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Synthesis of enantiomerically enriched (*S*)-(+)-2-aryl-4-pentenoic acids and (*R*)-(−)-2-aryl-4-pentenamides via microbial hydrolysis of nitriles, a chemoenzymatic approach to stereoisomers of α,γ-disubstituted γ-butyrolactones

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Abstract—In the presence of the nitrile hydratase/amidase-containing *Rhodococcus* sp. AJ270 whole cell catalyst, 2-aryl-4-pentenenitriles **1** underwent enantioselective hydrolysis under mild conditions to afford (*R*)-(−)-2-aryl-4-pentenoic acid amides **2** and (*S*)-(+)-2-aryl-4-pentenoic acids **3** in almost quantitative yield. The amidase involved in the cells shows very high *S*-enantioselectivity whereas the nitrile hydratase exhibits low to moderate *S*-enantioselectivity. The synthesis of stereoisomers of α,γ-disubstituted γ-butyrolactones from iodolactonization of (*S*)-(+)-2-aryl-4-pentenoic acid was demonstrated.

1. Introduction

Biocatalytic hydrolysis of nitriles has been shown to proceed through two distinct pathways: in the presence of a nitrilase,[1] nitriles undergo direct conversion to give carboxylic acids whereas a nitrile hydratase catalyzes the hydration of nitriles followed by the transformation into the corresponding acids with the aid of an amidase.[2] Biotransformations of nitriles using microbial whole cell catalysts have attracted much attention because they are effective, convenient and environmentally benign methods for the production of carboxylic acids and their amide derivatives. Microbial hydration of acrylonitrile to acrylamide, for instance, has become one of the largest industrial biotransformations in the world.[3] Recent endeavors by others[4] and us[5] have demonstrated that biotransformations of nitriles are also a unique complimentary addition to existing asymmetric chemical and enzymatic methods for the synthesis of carboxylic acids and their derivatives.

Rhodococcus sp. AJ270, a novel isolate from a soil sample,[6] appears to be a robust and useful nitrile hydratase/amidase-containing biocatalyst. Compared with other microbes reported, it displays broad enzymatic activity against almost all aromatic, heterocyclic and aliphatic nitriles. Both amides and acids can be obtained in high yields from the appropriate nitriles.[7] It also shows excellent regioselectivity in hydrolyzing aromatic dinitriles and a variety of aliphatic dinitriles bearing a suitably placed second chelating moiety.[8] Recently we have demonstrated that *Rhodococcus* sp. AJ270 is an efficient enantioselective biocatalytic system able to transform some racemic α-substituted arylacetonitriles[5a–c] and 2-arylcyclopropanecarbonitriles[5d,e] into the corresponding enantiomerically pure amides and acids. Our interest in understanding the mechanisms of enantioselective biotransformations of nitriles and in exploring this methodology to create unique and versatile chiral intermediates led us to investigate *Rhodococcus* sp. AJ270-catalyzed biotransformations of α-allyl arylacetonitriles, functionalized nitrile substrates. We wish to report herein a direct and convenient microbial production of 2-aryl-4-pentenoic acid derivatives and a new chemoenzymatic synthesis of optically active γ-butyrolactone derivatives.

2. Results and discussion

2.1. Biotransformations of 2-aryl-4-pentenenitriles

We first examined the reaction of 2-phenyl-4-pentenenitrile **1a**. Catalyzed by *Rhodococcus* sp. AJ270 cells under very mild conditions, **1a** underwent efficient and

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complete hydration reaction to form amide **2a** in a few hours. The conversion of amide **2a** into acid **3a** was slower, but highly enantioselective. After 2.5–3 days incubation, optically active (*R*)-(−)-2-phenyl-4-pentenamide **2a** and (*S*)-2-phenyl-4-pentenoic acid **3a** were obtained in excellent yield with high enantiomeric purity (Scheme 1 and Table 1). As illustrated in Table 1, increased amide conversion led to an increase in the enantiomeric excess (e.e.) of the amide **2a** and a decrease in the e.e. of the acid **3a**.

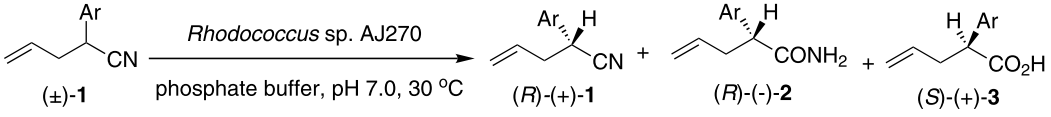
To test the generality of this biotransformation and also to gain a better understanding of enantioselectivity of nitrile hydratase and amidase, a number of 2-aryl-4-pentenenitrile analogs **1b–g** bearing different substituents in different positions were synthesized and subjected to biocatalytic hydrolysis. The results summarized in Table 1 showed a dramatic effect of the substituent on reaction rate. When a *para*-fluoro substituent was introduced into the benzene ring of the substrate, no detrimental influence was observed, as the hydrolysis of **1b** proceeded in a similar efficiency as to that of the parent nitrile **1a** to give enantiopure (*R*)-amide **2b** and (*S*)-acid **3b** in excellent yields. Introduction of other substituents such as chloro, methoxy and methyl at different positions of the benzene ring, however, resulted in slow conversions under identical reaction conditions. For example, after a week of exposure to the biocatalyst, the reaction mixtures of nitriles **1c** and **1e** still contained a considerable amount of the starting materials (entries 5 and 7). Only when the concentration of the substrate was halved and the incubation continued for a longer period, did the hydration reaction go to completion and high yields of the corresponding amide and acid were obtained. The presence of a methyl group at the *ortho*-position of the benzene ring retarded the enzymatic transformation of the amide into the acid, as biohydrolysis of nitrile **1g** after a week afforded amide **2g** in 93% yield.

Except for **1g**, almost all of the substrates, regardless of the nature of the substituent and the substitution pattern on the benzene ring, gave good to excellent e.e.s of (*R*)-amides (e.e. 99.2 to >99.5%) and (*S*)-acids (e.e. 87.4 to >99.5%). The recovered nitriles (*R*)-(+)-**1c** and (*R*)-(+)-**1e** were optically active, albeit with moderate e.e.s (47.0–59.1%).

2.2. Kinetic resolution of 2-phenyl-4-pentenamide

In order to shed further light on the stereochemistry of biotransformations of 2-aryl-4-pentenenitriles **1**, racemic 2-phenyl-4-pentenamide (±)-**2a** was employed as the substrate. After 67 h interaction with *Rhodococcus* sp. AJ270 cells, (±)-**2a** was resolved to give almost quantitative yields of (*R*)-**2a** and (*S*)-**3a** with 90.2 and 97.3% e.e., respectively (Scheme 2).

The absolute configuration of the carboxylic acids obtained was assigned as *S* on the basis of the measurement and comparison of their specific rotations with that of an authentic sample, (*S*)-(+)-2-phenyl-4-pentenoic acid ($[\alpha]_D^{25}=+84.6$),[9] assuming that the presence of a substituent on the benzene ring does not cause inversion between the direction of specific rotation and

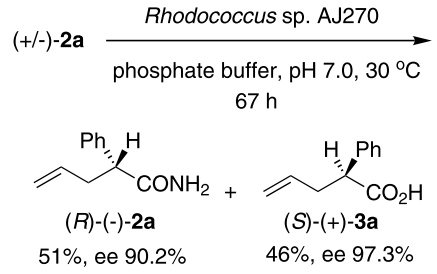


Scheme 1. Biotransformations of nitriles (±)-**1**.

Table 1. Biotransformations of racemic 2-arylpentenenitriles (±)-**1**

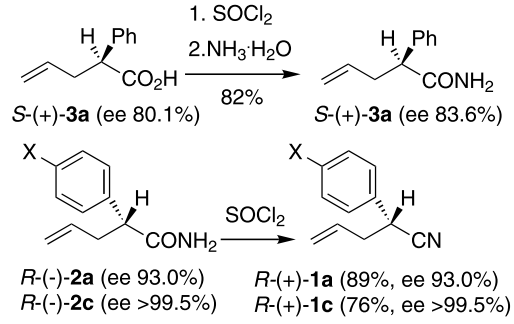
Entry	1	Ar	Conditions[a]	Nitrile (*R*)-(+)-**1**		Amide (*R*)-(−)-**2**		Acid (*S*)-(+)-**3**	
				Yield (%)[b]	E.e. (%)[c]	Yield (%)[b]	E.e. (%)[c]	Yield (%)[b]	E.e. (%)[c]
1	**1a**	C_6H_5	1 mmol, 58 h	–	–	62	70.8	38	>99.5
2	**1a**	C_6H_5	1 mmol, 69 h	–	–	49	99.2	49	96.8
3	**1b**	4-F-C_6H_4	1 mmol, 60 h	–	–	50	>99.5	50	99.3
4	**1c**	4-Cl-C_6H_4	1 mmol, 7 days	36	59.1	20	99.2	39	99.2
5	**1c**	4-Cl-C_6H_4	0.5 mmol, 6 days	Trace	–	44	99.3	50	>99.5
6	**1d**	4-MeO-C_6H_4	0.5 mmol, 73 h	–	–	47	>99.5	51	87.4
7	**1e**	4-Me-C_6H_4	1 mmol, 8 days	41	47.0	28	3.7	26	>99.5
8	**1e**	4-Me-C_6H_4	0.5 mmol, 7 days	–	–	49	>99.5	49	94.3
9	**1f**	3-Me-C_6H_4	0.5 mmol, 6 days	–	–	49	>99.5	49	>99.5
10	**1g**	2-Me-C_6H_4	0.5 mmol, 7 days	Trace	–	93	3.2	4	78.5

[a] *Rhodococcus* sp. AJ270 cells (2 g wet weight) in phosphate buffer (0.1 M. pH 7.0, 50 ml) were used. The reaction conditions were not optimized.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral stationary phase column.



Scheme 2. Kinetic resolution of amide (±)-**2a**.

configuration. The absolute configurations of optically active amides and nitriles were determined through intertransformations among (*S*)-(+)-acids **3**, (*R*)-(−)-amides **2** and (*R*)-(+)-nitriles **1**. For example, treatment of (*S*)-(+)-**3a** with thionyl chloride followed by ammonium hydroxide yielded (*S*)-(+)-amide **2a**, the antipode of the biotransformation product (*R*)-(−)-**2a**, while the chemical dehydration of (*R*)-(−)-**2a** (X = H) and **2c** (X = Cl) using thionyl chloride led to the formation of (*R*)-(+)-nitriles **1a** and **1c**, respectively (Scheme 3).



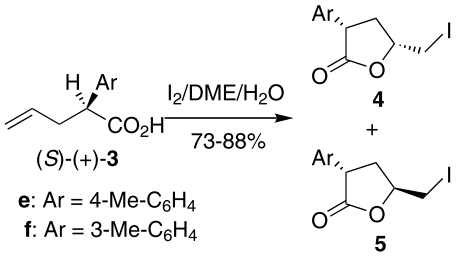
Scheme 3. Chemical transformations of acid and amide.

It has been generally believed that the amidase is an *S*-enantioselective hydrolyzing enzyme against amide substrates while the nitrile hydratase exhibits no or low enantioselectivity depending on the structure of the nitriles. The results obtained from the current study are consistent with this general rule; the amidase involved in *Rhodococcus* sp. AJ270 shows high *S*-enantioselectivity and the nitrile hydratase displays moderate *S*-enantioselection. Furthermore, the nitrile hydratase activity is dramatically affected by the electronic nature of the substituent while the amidase is sensitive to the substitution pattern on the benzene ring of the substrate, as exemplified by the sluggish hydration reaction of the substituted nitriles **1c**–**g** and very slow hydrolysis of amide **2g** along with the moderate e.e. of acid **3g** (Table 1). Moreover, the excellent enantioselectivity of the biotransformations of 2-aryl-4-pentenenitriles results from the combined effects of amidase and nitrile hydratase, with the former being the dominant one, since the e.e. achieved from the reaction of (±)-**1a** was higher than that from the kinetic resolution of (±)-**2a**. It is therefore obviously advantageous to apply biotransformations of nitriles rather than kinetic resolution of amides for the preparation of enantiopure (*S*)-2-arylpentenoic acids and (*R*)-2-aryl-4-pentenamides.

2.3. Synthesis of α,γ-disubstituted γ-lactones

The chiral γ-lactone functionality occurs widely in natural products and synthetic bioactive compounds, and it has been also used as the intermediate for the preparation of complex natural products.[10] Intramolecular lactonization of 2-substituted 4-pentenoic acids and their derivatives is an efficient approach to α,γ-disubstituted γ-lactones.[11] Though the iodolactonization has been studied[12] and, in some cases, good diastereoselectivity was obtained,[13] no investigation of lactonizations utilizing chiral 2-aryl-4-pentenoic acids and their derivatives has appeared in the literature until now. Recently, Silverman and his co-worker[14,15] reported that racemic *cis*- and *trans*-5-(aminomethyl)-3-aryldihydrofuran-2(3*H*)-ones, which were derived from amination of *cis*- and *trans*-3-aryl-5-(iodomethyl)dihydrofuran-2(3*H*)-ones, are a new class of reversible and irreversible monoamine oxidase-B (MAO-B) inactivators. Surprisingly, however, the authors did not examine the influence of molecular chirality on the bioactivity, most probably due to the lack of enantiopure compounds. With the enantiopure 2-aryl-4-pentenoic acids and amides in hand, we attempted their lactonization reactions to synthesize all stereoisomers of α,γ-disubstituted γ-lactones.

Following a literature method,[12] (*S*)-(+)-acids **3e** and **3f**, after treatment with iodine at ambient temperature, were converted into a mixture of (3*S*,5*R*)-3-(4- or 3-methylphenyl)-5-iodomethyl-γ-lactone **4** and (3*S*,5*S*)-3-(4- or 3-methylphenyl)-5-iodomethyl-γ-lactone **5** in the ratio of 2.5–2.7 to 1 in good yield (Scheme 4). Pure stereoisomers **4** and **5**, precursors to chiral MAO-B inactivators, were obtained readily from flash column chromatography.



Scheme 4. Iodolactonization of (*S*)-(+)-acids **3e** and **3f**.

3. Conclusions

Enantiopure 2-aryl-4-pentenoic acids and their derivatives are useful building blocks in organic synthesis. Previously these compounds were only available through a tedious resolution procedure using a chiral

base such as L-menthylamine[9] or (*S*)-α-phenylethylamine.[16] A multi-step asymmetric synthesis of (*S*)-2-phenyl-4-pentenoic acid has been attempted very recently using (2*R*,5*R*)-bis(methoxymethoxymethyl)-pyrrolidine as a chiral auxiliary, but the synthetic efficiency was far from satisfactory.[16] Our study has shown that *Rhodococcus* sp. AJ270 is an effective biocatalyst able to catalyze the enantioselective hydrolysis of 2-aryl-4-pentenenitriles and 2-aryl-4-pentenamides. Biotransformations of racemic 2-aryl-4-pentenenitriles provide a straightforward, convenient and powerful method for the preparation of (*S*)-2-aryl-4-pentenoic acids and (*R*)-2-aryl-4-pentenamides with high enantiomeric purity. It has also been revealed that both the amidase and the nitrile hydratase involved in microbial cells are (*S*)-enantioselective, and the overall excellent enantioselectivity of the biohydrolysis of nitriles results from the combined effects of the two enzymes, with the amidase being dominant one. The further application of enantioselective biotransformations of nitriles has been extended to the synthesis of enantiopure (3*S*,5*R*)- and (3*S*,5*S*)-3-(4- or 3-methylphenyl)-5-iodomethyl-γ-butyrolactones, important precursors of chiral reversible and irreversible monoamine oxidase-B inactivators, via the iodolactonization of the corresponding (*S*)-2-aryl-4-pentenoic acids.

4. Experimental

4.1. General

Both melting points, which were determined using a Reichert Kofler hot-stage apparatus, and boiling points are uncorrected. IR spectra were obtained on a Perkin–Elmer 782 instrument as liquid films or KBr discs. NMR spectra were recorded on a Bruker AM 300 spectrometer. Chemical shifts are reported in ppm and coupling constants are given in hertz. Mass spectra were measured on an AEI MS-50 mass spectrometer and microanalyses were carried out by the Analytical Laboratory of the Institute.

Polarimetry was carried out using an Optical Activity AA-10R polarimeter and the measurements were made at the sodium D-line with a 5 cm pathlength cell. Concentrations (*c*) are given in g/100 ml. The e.e. values of all products were obtained with a Shimadzu LC-10AVP HPLC system using a chiral stationary phase column with racemic samples as references.

4.2. Preparation of racemic 2-aryl-4-pentenenitriles 1[17]

Racemic 2-aryl-4-pentenenitriles **1** were prepared from allylation of arylacetonitriles under basic conditions in the presence of a phase transfer catalyst TEBA according to the literature.[17] All unknown nitriles were fully characterized by their spectroscopic data.

4.2.1. 2-Phenyl-4-pentenenitrile, 1a[17]. Yield 48%; oil; ν_{max} (KBr)/cm^{-1} 2241 (CN), 1643 (C=C); δ_H ($CDCl_3$) 7.42–7.31 (m, 5H, ArH), 5.88–5.74 (m, 1H, -C*H*=CH_2), 5.20 (d, J=15.1, 1H, *trans* -CH=CH*H*), 5.19 (d, J=11.3, 1H, *cis* -CH=C*H*H), 3.86 (t, J=7.3, 1H, CH), 2.69–2.59 (m, 2H, CH_2); δ_C ($CDCl_3$) 135.2, 132.6, 129.1, 128.0, 127.3, 120.3, 119.3, 39.8, 37.5; m/z (EI) 157 (M^+, 26%), 116 (100).

4.2.2. 2-(4-Fluorophenyl)-4-pentenenitrile, 1b. Yield 55%; oil; ν_{max} (KBr)/cm^{-1} 2242 (CN), 1643 (C=C); δ_H ($CDCl_3$) 7.32–7.25 (m, 2H, ArH), 7.06 (t, J=8.5, 2H, ArH), 5.83–5.70 (m, 1H, -C*H*=CH_2), 5.18 (d, J=10.1, 1H, *cis* -CH=C*H*H), 5.17 (d, J=17.2, 1H, *trans* -CH=CH*H*), 3.84 (t, J=7.2, 1H, CH), 2.68–2.53 (m, 2H, CH_2); δ_C ($CDCl_3$) 164.0, 160.7, 132.2, 131.8, 130.9, 120.1, 119.7, 116.2, 115.9, 39.8, 36.8; m/z (EI) 175 (M^+, 21%), 134 (100), 107 (15). Anal. found: C, 75.76; H, 6.23; N, 7.82. $C_{11}H_{10}FN$ requires: C, 75.41; H, 5.75; N, 7.99%.

4.2.3. 2-(4-Chlorophenyl)-4-pentenenitrile, 1c. Yield 46%; oil; ν_{max} (KBr)/cm^{-1} 2242 (CN), 1644 (C=C); δ_H ($CDCl_3$) 7.34 (d, J=8.3, 2H, ArH), 7.26 (d, J=8.6, 2H, ArH), 5.80–5.71 (m, 1H, -C*H*=CH_2), 5.18 (d, J=9.7, 1H, *cis* -CH=C*H*H), 5.17 (d, J=18.0, 1H, *trans* -CH=CH*H*), 3.82 (t, J=7.2, 1H, CH), 2.62–2.58 (m, 2H, CH_2); δ_C ($CDCl_3$) 134.0, 133.6, 132.1, 129.1, 128.6, 119.8, 119.6, 39.5, 36.7; m/z (EI) 193 (M^++2, 7), 191 (M^+, 23%), 152 (32), 150 (100). Anal. found: C, 69.01; H, 5.41; N, 7.58. $C_{11}H_{10}ClN$ requires: C, 68.94; H, 5.26; N, 7.31%.

4.2.4. 2-(4-Methoxyphenyl)-4-pentenenitrile, 1d.[18] Yield 47%; oil; ν_{max} (KBr)/cm^{-1} 2240 (CN), 1643 (C=C); δ_H ($CDCl_3$) 7.26 (d, J=8.8, 2H, ArH), 6.92 (d, J=8.3, 2H, Ar*H*), 5.88–5.74 (m, 1H, -C*H*=CH_2), 5.21 (d, J=14.6, 1H, *trans* -CH=CH*H*), 5.20 (d, J=11.7, 1H, *cis* -CH=C*H*H), 3.83 (s, 3H, CH_3), 3.82 (t, J=7.2, 1H, CH), 2.68–2.57 (m, 2H, CH_2); δ_C ($CDCl_3$) 159.4, 132.8, 128.5, 127.2, 120.6, 119.2, 114.4, 55.3, 39.9, 36.7; m/z (EI): 187 (M^+, 7%), 146 (100).

4.2.5. 2-(4-Methylphenyl)-4-pentenenitrile, 1e. Yield 43%; oil; ν_{max} (KBr)/cm^{-1} 2240 (CN), 1643 (C=C); δ_H ($CDCl_3$) 7.26 (d, J=8.4, 2H, Ar*H*), 7.20 (d, J=8.4, 2H, ArH), 5.87–5.78 (m, 1H, -C*H*=CH_2), 5.23 (d, J=11.1, 1H, *cis* -CH=C*H*H), 5.22 (d, J=16.8, 1H, *trans* -CH=CH*H*), 3.84 (t, J=7.0, 1H, CH), 2.67–2.62 (m, 2H, CH_2), 2.38 (s, 3H, CH_3); δ_C ($CDCl_3$) 138.0, 132.8, 132.3, 129.7, 127.2, 120.5, 119.3, 39.9, 37.1, 21.1; m/z (EI) 171 (M^+, 20%), 130 (100). Anal. found: C, 84.17; H, 7.65; N, 7.84. $C_{12}H_{13}N$ requires: C, 84.17; H, 7.65; N, 8.18%.

4.2.6. 2-(3-Methylphenyl)-4-pentenenitrile, 1f. Yield 44%; oil; ν_{max} (KBr)/cm^{-1} 2241 (CN), 1643 (C=C), 1609; δ_H ($CDCl_3$) 7.29–7.10 (m, 4H, ArH), 5.85–5.76 (m, 1H, -C*H*=CH_2), 5.20 (d, J=16.7, 1H, *trans* -CH=CH*H*), 5.19 (d, J=10.5, 1H, *cis* -CH=C*H*H), 3.81 (t, J=7.2, 1H, CH), 2.65–2.60 (m, 2H, CH_2), 2.37 (s, 3H, CH_3); δ_C ($CDCl_3$) 138.9, 135.2, 132.7, 128.9 (2C), 128.0, 124.4, 120.4, 119.2, 39.9, 37.4, 21.4; m/z (EI): 171 (M^+, 22%), 130 (100). Anal. found: C, 84.11; H 7.81; N 7.92. $C_{12}H_{13}N$ requires: C, 84.17; H, 7.65; N 8.18%.

4.2.7. 2-(2-Methylphenyl)-4-pentenenitrile, 1g. Yield 82%; oil; ν_{max} (KBr)/cm^{-1} 2240 (CN), 1643 (C=C); δ_H ($CDCl_3$) 7.45–7.18 (m, 4H, ArH), 5.92–5.78 (m, 1H, -C*H*=CH_2), 5.24 (d, J=17.9, 1H, *trans* -CH=CH*H*), 5.20 (d, J=9.9, 1H, *cis* -CH=C*H*H), 4.01 (dd, J=8.5, 6.1, 1H, CH), 2.65–2.53 (m, 2H, CH_2), 2.36 (s, 3H, CH_3); δ_C ($CDCl_3$) 134.9, 133.6, 132.8, 131.0, 128.2, 127.5, 126.8, 120.6, 119.2, 38.4, 34.3, 19.1; m/z (EI) 171 (M^+, 27%), 130 (100), 103 (44). Anal. found: C, 84.12; H, 7.89; N, 7.98. $C_{12}H_{13}N$ requires: C, 84.17; H, 7.65; N, 8.18%.

4.3. General procedure for the biotransformations of 2-aryl-4-pentenenitriles 1

To an Erlenmeyer flask (150 ml) with a screw cap was added *Rhodococcus* sp. AJ270 cells[5a] (2 g wet weight) and potassium phosphate buffer (0.1 M, pH 7.0, 50 ml), and the resting cells were activated at 30°C for 0.5 h with orbital shaking. 2-Aryl-4-pentenenitriles (Table 1) was added in one portion to the flask and the mixture was incubated at 30°C using an orbital shaker (200 rpm). The reaction, monitored by TLC, was quenched after the specified period of time (Table 1) by removing the biomass through a Celite pad filtration. The resulting aqueous solution was basified to pH 12 with aqueous NaOH (2 M). Extraction with ethyl acetate gave, after drying ($MgSO_4$), removing solvent and column chromatography, amide **2** and the unconverted nitrile **1**. The aqueous solution was then acidified using aqueous HCl (2 M) to pH 2 and extracted with ethyl acetate. Column chromatography gave pure acid **3**.

4.3.1. Microbial hydrolysis of 2-phenyl-4-pentenenitrile, 1a

4.3.1.1. (*R*)-2-Phenyl-4-pentenamide, 2a. Yield 49%; mp 73.5–74.5°C; $[\alpha]_D^{25}$=−83.4 (c 4.4, $CHCl_3$); e.e. 99.2% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3382, 3189 (NH_2), 1657 (C=O); δ_H ($CDCl_3$) 7.36–7.24 (m, 5H, Ar*H*), 5.78–5.64 (m, 2H, CON*H*H and -C*H*=CH_2), 5.64 (br. s, 1H, CONH*H*), 5.06 (d, J=17.0, 1H, *trans* -CH=CH*H*), 4.98 (d, J=10.2, 1H, *cis* -CH=C*H*H), 3.46 (t, J=7.6, 1H, CH), 2.94–2.85 (m, 1H, C*H*H), 2.57–2.47 (m, 1H, CH*H*); δ_C ($CDCl_3$) 175.8, 139.1, 135.5, 128.6, 127.8, 127.2, 116.7, 52.2, 36.9; m/z (EI) 175 (M^+, 7%), 132 (43), 131 (100), 116 (29), 91 (18.). Anal. found: C, 75.37; H, 7.26; N 8.07. $C_{11}H_{13}NO$ requires: C, 75.40; H, 7.48; N, 7.99%.

4.3.1.2. (*S*)-2-Phenyl-4-pentenoic acid, 3a.[9,16] Yield 49%; oil; $[\alpha]_D^{25}$=+79 (c 4.1, $CHCl_3$); e.e. 96.8% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3400–2600 (br., COOH), 1705 (C=O), 1643 (C=C); δ_H ($CDCl_3$) 10.07 (br. s, 1H, CO_2H), 7.34–7.27 (m, 5H, ArH), 5.78–5.67 (m, 1H, -C*H*=CH_2), 5.10 (d, J=17.2, 1H, *trans* -CH=CH*H*), 5.02 (d, J=10.2, 1H, *cis* -CH=C*H*H), 3.65 (t, J=7.5, 1H, CH), 2.89–2.79 (m, 1H, C*H*H), 2.59–2.49 (m, 1H, CH*H*); δ_C ($CDCl_3$): 179.6, 137.7, 134.7, 128.5, 127.9, 127.4, 117.1, 51.2, 36.9; m/z (EI): 176 (M^+, 3%), 135 (52), 131 (100), 130 (34), 129 (35), 128 (24), 115 (25), 107 (22), 91 (25). HRMS found: 175.0764 (M−H). $C_{11}H_{11}O_2$ requires: 175.0764.

Kinetic resolution of racemic 2-phenyl-4-pentenamide gave (*R*)-2-phenyl-4-pentenamide **2a** (yield 51%, e.e. 90.2%) and (*S*)-2-phenyl-4-pentenoic acid **3a** (yield 46%, e.e. 97.3%).

4.3.2. Microbial hydrolysis of 2-(4-fluorophenyl)-4-pentenenitrile, 1b

4.3.2.1. (*R*)-2-(4-Fluorophenyl)-4-pentenamide, 2b. Yield 50%; mp 57–58°C $[\alpha]_D^{25}$=−75.7 (c 4.9, $CHCl_3$); e.e. >99.5% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3422, 3330 (NH_2), 1655 (C=O); δ_H ($CDCl_3$) 7.20–7.15 (m, 2H, ArH), 6.91 (t, J=8.6, 2H, ArH), 6.29 (br. s, 1H, CON*H*H), 5.67 (br. s, 1H, CONH*H*), 5.68–5.55 (m, 1H, -C*H*=CH_2), 4.95 (d, J=17.6, 1H, *trans* -CH=CH*H*), 5.90 (d, J=10.7, 1H, *cis* -CH=C*H*H), 3.37 (t, J=7.6, 1H, CH), 2.79–2.69 (m, 1H, C*H*H), 2.43–2.34 (m, 1H, CH*H*); δ_C ($CDCl_3$) 175.8, 163.6, 160.4, 135.3, 135.0, 129.5, 129.4, 117.1, 115.7, 115.5, 51.6, 37.3; m/z (EI): 193 (M^+, 6%), 175 (22), 149 (35), 134 (100), 109 (25). Anal. found: C, 68.26; H, 6.25; N, 7.12. $C_{11}H_{12}FNO$ requires: C, 68.38; H, 6.26; N, 7.25%.

4.3.2.2. (*S*)-2-(4-Fluorophenyl)-4-pentenoic acid, 3b. Yield 50%; oil; $[\alpha]_D^{25}$=+67.3 (c 4.9, $CHCl_3$); e.e. 99.3% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3200–2600 (br., COOH), 1708 (C=O), 1643 (C=C); δ_H ($CDCl_3$) 11.50 (br. s, COOH), 7.37–7.33 (m, 2H, ArH), 7.08 (t, J=8.6, 2H, ArH), 5.80–5.69 (m, 1H, -C*H*=CH_2), 5.14 (d, J=17.4, 1H, *trans* -CH=C*H*H), 5.08 (d, J=10.5, 1H, *cis* -CH=C*H*H), 3.70 (t, J=7.8, 1H, CH), 2.92–2.82 (m, 1H, C*H*H), 2.61–2.52 (m, 1H, CH*H*); δ_C ($CDCl_3$) 179.9, 163.8, 160.6, 134.5, 133.4, 133.4, 129.7, 129.6, 117.6, 115.7, 115.4, 50.6, 37.1; m/z (EI) 194 (M^+, 4%), 153 (100), 149 (97), 133 (23), 125 (50), 109 (40), 97 (39). HRMS found: 193.0670 (M−H). $C_{11}H_{10}FO_2$ requires: 193.0670.

4.3.3. Microbial hydrolysis of 2-(4-chlorophenyl)-4-pentenenitrile, 1c

4.3.3.1. (*R*)-2-(4-Chlorophenyl)-4-pentenamide, 2c. Yield 44%; mp 99–100.3°C; $[\alpha]_D^{25}$=−71.0 (c 2.3, $CHCl_3$); e.e. 99.3% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3417, 3330 (NH_2), 1654 (C=O); δ_H ($CDCl_3$) 7.30 (d, J=8.0 2H, ArH), 7.24 (d, J=8.3, 2H, ArH), 5.99 (br. s, 1H, CON*H*H), 5.73–5.53 (m, 1H, -C*H*=CH_2), 5.53 (br. s, 1H, CONH*H*), 5.06 (d, J=18.6, 1H, *trans* -CH=CH*H*), 5.00 (d, J=10.9, 1H, *cis* -CH=C*H*H), 3.43 (t, J=7.5, 1H, CH), 2.90–2.80 (m, 1H, C*H*H), 2.53–2.46 (m, 1H, CH*H*); δ_C ($CDCl_3$) 175.1, 137.7, 135.2, 133.3, 129.4, 129.0, 117.3, 51.9, 37.3; m/z (EI) 211 (M^++2, 5), 209 (M^+, 14%), 168 (23), 167 (36), 166 (39), 165 (100), 153 (12), 150 (30), 142 (10), 140 (30), 131 (32), 130 (50), 129 (43), 128 (19), 127 (33), 125 (64). Anal. found: C, 62.84; H, 5.71; N, 6.48. $C_{11}H_{12}ClNO$ requires: C, 63.01; H, 5.77; N, 6.68%.

4.3.3.2. (*S*)-2-(4-Chlorophenyl)-4-pentenoic acid, 3c. Yield 50%; oil; $[\alpha]_D^{25}$=+49.78 (c 2.75, $CHCl_3$); e.e. >99.5% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3400–2800 (br., COOH), 1708 (C=O), 1644 (C=C); δ_H ($CDCl_3$) 10.41 (br. s, COOH), 7.37 (d, J=8.5, 2H, ArH), 7.32 (d, J=8.5, 2H, ArH), 5.80–5.69

(m, 1H, -C*H*=CH_2), 5.14 (d, J=18.2, 1H, *trans* -CH=CH*H*), 5.09 (d, J=10.8, 1H, *cis* -CH=C*H*H), 3.70 (t, J=7.6, 1H, CH), 2.92–2.82 (m, 1H, C*H*H), 2.73–2.53 (m, 1H, CH*H*); δ_C ($CDCl_3$) 179.3, 136.2, 134.4, 133.5, 129.4, 128.9, 117.6, 50.7, 37.0; m/z (EI) 212 (M^++2, 4), 210 (M^+, 11%), 171 (35), 169 (100), 167 (26), 165 (78), 143 (12), 141 (40), 129 (70), 128 (45), 77 (35). HRMS found: 209.0372 (M−H). $C_{11}H_{10}ClO_2$ requires: 209.0375.

4.3.4. Microbial hydrolysis of 2-(4-methoxyphenyl)-4-pentenenitrile, 1d

4.3.4.1. (*R*)-2-(4-Methoxyphenyl)-4-pentenamide, 2d. Yield 47%; mp 90.5–91.4°C; $[\alpha]_D^{25}=-84.1$ (c 2.45, $CHCl_3$); e.e. >99.5% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3410, 3340 (NH_2), 1632 (C=O); δ_H ($CDCl_3$) 7.21 (d, J=8.6, 2H, ArH), 6.87 (d, J=8.6, 2H, ArH), 5.74–5.65 (m, 1H, -C*H*=CH_2), 5.34 (br. s, 2H, $CONH_2$), 5.04 (d, J=17.6, 1H, *trans* -CH=CH*H*), 4.97 (d, J=10.1, 1H, *cis* -CH=C*H*H), 3.79 (s, 3H, CH_3), 3.41 (t, J=7.6, 1H, CH), 2.90–2.85 (m, 1H, C*H*H), 2.52–2.47 (m, 1H, CH*H*); δ_C ($CDCl_3$) 175.5, 158.7, 135.6, 131.1, 128.9, 116.6, 114.1, 55.1, 51.5, 37.0; m/z (EI) 205 (M^+, 14%), 164 (85), 161 (100), 146 (79), 136 (49), 121 (26), 108 (36), 91 (34), 77 (17). Anal. found: C, 70.03; H, 7.38; N, 6.79. $C_{12}H_{15}NO_2$ requires: C, 70.22; H, 7.37; N, 6.82%.

4.3.4.2. (*S*)-2-(4-Methoxyphenyl)-4-pentenoic acid, 3d. Yield 51%; mp 88–89.3°C; $[\alpha]_D^{25}=+71.0$ (c 2.45, $CHCl_3$); e.e. 87.4% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3400–2800 (br., COOH), 1718 (C=O), 1677 (C=C); δ_H ($CDCl_3$) 10.09 (br. s, COOH), 7.27 (d, J=8.6, 2H, ArH), 6.90 (d, J=8.5, 2H, ArH), 5.79–5.70 (m, 1H, -C*H*=CH_2), 5.11 (d, J=17.0, 1H, *trans* -CH=CH*H*), 5.05 (d, J=10.2, 1H, *cis* -CH=C*H*H), 3.82 (s, 3H, CH_3), 3.63 (t, J=7.7, 1H, CH), 2.88–2.78 (m, 1H, C*H*H), 2.58–2.51 (m, 1H, CH*H*); δ_C ($CDCl_3$) 179.8, 159.0, 135.0, 129.9, 129.1, 117.2, 114.1, 55.3, 50.5, 37.1; m/z (EI) 206 (M^+, 14%), 165 (100), 137 (22). Anal. found: C, 69.87; H, 6.85. $C_{12}H_{14}O_3$ requires: C, 69.89; H, 6.84%.

4.3.5. Microbial hydrolysis of 2-(4-methylphenyl)-4-pentenenitrile, 1e

4.3.5.1. (*R*)-2-(4-Methylphenyl)-4-pentenamide, 5e. Yield 49%; mp 85.5–87°C; $[\alpha]_D^{25}=-75.1$ (c 2.45, $CHCl_3$); e.e. >99.5% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3387, 3189 (NH_2), 1656 (C=O); δ_H ($CDCl_3$) 7.18 (d, J=8.3, 2H, ArH), 7.14 (d, J=8.2, 2H, ArH), 5.77–5.66 (m, 1H, -C*H*=CH_2), 5.64 (br. s, 1H, CON*H*H), 5.41 (br. s, 1H, CONH*H*), 5.04 (d, J=17.0, 1H, *trans* -CH=CH*H*), 4.97 (d, J=10.2, 1H, *cis* -CH=C*H*H), 3.43 (t, J=7.5, 1H, CH), 2.93–2.84 (m, 1H, C*H*H), 2.55–2.48 (m, 1H, CH*H*), 2.32 (s, 3H, CH_3); δ_C ($CDCl_3$) 175.4, 137.0, 136.0, 135.6, 129.4, 127.7, 116.6, 51.9, 36.8, 20.9; m/z (EI) 189 (M^+, 5%), 171 (4), 145 (100), 130 (39), 120 (19), 105 (39), 91 (14). Anal. found: C, 76.38; H, 7.90; N, 7.47. $C_{12}H_{15}NO$ requires: C, 76.16; H, 7.99; N, 7.40%.

4.3.5.2. (*S*)-2-(4-Methylphenyl)-4-pentenoic acid, 3e. Yield 49%; oil; $[\alpha]_D^{25}=+69.7$ (c 2.55, $CHCl_3$); e.e. 94.3% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3400–2800 (br., COOH), 1708 (C=O), 1643 (C=C); δ_H ($CDCl_3$) 10.00 (br. s, COOH), 7.23 (d, J=8.2, 2H, ArH), 7.17 (d, J=7.9, 2H, ArH), 5.80–5.68 (m, 1H, -C*H*=CH_2), 5.12 (d, J=17.6, 1H, *trans* -CH=CH*H*), 5.04 (d, J=10.2, 1H, *cis* -CH=C*H*H), 3.64 (t, J=7.6, 1H, CH), 2.89–2.79 (m, 1H, C*H*H), 2.58–2.49 (m, 1H, CH*H*), 2.36 (s, 3H, CH_3); δ_C 180.1, 137.7, 135.4, 135.2 129.8, 128.3, 117.5, 51.3, 37.3, 21.4; m/z (EI) 190 (M^+, 8%), 149 (100), 145 (8), 129 (35), 128 (29), 121 (36), 115 (17), 105 (16), 93 (30), 91 (24), 77 (23). HRMS found: 189.0922 (M−H). $C_{12}H_{13}O_2$ requires: 189.0921.

4.3.6. Microbial hydrolysis of 2-(3-methylphenyl)-4-pentenenitrile, 1f

4.3.6.1. (*R*)-2-(3-Methylphenyl)-4-pentenamide, 2f. Yield 49%; mp 70–70.5°C; $[\alpha]_D^{25}=-94.8$ (c 2.3, $CHCl_3$); e.e. >99.5% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3382, 3184 (NH_2), 1657 (C=O); δ_H ($CDCl_3$) 7.24–7.07 (m, 4H, ArH), 5.90 (br. s, 1H, CON*H*H), 5.78–5.65 (m, 1H, -C*H*=CH_2), 5.49 (br. s, 1H, CONH*H*), 5.05 (d, J=16.9, 1H, *trans* -CH=CH*H*), 4.98 (d, J=10.1, 1H, *cis* -CH=C*H*H), 3.43 (t, J=7.6, 1H, CH), 2.93–2.83 (m, 1H, C*H*H), 2.55–2.46 (m, 1H, CH*H*), 2.34 (s, 3H, CH_3); δ_C ($CDCl_3$) 175.4, 139.0, 138.4, 135.6, 128.5, 128.5, 128.0, 124.8, 116.6, 52.3, 36.9, 21.2; m/z (EI): 189 (M^+, 3%), 171 (9), 145 (100), 130 (65), 120 (16), 105 (38), 91 (19). Anal. found: C, 75.80; H, 7.99; N, 7.51. $C_{12}H_{15}NO$ requires: C, 76.16; H, 7.99; N, 7.40%.

4.3.6.2. (*S*)-2-(3-Methylphenyl)-4-pentenoic acid, 3f. Yield 49%; oil; $[\alpha]_D^{25}=+68.7$ (c 1.95, $CHCl_3$); e.e. >99.5% (HPLC analysis using a Chiralcel OD column); ν_{max} (KBr)/cm^{-1} 3400–2800 (br., COOH), 1707 (C=O), 1643 (C=C); δ_H ($CDCl_3$) 10.09 (br. s, COOH), 7.24–7.10 (m, 4H, ArH), 5.81–5.68 (m, 1H, -C*H*=CH_2), 5.12 (d, J=17.1, 1H, *trans* -CH=CH*H*), 5.04 (d, J=10.2, 1H, *cis* -CH=C*H*H), 3.63 (t, J=7.6, 1H, CH), 2.88–2.79 (m, 1H, C*H*H), 2.58–2.48 (m, 1H, CH*H*), 2.36 (s, 3H, CH_3); δ_C ($CDCl_3$) 180.1, 138.8, 138.3, 135.4, 129.1, 129.0, 128.7, 125.4, 117.5, 51.6, 37.4, 21.8; m/z (EI): 190 (M^+, 10%), 149 (63), 145 (100), 129 (27), 128 (21), 121 (28), 115 (15), 105 (16), 93 (30), 91 (22), 77 (21). HRMS found: 189.0923 (M−H). $C_{12}H_{13}O_2$ requires: 189.0921.

4.3.7. Microbial hydrolysis of 2-(2-methylphenyl)-4-pentenenitrile, 1g

4.3.7.1. (*R*)-2-(2-Methylphenyl)-4-pentenamide, 2g. Yield 93%; mp 86.5–88°C; $[\alpha]_D^{25}=-1.3$ (c 4.7, $CHCl_3$); e.e. 3.2% (HPLC analysis using a Chiralcel OD column); ν_{max} (KBr)/cm^{-1} 3399, 3197 (NH_2), 1652 (C=O); δ_H ($CDCl_3$) 7.34–7.19 (m, 4H, ArH), 6.32 (br. s, 1H, CON*H*H), 5.81–5.70 (m, 1H, -C*H*=CH_2), 5.48 (br. s, 1H, CONH*H*), 5.07 (d, J=17.3, 1H, *trans* -CH=CH*H*), 4.99 (d, J=10.1, 1H, *cis* -CH=C*H*H), 3.75 (t, J=7.5, 1H, CH), 2.96–2.87 (m, 1H, C*H*H), 2.58–2.48 (m, 1H, CH*H*), 2.36 (s, 3H, CH_3); δ_C ($CDCl_3$) 175.9, 137.3, 136.1, 135.7, 130.6, 127.0, 126.4, 116.5, 48.2, 36.4, 19.6; m/z (EI): 189 (M^+, 9%), 171 (8), 145 (100), 130 (55), 105 (47), 103 (30), 91 (22). Anal. found: C, 75.94; H, 7.98; N, 7.61. $C_{12}H_{15}NO$ requires: C, 76.16; H, 7.99; N, 7.40%.

4.3.7.2. (*S*)-2-(2-Methylphenyl)-4-pentenoic acid, 3g. Yield 4%; oil; $[\alpha]_D^{25}=+40$ (*c* 0.2, $CHCl_3$); e.e. 78.5% (HPLC analysis using a Chiralcel OJ column); ν_{max} (KBr)/cm^{-1} 3400–2800 (br., COOH), 1708 (C=O), 1643 (C=C); δ_H ($CDCl_3$) 7.32–7.09 (m, 4H, ArH), 5.78–5.68 (m, 1H, -C*H*=CH_2), 5.08 (d, *J*=17.0, 1H, *trans* -CH=CH*H*), 5.00 (d, *J*=10.1, 1H, *cis* -CH=C*H*H), 3.93 (t, *J*=7.6, 1H, CH), 2.88–2.78 (m, 1H, C*H*H), 2.53–2.43 (m, 1H, CH*H*), 2.38 (s, 3H, CH_3); δ_C ($CDCl_3$) 178.6, 136.4, 136.3, 136.1, 130.6, 127.3, 126.8, 126.5, 117.2, 46.4, 36.7, 19.9; *m*/*z* (EI) 190 (M^+, 8%), 149 (75), 145 (100), 129 (26), 128 (21), 121 (25), 115 (16), 105 (28), 93 (22), 91 (23), 77 (22). HRMS found: 189.0922 (M−H). $C_{12}H_{13}O_2$ requires: 189.0921.

4.4. Chemical transformation of (*S*)-2-phenyl-4-pentenoic acid into (*S*)-2-phenyl-4-pentenamide

A mixture of (*S*)-2-phenyl-4-pentenoic acid (0.2 mmol, e.e. 80.1%) and $SOCl_2$ (0.6 mmol) in anhydrous dichloromethane was heated under reflux for 4 h under N_2. After removal of excess $SOCl_2$ under vacuum, the residue was mixed with dichloromethane (2 ml) and then the mixture was added slowly to a cold solution of aqueous ammonium hydroxide solution. Pure (*S*)-2-phenyl-4-pentenamide was obtained after column chromatography. (*S*)-(+)-**2a**: yield 82%; mp 71–73.3°C; $[\alpha]_D^{25}=+70.3$ (*c* 1.45, $CHCl_3$); e.e. 83.6% (HPLC analysis using a Chiralcel OJ column). Spectral data were identical to that of (*R*)-(−)-**2a**.

4.5. Chemical dehydration of (*R*)-2-aryl-4-pentenamides 2a and 2c

To a solution of (*R*)-2-phenyl-4-pentenamide **2a** (0.142 mmol, e.e. 93.0%) or (*R*)-2-phenyl-2-(4-chlorophenyl)-4-pentenamide **2c** (0.15 mmol, e.e. >99.5%) in dry DMF was added a mixture of dry benzene (2.5 ml) and $SOCl_2$ (0.3 mmol). The mixture was stirred at room temperature until the amide was consumed. The reaction mixture was then mixed with crushed ice and extracted with benzene (3×30 ml). The organic layer was combined and washed sequentially with saturated aqueous $NaHCO_3$ solution and water. After column chromatography, the pure nitrile was obtained.

4.5.1. (*R*)-2-Phenyl-4-pentenenitrile, 1a. Yield 89%; oil; $[\alpha]_D^{25}=+42$ (*c* 1.05, $CHCl_3$); e.e. 93.0% (HPLC analysis using a Chiralcel OB column). Spectral data were identical to that of racemic **1a**.

4.5.2. (*R*)-2-(4-Chlorophenyl)-4-pentenenitrile, 1c. Yield 76%; oil; $[\alpha]_D^{25}=+27.3$ (*c* 1.1, $CHCl_3$); e.e. >99.5% (HPLC analysis using a Chiralcel OB column). Spectral data were identical to that of racemic **1a**.

4.6. Iodolactonization of (*S*)-2-arylpentenoic acids 3e and 3f[12]

To a mixture of **3e** (0.337 mmol) or **3f** (0.35 mmol), DME and water was added 1.1–2 equiv. of iodine, and the resulting mixture was stirred at room temperature until the acid was converted. After dilution with ether, the mixture was treated with saturated aqueous NaS_2O_3 solution and then extracted with ether. Column chromatography gave pure γ-lactone compounds **4** and **5**.

4.6.1. (3*S*,5*R*)-3-(4-Methylphenyl)-5-iodomethyl-γ-butyrolactone, 4e. Yield 53%; mp 82.1–82.7°C; $[\alpha]_D^{25}=+40$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1766 (C=O); δ_H ($CDCl_3$) 7.19 (s, 4H, ArH), 4.53–4.49 (m, 1H, COOCH), 3.92 (dd, *J*=12.5, 9.0, 1H, CHCOO), 3.50 (dd, *J*=10.4, 4.4, 1H, C*H*HI), 3.37 (dd, *J*=10.4, 7.3, 1H, CH*H*I), 2.98–2.89 (m, 1H, C*H*H), 2.35 (s, 3H, CH_3), 2.15 (q, *J*=10.0, 1H, CH*H*); δ_C ($CDCl_3$) 176.0, 137.4, 132.7, 129.4, 127.8, 76.0, 46.9, 38.3, 20.9, 6.5; *m*/*z* (EI) 316 (M^+, 15%), 145 (100). Anal. found: C, 45.76; H, 4.07. $C_{12}H_{13}IO_2$ requires: C, 45.59; H, 4.14%.

4.6.2. (3*S*,5*S*)-3-(4-Methylphenyl)-5-iodomethyl-γ-butyrolactone, 5e. Yield 20%; oil; $[\alpha]_D^{25}=+11.4$ (*c* 1.05, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1774 (C=O); δ_H ($CDCl_3$) 7.14–7.20 (m, 4H, ArH), 4.76–4.70 (m, 1H, COOCH), 3.98 (t, *J*=7.7, 1H, CHCOO), 3.45 (dd, *J*=10.4, 4.4, 1H, C*H*HI), 3.36 (dd, *J*=10.3, 7.4, 1H, CH*H*I), 2.63–2.54 (m, 2H, CH_2), 2.34 (s, 3H, CH_3); δ_C ($CDCl_3$) 176.4, 137.4, 133.4, 129.6, 127.2, 76.7, 45.2, 36.3, 20.9, 6.8; *m*/*z* (EI) 316 (M^+, 18%), 145 (100). HRMS found: 317.0032 (M+H). $C_{12}H_{14}IO_2$ requires: 317.0033.

4.6.3. (3*S*,5*R*)-3-(3-Methylphenyl)-5-iodomethyl-γ-butyrolactone, 4f. Yield 63%; oil; $[\alpha]_D^{25}=+33.7$ (*c* 3.5, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1779 (C=O); δ_H ($CDCl_3$) 7.27–7.08 (m, 4H, ArH), 4.53–4.45 (m, 1H, OCOOCH), 3.90 (dd, *J*=12.3, 9.0, 1H, CHCOO), 3.48 (dd, *J*=10.1, 4.4, 1H, C*H*HI), 3.38 (dd, *J*=10.1, 6.9, CH*H*I), 2.94–2.87 (m, 1H, C*H*H), 2.36 (s, 3H, CH_3), 2.12 (q, *J*=10.2, 1H, CH*H*); δ_C ($CDCl_3$) 176.1, 138.7, 136.0, 128.9, 128.6, 125.2, 76.2, 47.4, 38.5, 21.5, 6.8; *m*/*z* (EI) 316 (M^+, 15%), 186 (27), 145 (100). HRMS found: 317.0033 (M+H). $C_{12}H_{14}IO_2$ requires: 317.0033.

4.6.4. (3*S*,5*S*)-2-(3-Methylphenyl)-4-iodomethyl-γ-butyrolactone, 5f. Yield 25%; oil; $[\alpha]_D^{25}=+8.57$ (*c* 1.4, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1773 (C=O); δ_H ($CDCl_3$) 7.30–7.06 (m, 4H, ArH), 4.79–4.72 (m, 1H, COOCH), 3.99 (t, *J*=7.4, 1H, CHCOO), 3.46 (dd, *J*=10.4, 4.4, 1H, C*H*HI), 3.38 (dd, *J*=10.4, 7.4, 1H, CH*H*I), 2.64–2.56 (m, 2H, CH_2), 2.37 (s, 3H, CH_3); δ_C ($CDCl_3$) 176.6, 138.9, 136.7, 129.0, 128.6, 128.3, 124.5, 76.9, 45.8, 36.6, 21.5, 7.1; *m*/*z* (EI) 316 (M^+, 10%), 145 (100). HRMS found: 317.0031 (M+H). $C_{12}H_{14}IO_2$ requires: 317.0033.

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