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Vinyl Carbonates as Novel Alkoxycarbonylation Reagents in Enzymatic Synthesis of Carbonates.

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Abstract: *Carbonates could be obtained by enzymatic alkoxycarbonylation from vinyl carbonates, which are easily prepared from vinyl chloroformate. The reaction was catalyzed by Candida antarctica lipases, SP 435 and SP 435 A. The method could be also used for the synthesis of carbamates. When racemic alcohols were used, lipase catalyzed their resolution, and chiral carbonates were obtained with different enantiomeric excesses depending upon the structure of the alcohol.*

INTRODUCTION

The synthetic potential of enzymes in organic solvents has been well documented in the last few years.[1] Esterification and specially transesterification reactions have been the processes most commonly used in asymmetric transformations in organic synthesis.[2]

As a consequence of the numerous trials to improve the conversion and the regio- or enantioselectivity in these processes, several acylating agents have been used, such as, activated esters,[3] enol esters,[4] anhydrides[5] or oxime esters.[6] This together with the increasing of commercially available enzymes, provide organic chemists with a full set of tools to obtain selective processes.

Nevertheless tedious work up is often required in order to resolve a racemic compound; for this reason, the development of new versatile reagents, which can be recognized by the enzyme in a different way than the traditional ones, is a fundamental task nowadays.

The alkoxycarbonylation reaction, which has scarcely been investigated, resumes several of these characteristics. The carbonate ester derivatives have been used in the synthesis of fatty carbonate esters,[7] and in the resolution of chiral alcohols.[8] Their difference in structure respect to the esters has been useful in the resolution of methyl *N*-acetylpropranolol carbonate, not accessible in other ways.[9] In addition, we have prepared 3'-carbonates of 2'-deoxynucleosides through an enzymatic alkoxycarbonylation using *O*-

alkoxycarbonyloximes.[10]

We believed that the introduction of an irreversible leaving group, a vinyl moiety, in a carbonate structure could extend the versatility of this kind of reagents in enzymatic reactions. One of the most important compounds of this family, is the benzylvinyl carbonate due to the easy deprotection of the benzyloxycarbonyl group.

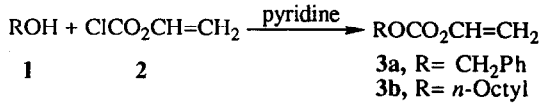
RESULTS AND DISCUSSION

Our interest in the development of new alkoxycarbonylating reagents, which could be used in enzyme catalyzed reactions, led us to prepare the benzylvinyl carbonate (**3a**) from the benzyl alcohol and vinyl chloroformate (Scheme I). Good yields of compounds (**3**) were obtained when a small excess of vinyl chloroformate was used.

As a preliminary experiment, *n*-octanol and isopropanol were submitted to react with 1 molar equivalent of vinyl carbonate (**3a**) in the presence of various lipases in diisopropyl ether or hexane (Scheme II). Of all our trials, the best results were obtained when two different lipases isolated from *Candida antarctica* (SP 435 and SP 435 A) were used in diisopropyl ether as solvent at room temperature. SP 435 showed the higher catalytic activity. Molecular sieves 4Å were used in order to avoid moisture, and the progress of the reaction was controlled by TLC. Small amounts (less than 5%) of a side product, dibenzylcarbonate, were detected. As one can see in Table I, both primary and secondary alcohols reacted under these conditions to give compounds (**5a-5b**) in good yields.

When CCL, PSL, or PPL were employed, the dibenzylcarbonate was the major product and only small quantities of products (**5a-5b**) were formed. We think that the reactive, benzylvinyl carbonate, was hydrolyzed with the water content of the enzyme, and the resulting carbonic acid decomposed to benzyl alcohol and CO_2. The benzyl alcohol competed with the nucleophile in the reaction to yield dibenzyl carbonate. The same results were obtained when the benzylvinyl carbonate was submitted to the same reaction conditions employing *Candida antarctica* lipase and small amounts of water. When attempts to reduce the water content of these enzymes (CCL, PSL and PPL) by means of molecular sieves were made, only a moderate increase in the yields of products (**5a-5b**) was obtained, due probably to the higher moisture of them. No reaction was observed when *Subtilisin Carlsberg* was the catalyst.

Scheme I.



Scheme II.

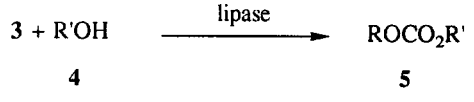


Table I. Carbonates (**5**) from vinyl carbonates (**3**) and different alcohols.

Entry	R	R'	Time, h	Yield (%)	lipase
5a	benzyl	*n*-octyl	1	94	SP 435
5a	benzyl	*n*-octyl	8	64	SP 435 A
5b	benzyl	*i*-propyl	15	90	SP 435
5b	benzyl	*i*-propyl	23	63	SP 435 A
5c	*n*-octyl	*n*-octyl	1	91	SP 435
5c	*n*-octyl	*n*-octyl	7	61	SP 435 A
5d	*n*-octyl	*i*-propyl	16	90	SP 435
5d	*n*-octyl	*i*-propyl	22	60	SP 435 A

Under the same reaction conditions (SP 435 and SP 435 A lipases, molecular sieves 4Å, room temperature, and diisopropyl ether) the alkyl vinyl carbonate (**3b**) was less reactive towards the enzymatic hydrolysis reaction, and dioctyl carbonate was not detected. From the yields of compounds (**5c-5d**), it seemed that the introduction of an alkyl chain in the substrate not affected essentially the overall performance of the enzyme (Table I).

The good results obtained in this alkoxycarbonylation reaction had encouraged us to extend this methodology to the resolution of racemic alcohols. Our aim was to confirm the utility of these substrates, the vinyl carbonates, which differ considerably in electronic structure of the currently employed esters, in the resolution of several alcohols. The reaction conditions are not essentially different from those previously described. A careful control of the reaction progress by ^{1}H-NMR allow us to optimize the e.e. for compounds (**5e-5j**).

Table II. Carbonates from (**3**) and racemic alcohols.

Entry	R	R'	Time, h	Conv. (%)	e.e., % (Conf.)	lipase	Solvent
5e	benzyl	2-butyl	14	48	60 (*R*)	SP 435	hexane
5e	benzyl	2-butyl	24	52	64 (*R*)	SP 435 A	hexane
5f	benzyl	2-octyl	26	43	90 (*R*)	SP 435	hexane
5f	benzyl	2-octyl	45	50	95 (*R*)	SP 435 A	hexane
5g	benzyl	1-(2-ethyl)-hexyl	17	44	<5	SP 435 A	$^iPr_2O$
5h	benzyl	1-phenyl ethyl	38	45	87 (*R*)	SP 435 A	$^iPr_2O$
5i	*n*-octyl	2-butyl	30	50	60 (*R*)	SP 435 A	$^iPr_2O$
5j	*n*-octyl	2-octyl	48	44	91 (*R*)	SP 435 A	$^iPr_2O$

As it is shown on the Table II both lipases are enantioselective towards the *R* enantiomer. With the more specific SP 435 A lipase the reaction times are longer and the e.e. higher. The enantioselectivity depended upon the alcohol structure, it was better with 2-octanol than with 2-butanol, with 2-ethylhexan-1-ol no enantioselectivity was obtained.

Finally, we tried to extend the same methodology to obtain carbamates due to the importance of the alkoxycarbonylation of amines in the synthesis of pharmacologically important molecules.[11] We chose a simple amine, like *N*-butylamine, to study the scope of this reaction.

The results were the same as for those for the alkoxycarbonylation of alcohols. Small amounts of dibenzyl carbonate were obtained when benzylvinyl carbonate (**3a**) was employed, while with *n*-octyl vinyl carbonate (**3b**), more inert to the hydrolysis, dioctyl carbonate was not detected (Scheme III).

Scheme III.

$$3 + n\text{-BuNH}_2 \xrightarrow{\text{lipase}} n\text{-BuNHCO}_2\text{R}$$

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Table III. Carbamates from (**3**) and *N*-butylamine.

Entry	R	Time, h	Yield (%)	lipase
6a	benzyl	6	58	SP 435
6a	benzyl	7	37	SP 435 A
6b	*n*-octyl	3	70	SP 435
6b	*n*-octyl	5	57	SP 435 A

Again the best results were achieved with SP 435 lipase and diisopropyl ether as solvent at room temperature. No reaction was observed, when the previously described biocatalysed processes were conducted in absence of enzyme.

CONCLUSION

In the present work we described an easy method to obtain carbonate of primary and secondary alcohols under mild conditions through an enzymatic alkoxycarbonylation. This method overcame some difficulties of others, like low reactivity of specialized reagents towards hindered alcohols, or operational complexity due to the use of phosgene. This methodology was also useful for the resolution of racemic alcohols. Chiral carbonates were obtained from moderated to high ee. In addition one example of carbamate formation is shown. The introduction of a benzyloxycarbonyl group through this enzymatic reaction is noteworthy.

EXPERIMENTAL

We used two lipases from *Candida antarctica* SP 435 and SP 435 A gifted by Novo Nordisk. All reagents were of commercially produced quality and were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under argon. For column chromatography, Merck silica gel 60/230-400 mesh was used. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a

Mattson 3000 Infrared Fourier transform spectrophotometer. ^1H and ^{13}C NMR were obtained with TMS (tetramethylsilane) as internal standard; using Bruker AC-300 (^1H-300 MHz and ^{13}C-75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett-Packard 5897 A spectrometer. Microanalyses were performed on a Perkin-Elmer 240B elemental analyser.

Determination of enantiomeric excess and absolute configuration was as follow: For carbonates (**5e-5h**) the e.e. and configuration were calculated in comparison with the optically active carbonate prepared from the appropriate chiral alcohol and benzyl chloroformate. For (**5i**) and (**5j**) enantiomerically pure compounds were prepared by enzymatic reaction of the appropriate chiral alcohol and carbonate (**3b**).(All these compounds gave satisfactory ^1H-, ^{13}C-NMR and mass spectra).

Synthesis of carbonates (3). General procedure.

To a solution of 35 mmol of alcohol (**1**) in 4ml of dry pyridine 50 mmol of vinyl chloroformate were slowly added under argon and 0° C. The solution was stirred during 30 min. for (**3a**) or 2 h. (**3b**). The solution was acidified with HCl (3 N) and extracted with dichloromethane; the organic layer was dried over sodium sulphate and distilled under vacuum (10^{-5} mm Hg) to yield pure (**3a**) or submitted to flash chromatography on silica using hexane-ethyl ether (95:5) for (**3b**). The final yields were 75 and 71 % for (**3a**) and (**3b**) respectly.

Benzylvinyl carbonate (3a): oil; IR (neat):$\upsilon_{c=o}$= 1759 cm^{-1}; (Found: C, 67.21; H, 5.57. $C_{10}H_{10}O_3$ requieres C, 67.39; H, 5.66); ^1H-NMR ($CDCl_3$) δ (ppm): 7.40 (s, 5H, aromatic), 7.10 (dd, 1H, CH), 5.20 (s, 2H, CH_2), 4.90 (dd, 1H, CH), 4.50 (dd, 1H, CH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 152.48 (C=O), 142.51 (CH), 134.57 (C), 128.44 (2 CH), 128.23 (CH), 97.55 (CH_2), 69.87 (CH_2); MS (EI, 70eV), m/z: 178 (M+), 91 (100.00), 77 (4.43).

***n*-Octylvinyl carbonate (3b):** oil; Rf=0.48 (hexane:ethyl ether 95:5); IR (neat): $\upsilon_{c=o}$= 1765 cm^{-1}; (Found: C, 65.77; H, 9.98. $C_{11}H_{20}O_3$ requieres C, 65.95; H, 10.07); ^1H-NMR ($CDCl_3$) δ (ppm): 7.10 (dd, 1H, CH), 4.90 (dd, 1H, CH), 4.50 (dd, 1H, CH), 4.20 (t, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.40-1.10 (m, 10H), 0.90 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 152.68 (C=O), 142.57 (CH), 97.23 (CH_2), 68.61 (CH_2); 31.65 (CH_2), 31.49 (CH_2), 29.04 (CH_2), 28.44 (CH_2), 25.53 (CH_2), 22.51 (CH_2), 13.89 (CH_3); MS (EI, 70 eV), m/z: 157 (1.77), 112 (22.29), 57 (100.00), 43 (79.67).

Synthesis of carbonates (5a-5d). General procedure.

To a solution of 1.25 mmol of carbonate (**3**) and 1.25 mmol of the appropiate alcohol in 15 ml of diisopropyl ether with 1.5 g of molecular sieves 4Å, SP 435 (40 mg) or SP 435A (40 mg) were added. The mixture was stirred at 25° C and controlled by TLC. The reaction was terminated by removal of the enzyme, and the organic solvent was evaporated under reduced pressure. The chromatographic separation on silica of the resulting residue yield the carbonates (**5**).

Benzyl-*n*-octyl carbonate (5a): oil; Rf=0.34 (hexane:ethyl ether 97.5:2.5); IR (neat): $\upsilon_{c=o}$= 1743 cm^{-1}; (Found: C, 72.35; H, 9.02. $C_{16}H_{24}O_3$ requieres C, 72.68; H, 9.16) ^1H-NMR ($CDCl_3$) δ (ppm): 7.40 (m, 5H, aromatic), 5.15 (s, 1H, CH_2), 4.15 (t, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.20-1.40 (m, 10H), 0.85 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 155.15 (C=O), 135.29 (C), 128.44 (CH), 128.34 (CH), 128.20 (CH), 69.29 (CH_2), 68.18 (CH_2), 31.65 (CH_2), 29.05 ($2CH_2$), 28.55 (CH_2), 25.58 (CH_2), 22.53 (CH_2), 13.97

(CH_3); MS (EI, 70 eV), m/z: 264 (M^+), 151 (17.00), 91 (100.00), 77 (12.12).

Benzylisopropyl carbonate (5b): oil; Rf=0.33 (hexane:ethyl ether 97:3); IR (neat): $\upsilon_{c=o}$= 1736 cm^{-1}; (Found: C, 67.82; H, 7.18. $C_{11}H_{14}O_3$ requieres C, 68.01; H, 7.27); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.35 (m, 5H, aromatic), 5.15 (s, 2H, CH_2), 4.90 (m, 1H, CH), 1.35 (d, 6H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.51 (C=O), 135.32 (C), 128.42 (CH), 128.29 (CH), 128.17 (CH), 71.93 (CH), 69.10 (CH_2), 21.64 (2 CH_3); MS (EI, 70 eV), m/z: 194 (M^+), 152 (32.94), 91 (100.00), 43 (15.72).

Dioctyl carbonate (5c): oil; Rf=0.32 (hexane:ethyl eter 97:3); IR (neat): $\upsilon_{c=o}$= 1746 cm^{-1}; (Found: C, 71.28; H, 11.96. $C_{17}H_{34}O_3$ requieres C, 71.27; H, 11.97); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.10 (t, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.10-1.50 (m, 10H), 0.90 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 155.31 (C=O), 67.91 (CH_2), 31.64 (CH_2), 29.07 (CH_2), 29.04 (CH_2), 28.55 (CH_2), 25.59 (CH_2), 22.51 (CH_2), 13.95 (CH_3); MS (EI, 70 eV), m/z: 175 (13.28), 112 (56.52), 71 (100.00).

***n*-Octylisopropyl carbonate (5d)**: oil; Rf=0.31 (hexane:ethyl ether 98:2); IR (neat): $\upsilon_{c=o}$= 1744 cm^{-1}; (Found: C, 66.43; H, 11.25. $C_{12}H_{24}O_3$ requieres C, 66.61; H, 11.19); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.80 (m, 1H, CH); 4.10 (t, 2H, CH_2); 1.65 (m, 2H, CH_2); 1.10-1.40 (m, 16H); 0.90 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.69 (C=O), 71.53 (CH), 67.71 (CH_2), 31.65 (CH_2), 29.07 (CH_2), 29.04 (CH_2), 28.57 (CH_2), 25.61 (CH_2), 22.51 (CH_2), 21.68 ($2CH_3$), 13.97 (CH_3); MS (CI, 70eV), m/z: 217 (M^+), 112 (18.86), 43 (100)

Synthesis of carbonates (5e-5j). General procedure.

To a solution of 1.2 mmol of carbonates (3) and 2 mmol of racemic alcohol in 15 mL of hexane or diisopropyl ether with 2 g of molecular sieves (4Å), 40 mg of SP 435 or SP 435 A lipase were added (see Table II). The reaction was monitored by TLC and was terminated, after approximately 45 % conversion of the alcohol, by filtered off the enzyme. The organic solvent was evaporated under reduce pressure and the chromatographic separation on silica gel of the resulting residue gave the carbonate.

***R*-(-)-Benzyl-2-butyl carbonate (5e)**: oil; Rf=0.22 (hexane:ethyl ether 97:3); $[\alpha]_D^{25}$ = -6.3 (c= 0.6, $CHCl_3$), e.e. 60%, (using SP 435), $[\alpha]_D^{25}$ = -6.7 (c= 0.7, $CHCl_3$), e.e. 64%, (using SP 435 A); IR (neat): $\upsilon_{c=o}$= 1749 cm^{-1}; (Found: C, 69.51; H, 7.68. $C_{12}H_{16}O_3$ requieres C, 69.19; H, 7.75); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.35 (m, 5H, aromatic), 5.15 (s, 2H, CH_2), 4,70 (m, 1H, CH), 1.65 (m, 2H, CH_2), 1.30 (d, 3H, CH_3), 0.95 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.85 (C=O), 135.43 (C), 128.53 (CH), 128.38 (CH), 128.23 (CH), 76.76 (CH_2), 69.24 (CH_2), 28.72 (CH_2), 19.33 (CH_3), 9.55 (CH_3); MS (EI, 70 eV), m/z: 208 (M^+), 152 (27.74), 108 (33.91), 91 (100.00), 57 (11.71).

***R*-(-)-Benzyl-2-octyl carbonate (5f)** : oil; Rf=0.38 (hexane:ethyl ether 97:3); $[\alpha]_D^{25}$ = -9.6 (c= 1.1, $CHCl_3$), e.e. 90% (using SP 435), $[\alpha]_D^{25}$ = -10.1 (c= 0.9, $CHCl_3$), e.e. 95% (using SP 435 A); IR (neat): $\upsilon_{c=o}$= 1744 cm-1; (Found: C, 72.39; H, 9.05. $C_{16}H_{24}O_3$ requieres C, 72.68; H, 9.16); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.35 (m, 5H, aromatic), 5.15 (s, 2H, CH_2), 4.70 (m, 1H, CH), 1.60 (m, 2H, CH_2), 1.40-1.15 (m, 11H), 0.90 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.73 (C=O), 135.36 (C), 128.40 (CH), 128.26 (CH),

128.11 (CH), 75.51 (CH), 69.11 (CH_2), 35.76 (CH_2), 31.58 (CH_2), 28.94 (CH_2), 25.11 (CH_2), 22.42 (CH_3), 19.76 (CH_2), 13.92 (CH_3); MS (EI, 70 eV), m/z: 264 (M^+), 152 (28.35), 108 (34.66), 91 (100.00).

Benzyl-1-(2-ethyl)-hexyl carbonate (5g): oil; Rf=0.78 (hexane:ethyl ether 8:2); $[\alpha]_D^{25=}$ 0 (c= 0.5, $CHCl_3$), e.e. 0% (using SP 435 A); IR (neat): $\upsilon_{c=o}$= 1746; (Found: C, 72.51; H, 9.56. $C_{16}H_{25}O_3$ requieres C, 72.40; H, 9.50); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.35 (m, 5H, aromatic), 5.15 (s, 2H, CH_2), 4.10 (dd, 2H, CH_2), 1.10-1.50 (m, 9H), 0.90 (t, 6H, $2CH_3$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 155.22 (C=O), 135.18 (C), 128.37 (CH), 128.27 (CH), 128.13 (CH), 70.42 (CH_2), 69.25 (CH_2), 38.65 (CH), 29.89 (CH_2), 28.67 (CH_2), 23.27 (CH_2), 22.73 (CH_2), 13.84 (CH_3), 10.70 (CH_3); MS (EI, 70 eV), m/z: 265 (M^+), 152 (19.75), 91 (100.00).

***R*-(+)-Benzyl-1-phenylethyl carbonate (5h):** oil; Rf= 0.78 (hexane:ethyl ether 8:2); $[\alpha]_D^{25=}$ +57.6 (c= 0.8, $CHCl_3$), e.e. 87% (using SP 435 A); IR (neat): $\upsilon_{c=o}$= 1746; (Found: C, 75.06; H, 6.34. $C_{13}H_{26}O_3$ requieres C, 74.97; H, 6.30); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.35 (m, 10H, aromatic), 5.70 (q, 1H, CH), 5.15 (d, 1H, CH_2, J= 12.0 Hz), 5.08 (d, 1H, CH_2, J=12.0 Hz), 1.60 (d, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.36 (C=O), 140.87 (C), 135.08 (C), 128.42 (2 CH), 128.34 (CH), 128.19 (CH), 128.00 (CH), 125.89 (CH), 76.48 (CH), 69.40 (CH_2), 22.22 (CH_3); MS (EI, 70 eV), m/z: 165 (23.86), 105 (100.00), 91 (60.09), 77 (38.96).

***R*-(-)-2-Butyl-*n*-octyl carbonate (5i):** oil; Rf=0.51 (hexane:ethyl ether 95:5); $[\alpha]_D^{25}$ = -3.7 (c= 0.7, $CHCl_3$), e.e. 60% (using SP 435 A); IR (neat): $\upsilon_{c=o}$= 1744; (Found: C, 67.97; H, 11.34. $C_{13}H_{26}O_3$ requieres C, 67.77; H, 11.38); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.70 (m, 1H, CH), 4.10 (t, 2H, CH_2), 1.50-1.80 (m, 4H, 2 CH_2), 1.20-1.50 (m, 13H), 1.00-0.80 (m, 6H, $2CH_3$),; ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.97 (C=O), 76.22 (CH), 67.74 (CH_2), 31.67 (CH_2), 29.10 (CH_2), 29.07 (CH_2), 28.68 (CH_2), 28.61 (CH_2), 25.64 (CH_2), 22.54 (CH_2), 19.31 (CH_3), 13.98 (CH_3), 9.53 (CH_3); MS (EI, 70 eV), m/z: 120 (1.18), 112 (16.77), 57 (100.00), 41 (42.68).

***R*-(-)-2-Octyl-*n*-octyl carbonate (5j):** oil; Rf=0.32 (hexane:ethyl ether 97:3); $[\alpha]_D^{25=}$ -4 (c=0.5, $CHCl_3$), e.e. 91% (using SP 435 A); IR (neat): $\upsilon_{c=o}$= 1744; (Found: C, 71.40; H, 11.90. $C_{17}H_{34}O_3$ requieres C, 71.27; H, 11.97); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.70 (m, 1H, CH), 4.10 (t, 2H, CH_2), 1.50-1.70 (m, 4H), 1.20-1.40 (m, 21H), 0.90 (t, 6H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.96 (C=O), 75.14 (CH), 67.75 (CH_2), 35.84 (CH_2), 31.69 (CH_2), 31.64 (CH_2), 29.12 (CH_2), 29.08 (CH_2), 29.02 (CH_2), 28.63 (CH_2), 25.66 (CH_2), 25.21 (CH_2), 22.55 (CH_2), 22.49 (CH_3), 19.85 (CH_2), 13.99 (2 CH_3); MS (EI, 70 eV), m/z: 129 (8.31), 112 (38.66), 71 (100.00), 57 (98.72).

***R*-(-)-Benzyl-2-butyl carbonate:** $[\alpha]_D^{25=}$ -10.5 (c= 0.3, $CHCl_3$).

***S*-(+)-Benzyl-2-octyl carbonate:** $[\alpha]_D^{25=}$ +10.7 (c= 0.6, $CHCl_3$).

***R*-(+)-Benzyl-1-phenylethyl carbonate:** $[\alpha]_D^{25=}$ +66.2 (c= 0.3, $CHCl_3$).

***R*-(-)-2-Butyl-*n*-octyl carbonate:** $[\alpha]_D^{25=}$ -6.1 (c= 0.6, $CHCl_3$).

***R*-(-)-*n*-Octyl-2-octyl carbonate:** $[\alpha]_D^{25}$= -4.4 (c= 1.1, $CHCl_3$).

Synthesis of carbamates (6). General procedure.

Carbonates (3) (1mmol) and *N*-butylamine (1mmol) were dissolved in 15 mL of diisopropyl ether with 1.5 g of molecular sieves and then 40 mg of SP 435 lipase were added. The reaction was controlled by TLC, and when all the carbonate disappeared, the enzyme was filtered off and the solvent evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel.

Benzyl-*N*-butyl carbamate (6a): oil; Rf=0.34 (hexane:ethyl ether 7:0); IR (neat): $\upsilon_{c=o}$= 1705 cm^{-1}; (Found: C, 69.24; H, 8.17; N, 6.34. $C_{12}H_{17}NO_2$ requieres C, 69.52; H, 8.27; N, 6.76); ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.35 (m, 5H, aromatic), 5.10 (s, 2H, CH_2), 4.75 (bs, 1H, NH), 3.20 (q, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.35 (m, 2H, CH_2), 0.90 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 156.34 (C=O), 136.57 (C), 128.31 (CH), 127.91 (CH), 127.86 (CH), 66.34 (CH_2), 40.63 (CH_2), 31.85 (CH_2), 19.72 (CH_2), 13.56 (CH_3); MS (EI, 70 eV), m/z: 207 (M^+), 108 (78.15), 91 (100.00), 77 (16.47).

***N*-Butyl-*n*-octyl carbamate (6b):** oil; Rf=0.53 (hexane:ethyl ether 7:3); IR (neat): $\upsilon_{c=o}$= 1721 cm^{-1}; (Found: C, 67.98; H, 11.83; N, 6.02. $C_{13}H_{27}NO_2$ requieres C, 68.06; H, 11.87; N, 6.11); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.65 (bs, 1H, NH), 4.00 (t, 2H, CH_2), 3.15 (q, 2H, CH_2), 1.70-1.10 (m, 16H), 0.90 (m, 6H, 2 CH_3); ^{13}C-NMR ($CDCl_3$) δ (ppm): 156.74 (C=O), 64.82 (CH_2), 40.62 (CH_2), 32.05 (CH_2), 31.70 (CH_2), 29.18 (CH_2), 29.12 (CH_2), 29.00 (CH_2), 25.81 (CH_2), 22.57 (CH_2), 19.81 (CH_2), 13.99 (CH_3), 13.65 (CH_3); MS (EI, 70 eV), m/z: 186 (12.29), 118 (100.00), 100 (5.64).

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