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Enantioselective synthesis of 4,5,6,7-tetrahydro-4-oxo-benzofuran-5-yl acetate and 1-benzyl-4,5,6,7-tetrahydro-4-oxo-1(H)-indol-5-yl acetate using chemoenzymatic methods

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Abstract

The chemoenzymatic synthesis of both of the enantiomers of pharmacologically interesting compounds such as 4,5,6,7-tetrahydro-4-oxo-benzofuran-5-yl acetate (**2a**), 4,5,6,7-tetrahydro-4-oxo-6,6-dimethylbenzofuran-5-yl acetate (**2b**), and their hydroxy derivatives **3a**, **3b**, 1-benzyl-4,5,6,7-tetrahydro-4-oxo-1(H)-indol-5-yl acetate (**5**), starting from 6,7-dihydrobenzofuran-4(5H)-one (**1a**), 6,7-dihydro-6,6-dimethylbenzofuran-4(5H)-one (**1b**), and 1-benzyl-6,7-dihydro-1H-indol-4(5H)-one (**4**) are reported. Manganese(III) acetate-mediated acetoxylation followed by the enzyme-mediated kinetic resolution of α′-acetoxy enone provides acetoxy and hydroxy derivatives in good yields and high enantiomeric excesses.

Keywords: Manganese(III) cetate; Indole; Benzofurane; Enzymatic resolution; Oxidation of enone

1. Introduction

The benzofuran type ring structures occur extensively among natural products, e.g. furocoumarins and furanoquinoline alkaloids [1]. Benzofuran derivatives are useful intermediates for the synthesis of drugs; it is also an intermediate for the synthesis of 4-hydroxyindole, which is a key intermediate for the synthesis of an arrhytmic agent, Pindalol [2]. The synthon, using 6,7-dihydro-1H-indol-4(5H)-one as a key intermediate, possesses potentiality that is applicable for the synthesis of a variety of 4-substituted indoles [3a,b]. It is therefore of considerable interest to develop efficient methods for the preparation of these compounds in enantiomerically pure forms.

In our ongoing work, we have presented procedures for the $Mn(OAc)_3$ mediated α′-acetoxylation of α,β-unsaturated ketones followed by the enzymatic and fungus-mediated resolution of acetoxy enones for the synthesis of enantiomerically pure α-hydroxy and α-acetoxy ketones [4]. The target compounds **2a**,**b**; **3a**,**b**; **4**; **5** are interesting compounds in chemical and pharmaceutical aspects [3c–g]. Herein we report an efficient chemoenzymatic route to the synthesis of the enantiomers of these compounds via $Mn(OAc)_3$ mediated α′-acetoxylation followed by enzymatic resolution.

2. Experimental

2.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in parts per million relative to $CDCl_3$ (^{1}H: $\delta = 7.27$), $CDCl_3$ (^{13}C: $\delta = 77.0$), and CCl_4 (^{13}C: $\delta = 96.4$) as internal standards. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda = 254$ nm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column. Optical rotations were measured with a Krüss P3002RS automatic polarimeter. Lipases PFL (Lipase from *Pseudomonas fluorescens*) BioChemika (95608); CAL (Lipase from *Candida antarctica*) BioChemika (62299),

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HPL (Hog pancreas lipase) BioChemika (62300); MML (Lipase from *Mucor miehei*) BioChemika (62298); AL (Lipase from *Aspergillus*) BioChemika (84205); RAL (Lipase from *Rhizopus arrhizus*) BioChemika (62305) are purchased from Fluka and all are from Lipase basic kit (62327) from Fluka.

2.1.1. Procedure for the synthesis of 1-benzyl-6,7-dihydro-1H-indol-4(5H)-one (4)

A solution of the 6,7-dihydrobenzofuran-4(5H)-one (6.2 mmol) and benzylamine (18.6 mmol) in 20% aqueous ethanol (5 ml) was heated in a sealed tube at 145–150 °C for 12 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 and dried over $MgSO_4$, concentrated, and chromatographed on silica gel. Elution with (1:1 EtOAc:Hexane) afforded 1-benzyl-4-oxo-4,5,6,7-tetrahydroindole (96% yield). The spectroscopic data (NMR, IR) are in accordance with the literature [5].

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

A solution of 10 mmol of benzofurane and (12.5 mmol) $Mn(OAc)_3$ in 110 ml benzene–acetic acid (100:10) were heated under reflux for 20–49 h. After all of the starting materials were consumed, the reaction mixture was extracted with ether and organic layer was washed with brine. The resulting organic phase was dried over $MgSO_4$, concentrated and purified by flash column chromatography (1:1 EtOAc:Hexane) to yield acetoxybenzofurane.

2.1.3. General procedure for the lipase-catalyzed kinetic resolution

Lipase (200–300 mg) was dissolved in 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 to shake at 37 °C. Conversion was monitored by TLC and HPLC up to 50%. After filtration the filtrate was extracted with dichloromethane, dried over $MgSO_4$, concentrated and purified by column chromatography (1:4 EtOAc:Hexane).

*2.1.4. (-)4,5,6,7-Tetrahydro-4-oxobenzofuran-5-yl acetate (−)-**2a***

(48.5 mg, 50%); $[\alpha]_D^{20} = -83$ (*c* 0.9, $CHCl_3$); HPLC: Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.80 ml min^{-1} 20 °C retention time: 67.76 min. IR ($CHCl_3$): $\nu = 1695$, 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.30 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 5.37 (dd, $J = 5.0$, 12.1 Hz, 1H, H-5), 6.60 (d, $J = 2.0$ Hz, 1H, H-3), 7.28 (d, $J = 2.0$ Hz, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 22.2, 28.2, 96.1, 107.1, 143.5, 165.1, 169.6, 187.6. Anal. Calcd. for $C_{10}H_{10}O_4$(194.18): C, 61.85; H, 5.19. Found: C, 61.59; H, 5.40.

*2.1.5. (+)6,7-Dihydro-5-hydroxybenzofuran-4(5H)-one (+)-**3a***

(36.5 mg, 48%); $[\alpha]_D^{20} = +62$ (*c* 0.1, $CHCl_3$); HPLC: Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.80 ml min^{-1} 20 °C retention time: 26.60 min. IR ($CHCl_3$): $\nu = 1682$, 3022, 3500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (m, 1H, H-6), 2.48 (m, 1H, H-6), 2.94 (m, 2H, CH_2), 4.16 (dd, $J = 5.1$, 12.7 Hz, 1H, H-5), 6.60 (d, $J = 2.0$ Hz, 1H, H-3), 7.27 (d, $J = 1.9$ Hz, 1H, H-2) ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 30.9, 96.2, 106.8, 119.0, 143.6, 166.5, 194.0. Anal. Calcd. for $C_8H_8O_3$(152.15): C, 62.33; H, 6.54. Found: C, 62.78; H, 6.44.

*2.1.6. (+)4,5,6,7-Tetrahydro-6,6-dimethyl-4-oxobenzofuran-5-yl acetate (+)-**2b***

(56.6 mg, 51%); $[\alpha]_D^{20} = +62$ (*c* 0.35, $CHCl_3$); HPLC: Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.80 ml min^{-1} 20 °C retention time: 61.12 min. IR ($CHCl_3$): $\nu = 1700$, 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 2.20 (s, 3H, $COCH_3$), 2.81 (d, $J = 17.28$ Hz, 1H, CH_2), 3.00 (d, $J = 17.28$ Hz, 1H, CH_2), 5.30 (s, 1H, H-5), 6.60 (m, 1H, H-3), 7.35 (m, 1H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.7, 27.2, 37.5, 39.1, 96.1, 106.8, 119.3, 143.4, 163.8, 169.7, 186.8. Anal. Calcd. for $C_{12}H_{14}O_4$(222.24): C, 64.85; H, 6.35. Found: C, 64.53; H, 6.33.

*2.1.7. (+)-6,7-Dihydro-5-hydroxy-6,6-dimethylbenzofuran-4(5H)-one (+)-**3b***

(36.0 mg, 40%); $[\alpha]_D^{20} = +133$ (*c* 0.6, $CHCl_3$); HPLC using Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.80 ml min^{-1} 20 °C 33.41 min. IR ($CHCl_3$): $\nu = 1687$, 3030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.79 (d, $J = 17.28$ Hz, 1H, CH_2), 2.90 (d, $J = 17.34$ Hz, 1H, CH_2), 3.69 (s, 1H, OH), 4.03 (s, 1H, H-5), 6.69 (m, 1H, H-3), 7.38 (m, 1H, H-2). ^{13}C NMR (100MHz, $CDCl_3$) δ 18.7, 27.7, 37.4, 41.1, 80.1, 106.5,143.4, 165.3, 193.3. Anal. Calcd. for $C_{10}H_{12}O_3$(180.2): C, 65.91; H, 7.74. Found: C, 65.63; H, 7.63.

*2.1.8. (+)1-Benzyl-4,5,6,7-tetrahydro-4-oxo-1H-indol-5-yl acetate (+)-**5***

(53.8 mg, 38%); $[\alpha]_D^{20} = +5$ (*c* 0.5, $CHCl_3$); HPLC: Chiralcell OJ column, UV detection at 254 nm, eluent: hexane/2-propanol = 65:35, flow 0.30 ml min^{-1} 20 °C retention time: 36.39 min. IR ($CHCl_3$): $\nu = 1682$, 1739 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.15–2.30 (m, 2H, CH_2), 2.69–2.85 (m, 2H, CH_2), 4.98 (s, 2H, CH_2Ph), 5.30 (dd, $J = 4.98$, 12 Hz, 1H, CHO), 6.50 (d, $J = 3.12$ Hz, H-3), 6.54 (d, $J = 3.06$ Hz, 1H, H-2), 6.86–7.27 (m, 5H, Ph) ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.9, 29.7, 50.6, 73.4, 96.1, 106.5, 120.4, 123.7, 126.3, 127.8, 128.1, 129.0, 136.0, 141.0, 169.9, 187.3. Anal. Calcd. for $C_{17}H_{17}NO_3$(283.32): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.12; H, 6.04; N, 5.23.

*2.1.9. X-ray crystal structure analysis of **5***

A single crystal suitable for X-ray structural analysis was obtained by EtOAc/hexane. A white crystal of dimensions 0.21 mm × 0.19 mm × 0.17 mm was mounted on a glass fiber. X-ray diffraction intensity data collection and cell refinement were performed on Rigaku R-AXIS RAPID IP diffractometer equipped with a graphite monochromator. A total of 4368 unique

reflections were collected using Mo Kα (λ = 0.71073 Å) radiation by the oscillation scan technique at 291(2) K, of which 3741 reflections had $I > 2\sigma(I)$ and were used in the structure solution and refinements. The corrections for Lp factors and empirical absorption were applied to the intensity data. The structure was solved by direct methods and refined on F^2 using a full-matrix least-squares technique (SHELXS-97 and SHELXL-97) [5]. The non-hydrogen atoms were also refined by a full-matrix least-squares technique, anisotropically, and hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 3741 observed reflections and 192 parameters. Convergence with unweighted and weighted agreement factors was achieved at $R = 0.088$ and $Rw = 0.104$ ($w = 1/[\sigma(F_0^2) + (0.0481P)^2 + 0.0000P]$) where $P = (F_0^2 + 2F_c^2)/3$, The maximum and minimum peaks on the final difference Fourier map correspond to 0.224 and −0.213e Å^3.

Crystal data for **5**: empirical formula, $C_{17}H_{17}NO_3$; formula weight, 283.3; calculated density, 1.30 g/cm^3; volume (V), 1443.9(2) Å^3; crystal system, monoclinic; space group, $P2_1/n$ (no.: 14); $Z = 4$; unit cell dimensions, $a = 6.869(5)$, $b = 18.265(5)$, $c = 11.682(5)$, $\beta = 99.875(5)$; absorption coefficient, 0.090 mm^{-1}; index ranges, $-8 \le h \le 6$, $-26 \le k \le 26$, $-16 \le l \le 16$; $F(0\,0\,0)$, 708; $\theta_{max} = 30.6$; GOF, 1.281.

Final atomic coordinates of the crystal, along with lists of anisotropic thermal parameters, hydrogen coordinates, bond lengths, and bond angles, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-606017. Data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223-336-033; e-mail: deposit@ccdc.cam.cn; web: http://www.ccdc.cam.ac.uk).

3. Results and discussion

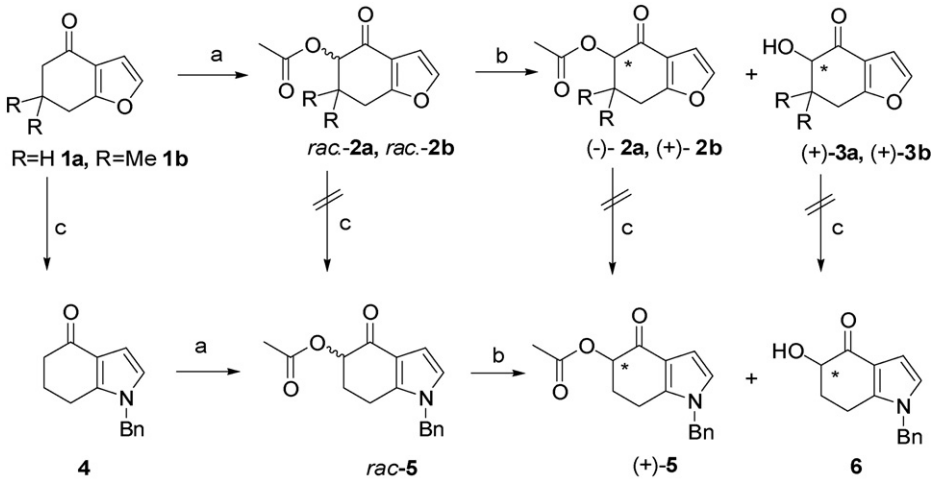
In an initial reaction (Scheme 1), the oxidation of 6,7-dihydrobenzofuran-4(5H)-one (**1a**) and 6,7-dihydro-6,6-dimethylbenzofuran-4(5H)-one (**1b**), which is synthesized starting from 5,5-dimethyl-1,3-cyclohexanedione and chloroacetaldehyde in the presence of a base according to the procedure in the literature [6], with manganese(III) acetate in benzene furnished the desired acetoxy derivative *rac*-**2a** and **2b** in 90 and 86% yields. Using the same oxidation procedure 1-benzyl-6,7-dihydro-1H-indol-4(5H)-one (**4**), which is synthesized starting from **1a** and benzylamine, is converted to its acetoxy derivative *rac*-**5** in a 66% yield as shown in Scheme 1.

In the course of a biotransformation, the stereoselective transformation of a substrate often takes place under mild and ecologically compatible conditions [7]. During the course of our studies on the biotransformations of *rac*-**2a** and **2b** the screening reactions were examined with various lipases.

There is a wide variety of enzymes for screening the enantioselective hydrolysis of acetoxy enone *rac*-**2a**. As shown in Table 1, we tested several enzymes (see Section 2.1), Amano PS, PFL, CAL, HPL, PPL, MML, AL, RAL in four different organic solvents (DMSO, THF, toluene and acetonitrile) for the kinetic resolution step, in which the following conditions provided the best results.

In a typical experiment for enzymatic hydrolysis *rac*-**2** was dissolved in an organic solvent, a phosphate buffer (pH 7.0) was then added and the mixture stirred at 35 °C in the presence of an enzyme. The reaction was monitored by TLC and HPLC with a chiral column using *rac*-**2a**, and *rac*-**3a** (synthesized from *rac*-**1a** with K_2CO_3/MeOH) as references. When an approximately 50% conversion was attained, the crude product was separated by flash column chromatography to provide (−)-**2a** and (+)-**3a**. According to the HPLC analysis the reactions provided the acetoxy enone (−)-**2a** in 16 to > 99% e.e. and hydroxy enone (+)-**3a** in 28 to > 99% e.e. Amano PS (with DMSO, THF, acetonitrile), PFL and HPL (in DMSO) exhibited high enantioselectivity for the remaining acetoxy enone (>99% e.e.) while MML (with DMSO, acetonitrile), PFL(with THF, acetonitrile), CAL (with DMSO) exhibited high enantioselectivity for the hydroxy enone (90 to > 99% e.e.) (Table 1).

As shown in Table 1, HPL, AL, and RAL exhibited solvent dependent reverse selectivity with high enantioselectivity for acetoxy enone (52 to > 99% e.e.) while RAL exhibited mod-



Scheme 1. (a) $Mn(OAc)_3$, AcOH, benzene, reflux; (b) enzyme; (c) benzylamine, EtOH/H_2O, heat.

Table 1
Enzymatic hydrolysis of 4,5,6,7-tetrahydro-4-oxo-benzofuran-5-yl acetate **2a**

Entry	Enzyme	Time (h)	Solvent	Acetate		Alcohol		Convergence[c] (%)	E[c]
				e.e.[a](%)	Yield[b](%)	e.e.[a](%)	Yield[b](%)		
1	Amano PS	1	DMSO	99	50	53	45	65	15
2	PFL	2	DMSO	99		84		54	59
3	CAL	60	DMSO	41		91		69	7
4	HPL	14	DMSO	99[d]		66		60	24
5	PPL	3	DMSO	66		72			
6	MML	3	DMSO	56	43	99	48	48	12
7	AL	2	DMSO	52		15		78	2.1
8	RAL	2	DMSO	16		36		31	2.5
9	Amano PS	1.5	THF	99		35		74	9.1
10	PFL	1.5	THF	18		92		16	28
11	AL	113	THF	31[d]		71		30	7.9
12	RAL	110	THF	9[d]		65		12	5.1
13	Amano PS	2.5	toluene	82		52		61	7.7
14	HPL	20	toluene	59		87		40	26
15	CAL	20	toluene	90		28		76	4.7
16	Amano PS	2	acetonitrile	99		52		66	15
17	PFL	2.5	acetonitrile	61		92		40	44
18	CAL	26	acetonitrile	24		85		22	15
19	MML	26	acetonitrile	85		93		48	74

[a] Determined by HPLC using Chiralcell OB column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.80 ml min^{-1} 20 °C, using racemic compounds as references.
[b] Isolated yield after flash column chromatography.
[c] See ref. [8].
[d] Reverse selectivity.

erately enantioselectivity for the hydroxy enone (65% e.e.). For the preparative scale, the synthesis of (−)-**2a** Amano PS, DMSO (Table 1, entry 1), and for (+)-**3a** MML in DMSO is used.

The above-mentioned conditions, as described for the enantioselective hydrolysis of *rac*-**2a** was screened for *rac*-**2b** with various enzymes in different solvents at pH 7.0. In many cases, the enzymes gave no reaction, which was may be due to the bulky groups on the ring. As shown in Table 2 Amano PS in THF exhibited high enantioselectivity for the acetoxy enone (99% e.e., 51% yield) and MJL in DMSO exhibited also high enantioselectivity for the hydroxy enone (97% e.e., 40% yield). Both conditions are used for the preparative scale synthesis of (+)-**2b** and (+)-**3b**. CCL and PFL in THF exhibited reverse selectivities for the product alcohol and remained acetate. For the preparative scale, the synthesis of (+)-**3b** MJL, DMSO (Table 2, entry1), and for (+)-**2b** Amano PS in DMSO is used.

Next, we examined the transformation of the commercially available **1a** into the 1-benzyl-4,5,6,7-tetrahydro-4-oxo-1(H)-indol-5-yl acetate **5**. When **1a** was heated with benzylamine in aqueous ethanol at 150 °C under pressure according to the published procedure 1-benzyl-6,7-dihydro-1H-indol-4(5H)-one (**4**) was produced in 96% yield [5]. The acetoxylation of indanone derivative **4** by using manganese(III) acetate afforded *rac*-**5** in 63% yield. Fig. 1a and b shows the molecular and crystal structure of the compound **5**.

Table 2
Enzymatic hydrolysis of 4,5,6,7-tetrahydro-4-oxo-6,6-dimethylbenzofuran-5-yl acetate *rac*-**2b**

Entry	Enzyme	Time (h)	Solvent	Acetate		Alcohol		Convergence (%)[c]	E[c]
				e.e.[a] (%)	Yield[b] (%)	e.e.[a] (%)	Yield[b] (%)		
1	MJL	18	DMSO	33		97	40	25	90
2	PPL	18	DMSO	32		81		28	12
3	PPL	141	THF	25		50		33	3.8
4	Amano PS	48	THF	>99	51	83		54	55
5	CCL	48	THF	84[d]		29		74	4.3
6	PFL	48	THF	74[d]		73		50	14
7	MJL	170	THF	14		39		26	2.6
8	HPL	48	THF	27		64		30	4.9

[a] Determined by HPLC using Chiralcell OB column, UV detection at 254 nm, eluent:hexane/2-propanol = 95:5, flow 0.80 ml min^{-1} 20 °C, using racemic compounds as references.
[b] Isolated yield after flash column chromatography.
[c] See ref. [8].
[d] Reverse selectivity.

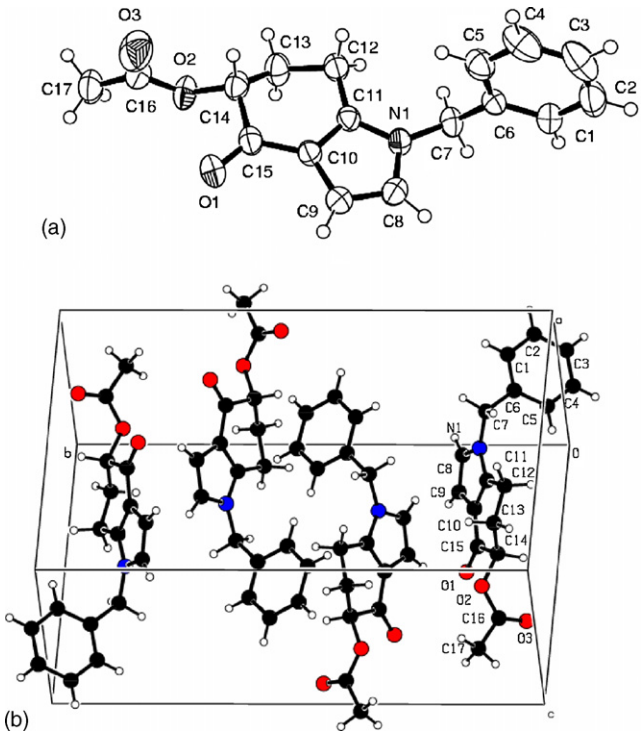


Fig. 1. (a) ORTEP view of 1-benzyl-4,5,6,7-tetrahydro-4-oxo-1(H)-indol-5-yl acetate **5** with displacement ellipsoids drawn at the 50% probability level. (b) Racemic mixture of both of the enantiomers in the unit cell. Selected bond lengths (Å), bond angles (°), and torsion angles (°): O_2–C_{14}, 1.450(2); O_1–C_{15}, 1.2278(2); N_1–C_{11}, 1.359(2); N_1–C_8, 1.384(3); N_1–C_7, 1.460(2); C_{14}–C_{13}, 1.510(3); C_6–C_7, 1.504(3); C_8–N_1–C_7, 123.6(2); N_1–C_7–C_6, 113.3(2); C_{13}–C_{14}–C_{15}, 114.6(2); C_{11}–C_{10}–C_{15}–O_1, 178.3(2); O_1–C_{15}–C_{14}–C_{13},152.3(2); C_{10}–C_{15}–C_{14}–O_2, 148.4(2).

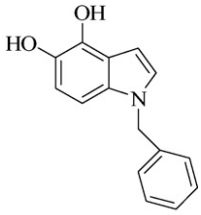
As described for *rac*-**2a**, the enantioselective hydrolysis of *rac*-**5** was screened with various enzymes in different solvents at pH 7.0. As shown in Table 3 only with Amano PS in DMSO and THF, CCL and PFL in DMSO observed conversion by monitoring of the reaction by HPLC with chiral column and TLC using *rac*-**5** as reference. We were not able to isolate the hydroxy derivative from enzyme hydrolysis, as well as from chemical hydrolysis. Only a trace amount of **6** could be detected by GC–MS. In addition to the starting material acetoxy derivative, a mixture of undefined products was formed. We applied several pH values for enzymatic hydrolysis process, but the problems were not solved. The acetoxy products with high enantioselectivity occurred successively however. The resolution was only possible with three enzymes but surprisingly Amano PS showed solvent dependent reverse selectivity. Amano PS in DMSO exhibited high enantioselectivity for the (+)-acetoxy enone (95% e.e., 38% yield) and Amano PS in THF exhibited high enantioselectivity for the (−)-acetoxy enone (83% e.e.) (Table 3).

Table 3
Enzymatic hydrolysis of 1-benzyl-4,5,6,7-tetrahydro-4-oxo-1(H)-indol-5-yl acetate *rac*-**5**

Entry	Enzyme	Reaction time (min)	Solvent	Acetate	
				e.e.[a] (%)	Yield[b] (%)
1	Amano PS	1160	DMSO	95	38
2	CCL	740	DMSO	13	
3	PFL	1515	DMSO	5	
4	Amano PS	1380	THF	83[c]	36

[a] Determined by HPLC using Chiralcell OJ column UV detection at 254 nm, eluent: hexane/2-propanol = 65:35, flow 0.30 ml min^{-1} 20 °C, using racemic compounds as references.
[b] Isolated yield after flash column chromatography.
[c] Reverse selectivity.

The indole formation reaction, which was described for the formation of **4**, is also applied to **2a** and **3a** [5] in which the mixture of the products were formed. According to the GC–MS and NMR results the only identifiable product was 1-benzyl-1H-indole-4,5-diol (**7**), which could be formed via tetrahydroindole formation followed by aromatization.



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4. Conclusion

4,5,6,7-Tetrahydro-4-oxo-benzofuran-5-yl acetate, 4,5,6,7-tetrahydro-4-oxo-6,6-dimethylbenzofuran-5-yl acetate are synthesized starting from 6,7-dihydrobenzofuran-4(5H)-one, 6,7-dihydro-6,6-dimethylbenzofuran-4(5H)-one via manganese(III) acetate-mediated acetoxylation. Enzyme catalyzed kinetic resolution of these racemic acetoxy derivatives furnished the corresponding enantiomers of acetoxy and hydroxy derivatives in high enantiomeric excesses. 6,7-dihydrobenzofuran-4(5H)-one is converted to its indole derivative by using benzylamine. This 1-benzyl-6,7-dihydro-1H-indol-4(5H)-one is acetoxylated and enzyme catalyzed kinetic resolution is applied. The acetoxy derivative is obtained in high e.e. It was not possible, however, to isolate the hydroxy derivative after resolution. This method provides a simple new entry to the synthesis of chiral benzofuranone and the indole type of ring structures in high e.e.

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