$NaHSO_4$ and was immediately distilled under reduced pressure with a Kugelrohr distillation apparatus (pot temperature 95 °C, 0.050 mm) to give 0.63 g (70%) of distillate that solidified at once, mp 45–46 °C. Anal. ($C_{12}H_{14}O$) C, H.

3,4-Dihydro-6-methoxy-7-methyl-2(1*H*)-naphthalenone (20b). To a cooled (ice bath), stirred solution of 0.5 g (0.003 mol) of **18b** in 20 mL of CH_2Cl_2 and 8 mL of saturated aqueous $NaHCO_3$ was added 0.65 g (80%, 0.003 mol) of 3-chloroperoxybenzoic acid over 5 min. The resulting mixture was stirred for an additional 10 min with cooling and then for 2.5 h at room temperature. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ and H_2O. Volatiles were removed under reduced pressure to give a white solid which was dissolved in 10 mL of EtOH and 5 mL of 2 N HCl and heated under reflux for 1.5 h. The resulting orange solution was cooled and extracted with three 50-mL portions of benzene. The pooled benzene extracts were dried (Na_2SO_4) and filtered, and the benzene was evaporated under reduced pressure to leave a reddish solid which was recrystallized from cyclohexane to give 0.4 g (70%) of white crystals, mp 84–85 °C. Anal. ($C_{12}H_{14}O_2$) C, H.

2-(Di-*n*-propylamino)-6-methoxy-7-methyltetralin Hydrochloride (22b). To a stirred solution of 0.3 g (0.0016 mol) of **20b** and 0.03 g (0.00016 mol) of *p*-toluenesulfonic acid in 20 mL of benzene was added 0.637 g (0.0063 mol) of di-*n*-propylamine. This solution was heated under reflux in a Dean–Stark apparatus to provide removal of H_2O. The cooled purple reaction mixture was immediately placed in a Parr hydrogenation vessel with 20 mL of absolute EtOH and 0.2 g of PtO_2, and this mixture was hydrogenated overnight at an initial pressure of 55 psig. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The oily residue was treated with ethereal HCl and the resulting solid was recrystallized from EtOH–Et_2O to yield 0.3 g (68%) of a light tan powder, mp 195–196 °C. Anal. ($C_{18}H_{30}ClNO$) C, H, N.

2-(Di-*n*-propylamino)-6-hydroxy-7-methyltetralin Hydrobromide (8). Compound **22b** (0.2 g, 0.00073 mol) in 11 mL of 48% HBr and 3 mL of AcOH was heated under reflux for 1.5 h. The volatiles were evaporated under reduced pressure to give a reddish solid which was recrystallized from EtOH–Et_2O to give 0.150 g (67%) of a light tan powder, mp 229–230 °C. Anal. ($C_{17}H_{28}BrNO$) C, H, N.

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Quinones. 4.† Novel Eicosanoid Antagonists: Synthesis and Pharmacological Evaluation

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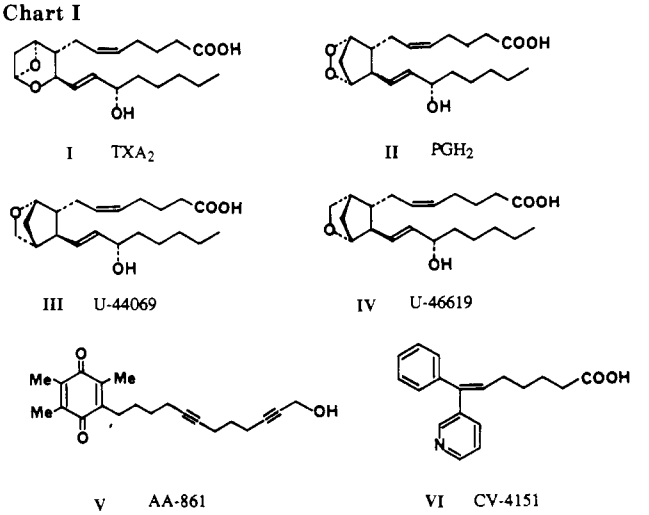
A new series of ω-phenyl-ω-quinonylalkanoic acids and related compounds was synthesized. The compounds were tested for their inhibitory effects on U-44069-induced contraction of the rabbit aorta. (±)-7-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid (**4d**) (AA-2414) with pA_2 value of 8.28 was one of the most potent compounds. Compound **4d** inhibited U-46619-induced contraction of the guinea pig lung (pA_2 = 8.29) and U-44069-induced aggregation of the guinea pig platelet ($IC_{50} = 3.5 \times 10^{-7}$ M). Compound **4d** displaced the binding of [^{3}H]U-46619 to guinea pig platelets ($IC_{50} = 7.4 \times 10^{-9}$ M). Compound **4d** also showed very potent inhibitory effects with an MED of 0.3 mg/kg (po) on U-46619-, LTD_4-, PAF-, or IgG_1-induced bronchoconstriction in guinea pigs. The enantiomers of **4d** were prepared. The *R*-(+) isomer **8a** was active in both in vitro and in vivo tests, but the *S*-(−) isomer **8b** was much less active. We concluded that the antiasthmatic effects of **4d** were based mainly on the TXA_2 receptor antagonistic action. In addition, compound **4d** showed potent inhibitory effects on PGD_2-, $PGF_{2\alpha}$-, and 11-*epi*-$PGF_{2\alpha}$-induced contraction of the guinea pig tracheal strips. The diverse inhibitory effects might be expressed in terms of eicosanoid-antagonistic activity.

Since the discoveries of thromboxane A_2 (TXA_2), prostaglandin I_2(PGI_2), and leukotrienes (LTs) during the period from 1975 to 1979, studies have clarified the physiological and pathological roles of the arachidonate cascade metabolites. Based on these discoveries, novel concepts for designing new drugs that specifically control and manipulate these metabolites have been developed. Our approach to the synthesis of target compounds that affect metabolites of the arachidonate cascade has focused on the synthesis of non-eicosanoid compounds (Chart I). We have found a potent and selective 5-lipoxygenase inhibitor, 2-(12-hydroxy-5,10-dodecadiynyl-3,5,6-trimethyl-1,4-benzoquinone (V, AA-861),[1] from studies on quinone derivatives with alkenyl and alkynyl groups in the side chain, and a potent and long-acting thromboxane synthetase inhibitor, (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenic acid (VI, CV-4151),[2] from the design of a series of ω-(3-pyridyl)alkenoic acids. Both compounds are in clinical trials.

Chart I



† Part 3 is ref 1b.
‡ Chemistry Laboratories.
§ Biology Laboratories.

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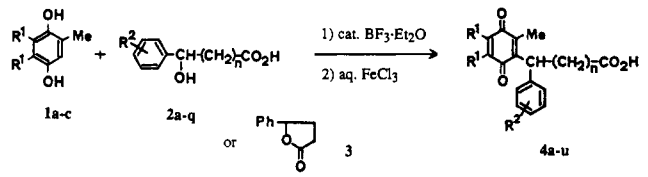
Table I. Physical Properties and Inhibitory Effects of Compounds 4a–u

compd	R^1	R^2	n	formula[a]	mp, °C	% yield	% inhibition[b,c] 10^{-5} M	10^{-6} M	10^{-7} M	3×10^{-8}, M	IC_{50},[d] μM
4a	Me	H	2	$C_{19}H_{20}O_4$	142–143	84	0				
4b	Me	H	3	$C_{20}H_{22}O_4$	144–145	78	24				
4c	Me	H	4	$C_{21}H_{24}O_4$	125–126	76	63				
4d	Me	H	5	$C_{22}H_{26}O_4$	128–129	73	99	99	49		0.10
4e	Me	H	6	$C_{23}H_{28}O_4$	94–95	71	98	0			3.2
4f	Me	H	7	$C_{24}H_{30}O_4$	125–127	71	94	0			3.4
4g	Me	H	8	$C_{25}H_{32}O_4$	48–50	64	41				
4h	MeO	H	5	$C_{22}H_{26}O_4$	92–93	70	0				
4i		H	5	$C_{24}H_{24}O_4$	137–138	36	100	99	20		0.24
4j	Me	*p*-Me	5	$C_{23}H_{28}O_4$	138–139	78	100	50			1.0
4k	Me	*o*-Me	5	$C_{23}H_{28}O_4$	156–158	59	99	0			3.2
4l	Me	*p*-Pr^i	5	$C_{25}H_{32}O_4$	135–137	72	4				
4m	Me	*p*-F	5	$C_{22}H_{25}FO_4$	141–142	80	100	100	96	20	0.048
4n	Me	*m*-F	5	$C_{22}H_{25}FO_4$	113–114	38	100	31			1.9
4o	Me	*p*-Cl	5	$C_{22}H_{25}ClO_4$	142–143	78	100	91	17		0.28
4p	Me	*p*-Br	5	$C_{22}H_{25}BrO_4$	148–150	70	94	36			1.7
4q	Me	*p*-MeO	5	$C_{23}H_{28}O_5$	110–111	78	100	3			3.0
4r	Me	*o*-MeO	5	$C_{23}H_{28}O_5$	152–153	27	0				
4s	Me	*m*-CF_3	5	$C_{23}H_{25}F_3O_4$	104–105	36	64				
4t	MeO	*p*-F	5	$C_{22}H_{25}FO_6$	121–122	70	99	0			3.2
4u		*p*-F	5	$C_{24}H_{23}FO_4$	132–133	30	100	100	78		

[a] Analyses (C, H) within ±0.3% of the calculated values. [b] Percent inhibition on U-44069 (10^{-7} M) induced contraction of the rabbit aorta. [c] Values are the mean of duplicate experiments. [d] Antagonist concentration that reduced U-44069-induced contraction of the rabbit aorta by 50%.

Scheme I



In this report, the synthesis, structure–activity relations, and pharmacological evaluation of a novel series of ω-phenyl-ω-quinonylalkanoic acids and related compounds are described. (±)-7-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid (**4d**) (AA-2414), which showed potent and long-acting antiasthmatic effects in guinea pigs (po) based mainly on TXA_2 receptor antagonistic action, has been selected for further pharmacological and clinical evaluation.

Chemistry

The synthesis of a series of ω-phenyl-ω-quinonylalkanoic acids **4a–u** was carried out by the acid-catalyzed coupling reaction between hydroquinones **1** and α-substituted benzyl alcohols **2** or the γ-lactone **3**, followed by ferric chloride oxidation using an application of the Jurd and Wong method[3] (Scheme I). The starting materials (**2,3**) were prepared with the Friedel–Crafts reaction or the Grignard reaction,[4] followed by sodium borohydride reduction and sodium hydroxide hydrolysis of the resulting ω-oxo-ω-(substituted-phenyl)alkanoates.

Modifications were made in the ω-phenyl moiety, the ω-quinonyl moiety, the alkylene chain length, the α-methylene group adjacent to the carboxyl group, as well as variation in choice of the substituent in the five-carbon chain as shown in Y of Chart II, and the carboxyl group. In the course of this work, the quinone compounds **5a,b**, **6a–h**, and **7a–e** were prepared as outlined in the following. The quinonylheptanoic acids **5a,b** were prepared by a Wittig coupling reaction using the aldehydes (**10,11**), followed by catalytic hydrogenation in the presence of 5% palladium charcoal and by oxidative demethylation[1b] of the resulting hydroquinone dimethyl ethers with cerium(IV) ammonium nitrate. The amides (**6d–g**, **7e**) were obtained by the coupling reaction between *p*-nitrophenyl esters of ω-phenyl-ω-quinonylalkanoic acids (**4a**, **4d**) and the appropriate amines. The analogue **7a**, in which the substitution on the α-methylene adjacent to the carboxyl group of **4d** was varied, was prepared from the reaction of ethyl isobutyrate with the iodide **12b** in the presence of lithium diisopropylamide. Treatment of sodium azide with the cyanide **13**, formed by displacement of the iodide **12c** with sodium cyanide in the presence of ammonium chloride, followed by oxidative demethylation, gave the tetrazole derivative **6h**.

To investigate the mechanism of action, two optically active compounds **8a,b** were prepared by optical resolution of **4d** using *S*-(−)- and *R*-(+)-α-phenethylamines, respectively. The optical purity of **8a,b** was calculated by chromatographic separation of **6c** (**4d** methyl ester) on a HPLC column using cellulose derivatives coated on silica gel for optical resolution of the racemates. The absolute configuration at the α-carbon was established by X-ray crystallographic analysis (Figure 1) of the *p*-bromoanilide **9** of the (+) isomer **8a**, synthesized by a mixed-anhydride method. The configuration was determined to be *R*-(+).

Further details are to be found in Tables I–III and the Experimental Section.

Pharmacological Results and Discussion

The compounds were initially tested for their inhibitory effects on U-44069[5] (10^{-7} M) induced contraction of the

(1) (a) Yoshimoto, T.; Yokoyama, C.; Ochi, K.; Yamamoto, S.; Maki, Y.; Terao, S.; Shiraishi, M. M. *Biochim. Biophys. Acta* **1982**, *713*, 470. (b) Shiraishi, M.; Terao, S. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1591. (c) Shiraishi, M.; Kato, K.; Ohkawa, S.; Terao, S. *J. Pharm. Dyn.* **1984**, *7*, s-95.
(2) (a) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishikawa, K. *J. Med. Chem.* **1985**, *28*, 287. (b) Imura, Y.; Terashita, Z.; Shibouta, Y.; Nishikawa, K. *J. Eur. Pharm.* In press. It is reported that CV-4151 shows the TXA_2 receptor antagonistic activity in addition to the TXA_2 synthetase inhibitory effect.
(3) Jurd, L.; Wong, R. Y. *Aust. J. Chem.* **1980**, *33*, 137.
(4) Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777.

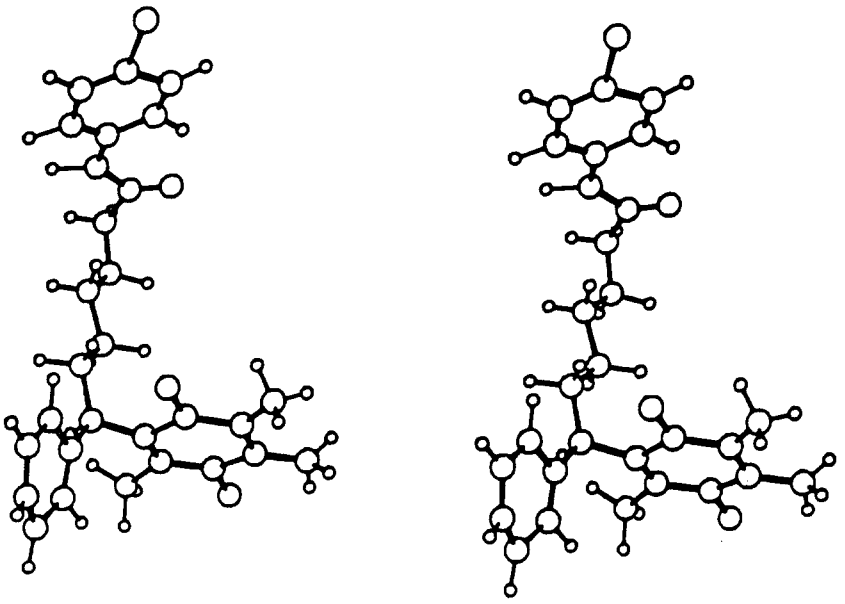
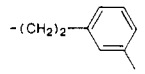
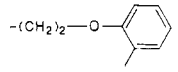


Figure 1. Stereoscopic pair of **9**.

Table II. Physical Properties and Inhibitory Effects of Compounds **5a–c**, **6a–h**, and **7a–e**

compd	R, X, or Y	formula[a]	mp, °C	% inhibition[b,c] 10^{-5} M	% inhibition[b,c] 10^{-6} M	% inhibition[b,c] 10^{-7} M	IC_{50},[d] μM
5a	H	$C_{16}H_{22}O_4$	70–71	8			
5b	Me	$C_{17}H_{24}O_4$	oil	0			
5c	2-thienyl	$C_{20}H_{24}O_4S$	116–117	100	65	0	0.76
6a	Me	$C_{22}H_{28}O_2$	oil	25			
6b	CH_2OH	$C_{22}H_{28}O_3$	oil	0			
6e	CO_2Me	$C_{23}H_{28}O_4$	54–55	95	36		1.4
6d	$CONH_2$	$C_{22}H_{27}NO_3$	105–106	6			
6e	$CONHPr^i$	$C_{25}H_{33}NO_3$	99–101	8			
6f	CONH(Me)Ph	$C_{30}H_{35}NO_3$	105–106	33			
6g	$CONHCH_2CO_2H$	$C_{24}H_{29}NO_5$	162–164	0			
6h	5-tetrazolyl	$C_{22}H_{26}N_4O_2$	128–130	2			
7a	$-(CH_2)_4C(Me)_2-$	$C_{24}H_{30}O_4$	112–113	12			
7b	$-(CH_2)_3C{\equiv}C-$	$C_{22}H_{22}O_4$	134–136	72			
7c		$C_{25}H_{24}O_4$	171–173	89	0		
7d		$C_{25}H_{24}O_5$	175–177	2			
7e	$-(CH_2)_2CONHCH_2-$	$C_{21}H_{23}NO_5$	145–146	0			

[a] Analyses (C, H, N) within ±0.3% of the calculated values. [b] Percent inhibition on U-44069 (10^{-7} M) induced contraction of the rabbit aorta. [c] Values are the mean of duplicate experiments. [d] Antagonist concentration that reduced U-44069-induced contraction of the rabbit aorta by 50%.

Table III. Physical Properties and Inhibitory Effects[a] of Compounds **8a,b** and **4d** in Vitro

compd	formula[b]	mp, °C	$[\alpha]_D$,[c] deg	op, % ee	pA_2[d,e]	pA_2[d,f]	IC_{50},[g] M	IC_{50},[h] M
8a	$C_{22}H_{26}O_4$	77–80	+24.8	96	8.60	8.80 ± 0.10	1.2×10^{-7}	2.1×10^{-9}
8b	$C_{22}H_{26}O_4$	77–80	−24.8	96	6.64[i]	6.53 ± 0.09[i]	1.3×10^{-5} [i]	2.1×10^{-7} [i]
4d					8.28	8.29 ± 0.09	3.5×10^{-7}	7.4×10^{-9}
U-46619 (IV)								3.1×10^{-8}

[a] Values are the mean ± SEM of four to six independent experiments or the mean of duplicate experiments when the SEM is not given. [b] Analyses (C, H) within ±0.3% of the calculated values. [c] (c 1, $CHCl_3$). [d] −log antagonist concentration that produced a 2-fold rightward shift of the U-44069 concentration–response curve. [e] The pA_2 values show the effects on U-44069-induced contraction of the rabbit aorta. [f] The pA_2 values show the effects on U-46619-induced contraction of guinea pig lung. [g] Antagonist concentration that reduced U-44069-induced aggregation of the guinea pig platelet by 50%. [h] Antagonist concentration that reduced the specific binding of [^{3}H]U-46619 to guinea pig platelets (TXA_2 receptor) by 50%. [i] The effects might result from 2% of **8a** contaminated in the sample.

rabbit aorta in vitro. The results are summarized in Tables I and II as percent inhibition at the various concentrations tested.

The first compound we synthesized, **4d**, exhibited a very potent effect in the in vitro test. To determine the compound with the highest potency in the assay system, we synthesized a series of ω-phenyl-ω-quinonylalkanoic acids **4a–g** with two to eight methylene groups. The highest potency appeared in compound **4d**, (±)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid, with five methylene groups. The in vitro potency of the com-

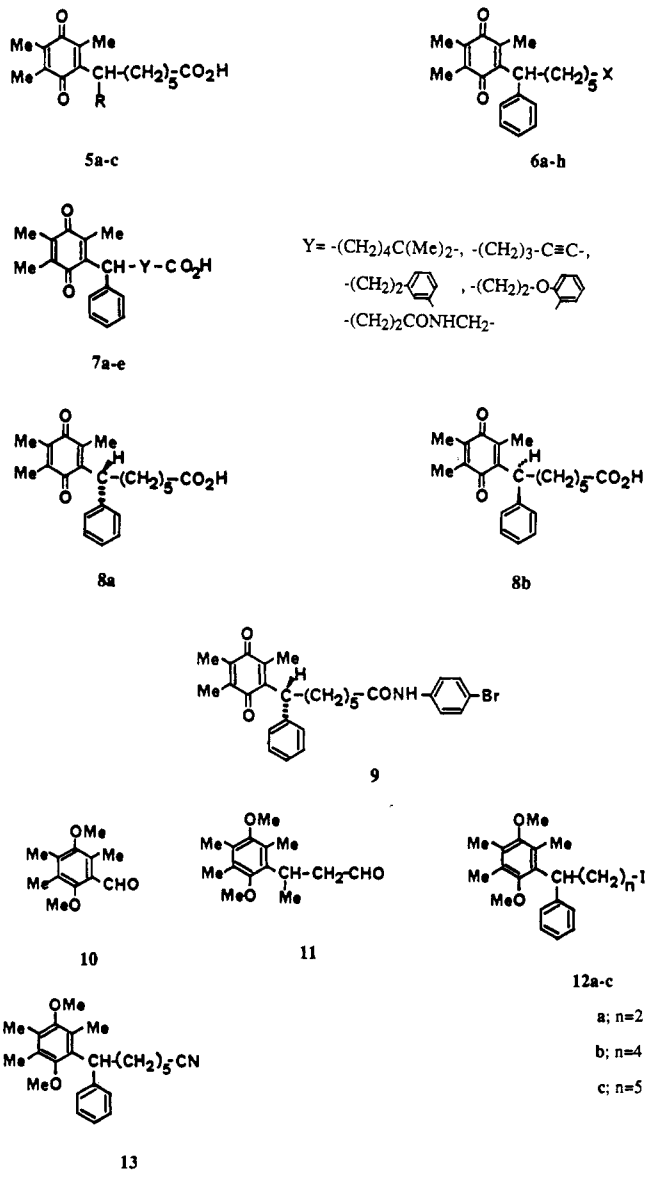
(5) The stable PGH_2 analogues, both U-44069 and U-46619, are thromboxane mimetics on the PGH_2/TXA_2 receptor: (a) Bundy, G. L. *Tetrahedron Lett.* **1975**, 1957. (b) Malmsten, C. *Life Sci.* **1976**, *18*, 169.

Table IV. Pharmacological Effects of Compounds **8a,b** and **4d** in Vivo

compd	mediator	% inhibition[a,e] 20 mg/kg	5 mg/kg	1.25 mg/kg	0.31 mg/kg	0.08 mg/kg	ID_{50},[b] mg/kg
8a	U-46619			93**[e]	75**	72**	
	LTD_4		80**	85**	85**	12	
8b	U-46619	68*[c]	47				
	LTD_4	65*[c]	27				
4d	U-46619			90**	89**	31	0.13
	LTD_4		94** (72**)[d]	77**	58**	24	0.19
	PAF		85**	94**	66**		
	IgG_1		91** (96**)[d]	85**	71**		0.20

[a] Present inhibition on U-46619-, LTD_4-, or PAF-induced bronchoconstriction in guinea pig or on IgG_1-mediated bronchoconstriction in actively sensitized guinea pig after the oral administration 1 h. The number of animals is eight. [b] The values represent the dose required to produce 50% inhibition of bronchoconstriction induced by U-46619, LTD_4, and IgG_1. [c] The effects might result from 2% of **8a** contaminated in the sample. [d] The number in parentheses shows percent inhibition 24 h after the oral administration of 5 mg/kg. The number of animals is eight. [e] Significance of differences: (*) $P < 0.05$, (**) $P < 0.01$.

Chart II



pounds **4a–g** depended on the number of methylene groups. In changes of the quinoyl moiety, the 3,5,6-trimethyl-1,4-benzoquinon-2-yl group appeared to be more effective when compared with compounds (**4d,h,i**) with the same number of methylene groups. Keeping the five-methylene chain length, the quinonyl moiety, and the terminal acid in the structure **4d**, we then determined the effects of the groups (R) substituted on the α-carbon of the quinone side chain (**5a–c**). Changing the phenyl group to the methyl or hydrogen greatly reduced potency. Variations at R showed that the phenyl group gave more favorable results. We next investigated the effects of other terminal groups (X) in place of the carboxyl group in the original molecule **4d** (**6a–h**). While the compound in which the chain was terminated with methoxycarbonyl was found to have significant activity, variations at X showed that the carboxylic acid was best. In addition, we investigated the effects of modifying the α-methylene group adjacent to the carboxyl group and of introducing a substituent in the five-carbon chain as shown in Y. Changing the methylene groups in **4d** to include other substituents (**7a–e**) resulted in a profound loss of potency. Finally, we determined the effects of phenyl-substitution changes, keeping the structure of the original compound **4d**. Variations at R_2 showed that the para substituent on the phenyl group was generally better than one at the ortho or meta position and that a halogen (particularly fluorine) atom or methyl group on the para position was as effective as a hydrogen atom. From these results and other factors[6] including acute toxicity in mice (po) and ease of synthesis, compound **4d** was chosen for the further pharmacological studies.

Compound **4d** and optically active compounds [**8a**, *R*-(+); **8b**, *S*-(−)] were examined for their various pharmacological effects as shown in Table III. We examined the effects of these compounds against U-44069-induced contraction of the rabbit aorta in vitro. The *R*-(+) isomer **8a** and **4d** inhibited the U-44069-induced contraction with pA_2 values of 8.60 and 8.28, respectively, but the *S*-(−) isomer **8b** was less active. The inhibitory effects of these compounds on U-46619[5]-induced contraction of the guinea pig lung in vitro were also similar; compounds **8a** and **4d** had high pA_2 values of 8.80 and 8.29, respectively, but compound **8b** was much less active. TXA_2, in addition to its powerful activity related to vascular and pulmonary smooth muscle contraction, shows potent activity in platelet aggregation. We tested these compounds for their effects on U-44069-induced aggregation of the guinea pig platelet in vitro (Table III). Compounds **8a** and **4d** strongly inhibited the aggregation dose dependently with IC_{50} values of 1.2×10^{-7} M and 3.5×10^{-7} M, respectively, whereas the effect of **8b** was weak. The inhibitory effects on the specific binding of [^{3}H]U-46619 to guinea pig platelets (TXA_2 receptor) in vitro were also examined (Table III). Derivatives **8a** and **4d** displaced the binding of [^{3}H]U-46619 dose dependently with IC_{50} values of 2.1×10^{-9} M and 7.4×10^{-9} M, respectively.

We next studied the inhibitory effects of **8a,b** and **4d**

(6) Further details will be published in *Prostaglandins*.

on U-46619-induced bronchoconstriction in guinea pigs in vivo (po). The results are summarized in Table IV as percent inhibition at the various doses tested. Compounds **8a** and **4d** showed very potent inhibitory effects, whereas compound **8b** was much less active. Compound **4d** also showed highly potent inhibitory effects on LTD_4 or platelet activating factor (PAF) induced bronchoconstriction in guinea pigs and/or on IgG_1-mediated bronchoconstriction in actively sensitized guinea pigs. Additionally, compound **4d** indicated long-lasting inhibitory effects on LTD_4-induced bronchoconstriction in guinea pigs and/or on IgG_1-mediated bronchoconstriction in actively sensitized guinea pigs (Table IV).

Arachidonate cascade metabolites, such as TXA_2, prostaglandin H_2 (PGH_2), PGD_2, $PGF_{2\alpha}$, 11-*epi*-$PGF_{2\alpha}$, and LTs are potent bronchoconstrictors.[7] Judging from the above-mentioned results of structure–activity relationships, we postulated that the potent antiasthmatic effects of **4d** with a minimum effective dose (MED) of 0.3 mg/kg (po) were based mainly on the receptor antagonistic action of TXA_2. To prove this assumption, several in vitro tests[6] of **4d** were carried out. Compounds **4d** and **8a,b** inhibited the production of 5-hydroxyeicosatetraenoic acid (5-HETE) from arachidonic acid by RBL-1 (rat basophilic leukemia) cells with IC_{50} values of 2.1×10^{-7} M, 3.1×10^{-7} M, and 1.9×10^{-7} M, respectively, but their effects were weaker than that of V ($IC_{50} = 2.0 \times 10^{-8}$ M).[1c] Thromboxane synthetase inhibitory effect of **4d** (horse platelet, 13% inhibition at 10^{-5} M) was much weaker than that of VI ($IC_{50} = 2.6 \times 10^{-8}$ M).[2a] Cyclooxygenase-inhibitory effect of **4d** (bovine vesicular gland, 20% inhibition at 10^{-4} M) was very weak. In addition, compound **4d** indicated neither anti-LTD_4 nor anti-PAF activities at 10^{-4} M (guinea pig lung membranes) and 10^{-5} M (rabbit platelets), respectively. From the pharmacological results, we concluded that the potent antiasthmatic effects of **4d** were based mainly on the TXA_2/PGH_2 receptor antagonistic action. Since the LT receptor antagonistic action of **4d** was lacking, we concluded that the LTD_4-induced bronchoconstriction in guinea pigs might occur through the formation and release of TXA_2 and the binding to its receptor.

Compound **4d** also showed potent inhibitory effects on PGD_2-, $PGF_{2\alpha}$-, and 11-*epi*-$PGF_{2\alpha}$-induced contraction of the guinea pig tracheal strips in vitro (pA_2 values 7.20, 5.71, and 7.79, respectively).[6] The diverse inhibitory effects of **4d** might be interpreted as an eicosanoid-antagonistic action on the basis of the binding assays. Compound **4d** showed an inhibitory effect on 5-lipoxygenase as well as a scavenging action[6] on active oxygen species. This effect could be associated with its quinone structure.[8] It is interesting to note that the introduction of a phenyl group on the α-carbon of the quinone-based 5-lipoxygenase inhibitor V has resulted in a new pharmacological profile. It is concluded that (±)-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid (**4d**), a non-eicosanoid compound, is a novel, highly potent, orally active, and long-acting eicosanoid antagonist. This compound possesses a variety of pharmacologically beneficial effects and is under clinical investigations for the treatment of asthma, allergy, and other diseases.

Experimental Section

Melting points were determined on a Yamaco micro-melting apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer at 90 MHz in $CDCl_3$ with tetramethylsilane as internal standard. When elemental analyses are given, results obtained were within ±0.3% of the theoretical values. Optical rotations were measured with a JASCO DIP-181 instrument. Silica gel used for column chromatography was from Merck (Silica gel 60, 70–230 mesh). THF and isopropyl ether (IPE) were distilled from calcium hydride before use. Solutions in organic solvents were dried over anhydrous $MgSO_4$. HPLC was carried out on a Hitachi 630-30 liquid chromatograph. CHIRALCEL OC (cellulose derivatives coated on silica gel, Daicel Chemical Industries, Ltd.) was used for analytical HPLC of optical resolution. Crystallographic analyses were performed by M. Takamoto and Y. Wada.

ω-Aryl-ω-hydroxyalkanoic Acids 2a–r and the Lactone 3. Method A. Thionyl chloride (92.0 mL, 1.28 mol) was added to a solution of 6-(ethoxycarbonyl)hexanoic acid[9] [bp 144–148 °C (5 mmHg); 120 g, 0.64 mol] in CH_2Cl_2 (200 mL) at ambient temperature. The mixture was brought to 50 °C, stirred for 2 h, and then the solvent was evaporated under reduced pressure. The residue was distilled to give ethyl 6-(chloroformyl)hexanoate (129 g, 98%), bp 90–91 °C (0.3 mmHg). This ester (41.3 g, 0.20 mol) was added dropwise to a stirred suspension of $AlCl_3$ (53.2 g, 0.20 mol) in benzene (71.0 mL, 0.80 mol) at 5 °C during 40 min. When addition was complete, the mixture was brought to 90 °C, stirred for 2 h, and then cooled. The reaction mixture was poured into a mixture of crushed ice (400 g) and concentrated HCl (40 mL), followed by stirring. After 20 min, the product was extracted with EtOAc (500 mL). The EtOAc was washed with saturated brine, dried, and evaporated. The residue was dissolved in EtOH (200 mL), to which was added concentrated H_2SO_4 (2 mL). The mixture was heated at 80 °C for 2 h and then cooled. To the reaction mixture was added aqueous $NaHCO_3$, and the EtOH was evaporated under reduced pressure. The product was extracted with EtOAc (400 mL). The EtOAc was washed with brine, dried, and evaporated. The residue (ethyl 6-benzoylhexanoate) was dissolved in MeOH (300 mL). After being cooled to 0 °C, $NaBH_4$ (4.5 g, 0.12 mol) was added portionwise to the solution during 10 min. The mixture was stirred for a further 30 min under the same conditions. The reaction mixture was quenched with Me_2CO, and the MeOH was evaporated under reduced pressure. EtOAc (400 mL) and water (300 mL) were added to the residue, and the EtOAc was washed with brine, dried, and evaporated. To the resulting product (ethyl 7-hydroxy-7-phenylheptanoate) was added a mixture of THF (200 mL) and 2.5 N NaOH (200 mL). The mixture was stirred at 70 °C for 3 h and then cooled. IPE (200 mL) and saturated brine (200 mL) were added to the mixture, and the aqueous layer was washed with IPE and acidified to pH 3 with 4 N HCl. The resulting product was extracted with EtOAc (500 mL). The extract was washed successively with water and brine, dried, and evaporated under reduced pressure to give 7-hydroxy-7-phenylheptanoic acid **2c** (42.2 g, 95%) as an oil: ^1H NMR δ 7.27 (m, 5 H), 6.31 (br s, 2 H), 4.61 (t, 1 H), 2.27 (t, 2 H), 1.8–1.2 (m, 6 H).

The compounds **2a,b**, **2d–l**, and **2r** were prepared by the similar method as described above from the corresponding materials: **2a** (R^2 = H, n = 3; oil), **2b** (R^2 = H, n = 4; oil), **2d** (R^2 = H, n = 6; oil), **2e** (R^2 = H, n = 7; oil), **2f** (R^2 = H, n = 8; oil), **2g** (R^2 = *p*-Me, n = 5; mp 62–64 °C), **2h** (R^2 = *p*-Pr^i, n = 5; oil), **2i** (R^2 = *p*-F, n = 5; mp 85–86 °C), **2j** (R^2 = *p*-Cl, n = 5; mp 97–98 °C), **2k** (R^2 = *p*-Br, n = 5; mp 87–89 °C), **2l** (R^2 = *p*-MeO, n = 5; mp 55–56 °C), **2r** [7-hydroxy-7-(2-thienyl)heptanoic acid; oil].

Method B. Ethyl 6-(3-fluorobenzoyl)hexanoate was prepared from 1-bromo-3-fluorobenzene (3.15 g, 18 mmol) according to the Mukaiyama et al. method[4] with use of the *S*-(2-pyridyl) thioester to yield 4.10 g of an oil (86%). The ethyl ester (3.99 g, 15 mmol) was treated similarly to method A to give 7-(3-fluorophenyl)-7-

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hydroxyheptanoic acid (**2o**, 3.50 g, 97%) as an oil: ^{1}H NMR δ 7.4–6.4 (m, 6 H), 4.62 (t, 1 H), 2.28 (t, 2 H), 1.9–1.1 (m, 8 H).

The compounds **2m,n** and **2p,q** were prepared by the same method as described above from the corresponding materials: **2m** (R^2 = *o*-Me, *n* = 5; oil), **2n** (R^2 = *o*-MeO, *n* = 5; oil), **2p** (R^2 = *m*-MeO, *n* = 5; oil), **2q** (R^2 = *m*-CF_3, *n* = 5; oil).

Method C. Crude ethyl 4-hydroxy-4-phenylbutyrate (containing the lactone **3**) was prepared by method A from ethyl 3-(chloroformyl)-propionate [bp 93–95 °C (15 mmHg); 16.5 g, 0.10 mol]. The compound was dissolved in 1,2-dichloroethane (150 mL), to which was added D-camphor-10-sulphonic acid (0.46 g, 2 mmol). The mixture was heated at 80 °C for 1 h, and then cooled. The 1,2-dichloroethane was washed in turn with aqueous $NaHCO_3$ and brine, dried, and evaporated under reduced pressure to give 4-phenyl-4-butanolide **3** (15.4 g, 95%) as an oil: ^{1}H NMR δ 7.35 (m, 5 H), 5.49 (dd, 1 H), 2.8–2.0 (m, 4 H).

ω-Aryl-ω-quinonylalkanoic Acids 4a–u and 5c and Compounds 6a,b and 7c. General Procedure. Boron trifluoride etherate (8.1 g, 57 mmol) was added dropwise to a mixture of trimethylhydroquinone (**1a**, 28.9 g, 190 mmol) and 7-hydroxy-7-phenylheptanoic acid (**2c**, 42.2 g, 190 mmol) in toluene (570 mL) at 60 °C during 20 min. The mixture was stirred for a further 2 h under the same conditions and then evaporated under reduced pressure. The residue was dissolved in THF (300 mL), to which was added 1.5 M $FeCl_3$ (300 mL) at room temperature. The mixture was stirred for 30 min and then concentrated under reduced pressure. The residue was extracted with EtOAc (500 mL). The extract was washed with brine and dried. The EtOAc was filtered through silica gel (100 g), and the silica gel was washed with EtOAc (300 mL). The combined EtOAc was evaporated under reduced pressure. The residue was recrystallized from EtOH to give 7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid, (**4d**, 49.0 g, 73%): ^{1}H NMR δ 8.50 (br s, 1 H), 7.24 (m, 5 H), 4.29 (t, 1 H), 2.32 (t, 2 H), 2.04 (s, 3 H), 2.4–2.0 (m, 2 H), 1.97 (s, 6 H), 1.8–1.1 (m, 8 H).

The preparation of **4r** was carried out in a 1,2-dichloroethane solvent at 80 °C for 2 h, followed by oxidation. The compounds **6a,b** and **7c** were prepared by a similar method as described above from the corresponding materials [1-phenylheptan-1-ol (oil), 7-hydroxy-7-phenylheptan-1-ol (oil), and 3-(3-hydroxy-3-phenylpropyl)benzoic acid (mp 120–122 °C), respectively].

7-(2,3,5-Trimethyl-1,4-benzoquinon-6-yl)octanoic Acid (5b). 3-(2,5-dimethoxy-3,4,6-trimethylphenyl)butanal (**11**, oil) was prepared by the coupling reaction between 1-bromo-2,5-dimethoxy-3,4,6-trimethylbenzene (mp 72–73 °C) and crotyl bromide by using the Snyder and Rapoport method,[10] followed by the hydroboration–oxidation[11] and the Swern oxidation[12] of the resulting 3-(2,5-dimethoxy-3,4,6-trimethylphenyl)-1-butene (oil): ^{1}H NMR δ 9.68 (t, 1 H), 3.83 (m, 1 H), 3.67 (s, 3 H), 3.60 (s, 3 H), 2.89 (dd, 2 H), 2.27 (s, 3 H), 2.16 (s, 6 H), 1.33 (d, 3 H). A stirred suspension of NaH (24 mmol, 60% mineral oil dispersion, washed with hexane to remove the oil and dried before use) in DMSO (30 mL) was heated at 80 °C for 1 h under Ar; the solution was then cooled. To the solution was added (3-carboxypropyl)triphenylphosphonium bromide (4.6 g, 11 mmol) portionwise at such a rate to keep a temperature of 25–30 °C. After the addition was completed, the mixture was stirred for 10 min at ambient temperature. To the mixture was added a solution of **11** (2.7 g, 11 mmol) in THF (5 mL) for 10 min and then the mixture was stirred under the same conditions for 2 h. When the reaction was completed, water (50 mL) and toluene (100 mL) were added, and then the mixture was shaken vigorously. The organic layer was partitioned and the aqueous layer was acidified to pH 4 with 2 N HCl. The resulting product was extracted with IPE. The extract was washed with water, dried, and concentrated. The residue was chromatographed on silica gel with IPE as eluent to give 7-(2,5-dimethoxy-3,4,6-trimethylphenyl)-4-octenoic acid (2.2 g, 68%) as a colorless oil. A solution of this compound 2.1 g, 6.3 mmol) in EtOAc (20 mL) was hydrogenated over 5% Pd–C (0.2 g) at ambient temperature under atmospheric pressure until 1 molar equiv of hydrogen had been absorbed. After the reaction was completed, the catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give 7-(2,5-dimethoxy-3,4,6-trimethylphenyl)octanoic acid (2.0 g, 95%) as a colorless oil. A solution of this compound 2.0 g, 6.0 mmol) in a mixture of 30% aqueous MeCN (20 mL) was cooled to 0–2 °C and treated dropwise with a cold solution of cerium(IV) ammonium nitrate (9.9 g) in 50% aqueous MeCN (20 mL) during 20 min. The mixture was stirred for a further 20 min under the same conditions. The product, obtained in the usual manner, was chromatographed on silica gel with IPE as eluent to give the acid **5b** (1.6 g, 88%) as a yellow oil: ^{1}H NMR δ 2.92 (m, 1 H), 2.30 (t, 3 H), 2.02 (s, 3 H), 1.99 (s, 6 H), 1.59 (m, 6 H), 1.21 (d, 3 H).

7-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)heptanoic Acid (5a). 2,5-Dimethoxy-3,4,6-trimethylbenzaldehyde (**10**, mp 85–86 °C) was obtained by treatment of 1,4-dimethoxy-2,3,5-trimethylbenzene with dichloromethyl methyl ether in the presence of titanium tetrachloride[13]: ^{1}H NMR δ 10.47 (s, 1 H), 3.76 (s, 3 H), 3.64 (s, 3 H), 2.48 (s, 3 H), 2.25 (s, 3 H), 2.20 (s, 3 H). Compound **5a** was prepared by the same method as described above from the aldehyde **10**. Overall yield: 52%; ^{1}H NMR δ 7.20 (br s, 1 H), 2.44 (t, 2 H), 2.34 (t, 2 H), 2.01 (s, 9 H), 1.8–1.2 (m, 8 H).

Preparation of Amides 6d–g and 7e. General Procedure. Dicyclohexyl carbodiimide (4.53 g, 22 mmol) was added to a solution of **4d** (7.08 g, 20 mmol) and *p*-nitrophenol (3.06 g, 22 mmol) in CH_2Cl_2 (70 mL) at 0 °C during 5 min. The mixture was stirred further for 30 min under the same conditions and for 1 h at ambient temperature. The CH_2Cl_2 was evaporated under reduced pressure. To the residue was added EtOAc (50 mL), which was left overnight at 5–6 °C. The precipitate was filtered off and the filtrate was evaporated in vacuo. The residue was crystallized from IPE to give 8.65 g (91%, mp 86–88 °C) of *p*-nitrophenyl 7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoate.

To a solution of this *p*-nitrophenyl ester (0.71 g, 1.5 mmol) in THF (7 mL) was added concentrated ammonia–water (1.0 mL). After the reaction mixture was stirred for 4 h at room temperature, the THF was evaporated in vacuo. To the residue was added an aqueous K_2CO_3, and the product was then extracted with EtOAc. The extract was washed with water, dried, and evaporated. The residue was crystallized from IPE to give 0.46 g (87%) of 7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanamide (**6d**): ^{1}H NMR δ 7.24 (m, 5 H), 5.95 (br d, 2 H), 4.29 (t, 1 H), 2.4–1.9 (m, 4 H), 2.04 (s, 3 H), 1.97 (s, 6 H), 1.8–1.1 (m, 6 H). **6e**: 81%; ^{1}H NMR δ 7.23 (m, 5 H), 5.50 (br d, 2 H), 4.29 (t, 1 H), 4.05 (m, 1 H), 2.3–1.9 (m 4 H), 2.03 (s, 3 H), 1.96 (s, 6 H), 1.8–1.1 (m, 6 H), 1.11 (d, 6 H). **6f** [using L-(−)-1-phenylethylamine]: 85%; ^{1}H NMR δ 7.27 (s, 5 H), 7.22 (m, 5 H), 5.91 (d, 1 H), 5.10 (m, 1 H), 4.27 (t, 1 H), 2.3–1.9 (m, 4 H), 2.02 (s, 3 H), 1.96 (s, 6 H), 1.8–1.1 (m, 6 H), 1.45 (d, 3 H).

Compounds **6g** and **7e** were prepared from the corresponding acids similarly to the above method with use of glycine benzyl ester instead of ammonia–water, followed by the deprotection (H_2/5% Pd–C) and the oxidation (1 M $FeCl_3$) in the usual manner. **6g**: 76%; ^{1}H NMR δ 7.60 (br s, 1 H), 7.23 (m, 5 H), 6.39 (t, 1 H), 4.28 (t, 1 H), 4.02 (d, 2 H), 2.3–1.9 (m, 4 H), 2.03 (s, 3 H), 1.97 (s, 6 H), 1.8–1.1 (m, 6 H). **7e**: 71%; ^{1}H NMR δ 9.63 (br s, 1 H), 7.23 (m, 5 H), 6.55 (t, 1 H), 4.32 (t, 1 H), 3.97 (d, 2 H), 2.7–2.1 (m, 4 H), 2.01 (s, 3 H), 1.95 (s, 6 H).

Methyl 7-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoate (6c). To a solution of **4d** (0.71 g, 2.0 mmol) in MeOH (10 mL) was added concentrated H_2SO_4 (0.02 mL), which was heated to reflux at 80 °C for 2 h. After being cooled, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (1 mL) and then the MeOH was evaporated in vacuo. The product, obtained in the usual manner, was chromatographed on silica gel with IPE as eluent to give the methyl ester **6c** (0.72 g, 98%): ^{1}H NMR δ 7.24 (m, 5 H), 4.29 (t, 1 H), 3.63 (s, 3 H), 2.3–1.9 (m, 2 H), 2.28 (t, 2 H), 2.04 (s, 3 H), 1.97 (s, 6 H), 1.8–1.1 (m, 6 H).

5-[6-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)-6-phenylhexyl]tetrazole (6h). 1-Iodo-6-(2,5-dimethoxy-3,4,6-trimethylphenyl)-6-phenylhexane (**12c**, oil) was prepared by the same method as shown in our previous report:[1b] ^{1}H NMR δ 7.20 (m,

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5 H), 4.55 (d, 1 H), 3.60 (s, 3 H), 3.24 (s, 3 H), 3.12 (t, 2 H), 2.3–1.9 (m, 2 H), 2.18 (s, 3 H), 2.15 (s, 3 H), 2.07 (s, 3 H), 1.79 (m, 2 H), 1.6–1.2 (m, 4 H). To a solution of **12c** (4.66 g, 10 mmol) in DMSO (40 mL) was added NaCN (1.23 g, 25 mmol). The mixture was stirred at 50 °C for 2 h. After being cooled, water (60 mL) and IPE (100 mL) were added to the reaction mixture. The IPE was washed with aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel with IPE–hexane (2:1) as eluent to give 6-(2,5-dimethoxy-3,4,6-trimethylphenyl)-6-phenylhexyl cyanide (**13**, 3.40 g, 93%) as a colorless oil.

A mixture of **13** (3.29 g, 9.0 mmol), NaN_3 (2.93 g, 45 mmol), and NH_4Cl (2.68 g, 45 mmol) in DMF (60 mL) was heated at 120–130 °C for 24 h. At this time, an additional portion of NaN_3 (1.76 g, 27 mmol) and NH_4Cl (1.44 g, 27 mmol) were added, and heating was continued for an additional 16 h. The reaction mixture was filtered hot and the filtrate was evaporated in vacuo. The residue was treated with dilute HCl and extracted with EtOAc. The EtOAc was washed with aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel with EtOAc–IPE (2:1) as eluent to give 5-[6-(2,5-dimethoxy-3,4,6-trimethylphenyl)-6-phenylhexyl]tetrazole (1.43 g, 39%) as a viscous oil.

A solution of this compound (1.43 g, 3.5 mmol) in a mixture of 30% aqueous MeCN (15 mL) was treated with a cold solution of cerium(IV) ammonium nitrate (5.75 g) in 50% aqueous MeCN (15 mL) according to the method used for the preparation of **5b** to give the quinone tetrazole **6h** (1.07 g, 81%): ^{1}H NMR δ 12.86 (br s, 1 H), 7.21 (m, 5 H), 4.27 (t, 1 H), 3.06 (t, 2 H), 2.3–2.0 (m, 2 H), 2.02 (s, 3 H), 1.96 (s, 6 H), 1.9–1.2 (m, 6 H).

2,2-Dimethyl-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic Acid (7a). 1-Iodo-5-(2,5-dimethoxy-3,4,6-trimethylphenyl)-5-phenylpentane (**12b**, oil) was prepared by the same method as shown in our previous report:[1b] ^{1}H NMR δ 7.20 (m, 5 H), 4.55 (dd, 1 H), 3.60 (s, 3 H), 3.22 (s, 3 H), 3.13 (t, 2 H), 2.5–1.9 (m, 2 H), 2.17 (s, 3 H), 2.14 (s, 3 H), 2.08 (s, 3 H), 1.86 (m, 2 H), 1.8–1.2 (m, 2 H). *n*-Butyllithium (1.6 M solution in hexane, 2.1 mL, 3.3 mmol) was added dropwise to a solution of diisopropylamine (0.50 mL, 3.6 mmol) in THF (5 mL) at −20 °C under Ar during 10 min, followed by the addition of a solution of ethyl isobutyrate (0.38 g, 3.3 mmol) in THF (4 mL) under the same conditions. The solution was stirred for 20 min and then a solution of **12b** (1.36 g, 3.0 mmol) in THF (14 mL) was added for 10 min. After the mixture was stirred at −20 to −10 °C for 1.5 h, the reaction was quenched with 1 N HCl. IPE and NaCl were added to extract the product. The extract was washed with aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel with IPE–hexane (1:4) as eluent to give ethyl 7-(2,5-dimethoxy-3,4,6-trimethylphenyl)-2,2-dimethyl-7-phenylheptanoate (1.20 g, 91%) as a colorless oil.

The ethyl ester was hydrolyzed with 2 N NaOH, followed by oxidative demethylation with cerium(IV) ammonium nitrate and worked up in the usual way to give the free acid **7a** (0.74 g, 72%): ^{1}H NMR δ 11.0 (br s, 1 H), 7.23 (m, 5 H), 4.27 (t, 1 H), 2.4–2.0 (m, 2 H), 2.04 (s, 3 H), 1.97 (s, 6 H), 1.6–1.1 (m, 6 H), 1.17 (s, 6 H).

7-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenyl-2-heptynoic Acid (7b). 7-(3,5,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenyl-2-heptyn-1-ol (mp 84–85 °C) was prepared according to the methods described in our previous report:[1b] ^{1}H NMR δ 7.25 (m, 5 H), 4.32 (t, 1 H), 4.21 (t, 2 H), 2.4–2.0 (m, 4 H), 2.05 (s, 3 H), 1.96 (s, 6 H), 1.93 (s, 1 H), 1.51 (m, 2 H). Jones' reagent (2.25 mL) was added dropwise to a solution of (1.01 g, 3.0 mmol) in acetone (15 mL) at room temperature during 15 min. After the mixture was stirred for 30 min, the acetone was concentrated. The residue was worked up in the usual way to give the 2-heptynoic acid **7b** (0.71 g, 68%): ^{1}H NMR δ 7.24 (m, 5 H), 5.70 (br s, 1 H), 4.31 (t, 1 H), 2.4–2.0 (m, 2 H), 2.38 (t, 2 H), 2.05 (s, 3 H), 1.97 (s, 6 H), 1.8–1.4 (m, 2 H).

2-[3-(2,3,5-Trimethyl-1,4-benzoquinon-6-yl)-3-phenylpropoxy]benzoic Acid (7d). 1-Iodo-3-(2,5-dimethoxy-3,4,6-trimethylphenyl)-3-phenylpropane (**12a**, oil) was prepared by the same method as shown in our previous report:[1b] ^{1}H NMR δ 7.21 (m, 5 H), 4.61 (dd, 1 H), 3.61 (s, 3 H), 3.16 (s, 3 H), 3.06 (t, 2 H), 2.81 (m, 2 H), 2.20 (s, 3 H), 2.17 (s, 3 H), 2.13 (s, 3 H). NaH (2.0 mmol, 60% mineral oil dispersion) was added to a solution of methyl 2-hydroxybenzoate (0.30 g, 2.0 mmol) in DMF (3 mL) under ice cooling, followed by stirring for 5 min. To the mixture was added a solution of **12a** 2.0 mmol in DMF (5 mL) and then the mixture was stirred at 50 °C for 2 h. After being cooled, the reaction mixture was quenched with 1 N HCl. The product, obtained in the usual manner, was chromatographed on silica gel with IPE–hexane (1:4) as eluent to give methyl 2-[3-(2,5-dimethoxy-3,4,6-trimethylphenyl)-3-phenylpropoxy]benzoate (0.80 g, 89%) as a colorless oil.

The methyl ester was hydrolyzed, followed by oxidative demethylation, and worked up in the usual way to give the acid **7d** (0.34 g, 47%): ^{1}H NMR δ 12.2 (br s, 1 H), 8.14 (dd, 1 H), 7.50 (m, 1 H), 7.29 (m, 5 H), 7.13 (d, 1 H), 6.92 (d, 1 H), 4.52 (t, 1 H), 4.24 (t, 2 H), 2.82 (m, 2 H), 2.07 (s, 3 H), 1.97 (s, 3 H), 1.93 (s, 3 H).

Resolution of (±)-7-(3,4,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic Acid (4d). To a solution of racemic **4d** (10.0 g, 28 mmol) in EtOAc (200 mL) was added L-(−)-phenylethylamine (3.41 g, 28 mmol) [Aldrich: $[\alpha]_D$ −39° (neat)]. After the mixture was stirred at room temperature for 1 h and allowed to stand for 2 h at room temperature, a yellow precipitate (7.23 g) was collected. This (−)-phenylethylamine salt was recrystallized four times from EtOAc to give yellow crystals (2.92 g). Further recrystallizations from EtOAc did not change the specific rotation of the free acid liberated from samples of the phenylethylamine salt after each recrystallization. The salt was treated with 1 N HCl, and the liberated acid was extracted with EtOAc. The EtOAc was washed with aqueous NaCl, dried, and evaporated in vacuo to give the (+)-rich **4d** (2.16 g): $[\alpha]_D$ +22.8° (*c* 1, $CHCl_3$); ee = 88%, determined by chromatographic separation of **6c** (**4d** methyl ester) on an HPLC column (CHIRALCEL OC). The sample for the determination of the optical purity was prepared by esterifying the free acid with CH_2N_2 in ether. The (+)-rich **4d** (2.16 g) was recrystallized from EtOH (11 mL) and the precipitate (racemic **4d**) was filtered off. The filtrate was evaporated in vacuo. The residue was crystallized from IPE to give the (+)-**4d** (**8a**) (1.67 g, 17%): $[\alpha]_D$ +24.8° (*c* 1, $CHCl_3$); 96% ee; ^{1}H NMR δ 9.70 (br s, 1 H), 7.24 (m, 5 H), 4.29 (t, 1 H), 2.4–2.0 (m, 2 H), 2.32 (t, 2 H), 2.04 (s, 3 H), 1.97 (s, 6 H), 1.8–1.1 (m, 6 H).

(−)-7-(3,4,6-Trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptanoic acid (**8b**) was prepared from racemic **4d** (10.0 g, 28 mmol) similarly to the above method with use of D-(+)-phenylethylamine (3.41 g, 28 mmol) [Aldrich: $[\alpha]_D$ +39° (neat)] instead of L-(−)-phenylethylamine. **8b** (1.70 g, 17%): $[\alpha]_D$ −24.8° (*c* 1, $CHCl_3$); 96% ee.

(7*R*)-(+)-4′-Bromo-7-(3,5,6-trimethyl-1,4-benzoquinon-2-yl)-7-phenylheptananilide (9). A solution if ethyl chloroformate (0.24 g, 2.2 mmol) in THF (2 mL) was added dropwise to a solution of **8a** (0.71 g, 2.0 mmol) in THF (10 mL) at −10 °C under Ar during 5 min, followed by the addition of a solution of Et_3N (0.31 mL) in THF (2 mL) under the same conditions. The mixture was stirred for 15 min and then a solution of 4-bromoaniline (0.36 g, 2.1 mmol) in THF (4 mL) was added at −10 °C for 5 min. After the mixture was stirred at −10 to 0 °C for 1 h, the THF was evaporated in vacuo. The residue was treated with dilute HCl and extracted with EtOAc. The EtOAc was washed in turn with aqueous K_2CO_3 and aqueous NaCl, dried, and concentrated. The residue was recrystallized from EtOAc–IPE (2:1) to give the anilide **9** (0.77 g, 76%), mp 163–164 °C; $[\alpha]_D$ +18.5° (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.4–7.1 (br s, 1 H), 7.38 (s, 4 H), 7.23 (m, 5 H), 4.29 (t, 1 H), 2.4–2.0 (m, 4 H), 2.03 (s, 3 H), 1.96 (s, 6 H), 1.9–1.1 (m, 6 H).

Biological Methods. In Vitro Experiments. Rabbit Aorta Contraction. New Zealand white rabbits (male, 2–3 kg) were killed and their thoracic aorta were placed in Krebs–Henseleit solution of the following composition (mM): NaCl, 118; KCl, 4.75; $CaCl_2$, 2.54; KH_2PO_4, 1.19; $MgSO_4$, 1.19; $NaHCO_3$, 12.5; and glucose, 10.0. Adhering fat and connective tissue were removed and spiral strips of the aorta were prepared. Each strip (2–3 mm in width, 3 cm in length) was mounted in an organ bath containing 20 mL of the Krebs–Henseleit solution, bubbled with 95% O_2–5% CO_2 gas at 37 °C. A resting tension of 2 g was isometrically recorded on an ink-writing polygraph (San-ei, RECTI-HORIZ-8k, Japan) via a force-displacement transducer (Nihon Kohden, Model SB-1T, Japan). The contractile response of the strip to U-44069 (2–6 nM), which causes about 50% of the contraction induced by 30 mM KCl, was examined in the absence or presence of drugs (final concentrations of drugs were from 10^{-5} to 10^{-8} M in 0.01%

DMSO). The aortic strip was treated with the agents for 10 min before the addition of U-44069.

Guinea Pig Lung Contraction. Strips of the guinea pig lungs were prepared. Each strip (3 × 3 × 20 mm) was mounted in an organ bath containing Krebs solution at 37 °C. The reaction medium was continuously aerated with 5% CO_2–95% O_2 gas. An initial tension of the strips was loaded at 2 g, and U-46619-induced contraction was isometrically recorded on a polygraph via a force-displacement transducer. Following priming, U-46619 dose–response curve was obtained with a cumulative dose schedule (six doses). The preparations were then washed at regular intervals until the resting base line had returned. After an appropriate rest period (about 1 h), the U-46619 dose–response curve was repeated in the presence of drugs. pA_2 values were obtained by the method of Tallarida and Murray.[14]

Guinea Pig Platelet Aggregation. Platelet-aggregation studies were done as described.[15] Blood was collected in 3.15% sodium citrate (1 mL for 9 mL of blood) by cardiac puncture from conscious male guinea pigs. Platelet-rich plasma (PRP) was obtained by centrifuging the blood at 3000 rpm for 5 s at room temperature. The platelet concentration was adjusted to 450000/μL with a photometer (Rikadenki, Platelet Aggregometer, Japan). The PRP (250 μL) was preincubated at 37 °C for 2 min and then incubated for 2 min with U-44069. The concentrations of the aggregating agent were used to obtain submaximal aggregation.

[^{3}H]U-46619 Binding to Guinea Pig Platelets. The experiments were done according to the methods described by Kattelman et al.[16] with slight modifications. A syringe containing 0.315% citrate anticoagulant and 1 mM aspirin as final concentrations was used to collect the blood by cardiac puncture from conscious guinea pigs. The PRP fraction was collected by centrifuging the blood at 3000 rpm for 5 s at room temperature and the obtained PRP was treated with 1 μM PGE_1 after which the platelet pellet was obtained by centrifuging the PRP at 3000 rpm for 5 min. The platelet concentration was adjusted to 660000/μL with a modified 25 mM Tris-HCl buffer (pH 7.4) containing 138 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, and 5.5 mM glucose. Platelets in 460 μL of the buffer were preincubated with drugs (20 μL) for 6 min at 25 °C and [^{3}H]U-46619 (20 μL, 0.037 μCi for guinea pig) were then added to the mixtures, and the preparations were incubated for 6 min. The binding reaction was stopped by adding 3 mL of ice-cold 25 mM Tris-HCl buffer. Platelets were isolated by vacuum filtration on glass filters (Whatman, GF/C filter). Each tube and filter were washed twice with 3 mL of ice-cold 25 mM Tris-HCl buffer. The radioactivity on the glass filter was measured using a liquid-scintillation counter [(Aloka, LSC-900, Japan, scintillator containing toluene (12 L), bis-MSB (12 g), DPO (180 g), and nonion (5.16 L)]. Nonspecific binding of [^{3}H]U-46619 to the platelet was estimated in the presence of 10^{-5} M unlabeled U-46619.

In Vivo Experiments. Experimental Allergic Asthma. IgG_1-mediated bronchoconstriction was examined in guinea pigs sensitized intraperitoneally with an emulsion of egg albumin (EA) (1 mg/kg) and Freund's complete adjuvant (FCA), according to the method of Orange and Moore.[17] Three weeks later, the animals from which the sera at 1:1000 dilution showed a positive 3-h passive cutaneous anaphylaxis (PCA) in guinea pigs were used. The bronchoconstriction in the animals which were anesthetized with urethane (1.5 g/kg, ip) and treated with gallamine triethiodide (1 mg/kg, iv) was measured by the overflow technique of Konzentt–Rössler.[18] The increase in respiratory overflow volume provoked by antigen challenge (EA, 1 mg/kg, iv) was expressed as percent of the maximal overflow volume (100%) obtained by obstruction of the trachea. Drugs suspended in a 5% gum arabic solution were given orally 1 h before antigen challenge.

Spasmogen-Induced Bronchoconstriction. The bronchoconstriction induced by U-46619 (10 μg/kg, iv), LTD_4 (10 μg/kg, iv), and/or PAF (10 μg/kg, iv) was examined by the Konzentt–Rössler method as described above. Drugs suspended in a 5% gum arabic solution were given orally 1 h before the spasmogen challenge.

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Supplementary Material Available: Tables listing crystal data and atomic coordinates of the bonded atoms of the (7*R*)-(+)-anilide **9** (5 pages); structure factor amplitudes of **9** (8 pages). Ordering information is given on any current masthead page.

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Benzofuro[2,3-*c*]pyridin-6-ols: Synthesis, Affinity for Opioid-Receptor Subtypes, and Antinociceptive Activity

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A general synthetic approach to a novel series of *cis*-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols is described together with their receptor-binding profile on opioid-receptor subtypes (μ, κ, δ). In addition, their in vivo antinociceptive activity was assessed. A number of the analogues synthesized showed potent affinity for opioid receptors and have potent antinociceptive activity in a mouse phenylquinone abdominal stretching model. In addition, the SAR for nitrogen substitution in the above series is explored with respect to the overall opioid receptor subtype binding profile. In general it was found that substituents which enhanced μ and κ binding affinity in the benzomorphan series had a similar effect in the benzofuropyridine series described in this manuscript. An overlap hypothesis topologically connecting the benzomorphan nucleus to the *cis*-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridine nucleus is also presented.

During the course of investigations directed toward the discovery of novel centrally acting analgetics, a series of *cis*-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols (**1**) was synthesized and evaluated both for affinity at

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