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Practical Enzymatic Route to Optically Active 3-Hydroxyamides. Synthesis of 1,3-Aminoalcohols

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Abstract: *Candida antarctica* lipase (CAL) is a very efficient catalyst for the enantioselective aminolysis of different racemic 3-hydroxyesters with aliphatic amines. The degree of enantioselectivity exhibited by the lipase depends on the substrate and nucleophile, but in the most cases, the *E* values obtained are very satisfactory. CAL also catalyzes the aminolysis of ethyl (±)-3,4-epoxybutyrate and the epoxyamide was achieved with high e.e. The chemical reduction of the 3-hydroxyamides obtained by enzymatic aminolysis yields the corresponding 1,3-aminoalcohols.

Introduction

The development of methods for the synthesis of amides is a goal for the organic chemists because the amide bond is present in a large range of compounds whose therapeutic activity is well known.[1] Although the direct conversion of esters to amides is an useful synthetic operation, in general, drastic reaction conditions such as high temperatures, long reaction times or strong alkali metal as catalysts,[2] which are not compatible with sensitive functionality, are required. Milder reaction conditions are used for the synthesis of ω-hydroxyamides by aminolysis of lactones either using metal amides[3] or catalysts.[4]

On the other hand, the application of biocatalysis in organic synthesis is at present a very advantageous alternative to the conventional methods, as proved by the current rich literature in this field.[5] With respect to the enzymatic aminolysis reaction, proteolytic enzymes such as α-chymotrypsin, papain or trypsin have been efficiently used for the peptide synthesis[6] and for the preparation of peptide C-terminal amides.[7] In addition, the capability of different lipases to catalyze peptide synthesis from D or L aminoacids has been investigated.[8] Lipases have several advantages over the proteolytic enzymes such as their stability in organic solvents and, most important, the no hydrolysis of peptide bond. This last advantage made the aminolysis reaction specially attractive for the resolution of racemic esters because the most usual methods, transesterification or esterification, often display the inconvenience of reversibility,[9] and so the removal of water is necessary by molecular

sieves,[10] or the use of activated esters[11] or oxime[12] esters. Nevertheless, the enantioselective properties of the lipases have much less been exploited in the amidation reaction.

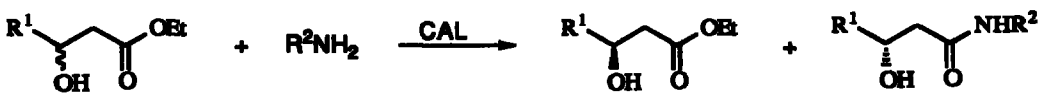
Over the last few years one of our objectives has been to investigate the enantioselective aminolysis reaction.[13] Currently, we are interested in the lipase catalyzed amidation of β-hydroxyesters. Both these substrates and the resulting β-hydroxyamides have a great importance as building blocks for the preparation of many bioactive natural products.[14] Moreover, the development of an efficient route towards optically active β-hydroxyamides could be very useful since they are precursors of 1,3-aminoalcohols, which possess pharmaceutical properties as antidepressants (Tomoxetine, Fluoxetine, and Nisoxetine)[15] and are starting materials in the synthesis of some antibiotics.[16]

Results and Discussion

In a preliminary communication[17] we have showed that *Pseudomonas cepacia* lipase and *Candida antarctica* lipase (CAL) catalyze the aminolysis of ethyl (±)-3-hydroxybutyrate (**1**). Both lipases displayed opposite stereochemical preference, but the most significant difference of behaviour was the degree of enantioselectivity exhibited. CAL, an acrylic resin supported lipase, proved to be the most efficient catalyst.

In order to widen the utility of this catalyst for the synthesis of a range of 3-hydroxyamides and to study the substrate structural requeriments of the lipase, we have investigated the amidation of different 3-hydroxyesters with varying sized amines (Scheme I). All the reactions are carried out in the same conditions as for **1**, that is, room temperature and dioxane as solvent.

Scheme 1



1	$R^1 = CH_3$	**4 a-e**	(*S*)-(+)-**1**	(*R*)-(-)-**5 a-e**
2	$= CH_2CH_3$		(*S*)-(+)-**2**	(*R*)-(-)-**6 a-e**
3	$= CH_2Cl$		(*R*)-(+)-**3**	(*S*)-(-)-**7 a-e**

The substrate has a strong influence on the catalytic activity of the enzyme. As it is shown in the Table, for the same nucleophile, for instance benzylamine, the change of a methyl for a chloromethyl group causes a noticeable increase of the rate of reaction. This fact is of particular importance in the case of ester **3**, since the nucleophilic substitution of the chloride by the amine could compete with the amidation if long reaction times were necessary. With respect to the nucleophile, the general trend is an increase in the reaction rate with the lengthening of the chain, as expected from the well-known fact that the more lipophilic is a substrate, the more efficiently is accepted by lipases.

In the most cases the enantiomeric ratios (*E* values)[18] calculated from the percentage of conversion[18]

and the ee[19] of substrate and product are very satisfactory. This means that by an adequate selection of the extent of conversion it should be possible to obtain the product with very high enantiomeric excesses. It is interesting to note the high E values (>100) obtained in the amidation of **1**, **2**, and **3** with benzyl-, octyl-, and dodecylamine, respectively. These nucleophiles should be chosen if the end is to get the ester with high optical and chemical yields.

Table. CA Lipase-Catalyzed Aminolysis of Esters 1-3

						Amide		Ester	
Ester	R^1	Amine	R^2	t, h	conv.[a] %	$[\alpha]_D^{22}$ (c, $CHCl_3$)	ee,[b] %	ee,[b] %	E[a]
1	CH_3	4a	*n*-Butyl	11	46	-27.5 (0.68)	79	67	17
		4b	Allyl	14	41	-30.6 (0.75)	75	52	12
		4c	Benzyl	21	45	-33.8 (0.96)	>99	82	>100
		4d	*n*-Octyl	1	20	-20.8 (0.97)	92	23	30
		4e	*n*-Dodecyl	1	26	-16.0 (0.99)	94	33	44
2	CH_3CH_2	4a	*n*-Butyl	5	56	-20.0 (0.92)	75	96	27
		4b	Allyl	1.5	48	-30.4 (1.10)	94	86	79
		4c	Benzyl	7	55	-21.1 (1.04)	82	>99	52
		4d	*n*-Octyl	1	29	-24.3 (1.05)	>99	40	>100
		4e	*n*-Dodecyl	1	40	-16.2 (0.99)	81	55	18
3	CH_2Cl	4a	*n*-Butyl	1	36	-24.7 (1.01)	92	52	43
		4b	Allyl	1.2	43	-24.3 (1.02)	90	68	39
				2	55	-20.4 (1.12)	80	98	40
		4c	Benzyl	2	50	-22.8 (0.97)	98	>99	>100
		4d	*n*-Octyl	1	41	-17.0 (1.00)	83	58	20
		4e	*n*-Dodecyl	1	35	-14.0 (1.03)	>99	53	>100

[a] See ref 18. [b] See ref 19.

We wish also to emphasize the results obtained in the reaction of the chloroester **3** with benzylamine; at 50% of conversion both amide and ester are obtained with e.e. >99% and 98% respectively. This chloroester has been used for the preparation of aminoacids such as L-carnitine,[20] and other cholesterol antagonist compounds.[21]

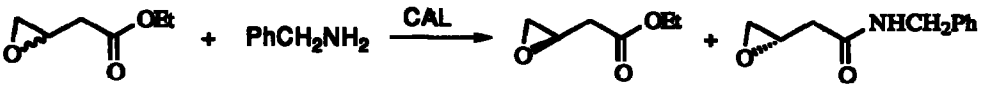
The high catalytic efficiency of the CAL in the aminolysis of these 3-hydroxyesters prompted us to test the aminolysis of another structurally relationed ester, ethyl (±)-3-hydroxy-3-phenylpropionate. Its amidation using benzylamine takes place with only 11% of conversion after 264 h, and the corresponding (*S*)-amide is obtained with moderate e.e. (66%, E = 15). When the reaction is conducted at 60°C, an increase of rate is observed (20% of conversion after 96 h), but at this temperature CAL displays a very low enantioselectivity (E =

1).

As one can deduce of the results, the behaviour of CAL is influenced by the substrate and the nucleophile. However, the lipase always exhibits the same stereochemical preference toward all the substrates. Probably, the hydroxyl group predetermines the accomodation of the ester in the binding domain of the enzyme.

On the other hand, we also thought of interest to check the catalytic potential of CAL in the aminolysis of ethyl (±)-3,4-epoxybutyrate (8), which was obtained from ethyl (±)-4-chloro-3-hydroxybutyrate according to the method developed by McClure.[22] This substrate is very sensitive to the presence of basic compounds; thus, when the epoxyester is allowed to react with benzylamine, the opening of the oxirane ring takes place. However, the reaction of 8 with benzylamine (4c) in presence of CAL as catalyst (Scheme 2) yields the 3,4-epoxyamide 9 and (*R*)-(8) with 84% e.e.[23] and 32% e.e.[23], respectively. In this reaction, 27% of conversion was achieved after 3 h, and the enantiomeric ratio was moderate ($E = 15$).

Scheme 2



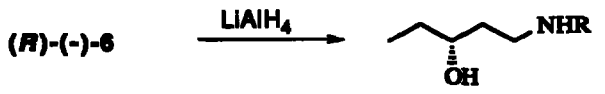
8 (*R*)-(+)-8 32% e.e. (*S*)-(-)-9 85% e.e.

It should be pointed out the economic efficiency of CAL in these processes, as proved by the fact that it could be recycled twenty times without appreciable loss of catalytic activity.

Finally, we have carried out the reduction of the 3-hydroxyamides obtained in the enzymatic reactions with lithium aluminum hydride (Scheme 3), using a 1:1.5 molar ratio hydroxyamide/hydride. The reactions are performed in dioxane as solvent at 65°C for 12 h, and the corresponding 1,3-aminoalcohols are obtained with 75-90% yield. On these reduction conditions, both the reduction of the chlorine group of 7, and the allyl group of amides 5b, 6b, and 7b, take place.

Scheme 3

(*R*)-(+)-10 a-e



(*R*)-(+)-11 a-e

a: R = *n*-butyl. b: R = *n*-propyl
c: R = benzyl. d: R = *n*-octyl
e: R = *n*-dodecyl.

Conclusions

In conclusion, we have developed a very simple and efficient method to obtain 3-hydroxyamides with very high optical and chemical yield from racemic 3-hydroxyesters, using *Candida antarctica* lipase as catalyst. This lipase also catalyzes the amidation of ethyl (±)-3,4-epoxybutyrate. These 3-hydroxyamides obtained are starting materials for the synthesis of optically active 1,3-aminoalcohols.

Experimental Section

General. *Candida antarctica* lipase, SP 435 A, was gifted by Novo Nordisk Co. All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Precoated TLC plates silica gel 60 F_{254} from Merck were used, and for column chromatography, Merck silica gel 60/230-400 mesh was used. Mp's were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1720-X FT Infrared spectrophotometer. ^{1}H- and ^{13}C-NMR were obtained with $CDCl_3$ as solvent and 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.

General Procedure for the Enzymatic Aminolysis of (±)-3-Hydroxyesters. 5 mmol of ester and 5 mmol of amine were added to a suspension of CA lipase (300 mg) in dioxane (20 mL) under nitrogen atmosphere. The mixture was shaken at 30°C and 250 rpm during the time indicated in Table. Then, the enzyme was filtered, washed with dichloromethane and the organic solvents were evaporated. The residue was subjected to column chromatography using hexane-ethyl acetate 1:1 as eluent.

(*R*)-*N*-Butyl-3-hydroxybutyramide (5a): oil; IR (neat) 1641 cm^{-1}; ^{1}H NMR δ 0.94 (t, 3H, J = 7.3, CH_3), 1.22 (d, 3H, J = 6.3, CH_3), 1.24-1.55 (m, 4H, $2CH_2$), 2.27 [dd, 1H, J = 4.2, J = 2.0, C*H*HC(O)NR], 2.35 [dd, 1H, J = 4.2, J = 0.8, CH*H*C(O)NR], 3.20 (q, 2H, J = 5.9, CH_2), 3.86 (bs, 1H, OH), 4.21 (m, 1H, C*H*OH), 5.90 (bs, 1H, NH); ^{13}C NMR δ 13.59 (CH_3), 19.94 (CH_3), 22.75 (CH_2), 31.41 (CH_2), 38.99 (CH_2), 43.81 (CH_2), 64.76 (CH), 172.38 (C=O); MS (70 eV) *m/z* 159 (M^+, 14), 43 (100). Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.79. Found: C, 60.44; H, 10.80; N, 8.75.

(*R*)-*N*-Allyl-3-hydroxybutyramide (5b): oil; IR (neat) 1631 cm^{-1}; ^{1}H NMR δ 1.24 (d, 3H, J = 6.0, CH_3), 2.31 [dd, 1H, J = 15.1, J = 8.0, C*H*HC(O)NR], 2.40 [dd, 1H, J = 15.1, J = 4.1, CH*H*C(O)NR], 3.00 (bs, 1H, OH), 3.80 (m, 2H, CH_2), 4.21(m, 1H, C*H*OH), 5.12-5.28 (m, 2H, $=CH_2$), 5.83 (m, 1H, CH=), 6.30 (bs, 1H, NH); ^{13}C NMR δ 22.66 (CH_3), 41.34 (CH_2), 43.93 (CH_2), 64.49 (CH), 115.74 (CH_2), 133.44 (CH), 172.29 (C=O); MS (70 eV) *m/z* 143 (M^+, 5), 57 (100). Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72;

H, 9.15; N, 9.78. Found: C, 58.84, H, 9.35, N, 9.75.

(*R*)-*N*-Benzyl-3-hydroxybutyramide (5c): mp 84-85°C; IR (KBr disk) 1639 cm^{-1}; ^{1}H-NMR δ 1.22 (d, 3H, *J* = 6.3, CH_3), 2.23-2.44 [m, 2H, $CH_2C(O)NR$], 4.21 (m, 1H, CH), 4.47 (d, 2H, *J* = 5.7, CH_2Ph), 6.22 (bs, 1H, NH), 7.23-7.42 (m, 5H, Ph); ^{13}C-NMR δ 22.78 (CH_3), 43.23 (CH_2), 43.81 (CH_2), 64.74 (CH), 127.40, 127.54, 128.58 ($CH_{aromatic}$), 137.91 ($C_{aromatic}$), 172.25 (C=O); MS (70 eV) *m/z* 193 (M^+, 3), 106 (100). Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.35; H, 7.90; N, 7.30.

(*R*)-3-Hydroxy-*N*-octylbutyramide (5d): mp 45-46°C; IR (KBr disk) 1637 cm^{-1}; ^{1}H NMR δ 0.87 (t, 3H, *J* = 6.2, CH_3), 1.20-1.50 (m, 15H, CH_3, $6CH_2$), 2.10-2.40 (m, 2H, CH_2), 3.24 (q, 2H, *J* = 6.6, CH_2), 3.90 (d, 1H, OH), 4.17 (m, 1H, C*H*OH), 5.80 (bs, 1H, NH); ^{13}C NMR δ 13.87 (CH_3), 22.40 (CH_2), 22.61 (CH_2), 26.70 (CH_2), 29.02 (CH_2), 29.29 (CH_2), 31.50 (CH_2), 39.20 (CH_2), 43.61 (CH_2), 64.64 (CH), 172.19 (C=O); MS (70 eV) *m/z* 215 (M^+, 18), 117 (100). Anal. Calcd. for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70; N, 6.50. Found: C, 66.81; H, 11.68; N, 6.58.

(*R*)-*N*-Dodecyl-3-hydroxybutyramide (5e): mp 65-66°C; IR (KBr disk) 1633 cm^{-1}; ^{1}H NMR δ 0.88 (t, 3H, *J* = 6.5, CH_3), 1.20-1.53 (m, 23H, CH_3, $10CH_2$), 2.10-2.40 (m, 2H, CH_2), 3.24 (q, 2H, *J* = 6.7, CH_2), 3.85 (bs, 1H, OH), 4.14 (m, 1H, C*H*OH), 5.81 (bs, 1H, NH); ^{13}C NMR δ 13.75 (CH_3), 22.32 (CH_2), 22.53 (CH_2), 26.67 (CH_2), 29.02 (CH_2), 29.31 (CH_2), 31.59 (CH_2), 39.08 (CH_2), 43.50 (CH_2), 64.55 (CH), 172.22 (C=O); MS (70 eV) *m/z* 271 (M^+, 10), 43 (100). Anal. Calcd. for $C_{16}H_{33}NO_2$: C, 70.80; H, 12.25; N, 5.16. Found: C, 70.68; H, 12.32; N, 5.36.

(*R*)-*N*-Butyl-3-hydroxyvaleramide (6a): mp 36-37°C; IR (KBr disk) 1649 cm^{-1}; ^{1}H NMR δ 0.90-0.95 (m, 6H, $2CH_3$), 1.22-1.61 (m, 6H, $3CH_2$), 2.24 [dd, 1H, *J* = 15.4, *J* = 8.9, C*H*HC(O)NR], 2.38 [dd, 1H, *J* = 15.4, *J* = 2.8, CH*H*C(O)NR], 3.23 (m, 2H, CH_2), 3.88 (m, 1H, CH), 4.27 (d, 1H, OH), 6.58 (bs, 1H, NH); ^{13}C NMR δ 9.44 (CH_3), 13.32 (CH_3), 19.65 (CH_2), 29.39 (CH_2), 31.10 (CH_2), 38.69 (CH_2), 41.50 (CH_2), 69.63 (CH), 172.28 (C=O); MS (70 eV) *m/z* 173 (M^+, 4), 57 (100). Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.31; H, 11.12; N, 8.01.

(*R*)-*N*-Allyl-3-hydroxyvaleramide (6b): mp 41-42°C; IR (KBr disk) 1633 cm^{-1}; ^{1}H NMR δ 0.95 (t, 3H, *J* = 7.4, CH_3), 1.42-1.66 (m, 2H, CH_2), 2.18-2.45 [m, 2H, $CH_2C(O)NR$], 3.71 (d, 1H, OH), 3.82-3.98 (m, 3H, CH, CH_2), 5.12-5.25 (m, 2H, $=CH_2$), 5.85 (m, 1H, CH=), 6.58 (bs, 1H, NH); ^{13}C NMR δ 9.56 (CH_3), 29.54 (CH_2), 41.41 (CH_2), 41.80 (CH_2), 69.72 (CH), 115.90 (CH_2), 133.64 (CH), 172.40 (C=O); MS (70 eV) *m/z* 157 (M^+, 2), 41 (100). Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.90. Found: C, 61.00; H, 9.54; N, 8.98.

(*R*)-*N*-Benzyl-3-hydroxyvaleramide (6c): mp 60-61°C; IR (KBr disk) 1631 cm^{-1}; ^{1}H-NMR δ 0.92 (t, 3H, *J* = 7.4, CH_3), 1.60 (m, 2H, CH_2), 2.27 [dd, 1H, *J* = 15.2, *J* = 8.9, C*H*HC(O)NR], 2.40 [dd, 1H, *J* = 15.2, *J* = 3.2, CH*H*C(O)NR], 3.63 (d, 1H, OH), 3.93 (m, 1H, CH), 4.41 (d, 2H, *J* = 5.7, CH_2Ph), 6.30 (bs, 1H, NH), 7.20-7.39 (m, 5H, Ph); ^{13}C-NMR δ 9.69 (CH_3), 29.67 (CH_2), 41.84 (CH_2), 43.13

(CH_2), 69.84 (CH), 127.29, 127.44, 128.50 ($CH_{aromatic}$), 137.90 ($C_{aromatic}$), 172.43 (C=O); MS (70 eV) *m/z* 207 (M+, 18), 91 (100). Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.26; N, 6.75. Found: C, 69.46; H, 8.07; N, 6.86.

(*R*)-3-Hydroxy-*N*-octylvaleramide (6d): mp 46-47°C; IR (KBr disk) 1631 cm^{-1}; ^1H NMR δ 0.84-0.99 (m, 6H, $2CH_3$), 1.27-1.60 (m, 14H, $7CH_2$), 2.18-2.42 (m, 2H, CH_2), 3.23 (q, 2H, *J* = 7.0, CH_2), 3.90 (m, 1H, C*H*OH), 4.08 (bs, 1H, OH), 6.26 (bs, 1H, NH); ^{13}C NMR δ 9.69 (CH_3), 13.97 (CH_3), 22.53 (CH_2), 26.81 (CH_2), 29.16 (CH_2), 29.45 (CH_2), 29.59 (CH_2), 31.73 (CH_2), 39.30 (CH_2), 41.72 (CH_2), 69.90 (CH), 172.40 (C=O); MS (70 eV) *m/z* 229 (M+, 12), 200 (100). Anal. Calcd. for $C_{13}H_{27}NO_2$: C, 68.07; H, 11.86; N, 6.10. Found: C, 68.23; H, 11.71; N, 6.15.

(*R*)-*N*-Dodecyl-3-hydroxyvaleramide (6e): mp 66-67°C; IR (KBr disk) 1631 cm^{-1}; ^1H NMR δ 0.84-1.00 (m, 6H, $2CH_3$), 1.19-1.58 (m, 22H, $11CH_2$), 2.20-2.33 (m, 2H, CH_2), 3.24 (q, 2H, *J* = 6.7, CH_2), 3.78 (d, 1H, *J* = 3.3, OH), 3.90 (m, 1H, C*H*OH), 5.84 (bs, 1H, NH); ^{13}C NMR δ 9.62 (CH_3), 13.85 (CH_3), 22.39 (CH_2), 26.72 (CH_2), 28.98 (CH_2), 29.02 (CH_2), 29.27 (CH_2), 29.57 (CH_2), 31.54 (CH_2), 39.20 (CH_2), 41.66 (CH_2), 69.83 (CH), 172.40 (C=O); MS (70 eV) *m/z* 285 (M+, 10), 131 (100). Anal. Calcd. for $C_{17}H_{35}NO_2$: C, 75.53; H, 12.35; N, 4.90. Found: C, 75.68; H, 12.48; N, 4.92.

(*S*)-*N*-Butyl-4-chloro-3-hydroxybutyramide (7a): mp 30-31°C; IR (KBr disk) 1637 cm^{-1}; ^1H NMR δ 0.91 (t, 3H, *J* = 7, CH_3), 1.20-1.59 (m, 4H, $2CH_2$), 2.49 (m, 2H, CH_2), 3.24 (q, 2H, CH_2), 3.60 (d, *J* = 5.4, 2H, CH_2Cl), 4.23 (m, 1H, C*H*OH), 4.50 (bs, 1H, OH), 6.30 (bs, 1H, NH); ^{13}C NMR δ 13.28 (CH_3), 19.61 (CH_2), 30.93 (CH_2), 38.87 (CH_2), 39.40 (CH_2), 47.98 (CH_2), 68.12 (CH), 171.04 (C=O); MS (70 eV) *m/z* 195 [(M+2)+, 3), 193 (M+, 9), 144 (100). Anal. Calcd. for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; N, 7.23. Found: C, 49.52; H, 8.40; N, 7.38.

(*S*)-*N*-Allyl-4-chloro-3-hydroxybutyramide (7b): mp 58-59°C; IR (KBr disk) 1649 cm^{-1}; ^1H NMR δ 2.50 [dd, 1H, C*H*HC(O)NR], 2.59 [dd, 1H, CH*H*C(O)NR], 3.59 (d, 2H, *J* = 8.0, CH_2Cl), 3.90 (t, 2H, *J* = 5.6, CH_2), 4.11 (bs, 1H, OH), 4.22 (m, 1H, C*H*OH), 5.12-5.30 (m, 2H, $=CH_2$), 5.74-5.96 (m, 1H, CH=), 6.20 (bs, 1H, NH); ^{13}C NMR δ 39.26 (CH_2), 41.62 (CH_2), 47.97 (CH_2), 68.26 (CH), 116.35 (CH_2), 133.40 (CH), 170.89 (C=O); MS (70 eV) *m/z* 177 (M+, 2),57 (100). Anal. Calcd. for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.80; N, 7.88. Found: C, 47.39; H, 6.69; N, 7.82.

(*S*)-*N*-Benzyl-4-chloro-3-hydroxybutyramide (7c): mp 85-86°C; IR (KBr disk) 1631 cm^{-1}; ^1H-NMR δ 2.54 (m, 2H, CH_2), 3.58 (d, 2H, *J* = 4.7, CH_2Cl), 4.23 (m, 1H, CH), 4.46 (d, 2H, *J* = 5.7, CH_2Ph), 6.27 (bs, 1H, NH), 7.23-7.39 (m, 5H, Ph); ^{13}C-NMR δ 38.61 (CH_2), 42.75 (CH_2), 47.32 (CH_2), 67.64 (CH), 126.79, 127.88 ($CH_{aromatic}$), 136.81 ($C_{aromatic}$), 170.24 (C=O); MS (70 eV) *m/z* 229 [(M+2)+, 4], 227 (M+, 12), 91 (100). Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.19; N, 6.15. Found: C, 57.87; H, 6.02; N, 6.20.

(*S*)-4-Chloro-3-hydroxy-*N*-octylbutyramide (7d): mp 57-58°C; IR (KBr disk) 1631 cm^{-1}; ^1H NMR δ 0.80 (t, 3H, *J* = 5.7, CH_3), 1.09-1.58 (m, 12H, $6CH_2$), 2.30-2.57 (m, 2H, CH_2), 3.06-3.24 (q, 2H,

J = 7.4, CH_2), 3.50 (m, 2H, CH_2Cl), 4.15 (m, 1H, C*H*OH), 4.80 (bs, 1H, OH), 6.71 (bs, 1H, NH); ^{13}C NMR δ 13.70 (CH_3), 22.24 (CH_2), 26.57 (CH_2), 28.82 (CH_2), 28.87 (CH_2), 29.00 (CH_2), 31.39 (CH_2), 39.27 (CH_2), 39.35 (CH_2), 47.99 (CH_2), 68.16 (CH), 171.08 (C=O); MS (70 eV) *m/z* 251 [(M+2)+, 2], 249 (M+, 6), 200 (100). Anal. Calcd. for $C_{12}H_{24}ClNO_2$: C, 57.70; H, 9.68; N, 5.60. Found: C, 57.58; H, 9.82; N, 5.55.

(*S*)-*N*-Dodecyl-4-chloro-3-hydroxybutyramide (7e): mp 80-81°C; IR (KBr disk) 1612 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.5, CH_3), 1.25-1.55 (m, 20H, $10CH_2$), 2.48 (m, 2H, CH_2), 3.26 (q, 2H, J = 6.6, CH_2), 3.49-3.65 (m, 2H, CH_2Cl), 4.12 (m, 1H, C*H*OH), 4.22 (d, 1H, OH), 5.82 (bs, 1H, NH); ^{13}C NMR δ 13.94 (CH_3), 22.48 (CH_2), 26.70 (CH_2), 29.06 (CH_2), 29.15 (CH_2), 29.23 (CH_2), 29.34 (CH_2), 29.37 (CH_2), 29.42 (CH_2), 31.70 (CH_2), 39.06 (CH_2), 39.38 (CH_2), 47.85 (CH_2), 68.37 (CH), 171.00 (C=O); MS (70 eV) *m/z* 307 [(M+2)+, 2], 305 (M+, 6), 150 (100). Anal. Calcd. for $C_{16}H_{32}ClNO_2$: C, 62.82; H, 10.54; N, 4.58. Found: C, 62.69; H, 10.35; N, 4.49.

(*S*)-*N*-Benzyl-3-hydroxy-3-phenylpropanamide: mp 105-106°C. $[\alpha]_D^{22}$ -34.7 (c, 0.49, $CHCl_3$), 66%e.e.; IR (Nujol) 1637 cm^{-1}; ^1H-NMR δ 2.60 [m, 2H, $CH_2C(O)NR$], 4.11 (d, 1H, OH), 4.43 (d, 2H, J = 5.7, CH_2Ph), 5.12 (m, 1H, CH), 6.15 (bs, 1H, NH), 7.10-7.45 (m, 10H, Ph); ^{13}C-NMR δ 43.27 (CH_2), 44.48 (CH_2), 70.71 (CH), 125.45, 127.37, 128.37, 128.55 ($CH_{aromatic}$), 137.66, 142.83 ($C_{aromatic}$), 171.54 (C=O); MS (70 eV) *m/z* 255 (M+, 6), 160 (100). Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.10; H, 6.53; N, 5.60.

(*S*)-*N*-Benzyl-3,4-epoxybutyramide (9): mp 69-70°C. $[\alpha]_D^{22}$ -43.0 (c, 0.54, $CHCl_3$), 85%e.e.; IR (KBr disk) 1647 cm^{-1}; ^1H-NMR δ 2.29 [dd, 1H, J = 6.6, J = 1.6, C*H*HC(O)NR], 2.50-2.75 [m, 2H, CH*H*C(O)NR, C*H*HO], 2.84 (t, 1H, J = 1.2, CH*H*O), 3.25 (m, 1H, CH), 4.19 (d, 2H, J = 1.8, CH_2Ph), 6.18 (bs, 1H, NH), 7.17-7.40 (m, 5H, Ph); ^{13}C-NMR δ 39.40 (CH_2), 43.23 (CH_2), 46.87 (CH_2), 48.66 (CH), 127.21, 127.41, 128.42 ($CH_{aromatic}$), 137.79 ($C_{aromatic}$), 169.23 (C=O); MS (70 eV) *m/z* 191 (M+, 6), 91 (100). Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.98; H, 6.87, N, 7.40.

General Procedure for the Reduction of 3-Hydroxyamides. 3-Hydroxyamide (8 mmol) was added to a suspension of $LiAlH_4$ (12 mmol) in anhydrous dioxane (20 mL). The mixture was stirred at 65°C for 12h, and then quenched by addition of MeOH. The organic solution was separated and the resulting solid was washed with water, dried with Na_2SO_4, and evaporated to yield the corresponding 1,3-aminoalcohol.

(*R*)-4-Butylamino-2-butanol (10a): Yield, 83%, oil. $[\alpha]_D^{22}$ +14.3 (c, 0.97, $CHCl_3$), 92% e.e.; ^1H NMR δ 0.92 (t, 3H, J = 7.8, CH_3), 1.16 (d, 3H, J = 7.4, CH_3), 1.21-1.68 (m, 6H, $3CH_2$), 2.48-3.06 (m, 4H, $2CH_2$), 3.63 (bs, 2H, NH, OH), 4.01 (m, 1H, C*H*OH). ^{13}C NMR δ 13.66 (CH_3), 20.08 (CH_2), 23.34 (CH_3), 31.19 (CH_2), 36.10 (CH_2), 48.14 (CH_2), 48.83 (CH_2), 68.80 (CH). MS (70 eV) *m/z* 145 (M+, 1), 45 (100). Anal. Calcd. for $C_8H_{19}NO$: C, 66.15; H, 13.18; N, 9.60. Found: C, 66.24; H, 13.09; N, 9.72.

(*R*)-4-Propylamino-2-butanol (10b): Yield, 76%, oil. $[\alpha]_D^{22}$ +17.0 (c, 0.93, $CHCl_3$), 90% e.e.;

^{1}H NMR δ 0.92 (t, 3H, J = 6.9, CH_3), 1.28 (d, 3H, J = 6.8, CH_3), 1.50 (m, 4H, CH_2), 2.41-3.08 (m, 4H, $2CH_2$), 3.50 (bs, 1H, OH), 3.96 (m, 1H, C*H*OH); ^{13}C NMR δ 11.50 (CH_3), 22.16 (CH_3), 23.50 (CH_2), 35.97 (CH_2), 48.12 (CH_2), 50.90 (CH_2), 68.89 (CH). MS (70 eV) *m/z* 131 (M^+, 1), 45 (100). Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.67. Found: C, 63.92, H, 13.12, N, 10.54.

(*R*)-4-Benzylamino-2-butanol (10c): Yield, 85%, oil. $[\alpha]_D^{22}$ +16.3 (c, 0.90, $CHCl_3$), >99% e.e.; ^{1}H-NMR δ 1.25 (d, 3H, J = 6.4, CH_3), 1.56 (m, 2H, CH_2), 2.72-3.05 (m, 2H, CH_2), 3.90 (d, 2H, J = 7.6, CH_2Ph), 3.39-3.56 (bs, 2H, NH, OH), 4.01 (m, 1H, C*H*OH), 7.22-7.43 (m, 5H, Ph); ^{13}C-NMR δ 23.78 (CH_3), 37.11 (CH_2), 47.86 (CH_2), 53.74 (CH_2), 68.85 (CH), 127.32, 128.38, 128.60 ($CH_{aromatic}$), 139.37 ($C_{aromatic}$). MS (70 eV) *m/z* 120 (M^+ -59, 8), 91 (34), 45 (100). Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.55; N, 7.81. Found: C, 73.76; H, 9.53; N, 7.97.

(*R*)-4-Octylamino-2-butanol (10d): Yield, 79%, oil. $[\alpha]_D^{22}$ +9.6 (c, 1.00, $CHCl_3$), 92% e.e.; ^{1}H NMR δ 0.96 (t, 3H, CH_3), 1.05-1.69 (m, 17H, CH_3, $7CH_2$), 2.42-3.05 (m, 4H, $2CH_2$), 3.92 (m, 1H, C*H*OH); ^{13}C NMR δ 13.76 (CH_3), 22.32 (CH_3), 23.25 (CH_2), 26.93 (CH_2), 28.91 (CH_2), 29.16 (CH_2), 29.54 (CH_2), 31.88 (CH_2), 36.31 (CH_2), 48.56 (CH_2), 49.33 (CH_2), 69.29 (CH). MS (70 eV) *m/z* 201 (M^+, 1), 102 (100), 44 (93). Anal. Calcd. for $C_{12}H_{27}NO$: C, 71.50; H, 13.50; N, 6.95. Found: C, 71.71; H, 13.68; N, 6.90.

(*R*)-4-Dodecylamino-2-butanol (10e): Yield, 81%, mp 56-57°C. $[\alpha]_D^{22}$ +15.2 (c, 0.71, $CHCl_3$), 94% e.e.; ^{1}H NMR δ 0.80-1.00 (m, 6H, $2CH_3$), 1.10-1.78 (m, 23H, NH, $11CH_2$), 2.40-3.09 (m, 4H, $2CH_2$), 3.70 (m, 2H, CH, OH); ^{13}C NMR δ 9.77 (CH_3), 13.91 (CH_3), 22.50 (CH_2), 27.05 (CH_2), 29.18 (CH_2), 29.38 (CH_2), 29.45 (CH_2), 29.68 (CH_2), 30.39 (CH_2), 31.74 (CH_2), 34.16 (CH_2), 48.82 (CH_2), 49.50 (CH_2), 74.87 (CH). MS (70 eV) *m/z* 257 (M^+, 2), 102 (100), 44 (83). Anal. Calcd. for $C_{16}H_{35}NO$: C, 74.64; H, 13.70; N, 5.44. Found: C, 74.60; H, 13.84; N, 5.37.

(*R*)-1-Butylamino-3-pentanol (11a): Yield, 84%, mp 49-50°C. $[\alpha]_D^{22}$ +17.0 (c, 1.06, $CHCl_3$), 75% e.e.; ^{1}H NMR δ 0.79-1.00 (m, 6H, $2CH_3$), 1.18-1.72 (m, 9H, NH, $4CH_2$), 2.44-3.08 (m, 4H, $2CH_2$), 3.67 (m, 1H, CH); ^{13}C NMR δ 9.38 (CH_3), 13.35 (CH_3), 19.80 (CH_2), 30.00 (CH_2), 31.38 (CH_2), 33.96 (CH_2), 48.15 (CH_2), 48.77 (CH_2), 73.95 (CH). MS (70 eV) *m/z* 159 (M^+, 3), 44 (100). Anal. Calcd. for $C_9H_{21}NO$: C, 67.87; H, 13.29; N, 8.79. Found: C, 67.75; H, 13.36; N, 8.89.

(*R*)-1-Propylamino-3-pentanol (11b): Yield, 75%, oil. $[\alpha]_D^{22}$ +13.4 (c, 1.25, $CHCl_3$), 94% e.e.; ^{1}H NMR δ 0.84-1.04 (m, 6H, CH_3), 1.32-1.78 (m, 6H, CH_2), 2.42-3.10 (m, 4H, CH_2), 3.61-4.00 (m, 2H, CH, OH); ^{13}C NMR δ 9.58 (CH_3), 11.31 (CH_3), 22.54 (CH_2), 30.20 (CH_2), 34.01 (CH_2), 48.48 (CH_2), 51.08 (CH_2), 74.53 (CH). MS (70 eV) *m/z* 145 (M^+, 3), 72 (100). Anal. Calcd. for $C_8H_{19}NO$: C, 66.15; H, 13.18; N, 9.64. Found: C, 66.30; H, 13.02; N, 9.70.

(*R*)-1-Benzylamino-3-pentanol (11c): Yield, 90%, oil. $[\alpha]_D^{22}$ +20.8 (c, 0.97, $CHCl_3$), 82%

e.e.; ^{1}H-NMR δ 0.88 (t, 3H, J = 6.4, CH_3), 1.10-1.65 (m, 4H, CH_2), 2.61-3.25 (m, 3H, CH_2, OH), 3.57-3.82 (m, 3H, CH_2Ph, CH), 7.19-7.35 (m, 5H, Ph); ^{13}C-NMR δ 10.57 (CH_3), 31.07 (CH_2), 35.16 (CH_2), 48.80 (CH_2), 54.38 (CH_2), 75.25 (CH), 127.69, 128.72, 129.01 ($CH_{aromatic}$), 140.02 ($C_{aromatic}$). MS (70 eV) *m/z* 193 (M+, 1), 91 (100). Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.43; H, 9.85; N, 7.30.

(*R*)-1-Octylamino-3-pentanol (11d): Yield, 78%, mp 46-47°C. $[\alpha]_D^{22}$ +18.8 (c, 1.03, $CHCl_3$), >99% e.e.; ^{1}H NMR δ 0.81-1.00 (m, 6H, $2CH_3$), 1.18-1.68 (m, 16H, $8CH_2$), 2.43-3.07 (m, 4H, $2CH_2$), 3.43 (bs, 1H, OH), 3.70 (m, 1H, CH); ^{13}C NMR δ 9.77 (CH_3), 13.90 (CH_3), 22.45 (CH_2), 27.03 (CH_2), 29.03 (CH_2), 29.28 (CH_2), 29.47 (CH_2), 30.37 (CH_2), 31.62 (CH_2), 33.94 (CH_2), 48.67 (CH_2), 49.39 (CH_2), 74.74 (CH). MS (70 eV) *m/z* 215 (M+, 4), 116 (67), 44 (100). Anal. Calcd. for $C_{13}H_{29}NO$: C, 74.49; H, 13.57; N, 6.50. Found: C, 74.30; H, 13.61; N, 6.59.

(*R*)-1-Dodecylamino-3-pentanol (11e): Yield, 80%, mp 56-57°C. $[\alpha]_D^{22}$ +9.1 (c, 1.00, $CHCl_3$), 81% e.e.; ^{1}H NMR δ 0.86 (t, 3H, J = 6.6, CH_3), 1.10-1.69 (m, 27H, CH_3, $12CH_2$), 2.42-3.05 (m, 4H, $2CH_2$), 3.22-3.58 (bs, 1H, OH), 3.95 (m, 1H, CH); ^{13}C NMR δ 13.61 (CH_3), 22.24 (CH_2), 23.10 (CH_3), 26.81 (CH_2), 28.88 (CH_2), 29.45 (CH_2), 31.45 (CH_2), 36.30 (CH_2), 48.36 (CH_2), 49.21 (CH_2), 68.90 (CH). MS (70 eV) *m/z* 271 (M+, 2), 116 (68), 44 (100). Anal. Calcd. for $C_{17}H_{37}NO$: C, 75.21; H, 13.73; N, 5.16. Found: C, 75.33; H, 13.60; N, 4.98.

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23.- The enantiomeric excess and the absolute configuration of **8** and **9** were determined by comparison of the observed rotation with that of an authentical sample prepared from ethyl (*R*)-(+)-4-chloro-3-hydroxybutyrate and (*S*)-(-)-*N*-benzyl-4-chloro-3-hydroxybutyramide respectively with Ag_2O.