Tetrahedron: *Asymmetry* 23 (2012) 1256–1261

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# A new chemoenzymatic approach to the synthesis of chiral 4-aryl-1,4-dihydro-2*H*-isoquinolines via the enzymatic resolution of 2-acetyl-4-phenyl-1,4-dihydro-2*H*-isoquinolin-3-one

Dominik Koszelewski [a], Malgorzata Cwiklak [a], Ryszard Ostaszewski [a,b,*]

[a] *Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224 Warsaw, Poland*
[b] *Industrial Chemistry Research Institute, Rydygiera 8, 01-793 Warsaw, Poland*

ARTICLE INFO

*Article history:*
Received 28 June 2012
Accepted 27 July 2012
Available online 17 September 2012

ABSTRACT

A new chemoenzymatic method is proposed for the synthesis of enantiomerically pure 4-phenyl-1,4-dihydro-2*H*-isoquinolines based on the enzymatic kinetic resolution of 2-acetyl-4-phenyl-1,4-dihydro-2*H*-isoquinolin-3-one. For the enzymatic resolution of the racemic substrate, readily available 'home made' animal liver acetone powders (LAPs) were used. Excellent enantioselectivity, exceeding 500, was achieved in a short reaction time upon application of turkey liver acetone powder as the biocatalyst. Reduction of obtained product led to the formation of amine (*R*)-**1**, which is hardly available using standard procedures. These results show that *N*-acetyl lactams are a new type of substrate for enzymatic biotransformations.



## 1. Introduction

A large number of bioactive molecules possessing a chiral tetrahydroisoquinoline (THIP) scaffold **1**–**3** and their asymmetric syntheses are reported in the literature.[1–5] For instance, nomifensine **4**[6,7] and dichlorofensine **5**[8] are of considerable interest due to their ability to inhibit the uptake of important central neurotransmitters such as serotonine, norepinephrine, or dopamine at postsynaptic receptors (Fig. 1). In most cases, only one enantiomer of these compounds demonstrates pharmacological activity. However, they are synthesized as racemic mixtures, and thus require an additional step for resolution into enantiomers.[9]

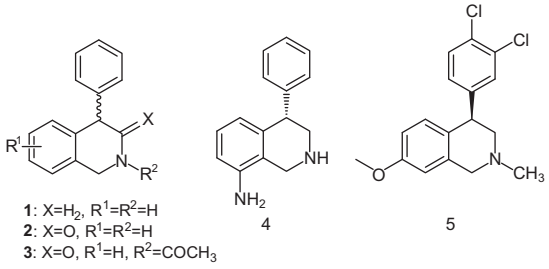



**Figure 1.** Bioactive compounds possessing the THIP scaffold.

The reported syntheses of target compound **1** are based on the reductive amination of substituted benzaldehydes with respective ethanolamines, followed by acid catalyzed cyclization of product obtained with methanesulfonic acid.[10] However, the arylethanolamines required for the first reaction are hardly available. Another method for the synthesis of **1** via *cis*- and *trans*-phenantridine is a time consuming multistep reaction and requires a chiral auxiliary.[11] Bourguignon et al. proposed a highly selective protonation of chiral lactam enolates of 4-substituted-1,4-dihydroisoquinolin-3-ones, which are obtained from isochroman-3-ones. However, this method demands deuterated ethanol.[12]

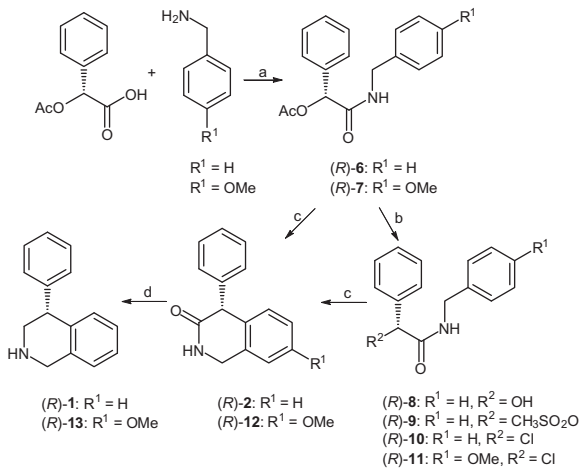
In recent years the use of hydrolytic enzymes for the resolution of different racemic compounds has been growing continuously.[13,14] The kinetic resolution of amides is a well-known procedure.[15] In order to enhance the reactivity of lactam **2**, its N-acetylated derivatives can be used. A literature search indicated that *N*-acetyl lactam esters were slowly hydrolyzed by esterases, which reduced its skin permeation.[16] This suggests, that they can be good substrates for enzymatic hydrolysis reactions.

## 2. Results and discussion

We were interested in a general synthetic method which could be applied for the synthesis of enantiomerically pure *N*–H and *N*-alkyl tetrahydroisoquinoline scaffolds. This scaffold can be obtained by the reduction of amides **2**, themselves available via stereoselective Friedel–Craft cyclization of optically active α-acetoxyamides. In Scheme 1, we propose a new synthetic route

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

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.07.013




**Scheme 1.** Synthesis of non-racemic 4-aryl-1,4-dihydro-2*H*-isoquinolines **1** and **13**. *Reagents and conditions:* (a) DCC / HOBt, $CH_2Cl_2$, 0 °C, rt, 24 h; (b) [(*R*)-**1** in (*R*)-**3**, NaOHaq/MeOH, ultrasounds], [(*R*)-**1** in (*R*)-**4**, $CH_3SO_2Cl/Et_3N$, $CH_2Cl_2$, reflux, 6 h], [(*R*)-**1** in (*R*)-**5** and (*R*)-**2** in (*R*)-**6** $SOCl_2$, $CH_2Cl_2$, rt, 2 h]; (c) Table 1, (d) $B_2H_6$, THF.

to obtain optically active lactam **2** and its derivative **12**. Enatiomerically pure amides (*R*)-**6** and (*R*)-**7** were prepared in a condensation reaction between (*R*)-acetoxymandelic acid with the appropriate benzylamine in 68% and 76% yields, respectively.

We applied the literature procedure to the cyclization of the already prepared amides (*R*)-**6** and (*R*)-**7** to obtain the corresponding lactams (*R*)-**2** and (*R*)-**12** (Table 1, entries 1 and 2). However, while both reactions proceeded in good chemical yield, racemization occurred and lactam **12** was obtained in 21% ee (Table 1, entry 2). For substrate (*R*)-**6**, the racemic product was obtained (Table 1, entry 1). Since racemization occurred upon cyclization the influence of the leaving group on the stereochemical course of the cyclization was studied (Table 1, entries 3–7). Using α-hydroxyamide (*R*)-**8** as the substrate and performing the reaction at −20 °C increased the yield, but again a racemic product was obtained (Table 1, entry 3). The use of polyphosphoric acid as a catalyst provided the desired product (*R*)-**2** in 51% yield and 31% enantiomeric excess (Table 1, entry 4). For the next set of experiments, α-substituted amides (*R*)-**9**, (*R*)-**10**, and (*R*)-**11** were prepared according to standard procedures. The application of Lewis acid catalysts for the cyclization provided the respective lactams in good yield but moderate ee (Table 1, entries 5–7).

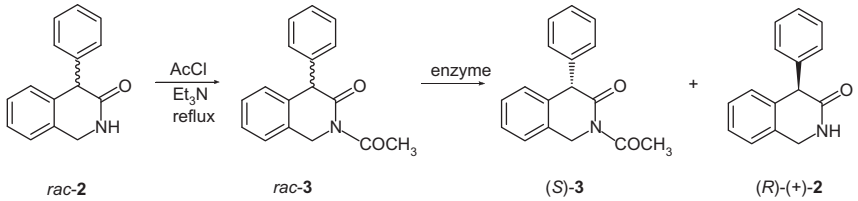
Functionalization of the acetoxy group in order to obtain a hydroxyl group did not influence the stereochemical course of the cyclization, and the product was obtained in 31% enantiomeric excess (Table 1, entry 4). After many trials we found that compound **2** could be obtained in good yield but the enantiomeric excess did not exceed 47% (Table 1, entry 5). Due to the fact that the target compound racemized under the cyclization conditions, we turned our attention to methods based on kinetic enzymatic kinetic resolution procedures, which nowadays are commonly used in organic laboratories. Experiments dedicated to the resolution of lactams **2** and **12** were completely unsuccessful. None of the commercially available protease catalyzed this reaction. Enantiomerically pure lactam **2** could be obtained upon application of the acetylated derivative 2-acetyl-4-phenyl-1,4-dihydro-2*H*-izochinolin-3-one **3** as a substrate to the enzymatic reactions. To the best of our knowledge, this approach has not been investigated before. Model compound *rac*-**3** was prepared by acetylation of 4-phenyl-1,4-dihydro-2*H*-isoquinolin-3-one *rac*-**2**, using acetyl chloride, in 85% yield. No attempts were made to optimize this reaction. This compound was used as a new type of substrate for the enzymatic kinetic resolution (Scheme 2).

After the screening of commercially available enzymes in a phosphate buffer (pH 7) and acetone, we chose two enzymes (lipase from wheat germ and lipase from *Pseudomonas cepacia*), which converted substrate **3** into the product. The influence of organic cosolvents (acetone, *t*-butylmethyl ether, ethyl ether) on the stereochemical course of reaction was then investigated (Table 2, entries 1–6). The product was obtained in excellent enantioselectivity in *t*-butylmethyl ether and diethyl ether in reaction catalyzed by *Pseudomonas cepacia* (Table 2, entries 5 and 6). However, the formation of an emulsion was observed, which strongly limited the use of the native lipase from *Pseudomonas cepacia*. In reactions catalyzed by the lipase from wheat germ, the increase in enantioselectivity was insubstantial (Table 2, entries 1–3). In order to avoid the formation of the emulsion in two phase system, we prepared a set of immobilized lipases from *Pseudomonas cepacia*. Immobilization was conducted in three ways: covalent

**Table 1**
Conditions of cyclization (c from Scheme 1)

| Entry | Sub. | Cat. | Solvent | *T* (°C) | Prod. | Y (%) | $[\alpha]_D$[b] | ee[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | (*R*)-**6** | $H_2SO_4$ | $CH_2Cl_2$ | 0 | **2** | 50 | — | 2 (*R*) |
| 2 | (*R*)-**7** | $H_2SO_4$ | $CH_2Cl_2$ | 0 | **12** | 43 | — | 21 |
| 3 | (*R*)-**8** | $H_2SO_4$ | $CH_2Cl_2$ | −20 | **2** | 85 | −1.3 | 2 (*R*) |
| 4 | (*R*)-**8** | PPA | — | 40 | | 51 | −8.2 | 31 (*R*) |
| 5 | (*R*)-**9** | $AlCl_3$ | $CH_2Cl_2$ | 40 | | 16 | −10.2 | 47 (*R*) |
| 6 | (*R*)-**10** | $ZnCl_3$ | $ClCH_2CH_2Cl$ | 80 | | 44 | −3.2 | 14 (*R*) |
| 7 | (*R*)-**11** | $ZnCl_3$ (3 equiv) | $ClCH_2CH_2Cl$ | 80 | **12** | 54 | −0.5 | 11 |

[a] Ee determined by HPLC on a Chiralcel OD-H column.
[b] Solvent: $CHCl_3$, 22 °C, *c* 1.0.




*rac*-**2** *rac*-**3** (*S*)-**3** (*R*)-(+)-**2**

**Scheme 2.** Enzymatic kinetic resolution of compound **3**.

**Table 2**
Conditions of the enzymatic kinetic resolution of **3**

| Entry | Substrate | Enzyme | Solvent | $t$ (h) | $c$[a] (%) | ee[b] (%) | $E$ |
|---|---|---|---|---|---|---|---|
| 1 | *rac*-**3** | Lipase from wheat germ | $Me_2CO$ | 6 | 50 | 19(*R*) | 2 |
| 2 | | Lipase from wheat germ | TBME | 20 | 46 | 47(*R*) | 4 |
| 3 | | Lipase from wheat germ | $Et_2O$ | 24 | 42 | 43(*R*) | 3 |
| 4 | | Lipase from *P. cepacia* (PcL) | $Me_2CO$ | 4 | 26 | 77(*S*) | 10 |
| 5 | | Lipase from *P. cepacia* | TBME | 24 | 36 | >99(*S*) | 350 |
| 6 | | Lipase from *P. cepacia* | $Et_2O$ | 24 | 28 | >99(*S*) | 290 |
| 7 | | PcL-Celit®545 | TBME | 5 | 17 | 45 | 3 |
| 8 | | PcL-chitosan, EDC | | 5 | 47 | 80 | 19 |
| 9 | | PcL-chitosan, EDC, GA | | 5 | 41 | 81 | 17 |
| 10 | | PcL-silica gel, cyanuric chloride | | 4 | 44 | 9 | 1 |
| 11 | | PcL-Zol-Gel AK, Sigma product | | 4 | 70 | 41 | 8 |
| 12 | | PcL-Zol-Gel, PTMS, Tween®80 | | 5 | 46 | 75 | 13 |
| 13 | | PcL-Zol-Gel, PTMS, PVA | | 5 | 28 | >99 | 290 |
| 14 | | PcL-Zol-Gel, L-Ph-O | | 5 | 86 | 15 | 3 |

[a] Determined by HPLC on a reverse phase column. Isolated yield in brackets.
[b] Ee determined by HPLC on a Chiralcel OD-H column. *E*-values calculated according to Chen et al.[24]

immobilization on chitosan, adsorption on Celite®545, and inclusion of a zole–gel matrix. Application of immobilized PcL with EDC hydrochloride and zole–gel matrix gave product (*R*)-**2** in moderate enantioselectivity (Table 2, entries 8, 9, and 12). However, the reaction time was substantially shorter when conducted with unimmobilized PcL. Immobilization of PcL with zole–gel matrix supported with polyvinyl acetate and propyl trimethoxysilane triggered enantioselectivity on level of 290 (Table 2, entry 13).

From an economical point of view, biotransformations using home made liver acetone powders (LAP)[17] are very important, because these biocatalysts are readily available and when used as substrates, accept a broad range of compounds.[18–20] For the next set of experiments, liver acetone powders (LAPs) were prepared according to a previously published protocol.[22] Fast TLC screening showed that crude powders obtained from pig (PLAP), rabbit (RLAP), chicken (CLAP), turkey (TLAP), and bovine (BLAP) livers are good biocatalysts for this enzymatic reaction. These enzymes were used for the model enzymatic kinetic resolution of *rac*-**3** performed in phosphate buffer (pH 8) containing 20% (v/v) of acetone. The progress of the enzymatic reactions was monitored by HPLC. The product obtained was separated and its enantiomeric excess was determined using HPLC. The results are summarized in Table 3.

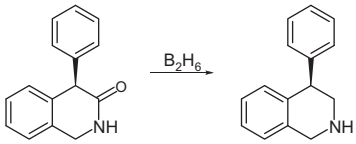
The liver acetone powders obtained from pig, chicken, and bovine LAPs were moderate biocatalysts and showed fair enantioselectivity (19–60% ee; Table 3, entries 1, 2, and 4). Better results were achieved when rabbit acetone liver powder was used and product was obtained in good yield and enantiomeric excess (Table 3, entry 5).

It is noteworthy that in this case, the obtained product possessed the opposite absolute configuration. The best result was reached when turkey LAP was used. In this case very good yield and excellent enantiomeric excess ($E$ >500) were achieved (Table 3, entry 3). The absolute configuration of compound **2** was assigned

**Table 3**
Enzymatic kinetic resolution of **3**

| Entry | Enzyme | $c$[a] (%) | ee[b] (%) | Conf. | $E$ |
|---|---|---|---|---|---|
| 1 | PLAP | 62 | 47 | (*S*) | 6.1 |
| 2 | CLAP | 62 | 60 | (*S*) | 17 |
| 3 | TLAP | 45 | 99 | (*R*) | >500 |
| 4 | BLAP | 58 (53) | 19 | (*R*) | 2 |
| 5 | RLAP | 41 | 84 | (*R*) | 21 |

[a] Determined by HPLC on a reverse phase column. Isolated yield in brackets.
[b] Ee determined by HPLC on a Chiralcel OD-H column. *E*-values calculated according to Chen et al.[24]




(*R*)-(−)-**2** (*R*)-(+)-**1** $[\alpha]_D$ = +1.2

**Scheme 3.** Reduction of lactam **2** leading to amine **1**.

by chemical correlation after reduction to 4-phenyl-1,2-dihydro-2*H*-isoquinolin **1** (Scheme 3). The positive value of the specific rotation was compared to the published data[23] and confirmed its (*R*)-configuration.

## 3. Conclusion

Studies on the synthesis of enantiopure THIP scaffold **1** based on a stereoselective Friedel–Crafts cyclization were performed and proved to be completely inefficient. Therefore, a new approach was proposed based on the enzymatic kinetic resolution of α-acetoxyamides which are readily available from their respective lactams. Our results clearly indicate that 2-acetyl-4-aryl-1,4-dihydro-2*H*-isoquinolin-3-ones are good substrates for hydrolases and the target compounds were obtained in excellent enantioselectivity upon application of native and immobilized enzymes. The procedure presented is simple, efficient, and can be readily extended to other substrates. This is a new and parallel approach to already known protease hydrolysis protocols.

## 4. Experimental

The HPLC analyses were performed on a Chiralcel 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.[13] All the chemicals were obtained from commercial chemical sources. The solvents were of analytical grade.

### 4.1. Immobilization of enzymes on Celite® 545

To a solution of supernatant (0.2 ml) in 50 mM of phosphate buffer (pH 7.4, 0.8 ml) was added Celite® 545 and stirred for

30 min at room temperature and dried over vacuum. The dry immobilizate was preserved at 4 °C.

### 4.2. Immobilization of enzymes in sol–gel matrix

Supernatant with appropriate addition: Tween® 80 (0.18 ml) and L-phenylalanine (20 mg) were mixed and then added to a solution of polyvinyl alcohol (100 μl, 4% v/v), sodium fluoride (50 μl, 1 M), and isopropyl alcohol (0.1 ml) and stirred. Next, alkyl silane (PTMS or *i*-BTMS) (2.5 mmol) and tetramethoxysilane (0.5 mmol, 75 μl) were added and stirred for 15 s. The mixture was left to dry in an open tube at room temperature. The obtained gel was washed with water (10 ml), isopropyl alcohol 10 ml), and *n*-pentane (10 ml). The gel was crumbled and the immobilizate was left to dry in an open tube at room temperature.

### 4.3. Immobilization of enzymes on chitosan with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide chlorohydride (EDC)

To the solution of 1 M sodium hydroxide containing 26% (v/v) ethyl alcohol was added dropwise chitosan 3% (v/v) in 1% (v/v) acetic acid and stirred. The mixture was then left for 3 h in room temperature. Chitosan was filtered and washed with water (500 ml).

Dry chitosan (114 mg) was placed in 3 ml of a 0.75% (v/v) solution of EDC in 25 °C. After 10 min the bed was separated, washed with water, and added to supernatant (0.8 ml) at room temperature for 1 h. The catalyst was then separated and washed with water (10 ml).

### 4.4. Preparation of cyclisation precursors

#### 4.4.1. (1*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl acetate (*R*)-6

*Procedure 1*. To a solution of (*R*)-*O*-acetoxymandelic acid (200 mg, 1 mmol) in anhydrous dichloromethane (4 ml) 1-hydroxybenztriazole (153 mg, 1.1 mmol) and 1,3-dicyclohexylcarbodiimide (233 mg, 1.1 mmol) were added. The mixture was cooled to 10 °C, then a solution of benzylamine or 4-methoxybenzylamine (1.1 mmol) in dichloromethane (1 ml) was added. The mixture was then stirred for 24 h at 20 °C. Dichloromethane (10 ml) was added and the residue of the carbamide was separated. The organic phase was washed with citric acid (10%, 3 × 10 ml), saturated sodium bicarbonate (3 × 10 ml), and brine (3 × 10 ml). The organic phase was dried over anhydrous magnesium sulfate and solvent was evaporated under vacuum. The crude was purified by crystallization from ethyl acetate/*n*-hexane. Product (*R*)-**6** was isolated in 68% yield; mp 90°C (ethyl acetate/*n*-hexane); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.28 (t, $J$ = 7.2 Hz, 3H), 2.20 (s, 3H), 4.06 (d, $J$ = 5.3 Hz, 2H), 4.22 (q, $J$ = 7.1 Hz, 2H), 6.13 (s, 1H), 6.72 (s, 1H), 7.30–7.52 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.5, 21.4, 41.6, 62.1, 75.7, 127.8, 129.0, 129.4, 168.7, 169.3, 169.7; $[\alpha]_D^{22} = -112.9$ (*c* 1.0, $CHCl_3$)[26] >99% ee (HPLC Chiralcel OD-H); enantiomeric excess was defined by HPLC with a chiral column; *n*-hexane/*i*-propanol; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_R$ = 6.32 min.

#### 4.4.2. (1*R*)-2-[(4-Methoxybenzyl)amino]-2-oxo-1-phenylethyl acetate (*R*)-7

Prepared according to procedure 1. Product (*R*)-**7** was isolated in 76% yield; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.15 (s, 3H), 3.79 (s, 3H), 4.30–4.50 (m, 2H), 6.09 (s, 1H), 6.40 (br s, 1H), 7.00 (d, $J$ = 8.6 Hz, 4H), 7.30–7.50 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): d 21.3, 43.2, 55.6, 75.8, 114.4, 127.7, 129.1, 129.3, 129.4, 130.0, 135.8, 159.4, 168.4; $[\alpha]_D^{22} = -101.5$ (*c* 1.0, $CHCl_3$) >99% e.e. (HPLC Chiralcel OD-H); Parametres of HPLC analysis: chiral column Chiralcel OD-H; *n*-hexane/*i*-propanol; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_R$ = 8.07 min.

#### 4.4.3. *N*-Benzyl-2-hydroxy-2-phenylethanamide *rac*-8

*Procedure 2*. To a solution of 2-(benzylamino)-2-oxo-1-phenylethyl acetate *rac*-**6** (1.4 mmol) in methanol (1 ml), sodium hydroxide (2 M, 1.5 ml) was added. The mixture was placed in an ultrasonic washer for 30 min. The alcohol was evaporated under vacuum, and the residue was acidified with hydrochloric acid (10%) to pH 7. The aqueous phase was extracted with chloroform (3 × 10 ml). The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was evaporated under vacuum. The crude product was purified by crystallization from ethyl acetate/*n*-hexane to obtain 0.4 g of the product in 90% yield; mp 95 °C, $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.90 (s, 1H), 4.52 (d, $J$ = 5.8 Hz, 2H), 5.13 (s, 1H), 6.75 (br s, 1H), 7.20–7.60 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 43.8, 74.5, 127.1, 127.9, 128.9, 129.0, 129.1, 137.9, 139.7, 172.4; IR ($cm^{-1}$): 1620 (C=O), 3215, 3277; HPLC analysis: chiral column Chiralcel OD-H; *n*-hexane/*i*-propanol; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 6.03 min.; $Rt_{(S)}$ = 6.43 min.

#### 4.4.4. (2*R*)-*N*-Benzyl-2-hydroxy-2-phenylethanamide (*R*)-8

Prepared according to procedure 2. Product (*R*)-**8** was isolated in 91% yield; mp 94–96 °C; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.90 (s, 1H), 4.52 (d, $J$ = 5.8 Hz, 2H), 5.13 (s, 1H), 6.75 (br s, 1H), 7.20–7.60 (m, 10H); IR ($cm^{-1}$): 1622 (C=O), 3220, 3281; $[\alpha]_D^{22} = -76.9$ (*c* 1.0, $CHCl_3$)[26]; HPLC analysis: chiral column Chiralcel OD-H, *n*-hexane/*i*-propanol; 6/4; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 6.03 min.

#### 4.4.5. (1*R*)-2-(Benzylamino)-2-oxo-1-phenylethyl methanesulfonate (*R*)-9

*N*-Benzyl-(2*R*)-hydroxyphenylacetamide (*R*)-**8** (568 mg, 2.35 mmol) was dissolved in anhydrous dichloromethane (5 ml) after which triethylamine (1.3 ml, 9 mmol) was added. The mixture was cooled to 0 °C and methane sulfonyl chloride (0.3 ml, 3.10 mmol) was added. The mixture was stirred at reflux, then the solvent was evaporated under vacuum. The crude product was purified by gel chromatography (*n*-hexane/ethyl acetate) to obtain 743 mg of the product in 99% yield; AE: calculated $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39, obtained: C, 60.09; H, 5.41; N, 4.25; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.88 (s, 3H), 4.42–4.68 (m, 2H), 6.00 (s, 1H), 6.86 (br s, 1H), 7.25–7.60 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 39.7, 43.9, 81.8, 128.1, 128.1, 129.2, 129.5, 130.3, 134.3, 167.0, 202.9; $[\alpha]_D^{22} = -108.8$ (*c* 0.6, $CHCl_3$); HPLC analysis: chiral column Chiralcel OD-H, *n*-hexane/*i*-PrOH; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 8.48 min.

#### 4.4.6. *rac*-*N*-Benzyl-2-chloro-2-phenylethanamide *rac*-10

*Procedure 3*. To a solution of *N*-benzyl-2-hydroxyphenylacetamide *rac*-**8** (1.045 g, 4.33 mmol) in anhydrous dichloromethane (5 ml) cooled to 0 °C, thionyl chloride (1 ml, 13 mmol) was added. The mixture was then stirred for 1.5 h at room temperature. The solvent was evaporated under vacuum. The crude product was purified by crystallization from *n*-hexane/ethyl acetate to obtain 1.125 g of in 85% yield; mp 95 °C (ethyl acetate/*n*-hexane) [Lit. 94.5–96.5]; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.59 (d, $J$ = 5.6 Hz, 2H), 5.50 (s, 1H), 7.10 (br s, 1H), 7.20–7.60 (m, 10H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 44.3, 62.0, 128.0, 128.1, 129.1, 129.2, 129.4, 137.3, 137.7, 167.6; IR (KBr) $cm^{-1}$: 1537, 1650 (C=O), 3336.

#### 4.4.7. (2*R*)-*N*-Benzyl-2-chloro-2-phenylethanamide (*R*)-10

Prepared according to procedure 3. Product was obtained in 83% yield; mp 91–93 °C (ethyl acetate/*n*-hexane); AE: calculated $C_{15}H_{14}ClNO$: C, 69.37; H, 5.43; N, 5.39, obtained: C, 69.15; H, 5.55; N, 5.16; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.59 (d, $J$ = 5.6 Hz, 2H), 5.50 (s, 1H), 7.10 (br s, 1H), 7.20–7.60 (m, 10H); $[\alpha]_D^{22} = -59.9$ (*c* 0.55, $CHCl_3$); HPLC analysis: chiral column Chiralcel OD-H, *n*-hexane/*i*-propanol; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 6.35 min.

#### 4.4.8. 2-Chloro-*N*-(4-methoxybenzyl)-2-phenylethanamide *rac*-11

Prepared according to procedure 3. Product *rac*-**11** was obtained in 90% yield; AE: calculated $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.57; N, 4.83, obtained: C, 66.41; H, 6.02; N, 5.82; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.8 (s, 3H), 4.43 (d, $J$ = 5.6 Hz, 2H), 5.40 (s, 1H), 6.90 (br s, 1H), 7.10 (dd, $J$ = 8.6 Hz, 4H), 7.30–7.50 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 43.9, 55.6, 62.1, 114.5, 128.0, 129.2, 129.4, 157.6.

#### 4.4.9. (2*R*)-2-Chloro-*N*-(4-methoxybenzyl)-2-phenylethanamide (*R*)-11

Prepared according to procedure 3. Product (*R*)-**11** was obtained in 83% yield; AE: calculated $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.57; N, 4.83, obtained: C, 66.41; H, 5.82; N, 4.82; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.8 (s, 3H), 4.43 (d, $J$ = 5.6 Hz, 2H), 5.40 (s, 1H), 6.90 (br s, 1H), 7.10 (dd, $J$ = 8.6 Hz, 4H), 7.30–7.50 (m, 5H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 43.9, 55.6, 62.1, 114.5, 128.0, 129.2, 129.4, 157.6; $[\alpha]_D^{22} = -66.4$ ($c$ 0.55, $CHCl_3$); HPLC analysis: chiral column Chiralcel OD-H; *n*-hexane/*i*-propanol; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 5.89 min.

#### 4.4.10. 4-Phenyl-1,4-dihydroisoquinolin-3(2*H*)-one *rac*-2

To a solution of *N*-benzyl-2-chlorophenylethanamide *rac*-**10** (500 mg, 1.2 mmol) in anhydrous 1,2-dichoroethane (5 ml) cooled to 0 °C, zinc chloride(II) (981 mg, 7.2 mmol) was added. The mixture was stirred at reflux for 36 h and then cooled to 0 °C. Next, distilled water (10 ml) was added. The mixture was extracted with chloroform. The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was evaporated under vacuum. The crude product was purified by gel chromatography with benzene to obtain 267 mg of *rac*-**2** in 65% yield; mp 198 °C (benzene) [Lit. 199–201][21] AE: calculated $C_{15}H_{13}NO + 0.5\ H_2O$: C, 77.56; H, 6.08; N, 6.03, obtained: C, 77.63; H, 5.83; N, 6.10%; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.55 (dd, $J$ = 5.6 Hz, 2H), 4.88 (s, 1H), 7.10 (br s, 1H), 7.12–7.50 (m, 9H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 45.4, 52.8, 125.8, 127.4, 127.5, 128.2, 129.2, 131.9, 173.0; HPLC analysis: chiral column Chiralcel OD-H; *n*-hexane/*i*-propanol; 6/4; 0.8 ml/min; 223 nm; $Rt_{(S)}$ = 11.22 min.; $Rt_{(R)}$ = 12.25 min.; IR (KBr) cm$^{-1}$: 1633, 3251; HR EI-MS $m/z$ $C_{15}H_{13}NO$ $[M]^{+\cdot}$: calculated 223.099; obtained: 223.099.

#### 4.4.11. (4*R*)-4-Phenyl-1,4-dihydroisoquinolin-3(2*H*)-one (*R*)-2

To a solution of appropriate amide (0.72 mmol) in anhydrous dichloromethane (1 ml) cooled to the appropriate temperature, sulfuric acid (1 ml) was added. The mixture was stirred for 4 h, then poured into crushed ice, neutralized with potassium carbonate, and extracted with chloroform (3 × 5 ml). The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was evaporated under vacuum. The product was purified by gel chromatography with *n*-hexane/ethyl acetate. HPLC analysis: chiral column Chiralcel OD-H; *n*-hexane/*i*-propanol; 6/4; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 12.25 min.

#### 4.4.12. 7-Methoxy-4-phenyl-1,4-dihydroisoquinolin-3(2*H*)-one *rac*-12

To a solution of 2-chloro-*N*-(4-methoxybenzyl)-2-phenylethantamide *rac*-**11** (180 mg, 0.61 mmol) in anhydrous 1,2-dichloroethane (10 ml) cooled to 0 °C, zinc chloride (244 mg, 1.8 mmol) was added. The mixture was stirred at reflux for 7 h. Next, it was cooled to 0 °C, and distilled water (10 ml) was slowly added. The aqueous phase was extracted with chloroform (3 × 5 ml). The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was evaporated under vacuum. The product was purified by gel chromatography with *n*-hexane/ethyl acetate to obtain 55 mg in 36% yield; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.76 (s, 3H), 4.35 (dd, $J$ = 5.6 Hz, 2H), 4.78 (s, 1H), 6.80 (br s, 1H), 6.90-7.450 (m, 8H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 25.2, 34.2, 52.9, 113.6, 113.7, 126.9, 127.5, 128.2, 128.6, 129.0, 136.8, 138.6, 159.5, 172.8; HPLC analysis: chiral column Chiralcel OD-H; *n*-hexane/*i*-propanol; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 13.73 min.; $Rt_{(S)}$ = 15.00 min.; IR (KBr) cm$^{-1}$: 1629, 3251; HR EI-MS $m/z$ $C_{16}H_{15}NO_2$ $[M]^{+\cdot}$: calculated 253.110; measured: 253.109.

#### 4.4.13. (4*R*)-7-Methoxy-4-phenyl-1,4-dihydroisoquinolin-3(2*H*)-one (*R*)-12

To a solution of (2*R*)-(−)-chloro-*N*-(4-methoxybenzyl)-2-phenylethanamide (*R*)-**11** (174 mg, 0.6 mmol) in 1,2-dichloroethane (10 ml) cooled to 0 °C, zinc chloride(II) (3 equivalents) was added (Table 1, entry 7). The mixture was stirred at 80 °C, then it was cooled to 0 °C and hydrochloric acid was added (10%, 10 ml). The aqueous phase was extracted with chloroform (3 × 5 ml). The combined organic phases were dried over anhydrous magnesium sulfate and the solvent was evaporated under vacuum. The product was purified by gel chromatography with *n*-hexane/ethyl acetate. HPLC analysis: chiral column Chiralcel OD-H; *n*-hexane/*i*-propanol; 6/4; v/v; 0.8 ml/min; 223 nm; $Rt_{(R)}$ = 13.73 min.

#### 4.4.14. 2-Acetyl-4-phenyl-1,4-dihydro-2*H*-izoquinolin-3-one *rac*-3

To a solution of 4-phenyl-1,4-dihydro-2*H*-izoquinolin-3-one *rac*-**2** (100 mg, 0.45 mmol) in dichloromethane (3 ml) were added potassium carbonate (100 mg) and 4-dimethylaminepyridine (10 mg) at room temperature. Next, acetyl chloride was added (0.1 ml, 1.35 mmol) and the solution was stirred at reflux for 3 h. The mixture was cooled to 0 °C, quenched with HCl (5%) to pH 1. The aqueous phase was extracted with chloroform (3 × 5 ml). The combined organic phase was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by gel chromatography by *n*-hexane/ethyl acetate as eluent. The product was isolated in 77% yield (92 mg). $R_f$ = 0.48 (*n*-hexane/ethyl acetate; 1/1; v/v); Elemental analysis: calculated $C_{17}H_{15}NO_2 + 1.3\ H_2O$: C, 70.72; H, 6.14; N, 4.85, measured: C, 70.67; H, 6.20; N, 4.35; 1H NMR (200 MHz, $CDCl_3$): $\delta$ 2.68 (s, 3H), 4.92 (dd, $J$ = 16.2 Hz, 2H), 5.11 (s, 1H), 7.15–7.53 (m, 9H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 27.7, 45.6, 56.5, 126.6, 128.1, 128.2, 128.3, 128.4, 128.8, 129.2, 132.9, 134.9, 135.4, 172.6, 173.2; HR EI-MS $m/z$ for $C_{17}H_{15}NO_2$ $[M]^{+\cdot}$: calculated 265.110; measured:265.109.

#### 4.4.15. 4-Phenyl-1,4-dihydro-2*H*-isoquinoline (*R*)-1

To a solution of 4-phenyl-1,4-dihydro-2*H*-izochinolin-3-one (*R*)-**2** (206 mg, 0.924 mmol, 47% ee) in dry tetrahydrofurane was added a solution of diborane complex in tetrahydrofuran (1 M, 4 ml, 1.84 mmol). The mixture was stirred at reflux for 6 h. HCl (6 M, 10 ml) was added, and the solvent was evaporated. The aqueous phase was washed with chloroform (3 × 5 ml), then basified with sodium hydroxide (6 M), and ethyl acetate was added (10 ml). The organic phase was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by gel chromatography with methylene chloride/methanol (24/1 = v/v) to obtain 70 mg of (*R*)-**1** in 36% yield as a pale yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.85 (s, 1H), 3.13 (dd, $J$ = 12.8, 6.5 Hz, 1H), 3.44 (dd, $J$ = 12.8, 5.3 Hz, 1H), 4.00–4.20 (m, 3H), 6.88 (d, $J$ = 7.0 Hz, 1H), 7.10–7.30 (m, 8H); HR EI-MS m/z for $C_{15}H_{15}N$ $[M]^{+\cdot}$: calculated 209.120; measured 209.119; IR (film): 1450, 2808, 3222; $[\alpha]_D^{22} = +1.2$ ($c$ 1.0, $CH_3OH$) {Lit. $[\alpha]_D$ = +11.1 ($c$ 1.0, $CH_3OH$) for the (*R*)-enantiomer}.[25]

#### 4.4.16. (4*R*)-7-Methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (*R*)-13

Thirty-one grams of (*R*)-**13** in 16% yield as a yellow oil was obtained; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.80 (s, 1H), 3.13 (d, $J$ = 6.5 Hz,

2H), 3.44 (dd, $J$ = 12.8, 5.3 Hz, 2H), 3.73 (s, 3H), 4.00–4.13 (m, 1H), 7.00 (d, $J$ = 7.0 Hz, 1H), 7.20–7.65 (m, 7H); $^{13}$C NMR (50 MHz, $CDCl_3$): d 45.4, 48.1, 52.3, 55.5, 113.7, 114.3, 126.7, 126.8, 127.1, 127.2, 127.3, 128.1, 128.7, 129.1, 129.4; HR EI-MS $m/z$ dla $C_{16}H_{18}NO$ $[M]^{+\cdot}$: calculated 240.139; measured 240.138.

### 4.4.17. Enzymatic kinetic resolution of *rac*-3

To a solution of 2-acetyl-4-phenyl-1,4-dihydro-2*H*-izoquinolin-3-one (*rac*-**3**) (35 mg, 0.12 mmol) in an acetone/buffer pH 8 mixture (10 ml, 1/4 = v/v), the enzyme was added. The mixture was then stirred for 2 h at room temperature. The enzyme was separated and washed with chloroform (3 × 2 ml) and phosphate buffer pH 8 (3 × 2 ml). The phases were separated and the aqueous phase was extracted with chloroform (3 × 2 ml). The combined organic phases were dried over magnesium sulfate, and then the solvent was evaporated under vacuum. The crude product was purified by gel chromatography.

## Acknowledgments

This work was supported by the State Committee for Scientific Research, KBN Grant PBZ-MIN-007/P04/2003 and by project 'Biotransformations for pharmaceutical and cosmetics industry' No. POIG.01.03.01-00-158/09-01 part-financed by the European Union within the European Regional Development Fund.

## References

1. Toome, V.; Blount, J. F.; Grethe, G.; Uskokovic, M. *Tetrahedron Lett.* **1970**, *11*, 49–52.
2. Cherpillod, C.; Omer, L. M. O. *J. Int. Med. Chem.* **1981**, *9*, 324–329.
3. Kihra, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543–1546.
4. Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2447–2453.
5. (a) Venkov, A. P.; Vodenicharov, D. M. *Synthesis* **1990**, 253; (b) Coote, J. S.; Davies, S. G. *J. Chem. Soc. Chem. Comm.* **1988**, 648–649; (c) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. J. *Chem. Soc., Perkin Trans. 1* **1989**, 2223–2228; (d) Wuenschen, B.; Nerdinger, S. *Eur. J. Org. Chem.* **1999**, 503–517; (e) Ruchirawat, S.; Tontoolarug, S.; Sahakitpichan, P. *Heterocycles* **2001**, *55*, 635; (f) Wang, S.; Onaran, M. B.; Seto, C. T. *Org. Lett.* **2010**, *12*, 2690–2693; (g) Coote, S. J.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Chem. Asian J.* **2010**, *5*, 589–604.
6. Dandridge, P. A.; Kaiser, C.; Brenner, M.; Gaitanopoulos, D.; Davis, L. D.; Webb, R. L.; Foley, J. J.; Sarau, H. M. *J. Med. Chem.* **1984**, *27*, 28–35.
7. Guillon, J.; Dallemagne, P.; Leveque, H.; Duval, R.; Rault, S. *Pharm. Sci.* **1997**, 325–327.
8. (a) Ulin, J.; Gee, A. D.; Malmborg, P.; Tedroff, J.; Långström, B. *Appl. Radiat. Isot.* **1989**, *40*, 171; (b) Kacztán, E. Z.; György, L.; Deák, G.; Seregi, A.; Dóda, M. *J. Med. Chem.* **1986**, *29*, 1189.
9. Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509–2516.
10. Tarby, C. M.; Kaltenbach, R. F., III; Huynh, T.; Pudzianowski, A.; Shen, H.; Ortega-Nanos, M.; Sheriff, S.; Newitt, J. A.; McDonnell, P. A.; Burford, N.; Fairchild, C. R.; Vaccaro, W.; Chen, Z.; Borzilleri, R. M.; Naglich, J.; Louis, J.; Lombardo, ; Gottardis, Marco; Trainor, G. L.; Roussell, D. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2095–2100.
11. Yamashita, M.; Yamada, K.; Tomida, K. *J. Am. Soc.* **2004**, *126*, 1954–1955.
12. Philippe, N.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Org. Lett.* **2000**, *2*, 2185–2188.
13. Philippe, N.; Denivet, F.; Vasse, J.; Santos, J.; Levacher, V.; Dupas, G. *Tetrahedron* **2003**, *59*, 8049.
14. Morgan, B.; Sarikonda, B. R.; Dodds, D. R.; Homman, M. J.; Vail, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3681–3690.
15. Aggarwal, V. K.; Astle, C. J.; Iding, H.; Wirz, B.; Rogers-Evans, M. *Tetrahedron Lett.* **2005**, *46*, 945–947.
16. Bonina, F. P.; Montenegro, L.; Trapani, G.; Franco, M.; Liso, G. *Inter. J. Pharm.* **1995**, *124*, 45–51.
17. Kobata, K.; Yoshikawa, K.; Kohashi, M.; Watanabe, T. *Tetrahedron Lett.* **1996**, *37*, 2784–2790.
18. Sanchez, R.; Luna, H.; Perez, H.; Manjarrez, N.; Solıs, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1399–1401.
19. Herdan, J.; Balilescu, M.; Cira, O. *J. Mol. Cat. A: Chemical* **1996**, *107*, 409–414.
20. Yoon, J. H.; Rhee, J. S. *Carbohydr. Res.* **2000**, *327*, 377–383.
21. Petrov, O. S.; Ognyanov, V. I.; Mollov, N. M. *Synth. Commun.* **1987**, 637–638.
22. Basavaian, D.; Dharma, R. P. *Synth. Commun.* **1994**, *24*, 925.
23. Kihara, M.; Ikeuchi, M.; Adachi, S.; Nagao, Y.; Moritoki, H.; Yamaguchi, M.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543–1546.
24. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
25. Kihara, M.; Ikeuchi, M.; Adachi, S.; Nagaro, Y.; Moritoki, H.; Taira, Z. *Chem. Pharm. Bull.* **1995**, *43*, 1543.
26. Choi, D.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **1996**, *4*, 2105–2114.