Ethyl (1*S*, 2*RS*)- and (1*S*,2*S*)-2-(2-chloro-propanoyloxy)propanoate. Preparation and hydrolysis

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Abstract: Ethyl (1*S*,2*RS*)-2-(2-chloropropanoyloxy)propanoate ((1*S*,2*RS*)-(**I**)) was obtained from *rac*-2-chloropropionyl chloride and ethyl L-lactate. (1*S*,2*S*)-(**I**) was also synthesized from (*S*)-2-chloropropionyl chloride and ethyl L-lactate with 93% d.e. (**I**) was undertaken hydrolysis by different media: NaOH/THF-H$_2$O, Na$_2$CO$_3$/THF-H$_2$O, LiOHxH$_2$O/THF-H$_2$O, 25% NaOH/H$_2$O, and weakly acidic ion-exchange resin Amberlite IRC748 dispersion in MeOH. (1*S*,2*RS*)-2-(2-Chloropropanoyloxy)propanoic acid (**II**) diastereomers were identified as products of acidic hydrolysis with the ionic resin. GC/MS, HPLC and HPLC/MS analyses of resulted products are presented.

Keywords: ethyl L-lactate, 2-chloropropionyl chloride, diastereomers, ethyl 2-(2-chloro-propanoyl-oxy)propanoate, hydrolysis

INTRODUCTION

Ethyl L-lactate (**IV**) was applied as a chiral auxiliary for selective esterification of racemic acid chlorides by R. D. Larsen et al. [1]. In 1989 reported an asymmetric transformation of racemic ibuprofen, going *via* tertiary amine-catalyzed addition of chiral alkohols (ethyl L-lactate, izobutyl (*R*)-lactate, (*R*)-pantolactone (**III**) to *rac*-2-arylpropionic acids, and resulted in *S* or *R* enantiomers of the respective esters with 94-99% diastereomeric excess.
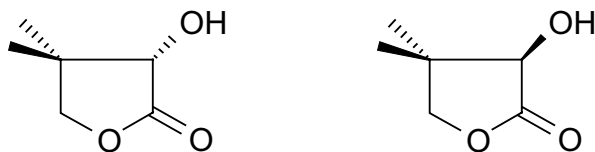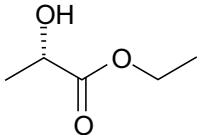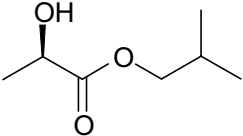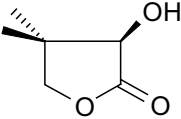
(*S*)- and (*R*)-pantolactone (**III**)
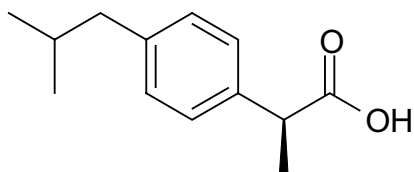
(*S*)-(+)-ibuprofen

Ethyl L-lactate was stated to provide the *S* stereochemistry at C2 chiral center. The character of substituents attached to the aromatic ring did not affect the reaction diastereoselectivity – as well electron donating 4-methoxyphenylketenes, as electron withdrawing 4-nitrophenylketenes established a similar and high selectivity. The best diastereoselectivities were obtained for the reactions done in solvents of low polarity (heptane, hexane, toluene). The less sterically hindered tertiary amines provided a more efficient generation of ketenes, thus – higher diastereoselectivities (trimethylamine, *N*-methylpyrrolidine: 94-99% d.e.). The authors compared the degree of diastereoselectivity vs. the temperature of reaction, and found only a 7% drop between the reaction performed at room temperature and at -78 °C. The optimum conditions with ethyl L-lactate were described as follows: -78 °C, concentration 0.02 M (obtained ibuprofen ester *S,S/R,S* as 98.6:1.4); the substrates were added as follows: the acid chloride was dropped at room temperature to the tertiary amine (300 mol %) dissolved in heptane or toluene to generate the ketene, next, at -78 °C the chiral alcohol (120 mol %) dissolved in the same solvent in concentration of 0.2 M was dropped. In all cases the (*S*)- and (*R*)-hydroxy esters provided predominantly *S* and *R* stereochemistry. (*R*)-Pantolactone (**III**) was found to be remarkable selective chiral auxiliary for asymmetric synthesis discussed by the authors. The obtained diastereoselectivities for described in the article chiral alkohols were as in Table 1.

Table 1. Diastereoselectivity of reaction of ketene derived from racemic ibuprofen with different chiral α-hydroxy esters

R*OH	Ratio of obtained diastereomers
	97 : 3 *S,S/ R,S*
	97 : 3 *R,R/S,R*
	>99 : 1 *R,R/S,R*

In 1992 the other authors (T. Durst and K. Koh) [2] reported the results of work on the reaction of (*R*)-pantolactone (**III**) with α-halogenated ketenes, afforded in the high yields and excellent diastereomeric excesses (d.e. 75 to > 95 %) of resulted α-haloesters. In most of the cases a new chiral center had *S* configuration.

The authors gave a representative procedure as follows: α-halo acid halide (1-5 mmol) in dry THF (15-20 mL) was added dropwise to a solution of (**III**) and dimethylethylamine (2 eq. each, 0.2 M in THF, at -78 °C) over a period of one hour. Next, the cold bath was removed and reaction was allowed to stir at room temperature for 15 min (reaction temperature rose to 10 °C). The rapid warming of such a reaction mixture was essential for obtaining products of high optical purity, since the slow warming caused in the loss of stereoselectivity, due to epimerization generated by the base excess. The authors stated also the influence of the kind of halogens in α-halo acid halides on the reaction diastereoselectivity: α-iodo acid chloride gave better results than α-bromo acid chloride, from the other side – acid bromides form the crucial for reaction selectivity, intermediate labile ketenes more efficiently than acid chlorides. The quantitative proportion of obtained diastereomers was determined by comparison of H-2 and H-2' protons signals detected in ^{1}H NMR spectra.

The configuration of obtained α-haloesters was established indirectly by performing the hydrolysis with lithium hydroxide, followed by comparison of the resulted acids optical rotation with the literature data. In most cases

(**III**) induced the *S* stereochemistry of a new generated chiral centre. The only described exception was *t*-butyl α-bromo ester hydrolizing to the respective acid with *R* stereochemistry. The synthesis of discussed α-haloesters is presented in Scheme 1.
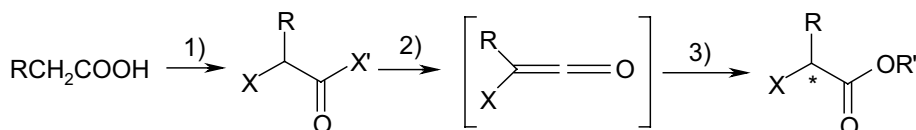
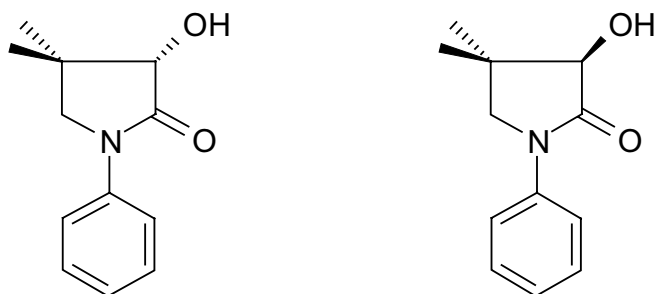X,X' = halogen
R = alkyl, aryl, cycloalkyl
1) oxalyl chloride
2) tertiary amine
3) (*R*)-pantolactone

Scheme 1. Generation of a new chiral center at C-2 in α-halo esters [2].

M. Calmes et al. in 1994 [3] reported the surprising base catalyst effect during asymmetric addition of pantolactone to methyl (3-benzoylphenyl ketene. Investigating the stereochemistry of addition of the ketene derived from racemic ketoprofen, to a chiral alkohol, they used (**III**) as a convenient, chiral auxiliary of natural origin. Ketene was formed in THF, at -10 °C, from the respective acid chloride and tertiary amine – TEA (1.1 eq.). A chiral alcohol was added after 3 h. It was shown that pantolactone is the only alcohol affording an excellent diastereoselectivity. Following the work of Larsen et al. [1] they also observed only a slight dependence of selectivity from temperature, if it was lower than -10 °C (max loss of selectivity, from -78 to -10 °C, was 2%). At room temperature the selectivity decreased to 15%. Stereochemistry dependence on the tertiary amine was proved by replacement of TEA by the different bases of various bulkiness, e.g.: pyridine, trimethylamine, *N*-methylmorpholine. During experiments, the order of components addition was also investigated. It was then shown that it did not significantly affect the diastereoselectivity. The less hindered nucleophilic bases (trimethylamine, triethylamine, NMM) induced the excellent diastereoselectivity for (*RR*) isomer; the hindered bases, as pyridine, afforded the opposite stereochemistry (*SR*), but with low diastereoselectivity (for instance in pyridine case, the ratio was 46:54, *RR/SR*).

On the basis of the already proposed mechanisms [2, 3] of the discussed asymmetric addition, the authors suggested simultaneous participation of two mechanisms in the process. The predominance of one on the other depends on

the character of the applied base. According to the first mechanism, reaction is proceeding through the addition of the amine to the previously formed ketene, followed by asymmetric protonation by a chiral alcohol. In the second mechanism, initially formed an amine-alkohol complex reacts with ketene affording an ion pair. The latter collapse results in the observed stereoselectivity. Schematically it was depicted as in Scheme 2. In case of the nucleophilic unhindered base, the first mechanism is promoted, and amine generates with ketene the least hindered enolate. Protonation with pantolactone is then highly stereoselective. When hindered base is used, the addition to ketene is disfavored, and complex amine-alkohol is formed. Since amine complexation should be done on the less hindered face of the alcohol, the reaction stereoselectivity can be affected and even reversed.

Mechanism 1: initial addition of amine on ketene

Mechanism 2: initial formation of amine-alkohol complex

Scheme 2. Two mechanisms involved in asymmetric addition of chiral alkohol to ketene [3].

The other authors, P. Camps et al. [4, 5] reported a synthesis of a new chiral auxiliary, related to pantolactone: racemic 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone (**IV**), its enzyme-catalyzed resolution to (*R*)- and (*S*)- enantiomers, and their subsequent application to the asymmetric synthesis of α-arylpropionic acids.

(*S*)- and (*R*)- 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone (**IV**)

In 1998 the same group of researchers [6] published the work concerning deracemization of *rac*-α-chlorocarboxylic acids by reaction of their acid chlorides with (*R*)- or (*S*)-(**IV**), followed by a mild basic hydrolysis. The best results were reached for (*S*)-2-chloropropionic acid (optical purity 99%). Working on the deracemization of *rac*-2-chloropropionyl chloride with (*S*)-(**IV**), performed in dichloromethane at -20 °C, they noticed a very strong effect of tertiary amine (2.2 equiv.) on reaction diastereoselectivity, what was in great accordance with data previously reported by the other authors for (*R*)- or (*S*)-(**III**). The highest diastereoselectivity (96%) was attained for reaction performed with triethylamine. The resulted ester possessed *R* stereochemistry on C2 (α) atom. Slightly lower diastereoselectivity was obtained for ethyldiizopropylamine (d.e. 49%), and *N*-methylmorpholine (d.e. 46%). In the case of hindered bases, as pyridine or its derivatives, the diastereoselectivities were very low (as 2%) and reversed (α *S*,3*S*). When (*R*)-(**IV**) was used, the main product obtained was diastereomer (α*S*,3*R*). After a mild hydrolysis with LiOH, the optically pure enantiomers of (*S*)-2-chloropropionic acid (with (*R*)-(**IV**), e.e. 98%, yield 86%)) or (*R*)-2-chloropropionic acid (with (*S*)-(**IV**), e.e. 99%, yield 85%) were obtained.

In the quoted above article of Calmes et al**.** [3]**,** a significant effect of the tertiary amine on the reaction course was explained by the formation of enolate (generated due to the addition of the amine to the previously formed ketene), and its further reaction with the chiral alcohol. For the case of the reaction conditions applied by Camps et al**.** [6], the acid chloride was added to a cold solution (-20 -0 °C) of enantiopure alcohol and amine (2 equiv.), so the ketene could not be previously formed. For that reason they proposed a dynamic kinetic resolution process as a possible alternative mechanism to explain a great influence of amine on the reaction: thus, a racemic acid chloride can give with an amine a racemic mixture of acylammonium cations, being one to the other in a rapid equilibrium *via* the corresponding *E*- and /or *Z*-enolates. The latter are formed

alternatively by the base addition to *in situ* generated ketene. A subsequent slow reaction of cations with chiral alcohol leads predominantly to one of two possible esters in a dynamic kinetic resolution, provided that alcohol reacts faster with one of cations. Schematically the authors set out the proposed mechanism as shown in Scheme 3.
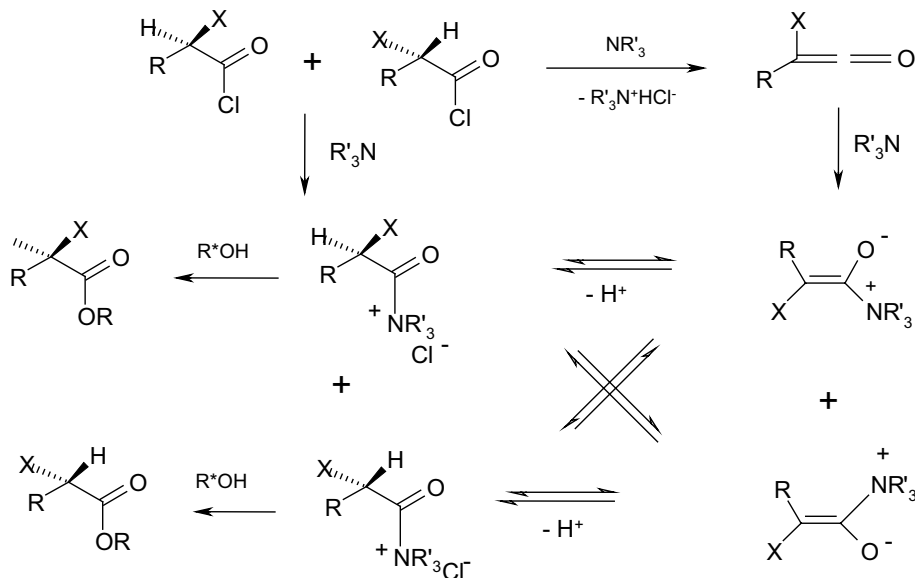

X = Cl, Br, phtalimido, aryl, etc.; R = alkyl; R'$_3$N = achiral tertiary amine;
R*OH = chiral enantiopure alkohol

Scheme 3. Possible mechanism for diastereoselective ester formation in the amine-induced reaction of chiral alcohols and racemic acid chlorides with a trisubstituted stereogenic center at the α-position [6].

On the basis of the literature data citied above [1-6] we conclude that ethyl L-lactate can be applied as a chiral auxiliary in asymmetric synthesis, as it was described by Larsen et al. [1]. Although not proving an excellent selectivity, especially when compared to the properties of (*R*)- or (*S*)-pantolactone (**III**) [2, 3] or its derivative (**IV**) [4-6], ethyl L-lactate remains a useful chiral tool. Considering the described above preparation of enantiomers of 2-chloropropionic acid [6], we investigated the possibility to perform a diastereoselective asymmetric transformation of racemic 2-chloropropionyl chloride with ethyl L-lactate as a chiral alcohol.

RESULTS

In this paper we present our works on the possibilities to deracemize *rac*-2-chloropropionic acid by the reaction of *rac*-2-chloropropionyl chloride with ethyl L-lactate, followed by the hydrolysis of the obtained ester (**I**). We also synthesized selectively a single (1*S*,2*S*)-(**I**), starting from (*S*)-2-chloropropionyl chloride and ethyl L-lactate. Mild basic hydrolysis of it allowed us to define its stereochemistry, based on a specific rotation of resulted 2-chloropropionic acid. Thus, with the known stereochemistry of a single (1*S*,2*S*)-(**I**), and its analytical (HPLC, GC/MS) determination, we could attribute the proper configuration to the obtained in other syntheses the diastereomeric pair of (1*S*,2*RS*)-(**I**).
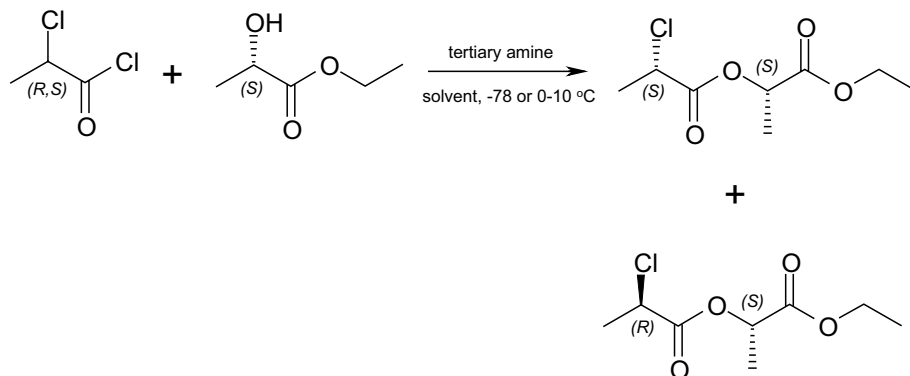
Scheme 4. Reaction of *rac*-2-chloropropionyl chloride with ethyl L-lactate.

For ester (**I**) preparation we applied conditions favorable for the ketene formation, as described by P. Camps et al. [6]. They performed a synthesis of enantiomerically pure (*R*)- or (*S*)-2-chloropropionic acid from *rac*-2-chloropropionyl chloride with a chiral auxiliary (*R*)- or (*S*)- (**IV**). *(R)*-(**IV**) generated S configuration in resulted (after hydrolysis) 2-chloropropionic acid.

On the ground of the existing literature data we assumed, that selective asymmetric synthesis of (**I**) from *rac*-2-chloropropionyl chloride and ethyl L-lactate, leading after hydrolysis to (*S*)-2-chloropropionic acid, should provide the predominant formation of (1*S*,2*S*)-(**I**), as it was described by R.D. Larsen et al. [1] for ibuprofen derivative. On the other hand, T. Durst and K. Koh [2] in their work on the synthesis of α-haloesters applied (*R*)-pantolactone (**III**), which undertaken the addition to α-halogenated acyl halogens, induced also *S* configuration at C2 carbon atom.

We decided to perform the synthesis of (**I**), under conditions favoring a ketene formation. Following the above mentioned literature data, we conducted the process, according to the procedure, as described: *rac*-2-chloropropionyl chloride in hexane was cooled to -78 °C and then, under inert gas atmosphere, 2 mol. equiv. of a tertiary amine (TEA) in hexane was dropped. Next, the cooling bath was removed and mixture was stirred at an ambient temperature for 2 h, followed by the succeding cooling to -78 °C and addition of 2 mol. equiv. of ethyl L-lactate solution in hexane. After 0.5 h the cooling bath was again removed and water was added to the reaction mixture, the organic layer was separated and concentrated. GC/MS determined the ratio of obtained (1*S*,2*RS*) diastereomers of (**I**) as 42.6:57.4, according to their appearance on chromatogram.

This reaction was done again in the similar conditions, but with different order of substrates addition: first TEA and ethyl L-lactate in hexane were cooled to -78 °C, and then *rac*-2-chloropropionyl chloride was dropped. In this case the obtained diastereomers ratio was practically the same – 42.1:57.9.
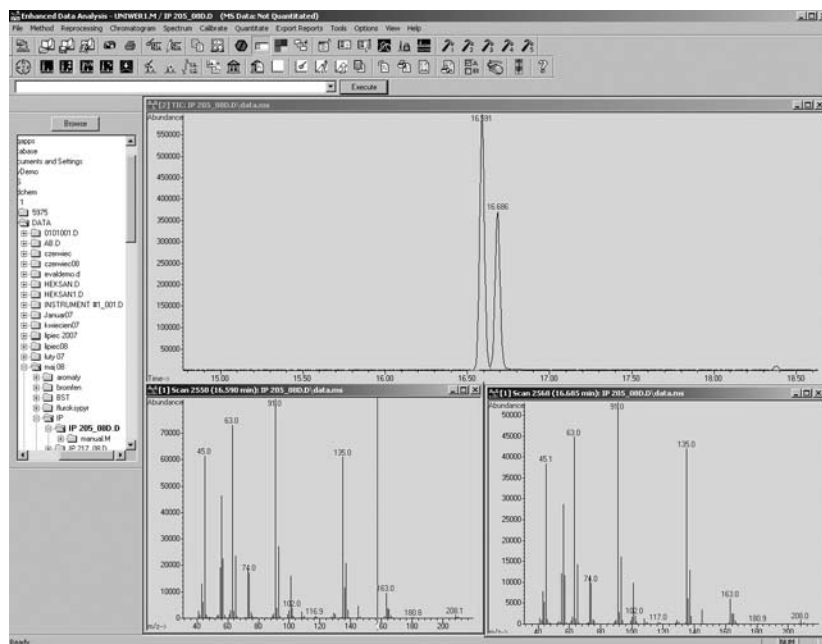

Figure 1. GC/MS chromatogram and spectra of *rac*-2-chloropropionyl chloride addition to ethyl L-lactate, at 0-10 °C, in dichloromethane, with TEA.

In continuing our trials to deracemize 2-chloropropionic acid using the discussed method, we also applied dichloromethane as a solvent, and performed the addition (in order of substrates: acid chloride added to a mixture of amine and chiral alcohol) at -78 °C, as well as at 0-10 °C, using TEA or pyridine as a base. One of the examples of GC/MS data for obtained (**I**) is presented in Figure 1. The resulted diastereomers ratio, estimated by GC/MS is depicted in Table 2.

Additionally, we synthesized (**I**) according to procedure described by R.T. Kelly et al. [7], when *rac* acid chloride was added directly to ethyl L-lactate at room temperature, without any solvent. The data obtained for this case are also included in Table 2.

Table 2. Diastereoselectivity ratio of the addition ethyl L-lactate to *rac*-2-chloropropionyl chloride

Tertiary amine	Temperature [°C]	Solvent	Ratio of (**I**) diastereomers (as they appeared on GC/MS or HPLC chromatograms)
1. -	ambient	-	41.2 : 58.8
2. TEA [A)]	0-10	dichloromethane	55.8 : 44.2
3. TEA [A)]	-78	dichloromethane	42.9 : 57.1
4. pyridine [A)]	-78	dichloromethane	51.1 : 48.9
5. TEA [A)]	-78	hexane	42.1 : 57.9
6. TEA [B)]	-78	hexane	42.6 : 57.4

[A)]   acid chloride added to the mixture of tertiary amine and chiral alkohol
[B)]   tertiary amine added to the acid chloride, followed by the addition of chiral alcohol

The results shown in Table 2 indicated a lack of selectivity for this addition, although there is a slight tendency to form the second appearing on chromatograms diastereomer, in the case of TEA use. But the same ratio was obtained for the direct addition of L-lactate to acid chloride at room temperature. In the case of 0-10 °C range, still almost not distinguishable proportions between diastereomers conversed in comparison to the others, what was also observable when pyridine was used as a base.

A proper configuration of each diastereomer was attributed by stereoselective synthesis of (1*S*, 2*S*)-(**I**) from ethyl L-lactate and (*S*)-(+)-2-chloropropionyl chloride [7-11]. Synthesis was done according to the known procedures [12-16], at the temperature range of 0-10 °C, in dichloromethane, using pyridine as a base. Reaction afforded predominantly in the single diastereomer, with approximate ratio as 3.5:96.5 (by HPLC). The obtained diastereomer was defined as having (1*S*,2*S*) stereochemistry by performing its mild hydrolysis with

Na$_2$CO$_3$/THF-H$_2$O, and acidification with 2 *M* HCl [3]. HPLC analysis (with internal standard: 2-chloropropionic acid of known purity) proved the presence of 70% of 2-chloropropionic acid in the post hydrolysis concentrate. The optical rotation of this product was $[\alpha]_D^{26.3}$=-16.8 (c=2.07, in methanol), what is in close accordance with the literature data for (*S*)-2-chloropropionic acid ($[\alpha]_D$=-16.5, c=1, in chloroform [17], $[\alpha]_D$=-12.4, c=2.7, in water [18]). The migration time of the resulted diastereomer was consistent with elution of second peak of the discussed diastereomeric pair in HPLC and GC/MS chromatograms. It made possible to determine a first appeared diastereomer as (1*S*,2*R*), and the second - as (1*S*,2*S*), respectively.

(*S*)-2-Chloropropionyl chloride was undertaken the reaction with ethyl L-lactate and TEA, at temperature range of 0-10 °C, in different solvents. The ratios of diastereomers in the obtained products are presented in Table 3.
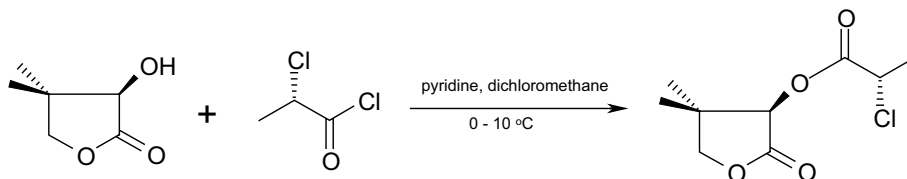
Table 3. Selectivity of the reaction of (*S*)-2-chloropropionyl chloride with ethyl L-lactate

Tertiary amine	Temperature [°C]	Solvent	Ratio of (**1**) diastereomers (1*S*,2*R* : 1*S*,2*S*) by HPLC
1. pyridine	0-10	dichloromethane	3.5 : 96.5
2. TEA	0-10	dichloromethane	40.7 : 59. 3
2. TEA	0-10	diethyl ether	18.5 : 81.5
3. TEA	0-10	hexane	1 : 1

The results above suggested that dichloromethane and a bulky base, such as pyridine, maintained the selectivity of reaction. When TEA was used in dichloromethane, selectivity decreased to 4:6 ratio, while TEA in diethyl ether supported it and racemization was not that high (2:8 ratio of diastereomers). In general, with TEA, dependently on the solvent applied, products consisted of diastereomers in different proportions, with racemization in hexane.

In continuing our investigations we decided to perform a similar addition of *rac* or (*S*)-2-chloropropionyl chloride to another chiral auxiliary – (*R*)-pantolactone (**III**) instead of ethyl L-lactate. The reaction was done in dichloromethane, at -78 °C or within the range of 0-10 °C, with pyridine or TEA. According to the literature data, we supposed, that this chiral tool applied should support the (*S*) configuration at C2 carbon atom of the considered acyl chloride. But also in the case of (*R*)-pantolactone we were not able to deracemize *rac*-2-chloropropionyl chloride under described above conditions. When (*S*)-2-chloropropionyl chloride was added to (*R*)-(**III**) the expected ester (**V**) was obtained selectively as a single product (GC/MS). When compared with peaks detected for product

of *rac* chloride with (*R*)-(**III**), it was attributed to the first peak appeared in chromatogram. The ratios of diastereomers obtained from the executed reactions are presented in Table 4.

Scheme 6. Synthesis of a single diastereomer of (**V**) from (*R*)-pantolactone (**III**) and (*S*)-2-chloropropionyl chloride.

Table 4. Selectivity of the reaction of (*S*)- and *rac*-2-chloropropionyl chloride with (*R*)-pantolactone (**III**) in dichloromethane

	2-CPA chloride	Tertiary amine	Temperature [°C]	Ratio of (**V**) diastereomers (1*R*,2*S*) : (1*R*,2*R*) by GC/MS
1.	(*S*)	pyridine	0-10	97 : 3 (d.e. 94%)
2.	(*S*)	TEA	0-10	88.4 : 11.6 (d.e. 76.8%)
3.	*rac*	pyridine	0-10	47 : 53
4.	*rac*	TEA	0-10	46.3 : 53.7
5.	*rac*	pyridine	-78	44 : 56
6.	*rac*	TEA	-78	44.7 : 55.3

Diastereomeric (1*S*,2*RS*)-(**I**) with known proportion of diastermers, and (1*S*,2*S*)-(**I**) were undertaken hydrolysis carried out with different agents. The basic hydrolysis in 25% NaOH aqueous solution led to the mixture of products. In a crude post hydrolysis solution was determined 2-chloropropionic acid and diastereomers of (1*S*,2*RS*)-2-(2-chloropropanoyloxy)propanoic acid (**II**) (HPLC, HPLC/MS). Na_2CO_3/THF-H_2O (HPLC chromatogram displayed in Figure 2).
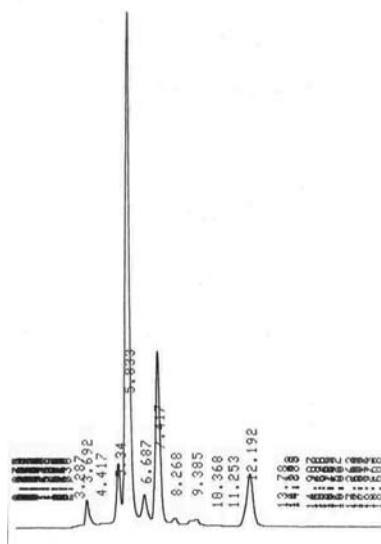
Figure 2. HPLC chromatogram of a mixture resulted after Na_2CO_3/THF-H_2O (1:1) hydrolysis of (1*S*,2*RS*)-(**I**); main visible peak attributes of 2-CPA.

NaOH/THF-H_2O or LiOH×H_2O/THF-H_2O application resulted mainly in 2-chloropropionic acid as a product. The contents of 2-CPA in the crude post hydrolysis concentrates for (1*S*,2*S*)- and (1*S*,2*RS*)-(**1**) was evaluated by HPLC, and is presented in Table 5.

Table 5. Quantity of 2-chloropropionic acid in crude product after basic hydrolyses

Base applied	2-CPA contents[%]	
	From (1*S*,2*RS*)-(**I**)	From (1*S*,2*S*)-(**I**)
25% NaOH aq./24 h	5	17
NaOH/THF-H_2O/24 h	51	54.8
Na_2CO_3/THF-H_2O/3 h	64.4	69.8
LiOHxH_2O/THF-H_2O/20 h	57	70.7

Hydrolysis of (**I**) by the ionic resin Amberlite IRC 748, disperged in methanol, led mainly to the acid (**II**) (Scheme 7).
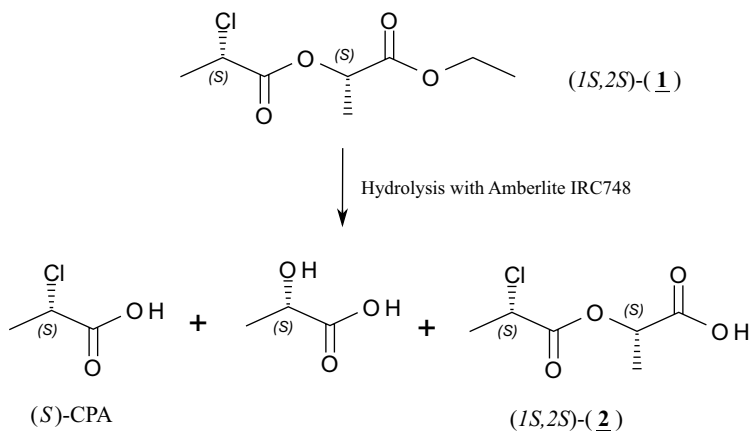
Scheme 7. Hydrolysis of (1*S*,2*S*)-(**I**) under acidic conditions with ionic resin Amberlite IRC 748 in methanol.

There is only a few published data concerning (**I**) or (**II**) [9-19]. The work of Clark and Emsley [19] is one of a very few publications, where the formation of (**II**) was described.

When (1*S*,2*RS*) diastereomeric pair was hydrolyzed, two separated peaks were obseverd on HPLC chromatograms. HPLC/MS results confirmed their structure as possessing the same molecular mass

(in negative scan type detected signals at *m/z* 179 [M-H$^+$]$^-$, corresponding to the molecular mass of (**II**)); the obtained spectra of HPLC/MS are presented in Figure 3. In the case of (1*S*,2*S*)-(**I**) after the similar acidic conditions hydrolysis, only single peak of acid (**II**) was detected by HPLC. As in hydrolysis process there was not involved any chiral centre, stereochemistry of resulted acid could be defined as the same as configuration of starting ester, i.e. (1*S*,2*S*). Consequently, by comparison of the migration time of acid (**II**) diastereomeric peaks, and migration time of a single peak of (1*S*,2*S*)-(**II**) on HPLC chromatogram, we distinguished the first acid peak eluted as (1*S*,2*S*)-(**II**) and the second – (1*S*,2*R*). This is opposite order as (**I**) diastereomers elution (the mobile phase: MeOH-H$_2$O (3:2) + 0.1% H$_3$PO$_4$, flow rate 1 mL/min).
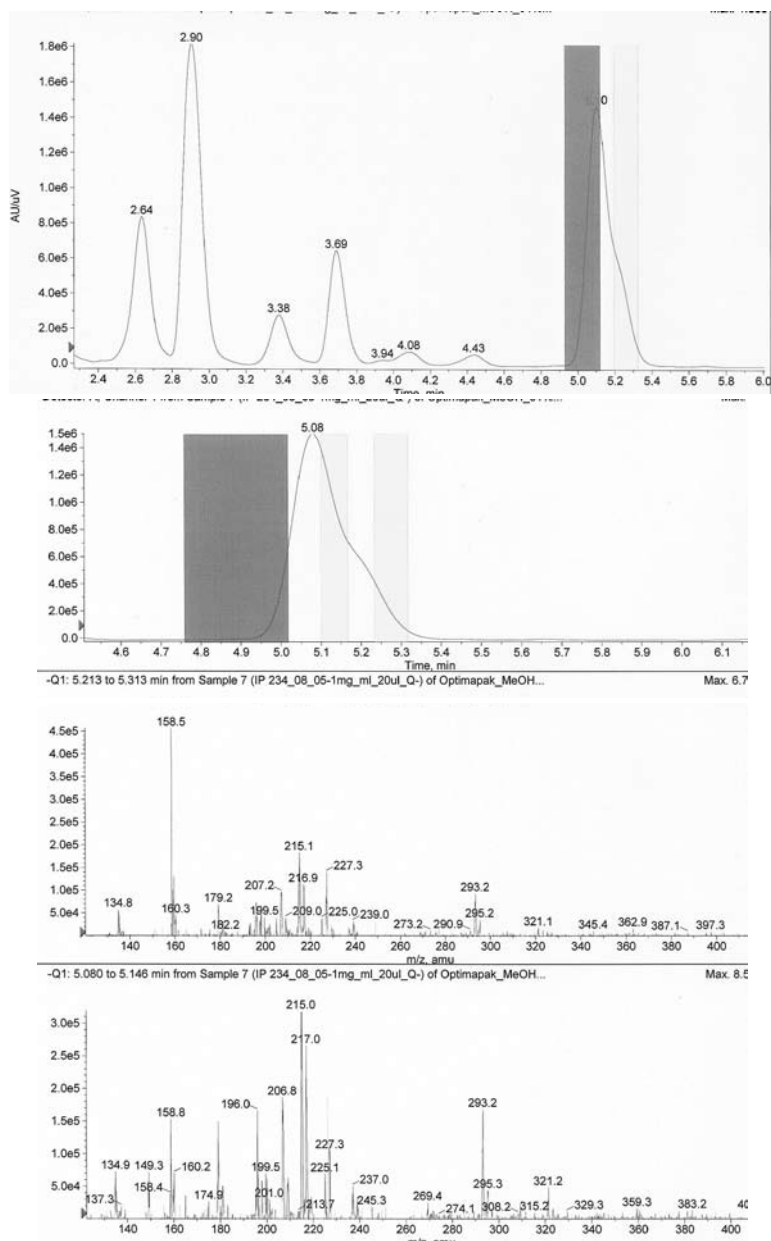
Figure 3. HPLC/MS chromatogram and mass spectra of (1*S*,2*S*)-(**II**) and (1*S*,2*R*)-(**II**), resulted from hydrolysis of (1*S*,2*RS*)-(**I**) in 25% NaOH aq.

When basic or acidic hydrolysis was carried out with 1:1 (1*S*,2*R*):(1*S*,2*S*)-(**I**), the ratio of obtained resolved acid diastereomers changed to the proportions as 2.5:1, and even 4:1, when considered order of their elution, i.e., for (1*S*,2*S*):(1*S*,2*R*), respectively. When the single stereoisomer (1*S*,2*S*)- (**I**) was hydrolyzed, the single peak of the respective (1*S*,2*S*) acid isomer was detected on chromatogram. These results made possible the assumption of faster hydrolytic degradation of (1*S*,2*R*)-(**I**) to the small molecules of lactic acid and 2-chloropropionic acid. In Figure 4 are presented HPLC chromatograms of discussed above products of acidic hydrolysis of (**I**).

A) B)

Figure 4.   HPLC chromatogram of: **A)** a single diastereomer (1*S*,2*S*)-(**II**) and **B)** a pair of diastereomers (1*S*,2*RS*)-(**II**) (obtained after acidic hydrolysis of (1*S*,2*S*)-(**I**) or (1*S*,2*RS*)-(**I**), respectively).

CONCLUSIONS

The synthesis of (1*S*,2*RS*)- and (1*S*,2*S*)-(**I**) was done from *rac* or (*S*)-2-chloropropionyl chloride and ethyl L-lactate, in presence of TEA or pyridine as a base. Hydrolysis of the resulted ester (**I**) was performed using different media. Basic hydrolysis with 25% NaOH aq. or acidic hydrolysis with ionic resin Amberlite IRC748 led to a mixture of 2-CPA and diastereomers of acid (**II**). Mild hydrolysis with LiOH × H_2O, Na_2CO_3 or NaOH solutions in THF-H_2O 1:1 or 2:1,

led mainly to 2-CPA acid. Structure of acid (**II**) was confirmed by HPLC/MS. The addition of (*R*)-pantolactone (**III**) to *rac* or (*S*)-2-chloropropionyl chloride was also conducted under similar conditions as for the synthesis of ester (**I**). The obtained ester (**V**) was characterized by GC/MS. Hydrolysis of (1*S*,2*S*)-(**I**) and hydrolysis of (1*R*,2*S*)-(**V**) with Na_2CO_3/THF-H_2O 1:1, gave mainly 2-CPA. The specific rotation of obtained 2-CP acids confirmed their S configuration, what led to conclusion that reaction of (*S*)-2-chloropropionyl chloride with both of mentioned above chiral alcohols applied supports the S configuration at C2 carbon atom. The attempts to deracemize *rac*-2-CPA by reaction of *rac*-2-chloropropionyl chloride with ethyl L-lactate or (*R*)-pantolactone failed.

EXPERIMENTAL

General procedures

rac-2-Chloropropionyl chloride (>95%), thionyl chloride (97%), triethylamine (>99%) were purchased from Sigma-Aldrich, pyridine (98%), ethyl L-lactate (>98%) – from Fluka, ethyl acetate p.a., dichloromethane p.a., diethyl ether p.a.- from POCh, magnesium sulfate anhydrous p.a., sodium hydroxide p.a., and hexane (fraction from petroleum) – from Chempur.

GC: Hewlett-Packard HP 6890 apparatus, injector coc type, detector FID, column Megabore HP-1 (15 m x 0.53 mm), film thickness 0.15 µm, temperature programme: 50 °C (3 min) – 220 °C (5°/min), detector temperature 270 °C. GC/MS: selective mass detector of Agilent Technologies type 5975B, coupled with gas chromatograph AT 6890 N, injector split-splitless, capillary column HP-5MS (30 m × 0.25 mm), film thickness 0.25 µm, MS mode: EI (70 eV) or CI (methane), temperature programme – GC: column temperature 100 °C (4 min) – 240 °C (5 °/min), 240 °C (20 min), detector temperature 230 °C – when MS analysis was carried on in EI mode, and: column temperature 50 °C (3 min) – 220 °C (5 °/min), 220 °C (10 min), detector temperature 240 °C – when CI technique was applied. HPLC: Shimadzu HPLC apparatus, type LC-100AT VP, column of Varian Omnispher C18 (150 x 4.6 mm) detector UV (220 nm); mobile phase: MeOH-H_2O (3:2) + 0.1% H_3PO_4, flow rate 1 mL/min. HPLC/MS: 4000 Qtrap apparatus of Applied Biosystems, column Optimapak C18, mobile phase: MeOH/0.1% HCOOH, flow 1 mL/min. FT/IR: Jasco FT/IR 420 apparatus, method – film between KBr plates. ^{1}H NMR**:** Varian 200 apparatus at 200 MHz, solvent - CDCl₃, internal standard – TMS, coupling constants J are done in Hz. Specific rotation: Atago automatic polarimeter, type AP 100.

(S)-(+)-2-Chloropropionyl chloride

To 0.34 mole of vigorously stirred (S)-2-CP acid (37.3 g) was carefully dropped 0.35 mole of thionyl chloride (41.6 g, 27.4 mL) at the temperature below 10 °C (ice bath). Next, the mixture was stirred and kept at 50 °C for 4 hours, until the end of HCl arising. Next, the solvent and residual volatiles were removed under reduced pressure. The crude acid chloride was distilled (b.p. 53 °C/100 mm Hg). After distillation 25 g of 97% (**GC**) product was obtained. Yield 57.5%; specific rotation: $[\alpha]_D^{25}$=3.66 (neat); **GC/MS** (EI) *m/z*: 129 (M+1), 123, 105, 97, 93, 91, 84, 77, 73, 71, 65, 63(100%), 60, 55, 49, 43.

Reaction of ethyl L-lactate with (S)-2-chloropropionyl chloride (synthesis of (1S,2S)-(I))

A) - with pyridine, in dichloromethane

(S)-2-chloropropionyl chloride (0.05 mole, 6.4 g) was slowly dropped to a stirred solution of ethyl L-lactate (0.06 mole, 7.1 g) and 0.055 mole of dry pyridine (4.35 g, 4.45 mL) in 100 mL of dry dichloromethane, at the temperature 0-10 °C (ice bath). The mixture was stirred for 1 h, followed by the addition of 100 mL of water. The layers were separated, and the organic layer was dried over anhydrous MgSO₄, filtered and concentrated to give 10.1 g of (**I**). Yield 97%, GC purity 81%, HPLC purity 84.4%; in HPLC chromatogram the quantitative proportions between peaks were as 3.5:96.5, respectively to their order of appearance; in GC/MS chromatogram the quantitative proportions between peaks were as 2.3:97.7, respectively to their order of appearance, GC/MS (EI): first peak (of (1S,2R) diastereomer – 8.5 min) and the second peak (of (1S,2S) diastereomer – 18.6 min) have the same spectra: *m/z* 208 (M⁺·), 181, 173, 163, 145, 135, 129, 117, 108, 101, 91(100%), 85, 79, 73, 63, 56, 45; ¹H NMR (CDCl₃, TMS) [ppm]: 1.247(t, 3H, J= 7.2, from ester CH₃), 1.521(d, 3H, J=7.2, from CH₃ at chiral carbon (2S): Cl-C*-(CH₃)(H)-C=O), 1.722(d, 3H, J=6.8, from CH₃ at chiral carbon (1S): -O-C*-(CH₃)(H)-C=O), 4.159(q, 2H, J=7.2, from ester CH₂), 4.443(q, 1H, J=7.0, from proton at chiral carbon (2S): Cl-C*(CH₃)(H)-C=O), 5.081(q, 1H, J=7.0, from proton at chiral carbon (1S): O-C*-(CH₃)(H)-C=O); in the ¹H NMR spectra were also detected signals (~2-3%) derived from the second stereoisomer present in these diastereomeric pair, i.e. (1S,2R) one: 4.455(q, 1H, J=7.2, from proton at chiral carbon (2R), 5.070 (q, 1H, J=7.2, from proton at chiral carbon (1S) $[\alpha]_D^{24.4}$=-48.83, c=2.13, in methanol.

B) - with TEA, in dichloromethane

When this reaction was performed in dichloromethane with TEA, instead the expected single (1*S*,2*S*)-stereoisomer, the diastereomeric pair (1*S*,2*RS*) of ECOPP was obtained. HPLC: two separated peaks in proportions as 40.7:59.3 in order of appearance, with retention times 9.1 min, and 9.7 min, respectively. GC/MS: two separated peaks in proportions 38.9:61.1, with retention times 16.6 min, and 16.7 min, respectively. By comparison to a single stereoisomer analysis it can be determined as ~4:6 for (1*S*,2*R*):(1*S*,2*S*).

C) - with TEA, in diethyl ether

When this reaction was performed in diethyl ether, with TEA, the diastereomeric pair (1*S*,2*RS*) of ECOPP was obtained. HPLC: two separated peaks in proportions as 18.5:81.5 in order of appearance, with retention times 9.2 min, and 9.8 min, respectively. GC/MS: two separated peaks in proportions 16:84, with retention times 18.5 min, and 18.7 min, respectively. By comparison to single stereoisomer analysis it can be determined as ~ 2:8 for (1*S*,2*R*):(1*S*,2*S*). ^{1}H NMR: (CDCl$_3$, TMS) [ppm]: 1.247(t, 3H, J= 7.2, from ester CH$_3$), 1.521 (80%) (d, 3H, J=7.2, J=1.0, from CH$_3$ at chiral carbon (2*S*): Cl-C*-(CH$_3$)(H)-C=O), 1.526 (20%) (d, 3H, J=7.2, J=1.0, from CH$_3$ at chiral carbon (2*R*): Cl-C*-(CH$_3$)(H)-C=O), 1.715 (20%) (d, 3H, J=7.2, J=1.0, from CH$_3$ at chiral carbon (1*S*): -O-C*(CH$_3$)(H)-C=O in (1*S*,2*R*) stereoisomer, 1.722 (80%) (d, 3H, J=6.8, J=1.0, from CH$_3$ at chiral carbon (1*S*): -O-C*-(CH$_3$)(H)-C=O in (1*S*,2*S*) stereoisomer), 4.157(q, 2H, J=7.2, from ester CH$_2$), 4.419 (20%) (q, 1H, J=7.2, J=4.4, from proton at chiral carbon (2*R*): Cl-C*-(CH$_3$)(H)-C=O), 4.441 (80%) (q, 1H, J=7.2, J=4.4, from proton at chiral carbon (2*S*): Cl-C*-(CH$_3$)(H)-C=O), 5.070 (20%) (q, 1H, J=7.2, J=2.2, from proton at chiral carbon (1*S*): O-C*-(CH$_3$)(H)-C=O) in (1*S*,2*R*) stereoisomer), 5.079 (80%)(q, 1H, J=7.2, J=2.2, from proton at chiral carbon (1*S*): O-C*-(CH$_3$)(H)-C=O) in (1*S*,2*S*) stereoisomer), $[\alpha]_D^{24.6}$=-48.07, c=2.16, in methanol.

D) - with TEA, in hexane

When this reaction was performed in similar conditions, but using hexane and TEA, the diastereomeric pair (1*S*,2*RS*) of ECOPP was obtained. HPLC: two separated peaks in proportions as 1:1 in order of appearance, with migration times 8.9 min and 9.5 min, respectively. GC/MS: two separated peaks in proportions as 46.4:53.6 in order of appearance, with migration times 16.6 min and 16.7 min, respectively. ^{1}H NMR: analogously to the spectra described above, proportions for signals of stereoisomers in diastereomeric pair (1*S*,2*RS*) as 1:1, in accordance to HPLC and GC/MS results. By comparison to

a single stereoisomer analysis it can be determined as ~1:1 for (1*S*,2*R*):(1*S*,2*S*), $[\alpha]_D^{24.4}$=-35.92, c=2.06, in methanol.

Reaction of ethyl L-lactate with *rac*-2-chloropropionyl chloride; (synthesis of (1*S*,2*RS*)-(I))

A) - without solvent, without tertiary amine

To a stirred ethyl L-lactate (80 mmol, 9.45 g) was added 77.5 mmol (10 g) of *rac*-2-chloropropionyl chloride, at ambient temperature. The gases formed during reaction were caught by a system of water and NaOH/water containing washers. After 12 h the reaction was finished, the crude product was dissolved in EtOAc (200 mL) and washed with 100 mL of water, then a solution was dried over MgSO₄, filtered and evaporated to obtain 12.9 g of product (yield 80%). Ratio of diastereomers by GC/MS was estimated as 41.2:58.8.

B) - with TEA, in dichloromethane, at 0-10 °C

Commercial *rac*-2-chloropropionyl chloride (0.094 mole, 12.0 g) was slowly dropped to a stirred solution of 1.1 equiv. of ethyl L-lactate (0.105 mole, 12.3 g) and 1.1 equiv. of TEA (10.35 g, 13.9 mL), dissolved in 75 mL of dichloromethane, at the temperature 0-10 °C (ice bath). The mixture was then stirred for 1 h, followed by the addition of 100 mL of water. The layers were then separated, and the organic layer was dried over anhydrous MgSO₄, filtered and concentrated in vacuo to give 17.8 g of product. Yield 91.3%, GC purity 98%. GC/MS (EI), *m/z*: first peak – 208 (M⁺˙), 163, 145, 135, 101, 91(100%), 74, 63, 55, 45, second peak – 208 (M⁺˙), 163, 145, 135, 101, 91(100%), 74, 63, 55, 45 – the quantitative proportions between peaks as 55.8:44.2 in order of appearance; HPLC: two separated peaks peaks in proportions as 52.4:47.6 in order of appearance, with retention times 9.05 min and 9.68 min, respectively; FT/IR[cm⁻¹]: 2989, 1750, 1448, 1182, 1098; ¹H NMR (CDCl₃, TMS) [ppm]: 1.24 (2t, 6H, J=7.0), 1.52 (2d, 6H, J= 7.0, J=1.0), 1.71 (2d, 6H, J=1.2, J=7.0), 4.14 (2q, 4H, J=2.7, J=7.0), 4.38(2q, 2H, J=2.3, J=7.0), 5.06 (2q, 2H, J=2.2, J=7.0), $[\alpha]_D^{24.4}$=-35.24, c=2.10, in methanol.

C) - in dichloromethane, at -78 °C
1. with pyridine

Ethyl L-lactate (5 mmol, 0.59 g) and pyridine (5.5 mmol, 0.44 g), dissolved in 25 mL of dry dichloromethane and stirred under inert gas (N₂) were cooled to -78 °C. Next, to the mixture was slowly dropped *rac*-2-chloropropionyl chloride (5.25 mmol, 0.66 g, 0.52 mL) in 25 mL of dichloromethane. After 2 h at -78 °C,

a cooling bath was removed, and the reaction was allowed to reach an ambient temperature. Water was then added (50 mL), and layers were separated. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated to obtain 0.86 g of product, as a colorless liquid (yield 82.7%). Diastereomers ratio by GC/MS: 51.1:48.9 (1*S,*2*R*:1*S,*2*S*), in order of their appearance at chromatogram.

2. with TEA

Ethyl L-lactate (5 mmol, 0.59 g) and TEA (5.5 mmol, 0.76 mL), dissolved in 25 mL of dry dichloromethane and stirred under inert gas (N_2) were cooled to -78 °C. Next, to the mixture was slowly dropped *rac*-2-chloropropionyl chloride (5.25 mmol, 0.66 g, 0.52 mL) in 25 mL of dichloromethane. After workup as described above, 0.87 g (yield 83.7%) of colorless oil was obtained. GC/MS results: ratio of diastereomers 42.9:57.1 (1*S,*2*R*:1*S,*2*S*) in order of their appearance at chromatogram.

D) - with TEA, in hexane, at -78 °C

1. To the rac-2-chloropropionyl chloride (50 mmol, 6.35 g) dissolved in 100 mL of dry hexane and stirred under inert gas (N_2) at -78 °C, was slowly dropped 2 equiv. of TEA (0.1 mol, 10.1 g, 13.7 mL) in 100 mL of hexane. The cooling bath was removed and the mixture was stirred for 2 h, next it was cooled again to -78 °C, and ethyl L-lactate (2 equiv., 0.1 mol 11.8 g) in 100 mL of hexane was added. Then, a cooling bath was removed and the mixture was stirred for 0.5 h, following by water addition (100 mL) and the layers separation. The water layer was additionally extracted with 50 mL of ethyl acetate, the organic layers were collected, dried over $MgSO_4$, filtered and solvent was evaporated. It was obtained 8.7 g of a clear colorless liquid (yield 83.7%). Diastereomers ratio by GC/MS: 42.6:57.4.

2. To the mixture of TEA (2 equiv., 0.1 mol, 10.1 g, 13.7 mL) and ethyl L-lactate (2 equiv., 0.1 mol 11.8 g) dissolved in 200 mL of dry hexane, and stirred under inert gas (N_2) at -78 °C, was slowly added (during 1 h) rac-2-chloropropionyl chloride (50 mmol, 6.35 g) in 100 mL of hexane. After addition, a cooling bath was removed, the mixture was stirred for an additional 0.5 h, followed by water (100 mL) addition and layers separation. After workup as described above, 9.8 g of clear colorless liquid was obtained (yield 94.2%). Ratio of diastereomers by GC/MS: 42.1:57.9.

Hydrolysis of (1*S*,2*S*)-(**I**)

1. with 25% NaOH aq.

To vigorously stirred 2 g of (1*S*,2*S*)-(**I**), cooled to 0-10 °C (ice bath), was slowly dropped 10 mL of 25% NaOH aq. and the mixture was stirred at ambient temperature for 24 h. The solution was then cooled again to 0 °C and acidified with 2N HCl to pH 1-2. A crude mixture was dissolved with 20 mL of methanol to increase the solubility of individuals. HPLC results: among the others was determined 17% of 2-CPA, 23.5% substance which can conform (**II**) single diastereomer.

2. with LiOH × H₂O/ THF-H₂O) (2:1)

5 mmol of of (1*S,2S*)-(**I**) (1.04 g) dissolved in 30 mL of THF/H₂O 2:1 was treated with 10 mmol (0.42 g) of LiOHxH₂O at room temperature. The mixture was stirred at this temperature for 20 h, concentrated in vacuo, and the residue was extracted with 25 mL of EtOAc. Water layer was then acidified with 2 *M* HCl to pH 1, and extracted with 2x30 mL of EtOAc. Organic layers were dried over MgSO₄, filtered and concentrated to obtain 0.85 g of product as a clear liquid. HPLC results: 70.7% 2-CPA.

3. with Na₂CO₃/THF-H₂O) (1:1)

10 mmol of (1*S*,2*S*)-(**I**) (2.08 g) was first dissolved in 50 mL of THF, and 20 mmol of Na₂CO₃ in 50 mL of H₂O was then added at room temperature. After 3 h reaction was finished, and the workup was done as described above to obtain 1.2 g of clear liquid. HPLC results: 69.8% of 2-CPA. Specific rotation: $[\alpha]_D^{26.3}$=-16.18, c=2.07, in methanol; $[\alpha]_D^{26.3}$=-16.75, c=2.09 in 2-propanol (for (*S*)-(–)-2-chloropropionic acid: $[\alpha]_D^{25}$=16.5, c=1, in chloroform [17]; $[\alpha]_D^{20}$=-12.4, c=2.7, in water [18].

4. with NaOH/THF-H₂O (2:1)

The procedure was done in similar way as described above; 5 mmol (1.04 g) of (1*S,2S*)-(**I**) was treated at 0 °C with 10 mmol (0.4 g) of NaOH dissolved in 30 mL of THF/H₂O, 2:1. After 24 h the reaction was finished and worked up to obtain 0.8 g of product. HPLC results: 54.8% of 2-CPA.

5. with Amberlite IRC 748/MeOH

2 g of (1*S*,2*S*)-<u>1</u> was stirred at the room temperature with 4 g of ionic resin Amberlite IRC 748 in 25 mL of methanol, for 24 h. The resin was next filtered off and the residual solution was analyzed by HPLC. Results by HPLC: among the others was determined 35% of 2-CPA, 49% of (**II**) single diastereomer.

Hydrolysis of (1*S*,2*RS*)-(I)

1. with 25% NaOH

To vigorously stirred 2 g of 1:1 (1*S*,2*RS*)-(**I**), cooled to 0-10 °C (ice bath), was slowly dropped 10 mL of 25% NaOH aq. and the mixture was stirred at ambient temperature for 24 h. The solution was then cooled again to 0 °C and acidified with 2N HCl to pH 1-2. A crude mixture was dissolved with 20 mL of methanol to increase the solubility of individuals. HPLC results: among the others was determined 5% of 2-CPA, 19.2% of first eluted (**II**) diastereomer, 8% of second eluted (**II**) acid diastereomer. Comparing to starting ester (**I**), proportions changed from 1:1 to 2.5:1. HPLC/MS results (in negative scan type), peaks in order of appearance: 2.24 min: not analyzed; 2.62 min (scanned from 2.707 to 2.774 min), *m/z*: 71.1, 80.8, 89.1 (M-H)$^-$ lactic acid, 94.9, 97.0, 112.6, 124.9 (M+Cl)$^-$ lactic acid, 127.0, 147.0, 148.9, 151.0, 170.9, 173.0, 176.1, 179.1, 196.0, 197.9, 199.9, 202.2, 226.7, 229.0, 241.0, 245.1, 249.1; 2.89 min (scanned from 2.941 to 3.008 min): 112.5, 114.2, 124.6, 126.2, 158.9, 161.2, 176.0, 197.1, 199.0, 219.0, 221.2, 226.5, 227.9, 251.1, 275.2; 3.36 min (scanned from 3.409 to 3.509 min): 83.4, 112.4, 158.8, 165.1, 175.0, 211.0, 227.5, 289.2; 3.67 min (scanned from 3.743 to 3.810 min): 89.4, 107.2 (M - H)$^-$ 2-chloropropionic acid,, 109.2, 117.0, 119.0, 143.1 (M+Cl)$^-$ 2-chloropropionic acid,, 147.1, 153.0, 155.1, 161.9, 162.9, 197.2, 199.2, 206.9, 209.0, 215.0, 217.1, 220.8, 223.1, 253.1, 255.0, 271.0, 273.0, 277.0, 279.1; 4.07 min: not analyzed; 5. 08 min – detected unregular peak, containing not resolved additional one inside (can correspond to two stereoisomers of (1*S*,2*RS*) diastereomeric pair of (**II**) acid) - scanning from 5.080 to 5.146 min: 160.2, 158.8, 149.3, 134.9, 179.2 (M - H)$^-$ (**II**) acid, 196.0, 206.8, 215.0 (M+Cl)$^-$ (**II**) acid – one of diastereomers; 217.0, 225.1, 227.3, 237.0, 293.2, 295.2, scanning from 5.213 to 5.313 min: 134.8, 158.5, 160.2, 179.2 (M - H)$^-$ (**II**) acid – second of diastereomers, 199.5, 207.2, 215.1 (M+Cl)$^-$ (**II**) acid, 216.9, 225.0, 227.3, 239.0, 293.2, 295.2.

2. with LiOH × H_2O/THF-H_2O (2:1)

(1*S*,2*RS*)-(**I**) (20 mmol, 4.16 g, ratio of (1*S*,2*R*):(1*S*,2*S*) as ~ 6:4) was dissolved in 120 mL of THF/H_2O 2:1, and then treated with 40 mmol (2 eq., 1.7 g) of LiOH × H_2O at room temperature. After 20 h reaction was finished and worked up as described above for (1*S*,2*S*)-(**I**) to obtain 3.2 g of a clear liquid. HPLC results: 57% of 2-CPA.

3. with Na$_2$CO$_3$ /THF-H$_2$O (1:1)

(1*S*,2*RS*)-(**I**) (10 mmol, 2.08 g, ratio of (1*S*,2*R*):(1*S*,2*S*) as ∼ 6:4) was dissolved in 50 mL of THF, and then treated with 20 mmol (2 eq., 2.12 g) of Na$_2$CO$_3$ in 50 mL of H$_2$O, at room temperature. After 3 h reaction was finished and worked up as described above for (1*S*,2*S*)-(**I**) to obtain 1 g of a clear liquid. HPLC results: 64.4% of 2-CPA.$[\alpha]_D^{25}$=0, c=2.03, in methanol.

4. with NaOH/ THF-H$_2$O) (2:1)

(1*S*,2*RS*)-(**I**) (10 mmol, 2.08 g, ratio of (1*S*,2*R*):(1*S*,2*S*) as ∼ 6:4) was dissolved in 60 mL of THF/H$_2$O 2:1, and then treated at 0 °C with 20 mmol (2 eq., 0.8 g) of NaOH. After 24 h of stirring at room temperature, the reaction was finished and worked up as described above to obtain 1.5 g of a colorless liquid. HPLC results: 51% of 2-CPA.

5. with Amberlite IRC 748 in MeOH

2 g of (1*S*,2*RS*)-(**I**) (1:1 ratio of (1*S*,2*R*):(1*S*,2*S*)) was stirred for 24 h at room temperature with 4 g of ionic resin Amberlite IRC 748 in 25 mL of methanol. The resin was next filtered off and the residual solution was analyzed by HPLC. Results by HPLC: among the others was determined 7% of 2-CPA, 33.5% of (**II**) first eluted diastereomer, 11.1% of second eluted (**II**) diastreomer. Comparing to starting ester (**I**), proportions of resulted (**II**) changed from 1:1 to 3:1.

Reaction of (R)-pantolactone (III) and *rac*-2-chloropropionyl chloride (preparation of (1R,2RS)-(V))

A) - in dichloromethane, at -78 °C

1. with pyridine: To 5 mmol of (*R*)-pantolactone (**III**) and 5.5 mmol of pyridine, dissolved in 25 mL of dry dichloromethane and cooled to -78 °C, 5 mmol of *rac*-2-chloropropionyl chloride in 25 mL of dichloromethane was added. Cooling bath was removed and the mixture was stirred for additional 4 h, and 50 mL of water was then added. After layers separation and workup, 1.05 g of product was obtained (95% of yield). Diastereomers ratio by GC/MS, in order of appearance on chromatogram: 44:56.

2. with TEA: When the reaction was done with TEA, 1.0 g (90.5% of yield) of product was obtained. Diastereomers ratio by GC/MS, in order of appearance on chromatogram – 44.7:55.3.

B) - in dichloromethane, at 0-10 °C
1. with pyridine: The reaction was done from the quantities and in a way as desribed above. Diastereomers ratio by GC/MS, in order of their appearance on chromatogram was as 47:53.

2. with TEA**:** Diastereomers ratio by GC/MS as 46.3:53.7.

Reaction of (R)-pantolactone (Ⅲ) and *(S)*-2-chloropropionyl chloride (synthesis of (1*R*,2*S*)-(Ⅴ))

A) - in dichloromethane, at 0-10 °C
1. with pyridine: The reaction was done from the quantities and in a way as in the above, at temperature of 0-10 °C. The resulted yield was of 91%. Diastereomers ratio by GC/MS, in order of their appearance on chromatogram was as 97:3 (d.e. 94%) $[\alpha]_D^{24.4}$=-10.75, c=2.14, in methanol.
2. with TEA: The reaction was done as above, with a yield of 91%. Diastereomers ratio by GC/MS, in order of their appearance on chromatogram was as 88.4:11.6 (d.e. 76.8%).

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