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Lipase-Catalyzed Synthesis of Optically Active Amides in Organic Media

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Abstract:. Lipases from *Candida cylindracea* and *Candida antarctica* catalyze the aminolysis of activated and nonactivated esters respectively. The degree of enantioselectivity depends on the amine.

Over the last few years the use of enzymes in organic solvents has occupied a position of particular prominence in the synthesis of optically active organic compounds.[1] It is now well established that biocatalytic transformations performed in organic media can be of great utility for certain types of processes that are difficult or impossible to carry out in water.[2]

Lipases have been the most commonly used enzymes in preparative organic chemistry because of their high stability in organic media and their ability to accept a great variety of substrates.[3] Thus, these hydrolytic enzymes have displayed a great efficiency for the preparation and resolution of chiral alcohols, esters and carboxylic acids through an esterification or transesterification reaction.[4] However, few reports on the lipase catalyzed preparation of chiral amides from racemic esters or amines have been reported.[5]

The protease subtilisin has shown that it can catalyze the aminolysis reaction of racemic amines and the nature of the solvent is essential in this enantioselective process.[6] This method has recently been applied for the resolution of (*R*)-1-aminoindane and (*R*)-1-(1-naphthyl)ethylamine in a continuous reactor, using 3-methyl-3-pentanol as solvent.[7]

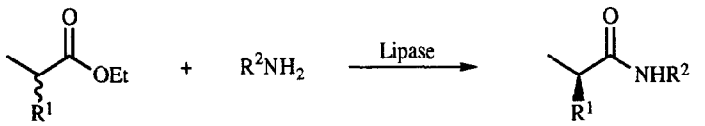
In recent years, our group has been investigating the potentiality of lipases to catalyze the aminolysis reaction in organic media.[5] In our work, we have shown the usefulness of this kind of process for the preparation of amides with two stereogenic centers,[8] propiolic amides,[9] chiral diamides,[10] optically active acrylic

amides[11] and chiral aminoalcohols.[12] Moreover, we have corroborated the influence of the structure of the ester in these enzymatic reactions.[13]

In addition, other groups have reported the preparation of *N*-octyl-alkanamides,[14] the acylation of primary amines[15] and recently, the formation of lactams from aminoesters through an intramolecular aminolysis reaction.[16]

Continuing with our work in this area, we have studied the CCL catalyzed aminolysis of ethyl (±)-2-chloropropionate with long chain aliphatic amines in order to investigate the behaviour of the CCL in the aminolysis of this substrate with a wide range of structurally different amines. The aminolysis of ethyl (±)-2-bromopropionate is also investigated. On the other hand, the potentiality of *Candida antarctica* lipase (CAL) to catalyze the aminolysis of 2-substituted propionic esters and aliphatic amines is reported.

Scheme



1 $R^1 = Cl$ **4** **5** $R^1 = Cl$

2 $R^1 = Br$ **6** $R^1 = Br$

3 $R^1 = Et$ **7** $R^1 = Et$

In an earlier paper, we have demonstrated that *Candida cylindracea* lipase (CCL) is a very useful catalyst for the preparation of chiral amides from ethyl (±)-2-chloropropionate,[17] and we have observed that the degree of enantioselectivity dramatically depends on the starting amine, but in all cases CC lipase exhibited its selectivity towards the *S* isomer of the ester. Similar results have been found in the aminolysis with octyl, decyl and dodecylamine. These reactions were carried out at room temperature because the noncatalyzed aminolysis happened slowly. In all the cases the (*S*)-amides were obtained with high to moderate enantiomeric excess.

This notably contrasts with the results obtained in the CCL catalyzed hydrolysis of octyl 2-chloropropionate[18] and in the esterification of the corresponding acid using 1-butanol,[19] for which the CCL was always selective towards the *R* isomer. In addition, whereas the presence of a substituent, for instance a methyl group, in the α position of the alcohol induces a reversal of enantioselectivity in the esterification reaction,[20] no change was observed in the aminolysis with amines such as α-methylbenzylamine, *sec*-butylamine and 2-aminoheptane;[8] CCL preferentially utilizes the *S* enantiomer of the ester again .

The uniform behaviour shown by the CCL in the aminolysis reaction might be due to conformational changes in the acyl binding domain induced by interaction of the amine with the enzyme. This effect could be the consequence of the basic properties of the amine more than that of the steric factors of the chain.

Table I. Amidation reaction of **1** and **2** with amines **4** catalyzed by CCL.[a]

Entry	R^2	t, h	conv., %	$[\alpha]_D^{25b}$	ee, %	Conf.
5a	Octyl	5	23	-10.0 (c, 0.97)	70	*S*
5b	Decyl	5	35	-9.9 (c, 1.02)	92	*S*
5c	Dodecyl	5.5	20	-5.7 (c, 1.02)	51	*S*
6a	Butyl	89	24	-10.2 (c, 0.80)	90	*S*
6b	Allyl	93	27	-3.8 (c, 0.82)	50	*S*
6c	Benzyl	95	30	-0.5 (c, 0.70)	<5	-
6d	Octyl	70	38	-6.0 (c, 0.72)	61	*S*
6e	Decyl	94	38	-6.5 (c, 0.65)	64	*S*
6f	Dodecyl	91	35	-3.6 (c, 0.6)	64	*S*

[a]Hexane was used as solvent. [b]Measured in $CHCl_3$.

When ethyl (±)-2-bromopropionate reacts with aliphatic amines at room temperature, the corresponding nucleophilic substitution product is obtained and the amide is not detected. If $AlCl_3$ is used as catalyst[21] in this reaction, the amide is formed but in very low yield. Taking into account the difficulties to obtain this kind of amides, we thought it of interest to try the CCL catalyzed aminolysis of the ester **2** in order to obtain optically active 2-bromopropionamides.

As one can see in Table I, longer reaction times than with **1** were neccessary. However, although the amides were obtained with different enantiomeric excesses, the selectivity of the enzyme did not change with the size of the amine.

Candida antarctica lipase has proved to be an efficient catalyst in the amidation reaction.[11,12] For this reason, and given that the CCL catalyzed aminolysis of **2** happens very slowly, we have checked the catalytic activity of this lipase in the aminolysis of this substrate. With all the amines tested, the reaction was very fast; for instance, with benzylamine the aminolysis took place with 60% of conversion after 1.5 h in dioxane, but in no case this enzyme was enantioselective.

Finally, we have investigated the aminolysis of ethyl (±)-2-methylbutyrate (**3**). Although CCL catalyzed the amidation when butylamine was used as nucleophile, longer reaction time and heating at 50°C were neccessary to get a percentage of conversion of 18%. Moreover, when other aliphatic amines were used, poorer results were achieved. Bearing in mind that amides from nonactivated esters are hard to obtain, we decided to try the aminolysis of **3** with CAL because of its higher catalytic activity. The results are collected in Table II. In all cases CAL was selective towards the *R* isomer of the ester but the enantiomeric excesses were only moderate.

Table II. Amidation reaction of 3 with amines 4 catalyzed by CAL.[a]

Entry	R^2	t, days	conv., %	$[\alpha]_D^{25b}$	ee, %	Conf.
7a	Benzyl	3	25	-6.8 (c, 1.05)	78	*R*
7b	Octyl	5	20	-6 0 (c, 0.99)	50	*R*
7c	Decyl	8	23	-3.7 (c, 0.96)	50	*R*
7d	Dodecyl	5	20	-4.6 (c, 0.70)	48	*R*
7e	Butyl	3	20	-6.0 (c, 0.85)	40	*R*
7f	Allyl	4	20	-6.7 (c, 0.95)	40	*R*

[a]Hexane was used as solvent. [b]Measured in $CHCl_3$.

The configuration of amides **5** and **7** and the ee of **7** were assigned by comparison of their optical rotations with authentical samples obtained from ethyl (*S*)-(-)-2-chloropropionate and (*S*)-(+)-2-methylbutyric anhydride. The configuration of amides **6** was determined by comparison with the amide obtained from enantiomeric pure 2-bromopropionyl chloride (prepared from (*R*)-(+)-2-bromopropionic acid and thionyl chloride) and the corresponding amine. The ee of compounds **5** and **6** were calculated by ^{1}H-NMR spectroscopy using the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium (III).

In conclusion, the enantioselectivity displayed by the CCL in the aminolysis of 2-chloropropionate is always the same independent of the size of the amine. This lipase also catalyzed the amidation of 2-bromopropionate with aliphatic amines with moderate enantioselectivity. *Candida antarctica* lipase catalyzes the aminolysis of 2-methylbutyrate with aliphatic amines.

EXPERIMENTAL

Candida cylindracea lipase, Type VII crude, was purchased from Sigma Chemical Co. *Candida antarctica* lipase (SP 435 L) was obtained from Novo Nordisk Co. All reagents were of commercial quality and were purchased from Aldrich Chemie. Solvents were distilled over a suitable desiccant and stored under argon. For column chromatography, Merck silica gel 60/230-400 mesh was used. Melting points 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 170-X Infrared Fourier transform 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 5897 A spectrometer. All the new compounds gave satisfactory elemental analysis and were performed by Microanalyses Perkin-Elmer 240. The extent of conversion was determined by gas chromatography and by ^{1}H-NMR.

***Candida cylindracea* lipase catalyzed aminolysis of ethyl (±)-2-chloropropionate.**

To a solution of 10 mmol of ethyl (±)-2-chloropropionate and 5 mmol of the corresponding amine in 30 mL of hexane was added CCL (4 g). The suspension was stirred at 30°C and 220 rpm for the time collected in Table I. When the reaction was terminated, the enzyme was filtered and washed with dichloromethane. Then, the organic solvents were evaporated under reduced pressure and the residue was subjected to flash chromatography on silica using hexane-ethyl acetate as eluent.

(*S*)-(-)-*N*-Octyl-2-chloropropionamide (5a): mp 27-28°C; IR (KBr) ν_{max}: 1655 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (t, 3H, CH_3), 1.15-1.65 (m, 12H, CH_2), 1.71 (d, 3H, CH_3), 3.25 (m, 2H, CH_2), 4.40 (q, 1H, CH), 6.62 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.93 (CH_3), 22.47 (CH_2), 22.63 (CH_3), 26.68 (CH_2), 29.00 (CH_2), 29.17 (CH_2), 31.62 (CH_2), 39.81 (CH_2), 55.92 (CH), 169.25 (C=O); MS m/z: 221 [(M+2)+, 4], 219 (M+, 13), 184 (M+-Cl, 93), 156 (100). Anal. Calcd. for $C_{11}H_{22}ClNO$: C, 60.12; H, 10.09; N, 6.37. Found: C, 60.21; H, 9.93; N, 6.56.

(*S*)-(-)-*N*-Decyl-2-chloropropionamide (5b): mp 32-33°C; IR (KBr) ν_{max}: 1655 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.80 (t, 3H, CH_3), 1.07-1.58 (m, 16H, CH_2), 1.66 (d, 3H, CH_3), 3.20 (m, 2H, CH_2), 4.35 (q, 1H, CH), 6.68 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.94 (CH_3), 22.50 (CH_2), 22.58 (CH_3), 26.63 (CH_2), 29.07 (CH_2), 29.11 (CH_2), 29.33 (CH_2), 31.70 (CH_2), 39.76 (CH_2), 55.84 (CH), 169.25 (C=O); MS m/z: 249 [(M+2)+, 2.7], 247 (M+, 8.6), 212 (M+-Cl, 89), 184 (100). Anal. Calcd. for $C_{13}H_{26}ClNO$: C, 63.01; H, 10.58; N, 5.65. Found: C, 63.23; H, 10.41; N, 5.68.

(*S*)-(-)-*N*-Dodecyl-2-chloropropionamide (5c): mp 49-50°C; IR (KBr) ν_{max}: 1651 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (t, 3H, CH_3), 1.15-1.65 (m, 20H, CH_2), 1.73 (d, 3H, CH_3), 3.27 (m, 2H, CH_2), 4.41 (q, 1H, CH), 6.65 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.90 (CH_3), 22.44 (CH_2), 22.46 (CH_3), 26.60 (CH_2), 29.03 (CH_2), 29.08 (CH_2), 29.11 (CH_2), 29.28 (CH_2), 29.34 (CH_2), 29.41 (CH_2), 31.69 (CH_2), 39.72 (CH_2), 55.67 (CH), 169.22 (C=O); MS m/z: 277 [(M+2)+, 2], 275 (M+, 6), 240 (M+-Cl, 67), 212 (100). Anal.Calcd. for $C_{15}H_{30}ClNO$: C, 65.31; H, 10.96; N, 5.07. Found: C, 65.57; H, 10.71; N, 4.86.

***Candida cylindracea* lipase catalyzed aminolysis of ethyl (±)-2-bromopropionate.**

To a solution of 5 mmol of ethyl (±)-2-bromopropionate and 5 mmol of the corresponding amine in 40 mL of hexane was added CCL (6 g). The suspension was stirred at 30°C and 220 rpm. Reaction was terminated by removal of the enzyme by filtration and the organic solvent evaporated under reduced pressure. The residue was subjected to flash chromatography on silica using hexane-ethyl acetate 3:1 as eluent.

(*S*)-(-)-*N*-Butyl-2-bromopropionamide (6a): mp 24-25°C; IR (KBr) ν_{max}: 1656 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (t, 3H, CH_3), 1.20-1.60 (m, 4H, CH_2), 1.86 (d, 3H, CH_3), 3.23 (m, 2H,

CH_2), 4.37 (q, 1H, CH), 6.50 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.46 (CH_3), 19.76 (CH_2), 23.03 (CH_3), 31.12 (CH_2), 39.68 (CH_2), 45.27 (CH), 169.02 (C=O); MS m/z: 209 [(M+2)+, <1), 207 (M+, <1), 128 (M+-Br, 11), 57 (100). Anal. Calcd. for $C_7H_{14}BrNO$: C, 40.40; H, 6.78; N, 6.73. Found: C, 40.56; H, 6.68; N, 6.96.

(*S*)-(-)-*N*-Allyl-2-bromopropionamide (6b): mp 35-36°C; IR (neat) ν_{max}: 1661 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.88 (d, 3H, CH_3), 3.90 (m, 2H, CH_2), 4.43 (q, 1H, CH), 5.12-5.30 (m, 2H, CH_2), 5.70-5.95 (m, 1H, CH), 6.65 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 22.51 (CH_3), 42.06 (CH_2), 44.06 (CH), 116.26 (CH_2), 133.10 (CH), 169.63 (C=O); MS m/z: 193 [(M+2)+, 1), 191 (M+, 1), 112 (M+-Br, 100). Anal. Calcd. for $C_6H_{10}BrNO$: C, 37.52; H, 5.25; N, 7.29. Found: C, 37.46; H, 5.43; N, 7.07.

(*S*)-(-)-*N*-Benzyl-2-bromopropionamide (6c): mp 93-94°C; IR (KBr) ν_{max}: 1651 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.91 (d, 3H, CH_3), 4.35-4.65 (m, 3H, CH and CH_2), 6.68 (bs, 1H, NH), 7.20-7.45 (m, 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ (ppm): 22.80 (CH_3), 43.77 (CH_2), 44.70 (CH), 127.32 (CH), 128.46 (CH), 137.24 (C), 169.06 (C=O); MS m/z: 162 (M+-Br, 100), 91 (80). Anal. Calcd. for $C_{10}H_{12}BrNO$: C, 49.61; H, 5.00; N, 7.29. Found: C, 49.36; H, 5.09; N, 7.02.

(*S*)-(-)-*N*-Octyl-2-bromopropionamide (6d): mp 51-52°C; IR (KBr) ν_{max}: 1647 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (t, 3H, CH_3), 1.15-1.60 (m, 12H, CH_2), 1.88 (d, 3H, CH_3), 3.24 (m, 2H, CH_2), 4.39 (q, 1H, CH), 6.41 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.90 (CH_3), 22.46 (CH_2), 23.16 (CH_3), 26.64 (CH_2), 29.03 (CH_2), 29.10 (CH_2), 31.60 (CH_2), 40.05 (CH_2), 45.47 (CH), 168.98 (C=O); MS m/z: 265 [(M+2)+, 1), 263 (M+, 1), 184 (M+-Br, 63), 86 (100). Anal. Calcd. for $C_{11}H_{22}BrNO$: C, 50.00; H, 8.39; N, 5.30. Found: C, 50.21; H, 8.16; N, 5.37.

(*S*)-(-)-*N*-Decyl-2-bromopropionamide (6e): mp 36-37°C; IR (KBr) ν_{max}: 1647 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.83 (t, 3H, CH_3), 1.10-1.65 (m, 16H, CH_2), 1.82 (d, 3H, CH_3), 3.22 (m, 2H, CH_2), 4.38 (q, 1H, CH), 6.62 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.83 (CH_3), 22.39 (CH_2), 22.93 (CH_3), 26.53 (CH_2), 28.99 (CH_2), 29.23 (CH_2), 31.59 (CH_2), 39.95 (CH_2), 45.14 (CH), 168.98 (C=O); MS m/z: 293 [(M+2)+, <1), 291 (M+, <1), 212 (M+-Br, 40), 86 (100). Anal. Calcd. for $C_{13}H_{26}BrNO$: C, 53.43; H, 8.97; N, 4.79. Found: C, 53.65; H, 9.19; N, 4.55.

(*S*)-(-)-*N*-Dodecyl-2-bromopropionamide (6f): mp 46-47°C; IR (KBr) ν_{max}: 1645 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.84 (t, 3H, CH_3), 1.10-1.60 (m, 20H, CH_2), 1.86 (d, 3H, CH_3), 3.23 (m, 2H, CH_2), 4.40 (q, 1H, CH), 6.45 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.96 (CH_3), 22.52 (CH_2), 23.16 (CH_3), 26.67 (CH_2), 29.10 (CH_2), 29.20 (CH_2), 29.36 (CH_2), 29.50 (CH_2), 31.76 (CH_2), 40.08 (CH_2),

45.47 (CH), 169.02 (C=O); MS m/z: 240 (M^+-Br, 30), 86 (100). Anal. Calcd. for $C_{15}H_{30}BrNO$: C, 56.25; H, 9.44; N, 4.37. Found: C, 56.01; H, 9.48; N, 4.51.

Enzymatic aminolysis of ethyl (±)-2-methylbutyrate: To a solution of ethyl (±)-2-methylbutyrate (5 mmol) and the corresponding amine (5 mmol) in 30 ml of solvent, CAL (150 mg) was added. The mixture was shaken at 30°C and 220 rpm. The reaction was stopped by removal of the enzyme by filtration. The organic solvent was evaporated and the residue was subjected to flash chromatography using hexane-ethyl acetate.

(*R*)-(-)-*N*-Benzyl-2-methylbutyramide (7a): mp 45-46°C; IR (KBr) ν_{max}: 1643 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (t, 3H, CH_3), 1.15 (d, 3H, CH_3), 1.44 (m, 1H, C*H*H), 1.70 (m, 1H, CH*H*), 2.13 (m, 1H, CH), 4.44 (d, 2H, CH_2), 5.83 (bs, 1H, NH), 7.20-7.40 (m, 5H, aromatic); ^{13}C-NMR ($CDCl_3$) δ (ppm): 11.81 (CH_3), 17.37 (CH_3), 27.15 (CH_2), 42.92 (CH), 43.13 (CH_2), 127.18 (CH), 127.54 (CH), 128.46 (CH), 138.45 (C), 176.41 (C=O); MS m/z: 191 (M^+, 43), 91 (100). Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.38; H, 8.78; N, 7.42.

(*R*)-(-)-*N*-Octyl-2-methylbutyramide (7b): mp 39-40°C; IR (KBr) ν_{max}: 1643 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.78-0.97 (m, 6H, CH_3), 1.13 (d, 3H, CH_3), 1.18-1.75 (m, 14H, CH_2), 2.04 (m, 1H, CH), 3.25 (m, 2H, CH_2), 5.40 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 11.77 (CH_3), 13.91 (CH_3), 17.44 (CH_3), 22.48 (CH_2), 26.79 (CH_2), 27.21 (CH_2), 29.05 (CH_2), 29.12 (CH_2), 29.60 (CH_2), 31.64 (CH_2), 39.21 (CH_2), 43.09 (CH), 176.30 (C=O); MS m/z: 213 (M^+, 51), 156 (100). Anal. Calcd. for $C_{13}H_{27}NO$: C, 73.18; H, 12.75; N, 6.57. Found: C, 72.92; H, 12.71; N, 6.70.

(*R*)-(-)-*N*-Decyl-2-methylbutyramide (7c): mp 44-45°C; IR (KBr) ν_{max}: 1642 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.80-0.95 (m, 6H, CH_3), 1.11 (d, 3H, CH_3), 1.18-1.75 (m, 18H, CH_2), 2.04 (m, 1H, CH), 3.23 (m, 2H, CH_2), 5.54 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 11.74 (CH_3), 13.88 (CH_3), 17.37 (CH_3), 22.44 (CH_2), 26.72 (CH_2), 27.15 (CH_2), 29.07 (CH_2), 29.36 (CH_2), 29.50 (CH_2), 31.64 (CH_2), 39.14 (CH_2), 42.85 (CH), 176.34 (C=O); MS m/z: 241 (M^+, 43), 184 (100). Anal.Calcd. for $C_{15}H_{31}NO$: C, 74.63; H, 12.94; N, 5.80. Found: C, 74.71; H, 12.81; N, 5.96.

(*R*)-(-)-*N*-Dodecyl-2-methylbutyramide (7d): mp 62-62°C; IR (KBr) ν_{max}: 1642 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.85-1.00 (m, 6H, CH_3), 1.12 (d, 3H, CH_3), 1.16-1.80 (m, 22H, CH_2), 2.04 (m, 1H, CH), 3.21 (m, 2H, CH_2), 5.50 (bs, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 11.88 (CH_3), 14.05 (CH_3), 17.52 (CH_3), 22.61 (CH_2), 26.81 (CH_2), 27.28 (CH_2), 29.21 (CH_2), 29.26 (CH_2), 29.46 (CH_2), 29.48 (CH_2), 29.55 (CH_2), 29.63 (CH_2), 31.83 (CH_2), 39.24 (CH_2), 43.27 (CH), 176.28 (C=O); MS m/z: 269 (M^+, 37), 57 (100). Anal. Calcd. for $C_{17}H_{35}NO$: C, 75.77; H, 13.09; N, 5.20. Found: C, 75.62; H, 13.22; N, 5.03.

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REFERENCES

1 Faber, K. *Biotransformations in Organic Chemistry*, Springer-Verlag. 1992. Davies, H.G.; Green, R. G.; Kelly, D. R.; Roberts, S. M. *Biotransformations in Preparative Organic Chemistry*, Academic Press. 1989.

2. Klibanov, A. M. *CHEMTECH*, **1986**, *16*, 354. Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci*, USA, **1985**, *82*, 3192.

3. Chen, C-S.; Sih, C. J. *Angew. Chem. Int Ed Engl* **1989**, *28*, 695

4. Klibanov, A. M. *Acc. Chem. Res* **1990**, *23*, 114. Boland, W.; Frölss, C.; Lorenz, M. *Synthesis* **1991**, 1049. Faber, K.; Riva, S. *Synthesis*, **1992**, 895.

5. Gotor, V. *Microbial Reagents in Organic Synthesis*. NATO ASI Series. **1992**, *381*, 199.

6. Kitaguchi, H.; Fitzpatrick, P. A.; Huber, J. E.; Klibanov, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 3094.

7. Gutman, A. L.; Meyer, E.; Kalerin, E., Polyak, F.; Sterling, J. *Biotechnology and Bioengineering* **1992**, *40*, 760.

8. Brieva, R.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Chem. Commun.*, **1990**, 1386.

9. Rebolledo, F.; Brieva, R.; Gotor, V. *Tetrahedron Lett.* **1989**, *30*, 5345.

10. Gotor, V.; García, M. J.; Rebolledo, F. *Tetrahedron: Asymmetry* **1990**, *1*, 277.

11. Puertas, S.; Brieva, R.; Rebolledo, F.; Gotor, V. *Tetrahedron*, in press.

12. García, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry*, **1992**, *3*, 1519.

13. García, M. J.; Brieva, R.; Rebolledo, F.; Gotor, V. *Biotechnology Lett.*, **1991**, *13*, 867.

14. Tuccio, B.; Ferré, E.; Comeau, L. *Tetrahedron Lett.*, **1991**, *32*, 2763.

15. Djeghaba, Z.; Deleuze, H.; De Jeso, B.; Messadi, D.; Maillard, B. *Tetrahedron Lett.*, **1991**, *32*, 761.

16. Gutman, A. L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett* **1992**, *33*, 3943.

17. Gotor, V.; Brieva, R.; Rebolledo, F. *Tetrahedron Lett* **1988**, *29*, 6973. Gotor, V.; Brieva, R.; González, C.; Rebolledo, F. *Tetrahedron* **1991**, *47*, 9207.

18. Cambou, B.; Klibanov, A. M. *Appl. Biochem. Biotechnol.*, **1984**, *9*, 255.

19. Kirchner, G.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc*, **1985**, *107*, 7072.

20. Holmberg, E.; Hult, K. *Biocatalysis*, **1992**, *5*, 289.

21. Bigg, D. C. H.; Lesimple, P. *Synthesis*, **1992**, 277.