antiedematous effects of the drugs were estimated in terms of percent inhibition.

PGE_2 Induced Edema. Six mice per group were used. Sixty minutes after oral administration of drugs (100 mg/kg), PGE_2 (20 μg/0.01 mL) was injected subcutaneously into the plantar surface of the right hind paw and the volume of the resulting edema was measured with a dial thickness gauge. The antiedematous effects of the drugs were estimated in terms of percent inhibition.

Gastrointestinal Ulceration Studies.[8] **Gastric Ulceration.** Mice were fasted for 24 h (with water ad libitum). Compounds were suspended in a methyl cellulose vehicle and administered orally by gavage in a volume of 0.5 mL/100 g of body weight. The animals were sacrificed after 4 h, and the stomachs were examined for lesions under a dissecting microscope.

Intestinal Ulceration: Compounds were administered to normal, fed rats by gavage for 3 consecutive days. The mice were sacrificed 24 h after the last dosing and examined for intestinal ulcers.

Statistical Analysis:[9] Student's *t*-test and analysis of variance [ANOVA, two factors (pharmacologic calculation system version 4.1)] were employed.

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Registry No. 1, 54903-09-2; 2, 54903-12-7; 3, 72766-68-8; 4, 95637-40-4; 5, 76751-95-6; 6, 139101-47-6; 7, 139101-48-7; 8, 139101-49-8; 9, 139101-50-1; 10, 139101-51-2; 11, 139101-52-3; 12, 139101-53-4; 13, 139101-54-5; 14, 139101-55-6; 15, 139101-56-7; 16, 139101-57-8; 17, 139101-58-9; 18, 139101-59-0; 19, 139101-60-3; 2-vinylpyridine, 100-69-6; 4-vinylpyridine, 100-43-6.

Supplementary Material Available: A table of IR and ^{1}H-NMR spectral data of compounds 6–19 (2 pages). Ordering information is given on any current masthead page.

(8) Sancilio, L. F.; Nolan, J. C.; Wagner, L. E.; Ward, J. W. The Analgesic and Antiinflammatory Activity and Pharmacologic Properties of Bromfenac. *Arzneim.-Forsch.* 1987, *37*, 513–519.

(9) Bliss, C. I.; White, C. In *The Vitamins*, 2nd ed.; Gyorgy, P., Pearson, W. N., Eds.; Academic Press: New York, 1967; Vol. 6, pp 50–78.

Development of 2,3-Dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (L-670,630) as a Potent and Orally Active Inhibitor of 5-Lipoxygenase

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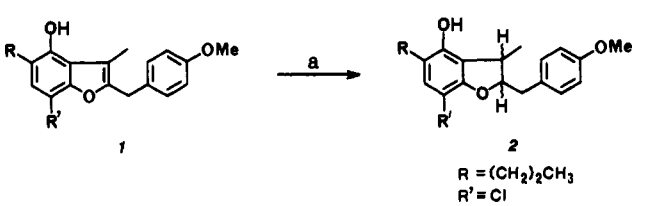
Leukotrienes are potent biological mediators of allergic and inflammatory diseases and are derived from arachidonic acid through the action of the 5-lipoxygenase. In this study, the syntheses and comparative biological activities of three series of 2,3-dihydro-2,6-disubstituted-5-benzofuranols with various substituents on position 3 are described. Compounds from each series were evaluated for their ability to inhibit the production of leukotriene B_4 (LTB_4) in human peripheral blood polymorphonuclear (PMN) leukocytes and the 5-lipoxygenase reaction in cell-free preparations from rat PMN leukocytes. The structure–activity relationships of each series in vitro and in vivo are presented. The bioavailability, metabolism, and toxicity profile of each series are discussed. The series with no substituent at position 3 was the most potent and among the compounds in that series 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (46, L-670,630) was chosen for further development.

Leukotrienes are potent biological mediators derived from arachidonic acid through the action of the 5-lipoxygenase. The peptidoleukotrienes LTC_4, LTD_4, and LTE_4, are potent spasmogenic agents and have been implicated in the pathology of allergic diseases. Leukotriene B_4, being a potent chemotactic agent, has been considered to be an important mediator of inflammation.[1] Thus, a selective inhibitor of 5-lipoxygenase could become a new class of therapeutic agents for the treatment of such conditions. Recently, a number of hydroxamic acid derivatives[2] and benzofuranols[3,4] have been reported to be potent 5-lipoxygenase inhibitors.

In our continuing quest for a potent and orally active inhibitor of 5-lipoxygenase, we were also interested in the 2,3-dihydrobenzofuranols, as an extension of our earlier work on the 4-benzofuranols.[4] We now report our studies in this area in which the structure–activity relationship of substitution pattern at positions 2, 3, 4, 5, and 6 are

Scheme I[a]



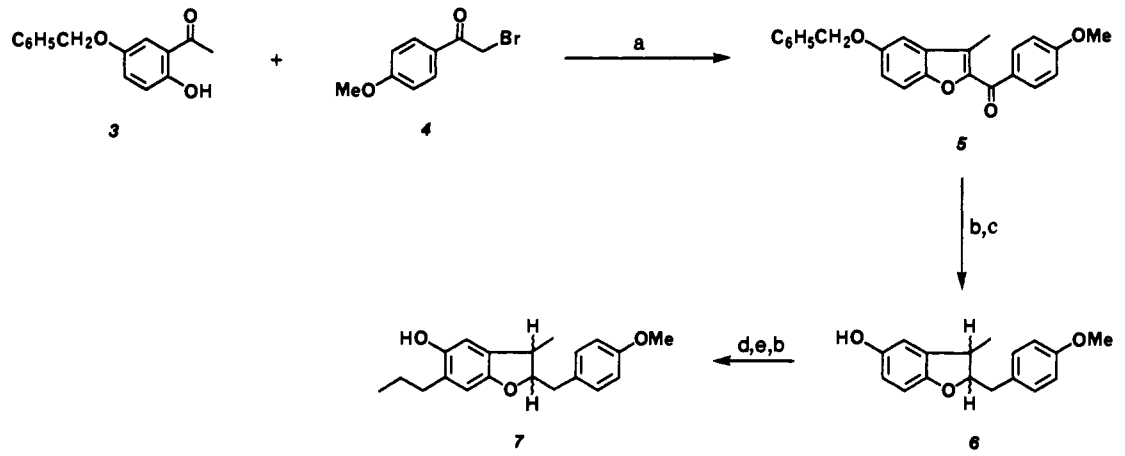
a) Et_3SiH, TFA

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.
§ Department of Biochemistry.
∥ Department of Animal Drug Metabolism.

(1) For reviews on the leukotrienes, see: (a) Rokach, J., Ed. *Leukotrienes and Lipoxygenases Chemical, Biological and Clinical Aspects.*; Elsevier: Amsterdam, 1989. (b) Taylor, G. W.; Clarke, S. R. The Leukotriene Biosynthetic Pathway a Target for Pharmacological Attack. *Trends Pharmacol. Sci.* 1986, 7, 100–103. (c) Sirois, P. Pharmacology of the Leukotrienes. *Adv. Lipid Res.* 1985, *21*, 79–101.

0022-2623/92/1835-1299$03.00/0

Scheme II[a]



a) K_2CO_3, acetone, △; b) H_2/Pd/C; c) Et_3SiH, TFA; d) $CH_2=CHCH_2Br$, K_2CO_3; e) $C_6H_4Cl_2$, △

explored, and the potential toxicity and metabolism considered. The results of these studies eventually led to the identification of 2,3-dihydro-2-(2-phenylethyl)-6-(3-phenoxypropyl)-5-benzofuranol (L-670,630) as a potent and orally active inhibitor of 5-lipoxygenase.

Chemistry

The first series of 2,3-dihydrobenzofuranols prepared were those originated from the 4-benzofuranols.[4] The furan ring was selectively reduced by triethylsilane in trifluoroacetic acid as shown in Scheme I. Preparation of the corresponding 2,3-dihydro-3-methyl-5-benzofuranol system is shown in Scheme II. Alkylation of 2-hydroxy-5-(benzyloxy)acetophenone (3) with 4-methoxyphenacyl bromide (4) gave after cyclization in situ the 5-(benzyloxy)benzofuran derivative 5 in 89% yield. Reductive deoxygenation of the ketone 5 by hydrogenation followed by reduction of the furan ring with concomitant deprotection using triethylsilane in trifluoroacetic acid gave the 2,3-dihydro-5-benzofuranol derivative 6 in 84% yield. Allylation of 6 followed by Claisen rearrangement and hydrogenation gave the 6-propyl derivative 7 in 82% yield.

For reasons of metabolic stability that will be discussed later, initial synthetic efforts were concentrated on compounds in the 2,3-dihydro-3,3-dimethyl-5-benzofuranol series whose syntheses are depicted in Schemes III and IV. Scheme III outlines the synthesis of the 3,3-dimethyl analogue of compound 7. Allylation of 4-methoxyphenol 8 with 3-methyl-2-butenyl bromide followed by Claisen rearrangement in refluxing dichlorobenzene in the presence of butyric anhydride and *N,N*-dimethylaniline gave a mixture containing 2-(1,1-dimethylallyl)-4-methoxyphenyl butyrate (9), 2-(1,2-dimethylallyl)-4-methoxyphenyl butyrate (10), and 4-methoxyphenyl butyrate (11). Epoxidation of 9 with *m*-chloroperbenzoic acid followed by base catalyzed hydrolysis of the butyrate and cyclization gave the 2,3-dihydro-2-(hydroxymethyl)-3,3-dimethyl-5-methoxybenzofuran (12a). The methoxy group was exchanged for a benzyloxy group and oxidation of the resulting alcohol 12b gave the corresponding aldehyde 13. Reaction of 13 with (4-methoxyphenyl)magnesium bromide followed by reductive deoxygenation of the resulting alcohol with sodium cyanoborohydride and zinc iodide gave the 2-(4-methoxybenzyl) derivative which after deprotection gave 14. Allylation of 14 followed by Claisen rearrangement gave the 6-allyl derivative 15. Reaction of 13 with the anion of diethyl (4-methoxybenzyl)phosphonate followed by hydrogenation of the resulting olefin gave the (4-methoxyphenyl)ethyl derivative 16 which was transformed to the 6-allyl derivative 17 as described above.

An alternative route to the 3,3-dimethyl series which is more general and facile is shown in Scheme IV. Allylation

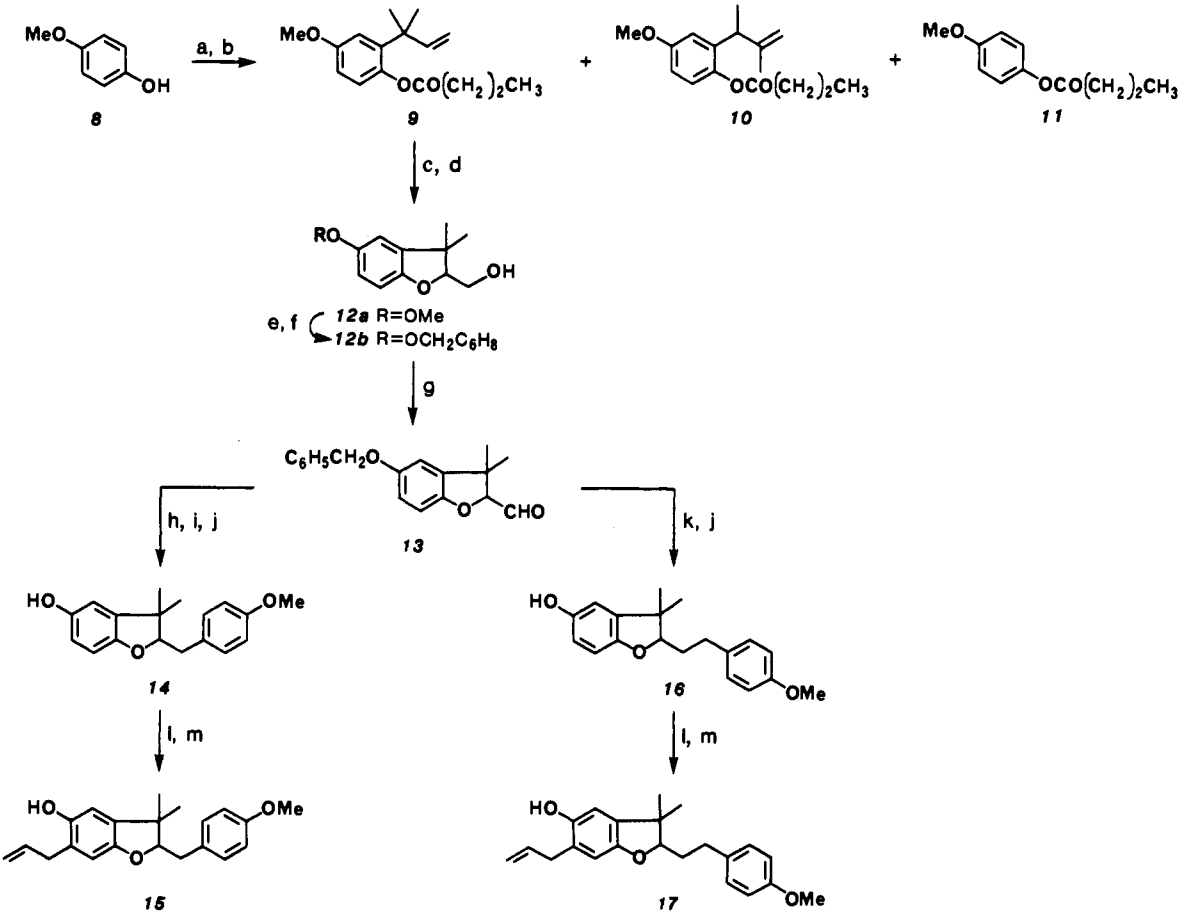
(2) (a) Summers, J. B.; Kim, K. H.; Mazdiyasni, H.; Holms, J. H.; Ratajczyk, J. D.; Stewart, A. O.; Dyer, R. D.; Carter, G. W. Hydroxamic Acid Inhibitors of 5-Lipoxygenase: Quantitative Structure-Activity Relationships. *J. Med. Chem.* **1990**, *33*, 992–998. (b) Summers, J. B.; Mazdiyasni, H.; Holms, J. H.; Ratajczyk, J. D.; Dyer, R. D.; Carter, G. W. Hydroxamic Acid Inhibitors of 5-Lipoxygenase. *J. Med. Chem.* **1987**, *30*, 574–580. (c) Summers, J. B.; Gunn, B. P.; Mazdiyasni, H.; Goetze, A. M.; Young, P. R.; Bouska, J. B.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. In Vivo Characterization of Hydroxamic Acid Inhibitors of 5-Lipoxygenase. *J. Med. Chem.* **1987**, *30*, 2121–2126. (d) Summers, J. B.; Gunn, B. P.; Martin, J. G.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Goetze, A. M.; Bouska, J. B.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. Orally Active Hydroxamic Acid Inhibitors of Leukotriene Biosynthesis. *J. Med. Chem.* **1988**, *31*, 3–5. (e) Summers, J. B.; Gunn, B. P.; Martin, J. G.; Martin, M. B.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Bouska, J. B.; Goetze, A. M.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. Structure-Activity Analysis of a Class of Orally Active Hydroxamic Acid Inhibitors of Leukotriene Biosynthesis. *J. Med. Chem.* **1988**, *31*, 1960–1964.

(3) (a) Hammond, M. L.; Kopka, I. E.; Zambias, R. A.; Caldwell, C. G.; Boger, J.; Baker, F.; Bach, T.; Luell, S.; MacIntyre, D. E. 2,3-Dihydro-5-benzofuranols as Antioxidant-Based Inhibitors of Leukotriene Biosynthesis. *J. Med. Chem.* **1989**, *32*, 1006–1020. (b) Hammond, M. L.; Zambias, R. A.; Chang, M. N.; Jensen, N. P.; McDonald, J.; Thompson, K.; Boulton, D. A.; Kopka, I. E.; Hand, K. M.; Opas, E. E.; Luell, S.; Bach, T.; Davies, P.; MacIntyre, D. E.; Bonney, R. J.; Humes, J. L. Antioxidant-Based Inhibitors of Leukotriene Biosynthesis. The Discovery of 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol, a Potent Topical Antiinflammatory Agent. *J. Med. Chem.* **1990**, *33*, 908–918.

(4) Lau, C. K.; Bélanger, P. C.; Scheigetz, J.; Dufresne, C.; Williams, H. W. R.; Maycock, A. L.; Guindon, Y.; Bach, T.; Dallob, A. L.; Denis, D.; Ford-Hutchinson, A. W.; Gale, P. H.; Hopple, S. L.; Letts, L. G.; Luell, S.; McFarlane, C. S.; MacIntyre, E.; Meurer, R.; Miller, D. K.; Piechuta, H.; Riendeau, D.; Rokach, J.; Rouzer, C. Synthesis and Structure-Activity Relationships of a Novel Class of 5-Lipoxygenase Inhibitors. 2-(Phenylmethyl)-4-Hydroxy-3,5-Dialkylbenzofurans: the Development of L-656,224. *J. Med. Chem.* **1989**, *32*, 1190–1197.

(5) Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Belanger, P. C. Ortho-Specific Alkylation of Phenols via 1,3,2-Benzodioxaborins. *Can. J. Chem.* **1989**, *67*, 1384–1387.

Scheme III[a]

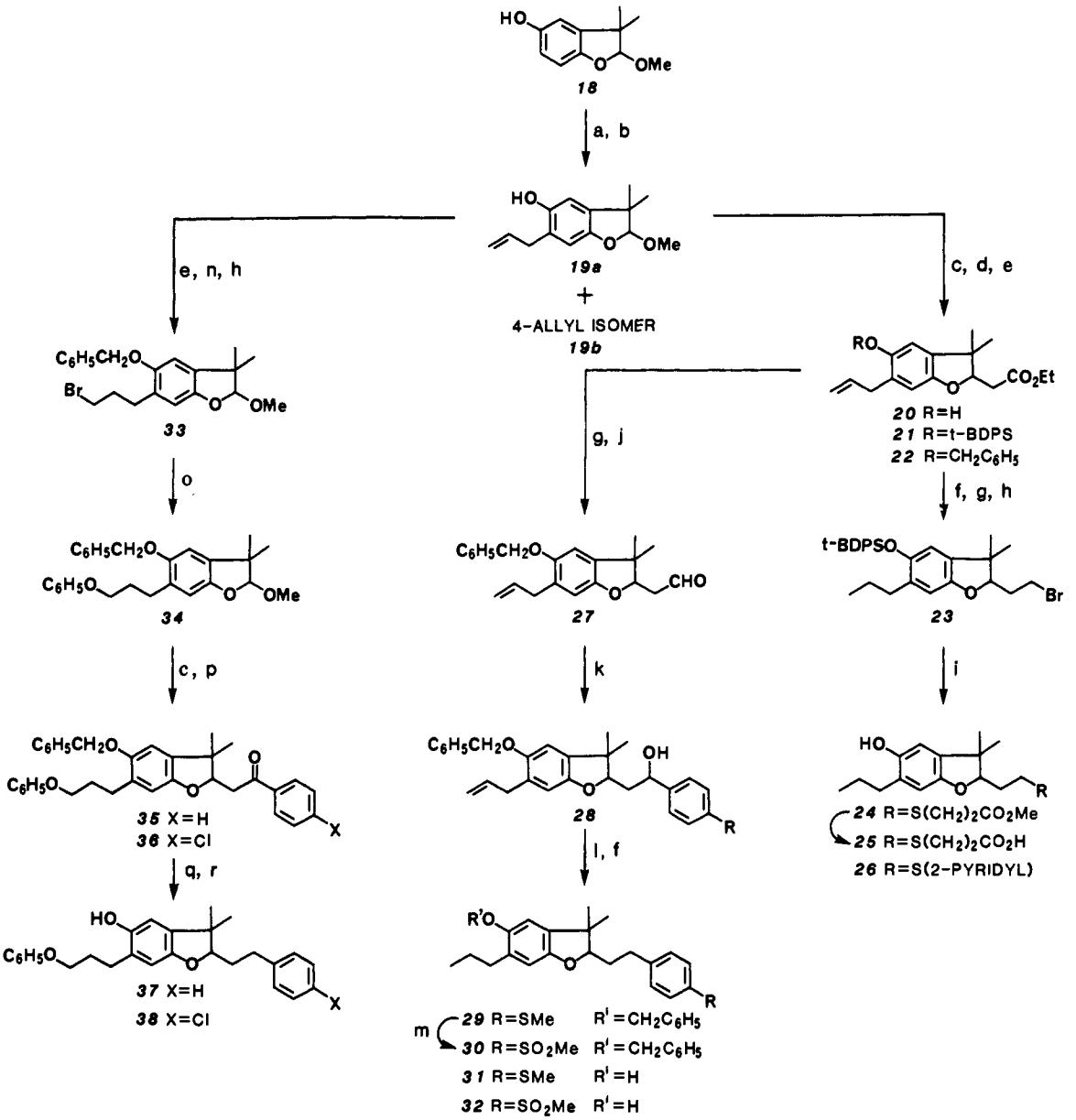


of 2,3-dihydro-3,3-dimethyl-2-methoxy-5-benzofuranol (18) followed by Claisen rearrangement gave a mixture of 6- and 4-allyl derivatives **19a** and **19b** in the ratio of 5:1, respectively. To provide a versatile synthesis of a wide range of substituents at position 2, compound **19a** was converted to the key intermediate ester **20** by first hydrolyzing the 2-methoxy acetal to the corresponding lactol and then reacting the latter with (carbethoxymethylene)triphenylphosphorane in refluxing tetrahydrofuran. The phenolic ester **20** was protected as the *tert*-butyldiphenylsilyl ether **21**. Hydrogenation of **21**, followed by reduction of the ester with lithium aluminum hydride gave an alcohol which was converted to the bromide **23** using carbon tetrabromide and triphenylphosphine. Displacement of the bromide with an alkyl or an aryl thiolate gave the corresponding thioether **24** and **26** after deprotection with tetrabutylammonium fluoride. Hydrolysis of the ester **24** gave the acid **25**. To prepare the 2-phenylethyl derivatives of the 3,3-dimethyl series, compound **20** was first protected as its benzyl ether **22**. Reduction of the ester to the alcohol as described earlier followed by oxidation of the alcohol with dimethyl sulfoxide and oxallyl chloride in dichloromethane gave the aldehyde **27**. Reaction of aldehyde **27** with [4-(methylthio)phenyl]magnesium bromide afforded alcohol **28** in 91% yield. Reductive deoxygenation of the alcohol with sodium cyanoborohydride in the presence of zinc iodide followed by hydrogenation of the olefin gave the 2-phenylethyl derivative **29** without debenzylation. Oxidation of **29** with *m*-chloroperbenzoic acid gave the corresponding sulfone **30**. Treatment of **29** and **30** with aqueous HCl in acetic acid gave **31** and **32**, respectively.

Introduction of substituents at position 6 was achieved by converting the benzyloxy derivative of **19a** to the bromide **33** via hydroboration and bromination. Displacement of the bromide with sodium phenoxide in DMF gave the phenoxypropyl derivative **34** (90%). Treatment of compound **34** with refluxing aqueous acetic acid liberated the free lactol which reacted with the appropriate diethyl (2-phenyl-2-oxoethyl)phosphonate to give ketones **35** and **36**, respectively. The ketones were reduced with triethylsilane in the presence of boron trifluoride etherate to give the corresponding phenylethyl derivatives **37** and **38** after deprotection with boron tribromide.

Synthetic access to the series with no substitution at position 3 is shown in Scheme V. On the basis of the structure–activity relationship of the 3,3-dimethyl series, phenylethyl substituents at position 2 were found to be optimum. Thus most of the synthetic efforts of the 3,3-unsubstituted series were directed toward the preparation of various substituents at position 6 after installing the phenylethyl group at position 2. Lithiation of 5-methoxybenzofuran (**39**) with *n*-butyllithium in tetrahydrofuran gave the 2-lithio derivative which reacted with phenylacetaldehyde to give the corresponding alcohol **40** in 90% yield. Reductive deoxygenation of the alcohol with *tert*-butylamine borane and aluminum chloride followed by reduction of the furan ring with triethylsilane in trifluoroacetic acid gave 58% of the 2,3-dihydro-2-(2-phenylethyl)benzofuran (**41**). Treatment of **41** with lithium ethylthiolate in DMF gave the phenol **42** (98%). Allylation of **42** followed by Claisen rearrangement gave a mixture of 6- and 4-allyl derivative **43a** and **43b** (70% and 22% respectively). Benzylation of **43a** followed by hydroboration with borane in tetrahydrofuran gave the alcohol **44** which was converted to the bromide **45** in a similar fashion as the other series shown in Scheme IV. Displacement of the bromide **45** with various phenoxides

Scheme IV[a]



a) CH_2=$CHCH_2Br$; b) $C_6H_5Cl_2$, △; c) AcOH/THF/H_2O; d) $(C_6H_5)_3PCHCO_2Et$; e) $C_6H_5CH_2Cl$ OR t-BDPSiCl; f) H_2/Pd/C; g) $LiAlH_4$; h) $(C_6H_5)_3P/CBr_4$, i) $^{\ominus}SR$: j) $(COCl)_2$, DMSO, k) $BrMgC_6H_4(4\text{-}SMe)$; l) $NaCNBH_3$, ZnI_2, m) mcpba; n) BH_3•THF; o) $^{\ominus}OC_6H_5$; p) $(OEt)_2P(O)CHC(O)C_6H_4(4\text{-}X)$; q) Et_3SiH, BF_3•Et_2O, r) BBr_3

and thiolates gave after deprotection compounds **46–53**. Allylation of **46** and **49** followed by Claisen rearrangement and then hydrogenation gave **54** and **55**, respectively.

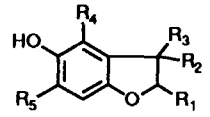
An alternative route to introduce substituents at position 6 is to react phenol **42** with an appropriate aldehyde in the presence of phenylboronic acid and propionic acid in refluxing toluene with concomitant removal of water to give the 2-phenyl-4*H*-1,3,2-benzodioxaborin derivatives **56–58**. Reduction of the latter with *tert*-butylamine borane and aluminum chloride gave the corresponding 6-substituted phenols **46**, **59**, and **60**. Oxidation of **60** with *m*-chloroperbenzoic acid gave sulfone **61**.

An alternate route was used to prepare the 2-phenylethyl group possessing a halogen substituent in the para position. With 5-methoxy-2-benzofurancarboxylic acid (**62**, Scheme VI) used as starting material, reduction of the acid with diisobutylaluminum hydride followed by oxidation of the resulting alcohol with manganese dioxide gave the aldehyde **63**. Reaction of **63** with (4-chlorobenzyl)phosphonium ylide gave the olefin **64**. Deprotection of the methyl ether with boron tribromide followed by reduction of both the olefin and the furan ring with triethylsilane in trifluoroacetic acid gave the dihydro compound **65**. Following the same procedure described above for converting compound **42** to compound **46**, compound **65** was transformed to compound **66**, the (4-chlorophenyl)ethyl analogue of **46**.

Results and Discussion

Structure–Activity Relationships in Vitro. Compounds that were selected for this study were evaluated for their potency to inhibit the formation of LTB_4 in human peripheral blood polymorphonuclear (PMN) leukocytes. The relative potencies are expressed by the mean IC_{50} values and summarized in Table I. Several com-

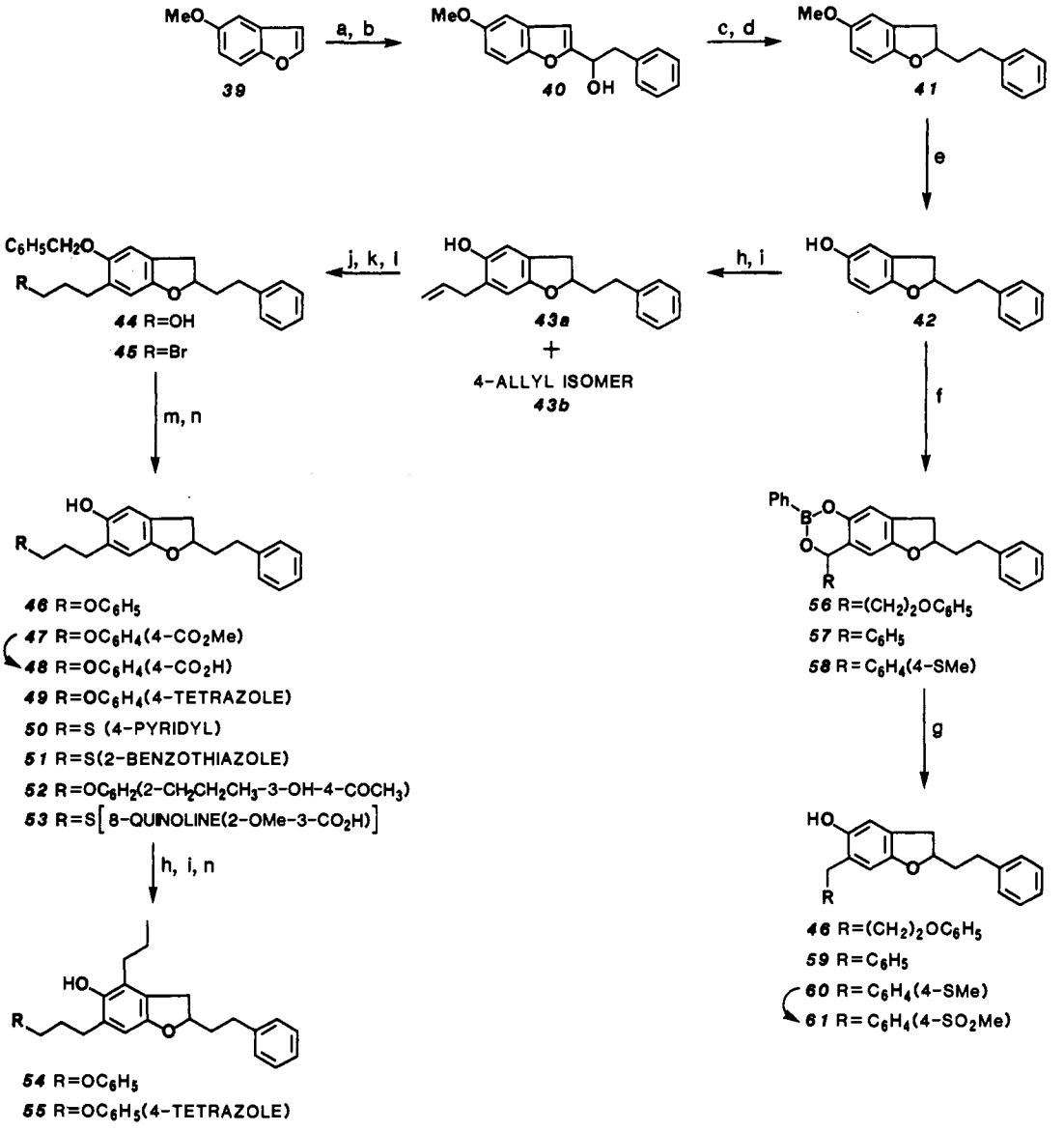
Table I. SAR of 2,3-Dihydro-5-benzofuranol in Vitro



compd	R_1	R_2	R_3	R_4	R_5	mp, °C	analyses[a]	IC_{50}, nM HPMN[b]	IC_{50}, nM 5-lipoxygenase[c]	methemoglobin formation %[d]
2								235		
6	$CH_2C_6H_4$(4-OMe)	H	CH_3	H	H			107[d]		6
7	$CH_2C_6H_4$(4-OMe)	H	CH_3	H	$CH_2CH_2CH_3$	oil		18	35	6
15	$CH_2C_6H_4$(4-OMe)	CH_3	CH_3	H	$CH_2CH{=}CH_2$	oil		49	164	1
17	$CH_2CH_2C_6H_4$(4-OMe)	CH_3	CH_3	H	$CH_2CH{=}CH_2$	oil		47	52	2
25	$(CH_2)_2S(CH_2)_2CO_2H$	CH_3	CH_3	H	$CH_2CH_2CH_3$	oil	$C_{16}H_{26}SO_4$	6968[d]		
26	$(CH_2)_2$S(2-pyridyl)	CH_3	CH_3	H	$CH_2CH_2CH_3$	oil		75	44	
31	$CH_2CH_2C_6H_4$(4-SMe)	CH_3	CH_3	H	$CH_2CH_2CH_3$	68		28[d]	92	
32	$CH_2CH_2C_6H_4$(4-SO_2Me)	CH_3	CH_3	H	$CH_2CH_2CH_3$	113	$C_{22}H_{28}SO_4$	176		
37	$CH_2CH_2C_6H_5$	CH_3	CH_3	H	$(CH_2)_3OC_6H_5$	65	$C_{27}H_{30}O_3$	38	40	6
38	$CH_2CH_2C_6H_4$(4-Cl)	CH_3	CH_3	H	$(CH_2)_3OC_6H_5$	oil		472[d]		3
42	$CH_2CH_2C_6H_5$	H	H	H	H	56	$C_{16}H_{16}O_2$	275		40
43a	$CH_2CH_2C_6H_5$	H	H	H	$CH_2CH{=}CH_2$	79	$C_{19}H_{20}O_2$	10	17	52
43b	$CH_2CH_2C_6H_5$	H	H	$CH_2CH{=}CH_2$	H	oil		38	25	18
46	$CH_2CH_2C_6H_5$	H	H	H	$(CH_2)_3OC_6H_5$	65	$C_{25}H_{26}O_3$	6	23	4
48	$CH_2CH_2C_6H_5$	H	H	H	$(CH_2)_3OC_6H_4$(4-CO_2H)	157	$C_{26}H_{26}O_5$	356	44	3
49	$CH_2CH_2C_6H_5$	H	H	H	$(CH_2)_3OC_6H_4$(4-tetrazolyl)	154	$C_{26}H_{26}N_4O_3$	201		1
50	$CH_2CH_2C_6H_5$	H	H	H	$(CH_2)_3$S(4-pyridyl)	140	$C_{24}H_{25}NO_2S$	14	8	6
51	$CH_2CH_2C_6H_5$	H	H	H	$(CH_2)_3$S(2-benzothiazolyl)	134	$C_{26}H_{25}NO_2S_2$	22	45	1
52	$CH_2CH_2C_6H_5$	H	H	H	$(CH_2)_3OC_6H_2$(2-$CH_2CH_2CH_3$-3-OH-4-$COCH_3$)	79	$C_{30}H_{34}O_5$	9	53	3
53	$CH_2CH_2C_6H_5$	H	H	H	$(CH_2)_3$S[8-quinolinyl(2-OMe-3-CO_2H)]	157	$C_{30}H_{29}NO_5S$	37	50	1
54	$CH_2CH_2C_6H_5$	H	H	$CH_2CH_2CH_3$	$(CH_2)_3OC_6H_5$	78	$C_{26}H_{32}O_3$	52	127	2
55	$CH_2CH_2C_6H_5$	H	H	$CH_2CH_2CH_3$	$(CH_2)_3OC_6H_4$(4-tetrazolyl)	155	$C_{26}H_{32}N_4O_3$	107	45	2
59	$CH_2CH_2C_6H_5$	H	H	H	$CH_2C_6H_5$	63	$C_{23}H_{22}O_2$	18	48	6
61	$CH_2CH_2C_6H_5$	H	H	H	$CH_2C_6H_4$(4-SO_2Me)	134	$C_{24}H_{24}O_4S$	190		5
66	$CH_2CH_2C_6H_4$(4-Cl)	H	H	H	$(CH_2)_3OC_6H_5$	oil	$C_{25}H_{25}ClO_3$	41	51	2.8
67	H	H	H	H	$(CH_2)_3OC_6H_5$			57		
70								>2000		
BW 755C								700		
A64077								1500	320	
NDGA[e]								85		

[a] Compounds were analyzed for C and H and analytical values were within ± 0.4% of calculated values. Compounds for which analyses are not indicated, purity was verified by TLC, HPLC, and mass spectrometry. [b] Concentration of compound required for 50% inhibition of LTB_4 production in human PMN compared with controls in the absence of drug. Reported values are an average of at least three determinations. The standard deviation for all experiments ranged between 15 and 50% of the mean value. [c] Concentration of compound required for 50% inhibition of arachidonic acid oxidation by rat 5-lipoxygenase. Reported values are derived from one to three titrations. [d] Reported values are based on single determination. [e] Nordihydroguaiaretic acid.

Scheme V[a]

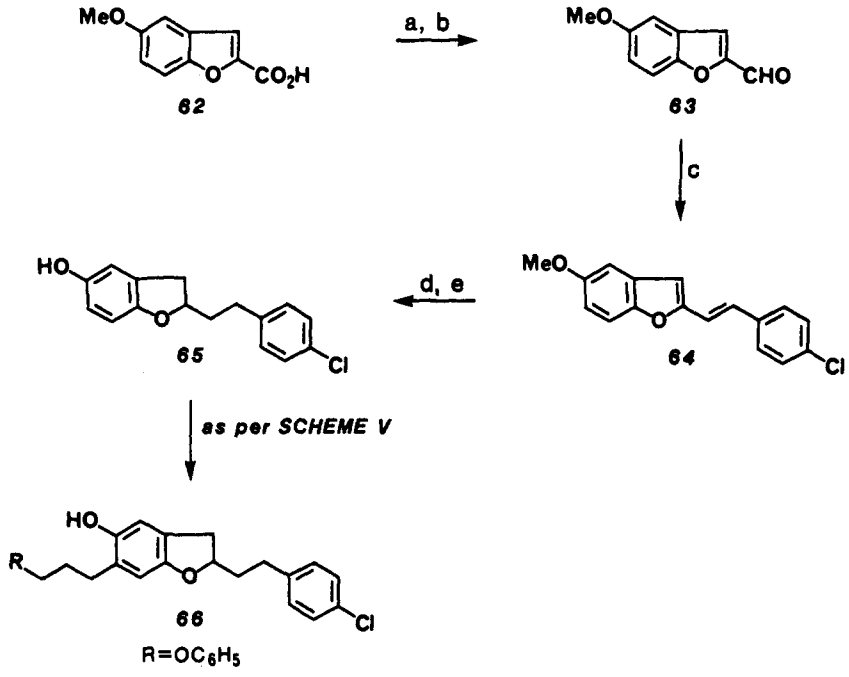


a) n-BuLi; b) $C_6H_5CH_2CHO$; c) t-$BuNH_2 \cdot BH_3/AlCl_3$; d) Et_3SiH/TFA; e) LiSEt, DMF; f) RCHO, $C_6H_5B(OH)_2$, EtCOOH, $C_6H_5CH_3$, △; g) t-$BuNH_2 \cdot BH_3/AlCl_3$; h) $CH_2=CHCH_2Br$; i) △, $C_6H_4Cl_2$; j) $C_6H_5CH_2Br$; k) $BH_3 \cdot THF$; l) $(C_6H_5)_3P/CBr_4$; m) $R^{\ominus}$; n) H_2/Pd/C

pounds in this series had IC_{50} values ranging between 6–30 nM and were more potent than the standard lipoxygenase inhibitors nordihydroguaiaretic acid (NDGA) (IC_{50} = 85 nM) and A-64077 (IC_{50} = 1.5 μM). In addition, Table I shows that the most potent inhibitors of LTB_4 production also inhibited the 5-lipoxygenase reaction in cell-free preparations from rat PMN leukocytes (IC_{50} value = 8–164 nM). As mentioned earlier, our interest in the 2,3-dihydrobenzofuranols originate from the 4-benzofuranols series of 5-lipoxygenase inhibitors that we described previously. For example, compound **2**, the 2,3-dihydrobenzofuran analogue of compound **1**, the most active compound in the 4-benzofuranol series[4] is already a fairly potent inhibitor of leukotriene production in the PMN leukocytes with an IC_{50} value of 235 nM. Moving the hydroxy group to position 5 increases the potency significantly. For example, compound **6** has an IC_{50} value of 107 nM even with no substituents on the phenol ring. Addition of the propyl substituent to position 6 (compound **7**) lowers the IC_{50} value to 18 nM. However, most of the dihydrobenzofuranols with mono substitution at position 2 and 3 were found to be unstable. They tended to oxidize back to the benzofuran when exposed to air. Thus similar compounds with a *gem*-dimethyl substituent at position 3 that would block the air oxidation were prepared. The 3,3-dimethyl analogue **15** was found to be a reasonably potent inhibitor with an IC_{50} value of 49 nM. Attempts to increase the lipophilicity of the substituents at position 2 (compounds **17** and **31**) or position 6 (compound **37**) lead to only slight increases in potency. Increasing the lipophilicity of both position 2 and 6 (compound **38**) has the opposite effect. An acid substituent at position 2 renders the compound inactive (compound **25**). Sulfone and pyridine substituents at position 2 (compounds **32** and **26**) are less active. These results, together with many other examples not reported here, seems to suggest that the 3,3-dimethyl series of compounds may be less potent than the analogous monomethyl series.

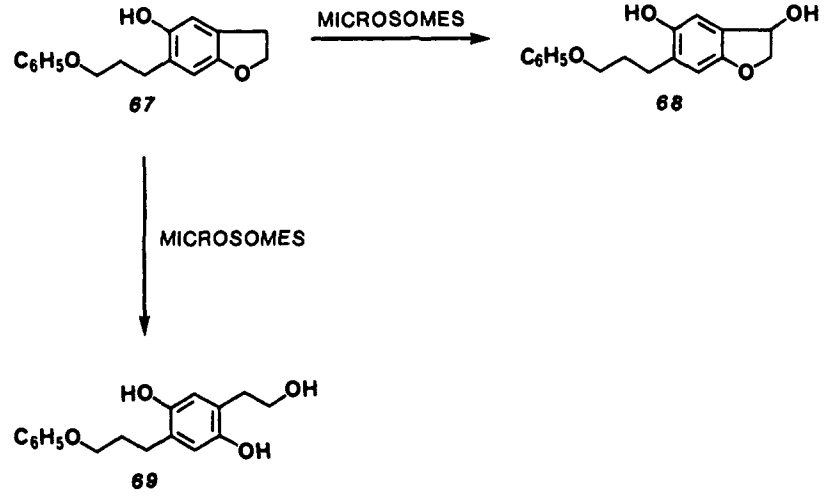
If the trend holds, the 3,3-unsubstituted series might be more potent. The 3,3-unsubstituted analogues, for exam-

Scheme VI[a]



a) DIBAL; b) MnO_2; c) $(C_6H_5)_3P{=}CHC_6H_4(4\text{-}Cl)$; d) BBr_3; e) Et_3SiH/TFA

Scheme VII



ple **46**, was found to be air stable and more potent than **37** (IC_{50} value of 6 and 38 nM respectively). However, some of the compounds in this series (example **42**, **43a**, and **43b**) caused methemoglobin formation in canine blood in vitro. This phenomenon has been observed before with other redox mechanism-based 5-lipoxygenase inhibitors.[6] Thus all subsequent compounds prepared in this series were tested for their ability to cause methemoglobin formation in vitro. As can be seen from the data of Table I, no correlation was observed between the ability of various compounds to inhibit leukotriene production and to cause methemoglobin formation.

The other problem involved with the 3,3-unsubstituted series was the potential metabolism at position 3. Compounds with no substitution at positions 2 and 3 (e.g. compound **67**[3a]) were found to be metabolized extensively in vitro (rat liver microsomes) and in vivo in rats. Rapid hydroxylation of **67** at position 3 was observed to give compound **68**. Prolonged incubation of compound **67** in the presence of rat liver microsomes gave the ring-opened hydroquinone **69** as shown in Scheme VII. However, metabolism was significantly reduced when large lipophilic substituents were placed at position 2 in both the 3,3-unsubstituted and the 3,3-dimethyl series. Figure 1 compares the relative stability of a representative compound from each series during incubation with rat liver microsomes. Both compound **38** and **66** were much more stable than compound **67**. Subsequent studies suggested that the increased metabolic stability of compounds **38** and **66** was probably due to the fact that they were poorer substrates for hepatic microsomal cytochrome P-450. It thus became

(6) (a) Fort, F. L.; Pratt, M. C.; Carter, G. W.; Lewkowski, J. P.; Heyman, I. A.; Cusick, P. K.; Kesterson, J. W. Heinz Bodies, Methemoglobinemia, and Hemolytic Anemia Induced in Rats by 3-Amino-1-[m-(trifluoromethyl)phenyl]-2-pyrazoline. *Fundam. Appl. Toxicol.* **1984**, *4*, 216–220. (b) Lau, C. K. et al. Unpublished results.

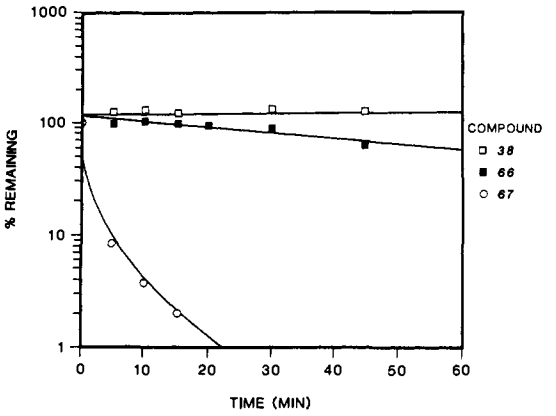


Figure 1. Metabolism of Dihydrobenzofuranols by microsomes. Compounds **38**, **66**, and **67** were incubated with rat liver microsomes at 37 °C in the presence of NADPH at various time periods up to 60 min. At the end of each period the reaction was stopped and extracted with EtOAc. The amount of substrate remaining was quantified by HPLC analysis of the concentrated organic extract.

clear that the 3,3-unsubstituted series is still viable as long as the 2-position is substituted with a large lipophilic group. On the basis of the structure–activity relationship of the 3,3-dimethyl series, it seems likely that the phenylethyl substituents at position 2 would also be optimum for the 3,3-unsubstituted series and yet resistant to degradation by microsomal enzymes. Thus, a major effort was directed to optimizing substituents on position 4 and 6 (while maintaining the 2-phenylethyl substituent constant) for in vitro and in vivo potency for this series. The results are summarized in Table I. In general, compounds with substituents at position 6 are slightly more potent than the corresponding 4-substituted analogues,[3a] as exemplified by compounds **43a** versus **43b**. Increase of lipophilicity from the allyl to the phenoxypropyl group gave a compound with an IC_{50} value below 10 nM (compound **46**). More importantly, it was found that compound **46** did not cause methemoglobin formation in contrast to its 6-allyl analogue (compound **43a**). The 6-benzyl analogue **59** is no more potent than **43a** but it is also inactive in the methemoglobin formation assay. It appears that compounds with bulky substituents at position 6 would not cause methemoglobin formation in canine blood. This was shown to be the case for other compounds prepared subsequently and the results are listed in Table I. Attempts to further increase the lipophilicity of compound **46** by adding a 4-chloro substituent to the phenylethyl substituent at position 2 (**66**) or adding a propyl group at position 4 resulted in decreased potency. Incorporation of an acid function at the end of the phenoxypropyl chain to mimic arachidonic acid and hopefully improve the pharmacokinetics of this series of compounds resulted in a significant reduction in activity (compound **48**). Converting the acid to the corresponding tetrazole **49** seems to improves the potency slightly. Adding back some lipophilicity by putting an extra propyl chain on position 4 (compound **55**) increases the potency further but still gives a compound that is substantially less active than **46**. Replacing the benzoic acid derivative with a quinolinic acid (compound **53**) increased the potency significantly to an IC_{50} value of 37 nM. A slightly acidic acetophenone derivative **52** is even more active with an IC_{50} value of 9 nM. Basic substituents such as the pyridyl propyl group in compound **50** also gave potent compounds (e.g. compound **50** has an IC_{50} value of 14 nM) but the benzothiazole compound **51** seems to be slightly less active. Compounds bearing other polar substituents like the sulfone **61** are much less active.

On the basis of the structure–activity relationship of the compounds described so far and many others not reported here, the optimum compounds that are resistant to microsomal metabolism and would not cause methemoglobin formation in canine blood are those 3,3-unsubstituted compounds that have large bulky lipophilic substituents at position 2 and 6. Basic and acidic groups can be tolerated at position 6.

The mechanism of action of these series of 5-lipoxygenase inhibitors has been studied briefly. They were shown to participate in a pseudoperoxidase reaction with 5-lipoxygenase and inhibition is probably achieved through reduction of the iron at the active site of the enzyme by these compounds.[7]

In Vivo Studies. Several of these inhibitors were evaluated for their oral activity in vivo by measuring their effect on antigen (ovalbumin)-induced bronchoconstriction in inbred, hyperreactive rats. Inbred rats were pretreated with methysergide (3 mg/kg, iv) and compounds were administered po 2 h prior to antigen challenge. The effect was measured as the percent inhibition of dyspnea duration compared to litter mate matched vehicle treated controls.[13] The results are summarized in Table II. A number of these compounds are very effective in blocking the duration of the antigen-induced bronchoconstriction response in hyperreactive rats with ED_{50} values in the range of 0.03–0.3 mg/kg. It is interesting to note that some of the more potent compounds in vivo are not the most potent in vitro and vice versa. For example, compound **55** with an ED_{50} value of 0.03 mg/kg in vivo has an IC_{50} value of only 107 nM in the HPMN assay. Compound **43a** having an IC_{50} value of 10 nM in the HPMN assay is barely active at 1.5 mg/kg in inhibiting antigen-induced dyspnea in hyperreactive rats. These findings may reflect the difference in bioavailability, drug disposition, and metabolism of individual compounds. Thus the bioavailability and plasma levels of some of these compounds in rats were measured after oral and iv dosing. The results are also summarized in Table II. In general the bioavailability (AUC_{po}/AUC_{iv}) and plasma level of these compounds are quite low. In some cases, no parent drug was detected. Since all the compounds are phenolic in nature and phenols are known to be metabolized in vivo mainly by conjugation to glucuronic acid to form phenol glucuronides,[8] it seemed quite likely that this series of compounds would be metabolized similarly. This was confirmed by treating the plasma samples from po-dosed animals with β-glucuronidase enzyme and then analyzing for parent compounds. The peak plasma levels of some of these compounds after β-glucuronidase treatment (total drug) vs untreated samples (free drug) are shown in Table II. As expected, the more lipophilic the compound, the greater is the extent of glucuronidation (for example, compound **15**, **46**, and **66**). Polar acidic compounds (**53** and **55**) tend to have higher ratio of free drugs which might explain the high in vivo potency of compound like **55** (ED_{50} = 0.03 mg/kg) in spite of its relatively low potency in vitro (IC_{50} value = 107 nM in the HPMN assay). However, these results did not account for the in vivo potency of compounds like **46** and **66** which have barely detectable free drugs in circulation. One possible explanation is that these

(7) Riendeau, D.; Falgueyret, J.-P.; Guay, J.; Ueda, N.; Yamamoto, S. Pseudoperoxidase Activity of 5-Lipoxygenase Stimulated by Potent Benzofuranol and N-hydroxyurea Inhibitors of the Lipoxygenase Reaction. *Biochem. J.* **1991**, *274*, 287–292.
(8) Dutton, G. J. Ed.; *Glucuronidation of Drugs and Other Compounds*; CRC Press: Boca Raton, Florida, 1980.

Table II. Effects of 2,3-Dihydro-5-hydroxybenzofurans on Antigen-Induced Dyspnea in Hyperreactive Inbred Rats

compd	dose,[a] mg/kg	inhibition of dyspnea, %[b]	p value[c]	ED_{50}, mg/kg	plasma level: free/total,[d] μM	bioavailability: free/total,[e] %
15	1.5[f]	68	<0.01		0/3.0	
17	1.5[f]	50	<0.05		0/0.7	
37	1.5[f]	48	<0.05			
43a	1.5	50	<0.01			
	0.5[g]	65	<0.01			
46	0.15[g]	55	<0.05	0.06	0.3/0.5	5/54
	0.05[g]	50	<0.02			
50	1.5	51	<0.05		1.0/3.0	11/10
52	0.5	50	<0.05		trace	
	0.5	69	<0.01			
53	0.15	72	<0.01	<0.05	1.0/3.4	3/4
	0.05	55	<0.01			
	0.5	64	<0.01			
55	0.15	61	<0.01	0.03	1.6/2.2	12/72
	0.05	52	<0.001			
	0.5[g]	53	<0.02			
59	0.15[g]	44	<0.02	0.3	1.6/3.8	44/76
	0.05[g]	44	<0.05			
	0.5[f]	74	<0.001			
66	0.15[f]	66	<0.01	0.07	0.3/3.1	6/27
	0.05[f]	56	<0.01			
	0.5	61	<0.02			
70	0.15	56	<0.02	0.05	0.0/7.0	0/20
	0.05	50	<0.02			

[a] Compounds were administered orally to a group of six rats 2 h prior to antigen challenge as suspensions in 1% methocel. [b] Inhibition (%) was calculated in terms of the reduction in duration in dyspnea in the drug-treated group compared to the control group. [c] p value compared to control. [d] Peak concentration of drugs in rat plasma after oral dosing at 20 mg/kg. Concentration of parent compound was measured before (free) and after (total) β-glucuronidase treatment. Only the peak levels are reported here. Each value is an average of three rats. The standard deviation of all experiments ranged between 5 to 20% of the mean value. [e] Bioavailability is a measure of $AUC_{po}/AUC_{iv} \times 100\%$ of parent compounds before (free) and after (total) β-glucuronidase treatment. [f] Compounds were administered as suspensions in 0.5% Tween 80 +0.4% methocel. [g] Compounds were administered as suspensions in 1% Methocel with 0.25% SDS.

Table III. Total Radioactivity (μg equiv/g) in Tissues of Male SD Rats Dosed Orally or Intravenously with ^{3}H-Labeled Compound 46 at 21 mg/kg[a]

time	Total Radioactivity (μg equiv/g) liver	kidney	lung	plasma	n
		a. orally			
5 min	12.12	9.12	473.13	7.74 ± 0.68	3
15 min	7.82	5.50	190.97	1.08 ± 0.90	3
30 min	3.92	0.85	4.11	1.09 ± 0.81	2
1 h	10.93	1.62	3.58	1.41 ± 1.22	3
2 h	13.12	2.20	2.22	2.64 ± 1.80	2
4 h	13.77	2.75	1.74	3.27 ± 1.32	2
24 h[b]	0.68	0.15	0.10	0.64	1
48 h[b]	0.11	0.03	0.09	0.82	1
		b. intravenously			
2 min	142.77	51.19	100.78	10.34 ± 1.8	2
10 min[b]	143.94	54.13	75.08	9.65 ± 1.4[c]	1
30 min[b]	41.11	22.75	56.91	5.81 ± 1.94[c]	1
1 h	26.77	11.78	40.77	3.34 ± 0.33	2
2 h	3.31	1.24	1.60	0.88 ± 0.81	2
4 h	9.87	2.82	5.00	1.18 ± 0.72	2

[a] Tissues from rats of the same group were composited by homogenization before combustion. Values are based on average of duplicated combustions of tissue homogenates. Two or three animals were used at all time points except those designated by *b*. [b] Only one rat of the group was analyzed for tissue radioactivity levels. [c] Plasma concentrations were from the mean of three rats.

Table IV. ^{3}H Compound 46 in Lung and Liver of Male SD Rats Dosed Orally at 21 mg/kg[a]

time	total radioactivity, μg/g	compound 46[a] %	compound 46[a] μg/g
	lung		
5 min	473	80.4	380
1 h	3.58	56.3	2.02
4 h	1.74	8.90	0.15
	liver[b]		
1 h	10.9	25.5	2.78
4 h	13.8	18.0	2.48

[a] Composite tissue homogenates were those described in Table IIIa. Percentage of compound 46 was determined by the amount of radioactivity eluted with 46 using RP-HPLC as described in Experimental Section. [b] Note that unlike the lung, radioactivity in liver and kidney does not decline between 1 and 4 h.

compounds may have a favorable tissue distribution in vivo. Compound 46 being the most potent compound in vitro was selected for further studies in this aspect.

Tritium-labeled compound 46 (in the phenoxy ring) was prepared,[9] and rats were dosed orally or by iv injection with the labeled compound at 21 mg/kg. In the oral study, the animals were sacrificed at 5, 15, 30 min, 1, 2, 4, 24, and 48 h post dose. The iv-dosed animals were sacrificed at 2, 10, 30 min, 1, 2, and 4 h post dose. Total radioactivity in plasma and tissues were determined. Concentrations of compound 46 in plasma and tissues of selected time points were also determined. Table III shows the total radioactivity levels in liver, lung, kidney, and plasma of orally and intravenously dosed animals. For orally dosed rats, high levels of radioactivity (473 μg equiv/g) was present in the lung as early as 5 min post dose which was 61 times higher than that in the plasma at this time point. In comparison, the level in the liver was 12.1 μg equiv/g, or approximately twice the plasma radioactivity. Of the radioactivity in the lung and plasma, ~80% and 94% was the parent compound, respectively. While high levels of radioactivity was found in the lung at the early time points when compound 46 was administered orally, the levels in the lung when dosed intravenously are lower and similar to those in other tissues. These results seem to suggest that compound 46 was rapidly absorbed after oral dosing and sequestered initially in the lung and then redistributed slowly to the

(9) Tritium-labeled compound 46 was kindly prepared by R. Chen of the Department of Animal Drug Metabolism of Merck Sharp and Dohme Research Laboratories, Rahway, NJ.

general circulation. This is supported by the high concentration of compound **46** in the lung at 5 min after oral dosing (380 μg/g of tissue, corresponding to 80.4% of the total radioactivity in the lung). By 1 h, the concentration had already declined substantially (to 2.02 μg/g of tissue or 56.3% of total radioactivity) to comparable levels as those in the plasma (Table IV). Also noticeable is that, after oral dosing of compound **46**, the total radioactivity in the lung, liver, kidney, and plasma reaches a trough around 30 min and then begins to climb again through 4 h. Similar result was also observed in the iv data whether this rebound of total activity (not the parent compound **46**) is due to enterohepatic circulation has not been investigated. On the basis of AUC (area under the plasma concentration vs time curve) of plasma total radioactivity from orally and iv-dosed animals, compound **46** was well absorbed. The compound, however, was cleared rapidly; by 1 h the level in the lung declined to 3.6 μg equiv/g (~2 times of plasma) with 56% (2.0 μg/g) of the radioactivity accounted for by compound **46** (Table IV). At this time point, concentration of compound **46** was similar in the liver and the lung while much lower concentrations were found in the plasma at 0.01 and 0.06 μg/mL for orally and intravenously dosed animals, respectively. As shown in Table IV, concentration of compound **46** was still at a reasonably high pharmacological level at 0.15 μg/g after 4 h considering the fact that its IC_{50} was 6 nM in the HPMN assay.

As mentioned earlier, compound **46** and similar compounds circulate largely as glucuronide conjugates in rats after oral dosing. These conjugates can be deconjugated in vitro by β-glucuronidase to regenerate the parent drug. It is possible that the circulating glucuronide conjugate serves as the source of free drug to the target organ and other tissues after deconjugation. To investigate if this phenomenon did exist, the glucuronide conjugate of compound **46** was prepared synthetically (compound **70**). Deconjugation of compound **70** and the in vivo conjugates of compound **46** isolated from rat plasma were examined in vitro using gastrointestinal (GI) homogenates. The GI tract homogenate was chosen for this study since it has been well established that GI (especially lower GI) is a rich source of glucuronidases. In addition, it was anticipated that deconjugation of the glucuronide may generate sufficiently high concentration for local therapeutic purposes (e.g. inflammatory bowel disease). Synthetic conjugate **70** (50 μg) was shown to regenerate the parent **46** partially when incubated with 260 units of β-glucuronidase or GI homogenate, <40% recovery. In comparison, the plasma conjugate **70** (<1.5 μg) was also partially converted to the parent (~60%) after incubation with GI homogenate (data not shown). The deconjugation reaction possibly involved enzymes (or gut bacteria) in addition to glucuronidases since addition of 500 μM of saccharolactone (an inhibitor of glucuronidase) to the incubate did not completely inhibit the deconjugation.

To demonstrate that deconjugation also occurs in vivo, synthetic glucuronide conjugate **70** was evaluated for its effect on antigen-induced bronchoconstriction in hyperreactive rats after oral dosing. The results are shown in Table II. The conjugate **70** which is inactive in vitro (Table I) is similarly potent in vivo as the parent compound **46** with similar ED_{50} value of 0.05 mg/kg po.

On the basis of all these findings, it is apparent that although compounds **46** and its analogues, produce little circulating parent compound in the blood, high concentrations of the free compounds in the target organ (the lung) could be achieved. The major circulating metabolite, glucuronic acid conjugate, may also be deconjugated in vivo in the GI tract to liberate more free drug to exert its therapeutic action. These observations may explain the high in vivo potency of compound **46** and similar compounds.

Characterization of Compound 46 (L-670,630). Overall, compound **46**, 2,3-dihydro-2-(2-phenylethyl)-6-(3-phenoxypropyl)-5-benzofuranol was found to have the best biological profile in vitro and in vivo. It is a potent inhibitor of leukotriene biosynthesis in intact human leukocytes (IC_{50} value = 6 nM) and of the 5-lipoxygenase reaction catalyzed by a cell-free preparation of rat leukocytes (IC_{50} value = 23 nM). The potency of the compound as an inhibitor of LTB_4 biosynthesis is comparable or better than that of previously described benzofuranol inhibitors such as L-656,224 (IC_{50} = 11 nM)[4] and L-651-896 (IC_{50} = 130 nM).[3] L-670,630 is much more efficient as an inhibitor of leukotriene biosynthesis and of 5-lipoxygenase than A-64077. Compound **46** is relatively inactive as an inhibitor of the porcine leukocyte 12-lipoxygenase (IC_{50} value = 7 uM) and partially purified 15-lipoxygenase from human leukocytes (IC_{50} value = 2.5 uM). When administered orally, compound **46** is a potent inhibitor of antigen-induced bronchoconstriction in inbred, hyperreactive rats with an ED_{50} value of 0.05 mg/kg po. Against ascaris antigen-induced bronchoconstriction in the squirrel monkeys, a po dose of 1 mg/kg of this compound caused a pronounced inhibition of the increase in pulmonary resistance (84%) and completely blocked the decrease in dynamic compliance (100%).[12] The present results showed that 2,3-dihydro-2-(2-phenylethyl)-6-(3-phenoxypropyl)-5-benzofuranol is a potent orally active inhibitor of leukotriene biosynthesis. Inhibitors of the 5-lipoxygenase pathway may be useful for the treatment of human bronchial asthma and other allergic and inflammatory diseases.

Experimental Section

Chemistry. Proton nuclear magnetic resonance spectra were obtained on a Bruker AM 250 spectrometer and proton chemical shifts are relative to tetramethylsilane (TMS) as internal standard. The infrared spectra were measured on a Perkin-Elmer 681 spectrophotometer. Melting points were measured on a Buchi 510 melting point apparatus in open capillary tubes and are uncorrected. Low-resolution mass spectral analyses were performed by the Morgan Schaffer Corporation, Montreal, and elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario. Where elemental analyses are reported only by symbols of the elements, results were within 0.4% of the theoretical. All reactions as well as column chromatography were monitored routinely with the aid of thin-layer chromatography using precoated silica gel GF plates (Analtech). High-performance liquid chromatography was carried out on a Waters WISP Model 710B liquid chromatograph equipped with a Waters data module M730 and fitted with a Waters reversed-phase C_{18} column with the following solvent systems: CH_3CN/H_2O (50:50 to 80:20 isocratic), flow rate 1.5 mL/min, with variable wavelength detector typically monitored at 300 nm.

7-Chloro-2,3-dihydro-2-(4-methoxybenzyl)-3-methyl-5-propyl-4-benzofuranol (2). To a solution of 7-chloro-2-(4-methoxybenzyl)-3-methyl-5-propyl-4-benzofuranol (0.1 g, 0.29 mmol) in trifluoroacetic acid (5 mL) was added triethylsilane (0.14 mL, 0.87 mmol). The reaction mixture was stirred at room temperature for a period of 18 h. The mixture was diluted with H_2O (20 mL) and neutralized with K_2CO_3 (solid). The solution was extracted with ethyl acetate and the combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane as eluent to yield 91% 7-chloro-2,3-dihydro-2-(4-methoxybenzyl)-3-methyl-5-propyl-4-benzofuranol (**2**): ^1H NMR δ 0.9 (t, 3 H, J = 6 Hz), 1.2 (d, 3 H, J = 6 Hz), 1.55 (m, 2 H), 2.45 (t, 2 H, J = 9 Hz), 2.65–3.5 (m, 3 H), 3.8 (s, 3 H), 4.5 (m, 2 H), 6.85

(m, 3 H), 7.2 (d, 2 H, J = 9 Hz).

5-(Benzyloxy)-2-(4-methoxybenzoyl)-3-methylbenzofuran (5). A mixture of 2-hydroxy-5-(benzyloxy)acetophenone (93 g, 380 mmol), 4-methoxyphenacyl bromide (88 g, 384 mmol), and potassium carbonate (106 g, 768 mmol) in acetone (1.5 L) was refluxed for 46 h. The reaction mixture was cooled and filtered. The filtrate was evaporated in vacuo. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane as eluent to yield 127 g (89%) of 5-(benzyloxy)-2-(4-methoxybenzoyl)-3-methylbenzofuran (5): ^{1}H NMR δ 2.55 (s, 3 H), 3.85 (s, 3 H), 5.1 (s, 2 H), 7.0 (d, 2 H, J = 9 Hz), 7.15 (m, 2 H), 7.45 (m, 6 H), 8.15 (d, 2 H, J = 9 Hz).

2,3-Dihydro-2-(4-methoxybenzyl)-3-methyl-5-benzofuranol (6). (a) A solution of 5 (5 g, 13.44 mmol) in ethanol (100 mL) was hydrogenated at 40 psi in a Parr apparatus in the presence of 5% palladium on carbon for a period of 1 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness. The product, 2-(4-methoxybenzoyl)-3-methyl-5-benzofuranol, was used as such in the next step.

(b) To a solution of 2-(4-methoxybenzoyl)-3-methyl-5-benzofuranol (3.8 g, 13.44 mmol) in trifluoroacetic acid (30 mL) was added triethylsilane (15 mL, 94 mmol). The reaction mixture was stirred at room temperature for a period of 18 h. The mixture was diluted with H_2O (50 mL) and neutralized with K_2CO_3 (solid). The solution was extracted with ethyl acetate and the combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane as eluent to yield 3 g (84%) of 2,3-dihydro-3-methyl-2-(4-methoxybenzyl)-5-benzofuranol (6): ^{1}H NMR δ 1.15 (d, 3 H, J = 6 Hz), 3.05 (m, 3 H), 3.78 (s, 3 H), 4.4 (q, 1 H), 4.72 (m, 1 H), 6.65 (s, 3 H), 6.85 (d, 2 H, J = 9 Hz), 7.2 (d, 2 H, J = 9 Hz).

2,3-Dihydro-2-(4-methoxybenzyl)-3-methyl-6-propyl-5-benzofuranol (7). (a) A mixture of 6 (16 g, 59.25 mmol), allyl bromide (10 g, 82.6 mmol), and K_2CO_3 (8.17 g, 59.2 mmol) in acetone (300 mL) was refluxed for a period of 18 h. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was chromatographed on silica gel using 5% ethyl acetate in hexane as eluent to yield 22 g (100%) of 5-(allyloxy)-2,3-dihydro-2-(4-methoxybenzyl)-3-methyl benzofuran: ^{1}H NMR δ 1.05 (d, 3 H, J = 6 Hz), 2.7–3.3 (m, 3 H), 3.7 (s, 3 H), 4.4 (m, 2 H), 5.1–5.3 (m, 2 H), 6.0 (m, 1 H), 6.6 (s, 3 H), 6.8 (d, 2 H, J = 9 Hz), 7.15 (d, 2 H, J = 9 Hz).

(b) A solution of 5-(allyloxy)-2,3-dihydro-2-(4-methoxybenzyl)-3-methylbenzofuran (22 g, 59 mmol) in dichlorobenzene (100 mL) was refluxed for a period of 18 h. The solution was concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to yield 18 g (82%) of 6-allyl-2,3-dihydro-2-(4-methoxybenzyl)-3-methyl-5-benzofuranol: ^{1}H NMR δ 1.05 (d, 3 H, J = 6 Hz), 2.6–3.2 (m, 3 H), 3.25 (d, 2 H), 3.7 (s, 3 H), 4.35 (m, 1 H), 4.65 (s, 1 H), 5.05 (m, 2 H), 6.0 (m, 1 H), 6.5 (s, 2 H), 6.8 (d, 2 H, J = 9 Hz), 7.15 (d, 2 H, J = 9 Hz).

(c) A solution of 6-allyl-2,3-dihydro-2-(4-methoxybenzyl)-3-methyl-5-benzofuranol (0.09 g, 0.29 mmol) in ethanol (5 mL) was hydrogenated in a Parr apparatus in presence of 5% palladium on carbon for a period of 1 h under 35 psi of pressure. The catalyst was removed by filtration, and the filtrate was concentrated to dryness. Chromatography gave 0.09 g (100%) of 2,3-dihydro-2-(4-methoxybenzyl)-3-methyl-6-propyl-5-benzofuranol (7): ^{1}H NMR δ 0.9 (t, 3 H, J = 9 Hz), 1.05 (d, 3 H, J = 6 Hz), 1.55 (m, 2 H), 2.4 (m, 2 H), 2.9 (m, 3 H), 3.65 (s, 3 H), 4.25 (q, 1 H, J = 6 Hz), 4.5 (s, 1 H), 6.4 (s, 2 H), 6.7 (d, 2 H, J = 9 Hz), 7.15 (d, 2 H, J = 9 Hz).

2-(Hydroxymethyl)-2,3-dihydro-3,3-dimethyl-5-methoxybenzofuran (12). (a) To a mixture of 4-methoxyphenol (62 g, 500 mmol), 3-methyl-2-buten-1-ol (4.3 g, 500 mmol), and diethyl azodicarboxylate (108 g, 625 mmol) in tetrahydrofuran (2 L) at 5 °C was added a solution of triphenylphosphine (163 g, 625 mmol) in tetrahydrofuran (500 mL) over 30 min. The mixture was then stirred at room temperature for 1 h and then concentrated in vacuo. The residue was triturated with 5% ethyl acetate in hexane. The solid was filtered off and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using 5% ethyl acetate in hexane as eluent to obtain 67 g (70%) of 3-methyl-2-buten-1-yl 4-methoxyphenyl ether as an oil: ^{1}H NMR δ 1.70 (s, 3 H), 1.76 (s, 3 H), 3.7 (s, 3 H), 4.36 (d, 2 H, J = 6 Hz), 5.23–5.6 (m, 1 H), 6.76 (s, 4 H).

(b) A mixture of 3-methyl-2-buten-1-yl 4-methoxyphenyl ether (42 g, 219 mmol) n-butyric anhydride (69 g, 438 mmol), and N,N-dimethylaniline (66 g, 547 mmol) in 1,2-dichlorobenzene (200 mL) was refluxed for 24 h under nitrogen atmosphere. After cooling to room temperature, water (100 mL) was added and the mixture stirred for 2 h. HCl (3 N, 200 mL) was then added followed by dichloromethane (100 mL). The organic layer was separated, washed with HCl (3 N, 200 mL), sodium bicarbonate (1 N, 300 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo until most of the 1,2-dichlorobenzene was driven off. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane to obtain 39.5 g (68%) of a mixture containing 2-(1,1-dimethylallyl)-4-methoxyphenyl n-butyrate (9), 2-(1,2-dimethylallyl)-4-methoxyphenyl n-butyrate (10), and 4-methoxyphenyl n-butyrate (11). The olefinic mixture was separated in the next step as their epoxides.

(c) To a mixture of 9, 10, and 11 (39.5 g) in dichloromethane (900 mL) was added in portions m-chloroperbenzoic acid (52 g, 300 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was cooled in an ice–water bath and calcium hydroxide (150 g) was added. After stirring for 15 min the mixture was filtered through a Celite pad and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane to obtain 20 g (47%) of 2-(1,1-dimethyl-2,3-epoxypropyl)-4-methoxyphenyl n-butyrate as an oil: ^{1}H NMR δ 1.03 (t, 3 H, J = 7.5 Hz), 1.2 (s, 3 H), 1.3 (s, 3 H), 1.6–2.0 (m, 2 H), 2.43–2.83 (m, 4 H), 3.06–3.20 (m, 1 H), 3.76 (s, 3 H), 6.6–7.06 (m, 3 H).

(d) To a solution of 2-(1,1-dimethyl-2,3-epoxypropyl)-4-methoxyphenyl n-butyrate (41 g, 147 mmol) in ethanol (600 mL) at 5 °C was added 0.5 M sodium ethoxide in ethanol (328 mL). The mixture was stirred for 30 min and then water added. The mixture was extracted with diethyl ether, back-washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 30 g (98%) of 2-(hydroxymethyl)-2,3-dihydro-3,3-dimethyl-5-methoxybenzofuran (12): mp 65–67 °C; ^{1}H NMR δ 1.13 (s, 3 H), 1.33 (s, 3 H), 1.96 (t, 1 H, J = 6 Hz), 3.6–3.93 (m, 5 H), 4.2–4.4 (m, 1 H), 6.5–6.8 (m, 3 H).

5-(Benzyloxy)-2,3-dihydro-3,3-dimethylbenzofuran-2-carboxyaldehyde (13). (a) To a solution of 12 (30 g, 144 mmol) in dichloromethane (1 L) at –78 °C was added dropwise 1 M boron tribromide in dichloromethane (300 mL). The mixture was permitted to warm to room temperature over 1 h and then recooled to 5 °C. Sodium bicarbonate (1 M) was added slowly and the mixture was stirred at room temperature until two clear layers were obtained. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 40% ethyl acetate in hexane as eluent to obtain 13.1 g (47%) of 2,3-dihydro-3,3-dimethyl-2-(hydroxymethyl)-5-benzofuranol: mp 79–80 °C; ^{1}H NMR δ 1.16 (s, 3 H), 1.36 (s, 3 H), 2.06 (t, 1 H, J = 6 Hz), 3.73–3.93 (m, 2 H), 4.23–4.46 (m, 1 H), 4.96 (s, 1 H) 6.5–6.6 (m, 3 H).

(b) A mixture of 2,3-dihydro-3,3-dimethyl-2-(hydroxymethyl)-5-benzofuranol (14 g, 72 mmol), potassium carbonate (21 g, 155 mmol), and benzyl chloride (19.5 g, 155 mmol) in methyl ethyl ketone was stirred at reflux for 18 h. The mixture was filtered through a Celite pad and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using 30% ethyl acetate as eluent to obtain 14.5 g (71%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-(hydroxymethyl)benzofuran: mp 55–58 °C; ^{1}H NMR δ 1.16 (s, 3 H), 1.36 (s, 3 H), 1.96 (t, 1 H, J = 6 Hz), 3.7–3.9 (m, 2 H), 4.26–4.46 (m, 1 H), 4.96 (s, 2 H), 6.63–6.76 (m, 3 H), 7.2–7.53 (m, 5 H).

(c) To a cold (–78 °C) solution of oxalyl chloride (1.78 g, 14 mmol) in CH_2Cl_2 (50 mL) was added DMSO (2.18 g, 28 mmol) in CH_2Cl_2 (10 mL) dropwise. This solution was stirred for 15 min. Then 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-(hydroxymethyl)benzofuran (2.0 g, 7 mmol) was added and the resulting mixture was stirred at –78 °C for 30 min. To the reaction mixture was added Et_3N (3.55 g, 35 mmol) and the temperature was raised to room temperature. Then H_2O (100 mL) was poured into the reaction mixture and stirred for 15 min. The organic phase was separated from the aqueous. The organic phase was concentrated in vacuo, and the residue was chromatographed on silica gel.

Elution with 15% ethyl acetate in hexane yielded 1.8 g (91%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethylbenzofuran-2-carboxyaldehyde (13): ^{1}H NMR δ 1.2 (s, 3 H), 1.5 (s, 3 H), 4.5 (d, 1 H, J = 1.5 Hz), 5.0 (s, 2 H), 6.75 (m, 3 H), 7.35 (m, 5 H), 9.8 (d, 1 H, J = 1.5 Hz).

6-Allyl-2,3-dihydro-3,3-dimethyl-2-(4-methoxybenzyl)-5-benzofuranol (15). (a) To a solution of 13 (1.8 g, 6.38 mmol) in tetrahydrofuran (50 mL) at 0 °C was added the Grignard reagent 4-methoxyphenyl magnesium bromide in tetrahydrofuran (0.85 M) (15 mL, 12.8 mmol) which was previously prepared by refluxing for 2 h a mixture of 4-bromoanisole (7.5 g, 0.40 mmol) and magnesium turnings (1 g, 41 mmol) in tetrahydrofuran (50 mL). The mixture was stirred for 2 h at room temperature and then excess HCl (1 N) was added. The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane as eluent to obtain 1.5 g (61%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[1-hydroxy-1-(4-methoxyphenyl)-methyl]benzofuran: ^{1}H NMR δ 0.9 (s, 3 H), 1.15 (s, 3 H), 2.75 (d, 1 H, J = 3 Hz), 3.8 (s, 3 H), 4.45 (d, 1 H), 4.9 (m, 1 H), 5 (s, 2 H), 6.7 (m, 3 H), 6.95 (d, 3 H, J = 9 Hz), 7.35 (m, 7 H).

(b) A solution of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[1-hydroxy-1-(4-methoxyphenyl)methyl]benzofuran (1.5 g, 3.8 mmol) in ethanol (40 mL) was hydrogenated in a Parr apparatus in the presence of 5% palladium on carbon for a period of 18 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane as eluent to obtain 0.056 g (5.2%) of 2,3-dihydro-3,3-dimethyl-2-(4-methoxybenzyl)-5-benzofuranol: ^{1}H NMR δ 1.1 (s, 3 H), 1.2 (s, 3 H), 2.85 (dd, J = 7.5 Hz, J' = 3 Hz), 3.75 (s, 3 H), 4.35 (dd, 1 H, J = 4.5 Hz), 4.9 (m, 1 H), 6.5 (s, 3 H), 6.85 (d, 2 H, J = 9 Hz), 7.15 (d, 2 H, J = 9 Hz).

(c) A mixture of 2,3-dihydro-3,3-dimethyl-2-(4-methoxybenzyl)-5-benzofuranol (0.056 g, 0.19 mmol), allyl bromide (0.033 g, 0.26 mmol), and K_2CO_3 (0.026 g, 0.19 mmol) in methyl ethyl ketone (5 mL) was refluxed for a period of 18 h. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was chromatographed on silica gel using 5% ethyl acetate in hexane as eluent to yield 0.05 g (78%) of 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-(4-methoxybenzyl)benzofuran.

(d) A solution of 5-(allyloxy)-2,3 dihydro-3,3-dimethyl-2-(4-methoxybenzyl)benzofuran (0.05 g, 0.15 mmol) in dichlorobenzene (5 mL) was refluxed for a period of 4 h. The solution was concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to yield 0.038 g (64%) of 6-allyl-2,3-dihydro-3,3-dimethyl-2-(4-methoxybenzyl)-5-benzofuranol (15): ^{1}H NMR δ 1.1 (s, 3 H), 1.2 (s, 3 H), 2.9 (m, 2 H), 3.3 (m, 2 H), 3.75 (s, 3 H), 4.3 (dd, 1 H, J = 6 Hz), 5.1 (m, 2 H), 5.7–6.25 (m, 1 H), 6.6 (s, 2 H), 6.9 (d, 2 H, J = 9 Hz), 7.25 (d, 2 H, J = 9 Hz).

2,3-Dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethyl]-5-benzofuranol (16). (a) To diethyl (4-methoxybenzyl)-phosphonate (0.6 g, 2.3 mmol) cooled at −78 °C in THF (20 mL) was added potassium hexamethyldisilazide (3.6 mL, 2.3 mmol) and the yellow solution was stirred for 30 min. Then 13 (0.2 g, 0.7 mmol) dissolved in 5 mL of THF was added to the phosphonate solution. The reaction mixture was warmed to 0 °C and stirred for 30 min. Subsequently the reaction mixture was acidified with HCl (1 N), diluted with brine, and extracted with ethyl acetate twice. The combined organic phases were dried (Na_2SO_4) and evaporated. The residue was concentrated in vacuo and was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane yielded 0.1 g, (37%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethenyl]benzofuran: ^{1}H NMR δ 1.1 (s, 3 H), 1.35 (s, 3 H), 3.7 (s, 3 H), 4.75 (d, 1 H, J = 9 Hz), 4.95 (s, 2 H), 6.25 (dd, 1 H, J = 12 Hz, J' = 7.5 Hz), 6.75 (m, 4 H), 7.35 (m, 5 H).

(b) A solution of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethenyl]benzofuran (0.1 g, 0.26 mmol) in ethanol (5 mL) was hydrogenated at 40 psi in a Parr apparatus in the presence of 5% palladium on carbon for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel using 20% ethyl acetate in hexane as eluant to yield 60 mg (78%) of 2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethyl]-5-benzofuranol (16): ^{1}H NMR δ 1.05 (s, 3 H), 1.18 (s, 3 H), 1.5–2.1 (m, 2 H), 2.4–3.1 (m, 2 H), 3.7 (s, 3 H), 4.1 (dd, 1 H, J = 9 Hz, J' = 3 Hz), 4.75 (m, 1 H), 6.55 (m, 3 H), 6.8 (d, 2 H, J = 9 Hz), 7.1 (d, 2 H, J = 9 Hz).

6-Allyl-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)-ethyl]-5-benzofuranol (17). (a) A mixture of 2,3 dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethyl]-5-benzofuranol (0.56 g, 1.8 mmol), allyl bromide (0.9 g, 7.5 mmol), and K_2CO_3 (1.03 g, 7.5 mmol) in methyl ethyl ketone (25 mL) was refluxed for a period of 1.5 h. The reaction mixture was cooled, filtered through Celite, and concentrated in vacuo. The residue was chromatographed on silica gel using 5% ethyl acetate in hexane as eluent to yield 0.35 g (55%) of 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethyl]benzofuran.

(b) A solution of 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2[2-(4-methoxyphenyl)ethyl]benzofuran (0.35 g, 1.03 mmol) in dichlorobenzene (6 mL) was refluxed for a period of 6 h. The solution was concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to yield 0.25 g (71%) of 6-allyl-2,3 dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethyl]-5-benzofuranol (17): ^{1}H NMR δ 1.05 (s, 3 H), 1.2 (s, 3 H), 1.6–2.0 (m, 2 H), 2.51–3.15 (m, 2 H), 3.35 (d, 2 H, J = 6 Hz), 3.75 (s, 3 H), 4.1 (dd, 1 H, J = 3 Hz), 5.1 (m, 2 H), 5.6–6.2 (m, 1 H), 6.55 (s, 1 H), 6.58 (s, 1 H), 6.8 (d, 2 H, J = 9 Hz), 7.15 (d, 2 H, J = 9 Hz).

2,3-Dihydro-3,3-dimethyl-2-methoxy-5-benzofuranol (18). 2,3-Dihydro-3,3-dimethyl-2-methoxy-5-benzofuranol was readily prepared from benzoquinone by the procedure of G. Allen, Jr.[10]

6-Allyl-2,3-dihydro-3,3-dimethyl-2-methoxy-5-benzofuranol (19a). (a) A mixture of 18 (74 g, 380 mmol), allyl bromide (92 g, 760 mmol), potassium carbonate (104 g, 760 mmol), and methyl ethyl ketone (500 mL) was refluxed for 4 h. The mixture was cooled and filtered through Celite, and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to yield 68 g (77%) of 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran, as an oil: ^{1}H NMR δ 1.26 (s, 3 H), 1.33 (s, 3 H), 3.53 (s, 3 H) 1.4–4.63 (m, 2 H), 5.0–5.63 (m, 2 H), 5.8–6.4 (m, 1 H), 6.73 (s, 2 H).

(b) A solution of 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran (68 g, 290 mmol) in 1,2-dichlorobenzene (136 mL) was refluxed under nitrogen atmosphere for 18 h. The mixture was concentrated in vacuo to remove most of the dichlorobenzene and the residue was chromatographed on silica gel using 5% ethyl acetate in hexane to obtain 51 g (75%) of 6-allyl-2,3-dihydro-3,3-dimethyl-2-methoxy-5-benzofuranol (19a) as an oil: ^{1}H NMR δ 1.24 (s, 3 H), 1.28 (s, 3 H), 3.28–3.40 (m, 2 H), 3.52 (s, 3 H), 4.87 (s, 1 H), 5.04–5.22 (m, 3 H), 5.88–6.07 (m, 1 H), 6.55–6.63 (m, 2 H). The more polar isomeric 4-allyl-2,3-dihydro-3,3-dimethyl-2-methoxy-5-benzofuranol (19b) 10 g (15%) was also isolated as an oil: ^{1}H NMR δ 1.40 (s, 3 H), 1.46 (s, 3 H), 3.0–3.66 (m, 5 H), 4.73–5.30 (m, 4 H), 5.73–6.33 (m, 1 H), 6.73 (s, 2 H).

6-Allyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol (20). (a) A mixture of 6-allyl-2,3-dihydro-3,3-dimethyl-2-methoxy-5-benzofuranol (19a, 20 g, 85 mmol), acetic acid (160 mL), and water (40 mL) was refluxed for 18 h. The mixture was concentrated in vacuo, and the residue chromatographed on silica gel using 20% ethyl acetate in hexane as eluent to obtain 17.8 g (94%) of 6-allyl-2,3 dihydro-2,5-dihydroxy-3,3-dimethylbenzofuran: mp 66–67 °C; ^{1}H NMR δ 1.23 (s, 3 H), 1.3 (s, 3 H), 3.16–3.46 (m, 2 H), 4.66–5.6 (m, 5 H), 5.7–6.26 (m, 1 H), 6.6 (s, 2 H).

(b) A mixture of 6-allyl-2,3-dihydro-2,5-dihydroxy-3,3-dimethylbenzofuran (30 g, 138 mmol), (carbethoxymethylene)triphenylphosphorane (125 g, 360 mmol), and tetrahydrofuran (650 mL) was refluxed for 20 h. The mixture was concentrated in vacuo and the residue chromatographed on silica gel using 30% ethyl acetate in hexane as eluent to obtain 33 g (82%) of 6-allyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol (20): ^{1}H NMR δ 1.1–1.4 (m, 9 H), 2.53–2.76 (m, 2 H), 3.2–3.4 (m, 2 H), 4.2 (q, 2 H, J = 13 Hz), 4.53–4.8 (m, 2 H), 4.93–5.3 (m, 2 H), 5.63–6.23 (m, 1 H), 6.36 (s, 1 H), 6.40 (s, 1 H).

(10) Allen, G., Jr. Condensation of Enamines with Substituted p-Benzoquinones. *J. Org. Chem.* 1968, *33*, 3346–3347.

2-(2-Bromoethyl)-5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-6-propylbenzofuran (23). (a) A mixture of 6-allyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol (5 g, 17 mmol), 10% palladium in charcoal (50 mg), and ethanol (50 mL) was hydrogenated at 50 psi for 2 h using a Parr apparatus. The mixture was filtered and concentrated to obtain 5 g (98%) of 6-propyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol as an oil: ^{1}H NMR δ 0.8–1.8 (m, 14 H), 2.4–2.8 (m, 4 H), 4.25 (q, 2 H, J = 6 Hz), 4.4 (s, 1 H), 4.65 (dd, 1 H, J = 9 Hz, J' = 6 Hz), 6.50 (s, 1 H), 6.55 (s, 1 H).

(b) A mixture of 6-propyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol (9.3 g, 32 mmol), *tert*-butylchlorodiphenylsilane (10.5 g, 38 mmol), (*N*,*N*-dimethylamino)pyridine (3.8 g, 32 mmol), and triethylamine (3.8 g, 38 mmol) in dichloromethane (250 mL) was stirred at room temperature for 18 h. Excess 20% citric acid solution was added and the mixture stirred for 10 min. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to obtain 19.5 g (98%) of 5-[(*tert*-butyldiphenylsilyl)oxy]-2-carbethoxymethyl-2,3-dihydro-3,3-dimethyl-6-propylbenzofuran as an oil which was used as such in the next step: ^{1}H NMR δ 0.5–1.9 (m, 22 H), 2.4–2.8 (m, 4 H), 4.25 (q, 2 H, J = 6 Hz(, 4.55 (dd, 1 H, J = 9 Hz, J' = 6 Hz), 6.0 (s, 1 H), 6.4 (s, 1 H), 7.15–8.0 (m, 10 H).

(c) To a mixture of lithium aluminum hydride (6 g, 159 mmol) in diethyl ether (750 mL) under N_2 was added a solution of 5-[(*tert*-butyldiphenylsilyl)oxy]-2-carbethoxymethyl-2,3-dihydro-3,3-dimethyl-6-propylbenzofuran (19 g, 32 mmol) in tetrahydrofuran (75 mL). After stirring for 1.5 h the mixture was decomposed slowly by addition of water (6.0 mL), 1 N NaOH (6.0 mL), and more water (18 mL). The solid was filtered over Celite and the filtrate concentrated. The residue was chromatographed using 30% ethyl acetate in hexane as eluent to obtain 14.8 g (95%) of 5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-2-(hydroxyethyl)-6-propylbenzofuran: mp 97–103 °C; ^{1}H NMR δ 0.5–2.3 (m, 25 H), 2.55–2.85 (m, 2 H), 3.5 (q, 2 H, J = 6 Hz), 3.85 (q, 2 H, J = 5 Hz), 4.15 (dd, J = 10 Hz, J' = 4.5 Hz), 6.1 (s, 1 H), 6.55 (s, 1 H), 7.2–7.95 (m, 10 H).

(d) Solid carbon tetrabromide (2.1 g, 6.4 mmol) was added in one portion to a solution of 5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-2-(hydroxyethyl)-6-propylbenzofuran (1.5 g, 3.2 mmol) and triphenylphosphine (1.6 g, 6.4 mmol) in dichloromethane (100 mL). The mixture was stirred for 15 min and then concentrated. The residue was extracted with diethyl ether and the solid filtered off over Celite. The filtrate was concentrated and the residue chromatographed using 15% ethyl acetate in hexane to obtain 3.2 g (92%) of the title compound: mp 89–90 °C; ^{1}H NMR δ 0.72 (s, 3 H), 0.9 (s, 3 H), 1.05 (t, 3 H, J = 9.3 Hz), 1.1 (s, 9 H), 1.6–1.8 (m, 2 H), 1.85–2.25 (m, 2 H), 2.6–2.75 (m, 2 H), 3.5–3.7 (m, 2 H), 4.2 (dd, 1 H, J = 12.5 Hz, J' = 3 Hz), 6.02 (s, 1 H), 6.57 (s, 1 H), 7.3–7.8 (m, 10 H).

2-[2-[(2-Carboxyethyl)thio]ethyl]-2,3-dihydro-3,3-dimethyl-6-propyl-5-benzofuranol (25). (a) Sodium hydride 50% dispersion (1.0 g, 21 mmol) was added to methyl 3-mercaptopropionate (2.6 g, 21 mmol) in dimethylformamide (60 mL). After stirring for 30 min, 2-(2-bromoethyl)-5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-6-propylbenzofuran (4 g, 7 mmol) was added and the mixture stirred for another 30 min. The mixture was poured into excess 20% citric acid solution and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated and the residue chromatographed using 10% ethyl acetate in hexane to yield 2.2 g (52%) of 5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-2-[2-[[2-(methoxycarbonyl)ethyl]thio]ethyl-6-propylbenzofuran as an oil: ^{1}H NMR δ 0.5–2.1 (m, 20 H), 2.4–3.0 (m, 8 H), 3.25–3.65 (m, 2 H), 4.7 (s, 3 H), 4.1 (dd, 1 H, J = 10 Hz, J' = 4.5 Hz), 6.1 (s, 1 H), 6.5 (s, 1 H), 7.2–7.9 (m, 10 H).

(b) To a solution 5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-2-[2-[[2-(methoxycarbonyl)ethyl]thio]-ethyl]-6-propylbenzofuran (1.5 g, 2.5 mmol) in tetrahydrofuran was added tetra-*n*-butylammonium fluoride (4.0 mL, 4 mmol) in tetrahydrofuran (1 M). The mixture was stirred for 5 min and then diluted with diethyl ether and water. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 20% ethyl acetate in hexane to give 820 mg (93%) of 2,3-dihydro-3,3-dimethyl-2-[2-[[2-(methoxycarbonyl)ethyl]thio]ethyl]-6-propyl-5-benzofuranol (24) as an oil: ^{1}H NMR δ 0.97 (t, 3 H, J = 5.5 Hz), 1.07 (s, 3 H), 1.29 (s, 3 H), 1.52–2.11 (m, 6 H), 2.44–3.0 (m, 8 H), 3.71 (s, 3 H), 4.23 (dd, 1 H, J = 11 Hz, J' = 3.7 Hz), 4.33 (s, 1 H), 6.55 (s, 2 H).

(c) A mixture of 2,3-dihydro-3,3-dimethyl-2-[2-[[2-(methoxycarbonyl)ethyl]thio]ethyl]-6-propyl-5-benzofuranol (24) (6.25 mg, 1.7 mmol), 10 N sodium hydroxide (1.0 mL), and methanol (10 mL) was stirred at room temperature for 1 h. The mixture was acodified with 20% citric acid solution and extracted with diethyl ether. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 80:15:5 hexane/ethyl acetate/acetic acid to obtain 600 mg (98%) of the title compound as an oil: ^{1}H NMR δ 0.97 (t, 3 H, J = 5.5 Hz), 1.09 (s, 3 H), 1.29 (s, 3 H), 1.5–1.71 (quintet, J = 5.5 Hz), 1.71–2.14 (m, 2 H), 2.52 (t, 2 H, J = 5.5 Hz), 2.61–3.0 (m, 6 H), 4.23 (dd, 1 H, J = 11.1 Hz, J' = 1.8 Hz), 6.52 (s, 1 H), 6.55 (s, 1 H).

2-[2-[(2-Pyridyl)thio]ethyl]-2,3-dihydro-3,3-dimethyl-6-propyl-5-benzofuranol (26). (a) Following the same procedure as for compound **25** part a but substituting 2-mercaptopyridine for methyl 3-mercaptopropionate, 2-(2-bromoethyl)-5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-6-propylbenzofuran (1.2 g, 2.1 mmol) was converted to 1.0 g (79%) of 5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-2-[2-[(2-pyridyl)-thio]ethyl]-6-propylbenzofuran as an oil: ^{1}H NMR δ 0.5–2.2 (m, 20 H), 2.5–2.85 (m, 2 H), 3.1–3.7 (m, 4 H), 4.15 (dd, 1 H, J = 12 Hz, J' = 3 Hz), 6.05 (s, 1 H), 6.55 (s, 1 H), 6.6–7.85 (m, 13 H), 8.45 (dd, 1 H, J = 6 Hz, J' = 1.5 Hz).

(b) Following the same procedure as for compound **25** part b 5-[(*tert*-butyldiphenylsilyl)oxy]-2,3-dihydro-3,3-dimethyl-2-[2-[(2-pyridyl)thio]ethyl]-6-propylbenzofuran (1.0 g, 1.7 mmol) was deprotected to give 540 mg (90%) of the title compound as an oil: ^{1}H NMR δ 1.0 (t, J = 7.4 Hz), 1.07 (s, 3 H), 1.29 (s, 3 H), 1.55–1.80 (m, 2 H), 1.89–2.23 (m, 2 H), 2.5 (t, J = 7.45 Hz), 3.20–3.62 (m, 2 H), 4.32 (dd, 1 H, J = 11.1 Hz, J' = 1.8 Hz), 4.4 (s, 1 H), 6.52 (s, 1 H), 6.56 (s, 1 H), 6.97 (t, 1 H, J = 5.5 Hz), 7.20 (d, 1 H, J = 7.45 Hz), 7.47 (t, 1 H, J = 5.5 Hz), 8.44 (d, 1 H, J = 5.5 Hz).

6-Allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-(formylmethyl)benzofuran (27). (a) To a solution of 6-allyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol (20) (11.9 g, 41 mmol) in tetrahydrofuran (500 mL) at 5 °C and under nitrogen atmosphere was added dropwise a 1.5 M solution in toluene of diisobutylaluminum hydride (110 mL, 164 mmol). The mixture was stirred for 10 min and then poured slowly into a stirring mixture of HCl (3 N, 300 mL) and ice (300 mL). After stirring for 30 min and the addition of ethyl acetate to facilitate separation, the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 30% ethyl acetate in hexane as eluent to obtain 9.9 g (97%) of 6-allyl-2,3-dihydro-3,3-dimethyl-2-(2-hydroxyethyl)-5-benzofuranol: mp 55–58 °C; ^{1}H NMR δ 0.96 (s, 3 H), 1.16 (s, 3 H), 1.56–2.33 (m, 3 H), 3.1–3.3 (m, 2 H), 3.66–4.30 (m, 3 H), 4.86–5.2 (m, 3 H), 5.6–6.23 (m, 1 H), 6.43 (s, 1 H), 6.46 (s, 1 H).

(b) A mixture of 6-allyl-2,3-dihydro-3,3-dimethyl-2-(2-hydroxyethyl)-5-benzofuranol (7.5 g, 30 mmol), potassium carbonate (12.4 g, 90 mmol), and benzyl chloride (11.3 g, 90 mmol) in methyl ethyl ketone (200 mL) was refluxed for 18 h. Another portion of benzyl chloride (2.75 g, 21 mmol) and potassium carbonate (3.1 g, 21 mmol) was added and refluxing continued for another 7 h. The mixture was cooled and filtered and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using 30% ethyl acetate in hexane as eluent to obtain 9.4 g (92%) of 6-allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-(2-hydroxyethyl)benzofuran, as an oil: ^{1}H NMR δ 1.13 (s, 3 H), 1.33 (s, 3 H), 1.73–2.3 (m, 3 H), 3.26–3.50 (m, 2 H), 3.93–4.06 (m, 2 H), 4.2–4.46 (m, 1 H), 4.86–5.23 (m, 4 H), 6.66 (s, 1 H), 6.73 (s, 1 H), 7.23–7.6 (m, 5 H).

(c) Dimethyl sulfoxide (1.71 g, 22 mmol) was added dropwise to oxalyl chloride (1.39 g, 11 mmol) in dichloromethane (125 mL) at −78 °C. To this mixture was added a solution of 6-allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-(2-hydroxyethyl)benzofuran (2.5 g, 7.4 mmol) in dichloromethane (25 mL). After the mixture was stirred for 20 min, triethylamine (4.4 g, 44 mmol) was added and the mixture brought up to room temperature and then diluted with water. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 2.8 g of

6-allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-(formylmethyl)benzofuran (27), as an oil which was used in the next step without further purification: ^{1}H NMR δ 1.1 (s, 3 H), 1.33 (s, 3 H), 2.43–3.03 (m, 2 H), 3.36 (d, 2 H, J = 7.4 Hz), 4.7 (dd, 1 H, J = 11 Hz, J' = 5.5 Hz), 4.83–5.23 (m, 4 H), 5.6–6.2 (m, 1 H), 6.63 (s, 1 H), 6.7 (s, 1 H), 7.13–7.56 (m, 5 H), 9.9 (t, 1 H, J = 1.86 Hz).

6-Allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-hydroxy-2-[4-(methylthio)phenyl]ethyl]benzofuran (28). To a solution of **27** (2.8 g, 7.4 mmol), in tetrahydrofuran (125 mL) at 5 °C was added the Grignard reagent [4-(methylthio)-phenyl]magnesium bromide in tetrahydrofuran (0.8 M) (19 mL, 15 mmol) which was previously prepared by refluxing for 2 h a mixture of 4-bromothioanisole (8.1 g, 40 mmol) and magnesium turnings (1 g, 41 mmol) in tetrahydrofuran (50 mL). The mixture was stirred for 1 h at room temperature and then excess HCl (1 N) was added. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 30% ethyl acetate as eluent to obtain 3.1 g (91%) of the title compound **28**, as an oil (erythro–threo isomer mixture): ^{1}H NMR δ 1.06 (s, 3 H), 1.23 (s, 3 H), 1.63–2.2 (m, 2 H), 2.3–2.56 (m, 4 H), 3.23–3.53 (m, 3 H), 4.06–4.6 (m, 1 H), 4.8–5.3 (m, 4 H), 5.7–6.26 (m, 1 H), 6.66 (s, 2 H), 6.8–7.73 (m, 9 H).

5-(Benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-[4-(methylthio)phenyl]ethyl]-6-propylbenzofuran (29). (a) A mixture of **28** (3.1 g, 6.7 mmol), zinc iodide (3.2 g, 10 mmol), and sodium cyanoborohydride (3.1 g, 50 mmol) in 1,2-dichloroethane (125 mL) was refluxed for 18 h under nitrogen atmosphere. The mixture was filtered and the filtrate stirred for 15 min with HCl (3 N, 50 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to obtain 750 mg (25%) of 6-allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-[4-(methylthio)phenyl]ethyl]benzofuran, as an oil: ^{1}H NMR δ 1.08 (s, 3 H), 1.28 (s, 3 H), 1.63–2.23 (m, 2 H), 2.15 (s, 3 H), 2.56–3.23 (m, 2 H), 3.3–3.5 (m, 2 H), 4.11 (dd, 1 H, J = 7.45 Hz, J' = 3.7 Hz), 4.86–5.2 (m, 4 H), 5.6–6.3 (m, 1 H), 6.63 (s, 1 H), 6.66 (s, 1 H), 6.93–7.63 (m, 9 H).

(b) A mixture of 6-allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-[4-(methylthio)phenyl]ethyl]benzofuran (744 mg, 1.6 mmol), ethanol (25 mL), ethyl acetate (25 mL), and 10% palladium on carbon (700 mg) was hydrogenated in a Parr apparatus for 1.5 h at 40 psi. The mixtured was filtered through Celite and the filtrate concentrated to provide 667 mg (89%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-[4-(methylthio)phenyl]-ethyl]-6-propylbenzofuran (**29**), as an oil: ^{1}H NMR δ 0.73–2.16 (m, 13 H), 2.36–3.16 (m, 7 H), 4.16 (dd, 1 H, J = 9.3 Hz, J' = 3.7 Hz), 5.0 (s, 2 H), 6.66 (s, 1 H), 6.70 (s, 1 H), 7.0–7.66 (m, 9 H).

2,3-Dihydro-3,3-dimethyl-2-[2-[4-(methylthio)phenyl]-ethyl]-6-propyl-5-benzofuranol (31). A mixture of **29** (55 mg, 0.123 mmol), acetic acid (4.5 mL), and HCl (6 N, 0.5 mL) was heated in an oil bath maintained at 115 °C for 1 h. The mixture was partitioned between diethyl ether and water. The ether layer was washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to provide 22 mg (50%) of the title compound **31**: mp 68–71 °C; ^{1}H NMR δ 0.7–2.3 (m, 13 H), 2.3–3.26 (m, 7 H), 4.0–4.56 (m, 2 H), 6.53 (s, 1 H), 6.6 (s, 1 H), 7.06–7.36 (m, 5 H).

2,3-Dihydro-3,3-dimethyl-2-[2-[4-(methylsulfonyl)-phenyl]ethyl]-6-propyl-5-benzofuranol (32). (a) To a solution of compound **29** (270 mg, 0.6 mmol) in dichloromethane (40 mL) at 5 °C was added 85% *m*-chloroperbenzoic acid (240 mg, 1.2 mmol). The mixture was stirred for 30 min at 5 °C and then 30 min more at room temperature. Excess calcium hydroxide was added, and after the mixture was stirred, the filtrate was concentrated to give 290 mg (98%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-[4-(methylsulfonyl)phenyl]ethyl]-6-propylbenzofuran as an oil: ^{1}H NMR δ 0.95 (t, 3 H, J = 6 Hz), 1.15 (s, 3 H), 1.35 (s, 3 H), 1.4–2.3 (m, 4 H), 2.6 (t, 2 H, J = 6 Hz), 2.85–3.35 (m, 2 H), 3.1 (s, 3 H), 4.15 (dd, 1 H, J = 10.5 Hz, J' = 4.5 Hz), 5.05 (s, 2 H), 6.65 (s, 1 H), 6.70 (s, 1 H), 7.2–7.6 (m, 7 H), 7.95 (d, 2 H, J = 9 Hz).

(b) By using the same procedure as for converting compound **29** to compound **31**, 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-[4-(methylsulfonyl)phenyl]ethyl]-6-propylbenzofuran (350 mg, 0.7 mmol) was converted to 150 mg (50%) of the title compound: mp 113–118 °C; ^{1}H NMR δ 0.95 (t, 3 H, J = 6 Hz), 1.1 (s, 3 H), 1.3 (s, 3 H), 1.35–2.2 (m, 4 H), 2.5 (t, 2 H, J = 6 Hz), 3.1 (s, 3 H), 2.8–3.2 (m, 2 H), 4.15 (dd, 1 H, J = 10.5 Hz, J' = 4.5 Hz), 4.55 (s, 1 H), 6.55 (s, 1 H), 6.60 (s, 1 H), 7.5 (d, 2 H, J = 9 Hz), 7.9 (d, 2 H, J = 9 Hz).

5-(Benzyloxy)-6-(3-bromopropyl)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran (33). (a) A mixture of **19a** (12 g, 51 mmol), potassium carbonate (20 g, 150 mmol), benzyl chloride (19 g, 150 mmol), and methyl ethyl ketone (300 mL) was refluxed for 22 h. The mixture was filtered through Celite and concentrated in vacuo, and the residue was chromatographed on silica gel using 5% ethyl acetate as eluent to obtain 15 g (90%) of 6-allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran, as an oil: ^{1}H NMR δ 1.24 (s, 3 H), 1.28 (s, 3 H), 3.28–3.40 (m, 2 H), 3.52 (s, 3 H), 4.73–5.33 (m, 5 H), 5.66–6.33 (m, 1 H), 6.66 (s, 2 H), 7.16–7.63 (m, 5 H).

(b) To a solution of 6-allyl-5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran (14 g, 43 mmol) in tetrahydrofuran at 0 °C was added dropwise over 15 min 1 M diborane in tetrahydrofuran (250 mL). The mixture was stirred for 75 min and then methanol (40 mL) was added dropwise followed by 1 N sodium hydroxide (50 mL) and 30% hydrogen peroxide (20 mL). After the mixture was stirred for 30 min, a solution of sodium sulfite (18 g, 3.0 mmol) in water (120 mL) was added slowly. Diethyl ether (500 mL) was then added. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude was chromatographed on silica gel using 20% ethyl acetate in hexane to yield 9.1 g (65%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-6-(3-hydroxypropyl)-2-methoxybenzofuran, as an oil: ^{1}H NMR δ 1.23 (s, 3 H), 1.30 (s, 3 H), 1.53–2.06 (m, 3 H), 2.70 (t, 2 H, J = 9.3 Hz), 3.36–3.70 (m, 5 H), 5.0 (s, 2 H), 5.03 (s, 1 H), 6.66 (s, 1 H), 6.70 (s, 1 H), 7.2–7.6 (m, 5 H).

(c) To a solution of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-6-(3-hydroxypropyl)-2-methoxybenzofuran (9.1 g, 28 mmol) and triphenylphosphine (14.7 g, 156 mmol) in dichloromethane (600 mL) was added carbon tetrabromide (18.5 g, 56 mmol). The mixture was stirred for 45 min and concentrated in vacuo. The residue was slurried with diethyl ether and the heterogeneous mixture filtered through Celite. The filtrate was concentrated in vacuo and the crude residue was chromatographed using 15% ethyl acetate in hexane to yield 7.7 g (68%) of 5-(benzyloxy)-6-(3-bromopropyl)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran (**33**), as an oil: ^{1}H NMR δ 1.26 (s, 3 H), 1.3 (s, 3 H), 1.93–2.33 (m, 2 H), 1.76 (t, 2 H, J = 7.4 Hz), 3.36 (t, 2 H, J = 7.4 Hz), 3.56 (s, 3 H), 5.0 (s, 2 H), 5.03 (s, 1 H), 6.7 (s, 2 H), 7.23–7.56 (m, 5 H).

5-(Benzyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxy-6-(3-phenoxypropyl)benzofuran (34). A solution of **33** (7.7 g, 19 mmol) in dimethylformamide (20 mL) was added under nitrogen atmosphere to a mixture of phenol (4.7 g, 50 mmol) and 50% sodium hydride dispersion (2.4 g, 50 mmol) in dimethylformamide (250 mL). The mixture was stirred at room temperature for 1 h and then poured into 20% citric acid solution (500 mL) and the lot extracted with diethyl ether. The organic layer was washed with water and 1 N sodium hydroxide (twice), dried ($MgSO_4$) filtered, and concentrated in vacuo to obtain 7.1 g (90%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxy-6-(3-phenoxypropyl)benzofuran (**34**), as an oil: ^{1}H NMR δ 1.23 (s, 3 H), 1.3 (s, 3 H), 1.9–2.26 (m, 2 H), 2.76 (t, 2 H, J = 7.4 Hz), 3.5 (s, 3 H), 3.93 (t, 2 H, J = 7.4 Hz), 5.0 (s, 2 H), 5.03 (s, 1 H), 6.6–7.63 (m, 12 H).

5-(Benzyloxy)-2,3-dihydro-2-(2-oxo-2-phenylethyl)-3,3-dimethyl-6-(3-phenoxypropyl)benzofuran (35). (a) A solution of **34** (7.1 g, 16.9 mmol), acetic acid (320 mL), and water (80 mL) was refluxed under nitrogen atmosphere for 18 h. The mixture was concentrated. The residue was dissolved in diethyl ether and washed with 1 N sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to provide 5.4 g (78%) of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-hydroxy-6-(3-phenoxypropyl)benzofuran, as an oil: ^{1}H NMR δ 1.26 (s, 3 H), 1.33 (s, 3 H), 1.86–2.26 (m, 1 H), 2.66–3.10 (m, 3 H), 3.93 (t, 2 H, J = 7.4 Hz), 5.0 (s, 2 H), 5.46 (d, 1 H, J = 7.4 Hz), 6.56–7.0 (m, 4 H), 7.1–7.6 (m, 8 H).

(b) To a solution of 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-hydroxy-6-(3-phenoxypropyl)benzofuran (1.5 g, 3.7 mmol) and diethyl (2-oxo-2-phenylethyl)phosphonate (6.0 g, 17.8 mmol) in dimethylformamide (22 mL) was added potassium *tert*-butoxide (3.0 g, 26.7 mmol) in one portion. The mixture was stirred at room temperature for 15 min and then heated in an oil bath at 110–120 °C for 2 h. The mixture was cooled, poured into HCl (1 N, 300 mL), and extracted with diethyl ether. The ether layer was washed twice with water, dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to provide 1.85 g (95%) of 5-(benzyloxy)-2-(2-oxo-2-phenylethyl)-2,3-dihydro-3,3-dimethyl-6-(3-phenoxypropyl)benzofuran (**35**), as an oil: ^{1}H NMR δ 1.2 (s, 3 H), 1.41 (s, 3 H), 2.0–2.14 (m, 2 H), 2.7–2.88 (m, 2 H), 3.13 (dd, 1 H, J = 16 Hz, J' = 3.7 Hz), 3.4–3.62 (m, 1 H), 3.95 (t, 2 H, J = 7.4 Hz), 4.94 (dd, 1 H, J = 11 Hz, J' = 5.5 Hz) 5.02 (s, 2 H), 6.62 (s, 1 H), 6.71 (s, 1 H), 6.79–7.0 (m, 2 H), 7.14–7.65 (m, 11 H), 8.02 (dd, 2 H, J = 9.3 Hz, J' = 1.8 Hz).

5-(Benzyloxy)-2-[2-(4-chlorophenyl)-2-oxoethyl]-2,3-dihydro-3,3-dimethyl-6-(3-phenoxypropyl)benzofuran (36). By following the same procedure described above for converting compound **34** to compound **35** but using diethyl (2-(4-chlorophenyl)-2-oxoethyl)phosphonate, the title compound **36** was obtained from compound **34** (yield, 1.5 g, 45%), as an oil: ^{1}H NMR δ 1.23 (s, 3 H), 1.4 (s, 3 H), 1.86–2.3 (m, 2 H) 2.66–3.26 (m, 4 H), 4.0 (t, 2 H, J = 7.4 Hz), 4.8–5.1 (m, 3 H), 6.6–7.06 (m, 4 H), 7.06–7.66 (m, 10 H), 8.0 (d, 2 H, J = 11.1 Hz).

2,3-Dihydro-3,3-dimethyl-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (37). A mixture of **35** (1.8 g, 3.5 mmol), anhydrous zinc iodide (1.7 g, 5.3 mmol), and sodium cyanoborohydride (1.6 g, 26 mmol) in 1,2-dichloroethane (75 mL) was stirred at reflux and under nitrogen atmosphere for 2 days. The mixture was filtered and the filtrate concentrated and chromatographed using 15% ethyl acetate in hexane to obtain 860 mg (60%) of 2,3-dihydro-3,3-dimethyl-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol: mp 65–69 °C; ^{1}H NMR δ 1.1 (s, 3 H), 1.26 (s, 3 H), 1.7–2.14 (m, 4 H), 2.52–3.11 (m, 4 H), 3.82–4.07 (m, 2 H), 4.14 (dd, 1 H, J = 11 Hz, J' = 3 Hz), 5.29 (s, 1 H), 6.55 (s, 1 H), 6.59 (s, 1 H), 6.80–7.0 (m, 2 H), 7.0–7.32 (m, 8 H).

2-[2-(4-Chlorophenyl)ethyl]-2,3-dihydro-3,3-dimethyl-6-(3-phenoxypropyl)-5-benzofuranol (38). (a) A mixture of **36** (1.2 g, 2.2 mmol), triethylsilane (50 mL), and boron trifluoride etherate (1.2 mL, 10 mmol) in 1,2-dichloroethane (50 mL) was stirred at room temperature for 3 h. The mixture was poured into water and extracted with diethyl ether. The ether layer was washed with 1 N sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 10% ethyl acetate in hexane as eluent to provide 780 mg (67%) of 5-(benzyloxy)-2-[2-(4-chlorophenyl)ethyl]-2,3-dihydro-3,3-dimethyl-6-(3-phenoxypropyl)benzofuran, as an oil: ^{1}H NMR δ 1.10 (s, 3 H), 1.28 (s, 3 H), 1.73–2.18 (m, 4 H), 2.65–3.09 (m, 4 H), 3.98 (t, 2 H, J = 7.4 Hz), 4.06–4.18 (m, 1 H), 5.04 (s, 2 H), 6.73 (s, 1 H), 6.74 (s, 1 H) 6.77–6.97 (m, 2 H), 7.03–7.46 (m, 12 H).

(b) To a solution of 5-(benzyloxy)-2-[2-(4-chlorophenyl)-ethyl]-2,3-dihydro-3,3-dimethyl-6-(3-phenoxypropyl)benzofuran (750 mg, 1.4 mmol) in dichloromethane (120 mL) at −78 °C was added dropwise 1 M boron tribromide in dichloromethane (1.7 mL). The mixture was stirred for 10 min, and then methanol (5 mL) was added followed by solid potassium carbonate (1 g, 7.2 mmol). The mixture was stirred at room temperature for 15 min and filtered and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to obtain 330 mg (53%) of 2-[2-(4-chlorophenyl)ethyl]-2,3-dihydro-3,3-dimethyl-6-(3-phenoxypropyl)-5-benzofuranol (**38**), as an oil: ^{1}H NMR δ 1.10 (s, 3 H), 1.28 (s, 3 H), 1.74–2.25 (m, 4 H), 2.62–3.12 (m, 4 H), 4.03 (t, 2 H, J = 7.4 Hz), 4.10–4.21 (m, 1 H), 5.3 (s, 1 H), 6.61 (s, 1 H), 6.64 (s, 1 H), 6.82–7.42 (m, 14 H).

2-(1-Hydroxy-2-phenylethyl)-5-methoxybenzofuran (40). To a solution of 5-methoxybenzofuran (**39**, 148 g, 1 mol) in tetrahydrofuran (2 L) at −78 °C was added dropwise 2.5 M *n*-butyllithium in hexane (420 mL, 1.05 mol). The mixture was stirred at −78 °C for 1.5 h and then phenyl acetaldehyde (144 g, 1.2 mol) was added over 15 min. The cooling bath was removed and the mixture permitted to gradually rise to 0 °C. Water (600 mL) was added. The ether layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude was chromatographed on silica gel (2 kg) using a solvent mixture of increasing polarity of 5%, 10%, 20%, and 30% ethyl acetate in hexane to provide 243 g (90%) of 2-(1-hydroxy-2-phenylethyl)-5-methoxybenzofuran (**40**): mp 69–70 °C; ^{1}H NMR δ 2.13 (d, 1 H, J = 3.7 Hz), 3.35–3.53 (m, 2 H) 3.88 (s, 3 H), 4.95–5.09 (m, 1 H), 6.53 (s, 1 H), 6.88 (dd, 1 H, J = 11 Hz, J' = 1.8 Hz), 7.0 (d, 1 H, J = 1.8 Hz), 7.13–7.46 (m, 6 H). Anal. ($C_{17}H_{16}O_3$) C, H.

5-Methoxy-2-(2-phenylethyl)benzofuran (41). To a mixture of aluminum chloride (204 g, 1.5 mol) in toluene (2.5 L) at 5 °C and under nitrogen atmosphere was added in 50-g portions of *tert*-butylamine–borane (200 g, 2.3 mol). After the mixture was stirred for 30 min, a solution of 2-(1-hydroxy-2-phenylethyl)-5-methoxybenzofuran (**40**, 238 g, 880 mmol) in toluene (600 mL) was added dropwise. The mixture was stirred at 5 °C for 2 h and then added in portions to a stirring ice cold mixture of 10% HCl acid (3 L). Stirring was continued until gas evolution had ceased. The organic layer was separated and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (2 kg) using 15% ethyl acetate as eluent to provide 129 g (58%) of 5-methoxy-2-(2-phenylethyl)benzofuran (**41**): mp 68–70 °C; ^{1}H NMR δ 3.07 (s, 4 H), 5.8 (s, 3 H), 6.29 (s, 1 H), 6.82 (dd, 1 H, J = 9.3 Hz, J' = 3 Hz), 6.95 (d, 1 H, J = 3 Hz), 7.14–7.37 (m, 6 H). Anal. ($C_{17}H_{16}O_2$) C, H.

2,3-Dihydro-2-(2-phenylethyl)-5-benzofuranol (42). (a) Trifluoroacetic acid (232 mL, 30 mol) was added over 15 min to a suspension of 5-methoxy-2-(2-phenylethyl)benzofuran (**41**, 128 g, 500 mmol) in triethylsilane (465 mL, 2.8 mol) at 5 °C. The mixture was stirred at 5 °C for 60 min and then at room temperature for 18 h. The mixture was concentrated in vacuo. The residue was dissolved in diethyl ether, washed with 1 N sodium hydroxide, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 5% ethyl acetate in hexane as eluent to provide 128 g (99%) of 2,3-dihydro-5-methoxy-2-(2-phenylethyl)benzofuran: ^{1}H NMR δ 1.88–2.25 (m, 2 H), 2.7–2.95 (m, 3 H), 3.25 (dd, 1 H, J = 16.7 Hz, J' = 9.3 Hz), 3.77 (s, 3 H), 4.67–4.82 (m, 1 H), 6.59–6.79 (m, 3 H), 7.13–7.37 (m, 5 H). Anal. ($C_{17}H_{18}O_2$) C, H.

(b) Ethanethiol (62 g, 1 mol) was added dropwise to lithium hydride (8 g, 1 mol) in dimethylformamide (700 mL) under nitrogen atmosphere. 2,3-Dihydro-5-methoxy-2-(2-phenylethyl)-benzofuran (126 g, 500 mmol) in dimethylformamide (200 mL) was then added in one portion and the mixture brought to reflux for 3 h. The mixture was poured into HCl (1 N) and extracted with diethyl ether. The ether layer was separated and backwashed with water twice, dried over $MgSO_4$, filtered, and concentrated in vacuo to obtain 123 g (98%) of 2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (**42**): mp 56–58 °C; ^{1}H NMR δ 1.88–2.25 (m, 2 H), 2.7–2.95 (m, 3 H), 3.25 (dd, 1 H, J = 16.7 Hz, J' = 9.3 Hz), 4.4 (s, 1 H), 4.67–4.82 (m, 1 H), 6.52–6.71 (m, 3 H), 7.14–7.37 (m, 5 H). Anal. ($C_{16}H_{16}O_2$) C, H.

6-Allyl-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (43a). (a) A mixture of 2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (**42**, 50 g, 208 mmol), potassium carbonate (55 g, 400 mmol), allyl bromide (48 g, 400 mmol), and acetone (500 mL) was refluxed for 18 h. The mixture was cooled, diluted with hexane (250 mL), and filtered through Celite. The filtrate was concentrated in vacuo and the residue chromatographed in silica gel using 10% ethyl acetate in hexane as eluent to provide 47.8 g (82%) of 5-(allyloxy)-2,3-dihydro-2-(2-phenylethyl)benzofuran as an oil: ^{1}H NMR δ 1.85–2.32 (m, 2 H), 3.0–4.5 (m, 3 H), 3.2 (dd, 1 H, J = 16.7 Hz, J' = 7.4 Hz), 4.35–4.59 (m, 2 H), 4.65–4.88 (m, 1 H), 5.35 (m, 1 H), 5.92–6.22 (m, 1 H), 6.56–6.89 (m, 3 H), 7.07–7.49 (m, 5 H).

(b) A mixture of 5-(allyloxy)-2,3-dihydro-2-(2-phenylethyl)-benzofuran (47 g, 167 mmol) in 1,2-dichlorobenzene (100 mL) was refluxed under nitrogen atmosphere for 21 h. The mixture was concentrated in vacuo to drive off most of the 1,2-dichlorobenzene and the residue was chromatographed on silica gel using 10% ethyl acetate in hexane as eluent to provide 41 g (87%) of pure isomer mixture. The isomer mixture was separated by chromatography on silica gel (2.5 kg) using 50% hexane in dichloromethane as eluent to obtain 6-allyl-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (**43a**) (32.7 g, 69.5%) and 4-allyl-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (**43b**) as an oil (10.4 g, 22%). **43a**:

mp 79–80 °C; ^{1}H NMR δ 1.86–2.26 (m, 2 H), 2.64–3.0 (m, 3 H), 3.20 (dd, 1 H, J = 18.6 Hz, J' = 9.3 Hz), 3.34 (d, 2 H, J = 3.7 Hz), 4.55 (s, 1 H), 4.64–4.86 (m, 1 H), 5.04–5.32 (m, 2 H), 5.86–6.13 (m, 1 H), 6.55 (s, 1 H), 6.65 (s, 1 H), 7.07–7.52 (m, 6 H). **43b**: ^{1}H NMR δ 1.86–2.26 (m, 2 H), 2.64–3.0 (m, 3 H), 3.2 (dd, 1 H, J = 18.6 Hz, J' = 9.3 Hz), 3.34 (d, 2 H, J = 3.7 Hz), 4.50 (s, 1 H), 4.67–4.86 (m, 1 H), 5.0–5.28 (m, 2 H), 5.82–6.07 (m, 1 H), 6.47–6.67 (m, 2 H), 7.1–7.43 (m, 6 H).

5-(Benzyloxy)-6-(3-bromopropyl)-2,3-dihydro-2-(2-phenylethyl)benzofuran (45). In a manner analogous to the production of compound **33** from compound **19a**, compound **45** is produced from compound **43a**: ^{1}H NMR δ 1.85–2.26 (m, 2 H), 2.14 (t, 2 H, J = 7.4 Hz), 2.67–2.97 (m, 5 H), 3.22 (dd, 1 H, J = 16.7 Hz, J' = 9.3 Hz), 3.40 (t, 1 H, J = 7.4 Hz), 4.67–5.7 (m, 1 H), 5.0 (s, 2 H), 6.64 (s, 1 H), 6.77 (s, 1 H), 7.14–7.52 (m, 10 H).

2,3-Dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (46). (a) Dry phenol (14 g, 152 mmol) was added to 50% sodium hydride dispersion (7 g, 145 mmol) in dimethylformamide (200 mL) under nitrogen atmosphere. After the mixture was stirred for 30 min, a solution of 6-(3-bromopropyl)-5-(benzyloxy)-2,3-dihydro-2-(2-phenylethyl)benzofuran (**45**, 8.7 g, 16.9 mmol) in dimethylformamide (25 mL) was added. The mixture was stirred at room temperature for 3 h, poured into excess HCl (1 N) and extracted with diethyl ether. The ether layer was washed with 1 N sodium hydroxide twice, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 5% ethyl acetate in hexane to yield 6.3 g (82%) of 5-(benzyloxy)-2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)benzofuran, as an oil: ^{1}H NMR δ 1.86–2.25 (m, 4 H), 1.15–2.95 (m, 5 H), 3.24 (dd, 1 H, J = 16 Hz, J' = 8.5 Hz), 3.96 (t, 3 H, J = 6.5 Hz), 4.6–4.83 (m, 1 H), 4.99 (s, 2 H), 6.65 (s, 1 H), 6.77 (s, 1 H), 6.80–7.0 (m, 2 H), 7.1–7.5 (m, 13 H).

(b) Boron tribromide solution (1 M) in dichloromethane (18.8 mL, 18.8 mmol) was added dropwise to a solution of 5-(benzyloxy)-2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)benzofuran in dichloromethane (300 mL) at −78 °C. The mixture was stirred for 10 min, and methanol (5 mL) was then added dropwise. The mixture was brought to room temperature and saturated sodium bicarbonate solution added. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane to yield 4.5 g (76%) of 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (**46**) mp 65–70 °C; ^{1}H NMR δ 1.86–2.24 (m, 4 H), 2.68–2.95 (m, 5 H), 3.2 (dd, 1 H, J = 15 Hz, J' = 7.4), 4.0 (t, 2 H, J = 5.5) 4.67–4.83 (m, 1 H), 5.21 (s, 1 H), 6.58 (s, 1 H), 6.67 (s, 1 H), 6.88–7.04 (m, 3 H), 7.13–7.39 (m, 7 H). Anal. ($C_{25}H_{26}O_3$) C, H.

Alternate Route to 2,3-Dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (46). (a) A mixture of **42** (18.4 g, 76 mmol), 3-phenoxypropionaldehyde (23 g, 153 mmol), phenylboronic acid (14.8 g, 121.4 mmol), and propionic acid (1.8 g) was refluxed in toluene (460 mL), with azeotropic removal of water (Dean-Stark apparatus), for 4 h. After the mixture was cooled to room temperature, a saturated solution of sodium bicarbonate was added and the mixture was stirred for 15 min. The mixture was extracted with ether, washed with brine (2×), dried over magnesium sulfate, and filtered. The filtrate was concentrated in vacuo. A white solid crystallized after trituration of the oily residue with ether/hexane. After filtration and air drying, 34 g (71.4 mmol, 94%) of 7,8-dihydro-2-phenyl-7-(2-phenylethyl)-4-(2-phenoxyethyl)-4*H*-furo[2,3-*g*]-1,3,2-benzodioxaborin (**56**) was obtained: mp 90–92 °C; ^{1}H NMR 1.89–2.07 (m, 1 H), 2.07–2.27 (m, 2 H), 2.34–2.48 (m, 1 H), 2.70–2.91 (m, 3 H), 3.27 (dd, 1 H, J = 15 Hz, J' = 9 Hz), 4.09–4.18 (m, 1 H), 4.25–4.36 (m, 1 H), 4.70–4.75 (m, 1 H), 5.45 (d br, 1 H), 6.49 (d, 1 H, J = 2 Hz), 6.90–6.97 (m, 3 H), 7.16–7.52 (m, 11 H), 7.94 (dd, 2 H, J = 7 Hz, J' = 2 Hz).

(b) To a suspension of aluminum chloride (26.86 g, 202 mmol) in dry methylene chloride (640 mL), at 0 °C, was added *tert*-butylamine–borane (35.07 g, 403 mmol) portionwise. After 10 min a clear solution was obtained and then compound **56** (32 g, 67.2 mmol) was added as a solid. The solution was stirred at 0 °C for 2 h and then slowly poured over ice (1900 mL) and concentrated HCl (128 mL) with vigorous stirring. The mixture was stirred until the bubbling stopped. The layers were separated, the aqueous layer was extracted with methylene chloride, the organic layers were combined and washed with brine (2×), dried over magnesium sulfate, and filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed using 15:85 ethyl acetate/hexane as eluant to give 14 g (37.4 mmol, 56%) of 2,3-dihydro-6-(3-phenyloxypropyl)-2-(2-phenylethyl)-5-benzofuranol (**46**) identical to the material obtained above.

6-[3-(4-Carboxyphenoxy)propyl]-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (48). (a) In a manner analogous to the production of compound **49a** but using methyl 4-hydroxybenzoate in place of 4-cyanophenol, compound **45** (1 g, 2.2 mmol) was converted to 5-(benzyloxy)-6-[3-(4-carbomethoxyphenoxy)propyl]-2,3-dihydro-2-(2-phenethyl)benzofuran as an oil: ^{1}H NMR δ 1.75–2.25 (m, 4 H), 2.65–2.95 (m, 5 H), 3.24 (dd, 1 H, J = 15 Hz, J' = 9 Hz), 3.9 (s, 3 H), 4.02 (t, 2 H, 11 Hz), 4.65–4.83 (m, 1 H), 5.0 (s, 2 H), 6.66 (s, 1 H), 6.80 (s, 1 H), 6.88 (d, 2 H, J = 7.4 Hz), 7.1–7.5 (m, 10 H), 7.96 (d, 2 H, J = 7.4 Hz).

(b) A mixture of 5-(benzyloxy)-6-[3-(4-carbomethoxyphenoxy)propyl]-2,3-dihydro-2-(2-phenethyl)benzofuran (1 g, 1.9 mmol) and 10% palladium on charcoal (100 mg) in a 1:1 mixture of ethyl acetate (25 mL) and ethanol (25 mL) was hydrogenated in a Parr apparatus at 45 psi for 18 h. The mixture was filtered, concentrated, and crystallized from diethyl ether to provide 800 mg (80%) of 6-[3-(4-carbomethoxyphenoxy)propyl]-2,3-dihydro-2-(2-phenethyl)-5-benzofuranol: mp 127–128 °C; ^{1}H NMR δ 1.86–2.22 (m, 4 H), 2.67–2.95 (m, 5 H), 3.22 (dd, 1 H, J = 18 Hz, J' = 9 Hz), 3.92 (s, 3 H), 4.04 (t, 2 H, J = 7.4 Hz), 4.7–4.8 (m, 1 H), 4.8 (s, 1 H), 6.58 (s, 1 H), 6.64 (s, 1 H), 6.94 (d, 2 H, J = 7.4 Hz), 7.14–7.38 (m, 5 H), 8.0 (d, 2 H, J = 7.4 Hz). Anal. ($C_{27}H_{28}O_5$) C, H.

(c) In a manner analogous to the production of compound **25c**, 6-[3-(4-carbomethoxyphenoxy)propyl]-2,3-dihydro-2-(2-phenethyl)-5-benzofuranol (700 mg, 1.6 mmol) was converted to 313 mg (46%) of the title compound: mp 157–160 °C; ^{1}H NMR δ 1.8–2.4 (m, 4 H), 2.6–2.95 (m, 5 H), 3.1–3.28 (dd, 1 H, J = 18 Hz, J' = 9 Hz), 4.06 (t, 2 H, J = 7.4 Hz), 4.6–4.8 (m, 1 H), 6.58 (s, 1 H), 6.66 (s, 1 H), 6.95 (d, 2 H, J = 7.4 Hz), 7.15–7.35 (m, 5 H), 8.04 (d, 2 H, J = 7.4 Hz).

2,3-Dihydro-2-(2-phenylethyl)-6-[3-[4-(1*H*-tetrazol-5-yl)-phenoxy]propyl]-5-benzofuranol (49). (a) 4-Cyanophenol (1.07 g, 9 mmol) was added in one portion to 50% sodium hydride dispersion (435 mg, 9 mmol) in dimethylformamide (30 mL) under nitrogen atmosphere. After the mixture stirred for 30 min, a solution of 6-(3-bromopropyl)-5-(benzyloxy)-2,3-dihydro-2-(2-phenylethyl)benzofuran (**45**, 1 g, 2.2 mmol) in dimethylformamide (5 mL) was added. The mixture was stirred at room temperature for 18 h. The mixture was poured into excess 20% citric acid solution and extracted with diethyl ether. The ether layer was back-washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 15% ethyl acetate in hexane as eluent to yield 1.06 g (95%) as an oil of 5-(benzyloxy)-6-[3-(4-cyanophenoxy)propyl]-2,3-dihydro-2-(2-phenylethyl)benzofuran: mp 154–157 °C; ^{1}H NMR δ 1.88–2.25 (m, 4 H), 2.67–2.95 (m, 4 H), 3.22 (dd, 1 H, J = 15 Hz, J' = 9 Hz), 3.98 (t, 2 H, J = 5.5 Hz), 4.67–4.83 (m, 1 H), 5.0 (s, 2 H), 6.62 (s, 1 H), 6.79 (s, 1 H), 6.85 (d, 2 H, J = 7.4 Hz), 7.15–7.46 (m, 10 H), 7.54 (d, 2 H, J = 7.4 Hz).

(b) A mixture of 5-(benzyloxy)-6-[3-(4-cyanophenoxy)-propyl]-2,3-dihydro-2-(2-phenylethyl)benzofuran (1 g, 2.0 mmol) and tri-*n*-butyltin azide (2.2 g, 6.6 mmol) was heated in an oil bath at 125 °C for 90 min. The total mixture was chromatographed on silica gel using 1:1 ethyl acetate in hexane and containing 10% acetic acid to yield 1.2 g of 5-(benzyloxy)-2,3-dihydro-2-(2-phenylethyl)-6-[3-[4-(1*H*-tetrazol-5-yl)phenoxy]propyl]benzofuran: ^{1}H NMR δ 1.82–2.24 (m, 4 H), 2.65–2.94 (m, 4 H), 3.24 (dd, 1 H, J = 15 Hz, J' = 9.3 Hz), 4.0 (t, 2 H, J = 7.4 Hz), 4.65–4.84 (m, 1 H), 5.0 (s, 2 H), 6.65 (s, 1 H), 6.79 (s, 1 H), 6.94 (d, 2 H, J = 9.3 Hz), 7.07–7.49 (m, 10 H), 7.89 (d, 2 H, J = 9.3 Hz).

(c) A mixture of 5-(benzyloxy)-2,3-dihydro-2-(2-phenylethyl)-6-[3-[4-(1*H*-tetrazol-5-yl)phenoxyl]propyl]benzofuran (450 mg, 0.84 mmol), HCl (6 N, 2 mL), and acetic acid (18 mL) was heated in an oil bath at 125 °C for 4 h and under nitrogen atmosphere. The mixture was concentrated in vacuo. The residue was chromatographed on silica gel using 30:70 ethyl acetate in hexane and containing 5% acetic acid to yield 251 mg (67%) of 2,3-dihydro-2-(2-phenylethyl)-6-[3-[4-(1*H*-tetrazol-5-yl)phenoxy]propyl]-5-benzofuranol: mp 154–157 °C; ^{1}H NMR δ 1.85–2.28

(m, 4 H) 2.59–2.97 (m, 4 H) 3.21 (dd, 1 H, J = 11 Hz, J' = 7.4 Hz), 4.04 (t, J = 3.7 Hz), 4.64–4.83 (m, 1 H), 6.58 (s, 1 H), 6.65 (s, 1 H), 7.03 (d, 2 H). Anal. ($C_{26}H_{26}N_4O_3$) C, H, N.

2,3-Dihydro-2-(2-phenylethyl)-6-[3-(4-pyridylthio)propyl]-5-benzofuranol (50). (a) In a manner analogous to the production of compound **49** but using 4-mercaptopyridine in place of 4-cyanophenol, compound **45** (1 g, 2.2 mmol) was converted to 750 mg (71%) of 5-(benzyloxy)-2,3-dihydro-2-(2-phenethyl)-6-[3-(4-pyridylthio)propyl]benzofuran: ^{1}H NMR δ 1.85–2.25 (m, 4 H), 2.65–3.05 (m, 7 H), 2.24 (dd, 1 H, J = 16.7 Hz, J' = 7.45 Hz), 4.65–4.85 (m, 1 H), 4.97 (s, 2 H), 6.6 (s, 1 H), 6.76 (s, 1 H), 6.97–7.5 (m, 7 H), 8.26 (d, 2 H, J = 3.7 Hz).

(b) A mixture of 5-(benzyloxy)-2,3-dihydro-2-(2-phenethyl)-6-[3-(4-pyridylthio)propyl]benzofuran (750 mg, 1.6 mmol) in acetic acid (18 mL) and 6 N hydrochloric acid (2.0 mL) was refluxed for 3 h. The mixture was cooled, diluted with 1 N sodium acetate (50 mL), and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, concentrated, and the residue was chromatographed on silica gel using 50% ethyl acetate in hexane to obtain 430 mg (70%) of the title compound: mp 140–143 °C; ^{1}H NMR δ 1.85–2.25 (m, 4 H), 2.27–2.9 (m, 5 H), 3.0 (t, 2 H, J = 11 Hz), 3.2 (dd, 1 H, J = 18 Hz, J' = 9 Hz), 4.65–4.82 (m, 1 H), 6.56 (s, 1 H), 6.64 (s, 1 H), 7.05–7.35 (m, 7 Hz), 8.32 (d, 2 H, J = 7.4 Hz). Anal. ($C_{24}H_{25}NSO_2$) C, H, N, S.

2-[[3-[2,3-Dihydro-2-(2-phenylethyl)-5-benzofuranol-6-yl]propyl]thio]benzothiazole (51). Following the same procedure described above for producing compound **50** from **45** and using 2-mercaptobenzothiazole (658 mg, 1.46 mmol), 2-[[3-[2,3-dihydro-5-(benzyloxy)-2-(2-phenylethyl)benzofuran-6-yl]-propyl]thio]benzothiazole (**51**) was isolated in 91% yield (712 mg). Without further characterization, the benzyl protecting group was cleaved by treating the latter (507 mg, 1.05 mmol) with HCl (6 N, 1.4 mL) and acetic acid (11 mL). The mixture was refluxed for 18 h. The mixture was concentrated in vacuo. The residue was chromatographed on silica gel (eluted with 20% ethyl acetate in hexane) to give 223 mg (50%) of the title compound: mp 134–136 °C; ^{1}H NMR δ 1.83–2.03 (m, 1 H), 2.03–2.25 (m, 3 H), 2.67–2.95 (m, 5 H) 3.20 (dd, 1 H, J = 15 Hz, J' = 9 Hz) 3.35 (t, 2 H, J = 6.3 Hz) 4.62–4.82 (m, 1 H), 5.24 (s, 1 H), 6.61 (s, 1 H) 6.67 (s, 1 H) 7.12–7.50 (m, 7 H), 7.75 (d, 1 H, J = 7 Hz), 7.94 (d, 1 H, J = 7 Hz). Anal. ($C_{26}H_{25}NO_2S_2$) C, H, N, S.

6-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (52). (a) Following the procedure described for the preparation of compound **46** from compound **42**, step a, compound **42** was reacted with 2,4-dihydroxy-3-propyl phenylmethyl ketone, followed by cleavage of the benzyl ether as in compound **53**, step b, afforded the title compound **52**: mp 79–81 °C; ^{1}H NMR δ 0.98 (t, 3 H, J = 7 Hz), 1.50–1.66 (m, 3 H), 1.88–2.21 (m, 4 H), 2.57 (s, 3 H), 2.64–2.91 (m, 6 H), 3.22 (dd, 1 H, J = 16 Hz, J' = 7 Hz), 4.06 (t, 2 H, J = 7 Hz), 4.68–4.79 (m, 1 H), 6.43 (d, 1 H, J = 8 Hz), 6.58 (s, 1 H), 6.63 (s, 1 H), 7.17–7.34 (m, 5 H), 7.58 (d, 1 H, J = 8 Hz).

6-[3-[(3-Carboxy-2-methoxyquinolin-7-yl)thio]propyl]-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (53). (a) A mixture of 6-(3-bromopropyl)-5-(benzyloxy)-2,3-dihydro-2-(2-phenylethyl)benzofuran (**45**, 823 mg, 1.8 mmol), 2-methoxy-3-carbomethoxy-7-mercaptoquinoline (700 mg, 2.8 mmol), and potassium carbonate (414 mg, 3.0 mmol) in methyl ethyl ketone (50 mL) was refluxed for a period of 60 min. The reaction mixture was cooled, filtered through Celite and concentrated in vacuo. The residue was chromatographed on silica gel using 20% ethyl acetate in hexane as eluent to yield 1.0 g (96%) of 5-(benzyloxy)-6-(3-[(3-carbomethoxy-2-methoxyquinolin-7-yl)thio]-propyl]-2,3-dihydro-2-(2-phenylethyl)benzofuran: mp 96–98 °C; ^{1}H NMR δ 1.88–2.21 (m, 4 H), 1.45–1.92 (m, 4 H), 3.01–3.15 (m, 2 H), 3.22 (dd, 1 H, J = 18 Hz, J' = 7.5 Hz), 3.95 (s, 3 H), 4.13 (s, 3 H), 4.65–4.79 (m, 1 H), 5.01 (s, 1 h), 6.64 (s, 1 H), 6.77 (s, 1 H), 7.13–7.46 (m, 11 H), 7.55–7.64 (m, 2 H) 8.55 (s, 1 H). Anal. ($C_{31}H_{31}NSO_5$) C, H, N, S.

(b) Methanesulfonic acid (0.5 mL) was added dropwise to a solution of 5-(benzyloxy)-6-[3-[(carbomethoxy-2-methoxyquinolin-7-yl)thio]propyl]-2,3-dihydro-2-(2-phenylethyl)benzofuran (1.1 g, 1.7 mmol), trifluoroacetic acid (11 mL), and thioanisole (3 mL) at 5 °C. The mixture was stirred for 30 min and then added in portions to an ice-cold stirring biphasic mixture of saturated sodium bicarbonate solution (150 mL), brine (25 mL), tetrahydrofuran (125 mL), and diethyl ether (25 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 30% ethyl acetate in hexane as eluent to yield 900 mg (95%) of 6-[[3-(3-carbomethoxy-2-methoxyquinolin-7-yl)thio]propyl]-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol, which was crystallized from diethyl ether: mp 112–114 °C; ^{1}H NMR δ 1.85–2.22 (m, 4 H), 2.65–2.92 (m, 4 H), 3.12 (t, 2 H, J = 3.7 Hz), 3.21 (dd, 1 H, J = 15 Hz, J' = 7.5 Hz), 3.94 (s, 3 H), 4.16 (s, 3 H), 4.48 (s, 1 H), 4.48–4.66 (m, 1 H), 6.58 (s, 1 H), 6.61 (s, 1 H), 7.12–7.34 (m, 6 H), 7.56–7.68 (m, 2 H), 8.55 (s, 1 H). Anal. ($C_{31}H_{31}NSO_5$) C, H, N, S.

(c) A mixture of 6-[3-[(3-carbomethoxy-2-methoxyquinolin-7-yl)thio]propyl]-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (794 mg, 1.5 mmol), methanol (12 mL), and 1 N sodium hydroxide (12 mL) was heated in an oil bath at 75 °C and under nitrogen atmosphere for 45 min. The mixture was concentrated in vacuo to remove most of the methanol and the residue was neutralized with excess of 25% ammonium acetate solution. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using 65:30:5 hexane/ethyl acetate/acetic acid as eluent to yield 165 mg (21%) of 6-[3-[(3-carboxy-2-methoxyquinolin-7-yl)thio]propyl]-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (**53**): mp 157–161 °C; ^{1}H NMR δ 1.77–2.27 (m, 4 H), 2.65–2.94 (m, 4 H), 3.06–3.27 (m, 3 H), 4.25 (s, 3 H), 4.62–4.79 (m, 1 H), 6.56 (s, 1 H), 6.68 (s, 1 H), 7.10–7.36 (m, 6 H), 7.62–7.73 (m, 2 H), 8.78 (s, 1 H). Anal. ($C_{30}H_{29}NSO_5$) C, H, N, S.

2,3-Dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-4-propyl-5-benzofuranol (54). Following the procedure described above for the conversion of compound **42** to compound **43**, allylation of compound **46**, followed by Claisen rearrangement and subsequent hydrogenation gave the title compound **54**: mp 78–87 °C; ^{1}H NMR δ 0.94 (t, 3 H, J = 7 Hz), 1.48–1.63 (m, 2 H), 1.89–2.22 (m, 4 H), 2.52 (t, 2 H, J = 8 Hz), 2.71–2.86 (m, 5 H), 2.19 (dd, 1 H, J = 15 Hz, J' = 8 Hz), 3.96 (t, 2 H, J = 6 Hz), 4.67–4.78 (m, 1 H), 5.18 (s, 1 H), 6.45 (s, 1 H), 6.83–6.99 (m, 3 H), 7.08–7.31 (m, 7 H). Anal. ($C_{28}H_{32}O_3$) C, H.

2,3-Dihydro-2-(2-phenylethyl)-4-propyl-6-[3-[4-(1*H*-tetrazol-5-yl)phenoxy]propyl]-5-benzofuranol (55). Following the procedure described above for the conversion of compound **42** to compound **49**, but using hydrogenated **43b** as starting material, the title compound **55** was obtained as a solid: mp 155–158 °C; ^{1}H NMR δ 0.91 (m, 3 H), 1.48–1.63 (m, 2 H), 1.94–2.15 (m, 4 H), 2.57 (dd, 2 H, J = 15 Hz, J' = 7 Hz), 2.72–2.86 (m, 4 H), 3.27 (m, 2 H), 4.12 (t, 2 H, J = 5 Hz), 4.61–4.73 (m, 1 H), 6.40 (s, 1 H), 7.11–7.30 (m, 7 H), 8.00–8.09 (m, 2 H). Anal. ($C_{29}H_{32}N_4O_3$) C, H, N.

6-Benzyl-2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (59). By using the alternative route methodology for the production of compound **46** but substituting benzaldehyde in place of 3-phenoxypropionaldehyde, 2,3-dihydro-2-(2-phenylethyl)-5-benzofuranol (**42**, 1.0 g, 4.3 mmol) was converted to 1.2 g (65%) of 7,8-dihydro-2,4-diphenyl-7-(2-phenethyl)-4*H*-furo[2,3-*g*]-1,3,2-benzodioxaborin as an oil. Without further purification this intermediate was reduced to give 720 mg (75%) of the title compound: mp 63–64 °C; ^{1}H NMR δ 1.8–2.21 (m, 2 H), 2.68–2.94 (m, 3 H), 3.22 (dd, 1 H, J = 16.7 Hz, J' = 7.45 Hz), 3.94 (s, 2 H), 4.25 (s, 1 H), 4.6–4.8 (m, 1 H), 6.5 (s, 1 H), 6.6 (s, 1 H), 7.1–7.3 (m, 10 H). Anal. ($C_{23}H_{22}O_2$) C, H.

2,3-Dihydro-6-[[4-(methanesulfonyl)phenyl]methyl]-2-(2-phenylethyl)-5-benzofuranol (61). (a) Following the procedure described above for the preparation of compound **59** but starting with 4-(methylthio)benzaldehyde, compound **42** was converted to 2,3-dihydro-6-[4-(methylthio)benzyl]-2-(2-phenylethyl)-5-benzofuranol (**60**): mp 100–102 °C.

(b) To a solution of 2,3-dihydro-6-[4-(methylthio)benzyl]-2-(2-phenylethyl)-5-benzofuranol (**60**, 3.1 g, 8.2 mmol) in methylene chloride at 0 °C was added *m*-chloroperbenzoic acid (3.65 g, 21.2 mmol). The mixture was stirred for 2 h and then 4 g of calcium hydroxide was added and stirred continuously for another 20 min at 0 °C. After filtration on Celite and evaporation of the solvent the residue was chromatographed on silica gel using 40% of ethyl acetate in hexane to yield 1.48 g (44%) of title compound **61** as a solid: mp 134–135 °C; ^{1}H NMR δ 1.93–2.31 (m, 2 H), 2.72–2.98 (m, 4 H), 3.04 (s, 3 H), 3.24 (dd, 1 H, J = 14 Hz, J' = 8 Hz), 4.02

(s, 2 H), 4.55 (s, 1 H), 4.79 (m, 1 H), 4.56 (s, 1 H), 6.68 (s, 1 H), 7.18–7.34 (m, 5 H), 7.48 (d, 2 H, J = 8 Hz), 7.89 (d, 2 H, J = 8 Hz). Anal. ($C_{24}H_{24}OS$) C, H, S.

5-Methoxybenzofuran-2-carboxaldehyde (63). (a) To a solution of 5-methoxybenzofuran-2-carboxylic acid (10.0 g, 52 mmol) in THF (300 mL) cooled at −78 °C was added diisobutylaluminum hydride (120 mL, 182 mmol) via a syringe. The reaction mixture temperature was raised to room temperature, and the solution was stirred for 3 h. The mixture was poured into a saturated solution of ammonium chloride (500 mL) and was stirred for 15 min and then was acidified with HCl (6 N). This mixture was extracted with ethyl acetate (2 × 500 mL). The combined organic extract was concentrated in vacuo. The residue was chromatographed on silica gel using 30% ethyl acetate in hexane to yield 2-(hydroxymethyl)-5-methoxybenzofuran (6.5 g, 71%).

(b) To a solution of 2-(hydroxymethyl)-5-methoxybenzofuran (16.0 g, 90 mmol) in ethyl acetate (1 L) was added MnO_2 (78 g, 900 mmol). The reaction mixture was stirred at room temperature for 3 h. Then this suspension was filtered through celite and concentrated in vacuo. The filtrate yielded 5-methoxybenzofuran-2-carboxaldehyde (**63**, 9.5 g, 60%): ^{1}H NMR δ 3.85 (s, 3 H), 7.15 (m, 2 H), 7.45 (m, 2 H), 9.8 (s, 1 H).

2-[2-(4-Chlorophenyl)ethenyl]-5-methoxybenzofuran (64). To anhydrous ethanol (50 mL) was added sodium (2.58 g, 0.112 mol) portionwise at room temperature. The mixture was stirred until the sodium was completely dissolved. To this cooled solution (0 °C) was added (4-chlorobenzyl)triphenylphosphonium chloride (45.6 g, 0.108 mol), and the mixture was stirred for 30 min. To the resulting phosphorane was added 5-methoxybenzofuran-2-carboxaldehyde (**63**, 9.5 g, 54 mmol) and the reaction mixture was stirred at 0 °C for 3 h. The mixture was acidified with HCl (1 N) and concentrated in vacuo. The residue was chromatographed on silica gel using 5% ethyl acetate in hexane to yield 6.5 g (41%) of **64** as a mixture of cis/trans isomers: ^{1}H NMR δ 3.75 (2s, 3 H, cis/trans mixture), 6.45 (m, 2 H), 6.7–7.0 (m, 2 H), 7.1–7.5 (m, 6 H).

2-[2-(4-Chlorophenyl)ethyl]-2,3-dihydro-5-benzofuranol (65). (a) To a solution of **64** (6.5 g, 22.8 mmol) in CH_2Cl_2 (500 mL) at −78 °C was added BBr_3 (68.5 mL, 68.5 mmol) dropwise. The reaction mixture was stirred for 1 h at −78 °C, and then methanol (150 mL) was added dropwise. The methanol mixture was concentrated in vacuo. The residue was chromatographed on silica gel using 15% acetate in hexane to yield 4.7 g (76%) of 2-[2-(4-chlorophenyl)ethenyl]-5-benzofuranol: ^{1}H NMR δ 6.5–7.5 (m, 10 H), 7.9 (s, 1 H).

(b) To a solution of 2-[2-(4-chlorophenyl)ethenyl]-5-benzofuranol (4.65 g, 17.2 mmol) in THF (25 mL) was added triethylsilane (8.23 mL, 51.6 mmol) as a reactant. The resultant reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O, then neutralized with potassium carbonate (solid), extracted with ethyl acetate (100 mL × 2), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane yielded 2.5 g, (53%) of **65**: ^{1}H NMR δ 1.65–2.2 (m, 2 H), 2.5–2.9 (m, 3 H), 3.2 (m, 1 H), 4.7 (m, 1 H), 4.8 (s, 1 H), 6.6 (s, 3 H), 7.2 (m, 4 H).

2-[2-(4-Chlorophenyl)ethyl]-2,3-dihydro-6-(3-phenoxypropyl)-5-benzofuranol (66). Following the same procedure described above for converting compound **42** to **46**, compound **65** was transformed to compound **66**: ^{1}H NMR δ 1.6–2.2 (m, 4 H), 2.5–2.85 (m, 5 H), 3.1 (s, 1 H), 3.9 (t, 2 H, J = 6 Hz), 4.6 (m, 1 H), 5.2 (s, 1 H), 6.5 (d, 2 H), 6.8 (m, 3 H), 7.1 (m, 6 H). Anal. ($C_{25}H_{25}O_3Cl$) C, H, Cl.

2,3-Dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranyl β-D-Glucopyranosiduronic Acid (70). (a) To a solution of 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenethyl)-5-benzofuranol (373 mg, 1 mmol) in dichloromethane (4 mL) at 0 °C and under nitrogen atmosphere was added silver trifluoromethanesulfonate (650 mg, 2.5 mmol). After stirring for 15 min, methyl (tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate[14] (642 mg, 1.6 mmol) in dichloromethane (4 mL) was added dropwise over 10 min. The mixture was stirred for 15 min and then saturated sodium chloride solution (10 mL) was added. The mixture was filtered as such, and the salts were washed with dichloromethane (25 mL). The organic layer of the filtrate was separated, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed using 40% ethyl acetate in hexane to provide 540 mg (78%) of methyl [2-(2-phenylethyl)-6-(3-phenoxypropyl)-2,3-dihydrobenzofuran-5-yl tri-*O*-acetyl-β-D-glucopyranosid]uronate as an oil: ^{1}H NMR δ 1.82–2.2 (m, 9 H), 2.52–2.92 (m, 5 H), 3.13–3.31 (m, 1 H), 3.73 (s, 3 H), 3.92 (t, 2 H, J = 7.4 Hz), 4.02–4.14 (m, 2 H), 4.62–4.82 (m, 1 H), 4.88–5.04 (m, 1 H), 5.19–5.43 (m, 4 H), 6.59 (s, 1 H), 6.74–7.0 (m, 4 H), 7.11–7.40 (m, 7 H).

(b) A mixture of methyl [2-(2-phenylethyl)-6-(3-phenoxypropyl)-2,3-dihydrobenzofuran-5-yl tri-*O*-acetyl-β-D-glucopyranosid]uronate (529 mg, 0.76 mmol) and 1 N sodium hydroxide (8 mL) in methanol (25 mL) was stirred at room temperature for 30 min. The mixture was acidified with excess 1 N hydrochloric acid containing brine and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 5% acetic acid in ethyl acetate to obtain 306 mg (73%) of the title compound: mp 59–61 °C; ^{1}H NMR δ 1.83–2.20 (m, 4 H), 2.6–2.94 (m, 5 H), 3.2 (dd, 1 H, J = 16 Hz, J' = 7.4 Hz), 3.6–4.07 (m, 6 H), 4.6–4.8 (m, 2 H), 6.58 (s, 1 H), 6.8–7.35 (m, 11 H).

Biological Methods. Human Polymorphonuclear Leukocytes. The potency of the compounds as inhibitors of LTB_4 biosynthesis was determined using Ca^{2+}-ionophore-activated human leukocytes as previously described.[4] Inhibitors were preincubated for 2 min at 37 °C with freshly prepared polymorphonuclear leukocytes from human blood (5×10^5 cells/mL). The cells were then stimulated with Ca^{2+}-ionophore A23187 (10 μM) and the level of LTB_4 released after 5 min was determined by radioimmunoassay. IC_{50} values were derived from nonlinear regression analysis of five-point titrations.

Rat Leukocyte 5-Lipoxygenase. 5-Lipoxygenase activity was measured from the conversion of [^{14}C]arachidonic acid to 5-HETE and 5,12-diHETES with the 10000g supernatant fraction from rat PMN leukocytes.[15] The activity of 5-lipoxygenase was calculated from the percentage of conversion of arachidonic acid to 5-HETE and 5,12-diHETEs after the 10 min incubation. IC_{50} values were derived by linear regression analysis.

Measurement of Methemoglobin Formation. Compounds were dissolved in 30 μL dimethyl sulfoxide and added to 0.3 mL of fresh canine venous blood containing heparin (Sigma Chemical Co., MO, 160 IU/mL) to give final concentrations of 200 μg/mL. Blood containing test compounds, or dimethyl sulfoxide alone, was mixed and incubated at 37 °C for 45 min. The incubate was diluted 1:80 volume/volume with 150 mM potassium phosphate buffer, pH 6.6, and centrifuged at 12000g for 3 min. Duplicate 275-μL aliquots of the supernatant were transferred to a microtitre plate (Immulon I, Dynatech Laboratories, VA), and 10 μL of a 20% (weight/volume) potassium ferricyanide solution in deionized water was added to one of the duplicates to induce maximum methemoglobin formation. After gentle mixing for 2 min at 21 °C, absorbance was assessed at 630 nm (Model 580, Dynatech, VA). Ten microliters of a 5% (weight/volume) potassium cyanide solution in deionized water was then added, and the absorbance again assessed after a further 5-min incubation. Methemoglobin formation was assessed by the difference in absorbance in the absence and presence of potassium cyanide, and normalized by comparison with formation in the presence of potassium ferricyanide (% MetHb).

Effects on Antigen-Induced Dyspnea in Hyperreactive Rats. Aerosol challenge with ovalbumin using a DeVilbiss nebulizer and subsequent recordings of respiratory patterns by a pneumotachograph were carried out in clear plastic boxes as previously described.[11,12] Detailed descriptions of how the duration of dyspnea has been defined and measured have been given by Piechuta et al.[13] Rats were pretreated po with either a sus-

(11) Brunet, G.; Piechuta, H.; Hamel, R.; Holme, G.; Ford-Hutchinson, A. W. Respiratory Responses to Leukotrienes and Biogenic Amines in Normal and Hyperreactive Rats. *J. Immunol.* 1983, *131*, 434–438.

(12) McFarlane, C. S.; Piechuta, H.; Hall, R. A.; Ford-Hutchinson, A. W. Effects of a Contractile Prostaglandin Antagonist (L-640,035) upon Allergen-Induced Bronchoconstriction in Hyperreactive Rats and Conscious Squirrel Monkeys. *Prostaglandins* 1984, *28*, 173–182.

pension of drug or vehicle alone (0.4% Methocel and 0.5% Tween 80, 10 mL/kg) at 2 h prior to the aerosol of antigen. Rats were also pretreated with methysergide (3 mg/kg, iv) 5 min prior to exposure to antigen. Statistical analysis was carried out by Student's t test and ED_{50} values were derived by linear regression analysis.

Effect of Oral Administration of Compound 46 on Ascaris Antigen-Induced Bronchoconstriction in Conscious Squirrel Monkeys. Squirrel monkeys (*Saimiri sciureus*) which were trained to sit in restraining chairs and breathe through a face mask with a history of reproducible bronchoconstrictor responses to Ascaris antigen aerosol challenge were used in these experiments.[12] Three monkeys were fasted overnight for 18 h and were then pretreated with L-670,630 at a dose of 1.0 mg/kg orally in 1% Methocel, as vehicle. Three hours later, the monkeys were challenged with antigen (1:25 dilution) aerosol for 10 min. Diluted antigen solution was obtained from a stock volume of a 1:10 solution which contained 172 000 to 182 000 PNU/mL (protein nitrogen units/mL) (Greer Laboratories Inc. Lenoir, NC). Antigen aerosol was generated by a Model 25, DeVilbiss ultrasonic nebulizer which was connected to the face mask through which the animals breathe. Response changes in airway resistance (R_L) and in dynamic compliance (C_{dyn}) after inhalation challenge were measured by an on-line Buxco Electronics pulmonary mechanics analyzer, Model 6, for 60 min post antigen challenge.

The results showed that compound **46** inhibited the bronchoconstriction induced by antigen aerosol challenge. Increases in airway resistance (R_L) and the fall in dynamic compliance (C_{dyn}) which normally occurred following challenge were significantly inhibited. Mean values for airway resistance (R_L) were reduced by 83.9% ($p < 0.05$) and dynamic compliance (C_{dyn}) by 100% ($p < 0.02$) for greater than 60 min post challenge.

Measurement of Plasma Level and Bioavailability of Dihydrobenzofuranols. Male Sprague-Dawley rats (3) were starved overnight and dosed orally with the compound at 20 mg/kg as a suspension in 1% Methocel (1 mL/100 g). Blood was taken from the jugular vein at 0, 30 min, 1, 2, 4, and 6 h after dosing. In the iv studies, compounds were dissolved in PEG 400 and injected intraveneously in the jugular vein at a dose of 5 mg/kg (dose volume = 0.1 mL/100 g). Blood was taken from the jugular vein at 0, 5, 15, 30 min, 1, 2, 4, and 6 h after dosing. Blood was centrifuged and plasma was collected. To 100 μL of each plasma sample was added an equal volume of acetonitrile to precipitate the protein. An aliquot (50–100 μL) of the supernatant after centrifugation was subjected to reversed-phase HPLC. The parent compound was quantitated from the area of the corresponding peak, relative to the standard (plasma sample at time 0 min, spiked with varying concentration of the compound). To another 100 μL of the same plasma sample was added an equal volume of a solution of β-glucuronidase (Sigma, type VII from *Escherichia coli*, 200 units/mL, pH 6.8, Tris buffer). The solution was incubated at 37 °C for 2 h. Equal volume of acetonitrile was then added. The mixture was agitated and centrifuged. The supernatant was analyzed by HPLC for parent compound (total drug present).

Metabolism Studies. Microsomal Metabolism of Dihydrobenzofuranols. Liver microsomes from untreated rats were prepared as previously described.[16] Typical incubation mixtures contained 100 μmol potassium phosphate, pH 7.4, 6 μmol $MgCl_2$, microsomal protein (2–3 mg/mL), substrate (compounds **38**, **66**, and **67**, ~25 μM), and a NADPH regenerating system (1 μmol NADP, 10 μmol glucose 6-phosphate, 0.7 units of glucose-6-phosphate dehydrogenase) in final volume of 2 mL. The incubation was carried out at 37 °C at various time periods up to 60 min. At the end of the incubation period, the reaction was stopped by the addition of an equal volume of ethyl acetate, together with an internal standard for the quantification of the substrate. The ethyl acetate extract was recovered, evaporated to dryness, and reconstituted in MeOH before HPLC analysis.

For isolation of metabolites, compound **67** was incubated as described above except that the total volume of incubation mixture was 40 mL and the time of incubation was 18 min. After the incubate was extracted with 2 × 80 mL of ethyl acetate, the extracts were combined, evaporated, and redissolved in 3 × 1 mL of $MeOH/CH_3CN$ (60:40). The solution was filtered through a sintered glass funnel before aliquots were analyzed with HPLC using Zorbax ODS column, eluted isocratically with $CH_3OH/CH_3CN/H_2O$ (36:24:40, v/v/v) at 1 mL/min and UV absorbance was monitored at 300 nm. Metabolites **68** and **69** were isolated by repetitive HPLC chromatography of several separate incubations to provide samples for spectral analysis. Compound **68**: m/z 286, 176, 149; ^1H NMR (400 MHz, C_6D_6) selected signals δ 1.82 (m, 2 H), 2.61 (t, 2 H), 3.58 (t, 2 H), 4.03 (m, 2 H), 4.74 (br t, 1 H), 6.45 (s, 1 H), 6.68 (s, 1 H). Compound **69**: m/z 288, 194, 176, 163; ^1H NMR selected signals δ 1.83 (m, 2 H), 2.42 (t, 2 H), 2.64 (t, 2 H), 3.20 (m, 2 H), 3.59 (t, 2 H).

In Vivo Metabolism of Compound 46. Male Sprague-Dawley rats were dosed by gavage or by iv injection via the femoral vein with ^3H compound **46** in PEG-400 at 21 mg/kg of body weight and at a specific activity of 3.96 μCi/mg. In the oral study, the animals were sacrificed at 5, 15, 30 min, 1, 2, 4, 24, and 48 h post dose. The iv-dosed animals were sacrificed at 2, 10, 30 min, 1, 2, and 4 h post dose. Total radioactivity in tissues were determined by combustion of aqueous tissue homogenates. Plasma and tissues were extracted with methanol, and the recovered radioactivity was analyzed by HPLC. The concentration of the parent compound was calculated on the basis of radioactivity recovered from HPLC column eluent corresponding to the retention time of compound **46**. HPLC condition: Zorbax C-18 column eluted isocratically with a mobile phase consisting of $CH_3CN/MeOH/H_2O$ (45:30:25, v/v/v) at 1 mL/min. Recoveries of methanolic extraction in all samples were 85–100%.

Deconjugation of Compound 70 by β-Glucuronidase or GI Homogenate. Compound **70** (25 μg) or rat plasma (0.2–1.4 μg) was incubated with either β-glucuronidase (from *E. coli*, 260 units) or 250 μL of rat GI homogenate in 1 mL 0.2 M sodium phosphate buffer, pH 5.0 for 1 h at 37 °C. Control samples were incubated with buffer alone. GI homogenate was prepared by homogenizing the GI tract (30 gm) of a male Sprague-Dawley rat in phosphate buffer (1:4, w/w). At the end of incubation, the incubate was extracted with ethyl acetate and centrifuged and the supernatant evaporated to dryness. The extract was redissolved in MeOH prior to HPLC analysis.

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Registry No. **1**, 102612-16-8; **2**, 139201-22-2; **3**, 30992-63-3; **4**, 2632-13-5; **5**, 138854-37-2; **5** alcohol, 139201-23-3; **6**, 138854-00-9; **6** allyloxy, 138854-39-4; **6** 6-allyl, 138854-40-7; **7**, 139201-24-4; **8**, 150-76-5; **9**, 139201-25-5; **10**, 139201-26-6; **11**, 14617-95-9; **12a**, 138854-49-6; **12b**, 138854-51-0; **13**, 138854-52-1; **14**, 129201-27-0; **15**, 129201-28-1; **16**, 138854-04-3; **17**, 139201-29-9; **18**, 13380-24-0; **19a**, 138854-54-3; **19a** benzyl ether, 138854-69-0; **19b**, 138854-70-3; **20**, 138854-63-4; **20** 2-hydroxy ethyl, 138854-64-5; **21**, 139201-30-2; **23**, 139201-31-3; **23** alcohol, 139201-32-4; **24**, 139201-33-5; **24** *t*-BDPSO ether, 139201-37-9; **25**, 139201-34-6; **26**, 139201-35-7; **26** *t*-BDPSO ether, 139201-36-8; **27**, 138854-66-7; **27** alcohol, 139201-38-0; **28**, 139201-39-1; **29**, 138854-69-0; **29** 6-allyl, 138854-68-9; **30**, 139201-40-4; **31**, 138854-06-5; **32**, 139201-41-5; **33**, 138854-57-6; **33** alcohol, 138854-56-5; **34**, 138854-58-7; **34** alcohol, 138854-59-8; **35**, 139201-42-6; **36**, 138854-60-1; **37**, 139201-43-7; **38**, 138854-05-4; **38** benzyl ether, 138854-61-2; **39**, 13391-28-1; **40**, 139201-44-8; **41**, 139201-45-9; **42**, 133174-25-1; **42**

(13) Piechuta, H.; Smith, M. E.; Share, N. N.; Holme, G. The Respiratory Response of Sensitized Rats to Challenge with Antigen Aerosols. *Immunology* **1979**, *38*, 385–392.
(14) Bollenback, G. N.; Long, J. W.; Benjamin, D. G.; Lindquist, J. A. The Synthesis of Aryl-D-Glucopyranosiduronic Acids. *J. Am. Chem. Soc.* **1955**, *77*, 3310–3315.
(15) Riendeau, D.; Leblanc, Y. Modulation of Rat Polymorphonuclear Leukocyte 5-Lipoxygenase Activity by 5-HPETE and NADH-Dependent Flavin Inhibition. *Biochem. Biophys. Res. Commun.* **1986**, *141*, 534–540.
(16) Lu, A. Y. H.; Levin, W. Partial Purification of Cytochromes P-450 and P-448 from Rat Liver Microsomes. *Biochem. Biophys. Res. Commun.* **1972**, *46*, 1334–1339.

methyl ether, 138854-08-7; **42** allyl ether, 138854-09-8; **43a**, 138853-84-6; **43b**, 138853-85-7; **43b** hydrogenated, 139201-46-0; **44**, 139201-47-1; **45**, 138854-18-9; **45** 4-cyanophenoxy derivative, 138854-19-0; **46**, 133174-26-2; **46** benzyl ether, 138854-30-5; **47**, 139201-48-2; **47** benzyl ether, 138854-35-0; **48**, 139201-49-3; **49**, 138853-91-5; **49** benzyl ether, 138854-20-3; **50**, 139201-50-6; **50** benzyl ether, 139201-51-7; **51**, 138853-98-2; **51** benzyl ether, 139201-52-8; **52**, 139201-53-9; **53**, 139201-54-0; **53** benzyl ether, methyl ester, 138854-21-4; **53** methyl ester, 138854-22-5; **54**, 139201-55-1; **55**, 139201-56-2; **56**, 138854-29-2; **57**, 139201-57-3; **58**, 139201-58-4; **59**, 139201-59-5; **60**, 139201-60-8; **61**, 139201-61-9; **62**, 10242-08-7; **63**, 23145-19-9; **63** alcohol, 37603-26-2; (*E*)-**64**, 139201-62-0; (*Z*)-**64**, 139201-64-2; (*E*)-**64** alcohol, 139201-63-1; (*Z*)-**64** alcohol, 139201-65-3; **65**, 138853-86-8; **66**, 138853-90-4; **67**, 119794-95-5; **68**, 139201-66-4; **69**, 139201-67-5; **70**, 139242-71-0; **70** tri-*O*-acetyl methyl ester, 139201-68-6; LTB_4, 71160-24-2; p-$(OEt)_2P(O)CH_2C(O)C_6H_4Cl$, 18276-82-9; allyl bromide, 106-95-6; 3-methyl-2-buten-1-yl 4-methoxyphenyl ether, 34125-69-4; 3-methyl-2-buten-1-ol, 556-82-1; 2-(1,1-dimethyl-2,3-epoxypropyl)-4-methoxyphenyl *n*-butyrate, 138854-48-5; 2,3-dihydro-3,3-dimethyl-2-(hydroxymethyl)-5-benzofuranol, 138854-50-9; (4-methoxyphenyl)magnesium bromide, 13139-86-1; 4-bromoanisole, 104-92-7; 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[1-hydroxy-1-(4-methoxyphenyl)methyl]benzofuran, 139201-69-7; 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-(4-methoxybenzyl)-benzofuran, 139201-70-0; diethyl (4-methoxybenzyl)phosphonate, 1145-93-3; benzyl chloride, 100-44-7; 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethenyl]benzofuran, 138854-03-2; 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethyl]benzofuran, 139201-71-1; 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran, 138854-53-2; 6-allyl-2,3-dihydro-2,5-dihydroxy-3,3-dimethylbenzofuran, 138854-62-3; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; 6-propyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol, 139201-72-2; methyl 3-mercaptopropionate, 2935-90-2; 2-mercaptopyridine, 2637-34-5; [4-(methylthio)phenyl]magnesium bromide, 18620-04-7; 4-bromothioanisole, 104-95-0; phenol, 108-95-2; diethyl (2-oxo-2-phenylethyl)phosphonate, 3453-00-7; phenyl acetaldehyde, 122-78-1; 3-phenoxypropionaldehyde, 22409-86-5; methyl 4-hydroxybenzoate, 99-76-3; 4-cyanophenol, 767-00-0; 4-mercaptopyridine, 4556-23-4; 2-mercaptobenzothiazole, 149-30-4; 2,4-dihydroxy-3-propyl phenylmethyl ketone, 40786-69-4; 2-methoxy-3-carbomethoxy-7-mercaptoquinoline, 95903-63-2; benzaldehyde, 100-52-7; (4-chlorobenzyl)triphenylphosphonium chloride, 1530-39-8; 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenethyl)-5-benzofuranol, 133174-26-2; methyl (tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate, 21085-72-3; 5-lipoxygenase, 80619-02-9.

Communications to the Editor

Intriguing Structure–Activity Relations Underlie the Potent Inhibition of HIV Protease by Norstatine-Based Peptides†

Human immunodeficiency virus (HIV) protease represents a compelling anti-viral target in that potent and specific inhibitors of this enzyme can be designed rationally using contemporary mechanistic and structural motifs.[1-3] Indeed, cell culture studies using inhibitors of HIV protease have established that this enzyme is essential for viral replication and infectivity, thereby providing a plausible biochemical rationale for the treatment of AIDS.[4] In accord with its role as an aspartyl proteinase, the enzyme has been profoundly inhibited by numerous peptide analogues incorporating features which mimic the proposed tetrahedral intermediates that are formed upon hydration of amide substrates of this class of proteinases.[5-11]

Yet, examples of (hydroxymethyl)carbonyl-based inhibitors (e.g. norstatine) of HIV protease have been conspicuously lacking until recently, when Raju and Deshpande[12] reported a number of moderately potent compounds $K_i \geq 3.3$ μM, and Mimoto et al.[13] described a heptapeptide, as well as a truncated variant,[14] with potent activity against synthetic [Ala^{67,95}] HIV protease. Their reports have prompted us to disclose a series of small phenylnorstatine-based peptides extending from the P_2 to P_1' positions, and having N and C terminals protected. With L-proline at the P_1' position and *S* stereochemistry of the (hydroxymethyl)carbonyl component (Table I), these inhibitors, prepared according to Scheme I,[15,16] exhibit impressive potency in the nanomolar range (IC_{50} = 0.58–7.4 nM).[17]

Specifically, the truncated peptide (1) possesses submicromolar activity (IC_{50} = 460 nM), which can be improved by extending the main chain in the N-terminal direction with either valine or asparagine at the P_2 position. Subnanomolar inhibition is achieved by capping the N-terminus with a (naphthyloxy)acetyl protecting group (cf.

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(1) Debouck, C.; Metcalf, B. W. Human Immunodeficiency Virus Protease: A Target for AIDS Therapy. *Drug Dev. Res.* **1990**, *21*, 1–17.

(2) Kräusslich, H.-G.; Wimmer, E. Viral Proteinases. *Annu. Rev. Biochem.* **1988**, *57*, 701–754.

(3) McQuade, T. J.; Tomasselli, A. G.; Liu, L.; Karacostas, V.; Moss, B.; Sawyer, T. K.; Heinrikson, R. L.; Tarpley, W. G. A Synthetic HIV-1 Protease Inhibitor with Antiviral Activity Arrests HIV-Like Particle Maturation. *Science* **1990**, *247*, 454–456.

(4) Meek, T. D.; Lambert, D. M.; Dreyer, G. B.; Carr, T. J.; Tomaszek, T. A., Jr.; Moore, M. L.; Strickler, J. E.; Debouck, C.; Hyland, L. J.; Matthews, T. J.; Metcalf, B. W.; Petteway, S. R. Inhibition of HIV-1 Protease in Infected T-Lymphocytes by Synthetic Peptide Analogues. *Nature* **1990**, *343*, 90–92.

(5) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. Rational Design of Peptide-Based HIV Proteinase Inhibitors. *Science* **1990**, *248*, 358–361.

(6) Rich, D. H.; Sun, C.-Q.; Prasad, J. V. N. V.; Pathiasseril, A.; Toth, M. V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Houseman, K. Effect of Hydroxyl Group Configuration in Hydroxyethylamine Dipeptide Isosteres on HIV Protease Inhibition . Evidence For Multiple Binding Modes. *J. Med. Chem.* **1991**, *34*, 1222–1225.

(7) Ashorn, P.; McQuade, T. J.; Thaisrivongs, S.; Tomasselli, A. G.; Tarpley, W. G.; Moss, B. An Inhibitor of the Protease Blocks Maturation of Human and Simian Immunodeficiency Viruses and Spread of Infection. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 7472–7476.

(8) Grobelny, D.; Wondrak, E. M.; Galardy, R. E.; Oroszlan, S. Selective Phosphinate Transition-State Analogue Inhibitors of the Protease of Human Immunodeficiency Virus. *Biochem. Biophys. Res. Commun.* **1990**, *169*, 1111–1116.

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