Asymmetric Synthesis and Determination of the Absolute Configuration of FK584, an Agent for the Treatment of Overactive Detrusor

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FK584[(−)-*N*-*tert*-butyl-4,4-diphenyl-2-cyclopentenylamine hydrochloride, (−)-4·HCl], a potential candidate for the treatment of overactive detrusor, was synthesized in a 4-step approach starting with Sharpless oxidation of cyclopentenol 6 (kinetic resolution). This epoxidation is a rare case in that the empirical rule does not work. Regio- and stereoselective introduction of *tert*-butylamine to the obtained epoxycyclopentanol 5 and subsequent conversion of the resulting diol to an olefin completed the synthesis. The absolute configuration of FK584 was determined to be *S* by X-ray crystallographic analysis of the salt of *S*-(+)-mandelic acid.

Key words FK584; *N*-*tert*-butyl-4,4-diphenyl-2-cyclopentenylamine; overactive detrusor; Sharpless oxidation

We earlier reported[1] that FK584 has good pharmacological properties for the treatment of overactive detrusor and its clinical development is in progress. In the course of developing a new clinical agent, pharmacokinetic studies are necessary which require radiolabelled compound. The synthesis of FK584[1] was carried out by optical resolution of the synthetic racemate but this method is not applicable to the synthesis of radiolabelled compound. Consequently, we pursued an asymmetric synthesis of FK584 by two different methods, A and B, using 2-methyl-[2-^{14}C]-propylamine as a labelled precursor which is available from the Amersham Company (Fig. 1). Method A consists of the introduction of *tert*-butylamine to π-allylpalladium **3** generated from cyclopentenyl acetate **1** or **2**, while method B involves the introduction of *tert*-butylamine to 5,5-diphenyl-2,3-epoxycyclopentan-1-ol (**5**) and subsequent conversion to the required final product. Herein, we report the details of the asymmetric synthesis of FK584 and its absolute configuration.

Our initial attempt at the synthesis of FK584 involved a kinetic resolution of **6**[1] or **7**[2] with lipase PS (Amano) and isopropenyl acetate to afford optically active cyclopentenol (+)-**7** and cyclopentenyl acetate (−)-**2**, respectively, and the results are shown in Table 1 (Chart 1).[3] In the case of **6**, no reaction occurred, probably due to too large steric hindrance of the diphenyl group in the α-position of the hydroxyl group. With chiral cyclopentenyl acetate (−)-**2** in hand, the regio- and stereoselective introduction of *tert*-butylamine to it by a double inversion reaction using palladium catalyst[4] was investigated (Chart 2). For convenience, we first attempted the reaction with racemic cyclopentenyl acetate **1** which was prepared by acetylation of **6**: a mixture of compound **1** (1 mol), tetrakis triphenylphosphine palladium (0.05 mol), *tert*-butylamine (1 mol) and triethylamine (1 mol) in tetrahydrofuran (THF) was stirred at room temperature overnight under nitrogen atmosphere to afford cyclopentadiene **8**[5] in 68% yield and no desired product was detected by ^{1}H-NMR measurement. Elimination probably occurred *via* σ-allylpalladium equilibrated with π-allylpalladium through the action of the amine as base. This idea was partly supported by the result that in the case of a neutral nucleophile (azide),[6] regioselec-

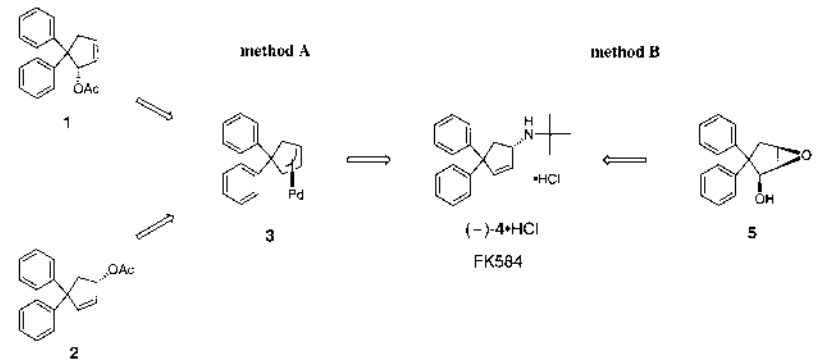

Fig. 1

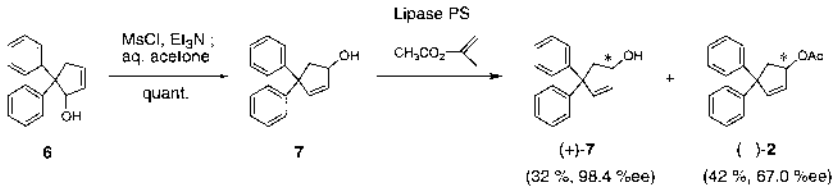

Chart 1

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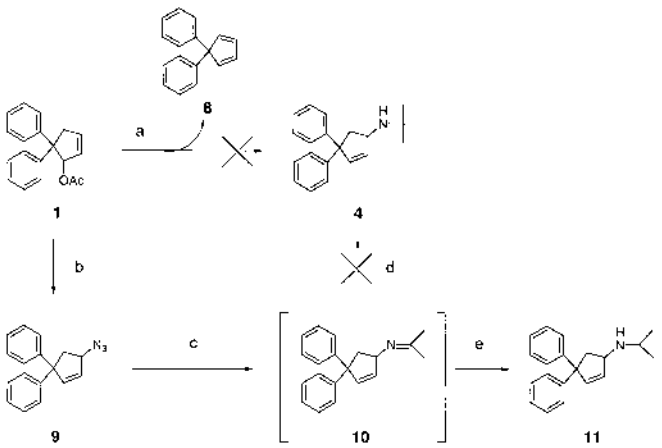
Table 1. Kinetic Resolution of Cyclopentenol **7**

Run	Reaction condition	**7**			**2**		
		Yield (%)	$[\alpha]_D$	+/−[a)]	Yield (%)	$[\alpha]_D$	+/−[b)]
1	40 °C, 41 h	60	+57.8 (c=2.18, MeOH)	75.1/24.9	37	−86.3 (c=1.50, MeOH)	8.8/91.2
2	40 °C, 110 h	32	+113.4 (c=0.63, MeOH)	99.2/0.8	42	−72.9 (c=0.98, MeOH)	16.5/83.5

a, *b*) The enantiomer ratio of compounds **7** and **2** was determined by HPLC analysis as described in the Experimental section.



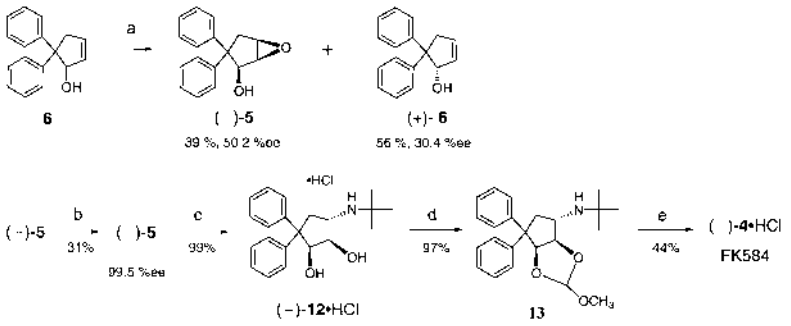
(a) $Pd(PPh_3)_4$ (cat.), *tert*-$BuNH_2$; (b) $Pd(PPh_3)_4$ (cat.), NaN_3, aq. THF; (c) Ph_3P, acetone; (d) CH_3MgI or CH_3MgI, $BF_3{\cdot}OEt_2$; (e) $NaBH_4$

Chart 2

tive substitution occurred to afford an azide derivative **9** in 79% yield. The hindered nature of the diphenyl group is probably responsible for this selectivity. Since ^{14}C-methyl magnesium iodide is also available, we pursued an alternate route to **4** from **9**: reaction of methyl magnesium iodide and an imine **10** which was prepared by Staudinger reaction of the azide **9** with triphenylphosphine and acetone. The imine **10** was identified as amine **11** by reducing it with sodium borohydride. Contrary to our expectations, *in situ* treatment of the imine **10** with methyl magnesium iodide in the absence or presence of Lewis acid (boron trifluoride etherate)[7] afforded a complex mixture and no desired product was obtained.

This result led us to pursue method B starting with an asymmetric epoxidation of cyclopentenol **6** by Sharpless oxidation[8] (Chart 3). A mixture of cyclopentenol **6** (1 mol), dimethyl D-(−)-tartrate (0.2 mol), *tert*-butylhydroperoxide (0.50 mol), titanium(IV) isopropoxide (0.15 mol) and 4-Å molecular sieves (MS4A) was stirred at −10 °C for 2 d to afford (−)-**5**[9] and (+)-**6** in 39.2% and 56.4% yield, respectively.[10] The enantiomeric excess of these compounds was determined to be 50.2% for (−)-**5** and 30.4% for (+)-**6** by HPLC analysis; fortunately, purification of (−)-**5** was accomplished by removing the more crystallizable racemate from ethyl acetate (EtOAc). According to the empirical rule,[11] the absolute configuration of (−)-5,5-diphenyl-2,3-epoxycyclopentan-1-ol ((−)-**5**) was believed to be 1*R*, 2*R*, 3*S*. However, applying the proposed structure of the 'loaded' catalyst at the time of oxygen transfer in the Sharpless oxidation of an allylic alcohol, the absolute configuration of (−)-**5** was thought to be 1*S*, 2*S*, 3*R* (the antipode). The reason was that the restricted conformation of the substrate and contact between the large diphenyl group adjacent to the hydroxyl of the substrate and the ligand ester group of the active epoxidation catalyst seriously impede the necessary approach of alkene of (1*S*)-**6** to the oxidant as shown in Fig. 2 (in the path which would yield 1*R*, 2*R*, 3*S* according to the empirical rule). The absolute configuration of (−)-**5** was not determined at this point and conversion of (−)-**5** to the objective compound **4** proceeded. Reaction of (−)-**5** (99.5% ee) with *tert*-butylamine in the presence of titanium(IV) isopropoxide,[12] followed by treatment with 3 N hydrochloric acid afforded cyclopentenylamine hydrochloride (−)-**12**·HCl (>99.4% ee) in 99% yield. The C-3 opened product was the only isomer detected by ^{1}H-NMR analysis and a stereoelectronic effect through an intramolecular coordination of a cyclopentanoyltitanium to the epoxide oxygen atom was probably responsible for the regio- and stereoselectivity. Conversion of (−)-**12**·HCl to **4** was carried out by the following procedure: 1) treatment of (−)-**12**·HCl with methyl orthoformate in the presence of catalytic amount of *p*-toluenesulfonic acid (TsOH) to afford orthoester **13** as a 10 : 1 diastereomer mixture[13] (97% yield); 2) refluxing of a mixture of **13**, acetic acid and a catalytic amount of acetic anhydride in xylene,[14] followed by salt formation with hydrogen chloride to afford (−)-**4**·HCl (>99.8% ee) in 44% isolated yield. Synthetic **4**·HCl showed all spectroscopic data to be in accord with the reported values,[1] including the sign of the optical rotation; this means that asymmetric synthesis of FK584 ((−)-**4**·HCl) was completed in a 3-step approach starting with (−)-**5** which was obtained by Sharpless oxidation of cyclopentenol **6** with dimethyl D-(−)-tartrate, *tert*-butylhydroperoxide, titanium(IV) isopropoxide and MS4A.

The absolute configuration of FK584 was determined to be *S* by X-ray crystallographic analysis of the salt of (*S*)-(+)-mandelic acid as shown in Fig. 3. Based on this result and the fact that regio- and stereoselective conversion of (−)-**5** to the (*S*)-(−)-**4**·HCl was attained, the absolute configuration of (−)-**5** was confirmed to be 1*S*, 2*S*, 3*R*. The proposed structure of 'loaded' catalyst at the time of oxygen transfer state of allylic alcohol was confirmed to work well in this conformationally restricted cyclopentenol case and to afford moderate optical purity. However, the reaction time of the epoxidation was much longer than that of the usual allylic alcohol, probably due to the poor fit to the requirements of the active epoxidation catalyst as in the case of allylic alcohols having *cis*-3-substituents. According to method B, (*S*)-*N*-{2-methyl-[2-^{14}C]-propyl}-4,4-diphenyl-2-cyclopentenylamine hydrochloride (^{14}C-FK584, 303 MBq/mmol) was synthesized from (−)-**5** and 2-methyl-[2-^{14}C]-propylamine, and pharma-



(a) $(CH(OH)CO_2CH_3)_2$ (0.2 eq.), MS 4A, $Ti(O\text{-}iso\text{-}Pr)_4$ (0.15 eq.), *tert*-BuOOH (0.5 eq.); (b) Recrystallization; (c) $Ti(O\text{-}iso\text{-}Pr)_4$, *tert*-$BuNH_2$; 3N HCl; (d) $CH(OCH_3)_3$, $TsOH•H_2O$ (cat.); (e) $(CH_3CO)_2O$, CH_3CO_2H; HCl

Chart 3

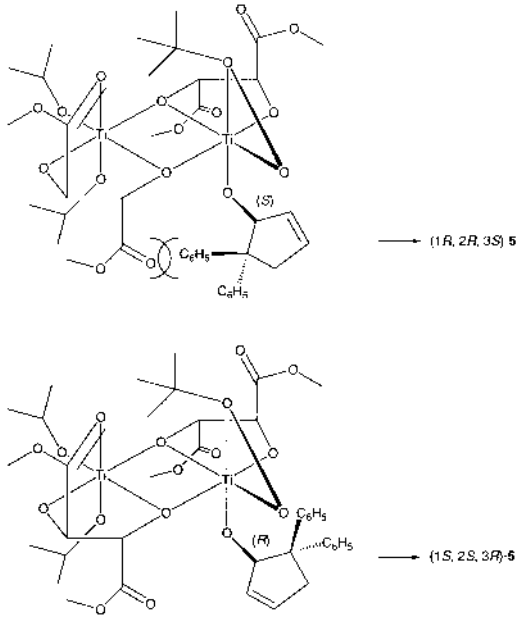


Fig. 2

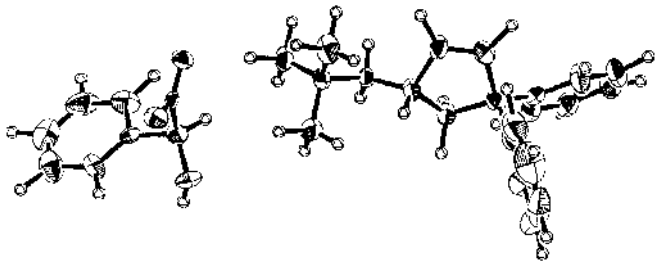


Fig. 3. ORTEP Drawing of the Crystal Structure of (−)-**4**·(*S*)-(+)-Manderate Determined by X-Ray Crystallographic Analysis

cokinetic studies are currently ongoing.

In conclusion, (1*S*,2*S*,3*R*)-(−)-5,5-diphenyl-2,3-epoxycyclopentan-1-ol ((−)-**5**) was synthesized by Sharpless oxidation of cyclopentenol **6** (kinetic resolution) in a rare case in which the empirical rule did not work. Regio- and stereoselective introduction of *tert*-butylamine to the obtained (−)-**5** and subsequent conversion of the resulting diol to an olefin afforded FK584. The absolute configuration of FK584 was determined to be *S* by X-ray crystallographic analysis of the salt of (*S*)-(+)-mandelic acid.

Experimental

All melting points were determined in open glass capillaries on a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi R-90H or a Bruker AC-200P NMR spectrometer with tetramethylsilane as an internal standard (δ value, ppm). Mass (MS) spectra were recorded on a JEOL JMS D-300 MS spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400CHN elemental analyzer.

(Method A) 4,4-Diphenyl-2-cyclopenten-1-ol (7) Methanesulfonyl chloride (MsCl) (0.79 ml, 10.2 mmol) and triethylamine (1.42 ml, 10.2 mmol) were successively added to a solution of **6** (2.00 g, 8.46 mmol) in acetone (20 ml) below −5 °C and the whole was stirred for 0.5 h. The mixture was poured into ice water (20 ml) and the mixture was stirred for 15 min. Brine and EtOAc were added to the mixture and the organic layer was separated, washed with brine, dried over sodium sulfate (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of *n*-hexane and EtOAc (5 : 1) to afford **7** (2.00 g, 100%) as an oil. The physical data of this compound was identical to those of **7** reported in the preceding paper.[1)]

(−)-4,4-Diphenyl-2-cyclopentenyl Acetate [(−)-2] A mixture of **7** (0.30 g, 1.27 mmol) and lipase PS (Amano, 0.70 g) in isopropenyl acetate (2.20 ml) was stirred at 40 °C for 41 h; then the lipase was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of *n*-hexane and EtOAc (20 : 1) to afford (+)-**7** (0.18 g, 60%) and (−)-**2** (0.13 g, 37%) as oils, respectively. (+)-**7**: $[\alpha]_D^{24}$ +57.9° (c=2.18, MeOH). IR (neat): 3350 cm^{-1}. NMR ($CDCl_3$, 200 MHz): δ 1.61 (1H, s), 2.40 (1H, dd, J=4.7, 13.8 Hz), 3.00 (1H, dd, J=6.9, 13.8 Hz), 4.90—5.10 (1H, br s), 5.97 (1H, dd, J=2.0, 5.6 Hz), 6.38 (1H, dd, J=1.1, 5.6 Hz), 7.10—7.42 (10H, m). MS *m/z*: 236 (M^+). The enantiomeric excess of this compound was determined to be 50.2% by HPLC analysis (column, CHIRALCEL-OD (Daicel) 4.6× 250 mm; eluent, 20 : 1 *n*-hexane–EtOH mixture; flow rate, 1.0 ml/min; detector, 220 nm; t_R of (+)-**7**, 10.6 min; t_R of (−)-**7**, 16.0 min). (−)-**2**: $[\alpha]_D^{24}$ −86.3° (c=1.50, MeOH). IR (neat): 1730 cm^{-1}. NMR ($CDCl_3$, 200 MHz): δ 2.03 (3H, s), 2.47 (1H, dd, J=5.0, 14.2 Hz), 3.12 (1H, dd, J=7.2, 14.2 Hz), 5.80—5.92 (1H, m), 5.95 (1H, dd, J=2.0, 5.5 Hz), 6.44 (1H, dd, J=1.2, 5.5 Hz), 7.10—7.38 (10H, m). MS *m/z*: 278 (M^+). The enantiomeric excess of this compound was determined to be 82.4% by HPLC analysis (column, CHIRALCEL-OD (Daicel) 4.6×250 mm; eluent, 100 : 1 *n*-hexane–EtOH mixture; flow rate, 1.0 ml/min; detector, 220 nm; t_R of (−)-**2**, 6.9 min; t_R of (+)-**2**, 8.1 min).

5,5-Diphenyl-2-cyclopentenyl Acetate (1) Acetic anhydride (0.84 ml, 8.90 mmol) and a catalytic amount of 4-dimethylaminopyridine were added to a solution of **6** (0.70 g, 2.96 mmol) in pyridine (5 ml) at room temperature. Stirring was continued for 30 min, then the pH of the reaction mixture was adjusted to 1.0 with dilute HCl and extracted with EtOAc. The extract was washed with brine, dried over magnesium sulfate ($MgSO_4$), and evaporated *in vacuo* to afford **1** (0.82 g, 100%) as an oil. IR (neat): 1720 cm^{-1}. NMR ($CDCl_3$, 200 MHz): δ 1.68 (3H, s), 2.80—3.00 (1H, m), 3.48—3.70 (1H, m), 6.00—6.10 (1H, m), 6.14—6.26 (1H, m), 6.49 (1H, s), 7.10—7.35 (10H, m). MS *m/z*: 278 (M^+).

4,4-Diphenyl-2-cyclopentenyl Azide (9) A mixture of **1** (216 mg, 0.78 mmol), sodium azide (84 mg, 1.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (62 mg, 0.05 mmol) in a mixture of THF (3 ml) and water (1.5 ml) was stirred at room temperature for 14.5 h under an argon at-

mosphere. EtOAc was added to the solution and the organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of *n*-hexane and EtOAc (100 : 1) to afford **9** (0.16 g, 78%) as an oil. IR (neat): 2100 cm^{-1}. NMR ($CDCl_3$, 90 MHz): δ 2.45 (1H, dd, J=6, 14 Hz), 3.05 (1H, dd, J=14, 8 Hz), 4.42—4.70 (1H, m), 5.90 (1H, dd, J=2, 6 Hz), 6.42 (1H, dd, J=1, 6 Hz), 6.95—7.30 (10H, m). MS *m/z*: 261 (M^+), 232, 219.

***N*-Isopropyl-4,4-diphenyl-2-cyclopentenylamine Methanesulfonate (11·MsOH)** Triphenylphosphine (330 mg, 1.26 mmol) was added to a solution of **9** (300 mg, 1.15 mmol) in acetone (3 ml) at room temperature and the whole was refluxed for 21 h. After cooling, the solvent was removed by evaporation and the residue was dissolved in MeOH (3 ml). Sodium borohydride (220 mg, 5.81 mmol) was added to the solution and the whole was stirred for 20 min. Brine and EtOAc were then added to the mixture and the organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel with a mixture of chloroform ($CHCl_3$) and methanol (MeOH) (50 : 1) to afford **11** (0.26 g) as an oil. MsOH (92 mg, 0.95 mmol) in MeOH was added to a solution of the free amine **11** obtained in the above manner (0.26 g) in $CHCl_3$ and the solution was evaporated *in vacuo*. The residue was triturated with a mixture of diethyl ether and EtOAc to afford **11**·MsOH (260 mg, 61%), mp 148—150 °C. *Anal*. Calcd for $C_{21}H_{27}NSO_3 \cdot 0.4H_2O$: C, 66.25; H, 7.35; N, 3.67. Found : C, 66.35; H, 7.26; N, 3.57. IR (nujol): 2700, 2510, 2470, 1610, 1490 cm^{-1}. NMR ($CDCl_3$, 200 MHz): δ 1.38 (3H, d, J=6.2 Hz), 1.39 (3H, d, J=6.2 Hz), 2.52 (3H, s), 2.64 (1H, dd, J=8.7, 13.0 Hz), 3.19 (1H, dd, J=6.7, 13.0 Hz), 3.20—3.50 (1H, m), 4.35 (1H, br s), 6.12 (1H, d, J=5.7 Hz), 6.42 (1H, d, J=5.7 Hz), 7.10—7.40 (10H, m), 8.75 (2H, br s).

(Method B) (1*S*,2*S*,3*R*)-(−)-5,5-Diphenyl-2,3-epoxycyclopentan-1-ol ((−)-5) Titanium(IV) isopropoxide (22.70 ml, 76.3 mmol) was added to a suspension of **6** (120.09 g, 508 mmol), dimethyl D-(−)-tartrate (18.10 g, 102 mmol) and molecular sieves 4A (activated powder, 24.00 g) in CH_2Cl_2 (1200 ml) at −10—−9 °C under nitrogen atmosphere. Stirring was continued for 2 h, then *tert*-butyl hydroperoxide (3.0 M solution in 2,2,4-trimethylpentane, 85.00 ml) was added to the suspension and the whole was stirred at −10 °C for 2 d. The mixture was poured into 0.4 N HCl (1550 ml) and the resulting emulsion was filtered through a celite pad. The organic layer was separated and the aqueous layer was extracted with dichloromethane (CH_2Cl_2). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of CH_2Cl_2 and EtOAc (1 : 0 to 0 : 1) to afford (+)-**6** (67.73 g), $[\alpha]_D^{21.2}$ +100.8° (c=1.19, MeOH) and (−)-**5** (50.20 g), $[\alpha]_D^{22.4}$ −150.5° (c=0.63, CH_2Cl_2).

The crude product (−)-**5** was purified as follows: The crude product (50.03 g) was recrystallized from EtOAc (150 ml) to afford its racemate (16.46 g, mp 140—141 °C, $[\alpha]_D^{18}$ −4.2° (c=0.61, CH_2Cl_2). *Anal*. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found : C, 80.74; H, 6.36. IR (nujol): 3400, 1100 cm^{-1}. NMR ($CDCl_3$, 200 MHz): δ 1.62 (1H, d, J=12.2 Hz), 2.41 (1H, d, J=15.2 Hz), 3.46 (1H, d, J=15.2 Hz), 3.65 (2H, s), 4.96 (1H, d, J=12.2 Hz), 7.04—7.36 (10H, m)). The filtrate was evaporated *in vacuo* and the residue was recrystallized from EtOAc (50 ml) to afford racemate (1.42 g, $[\alpha]_D^{16}$ −5.7° (c=0.53, CH_2Cl_2)). The filtrate was evaporated *in vacuo* and the residue was stirred in a mixture of *n*-hexane (100 ml) and petroleum ether (20 ml). The resulting precipitates were collected by filtration to afford (−)-**5** (25.67 g, $[\alpha]_D^{16}$ −298.6° (c=0.52, CH_2Cl_2)). This compound was recrystallized from EtOAc (25 ml) to afford pure (−)-**5** (15.51 g, 12%), mp 97—98 °C. $[\alpha]_D^{18}$ −300.2° (c=0.48, CH_2Cl_2). *Anal*. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found : C, 80.94; H, 6.48. IR (nujol): 3420 cm^{-1}. NMR ($CDCl_3$, 200 MHz): δ 1.61 (1H, d, J=12.3 Hz), 2.42 (1H, dd, J=15.2, 1.3 Hz), 3.47 (1H, d, J=15.2 Hz), 3.61—3.70 (2H, m), 4.97 (1H, dd, J=12.3, 1.3 Hz), 7.05—7.40 (10H, m). The enantiomeric excess of this compound was determined to be 99.5% by HPLC analysis (column, SUMIPAX OA-4500 (Sumitomo) 4.6×250 mm; eluent, 25 : 1 *n*-hexane–EtOH mixture; flow rate, 1.0 ml/min; detector, 220 nm; t_R of (−) isomer, 8.9 min; t_R of (+) isomer, 9.9 min). The enantiomeric excess of the compound (+)-**6** was determined to be 30.4% by HPLC analysis (column, CHIRALCEL-OD (Daicel) 4.6×250 mm; eluent, 50 : 1 *n*-hexane–EtOH mixture; flow rate, 1.0 ml/min; detector, 220 nm; t_R of (−) isomer, 10.1 min; t_R of (+) isomer, 12.5 min).

(1*S*,2*R*,3*S*)-(−)-3-*tert*-Butylamino-5,5-diphenylcyclopentane-1,2-diol Hydrochloride [(−)-12·HCl] Titanium(IV) isopropoxide (2.15 ml, 7.22 mmol) was added to a solution of (−)-**5** (1.40 g, 5.55 mmol) in a mixture of CH_2Cl_2 (14 ml) and isopropyl alcohol (5.6 ml) with ice bath cooling. Stirring was continued for 30 min, then *tert*-butylamine (0.70 ml, 6.66 mmol) was added to the solution and the whole was stirred at room temperature overnight. The solution was evaporated *in vacuo* and the residue was dissolved in diethyl ether. 3 N HCl was added to the solution in an ice bath and the whole was stirred for 3 h. The resulting precipitates were collected by filtration, washed with diethyl ether and dried to afford (−)-**12**·HCl (1.98 g, 99%), mp 279—281°C (dec.). *Anal*. Calcd for $C_{21}H_{27}NO_2 \cdot HCl \cdot H_2O$: C, 66.39; H, 7.96; N, 3.69. Found : C, 66.27; H, 8.21; N, 3.60. $[\alpha]_D^{22}$ −70.5° (c=0.37, MeOH). IR (nujol): 3520, 3320 cm^{-1}. NMR (DMSO-d_6, 200 MHz): δ 1.36 (9H, s), 2.63 (1H, dd, J=14.0, 7.7 Hz), 3.12 (1H, dd, J=14.0, 9.9 Hz), 3.48—3.72 (1H, br s), 4.09—4.26 (1H, m), 4.68—4.84 (1H, m), 5.15 (1H, d, J=5.8 Hz), 5.23 (1H, d, J=4.9 Hz), 7.00—7.50 (10H, m), 8.60—8.78 (1H, m), 9.00—9.18 (1H, m). The enantiomeric excess of the compound (−)-**12**·HCl was determined to be >99.4% by HPLC analysis (column, CHIRALCEL-OD (Daicel) 4.6×250 mm; eluent, 9 : 1 *n*-hexane–EtOH mixture; flow rate, 1.0 ml/min; detector, 220 nm; t_R of (+) isomer, 6.5 min; t_R of (−) isomer, 8.0 min).

(*S*)-(−)-*N*-*tert*-Butyl-4,4-diphenyl-2-cyclopentenylamine Hydrochloride ((−)-4·HCl, FK584) Trimethyl orthoformate (2.80 ml, 25.6 mmol) was added to a suspension of (−)-**12** (1.85 g, 5.11 mmol) and TsOH monohydrate (0.10 g, 0.51 mmol) in CH_2Cl_2 (18.5 ml) and the whole was stirred at room temperature for 2 h. Then, the mixture was evaporated *in vacuo* and 1 N NaOH solution (18.5 ml) and EtOAc were added to the residue. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (50 : 1) to afford **13** (1.83 g, 97%) as an oil. IR (neat): 3350, 1735, 1600, 1580, 1490, 1445, 1365 cm^{-1}. NMR ($CDCl_3$, 200 MHz) for a major diastereomer A: δ 1.01 (9H, s), 2.12 (1H, dd, J=5.1, 13.2 Hz), 3.13 (1H, dd, J=7.5, 13.2 Hz), 3.25 (3H, s), 3.35—3.51 (1H, m), 4.67 (1H, d, J=6.0 Hz), 5.41 (1H, s), 5.58 (1H, d, J=6.0 Hz), 7.06—7.36 (10H, m). NMR ($CDCl_3$, 200 MHz) for a minor diastereomer B: δ 0.92 (9H, s), 2.12 (1H, dd, J=5.1, 13.2 Hz), 3.13 (1H, dd, J=7.5, 13.2 Hz), 3.15 (3H, s), 3.35—3.51 (1H, m), 4.76 (1H, d, J=5.5 Hz), 5.46 (1H, d, J=5.5 Hz), 5.70 (1H, s), 7.06—7.36 (10H, m). The ratio of the diastereomer A/B was 10/1. MS *m/z*: 367 (M^+), 352. To a solution of **13** (0.80 g, 2.18 mmol) in xylene (16 ml) was added acetic acid (0.69 ml, 12.05 mmol) and acetic anhydride (0.04 ml, 0.42 mmol) and the whole was refluxed for 3.5 h. After cooling, 1.5 N of NaOH solution (20 ml) and EtOAc were added to the solution. The organic layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and MeOH (30 : 1) to afford (−)-**4** (0.58 g) as an oil. A 4 N solution of HCl in EtOAc (0.55 ml) was added to a solution of (−)-**4** (0.58 g) in a mixture of isopropyl alcohol (1.2 ml) and EtOAc (5.8 ml) and the whole was stirred at 0 °C for 3.5 h. The resulting precipitates were collected by filtration and dried to afford (−)-**4**·HCl (0.32 g, 44%, >99.8% ee). The physical data of this compound was identical with those of FK584 reported in the preceding paper.[1)]

X-Ray Crystallography of (−)-4·(*S*)-(+)-Manderate A mixture of (−)-**4** (1.00 g, 3.43 mmol) and (*S*)-(+)-manderic acid (522 mg, 3.43 mmol) in isopropyl alcohol (20 ml) was refluxed and the obtained solution was cooled to room temperature overnight. The resulting precipitates were collected by filtration and dried to give (−)-**4**·(*S*)-(+)-manderate (1.40 g, 92%) as crystals, mp 151—155 °C (recrystallized from ethanol). $[\alpha]_D^{20}$ −102.0° (c=1.03, MeOH). *Anal*. Calcd for $C_{29}H_{33}O_3N$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.56; H, 7.69; N, 3.12. IR (nujol): 3090, 2800—2300, 1615, 1575 cm^{-1}. NMR (DMSO-d_6, 200 MHz): δ 1.24 (9H, s), 2.31 (1H, dd, J=7.9, 13.4 Hz), 3.22 (1H, dd, J=7.1, 13.4 Hz), 4.27 (1H, br t, J=7.4 Hz), 4.60 (1H, s), 5.94 (1H, br d, J=5.7 Hz), 6.58 (1H, dd, J=5.7, 1.9 Hz), 7.15—7.40 (15H, m). Crystal data of (−)-**4**·(*S*)-(+)-manderate were as follows: $C_{29}H_{33}O_3N$, monoclinic, $P2_1$ (#4), a=8.328 (2) Å, b=10.306 (1) Å, c=14.568 (1) Å, β=98.91 (1)°, V=1235.2 (3) Å^3, Z=2, D_{calcd}=1.193 g/cm^3, $F_{(000)}$=476.00, μ (Mo$K\alpha$)=5.68 cm^{-1}. Intensities were collected on a Rigaku AFC5R diffractometer with graphite monochromated Cu$K\alpha$ radiation (λ=1.54178 Å), and 2185 unique reflections with $I_0 \geqq 3\sigma_I$ were obtained using the $\omega-2\theta$ scanning method within $6° \leqq 2\theta \leqq 130°$. The structure was solved using MULTAN 84 based on direct methods, and refined. The final R value was 0.058. An ORTEP drawing of (−)-**4**·(*S*)-(+)-manderate is shown in Fig. 3.

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References and Notes

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2) This compound was obtained by reducing 4,4-diphenyl-2-cyclopenten-1-one with diisopropyl aluminum hydride as reported[1)] or, more conveniently, from **6** by treatment with MsCl and triethylamine, followed by quenching with water in quantitative yield.
3) Lipase PS shows a preference for the (*R*)-configuration, so the absolute configuration of (+)-**7** and (−)-**2** was believed to be *S* and *R*, respectively, however, we have not determined these configurations. *a*) Kazlauskas R. J., Weissfloch A. N. E., Rappaport A. T., Cuccia L. A., *J. Org. Chem.*, **56**, 2656—2665 (1991); *b*) Cygler M., Grochulski P., Kazlauskas R. J., Schrag J. D., Bouthillier F., Rubin B., Serreqi A. N., Gupta A. K., *J. Am. Chem. Soc.*, **116**, 3180—3186 (1994).
4) The oxidative addition forming π-allylpalladium usually proceeds with inversion of the configuration, while the stereochemistry at the nucleophilic substitution of the π-allylpalladium is dependent upon the nature of the nucleophile. When dimethylamine was used as a nucleophile, it attacked the π-allyl ligand from the side opposite the palladium. *a*) For reviews, see: Frost C. G., Howarth J., Williams J. M. J., *Tetrahedron Asymmetry*, **3**, 1089—1122 (1992); Godleski S. A., "Comprehensive Organic Synthesis," ed. by Trost B. M., Fleming I., Pergamon Press, Oxford, 1991, Vol. 4, Chapter 3.3, pp. 585—661; Consiglio G., Waymouth R. M., *Chem. Rev.*, **89**, 257—276 (1989); *b*) Hayashi T., Konishi M., Kumada M., *J. Chem. Soc.*, *Chem. Commun.*, **1984**, 107—108 and references cited therein.
5) IR (neat): 3060, 3025, 2950 cm^{-1}. NMR ($CDCl_3$, 90 MHz): δ 6.36 (2H, br d, J=6 Hz), 6.80 (2H, br d, J=6 Hz), 7.20 (10H, s). MS *m*/*z*: 218 (M^+).
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8) Kinetic resolution of 2-cyclopenten-1-ol by Sharpless oxidation was described in reference 8*d* as unpublished results, however, no reaction conditions including the absolute configuration of the tartrate were available. *a*) Katsuki T., Sharpless K. B., *J. Am. Chem. Soc.*, **102**, 5974—5976 (1980); *b*) Rossiter B. E., "Asymmetric Synthesis," ed. by Morrison J. D., Academic Press, New York, 1985, Vol. 5, Chapter 7, pp. 193—246; *c*) Finn M. B., Sharpless K. B., "Asymmetric Synthesis," ed. by Morrison J. D., Academic Press, New York, 1985, Vol. 5., Chapter 8, pp. 247—308; *d*) Johnson R. A., Sharpless K. B., "Comprehensive Organic Synthesis," ed. by Trost B. M., Fleming I., Pergamon Press, Oxford, 1991, Vol. 7, Chapter 3.2, pp. 389—436.
9) Nuclear Overhauser effects were observed between hydrogens at the C-1, C-2, C-3, and C-4 positions by a NOESY experiment of (−)-**5**, so the relative configuration of the hydroxyl group and the epoxide is *cis*.
10) Opposite results ((+)-**5**, (−)-**6**) were obtained with dimethyl L-(+)-tartrate. (+)-**5**: 39%, 58.4% ee, $[\alpha]_D^{22}$ +175.8° (*c*=0.50, CH_2Cl_2). (−)-**6**: 59%, 38.0% ee, $[\alpha]_D^{22}$ +127.4° (*c*=0.52, MeOH).
11) The empirical rule in Sharpless oxidation is that the allylic alcohol with a C-1 substituent is drawn so that the olefinic carbons and the hydroxyl lie in the plane of the paper, and the carbinol carbon is at the lower right, D-(−)-tartrates mediate delivery of the oxygen atom from the top face, so one enantiomer having the C-1 substituent oriented away from the direction of oxygen delivery, *i.e.*, (1*S*)-**6** was thought to be oxidized much faster than the other enantiomer. The kinetic resolutions of 2-cyclohexen-1-ol and 2-cyclohepten-1-ol with 1 eq of titanium(IV) isopropoxide, 1.2 eq of diisopropyl L-(+)-tartrate and 0.6 eq of *tert*-butylhydroperoxide at −20 °C afforded (1*R*)-2-cyclohexen-1-ol and (1*R*)-2-cyclohepten-1-ol, respectively, in accord with the empirical rule. Martin V. S., Woodard S. S., Katsuki T., Yamada Y., Ikeda M., Sharpless K. B., *J. Am. Chem. Soc.*, **103**, 6237—6240 (1981).
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