Lipase-Mediated Resolution of *trans*-1-Azidoindan-2-ol: A New Route to Optically Pure *cis*-1-Aminoindan-2-ol

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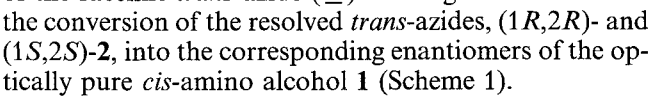
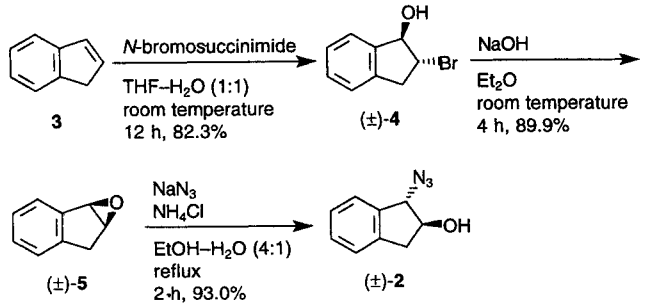
Optically pure *trans*-1-azidoindan-2-ol has been prepared in both enantiomeric forms via lipase-mediated kinetic transesterification in organic solvent. A route to optically pure *cis*-1-aminoindan-2-ol has also been developed by using the optically pure *trans*-azido-alcohol thus obtained.

Optically pure *cis*-1-aminoindan-2-ol **(1)** is an important compound from both medicinal and chemical viewpoints. The HIV protease inhibitor L-735524 contains (−)-(1*S*,2*R*)-enantiomer (1*S*,2*R*)-**1** as a key component,[1] while both enantiomers are utilized as chiral auxiliaries and ligands.[2] Since there are a limited number of efficient methods for the preparation of the optically pure amine **1**, we examined the resolution of racemic *trans*-1-azidoindan-2-ol [(±)-**2**] intending to use the resolved product as a precursor for optically pure *cis*-1-aminoindan-2-ol[3] **(1)**. We now report the details of our successful investigation of the lipase-mediated kinetic transesterification of the racemic *trans*-azide (±)-**2** in organic solvent[4] for the conversion of the resolved *trans*-azides, (1*R*,2*R*)- and (1*S*,2*S*)-**2**, into the corresponding enantiomers of the optically pure *cis*-amino alcohol **1** (Scheme 1).

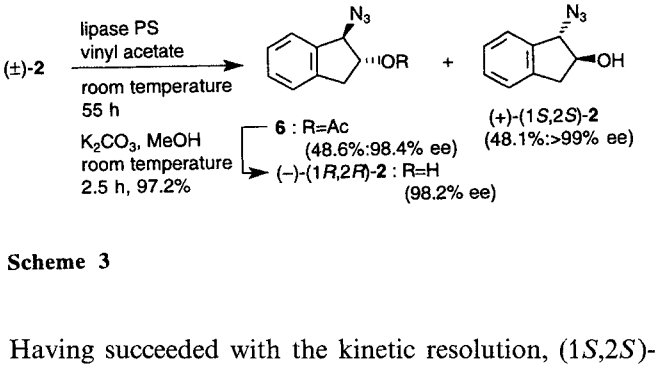


Scheme 1

Racemic *trans*-1-azidoindan-2-ol [(±)-**2**] was prepared in 68.7% overall yield from indene **3** via a sequential formation of the bromohydrin[5,6] **4** and the racemic epoxide[6] **5** (Scheme 2). As a preliminary experiment, we first examined the resolution of 1 mmol of the racemic azido alcohol (±)-**2** in *tert*-butyl methyl ether containing 10 mmol of vinyl acetate in the presence of each of five lipases (immobilized on support: 100 mg) (Table). Since lipase PS (*Pseudomonas* sp., Amano) seemed to be the most promising among those tested, we further examined the resolution using lipase PS which exhibited much better enantiomeric discrimination when it was used in lesser amount. Thus, when 1 mmol of (±)-**2** was treated with 10 mg of lipase PS in *tert*-butyl methyl ether for 55 hours at room temperature, (1*R*,2*R*)-acetate **6** was obtained in 48.1% yield with 94.5% ee leaving the unreacted (1*S*,2*S*)-alcohol **2** with 46.6% recovery in optically pure state (> 99% ee) (Table 1, entry 4). Optical yield of the acetate **6** was improved in a 25 mmolar scale resolution which gave (1*R*,2*R*)-acetate **6** in 98.4% ee and the optically pure alcohol (1*S*,2*S*)-**2** both in excellent yields. The (1*R*,2*R*)-acetate **6** was transformed into (1*R*,2*R*)-alcohol **2** in 97.2% yield on methanolysis in the presence of potassium carbonate without losing the original chiral integrity (98.2% ee) (Scheme 3).



Scheme 2



Scheme 3

Having succeeded with the kinetic resolution, (1*S*,2*S*)-alcohol **2** was transformed into the (1*S*,2*S*)-methanesulfonate **7** in 94.5% yield. Similarly, the optically enriched (1*R*,2*R*)-alcohol **2** (98.2% ee) furnished the optically pure (1*R*,2*R*)-methanesulfonate **7** (> 99% ee) in 89.4% yield after recrystallization. Inversion of the chirality at the C-2 center of the mesylate **7** was found to be difficult under conventional nucleophilic displacement conditions. Thus, (1*R*,2*R*)-mesylate **7**, on reflux with potassium acetate in dimethylformamide, gave the inverted (1*R*,2*S*)-acetate **8** in less than 15% yield losing some original chiral integrity (~ 96.5% ee). Similarly, the solvolysis of **7** in hot acetic acid in the presence of cesium fluoride[7] gave only 20% yield of **8** though it preserved optical purity. The best yield so far obtained was 63.7% when **7** was refluxed with cesium acetate in toluene in the presence of 18-crown-6.[8]

We, therefore, employed Mitsunobu conditions[9] to carry out the inversion in a more straightforward way. Thus, treatment of (1*S*,2*S*)-alcohol **2** with 4-nitrobenzoic acid[10] in the presence of diethyl azodicarboxylate (DEAD) and

Table. Kinetic Transesterification of Racemic *trans*-1-Azidoindan-2-ol [(±)-**2**][a]

Entry	Lipase[b] (mg/mmol)	Solvent	Time (h)	(+)-(1*S*,2*S*)-Alcohol **2**		(−)-(1*R*,2*R*)-Acetate **6**	
				Yield (%)	ee (%)[c]	Yield (%)	ee (%)[d]
1	PS (100)	*t*-BuOMe	46	42.8	> 99	58.6	77.2
2	PS (100)	CH_2Cl_2	48	48.0	> 99	48.7	92.3
3	PS (100)	hexane	48	37.1	> 99	58.5	71.0
4	PS (10)	*t*-BuOMe	48	46.6	> 99	48.1	94.5
5	OF (100)	*t*-BuOMe	127	83.0	5.4	13.4	36.1
6	MY (100)	*t*-BuOMe	127	69.6	33.2	26.2	61.8
7	AY (100)	*t*-BuOMe	127	64.3	31.9	26.6	59.0
8	LIP (100)	*t*-BuOMe	22	10.6	87.5	83.8	13.1

[a] Reaction was carried out using (±)-**2** (1 mmol) in solvent (10 mL) containing vinyl acetate (10 mmol) at r.t.
[b] PS: *Pseudomonas* sp. (Amano); OF; *Candida cylindraceae* (Meito); MY: *Candida cylindraceae* (Meito); AY: *Candida rugosa* (Amano); LIP: *Pseudomonas aeruginosa* (Toyobo).
[c] Optical purity was determined by HPLC using a chiral column (CHIRALCEL OD, *i*-PrOH/hexane, 5 : 95).
[d] Optical purity was determined by HPLC using a chiral column (CHIRALCEL OD, *i*-PrOH/hexane, 3 : 97).

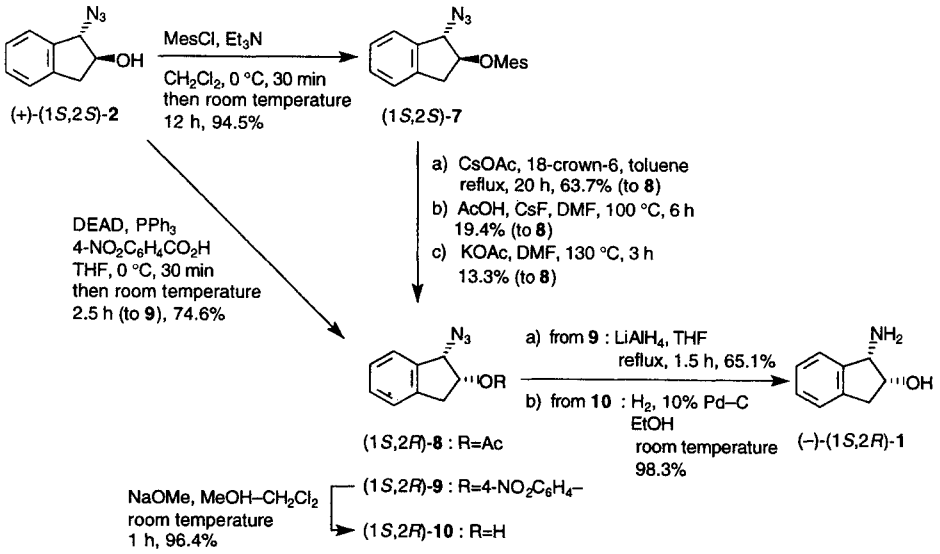
triphenylphosphine furnished the inverted (1*S*,2*R*)-4-nitrobenzoate **(9)** in 74.6% yield without loss of optical purity. The optically enriched (1*R*,2*R*)-alcohol **2** (98.4% ee), on the other hand, gave the inverted (1*R*,2*S*)-4-nitrobenzoate **(9)** in optically pure state in 80.8% yield on the same inversion conditions followed by recrystallization. Removal of the benzoate group was best carried out by treating (1*S*,2*R*)-**9** with sodium methoxide to give (1*S*,2*R*)-*cis*-1-azidoindan-2-ol **(10)** in 96.4% yield. Under the same conditions (1*R*,2*S*)-**9** afforded (1*R*,2*S*)-*cis*-1-azidoindan-2-ol **(10)** in 96.7% yield. Finally, (1*S*,2*R*)-azide **10** was hydrogenated on palladized carbon to give (1*S*,2*R*)-*cis*-1-aminoindan-2-ol **(1)** in 98.3% yield. The enantiomeric (1*R*,2*S*)-*cis*-1-aminoindan-2-ol **(1)** was obtained in 94.0% yield from (1*R*,2*S*)-azide **10** by the same treatment.

The amino alcohol **1** was also obtained in a single step from (1*S*,2*R*)-benzoate **9** on treatment with lithium aluminum hydride in refluxing tetrahydrofuran, but the yield of (1*S*,2*R*)-*cis*-1-aminoindan-2-ol **(1)** was less satisfactory (~ 65.1%) (Scheme 4).

In conclusion, we have developed a practical method for the resolution of the racemic *trans*-1-azidoindan-2-ol **(2)** and for the synthesis of both enantiomers of *cis*-1-aminoindan-2-ol **(1)**, a medicinally and chemically important compound, by employing lipase-mediated kinetic transesterification.

Melting points are uncorrected. IR spectra were recorded on a JASCO-IR-700 spectrometer. ^1H NMR spectra were recorded on a Gemini 2000 (300 MHz) and a JNM-GX500 (500 MHz). Mass spectra were JEOL JMS-DX303 instrument. Optical purities were determined on a Gilson Model-307 instrument equipped with a chiral column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

(±)-*trans*-1-Azidoindan-2-ol [(±)-2]:
i) (±)-trans-2-Bromoindan-1-ol [(±)-**4**]:
To a stirred solution of indene **3** (11.6 g, 0.1 mol) in 50% aq THF (200 mL) was added *N*-bromosuccinimide (19.58 g, 0.11 mol) portionwise at r.t. After 12 h, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 75 mL). The combined organic layer was washed with 5% $Na_2S_2O_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to leave a crystalline mass which was recrystallized from EtOH to give (±)-**4**



Scheme 4

as colorless needles; yield: 17.45 g (82.3%); mp 130–131 °C (Lit.[5] 130–131 °C).

ii) (±)-Epoxyindane [(±)-**5**]:

To a stirred solution of the bromohydrin (±)-**4** (6.36 g, 30 mmol) in Et_2O (100 mL) was added powdered NaOH (3.0 g, 75 mmol) at r.t. After 4 h, water (40 mL) was added to the mixture and the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined Et_2O layer was washed with brine (40 mL), dried ($MgSO_4$), and evaporated under reduced pressure to leave the crude epoxide (±)-**5** (3.56 g, 89.9%) which was used for the next reaction.

iii) (±)-trans-1-Azidoindan-2-ol [(±)-**2**]:

A mixture of the epoxide (±)-**5** (3.56 g, 27.0 mmol), NH_4Cl[11] (2.25 g, 42 mmol) and NaN_3 (2.73 g, 42 mmol) in 80% aq EtOH (90 mL) was refluxed for 2 h. After cooling, water (30 mL) was added to the mixture and the mixture was extracted with EtOAc (3 × 50 mL). The extract was washed with brine (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure to leave a crude product which was chromatographed on silica gel (80 g, eluent: EtOAc/hexane, 1:5) to give (±)-**2** as a low melting solid; yield: 4.39 g (93.0%); mp ~ 30 °C.

IR (film): ν = 3348, 2098 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, 1H, J = 6.71 Hz), 7.23–7.33 (m, 3H), 4.70 (d, 1H, J = 4.88 Hz), 4.47–4.53 (m, 1H), 3.31 (dd, 1H, J = 15.87, 6.71 Hz), 2.87 (dd, 1H, J = 15.87, 6.11 Hz), 2.19 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.77 (s), 137.86 (s), 129.16 (d), 127.36 (d), 125.30 (d), 124.69 (d), 78.53 (d), 71.77 (d), 38.85 (t).

Kinetic Acetylation of Racemic *trans*-1-Azidoindan-2-ol [(±)-2]:

A suspension of (±)-**2** (4.35 g, 24.9 mmol), vinyl acetate (13.6 mL, 147.5 mmol), and lipase PS-on-Celite (*Pseudomonas* sp., Amano) (250 mg) in *tert*-BuOMe (150 mL) was stirred at r.t. for 55 h. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (100 g, eluent: EtOAc/hexane, 1:8) to give (1*R*,2*R*)-*trans*-2-acetoxy-1-azidoindane [(1*R*,2*R*)-**6**] as a colorless oil and (1*S*,2*S*)-*trans*-1-azidoindan-2-ol [(1*S*,2*S*)-**2**] as a colorless oil (eluent: EtOAc/hexane, 1:4).

(−)-(1R,2R)-trans-2-Acetoxy-1-azidoindane [(*1R,2R*)-**6**]:

Yield: 2.62 g (48.6%); $[\alpha]_D^{29}$ − 91.6 (c = 2.6, $CHCl_3$). Optical purity was determined to be 98.4% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 3:97).

IR (film): ν = 2102, 1745 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, 1H, J = 7.32 Hz), 7.29–7.37 (m, 2H), 7.27 (d, 1H, J = 4.88 Hz), 5.35 (ddd, 1H, J = 6.71, 4.88, 4.27 Hz), 4.87 (d, 1H, J = 4.27 Hz), 3.49 (dd, 1H, J = 16.48, 6.71 Hz), 2.89 (dd, 1H, J = 16.48, 4.27 Hz), 2.09 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.38 (s), 139.82 (s), 137.38 (s), 129.42 (d), 127.46 (d), 125.18 (d), 124.70 (d), 79.37 (d), 69.35 (d), 36.76 (t), 20.89 (q).

MS: m/z = 175 (M^+ − 42), 43 (100%).

HRMS: m/z = calc. for $C_9H_9N_3O$ 175.0746, found 175.0766.

(+)-(1S,2S)-trans-1-Azidoindan-2-ol [(*1S,2S*)-**2**]:

Yield: 2.09 g (48.1%); $[\alpha]_D^{30}$ + 78.3 (c = 1.9, $CHCl_3$). Optical purity was determined to be > 99% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 5:95).

IR (film): ν = 3364, 2096 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, 1H, J = 6.71 Hz), 7.23–7.33 (m, 3H), 4.70 (d, 1H, J = 4.89 Hz), 4.47–4.54 (m, 1H), 3.31 (dd, 1H, J = 15.87, 6.71 Hz), 2.88 (dd, 1H, J = 15.87, 6.11 Hz), 2.18 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.79 (s), 137.90 (s), 129.18 (d), 127.39 (d), 125.33 (d), 124.71 (d), 78.59 (d), 71.82 (d), 38.90 (t).

MS: m/z = 175 (M^+), 91 (100%).

HRMS: m/z = calc. for $C_9H_9N_3O$ 175.0746, found 175.0719.

(−)-(1R,2R)-trans-1-Azidoindan-2-ol [(1R,2R)-2]:

To a stirred solution of (1*R*,2*R*)-**6** (98.4% ee; 3.93 g, 18.1 mmol) in MeOH (100 mL) was added K_2CO_3 (7.51 g, 54.4 mmol) at r.t. After 2.5 h, the mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was dissolved in H_2O (30 mL) and the solution was extracted with EtOAc (3 × 50 mL). The combined extract was washed with brine (30 mL), dried ($MgSO_4$), evaporated under reduced pressure and chromatographed on silica gel (100 g, eluent: EtOAc/hexane, 1:4) to give the alcohol (1*R*,2*R*)-**2** as a colorless oil; yield: 3.08 g (97.2%); $[\alpha]_D^{30}$ − 77.9 (c = 2.8, $CHCl_3$). Optical purity was determined to be 98.2% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 5:95). Spectroscopic data were identical with those of (1*S*,2*S*)-**2**.

(+)-(1S,2S)-trans-1-Azido-2-methanesulfonyloxyindane [(1S,2S)-7]:

To a stirred solution of (1*S*,2*S*)-**2** (> 99% ee; 1.07 g, 6.1 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (1.7 mL, 12.2 mmol) at 0 °C, followed by $MeSO_2Cl$ (0.71 mL, 9.2 mmol) at the same temperature and was stirred at the same temperature for 30 min. After stirring at r.t. for 12 h, the mixture was diluted with CH_2Cl_2 (30 mL) and the solution was washed with 5% HCl (15 mL), 5% $NaHCO_3$ (15 mL), brine (15 mL), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (80 g, eluent: EtOAc/hexane, 1:6) to give a crystalline solid which was recrystallized from benzene/hexane to give (1*S*,2*S*)-**7** as colorless needles; yield: 1.46 g (94.5%); mp 73–74 °C; $[\alpha]_D^{31}$ + 71.84 (c = 1.0, $CHCl_3$). Optical purity was determined to be > 99% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 1:9).

IR (Nujol): ν = 2098, 1332 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, 1H, J = 6.71 Hz), 7.31–7.39 (m, 2H), 7.27 (d, 1H, J = 8.55 Hz), 5.19 (ddd, 1H, J = 6.72, 5.49, 4.88 Hz), 5.02 (d, 1H, J = 4.88 Hz), 3.51 (dd, 1H, J = 16.48, 6.72 Hz), 3.17 (dd, 1H, J = 16.48, 5.49 Hz), 3.13 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.39 (s), 136.42 (s), 129.81 (d), 127.96 (d), 125.28 (d), 124.64 (d), 84.79 (d), 69.35 (d), 38.41 (q), 37.12 (t).

MS: m/z = 211 (M^+ − 42), 129 (100%).

Anal. ($C_{10}H_{11}N_3O_3S$): Calc. C, 47.42; H, 4.38; N, 16.60; S, 12.63. Found C, 47.23; H, 4.59; N, 16.44; S, 12.60.

By the same method, the enantiomeric (1*R*,2*R*)-**2** (98.2% ee) was converted into (−)-(1*R*,2*R*)-1-azido-2-methanesulfoxyindane [(1*R*,2*R*)-**7**] as colorless needles in 89.4%; mp 71.5–72.0 °C; $[\alpha]_D^{30}$ − 69.06 (c = 1.0, $CHCl_3$) (> 99% ee by HPLC using CHIRALCEL OD, eluent: *i*-PrOH/hexane, 1:9). Spectral data were identical to those of (+)-(1*S*,2*S*)-**7**.

Anal. ($C_{10}H_{11}N_3O_3S$): Calc. C, 47.42; H, 4.38; N, 16.60; S, 12.63. Found C, 47.48; H, 4.33; N, 16.42; S, 12.41.

(1S,2R)- and (1R,2S)-cis-2-Acetoxy-1-azidoindane [(1S,2R)- and (1R,2S)-8]:

a) (*1R,2S*)-*cis-2-Acetoxy-1-azidoindane* [(*1R,2S*)-**8**] from (*1R,2R*)-*1-Azido-2-methanesulfoxyindane* [(*1R,2R*)-**7**]:

A stirred mixture of (1*R*,2*R*)-**7** (759 mg, 3 mmol), CsOAc (2.88 g, 15 mmol), and 18-crown-6 (1.32 g, 3 mmol) in toluene (25 mL) was refluxed for 20 h. After cooling, the mixture was diluted with EtOAc (30 mL) and the mixture was washed with brine (15 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (70 g, eluent: EtOAc/hexane, 1:8) to give the *cis*-acetate (1*R*,2*S*)-**8** as a pale yellow oil; yield: 415 mg (63.7%); $[\alpha]_D^{30}$ − 25.54 (c = 1.5, $CHCl_3$). Optical purity was determined to be > 99% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 5:95).

IR (film): ν = 2102, 1742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, 1H, J = 7.33 Hz), 7.27–7.38 (m, 3H), 5.53 (q, 1H, J = 6.11 Hz), 4.87 (d, 1H, J = 5.49 Hz), 3.23 (dd, 1H, J = 16.48, 6.72 Hz), 3.13 (dd, 1H, J = 16.48, 5.50 Hz), 2.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.50 (s), 139.49 (s), 137.48 (s), 129.45 (d), 127.50 (d), 125.23 (d), 124.96 (d), 75.27 (d), 65.19 (d), 36.16 (t), 20.69 (q).

MS: m/z = 175 ($M^+ - 42$), 43 (100%).

HRMS: m/z = calc. for $C_9H_9N_3O$ 175.0746, found 175.0723.

*b) (1S,2R)-cis-2-Acetoxy-1-azidoindane [(1S,2R)-**8**] from (1S,2S)-1-Azido-2-methanesulfonyloxyindane [(1S,2S)-**7**]:*

A stirred mixture of (1S,2S)-**7** (253 mg, 1 mmol), CsF (760 mg, 5 mmol), and HOAc (300 mg, 5 mmol) in DMF (10 mL) was heated at 100 °C for 1 h. After cooling, the mixture was poured into ice-water and extracted with EtOAc (3 × 20 mL). The extract was washed with 5% $NaHCO_3$ (15 mL), brine (15 mL), dried ($MgSO_4$), evaporated under reduced pressure and chromatographed on silica gel (70 g, eluent: EtOAc/hexane, 1:8) to give (1S,2R)-**8** as a pale yellow oil; yield: 42 mg (19.4%). Optical purity was determined to be > 99% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 5:95). Spectral data were identical with those of optically pure (1R,2S)-**8** obtained by method a).

*c) (1R,2S)-cis-2-Acetoxy-1-azidoindane [(1R,2S)-**8**] from (1R,2R)-1-Azido-2-methanesulfoxyindane [(1R,2R)-**7**]:*

A stirred mixture of (1R,2R)-**7** (580 mg, 2.29 mmol) and KOAc (2.25 g, 22.9 mmol) in DMF (16 mL) was refluxed at 130 °C for 3 h. After cooling, the mixture was poured in ice-water (15 mL) and extracted with EtOAc (3 × 20 mL). The extract was washed with brine (15 mL), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (70 g, eluent: EtOAc/hexane, 1:8) to give (1R,2S)-**8** as a pale yellow oil; yield: 66 mg (13.3%). Optical purity was determined to be 96.5% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 5:95). Spectral data were identical to those of optically pure (1R,2S)-**8**, obtained by method a).

(−)-(1S,2R)-*cis*-1-Azido-2-(4-nitrobenzoyloxy)indane [(1S,2R)-9]:
To a stirred solution of (1S,2S)-**2** (1.91 g, 11.2 mmol) and 4-nitrobenzoic acid (3.74 g, 22.4 mmol) in THF (40 mL) was added dropwise Ph_3P (5.89 g, 22.4 mmol) in THF (20 mL) and diethyl azodicarboxylate (3.91 g, 22.4 mmol) in THF (20 mL) at 0 °C at the same time during 20 min and the mixture was stirred for 30 min at the same temperature, and 2.5 h at r.t. The mixture was evaporated under reduced pressure to leave the residue which was chromatographed on silica gel (100 g, eluent: EtOAc/hexane, 1:8) to give the benzoate (1S,2R)-**9** as colorless prisms; yield: 2.71 g (74.6%); mp 133.5–134.0 °C (CH_2Cl_2/EtOH); $[\alpha]_D^{31}$ −42.87 (c = 0.9, $CHCl_3$). Optical purity was determined to be > 99% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 1:9).

IR (Nujol): ν = 2086, 1720, 1524, 1350 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (d, 2H, J = 9.15 Hz), 8.25 (d, 2H, J = 9.16 Hz), 7.46 (d, 1H, J = 7.32 Hz), 7.32–7.42 (m, 3H), 5.80 (dt, 1H, J = 6.71, 5.50 Hz), 5.02 (d, 1H, J = 6.11 Hz), 3.40 (dd, 1H, J = 16.48, 6.72 Hz), 3.30 (dd, 1H, J = 16.48, 5.50 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.33 (s), 150.70 (s), 139.27 (s), 137.20 (s), 134.91 (s), 130.99 (d), 129.78 (d), 127.80 (d), 125.40 (d), 125.11 (d), 123.58 (s), 76.66 (d), 65.49 (d), 36.39 (t).

MS: m/z = 282 ($M^+ - 42$), 150 (100%).

Anal. ($C_{16}H_{12}N_4O_4$): Calc. C, 59.24; H, 3.73; N, 17.28. Found C, 58.86; H, 3.70; N, 17.21.

Similarly, the optically enriched (1R,2R)-**2** (98.4% ee) afforded (+)-(1R,2S)-*cis*-1-azido-2-(4-nitrobenzoyloxy)indane [(1R,2S)-**9**] in 80.8% yield with > 99% ee by HPLC after recrystallization; mp 134–135 °C; $[\alpha]_D^{30}$ + 42.72 (c = 1.1, $CHCl_3$). Spectroscopic data were identical with those of (1S,2R)-**9**.

(+)-1(S,2R)-*cis*-1-Azidoindan-2-ol [(1S,2R)-10]:
To a stirred solution of NaOMe in MeOH, prepared in situ by addition of Na (230 mg, 10 mg atom) to MeOH (20 mL), was added dropwise a solution of the *cis*-benzoate (1S,2R)-**9** (1.086 g, 3.35 mmol) in CH_2Cl_2 (15 mL) at r.t. and the mixture was kept stirring for 1 h at the same temperature. The mixture was evaporated under reduced pressure and the residue, after addition of brine, (20 mL) was extracted with CH_2Cl_2 (2 × 30 mL) and dried over ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on silica gel (80 g, eluent: EtOAc/hexane, 1:6) to give the *cis*-alcohol (1S,2R)-**10** as a colorless oil; yield: 565 mg (96.4%); $[\alpha]_D^{27}$ + 85.85 (c = 2.0, $CHCl_3$). Optical purity was determined to be > 99% ee by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 5:95).

IR (film): ν = 3394, 2102 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.43 (m, 4H), 4.79 (d, 1H, J = 5.49 Hz), 4.55–4.65 (m, 1H), 3.17 (dd, 1H, J = 15.93, 6.32 Hz), 2.95 (dd, 1H, J = 15.93, 6.04 Hz), 2.36 (d, 1H, J = 7.97 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.77 (s), 137.87 (s), 129.66 (d), 127.41 (d), 125.71 (d), 125.24 (d), 74.17 (d), 67.84 (d), 38.99 (t).

MS: m/z = 175 (M^+), 130 (100%).

HRMS: m/z = calc. for $C_9H_9N_3O$ 175.0746, found 175.0720.

Using the same treatment, (1R,2S)-**9** was converted to (−)-(1R,2S)-*cis*-1-azidoindan-2-ol [(1R,2S)-**10**] in 96.7% yield; $[\alpha]_D^{28}$ −85.19 (c = 1.6, $CHCl_3$). Spectral data were identical with those of (+)-(1S,2R)-**10**.

(−)-(1S,2R)-*cis*-1-Aminoindan-2-ol [(1S,2R)-1]:
A solution of (1S,2R)-**10** (550 mg, 3.14 mmol) in EtOH (15 mL) was hydrogenated on 10% Pd−C (30 mg) with 1 bar of H_2 for 2 h. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure to give (1S,2R)-**1** as colorless prisms, yield: 460 mg (98.3%); mp 116–117 °C (from hexane/CH_2Cl_2); $[\alpha]_D^{30}$ −61.08 (c = 0.3, $CHCl_3$) [Lit.[12] mp 116–117 °C, $[\alpha]_D^{30}$ −61.5° (c = 0.478, $CHCl_3$)].

IR (Nujol): ν = 3342, 3290 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.33 (m, 1H), 7.24 (br d, 3H, J = 2.45 Hz), 4.39 (dt, 1H, J = 5.50, 3.05 Hz), 4.34 (d, 1H, J = 5.49 Hz), 3.09 (dd, 1H, J = 16.48, 5.50 Hz), 2.95 (dd, 1H, J = 16.48, 3.06 Hz), 2.22 (br s, 3H exchangeable with D_2O).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.37 (s), 140.56 (s), 127.85 (d), 126.87 (d), 125.19 (d), 123.96 (d), 73.18 (d), 58.70 (d), 39.09 (t).

Similarly (1R,2S)-**10** afforded [(1R,2S)-**1**] in 94.0% yield; mp 114–116 °C (hexane/CH_2Cl_2); $[\alpha]_D^{30}$ + 63.69 (c = 0.8, $CHCl_3$) [Lit.[12] mp 115–116 °C, $[\alpha]_D^{30}$ + 65.12 (c = 0.238, $CHCl_3$)]. Spectral data were identical with those of (−)-(1S,2R)-**1**.

Direct Conversion of (1S,2R)-*cis*-1-Azido-(4-nitrobenzoyloxy)indane [(1S,2R)-9] into (−)-(1S,2R)-*cis*-1-Aminoindan-2-ol [(1S,2R)-1]:
To a stirred suspension of $LiAlH_4$ (228 mg, 6 mmol) in THF (20 mL) was added (1S,2R)-**9** (648 mg, 2 mmol) in THF (10 mL) at 0 °C and the mixture was kept stirring at the same temperature for 15 min and then at refluxing temperature for 1.5 h. After cooling, the mixture was treated with 30% NH_4OH (8 mL) and filtered through a Celite pad. The filtrate was evaporated under reduced pressure and the residue was treated with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (50 g, eluent: CH_2Cl_2/MeOH, 9:1) to give (1S,2R)-**1**, yield: 194 mg (65.1%); mp 113–114 °C (hexane/CH_2Cl_2); $[\alpha]_D^{29}$ −57.47 (c = 0.5, $CHCl_3$). Spectral data were identical with those of an authentic material.

(1) For example:
Vacca, J.; Dorsey, B.; Levin, R.; McDaniel, S.; Darke, P.; Zugary, J.; Schleif, W.A.; Quintero, J.; Sardana, V.; Lin, J.; Chen, J.-W.; Ostovic, D.; Anderson, P.S.; Emini, E.A.; Huff, J.R. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4096.
(2) Recent examples:
(a) Davies, I.W.; Senanayake, C.H.; Castonguay, L.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 7619.

(b) Simone, B.D.; Savoia, D.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1995**, *6*, 301.
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(3) Recent examples:
(a) Senanayake, C.H.; DiMichele, L.M.; Liu, J., Fredenburgh, L.E.; Ryan, K.M.; Roberts, F.E.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 7615.
(b) Takahashi, M.; Koike, R.; Ogasawara, K. *Chem. Pharm. Bull.* **1995**, *43*, 1585.
(c) Senanayake, C.H.; Roberts, F.E.; DiMichele, L.M.; Ryan, K.M.; Liu, J.; Fredenburgh, L.E.; Foster, B.S.; Douglas, A.W.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *Tetrahedron Lett.* **1995**, *36*, 3993.

(4) A pertinent monograph:
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(7) Sato, T.; Otera, J. *Synlett* **1995**, 336.

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(9) (a) Mitsunobu, O. *Synthesis* **1981**, 1.
(b) Hughes, D.L. *Org. React.* **1992**, *42*, 335.

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(11) Hönig, H.; Seufer Wasserthal, P.; Weber, H. *Tetrahedron* **1990**, *46*, 3841.

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