Enantioselective Biotransformation of 1-Isopropylnaphthalene in Rabbits

Takashi MATSUMOTO,^{*,a} Takashi ISHIDA,^b Yoshio TAKEDA,^a Kimiko SOH,^a Ikumi KUBO,^a and Mitsuo SAKAMOTO^a

Faculty of Integrated Arts and Sciences, The University of Tokushima,^a Minamijosanjima, Tokushima 770, Japan and Hiroshima Institute of Technology,^b 1-1 Miyake 2-chome, Saeki-ku, Hiroshima 731-51, Japan.

Received August 31, 1994; accepted October 28, 1994

1-Isopropylnaphthalene (**1**) was administered orally to rabbits and the following eight metabolites, 2-(1-naphthyl)-2-propanol (**7**), 2-(1-naphthyl)-1-propanol (**8**: $R/S=83:17$), 2-(1-naphthyl)-1,2-propanediol (**9**: $R/S=40:60$), 4-isopropyl-1,2-naphthoquinone (**10**), 4-isopropyl-1-naphthol (**11**), 4-isopropyl-2-naphthol (**12**), 5-isopropyl-2-naphthol (**13**), and 2-(1-naphthyl)propanoic acid (**14'**) as its methyl ester (**14**: $R/S=52:48$), were isolated from urine. Among them, three metabolites (**8**, **9**, and **14**), possessing an asymmetric carbon atom in the molecule, were formed enantioselectively and five metabolites (**7**, **10**, **11**, **12**, and **13**) were formed regioselectively. The presumed metabolic pathways of 1-isopropylnaphthalene (**1**) in rabbits leading to these metabolites are discussed.

Key words enantioselective metabolism; 1-isopropylnaphthalene; rabbit

Alkylaromatic compounds have been widely used as heat-transfer agents or printing materials as one of the substitutes for polychlorinated biphenyls. Among them, 1-isopropylnaphthalene (**1**) is used in many industrial materials such as color-forming compounds,¹⁾ jet-printing media,²⁾ or pressure-sensitive copying paper.^{3,4)} Its positional isomer, 2-isopropylnaphthalene (**2**) is used for the same purposes, and recently its biotransformation in rats^{5–7)} and rabbits,⁸⁾ was reported by Kojima *et al.* However, their study did not deal with the stereochemistry of the metabolites. Recently, compound **1** was found as one of the polycyclic aromatic hydrocarbons in Kuwaiti gas oil,⁹⁾ barbecue briquettes,¹⁰⁾ and even in drinking water.¹¹⁾ Thus, knowledge of the metabolism of compound **1** is very important from environmental, pharmacological and toxicological points of view.

We have reported the enantioselective biotransformation of several isopropylaromatic and related compounds, (+)-dehydroabiatic acid (**3**),¹²⁾ *p*-cymene (**4**),¹³⁾ cumene (**5**),¹⁴⁾ and 4-isopropenyltoluene (**6**),¹⁵⁾ in rabbits. The present study is a continuation of our systematic research on the stereoselective biotransformation of isopropylaromatic compounds. This is the first report on the enantioselective biotransformation of isopropylnaphthalenes.

Metabolism of 1-Isopropylnaphthalene 1-Isopropylnaphthalene (**1**) (11.00 g) was administered orally to rabbits and the urinary metabolites (after β -glucuronidase: arylsulfatase treatment and extraction with chloroform) were separated into neutral, phenolic, and acidic portions. The neutral portion was separated into four compounds, A (0.719 g), B (0.640 g), C (0.149 g), and D (0.183 g) by silica gel column chromatography. The phenolic portion

was chromatographed on silica gel to give compound E (0.347 g) and a mixture (*ca.* 1:1, 0.240 g) of compounds F and G. The acidic portion was esterified with diazomethane and the product was purified by silica gel column chromatography to give compound H (0.308 g).

Compound A (**7**): The mass spectrum gave a molecular ion peak at m/z 186.1035 (M^+), corresponding to the formula $C_{13}H_{14}O$, and the infrared (IR) spectrum showed absorption bands at 3600 and 3420 cm^{-1} due to a hydroxyl group. The proton nuclear magnetic resonance (1H -NMR) spectrum ($CDCl_3$) showed a singlet signal at δ 1.86 (7H) due to two tertiary methyl groups and a hydroxyl group, and two multiplets at δ 7.36–7.95 (6H) and 8.74–8.91 (1H) due to aromatic protons. From these spectral data, the structure of compound A was assigned as 2-(1-naphthyl)-2-propanol¹⁶⁾ (**7**).

Compound B (**8**): $[\alpha]_D -5.27^\circ$ (C_6H_6). The mass spectrum gave a molecular ion peak at m/z 186.1042 (M^+), corresponding to the formula $C_{13}H_{14}O$, and the IR spectrum showed hydroxyl bands at 3580 and 3400 cm^{-1} . The 1H -NMR spectrum ($CDCl_3$) showed signals at δ 1.43 (3H, d, $J=6.7$ Hz), 1.49 (1H, s), 3.88 (1H, m), 3.80 and 3.96 (each 1H, d, $J=7.6$ Hz), and 7.34–8.24 (7H, m) due to a secondary methyl group, a hydroxyl group, a methine proton, a methylene group having a hydroxyl group, and aromatic protons, respectively. These spectral data suggested that one of the isopropyl methyl groups in 1-isopropylnaphthalene (**1**) was replaced by a hydroxyl group. Thus, the structure of compound B was assigned as (–)-2-(1-naphthyl)-1-propanol¹⁶⁾ (**8**). The enantiomeric ratio^{17,18)} of compound B was $R/S=83:17$.

Compound C (**9**): $[\alpha]_D -1.12^\circ$ ($CHCl_3$). The mass

* To whom correspondence should be addressed.

Chart 1

spectrum gave a molecular ion peak at m/z 202.1003 (M^+), corresponding to the formula $C_{13}H_{14}O_2$, and the IR spectrum showed hydroxyl bands at 3550 and 3390 cm^{-1} . The 1H -NMR ($CDCl_3$) showed the presence of a tertiary methyl group at δ 1.79 (3H, s), two hydroxyl groups at δ 2.15 (2H, brs), a methylene group at δ 3.84 and 4.29 (each 1H, d, $J=11.4$ Hz), and seven aromatic protons at δ 7.27–8.73 (7H, m). From these spectral data, the structure of compound C was assigned as (–)-2-(1-naphthyl)-1,2-propanediol¹⁶⁾ (**9**). In order to determine the enantiomeric ratio of compound C, the following correlation was carried out. Treatment of compound C with *p*-toluenesulfonyl chloride in pyridine at room temperature gave a monotosylate (**15**), which was treated with sodium methoxide at 0–5 °C to give an epoxide (**16**). This epoxide was then submitted to catalytic hydrogenolysis in ethanol using palladium on carbon and sodium hydroxide to give the known 2-(1-naphthyl)-1-propanol^{16,17)} (**8**), whose optical rotation was $[\alpha]_D +1.66^\circ$ (C_6H_6). Therefore, the enantiomeric ratio¹⁸⁾ of **8** was $R/S=40:60$. Mitsui and Imaizumi¹⁹⁾ have reported that the hydrogenolysis of α -alkylstyrene oxides proceeds by predominant inversion of the configuration using a palladium-on-carbon catalyst in the presence of base. Application of Mitsui's rule to the epoxide **16** suggested that the stereochemistry of **16** was *S*. Thus, the stereochemistry of compound C was also assigned as *S* (Chart 1).

Compound D (10): The mass spectrum gave a molecular ion peak at m/z 200.0839 (M^+), corresponding to the formula $C_{13}H_{12}O_2$, and the IR spectrum showed a quinone band at 1660 cm^{-1} . The 1H -NMR spectrum

($CDCl_3$) indicated the presence of an isopropyl group at δ 1.33 (6H, d, $J=6.7$ Hz) and 3.25 (1H, m, $J=6.7$ Hz), an olefinic proton at δ 6.43 (1H, s), and four aromatic protons at δ 7.45–8.25 (4H, m). Thus, the structure of compound D was assigned as 4-isopropyl-1,2-naphthoquinone (**10**).

To obtain further confirmation of the structure of compound D, the following reaction was carried out. Treatment of compound D with acetic anhydride in the presence of zinc powder at room temperature produced a diacetate (**17**), whose mass spectrum gave a molecular ion peak at m/z 286.1221 (M^+), corresponding to the formula $C_{17}H_{18}O_4$. The 1H -NMR spectrum ($CDCl_3$) of **17** showed the presence of an isopropyl group at δ 1.39 (6H, d, $J=6.7$ Hz) and 3.73 (1H, m, $J=6.7$ Hz), two acetoxyl groups at δ 2.33 and 2.44 (each 3H, s), and five aromatic protons at δ 7.22 (1H, s) and 7.41–8.20 (4H, m).

Compound D (10) was also obtained from compound E (**11**) by oxidation with Fremy's salt (potassium nitrosodisulfonate) in the presence of potassium dihydrogenphosphate in aqueous *N,N*-dimethylformamide (DMF).

Compound E (11): The mass spectrum gave a molecular ion peak at m/z 186.1044 (M^+), corresponding to the formula $C_{13}H_{14}O$, and the IR spectrum showed hydroxyl bands at 3600 and 3300 cm^{-1} . The 1H -NMR spectrum ($CDCl_3$) indicated the presence of an isopropyl group at δ 1.37 (6H, d, $J=6.7$ Hz) and 3.66 (1H, m, $J=6.7$ Hz), a phenolic hydroxyl group at δ 5.21 (1H, s), two *ortho*-coupling aromatic protons at δ 6.77 (1H, d, $J=7.9$ Hz) and 7.23 (1H, d, $J=7.9$ Hz), and four other aromatic protons at δ 7.41–7.65 and 7.94–8.32 (each 2H, m). Acetylation of compound E with acetic anhydride in pyridine afforded a monoacetate (**18**). The mass spectrum

of **18** gave a molecular ion peak at m/z 228.1127 (M^+), corresponding to the formula $C_{15}H_{16}O_2$. Thus, the structure of compound E was assigned as 4-isopropyl-1-naphthol (**11**), whose IR and 1H -NMR spectra were identical with those of an authentic sample.²⁰⁾

Compounds F (**12**) and G (**13**): Phenolic compounds, F and G, were obtained as a mixture (*ca.* 1 : 1), whose mass spectrum gave a molecular ion peak at m/z 186.1054 (M^+), corresponding to the formula $C_{13}H_{14}O$. The IR spectrum of the mixture showed hydroxyl bands at 3580 and 3340 cm^{-1} , and the 1H -NMR spectrum ($CDCl_3$) showed the presence of an isopropyl group at δ 1.37 (6H, d, $J=6.7$ Hz) and 3.70 (1H, m, $J=6.7$ Hz), a phenolic hydroxyl group at δ 5.19 (1H, brs), and six aromatic protons at δ 7.00–8.12 (6H, m).

A mixture of compounds F and G was treated with acetic anhydride in pyridine to give a mixture of monoacetates (**19** and **20**), whose IR spectrum showed an absorption band at 1750 cm^{-1} and whose mass spectrum gave a molecular ion peak at m/z 228.1146 (M^+), corresponding to the formula $C_{15}H_{16}O_2$. The 1H -NMR spectrum ($CDCl_3$) of the mixture (**19** and **20**) showed signals due to an isopropyl group at δ 1.38 (6H, d, $J=7.0$ Hz) and 3.72 (1H, m, $J=7.0$ Hz), an acetoxyl group at δ 2.32 (3H, s), and six aromatic protons at δ 7.15–8.20 (6H, m).

A mixture (*ca.* 1 : 4) of compounds F and G, obtained from repeated column chromatography on silica gel, was also treated with methyl iodide and anhydrous potassium carbonate in refluxing ethyl methyl ketone to give a mixture (*ca.* 1 : 4) of monomethyl ethers (**21** and **22**), whose mass spectrum gave a molecular ion peak at m/z 200.1182 (M^+), corresponding to the formula $C_{14}H_{16}O$. In the 1H -NMR spectrum (400 MHz, $CDCl_3$) of the mixture, the minor compound (**21**) showed signals due to an isopropyl group at δ 1.38 (6H, d, $J=6.8$ Hz) and 3.70 (1H, m, $J=6.8$ Hz), a methoxyl group at δ 3.92 (3H, s), two *meta*-coupling aromatic protons at δ 6.99 (1H, d, $J=2.4$ Hz) and 7.09 (1H, d, $J=2.4$ Hz), and four aromatic protons at δ 7.36–7.44 (2H, m), 7.75 (1H, br d, $J=7.3$ Hz), and 8.03 (1H, d, $J=9.3$ Hz). In the 1H -NMR spectrum of **21**, differential nuclear Overhauser effects (NOE's) were observed between an isopropyl methyl signal at δ 1.38 and aromatic proton signals at δ 7.09 and 8.03, and between a methoxyl signal at δ 3.92 and an aromatic proton signal at δ 6.99 (Fig. 1). From these spectral data, the structure of **21** was assigned as 4-isopropyl-2-methoxynaphthalene. On the other hand, the major compound (**22**) showed signals due to an isopropyl group at δ 1.39 (6H, d, $J=6.8$ Hz) and 3.70 (1H, m, $J=6.8$ Hz), a methoxyl group at δ 3.92 (3H, s), and six aromatic protons at δ 7.15 (1H, d, $J=2.4$ Hz), 7.17 (1H, dd, $J=2.4, 9.3$ Hz), 7.27 (1H, d, $J=8.3$ Hz), 7.41 (1H, t, $J=8.3$ Hz), 7.59 (1H, d, $J=8.3$ Hz), and 8.03 (1H, d, $J=9.3$ Hz). In the 1H -NMR spectrum of **22**, differential NOE's were also observed between an isopropyl methyl signal at δ 1.39 and aromatic proton signals at δ 7.27 and 8.03, and between a methoxyl signal at δ 3.92 and aromatic proton signals at δ 7.15 and 7.17 (Fig. 1). From these spectral data, the structure of **22** was assigned as 5-isopropyl-2-methoxynaphthalene. Thus, the structures of compounds F and G were

Fig. 1. Differential NOE Spectra of Methyl Ethers (**21** and **22**) of Metabolites F and G

conclusively assigned as 4-isopropyl-2-naphthol (**12**) and 5-isopropyl-2-naphthol (**13**), respectively.

Compound H (**14**): $[\alpha]_D -6.69^\circ$ (C_6H_6). The mass spectrum gave a molecular ion peak at m/z 214.0988 (M^+), corresponding to the formula $C_{14}H_{14}O_2$, and the IR spectrum showed an absorption band at 1720 cm^{-1} due to an ester group. The 1H -NMR spectrum ($CDCl_3$) indicated the presence of a secondary methyl group at δ 1.65 (3H, d, $J=7.0$ Hz), a methoxycarbonyl group at δ 3.64 (3H, s), a methine proton at δ 4.51 (1H, q, $J=7.0$ Hz), and seven aromatic protons at δ 7.41–8.16 (7H, m). Reduction of compound H with lithium aluminum hydride in ether afforded (–)-2-(1-naphthyl)-1-propanol¹⁶⁾ (**8**), $[\alpha]_D -0.53^\circ$ (C_6H_6), whose IR and 1H -NMR spectra were identical with those of compound B. Thus, the structure of compound H was assigned as methyl (–)-2-(1-naphthyl)propanoate (**14**) and the corresponding 2-(1-naphthyl)propanoic acid (**14'**) was the metabolite. The enantiomeric ratio^{17,18)} of compound H was $R/S=52:48$.

Metabolism of 2-(1-Naphthyl)-2-propanol (7), (±)-2-(1-Naphthyl)-1-propanol (8), and (±)-2-(1-Naphthyl)propanoic Acid (14') a) 2-(1-Naphthyl)-2-propanol¹⁶⁾ (**7**) (9.000 g) was administered orally to rabbits. The crude urinary product was purified by silica gel column chromatography to give recovered **7** (4.368 g) and a small amount of (–)-2-(1-naphthyl)-1,2-propanediol (**9**) (0.152 g), $[\alpha]_D -1.90^\circ$ ($CHCl_3$), whose IR and 1H -NMR spectra were identical with those of compound C.¹⁶⁾ The enantiomeric ratio¹⁸⁾ of the metabolite **9** was $R/S=34:66$.

b) (±)-2-(1-Naphthyl)-1-propanol¹⁶⁾ (**8**) (5.500 g) was administered orally to rabbits. The crude urinary product was separated into neutral and acidic portions. The neutral portion was chromatographed on silica gel to give an optically active alcohol (0.734 g), $[\alpha]_D -6.33^\circ$ (C_6H_6), whose IR and 1H -NMR spectra were identical with those of the starting alcohol (**8**). The enantiomeric ratio¹⁸⁾ of the recovered alcohol (**8**) was $R/S=89:11$.

The acidic portion was esterified with diazomethane. The product was chromatographed on silica gel to give an ester (1.220 g), $[\alpha]_D +69.05^\circ$ (C_6H_6), whose IR and 1H -NMR spectra were identical with those of compound H (**14**). The enantiomeric ratio¹⁸⁾ of the ester (**14**) was $R/S=28:72$.

c) (±)-2-(1-Naphthyl)propanoic acid (**14'**) (6.368 g) was converted into the sodium salt (**14''**), which was administered orally to rabbits. The crude urinary product was esterified with diazomethane and the resulting ester was chromatographed on silica gel to give an optically active ester (3.820 g), $[\alpha]_D +4.49^\circ$ (C_6H_6), whose IR and 1H -NMR spectra were identical with those of compound

H (**14**). The enantiomeric ratio¹⁸⁾ of the ester (**14**) was $R/S=49:51$.

Discussion

In the biotransformation of aryl isopropyl groups (*p*-cymene, cumene, and (+)-dehydroabiatic acid), we have reported the following common metabolic routes¹²⁻¹⁴⁾: (1) the formation of dimethylcarbinol (ω -1 oxidation), (2) the formation of primary alcohol (ω -oxidation), (3) the formation of *S*-rich carboxylic acid from the primary alcohol (ω -oxidation).

In the present study, 1-isopropyl-naphthalene (**1**) was administered orally to rabbits and the following eight metabolites, 2-(1-naphthyl)-2-propanol (A=**7**), 2-(1-naphthyl)-1-propanol (B=**8**), 2-(1-naphthyl)-1,2-propanediol (C=**9**), 4-isopropyl-1,2-naphthoquinone (D=**10**), 4-isopropyl-1-naphthol (E=**11**), 4-isopropyl-2-naphthol (F=**12**), 5-isopropyl-2-naphthol (G=**13**), and 2-(1-naphthyl)-propanoic acid (**14'**) as its methyl ester (H=**14**), were isolated from urine. The proposed metabolic pathways of 1-isopropyl-naphthalene (**1**) leading to these metabolites are shown in Chart 2.

Firstly, the enzymatic oxidation of 1-isopropyl-naphthalene (**1**) could occur by three different metabolic routes (a, b, and c). In route a, the ω -1 position is first oxidized to give a tertiary alcohol (**7**), whose methyl group is further oxidized to give the corresponding propanediol (**9**). In route b, the ω -position of **1** is first oxidized and the resulting primary alcohol (**8**) is then oxidized to give a propanoic acid derivative (**14'**). Oral administrations of these intermediate metabolites **7** and **8** to rabbits were also carried out separately, affording the metabolites **9** and **14'**, respectively. Thus, the operation of these metabolic routes, a and b, was confirmed. In route c, the naphthalene ring was oxidized regioselectively to give an *ortho*-quinone (**10**)

and three naphthols (**11**, **12**, and **13**). All three metabolites (**8**, **9**, and **14**) possessing an asymmetric carbon atom in the molecule showed optical activity. The enantiomeric ratios of these optically active metabolites, **8**, **9**, and **14** were $R/S=83:17$, $40:60$, and $52:48$, respectively. In the formation of the primary alcohol **8** from compound **1**, the *R*-enantiomer was predominant. This observation was coincident with our previous metabolic studies.^{13,14)} In the previous papers,^{13,14,21)} we further reported a chiral inversion from the *R*-primary alcohol to the *S*-carboxylic acid. However, in the present metabolism, the conversion of the primary alcohol **8** to the carboxylic acid **14'** was enantioselective and the chiral inversion was not found. This result might be explained by the existence of repulsive forces between the isopropyl group and the *peri*-position H in compound **1**. This could interfere with the free rotation of the isopropyl group. The enantiomeric ratio of the metabolite **14** obtained from **1** was $R/S=52:48$, while that obtained from ($\pm$)-**8** was $R/S=28:72$. However, the reason for this difference of the enantiomeric ratios is unknown at present. In addition, the 1,2-propanediol metabolite **9** was also isolated. This diol was only found in the biotransformation of 4-isopropenyltoluene (**6**). In the case of compound **6**, the formation of the diol, 2-(*p*-tolyl)-1,2-propanediol (**24**), can be easily explained in terms of epoxide (**23**) formation¹⁵⁾ (Chart 3). However, the formation of the diol **9** from compound **1** is considered to be the result of ω -oxidation of the *gem*-dimethylcarbinol group in the metabolite **7**. Furthermore, in compound **1**, the aromatic ring was regioselectively oxidized into a naphthoquinone (**10**) and three naphthols (**11**, **12**, and **13**), although no phenolic metabolite was found in the metabolism of *p*-cymene (**4**), cumene (**5**), or 4-isopropenyltoluene (**6**). From the viewpoint of biotransformation of the naphthalene ring,

Chart 2. Metabolic Pathways of 1-Isopropyl-naphthalene in Rabbits

Chart 3

Chart 4

the formation of a naphthoquinone (10) is very interesting. A quinone is usually thought to be formed through three steps²²⁻²⁵: (1) oxidation of a double bond of an aromatic ring to form an epoxide, (2) hydration of the epoxide to a dihydrodiol, (3) oxidation of the dihydrodiol to a quinone; or independently, (4) oxidation from *ortho*-dihydric phenol, which might be formed as an intermediate from two phenols (11 and 12).

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were measured on a Shimadzu IR-400 spectrometer in chloroform, and the optical rotations were measured with a JASCO DIP-360 digital polarimeter. The mass spectra were recorded on a JEOL JMS-D300 spectrometer. The ¹H-NMR spectra were recorded with a Hitachi R-1500 spectrometer (60 MHz) in deuteriochloroform using tetramethylsilane as an internal standard unless otherwise stated, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Column chromatography was performed using Merck silica gel (0.063–0.200 mm).

Material According to our previous method,¹⁶ 2-(1-naphthyl)-2-propanol (7), (±)-2-(1-naphthyl)-1-propanol (8), and 1-isopropenyl-naphthalene (26) were prepared from 1-acetonaphthone (25).

Synthesis of 1-Isopropynaphthalene (1) A mixture of 1-isopropenyl-naphthalene (26) (11.490 g) and 5% Pd-C (500 mg) in ethyl acetate (70 ml) was stirred at room temperature under an atmosphere of hydrogen for 5.5 h. The mixture was filtered and the filtrate was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using hexane as an eluent, to give 1-isopropynaphthalene (1) (11.243 g; 96.7% yield). ¹H-NMR δ: 1.40 (6H, d, *J*=6.7 Hz, –CH(CH₃)₂), 3.77 (1H, m, *J*=6.7 Hz, –CH(CH₃)₂), 7.24–8.22 (7H, m, aromatic protons).

Synthesis of 1-Propanoylnaphthalene (29) A solution of 1-naphthaldehyde (27) (7.500 g) in dry ether (38 ml) was added to a stirred solution of ethylmagnesium iodide (prepared from magnesium turnings (1.283 g) and ethyl iodide (4.58 ml) in dry ether (20 ml)) at room temperature for 30 min. The mixture was further stirred at room temperature for 30 min, poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude alcohol (28) (8.940 g). IR: 3600, 3410 cm⁻¹. ¹H-NMR δ: 1.02 (3H, t, *J*=7.0 Hz, –CH₃), 1.92 (2H, m, –CH₂–), 5.40 (1H, t, *J*=6.2 Hz, –CH(OH)–), 7.31–8.21 (7H, m, aromatic protons).

A mixture of the crude alcohol (28) (8.940 g) and pyridinium chlorochromate (15.520 g) in dichloromethane (230 ml) was stirred at room temperature for 1.5 h. After addition of ethyl acetate and aqueous sodium hydrogencarbonate, the mixture was extracted with ethyl acetate.

The ethyl acetate extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using hexane-chloroform (3:7) as an eluent, to give a ketone (29) (7.006 g; 79.1% yield from 27). IR: 1675 cm⁻¹. ¹H-NMR δ: 1.28 (3H, t, *J*=7.3 Hz, –CH₃), 3.08 (2H, q, *J*=7.3 Hz, –CH₂–), 7.47–8.05 (6H, m) and 8.50–8.65 (1H, m) (aromatic protons). *Anal.* Calcd for C₁₃H₁₂O: C, 84.75; H, 6.57. Found: C, 84.61; H, 6.70.

Synthesis of Methyl (±)-2-(1-Naphthyl)propanoate (14) A stirred mixture of the ketone (29) (10.862 g), lead tetraacetate (90%, 30.500 g), and perchloric acid (60%, 14.9 ml) in trimethyl orthoformate (220 ml) was heated at 50°C for 2 h according to the method of Fujii *et al.*²⁶ The mixture was evaporated *in vacuo* to remove the trimethyl orthoformate. The residue was diluted with chloroform and washed with water. The dried solution was evaporated *in vacuo*. The crude product was chromatographed on silica gel (200 g), using hexane–benzene (3:7) as an eluent, to give (±)-14 (11.539 g; 91.3% yield). IR: 1720 cm⁻¹. ¹H-NMR δ: 1.65 (3H, d, *J*=7.0 Hz, –CH₃), 3.64 (3H, s, –CO₂CH₃), 4.51 (1H, q, *J*=7.0 Hz, –CH(CH₃)–), 7.41–8.16 (7H, m, aromatic protons). *Anal.* Calcd for C₁₄H₁₄O₂: C, 78.48; H, 6.59. Found: C, 78.39; H, 6.52.

Synthesis of (±)-2-(1-Naphthyl)propanoic Acid (14') A mixture of the racemic ester (14) (11.866 g) and aqueous sodium hydroxide (8%, 55.4 ml) in methanol (71 ml) was refluxed for 2 h and then evaporated *in vacuo* to remove the methanol. The residue was washed with ether, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was recrystallized from acetone–hexane to give (±)-14' (8.375 g; 75.5% yield), mp 150–151°C (lit.,¹⁷) mp 150–151°C. IR: 3600–2300, 1700 cm⁻¹. ¹H-NMR δ: 1.66 (3H, d, *J*=7.0 Hz, –CH₃), 4.53 (1H, q, *J*=7.0 Hz, –CH(CH₃)–), 7.25–8.17 (7H, m, aromatic protons). The mother liquor of recrystallization was evaporated *in vacuo* and the residue was chromatographed on silica gel (25 g), using chloroform as an eluent, to give additional (±)-14' (1.310 g; 11.8% yield).

Administration of 1-Isopropynaphthalene to Rabbits and Extraction of Urinary Metabolites Five female rabbits (Japanese White strain, each 3.0–3.5 kg) were used.

1-Isopropynaphthalene (1) (11.000 g) emulsified in aqueous Tween 80 (polyoxyethylene sorbitan monooleate) solution (0.001%, 100 ml) was administered orally at a dose of 2.20 g/rabbit to five rabbits after 1 d of starvation. After drug administration, food (Oriental Rabbit Food, CR-2) and water were given freely to the rabbits. For isolation of the metabolites, each rabbit was kept in a metabolic cage in which urine and feces were separated. Urine was collected daily for 2 d under a toluene layer at room temperature, then mixed, centrifuged to remove contaminants (hairs and feces), and stored at 0°C until analysis. The urine (1800 ml) was adjusted to pH 5.0 with phosphate buffer, incubated with β-glucuronidase: arylsulfatase (4.5 ml of *Helix pomatia* enzyme (Boehringer-Mannheim, Germany)) at 37°C for 24 h. The urinary

aqueous solution was then adjusted to pH 2–3 with dilute hydrochloric acid and extracted with chloroform. The chloroform extract was washed successively with aqueous sodium hydrogencarbonate, aqueous sodium hydroxide, and water. The chloroform solution was dried over sodium sulfate and evaporated *in vacuo* to give a neutral portion (4.856 g) as a dark brown oil. The aqueous sodium hydroxide washing was acidified with dilute hydrochloric acid and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give a phenolic portion (1.359 g) as a dark brown oil. The aqueous sodium hydrogencarbonate washing was also acidified with dilute hydrochloric acid and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give an acidic portion (0.963 g) as a dark solid.

Isolation of Metabolites The neutral portion (4.856 g) was purified by repeated column chromatography on silica gel (50–100 times the sample weight in each case), using hexane–chloroform (2:3, 3:7), chloroform, and ether–chloroform (1:1) as eluents to give four compounds, A, B, C, and D.

The phenolic portion (1.359 g) was also purified by repeated column chromatography on silica gel (50–100 times the sample weight in each case), using hexane–chloroform (1:1) as an eluent, to give three compounds, E, F, and G.

The acidic portion (0.963 g) was esterified with an ethereal diazo-methane solution at room temperature for 1 h. The ether solution was washed with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by repeated column chromatography on silica gel (50–100 times the sample weight in each case), using hexane–chloroform (7:3) as an eluent to give compound H.

a) Compound A was isolated from the hexane–chloroform (2:3) fraction as a solid (0.719 g), mp 83–85 °C (from acetone–hexane). HRMS *m/z*: Found: 186.1035 (M^+). Calcd for $C_{13}H_{14}O$: M , 186.1045. Compound A was identified as 2-(1-naphthyl)-2-propanol (**7**) by comparisons of its spectra (IR and 1H -NMR) with those of a synthetic sample.¹⁶⁾

b) Compound B was isolated from the hexane–chloroform (2:3) fraction as an oil (0.640 g), $[\alpha]_D^{25} -5.27^\circ$ (C_6H_6 , $c=1.58$) and -18.45° ($CHCl_3$, $c=1.55$). HRMS *m/z*: Found: 186.1042 (M^+). Calcd for $C_{13}H_{14}O$: M , 186.1045. It was identified as (–)-2-(1-naphthyl)-1-propanol (**8**) by comparisons of its spectra (IR and 1H -NMR) with those of a synthetic sample.¹⁶⁾ The enantiomeric ratio^{17,18)} of compound B was $R/S=83:17$.

c) Compound C was isolated from the ether–chloroform (1:1) fraction as an oil (0.149 g), $[\alpha]_D^{25} -1.12^\circ$ ($CHCl_3$, $c=3.22$). HRMS *m/z*: Found: 202.1003 (M^+). Calcd for $C_{13}H_{14}O_2$: M , 202.0994.

A solution of compound C (77 mg) and *p*-toluenesulfonyl chloride (88 mg) in pyridine (1.0 ml) was allowed to stand at room temperature for 48 h. The mixture was poured into a mixture of ice and dilute hydrochloric acid, and the whole was extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude monotosylate (**15**) (120 mg). IR 3580, 3400 cm^{-1} . 1H -NMR δ : 1.83 (3H, s, $-CH_3$), 2.20 (1H, s, $-OH$), 2.40 (3H, s, $-CH_3$), 4.31 and 4.61 (each 1H, d, $J=10.1$ Hz, $-CH_2O-$), 7.12–8.56 (11H, m, aromatic protons).

A solution of sodium methoxide (21 mg) in methanol (1.0 ml) was added to a stirred solution of the crude tosylate (**15**) (120 mg) in dry ether (1.0 ml) with cooling in ice-water bath. The mixture was further stirred for 1 h and then diluted with ether. The precipitate was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was extracted with ether and the ether extract was evaporated *in vacuo* to give a crude epoxide (**16**) (60 mg). 1H -NMR δ : 1.79 (3H, s, $-CH_3$), 2.95 and 3.15 (each 1H, d, $J=5.4$ Hz, $-CH_2O-$), 7.25–8.25 (7H, m, aromatic protons).

A mixture of 10% Pd–C (30 mg) and alcoholic sodium hydroxide (2%, 0.3 ml) in ethanol (5.0 ml) was stirred at room temperature for 1 h. After addition of a solution of the crude epoxide (**16**) (60 mg) in ethanol (5.0 ml), the mixture was stirred at room temperature under an atmosphere of hydrogen for 4 h. The mixture was filtered and the filtrate was acidified with acetic acid. The acidic solution was evaporated *in vacuo* and the residue was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using chloroform as an eluent, to give an alcohol (**8**) (33 mg), $[\alpha]_D^{25} +1.66^\circ$ (C_6H_6 , $c=1.63$) and $+5.75^\circ$ ($CHCl_3$, $c=1.48$). The IR and 1H -NMR spectra were identical with those of 2-(1-naphthyl)-1-propanol.^{16,17)} The enantiomeric ratio¹⁸⁾ of

the alcohol **8** was $R/S=40:60$.

d) Compound D was isolated from the hexane–chloroform (3:7) fraction as a solid (0.183 g), mp 101–103 °C (from hexane). HRMS *m/z*: Found: 200.0839 (M^+). Calcd for $C_{13}H_{12}O_2$: M , 200.0837. A mixture of compound D (31 mg) and zinc powder (50 mg) in acetic anhydride (0.5 ml) was stirred at room temperature for 1.5 h. The mixture was diluted with ether and then filtered to remove the zinc powder. The filtrate was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using hexane–chloroform (1:4) as an eluent, to give a diacetate (**17**) (27 mg). IR: 1760 cm^{-1} . HRMS *m/z*: Found: 286.1221 (M^+). Calcd for $C_{17}H_{18}O_4$: M , 286.1205. From the IR and 1H -NMR spectra, the structure of compound D was assigned as 4-isopropyl-1,2-naphthoquinone (**10**).

e) Compound E was isolated from the hexane–chloroform (1:1) fraction as an oil (0.347 g). IR: 3600, 3300 cm^{-1} . HRMS *m/z*: Found: 186.1044 (M^+). Calcd for $C_{13}H_{14}O$: M , 186.1045. The IR and 1H -NMR spectra of compound E were identical with those of authentic 4-isopropyl-1-naphthol²⁰⁾ (**11**).

A solution of compound E (50 mg) and acetic anhydride (0.5 ml) in pyridine (0.5 ml) was heated at 70–75 °C for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (15 g), using hexane–chloroform (1:1) as an eluent, to give a monoacetate (**18**) (41 mg), HRMS *m/z*: Found: 228.1127 (M^+). Calcd for $C_{15}H_{16}O_2$: M , 228.1150. IR: 1750 cm^{-1} . 1H -NMR δ : 1.39 (6H, d, $J=6.7$ Hz, $-CH(CH_3)_2$), 2.45 (3H, s, $-OCOCH_3$), 3.73 (1H, m, $J=6.7$ Hz, $-CH(CH_3)_2$), 7.18 (1H, d, $J=7.9$ Hz), 7.41 (1H, d, $J=7.9$ Hz), 7.42–7.65 (2H, m), and 7.82–8.29 (2H, m) (aromatic protons).

Conversion of compound E into compound D: A stirred solution of compound E (**11**) (40 mg) in DMF (4.8 ml) was protected from light with aluminum foil. After addition of a solution of Fremy's salt (potassium nitrosodisulfonate) (289 mg) and potassium dihydrogenphosphate (111 mg) in water (11.1 ml), the mixture was stirred at room temperature under a stream of nitrogen for 3 h. The mixture was poured into dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using chloroform as an eluent, to give a quinone (38 mg; 88.4% yield), which was recrystallized from hexane to give red crystals, mp 101–103 °C. IR: 1660 cm^{-1} . 1H -NMR δ : 1.33 (6H, d, $J=6.7$ Hz, $-CH(CH_3)_2$), 3.25 (1H, m, $J=6.7$ Hz, $-CH(CH_3)_2$), 6.44 (1H, s, olefinic proton), 7.45–8.23 (4H, m, aromatic protons). The IR and 1H -NMR spectra of the quinone were identical with those of compound D.

f) A mixture of compounds F and G (*ca.* 1:1) was isolated from the hexane–chloroform (1:1) fraction as an oil (0.240 g), IR: 3580, 3340 cm^{-1} . HRMS *m/z*: Found: 186.1054 (M^+). Calcd for $C_{13}H_{14}O$: M , 186.1045.

A mixture of compounds F and G (37 mg) was acetylated with acetic anhydride (0.3 ml) in pyridine (0.3 ml) at 65–70 °C for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (10 g), using hexane–chloroform (1:1) as an eluent, to give a mixture of the corresponding monoacetates (**19** and **20**) (34 mg), IR: 1750 cm^{-1} . HRMS *m/z*: Found: 228.1146 (M^+). Calcd for $C_{15}H_{16}O_2$: M , 228.1150.

A mixture of compounds F and G (*ca.* 1:4, 50 mg) was methylated with methyl iodide (0.1 ml) and anhydrous potassium carbonate (1.0 g) in refluxing ethyl methyl ketone (2.0 ml) for 5 h. The mixture was cooled, diluted with ether, and washed with water. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using hexane–chloroform (1:1) as an eluent, to give a mixture of the corresponding monomethyl ethers (**21** and **22**) (*ca.* 1:4, 40 mg). HRMS *m/z*: Found: 200.1182 (M^+). Calcd for $C_{14}H_{16}O$: M , 200.1201. From the 1H -NMR (400 MHz) and its NOE difference spectra (Fig. 1), the structures of the monomethyl ethers, **21** and **22**, were assigned as 4-isopropyl-2-methoxynaphthalene and 5-isopropyl-2-methoxynaphthalene, respectively. Thus, the structures of compounds F and G were conclusively assigned as 4-isopropyl-2-naphthol (**12**) and 5-isopropyl-2-naphthol (**13**), respectively.

g) Compound H was isolated from the hexane–chloroform (7:3) fraction as an oil (0.308 g), $[\alpha]_D^{25} -6.69^\circ$ (C_6H_6 , $c=1.08$) and -4.96° ($CHCl_3$, $c=1.37$). HRMS *m/z*: Found: 214.0988 (M^+). Calcd for $C_{14}H_{14}O_2$: M , 214.0994. It was identified as methyl (–)-2-(1-naphthyl)propanoate (**14**) by comparisons of its spectra (IR and 1H -NMR) with those of a synthetic sample. The enantiomeric ratio^{17,18)} of compound H was $R/S=52:48$.

A mixture of compound H (123 mg) and lithium aluminum hydride (60 mg) in dry ether (4.0 ml) was stirred at room temperature for 1.5 h. The mixture was poured into ice-dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (10 g), using chloroform as an eluent, to give an alcohol (90 mg; 84.1% yield), $[\alpha]_D -0.53^\circ$ (C_6H_6 , $c=3.76$) and -1.22° ($CHCl_3$, $c=3.93$), whose IR and 1H -NMR spectra were identical with those of compound B (8). The enantiomeric ratio^{17,18)} of the alcohol was $R/S=53:47$.

Metabolism of 2-(1-Naphthyl)-2-propanol (7), ($\pm$)-2-(1-Naphthyl)-1-propanol (8), and ($\pm$)-2-(1-Naphthyl)propanoic Acid (14) a) A suspension of 2-(1-naphthyl)-2-propanol (7) (9.000 g) and β -cyclodextrin (27.0 g) in water (150 ml) was administered orally to five female rabbits after 1 d of starvation. After drug administration, food and water were given freely to the rabbits. Urine was collected daily for 2 d under a toluene layer at room temperature, then mixed, centrifuged to remove contaminants, and stored at $0^\circ C$ until analysis. The urine was adjusted to pH 5.0 with phosphate buffer, incubated with β -glucuronidase: arylsulfatase (4.5 ml of *Helix pomatia* enzyme) at $37^\circ C$ for 48 h. The urinary aqueous solution was then adjusted to pH 2–3 with dilute hydrochloric acid and extracted with chloroform. The chloroform extract was separated into neutral (5.193 g), phenolic (0.651 g), and acidic (1.126 g) portions.

The neutral portion (5.193 g) was chromatographed on silica gel (100 g), using chloroform as an eluent, to give recovered 2-(1-naphthyl)-2-propanol (7) (4.368 g), mp $83-85^\circ C$ (from acetone-hexane). Further elution with ether-chloroform (3:97) afforded a diol (0.152 g), $[\alpha]_D -1.90^\circ$ ($CHCl_3$, $c=3.41$), whose IR and 1H -NMR spectra were identical with those of the authentic 2-(1-naphthyl)-1,2-propanediol¹⁶⁾ (9). The enantiomeric ratio¹⁸⁾ of the diol was $R/S=34:66$.

The phenolic and acidic portions were each submitted to silica gel column chromatography, but no naphthalene compound was isolated.

b) ($\pm$)-2-(1-Naphthyl)-1-propanol (8) (5.500 g) emulsified in aqueous Tween 80 solution (0.003%, 90 ml) was administered orally to six female rabbits after 1 d of starvation. After drug administration, food and water were given freely to the rabbits. Urine was collected daily for 2 d under a toluene layer at room temperature and then treated as described in a). The crude product was separated into neutral (1.874 g), phenolic (0.586 g) and acidic (3.518 g) portions.

The neutral portion (1.874 g) was chromatographed on silica gel (220 g), using chloroform as an eluent, to give an alcohol (0.734 g), $[\alpha]_D -6.33^\circ$ (C_6H_6 , $c=3.96$), whose IR and 1H -NMR spectra were identical with those of the starting 2-(1-naphthyl)-1-propanol (8). The enantiomeric ratio¹⁸⁾ of the alcohol (8) was $R/S=89:11$.

The acidic portion (3.518 g) was esterified with an ethereal diazomethane solution at room temperature for 1 h. The crude product was chromatographed on silica gel (200 g), using hexane-chloroform (3:2) as an eluent, to give an ester (1.220 g), $[\alpha]_D +69.05^\circ$ (C_6H_6 , $c=6.39$), whose IR and 1H -NMR spectra were identical with those of authentic methyl 2-(1-naphthyl)propanoate (14). The enantiomeric ratio¹⁸⁾ of the ester was $R/S=28:72$.

The phenolic portion was also submitted to silica gel column chromatography, but no naphthalene compound was isolated.

c) A solution of ($\pm$)-2-(1-naphthyl)propanoic acid (14') (6.368 g) in ethanol (64 ml) was neutralized with aqueous sodium hydroxide using phenolphthalein as an indicator. The solution was evaporated *in vacuo* to give a racemic sodium salt (14'').

The above sodium salt (14'') emulsified in aqueous Tween 80 solution (0.005%, 100 ml) was administered orally to five female rabbits after 1 d of starvation. After drug administration, food and water were given freely to the rabbits. Urine was collected daily for 2 d under a toluene

layer at room temperature and then treated as described in a). The crude metabolite was esterified with an ethereal diazomethane solution at room temperature for 30 min. The crude ester was chromatographed on silica gel (300 g), using hexane-chloroform (3:7) as an eluent, to give an ester (3.820 g), $[\alpha]_D +4.49^\circ$ (C_6H_6 , $c=20.04$), whose IR and 1H -NMR spectra were identical with those of authentic methyl 2-(1-naphthyl)propanoate (14). The enantiomeric ratio¹⁸⁾ of the ester was $R/S=49:51$.

References and Notes

- 1) Fuji Xerox Co. Ltd., Japan. Kokai Tokkyo Koho JP 59106991 (84106991) [*Chem. Abstr.*, **102**, 140949r (1985)].
- 2) Oki Electric Industry Co. Ltd. Carbon Paper Co. Ltd., Japan. Kokai Tokkyo Koho JP 5971372 (8471372) [*Chem. Abstr.*, **101**, 112592e (1984)].
- 3) Kanzaki Paper Mfg. Co. Ltd., Japan. Kokai Tokkyo Koho JP 5979790 (8479790) [*Chem. Abstr.*, **102**, 158134f (1985)].
- 4) Denki Kagaku Kogyo K. K., Japan. Kokai Tokkyo Koho JP 59198190 (84198190) [*Chem. Abstr.*, **102**, 158139m (1985)].
- 5) S. Kojima, K. Maruyama, *Eisei Kagaku*, **25**, 327 (1979).
- 6) S. Kojima, K. Maruyama, T. Babasaki, *Drug Metab. Dispos.*, **8**, 463 (1980).
- 7) S. Kojima, T. Honda, T. Babasaki, M. Kiyozumi, M. Nakagawa, *Eisei Kagaku*, **30**, 91 (1984).
- 8) T. Honda, A. Fukada, M. Kiyozumi, S. Kojima, *Eur. J. Drug Metab. Pharmacol.*, **12**, 11 (1987).
- 9) M. J. Ijam, S. Y. Al-Oatami, S. F. Arif., *Prepr. Am. Chem. Soc. Div. Pet. Chem.*, **35**, 821 (1990) [*Chem. Abstr.*, **114**, 46161d (1991)].
- 10) S. C. Kushwaha, S. G. Clarkson, K. A. Mehkeri, *J. Food Sat.*, **7**, 177 (1985) [*Chem. Abstr.*, **104**, 74182y (1986)].
- 11) Jieying Tu, Daixian Chen, Xiaoping Shu, Mingbao Meng, *Huanjing Huaxue*, **5**, 60 (1986) [*Chem. Abstr.*, **106**, 22946x (1987)].
- 12) T. Matsumoto, N. Hayashi, T. Ishida, Y. Asakawa, *J. Pharm. Sci.*, **79**, 540 (1990).
- 13) T. Matsumoto, T. Ishida, T. Yoshida, H. Terao, Y. Takeda, Y. Asakawa, *Chem. Pharm. Bull.*, **40**, 1721 (1992).
- 14) T. Ishida, T. Matsumoto, *Xenobiotica*, **22**, 1291 (1992).
- 15) T. Matsumoto, T. Ishida, Y. Takeda, J. Yagi, *Biol. Pharm. Bull.*, **17**, 1441 (1994).
- 16) T. Matsumoto, Y. Takeda, E. Iwata, M. Sakamoto, T. Ishida, *Chem. Pharm. Bull.*, **42**, 1191 (1994).
- 17) R. Menicagli, O. Piccolo, L. Lardicci, M. L. Wis, *Tetrahedron*, **35**, 1301 (1979).
- 18) The ratio of enantiomeric isomers was determined by comparisons of the sign and value of specific rotation with those given in the literature.^{16,17)}
- 19) S. Mitsui, S. Imaizumi, *Nippon Kagaku Zasshi*, **86**, 219 (1965).
- 20) T. Matsumoto, S. Imai, N. Yamamoto, *Bull. Chem. Soc. Jpn.*, **61**, 911 (1988).
- 21) In studies on the metabolism of *p*-cymene¹³⁾ and cumene,¹⁴⁾ 2-(*p*-tolyl)propanoic acid ($R/S=0:100$) and 2-phenylpropanoic acid ($R/S=1:99$) were isolated.
- 22) R. F. Newbold, P. Brookes, *Nature* (London), **261**, 52 (1976).
- 23) P. G. Wislocki, A. W. Wood, R. L. Chang, W. Levin, H. Yagi, O. Hernandez, D. M. Jerina, A. H. Conney, *Biochem. Biophys. Res. Commun.*, **68**, 1006 (1976).
- 24) A. W. Wood, P. G. Wislocki, R. L. Chang, W. Levin, A. Y. H. Lu, H. Yagi, O. Hernandez, D. M. Jerina, A. H. Conney, *Cancer Res.*, **36**, 3358 (1976).
- 25) J. E. Rice, N. G. Geddie, E. J. Lavoie, *Chem. Biol. Interact.*, **63**, 227 (1987).
- 26) K. Fujii, K. Nakao, T. Yamauchi, *Synthesis*, **1982**, 456.