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Multicomponent diversity and enzymatic enantioselectivity as a route towards both enantiomers of α-amino acids—a model study

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Abstract—A model study on a new, enantioconvergent method for the synthesis of chiral, nonracemic α-amino acids is presented. α-Acetoxyamides obtained in a Passerini multicomponent reaction are selectively hydrolyzed by *Wheat Germ* lipase. Studies on conversion of the thus obtained, enantiomerically enriched α-hydroxyamides into α-aminoamides are presented. Products of these reactions are then hydrolyzed to give α-amino acids.

1. Introduction

Synthesis of enantiomerically enriched α-amino acids has drawn interest since the beginning of asymmetric synthesis, resulting in the development of many widely used protocols.[1] Today the stereocontrolled synthesis of these compounds is also a matter of crucial importance, due to their wide applicability in medicine,[2] asymmetric catalysis[3] and bioanalysis.[4]

Enzymatic asymmetric catalysis is also widely used for the preparation of α-amino acids.[5] Such syntheses are usually easier and cheaper than their chemical analogues[6] and more readily fulfill the requirements of green chemistry.[7]

The goal of this study was to establish a new chemoenzymatic method for the preparation of enantiomerically enriched α-amino acids. Such a method should possess certain features, which include: a possibility of convenient introduction of diverse modifications (in order to adjust the synthetic method towards the synthesis of various structures); easy accessibility of the substrate and finally high enantioselectivity of the enzymatic step. Other features include a high yield and a low amount of racemisation in synthetic transformations. Generation of both enantiomers of desired product, which is a key feature in bioactivity screening studies, is also necessary.

Our general synthetic concept is presented in Figure 1. In order to fulfill the first of the above mentioned requirements, we have decided to employ the Passerini multicomponent reaction as a first step, leading to substrate **D** for enzymatic hydrolysis. This enables us to use the easily accessible aldehydes **A** as starting materials. It also allows convenient introduction of diverse R′ and R″ moieties (from isocyanide **B** and carboxylic acid **C**), which determine the enantioselectivity of enzymatic hydrolysis and success of further transformations. A large number of possible structures for **B** and **C** allows the adjustment of the synthetic method to the synthesis of various α-amino acids **F**. In case of a need for a single enantiomer of the product, a simple protocol for the transformation of alcohols **E** into esters **D** with inversion of the configuration inversion is also established.

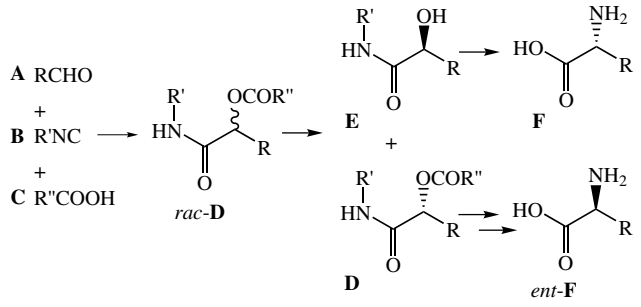

Figure 1. General synthetic concept.

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2. Results and discussion

Phenylalanine was chosen as a target compound for the model study (Scheme 1). Our first goal was to examine the possibility of enantioselective, enzymatic hydrolysis of the racemic precursor of the target compound.

Compound *rac*-**4** was obtained in a Passerini reaction between phenylacetic aldehyde **1**, *p*-methoxybenzyl isocyanide **2** and acetic acid **3**. Initially, a group of lipases was tested. The group consisted of *Wheat Germ* lipase, Novozym 435A, Porcine Pancrease lipase, *Candida rugosa* lipase, Amano AK Lipase, *Rhizopus niveus* lipase, *Candida lypholytica* lipase, *Pseudomonas cepacia* lipase and Pig Liver esterase. Of the enzymes tested, only *Wheat Germ* lipase performed the hydrolysis. Our previous study has shown that the stereochemical outcome of these reactions depends strongly on the co-solvent used. The results of the optimization study are shown in Table 1.

The enzyme has shown the highest enantioselectivity (55, as counted from the conversion-independent equation) when ethyl ether (Table 1, entry 4) was used as a co-solvent. Finally, this method was used in our model study.

In order to assign the configuration of the products of enzymatic hydrolysis, compounds (*S*)-**4** and (*S*)-**5** were synthesized from commercially available, enantiomerically pure phenylalanine, using procedures well described in synthetic literature.[8,9]

It should be emphasized that enzymatic kinetic resolution yields both enantiomers of desired product in yields lower than 50%. This is advantageous, when both enantiomers are required, but in case of demand for a single enantiomer, a method for more effective synthesis had to be established.

This goal was achieved by a transformation of one of the products of enzymatic hydrolysis into another (Scheme 1, syntheses c and d). Namely, (*R*)-**5** was prepared in an enantioconvergent way both from (*R*)-**4** by basic hydrolysis (99% yield) and from (*S*)-**5** by an effective (93% overall yield) sequence of simple synthetic steps. Inversion of configuration was obtained in an S_N2 reaction of *p*-toluenesulfonyl ester of alcohol **5** with caesium acetate. Other sulphonyl esters (i.e., mesylate and triflate) were also investigated, but gave poorer yields or led to racemisation of the product.

Table 1. Enzymatic hydrolysis optimization study

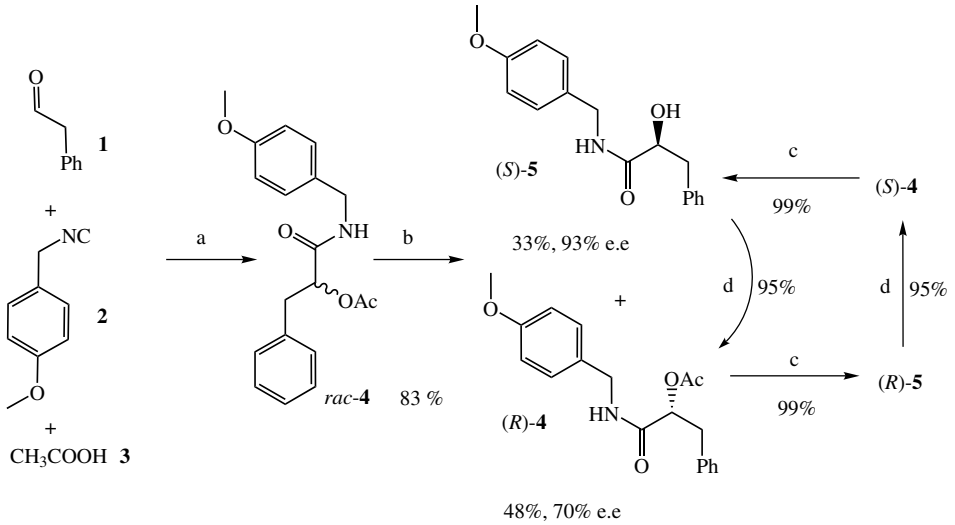
No	Co-solvent[a]	Time	Product	Yield/%	ee[b]/%	*E*
1	*c*-Hex	30 d	(*S*)-**5**	22	28.0	2
			(*R*)-**4**	74	3.0	
2	*i*-Pr_2O	48 h	(*S*)-**5**	33	54.4	6
			(*R*)-**4**	40	58.7	
3	TBME	30 h	(*S*)-**5**	42	87.8	35
			(*R*)-**4**	44	76.5	
4	Et_2O	48 h	(*S*)-**5**	33	92.7	55
			(*R*)-**4**	49	69.8	

[a]Abbreviations used: TBME—*tert*-butyl-methyl-ether, *c*-Hex—cyclohexane.
[b] Determined by HPLC with Daicel Chiracel OD-H column.

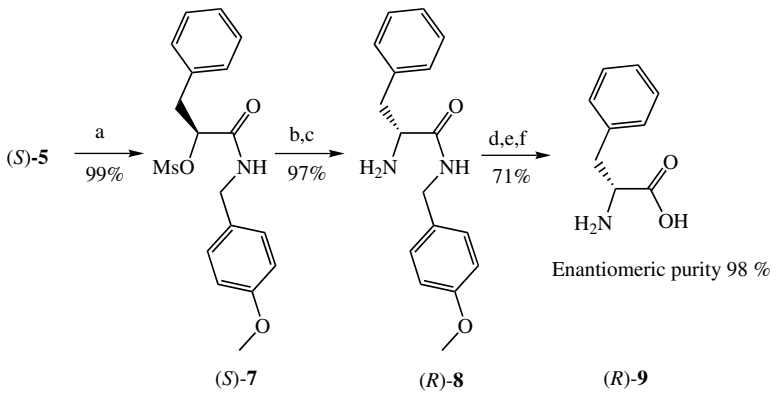
The same enantioconvergent procedure (Scheme 1) leads to the preparation of (*S*)-**5** in a satisfying yield.

To complete the model study of α-amino acid preparation, it was necessary to establish a convenient method of transformation of alcohol (*S*)-**5** into target compound [(*R*)-**8**, Scheme 2]. In the model study, compound (*S*)-**5** was transformed into methanesulfonic acid ester (*R*)-**7**. S_N2 reaction of this ester with sodium azide in the presence of DABCO, DMAP and crown ether afforded an azide, which was conveniently reduced with hydrogen and a palladium catalyst to give compound (*R*)-**8**. The yield of these steps was almost quantitative (96% over three steps).

Acidic hydrolysis of (*R*)-**8** afforded α-amino acid (*R*)-**9**. Conventional methods of purification (crystallization,



Scheme 1. Synthesis of alcohol **5**. Reagents and conditions: (a) DCM, 20 °C, 48 h; (b) lipase from *Wheat Germ*, phosphate buffer 7.0/Et_2O (8:2), 20 °C, 48 h; (c) NaOH, methanol/water, ultrasound; (d) (1) TosCl, Et_3N, DCM, 20 min; (2) CsOAc, crown ether, DMF, 66 h.



Scheme 2. Synthesis of amino acid **9**. Reagents and conditions: (a) MsCl, Et_3N, DMAP, DCM, 20 °C, 30 min; (b) NaN_3, DABCO, DMAP, benzo-15-crown-5, 40 °C, 24 h; (c) H_2, Pd/C, methanol, 4 h; (d) 6 M HCl, reflux, 20 h; (e) CbzCl, 4 N NaOH, 1 N $NaHCO_3$; (f) H_2, Pd/C, methanol.

ion-exchange chromatography) did not yield analytically pure compounds, therefore, the purification of material obtained was performed by in situ introduction of benzyloxycarbonyl (Cbz) moiety, extraction of the protected compound and reductive cleavage of the protecting group. The enantiomeric purity of thus obtained target compound was 98%.

3. Conclusion

A model study on a new, chemoenzymatic procedure for the preparation of both enantiomers of uncoded α-amino acids is presented. Starting aldehyde (Fig. 1, **A**) was transformed into α-acetoxyamide (*rac*-**D**), which was hydrolyzed by *Wheat Germ* lipase into enantiomerically enriched alcohol (**E**). An enantioconvergent approach enables a synthesis of both enantiomers of alcohol **E** in a high yield. A method for the transformation of alcohol (**E**) into target α-amino acid (**F**) was also established. Depending on the synthetic path chosen, preparation of either **F** or ***ent*-F** is possible.

4. Experimental

Optical rotations were measured with a JASCO DIP-360 polarimeter. NMR spectra were measured with Varian 200 GEMINI and Varian 400 GEMINI spectrometer. TLCs were performed with silica gel 60 (230–400 mesh, Merck) and silica gel 60 PF254 (Merck), respectively. HPLC experiments were carried out on DAICEL CHIRACEL OD-H column with a pre-column, eluent: hexane/*iso*-propanol 9:1 (v/v), flow: 1 ml/min. CHN analysis was performed on Perkin–Elmer 240 Elemental Analyzer and CHNS analysis on Heraeus Vario EL III apparatus.

4.1. Acetic acid *rac*-1-(4-methoxy-benzylcarbamoyl)-2-phenyl-ethyl ester *rac*-4

To a solution of acetic acid (2 mmol, 172 μl) in DCM (1 ml) were added phenylacetic aldehyde (2.2 mmol, 225 μl) and (*p*-methoxy)benzylisocyanide (2.14 mmol, 315 mg, solution in 1 ml of DCM) in room temperature. After 90 h the solvent was evaporated and the product was purified by flash chromatography (silica gel, hexane–ethyl acetate, 4:1 v/v). Yield: 89%. Mp 79–81 °C (ethyl acetate/hexane); $R_f = 0.68$ (ethyl acetate/hexane; 4:6; v/v). Anal. $C_{19}H_{21}NO_4$ requires: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.75; H, 6.49; N, 4.28; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H, CH_3CO), 3.21 (m, 2H, CH_2NH), 3.79 (s, 3H, CH_3O), 4.33 (m, 2H, CH_2CHO), 5.41 (t, 1H, $J = 6$ Hz, C*H*C(O)), 6.10 (s, 1H, N*H*), 6.80–7.26 (m, 9H, 2Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.93, 37.59, 42.60, 55.23, 74.34. 113.98, 126.89, 128.37, 129.02, 129.56, 129.64, 135.74, 159.00, 168.64, 169.36; Retention time of enantiomers: $T_R = 11.993$ min, $T_S = 13.573$ min.

4.2. Enzymatic hydrolysis of *rac*-4

Ester *rac*-**4** (50 mg) was dissolved in 10 ml of solvent (water/co-solvent, 8:2, v/v). Lipase from wheat germ (E.C. 3.1.1.3, 3 mg) was added in one portion to the suspension and stirred in a shaker at 300 rpm at room temperature for the amount of time given in Table 1. Extraction with ethyl acetate, concentration in vacuo and purification of the resulting residue by flash chromatography (silica gel, hexane–ethyl acetate) afforded ester (*R*)-**4** and alcohol (*S*)-**5**. Analysis for the products of hydrolysis in water/ethyl ether (Table 1, entry 4): Ester (*R*)-**4**: yield 48%. Ee_R (HPLC): 70%. Other analysis consistent with *rac*-**4**. Alcohol (*S*)-**5**: yield 33%. Ee_S (HPLC): 93%; mp 78–80 °C (ethyl acetate/hexane); $R_f = 0.43$ (ethyl acetate/hexane; 4:6; v/v). Anal. $C_{17}H_{19}NO_3$ requires: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.62; H, 6.76; N, 4.87. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (br s, 1H, O*H*), 2.90 (dd, 1H, $J = 13.9$, 8.2 Hz, CH_2CHO), 3.23 (dd, 1H, $J = 13.9$, 4.1 Hz, CH_2CHO), 3.72 (s, 2H, CH_3), 4.32 (m, 3H, ArCH_2N, C*H*OH), 6.77 (s, 1H, NH), 6.80–7.31 (m, 9H, 2Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.00, 42.72, 55.43, 72.97, 114.14, 127.08, 128.82, 129.23, 129.69, 130.00, 136.90, 159.10, 172.50. Retention time of enantiomers: $T_R =$ 9.745 min, $T_S = 10.625$ min.

4.3. Chemical hydrolysis of (*R*)-4

Ester (*R*)-**4** (50 mg, 0.15 mmol) was dissolved in 3 ml of methanol. Aqueous NaOH solution (4 M, 0.10 ml) was

added and the mixture was sonicated for 30 min. The solvent was evaporated, the residue was brought up in HCl (1 M, 5 ml) and washed with ethyl acetate (3 × 5 ml). Combined organic layers were dried ($MgSO_4$), and the solvent was evaporated, to yield product (42.5 mg, 99%). $R_f = 0.43$ (ethyl acetate/hexane; 4:6; v/v). Anal. $C_{17}H_{19}NO_3$ requires: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.62; H, 6.76; N, 4.87; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (br s, 1H, O*H*), 2.90 (dd, 1H, $J = 13.9$, 8.2 Hz, CH_2CHO), 3.23 (dd, 1H, $J = 13.9$, 4.1 Hz, CH_2CHO), 3.72 (s, 2H, CH_3), 4.32 (m, 3H, ArCH_2N, C*H*OH), 6.77 (s, 1H, NH), 6.80–7.31 (m, 9H, 2Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.00, 42.72, 55.43, 72.97, 114.14, 127.08, 128.82, 129.23, 129.69, 130.00, 136.90, 159.10, 172.50.

4.4. Chemical hydrolysis of *rac*-4

The above described conditions yielded *rac*-**4**. Retention times of enantiomers: $T_R = 9.745$ min, $T_S = 10.625$ min.

4.5. Acetic acid (*S*)-1-(4-methoxy-benzylcarbamoyl)-2-phenyl-ethyl ester (*R*)-4

To a stirred solution of (*S*)-2-hydroxy-*N*-(4-methoxy-benzyl)-3-phenyl-propionamide (*S*)-**5** (400 mg, 1.40 mmol, >99% ee, $[\alpha]_D^{25} = -71.1$ (*c* 1.0, chloroform) as obtained in the correlation study; for general procedure see Refs. 8 and 9) in DCM (8 ml) were added triethylamine (580 μl, 4.20 mmol) and *p*-toluenesulfonyl chloride (400 mg, 2.10 mmol). After 18 min, the solvent was evaporated and the product was purified by flash chromatography (silica gel, hexane–ethyl acetate, 8:2) to give 590 mg (96%) of toluene-4-sulfonic acid (*S*)-1-(4-methoxy-benzylcarbamoyl)-2-phenyl-ethyl ester. Yield: 96%; mp 96 °C (ethyl acetate/hexane); $R_f = 0.71$ (hexane–ethyl acetate; 4:6; v/v); $[\alpha]_D^{25} = -50.4$ (*c* 1.0, chloroform). Anal. $C_{24}H_{25}NO_5S$ requires: C, 65.58; H, 5.73; N, 3.19. Found: C, 65.79; H, 5.76; N, 3.11; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H, ArCH_3), 3.05 (dd, 1H, $J = 14.4$, 7.2 Hz, CH_2CHO), 3.17 (dd, 1H, $J = 14.4$, 4.0 Hz, CH_2CHO), 3.80 (s, 3H, CH_3O), 4.25–4.33 (m, 2H, ArCH_2N), 5.02 (dd, 1H, $J = 7.2$, 4.0 Hz, C*H*C(O)), 6.43 (s, 1H, NH), 6.80–7.53 (m, 13H, 3Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.63, 38.36, 42.74, 55.24, 80.62, 113.96, 126.86, 127.73, 128.34, 128.91, 129.17, 129.71, 129.89, 132.14, 134.63, 145.22, 158.98, 167.46. A sample of this compound (100 mg, 0.227 mmol) was dissolved in DMF (2 ml). Caesium acetate (88 mg, 0.45 mmol) and benzo-17-crown-5 (10 mg) were added in one portion. The mixture was stirred for 66 h in 50 °C, and then poured into water (20 ml). This mixture was extracted with ethyl acetate (3 × 15 ml). The collected organic phases were dried ($MgSO_4$) and the solvent was evaporated. The product was purified by flash chromatography (silica gel, hexane–ethyl acetate 1:1) to give 73.5 mg (99%). Ee_R (HPLC): >99%. Other analyses were consistent with *rac*-**4**.

4.6. Methanesulfonic acid (*S*)-1-(4-methoxy-benzylcarbamoyl)-2-phenyl-ethyl ester (*S*)-7

(*S*)-2-Hydroxy-*N*-(4-methoxy-benzyl)-3-phenyl-propionamide (*S*)-**5** (571 mg, 2.00 mmol, from correlation study, see the procedure above) was dissolved in DCM (6 ml). Triethylamine (1.12 ml, 8.00 mmol) and methanesulfonyl chloride (232 μl, 3.00 mmol) were added in one portion. The mixture was stirred for 30 min, the solvent was evaporated and the product was purified by flash chromatography (silica gel, hexane–ethyl acetate, 4:6, v/v). Yield: 99%. $R_f = 0.60$ (hexane–ethyl acetate; 4:6; v/v); mp 119–120 °C (ethyl acetate/hexane); $[\alpha]_D^{25} = -66.1$ (*c* 1.0, chloroform). Anal. $C_{18}H_{21}NO_5S$ requires: C, 59.49; H, 5.82; N, 3.58. Found: 59.48; H, 5.86; N, 3.88; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3SO_2), 3.12 (dd, 1H, $J = 14.4$, 9.1 Hz, CH_2CHO), 3.53 (dd, 1H, $J = 14.4$, 3.6 Hz, CH_2CHO), 3.86 (s, 3H, CH_3O), 4.42–4.50 (m, 2H, ArCH_2N), 5.22 (dd, 1H, $J = 9.1$, 3.6 Hz, C*H*C(O)), 6.67 (s, 1H, N*H*), 6.89–7.43 (m, 9H, 2Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.89, 38.71, 43.07, 55.42, 81.66. 114.21, 127.60, 128.89, 129.08, 129.87, 135.64, 167.56.

4.7. (*R*)-2-Amino-*N*-(4-methoxy-benzyl)-3-phenyl-propionamide (*R*)-8

To a solution of methanesulfonic acid (*S*)-1-(4-methoxy-benzylcarbamoyl)-2-phenyl-ethyl ester (*S*)-**7** (200 mg, 0.55 mmol) in DCM (3 ml) were added 1,4-diaza-bicyclo[2.2.2]octane (102 mg, 0.90 mmol), 4-dimehylaminopyridine (10 mg), sodium azide (1 mmol) and benzo-15-crown-5 (10 mg). After 20 h the desired azide was purified by flash chromatography (silica gel, hexane–ethyl acetate, 4:1, v/v). Yield: 98%. $R_f = 0.83$ (hexane–ethyl acetate; 4:6; v/v) $[\alpha]_D^{25} = -21.8$ (*c* 1.0; chloroform). Anal. $C_{17}H_{18}N_4O_2$ requires: 65.79; H, 5.85; N, 18.05. Found C, 65.60; H, 6.08; N, 17.95; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (dd, 1H, $J = 8.0$, 14.4 Hz, PhCH_2), 3.35 (dd, 1H, $J = 4.4$, 14.4 Hz, PhCH_2), 3.86 (s, 3H, CH_3O), 4.22 (dd, 1H, $J = 4.4$, 8.0 Hz, C*H*N$_3$), 4.30–4.37 (m, 2H, PhCH_2NH), 6.48 (br s, 1H, N*H*), 6.82–7.29 (m, 9H, 2Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.44, 42.93, 55.24, 65.43, 114.02, 127.15, 128.61, 129.90, 129.41, 129.50, 136.00, 159.04, 168.19. A sample of this compound (0.37 mmol, 115 mg) was dissolved in methanol (8 ml). To this mixture 10% Pd/C (10 mg) was added and hydrogen was fluxed through the solution (from a rubber balloon through a needle) for a period of 2 h. The reaction mixture was then filtered through a bed of Celite and the solvent was evaporated, to give white crystals (104 mg, 99%). Mp 84–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 2H, NH_2), 2.73 (dd, 1H, $J = 9.2$, 13.6 Hz, PhCH_2CH), 3.25 (dd, 1H, $J = 4.0$, 13.6 Hz, PhCH_2CH), 3.63 (dd, 1H, $J = 4.0$, 8.8 Hz, C*H*NH$_2$), 3.77 (s, 3H, CH_3O), 4.30–4.40 (m, 2H, PhCH_2NH), 6.82–7.31 (m, 9H, 2Ar*H*), 7.56 (s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.82, 42.43, 55.11, 56.27, 113.82, 126.63, 128.54, 128.83, 128.92, 129.19, 130.30, 137.68, 158.73, 173.77.

4.8. (*R*)-Phenylalanine (*R*)-9

(*R*)-2-Amino-*N*-(4-methoxy-benzyl)-3-phenylpropionamide (*R*)-**8** (180 mg, 0.63 mmol) was refluxed in 6 M HCl (10 ml) for 20 h. The solvent was then removed and the residue was dissolved in 4 N NaOH (6 ml) and 1 M $NaHCO_3$ (1.5 ml) and benzyl chloroformate (0.50 mmol, 72 μl). After 20 h, another portion of benzyl chloroformate was added

(0.50 mmol, 72 μl). After 43 h, the reaction mixture was washed with ethyl ether (2 × 25 ml). Collected organic phases were washed with 1 M NaOH (2 × 20 ml). Collected aqueous fractions were slowly poured into a stirred mixture of 4 M HCl (50 ml) and ethyl acetate (80 ml). Aqueous phase was washed with ethyl acetate (2 × 20 ml). Collected organic phases were dried ($MgSO_4$) and the solvent was evaporated. The residue was dissolved in methanol (10 ml). To this mixture 10% Pd/C (10 mg) was added and hydrogen was fluxed through the solution for 2 h. Then the reaction mixture was filtered through a bed of Celite and the solvent was evaporated, to give white crystals (74 mg, 71%). $[\alpha]_D^{25} = -7.3$ (*c* 1.0, acetic acid, lit.:[10] −7.5, enantiomeric purity: 98%); ESI MS(−): 164.1 $(M-H^+)^-$, 100%.

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