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Preparation of Enantiomerically Pure *trans*- and *cis*-2-(1-Naphthyl)cyclohexan-1-ols

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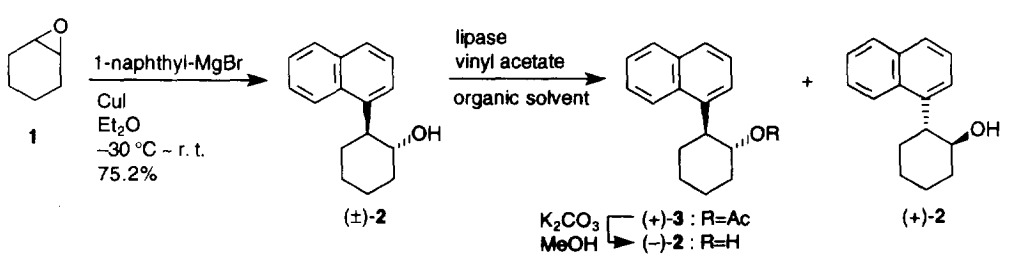
Abstract: Lipase-mediated treatment of racemic *trans*-2-(1-naphthyl)cyclohexan-1-ol with vinyl acetate allows clear-cut enantiospecific kinetic acetylation to give (+)-(1*R*,2*S*)-acetate in excellent chemical and enantiomeric excesses leaving (+)-(1*S*,2*R*)-alcohol in an excellent enantiomeric purity and excellent recovery. The enantiomerically pure alcohol obtained is transformed into the diastereomeric alcohol neatly *via* the Mitsunobu inversion reaction.

Enantiomerically pure *trans*-2-phenylcyclohexan-1-ol (**2**) has been found to be a powerful chiral auxiliary in the construction of a wide variety of chiral target molecules.[1] Because its efficiency in stereocontrol is presumed to be due to the bulkiness and the electronic effect of the phenyl functionality, we were interested in the preparation of an alternative carrying a bulkier naphthyl group in place of the phenyl group. We, thus, examined resolution of racemic *trans*-2-(1-naphthyl)cyclohexan-1-ol [(±)-**2**] using lipase as a catalyst. We employed lipase-mediated kinetic acetylation in an organic solvent rather than kinetic deacylation in an aqueous solution taking into account of low solubility of the substrate in an aqueous medium.[2] We wish to report here the results which brought about clear-cut enantioselective acylation of the racemic substrate leading to an efficient preparation of both enantiomeric *trans*-2-(1-naphthyl)cyclohexan-1-ol (**2**) and the diastereomeric *cis*-2-(1-naphthyl)cyclohexan-1-ol (**5**).

The racemic *trans*-alcohol (±)-**2** was prepared in a satisfactory yield by reaction of commercially available cyclohexene oxide[3] (**1**) and 1-naphthylmagnesium bromide[4] in ether in the presence of copper(I) iodide.[5] Racemic substrate (±)-**2** thus obtained was next treated with vinyl acetate in an organic solvent[6] in the presence of a lipase shown. Among the lipases tested lipase PS (*Pseudomonas* sp., Amano) and lipase LIP (*Pseudomonas aeruginosa*, Toyobo) exhibited the best results when *tert*-butyl methyl ether was used as solvent. The ethers, particularly, *tert*-butyl methyl ether, were found to be more suitable solvents than both benzene and dichloromethane under the same conditions (**Table 1**). Typically, treatment of (±)-**2** with 10 equivalents of vinyl acetate in *tert*-butyl methyl ether (ca. 3%) in the presence of lipase PS-on-Celite (200 mg/mmol of the substrate) at room temperature, the kinetic acylation completed after 14 days to give (1*R*,2*S*)-2-(1- naphthyl)-



Scheme 1

Table 1. Lipase-mediated Kinetic Acetylation of Racemic *trans*-2-(1-Naphthyl)cyclohexan-1-ol [(±)-**2**]

Entry	Lipase[a]	Solvent[a]	Acetate [(+)-**3**] (%)	ee[b] (%)	Alcohol [(+)-**2**] (%)	ee[b] (%)
1	OF[c]	benzene	88.4	11.5	11.8	97.2
2	OF	CH_2Cl_2	99.0	2.9	1.1	92.8
3	OF	Et_2O	61.9	59.8	38.4	98.8
4	OF	*t*-BuOMe	61.2	62.8	38.8	98.0
5	PS[c]	benzene	67.2	57.0	32.5	>99
6		CH_2Cl_2	86.7	16.6	13.3	>99
7	PS	Et_2O	50.6	98.4	49.0	99.0
8	PS	*t*-BuOMe	50.0	>99	49.7	98.8
9	MY[c]	*t*-BuOMe	92.0	7.5	4.5	98.4
10	LIP[c]	*t*-BuOMe	49.6	98.6	50.4	99.6

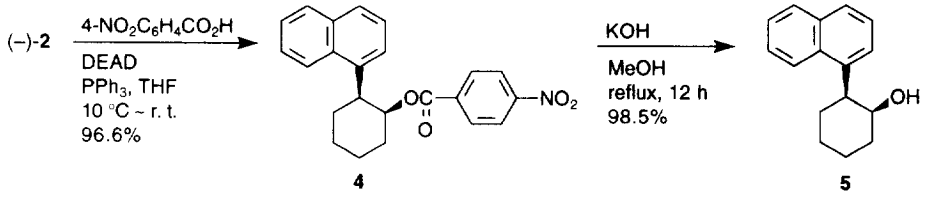
a. All reactions were carried out using 1 mmol of (±)-**2** in the presence of 100 mg of a lipase in 10 ml of an organic solvent at room temperature for 160 h.

b. Enantiomeric excesses were determined by HPLC using a chiral column (CHIRALCEL OD; *i*-PrOH/hexane, 3:97 v/v for **3** and *i*-PrOH/hexane, 1:9 v/v for **2**).

c. OF=*Candida cylindraceae*-on-Celite (Meito). PS=*Pseudomonas* sp.-on-Celite (Amano). MY=*Candida cylindraceae*-on-Celite (Meito). LIP=*Pseudomonas aeruginosa*-on-Hyflo Super-Cel (Toyobo).

cyclohexan-1-yl acetate [(+)-**3**] in 49.7% yield leaving unreacted (1*S*,2*R*)-2-(1-naphthyl)cyclohexan-1-ol [(+)-**2**] in 50.0% recovery with 98.8 and >99% ee of optical purities which were determined by HPLC using a chiral column. The acetate [(+)-**3**] containing a small amount of the enantiomer was easily purified by a single recrystallization to give the enantiomerically pure material. Transformation of the acetate (+)-**3** into the enantiomerically pure alcohol (−)-**2** was readily carried out by alkaline methanolysis at room temperature in an excellent yield.

Transformation of the *trans*-alcohol **2** into the diastereomeric *cis*-alcohol **5** was also carried out without difficulty by employing the Mitsunobu reaction.[7] Thus, treatment of the *trans*-(1*R*,2*S*)-1-(1-naphthyl)cyclohexan-1-ol [(−)-**2**] with 4-nitrobenzoic acid[8] in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) allowed substitution of the hydroxy group by the benzoate group to give *cis*-(1*S*,2*S*)-2-(1-naphthyl)cyclohexan-1-yl 4-nitrobenzoate (**4**), excellently, which on saponification furnished the enantiomerically pure *cis*-(1*S*,2*S*)-2-(1-naphthyl)cyclohexan-1-ol (**5**).



4 **5**

Scheme 2

Enantiocontrolled synthesis using the optically active *trans*- and *cis*-2-(1-naphthyl)cyclohexan-1-ols is presently under investigation.

Experimental

M. ps were determined on a Yanagimoto hotstage instrument and are uncorrected. IR spectra were recorded on a JASCO-IR-700 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-GX-500 (500

MHz) spectrometer. Enantiomeric rotations were measured with a JASCO-DIP-370 digital polarimeter. Optical purities were determined on a Gilson Model-307 instrument equipped with a chiral column.

Racemic *trans*-2-(1-Naphthyl)cyclohexan-1-ol [(±)-2]: To a stirred refluxing suspension of Mg (730 mg, 0.03 atom) in Et_2O (20 ml) was added dropwise 1-bromonaphthalene (5.18 g, 25 mmol). After refluxing for 1 h, benzene (10 ml) was added to the solution without cooling. After cooling to r. t. the solution was added to the cooled suspension of CuI (4.73 g, 25 mmol) in Et_2O (15 ml) with stirring at –30 °C. After 20 min, to this mixture was added cyclohexene oxide (2.77 g, 28.3 mmol) in Et_2O (10 ml) dropwise at the same temperature. After 30 min at the same temperature, the temperature was gradually raised to room temperature and the stirring was continued for 12 h at the same temperature. The mixture was treated with aq. sat. NH_4Cl and filtered through a Celite pad. The organic layer was separated, dried over $MgSO_4$, evaporated under reduced pressure and chromatographed on silica gel (100 g, eluent: AcOEt/hexane, 1:8 v/v) to give the *trans*-alcohol (±)-**2** (4.25 g, 75.2%) as colorless prisms, mp 132-134 °C (Et_2O-hexane) (lit.: mp 134-135 °C[9]; mp 129-130 °C[10]).

Kinetic Acetylation of Racemic *trans*-2-(1-Naphthyl)cyclohexan-1-ol [(±)-2]: Typical procedure A suspension of (±)-**2** (9.72 g, 43 mmol), vinyl acetate (40.0 ml, 430 mmol), and lipase PS-on-Celite (*Pseudomonas* sp., Amano) (8.6 g) in *tert*-BuOMe (350 ml) was stirred at room temperature for 14 days. After filtration through a Celite pad, the filtrate was evaporated under reduced pressure and chromatographed on silica gel (250 g, eluent: AcOEt/hexane, 1:8 v/v) to give the acetate (+)-**3** (5.69 g, 49.4%, 97.8% ee) and the alcohol (+)-**2** (4.86 g, 49.9%, >99% ee). Optical purities were determined by HPLC using a chiral column (CHIRALCEL OD, eluent: *i*-PrOH/hexane, 3:97 v/v for **3** and 1:9 v/v for **2**). The absolute configuration of the products were identical with those of the reported[2] and were also confirmed by the modified Mosher method based on the ^1H NMR (500 Mhz) analysis of the MTPA esters.[11]

(1*R*,2*S*)-2-(1-naphthyl)cyclohexan-1-yl acetate [(+)-3]: mp 76.5-77.5 °C (Et_2O-hexane); $[\alpha]_D^{26}$ +32.64 (*c* 1.05, $CHCl_3$) (>99% ee by HPLC using CHIRALCEL OD).

IR (Nujol): v=1723 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=8.16 (1H, d, *J*=8.54 Hz), 7.85 (1H, d, *J*=7.93 Hz), 7.70 (1H, d, *J*=7.93 Hz), 7.54-7.37 (4H, m), 5.25 (1H, m), 3.61 (1H, m), 2.27-2.18 (1H, m), 2.12-2.05 (1H, m), 1.98-1.90 (1H, m), 1.87-1.80 (1H, m), 1.59 (3H, s), 1.64-1.44 (4H, m). MS: *m/z*=268 (M^+), 208 (100%).

(1*S*,2*R*)-2-(1-naphthyl)cyclohexan-1-ol [(+)-2]: mp 100-101 °C (Et_2O-hexane); $[\alpha]_D^{26}$ +78.73 (*c* 1.00, $CHCl_3$) (>99% ee by HPLC using CHIRALCEL OD). IR (Nujol): v=3522 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=8.21 (1H, d, *J*=8.55 Hz), 7.87 (1H, d, *J*=8.55 Hz), 7.75 (1H, dd, *J*=7.33, 2.44 Hz), 7.56-7.45 (4H, m), 4.00 (1H, br s), 3.41 (1H, br s), 2.26-2.21 (1H, m), 2.02-1.91 (1H, m), 1.82 (1H, br s), 1.64-1.43 (6H, m). MS: *m/z*=226 (M^+), 141 (100%).

Methanolysis of the Enantiomerically Pure Acetate (+)-3: A solution of (+)-**3** (3.11 g, 11.6 mmol) and K_2CO_3 (4.80 g, 34.8 mmol) in MeOH (50 ml) was stirred at room temperature for 20 h. After evaporation of the solvent under reduced pressure, the residue was treated with water and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed on silica gel (90 g, eluent: AcOEt/hexane, 1:5 v/v) to give (1*R*,2*S*)-2-(1-naphthyl)cyclohexan-1-ol [(–)-**2**] (2.54 g, 96.8%) as colorless prisms; mp 100-100.5 °C (Et_2O-hexane), $[\alpha]_D^{26}$ –72.61 (*c* 1.03, $CHCl_3$) (>99% ee by HPLC using CHIRALCEL OD). Spectral data were identical with those of (+)-**2**.

The Mitsunobu Reaction of the Optically Pure Alcohol (–)-2: To a stirred solution of the (1*R*,2*S*)-*trans*-alcohol (–)-**2** (1.81 g, 8 mmol), 4-nitrobenzoic acid (2.67 g, 16 mmol), and triphenylphosphine (4.21 g, 16 mmol) in THF (35 ml) was added dropwise a solution of diethyl azodicarboxylate (DEAD) (2.79 g, 16 mmol) in THF (35 ml) below 10 °C and the mixture was further stirred at room temperature for 12 h. The mixture was evaporated under reduced pressure and chromatographed on silica gel (100 g, elution: AcOEt/hexane, 1:8 v/v) to give (1*S*,2*S*)-*cis*-2-(1-naphthyl)cyclohexan-1-yl 4-nitrobenzoate (**4**) (2.90 g, 96.6%) as pale yellow prisms; mp 131-132 °C (AcOEt-hexane), $[\alpha]_D^{26}$ +504.74 (*c* 1.53, $CHCl_3$) (>99% ee by HPLC using CHIRALCEL OD). IR (Nujol): v=1717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=8.24 (2H, d, *J*=8.55 Hz), 8.07 (2H, d, *J*=9.16 Hz), 8.06 (1H, d, *J*=7.32 Hz), 7.84 (1H, d, *J*=7.93 Hz), 7.66 (1H, d, *J*=8.54 Hz), 7.56 (1H, td, *J*=6.71, 1.22 Hz), 7.48 (1H, dd, *J*=7.94, 7.32 Hz), 7.40 (1H, d, *J*=6.71 Hz), 7.28 (1H, dd, *J*=7.94, 7.32 Hz), 5.59 (1H, br s), 3.79 (1H, br d, *J*=12.21 Hz), 2.48 (1H, qd, *J*=12.82, 3.66 Hz), 2.32-2.25 (1H, m), 2.16-2.07 (1H, m), 2.00-1.88 (2H, m), 1.81-1.63 (3H, m). MS: *m/z*=375 (M^+), 141 (100%).

Anal. Calcd for $C_{23}H_{21}NO_4$: C 73.57 H, 5.64 N, 3.73
Found: 73.34 5.71 3.72

Hydrolysis of the *cis*-Benzoate 4: A solution of 4 (2.27 g, 6.05 mmol) and KOH (3.39 g, 60.5 mmol) in MeOH (45 ml) was refluxed for 12 h. After cooling the mixture was evaporated under reduced pressure and the residue after dilution with water was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and chromatographed on silica gel (100 g, eluent: AcOEt/hexane, 1:5 v/v) to give *cis*-(1*S*,2*S*)-2-(1-naphthyl)cyclohexan-1-ol (**5**) (1.35 g, 98.5%) as a colorless oil; $[\alpha]_D^{30}$ +160.48 (*c* 0.49, $CHCl_3$) (>99% ee by HPLC using CHIRALCEL OD). Spectral data were virtually identical with those reported for (±)-**5**.[8] IR (film): v=3448 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=8.03 (1H, d, *J*=7.94 Hz), 7.87 (1H, d, *J*=7.93 Hz), 7.75 (1H, d, *J*=7.93 Hz), 7.55-7.41 (4H, m), 4.15 (1H, br s), 3.63 (1H, br d, *J*=12.82 Hz), 2.31 (1H, qd, *J*=12.82, 3.66 Hz), 2.09-1.95 (2H, m), 1.84-1.73 (2H, m), 1.69-1.49 (3H, m), 1.16 (1H, br s). MS: *m/z*=226 (M^+), 141 (100%).

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