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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

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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.

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 a key 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.

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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 $CDCl_3$ (^1H: $\delta = 7.27$), $CDCl_3$ (^{13}C: $\delta = 77.0$) and CCl_4 (^{13}C: $\delta = 96.4$) 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 ($\lambda = 254$ 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 h [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%, colorless crystals, (mp: 81 °C). IR ($CHCl_3$): $\nu = 1647, 2926\ cm^{-1}$. ^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 ($CHCl_3$): $\nu = 1657, 1737, 2967\ cm^{-1}$. ^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%, colorless crystals (mp: 156.6 °C). IR ($CHCl_3$): $\nu = 1644, 2961, 3312\ cm^{-1}$; ^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.