*Chinese Journal of Chemistry*, **2004**, *22*, 775—778

**Communication**

# An Improved Method for the Synthesis of Optically Active Tomoxetines and Fluoxetines

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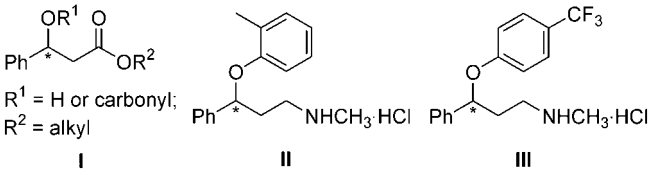
A chemoenzymatic approach was applied to the preparation of chiral 3-hydroxy-3-arylpropionates and 3-hydroxy-4,4,4-trifluorobutanoate that are potential precursors for certain chiral pharmaceuticals including chiral tomoxetines and fluoxetines.

**Keywords** 3-hydroxy-3-arylpropionate, 3-hydroxy-4,4,4-trifluorobutanoate, *Candia rugosa* lipase (*CRL*), tomoxetine, fluoxetine

Optically active 3-hydroxy-3-arylcarboxylates are synthetically important and highly functionalized chiral synthons. The 3-hydroxy-3-phenylpropionate (**I**) is of particular interest as potential precursors of optically pure tomoxetine hydrochloride (**II**) and fluoxetine hydrochloride (**III**), which are important pharmaceuticals for the treatment of psychiatric disorders (depression, anxiety, alcoholism) and metabolic problems (obesity, bulimia).[1] Meanwhile (*R*)-tomoxetine (**II**) is the first norepinephrine reuptake-inhibiting anti-depressant which does not possess strong affinity for either $\alpha$- or $\beta$-adrenergic receptors.[1a,2]




**I** **II** **III**

Consequently, the preparation of optically active 3-hydroxy-3-arylcarboxylates has attracted much interest.[3] There have been many reports concerning the asymmetric synthesis of those compounds. For example, catalytic asymmetric reduction of the corresponding $\beta$-keto carboxylates,[3d,4] aldol,[5] Reformatsky,[6] Diels-Alder,[7] organocopper conjugate addition reactions,[8] and even Pd-catalyzed kinetic resolution.[9] However, the drawbacks of these synthetic routes are significant, that include harsh reaction conditions, expensive reagents, low chemical yields and poor optical purity especially the widespread need for stoichiometric chiral reagents.[4-9]

Using the biological method is another alternative way to synthesize those chiral molecules.[3d,3f,10] Kumar's[3d] and Chenevert's[3f] groups utilized bakers' yeast to reduce $\beta$-keto carboxylates in water to obtain corresponding chiral $\beta$-hydroxy esters with low yields and poor enantiomeric excess. Boaz's[10a] and Schneider's group[10b] used lipase to hydrolyze 3-phenyl-3-hydroxycarboxylates and chloroacetate in buffer, but the results were not encouraging either. The other groups[10c-e] obtained the precursor of title compounds via lipase-catalyzed acetylation of hydroxy-compounds, such as 1-phenyl-3-buten-1-ol,[10c] 3-chloro-1-phenylpropan-1-ol[10d] and 3-hydroxy-3-phenyl-propionitrile.[10e] Though the results were better but the chemical yields were not so good. Therefore improvement of the method of synthesis of such molecules seems necessary. Our group has exploited baker's yeast-mediated enantioreduction for preparing some optically active $\gamma$-hydroxy-$\beta$-ketophosphonates and $\delta$-hydroxy-$\beta$-ketophosphonates.[11] Nevertheless we also used *Candia antartic* lipase B (*CALB*) and crude *Candia rugosa* lipase (*CRL*) to resolve hydroxyphophonates and aminophosphonates attaining corresponding chiral compounds.[12]

Chiral ethyl 3-hydroxy-4,4,4-trifluorobutyrate is necessary in an established synthetic method for the production of *L*-carbinol as a precursor of novel fluorinated pharmaceuticals, such as the anti depressant beloxatone.[13]

As an extension of our study, we herein wish to report such a simple and useful method for the chemoenzymatic preparation of both enantiomers, 3-hydroxy-3-arylpropionates (**I**) and 3-hydroxy-4,4,4-trifluorobutyrate in high optical purity and chemical yields.

A simple preparation of 3-hydroxy-3-aryl-carboxylates (**1**) was therefore as the essential requirement. An aldol reaction between acetate and arylaldehydes in the presence of LDA readily afforded the achiral compounds (**1**) (Scheme 1).

In our previous work, we successively resolved the

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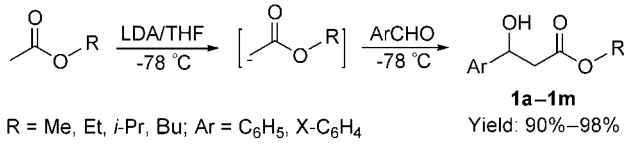
Received March 4, 2004; revised and accepted May 10, 2004.
Project supported by the National Natural Science Foundation of China (Nos. 20272075 and 20372076).

**Scheme 1**




2-hydroxy-2-arylethanephosphonates by crude *CRL* in diisopropyl ether.[12a] Because of the similarity of phosphonates and carboxylates, this strategy was successfully applied to resolve 3-hydroxy-3-arylcarboxylates.

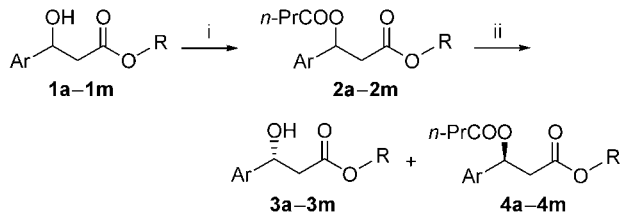
Direct butyrylation of 3-hydroxy-3-arylpropionates using DCC/butyric acid system afforded the butyryl derivatives in above 90% yields. They could be enantioselectively hydrolyzed to the corresponding (*R*)-alcohols by *CRL* in diisopropyl ether pre-equilibrated with 1.2 mol/L aqueous $MgCl_2$.

As demonstrated by our experimental data, in corresponding with the 2-hydroxy-2-arylethanephosphonates, the overall yields of the *CRL*-catalyzed reaction were remarkably increased and the reaction time was significantly shortened, though the enantioselectivity of *CRL* decreased a little bit. It was worthy to point out that our efforts to improve the enantioselectivity of *CRL* by increasing the bulky degree of the ester group were unsuccessful.

If we could determine the absolute configuration of one of the products (**3a**—**3m**, **4a**—**4m**), the absolute configuration of other molecules was thus deduced. Substantially, the absolute configuration of one of hydrolyzed alcohols ethyl 3-hydroxy-3-phenylpropionate (**3c**) was determined based on the optical rotation $[\alpha]_D^{20}$ +48.7 (*c* 1.4, $CHCl_3$), {lit.[10a] (*S*)-**3c**: $[\alpha]_D^{20}$ −50.8 (*c* 1.0, $CHCl_3$) and lit.[14] $[\alpha]_D^{20}$ +40.0 (*c* 2.8, $CHCl_3$)} (Scheme 2 and Table 1).

In our study, we found that the same enantioseclectivity of *CRL*-catalyzed hydrolysis was kept when the aryl groups of 2-hydroxy-2-arylethanephosphonates were replaced by a trifluoromethyl moiety.[12b] Analogously, we synthesized the chiral ethyl 3-hydroxy-4,4,4-trifluorobutyrate that has potential applications to novel fluorinated pharmaceuticals, such as the antidepressant beloxatone[13] (Scheme 3).

**Scheme 2**




**Scheme 3**

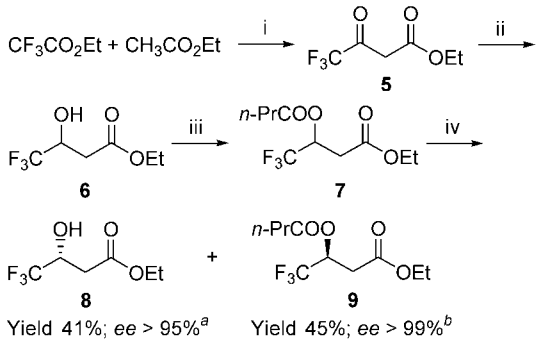



**Table 1** *CRL* catalyzed enantioselective hydrolysis of **2a**—**2m**

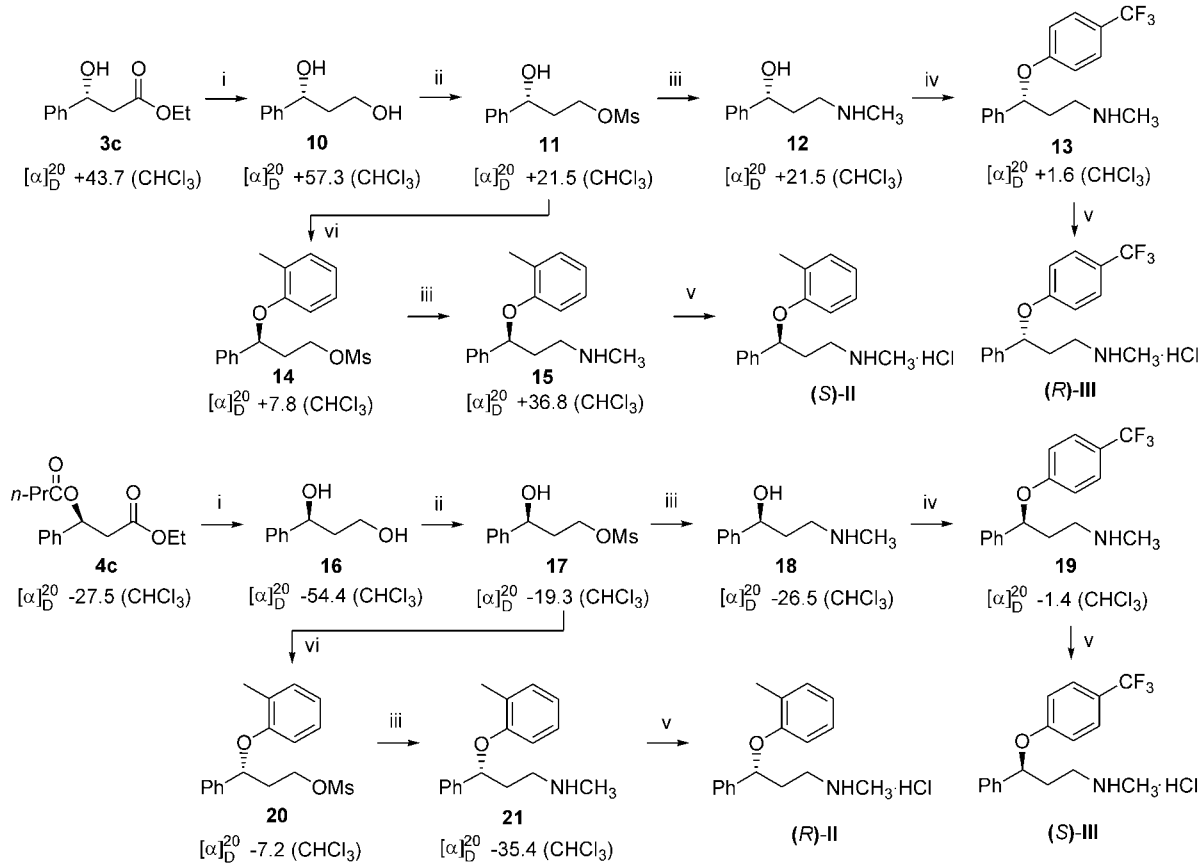
| Entry | R | Ar | Yield of **2**/% | Reaction time/h | **3** | | **4** | | $E^b$ |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Yield/% | $ee^a$/% | Yield/% | $ee^a$/% | |
| **a** | Me | $C_6H_5$ | 94 | 24 | 48 | 87 | 44 | 92 | >68 |
| **b** | Me | 4-$MeOC_6H_4$ | 93 | 24 | 44 | >99 | 47 | 92 | >150 |
| **c** | Et | $C_6H_5$ | 95 | 24 | 43 | >99 | 48 | 92 | >150 |
| **d** | Et | 4-$MeC_6H_4$ | 93 | 24 | 42 | 95 | 44 | 93 | >100 |
| **e** | Et | 4-$MeOC_6H_4$ | 95 | 24 | 47 | 86 | 44 | 91 | >60 |
| **f** | Et | 2-Furyl | 91 | 24 | 51 | 75 | 40 | 90 | >45 |
| **g** | Et | 2-$ClC_6H_4$ | 92 | 24 | 46 | 95 | 41 | 99 | >150 |
| **h** | Et | 4-$FC_6H_4$ | 94 | 24 | 41 | >99 | 49 | 87 | >100 |
| **i** | Et | 2,4-$Cl_2C_6H_3$ | 90 | 24 | 46 | 94 | 42 | >99 | >150 |
| **j** | Et | 4-$O_2NC_6H_4$ | 96 | 24 | 43 | 92 | 43 | >99 | >150 |
| **k** | *i*-Pr | $C_6H_5$ | 93 | 24 | 44 | 94 | 48 | 82 | >50 |
| **l** | *i*-Pr | 4-$MeOC_6H_4$ | 92 | 24 | 45 | 76 | 46 | 77 | >20 |
| **m** | Bu | $C_6H_5$ | 95 | 24 | 42 | 93 | 47 | 87 | >50 |

[a] The *ee* values were determined by the chiral HPLC (CHIRALPAK AD, OD, AS). [b] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[15]

The absolute configuration of the hydrolyzed alcohol **8** was determined based on the optical rotation of ethyl 3-hydroxy-4,4,4-trifluorobutyrate **8** $[\alpha]_D^{20}$ +20.8 (*c* 0.7, $CHCl_3$) {lit.[16a] (*S*)-**8**: $[\alpha]_D^{20}$ −18.4 (*c* 2.85, $CHCl_3$); lit.[16b] (*R*)-**8**: $[\alpha]_D^{20}$ +21.8 (*c* 1.25, $CHCl_3$); lit.[16c] (*R*)-**8**: $[\alpha]_D^{25}$ +20.8 (*c* 1.2, $CHCl_3$)}.

The optically active carboxylic acid and ester could be directly converted to the four known chiral tomoxetine hydrochloride (**II**) and fluoxetine hydrochloride (**III**). And we selected one group of the highest enantiomeric excess to prepare the title compounds. Finally, we were successively to prepare (*R*)-tomoxetine **21**, (*S*)-tomoxetine **15**, (*R*)-fluoxetine **13** and (*S*)-fluoxetine **19**. Upon acidification with HCl (gas) in ether both enantiomers of tomoxetine and fluoxetine hydrochloride were obtained. (*R*)-**II**: m.p. 160—161 ℃, $[\alpha]_D^{20}$ −38.8 (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20}$ −41.0 (*c* 1.0, MeOH), $[\alpha]_D^{20}$ −40.4 (*c* 1.0, EtOH) {lit.[3b] m.p. 162—164 ℃, $[\alpha]_D^{20}$ −41.37 (*c* 1.02, MeOH), $[\alpha]_D^{20}$ −40.9 (*c* 0.94, EtOH)}. (*S*)-**II**: m.p. 162—163 ℃, $[\alpha]_D^{20}$ +40.9 (*c* 1.2, $CHCl_3$), $[\alpha]_D^{20}$ +43.1 (*c* 1.0, MeOH), $[\alpha]_D^{20}$ +42.7 (*c* 1.0, EtOH) {lit.[3b] m.p. 162—164 ℃, $[\alpha]_D^{20}$ 43.2 (*c* 0.81, MeOH), $[\alpha]_D^{20}$ +40.5 (*c* 1.06, EtOH)}. (*R*)-**III**: m.p. 141—142 ℃, $[\alpha]_D^{20}$ −14.1 (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20}$ +11.0 (*c* 1.0, $H_2O$) {lit.[3b] m.p. 140−142 ℃, lit.[3f] $[\alpha]_D^{25}$ −14.8 (*c* 1.1, $CHCl_3$)}. (*S*)-**III**: m.p. 139—140 ℃, $[\alpha]_D^{20}$ +12.8 (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20}$ −10.0 (*c* 1.0, $H_2O$) {lit.[3b] 140—142 ℃, lit.[3f] $[\alpha]_D^{25}$ +14.0 (*c* 1.0, $CHCl_3$), $[\alpha]_D^{20}$ −10.2 (*c* 1.0, $H_2O$)} (Scheme 4).

**Scheme 4**




(i) $LiAlH_4$, THF, -10–0 °C,1 h; (ii) MsCl, $Et_3N$, ether, -10–0 °C, 2 h; (iii) 25% aqueous $CH_3NH_2$, THF, 65--70 °C, 3 h; (iv) NaH, DMSO, 55 °C, 45 min; *p*-chlorobenzotrifluoride, 90–100 °C,1.5 h; (v) HCl (gas), ether; (vi) *o*-cresol, DEAD, ether, -10 °C, 2.5 h

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(E0403043 PAN, B. F.)