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Candida Rugosa lipase-catalyzed kinetic resolution of β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates

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Abstract—A simple and convenient method was reported for the preparation of optically active β-hydroxy-β-arylpropionates, δ-hydroxy-δ-aryl-β-oxo-pentanoates and their butyryl derivatives via CRL-catalyzed hydrolysis. The optically active products are potential precursors of some chiral pharmaceuticals and natural products.
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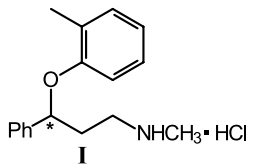
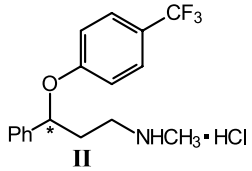
1. Introduction

Optically active β-hydroxy-β-arylpropionates and the derivatives thereafter are synthetically important and highly functionalized chiral synthons, of which the chiral β-hydroxy-β-arylpropionates are precursors of enantiopure pharmaceuticals including enantiomers of tomoxetine hydrochloride (**I**) and fluoxetine hydrochloride (**II**). The racemic **I** and **II** are pharmaceuticals for treatment of psychiatric disorders (depression, anxiety, alcoholism) and metabolic problems (obesity, bulimia).[1] Meanwhile, (*R*)-tomoxetine (**I**) is the first norepinephrine reuptake-inhibiting anti-depressant which does not possess strong affinity for either α- or β-adrenergic receptors.[1a,2]



I



II

On other hand, optically active δ-hydroxy-δ-aryl-β-oxo-pentanoates can be converted to 6-substituted-4-hydroxy lactones and also reacted with an equivalent of aldehydes via a tandem Knovenenagel reaction in the presence of $BF_3 \cdot Et_2O$ to give single diasetereomers of highly substituted tetrahydropyran-4-ones, which are key precursors of many natural products, such as compactin and mevinolin,[3] manoalide,[4] compaction and (+)-dihydrocompaction,[5] (−)-pestalotin,[6] bryostatin,[7] and so on.

Since optically active β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates have practical and potential uses in organic reactions and chiral pharmaceuticals, synthetic study of these molecules has therefore attracted considerable interest. The preparation of chiral β-hydroxy-β-arylpropionates was mainly focused on catalytic asymmetric[8] and biological reduction[9] of corresponding β-keto carboxylates. As examples for preparation of optically active δ-hydroxy-δ-aryl-β-oxo-pentanoates, 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene was reacted with chiral acetals through a distereselective addition[10] or with aldehydes via an asymmetric aldol condensation catalyzed by Ti(IV)/BINOL complex.[11] Another method used an enantioselective reaction of diketene with aldehydes through a chiral Schiff's base–titanium alkoxide complex.[12]

The drawbacks of above synthetic routes include harsh reaction conditions, expensive reagents, poor chemical yields and low optical purity.[8–12] An alternative way to synthesize these chiral molecules is based on biocatalytic kinetic resolution, which has attracted the interest of synthetic chemists because of the high-, regio- and stereoselectivity.[13] Our group has exploited baker's yeast-mediated enantioreduction for preparation of some optically active γ-hydroxy-β-ketophosphonates and δ-hydroxy-β-ketophosphonates.[14] In addition we also used *Candia Antartic* lipase B (CALB) and crude *Candia Rugosa* lipase

Keywords: β-Hydroxy-β-arylpropionates; δ-Hydroxy-δ-aryl-β-oxo-pentanoates; *Candia Rugosa* lipase (CRL); Enantioselectivity; Hydrolysis.
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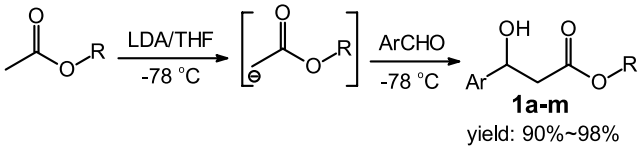
(CRL) to resolve hydroxyphophonates and aminophosphonates to obtain chiral compounds.[15]

In this paper, we wish to report our experimental results on CRL-catalyzed enantioselective hydrolysis and alcoholysis for the preparation of chiral hydroxycarboxylates bearing aryl groups.

2. Results and discussion

First, the racemic β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates were synthesized via a convenient and simple method with high yields (Schemes 1 and 2)

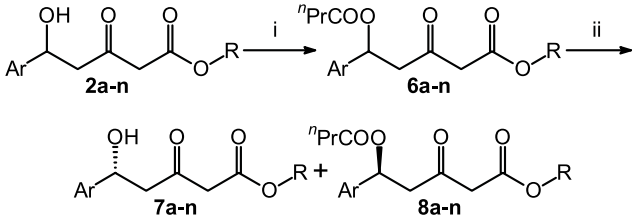


R=Me, Et, *i*-Pr, Bu; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

Scheme 1.

In our previous work,[15a,c,f] we successfully resolved β-hydroxy-β-arylethylphosphonates and δ-hydroxy-δ-aryl-β-oxo-butylphosphonates by crude CRL in diisopropyl ether. Because of the similarity of phosphonates and carboxylates, this strategy was successfully applied to resolve compounds **1a**–**m** and **2a**–**n**.

Direct butyrylation of **1a**–**m** and **2a**–**n** using DCC/butyric acid system afforded the butyryl derivatives in above 90% yields. The resulted products could be enantioselectively hydrolyzed to corresponding (*R*)-alcohols and (*S*)-esters by crude CRL in diisopropyl ether pre-equilibrated with 1.2 mol/L aqueous $MgCl_2$. (Schemes 3 and 4, Tables 1 and 2)



R=Me, Et; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

(i) $^{n}PrCO_2H$/DCC/DMAP(cat.)/CH_2Cl_2, rt, 1~2h;

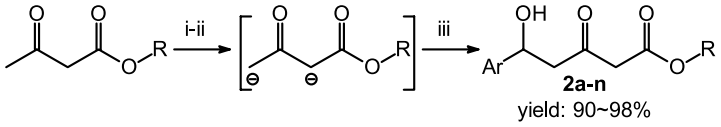
(ii) *CRL*/$^{i}Pr_2O$-H_2O, 30 °C, 24h.

Scheme 4.

Comparing the data in Table 1 with that of corresponding β-hydroxy-β-arylethylphosphonates,[15a,f] we found that the overall yields of CRL-catalyzed reaction were dramatically increased and reaction time was significantly shortened. However, the enantioselectivity of CRL decreased a little bit. Efforts to improve it by changing the bulky degree of the ester groups were unsuccessful.

Similar results were obtained and shown on Table 2. The enantioselectivity of CRL were very good in comparison to that for corresponding δ-hydroxy-δ-aryl-β-oxo-butylphosphonates.[15c]

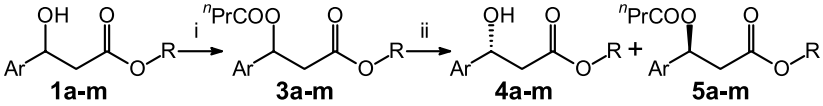
Due to the similarity of the substrates **3a**–**m** and **6a**–**n**, the enantioselectivity of the resolution reaction catalyzed by CRL are identical. Consequently, if the absolute configuration of one of the products **4a**–**m** and **5a**–**m** or **7a**–**n** and **8a**–**n** was determined, the stereochemistry of the other molecules could be deduced. Subsequently, the absolute configuration of hydrolyzed the ethyl β-hydroxy-β-phenyl-propionate (**4c**) and methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoate (**7a**) was determined by optical rotation. The optical rotation of **4c** is $[\alpha]_D^{20}=+48.7$ (*c* 1.4, $CHCl_3$) {literature[9a] (*S*)-**1c**: $[\alpha]_D^{20}=-50.8$ (*c* 1.0, $CHCl_3$) and literature[17] (*R*)-**1c**: $[\alpha]_D^{22}=+40.0$ (*c* 2.8, $CHCl_3$)} and **7a** is $[\alpha]_D^{20}=+58.1$ (*c*=1.0, $CHCl_3$) {literature[11a] (*R*)-**2a**:



R=Me, Et; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

(i) NaH/THF, 0 °C, 0.5h; (ii) BuLi/THF, ice-salt bath, 0.5h;
(iii) ArCHO/THF, ice-salt bath, 1.0~2.0h.

Scheme 2.



R=Me, Et, *i*-Pr, Bu; Ar=X-C_6H_4 (X=H, Me, MeO, F, Cl, O_2N) etc..

(i) $^{n}PrCO_2H$/DCC/DMAP(cat.)/CH_2Cl_2, rt, 1~2h; (ii) *CRL*/$^{i}Pr_2O$-H_2O, 30 °C, 24h.

Scheme 3.

Table 1. CRL catalyzed enantioselective hydrolysis of **3a–m**

Entry	R	Ar	Yield of **3** (%)	**4**		**5**		E^a
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
a	Me	C_6H_5	94	48	86.9	44	92.0	>68
b	Me	4-$MeOC_6H_4$	93	44	>99	47	92.0	>150
c	Et	C_6H_5	95	43	>99	48	91.9	>150
d	Et	4-MeC_6H_4	93	42	94.5	44	95.3	>100
e	Et	4-$MeOC_6H_4$	95	47	85.9	44	90.6	>60
f	Et	2-Furyl	91	51	75.1	40	90.2	>45
g	Et	2-ClC_6H_4	92	46	95.4	41	98.6	>150
h	Et	4-FC_6H_4	94	41	93.7	49	86.8	>100
i	Et	2,4-$Cl_2C_6H_3$	90	46	93.7	42	>99	>150
j	Et	4-$O_2NC_6H_4$	96	43	91.6	43	99.6	>150
k	*i*-Pr	C_6H_5	93	44	93.6	48	81.9	>50
l	*i*-Pr	4-$MeOC_6H_4$	92	45	75.7	46	76.7	>20
m	*n*-Bu	C_6H_5	95	42	93.0	47	86.8	>50

[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[16]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK AD, OD, AS).

Table 2. CRL catalyzed enantioselective hydrolysis of **6a–n**

Entry	R	Ar	Yield of **6** (%)	**7**		**8**		E^a
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
a	Me	C_6H_5	92	46	97.0	47	99.9	>200
b	Me	4-MeC_6H_4	91	46	98.6	47	99.9	>200
c	Me	4-$MeOC_6H_4$	93	45	99.9	46	96.0	>200
d	Me	2-Furyl	94	54[c]	52.0	39[c]	98.1	>80
e	Me	2-BrC_6H_4	91	47	99.8	47	97.5	>200
f	Me	4-FC_6H_4	96	48	97.7	46	97.2	>200
g	Me	2,4-$Cl_2C_6H_3$	94	46	98.1	47	94.9	>200
h	Me	4-$O_2NC_6H_4$	93	46	99.9[d]	48	91.9	>200
i	Et	C_6H_5	94	47	99.7	47	99.7	>200
j	Et	4-MeC_6H_4	91	47	98.6	46	99.9	>200
k	Et	4-$MeOC_6H_4$	92	45	97.2	47	99.6	>200
l	Et	2-Furyl	94	46	89.6	48	84.9	>100
m	Et	2,4-$Cl_2C_6H_3$	93	45	99.1	49	99.9	>200
n	Et	4-$O_2NC_6H_4$	93	45	99.8	45	/[e]	/

[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[16]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK AD, OD, AS).
[c] The reaction time was too long.
[d] The ee values of **7h** was determined by **8h**.
[e] **8n** can not be determined by chiral HPLC.

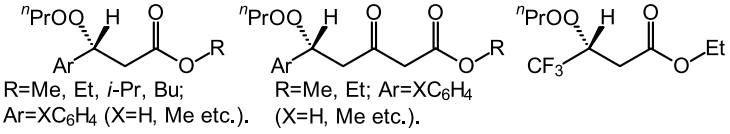
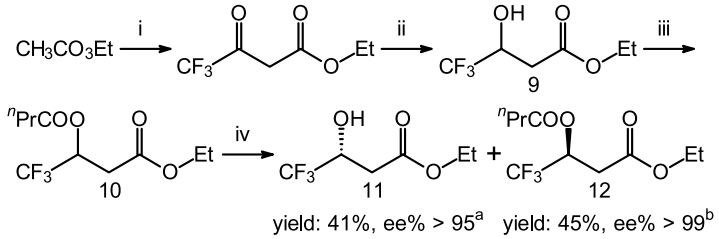


Figure 1. The preferential configuration of CRL-catalyzed hydrolysis.



a, the ee values of 11 was determined by ^{19}F NMR spectrum;
b, the ee values of 12 was determined by chiral HPLC.

(i) CF_3CO_2Et/EtONa/EtOH, reflux, 10h; (ii) $NaBH_4$, rt, 0.5h; (iii) $^nPrCO_2H$/DCC/DMAP(cat.)/CH_2Cl_2, rt, 1.5h; (iv) *CRL*/$^iPr_2O$-H_2O, 30 °C, 24h.

Scheme 5.

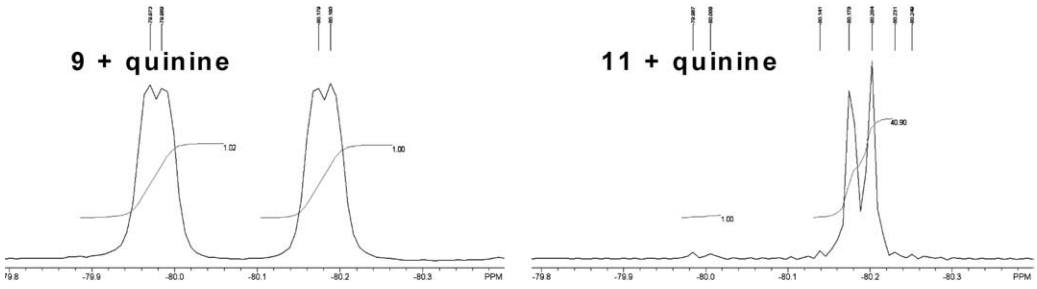


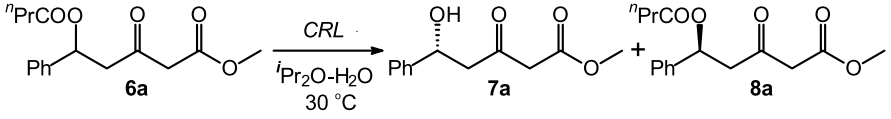
Figure 2. ^{19}F NMR spectrum of **9**+quinine and **11**+quinine.

$[\alpha]_D^{25}=+57.1$ ($c=1.0$, $CHCl_3$) and literature[11b] (*S*)-**2a** $[\alpha]_D^{25}=-46.0$ ($c=1.0$, $CHCl_3$)}.

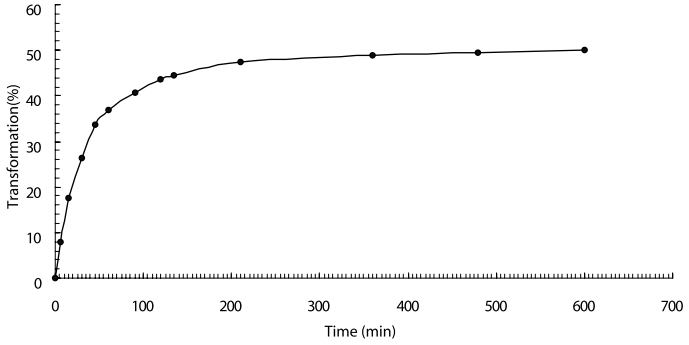
Based on the optical rotation data, the absolute configuration of products **4a**–**m** and **5a**–**m** or **7a**–**n** and **8a**–**n** was thus determined. So, the enantioselectivity of CRL-catalyzed hydrolysis of substrates **3a**–**m** and **6a**–**n** was consequently deduced (Fig. 1).

It was found that the enantioselectivity of CRL-catalyzed hydrolysis was kept almost identical. When the aryl group of β-hydroxy-β-arylethylphosphonates was replaced by a trifluoromethyl moiety,[15b] similar outcomes were observed. These trifluoromethyl analog are the precursors of novel fluorinated pharmaceuticals, such as the antidepressant beloxatone,[18] chiral ethyl 3-hydroxy-4,4,4-trifluorobutyrate was synthesized. (Scheme 5 and Fig. 2)

The absolute configuration of product **11** was also determined by optical rotation with an $[\alpha]_D^{20}=+20.8$ (c 0.7, $CHCl_3$) {literature[18c] (*S*)-**9**: $[\alpha]_D^{20}=-18.4$ (c 2.85, $CHCl_3$); literature[18b] (*R*)-**9**: $[\alpha]_D^{20}=+21.8$ (c 1.25, $CHCl_3$); literature[19] (*R*)-**9**: $[\alpha]_D^{25}=+20.1$ (c 1.2, $CHCl_3$)}. Based on the above data, the enantioselectivity of CRL-catalyzed hydrolysis was also deduced as shown in Figure 1.

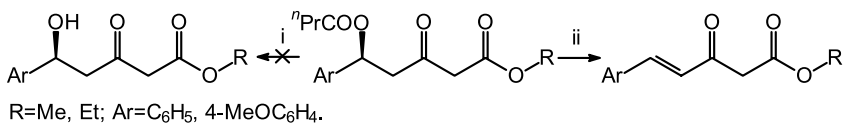


Scheme 6.



time (min)	transformation (%)	time (min)	transformation (%)	time (min)	transformation (%)	time (min)	transformation (%)
6	8.0	45	33.6	120	43.7	360	49.0
15	17.5	60	36.9	135	44.6	480	49.5
30	26.2	90	40.8	210	47.4	600	50.0

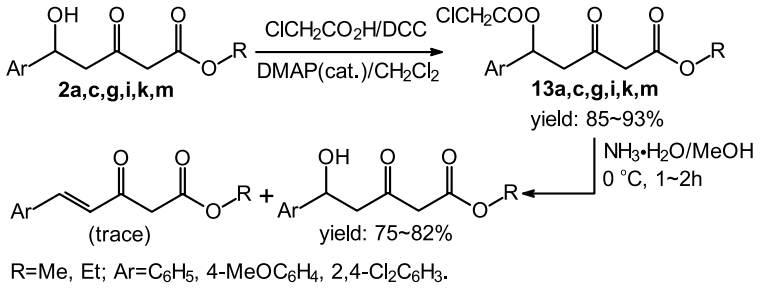
Figure 3. The curve between the transformation and reaction time of CRL-catalyzed hydrolysis of substrate **6a** (transformation was determined by ^{1}H NMR spectrum, because of big difference of chemical shift of δ-H between the product **7a** (δ_H: ~5.20 ppm) and **8a** (δ_H: ~6.20 ppm)).



R=Me, Et; Ar=C_6H_5, 4-$MeOC_6H_4$.

(i) lipase/H_2O; (ii) base/solvent.

Scheme 7.



Scheme 8.

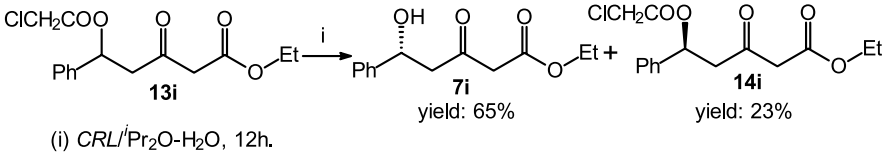
Due to the slow reaction rate of CRL-catalyzed hydrolysis of hydroxycarboxylates bearing aryl groups, we were able to investigate the kinetics of the transformation at 30 °C. (Scheme 6 and Fig. 3)

Although good results of CRL-catalyzed hydrolysis of δ-hydroxy-δ-aryl-β-oxo-pentanoates were achieved, we still met difficulty of transforming the chiral butyryl esters into corresponding optically active alcohols. Chemical hydrolysis only provided elimination products. It is necessary to point out that our trials to furnish this transformation by enzyme-catalyzed hydrolysis including CALB, IM, PS-30, PPL, GM as well as AY failed. (Scheme 7)

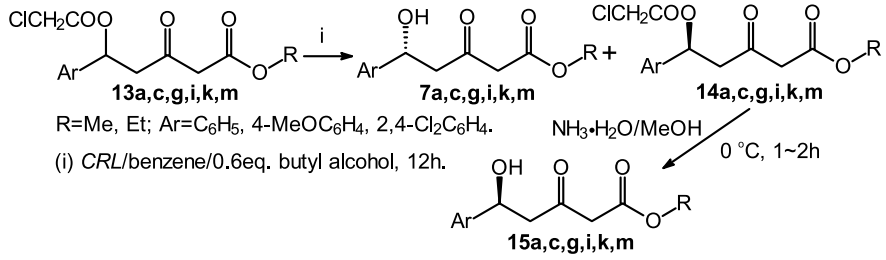
Some chloroacetyl esters were reported to transform into corresponding alcohols under weak basic conditions, such as Et_3N, $NH_3 \cdot H_2O$, K_2CO_3 etc.,[20] and such treatment also good for our substrates. The chloroacetyl esters formed by conventional method (DCC/chloroacetic acid) gave corresponding alcohols upon treatment with aqueous NH_3 in MeOH with excellent yield. (Scheme 8)

Since this method solved the problem of elimination of butyryl esters, and if the chloroacetyl esters could be resolved, the enantiomers of δ-hydroxy-δ-aryl-β-oxo-pentanoates were obtained.

Based on above idea, we first enantioselectively hydrolyzed the chloroacetyl esters catalyzed by crude CRL in diisopropyl ether preequilibrated with 1.2 M $MgCl_2$ solution. Although this enantioselective hydrolysis reaction successfully proceeded, the enantioselectivity was worse than their butyryl counterparts. (Scheme 9).



Scheme 9.

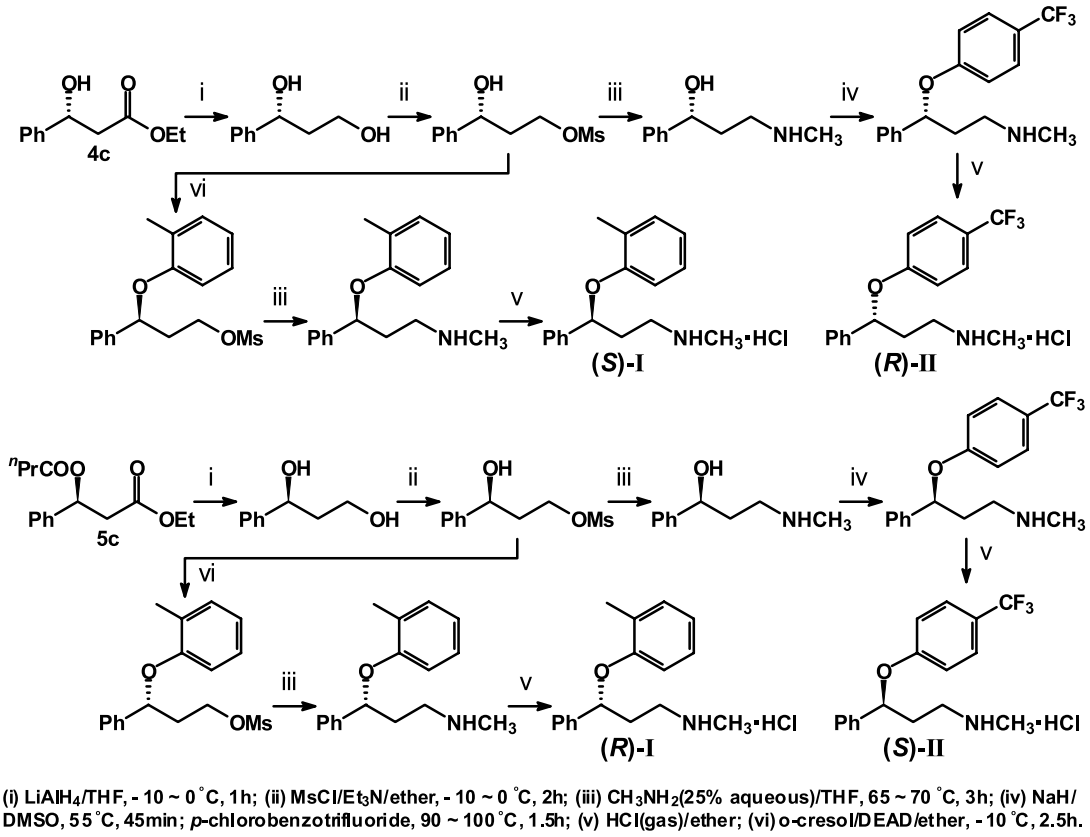


Scheme 10.

Table 3. CRL catalyzed enantioselective alcoholysis of **13a**,**c**,**g**,**i**,**k**,**m**

Entry	R	Ar	Yield of **14** (%)	**7**		**15**		E^a
				Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	
a	Me	C_6H_5	48	45	78.6	76	88.7	>80
c	Me	4-$MeOC_6H_4$	49	46	86.5	78	94.9	>100
g	Me	2,4-$Cl_2C_6H_3$	46	43	92.0	70	90.6	>100
i	Et	C_6H_5	49	44	95.4	82	>99	>100
k	Et	4-$MeOC_6H_4$	49	45	96.7	79	>99	>100
m	Et	2,4-$Cl_2C_6H_3$	44	42	>99	71	97.3	>100

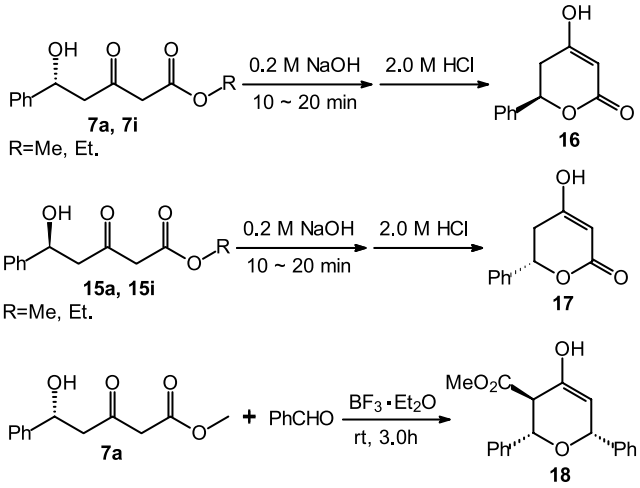
[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[16]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK AD, OD, AS).



Scheme 11.

Another alternative method to improve enantioselectivity was alcoholysis, and our group has prepared optically active 1- or 2-hydroxyalkanephosphonates through butyl alcoholysis reaction of corresponding chloroacetyl esters catalyzed by CALB and IM.[21] Fortunately, this method is successfully used in our substrates catalyzed by crude CRL. (Scheme 10 and Table 3).

After successful completion of the CRL-catalyzed hydrolysis/alcoholysis of substrates **3a**–**m**, **6a**–**n** and **13a**–**m**, we utilized the optically active products to synthesize some chiral pharmaceuticals and precursors of natural products. In the introduction, we stated the extremely useful chiral pharmaceuticals tomoxetine hydrochloride (**I**) and fluoxetine hydrochloride (**II**). We therefore selected one couple of the highest enantiomeric excess (**4c** and **5c**) to prepare them. We also transformed several chiral products (**7a**, **7i**, **15a** and **15i**) into optically active precursors of natural products, such as chiral 4-hydroxy-6-phenyll-5,6-dihydro-2-pyones (**16** and **17**) and methyl 4-oxo-2,6-diphenyl-tetrahydro-pyran-3-carboxylatete (**18**). (Schemes 11 and 12).



Scheme 12.

3. Conclusion

In summary, β-hydroxy-β-arylpropionates and δ-hydroxy-δ-aryl-β-oxo-pentanoates were successfully resolved by CRL-catalyzed hydrolysis to furnish optically active β-hydroxy-β-arylpropionates, δ-hydroxy-δ-aryl-β-oxo-pentanoates and their butyryl derivatives, which are useful precursors of chiral pharmaceuticals, such as tomoxetine hydrochloride (**I**) and fluoxetine hydrochloride (**II**).

4. Experimental

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard); ^{19}F NMR spectra were taken on the same spectrometer using CF_3COOH as external standard.

CRL (901 units/mg) was purchased from Sigma Chemical Co.

The chiral liquid chromatography system: Waters 515 HPLC pump; UV Waters 2487 Dual λ Absorbance Detector, 254 nm; Penelson Network chromatography interface NCI 900, Turbohrom Navigator data station software; column dimensions: 0.46 cm×25 cm; the flow rate: 0.7 mL/min; eluent: hexane–isopropanol=9:1–8:2 (v/v).

4.1. General procedure for the preparation of β-hydroxy-β-arylpropionates 1a–m

To a solution of diisopropyl amine (1.82 g, 18 mmol) in dry THF (20 mL) was added butyllithium (in hexane 1.6 M, 11.3 mL, 18 mmol) at −78 °C under nitrogen. The mixture was kept at this temperature for 1 h, then a mixture of acetate (15 mmol) and dry THF (10 mL) was added at low temperature. After it stirred for 1 h at −78 °C, a mixture of aldehyde (18 mmol) and dry THF (10 mL) was added. After the mixture was stirred for another 1 h, saturated NH_4Cl solution was added and the aqueous layer was extracted with ethyl acetate (3×30 mL), the combined extracts were dried and evaporated in vacuum. The residue was subjected to flash chromatography to furnish the racemic β-hydroxy-β-arylpropionates **1a**–**m**.

4.2. General procedure for preparation of δ-hydroxy-δ-aryl-β-oxo-pentanoates (2a–n)

To a suspension of sodium hydride (80%, 0.54 g, 18 mmol) in dry THF (8 mL) was added acetoacetate (15 mmol) under nitrogen, after 30 min at rt, butyllithium (in hexane 1.6 M, 11.3 mL, 18 mmol) was added at −15–10 °C (ice-salt bath). The mixture was kept this temperature for 30 min, then aldehydes (18 mmol) was added at this temperature. After the mixture was stirred for 1–2 h at low temperature, saturated NH_4Cl (30 mL) was added and the aqueous was extracted with ethyl acetate (3×30 mL). The combined extracts was dried and evaporated in vacuum. The residues were subjected to flash chromatography to furnish the δ-hydroxy-δ-aryl-β-oxo-pentanoates (**2a**–**n**).

4.3. General procedure for the preparation of β-butyryloxy-β-arylpropionates (3a–m), δ-butyryloxy-δ-aryl-β-oxo-pentanoates (6a–n) and δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (15a,c,g,i,k,m)

In a 25 mL bottle were added substrates **1a**–**m** (or **2a**–**n**) (1 mmol), *n*-butyric acid (or chloroacetic acid) (1.2 mmol), DCC (248 mg, 1.2 mmol), DMAP (5 mg) and CH_2Cl_2 (10 mL). After the starting material was almost consumed at rt (about 1–2 h), diethyl ether (10 mL) was added and the precipitate was filtered off. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the corresponding butyryl derivatives of which yields are listed in Tables 1 and 2.

4.4. General procedure of CRL-catalyzed enantioselective hydrolysis of β-butyryloxy-β-arylpropionates (3a–m)

Substrates **3a**–**m** (100 mg) and CRL (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 24 h at 30 °C, and filtered off the CRL that could be reuse and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **4a**–**m** and unreacted esters **5a**–**m**. The yields are listed in Table 1.

4.4.1. (3*R*) Methyl β-hydroxy-β-phenyl propionate (4a).[8i,22] Colorless oil; $[\alpha]_D^{20}=+46.9$ (*c* 1.2, $CHCl_3$). ν_{max}(liquid film) 3464, 3032, 2955, 1737, 1439, 1201, 1062, 1026, 763, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.27 (5H, m, C_6H_5), 5.14 (1H, dd, $J=7.5$, 8.7 Hz, PhC*H*CH_2), 3.73 (3H, s, OCH_3), 2.83–2.69 (2H, m, PhCHCH_2CO); *m*/*z* (EI) 180 (41, M^+), 120 (12), 107 (100), 105 (29), 79 (68), 77 (44), 51 (15), 43 (13%).

4.4.2. (3*S*) Methyl β-butyryloxy-β-phenyl propionate (5a). Colorless oil; $[\alpha]_D^{20}=-45.9$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3036, 2967, 2878, 1745, 1170, 1004, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.26 (5H, m, C_6H_5), 6.18 (1H, dd, $J=4.8$, 9.0 Hz, PhC*H*CH_2), 3.67 (3H, s, OCH_3), 2.97 (1H, dd, $J=9.0$, 15.6 Hz, PhCHCH_2CO), 2.76 (1H, dd, $J=5.4$, 15.6 Hz, PhCHCH_2CO), 2.29 (2H, t, $J=8.1$ Hz, $COCH_2CH_2CH_3$), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 0.91 (3H, t, $J=8.1$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 250 (1, M^+), 179 (100), 147 (20), 131 (14), 121 (37), 105 (62), 77 (16), 71 (47), 43 (33%). Found: C, 66.99; H, 7.31. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25.

4.4.3. (3*R*) Methyl β-hydroxy-β-(*p*-methoxyphenyl) propionate (4b).[23] Colorless oil; $[\alpha]_D^{20}=+36.4$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3482, 3003, 2955, 2839, 1738, 1614, 1515, 1249, 1033, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, $J=6.9$ Hz, C_6H_4), 6.82 (2H, d, $J=6.6$ Hz, C_6H_4), 5.02 (1H, dd, $J=4.5$, 9.3 Hz, ArC*H*CH_2), 3.74 (3H, s, CO_2CH_3), 3.65 (3H, s, OCH_3), 2.76–2.58 (2H, m, ArCHCH_2CO); δ_{13}C(75.5 MHz, $CDCl_3$) 173.07, 159.54, 135.31, 127.36, 114.28, 70.33, 55.64, 52.23, 43.70; *m*/*z* (EI) 210 (15, M^+), 179 (3), 137 (100), 135 (12), 109 (23), 94 (13), 77 (14), 65 (4%).

4.4.4. (3*S*) Methyl β-butyryloxy-β-(*p*-methoxyphenyl) propionate (5b). Colorless oil; $[\alpha]_D^{20}=-60.7$(*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2965, 2939, 2878, 1744, 1517, 1173, 832 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, $J=7.2$ Hz, C_6H_4), 6.87 (2H, d, $J=7.5$ Hz, C_6H_4), 6.13 (1H, dd, $J=5.4$, 9.3 Hz, ArC*H*CH_2), 3.80 (3H, s, CO_2CH_3), 3.66 (3H, s, OCH_3), 2.98 (1H, dd, $J=6.9$, 15.6 Hz, ArCHCH_2CO), 2.74 (1H, dd, $J=5.4$, 15.9 Hz, ArCHCH_2CO), 2.26 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.65–1.58 (2H, m, $COCH_2CH_2CH_3$), 0.90 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 280 (15, M^+), 209 (100), 193 (14), 151 (59), 137 (62), 135 (88), 119 (11), 77 (11), 71 (41%). Found: C, 64.15; H, 7.41. $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19.

4.4.5. (3*R*) Ethyl β-hydroxy-β-phenyl propionate (4c).[8i,24] Colorless oil; $[\alpha]_D^{20}=+43.7$ (*c* 1.4, $CHCl_3$). ν_{max}(liquid film) 3461, 2984, 2938, 1734, 1197, 1162, 1028, 761, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 5.13 (1H, dd, $J=4.5$, 8.1 Hz, PhC*H*CH_2), 4.18 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.11 (1H, s, O*H*), 2.81–2.67 (2H, m, PhCHCH_2CO), 1.26 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m*/*z* (EI)

194 (100, M^+), 165 (6), 147 (13), 120 (19), 107 (97), 105 (65), 79 (49), 77 (38), 60 (11%).

4.4.6. (3*S*) Ethyl β-butyryloxy-β-phenyl propionate (5c). Colorless oil; $[\alpha]_D^{20}=-27.5$(*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3037, 2969, 2877, 1742, 1457, 1255, 1172, 1028, 763, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.26 (5H, m, C_6H_5), 6.18 (1H, dd, *J*=5.1, 9.0 Hz, PhC*H*CH_2), 4.10 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 2.95 (1H, dd, *J*=9.0, 15.3 Hz, PhCHCH_2CO), 2.74 (1H, dd, *J*=5.1, 15.9 Hz, PhCHCH_2CO), 2.30 (2H, t, *J*=7.8 Hz, CO$CH_2CH_2CH_3$), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 1.22 (3H, t, *J*=7.5 Hz, OCH_2CH_3), 0.91 (3H, t, *J*=7.5 Hz, $COCH_2CH_2CH_3$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.7, 170.1, 139.9, 129.0, 128.7, 126.95, 72.3, 61.1, 42.0, 36.6, 18.8, 14.5, 14.0; *m/z* (EI) 264 (1, M^+), 193 (100), 147 (28), 131 (17), 121 (37), 105 (76), 77 (15), 71 (42), 43 (28%). Found: C, 68.18; H, 7.63. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63.

4.4.7. (3*R*) Ethyl β-hydroxy-β-(*p*-methylphenyl) propionate (4d).[8i,25] Colorless oil; $[\alpha]_D^{20}=+42.5$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3464, 2983, 2927, 1735, 1373, 1160, 1041, 819 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J*=8.4 Hz, C_6H_4), 7.16 (2H, d, *J*=7.8 Hz, C_6H_4), 5.09 (1H, dd, *J*=4.2, 9.0 Hz, ArC*H*CH_2), 4.17 (2H, q, *J*=7.5 Hz, OCH_2CH_3), 3.14 (1H, s, O*H*), 2.79–2.63 (2H, m, ArCHCH_2CO), 2.34 (3H, s, ArCH_3), 1.26 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 208 (31, M^+), 193 (14), 134 (7), 121 (100), 119 (42), 105 (9), 93 (38), 91 (34), 77 (17%).

4.4.8. (3*S*) Ethyl β-butyryloxy-β-(*p*-methylphenyl) propionate (5d). Colorless oil; $[\alpha]_D^{20}=-46.5$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2969, 2877, 1743, 1174, 1027, 817 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J*=8.1 Hz, C_6H_4), 7.15 (2H, d, *J*=7.8 Hz, C_6H_4), 6.15 (1H, dd, *J*=5.7, 9.0 Hz, ArC*H*CH_2), 4.12 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 2.95 (1H, dd, *J*=7.2, 14.4 Hz, ArCHCH_2CO), 2.73 (1H, dd, *J*=5.1, 15.6 Hz, ArCHCH_2CO), 2.33 (3H, s, ArCH_3), 2.27 (2H, t, *J*=7.8 Hz, CO$CH_2CH_2CH_3$), 1.66–1.58 (2H, m, $COCH_2CH_2CH_3$), 1.22 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.90 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 278 (2, M^+), 207 (86), 191 (52), 149 (25), 145 (17), 119 (100), 177 (20), 91 (21), 71 (30), 43 (42%). Found: C, 69.07; H, 7.90. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97.

4.4.9. (3*R*) Ethyl β-hydroxy-β-(*p*-methoxylphenyl) propionate (4e).[8i,26] Colorless oil; $[\alpha]_D^{20}=+26.5$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 3461, 2981, 2908, 1732, 1613, 1515, 1249, 1176, 1035, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28 (2H, d, *J*=7.5 Hz, C_6H_4), 6.88 (2H, d, *J*=6.9 Hz, C_6H_4), 5.08 (1H, dd, *J*=4.2, 9.0 Hz, ArC*H*CH_2), 4.18 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 2.80–2.63 (2H, m, ArCHCH_2CO), 1.26 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 224 (12, M^+), 179 (4), 138 (9), 137 (100), 135 (18), 109 (18), 94 (8), 77 (10), 65 (3%).

4.4.10. (3*S*) Ethyl β-butyryloxy-β-(*p*-methoxylphenyl) propionate (5e). Colorless oil; $[\alpha]_D^{20}=-54.2$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2968, 2938, 2877, 1741, 1517, 1251, 1174, 1034, 833 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, *J*=6.9 Hz, C_6H_4), 6.86 (2H, d, *J*=6.6 Hz, C_6H_4), 6.13 (1H, dd, *J*=5.7, 9.0 Hz, ArC*H*CH_2), 4.11 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 2.96 (1H, dd, *J*=9.3, 15.3 Hz, ArCHCH_2CO), 2.73 (1H, dd, *J*=4.8, 15.3 Hz, ArCHCH_2CO), 2.26 (2H, t, *J*=7.8 Hz, CO$CH_2CH_2CH_3$), 1.65–1.55 (2H, m, $COCH_2CH_2CH_3$), 1.21 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.88 (3H, t, *J*=7.5 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 294 (12, M^+), 223 (96), 207 (14), 177 (8), 161 (21), 150 (16), 137 (47), 135 (100), 119 (11), 71 (25%). Found: C, 65.26; H, 7.47. $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.53.

4.4.11. (3*R*) Ethyl β-hydroxy-β-furan-2-yl propionate (4f).[27] Colorless oil; $[\alpha]_D^{20}=+15.0$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3455, 2985, 2938, 1734, 1374, 1210, 1164, 1014, 742 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.36 (1H, m, C_4H_3O), 6.34–6.32 (1H, m, C_4H_3O), 6.28–6.26 (1H, m, C_4H_3O), 5.13 (1H, dd, *J*=4.8, 8.1 Hz, ArC*H*CH_2), 4.18 (2H, q, *J*=7.5 Hz, OCH_2CH_3), 3.43 (1H, s, O*H*), 2.94–2.78 (2H, m, ArCHCH_2CO), 1.27 (3H, t, *J*=7.2 Hz, OCH_2CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.13, 155.39, 142.47, 110.58, 106.55, 64.45, 61.24, 40.42, 14.44; *m/z* (EI) 184 (20, M^+), 155 (4), 137 (14), 110 (16), 97 (100), 95 (46), 88 (4), 69 (7), 60 (6%).

4.4.12. (3*S*) Ethyl β-butyryloxy-β-furan-2-yl propionate (5f). Colorless oil; $[\alpha]_D^{20}=-94.2$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2879, 1744, 1376, 1287, 1172, 1014, 746 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.37 (1H, m, C_4H_3O), 6.38–6.26 (3H, m, C_4H_3O, ArC*H*CH_2), 4.13 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 3.09 (1H, dd, *J*=8.4, 15.6 Hz, ArCHCH_2CO), 2.91 (1H, dd, *J*=5.7, 15.6 Hz, ArCHCH_2CO), 2.27 (2H, t, *J*=7.2 Hz, CO$CH_2CH_2CH_3$), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 1.23 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.91 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.71, 169.81, 151.76, 143.04, 110.72, 109.18, 65.01, 61.18, 38.13, 36.44, 18.72, 14.46, 13.84; *m/z* (EI) 254 (4, M^+), 183 (100), 167 (11), 137 (50), 121 (21), 115 (23), 110 (19), 95 (46), 71 (33), 43 (22%). Found: C, 61.43; H, 7.36. $C_{13}H_{18}O_5$ requires C, 61.41; H, 7.13.

4.4.13. (3*R*) Ethyl β-hydroxy-β-(*o*-chlorophenyl) propionate (4g).[28] Colorless oil; $[\alpha]_D^{20}=+80.3$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 3481, 2984, 2938, 1735, 1441, 1193, 1033, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.63 (1H, d, *J*=6.6 Hz, C_6H_4), 7.35–7.22 (3H, m, C_6H_4), 5.49 (1H, d, *J*=9.6 Hz, ArC*H*CH_2), 4.20 (2H, q, *J*=7.5 Hz, OCH_2CH_3), 3.63 (1H, s, O*H*), 2.86 (1H, dd, *J*=2.7, 16.8 Hz, ArCHCH_2CO), 2.58 (1H, dd, *J*=9.6, 16.5 Hz, ArCHCH_2CO), 1.28 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 228 (6, M^+), 193 (65), 147 (10), 143 (29), 141 (100), 139 (41), 113 (15), 105 (15), 88 (25), 77 (50), 60 (17%).

4.4.14. (3*S*) Ethyl β-butyryloxy-β-(*p*-methoxylphenyl) propionate (5g). Colorless oil; $[\alpha]_D^{20}=-5.6$ (*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 2970, 2938, 2878, 1751, 1375, 1172, 1019, 759 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.34 (2H, m, C_6H_4), 7.28–7.22 (2H, m, C_6H_4), 6.51 (1H, dd, *J*=5.1, 8.7 Hz, ArC*H*CH_2), 4.15 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 2.86–2.81 (2H, m, ArCHCH_2CO), 2.34 (2H, t, *J*=7.2 Hz, CO$CH_2CH_2CH_3$), 1.70–1.62 (2H, m, $COCH_2CH_2CH_3$), 1.24 (3H, t, *J*=7.5 Hz, OCH_2CH_3), 0.93 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 299 (21, $M^+ + 1$), 263 (74), 227 (36), 211 (63), 193 (14), 175 (58), 169 (63), 165 (30), 139 (70), 71 (86), 43 (100%). Found: C, 60.21; H, 6.34. $C_{15}H_{19}O_4Cl$ requires C, 60.30; H, 6.41.

4.4.15. (3*R*) Ethyl β-hydroxy-β-(*p*-fluorophenyl) propionate (4h).[25] Colorless oil; $[\alpha]_D^{20}=+38.8$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3455, 2985, 2908, 1733, 1606, 1512, 1223, 1158, 838 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34 (2H, dd, *J*= 3.3, 9.0 Hz, C_6H_4), 7.03 (2H, t, *J*=6.6 Hz, C_6H_4), 5.10 (1H, dd, *J*=4.5, 8.1 Hz, ArC*H*CH_2), 4.18 (2H, q, *J*=7.5 Hz, O*C*H_2CH_3), 3.22 (1H, s, O*H*), 2.78–2.63 (2H, m, ArCHCH_2-CO), 1.26 (3H, t, *J*=7.2 Hz, OCH_2CH_3); *m/z* (EI) 212 (22, M^+), 195 (38), 165 (6), 153 (22), 138 (9), 125 (100), 123 (74), 97 (69), 88 (36), 77 (27), 60 (27%).

4.4.16. (3*S*) Ethyl β-butyryloxy-β-(*p*-fluorophenyl) propionate (5h). Colorless oil; $[\alpha]_D^{20}=-37.7$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2879, 1743, 1514, 1175, 1160, 838 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (2H, dd, *J*=5.4, 8.7 Hz, C_6H_4), 7.04 (2H, t, *J*=8.7 Hz, C_6H_4), 6.15 (1H, dd, *J*=5.4, 9.0 Hz, ArC*H*CH_2), 4.12 (2H, q, *J*=7.5 Hz, O*C*H_2CH_3), 2.96 (1H, dd, *J*=9.0, 15.9 Hz, ArCHCH_2CO), 2.73 (1H, dd, *J*=5.7, 15.9 Hz, ArCHCH_2CO), 2.28 (2H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$), 1.70–1.57 (2H, m, $COCH_2$-CH_2CH_3), 1.23 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.90 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 282 (10, M^+), 211 (96), 165 (31), 149 (20), 138 (7), 123 (100), 119 (8), 95 (10), 71 (77), 43 (87%). Found: C, 63.93; H, 6.96. $C_{15}H_{19}O_4F$ requires C, 63.82; H, 6.78.

4.4.17. (3*R*) Ethyl β-hydroxy-β-(*o*,*p*-dichlorophenyl) propionate (4i).[29] Colorless oil; $[\alpha]_D^{20}=+58.1$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3473, 2984, 2908, 1720, 1591, 1471, 1375, 1192, 868, 823 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (1H, d, *J*=8.7 Hz, C_6H_3), 7.35–7.26 (2H, m, C_6H_3), 5.42 (1H, dd, *J*=2.1, 9.6 Hz, ArC*H*CH_2), 4.17 (2H, q, *J*= 7.5 Hz, O*C*H_2CH_3), 2.82 (1H, dd, *J*=3.0, 16.5 Hz, ArCHCH_2CO), 2.53 (1H, dd, *J*=9.6, 16.5 Hz, ArCHCH_2-CO), 1.28 (3H, t, *J*=7.2 Hz, OCH_2CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.62, 139.13, 134.13, 132.29, 129.42, 128.54, 127.88, 67.01, 61.50, 60.85, 41.77, 14.51; *m/z* (EI) 263 (1, M^+), 227 (36), 177 (55), 175 (100), 173 (39), 139 (14), 111 (40), 88 (50), 75 (19), 43 (19%).

4.4.18. (3*S*) Ethyl β-butyryloxy-β-(*o*,*p*-dichlorophenyl) propionate (5i). Colorless oil; $[\alpha]_D^{20}=-12.3$ (*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 2970, 2938, 2878, 1708, 1475, 1376, 1168, 1022, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.23 (3H, m, C_6H_3), 6.44 (1H, dd, *J*=5.4, 8.1 Hz, ArC*H*CH_2), 4.15 (2H, q, *J*=6.9 Hz, O*C*H_2CH_3), 2.82–2.79 (2H, m, ArCHCH_2CO), 2.33 (2H, t, *J*=7.8 Hz, $COCH_2CH_2CH_3$), 1.70–1.61 (2H, m, $COCH_2CH_2CH_3$), 1.25 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 0.93 (3H, t, *J*= 6.9 Hz, $COCH_2CH_2CH_3$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.4, 169.7, 136.4, 134.8, 133.2, 130.0, 128.4, 127.9, 67.0, 61.3, 40.3, 36.4, 18.7, 14.5, 14.0; *m/z* (EI) 332 (1, M^+), 297 (7), 263 (26), 261 (39), 215 (10), 209 (9), 199 (10), 175 (32), 173 (43), 71 (100), 43 (60%). Found: C, 54.37; H, 5.65. $C_{15}H_{18}O_4Cl_2$ requires C, 54.07; H, 5.44.

4.4.19. (3*R*) Ethyl β-hydroxy-β-(*p*-nitrophenyl) propionate (4j).[30] Colorless oil; $[\alpha]_D^{20}=+23.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3480, 2985, 1732, 1522, 1349, 1195, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.22 (2H, d, *J*=6.9 Hz, C_6H_4), 7.57 (2H, d, *J*=9.0 Hz, C_6H_4), 5.24 (1H, dd, *J*=5.1, 7.5 Hz, ArC*H*CH_2), 4.20 (2H, q, *J*=6.9 Hz, O*C*H_2CH_3), 3.79 (1H, s, O*H*), 2.81–2.64 (2H, m, ArCHCH_2CO), 1.28 (3H, t, *J*=6.9 Hz, OCH_2CH_3); *m/z* (EI) 239 (30, M^+), 210 (17), 192 (34), 165 (29), 152 (75), 150 (100), 134 (10), 105 (21), 88 (46), 77 (34), 43 (22%).

4.4.20. (3*S*) Ethyl β-butyryloxy-β-(*p*-nitrophenyl) propionate (5j). Colorless oil; $[\alpha]_D^{20}=-36.6$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2878, 1743, 1608, 1526, 1349, 1169, 857 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.22 (2H, d, *J*= 6.9 Hz, C_6H_4), 7.55 (2H, d, *J*=7.5 Hz, C_6H_4), 6.22 (1H, dd, *J*=5.4, 8.1 Hz, ArC*H*CH_2), 4.14 (2H, q, *J*=6.9 Hz, O*C*H_2CH_3), 2.97 (1H, dd, *J*=8.7, 15.9 Hz, ArCHCH_2CO), 2.78 (1H, dd, *J*=5.7, 15.9 Hz, ArCHCH_2CO), 2.34 (2H, t, *J*=7.5 Hz, $COCH_2CH_2CH_3$), 1.71–1.58 (2H, m, $COCH_2$-CH_2CH_3), 1.24 (3H, t, *J*=7.5 Hz, OCH_2CH_3), 0.92 (3H, t, *J*=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 309 (1, M^+), 264 (4), 238 (50), 222 (100), 192 (25), 176 (48), 150 (54), 134 (51), 103 (9), 71 (91), 43 (45%). Found: C, 58.42; H, 6.17; N, 4.74. $C_{15}H_{19}NO_6$ requires C, 58.25; H, 6.19; N, 4.53.

4.4.21. (3*R*) Isopropyl β-hydroxy-β-phenyl propionate (4k).[8i,31] Colorless oil; $[\alpha]_D^{20}=+39.4$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3462, 3033, 2983, 2937, 1731, 1455, 1375, 1198, 1109, 761, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.25 (5H, m, C_6H_5), 5.14–5.01 (2H, m, PhC*H*CH_2, O*C*$H(CH_3)_2$), 3.31 (1H, s, O*H*), 2.80–2.62 (2H, m, PhCHCH_2CO), 1.22 (6H, d, *J*=6.3 Hz, $OCH(CH_3)_2$); *m/z* (EI) 208 (15, M^+), 165 (41), 149 (11), 147 (19), 137 (7), 120 (7), 107 (100), 79 (50), 43 (23%).

4.4.22. (3*S*) Isopropyl β-butyryloxy-β-phenyl propionate (5k). Colorless oil; $[\alpha]_D^{20}=-41.8$(*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 3067, 2980, 2938, 1740, 1376, 1274, 1172, 1109, 1007, 763, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 6.18 (1H, dd, *J*=5.4, 9.0 Hz, PhC*H*CH_2), 5.04–4.95 (1H, m, O*C*$H(CH_3)_2$), 2.93 (1H, dd, *J*=9.0, 15.3 Hz, PhCHCH_2CO), 2.72 (1H, dd, *J*=5.1, 15.3 Hz, PhCHCH_2CO), 2.90 (2H, t, *J*=7.5 Hz, $COCH_2$-CH_2CH_3), 1.69–1.57 (2H, m, $COCH_2CH_2CH_3$), 1.20 (6H, t, *J*=7.5 Hz, $OCH(CH_3)_2$), 0.90 (3H, t, *J*=7.2 Hz, $COCH_2$-CH_2CH_3); *m/z* (EI) 278 (1, M^+), 207 (66), 165 (100), 147 (41), 131 (28), 120 (12), 105 (57), 71 (69), 43 (50%). Found: C, 69.06; H, 7.84. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97.

4.4.23. (3*R*) Isopropyl β-hydroxy-β-(*p*-methoxylphenyl) propionate (4l). Colorless oil; $[\alpha]_D^{20}=+32.1$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 3482, 2982, 2938, 2838, 1729, 1614, 1515, 1249, 1109, 1035, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29 (2H, d, *J*=9.3 Hz, C_6H_4), 6.88 (2H, d, *J*= 9.3 Hz, C_6H_4), 5.15–5.01 (2H, m, ArC*H*CH_2, O*C*$H(CH_3)_2$), 3.80 (3H, s, O*C*H_3), 2.73 (1H, dd, *J*=8.7, 16.2 Hz, ArCHCH_2CO), 2.64 (1H, dd, *J*=3.9, 16.5 Hz, ArCHCH_2-CO), 1.23 (6H, d, *J*=6.0 Hz, $OCH(CH_3)_2$); δ_{13}C(75.5 MHz, $CDCl_3$) 172.3, 159.5, 135.3, 127.4, 114.2, 70.4, 68.7, 55.6, 44.1, 22.1; *m/z* (EI) 238 (12, M^+), 195 (10), 179 (7), 137 (100), 135 (49), 109 (20), 94 (9), 77 (12), 43 (9%). Found: C, 65.31; H, 7.54. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61.

4.4.24. (3*S*) Isopropyl β-butyryloxy-β-(*p*-methoxylphenyl) propionate (5l). Colorless oil; $[\alpha]_D^{20}=-46.3$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 2979, 2938, 2878, 1740, 1614, 1517, 1376, 1303, 1174, 1110, 833 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, *J*=6.6 Hz, C_6H_4), 6.86 (2H, d, *J*=6.6 Hz, C_6H_4), 6.13 (1H, dd, *J*=5.4, 9.3 Hz,

ArC*H*CH_2), 5.05–4.93 (1H, m, OC*H*$(CH_3)_2$), 3.79 (3H, s, OCH_3), 2.93 (1H, dd, J=9.0, 15.9 Hz, ArCHCH_2CO), 2.70 (1H, dd, J=5.7, 15.0 Hz, ArCHCH_2CO), 2.26 (2H, t, J=7.5 Hz, COC$H_2$$CH_2CH_3$), 1.65–1.58 (2H, m, $COCH_2$CH_2-CH_3), 1.19 (6H, t, J=6.6 Hz, OCH(CH_3)$_2$), 0.90 (3H, t, J=6.9 Hz, $COCH_2CH_2$CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.8, 169.7, 159.9, 131.9, 128.4, 114.3, 72.1, 68.5, 55.6, 42.1, 36.7, 22.1, 18.8, 14.0; *m*/*z* (EI) 308 (11, M^+), 237 (60), 195 (78), 177 (9), 161 (30), 150 (19), 137 (47), 135 (100), 119 (8), 71 (44), 43 (59%). Found: C, 66.21; H, 7.78. $C_{17}H_{24}O_5$ requires C, 66.21; H, 7.84.

4.4.25. (3*R*) *n*-Butyl β-hydroxy-β-phenyl propionate (4m).[8i,32] Colorless oil; $[\alpha]_D^{20}=+28.3$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 3464, 2962, 2935, 1733, 1271, 1195, 1165, 1061, 761, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 5.12 (1H, dd, J=4.5, 8.4 Hz, PhC*H*CH_2), 4.12 (2H, t, J=6.6 Hz, O$CH_2CH_2CH_2CH_3$), 3.22 (1H, s, O*H*), 2.77 (1H, dd, J=8.1, 15.9 Hz, PhCHCH_2CO), 2.69 (1H, dd, J=4.5, 16.5 Hz, PhCHCH_2CO), 1.63–1.56 (2H, m, OCH_2C$H_2CH_2CH_3$), 1.39–1.31 (2H, m, OCH_2CH_2CH_2-CH_3), 0.92 (3H, t, J=7.2 Hz, $OCH_2CH_2CH_2$CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.8, 143.1, 128.9, 128.1, 126.1, 70.7, 65.1, 43.8, 31.0, 19.5, 14.1; *m*/*z* (EI) 272 (48, M^+), 165 (14), 147 (27), 120 (18), 107 (100), 105 (85), 79 (50), 77 (34), 56 (19%).

4.4.26. (3*S*) *n*-Butyl β-butyryloxy-β-phenyl propionate (5m). Colorless oil; $[\alpha]_D^{20}=-32.9$(*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 2964, 2927, 2876, 1743, 1274, 1170, 1028, 763, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.27 (5H, m, C_6H_5), 6.17 (1H, dd, J=4.8, 9.3 Hz, PhC*H*CH_2), 4.08 (2H, t, J=6.3 Hz, O$CH_2CH_2CH_2CH_3$), 2.97 (1H, dd, J=9.0, 15.6 Hz, PhCHCH_2CO), 2.75 (1H, dd, J=5.1, 15.3 Hz, PhCHCH_2-CO), 2.29 (2H, t, J=7.5 Hz, COC$H_2CH_2CH_3$), 1.71–1.52 (4H, m, $COCH_2$CH_2CH_3, OCH_2C$H_2CH_2CH_3$), 1.40–1.28 (2H, m, OCH_2CH_2CH_2CH_3), 0.94–0.88 (6H, m, $COCH_2$-CH_2CH_3, $OCH_2CH_2CH_2$CH_3); δ_{13}C(75.5 MHz, $CDCl_3$) 172.7, 170.3, 139.9, 129.0, 128.7, 126.9, 72.4, 65.0, 42.0, 36.6, 31.0, 19.4, 18.89, 14.1, 14.0; *m*/*z* (EI) 293 (19, M^+), 221 (38), 205 (100), 163 (46), 147 (13), 105 (35), 77 (12), 71 (24), 57 (39%). Found: C, 69.67; H, 8.11. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27.

4.5. General procedure of CRL-catalyzed enantioselective hydrolysis of δ-butyryloxy-δ-aryl-β-oxo-pentanoates (6a–n)

Substrates **6a**–**n** (150 mg) and CRL (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 24 h at 30 °C, and filtered off the CRL that could be reuse and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **7a**–**n** and unreacted esters **8a**–**n**. The yields are listed in Table 2.

4.5.1. (5*R*) Methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7a).[33] Colorless oil; $[\alpha]_D^{20}=+58.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3497, 3064, 3033, 2956, 1745, 1714, 1439, 1327, 1156, 753, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 5.18 (1H, dd, J=5.7, 9.0 Hz, $COCH_2$-C*H*OH), 3.73 (3H, s, OCH_3), 3.51 (2H, s, COCH_2CO_2), 3.05–2.86 (3H, m, O*H*, COCH_2CHOH); *m*/*z* (EI) 222 (4, M^+), 204 (43), 149 (24), 144 (25), 131 (36), 116 (77), 107 (98), 105 (71), 79 (100), 77 (75), 43 (24%).

4.5.2. (5*S*) Methyl δ-butyryloxy-δ-phenyl-β-oxo-pentanoates (8a). Colorless oil; $[\alpha]_D^{20}=-36.5$ (*c* 1.5, $CHCl_3$). ν_{max} (liquid film) 3066, 2967, 2878, 1741, 1324, 1552, 1174, 753, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.26 (5H, m, C_6H_5), 6.20 (1H, dd, J=4.8, 8.7 Hz, $COCH_2$-C*H*OCO), 3.72 (3H, s, OCH_3), 3.46 (2H, s, COCH_2CO_2), 3.22 (1H, dd, J=8.7, 16.8 Hz, COCH_2CHOCO), 2.97 (1H, dd, J=4.8, 16.8 Hz, COCH_2CHOCO), 2.28 (2H, t, J=7.5 Hz, COC$H_2CH_2CH_3$), 1.68–1.58 (2H, m, $COCH_2$CH_2-CH_3), 0.90 (3H, t, J=7.5 Hz, $COCH_2CH_2$CH_3); *m*/*z* (EI) 274 (4, M^+-H_2O), 221 (39), 189 (52), 144 (15), 131 (27), 108 (88), 101 (27), 77 (22), 71 (100), 43 (81%). Found: C, 65.67; H, 7.02. $C_{16}H_{20}O_5$ requires C, 65.74; H, 6.90.

4.5.3. (5*R*) Methyl δ-hydroxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (7b). Colorless oil; $[\alpha]_D^{20}=+58.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3496, 3025, 2955, 1747, 1715, 1516, 1438, 1325, 821 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, J=8.1 Hz, C_6H_4), 7.16 (2H, d, J=7.8 Hz, C_6H_4), 5.14 (1H, dd, J=3.3, 9.0 Hz, $COCH_2$C*H*OH), 3.73 (3H, s, OCH_3), 3.50 (2H, s, COCH_2CO_2), 2.99 (1H, dd, J=9.3, 17.1 Hz, COCH_2CHOH), 2.87 (1H, dd, J=3.6, 17.1 Hz, COCH_2CHOH), 2.34 (3H, s, ArCH_3); *m*/*z* (EI) 236 (4, M^+), 218 (33), 163 (16), 159 (10), 145 (23), 121 (100), 119 (40), 117 (14), 93 (52), 91 (47), 77 (25%). Found: C, 66.06; H, 7.03. $C_{13}H_{16}O_4$ requires C, 66.09, H, 6.83.

4.5.4. (5*S*) Methyl δ-butyryloxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (8b). Colorless oil; $[\alpha]_D^{20}=-46.4$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 2964, 2876, 1738, 1516, 1174, 1085, 817 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, J=7.8 Hz, C_6H_4), 7.15 (2H, d, J=8.4 Hz, C_6H_4), 6.16 (1H, dd, J=5.1, 8.7 Hz, $COCH_2$C*H*OCO), 3.72 (3H, s, OCH_3), 3.45 (2H, s, COCH_2CO_2), 3.21 (1H, dd, J=8.7, 17.1 Hz, COCH_2CHOCO), 2.95 (1H, dd, J=4.8, 17.1 Hz, COCH_2-CHOCO), 2.33 (3H, s, ArCH_3), 2.28 (2H, t, J=7.2 Hz, COC$H_2CH_2CH_3$), 1.71–1.58 (2H, m, $COCH_2$CH_2CH_3), 0.89 (3H, t, J=7.2 Hz, $COCH_2CH_2$CH_3); *m*/*z* (EI) 288 (2, M^+-H_2O), 235 (35), 218 (9), 203 (43), 159 (7), 145 (27), 119 (100), 101 (17), 71 (60), 43 (37%). Found: C, 66.76; H, 7.20. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24.

4.5.5. (5*R*) Methyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7c).[11a] Colorless oil; $[\alpha]_D^{20}=+54.8$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 3496, 3003, 2957, 2840, 1746, 1715, 1615, 1515, 1250, 1033, 836 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27 (2H, d, J=9.0 Hz, C_6H_4), 6.87 (2H, d, J=8.4 Hz, C_6H_4), 5.12 (1H, dd, J=3.3, 9.3 Hz, $COCH_2$C*H*OH), 3.79 (3H, s, ArOCH_3), 3.73 (3H, s, CO_2CH_3), 3.50 (2H, s, COCH_2CO_2), 2.99 (1H, dd, J=9.0, 17.4 Hz, COCH_2CHOH), 2.85 (1H, dd, J=3.0, 17.4 Hz, COCH_2CHOH); *m*/*z* (EI) 252 (3, M^+), 234 (6), 179 (4), 161 (8), 137 (100), 135 (19), 109 (19), 94 (10), 77 (12), 65 (4%).

4.5.6. (5*S*) Methyl δ-butyryloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (8c). Colorless oil; $[\alpha]_D^{20}=-48.6$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2966, 2939, 2878, 1739, 1614, 1516, 1251, 1174, 1033, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29 (2H, d, J=8.7 Hz, C_6H_4), 6.87 (2H, d, J=6.6 Hz,

C_6H_4), 6.15 (1H, dd, J=4.8, 9.0 Hz, $COCH_2CHOCO$), 3.79 (3H, s, $ArOCH_3$), 3.72 (3H, s, CO_2CH_3), 3.45 (2H, s, $COCH_2CO_2$), 3.22 (1H, dd, J=9.0, 17.1 Hz, $COCH_2$-CHOCO), 2.96 (1H, dd, J=5.1, 17.1 Hz, $COCH_2CHOCO$), 2.25 (2H, t, J=7.8 Hz, $COCH_2CH_2CH_3$), 1.63–1.56 (2H, m, $COCH_2CH_2CH_3$), 0.89 (3H, t, J=7.2 Hz, $COCH_2CH_2$-CH_3); *m/z* (EI) 322 (5, M^+), 251 (27), 234 (15), 219 (25), 207 (9), 161 (52), 137 (67), 135 (100), 101 (16), 71 (36%). Found: C, 63.11; H, 7.13. $C_{17}H_{22}O_6$ requires C, 63.34; H, 6.88.

4.5.7. (5*R*) Methyl δ-hydroxy-δ-furan-2-yl-β-oxo-pentanoates (7d).[34] Colorless oil; $[\alpha]_D^{20}=+23.2$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3482, 3124, 2957, 1745, 1716, 1439, 1327, 1151, 1012, 747 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.36 (1H, m, C_4H_3O), 6.34–6.32 (1H, m, C_4H_3O), 6.28 (1H, d, J=3.6 Hz, C_4H_3O), 5.20 (1H, dd, J=3.6, 8.7 Hz, $COCH_2CHOH$), 3.74 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2$-CO_2), 3.17 (1H, dd, J=9.0, 17.4 Hz, $COCH_2CHOH$), 3.03 (1H, dd, J=3.6, 17.4 Hz, $COCH_2CHOH$); *m/z* (EI) 212 (20, M^+), 180 (17), 152 (10), 139 (20), 121 (26), 116 (25), 110 (29), 97 (100), 95 (20), 69 (16%).

4.5.8. (5*S*) Methyl δ-butyryloxy-δ-furan-2-yl-β-oxo-pentanoates (8d). Colorless oil; $[\alpha]_D^{20}=-95.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2968, 2879, 1737, 1438, 1326, 1174, 1014, 749 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.36 (1H, m, C_4H_3O), 6.38–6.27 (3H, m, C_4H_3O, $COCH_2CHOCO$), 3.74 (3H, s, OCH_3), 3.49 (2H, s, $COCH_2CO_2$), 3.32 (1H, dd, J=8.4, 17.4 Hz, $COCH_2CHOCO$), 3.16 (1H, dd, J=5.4, 17.4 Hz, $COCH_2CHOCO$), 2.25 (2H, t, J=7.5 Hz, $COCH_2$-CH_2CH_3), 1.69–1.54 (2H, m, $COCH_2CH_2CH_3$), 0.89 (3H, t, J=7.5 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 282 (1, M^+), 211 (52), 179 (100), 162 (9), 137 (41), 121 (36), 101 (33), 94 (36), 71 (68), 43 (51%). Found: C, 59.59; H, 6.44. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.43.

4.5.9. (5*R*) Methyl δ-hydroxy-δ-(*o*-bromophenyl)-β-oxo-pentanoates (7e). Colorless oil; $[\alpha]_D^{20}=+79.5$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 3522, 2981, 2947, 2920, 1735, 1698, 1440, 1331, 1196, 1144, 1006, 749 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (1H, d, J=6.6 Hz, C_6H_4), 7.51 (1H, d, J=7.8 Hz, C_6H_4), 7.35 (1H, t, J=7.5 Hz, C_6H_4), 7.13 (1H, t, J=7.2 Hz, C_6H_4), 5.49 (1H, dd, J=1.8, 9.6 Hz, $COCH_2CHOH$), 3.79 (3H, s, OCH_3), 3.54 (2H, s, $COCH_2$-CO_2), 3.09 (1H, dd, J=2.4, 17.7 Hz, $COCH_2CHOH$), 2.78 (1H, dd, J=9.6, 17.7 Hz, $COCH_2CHOH$); *m/z* (EI) 284 (14, M^+-H_2O), 282 (14, M^+-H_2O), 221 (11), 203 (54), 187 (48), 185 (69), 157 (20), 116 (100), 105 (20), 84 (26), 77 (78), 59 (19%). Found: C, 47.88; H, 4.56. $C_{12}H_{13}BrO_4$ requires C, 47.86; H, 4.35.

4.5.10. (5*S*) Methyl δ-butyryloxy-δ-(*o*-bromophenyl)-β-oxo-pentanoates (8e). Colorless oil; $[\alpha]_D^{20}=-0.92$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3066, 2967, 2937, 2877, 1743, 1438, 1250, 1174, 1086, 757 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54 (1H, d, J=8.1 Hz, C_6H_4), 7.37–7.28 (2H, m, C_6H_4), 7.15 (1H, dt, J=2.1, 8.1 Hz, C_6H_4), 6.47 (1H, t, J=6.3 Hz, $COCH_2CHOCO$), 3.73 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2CO_2$), 3.50 (2H, d, J=6.3 Hz, $COCH_2CHOCO$), 2.33 (2H, t, J=7.5 Hz, $COCH_2CH_2CH_3$), 1.71–1.59 (2H, m, $COCH_2CH_2CH_3$), 0.93 (3H, t, J=7.2 Hz, $COCH_2CH_2$-CH_3); *m/z* (EI) 301 (5, $M^+-{}^n$PrCO), 299 (5, $M^+-{}^n$PrCO), 291 (20), 269 (11), 209 (10), 203 (100), 183 (31), 101 (37), 71 (77), 59 (17), 43 (43%). Found: C, 51.98; H, 5.20. $C_{16}H_{19}BrO_5$ requires C, 51.77; H, 5.16.

4.5.11. (5*R*) Methyl δ-hydroxy-δ-(*p*-fluorophenyl)-β-oxo-pentanoates (7f). Colorless oil; $[\alpha]_D^{20}=+52.6$ (*c* 1.4, $CHCl_3$). ν_{max} (liquid film) 3503, 2957, 1747, 1716, 1606, 1512, 1223, 840 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.28 (2H, m, C_6H_4), 7.03 (2H, t, J=6.9 Hz, C_6H_4), 5.15 (1H, dd, J=2.7, 9.0 Hz, $COCH_2CHOH$), 3.72 (3H, s, OCH_3), 3.50 (2H, s, $COCH_2CO_2$), 2.97 (1H, dd, J=9.0, 17.4 Hz, $COCH_2CHOH$), 2.87 (1H, dd, J=3.6, 17.4 Hz, $COCH_2$-$CHOH$); *m/z* (EI) 240 (2, M^+), 222 (27), 180 (9), 167 (21), 162 (15), 149 (32), 125 (100), 123 (65), 116 (64), 97 (77), 85 (25%). Found: C, 60.09; H, 5.63. $C_{12}H_{13}FO_4$ requires C, 60.00; H, 5.45.

4.5.12. (5*S*) Methyl δ-butyryloxy-δ-(*p*-fluorophenyl)-β-oxo-pentanoates (8f). Colorless oil; $[\alpha]_D^{20}=-31.7$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 2967, 2939, 2879, 1741, 1513, 1228, 1177, 1085, 839 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.31 (2H, m, C_6H_4), 7.03 (2H, t, J=6.9 Hz, C_6H_4), 6.17 (1H, dd, J=5.1, 8.7 Hz, $COCH_2CHOCO$), 3.72 (3H, s, OCH_3), 3.45 (2H, s, $COCH_2CO_2$), 3.22 (1H, dd, J=8.7, 16.8 Hz, $COCH_2CHOCO$), 2.97 (1H, dd, J=5.4, 17.1 Hz, $COCH_2CHOCO$), 2.27 (2H, t, J=7.2 Hz, $COCH_2CH_2CH_3$), 1.70–1.57 (2H, m, $COCH_2CH_2CH_3$), 0.90 (3H, t, J=7.2 Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 292 (3, M^+-H_2O), 239 (69), 222 (16), 207 (100), 162 (14), 149 (36), 123 (90), 122 (38), 101 (41), 71 (83%). Found: C, 62.05; H, 6.30. $C_{16}H_{19}O_5F$ requires C, 61.93; H, 6.17.

4.5.13. (5*R*) Methyl δ-hydroxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7g). Colorless oil; $[\alpha]_D^{20}=+79.3$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3524, 2982, 2951, 1737, 1695, 1442, 1336, 1087, 1006, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (1H, d, J=8.1 Hz, C_6H_3), 7.36–7.27 (2H, m, C_6H_3), 5.49 (1H, dd, J=2.4, 9.6 Hz, $COCH_2CHOH$), 3.75 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2CO_2$), 3.06 (1H, dd, J=2.7, 17.7 Hz, $COCH_2CHOH$), 2.77 (1H, dd, J=9.9, 17.7 Hz, $COCH_2CHOH$); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 202.9, 167.7, 139.1, 134.1, 132.1, 129.4, 128.5, 128.0, 66.5, 52.9, 49.9, 49.8; *m/z* (EI) 274 (15, M^+-H_2O), 272 (23, M^+-H_2O), 237 (17), 177 (53), 175 (100), 173 (39), 147 (17), 116 (96), 111 (52), 84 (29), 74 (35%). Found: C, 49.60; H, 4.36. $C_{12}H_{12}Cl_2O_4$ requires C, 49.51; H, 4.15.

4.5.14. (5*S*) Methyl δ-butyryloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (8g). Colorless oil; $[\alpha]_D^{20}=-15.2$ (*c* 1.6, $CHCl_3$). ν_{max} (liquid film) 3095, 2967, 2878, 1745, 1592, 1774, 1247, 1172, 1103, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.24 (3H, m, C_6H_3), 6.45 (1H, dd, J=3.9, 8.4 Hz, $COCH_2CHOCO$), 3.74 (3H, s, OCH_3), 3.51 (2H, s, $COCH_2CO_2$), 3.18–3.03 (2H, m, $COCH_2CHOCO$), 2.32 (2H, t, J=7.5 Hz, $COCH_2CH_2CH_3$), 1.69–1.60 (2H, m, $COCH_2CH_2CH_3$), 0.92 (3H, t, J=7.2 Hz, $COCH_2CH_2$-CH_3); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 198.6, 173.4, 172.5, 136.4, 134.8, 132.9, 130.0, 128.3, 127.9, 68.1, 52.9, 51.7, 49.5, 47.7, 36.4, 18.7, 14.0; *m/z* (EI) 325 (3, M^+-Cl), 291 (15), 289 (23), 257 (32), 237 (29), 215 (9), 199 (12), 173 (46), 101 (39), 71 (100), 43 (55%). Found: C, 53.38; H, 5.07. $C_{16}H_{18}Cl_2O_5$ requires C, 53.20; H, 5.02.

4.5.15. (5*R*) Methyl δ-hydroxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (7h).[11] Colorless oil; $[\alpha]_D^{20}=+49.8$ (*c* 1.0, $CHCl_3$). ν_{max}(liquid film) 3535, 2959, 2893, 1735, 1707, 1514, 1347, 1190, 100, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (2H, d, $J=9.0$ Hz, C_6H_4), 7.55 (2H, d, $J=8.7$ Hz, C_6H_4), 5.32 (1H, t, $J=6.0$ Hz, $COCH_2CHOH$), 3.75 (3H, s, OCH_3), 3.54 (2H, s, $COCH_2CO_2$), 2.99 (2H, d, $J=6.0$ Hz, $COCH_2CHOH$); *m/z* (EI) 250 (13, M^+-OH), 235 (44), 218 (21), 207 (14), 194 (14), 176 (27), 165 (20), 152 (75), 151 (90), 116 (100), 101 (32), 74 (64%).

4.5.16. (5*S*) Methyl δ-butyryloxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (8h). Colorless oil; $[\alpha]_D^{20}=-27.8$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2968, 2878, 1744, 1524, 1349, 1172, 1087, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.20 (2H, d, $J=6.9$ Hz, C_6H_4), 7.54 (2H, d, $J=6.6$ Hz, C_6H_4), 6.26 (1H, dd, $J=5.1$, 8.1 Hz, $COCH_2CHOCO$), 3.73 (3H, s, OCH_3), 3.48 (2H, s, $COCH_2CO_2$), 3.27 (1H, dd, $J=8.1$, 17.4 Hz, $COCH_2CHOCO$), 3.03 (1H, dd, $J=5.1$, 17.4 Hz, $COCH_2CHOCO$), 2.32 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.78–1.58 (2H, m, $COCH_2CH_2CH_3$), 0.91 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 319 (2, M^+-H_2O), 266 (29), 250 (29), 234 (53), 218 (63), 176 (55), 150 (43), 101 (40), 101 (16), 71 (100), 43 (56%). Found: C, 56.88; H, 5.84; N, 3.92. $C_{16}H_{19}NO_7$ requires C, 56.97; H, 5.68; N, 4.15.

4.5.17. (5*R*) Ethyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7i).[35] Colorless oil; $[\alpha]_D^{20}=+50.8$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3489, 3033, 2984, 2908, 1741, 1715, 1321, 1193, 1030, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 5.17 (1H, dd, $J=3.6$, 5.7 Hz, $COCH_2CHOH$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 2.99 (1H, dd, $J=9.0$, 17.1 Hz, $COCH_2CHOH$), 2.88 (1H, dd, $J=3.6$, 17.1 Hz, $COCH_2CHOH$), 1.26 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 236 (4, M^+), 218 (37), 189 (8), 162 (17), 144 (30), 131 (54), 130 (75), 107 (99), 105 (100), 84 (44), 79 (99), 77 (83%).

4.5.18. (5*S*) Ethyl δ-butyryloxy-δ-phenyl-β-oxo-pentanoates (8i). Colorless oil; $[\alpha]_D^{20}=-35.8$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3066, 2969, 2877, 1741, 1369, 1252, 1175, 1091, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.26 (5H, m, C_6H_5), 6.21 (1H, dd, $J=4.5$, 8.7 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.44 (2H, s, $COCH_2CO_2$), 3.23 (1H, dd, $J=9.0$, 17.1 Hz, $COCH_2CHOCO$), 2.98 (1H, dd, $J=4.5$, 17.1 Hz, $COCH_2CHOCO$), 2.28 (2H, t, $J=8.1$ Hz, $COCH_2CH_2CH_3$), 1.71–1.58 (2H, m, $COCH_2CH_2CH_3$), 1.27 (3H, t, $J=7.5$ Hz, OCH_2CH_3), 0.89 (3H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 306 (5, M^+), 251 (27), 234 (15), 219 (25), 207 (9), 161 (52), 137 (67), 135 (100), 101 (16), 71 (36%). Found: C, 66.34; H, 7.21. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24.

4.5.19. (5*R*) Ethyl δ-hydroxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (7j). Colorless oil; $[\alpha]_D^{20}=+47.9$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 3491, 2984, 1743, 1714, 1320, 1033, 821 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24 (2H, d, $J=8.1$ Hz, C_6H_4), 7.15 (2H, d, $J=8.4$ Hz, C_6H_4), 5.24 (1H, dd, $J=3.0$, 9.0 Hz, $COCH_2CHOH$), 4.18 (2H, q, $J=6.6$ Hz, OCH_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 2.99 (1H, dd, $J=9.0$, 17.1 Hz, $COCH_2CHOH$), 2.87 (1H, dd, $J=3.3$, 17.1 Hz, $COCH_2CHOH$), 2.33 (3H, s, $ArCH_3$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 250 (5, M^+), 232 (36), 163 (20), 145 (33), 130 (46), 121 (100), 119 (58), 93 (59), 91 (55), 77 (29%). Found: C, 67.04; H, 7.36. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25.

4.5.20. (5*S*) Ethyl δ-butyryloxy-δ-(*p*-methylphenyl)-β-oxo-pentanoates (8j). Colorless oil; $[\alpha]_D^{20}=-38.8$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2969, 2937, 2877, 1740, 1319, 1251, 1176, 1087, 817 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25 (2H, d, $J=8.1$ Hz, C_6H_4), 7.15 (2H, d, $J=7.8$ Hz, C_6H_4), 6.17 (1H, dd, $J=4.8$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.43 (2H, s, $COCH_2CO_2$), 3.22 (1H, dd, $J=8.4$, 16.8 Hz, $COCH_2CHOCO$), 2.96 (1H, dd, $J=4.8$, 16.8 Hz, $COCH_2CHOCO$), 2.33 (3H, s, $ArCH_3$), 2.27 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.70–1.56 (2H, m, $COCH_2CH_2CH_3$), 1.26 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.90 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 302 (4, M^+-H_2O), 249 (34), 232 (9), 203 (50), 159 (9), 145 (25), 119 (100), 91 (16), 71 (53), 43 (39%). Found: C, 67.30; H, 7.76. $C_{18}H_{24}O_5$ requires C, 67.48; H, 7.55.

4.5.21. (5*R*) Ethyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7k).[36] Colorless oil; $[\alpha]_D^{20}=+42.9$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3502, 2983, 2839, 1741, 1515, 1249, 1033, 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28 (2H, d, $J=6.9$ Hz, C_6H_4), 6.88 (2H, d, $J=6.6$ Hz, C_6H_4), 5.13 (1H, dd, $J=3.6$, 9.0 Hz, $COCH_2CHOH$), 4.19 (2H, q, $J=7.5$ Hz, OCH_2CH_3), 3.81 (3H, s, OCH_3), 3.48 (2H, s, $COCH_2CO_2$), 3.00 (1H, dd, $J=9.0$, 17.4 Hz, $COCH_2CHOH$), 2.88 (1H, dd, $J=3.6$, 17.4 Hz, $COCH_2CHOH$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 266 (2, M^+), 248 (7), 179 (4), 161 (10), 137 (100), 135 (22), 109 (19), 94 (10), 77 (13%).

4.5.22. (5*S*) Ethyl δ-butyryloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (8k). Colorless oil; $[\alpha]_D^{20}=-47.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2968, 2938, 2877, 2840, 1739, 1614, 1516, 1251, 1175, 1034, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29 (2H, d, $J=6.6$ Hz, C_6H_4), 6.86 (2H, d, $J=6.6$ Hz, C_6H_4), 6.16 (1H, dd, $J=5.1$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 3.43 (2H, s, $COCH_2CO_2$), 3.23 (1H, dd, $J=8.4$, 16.8 Hz, $COCH_2CHOCO$), 2.96 (1H, dd, $J=4.8$, 16.8 Hz, $COCH_2CHOCO$), 2.50 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.65–1.56 (2H, m, $COCH_2CH_2CH_3$), 1.28 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.89 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); *m/z* (EI) 336 (3, M^+), 265 (32), 248 (15), 219 (39), 207 (10), 161 (43), 137 (57), 135 (100), 71 (79), 43 (24%). Found: C, 64.18; H, 7.28. $C_{18}H_{24}O_6$ requires C, 64.27; H, 7.19.

4.5.23. (5*R*) Ethyl δ-hydroxy-δ-furan-2-yl-β-oxo-pentanoates (7l). Colorless oil; $[\alpha]_D^{20}=+32.2$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3484, 2985, 1741, 1716, 1370, 1321, 1151, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.36 (1H, m, C_4H_3O), 6.35–6.28 (2H, m, C_4H_3O), 5.21 (1H, dd, $J=3.6$, 8.4 Hz, $COCH_2CHOH$), 4.21 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.51 (2H, s, $COCH_2CO_2$), 3.18 (1H, dd, $J=8.7$, 17.7 Hz, $COCH_2CHOH$), 3.05 (1H, dd, $J=3.6$, 17.7 Hz, $COCH_2CHOH$), 1.29 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m/z* (EI) 226 (22, M^+), 180 (24), 152 (140), 139 (21), 130 (24), 121 (34), 110 (41), 97 (100), 95 (26), 84 (16%). Found: C, 58.20; H, 6.39. $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.24.

4.5.24. (5*S*) Ethyl δ-butyryloxy-δ-furan-2-yl-β-oxo-pentanoates (8l). Colorless oil; $[\alpha]_D^{20}=-94.5$ (*c* 1.3, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2878, 1743, 1251, 1174, 1093, 1015, 748 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.28 (1H, m, C_4H_3O), 6.38–6.28 (3H, m, C_4H_3O, $COCH_2CHOCO$), 4.20 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 3.33 (1H, dd, $J=8.1$, 17.1 Hz, $COCH_2CHOCO$), 3.16 (1H, dd, $J=4.8$, 17.1 Hz, $COCH_2CHOCO$), 2.25 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.68–1.58 (2H, m, $COCH_2CH_2CH_3$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3), 0.90 (3H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 296 (1, M^+), 225 (48), 219 (7), 203 (50), 179 (100), 137 (40), 121 (24), 95 (19), 71 (34), 43 (30%). Found: C, 60.82; H, 6.95. $C_{15}H_{20}O_6$ requires C, 60.80; H, 6.80.

4.5.25. (5*R*) Ethyl δ-butyryloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7m). Colorless oil; $[\alpha]_D^{20}=+75.3$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3320, 2979, 2938, 1747, 1712, 1473, 1407, 1135, 1030, 821 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, d, $J=9.0$ Hz, C_6H_3), 7.57–7.28 (2H, m, C_6H_3), 5.50 (1H, dd, $J=2.1$, 9.3 Hz, $COCH_2CHOH$), 4.22 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.52 (2H, s, $COCH_2CO_2$), 3.42 (1H, d, $J=5.2$ Hz, $COCH_2CHOH$), 3.08 (1H, d, $J=16.2$ Hz, $COCH_2CHOH$), 1.30 (3H, t, $J=7.8$ Hz, OCH_2CH_3); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 203.0, 167.2, 139.1, 134.1, 132.1, 129.4, 128.6, 127.9, 66.5, 62.1, 50.1, 49.9, 14.5; *m*/*z* (EI) 288 (15, M^+-H_2O), 286 (22, M^+-H_2O), 251 (16), 212 (17), 199 (19), 175 (100), 147 (15), 130 (89), 111 (50), 88 (35), 75 (20%). Found: C, 51.26; H, 4.59; $C_{13}H_{14}Cl_2O_4$ requires C, 51.17; H, 4.62.

4.5.26. (5*S*) Ethyl δ-butyryloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (8m). Colorless oil; $[\alpha]_D^{20}=-16.8$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 2970, 2937, 2878, 1745, 1475, 1369, 1244, 1173, 824 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.23 (3H, m, C_6H_3), 6.45 (1H, dd, $J=5.2$, 8.4 Hz, $COCH_2CHOCO$), 4.20 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.48 (2H, s, $COCH_2CO_2$), 3.09–2.98 (2H, m, $COCH_2CHOCO$), 2.32 (2H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$), 1.69–1.60 (2H, m, $COCH_2CH_2CH_3$), 1.30 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.93 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); $\delta_{13}C$(75.5 MHz, $CDCl_3$) 198.75, 172.45, 167.10, 136.45, 134.76, 132.93, 129.99, 128.31, 127.92, 68.12, 61.95, 49.78, 47.63, 36.46, 18.72, 14.54, 13.98; *m*/*z* (EI) 358 (1, M^+-H_2O), 356 (3, M^+-H_2O), 305 (19), 303 (29), 259 (34), 257 (51), 251 (37), 215 (16), 199 (17), 175 (36), 71 (100), 43 (56%). Found: C, 54.56; H, 5.39; $C_{17}H_{20}Cl_2O_5$ requires C, 54.41; H, 5.37.

4.5.27. (5*R*) Ethyl δ-hydroxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (7n). Colorless oil; $[\alpha]_D^{20}=+37.8$ (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3364, 3086, 2981, 1741, 1517, 1349, 1136, 1023, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (2H, d, $J=8.7$ Hz, C_6H_4), 7.56 (2H, d, $J=8.7$ Hz, C_6H_4), 5.32 (1H, dd, $J=3.0$, 9.6 Hz, $COCH_2CHOH$), 4.22 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 3.52 (2H, s, $COCH_2CO_2$), 2.99 (2H, d, $J=6.3$ Hz, $COCH_2CHOH$), 1.28 (3H, t, $J=6.9$ Hz, OCH_2CH_3); *m*/*z* (EI) 263 (3, M^+-H_2O), 235 (66), 221 (33), 192 (13), 176 (32), 165 (24), 152 (78), 151 (93), 150 (100), 130 (91), 77 (42%). Found: C, 55.52; H, 5.39; N, 4.89. $C_{13}H_{15}NO_6$ requires C, 55.51; H, 5.38; N, 4. 98.

4.5.28. (5*S*) Ethyl δ-butyryloxy-δ-(*p*-nitrophenyl)-β-oxo-pentanoates (8n). Colorless oil; $[\alpha]_D^{20}=-30.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2970, 2939, 2878, 1743, 1524, 1349, 1172, 856 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (2H, d, $J=8.1$ Hz, C_6H_4), 7.53 (2H, d, $J=8.7$ Hz, C_6H_4), 6.26 (1H, dd, $J=5.1$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 3.45 (2H, s, $COCH_2CO_2$), 3.26 (1H, dd, $J=8.4$, 17.7 Hz, $COCH_2CHOCO$), 3.00 (1H, dd, $J=5.4$, 17.7 Hz, $COCH_2CHOCO$), 2.31 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.69–1.59 (2H, m, $COCH_2CH_2CH_3$), 1.25 (3H, t, $J=7.2$ Hz, OCH_2CH_3), 0.90 (3H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$); *m*/*z* (EI) 333 (3, M^+-H_2O), 280 (26), 264 (25), 234 (56), 218 (64), 190 (23), 176 (59), 150 (40), 134 (25), 71 (100), 43 (75%). Found: C, 58.34; H, 5.82; N, 4.11. $C_{17}H_{21}NO_7$ requires C, 58.11; H, 6.02; N, 3.99.

4.6. General procedure of CRL-catalyzed enantioselective alcoholysis of δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (13a,c,g,i,k,m) and chemical hydrolysis of chiral δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (14a,c,g,i,k,m)

Substrates **13a**,**c**,**g**,**i**,**k**,**m** (0.5 mmol), butyl alcohol (23 mg, 0.31 mmol) and CRL (30 mg) were added anhydrous benzene (3 mL). The mixture was stirred 12 h at 30 °C, and filtered off the CRL that could be reused and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **7a**–**m** and unreacted esters **14a**,**c**,**g**,**i**,**k**,**m**. The yields are listed in Table 3.

Chiral δ-chloroacetyloxy-δ-aryl-β-oxo-pentanoates (**14a**,**c**,**g**,**i**,**k**,**m**) (0.1 mmol), methyl alcohol (3 mL) and ammonium hydroxide (5 drops) were stirred at 0 °C for 2 h, then ethyl acetate (5 mL) and brine (3 mL) were added, and water phase was washed with ethyl acetate (5 mL) again. The combined organic phase was dried and solvent was removed in vacuum, and the residue was subjected to flash chromatography to afford optical active **15a**,**c**,**g**,**i**,**k**,**m**. The yields are listed in Table 3.

4.6.1. (5*R*) Methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7a).[33] Colorless oil; $[\alpha]_D^{20}=+56.7$ (*c* 1.0, $CHCl_3$).

4.6.2. (5*S*) Methyl δ-chloroacetyloxy-δ-phenyl-β-oxo-pentanoates (14a). Colorless oil; $[\alpha]_D^{20}=-38.1$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3036, 2957, 1749, 1722, 1322, 1170, 993, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.26 (5H, m, C_6H_5), 6.27 (1H, dd, $J=4.5$, 8.4 Hz, $COCH_2CHOCO$), 4.06 (2H, s, $ClCH_2CO$), 3.72 (3H, s, OCH_3), 3.53 (2H, s, $COCH_2CO_2$), 3.31 (1H, dd, $J=9.0$, 17.4 Hz, $COCH_2CHOCO$), 3.02 (1H, dd, $J=4.5$, 17.4 Hz, $COCH_2CHOCO$),; *m*/*z* (EI) 280 (13, M^+-H_2O), 221 (39), 204 (40), 189 (50), 144 (28), 131 (100), 105 (98), 101 (32), 77 (59), 59 (22%). Found: C, 56.55; H, 5.32. $C_{14}H_{15}ClO_5$ requires C, 56.29; H, 5.06.

4.6.3. (5*S*) Methyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (15a).[33] Colorless oil; $[\alpha]_D^{20}=-54.3$ (*c* 1.2, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.4. (5*R*) Methyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7c).[11a] Colorless oil; $[\alpha]_D^{20}=+51.9$ (*c* 1.0, $CHCl_3$).

4.6.5. (5*S*) Methyl δ-chloroacetyloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (14c). Colorless oil; $[\alpha]_D^{20}=-49.7$ (*c* 2.0, $CHCl_3$). ν_{max} (liquid film) 3007, 2958, 2841, 1749, 1722, 1517, 1252, 1175, 1031, 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32 (2H, d, $J=9.3$ Hz, C_6H_4), 6.88 (2H, d, $J=9.3$ Hz, C_6H_4), 6.23 (1H, dd, $J=4.8$, 8.7 Hz, $COCH_2CHOCO$), 4.03 (2H, s, $ClCH_2CO$), 3.80 (3H, s, $ArOCH_3$), 3.72 (3H, s, CO_2CH_3), 3.47 (2H, s, $COCH_2CO_2$), 3.31 (1H, dd, $J=8.7$, 17.4 Hz, $COCH_2CHOCO$), 3.01 (1H, dd, $J=4.5$, 17.4 Hz, $COCH_2CHOCO$); *m*/*z* (EI) 328 (3, M^+), 234 (22), 175 (18), 161 (100), 137 (61), 135 (46), 101 (15), 77 (20), 59 (12%). Found: C, 55.02; H, 5.51. $C_{15}H_{17}ClO_6$ requires C, 54.80; H, 5.21.

4.6.6. (5*S*) Methyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (15c).[11a] Colorless oil; $[\alpha]_D^{20}=-50.5$ (*c* 2.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.7. (5*R*) Methyl δ-hydroxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7g). Colorless oil; $[\alpha]_D^{20}=+73.3$ (*c* 2.4, $CHCl_3$).

4.6.8. (5*S*) Methyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (14g). Colorless oil; $[\alpha]_D^{20}=-13.7$ (*c* 1.9, $CHCl_3$). ν_{max} (liquid film) 3007, 2972, 2858, 1753, 1712, 1411, 1327, 1317, 1197, 1001, 865, 798 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.26 (3H, m, C_6H_3), 6.53 (1H, dd, $J=3.9$, 9.0 Hz, $COCH_2CHOCO$), 4.11 (2H, s, $ClCH_2CO$), 3.75 (3H, s, OCH_3), 3.51 (2H, s, $COCH_2CO_2$), 3.19 (1H, dd, $J=9.0$, 18.0 Hz, $COCH_2CHOCO$), 3.07 (1H, dd, $J=3.6$, 17.7 Hz, $COCH_2CHOCO$); $\delta_{13}C$ (75.5 MHz, $CDCl_3$) 198.4, 167.4, 166.2, 135.3, 135.3, 133.0, 130.1, 128.4, 128.1, 69.9, 52.9, 49.5, 47.3, 41.0; *m*/*z* (EI) 348 (9, M^+-H_2O), 257 (19), 237 (100), 199 (37), 175 (77), 137 (21), 101 (71), 77 (51), 59 (40%). Found: C, 46.02; H, 3.80. $C_{14}H_{13}Cl_3O_5$ requires C, 45.74; H, 3.56.

4.6.9. (5*S*) Methyl δ-hydroxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (15g). Colorless oil; $[\alpha]_D^{20}=-73.0$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.10. (5*R*) Ethyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (7i).[35] Colorless oil; $[\alpha]_D^{20}=+47.6$ (*c* 1.3, $CHCl_3$).

4.6.11. (5*S*) Ethyl δ-chloroacetyloxy-δ-phenyl-β-oxo-pentanoates (14i). Colorless oil; $[\alpha]_D^{20}=-40.6$ (*c* 2.0, $CHCl_3$). ν_{max} (liquid film) 3067, 3036, 2985, 2910, 1745, 1721, 1411, 1370, 1171, 1030, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.27 (5H, m, C_6H_5), 6.28 (1H, dd, $J=4.5$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.06 (2H, s, $ClCH_2CO$), 3.43 (2H, s, $COCH_2CO_2$), 3.32 (1H, dd, $J=9.0$, 17.4 Hz, $COCH_2CHOCO$), 3.03 (1H, dd, $J=4.2$, 17.4 Hz, $COCH_2CHOCO$), 1.28 (3H, t, $J=7.2$ Hz, OCH_2CH_3); *m*/*z* (EI) 294 (9, M^+-H_2O), 259 (12), 218 (21), 189 (69), 145 (19), 131 (78), 107 (59), 105 (100), 77 (60), 51 (15%). Found: C, 57.50; H, 5.64. $C_{15}H_{17}ClO_5$ requires C, 57.61; H, 5.48.

4.6.12. (5*S*) Ethyl δ-hydroxy-δ-phenyl-β-oxo-pentanoates (15i).[35] Colorless oil; $[\alpha]_D^{20}=-46.6$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.13. (5*R*) Ethyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (7k).[36] Colorless oil; $[\alpha]_D^{20}=+40.5$ (*c* 2.0, $CHCl_3$).

4.6.14. (5*S*) Ethyl δ-chloroacetyloxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (14k). Colorless oil; $[\alpha]_D^{20}=-62.7$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2940, 2911, 2841, 1737, 1613, 1516, 1250, 1178, 1031, 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, $J=6.9$ Hz, C_6H_4), 6.88 (2H, d, $J=7.2$ Hz, C_6H_4), 6.23 (1H, dd, $J=4.5$, 8.4 Hz, $COCH_2CHOCO$), 4.18 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.03 (2H, s, $ClCH_2CO$), 3.80 (3H, s, OCH_3), 3.47 (2H, s, $COCH_2CO_2$), 3.32 (1H, dd, $J=9.0$, 17.7 Hz, $COCH_2CHOCO$), 3.02 (1H, dd, $J=8.1$, 17.1 Hz, $COCH_2CHOCO$), 1.28 (3H, t, $J=7.5$ Hz, OCH_2CH_3); *m*/*z* (EI) 342 (2, M^+), 265 (4), 248 (14), 219 (20), 175 (16), 161 (100), 137 (96), 135 (92), 119 (12), 77 (29%). Found: C, 55.97; H, 5.60. $C_{16}H_{19}ClO_6$ requires C, 56.06; H, 5.59.

4.6.15. (5*S*) Ethyl δ-hydroxy-δ-(*p*-methoxylphenyl)-β-oxo-pentanoates (15k).[36] Colorless oil; $[\alpha]_D^{20}=-38.7$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.6.16. (5*R*) Ethyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (7m). Colorless oil; $[\alpha]_D^{20}=+65.9$ (*c* 1.0, $CHCl_3$).

4.6.17. (5*S*) Ethyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (14m). Colorless oil; $[\alpha]_D^{20}=-6.8$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 31.05, 2980, 2939, 1763, 1741, 1710, 1413, 1314, 1186, 1089, 1029, 825 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.25 (3H, m, C_6H_3), 6.53 (1H, dd, $J=3.6$, 9.0 Hz, $COCH_2CHOCO$), 4.20 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 4.08 (2H, s, $ClCH_2CO$), 3.49 (2H, s, $COCH_2CO_2$), 3.19 (1H, dd, $J=9.0$, 17.7 Hz, $COCH_2CHOCO$), 3.02 (1H, dd, $J=3.9$, 17.7 Hz, $COCH_2CHOCO$), 1.30 (3H, t, $J=6.9$ Hz, $COCH_2CH_2CH_3$); $\delta_{13}C$ (75.5 MHz, $CDCl_3$) 198.4, 167.0, 166.2, 135.3, 135.3, 133.0, 130.2, 128.4, 128.1, 67.0, 62.1, 49.8, 47.3, 41.0, 14.5; *m*/*z* (EI) 362 (10, M^+-H_2O), 259 (19), 251 (100), 215 (13), 199 (40), 175 (72), 137 (19), 115 (30), 102 (15), 77 (55), 69 (18%). Found: C, 47.41; H, 4.19; $C_{15}H_{15}Cl_3O_5$ requires C, 47.21; H, 3.96.

4.6.18. (5*S*) Ethyl δ-chloroacetyloxy-δ-(*o*,*p*-dichlorophenyl)-β-oxo-pentanoates (15m). Colorless oil; $[\alpha]_D^{20}=-65.4$ (*c* 1.0, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.7. CRL-catalyzed enantioselective hydrolysis ethyl 3-butyryloxy-4,4,4-trifluorobutyrate (10)

4.7.1. Preparation of ethyl 3-hydroxy-4,4,4-trifluorobutyrate (9). Sodium (3.45 g, 0.15 mol) was dissolved in absolute ethanol (15 mL), and to this mixture was added CH_3CO_2Et (8.8 g, 0.10 mol) and CF_3CO_2Et (14.2 g, 0.10 mol). The mixture was heated under refluxed for 48 h, then cooled to rt and hydrolyzed with minimum of 10 N H_2SO_4, yielding a mixture of ester and its hydrate, bp 100–130 °C/760 mm Hg. Reduction of this mixture with $NaBH_4$ gave ethyl 3-hydroxy-4,4,4-trifluorobutyrate 15.4 g (83%).

4.7.2. Preparation of diethyl ethyl 3-butyryloxy-4,4,4-trifluorobutyrate (10). In a 25 mL bottle were added substrate **9** (0.186 g, 1 mmol), *n*-butyric acid (0.11 mL, 1.2 mmol), DCC (248 mg, 1.2 mmol), DMAP (5 mg) and CH_2Cl_2 (10 mL). After the starting material was almost consumed at rt (about 1–2 h), diethyl ether (10 mL) was added and the precipitate was filtered off. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to give ethyl 3-butyryloxy-4,4,4-trifluorobutyrate 2.43 g (95%).

4.7.3. CRL-catalyzed enantioselective hydrolysis ethyl 3-butyryloxy-4,4,4-trifluorobutyrate (10). Substrate **10** (100 mg) and CRL (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 24 h at 30 °C, and filtered off the CRL that could be reused and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford the hydrolyzed alcohols **11** (41%) and unreacted esters **12** (45%).

4.7.3.1. (3*R*) Ethyl 3-hydroxy-4,4,4-trifluorobutanozte (11).[19] Colorless oil; $[\alpha]_D^{20}=+20.8$ (*c* 0.7, $CHCl_3$). ν_{max} (liquid film) 3463, 2990, 2945, 1725, 1305, 1171, 1021, 880, 662 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.48–4.42 (1H, m, CF_3CHCH_2), 4.22 (2H,q, $J=7.5$ Hz, OCH_2CH_3), 3.60 (1H, s, O*H*), 2.78–2.63 (2H, m, CF_3CHCH_2), 1.30 (3H, t, $J=7.2$ Hz, OCH_2CH_3); $\delta_{19}F$ (120 MHz, $CDCl_3$) −80.21, −80.23; *m/z* (EI) 186 (2, M^+), 159 (24), 141 (100), 117 (27), 113 (16), 99 (10), 77 (8), 71 (28), 69 (14), 43 (51%).

4.7.3.2. (3*S*) Ethyl 3-butyryloxy-4,4,4-trifluorobutanozte (12). Colorless oil; $[\alpha]_D^{20}=+6.3$ (*c* 0.8, $CHCl_3$). ν_{max} (liquid film) 2976, 2943, 1882. 1768, 1747, 1183, 1139, 1049, 1027, 659 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.84–5.77 (1H, m, CF_3CHCH_2), 4.18 (2H, q, $J=6.9$ Hz, OCH_2CH_3), 2.84–2.71 (2H, m, CF_3CHCH_2), 2.37 (2H, t, $J=7.2$ Hz, $COCH_2CH_2CH_3$), 1.74–1.62 (2H, m, $COCH_2CH_2CH_3$), 1.26 (3H, t, $J=6.6$ Hz, OCH_2CH_3), 0.94 (3H, t, $J=7.5$ Hz, $COCH_2CH_2CH_3$); $\delta_{19}F$ (120 MHz, $CDCl_3$) −78.0, −78.0; *m/z* (EI) 256 (1, M^+), 228 (14), 211 (6), 187 (4), 141 (8), 123 (11), 71 (100), 70 (16), 43 (35%); HRMS (EI): M^+ found: 256.0918. $C_{10}H_{15}O_4F_3$ requires 256.0922.

4.8. Preparation of chiral tomoxetine hydrochloride (I) and fluoxetine hydrochloride (II)

4.8.1. Preparation of (1*R*) 1-phenylpropane-1,3-diol and (1*S*) 1-phenylpropane-1,3-diol. In a 50 mL flask were added (3*R*) ethyl β-hydroxy-β-phenyl propionate (**4c**) (0.39 g, 2 mmol) (or (3*S*) ethyl β-butyryloxy-β-phenyl propionate (**5c**) (0.53 g, 2 mmol)), THF (15 mL) and $LiAlH_4$ (0.11 g, 3 mmol) (or 0.18 g, 5 mmol). After the mixture was stirred at room temperature for 1 h, 5 mL aqueous HCl was added and THF was removed under reduced pressure. Then the solution was extracted with EtOAc (3×5 mL), the combine extracts were dried and evaporated in vacuum. The residue was subjected to flash chromatography to obtain (1*R*) 1-phenylpropane-1,3-diol 0.28 g, yield: 92%. (or (1*S*) 1-phenylpropane-1,3-diol 0.29 g, yield: 95%).

(1R) 1-Phenylpropane-1,3-diol.[9g,37] Colorless oil; $[\alpha]_D^{20}=+57.4$ (*c* 1.65, $CHCl_3$). ν_{max} (liquid film) 3349, 3032, 2974, 1494, 1454, 1050, 726, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.21 (5H, m, C_6H_5), 4.84 (1H, dd, $J=4.2$, 8.4 Hz, $PhCHCH_2$), 4.00 (1H, s, O*H*), 3.76–3.66 (2H, m, $CHCH_2CH_2OH$), 3.58 (1H, s, O*H*), 1.94–1.79 (2H, m, $PhCHCH_2CH_2$); *m/z* (EI) 152 (M^+, 19), 133 (11), 107 (100), 105 (32), 79 (72), 77 (49), 51 (13), 43 (7%).

(1S) 1-Phenylpropane-1,3-diol. Colorless oil; $[\alpha]_D^{20}=-57.4$ (*c* 1.20, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.2. Preparation of (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate and (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate. In a 25 mL flask were added (1*R*) 1-phenylpropane-1,3-diol (or (1*S*) 1-phenylpropane-1,3-diol) (0.30 g, 2 mmol), Et_3N (0.13 g, 3.6 mmol) and anhydrous Et_2O (10 mL), and at ice-salt bath the mixture of methanesulfonyl chloride (0.26 g, 2.3 mmol) and 5 mL Et_2O were added. After the mixture was stirred at this low temperature for 1 h, then at ice-water bath for another 2 h. The reaction was terminated through adding 10 mL saturated NH_4Cl. The water phase was extracted with EtOAc (3×5 mL), the combine extracts were dried and evaporated in vacuum. The residue was subjected to flash chromatography to obtain (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate (or (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate) 0.39 g, yield: 85%.

(3R) 3-Phenyl-3-hydroxypropyl methanesulfonate.[9g,37] Colorless oil; $[\alpha]_D^{20}=+21.5$ (*c* 2.00, $CHCl_3$). ν_{max} (liquid film) 3532, 3031, 2939, 1352, 1174, 975, 927, 703 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5H, m, C_6H_5), 4.84 (1H, dt, $J=2.4$, 6.6 Hz, $PhCHCH_2$), 4.48–4.40 (1H, m, $CHCH_2CH_2O$), 4.28–4.21 (1H, m, $CHCH_2CH_2O$), 2.97 (3H, s, $CH_2OSO_2CH_3$), 2.62 (1H, s O*H*), 2.10 (2H, dd, $J=6.6$, 12.3 Hz, $PhCHCH_2CH_2$); *m/z* (EI) 230 (M^+, 2), 133 (47), 107 (100), 105 (66), 79 (71), 77 (43), 51 (9), 43 (3%).

(3S) 3-Phenyl-3-hydroxypropyl methanesulfonate. Colorless oil; $[\alpha]_D^{20}=-19.3$ (*c* 1.65, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.3. Preparation of (1*R*) 3-(methylamino)-1-phenyl-1-propanol and (1*S*) 3-(methylamino)-1-phenyl-1-propanol. A solution of (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate (or (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate) (0.23 g, 1 mmol) and methylamine (6 mL, 25% solution in water) in THF (6 mL) was heated at 60–65 °C in a pressure tube for 4 h. After cooling, the solvent was evaporated in vacuum. And the residue was dissolved in 8 mL aqueous HCl, then was extracted with EtOAc (1× 10 mL). The water phase was neutralized with Na_2CO_3 to alkaline (pH>10), and extracted with ether (3×10 mL). The combined extracts was dried and evaporated under reduced pressure to get (1*R*) 3-(methylamino)-1-phenyl-1-propanol (or (1*S*) 3-(methylamino)-1-phenyl-1-propanol) 0.133 g, yield: 80% (0.136 g, yield: 82%).

(1R) 3-(Methylamino)-1-phenyl-1-propanol.[9g,37] Colorless oil; $[\alpha]_D^{20}=+29.3$ (*c* 1.05, $CHCl_3$). ν_{max} (liquid film) 3402, 3032, 2825, 1469, 1194, 1045, 774, 704 cm^{-1}; δ_H

(300 MHz, $CDCl_3$) 7.41–7.21 (5H, m, C_6H_5), 4.93 (1H, dd, $J=3.0$, 9.0 Hz, PhC*H*CH_2), 2.92–2.81 (2H, m, $CHCH_2$-CH_2NH), 2.44 (3H, d, $J=4.2$ Hz, CH_2NHCH_3), 1.90–1.72 (2H, m, $PhCHCH_2CH_2$); *m/z* (EI) 165 (M^+, 9), 133 (7), 107 (3), 104 (12), 79 (9), 77 (17), 58 (11), 51 (7), 44 (100%).

(1S) 3-(Methylamino)-1-phenyl-1-propanol. Colorless oil; $[\alpha]_D^{20}=-23.0$ (*c* 1.55, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.4. Preparation of (*R*) fluoxetine and (*S*) fluoxetine. To a solution of (1*R*) 3-(methylamino)-1-phenyl-1-propanol (or (1*S*) 3-(methylamino)-1-phenyl-1-propanol) (83 mg, 0.5 mmol) in dry DMSO (3 mL) was added 80% NaH (30 mg, 1 mmol). The mixture was reacted at 55 °C for 30 min. Then trifluoromethyl-*p*-chlorobenzene (135 mg, 0.75 mmol) in 1 mL dry DMSO was added, the mixture was stirred at 90–100 °C for 1.5 h. After cooling dilution with ether, the mixture was washed with brine, dried and concentrated under vacuum. The residue was subjected to flash chromatography to obtain (*R*) fluoxetine (or (*S*) fluoxetine) 130 mg, yield: 84% (or 130 mg, yield: 84%).

(R) Fluoxetine.[9g,35] Colorless oil; $[\alpha]_D^{20}=+1.2$ (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3314, 3034, 2948, 2800, 1616, 1518, 1330, 1252, 1112, 1069 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42 (2H, d, $J=8.4$ Hz, C_6H_4), 7.34–7.25 (5H, m, C_6H_5), 6.90 (2H, d, $J=8.7$ Hz, C_6H_4), 5.31 (1H, dd, $J=4.8$, 8.4 Hz, PhC*H*CH_2), 2.75 (2H, t, $J=6.9$ Hz, $CHCH_2CH_2NH$), 2.44 (3H, s, CH_2NHCH_3), 2.25–2.17 (1H, m, $PhCHCH_2CH_2$), 2.08–1.99 (1H, m, $PhCHCH_2CH_2$), 1.86 (1H, s, N*H*); *m/z* (EI) 309 (M^+, 18), 251 (3), 183 (4), 104 (12), 164 (5), 148 (9), 104 (14), 91 (9), 77 (7), 44 (100%). Found: C, 66.29; H, 6.02; N, 4.77. $C_{17}H_{18}F_3NO$ requires C, 66.01; H, 5.87; N, 4.53.

(S) Fluoxetine. Colorless oil; $[\alpha]_D^{20}=-1.4$ (*c* 1.70, $CHCl_3$). Found: C, 66.07; H, 5.92; N, 4.80. $C_{17}H_{18}F_3NO$ requires C, 66.01; H, 5.87; N, 4.53. All of its other spectrums were identical with its enantiomer.

4.8.5. Preparation of (*R*) fluoxetine hydrochloride ((*R*)-II) and (*S*) fluoxetine hydrochloride ((*S*)-II). The oil (*R*) fluoxetine (or (*S*) fluoxetine) (42 mg, 0.14 mmol) was dissolved in ether and acidified with HCl (gas). The solution was concentrated to give a solid (*R*) fluoxetine hydrochloride ((*R*)-**II**) (or (*S*) fluoxetine hydrochloride ((*S*)-**II**)) 46 mg, yield: 98% (or 46 mg, yield: 98%).

(R) Fluoxetine hydrochloride ((*R*)-**II**).[9g,37] White solid; mp 140–141 °C; $[\alpha]_D^{20}=-10.1$ (*c* 1.00, $CHCl_3$); $[\alpha]_D^{20}=+12.0$ (*c* 1.00, H_2O). ν_{max} (liquid film) 3016, 2962, 2793, 2733, 2455, 1616, 1518, 1331, 1243, 1164, 1109, 1070, 843, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.64 (2H, s, N*H*,*H*Cl), 7.42 (2H, d, $J=8.4$ Hz, C_6H_4), 7.39–7.24 (5H, m, C_6H_5), 6.90 (2H, d, $J=8.7$ Hz, C_6H_4), 5.46 (1H, dd, $J=4.2$, 7.8 Hz, PhC*H*CH_2), 3.23–3.04 (2H, m, $CHCH_2CH_2NH$), 2.63 (3H, s, CH_2NHCH_3), 2.56–2.38 (2H, m, $PhCHCH_2CH_2$); *m/z* (EI) 309 (M^+-HCl, 6), 252 (1), 183 (2), 162 (2), 148 (4), 104 (8), 91 (5), 77 (4), 59 (4), 44 (100%). Found: C, 59.12; H, 5.50; N, 4.32. $C_{17}H_{19}ClF_3NO$ requires C, 59.05; H, 5.54; N, 4.05.

(S) Fluoxetine hydrochloride ((*S*)-**II**). White solid; mp 140–141 °C; $[\alpha]_D^{20}=+8.5$ (*c* 1.00, $CHCl_3$); $[\alpha]_D^{20}=+9.0$ (*c* 1.00, H_2O). Found: C, 59.09; H, 5.49; N, 4.73. $C_{17}H_{19}ClF_3NO$ requires C, 59.05; H, 5.54; N, 4.05. All of its other spectrums were identical with its enantiomer.

4.8.6. Preparation of (3*S*) 3-phenyl-3-(2-methylphenoxy)-propyl methanesulfonate and (3*R*) 3-phenyl-3-(2-methyl-phenoxy)propyl methanesulfonate. To a solution of PPh_3 (0.39 g, 1.5 mmol), *o*-cresol (0.22 g, 2 mmol) and anhydrous ether (8 mL) was added DEAD (40% solution in toluene, 0.66 g, 1.5 mmol) at ice-salt bath. After reacted at this temperature for 30 min, (3*R*) 3-phenyl-3-hydroxypropyl methanesulfonate (or (3*S*) 3-phenyl-3-hydroxypropyl methanesulfonate) (0.23 g, 1 mmol) was added to this reaction mixture. The mixture was kept this temperature for another 1 h, then at ice-water bath for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography to obtain (3*S*) 3-phenyl-3-(2-methylphenoxy)propyl methanesulfonate (or (3*R*) 3-phenyl-3-(2-methylphenoxy)propyl methanesulfonate) 0.26 g, yield: 80% (or 0.25 g, 78%).

(3S) 3-Phenyl-3-(2-methylphenoxy)propyl methanesulfonate.[37] Colorless oil; $[\alpha]_D^{20}=+7.8$ (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3065, 3030, 2938, 1493, 1357, 1239, 1176, 970, 753, 702 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.25 (5H, m, C_6H_5), 7.20 (1H, d, $J=7.5$ Hz, C_6H_4), 6.96 (1H, t, $J=7.8$ Hz, C_6H_4), 6.81 (1H, t, $J=7.8$ Hz, C_6H_4), 6.60 (1H, d, $J=8.1$ Hz, C_6H_4), 5.33 (1H, dd, $J=4.5$, 8.4 Hz, PhC*H*CH_2), 4.51–4.35 (2H, m, $CHCH_2CH_2OSO_2$), 2.90 (3H, s, CH_2-OSO_2CH_3), 2.42–2.25 (2H, m, $PhCHCH_2CH_2$), 2.32 (3H, s, $ArCH_3$); *m/z* (EI) 320 (M^+, 3), 224 (4), 213 (2), 117 (100), 108 (7), 91 (7), 79 (6), 77 (6), 65 (2%).

(3R) 3-Phenyl-3-(2-methylphenoxy)propyl methanesulfonate. Colorless oil; $[\alpha]_D^{20}=-7.8$ (*c* 1.70, $CHCl_3$). All of its spectrums were identical with its enantiomer.

4.8.7. Preparation of (*S*) tomoxetine and (*R*) tomoxetine. The reaction process was identical with preparation of (1*R*) 3-(methylamino)-1-phenyl-1-propanol and (1*S*) 3-(methyl-amino)-1-phenyl-1-propanol. We obtained (*S*) tomoxetine 0.212 g, yield: 83% and (*R*) tomoxetine 0.209 g, yield: 82%.

(S) Tomoxetine.[35] Colorless oil; $[\alpha]_D^{20}=+36.8$ (*c* 0.50, $CHCl_3$). ν_{max} (liquid film) 3320, 3064, 2947, 2794, 1493, 1240, 1120, 750, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34–7.22 (5H, m, C_6H_5), 7.12 (1H, d, $J=6.9$ Hz, C_6H_4), 6.96 (1H, t, $J=8.1$ Hz, C_6H_4), 6.77 (1H, t, $J=7.2$ Hz, C_6H_4), 6.60 (1H, d, $J=8.4$ Hz, C_6H_4), 5.59 (1H, dd, $J=4.2$, 8.1 Hz, PhC*H*CH_2), 2.80 (2H, t, $J=7.2$ Hz, $CHCH_2CH_2N$), 2.43 (3H, s, CH_2NHCH_3), 2.32 (3H, s, $ArCH_3$), 2.22–2.02 (3H, m, N*H*,$PhCHCH_2CH_2$); *m/z* (EI) 255 (M^+, 17), 151 (18), 148 (32), 108 (9), 104 (11), 91 (11), 77 (14), 44 (100%). Found: C, 80.21; H, 8.09; N, 5.52. $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.49.

(R) Tomoxetine. Colorless oil; $[\alpha]_D^{20}=-35.4$ (*c* 0.55, $CHCl_3$). Found: C, 80.00; H, 8.15; N, 5.62. $C_{17}H_{21}NO$ requires C, 79.96; H, 8.29; N, 5.49. All of its other spectrums were identical with its enantiomer.

4.8.8. Preparation of (*S*) tomoxetine hydrochloride ((*S*)-I) and (*R*) tomoxetine hydrochloride ((*R*)-I). The reaction process was identical with preparation (*R*) fluoxetine hydrochloride ((*R*)-**II**) and (*S*) fluoxetine hydrochloride ((*S*)-**II**). And we obtained *S*) tomoxetine hydrochloride ((*S*)-**I**) 41 mg, yield: 99% and (*R*) tomoxetine hydrochloride ((*R*)-**I**) 41 mg, yield: 99%.

(S) Tomoxetine hydrochloride ((*S*)-**I**).[37] White solid; mp 162–163 °C; $[\alpha]_D^{20}=+40.9$ (*c* 1.18, $CHCl_3$); $[\alpha]_D^{20}=+43.1$ (*c* 1.00, MeOH); $[\alpha]_D^{20}=+42.6$ (*c* 1.18, EtOH). ν_{max} (liquid film) 3018, 2961, 2761, 2717, 1493, 1235, 1118, 1037, 767, 711 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.64 (2H, s, N*H*,*H*Cl), 7.34–7.21 (5H, m, C_6H_5), 7.10 (1H, d, $J=7.5$ Hz, C_6H_4), 6.94 (1H, t, $J=7.8$ Hz, C_6H_4), 6.77 (1H, t, $J=7.5$ Hz, C_6H_4), 6.59 (1H, d, $J=8.4$ Hz, C_6H_4), 5.37 (1H, t, $J=6.6$ Hz, PhC*H*CH_2), 3.15–3.11 (2H, t, $J=7.2$ Hz, $CHCH_2CH_2N$), 2.60 (3H, s, CH_2NHCH_3), 2.53–2.47 (2H, m, $PhCHCH_2CH_2$), 2.30 (3H, s, $ArCH_3$); *m/z* (EI) 255 (M^+-HCl, 5), 197 (1), 151 (9), 148 (16), 115 (3), 104 (7), 91 (7), 77 (8), 44 (100%). Found: C, 70.05; H, 7.85; N, 5.02. $C_{17}H_{22}ClNO$ requires C, 69.97; H, 7.60; N, 4.80.

(R) Tomoxetine hydrochloride ((*R*)-**I**). White solid; mp 161–162 °C; $[\alpha]_D^{20}=-34.9$ (*c* 1.18, $CHCl_3$); $[\alpha]_D^{20}=-39.0$ (*c* 1.00, MeOH); $[\alpha]_D^{20}=-38.4$ (*c* 1.18, EtOH). Found: C, 69.98; H, 7.75; N, 4.99. $C_{17}H_{22}ClNO$ requires C, 69.97; H, 7.60; N, 4.80. All of its other spectrums were identical with its enantiomer.

4.9. Prepraration of (*R*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (16) and (*S*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (17).[38]

In a 25 mL flask was added substrates **7a** or **7i** (**15a** or **15i**) (0.1 mmol) and 0.2 M solution of NaOH. After the mixture was stirred for 20 min, 2.0 M solution of HCl was added and the PH values <2. The solid was filtered and dried to get (*R*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (**16**) (or (*R*) 4-hydroxy-6-aryl-5,6-dihydro-2-pyones (**17**)) 19 mg, yield: 98%.

(R) 4-Hydroxy-6-aryl-5,6-dihydro-2-pyones (**16**). White solid; mp 124–125 °C; $[\alpha]_D^{20}=+96.3$ (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3038, 2899, 1720, 1292, 1012, 756, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48–7.27 (5H, m, C_6H_6), 5.72 (1H, dd, $J=3.9$, 9.6 Hz, PhC*H*OCO), 3.69 (1H, d, $J=18.9$ Hz, COC*H*=COH), 3.49 (1H, d, $J=18.9$ Hz, COCH=CO*H*), 2.93 (2H, dq, $J=4.2$, 9.9, 18.3 Hz, PhC*H*CH_2C=); *m/z* (EI) 190 (64, M^+), 144 (2), 131 (4), 105 (72), 104 (100), 103 (28), 84 (58), 78 (28), 77 (32), 51 (9%). Found: C, 69.45; H, 5.50. $C_{11}H_{10}O_3$ requires C, 69.46; H 5.30.

(S) 4-Hydroxy-6-aryl-5,6-dihydro-2-pyones (**17**). White solid; mp 124–125 °C; $[\alpha]_D^{20}=-95.3$ (*c* 1.00, $CHCl_3$). Found: C, 69.29; H, 5.55. $C_{11}H_{10}O_3$ requires C, 69.46; H 5.30. All of its other spectrums were identical with its enantiomer.

4.10. Preparation of (*R*) methyl 4-oxo-2,6-diphenyl-tetrahydropyran-3-carboxylatete (18).[39]

In 25 mL flask was added substrate **7a** (111 mg, 0.5 mmol), benzaldehyde (66 mg, 0.63 mmol), $BF_3\cdot Et_2O$ (119 mg, 0.75 mmol) and CH_2Cl_2 (4 mL). After the mixture was reacted 3 h, ethyl acetate (35 mL) was added then washed with saturated $NaHSO_3$ solution (3×10 mL) and brine (2×10 mL). The organic phase dried and solvent was removed under reduced pressure, and the residues were purified by flash chromatography to give (*R*) methyl 4-oxo-2,6-diphenyl-tetrahydropyran-3-carboxylatete (**14**) 132 mg, yield: 85%.

Colorless oil; $[\alpha]_D^{20}=+23.7$ (*c* 1.30, $CHCl_3$). ν_{max} (liquid film) 3063, 3034, 2952, 1748, 1718, 1454, 1274, 1139, 1070, 761, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) .42–7.19 (10H, m, C_6H_5), 5.05 (1H, d, $J=10.8$ Hz, PhC*H*CHCO), 4.87 (1H, dd, $J=3.3$, 10.8 Hz, PhC*H*CH_2CO), 3.69 (1H, d, $J=10.8$ Hz, COC*H*CHPh), 3.57 (3H, s, OCH_3), 2.81–2.65 (2H, m, $PhCHCH_2CO$); *m/z* (EI) 310 (7, M^+), 278 (7), 233 (14), 204 (16), 201 (16), 172 (32), 145 (15), 131 (49), 104 (100), 77 (32%). Found: C, 73.52; H, 5.89. $C_{19}H_{18}O_4$ requires C, 73.53; H, 5.85.

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