of 3:1:1 HOAc/H_2O/THF at 45 °C for 3.5 h. The crude product was chromatographed on silica gel (2% MeOH, 98% EtOAc) to give **2f** in 50% yield from **3**: ^{1}H NMR δ 1.18 (s, C-16 CH_3), 2.71 (dd, J = 19, 8 Hz, C-10H), 3.60 (m, C-20H's), 3.67 (s, OCH_3), 4.01 (q, J = 8 Hz, C-11H), 5.31 (m, C-4,5H's), 5.35 (dd, J = 15, 8 Hz, C-13H), 5.72, 5.74 (2 dt, J = 15, 7 Hz, C-14H, diastereomers[6]). Anal. ($C_{22}H_{36}O_6$) C, H.

Gastric Antisecretory Studies. Prostaglandins were dissolved in absolute ethanol (1 mg/mL) and stored at -10 °C. Dilutions for administration were made in all studies with phosphate buffer (pH 7.4) so that the final ethanol concentration did not exceed 20%.

Antisecretory studies were done as previously described for enisoprost.[13] Briefly, adult female beagles, weighing 6-11 kg, with innervated (Pavlov) gastric pouches, were food deprived with access to water 24 h prior to experiments. Following a 30-min basal collection period, prostaglandin in isosmotic phosphate buffer (pH 7.4) or vehicle was administered into the pouch through a Thomas cannula. Thirty minutes later the gastric pouch was emptied and gastric secretion was stimulated by feeding 10-12 oz of canned dog food (Evanger's Dog and Cat Food Co. Inc., Wheeling, IL). Gastric juice samples were collected over a 4-h period at 30-min intervals. Total acid output (mequiv/30 min) was determined for each collection period by multiplying the volume of secretion (mL/30 min) and the acidity (mequiv/L). For new compounds, percent reduction of total acid output from control was calculated over each 4-h experiment for four to six doses and 2-12 dogs were used for each dose. ED_{50} values and 95% confidence limits were determined from inhibition of secretion curves.

Single doses of prostaglandins that caused approximately 80% inhibition of secretion for the second collection period (60-90 min after dosing, the time of peak acid secretion in control experiments) were used to determine duration of effect. Statistical differences among prostaglandins at each collection time were determined by ANOVA after transformation of percent inhibition values (PIV) by the function arcsine ($\sqrt{PIV}$).[14]

Diarrheal Studies. Adult Charles River male rats weighing 210-230 g were individually housed and fasted with water available ad libitum for 24 h prior to the test. The animals (N = 6-12) received logarithmically graded prostaglandin doses orally. Immediately after administration, the animals were returned to their cages, and diarrhea, if any, was assessed on an all or none basis for 8 h after drug treatment. The ED_{50} and relative potency values were calculated by the logistic method of Berkson.[15,16]

Acknowledgment. We thank C. Anglin and J. Casler for technical assistance in the antisecretory studies, R. Bianchi and C. Ponte for performing the diarrheal studies, the group of E. Hajdu for spectral data, L. Swenton for assistance in interpretation of spectral data, the group of E. Zielinski for microanalyses, L. Householder for artwork, and D. Weiman and J. Fraser for typing the manuscript.

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2,3-Dihydro-5-benzofuranols as Antioxidant-Based Inhibitors of Leukotriene Biosynthesis

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The enzymes that catalyze the oxidative metabolism of arachidonic acid have provided fertile ground for the development of useful therapeutic agents for nearly a quarter century. Inhibitors of the enzyme cyclooxygenase prevent the formation of the prostaglandins and thromboxanes and are clinically useful antiinflammatories and peripheral analgesics. More recently it has been discovered that the enzyme 5-lipoxygenase is the first step in the formation of a series of biologically important metabolites of arachidonic acid, the leukotrienes. Evidence suggests that an inhibitor of 5-lipoxygenase may be a useful therapeutic agent in the treatment of asthma, immediate hypersensitivity, and inflammation. Various antioxidants have been examined as inhibitors of 5-lipoxygenase in vitro. We were intrigued by recent reports that the 2,3-dihydro-5-benzofuranol ring system maximizes the stereoelectronic effects necessary for efficient hydrogen atom abstraction by peroxyl radicals. In this study we describe the synthesis of over 50 new 2,3-dihydro-5-benzofuranols and their biological evaluation as inhibitors of leukotriene biosynthesis in isolated human polymorphonuclear leukocytes. We show that the 2,3-dihydro-5-benzofuranol ring system, although not a potent inhibitor of leukotriene biosynthesis in itself, can provide a useful template for the design of antioxidant-based inhibitors of leukotriene biosynthesis. Furthermore, within a structural class the potency of a given analogue can be predicted on the basis of its overall calculated lipophilicity (log P). The data are interpreted in terms of a model in which the observed inhibition by this class of inhibitors is dependent on the intrinsic ability of the antioxidant to reduce the enzyme and on the fraction of the inhibitor that is partitioned into the membrane.

The enzymes that catalyze the oxidative metabolism of arachidonic acid have provided fertile ground for the development of useful therapeutic agents for nearly a quarter century. Inhibitors of the enzyme cyclooxygenase prevent the formation of the prostaglandins and thromboxanes and are clinically useful antiinflammatories and peripheral analgesics.[1] More recently it has been discovered that the enzyme 5-lipoxygenase is the first step in the formation of a series of biologically important metabolites of arachidonic acid, the leukotrienes[2] (Figure 1). In particular leukotriene C_4 (LTC_4) and LTD_4 have been identified as the slow reacting substance of anaphylaxis (SRSA) and cause a prolonged contraction of bronchial smooth muscle.[3]

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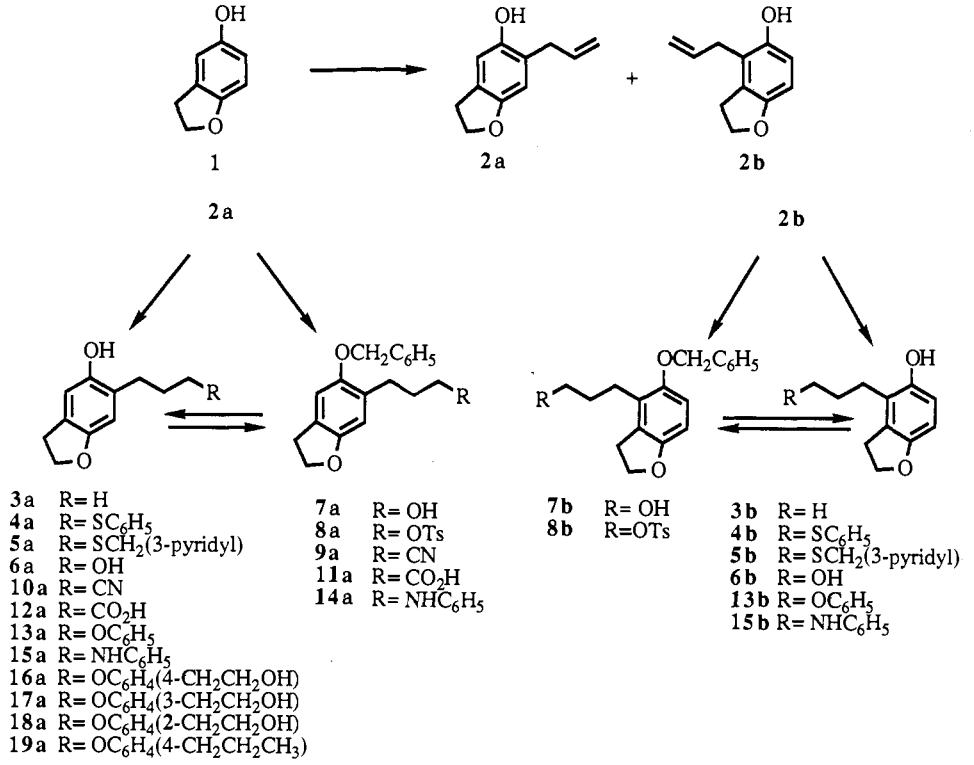
Scheme I



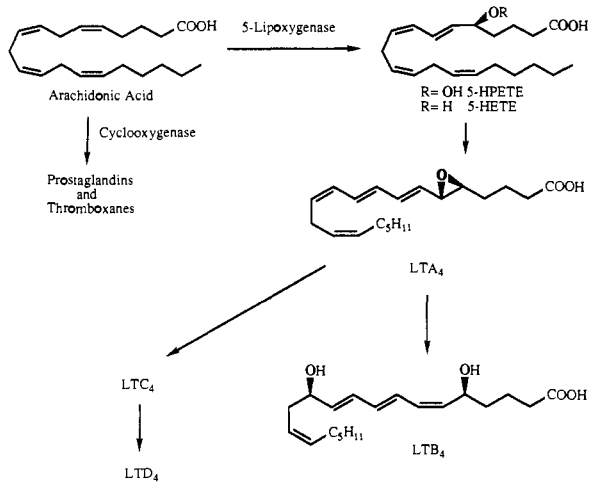


Figure 1. The arachidonic acid cascade.

Another metabolite, LTB_4, has been shown to be a powerful chemotactic agent for a variety of cell types.[4] Taken together this evidence suggests that an inhibitor of 5-lipoxygenase may be a useful therapeutic agent in the treatment of asthma, immediate hypersensitivity, and inflammation.

Various strategies have been employed in attempts to develop useful inhibitors of 5-lipoxygenase.[5] Analogues of arachidonic acid,[6] 5-HPETE,[7] 5-HETE,[8] and 15-HETE[9] have been described. Since 5-lipoxygenase presumably contains an iron atom in the active site,[10] metal chelators such as hydroxamic acid derivatives have been used to inhibit 5-lipoxygenase both in vitro[7,11] and in vivo.[12] Finally various antioxidants such as AA-861,[13] 3-*tert*-butyl-4-hydroxyanisole,[14] α-tocopherol,[14] caffeic acid,[15] and a series of gingerol derivatives[16] have been examined in vitro. We were intrigued by recent reports that the 2,3-dihydro-5-benzofuranol ring system maximizes the stereoelectronic effects necessary for efficient hydrogen atom abstraction by peroxyl radicals.[17] This, combined with earlier results from our laboratories,[18] suggested that 2,3-

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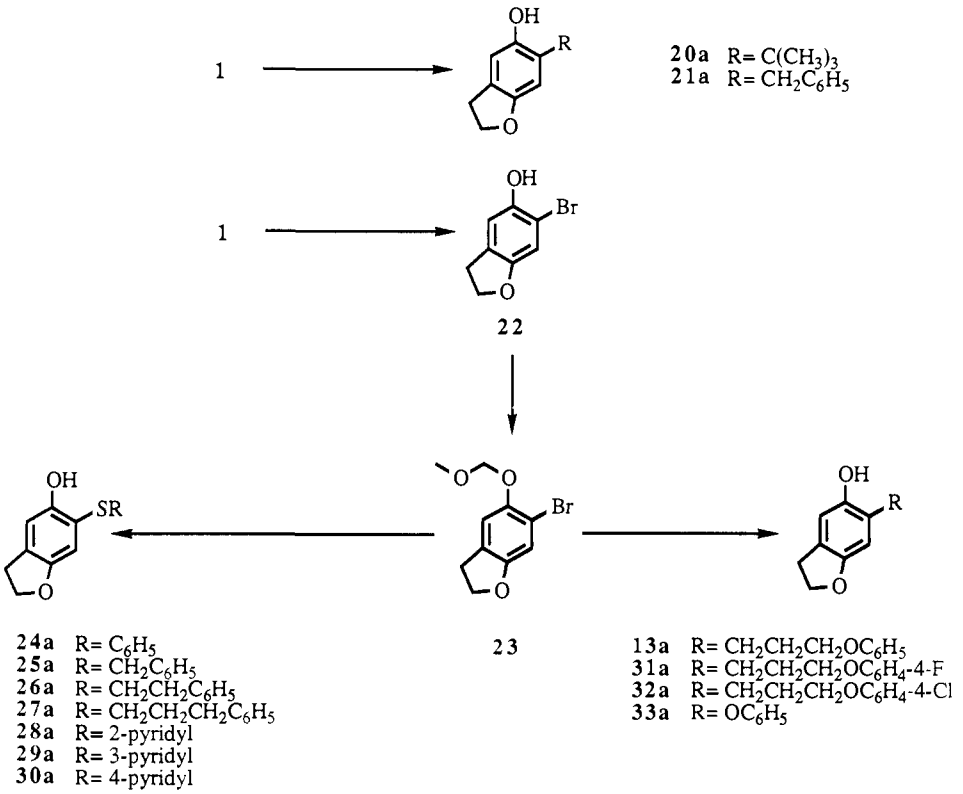
Scheme II



dihydro-5-benzofuranol (1) might provide a useful template for the design of potent antioxidant-based inhibitors of 5-lipoxygenase.

Chemistry

The preparation of the 2,3-dihydro-5-benzofuranols synthesized in this study are shown schematically in Schemes I–IV. Alkylation of 1 with allyl bromide followed by thermal Claisen rearrangement afforded a 2:1 mixture of **2a** and **2b** (Scheme I). Lewis acid catalyzed Claisen rearrangement of 1 using boron trichloride in methylene chloride[19] gave **2a** in 80% isolated yield. Only 5% of **2b** was isolated from this reaction. The allyl compound (**2a**) was easily reduced to **3a** by catalytic hydrogenation or directly functionalized under free-radical conditions[20] with either thiophenol or 3-(methylthio)pyridine[21] to afford **4a** (63%) and **5a** (63%), respectively. Hydroboration of **2a** with borane–methyl sulfide in ether followed by alkaline hydrogen peroxide oxidation gave the primary alcohol **6a** (41%). Attempts to hydroborate **2a** with commercial borane in tetrahydrofuran led, upon oxidation, to complex mixtures that were not preparatively useful. Quenching the monosodium salt (NaH, THF) of **6a** with benzyl bromide gave **7a** (90%), which was directly converted to the primary tosylate (**8a**, 72%). Displacement of the tosylate with sodium cyanide in ethanol proceeded uneventfully to give **9a** (85%), which could be catalytically hydrogenated to the phenol **10a** (78%). Alternatively hydrolysis of **9a** afforded the carboxylic acid **11a** (32%), which was efficiently deprotected to the butyric acid derivative **12a** (98%). Reaction of **8a** with sodium phenoxide (DMF, 80 °C) followed by deprotection afforded **13a** (52%). Nucleophilic displacement with lithium anilide in tetrahydrofuran containing a small amount of dimethyl sulfoxide gave **14a** (71%), which was deprotected in only moderate yield to afford **15a** (47%). Reaction of **8a** with the monolithium salts of the three isomeric 2-(hydroxyethyl)phenols and 4-propylphenol afforded, after debenzylation, **16a–19a** in low to moderate yield. In an identical fashion to that described above for the 6-allyl compound **2a**, the minor isomer from the thermal Claisen rearrangement (**2b**) provided synthetic access to a short series of 4-substituted 2,3-dihydro-5-benzofuranols (**3b–6b**, **15b**) for structure activity purposes.

As shown in Scheme II direct electrophilic alkylation of 1 with *tert*-butyl alcohol in benzene using sulfuric acid as catalyst gave a mixture of **20a** (43%) and the corresponding 7-*tert*-butyldihydrobenzofuranol (**20c**, 25%).[22] Under essentially identical conditions alkylation of 1 with benzyl alcohol gave a complex mixture of products from which **21a** could be isolated in low yield. Bromination[23] of 1 afforded **22** as the exclusive regioisomer,[24] which, in contrast to a previous report,[23] was a stable solid in our hands. Protection of **22** as the methoxymethyl ether[25] gave **23**, which was readily converted to the 6-lithio derivative by treatment with either *n*-butyllithium or *tert*-butyllithium. Quenching the lithium reagent with a series of disulfides afforded, after deprotection, the 6-thio analogues

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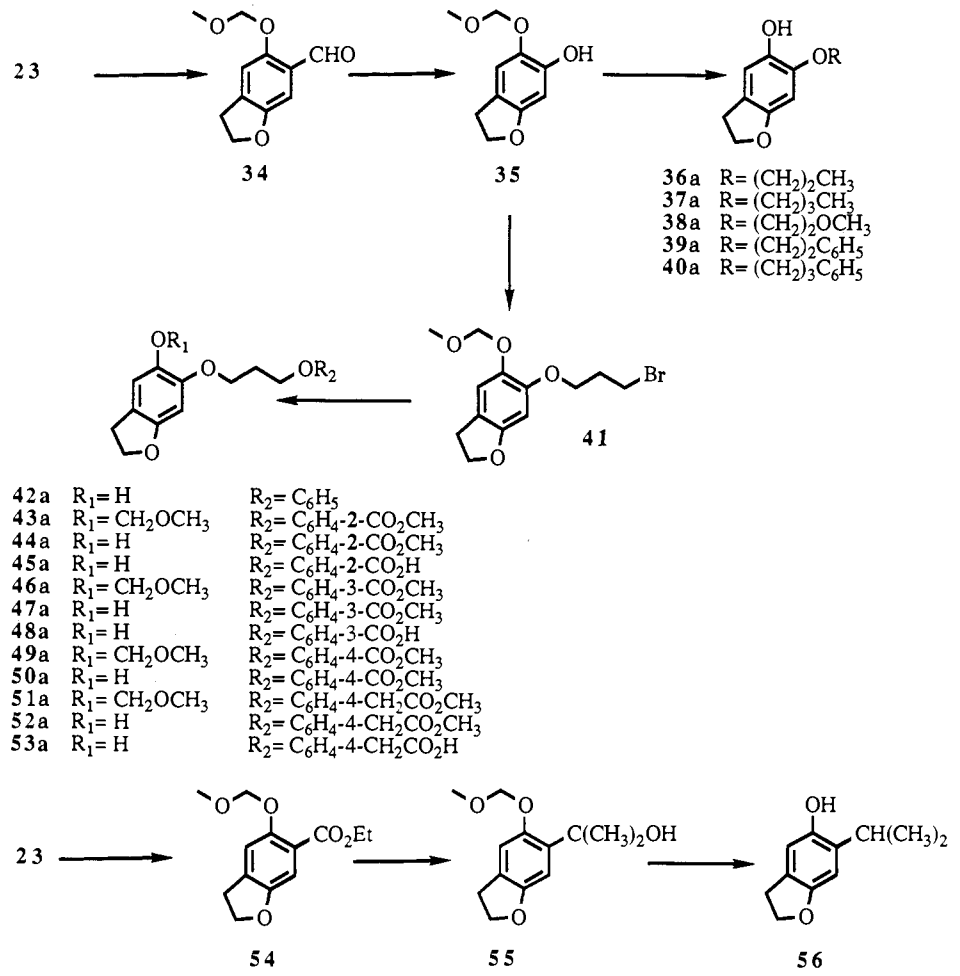
Scheme III



24a–30a in overall yields ranging from 15 to 50%. Alternatively the lithio anion of **23** could be alkylated with iodides and deprotected to give **13a** (52%), **31a** (19%), and **32a** (42%). Ullmann[26] coupling of **23** with phenol in the presence of cupric oxide and pyridine afforded, after deprotection, the diaryl ether **33a** (34%).

Synthetic access to 6-substituted alkyl ether analogues of **1** is depicted in Scheme III. Acylation of the lithio anion of **23** gave the aldehyde **34** (70%), which was oxidized with *p*-nitroperbenzoic acid[27] and hydrolyzed to afford **35** (57%). The monoprotected catechol **35** was alkylated with allyl bromide and potassium carbonate in acetone, which, after hydrogenation and deprotection, gave **36a** (66%). In an identical fashion alkylation of **35** with the requisite alkyl bromides gave after deprotection the ethers **37a–40a** in 44–69% overall yields. Alkylation of the sodium alkoxide of **35** in dimethylformamide with 5 equiv of 1,3-dibromopropane afforded **41** (44%).

Alkylation of sodium phenoxide with **41** in dimethylformamide followed by deprotection gave **42a** (30%). In an analogous fashion alkylation of the sodium salts of the three isomeric methyl hydroxybenzoates and methyl 4-hydroxyphenylacetate with **41** gave **43a**, **46a**, **49a**, and **51a** in excellent yield. The methoxymethyl ethers were removed with dilute methanolic HCl to give the deprotected methyl esters **44a**, **47a**, **50a**, and **52a** in 50–60% yields. Alternatively the esters (**43a**, **46a**, and **51a**) were saponified and the crude carboxylic acids deprotected in dilute aqueous HCl containing tetrahydrofuran as a cosolvent to give **45a**, **48a**, and **53a** in 32–51% overall yields.

Introduction of a branched chain at the 6-position was also achieved from the bromide **23**. Addition of the lithio anion of **23** to ethyl chloroformate gave the ethyl ester **54** (94%), which was treated with an small excess of methyllithium to afford the dimethylcarbinol **55** (66%). Attempts to reduce **55** by hydrogenolysis or by acid-catalyzed elimination were unsuccessful. However, lithium ammonia reduction[28] proceeded cleanly to give, after deprotection, **56** (62%).

In order to assess the effect of increasing steric congestion about the phenol, a short series of 4,6-disubstituted 2,3-dihydro-5-benzofuranols were prepared as shown in Scheme IV. Formylation of the previously described benzofuranone **57**[29] with sodium hydride and ethyl formate[30] in toluene gave **58**. The 6-formyl derivative **58** was then converted to the enol silyl ether and added directly to a −78 °C solution of methyllithium.[31] After mild acidic hydrolysis the 4-methyl compound **59** was obtained in virtually quantitative yield. Oxidation with DDQ afforded **60** (80%), which was converted to the phenol **61** in 71% yield by Baeyer–Villager reaction followed by saponification. Hydrogenation over 10% palladium on carbon gave

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Table I. Inhibition of LTB_4 Biosynthesis in Human PMNs by 6-Substituted 2,3-Dihydro-5-benzofuranols

compd	R_6	IC_{50}, nM	log P calcd	formula	mp, °C	anal.
1	H	4000	1.7	$C_6H_8O_2$	111–112	C, H
2a	CH_2CHCH_2	480	2.9	$C_{11}H_{12}O_2$	80–82	C, H
3a	$CH_2CH_2CH_3$	290	3.4	$C_{11}H_{14}O$	73–74	C, H
4a	$(CH_2)_3SC_6H_5$	19	4.9	$C_{17}H_{18}O_2S$	oil	C, H, S
5a	$(CH_2)_3SCH_2$(3-pyridyl)	280	3.3	$C_{17}H_{19}NO_2S$	130–131	C, H, N, S
6a	$(CH_2)_3OH$	10000	1.4	$C_{11}H_{14}O_3$	103–104	C, H
10a	$CH_2CH_2CH_2CN$	1400	1.8	$C_{12}H_{13}NO_2$	77–78	C, H, N
12a	$CH_2CH_2CH_2CO_2H$	NA[a]	b	$C_{12}H_{14}O_4 \cdot 0.3H_2O$	121–123	C, H
13a	$(CH_2)_3OC_6H_5$	57	4.3	$C_{17}H_{18}O_3$	114–115	C, H
15a	$(CH_2)_3NHC_6H_5$	140	3.8	$C_{17}H_{19}NO_2$	132–133	C, H, N
16a	$(CH_2)_3OC_6H_4$-4-$(CH_2)_2OH$	340	3.5	$C_{19}H_{22}O_4$	116–117	C, H
17a	$(CH_2)_3OC_6H_4$-3-$(CH_2)_2OH$	60	3.5	$C_{19}H_{22}O_4$	71–72	C, H
18a	$(CH_2)_3OC_6H_4$-2-$(CH_2)_2OH$	290	3.5	$C_{19}H_{22}O_4 \cdot 0.2H_2O$	131–132	C, H
19a	$(CH_2)_3OC_6H_4$-4-$(CH_2)_2CH_3$	9	6.0	$C_{20}H_{24}O_3$	101–102	C, H
20a	$C(CH_3)_3$	790	3.7	$C_{12}H_{16}O_2$	148–149	C, H
21a	$CH_2C_6H_5$	280	3.9	$C_{15}H_{14}O_2$	133–135	C, H
24a	SC_6H_5	140	4.1	$C_{14}H_{12}O_2S$	80–81	C, H, S
25a	$SCH_2C_6H_5$	110	4.1	$C_{15}H_{14}O_2S$	50–52	C, H, S
26a	$S(CH_2)_2C_6H_5$	66	4.4	$C_{16}H_{16}O_2S$	oil	C, H, S
27a	$S(CH_2)_3C_6H_5$	28	4.9	$C_{17}H_{18}O_2S$	oil	C, H, S
28a	S(2-pyridyl)	2800	2.8	$C_{13}H_{11}NO_2S$	126–127	C, H, N, S
29a	S(3-pyridyl)	1200	2.8	$C_{13}H_{11}NO_2S$	181–183	C, H, N, S
30a	S(4-pyridyl)	2600	2.8	$C_{13}H_{11}NO_2S$	184–185	C, H, N, S
31a	$(CH_2)_3OC_6H_4$-4-F	28	4.5	$C_{17}H_{17}O_3F$	125–126	C, H
32a	$(CH_2)_3OC_6H_4$-4-Cl	55	5.1	$C_{17}H_{17}O_3Cl \cdot 0.2H_2O$	116–118	C, H
33a	OC_6H_5	420	3.7	$C_{14}H_{12}O_3$	125–127	C, H
36a	$OCH_2CH_2CH_3$	470	2.6	$C_{11}H_{14}O_3$	125–126	C, H
37a	$O(CH_2)_3CH_3$	180	3.1	$C_{12}H_{16}O_3$	62–63	C, H
38a	$O(CH_2)_2OCH_3$	3200	1.3	$C_{11}H_{14}O_4$	60–62	C, H
39a	$O(CH_2)_2C_6H_5$	120	3.6	$C_{16}H_{16}O_3$	88–90	C, H
40a	$O(CH_2)_3C_6H_5$	51	4.2	$C_{17}H_{18}O_3$	110–112	C, H
42a	$O(CH_2)_3OC_6H_5$	320	3.4	$C_{17}H_{18}O_4 \cdot 0.25H_2O$	106–107	C, H
44a	$O(CH_2)_3OC_6H_4$-2-CO_2CH_3	47	3.4	$C_{19}H_{20}O_6$	96–97	C, H
45a	$O(CH_2)_3OC_6H_4$-2-CO_2H	NA[a]	b	$C_{18}H_{18}O_6 \cdot 0.25H_2O$	125–127	C, H
47a	$O(CH_2)_3OC_6H_4$-3-CO_2CH_3	68	3.7	$C_{19}H_{20}O_6 \cdot 0.25H_2O$	93–95	C, H
48a	$O(CH_2)_3OC_6H_4$-3-CO_2H	5100	b	$C_{18}H_{18}O_6$	160–161	C, H
50a	$O(CH_2)_3OC_6H_4$-4-CO_2CH_3	71	3.7	$C_{19}H_{20}O_6$	133–135	C, H
52a	$O(CH_2)_3OC_6H_4$-4-$CH_2CO_2CH_3$	120	3.1	$C_{20}H_{22}O_6$	108–110	C, H
53a	$O(CH_2)_3OC_6H_4$-4-CH_2CO_2H	NA[a]	b	$C_{19}H_{20}O_6 \cdot 0.25H_2O$	156–158	C, H
56a	$CH(CH_3)_2$	300	3.3	$C_{11}H_{14}O_2$	98–99	C, H
phenidone		8000				
nordihydroguaiaretic acid (NDGA)		210				

[a] Not active. Less than 50% inhibition at a concentration 10 μg/mL. [b] Not calculated.

Table II. Inhibition of LTB_4 Biosynthesis in Human PMNs by 4-Substituted 2,3-Dihydro-5-benzofuranols

compd	R_4	IC_{50}, nM	log P calcd	formula	mp, °C	anal.
2b	CH_2CHCH_2	2100	2.9	$C_{11}H_{12}O_2$	oil	C, H
3b	$CH_2CH_2CH_3$	1000	3.4	$C_{11}H_{14}O_2$	37–38	C, H
4b	$(CH_2)_3SC_6H_5$	120	4.9	$C_{17}H_{18}O_2S$	87–88	C, H, S
5b	$(CH_2)_3SCH_2$(3-pyridyl)	2000	3.3	$C_{17}H_{19}NO_2S$	116–118	C, H, N, S
6b	$(CH_2)_3OH$	33000	1.4	$C_{11}H_{14}O_3$	108–110	C, H
13b	$(CH_2)_3OC_6H_5$	290	4.3	$C_{17}H_{18}O_3$	107–108	C, H
15b	$(CH_2)_3NHC_6H_5$	1400	3.8	$C_{17}H_{19}NO_2$	117–118	C, H, N
68	$C(CH_3)_2$	730[a]	3.7	$C_{12}H_{16}O_2$	184–185	C, H

[a] IC_{50} based on a single titration.

the dihydrobenzofuranol **62**[32] (94%), which was alkylated with allyl bromide and thermally rearranged to the 6-allyl analogue **63** (83%). This material was then hydrogenated or alkylated under free-radical conditions to afford **64** (92%) and **65** (70%), respectively. Alternatively **64** could be prepared from **3a**. Bromination of **3a** gave **66** (46%), which was converted to the methoxymethyl ether **67** (82%). The protected bromide **67** was converted to the lithium salt with *n*-butyllithium in tetrahydrofuran at −78 °C and quenched with an excess of methyl iodide. Acidic hydrolysis afforded **64** in 56% yield. The sterically encumbered analogue **70** was prepared from the known phenol **68**[22] by alkylation with allyl bromide and thermal Claisen rearrangement to give **69** (53%). Simple hydrogenation then afforded **70** (73%).

Results

The 2,3-dihydro-5-benzofuranols prepared in this study were evaluated for their ability to inhibit the production of LTB_4 in isolated human polymorphonuclear leukocytes (PMNs).[33] Leukotriene biosynthesis was initiated with

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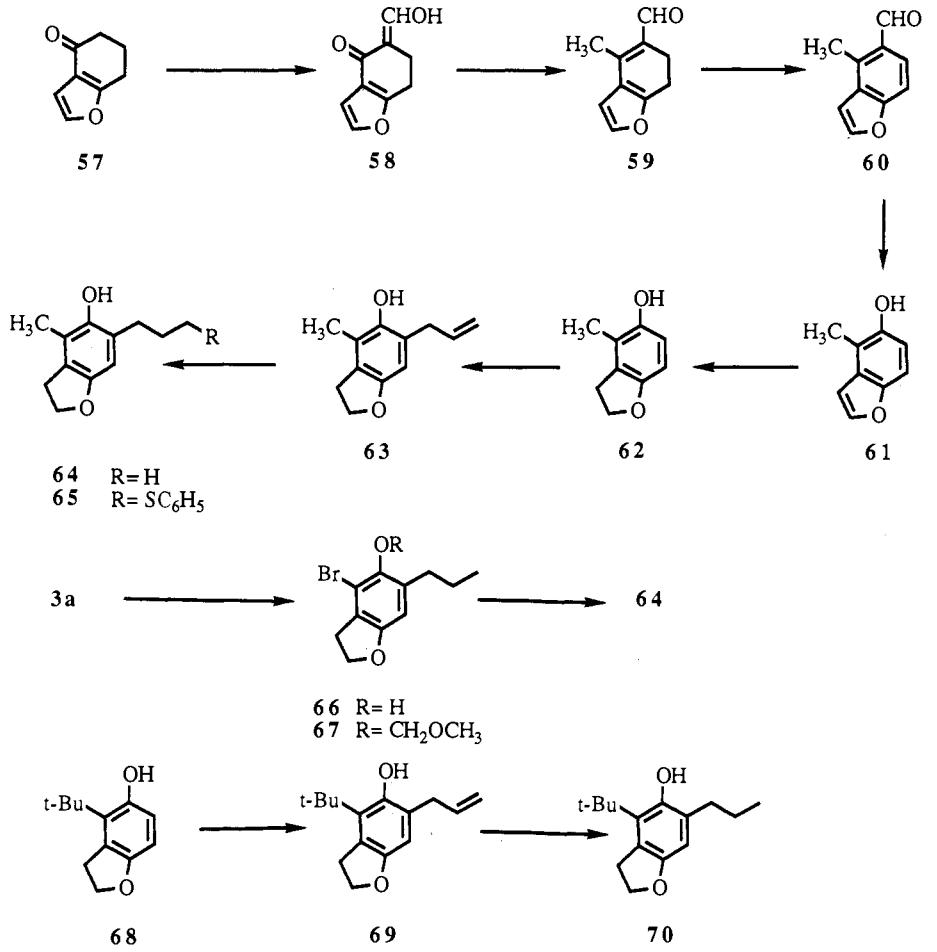
Scheme IV



calcium ionophore A23187 and LTB_4 concentration measured by radioimmunoassay.[34] The log of the octanol/water partition coefficients (log *P*) were estimated by calculation[35] using commercially available software.[36] The results are tabulated for 6-substituted 2,3-dihydro-5-benzofuranols in Table I while the results for 4-substituted analogues are shown in Table II.

Early on in our synthetic efforts certain general structure–activity trends became apparent. Substitution at either the 4- or 6-position improved activity with respect to the unsubstituted ring system 1. For isomeric compounds, substitution at the 6-position was generally more favorable than substitution at the 4-position. Even simple 6-substituted analogues such as the allyl and propyl analogues **2a** and **3a** were quite respectable inhibitors of leukotriene biosynthesis. As our synthetic studies progressed a striking relationship between the log of the partition coefficient (log *P*) and LTB_4 biosynthesis inhibition became apparent.[37] This relationship is shown graphically in Figure 2. The linear dependence of log IC_{50} on log P[37a] extends over 3 orders of magnitude in biological activity and 5 orders of magnitude in partition coefficient. The relationship is structurally specific in that different, but nearly parallel, lines are obtained for 6-substituted and 4-substituted 2,3-dihydro-5-benzofuranols. For this reason we focused our efforts on the preparation of a series of the more active 6-substituted 2,3-dihydro-5-benzofuranols. On the one hand we hoped to use this relationship to maximize the activity of our inhibitors, while on the other hand we

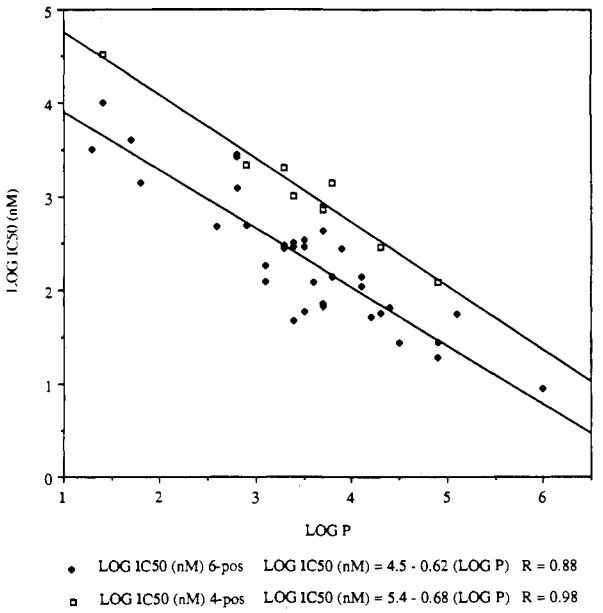


Figure 2. The linear dependence of the log of the IC_{50} for leukotriene biosynthesis inhibition on the calculated log of the octanol/water partition coefficient (log *P*).

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Table III. Inhibition of LTB_4 Biosynthesis in Human PMNs by 4,6-Disubstituted 2,3-Dihydro-5-benzofuranols

compd	R_4	R_6	IC_{50}, nM	log P calcd	formula	mp, °C	anal.
63	CH_3	CH_2CHCH_2	130	3.5	$C_{12}H_{14}O_2$	60–61	C, H
64	CH_3	$CH_2CH_2CH_3$	160	4.1	$C_{12}H_{16}O_2$	72–73	C, H
65	CH_3	$(CH_2)_3SC_6H_5$	19	5.9	$C_{18}H_{20}O_2S$	80–81	C, H, S
66	Br	$CH_2CH_2CH_3$	65	4.3	$C_{12}H_{15}BrO_2$	42–43	C, H, Br
70	$C(CH_3)_3$	$CH_2CH_2CH_3$	430[a]	5.4	$C_{15}H_{22}O_2$	129–130	C, H

[a] IC_{50} based on a single titration.

sought to find analogues that would be more potent than predicted on the basis of lipophilicity alone.

One of our initial thoughts was that the correct placement of local hydrophilicity might lead to a compound with increased activity. For this reason we prepared **12a** as an analogue in which the phenolic hydroxyl would mimic the hydroperoxyl present in 5-HPETE. This compound was completely devoid of activity. Other attempts to include a charged carboxylic acid in the structure such as **45a**, **48a**, and **53a** likewise showed little or no activity. Interestingly the corresponding esters **44a**, **47a**, **50a**, and **52a**, as predicted on the basis of lipophilicity, were quite potent inhibitors. Inclusion of an uncharged hydroxyl group as a hydrogen bond donor were likewise disappointing. For example the hydrocarbon **3a** is 20 times as potent as the alcohol **6a**. Attachment of the hydroxyl group to the end of a long lipophilic chain as shown in **16a**, **17a**, and **18a** led as expected to potent inhibitors of LTB_4 synthesis with some evidence that the meta-substituted analogue **17a** was more potent than its isomers **16a** and **18a**. It should be noted however that the isosteric analogue **19a** in which the hydroxyl of **16a** was replaced with a methyl group was even more potent (IC_{50} = 9 nM).

A series of weakly basic analogues were synthesized in the hope of finding a structurally specific position for a hydrogen bond acceptor. A pyridine nitrogen was attached at the end of a long chain as in **5a** or closer to dihydrobenzofuranol ring as in **28a**, **29a**, or **30a**. In both cases the compounds were no more potent than predicted on the basis of lipophilicity alone. Likewise an aniline nitrogen such as **15a** resulted in a compound of predictable activity. Even the use of an ether linkage as a potential hydrogen bond acceptor as in **38a** resulted in a substantial loss of biological activity when compared to the isosteric hydrocarbon **37a**.

Another attempt to increase the potency of this series of compounds involved the attachment of heteroatoms directly to the dihydrobenzofuranol ring. As can be seen from a comparison of compounds **24a–27a** with sulfur as the heteroatom or **33a**, **39a**, and **40a** with oxygen as the heteroatom, the activity increased as the length of the side chain increased. However the comparison of compounds in which the heteroatom is attached directly to the 6-position of the dihydrobenzofuranol ring with isomeric compounds in which the heteroatom is at a distal position shows no change in activity can be attributed to this substitution. For example **4a** and **27a** show essentially identical activity and the same result is obtained by comparing **13a** and **40a**. The difference in activity between **4a** and **13a** on the one hand and **27a** and **40a** on the other is well accounted for by differences in lipophilicity.

The effect of steric congestion near the phenolic hydroxyl was addressed in two ways. In the first case steric bulk was increased by preparing the branched chain analogues **20a** and **56a**. Comparing the biological activity of **3a**, **56a**, and **20a**, it is apparent that increasing steric bulk at the 6-position results in a slight decrease in biological activity. However at the already sterically more encumbered 4-position, the 4-*tert*-butyl analogue **68** appears to retain the activity that would be predicted for this material on the basis of lipophilicity.

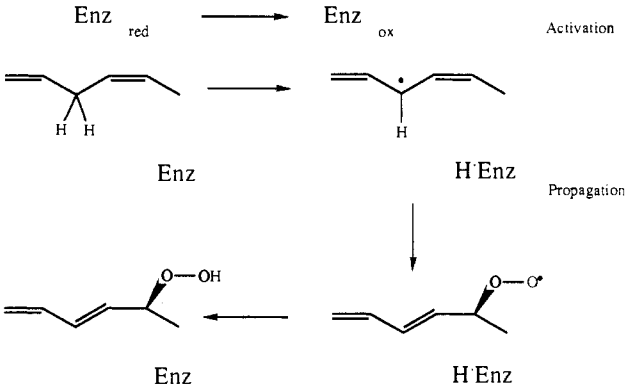

Figure 3. A schematic representation of a free-radical mechanism for 5-lipoxygenase.

Since the 4-position appeared less sensitive to steric congestion, a short series of 4,6-disubstituted 2,3-dihydro-5-benzofuranols was prepared. The biological activity of these materials is shown in Table III. As can be seen by comparing **64** to **65**, increasing lipophilicity continues to increase the potency of these compounds. A comparison of **3a**, **64**, **66**, and **70** showed the effect of steric bulk on the ability of these compounds to inhibit LTB_4 biosynthesis. A relatively small substituent such as the methyl group in **64** or a polarizable substituent such as the bromo group in **66** resulted in an increase in potency which is probably best explained on the basis of increased lipophilicity. However the more sterically demanding *tert*-butyl analogue **70** is substantially less active than either **64** or **66**, indicating that the biological activity is sensitive to the steric environment near the phenol.

Discussion

In this study we have shown that the 2,3-dihydro-5-benzofuranol ring system, although not a potent inhibitor of leukotriene biosynthesis in itself, can provide a useful template for the design of potent antioxidant-based inhibitors of leukotriene biosynthesis. Indeed **19a** is among the most potent inhibitors of leukotriene biosynthesis yet described. Furthermore, within a structural class the potency of a given analogue can be predicted on the basis of its overall calculated lipophilicity (log *P*). These results can be rationalized on the basis of a free-radical mechanism for 5-lipoxygenase (Figure 3).[38] In such a scenario the metabolism of arachidonic acid is initiated after an oxidative activation of the enzyme. Although the nature of this activation is unclear, evidence for other lipoxygenases[39] and 5-lipoxygenase[40,41] suggests that the addition of lipid

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hydroperoxide can eliminate the kinetic lag phase associated with this activation. One might expect an efficient antioxidant such as those synthesized in this study to reduce the activated enzyme species[42] directly or to intercept the pentadienyl or hydroperoxyl radical intermediates on the enzyme surface. The net result of any of these reductions is an enzyme left in an improper oxidation state to continue the free radical chain process.

The linear dependence of the log of the IC_{50} on the log of the partition coefficient is best interpreted as resulting from the partitioning of the inhibitor between free solution and the cell membrane. Recent evidence[43] suggests that upon activation the 5-lipoxygenase enzyme migrates from the cytosol to the membrane where metabolism of arachidonic acid takes place. Since an increase in lipophilicity would increase the concentration of inhibitor present in the cell membrane, it would seem reasonable that the apparent in vitro activity would increase with increasing lipophilicity. What emerges then is a picture of this class of antioxidant-based inhibitors of leukotriene biosynthesis in which the observed inhibition is dependent on the intrinsic ability of the antioxidant to reduce the enzyme and on the fraction of the inhibitor that is partitioned into the membrane. A similar phenomenon has been described[44] in a completely nonenzymatic system for the inhibition of the free-radical oxidation of linoleic acid with antioxidants in micelles. It is likely that this effect of lipophilicity on the inhibition of leukotriene biosynthesis will be general for all classes of 5-lipoxygenase inhibitors.

Experimental Section

All reagents and solvents were analytical reagent grade and were used without further purification unless otherwise noted. Tritiated LTB_4 ([^{3}H]LTB_4:[5,6,8,9,11,12,14,15-^{3}H]LTB_4 (223 Ci/mmol)) was obtained from Amersham International. LTB_4 was obtained from Dr. J. Rokach, Merck-Frosst, Montreal, Canada. The LTB_4 antiserum was obtained from Dr. R. N. Young, Merck-Frosst. Dry tetrahydrofuran refers to solvent freshly distilled from sodium benzophenone ketyl. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained on a Varian XL 200 instrument as solutions in deuteriochloroform using tetramethylsilane (TMS, δ 0.00) as internal standard. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed at the Merck analytical laboratory. Flash chromatography was performed essentially as described in the literature[45] using Kieselgel 60 (EM Science, 230–400 mesh) as stationary phase. Preparative HPLC refers to separations performed on a Waters PrepLC 500A instrument using Waters PrepPAK-500/SILICA cartridges as stationary phase. Analytical thin-layer chromatography (TLC) was performed with silica gel GHLF plates of 0.25-mm thickness obtained from Analtech Inc.

2,3-Dihydro-5-benzofuranol (1). The preparation of 1 has been described.[23,46,47] 1: mp 111–112 °C (lit.[23] mp 111–112 °C); ^{1}H NMR δ 6.73 (d, 1 H, J = 2 Hz), 6.65 (d, 1 H, J = 8 Hz), 6.54 (dd, 1 H, J = 8, 2 Hz), 4.56 (t, 2 H, J = 8 Hz), 4.52 (s, 1 H), 3.16 (t, 2 H, J = 8 Hz).

2,3-Dihydro-6-propen-3-yl-5-benzofuranol (2a) and 2,3-Dihydro-4-propen-3-yl-5-benzofuranol (2b). A. Allylation of 1. To a mechanically stirred mixture of 1 (35.00 g, 257 mmol) and anhydrous potassium carbonate (175.00 g, 1.27 mol) in acetone (750 mL) was added allyl bromide (63 mL, 88.0 g, 728 mmol) and the mixture heated to reflux for 16 h. The reaction mixture was allowed to cool, and the salts were removed by filtration. The filtrate was concentrated and distilled to give the allyl ether (41.40 g, 92%): bp 102 °C (0.9 mmHg).

B. Thermal Claisen Rearrangement of the Allyl Ether. The allyl ether (3.50 g, 19.8 mmol) was heated to 200 °C under nitrogen until starting material was consumed by TLC (20% ethyl acetate in hexane as eluant, 2 h). After cooling, the residue was purified by flash chromatography using 10% ethyl acetate in hexane as eluant to afford, in order of elution, **2b** (0.800 g, 23%) and **2a** (1.400 g, 40%). **2a**: ^{1}H NMR δ 6.73 (s, 1 H), 6.55 (s, 1 H), 5.97 (m, 1 H), 5.18 (m, 1 H), 5.12 (m, 1 H), 4.65 (br s, 1 H), 4.51 (t, 2 H, J = 9 Hz), 3.34 (br d, 2 H, J = 7 Hz), 3.15 (t, 2 H, J = 9 Hz). **2b**: ^{1}H NMR δ 6.59 (d, 1 H, J = 8 Hz), 6.53 (d, 1 H, J = 8 Hz), 5.98 (m, 1 H), 5.13 (br s, 1 H), 5.06 (br d, 1 H, J = 6 Hz), 4.53 (t + br s, 3 H, J = 9 Hz), 3.36 (br d, 2 H, J = 6 Hz), 3.13 (t, 2 H, J = 9 Hz).

C. Lewis Acid Catalyzed Claisen Rearrangement of the Allyl Ether. To a −20 °C solution of boron trichloride (1 M in methylene chloride, 240 mL, 240 mmol) was added dropwise a solution of the allyl ether (38.50 g, 219 mmol) in methylene chloride (400 mL). Upon completion of the addition the reaction mixture was allowed to slowly warm to room temperature over 2 h and then carefully poured into ice water (1000 mL). The layers were separated, and the aqueous layer was reextracted with methylene chloride (2 × 200 mL). The combined organic layers were washed sequentially with water (500 mL) and 20% NaCl (500 mL). After drying (Na_2SO_4), hexane (400 mL) was added and the mixture concentrated on a hot plate to a total volume of 300 mL. The mixture was allowed to crystallize in the freezer. Filtration afforded **2a** (27.19 g). The mother liquors (8.5 g) were purified by preparative HPLC using 10% ethyl acetate in hexane as eluant to give in order of elution **2b** (1.38 g, 4%), **2a** (3.56 g, total yield 30.75 g, 80%), and 1 (1.36 g, 5%).

2,3-Dihydro-6-propyl-5-benzofuranol (3a). A solution of **2a** (10.00 g, 56.8 mmol) in absolute ethanol (100 mL) was hydrogenated over 10% palladium-on-carbon catalyst (0.500 g) at 3 atm pressure. After the requisite amount of hydrogen had been taken up (30 min) the catalyst was removed by filtration through Celite and the fitrate concentrated. Preparative HPLC using 10% ethyl acetate in hexane as eluant gave **3a** (8.15 g, 81%): ^{1}H NMR δ 6.66 (s, 1 H), 6.56 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 4.26 (s, 1 H), 3.15 (t, 2 H, J = 8 Hz), 2.63 (t, 2 H, J = 8 Hz), 1.60 (m, 2 H), 0.98 (t, 3 H, J = 8 Hz).

2,3-Dihydro-4-propyl-5-benzofuranol (3b). In an analogous manner to that described above for **3a**, **2b** (0.300 g, 1.70 mmol) was hydrogenated over 10% palladium on carbon (0.020 g) to give **3b** (0.210 g, 69%): ^{1}H NMR δ 6.61 (d, 1 H, J = 6 Hz), 6.58 (d, 1 H, J = 6 Hz), 4.62 (t, 2 H, J = 8 Hz), 3.01 (t, 2 H, J = 8 Hz), 2.63 (t, 2 H, J = 6 Hz), 1.68 (m, 2 H), 1.05 (t, 3 H, J = 6 Hz).

2,3-Dihydro-6-(3-thiophenoxypropyl)-5-benzofuranol (4a). To a solution of **2a** (0.600 g, 3.40 mmol) in thiophenol (1.5 mL) was added AIBN (0.150 g) and the mixture heated at 90 °C for 8 h. The mixture was cooled and the excess thiophenol removed under reduced pressure. Flash chromatography using 20% ethyl acetate in hexane as eluant gave in order of elution **2a** (0.110 g, 18%) and **4a** (0.610 g, 63%). **4a**: ^{1}H NMR δ 7.50–7.10 (m, 5 H), 6.68 (s, 1 H), 6.54 (s, 1 H), 4.68 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 3.14 (t, 2 H, J = 8 Hz), 2.96 (t, 2 H, J = 6 Hz), 2.72 (t, 2 H, J = 6 Hz), 1.96 (m, 2 H).

2,3-Dihydro-4-(3-thiophenoxypropyl)-5-benzofuranol (4b). In a manner analogous to that described for **4a**, **2b** (1.00 g, 5.67 mmol) was treated with thiophenol (3 mL) and AIBN (0.260 g) to give **4b** (0.900 g, 56%) and recovered **2b** (0.11 g, 11%). **4b**: ^{1}H NMR δ 7.36–7.14 (m, 5 H), 6.55 (d, 1 H, J = 6 Hz), 6.50 (d, 1 H, J = 6 Hz), 4.66 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 3.11 (t, 2 H, J = 8 Hz), 2.97 (t, 2 H, J = 6 Hz), 2.74 (t, 2 H, J = 6 Hz), 1.95 (m, 2 H).

2,3-Dihydro-6-[3-[3-(methylthio)pyridyl]propyl]-5-benzofuranol (5a). In a manner analogous to that described for **4a**, **2a** (0.375 g, 2.13 mmol) was treated with 3-(methylthio)pyridine[21] (1.05 g, 8.38 mmol) and AIBN (0.088 g) to afford **5a** (0.402 g, 63%): ^{1}H NMR δ 8.56 (s, 1 H), 8.51 (d, 1 H, J = 5 Hz), 7.78 (d, 1 H, J

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(47) Alternatively 1 can be prepared by catalytic hydrogenation of 5-hydroxybenzofuran. For the preparation of 5-hydroxybenzofuran, see: Rene, L.; Royer, R. *Bull. Chem. Soc. Fr.* **1973**, 2355.

= 6 Hz), 7.34 (dd, 1 H, J = 7, 5 Hz), 6.74 (s, 1 H), 6.50 (s, 1 H), 5.12 (br s, 1 H), 4.50 (t, 2 H, J = 7 Hz), 3.70 (s, 2 H), 3.12 (t, 2 H, J = 7 Hz), 2.66 (t, 2 H, J = 6 Hz), 2.45 (t, 2 H, J = 6 Hz), 1.88 (quintet, 2 H, J = 6 Hz).

2,3-Dihydro-4-[3-[3-(methylthio)pyridyl]propyl]-5-benzofuranol (5b). In a manner analogous to that described for **4a**, **2b** (0.350 g, 1.99 mmol) was treated with 3-(methylthio)pyridine[21] (0.97 g, 7.76 mmol) and AIBN (0.082 g) to afford **5b** (0.400 g, 67%): ^{1}H NMR δ 8.56 (s, 1 H), 8.49 (d, 1 H, J = 4 Hz), 7.77 (d, 1 H, J = 6 Hz), 7.36 (dd, 1 H, J = 6, 4 Hz), 6.63 (d, 1 H, J = 8 Hz), 6.49 (d, 1 H, J = 8 Hz), 4.56 (t, 2 H, J = 8 Hz), 3.72 (s, 2 H), 3.10 (t, 2 H, J = 8 Hz), 2.86 (t, 2 H, J = 6 Hz), 2.45 (t, 2 H, J = 6 Hz), 1.86 (quintet, 2 H, J = 6 Hz).

2,3-Dihydro-6-(3-hydroxypropyl)-5-benzofuranol (6a). To a 5 °C solution of **2a** (15.00 g, 88.0 mmol) in ether (125 mL) was added neat borane–methyl sulfide (5.4 mL, 4.33 g, 56.9 mmol) and the mixture allowed to stir at room temperature for 1 h. Absolute ethanol (100 mL) was added followed by 2.5 N NaOH (155 mL). The solution was cooled to 5 °C and 30% hydrogen peroxide (14.1 mL) was added dropwise. The resulting mixture, which had warmed to 25–30 °C during the peroxide addition, was allowed to stir for 30 min. The reaction was then worked up by diluting with water (300 mL) and extracting with ether (3 × 200 mL). The combined ether extracts were washed sequentially with water and 20% NaCl, dried ($MgSO_4$), and concentrated. Recrystallization from chloroform gave **6a** (5.08 g). Chromatography of the mother liquors using 40% ethyl acetate in hexane as eluant afforded additional **6a** (2.02 g, total yield 7.08 g, 41%): ^{1}H NMR δ 6.75 (s, 1 H), 6.56 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 3.66 (t, 2 H, J = 6 Hz), 3.17 (t, 2 H, J = 8 Hz), 2.74 (t, 2 H, J = 8 Hz), 1.86 (m, 2 H).

2,3-Dihydro-4-(3-hydroxypropyl)-5-benzofuranol (6b). In a manner analogous to that described above for **6a**, **2b** (3.00 g, 16.8 mmol) was treated with borane–methyl sulfide (1.08 mL, 0.865 g, 11.3 mmol) to afford **6b** (1.81 g, 55%): ^{1}H NMR δ 6.73 (d, 1 H, J = 8 Hz), 6.63 (d, 1 H, J = 8 Hz), 4.09 (t, 2 H, J = 6 Hz), 4.00 (d, 1 H, J = 8 Hz), 3.93 (d, 1 H, J = 4 Hz), 2.87 (t, 2 H, J = 6 Hz), 2.67 (t, 2 H, J = 6 Hz), 2.03 (m, 2 H).

2,3-Dihydro-6-(3-hydroxypropyl)-5-(benzyloxy)benzofuran (7a). Sodium hydride (60% dispersion in mineral oil, 0.678 g, 16.95 mmol) was washed with petroleum ether and then suspended in dry tetrahydrofuran (15 mL) and cooled in an ice bath. A solution of **6a** (3.00 g, 15.4 mmol) in dry tetrahydrofuran (16 mL) was added dropwise to the sodium hydride suspension. When the hydrogen evolution had ceased, benzyl bromide (3.03 g, 17.7 mmol) was added dropwise and the mixture allowed to stir at room temperature overnight. The reaction was diluted with hexane (20 mL) and filtered, and the filtrate was concentrated. The residue was taken up in ether (50 mL), washed with 2 N HCl and brine, dried ($MgSO_4$), and concentrated to give **7a** (3.97 g, 90%): ^{1}H NMR δ 7.50–7.30 (m, 5 H), 6.86 (s, 1 H), 6.66 (s, 1 H), 5.04 (s, 2 H), 4.57 (t, 2 H, J = 8 Hz), 4.60 (t, 1 H, J = 6 Hz), 4.56 (t, 1 H, J = 6 Hz), 3.18 (t, 2 H, J = 8 Hz), 2.72 (t, 2 H, J = 6 Hz), 1.81 (quintet, 2 H, J = 6 Hz).

2,3-Dihydro-4-(3-hydroxypropyl)-5-(benzyloxy)benzofuran (7b). In a manner analogous to that described above for **7a**, **6b** (1.44 g, 7.41 mmol) was alkylated with benzyl bromide (1.50 g, 11.66 mmol) to give **7b** (1.81 g, 86%): ^{1}H NMR δ 7.50–7.30 (m, 5 H), 6.70 (d, 1 H, J = 8 Hz), 6.58 (d, 1 H, J = 8 Hz), 5.02 (s, 2 H), 4.58 (t, 2 H, J = 8 Hz), 3.56 (t, 2 H, J = 6 Hz), 3.18 (t, 2 H, J = 8 Hz), 2.74 (t, 2 H, J = 6 Hz), 1.94 (quintet, 2 H, J = 8 Hz).

2,3-Dihydro-6-(3-hydroxypropyl)-5-(benzyloxy)benzofuran Tosylate (8a). To a 0 °C solution of **7a** (1.16 g, 4.07 mmol) in dry pyridine (3 mL) was added *p*-toluenesulfonyl chloride (0.707 g, 3.72 mmol) and the mixture allowed to warm to room temperature and stir for 1 h. The reaction mixture was poured into ice water (25 mL) and acidified with 2 N HCl. The resulting precipitate was collected by filtration, washed with water (2 × 5 mL), and vacuum dried to give **8a** (1.28 g, 72%): ^{1}H NMR δ 7.77 (d, 2 H, J = 8 Hz), 7.42–7.35 (m, 5 H), 7.32 (d, 2 H, J = 8 Hz), 6.79 (s, 1 H), 6.46 (s, 1 H), 5.00 (s, 2 H), 4.53 (t, 2 H, J = 8 Hz), 4.05 (t, 2 H, J = 6 Hz), 3.15 (t, 2 H, J = 8 Hz), 2.64 (t, 2 H, J = 6 Hz), 2.46 (s, 3 H), 1.92 (quintet, 2 H, J = 6 Hz).

2,3-Dihydro-4-(3-hydroxypropyl)-5-(benzyloxy)benzofuran Tosylate (8b). In a manner analogous to that described for **8a**, **7b** (1.64 g, 5.71 mmol) was treated with *p*-toluenesulfonyl chloride (1.19 g, 6.24 mmol) to give **8b** (1.65 g, 66%): ^{1}H NMR δ 7.72 (d, 2 H, J = 8 Hz), 7.34 (m, 5 H), 7.30 (d, 2 H, J = 8 Hz), 6.64 (d, 1 H, J = 8 Hz), 6.53 (d, 1 H, J = 8 Hz), 4.97 (s, 2 H), 4.50 (t, 2 H, J = 8 Hz), 4.04 (t, 2 H, J = 6 Hz), 3.10 (t, 2 H, J = 6 Hz), 2.92 (quintet, 2 H, J = 6 Hz).

4-[2,3-Dihydro-5-(benzyloxy)benzofuran-6-yl]butyronitrile (9a). A mixture of **8a** (1.28 g, 2.91 mmol) and sodium cyanide (0.300 g, 6.12 mmol) in 95% ethanol (5 mL) and dimethylformamide (1 mL) was heated to reflux until the starting tosylate was no longer present by TLC (30% ethyl acetate in hexane as eluant). The reaction was worked up by pouring into water and extracting with ethyl acetate. The organic extract was washed with water and 20% NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using 25% ethyl acetate in hexane as eluant to give **9a** as an oil (0.770 g, 85%): ^{1}H NMR δ 7.34–7.20 (m, 5 H), 6.84 (s, 1 H), 6.61 (s, 1 H), 5.04 (s, 2 H), 4.56 (t, 2 H, J = 8 Hz), 3.18 (t, 2 H, J = 8 Hz), 2.75 (t, 2 H, J = 6 Hz), 2.30 (t, 2 H, J = 6 Hz), 1.95 (quintet, 2 H, J = 6 Hz).

4-(2,3-Dihydro-5-hydroxybenzofuran-6-yl)butyronitrile (10a). A portion of the above oil (0.290 g, 1.01 mmol) in absolute ethanol (2.0 mL) was deprotected by hydrogenation over 10% palladium on carbon (0.020 g) at atmospheric pressure. The catalyst was removed by filtration and the filtrate concentrated and chromatographed with 20% ethyl acetate in hexane as eluant to give **10a** (0.159 g, 78%): ^{1}H NMR δ 6.64 (s, 1 H), 6.54 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 3.16 (t, 2 H, J = 8 Hz), 2.72 (t, 2 H, J = 6 Hz), 2.54 (t, 2 H, J = 6 Hz), 1.98 (m, 2 H).

4-[2,3-Dihydro-5-(benzyloxy)benzofuran-6-yl]butyric Acid (11a). To a solution of potassium hydroxide (85%, 0.724 g, 10.00 mmol) in water (2 mL) and ethanol (2 mL) was added **9a** (0.290 g, 1.01 mmol) and the mixture heated to reflux for 18 h. The reaction mixture was cooled, acidified with 2 N HCl, and extracted with ether. The extract was dried ($MgSO_4$) and concentrated to a solid (0.140 g). Recrystallization from hexane/ether gave pure **11a** (0.100 g, 32%): mp 121–122 °C; ^{1}H NMR δ 7.46–7.30 (m, 5 H), 6.81 (s, 1 H), 6.62 (s, 1 H), 5.00 (s, 2 H), 4.54 (t, 2 H, J = 8 Hz), 4.18 (t, 2 H, J = 8 Hz), 2.70 (t, 2 H, J = 6 Hz), 2.47 (t, 2 H, J = 6 Hz) 1.96 (quintet, 2 H, J = 6 Hz).

4-(2,3-Dihydro-5-hydroxybenzofuran-6-yl)butyric Acid (12a). To a solution of **11a** (0.100 g, 0.32 mmol) in absolute ethanol (1 mL) was added 10% palladium on carbon (0.015 g) and the mixture hydrogenated at atmospheric pressure overnight. The catalyst was removed by filtration and the filtrate concentrated to give **12a** (0.068 g, 98%): ^{1}H NMR δ 6.70 (s, 1 H), 6.54 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 3.16 (t, 2 H, J = 8 Hz), 2.62 (t, 2 H, J = 6 Hz), 2.44 (t, 2 H, J = 6 Hz), 1.92 (m, 2 H).

2,3-Dihydro-6-(3-phenoxypropyl)-5-benzofuranol (13a). A. Alkylation of Sodium Phenoxide with 8a. A solution of **8a** (0.440 g, 1.01 mmol) in dry dimethylformamide (1 mL) was added to a solution of sodium phenoxide (0.140 g, 1.20 mmol) and the mixture heated to 80 °C for 3 h. The reaction mixture was cooled, poured into water, and extracted with ether. The ether extracts were washed sequentially with water and 20% NaCl, dried (Na_2SO_4), and concentrated. Flash chromatography gave a purified benzyl ether (0.210 g, mp 81–82 °C) which was directly deprotected as described above for **12a** to give **13a** (0.140 g, 52%): ^{1}H NMR δ 7.28 (m, 2 H), 6.95 (m, 3 H), 6.71 (s, 1 H), 6.57 (s, 1 H), 5.19 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 3.99 (t, 2 H, J = 6 Hz), 3.15 (t, 2 H, J = 8 Hz), 2.78 (t, 2 H, J = 6 Hz), 2.09 (m, 2 H).

B. Alkylation of 22 with Phenoxypropyl Iodide. To a −78 °C solution of **22** (18.20 g, 70.44 mmol) in dry tetrahydrofuran (350 mL) was added dropwise a solution of *tert*-butyllithium (1.7 M in hexane, 83 mL, 141 mmol) over 20 min. The mixture was allowed to stir at −78 °C for 10 min and then a solution of phenoxypropyl iodide[48] (20.2 g, 77.47 mmol) in tetrahydrofuran (80 mL) was added rapidly by syringe. The mixture was allowed to warm to room temperature and stir for 3 h and then poured into 20% NaCl (1000 mL). Ether (500 mL) was added, and the layers were separated. The aqueous layer was reextracted with ether (2 × 300 mL), and the combined extracts were washed with 20%

(48) Phenoxypropyl iodide was prepared from the commercially available bromide by treatment with sodium iodide (1.5 equiv) in acetone. Yield: 76% bp 100–102 °C (0.4 mmHg).

NaCl (500 mL), dried ($MgSO_4$), and concentrated. The residue was taken up in methanol (750 mL), concentrated HCl (15 mL) was added, and the mixture was allowed to stir overnight at room temperature. Concentration of the methanol to a total volume of 200 mL, followed by cooling in an ice bath, gave **13a** (5.80 g) as an off white solid. The mother liquors were concentrated, taken up in ethyl acetate, washed with 5% $NaHCO_3$, and dried ($MgSO_4$). The ethyl acetate extract was concentrated and chromatographed with 0.5% ethyl acetate in methylene chloride as eluant to give **13a** (4.00 g, total yield 9.80 g, 52%).

2,3-Dihydro-4-(3-phenoxypropyl)-5-benzofuranol (13b). In a manner analogous to that described above for **13a**, sodium phenoxide (0.167 g, 1.44 mmol) was alkylated with **8b** (0.500 g, 1.20 mmol) and then deprotected to give **13b** (0.195 g, 50%): ^1H NMR δ 7.30–7.20 (m, 2 H), 7.00–6.86 (m, 3 H), 6.65 (d, 1 H, J = 6 Hz), 6.48 (d, 1 H, J = 6 Hz), 5.05 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 3.98 (t, 2 H, J = 6 Hz), 3.12 (t, 2 H, J = 8 Hz), 2.80 (t, 2 H, J = 6 Hz), 2.08 (m, 2 H).

***N*-Phenyl-3-[2,3-dihydro-5-(benzyloxy)benzofuran-6-yl]propylamine (14a).** To a −78 °C solution of lithium anilide, prepared from aniline (0.217 g, 2.33 mmol) and *n*-butyllithium (1.6 M in hexane, 1.46 mL, 2.33 mmol), in tetrahydrofuran (2 mL) was added a solution of **8a** (0.980 g, 2.23 mmol). Dimethyl sulfoxide (0.1 mL) was added and the mixture was allowed to stir at room temperature for 1 h. The reaction mixture was poured into water and extracted with ether (2×). The extracts were dried ($MgSO_4$) and concentrated to afford **14a** (0.570 g, 71%): ^1H NMR δ 7.44–7.22 (m, 5 H), 7.06 (t, 2 H, J = 8 Hz), 6.76 (s, 1 H), 6.58 (s, 1 H), 6.58 (t, 1 H, J = 8 Hz), 6.36 (d, 1 H, J = 8 Hz), 4.93 (s, 2 H), 4.46 (t, 2 H, J = 8 Hz), 3.70–3.50 (br s, 1 H), 3.10 (t, 2 H, J = 8 Hz), 3.05 (t, 2 H, J = 6 Hz), 2.65 (t, 2 H, J = 6 Hz), 1.82 (quintet, 2 H, J = 6 Hz).

***N*-Phenyl-3-(2,3-dihydro-5-hydroxybenzofuran-6-yl)propylamine (15a).** A solution of **14a** (0.800 g, 2.22 mmol) in absolute ethanol (5 mL) containing acetic acid (1 mL) was hydrogenated over 10% palladium on carbon (0.040 g) at 3 atm for 8 h. The catalyst was removed by filtration and the filtrate diluted with water (10 mL) and ether (10 mL). The mixture was neutralized with solid $NaHCO_3$, and the layers were separated. The aqueous layer was reextracted with ether (4 × 10 mL), and the combined ether extracts were dried ($MgSO_4$) and concentrated. Flash chromatography using 25% ethyl acetate in hexane as eluant afforded **15a** (0.280 g, 47%): ^1H NMR δ 7.20 (m, 2 H), 6.81 (m, 1 H), 6.74 (s, 1 H), 6.70 (br s, 2 H, $W_{0.5}$ = 6 Hz), 6.54 (s, 1 H), 4.62 (t, 2 H, J = 8 Hz), 3.19 (t, 2 H, J = 8 Hz), 3.08 (t, 2 H, J = 6 Hz), 2.76 (t, 2 H, J = 6 Hz), 1.96 (m, 2 H).

***N*-Phenyl-3-(2,3-dihydro-5-hydroxybenzofuran-4-yl)propylamine (15b).** As described above for **14a**, **8b** (1.08 g, 2.46 mmol) was treated with lithium anilide and deprotected to give **15b** (0.280 g, 42%): ^1H NMR δ 7.15–7.05 (m, 2 H), 6.82 (t, 1 H, J = 8 Hz), 6.72 (dd, 2 H, J = 6, 1 Hz), 6.58 (d, 1 H, J = 6 Hz), 6.51 (d, 1 H, J = 6 Hz), 4.55 (t, 2 H, J = 8 Hz), 3.12 (m, 2 H), 2.80 (t, 2 H, J = 8 Hz), 1.97 (m, 2 H).

2,3-Dihydro-6-[3-[4-(2-hydroxyethyl)phenoxy]propyl]-5-benzofuranol (16a). To a solution of 4-hydroxyphenethyl alcohol (0.249 g, 1.80 mmol) in dry tetrahydrofuran (3 mL) was added *n*-butyllithium (1.6 M in hexane, 1.13 mL, 1.85 mmol) and the mixture allowed to stir for 10 min. The solvent was removed under reduced pressure and the residue resuspended in dimethyl sulfoxide (3 mL) containing tetramethylethylenediamine (0.45 mL, 3 mmol). To the resulting solution was added **8a** (0.657 g, 1.50 mmol) and the mixture stirred at room temperature for 16 h. The mixture was poured into water (50 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$), concentrated, and purified by flash chromatography (40% ethyl acetate in hexane as eluant) to give a solid (0.500 g, mp 101–102 °C). This material was hydrogenated as a solution in ethanol (10 mL) over 10% palladium on carbon (0.035 g). After filtration and concentration the crude hydrogenation product was recrystallized from ethyl acetate/hexane to give **16a** (0.198 g, 42%): ^1H NMR δ 7.16 (d, 2 H, J = 10 Hz), 6.87 (d, 2 H, J = 10 Hz), 6.70 (s, 1 H), 6.56 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 3.97 (t, 2 H, J = 6 Hz), 3.84 (t, 2 H, J = 6 Hz), 3.14 (t, 2 H, J = 8 Hz), 2.9–2.7 (m, 4 H), 2.18 (s, 1 H), 2.08 (m, 2 H).

2,3-Dihydro-6-[3-[3-(2-hydroxyethyl)phenoxy]propyl]-5-benzofuranol (17a). In a manner analogous to that described for **16a**, **8a** (0.657 g, 1.50 mmol) was treated with the monolithium salt of 3-hydroxyphenethyl alcohol and deprotected to afford **17a** (0.210 g, 44%): ^1H NMR δ 7.24 (s, 1 H), 6.84–6.72 (m, 3 H), 6.70 (s, 1 H), 6.55 (s, 1 H), 4.50 (t, 2 H, J = 8 Hz), 3.98 (t, 2 H, J = 6 Hz), 3.86 (t, 2 H, J = 6 Hz), 3.14 (t, 2 H, J = 8 Hz), 2.84 (t, 2 H, J = 6 Hz), 2.76 (t, 2 H, J = 6 Hz), 2.06 (m, 2 H).

2,3-Dihydro-6-[3-[2-(2-hydroxyethyl)phenoxy]propyl]-5-benzofuranol (18a). In a manner analogous to that described for **16a**, **8a** (0.657 g, 1.5 mmol) was treated with the monolithium salt of 2-hydroxyphenethyl alcohol and deprotected to afford **18a** (0.040 g, 8%): ^1H NMR δ 7.30–7.14 (m, 2 H), 6.93 (d, 1 H, J = 8 Hz), 6.86 (d, 1 H, J = 8 Hz), 6.70 (s, 1 H), 6.58 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 4.03 (t, 2 H, J = 6 Hz), 3.90 (t, 2 H, J = 6 Hz), 3.16 (t, 2 H, J = 8 Hz), 2.97 (t, 2 H, J = 6 Hz), 2.80 (t, 2 H, J = 6 Hz), 2.6–2.3 (br s, 2 H, $W_{0.5}$ = 30 Hz), 2.10 (m, J = 2 Hz).

2,3-Dihydro-6-[3-(4-propylphenoxy)propyl]-5-benzofuranol (19a). In a manner analogous to that described for **16a**, **8a** (0.438 g, 1.0 mmol) was treated with the lithium salt of 4-propylphenol and deprotected to afford **19a** (0.015 g, 5%): ^1H NMR δ 7.10 (d, 2 H, J = 10 Hz), 6.88 (d, 2 H, J = 10 Hz), 6.72 (s, 1 H), 6.58 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 3.98 (t, 2 H, J = 6 Hz), 3.16 (t, 2 H, J = 8 Hz), 2.78 (t, 2 H, J = 6 Hz), 2.54 (t, 2 H, J = 6 Hz), 2.08 (m, 2 H), 1.60 (t, 2 H, J = 6 Hz), 0.94 (t, 3 H, J = 6 Hz).

2,3-Dihydro-6-*tert*-butyl-5-benzofuranol (20a). To a solution of 1 (1.00 g, 7.35 mmol) and *tert*-butyl alcohol (0.82 g, 11.00 mmol) in benzene (20 mL) was added concentrated H_2SO_4 (0.20 mL) and the mixture heated to 60 °C. After 1 h an additional portion of *tert*-butyl alcohol (0.82 g, 11.00 mmol) and concentrated H_2SO_4 (0.2 mL) was added and heating continued for another 1.5 h. At this point starting material had been consumed and two products were apparent by TLC (3:1 methylene chloride/hexane). The reaction mixture was diluted with ether (30 mL) and quenched with 5% $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was back-extracted with an additional portion of ether (25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography using 3:1 methylene chloride/hexane as eluant afforded in order of elution **20a** (0.600 g, 43%) and 2,3-dihydro-7-*tert*-butyl-5-benzofuranol (**20c**, 0.350 g, 25%). **20a**: mp 146.5–148 °C; ^1H NMR δ 6.74 (s, 1 H), 6.55 (s, 1 H), 4.50 (t, 2 H, J = 8 Hz), 4.39 (s, 1 H), 3.12 (t, 2 H, J = 8 Hz), 1.37 (s, 9 H). **20c**: mp 107–109 °C; ^1H NMR δ 6.54 (br s, 2 H), 4.50 (t, 2 H, J = 8 Hz), 4.30 (s, 1 H), 3.09 (t, 2 H, J = 8 Hz), 1.31 (s, 9 H). Anal. ($C_{12}H_{16}O_2$) C, H.

2,3-Dihydro-6-(phenylmethyl)-5-benzofuranol (21a). In a manner analogous to that described for **20a**, compound 1 (1.00 g, 7.35 mmol) was treated with benzyl alcohol (0.874 g, 8.09 mmol) in benzene (25 mL) containing H_2SO_4 (0.20 g) to afford, after flash chromatography (15% ethyl acetate in hexane as eluant) and crystallization from hexane/methylene chloride, compound **21a** (0.100 g, 6%): ^1H NMR δ 7.36–7.18 (m, 5 H), 6.69 (s, 1 H), 6.58 (s, 1 H), 4.54 (t, 2 H, J = 9 Hz), 4.25 (s, 1 H), 3.95 (s, 2 H), 3.15 (t, 2 H, J = 9 Hz).

2,3-Dihydro-6-bromo-5-benzofuranol (22). A 3-L three-neck flask fitted with a mechanical stirrer was charged with 1 (100.0 g, 735 mmol) in methylene chloride (1500 mL) and a solution of bromine (122 g, 763 mmol) in dichloromethane (total volume 250 mL) was added dropwise over 1.5 h. Upon completion of the addition the mixture was allowed to stir at room temperature and then worked up in two batches as follows. Approximately half of the reaction mixture was poured into 5% $NaHCO_3$ (2000 mL) and the resulting mixture allowed to stir for 30–60 min. The layers were separated, and the aqueous layer was extracted with methylene chloride (500 mL). The combined organic extracts were washed with 5% $NaHSO_3$ (500 mL), dried with $MgSO_4$, and filtered and all the organic fractions combined. The product crystallized upon concentration and was therefore triturated in small batches to afford **22** (103.38 g, 76.9%) as a tan solid: mp 115–117 °C; ^1H NMR δ 6.87 (s, 1 H), 6.86 (s, 1 H), 5.11 (br s, 1 H), 4.55 (t, 2 H, J = 8 Hz), 3.13 (t, 2 H, J = 8 Hz). Anal. ($C_8H_7BrO_2$) C, H, Br.

2,3-Dihydro-6-bromo-5-benzofuranol Methoxymethyl Ether (23). A flame-dried 1000-mL three-neck flask fitted with an internal thermometer, a magnetic stirrer, and a 250-mL dropping funnel was charged with sodium hydride (60% dispersion

in mineral oil, 11.17 g, 279 mmol) and dimethylformamide (dried over molecular sieves, 200 mL). A solution of **22** (50.00 g, 233 mmol) in dimethylformamide (100 mL) was added dropwise such that the reaction temperature did not exceed 40 °C (addition time was approximately 30 min). When hydrogen evolution had ceased, an ice bath was added and chloromethyl methylether (22.47 g, 279 mmol) was added dropwise at 25 °C. Upon completion of the addition the reaction mixture was allowed to stir at room temperature for 2 h and then quenched by pouring into water (1000 mL). The mixture was extracted with ether (3 × 300 mL), and the combined organic extracts were washed sequentially with water (2 × 500 mL) and 20% NaCl (300 mL), dried (Na_2SO_4), and concentrated. Distillation afforded **23** (55.42 g, 91.9%) as a colorless liquid: bp 132–140 °C (0.2 mmHg); ^{1}H NMR δ 7.02 (s, 1 H), 6.96 (s, 1 H), 5.12 (s, 2 H), 4.56 (t, 2 H, J = 9 Hz), 3.54 (s, 3 H), 3.14 (t, 2 H, J = 9 Hz).

2,3-Dihydro-6-(phenylthio)-5-benzofuranol (24a). To a solution of **23** (3.00 g, 11.6 mmol) in dry tetrahydrofuran (50 mL) at −60 °C was added dropwise a solution of *n*-butyllithium (1.57 M in hexane, 8.25 mL, 13.0 mmol) and the mixture allowed to stir for 20 min. To the resulting white suspension was added dropwise a solution of diphenyl disulfide (4.00 g, 18.5 mmol) in tetrahydrofuran (20 mL) and the mixture allowed to stir for 20 min at −60 °C and then warmed to room temperature over 40 min. The reaction mixture was poured into water (150 mL) and extracted with ether (3 × 100 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The crude product (5.0 g) was purified by preparative HPLC using 10% ethyl acetate in hexane as eluant and then directly deprotected in methanol (40 mL) containing concentrated HCl (0.25 mL) at 50 °C for 3 h. Most of the methanol was removed in vacuo and the residue partitioned between ethyl acetate (75 mL) and water (25 mL). The organic extract was washed with an additional portion of water (25 mL), dried (Na_2SO_4), and concentrated. Flash chromatography using 10% ethyl acetate in hexane afforded **24a** (1.40 g, 49%). Recrystallization from hexane gave an analytical sample: ^{1}H NMR δ 7.28–7.10 (m, 5 H), 6.95 (s, 1 H), 6.93 (s, 1 H), 6.18 (s, 1 H), 4.56 (t, 2 H, J = 7 Hz), 3.24 (t, 2 H, J = 7 Hz).

2,3-Dihydro-6-[(phenylmethyl)thio]-5-benzofuranol (25a). In a manner analogous to that described for **24a**, **23** (1.00 g, 3.86 mmol) was alkylated with dibenzyl disulfide (1.32 g, 5.34 mmol) and deprotected to give **25a** (0.400 g, 40%): ^{1}H NMR δ 7.30–7.22 (m, 3 H), 7.16–7.10 (m, 2 H), 6.80 (s, 1 H), 6.74 (s, 1 H), 6.18 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 3.84 (s, 2 H), 3.18 (t, 2 H, J = 8 Hz).

2,3-Dihydro-6-[(phenylethyl)thio]-5-benzofuranol (26a). In a manner analogous to that described for **24a**, **23** (1.50 g, 5.79 mmol) was alkylated with diphenethyl disulfide (1.90 g, 6.93 mmol) and deprotected to give **26a** (0.240 g, 15%): ^{1}H NMR δ 7.24 (m, 5 H), 6.90 (s, 1 H), 6.88 (s, 1 H), 6.31 (s, 1 H), 4.55 (t, 2 H, J = 8 Hz), 3.21 (t, 2 H, J = 8 Hz), 2.90 (m, 4 H).

2,3-Dihydro-6-[(phenylpropyl)thio]-5-benzofuranol (27a). In a manner analogous to that described for **24a**, **23** (1.00 g, 3.86 mmol) was alkylated with diphenpropyl disulfide (1.62 g, 5.34 mmol) and deprotected to give **27a** (0.254 g, 23%): ^{1}H NMR δ 7.30–7.08 (m, 5 H), 6.84 (s, 1 H), 6.83 (s, 1 H), 6.16 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 3.19 (t, 2 H, J = 8 Hz), 2.76–2.64 (m, 4 H), 1.90 (quintet, J = 6 Hz).

2,3-Dihydro-6-(2-pyridylthio)-5-benzofuranol (28a). In a manner analogous to that described for **24a**, **23** (1.00 g, 3.86 mmol) was alkylated with di-2-pyridyl disulfide (1.39 g, 6.17 mmol) and deprotected to give **28a** (0.410 g, 43%): ^{1}H NMR δ 8.82 (s, 1 H), 8.40 (d, 1 H, J = 5 Hz), 7.55 (t, J = 5 Hz), 7.19–7.06 (m, 2 H), 6.98 (s, 1 H), 6.92 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 3.22 (t, 2 H, J = 8 Hz).

2,3-Dihydro-6-(3-pyridylthio)-5-benzofuranol (29a). In a manner analogous to that described for **24a**, **23** (0.62 g, 2.39 mmol) was alkylated with di-3-pyridyl disulfide[49] (0.732 g, 3.32 mmol) and deprotected to give **29a** (0.290 g, 50%): ^{1}H NMR δ 8.41 (br d, 1 H, J = 7 Hz), 7.16 (dd, 1 H, J = 5, 7 Hz), 6.96 (s, 1 H), 6.91 (s, 1 H), 6.24 (br s, 1 H), 4.58 (t, 2 H, J = 8 Hz), 3.25 (t, 2 H, J = 8 Hz).

2,3-Dihydro-6-(4-pyridylthio)-5-benzofuranol (30a). In a manner analogous to that described for **24a**, **23** (1.00 g, 3.86 mmol) was alkylated with di-4-pyridyl disulfide (1.18 g, 5.34 mmol) and deprotected to give **30a** (0.330 g, 35%): ^{1}H NMR δ 8.35 (dd, 2 H, J = 5, 1 Hz), 6.99 (s, 1 H), 6.92 (dd, 2 H, J = 5, 1 Hz), 6.88 (s, 1 H), 6.02 (br s, 1 H), 4.59 (t, 2 H, J = 9 Hz), 3.28 (t, 2 H, J = 9 Hz).

2,3-Dihydro-6-[3-(4-fluorophenoxy)propyl]-5-benzofuranol (31a). In a manner analogous to that described above for **13a**, **23** (6.78 g, 26.1 mmol) was converted to its lithium salt with *tert*-butyllithium (1.7 M in pentane, 33.3 mL, 56.6 mmol) and alkylated with (4-fluorophenoxy)propyl iodide[50] (7.33 g, 26.1 mmol). The crude alkylation product was deprotected to give **31a** (1.45 g, 19%): ^{1}H NMR δ 7.02–6.88 (m, 2 H), 6.88–6.78 (m, 2 H), 6.68 (s, 1 H), 6.55 (s, 1 H), 4.50 (t, 2 H, J = 8 Hz), 3.92 (t, 2 H, J = 6 Hz), 3.12 (t, 2 H, J = 8 Hz), 2.74 (t, 2 H, J = 6 Hz), 2.06 (m, 2 H).

2,3-Dihydro-6-[3-(4-chlorophenoxy)propyl]-5-benzofuranol (32a). In a manner analogous to that described above for **13a**, **23** (4.97 g, 19.18 mmol) was converted to its lithium salt with *tert*-butyllithium (1.7 M in pentane, 22.6 mL, 38.4 mmol) and alkylated with (4-chlorophenoxy)propyl iodide[50] (6.26 g, 21.1 mmol). The crude alkylation product was deprotected to give **32a** (2.45 g, 42%): ^{1}H NMR δ 7.16 (m, 2 H), 6.85 (m, 2 H), 6.70 (s, 1 H), 6.58 (s, 1 H), 4.92 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 3.98 (t, 2 H, J = 6 Hz), 3.18 (t, 2 H, J = 8 Hz), 2.77 (t, 2 H, J = 6 Hz), 2.10 (m, 2 H).

2,3-Dihydro-6-phenoxy-5-benzofuranol (33a). A mixture of **23** (1.00 g, 3.86 mmol), phenol (0.36 g, 3.86 mmol), and freshly ground potassium carbonate (1.60 g, 11.58 mmol) in dry pyridine (6 mL) was heated to 120 °C under nitrogen. Cupric oxide (0.316 g, 3.97 mmol) was added, the temperature raised to 150 °C, and the mixture allowed to stir for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate (50 mL) and filtered through Celite. The filtrate was washed sequentially with 2 N HCl (2 × 25 mL), 1 N NaOH (50 mL), and 20% NaCl (50 mL), dried (Na_2SO_4), and concentrated to a dark oil (0.87 g). The oil was taken up in methanol (25 mL) containing concentrated HCl (0.3 mL) and the methoxymethyl ether removed at 40 °C for 1 h. The reaction mixture was poured into 5% $NaHCO_3$ (150 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Flash chromatography using 10% ethyl acetate in hexane as eluant gave **33a** (0.325 g, 34%): ^{1}H NMR δ 7.38–7.26 (m, 5 H), 7.16–6.98 (m, 3 H), 6.91 (s, 1 H), 6.39 (s, 1 H), 5.13 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 3.18 (t, 2 H, J = 8 Hz).

2,3-Dihydro-5-hydroxybenzofuran-6-carboxaldehyde Methoxymethyl Ether (34). To a solution of **23** (34.50 g, 133 mmol) in dry tetrahydrofuran (325 mL) at −70 °C was added *n*-butyllithium (1.57 M in hexane, 95 mL, 149 mmol) dropwise such that the reaction temperature did not exceed −60 °C during the addition. The mixture was allowed to stir for 20 min at −70 °C and then dry dimethylformamide (42 mL) was added dropwise (T_{int} < −60 °C). The mixture was stirred for 1 h and then allowed to warm to 0 °C over 40 min. The mixture was poured into water (1000 mL) and, after stirring for 1 h, extracted with ether (3 × 500 mL). The combined extracts were washed with water (500 mL) and 20% NaCl (500 mL), dried ($MgSO_4$), and concentrated. Purification by preparative HPLC using 20% ethyl acetate in hexane as eluant gave **34** (19.32 g, 70%) as a yellow solid: mp 64–65 °C; ^{1}H NMR δ 10.41 (s, 1 H), 7.20 (s, 1 H), 7.13 (s, 1 H), 5.24 (s, 2 H), 4.59 (t, 2 H, J = 9 Hz), 3.53 (s, 3 H), 3.25 (t, 2 H, J = 9 Hz).

2,3-Dihydro-5,6-benzofurandiol 5-Methoxymethyl Ether (35). To a solution of **34** (1.50 g, 7.20 mmol) in methylene chloride (50 mL) was added *p*-nitroperoxybenzoic acid (2.64 g, 12.25 mmol) and the mixture refluxed under nitrogen for 24 h. The reaction mixture was cooled and concentrated, and the residue was taken up in ethyl acetate (100 mL). The solution was washed sequentially with 5% $NaHCO_3$ (3 × 50 mL), 5% Na_2SO_3 (2 × 50 mL), and 20% NaCl (50 mL), dried (Na_2SO_4), and concentrated to give a crude formate ester (1.42 g). The green oil was then taken

(49) Wolfgang, W.; Hell, P. M. *Liebigs Ann. Chem.* **1969**, *727*, 35.

(50) The *p*-fluorophenoxy iodide and *p*-chlorophenoxy iodide were prepared from the substituted phenols by treatment with 1,3-dibromopropane as described for **41** followed by displacement of the bromide with sodium iodide in acetone.

up in methanol (50 mL) and saponified with aqueous KOH (0.430 g in 2 mL water). After 1 h at room temperature, the methanol was removed and the residue diluted with water (50 mL). The aqueous solution was carefully acidified with 2 N HCl and then extracted with ethyl acetate (50 mL). The organic layer was washed with water (50 mL) and 5% Na_2SO_3 (2 × 50 mL), dried (Na_2SO_4), and concentrated to a dark oil. Flash chromatography using 20% ethyl acetate in hexane as eluant gave **35** (0.810 g, 57%) as a pale oil which darkened on standing: ^{1}H NMR δ 6.95 (s, 1 H), 6.45 (s, 1 H), 6.02 (s, 1 H), 5.11 (s, 2 H), 4.55 (t, 2 H, J = 9 Hz), 3.53 (s, 3 H), 3.11 (t, 2 H, J = 9 Hz).

2,3-Dihydro-6-(allyloxy)-5-benzofuranol Methoxymethyl Ether. To a mechanically stirred mixture of **35** (0.300 g, 1.44 mmol) and K_2CO_3 (1.80 g, 12.96 mmol) in acetone (60 mL) was added allyl bromide (0.436 g, 3.60 mmol) and the mixture heated to reflux for 4 h. The reaction mixture was cooled and filtered, and the filtrate was concentrated. The residue was taken up in ethyl acetate, washed with water, dried (Na_2SO_4), and concentrated to give a clear oil (0.364 g, quantitative).

2,3-Dihydro-6-(allyloxy)-5-benzofuranol Methoxymethyl Ether. To a mechanically stirred mixture of **35** (0.300 g, 1.44 mmol) and K_2CO_3 (1.80 g, 12.96 mmol) in acetone (60 mL) was added allyl bromide (0.436 g, 3.60 mmol) and the mixture heated to reflux for 4 h. The reaction mixture was cooled and filtered, and the filtrate was concentrated. The residue was taken up in ethyl acetate, washed with water, dried (Na_2SO_4), and concentrated to give a clear oil (0.364 g, quantitative).

2,3-Dihydro-6-(propyloxy)-5-benzofuranol (36a). The crude allyl ether (0.250 g, 1.01 mmol) was dissolved in absolute ethanol (15 mL) and hydrogenated at 3 atm over 10% palladium-on-carbon catalyst (0.030 g). After 20 min hydrogen uptake was complete and the reaction mixture was filtered through Celite, and the filtrate was concentrated to give the crude hydrogenation product (0.220 g) as a white solid. This material was taken up in methanol (25 mL) containing concentrated HCl (0.1 mL) and heated to 45 °C for 90 min. The solution was cooled and most of the methanol removed by concentration. The remaining material was taken up in ethyl acetate (50 mL), washed with 5% $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated. Flash chromatography using 10% ethyl acetate in hexane as eluant gave **36a** (0.130 g, 66%). Recrystallization from hexane gave an analytical sample: ^{1}H NMR δ 6.79 (s, 1 H), 6.42 (s, 1 H), 5.24 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 3.97 (t, 2 H, J = 7 Hz), 3.13 (t, 2 H, J = 8 Hz), 1.82 (sextet, 2 H, J = 7 Hz), 1.04 (t, 3 H, J = 7 Hz).

2,3-Dihydro-6-(butyloxy)-5-benzofuranol (37a). To a mechanically stirred mixture of **35** (0.350 g, 1.68 mmol) and K_2CO_3 (2.20 g, 15.9 mmol) in acetone (60 mL) was added butyl bromide (1.40 g, 10.00 mmol) and the mixture heated to reflux for 16 h. The reaction mixture was cooled and filtered, and the filtrate was concentrated. Flash chromatography (10% ethyl acetate in hexane as eluant) gave the methoxymethyl ether (0.364 g) which was deprotected as a solution in methanol (30 mL) containing concentrated HCl (0.5 mL) at 55 °C. The mixture was concentrated, diluted with water (50 mL), and extracted with ether (2 × 25 mL). The ether extracts were washed with 5% $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated. Flash chromatography afforded **37a** (0.240 g, 69%) as a white solid: ^{1}H NMR δ 6.79 (s, 1 H), 6.41 (s, 1 H), 5.24 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 4.00 (t, 2 H, J = 6 Hz), 3.13 (t, 2 H, J = 8 Hz), 1.80 (quintet, 2 H, J = 6 Hz), 1.49 (sextet, 2 H, J = 7 Hz), 0.98 (t, 3 H, J = 7 Hz).

2,3-Dihydro-6-(2-methoxyethoxy)-5-benzofuranol (38a). In a manner analogous to that described for **37a**, **35** (0.350 g, 1.68 mmol) was alkylated with 2-methoxyethyl bromide (0.580 g, 4.20 mmol) and deprotected to give **38a** (0.155 g, 44%): ^{1}H NMR δ 6.79 (s, 1 H), 6.46 (s, 1 H), 6.08 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 4.14 (t, 2 H, J = 5 Hz), 3.69 (t, 2 H, J = 5 Hz), 3.46 (s, 3 H), 3.14 (t, 2 H, J = 8 Hz).

2,3-Dihydro-6-(2-phenylethoxy)-5-benzofuranol (39a). In a manner analogous to that described for **37a**, **35** (0.233 g, 1.12 mmol) was alkylated with phenethyl bromide (0.518 g, 2.80 mmol) and drprotected to give **39a** (0.140 g, 49%): ^{1}H NMR δ 7.38–7.24 (m, 5 H), 6.77 (s, 1 H), 6.44 (s, 1 H), 5.07 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 4.23 (t, 2 H, J = 6 Hz), 3.18–3.06 (m, 4 H).

2,3-Dihydro-6-(3-phenylpropoxy)-5-benzofuranol (40a). In a manner analogous to that described for **37a**, **35** (0.350 g, 1.68 mmol) was alkylated with 3-bromo-1-phenylpropane (0.836 g, 4.20 mmol) and deprotected to give **40a** (0.280 g, 62%): ^{1}H NMR δ 7.34–7.15 (m, 5 H), 6.97 (s, 1 H), 6.37 (s, 1 H), 5.10 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 4.00 (t, 2 H, J = 6 Hz), 3.12 (t, 2 H, J = 8 Hz), 2.81 (t, 2 H, J = 6 Hz), 2.14 (quintet, 2 H, J = 6 Hz).

2,3-Dihydro-6-(3-bromopropoxy)-5-benzofuranol Methoxymethyl Ether (41). To a suspension of sodium hydride (60% dispersion, 0.728 g, 18.2 mmol) in dry dimethylformamide (20 mL) under nitrogen was added a solution of **35** (3.57 g, 18.2 mmol) in dimethylformamide (20 mL) dropwise over 30 min. After hydrogen evolution was complete the resulting solution of sodium alkoxide was added dropwise over 90 min to a solution of 1,3-dibromopropane (18.37 g, 91 mmol) in dimethylformamide (20 mL). The mixture was allowed to stir for 2 h and then poured into water (200 mL) and extracted with ethyl acetate (4 × 30 mL). The combined extracts were washed with water (200 mL), dried (Na_2SO_4), and concentrated. Preparative HPLC using 15% ethyl acetate as eluant gave 41 (2.56 g, 44%) as an oil: ^{1}H NMR δ 6.98 (s, 1 H), 6.48 (s, 1 H), 5.08 (s, 2 H), 4.57 (t, 2 H, J = 7 Hz), 4.12 (t, 2 H, J = 5 Hz), 3.63 (t, 2 H, J = 5 Hz), 3.54 (s, 3 H), 3.15 (t, 2 H, J = 7 Hz), 2.33 (quintet, 2 H, J = 5 Hz).

2,3-Dihydro-6-(3-phenoxypropoxy)-5-benzofuranol (42a). To a suspension of sodium hydride (60% dispersion, 0.019 g, 0.47 mmol) in dry dimethylformamide (4 mL) was added phenol (0.045 g, 0.47 mmol) and the mixture allowed to stir until hydrogen evolution had ceased. A solution of 41 (0.150 g, 0.47 mmol) in dry dimethylformamide (2 mL) was added dropwise and the mixture heated to 60 °C for 1 h. The mixture was cooled, diluted with water (50 mL), and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and 20% NaCl (20 mL), dried (Na_2SO_4), and concentrated. The residue was deprotected in methanol (20 mL) containing concentrated HCl (0.2 mL) at 55 °C for 1 h. The methanol was removed by concentration, and the residue was partitioned between water (50 mL) and ethyl acetate (25 mL). The aqueous layer was reextracted with ethyl acetate (2 × 25 mL), and the combined organic extracts were washed sequentially with 5% $NaHCO_3$ (25 mL), water (25 mL), and 20% NaCl (25 mL). The extracts were dried (Na_2SO_4) and concentrated, and the crude product was purified by flash chromatography using 10% ethyl acetate in hexane as eluant. Further purification was achieved by recrystallization from hexane to afford **42a** (0.040 g, 30%): ^{1}H NMR δ 7.30 (m, 2 H), 6.94 (m, 3 H), 6.79 (s, 1 H), 6.45 (s, 1 H), 5.32 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 4.27 (t, 2 H, J = 6 Hz), 4.22 (t, 2 H, J = 6 Hz), 3.13 (t, 2 H, J = 8 Hz), 2.28 (quintet, 2 H, J = 6 Hz).

2-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid Methyl Ester Methoxymethyl Ether (43a). In a manner analogous to that described for **42a**, methyl salicylate (0.288 g, 1.89 mmol) was alkylated with 41 (0.600 g, 1.89 mmol) to give **43a** (0.448 g, 61%) as an off-white solid: ^{1}H NMR δ 7.84 (dd, 1 H, J = 8, 2 Hz), 7.50 (td, 1 H, J = 8, 2 Hz), 7.04 (m, 3 H), 6.56 (s, 1 H), 5.10 (s, 2 H), 4.61 (t, 2 H, J = 8 Hz), 4.30 (m, 4 H), 3.92 (s, 3 H), 3.56 (s, 3 H), 3.18 (t, 2 H, J = 8 Hz), 2.38 (quintet, 2 H, J = 6 Hz).

2-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid Methyl Ester (44a). A solution of **43a** (0.102 g, 0.26 mmol) was deprotected in methanol (10 mL) containing concentrated HCl (0.15 mL) as described above for **42a** to afford **44a** (0.055 g, 61%): ^{1}H NMR δ 7.82 (dd, 1 H, J = 8, 2 Hz), 7.47 (dt, 1 H, J = 7, 2 Hz), 7.00 (t, 1 H, J = 7 Hz), 6.98 (d, 1 H, J = 7 Hz), 6.78 (s, 1 H), 6.48 (s, 1 H), 5.41 (br s, 1 H), 4.53 (t, 2 H, J = 7 Hz), 4.29 (t, 2 H, J = 6 Hz), 4.24 (t, 2 H, J = 6 Hz), 3.89 (s, 3 H), 3.13 (t, 2 H, J = 7 Hz), 2.34 (quintet, 2 H, J = 6 Hz).

2-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid (45a). To a solution of **43a** (0.305 g, 0.79 mmol) in methanol (20 mL) was added a solution of NaOH (0.100 g, 2.5 mmol) in water (3 mL). The mixture was heated to reflux for 3 h. The reaction mixture was cooled and diluted with water (60 mL). The aqueous solution was carefully acidified to pH 5 with 2 N HCl and the carboxylic acid isolated by filtration (0.192 g, mp 126–127 °C). The crude acid was dissolved in a mixture of tetrahydrofuran (10 mL) and water (2 mL). Concentrated HCl (0.3 mL) was added and the mixture heated to 60 °C for 3 h. The reaction mixture was concentrated and the residue partitioned between water (20 mL) and methylene chloride (20 mL). The

aqueous layer was reextracted with methylene chloride (2 × 25 mL). The combined extracts were washed with water (2 × 25 mL), dried (Na_2SO_4), and concentrated. Recrystallization from methylene chloride/hexane gave **45a** (0.122 g, 47%): ^{1}H NMR δ 8.09 (dd, 1 H, J = 8, 2 Hz), 7.68 (td, 1 H, J = 8, 2 Hz), 7.26 (t, 1 H, J = 8 Hz), 7.17 (d, 1 H, J = 8 Hz), 6.92 (s, 1 H), 6.54 (s, 1 H), 4.64 (t, 2 H, J = 8 Hz), 4.55 (t, 2 H, J = 6 Hz), 4.34 (t, 2 H, J = 6 Hz), 3.34 (t, 2 H, J = 8 Hz), 2.56 (quintet, 2 H, J = 6 Hz).

3-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid Methyl Ester Methoxymethyl Ether (46a). In a manner analogous to that described for **42a**, methyl 3-hydroxybenzoate (0.240 g, 1.58 mmol) was alkylated with **41** (0.500 g, 1.58 mmol) to give **46a** (0.613 g, quantitative) as an oil: ^{1}H NMR δ 7.62 (d, 1 H, J = 7 Hz), 7.54 (d, 1 H, J = 2 Hz), 7.32 (t, 1 H, J = 7 Hz), 7.10 (dd, 1 H, J = 7, 2 Hz), 6.96 (s, 1 H), 6.48 (s, 1 H), 5.07 (s, 2 H), 4.52 (t, 2 H, J = 8 Hz), 4.23 (t, 2 H, J = 6 Hz), 4.18 (t, 2 H, J = 6 Hz), 3.92 (s, 3 H), 3.14 (t, 2 H, J = 8 Hz), 2.30 (quintet, (quintet, 2 H, J = 6 Hz).

3-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid Methyl Ester (47a). A solution of **46a** (0.158 g, 0.40 mmol) was deprotected in methanol (15 mL) containing concentrated HCl (0.20 mL) as described above for **42a** to afford **47a** (0.078 g, 60%): ^{1}H NMR δ 7.65 (d, 1 H, J = 7 Hz), 7.59 (d, 1 H, J = 2 Hz), 7.46 (d, 1 H, J = 7 Hz), 7.12 (dd, 1 H, J = 7, 2 Hz), 6.80 (s, 1 H), 6.46 (s, 1 H), 5.33 (s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 4.23 (t, 4 H, J = 6 Hz), 3.94 (s, 3 H), 3.14 (t, 2 H, J = 8 Hz), 2.30 (quintet, 2 H, J = 6 Hz).

3-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid (48a). In a manner analogous to that described above for **45a**, **47a** (0.440 g, 1.13 mmol) was saponified and deprotected to give **48a** (0.167 g, 51%): ^{1}H NMR δ 7.74 (d, 1 H, J = 7 Hz), 7.64 (d, 1 H, J = 2 Hz), 7.40 (t, 1 H, J = 7 Hz), 7.18 (dd, 1 H, J = 7, 2 Hz), 6.81 (s, 1 H), 6.48 (s, 1 H), 4.57 (t, 2 H, J = 8 Hz), 4.24 (t, 4 H, J = 5 Hz), 3.14 (t, 2 H, J = 8 Hz), 2.33 (quintet, 2 H, J = 5 Hz).

4-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid Methyl Ester Methoxymethyl Ether (49a). In a manner analogous to that described for **42a**, methyl 4-hydroxybenzoate (0.240 g, 1.58 mmol) was alkylated with **41** (0.500 g, 1.58 mmol) to give **49a** (0.590 g, 96%) as an oil: ^{1}H NMR δ 7.99 (d, 2 H, J = 8 Hz), 6.98 (s, 1 H), 6.94 (d, 2 H, J = 8 Hz), 6.48 (s, 1 H), 5.06 (s, 2 H), 4.57 (t, 2 H, J = 8 Hz), 4.24 (t, 2 H, J = 6 Hz), 4.18 (t, 2 H, J = 6 Hz), 3.90 (s, 3 H), 3.51 (s, 3 H), 3.14 (t, 2 H, J = 8 Hz), 2.30 (quintet, 2 H, J = 6 Hz).

4-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzoic Acid Methyl Ester (50a). A solution of **49a** (0.580 g, 1.49 mmol) was deprotected in methanol (30 mL) containing concentrated HCl (0.25 mL) as described above for **42a** to afford **50a** (0.331 g, 64%): ^{1}H NMR δ 7.99 (d, 2 H, J = 8 Hz), 6.93 (d, 2 H, J = 8 Hz), 6.79 (s, 1 H), 6.45 (s, 1 H), 5.25 (br s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 4.23 (t, 4 H, J = 6 Hz), 3.90 (s, 3 H), 3.13 (t, 2 H, J = 8 Hz), 2.31 (quintet, 2 H, J = 6 Hz).

4-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzeneacetic Acid Methyl Ester Methoxymethyl Ether (51a). In a manner analogous to that described for **42a**, methyl 4-hydroxyphenylacetate (0.236 g, 1.42 mmol) was alkylated with **41** (0.450 g, 1.42 mmol) to give crude **51a** (0.589 g, quantitative) as an oil. This material was taken on without further purification: ^{1}H NMR δ 7.18 (d, 2 H, J = 8 Hz), 6.97 (s, 1 H), 6.66 (d, 2 H, J = 8 Hz), 6.47 (s, 1 H), 5.06 (s, 2 H), 4.56 (t, 2 H, J = 8 Hz), 4.17 (t, 4 H, J = 6 Hz), 3.70 (s, 3 H), 3.58 (s, 2 H), 3.52 (s, 3 H), 3.14 (t, 2 H, J = 8 Hz), 2.27 (quintet, 2 H, J = 6 Hz).

4-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzeneacetic Acid Methyl Ester Methoxymethyl Ether (51a). In a manner analogous to that described for **42a**, methyl 4-hydroxyphenylacetate (0.236 g, 1.42 mmol) was alkylated with **41** (0.450 g, 1.42 mmol) to give crude **51a** (0.589 g, quantitative) as an oil. This material was taken on without further purification: ^{1}H NMR δ 7.18 (d, 2 H, J = 8 Hz), 6.97 (s, 1 H), 6.66 (d, 2 H, J = 8 Hz), 6.47 (s, 1 H), 5.06 (s, 2 H), 4.56 (t, 2 H, J = 8 Hz), 4.17 (t, 4 H, J = 6 Hz), 3.70 (s, 3 H), 3.58 (s, 2 H), 3.52 (s, 3 H), 3.14 (t, 2 H, J = 8 Hz), 2.27 (quintet, 2 H, J = 6 Hz).

4-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzeneacetic Acid Methyl Ester (52a). A solution of **51a** (0.250 g, 0.62 mmol) was deprotected in methanol (25 mL) containing concentrated HCl (0.20 mL) as described above for **42a** to afford **52a** (0.115 g, 52%): ^{1}H NMR δ 7.21 (d, 2 H, J = 7 Hz), 6.90 (d, 2 H, J = 7 Hz), 6.80 (s, 1 H), 6.46 (s, 1 H), 5.32 (br s, 1 H), 4.54 (t, 2 H, J = 8 Hz), 4.22 (t, 2 H, J = 5 Hz), 4.16 (t, 2 H, J = 5 Hz), 3.70 (s, 3 H), 3.59 (s, 2 H), 3.13 (t, 2 H, J = 8 Hz), 2.28 (quintet, 2 H, J = 5 Hz).

4-[3-[(2,3-Dihydro-5-hydroxy-6-benzofuranyl)oxy]propoxy]benzeneacetic Acid (53a). In a manner analogous to that described above for **45a**, **51a** (0.310 g, 0.77 mmol) was saponified and deprotected to give **53a** (0.085 g, 32%): ^{1}H NMR δ 7.26 (d, 2 H, J = 8 Hz), 6.94 (d, 2 H, J = 8 Hz), 6.84 (s, 1 H), 6.49 (s, 1 H), 5.37 (br s, 1 H), 4.59 (t, 2 H, J = 8 Hz), 4.25 (t, 2 H, J = 6 Hz), 4.20 (t, 2 H, J = 6 Hz), 3.65 (s, 2 H), 3.19 (t, 2 H, J = 8 Hz), 2.33 (quintet, 2 H, J = 6 Hz).

2,3-Dihydro-5-hydroxybenzofuran-6-carboxylic Acid Ethyl Ester Methoxymethyl Ether (54). A solution of **23** (58.8 g, 227 mmol) in tetrahydrofuran (250 mL) was cooled with a dry ice acetone bath to −60 °C and then a solution of n-butyllithium (2.5 M in hexanes, 250 mmol) was added dropwise via a cannula. The reaction mixture was not allowed to exceed −50 °C during the addition. Upon completion of the addition the mixture was allowed to stir for 30 min with dry ice acetone cooling and then cannulated with a Flex-Needle into a dry ice acetone cooled solution of ethyl chloroformate (24 mL, 27.1 g, 250 mmol) in tetrahydrofuran (200 mL) over 90 min. During the addition the reaction temperature was maintained at −65 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture allowed to warm to room temperature over 1 h. The reaction was then worked up by pouring into 5% $NaHCO_3$ (1600 mL) and the resulting mixture saturated with NaCl. Ether (500 mL) was added, and the layers were separated. The aqueous layer was reextracted with ether (500 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated to afford **54** (54.05 g, 94%) as an oil which was used without further purification: ^{1}H NMR δ 7.17 (1 H, s), 7.06 (1 H, s), 5.14 (2 H, s), 4.58 (t, 2 H, J = 8.5 Hz), 4.34 (q, 2 H, J = 7 Hz), 3.54 (s, 3 H), 3.22 (t, 2 H, J = 8.5 Hz), 1.37 (t, 3 H, J = 7 Hz).

2,3-Dihydro-5-(methoxymethoxy)-6-(1-hydroxy-1-methylethyl)benzofuran (55). A solution of methyllithium (1.4 M in ether, 21.4 mL, 30 mmol) was cooled to −70 °C under nitrogen and then a solution of **54** (2.50 g, 10.0 mmol) in ether (6 mL) was added dropwise via syringe at a rate such that the internal temperature did not exceed −60 °C. Upon completion of the addition, the mixture was stirred at −78 °C for 45 min and then allowed to warm to 0 °C slowly. The reaction was worked up by pouring into water (50 mL) and separating the layers. The aqueous layer was reextracted with an additional portion of ether (50 mL), and the combined organic extracts were washed with 20% NaCl (50 mL), dried ($MgSO_4$), and concentrated. The resulting crude product began to slowly crystallize. Trituration with hexane afforded **55** (1.56 g, 65.5%) as a white solid: mp 84 °C; ^{1}H NMR δ 7.06 (s, 1 H), 6.81 (s, 1 H), 5.24 (s, 2 H), 4.55 (t, 2 H, J = 9 Hz), 4.12 (s, 1 H), 3.53 (s, 3 H), 3.18 (t, 2 H, J = 9 Hz), 1.60 (s, 6 H).

2,3-Dihydro-6-(1-methylethyl)-5-benzofuranol (56). An oven-dried 50-mL three-neck flask equipped with a dry ice acetone condenser and a gas inlet was flushed with nitrogen and then anhydrous ammonia (5 mL) was condensed in. Dry tetrahydrofuran (4 mL) was added followed by lithium wire (0.041 g, 5.91 mmol, in three pieces). A deep blue color was immediatedly observed. A solution of **55** (0.412 g, 1.73 mmol) in dry tetrahydrofuran (4 mL) was then added dropwise in portions. Whenever the blue color was quenched, the addition was suspended until the blue color returned. The total addition time was about 20 min. Upon completion of the addition, the blue color returned and the mixture was allowed to stir at refluxing ammonia temperature for 10 min. The reaction was quenched by the portionwise addition of ammonium chloride (0.471 g) and the ammonia allowed to evaporate. The resulting mixture was partitioned between ether (50 mL) and 10% NaCl (100 mL). The aqueous fraction was reextracted with an additional portion of ether, and the combined extracts were dried ($MgSO_4$) and concentrated to a pale oil (0.320 g). Chromatography through a short column of flash silica gel using 7% ethyl acetate in hexane as eluant afforded a colorless liquid (0.256 g). This material was deprotected in methanol (10 mL) containing concentrated HCl (0.20 mL) at 55 °C to give **56** (0.190 g, 62%) as a white solid. Recrystallization from hexane afforded an analytical sample: ^{1}H

NMR δ 6.59 (s, 2 H), 4.45 (t, 2 H, J = 9 Hz), 4.23 (s, 1 H), 3.06 (m, 3 H, J = 9, 7 Hz), 1.15 (d, 6 H, J = 7 Hz).

4,5,6,7-Tetrahydro-4-oxobenzofuran-5-carboxaldehyde (58). To a mechanically stirred solution of ethyl formate (394 g, 5.35 mol) in dry toluene (900 mL) was added sodium hydride (97%, 64.0 g, 2.67 mol). A solution of **57** (120.0 g, 0.88 mol) in toluene (100 mL) was then added dropwise over 30 min. During the exothermic addition a thick precipitate is deposited. The reaction mixture was allowed to stir for 3.5 h and then carefully quenched by the dropwise addition of 5% H_2SO_4 (2000 mL). The layers were separated, and the aqueous layer was reextracted with toluene (300 mL). The combined organic extracts were washed with 20% NaCl (2 × 500 mL), dried (Na_2SO_4), and concentrated. Trituration from hexane (120 mL) and toluene (70 mL) afforded **58** (60 g). Further trituration of the mother liquors with ether provided an additional 42 g of **58** (total yield 102 g, 71%): mp 74–76 °C (lit.[30b] mp 77–78 °C).

4-Methyl-6,7-dihydrobenzofuran-5-carboxaldehyde (59). To a solution of **58** (9.28 g, 56.5 mmol) and triethylamine (12 mL, 86.1 mmol) in dry tetrahydrofuran (110 mL) at 0 °C was added dropwise trimethylsilyl chloride (9.28 mL, 73.1 mmol). A thick precipitate formed during the addition. The reaction mixture was allowed to warm to room temperature and then transferred via a cannula into a −78 °C solution of methyllithium (1.4 M in ether, 120 mL, 168 mmol) and tetrahydrofuran (85 mL). Upon completion of the addition the reaction mixture was allowed to warm to −20 °C and then quenched by the careful addition of water (9 mL). The resulting mixture was poured into 2 N HCl (185 mL) and the two-phase mixture allowed to stir for 3 h. The aqueous phase was saturated with NaCl, and the layers were separated. The aqueous phase was reextracted with ethyl acetate (100 mL), and the organic layers were washed with 20% NaCl (100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford **59** (9.06 g, 99%) as an oil which slowly solidified on standing: ^{1}H NMR δ 10.15 (s, 1 H), 7.32 (d, 1 H, J = 1.5 Hz), 6.49 (d, 1 H, J = 1.5 Hz), 7.29 (s, 4 H), 2.39 (s, 3 H).

4-Methylbenzofuran-5-carboxaldehyde (60). To a suspension of dichlorodicyano-1,4-benzoquinone (60.8 g, 267 mmol) in dioxane (220 mL) was added a solution of **59** (36.82 g, 227 mmol) in dioxane (220 mL) over 2.5 h. The mixture was allowed to stir an additional 20 min and then diluted with methylene chloride (450 mL). The mixture was filtered through Celite to remove the hydroquinone and the filter cake was washed with an additional portion of methylene chloride (450 mL). The filtrate was concentrated and chromatographed through a large (9-cm diameter) column of flash silica gel. Elution with 10% ethyl acetate in hexane gave **60** (29.17 g, 80%) as a pale peach solid: mp 66–67 °C; ^{1}H NMR δ 10.39 (s, 1 H), 7.81 (d, 1 H, J = 8 Hz), 7.70 (d, 1 H, J = 2 Hz), 7.46 (d, 1 H, J = 8 Hz), 6.93 (dd, 1 H, J = 2, 1 Hz), 2.86 (s, 3 H).

4-Methyl-5-benzofuranol (61). To a solution of **60** (33.06 g, 206 mmol) in methylene chloride (580 mL) was added 80% *m*-chloroperbenzoic acid (52.0 g, 211 mmol) and the mixture heated at reflux for 17 h. The reaction mixture was allowed to cool, diluted with ethyl acetate (580 mL), and extracted with 5% $NaHCO_3$ (290 mL) and the combined organic layers dried ($MgSO_4$) and concentrated. The resulting yellow oil (47 g) was taken up in methanol (700 mL) and 2.5 N NaOH (185 mL, 462 mmol) was added. The mixture was stirred at room temperature for 20 min, cooled with an ice bath, and acidified with 2 N HCl (810 mL). The resulting mixture was saturated with NaCl and extracted with ethyl acetate (3 × 1200 mL). The combined extracts were washed with 20% NaCl (2 × 900 mL), dried ($MgSO_4$), and concentrated. The resulting dark oil (51 g) was chromatographed through a large (9-cm diameter) column of flash silica gel. Elution with 12.5% ethyl acetate in hexane afforded **61** (21.81 g, 71.4%) as an off-white solid: mp 79–81 °C; ^{1}H NMR δ 7.57 (d, 1 H, J = 2 Hz), 7.20 (d, 1 H, J = 8.5 Hz), 6.77 (d, 1 H, J = 8.5 Hz), 6.72 (dd, 1 H, J = 2, 1 Hz), 4.54 (s, 1 H), 2.39 (s, 3 H).

2,3-Dihydro-4-methyl-5-benzofuranol (62). A solution of **61** (1.86 g, 12.6 mmol) in absolute ethanol (50 mL) was hydrogenated over 10% palladium-on-carbon catalyst (0.10 g) at 3 atm of pressure. After the required amount of hydrogen had been taken up (overnight), the catalyst was removed by filtration and washed with an additional portion of absolute ethanol (20 mL). The combined filtrate and washings were concentrated to a white crystalline solid (1.88 g). Recrystallization from toluene gave **62** (1.77 g, 94%): mp 113–114 °C (lit.[32] mp 111–112 °C); ^{1}H NMR δ 6.54 (d, 1 H, J = 8 Hz), 6.48 (d, 1 H, J = 8 Hz), 4.55 (t, 2 H, J = 8 Hz), 4.36 (s, 1 H), 3.12 (t, 2 H, J = 8 Hz), 2.16 (s, 3 H). Anal. ($C_9H_{10}O_2$) C, H.

2,3-Dihydro-4-methyl-6-propen-3-yl-5-benzofuranol (63). In a manner analogous to that described above for **2a**, compound **62** (1.00 g, 6.66 mmol) was alkylated with allyl bromide (1.76 g, 14.6 mmol) to give the allyl ether. The allyl ether (1.23 g) was thermally rearranged in 1,2-dichlorobenzene (8 mL) at 190 °C for 3.5 h to afford, after chromatographic purification, compound **63** (1.05 g, 83%). Recrystallization from hexane gave an analytical sample: ^{1}H NMR δ 6.42 (s, 1 H), 5.97 (ddt, J = 17, 10, 6 Hz), 5.17 (dq, 1 H, J = 17, 1.5 Hz), 5.15 (dq, 1 H, J = 10, 1.5 Hz), 4.54 (s, 1 H), 4.53 (t, 2 H, J = 8 Hz), 3.34 (d, 2 H, J = 6 Hz), 3.10 (t, 2 H, J = 8 Hz), 2.16 (s, 3 H).

2,3-Dihydro-4-methyl-6-propyl-5-benzofuranol (64). A solution of **63** (0.500 g, 2.63 mmol) in absolute ethanol (25 mL) was hydrogenated over 5% palladium on carbon (0.060 g) at 3 atm of pressure. After hydrogen uptake was complete (30 min), the catalyst was removed by filtration through Celite. The filter cake was washed with an additional portion of ethanol (30 mL), and the combined filtrate and washings were concentrated to a white crystalline solid. Recrystallization from hexane gave **64** (0.463 g, 92%): ^{1}H NMR δ 6.44 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 4.19 (s, 1 H), 3.10 (t, 2 H, J = 8 Hz), 2.52 (t, 2 H, J = 7.5 Hz), 2.17 (s, 3 H), 1.62 (sextet, 2 H, J = 7.5 Hz), 0.97 (t, 3 H, J = 7.5 Hz).

2,3-Dihydro-4-methyl-6-(3-thiophenoxypropyl)-5-benzofuranol (65). A mixture of **63** (0.150 g, 0.79 mmol), thiophenol (0.5 mL, 0.54 g, 4.88 mmol), and AIBN (0.025 g) was heated to 90 °C for 3.5 h and then 100 °C for 4 h. The reaction mixture after cooling was purified by flash chromatography using 0–10% ethyl acetate in hexane as eluant. Recrystallization from hexane containing a small amount of toluene afforded **65** (0.165 g, 70%) as fluffy white needles: ^{1}H NMR δ 7.40–7.12 (m, 5 H), 6.41 (s, 1 H), 4.57 (s, 1 H), 4.52 (t, 2 H, J = 8.5 Hz), 3.09 (t, 2 H, J = 8.5 Hz), 2.94 (t, 2 H, J = 7 Hz), 2.71 (t, 2 H, J = 7 Hz), 2.16 (s, 3 H), 1.94 (quintet, 2 H, J = 7 Hz).

2,3-Dihydro-4-bromo-6-propyl-5-benzofuranol (66). To a cooled (10 °C) solution of **3a** (5.00 g, 28.1 mmol) in methylene chloride (50 mL) was added dropwise a solution of bromine (4.75 g, 29.72 mmol) in methylene chloride (50 mL) and the mixture allowed to stir for 1 h. The reaction mixture was then poured into 5% $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer reextracted with an additional portion of methylene chloride. The combined organic layers were washed sequentially with 5% $NaHSO_3$ (100 mL) and 20% NaCl (100 mL) and then dried (Na_2SO_4) and concentrated. Preparative HPLC using 3% ethyl acetate in hexane as eluant gave **66** (3.31 g, 46%) as an oil: ^{1}H NMR δ 6.52 (s, 1 H), 5.14 (s, 1 H), 4.55 (t, 2 H, J = 9 Hz), 3.16 (t, 2 H, J = 9 Hz), 2.60 (t, 2 H, J = 7 Hz), 1.62 (tq, 2 H, J = 7 Hz), 0.95 (t, 3 H, J = 7 Hz).

2,3-Dihydro-4-bromo-6-propyl-5-benzofuranol Methoxymethyl Ether (67). To a suspension of sodium hydride (60% dispersion in mineral oil, 0.373 g, 9.33 mmol) in dry dimethylformamide (20 mL) was added **66** (2.00 g, 7.78 mmol) in portions. After hydrogen evolution had ceased, a solution of chloromethyl methyl ether (0.751 g, 9.33 mmol) in dry dimethylformamide (5 mL) was added dropwise and the solution allowed to stir at room temperature for 2 h. The reaction mixture was poured into water (200 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were washed sequentially with water (2 × 50 mL) and 20% NaCl (50 mL), dried (Na_2SO_4), and concentrated. The crude oil was purified by preparative HPLC using 3% ethyl acetate in hexane as eluant to afford **67** (1.91 g, 82%) as a colorless oil: ^{1}H NMR δ 6.55 (s, 1 H), 5.01 (s, 2 H), 4.60 (t, 2 H, J = 9 Hz), 3.64 (s, 3 H), 3.20 (t, 2 H, J = 9 Hz), 2.63 (t, 2 H, J = 7 Hz), 1.61 (m, 2 H), 0.97 (t, 3 H, J = 6 Hz).

2,3-Dihydro-4-methyl-6-propyl-5-benzofuranol (64) by Alkylation of 67. To a solution of **67** (0.757 g, 2.51 mmol) in dry tetrahydrofuran (15 mL) at −78 °C was added *n*-butyllithium (2.5 M in hexane, 1.2 mL, 3.0 mmol) dropwise over about 5 min. The mixture was allowed to stir for 30 min and then methyl iodide (0.80 mL, 1.824 g, 12.85 mmol) was added all at once. An immediate exotherm was observed. The mixture was allowed to stir

at -78 °C for 30 min and then the cooling bath was removed and the mixture allowed to stir at room temperature for 2 h. The reaction mixture was poured into water (100 mL) and ether (50 mL) and the resulting mixture saturated with NaCl. The organic layer was removed and the aqueous layer reextracted with ether (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to a pale yellow oil (0.560 g, 94%). The crude product was taken up in methanol (50 mL) and the MOM ether removed by the addition of concentrated HCl (0.5 mL). The mixture was allowed to stir at 55 °C for 2 h. After cooling to room temperature, the reaction mixture was worked up by addition of 5% $NaHCO_3$ (3 mL) and concentrated in vacuo. After most of the methanol had been removed, the residue was partitioned between water and ether and the aqueous fraction reextracted with ether. The combined organic extracts were dried concentrated and chromatographed (10% ethyl acetate in hexane as eluant) to afford **64** (0.270 g, 56%) as a white crystalline solid and **3a** (0.050 g). Recrystallization of **64** from hexane afforded a sample identical with that prepared by hydrogenation of **63**.

2,3-Dihydro-4-*tert*-butyl-6-propen-3-yl-5-benzofuranol (69). To a suspension of sodium hydride (60% dispersion in mineral oil, 0.160 g, 3.99 mmol) in dry dimethylformamide (4.5 mL) was added a solution of **68**[22] (0.511 g, 2.66 mmol) in dimethylformamide (4 mL). After hydrogen evolution had ceased, a solution of allyl bromide (0.483 g, 3.99 mmol) in dimethylformamide (4 mL) was added and the mixture heated to 50 °C under nitrogen. After 1 h the reaction mixture was poured into 20% NaCl (125 mL) and extracted with ether (3 × 40 mL). The combined extracts were dried and concentrated to give a crude allyl ether (0.656 g). This material was taken up in 1,3-dichlorobenzene (6 mL) and heated to reflux under nitrogen for 16 h. Purification by flash chromatography using 2% ethyl acetate in hexane as eluant gave **69** (0.327 g, 53%) as a pale yellow solid: mp 92-95 °C; ^{1}H NMR δ 6.53 (s, 1 H), 6.06 (m, 1 H), 5.28 (m, 1 H), 5.22 (m, 1 H), 4.80 (s, 1 H), 4.46 (t, 2 H, J = 8 Hz), 3.48 (t, 2 H, J = 8 Hz), 3.38 (d, 2 H, J = 6 Hz), 1.50 (s, 9 H).

2,3-Dihydro-4-*tert*-butyl-6-propyl-5-benzofuranol (70). To a solution of **69** (0.230 g, 0.99 mmol) in absolute ethanol (12 mL) was added 10% palladium on carbon (0.020 g) and the solution hydrogenated at 3 atm of pressure. After 30 min the catalyst was removed by filtration through Celite and the filter cake washed with a small portion of ethanol. The combined filtrate and washings were concentrated to afford a crude product (0.210 g). Recrystallization from aqueous ethanol gave **70** (0.170 g, 73%) as a white solid: ^{1}H NMR δ 6.54 (s, 1 H), 4.46 (br s, 1 H), 4.44 (t, 2 H, J = 8 Hz), 3.47 (t, 2 H, J = 8 Hz), 2.52 (t, 2 H, J = 8 Hz), 1.66 (quintet, 2 H, J = 8 Hz), 1.51 (s, 9 H), 1.04 (t, 3 H, J = 8 Hz).

Human PMN LTB_4 Assay. A. Preparation of Human PMN. Human blood was obtained by antecubital venepuncture from consenting volunteers who denied having taken medication within the previous 7 days. The blood was immediately added to 10% (v/v) trisodium citrate (0.13 M) or 5% (v/v) sodium heparin (1000 IU/mL). PMNs were isolated from anticoagulated blood by dextran sedimentation and centrifugation through Ficoll-Hypaque (specific gravity 1.077), essentially as described.[33] Contaminating erythrocytes were removed by lysis following exposure to ammonium chloride (0.16 M) in Tris buffer (pH 7.65), and the PMNs resuspended at 5×10^5 cells/mL in HEPES (15 mM) buffered Hanks balanced salt solution containing Ca^{2+} (1.4 mM) and Mg^{2+} (0.7 mM), pH 7.4. Viability was assessed by Trypan blue exclusion and was typically greater than 98%.

B. Generation and Radioimmunoassay of LTB_4. PMNs (0.5 mL; 2.5×10^5 cells) were placed in plastic tubes and incubated (37 °C, 2 min) with test compounds at the desired concentration or vehicle control (DMSO, final concentration 0.2%). The synthesis of LTB_4 was initiated by the addition of calcium ionophore A23187 (final concentration 10 μM) or vehicle in control samples and allowed to proceed for 5 min at 37 °C. The reactions were then terminated by the addition of cold methanol (0.25 mL) and samples of the entire PMN reaction mixture were removed for radioimmunoassay of LTB_4.

Samples (50 μL) of authentic LTB_4 of known concentration in radioimmunoassay buffer (RIA) buffer (potassium phosphate 1 mM; disodium EDTA 0.1 mM; Thimerosal 0.025 mM; gelatin 0.1%, pH 7.3) or PMN reaction mixture diluted 1:1 with RIA buffer were added to reaction tubes. Thereafter [^{3}H]LTB_4 (10 nCu in 100 μL of RIA buffer) and LTB_4 antiserum (100 μL of a 1:3000 dilution in RIA buffer) were added and the tubes vortexed. Reactants were allowed to equilibrate by incubation overnight at 4 °C. To separate antibody-bound from free LTB_4, aliquots (50 μL) of activated charcoal (3% activated charcoal in RIA buffer containing 0.25% Dextran T-70) were added and the tubes vortexed and allowed to stand at room temperature for 10 min prior to centrifugation (1500g, 10 min, 4 °C). The supernatants containing antibody-bound LTB_4 were decanted into vials, and Aquasol 2 (4 mL) was added. Radioactivity was quantified by liquid scintillation spectrometry. Preliminary studies established that the amount of methanol carried into the radioimmunoassay did not influence the results. The specificity of the antiserum and the sensitivity of the procedure have been described in detail elsewhere.[34] The amount of LTB_4 produced in test and control (ca. 20 ng/10^6 cells) samples were calculated. Inhibitory dose-response curves were constructed from five point titrations using a four-parameter algorithm and from these the IC_{50} values were determined. Unless otherwise noted, all compounds were tested in at least duplicate and the reported IC_{50} values reflect the mean value of all the IC_{50}s obtained.

Acknowledgment. We thank Dr. Stanley Wright of Dev Labs, Hoddeston, England, for a generous gift of 2,3-dihydro-5-benzofuranol (**1**) and for helpful procedures including the Lewis acid catalyzed Claisen rearrangement of **1** and the preparation of **4a** and **6a**.

Benzodiazepine Receptor Binding Activity of 6,9-Disubstituted Purines

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A series of 6,9-disubstituted purines were tested for their ability to bind to the benzodiazepine receptor in rat brain tissue. One of the most active compounds was 9-(3-aminobenzyl)-6-(dimethylamino)-9*H*-purine (**44**) with an IC_{50} = 0.9 μM, which was only 4.5-fold higher than the IC_{50} for chlordiazepoxide. Substitution of a 3-aminobenzyl or 3-hydroxybenzyl group at the 9-position of 6-(dimethylamino)purine led to over a 50-fold increase in receptor affinity. Compound **44** did not exhibit significant anxiolytic activity, nor did anticonvulsant activity correlate with relative receptor binding affinity.

The benzodiazepines (BZs) are a class of centrally acting drugs with broad therapeutic application as anxiolytics, hypnotics, muscle relaxants, and anticonvulsants.[1] High-affinity binding sites or receptors for BZs have been

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0022-2623/89/1832-1020$01.50/0