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A number of novel 2-substituted 2,3-dihydro-5-benzofuranols optionally protected on 5-OH group have been prepared *via* a simple two step route to racemic 2,3-dihydro-5-hydroxy-2-benzofuranacetic acids from hydroquinones and 4-bromocrotonates.

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Introduction.

Vitamin E-like compounds have recently received much attention because of their considerable activity as free-radical scavenger agents and, more particularly, as lipo-peroxidation inhibitors [1].

Various attempts to maximize antioxidant potency of phenols related to tocopherols have led to the development of a model which, based on some stereoelectronic factors such as the orientation of the 2p-type lone pair on the ring oxygen, ensures an optimum for chain-breaking capacity to 2,3-dihydro-5-benzofuranols [2].

Such a template, although known for several decades [3], seems not to have been fully explored from a biological point of view, in spite of the huge potential utility of antioxidants in many therapeutic fields [4,5]. A notable exception in this context is the recognized activity of many 2,3-dihydro-5-benzofuranols as inhibitors of leukotriene biosynthesis [6].

As a primary part of a research program on new anti-inflammatory/antioxidizing agents for the respiratory tract, we focused our attention on the 5-hydroxycoumaran nucleus. The main goal we pursued was to appropriately combine 5-OH-generating protecting groups with a suitable 2-substitution pattern, which may eventually give a contribution to the overall profile of biological activity.

Previously reported synthetic entries to that ring system allowed only simple alkyl groups (notably a gem-dimethyl group [7]) to be introduced in position 2, or they are inconvenient on a large scale preparation. Most commonly,

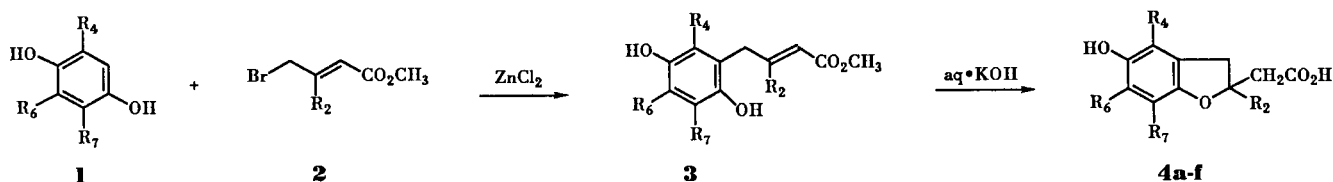
Claisen rearrangement of 4-allyloxyphenol derivatives, followed by a ring-closure reaction of the resulting allylhydroquinone, leads to the target nucleus [8]. That obvious synthetic strategy has the disadvantage to require previous selective protection of one of the hydroxy groups of the starting hydroquinone, thus adding additional steps to the overall process.

We wish to report here a short, straightforward route to racemic 2,3-dihydro-5-hydroxy-2-benzofuranacetic acids **4** *via* direct Friedel-Crafts alkylation of a suitable hydroquinone **1** with methyl 4-bromocrotonate **2** and subsequent hydrolytic cyclization of the resulting 4-aryl-2-butenolate **3**. The compound **4a** was the key substrate for further manipulations on positions 2 and 5 that gave rise to a broad range of substances having widely modulated physicochemical properties.

Results and Discussion.

The general synthetic route to compounds **4a-f** (Table 1) has been outlined in Scheme 1. Zinc chloride as the Friedel-Crafts catalyst was satisfactory for preparative purposes; the choice of solvent, on the other hand, was of crucial importance. A broad search disclosed that hydrocarbon solvents having bp > 90° could improve yields of **4** to the optimum, despite the low solubility of hydroquinones **1** in these media. The rather intractable reaction mixture was then submitted to hydrolytic cyclization in an alkaline environment: a strong reducing agent such as sodium dithionite was added to the mixture in order to mini-

Scheme 1



mize spontaneous oxidation to the benzoquinone **5**. Nucleophilic attack of phenolate anion on the β -carbon of the butenoic moiety occurs readily and selectively, with no detectable chroman-2-carboxylic acid formation. 6-Member ring closure was instead noticed in the isolation of 6-hydroxy-3,5,7,8-tetramethyl-2*H*-1-benzopyran-2-one **6** as the main by-product from **1a** + **2a**. Its structural assignment was based on ir, ms, ^1H - and ^{13}C -nmr data of the corresponding 6-acetoxy derivative **7** (see the Experimental), and particularly on reported different chemical shifts of H3 and H4 in similar coumarins [9]. The extensive rearrangement of the 2-butenic chain leading to the formation of **6** (Scheme 2) may be reasonable by explained through a Lewis acid-assisted electrophilic aromatic substitution by the bromocrotonate in its β -position rather than in the γ -position. Subsequent departure of bromide and 1-3 migration of the γ -carbon *via* a transient cyclopropane intermediate [10] gave rise to the 3-aryl-2-methylacrylate, with the double bond in the most stable position. Final lactonization to **6** was driven by the conjugation of the resulting coumarin.

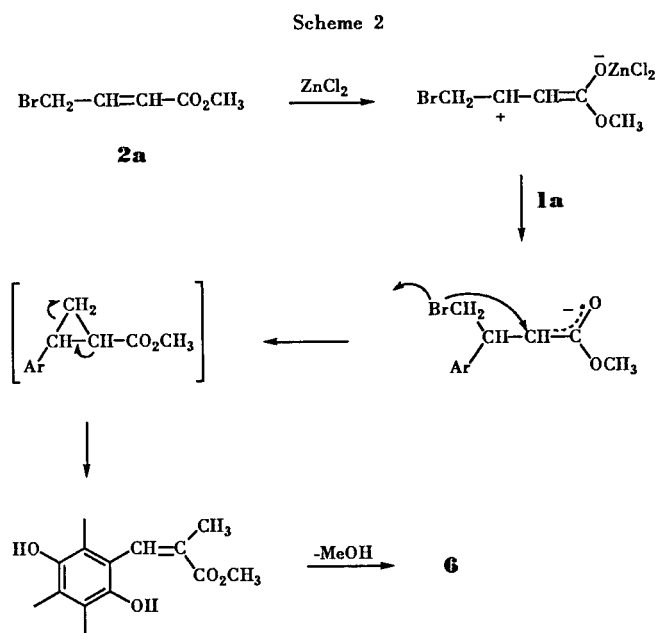


Table 1

(±)-2,3-Dihydro-5-hydroxy-2-benzofuranacetic Acids **4**

Compound No.	R ²	R ⁴	R ⁶	R ⁷	Mp, °C
4a	H	Me	Me	Me	174-175
4b	H	Me	Me	H	152-153
4c	H	Me	H	Me	174-175
4d	H	H	Me	Me	171-172
4e	H	Me	OMe	OMe	141-142
4f [a]	Me	Me	Me	Me	184-185

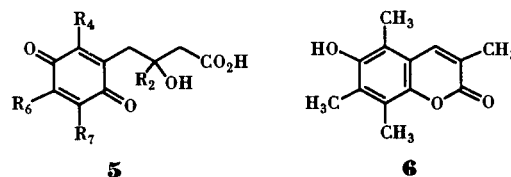
[a] Reference [8b].

A first series of derivatives of **4a** consisting mainly of esters and amides of the 2-acid-containing group (Table 2, compounds **8-25**) could be provided by well-known preparative methods involving preventative acylation or alkylation of the 5-hydroxy group. The list also included non-hydrolysable ketones **26** and **27** obtained from Friedel-Crafts acylation of thiophene and 2-bromothiophene, respectively. A wider range of compounds derived from the reduction of the carboxylic group gave 2-benzofuranethanols **28-33**. Various manipulations of the hydroxyethyl side chain allowed halides **35** and **36**, amines **37-43**, amides **44** and **45**, heteroaromatic thioethers **46-49**, thioesters **50** and **51**, thiol **52** and aryl ether **61** to be obtained in fair to good yields. Moreover, fine adjustment of overall lipophilicity was achieved by the synthesis of homologues acids **56** and **57**, whilst tertiary alcohols **58-60** were prepared with the aim to enhance metabolic stability of the side chain. Scheme 3 summarizes synthetic patterns for the entire range of compounds deriving from **4a**.

Racemic solutions of acids **4a**, **8** and **10** were accomplished by means of fractional recrystallization of their (*S*)- or (*R*)- α -methylbenzylamine salts. Attempts to achieve enzymatic resolutions with the use of Lipase from *Candida cylindracea* were unsuccessful.

In summary, we have described the synthesis of many novel 2-substituted 2,3-dihydro-5-benzofuranols optionally protected on the phenolic hydroxyl. Their common precursor **4a** was obtained by a simple two-step process starting from commercially available substrates.

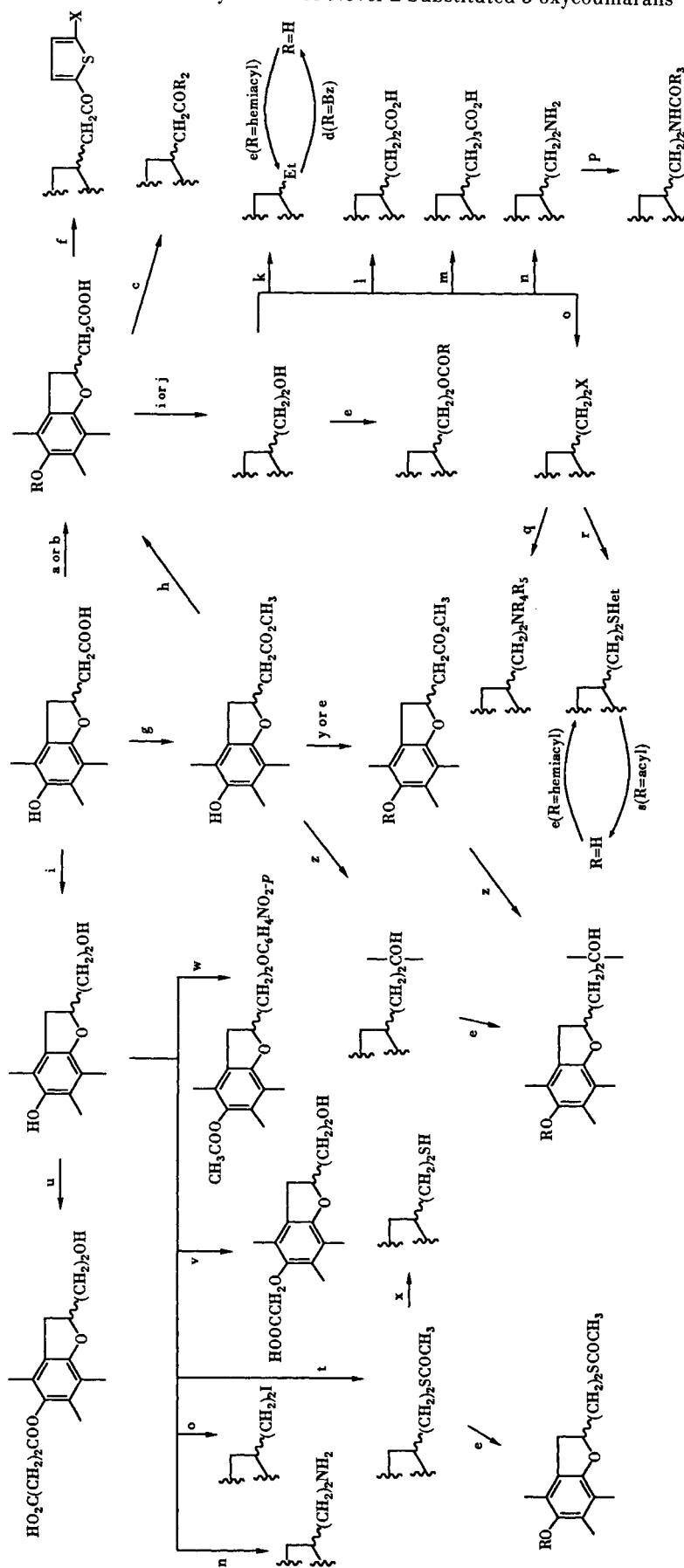
Many of the compounds presented here should by potent *in vivo* radical scavenger agents. On the basis of the overall profile of activity, **8** (IRFI 016) [12], **10** (IRFI 048) and **51** (IRFI 042) have been selected for clinical development as anti-oxidizing drugs for the respiratory tract. In addition, several members of this series are under active investigation as potential anti-ischemic agents.



EXPERIMENTAL

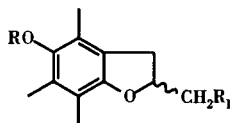
Melting points were determined in a Büchi 535 apparatus (uncorrected) or by differential scanning calorimetry on a Perkin Elmer DSC 7 instrument (see Table 2). The ^1H nuclear magnetic resonance (nmr) spectra were obtained on a Varian EM 360L instrument using tetramethylsilane (TMS, δ 0.00) as the internal standard. Infrared spectra were recorded on a Perkin Elmer 881 spectrophotometer as potassium bromide pellets unless other-

Scheme 3 [a]



a] Reagents and conditions: (a) anhydride, catalytic H_2SO_4 ; (b) R_2SO_4 or RX , KOH , acetone; (c) aq KOH ; (d) H_2 , Pd/C , EtOH ; (e) anhydride, KOH , DMF ; (f) $(1) (\text{COCl})_2$, C_6H_6 ; (g) H_2SO_4 , MeOH ; (h) $(1) \text{ROH}$, PPh_3 , DIAD ; (i) LiAlH_4 , THF ; (j) $(1) (\text{COCl})_2$, C_6H_6 ; (k) $(1) \text{NaBH}_4$, dioxane; (l) P-TsCl , Py , 0°C ; (m) $(1) \text{LiAlH}_4$, THF ; (n) P-TsCl , Py , 0°C ; (o) aq NaOH ; (p) P-TsCl , Py , 0°C ; (q) $\text{R}_4\text{R}_5\text{NH}$, EtOH ; (r) H_2 , Pd/C , EtOH ; (s) aq NaOH ; (t) MeCO_2SH , PPh_3 , DIAD , THF ; (u) P-TsCl , Py , 0°C ; (v) R_3COCl , Et_3N , CH_2Cl_2 ; (w) $\text{Br-CH}_2\text{CO}_2\text{Et}$, K_2CO_3 , DMF ; (x) aq NaOH ; (y) RX , KOH , DMF ; (z) MeMgI , Et_2O .

Table 2
Substituted 2,3-dihydro-4,6,7-trimethylbenzofurans



Compound No.	R	R ₁	Mp, °C	Recrystallization solvent [a]	Synthetic route (Scheme 3)
8	MeCO	CO ₂ H	183.4 [b]	IA	a
9	EtCO	CO ₂ H	148-150	B/Hep	a
10	Me	CO ₂ H	135.4 [b]	IA	b
11	i-Pr	CO ₂ H	118.1 [b]	B/H	g,h
12	MeCO	CO ₂ Et	76-77	[c]	a,c
13	MeCO	CO ₂ (CH ₂) ₇ Me	43-44	[c]	a,c
14	MeCO	CO ₂ (CH ₂) ₁₇ Me	58-59	[c]	a,c
15	MeCO	CO ₂ (CH ₂) ₂ NMe ₂	165-167	EA/M	a,c
16	MeCO	CO ₂ (CH ₂) ₂ -morpholin-4-yl	189-191	EA/E	a,c
17	MeCO	CO ₂ (CH ₂) ₂ -piperazin-1-yl-4-Me	208.8 [b]	I	a,c
18	MeCO	CO ₂ (CH ₂) ₂ -piperidin-1-yl	168.4 [b]	EA/M	a,c
19 [d]	H	CO ₂ Me	121-122	EA/H	g
20	HO ₂ C(CH ₂) ₂ CO	CO ₂ Me	154-156	B	g,e
21	MeCO	CO-piperazin-1-yl-4-Me	238-239	EA/M	a,c
22	MeCO	CONH(CH ₂) ₂ -morpholin-4-yl	149-151	[c]	a,c
23	Me	CO ₂ Me	50-51	B	b
24	Me	CO ₂ (CH ₂) ₂ -morpholin-4-yl	181.4 [b]	EA/M	b,c
25	Me	CO ₂ (CH ₂) ₂ -piperidin-4-yl	167.4 [b]	EA/M	b,c
26	MeCO	CO-thien-2-yl	132-133	B/H	a,f
27	MeCO	CO-thien-2-yl-5-Br	142.2 [b]	B/H	a,f
28	H	CH ₂ OH	124-125	B	i
29	Me	CH ₂ OH	74-76	B	b,i
30	PhCH ₂	CH ₂ OH	92.9 [b]	H	g,y,i
31	MeCO	CH ₂ OH	136-138	IA	aj
32	HO ₂ C(CH ₂) ₂ CO	CH ₂ OH	132-134	IA	i,u
33	HO ₂ CCH ₂	CH ₂ OH	149.8 [b]	EA/H	i,v
34	Me	CH ₂ OCO(CH ₂) ₂ CO ₂ H	83.0 [b]	H	b,i,e
35	H	CH ₂ I	97.0 [b]	[c]	i,o
36	MeCO	CH ₂ Br	oil		aj,o
37	MeCO	CH ₂ -morpholin-4-yl	185.3 [b]	EA/M	aj,o,q
38	MeCO	CH ₂ -piperidin-1-yl	199.3 [b]	EA/M	aj,o,q
39	MeCO	CH ₂ -piperazin-1-yl-4-Me	oil		aj,o,q
40	H	CH ₂ NH ₂	197-199	[e]	in
41	PhCH ₂	CH ₂ NH ₂	192-193	EA/M	g,y,i,n
42	PhCH ₂	CH ₂ -morpholin-4-yl	196-198	EA/M	g,y,i,o,q
43	PhCH ₂	CH ₂ NEt ₂	164-166	EA/M	g,y,i,o,q
44	MeCO	CH ₂ NHCO(CH ₂) ₁₄ Me	114.3 [b]	[c]	aj,n,p
45	PhCH ₂	CH ₂ NHCOPh(OMe) ₃ -3,4,5	171-173	EA/E	g,y,i,n,p
46	Me	CH ₂ S-thiazolin-2-yl	167.5 [b]	[e]	b,i,o,r
47	Me	CH ₂ S-pyrimidin-2-yl	oil		b,i,o,r
48	Me	CH ₂ S-imidazol-2-yl-1-Me	57-59	EA/M	b,i,o,r
49	HO ₂ C(CH ₂) ₂ CO	CH ₂ S-benzothiazol-2-yl	90.0 [b]	B/H	aj,o,r,s,e
50	H	CH ₂ SCOMe	89-91	H	i,t
51	HO ₂ C(CH ₂) ₂ CO	CH ₂ SCOMe	101.7 [b]	E/W	i,t,e
52	H	CH ₂ SH	108-110	B	i,t,x
53	PhCH ₂	Me	65-67	[c]	g,y,i,k
54	H	Me	73-75	[c]	g,y,i,k,d
55	HO ₂ C(CH ₂) ₂ CO	Me	156.5 [b]	B	g,y,i,k,d,e
56	Me	CH ₂ CO ₂ H	109.8 [b]	A/W	b,i,l
57	Me	(CH ₂) ₂ CO ₂ H	127.6 [b]	E/W	b,i,m
58	Me	CMe ₂ OH	72.5 [b]	H	g,y,z
59	H	CMe ₂ OH	113-115	EA/H	g,z
60	HO ₂ C(CH ₂) ₂ CO	CMe ₂ OH	129.8 [b]	B/Hep	g,z,e
61	MeCO	CH ₂ OPhNO ₂ -4	130.9 [b]	E	i,w

[a] IA = isopropyl acetate, B = benzene, Hep = *n*-heptane, H = *n*-hexane, EA = ethyl acetate, M = methanol, E = ethanol, I = 2-propanol, W = water, A = acetone. [b] Differential scanning calorimetry mp (onset). [c] purified by tlc or column chromatography. [d] Reference [11]. [e] hydrochloride precipitated in ethereal or ethanolic hydrogen chloride.

wise noted. The ^{13}C nmr and ms spectra of compound **7** were obtained on Bruker WM 300 and Kratos MS80 instruments, respectively. Analyses were carried out on a Carlo Erba 1106 analyzer.

Thin layer chromatography was accomplished on Merck pre-coated silica gel 60 F₂₅₄ plates; the spots were detected under a 254 nm light source and by spraying with a potassium permanganate solution. Flash chromatography was performed on Kieselgel 60, 230-400 mesh (Merck).

Starting hydroquinones **1a-e** were either commercially available or were prepared from the corresponding phenols as described elsewhere [13], except for 2,3-dimethoxy-5-methylhydroquinone (**1e**, ir: 3433 cm^{-1}), obtained by sodium borohydride/methanol reduction of the corresponding benzoquinone. Methyl 4-bromo-3-methyl-2-butenolate (*E/Z*) was prepared from 3,3-dimethylacrylic acid according to the known procedure [14] for allylic bromination.

General Procedure for the Preparation of ($\pm$)-2,3-Dihydro-5-hydroxy-2-benzofuranacetic Acid (**4**).

A mixture of the appropriate hydroquinone **1** (10 mmoles) and anhydrous zinc chloride (1.7 mmoles) in *n*-heptane (10 ml) was refluxed under nitrogen and treated dropwise with 6.3 mmoles of **2** (methyl 4-bromo-2-butenolate for **4a-e** or methyl 4-bromo-3-methyl-2-butenolate for **4f**) under vigorous stirring. After 2 hours the suspension was cooled and evaporated under vacuum. The resulting oily residue containing the 4-aryl-2-butenolate **3** was treated with aqueous 20% potassium hydroxide (22 ml) and sodium hydrosulfite (8.4 mmoles). The reaction mixture was refluxed under nitrogen for 2.5 hours, then it was cooled, acidified with concentrated hydrochloric acid to pH 3, and extracted with ethyl acetate. The organic layer was washed twice with brine, then re-extracted with saturated sodium bicarbonate. The aqueous phase was then acidified and the resulting precipitate filtered, washed with water and dried.

Pure compounds **4a-f** were obtained by flash chromatography (eluant carbon tetrachloride:acetic acid 9:1) followed by recrystallization from ethyl acetate:*n*-hexane. The mp are listed in Table I.

($\pm$)-2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuranacetic Acid (**4a**).

This compound was obtained in 56% yield and had ir: 3402, 1711 cm^{-1} ; uv (ethanol): λ_{max} 294 nm (ϵ 3,915); ^1H nmr (DMSO- d_6): δ 12.2 (sb, 1H), 7.4 (sb, 1H), 5.35-4.85 (m, 1H), 3.55-2.75 (m, 2H), 2.65 (d, 2H), 2.05 (s, 6H), 2.0 (s, 3H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C, 66.09; H, 6.82. Found: C, 66.15; H, 6.84.

($\pm$)-2,3-Dihydro-5-hydroxy-4,6-dimethyl-2-benzofuranacetic Acid (**4b**).

This compound was obtained in 49% yield and had ir: 3407, 1712 cm^{-1} ; ^1H nmr (methanol- d_4): δ 6.3 (s, 1H), 5.3-4.85 (m, 1H), 3.4-2.8 (m, 2H), 2.7 (d, 2H), 2.1 (s, 3H), 2.05 (s, 3H).

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35. Found: C, 64.92; H, 6.46.

($\pm$)-2,3-Dihydro-5-hydroxy-4,7-dimethyl-2-benzofuranacetic Acid (**4c**).

This compound was obtained in 51% yield and had ir: 3294, 1704 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 7.6 (sb, 2H), 6.3 (s, 1H), 5.2-4.85 (m, 1H), 3.5-2.8 (m, 2H), 2.7 (d, 2H), 2.0 (s, 6H).

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35. Found: C, 64.49; H, 6.50.

($\pm$)-2,3-Dihydro-5-hydroxy-6,7-dimethyl-2-benzofuranacetic Acid (**4d**).

This compound was obtained in 54% yield and had ir: 3332, 1707 cm^{-1} ; ^1H nmr (methanol- d_4): δ 6.5 (s, 1H), 5.2-4.85 (m, 1H), 3.5-2.8 (m, 2H), 2.7 (d, 2H), 2.05 (s, 6H).

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35. Found: C, 64.73; H, 6.40.

($\pm$)-2,3-Dihydro-6,7-dimethoxy-5-hydroxy-4-methyl-2-benzofuranacetic Acid (**4e**).

This compound was obtained in 41% yield and had ir: 3467, 1700 cm^{-1} ; ^1H nmr (methanol- d_4): δ 5.3-4.8 (m, 2H), 3.8 (s, 3H), 3.75 (s, 3H), 3.5-2.8 (m, 2H), 2.7 (d, 2H), 2.0 (s, 3H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_6$: C, 58.20; H, 6.01. Found: C, 58.39; H, 6.36.

($\pm$)-2,3-Dihydro-5-hydroxy-2,4,6,7-tetramethyl-2-benzofuranacetic Acid (**4f**).

This compound was obtained in 62% yield and had ir: 3566, 1713 cm^{-1} ; ^1H nmr (methanol- d_4): δ 3.5-3.0 (m, 2H), 2.7 (s, 2H), 2.1 (s, 6H), 2.0 (s, 3H), 1.5 (s, 3H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25. Found: C, 67.16; H, 7.37.

($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetic Acid (**8**).

To a suspension of crude **4a** (17.4 g, 75% purity) in acetic anhydride (40 ml) was added 4 drops of concentrated sulfuric acid. The mixture was kept under stirring at 80° in an inert atmosphere for 4 hours. After cooling, ice (40 g) was added and the mixture was then stirred overnight. The precipitation was completed by adding more water. The solid was collected by filtration, dried, decolorized and recrystallized twice, yield 13.0 g (84%); ir: 1763, 1713 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 9.5 (s, 1H), 5.3-4.8 (m, 1H), 3.5-2.7 (m, 4H), 2.3 (s, 3H), 2.1 (s, 3H), 2.0 (s, 6H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.74; H, 6.52; O, 28.74. Found: C, 64.78; H, 6.56; O, 28.58.

6-Acetyloxy-3,5,7,8-tetramethyl-2H-1-benzopyran-2-one (**7**).

This compound was isolated from the mother liquors derived from the recrystallization of the above acetoxy acid and was purified by column chromatography (eluant carbon tetrachloride:acetic acid 95:5) followed by preparative tlc; ir: 1776, 1761, 1208 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.15 (q, 1H, 4-H, $J = 7.5$ Hz), 2.45 (d, 3H, 3-Me, $J = 7.5$ Hz), 2.3 (s, 3H), 2.2 (s, 6H), 2.1 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 11.91 (q), 13.11 (q), 13.20 (q), 15.29 (q), 20.44 (q), 118.10 (s), 119.20 (s), 122.77 (s), 125.44 (s), 130.69 (s), 143.27 (d), 143.87 (s), 148.88 (s), 167.05 (s), 169.30 (s); ms: (m/z) 260 (M^+), 218 ($\text{M}^+ - \text{CH}_2\text{CO}$), 190 (218 - CO), 175 (190 - CH_3).

Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{O}_4$: C, 69.22; H, 6.20. Found: C, 69.27; H, 5.99.

($\pm$)-2,3-Dihydro-5-propionyloxy-4,6,7-trimethyl-2-benzofuranacetic Acid (**9**).

This compound was prepared in 84% yield in an analogous manner to that described for **8**; ir: 1746, 1710 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 11.0 (sb, 1H), 5.35-4.85 (m, 1H), 3.35-2.55 (m,

6H), 2.0 (s, 3H), 1.9 (s, 6H), 1.2 (t, 3H).

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 66.01; H, 6.83.

Ethyl ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (**12**).

A suspension of **8** (3.83 g) in benzene (30 ml) was treated dropwise with oxalyl chloride (6.2 ml) at 50° for 1 hour. Evaporation of the solvent gave ($\pm$)-5-acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetyl chloride (ir: 1804 cm^{-1}). To a solution of the above-mentioned acid chloride (4.08 g) in dry tetrahydrofuran (15 ml), pyridine (1.3 ml, 1.2 molar excess) and ethanol (1.2 ml, 1.5 molar excess) were added. The mixture was stirred at room temperature for 1 hour, then the solvent was evaporated and the residue was partitioned between acidulated water and ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate, brine, dried and evaporated to afford crude ethyl ester. Flash chromatography (eluant dichloromethane:ethyl acetate 9:1) gave pure **12** (3.54 g, 84%); ir: 1755, 1725 cm^{-1} ; 1H nmr (deuteriochloroform): δ 5.35-4.85 (m, 1H), 4.2 (q, 2H), 3.55-2.55 (m, 4H), 2.3 (s, 3H), 2.05 (s, 3H), 2.00 (s, 6H), 1.25 (t, 3H).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.40; H, 7.36.

The following were similarly prepared:

n-Octyl ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (**13**).

This compound (4.1 g, 82%) had ir: 1762, 1737 cm^{-1} ; 1H nmr (deuteriochloroform): δ 5.35-4.85 (m, 1H), 4.1 (t, 2H), 3.55-2.65 (m, 4H), 2.3 (s, 3H), 2.05 (s, 3H), 2.0 (s, 6H), 1.6-1.1 (m, 12H), 0.85 (m, 3H).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.77. Found: C, 71.07; H, 9.17.

n-Octadecyl ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (**14**).

This compound (145 mg, 84%) had ir: 1746, 1723 cm^{-1} ; 1H nmr (deuteriochloroform): δ 5.35-4.85 (m, 1H), 4.1 (t, 2H), 3.35-2.65 (m, 4H), 2.3 (s, 3H), 2.05 (s, 3H), 1.95 (s, 6H), 1.5-1.2 (m, 32H), 0.8 (m, 3H).

Anal. Calcd. for $C_{33}H_{54}O_5$: C, 74.67; H, 10.25. Found: C, 74.62; H, 10.24.

2-(*N,N*-Dimethylamino)ethyl ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (**15**).

To a solution of 5-acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetyl chloride (3.0 g, 10 mmoles, prepared as described above) in dry tetrahydrofuran (7 ml), *N,N*-dimethylethanolamine (1.0 ml, 10 mmoles) was added. The mixture was stirred at room temperature for 1 hour, after which time the solvent was removed *in vacuo*. The residue was partitioned between aqueous bicarbonate and ether. The organic layer was washed with brine, dried and concentrated *in vacuo*. Treatment with ethereal hydrogen chloride afforded crystalline **15** as the hydrochloride salt. After recrystallization 2.6 g (66%) was obtained; ir: 2650, 1753, 1742 cm^{-1} ; 1H nmr (methanol- d_4): δ 5.7-4.8 (m, 1H), 4.5-4.3 (m, 2H), 3.65-2.75 (m, 6H), 2.9 (s, 6H), 2.3 (s, 3H), 2.05 (s, 3H), 1.95 (s, 6H).

Anal. Calcd. for $C_{19}H_{27}NO_5 \cdot HCl$: C, 59.14; H, 7.31; N, 3.63. Found: C, 59.02; H, 7.51; N, 3.52.

The following were similarly prepared:

2-(4-Morpholinyl)ethyl ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (**16**).

This compound (2.38 g, 69%) had ir: 2556, 2455, 1753, 1738 cm^{-1} ; 1H nmr (methanol- d_4): δ 5.4-4.9 (m, 1H), 4.6-4.35 (tb, 2H), 4.15-3.75 (tb, 4H), 3.6-2.6 (m, 10H), 2.3 (s, 3H), 2.05 (s, 3H), 1.95 (s, 6H).

Anal. Calcd. for $C_{21}H_{29}NO_6 \cdot HCl$: C, 58.94; H, 7.06; N, 3.27. Found: C, 58.99; H, 7.01; N, 3.28.

2-(4-Methyl-1-piperazinyl)ethyl ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (**17**).

This compound (6.0 g, 68%) had ir: 3455, 1752 cm^{-1} ; 1H nmr (methanol- d_4): δ 5.3-4.9 (m, 1H), 4.7-4.4 (m, 2H), 3.8-3.6 (m, 8H), 3.0 (s, 3H), 3.3-2.8 (m, 4H), 2.3 (s, 3H), 2.05 (s, 3H), 1.95 (s, 6H).

Anal. Calcd. for $C_{22}H_{32}N_2O_5 \cdot 2HCl$: C, 55.35; H, 7.18; N, 5.87; Cl, 14.85. Found: C, 54.44; H, 7.34; N, 5.64; Cl, 14.68.

2-(1-Piperidinyl)ethyl ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (**18**).

This compound (14.2 g, 77%) had ir: 1757, 1732 cm^{-1} ; 1H nmr (deuteriochloroform): δ 5.3-4.9 (m, 1H), 4.7-4.4 (tb, 2H), 3.7-2.8 (m, 8H), 2.9 (d, 2H), 2.3 (s, 3H), 2.05 (s, 3H), 2.0 (s, 6H).

Anal. Calcd. for $C_{22}H_{31}NO_5 \cdot HCl$: C, 62.03; H, 7.57; N, 3.29; Cl, 8.32. Found: C, 61.85; H, 7.93; N, 3.17; Cl, 8.30.

1-[($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetyl]-4-methylpiperazine (**21**).

This compound (2.9 g, 69%) had ir: 1754, 1655 cm^{-1} ; 1H nmr (deuteriochloroform): δ 5.3-4.9 (m, 1H), 4.2-3.7 (m, 4H), 3.6-2.7 (m, 8H), 2.8 (s, 3H), 2.3 (s, 3H), 2.05 (s, 3H), 1.95 (s, 6H).

Anal. Calcd. for $C_{20}H_{28}N_2O_4 \cdot HCl$: C, 60.52; H, 7.44; N, 7.06. Found: C, 60.23; H, 7.36; N, 7.09.

N-[2-(4-Morpholinyl)ethyl] ($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetamide (**22**).

This compound (2.9 g, 75% isolated as the free base and purified by flash chromatography, eluant chloroform:methanol 95:5) had ir: 1752, 1643 cm^{-1} ; 1H nmr (deuteriochloroform): δ 6.6 (tb, 1H), 5.3-4.8 (m, 1H), 3.7 (t, 4H), 3.5-2.4 (m, 12H), 2.3 (s, 3H), 2.1 (s, 3H), 1.95 (s, 3H).

Anal. Calcd. for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found: C, 64.13; H, 7.80; N, 7.14.

($\pm$)-2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranacetic Acid (**10**) and the Methyl Ester **23**.

Potassium hydroxide powder (7.0 g) was added to a solution of crude **4a** (10 g of 75% purity) in dry acetone (60 ml) at 5° with stirring. The resulting suspension was treated, still at 5°, with dimethyl sulfate (10 ml) in acetone (10 ml). The mixture was then slowly brought to room temperature and stirred for 2.5 hours. Evaporation of the solvent and partitioning of the residue between acidified water and ethyl acetate, followed by the usual work-up of the organics, gave an oily product which was purified by flash chromatography (eluant *n*-hexane:ethyl acetate 9:1) and optionally recrystallized. 7.1 g (85%) of **23** was obtained; ir: 1740 cm^{-1} ; 1H nmr (deuteriochloroform): δ 5.35-4.85 (m, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.4-2.5 (m, 4H), 2.15 (s, 6H), 2.05 (s, 3H).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.92; H, 7.58.

Alkaline hydrolysis of **23** (2*N* sodium hydroxide, room temper-

ature, 1 hour) gave **10** in quantitative yield; ir: 1702 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.3 (sb, 1H), 5.3-4.9 (m, 1H), 3.65 (s, 3H), 3.4-2.7 (m, 4H), 2.2 (s, 6H), 2.1 (s, 3H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25. Found: C, 67.10; H, 7.56.

2-(4-Morpholinyl)ethyl and 2-(1-Piperidinyl)ethyl ($\pm$)-2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranacetates **24** and **25**.

5-Methoxy acid **10** was converted to the acid chloride (ir: 1798 cm^{-1}) in the same way as that described for the 5-acyloxy acid **8**. Esterifications with 2-(4-morpholino)ethanol or 2-(1-piperidino)ethanol were performed in an analogous manner to that indicated for **16** and **18**, respectively.

Compound **24** (2.2 g, 66%) had ir: 1742 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.2-4.8 (m, 1H), 4.7 (tb, 2H), 4.05 (tb, 4H), 3.6 (s, 3H), 3.55-2.9 (m, 8H), 2.8 (d, 2H), 2.15 (s, 6H), 2.0 (s, 3H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_5 \cdot \text{HCl}$: C, 60.07; H, 7.56; N, 3.50. Found: C, 59.94; H, 7.69; N, 3.35.

Compound **25** (3.17 g, 73%) had ir: 2536, 1740 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.2-4.8 (m, 1H), 4.65 (t, 2H), 3.6 (s, 3H), 3.5-2.9 (m, 8H), 2.8 (d, 2H), 2.15 (s, 6H), 2.0 (s, 3H), 1.9-1.65 (m, 6H).

Anal. Calcd. for $\text{C}_{21}\text{H}_{31}\text{NO}_4 \cdot \text{HCl}$: C, 63.38; H, 8.10; N, 3.53. Found: C, 63.57; H, 8.41; N, 3.39.

Methyl ($\pm$)-2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuranacetate (**19**).

To a cooled solution of **4a** (2.0 g) in methanol (130 ml), concentrated sulfuric acid (11 ml) was added. The mixture was refluxed under nitrogen for 1 hour; after concentrating *in vacuo*, water and ethyl acetate were added. The organic extracts were washed with brine, dried over sodium sulfate and concentrated to afford 2.1 g (100%) of solid. This material was finally recrystallized to afford pure **19**; ir: 3423, 1731 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.3-4.8 (m, 1H), 3.7 (s, 3H), 3.6-2.6 (m, 4H), 2.1 (s, 9H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25. Found: C, 67.04; H, 7.26.

($\pm$)-2,3-Dihydro-2-(methoxycarbonyl)methyl-4,6,7-trimethyl-5-benzofuranol Hemisuccinate (**20**).

A mixture of **19** (2.5 g, 10 mmoles) and potassium hydroxide powder (0.62 g, 11 mmoles) in dimethylformamide (20 ml) was treated dropwise with a solution of succinic anhydride (1.1 g, 11 mmoles) in dimethylformamide (10 ml) and stirred at room temperature in a nitrogen atmosphere for 1 hour. The mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organics were washed twice with brine, dried and evaporated, to afford 3.5 g of a beige solid, which was recrystallized to give pure **20** in 93% yield; ir: 1741, 1731, 1694 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 10.5 (sb, 1H), 5.35-4.85 (m, 1H), 3.7 (s, 3H), 3.4-2.6 (m, 8H), 2.05 (s, 3H), 1.95 (s, 6H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{O}_7$: C, 61.71; H, 6.33. Found: C, 61.51; H, 6.20.

($\pm$)-2,3-Dihydro-5-isopropoxy-4,6,7-trimethyl-2-benzofuranacetic Acid (**11**).

To a solution of **19** (5.0 g, 20 mmoles) in dichloromethane (80 ml) were added 2-propanol (2.3 ml, 30 mmoles), triphenylphosphine (7.8 g, 30 mmoles) and diisopropyl azodicarboxylate (5.9 ml, 30 mmoles). The mixture was stirred at room temperature overnight. Evaporation of the solvent gave an oily residue that was chromatographed (eluant *n*-hexane:ethyl acetate 95:5) to give

4.2 g (72%) of methyl ($\pm$)-2,3-dihydro-5-isopropoxy-4,6,7-trimethyl-2-benzofuranacetate (ir: 1742 cm^{-1}). Ester hydrolysis (1N sodium hydroxide, acetone, room temperature, 1 hour) followed by recrystallization of crude acid, gave pure **11** in quantitative yield; ir: 1700 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 10.6 (s, 1H), 5.3-4.9 (m, 1H), 4.2-3.5 (m, 1H), 3.4-2.7 (m, 4H), 2.2 (s, 6H), 2.1 (s, 3H), 1.3 (d, 6H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_4$: C, 69.04; H, 7.97. Found: C, 69.07; H, 8.13.

2-[($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetyl]thiophene (**26**).

To a solution of 7.5 g of 5-acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetyl chloride (25 mmoles, prepared as described previously) in benzene (50 ml), thiophene (2.0 ml, 25 mmoles) and tin(IV) chloride (2.9 ml, 25 mmoles) were added. After 2 hours of stirring at room temperature, water (100 ml) and 6N hydrochloric acid (25 ml) were added to the mixture, that was then extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, and evaporated to dryness. The crude product (8.1 g) was purified by flash chromatography (eluant carbon tetrachloride:ethyl acetate 9:1); final recrystallization gave pure **26** (4.2 g, 48%); ir: 1746, 1657 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.7-7.5 (m, 2H), 7.15-6.95 (m, 1H), 5.5-5.0 (m, 1H), 3.7-2.8 (m, 4H), 2.3 (s, 3H), 2.05 (s, 3H), 2.0 (s, 6H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_4\text{S}$: C, 66.26; H, 5.85. Found: C, 66.35; H, 5.95.

2-[($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetyl]-5-bromothiophene (**27**).

This compound (2.97 g, 48%) was similarly prepared from 2-bromothiophene; ir: 1740, 1666 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.4 (d, 1H), 7.05 (d, 1H), 5.5-5.0 (m, 1H), 3.6-2.7 (m, 4H), 2.3 (s, 3H), 2.05 (s, 3H), 2.0 (s, 6H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{BrO}_4\text{S}$: C, 53.91; H, 4.52; Br, 18.87. Found: C, 54.03; H, 4.67; Br, 18.55.

($\pm$)-2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuranethanol (**28**).

A solution of **4a** (3.4 g, 14 mmoles) in dry tetrahydrofuran (35 ml) was added dropwise to a suspension of lithium aluminium hydride (1.1 g) in dry tetrahydrofuran (20 ml). The mixture was refluxed under a nitrogen atmosphere for 1 hour, then it was cooled and cautiously treated first with ethyl acetate (11 ml) and then with 6N hydrochloric acid. The resulting solution was extracted with ethyl acetate; the organics were then washed with brine, saturated bicarbonate, and brine again. After drying over sodium sulfate, the solvent was evaporated, leaving 3.1 g (98%) of a cream solid. Final recrystallization afforded pure **28**; ir: 3284, 1055 cm^{-1} ; ^1H nmr (methanol- d_4): δ 5.1-4.4 (m, 2H), 3.7 (t, 2H), 3.3-2.6 (m, 2H), 2.1 (s, 6H), 2.0 (s, 3H), 1.85 (m, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_3$: C, 70.24; H, 8.16. Found: C, 69.99; H, 8.23.

($\pm$)-2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranethanol (**29**).

This compound was similarly prepared in 89% yield starting from **10**; ir: 3382, 1239 cm^{-1} ; ^1H nmr (carbon tetrachloride): δ 5.0-4.5 (m, 1H), 4.4 (s, 1H), 3.7 (t, 2H), 3.5 (s, 3H), 3.3-2.4 (m, 2H), 2.05 (s, 6H), 2.0 (s, 3H), 2.0-1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3$: C, 71.16; H, 8.53. Found: C, 71.06; H, 8.65.

($\pm$)-5-Benzoyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranethanol (**30**).

Benzoylation of **19** was performed in the usual way (1.5 molar excess of benzyl bromide and potassium carbonate, dimethylformamide, room temperature, 24 hours). The resulting methyl ($\pm$)-5-benzoyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetate (ir: 3035, 1731 cm^{-1}) was reduced with lithium aluminium hydride (or diisobutyl aluminium hydride) as described for the preparation of **28**, obtaining 3.81 g (71% yield from **19**) of pure **30**; ir: 3359 cm^{-1} ; ^1H nmr (carbon tetrachloride): δ 7.5-7.2 (m, 5H), 5.1-4.6 (m, 1H), 4.7 (s, 2H), 4.3 (s, 1H), 3.7 (t, 2H), 3.3-2.6 (m, 2H), 2.1 (s, 6H), 2.0 (s, 3H), 2.0-1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_3$: C, 76.89; H, 7.74. Found: C, 77.22; H, 7.82.

($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranethanol (**31**).

To a solution of ($\pm$)-5-acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranacetyl chloride (10.6 g, 36 mmoles, prepared as described previously) in dry dioxane (120 ml), 7.0 g of sodium borohydride were added portionwise. The mixture was stirred at room temperature overnight; water and 6N hydrochloric acid were then added and the resulting solution was extracted with ethyl acetate. The organic layer was washed with saturated bicarbonate and brine, dried and evaporated to leave 9.8 g of crude product. Column chromatography (eluant chloroform:methanol 95:5) followed by recrystallization afforded pure **31** in 77% yield; ir: 3396, 1755 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.1-4.6 (m, 1H), 4.2 (s, 1H), 3.7 (t, 2H), 3.3-2.5 (m, 2H), 2.3 (s, 3H), 2.1 (s, 3H), 2.0 (s, 6H), 2.0-1.7 (m, 2H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.16; H, 7.63. Found: C, 68.31; H, 7.65.

($\pm$)-2,3-Dihydro-2-(2-hydroxyethyl)-4,6,7-trimethyl-5-benzofuranol 5-Hemisuccinate (**32**).

To a cooled solution of **28** (21.3 g, 0.096 mole) in dimethylformamide (42 ml), imidazole (16.3 g, 0.240 mole) and *t*-butyldimethylsilyl chloride (17.4 g, 0.110 mole) were added. The mixture was stirred for 15 minutes under nitrogen, then potassium hydroxide (13.4 g) was added. After 1 hour of stirring at room temperature the mixture was treated dropwise with a solution of succinic anhydride (11.5 g, 0.115 mole) in dimethylformamide (100 ml). The reaction was complete in 1 hour; final deprotection was performed by treatment with 6N hydrochloric acid (80 ml). Extraction with ethyl acetate was followed by washing with water and re-extraction with saturated sodium bicarbonate. Acidification of the aqueous phase led to the precipitation of a gummy solid, that was filtered under suction, dried and recrystallized to give pure **32** (13.2 g, 43%); ir: 1731, 1713 cm^{-1} ; ^1H nmr (methanol- d_4): δ 5.0-4.5 (m, 1H), 3.75 (t, 2H), 3.4-2.5 (m, 6H), 2.1 (s, 3H), 2.0 (s, 6H), 2.0-1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{O}_6$: C, 63.34; H, 6.88. Found: C, 63.61; H, 6.60.

($\pm$)-5-(Carboxymethoxy)-2,3-dihydro-4,6,7-trimethyl-2-benzofuranethanol (**33**).

Alkylation of the 5-hydroxy group of **28** was performed under standard conditions (1.5 molar excess of ethyl bromoacetate and potassium carbonate, dimethylformamide, room temperature, 24 hours). Saponification of the resulting ($\pm$)-5-(carboethoxymethoxy)-2,3-dihydro-4,6,7-trimethyl-2-benzofuranethanol (ir: 1731

cm^{-1}) was carried out with 2N sodium hydroxide in acetone at room temperature (30 minutes) and gave crude **33**. Recrystallization afforded the pure product in 76% yield from **28**; ir: 3471, 1746 cm^{-1} ; ^1H nmr (methanol- d_4): δ 5.0-4.5 (m, 1H), 4.2 (s, 2H), 3.6 (t, 2H), 3.4-2.6 (m, 2H), 2.1 (s, 6H), 2.0 (s, 3H), 2.0-1.7 (m, 2H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_5$: C, 64.27; H, 7.19. Found: C, 64.11; H, 7.32.

($\pm$)-2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranethanol Hemisuccinate (**34**).

Acylation of the alcoholic side chain of **29** was performed essentially as described before for the synthesis of **20** from **19**. Pure **34** was obtained in 91% yield; ir: 1723 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 10.35 (s, 1H), 5.0-4.5 (m, 1H), 4.3 (t, 2H), 3.6 (s, 3H), 3.5-2.7 (m, 2H), 2.7-2.5 (m, 4H), 2.1 (s, 6H), 2.05 (s, 3H), 2.0-1.7 (m, 2H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_6$: C, 64.27; H, 7.19. Found: C, 64.26; H, 7.46.

($\pm$)-2,3-Dihydro-2-(2-iodoethyl)-4,6,7-trimethyl-5-benzofuranol (**35**).

A mixture of **28** (3.1 g, 14 mmoles), triphenylphosphine (5.5 g, 21 mmoles), and imidazole (1.4 g, 21 mmoles) in 60 ml of toluene was treated with iodine (4.4 g, 17 mmoles). The slurry was stirred at 60° for 2.5 hours, then the solids were filtered and the mother liquors were washed with saturated sodium bicarbonate. The organic layer was finally dried and evaporated. The crude residue was chromatographed (eluant *n*-hexane:acetone 95:5) to obtain 3.0 g (64%) of pure **35**; ir: 3403, 1195 cm^{-1} ; ^1H nmr (carbon tetrachloride): δ 4.9-4.4 (m, 1H), 4.0 (s, 1H), 3.2 (t, 2H), 3.0-2.5 (m, 2H), 2.2 (m, 2H), 2.1 (s, 9H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{IO}_2$: C, 47.00; H, 5.16. Found: C, 46.98; H, 5.14.

($\pm$)-2-(2-Bromoethyl)-2,3-dihydro-4,6,7-trimethyl-5-benzofuranol Acetate (**36**).

Bromination of **31** (1.86 g) to afford **36** was performed following the same procedure described above, using 1.2 molar excess of bromine. A clear oil (1.53 g, 66%) was obtained; ir (neat): 1760, 1206 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.1-4.6 (m, 1H), 3.5 (t, 2H), 3.4-2.4 (m, 2H), 2.3 (s, 3H), 2.1 (s, 3H), 2.0 (s, 6H), 1.9-1.7 (m, 2H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{BrO}_3$: C, 55.06; H, 5.85. Found: C, 54.81; H, 6.22.

($\pm$)-2,3-Dihydro-4,6,7-trimethyl-2-[2-(4-morpholinyl)ethyl]-5-benzofuranol Acetate (**37**).

A mixture of **36** (3.0 g) and morpholine (1.7 ml, 2.2 equivalents) in absolute ethanol (60 ml) was refluxed under stirring for 8 hours. The resulting solution was then concentrated *in vacuo*, and saturated sodium bicarbonate and ether were added. After partitioning, the organic layer was washed with water and brine, dried and concentrated. The addition of ethereal hydrogen chloride resulted in the precipitation of **37** (3.0 g, 88%) as the hydrochloride; ir: 1760 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.0-4.6 (m, 1H), 4.1 (t, 4H), 3.4-2.7 (m, 8H), 2.5-2.2 (m, 2H), 2.3 (s, 3H), 2.1 (s, 3H), 1.95 (s, 6H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{27}\text{NO}_4 \cdot \text{HCl}$: C, 61.70; H, 7.63; N, 3.79; Cl, 9.58. Found: C, 61.76; H, 7.80; N, 3.58; Cl, 9.28.

The following were similarly prepared:

($\pm$)-2,3-Dihydro-4,6,7-trimethyl-2-[2-(1-piperidinyl)ethyl]-5-benzofuranol Acetate (**38**).

This compound (2.2 g, 85%) had ir: 1754, 1222 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.0-4.6 (m, 1H), 3.6-2.2 (m, 14H), 2.3 (s, 3H), 2.1 (s, 3H), 1.95 (s, 6H), 1.9-1.6 (m, 2H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_3 \cdot \text{HCl}$: C, 65.29; H, 8.22; N, 3.81; Cl, 9.64. Found: C, 65.32; H, 8.49; N, 3.53; Cl, 9.62.

($\pm$)-2,3-Dihydro-4,6,7-trimethyl-2-[2-(4-methyl-1-piperazinyl)ethyl]-5-benzofuranol Acetate (**39**).

This compound (1.5 g, 94%, isolated as free base) had ir (neat): 1750 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.0-4.6 (m, 1H), 3.4-2.6 (m, 2H), 2.6-2.35 (m, 10H), 2.4 (s, 3H), 2.3 (s, 3H), 2.15 (s, 6H), 2.1 (s, 3H), 2.05-1.7 (m, 2H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.18; H, 8.68; N, 8.16.

($\pm$)-2-(2-Aminoethyl)-2,3-dihydro-4,6,7-trimethyl-5-benzofuranol (**40**).

A mixture of **28** (222 mg, 1 mmole), phthalimide (162 mg, 1.1 mmoles), and triphenylphosphine (393 mg, 1.5 mmoles) in dry tetrahydrofuran (2 ml) was cooled at 0° and treated portionwise with diisopropyl azodicarboxylate (0.3 ml, 1.5 mmoles). The solution was stirred at room temperature for 3 hours, the solvent was evaporated, and the residue was purified by preparative tlc (eluant chloroform:ethyl acetate 9:1), obtaining 123 mg (35%) of *N*[($\pm$)-2-(2,3-dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuran-1-yl)ethyl]phthalimide; ir: 1772, 1716 cm^{-1} . This material was dissolved in absolute ethanol (1 ml) and tetrahydrofuran (1 ml) and treated with hydrazine hydrate (0.05 ml). The mixture was refluxed for 2 hours; after cooling, the precipitated phthalhydrazide was filtered away and the filtrate evaporated. The residue was dissolved in chloroform and treated with ethereal hydrogen chloride until precipitation was complete, obtaining, after filtration, **40** (66 mg, 73%) as colorless crystals; ir: 3410, 3059 cm^{-1} ; ^1H nmr (deuterium oxide): δ 5.0-4.6 (m, 1H), 3.4-2.7 (m, 4H), 2.3-2.1 (m, 2H), 2.1 (s, 6H), 2.0 (s, 3H).

Anal. Calcd. for $\text{C}_{31}\text{H}_{19}\text{NO}_2 \cdot \text{HCl}$: C, 60.58; H, 7.82; N, 5.43. Found: C, 60.32; H, 7.91; N, 5.39.

($\pm$)-5-Benzyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranethanamine (**41**).

This compound was similarly prepared in 91% yield from **30** and had ir: 3032, 1236 cm^{-1} ; ^1H nmr (methanol- d_4): δ 7.5-7.2 (m, 5H), 5.0-4.6 (m, 1H), 4.7 (s, 2H), 3.4-2.7 (m, 4H), 2.4-2.2 (m, 2H), 2.2 (s, 6H), 2.1 (s, 3H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_2 \cdot \text{HCl}$: C, 69.05; H, 7.53; N, 4.03. Found: C, 69.00; H, 7.43; N, 4.25.

($\pm$)-5-Benzyloxy-2,3-dihydro-2-[2-(4-morpholinyl)ethyl]-4,6,7-trimethylbenzofuran (**42**).

Bromination of the alcoholic side chain of **30** was performed essentially in the same way to that indicated for **36**. The resulting ($\pm$)-2-(2-bromoethyl)-5-benzyloxy-2,3-dihydro-4,6,7-trimethylbenzofuran (ir: 3034, 1594 cm^{-1}) was reacted with morpholine in an analogous fashion to that described for **37**. Pure **42** was obtained as hydrochloride in 75% overall yield; ir: 2600 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.5-7.2 (m, 5H), 5.1-4.5 (m, 1H), 4.7 (s, 2H), 4.8-4.3 (m, 4H), 3.5-2.6 (m, 8H), 2.4-2.2 (m, 2H), 2.2 (s, 6H), 2.1 (s, 3H).

Anal. Calcd. for $\text{C}_{22}\text{H}_{31}\text{NO}_3 \cdot \text{HCl}$: C, 68.97; H, 7.72; N, 3.35. Found: C, 68.59; H, 7.63; N, 3.09.

($\pm$)-5-Benzyloxy-2,3-dihydro-4,6,7-trimethyl-*N,N*-diethyl-2-benzofuranethanamine (**43**).

A solution of the above, mentioned ($\pm$)-2-(2-bromoethyl)-5-benzyloxy-2,3-dihydro-4,6,7-trimethylbenzofuran (122 mg, 0.32 mmole) in diethylamine (1 ml) was refluxed for 1 hour. The work-up of the reaction followed the same procedure indicated for the preparation of **37**. Pure **43** (100 mg, 76%) was obtained as hydrochloride; ir: 2646, 2442, 1079 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.5-7.2 (m, 5H), 5.1-4.7 (m, 1H), 4.7 (s, 2H), 3.5-2.7 (m, 8H), 2.5-2.3 (m, 2H), 2.2 (s, 6H), 2.1 (s, 3H), 1.4 (t, 6H).

Anal. Calcd. for $\text{C}_{24}\text{H}_{33}\text{NO}_2 \cdot \text{HCl}$: C, 71.35; H, 8.48; N, 3.47. Found: C, 71.04; H, 8.16; N, 3.18.

($\pm$)-*N*-[2-(5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuran-1-yl)ethyl]palmitamide (**44**).

A solution of ($\pm$)-5-acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranethanamine (1.7 g, prepared from **31** in the same manner as **40**; it had ir: 1757 cm^{-1}) in chloroform (30 ml) and triethylamine (0.95 ml, 1.2 equivalents) was treated portionwise with palmitoyl chloride (2.14 ml, 1.1 equivalents). The mixture was stirred at room temperature for 1 hour; after washing with 1*N* hydrochloric acid, saturated sodium bicarbonate, and water, the chloroform solution was dried and evaporated to dryness. Chromatography of the residue (eluant carbon tetrachloride:ethyl acetate 9:1) gave pure **44** (2.65 g, 82%); ir: 3306, 1756 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 6.2 (sb, 1H), 5.0-4.5 (m, 1H), 3.5 (tb, 2H), 3.4-2.6 (m, 4H), 2.3 (s, 3H), 2.1 (s, 3H), 2.0 (s, 6H), 2.0-1.7 (m, 2H), 1.5-1.2 (m, 26H), 0.95 (tb, 3H).

Anal. Calcd. for $\text{C}_{31}\text{H}_{51}\text{NO}_4$: C, 74.21; H, 10.24; N, 2.79. Found: C, 74.37; H, 10.33; N, 2.66.

($\pm$)-*N*-[2-(5-Benzyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuran-1-yl)ethyl]-3,4,5-trimethoxybenzamide (**45**).

This compound was similarly prepared in 71% yield from **41** and 3,4,5-trimethoxybenzoyl chloride; ir: 3271, 1684, 1543 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.4-7.2 (m, 5H), 7.0 (s, 2H), 6.8 (t, 1H), 5.1-4.7 (m, 1H), 4.7 (s, 2H), 3.8 (s, 9H), 3.8-3.4 (m, 2H), 3.2-2.7 (m, 2H), 2.2 (s, 6H), 2.1 (s, 3H), 2.1-1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{30}\text{H}_{35}\text{NO}_6$: C, 71.27; H, 6.98; N, 2.77. Found: C, 71.11; H, 6.90; N, 2.73.

($\pm$)-2-(2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuran-1-yl)ethylthio-2-thiazoline (**46**).

A solution of 2-mercapto-2-thiazoline (1.28 g, 11 mmoles) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.74 ml, 12 mmoles) in benzene (20 ml) was treated with a benzene solution of ($\pm$)-2-(2-bromoethyl)-2,3-dihydro-5-methoxy-4,6,7-trimethylbenzofuran (2.91 g, 10 mmoles, ir: 1208 cm^{-1} , prepared from **29** by the method previously described for the conversion **31** $\rightarrow$ **36**). The mixture was stirred at room temperature for 2 hours; the precipitated DBU·HBr was filtered and the filtrate was evaporated to dryness, leaving a crude residue that was purified by flash chromatography (eluant *n*-hexane:ethyl acetate 8:2). Treatment of the resulting oily product with ethereal hydrogen chloride afforded 2.72 g (75%) of pure **46** as hydrochloride salt; ir: 1570, 1239 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.0-4.7 (m, 1H), 4.5 (t, 2H), 3.9-3.4 (m, 4H), 3.6 (s, 3H), 3.25-2.75 (m, 3H), 2.4-2.1 (m, 2H), 2.1 (s, 6H), 2.0 (s, 3H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{23}\text{NO}_2\text{S}_2 \cdot \text{HCl}$: C, 54.60; H, 6.47; N, 3.75. Found: C, 54.53; H, 6.64; N, 3.59.

The following were similarly prepared:

($\pm$)-2-(2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranyl)ethylthio-2-pyrimidine (**47**).

This compound (116 mg, 70%, isolated as free base) had ir (neat): 1080 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.5 (d, 2H), 6.9 (t, 1H), 5.1-4.6 (m, 1H), 3.8 (s, 3H), 3.3 (t, 2H), 3.2-2.6 (m, 2H), 2.1 (s, 6H), 2.05 (s, 3H), 2.0-1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.35; H, 6.67; N, 8.45.

($\pm$)-2-(2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranyl)ethylthio-1-methylimidazole (**48**).

This compound (2.04 g, 55%) had ir: 2827, 1238, 1081 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.6-7.2 (m, 2H), 5.2-4.6 (m, 1H), 3.85 (s, 3H), 3.7 (t, 2H), 3.6 (s, 3H), 3.4-2.5 (m, 2H), 2.3-1.9 (m, 2H), 2.1 (s, 6H), 2.05 (s, 3H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{S}\cdot\text{HCl}$: C, 58.60; H, 6.83; N, 7.59. Found: C, 58.71; H, 6.93; N, 7.58.

($\pm$)-2-[2-(2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuranyl)-ethylthio]benzothiazole Hemisuccinate (**49**).

($\pm$)-2-(5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranyl)-ethylthio-2-benzothiazole (prepared from **36** and 2-mercapto-benzothiazole in the same manner as described above; it had ir: 3063, 1763, 1713 cm^{-1}) was hydrolyzed to the 5-hydroxybenzofuranyl derivative in the usual manner (4 equivalents of 1N sodium hydroxide, acetone, room temperature, 2 hours), and the resulting product was reacted crude with succinic anhydride in dimethylformamide as described for the conversion **19** $\rightarrow$ **20**. Pure **49** was obtained in 47% overall yield; ir: 1718, 1712 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 10.0 (s, 1H), 7.9-7.6 (m, 2H), 7.5-7.1 (m, 2H), 5.1-4.7 (m, 1H), 3.5 (t, 2H), 3.2-2.6 (m, 6H), 2.4-2.15 (m, 2H), 2.1 (s, 3H), 1.95 (s, 6H).

Anal. Calcd. for $\text{C}_{24}\text{H}_{25}\text{NO}_5\text{S}_2$: C, 61.13; H, 5.34; N, 2.97. Found: C, 61.11; H, 5.59; N, 2.54.

($\pm$)-2-[2-(Acetylthio)ethyl]-2,3-dihydro-4,6,7-trimethyl-5-benzofuranol (**50**).

Diisopropyl azodicarboxylate (4.2 ml, 21 mmoles) was added to a solution of triphenylphosphine (5.5 g, 21 mmoles) in dry tetrahydrofuran (80 ml) with stirring at 0° under nitrogen. After 1 hour a solution of **28** (3.1 g, 14 mmoles) and thiolacetic acid (1.5 ml, 21 mmoles) in dry tetrahydrofuran (30 ml) was added and the reaction was then allowed to warm to room temperature. Upon completion of the reaction (about 1 hour) the solvent was removed and the residue taken up in ether (50 ml). After cooling, the insoluble material was removed. The filtrate was washed with 2N hydrochloric acid (3 x 35 ml), brine, saturated sodium bicarbonate (3 x 35 ml), and brine again; the organic layer was dried and evaporated. The residue was treated with petroleum ether: ethyl acetate 3:1 (30 ml) and cooled; the resulting white solid was filtered and the filtrate concentrated *in vacuo* to a red oil (5.9 g), which was finally chromatographed (eluant *n*-hexane:acetone 9:1) and recrystallized, to afford 3.1 g (80%) of a white solid; ir: 3406, 1686 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.1-4.5 (m, 2H), 3.4-2.6 (m, 4H), 2.3 (s, 3H), 2.1 (s, 9H), 2.0-1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{S}$: C, 64.26; H, 7.20. Found: C, 64.29; H, 7.30.

($\pm$)-2-[2-(Acetylthio)ethyl]-2,3-dihydro-4,6,7-trimethyl-5-benzofuranol Hemisuccinate (**51**).

Acylation of **50** with succinic anhydride followed a similar pro-

cedure to that described for the synthesis of **20**, and gave the title product in 92% yield; ir: 1747, 1710, 1693 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 10.3 (s, 1H), 5.1-4.5 (m, 1H), 3.6-2.6 (m, 8H), 2.3 (s, 3H), 2.1 (s, 3H), 1.95 (s, 6H), 1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{24}\text{O}_6\text{S}$: C, 59.98; H, 6.36. Found: C, 59.99; H, 6.37.

($\pm$)-2,3-Dihydro-2-(2-mercaptoethyl)-4,6,7-trimethyl-5-benzofuranol (**52**).

To a solution of **50** (5.1 g, 18 mmoles) in acetone (90 ml) was added 25% aqueous ammonia solution (20 ml) and the mixture was stirred at room temperature under nitrogen atmosphere for 16 hours. Next, the mixture was acidified with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was then washed with brine, dried and evaporated to dryness, obtaining 5.2 g of a cream solid. Recrystallization afforded 4.3 g (100%) of product, containing the -S-S- dimer as the only detectable impurity; ir: 3351, 1237 cm^{-1} ; ^1H nmr (DMSO- d_6): δ 5.1-4.4 (m, 1H), 3.5 (sb, 1H), 3.2-2.6 (m, 4H), 2.1 (m, 2H), 2.0 (s, 6H), 1.95 (s, 3H), 1.2 (t, 1H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2\text{S}$: C, 65.51; H, 7.61. Found: C, 65.53; H, 7.45.

($\pm$)-5-Benzyloxy-2-ethyl-2,3-dihydro-4,6,7-trimethylbenzofuran (**53**).

p-Toluenesulfonyl chloride (2.57 g, 13 mmoles) was added to an ice-cooled solution of **30** (3.5 g, 11 mmoles) in pyridine (11 ml). The mixture was stirred at 0° for 3 hours, then acidified with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, dried and evaporated to leave 4.35 g (85%) of ($\pm$)-5-benzyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuranethanol *p*-toluenesulfonate; ir: 1359, 1177 cm^{-1} . To a suspension of lithium aluminium hydride (1.3 g) in dry tetrahydrofuran (20 ml) was added dropwise a solution of the above-mentioned tosylate (4.0 g) in dry tetrahydrofuran (30 ml). After having been stirred for 30 minutes the mixture was quenched with 2N hydrochloric acid until hydrogen evolution ceased; metal hydroxides were then filtered, resuspended in ether and filtered again. The combined filtrates were finally washed with brine, dried and evaporated to dryness, obtaining 2.54 g (100%) of **53**, pure enough for next reaction. An analytically pure specimen was obtained by preparative tlc (eluant *n*-hexane:ethyl acetate 9:1); ir: 1595, 1237 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.5-7.1 (m, 5H), 4.8-4.4 (m, 1H), 4.7 (s, 2H), 3.3-2.5 (m, 2H), 2.2 (s, 6H), 2.1 (s, 3H), 1.9-1.5 (m, 2H), 1.0 (t, 3H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_2$: C, 81.04; H, 8.16. Found: C, 80.89; H, 8.09.

($\pm$)-2-Ethyl-2,3-dihydro-4,6,7-trimethyl-5-benzofuranol (**54**).

Debenzylation of **53** (2.6 g) was performed with 10% palladium-on-carbon (0.3 g) in absolute ethanol (50 ml) under 70 psi of hydrogen at 40°. Filtration of the catalyst over Celite and evaporation of the filtrate left 1.4 g (77%) of **54**, pure enough for synthetic purposes. An analytically pure specimen was obtained by tlc (eluant dichloromethane:ethyl acetate 9:1); ir: 3378 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 4.9-4.5 (m, 1H), 4.2 (s, 1H), 3.3-2.7 (m, 2H), 2.1 (s, 6H), 2.0 (s, 3H), 1.8-1.5 (m, 2H), 1.1 (t, 3H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.69; H, 8.79. Found: C, 75.66; H, 8.72.

($\pm$)-2-Ethyl-2,3-dihydro-4,6,7-trimethyl-5-benzofuranol Hemisuccinate (**55**).

Reaction between **54** and succinic anhydride was performed essentially as described for **20**, and gave the title product in 96% yield; ir: 1748, 1697 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 9.4 (s, 1H), 4.9-4.5 (m, 1H), 3.4-2.6 (m, 6H), 2.1 (s, 3H), 2.0 (s, 6H), 1.9-1.5 (m, 2H), 1.0 (t, 3H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{22}\text{O}_5$: C, 66.65; H, 7.24. Found: C, 66.60; H, 7.51.

($\pm$)-3-(2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranyl)-propionic Acid (**56**).

A solution of 6.25 g (16 mmoles) of ($\pm$)-2,3-dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranethanol *p*-toluenesulfonate (prepared from **29** as described in the first step of the synthesis of **53**; it had ir: 1356, 1179 cm^{-1}) in 95° ethanol:dimethylformamide 5:1 (40 ml) was treated with 1.6 g of sodium cyanide. The mixture was refluxed for 1.5 hours, cooled and partitioned between water and ethyl acetate. The organic layer was washed with brine, dried and evaporated to give 4.0 g (100%) of ($\pm$)- β -(2,3-dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranyl)propionitrile (ir: 2244, 1236, 1079 cm^{-1}), that was finally refluxed in 55 ml of ethanolic potassium hydroxide (5*N* in 70% ethanol) for 4 hours, affording, after acidification and extraction of the mixture followed by usual work-up of the organics, 3.8 g (88%) of crude product. Decolorization and recrystallization finally gave pure **56**; ir: 1698 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 10.45 (s, 1H), 5.0-4.5 (m, 1H), 3.6 (s, 3H), 3.5-2.8 (m, 2H), 2.5 (tb, 2H), 2.1 (s, 6H), 2.0 (s, 3H), 2.0-1.8 (m, 2H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.16; H, 7.63. Found: C, 68.24; H, 7.53.

($\pm$)-4-(2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranyl)-butyric Acid (**57**).

A dichloromethane solution of dimethyl sulfoxide (4.2 ml in 12 ml) was added to a cooled (-60°) dichloromethane solution of oxalyl chloride (2.3 ml in 62 ml). 5.9 g (25 mmoles) of **29** dissolved in dichloromethane (25 ml) and 17 ml of triethylamine were introduced into the mixture after 10 minutes and 25 minutes, respectively. The reaction was then warmed to room temperature and quenched with water; after partitioning, the dichloromethane layer was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate and brine, in that order. The extracts were finally dried and evaporated; the residue was chromatographed (eluant *n*-hexane:acetone 9:1), affording 2.6 g (44%) of pure ($\pm$)-2,3-dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranacetaldehyde; ir: 2730, 1725 cm^{-1} . A solution of this aldehyde (2.6 g, 11 mmoles) and carbethoxymethylenetriphenylphosphorane (6.6 g, 19 mmoles) in dioxane (260 ml) was refluxed for 7 hours, then evaporated. The residue was chromatographed (eluant *n*-hexane:acetone 9:1), to give 3.17 g (95%) of ethyl 4-(2,3-dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranyl)-2-butenate; ir: 1722, 1657 cm^{-1} . Catalytic hydrogenation (10% palladium-on-carbon, ethanol, 60 psi of hydrogen), followed by saponification of the resulting saturated ester, finally gave the title product. Recrystallization afforded 2.9 g (42%) of pure **57**; ir: 1700 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 10.6 (s, 1H), 4.9-4.5 (m, 1H), 3.6 (s, 3H), 3.4-2.8 (m, 2H), 2.4 (tb, 2H), 2.1 (s, 6H), 2.05 (s, 3H), 2.0-1.65 (m, 4H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_4$: C, 69.04; H, 7.97. Found: C, 68.94; H, 7.64.

($\pm$)- α,α -Dimethyl-2,3-dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuranethanol (**58**).

Iodomethane (2.7 ml, 43 mmoles) was added dropwise to a suspension of magnesium (1.1 g, 45 mmoles) in dry ether (50 ml).

After 20 minutes the mixture was treated with a solution of **23** (4.6 g, 17 mmoles) in dry ether (100 ml) and stirred for 1 hour; saturated ammonium chloride was then added to quench the reaction. After partitioning, the organics were washed with brine, dried and evaporated; the residue was chromatographed (eluant chloroform:ethyl acetate 9:1), obtaining 4.4 g (95%) of product. Recrystallization finally afforded pure **58**; ir: 1239, 1196 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 5.2-4.7 (m, 1H), 3.6 (s, 3H), 3.4-2.6 (m, 2H), 2.9 (s, 1H), 2.1 (s, 6H), 2.0 (s, 3H), 1.8 (d, 2H), 1.35 (s, 3H), 1.3 (s, 3H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_3$: C, 72.69; H, 9.15. Found: C, 72.80; H, 9.13.

($\pm$)- α,α -Dimethyl-2,3-dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuranethanol (**59**).

The title product was obtained from **19** following the same procedure described above, yield 3.0 g (67%); ir: 3440, 1235 cm^{-1} ; ^1H nmr (methanol- d_4): δ 5.1-4.7 (m, 1H), 3.5-2.6 (m, 2H), 2.1 (s, 6H), 2.0 (s, 3H), 1.75 (d, 2H), 1.35 (s, 3H), 1.3 (s, 3H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_3$: C, 71.97; H, 8.86. Found: C, 71.90; H, 8.77.

($\pm$)- α,α -Dimethyl-2,3-dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuranethanol 5-Hemisuccinate (**60**).

Reaction between **59** and succinic anhydride was carried out in a similar way to that described for **20**. Pure **60** was obtained in 85% yield after flash chromatography (eluant chloroform:acetic acid 98:2) and recrystallization; ir: 3433, 1729 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.2 (s, 2H), 5.2-4.7 (m, 1H), 3.6-2.5 (m, 6H), 2.05 (s, 3H), 1.95 (s, 6H), 1.9-1.6 (m, 2H), 1.35 (s, 3H), 1.3 (s, 3H).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_6$: C, 65.13; H, 7.48. Found: C, 65.20; H, 7.83.

($\pm$)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-[2-(*p*-nitrophenyloxy)ethyl]benzofuran (**61**).

To a suspension of 1.7 g (42 mmoles) of 60% sodium hydride in dimethylformamide (40 ml) were added 8.7 g (39 mmoles) of **28**. After 30 minutes the mixture was treated with MEM chloride (4.5 ml, 39 mmoles) in benzene (24 ml) and stirred for 1 hour. The resulting mixture was then added to a suspension of 3.4 g (84 mmoles) of 60% sodium hydride in dimethylformamide (24 ml) and the overall was stirred for 30 minutes at 60° . *p*-Chloronitrobenzene (12.4 g, 78 mmoles) was then added and the reaction mixture was kept under stirring at 60° for 2 hours, then poured into ice water. The resulting mixture was then extracted twice with ethyl acetate; the combined extracts were washed with brine (2 x 30 ml), dried and evaporated. Flash chromatography of the residue (eluant chloroform:ethyl acetate 98:2) gave 12.0 g of ($\pm$)-2,3-dihydro-5-(2-methoxyethoxymethoxy)-4,6,7-trimethyl-2-[2-(*p*-nitrophenyloxy)ethyl]benzofuran; ir: 1260, 1222 cm^{-1} . A solution of this material in acetic acid (75 ml) containing 1.5 g of 10% sulfuric acid was stirred at 60° for 1 hour. Water and saturated sodium bicarbonate were then added to neutrality: the mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried and evaporated to dryness, leaving 9.5 g of a cream solid (67% yield from **28**). Pure **61** was obtained by recrystallization; ir: 1746, 1262, 1219 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 8.1 (d, 2H), 6.9 (d, 2H), 5.2-4.7 (m, 1H), 4.3 (t, 2H), 3.4-2.7 (m, 2H), 2.3-2.0 (m, 2H), 2.3 (s, 3H), 2.1 (s, 3H), 2.0 (s, 6H).

Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_6$: C, 65.44; H, 6.01; N, 3.63. Found: C, 65.53; H, 6.31; N, 3.33.

(+)- and (-)-2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2-benzofuran-acetic Acids (+)- and (-)-**4a**.

Equimolar amounts of racemic ($\pm$)-**4a** and (*S*)-(-)- α -methylbenzylamine were dissolved in ether:ethanol 7:1 (5 ml/mmol); the mixture was kept at -20° for 1 hour, then the resulting white solids were collected by filtration. The diastereomeric salt mixture was recrystallized three times with methanol:ethyl acetate 1:2 and finally converted to the acid to afford (-)-**4a**, mp (DSC) 178.6° ; $[\alpha]_D^{20} = -19.5^\circ$ (c 0.051, ethanol); ^1H nmr spectrum was identical with that of ($\pm$)-**4a**.

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C, 66.09; H, 6.82. Found: C, 65.70; H, 7.06.

The opposite enantiomer (+)-**4a** was similarly prepared from ($\pm$)-**4a** and (*R*)-(+)- α -methylbenzylamine. It had mp (DSC) 179.2° ; $[\alpha]_D^{20} = +19.3^\circ$ (c 0.126, ethanol); ^1H nmr was identical with that of ($\pm$)-**4a**.

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_4$: C, 66.09; H, 6.82. Found: C, 65.84; H, 7.10.

(+)- and (-)-5-Acetyloxy-2,3-dihydro-4,6,7-trimethyl-2-benzofuran-acetic Acids (+)- and (-)-**8**.

Acetylation of (+)- and (-)-**4a** were carried out in the same manner as described for the racemic compound to give (+)- and (-)-**8**, respectively. Compound (+)-**8** had mp (DSC) 157.2° ; $[\alpha]_D^{20} = +23.3^\circ$ (c 0.021, ethanol); ^1H nmr spectrum was identical with that of ($\pm$)-**8**.

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.74; H, 6.52. Found: C, 64.69; H, 6.53.

Enantiomer (-)-**8** had mp (DSC) 158.7° ; $[\alpha]_D^{20} = -23.0^\circ$ (c 0.065, ethanol); ^1H nmr spectrum was identical with that of ($\pm$)-**8**.

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_5$: C, 64.74; H, 6.52. Found: C, 64.45; H, 6.86.

(+)- and (-)-2,3-Dihydro-5-methoxy-4,6,7-trimethyl-2-benzofuran-acetic Acids (+)- and (-)-**10**.

Racemic ($\pm$)-**10** was salfied with (*S*)-(-)- α -methylbenzylamine in methanol:ether; the diastereomeric salt was recrystallized twice in the same solvent mixture and finally converted to (-)-**10**, mp (DSC) 136.6° ; $[\alpha]_D^{20} = -21.6^\circ$ (c 0.102, ethanol); ^1H nmr spectrum was identical with that of ($\pm$)-**10**.

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25. Found: C, 67.33; H, 7.40.

Enantiomer (+)-**10** was similarly prepared from ($\pm$)-**10** and (*R*)-(+)- α -methylbenzylamine, mp (DSC) 136.1° ; $[\alpha]_D^{20} = +21.5^\circ$ (c 0.046, ethanol); ^1H nmr spectrum was identical with that of ($\pm$)-**10**.

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25. Found: C, 67.36; H, 7.40.

We tentatively assigned the (*S*)-configuration to (-)-**4a**, (-)-**8** and (-)-**10** and the (*R*)-configuration to their (+)-antipodes on the basis of close structural relationships with the enantiomers of 6-hydroxy-2,5,7,8-tetramethylchroman-2-acetic acid, whose absolute configuration was unequivocally determined [15]. To further support this assignment, note that our resolution procedure was similar to that described for preparing the enantiomers of the above-mentioned chiral acid [16].

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