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Optical Resolution and Determination of Absolute Configuration of (±)-2-[4-(2-Oxocyclopentylmethyl)phenyl]propionic Acids

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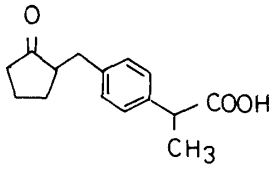
The title compound, which was newly synthesized, showed good anti-inflammatory and analgesic activities. Optical resolution was performed by the following procedures: 1) condensation of the acid with (−)-1-phenylethylamine followed by separation of diasteromeric amides; 2) reduction of the cyclopentanone moiety and then acylation with optically active acid; 3) separation of epimeric esters followed by saponification of esters; 4) oxidation of alcohols to ketones; 5) saponification of amides. The absolute configurations of the four optically active compounds thus obtained were confirmed by circular dichroism spectroscopy.

Keywords——anti-inflammatory agent; 2-arylpropionic acid derivative; optical resolution; absolute configuration; CD; ORD

(±)-2-[4-(2-Oxocyclopentylmethyl)phenyl]propionic acid (**1**)[1] is a newly synthesized 2-arylpropionic acid derivative having potent anti-inflammatory and analgesic activities.[2]

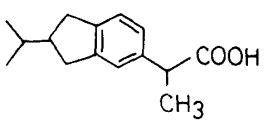


1

Chart 1

Among 2-arylpropionic acid derivatives having anti-inflammatory activity, differences of pharmacological activities between their enantiomers are often observed.[3] Thus, in order to investigate the pharmacological activities and metabolic pathway of **1**, it is very important to synthesize the four optically active compounds. In this paper, we describe the optical resolution and determination of the absolute configurations of the four enantiomers of **1**.

In the previous paper, we reported the optical resolution of 2-(2-isopropylindan-5-yl)propionic acid (**2**).[4] Using a similar method, we tried to synthesize 1-phenylethylamide



2

Chart 2

derivatives of **1** for optical resolution. Condensation of **1** with (−)-(1*S*)-1-phenylethylamine was carried out in the presence of triphenylphosphine and 2,2′-dipyridyl disulfide in dichloromethane at room temperature. High pressure liquid chromatography (HPLC) of the

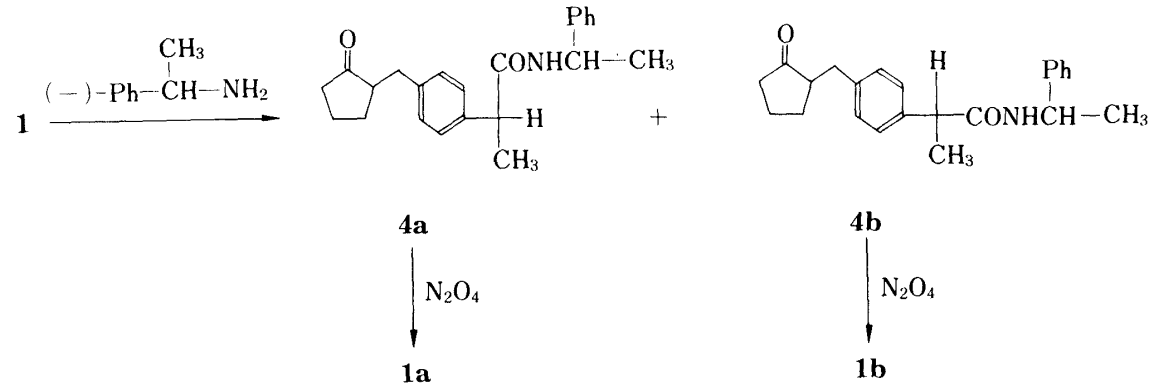


Chart 3

reaction products showed two peaks due to two kinds of amides. These were separated by preparative medium pressure liquid chromatography (MPLC) (Si-60 Lobar column) to afford (−)-*N*-[(1*S*)-1-phenylethyl]-(2*R*)-2-[4-(2-oxocyclopentylmethyl)phenyl]propionamide (**4a**) ($[\alpha]_D^{20}$ −61.4°, mp 122—124 °C) and (−)-*N*-[(1*S*)-1-phenylethyl]-(2*S*)-2-[4-(2-oxocyclopentylmethyl)phenyl]propionamide (**4b**) ($[\alpha]_D^{20}$ −27.9°, mp 100—102 °C) as crystals. The structures of the amides, **4a** and **4b**, were assigned on the basis of the following data and elemental analysis. The infrared (IR) spectra of both **4a** and **4b** showed an amide band at 1650 cm^{-1} and a carbonyl absorption at 1740 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of **4a** exhibited two methyl proton peaks at 1.34 (doublet) and 1.48 ppm (doublet), and two methine proton peaks at 3.50 (quartet) and 5.09 ppm (quintet). Compound **4b** had the corresponding methyl proton peaks at 1.39 and 1.48 ppm and methine proton peaks at 3.53 and 5.10 ppm. According to the literature,[5] the less polar (−)-(1*S*)-1-phenylethylamide of a 2-arylpropionic acid generally has *R*-configuration at the 2-position of propionic acid and the more polar amide has *S*-configuration. Consequently, the less polar amide **4a** may have *R*-configuration and the more polar **4b** may have *S*-configuration.

The amide bond cleavage of **4a** and **4b** was performed by diazotization with N_2O_4 followed by thermal decomposition to afford the corresponding acids **1a** ($[\alpha]_D^{20}$ −40.1°, mp 57—59 °C) and **1b** ($[\alpha]_D^{20}$ 40.3°, mp 57—59 °C).

Optical rotatory dispersion (ORD) and circular dichroism (CD) spectra of **1a** and **1b** are shown in Figs. 1 and 2. As observed in the ORD spectra, **1a** showed a negative Cotton effect

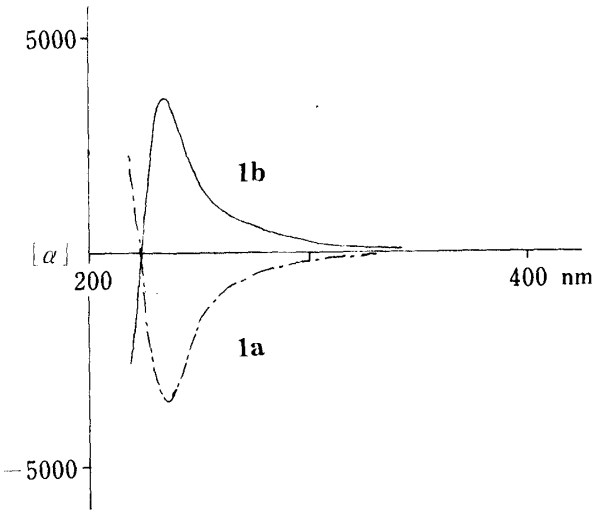


Fig. 1. ORD Spectra of **1a** and **1b**

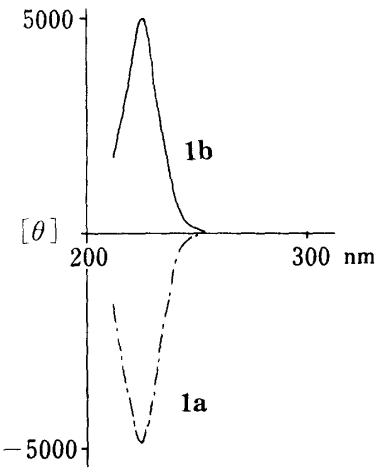
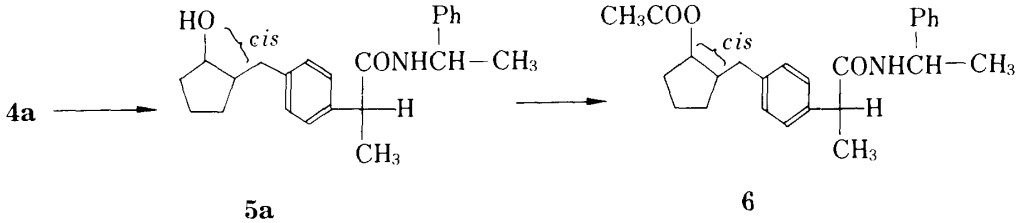


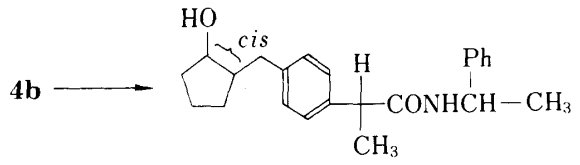
Fig. 2. CD Spectra of **1a** and **1b**

([α] (nm): −3400° (234))[6] and **1b** displayed a positive Cotton effect ([α] (nm): 3400° (234)). From these results, the configurations of the 2-position of the propionic acid moiety of **1a** and **1b** were confirmed to be *R* and *S*, respectively.

Due to the small chirality effect of the optically active 1-phenylethylamide moiety, many attempts to separate the enantiomers (2-position of cyclopentanone) were unsuccessful, including recycle chromatography by HPLC. Consequently, the amide **4a** was reduced with potassium tri-*sec*-butyl borohydride, which might give the *cis* conformational alcohol by reduction of the 2-substituted cyclopentanone,[7] to afford (−)-*N*-[(1*S*)-1-phenylethyl]-(2*R*)-2-[4-(*cis*-2-hydroxycyclopentylmethyl)phenyl]propionamide (**5a**) ($[\alpha]_D^{20}$ −61.4°, mp 110 °C). The evidence that the alcohol, **5a**, has *cis*-configuration will be discussed in the following paper.[8]



5a **6**



5b

Chart 4

Acetylation of **5a** with acetic anhydride in the presence of a catalytic amount of triethylamine gave (−)-*N*-[(1*S*)-1-phenylethyl]-(2*R*)-2-[4-(*cis*-2-acetoxycyclopentylmethyl)-phenyl]propionamide (**6**) as an oil. HPLC of **6** showed two peaks (1 : 1) after 6 cycles of chromatography. This fact suggested the existence of epimers due to *cis*-substituted cyclopentanol. Separation of these two peaks, however, was very difficult owing to their very close proximity.

In order to isolate these enantiomers, an optically active group, the (−)-(*S*)-α-methoxy-α-trifluoromethylphenylacetyl group, was introduced into the cyclopentanol moiety of **5a** instead of the acetyl group. Compound **5a** was treated with (−)-(*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl) in pyridine at 0 °C for 24 h to give the MTPA esters. The MTPA esters were analyzed by HPLC using a μPorasil column (1/4 in × 1 foot) (eluted with hexane–ethyl acetate (10 : 90) at a flow rate of 3 ml/min). HPLC showed two peaks (1 : 1) at retention times of 20 and 21 min. These two very close peaks were separated on a semi-prep μPorasil column (3/8 in × 1 foot) to afford (+)-*N*-[(1*S*)-1-phenylethyl]-(2*R*)-2-{4-[*cis*-(1*S*, 2*S*)-2-*O*-((α*S*)-α-methoxy-α-trifluoromethylphenylacetyl)cyclopentylmethyl]-phenyl}propionamide (**7a**) ($[\alpha]_D^{20}$ 46.3°, mp 97—98 °C) and (−)-*N*-[(1*S*)-1-phenylethyl]-(2*R*)-2-{4-[*cis*-(1*R*, 2*R*)-2-*O*-((α*S*)-α-methoxy-α-trifluoromethylphenylacetyl)cyclopentylmethyl]phenyl}propionamide (**7b**) ($[\alpha]_D^{20}$ −81.9°, mp 85—88 °C) as crystals. Compounds **7a** and **7b** displayed new methoxy signals at 3.60 and 3.55 ppm, respectively, in the NMR.

The other amide **4b** was treated in the same way as **4a** to produce a mixture of two compounds (**7c** and **7d**) *via* **5b**. HPLC of the reaction mixture showed two very close peaks due to (+)-*N*-[(1*S*)-1-phenylethyl]-(2*S*)-2-{4-[*cis*-(1*S*, 2*S*)-2-*O*-((α*S*)-α-methoxy-α-tri-

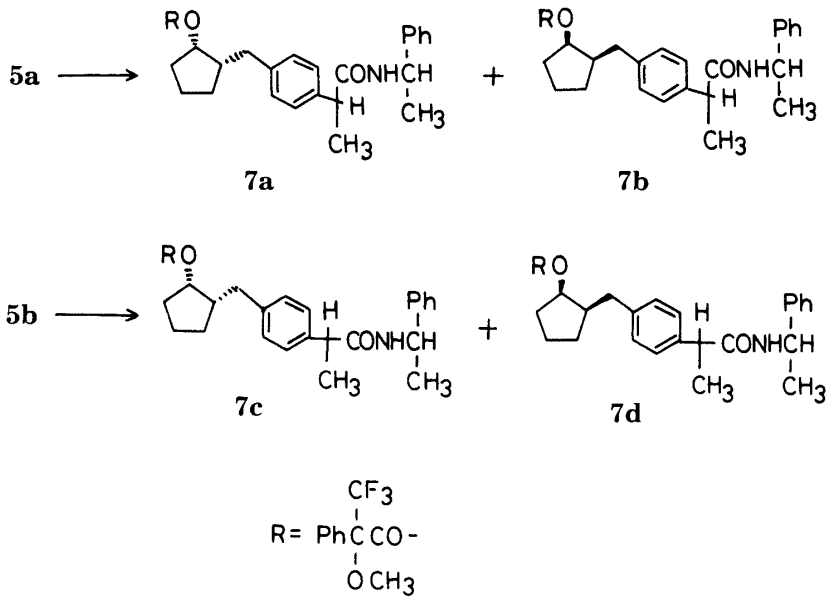


Chart 5

fluoromethylphenylacetyl)cyclopentylmethyl]phenyl}propionamide (**7c**) ($[\alpha]_D^{20}$ 36.8°, mp 99—102 °C) and (−)-*N*-[(1*S*)-phenylethyl]-(2*S*)-2-{4-[*cis*-(1*R*, 2*R*)-2-*O*-((α*S*)-α-methoxy-α-trifluoromethylphenylacetyl)cyclopentylmethyl]phenyl}propionamide (**7d**) ($[\alpha]_D^{20}$ −18.3°, mp 78—81 °C), and these products were separated by preparative HPLC. The NMR spectra of **7c** and **7d** showed the methoxy peaks at 3.60 and 3.50 ppm, respectively, each as a singlet.

Thus the desired four optically active *cis* isomers having protective groups (**7a**, **7b**, **7c** and **7d**) were obtained. After removal of the acyl group, oxidation of the hydroxy group and saponification of the amide group, the corresponding optically active acids (**1**) were obtained.

Hydrolysis of **7a** with two equivalents of sodium hydroxide in methanol yielded two alcohols, (−)-*N*-[(1*S*)-1-phenylethyl]-(2*R*)-2-[4-(*cis*-(1*S*, 2*S*)-2-hydroxycyclopentylmethyl)-phenyl]propionamide (**5c**) and (−)-*N*-[(1*S*)-1-phenylethyl]-(2*S*)-2-[4-(*cis*-(1*S*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionamide (**5e**), which were separated by preparative HPLC. This result suggested that the C-2 position of propionic acid underwent racemization during the saponification under the conditions employed. Likewise, hydrolysis of **7b**, **7c** and **7d** gave two alcohols (**5d** and **5f**, **5c** and **5e**, and **5d** and **5f**, respectively) under the same reaction conditions. The relationships between the esters (**7**) and alcohols (**5**) are shown in Chart 6, and the physical properties of these alcohols are shown in Table I.

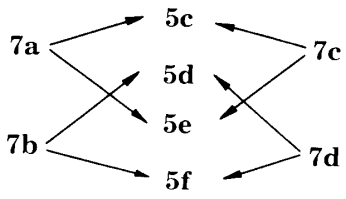


Chart 6

Jones oxidation of **5c**, **5d**, **5e** and **5f** gave the ketones (**4c**, **4d**, **4e** and **4f**, respectively), whose physical properties are shown in Table II. The four optically pure ketones (**4c**, **4d**, **4e**

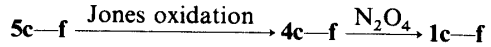
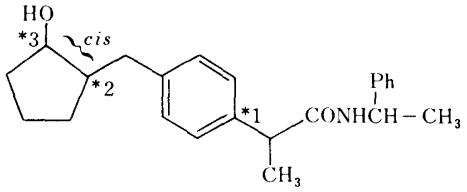


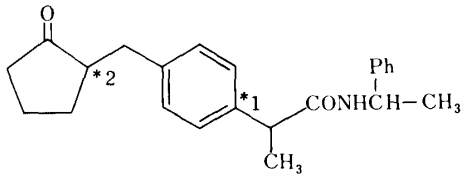
Chart 7

TABLE I. Physicochemical Properties of **5a—f**



Compd.	Configuration			mp (°C)	$[\alpha]_D^{20}$ (*c*, ethanol)
	*3	*2	*1		
5a	*RS*	*RS*	*R*	135—138	−67° (0.75)
5b	*RS*	*RS*	*S*	110—115	−25° (0.71)
5c	*S*	*S*	*R*	142—143	−68° (0.58)
5d	*R*	*R*	*R*	160—162	−65.5° (0.60)
5e	*S*	*S*	*S*	116—118	−22.5° (0.61)
5f	*R*	*R*	*S*	121—123	−28.5° (0.60)

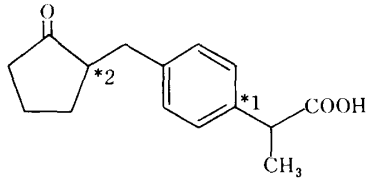
TABLE II. Physicochemical Properties of **4a—f**



Compd.	Configuration		Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (*c*, ethanol)
	*2	*1			
4a	*SR*	*R*	43[a]	122—124	−61.4° (0.16)
4b	*SR*	*S*	40[a]	100—102	−27.9° (0.12)
4c	*S*	*R*	48[b]	113—114	−163° (0.65)
4d	*R*	*R*	51[b]	138—139	29.8° (0.87)
4e	*S*	*S*	49[b]	110—111	−119° (0.61)
4f	*R*	*S*	45[b]	114—115	62° (0.81)

a) Yield from **1**. *b*) Yield from **5**.

TABLE III. Physicochemical Properties of **1a—f**



Compd.	Configuration		Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (*c*, ethanol)
	*2	*1			
1a	*RS*	*R*	50	57—59	−40.1° (0.55)
1b	*RS*	*S*	58	57—59	40.3° (0.55)
1c	*S*	*R*	60	61—62	−155° (0.16)
1d	*R*	*R*	53	64—65	95.5° (0.14)
1e	*S*	*S*	50	64—65	−91.3° (0.14)
1f	*R*	*S*	54	61—62	161° (0.15)

and **4f**) thus obtained were treated with N_2O_4 under the same reaction conditions as employed for **4a** to produce the parent acids (**1c**, **1d**, **1e** and **1f**, respectively). The physical properties of these acids are shown in Table III; the absolute values of $[\alpha]_D$ of each pair (**1c** and **1f**, **1d** and **1e**) did not agree exactly, and this was ascribed to partial racemization in the solution. Accordingly, we investigated the tendency to racemization of **1c**—**f**. The $[\alpha]_D$ values changed to about $-40°$ for **1c** and **1d**, and to about $+40°$ for **1e** and **1f** immediately after addition of a trace of acid or base to the methanol solution of **1c**, **1d**, **1e** and **1f**. These facts suggested that the C-2 position of cyclopentanone racemized easily.

For the determination of the purity of the optically active compounds, **1d** was again led to **7d** *via* **4d** and **5d** by the same separation procedure as mentioned above. The NMR and HPLC spectra of the product (**7d**) derived from **1d** were superimposable on those of the compound prepared from **1**. Other acids (**1c**, **1e** and **1f**) were also treated as mentioned above to give almost pure products (**7c**, **7e** and **7f**). These results suggested that **1c**—**f** were almost optically pure compounds.

The enantiomeric relationships between **1c** and **1f**, and between **1d** and **1e** were made clear by the ORD spectra shown in Fig. 3. Furthermore, determination of the absolute configurations of these compounds was done from the CD spectra as shown in Fig. 4.

The absolute configurations of the 2-position of propionic acid (*1 in Table III) and the

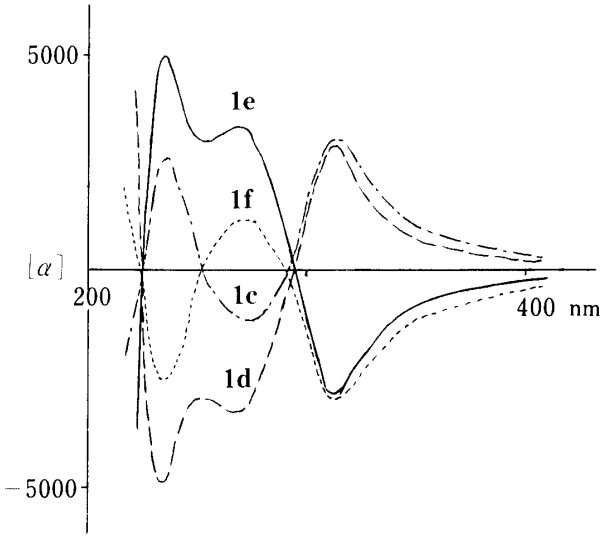


Fig. 3. ORD Spectra of **1c**—**f**

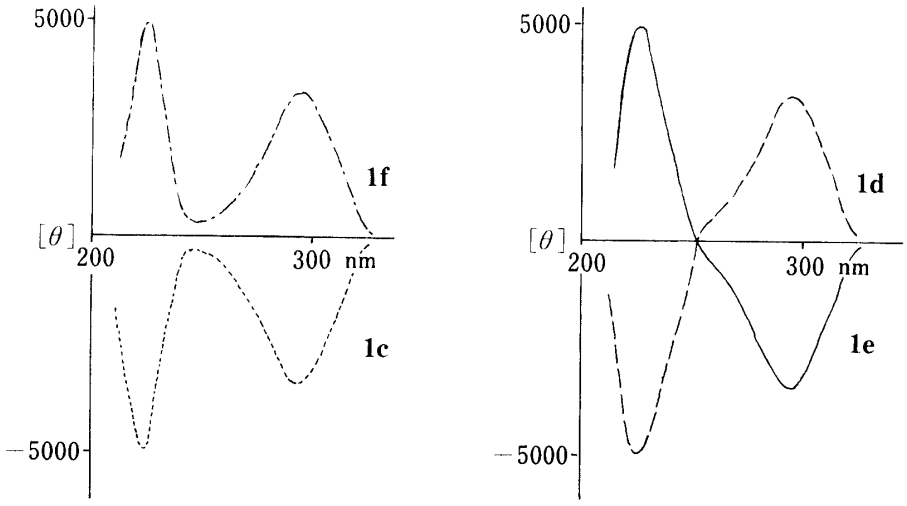


Fig. 4. CD Spectra of **1c**—**f**

2-position of cyclopentanone (*2 in Table III) in **1c** were determined to be *R* and *S*, respectively, by comparison with the spectra of (+)-(2*S*)-2-phenylpropionic acid having positive CD at 223 nm[9] and (−)-(2*R*)-2-methylcyclopentanone having negative CD at 298 and 302 nm.[10] Thus, **1c** was concluded to be (2*R*)-2-[4-((2*S*)-2-oxocyclopentylmethyl)-phenyl]propionic acid. The absolute configurations of the other three compounds (**1d**, **1e** and **1f**) were concluded to be *R*, *R* for **1d**, *S*, *S* for **1e** and *S*, *R* for **1f** (*S*, *R* correspond to *1, *2 in Table III).

These optically pure compounds are currently being tested for biological activity and metabolic behavior, and the results will be reported elsewhere.

Experimental

Melting points were determined with a Büchi melting point apparatus and are uncorrected. IR spectra were determined on a JASCO IRA-2 grating IR spectrometer and mass spectra (MS) were recorded on a JEOL JMS-01S spectrometer. ^{1}H-NMR spectra were measured with a Varian EM-390 or T-60 machine. High pressure liquid chromatography was performed on a Waters ALC-401 machine with μPorasil for analysis and semi prep μPorasil (3/8 in × 1 foot) or a Lobar column (Si-60, Merck Co., Ltd.) for preparation. Optical rotations were measured on a Perkin-Elmer 241 spectrometer and ORD and CD spectra were recorded on a JASCO J-20 spectrometer. All organic extracts were dried over anhydrous sodium sulfate.

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*R*)-2-[4-(2-oxocyclopentylmethyl)phenyl]propionamide (4a) and (−)-*N*-[(1*S*)-1-Phenylethyl]-(2*S*)-2-[4-(2-oxocyclopentylmethyl)phenyl]propionamide (4b)——A dichloromethane (50 ml) solution of 2.46 g of **1** was mixed with 2.4 g of 2,2′-dipyridyl disulfide, 2.8 g of triphenylphosphine and 1.21 g of (−)-(1*S*)-1-phenylethylamine. The reaction mixture was kept at 0 °C for 30 min and then concentrated *in vacuo*. The residue was chromatographed on silica gel (eluted with hexane–ethyl acetate (7 : 3)). The amide was further purified on an Si-60 Lobar column to give 1.5 g of the amide **4a** and 1.4 g of **4b**. **4a**: mp 122—124 °C, $[\alpha]_D^{20}$ −61.4° (*c*=0.16% EtOH), IR (Nujol): 3250, 1740, 1650 cm^{-1}. *Anal.* Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.89; H, 7.90; N, 3.98. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, *J*=7 Hz), 1.48 (3H, d, *J*=7 Hz), 1.5—2.7 (9H, m), 3.12 (1H, m), 3.50 (1H, q, *J*=7 Hz), 5.09 (1H, quintet, *J*=7 Hz), 5.55 (1H, br s), 7.20 (4H, s), 7.26 (5H, s). **4b**: mp 100—102 °C, $[\alpha]_D^{20}$ −27.9° (*c*=0.12% EtOH), IR (Nujol): 3280, 1740, 1650 cm^{-1}. *Anal.* Calcd for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01. Found: C, 79.11; H, 7.65; N, 3.88. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, *J*=7 Hz), 1.48 (3H, d, *J*=7 Hz), 1.5—2.7 (9H, m), 3.12 (1H, m), 3.53 (1H, q, *J*=7 Hz), 5.10 (1H, quintet, *J*=7 Hz), 5.55 (1H, br s), 7.16 (4H, s), 7.16 (5H, s).

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*R*)-2-[4-(*cis*-2-hydroxycyclopentylmethyl)phenyl]propionamide (5a)——A solution of 349 mg of **4a** in 1 ml of absolute tetrahydrofuran cooled to −78 °C under nitrogen was treated dropwise with 5 ml of 0.5 M tetrahydrofuran (THF) solution of potassium tri-*sec*-butyl borohydride. After standing for 1 h at 0 °C, the reaction mixture was quenched by the addition of 20 ml of 0.2 N HCl and extracted with ether. The solvent was removed under reduced pressure to leave an oily residue which was purified by silica gel column chromatography. Recrystallization from ether–hexane gave 243 mg of **5a** as crystals. (Melting point and optical rotation value are shown in Table I.) *Anal.* Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.40; H, 8.12; N, 3.88. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, *J*=7 Hz), 1.44 (3H, d, *J*=7 Hz), 1.5 (1H, br s, OH), 1.5—3.0 (9H, m), 3.50 (1H, q, *J*=7 Hz), 4.10 (1H, m), 5.13 (1H, quintet, *J*=7 Hz), 5.50 (1H, m), 7.25 (9H, s).

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*S*)-2-[4-(*cis*-2-hydroxycyclopentylmethyl)phenyl]propionamide (5b)——The reaction of 349 mg of **4b** and 5 ml of 0.5 M THF solution of potassium tri-*sec*-butyl borohydride gave 246 mg of **5b** as crystals. (Melting point and optical rotation value are shown in Table I.) *Anal.* Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.52; H, 8.22; N, 3.92. ^{1}H-NMR ($CDCl_3$) δ: 1.2 (1H, br s, OH), 1.38 (3H, d, *J*=7 Hz), 1.50 (3H, d, *J*=7 Hz), 1.5—3.0 (9H, m), 3.53 (1H, q, *J*=7 Hz), 4.06 (1H, m), 5.14 (1H, quintet, *J*=7 Hz), 5.50 (1H, m), 7.20 (9H, s).

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*R*)-2-[4-(*cis*-2-acetoxycyclopentylmethyl)phenyl]propionamide (6)——Compound **5a** (100 mg) was dissolved in 1 ml of acetic anhydride containing 1 drop of triethylamine. The reaction mixture was kept at room temperature overnight. The solvent was evaporated off under reduced pressure to leave an oily acetate, which was purified by silica gel chromatography to give 94 mg of pure acetate as an oil. *Anal.* Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.11; H, 7.75; N, 3.78. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, *J*=7 Hz), 1.46 (3H, d, *J*=7 Hz), 1.90 (3H, s). 1.50—3.0 (9H, m), 3.50 (1H, q, *J*=7 Hz), 4.80 (1H, m), 5.10 (1H, quintet, *J*=7 Hz), 5.70 (1H, br s), 7.13 (4H, s), 7.20 (5H, s).

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*R*)-2-{4-[*cis*-(1*S*, 2*S*)-2-*O*-(α*S*)-α-methoxy-α-trifluoromethylphenylacetyl)-cyclopentylmethyl]phenyl}propionamide (7a) and (−)-*N*-[(1*S*)-1-Phenylethyl]-(2*R*)-2-{4-[*cis*-(1*R*, 2*R*)-2-*O*-(α*S*)-α-methoxy-α-trifluoromethylphenylacetyl)cyclopentylmethyl]phenyl}propionamide (7b)——To a well stirred mixture of 100 mg of alcohol (**5a**) and 1.0 ml of pyridine was added 150 mg of (−)-(1*S*)-1-methoxy-1-trifluoromethyl-

phenylacetyl chloride under ice cooling. After standing overnight at 0 °C, the reaction mixture was quenched by the addition of 10 ml of water and extracted with ether. The extracts were washed with 2 ml of 10% HCl and evaporated *in vacuo*. The resulting oil was purified by silica gel chromatography to afford a mixture (150 mg) of **7a** and **7b**. Separation of **7a** and **7b** was performed by HPLC with semi prep μPorasil (eluted with hexane–ethyl acetate (85 : 15) at a flow rate of 6 ml/min).

Compound **7a** was recrystallized from ether–hexane to give 47 mg of crystals, mp 97—98 °C, $[\alpha]_D^{20}$ 46.3 ° (c=0.43, EtOH). *Anal.* Calcd for $C_{33}H_{36}F_3NO_4$: C, 69.76; H, 6.34; N, 2.47. Found: C, 69.63; H, 6.48; N, 2.26. MS *m/e*: 567 (M^+), 410, 334, 187, 186 (base). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, J=7 Hz), 1.49 (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.50 (1H, q, J=7 Hz), 3.60 (3H, s), 5.10 (1H, quintet, J=7 Hz), 5.30 (1H, br s, NH), 5.46 (1H, br s), 7.0—7.6 (14H, m). Compound **7b** was recrystallized from ether–hexane to give 38 mg of crystals, mp 85—88 °C, $[\alpha]_D^{20}$ −81.9 ° (c= 0.45, EtOH). *Anal.* Calcd for $C_{33}H_{36}F_3NO_4$: C, 69.76; H, 6.34; N, 2.47. Found: C, 69.92; H, 6.41; N, 2.22. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, J=7 Hz), 1.49 (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.50 (1H, q, J=7 Hz), 3.55 (3H, s), 5.10 (1H, quintet, J=7 Hz), 5.30 (1H, br s, NH), 5.46 (1H, br s), 7.0—7.6 (14H, m). MS *m/e*: 567 (M^+), 410, 334, 187, 186 (base).

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*S*)-2-{4-(*cis*-(1*S*, 2*S*)-2-*O*-((α*S*)-α-methoxy-α-trifluoromethylphenylacetyl)-cyclopentylmethyl]phenyl}propionamide (7c) and (−)-*N*-[(1*S*)-1-Phenylethyl]-(2*S*)-2-{4-[*cis*-(1*R*, 2*R*)-2-*O*-((α*S*)-α-methoxy-α-trifluoromethylphenylacetyl)cyclopentylmethyl]phenyl}propionamide (7d)——The reaction of 100 mg of **5b** and 150 mg of (−)-(1*S*)-1-methoxy-1-trifluoromethylphenylacetyl chloride gave 53 mg of **7c** and 34 mg of **7d** by the same procedure as mentioned above.

Compound **7c** was recrystallized from ether–hexane to give 37 mg of crystals, mp 99—102 °C, $[\alpha]_D^{20}$ 36.8 ° (c= 0.45, EtOH). *Anal.* Calcd for $C_{33}H_{36}F_3NO_4$: C, 69.76; H, 6.34; N, 2.47. Found: C, 69.74; H, 6.33; N, 2.43. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.48 (1H, q, J=7 Hz), 3.60 (3H, s), 5.06 (1H, quintet, J=7 Hz), 5.25 (1H, br s, NH), 5.50 (1H, br s), 7.07—7.6 (14H, m). MS *m/e*: 567 (M^+), 410, 334, 187, 186 (base). Compound **7d** was recrystallized from ether–hexane to give 33 mg of crystals, mp 78—81 °C, $[\alpha]_D^{20}$ −18.3 ° (c=0.43, EtOH). *Anal.* Calcd for $C_{33}H_{36}F_3NO_4$: C, 69.76; H, 6.34; N, 2.47. Found: C, 69.52; H, 6.56; N, 2.35. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=7 Hz), 1.48, (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.48 (1H, q, J=7 Hz), 3.50, (3H, s), 5.06 (1H, quintet, J=7 Hz), 5.25 (1H, br s, NH), 5.50, (1H, br s), 7.0—7.6 (14H, m). MS *m/e*: 567 (M^+), 410, 334, 187, 186 (base).

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*R*)-2-[4-(*cis*-(1*S*, 2*S*)-2-hydroxycyclopentyl methyl)phenyl]propionamide (5c) and (−)-*N*-[(1*S*)-1-Phenylethyl]-(2*S*)-2-[4-(*cis*-(1*S*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionamide (5e)——A solution of 100 mg of **7a** and 50 mg of NaOH in 1 ml of methanol was stirred at room temperature overnight. After addition of 1 ml of water, methanol was removed under reduced pressure. The residual aqueous layer was extracted with ether and the solvent was removed *in vacuo*. The resulting precipitate was collected. Further purification was achieved by HPLC with a semi prep μPorasil column; elution with hexane–ethyl acetate (7 : 3) gave two amides **5c** and **5e**. Compound **5c** was recrystallized from ether–hexane to give 37 mg of crystals. (Melting points and optical rotation values of **5a—f** are given in Table I.) *Anal.* Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.50; H, 8.20; N, 3.83. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.48 (1H, q, J=7 Hz), 3.60 (3H, s), 5.06 (1H, quintet, J=7 Hz), 5.25 (1H, br s, NH), 5.50 (1H, br s), 7.0—7.6 (14H, m). Compound **5e** was recrystallized from ether–hexane to give 37 mg of crystals. *Anal.* Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.43; H, 8.15; N, 3.73. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.48 (1H, q, J=7 Hz), 3.60 (3H, s), 5.06 (1H, quintet, J=7 Hz), 5.25 (1H, br s, NH), 5.50 (1H, br s), 7.0—7.6 (14H, m).

(−)-*N*-[(1*S*)-1-Phenylethyl]-(2*R*)-2-[4-(*cis*-(1*R*, 2*R*)-2-hydroxycyclopentylmethyl)phenyl]propionamide (5d) and (−)-*N*-[(1*S*)-1-Phenylethyl]-(2*S*)-2-[4-(*cis*-(1*R*, 2*R*)-2-hydroxycyclopentylmethyl)phenyl]propionamide (5f)——Compound **7b** (100 mg) was saponified with NaOH by the same procedure as mentioned above to give **5d** and **5f**. Compound **5d** was recrystallized from ether–hexane to give 37 mg of crystals. *Anal.* Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.53; H, 8.25; N, 3.93. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.48 (1H, q, J=7 Hz), 3.60 (3H, s), 5.06 (1H, quintet, J=7 Hz), 5.25 (1H, br s NH), 5.50 (1H, br s), 7.0—7.6 (14H, m).

Compound **5f** was recrystallized from ether–hexane to give 37 mg of crystals. *Anal.* Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.43; H, 8.10; N, 3.74. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.3—3.0 (9H, m), 3.48 (1H, q, J=7 Hz), 3.60 (3H, s), 5.06 (1H, quintet, J=7 Hz), 5.25 (1H, br s, NH), 5.50 (1H, br s), 7.0—7.6 (14H, m).

Jones Oxidation of 5c, 5d, 5e and 5f (Synthesis of 4c, 4d, 4e and 4f)——Jones reagent was added dropwise to a stirred solution of 100 mg of **5** in 1.0 ml of acetone until a yellow color remained. After 10 min, the reaction mixture was diluted with 10 ml of water and extracted with ether. The extracts were washed with water and the solvent was evaporated off. The residue was chromatographed on silica gel to produce **4** as a solid. Recrystallization from hexane–ethyl acetate gave pure **4** as prisms. (Melting points, optical rotation values and yields are given in Table II.) **4c**: *Anal.* Calcd for $C_{23}H_{27}NO_2$: C, 79.12; H, 7.79; N, 4.01. Found: C, 79.12; H, 7.74; N, 3.92. The NMR spectrum of **4c** was identical with that of **4a**. **4d**: *Anal.* Calcd for $C_{23}H_{27}NO_2$: C, 79.12; H, 7.79; N, 4.01. Found: C, 79.12; H, 7.74; N,

4.16. The NMR spectrum of **4d** was identical with that of **4b**. **4e**: *Anal.* Calcd for $C_{23}H_{27}NO_2$: C, 79.12; H, 7.79; N, 4.01. Found: C, 78.95; H, 7.81; N, 4.07. The NMR spectrum of **4e** was identical with that of **4a**. **4f**: *Anal.* Calcd for $C_{23}H_{27}NO_2$: C, 79.12; H, 7.79; N, 4.01. Found: C, 79.20; H, 7.74; N, 4.19. The NMR spectrum of **4f** was identical with that of **4b**.

Amide Bond Cleavage of 4a, 4b, 4c, 4d, 4e and 4f (Synthesis of 1a, 1b, 1c, 1d, 1e and 1f)——A stirred suspension of 700 mg of sodium acetate in 3 ml of carbon tetrachloride (CCl_4) at −78 °C was treated with 0.4 ml of N_2O_4 (1.5 M CCl_4 solution). After 15 min, the stirred yellow suspension was treated dropwise with a solution of 100 mg of **4** in 0.5 ml of CCl_4 at 0 °C and kept for 2 h. The reaction mixture was then diluted with 3 ml of water and extracted with ether. The solvent was evaporated off under reduced pressure and the residual oil was dissolved in 3 ml of CCl_4. This solution was refluxed for 1 h. The solvent was evaporated off *in vacuo* and the residue was chromatographed on 0.5 g of silica gel to give the parent acid **1**. (Melting points, optical rotation values and yields are given in Table III.) MS *m/e*: 246 (M^+), 201, 200, 163, 117, 116 (base). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, d, J=7 Hz), 1.5—2.7 (8H, m), 3.0—3.3 (1H, m), 3.71 (1H, q, J=7 Hz), 7.15 (2H, d, J=9 Hz), 7.27 (2H, d, J=9 Hz), 11.0 (1H, br s, OH). **1a**: *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.85; H, 7.27. ORD (c=0.12, methanol) [α] (nm): −3600 (234) (peak). CD (c=0.12, methanol) [θ] (nm): −5000 (226) (negative maximum). **1b**: *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.98; H, 7.22. ORD (c=0.12, methanol) [α] (nm): 3600 (234) (peak). CD (c=0.12, methanol) [θ] (nm): 5000 (226) (positive maximum). **1c**: *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.12; H, 7.32. ORD (c=0.12, methanol) [α] (nm): −3000 (312) (peak), −1240 (276) (peak), 2600 (234) (peak). CD (c=0.12, methanol) [θ] (nm): −3400 (295) (negative maximum), −5000 (226) (negative maximum). **1d**: *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.05; H, 7.28. ORD (c=0.12, methanol) [α] (nm): 2900 (312) (peak), −3250 (268) (peak), −3000 (252), −4900 (234) (peak). CD (c=0.12, methanol) [θ] (nm): 3400 (295) (positive maximum), −5000 (226) (negative maximum). **1e**: *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.30; H, 7.23. ORD (c=0.12, methanol) [α] (nm): −2900 (312) (peak), 3250 (268) (peak), 2900 (252), 4900 (234) (peak). CD (c=0.12, methanol) [θ] (nm): −3400 (295) (negative maximum), 5000 (226) (positive maximum). **1f**: *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.01; H, 7.30. ORD (c=0.12, methanol) [α] (nm): −3000 (312) (peak), 1240 (276) (peak), −2600 (234) (peak). CD (c=0.12, methanol) [θ] (nm): 3400 (295) (positive maximum), 5000 (226) (positive maximum).

References

1) Sankyo Co., Ltd., Japan Patent 38906 (1977).
2) E. Misaka, T. Yamaguchi, Y. Iizuka, K. Kamoshida, T. Kojima, K. Kobayashi, Y. Endo, Y. Misawa, S. Kobayashi and K. Tanaka, *Oyo Yakuri*, **21**, 753 (1981).
3) T. Y. Shen, *Angew. Chem. Int. Ed. Engl.*, **11**, 460 (1972); J. S. Kaltenbronn, *J. Med. Chem.*, **16**, 490 (1973); S. Noguchi, S. Kishimoto, I. Minamida and M. Obayashi, *Chem. Pharm. Bull.*, **22**, 529 (1974); Z. N. Gaut, H. Baruth, L. O. Randall, C. Ashley and J. R. Paulsrud, *Prostaglandins*, **10**, 59 (1975); S. S. Adams, P. Bresloff and C. G. Mason, *J. Pharm. Pharmacol.*, **28**, 256 (1976).
4) S. Naruto and A. Terada, *Chem. Pharm. Bull.*, **26**, 1486 (1978).
5) G. Helmchen, H. Volter and W. Schuhle, *Tetrahedron Lett.*, **1977**, 1417.
6) C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, **1939**, 916.
7) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972); G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 4745 (1975).
8) S. Naruto and A. Terada, *Chem. Pharm. Bull.*, **31**, 4319 (1983).
9) G. Barth, W. Voelter, H. S. Mosher, E. Bunnenberg and C. Djerassi, *J. Am. Chem. Soc.*, **92**, 875 (1970).
10) J. J. Partridge, N. K. Chadha and M. R. Uskokovic, *J. Am. Chem. Soc.*, **95**, 532 (1973).