Regioselective Lipase-Catalysed Amidation of Dicarboxylic *N*-Blocked Amino Acid Diesters − Effect of the Side-Chain Length

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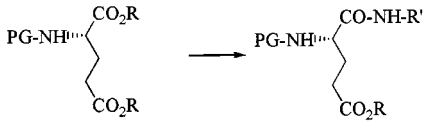
Diethyl esters of both (*R*)- and (*S*)-*N*-blocked α-aminoadipic and α-aminopimelic acids yield exclusively the ω-monoamide when they are subjected to amidation catalysed by the lipase B of *Candida antarctica* in anhydrous diisopropyl ether. These results are in contrast to the α-monoamide yielded by the equivalent L-glutamic derivatives under the same experimental conditions. These results show that the length of the side chain plays a crucial role in the regioselectivity of the reaction.

Introduction

Although a less frequent reaction than lipase-catalysed transesterification in organic solvents, amides can also be formed when amines, instead of alcohols, are used as nucleophiles under the same experimental conditions. A few commercial lipases have been described to successfully catalyse amidations: porcine pancreatic,[1] *Pseudomonas cepacia,*[2] *Candida rugosa*[3] and others but, since the recent work by Gotor et al.,[4] the enzyme of choice seems to be the *Candida antarctica* lipase B (CAL).

One of the most remarkable characteristics of the enzymatic reactions is their high regioselectivity between identical functional groups located in chemically different regions of the same molecule. Amino acid derivatives are a generally cheap and easily available source of chiral building blocks[5] in organic synthesis but the use of dicarboxylic amino acids such as aspartic and glutamic acids presents the problem of distinguishing between the two carboxylic groups. This is usually carried out by a time-consuming series of selective protecting-deprotecting steps, in a classical organic synthesis, with consequent reductions in the final yield. A line of our research deals with the regioselective CAL-catalysed amidation of diesters of *N*-protected dicarboxylic amino acids and the effect of changing a unique part of the substrate on the rate and selectivity of the reaction. After a general survey,[6] we studied the influence of the *N*-protecting group[7] when *(S)*-glutamic[8] acid diesters **1** were used as acyl donors, and we found that, while the reaction rate depended on the ester, amine or protecting group used, the regioselectivity was not affected and α-monoamides **2** were obtained in all cases (Scheme 1). In this paper we report the effect on the regioselectivity and reactivity of the reaction produced by a longer side chain than that of glutamic acid by studying the amidation of some *N*-protected *(S)*-, *(R)*- and *(R,S)*-α-aminoadipic **3** and *(R,S)*-α-aminopimelic **4** acids (side chain enlarged by one and two methylene groups, respectively) diethyl esters under the same experimental conditions.



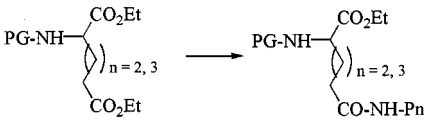
1 **2**

Scheme 1. CAL-catalysed amidation of diethyl (*S*)-glutamic acid derivatives

Results and Discussion

The preparatory part of this work was the synthesis of the substrates, *N*-protected diesters, from the commercial free amino acids as racemic or enantiopure forms, applying standard synthetic methods.[9] Based on our previous results with (*S*)-glutamic derivatives,[7] the selected substrates were:

- *N*-carbamates: benzyloxycarbonyl (*R*)- and (*S*)-**3a** and (*R,S*)-**4a**,
- Aliphatic *N*-amides, small acetyl (*R*)- and (*S*)-**3b** and (*R,S*)-**4b**, and bulky pivaloyl {Piv: 2,2-dimethylpropionyl} (*R*)- and (*S*)-**3c** and (*R,S*)-**4c**.
- *N*-Amides bearing an aromatic ring at increasingly greater distance from the chiral centre: *N*-benzoyl (*R,S*)-**3d**, *N*-phenyacetyl (*R,S*)-**3e** and *N*-benzylacetyl (*R,S*)-**3f**.



3, 4 **5, 6**

Scheme 2. CAL-catalysed amidation of diethyl *N*-protected α-aminoadipic and α-aminopimelic derivatives; derivatives **3** and **5**: (*R*)-, (*S*)- and (*R,S*)-α-aminoadipic (n = 2); **4** and **6**: (*R,S*)-α-aminopimelic (n = 3); PG (protecting group): **a**, Cbz; **b**, Ac; **c**, Piv; **d**, Bzl; **e**, PhAc; **f**, BnAc

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Table 1. CAL-catalysed ω-monoamidations of **3** and **4** derivatives, analytical scale, HPLC data

Time (min)	(*R*)-**5a**	(*S*)-**5a**	(*R*)-**5b**	(*S*)-**5b**	(*R*)-**5c**	(*S*)-**5c**	(*R,S*)-**5d**	(*R,S*)-**5e**	(*R,S*)-**5f**	(*R,S*)-**6a**	(*R,S*)-**6b**	(*R,S*)-**6c**
15	46.5	39.7	62.7	63.2	27.7	50.7	35.6	33.5	46.2	58.1	67.0	55.9
30	65.0	57.5	76.8	77.0	46.5	61.4	47.4	47.8	62.4	75.0	79.1	66.2
45	73.0	66.2	84.0	87.9	54.3	67.8	55.0	59.8	73.8	84.9	84.6	71.0
60	79.8	73.0	90.3	96.9	58.4	73.3	61.5	64.5	79.0	88.8	90.7	74.6

The reactions were initially carried out on an analytical scale in 2 mL screw-cap vials containing a suspension of the enzyme and molecular sieves 4Å in a diisopropyl ether solution of the acyl donor **3** or **4**, *n*-pentylamine and *N*-methylacetanilide or *N*-methylbutyranilide as internal standard. These mixtures were incubated at 60 °C in an orbital shaker and periodically analysed by HPLC (Table 1).

In all cases, **3** and **4** were each converted into a single product, although at different reaction rates, while the blank reactions without enzyme remained unchanged. Subsequently the reactions were performed on a preparative scale and the products isolated and structurally analysed by ^{1}H and ^{13}C NMR spectroscopy; all the products obtained were the corresponding ω-monoamides **5** and **6**

Table 2. ^{1}H NMR spectroscopic data for *N*-protected α-aminoadipic and α-aminopimelic acid derivatives (200 MHz, $CDCl_3$, δ ppm)

Comp.	Amino acid side chain						OEt		*n*-Pentylamine		
	α-CH	β-CH_2	γ-CH_2	δ-CH_2	ε-CH_2	α-NH	CH_2	CH_3	NH	N−CH_2	CH_3
(*S*)-3a	4.29	1.81 1.61	1.61	2.25	–	5.33	4.04 4.12	1.20 1.17	–	–	–
(*S*)-5a	4.25	1.77 1.61	1.61	2.11	–	5.79	4.10	1.18	5.55	3.12	0.81
(*R*)-3a	4.26	1.80 1.61	1.61	2.23	–	5.54	4.11 4.03	1.15 1.19	–	–	–
(*R*)-5a	4.29	1.82 1.68	1.68	2.17	–	5.49	4.16	1.24	5.62	3.17	0.86
(*S*)-3b	4.50	1.77 1.58	1.58	2.23	–	6.36	4.11 4.03	1.19 1.16	–	–	–
(*S*)-5b	4.50	1.78 1.61	1.61	2.18	–	6.48	4.13	1.25	5.85	3.16	0.84
(*R*)-3b	4.50	1.76 1.58	1.58	2.26	–	6.49	4.14 4.03	1.19 1.20	–	–	–
(*R*)-5b	4.48	1.62 1.78	1.62	2.18	–	6.49	4.13	1.22	5.88	3.15	0.83
(*S*)-3c	4.49	1.83 1.61	1.61	2.27	–	6.22	4.14 4.06	1.19 1.23	–	–	–
(*S*)-5c	4.49	1.82 1.63	1.63	2.16	–	6.38	4.16	1.23	5.84	3.17	0.85
(*R*)-3c	4.48	1.82 1.59	1.59	2.25	–	6.21	4.12 4.04	1.21 1.24	–	–	–
(*R*)-5c	4.50	1.85 1.55	1.63	2.16	–	6.38	4.19	1.22	5.76	3.21	0.88
(*R,S*)-3d	4.75	1.95 1.73	1.73	2.32	–	6.81	4.21 4.08	1.21 1.27	–	–	–
(*R,S*)-5d	4.73	1.94 1.75	1.75	2.24	–	7.13	4.21	1.27	5.73	3.19	0.84
(*R,S*)-3e	4.56	1.81 1.59	1.59	2.27	–	6.04	4.15 4.10	1.27 1.20	–	–	–
(*R,S*)-5e	4.55	1.81 1.61	1.61	2.13	–	6.29	4.15	1.23	5.72	3.18	0.89
(*R,S*)-3f	4.56	1.78 1.54	1.54	2.25	–	6.06	4.16 4.10	1.25 1.24	–	–	–
(*R,S*)-5f	4.54	1.79 1.59	1.59	2.14	–	6.34	4.17	1.26	5.77	3.21	0.89
(*R,S*)-4a	4.32	1.77 1.61	1.61	1.35	2.25	5.32	4.14 4.08	1.25 1.21	–	–	–
(*R,S*)-6a	4.28	1.72 1.61	1.61	1.44	2.10	5.42	4.14	1.26	5.61	3.16	0.84
(*R,S*)-4b	4.51	1.72 1.56	1.56	1.29	2.22	6.16	4.12 4.04	1.20 1.17	–	–	–
(*R,S*)-6b	4.53	1.72 1.61	1.61	1.30	2.12	6.23	4.14	1.23	5.65	3.17	0.85
(*R,S*)-4c	4.48	1.79 1.56	1.56	1.27	2.21	6.12	4.11 4.03	1.20 1.23	–	–	–
(*R,S*)-6c	4.38	1.72 1.53	1.53	1.22	2.04	6.21	4.05	1.14	6.10	3.07	0.76

(Scheme 2) while no traces of the α-mono- or diamide were detected.

A methylene link is not a great length enlargement in a hydrocarbon chain and it normally produces little, if any, effect in a chemical reaction, although it may induce an important change in an enzyme-catalysed transformation. The distance[10] from the ω-carbonyl group to the substituted chiral carbon in a fully extended chain is only increased from 3.85 Å (glutamic acid) to 5.01 Å (α-aminoadipic acid) and 6.81 Å (α-aminopimelic acid) but, in these CAL-catalysed amidations, these small enlargements produced an enormous change in the regioselectivity from α- to ω-monoamides, with both (*R*)- and (*S*)-enantiomers. Work is currently in progress to explain the reactivity and selectivity data of all the dicarboxylic amino acids studied, by CAL active-site X-ray crystallography[11] and computer assisted modeling[12] studies.

Table 3. ^{13}C NMR spectroscopic data for *N*-protected α-aminoadipic and α-aminopimelic acid derivatives (50 MHz, $CDCl_3$, δ ppm)

Comp.	Amino acid side chain						OEt		*n*-Pentylamine		
	α-CH	β-CH_2	γ-CH_2	δ-CH_2	ε-CH_2	CO	CH_2	CH_3	N-CH_2	CH_3	CH_2
(*S*)-3a	53.50	31.74	20.46	33.40	–	172.05 172.81	60.18 61.29	14.02 13.95	–	–	–
(*S*)-5a	53.37	31.69	21.36	35.51	–	172.13 172.13	61.37	13.99	39.36	13.83	29.15, 28.92 22.16
(*R*)-3a	53.49	31.69	20.47	33.38	–	172.05 172.81	60.17 61.26	14.02 13.94	–	–	–
(*R*)-5a	53.37	32.08	21.40	35.62	–	172.11 172.17	61.48	14.08	39.45	13.90	29.24, 28.27 22.27
(*S*)-3b	51.73	31.53	20.44	33.40	–	172.28 172.96	61.33 60.24	14.05 13.99	–	–	–
(*S*)-5b	51.68	31.70	21.43	35.46	–	172.33 172.34	61.41	14.08	39.44	13.88	29.20, 28.98 22.25
(*R*)-3b	51.77	31.58	20.45	33.43	–	172.30 173.04	61.41 60.31	14.09 14.03	–	–	–
(*R*)-5b	51.65	31.67	21.42	35.44	–	172.33 172.34	61.43	14.08	39.43	13.90	29.19, 28.98 22.26
(*S*)-3c	51.67	31.57	20.46	33.43	–	172.43 173.02	61.34 60.27	14.10 14.03	–	–	–
(*S*)-5c	51.38	31.68	21.51	35.26	–	172.36 172.42	61.31	14.00	39.33	13.82	29.05, 28.82 22.19
(*R*)-3c	51.66	31.55	20.45	33.41	–	172.41 173.00	61.32 60.27	14.09 14.03	–	–	–
(*R*)-5c	51.26	32.00	21.64	35.46	–	172.60 172.41	61.52	14.13	39.46	13.96	29.29, 29.05 22.32
(*R,S*)-3d	52.27	31.66	20.49	33.46	–	172.28 173.08	61.55 60.34	14.09 14.09	–	–	–
(*R,S*)-5d	51.51	31.58	21.29	35.37	–	172.20 172.28	61.38	14.03	39.41	13.88	29.13, 28.96 22.24
(*R,S*)-3e	51.74	31.32	20.33	33.28	–	171.84 172.82	61.25 60.15	14.01 13.89	–	–	–
(*R,S*)-5e	51.60	31.68	21.43	35.42	–	172.03 172.25	61.46	14.03	39.41	13.90	29.19, 28.98 22.26
(*R,S*)-3f	51.72	31.66	20.34	33.48	–	172.17 172.96	61.41 60.29	14.06 15.15	–	–	–
(*R,S*)-5f	51.51	31.58	21.29	35.37	–	172.20 172.28	61.38	14.03	39.41	13.88	29.19, 28.96 22.24
(*R,S*)-4a	53.69	32.30	24.39	24.59	33.91	172.31 173.26	61.34 60.19	14.13 14.06	–	–	–
(*R,S*)-6a	53.70	32.30	24.75	25.10	36.27	172.43 173.30	61.34	14.05	39.41	13.87	29.22, 28.97 22.24
(*R,S*)-4b	51.92	32.12	24.39	24.60	33.89	172.52 173.36	61.40 60.24	14.15 14.09	–	–	–
(*R,S*)-6b	51.97	32.12	24.76	25.07	36.22	172.51 172.52	61.39	14.11	39.45	13.91	29.25, 29.00 22.28
(*R,S*)-4c	51.73	31.96	24.33	24.57	33.84	172.59 173.22	61.24 60.11	14.07 14.00	–	–	–
(*R,S*)-6c	51.73	31.80	24.71	24.98	35.98	172.42 172.48	61.11	13.88	39.22	13.73	29.05, 28.82 22.08

The reactivity of the substrates is not significantly affected by the configuration of the chiral carbon atom or the structure of the protecting group. Considering the conversion at 15 minutes as a suitable value for comparing the reaction rates (see Table 1), the differences induced by the steric and electronic features of the *N*-protecting groups, although present, are not very important. Steric hindrance appears to be the driving effect and, unlike (*S*)-glutamic derivatives, the amides **5b** and (*S*)-**5c** react faster than the carbamates **5a**. The configuration of the chiral carbon only appears to have a great effect when it is associated with a bulky *N*-protecting group such as pivaloyl − (*R*)-**5c** reacts much more slowly than (*S*)-**5c**. The steric effect of the phenyl group decreases when the distance to the chiral carbon increases, probably due to the higher flexibility of the longer joining chain. In the three cases studied, pimelic derivatives **6a−c** react faster than their counterparts **5a−c**.

Structural elucidation

The structures of all new compounds were elucidated according to analytical and spectroscopic (^{1}H and ^{13}C NMR) data which are collected in Tables 2 and 3. Two-dimensional pulse sequences such as HMQC or HMBC have been employed for the unequivocal determination of all chemical shifts.

The monoamidation position was determined from the chemical shift displacement rule of ester-amide dicarboxylic amino acids previously determined in our group[6] − amide substitution at one of the carboxylate moieties produces an upfield shift of the adjacent C*H* or CH_2 protons of about 0.15 ppm, while deshielding the respective carbon atoms by 0.9 to 1.5 ppm. With respect to the new aminoadipic and aminopimelic ester-amide derivatives (compounds **5a−f** and **6a−f**), higher chemical shifts differences in both the ^{1}H and ^{13}C NMR spectra for the signals of the side chain methylene moiety (δ-CH_2 or ε-CH_2 respectively) were observed, thus indicating a regioselective monoamidation on the side chain and not in the α position.

Experimental Section

General: Elemental analyses were performed on a Perkin−Elmer 240C equipment. Melting points were determined with a Reichert-Jung apparatus equipped with a microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian-Gemini-200 or a Varian XL-300 spectrometer. Optical rotations were determined on a Perkin−Elmer 241-C polarimeter. Analytical HPLC was performed on a Beckman Chromatograph equipped with a Deltapak C_{18} 5μ (3.9 × 15 mm) column and a UV detector. The eluent employed was water/acetonitrile plus 0.5 mL/l of trifluoroacetic acid at a 1 mL/min flow rate (ratio and wavelength are specified in each case). Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F254 (Merck). Chromatographic separations were performed on columns using the flash chromatographic technique on silica gel 230−240 mesh (Merck). Diisopropyl ether was refluxed over sodium wire, distilled and stored over molecular sieves 4Å. *n*-Pentylamine was obtained from commercial sources, distilled and stored over KOH pellets. The rest of the commercial chemicals were used without further purification. Novozym 435, a Novo Nordisk commercial immobilised preparation of CAL, was used as received.

Synthesis of Substrates a−c: Hydrogen chloride was bubbled through a suspension of the corresponding free amino acid (1 g) in absolute EtOH (40 mL) for one hour. The resulting clear solution was stirred at room temperature for 48 hours and then the solvent was evaporated under vacuum. The residue was extracted with a mixture of aqueous $NaHCO_3$ (40 mL) and CH_2Cl_2 (40 mL). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to dryness. The diester thus formed was reacted with the corresponding acyl chloride (1.5 equiv.) by adding it dropwise to an ice-cooled suspension of the diester in pyridine (2 equiv.) and water (5 mL). The reactions were stirred at room temperature for 16 h and then HCl 1 N (6 mL) was added, the mixture stirred and extracted with CH_2Cl_2, then with a solution of $NaHCO_3$ and finally with water. The organic solution was dried (Na_2SO_4), the solvent evaporated and the final residue chromatographed, where necessary, to obtain a single peak (HPLC), using hexane/ethyl acetate as eluents. In the case of Cbz derivatives, an additional purification step using circular chromatography (CH_2Cl_2/acetone, 40:1) was performed.

(*S*)-*N*-Cbz-2-aminoadipic Acid Diethyl Ester (*S*)-3a: 28%. Colorless syrup. − $[\alpha]_D$: +7.8° (*c* = 1, $CHCl_3$). − $C_{18}H_{25}NO_6$ (351.17): calcd. C. 61.52, H. 7.17, N. 3.99; found C. 61.43, H. 7.05, N. 4.10

(*R*)-*N*-Cbz-2-aminoadipic Acid Diethyl Ester (*R*)-3a: 30%. Colorless syrup. − $[\alpha]_D$: −6.9° (*c* = 1, $CHCl_3$). − $C_{18}H_{25}NO_6$ (351.17): calcd. C. 61.52, H. 7.17, N. 3.99; found C. 61.55, H. 7.19, N. 4.03.

(*S*)-*N*-Acetyl 2-aminoadipic Acid Diethyl Ester (*S*)-3b: 58%. Colorless syrup. − $[\alpha]_D$: + 26.0° (*c* = 1, $CHCl_3$). − $C_{12}H_{21}NO_5$ (259.30): calcd. C. 55.58, H. 8.16, N. 5.40; found C. 55.75, H. 8.07, N. 5.53.

(*R*)-*N*-Acetyl 2-aminoadipic Acid Diethyl Ester (*R*)-3b: 53%. Colorless syrup. − $[\alpha]_D$: −24.20° (*c* = 1, $CHCl_3$). − $C_{12}H_{21}NO_5$ (259.30): calcd. C. 55.58, H. 8.16, N. 5.40; found C. 55.43, H. 8.22, N. 5.32.

(*S*)-*N*-Pivaloyl-2-aminoadipic Acid Diethyl Ester (*S*)-3c: 49%. Colorless syrup. − $[\alpha]_D$: +13.8° (*c* = 1, $CHCl_3$). − $C_{15}H_{27}NO_5$ (301.38): calcd. C. 59.78, H. 9.03, N. 4.65; found C. 59.89, H. 9.15, N. 4.73

(*R*)-*N*-Pivaloyl-2-aminoadipic Acid Diethyl Ester (*R*)-3c: 50%. Colorless syrup. − $[\alpha]_D$: −13.4° (*c* = 1, $CHCl_3$). − $C_{15}H_{27}NO_5$ (301.38): calcd. C. 59.78, H. 9.03, N. 4.65; found C. 60.02, H. 9.12, N. 4.58.

(*R*,*S*)-*N*-Cbz-2-aminopimelic Acid Diethyl Ester (*R*,*S*)-4a: 73%. Colorless syrup. − $C_{19}H_{27}NO_6$ (365.18): calcd. C. 62.45, H. 7.45, N. 3.83; found C. 62.30; H. 7.51, N. 3.76.

(*R*,*S*)-*N*-Acetyl-2-aminopimelic Acid Diethyl Ester (*R*,*S*)-4b: 83%. Colorless syrup. − $C_{13}H_{23}NO_5$ (273.33): calcd. C. 57.13, H. 8.48, N. 5.12; found C. 56.96, H. 8.53, N. 5.00.

(*R*,*S*)-*N*-Pivaloyl-2-aminopimelic Acid Diethyl Ester (*R*,*S*)-4c: 65%. Colorless syrup. − $C_{16}H_{29}NO_5$ (315.41): calcd. C. 60.93, H. 9.27, N. 4.44; found C. 61.07, H. 9.25, N. 4.38.

Synthesis of Substrates d−f: Diethyl ether (10 mL) was added to a solution (10 mL) of *(R,S)*-2-aminoadipic acid (400 mg, 2.48 mmol) in aqueous NaOH (300 mg, 7.5 mmol) and the mixture cooled in an ice bath. Then, a solution of the corresponding acyl chloride (1.2 equiv.) in diethyl ether (10 mL) was added dropwise with vigorous stirring. After 3 h the ethereal layer was discarded and the aqueous phase washed twice with diethyl ether and then taken to

pH 3.5 with HCl 2 N. After extracting with EtOAc (5 × 20 mL) and drying the organic phase (Na_2SO_4), the solvent was evaporated to dryness. The diacid formed was esterified by adding ethanol (10 mL) and $SOCl_2$ (4 equiv.) dropwise, left to react at room temperature for one hour and then refluxed for 30 minutes, the solvent removed and the final residue chromatographed (hexane/EtOAc)

(*R*,*S*)-*N*-Benzoyl-2-aminoadipic Acid Diethyl Ester (*R*,*S*)-3d: 73%. Colorless syrup. − $C_{17}H_{23}NO_5$ (321.37): calcd. C. 63.54, H. 7.21, N. 4.36; found C. 63.72, H. 7.13, N. 4.30.

(*R*,*S*)-*N*-Phenylacetyl-2-aminoadipic Acid Diethyl Ester (*R*,*S*)-3e: 32%. Colorless syrup. − $C_{18}H_{25}NO_5$ (335.39): calcd. C. 64.46, H. 7.51, N. 4.18; found C. 64.62, H. 7.55, N. 4.16.

(*R*,*S*)-*N*-Phenylpropionyl-2-aminoadipic Acid Diethyl Ester (*R*,*S*)-3f: 37%. Colorless syrup. − $C_{19}H_{27}NO_5$ (349.42): calcd. C. 65.31, H. 7.79, N. 4.01; found C. 65.24, H. 7.88, N. 3.97.

Enzymatic reactions. General Procedure: CAL (50 mg/mL) and molecular sieves 4Å (50 mg/mL) were added to a diisopropyl ether solution containing the corresponding substrate (20 mM) and *n*-pentylamine (50 mM) and the resulting mixture was incubated at 60 °C in an orbital shaker at 250 r.p.m. The reactions were initially performed on an analytical scale in 2 mL screw-cap vials containing also an internal standard (*N*-methylacetanilide or *N*-methylbutyranilide, 5 mM). Aliquots (20 μL) were periodically withdrawn and analysed by HPLC (conditions specified for each case). Blank reactions without enzyme were also checked in all cases but no chemical changes were observed. Preparative reactions were carried out under the same experimental conditions on a 100 mg scale. When the reaction was complete, the enzyme and molecular sieves were filtered off and washed with acetonitrile, methanol and dichloromethane. The combined organic extracts were evaporated and the residue chromatographed (hexane/EtOAc).

(*S*)-*N*-Cbz-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*S*)-5a: 71%. Colorless solid, m.p. 82−83 °C. − $[\alpha]_D$: +5.8° (*c* = 1, $CHCl_3$). − HPLC: λ = 215 nm, water/acetonitrile 60:40. − $C_{21}H_{32}N_2O_5$ (392.49): calcd. C. 64.26, H. 8.22, N. 7.14; found C. 64.02, H. 8.35, N. 6.98.

(*R*)-*N*-Cbz-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*R*)-5a: 64%. Colorless solid, m.p. 82−83 °C. − $[\alpha]_D$: −5.4° (*c* = 1, $CHCl_3$). − HPLC: λ = 215 nm, water/acetonitrile 60:40. − $C_{21}H_{32}N_2O_5$ (392.49): calcd. C. 64.26, H. 8.22, N. 7.14; found C. 63.95, H. 8.27, N. 7.12.

(*S*)-*N*-Acetyl-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*S*)-5b: 69%. Colorless solid, m.p. 69−71 °C. − $[\alpha]_D$: +10.7° (*c* = 1, $CHCl_3$). λ = 200 nm, water/acetonitrile 85:15. − $C_{15}H_{28}N_2O_4$ (300.39): calcd. C. 59.97, H. 9.40, N. 9.33; found C. 59.67, H. 9.42, N. 9.28.

(*R*)-*N*-Acetyl-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*R*)-5b: 89%. Colorless solid, m.p. 71−72 °C. − $[\alpha]_D$: −11.5° (*c* = 1, $CHCl_3$). − HPLC: λ = 200 nm, water/acetonitrile 85:15. − $C_{15}H_{28}N_2O_4$ (300.39): calcd. C. 59.97, H. 9.40, N. 9.33; found C. 59.93, H. 9.45, N.9.30.

(*S*)-*N*-Pivaloyl-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*S*)-5c: 68%. Colorless solid, m.p. 84−85 °C. − $[\alpha]_D$: +5.4° (*c* = 1, $CHCl_3$). − HPLC: λ = 200 nm, water/acetonitrile 73:27. − $C_{18}H_{34}N_2O_4$ (342.47): calcd. C. 63.13 H. 10.01, N. 8.18; found C. 63.37, H. 10.30, N. 8.24.

(*R*)-*N*-Pivaloyl-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*R*)-5c: 87%. Colorless solid, m.p. 86−87 °C. − $[\alpha]_D$: −4.7° (*c* = 1, $CHCl_3$). − HPLC: λ = 200 nm, water/acetonitrile 73:27. − $C_{18}H_{34}N_2O_4$ (342.47): calcd. C. 63.13 H. 10.01, N. 8.18; found C. 63.40, H. 10.25, N. 8.05.

(*R*,*S*)-*N*-Benzoyl-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*R*,*S*)-5d: 80%. Colorless solid, m.p. 97−99 °C. − HPLC: λ = 215 nm, water/acetonitrile 70:30. − $C_{20}H_{30}N_2O_4$ (362.46): calcd. C. 66.27, H. 8.34, N. 7.73; found C. 66.32, H. 8.51, N. 7.71.

(*R*,*S*)-*N*-Phenylacetyl-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*R*,*S*)-5e: 61%. Colorless solid, m.p. 74−76 °C. − HPLC: λ = 215 nm, water/acetonitrile 70:30. − $C_{21}H_{32}N_2O_4$ (376.49): calcd. C. 66.99, H. 8.57, N. 7.44; found C. 66.89, H. 8.62, N. 7.40.

(*R*,*S*)-*N*-[3-(Phenylpropionyl)]-2-aminoadipic Acid 1-Ethyl Ester-6-pentylamide (*R*,*S*)-5f: 80%. Colorless solid, m.p. 85−87 °C. − HPLC: λ = 215 nm, water/acetonitrile 65:35. − $C_{22}H_{34}N_2O_4$ (390.52): calcd. C. 67.66, H. 8.78, N. 7.17; found C. 67.75, H. 8.89, N. 7.12.

(*R*,*S*)-*N*-Cbz-2-aminopimelic Acid 1-Ethyl Ester-7-pentylamide (*R*,*S*)-6a: 92%. Colorless solid, m.p. 52−53 °C . − HPLC: λ = 215 nm, water/acetonitrile 60:40. − $C_{22}H_{34}N_2O_5$ (406.52): calcd. C 65.00, H. 8.43, N. 6.89; found C 64.75, H. 8.63, N. 7.10.

(*R*,*S*)-*N*-Acetyl-2-aminopimelic Acid 1-Ethyl Ester-7-pentylamide (*R*,*S*)-6b: 80%. Colorless solid, m.p. 75−76 °C. − HPLC: λ = 200 nm, water/acetonitrile 80:20. − $C_{16}H_{30}N_2O_4$ (314.42): calcd. C. 61.12, H. 9.62, N. 8.91; found 61.13, H. 9.84, N. 8.77.

(*R*,*S*)-*N*-Pivaloyl-2-aminopimelic Acid 1-Ethyl Ester-7-pentylamide (*R*,*S*)-6c: 99%. Colorless syrup. − HPLC: λ = 200 nm, water/acetonitrile 73:27. − $C_{19}H_{36}N_2O_4$ (356.50): calcd. C. 64.01, H. 10.18, N. 7.86; found C. 64.19, H. 10.33, N. 7.97.

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