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# The studies on chemoenzymatic synthesis of Femoxetine

Anna Brodzka, Dominik Koszelewski, Ryszard Ostaszewski*

*Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224 Warsaw, Poland*

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ABSTRACT

The studies on enzymatic kinetic resolution of 3-phenyl-4-pentenoic acid esters were performed. The obtained results demonstrated that the careful choice of biocatalyst and a reaction type are very important for successful enzymatic kinetic resolution. Kinetic resolution provides 3-phenyl-4-pentenoic acid (**1**) with good enantioselectivity upon esterification. That product was used as a substrate for formal synthesis of two biologically relevant compounds Femoxetine and LG 121071.



## 1. Introduction

The synthesis of enantiomerically pure drugs is of great importance for both academia and pharmaceutical industry [1]. Among others 3-phenyl-4-pentenoic acid (**1**) is a valuable building block for the synthesis of drugs and biologically active compounds (Scheme 1) [2].

The enantiomerically pure acid **1** is an important substrate for synthesis of several biologically active compounds like Femoxetine (**8**) [3], (*R*)-3-phenylpentenoic acid (**9**) – the key intermediate in synthesis of LG 121071 a modulator of androgen receptors [4] and 3-phenylGABA whose biological activity has been related to (*R*)-enantiomer [5].

Enantiomer *S* of 3-phenyl-4-pentenoic acid is also an important intermediate for the antitumor antibiotic methylenolactocin [6,7]. Previously, enantiomerically pure 3-phenyl-4-pentenoic acid (**1**) was synthesized by chemical routes in multistep syntheses [2,8,6]. Enantioselective biotransformations of racemic 3-arylpent-4-enenitriles catalyzed by *Rhodococcus erythropolis* AJ270 to acid **1** by a nitrile hydratase/amidase containing microbial whole-cell catalyst was reported to proceeds with good yield but the enantiomeric excess of this product did not exceed 92.5% [9]. Also the preparation of substrate for biotransformation was cumbersome. Despite of this, the fermentative methods are expensive and difficult to carry out in chemical laboratories.

## 2. Results and discussion

The aim this study was to determine the conditions for enzymatic kinetic resolution of 3-phenyl-4-pentenoic acid esters (**2a**–**c**) for Femoxetine synthesis. Previously we have found that enzymes can be used for stereocontrolled, chemoenzymatic synthesis of unnatural peptides [10], for the kinetic resolution of the α-acetoxyamides [11] and for desymmetrization of 3-arylglutaric acid anhydrides [12]. Racemic acid **1** was obtained according to the literature procedure from cinnamyl alcohol and triethyl orthoacetate with 86% yield [13]. The parent esters were obtained from acid chloride and corresponding aliphatic alcohol (Scheme 2).

### 2.1. Enzymatic hydrolysis of ethyl 3-phenyl-4-pentenoate

In the study on enzymatic kinetic resolution (EKR) of esters **2** commercially available enzymes were examined according to Scheme 3. Reactions were conducted in buffer (pH 7.0) containing 20 vol.% of acetone, keeping enzyme/substrate ratio – 1:1.

In most cases poor results were obtained. Even for widely used biocatalyst Novozym 435 the enantioselectivity of reaction was close to 1 (Table 1, entry 1). More promising results were obtained for crude biocatalyst delivered from animal tissue. Liver acetone powders (LAP) are widely used in organic synthesis, such as the synthesis of cyclohexyl based chiral auxiliaries [14], α-acetoxyamides [11], α-hydroxy-β,γ-unsaturated esters [15], capsaicin analogs [16] and trans-1-acetoxy-2-aryloxycyclohexanes [17]. Also the application of LAP for the synthesis of stereogenic carbon center was recently reviewed [18]. In our study eight various acetone powders [pig liver acetone powder (PLAP), beef liver acetone powder

* Corresponding author. Tel.: +48 22 343 2120; fax: +48 22 632 66 81.
*E-mail address:* rysza@icho.edu.pl (R. Ostaszewski).

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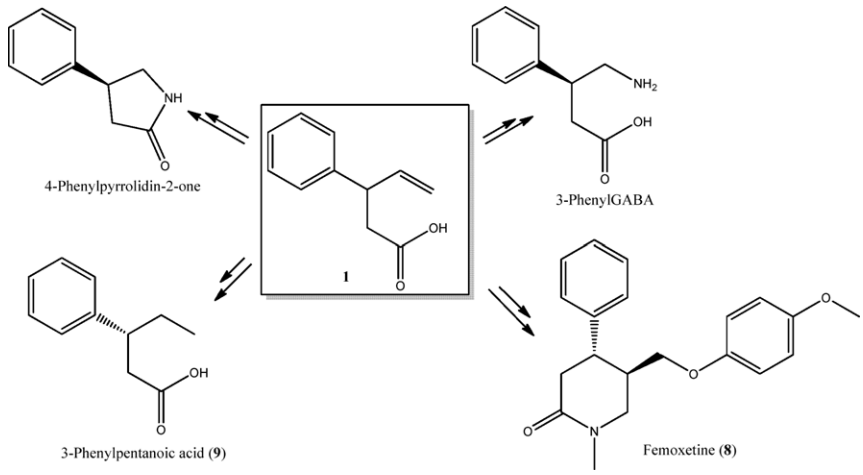
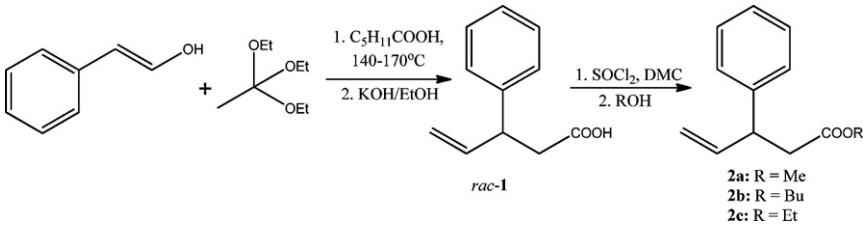



**Scheme 1.** Signification of 3-phenyl-4-pentenoic acid.




**Scheme 2.** Synthesis of racemic acid (**1**) and its esters (**2a**–**c**).

(BLAP), rabbit liver acetone powder (RLAP), wild boar liver acetone powder (WLAP), chicken liver acetone powder (CLAP), duck liver acetone powder (DLAP), turkey liver acetone powder (TLAP), goose liver acetone powder (GLAP)] were screened.

The experimental data shows that in a hydrolysis reaction of butyl ester **2b** catalyzed by CLAP and WLAP acid **1** was obtained with the highest enantioselectivity (Table 1, entries 5 and 6). When methyl ester of compound **1** was hydrolyzed we observed decease of enantioselectivity.

Our studies on the effect of the length of ester on enantioselectivity are congruent with the literature data [19].

**Table 1**
Enzymatic kinetic resolution of ester **2a**–**c** catalyzed by acetone powders.

| Entry | Acetone powder | *R* | Time (h) | *c* (%)[a] | % ee[b] (*R*)-**2** | *E*[d] |
|---|---|---|---|---|---|---|
| 1 | Novozym 435 | Et | 24 | 44 | 8 | 1 |
| 2 | PLAP | Bu | 3 | 21 | 19 | 8 |
| 3 | BLAP | Bu | 4 | 25 | 18 | 4 |
| 4 | RLAP | Bu | 4 | 20 | 12 | 3 |
| 5 | WLAP | Bu | 4 | 24 | 21 | 24 |
| 6 | CLAP | Bu | 5 | 23 | 27[c] | 25 |
| 7 | DLAP | Bu | 5 | 27 | 18 | 3 |
| 8 | TLAP | Bu | 6 | 17 | 13 | 5 |
| 9 | GLAP | Bu | 5 | 22 | 12 | 3 |
| 10 | PLAP | Me | 2 | 27 | 1 | 1 |
| 11 | WLAP | Me | 2 | 32 | 16 | 2 |
| 12 | CLAP | Me | 3 | 21 | 19 | 7 |

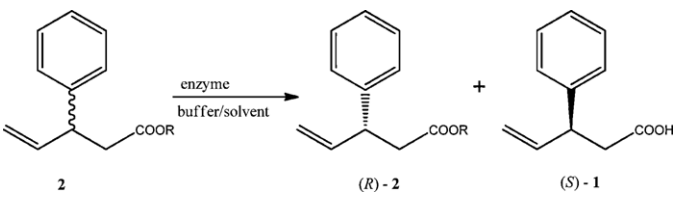
[a] Determined by HPLC on RP-C18 column.
[b] Determined by HPLC on the Daicel Chiracel OD-H column.
[c] (*S*)-**1** acid $[\alpha]_D = -7.5$ ($c = 1.0$, PhH).
[d] Calculated according to Chen et al. [20], using the equation: $E = (\ln[(1-c)(1-ee_s)])/(\ln[(1-c)(1+ee_s)])$.

### 2.2. Enzymatic esterification of 3-phenyl-4-pentenoic acid

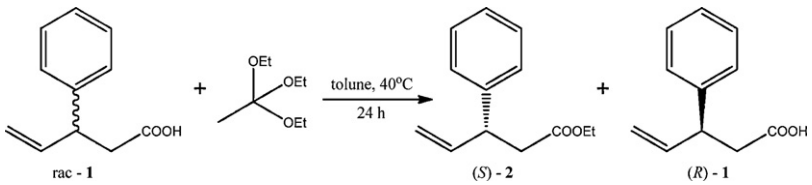
In the above studies we did not obtain satisfactory results, so we decided to perform enzymatic kinetic resolution using the esterification reaction. In this reaction triethyl orthoacetate was used as a donor of alcoholate group. Addition of an orthoester biases the equilibrium in favor of the ester side, due to consumption of water formed through hydrolysis of the orthoester. At first, the racemic ester was obtained by this methodology [21].

Next, we have focused our attention on the synthesis of chiral non-racemic ethyl 3-phenyl-4-pentenoate. In this study several commercially available and one immobilized lipase [immobilized lipase from *Candida antarctica* (*Novo sp 435A*)] together with six different acetone powders were screened as biocatalysts for esters (**2**) synthesis. These reactions were conducted in an toluene at 40 °C for 24 h (Scheme 4). The obtained results were shown in Table 2.

We found that the majority of tested enzymes exhibited enantioselectivity (Table 2). A few enzymes (lipases from: *Candida rugosa*; *Novo sp 435 A; BLAP, WLAP*) (Table 2, entries 8, 9, 13 and 16) exhibited low enantioselectivity and several enzymes (lipases from: *Penicillium roqueforti*, *Aspergillus*, *Wheat germ*, *Pseudomonas sp.*, *Mucor miehei*; *TLAP*, *JLAP*, *BKAP*, *GLAP*) (Table 2, entries 2–4, 6, 7 and 11–14) exhibited good enantioselectivity. We decided to scale-up selected enzymatic esterification of racemic




**Scheme 3.** EKR of esters 3-phenyl-4-pentenoic acid (**1**).




**Scheme 4.** Enantioselective synthesis of ethyl 3-phenyl-4-pentenoate.

**Table 2**
Results obtained in enzymatic esterification 3-phenyl-4-pentenoic acid with triethyl orthoacetate.[a]

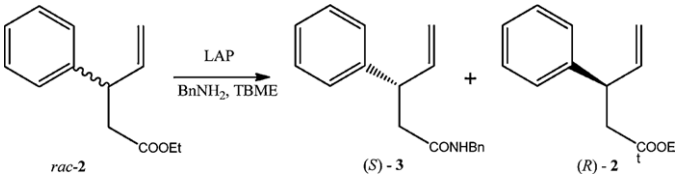
| Entry | Enzyme | Product | *c* (%)[b] | % ee[c] | *E*[d] |
|---|---|---|---|---|---|
| 1 | – | **2c** | 11 | – | – |
| 2 | *Penicilium roqueforti* | (*S*)-**2c** | 52 | 90 | 76 |
| 3 | *Aspergillus* | (*S*)-**2c** | 23 | 92 | 34 |
| 4 | *Wheat germ* | (*S*)-**2c** | 45 | 93 | 63 |
| 5 | *Pseudomonas cepacia* | (*S*)-**2c** | 15.4 | 92 | 30 |
| 6 | *Pseudomonas sp* | (*S*)-**2c** | 37.5 | 93 | 50 |
| 7 | *Mucor miehei* | (*S*)-**2c** | 40.9 | 91 | 40 |
| 8 | *Candida rugosa* | (*S*)-**2c** | 30.1 | 90 | 29 |
| 9 | *Novo sp 435 A* | (*S*)-**2c** | 57 | 69 | 17 |
| 10 | BLAP | (*S*)-**2c** | 24 | 90 | 26 |
| 11 | TLAP | (*S*)-**2c** | 54 | 82 | 41 |
| 12 | JLAP[f] | (*S*)-**2c** | 52 | 83 | 32 |
| 13 | BKAP[g] | (*S*)-**2c** | 25.7 | 93 | 37 |
| 14 | GLAP | (*S*)-**2c** | 25 | 97 | 82 |
| 15[e] | GLAP | (*S*)-**2c** | 50 | 80 | 22 |
| 16 | WLAP | (*S*)-**2c** | 29.1 | 83 | 16 |

[a] *Conditions*: **1** (1 mmol), **4b** (3 mmol), toluene (1.21 ml), the enzyme (10 mg), 35–40 °C, 24 h.
[b] Determined by HPLC on RP-C18 column.
[c] Determined by HPLC on the Daicel Chiracel OD-H column.
[d] Calculated according to Chen et al. [20], using the equation: $E = (\ln[1 - c(1 + ee_p)])/(\ln[1 - c(1 - ee_p)])$.
[e] Reaction was prepared in larger scale, conditions: **1** (10 mmol), **4b** (30 mmol), toluene (12.1 ml), the enzyme (100 mg), 35–40 °C, 24 h.
[f] JLAP – deer liver acetone powder.
[g] BKAP – beef kidney acetone powder.

3-phenyl-4-pentenoic acid (Table 2, entry 15). Unexpectedly, the reaction in larger scale under the same conditions proceeded with higher rate than in small scale (Table 2, entry 14). Shortening reaction time provided product with the same enantioselelctivity in large scale.

### 2.3. Chemoenzymatic synthesis of Femoxetine

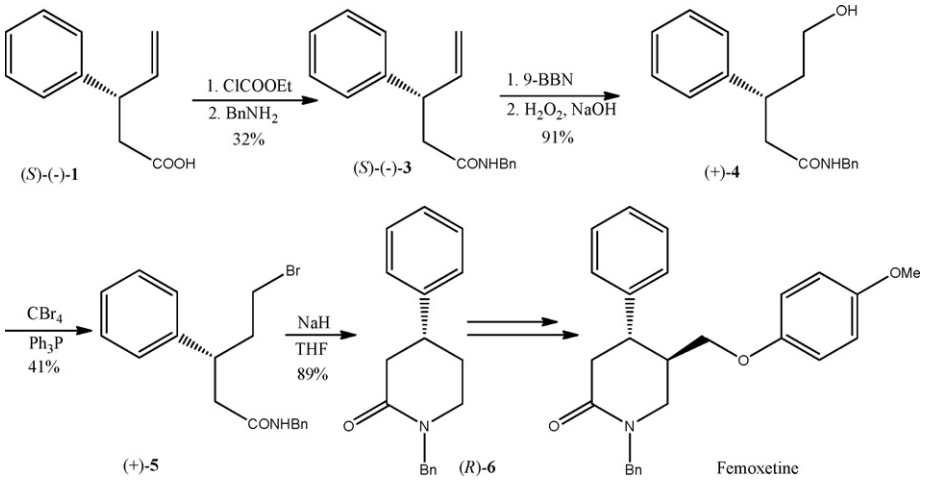
Efficient enzymatic kinetic resolution of esters **2** provides large amount of chiral acid **1** which can be used as a convenient building block for synthesis of Femoxetine®. The reaction of optically pure acid (*S*)-**1** with ethyl chloroformate and benzylamine leads to formation of amide (*S*)-**3** in 32% yield. Several attempts were made to optimize this reaction without satisfactory result. Reaction of amide **3** with 9-BBN followed by oxidation ($H_2O_2$) leads to formation of alcohol **4** in 91% yield. Next, Appel reaction provides bromide **5** (41% yield) whose cyclization lets to formation of (*S*)-N-benzyl-4-phenyl-2-piperidinone (**6**) in 89% yield (Scheme 5) [22]. Specific rotation of obtained compound (+36.2) compared to literature data (+35.0) fully confirms the absolute configuration of our product and its enantiomeric purity [6]. Since the next reactions leading to Femoxetine® are known in literature this is the formal synthesis of this bioactive molecule [23,24].



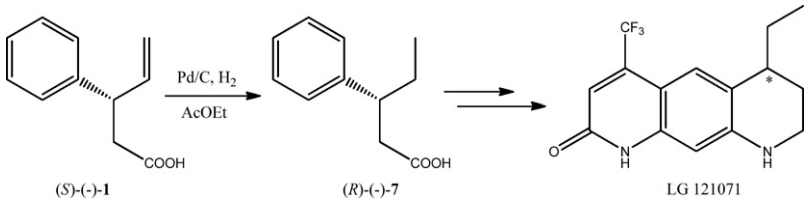

**Scheme 6.** Aminolysis of ethyl ester of 3-phenyl-4-pentenoic acid (**2c**).

This short and efficient synthesis of Femoxetine® based on acid **1** clearly demonstrates the synthetic potential of this chiral auxiliary. The formation of amide **3** from acid **1**, the first step in reaction sequence (Scheme 5) proceeds in relatively low yield what greatly diminishes the overall yield. The same chiral product can be directly obtained from racemic ester **2** upon enantioselective enzymatic aminolysis. It is already known that enzymatic kinetic resolution of ester based on aminolysis reaction is also catalyzed by liver acetone powders [25]. Therefore, we examined a suitability of obtained acetone powders in aminolysis reaction of racemic ester **2c** with benzyl amine according to Scheme 6.

All reactions were conducted in *tert*-butylmethyl ether at 30 °C. The experimental data show that enzymes which catalyze this




**Scheme 5.** Formal synthesis of (*R*)-N-benzyl-4-phenyl-2-piperidinone.




**Scheme 7.** Synthesis of (*R*)-3-phenylpentanoic acid (**7**).

reaction are present in six acetone powders (PLAP, BLAP, TLAP, RLAP, WLAP, CLAP).

Amide **3** with the highest optically purity was obtained when pig liver acetone powder (PLAP) ($[\alpha]_D$ = +7.56 in $CHCl_3$, $c$ = 1.0) and wild boar liver acetone powder (WLAP) ($[\alpha]_D$ = −7.00 in $CHCl_3$, $c$ = 1.0) were used in aminolysis reaction. Comparing the value of the specific rotation of these products to the value of specific rotation of amide obtained at an earlier stage (−7.10 in $CHCl_3$, $c$ = 1.0, Scheme 5) we estimated that these compounds were obtained with enantiomeric excess over 95%.

It is interesting to note that upon proper choice of biocatalyst both enantiomers of amide **3** are readily available. Amide (*R*)-**3** was obtained when PLAP was used as a biocatalyst, whereas in reaction catalyzed by WLAP product (*S*)-**3** was formed.

### 2.4. Synthesis of (R)-3-phenylpentanoic acid (7)

Obtained, optically pure acid (*S*)-**1** was used as a substrate to the synthesis of (*R*)-3-phenylpentanoic acid (**7**). This acid is a building block for synthesis of LG 121071 which is an efficient modulator of androgen receptors [4].

Acid (*S*)-**1** was reduced by hydrogen/palladium to (*R*)-3-phenylpentanoic acid (**7**) (yield 77%) (Scheme 7). Specific rotation of obtained compound was −47.3 which is almost identical to literature data (−48.0) which is observed for 99% enantiomeric excess [26].

## 3. Conclusions

The studies on enzymatic kinetic resolution of 3-phenyl-4-pentenoic acid were performed. Application of commercially available enzymes as biocatalysts for enzymatic hydrolysis was unsuccessful and respective reactions proceed with low enantioselectivity. Home made liver acetone powders were found to be much more efficient biocatalysts. However, the enzymatic hydrolysis gives better results for other class of substrates – 3-aryl alkanoic acids [27]. The second approach – enzymatic esterification was more efficient, the product was obtain with excellent enantioselectivity. Under optimal conditions desired optically pure acid **1** was obtained in good yield and high enantiomeric excess and used as a substrate for formal synthesis of Femoxetine and LG 121071. Six step synthesis of lactam (*R*)-**6**, an important intermediate for Femoxetine provide target compound proceeds in 11% overall yield. The attempts made to shorten this synthesis by enantioselective aminolysis of racemic ester **2c** using benzyl amine and enzymes proved to be unsuccessful.

Reduction of carbon double bond present in structure of optically pure acid **1** provides (*R*)-3-phenylpentanoic acid (**7**), an important intermediate in LG 121071 synthesis in 77% yield.

The studies demonstrate that enzymatic procedures can be successfully combined with chemical transformation leading to biologically relevant compound.

## 4. Experimental

### 4.1. General

The HPLC analyses were performed on a Chiracel OD-H column (4.6 mm × 250 mm, from Diacel Chemical Ind., Ltd.) equipped with a pre-column (4 mm × 10 mm, 5 m) using an LC-6A Shimadzu apparatus with UV SPD-6A detector and Chromatopac C-R6A analyser. The elemental analyses were performed on CHN Perkin-Elmer 240 apparatus. All the reactions were monitored by TLC on Merck silica gel Plates 60 F254. The acetone powders were prepared in our laboratory [28]. All the chemicals were obtained from commercial chemical sources. The solvents were of analytical grade.

### 4.2. Synthesis of 3-phenyl-4-pentenoic acid (1)

3-Phenyl-4-pentenoic acid was synthesized according to the method described by Bermejo Gonzalez and Bartlett [13]. A mixture of cynnamyl alcohol (0.25 mol; 33.7 g), triethyl orthoacetate (0.25 mol; 46.1 ml), and hexanoic acid (1.5 mmol; 0.19 ml) was heated in an oil bath. The solution was placed in a flask with Claisen head (for distilling off ethanol), condenser and thermometer. After 3 h 0.1 ml of hexanoic acid was added. Additional portion (0.1 ml) hexanoic acid was added at 3.5 and 4.5 h. After 6 h the temperature rose to 166 °C. After this time 27 ml of ethanol distilled off and TLC analysis indicates that no cinnamyl alcohol remains.

The mixture was cooled, and a solution of potassium hydroxide (0.35 mol; 19.7 g) in water (25 ml), and methanol (75 ml) were added. The mixture was heated under reflux for 1 h under nitrogen. After cooling, the solution was washed with ethyl ether and acidified with concentrated HCl to pH 1. The acidic solution was extracted with ethyl ether (3×) and organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure.

The crude acid was purified by crystallization from hexane (86% yield) to give product melting at 46 °C [13]. $^1$H NMR (200 MHz, $CDCl_3$): 2.74 (dd, $J$ = 15.0, 7.5 Hz, 1H), 2.78 (dd, $J$ = 15.0, 7.8 Hz, 1H), 3.90 (q, $J$ = 7.2 Hz, 1H), 5.00–5.18 (m, 2H), 5.90–6.10 (m, 1H), 7.19–7.40 (m, 5H); $^{13}$C NMR (200 MHz, $CDCl_3$): 40.2, 45.5, 115.3, 127.1, 127.8, 128.9, 140.2, 142.2, 178.3.

### 4.3. Synthesis of 3-phenylpentanoic acid (7)

A solution of 3-phenyl-4-pentenoic acid (2.30 mmol) in ethyl acetate (50 ml) and catalytic amount of Pd/C (5 mg) were placed under hydrogen under pressure 50 psi. The catalyst was filtered off and solvent was evaporated under vacuum. The crude acid was purified by crystallization from hexane (77% yield) to give product melting at 61 °C [27]. Elemental analysis: calcd. for $C_{11}H_{14}O_2$: C, 74.13%, H, 7.92%, found: C, 74.15%, H, 8.07%; $^1$H NMR (200 MHz, $CDCl_3$): 0.78 (t, $J$ = 7.14, 3H), 1.40–1.80 (m, 2H), 2.61 (dd, $J$ = 15.0, 7.5 Hz, 1H), 2.65 (dd, $J$ = 15.0, 7.8 Hz, 1H), 2.90–3.1 (m, 1H), 7.10–7.40 (m, 5H), 7.19–7.40; $^{13}$C NMR (50 MHz, $CDCl_3$): 12.2, 29.4, 41.4, 43.8, 126.8, 127.7, 128.7, 143.8, 178.8.

### 4.4. Synthesis of (−)-(R)-3-phenylpentanoic acid ((R)-**7**)

A solution of (*R*)-3-phenyl-4-pentenoic acid with 92% ee ($[\alpha]_D = -11.8$, $c = 0.5$, PhH) (2.30 mmol) in ethyl acetate (950 ml) and catalytic amount of Pd/C (5 mg) were placed under hydrogen under pressure 50 psi. The catalyst was filtered off and solvent was evaporated under vacuum. The crude acid was purified by crystallization from hexane (77% yield) to give product melting at 61 °C [29]. Product (*R*)-(−) ($[\alpha]_D = -47.3$, $c = 0.5$, PhH).

### 4.5. Synthesis of ethyl-3-phenyl-4-pentenoate (**2c**)

To the solution of 3-phenyl-4-pentenoic acid (**1**) (9.81 mmol) in methylene chloride (3 ml) thionyl chloride was dropped (9.87 mmol). The mixture was stirring for 2 h in room temperature. Next, dry ethanol (85.6 mmol) was added and the mixture was stirring for 3 h. The solvent excess was evaporated under vacuum. The crude product was purified by silica gel flash chromatography using hexane/ethyl acetate (99.5/0.5; v/v) as an eluent to afford the product **2c** as a colorless oil (92% yield); HPLC analysis [hexane/*i*-PrOH; 9:1; λ = 232 nm; 1.0 ml/min] $t_R(S) = 9.77$ min; $t_R(R) = 11.03$ min. $^1$H NMR (200 MHz, $CDCl_3$): 1.16 (t, $J = 7.2$ Hz, 3H), 2.70 (dd, $J = 15.0$, 7.5 Hz, 1H), 2.74 (dd, $J = 15.0$, 7.8 Hz, 1H), 3.86 (q, $J = 7.2$ Hz, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 5.04 (m, 1H), 5.09 (m, 1H), 5.98 (ddd, $J = 17.4$, 10.2, 7.2 Hz, 1H), 7.29 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): 14.1, 40.3, 45.6, 60.3, 114.7, 126.7, 127.6, 128.5, 140.3, 142.5, 171.7 [30].

### 4.6. Synthesis of methyl 3-phenyl-4-pentenoate (**2a**)

Ester **2a** was obtained in the similar way as product **2c**. Yield: 90%. $^1$H NMR (200 MHz, $CDCl_3$): 2.74 (dd, $J = 15.1$, 7.7 Hz, 1H), 2.78 (dd, $J = 15.1$, 7.7 Hz, 1H), 3.62 (s, 3H), 3.89 (q, $J = 7.7$ Hz, 1H), 5.01–5.15 (m, 2H), 5.90–6.10 (m, 1H), 7.15–7.38 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): 40.4, 45.8, 51.9, 115.1, 127.0, 127.8, 128.9, 140.5, 142.7, 172.6 [31].

### 4.7. Synthesis of butyl 3-phenyl-4-pentenoate (**2b**)

Ester **2b** was obtained in the similar way as products **2a** and **2c**. Yield: 80%. $^1$H NMR (200 MHz, $CDCl_3$): 0.94 (t, $J = 7.1$ Hz, 3H), 1.20–1.75 (m, 4H), 2.74 (dd, $J = 15.1$, 7.7 Hz, 1H), 2.78 (dd, $J = 15.1$, 7.7 Hz, 1H), 3.79–4.15 (m, 3H), 4.98–5.17 (m, 2H), 5.87–6.07 (m, 1H), 7.18–7.38 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): 19.3, 31.8, 40.6, 45.9, 62.3, 64.6, 115.0, 126.9, 127.8, 128.8, 140.5, 142.7, 172.6; ESI-MS HR, $[M]^+$, calcd for $C_{15}H_{20}O_2$: 232.146, found (*m*/*z*): 232.147.

### 4.8. Synthesis of racemic ethyl 3-phenyl-4-pentenoate (**2c**)

**2c** was synthesized as described by Gopalan [21].

To the solution of 3-phenyl-4-pentenoic acid (1 mmol) in toluene, triethyl orthoacetate (3 mmol) was added. The reaction mixture was heated under reflux (110 °C) for 24 h. After cooling, hydrochloric acid was added (2 M, 1.1 ml). The organic layer was washed with saturated sodium bicarbonate (1×), brine (1×) and dried over anhydrous $MgSO_4$. The excess of reagents and solvent were evaporated under vacuum. The crude product was purified by silica gel flash chromatography using hexane/ethyl acetate (99.5/0.5; v/v) as an eluent to afford the product **2c** as a colorless oil; $R_f = 0.8$ (hexane/EtOAc, 8:2; v/v); HPLC analysis [hexane/*i*-PrOH; 9:1; λ = 232 nm; 1.0 ml/min] $t_R(R) = 4.30$ min; $t_R(S) = 5.3$ min.

### 4.9. Enantioselective synthesis of ethyl 3-phenyl-4-pentenoate (**2c**)

To the solution of 3-phenyl-4-pentenoic acid (1 mmol) in toluene, triethyl orthoacetate (3 mmol) and enzyme (10 mg) were added. The reaction mixture was stirring for 24 h at 35–40 °C. After cooling, 2 M HCl was added (1.1 ml). The organic layer was washed saturated $NaHCO_3$ (1×) and brine (1×), and dried over anhydrous $MgSO_4$. The excess of reagent and solvent were evaporated under vacuum.

The crude product was purified by silica gel flash chromatography using hexane/ethyl acetate (99.5/0.5; v/v) as an eluent to afford the product **2c** as a colorless oil; $R_f = 0.8$ (hexane/EtOAc, 8:2; v/v); HPLC analysis [hexane/*i*-PrOH; 9:1; λ = 232 nm; 1.0 ml/min] $t_R(R) = 4.30$ min; $t_R(S) = 5.30$ min.

### 4.10. Enantioselective synthesis of ethyl 3-phenyl-4-pentenoate (**2c**) in gram scale

To the solution of 3-phenyl-4-pentenoic acid (10 mmol) in toluene, triethyl orthoacetate (30 mmol) and GLAP (100 mg) were added. The reaction mixture was stirring for 24 h at 35–40 °C. After cooling, 2 M HCl was added (11 ml). The organic layer was washed saturated $NaHCO_3$ (1×) and brine (1×), and dried over anhydrous $MgSO_4$. The excess of reagent and solvent were evaporated under vacuum.

The crude product was purified by silica gel flash chromatography using hexane/ethyl acetate (99.5/0.5; v/v) as an eluent to afford the product **2c** as a colorless oil (50% yield). Elemental analysis: calcd. for $C_{13}H_{16}O_2$: C, 76.44%, H, 7.90%, found: C, 76.31%, H, 7.79%; $R_f = 0.8$ (hexane/EtOAc, 8:2; v/v); HPLC analysis [hexane/*i*-PrOH; 9:1; λ = 232 nm; 1.0 ml/min] $t_R(R) = 4.30$ min; $t_R(S) = 5.30$ min; ee = 80%. Shorter reaction time, 16 h, provide ester with 99% ee.

### 4.11. Synthesis of benzyl amide of (S)-3-phenyl-4-pentenoic acid ((S)-**3**)

To the solution of (*S*)-3-phenyl-4-pentenoic acid ((*S*)-**1**), ($[\alpha]_D = -11.8$, $c = 0.5$, PhH) (0.5 mmol) in methylene chloride (5 ml) triethylamine (7.36 mmol) was added followed by ethyl chloroformate (1.8 mmol). The mixture was stirring in room temperature for 3 h, filtrated through celite and benzylamine (6.31 mmol) was added. After stirring in room temperature for 3 h. the reaction mixture was washed with water (3 × 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by crystallization from ethyl acetate/hexane (32% yield).

Elemental analysis: calcd. for $C_{18}H_{19}NO$: C, 81.48%, H, 7.22%, N, 5.28%, found: C, 81.52%, H, 7.46%, N, 5.26%; $^1$H NMR (200 MHz, $CDCl_3$): 2.57–2.82 (m, 2H), 3.91–4.09 (m, 1H), 4.10–4.52 (m, 2H), 5.02–5.25 (m, 2H), 5.84–6.20 (m, 2H), 7.00–7.18 (m, 2H), 7.20–7.50 (m, 8H); $^{13}$C NMR (50 MHz, $CDCl_3$): 43.1, 43.7, 46.3, 115.1, 127.0, 127.5, 127.8, 127.9, 128.8, 128.9, 138.3, 140.7, 142.8, 171.2; $[\alpha]_D = -7.1$ ($c = 1.0$, $CHCl_3$).

### 4.12. Synthesis of benzyl amide of (+)-3-phenyl-5-hydroxypentanoic acid (**4**)

To the solution of benzyl amide of (*S*)-3-phenyl-4-pentenoic acid ((*S*)-**3**) (0.70 mmol) in dry tetrahydrofurane (7 ml) 9-BBN (3.44 mmol) was added and reaction mixture was stirred in room temperature. After 12 h. solution of sodium hydroxide (2 M, 2 ml) and hydrogen peroxide (10%, 2 ml) were dropped and the reaction mixture was treated by ultrasound for 20 min. Then the solution was acidified with 2 M HCl to pH 2 and distilled water (100 ml) was added. Reaction mixture was extracted with ethyl acetate (3 × 30 ml) and combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by silica gel flash chromatography using hexane/ethyl acetate as an eluent (91% yield); $^1$H NMR (200 MHz, $CDCl_3$): 1.80–1.93 (m, 3H),

2.24 (s, 1H), 2.37–2.62 (m, 2H), 3.20–3.40 (m, 1H), 3.40–3.60 (m, 2H), 4.00–4.40 (m, 2H), 5.68 (s, 1H), 6.88–7.00 (m, 2H), 7.09–7.32 (m, 8H); $^{13}$C NMR (50 MHz, $CDCl_3$): 36.6, 39.3, 39.4, 43.8, 44.2, 60.7, 127.0, 127.6, 127.7, 127.8, 128.9, 129.1, 138.2, 144.1, 172.0; $[\alpha]_D$ = +1.9 ($c$ = 1.5, $CHCl_3$).

### 4.13. Synthesis of benzyl amide of (+)-3-(4′-fluorophenyl)-4-bromopentanoic acid (**5**)

To the solution of benzyl amide of (+)-3-phenyl-5-hydroxypentanoic acid (**4**) (0.53 mmol) in dry methylene chloride (5 ml) triphenylphosphine (0.63 mmol) and tetrabromomethane (0.64 mmol) were added. The mixture was stirring in room temperature for 24 h. and the solvent excess was evaporated under vacuum. The crude product was purified by silica gel flash chromatography using hexane/ethyl acetate as an eluent (41% yield); Elemental analysis: calcd. for $C_{18}H_{20}NOBr$: C, 62.44%, H, 5.82%, N, 4.05%, found: C, 62.38%, H, 5.99%, N, 4.03%; $^1$H NMR (200 MHz, $CDCl_3$): 2.12–2.42 (m, 2H), 2.48–2.72 (m, 2H), 3.12–3.55 (m, 3H), 5.59 (s, 1H), 6.98–7.12 (m, 2H), 7.21–7.44 (m, 8H); $^{13}$C NMR (50 MHz, $CDCl_3$): 36.6, 39.3, 39.4, 43.8, 44.2, 60.7, 127.0, 127.6, 127.7, 127.8, 128.9, 129.1, 138.2, 144.1, 172.0; $[\alpha]_D$ = +20.1 ($c$ = 1.0, $CHCl_3$).

### 4.14. Synthesis of N-benzyl-(R)-4-phenyl-2-piperidinone (**6**)

To the solution of benzyl amide of (+)-3-(4′-fluorophenyl)-4-bromopentanoic acid (**5**) (0.15 mmol) in dry tetrahydrofunane (10 ml) sodium hydroxide (0.30 mmol) was added and reaction mixture was stirred in 85 °C for 24 h. After that methanol was added (2 ml) and solvent excess evaporated under vacuum. The residue was dissolved in water and extracted with ethyl acetate (3 × 15 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by crystallization from hexane/ethyl acetate (89% yield).

Elemental analysis: calcd. for $C_{18}H_{19}NO$: C, 81.48%, H, 7.22%, N, 5.28%, found: C, 81.64%, H, 7.435%, N, 5.34%; $^1$H NMR (200 MHz, $CDCl_3$): 1.80–2.15 (m, 2H), 2.48–2.90 (m, 2H), 3.00–3.20 (m, 1H), 3.21–3.40 (m, 2H), 4.65 (dd, $J$ = 15.0, 7.0 Hz, 2H), 7.10–7.40 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$): 30.5, 38.9, 39.7, 46.6, 50.3, 126.7, 127.0, 127.7, 128.4, 128.8, 128.9, 137.3, 143.6, 169.5; $[\alpha]_D$ = +36.2 ($c$ = 1.12, $CHCl_3$).

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