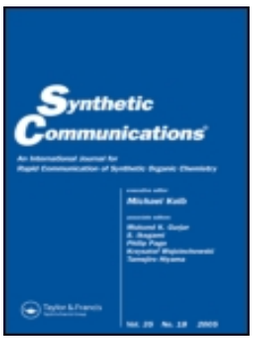

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LIPASE-CATALYZED ACETYLATION OF *tert*-BUTYL *N*-(2-HYDROXY-3-PHENOXYPROPOXY)CARBAMATES—PREPARATION OF OPTICALLY ACTIVE AMINOOXYPROPANOLS

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ABSTRACT

A simple method was developed for the preparation of optically active-3-aryloxy-1-aminooxy-2-propanols by a lipase-catalyzed kinetic resolution of racemic mixtures of their *N*-*tert*-butylcarbamate-protected derivatives.

Many types of optically active amino alcohols, but not aminooxy alcohols, have been obtained to data and used in pharmacy, cosmetics, etc., as well as chiral auxiliares in organic synthesis. It may be expected therefore that β-aminooxy alcohols of the general formula **1** in an optically active form will prove to be valuable synthons or chiral auxiliaries in the synthesis of new biologically active compounds.

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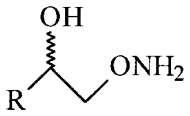
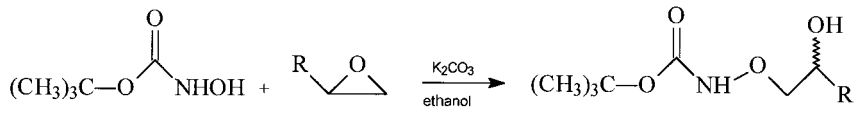


1

For example, some alkoxyamino groups are known as common fragments of the semisynthetic cephalosporin antibiotics of the second and third generation, such as: cefmenoxime, ceftriaxone, cefuroxime, ceftazidime, or of a synthetic monobactam antibiotic aztreonam.[1] However, none of the known antibiotic molecules contains a β-aminooxy alcohol fragment and to the best of our knowledge optically active β-aminooxy alcohols have been described only by us.[2,3]

In the research on a lipase-catalyzed kinetic separation of the enantiomers of β-aminooxy alcohols we were looking for a suitable protection of the amino function. In the preliminary experiments the protection by the phthaloyl and *iso*-propylidene groups was investigated.[2] Simple protection and deprotection procedures and very low cost of the substrates were considered as the main advantages of these groups. However, when some popular commercial lipase preparations were used in the experiments, the optical purities of the separated enantiomers were not always satisfactory. For that reason we decided to investigate the lipase-catalyzed kinetic resolution of some β-aminooxy alcohols with their amino function protected with the *tert*-butylcarbamate group. According to the literature,[4,5] *tert*-butyl *N*-hydroxycarbamate (**2**) can be easily prepared from hydroxylamine and *tert*-butoxycarbonyl azide. When the commercially available di-*tert*-butyl dicarbonate was used instead of the azide, the yield of **2** was by almost 20% higher. In the second step the prepared carbamate was made to react with some epoxides. As it is known,[6] the acylation or alkoxycarbonylation of hydroxylamine occurs at the nitrogen atom. However, further reaction with a mono-*N*-substituted hydroxylamine takes place either on the hydroxyl group if the *N*-substituent is electron-withdrawing or on the nitrogen atom if the substituent has the electron-donating properties. The reactions of monosubstituted epoxides with stoichiometric amounts of the potassium salt of *tert*-butyl *N*-hydroxycarbamate were carried out at room temperature in an ethanol solution to yield the appropriate 1,2-diols with a carbamoyl-protected primary hydroxy group and a free secondary hydroxy group (Scheme 1).

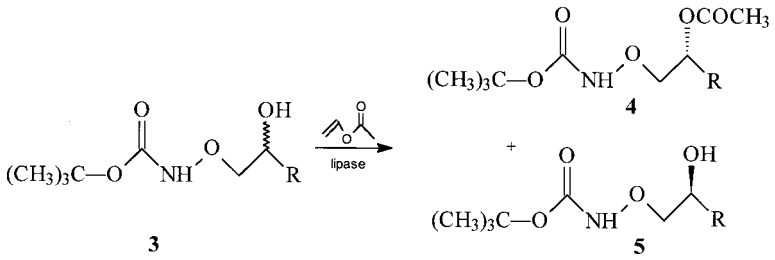
The yields and properties of the prepared *tert*-butyl carbamates of the general formula **3** as well as their ^{1}H NMR and IR spectral data are presented in Table 1.



2 **3**

R= $C_6H_5OCH_2$ **(a)**
4-CH_3-$C_6H_4OCH_2$ **(b)**
1-$C_{10}H_7OCH_2$ **(c)**
C_6H_5 **(d)**

Scheme 1.



Scheme 2.

The prepared *N*-(2-hydroxyalkoxy)-*tert*-butyl carbamates (**3**) were subjected to the lipase-catalyzed esterification with an excess of vinyl acetate as the acyl donor. The reactions were carried out in a *tert*-butyl methyl ether solution. In the preliminary experiments, *tert*-butyl *N*-(2-hydroxy-3-phenoxypropoxy)carbamate (**3a**) was the substrate and the lipase preparations used were: Amano PS (*Pseudomonas cepacia*), Amano 20 (*Pseudomonas fluorescens*), and Novozym 435 (*Candida antarctica*). With all three lipases the reactions were very slow at room temperature; the slowest was that with Amano PS, but this enzyme gave the product of a highest enantiomeric excess. All the reactions were monitored by TLC and the conversion degree (c%) was determined by HPLC (Scheme 2).

The mixtures of the resulting acetates (**4**) and unchanged alcohols (**5**) were separated by a column chromatography on silica gel; the results are presented in Table 2, and the spectral data of the resulting acetoxycarbamates in Table 3.

As it may be seen, the fastest reaction was that with Novozym 435 but its enantioselectivity E was very poor. On the other hand, the use of Amano PS looked very promising. For this reason, the acetylations of

Table 1. Yields and Properties of the Synthesized Carbomates of the General Formula **3**

No	Yield (%)	M.p. (°C)	Analysis Calculated %C	%H	%N	Found %C	%H	%N	^{1}H NMR (δ ppm, $CDCl_3$)	IR (Nujol, cm^{-1})
3a	47	82–84	59.13	7.79	4.92	59.14	7.45	4.80	1.49 (s, 9H); 3.90–4.10 (m, 4H); 4.21–4.40 (m, 2H); 6.88–7.38 (m, 5H); 7.38 (bs, 1H).	3310; 3200; 1690; 1580.
3b	52	76–78	60.38	8.11	4.69	60.44	7.83	4.53	1.49 (s, 9H); 2.22 (s, 3H); 3.40 (bs, 1H); 3.91–4.11 (m, 4H); 4.20–4.28 (m, 1H); 6.81–7.40 (m, 4H); 7.41 (bs, 1H).	3300; 3180; 1700; 1580.
3c	45	118–120	64.84	6.95	4.20	64.57	7.16	4.20	1.50 (s, 9H); 4.07–4.32 (m, 4H); 4.40–4.49 (m, 2H); 6.80–8.25 (m, 7H); 7.46 (bs, 1H).	3360; 3290; 1700; 1580.
3d	49	80–82	61.87	7.18	5.55	62.18	7.59	5.39	1.48 (s, 9H); 2.17 (s, 1H); 3.58–4.30 (m, 2H); 4.84 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 8.2$ Hz); 7.14 (bs, 1H); 7.20–7.35 (m, 5H).	3500–3200; 1730; 1580.

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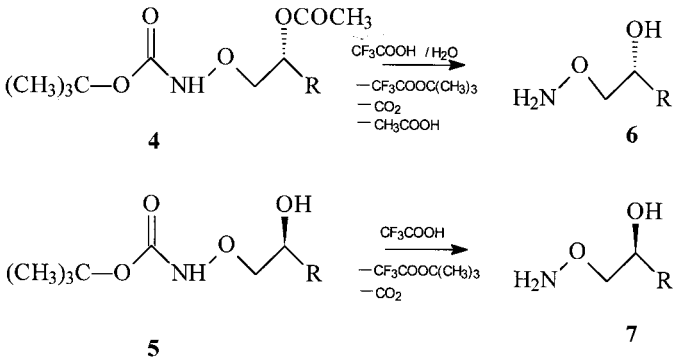
the remaining three carbamates (**3b**, **3c**, **3d**) were catalyzed by Amano PS; the results are collected in Tables 2 and 3. The enantioselectivities of the reactions were good with the exception of that with compound **3d** as the substrate. This can be easily explained since in the case of styrene oxide, as found by Kliegel,[7] the anion attacks the phenyl-substituted carbon atom to yield the corresponding primary alcohol.

The *tert*-butylcarbamate protecting groups of the separated enantiomers of *N*-(2-acetoxy-3-phenoxypropoxy)carbamates (**4**) and *N*-(2-hydroxy-3-phenoxypropoxy)carbamates (**5**) were easily removed by dissolving the compounds in an excess of trifluoroacetic acid at room temperature. Under these conditions the acetyl group was also removed thus yielding free aminooxy alcohols **6** and **7**, respectively (Scheme 3).

The aminooxy alcohols **6** and **7** were isolated as hydrochlorides by treating the reaction mixtures with a solution of hydrogen chloride in diethyl ether. The melting points of the aminooxy alcohol hydrochlorides prepared by this method were identical with those obtained[2] with the phthaloyl or *iso*-propylidene protecting groups, but the yields were considerably higher. In addition, their optical purities (Table 4) were much higher than those prepared previously.[2]

The signs of optical rotation were consistent with those previously determined[2] for the hydrochlorides **6a**–**c** and **7a**–**c**. Taking into account enantioselectivities of the used lipases and comparing the optical rotation data with those available for other β-aminooxy alcohols prepared by the enantiomer separation[2] and by the stereoselective reduction[3] of the appropriate ketone (for which the X-ray structure was determined) we presume the levorotatory aminooxy alcohol hydrochlorides posses (*S*) configuration at the stereogenic center.



Scheme 3.

Table 2. Results of the Lipase-Catalyzed Acetylation of the *tert*-Butylcarbamates of the General Formula **3**

Substrate No.	Lipase	Reaction Time (h)	Conversion (%)	*E*	Acetate (**4**)			Unreacted Alcohol (**5**)		
					$[\alpha]_D^{20}$	ee (%)	Yield (%)	$[\alpha]_D^{20}$	ee (%)	Yield (%)
3a	Amano PS	120	51	65	+14	86	47	+6	92	46
3a	Amano 20	96	53	27	+12	79	49	+6	90	41
3a	Novozym 435	24	49	4	+6	46	45	+2.5	44	48
3b	Amano PS	168	48	38	+25	87	47	+1	81	49
3c	Amano PS	504	37	>100	+17	99	33	+5	59	60
3d	Amano PS	192	75	_*	+4	_*	70	+3	_*	23

*No enantiomer separation on the HPLC column used.

Table 3. ^{1}H NMR Chemical Shifts and Characteristic Ir Bands of the Acetoxycarbamates of the General Formula **4**

No.	^{1}H NMR (δ ppm, $CDCl_3$)	IR (cm^{-1}, film)
4a	1.47 (s, 9H); 2.13 (s, 3H); 4.08–4.14 (m, 4H); 5.45–5.55 (m, 1H); 6.87–7.38 (m, 5H); 7.44 (bs, 1H).	3300; 1730; 1720; 1580.
4b	1.48 (s, 9H); 2.13 (s, 3H); 2.20 (s, 3H); 4.10–4.14 (m, 4H); 5.48–5.59 (m, 1H); 6.83–7.18 (m, 4H); 7.44 (bs, 1H).	3300; 1730; 1720; 1580.
4c	1.48 (s, 9H); 2.15 (s, 3H); 4.22 (d, 2H, $J = 5.2$ Hz); 4.32 (d, 2H, $J = 4.6$ Hz); 5.63–5.73 (n, 1H); 6.78–8.22 (m, 7H); 7.46 (bs, 1H).	3300; 1740; 1720; 1570.
4d	1.44 (s, 9H); 2.10 (s, 3H); 4.35 (dd, 1H, $J_1 = 12.3$ Hz, $J_2 = 7.1$ Hz); 4.38 (dd, $J_1 = 12.3$ Hz, $J_2 = 4.0$ Hz); 6.17 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz); 7.34–7.38 (m, 5H); 7.58 (bs, 1H).	3300; 1740; 1720; 1600.

Table 4. The Yields and Properties of the 2-Hydroxy-3-substituted Propoxyamine Hydrochlorides of the General Formulas **6** and **7**

		Enantiomer **6** (from Acetate)			Enantiomer **7** (from Alcohol)		
No.	M.p. (°C)	Yield (%)	ee (%)	$[\alpha]_D^{20}$	Yield (%)	ee (%)	$[\alpha]_D^{20}$
6a and **7a**	120–122	75	86	+10.5	89	92	−11.0
6b and **7b**	132–134	82	57	+12.5	91	81	−11.8
6c and **7c**	192–194	53	99	+15.0	85	59	−8.9

Because of its preparative simplicity the above presented method may turn out to be useful in the preparation of other optically active aminooxy alcohols.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer in $CDCl_3$ solution. IR spectra were taken on a Carl Zeiss Specord M80 instrument. Optical rotation measurements were recorded on P20 Bellingham and Stanley polarimeter. HPLC analyses were performed on a

Thermo-Separation products P-100 instrument. The element analyses were determined on a Perkin-Elmer apparatus. The determination of the products purity, and reactions monitoring were accomplished by TLC on Silica Gel 60 F_{254} plates and the column chromatography on Silica Gel 60 (less than 230 mesh). Lipases Amano AK, Amano PS and Amano 20 were generously provided by Amano Japan, while the Novozym SP-435 by Novo-Nordisk, Enzyme Business, Poland.

General Method for the Preparation of *tert*-Butyl *N*-(2-Hydroxy-3-phenoxypropoxy)carbamates

The appropriate 2-substituted oxirane (0.055 mol) was added dropwise to a stirred solution of *tert*-butyl *N*-hydroxycarbamate (6.65 g, 0.05 mol) and K_2CO_3 (2.08 g, 0.05 mol) in 100 ml of 96% ethanol. The mixture was stirred overnight at room temperature and the volatile materials were completely removed under reduced pressure. The inorganic compounds were washed out with water and the organic residue was extracted with three 50 mL portions of chloroform. The combined extracts were dried over $MgSO_4$ and the solvent was removed. Crystallization from an ethyl acetate/hexane (3 : 1) mixture afforded colorless crystals. The yields and properties of the prepared compounds are collected in Table 1.

Enzymatic Acetylation of *tert*-Butyl *N*-(2-Hydroxy-3-phenoxypropoxy)carbamates

Vinyl acetate (0.93 g, 1 mL, 0.1 mol) was added to the stirred solution of the appropriate racemic alcohol (1 g, 0.004 mol) and the enzyme (lipase Amano AK, 1 g) in methyl *tert*-butyl ether (30 mL). The mixture was stirred at room temperature for several hours, the enzyme was removed by filtration, and the solvent was evaporated under reduced pressure. The remaining mixture of the substrate (alcohol) and the corresponding acetate was separated by a column chromatography on silica gel with a hexane/ethyl acetate mixture (1 : 3) as the eluent. The results of the lipase catalyzed acetylation are collected in Table 2.

Acidolysis of *tert*-Butyl-(+)-*N*-(2-Hydroxy-3-phenoxypropoxy) and (+)-*N*-(2-Acetoxy-3-phenoxypropoxy)carbamates

Trifluoroacetic acid (1.48 g, 1 mL, 0.013 mol) was added to the stirred solution of the appropriate *tert*-butyl (+)-*N*-(2-hydroxy-3-phenoxyprop-

oxy)-or(+)-*N*-(2-acetoxy-3-phenoxypropoxy)carbamate (1 g, ca. 0.004 mol) in 10 mL of diethyl ether. The mixture was stirred for 1 h at room temperature, whereupon 20 mL of 29% HCI in diethyl ether was added to precipitate the product which was separated by filtration and washed with a cold diethyl ether/isopropanol (2 : 1) mixture. The yields and properties of the prepared compounds are collected in Table 4.

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