Benzofurans. Improved Syntheses of Bufuralol, 7-Ethyl-2-(2-*tert*-butylamino-1-hydroxyethyl)benzofuran, and 1''-Oxobufuralol, 7-Acetyl-2-(2-*tert*-butylamino-1-hydroxyethyl)benzofuran

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An improved laboratory scale synthesis of bufuralol (**1**) and 1''-oxobufuralol (**4**) was accomplished. The intermediate benzofurans were prepared *via* aromatization of 2,3-dihydrobenzofurans or by a one-step acid-catalyzed cyclization from 2,2-diethoxyethyl 4-bromo-6-ethyl-2-formylphenyl ether (**23**). Base-catalyzed cyclization of 3-(5-bromo-3-ethyl-2-hydroxyphenyl)-1,2-epoxypropane (**16**) provided the key intermediate, 5-bromo-7-ethyl-2-hydroxymethyl-2,3-dihydrobenzofuran (**17**). Selective functionalization of the C-2 and C-7 positions of the benzofuran ring system was accomplished to afford both **1** and **4**.

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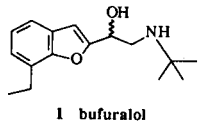
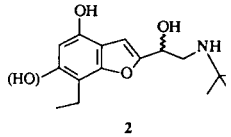
Bufuralol (**1**) is an antihypertensive agent with potent, nonselective β-adrenoreceptor antagonist properties [1]. In man and animals, it is metabolized to approximately fifteen different products *via* oxidative pathways [2]. These metabolites include two phenols **2**, benzylic alcohols **3** and the corresponding 1''-oxobufuralols **4**, of which the diastereomeric alcohols and the enantiomeric ketones could contribute to the observed pharmacological effects of the parent drug [3,4]. The oxidative metabolism of bufuralol exhibits genetic polymorphism of the debrisoquine-sparteine type [4-9], a phenomenon that seems to be associated with enzymatic hydroxylation by a single isozyme, cytochrome P-450 IID6, sometimes called cytochrome P-450-DB. This enzyme, which is deficient or defective in 5-8% of causasian populations, has been the subject of intense investigation.

Bufuralol (**1**) is an important substrate for the study of the oxidative transformations catalyzed by cytochrome P-450 IID6, and because it is a chiral molecule, stereoselective aspects of its metabolism are potentially important parameters to be examined in these transformations. In order to begin a study of the stereochemical features of these pathways, easily obtained quantities of bufuralol (**1**) and 1''-oxobufuralol (**4**) were needed. In this paper, efficient routes to both of these compounds are reported.



1 bufuralol



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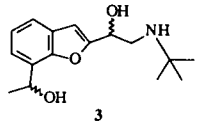

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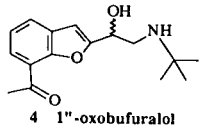
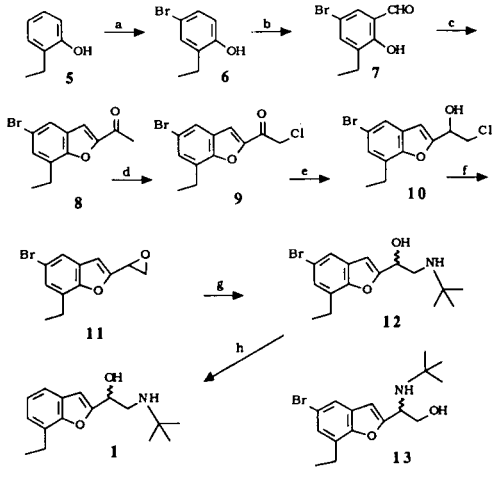


4 1''-oxobufuralol

The previously reported synthesis of bufuralol, outlined in Scheme 1 [11], is lengthy and is reported to occur in only about 4 per cent overall yield. Key problematic steps are the *ortho* formylation of **6** and the reaction of the resulting salicyladehyde **7** with chloroacetone to form benzofuran **8**. Each of these reactions occurs in less than 50% yield, with considerable amounts of intractable by-products.



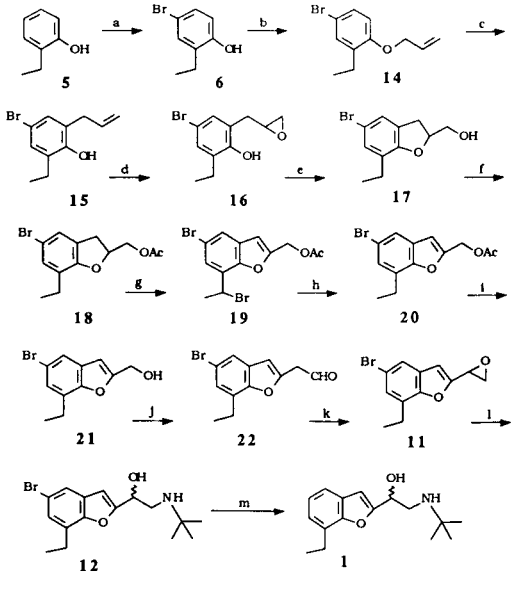
SCHEME 1. Synthesis of bufuralol [11].

Reagents: a. Br_2, AcOH; b. $(CH_2)_6N_4$, $(HCHO)_n$, AcOH, H_2SO_4; c. chloroacetone, NaOH, MeOH; d. SO_2Cl_2, $CHCl_3$; e. $NaBH_4$, MeOH; f. NaH, THF, 0°; g. *tert*-butylamine, MeOH; h. H_2, Pd-C, EtOH, 25°C, one atm.

The reported synthesis of 1''-oxobufuralol (**4**) is even more problematic. Its synthesis depends on bufuralol (**1**), which after protection of the amino alcohol side-chain, is brominated at the benzylic position, and the halide is displaced hydrolytically. Subsequent oxidation and finally deprotection of the side chain yields **4** in a five-step process reported to occur in 20-30% yield from bufuralol (**1**) [10], thus in about 1 percent overall yield.

The improved synthesis of **1** is outlined in Scheme 2. A key feature of this method is construction of dihydrofuran derivative **17** from the Claisen rearrangement product of the allyl ether of phenol **6**. Bromination of 2-ethylphenol

(**5**) in glacial acetic acid provided 4-bromo-2-ethylphenol (**6**) (89%) [13]. Allyl ether **14** was obtained from phenol **6** by alkylation using potassium *tert*-butoxide in *tert*-butyl alcohol and allyl bromide (92%). The Claisen rearrangement of the allyl ether was carried out in *N,N*-dimethylaniline (194°) to give phenol **15** (82%). The rearrangement of the allyl group to the 4-position is prevented by the presence of the 4-bromo substituent in **14**. Expoxidation of **15** with *m*-chloroperbenzoic acid in methylene chloride in the dark gave the epoxide **16** (84%). Treatment of **16** with 5% potassium hydroxide in 70% aqueous dimethyl sulfoxide resulted in the intramolecular opening of the epoxide by the phenolate anion [14], forming dihydrobenzofuran **17** (75%).



SCHEME 2. Improved synthesis of bufuralol.

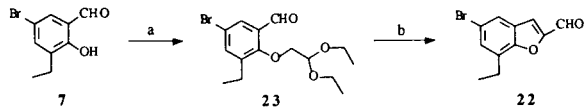
Reagents: a. Br_2, AcOH, 5-8°; b. *tert*-BuOK, *tert*-BuOH, allyl bromide, reflux; c. N,N-dimethylaniline, reflux; d. MCPBA, CH_2Cl_2, 0-25°; e. KOH, dimethylsulfoxide, H_2O, 25°; f. AcCl, 4-DMAP, CH_2Cl_2, Et_3N, 25°; g. N-bromosuccinimide, CCl_4, reflux; h. $NaBH_3CN$, HMPA, 70°; i. K_2CO_3, MeOH, 25°; j. Swern oxidation; k. $Me_3S^+I^-$, DMSO, THF, NaH; l. *tert*-butylamine, MeOH, benzene, reflux; m. H_2, Pd-C, EtOH, 1 atm.

Conversion of **17** to benzofuran **20** was accomplished in three steps. Acetylation of **17** gave acetate ester **18** (96%). Bromination of **18** using *N*-bromosuccinimide in refluxing carbon tetrachloride, in the presence of benzoyl peroxide as the radical initiator, proceeded with aromatization of the dihydrofuran ring by bromination-dehydrobromination and benzylic bromination of the 7-ethyl group to form benzofuran **19** (crude product in 90% yield). The bromination-dehydrobromination process was controlled by addition of *N*-bromosuccinimide in several portions in order to keep the available concentration of free bromine low. The 7-bromoethyl group of **19** was selectively reduced with sodium cyanoborohydride in hexamethyl phosphoramide [15] to give benzofuran **20** in 73% yield. Our attempts to directly dehydrogenate **18** with either DDQ or active manganese dioxide provided **20**, but only in yields of 10-15%.

Subsequent steps utilized the hydroxymethyl group at C-2 to elaborate the amino alcohol side-chain in **1**. Deacetylation of **20** was carried out in absolute methanol in the presence of potassium carbonate (98%). Superhydride reduction [16] of **19** also gave **21**, but in 53% yield. Aldehyde **22** was obtained (82%) by Swern oxidation of the 2-hydroxymethylbenzofuran **21**. Using active manganese dioxide in benzene and ether for this oxidation gave only a very low yield of **22** (<20%). Also, attempted direct oxidation of **17** to **22** with DDQ or active manganese dioxide also gave only a 10-15% yield of **22**.

Conversion of aldehyde **22** to epoxide **11** was achieved in 78% yield by methylene transfer using dimethylsulfonium methylide in tetrahydrofuran-dimethyl sulfoxide [18]. Opening of the epoxide **11** by *tert*-butylamine was performed in a methanol-benzene (50:50) mixture with an excess of the amine [11]. As reported, this reaction gave 56% of **12** and 5% of the unwanted regioisomer **13**. The 5-bromo substituent in **11** has a favorable directing effect in opening at the terminal position of the epoxide by the amine to afford the required amino alcohol **12** [11]. Hydrogenolysis of the 5-bromo substituent of **12** gave bufuralol **1** (93%) [11]. The overall yield from **6** to **1** is nearly 10%, an improvement over the reported 4% yield. However, the process is a long, multistep procedure. Thus, improvements were sought to obtain a more efficient process.

Having established that aldehyde **22** is a suitable intermediate for the synthesis of **1**, a short, direct route to it was found (Scheme 3). It was obtained in two steps from salicylaldehyde **7**, an intermediate in the reported synthesis, *via* *O*-alkylated derivative **23**. Salicyladehyde **7** was obtained by the modified Duff reaction, as reported in the literature [11], but in higher yield (61%). The *O*-alkylation of substituted salicylaldehyde **7** with bromoacetaldehyde diethyl acetal in dimethylformamide in the presence of potassium carbonate gave **23** in 80% yield. Subsequent acid-catalyzed intramolecular aldol condensation [17] provided the benzofuran aldehyde **22** in 49% yield. This process is a shorter and more direct route from **6** to **22**, 45% yield in two steps, rather than a nine step procedure.

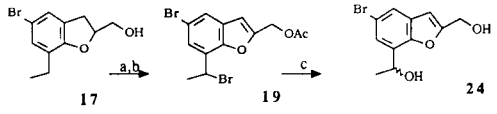


SCHEME 3.

Reagents: a. Bromoacetaldehyde diethyl acetal, K_2CO_3, DMF, reflux; b. TFA, reflux.

An improved synthesis of 1''-oxobufuralol (**4**) was also developed. Its preparation utilized dihydrobenzofuran **17**, an intermediate in the bufuralol synthesis (Scheme 2), and thus does not require bufuralol (**1**) as the starting material.

In model reactions, acetylation of **17** and bromination (*N*-bromosuccinimide) of **18** gave brominated benzofuran **19** (Scheme 4). Hydrolysis of **19** under alkaline conditions gave the diol **24**. This diol has the functional groups necessary to reach **4**, but selective protection of the alcohols was required to complete the process.



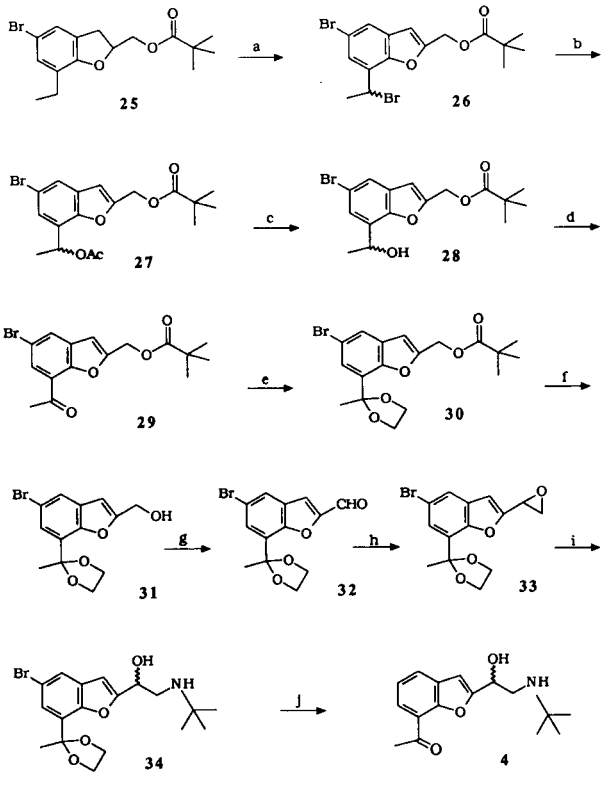
SCHEME 4.

Reagents: a. Ac_2O; b. N-bromosuccinimide; c. H_2O, NaOH.

In order to selectively obtain and transform the benzylic secondary hydroxyl group in **24**, a more hindered ester was added as a protecting group to the primary alcohol in **17**. Dihydrobenzofuran carbinol **17** was converted to its pivaloyl ester **25** (Scheme 5). Benzofuran **26** was prepared by bromination (*N*-bromosuccinimide) of **25** in refluxing carbon tetrachloride. During this reaction, both benzylic positions were monobrominated, and dehydrobromination to the furan ring occurred. Diester **27** was then obtained by displacement of the benzylic bromide **26** with mercuric acetate in refluxing acetic acid [19]. Treatment of the diester **27** with anhydrous ammonia in absolute methanol selectively removed the acetate ester protecting group producing **28**, with the pivaloyl ester intact [20]. Swern oxidation of the resulting hydroxy ester **28** gave the keto-ester **29**, which was then protected as its ethylene acetal **30** for subsequent steps. These protection steps were necessary because the analogous step in the conversion of substituted benzofuran-2-carboxaldehyde to the corresponding epoxide (**22** to **11**) was unsuccessful in the presence of the carbonyl group at the 1″-position. Hydrolysis of the pivaloyl ester in **30** under basic conditions provided the alcohol **31**, and subsequent oxidation using Collins reagent prepared by Ratcliffe procedure [21] afforded aldehyde **32**.

Conversion of **32** to **4**, followed by steps analogous to the preparation of bufuralol **1**, completed the synthesis. The benzofuran epoxide **33** was prepared from aldehyde **32** using dimethylsulfonium methylide [18]. Opening of the epoxide in benzene-methanol (50:50) with an excess of *tert*-butylamine gave the amino alcohol **34**. Reductive debromination of **34** was carried out in the presence of 5% palladium on carbon in absolute ethanol and triethylamine (one atmosphere), without either cleavage of the acetal group or reduction of the benzofuran ring. The debrominated acetal intermediate was then treated with aqueous 5% hydrochloric acid in acetone to hydrolyze the acetal affording the desired 1″-oxobufuralol (**4**).

In summary, efficient syntheses of bufuralol (**1**) and 1″-oxobufuralol (**4**) have been accomplished from readily available starting materials. The process seem readily adaptable to preparation of other substituted benzofurans.



Scheme 5.

Reagents: a. N-bromosuccinimide, CCl_4, reflux; b. $Hg(OAc)_2$, AcOH, reflux; c. ammonia, MeOH; d. Swern oxidation; e. TsOH, ethylene glycol, benzene, reflux; f. NaOH, THF, H_2O; g. CrO_3, pyridine, dichloromethane; h, NaH, DMSO, THF, $Me_3S^+ I^-$; i. benzene, MeOH; *tert*-butylamine, reflux; j. H_2, 5% Pd·C, 15 psi, EtOH, Et_3N.

EXPERIMENTAL

General Methods.

High-field ^1H and ^{13}C nmr spectra were obtained on a Varian VXR-300 spectrometer. Chemical shifts are expressed in δ downfield from tetramethylsilane (δ 0.0). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. EI and FAB mass spectra were obtained on a VG-70SEQ mass spectrometer. Infrared spectra were recorded on a Perkin Elmer 1610 FTIR. Analytical thin-layer chromatography (tlc) was carried out on Merck silica gel 60 F_{254} tlc plates (0.25-mm thickness), and the spots were detected by a uv lamp (254 nm). Merck silica gel 60 (230-400 mesh ASTM) was used for flash-column chromatography. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrectred. Unless otherwise specified, concentration of reaction mixtures or extracts was carried out on a Büchi rotary evaporator at aspirator pressure. Tetrahydrofuran was distilled under

argon from sodium metal with benzophenone as an indicator. Pre-purified nitrogen was dried by passing through a 2-foot column packed with indicating Drierite and potassium hydroxide. All glassware was oven dried. All ractions were carried out under a nitrogen atmosphere.

4-Bromo-2-ethylphenyl Allyl Ether (**14**).

To a cooled (ice-water) mixture of potassium *tert*-butoxide (65.00 g, 0.58 mole) in 300 ml of *tert*-butyl alcohol, **6** [13] (98.00 g, 0.49 mole) was added in 100 ml of *tert*-butyl alcohol under nitrogen with stirring. The mixture was refluxed for 0.5 hour and then cooled to below 60°. Allyl bromide (96.20 g, 0.80 mole) in 100 ml of *tert*-butyl alcohol was added dropwise to the mixture with cooling, as required. After the addition was complete, the reaction mixture was refluxed for an additional 8 hours, cooled, and the solvent was evaporated. The residue was dissolved in 750 ml of dichloromethane and wahsed with water to remove inorganic material. The organic phase was then dried (sodium sulfate), filtered and evaporated. The red-brown liquid obtained was distilled (bp 128-130°, 2.2 mm of mercury) to give **14** (108.12 g, 92%) as a pale brown oil; ^{1}H nmr (deuteriochloroform): δ 7.24 (1 H, d, J = 2.6 Hz), 7.22 (1 H, dd, J = 8.5, 2.6 Hz), 6.67 (1 H, d, J = 8.5 Hz), 6.03 (1 H, m), 5.34 (1 H, dd, J = 17.3, 1.6 Hz), 5.27 (1 H, dd, J = 10.5, 1.6 Hz), 4.50 (2 H, d, J = 5.0 Hz), 2.63 (2 H, q, J = 7.5 Hz), 1.19 (3 H, t, J = 7.5 Hz), ^{13}C nmr (deuteriochloroform): δ 155.16, 135.05, 132.95, 131.53, 129.03, 116.93, 112.89, 112.67, 68.71, 23.14, 13.84; ir (neat): 3081, 2966, 1487, 1454, 1280, 1243, 1228, 1182, 1137, 1022, 997, 924, 879, 803 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{11}H_{13}OBr$: 240.0149. Found: 240.0144.

2-Allyl-4-bromo-6-ethylphenol (**15**).

The allyl ether **14** (95.50 g, 0.40 mole) was refluxed in *N,N*-dimethylaniline (500 ml) at 193° for 2.5 hours under nitrogen in the dark. The mixture was then cooled to ambient temperature, placed in diethyl ether (750 ml), washed with aqueous 10% hydrochloric acid to remove the *N,N*-dimethylaniline, and then washed with water again. The organic phase was dried (sodium sulfate), filtered and evaporated. The crude product was flash chromatographed on silica gel eluting with dichloromethane and hexane (30:70) to give **15** (78.31 g, 82%) as a pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 7.15 (1 H, d, J = 2.3 Hz), 7.08 (1 H, d, J = 2.3 Hz), 5.97 (1 H, m), 5.22 (1 H, d, J = 1.6 Hz), 5.18 (1 H, dd, J = 6.5, 1.6 Hz), 4.96 (1 H, s, OH), 3.37 (2 H, d, J = 6.3 Hz), 2.59 (2 H, q, J = 7.5 Hz), 1.21 (3 H, t, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 151.02, 135.40, 132.46, 130.13, 129.97, 126.52, 117.12, 112.42, 35.24, 22.96, 13.72; ir (neat): 3544 (OH), 3077, 2988, 2933, 2877, 1633, 1605, 1461, 1372, 1316, 1255, 1183, 1061, 994, 922, 861, 794, 755, 716 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{11}H_{13}OBr$: 240.0149. Found: 240.0134.

3-(4-Bromo-3-ethyl-2-hydroxyphenyl)-1,2-epoxypropane (**16**).

To a solution of (50-60%) *m*-chloroperbenzoic acid (58.20 g, 169 mmoles) in 260 ml of dichloromethane under nitrogen in the dark at 0°, **15** (35.00 g, 145 mmoles) was added in 250 ml of dichloromethane with stirring. The reaction mixture was allowed to warm to ambient temperature (22°) and was stirred for an additional 20 hours. The dichloromethane solution was then washed with aqueous 5% sodium bicarbonate and with water. The organic phase was dried (sodium sulfate), filtered and evaporated to give **16** (31.34 g, 84%) as a pale yellow viscous oil; ^{1}H nmr (deuteriochloroform): δ 7.17 (1 H, d, J = 2.4 Hz), 7.06 (1 H, d, J = 2.4 Hz), 3.28 (1 H, m), 3.17 (1 H, dd, J = 13.3, 2.3 Hz), 2.93 (1 H, dd, J = 4.3, 4.0 Hz), 2.73 (1 H, dd, J = 4.3, 4.7 Hz), 2.63 (1H, dd, J = 13.3, 7.6 Hz), 2.63 (2 H, q, J = 7.5 Hz), 1.19 (3 H, t, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 152.53; 134.31, 130.81, 130.57, 124.70, 111.86, 53.56, 48.21, 34.79, 23.20, 13.87; ms: HR-EI (m/z) Calcd. for $C_{11}H_{13}O_2Br$: 256.0098. Found: 256.0092.

5-Bromo-7-ethyl-2-hydroxymethyl-2,3-dihydrobenzofuran (**17**).

To **16** (30.00 g, 117 mmoles), a solution of potassium hydroxide (4.00 g, 71 mmoles) in 75 ml of dimethyl sulfoxide and 25 ml of water under nitrogen was added with cooling, and the mixture was stirred for 3 hours at ambient temperature (23°). Dichloromethane (500 ml) was then added, and the organic phase was washed with a saturated sodium chloride solution. The dichloromethane solution was dried (sodium sulfate), filtered and evaporated. The residual oil was flash chromatographed on a short column of silica gel eluting with ethyl acetate-hexane (80:20) to give **17** (22.50 g, 75%) as a pale brown oil; ^{1}H nmr (deuteriochloroform): δ 7.11 (1 H, s), 7.01 (1 H, s), 4.91 (1 H, m), 3.85 (1 H, dd, J = 12.1, 3.4 Hz), 3.72 (1 H, dd, J = 12.1, 6.1 Hz), 3.23 (1 H, dd, J = 15.8, 9.4 Hz), 3.51 (1 H, dd, J = 15.8, 7.6 Hz), 2.56 (2 H, q, J = 7.5 Hz), 1.19 (3 H, t, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 156.10, 129.93, 128.01, 127.56, 125.06, 112.13, 83.03, 64.56, 31.30, 22.69, 13.70; ir (neat): 3377, 2966, 2922, 2866, 1650, 1611, 1583, 1461, 1427, 1372, 1333, 1301, 1269, 1183, 1098, 1055, 1018, 975, 948, 900, 858, 826, 767, 735, 702 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{11}H_{13}O_2Br$: 256.0098. Found: 256.0095.

5-Bromo-7-ethyl-2-acetoxymethyl-2,3-dihydrobenzofuran (**18**).

To a solution of triethylamine (22.3 ml, 168.00 mmoles), 4-dimethylaminopyridine (2.00 g, 16 mmoles) and acetyl chloride (12.0 ml, 168 mmoles) in 300 ml dichloromethane at 0°, under nitrogen, **17** was added (36.00 g, 140 mmoles) in 200 ml of dichloromethane with stirring. After the addition, the mixture was allowed to warm to ambient temperature (22°) and stirred for 8 hours. The dichloromethane solution was washed with aqueous 5% hydrochloric acid, then with water and dried (sodium sulfate). The solution was filtered and evaporated, and the remaining dark brown oil was flash chromatographed on silica gel eluting with hexane-ethyl acetate (50:50) to give **18** (40.21 g, 96%) as a pale brown oil; ^{1}H nmr (deuteriochloroform): δ 7.10 (1 H, s), 7.07 (1 H, s), 4.97 (1 H, m), 4.28 (1 H, dd, J = 12.0, 4.2 Hz), 4.21 (1 H, dd, J = 12.0, 6.0 Hz), 3.29 (1 H, dd, J = 15.9, 9.5 Hz), 2.97 (1 H, dd, J = 15.9, 7.0 Hz), 2.55 (2 H, q, J = 7.6 Hz), 2.07 (3 H, s), 1.18 (3 H, t, J = 7.6 Hz); ^{13}C nmr (deuteriochloroform): δ 170.52, 156.17, 130.12, 127.78, 127.31, 124.94, 112.16, 79.84, 65.45, 32.10, 22.74, 20.74, 13.66: ir (neat) 3466, 2966, 2922, 2877, 1744 (C=O), 1611, 1455, 1366, 1233, 1183, 1044, 983, 955, 916, 866, 766, 733, 638 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{13}H_{15}O_3Br$: 298.0204. Found: 298.0204.

2-Acetoxymethyl-5-bromo-7-(1-bromoethyl)benzofuran (**19**).

The reaction was carried out under nitrogen with efficient stirring and was illuminated with a 200-W lamp. A solution of **18** (21.00 g, 70 mmoles) in 500 ml of carbon tetrachloride was refluxed with benzoyl peroxide (0.50 g, 2 mmoles) and *N*-bromosuccinimide (25.00 g, 140 mmoles) added in five equal portions. When the mixture was free of the bromine color after each addition of *N*-bromosuccinimide, it was cooled to ambient temperature and the next portion of *N*-bromosuccinimide and benzoyl peroxide was added. After the final addition was complete, the mixture was cooled to ambient temperature and washed with

water. The organic phase was then dried (sodium sulfate), filtered and evaporated to obtain **19** (24.14 g, 91%) as a viscous red-brown oil, which was used without further purification. A portion was flash chromatographed on silica gel eluting with hexane-ethyl acetate (40:60) to obtain a sample for spectral data on **19** as a pale brown oil; ^{1}H nmr (deuteriochloroform): δ 7.66 (1 H, s), 7.57 (1 H, s), 6.77 (1 H, s), 5.67 (1 H, q, J = 6.9 Hz), 5.26 (2 H, s), 2.18 (6 H, overlapping d and s).

2-Acetoxymethyl-5-bromo-7-ethylbenzofuran (**20**).

A solution of sodium cyanoborohydride (29.00 g, 461 mmoles) and **19** (55.00 g, 146 mmoles) in 200 ml of hexamethylphosphoramide was heated at 70° for 10 hours under nitrogen with stirring. The mixture was then dissolved in 300 ml of diethyl ether and washed with water, dried (sodium sulfate) and evaporated. The residue was flash chromatographed eluting with hexane-ethyl acetate (50:50) to obtain **20** as a pale yellow viscous oil; ^{1}H nmr (deuteriochloroform): δ 7.51 (1 H, s), 7.23 (1 H, s), 6.69 (1 H, s), 5.18 (2 H, s), 2.89 (2 H, q, J = 7.7 Hz), 2.12 (3 H, s), 1.33 (3 H, t, J = 7.7 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 169.43, 153.02, 151.70, 129.15, 128.99, 126.02, 121.14, 115.27, 106.40, 57.81, 22.07, 20.31, 13.57; ms: HR-EI (m/z) Calcd. for $C_{13}H_{13}O_3Br$: 296.0048. Found: 296.0061.

5-Bromo-7-ethyl-2-hydroxymethylbenzofuran (**21**).

A solution of **20** (36.29 g, 122 mmoles) in 300 ml of absolute methanol was stirred with potassium carbonate (33.75 g, 244 mmoles) under nitrogen at 22° for 2 hours. The mixture was filtered and most of the solvent was evaporated. The residue was placed in 300 ml of dichloromethane, washed with water, dried (sodium sulfate), and the solvent was evaporated. The viscous liquid obtained was flash chromatographed on silica gel eluting with hexane-ethyl acetate (40:60) to give **21** (30.63 g, 98%) as pale brown crystals, mp 50-51°; ^{1}H nmr (deuteriochloroform): δ 7.49 (1 H, d, J = 1.8 Hz), 7.21 (1 H, d, J = 1.8 Hz), 6.58 (1 H, s), 4.76 (2 H, s), 2.88 (2 H, q, J = 7.6 Hz), 2.07 (1 H, br s, OH), 1.32 (3 H, t, J = 7.6 Hz); ^{13}C nmr (deuteriochloroform): δ 157.03, 152.11, 129.29, 129.23, 126.11, 120.91, 115.69, 103.57, 103.52, 57.82, 22.53, 13.82 [24]; ir (potassium bromide): 3210, 2970, 2924, 2877, 1718, 1585, 1452, 1414, 1357, 1325, 1208, 1180, 1142, 1077, 1022, 966, 930, 866, 852, 809, 791, 753, 713, 641 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{11}H_{11}O_2Br$: 253.9942. Found: 253.9935.

5-Bromo-7-ethyl-2-formylbenzofuran (**22**).

A. Swern Oxidation of **21**.

To a 2*M* oxalyl chloride solution in dichloromethane (45 ml, 90 mmoles) at −60° dry dimethyl sulfoxide (8 ml, 112 mmoles) was added in 50 ml of dichloromethane under nitrogen with stirring. Alcohol **21** (20.00 g, 78 mmoles) in 100 ml of dichloromethane was added to the mixture at −60°, and the mixture was stirred for 1 hour. Triethylamine (30 ml, 216 mmoles) was then added and stirring was continued for an additional 0.5 hour at −60°. The reaction mixture was then allowed to warm to ambient temperature, 100 ml of dichloromethane was added, and the mixture was washed with aqueous 5% hydrochloric acid, water, aqueous 5% sodium carbonate and with water again. The orgainc phase was then dried (sodium sulfate), filtered and evaporated. The product obtained was recrystallized from cyclohexane to give **22** (16.13 g, 81%) as pale yellow crystals, mp 86-88°; ^{1}H nmr (deuteriochloroform): δ 9.88 (1 H, s), 7.72 (1 H, d, J = 1.8 Hz), 7.49 (1 H, s), 7.44 (1 H, d, J = 1.8 Hz), 2.97 (2 H, q, J = 7.5 Hz), 1.36 (3 H, t, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 179.36, 153.39, 152.86, 130.93, 130.64, 127.77, 123.12, 117.14, 116.49, 22.49, 13.70; ir (potassium bromide): 3125, 3069, 2970, 2934, 2875, 1672 (C=O), 1588, 1558, 1458, 1431, 1410, 1377, 1337, 1312, 1191, 1124, 1097, 1080, 938, 871, 805 cm^{-1}.

Anal. Calcd. for $C_{11}H_9O_2Br$: C, 52.20; H, 3.58. Found: C, 52.38; H, 3.55.

B. From Acetal **23**.

A solution of **23** (27.9 g, 81 mmoles) in 100 ml of trifluoroacetic acid was heated at reflux for 15 minutes under nitrogen. The mixture was then cooled to room temperature and was placed in 250 ml of diethyl ether. The organic phase was washed with water, aqueous 5% sodium carbonate, dried (sodium sulfate), filtered and evaporated. The crude product obtained was flash chromatographed on silica gel eluting with ethyl acetate-hexane (10:90) and recrystallized from cyclohexane to give **22** (10.1 g, 49%) as pale yellow crystals, mp 86-88°. Spectral data were identical to data on **22** prepared by oxidation of the alcohol **21**.

5-Bromo-7-ethyl-2-(1,2-epoxyethyl)benzofuran (**11**).

To a 2*M* solution of sodium methylsulfinylmethide [25] (25 ml, 50 mmoles) in 12 ml of dimethyl sulfoxide and 13 ml of tetrahydrofuran at 0° under nitrogen was added trimethylsulfonium iodide (11.23 g, 55 mmoles) in 40 ml of dimethyl sulfoxide-tetrahydrofuran (50:50) over five minutes. The solution was stirred for two minutes and **22** (12.27 g, 49 mmoles) in 75 ml of tetrahydrofuran was added to the mixture at 0°. The reaction mixture was then stirred for an additional 30 minutes at 0° and at ambient temperature (24°) for 1 hour. The mixture was diluted with water, and was then extracted with 300 ml of dichloromethane. The organic phase was dried (sodium sulfate), filtered and evaporated. Crystallization from petroleum ether, bp 35-60°, gave **11** (10.36 g, 80%) as a pale yellow crystals, mp 47-48° (lit 46-48° [11]); ^{1}H nmr (deuteriochloroform): δ 7.54 (1 H, d, J = 1.9 Hz), 7.27 (1 H, d, J = 1.9 Hz), 6.77 (1 H, s), 4.04 (1 H, dd, J = 4.1, 2.6 Hz), 3.38 (1 H, dd, J = 5.5, 2.6 Hz), 3.27 (1 H, dd, J = 5.5, 4.1 Hz), 2.91 (2 H, q, J = 7.5 Hz), 1.36 (3 H, t, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 153.54, 152.00, 129.32, 129.13, 126.48, 120.82, 115.90, 105.68, 48.28, 46.38, 22.51, 13.75.

5-Bromo-2-(2-*tert*-butylamino-1-hydroxyethyl)-7-ethylbenzofuran (**12**).

A solution of **11** (10.5 g, 39.4 mmoles) in 110 ml of benzene-methanol (50:50) was heated at reflux with *tert*-butyl amine (27 ml, 256.9 mmoles) under nitrogen for 14 hours. The mixture was then cooled and solvent was evaporated. Crystallization from benzene-cyclohexane gave **12** as white crystals, mp 92-93° (lit 91-92° [11]). The hydrochloride salt of **12** (8.29 g, 56%) was obtained from ethanolic hydrochloric acid and crystallized from acetone-cyclohexane to give white crystals, mp 186-188°; ^{1}H nmr (deuteriomethanol): δ 7.63 (1 H, s), 7.31 (1 H, s), 6.93 (1 H, s), 5.20 (1 H, dd, J = 9.4, 3.4 Hz), 3.51 (1 H, dd, J = 3.4, 12.3 Hz), 3.39 (1 H, dd, J = 9.3, 12.3 Hz), 2.96 (1 H, q, J = 7.4 Hz), 1.49 (9 H, s), 1.38 (3 H, t, J = 7.4 Hz); ^{13}C nmr (deuteriochloroform): δ 155.86, 152.00, 129.25, 128.99, 126.31, 121.10, 115.97, 103.82, 63.66, 57.87, 46.34, 25.89, 22.40, 13.73; ir (potassium bromide): (free base) 3288, 3121 (OH), 2963, 2877, 2844, 2766, 1588, 1455, 1409, 1383, 1368, 1340, 1278, 1225, 1214, 1180, 1144, 1113, 1095, 1056, 1024, 964, 954, 888, 853, 819, 797, 739 cm^{-1}.

The gummy residue obtained after evaporation of the mother

liquors from crystallization of **12** was treated with ethanolic hydrochloric acid and evaporated. Fractional crystallization of the product from ethyl acetate-cyclohexane gave the minor isomer **13** (0.74 g, 5%) as white crystals of the hydrochloride salt, mp 195-196° (lit 198° [11]); ^{1}H nmr (acetone-d_6-deuterated water): δ 7.69 (1 H, d, J = 1.8 Hz), 7.33 (1 H, d, J = 1.8 Hz), 7.27 (1 H, s), 4.86 (1 H, dd, J = 6.4, 5.2 Hz), 4.25 (1 H, dd, J = 12.0, 6.6 Hz), 4.13 (1 H, dd, J = 12.0, 5.2 Hz), 2.95 (2 H, q, J = 7.5 Hz), 1.45 (9 H, 2), 1.33 (3 H, t, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 151.56, 149.83, 129.62, 129.02, 127.29, 121.69, 116.46, 107.59, 62.73, 59.78, 56.04, 26.61, 22.71, 13.93.

2-(2-*tert*-Butylamino-1-hydroxyethyl)-7-ethylbenzofuran Hydrochloride (Bufuralol Hydrochloride) (**1**).

A solution of the hydrochloride salt of **12** (8.0 g, 21.3 mmoles) in 200 ml of ethanol with 3.0 g of 5% palladium on carbon was reduced under 15 psi initial hydrogen pressure. When the theoretical amount of hydrogen was absorbed (15 minutes), the catalyst was removed by filtration and washed with ethanol. The ethanolic solution was evaporated, and the residue was partitioned between 50 ml of aqueous 10% sodium hydroxide and ethyl acetate (200 ml). The organic extract was washed with water, dried (sodium sulfate), filtered and evaporated. The oily residue was treated with ethanolic hydrochloric acid and was crystallized from cyclohexane-diethyl ether to give **1** (5.9 g, 93%) as white crystals, mp 122-123° (lit 146° [11,23]); ^{1}H nmr (deuteriomethanol): δ 7.37 (1 H, dd, J = 6.9, 2.1 Hz), 7.10 (2 H, m), 6.84 (1 H, s), 5.10 (1 H, dd, J = 9.3, 3.4 Hz), 3.41 (1 H, dd, J = 12.5, 3.4 Hz), 3.32 (1 H, dd, J = 12.5, 9.3 Hz), 2.89 (2 H, q, J = 7.6 Hz), 1.40 (9 H, s), 1.30 (3 H, t, J = 7.6 Hz); ^{13}C nmr (deuteriomethanol): δ 156.88, 154.64, 128.86, 128.65, 124.78, 124.20, 119.80, 105.32, 65.03, 58.53, 46.85, 25.79, 23.74, 14.77; ir (potassium bromide): 3288 (OH), 2970, 2872, 2772, 2508, 2402, 1581, 1481, 1458, 1425, 1403, 1380, 1317, 1278, 1180, 1097, 1006, 962, 939, 852, 823, 751 cm^{-1}.

Anal. Calcd. for $C_{16}H_{24}NO_2Cl$: C, 64.53; H, 8.12; N, 4.70. Found: C, 64.08; H, 7.89; N, 4.94.

5-Bromo-3-ethylsalicylaldehyde (**7**).

A mixture of 4-bromo-2-ethylphenol (**6**) (149.0 g, 0.74 mole), hexamethylenetetramine (56.0 g, 0.40 mole) and paraformaldehyde (56.0 g, 1.87 moles) was heated to 100° under nitrogen. At this temperature, 220 ml of glacial acetic acid was added slowly over 90 minutes. The temperature was then increased to 120-130° and 60 ml of concentrated sulfuric acid was added slowly over 2 hours. After 15 minutes, heating was discontinued and water (1600 ml) was added to the cooling mixture. The mixture was then stirred at ambient temperature (25°) for 18 hours. The yellow precipitate that formed was filtered, washed and dried. Crystallization from petroleum ether, bp 35-60°, gave **7** (103.4 g, 61%) as pale yellow crystals, mp 47-48° (lit 43-45° [11]); ^{1}H nmr (deuteriochloroform): δ 11.19 (1 H, s, OH), 9.81 (1 H, s), 7.50 (1 H, s), 7.48 (1 H, s), 2.67 (2 H, q, J = 7.5 Hz), 1.22 (3 H, t, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 195.35, 158.46, 138.45, 135.29, 132.81, 120.95, 110.94, 22.10, 13.34; ir (potassium bromide): 3155 (OH), 2966, 2922, 2855, 1693, 1649 (C=O), 1605, 1441, 1375, 1309, 1265, 1221, 1199, 1144, 1069, 1012, 930, 914, 864, 738, 710 cm^{-1}.

2,2-Diethoxyethyl (4-Bromo-6-ethyl-2-formyl)phenyl Ether (**23**).

Bromoacetaldehyde diethyl acetal (5.76 g, 29 mmoles) and anhydrous potassium carbonate (3.42 g, 25 mmoles) was added to a solution of **7** (5.20 g, 23 mmoles) in 11 ml of *N,N*-dimethylformamide. The mixture was refluxed for 90 minutes, under nitrogen, cooled to room temperature and poured into water. The mixture was then extracted with diethyl ether (200 ml), and the organic phase was washed with water, dried (sodium sulfate), filtered and evaporated to obtain **23** (6.40 g, 80%) as an oil which was used without further purification; ^{1}H nmr (deuteriochloroform): δ 10.34 (1 H, s), 7.78 (1 H, d, J = 2.5 Hz), 7.56 (1 H, d, J = 2.4 Hz), 4.84 (1 H, t, J = 5.1 Hz), 3.96 (2 H, d, J = 5.1 Hz), 3.74 (2 H, m), 3.63 (2 H, m), 2.73 (2 H, q, J = 7.5 Hz), 1.25 (9 H, m); ^{13}C nmr (deuteriochloroform): δ 189.03, 158.72, 140.51, 137.95, 130.48, 128.72, 117.73, 100.41, 76.24, 62.82, 22.18, 15.25, 14.32; ir (neat): 3055, 2977, 2933, 2888, 2755, 1688 (C=O), 1572, 1455, 1388, 1344, 1244, 1216, 1138, 1072, 1016, 944, 911, 883, 794 cm^{-1}.

5-Bromo-7-(1-hydroxyethyl)-2-hydroxymethylbenzofuran (**24**).

To a solution of crude **19** (3.00 g, 7.9 mmoles) in 150 ml of tetrahydrofuran, a solution of potassium hydroxide (3.00 g, 53.5 mmoles) in 20 ml of water was added at ambient temperature (23°). The mixture was stirred for 8 hours under nitrogen. Most of the tetrahydrofuran was evaporated, and the residue was extracted with dichloromethane (200 ml). The organic phase was washed with water, dried (sodium sulfate), filtered, and evaporated. The residue was crystallized from chloroform-hexane to afford **24** as white crystals, mp 142-143°; ^{1}H nmr (deuteriomethanol): δ 7.58 (1 H, d, J = 2.0 Hz), 7.45 (1 H, d, J = 2.0 Hz), 6.68 (1 H, s), 5.30, (1 H, q, J = 6.5 Hz), 4.67 (2 H, s), 1.55 (3 H, d, J = 6.5 Hz); ^{13}C nmr (deuteriomethanol): δ 160.10, 151.67, 133.03, 131.67, 124.26, 123.12, 116.83, 104.13, 65.48, 57.88, 24.27; ir (potassium bromide): 3355 (OH), 3222 (OH), 2966, 2922, 2877, 1655, 1577, 1444, 1394, 1366, 1344, 1288, 1233, 1216, 1183, 1138, 1116, 1072, 1028, 1005, 933, 894, 872, 788, 755, 683 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}O_3Br$: C, 48.73; H, 4.09. Found: C, 48.59; H, 3.97.

5-Bromo-7-ethyl-2-trimethylacetoxymethyl-2,3-dihydrobenzofuran (**25**).

To a solution of triethylamine (45 ml, 324 mmoles), 4-dimethylaminopyridine (2.00 g, 16 mmole) and trimethylacetyl chloride (35.2 ml, 286 mmoles) in 200 ml of dichloromethane at 0° under nitrogen, **17** (73.5 g, 286 mmoles) in 500 ml of dichloromethane was added with stirring. The mixture was then allowed to warm to room temperature and stirred for 10 hours. The dichloromethane solution was then washed with aqueous 5% hydrochloric acid, water and dried (sodium sulfate). The solution was filtered and evaporated, and the brown oil was flash chromatographed on silica gel eluting with hexane-ethyl acetate (60:35) to give **25** (79.9 g, 82%) as a pale brown oil; ^{1}H nmr (deuteriochloroform): δ 7.10 (1 H, s), 7.06 (1 H, s), 4.98 (1 H, m), 4.30 (1 H, dd, J = 11.7, 3.9 Hz), 4.20 (1 H, dd, J = 11.7, 5.1 Hz), 3.31 (1 H, dd, J = 15.9, 9.6 Hz), 2.99 (1 H, dd, J = 15.9, 6.3 Hz), 2.54 and 2.53 (2 H, q, J = 7.5 Hz), 1.17 (3 H, t, J = 7.5 Hz), 1.12 (9 H, s); ^{13}C nmr (deuteriochloroform): δ 177.88, 156.42, 130.08, 127.51, 127.38, 124.85, 111.99, 79.82, 65.45, 38.77, 32.01, 26.99, 22.89, 13.71; ir (neat): 2970, 2935, 2873, 1731 (C=O), 1595, 1479, 1460, 1397, 1366, 1329, 1282, 1183, 1152, 1036, 986, 911, 863, 833, 768, 734 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{16}H_{21}O_3Br$: 340.0674. Found: 340.0652.

5-Bromo-7-(1-bromoethyl)-2-trimethylacetoxymethylbenzofuran (**26**).

The reaction was carried out under nitrogen with efficient stirring and illumination with a 200-W lamp. A solution of **25** (26.5 g, 78 mmoles) and benzoyl peroxide (0.50 g, 2 mmoles) in 500 ml of carbon tetrachloride was heated to reflux, and *N*-bromosuccinimide (27.6 g, 155 mmoles) was added in five equal portions. When the mixture was free of bromine color after the initial addition, it was cooled to ambient temperature and the next portion of *N*-bromosuccinimide and benzoyl peroxide was added. After the final addition, the mixture was cooled to ambient temperature and was washed with water. The organic phase was then dried (sodium sulfate), filtered and evaporated to obtain **26** (30.8 g, 95%) as a viscous red-brown oil, which was used without further purification. A portion was flash chromatographed on silica gel eluting with hexane-ethyl acetate (30:60) to obtain **26** (with some decomposition) as a pale brown oil; ^{1}H nmr (deuteriochloroform): δ 7.64 (1 H, d, J = 1.9 Hz), 7.50 (1 H, d, J = 1.9 Hz), 6.69 (1 H, s), 5.59 (1 H, q, J = 6.9 Hz), 5.22 (2 H, s), 2.14 (3 H, d, J = 6.9 Hz), 1.23 (9 H, s).

5-Bromo-7-(1-acetoxyethyl)-2-trimethylacetoxymethylbenzofuran (**27**).

To a solution of crude **26** (30.0 g, 72 mmoles) in 150 ml glacial acetic acid, mercuric acetate (22.9 g, 71 mmoles) was added, and the mixture was refluxed for two hours with stirring. The cooled mixture was then taken in 350 ml diethyl ether, washed with water, dried (sodium sulfate), filtered and evaporated. The residue was flash chromatographed on silica eluting with hexane-ethyl acetate (30:70) to give **27** (17.4 g, 61%) as a viscous pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 7.62 (1 H, d, J = 1.8 Hz), 7.39 (1 H, d, J = 1.8 Hz), 6.68 (1 H, s), 6.29 (1 H, q, J = 6.6 Hz), 5.20 (2 H, s), 2.12 (3 H, s), 1.63 (3 H, d, J = 6.6 Hz), 1.23 (9 H, s); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 176.47, 169.12, 153.91, 149.92, 129.99, 127.03, 123.88, 123.18, 115.14, 105.65, 66.76, 66.70 [24], 57.84, 38.20, 26.66, 20.65, 20.39; ir (neat): 3455, 3116, 3078, 2977, 2935, 2872, 1739 (C=O), 1640, 1608, 1587, 1535, 1480, 1397, 1369, 1323, 1278, 1233, 1143, 1090, 1033, 967, 939, 860, 820, 799, 757 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{18}H_{21}O_5Br$: 396.0572. Found: 396.0547.

5-Bromo-2-trimethylacetoxymethyl-7-(1-hydroxyethyl)benzofuran (**28**).

To a solution of **27** (36.8 g, 93 mmoles) in 100 ml of absolute methanol at 0°, 100 ml of absolute methanol, which had been saturated with gaseous ammonia at 0°, was added. The mixture was allowed to warm to room temperature (25°) and stirred for 10 hours under nitrogen. The solvent was then evaporated, and the residue was flash chromatographed on silica gel eluting with hexane-ethyl acetate (1:2) to give **28** (28.3 g, 86%) as cream colored crystals, mp 64-65° (chloroform-hexane); ^{1}H nmr (deuteriochloroform): δ 7.57 (1 H, d, J = 1.8 Hz), 7.48 (1 H, d, J = 1.8 Hz), 6.67 (1 H, s), 5.33 (1 H, q, J = 6.4 Hz), 5.19 (2 H, s), 1.61 (3 H, d, J = 6.4 Hz), 1.22 (9 H, s); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 176.63, 153.54, 149.74, 132.86, 129.52, 123.41, 121.88, 115.32, 105.67, 63.05, 58.00, 38.29, 26.77, 24.14; ir (neat): 3442 (OH), 3114, 2973, 2933, 2872, 1733 (C=O), 1607, 1587, 1480, 1457, 1398, 1376, 1279, 1230, 1147, 1070, 1032, 965, 942, 896, 859, 817, 781, 757 cm^{-1}; ms: HR-EI (m/z) Calcd. for $C_{16}H_{19}O_4Br$: 354.0466. Found: 354.0456.

7-Acetyl-5-bromo-2-trimethylacetoxymethylbenzofuran (**29**).

To a 2*M* oxalyl chloride solution (31 ml, 62 mmoles) in dichloromethane at −60° was added dry dimethyl sulfoxide (5 ml, 70 mmoles) in 50 ml of dichloromethane under nitrogen with stirring. Alcohol **28** (20.0 g, 56 mmoles) in 100 ml of dichloromethane was added to the mixture at −60° and stirred for 1 hour. After the addition of triethylamine (25 ml, 180 mmoles), it was stirred for an additional 0.5 hour at −60° and then allowed to warm to ambient temperature. Dichloromethane (100 ml) was added, and the extract was washed with aqueous 5% hydrochloric acid, water, aqueous 5% sodium carbonate, and water again. The organic phase was then dried (sodium sulfate), filtered and evaporated. The product obtained was recrystallize d from chloroformcyclohexane to give **29** (14.8 g, 78%) as pale yellow crystals, mp 88-89°; ^{1}H nmr (deuteriochloroform): δ 7.99 (1 H, d, J = 2.0 Hz), 7.86 (1 H, d, J = 2.0 Hz), 6.77 (1 H, s), 5.26 (2 H, s), 2.83 (3 H, s), 1.24 (9 H, s); ^{13}C nmr (deuteriomethanol): δ 195.75, 178.92, 156.29, 133.18, 129.83, 128.58, 124.05, 116.94, 106.63, 59.16, 39.89, 30.87, 27.53; ir (potassium bromide): 3096, 2974, 2933, 2866, 1736 (C=O), 1585, 1478, 1405, 1365, 1315, 1272, 1247, 1200, 1151, 1137, 985, 961, 936, 877, 837, 751, 567 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}O_4Br$: C, 54.41; H, 4.85. Found: C, 54.15; H, 4.74.

2-(5-Bromo-2-trimethylacetoxymethylbenzofuran-7-yl)-2-methyl-1,3-dioxolane (**30**).

To a solution of **29** (12.6 g, 37 mmoles) in 150 ml of benzene was added *p*-toluenesulfonic acid (0.5 g, 2.6 mmoles) and ethylene glycol (6 ml, 107 mmoles). The mixture was heated at reflux under nitrogen for 4 hours, and water formed during the reaction was removed azeotropically using a Dean-Stark trap. The mixture was cooled and poured into 100 ml of aqueous 10% sodium carbonate solution and extracted with 250 ml of dichloromethane. The organic phase was washed with water, dried (sodium sulfate), filtered and evaporated. The residue obtained was crystallized from benzene-cyclohexane to give **30** (14.4 g, 97%) as off-white crystals, mp 81-82°; ^{1}H nmr (deuteriochloroform): δ 7.63 (1 H, d, J = 2.0 Hz), 7.51 (1 H, d, J = 2.0 Hz), 6.67 (1 H, s), 5.23 (2 H, s), 4.11 (2 H, m), 3.90 (2 H, m), 1.85 (3 H, s), 1.23 (9 H, s); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 176.52, 153.83, 149.71, 130.81, 128.56, 123.69, 123.49, 114.73, 106.06, 105.31, 64.40, 57.92, 38.23, 26.70, 25.47; ir (potassium bromide): 3100, 3077, 2968, 2933, 2888, 1716 (C=O), 1611, 1588, 1477, 1405, 1377, 1316, 1283, 1233, 1194, 1155, 1133, 1044, 961, 938, 872, 816, 761, 688 cm^{-1}.

Anal. Calcd. for $C_{18}H_{21}O_5Br$: C, 54.42; H, 5.33. Found: C, 53.84; H, 5.26.

2-(5-Bromo-2-hydroxymethylbenzofuran-7-yl)-2-methyl-1,3-dioxolane (**31**).

To a solution of **30** (12.0 g, 30 mmoles) in 200 ml of tetrahydrofuran was added sodium hydroxide (5.0 g, 125 mmoles) in 35 ml of water at 24°, and the mixture was stirred under nitrogen for 4 hours. The reaction mixture was then extracted with 300 ml of dichloromethane. The organic phase was washed with aqueous saturated sodium chloride solution, with water, and dried (sodium sulfate), filtered and evaporated under reduced pressure. The residue was recrystallized from chloroform-cyclohexane to give **31** (8.7 g, 91%) as cream colored crystals, mp 110-111°; ^{1}H nmr (deuteriochloroform): δ 7.62 (1 H, d, J = 2.0 Hz), 7.49 (1 H, d, J = 2.1 Hz), 6.63 (1 H, s), 4.81 (2 H, s), 4.10 (2 H, m), 3.88 (2 H, m), 1.85 (3 H, s); ^{13}C nmr (deuteriochloroform): δ 158.18, 150.04, 130.99, 128.00, 123.79, 123.53, 115.38, 107.01, 102.86, 64.74, 57.59, 25.88; ir (potassium bromide): 3450, 3112, 3070, 2986, 2893, 1606, 1585, 1402, 1374, 1320, 1237, 1222, 1200, 1142, 1105,

1039, 1024, 952, 930, 866, 781, 760 cm^{-1}; ms: HR-FAB (m/z) (MH^+) Calcd. for $C_{13}H_{13}O_4Br$: 313.0075. Found: 313.0054.

Anal. Calcd. for $C_{13}H_{13}O_4Br$: C, 49.86; H, 4.18. Found: C, 49.85; H, 4.12.

2-(5-Bromo-2-formylbenzofuran-7-yl)-2-methyl-1,3-dioxolane (**32**).

To a solution of anhydrous pyridine (23 ml, 284 mmoles) in 150 ml of dichloromethane at 5° under nitrogen was added chromium trioxide (14.2 g, 142 mmoles) in one portion. The mixture was stirred for 5 minutes at 5° and then allowed to warm to room temperature (23°) over 1 hour. A solution of **31** (7.4 g, 24 mmoles) in 50 ml of dichloromethane was added rapidly, and then stirred for 30 minutes. The mixture was filtered and the residue was washed with 100 ml of dichloromethane. The dichloromethane solution was washed with aqueous 5% sodium carbonate solution and water. The organic phase was then dried (sodium sulfate), filtered and evaporated. The residue was crystallized from chloroform-cyclohexane to give **32** (5.2 g, 70%) as pale yellow crystals, mp 134-136°; ^1H nmr (deuteriochloroform): δ 9.95 (1 H, s), 7.84 (1 H, d, J = 2.1 Hz), 7.61 (1 H, d, J = 2.0 Hz), 7.50 (1 H, s), 4.13 (2 H, m), 3.91 (2 H, m), 1.89 (3 H, s); ^{13}C nmr (deuteriochloroform): δ 179.84, 153.37, 151.43, 129.99, 129.38, 128.42, 125.73, 116.83, 114.25, 106.64, 64.96, 25.83; ir (potassium bromide): 3077, 2988, 2877, 1677 (C=O), 1561, 1444, 1400, 1366, 1338, 1305, 1238, 1216, 1200, 1155, 1116, 1044, 950, 888, 861, 788, 761, 727, 688 cm^{-1}; ms: HR-FAB (m/z) (MH^+) Calcd. for $C_{13}H_{11}O_3Br$: 310.9918. Found: 310.9915.

Anal. Calcd. for $C_{13}H_{11}O_3Br$: C, 50.19; H, 3.56. Found: C, 49.89; H, 3.57.

2-(1,2-Epoxyethyl)-5-bromobenzofuran-7-yl)-2-methyldioxolane (**33**).

To a 2*M* solution of sodium methylsulfinylmethide [25] (13 ml, 26 mmoles) in 6 ml of dimethyl sulfoxide and 7 ml of tetrahydrofuran at 0° under nitrogen was added trimethylsulfonium iodide (6.1 g, 28 mmoles) in 30 ml of dimethysulfoxide-tetrahydrofuran (50:50) in 5 minutes. The solution was stirred for 2 minutes and **32** (8.0 g, 26 mmoles) in 60 ml of tetrahydrofuran was added to the mixture at 0°. The reaction mixture was then stirred for an additional 30 minutes at 0° and at ambient temperature (25°) for 1 hour. The mixture was diluted with water and extracted with 200 ml of dichloromethane. The organic phase was dried (sodium sulfate), filtered and evaporated. Polar by-products were precipitated from cyclohexane-benzene. Evaporation gave **33** (5.6 g, 67%) as pale yellow viscous oil which was used without further purification; ^1H nmr (deuteriochloroform): δ 7.62 (1 H, d, J = 2.0 Hz), 7.50 (1 H, d, J = 2.0 Hz), 6.71 (1 H, s), 4.12 (2 H, m), 4.04 (1 H, dd, J = 4.0, 2.7 Hz), 3.88 (2 H, m), 3.29 (1 H, dd, J = 5.5, 2.7 Hz), 3.23 (1 H, dd, J = 5.5, 4.0 Hz), 1.84 (3 H, s); ^{13}C nmr (deuteriochloroform): δ 154.81, 130.78, 128.45, 124.57, 124.38, 123.45, 115.66, 106.87, 104.39, 64.83, 48.81, 46.35, 25.87; ms: HR-EI (m/z) Calcd. for $C_{14}H_{13}O_4Br$: 323.9997. Found: 323.9985.

2-[(2-*tert*-Butylamino-1-hydroxyethyl)-5-bromobenzofuran-7-yl]-2-methyl-1,3-dioxolane (**34**).

A solution of crude **33** (5.0 g, 15 mmoles) in 100 ml of benzene-methanol (50:50) was heated at reflux with *tert*-butylamine (40 ml, 380 mmoles) under nitrogen for 16 hours. The mixture was then cooled, and the solvent was evaporated. Polar by-products were precipitated from benzene-cyclohexane. After evaporation, the product was crystallized from benzene-petroleum ether (bp 35-60°) to give **34** (3.1 g, 51%) as a white amorphous powder, mp 132-133°; ^1H nmr (deuteriomethanol): δ 7.60 (1 H, d, J = 2.0 Hz), 7.46 (1 H, d, J = 2.0 Hz), 6.63 (1 H, s), 4.86 (1 H, dd, J = 6.3, 4.1), 4.11 (2 H, m), 3.89 (2 H, m), 3.07 (1 H, dd, J = 11.9, 4.5 Hz), 2.97 (1 H, dd, J = 11.9, 6.3 Hz), 1.83 (3 H, s), 1.12 (9 H, s); ^{13}C nmr deuteriochloroform): δ 160.43, 149.88, 131.05, 128.09, 123.54, 123.33, 115.30, 106.91, 101.93, 66.13, 64.73, 50.36, 46.32, 28.92, 25.87; ir (potassium bromide): 3288, (NH), 3111 (OH), 3000, 2988, 2966, 2922, 2888, 2844, 1588, 1444, 1405, 1372, 1322, 1222, 1194, 1144, 1094, 1033, 966, 950, 872, 844, 817, 777, 755, 727, 694, 624 cm^{-1}; ms: HR-EI (m/z) (M^+-H_2O) Calcd. 379.0783. Found: 379.0781.

7-Acetyl-2-[2-(*tert*-butylamino)-1-hydroxyethyl]benzofuran Hydrochloride (1''-Oxbufuralol Hydrochloride) (**4**).

A solution of **34** (3.0 g, 7.5 mmoles) in 150 ml of ethanol containing 1 ml of triethylamine and 1.5 g of 5% palladium on carbon was reduced under 15 psi hydrogen pressure. When the theoretical amount of hydrogen was absorbed, the hydrogenolysis was stopped. The catalyst was removed by filtration and extracted with ethanol (100 ml). The ethanolic solution was evaporated, and the residue was dissolved in 10 ml of acetone. Then 5 ml of aqueous 10% hydrochloric acid was added and the mixture was stirred for 30 minutes. After the acetone was evaporated, the mixture was made alkaline with aqueous 10% sodium hydroxide solution and then extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with water, dried (sodium sulfate), and evaporated to give **4** (1.27 g, 84%) as a pale brown oil. The hydrochloride salt of **4** was prepared from a solution of hydrogen chloride in methanol as a semi-solid; ^1H nmr (deuteriochloroform): δ 7.81 (1 H, d, J = 7.7, 1.3 Hz), 7.68 (1 H, d, J = 1.3, 7.7 Hz), 7.26 (1H, t, J = 7.7 Hz), 6.85 (1 H, s), 5.66 (1 H, m), 3.48 (1 H, m), 3.36 (1 H, m), 2.77 (3 H, s), 1.55 (9 H, s); ^{13}C nmr (deuteriochloroform): δ 195.95, 156.10, 152.65, 129.26, 126.45, 125.39, 122.83, 121.87, 104.04, 63.57, 57.91, 46.26, 30.31, 25.83; FTIR (neat): 3311 (OH0, 2977, 2777, 1677 (C=O), 1594, 1477, 1444, 1416, 1372, 1355, 1277, 1200, 1122, 1061, 966, 922, 822, 750, 727 cm^{-1}.

Anal. Calcd. for $C_{20}H_{25}NO_7$ (maleic acid salt[10]): C, 61.37; H, 6.44; N, 3.58. Found: C, 60.92; H, 6.51; N, 3.50.

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