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Efficient and practical synthesis of both enantiomers of 3-phenylcyclopentanol derivatives

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Abstract—An efficient, multigram scale synthesis of the respective optical isomers of 3-(substituted-phenyl) cyclopentanols was achieved by a lipase-catalyzed transesterification (kinetic resolution) in organic medium. This enzymatic reaction proceeded with great efficiency as measured by chemical yield and enantioselectivity. The racemic *cis*-alcohol **3** was successfully resolved to yield (1*R*,3*S*)-acetate **7** and the corresponding (1*S*,3*R*)-alcohol **3**. The utility of this procedure was demonstrated by the practical syntheses of the biologically active compounds. The (1*R*,3*S*)-acetate **7** and the (1*S*,3*R*)-alcohol **3** were converted into orally active 5-lipoxygenase inhibitors, respectively, without loss of optical purity. © 2002 Published by Elsevier Science Ltd.

1. Introduction

5-Lipoxygenase,[1] (5-LO) is an enzyme that metabolizes arachidonic acid to a group of biologically active lipids known as leukotrienes. The leukotrienes are extremely potent substances that elicit a wide variety of biological effects,[2] often at nano-molar to pico-molar concentrations. An agent that selectively inhibits the action of 5-LO is expected to have therapeutic value for the treatment of acute and chronic inflammatory conditions.[3] Already, the therapeutic benefits of 5-LO inhibitors have been demonstrated for asthma.[4]

Previously, we reported on a series of substituted *N*-cyclopentyl-*N*-hydroxyureas, **1a** and **1b** (Fig. 1).[5] These compounds, prepared as racemates, exhibited good potency as 5-LO inhibitors, both in vitro and in vivo. The preliminary biological evaluations of each enantiomer, isolated in small amounts (~20 mg) using chiral HPLC, indicate that the (+)-enantiomer is substantially more potent than the corresponding (−)-enantiomer.

Further detailed investigations required an efficient, multigram scale synthesis of each enantiomer. Optically active 3-substituted phenyl cyclopentanols were chosen as the key synthetic intermediates. We wish to report here the first asymmetric synthesis of the respective optical isomers by exploiting an enzyme-catalyzed transesterification (kinetic resolution) of 3-substituted phenyl cyclopentanol, employing porcine pancreas lipase (PPL).

2. Results and discussion

2.1. Diastereoselective reduction of the chiral cyclopentenone 2

Many efforts have been devoted to the development of efficient methodologies for the preparation of enantiomerically pure 3-arylcyclopentanones. A successful approach, developed by Posner,[6a] utilizes a neighboring group effect to direct the stereoselectivity at the anomeric center. An efficient catalytic process has recently been reported by Miyaura and Hayashi and involves the rhodium-catalyzed 1,4-addition of phenylboronic acid to 2-cyclopentene-1-one with excellent enantioselectivity and in high yield.[6a,c]

To prepare the desired 3-arylcyclopentanols, the diastereoselective reduction of optically active 3-arylcyclopentanone[6]

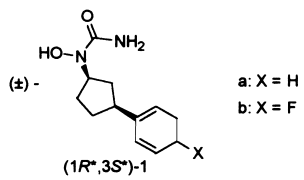

Figure 1. 1,5-Lipoxygenase inhibitors.

Keywords: 5-lipoxygenase inhibitors; kinetic resolution; lipase-catalyzed transesterification; optically active-3-phenylcyclopentanol derivatives.

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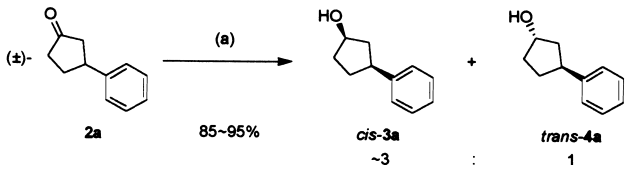


Scheme 1. *Reagents*: (a) DIBAL, toluene, −78°C or LiAl[O^{t}Bu]$_3$H, THF, −78°C.

was initially investigated. Disappointingly, hydride reduction of 3-phenylcyclopentanone,[7] (**2a**) did not proceed with good diastereoselectivity for either the *cis* or *trans*-alcohol. Even when DIBAL or LiA1[O^{t}Bu]$_3$H was used as the reducing agent, at low temperature, the diastereoselectivity of the reduction was not satisfactory (*cis*-**3a**: *trans*-**4a**=~3:1) (Scheme 1). Furthermore, it was difficult to obtain preparative quantities of a single diastereomer from a ~3:1 mixture of **3a** and **4a** by column chromatography.

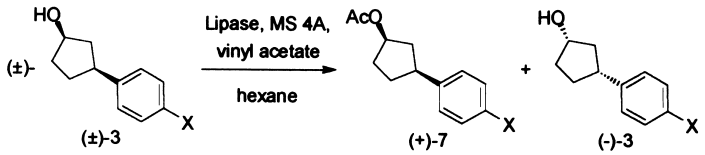
2.2. Enzymatic transesterification of the *cis*-3-arylcyclopentan-1-o1 3

As an alternative approach, the lipase-catalyzed kinetic resolution of pure *cis*-3-phenylcyclopentan-1-ol (**3**) was explored. Biocatalysts are powerful tools for the preparation of chiral compounds that are not obtained easily by conventional chemical asymmetric synthesis.[8] In particular, lipase-catalyzed transesterification in organic media is considered to be a practical method to prepare large quantities of optically active alcohols.[9]

The requisite *cis*-alcohol **3** was readily prepared from 3-aryl-2-cyclopenten-1-one[10] in four steps, as illustrated below (Scheme 2). Thus, the chemoselective 1,2-reduction[11] of cyclopentenone **5** with $NaBH_4$–$CeCl_3$ followed by immediate allylic alcohol. The direct hydrogenation of the allylic alcohol was unsuccessful, however, in constrast, silylation of the hydroxyl group provided the formation of desired **6** in quantitative yield. Fluoride ion mediated desilylation of **6** gave a 10:1 diastereomeric mixture of *cis*-**3** and *trans*-**4**, respectively. Pure *cis*-alcohol **3** was then obtained after column chromatography.

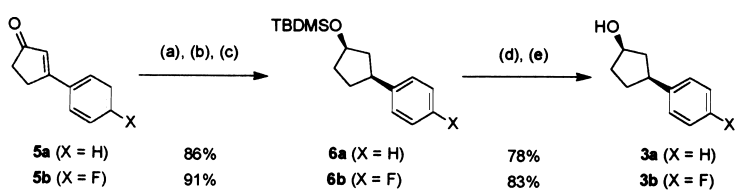
For the transesterification of (±)-*cis*-**3**, stereoselectivity and activity screening of several commercially available lipases was carried out using vinyl acetate as an irreversible acyl transfer reagent (vinyl alcohol undergoes irreversible tautomerisation to acetaldehyde). The results are summarized in Table 1. Among the lipases examined, *Pseudomonas cepacia* lipase (Amano PS) and PPL exhibited good stereoselectivity (entries 1, 2, 5, and 6), while *Pseudomonas fluorescens* lipase (L 056P) gave unsatisfactory results (entries 3 and 7). In the case of *Candida rugosa* lipase (Amano AY), the transesterification did not progress and the racemic starting material (±)-*cis*-**3** was recovered (entries 4 and 8). In the PPL mediated transesterification, excellent selectivity for both (±)-*cis*-**3a** and **3b** was achieved. Notably, PPL was superior to Amano PS since only the favored antipode acetylated, while the unfavored antipode showed almost no reaction during the 4 h incubation (entries 1 vs 2 and 5 vs 6). The resulting *cis*-acetates **7a** (97% ee, E=134) and **7b** (>98% ee, E=298) were isolated in high

Table 1. Enzymatic resolution of (±)-*cis*-**3**

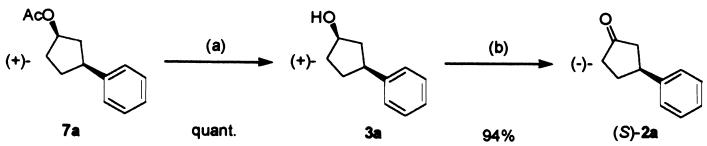


Entry	**3**	X	Lipase	Time (h)	(+)-**7**, % ee (% yield)[a]	(−)-**3**, % ee (% yield)[a]	E[b]
1	**a**	H	Amano PS	4	83 (50)	96 (39)	42
2	**a**	H	PPL	4	97 (37)	68 (51)	134
3	**a**	H	L 056P	4	90 (39)	79 (44)	46
4	**a**	H	Amano AY	4	(0)	(93)	–
5	**b**	F	Amano PS	4	93 (24)	39 (64)	40
6	**b**	F	PPL	4	>98 (29)	41 (63)	298
7	**b**	F	L 056P	4	78 (34)	nd (32)	–
8	**b**	F	Amano AY	4	(0)	(95)	–
9	**a**	H	PPL	24	95 (48)	98 (42)	180
10	**b**	F	PPL	24	96 (48)	>98 (44)	259
11[c]	**a**	H	PPL	24	>98 (30)	47 (58)	317

[a] Isolated yield.
[b] $E = \boldsymbol{ln}[1 - c(1 + ee_p)/\ln[1 - c((1 - ee_p)$, c=ee_a/ee_s+ee_p; cfs. Ref. 9b and 12.
[c] Transesterification was performed without hexane.



Scheme 2. *Reagents*: (a) $NaBH_4$, $CeCl_3$, MeOH; (b) TBDMSCl, imidazole, DMF; (c) H_2, Pd–C (5%), MeOH; (d) Bu_4NF, THF; (e) column chromatography.



Scheme 3. *Reagents*: (a) K_2CO_3, MeOH; (b) PCC, CH_2Cl_2.

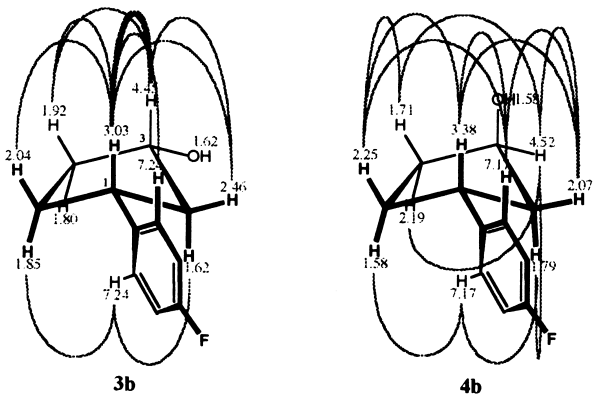


Figure 2. Key PNOESY experiments (⌢) of **3b** and **4b** in $CDCl_3$.

yield (34 and 37%, respectively). Also, in the reaction without hexane, the *cis*-acetate **7a** (>98% ee, E=317) was obtained in 30% yield (entry 11). In 24 h reactions, both (±)-*cis*-**3a** and **3b** gave optically active *cis*-**3a** (98% ee, E=180) and **3b** (>98% ee, E=259) in high yield (42 and 44%, respectively). It seems that a prolonged reaction time does not have a negative effect on the stereoselectivity and the undesired acetate is scarcely observed, even after 24 h (entries 9 and 10).

2.3. Determination of the stereochemistry of cyclopentanols 3a and 3b

The absolute configuration of the acetylated product (+)-**7a** was determined by the following two steps. First, the *cis*-relative stereochemistry (1R^*,3S^*) at C(1) and C(3) of 3-phenylcyclopentanol (**3a**) was assigned by comparing the ^1H and ^{13}C NMR chemical shift data of **3a** with those reported in the literature.[13] Next, (+)-**7a** was converted to **2a** (Scheme 3) and compared with known material to determine the absolute configuration at C(3). The hydrolysis of acetate (+)-**7a** (78% ee) was easily carried out with K_2CO_3 in methanol to give alcohol (+)-**3a**. The secondary hydroxyl group of alcohol (+)-**3a** was then oxidized with pyridinium chlorochromate (PCC) in dichloromethane to generate the desired 3-phenylcyclopentanone (**2a**). The sign of the optical rotation of the ketone **2a** ($[\alpha]_D$=−61.4° (*c* 0.68, $CHCl_3$)) was the same as the literature value for (3*S*)-3-phenylcyclopentanone ($[\alpha]_D$=−84.9° (*c* 0.72, $CHCl_3$)).[14] Therefore, the acetylated product (+)-**7a** had the (1*R*,3*S*) configuration, and the stereogenic reaction center had a (1*R*) configuration.

In the case of acetate (+)-**7b**, the relative configuration of the hydroxyl and *p*-fluorophenyl group in **3b** was determined by a comparison of the phase sensitive NOESY spectra of **3b** with its diastereomer **4b**. An NOE interaction was observed between the protons at C(l) and C(3) of cyclopentane ring for **3b** and no such interaction was observed for **4b** (Fig. 2). Therefore, the alcohol **3b** has the *cis*-stereochemistry (1R^*,3S^*) at C(l) and C(3).

The absolute configuration of the stereogenic center C(1) was determined by the application of the advanced Mosher's method, using MαNP [2-methoxy-2-(1-naphthyl)propionic acid] as a chiral anisotropic reagent.[15]

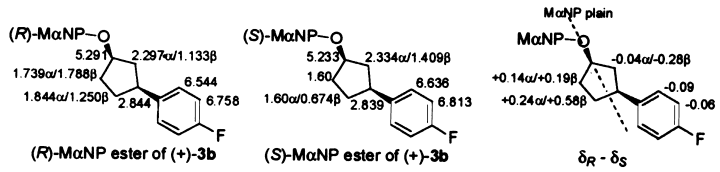
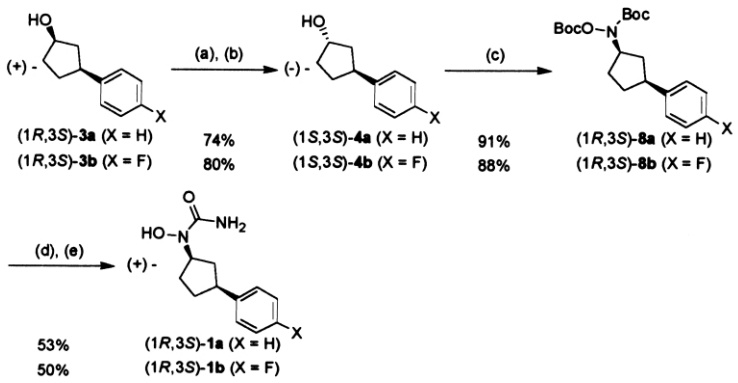


Figure 3. ^1H NMR assignment of MαNP ester and chemical shift difference ($\delta_R-\delta_S$).



Scheme 4. *Reagents*: (a) $PhCO_2H$, DEAD, PPh_3, THF; (b) NaOH aq., MeOH; (c) HN(Boc)OBoc, DEAD, PPh_3, THF; (d) trifluoroacetic acid, CH_2Cl_2; (e) TMSNCO, THF.

The requisite MαNP esters, were prepared by acylation of (+)-**3b** (obtained after hydrolysis of the acetate (+)-**7b**) with (*R*) and (*S*)-MαNP acid in the presence of DCC and DMAP. Their proton chemical shifts were assigned by COSY and phase sensitive NOESY, and the chemical shift difference ($\delta_R-\delta_S$) for each corresponding proton was calculated as shown in Fig. 3. Looking at the molecule from MαNP direction, the chemical shift differences of the right-hand side of MαNP plain are positive and those of the other side are negative. Therefore the MαNP ester should have a β-direction (*R*-configuration). Hence, the resolved stereogenic center C(1) of acetate (+)-**7b** would also have a (1*R*) configuration. In conjunction with the stereochemical assignment of the *cis*-stereochemistry of **3b**, these results confirmed the (1*R*,3*S*) configuration of acetylated product (+)-**7b**. The absolute stereochemistry of (−)-**3b** was also determined as (1*S*,3*R*) in the same manner, in which the positive and negative sides to MαNP plain were opposite to those in (+)-**3b** case.

2.4. Application to large scale synthesis

On large-scale, the simplicity of the reaction resulted in an efficient resolution. Under optimized conditions, the kinetic resolution of 55.8 g of *cis*-3-(4-fluorophenyl)cyclopentanol (**3b**) for 4 h provided 26.6 g of (+)-(1*R*,3*S*)-3-(4-fluorophenyl)cyclopentyl acetate (**7b**), that showed excellent enantiomeric purity (>98% ee). (1*R*,3*S*)-Acetate (+)-**7b** was easily hydrolyzed by means of K_2CO_3 in methanol to yield 21.7 g (39% from (±)-**3b**) of (1*R*,3*S*)-alcohol (+)-**3b**. Re-incubation of the recovered intact *cis*-alcohol **3b** (32.1 g) into the reaction medium, followed by 24 h of transesterification, afforded 25.4 g (46% from (±)-**3b**) of (1*S*,3*R*)-alcohol (−)-**3b**, that showed excellent enantiomeric purity (>98% ee).

2.5. Conversion to the biologically active compound

After having secured the requisite optically active intermediate alcohols, elaboration to the respective target compounds proved uneventful. Thus, double inversion of (1*R*,3*S*)-alcohol (+)-**3** employing Mitsunobu's procedure[16] ((1) $PhCO_2H$, PPh_3–DEAD (2) hydrolysis (3) HN(Boc)O-Boc, PPh_3–DEAD)) gave an excellent yield of the corresponding di-Boc protected hydroxylamine **8**. Acid hydrolysis of the *tert*-butoxycarbonyl functionality (trifluoroacetic acid in CH_2Cl_2) and subsequent treatment with trimethylsilylisocyanate furnished the desired hydroxyurea (+)-**1**. The corresponding (−)-enantiomer, (−)-**1**, was synthesized in an analogous manner to prepare hydroxyurea (+)-**1** from (1*S*,3*R*)-alcohol **3** (Scheme 4).

3. Conclusion

Both enantiomers of *cis*-3-(substituted-phenyl)cyclopentanols have been obtained in optically active form by a lipase-catalyzed transesterification in organic medium. The enzyme catalyst, PPL, is readily available, inexpensive, and environmentally benign and can be used under mild reaction conditions. Additionally, the derived cyclopentanols can easily be transformed into the corresponding cyclopentanones without loss of optical purity. This enzyme mediated synthesis provides an additional example of one of the more powerful methods for the practical preparation of optically pure chiral synthons for the construction of biologically important molecules.

4. Experimental

4.1. General methods

Instruments. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-LA 270 spectrometer system at 270 MHz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-LA 270 spectrometer system at 67.8 MHz. Chemical shifts are reported as δ values in ppm from tetramethylsilane as internal standard. COSY and phase sensitive NOESY spectra were recorded on a Bruker AVANCE 600 NMR spectrometer system at 600 MHz with standard 5 mm probe or 2.5 mm micro-probe. IR spectra were recorded on a Shimadzu IR-470 infrared spectrometer. Low-resolution mass spectra (ESI) were recorded on a Waters/Micromass ZMD mass spectrometer. High resolution mass spectra (EI) were recorded on a JEOL JMS-700 spectrometer (MStation) with direct inlet mode, and reported in *m/z*. Optical rotations were measured using a JASCO DIP-370 Digital Polarimeter. All melting points were measured in open capillary tubes with Büch 535 or 520 apparatus and are uncorrected. Elemental analyses (CHN) were carried out on a Thermo Finnigan elemental analyzer EA 1110.

Materials. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel coated glass plates 60 F_{254} (Merck, Art5719). For flash column chromatography, Merck Silicagel 60 (230–400 mesh ASTM) was used. *C. rugosa* lipase (Amano AY) and *P. cepacia* lipase (Amano PS) were supplied by Amano Pharmaceutical CO., Ltd. Porcine pancrease lipase (PPL) (EC 3.1.1.3) was obtained from Sigma. *P. fluorescens* lipase (L 056P) was obtained from BIOCATALYSTS LTD. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Wako Pure Chemical Industries, Ltd. All other materials were purchased from Nacalai Tesque, Inc, Tokyo Kasei Kogyo Co, Ltd, Wako Pure Chemical Industries, Ltd, and Aldrich Chemical Co, Inc and were used as received.

4.1.1. *tert*-Butyl[[*cis*-3-(4-fluorophenyl)cyclopentyl]oxy]-dimethylsilane (6b). To a cooled (0°C) mixture of 3-(4-fluorophenyl)cyclopent-2-en-l-one[10c] (**5b**; 96 g, 546 mmol) and cerium (III) chloride heptahydrate (208 g, 560 mmol) in MeOH (2000 ml) was added $NaBH_4$, (21.2 g, 560 mmol) in small portions over a 30 min period. The mixture was allowed to warm to room temperatue and stirred for 1 h. The reaction was quenched by the addition of ice-cold water (500 ml), and then the volatiles were removed under reduced pressure. The residue was extracted with EtOAc (1000 ml). The organic extracts were washed with brine (300 ml), dried over Na_2SO_4, and concentrated in vacuo to yield 97 g of the corresponding 3-(4-fluorophenyl)cyclopent-2-en-l-ol as yellow solids.

To a cooled (0°C) solution of the allylic alcohol (97 g) in

anhydrous DMF (400 ml) was added successively imidazole (38.1 g, 560 mmol) and *tert*-butyldimethylsilyl chloride (84.4 g, 560 mmol). The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (1000 ml). The whole mixture was washed with water (500 ml), 1N-HCl (500 ml), saturated aqueous $NaHCO_3$ (500 ml), and brine (300 ml). The organic phase was dried over Na_2SO_4, and concentrated to afford 142 g of the corresponding *tert*-buty1[[3-(4-fluorophenyl)cyclopent-2-en-l-yl]oxy]dimethylsilane as a brown oil.

A suspension of the silylated cyclopentenol and 5% Pd/C (10 g) in EtOAc (400 ml) was stirred under H_2 atmosphere for 8 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to afford 138.5 g (86% for three steps) of *tert*-butyl[[3-(4-fluorophenyl)-cyclopentyl]oxy]dimethylsilane (**6b**) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.29–7.20 (m, 2H), 6.95 (t, J=8.8 Hz, 2H), 4.41–4.30 (m, 1H), 3.06–2.93 (m, 1H), 2.38–2.26 (m, 1H), 2.07–1.91 (m, 1H), 1.88–1.72 (m, 3H), 1.67–1.55 (m, 1H), 0.91 (s, 9H), 0.07 (s, 6H); HRMS (EI) calcd for $C_{17}H_{26}OFSi$ $(M-H)^+$ 293.1737, found 293.1726.

4.1.2. *tert*-Butyl[*cis*-3-phenylcyclopentyl)oxy]dimethylsilane (6a). *tert*-Butyl[(*cis*-3-phenylcyclopentyl)oxy]-dimethylsilane (**6a**) was prepared from the corresponding 3-phenyl-2-cyclopenten-1-one[10a,b] (**5a**) in 86% yield as a light brown oil in a similar manner as described for the preparation of *cis*-**6b**: ^{1}H NMR ($CDCl_3$) δ 7.34–7.10 (m, 5H), 4.41–4.26 (m, 1H), 3.07–2.94 (m, 1H), 2.34–2.20 (m, 1H), 2.17–1.56 (m, 5H), 0.90 (s, 9H), 0.08 (s, 6H); HRMS (EI) calcd for $C_{17}H_{28}OSi$ 276.1910, found 276.1910.

4.1.3. *cis*-3-(4-Fluorophenyl)cyclopentanol (3b). To a cooled (0°C) solution of *tert*-butyl[[3-(4-fluorophenyl)-cyclopentyl]oxy]dimethylsilane (**6b**, 9.4 g, 30 mmol) in THF (100 ml) was added a solution of *n*-Bu_4NF (1 M solution in THF, 40 ml). The reaction mixture was stirred for 1 h at room temperature. The mixture was diluted with EtOAc (100 ml). The whole mixture was washed with brine (100 ml), dried over or $MgSO_4$, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 300 g, hexane/EtOAc (3/1)) afforded 4.5 g (83%) of *cis*-3-(3-fluorophenyl)cyclopentan-1-ol (**3b**) as a colorless oil and 615 mg (11%) of diastereomeric mixture (*cis*/*trans*=1:1) of **3b**: *cis*-**3b**; ^{1}H NMR ($CDCl_3$,) δ 7.23 (dd J=8.8, 5.4 Hz, 2H), 6.96 (t, J=8.8 Hz, 2H), 4.50–4.38 (m, 1H), 3.52–2.94 (m, 1H), 2.52–2.37 (m, 1H), 2.08–1.77 (m, 4H), 1.68–1.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.2 (d, J=242 Hz), 141.3 (d, J=3 Hz), 128.5 (d, J=8 Hz), 115.0 (d, J=21 Hz), 73.5, 44.1, 43.5, 36.0, 32.8; HRMS (EI) calcd for $C_{11}H_{13}NOF$ 180.0950, found 180.0955.

4.1.4. *cis*-3-Phenylcyclopentanol (3a). *cis*-3-Phenylcyclopentanol (**3a**) was prepared from the corresponding *tert*-butyl[(*cis*-3-phenylcyclopentyl)oxy]dimethylsilane (**6a**) in 78% yield as a colorless oil in a similar manner as described for the preparation of *cis*-**3b**: ^{1}H NMR ($CDCl_3$) δ 7.38–7.13 (m, 5H), 4.51–4.40 (m, 1H), 3.13–2.99 (m, 1H), 2.52–2.40 (m, 1H), 2.11–1.60 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 145.65, 128.34, 127.13, 125.94, 73.65, 44.23, 44.00, 36.06, 32.63; HRMS (EI) calcd for $C_{11}H_{13}NOF$ 162.1045, found 162.1027.

4.2. General procedure of lipase-catalyzed transesterification

A mixture of powdered 4 Å molecular sieves (30 mg), (±)-*cis*-cyclopentanol (**3**, 0.3 mmol), and vinyl acetate (2 ml) in hexane (2 ml) was stirred at room temperature for 10 min. To this mixture was added a powder of lipase (20 mg) in one portion. The reaction mixture was stiffed vigorously at room temperature. After an appropriate time, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated in vacuo to afford a crude mixture. The mixture was separated by silica-gel column chromatography to afford corresponding acetate (**7**) and unacetylated alcohol (**3**).

4.2.1. (+)-(1*R*,3*S*)-3-(4-Fluorophenyl)cyclopentyl acetate (7b) and (−)-(1*S*,3*R*)-3-(4-fluorophenyl)cyclopentanol (3b). A mixture of powdered 4 Å molecular sieves (33.6 g), (±)-*cis*-3-(4-fluorophenyl)cyclopentanol (**3b**; 55.8 g, 310 mmol), and vinyl acetate (2240 ml) in hexane (2240 ml) was stirred for 10 min at room temperature. To this mixture was added PPL, (Sigma, Lipase from Porcine Pancreas; 22.4 g) in small portions. The reaction mixture was stirred vigorously at room temperature. After 4 h, the reaction mixture was filtered through a pad of celite, and the filtrate was concentrated in vacuo to afford a crude mixture. The mixture was separated by silica-gel column chromatography (SiO_2, 1700 g; hexane/EtOAc (10/1 and then 3/1)) to afford 26.6 g (39%) of optically pure (>98% ee) (+)-(1*R*,3*S*)-3-(4-fluorophenyl)cyclopentyl acetate (**7b**) as a colorless oil and 32.1 g of an unreacted alcohol **3b**. The optical purity of the acetate **7b** was determined by chiral HPLC analysis (column, CHIRALCEL OJ-H; eluent, hexane/2-propanol (95/5); flow rate, 0.5 ml/min; t_R 13.0 min (1*R*,3*S*) and 14.6 min (1*S*,3*R*)): (+)-(1*R*,3*S*)-**7b** (>98% ee); $[\alpha]_D$=+16.6° (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.24–7.15 (m, 2H), 6.98 (t, J=8.8 Hz, 2H), 5.28–5.18 (m, 1H), 3.12–296 (m, 1H), 2.61–2.49 (m, 1H), 2.12–1.60 (m, 5H), 2.06 (s, 3H); HRMS (EI) calcd for $C_{13}H_{I5}O_2F$ 222.1056, found 222.1062.

The recovered alcohol (32.1 g) was subjected to the above mentioned reaction conditions for 24 h. An analogous work-up and purification by silica-gel column chromatography (SiO_2, 800 g; hexane/EtOAc (2/1)) gave 25.4 g (46% from racemate) of optically pure (>98% ee) (−)-(1*S*,3*R*)-3-(4-fluorophenyl)cyclopentanol (**3b**) as a colorless oil and 7.2 g (10%) of 97% ee (+)-(1*R*,3*S*)-3-(4fluorophenyl)cyclopentyl acetate (**7b**) as a colorless oil. Cyclopentanol **3b** could not be separated by chiral HPLC under a variety of conditions, and hence the optical purity was determined from the derived acetate **7b**, that was obtained from **3b** by the treatment with Ac_2O, pyridine, and DMAP in CH_2Cl_2: (−)-(1*S*,3*R*)-3b (>98% ee); $[\alpha]_D$=−8.1° (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.28–7.19 (m, 2H), 6.94 (t, J=8.8 Hz, 2H), 4.50–4.39 (m, 1H), 3.12–2.96 (m, 1H), 2.62–2.48 (m, 1H), 2.10–1.54 (m, 6H).

4.2.2. MαNP esters of (+)-3b and (−)-3b. Cyclopentanol (+)-**3b** (0.50 mg, 2.8 μmol) was treated with 10 μmol of (*S*)-MαNP [2-methoxy-2-(1-naphthyl)propionic acid], 10 μmol of DCC, and 10 μmol of DMAP in 2000 μl of CH_2Cl_2, at room temperature, for 22 h. Purification by

preparative TLC afforded the pure (*S*)-MαNP ester of (+)-**3b** (0.84 mg, 2.1 μmol): R_f=0.55 ($CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.40 (1H, m), 7.85 (1H, br d, *J*=8.1 Hz), 7.82 (1H, m), 7.6), 6.81 (2H, t, *J*=8.7 Hz), 6.64 (2H, dd, *J*=8.6, 5.4 Hz), 5.23 (1H, m), 3.12 (3H, s), 6 (1H, dd, *J*=7.2, 1.0 Hz), 7.52 (1H, dd, *J*=8.1, 7.4 Hz), 7.45 (1H, m), 7.44 (1H, m), 2.84 (1H, m), 2.33 (1H, ddd, *J*=14.7, 10.0, 6.3 Hz), 2.00 (3H, s), 1.60 (3H, m), 1.41 (1H dddd, *J*=12.6, 7.6, 2.7, 1.27 Hz), 0.68 (1H, m).

The pure (*R*)-MαNP ester (0.88 mg, 2.2 μmol) was also obtained from (+)-**3b** in a similar manner as described for the preparation of (*S*)-MαNP ester: R_f=0.55 ($CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (1H, m), 7.88 (1H br d, *J*=8.1 Hz), 7.87 (1H, m), 7.65 (1H, dd, *J*=72, 1.0 Hz), 7.51 (1H, dd, *J*=8.1, 7.4 Hz), 7.46 (1H, m), 7.45 (1H, m), 6.76 (2H, t, *J*=8.7 Hz), 6.55 (2H, dd, *J*=8.6, 5.4 Hz), 5.29 (1H, tt, *J*=6.5, 3.0 Hz), 3.10 (3H, s), 2.84 (1H, br pent., *J*=8.1 Hz), 2.30 (1H ddd, *J*=14.7, 9.6, 6.5 Hz), 2.00 (3H, s), 1.84 (1H, m), 1.79 (1H, m), 1.74 (1H, m), 1.25 (1H, m), 1.13 (1H, dddd, *J*=14.8, 8.4, 3.0, 1.4 Hz).

The (*S*)-MαNP ester (0.89 mg, 2.3 μmol) and (*R*)-MαNP ester (0.85 mg, 2.2 μmol) of (−)-**3b** were also prepared in a similar manner. The ^{1}H NMR spectrum of the MαNP esters was perfectly identical to that of the corresponding enantiomers.

4.2.3. (+)-(1*R*,3*S*)-3-Phenylcyclopentyl acetate (7a) and (−)-(1*S*,3*R*)-3-phenylcyclopentanol (3a). A mixture of powdered 4 Å molecular sieves (300 mg) and (±)-*cis*-3-phenylcyclopentanol (**3a**; 400 mg, 2.5 mmol) in vinyl acetate (20 ml) was stirred at room temperature for 10 min. To this mixture was added PPL (200 mg), and the reaction mixture was stirred vigorpusly at room temperature for 24 h (entry 11). The reaction mixture was then diluted with chloroform (50 ml) and filtered through a pad of celite. The filtrate was concentrated in vacuo to afford a crude mixture. The mixture was separated by silica-gel column chromatography (SiO_2, 20 g; hexane/EtOAc (10/1 and then 3/1)) to afford 152 mg (30%) of optically pure (>98% ee) (+)-(1*R*,3*S*)-3-phenylcyclopentyl acetate (**7a**) as a colorless oil (the optical purity of **7a** was determined after hydrolysis to **3a**) and 232 mg (58%) of 47% ee (−)-(1*S*,3*R*)-cyclopentanol **3a** as a colorless oil. The optical purity of the alcohol **3a** was determined by chiral HPLC analysis (column, CHIRALPAK AD-H; eluent, hexane/EtOH (95/5); flow rate, 1.0 ml/min; t_R 9.2 min (1*R*,3*S*) and 10.4 min (1*R*,3*S*)): (+)-(1*R*,3*S*)-**7a** (>98% ee): $[\alpha]_D$=+19.0° (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.35–7.22 (m, 5H), 5.30–5.18 (m, 1H), 3.22–2.99 (m, 1H), 2.63–2.50 (m, 1H), 2.05 (s, 3H), 2.12–1.71 (m, 5H); HRMS (EI) calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1133.

A mixture of powdered 4 Å molecular sieves (150 mg), (±)-*cis*-**3a** (200 mg, 1.2 mmol), and vinyl acetate (10 ml) in hexane (10 ml) was stirred at room temperature for 10 min. To this mixture was added PPL (100 mg), and the reaction mixture was stirred vigorously at room temperature for 24 h (entry 9). An analogous work-up and purification afforded 84 mg (42%) of 98% ee (−)-(1*S*,3*R*)-3-phenylcyclopentanol (**3a**) as a colorless oil and 121 mg (48%) of 95% ee (+)-(1*R*,3*S*)-3-phenylcyclopentyl acetate (**7a**) as a colorless oil: (−)-(1*S*,3*R*)-**3a** (98% ee); $[\alpha]_D$=−8.7° (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.36–7.12 (m, 5H), 4.51–4.41 (m, 1H), 3.13–2.97 (m, 1H), 2.51–2.40 (m, 1H), 2.10–1.57 (m, 6H).

4.2.4. (−)-(*S*)-3-Phenylcyclopentanone (2a).[14] To a solution of 78% ee (+)-3-phenylcyclopentyl acetate (**7a**; 86 mg, 0.42 mmol) in MeOH (5 ml) was added K_2CO_3 (300 mg, 2.2 mmol) in one portion. The mixture was stirred at room temperature for 3 h. The volatiles were removed under reduced pressure, and the residue was diluted with 30 ml of water. The aqueous mixture was extracted with EtOAc (50 ml). The organic phase was washed with brine (30 ml), dried over $MgSO_4$, and concentrated in vacuo to afford 70 mg of crude (+)-3-phenylcyclopentanol (**3a**).

To a suspension of pyridinium chlorochromate (PCC) (135 mg, 0.63 mmol) in dry CH_2Cl_2 (2 ml) was added a solution of the alcohol (+)-**3a** in dry CH_2Cl_2 (2 ml). The mixture was stirred vigorously at room temperature for 2 h. The reaction mixture was suspended in diethyl ether (50 ml) and then passed through a short Florisil (Nacalai Tesque, 60–100 mesh) column. The solvent was removed from the eluate to furnish 63 mg (94%) of 3-phenylcyclopentanone (**2a**) as a colorless oil: $[\alpha]_D$=−61.4° (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39–7.20 (m, 5H), 3.53–3.34 (m, 1H), 2.74–2.63 (m, 1H), 2.60–2.23 (m, 1H), 2.35–1.61 (m, 1H). The spectral data are identical with those in the literature.[14]

4.2.5. (+)-(1*S*,3*S*)-3-(4-Fluorophenyl)cyclopentanol (4b). To a solution of (+)-(1*R*,3*S*)-3-(4-fluorophenyl)cyclopentyl acetate (**7b**; 379 mg, 1.7 mmol) in MeOH (50 ml) was added K_2CO_3 (1.2 g, 8.5 mmol). The reaction mixture was stirred for 3 h at room temperature. The volatiles were removed under reduced pressure, and the residue was diluted with 100 ml of water. The aqueous mixture was extracted with EtOAc (100 ml). The organic layer was washed with brine (50 ml), dried over $MgSO_4$, and concentrated in vacuo to afford crude (+)-(1*R*,3*S*)-3-(4-fluorophenyl)cyclopentanol (**3b**).

To a stirred solution of the alcohol (+)-(1*R*,3*S*)-**3b** (299 mg, 1.7 mmol), benzoic acid (224 mg, 2.0 mmol), and triphenylphosphine (525 mg, 2.0 mmol) in THF (25 ml) was added dropwise diethyl azodicarboxylate (435 mg, 2.5 mmol) in THF (5 ml) at 0°C under an argon atmosphere. The mixture was stirred for 1 h at room temperature, and then the volatiles were removed under reduced pressure. The residue was suspended in Et_2O, and insoluble material was removed by filtration. The ether layer was concentrated in vacuo to afford crude (1*S*,3*S*)-3-(4-fluorophenyl)cyclopentyl benzoate.

To a solution of the crude benzoate (1.2 g, 1.7 mmol) in MeOH (30 ml) was added an aqueous solution of KOH (560 mg in 5 ml of water). The mixture was stirred for 12 h at room temperature. The volatiles were removed under reduced pressure, and the residue was diluted with water (50 ml). The aqueous mixture was extracted with EtOAc (100 ml). The organic layer was washed with brine (50 ml), dried over $MgSO_4$, and concentrated in vacuo. The residual oil was purified by flash chromatography (SiO_2, 80 g; hexane/EtOAc (2/1)) to afford 245 mg (80%) of (+)-(1*S*,3*S*)-3-(4-fluorophenyl)cyclopentanol (**4b**) as a colorless

oil. The optical purity, determined by HPLC analysis (column, CHIRALPAK AS; eluent, hexane/2-propanol (95/5); flow rate, 0.5 ml/min; t_R 16.1 min (1*S*,3*S*) and 17.9 min (1*R*,3*R*)), was >98% ee: $[\alpha]_D$=+11.4° (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.18 (dd, *J*=8.7, 5.4 Hz, 2H), 6.97 (t, *J*=8.7 Hz, 2H), 4.56–4.50 (m, 1H), 3.45–3.30 (m, 1H), 2.31–2.12 (m, 2H), 2.12–2.02 (m, 1H), 1.85–1.47 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 161.2 (d, *J*=242 Hz), 141.0 (d, *J*=3 Hz), 128.3 (d, *J*=8 Hz), 115.0 (d, *J*=20 Hz), 73.6, 44.4, 42.2, 35.6, 32.7; HRMS (EI) calcd for $C_{11}H_{13}NOF$ 180.0950, found 180.0952.

4.2.6. (+)-(1*S*,3*S*)-3-Phenylcyclopentanol (4a). (+)-(1*S*,3*S*)-3-Phenylcycloperntanol (**4a**) was prepared from the corresponding (+)-(1*R*,3*S*)-3-phenylcyclopentyl acetate (**7a**) in 74% yield as a colorless oil in a similar manner as described for the preparation of (+)-(1*S*,3*S*)-**4b**. The optical purity, determined by HPLC analysis (column, CHIRALCEL OG; eluent, hexane/2-propanol (90/10); flow rate, 0.5 ml/min; t_R 12.9 min (1*S*,3*S*) and 14.8 min (1*R*,3*R*), was >98% ee: $[\alpha]_D$=+12.7° (*c* 1.00, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.37–7.14 (m, 5H), 4.56–4.49 (m, 1H), 3.48–3.30 (m, 1H), 2.35–2.06 (m, 3H), 1.90–1.53 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 145.49, 129.33, 127.02, 125.92, 73.70, 44.27, 42.90, 35.69, 32.61; HRMS (EI) calcd for $C_{11}H_{13}NOF$ 162.1045, found 162.1042.

4.2.7. *N*,*O*-Bis(*tert*-butoxycarbonyl)-*N*-[(1*R*,3*S*)-3-(4-fluorophenyl)cyclopentyl] hydroxylamine (8b). To a stirred solution of (+)-(1*S*,3*S*)-3-(4-fluorophenyl)cyclopentanol (**4b**; 245 mg, 1.4 mmol), *N*,*O*-bis-(*tert*-butoxycarbonyl)hydroxylamine (400 mg, 1.7 mmol), and triphenylphosphine (450 mg, 1.7 mmol) in THF (25 ml) was added dropwise diethyl azodicarboxylate (350 mg, 2.0 mmol) in THF (5 ml) at 0°C under and argon atmosphere. After completion of addition, the mixture was stirred for 1 h at room temperature, an then the volatiles were removed under reduced pressure. Chromatographic removal of triphenylphosphine oxide provided 489 mg (88%) of *N*,*O*-bis(*tert*-butoxycarbonyl)-*N*-[(1*R*,3*S*)-3-(4-fluorophenyl)-cyclopentyl]hydroxylamine, (**8b**) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.24–7.16 (m, 2H), 6.97 (t, *J*=8.8 Hz, 2H), 4.81–4.62 (m, 1H), 3.09–2.88 (m, 1H), 2.42–2.22 (m, 1H), 2.10–1.35 (m, 23H). This material was used for the next steps without further purification.

4.2.8. *N*,*O*-Bis(*tert*-butoxycarbonyl)-*N*-[(1*R*,3*S*)-3-phenylcyclopentyl]hydroxylamine(8a). *N*,*O*-Bis(*tert*-butoxycarbonyl)-*N*-[(1*R*,3*S*)-3-phenylcyclopentyl]-hydroxylamine (**8a**) was prepared from the corresponding (+)-(1*S*,3*S*)-3-phenylcyclopentanol (**4a**) in 91% yield as yellow oil in a similar manner as described for the preparation of **8b**: ^{1}H NMR ($CDCl_3$) δ 7.38–7.17 (m, 5H), 4.80–4.65 (m, 1H), 3.12–2.93 (m, 1H), 2.53–2.28 (m, IH), 2.11–1.65 (m, 5H), 1.50–1.40 (m, 18H). This material was used for the next steps without further purification.

4.2.9. (+)-*N*-[(1*R*,3*S*)-3-(4-Fluorophenyl)cyclopentyl]-*N*-hydroxyurea (1b). To a stirred solution of *N*,*O*-bis(*tert*-butoxycarbonyl)-*N*-[(1*R*,3*S*)-3-(4-fluorophenyl)-cyclopentyl]hydroxylamine (**8b**; 489 mg, 1.2 mmol) in CH_2Cl_2 (10 ml) was added trifluoroacetic acid (4 ml). The mixture was stirred for 1 h at room temperature. The volatiles were removed under reduced pressure, and the residue was diluted with HtOAc (50 ml). The organic layer was washed with water (30 ml), sat. aqueous $NaHCO_3$ solution (30 ml), and brine (50 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuoto afford crude (1*R*,3*S*)-3-(4-fluorophenyl)cyclopentylhydroxylamine as white solids.

To a solution of the crude hydroxylamine (234 mg, 1.2 mmol) in THF (10 ml) was added trimethylsilyl isocyanate (0.3 ml, 2.0 mmol) at room temperature. The reaction mixture was stirred for 30 min. Volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography (SiO_2, 30 g; $CHCl_3$/acetone (3/2)). Recrystallization from EtOAc afforded 142 mg (50%) of (+)-*N*-[(1*R*,3*S*)-3-(4-Fluorophenyl)cyclopentyl]-*N*-hydroxyurea (**1b**) as a white powder. The optical purity, determined by HPLC analysis (column, CHIRALCEL OJ; eluent, hexane/2-propanol (90/10); flow rate, 0.5 ml/min; t_R 13.1 min (1*S*,3*R*) and 17.6 min (1*R*,3*S*), was >98% ee: $[\alpha]_D$=+22.2° (*c* 0.5, EtOH); mp 139.2–140.2°C; IR (KBr) ν 3400, 3250, 1650, 1620, 1510,1400,1220, 840 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.09 (s, 1H), 7.31–7.24 (m, 2H), 7.10 (t, *J*=9.0 Hz, 2H), 6.28 (s, 2H), 4.73–4.60 (m, 1H), 3.04–2.88 (m, 1H), 2.11–1.53 (m, 6H); MS (ESI) *m*/*z* 239 (MH^+), 237 ($[M-H]^-$); Anal. calcd for $C_{12}H_{15}N_2O_2F$: C, 60.49; H, 6.35; N, 11.76. Found: C, 60.18; K 6.33; N, 11.69.

4.2.10. (−)-*N*-[(1*S*,3*R*)-3-(4-Fluorophenyl)cyclopentyl]-*N*-hydroxyurea (1b). (−)-*N*-[(1*S*,3*R*)-3-(4-Fluorophenyl)-cyclopenty1]-*N*-hydroxyurea (**1b**) was prepared from the corresponding (−)-(1*S*,3*R*)-alcohol **3b** as a white powder in a similar manner as described for the ion of (+)-(1*R*,3*S*)-**1b**. The optical purity determined by HPLC analysis (column, CMRALCEL OJ; eluent, hexane/2-propanol (90/10); flow rate, 0.5 ml/min; t_R 13.1 min (1*S*,3*R*) and 17.6 min (1*R*,3*S*)), was >98% ee: $[\alpha]_D$=−22.4° (*c* 0.5, EtOH); mp 139.0–140.4°C; IR (KBr) ν 3400, 3350, 1650, 1510, 1400, 1220, 950 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.09 (s, 1H), 7.32–7.24 (m, 2H), 7.10 (m, 2H), 6.29 (br.s, 2H), 4.75–4.58 (m, 1H), 3.05–2.88 (m, 1H), 2.09–1.56 (m, 6H); MS (ESI) *m*/*z* 239 (MH^+), 237 ($[M-H]^-$); Anal. calcd for $C_{12}H_{15}N_2O_2F$: C, 60.49; H, 6.35; N, 11.76. Found: C, 60.45; H, 6.50; N, 11.72.

4.2.11. (+)-*N*-Hydroxy-*N*-[(1*R*,3*S*)-3-phenylcyclopentyl] urea (1a). (+)-*N*-Hydroxy-*N*-[(1*R*,3*S*)-3-phenylcyclopentyl]urea (**1a**) was prepared from the corresponding *N*,*O*-bis(*tert*-butoxycarbonyl)-*N*-[(1*R*,3*S*)-3-phenylcyclopentyl]hydroxylamine (**8a**) in 53% yield as a white powder in a similar manner as described for the preparation of (+)-(1*R*,3*S*)-**1b**. The optical purity, determined by HPLC analysis (column, CHIRALCEL OJ; eluent, hexanen/2-propanol (80/20); flow rate, 1.0 ml/min; t_R 7.0 min (1*S*,3*R*) and 12.0 min (1*R*,3*S*)), was >98% ee: $[\alpha]_D$=+26.2° (*c* 0.5, EtOH); mp 126.1–126.9°C; IR (KBr) ν 3480, 3350, 3300, 1810, 1580, 1450, 1150, 1070, 760, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.10 (s, 1H), 7.31–7.16 (m, 5H), 6.28 (s, 2H), 4.70–4.60 (m, 1H), 2.95–2.90 (m, 1H), 2.06–1.58 (m, 6H); MS (ESI) *m*/*z* 221 (MH^+), 219 ($[M-H]^-$); Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.18; M 7.41; N, 12.41.

4.2.12. (−)-*N*-Hydroxy-*N*-[(1*S*,3*R*)-3-phenylcyclopentyl] urea (1a). (−)-*N*-Hydroxy-*N*-[(1*S*,3*R*)-3-phenylcyclopen-

tyl]urea (**1a**) was prepared from the corresponding (−)-(1*S*,3*R*) alcohol **3a** as a white powder in a similar manner as described for the preparation of (+)-(1*R*,3*S*)-**1a**. The optical purity, determined by HPLC analysis (column, CHIRALCEL OJ; eluent, hexane/2-propanol (80/20); flow rate, 1.0 ml/min; t_R 7.0 min (1*R*,3*S*) and 12.0 min (1*R*,3*S*)), was >98% ee: $[\alpha]_D=-27.2°$ (*c* 0.5, EtOH); mp 125.8–126.8°C; IR (KBr) ν 3480, 3350, 3300, 1610, 1580, 1450, 1150, 1070, 760, 700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.12 (s, 1H), 7.31–7.16 (m, 5H), 6.28 (s, 2H), 4.70–4.60 (m, 1H), 2.93–2.88 (m, 1H), 2.10–1.55 (m, 6H); MS (ESI) *m/z* 221 (MH^+), 219 ($[M-H]^-$); Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.24; H 7.41; N, 12.39.

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