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TETRAHEDRON: *ASYMMETRY*

# Introduction of a quaternary stereogenic center to oxindole using cholinesterase-catalyzed asymmetric hydrolysis

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**Abstract**—Prochiral diesters bearing an oxindole skeleton were efficiently prepared from oxindole. Cholinesterase-catalyzed hydrolysis of prochiral dipropionate afforded an optically active monoalcohol of 95% e.e. The obtained monoalcohol might find use as a versatile intermediate in the enantioselective synthesis of indole alkaloids. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Synthesis of quaternary stereogenic centers remains a challenge for synthetic organic chemists.[1] Some methods, such as diastereoselective reaction using chiral auxiliaries, enantioselective reaction using transition-metals, and enzymatic procedures, have been reported for the formation of quaternary stereogenic centers with stereoselectivity.[2] Among them, enzymatic methods are attractive to many organic and medicinal chemists because enzymatic reactions require only mild reaction conditions, react with high selectivity and accept a wide range of substrates.[3] The formation of a quaternary stereogenic center from either a prochiral or *meso* compound by enzymatic methods has been reported by several groups, including us.[4] However, such induction in an indole skeleton by enzymatic methods has not yet been studied. Oxindoles bearing a quaternary stereogenic carbon[5] are found in natural products, such as spirotryprostatins[6] and horsfiline[7] (Fig. 1), and are also regarded as chiral building blocks in indole syntheses.[5] Herein, we report the asymmetric hydrolysis of prochiral 3,3-bis(acyloxymethyl)-2-oxindole, which is a potential chiral building block in the synthesis of the aforementioned natural products.

## 2. Results and discussion

Prochiral diesters **3** for enzymatic hydrolysis were prepared from oxindole (Scheme 1). Initially, oxindole was protected as its methoxymethyl (MOM) amide by treatment with MOMCl in 63% yield. After several attempts the C-(3) position of the oxindole skeleton was successfully dihydroxymethylated by treatment with paraformaldehyde in the presence of $K_2CO_3$ to afford the diol **2** in 96% yield. The obtained diol **2** was converted into the prochiral diesters **3** by acylation with acid anhydrides (**3a**: acetic anhydride, 80%; **3b**: propionic anhydride, 85%; **3c**: butyric anhydride, 32%; **3d**:

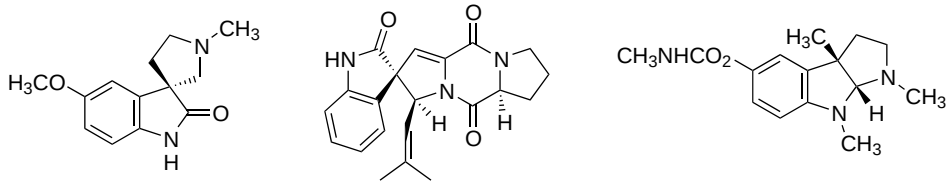


**Figure 1.**

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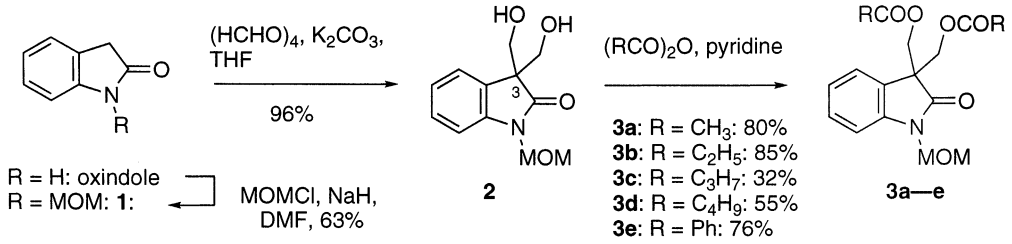



**Scheme 1.**

valeric anhydride, 55%; **3e**: benzoic anhydride, 76%, respectively).

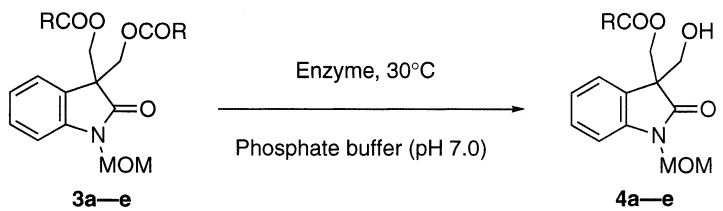
The introduction of the quaternary stereogenic carbon was first attempted by enzymatic transesterification of diol **2** using *Pseudomonas cepacia* lipase (PCL, Amano PS);[4c,8] unfortunately the transesterification reaction did not proceed.

We next examined the hydrolysis of diesters **3** using four hydrolytic enzymes. The enzymatic hydrolysis was performed in 0.1 M phosphate buffer (pH 7.0) at 30°C and terminated when diol **2** was formed as indicated by TLC. The results of hydrolyses are summarized in Table 1. The enantiomeric excess (% e.e.) of the hydrolyzed products was determined by HPLC using (±)-**4** as reference standards. In the case of prochiral diacetate **3a**, hydrolysis using PCL did not proceed at all, but hydrolyses by PLE, PPL, and cholinesterase[4a,9] afforded monoalcohol **4a** in 8–53% chemical yields. Disappointingly, the obtained monoalcohol **4a** had low e.e. (entries 2–4, 30–47% e.e.).

The bulk of the acyl function is known to affect the enantioselectivity of enzymatic hydrolysis reactions.[3] This led us to examine the enzymatic hydrolysis of the dipropionate **3b**. Hydrolysis of **3b** using cholinesterase afforded the monoalcohol **4b** in 20% yield with a moderate e.e. of 70%. The hydrolysis of **3b** with PLE or PPL afforded **4b** with low e.e. These results encouraged us to further study the effect of the acyl function on the selectivity of reactions with cholinesterase.

Dibutyrate **3c**, divalerate **3d**, and dibenzoate **3e** were examined in the cholinesterase reactions (entries 8–12), but hydrolysis of these diacylates **3c**–**3e** either afforded monoalcohols with very low e.e. (entries 8–10), or did not proceed (entries 11 and 12). Therefore, we focused our attention on optimization of the reaction between dipropionate **3b** and cholinesterase. After varying the

**Table 1.**

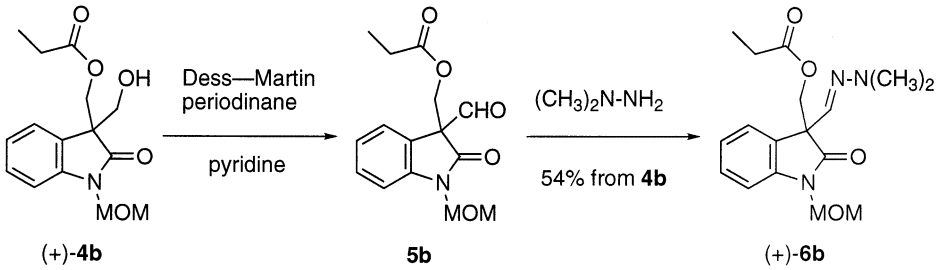



| Entry | Substrate | Enzyme[a] | Time | Monoalcohol (**4**) | | | Recovery (%) |
|---|---|---|---|---|---|---|---|
| | | | | Yield (%) | e.e.[b] (%) | Sign of [α] | |
| 1 | **3a**: R = $CH_3$ | PCL | 48 | 0 | – | – | 100 |
| 2 | **3a**: R = $CH_3$ | PLE | 1 | 53 | 31 | (−) | 40 |
| 3 | **3a**: R = $CH_3$ | PPL | 9 | 34 | 47 | (+) | 53 |
| 4 | **3a**: R = $CH_3$ | Cholinesterase | 5 | 8 | 30 | (+) | 59 |
| 5 | **3b**: R = $C_2H_5$ | PLE | 0.25 | 47 | 41 | (−) | 20 |
| 6 | **3b**: R = $C_2H_5$ | PPL | 26 | 27 | 12 | (+) | 58 |
| 7 | **3b**: R = $C_2H_5$ | Cholinesterase | 8 | 20 | **70** | (+) | 77 |
| 8 | **3c**: R = $C_3H_7$ | PLE | 1.5 | 13 | 46 | (−) | 49 |
| 9 | **3d**: R = $C_4H_9$ | Cholinesterase | 55 | 3 | 2 | (+) | 78 |
| 10 | **3e**: R = Ph | Cholinesterase | 82 | 1 | 26 | – | 81 |
| 11 | **3e**: R = Ph | PLE | 48 | 0 | – | – | 100 |
| 12 | **3e**: R = Ph | PPL | 48 | 0 | – | – | 100 |
| 13 | **3b**: R = $C_2H_5$ | Cholinesterase | 120 | 38 | **95** | (+) | 40[c] |

[a] Enzymes: PCL, *Pseudomonas cepacia* lipase; PPL, porcine pancreatic lipase; PLE, pig liver esterase; cholinesterase, cholinesterase from electric eel.

[b] HPLC: column, Daicel Chiralpak AD; eluent, hexane/*i*-PrOH = 80/1; flow rate, 0.5 ml/min; detection, UV (254 nm).

[c] Prochiral diol **2** was isolated in 16% yield.




**Scheme 2.**

reaction temperature and investigating the effect of added co-solvents in several reactions, we found that hydrolysis of **3b** using cholinesterase afforded monoalcohol **4b** with high 95% e.e. and 38% yield by an extended reaction time of 5 days. The monoalcohol **4b** was isolated with the recovered dipropionate **3b** (40%) and the diol **2** (16%). The improvement in e.e. may result from kinetic resolution of the monoalcohol **4b**. (Taking into consideration the recovered dipropionate **3b** and the diol **2**, the yield of the homochiral monoalcohol **4b** was 86%.)

In the formation of the aldehyde **5b** (Scheme 2), oxidation of the free hydroxyl group of (+)-**4b** was attempted by several methods including PCC, PDC, and Swern oxidations. However, using these reagents the oxidation afforded a complex mixture. Finally, it was found that oxidation with Dess–Martin periodinane afforded aldehyde **5b**, which was unstable at room temperature; therefore, the aldehyde was isolated as its dimethylhydrazone derivative (+)-**6b** in 54% yield.

## 3. Conclusion

Prochiral diesters **3** bearing an indole skeleton were prepared from oxindole. Enzymatic hydrolysis of dipropionate **3b** using cholinesterase from electric eel proceeded in enantioselective manner to afford the optically active monoalcohol (+)-**4b** of 95% e.e. Synthesis of natural products using (+)-**4b** is currently underway.

## 4. Experimental

$^1$H NMR spectra were determined at 270 MHz unless otherwise noted. $CH_2Cl_2$ was distilled from $P_2O_5$. THF was purchased from Kanto Chemical Corp., and used without distillation. PLE, PPL, and cholinesterase from electric eel were purchased from Sigma Corp., and PCL (Amano PS) was given by Amano Pharmaceutical Corp. (Japan), and all were used as received. Infrared spectra were recorded on a Jasco A-100 spectrometer (KBr or neat). EIMS, FABMS, and HRMS spectra were taken on a Jeol JMS 610H or Jeol SX102 spectrometer.

### 4.1. 1-(Methoxymethyl)-2-oxindole 1

A solution of oxindole (100 mg, 0.75 mmol) in DMF (1.5 mL) was added dropwise to a stirred suspension of NaH (60% oil dispersion, 97 mg 2.4 mmol) in DMF (1.5 mL) at 0°C, and the mixture stirred for 15 min. Methoxymethyl chloride (0.2 mL, 2.7 mmol) was added dropwise to the stirred solution, and the solution was stirred for 3 h at room temperature. The solution was neutralized with 10% aqueous HCl, extracted with EtOAc, washed with brine, and dried over $Na_2SO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (30% EtOAc in hexane) to give **1** (84 mg, 63%) as a colorless solid: mp 75–77°C; IR (KBr) 1710 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 7.24–7.31 (m, 2H), 7.01–7.11 (m, 2H), 5.13 (s, 2H), 3.61 (s, 2H), 3.35 (s, 3H); EIMS $m/z$: 177 ($M^+$, 40), 146 (89), 43 (100).

### 4.2. 3,3-Bis(hydroxymethyl)-1-(methoxymethyl)-2-oxindole 2

A mixture of **1** (568 mg, 3.2 mmol), $K_2CO_3$ (1.4 g, 10 mmol), and $(HCHO)_4$ (1.9 g, 18 mmol) in THF (30 mL) was stirred at room temperature for 10 min. The mixture was neutralized with 10% aqueous HCl, extracted with EtOAc, washed with brine, and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (80% EtOAc in hexane) to afford **2** (729 mg, 96%) as colorless solid: mp 98–101°C; IR (KBr) 3400 (br), 1680 cm$^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 7.32–7.38 (m, 2H), 7.08–7.18 (m, 2H), 5.16 (s, 2H), 3.96–4.10 (m, 4H), 3.32 (s, 3H), 2.23–2.27 (m, 2H); EIMS $m/z$: 237 ($M^+$, 34), 206 (100); FAB(+)HRMS calcd for $C_{12}H_{16}NO_4$ ($M^+$+H) 238.1079, found 238.1079.

### 4.3. 3,3-Bis(acetoxymethyl)-1-(methoxymethyl)-2-oxindole 3a

A solution of **2** (40 mg, 0.168 mmol), pyridine (0.05 mL, 0.672 mmol), and $Ac_2O$ (0.05 mL, 0.504 mmol) in $CH_2Cl_2$ (1 mL) was stirred at room temperature for 4 h. The solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% EtOAc in hexane) to give **3a** (43 mg, 80%) as a colorless oil: IR (neat) 1740, 1710 cm$^{-1}$; $^1$H NMR

($CDCl_3$): $\delta$ 7.29–7.37 (m, 2H), 7.06–7.14 (m, 2H), 5.17 (s, 2H), 4.65 (d, $J=10.8$ Hz, 2H), 4.26 (d, $J=10.8$ Hz, 2H), 3.33 (s, 3H), 1.93 (s, 6H); FAB(+)HRMS calcd for $C_{16}H_{19}NO_6$ ($M^+$) 321.1213, found 321.1187.

### 4.4. 1-(Methoxymethyl)-3,3-bis(propionyloxymethyl)-2-oxindole 3b

Compound **3b** was prepared from **2** and propionic anhydride, analogously to the preparation of **3a**: a colorless oil; 85%; IR (neat) 1730 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.05–7.36 (m, 4H), 5.17 (s, 2H), 4.69 (d, $J=11.2$ Hz, 2H), 4.25 (d, $J=11.2$ Hz, 2H), 3.34 (s, 3H), 2.18 (q, $J=7.6$ Hz, 2H), 2.17 (q, $J=7.6$ Hz, 2H), 0.97 (t, $J=7.6$ Hz, 6H); FAB(+)HRMS calcd for $C_{18}H_{23}NO_6$ ($M^+$) 349.1525, found 349.1528.

### 4.5. 3,3-Bis(butyryloxymethyl)-1-(methoxymethyl)-2-oxindole 3c

Compound **3c** was prepared from **2** and butyric anhydride analogously to the preparation of **3a**: a colorless oil; 32%; IR (neat) 1730 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.27–7.36 (m, 2H), 7.05–7.12 (m, 2H), 5.17 (s, 2H), 4.70 (d, $J=10.9$ Hz, 2H), 4.24 (d, $J=10.9$ Hz, 2H), 3.34 (s, 3H), 2.14 (t, $J=7.6$ Hz, 4H), 1.46 (sextet, $J=7.5$ Hz, 4H), 0.78 (t, $J=7.6$ Hz, 6H); FABMS $m/z$: 377 ($M^+$).

### 4.6. 1-(Methoxymethyl)-3,3-bis(pentanoyloxymethyl)-2-oxindole 3d

Compound **3d** was prepared from **2** and valeric anhydride analogously to the preparation of **3a**: a colorless oil; 55%; IR (neat) 1730 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.27–7.35 (m, 2H), 7.04–7.12 (m, 2H), 5.17 (s, 2H), 4.70 (d, $J=11.0$ Hz, 2H), 4.23 (d, $J=11.0$ Hz, 2H), 3.34 (s, 3H), 2.15 (t, $J=7.6$ Hz, 4H), 1.34–1.45 (m, 4H), 1.08–1.19 (m, 4H), 0.80 (t, $J=7.3$ Hz, 6H); FABMS $m/z$: 406 ($M^+$+H).

### 4.7. 3,3-Bis(benzoyloxymethyl)-1-(methoxymethyl)-2-oxindole 3e

Compound **3e** was prepared from **2** and benzoic anhydride analogously to the preparation of **3a**: colorless solids; 76%; mp 108–111°C; IR (KBr) 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.84–7.88 (m, 4H), 7.50–7.57 (m, 2H), 7.30–7.47 (m, 6H), 7.06–7.14 (m, 2H), 5.21 (s, 2H), 4.92 (d, $J=10.9$ Hz, 2H), 4.79 (d, $J=10.9$ Hz, 2H), 3.32 (s, 3H); FABMS $m/z$: 446 ($M^+$+H).

### 4.8. (+)-[3-(Hydroxymethyl)-1-(methoxymethyl)-2-oxoindolin-3-yl]methyl propionate 4b

A suspension of **3b** (55 mg, 0.16 mmol) and cholinesterase (0.2 mg) in phosphate buffer (0.1 M, pH = 7.0, 6.0 mL) was stirred at 30°C for 120 h. The solution was extracted with EtOAc, and dried over $Na_2SO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% EtOAc in hexane afforded the recovered **3b** (23 mg, 40%), with 50% EtOAc in hexane afforded **4b** (18 mg, 38%), and with 80% EtOAc in hexane gave diol **2** (6 mg, 16%). **4b**: a colorless oil; 95% e.e.; $[\alpha]_D^{25}$ +49.0 ($c$ 0.27, $CHCl_3$); IR (neat) 3450 (br), 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.30–7.37 (m, 2H), 7.07–7.26 (m, 2H), 5.19 (d, $J=10.9$ Hz, 1H), 5.14 (d, $J=10.9$ Hz, 1H), 4.73 (d, $J=10.9$ Hz, 1H), 4.37 (d, $J=10.9$ Hz, 1H), 3.85–4.02 (m, 2H), 3.33 (s, 3H), 2.33 (br s, 1H), 2.18 (q, $J=7.6$ Hz, 1H), 2.17 (q, $J=7.6$ Hz, 1H), 0.97 (t, $J=7.6$ Hz, 3H); FAB(+)HRMS calcd for $C_{15}H_{20}NO_5$ ($M^+$+H) 294.1341, found 294.1336.

### 4.9. (+)-[3-(Hydroxymethyl)-1-(methoxymethyl)-2-oxoindolin-3-yl]methyl acetate 4a

Hydrolysis of **3a** by PPL afforded **4a** (34%, 47% e.e.) as a colorless oil: $[\alpha]_D^{25}$ +19.5 ($c$ 0.89, $CHCl_3$); IR (neat) 3480 (br), 1720 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.20–7.37 (m, 2H), 7.07–7.27 (m, 2H), 5.19 (d, $J=10.9$ Hz, 1H), 5.14 (d, $J=10.9$ Hz, 1H), 4.68 (d, $J=10.9$ Hz, 1H), 4.40 (d, $J=10.9$ Hz, 1H), 3.84–4.10 (m, 2H), 3.32 (s, 3H), 2.50 (br, 1H), 1.91 (s, 3H); EIMS $m/z$: 279 ($M^+$, 68), 248 (100).

### 4.10. (−)-[3-(Hydroxymethyl)-1-(methoxymethyl)-2-oxoindolin-3-yl]methyl butyrate 4c

Hydrolysis of **3c** by PLE afforded **4c** (13%, 46% e.e.) as a colorless oil: $[\alpha]_D^{25}$ −18.3 ($c$ 0.27, $CHCl_3$); IR (neat) 3450 (br), 1720 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.26–7.37 (m, 2H), 7.06–7.15 (m, 2H), 5.18 (d, $J=10.9$ Hz, 1H), 5.15 (d, $J=10.9$ Hz, 1H), 4.75 (d, $J=11.0$ Hz, 1H), 4.37 (d, $J=11.0$ Hz, 1H), 3.99 (dd, $J=9.2$, 11.2 Hz, 1H), 3.87 (dd, $J=3.6$, 11.2 Hz, 1H), 3.34 (s, 3H), 2.32 (m, 1H), 2.13 (t, $J=7.4$ Hz, 1H), 2.12 (t, $J=7.4$ Hz, 1H), 1.44 (sextet, $J=7.4$ Hz, 2H), 0.77 (t, $J=7.4$ Hz, 3H); FABMS $m/z$: 308 ($M^+$+H).

### 4.11. (+)-[3-Dimethylhydrazonomethyl)-1-(methoxymethyl)-2-oxoindolin-3-yl]methyl propionate 6b

A solution of **4b** (18 mg, 61 μmol) in $CH_2Cl_2$ (0.5 mL) was added dropwise to the stirred solution of Dess–Martin periodinane (130 mg, 0.31 mmol) in $CH_2Cl_2$ (1 mL) at 0°C, and the solution was stirred for 2 h. Then a solution of dimethylhydrazine (4.0 mg, 66 μmol) in $CH_2Cl_2$ (0.5 ml) was added dropwise at 0°C and the mixture was stirred for 1 h. The solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% EtOAc in hexane) to leave **6b** (11 mg, 54%, 95% e.e.) as a colorless oil: $[\alpha]_D^{21}$ +44.2 ($c$ 0.70, $CHCl_3$); IR (neat) 1710 (br), 1610 $cm^{-1}$; $^1H$ NMR: $\delta$ 7.26–7.37 (m, 2H), 7.05–7.13 (m, 2H), 6.36 (s, 1H), 5.22 (d, $J=10.9$ Hz, 1H), 5.12 (d, $J=10.9$ Hz, 1H), 4.93 (d, $J=10.9$ Hz, 1H), 4.48 (d, $J=10.9$ Hz, 1H), 3.35 (s, 3H), 2.78 (s, 6H), 2.08 (m, 2H), 0.85 (t, $J=7.6$ Hz, 3H); EI-HRMS calcd for $C_{17}H_{23}N_3O_4$ ($M^+$) 333.1688, found 333.1676.

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