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Enantioselective hydrolysis of various racemic α-substituted arylacetonitriles using *Rhodococcus* sp. CGMCC 0497

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Abstract—The enantioselective hydrolysis of 17 racemic α-substituted arylacetonitriles by *Rhodococcus* sp. CGMCC 0497 is described. The corresponding (*R*)-amides and (*S*)-acids were obtained with excellent enantiomeric excess in most cases. The effect of steric and electronic factors on the outcome of the reactions are discussed here. The results prove that nitrile-converting enzymes are efficient tools for the synthesis of sterically unencumbered chiral α-arylpropionic acids and amides. © 2002 Published by Elsevier Science Ltd.

1. Introduction

α-Arylpropionic acids are related to the non steroidal anti-inflammatory profen drugs. All profens other than naproxen have been sold as racemic mixtures. However, the claim that the (*S*)-(+)-isomer may have advantages over the racemate has prompted frantic efforts to examine all profens for racemic switch potential.[1]

Among enzymatic methods, nitrile-converting enzymes as well as esterases or lipases can achieve this goal. However, compared with esterases or lipases, the studies on nitrile-converting enzymes are relatively few.[2] Although studied by a number of groups, the tested substrates for this class of enzyme are very limited.[3] Until now, there has been no detailed report on the substrate adaptability, which gives an impression that nitrile-converting enzymes are not a generally accepted and efficient means for the synthesis of chiral α-arylpropionic acids. In fact, nitrile hydratase has been successfully applied in the production of arylamides for many years,[4] which proves that nitrile-converting enzymes can be powerful tools in organic syntheses. In order to exploit this potential, we were interested in the study of nitrile-converting enzymes in detail with regard to their ability to convert racemic α-substituted arylacetonitriles to the corresponding chiral amides and acids.

We have screened and optimized the culture conditions for the strain *Rhodococcus* sp. CGMCC 0497, which was isolated by our group and proved to have high nitrile-converting activity and enantioselectivity.[5] As an extension of these findings, we now report the results obtained in a detailed investigation on the synthetic usefulness and limitation of this biocatalysts. Herein, we report a study in which 17 cyano compounds were hydrolyzed to the corresponding amides and acids using *Rhodococcus* sp. CGMCC 0497 as the catalyst. Excellent enantiomeric excesses were achieved in most cases.

2. Results and discussion

In order to gain meaningful results, we used the fresh microorganism cultivated under the optimal conditions. The enantiomeric excesses of amides **b** and acids **c** were determined by means of chiral HPLC or chiral GC analysis after conversion to the corresponding methyl, ethyl or isopropyl esters. The configurations of the products were obtained by comparing the sign of specific rotations with those reported in the literature. The recovered nitrile **15a** was converted to the corresponding methyl ester by chemical reaction and its configuration was thus assigned by comparing the retention time of this ester with the samples derived from the corresponding (*R*)-amide or (*S*)-acid using chiral HPLC. The enantiomeric excess of the recovered **15a** was determined directly by chiral HPLC.

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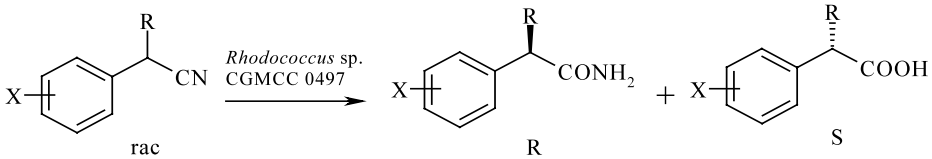
We first tested 14 nitriles with phenylacetonitrile as the basic structure bearing variety of substituents at the benzene ring and the α-position (Scheme 1). As shown in Table 1, the hydrolysis of all of the nitrile compounds proceeded smoothly and completely. In all cases, (*R*)-amides and (*S*)-acids were obtained and the total isolated yields of both products reached at least 90%.

The influence of the substituent at the α-position (Table 1, entries 1–3) has been reported by Wang et al.[6] They reported incomplete conversion when a bulky and conformationally flexible group was introduced. Under our reaction conditions, the same substrate **3a** was hydrolyzed effectively to the amide as well as **1a** and **2a**, but the conversion of amide to acid was rather slow and prolonged reaction time hardly had any effect. It is obvious that the significant effect of steric factors still exists. At the α-position, the larger the substituent is, the more time was needed to achieve the same yield of acid. Moreover, a decrease in enantioselectivity was observed when the substituent was too large, as demonstrated by the fact that the e.e. of acid **3c** was 96% when the yield was only 14%, while the e.e. values of **1c** and **2c** were 96 and 99% and the yields reached 48 and 38%, respectively. The enantiomeric ratio (*E*) calculated according to the enantiomeric excess of the acids fraction for entry 1 was 146, for entry 2 was 371, and for entry 3 was only 57. It can be inferred that substituents larger than *n*-Pr will give worse results.

Most probably for a similar reason, the position of the substituent on the benzene ring also plays an important role on the rate and selectivity of the reaction. As shown in Table 1, hydrolysis of *ortho*-substituted **5a** proceeded not only much more slowly than the corresponding *meta*- and *para*-substituted substrates, **6a** and **7a**, but also with a significant reduction in the enantioselectivity. This is also shown in the reaction of **8a** versus **9a** and **10a**. The Cl atom is relatively small, hence the yield of acid **8c** could reach 46%, while the methoxy group is much larger and the hydrolysis of amide **5b** to acid **5c** was too slow to reach the termination of resolution.

The steric effects of *meta*-substitution only resulted in a decrease in the reaction rate but not in enantioselectivity (Table 1, entries 6 and 9). The e.e. value of the products were all above 97%, the same level as the *para*-substituted ones, while the reaction time was prolonged compared with the *para*-substituted ones.

Except the nitro-substituted cyano compounds, all *para*-substituted substrates gave two products with excellent enantioselectivity of 96% up to 100%, whether the substituents were electron-donating, such as methoxy and methyl groups (Table 1, entries 7 and 14) or electron-withdrawing halogen groups (Table 1, entries 10–13). The reaction time ranged from 3.5 to 7 h.



Scheme 1.

Table 1. Enantioselective hydrolysis of nitriles with phenylacetonitrile as the basic structure by *Rhodococcus* sp. CGMCC 0497

Entry	Substrate **A**	X	R	Time (h)	(*R*)-Amide **b**		(*S*)-Acid **c**	
					Yield (%)	E.e. (%)	Yield (%)	E.e. (%)
1	**1**	H	CH_3	3	42	97[a]	48	96
2	**2**	H	Et	34	50	97[a]	38	99
3	**3**	H	*n*-Pr	50	80	13[b]	14	96
4	**4**	4′-NO_2	CH_3	5.5	47	86[a]	44	90
5	**5**	2′-OMe	CH_3	34	65	34[c]	28	91
6	**6**	3′-OMe	CH_3	10	42	>99[c]	49	>98
7	**7**	4′-OMe	CH_3	5	43	100[d]	50	98
8	**8**	2′-Cl	CH_3	30	45	50[a]	46	55
9	**9**	3′-Cl	CH_3	12	43	>99[c]	48	97
10	**10**	4′-Cl	CH_3	7	46	>98[a]	48	>98
11	**11**	4′-F	CH_3	4	45	>99[c]	47	>98
12	**12**	4′-Br	CH_3	5	45	>98[c]	46	96
13	**13**	4′-I	CH_3	3.5	42	>99[c]	50	97
14	**14**	4′-CH_3	CH_3	7	47	99[c]	46	100

[a] E.e. values of the corresponding ethyl esters determined by chiral HPLC.
[b] E.e. values of the corresponding methyl esters determined by chiral GC.
[c] E.e. values of the corresponding methyl esters determined by chiral HPLC.
[d] E.e. values of the corresponding isopropyl esters determined by chiral HPLC.

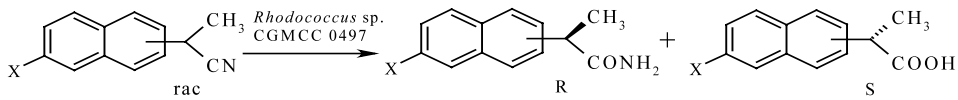
The nitro group is a distinct substituent exerting a strong electron-withdrawing effect. Treatment of the supernatant reaction mixture with 2N aq. NaOH before extraction could cause partial racemization of the products **4b** and **4c**, so satd aq. $NaHCO_3$ solution was used instead, or direct acidification followed by extraction of both products was carried out. The result indicated that a strong electron-withdrawing group may have some unfavorable effect on the enantioselectivity of the enzyme, but not on the activity.

In general, steric effects exerted more influence on the activity and enantioselectivity of the nitrile-converting enzymes in *Rhodococcus* sp. CGMCC 0497 than electronic effects did. To shed more light on the effects of steric factors on the course of this reaction, nitriles **15a**, **16a** and **17a** with a naphthene ring as the basic structure were prepared and subjected to the hydrolysis catalyzed by *Rhodococcus* sp. CGMCC 0497 (Scheme 2). The results listed in Table 2 show that β-naphthyl substituted cyano compounds **16a** and **17a**, structurally similar to *para*- and *meta*-disubstituted substrate in Table 1, were hydrolyzed to the corresponding (*R*)-amide and (*S*)-acid completely though with a little decrease of enantioselectivity (Table 2, entries 4 and 5). While the α-naphthyl substituted compound, **15a**, which is structurally similar to the *ortho*- and *meta*-disubstituted substrate, could not be hydrolyzed completely even after 168 h. Moreover, to our surprise, the amide **15b** was of the same configuration as that of the acid **15c**. (*S*)-Amide, instead of (*R*)-amide, was generated. Consequently, the recovered nitrile **15a** was confirmed to be of *R*-configuration (Table 2, entries 1 and 2).

This result is reasonable and can be explained by the combination of nitrile hydratase and amidase, both of which are *S*-selective toward their substrates, **15a** and **15b**, respectively. When racemic amide **15b** was used as the substrate directly in order to test the amidase independently, low activity and enantioselectivity was found (Table 2, entry 3). The yield of acid only reached 28% within 168 h, but the configuration of recovered amide was *R*, in accordance with the resolution rule.

Thus, with these 17 cyano compounds of different electronic and steric characteristics studied, we could infer that our nitrile-converting enzymes from *Rhodococcus* sp. CGMCC 0497 are effective tools for the conversion of most α-substituted arylacetonitriles with relatively low steric hindrance to the corresponding amides and acids with excellent enantiomeric excess.

Esterification of (*S*)-(+)-2-(4′-bromophenyl)propanoic acid **12c** and the hydrolyzed product of (*R*)-(−)-2-(4′-bromophenyl)propionamide **12b** using tropine afforded enantiopure (+)-PG_9 and (−)-PG_9 with retention of configuration (Scheme 3), which have been shown to be potent analgesic and cognition-enhancing drugs by Gualtier et al.[7] The racemic mixture and the enantiopure compounds have different effects. The study is far from thorough, partly due to problems in obtaining sufficient quantities of both enantiomers of PG_9 with satisfactory enantiomeric purity. However, our study afforded an efficient method to both enantiomers with enantiomeric excess higher than 96%.



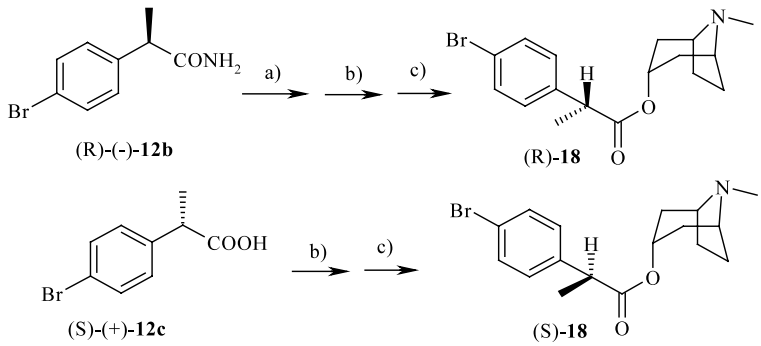
15, α-Naphthyl; **16** , **17**, β-Naphthyl

Scheme 2.

Table 2. Enantioselective hydrolysis of nitriles and (±)-2-(1′-naphthyl)propionamide **15b** with a naphthene ring as the basic structure by *Rhodococcus* sp. CGMCC 0497

Entry	Substrate	X	Time (h)	Amide **b**		Acid **c**	
				Yield (%)	E.e. (%)	Yield (%)	E.e. (%)
1[a]	**15a**	H	96	41	90 *S*[d]	12	93 *S*
2[b]	**15a**	H	168	45	63 *S*	16	48 *S*
3	**15b**	H	168	65	21 *R*	28	78 *S*
4	**16a**	H	24	52	69 *R*[e]	40	98 *S*
5[c]	**17a**	OMe	32	52	75 *R*[e]	43	99 *S*

[a] (*R*)-Substrate recovered with a yield of 38% and e.e. of 80%.
[b] (*R*)-Substrate recovered with a yield of 25% and e.e. of 98%.
[c] The product **17c** is the famous anti-inflammatory drug (*S*)-naproxen.
[d] E.e. values of the corresponding methyl esters determined by chiral HPLC.
[e] E.e. values of the corresponding ethyl esters determined by chiral HPLC.



Scheme 3. *Reagents and conditions*: (a) CH_2Cl_2, HCl; (b) $SOCl_2$, 80°C, 2 h; (c) $CHCl_3$, tropine, 80°C, 8 h.

3. Experimental

3.1. Materials and methods

The commercially available reagents were used without further purification. Melting points were determined on a Mettler FP62 and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 (90 MHz), Bruker AMX-300 (300 MHz), or Bruker AMX-400 (400 MHz) spectrometer at room temperature with TMS as internal standard. Chemical shifts in ppm were positive for upfield shifts. IR spectra were recorded neat or in KBr and measured in cm^{-1}, using a Shimadzu IR-440 IR spectrophotometer. EI-MS spectra were recorded on an HP 5989A. High resolution mass spectra were obtained on a Finnigan MAT8430. Microanalyses were carried out on an Italian Carlo-Erba 1106. Polarimetry was carried out using an optical activity Perkin Elmer 241ML polarimeter and the measurements were made at the sodium D-line with a 10 cm pathlength cell. Concentrations (c) are given in g/100 ml. Enantiomeric excesses: chiral HPLC was conducted with a PE NELSON NCI900 using Chiralcel OJ, OD or Chiralpak AS columns at a flow rate of 0.7 ml/min with 2-propanol/hexane as the mobile phase. Chiral GC separations were conducted with an R_t-βDex column using nitrogen as the carrier gas.

Racemic nitriles **1a**, **8a**, **9a**, **10a**, **14a**[8] were prepared following the literature methods but were carried out in THF at −75°C using t-BuOK as a base. **2a**, **3a**, **5a**, **6a**, **7a**, **15a**, **16a**, **17a**[9] and **4a**, **11a**, **12a**, **13a**[10] were prepared following the literature methods.

Racemic amide **15b** was obtained from chemical hydrolysis of **15a**.[11]

3.2. Analytical procedure for the determination of enantiomeric excess: general procedure

Amides **b** in methanol, ethanol or isopropanol were treated with catalytic conc. sulfuric acid under gentle reflux for 3 h to yield the corresponding esters. Acids **c** in dichloromethane was treated with 1 equiv. of dicyclohexylcarbodiimide, 3 equiv. of methanol, ethanol or isopropanol and catalytic 4-dimethylaminopyridine at rt for 1 h to achieve the esters and the esters were subjected to chiral HPLC or GC.

3.3. General procedure with whole cells

A suspension of washed wet cells (10 g) and aq. potassium phosphate buffer (pH 7.0, 0.1 mM, 40 mL) was incubated at 30°C for 30 min with continuous magnetic stirring before the addition of the substrate, a solution of 2-phenylpropionitrile or 2-phenylpropionamide (100 mg) in tetrahydrofuran (200 μL). The reaction, monitored by thin layer chromatography, was quenched after a period of time by centrifugation using an HIMAC centrifuge CR20B2 (Hitachi, Japan) with a RPR20-4-154 rotor (7800g, 30 min, 20°C), the resulting supernatant was basified with 2N aq. NaOH to pH 12 (for substrate **4a**, satd $NaHCO_3$ solution was used instead), and extracted with diethyl ether. The organic solutions, after drying ($MgSO_4$) and concentration, gave the amide and unreacted nitrile. The separation of amide and nitrile was effected by column chromatography. The aqueous solution was then acidified using 3N HCl to pH 2 and extracted with diethyl ether. Acid was obtained after removal of the solvent under reduced pressure.

3.3.1. (*R*)-(−)-2-Phenylpropionamide 1b. White crystal, mp 90–91°C lit.:[6] 90–92°C; $[\alpha]_D^{25}=-54.7$ (c 2.0, $CHCl_3$) lit.:[6] >99% e.e., $[\alpha]_D^{25}=-53.4$ (c 4.13, $CHCl_3$), *R*, e.e. 97%; ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.49 (s, 5H, Ar-H), 5.5 (br s, 2H, NH_2), 3.63 (q, 1H, $J=8$ Hz, CH), 1.55 (d, 3H, $J=8$ Hz, CH_3); IR (KBr): 3056, 3199 (NH_2), 1656 (C=O) cm^{-1}; EIMS m/z: 150 ($M+1^+$, 3%), 149 (M^+, 8), 105 ($M-CONH_2^+$, 100).

3.3.2. (*S*)-(+)-2-Phenylpropanoic acid 1c. Colorless oil, $[\alpha]_D^{25}=+66.1$ (c 1.8, $CHCl_3$) lit.:[6] 90% e.e., $[\alpha]_D^{25}=+61.8$ (c 4.27, $CHCl_3$), *S*, e.e. 96%; ^{1}H NMR (90 MHz, CCl_4): δ 11.4 (s, 1H, COOH), 7.17 (s, 5H, Ar-H), 3.56 (q, 1H, $J=8$ Hz, CH), 1.39 (d, 3H, $J=8$ Hz, CH_3); IR (neat): 2870–3110 (br, COOH), 1706 (C=O) cm^{-1}; EIMS m/z: 150 (M^+, 27%), 105 ($M-COOH^+$, 100).

3.3.3. (*R*)-(−)-2-Phenylbutyramide 2b. White crystal, mp 77–79°C lit.:[6] 74–76°C; $\alpha_D^{26}=-55.8$ (c 1.8, $CHCl_3$) lit.:[6] 96% e.e., $[\alpha]_D^{25}=-56.5$ (c 6.99, $CHCl_3$), *R*, e.e. 97%; ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.36 (s, 5H, Ar-H), 5.95 (br s, 2H, NH_2), 3.33 (t, 1H, $J=8$ Hz, CH), 2.46–1.49 (m, 2H, CH_2), 0.92 (t, 3H, $J=8$ Hz, CH_3); IR (KBr): 3391, 3175 (NH_2), 1653 (C=O) cm^{-1}; EIMS m/z: 164 ($M+1^+$, 5%), 163 (M^+, 10), 91 (100).

3.3.4. (*S*)-(+)-2-Phenylbutyric acid 2c. Colorless oil, $[\alpha]_D^{26}=+59.9$ (*c* 1.7, $CHCl_3$) lit.:[6] >99% e.e., $[\alpha]_D^{25}=+61.3$ (*c* 4.97, $CHCl_3$), *S*, e.e. 99%; ^1H NMR (90 MHz, CCl_4): δ 10.62 (s, 1H, COOH), 7.26 (s, 5H, Ar-H), 3.39 (t, 1H, $J=8$ Hz, CH), 2.41–1.43 (m, 2H, CH_2), 0.93 (t, 3H, $J=8$ Hz, CH_3); IR (neat): 2865–3110 (OH), 1708 (C=O) cm^{-1}; EIMS *m*/*z*: 164 (M^+, 27%), 91 (100).

3.3.5. (*R*)-(−)-2-Phenylvaleramide 3b. White crystal, mp 78–80°C lit.:[6] 78–79°C; $[\alpha]_D^{23}=-11.8$ (*c* 4.0, $CHCl_3$) lit.:[6] 41% e.e., $[\alpha]_D^{25}=+39.9$ (*c* 5.80, $CHCl_3$), *S*, e.e. 13%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H, Ar-H), 5.67 (br s, 1H, NH), 5.41 (br s, 1H, NH), 3.39 (t, 1H, $J=7.2$ Hz, CH), 2.18–2.06 (m, 1H, CH), 1.82–1.70 (m, 1H, CH), 1.34–1.19 (m, 1H, CH_2), 0.91 (t, 3H, $J=7.3$ Hz, CH_3); IR (KBr): 3409, 3188 (NH_2), 1651 (C=O) cm^{-1}; EIMS *m*/*z*: 178 ($M+1^+$, 1%), 177 (M^+, 0.3), 91 (100).

3.3.6. (*S*)-(+)-2-Phenylvaleric acid 3c. Colorless oil, $[\alpha]_D^{23}=+54.5$ (*c* 1.0, $CHCl_3$) lit.:[6] >99% e.e., $[\alpha]_D^{25}=+55.0$ (*c* 1.09, $CHCl_3$), *S*, e.e. 96.4%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.22 (m, 5H, Ar-H), 3.54 (t, 1H, $J=7.7$ Hz, CH), 2.06–2.01 (m, 1H, CH), 1.80–1.72 (m, 1H, CH), 1.34–1.23 (m, 2H, CH_2), 0.91 (t, 3H, $J=7.3$ Hz, CH_3); IR (neat): 3100–2650 (br, OH), 1706 (C=O) cm^{-1}; EIMS *m*/*z*: 178 (M^+, 27%), 91 (100).

3.3.7. (*R*)-(−)-2-(4′-Nitrophenyl)propionamide 4b. Pale yellow crystal, mp 118–119°C; $[\alpha]_D^{25}=-41.0$ (*c* 1.74, $CHCl_3$), e.e. 86%; ^1H NMR (90 MHz, $CDCl_3$): δ 7.52, 8.32 (AB, 4H, $J=8$ Hz, Ar-H), 5.83 (br s, 2H, NH_2), 3.72 (q, 1H, $J=8$ Hz, CH), 1.56 (d, 3H, $J=8$ Hz, CH_3); IR (KBr): 3455, 3283 (NH_2), 3202, 1675 (C=O), 1515, 1350 (NO_2) cm^{-1}; EIMS *m*/*z*: 195 ($M+1^+$, 46%), 151 ($M+1-CONH_2^+$, 86), 91 (100).

3.3.8. (*S*)-(+)-2-(4′-Nitrophenyl)propanoic acid 4c. Pale yellow crystal, mp 96–97°C; $[\alpha]_D^{25}=+62.3$ (*c* 1.07, $CHCl_3$), e.e. 90%; ^1H NMR (90 MHz, CCl_4): δ 10.59 (s, 1H, COOH), 7.47–8.27 (AB, 4H, $J=9$ Hz, Ar-H), 3.83 (q, 1H, $J=8$ Hz, CH), 1.59 (d, 3H, $J=8$ Hz, CH_3); IR (KBr): 2730–3150 (br, OH), 1675 (C=O), 1515, 1350 (NO_2) cm^{-1}; EIMS *m*/*z*: 195 (M^+, 24%), 150 ($M-COOH^+$, 100).

3.3.9. (*R*)-(−)-2-(2′-Methoxyphenyl)propionamide 5b. White crystal, mp 134–135°C; $[\alpha]_D^{22}=-41.5$ (*c* 1.23, $CHCl_3$), e.e. 34.2%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.23 (m, 2H, Ar-H), 6.98 (dd, 1H, $J_1=J_2=7.5$ Hz, ArH), 6.90 (d, 1H, $J=8.2$ Hz, ArH), 5.66 (s, 2H, NH_2), 3.88 (s, 3H, OCH_3), 4.04 (q, 1H, $J=7.1$ Hz, CH), 1.48 (d, 3H, $J=7.1$ Hz, CH_3); IR (KBr): 3393, 3196 (NH_2), 1648 (C=O) cm^{-1}; EIMS *m*/*z*: 179 (M^+, 22%), 135 ($M-CONH_2^+$, 100). Anal. calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.15; H, 7.28; N, 7.81%.

3.3.10. (*S*)-(+)-2-(2′-Methoxyphenyl)propanoic acid 5c. White solid, mp 95–96°C lit.:[12] 94–95°C; $[\alpha]_D^{22}=+60.3$ (*c* 0.9, $CHCl_3$) lit.:[12] 67% e.e., $[\alpha]_D=-46$ (c, $CHCl_3$), *R*, e.e. 91.4%; ^1H NMR (90 MHz, CCl_4): δ 10.73 (s, 1H, COOH), 7.35–7.0 (m, 2H, Ar-H), 7.0–6.65 (m, 2H, ArH), 3.8 (s, 3H, OCH_3), 4.01 (q, 1H, $J=7$ Hz, CH), 2.43 (d, 3H, $J=7$ Hz, CH_3); IR (KBr): 3050–2750 (br, OH), 1702 (C=O) cm^{-1}; EIMS *m*/*z*: 180 (M^+, 29%), 135 ($M-COOH^+$, 100).

3.3.11. (*R*)-(−)-2-(3′-Methoxyphenyl)propionamide 6b. White crystal, mp 97–98°C; $[\alpha]_D^{16}=-46.4$ (*c* 1.7, $CHCl_3$), e.e. 99.6%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.25 (m, 1H, Ar-H), 6.91–6.81 (m, 3H, ArH), 5.53 (s, 1H, NH), 5.35 (s, 1H, NH), 3.81 (s, 3H, OCH_3), 3.58 (q, 1H, $J=7.2$ Hz, CH), 1.52 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3265, 3206 (NH_2), 1689 (C=O) cm^{-1}; EIMS *m*/*z*: 180 ($M+1^+$, 18%), 179 (M^+, 79), 135 ($M-CONH_2^+$, 100). Anal. calcd for $C_{10}H_{13}NO_2$ C, 67.02; H, 7.31; N, 7.81; Found: C, 66.99; H, 7.27; N, 7.74%.

3.3.12. (*S*)-(+)-2-(3′-Methoxyphenyl)propanoic acid 6c. Colorless oil, $[\alpha]_D^{16}=+60.5$ (*c* 1.9, $CHCl_3$) lit.:[13,14] 62% e.e., $[\alpha]_D=-34$ (c, $CHCl_3$), *R*, 97.5% e.e., $[\alpha]_D=+62.3$ (*c* 1, $CHCl_3$), *S*, e.e. 98.2%; ^1H NMR (400 MHz, $CDCl_3$): δ 10.39 (br s, 1H, OH), 7.27–7.21 (m, 1H, Ar-H), 691–6.85 (m, 2H, Ar-H), 6.80–6.78 (m, 1H, Ar-H), 3.81 (s, 3H, OCH_3), 3.70 (q, 1H, $J=7.1$ Hz, CH), 1.52 (d, 3H, $J=7.1$ Hz, CH_3); IR (neat): 3050–2850 (br, OH), 1708 (C=O) cm^{-1}; EIMS *m*/*z*: 180 (M^+, 29%), 135 ($M-COOH^+$, 100).

3.3.13. (*R*)-(−)-2-(4′-Methoxyphenyl)propionamide 7b. White crystal, mp 126–127°C; $[\alpha]_D^{25}=-83.2$ (*c* 1, $CHCl_3$), e.e. 100%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–6.85 (AB, 4H, $J=8.5$ Hz, Ar-H), 6.15 (s, 1H, NH_2), 5.44 (s, 1H, NH_2), 3.79 (s, 3H, OCH_3), 3.52 (q, 1H, $J=7.1$ Hz, CH), 1.48 (d, 3H, $J=7.1$ Hz, CH_3); IR (KBr): 3347, 3170 (NH_2), 1662 (C=O) cm^{-1}; EIMS *m*/*z*: 180 ($M+1^+$, 4%), 179 (M^+, 9), 135 ($M-CONH_2^+$, 100).

3.3.14. (*S*)-(+)-2-(4′-Methoxyphenyl)propanoic acid 7c. White solid, mp 71–72°C lit.:[15] 74–77°C; $[\alpha]_D^{25}=+69.1$ (*c* 2, EtOH) lit.:[15] 87.3% e.e., $[\alpha]_D^{22}=-61.5$ (*c* 1.15, EtOH), R, e.e. 98%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.23–6.84 (AB, 4H, $J=8.7$ Hz, Ar-H), 3.78 (s, 3H, OCH_3), 3.68 (q, 1H, $J=7.2$ Hz, CH), 1.48 (d, 3H, $J=7.1$ Hz, CH_3); IR (KBr): 3500–2800 (br, OH), 1723 (C=O) cm^{-1}; EIMS *m*/*z*: 180 ($M+1^+$, 4%), 179 (M^+, 9), 135 ($M-CONH_2^+$, 100).

3.3.15. (*R*)-(−)-2-(2′-Chlorophenyl)propionamide 8b. White crystal, mp 121–122°C; $[\alpha]_D^{13}=-48.2$ (*c* 1.6, $CHCl_3$), e.e. 50%; ^1H NMR (90 MHz, $CDCl_3$): δ 7.71–6.9 (m, 4H, Ar-H), 5.65 (br, s, 2H, NH_2), 4.14 (q, 1H, $J=7$ Hz, CH), 1.52 (d, 3H, $J=7$ Hz, CH_3); IR (KBr): 3400, 3203 (NH_2), 1658 (C=O) cm^{-1}; EIMS *m*/*z*: 186 ($M+3^+$, 5%), 184 ($M+1^+$, 14), 148 ($M-Cl^+$, 100), 141 ($M+2-CONH_2^+$, 13), 139 ($M-CONH_2^+$, 34). Anal. calcd for $C_9H_{10}ClNO$: C, 58.87; H, 5.49; Cl, 19.31; N, 7.63. Found: C, 58.82; H, 5.74; Cl, 19.22; N, 7.53%.

3.3.16. (*S*)-(+)-2-(2′-Chlorophenyl)propanoic acid 8c. White solid, mp 85–86°C; $[\alpha]_D^{13}=+32.8$ (*c* 1.31, $CHCl_3$), e.e. 55%; ^1H NMR (90 MHz, CCl_4): δ 11.33 (s, 1H, COOH), 7.5–6.9 (m, 4H, Ar-H), 4.25 (q, 1H, $J=7$ Hz, CH), 1.53 (d, 3H, $J=7$ Hz, CH_3); IR (KBr): 3050–2650 (br, OH), 1704 (C=O) cm^{-1}; EIMS *m*/*z*: 186 ($M+2^+$,

6%), 184 (M^+, 16), 149 (M–Cl^+, 57), 141 (M+2–$COOH^+$, 33), 139 (M–$COOH^+$, 100); HRMS (EI) calcd for $C_9H_9O_2Cl$: 184.02911, Found 184.02735.

3.3.17. (*R*)-(−)-2-(3′-Chlorophenyl)propionamide 9b. White crystal, mp 98–99°C; $[\alpha]_D^{18.5}=-73.3$ (*c* 1.22, $CHCl_3$), e.e. 99.2%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1H, Ar-H), 7.29–7.25 (m, 2H, Ar-H), 7.22–7.20 (m, 1H, Ar-H), 5.46 (br, s, 1H, NH), 5.24 (br s, 1H, NH), 3.57 (q, 1H, $J=7.2$ Hz, CH), 1.52 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3351, 3199 (NH_2), 1643 (C=O) cm^{-1}; EIS *m/z*: 185 (M+2$^+$, 8%), 183 (M^+, 22), 142 (32), 141 (37), 140 (97), 139 (M–$CONH_2^+$, 86), 105 (100). Anal. calcd for $C_9H_{10}ClNO$: C, 58.87; H, 5.49; Cl, 19.31; N, 7.63. Found: C, 58.56; H, 5.43; Cl, 19.70; N, 7.62%.

3.3.18. (*S*)-(+)-2-(3′-Chlorophenyl)propanoic acid 9c. Colorless oil, $[\alpha]_D^{12}=+53.9$ (*c* 1.2, $CHCl_3$) lit.:[16] 81% e.e., $[\alpha]_D^{25}=+41.0$ (*c* 1.0, $CHCl_3$), *S*, e.e. 97.4%; ^1H NMR (300 MHz, $CDCl_3$): δ 11.32 (br s, 1H, OH), 7.24 (s, 1H, Ar-H), 7.19–7.10 (m, 3H, Ar-H), 3.62 (q, 1H, $J=7.2$ Hz, CH), 1.46 (d, 3H, $J=7.2$ Hz, CH_3); IR (neat): 3100–2850 (br, OH), 1710 (C=O) cm^{-1}; EIMS *m/z*: 186 (M+2$^+$, 10%), 184 (M^+, 30), 149 (M–Cl^+, 12.1), 141 (M+2–$COOH^+$, 38), 139 (M^+–COOH, 100).

3.3.19. (*R*)-(−)-2-(4′-Chlorophenyl)propionamide 10b. White crystal, mp 101–102°C; $[\alpha]_D^{18}=-47.9$ (*c* 1.1, $CHCl_3$), e.e. 98.5%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30, 7.25 (AB, 4H, $J=8.4$ Hz, Ar-H), 5.94 (br, s, 1H, NH), 5.43 (br, s, 1H, NH), 3.56 (q, 1H, $J=7.2$ Hz, CH), 1.47 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3393, 3220 (NH_2), 1654 (C=O) cm^{-1}; EIMS *m/z*: 185 (M+2$^+$, 6%), 184 (M+1$^+$, 6), 183 (M^+, 17), 141 (M+2–$CONH_2^+$, 38), 140 (45), 139 (M–$CONH_2^+$, 100).

3.3.20. (*S*)-(+)-2-(4′-Chlorophenyl)propanoic acid 10c. White solid, mp 77–78°C; $[\alpha]_D^{18}=+66.3$ (*c* 0.9, $CHCl_3$), e.e. 98.5%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.29, 7.24 (AB, 4H, $J=8.5$, Ar-H), 3.69 (q, 1H, $J=7.2$ Hz, CH), 1.50 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3100–2750 (br, OH), 1704 (C=O) cm^{-1}; EIMS *m/z*: 186 (M+2$^+$, 12%), 184 (M^+, 32), 141 (M+2–$COOH^+$, 36), 139 (M–$COOH^+$, 100).

3.3.21. (*R*)-(−)-2-(4′-Fluorophenyl)propionamide 11b. White crystal, mp 103–104°C; $[\alpha]_D^{16}=-56.6$ (*c* 1.0, $CHCl_3$), e.e. 99.1%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.25 (m, 2H, Ar-H), 7.04–7.00 (m, 2H, Ar-H), 5.94 (br, s, 1H, NH), 5.42 (br s, 1H, NH), 3.57 (q, 1H, $J=7.2$ Hz, CH), 1.49 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3353, 3197 (NH_2), 1650 (C=O) cm^{-1}; EIMS *m/z*: 168 (M+1$^+$, 36%), 167 (M^+, 18), 124 (41), 123 (M–$CONH_2^+$, 100). Anal. calcd for $C_9H_{10}FNO$: C, 64.66; H, 6.03; N, 8.38; F, 11.36. Found: C, 64.68; H, 5.98; N, 8.14; F, 11.46%.

3.3.22. (*S*)-(+)-2-(4′-Fluorophenyl)propanoic acid 11c. White solid, mp 51–52°C; $[\alpha]_D^{18}=+53.5$ (*c* 0.62, $CHCl_3$), e.e. 98.4%; ^1H NMR (300 MHz, $CDCl_3$): δ 11.20 (br s, 1H, OH), 7.24–7.19 (m, 2H, Ar-H), 6.96–6.90 (m, 2H, Ar-H), 3.61 (q, 1H, $J=7.2$ Hz, CH), 1.43 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3150–2780 (br, OH), 1710 (C=O) cm^{-1}; EIMS *m/z*: 168 (M^+, 28%), 123 (M–$COOH^+$, 100).

3.3.23. (*R*)-(−)-2-(4′-Bromophenyl)propionamide 12b. White crystal, mp 107–108°C; $[\alpha]_D^{22}=-53.6$ (*c* 2.0, $CHCl_3$), e.e. 98.3%; ^1H NMR (90 MHz, $CDCl_3$): δ 7.16, 7.48 (AB, 4H, $J=9$ Hz, Ar-H), 5.63 (br s, 2H, NH_2), 3.55 (q, 1H, $J=7$ Hz, CH), 1.47 (d, 3H, $J=7$ Hz, CH_3); IR (KBr): 3395, 3200 (NH_2), 1657 (C=O) cm^{-1}; EIMS *m/z*: 229 (M+2$^+$, 20%), 227 (M^+, 20), 185 (M+2–$CONH_2^+$, 96), 183 (M–$CONH_2^+$, 96), 104 (100). Anal. calcd for $C_9H_{10}BrNO$: C, 47.32; H, 4.42; N, 6.12 Br, 35.03; $C_{10}H_{13}NO_2$. Found: C, 47.50; H, 4.42; Br, 35.20; N, 6.00%.

3.3.24. (*S*)-(+)-2-(4′-Bromophenyl)propanoic acid 12c. White solid, mp 88–90°C lit.:[17] 88–92°C; $[\alpha]_D^{22}=+46.9$ (*c* 1.5, MeOH) lit.:[7a] 93.9% e.e. $[\alpha]_D=+46$ (MeOH), *S*, e.e. 96%; ^1H NMR (400 MHz, $CDCl_3$): δ 10.75 (br, s, 1H, COOH), 7.43, 7.18 (AB, 4H, $J=8.5$ Hz, Ar-H), 3.66 (q, 1H, $J=7.1$ Hz, CH), 1.49 (d, 3H, $J=7.1$ Hz, CH_3); IR (KBr): 3050–2870 (br, OH), 1702 (C=O) cm^{-1}; EIMS *m/z*: 230 (M+2$^+$, 35%), 228 (M^+, 34), 185 (M+2–$COOH^+$, 98), 183 (M–$COOH^+$, 100), 149 (M–Br^+, 4).

3.3.25. (*R*)-(−)-2-(4′-Iodophenyl)propionamide 13b. White crystal, mp 144–145°C; $[\alpha]_D^{16.5}=-39.8$ (*c* 0.25, $CHCl_3$), e.e. 99.2%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68, 7.08 (AB, 4H, $J=8.3$ Hz, Ar-H), 5.40 (br s, 1H, NH), 5.30 (br s, 1H, NH), 3.54 (q, 1H, $J=7.2$ Hz, CH), 1.50 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3393, 3202 (NH_2), 1638 (C=O) cm^{-1}; EIMS *m/z*: 276 (M+1$^+$, 28%), 275 (M^+, 44), 231 (M–$CONH_2^+$, 100), 148 (M–I^+, 6). Anal. calcd for $C_9H_{10}INO$: C, 39.30; H, 3.66; I, 46.13; N, 5.09. Found: C, 39.19; H, 3.60; I, 46.04; N, 4.97%.

3.3.26. (*S*)-(+)-2-(4′-Iodophenyl)propanoic acid 13c. White crystal, mp 137–138°C lit.:[18] 139–140°C; $[\alpha]_D^{16.5}=+40.8$ (*c* 1.5, $CHCl_3$) lit.:[18] 96% e.e. $[\alpha]_D=+39.0$ (*c* 2.45, $CHCl_3$), *S*, e.e. 96.7%; ^1H NMR (400 MHz, $CDCl_3$): δ 10.86 (br, s, 1H, COOH), 7.62, 7.05 (AB, 4H, $J=8.3$ Hz, Ar-H), 3.64 (q, 1H, $J=7.1$ Hz, CH), 1.48 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3084 (br, OH), 1713 (C=O) cm^{-1}; EIMS *m/z*: 277 (M+1$^+$, 10%), 276 (M^+, 75), 232 (12), 231 (M–$COOH^+$, 100).

3.3.27. (*R*)-(−)-2-(4′-Methylphenyl)propionamide 14b. White crystal, mp 94–95°C lit.:[19] 105–106°C; $[\alpha]_D^{14}=-46.3$ (*c* 1.6, $CHCl_3$) lit.:[19] >95% e.e. $[\alpha]_D=-49.7$ (*c* 1.14, $CHCl_3$), *R*, e.e. 98.9%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19, 7.15 (AB, 4H, $J=8.1$ Hz, Ar-H), 5.69 (br, s, 1H, NH), 5.30 (br, s, 1H, NH), 3.55 (q, 1H, $J=7.2$ Hz, CH), 2.33 (s, 3H, CH_3), 1.49 (d, 3H, $J=7.2$ Hz, CH_3). IR (KBr): 3355, 3179 (NH_2), 1659 (C=O) cm^{-1}; EIMS *m/z*: 164 (M+1$^+$, 5%), 163 (M^+, 12), 120 (28), 119 (M–$CONH_2^+$, 100).

3.3.28. (*S*)-(+)-2-(4′-Methylphenyl)propanoic acid 14c. White solid, mp 67–68°C lit.:[19] 48–49°C; $[\alpha]_D^{14}=+66.4$ (*c* 0.71, $CHCl_3$) lit.:[19] >95% e.e. $[\alpha]_D=+66.0$ (*c* 0.7, $CHCl_3$), *S*, e.e. 100%; ^1H NMR (400 MHz, $CDCl_3$): δ 11.35 (br s, 1H, OH), 7.16, 7.08 (AB, 4H, $J=7.9$ Hz,

Ar-H), 3.64 (q, 1H, $J=7$ Hz, CH), 2.23 (s, 3H, CH_3), 1.48 (d, 3H, $J=7.1$ Hz, CH_3); IR (KBr): 3100–2750 (br, OH), 1703 (C=O) cm^{-1}; EIMS m/z: 164 (M^+, 25%), 119 ($M-COOH^+$, 100).

3.3.29. (*R*)-(+)-2-(1′-Naphthyl)propionitrile (*R*)-(+)-15a. Colorless viscous oil, $[\alpha]_D^{15}=+48.8$ (*c* 1.25, $CHCl_3$), e.e. 80.3%; 168 h (25%) $[\alpha]_D^{15}=+59.6$ (*c* 0.8, $CHCl_3$), e.e. 98%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.89–7.84 (4H, Ar-H), 7.80–7.78 (1H, Ar-H), 7.68–7.66 (1H, Ar-H), 7.56–7.43 (m, 3H, Ar-H), 4.56 (q, 1H, $J=7.2$ Hz, CH), 1.75 (d, 3H, $J=7.2$ Hz, CH_3); IR (film): 2242 (CN); EIMS m/z: 182 ($M+1^+$, 10), 181 (M^+, 47), 166 ($M-CH_3^+$, 100).

3.3.30. (*S*)-(+)-2-(1′-Naphthyl)propionamide (*S*)-(+)-15b. White crystal, mp 136–138°C lit.:[20] 133–138°C; $[\alpha]_D^{18}=+66.3$ (*c* 1.2, Me_2CO/phH 1/1, v/v) e.e. 90.3%; $[\alpha]_D^{18}=+46.9$ (*c* 1.2, Me_2CO/phH 1/1, v/v) lit.:[20] $[\alpha]_D^{25}=-74.0$ (*c* 2.073, Me_2CO/phH 1/1, v/v), *R*, e.e. 63.2%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, 1H, $J=8.2$ Hz, Ar-H), 7.88–7.86 (m, 1H, Ar-H), 7.80 (d, 1H, $J=8$ Hz, Ar-H), 7.56–7.44 (m, 4H, Ar-H), 5.40 (br s, 1H, NH), 5.22 (br s, 1H, NH), 4.32 (q, 1H, $J=7.2$ Hz, CH), 1.70 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3384, 3197 (NH_2), 1656 (C=O) cm^{-1}; EIMS m/z: 200 ($M+1^+$, 13%), 199 (M^+, 37), 156 (33), 155 ($M-CONH_2^+$, 100).

3.3.31. (*R*)-(−)-2-(1′-Naphthyl)propionamide (*R*)-(−)-15b. $[\alpha]_D^{18}=-16.7$ (*c* 1.0, Me_2CO/phH 1/1, v/v) e.e. 63.2%,

3.3.32. (*S*)-(+)-2-(1′-Naphthyl)propanoic acid 15c. White solid, mp 64–66°C lit.:[20] 60°C; $\alpha_D^{18}=+133.6$ (*c* 0.5, $CHCl_3$), e.e. 93.2%; 168 h (16%) $\alpha_D^{18}=+$(c 0.5, $CHCl_3$) lit.:[15] 87% e.e., $\alpha_D^{25}=+125.7$ (*c* 0.35, $CHCl_3$), S, e.e. 47.7%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, 1H, $J=8.5$ Hz, Ar-H), 7.83 (d, 1H, $J=7.9$ Hz, Ar-H), 7.74 (d, 1H, $J=8.1$ Hz, Ar-H), 7.53–7.41 (m, 4H, Ar-H), 4.51 (q, 1H, $J=7.2$ Hz, CH), 1.67 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 2550–3070 (br, COOH), 1702 (C=O) cm^{-1}; EIMS m/z: 200 (M^+, 2%), 155 ($M-COOH^+$, 2), 123 (100), 105 (96).

3.3.33. (*R*)-(−)-2-(2′-Naphthyl)propionamide 16b. White crystal, mp 141–143°C lit.:[20] 135–142°C; $[\alpha]_D^{25}=-22.1$ (*c* 1.6, Me_2CO) lit.:[20] $[\alpha]_D^{25}=-31.10$ (*c* 1.045, Me_2CO), *R*, e.e. 69.3%; ^1H NMR (90 MHz, $CDCl_3$): δ 7.60–7.98 (m, 4H, Ar-H), 7.30–7.60 (m, 3H, Ar-H), 5.60 (br s, 2H, NH_2), 3.80 (q, 1H, $J=8$ Hz, CH), 1.60 (d, 3H, $J=8$ Hz, CH_3); IR (KBr): 3349, 3192 (NH_2), 1652 (C=O) cm^{-1}; EIMS m/z: 199 (M^+, 28%), 156 (25), 155 ($M-CONH_2^+$, 100).

3.3.34. (*S*)-(+)-2-(2′-Naphthyl)propanoic acid 16c. White solid, mp 140–142°C lit.:[20] 135–143°C; $[\alpha]_D^{26}=+65.0$ (*c* 0.65, EtOH) lit.:[20] $[\alpha]_D^{25}=+65.35$ (*c* 0.812, EtOH), *S*, e.e. 98%; ^1H NMR (90 MHz, $CDCl_3$): δ 11.09 (s, 1H, COOH), 7.54–7.91 (m, 4H, Ar-H), 7.07–7.54 (m, 3H, Ar-H), 3.85 (q, 1H, $J=8$ Hz, CH), 1.59 (d, 3H, $J=8$ Hz, CH_3); IR (KBr): 2800–3080 (br, COOH), 1698 (C=O) cm^{-1}; EIMS m/z: 200 (M^+, 44%), 155 ($M-COOH^+$, 100).

3.3.35. (*R*)–(−)-2-(6′-Methoxy-2′-naphthyl)propionamide 17b. White crystal, mp 174–176°C lit.:[21] 173–176°C; $[\alpha]_D^{25}=-16.3$ (*c* 1.2, $CHCl_3$) lit.:[21] $[\alpha]_D^{25}=+20$ (*c* 1, $CHCl_3$, S, e.e. 75%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.68 (m, 4H, Ar-H), 7.41–7.38 (m, 1H, Ar-H), 7.18–7.12 (m, 2H, Ar-H), 5.45 (br s, 1H, NH), 5.34 (br s, 1H, NH), 3.92 (s, 3H, OMe), 3.74 (q, 1H, $J=7.2$ Hz, CH), 1.60 (d, 3H, $J=7.2$ Hz, CH_3); IR (KBr): 3350, 3170 (NH_2), 1661 (C=O) cm^{-1}; EIMS m/z: 230 ($M+1^+$, 8%), 229 (M^+, 36), 186 (22), 185 ($M-CONH_2^+$, 100).

3.3.36. (*S*)-(+)-2-(6′-Methoxy-2′-naphthyl)propanoic acid 17c. White solid, mp 150–152°C lit.:[22] 155–157°C; $[\alpha]_D^{26}=+64.9$ (*c* 1.8, $CHCl_3$) lit.:[22] $[\alpha]_D^{25}=-67.2$ (*c* 1.096, $CHCl_3$, R, e.e. 99%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 3H, $J=8.7$ Hz, Ar-H), 7.41 (d, 1H, $J=8.8$ Hz, Ar-H), 7.14–7.10 (m, 2H, Ar-H), 4.02 (s, 3H, OMe), 3.87 (q, 1H, $J=7.1$ Hz, CH), 1.6 (d, 3H, $J=7.1$ Hz, CH_3); IR (KBr): 3196 (br, OH), 1729 (C=O) cm^{-1}; EIMS m/z: 230 (M^+, 48%), 185 (M^+-COOH, 100).

3.4. Esterification of 12c and the hydrolyzed product of 12b using tropine

3.4.1. (*R*)-(−)-Tropanyl 2-(4′-bromophenyl)propionate (*R*)-18. The amide **12b** (0.2 mmol) was dissolved in CH_2Cl_2 (1 mL) and 8N aq. HCl (2 mL) was added. The mixture was stirred for 8 h at 90°C. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate. The organic solutions, after washing (satd brine), drying ($MgSO_4$) and concentration, gave the acid (42 mg, 92%). The reaction of the (*R*)-acid sequentially with $SOCl_2$ and tropine[7a] gave (*R*)-**18**. Pale yellow oil, $[\alpha]_D^{17}=-16.5$ (*c* 1.3, EtOH) lit.:[7a] 90% e.e., $[\alpha]_D^{20}=-14.6$ (abs. EtOH), *R*, e.e. 98.3%; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45, 7.17 (AB, 4H, $J=8.4$ Hz, Ar-H), 4.96 (t, 1H, $J=5.3$ Hz, CHO), 3.61 (q, 1H, $J=7.2$ Hz, CH), 3.10 (t, 1H, $J=3.3$ Hz, CHN), 3.03 (t, 1H, $J=3.1$ Hz, CHN), 2.26 (s, 3H, NMe), 2.26–2.09 (m, 2H, CH_2), 1.86–1.62 (m, 4H, $2CH_2$), 1.48 (d, 3H, $J=7.2$ Hz, CH_3), 1.36–1.53 (m, 2H, CH_2). IR (film): 1729 (C=O) cm^{-1}; EIMS m/z: 353 (M^++2, 8%), 351 (M^+, 8), 185 (4), 183 (4), 124 (100).

3.4.2. (*S*)-(+)-Tropanyl 2-(4′-bromophenyl)propionate (*S*)-18. The reaction of (*S*)-2-(4′-bromophenyl)-propionate acid sequentially with $SOCl_2$ and tropine[7a] gave (*S*)-**18**. $[\alpha]_D^{17}=+15.3$ (*c* 1.1, EtOH) lit.:[7a] 94% e.e., $[\alpha]_D^{20}=+16.0$ (abs. EtOH), *S*, e.e. 96%,

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