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Stereoselective synthesis of optically active 1-benzyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indol-7-yl acetate and 1-benzyl-7-hydroxy-6,6-dimethyl-6,7-dihydro-1*H*-indol-4*(5H)*-one through lipase-catalyzed esterification and transesterification processes

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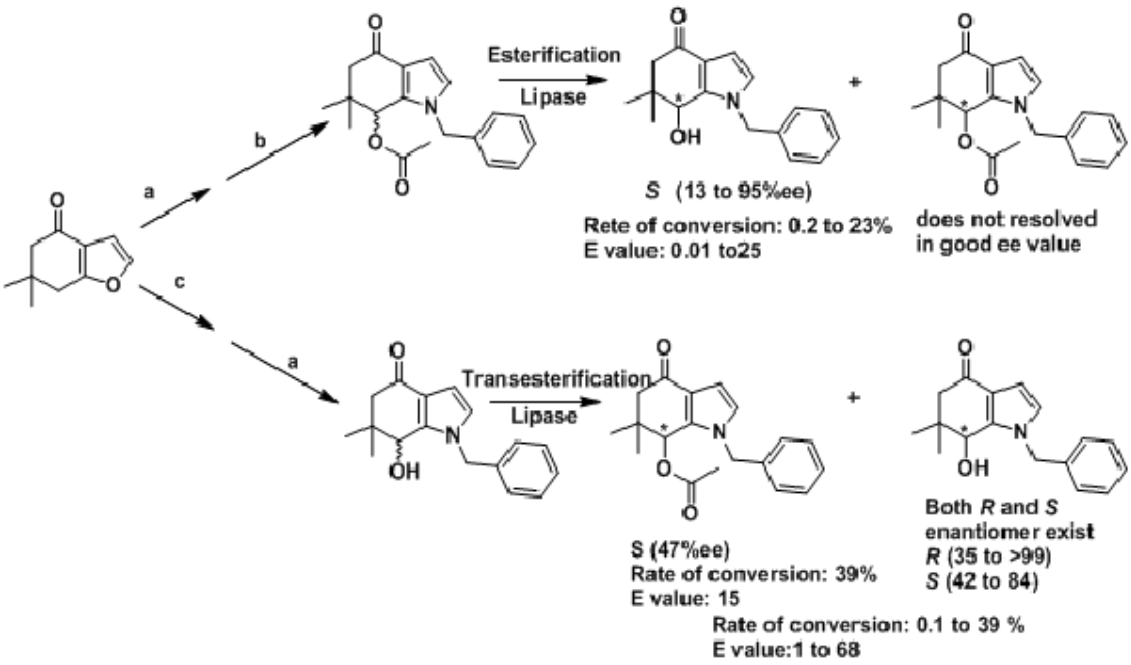

a) Benzylamine, EtOH/H_2O, heat; b) $KMnO_4$, Benzene/ AcOH, reflux; c) $Mn(OAc)_3$, AcOH, benzene, reflux

Stereoselective synthesis of optically active 1-benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indol-7-yl acetate and 1-benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one through lipase-catalyzed esterification and transesterification processes 71042

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Abstract

The enantioselective synthesis of 1-benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indol-7-yl acetate **(4)** and 1-benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one (**5**), which are important intermediates in pharmaceutical industry, was carried out for the first time, both by enzyme-mediated hydrolysis and transesterification reactions with high enantiomeric excesses in the presence of various lipases. In either case S enantiomer of (**5**) was obtained with high enantiomeric excesses at low rate of conversion and E value. However, R enantiomer of (**5**) was also obtained by transesterification reaction with high optical purity. In the transesterification reaction of (**rac-5a**) with several lipases in different solvent systems in the peresence of DMAP as an additive and vinyl acetate, E value of the reaction were raised for some enzyme and solvent combination (THF-MJL with >99 %ee and E value:41; for acetonitrile–MJL with 91 % ee and E value:51; for acetonitrile-Amano with 99 %ee, E value:68) showed R-(**5)** selectivity. Furthermore the conversion value was also increased. The best conversion of the transesterification reaction was 39% with DMSO-HPL showed 73% ee and E value:15 for R-(**5**) selectivity and 47% for S-(**4**) selectivity. The two procedures can therefore be considered as complementary with respect to the final composition.

Keywords: indole; enzyme-mediated hydrolysis; transesterification

1. Introduction

Enzymatic catalysis has recently been successfully used for the optical resolution of different extremely functionalized chiral molecules such as amino acids, diols, diesters, and hydroxy acids. Surprisingly very little notice has been paid to the enzymatic resolution of chiral tetrahydro indol derivatives in spite of their importance as products have become important targets in the pharmaceutical industry[1, 2]. The indol derivatives are useful not only as akey intermediate for synthesis of Pindolol, which is an excellent drug prevention and treatment of arrhythmia, but also as an intermediate for preparing various kinds of drugs, such as antibiotics, antipsycotic agents and blood platelet aggregation inhibitors. The biological activity of 4-oxo-tetrahydroindol derivatives and their structural relationship to indoles make these compounds important targets in drug industry[3, 4].

In our previous investigations, we reported the preparation of enantiopure α′-acetoxy and α′-hydroxy-4-oxo-tetrahydroindole derivatives using lipase enzyme-mediated hydrolysis

reactions [5]. To the best of our knowledge, there has been no research carried out on the kinetic resolution of γ-acetoxy-4-oxo-tetrahydroindole and γ-hydroxy-4-oxo-tetrahydroindole derivatives. It is therefore of notable interest to improve enabled methods for the preperation of these indole derivatives. In this paper, we report the synthesis of the enantiomers of γ-acetoxy and γ-hydroxy-4-oxo-tetrahydroindole derivatives, using enantioselective esterification and transesterification reactions.

2. Experimental

2.1. Materials and methods

NMR spectra were obtained on a Bruker Avance III spectrometer at 500 MHz. Chemical shifts, δ, are reported in parts per million relative to $CDCl_3$ (^{1}H:δ=7.27), $CDCl_3$ (^{13}C:δ=77.0) and CCl_4 (^{13}C:δ=96.4) as internal standards. Column chromatography was performed on silica gel 60 (40-63 μm). TLC was carried out on silica gel, $60F_{254}$ (Merck), and the spots were observed with UV light (λ=254 nm). IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR Spectrometer. Enantiomeric excesses were identified by HPLC analysis using an Agilent 1100 Series supplied with a suitable chiral phase column. The lipases CCL (lipase from *Candida cyclindracea*) BioChemika (62316), PFL (lipase from *Pseudomonas fluorecens*) BioChemika (95608), CAL (lipase from *Candida antarctica*) BioChemika (62299), HPL (Hog pancreas lipase) BioChemika (62300), MJL (lipase from *Mucor javanicus*) BioChemika (62304), PCL (lipase from *Pseudomonas cepacia*) (62309), RAL (*Rhizopus arrhizus* lipase) BioChemika (62305) were taken from a Fluka lipase basic kit (62327). Amano PS, from *Burkholderia cepacia (Pseudomonas cepacia)* was obtained from Aldrich (534641). Optical rotations were determined with a Dr.Kernchen elektronic-automation Sucromatdigital automatic saccharimeter. Mass spectra were recorded with an Agilent 7890A GC system using an Agilent 5975C VLMSD having a triple-axis detector with an HP-5 capillary GC column (30 m length, 0.32 mmID, 0.25 μm film thickness).

2.2. General procedure for $Mn(OAc)_3$ oxidation

7.5 mmol $Mn(OAc)_3$ in 100 ml benzene-acetic acid (10:1) were refluxed. To this solution, 1.8 mmol of benzofuranone was added and reflux was continued for 37-40 h. After all of the starting material was consumed, the reaction mixture was extracted with ether and the organic layer was washed with brine. The resulting organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (1:5 EtOAc:hexane) to yield acetoxy-benzofuranone.

2.3. General procedure for the synthesis of indole derivatives

Alkylamine (18,7 mmol) and benzofuranone (6,25 mmol) in 20% aqueous ethanol (5 ml) was heated at 145-150°C in a sealed tube for 12 hours [14]. The reaction mixture was poured into water, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under vacuum. The crude products were purified by column chromatography (1:2 EtOAc:hexane) elution to yield the indole derivatives.

2.4. Procedure for the synthesis of 1-benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indol-7-yl-acetate

A solution of 3 mmol of $KMnO_4$ in 100 ml benzene-acetic acid (10:1) was stirred under reflux (Dean-Stark apparatus). When the purple color of $KMnO_4$ turns brown, 1 mmol of indole derivative was added and reflux was continued [16]. The reaction was monitored by TLC. After all the starting material was consumed, the reaction mixture was extracted with ether and the organic layer was neutralized with $NaHCO_3$. The resulting organic phase was dried over $MgSO_4$, concentrated and purified by column chromatography (1:6 EtOAc:hexane) to yield (25 %) of the γ-acetoxy-indole derivative.

2.5. General procedure for the lipase-catalyzed kinetic resolution

Lipase (200-300 mg) was dissolved in a phosphate buffer (pH=7,30 ml) and added to a solution of the pure substrate (0.5 mmol) in solvent (3 mL) and the reaction mixture left agitating at 37°C. Conversion (up to 50%) was monitored by TLC and HPLC. After this, the filtrate was extracted with chloroform, dried over $MgSO_4$, concentrated, and purified by column chromatography (1:2 EtOAc:hexane).

2.6. General procedure for the lipase-catalyzed transesterification in the presence of additives

A solution of *rac*-**5** (0.5 mmol) in solvent (1 ml) or without solvent was stirred at RT with vinyl acetate (10 mmol) and 2.5 mmol DMAP. To this solution, lipase (200-300 mg) was added and the reaction mixture left agitating at 37°C. The reaction was monitored by TLC and HPLC. When 50% conversion was attained, the reaction was terminated. After filtration, the filtrate was extracted with chloroform, dried over $MgSO_4$, concentrated, and separated by column chromatography (1:2 EtOAc:hexane).

*2.7. 1-Benzyl-6,7-dihydro-6,6-dimethyl-1H-indol-4(5H)-one (**3**)*

Yield: 888 mg, 56%, colourless crystals, (mp: 81°C). IR ($CHCl_3$): ν=1647, 2926 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.00 (s, 6H, CH_3), 2.29 (s, 2H, CH_2), 2.43 (s, 2H, CH_2), 4.98 (s, 2H, CH_2Ph), 6.52 (d, *J*=3.00 Hz, 1H, H-3), 6.57 (d, *J*=3.00 Hz, 1H, H-2), 6.94-7.29 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.64; 35.57; 35.75; 50.45; 51.77; 105.64; 120.04; 123.24; 126.35; 127.91; 128.07; 128.78; 128.98; 136.70; 142.70; 193.76

*2.8. 1-Benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indol-7-yl-acetate (**4**)*

Yield: 99.50 mg, 64%. IR ($CHCl_3$): ν=1657, 1737, 2967 cm^{-1}.^1H-NMR (500 MHz, $CDCl_3$): δ 0.98 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.83 (s, 3H, $COCH_3$), 2.20 (d, *J*=16.65 Hz, 1H, CH_2), 2.81 (d, *J*=16.65 Hz, 1H, CH_2), 5.13 (d, *J*=16.254 Hz, 1H, CH_2-Ph), 5.24 (d, *J*=16.254 Hz, 1H, CH_2-Ph), 5.83 (s, 1H, CHO), 6.65 (d, *J*=3.001 Hz, 1H, H-3), 6.75 (d, *J*=2.951 Hz, 1H, H-2), 6.95-7.35 (m, 5H, Ph). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 20.44; 25.64; 25.77; 38.78; 47.46; 50.57; 68.48; 105.99; 121.74; 125.20; 126.15; 127.78; 128.83; 137.03; 138.29; 170.54; 193.38. Anal.Calcd. for $C_{19}H_{21}NO_3$ (311.37): C, 73.29; H, 6.80; N, 4.50. Found: C, 72.15; H, 7.02; N, 4.42. GC/MS (m/z) 311.2 (M^+), 252.1, 213.1, 178.1, 168.1, 91.1

*2.9. 1-Benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one (**5**)*

Yield: 872 mg, 52%, colourless crystals (mp:156.6°C). IR ($CHCl_3$): ν=1644, 2961, 3312 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$) δ 0.90 (s, 3H, -CH_3), 1.10 (s, 3H, -CH_3), 2.08 (d, *J*=16.51 Hz, 1H, CH_2), 2.69 (d, *J*=16.55 Hz, 1H, CH_2), 4.33 (s, 1H, H-7), 5.14 (d, *J*=15.90 Hz, 1H,

CH_2Ph), 5.28 (d, *J*=15.95 Hz, 1H, CH_2Ph), 6.50 (d, *J*=3.00 Hz, 1H, H-3), 6.62 (d, *J*=3.05 Hz, 1H, H-2), 7.05-7.34 (m, 5H, Ph). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 25.25; 26.15; 39.64; 47.19; 50.56; 69.06; 69.09; 105.55; 119.83; 124.48; 126.66; 127.96; 128.95; 129.27; 137.06; 142.43; 194.52. Anal.Calcd for $C_{17}H_{19}NO_2$ (269.34): C, 75.81; H, 7.11; N, 5.20. Found: C, 75.11; H, 7.27; N, 5.16. GC/MS (m/z) 269.0 (M^+), 253.2, 197.1, 168.0, 106.0, 91.1

*2.10. (S)1-Benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one (**5**)*

(65.9 mg, 49%); $[\alpha]^{20}_D$= -2.68 (*c* 0.01, $CHCl_3$); HPLC: Chiralcell OD-H column, UV detection at 254 nm, eluent: hexane/2-propanol=98:2, flow 1.0 ml min^{-1} 20^{o}C retention time: 4.1 min.

*2.11. (R)1-Benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one (**5**)*

(68.9 mg, 51%); $[\alpha]^{20}_D$= +23.08 (*c*0.0013, EtOAc); HPLC: Chiralcell OD-H column, UV detection at 254 nm, eluent: hexane/2-propanol=98:2, flow 1.0 ml min^{-1} 20^{o}C retention time: 4.5 min.

*2.12. X-ray crystal structure analysis of **3** and (rac-**5a)***

For the crystal structure determination, a single crystal of compounds **(3)** and (*rac*-**5a)** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and oscillation scans technique with Δ*w* = 5º for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software [6]. The structures were solved by direct methods using SHELXS-97 [7] and refined by a full-matrix least-squares procedure using the program SHELXL-9721. H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for **(3)***: $C_{17}H_{19}NO$, crystal system, space group: monoclinic, $P2_1/n$; (no:14); unit cell dimensions: *a* = 6.3605(2), *b* = 24.8456(2), *c* = 9.0033(3) Å, *α*= 90, *β* = 93.088(2), *γ* = 90 Å; volume: 1420.73(8) Å^3; Z = 4; calculated density: 1.184 g/cm^3; absorption coefficient: 0.073 mm^{-1} ; *F*(000): 544; *θ*-range for data collection 2.4–26.4º ; refinement method: full matrix least-square on F^2; data/parameters: 1387/175; goodness-of-fit on F^2: 1.014; final *R*-indices [I > 2σ(I)]: R_1 = 0.056, wR_2 = 0.133; largest diff. peak and hole: 0.135 and -0.130 e Å^{-3}. CCDC: 895984. *Crystal data for (**rac-5)***: $C_{17}H_{19}NO_2$, crystal system, space group: monoclinic, $P2_1/n$; (no:14); unit cell dimensions: *a* = 12.2872(4), *b* = 7.3242(2), *c* =16.5399(5) Å, *α*= 90, *β* = 93.049(4), *γ* = 90 Å; volume: 1486.38(8) Å^3; Z = 4; calculated density: 1.204 g/cm^3; absorption coefficient: 0.079 mm^{-1} ; *F*(000): 576; *θ*-range for data collection 2.1–30.5º ; refinement method: full matrix least-square on F^2; data/parameters: 1857/184; goodness-of-fit on F^2: 1.016; final *R*-indices [I > 2r(I)]: R_1 = 0.0761, wR_2 = 0.171; largest diff. peak and hole: 0.178 and -0.195 e Å^{-3}. CCDC: 895813

Crystallographic data were deposited in CSD under CCDC registration number. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

3. Results and discussion

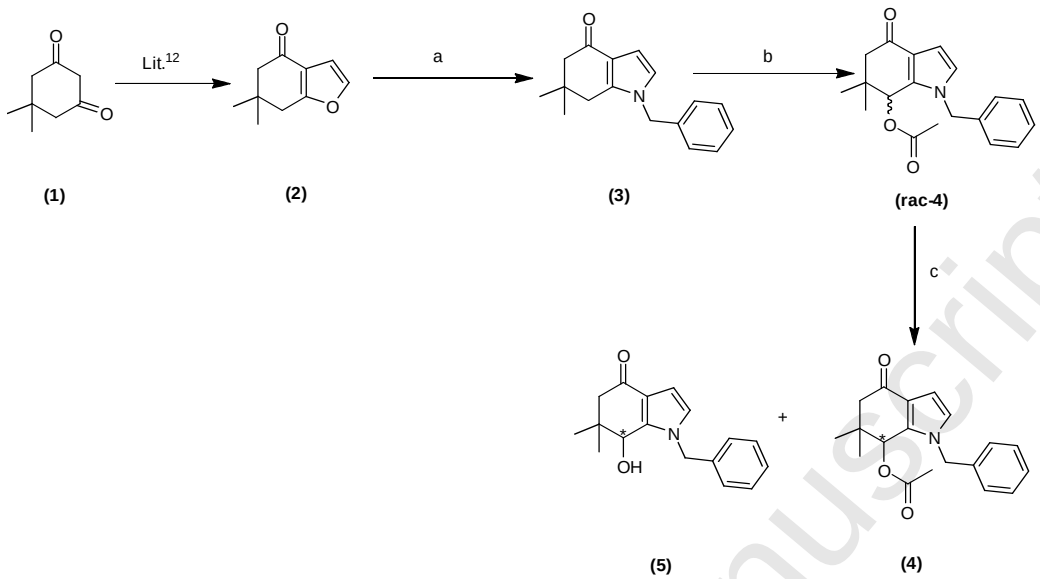
Commercially available 5,5-dimethyl-1,3-cyclohexanedione (**1**) were converted to the 6,7-dihydro-6,6-dimethyl benzofuranone (**2**) using the method of Matsumoto and Watanabe [8]. As an initial synthetic procedure (Scheme1), treatment of 6,7-dihydro-6,6-dimethyl benzofuranone (**2**) with benzylamine, in aqueous ethanol at 150ºC under pressure, [8,9] produces 1-benzyl-6,7-dihydro-6,6-dimethyl-1H-indol-4(5H)one (**3**) with a 56% yield. The single crystal structure of the compound (**3**) has been obtained.

Then the oxidation of 1-benzyl-6,7-dihydro-6,6-dimethyl-1H-indol-4(5H)-one (**3**) in the precence of 3 equivalents of $KMnO_4$ in benzene-acetic acid (10:1) medium is converted to γ-acetoxy-1-benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indole derivative (*rac*-**4**) in a 64% yield in the presence of a base according to the procedure in the literatüre [10] as shown in Scheme 1.

It is known that several studies on sources of $Mn(OAc)_3$ oxidation are designated in the literature. In general, manganese (III) acetate oxidations are identified by α′-regioselectivity [11,12,13].

In our previous work, we also showed the selective oxidations of enones by $Mn(OAc)_3$ oxidation [14]. Here, we tried this method for acetoxylation of our indol derivatives, however we have not any acetoxylation product. So we decided to try another method for acetoxylation of indol derivatives.

The selective oxidation of enones also leading to α′-acetoxy enones by potasium permanganate/carboxylic acid in an organic solvent with high yield according to Demir etal [10]. Herein we showed, for the first time, that potassium permanganate method in our indol system and we realize that, when we used $KMnO_4$/acetic acid method in our indole system, we got only γ-acetoxy product (*rac*-**4**) instead of α'-acetoxy product (Scheme 1).



Scheme1. a) Benzylamine, EtOH/H_2O, heat; b) $KMnO_4$, Benzene/AcOH, reflux; c) Enzyme, solvent, pH=7, 37°C

In the course of biotransformation, enzymatic catalysis has been recently succefully used for the optical resolution of various functionalized chiral molecules on a large scale such as alcohols, carboxylic acids and esters in organic solvents [15a]. During the course of our studies on the biotransformation of *rac*-**4** the screening reactions were examined with varied lipases.

In order to determine the enzyme that gives the best results, screening with seven different enzymes (Amano PS, CCL, PFL, CAL, HPL, MJL, and PCL) was carried out as shown in Table 1. They were tested in four different organic solvents (DMSO, THF, acetonitrile, toluene) for the kinetic resolution step.

In a distinctive experiments for enzymatic hydrolysis *rac*-**4** was dissolved in an organic solvent, a phosphate buffer (pH 7.0) was then added the mixture stirred at 37°C in the presence of an enzyme (Scheme 1).

The compound *rac*-**4** was also hydrolyzed chemically, to understand which peak in the HPLC spectra corresponds to the hydroxyl enone. This chemical hydrolysis was carried out using K_2CO_3 in methanol [15a,b]. The reaction was monitored by TLC and HPLC with a chiral column using *rac*-**4** and corresponding hydroxyl enone as a reference. When an approximately 50% conversion was obtained, the crude product was separated by flash column chromatography to ensure both enantiomers of 4 and 5.

According to the HPLC analysis the reaction provided enantioselectivity for the hydroxy indol (-)-**5** in 13 to 95% e.e. (Table 1)

For the preparative scale, the synthesis of **(-)-5** γ-hydroxy-1-benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indole (Table 1, entry 5) was used which was obtained the best result from PFL (*Pseudomonas fluorescens* lipase) enzyme in DMSO with high enantiomeric

excesses (95% ee, 49% yield). The acetoxy enantiomer, however, does not resolve in good enantiomeric excesses. This may be due to the presence of bulky groups on the ring.

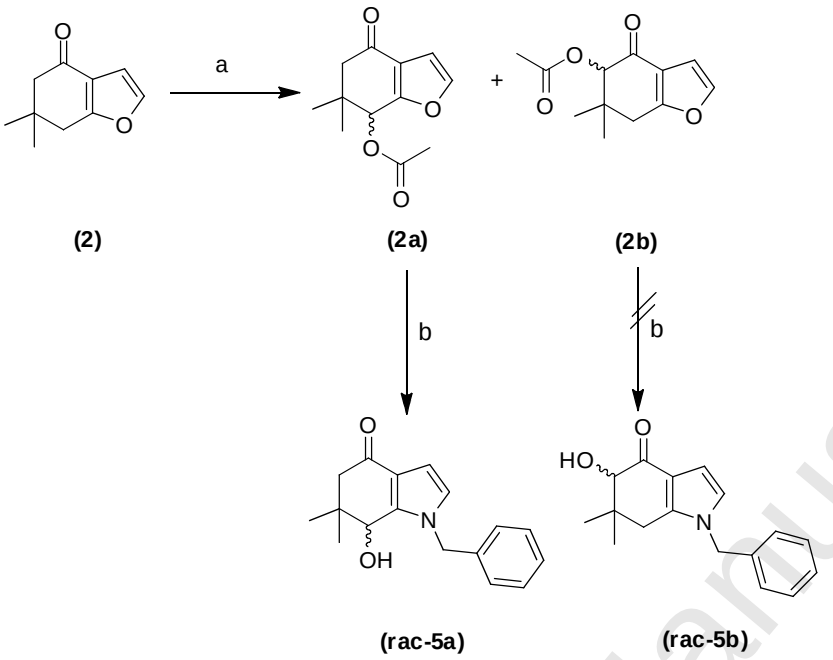
Table 1. Enzymatic hydrolysis of 1-benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indol-7-yl-acetate (*rac*-**4**)

Entry	Enzyme	Time(h)	Solvent	Alcohol		Acetate	Conversion	E[c]
				e.e[a](%)	Yield[b]	e.e[a] (%)	%	
1	PCL	48	DMSO	86		9.6	10	15
2	MJL	30.5	DMSO	81		0.55	0.67	0.009 7
3	CCL	72	DMSO	74		8.7	10.5	7.13
4	HPL	30.5	DMSO	71		8.2	10.4	6.3
5	PFL	72	DMSO	95	49	1.7	1.76	1.6
6	Amano PS	192	DMSO	59		8.4	12	4.2
7	MJL	21.5	THF	74		0.15	0.20	7
8	CCL	21.5	THF	84		4	4.5	13
9	HPL	20	THF	79		2.5	3	5.6
10	PFL	6.5	THF	13		3.8	23	1.36
11	Amano PS	96	THF	82		3	3.5	10.8
12	CAL	21.5	THF	74		1	1.5	6.5
13	MJL	29	Toluene	59		0.15	0.25	3
14	CCL	29	Toluene	85		0.4	0.5	9
15	HPL	45	Toluene	57		0.13	0.2	6
16	PFL	27.5	Toluene	51		0.07	1	1
17	CAL	47.5	Toluene	76		1	1.2	10.5
18	MJL	3.1	Acetonitrile	78		0.9	1.1	10
19	CCL	3	Acetonitrile	81		0.12	0.13	25
20	HPL	3.1	Acetonitrile	89		0.24	0.27	17
21	PFL	3.1	Acetonitrile	70		1.2	1.7	6
22	CAL	3	Acetonitrile	76		1	1.4	6

[a] Determined by HPLC using Chiralcell OD-H column, UV detection at 254 nm, eluent: hexane\2 propanol =98:2, flow 1.0 ml min^{-1} 20^{o}C, using racemic compounds as references.
[b] Isolated yield after flash column chromatography.
[c] See ref. [18]

We next investigated the transesterification of *rac*-**5a** under different conditions as another alternative route (Scheme 3).

Thus, we examined the transformation of 6,7-dihydro-6,6-dimethyl benzofuranone (**2**) into the 4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-benzofuran-7-yl acetate (**2a**) (major product) and 4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-benzofuran-5-yl acetate (**2b**) (minor product) using manganese (III) acetate oxidation procedure as shown in Scheme 2.



Scheme 2. a) $Mn(OAc)_3$, AcOH, benzene, reflux; b) Benzylamine, $EtOH/H_2O$, heat

As we reported in a previous study [16], when the reaction time was 20 hours, only 4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-benzofuran-5-yl acetate (**2b**) was produced. In this work, we realized that when we increased the reaction time, we obtained two products, **2a** as the major, and **2b** as the minor product. Because of separation problem of these two products, the mixture of the two was used for obtaining the indole derivatives [8]. From this reaction, 1-benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one (*rac*-**5a**) was obtained in high yield (52%) as shown in Scheme 2. The single crystal structure of the compound *rac*-**5a** is shown in Figures 2a and b.

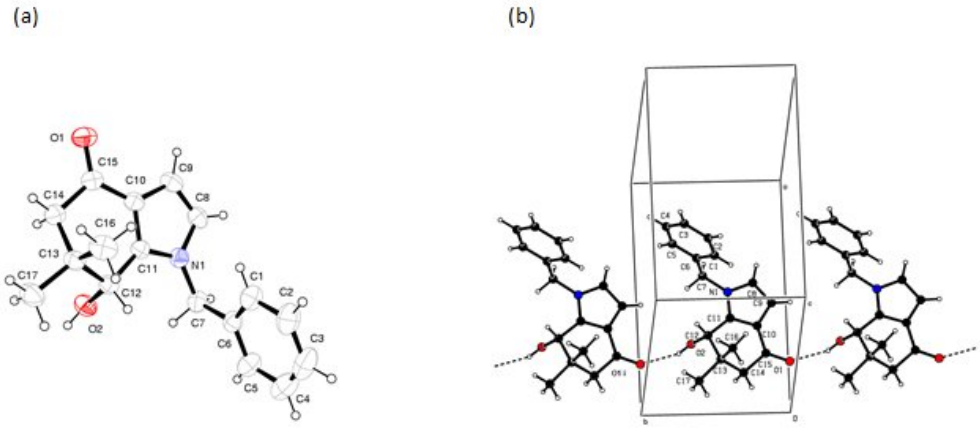
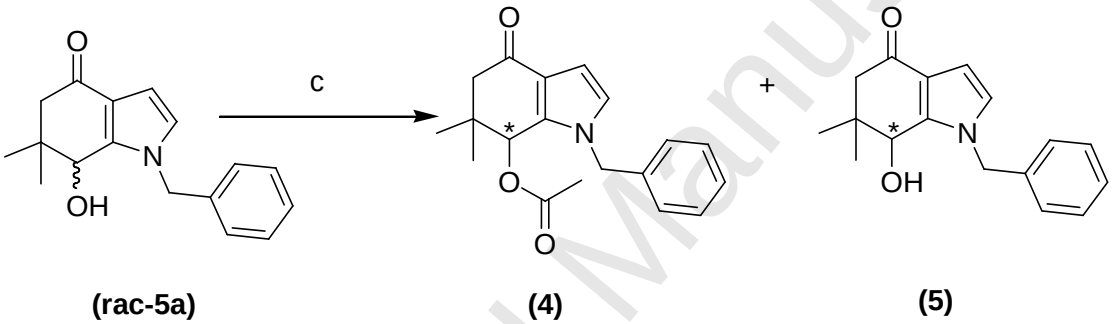


Figure 2. (a) ORTEP drawing of the molecule 1-benzyl-7-hydroxy-6,6-dimethyl-6,7-dihydro-1H-indol-4(5H)-one (*rac*-**5a**). Thermal ellipsoids are shown at 50% probability level. C12(R). (b) *H*-bonding pattern (dashed lines) along the *b*-axis in the unit cell. O2-H···O1^{i} = 2.815(3) Å, <(O2-H···O1^{i})=159º (Symmetry code i=x, 1+y,z).

Then we have studied transesterification reaction of *rac*-**5a,** with several lipases in different solvents (DMSO, toluene, THF, acetonitrile) or without solvent were explored. In all cases, only trace amounts of the products were formed.

It is known that the addition of crown ethers, amino alcohols, and certain bases, is well known to influence the hydrolysis of esters; bases also increase the rate of transesterification in the presence of enzymes in apolar organic solvents [17]. Enzyme mediated transesterification was achieved using several bases (DMAP, 2,4-lutidine, 2,6-lutidine and pyridine). DMAP, in particularly is the most basic additives according to the others. It is considerably enhanced the reaction rate. This was the idea behind the approach we adopted. Therefore we decided to use DMAP as an additive.



(rac-5a) **(4)** **(5)**

Scheme 3. c) Enzyme, vinyl acetate, additive (DMAP)

In the transesterification of *rac*-**5a,** was performed with various enzymes, in different solvents (DMSO, THF, acetonitrile, toluene), using vinyl acetate as the acetyl source and the reaction to take place in a matter of hours, in the presence of DMAP(5 equiv) as is shown in Table 2. From the lipases examined, it is observed that the MJL in THF, CAL in THF and Amano PS in acetonitrile gave better conversions with reverse selectivity (>99% ee). These enzyme solvent systems preferentially recognized the (R)-**5** enantiomers.

Table 2. Transesterification of 1-benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one (*rac*-**5a)** with solvent

Entry	Enzyme	Solvent	Additive	Time(h)	Alcohol		Acetate		Conversion	E[c]
					ee[a] (%)	Yield[b] (%)	ee[a] (%)	Yield[b] (%)	%	
1	Amano	DMSO	DMAP	11	82[d]		0.2		0.2	5
2	CCL	DMSO	DMAP	23	69[d]		8		0.1	6
3	CAL	DMSO	DMAP	23	75[d]		0.6		0.8	1
4	HPL	DMSO	DMAP	11	73[d]		47		39	15
5	Amano	THF	DMAP	11	80[d]		5		6	9
6	MJL	THF	DMAP	23	>99[d]	49	5		5	41
7	HPL	THF	DMAP	23	87[d]		9		9	15
8	CAL	THF	DMAP	23	>99[d]		1		1	2
9	RAL	THF	DMAP	23	86[d]		3		3	16
10	HPL	Toluene	DMAP	23	69[d]		0.1		0.1	2
11	CAL	Toluene	DMAP	23	35[d]		3		8	2
12	Amano	Acetonitrile	DMAP	21	99[d]		3		3	68
13	MJL	Acetonitrile	DMAP	22,5	91[d]		4		4	51
14	PFL	Acetonitrile	DMAP	7	62		0.7		1	1
15	CCL	Acetonitrile	DMAP	22,5	75		0.5		0.7	6
16	CAL	Acetonitrile	DMAP	22,5	84		0.05		0.06	16
17	HPL	Acetonitrile	DMAP	8	53		1		2	3
18	RAL	Acetonitrile	DMAP	23	77[d]		11		13	9

[a] Determined by HPLC using Chiralcell OD-H column, UV detection at 254 nm, eluent: hexane\2-propanol=98:2, flow 1.0 ml min^{-1} 20°C, using racemic compounds as references.
[b] Isolated yield after flash column chromatography.
[c] See ref. [18]
[d] Reverse selectivity

Furthermore, the effect of solvents were also investigated and it was observed that the lipases from MJL in acetonitrile (91% ee), RAL in THF (86% ee), RAL in acetonitrile (77% ee), Amano PS in THF (80 % ee), CCL in DMSO (69 % ee), HPL in DMSO (73 % ee), HPL in THF (87 % ee), HPL in toluene (69 % ee), CAL in DMSO (75 % ee), CAL in THF (99% ee), and CAL in toluene (35% ee) all exhibited solvent dependent reverse selectivity and **(R)-5** was obtained. However, the lipases from PFL in acetonitrile (62 % ee), CCL in acetonitrile (75% ee), CAL in acetonitrile (84 % ee), and HPL in acetonitrile (53% ee) showed **(S)-5** selectivity. These results clearly showed that solvent dependent substrate selectivity for *rac*-**5a**.

For the preperative scale, the synthesis of **(R)-5** MJL in THF (Table 2, entry 6) is used and the product obtained in 49% yield.

In addition, different lipases were also screened for resolving *rac*-**5a** in the enantioselective transesterification of the γ-hydroxy-4-oxo-tetrahydroindole derivative (**5**), by using vinyl acetate as an benign acyl donor and DMAP used as an additive, without solvent, as shown in Table 3.

Table 3. Transesterification of 1-benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1*H*-indol-4(5*H*)-one (*rac*-**5)** without solvent

Entry	Enzyme	Solvent	Additive	Time (h)	Alcohol	Acetate	Conversion[b]	E[b]
					ee[a] (%)	ee[a] (%)	%	
1	Amano	-	DMAP	7,5	52	6	10	4
2	MJL	-	DMAP	23	82[d]	24	23	12
3	PFL	-	DMAP	7,5	85	0.8	1	9
4	CAL	-	DMAP	23	90[d]	7	7	21
5	HPL	-	DMAP	8	42	1	2	3

[a] Determined by HPLC using Chiralcell OD-H column, UV detection at 254 nm, eluent: hexane\2-propanol=98:2, flow 1.0 ml min^{-1} 20°C, using racemic compounds as references.
[b] See ref. [18]
[c] Reverse selectivity

From this data it can be seen that the lipases, CAL with 90% enantiomeric excess, and MJL with 82% enantiomeric excess, exhibit reverse selectivity and **(R)-5** is obtained. However, the lipase from Amano PS with 52 % enantiomeric excess, PFL with 85 % enantiomeric excess and HPL with 42% enantiomeric excess show **(S)-5** selectivity.

This clearly suggests that both esterification and transesterification processes leads to very effective kinetic resolution as demonstrated by the high enantiomeric excess values, but surprisingly in the transesterification reaction reverse selectivity is also observed. In the transesterification process, only HPL in DMSO showed limited selectivity for acetoxy enone (-)-**4** (47% ee, Table 2) while in the esterification reaction any selectivity for acetoxy enone values was extremely low.

In this paper we report two strategies for enzymatic resolution of 4-oxo-tetrahydroindol derivatives. If it is considered to the first strategies according to the Scheme 1, 1-benzyl-6,7-dihydro-6,6-dimethyl-1H-indol-4(5H)one (**3**) has been synthesized by using indol formation procedure (benzylamine in aqueous EtOH at 150ºC under pressure) with a good yield (56 %). In the acetoxylation step which has been easily performed the desired product (*rac*-**4**) in the presence of $KMnO_4$/ acetic acid method in our indol system, surprisingly, we got only γ-acetoxy-4-oxo-tetrahydroindole derivative. Nevertheless the yield of *rac*-**4** was very low (25%). Furthermore, we tested a series of enzymes and solvents for the enantioselective hydrolysis of acetoxy enone *rac*-**4,** provided only R enantiomer for hydroxyl enone but the acetoxy enantiomer was not resoved in good enantiomeric excesses shown in Table1.

In the second route (Scheme 2), firstly acetoxylation of benzofuranone derivative was synthesized in the presence of $Mn(OAc)_3$, AcOH method. We previously synthesized of (**2b**) with very high yield and high regioselectivity, when the reaction time was 20 hours. Then, we suggest that, $Mn(OAc)_3$, AcOH method which has been generated i) high regioselectivity for α-acetoxy benzofuranone derivatives when the reaction time is 20 hours, ii) high regioselectivity for γ-acetoxy benzofuranone, when the reaction time is 40 hours. The second route showed that the **2a** was obtained with very high yield (86%). After treatment of indol procedure with benzylamine *rac*-**5a** was obtained in high yield (52%). This routes could be usefull for transesterification reactions results. In the transesterification reaction of *rac*-**5a,** both of R and S enantiomer could be obtained for hydroxyl enantiomer with high enantioselectivity, high conversion value and high E values with respect to the esterification

reactions. Additionally, in the transesterification reactions, the acetoxy enantiomer also resolved in 47%ee and high rate of conversion (39), high E value (15) according to overall enzymatic route as is shown in Table 2.

4. Conclusion

This work presents the first effective synthesis of γ-acetoxy-4-oxo-tetrahydroindole **(4)** and γ-hydroxy-4-oxo-tetrahydroindole **(5)** derivatives, which are important targets in the drug industry, through enzymatic kinetic resolution. The enantioselective synthesis of 1-benzyl-4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-1H-indol-7-yl acetate **(4)** was carried out with a 47% enantiomeric excess via a transesterification process, the esterification reaction showed very low selectivity. The enantioselective synthesis of 1-benzyl-6,7-dihydro-7-hydroxy-6,6-dimethyl-1H-indol-4(5H)-one (**5**) was realized in both the lipase-catalyzed esterification and transesterification reactions with high enantiomeric excesses. Generally much better results were achieved when transesterification reaction was conducted with specific lipases in certain solvent systems. In the transesterification reaction both **(S)-5** and **(R)-5** enantiomers were obtained as alcohols whereas, in the enzyme-mediated hydrolysis of *rac*-**4** only the **(S)-5** enantiomer was obtained as an alcohol in high optical purity. Therefore, esterification and transesterification can be considered as complementary with respect to the final product composition. This method enables a simple new entry to the synthesis of γ-acetoxy-4-oxo-tetrahydro indol derivatives, which are important precursors for farmacologically interesting compound.

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