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CAL-B-catalyzed resolution of some pharmacologically interesting β-substituted isopropylamines

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Abstract—Some pharmacologically active amines such as amphetamine, the isomeric *o*-, *m*- and *p*-methoxyamphetamines, 4-phenylbutan-2-amine and mexiletine, as well as their corresponding acetamides, have been prepared in high yields and with very high enantiomeric excesses. The method consists of the *Candida antarctica* lipase B (CAL-B)-mediated enantioselective acetylation of racemic amines using ethyl acetate as solvent and acyl donor. The enzyme follows Kazlauskas' rule with all amines, (*R*)-amides being obtained as the major enantiomer in all cases. From the conversion values measured for both enantiomers, it can be deduced that the size of the substituents attached to the stereocenter is responsible for the enantioselectivity and rate of some of these reactions.

1. Introduction

Optically active amines bearing the stereogenic center at the α-position are important compounds because of their broad range of applications and their pharmacological properties.[1] They have been used as chiral auxiliaries, resolving agents and building blocks for the preparation of natural and unnatural compounds. In most cases, the pharmacological activities of these amines are related to the configuration of the stereogenic center. Thus, (*S*)-amphetamine [1-phenylpropan-2-amine, **1** (Fig. 1)] has greater pharmacological activity as stimulant[2] and hyperthermic[3] agent than its (*R*)-enantiomer; (*R*)-*p*-methoxyamphetamine **4** is a constituent of (*R*,*R*)-formoterol, a potent bronchodilator;[4] and (*R*)-4-phenylbutan-2-amine **5** is a precursor of the antihypertensive dilevalol,[5] the active isomer of labetalol.[6] In addition, mexiletine [1-(2,6-dimethylphenoxy)propan-2-amine, **6**] is an antiarrhythmic agent, whose (*R*)-enantiomer is more potent for experimental arrhythmias[7] and in binding studies on cardiac sodium channels[8] than its (*S*)-counterpart.

In this regard, the development of methods to access enantiomerically enriched amines is of special interest. Resolution of some of these amines has been carried out by fractional crystallization or distillation of the diastereomeric salts,[9a,d] chromatographic separation of diastereomeric amides,[9b] or by microbial hydrolysis of an *N*-acyl derivative.[9c,e] We wish to report herein an

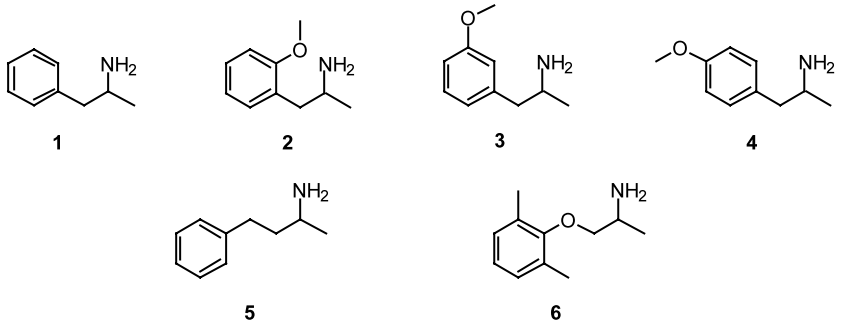

Figure 1.

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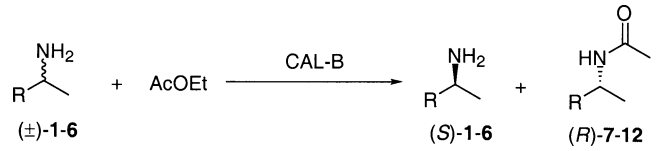
Table 1. CAL-B catalyzed enantioselective acylation of amines (±)-**1-6** with ethyl acetate



(±)-**1-6** (*S*)-**1-6** (*R*)-**7-12**

Amine	Amide	*t* (h)	*c*[a] (%)	Substrate [(*S*)-**1**–**6**]		Product [(*R*)-**7**–**12**]		*E*[c]	(*R*)-**7**–**12**[d] e.e. (%)
				Yield[b]	E.e. (%)	Yield[b]	E.e. (%)		
1	**7**	7	45	75	73	90	89	37	99
2	**8**	8	50	95	93	98	92	79	Enantiopure
3	**9**	11	52	88	96	97	89	70	98
4	**10**	22	55	97	99	99	82	52	98
5	**11**	4	51	76	90	99	86	41	99
6	**12**	21	52	81	99	94	92	123	Enantiopure

[a] Deduced from the e.e.s of the substrate (e.e.$_s$) and the product (e.e.$_p$): $c = \text{e.e.}_s/(\text{e.e.}_s+\text{e.e.}_p)$.
[b] Calculated taking into account the percentage of conversion *c*.
[c] Enantiomeric ratio calculated according to Sih et al.[12]
[d] After recrystallization (see text).

alternative method for the resolution of the pharmacologically interesting amines (shown in Fig. 1) by *Candida antarctica* lipase B (CAL-B)-catalyzed enantioselective acylation. This methodology has proved very useful in the resolution of racemic amines and in the aminolysis and ammonolysis of racemic esters.[10] From the results obtained in this kind of reaction, together with those obtained with the structurally analogous racemic secondary alcohols in transesterification processes, it can be deduced that α,α-disubstituted methylamines bearing a medium-sized substituent (a methyl group) and a large-sized one (as those of the amines of the present study) could be adequate substrates for CAL-B. Moreover, with this study we hope to widen the knowledge of the structural requirements of this lipase in aminolysis processes.

2. Results and discussion

Racemic amines **1**–**5** were obtained by reductive amination of the corresponding ketone using ammonium formate and 10% Pd–C as catalyst. Racemic mexiletine **6** is commercially available as its hydrochloride.

2.1. Enzymatic resolution of (±)-1–6

The resolution of the racemic amines (±)-**1**–**6** was carried out by CAL-B (Novozym 435) catalyzed enantioselective acylation, using the most simple reaction conditions, that is, employing ethyl acetate as the acyl donor and solvent.[11] Under these conditions the enzyme catalyzed acylation of the (*R*)-enantiomer of the amine preferentially, the resulting (*R*)-acetamides **7**–**12** and the remaining (*S*)-amines being easily separated by selective extraction. The results are collected in Table 1. All yields, calculated taking into account the percentage of conversion (*c*), were very high, especially those of the amides. With respect to the enantioselectivity, the *E* values vary with the structure, but they go from moderate to high, thus allowing substrates to be obtained with very high e.e. for conversions near to 50%. Since in most cases the conversions are higher than 50%, the amides were obtained with moderate to high e.e. Nevertheless, these enantiomeric excess values could be improved significantly after recrystallization from hexane/chloroform. Thus, as shown in the last column of Table 1, amides were finally obtained with e.e. >98%.

2.2. Influence of the substituents on the enantioselectivity and the reaction rate

The stereochemical preference of CAL-B with amines **1**–**6** is similar to that seen with racemic secondary alcohols, the enzyme following in all cases Kazlauskas' rule.[13] As a consequence of this rule and of some molecular modeling studies, an empirical model has been established for the active site of this enzyme.[14] The model is usually represented by means of two pockets of different size, the smallest one (the stereoselectivity pocket) being of limited size. Fig. 2a represents the binding mode of the substituents of the (*R*)-amines **1**–**6**: the large substituent (L), which bears an aromatic ring, in the large pocket, and the medium one (M, always a methyl group) in the small pocket, thus suitably orienting the nucleophilic amino group towards the internal upper region of the model, where it coordinates with

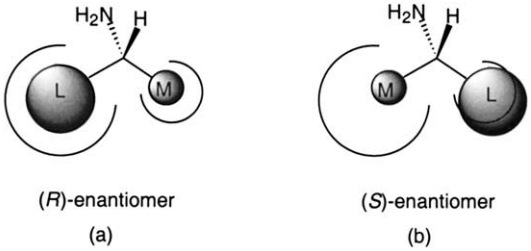


Figure 2. Active site model for CAL-B. Representation of binding modes of (*R*)-amines (a) and (*S*)-amines (b).

Table 2. Relative reactivities of (*R*)- and (*S*)-**1**–**6** and **13** in the CAL-B catalyzed aminolyses[a]

Entry	R	Substrate (e.e.$_s$, %)	Product (e.e.$_p$, %)	c[b]	c_R[c]	c_S[c]	E[d]
1	Bn	**1** (73)	**7** (89)	45	85	5.1	37
2	*o*-MeOBn	**2** (87)	**8** (93)	48	93	3.3	79
3	*m*-MeOBn	**3** (87)	**9** (92)	49	94	4.0	68
4	*p*-MeOBn	**4** (84)	**10** (91)	48	92	4.2	59
5	$Ph(CH_2)_2$	**5** (98)	**11** (78)	56	99	12.2	36
6	2,6-$Me_2C_6H_3OCH_2$	**6** (74)	**12** (96)	44	86	1.8	109
7	Ph	**13** (65)	**14** (97)	40	79	1.2	128

[a] Reaction time, 7 h.
[b] (%) Deduced from the e.e.s of the substrate (e.e.$_s$) and the product (e.e.$_p$): $c = e.e._s/(e.e._s + ee_p)$.
[c] (%) Determined from c and e.e.$_p$: $c_R = c\ (1+e.e._p)$; $c_S = c\ (1-e.e._p)$, where the subscripts R and S represent here the fast- and the slow-reacting enantiomers, respectively.
[d] Enantiomeric ratio calculated according to Sih et al.[12]

the carbonyl group of an acetylated serine residue. Fig. 2b represents the binding mode of the (*S*)-amines **1**–**6** with their amino group correctly oriented.

Let us now consider with some detail the validity of this model for the reactions described herein. Being aminolysis reactions, they are irreversibly catalyzed by CAL-B, in such a way that, for equal reaction times, each conversion value (c) is indicative of the reaction rate. Thus, we will next use the conversion values (overall, c; for the fast-reacting (*R*)-enantiomer, c_R; for the slow-reacting (*S*)-enantiomer, c_S) obtained after a reaction time of 7 h. These results are summarized in Table 2. As it can be expected, only small differences in the E values are observed when compared with those contained in Table 1. The results obtained with (±)-1-phenylethanamine **13** are also included in Table 2 for comparison purposes.

The reaction rates for the isomeric methoxyamphetamines (Table 2, entries 2–4) are very similar, as deduced from their virtually identical conversion values. In addition, the position of the methoxy group in the aromatic ring has some influence on the enantioselectivity; substitution at the *ortho* position seems to be most favorable to reaction, in contrast with that observed for other lipases.[15] As can be reasoned from the c_R and c_S values obtained for these amines, all of the methoxybenzyl groups are similarly accommodated in both pockets.

Amphetamine (entry 1) shows a lower E value than those of its methoxy analogous, which is due to the fact that (*R*)-methoxyamphetamines react faster than (*R*)-amphetamine and that (*S*)-amphetamine is transformed more quickly than (*S*)-methoxyamphetamines. In the same way, the higher E value for mexiletine (entry 6) is mainly a consequence of the slower reactivity of its (*S*)-enantiomer. These results can be explained to a large extent on the basis of the size of the substituents attached to the stereocenter and the size of the small pocket. Thus, the benzyl group present in amphetamine is smaller than a methoxybenzyl group and, consequently, is better accommodated in the small pocket. On the contrary, when the L-substituent of the mexiletine **6** has to occupy this pocket, more significant steric repulsions take place. This is clearly reflected in the low c_S value for this amine (entry 6).

However, the traditional model partially fails when applied to the comparison between (±)-1-phenylethanamine (**13**, entry 7), amphetamine (entry 1) and 4-phenylbutan-2-amine (entry 5). The corresponding c_R values decrease consistently in the series **5**>**1**>**13**, i.e. according to the rule that the larger the L-substituent is ($PhCH_2CH_2$>$PhCH_2$>Ph), the better the steric interaction with the large pocket. Nevertheless, the c_S values for these amines vary in opposite sense to that expected. Taking into account the electronic similarity of these substituents, the observed differences can neither be attribute to electronic effects. We think that the distinct ability of the mentioned groups to adopt different conformations in the active site of the CAL-B could play a key role in the rate of transformation of the (*S*) enantiomer. Thus, the phenylethyl group is the substituent with more conformational mobility and so, (*S*)-4-phenylbutan-2-amine (**5**) could have more facility that amines **1** and **13** to adopt an appropriate conformation to be accommodated in the active site of the enzyme. Probably, a new binding mode of the (*S*)-enantiomer could be considered for this kind of substrate.

2.3. Determination of the enantiomeric excesses and assignment of the absolute configuration

The enantiomeric excesses of amides (*R*)-**7**-**12** and **14** were determined by chiral HPLC (see Section 4.4 for the conditions of the analyses). The e.e.s of the (*S*)-amines **1**–**6** and **13** were determined after their transformation in the corresponding acetamide derivatives (acetyl chloride, DMAP, dichloromethane), and further analysis by chiral HPLC.

The (*S*)-configuration for the remaining amine **6**, isolated from the enzymatic reaction, as well as the (*R*)-configuration for the amide **11**, were assigned by comparison of the sign of their specific rotations with the published data (see Sections 4.3.6 and 4.3.11, respectively). In order to assign the (*S*)-configuration for the remaining amines **1** and **4**, they were transformed into the corresponding hydrochloride salts, and their specific rotation values compared with the literature data (see Sections 4.3.1 and 4.3.4).

The (*S*)-configurations of the remaining *o*-methoxy and *m*-methoxyamphetamine [(*S*)-**2** and (*S*)-**3**, respectively] were determined by application of the modified Mosher's method.[16] For the MTPA amides, the working model has been established to be analogous to that usual for esters of secondary alcohols.[16a] The conformations of both diastereomeric pairs of (*R*)-MTPA amides *l*-, *u*-**15**, and *l*-, *u*-**16**, derived from (±)-**2** and (±)-**3**, respectively, are represented in Table 3. Moreover, the δ values (^{1}H NMR) for some groups of the amine moiety, that is, the α-methyl (Me-1) and methoxy (MeO-2) groups, and the corresponding $\Delta\delta$ (*l*–*u*) values, are also collected. In both cases, the differential shielding obtained for the above mentioned groups are in good agreement with the previous findings.[9b,16b] In addition, the presence of the aromatic ring in the amine moiety shields, in both cases, the methoxy group of the acid moiety (MeO-3) in the *l*-diastereomers, but not in the *u*-diastereomers. This shielding effect also corroborates the (*S*)-configuration assigned to the remaining amines **2** and **3**. Thus, chemical shifts obtained for the (*R*)-MTPA amides derived from the remaining amines isolated in the enzymatic reactions are identical to those of the *u*-diastereomer.

3. Conclusion

We have demonstrated the utility of the CAL-B catalyzed enantioselective acylation of racemic amines in the resolution of some pharmacologically interesting β-substituted isopropylamines. The enantioselectivities—moderate to high—of these processes allowed the isolation of the remaining amines in very high yields and enantiomeric excesses. In all cases, amides were obtained with >98% e.e. after a simple recrystallization of the enzymatic product. In addition, we have shown that the enantioselectivity and reaction rates observed for some of these amines can be explained on the basis of the active site model proposed for CAL-B. However, some limitations to the model have also been found.

4. Experimental

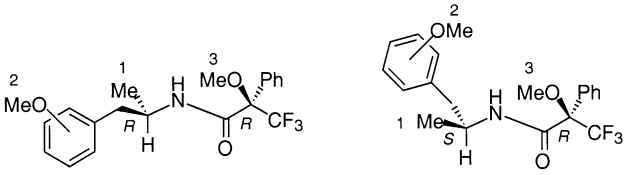
4.1. General

Lipase B from *C. antarctica*, Novozym 435, was a gift from Novo Nordisk Co. and was employed without any further treatment. Solvents were of spectrophotometric grade and they were stored with 4 Å molecular sieves under nitrogen prior to use. (±)-Mexiletine was purchased as its chlorohydrate from Aldrich. The other racemic amines were obtained by reductive amination of the corresponding ketone (vide infra). ^{1}H and ^{13}C NMR spectra were obtained with a Bruker DPX 300 (^{1}H 300 MHz and ^{13}C 75.5 MHz) and with a Bruker AC-200 (^{1}H 200 MHz and ^{13}C 50.3 MHz) spectrometers, using $CDCl_3$ as solvent.

4.2. Synthesis of racemic amines (±)-1–5. General procedure

A slight modification of a reported method[17] was adopted for the synthesis of these compounds. To a solution of the ketone (20 mmol) in deoxygenated methanol (52 mL), water (6 mL) and ammonium formate (0.21 mol) were added. After complete dissolution, 10% Pd–C (0.80 g, 0.75 mmol) was added and the mixture stirred at room temperature until disappearance of the ketone (TLC control, ethyl acetate: methanol, 4:1). Then, the catalyst was filtered on Celite®, washed with methanol and the solvents were evaporated. The residue was treated with conc. aq. HCl (4 mL) and water (30 mL) and extracted with diethyl ether (2×20 mL). Aqueous phase was treated with solid NaOH until pH basic, and extracted with diethyl ether (3×25 mL). Evaporation of the organic phase yielded the corresponding amine. A second fraction of amine was obtained by continuous extraction of the basic aqueous phase (dichloromethane, 14 h). Crude amine was purified by distillation under reduced pressure. Distillation temperatures (0.5 Torr) and yields of the amine are as follows: **1** (45°C, 80%), **2** (68°C, 75%), **3** (72°C, 72%), **4** (60°C, 79%) and **5** (50°C, 74%).

Table 3. (*R*)-MTPA amides **15** (*o*-MeO) and **16** (*m*-MeO) derived from (±)-**2** and (±)-**3**. Chemical shifts (δ, ppm) of some selected signals (^{1}H NMR, 300 MHz)



		(*R*)-MTPA amides *l*-**15** and *l*-**16**, δ (ppm)			(*R*)-MTPA amides *u*-**15** and *u*-**16**, δ (ppm)			$\Delta\delta$ (*l*−*u*) (ppm)		
Amine	Amide	Me-1	MeO-2	MeO-3	Me-1	MeO-2	MeO-3	Me-1	MeO-2	MeO-3
(±)-**2**	**15**	1.20	3.80	3.20	1.28	3.69	3.32	−0.08	+0.11	+0.12
(±)-**3**	**16**	1.18	3.81	3.27	1.25	3.75	3.32	−0.07	+0.06	+0.05

4.3. Typical procedure for the enzymatic acetylation of amines (±)-1–6

To a mixture of racemic amine (3.0 mmol) and CAL-B (300 mg) under a nitrogen atmosphere, was added ethyl acetate (15 mL). The resulting mixture was shaken at 28°C and 200 rpm for the time shown in Table 1. The enzyme was filtered, washed with ethyl acetate and the solvent was evaporated under reduced pressure. The residue was treated with 3N aq. H_2SO_4 (20 mL) and extracted with dichloromethane (3×15 mL). Aqueous phase was treated with solid NaOH until pH basic, and extracted with dichloromethane (4×20 mL). Evaporation of both organic phases yielded the pure amide (as a white solid) and the amine, respectively. In order to avoid the oxidation of the amines, they were stored under nitrogen atmosphere or transformed into the corresponding hydrochloride (by addition of conc. aq. HCl, ethanol and evaporation to dryness).

4.3.1. (*S*)-1-Phenylpropan-2-amine, 1. $[\alpha]_D^{20}$ +31.0 (*c* 0.95, $CHCl_3$) 73% e.e. ^{1}H NMR (200 MHz) δ 7.40–7.15 (m, 5H), 3.17 (m, 1H), 2.73 (dd, 1H, $J=5.5$ and 13.3 Hz), 2.52 (dd, 1H, $J=7.8$ and 13.3 Hz), 1.19 (s, 2H, NH_2), 1.13 (d, 3H, $J=6.3$ Hz) ppm. ^{13}C NMR (75.5 MHz) δ 139.4 (C), 128.9 (CH), 128.1 (CH), 125.9 (CH), 48.2 (CH), 46.4 (CH_2), 23.3 (CH_3) ppm. MS (ESI$^+$) *m*/*z* (rel. intensity): 136 [(M+H), 100], 119 (20). Hydrochloride salt of (*S*)-**1**: $[\alpha]_D^{20}$ +23.7 (*c* 0.34, H_2O) 84% e.e. Lit.[18] for (*R*)-(−)-**1**×HCl: $[\alpha]_D^{25}$ −27.2 (*c* 2, H_2O) 100% e.e.

4.3.2. (*S*)-1-(*o*-Methoxyphenyl)propan-2-amine, 2. $[\alpha]_D^{20}$ +31.8 (*c* 1.00, $CHCl_3$) 93% e.e. ^{1}H NMR (200 MHz) δ 7.30–7.10 (m, 2H), 6.95–6.80 (m, 2H), 3.82 (s, 3H), 3.20 (m, 1H), 2.75 (dd, 1H, $J=5.5$ and 12.9 Hz), 2.54 (dd, 1H, $J=8.0$ and 12.9 Hz), 1.29 (s, 2H, NH_2), 1.11 (d, 3H, $J=6.7$ Hz) ppm. ^{13}C NMR (75.5 MHz) δ 157.4 (C), 130.8 (CH), 127.8 (C), 127.2 (CH), 120.0 (CH), 110.0 (CH), 54.9 (CH_3), 46.8 (CH), 40.9 (CH_2), 23.3 (CH_3) ppm. MS (ESI$^+$) *m*/*z* (rel. intensity): 166 [(M+H), 100], 149 (18).

4.3.3. (*S*)-1-(*m*-Methoxyphenyl)propan-2-amine, 3. $[\alpha]_D^{20}$ +33.5 (*c* 1.00, $CHCl_3$) 96% e.e. ^{1}H NMR (200 MHz) δ 7.25–7.12 (m, 1H), 6.80–6.68 (m, 3H), 3.76 (s, 3H), 3.15 (m, 1H), 2.67 (dd, 1H, $J=5.3$ and 13.3 Hz), 2.45 (dd, 1H, $J=8.2$ and 13.3 Hz), 1.19 (s, 2H, NH_2), 1.09 (d, 3H, $J=6.3$ Hz) ppm. ^{13}C NMR (75.5 MHz) δ 159.2 (C), 140.9 (C), 128.8 (CH), 121.1 (CH), 114.4 (CH), 111.0 (CH), 54.5 (CH_3), 47.9 (CH), 46.3 (CH_2), 23.1 (CH_3) ppm. MS (ESI$^+$) *m*/*z* (rel. intensity): 166 [(M+H), 100], 149 (18).

4.3.4. (*S*)-1-(*p*-Methoxyphenyl)propan-2-amine, 4. $[\alpha]_D^{20}$ +35.2 (*c* 0.95, $CHCl_3$) 99% e.e. ^{1}H and ^{13}C NMR data were in agreement with the literature.[11] MS (ESI$^+$) *m*/*z* (rel. intensity): 166 [(M+H), 100], 149 (48). Hydrochloride salt of (*S*)-**4**: $[\alpha]_D^{20}$ +22.6 (*c* 2.00, H_2O) 99% e.e. Lit.[18] for (*R*)-(−)-**4**×HCl: $[\alpha]_D^{25}$ −22.5 (*c* 2, H_2O) 100% e.e.

4.3.5. (*S*)-4-Phenylbutan-2-amine, 5. $[\alpha]_D^{20}$ +6.4 (*c* 0.47, $CHCl_3$) 98% e.e. ^{1}H NMR (200 MHz) δ 7.48–7.12 (m, 5H), 2.93 (sext, 1H, $J=6.6$ Hz), 2.81–2.54 (m, 2H), 1.78–1.57 (m, 2H), 1.35 (s, 2H, NH_2), 1.09 (d, 3H, $J=6.6$ Hz) ppm. ^{13}C NMR (75.5 MHz) δ 142.0 (C), 128.0 (CH), 125.4 (CH), 46.1 (CH), 41.5 (CH_2), 32.5 (CH_2), 23.7 (CH_3) ppm. MS (ESI$^+$) *m*/*z* (rel. intensity): 150 [(M+H), 100].

4.3.6. (*S*)-1-(2,6-Dimethylphenoxy)propan-2-amine, 6. $[\alpha]_D^{20}$ +3.0 (*c* 1.05, $CHCl_3$) 99% e.e. Lit.[19] for (*R*)-(−)-**6**: $[\alpha]_D^{20}$ −2.7 (*c* 4.7, $CHCl_3$) 96% e.e. ^{1}H NMR data were in agreement with the literature.[9a] ^{13}C NMR (75.5 MHz) δ 155.2 (C), 130.4 (C), 128.6 (CH), 123.5 (CH), 77.9 (CH_2), 47.0 (CH), 19.5 (CH_3), 16.0 (CH_3) ppm. MS (ESI$^+$) *m*/*z* (rel. intensity): 202 [(M+Na), 20], 180 [(M+H), 100].

4.3.7. (*R*)-*N*-(1-Phenylpropan-2-yl)ethanamide, 7. $[\alpha]_D^{20}$ +37.6 (*c* 1.00, $CHCl_3$), 89% e.e. Recrystallized from hexane-chloroform: mp 123–125°C, $[\alpha]_D^{20}$ +44.0 (*c* 0.80, $CHCl_3$), 99% e.e. IR (KBr) *v* 3248 and 1637 cm^{-1}. ^{1}H NMR (200 MHz) δ 7.40–7.12 (m, 5H), 5.48 (bs, 1H, NH), 4.27 (m, 1H), 2.92–2.65 (m, 2H), 1.95 (s, 3H), 1.12 (d, 3H, $J=6.6$ Hz) ppm. ^{13}C NMR (75.5 MHz) δ 169.3 (C=O), 137.8 (C), 129.2 (CH), 128.2 (CH), 126.2 (CH), 46.0 (CH), 42.2 (CH_2), 23.3 (CH_3), 19.8 (CH_3) ppm. MS (ESI$^+$) *m*/*z* (rel. intensity) 216 [(M+K), 23], 200 [(M+Na), 100], 178 [(M+H), 15].

4.3.8. (*R*)-*N*-[1-(*o*-Methoxyphenyl)propan-2-yl]ethanamide, 8. Recrystallized from hexane–chloroform: mp 101–102°C, $[\alpha]_D^{20}$ +29.8 (*c* 1.05, $CHCl_3$) enantiopure. IR (KBr) *v* 3310 and 1634 cm^{-1}. ^{1}H and ^{13}C NMR data were in agreement with those published for the racemic sample.[20] MS (ESI$^+$) *m*/*z* (rel. intensity) 246 [(M+K), 10], 230 [(M+Na), 100], 208 [(M+H), 15], 166 (53).

4.3.9. (*R*)-*N*-[1-(*m*-Methoxyphenyl)propan-2-yl]ethanamide, 9. $[\alpha]_D^{20}$ +34.0 (*c* 1.00, $CHCl_3$) 89% e.e. Recrystallized from hexane-chloroform: mp 83–85°C. $[\alpha]_D^{20}$ +37.6 (*c* 1.00, $CHCl_3$) 98% e.e. IR (KBr) *v* 3317 and 1637 cm^{-1}. ^{1}H and ^{13}C NMR data were in agreement with those published for the racemic sample.[20] MS (ESI$^+$) *m*/*z* (rel. intensity) 246 [(M+K), 33], 230 [(M+Na), 100], 208 [(M+H), 16].

4.3.10. (*R*)-*N*-[1-(*p*-Methoxyphenyl)propan-2-yl]ethanamide, 10. $[\alpha]_D^{20}$ +36.2 (*c* 0.95, $CHCl_3$) 82% e.e. Recrystallized from hexane–chloroform: mp 94–96°C, $[\alpha]_D^{20}$ +41.9 (*c* 1.00, $CHCl_3$) 98% e.e. IR, ^{1}H and ^{13}C NMR data were in agreement with the literature.[11] MS (ESI$^+$) *m*/*z* (rel. intensity) 246 [(M+K), 29], 230 [(M+Na), 100], 208 [(M+H), 7], 166 (32).

4.3.11. (*R*)-*N*-(4-Phenylbutan-2-yl)ethanamide, 11. $[\alpha]_D^{20}$ +33.6 (*c* 1.00, EtOH) 86% e.e. Lit.[21] for (*S*)-(−)-**11**: $[\alpha]_D^{22}$ −31.5 (*c* 1.24, EtOH) 86% e.e. Recrystallized from hexane–chloroform: mp 74–75°C. $[\alpha]_D^{20}$ +37.5 (*c* 1.00, EtOH) 99%. IR (neat) *v* 3281 and 1645 cm^{-1}. ^{1}H NMR (200 MHz) δ 7.38–7.12 (m, 5H), 5.55 (bs, 1H, NH), 4.05 (m, 1H), 2.66 (m, 2H), 1.95 (s, 3H), 1.87–1.67 (m,

2H), 1.18 (d, 3H, $J=6.6$ Hz) ppm. ^{13}C NMR (75.5 MHz) δ 169.4 (C=O), 141.4 (C), 127.93 (CH), 127.87 (CH), 125.4 (CH), 44.6 (CH), 38.0 (CH_2), 32.1 (CH_2), 22.8 (CH_3), 20.5 (CH_3) ppm. MS (ESI$^+$) m/z (rel. intensity) 230 [(M+K), 20], 214 [(M+Na), 100], 192 [(M+H), 5].

4.3.12. (*R*)-*N*-[1-(2,6-Dimethylphenoxy)propan-2-yl]-ethanamide, 12. $[\alpha]_D^{20}$ +35.7 (*c* 1.05, $CHCl_3$) 92% e.e. Recrystallized from hexane–chloroform: mp 101–102°C. $[\alpha]_D^{20}$ +48.1 (*c* 1.05, $CHCl_3$) enantiopure. IR (KBr) ν 3289 and 1649 cm^{-1}. ^{1}H NMR data were in agreement with the literature.[19] ^{13}C NMR (75.5 MHz) δ 169.4 (C=O), 154.7 (C), 130.5 (C), 128.8 (CH), 123.9 (CH), 73.7 (CH_2), 45.2 (CH), 23.2 (CH_3), 17.5 (CH_3), 15.9 (CH_3) ppm. MS (ESI$^+$) m/z (rel. intensity) 260 [(M+K), 13], 244 [(M+Na), 100], 222 [(M+H), 11], 180 (52).

4.4. Chiral HPLC conditions for amides (±)-7–12 and (±)-14

Amide (±)-**7**: Chiralcel OD column (20°C), hexane: propan-2-ol, 96:4, 0.8 mL/min, t_R 22.18 (*S*) and 25.84 (*R*) min, $R_S=2.1$. Amide (±)-**8**: Chiralcel OD column (20°C), hexane: propan-2-ol, 94:6, 0.8 mL/min, t_R 23.52 (*R*) and 26.76 (*S*) min, $R_S=1.6$. Amide (±)-**9**: Chiralcel OD column (20°C), hexane: propan-2-ol, 95:5, 0.8 mL/min, t_R 21.42 (*S*) and 26.14 (*R*) min, $R_S=2.4$. Amide (±)-**10**: Chiralcel OB-H column (20°C), hexane:propan-2-ol, 92:8, 0.8 mL/min, t_R 21.19 (*S*) and 28.21 (*R*) min, $R_S=3.8$. Amide (±)-**11**: Chiralcel OD–H column (20°C), hexane: propan-2-ol, 96:4, 0.5 mL/min, t_R 50.12 (*R*) and 63.51 (*S*) min, $R_S=2.4$. Amide (±)-**12**: Chiralcel OD column (20°C), hexane: propan-2-ol, 90:10, 0.8 mL/min, t_R 8.82 (*R*) and 17.87 (*S*) min, $R_S=5.8$. Amide (±)-**14**: Chiralcel OB-H column (20°C), hexane: propan-2-ol, 85:15, 0.5 mL/min, t_R 7.23 (*S*) and 9.76 (*R*) min, $R_S=1.5$.

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