.06 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 1.92–2.03 (m, 2H, CH_2), 2.24 (s, 6H, $ArCH_3$), 4.42 (t, 1H, *J* = 5.5, CH), 6.96 (s, 2H, aromatic), 9.42 (broad s, 1H, COOH).

3.8. General procedure for the hydrolysis of imides 8a–d

To a stirred solution of **8** (more polar or less polar diastereomer) (1.0 equiv.) in 4:1 THF/H_2O (25 ml/mmol) was added H_2O_2 (30% solution in water, 4.16 equiv.) and after 5 min LiOH (1.63 equiv.) in H_2O (3.0 ml/mmol). The mixture was stirred overnight at room temperature. After quenching with aqueous Na_2SO_3 (0.6 M), the THF was evaporated, and the mixture extracted twice with CH_2Cl_2. The organic extracts were concentrated in vacuo to obtain the chiral auxiliary ***S*-4**. 2 N HCl was added to the aqueous layer until pH = 1, and the precipitate extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give the optically active acids **1a–d**.

(R)-2-(p-Chlorophenoxy)-propanoic acid ***R*-1a** [4] (from imide **2*R*,4'*S*-8a**). Yield: 82%. $[\alpha]_D^{25}$ +36.5 (*c* 1.4, MeOH), lit. [14] $[\alpha]_D^{25}$ +34.1.

(S)-2-(p-Chlorophenoxy)-propanoic acid ***S*-1a** [4] (from imide **2*S*,4'*S*-8a**). Yield: 99%. $[\alpha]_D^{25}$ −33.2 (*c* 2.8, MeOH), lit. [14] $[\alpha]_D^{25}$ −34.9.

(R)-2-(p-Chlorophenoxy)-butanoic acid ***R*-1b** [4] (from imide **2*R*,4'*S*-8b**). Yield: 94%. $[\alpha]_D^{25}$ +41.1 (*c* 1.3, MeOH), lit. [4] $[\alpha]_D^{20}$ +41.5.

(S)-2-(p-Chlorophenoxy)-butanoic acid ***S*-1b** [4] (from imide **2*S*,4'*S*-8b**). Yield: 95%. $[\alpha]_D^{25}$ −41.4 (*c* 1.7, MeOH), lit. [4] $[\alpha]_D^{20}$ −43.0.

(R)-2-(p-Chlorophenoxy)-pentanoic acid ***R*-1c** (from imide **2*R*,4'*S*-8c**). Yield: 78%. $[\alpha]_D^{25}$ +34.5 (*c* 1.3, MeOH).

(S)-2-(p-Chlorophenoxy)-pentanoic acid ***S*-1c** [1] (from imide **2*S*,4'*S*-8c**). Yield: 92%. $[\alpha]_D^{25}$ −31.7 (*c* 1.2, MeOH), lit. [1] $[\alpha]_D^{20}$ −38.0.

Optically active 2-(o,o'-dimethyl-p-chlorophenoxy)-butanoic acid (**1d**) (from less polar **8d**). Yield: 60% (oil). $[\alpha]_D^{25}$ +17.9 (*c* 2.9, MeOH). IR (KBr): 1180, 1450, 1710, 3100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.06 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 1.92–2.03 (m, 2H, CH_2), 2.24 (s, 6H, $ArCH_3$), 4.42 (t, 1H, *J* = 5.5, CH), 6.96 (s, 2H, aromatic), 9.42 (broad s, 1H, COOH).

Optically active 2-(o,o'-dimethyl-p-chlorophenoxy)-butanoic acid (**1d**) (from more polare **8d**). Yield: 62% (oil). $[\alpha]_D^{25}$ −21.3 (*c* 1.3, MeOH).

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