The Enantioselective Metabolism of *p*-Cymene in Rabbits

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***p*-Cymene (1) was metabolized in rabbits and the following four optically active metabolites, 2-(*p*-tolyl)-1-propanol (3′: *R*/*S*=65:35), 2-(*p*-tolyl)propanoic acid (5′: *R*/*S*=0:100), *p*-(2-hydroxy-1-methylethyl)benzoic acid (6′: *R*/*S*=91:9) and *p*-(1-carboxyethyl)benzoic acid (8′: *R*/*S*=30:70), were isolated in addition to three optically inactive metabolites, 2-(*p*-tolyl)-2-propanol (2), *p*-isopropylbenzoic acid (4′), and *p*-(1-hydroxy-1-methylethyl)benzoic acid (7′). The presumed metabolic pathways of *p*-cymene in rabbits were confirmed by the administration of the intermediate metabolites (2, 3′, 4′, and 5′). The enantiomeric ratios of the metabolites, 3′ and 6′, suggested that ω-hydroxylations of the isopropyl group in 1 and 4′ occurred preferentially at the *pro-S* methyl group. In the metabolism of 1, the *S*-isomers are predominant in the propanoic acid derivatives, but the *R*-isomers are rich in the propanol derivatives. It is of interest that the metabolism of 4′, however, produced predominantly the corresponding propanol derivative (6′; *R*/*S*=91:9) and propanoic acid derivative (8′; *R*/*S*=80:20) possessing the same *R*-configuration. Some optically active *p*-cymene derivatives were also synthesized as standard compounds.**

Keywords enantioselective metabolism; *p*-cymene; rabbit; 2-(*p*-tolyl)-1-propanol; 2-(*p*-tolyl)propanoic acid; *p*-(2-hydroxy-1-methylethyl)benzoic acid; *p*-(1-carboxyethyl)benzoic acid

Xenobiotics are metabolized in different ways according to their configuration (*R* or *S*), and since different enantiomers of drugs and their metabolites may have quantitatively or qualitatively different physiological actions, studies of enantioselectivity in xenobiotic metabolism can be of considerable practical importance.

p-Cymene (**1**) is a component of the essential oil of many plants, and its metabolism in mammals and in microorganisms has been reported by Southwell *et al.*,[1] Ishida *et al.*,[2] Walde *et al.*,[3] and Madhyastha and Bhattacharyya.[4] Nevertheless, the stereochemistry of the metabolites of *p*-cymene has not been studied. Metabolism of the aromatic isopropyl group was studied in 4-isopropylbiphenyl[5] and 2-isopropylnaphthalene,[6] but again, the stereochemistry was not reported. Recently, the metabolism in rabbits of (+)-dehydroabietic acid, a diterpene possessing an aromatic isopropyl group, was studied by us[7] and the stereochemistry of ten metabolites was elucidated. As an extension of the previous work,[2,7] we report here the regio- and stereo-selective metabolism of *p*-cymene (**1**) in rabbits. This is the first report on enantioselectivity in the metabolism of *p*-cymene in mammals.

Metabolism of *p*-Cymene *p*-Cymene (**1**) (10.00 g) was administered orally to rabbits and the urinary metabolites (after β-glucuronidase: arylsulfatase treatment and extraction with ether) were separated into neutral and acidic portions. The neutral portion was acetylated with acetic anhydride in pyridine and then chromatographed on silica gel to give two compounds, A (0.187 g) and B (0.166 g). The acidic portion was esterified with diazomethane and the product was separated into five compounds, C (0.597 g), D (1.416 g), E (1.066 g), F (0.285 g), and G (1.093 g), by silica gel column chromatography.

Compound A (**2**): The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed three singlet signals at δ 1.56 (6H) due to two tertiary methyl groups, at δ 1.75 (1H) due to a hydroxyl group, and at δ 2.35 (3H) due to an aromatic methyl group, and two doublet signals at δ 7.17 (2H, J=9 Hz) and 7.39 (2H, J=9 Hz) due to aromatic protons. The infrared (IR) spectrum showed hydroxyl bands at 3600 and 3530 cm^{-1}. From these spectral data, the structure of compound A was assigned as 2-(*p*-tolyl)-2-propanol (**2**).

Compound B (**3**): $[\alpha]_D$ +2.0° ($CHCl_3$). The ^{1}H-NMR spectrum showed signals at δ 1.26 (3H, d), 1.99 (3H, s), 2.32 (3H, s), 3.05 (1H, m), 4.12 (2H, d), and 7.09 (4H, s) due to a secondary methyl group, an acetoxyl methyl group, an aromatic methyl group, a methine proton, a methylene group, and aromatic protons, respectively. These spectral data suggested that one of the isopropyl methyl groups in *p*-cymene was replaced by an acetoxyl group. Thus, the structure of compound B was assigned as (+)-2-(*p*-tolyl)-1-propanol acetate (**3**). Treatment of **3** with lithium aluminum hydride in ether afforded a metabolite, (+)-2-(*p*-tolyl)-1-propanol (**3′**), whose optical rotation was $[\alpha]_D$ +5.1° ($CHCl_3$). Therefore, the enantiomeric ratio[8] of **3′** was *R* (**3′a**)/*S*(**3′b**)=65:35.

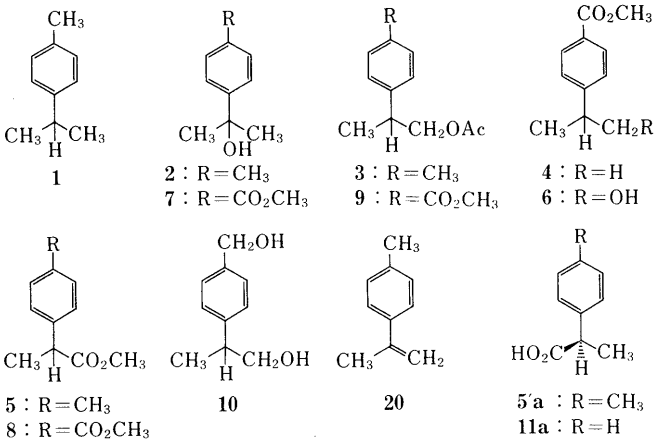
Compound C (**4**): The ^{1}H-NMR spectrum showed the presence of an isopropyl group at δ 1.28 (6H, d) and 2.97 (1H, m), a methoxycarbonyl group at δ 3.91 (3H, s), and four aromatic protons at δ 7.25 and 7.95 (each 2H and d). Thus, the structure of compound C was assigned as methyl *p*-isopropylbenzoate (**4**), and the corresponding *p*-isopropylbenzoic acid (**4′**) was obtained as a metabolite.

Compound D (**5**): $[\alpha]_D$ +82.2° ($CHCl_3$). The ^{1}H-NMR spectrum showed the presence of a secondary methyl group at δ 1.50 (3H, d), an aromatic methyl group at δ 2.33 (3H, s), a methoxycarbonyl group at δ 3.65 (3H, s), and four aromatic protons at δ 7.15 (4H, s). Thus, the structure of compound D was assigned as methyl (+)-2-(*p*-tolyl)-propanoate (**5**) and the corresponding 2-(*p*-tolyl)propanoic acid (**5′**) was obtained as a metabolite. Reduction of **5** with lithium aluminum hydride in ether afforded (−)-2-(*p*-tolyl)-1-propanol (**3′**), whose optical rotation was $[\alpha]_D$ −16.6° ($CHCl_3$). Therefore, the enantiomeric ratio[8] of this propanol derivative (**3′**) was *R*(**3′a**)/*S*(**3′b**)=0:100. This means that the metabolite **5′** was a pure *S*-isomer.

Compound E (**6**): $[\alpha]_D$ +13.6° ($CHCl_3$). The ^{1}H-NMR spectrum showed the presence of a secondary methyl group at δ 1.27 (3H, d), a methine proton at δ 3.00 (1H, m), a methylene group having a hydroxyl group at δ 3.73 (2H, d), a methoxycarbonyl group at δ 3.89 (3H, s), and four aromatic protons at δ 7.29 and 7.97 (each 2H and d). Thus, the structure of compound E was assigned as methyl (+)-*p*-(2-hydroxy-1-methylethyl)benzoate (**6**) and the corresponding *p*-(2-hydroxy-1-methylethyl)benzoic acid (**6′**) was obtained as a metabolite. The enantiomeric ratio[8] of **6** was *R*(**6a**)/*S*(**6b**)=91:9. Acetylation of **6** with acetic anhydride in pyridine afforded a monoacetate (**9**), $[\alpha]_D$ +13.0° ($CHCl_3$).

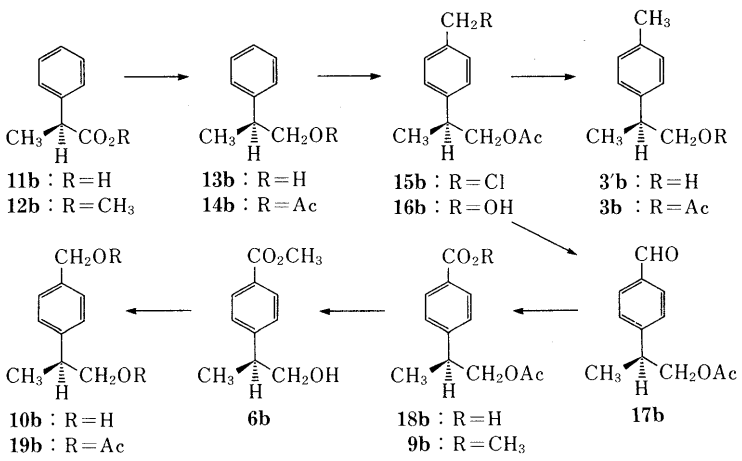
Compound F (**7**): The ^{1}H-NMR spectrum showed the presence of two tertiary methyl groups at δ 1.62 (6H, s), a hydroxyl group at δ 2.15 (1H, br s), a methoxycarbonyl group at δ 3.90 (3H, s), and four aromatic protons at δ 7.51 and 7.98 (each 2H and d). Thus, the structure of compound F was assigned as methyl *p*-(1-hydroxy-1-methylethyl)benzoate (**7**) and the corresponding *p*-(1-hydroxy-1-methylethyl)benzoic acid (**7′**) was obtained as a metabolite.

Compound G (**8**): $[\alpha]_D$ +26.4° ($CHCl_3$). The ^{1}H-NMR spectrum showed the presence of a secondary methyl group at δ 1.51 (3H, d), two methoxycarbonyl groups at δ 3.66 and 3.90 (each 3H and s), a methine proton at δ 3.79 (1H, m), and four aromatic protons at δ 7.37 and 7.99 (each 2H and d). Thus, the structure of compound G was assigned as methyl (+)-*p*-[1-(methoxycarbonyl)ethyl]-benzoate (**8**) and the corresponding *p*-(1-carboxyethyl)-benzoic acid (**8′**) was obtained as a metabolite. The dimethyl ester (**8**) was reduced with lithium aluminum hydride in tetrahydrofuran to give a diol (**10**), whose optical rotation was $[\alpha]_D$ −6.5° ($CHCl_3$). Therefore, the enantiomeric ratio[8] of **10** was *R*(**10a**)/*S*(**10b**)=30:70.



Metabolism of 2-(*p*-Tolyl)-2-propanol (2), (±)-2-(*p*-Tolyl)-1-propanol (3′), *p*-Isopropylbenzoic Acid (4′), and (±)-2-(*p*-Tolyl)propanoic Acid (5′) Each compound was administered orally to rabbits. The crude urinary product was esterified with diazomethane and then purified by column chromatography on silica gel to give the following metabolites. a) 2-(*p*-Tolyl)-2-propanol (**2**) produced the metabolite F (**7**). b) (±)-2-(*p*-Tolyl)-1-propanol (**3′**) produced the metabolites, D (**5**), E (**6**), and G (**8**). c) *p*-Isopropylbenzoic acid (**4′**) produced the metabolites, E (**6**), F (**7**), and G (**8**). d) (±)-2-(*p*-Tolyl)propanoic acid (**5′**) produced the metabolite G (**8**).

Synthesis of Optically Active *p*-Cymene Derivatives Some optically-active *p*-cymene derivatives were synthesized as standard compounds. Esterification of (*S*)-(+)-2-phenylpropanoic acid (**11b**) with diazomethane, followed by reduction of the resulting ester (**12b**) with lithium aluminum hydride in ether afforded (*S*)-(−)-2-phenyl-1-propanol (**13b**), which was converted into an acetate (**14b**) with acetic anhydride in pyridine. Chloromethylation of **14b** with chloromethyl methyl ether and anhydrous aluminum chloride in carbon tetrachloride at 0 °C produced a chloromethyl derivative (**15b**). The ^{1}H-NMR spectrum of **15b** showed a singlet signal at δ 4.48 (2H) due to a chloromethyl group and two doublet signals at δ 7.12 (2H, J=8 Hz) and 7.25 (2H, J=8 Hz) due to *ortho*-coupling aromatic protons. These spectral data suggested the presence of a chloromethyl group at the *para* position in **15b**. Compound **15b** was refluxed with lithium aluminum hydride in dry tetrahydrofuran to give (*S*)-(−)-2-(*p*-tolyl)-1-propanol (**3′b**), which was further converted into the corresponding acetate (**3b**). Treatment of the chloromethyl compound (**15b**) with silver nitrate in aqueous acetone at room temperature afforded a benzyl alcohol derivative (**16b**), which was oxidized with Jones reagent in acetone to give a mixture of aldehyde (**17b**) and acid (**18b**). The acid (**18b**) was esterified with diazomethane and the resulting ester (**9b**) was hydrolyzed with dilute hydrochloric



acid in refluxing methanol to give methyl (*S*)-(−)-*p*-(2-hydroxy-1-methylethyl)benzoate (**6b**). This ester (**6b**) was further converted into a diacetate (**19b**) *via* a diol (**10b**) by lithium aluminum hydride reduction and subsequent acetylation.

Discussion

As the metabolites of *p*-cymene (**1**) in rabbits, four optically active metabolites, 2-(*p*-tolyl)-1-propanol (**3′**), 2-(*p*-tolyl)propanoic acid (**5′**), *p*-(2-hydroxy-1-methylethyl)-benzoic acid (**6′**), and *p*-(1-carboxyethyl)benzoic acid (**8′**), were isolated, in addition to three optically inactive metabolites, 2-(*p*-tolyl)-2-propanol (**2**), *p*-isopropylbenzoic acid (**4′**), and *p*-(1-hydroxy-1-methylethyl)benzoic acid (**7′**). The metabolic pathways of *p*-cymene leading to these metabolites are proposed to be as shown in Chart 1.

Firstly, the enzymatic introduction of molecular oxygen into *p*-cymene might occur by three different metabolic routes (a, b, and c). In route a, the benzylic methine carbon position is first oxidized to give a tertiary alcohol (**2**), whose benzylic methyl carbon position is further oxidized to give *p*-(1-hydroxy-1-methylethyl)benzoic acid (**7′**). In route b, on the contrary, the benzylic methyl carbon position is first oxidized and the resulting *p*-isopropylbenzoic acid (**4′**) is then oxidized at the benzylic methine carbon position to give the metabolite **7′**. The oral administration of these intermediate metabolites **2** and **4′** to rabbits was also carried out separately and the same metabolite **7′** was obtained from both experiments. Thus, the metabolic routes, a and b, were confirmed. In the metabolism of **2**, a small amount of an isopropenyl compound (**20**) was also isolated. However, this compound (**20**) is probably an artifact which might be produced by dehydration of the tertiary hydroxyl group in **2** during the extraction of the crude metabolites under acidic conditions. The metabolic route c involves ω-hydroxylation of an isopropyl group and this oxidation produced a primary alcohol (**3′**), which is further oxidized to the corresponding acid (**5′**). Subsequent oxidations at the benzylic methyl carbon position in the metabolites, **3′** and **5′**, produced the benzoic acid derivatives, **6′** and **8′**, respectively. The metabolite **6′** was also produced from the metabolite **4′** by ω-hydroxylation of an isopropyl group and this was further oxidized to the metabolite **8′**. These metabolic routes were also confirmed by the oral administration of (±)-2-(*p*-tolyl)-1-propanol (**3′**), *p*-isopropylbenzoic acid (**4′**), and (±)-2-(*p*-tolyl)propanoic acid (**5′**) to rabbits. Four metabolites (**3′**, **5′**, **6′**, and **8′**) possessing an asymmetric carbon atom in the molecule showed optical activity. This indicates that the enzymatic oxidation of *p*-cymene in rabbits occurred stereoselectively. It is of interest that the enantiomeric ratio of the metabolite **3′** possessing a primary hydroxyl group was *R*/*S*=65:35, whereas that of the metabolite **5′** possessing a carboxyl group was *R*/*S*=0:100. These enantiomeric ratios suggested that the inversion of chirality occurred during the transformation of the metabolite **3′** to the metabolite **5′**. This can be explained as follows: that is, the *R*-alcohol (**3′**) was first oxidized to the *R*-acid (**5′a**), which was then stereospecifically inverted to the *S*-acid (**5′**). Such inversion has been reported in the metabolism of some anti-inflammatory agents, (*R*)-(−)-ibuprofen in humans,[9] (*R*)-(−)-cicloprofen in rats and monkeys,[10] (*R*)-(−)-benoxaprofen in rats and humans,[11,12] and (*R*)-(−)-2-phenylpropanoic acid (**11a**) in rats.[13] The enantiomeric ratio of the metabolite **6′** was *R*/*S*=91:9, whereas that of the metabolite **8′** was *R*/*S*=30:70. On the other hand, the oral administration of *p*-isopropylbenzoic acid (**4′**), an intermediate metabolite, to rabbits produced two optically active metabolites, **6′** and **8′**: their enantiomeric ratios were respectively *R*/*S*=91:9 and 80:20, suggesting that in the metabolism of **4′** almost no stereochemical inversion occurred during the oxidation of the alcohol **6′** to the acid **8′**. This was in contrast to the oxidation of the alcohol **3′** to the acid **5′**. Therefore, it appears that the metabolite **8′** from *p*-cymene was largely derived from the metabolite **5′**. The enantiomeric ratios of the metabolites, **3′** and **6′**, indicated that ω-hydroxylations of the isopropyl group in *p*-cymene (**1**) and *p*-isopropylbenzoic acid (**4′**) occurred preferentially in the *pro-S* methyl group. It is also confirmed that *p*-cymene does not undergo ring-hydroxylation in rabbits.[2] Enzymatic reactions are generally said to be stereospecific, but the present study has made it clear that the present reactions *in vivo* were relatively stereoselective and not stereospecific. The metabolism of *p*-cymene in rabbits was stereochemically different from that of (+)-dehydroabietic acid in rabbits.[7] It is very interesting that the regio- and stereo-selectivities of aromatic isopropyl group metabolism are dependent on the structure of the original compounds.

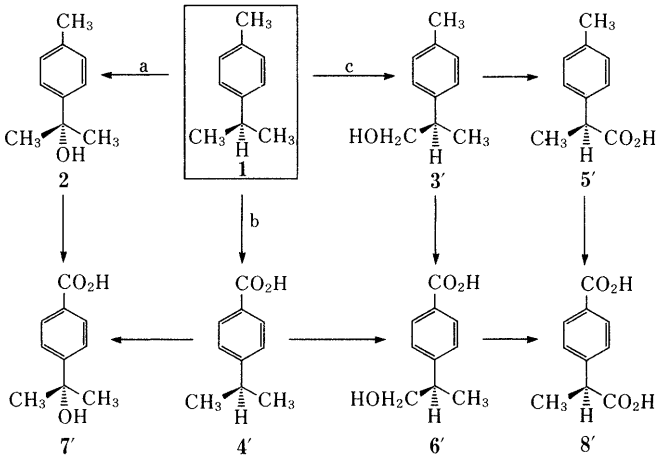


Chart 1. Metabolic Pathways of *p*-Cymene in Rabbits

Experimental

The IR spectra and optical rotations were measured in chloroform, and the ^{1}H-NMR spectra in deuteriochloroform at 90 MHz with tetramethylsilane as an internal standard, unless otherwise stated; s, singlet; br s, broad singlet; d, doublet; dd, double doublet; q, quartet; m, multiplet. The column chromatography was performed using Merck silica gel (0.063 mm).

Materials *p*-Cymene (**1**), *p*-isopropylbenzoic acid (**4′**), methyl *p*-toluate, and *p*-methylpropiophenone were purchased from Tokyo Kasei Co., Japan. 2-(*p*-Tolyl)-2-propanol (**2**), (±)-2-(*p*-tolyl)-1-propanol (**3′**), and (±)-2-(*p*-tolyl)propanoic acid (**5′**) were synthesized as follows.

a) 2-(*p*-Tolyl)-2-propanol (2) A solution of methyl *p*-toluate (6.00 g) in dry ether (20 ml) was added dropwise to a stirred solution of methylmagnesium iodide (prepared from magnesium turnings (2.33 g) and methyl iodide (6.15 ml) in dry ether (35 ml)) under reflux for 30 min. The mixture was further refluxed 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. The crude product was chromatographed on silica gel (30 g), using benzene–ether (97 : 3) as an eluent, to give **2** (5.96 g, 99.3% yield). MS *m/z*: 150 (M^+). IR: 3600, 3530 cm^{-1}. ^{1}H-NMR δ: 1.56 (6H, s, $-C(C\underline{H}_3)_2OH$), 1.75 (1H, s, –OH), 2.35 (3H, s, $-CH_3$), 7.17 and 7.39 (each 2H, d, $J=9$ Hz, aromatic protons).

b) (±)-2-(*p*-Tolyl)-1-propanol (3′) A suspension of **2** (4.095 g) in dilute sulfuric acid (2%, 20 ml) was refluxed for 80 min. The mixture was cooled 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 (80 g), using hexane as an eluent, to give an isopropenyl compound (**20**) (3.474 g, 96.4% yield). ^{1}H-NMR δ: 2.11 (3H, m, $-C(=CH_2)C\underline{H}_3$), 2.32 (3H, s, $-CH_3$), 5.00 (1H, m) and 5.31 (1H, s) ($=CH_2$), 7.11 and 7.35 (each 2H, d, $J=8$ Hz, aromatic protons).

A solution of tetrahydrofuran–borane (1 : 1) addition compound (1 mol dm^{-3}: 20.0 ml) was added to a stirred solution of **20** (4.06 g) in dry tetrahydrofuran (40 ml) at -15 to -10 °C for 20 min under a stream of nitrogen. The mixture was stirred at 0—5 °C for 3 h, and the following compounds were added successively: aqueous tetrahydrofuran (50%, 8.6 ml), aqueous sodium hydroxide (12%, 8.6 ml), and hydrogen peroxide (30%, 8.6 ml) at -15 to -5 °C. The mixture was stirred at -5—0 °C for 30 min and at room temperature for 1 h, then diluted with brine, 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 (100 g), using benzene–ether (95 : 5) as an eluent, to give (±)-**3′** (3.91 g, 84.8% yield). ^{1}H-NMR δ: 1.21 (3H, d, $J=7$ Hz, $-CH(C\underline{H}_3)-$), 1.44 (1H, s, –OH), 2.30 (3H, s, $-CH_3$), 2.87 (1H, m, $J=7$ Hz, $-C\underline{H}(CH_3)-$), 3.63 (2H, d, $J=7$ Hz, $-C\underline{H}_2OH$), 7.10 (4H, s, aromatic protons). *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.68; H, 9.52.

c) (±)-2-(*p*-Tolyl)propanoic Acid (5′) According to the method of Fujii *et al.*,[14] a stirred mixture of *p*-methylpropiophenone (9.91 g), lead tetraacetate (95.5%, 32.7 g), and perchloric acid (70%, 14.4 ml) in trimethyl orthoformate (395 ml) was heated at 50 °C for 2 h. The crude product was chromatographed on silica gel (200 g), using hexane–benzene (1 : 1) as an eluent, to give methyl (±)-2-(*p*-tolyl)propanoate (**5**) (10.94 g, 91.8% yield). ^{1}H-NMR (60 MHz, CCl_4) δ: 1.40 (3H, d, $J=7$ Hz, $-CH(C\underline{H}_3)-$), 2.27 (3H, s, $-CH_3$), 3.50 (1H, m, $J=7$ Hz, $-C\underline{H}(CH_3)-$), 3.55 (3H, s, $-CO_2CH_3$), 6.95 (4H, s, aromatic protons).

A mixture of (±)-**5** (5.52 g) and aqueous sodium hydroxide solution (12%, 20 ml) in methanol (20 ml) was refluxed for 2 h. The crude product was chromatographed on silica gel (30 g, Mallinckrodt CC-4), using benzene and benzene–ether (95 : 5) as eluents, to give an acid (±)-**5′** (4.68 g, 92.1% yield).

A solution of (±)-**5** (5.157 g) in dry ether (65 ml) was reduced with lithium aluminum hydride (829 mg) at room temperature for 1.5 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (70 g), using benzene–ether (97 : 3) as an eluent, to give (±)-2-(*p*-tolyl)-1-propanol (**3′**) (4.238 g, 97.5% yield).

Administration of *p*-Cymene to Rabbits and Extraction of Urinary Metabolites Four rabbits (Japanese White strain, two male and two female rabbits, each 2.5—3.0 kg) were used as experimental animals. *p*-Cymene (10.00 g) suspended in aqueous sodium sorbitate (Tween 80) solution (0.02%, 100 ml) was administered orally at a dose of 2.5 g/rabbit to the four 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 metabolism cage in which urine and feces were separated. Urine was collected daily for 3 d under a toluene layer at room temperature, mixed together (24—72 h), centrifuged to remove contaminants (hairs and feces), and mixed together (24—72 h), centrifuged to remove contaminants (hairs and feces), and stored at 0 °C until analysis. The urine was adjusted to pH 5.0 with phosphate buffer, incubated with β-glucuronidase : arylsulfatase (3 ml of *Helix pomatia* enzyme (Boehringer–Mannheim, West Germany)/1 l of fresh urine) at 37 °C for 48 h, and extracted with ether for 48 h. The ether extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give a neutral portion. The urinary aqueous solution from the above ether extraction was further adjusted to pH 3.0 with dilute hydrochloric acid and extracted with ether for 48 h. The ether extract was washed successively with dilute hydrochloric acid and water, dried over sodium sulfate, and evaporated *in vacuo* to give an acidic portion.

Isolation of Metabolites The neutral portion (816 mg) was chromatographed on a Sephadex column using chloroform–methanol (1 : 1) as an eluent, to give a mixture of alcohols (574 mg). Since the separation of these alcohols was difficult, the mixture was treated with acetic anhydride (3.0 ml) in pyridine (3.0 ml) at room temperature for 20 h. After the usual work-up, the product was chromatographed on silica gel (40 g), using benzene and benzene–ether (97 : 3) as eluents, to give two compounds, A and B.

The acidic portion was esterified with an ethereal diazomethane solution at room temperature for 1 h. The ether solution was washed successively with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue (8.252 g) was purified by repeated column chromatography on silica gel (50—100 times the sample weight in each case), using hexane–benzene (8 : 2, 1 : 1), benzene, and benzene–ether (99 : 1, 97 : 3, 9 : 1, 85 : 15) as eluents to give the following five compounds, C, D, E, F, and G.

a) Compound A was isolated from the benzene–ether (97 : 3) fraction as an oil (187 mg) and identified as 2-(*p*-tolyl)-2-propanol (**2**) by comparison of its spectra (IR and ^{1}H-NMR) with those of the synthetic sample.

b) Compound B was isolated from the benzene fraction as an oil (166 mg), $[\alpha]_D$ +2.0° ($c=9.13$), and identified as 2-(*p*-tolyl)-1-propanol acetate (**3**) by comparison of its spectra (IR and ^{1}H-NMR) with those of the synthetic sample. The enantiomeric ratio[8] of compound B was *R*(**3a**)/*S*(**3b**) = 65 : 35.

A solution of compound B (80.5 mg) in dry ether (3.0 ml) was reduced with lithium aluminum hydride (30.0 mg) at room temperature for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (15 g), using benzene–ether (85 : 15) as an eluent, to give an alcohol (58.6 mg), $[\alpha]_D$ +5.1° ($c=2.43$). The IR and ^{1}H-NMR spectra of the alcohol were identical with those of the synthetic 2-(*p*-tolyl)-1-propanol (**3′**). The enantiomeric ratio[8] of the alcohol (**3′**) was *R*(**3′a**)/*S*(**3′b**) = 65 : 35.

c) Compound C was isolated from the hexane–benzene (1 : 1) fraction as an oil (597 mg), MS *m/z*: 178 (M^+), IR: 1715 cm^{-1}, and identified as methyl *p*-isopropylbenzoate (**4**) by comparison of its spectra (IR and ^{1}H-NMR) with those of the authentic sample.

d) Compound D was isolated from the hexane–benzene (1 : 1) fraction as an oil (1.416 g), MS *m/z*: 178 (M^+), $[\alpha]_D$ +82.2° ($c=4.99$), IR: 1730 cm^{-1}, and identified as methyl 2-(*p*-tolyl)propanoate (**5**) by comparison of its spectra (IR and ^{1}H-NMR) with those of the synthetic sample. *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.36; H, 7.80.

A solution of compound D (154.0 mg) in dry ether (3.0 ml) was reduced with lithium aluminum hydride (33.0 mg) at room temperature for 1.5 h. The crude product was purified by column chromatography on silica gel (10 g), using benzene–ether (9 : 1) as an eluent, to give an alcohol (119.7 mg), $[\alpha]_D$ −16.6° ($c=3.09$). The IR and ^{1}H-NMR spectra of the alcohol were identical with those of the synthetic 2-(*p*-tolyl)-1-propanol (**3′**). The enantiomeric ratio[8] of the alcohol (**3′**) was *R*(**3′a**)/*S*(**3′b**) = 0 : 100.

e) Compound E was isolated from the benzene–ether (85 : 15) fraction as an oil (1.066 g). MS *m/z*: 194 (M^+). $[\alpha]_D$ +13.6° ($c=6.05$). IR: 3600, 3450, 1715 cm^{-1}. The IR and ^{1}H-NMR spectra of compound E were identical with those of the synthetic methyl *p*-(2-hydroxy-1-methylethyl)benzoate (**6**). The enantiomeric ratio[8] of compound E was *R*(**6a**)/*S*(**6b**) = 91 : 9.

A solution of compound E (110.0 mg) and acetic anhydride (0.5 ml) in pyridine (0.5 ml) was heated at 70—80 °C for 1 h. After the usual work-up, the crude product was chromatographed on silica gel (12 g), using benzene–ether (97 : 3) as an eluent, to give a monoacetate (114.2 mg), $[\alpha]_D$ +13.0° ($c=5.62$). IR 1725 cm^{-1}. The IR and ^{1}H-NMR spectra of the acetate were identical with those of the synthetic methyl *p*-(2-acetoxy-1-methylethyl)benzoate (**9b**). The enantiomeric ratio[8] of the acetate was *R*(**9a**)/*S*(**9b**) = 91 : 9.

f) Compound F was isolated from the benzene–ether (85 : 15) fraction as an oil (285 mg). MS *m/z*: 194 (M^+). IR: 3580, 3450, 1715 cm^{-1}. ^{1}H-NMR δ: 1.62 (6H, s, $-C(C\underline{H}_3)_2-$), 2.15 (1H, br s, –OH), 3.90 (3H, s, $-CO_2CH_3$), 7.51 and 7.98 (each 2H, d, $J=9$ Hz, aromatic protons). From these spectral data, the structure of compound F was assigned as methyl *p*-(1-hydroxy-1-methylethyl)benzoate (**7**). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.30; H, 7.39.

g) Compound G was isolated from the benzene fraction as an oil (1.093 g). MS *m/z*: 222 (M^+). $[\alpha]_D$ +26.4° ($c=4.54$). IR: 1725 cm^{-1}. ^{1}H-NMR δ: 1.51 (3H, d, $J=7$ Hz, $-CH(C\underline{H}_3)-$), 3.66 and 3.90 (each 3H, s, 2-CO_2CH_3), 3.79 (1H, q, $J=7$ Hz, $-C\underline{H}(CH_3)-$), 7.37 and 7.99 (each 2H, d, $J=9$ Hz, aromatic protons). From these spectral data, the structure of compound G was assigned as methyl *p*-[1-(methoxycarbonyl)ethyl]-benzoate (**8**). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.60; H, 6.48.

A solution of compound G (155.0 mg) in dry tetrahydrofuran (4.5 ml) was reduced with lithium aluminum hydride (45.0 mg) at room temperature for 1.5 h. After the usual work-up, the crude product was chromatographed on silica gel (10 g), using benzene–ether (6 : 4) as an eluent, to give a diol

(109.0 mg), $[\alpha]_D$ −6.5° (c=2.34). IR: 3610, 3420 cm^{-1}. The IR and ^{1}H-NMR spectra of the diol were identical with those of the synthetic (*S*)-(−)-2-[*p*-(hydroxymethyl)phenyl]-1-propanol (**10b**). The enantiomeric ratio[8] of the diol was *R*(**10a**)/*S*(**10b**)=30:70.

Metabolism of 2-(*p*-Tolyl)-2-propanol (2), (±)-2-(*p*-Tolyl)-1-propanol (3′), *p*-Isopropylbenzoic Acid (4′), and (±)-2-(*p*-Tolyl)propanoic Acid (5′) a) 2-(*p*-Tolyl)-2-propanol (**2**) (3.600 g) suspended in aqueous sodium sorbitate (Tween 80) solution was administered orally to two rabbits after 1 d of starvation. Urine was collected for 2 d, adjusted to pH 5.0, and enzymatically degraded at 37 °C for 48 h. The mixture was acidified to pH 2.0 and extracted with ether. The ether extract was washed successively with dilute hydrochloric acid and brine, esterified with an ethereal diazomethane solution, and evaporated *in vacuo*. The residue was chromatographed on silica gel (150 g), using benzene as an eluent, to give *p*-isopropenyltoluene (**20**) (210 mg), whose spectra (IR and ^{1}H-NMR) were identical with those of the synthetic sample. Further elution with benzene–ether (97:3 and then 9:1) afforded recovered **2** (289 mg) and methyl *p*-(1-hydroxy-1-methylethyl)benzoate (compound F, 1.702 g) (**7**).

b) (±)-2-(*p*-Tolyl)-1-propanol (**3′**) (3.500 g) suspended in aqueous sodium sorbitate (Tween 80) solution was administered orally to two rabbits after 1 d of starvation. After work-up as described in a), the crude product was esterified with diazomethane and purified by repeated column chromatography on silica gel, using benzene as an eluent, to give methyl 2-(*p*-tolyl)propanoate (compound D, 783 mg) (**5**), $[\alpha]_D$ +72.7° (c=2.25), *R*/*S*=6:94, and methyl *p*-[1-(methoxycarbonyl)ethyl]benzoate (compound G, 470 mg) (**8**), $[\alpha]_D$ +35.7° (c=5.33). Elution with benzene–ether (99:1 and 97:3) afforded recovered **3′** (529 mg), $[\alpha]_D$ +10.6° (c=3.29), *R*(**3′a**)/*S*(**3′b**)=82:18. Further elution with benzene–ether (95:5 and 9:1) afforded methyl *p*-(2-hydroxy-1-methylethyl)benzoate (compound E, 146 mg) (**6**). Each of compounds **5** and **8** was reduced with lithium aluminum hydride at room temperature for 1.5 h to give an alcohol (**3′**), $[\alpha]_D$ −13.5° (c=3.10), *R*(**3′a**)/*S*(**3′b**)=9:91, and a diol (**10**), $[\alpha]_D$ −9.11° (c=1.57), *R*(**10a**)/*S*(**10b**)=22:78, respectively.

c) Sodium salt of *p*-isopropylbenzoic acid (**4′**) (10.00 g) was dissolved in water (100 ml) and administered orally to four rabbits after 1 d of starvation. After work-up as described in a), the esterified product was purified by repeated column chromatography on silica gel, using benzene as an eluent, to give methyl *p*-isopropylbenzoate (**4**) (866 mg) and methyl *p*-[1-(methoxycarbonyl)ethyl]benzoate (compound G, 512 mg) (**8**), $[\alpha]_D$ −36.5° (c=6.04). Further elution with benzene–ether (9:1) afforded methyl *p*-(1-hydroxy-1-methylethyl)benzoate (compound F, 782 mg) (**7**) and methyl *p*-(2-hydroxy-1-methylethyl)benzoate (compound E, 3.140 g) (**6**), $[\alpha]_D$ +13.7° (c=10.60), *R*(**6a**)/*S*(**6b**)=91:9.

A solution of compound G (**8**) (111.1 mg) in dry tetrahydrofuran (4.0 ml) was reduced with lithium aluminum hydride (38.0 mg) at room temperature for 1.5 h. After the usual work-up, the crude product was chromatographed on silica gel (10 g), using benzene–ether (6:4) as an eluent, to give a diol (**10**) (36.8 mg), $[\alpha]_D$ +9.6° (c=1.53), *R*(**10a**)/*S*(**10b**)=80:20.

d) The sodium salt of (±)-2-(*p*-tolyl)propanoic acid (**5′**) (4.584 g) was dissolved in water (40 ml) and administered orally to two rabbits after 1 d of starvation. After work-up as described in a), the crude product was esterified with an ethereal diazomethane solution and purified by column chromatography on silica gel, using chloroform as an eluent, to give methyl 2-(*p*-tolyl)propanoate (**5**) (2.029 g), $[\alpha]_D$ +38.1° (c=2.56), *R*/*S*=27:73, and methyl *p*-[1-(methoxycarbonyl)ethyl]benzoate (compound G, 1.265 g) (**8**), $[\alpha]_D$ +10.3° (c=2.91).

A solution of **5** (1.051 g) in dry ether (20 ml) was reduced with lithium aluminum hydride (168 mg) at room temperature for 1.5 h. The crude product was chromatographed on silica gel (15 g), using chloroform as an eluent, to give 2-(*p*-tolyl)-1-propanol (**3′**) (634 mg), $[\alpha]_D$ −7.97° (c=4.01), *R*(**3′a**)/*S*(**3′b**)=26:74.

A solution of **8** (470 mg) in dry tetrahydrofuran (15 ml) was reduced with lithium aluminum hydride (104 mg) at room temperature for 1.5 h. The crude product was chromatographed on silica gel (15 g), using chloroform–ether (7:3) as an eluent, to give a diol (**10**) (316 mg), $[\alpha]_D$ −2.87° (c=3.63), *R*(**10a**)/*S*(**10b**)=41:59.

Synthesis of Optically Active *p*-Cymene Derivatives. (*S*)-(−)-2-Phenyl-1-propanol (13b) and Its Acetate (14b) A solution of (*S*)-(+)-2-phenylpropanoic acid (Aldrich, $[\alpha]_D$ +76.6° ($CHCl_3$)) (**11b**) (500 mg) in ether (10 ml) was esterified with an ethereal diazomethane solution at room temperature for 30 min to give a methyl ester (**12b**) (490 mg), $[\alpha]_D$ +80.9° (c=4.70). IR: 1730 cm^{-1}. ^{1}H-NMR (60 MHz, CCl_4) δ: 1.46 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 3.43—3.79 (1H, m, –C<u>H</u>(CH$_3$)–), 3.62 (3H, s, –CO_2CH_3), 7.25 (5H, s, aromatic protons).

A solution of **12b** (490 mg) in dry ether (10 ml) was treated with lithium aluminum hydride (90 mg) at room temperature for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (10 g), using benzene–ether (92:8) as an eluent, to give **13b** (383 mg, 94.2% yield), $[\alpha]_D$ −13.6° (c=8.12). IR: 3600, 3430 cm^{-1}. ^{1}H-NMR δ: 1.21 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 2.14 (1H, br s, –OH), 2.81 (1H, m, J=7 Hz, –C<u>H</u>(CH$_3$)–), 3.47 (2H, d, J=7 Hz, –C<u>H</u>$_2$OH), 7.13 (5H, s, aromatic protons).

A solution of **13b** (382.6 mg) and acetic anhydride (2.0 ml) in pyridine (2.0 ml) was heated at 70—80 °C for 1.5 h. After the usual work-up, the crude product was chromatographed on silica gel (10 g), using hexane–chloroform (6:4) as an eluent, to give an acetate (**14b**) (442.6 mg, 88.4% yield), $[\alpha]_D$ −2.8° (c=10.09). IR: 1730 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.28 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 1.92 (3H, s, –$OCOCH_3$), 3.04 (1H, m, –C<u>H</u>(CH$_3$)–), 4.01 and 4.15 (each 1H, dd, J=10, 7 Hz, –C<u>H</u>$_2$OAc), 7.18 (5H, s, aromatic protons). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.29; H, 7.75.

(*S*)-(−)-*p*-(2-Acetoxy-1-methylethyl)benzyl Chloride (15b) Anhydrous aluminum chloride (161 mg) was added to a stirred solution of **14b** (108.0 mg) and chloromethyl methyl ether (0.09 ml) in carbon tetrachloride (1.0 ml) at 0—5 °C and the mixture was stirred at this temperature for 30 min. The reaction mixture was diluted with ether, 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*. The crude product was chromatographed on silica gel (15 g), using hexane–chloroform (6:4) as an eluent, to give a chloromethyl compound (**15b**) (91.2 mg, 66.4% yield), $[\alpha]_D$ −10.9° (c=5.49). IR: 1730 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.25 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 1.91 (3H, s, –$OCOCH_3$), 3.03 (1H, m, –C<u>H</u>(CH$_3$)–), 3.98 and 4.14 (each 1H, dd, J=10, 7 Hz, –C<u>H</u>$_2$OAc), 4.48 (2H, s, –CH_2Cl), 7.12 and 7.25 (each 2H, d, J=8 Hz, aromatic protons).

(*S*)-(−)-2-(*p*-Tolyl)-1-propanol (3′b) and Its Acetate (3b) Lithium aluminum hydride (17 mg) was added to a stirred solution of **15b** (50.0 mg) in dry tetrahydrofuran (1.5 ml) with cooling in a water-bath. The mixture was refluxed for 3 h, poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel (5 g), using benzene–ether (85:15) as an eluent, to give an alcohol (**3′b**) (32.6 mg, 98.4% yield), $[\alpha]_D$ −16.6° (c=1.51). IR: 3590, 3440 cm^{-1}. ^{1}H-NMR δ: 1.24 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 1.36 (1H, br s, –OH), 2.31 (3H, s, –CH_3), 2.89 (1H, m, J=7 Hz, –C<u>H</u>(CH$_3$)–), 3.65 (2H, d, J=7 Hz, –C<u>H</u>$_2$OH), 7.10 (4H, s, aromatic protons). *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.70; H, 9.55.

A solution of **3′b** (22.6 mg) and acetic anhydride (0.3 ml) in pyridine (0.3 ml) was heated at 70—80 °C for 1 h. After the usual work-up, the crude product was chromatographed on silica gel (5 g), using benzene as an eluent, to give an acetate (**3b**) (19.5 mg, 67.4% yield), $[\alpha]_D$ −6.5° (c=0.93). IR: 1725 cm^{-1}. ^{1}H-NMR δ: 1.26 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 1.99 (3H, s, –$OCOCH_3$), 2.31 (3H, s, –CH_3), 3.05 (1H, m, J=7 Hz, –C<u>H</u>(CH$_3$)–), 4.12 (2H, d, J=7 Hz, –C<u>H</u>$_2$OAc), 7.08 (4H, s, aromatic protons). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.78; H, 8.25.

(*S*)-(−)-*p*-(2-Acetoxy-1-methylethyl)benzyl Alcohol (16b) A mixture of **15b** (136.4 mg) and silver nitrate (277 mg) in aqueous acetone (50%, 10 ml) was stirred at room temperature for 3 h, diluted with ether, and then filtered. The filtrate was washed with water, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel (7 g), using hexane–benzene (3:7) as an eluent, to give the recovered **15b** (57.2 mg). Further elution with benzene–ether (85:15) afforded an alcohol (**16b**) (66.8 mg, 53.3% yield), $[\alpha]_D$ −9.6° (c=3.11). IR: 3610, 3450, 1730 cm^{-1}. ^{1}H-NMR δ: 1.26 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 1.96 (3H, s, –$OCOCH_3$), 2.27 (1H, s, –OH), 3.07 (1H, m, J=7 Hz, –C<u>H</u>(CH$_3$)–), 4.13 (2H, d, J=7 Hz, –C<u>H</u>$_2$OAc), 4.62 (2H, s, –C<u>H</u>$_2$OH), 7.15 and 7.29 (each 2H, d, J=8 Hz, aromatic protons). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.50; H, 7.63.

Oxidation of 16b with Jones Reagent A solution of **16b** (82.5 mg) in acetone (3.0 ml) was oxidized with Jones reagent (1 mol dm^{-3}, 0.45 ml) at room temperature for 2 h. The mixture was diluted with ether, washed successively with brine, aqueous sodium hydrogencarbonate solution, and brine. The dried solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (5 g), using benzene–ether (85:15) as an eluent, to give an aldehyde (**17b**) (9.2 mg, 11.3% yield), $[\alpha]_D$ −21.6° (c=1.23). IR: 2740, 1735, 1702 cm^{-1}. ^{1}H-NMR δ: 1.32 (3H, d, J=7 Hz, –CH(C<u>H</u>$_3$)–), 1.99 (3H, s, –$OCOCH_3$), 3.18 (1H, m, J=7 Hz, –C<u>H</u>(CH$_3$)–), 4.20 (2H, d, J=7 Hz, –C<u>H</u>$_2$OAc), 7.38 and 7.84 (each 2H, d, J=8 Hz, aromatic protons), 10.18 (1H, s, –CHO).

The above alkaline washing was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel (8 g, Mallinckrodt CC-4), using benzene–ether (9 : 1) as an eluent, to give an acid (**18b**) (61.1 mg, 69.4% yield), $[\alpha]_D$ −17.1° (c=2.26). IR: 3600—2400, 1728, 1692 cm^{-1}. ^{1}H-NMR δ: 1.31 (3H, d, J=7 Hz, –CH(C$\underline{H}_3$)–), 2.00 (3H, s, –OCOCH_3), 3.19 (1H, m, J=7 Hz, –C$\underline{H}$(CH$_3$)–), 4.20 (2H, d, J=7 Hz, –C$\underline{H}_2$OAc), 7.34 and 8.06 (each 2H, d, J=8 Hz, aromatic protons), 9.89 (1H, br s, –CO_2H). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.64; H, 6.61.

The aldehyde **17b** (24 mg) in acetone (1.0 ml) was also oxidized with Jones reagent (2.5 mol dm^{-3}, 0.1 ml) at room temperature for 2 h to give an acid (**18b**) (21 mg, 81.2% yield).

Methyl (*S*)-(−)-*p*-(2-Hydroxy-1-methylethyl)benzoate (6b) and Its Acetate (9b) A solution of the acid **18b** (41.0 mg) in ether (5.0 ml) was treated with an ethereal diazomethane solution at room temperature for 30 min and the crude product was chromatographed on silica gel (6 g), using benzene–ether (9 : 1) as an eluent, to give an ester (**9b**) (40.7 mg, 93.4% yield), $[\alpha]_D$ −15.9° (c=1.96). IR: 1725 cm^{-1}. ^{1}H-NMR δ: 1.29 (3H, d, J=7 Hz, –CH(C$\underline{H}_3$)–), 1.98 (3H, s, –OCOCH_3), 3.16 (1H, m, J=7 Hz, –C$\underline{H}$(CH$_3$)–), 3.89 (3H, s, –CO_2CH_3), 4.18 (2H, d, J=7 Hz, –C$\underline{H}_2$OAc), 7.28 and 7.98 (each 2H, d, J=9 Hz, aromatic protons). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.29; H, 6.70.

A solution of **9b** (51.3 mg) and dilute hydrochloric acid (15%, 0.2 ml) in methanol (2.0 ml) was refluxed for 1 h. After cooling, the solution was diluted with ether, washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel (6 g), using benzene–ether (85 : 15) as an eluent, to give an alcohol (**6b**) (39.8 mg, 94.3% yield), $[\alpha]_D$ −16.7° (c=1.38). IR: 3600, 3465, 1720 cm^{-1}. ^{1}H-NMR δ: 1.27 (3H, d, J=7 Hz, –CH(C$\underline{H}_3$)–), 1.89 (1H, s, –OH), 2.97 (1H, m, J=7 Hz, –C$\underline{H}$(CH$_3$)–), 3.70 (2H, d, J=7 Hz, –C$\underline{H}_2$OH), 3.89 (3H, s, –CO_2CH_3), 7.29 and 7.97 (each 2H, d, J=8 Hz, aromatic protons). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.31; H, 7.53.

2-[*p*-(Hydroxymethyl)phenyl]-1-propanol (10b) and Its Diacetate (19b) A solution of the alcohol (**6b**) (28.0 mg) in dry tetrahydrofuran (2.0 ml) was reduced with lithium aluminum hydride (11 mg) at room temperature for 1.5 h. The crude product was chromatographed on silica gel (6 g), using benzene–ether (4 : 6) as an eluent, to give a diol (**10b**) (23.2 mg, 96.8% yield), $[\alpha]_D$ −16.1° (c=1.15). IR: 3610, 3420 cm^{-1}. ^{1}H-NMR δ: 1.22 (3H, d, J=7 Hz, –CH(C$\underline{H}_3$)–), 2.05 (2H, br s, 2-OH), 2.90 (1H, m, J=7 Hz, –C$\underline{H}$(CH$_3$)–), 3.62 (2H, d, J=7 Hz, –C$\underline{H}_2$OH), 4.58 (2H, s, –C$\underline{H}_2$OH), 7.16 and 7.28 (each 2H, d, J=8 Hz, aromatic protons). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.11; H, 8.34.

A solution of **10b** (23.2 mg) and acetic anhydride (0.5 ml) in pyridine (0.5 ml) was heated at 70—80 °C for 1 h. The crude product was chromatographed on silica gel (7 g), using benzene–ether (9 : 1) as an eluent, to give a diacetate (**19b**) (30.6 mg, 87.6% yield), $[\alpha]_D$ −9.9° (c=1.37). IR: 1735, 1725 cm^{-1}. ^{1}H-NMR δ: 1.28 (3H, d, J=7 Hz, –CH(C$\underline{H}_3$)–), 1.99 and 2.07 (each 3H, s, 2-OCOCH_3), 3.09 (1H, m, J=7 Hz, –C$\underline{H}$(CH$_3$)–), 4.12 (2H, d, J=7 Hz, –C$\underline{H}_2$OAc), 5.03 (2H, s, –C$\underline{H}_2$OAc), 7.18 and 7.30 (each 2H, d, J=8 Hz, aromatic protons). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.36; H, 7.12.

A solution of **16b** (8.2 mg) and acetic anhydride (0.2 ml) in pyridine (0.2 ml) was heated at 70—80 °C for 1 h to give a diacetate (**19b**) (9.3 mg, 94.4% yield).

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