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Synthesis of the Eight Possible Optically Active Isomers of 2-[4-(2-Hydroxycyclopentylmethyl)phenyl]propionic Acid

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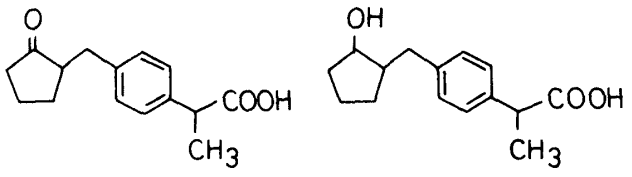
A recently synthesized compound, (±)-2-[4-(2-oxocyclopentylmethyl)phenyl]propionic acid, had good anti-inflammatory and analgesic activities. One of the metabolites of this compound showed more potent prostaglandin synthetase inhibitory activity than the parent acid. For the structural determination and absolute configurational assignment of the metabolites, we synthesized the eight possible title alcohols and carried out stereochemical assignment of these alcohols.

Keywords——anti-inflammatory agent; 2-arylpropionic acid; absolute configuration; reduction; metabolite

Previously, we reported the optical resolution and determination of the absolute configuration of (±)-2-[4-(2-oxocyclopentylmethyl)phenyl]propionic acid (**1**),[1] which has good anti-inflammatory and analgesic activities.[2]

In the metabolic pathway, it is reasonable to suppose that the cyclopentanone moiety of **1** may be reduced to cyclopentanol (**2**). In fact, the mass spectra (MS) of metabolites of **1** suggested the presence of **2**, which has more active prostaglandin synthetase inhibitory activity[3] than the parent acid, **1**. As a part of a study on **1**, we have attempted to determine the configuration of the cyclopentanol moiety (*cis* or *trans*) of **2**, and to synthesize the eight possible optically active alcohols (which have three asymmetric carbons).



1 **2**

Chart 1

Sodium cyanoborohydride reduction of **1** gave (±)-2-[4-(*cis*-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**3**) and (±)-2-[4-(*trans*-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**4**), almost quantitatively. The ratio of **3** to **4** was approximately 1 : 4.

In contrast, potassium tri-*sec*-butyl borohydride reduction of **1** afforded only the *cis* alcohol, **3**, in 80% yield. MS of both **3** and **4** displayed a molecular ion peak at $m/z = 248$ and a dehydration peak at 230. The infrared (IR) spectra of both **3** and **4** showed no carbonyl absorption in the 1740 cm^{-1} region. The nuclear magnetic resonance (NMR) spectrum of **3** showed the signal of a methine proton peak adjacent to the hydroxy group at 4.08 ppm as a multiplet. The corresponding proton peak of **4** was observed at 3.85 ppm as a multiplet. Esterification of **3** and **4** with diazomethane gave the corresponding esters, methyl (±)-2-[4-(*cis*-2-hydroxycyclopentylmethyl)phenyl]propionate (**5**) and methyl (±)-2-[4-(*trans*-2-

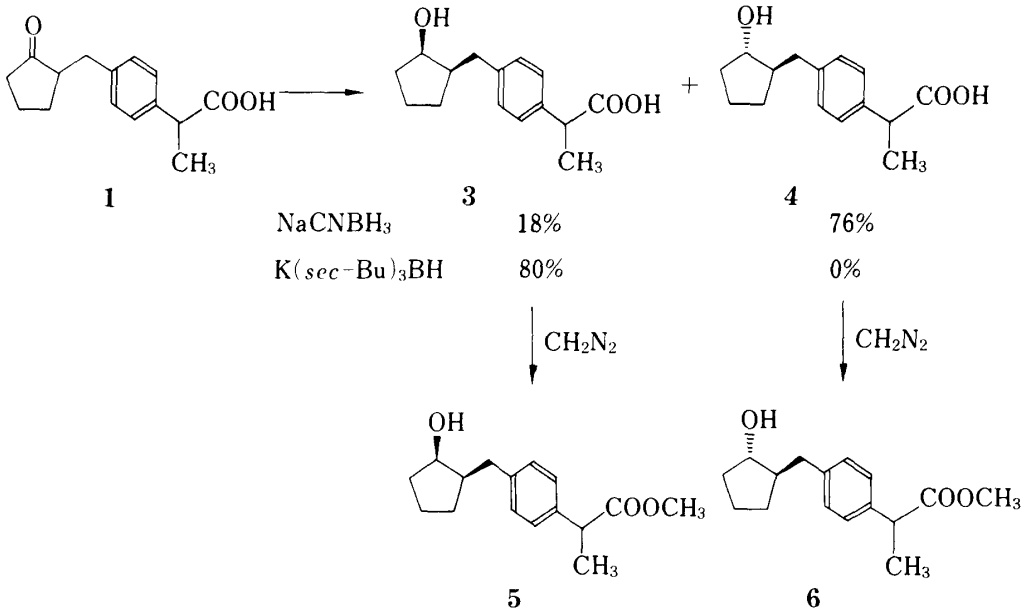
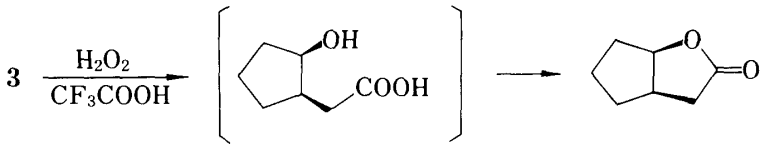


Chart 2

hydroxycyclopentylmethyl)phenyl]propionate (**6**). The NMR spectrum of **5** showed a deuterium oxide-exchangeable broad hydroxy proton peak at 3.90 ppm and a methine proton signal at 3.90 ppm as a multiplet. In the cace of **6**, the corresponding proton peaks were seen at 4.10 and 3.65 ppm. From a consideration of the conformational analysis of 2-substituted cyclopentanols in relation to NMR spectra,[4] **3** and **4** were assumed to be *cis* and *trans*, respectively. In order to confirm the conformational assignment of the alcohols, **3** and **4**, exhaustive oxidation of compound **3** was carried out with 30% H_2O_2 in trifluoroacetic acid[5] to afford *cis*-hexahydro-2*H*-cyclopenta(*b*)furan-2-one (**8**) in 10% yield, *via* *cis*-2-hydroxycyclopentylacetic acid (**7**). The structure of **8** was confirmed by comparison with an authen-



7 8

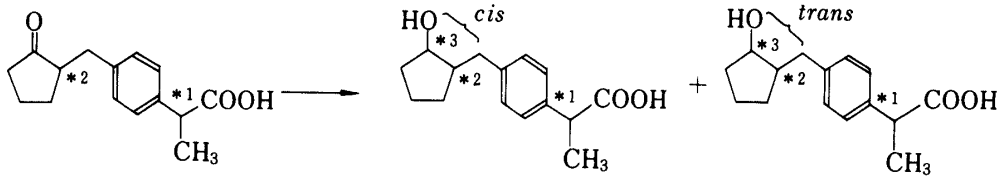
Chart 3

tic sample which was synthesized by the reported procedure.[6] In contrast, oxidation of **4** under the same reaction condition did not give **8**. From the oxidation results, the conformation was unambigously concluded to be *cis* for **3** and *trans* for **4**.

Next, (2*R*)-2-[4-((1*S*)-2-oxocyclopentylmethyl)phenyl]propionic acid (**1a**), which was previously synthesized by us,[1] was reduced with sodium cyanoborohydride in methanol to afford (2*R*)-2-[4-((1*S*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**3a**) and (2*R*)-2-[4-((1*R*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**4a**). Compounds **3a** and **4a** were separated by medium pressure liquid chromatography (MPLC) on an acetic acid-deactivated Si-60 Lobar column. Compound **3a** was recrystallized from ether–hexane (mp 105—106 °C, $[\alpha]_D$ −37°). Pure **4a** was similarly obtained by recrystallization from ether–hexane (mp 80—82 °C, $[\alpha]_D$ −76°).

Three other optically pure pentanones (**1b**, **1c** and **1d**) which were also synthesized by us[1]

TABLE I. Physical Properties of **3a—d** and **4a—d**



1 **3** **4**

Compd. No.	*2	*1	Compd. No.	*3	*2	*1	mp (°C)	$[\alpha]_D^{20}$ (*c*, ethanol)
1a	*S*	*R*	**3a**	*S*	*S*	*R*	105—106	−37° (0.15)
1b	*R*	*S*	**3b**	*R*	*R*	*S*	110—111	36° (0.15)
1c	*R*	*R*	**3c**	*R*	*R*	*R*	109—110	−66° (0.14)
1d	*S*	*S*	**3d**	*S*	*S*	*S*	110—111	62° (0.15)

Compd. No.	*3	*2	*1	mp (°C)	$[\alpha]_D^{20}$ (*c*, ethanol)
4a	*R*	*S*	*R*	80—82	−76° (0.15)
4b	*S*	*R*	*S*	87—88	72° (0.15)
4c	*S*	*R*	*R*	106—107	−17° (0.16)
4d	*R*	*S*	*S*	75—76	17° (0.16)

were reduced to give the corresponding *cis* (**3b**, **3c** and **3d**) and *trans* (**4b**, **4c** and **4d**) alcohols. These results and the physical properties are summarized in Table I.

By comparison of the retention times on high pressure liquid chromatography (HPLC) of the metabolites and the synthesized authentic alcohols, the main metabolite of **1** was concluded to be the *trans* alcohol (**4b**) having *S*, *R*, *S* configuration (*S*, *R*, *S* correspond to *1, *2, *3 in Table I); this product was a more active inhibitor of prostaglandin synthetase than the parent acid **1**. Details of the separation, identification[7] and biological activities of the metabolites 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 MS were recorded on a JEOL JMS-01S spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a Varian EM-390 or T-60. HPLC was performed on a Waters ALC-401 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. All organic extracts were dried over anhydrous sodium sulfate.

Reduction of (±)-2-[4-(2-Oxocyclopentylmethyl)phenyl]propionic Acid (1) with Potassium Tri-*sec*-butyl Borohydride——A solution of **1** (246 mg) in 1 ml of absolute tetrahydrofuran (THF) cooled to −78 °C was treated dropwise with 5 ml of a 0.5 M THF solution of potassium tri-*sec*-butyl borohydride under nitrogen. After being stirred 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 (±)-2-[4-(*cis*-2-hydroxycyclopentylmethyl)phenyl]-propionic acid (**3**) (197 mg) as crystals. mp 125—128 °C. *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H, 8.00. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=7 Hz), 1.5—2.2 (7H, m), 2.5—3.0 (2H, m), 3.70 (1H, q, J=7 Hz), 4.08 (1H, m), 6.45 (2H, s), 7.22 (4H, s). MS *m/z*: 248 (M^+), 230, 186, 91 (base).

Reduction of (±)-2-[4-(2-Oxocyclopentylmethyl)phenyl]propionic Acid (1) with $NaCNBH_3$——A solution of **1** (246 mg) and $NaCNBH_3$ (100 mg) in 2 ml of methanol was stirred at 0 °C for 40 min at pH 3 (adjusted with 6 N HCl). After addition of 10 ml of water, the reaction mixture was extracted with ether. The solvent was evaporated off under

reduced pressure to give an oily residue. The residue was subjected to chromatography on an deactivated Lobar column to afford pure **3** (45 mg) and (±)-2-[4-(*trans*-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**4**) (188 mg). Compound **3** was identical with the product obtained by tri-*sec*-butyl borohydride reduction of **1**. Compound **4** was recrystallized from ether–hexane. mp 108—113 °C. *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: 72.58; H, 8.08. ^{1}H-NMR ($CDCl_3$): 1.48 (3H, d, J=7 Hz), 1.5—2.2 (7H, m), 2.3—2.9 (2H, m), 3.70 (1H, q, J=7 Hz), 3.85 (1H, m), 6.48 (2H, s), 7.20 (4H, q, J=9 Hz), MS *m/z*: 248 (M^+), 230, 186, 91 (base).

Reduction of (2*R*)-2-[4-((1*S*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1a) with Potassium Tri-*sec*-butyl Borohydride——A solution of **1a** (246 mg) in 1 ml of absolute THF cooled to −78 °C was treated dropwise with 5 ml of a 0.5 M THF solution of potassium tri-*sec*-butyl borohydride under nitrogen. After 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 (2*R*)-2-[4-(*cis*-(1*S*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**3a**) as crystals (163 mg). mp 105—107 °C. $[\alpha]_D^{20}$ −37° (c=0.15, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.35; H, 7.98. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=7 Hz), 1.5—2.2 (7H, m), 2.5—3.0 (2H, m), 3.70 (1H, q, J=7 Hz), 4.08 (1H, m), 6.15 (2H, br s, OH), 7.22 (4H, s). MS *m/z*: 248 (M^+), 230, 186, 91 (base).

Reduction of (2*S*)-2-[4-((1*R*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1b) with Potassium Tri-*sec*-butyl Borohydride——The reaction of **1b** (246 mg) and potassium tri-*sec*-butyl borohydride (5 ml) in 0.5 M THF solution according to the procedure mentioned above gave (2*S*)-2-[4-(*cis*-(1*R*, 2*R*)-2-hydroxycyclopentylmethyl)phenyl]-propionic acid (**3b**) (137 mg). mp 110—111 °C. $[\alpha]_D^{20}$ 36° (c=0.15, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.45; H, 8.10.

Reduction of (2*R*)-2-[4-((1*R*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1c) with Potassium Tri-*sec*-butyl Borohydride——The reaction of **1c** (246 mg) and potassium tri-*sec*-butyl borohydride (5 ml) in 0.5 M THF solution according to the procedure described for **1a** gave (2*R*)-2-[4-(*cis*-(1*R*, 2*R*)-2-hydroxycyclopentylmethyl)phenyl]-propionic acid (**3c**) (154 mg). mp 109—110 °C. $[\alpha]_D^{20}$ −66° (c=0.14, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 8.05.

Reduction of (2*S*)-2-[4-((1*S*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1d) with Potassium Tri-*sec*-butyl Borohydride——The reaction of **1d** (246 mg) and potassium tri-*sec*-butyl borohydride (5 ml) in 0.5 M THF solution according to the procedure described for **1a** gave (2*S*)-2-[4-(*cis*-(1*S*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]-propionic acid (**3d**) (147 mg). mp 110—111 °C. $[\alpha]_D^{20}$ 62° (c=0.15, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.43; H, 8.00.

***cis*-Hexahydro-2*H*-cyclopenta(*b*)furan-2-one (8)**——A mixture of **3** (1 g), 30% H_2O_2 (7 ml) and trifluoroacetic acid (10 ml) was refluxed for 1.5 h. After cooling, the reaction mixture was poured into 50 ml of water and extracted with ether. The extracts were washed with $NaHCO_3$ solution, and evaporated. The residue was chromatographed on silica gel to give **8** (50 mg) as an oil. IR (Nujol): 1780 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—3.0 (9H, m), 5.0 (1H, m).

Reduction of (2*R*)-2-[4-((1*S*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1a) with $NaCNBH_3$——A solution of **1a** (246 mg) and $NaCNBH_3$ (100 mg) in 2 ml of methanol was stirred at 0 °C for 40 min at pH 3. After addition of 10 ml of water, the reaction mixture was extracted with ether and subjected to AcOH-deactivated Lobar column chromatography to give **3a** (35 mg) and (2*R*)-2-[4-(*trans*-(1*S*, 2*R*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**4a**) (180 mg). Compound **3a** was identical with the potassium tri-*sec*-butyl borohydride reduction product of **1a**. Compound **4a** was recrystallized from ether–hexane. mp 80—82 °C. $[\alpha]_D^{20}$ −76° (c=0.15, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.53; H, 8.05. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=7 Hz), 1.5—2.2 (7H, m), 2.3—2.9 (2H, m), 3.70 (1H, q, J=7 Hz), 3.85 (1H, m), 5.95 (2H, br s), 7.20 (4H, q, J=9 Hz). MS *m/z*: 248 (M^+), 230, 186, 91 (base).

Reduction of (2*S*)-2-[4-((1*R*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1b) with $NaCNBH_3$——The reaction of **1b** (246 mg) and $NaCNBH_3$ (100 mg) according to the procedure described for **1a** gave **3b** (35 mg) and (2*S*)-2-[4-(*trans*-(1*R*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**4b**) (165 mg). Compound **3b** was identical with the potassium tri-*sec*-butyl borohydride reduction product of **1b**. Compound **4b** was recrystallized from ether–hexane. mp 87—88 °C. $[\alpha]_D^{20}$ 72° (c=0.15, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.10.

Reduction of (2*R*)-2-[4-((1*R*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1c) with $NaCNBH_3$——The reaction of **1c** (246 mg) and $NaCNBH_3$ (100 mg) according to the procedure described for **1a** gave **3c** (38 mg) and (2*R*)-2-[4-(*trans*-(1*R*, 2*S*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**4c**) (170 mg). Compound **3c** was identical with the potassium tri-*sec*-butyl borohydride reduction product of **1c**. Compound **4c** was recrystallized from ether–hexane. mp 106—107 °C. $[\alpha]_D^{20}$ −17° (c=0.16, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12, Found: C, 72.64; H, 8.12.

Reduction of (2*S*)-2-[4-((1*S*)-2-Oxocyclopentylmethyl)phenyl]propionic Acid (1d) with $NaCNBH_3$——The reaction of **1d** (246 mg) and $NaCNBH_3$ (100 mg) according to the procedure described for **1a** gave **3d** (36 mg) and (2*S*)-2-[4-(*trans*-(1*S*, 2*R*)-2-hydroxycyclopentylmethyl)phenyl]propionic acid (**4d**) (177 mg). Compound **3d** was identical with the potassium tri-*sec*-butyl borohydride reduction product of **1d**. Compound **4d** was recrystallized from ether–hexane. mp 75—76 °C. $[\alpha]_D^{20}$ 17° (c=0.16, ethanol). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H,

8.09.

Methyl (±)-2-[4-(*cis*-2-Hydroxycyclopentylmethyl)phenyl]propionate (5)——Diazomethane ethereal solution (5 ml, 3 mmol) was added to a solution of **3** (246 mg) in ether (5 ml) at 0 °C. After 5 min, the solvent was evaporated off and the residue was subjected to silica gel column chromatography to afford **5** (230 mg) as an oil. *Anal.* Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.02; H, 8.40. MS *m/z*: 262 (M^+), 244, 185 (base). ^{1}H-NMR (DMSO-d_6) δ: 1.39 (3H, d, J=7 Hz), 1.3—3.0 (10H, m), 3.58 (3H, s), 3.66 (1H, q, J=7 Hz), 3.90 (2H, br s, OH and –CH–), 7.15 (4H, s).

Methyl (±)-2-[4-(*trans*-2-Hydroxycyclopentylmethyl)phenyl]propionate (6)——The reaction of **4** (246 mg) and diazomethane ethereal solution (5 ml, 3 mmol) according to the procedure mentioned above gave **6** (220 mg) as an oil. *Anal.* Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.22; H, 8.53. MS *m/z*: 262 (M^+), 244, 185 (base). ^{1}H-NMR (DMSO-d_6) δ: 1.39 (3H, d, J=7 Hz), 1.3—3.0 (10H, m), 3.60 (3H, s), 3.65 (1H, m), 3.72 (1H, q, J=7 Hz), 4.10 (1H, br s, OH), 7.15 (4H, s).

References

1) S. Naruto and A. Terada, *Chem. Pharm. Bull.*, **31**, 4286 (1983).
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) K. Matsuda, K. Onishi, T. Sha, M. Yamazaki, Y. Tanaka and K. Tanaka, *Jpn. J. Inflamm.*, **2**, 263 (1982).
4) R. K. Segal, R. U. Koenigsberger and T. J. Howard, *Tetrahedron Lett.*, **1973**, 1703.
5) N. C. Deno, B. A. Grigger, L. A. Messer, M. D. Meyer and S. G. Stroud, *Tetrahedron Lett.*, **1977**, 1703.
6) S. Dev and C. Rai, *Tetrahedron*, **30**, 819 (1974).
7) S. Naruto, Y. Tanaka, R. Hayashi and A. Terada, *Chem. Pharm. Bull.*, "submitted."