Lipase-catalysed Enantioselective Acylation of *N*-Protected or Unprotected 2-Aminoalkan-1-ols

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Porcine pancreatic lipase (PPL) catalysed the acylation of 2-aminoalkan-1-ols; the enantiospecificity depends on the starting amino alcohol. The catalytic activity of the enzyme was markedly improved when the benzyl carbamate derivatives were used as substrates; in general, the enzyme displayed a high enantiospecificity.

Optically active amino alcohols are constituents of many biologically and pharmacologically important compounds. They represent important structural features of natural products such as adrenaline, β-adrenergic receptor blockers and local anaesthetics.

The most widely used synthesis of β-amino alcohols is by reduction of amino acid derivatives.[1] Other methods using formamidines have been applied, for example, for the preparation of propranolol.[2] In addition, ephedrine and related optically active β-amino alcohols have been prepared from *O*-protected cyanohydrins.[3]

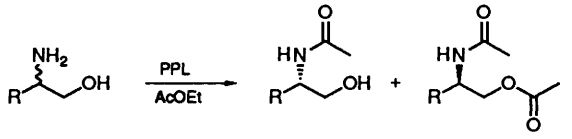
The use of enzymes in organic solvents for the resolution of chiral organic compounds is widespread and very efficient in many cases.[4] This methodology has been carried out successfully for the resolution of 1,2-amino alcohols. Thus, enzymatic hydrolysis and transesterification reactions can be applied for the preparation of β-adrenergic blockers.[5]

An efficient resolution of 2-aminobutan-1-ol and 2-aminopropan-1-ol has been described by Francalanci and co-workers through enzymatic hydrolysis of their ester derivatives or through transesterification.[6] Both procedures are carried out by protecting the amino group as an *N*-ethoxycarbonyl derivative. In a preliminary communication,[7] we reported that porcine pancreatic lipase (PPL) can catalyze the enantioselective amide bond formation and esterification of 2-aminobutan-1-ol and amide bond formation of 1-aminopropan-2-ol.

In this paper we report the enzymatic acylation of other 2-aminoalkan-1-ols, under the same reaction conditions as with 2-aminobutan-1-ol, in order to study the influence of the substrate. Furthermore, we have investigated the influence of the substituent on the amino group in the enantiospecificity of the enzymatic esterification; for this purpose, we have used 2-benzyloxycarbonylaminoalkan-1-ols as substrates because the benzyloxycarbonyl group is easily released under very mild conditions. Finally, we have tried the resolution of these substrates using acetone *O*-(benzyloxycarbonyl)oxime as acyl donor and different lipases.

The resolution of 2-aminobutan-1-ol was successfully achieved in ethyl acetate when PPL was used as catalyst.[7] In this reaction the conversions into amide and into amido ester were the same, and the enantiomeric excess of both derivatives was very high. Taking this result into account, it is possible that the amidation reaction was not enantioselective and that the transesterification took place with high enantiospecificity because the amide and the amido ester have reverse configurations.

We have applied this enzymatic reaction to other 2-aminoalkan-1-ols such as 2-aminopropan-1-ol, 2-aminopentan-1-ol and 2-aminohexan-1-ol (Scheme 1). A summary of the results obtained is collected in Table 1, in which the influence of the substrate structure on the enantiospecificity can be seen. It is worth noting that the recovered amino alcohols were racemic.



(±)-**1a-d** (*S*)-(−)-**2a-d** (*R*)-(+)-**3a-d**

a: R = CH_3
b: R = C_2H_5
c: R = C_3H_7
d: R = C_4H_9

Scheme 1

Again inspection of the conversions and the e.e. entries did not allow us to elucidate the origin of the enantioselectivity (amidation or transesterification step).

In order to determine whether the enantiospecificity arose from the amidation or the transesterification step, it would have been necessary to *O*-acylate selectively the amino alcohol and then, to carry out the enzymatic reaction with this substrate. This was not possible because intramolecular transfer of the acetyl group in the *O*-acyl derivative to the amino function took place very rapidly. This transfer may have taken place in the enzymatic reaction, too.

On the other hand, we have studied the transesterification of (±)-**2a** and (±)-**2b** (these compounds are easily obtained from the corresponding 2-aminoalkan-1-ol and acetone *O*-acetyloxime[8]). The results are collected in Table 2. It is seen that the transesterification took place enantiospecifically, no apparent influence of the substrate structure being observed.

In the enzymatic esterification of 2-aminoalkan-1-ols with ethyl acetate there may possibly be competition from the concurrent amidation[9] of reverse enantiospecificity with respect to the one of the esterification, as well as the fast transfer of the acetyl group mentioned before.

In order to get a more efficient resolution of these 2-aminoalkan-1-ols, we have checked the enzymatic reaction using the corresponding benzyl carbamates as substrates.

The reaction of oxime esters with bifunctional compounds such as amino alcohols was a very simple and efficient reaction for the selective protection of the amino group.[8] We have carried out the reactions between 2-aminoalkan-1-ols and acetone *O*-(benzyloxycarbonyl)oxime and only the corresponding *O*-benzyl carbamates were obtained. We have used this protecting group because of its easy release under mild conditions.

The enzymatic transesterification of compounds **4a–d** was carried out using ethyl acetate as solvent and acyl donor, and porcine pancreatic lipase (PPL) as catalyst (Scheme 2). The results obtained are summarized in Table 3. As can be seen, the

Table 1 Reaction of compounds (±)-**1a–d** with ethyl acetate catalyzed by PPL

		(*S*)-(−)-**2**			(*R*)-(+)-**3**		
Entry	Reaction time (h)	Conv. (%)[a]	$[\alpha]_D^{22b}$	E.e. (%)	Conv. (%)[a]	$[\alpha]_D^{22b}$	E.e. (%)
1a	24.5	52	−5.1	18	28	+35.8	67
1b	20	37	−44.0[c]	95	37.6	+61.0[c]	95
1c	24.5	37	−11.9	41	21	0	0
1d	24	31	−7.8	32	34	+10.6	27

[a] Determined by ^{1}H NMR of the mixture. [b] Measured in $CHCl_3$. [c] The configuration of **2b** and **3b** were incorrectly assigned in the preliminary communication.[7,11]

Table 2 Reaction of compounds (±)-**2a–b** with ethyl acetate catalyzed by PPL.

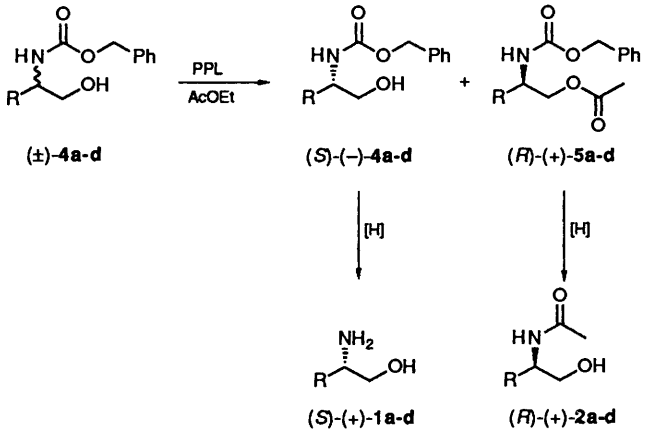
			(*S*)-(−)-**2**		(*R*)-(+)-**3**	
Entry	Reaction time (h)	Conv. (%)[a]	$[\alpha]_D^{22b}$	E.e. (%)	$[\alpha]_D^{22b}$	E.e. (%)
2a	4	55	−25.3	87	+30.9	58
2b	4	62	−39.3	87	+33.8	53

[a] Determined by ^{1}H NMR of the mixture. [b] Measured in $CHCl_3$.

Table 3 PPL-catalyzed transesterification of (±)-**4a–d** in ethyl acetate

			(*S*)-(−)-**4**		(*R*)-(−)-**5**	
Entry	Reaction time (h)	Conversion (%)[a]	$[\alpha]_D^{22b}$	E.e. (%)	$[\alpha]_D^{22b}$	E.e. (%)
4a	10	53	−5.0	85	+12.1	73
4b	16	54	−23.4	83	+25.2	78
4c	10.5	51	−21.2	99	+25.8	99
4d	9	51	−19.8	95	+23.6	95

[a] Determined by ^{1}H NMR of the mixture. [b] Measured in $CHCl_3$.



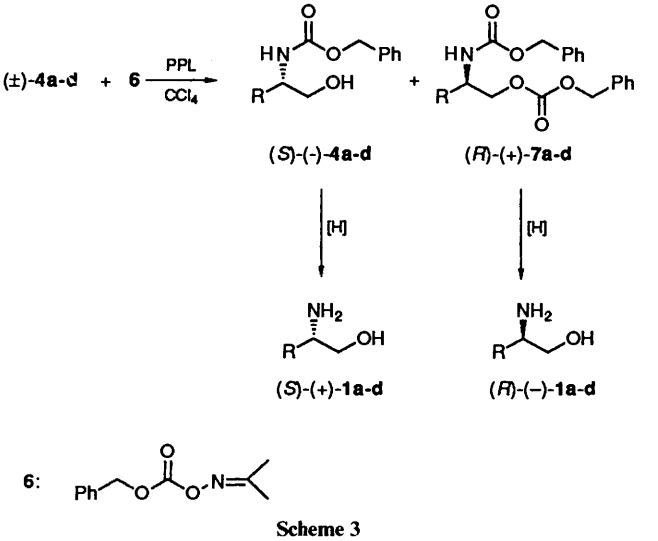
(±)-**4a-d** (*S*)-(−)-**4a-d** (*R*)-(+)-**5a-d** (*S*)-(+)-**1a-d** (*R*)-(+)-**2a-d**

Scheme 2

enzyme showed very high catalytic activity with the substrate **4c**, the reaction taking place with 51% conversion after 10.5 h, and both compounds (substrate and product) being obtained with an enantiomeric excess >95%. Similar results were achieved with the substrate **4d**. In these cases, it was not necessary to stop the reaction at different percentages of conversion to obtain the maximal optical purity for the substrate and the product.

The benzyloxycarbonyl group of compounds (*S*)-(−)-**4a–d** was easily removed under a hydrogen atmosphere or with cyclohexa-1,4-diene[10] as hydrogen donor using 20% palladium–carbon as catalyst. The corresponding (*S*)-(+)-2-aminoalkan-1-ols thus obtained had optical purities identical with those of compounds (*S*)-(−)-**4a–d**. The hydrogenolysis of (*R*)-(+)-**5a–d** yielded the corresponding (*R*)-(+)-2-acetylaminoalkan-1-ols due to the rapid transfer of the acetyl moiety from the hydroxy to the amino group, no racemization being observed in this process.

We have studied the enzymatic reaction of compounds (±)-**4a–d** in CCl_4 using acetone *O*-(benzyloxycarbonyl)oxime **6** as acylating reagent (Scheme 3) and the results are collected in Table 4. These reactions were slower than when ethyl acetate was used as acyl donor and, in general, their optical yields were lower. However, note that the reaction of (±)-**4a** yielded (*R*)-(+)-**7a** with a very satisfactory e.e. (92%) and with a high percentage of conversion (40%). Therefore, this method was



(*S*)-(−)-**4a-d** (*R*)-(+)-**7a-d** (*S*)-(+)-**1a-d** (*R*)-(−)-**1a-d**

6:

Scheme 3

Table 4 Reaction of compounds (±)-**4a–d** with **6** catalyzed by PPL.

			(*S*)-(−)-**4**		(*R*)-(+)-**7**	
Entry	Reaction time (h)	Conversion (%)[a]	$[\alpha]_D^{22}$[b]	E.e. (%)	$[\alpha]_D^{22}$[b]	E.e. (%)
4a	14.5	40	−4.5	77	+16.7	92
4b	17	37	−16.4	58	+31.7	71
4c	15	29	−6.4	31	+27.7	99
4d	12	21	−5.8	28	+22.0	84

[a] Determined by ^{1}H NMR of the mixture. [b] Measured in $CHCl_3$.

more adequate than those mentioned before for the resolution of 2-aminopropan-1-ol (see entries for **1a** and **4a** in Tables 1 and 3 respectively). The hydrogenolysis of (*S*)-(−)-**4a–d** and (*R*)-(+)-**7a–d** yielded (*S*)-(+)-**1a–d** and (*R*)-(−)-**1a–d** respectively, no racemization being observed during the process.

Finally, we have checked the potential of other enzymes such as *Candida cylindracea* lipase (CCL) and *Candida antarctica* lipase to catalyze the reaction of (±)-**4a–d** with the carbonate **6**, but the activity of these enzymes in CCl_4 was lower than that exhibited by PPL. A little amount of the corresponding acetonoximecarbonylester derivative was obtained in these processes when CCL was used as catalyst.

Experimental

Porcine pancreatic (Type II crude) and *Candida cylindracea* (Type VII crude) lipases were purchased from Sigma Chemical Co. *Candida antarctica* lipase, SP 435 A + B, was a gift from Novo Nordisk Co. All reagents were of commercial quality and were purchased from Aldrich Chemie. *N*-Benzyloxycarbonyl derivatives of (±)-2-aminoalkan-1-ols, compounds (±)-**4a–d**, were obtained by the procedure described for the preparation of (±)-2-benzyloxycarbonylaminobutan-1-ol.[8] Solvents were distilled over an adequate desiccant and stored under argon. For column chromatography, Merck silica gel 60/230–400 mesh was used. M.p.s were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations, measured on a Perkin–Elmer 241 polarimeter, are recorded in units of 10^{-7} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin–Elmer 1720-X FT Infrared spectrophotometer. ^{1}H- and ^{13}C NMR were obtained with TMS (tetramethylsilane) as internal standard; using a Bruker AC-300 (^{1}H 300 MHz and ^{13}C 75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett-Packard 5987 A spectrometer. Microanalyses were performed on a Perkin–Elmer 240B elemental analyser. The yield of every compound has been calculated based on the percentage of conversion.

Configuration and E.e. Determination of the Compounds described.—The configuration and e.e of 2-aminopropan-1-ol and 2-aminobutan-1-ol derivatives were assigned by comparison of their optical rotation with authentic samples obtained from (*S*)-(+)-2-aminopropan-1-ol and (*R*)-(−)-2-aminobutan-1-ol. The configuration assignment for 2-aminopentan-1-ol and 2-aminohexan-1-ol derivatives was made by analogy with the other amino alcohols, and the e.e. was calculated by ^{1}H NMR spectroscopy using the chiral shift reagent tris[3-trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) or from the Mosher's ester derivative, for which, the difference in the chemical shifts of the diastereoisomeric mixture was enhanced by addition of the achiral shift reagent Eu(fod)$_3$.

Reaction of (±)-2-Aminoalkan-1-ols **1** *with Ethyl Acetate-catalyzed by PPL: General Procedure.*—PPL (5 g) was added to a solution of compound **1** (5 mmol) in ethyl acetate (35 cm^3) and the mixture was stirred at 30 °C (reaction times collected in Table 1). When the reaction was complete, the enzyme was filtered off and washed with ethyl acetate and dichloromethane. The combined filtrate and washings were evaporated, and chromatographic separation on silica (eluent: ethyl acetate–methanol 95:3) of the resulting residue yielded (*S*)-(−)-**2** and (*R*)-(+)-**3**.

(*S*)-(−)-2-*Acetylaminopropan*-1-*ol* (*S*)-(−)-**2a**. Yield, 65%, R_f 0.12, oil; $[\alpha]_D^{22}$ −5.1 (*c*, 0.92), 18% e.e. (Found: C, 51.2; H, 9.5; N, 11.95. $C_5H_{11}NO_2$ requires C, 51.26; H, 9.46; N, 11.96); ν_{max}(neat)/cm^{-1} 1654 (C=O); δ_H($CDCl_3$) 1.17 (d, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 3.51 (dd, 1 H, C*H*HOH), 3.65 (dd, 1 H, CH*H*OH), 3.75 (br s, 1 H, OH), 4.03 (m, 1 H, CH), 6.31 (br s, 1 H, NH); δ_C($CDCl_3$) 16.5 (CH_3), 22.7 (CH_3), 47.1 (CH), 65.5 (CH_2) and 170.9 (C=O); *m*/*z* 118 [(M + 1)$^+$, <1%] and 86 (100).

(*R*)-(+)-2-(*Acetylamino*)*propyl acetate* (*R*)-(+)-**3a**. Yield, 57%, R_f 0.40, m.p. 56–58 °C; $[\alpha]_D^{22}$ +35.8 (*c*, 0.85), 67% e.e. (Found: C, 52.8; H, 8.3; N, 8.8. $C_7H_{13}NO_3$ requires C, 52.82; H, 8.23; N, 8.80); ν_{max}(Nujol)/cm^{-1} 1740 and 1655 (C=O); δ_H($CDCl_3$) 1.18 (d, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 4.01 (dd, 1 H, C*H*HOH), 4.12 (dd, 1 H, CH*H*OH), 4.29 (m, 1 H, CH) and 4.78 (br s, 1 H, NH); δ_C($CDCl_3$) 16.8 (CH_3), 20.4 (CH_3), 22.8 (CH_3), 43.8 (CH), 66.5 (CH_2) 169.7 and 170.7 (C=O); *m*/*z* 159 (M$^+$, <1%) and 86 (100).

(*S*)-(−)-2-*Acetylaminopentan*-1-*ol* (*S*)-(−)-**2c**. Yield: 95%, R_f 0.20, oil; $[\alpha]_D^{22}$ −11.9 (*c*, 0.81), 41% e.e. (Found: C, 57.9; H, 10.45; N, 9.7. $C_7H_{15}NO_2$ requires C, 57.90; H, 10.41; N, 9.65); ν_{max}(neat)/cm^{-1} 1651 (C=O); δ_H($CDCl_3$) 0.91 (t, 3 H, CH_3), 1.28–1.60 (m, 4 H, CH_2), 2.01 (s, 3 H, CH_3), 3.05 (br s, 1 H, OH), 3.55 (dd, 1 H, C*H*HOH), 3.69 (dd, 1 H, CH*H*OH), 3.95 (m, 1 H, CH) and 5.96 (br s, 1 H, NH); δ_C($CDCl_3$) 13.4 (CH_3), 18.7 (CH_2), 22.5 (CH_3), 32.7 (CH_2), 50.9 (CH), 63.8 (CH_2) and 170.7 (C=O); *m*/*z* 145 (M$^+$, 2%), 72 (84) and 43 (100).

(±)-2-(*Acetylamino*)*pentyl acetate* (±)-**3c**. Yield, 90%, R_f 0.48, m.p. 61–63 °C (Found: C, 57.7; H, 9.2; N, 7.5. $C_9H_{17}NO_3$ requires C, 57.73; H, 9.15; N, 7.48); ν_{max}(Nujol)/cm^{-1} 1740 and 1649 (C=O); δ_H($CDCl_3$) 0.92 (t, 3 H, CH_3), 1.22–1.57 (m, 4 H, CH_2), 1.99 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 4.11 (m, 3 H, CH, CH_2OH) and 4.78 (br s, 1 H, NH); δ_C($CDCl_3$) 13.6 (CH_3), 18.8 (CH_2), 20.6 (CH_3), 23.0 (CH_3), 33.3 (CH_2), 47.8 (CH), 65.7 (CH_2) 169.7 and 170.8 (C=O); *m*/*z* 187 (M$^+$, 1%), 114 (65) and 72 (100).

(*S*)-(−)-2-*Acetylaminohexan*-1-*ol* (*S*)-(−)-**2d**. Yield: 95%, R_f 0.22, m.p. 59–60 °C; $[\alpha]_D^{22}$ −7.8 (*c*, 0.92), 32% e.e. (Found: C, 60.3; H, 10.75; N, 8.8. $C_8H_{17}NO_2$ requires C, 60.35; H, 10.76; N, 8.80); ν_{max}(KBr)/cm^{-1} 1653 (C=O); δ_H($CDCl_3$) 0.90 (t, 3 H, CH_3), 1.21–1.62 (m, 6 H, CH_2), 2.01 (s, 3 H, CH_3), 3.30 (br s, 1 H, OH), 3.56 (dd, 1 H, C*H*HOH), 3.69 (dd, 1 H, CH*H*OH), 3.91 (m, 1 H, CH) and 5.80 (br s, 1 H, NH); δ_C($CDCl_3$) 13.7 (CH_3), 22.4 (CH_2), 23.0 (CH_3), 28.0 (CH_2), 30.6 (CH_2), 51.5 (CH), 64.6 (CH_2) and 171.0 (C=O); *m*/*z* 160 [(M + 1)$^+$, 1%] and 86 (100).

(*R*)-(+)-2-(*Acetylamino*)*hexyl acetate* (*R*)-(+)-**3d**. Yield: 93%, R_f 0.55, m.p. 58–60 °C; $[\alpha]_D^{22}$ +10.6 (*c*, 0.705), 27% e.e. (Found: C, 59.65; H, 9.5; N, 7.0. $C_{10}H_{19}NO_3$ requires C, 59.68; H, 9.52; N, 6.96); ν_{max}(KBr)/cm^{-1} 1732 and 1649 (C=O); δ_H($CDCl_3$) 0.90 (t, 3 H, CH_3), 1.21–1.62 (m, 6 H, CH_2), 1.99 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 4.09 (m, 3 H, CH, CH_2OH)

and 5.69 (br s, 1 H, NH); $\delta_C(CDCl_3)$ 13.6 (CH_3), 20.5 (CH_3), 22.1 (CH_2), 22.9 (CH_3), 27.6 (CH_2), 30.8 (CH_2), 47.9 (CH), 65.6 (CH_2), 169.8 and 170.7 (C=O); *m/z* 201 (M^+, 1%), 86 (54) and 43 (100).

Enzymatic Esterification of (±)-2-*Benzyloxycarbonylaminoalkan*-1-*ols* **4**: *General Procedure*.—To a solution (±)-**4** (1 mmol) in ethyl acetate (20 cm^3) was added PPL (1 g). The suspension was stirred at 30 °C. When the reaction was complete, the enzyme was filtered off and washed with ethyl acetate and dichloromethane. The combined organic filtrate and workings were evaporated and flash chromatography on silica of the residue (eluent: ether–hexane 3:1), yielded the corresponding (*S*)-(−)-**4** and (*R*)-(+)-**5**.

(*S*)-(−)-2-*Benzyloxycarbonylaminopropan*-1-*ol* (*S*)-(−)-**4a**. Yield: 97%, R_f 0.18, m.p. 62–64 °C; $[\alpha]_D^{22}$ −5.0 (*c*, 0.48), 85% e.e. (Found: C, 63.2; H, 7.25; N, 6.7. $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.23; N, 6.69); ν_{max}(KBr)/cm^{-1} 1692 (C=O); $\delta_H(CDCl_3)$ 1.16 (d, 3 H, CH_3), 2.40 (br s, 1 H, OH), 3.53 (m, 1 H, C*H*HOH), 3.66 (m, 1 H, CH*H*OH), 3.83 (m, 1 H, CH), 4.92 (br s, 1 H, NH), 5.10 (s, 2 H, PhCH_2) and 7.35 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 17.2 (CH_3), 48.9 (CH), 66.6 (CH_2), 66.8 (CH_2), 128.0, 128.1, 128.5 (CH_{arom}), 136.3 (C_{arom}) and 156.5 (C=O); *m/z* 209 (M^+, 1%), 178 (14) and 91 (100).

(*R*)-(+)-2-(*Benzyloxycarbonylamino*)*propyl acetate* (*R*)-(+)-**5a**. Yield, 99%, R_f 0.46, m.p. 60–62 °C; $[\alpha]_D^{22}$ +12.1 (*c*, 0.56), 73% e.e. (Found: C, 62.1; H, 6.85; N, 5.6. $C_{13}H_{17}NO_4$ requires C, 62.14; H, 6.82; N, 5.57); ν_{max}(KBr)/cm^{-1} 1732 and 1693 (C=O); $\delta_H(CDCl_3)$ 1.18 (d, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 4.04 (m, 3 H, CH, CH_2OAc), 4.91 (br s, 1 H, NH), 5.09 (s, 2 H, PhCH_2) and 7.34 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 17.8 (CH_3), 21.0 (CH_3), 46.3 (CH), 66.9 (CH_2), 67.3 (CH_2), 128.3, 128.7 (CH_{arom}), 136.7 (C_{arom}), 155.9 and 171.2 (C=O); *m/z* 251 (M^+, 2%), 178 (7) and 91 (100).

(*S*)-(−)-2-*Benzyloxycarbonylaminobutan*-1-*ol* (*S*)-(−)-**4b**. Yield: 92%, R_f 0.21, m.p. 37–39 °C; $[\alpha]_D^{22}$ −23.4 (*c*, 0.71), 83% e.e. (Found: C, 64.5; H, 7.6; N, 6.25. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.67; N, 6.27); ν_{max}(KBr)/cm^{-1} 1694 (C=O); $\delta_H(CDCl_3)$ 0.94 (t, 3 H, CH_3), 1.40–1.72 (m, 2 H, CH_2), 2.25 (br s, 1 H, OH), 3.54–3.78 (m, 3 H, CH, CH_2OH), 4.94 (br s, 1 H, NH), 5.10 (s, 2 H, PhCH_2) and 7.34 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 10.2 (CH_3), 24.1 (CH_2), 54.4 (CH), 64.3 (CH_2), 66.5 (CH_2), 127.8, 127.9, 128.3 (CH_{arom}), 136.3 (C_{arom}) and 156.8 (C=O); *m/z* 223 (M^+, 1%), 192 (16) and 91 (100).

(*R*)-(+)-2-(*Benzyloxycarbonylamino*)*butyl acetate* (*R*)-(+)-**5b**. Yield: 96%, R_f 0.53, m.p. 66–67 °C; $[\alpha]_D^{22}$ +25.2 (*c* 0.52), 78% e.e. (Found: C, 63.4; H, 7.3; N, 5.4. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28); ν_{max}(KBr)/cm^{-1} 1744 and 1690 (C=O); $\delta_H(CDCl_3)$ 0.95 (t, 3 H, CH_3), 1.53 (m, 2 H, CH_2), 2.03 (s, 3 H, CH_3), 3.83 (m, 1 H, CH), 4.09 (m, 2 H, CH_2OAc), 4.79 (br s, 1 H, NH), 5.10 (s, 2 H, PhCH_2) and 7.35 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 10.2 (CH_3), 20.7 (CH_3), 24.8 (CH_2), 51.6 (CH), 65.7 (CH_2), 66.8 (CH_2), 128.1, 128.5 (CH_{arom}), 136.4 (C_{arom}), 156.0 and 170.9 (C=O); *m/z* 265 (M^+, 1%), 192 (11) and 91 (100).

(*S*)-(−)-2-*Benzyloxycarbonylaminopentan*-1-*ol* (*S*)-(−)-**4c**.—Yield: 99%, R_f 0.26, m.p. 71–73 °C; $[\alpha]_D^{22}$ −21.2 (*c*, 0.53), 99% e.e. (Found: C, 65.8; H, 8.1; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90); ν_{max}(KBr)/cm^{-1} 1691 (C=O); $\delta_H(CDCl_3)$ 0.93 (t, 3 H, CH_3), 1.32–1.58 (m, 4 H, CH_2), 2.24 (br s, 1 H, OH), 3.57 (m, 1 H, CH), 3.70 (m, 2 H, CH_2OH), 4.85 (br s, 1 H, NH), 5.10 (s, 2 H, PhCH_2) and 7.35 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 13.9 (CH_3), 19.1 (CH_2), 33.5 (CH_2), 53.0 (CH), 65.3 (CH_2), 66.8 (CH_2), 128.0, 128.1, 128.5 (CH_{arom}), 136.3 (C_{arom}) and 156.8 (C=O); *m/z* 237 (M^+, 1%), 206 (16) and 91 (100).

(*R*)-(+)-2-(*Benzyloxycarbonylamino*)*pentyl acetate* (*R*)-(+)-**5c**. Yield: 99%, R_f 0.57, m.p. 47–49 °C; $[\alpha]_D^{22}$ +25.8 (*c*, 0.59), 99% e.e. (Found: C, 64.5; H, 7.6; N, 5.1. $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01); ν_{max}(KBr)/cm^{-1} 1733 and 1689 (C=O); $\delta_H(CDCl_3)$ 0.93 (t, 3 H, CH_3), 1.32–1.58 (m, 4 H, CH_2), 2.03 (s, 3 H, CH_3), 3.95 (m, 1 H, CH), 4.08 (m, 2 H, CH_2OAc), 4.80 (br s, 1 H, NH), 5.10 (s, 2 H, PhCH_2) and 7.35 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 13.7 (CH_3), 18.8 (CH_2), 20.6 (CH_3), 33.7 (CH_2), 49.8 (CH), 66.0 (CH_2), 66.6 (CH_2), 128.0, 128.3 (CH_{arom}), 136.3 (C_{arom}), 155.8 and 170.8 (C=O); *m/z* 279 (M^+, 1%), 206 (12) and 91 (100).

(*S*)-(−)-2-*Benzyloxycarbonylaminohexan*-1-*ol* (*S*)-(−)-**4d**. Yield: 96%, R_f 0.30, m.p. 76–78 °C; $[\alpha]_D^{22}$ −19.8 (*c*, 0.54), 95% e.e. (Found: C, 66.9; H, 8.4; N, 5.6. $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57); ν_{max}(KBr)/cm^{-1} 1689 (C=O); $\delta_H(CDCl_3)$ 0.90 (t, 3 H, CH_3), 1.29–1.60 (m, 6 H, CH_2), 2.21 (br s, 1 H, OH), 3.59 (m, 1 H, CH), 3.71 (m, 2 H, CH_2OH), 4.89 (br s, 1 H, NH), 5.12 (s, 2 H, PhCH_2) and 7.38 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 13.9 (CH_3), 22.5 (CH_2), 28.1 (CH_2), 31.1 (CH_2), 53.3 (CH), 65.5 (CH_2), 66.8 (CH_2), 128.0, 128.1, 128.5 (CH_{arom}), 136.3 (C_{arom}) and 156.8 (C=O); *m/z* 251 (M^+, 1%), 220 (11) and 91 (100).

(*R*)-(+)-2-(*Benzyloxycarbonylamino*)*hexyl acetate* (*R*)-(+)-**5d**. Yield: 95%, R_f 0.60, m.p. 66–68 °C; $[\alpha]_D^{22}$ +23.6 (*c*, 0.59), 95% e.e. (Found: C, 65.5; H, 7.9; N, 4.8. $C_{16}H_{23}NO_4$ requires C, 65.51; H, 7.90; N, 4.77); ν_{max}(KBr)/cm^{-1} 1733 and 1691 (C=O); $\delta_H(CDCl_3)$ 0.92 (t, 3 H, CH_3), 1.28–1.58 (m, 6 H, CH_2), 2.05 (s, 3 H, CH_3), 3.91 (m, 1 H, CH), 4.09 (m, 2 H, CH_2OAc), 4.78 (br s, 1 H, NH), 5.12 (s, 2 H, PhCH_2) and 7.36 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 13.8 (CH_3), 20.6 (CH_3), 22.3 (CH_2), 27.7 (CH_2), 31.3 (CH_2), 50.1 (CH), 66.0 (CH_2), 66.5 (CH_2), 127.9, 128.0, 128.4 (CH_{arom}), 136.4 (C_{arom}), 155.9 and 170.8 (C=O); *m/z* 293 (M^+, 2%), 220 (5) and 91 (100).

Reactions of Compounds (±)-**4** *with Acetone* O-(*Benzyloxycarbonyl*)*oxime* **6** *catalyzed by PPL: General Method*.—Compounds **4** (0.5 mmol) and **6** (0.103 g, 0.5 mmol) were dissolved in CCl_4 (20 cm^3) and then PPL (0.5 g) was added. After the mixture had been stirred at 30 °C (reaction time is collected in Table 4), the enzyme was filtered off and washed with dichloromethane. The combined filtrate of washings were evaporated, and chromatographic separation on silica of the resulting residue yielded (*S*)-(−)-**4** and (*R*)-(+)-**7**.

(*R*)-(+)-*Benzyl* 2-(*benzyloxycarbonylamino*)*propyl carbonate* (*R*)-(+)-**7a**. Yield: 97%, R_f 0.23 (dichloromethane–ether–hexane 4:0.2:3), m.p. 73–75 °C; $[\alpha]_D^{22}$ +16.7 (*c*, 0.52), 92% e.e. (Found: C, 66.5; H, 6.1; N, 4.1. $C_{19}H_{21}NO_5$ requires C, 66.46; H, 6.16; N, 4.08); ν_{max}(KBr)/cm^{-1} 1750 and 1661 (C=O); $\delta_H(CDCl_3)$ 1.21 (d, 3 H, CH_3), 3.95–4.25 (m, 3 H, CH, CH_2OCO$_2$CH_2Ph), 4.95 (br s, 1 H, NH), 5.10 (s, 2 H, PhCH_2), 5.18 (s, 2 H, PhCH_2) and 7.39 (m, 10 H, Ph); $\delta_C(CDCl_3)$ 17.3 (CH_3), 45.9 (CH), 66.7 (CH_2), 69.8 (CH_2), 70.4 (CH_2), 128.0, 128.3, 128.4, 128.5 (CH_{arom}), 134.9, 136.3 (C_{arom}), 155.0 and 155.5 (C=O); *m/z* 252 (M^+ − CH_2Ph, 3%) and 91 (100).

(*R*)-(+)-*Benzyl* 2-(*benzyloxycarbonylamino*)*butyl carbonate* (*R*)-(+)-**7b**. Yield: 92%, R_f 0.58 (ether–hexane 3:1), m.p. 51–53 °C; $[\alpha]_D^{22}$ +31.7 (*c*, 0.64), 71% e.e. (Found: C, 67.2; H, 6.5; N, 4.0. $C_{20}H_{23}NO_5$ requires C, 67.21; H, 6.49; N, 3.92); ν_{max}(KBr)/cm^{-1} 1738 and 1692 (C=O); $\delta_H(CDCl_3)$ 0.94 (t, 3 H, CH_3), 1.56 (m, 2 H, CH_2), 3.82 (m, 1 H, CH), 4.18 (m, 2 H, CH_2OCO$_2$CH_2Ph), 4.86 (br s, 1 H, NH), 5.09 (s, 2 H, PhCH_2), 5.14 (s, 2 H, PhCH_2) and 7.33 (m, 10 H, Ph); $\delta_C(CDCl_3)$ 10.2 (CH_3), 24.4 (CH_2), 51.5 (CH), 66.6 (CH_2), 69.0 (CH_2), 69.7 (CH_2), 128.0, 128.3, 128.4, 128.5 (CH_{arom}), 134.9, 136.3 (C_{arom}), 155.0 and 155.9 (C=O); *m/z* 357 (M^+, 1%) and 91 (100).

(*R*)-(+)-*Benzyl* 2-(*benzyloxycarbonylamino*)*pentyl carbonate* (*R*)-(+)-**7c**. Yield: 95%, R_f 0.25 (ether–hexane 2:3), m.p. 64–66 °C; $[\alpha]_D^{22}$ +27.7 (*c*, 0.61), 99% e.e. (Found: C, 67.9; H, 6.8; N, 3.75. $C_{21}H_{25}NO_5$ requires C, 67.91; H, 6.78; N, 3.77); ν_{max}(KBr)/cm^{-1} 1737 and 1686 (C=O); $\delta_H(CDCl_3)$ 0.94 (t, 3

H, CH_3), 1.30–1.60 (m, 4 H, CH_2), 3.91 (m, 1 H, CH), 4.19 (m, 2 H, $CH_2OCO_2CH_2Ph$), 4.85 (br s, 1 H, NH), 5.10 (s, 2 H, $PhCH_2$), 5.18 (s, 2 H, $PhCH_2$) and 7.38 (m, 10 H, Ph); $\delta_C(CDCl_3)$ 13.7 (CH_3), 18.9 (CH_2), 33.5 (CH_2), 49.8 (CH), 66.7 (CH_2), 69.4 (CH_2), 69.7 (CH_2), 128.0, 128.3, 128.4, 128.5 (CH_{arom}), 135.0, 136.3 (C_{arom}), 155.0 and 155.8 (C=O); *m/z* 280 ($M^+ - CH_2Ph$, 4%) and 91 (100).

(R)-(+)-Benzyl 2-(benzyloxycarbonylamino)hexyl carbonate *(R)*-(+)-**7d**. Yield: 95%, R_f 0.24 (ether–hexane 1:2), m.p. 60–62 °C; $[\alpha]_D^{22}$ +22.0 (*c*, 0.55), 84% e.e. (Found: C, 68.5; H, 7.1; N, 3.7. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.06; N, 3.63); ν_{max}(KBr)/cm^{-1} 1744 and 1686 (C=O); $\delta_H(CDCl_3)$ 0.91 (t, 3 H, CH_3), 1.21–1.64 (m, 6 H, CH_2), 3.89 (m, 1 H, CH), 4.19 (m, 2 H, $CH_2OCO_2CH_2Ph$), 4.88 (br s, 1 H, NH), 5.09 (s, 2 H, $PhCH_2$), 5.18 (s, 2 H, $PhCH_2$) and 7.35 (m, 10 H, Ph); $\delta_C(CDCl_3)$ 13.8 (CH_3), 22.3 (CH_2), 27.8 (CH_2), 31.1 (CH_2), 50.1 (CH), 66.7 (CH_2), 69.4 (CH_2), 69.7 (CH_2), 128.0, 128.3, 128.4, 128.5 (CH_{arom}), 135.0, 136.3 (C_{arom}), 155.0 and 155.8 (C=O); *m/z* 294 ($M^+ - CH_2Ph$, 2%) and 91 (100).

Hydrogenolysis of the O-Benzyloxycarbonyl Derivatives.—These reactions were carried out as it was described by Felix *et al.*[10] From compounds *(R)*-(+)-**5a–d** were obtained the corresponding amides *(R)*-(+)-**2a–d** in 80–90% yield. No racemization was observed.

From compounds *(S)*-(−)-**4a–d** and *(R)*-(+)-**7a–d** were obtained *(S)*-(+)-**1a–d** and *(R)*-(−)-**1a–d** respectively; yields, 85–90%. *(S)*-(+)-**1a**, $[\alpha]_D^{22}$ +19.0 (*c*, 2.15, EtOH), 85% e.e.; Aldrich catalogue $[\alpha]_D^{20}$ +18.0 (neat), 98%. *(S)*-(+)-**1b**, $[\alpha]_D^{22}$ +10.5 (*c*, 2.05, EtOH), 83% e.e.; Aldrich catalogue $[\alpha]_D^{20}$ +10.0 (neat), 98%. *(S)*-(+)-**1c**, $[\alpha]_D^{22}$ +6.5 (*c*, 0.38, $CHCl_3$), 99% e.e. *(S)*-(+)-**1d**, $[\alpha]_D^{22}$ +12.3 (*c*, 0.56, $CHCl_3$), 95% e.e.

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