Stereoselective Synthesis and Thromboxane A_2 (TXA_2) Receptor Antagonistic Activity of Optically Active Phenol Derivatives

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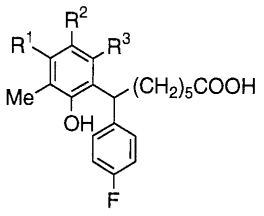
Enantiomers of four potent nonprostanoid thromboxane A_2 (TXA_2) receptor antagonists, (±)-7-(4-fluorophenyl)-7-(2-hydroxyphenyl)heptanoic acids (1—4), were synthesized stereoselectively by direct *ortho*-alkylation of phenols under modified Mitsunobu conditions. The reaction of 5 eq of phenols (6a—c) with 1 eq of (*S*)- or (*R*)-methyl 7-(4-fluorophenyl)-7-hydroxyheptanoate ((*S*)- or (*R*)-7) afforded ortho-alkylated phenol derivatives (6a—c) enantioselectively in 33 to 42% chemical yield and 90 to 93% ee. In these compounds, the (*R*)-enantiomers (1—4) exhibited potent TXA_2 receptor antagonistic activity and the (*S*)-isomer (3) was much less active. In particular, compound (*R*)-3 strongly inhibited U-46619-induced human platelet aggregation (IC_{50} = 48 nM), and also showed a very potent inhibitory effect with a minimum effective dose (MED) of 0.3 mg/kg (*p.o.*) on U-46619-induced bronchoconstriction in guinea pigs.

Key words *ortho*-substituted phenol; TXA_2 receptor antagonist; enantioselective synthesis; Mitsunobu reaction

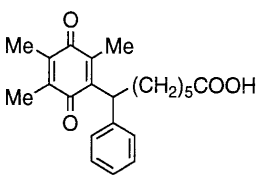
Thromboxane A_2[1] (TXA_2), an unstable metabolite of arachidonic acid, is a potent inducer of platelet aggregation,[2] and vascular and pulmonary smooth muscle contraction.[3] Consequently, TXA_2 may be involved in a variety of cardiovascular and respiratory diseases,[4] and a number of TXA_2 receptor antagonists[5] have been developed for the treatment of these diseases. In our continuing synthetic and pharmacological investigations of nonprostanoid compounds, we have already reported novel phenol derivatives, (±)-7-(4-fluorophenyl)-7-(2-hydroxyphenyl)heptanoic acids (for example, **1**—**4**), which exhibited potent TXA_2 receptor antagonistic activity.[6] These compounds were designed on the basis of considering the structures of TXA_2 and the hydroquinone form of (±)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid (**5**, AA-2414),[7] which is awaiting approval for clinical use in Japan (Fig. 1). In our previous paper, we demonstrated that phenol derivatives with a carbonyl or hydroxymethyl group at the 4-position of the phenol ring are orally active nonprostanoid TXA_2 receptor antagonists which possess potent activities in various species and tissues, and that the carbonyl or hydroxymethyl oxygen might interact with one of the TXA_2 receptor sites. Such an interaction between the TXA_2 receptor site and the carbonyl or hydroxymethyl oxygen of phenol derivatives was supported by the results of an investigation of the receptor–ligand interaction by use of molecular modeling of human TXA_2 receptor.[8]

Compounds (**1**—**4**) are racemates which possess one asymmetric carbon at the 7-position of the heptanoic acids. To determine the differences between the interaction of the receptor with the two enantiomers of phenol derivatives, we investigated the stereoselective synthesis of these phenol derivatives which have a diarylmethane moiety. Preparation of compounds having two bulky groups adjacent to the asymmetric carbon was greatly restricted because of their large steric hindrance. These compounds were prepared by the acid-catalyzed Friedel–Crafts type alkylation of hydroquinones or phenols with α-substituted benzyl alcohols, which are less affected by steric hindrance.[6,7] In general, it is difficult to control the stereochemistry in the Friedel–Crafts reaction. A few examples of stereoselective Friedel–Crafts alkylation have been reported, but these were limited to aliphatic substrates, and the regioselectivity was low.[9] In exploratory studies for stereoselective introduction of a carbon chain to the phenol nucleus, we found that *ortho*-substituted phenol derivatives (III) with high optical activity could be obtained directly by means of the Mitsunobu reaction between an appropriate phenol(I) and an optically active benzyl alcohol (II) (Chart 1).[10] In this reaction, the use of excess phenol stimulated the formation of the *ortho*-substituted compound, and the chemical yield was well balanced with the optical purity when 5 eq of phenol was reacted with 1 eq of alcohol in a solvent such as dichloroethane or toluene. In addition, the establishment of the absolute configuration at the asymmetric carbon by X-ray crystallographic analysis of the brominated product confirmed that stereochemical inversion of the asymmetric center took place in this reaction as well as the usual Mitsunobu reaction.

Herein, we report the synthesis of optically active 7-(4-fluorophenyl)-7-(2-hydroxyphenyl)heptanoic acids



	R^1	R^2	R^3
1;	Me	CHO	Me
2;	Me	Ac	Me
3;	Me	-CO(CH2)2-	
4;	-(CH2)3-		Me



5; AA-2414

Fig. 1

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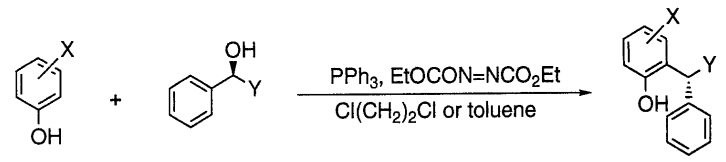

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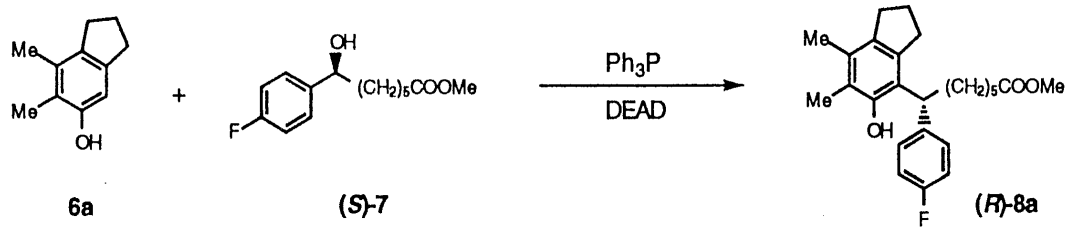
Chart 1

Table 1. Direct *ortho*-Alkylation of Indanol (**6a**) with (*S*)-**7**[a]



6a (*S*)-**7** (*R*)-**8a**

Entry	Amount of **6a** [**6a**]/[(*S*)-**7**]	Solvent	Temperature (°C)	Yield of **8a** (%)	ee of **8a**[b] (% ee)
1	1	$Cl(CH_2)_2Cl$	10	19	95
2	3	$Cl(CH_2)_2Cl$	10	34	94
3	5	$Cl(CH_2)_2Cl$	10	38	93
4	5	$Cl(CH_2)_2Cl$	25	36	91
5	3	Toluene	10	28	97
6	5	Toluene	10	28	97

a) Enantiomeric excess of (*S*)-**7** was 98% ee. *b*) Enantiomeric excess was determined by HPLC with Chiralcel OD.

(**1**—**4**) by the direct *ortho*-alkylation of phenols with optically active benzyl alcohols under the Mitsunobu conditions, and discuss the TXA_2 receptor antagonistic activity of these compounds.

Chemistry

To apply the results of a model reaction[10] using 2,3,5-trimethylphenol (**6b**) and (*R*)-1-phenylbutanol to benzyl alcohol ((*S*)- or (*R*)-**7**) having a long side chain with an ester group, conditions were examined for the reaction of indanol (**6a**) and alcohol ((*S*)-**7**) (Table 1). The results were similar to those obtained in the reaction of phenol (**6b**) and (*R*)-phenylbutanol. That is, 1) use of excess phenol favored the production of *ortho*-alkylated phenol in dichloroethane (entries 1—3). Compound **8a** was obtained in 19% or 38% yield when 1 eq or 5 eq of **6a** was reacted respectively, whereas no difference was observed in toluene. 2) Both chemical yield and enantiomeric excess were higher at 10 °C than at 25 °C (entries 3, 4). 3) The enantiomeric excess (97% ee) of *ortho*-alkylated phenol was higher in toluene than in dichloroethane, but the chemical yield (28%) was lower in toluene (entry 3, 6). In the reaction of (*R*)-1-phenylbutanol, chemical yield (40%) and optical purity (99% ee) were higher than those (37%, 94% ee) obtained in dichloroethane. The differences might have been due to the interaction of the methoxycarbonyl group of **7** with phosphonium ion or phenoxide anion in toluene. Considering these results, the following reaction conditions were employed for the synthesis of phenol derivatives which possess potent TXA_2 antagonistic activity; 5 eq of phenol (**6a**—**c**) was reacted with optically active benzyl alcohol ((*S*)- or (*R*)-**7**) in dichloroethane at 10 °C.

The optically active benzyl alcohols ((*S*)- or (*R*)-**7**) were prepared by enantioselective borane reduction of methyl 7-(4-fluorophenyl)-7-oxoheptanoate by oxazaborolidines.[11] Enantiomeric excesses of (*S*)- and (*R*)-**7** were 98 and 96%ee, respectively (Chart 2).

The results of the Mitsunobu reaction carried out under the conditions described above are shown in Table 2. Each of the phenol derivatives (**8a**—**c**) was obtained in a yield of 33 to 42% and the enantiomeric excesses were 90 to 93% ee. The enantiomeric excesses of (*R*)-**8a**, (*S*)-**8a** and (*R*)-**8b** were raised to 98 to >99% ee by further purification. The optical rotation properties of these compounds are also shown in Table 2.

The target phenol derivatives, which have potent TXA_2 antagonistic activity, were synthesized from compounds **8a**—**c** (Charts 3—5). Formylation of (*R*)-**8b** with Cl_2CHOCH_3–$TiCl_4$[12] in dichloromethane at −10 to −12 °C gave the 4-formylphenol (**9**) in a yield of 75%, and subsequent hydrolysis in THF–1 N NaOH produced (*R*)-**1** in 93% yield.

The reaction of the protected compound (**10**) with MeMgBr gave the alcohol (**11**) in 94% yield as a mixture of diastereomers. Pyridinium chlorochromate (PCC) oxidation of **11** and subsequent deprotection of **12** with BBr_3 provided **2** in good yield.

The indanone derivative ((*R*)-**3**) was prepared by oxidation of indane ((*R*)-**8a**) and subsequent hydrolysis of (*R*)-**13**. Oxidation of **8a** with PCC[13] occurred to the greatest extent in toluene at 0 °C among the conditions

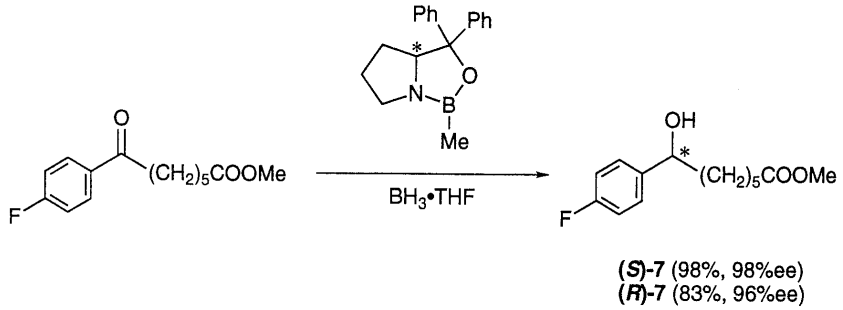
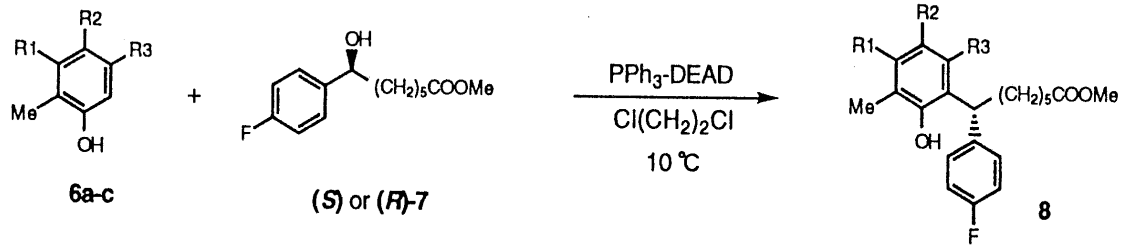


Chart 2

Table 2. Direct *ortho*-Alkylation of Phenols (**6a**—**c**) with (*S*)- and (*R*)-**7** and Physical Properties of Products (**8**)



Entry	Phenol **6**				7[a] Config.	Product **8**			
		R^1	R^2	R^3			Yield (%)	ee (%)	$[\alpha]_D$[b]
1	**6a**	Me	$-(CH_2)_3-$		(*S*)	(*R*)-**8a**	38	93	+104.1° (*c*=1.00)[d]
2	**6a**	Me	$-(CH_2)_3-$		(*R*)	(*S*)-**8a**	33	90	−104.8° (*c*=1.00)[d]
3	**6b**	Me	H	Me	(*S*)	(*R*)-**8b**	34	91	+115.5° (*c*=0.65)[e]
4	**6c**	$-(CH_2)_3-$		Me	(*S*)	(*R*)-**8c**	42	93	+107.8° (*c*=0.74)

a) Enantiomeric excesses of (*S*)- and (*R*)-**7** were 98 and 96% ee, respectively. *b*) The $[\alpha]_D$ was measured in $CHCl_3$. *c*) $[\alpha]_D$ was measured after purification. The ee after purification was 99% ee. *d*) $[\alpha]_D$ was measured after purification. The ee after purification was >99% ee. *e*) $[\alpha]_D$ was measured after purification. The ee after purification was 98% ee.

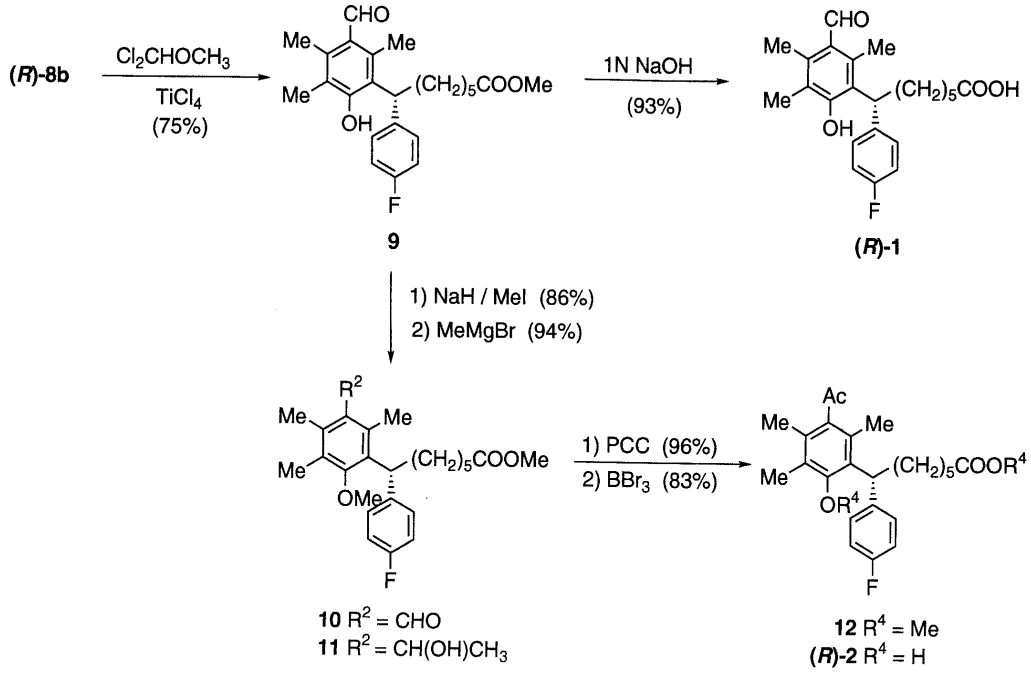
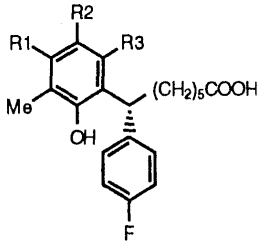


Chart 3

examined. Appreciable amounts of a by-product in which the benzilic methine carbon was oxidized were produced in other solvents and at higher temperature. The (*S*)-isomer of **3** was prepared by the same procedure as used for the (*R*)-isomer.

The indane derivative ((*R*)-**8c**) was hydrolyzed to give

Table 3. Physical Data of Phenol Derivatives (**1**—**4**)



Compd. No.	R^1	R^2	R^3	mp (°C)	Recrystn. solvent	Optical purity % ee[a]	Optical rotation $[\alpha]_D$
(*R*)-**1**	Me	CHO	Me	147—149	EtOH–H_2O	99	+170.5° (*c*=0.51, $CHCl_3$, 27[b])
(*R*)-**2**	Me	Ac	Me	99—101	AcOEt–hexane	99	+129.1° (*c*=1.01, $CHCl_3$, 27)
(*R*)-**3**	Me	$-CO(CH_2)_2-$		184 (dec.)	EtOH–H_2O	>99	+84.9° (*c*=0.92, DMSO, 20)
(*S*)-**3**	Me	$-CO(CH_2)_2-$		184 (dec.)	EtOH–H_2O	>99	−84.8° (*c*=0.90, DMSO, 20)
(*R*)-**4**	$-(CH_2)_3-$		Me	132—133	EtOH–H_2O	98	+123.4° (*c*=1.01, $CHCl_3$, 27)

a) The enantiomeric excess was measured by HPLC with Ultron ES-OVM. *b*) The last number in parenthesis shows the measurement temperature.

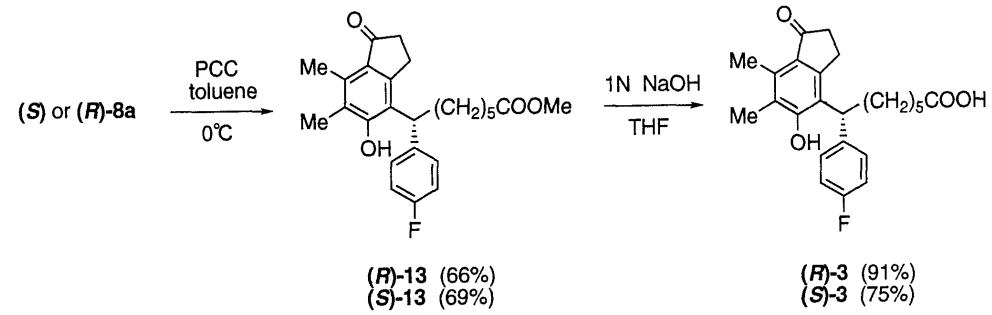


Chart 4

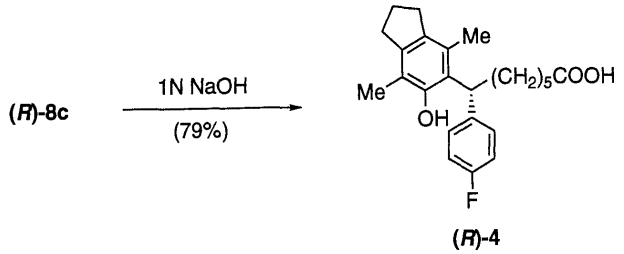


Chart 5

(*R*)-**4** in 79% yield.

The physical properties of these compounds (**1**—**4**) are summarized in Table 3. In the determination of enantiomeric excess of (*R*)- or (*S*)-**3** by HPLC, the antipode was not detected.

Biological Activity

TXA_2 receptor antagonistic activity of the optically active phenol derivatives (**1**—**4**) was tested by evaluating their inhibitory effects on U-46619-induced human platelet aggregation *in vitro*. The results are summarized in Table 4 as IC_{50} values. The activities of the corresponding racemates[6] and nonprostanoid TXA_2 receptor antagonist BM-13505[14] (**14**) are also listed for comparison. These optically active compounds exhibited potent TXA_2 receptor antagonistic activity; they were 1.4 to 1.7 times more potent than the racemates. The indanone derivative ((*R*)-**3**, IC_{50}=48 nM) and acetyl derivative ((*R*)-**2**, IC_{50}=45 nM) exhibited potent activity, as did the racemates, whereas the (*S*)-isomer of **3** was much less active.

Table 4. Inhibition of U-46619-Induced Human Platelet Aggregation

Compound[a]	IC_{50} (nM)[b,c]
(*R*)-**1**	180
(±)-**1**	310
(*R*)-**2**	45
(±)-**2**	69
(*R*)-**3**	48
(±)-**3**	78
(*S*)-**3**	>3000
(*R*)-**4**	200
(±)-**3**	310
14 (BM-13505)	640

a) Structures are given in Table 3. *b*) IC_{50} is the concentration of compound required to inhibit aggregation of human platelets by 50%. *c*) Number of experiments was 3 to 5.

In addition, the inhibitory effects on U-46619-induced bronchoconstriction in guinea pigs of the racemate and enantiomers of **3** were examined (*in vivo*, *p.o.*). The results are summarized as percent inhibition at the various doses tested (Table 5). Compound (*R*)-**3** exhibited more potent activity than the racemate (**3**), in accordance with the results obtained *in vitro*. The minimum effective dose (MED) of (*R*)-**3** was 0.3 mg/kg (*p.o.*), whereas (*S*)-**3** showed no activity in this assay. These results are

Table 5. Inhibitory Effects on U-46619-Induced Bronchoconstriction in Guinea Pigs *in Vivo*

Compd.[b]	% inhibition[a]				
	20[c]	5[c]	1.25[c]	0.31[c]	0.08[c]
(*R*)-**3**	—[f]	—	84[d]** (6)[e]	84** (6)	64 (5)
(±)-**3**	—	81** (7)	64** (7)	34 (6)	—
(*S*)-**3**	30 (6)	11 (6)	—	—	—

a) Percent inhibition after oral administration. *b*) Structures are given in Table 3. *c*) Dose of drug (mg/kg). *d*) Significance of differences (Dunnett's test): * $p<0.05$, ** $p<0.01$ (*vs.* control). *e*) The numbers in parentheses show the numbers of animals tested. *f*) Not tested.

consistent with those in the case of AA-2414.

In conclusion, optically active phenol derivatives (98—>99% ee) were synthesized by stereoselective introduction of a carbon chain into the *ortho*-position of phenols under Mitsunobu conditions. The (*R*)-derivatives exhibited potent TXA_2 receptor antagonistic activity on human platelets. The (*S*)-isomers showed poor activity. (*R*)-(+)-7-(4-Fluorophenyl)-7-(5-hydroxy-6,7-dimethyl-1-oxoindan-4-yl)-heptanoic acid ((*R*)-**3**), a nonprostanoid compound, was a highly potent, orally active TXA_2 receptor antagonist.

Experimental

Infrared (IR) spectra were taken on a Hitachi 215 spectrometer. Mass spectra were obtained on a JEOL JMS-AX 505W spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra unless otherwise specified were recorded on a Varian Gemini 200 instrument at 200 MHz in $CDCl_3$ with tetramethylsilane as an internal standard, and signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Melting points were obtained with a Yanaco micro melting apparatus and the data are uncorrected. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter. For thin-layer chromatography (TLC), precoated silica gel plates (Merck 60 F254, 0.2 mm) were used. Solutions in organic solvents were dried over anhydrous $MgSO_4$. Column chromatography was carried out on silica gel (Wakogel C-300, particle size 45—75 μm) by the flash chromatography technique.

General Procedure for the *ortho*-Alkylation of Phenols A solution of 95% diethyl azodicarboxylate (DEAD) (0.35 ml, 2.2 mmol) in 1,2-dichloroethane (5 ml) was added dropwise over 30 min to a solution of a phenol (5.9 mmol), methyl (*S*)- or (*R*)-7-(4-fluorophenyl)-7-hydroxyheptanoate ((*S*)-7 or (*R*)-7) (0.30 g, 1.2 mmol), and triphenylphosphine (0.46 g, 1.8 mmol) in 1,2-dichloroethane (20 ml) at 10 °C. The mixture was stirred for 1 h. After filtration, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford a desired *ortho*-alkylated phenol.

Methyl (*R*)-7-(4-Fluorophenyl)-7-(2-hydroxy-3,4,6-trimethylphenyl)-heptanoate ((*R*)-8b) A colorless oil (34%). $[\alpha]_D^{20}$ +108.2° (c=0.91, $CHCl_3$). 91% ee (Chiralcel OD, hexane–EtOH (990 : 10), 0 °C). This compound was purified to 98% ee by removing crystals of the racemate from *n*-hexane. A colorless oil. $[\alpha]_D^{20}$ +115.5° (c=0.65, $CHCl_3$). *Anal.* Calcd for $C_{23}H_{29}FO_3$: C, 74.17; H, 7.85. Found: C, 73.65; H, 7.78. MS *m/z*: 372 (M^+, 22), 340 (8), 243 (100), 213 (6). IR (neat): 3530, 2940, 1738, 1725, 1509, 1222 cm^{-1}. ^{1}H-NMR δ: 1.10—1.80 (6H, m), 1.90—2.44 (4H, m), 2.03 (3H, s), 2.21 (3H, s), 2.31 (3H, s), 3.65 (3H, s), 4.33 (1H, t, J=7.8 Hz), 4.56 (1H, s), 6.62 (1H, s), 6.94—7.05 (2H, m), 7.23—7.33 (2H, m).

Methyl (*R*)-7-(4-Fluorophenyl)-7-(5-hydroxy-6,7-dimethylindan-5-yl)-heptanoate ((*R*)-8a) A colorless oil (38%). 90% ee (Chiralcel OD, hexane–EtOH (990 : 10), 0 °C). This compound was purified to 99% ee by removing crystals of the racemate from *n*-hexane. Colorless crystals. mp 58—59 °C. $[\alpha]_D^{24}$ +104.1° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{31}FO_3$: C, 75.35; H, 7.84. Found: C, 75.19; H, 7.89. MS *m/z*: 398 (M^+, 3), 237 (2), 205 (7), 187 (13), 162 (100), 147 (16), 109 (26). IR (neat): 3455, 2935, 1742, 1725, 1505, 1219, 1168 cm^{-1}. ^{1}H-NMR δ: 1.14—1.46 (4H, m), 1.52—1.68 (2H, m), 1.92—2.32 (6H, m), 2.08 (3H, s), 2.16 (3H, s), 2.68—3.03 (4H, m), 3.65 (3H, s), 4.23 (1H, t, J=8.3 Hz), 4.40 (1H, s), 6.89—7.02 (2H, m), 7.23—7.35 (2H, m).

Methyl (*S*)-7-(4-Fluorophenyl)-7-(5-hydroxy-6,7-dimethylindan-5-yl)-heptanoate ((*S*)-8a) A colorless oil (33%). 90% ee (Chiralcel OD, hexane–EtOH (950 : 50), 0 °C). This compound was purified to >99% ee by removing crystals of the racemate from *n*-hexane. Colorless crystals. mp 59—60 °C. $[\alpha]_D^{22}$ −104.8° (c=1.00, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{31}FO_3$: C, 75.35; H, 7.84. Found: C, 75.60; H, 7.71.

Methyl (*R*)-7-(4-Fluorophenyl)-7-(6-hydroxy-4,7-dimethylindan-5-yl)-heptanoate ((*R*)-8c) A colorless oil (42%). *Anal.* Calcd for $C_{25}H_{31}FO_3$: C, 75.35; H, 7.84. Found: C, 75.32; H, 7.78. HR-MS Calcd for $C_{25}H_{31}FO_3$: 398.2257. Found: 398.2251. $[\alpha]_D^{26}$ +107.8° (c=0.74, $CHCl_3$). 93% ee (Chiralcel OD, hexane–EtOH (990 : 10), 0 °C). MS *m/z*: 398 (M^+, 33), 366 (6), 338 (2), 269 (100), 241 (3), 199 (4), 162 (7). IR (neat): 3540, 2945, 1740, 1724, 1510, 1460, 1222 cm^{-1}. ^{1}H-NMR δ: 1.14—1.46 (4H, m), 1.52—1.68 (2H, m), 1.94—2.33 (6H, m), 2.04 (3H, s), 2.22 (3H, s), 2.78—2.90 (4H, m), 3.64 (3H, s), 4.35 (1H, s), 4.38 (1H, t, J=8.1 Hz), 6.88—7.01 (2H, m), 7.20—7.32 (2H, m).

Methyl (*R*)-7-(4-Fluorophenyl)-7-(3-formyl-6-hydroxy-2,4,5-trimethylphenyl)heptanoate ((*R*)-9) A solution of $TiCl_4$ (0.76 ml) in dichloromethane (3 ml) was added dropwise to a solution of methyl (*R*)-7-(4-fluorophenyl)-7-(2-hydroxy-3,4,6-trimethylphenyl)heptanoate ((*R*)-**8b**, 0.8 g, 2.1 mmol) and dichloromethyl methyl ether (0.62 ml) in dichloromethane (10 ml) in the temperature range of −10 to −12 °C. The whole was stirred for 20 min and poured into ice-water. The mixture was extracted with chloroform, and the residue was recrystallized from chloroform–hexane to afford (*R*)-**9** (0.63 g, 75%) as colorless crystals. mp 66—70 °C. *Anal.* Calcd for $C_{24}H_{29}FO_4$: C, 71.98; H, 7.30. Found: C, 70.87, H, 7.28. $[\alpha]_D^{27}$ +161.0° (c=1.04, $CHCl_3$). 99.6% ee (Chiralcel OD, hexane–EtOH (980 : 20), 0 °C). MS *m/z*: 400 (M^+, 32), 385 (8), 372 (16), 340 (5), 285 (12), 271 (100), 243 (53). IR (KBr): 3400, 2925, 1732, 1662, 1550, 1508, 1175 cm^{-1}. ^{1}H-NMR δ: 1.06—1.47 (4H, m), 1.52—1.73 (2H, m), 1.96—2.38 (4H, m), 2.10 (3H, s), 2.45 (3H, s), 2.54 (3H, s), 3.65 (3H, s), 4.56 (1H, dd, J=6.6, 8.8 Hz), 5.08 (1H, s), 6.95—7.06 (2H, m), 7.19—7.30 (2H, m), 10.58 (1H, s).

Methyl (*R*)-7-(4-Fluorophenyl)-7-(3-formyl-6-methoxy-2,4,5-trimethylphenyl)heptanoate ((*R*)-10) A solution of (*R*)-7-(4-fluorophenyl)-7-(3-formyl-6-hydroxy-2,4,5-trimethylphenyl)heptanoic acid ((*R*)-**9**, 5.0 g, 12.9 mmol) in dimethylformamide (DMF) (20 ml) was added dropwise to a stirred suspension of 60% NaH (1.1 g, 27.2 mmol, washed three times with hexane) in DMF (30 ml) at 0 °C. The mixture was stirred at room temperature for 30 min, then MeI (3.9 g, 27.2 mmol) was added dropwise at 0 °C, and the mixture was stirred for 1.5 h at room temperature. Water was slowly added and the whole was extracted with ethyl acetate. The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on silica gel to yield (*R*)-**10** (4.6 g, 86%) as a colorless oil. *Anal.* Calcd for $C_{25}H_{31}FO_4$: C, 72.44; H, 7.54. Found: C, 72.14; H, 7.69. $[\alpha]_D^{26}$ +119.7° (c=1.04, $CHCl_3$). MS *m/z*: 414 (M^+, 25), 402 (11), 285 (17), 257 (30), 109 (100). IR (neat): 2940, 1738, 1690, 1560, 1510, 1288, 1224, 1100 cm^{-1}. ^{1}H-NMR δ: 1.04—1.46 (4H, m), 1.52—1.68 (2H, m), 1.87—2.53 (4H, m), 2.21 (3H, s), 2.31 (3H, s), 2.42 (3H, s), 3.31 (3H, s), 3.65 (3H, s), 4.60 (1H, t, J=7.7 Hz), 6.87—7.01 (2H, m), 7.09—7.23 (2H, m), 10.58 (1H, s).

Methyl (*R*)-7-(4-Fluorophenyl)-7-[3-(1-hydroxyethyl)-6-methoxy-2,4,5-trimethylphenyl]heptanoate ((*R*)-11) Anhydrous tetrahydrofuran (THF) (90 ml) was added dropwise to a 1 M solution of MeMgBr in THF (54.3 ml) at −78 °C, then methyl (*R*)-7-(4-fluorophenyl)-7-(3-formyl-6-methoxy-2,4,5-trimethylphenyl)heptanoate ((*R*)-**10**, 4.5 g, 10.9 mmol) in anhydrous THF (20 ml) was added dropwise at the same temperature. The mixture was stirred for 30 min, quenched with aqueous $KHSO_4$, and extracted with EtOAc. The organic layer was washed with water, dried and evaporated. The residue was chromatographed on silica gel with EtOAc–hexane (1 : 5) to yield (*R*)-**11** (4.4 g, 94%) as a colorless oil. *Anal.* Calcd for $C_{26}H_{35}FO_4$: C, 72.53; H, 8.19. Found: C, 72.14: H, 8.19. $[\alpha]_D^{25}$ +97.6° (c=1.02, $CHCl_3$). MS *m/z*: 430 (M^+, 16), 412 (82), 397 (27), 283 (68), 109 (100). IR (neat): 3460, 2935, 1736, 1508, 1222 cm^{-1}. ^{1}H-NMR δ: 1.05—1.46 (4H, m), 1.50—1.77 (2H, m), 1.55 (3H, d, J=6.8 Hz), 1.70 (1H, s), 1.91—2.52 (4H, m), 2.18 (3H, s), 2.38 (3H, s), 2.39 (3H, s), 3.31 (3H, s), 3.64 (3H, s), 4.54—4.66 (1H, m), 5.43 (1H, q, J=7.0 Hz), 6.84—6.98 (2H, m), 7.09—7.21 (2H, m).

Methyl (*R*)-7-(3-Acetyl-6-methoxy-2,4,5-trimethylphenyl)-7-(4-fluorophenyl)heptanoate ((*R*)-12) Methyl (*R*)-7-(4-fluorophenyl)-7-[3-(1-hydroxyethyl)-6-methoxy-2,4,5-trimethylphenyl]heptanoate ((*R*)-**11**, 4.1 g, 9.5 mmol) in dichloromethane (10 ml) was added in one portion to a

solution of PCC (3.3 g, 15.2 mmol) in dichloromethane (20 ml) at room temperature and the mixture was stirred at the same temperature for 2 h. Diethyl ether (50 ml) was added. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel to afford (*R*)-**12** (3.9 g, 96%) as a colorless oil. *Anal.* Calcd for $C_{26}H_{33}FO_4$: C, 72.87; H, 7.76. Found: C, 72.21; H, 7.93. $[\alpha]_D^{26}$ +102.9° (*c*=1.02, $CHCl_3$). MS *m/z*: 428 (M^+, 17), 413 (14), 385 (37), 353 (25), 335 (9), 299 (15), 257 (17), 163 (28), 109 (100). IR (neat): 2935, 1738, 1700, 1508, 1350, 1302, 1220, 1160 cm^{-1}. ^{1}H-NMR δ: 1.11—1.73 (6H, m), 1.86—2.38 (4H, m), 2.01 (3H, s), 2.11 (3H, s), 2.15 (3H, s), 2.44 (3H, s), 3.27 (3H, s), 3.65 (3H, s), 4.50 (1H, t, *J*=6.6 Hz), 6.86—7.00 (2H, m), 7.21—7.23 (2H, m).

Methyl (*R*)-7-(4-Fluorophenyl)-7-(5-hydroxy-6,7-dimethyl-1-oxoindan-4-yl)heptanoate ((*R*)-13) A mixture of PCC (43.3 g, 40.2 mmol) and Celite (52 g) was added to a solution of methyl (*R*)-7-(6,7-dimethyl-5-hydroxyindan-4-yl)-7-(4-fluorophenyl)heptanoate ((*R*)-**8a**, 16.0 g, 40.2 mmol) in toluene (640 ml) at 0 °C under argon, and the mixture was stirred for 23 h at the same temperature. Isopropyl alcohol was added and the reaction mixture was filtered. The insoluble material was washed with toluene. The washings and filtrate were combined, washed with water, dried, and evaporated. The residue was purified by column chromatography on silica gel with EtOAc–hexane to afford (*R*)-**13** (10.9 g, 66%) as colorless crystals. mp 135—136 °C. *Anal.* Calcd for $C_{25}H_{29}FO_4$: C, 72.79; H, 7.09. Found: C, 72.60; H, 7.12. $[\alpha]_D^{24}$ +130.6° (*c*=1.00, $CHCl_3$). MS *m/z*: 412 (M^+, 38), 381 (4), 297 (20), 283 (100), 226 (3), 189 (3). IR (KBr): 3300, 2945, 1735, 1663, 1573, 1506, 1339, 1218, 1142 cm^{-1}. ^{1}H-NMR δ: 1.10—1.71 (6H, m), 2.01—2.34 (4H, m), 2.12 (3H, s), 2.62 (3H, s), 2.64 (2H, t, *J*=5.8 Hz), 2.80—3.12 (2H, m), 3.65 (3H, s), 4.31 (1H, dd, *J*=6.0, 9.5 Hz), 5.35 (1H, br), 6.94—7.07 (2H, m), 7.23—7.34 (2H, m).

Methyl (*S*)-7-(4-Fluorophenyl)-7-(5-hydroxy-6,7-dimethyl-1-oxoindan-4-yl)heptanoate ((*S*)-13) In the same manner as described for the preparation of (*R*)-**13**, (*S*)-**13** was obtained as colorless crystals (69%). mp 135—136 °C. $[\alpha]_D^{24}$ −130.6° (*c*=1.00, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{29}FO_4$: C, 72.79; H, 7.09. Found: C, 72.68; H, 7.04.

(*R*)-7-(3-Acetyl-6-hydroxy-2,4,5-trimethylphenyl)-7-(4-fluorophenyl)-heptanoic Acid ((*R*)-2) A solution of methyl (*R*)-7-(3-acetyl-6-methoxy-2,4,5-trimethylphenyl)-7-(4-fluorophenyl)heptanoate ((*R*)-**12**, 2.0 g, 4.7 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of BBr_3 (2.0 ml, 5.3 g, 21.0 mmol) in CH_2Cl_2 (30 ml) at −78 °C. The solution was allowed to warm slowly to room temperature and stirred for 5 h. Ice-water was added to the mixture at 0 °C . The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc–hexane to afford (*R*)-**2** (1.56 g, 83%) as colorless crystals. mp 99—101 °C. *Anal.* Calcd for $C_{24}H_{29}FO_4$: C, 71.98; H, 7.30. Found: C, 71.96; H, 7.25. $[\alpha]_D^{27}$ +129.1° (*c*=1.01, $CHCl_3$). 99% ee (Ultron ES-OVM, EtOH–0.02 M KH_2PO_4 (pH 3.5) (35:65), r.t.). MS *m/z*: 400 (M^+, 32), 385 (18), 367 (10), 339 (10), 285 (100). IR (KBr): 3420, 2930, 1702, 1685, 1506, 1220 cm^{-1}. ^{1}H-NMR δ: 1.14—1.46 (4H, m), 1.53—1.70 (2H, m), 1.96—2.35 (4H, m), 2.04 (3H, s), 2.11 (3H, s), 2.48 (3H, s), 4.39 (1H, t, *J*=7.5 Hz), 4.59 (1H, br), 6.90—7.04 (2H, m), 7.19—7.31 (2H, m).

(*R*)-7-(4-Fluorophenyl)-7-(3-formyl-6-hydroxy-2,4,5-trimethylphenyl)-heptanoic Acid ((*R*)-1) A solution of methyl (*R*)-7-(4-fluorophenyl)-7-(3-formyl-6-hydroxy-2,4,5-trimethyl)heptanoate ((*R*)-**9**, 0.55 g, 1.4 mmol) in THF (6 ml) was treated with 1 N NaOH (2.9 ml) for 14 h at room temperature. Then 1 N HCl (2.9 ml) was added and the whole was extracted with ethyl acetate. The organic layer was washed with water, dried, and evaporated. The residue was recrystallized from acetonitrile to provide (*R*)-**1** (0.49 g, 93%) as colorless crystals. mp 147—149 °C. *Anal.* Calcd for $C_{23}H_{27}FO_4$: C, 71.48; H, 7.04. Found: C, 71.54: H, 7.06. $[\alpha]_D^{27}$ +170.5° (*c*=0.51, *CHCl*$_3$). 98.7% ee (Ultron ES-OVM, EtOH–0.02 M KH_2PO_4 (pH 3.5) (35:65), r.t.). MS *m/z*: 386 (M^+, 24), 368 (13), 340 (9), 271 (100), 243 (17). IR (KBr): 3420, 2870, 1705, 1670, 1554, 1510 cm^{-1}. ^{1}H-NMR (DMSO) δ: 0.96—1.62 (6H, m), 2.00—2.28 (4H, m), 2.10 (3H, s), 2.36 (6H, s), 4.58 (1H, br), 6.96—7.30 (4H, m), 8.85 (1H, s), 10.44 (1H, s), 11.95 (1H, br).

(*R*)-7-(4-Fluorophenyl)-7-(5-hydroxy-6,7-dimethyl-1-oxoindan-4-yl)-heptanoic Acid ((*R*)-3) In the same manner as described for the preparation of (*R*)-**1**, (*R*)-**3** was obtained as colorless crystals (91%). mp 184 °C (dec.) *Anal.* Calcd for $C_{24}H_{27}FO_4$: C, 72.34; H, 6.83. Found: C, 72.25; H, 6.75. $[\alpha]_D^{20}$ +84.9° (*c*=0.92, DMSO). >99% ee (Ultron ES-OVM, EtOH–0.02 M KH_2PO_4 (pH 3.5) (35:65), r.t.). MS *m/z*: 398 (M^+, 27), 380 (4), 297 (10), 283 (100), 271 (4), 241 (4), 141 (5). IR (KBr): 3250, 2925, 1703, 1665, 1573, 1508, 1220, 1145 cm^{-1}. ^{1}H-NMR δ: 1.09—1.84 (6H, m), 2.09—2.36 (4H, m), 2.14 (3H, s), 2.44—3.06 (4H, m), 2.60 (3H, s), 4.35 (1H, t, *J*=7.7 Hz), 6.80 (1H, br), 6.88—7.02 (2H, m), 7.22—7.35 (2H, m).

(*S*)-7-(4-Fluorophenyl)-7-(5-hydroxy-6,7-dimethyl-1-oxoindan-4-yl)-heptanoic Acid ((*S*)-3) In the same manner as described for the preparation of (*R*)-**1**, (*S*)-**3** was obtained as colorless crystals (75%). mp 184 °C (dec.). *Anal.* Calcd for $C_{24}H_{27}FO_4$: C, 72.34; H, 6.83. Found: C, 72.43; H, 6.81. $[\alpha]_D^{20}$ −84.8° (*c*=0.90, DMSO). >99% ee (Ultron ES-OVM, EtOH–0.02 M KH_2PO_4 (pH 3.5) (35:65), r.t.).

(*R*)-7-(6-Hydroxy-4,7-dimethylindan-5-yl)-7-(4-fluorophenyl)heptanoic Acid ((*R*)-4) In the same manner as described for the preparation of (*R*)-**1**, (*R*)-**4** was obtained as colorless crystals (79%). mp 132—133 °C. *Anal.* Calcd for $C_{24}H_{29}FO_3$: C, 74.97; H, 7.60. Found: C, 74.83: H, 7.44. $[\alpha]_D^{27}$ +123.4° (*c*=1.01, $CHCl_3$). 98% ee (Ultron ES-OVM, EtOH–0.02 M KH_2PO_4 (pH 3.5) (35:65), r.t.). MS *m/z*: 384 (M^+, 27), 366 (5), 338 (7), 269 (100), 162 (6), 109 (11). IR (KBr): 3545, 2930, 1700, 1503, 1219 cm^{-1}. ^{1}H-NMR δ: 1.10—1.80 (6H, m), 1.94—2.39 (6H, m), 2.05 (3H, s), 2.23 (3H, s), 2.78—2.93 (4H, m), 3.80—4.90 (1H, br), 4.39 (1H, t, *J*=7.1 Hz), 6.90—7.35 (2H, m), 7.21—7.35 (2H, m).

Methyl (*S*)-7-(4-Fluorophenyl)-7-hydroxyheptanoate ((*S*)-7) A solution of 1 M borane–THF complex in THF (4 ml) was added dropwise to a solution of (*R*)-3,3-diphenyl-1-methyltetrahydro-1*H*,3*H*-pyrro[1,2-*c*]-[1,3,2]oxazaborole (1.1 g, 4.7 mmol) in anhydrous THF (20 ml) at 0 °C with stirring under an argon atmosphere. To this solution were added simultaneously a solution of ethyl 7-(4-fluorophenyl)-7-oxoheptanoate (10.0 g, 39.6 mmol) in THF (20 ml) and a solution of 1 M borane–THF complex in THF (20 ml) at 0 °C for 25 min. The reaction mixture was stirred for 30 min at the same temperature and complex was decomposed by the addition of MeOH (20 ml) with stirring. After 30 min, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with EtOAc–hexane to yield (*S*)-**11** (9.9 g, 98%) as a colorless oil. *Anal.* Calcd. for $C_{14}H_{19}FO_3$: C, 66.12; H, 7.53. Found: C, 66.12; H, 7.61. $[\alpha]_D^{28}$ −23.9 (*c*=1.04, $CHCl_3$); 98% ee (Chiralcel OB, EtOH–hexane (80:920), r.t.). MS *m/z*: 254 (M^+, 7), 205 (7), 187 (8), 130 (90), 125 (100), 109 (20), 97 (30), 87 (81). IR (neat): 3440, 2940, 1740, 1510, 1222 cm^{-1}. ^{1}H-NMR δ: 1.17—1.98 (9H, m), 2.29 (2H, t, *J*=7.4 Hz), 3.65 (3 H, s), 4.65 (1 H, t, *J*=6.7 Hz), 6.96—7.08 (2 H, m), 7.26—7.36 (2 H, m).

Methyl (*R*)-7-(4-Fluorophenyl)-7-hydroxyheptanoate ((R)-7) In the same manner as described for the preparation of (*S*)-**7**, (*R*)-**7** (83%) was obtained as a colorless oil. *Anal.* Calcd for $C_{14}H_{19}FO_3$: C, 66.12; H, 7.53. Found: C, 65.90: H, 7.55. $[\alpha]_D^{28}$ −23.9 (*c*=1.01, $CHCl_3$); 96% ee (Chiralcel OB, EtOH–hexane (80:920), r.t.).

Biological Methods. U-46619-Induced Human Platelet Aggregation The platelet Aggregation study was done as described before.[15] Blood was collected in 3.8% sodium citrate (1 ml for 9 ml of blood) by cardiac puncture from healthy male volunteers who had taken no medication for at least 10 d prior to blood collection. Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) were obtained from the blood by centrifugation at 1000 × *g* for 5 s and at 1000 × *g* for 10 min at room temperature, respectively. The platelet density of PRP was adjusted to 400000 platelets/μl with PPP. Platelet aggregation was measured with a photometer (Hematracer 6, Niko Bioscience, Japan) according to the method described by Born.[16] The PRP (250 μl) was preincubated at 37 °C for 2 min and then incubated for 2 min with a phenol derivative, or the vehicle (25 μl) followed by stimulation with U-46619 (25 μl). The concentration of U-46619 used was such as to give submaximal aggregation (U-46619: 1—3 μM).

U-46619-Induced Bronchoconstriction in Guinea Pig Male Hartley guinea pigs were used for experiments. A guinea pig anesthetized with urethane (1.5 g/kg, i.p.) was fixed in a dorsal position, subjected to tracheotomy and connected to a respirator through a cannula. A branch of the tracheal cannula was connected to a respirator (Harvard Apparatus rodent respirator, Type 680) at the rate of 70 strokes/min with a constant volume of 3 to 5 ml.

Inflation pressure was kept constant at 10 cm H_2O. After treatment with gallamine triethiodide (1 mg/kg, i.v.), U-46619 (10 μg/kg) through a carotid cannula, the airway resistance was measured by the overflow technique using the Konzett–Rössler method.[17] Drugs suspended in a 5% gum arabic solution were given orally 1 h before the treatment with U-46619.

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References and Notes

1) Hamberg M., Svensson J., Samuelsson B., *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994—2998 (1975).
2) Svensson J., Hamberg M., Samuelsson B., *Acta Physiol. Scand.*, **98**, 285—294 (1976).
3) Hamberg M., Hedqvist P., Strandberg K., Svensson J., Samuelsson B., *Life Sci.*, **16**, 451—562 (1975); Svensson J., Strandberg K., Tuvemo T., Hamberg M., *Prostaglandins*, **14**, 425—436 (1977).
4) Fitzgerald G. A., Branch R. A., Jackson E. K., Roberts R. L., Knapp H. R., Oates J. A., *N. Engl. J. Med.*, **319**, 689—698 and 761—767 (1988).
5) Cross P. E., "Antithrombotic Agents. In Annual Report on Medicinal Chemistry," Vol. 17, ed. by Hess H-J., Academic Press; New York, 1982, Chapter 9, pp. 79—88; Cross P. E., Dickinson R. P., "Thromboxane Sythetase Inhibitors and Antagonists. In Annual Report on Medicinal Chemistry," Vol. 22, ed. by Bailey D. M., Academic Press, New York, 1987, Chapter 10, p. 95; Hall S. E., *Med. Res. Rev.*, **11**, 503—579 (1991); Davis-Bruno K. L., Halushka P. V., *Adv. Drug Res.*, **25**, 173—202 (1994).
6) Fukumoto S., Shiraishi M., Terashita Z., Ashida Y., Inada Y., *J. Med. Chem.*, **35**, 2202—2209 (1992).
7) Shiraishi M., Kato K., Terao S., Ashida Y., Terashita Z., Kito G., *J. Med. Chem.*, **32**, 2214—2221 (1989).
8) Yamamoto Y., Kamiya K., Terao S., *J. Med. Chem.*, **36**, 820—825 (1993).
9) Nakajima T., Masuda S., Kondo T., Nakamoto Y., Suga S., *Bull. Chem. Soc. Jpn.*, **52**, 2377—2382 (1979); Piccolo O., *J. Org. Chem.*, **56**, 183—187 (1991).
10) Fukumoto S., Fukushi S., Terao S., Shiraishi M., *J. Chem. Soc., Perkin Trans. 1*, submitted for publication.
11) Corey E. J., Bakshi R. K., Shibata S., *J. Am. Chem. Soc.*, **109**, 5551—5553 (1987); Corey E. J., Bakshi R. K., Shibata S., Chen C. -P., Singh V. K., *ibid.*, **109**, 7925—7926 (1987).
12) Reiche A., Gross H., Höft E., *Chem. Ber.*, **93**, 88—94 (1960).
13) Rathore R., Saxena N., *Synth. Commun.*, **16**, 1493—1498 (1986).
14) Staiger C., Uebis V., Kaufman B., Brindley F., Neugebauer G., *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **332**, Deutsche Pharmakologische Gesellschaft 27th Spring Meeting Abstracts, 385 (1986); Yanagisawa A., Smith J. A., Brezinski M. E., Lefer A. M., *Eur. J. Pharmacol.*, **133**, 89—96 (1987).
15) Terashita Z., Tsushima S., Yoshioka Y., Nonura H., Inada Y., Nishikawa K., *Life Sci.*, **32**, 1975—1982 (1983).
16) Born G. V., *Nature* (London), **194**, 927—929 (1962).
17) Konzett H., Rössler R., *Arch. Exp. Pathol. Pharmakol.*, **195**, 71—74 (1940).