Lipase-Mediated Resolution of Inden-1-ol

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Optically pure inden-1-ol has been obtained efficiently in both enantiomeric forms *via* kinetic deacylation of racemic 1-acetoxyindene using lipase PS.

Key words lipase-mediated kinetic resolution; inden-1-ol,1-acetoxyindene; *cis*-1-aminoindan-2-ol

Optically active inden-1-ol (**1**) has potential utility as a key starting material for the preparation of HIV-1 protease inhibitors such as L-735,524 and L-754,394.[1] Synthesis of optically active inden-1-ol (**1**), however, has been little studied and only one enantiotopical preparation[2] has been reported so far. The preparation described was accomplished by kinetic hydrolysis of the racemic 1-acetoxyindene (±)-**2** using a mold, *Rhizopus nigricans*, which gave (−)-**1** in 46% yield with 97% ee; the configuration of the product was determined by using the Harada–Nakanishi exciton chirality method.[3] Since no strict evidence supporting the claimed optical purity or the stereochemistry was presented, we examined the resolution of racemic inden-1-ol (±)-**1** to establish a more expedient procedure by employing lipase-mediated kinetic acylation and deacylation reactions.[4]

We first examined the kinetic acetylation of racemic inden-1-ol (±)-**1** with vinyl acetate in an organic solvent in the presence of a lipase. However, no practically satisfactory conditions could be established, though partial optical resolution was observed using lipase PS-on-Celite (*Pseudomonas* sp., Amano) (*ca.* 22% ee) (Chart 1). In this examination, both the chirality and optical purity of the products were found to be readily evaluative by HPLC analysis using a chiral column.

We next examined the kinetic deacetylation of racemic 1-acetoxyindene (±)-**2** in a phosphate buffer-acetone solution in the presence of a lipase.[5] Among various enzymes tested, lipase PS (*Pseudomonas* sp., Amano) gave the best result. From 10 mg/mmol of the racemic acetate (±)-**2**, (*R*)-inden-1-ol [(*R*)-**1**] was obtained in 46% yield in 94% ee, with recovery of optically pure (*S*)-1-acetoxyindene [(*S*)-**2**] in 45% yield after 48 h. Optically pure (*R*)-inden-1-ol [(*R*)-**1**] could be obtained in 29% yield leaving the (*S*)-acetate [(*S*)-**2**] in 86% ee with 42% recovery if the reaction was terminated after 24 h. Comparing the optical rotation values, there is a considerable difference between the reported value for (*R*)-**1** [$[\alpha]_D$ −164° ($CHCl_3$) for 97% ee[2]] and the present value for (*R*)-**1** [$[\alpha]_D^{31}$ −225.5° ($CHCl_3$) for 94% ee], though the signs of the optical rotation were identical. The enantiomeric (*S*)-alcohol (*S*)-**1** was obtained in 70% yield on methanolysis of the (*S*)-acetate (*S*)-**2**, accompanied with 19% of the isomerization product, 1-indanone.

Having accomplished the resolution of inden-1-ol (**1**), we examined the transformation of the optically pure acetate (*S*)-**2** into known *cis*-1-aminoindan-2-ol to confirm the absolute configuration of the resolution products unambiguously, as well as to establish an alternative route to the key starting material for the desired HIV-1 protease inhibitors.[1]

Unfortunately, epoxidation of the (*S*)-acetate **2** did not proceed in a stereoselective manner. When (*S*)-**2** was treated with *m*-chloroperbenzoic acid (*m*CPBA), a mixture of the *anti*-epoxide **3** and the *syn*-epoxide **4** was obtained as a readily separable 1 : 1 mixture in 80% total yield. The structures of these compounds were readily distinguished

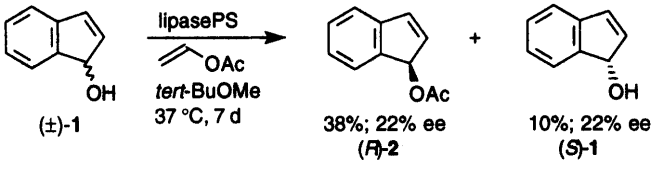

Chart 1

Table 1. Kinetic Deacylation of Racemic 1-Acetoxyindene[a]

Entry	Lipase[b] (mg/mmol of **2**)	Time (h)	(*S*)-**1** Yield (%) : ee[d] (%)	(*R*)-**2** Yield (%) : ee[c] (%)
1	MY (100)	2	11 : 88	67 : 17
2	OF (100)	2	25 : 75	51 : 46
3	AY (100)	2	12 : 87	64 : 22
4	PPL (100)	2	3 : 85	75 : 7
5	PS (100)	2	28 : 97	47 : 63
6	PS (10)	3	20 : >99	58 : 39
7	PS (10)	24	29 : 98	42 : 86
8	PS (10)	48	46 : 94	45 : >99

a) Reactions were carried out in a mixture of 0.1 M phosphate buffer and acetone (9 : 1, v/v) (10 ml/mmol of **2**) at 37 °C. *b*) MY (*Candida cylindracea*, Meito), OF (*Candida cylindracea*, Meito), AY (*Candida rugosa*, Amano), PPL (Porcine pancreatic lipase, Sigma), PS (*Pseudomonas*, sp., Amano). *c*) Determined by HPLC using a chiral column (Chiralcel OD, 1% iso-PrOH/hexane). *d*) Determined by HPLC using a chiral column (Chiralcel OD, 3% iso-PrOH/hexane).

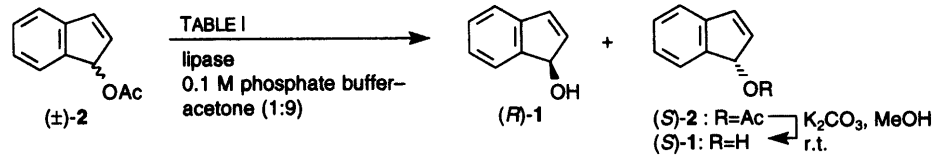

Chart 2

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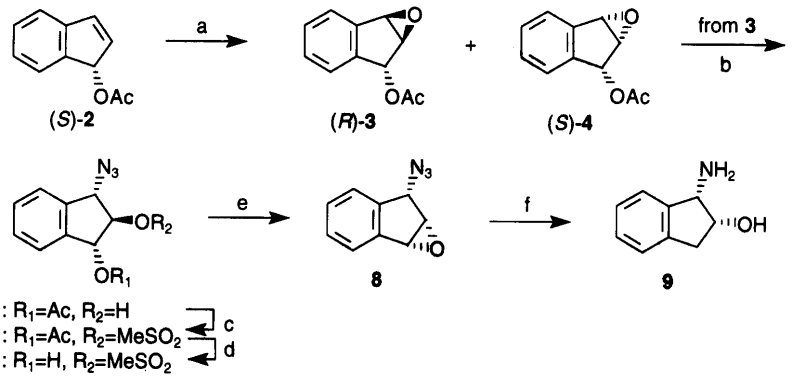

Reagents and conditions: a) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C—r.t., b) NaN_3, NH_4Cl, aq. DMF, 80 °C, c) MesCl, Et_3N, CH_2Cl_2, 0 °C, d) K_2CO_3, MeOH, r.t., e) NaH, THF, r.t., f) H_3(3 kg/cm^2), 10% Pd–C, EtOH.

Chart 3

from the ^{1}H-NMR spectra which exhibited the benzylic-acetoxy methine protons at δ 6.09 as a singlet for the *anti*-isomer **3** and at δ 6.05 as a doublet (J=2.4 Hz) for the *syn*-isomer **4**, as expected from their dihedral angles. In contrast, the epoxidation of the (*R*)-alcohol (*R*)-**1** under the same conditions, as well as under the Sharpless conditions[6] using vanadium(II) acetylacetonate and *tert*-butyl hydroperoxide resulted in complete decomposition of the starting material.

The *anti*-epoxide **3** separated was then exposed to an excess of sodium azide (5 eq) in hot aqueous *N*,*N*-dimethylformamide (DMF) (8:1, v/v) containing an equimolar amount of ammonium chloride[7] to afford regioselectively the acetoxy-azide **5** in 97.7% yield as a single product. On sequential methanesulfonylation and methanolysis, the acetoxy-azide **5** afforded the hydroxy-methanesulfonate **7**, which was immediately treated with sodium hydride to furnish the epoxy-azide **8** in 96.5% overall yield. Finally, **8** was hydrogenated under medium pressure of hydrogen (3 kg/cm^2) on palladized charcoal to initiate reduction of the azide functionality and regioselective hydrogenolysis of the epoxide bond, affording *cis*-1-aminoindan-2-ol[8] **9** in 69% yield. Since the product was found to have 1*S*,2*R*-configuration by comparison of its sign of rotation with that reported,[8] the structures of the resolution products have been established unambiguously. The present results, at the same time, confirm the validity of the assignment[2] based on the Harada–Nakanishi exciton chirality method.[3]

In conclusion we have developed an efficient method for the resolution of racemic inden-1-ol by employing lipase-mediated kinetic deacylation reaction. Moreover, we have determined the absolute configuration of the products unambiguously by transformation of the optically pure (*S*)-acetate into (1*S*,2*R*)-*cis*-1-aminoindan-2-ol, a key starting material of HIV-1 protease inhibitors,[1,9] as well as a chiral auxiliary.[10] A more efficient procedure for the transformation of the optically pure products into optically pure *cis*-1-aminoindan-2-ol is under investigation.

Experimental

IR spectra were recorded on a JASCO-IR-700 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GX500 spectrometer (500 MHz). Mass spectra were measured on a JEOL DX303 instrument. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Optical purities were determined on a Gilson Model 370 instrument equipped with a chiral column.

Typical Example of Kinetic Acetylation of Racemic Inden-1-ol (±)-1 A suspension of racemic inden-1-ol[11] (±)-**1** (100 mg, 0.76 mmol), vinyl acetate (0.13 mg, 1.15 mmol), and lipase PS-on-Celite (75.6 mg, 100 mg/mmol of **1**) in *tert*-BuOMe (10 ml) was stirred at 37 °C for 7 d. The suspension was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (eluent: AcOEt–hexane, 1:10, v/v) to give (*R*)-1-acetoxyindene [(*R*)-**2**], 50 mg (38.0%), as a pale yellow oil and (*S*)-inden-1-ol [(*S*)-**1**], 10 mg (10.0%), as a colorless solid. Optical purities of the products were determined to be 22% ee for (*R*)-**2** and 22% ee for (*S*)-**1** by HPLC using a chiral column (or Chiralcel OD, eluent: iso-PrOH–hexane, 1% (v/v) or 3% v/v).

Typical Example of Kinetic Deacetylation of Racemic 1-Acetoxyindene (±)-2 A suspension of racemic 1-acetoxyindene (±)-**2** (1.0 g, 5.75 mmol) and lipase PS (57.5 mg, 10 mg/mmol of (±)-**2**) in acetone–phosphate buffer (0.1 M) mixture (1:9, v/v, 58 ml) was stirred at 37 °C for 48 h. The suspension was filtered through a Celite pad and the filtrate was extracted with Et_2O. The extract was dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed on silica gel (eluent: AcOEt–hexane, 1:10, v/v) to give (*S*)-1-acetoxyindene [(*S*)-**2**], 446 mg (44.6%), $[\alpha]_D^{25}$ +82.3° (c=0.21, $CHCl_3$), as a pale yellow oil and (*R*)-inden-1-ol [(*R*)-**1**], 350 mg (46.1%), $[\alpha]_D^{31}$ −225.5° (c=0.10, $CHCl_3$), as a colorless solid. Optical purities of the products were determined to be >99% ee for (*S*)-**2** and >94% ee for (*R*)-**1** by HPLC using a chiral column (Chiralcel OD, eluent: iso-PrOH–hexane, 1% (v/v) or 3% (v/v)).

Methanolysis of (*S*)-1-Acetoxyindene [(S)-2] A stirred solution of the optically enriched (*S*)-acetate (*S*)-**2** (97% ee, 510 mg, 2.93 mmol) in MeOH (10 ml) was treated wtih K_2CO_3 (238 mg, 1.7 mmol) at room temperature. After 15 min at the same temperature, the mixture was diluted with Et_2O and filtered through a Celite pad. The filtrate was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed on silica gel (eluent: AcOEt–hexane, 1:5, v/v) to give 1-indanone, 74 mg (19.1%), and (*S*)-inden-1-ol [(*S*)-**1**], 273 mg (70.6%), $[\alpha]_D^{27}$ +246.9° (c=0.46, $CHCl_3$), as a colorless solid. Optical purity was determined to be 98% ee by HPLC using a chiral column (Chiralcel OD, eluent: iso-PrOH–hexane, 3% (v/v)). Spectral data were identical with those of (*R*)-**1**.

Epoxidation of (*S*)-1-Acetoxyindene (S)-2 *m*CPBA (3.83 g, 15.5 mmol) was added portionwise to a stirred suspension of (*S*)-1-acetoxyindene (*S*)-**2** (>99% ee, 1.80 g, 10.3 mmol) and $NaHCO_3$ (2.61 g, 31.0 mmol) in CH_2Cl_2 (150 ml) at 0 °C. After the addition, the suspension was further stirred for 24 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and the organic layer was separated. It was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave a residue. The residue was taken up into Et_2O and the ethereal layer was washed with 2% aqueous NaOH, water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel (eluent: AcOEt–hexane, 1:9, v/v) to give the *anti*-epoxide, (1*R*,2*S*,3*S*)-1-acetoxy-

2,3-epoxyindane (**3**), 784 mg (39.9%), mp 84 °C, $[\alpha]_D^{26}$ −138.2° (c=0.96, $CHCl_3$), as a colorless amorphous solid and the *syn*-epoxide, (1*R*,2*R*,3*R*)-1-acetoxy-2,3-epoxyindane (**4**), 784 mg (39.9%), mp 74 °C, $[\alpha]_D^{26}$ +113.2° (c=0.84, $CHCl_3$), as colorless prisms.

3: IR (film): 1743 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.12 (s, 3H), 4.15 (d, 1H, J=2.4 Hz), 4.33 (br s, 1H), 6.09 (s, 1H), 7.31—7.37 (m, 1H), 7.45—7.50 (m, 1H), 7.53—7.58 (m, 2H). MS m/z (%): 190 (M^+), 148 (100). HRMS m/z: 190.0611 ($C_{11}H_{10}O_3$ requires 190.0630). *Anal.* Calcd for $C_{11}H_{10}O_3$: C, 69.45; H, 5.30. Found: C, 69.43; H, 5.22.

4: IR (film): 1733 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 4.20—4.24 (m, 2H), 6.05 (d, 1H, J=2.4 Hz), 7.28—7.37 (m, 3H), 7.48 (d, 1H, J=7.3 Hz). MS m/z (%): 190 (M^+), 148 (100). HRMS m/z: 190.0626 ($C_{11}H_{10}O_3$ requires 190.0630). *Anal.* Calcd for $C_{11}H_{10}O_3$: C, 69.45; H, 5.30. Found: C, 69.55; H, 5.31.

(1*R*,2*R*,3*S*)-1-Acetoxy-3-azido-2-hydroxyindane (5) A mixture of the *anti*-epoxide (**3**) (520 mg, 2.74 mmol), NaN_3 (890 mg, 13.7 mmol), and NH_4Cl (293 mg, 5.47 mmol) in aqueous DMF (8 : 1, v/v, 20 ml) was stirred at 80 °C for 2 h. After cooling, the mixture was diluted with brine and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, evaporated and chromatographed on silica gel (eluent: AcOEt–hexane, 1 : 4, v/v) to give the azide-alcohol (**5**) as colorless crystals, 623 mg (97.7%), mp 53 °C, $[\alpha]_D^{27}$ +84.4° (c=0.87, $CHCl_3$). IR (film): 3500, 2098, 1739 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 3.95 (d, 1H, J=1.8 Hz), 4.40 (ddd, 1H, J=6.1, 5.5, 1.8 Hz), 4.76 (d, 1H, J=6.1 Hz), 5.76 (d, 1H, J=5.5 Hz), 7.35 (d, 1H, J=7.3 Hz), 7.38—7.46 (m, 3H). MS m/z (%): 173 (M^+−60), 43 (100). HRMS m/z: 173.0605 ($C_9H_7N_3O$ requires 173.0590). *Anal.* Calcd for $C_{11}H_{10}N_3O_3$: C, 55.63; H, 4.76; N, 18.02. Found: C, 56.36; H, 4.83; N, 17.97.

(1*R*,2*R*,3*S*)-1-Acetoxy-3-azido-2-methanesulfonyloxyindane (6) Methanesulfonyl chloride (0.18 ml, 2.34 mmol) was added dropwise to a stirred solution of the azide-alcohol (**5**) (435 mg, 1.95 mmol) and Et_3N (0.65 ml, 4.68 mmol) in CH_2Cl_2 (15 ml) at 0 °C. After 5 min at the same temperature, the reaction was quenched by addition of water and the organic layer was separated. The organic layer was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed on silica gel (eluent: AcOEt–hexane, 1 : 2, v/v) to give the methanesulfonate (**6**) as colorless crystals, 601 mg (99.1%), mp 59 °C, $[\alpha]_D^{29}$ −25.5° (c=1.05, $CHCl_3$). IR (film): 2098, 1734 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.20 (s, 3H), 3.19 (s, 3H), 4.90 (d, 1H, J=5.5 Hz), 5.17 (dd, 1H, J=5.5, 4.9 Hz), 6.26 (d, 1H, J=4.3 Hz), 7.34 (d, 1H, J=7.9 Hz), 7.42—7.51 (m, 3H). MS m/z (%): 215 (M^+−96), 43 (100). HRMS m/z: 215.0712 ($C_{11}H_9N_3O_2$ requires 215.0694).

(1*S*,3*S*,3*R*)-1-Azido-2,3-epoxyindane (8) A stirred solution of **6** (530 mg, 1.70 mmol) in MeOH (20 ml) was treated with K_2CO_3 (259 mg, 1.87 mmol) portionwise at room temperature. After 10 min, water was added to the solution and the mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to leave the crude alcohol **7** (457 mg), which was used immediately for the next reaction.

The crude **7** was dissolved in tetrahydrofuran (THF, 6 ml) and the solution was added dropwise to a stirred suspension of NaH (60% oil dispersion, 88 mg, 2.22 mmol) in THF (2 ml) at room temperature. Stirring was continued at the same temperature for 30 min, then the reaction was quenched by addition of brine and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed on silica gel (eluent: AcOEt–hexane, 1 : 9, v/v) to give the epoxide **8** as colorless crystals, 291 mg (99.7%), mp 69 °C, $[\alpha]_D^{29}$ −360.2° (c=0.71, $CHCl_3$). IR (film): 2094 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.19 (t, 1H, J=2.4 Hz), 4.22 (d, 1H, J=2.4 Hz), 4.54 (br d, 1H, J=2.4 Hz), 7.30—7.43 (m, 3H), 7.51 (d, 1H, J=7.3 Hz). MS m/z (%): 173 (M^+), 131 (100). HRMS m/z: 173.0579 ($C_9H_7N_3O$ requires 173.0589).

***cis*-(1*S*,2*R*)-1-Aminoindan-2-ol (9)** A solution of the epoxy-azide **8** (100 mg, 0.58 mmol) in EtOH (10 ml) containing $CHCl_3$ (0.3 ml) was hydrogenated in the presence of 10% Pd–C (15 mg) under pressure (H_2, 3 kg/cm^2) for 6 h at room temperature using a Parr apparatus. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to leave the amino-alcohol **9** as the hydrochloride. After having been made alkaline by addition of 5% NaOH, the mixture was extracted with CH_2Cl_2 and the extract was dried over $MgSO_4$, and evaporated under reduced pressure to leave a crystalline residue which was recrystallized from CH_2Cl_2–hexane to give pure *cis*-(1*S*,2*R*)-1-aminoindan-2-ol (**9**) as colorless crystals, 59 mg (69.0%), mp 105 °C, $[\alpha]_D^{31}$ −62.0° (c=0.90, $CHCl_3$) [lit.[8]: mp 116—117 °C, $[\alpha]_D^{25}$ −61.5° (c=0.478, $CHCl_3$)]. IR (film): 3336 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.22 (br s, 3H), 2.95 (dd, 1H, J=16.5, 3.1 Hz), 3.10 (dd, 1H, J=16.5, 5.5 Hz), 4.32 (br d, 1H, J=4.9 Hz), 4.36—4.41 (m, 1H), 7.22—7.32 (m, 4H). MS m/z (%): 149 (M^+), 104 (100). HRMS m/z: 149.0828 ($C_9H_7N_3O$ requires 149.0841).

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