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Synthesis of optically active aminooxy alcohols

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Abstract

Racemic secondary alcohols with an *N*-protected oxyamino function in the β-position were prepared by a base-catalyzed epoxide ring opening with *N*-hydroxyphthalimide or acetone oxime. The enantiomers were separated with a good selectivity by a lipase-catalyzed acetylation of the racemates with vinyl acetate. The protecting group of the aminooxy alcohol was split off by a hydrochloric acid hydrolysis to yield the hydrochloride of one of the enantiomeric forms of the title compounds.

Keywords: Aminooxy alcohols; Hydroxylamine derivatives; Hydroxyisoxazolidine; Secondary alcohols; Lipase-catalyzed acetylation; Enantiomers separation

1. Introduction

The optically active amino alcohols are constituents of many biologically and pharmacologically important compounds. The most widely used synthesis of optically pure β-amino alcohols consists in the reduction of the amino acid derivatives [1,2]. Chiral cyanohydrins are another convenient substrates since their reduction with lithium aluminum hydride results in the formation of the derivatives of 1,2-aminoethanol [3,4]. There are also known methods using formamidines as, for example, in the synthesis of propranolol [5]. Optically active α-chloro-, α-bromo-, α-nitro-, and α-azidohydrins are other potential precursors, which may be used as starting materials for 1,2-amino alcohols. Unfortunately, none of these methods can be applied to the preparation of optically active aminooxy alcohols which seem to be very interesting building blocks in the search for novel biologically active compounds.

A highly attractive method for the preparation of pure enantiomers consists in the use of biocatalysts, either in an enzyme-catalyzed preparation of chiral compounds from achiral substrates or in an enzymatic resolution of racemic mixtures. The last method was successfully applied to the preparation of optically active amino alcohols in quite a number of cases [6–15] and its possible application to the preparation of optically active aminooxy alcohols looks rather promising. To the best of our knowledge, optically active aminooxy alcohols have not been prepared to date, although some optically active hydroxylamine derivatives having no alcohol function have been synthesized by routine transformations of the corresponding optically active substrates

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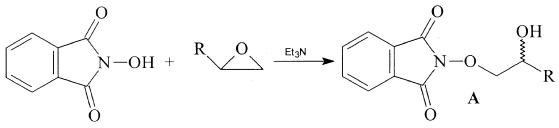


Scheme 1. Synthesis of *N*-(2-substituted-2-hydroxyethoxy)-phthalimides.

[16–19]. In the preparation of the *O*-substituted hydroxylamines, hydrolysis of the appropriately *O*-substituted oximes or hydroxyphthalimides is used most frequently [20–22]. This method has also been used in the present investigation.

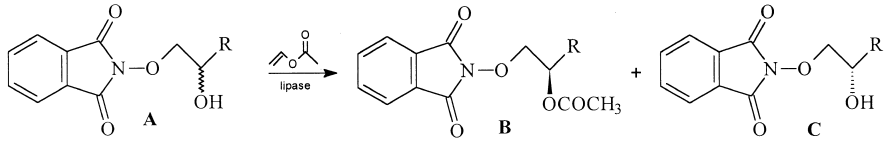
2. Results and discussion

The starting *N*-(2-substituted-2-hydroxyethoxy)-phthalimides **A** were prepared from the appropriate epoxides [20,23,24] and *N*-hydroxyphthalimide according to the known procedure (Scheme 1). However, in accord with the results reported by Kliegel [25], when styrene oxide was used in this reaction the attack of the *N*-hydroxyphthalimide-derived anion was directed towards the phenyl-substituted carbon atom to yield a primary alcohol, *N*-(2-hydroxy-1-phenylethoxy)phthalimide. The prepared *N*-(hydroxyalkoxy)phthalimides **A** were purified by column chromatography or recrystallization. Their yields and physicochemical properties are presented in the Experimental part.

A lipase-catalyzed transesterification with vinyl acetate in a *tert*-butyl methyl ether solution at 23–26°C was used to kinetically resolve the racemic **A** into the corresponding enantiomers (Scheme 2).

In the preliminary experiments, the catalytic efficacies of some lipases were evaluated and compared with one another. Thus, Novozym SP-435 (lipase B from *Candida antarctica*) was found to be the best catalyst in the reaction with **A**1 and **A2**, lipase Amano PS (*Pseudomonas cepacia*), with **A**3 and **A**6, and lipase Amano AK (*Pseudomonas sp.*), with **A**4 and **A**5. Detailed results of these reactions are presented in Table 1, whereas the ^{1}H NMR chemical shift data of the reaction products (**B** and **C**), in the Experimental part.

The reaction time was set separately for each substrate depending on its reactivity. The conversion degree was determined by analyzing the ^{1}H NMR spectra of crude reaction mixtures. Column chromatography was used in order to separate the prepared acetates from the unreactive alcohol enantiomer. The enantiomeric excesses (ee %) of the

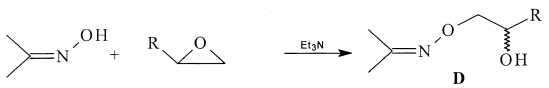


Scheme 2. Lipase-catalyzed acetylation of *N*-(2-substituted-2-hydroxyethoxy)phthalimides.

Table 1
Results of the lipase-catalyzed acetylations of *N*-hydroxyalkoxyphthalimides **A** (1–6)

No.	*R*	Lipase	Reaction time (h)	Conversion (%)	E	Ester **B** (product)				Alcohol **C** (substrate)		
						ee (%)	α_D^{20}	Yield (%)	m.p.(°C)	ee (%)	α_D^{20}	Yield (%)
1	CH_3	Novozym 435	23	45	>100	98	−4.6	40	72–74	80	+32	42
2	$ClCH_2$	Novozym 435	72	43	>100	99	+5.2	41	oil	77	+5.7	46
3	$CH_2=CHCH_2OCH_2$	Amano PS	40	50	7.2	60	0	45	48–49	60	+25	43
4	$CH_3(CH_2)_3OCH_2$	Amano AK	36	51	25	81	0	49	oil	86	+29	45
5	$C_6H_5OCH_2$	Amano AK	120	33	28	90	−67	30	98–99	44	+22	57
6	C_6H_5[a]	Amano PS	24	71	1.6	13	−18	60	80–81	32	+50	25

[a] Primary hydroxyl group.



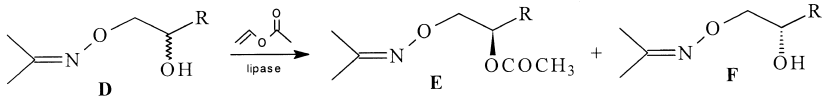
Scheme 3. Synthesis of *O*-(2-substituted-2-hydroxyethyl)acetone oximes.

separated acetates and alcohols were determined by HPLC on a Chiracel ODH chiral column while enantioselectivity (E) of the reaction was calculated with the aid of the generally known equations [26]. Although the absolute configuration of the separated enantiomers was not determined, the kinetically preferred formation of (*R*)-acetates had to be expected in accord with the Kazlauskas' rule [27]. Best results were obtained with the compounds **A**1 and **A2** and the Novozym SP-435 lipase: the enantiomeric excesses of the esters **B** were very high and those of the alcohols **C** quite acceptable, while enantioselectivity of the reactions was excellent. Separation of these compounds with the use of the Amano AK and Amano PS lipases gave inferior results.

Acetylation of compounds **A**3–**A**6 proceeded with a much lower enantioselectivity. Thus, only racemates of the acetates **B**3–**B**6 were obtained with Novozym SP-435 as the catalyst. The relative bulkiness of the substituent *R* may be here considered as one of the possible reasons for the loss of enantioselectivity since it is known that kinetic separations of secondary alcohols are most effective with substrates having substituents of different size and polarity on the stereogenic center [28]. In order to verify this assumption, racemic mixtures of acetone oxime *O*-(2-hydroxy-2-substituted)ethyl ethers (**D**) were synthesized from acetone oxime and the appropriately substituted oxirane (Scheme 3) [21]. Upon purification by column chromatography with a hexane–ethyl acetate mixture (6:1) they were obtained as viscous oils. Their yields and physicochemical data are collected in Table 6 while the ^{1}H NMR spectral data of **D** and of their acetates (**E**) are presented in Table 7 in the Experimental part.

The kinetic separation of the enantiomers of **D** was effected by acetylation with vinyl acetate at room temperature in the presence of the Amano PS lipase which was selected after testing four lipase preparations (those referred to earlier and Amano 20) in the reaction with the compound 7**D**. The appropriate optically active acetates **E** and the not reacting alcohol enantiomer **F** were obtained as viscous oils (Scheme 4). Detailed results of the separation are collected in Table 2.

The results presented in Tables 1 and 2 show that the enantiomer separations were more effective in the case of the *o*-phthaloyl-protected (**A**) than in that of the isopropylidene-protected (**D**) compounds. The

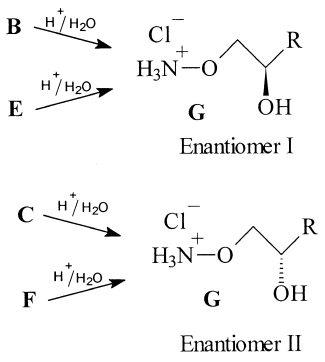


Scheme 4. Lipase-catalyzed acetylation of *O*-(2-substituted-2-hydroxyethyl)acetone oximes.

Table 2
The results of the lipase-catalyzed enantiomers separation of the acetone oxime-derived alcohols of the general structure **D**

No.	*R*	Reaction time (h)	Conversion (%)	E	Acetate (**E**)			Alcohol (**F**)		
					ee (%)	α_D^{20}	Yield (%)	ee (%)	α_D^{20}	Yield (%)
7	$C_6H_5OCH_2$	120	47	17	80	+13.6	45	71	+12	51
8	3-CH_3–$C_6H_4OCH_2$	144	50	51	89	+7	49	92	+14	47
9	4-CH_3–$C_6H_4OCH_2$	120	44	14	77	+8.3	41	60	+9.3	52
10	2-Cl–$C_6H_4OCH_2$	48	66	1	2	+2.5	62	1	+2.5	32
11	1-Naphthyl-OCH_2	144	49	12	71	+10	48	70	+12	50
12	C_6H_5[a]	48	58			+7	56		+9	40

[a] No enantiomers separation on the used chiral column.

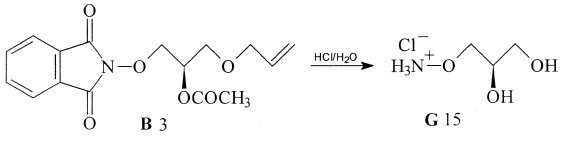


Scheme 5. Hydrolysis of *N*-(2-substituted-2-acetoxyethoxy)phthalimides (**B**), *O*-(2-substituted-2-acetoxyethyl)acetone oximes (**E**) and their not acetylated derivatives (**C**) and (**F**), respectively.

difference in the size of the substituents in the close neighborhood of the hydroxy group, greater in **A** than in **D**, may be responsible for the effect.

Hydrolysis with a dilute (1:1) hydrochloric acid was used to remove the *o*-phthaloyl and isopropylidene groups introduced as a protection in the preparation of the optically active oxyamino alcohols and their acetates **B**, **C**, **E**, and **F**. With the phthalimide derivatives **B** and **C** the hydrolysis was carried out at room temperature, whereas heating at 60–70°C was required in the case of the oxime derivatives **E** and **F**. Hydrolysis of the acetates (**B** and **E**) removed also the acetyl groups. Unexpectedly, hydrolysis of the allyloxymethyl derivatives **B**3 and **C**3 yielded enantiomers of 3-aminooxy-1,2-dihydroxypropane hydrochlorides (**G**15) Schemes 5 and 6.

The yields and physicochemical and spectroscopic properties of the optically active aminooxy alcohol hydrochlorides of the general formula **G** are presented in the Tables 8 and 9 (in the Experimental part), while the optical rotations and enantiomeric excesses (ee) are summarized in Table 3. The optically active aminooxy alcohol hydrochlorides obtained from the acetates **B** and **E** are denoted as



Scheme 6. Hydrolysis of *N*-(2-acetoxy-3-propen-2-oxy)propoxyphthalimide.

Table 3
Optical rotations and enantiomeric excesses (ee) of the aminooxy alcohol hydrochlorides of the general formula **G**

No.	*R*	Enantiomer I		Enantiomer II	
		α_D^{20}	ee (%)	α_D^{20}	ee (%)
13	CH_3	−19	98	+18	80
14	$ClCH_2$[a]	−10	99	+7.5	72
15	$HOCH_2$	−5	60	[b]	60
16	$CH_3(CH_2)_3OCH_2$	−2.5	81	[b]	86
17	$C_6H_5OCH_2$	+10	80	−8	70
18	1-Naphthyl-OCH_2	+11	71	−8.5	70
19	3-CH_3−$C_6H_4OCH_2$	[b]	92	−8	88
20	4-CH_3−$C_6H_4OCH_2$	+11	77	−8.5	60

[a] 4-Hydroxyisoxazolidine hydrochloride (formula **H**).
[b] Not measured.

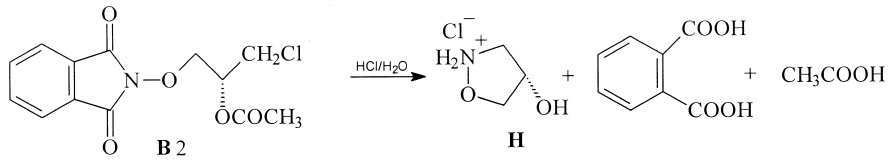
enantiomer I, while those from the unreacted alcohols as enantiomer II.

Hydrolysis of *N*-(3-chloro-2-hydroxypropoxy)-phthalimide (compound **C**2) and N-(3-chloro-2-acetoxypropoxy)phthalimide (**B**2) failed to yield the expected enantiomers of *O*-(3-chloro-2-hydroxypropyl) hydroxylamine (Scheme 7). The enantiomers of 4-hydroxyisoxazolidine hydrochloride (**H**) formed by an intramolecular cyclization of the chlorohydroxylamine were obtained instead. Details of the latter reaction are the subject of a separate paper, which reports also on the separation of the enantiomers of **H** [29].

The results presented above indicate that kinetic acetylation of chiral aminooxy alcohols with the aid of lipase preparations may be considered as a relatively simple preparative method of separating the enantiomers of these compounds. Further transformations may lead to other hydroxylamine derivatives that have not been prepared to date. Although the optical purity (ee) of the products is not very high, it is still comparable with those noted in most reactions of kinetic enzymatic resolutions. Determination of the absolute configuration on the stereogenic center of the alcohols calls for further investigations.

3. Experimental

^{1}H NMR spectra were recorded on a Varian 200 MHz spectrometer. IR spectra were taken on a Carl



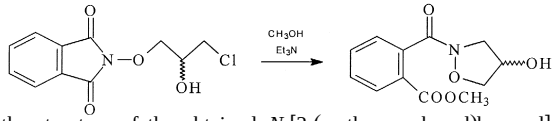
Scheme 7. Hydrolysis of *N*-(3-chloro-2-acetoxypropoxy)phthalimide.

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 elemental analyses were determined on a Perkin-Elmer apparatus. The determination of the

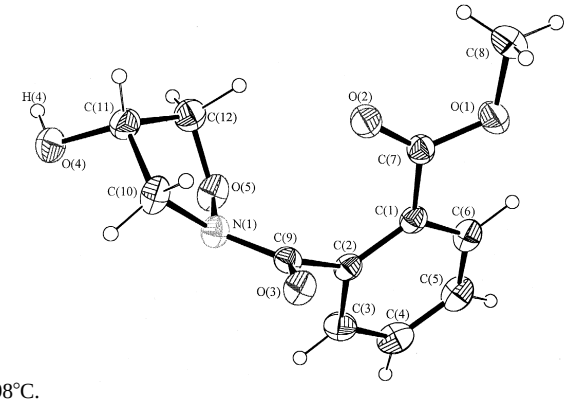
Table 4
Yields and properties of the synthesized *N*-(2-substituted-2-hydroxyethoxy)phthalimides of the general formula **A**

No.	*R*	Yield (%)	m.p. (°C)	IR ν_{OH}, ν_{CO} (cm^{-1})	Analyses					
					Calculated			Found		
					%C	%H	%N	%C	%H	%N
A1	CH_3	58	94–96[a]	3500; 1780–1780	59.73	5.01	6.33	59.72	4.99	6.51
A2	$ClCH_2$	51	70–72[b]	3500; 1650–1780	51.68	3.94	5.48	51.80	3.84	5.56
A3	$CH_2=CHCH_2OCH_2$	59	oil	3500; 1690–1790	60.40	5.43	5.03	60.64	5.55	4.95
A4	$CH_3(CH_2)_3OCH_2$	61	oil	3500; 1700–1790	61.42	6.53	4.78	61.11	6.31	4.64
A5	$C_6H_5OCH_2$	49	103–105	3510; 1730–1780	65.17	4.83	4.47	64.88	4.72	4.31
A6	C_6H_5	35	120–122[c]	3100–3500; 1730	67.84	4.63	4.94	67.59	4.54	4.90

The difference between the m.p. value of **A2** recorded by us and that reported in the literature [24] prompted us to find further evidence for the proposed structure. It was obtained by cyclization of the *N*-(3-chloro-2-acetoxypropoxy)phthalimide **(A2)** according to the scheme:



followed by X-ray determination of the structure of the obtained *N*-[2-(methoxycarbonyl)benzoyl]-4-hydroxyisoxazolidine. The ORTEP diagram is presented below.



[a] Literature [20] gives m.p. 96–98°C.
[b] Literature [24] m.p. 111–113°C.
[c] According to the literature [25] the compound is a primary alcohol and melts at 116–117°C. IR spectra were taken in Nujol.

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.

3.1. *N*-(2-Substituted-2-hydroxyethoxy)phthalimides (**A**1, **A**3–6)

N-(2-Substituted-2-hydroxyethoxy)phthalimides (**A**1, **A**3–6) were prepared from the appropriate epoxides and *N*-hydroxyphthalimide according to the procedure given by Kliegel [20]. The results are summarized in Table 4.

3.2. *N*-(2-Hydroxy-3-chloropropoxy)phthalimide (**A2**)

Epichlorhydrin (5.31 g, 57 mmol) was added dropwise at room temperature to a stirred solution of *N*-hydroxyphthalimide (8.57 g, 50 mmol) and triethylamine (5 ml) in 45 ml of dioxane. The mixture was heated for 9 h at 45–50°C. Upon cooling 50 ml of a 10% aqueous Na_2CO_3 solution was added and the mixture was extracted with chloroform. Subsequent drying and evaporation of the solvent left an oily residue, which was purified by recrystallization from ethyl acetate. Its physicochemical properties and yield are given in Table 4.

3.3. *N*-[2-(Methoxycarbonyl)benzoyl]4-hydroxyisoxazolidine

N-(2-Hydroxy-3-chloropropoxy)phthalimide (1 g, 4 mmol) was added to a stirred solution of triethylamine (1 ml) in 20 ml of methanol. After stirring for 1 h at room temperature the solvent was evaporated under reduced pressure. Water (30 ml) was added to the residue, and the mixture was extracted with chloroform and dried over sodium sulfate. After evaporation of the chloroform the oily residue was crystallized from ethyl acetate to yield colorless crystals, melting point (m.p.) 112–114°C, in 96% yield. The m.p. reported in Ref. [24] is also 112–114°C.

Table 5
M^1H NMR spectral data of compounds of the general formula **A** and **B**

No.	*R*	^{1}H NMR: δ ppm ($CDCl_3$)
A1	CH_3	1.17 (d, 3H, $J = 6.2$ Hz); 3.87–4.25 (m, 4H); 7.76–7.89 (m, 4H)
B1	CH_3	1.35 (d, 3H, $J = 6.6$ Hz); 2.08 (s, 3H); 4.21–4.25 (m, 2H); 5.15–5.30 (m, 1H); 7.75–7.95 (m, 4H)
A2	$ClCH_2$	3.69 (d, 2H, $J = 5.4$ Hz); 4.09–4.42 (m, 4H); 7.76–7.89 (m, 4H)
B2	$ClCH_2$	2.12 (s, 3H); 3.89 (dd, 1H, $J_1 = 11.4$ Hz, $J_2 = 4.8$ Hz); 3.93 (dd, 1H, $J_1 = 11.4$ Hz, $J_2 = 5.2$ Hz); 4.39 (dd, 1H, $J_1 = 11.3$ Hz, $J_2 = 5.6$ Hz); 5.45 (dd, 1H, $J_1 = 11.3$ Hz, $J_2 = 5.0$ Hz); 5.27–5.32 (m, 1H); 7.75–7.92 (m, 4H)
A3	$CH_2 = CHCH_2OCH_2$	3.18 (bs, 1H); 3.54–3.59 (m, 2H); 3.82–4.37 (m, 5H); 5.12–5.29 (m, 2H); 5.76–5.98 (m, 1H); 7.70–7.85 (m, 4H)
B3	$CH_2 = CHCH_2OCH_2$	2.07 (s, 3H); 3.68–3.71 (m, 2H); 3.97–4.01 (m, 2H); 4.25–4.50 (m, 2H); 5.05–5.26 (m, 3H); 5.78–5.98 (m, 1H); 7.70–7.82 (m, 4H)
A4	$CH_3(CH_2)_3OCH_2$	0.84 (t, 3H, $J = 7.2$ Hz); 1.20–1.57 (m, 4H); 3.38–3.54 (m, 5H); 4.05–4.31 (m, 3H); 7.68–7.95 (m, 4H)
B4	$CH_3(CH_2)_3OCH_2$	0.87 (t, 3H, $J = 7.0$ Hz); 1.20–1.59 (m, 4H); 2.09 (s, 3H); 3.36–3.56 (m, 2H); 3.68 (d, 2H, $J = 5.0$ Hz); 4.33 (dd, 1H, $J_1 = 11.1$ Hz, $J_2 = 6.4$ Hz); 4.42 (dd, 1H, $J_1 = 11.1$ Hz, $J_2 = 4.0$ Hz); 5.19–5.29 (m, 1H); 7.64–7.85 (m, 4H)
A5	$C_6H_5OCH_2$	3.53 (bs, 1H); 4.08–4.51 (m, 5H); 6.88–7.95 (m, 9H)
B5	$C_6H_5OCH_2$	2.11 (s, 3H); 4.30 (d, 2H, $J = 4.7$ Hz); 4.49 (dd, 1H, $J_1 = 11.1$ Hz, $J_2 = 6.1$ Hz); 4.56 (dd, 1H, $J_1 = 11.1$ Hz, $J_2 = 4.1$ Hz); 5.42–5.55 (m, 1H); 6.91–7.81 (m, 9H)
A6	C_6H_5	3.35 (bs, 1H); 4.03–4.50 (m, 3H); 6.88–7.88 (m, 9H)
B6	C_6H_5	2.08 (s, 3H); 4.48 (dd, 1H, $J_1 = 12.7$ Hz, $J_2 = 4.2$ Hz); 4.54 (dd, 1H, $J_1 = 12.7$ Hz, $J_2 = 7.4$ Hz); 5.58 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 7.4$ Hz); 7.35–7.82 (m, 9H)

Table 6
The yields and properties of the *O*-(2-substituted-2-hydroxyethyl)acetone oximes (**D**)

No.	*R*	Yield (%)	IR (cm^{-1}) ν_{OH}, $\nu_{C=N}$	Analyses					
				Calculated			Found		
				%C	%H	%N	%C	%H	%N
7	$C_6H_5OCH_2$	70	3460, 1590	64.55	7.67	6.27	64.40	7.65	6.12
8	3-$CH_3C_6H_4OCH_2$	56	3450, 1580	65.79	8.07	5.90	65.78	7.97	5.47
9	4-$CH_3C_6H_4OCH_2$	65	3440, 1600	65.79	8.07	5.90	65.62	7.88	5.53
10	2-$ClC_6H_4OCH_2$	51	3450, 1580	55.90	6.26	5.44	55.63	6.08	5.19
11	(1-$C_{10}H_7$)OCH_2	47	3400, 1580	70.30	7.00	5.12	70.00	6.97	4.87
12	C_6H_5[a]	61	3420, 1490	68.37	7.82	7.25	68.07	7.93	7.53

[a] Literature [21] gives b.p. 121–125°C/1mm Hg.

*3.4. General procedure for the lipase-catalyzed acetylation of N-(2-substituted-2-hydroxyethoxy)-phthalimides (**A**)*

The appropriate alcohol (15 mmol) was dissolved in 50 ml of *tert*-butyl methyl ether, and 32 mmol (2.79 g, 3 ml) of vinyl acetate followed by 1.5 g of the appropriate lipase were added. The mixture was stirred in closed flask at temperature 23–26°C for the indicated period of time. The enzyme was removed by filtration, and the residue after the solvent evaporation was separated on the silica gel column with ethyl acetate/hexane 1:4 mixture.

The yields and properties of the obtained acetates (**B**) and alcohols (**C**) are collected in Table 1, while their ^{1}H NMR chemical shift data in Table 5.

*3.5. O-(2-Substituted-2-hydroxyethyl)acetone oximes (**D**7–12)*

O-(2-Substituted-2-hydroxyethyl)acetone oximes (**D**7–12) were prepared according to [21] and puri-

Table 7
M^{1}H NMR spectral data of compounds of the general formula **D** and **E**

No.	*R*	^{1}H NMR: δ ppm ($CDCl_3$)
D7	$C_6H_5OCH_2$	1.92 (s, 3H); 1.94 (s, 3H); 2.93 (bs, 1H); 3.39–4.10 (m, 2H); 4.21–4.35 (m, 3H); 6.85–7.35 (m, 5H)
E7	$C_6H_5OCH_2$	1.84 (s, 3H); 1.87 (s, 3H); 2.09 (s, 3H); 4.00–4.40 (m, 4H); 5.40–5.52 (m, 1H); 6.85–7.33 (m, 5H)
D8	3-CH_3-$C_6H_4OCH_2$	1.87 (s, 3H); 1.88 (s, 3H); 2.32 (s, 3H); 3.40 (bs, 1H); 4.00–4.29 (m, 5H); 6.70–7.20 (m, 4H)
E8	3-CH_3-$C_6H_4OCH_2$	1.83 (s, 3H); 1.86 (s, 3H); 2.09 (s, 3H); 2.32 (s, 3H); 4.09–4.29 (m, 4H); 5.37–5.47 (m, 1H); 6.68–7.20 (m, 4H)
D9	4-CH_3-$C_6H_4OCH_2$	1.88 (s, 3H); 1.89 (s, 3H); 2.23 (s, 3H); 4.03 (d, 2H, $J = 5.8$ Hz); 4.15–4.35 (m, 4H); 6.81–7.15 (m, 4H)
E9	4-CH_3-$C_6H_4OCH_2$	1.84 (s, 3H); 1.86 (s, 3H); 2.09 (s, 3H); 2.22 (s, 3H); 4.00–4.32 (m, 4H); 5.43–5.53 (m, 1H); 6.77–7.18 (m, 4H)
D10	2-Cl-$C_6H_4OCH_2$	1.88 (s, 3H); 1.89 (s, 3H); 2.79–3.00 (bs, 1H); 3.95–4.14 (m, 2H); 4.19–4.33 (m, 3H); 6.84–7.39 (m, 4H)
E10	2-Cl-$C_6H_4OCH_2$	1.81 (s, 3H); 1.82 (s, 3H); 1.83 (s, 3H); 1.84 (s, 3H); 2.10 (s, 3H); 4.15 (dd, 1H, $J_1 = 10.6$ Hz, $J_2 = 5.6$ Hz); 4.24 (dd, 1H, $J_1 = 10.6$ Hz, $J_2 = 4.2$ Hz); 4.32 (d, 1H, $J = 5.2$ Hz); 4.39 (d, 1H, $J = 5.2$ Hz); 5.41–5.52 (m, 1H); 6.87–7.45 (m, 4H)
D11	1-Naphthyl-OCH_2	1.89 (s, 3H); 1.90 (s, 3H); 2.78 (bs, 1H); 4.15–4.57 (m, 5H); 6.82–8.29 (m, 7H)
E11	1-Naphthyl-OCH_2	1.85 (s, 3H); 1.87 (s, 3H); 2.12 (s, 3H); 4.23–4.40 (m, 4H); 5.58–5.68 (m, 1H); 6.77–8.27 (m, 7H)
D12	C_6H_5	1.87 (s, 3H); 1.96 (s, 3H); 2.90 (bs, 1H); 3.82 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 2.2$ Hz); 3.93 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 5.4$ Hz); 5.25 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 5.4$ Hz); 7.25–7.35 (m, 5H)
E12	C_6H_5	1.83 (s, 3H); 1.93 (s, 3H); 2.05 (s, 3H); 4.29 (dd, 1H, $J_1 = 11.6$ Hz, $J_2 = 4.4$ Hz); 4.38 (dd, 1H, $J_1 = 11.6$ Hz, $J_2 = 7.4$ Hz); 5.30 (dd, 1H, $J_1 = 4.4$ Hz, $J_2 = 7.4$ Hz); 7.30–7.36 (m, 5H)

Table 8
Yields and properties of the aminooxy alcohol hydrochlorides of the general formula **G**

No.	*R*	Yield (%)	m.p. (°C)	Analyses					
				Calculated			Found		
				%C	%H	%N	%C	%H	%N
13	CH_3	70	114–116	28.24	7.90	10.98	28.45	7.55	10.90
14	$ClCH_2$[a]	73	146–148	28.70	6.42	11.16	28.90	6.05	10.99
15	$HOCH_2$	62	56–58	25.10	7.02	9.76	25.61	6.76	9.42
16	$CH_3(CH_2)_3OCH_2$	87	sirup	42.11	9.09	7.01	41.93	8.93	6.83
17	$C_6H_5OCH_2$	61	120–122	49.21	6.42	6.38	49.22	6.15	6.09
18	1-Naphthyl-OCH_2	59	192–194	57.89	5.98	5.19	57.52	5.89	4.90
19	3-CH_3–$C_6H_4OCH_2$	72	132–134	51.39	6.90	5.99	51.42	6.78	5.91
20	4-CH_3–$C_6H_4OCH_2$	66	142–144	51.39	6.90	5.99	53.01	6.88	6.02

[a] 4-Hydroxyisoxazolidine hydrochloride (formula **H**).

fied by column chromatography on silica gel with an ethyl acetate/hexane 1:4 mixture. The yields and properties of the prepared acetoxime derivatives (**D**) are summarized in Table 6.

*3.6. Lipase-catalyzed acetylation of O-(2-substituted-2-hydroxyethyl)acetone oximes (**D**)*

To the solution of 20 mmol of the appropriate alcohol in 50 ml of *tert*-butyl methyl ether 42 mmol (3.44 g, 3.7 ml) of vinyl acetate followed by 2 g of Amano PS lipase were added. The mixture was stirred in a closed flask at room temperature for indicated period of time. The enzyme was removed by filtration, and the residue after the solvent evaporation was separated on the silica gel column with ethyl acetate/hexane 1:6 mixture. The yields and properties of the obtained acetates (**E**) and alcohols (**F**) are summarized in Table 2, and their ^{1}H NMR chemical shift data in Table 7.

*3.7. General method for hydrolysis of the compounds **B**, **C**, **E**, and **F***

N-(2-Substituted-2-acetoxyethoxy)phthalimide (**B**, 2.5 mmol) or *N*-(2-substituted-2-hydroxy)phthalimide (**C**, 2.5 mmol) was dissolved in 5 ml of 16% aqueous HCl solution and stirred for 6 h at room temperature. After evaporation of the acid under reduced pressure the resulting aminooxy alcohol hydrochloride was recrystallized from an isopropanol–ethyl ether 1:6 mixture.

Table 9
M^{1}H NMR spectra of aminooxy alcohol hydrochlorides of the general formula **G**

No.	δ ppm in DMSO-d_6
13	1.00–1.03 (m, 3H); 3.61 (bs, 2H); 3.79–3.89 (m, 4H)
14[a]	3.36 (d, 1H, $J = 11.2$ Hz); 3.47 (dd, 1H, $J_1 = 11.2$ Hz, $J_2 = 4.6$ Hz); 4.02 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 3.6$ Hz); 4.07 (d, 1H, $J = 8.4$ Hz); 4.76–4.81 (m, 1H)
15[b,c]	3.52–3.68 (m, 2H); 3.94–4.21 (m, 3H)
16[b]	0.89 (t, 3H, $J = 7.4$ Hz); 1.24–1.43 (m, 2H); 1.49–1.63 (m, 2H); 3.53–3.60 (m, 4H); 4.04–4.22 (m, 3H)
17	3.40 (bs, 2H); 3.91–4.17 (m, 6H); 6.89–7.28 (m, 5H); 11.20 (bs, 2H)
18	3.42 (bs, 2H); 4.11–4.34 (m, 6H); 6.93–8.26 (m, 7H); 11.05 (bs, 2H)
19[b]	2.34 (s, 3H); 4.05–4.36 (m, 5H); 6.83–6.95 (m, 3H); 7.28 (dd, 1H, $J_1 = J_2 = 8$ Hz)
20[b]	2.25 (s, 3H); 4.06–4.22 (m, 2H); 4.25–4.46 (m, 3H); 6.96–7.03 (m, 2H); 7.21–7.29 (m, 2H)

[a] 4-Hydroxyisoxazolidine hydrochloride (formula **H**).
[b] The spectra taken in D_2O solution.
[c] In ^{13}C NMR spectrum taken in D_2O solution, $\delta = 62.40$; 69.92; 73.13 ppm.

The hydrolysis of the acetoxime derivatives **E** and **F** required refluxing of the mixtures for 20 min.

The yields, physicochemical, and spectroscopic properties of the prepared aminooxy alcohol hydrochlorides (**G**) are given in Tables 8 and 9.

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