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Chemoenzymatic Synthesis of Enantioenriched (*R*)- and (*S*)-Aryloxyalkanoic Herbicides

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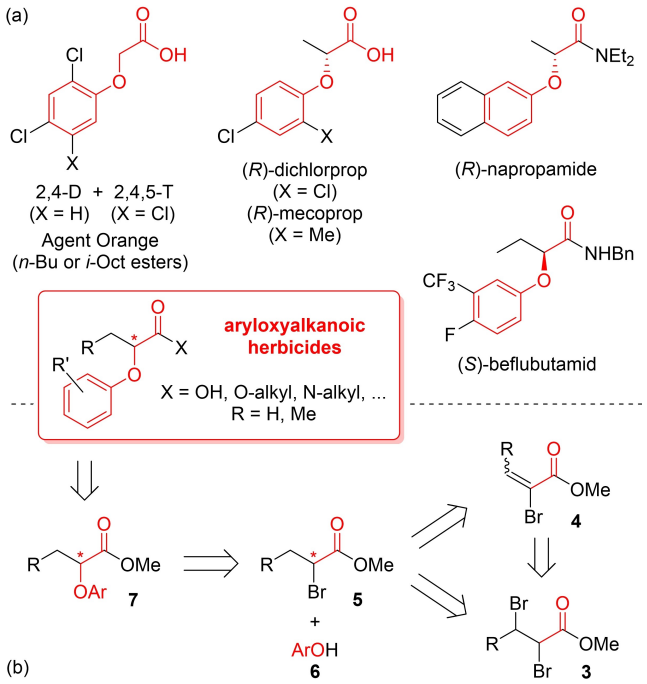
The combination of a biocatalytic asymmetric C=C reduction with a simple sequence of chemical transformations was implemented in a new chemoenzymatic synthesis of various substituted aryloxyalkanoic acids, used as weed-killing agrochemicals or chiral precursors. By careful selection of the biocatalyst, either enantiomer of the product could be obtained in good yield and moderate to good ee. The method relies on the use of simple and commercially available starting materials, and requires neither purified enzymes nor chromatographic separations.

Introduction

Aryloxyalkanoic herbicides (also commonly referred to as phenoxy herbicides) are a class of agrochemicals of widespread use for the protection of cereals and monocotyledonous crops from broad-leaf weeds. Their structure (Scheme 1a) is derived from phenoxyacetic acid and their activity is based on mimicking the growth hormone indoleacetic acid.

The first members of this class of compounds were synthesized in the 1940s and were rapidly adopted all over the world, especially in the US.[1] Among the oldest and the most studied, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), either as free acids or in the form of their esters or salts, were employed broadly in commercial formulations of herbicides for industrial agriculture. Their action was so rapid and effective that they even found application for tactical military use as defoliants to clear vegetation and foliage that provides cover to the enemy. A range of military preparations for this purpose became known as the "rainbow herbicides", mixtures nicknamed after the color of their containers: for instance, the most notorious Agent Orange (Scheme 1a), used heavily in the Vietnam War,[2] consisted of a 50:50 mixture of 2,4-D and 2,4,5-T as *n*-butyl esters (later replaced by *i*-octyl esters).



Scheme 1. (a) Representative examples of commercial chiral aryloxyalkanoic herbicides in their most active enantiomeric form (the common phenoxyacetic acid skeleton is shown in red). (b) Retrosynthetic route proposed in this work.

Due to multiple concerns on the toxic effects for human health (possibly due to dioxin contamination), strict regulations had been applied on the use of 2,4,5-T: from 1985 its use is forbidden in the US by the Environmental Protection Agency and its international trade is restricted by the Rotterdam Convention. Nevertheless, this class of agrochemicals is still heavily relied upon, with 2,4-D (which showed no evidence of risk to human health under intended conditions of use) still being the most employed herbicide in the US market.[3]

Extensive chemical development over the past decades led to aryloxyalkanoic acids and derivatives with decreased toxicity and environmental hazard, which are currently available on the

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market, including analogs with an additional methyl group, such as dichlorprop, mecoprop and napropamide (Scheme 1a). Those are currently sold as mixtures of both enantiomers, but only the (*R*)-enantiomer is responsible for their biological activity.[4] On the other hand, for the related herbicide beflubutamid, bearing an ethyl side-chain, both enantiomers show weed-killing activity, but the (*S*)-enantiomer is more than 1000 times more active than its antipode.[5] Multiple examples of similar molecules have been developed and commercialized as single enantiomers (e.g., fluazifop and other aryloxyphenoxy derivatives), generating considerable interest in the development of efficient and sustainable stereoselective syntheses of such compounds.

Indeed, in the last decades, the chemical industry has been subjected to a consistent and urgent pressure to develop and adopt more sustainable manufacturing processes, with particular regard to the reduction of greenhouse gas emission, waste output and replacement of toxic and dangerous reagents. The agrochemical sector is being profoundly affected by such trends as well.[6] The introduction of enzyme catalysis in the development of synthetic procedures, especially for the preparation of commercially valuable products such as biologically active molecules, agrochemicals and pharmaceuticals is now one of the primary options in the design of new synthetic strategies.[7]

Specifically, in the case of agrochemicals such as aryloxyalkanoic herbicides, the exploitation of the stereoselectivity of an enzymatic transformation appears an elite strategy for the synthesis of the more active enantiomer. As such, in an attempt to design a novel chemoenzymatic synthesis of both enantiomers of this class of molecules (Scheme 1b) we selected α-bromoalkanoates **5** as the key chiral intermediate, from which the target can be obtained by nucleophilic substitution followed by hydrolysis. Chiral α-bromoesters **5** can be obtained by stereoselective bioreduction of α-bromo-α,β-unsaturated esters **4**, mediated by ene-reductases (ERs) belonging to the family of Old Yellow Enzymes (OYEs), versatile biocatalysts for enantioselective reductions of C=C double bonds activated by electron-withdrawing groups.[8] The ER-mediated reduction of bromoesters **4** is known to proceed in good yield and selectivity.[9,10] Alternatively, and even more efficiently, esters **5** can be prepared in a one-pot system from α,β-dibromoesters **3** by *in situ* dehydrohalogenation followed by bioreduction.[11] The latter approach was selected for the simpler one-pot procedure and for the additional advantage to avoid the need for chromatographic purification and/or separation of the (*E*/*Z*)-diastereoisomers of **4**. In fact, previously reported bioreduction data on compounds related to **4** showed that both diastereoisomers are accepted by classical OYEs, affording the same enantiomer of the product (with (*S*)-configuration) with only minor difference in ee values (95–97% from (*Z*), 87–93% from (*E*)), while this is not the case for α-chloroester analogs.[9–11] Therefore, separation of (*E*/*Z*)-diastereoisomers was likely to be unnecessary.

Results and Discussion

The enantioselective reduction of activated C=C bonds mediated by ERs is a hugely expanding field of interest for synthetic applications, from lab to industrial scale.[12] These enzymes are able to accept a broad range of alkene substrates in which the C=C bond is conjugated with at least one electron-withdrawing group (EWG), and their enantioselectivity is often remarkably high. In the recent years, a large number of ERs from different species (bacteria, fungi, plants, etc.) have been discovered and fully characterized. This, in addition to multiple efforts in developing efficient mutants of wild-type enzymes with protein engineering approaches and other substrate-based engineering techniques, has opened up many possibilities to exploit and improve the excellent substrate scope and selectivity of these biocatalysts.[13]

In the past, ours and other research groups studied extensively the ER-mediated reductions of classes of C=C bonds activated by weak EWGs, which normally require more than one activating group to proceed efficiently (e.g., diesters,[14] cyanoesters,[15] and so on). However, in spite of the fact that one carboxylic ester group is often insufficient to activate the C=C bond, it was observed that the presence of a halogen atom (Br or Cl) at the α-position, as in **4**, greatly favors the reaction.[9,10] The enantioenriched products have been exploited for the synthesis of a range of pharmaceuticals and fine chemicals. Shortly after, Faber and co-workers showed that saturated dibromoesters (such as **3**) could be employed as convenient precursors of the substrate for the biotransformation, since they undergo spontaneous dehydrohalogenation in the presence of phosphate buffer to afford the unsaturated α-bromoesters **4**, which are then reduced *in situ* by the enzyme under the same conditions, in an elegant and simple reductive dehalogenation process.[11] Building on this knowledge, we envisaged the chemoenzymatic route to chiral aryloxyalkanoic herbicides herein described (Scheme 2).

The C3 skeleton of (*R*)-aryloxypropanoic acids such as (*R*)-dichlorprop and (*R*)-mecoprop can be derived from methyl acrylate **2a**, converted firstly to methyl 2,3-dibromopropanoate **3a** by addition of bromine.

Dibromoester **3a** was used as a substrate for the one-pot spontaneous dehydrohalogenation (to yield **4a**) and stereoselective reduction to **5a**, using our in-house library of ERs produced recombinantly in *E. coli* and purified.[16] The screening-scale reactions (1 mL final volume) were performed with 5 mM substrate in 50 mM potassium phosphate buffer, pH 7.0, in the presence of 0.1 mM $NADP^+$ and 1 U mL^{-1} glucose dehydrogenase (GDH) for the regeneration of the NADPH cofactor at the expense of glucose (20 mM). The results are reported in Table 1a. The substrate was well-accepted by several of the enzymes tested, and the desired enantiomer (*S*)-**5a**, required for the synthesis of the (*R*)-configured target molecules, could be obtained with excellent enantioselectivity only using OYE1-3 from *Saccharomyces pastorianus* and *S. cerevisiae*, in line with literature data.[11] Considering the slightly superior performance of OYE3, the latter was selected for this step on a preparative scale, yielding (*S*)-**5a** with a 97% ee.

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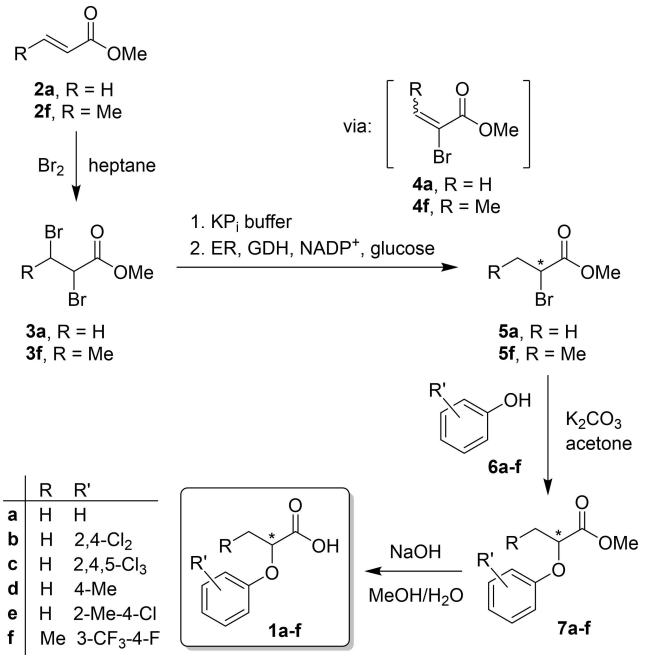
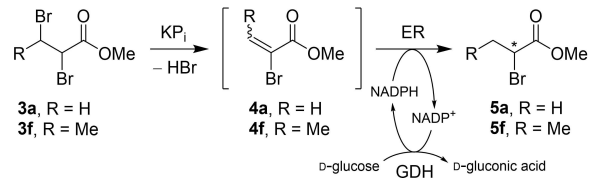


Scheme 2. Chemoenzymatic synthesis of enantioenriched aryloxyalkanoic herbicides.

Table 1. Screening of ene-reductases for the conversion of dibromoesters **3a,f** into bromoesters **5a,f**.



3a, R = H; **3f**, R = Me — **4a**, R = H; **4f**, R = Me — **5a**, R = H; **5f**, R = Me

Enzyme	Conv. **3a** [%][a]	ee **5a** [%][b]	Conv. **3f** [%][a]	ee **5f** [%][b]
■(a) Wild-type ERs				
OYE1	>99	93 (*S*)	>99	90 (*S*)
OYE2	>99	92 (*S*)	98	88 (*S*)
OYE3	>99	**97 (*S*)**	95	93 (*S*)
OYE2.6	<1	n.d.[c]	<1	n.d.[c]
KmOYE	10	n.d.[c]	6	n.d.[c]
SeOYE	<1	n.d.[c]	<1	n.d.[c]
YqjM	>99	48 (*R*)	80	62 (*R*)
■(b) Variants of YqjM				
YqjM C26H	>99	56 (*R*)	5	n.d.[c]
YqjM C26N	>99	71 (*R*)	8	47 (*R*)
YqjM I69A	35	75 (*R*)	<1	n.d.[c]
YqjM I69Y	>99	78 (*R*)	20	45 (*R*)
YqjM H167A	23	79 (*R*)	38	**96 (*R*)**

[a] Determined by GC-MS. [b] Determined by GC on chiral stationary phase. Absolute configuration was assigned by comparison with literature data. [c] n.d. = not determined.

However, in order to make the process less expensive, both OYE3 and GDH were employed as crude cell lysates, without side-products being detected. Furthermore, an attempt of increasing the substrate loading substantially (up to 100 mM) resulted in a much slower reaction rate and faster deactivation of the enzyme. The problem was circumvented by performing the two steps telescopically: firstly the dibromoester **3a** was incubated in buffer (at a slightly higher temperature, 40 °C) until completion of the dehydrohalogenation as assessed by GC-MS, neutralising the acidic pH with aqueous NaOH at regular intervals to avoid excessive accumulation of HBr. Then, enzymes and cofactor for the bioreduction were added to the mixture which was incubated at 30 °C. This approach proved to be more effective, affording complete conversion of **3a** to (*S*)-**5a** up to a substrate loading of 85 mM (250 mg).

After the enzymatic reduction, the optically enriched bromoester (*S*)-**5a** was submitted to nucleophilic substitution with phenol (**6a**) in the presence of K_2CO_3, to give the corresponding phenoxyester (*R*)-**7a** with inversion of configuration. Acetone was selected as the best option as a relatively green solvent, able to support the S_N2 mechanism and easily removed by distillation (unlike the better suited alternatives DMSO and DMF). The reaction was carried out under reflux until complete conversion by GC-MS. The resulting phenoxyester (*R*)-**7a**, was recovered by extraction and submitted directly to alkaline hydrolysis in methanol/water at ambient temperature, to yield the corresponding phenoxyacid (*R*)-**1a**, unsubstituted analog of this class of herbicides. The product was recrystallized from EtOH/H_2O, affording pure (*R*)-**1a** in 73% overall yield, calculated from **2a**.

The same procedure was also applied to a selection of different phenols **6b–e**, leading to commercially relevant molecules (*R*)-dichlorprop ((*R*)-**1b**), the related analogue of 2,4,5-T ((*R*)-**1c**) and (*R*)-mecoprop ((*R*)-**1e**), in 40–82% isolated yield (Table 2).

In order to assess the optical purity of those products, the same two-step sequence for the nucleophilic substitution and hydrolysis was also performed on commercially available *rac*-**5a**, to give samples of *rac*-**1a–e** to be used as standards in the analytical determination of the optical purity. HPLC analysis on a chiral stationary phase of the (*R*)-products showed lower ee values (72–96%), ascribed to partial racemisation of the bromoester (*S*)-**5a** under the substitution conditions. Indeed, less severe racemisation was observed for those substitution reactions which proceeded more quickly (particularly with the chlorinated phenols). Attempts to optimise the reaction with other solvents or at different temperatures and concentrations, inspired by previous literature reports of similar substitutions on racemic substrates,[17] were unsuccessful, affording either worse or comparable ee values. Nonetheless, the imperfect optical purity of the products is less concerning than, for

Table 2. Preparative-scale stereoselective synthesis of aryloxyalkanoic herbicides.

Prod.	R	R'	Enzyme	Isol. yields [%]	ee [%][a]
1a	H	H	OYE3	73	75 (*R*)
1b	H	2,4-Cl_2	OYE3	40	88 (*R*)
1c	H	2,4,5-Cl_3	OYE3	75	96 (*R*)
1d	H	4-Me	OYE3	78	72 (*R*)
1e	H	2-Me-4-Cl	OYE3	82	76 (*R*)
1f	Me	3-CF_3-4-F	YqjM H167A	67	68 (*S*)

[a] Determined by HPLC on a chiral stationary phase.

instance, in the field of pharmaceutical synthesis. Indeed, several of these herbicides (and many chiral agrochemicals in general) are currently sold as racemates, so, even a partially enantioenriched product may be considered for commercial use to decrease the application rates at similar field performance,[5b] and lower the environmental burden.

On the other hand, the same approach (Scheme 2) was also extended to the homolog aryloxybutanoic herbicides, such as (*S*)-beflubutamid. The C4 skeleton was derived from methyl crotonate **2f**, converted to methyl 2,3-dibromobutanoate **3f**.

Besides the longer aliphatic side-chain, which does not alter considerably the synthetic route, it is noteworthy that the active enantiomer of this class of agrochemicals is the antipode, therefore an enantiodivergent ER is required. In the absence of enzymes, the spontaneous dehydrohalogenation of **3f** in buffer solution as described previously afforded almost exclusively (*E*)-**4f** (*E*/*Z* diastereomeric ratio 93:7). After the preliminary screening reactions performed on **3f** in the presence of ERs (Table 1a), no enzyme in our library was found able to produce (*R*)-2-bromobutanoate (*R*)-**5f** with a satisfactory ee. The highest optical purity was obtained with YqjM, the OYE from *Bacillus subtilis*, which showed inverted selectivity within respect to canonical OYEs, despite the modest 62% ee. Expecting a further decrease of this value in the subsequent nucleophilic substitution, it was clearly necessary to identify a better enzyme for the stereospecific reduction step. Therefore, we envisaged to improve the enantioselectivity of the enzyme by site-directed mutagenesis. With the recent improvements in the quality and reduction in the costs of molecular biology techniques, enzyme engineering has become efficient, affordable and fast. Indeed, an ever-increasing number of studies focused on the improvement of the stereoselectivity of ERs have appeared in the literature, as recently reviewed in an excellent and comprehensive survey.[18] Five potentially beneficial mutations to be implemented in the sequence of YqjM were selected (C26H, C26N, I69A, I69Y, H167A), according to previous mutagenesis studies on this enzyme,[19,20] which could possibly afford (*R*)-**5f** in higher enantiopurity. After site-directed mutagenesis (see Supporting Information), the five variants were overproduced recombinantly in *E. coli* as previously done for the wild-type enzyme. Under identical screening conditions, the conversion of **3f** to (*R*)-**5f** was tested also with the variants (Table 1b). In spite of the lower conversion (38%), the variant YqjM H167 A showed a very promising improvement in the stereoselectivity, affording the (*R*)-enantiomer of the product in 96% ee. In an attempt to improve the selectivity and/or conversions further, several double mutants were also generated (C26H/I69Y, C26N/I69A, I69A/H167A, I69Y/H167A, see Supporting Information), selected on the basis of a successful enantioselectivity switch reported for a structurally related substrate, methyl α-(hydroxymethyl)acrylate.[19] Disappointingly, no conversion could be observed with **3f** (see Supporting Information for the screening data of **3a** and **3f**) proving that the results of successful mutagenesis studies often cannot be transferred directly, even to related targets. Nonetheless, the optical purity of 96% achieved with the single variant H167A was judged more than satisfactory for the following steps.

The reductive dehalogenation of **3f** with YqjM H167A was scaled up to 250 mg substrate, with increased enzyme loading in order to achieve complete conversion to (*R*)-**5f**, as determined by GC-MS. The isolated product was submitted to the same S_N2 conditions optimised for the shorter homolog, using 4-fluoro-3-(trifluoromethyl)phenol **6f**, to yield aryloxybutanoic ester (*S*)-**7f** with inversion of configuration. Alkaline hydrolysis afforded aryloxybutanoic acid (*S*)-**1f**, precursor (and main metabolite[5]) of (*S*)-beflubutamid in 67% isolated yield from **2f** (Table 2). HPLC analysis on chiral stationary phase revealed an enantiomeric excess of 68% (reference material *rac*-**1f** was synthesized from commercially available ethyl 2-bromobutyrate according to the same S_N2 and hydrolysis procedure, see Supporting Information). Attempts to improve the final enantiopurity by further optimizing the reaction conditions were unsuccessful. The significant reduction in ee observed for the final product, compared to the excellent value of the bromoester after the bioreduction, could be ascribed to a more severe partial racemization occurring during the longer reaction time required by the S_N2 step, likely because of the increased steric hindrance of **5f** compared to **5a**.

Conclusion

An alternative approach for the enantioselective synthesis of chiral aryloxyalkanoic herbicides and their analogs and metabolites has been proposed, in an effort to design a more sustainable, selective and safe route to the active enantiomer of this class of agrochemicals. Starting from inexpensive commercially available materials, our multistep chemoenzymatic process relies upon an asymmetric reductive dehalogenation mediated by ene-reductase enzymes followed by nucleophilic substitution and hydrolysis.

With a suitable selection and/or engineering of the biocatalyst, the system can afford either enantiomer of the target molecule, opening up a new route to auxin-like (*R*)-aryloxypropanoic and (*S*)-aryloxybutanoic acids. The procedure has been demonstrated for the synthesis of the most commercially successful herbicides of these classes, i.e. (*R*)-dichlorprop, (*R*)-mecoprop and (*S*)-beflubutamid (obtained in up to 82% yield), but it may be easily extended to other derivatives more recently developed classes such as the aryloxyphenoxy acetyl-CoA carboxylase inhibitors (e.g., (*R*)-fluazifop and (*R*)-fenoxaprop).

In spite of the imperfect final enantiopurity of the products obtained (67-96%), due to a partial racemization of the intermediate bromoester which could not be suppressed, the procedure is simple and cost-effective, since it requires only enzymes in the form of crude lysates and inexpensive substrates. Furthermore, none of the steps requires chromatographic purifications.

Experimental section

General

^{1}H, ^{13}C and $^{19}F\{^{1}H\}$ NMR spectra were recorded on a 400 MHz spectrometer at room temperature unless otherwise specified, using as an internal standard TMS for ^{1}H and residual solvent for ^{13}C. Chemical shifts δ are expressed in ppm relative to the reference, *J* values are given in Hertz. GC-MS analyses were performed using a HP-5MS column (30 m × 0.25 mm × 0.25 μm) installed on a HP 7890A gas chromatograph. The following temperature program was employed: 60 °C (1 min)/6 °C min^{-1}/150 °C (1 min)/ 12 °C min^{-1}/280 °C (5 min). The enantiomeric excess values of compounds **5 a,f** were determined by GC analysis, using a DAcTBSil.BetaCDX 0.25 μm × 0.25 mm × 25 m column (Mega, Italy), installed on a HP 6890 gas chromatograph, according to the following temperature programs: 50 °C (3 min) 5 °C min^{-1}/130 °C/ 90 °C min^{-1}/220 °C (2 min).

The enantiomeric excess values of products **1 a-f** were determined by HPLC analysis on a CHIRAL ART Amylose-SA (150 mm x 4.6 mm × 5 μm, YMC) for compounds **1 a-e** and on a Lux® 5 μm Cellulose-3 (150 mm x 4.6 mm × 5 μm, Phenomenex) for compound **1 f**, using the following conditions: *n*-hexane/*i*-PrOH 99:1 + 0.1 % TFA, λ = 210 nm, 1 mL min^{-1}.

General procedure for screening-scale conversion of 3 a,f

The reaction mixtures contained 50 mM KP_i pH 7.0, 5 mM substrate **3 a,f**, 20 mM glucose, 0.1 mM $NADP^+$, 1 U glucose dehydrogenase from *B. megaterium* and 50 μL of purified ER or 150 μL of crude cell-free extract of YqjM wt or variant (final volume 1 mL). The mixtures were incubated for 24 h at 30 °C under gentle shaking, then extracted with EtOAc (2 × 200 μL). The combined organic phase was dried over anhydrous Na_2SO_4 and analyzed by GC-MS.

Chemoenzymatic synthesis of (*R*)-aryloxyacids (*R*)-1 a–e from dibromoester 3 a using OYE3

A solution of dibromoester **3 a** (250 mg, 1.02 mmol) in *i*PrOH (200 μL) was added to a KP_i solution (200 mM, pH 7.0, final volume 5 mL) and incubated at 40 °C, with gentle shaking. The pH was monitored periodically and adjusted to pH 7.0 with aq. NaOH (4 M) until complete dehydrohalogenation (monitored by GC-MS). To the solution of **4 a** obtained was then added the reaction mixture for the enzymatic reduction containing glucose (4 equiv.), $NADP^+$ (7 mg), OYE3 cell-free extract (3 mL), GDH cell-free extract (1 mL) and KP_i (50 mL, pH 7.0, 2 mL), giving a total reaction volume of approx. 12 mL. The reaction was incubated overnight in an orbital shaker at 30 °C, 150 rpm, until complete conversion (by GC-MS). The mixture was then extracted with Et_2O (3 × 5 mL) and the combined organic phase containing (*S*)-**5 a** was dried on anhydrous Na_2SO_4. The majority of the solvent was removed under reduced pressure and the residue was added to a stirred suspension of the suitable phenol **6 a-e** (1.12 mmol, 1.1 equiv.) and K_2CO_3 (0.42 g, 3.06 mmol, 3 equiv.) in acetone (50 mL). The resulting mixture was heated under reflux in a sand bath for 2–4 h and monitored by GC-MS until complete conversion. After partial removal of the solvent under reduced pressure, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water (1 × 10 mL) and brine (1 × 10 mL), and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the corresponding 2-aryloxyester (*S*)-**7 a-e**. The latter was dissolved in MeOH (20 mL) under magnetic stirring, NaOH (82 mg, 2.04 mmol, 2 equiv.) dissolved in a minimal amount of water (1 mL) was added dropwise and the mixture was stirred at r.t. overnight. After removal of most of the solvent under reduced pressure, the mixture was acidified with aqueous HCl (2 M) until pH < 2.0, causing the precipitation of the crude aryloxyacid. The latter was recrystallized from a EtOH/H_2O mixture to yield the pure product.Characterization data is provided in the Supporting Information.

Chemoenzymatic synthesis of (*S*)-aryloxyacid (*S*)-1 f from dibromoester 3 f using YqjM H167A

A solution of dibromoester **3 f** (250 mg, 1.02 mmol) in *i*PrOH (200 μL) was added to a KP_i solution (200 mM, pH 7.0, final volume 12 mL) and incubated at 40 °C, with gentle shaking. The pH was monitored periodically and adjusted to pH 7.0 with aq. NaOH (4 M) until complete dehydrohalogenation (monitored by GC-MS). To the solution of **4 a** obtained was then added the reaction mixture for the enzymatic reduction containing glucose (4 equiv.), $NADP^+$ (7 mg), YqjM H167A cell-free extract (35 mL), GDH cell-free extract (8 mL), giving a total reaction volume of approx. 55 mL. The reaction was incubated overnight in an orbital shaker at 30 °C, 150 rpm, until complete conversion (by GC-MS). The extraction of the reaction mixture to yield a solution of (*R*)-**5 f** and the procedures for the following two steps are identical to the chemoenzymatic procedure reported above. For the substitution step, phenol **6 f** was used. After the hydrolysis step, the majority of the solvent was removed under reduced pressure, the mixture was acidified with aqueous HCl (2 M) until pH < 2.0 and the product was recovered by extraction with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Characterization data is provided in the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Agrochemicals · Biocatalysis · Enzymes · Green chemistry · Stereoselective synthesis

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