Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2283–2287

TETRAHEDRON: *ASYMMETRY*

Efficient enzymatic kinetic resolution of 4-hydroxytetralone and 3-hydroxyindanone

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Received 10 June 2001; accepted 11 September 2001

Abstract—Both enantiomers of 4-acetoxy- and 4-hydroxytetralone have been obtained with high enantiomeric purity by kinetic resolution using enzymes. 3-Hydroxyindanone was successfully resolved using enzymatic transesterification. The absolute configuration of the products were established by literature precedence. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Chiral 4-hydroxytetralone and 3-hydroxyindanone are important intermediates for the synthesis of biologically active compounds. The chiral 1,4-disubstituted tetralin unit is found in the antidepressant molecule, Sertraline.[1] Several natural products like catalponol,[2] isocatalponol,[2] isoshinanolone[3] and palmarumycin CP_4[4] also contain the 4-hydroxytetralone unit (Fig. 1). Of these, palmarumycin CP_4 possesses potent antifungal activity. The chiral 1,2-substituted indane moiety is present in the anti-HIV agent indinavir[5] and the chiral 1,3-disubstituted indane unit is found in indatraline,[6] a non-selective monoamine reuptake inhibitor.

Lipases are extensively used for the synthesis of enantiomerically pure compounds via resolution of racemic mixtures.[7] The high stereoselectivity shown by low cost, partially purified enzymes combined with high catalytic activity in organic media make them very useful catalysts for enantiomeric resolution. The great importance of the two structural units **1** and **3** led us to explore an enzymatic resolution method for obtaining them in enantiomerically pure form.

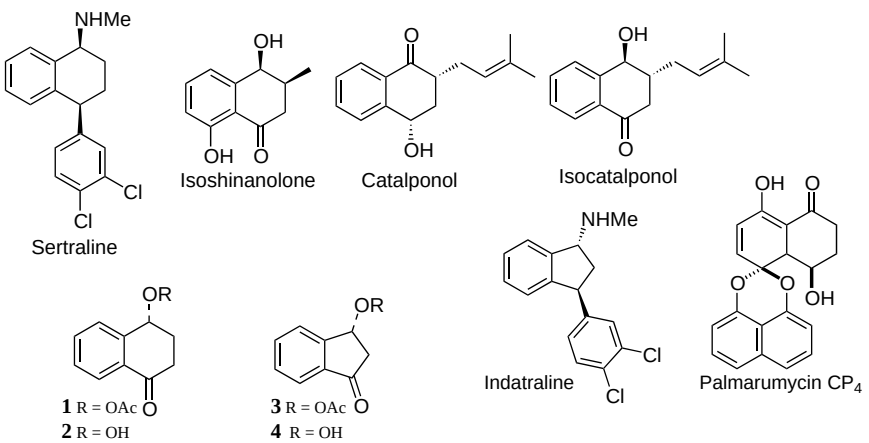

Figure 1.

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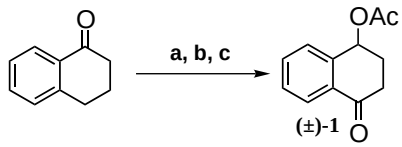
PII: S0957-4166(01)00404-9

2. Results and discussion

Commercially available 1-tetralone was converted to the racemic starting material 4-acetoxytetralone (±)-**1** in three steps viz. (i) reduction with sodium borohydride (ii) acetylation and (iii) oxidation with $KMnO_4$[8] as shown in Scheme 1. Following the usual practice for kinetic resolution, the enzymatic ester hydrolysis of (±)-**1** was investigated using the three readily available enzymes lipase *Amano PS*, *Candida cylindracea* lipase (CCL) and *Porcine pancreatic* lipase (PPL). Surprisingly, all the three enzymes effected hydrolysis, with PPL and lipase *Amano PS* exhibiting high enantioselectivity. The acetate (−)-**1** was obtained in >96% e.e.[9] The results are shown in Table 1.

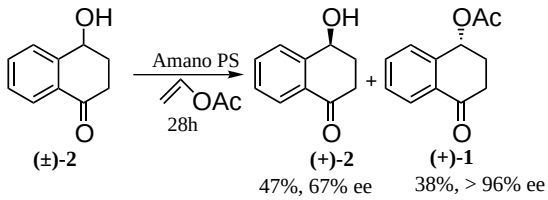
In a typical experiment, for enzymatic hydrolysis the racemic acetate was dissolved in acetonitrile (0.5 mL), phosphate buffer (pH 7.0, ~20 mL) was added and the mixture was stirred at room temperature in the presence of the enzyme (1.5 mass equivalents). The progress of the reaction was followed by tlc analysis and when approximately 50% conversion was attained, the products were isolated by extraction with ethyl acetate and the products viz. chiral acetate (−)-**1** and the enriched 4-hydroxytetralone (−)-**2** were separated by column chromatography. The e.e. of the hydrolysed product was determined by ^1H NMR spectral analysis of the corresponding Mosher's ester.[11] In the case of acetates, base-catalysed hydrolysis was carried out and the Mosher's ester was prepared.



Scheme 1. (a) $NaBH_4$, MeOH, 0°C–rt; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2 (90% yield for two steps); (c) $KMnO_4$, $MgSO_4 \cdot 7H_2O$, acetone, water (64% yield).

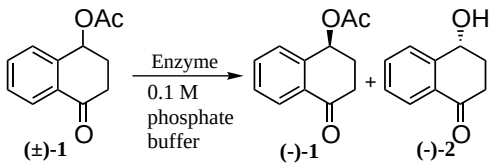
Since the hydrolytic activity of the lipases is different from their transesterification activity, it was of interest to study the enzymatic transesterification of 4-hydroxytetralone. Accordingly, the racemic hydroxy compound (±)-**2** was prepared by hydrolysis of the acetate (±)-**1** using K_2CO_3 in methanol (30°C, 15 min, 94% yield). In enzymatic transesterification studies of (±)-**2** using vinyl acetate as the acyl donor, the best result was obtained on using lipase *Amano PS* (<15% conversion was obtained with PPL and CCL even after 6 days) which showed an enantioselectivity of $E = 98$ (Scheme 2). Since the enzyme has same preference in hydrolysis and transesterification, the products obtained had complementary stereochemistry leading to (+)-**1** with >96% e.e. and (+)-**2** with 67% e.e. In a typical enzymatic transesterification reaction, the hydroxy compound (±)-**2** was dissolved in an excess of vinyl acetate and stirred in presence of the enzyme. When nearly 50% conversion had reached, the enzyme was filtered off, the solvent was removed under reduced pressure and the crude product was purified by column chromatography.

The absolute stereochemistry of the products was confirmed by synthesising (*R*)-1-acetoxytetralin using literature procedure[12] followed by oxidation with $KMnO_4$ to give the (4*R*)-acetoxytetralone. On comparison of optical rotation values, it became clear that enzymatic hydrolysis with all three enzymes led to the (*R*)-alcohol, whereas transesterification led to the (*R*)-acetate.



Scheme 2.

Table 1. Enzymatic hydrolysis of 4-acetoxytetralone **1**



No.	Enzyme	Reaction time (h)	Conversion c[a] (%)	Acetate		Alcohol		E[d]
				E.e.[b] (%)	Yield[c] (%)	E.e.[b] (%)	Yield[c] (%)	
1	CCL	25	58	92	46	67	54	16
2	PPL	48	50	>96	44	95	47	151
3	*Amano PS*	22	51	>96	48	91	54	69

[a] $c = \text{e.e.}_s/(\text{e.e.}_s + \text{e.e.}_p)$.
[b] Determined from ^1H NMR of the corresponding Mosher's ester.
[c] Isolated yield after column chromatography.
[d] Ref. 10.

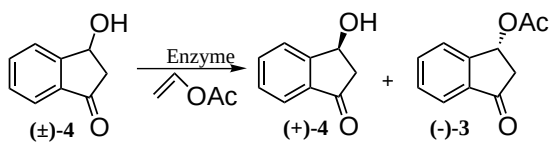
Using the three-step methodology as described already for the synthesis of (±)-**1**, 3-acetoxyindanone (±)-**3** was prepared starting from indan-1-one. However, enzymatic hydrolysis of the acetate in phosphate buffer led to elimination of acetic acid ultimately giving indenone. Therefore, 3-hydroxyindanone (±)-**4** was synthesised through acid catalysed hydrolysis of (±)-**3**. Enzymatic transesterification was carried out using vinyl acetate as the acyl donor (Scheme 3). While PPL was unable to effect transesterification, both CCL and *Amano PS* lipases were found to catalyse the reaction. Using lipase *Amano PS*, (+)-**4** was obtained in 41% yield and >96% e.e. In this case, the e.e. was determined through ^{1}H NMR experiments using Eu(hfc)$_3$ as chiral shift reagent. The results are summarised in Table 2.

In conclusion, we have developed an efficient asymmetric synthesis of 4-hydroxy/acetoxytetralone as well as 3-hydroxy and 3-acetoxyindanone by applying an enzymatic resolution methodology. As these compounds bear two useful functional groups, it is expected that they will serve as chiral building blocks for the synthesis of natural products and biologically active compounds.

3. Experimental

3.1. General

IR spectra were run on a Bomem MB-Series FT-IR spectrophotometer. NMR spectra were obtained using chloroform-*d* as solvent on Bruker DPX 300. Chemical shifts are given in δ scale with TMS as internal reference. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter using sodium vapour lamp and the rotations were taken in $CHCl_3$. CCL was purchased from Aldrich, PPL from Sigma and lipase *Amano PS* (*Pseudomonas cepacia*) from Amano pharmaceutical Co. Enantiomeric ratio E was calculated using Sih's method.[10] Analytical thin layer chromatography was performed on silica gel GF_{254} TLC plates. Purification by gravity column chromatography was carried out using silica gel (100–200 mesh). Mixtures of ethyl acetate and petroleum ether were used as eluent.



Scheme 3.

3.2. $KMnO_4$ oxidation of 1-tetralin acetate

To a cooled solution of 1-acetoxytetralin (0.67 g, 3.54 mmol) in acetone (15 mL) was added $MgSO_4 \cdot 7H_2O$ (2.08 g, 8.43 mmol) and water (5 mL). To this mixture $KMnO_4$ (2.88 g, 18.30 mmol) was added in small portions over 1 hour and stirred further for 4 h at room temperature. The solid was filtered off and the filtrate was treated with saturated solution of potassium metabisulphate. The resulting mixture was again filtered and the filtrate was extracted with dichloromethane (3×25 mL). The combined extract was washed with distilled water, saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was chromatographed on silica gel column. Elution with petroleum ether–ethyl acetate mixture (85:15) gave the product (±)-**1** as an oil (0.46 g, 64%). IR (neat): 2956, 1736, 1690, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3H), 2.26–2.45 (m, 2H), 2.68 (ddd, 1H, $J_1=17.5$ Hz, $J_2=6.9$ Hz, $J_3=4.8$ Hz), 2.94 (ddd, 1H, $J_1=17.4$ Hz, $J_2=9.5$ Hz, $J_3=5.1$ Hz), 6.14 (dd, 1H, $J_1=5.8$ Hz, $J_2=3.8$ Hz), 7.44–7.49 (m, 2H), 7.56–7.61 (m, 1H), 8.04–8.07 (m, 1H); ^{13}C NMR ($CDCl_3$): 21.11, 28.37, 34.28, 68.98, 127.09, 128.24, 128.94, 131.89, 133.83, 140.60, 170.37, 196.72; HRMS (M^+): 204.0797, $C_{12}H_{12}O_3$ requires 204.0786.

3.3. Enzymatic hydrolysis of 4-acetoxytetralone (±)-1

Racemic **1** (243 mg, 1.19 mmol) was dissolved in CH_3CN (0.5 mL). To this was added phosphate buffer (0.1 M, pH 7.0, 20 mL) and lipase PPL (362 mg). After stirring the reaction mixture for 2 days at room temperature (30°C), the reaction mixture was treated with saturated brine (3 mL) and filtered through Celite pad. The filtrate was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ solution, distilled water and brine and dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (petroleum ether–ethyl acetate 85:15–80:20) to get the product acetate (*S*)-(−)-**1** (106 mg, 44%) and alcohol (*R*)-(−)-**2** as a white solid (114 mg, 47%). The spectral characteristics of the acetate were comparable to that of the racemic acetate. (*S*)-(−)-**1**; e.e. >96%, $[\alpha]_D^{27}$−80.4 (*c*, 1.0, $CHCl_3$). (*R*)-(−)-**2**; e.e. 95%, $[\alpha]_D^{27}$−35.5 (*c*, 1.0, $CHCl_3$); mp: 41–43°C; IR (neat): 3405, 1679, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.13–2.46 (m, 3H), 2.61 (ddd, $J_1=17.2$ Hz, $J_2=9.6$ Hz, $J_3=4.6$ Hz), 2.94 (ddd, $J_1=17.4$ Hz, $J_2=7.4$ Hz, $J_3=4.5$ Hz), 4.99 (dd, $J_1=5.0$ Hz, $J_2=3.7$ Hz), 7.39–7.45 (m, 1H), 7.60–7.61 (m, 2H), 8.02 (d, 1H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$): 32.05, 35.11, 67.82, 126.99, 127.12,

Table 2. Enzymatic transesterification of racemic 3-hydroxyindanone **4**

No.	Enzyme	Reaction time	Conversion, *c* (%)	Acetate		Alcohol		*E*
				E.e. (%)	Yield (%)	E.e. (%)	Yield (%)	
1	CCL	35 h	41	73	29	51	63	16
2	PPL	7 days	–	–	–	–	91	–
3	*Amano PS*	25 h	53	85	43	>96	41	48

128.33, 131.12, 134.08, 145.32, 197.49. Anal. calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.41; H, 6.13.

3.4. Enzymatic transesterification of 4-hydroxytetralone

To a solution of (±)-**2** (133 mg, 0.65 mmol) in vinyl acetate (7 mL) was added lipase *Amano PS* (203 mg) and the mixture stirred at room temperature for 28 h. The enzyme was then filtered off and the solvent was evaporated. The crude product was subjected to column chromatography to get acetate (*R*)-(+)-**1** (64 mg, 38%), e.e. >96%, $[\alpha]_D^{27}$ 77.1 (*c*, 0.9, $CHCl_3$) and alcohol (*S*)-(+)-**2** (62 mg, 47%), e.e. 67%, $[\alpha]_D^{27}$ 23.5 (*c*, 0.7, $CHCl_3$).

3.5. Hydrolysis of (−)-1 using K_2CO_3

The following procedure is representative: acetate (−)-**1** (60 mg, 0.29 mmol) was dissolved in methanol (5 mL) containing a few drops of water and K_2CO_3 (46 mg, 0.33 mmol) was added and the mixture stirred at rt for 10 min. The reaction mixture was concentrated to remove methanol, diluted with water and extracted with dichloromethane. The crude product was purified by column chromatography to yield the product (42 mg, 88%). The spectral data was identical with that prepared earlier.

3.6. Determination of the e.e. of alcohol 2 by making the corresponding Mosher's ester

To a solution of (±)-**2** (31 mg, 0.19 mmol) in dry CH_2Cl_2 (1.5 mL) was added DMAP (4 mg, 0.03 mmol) and Mosher's acid (52 mg, 0.22 mmol). The mixture was cooled in an ice bath and DCC (58 mg, 0.28 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirring was continued until the alcohol was completely converted to the ester as evident from tlc (28 h). The reaction mixture was worked up by filtering out the dicyclohexyl urea formed in the reaction and the filtrate was concentrated and purified by column chromatography (eluent petroleum ether–ethyl acetate 95:5). The chromatography yielded the ester (67 mg, 93%). ^{1}H NMR ($CDCl_3$): 2.36–2.82 (m, 4H), 3.47, 3.52 (s, 3H, -OMe of the two diastereomeric ester), 6.31–6.33 (m, 1H), 7.29–7.61 (m, 8H), 8.05 (uneven triplet, 1H).

The same procedure was used for making Mosher's ester of optically enriched alcohols.

3.7. $KMnO_4$ oxidation of 1-acetoxyindane

Procedure was the same as in the case of (±)-**1**. The title compound was prepared from acetoxyindane in 80% yield as a yellow oily liquid. IR (neat): 2937, 1738, 1723, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$:CCl_4, 7:3): 2.13 (s, 3H), 2.78 (dd, 1H, J_1 = 19.2 Hz, J_2 = 2.6 Hz), 3.18 (dd, J_1 = 19.2 Hz, J_2 = 7.1 Hz), 6.36 (dd, J_1 = 6.9 Hz, J_2 = 2.4 Hz), 7.59 (m, 1H), 7.68 (m, 2H), 7.79 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$:CCl_4, 7:3): 20.92, 43.72, 69.77, 123.34, 126.77, 129.90, 135.09, 137.08, 151.36, 170.64, 201.56; HRMS (M^+): 190.0618, $C_{11}H_{10}O_3$ requires 190.0630.

3.8. Acid-catalyzed hydrolysis of (±)-3

To a solution of acetoxyindanone (±)-**3** (286 mg, 1.50 mmol) in acetone (10 mL), 20% HCl (10 mL) was added and stirred at room temperature for 24 h. The reaction mixture was treated with $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×10 mL). The extract was finally dried over anhydrous Na_2SO_4. After removal of the solvent and purification by column chromatography (petroleum ether:ethyl acetate, 80:20) yielded (±)-**4** as a colorless oil (189 mg, 85%). IR (neat): 3393, 1699, 1601 cm^{-1}; ^{1}H NMR ($CDCl_3$:CCl_4, 7:3): 2.49 (dd, 1H, J_1 = 18.9 Hz, J_2 = 2.7 Hz), 2.99 (dd, 1H, J_1 = 18.9 Hz, J_2 = 6.8 Hz), 3.28 (brs, 1H), 5.29 (m, 1H), 7.38 (m, 1H), 7.59 (m, 3H); ^{13}C NMR ($CDCl_3$:CCl_4, 7:3): 47.07, 68.38, 123.23, 125.94, 129.37, 135.24, 136.29, 155.30, 203.40; HRMS (M^+): 148.0539, $C_9H_8O_2$ requires 148.0524.

3.9. Enzymatic transesterification of 3-hydroxyindanone

To a solution of 3-hydroxyindanone (±)-**4** (58 mg, 0.39 mmol) in vinyl acetate (5 mL) was added lipase *Amano PS* (89 mg). After stirring for 25 h, the reaction mixture was filtered and concentrated in vacuo. Purification by column chromatography gave acetate (*R*)-(−)**3** (32 mg, 43%) e.e. 85%; $[\alpha]_D^{27}$ −8.9 (*c*, 1.2, $CHCl_3$) and alcohol (*S*)-(+)-**4** (24 mg, 41%), e.e. >96%; $[\alpha]_D^{27}$ 99.5 (*c*, 0.9, $CHCl_3$).

3.10. Determination of the e.e. of 3 by using the chiral shift reagent, $Eu(hfc)_3$

Good separation of the methyl signals ($OCOCH_3$) of the two enantiomers were achieved by the sequential addition of $Eu(hfc)_3$ (5 mg) to a solution of racemic (±)-**3** (5 mg) in $CDCl_3$ (0.5 mL). Baseline separation of the methyl signals were obtained with 25 mg of shift reagent. The difference in chemical shifts of the CH_3 of acetate (±)-**3** was found to be 0.118 ppm. The hydroxy compound (+)-**4** was converted to the acetate (using Ac_2O, Et_3N, and DMAP) and its e.e. determined by NMR as above.

Acknowledgements

The authors thank Dr. A. T. Anilkumar for a gift of the lipase *Amano PS*. S.J. thanks the CSIR, New Delhi for research fellowship.

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