Cell Viability Assay in HIV-1 Infected and Uninfected CEM Cells. Cell viability was determined by a tetrazolium (XTT) assay.[33]

Acknowledgment. This investigation was supported by Contract NO1-CM-17513, awarded by the National Cancer Institute, DHHS. The antiviral results in CEM cells were obtained under the auspices of the Developmental Therapeutics Program, Drug Synthesis and Chemistry Branch, Dr. Ven L. Narayanan, Chief, and the results provided by Dr. John P. Bader, Chief, Antiviral Evaluations Branch, Special Assistant for AIDS Antiviral Evaluations. The work of E.D.C. is supported by the AIDS Basic Research Programme of the European Community and grants from the Belgian F.G.W.O. (Fonds voor Geneeskundig Wetenschappelijk Onderzoek) and the Belgian G.O.A. (Geconcerteerde Onderzoeksacties).

Supplementary Material Available: Molecular modeling parameters for ATA structure 11 (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Regioselective Introduction of Carbon-3 Substituents to 5-Alkyl-7-methoxy-2-phenylbenzo[*b*]furans: Synthesis of a Novel Adenosine A_1 Receptor Ligand and Its Derivatives[1]

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By maintaining the balance between the electronic requirements, the stereochemical restrictions as well as the kinetic and thermodynamic factors, the unprecedented regioselective electrophilic aromatic substitution of formyl and nitro groups to carbon-3 of 5-alkyl-7-methoxy-2-phenylbenzo[*b*]furans have been achieved. Subsequent transformation of the resulting formyl group into methyl, hydroxymethyl, 1-hydroxyethyl, and cyano groups are also described.

Introduction

Considerable attention has been devoted recently to the potential therapeutic properties of *Salvia miltiorrhiza* Bunge (Danshen), whose aqueous extracts have been used widely in China to treat acute myocardiac infarction and angina pectoris.[3] In the course of our own evaluation of the pharmacological profile of the aqueous extracts of Danshen, we observed a significant inhibition of [^{3}H]-phenylisopropyladenosine binding to the adenosine A_1 receptor on bovine cerebral cortex membranes.[1b] In the hope of identifying potential cardiovascular compounds,[4] we have initiated a program to isolate the active component from Danshen, being monitored by the adenosine A_1 radioligand binding assay.[5,6] A new compound, 5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (**1**), with an exceedingly high potency (IC_{50} = 17 nM), was isolated as a yellowish oil.[1b] It is noteworthy that one of the most potent A_1-selective adenosine antagonists,[7-10] namely 1,3-dipropyl-8-cyclopentylxanthine (CPX) (**2**), shows extremely high A_1 affinity (IC_{50} = 0.92 nM).[11,12] Another well-known adenosine antagonist is 4-amino-8-hydroxytriazoloquinazoline (**3**).[13,14]

Unlike **2** and **3**, which are nitrogen-containing compounds, compound **1** has a skeleton devoid of nitrogen but is strikingly similar peripherally to **2** and **3**. Compound **1** therefore provides a new kind of structure having a high A_1 receptor antagonist activity and is relatively soluble in water. We report here the total synthesis of **1** as well as

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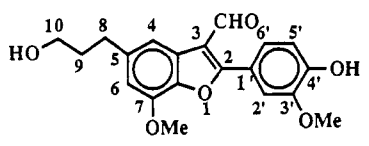

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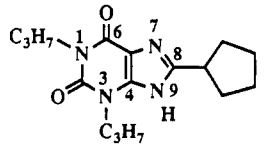
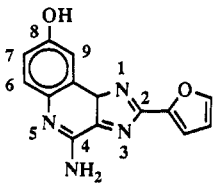


2



3

the synthesis of its derivatives.

Results and Discussion

1. Synthesis of 5-(3-Hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (1). Due to the antifungal activities of certain hydroxy- and methoxy-substituted 2-phenylbenzo[*b*]furans,[15] many synthetic methods for preparing such compounds have been reported.[16] Considering the structural character of compound 1 and comparing all the methods for the construction of 2-phenylbenzo[*b*]furans, our strategy to be employed for the synthesis of compound 1 was based on the method of the egonol synthesis, which was reported by Stevenson[17] adopting Castro's route.[18]

Despite the fact that the syntheses of 2,5,7-trisubstituted benzo[*b*]furans are well-documented, a direct and regioselective introduction of a formyl group to the C-3 position in these electron-rich benzo[*b*]furans is not available. In our particular case, we are guided by the desire to develop a simple regioselective formylation, thereby facilitating the total synthesis of our target molecule 1. It is expected that our strategy may provide a convenient new entry to 2,5,7-trisubstituted benzo[*b*]furan-3-carbaldehydes which are of special interest in our pharmaceutical research program. The route for the synthesis of compound 1 is depicted in Scheme I.

A key feature of this synthetic program is the conventional coupling reaction based on the egonol synthesis[17] starting from cuprous acetylide 11 and phenyl bromide 6. As expected, the benzo[*b*]furan 12 with the desired skeleton was generated. The synthesis of compound 11 was achieved by the following steps. Thus, ketone 7 was first protected with a benzyl group to give compound 8,[19] which was then converted by a Vilsmeier reaction[20] to β-phenyl-β-chloroacrylaldehyde 9. On treatment with hot aqueous sodium hydroxide,[20] aldehyde 9 furnished alkyne 10, presumably via a base-promoted fragmentation reaction. The cuprous acetylide 11 was obtained from 10 by treatment with cupric sulfate and hydroxylamine hydrochloride in ammonium hydroxide.[21] The phenylpropionate 6 was prepared from 5-bromovanillin (5)[22] through a Doebner–Knoevenagel reaction.[23,24] Coupling of cuprous acetylide 11 with bromophenol 6 yielded compound 12.[25] Hydrogenolysis of 12 provided phenol 13[26] which underwent reduction to give the alcohol 14.[27] Alcohol 14 was converted to acetoxy compound 15. Subsequent selective deprotection of 15 gave the phenol 16. The regioselective introduction of an aldehyde group to the C-3 position of 16 is not trivial. Vilsmeier reaction[20] afforded a C-4 aldehyde as the only product (vide infra, Scheme IX). The C-3 formylation was eventually achieved by a Gattermann reaction utilizing the Adams' reagent,[28] which yielded 17 (51%) and the presumably C-4 formylation product 18 (8%) in the ratio 7:1 according to the ^{1}H-NMR spectral analysis. Compound 18 was not isolated and was easily removed from 17 by means of column chromatography due to its higher polarity as compared to 17. Finally, hydrolysis of 17 provided our target molecule 1 as a yellowish amorphous solid, mp 77–77.5 °C, which is spectrometrically identical in all aspects to the natural product.

2. Modification of Compound 1. On the basis of the skeleton of compound 1 and on the unique regiochemistry of 2-phenylbenzo[*b*]furans discussed in the following section, several related compounds have been synthesized in order to delineate the structure–activity relationship (SAR) of compound 1 with adenosine A_1 receptor. Our first target molecule was compound 20 (Scheme II). Thus, compound 13 was first treated with the Adams' reagent[28] to afford regioselectively 19, which was saponified to give compound 20.

Our next experiments were to convert the aldehyde group of compound 1 to a hydroxymethyl group and a methyl group (Scheme III). Compound 1 was subjected to reduction by lithium aluminum hydride or catalytic hydrogenation[29] to afford compound 21. Interestingly, hydrogenation of compound 1 in an acidic medium yielded

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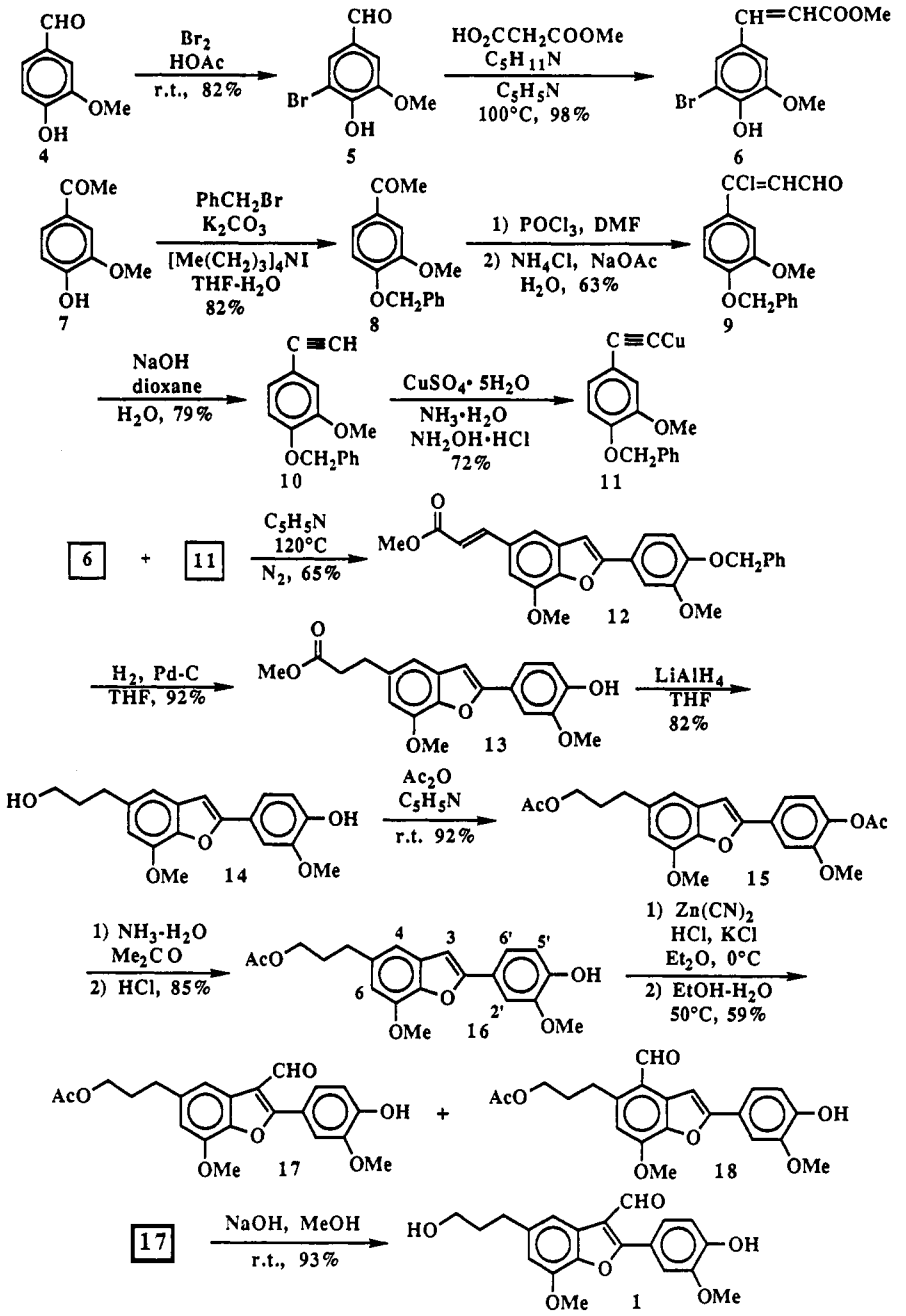
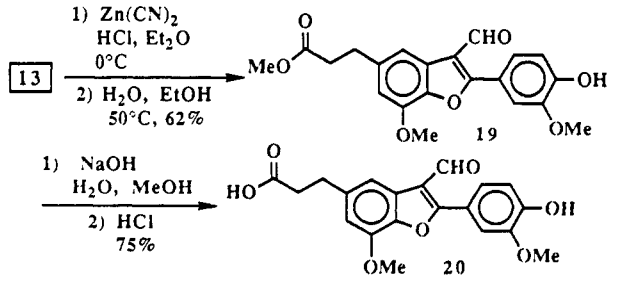
Scheme I



Scheme II



the 3-methyl-substituted analog **22**. This conversion was probably due to an acid-catalyzed dehydration of compound **21**, which was followed by hydrogenation to compound **22**.[30] We also reduced **19** to the corresponding hydroxymethyl compound **23** and methyl compound **24**, respectively.

Compound **17** was also prepared from **12** via a three-step route, as shown in Scheme IV. Thus, reduction of the α,β-unsaturated ester side chain of **12** furnished **25**, which was protected to afford acetate **26**. A formylation reaction eventually converted **26** into **17**, with concomitant loss of the benzyl group. Using compound **12** as a substrate, compound **27** was expectedly realized (Scheme IV) and was then saponified to afford **28**.

Several methods which had been proven effective for the oxidation of an aldehyde to an acid[31] failed to deliver an acid from **29**, which was obtained from **17**, owing presumably to the interference of the sterically hindered and

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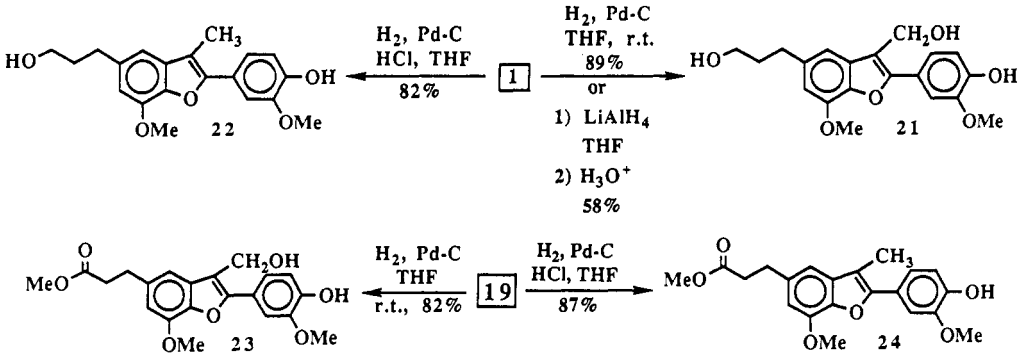
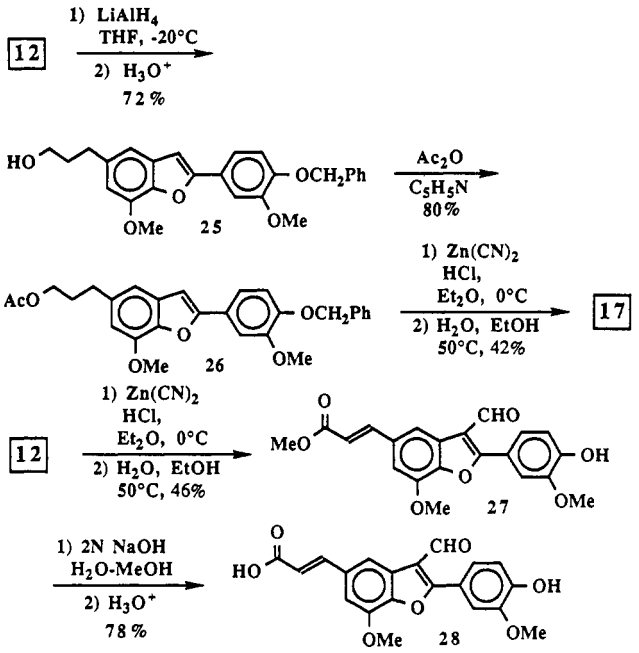
Scheme III



Scheme IV



oxidant-sensitive 2-phenyl group. Diacetate **29** was thus allowed to undergo a radical mediated oxidation,[32] following a literature procedure.[33] However, the only separable product was the 4-bromo-substituted compound **30**, which was isolated in a meager 5% yeild (Scheme V). On the other hand, compound **31** was obtained in 85% yield via treatment of compound **29** with methyllithium.

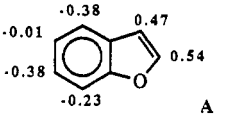
Our next target was compound **34** (Scheme VI). In our hands, diol **14** gave only the undesired **32** via acetylation with acetic anhydride.[34] Subsequent saponification as anticipated converted **32** to **33**. The C-3 acetylated compound **34** was also obtained albeit in only a trace amount during our chromatographic separation of **33**.

The pharmacometabolic result demonstrated that compound **1** was easily metabolized owing to its fragile aldehyde functional group.[35] We reasoned that a comparatively more stable electron-withdrawing group such as a nitro group at C-3 would be appropriate both electronically and spatially. Thus, a nitro group was introduced by a conventional nitration,[34] starting from compound **26** (Scheme VII). After nitration, compound **35** was debenzylated to give **36**, which was saponified to provide the desired **37**.

A cyano group was also introduced to C-3 by an aldehyde transformation route (Scheme VIII). Thus, compound **17** was first allowed to condense with hydroxylamine hydrochloride to give oxime **38**, which was then dehydrated with acetic anhydride to form **39**. Saponification of **39** provided **40**.

Our last target was compound **41**. The purpose for the synthesis of this compound is to examine the influence of a C-4 substituent on the bioactivity. Taking the steric effect into consideration (vide infra), we revolved to the use of the Vilsmeier reagent[36] as an electrophile, which would react via a bulky intermediate. In this way, substrate **14** gave **41** as the only product (Scheme IX). In striking contrast, a formyl group was introduced into the C-3 position of 2-phenylbenzo[*b*]furan under a Vilsmeier condition.[37] It is thus likely that the substitution of **14** was influenced by more subtle factors, such as that from the 3-hydroxypropyl group, which might be able to direct substitution at C-4 via polar interaction.

3. Regioselectivity of Benzo[*b*]furans toward Electrophiles. (a) Electronic Factors. It is appropriate to note that the regioselectivity for the C-3 formylation of **16** (Scheme I), **13** (Scheme II), **26** (Scheme IV), and **12** (Scheme IV) by a Gattermann–Adams reaction as well as the C-3 nitration of **26** (Scheme VII) were obtained through a correct guidance by frontier orbital theory and a 2D NMR spectral analysis. According to the frontier orbital theory, the frontier electron populations of an unsubstituted benzo[*b*]furan are represented as illustrated in structure A.[38] It should be noted that the more positive the numerical values, the more reactive is the corresponding carbon toward electrophiles.



A

In our case, the C-2 position of benzofuran is substituted by a phenyl group, thus, the C-3 position would become the most reactive. On the other hand, the technique of 2D ^{13}C–^{1}H COSY (supplementary material) is used in order to ascertain the carbon-13 absorption signals of C-3 (δ 99.9), C-4 (δ 112.3), C-6 (δ 107.5), and C-5′ (δ 114.8) of **16**. The result of this study unequivocally supports the notion that the electron density at C-3 is higher than those at C-4, C-6, and C-5′.

The mesomeric factor of the substituted 2-phenyl group also plays a pivotal role in the regiochemistry of C-3 versus C-4 substitution. The generation of a mixture of **17** and

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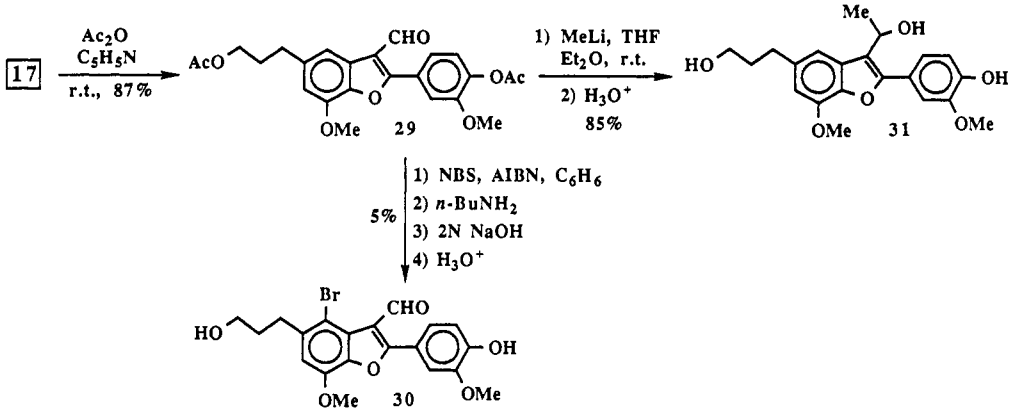
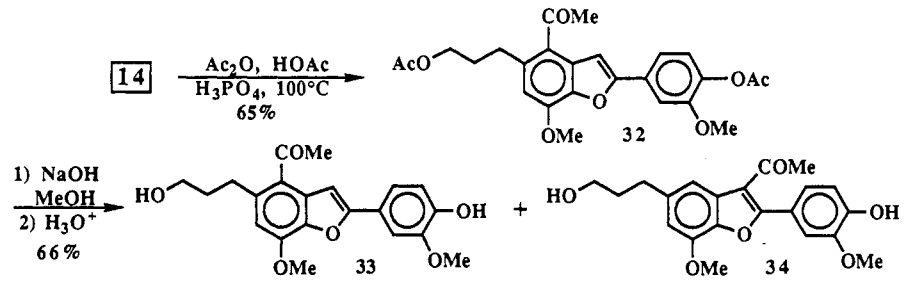
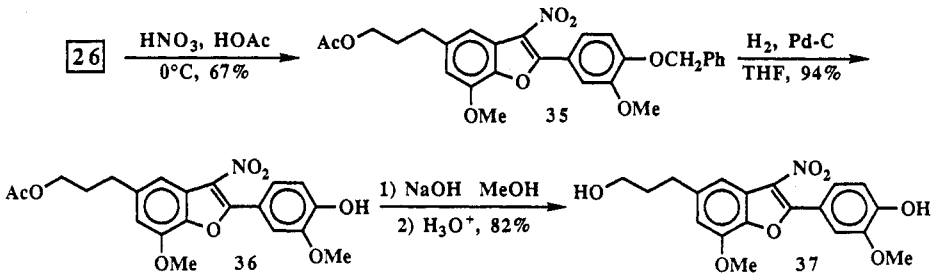
Scheme V



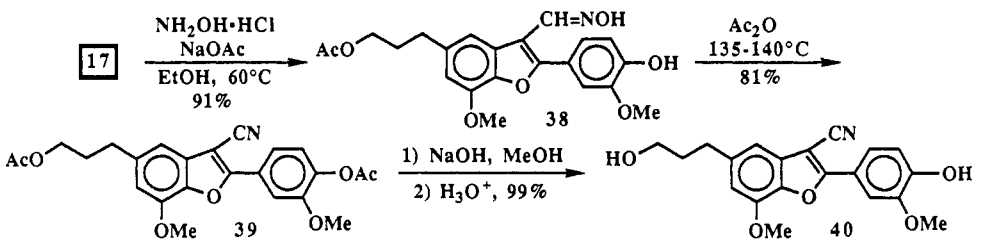
Scheme VI



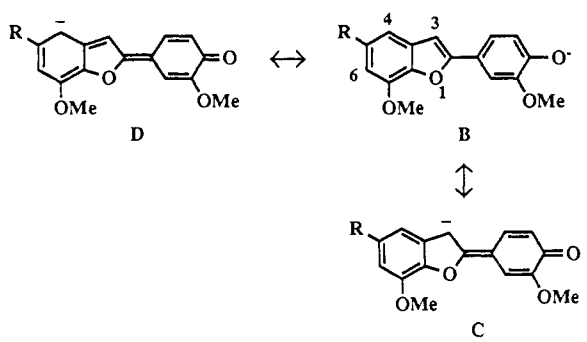
Scheme VII



Scheme VIII

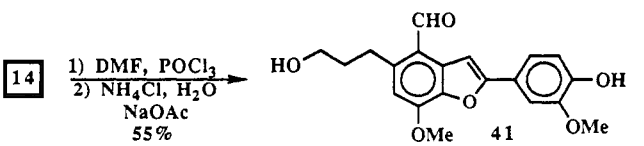


18 from 16 through the Gattermann–Adams formylation is possibly due to the fact that phenol is relatively acidic and the negative charge of the phenolate oxygen is easily delocalized, as depicted in structures B, C, and D. As a



result, the benzo[*b*]furan nucleus becomes more electron

Scheme IX



rich and is likely less regioselective toward electrophilic substitution. Using a similar argument, owing to its higher reactivity, the use of compound **16** as substrate failed to give **37** as a single product. Experimental results showed that a mixture of C-3 and C-4 nitro compounds was generated in a ratio of approximately 3:2 according to a proton NMR analysis.[39]

It is also of interest to reiterate the aforementioned 2D ^{13}C–^{1}H COSY results, which imply that all the unsubsti-

(39) Yang, Z.; Wong, H. N. C. unpublished experiments.

tuted carbons of the benzo[b]furan moiety are more electron rich than the C-5′ carbon. Such characteristic feature ensures that all electrophilic substitutions would not take place on C-5′ of the hydroxyphenyl ring.

As substantiated in the generation of **27** from **12** (Scheme IV) as well as **17** (Scheme IV) and **35** (Scheme VII) from **26**, appropriate protection of the hydroxyl group of the 2-phenyl ring as benzyloxy group led to an overall diminuation of the benzo[b]furan ring electron density, thereby enhancing C-3 regioselectivity. Furthermore, based on the results that benzyloxy substitution (viz **12** and **26**) (Scheme IV) gave exclusive C-3 formylation under the Gattermann–Adams condition (viz **27** and **17**, respectively) whereas the same reaction converted the unprotected **16** to a mixture of **17** and **18**, it is therefore logical to presume that the formylation step should occur prior to debenzylation.

(b) Steric Factors. Steric effect is another important factor governing the regioselectivity of electrophilic substitution. It has been recorded that a C-2 alkyl or phenyl substituent causes steric hindrance to substitution on the C-3 position.[40,41] As a result, despite the fact that C-3 is the most electron rich, a bulky electrophile such as the Vilsmeier reagent[36] (viz **14** → **41**) (Scheme IX) and the Friedel–Crafts reagent[34] (viz **14** → **32**) (Scheme VI) will be favorable for C-4 substitution, while smaller intermediates such as a nitronium ion[34] (viz **26** → **35**) (Scheme VII) or that generated from the Gattermann–Adams reagent[28] (Schemes I, II, and IV) gave preferentially C-3 substitution.[40,41]

(c) Kinetic versus Thermodynamic Factors. Although less obvious, it is evident from the results obtained so far that relatively high temperature reactions (100 °C) (i.e. **14** → **32** and **14** → **41**) (Schemes VI and IX) led to essentially C-4 substitution, while 0 °C reactions (i.e. **16** → **17**, **13** → **19**, **12** → **27**, **26** → **17**, and **26** → **35**) (Schemes I, II, IV, and VII) gave mainly C-3 substitution. A possible conclusion that can be deduced from these outcomes is that the C-3 and C-4 substitution pattern might also be explained by kinetic control versus thermodynamic control arguments.

Conclusion

We have shown that by maintaining the balance between the electronic requirements, the stereochemical restrictions as well as the kinetic and thermodynamic factors, formyl, acetyl, and nitro groups can be imparted regioselectively to either carbon-3 or carbon-4 of 5-alkyl-7-methoxy-2-phenylbenzo[b]furans. Subsequent chemical modifications thus converted the formyl group to other functional groups such as hydroxymethyl, methyl, 1-hydroxyethyl and cyano groups.

The pharmacological analysis of the compounds synthesized will be reported elsewhere in due course.

Experimental Section

5-Bromovanillin (5).[22] To a solution of vanillin (**4**) (100 g, 0.65 mol) in HOAc (200 mL), Br_2 (105 g, 0.69 mol) in HOAc (200 mL) was added at rt for 1 h. Bromovanillin (**5**) was separated during the process. Water (50 mL) was added to the mixture, and the solid was filtered off and then recrystallized from EtOH (95%) to give white crystals of **5** (125 g, 82%), mp 162–163 °C [lit.[22] mp 163–164 °C].

Methyl 3-Methoxy-4-hydroxy-5-bromocinnamate (6).[23] 5-Bromovanillin (**5**) (9.2 g, 0.04 mol), monomethyl malonate[24] (9.6 mL, 0.08 mol), and pyrrolidine (0.5 mL, 6 mmol) were mixed in dry pyridine (20 mL), and the mixture was heated at 100 °C for 6 h and then was allowed to cool to rt. The solvent was removed in vacuum, and the residue was mixed with 2 N HCl (60 mL) and EtOAc (100 mL). The organic layer was separated, first washed with brine (2 × 10 mL), and then dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was recrystallized from $CHCl_3/C_6H_{14}$ (1:1) to give the purified product **6** as a white solid (11.2 g, 98%), mp 107–109 °C: ^1H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.93 (s, 3 H), 6.30 (d, J = 16 Hz, 1 H), 6.95 (d, J = 1.7 Hz, 1 H), 7.30 (d, J = 1.7 Hz, 1 H), 7.54 (d, J = 16 Hz, 1 H); MS m/e 287 (M^+).

Anal. Calcd for $C_{11}H_{11}O_4Br$: C, 46.02; H, 3.86. Found: C, 45.98; H, 3.71.

3-Methoxy-4-(benzyloxy)acetophenone (8). To a solution of K_2CO_3 (27.6 g, 0.2 mol) in H_2O (75 mL) was added 3-methoxy-4-hydroxyacetophenone (**7**) (33 g, 0.2 mol). The resulting solid was partially dissolved in THF (350 mL). A solution of benzyl bromide (34.2 g, 0.2 mol) and tetrabutylammonium iodide (1 g) in THF (50 mL) was then added to the reaction mixture. After refluxing at 80 °C for 10 h with stirring, the mixture was allowed to cool to rt, and the organic layer was separated. The organic solvent was removed in vacuum, and the residue was dissolved in $CHCl_3$ (500 mL). The solution was washed with brine (2 × 50 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed, and the residual solution (100 mL) was then combined with C_6H_{14} (100 mL). The resulting needle-shaped crystals were recrystallized ($EtOAc/C_6H_{14}$, 1:1) to give **8** (42 g, 82%) as needles, mp 86–89 °C: ^1H NMR ($CDCl_3$) δ 2.53 (s, 3 H), 3.93 (s, 3 H), 5.22 (s, 2 H), 6.88 (d, J = 8.4 Hz, 1 H), 7.30–7.53 (m, 7 H); MS m/e 256 (M^+).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.47; H, 6.15.

β-(3-Methoxy-4-(benzyloxy)phenyl)-β-chloroacrolein (9).[20] To a solution of compound **8** (51 g, 0.2 mol) in DMF (200 mL) was added dropwise the Vilsmeier reagent [prepared by dropwise addition of $POCl_3$ (80 g, 0.52 mol) to DMF (80 mL) at 0 °C] during 1 h at 0 °C. The solution was stirred at the same temperature for 20 min and then at 65 °C for 10 h. The mixture was poured into an ice–H_2O solution (2 L) containing NaOAc (250 g) and NH_4Cl (300 g), and then the resulting mixture was allowed to stand overnight. The crystallized solids were filtered off and purified by chromatography twice on a silica gel column (300 g, $EtOAc/C_6H_{14}$, 1:3) to give a yellowish solid **9** (38 g, 63%), mp 99–101 °C: ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H), 5.21 (s, 2 H), 6.61 (d, J = 6.9 Hz, 1 H), 6.92 (d, J = 10.6 Hz, 1 H), 7.24–7.45 (m, 7 H), 10.12 (d, J = 6.9 Hz, 1 H); MS m/e 303 (M^+).

Anal. Calcd for $C_{17}H_{15}O_3Cl$: C, 67.44; H, 4.99. Found: C, 67.15; H, 4.88.

(3-Methoxy-4-(benzyloxy)phenyl)acetylene (10).[20] A solution of compound **9** (45 g, 0.15 mol) in dioxane (700 mL) was added dropwise to a vigorously stirred hot solution of NaOH (70 g, 1.75 mol) in H_2O (550 mL), and this mixture was continuously stirred at 80 °C for 2 h. The mixture was then concentrated in vacuum, and the residual solution was extracted with Et_2O (3 × 200 mL). The organic layer was washed with brine (3 × 50 mL) and dried over anhydrous Na_2SO_4. The ethereal extract was evaporated to dryness, and the residue was chromatographed on a silica gel column (500 g, 70–230 mesh, $CHCl_3$ containing 30% C_6H_{14}) to give **10** as a white solid (28 g, 79%), mp 87.5–88.0 °C: ^1H NMR ($CDCl_3$) δ 2.99 (s, 1 H), 3.88 (s, 3 H), 5.16 (s, 2 H), 6.81 (d, J = 8.6 Hz, 1 H), 7.01 (d, J = 1.8 Hz, 1 H), 7.03 (dd, J = 8.6, 1.8 Hz, 1 H), 7.30–7.44 (m, 5 H); MS m/e 328 (M^+).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.55; H, 6.01.

Cuprous (3-Methoxy-4-(benzyloxy)phenyl)acetylide (11).[21] A mixture of $CuSO_4 \cdot H_2O$ (14 g, 56 mmol) and 28% NH_4OH (56 mL) was stirred magnetically for a short time in a 2-L Erlenmeyer flask under N_2. After addition of distilled H_2O (225 mL), solid $NH_2OH \cdot HCl$ (7.8 g, 0.15 mol) was added. The dark blue solution then turned lighter and was cooled in an ice bath. After approximately 5 min, compound **10** (13.5 g, 56 mmol) in a solution of THF (50 mL) and EtOH (50 mL) was added, the yellowish cuprous acetylide formed immediately, and the precipitate was filtered off and then washed successively with H_2O (5 × 100 mL), EtOH (5 × 100 mL), and Et_2O (5 × 100 mL). The solid was dried

(40) Arventiev, B.; Offenberg, H. *Analele Stiint. Univ. "A.I. Cuza", Iasi Sect. I.* **1963**, *9*, 225–232; *Chem. Abstr.* **1964**, *60*, 15809e.
(41) Bisagni, M.; Buu-Hoi, N. P.; Royer, R. *J. Chem. Soc.* **1955**, 3688–3695.

for 6 h at 65 °C in vacuum in a rotary evaporator to give product 11 (11.6 g, 72%) as a yellowish solid: mp 188–190 °C dec. This compound was used immediately in other experiments and was not purified further.

5-(2-(Methoxycarbonyl)-*trans*-ethenyl)-7-methoxy-2-(3′-methoxy-4′-(benzyloxy)phenyl)benzo[*b*]furan (12).[25] Compound 11 (7.82 g, 0.02 mol) was dissolved in pyridine (50 mL) in a three-neck flask, and the reaction system was equipped with a N_2 inlet and a reflux condenser connected to a glycerine trap and then was thoroughly flushed with N_2 before use. A solution of bromide 6 (5.6 g, 0.02 mol) in pyridine (50 mL) was added to the above solution with magnetical stirring under N_2, and the mixture was stirred at 115 °C for 20 h and then evaporated to dryness in vacuum. The residue was dissolved in $CHCl_3$ (150 mL), and the solution was washed with H_2O (15 mL) and then dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuum, and the residue was chromatographed on a silica gel column (300 g, C_6H_{14}/EtOAc, 3:1) to give a raw product, which was recrystallized from $CHCl_3$ to give a white solid of 12 (6.9 g, 65%), mp 152–153 °C: ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3 H), 3.99 (s, 3 H), 4.06 (s, 3 H), 5.20 (s, 2 H), 6.41 (d, J = 15.9 Hz, 1 H), 6.88 (s, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 6.96 (s, 1 H), 7.32–7.44 (m, 7 H), 7.45 (d, J = 8.7 Hz, 1 H), 7.77 (d, J = 15.9 Hz, 1 H); MS m/e 446 (M^+).

Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.71; H, 5.35.

5-(2-(Methoxycarbonyl)ethyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (13).[26] A solution of the α,β-unsaturated ester 12 (1 g, 2.24 mmol) and 5% Pd–C (20 mg) in THF (15 mL) was stirred under H_2 at rt for 10 h. TLC ($CHCl_3/C_6H_{14}$, 1:2) indicated that the starting material disappeared. The mixture was filtered through a short silica gel column (THF) to remove the catalyst, the filtrate was evaporated to dryness in vacuum, and then the residue was purified by flash chromatography on a silica gel column (20 g, $CHCl_3/C_6H_{14}$, 1:2) to give colorless oil of 13 (0.74 g, 92%): ^{1}H NMR ($CDCl_3$) δ 2.68 (t, J = 7.8, 7.8 Hz, 2 H), 3.01 (t, J = 7.8, 7.8 Hz, 2 H), 3.68 (s, 3 H), 3.95 (s, 3 H), 4.01 (s, 3 H), 5.96 (br s, 1 H), 6.62 (d, J = 1.4 Hz, 1 H), 6.79 (s, 1 H), 6.96 (d, J = 1.4 Hz, 1 H), 6.96 (d, J = 8.1 Hz, 1 H), 7.35 (d, J = 2.0 Hz, 1 H), 7.37 (dd, J = 8.1, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 156.5, 146.8, 146.4, 144.8, 136.2, 131.3, 123.0, 118.9, 114.8, 112.2, 107.8, 107.3, 100.0, 56.1, 51.5, 36.2, 31.3; MS m/e 356 (M^+).

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 66.92; H, 5.56.

5-(3-Hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (14).[27] To a solution of compound 13 (4.73 g, 14 mmol) in THF (100 mL) was added $LiAlH_4$ (0.64 g, 17 mmol) at 0 °C. The mixture was stirred at rt for 4 h, decomposed with an ice–H_2O solution of 5% H_2SO_4, and then extracted with EtOAc (3 × 50 mL). The organic layer was evaporated to dryness, the residue was dissolved in EtOAc (100 mL), and the organic solution was washed with brine (2 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 100 g, $CHCl_3$/EtOH, 98:2) to give 14 (3.57 g, 82%) as a white solid, mp 78.0–78.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 2 H), 2.78 (t, J = 7.8, 7.8 Hz, 2 H), 3.72 (t, J = 6.4, 6.4 Hz, 2 H), 3.98 (s, 3 H), 4.03 (s, 3 H), 5.82 (s, 1 H), 6.64 (s, 1 H), 6.81 (s, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 6.98 (s, 1 H), 7.37 (d, J = 1.9 Hz, 1 H), 7.39 (dd, J = 8.0, 1.9 Hz, 1 H); MS m/e 328 (M^+).

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.81; H, 6.05.

5-(3-Acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-acetoxyphenyl)benzo[*b*]furan (15). To a solution of compound 14 (3.28 g, 0.01 mol) in pyridine (15 mL) was added Ac_2O (4 mL), and the mixture was stirred at rt for 18 h. The solvent was removed in vacuum (60 °C), and the residue was chromatographed on a silica gel column (230–400 mesh, 200 g, $CHCl_3/C_6H_{14}$, 2:1) to give compound 15 (3.76 g, 91%) as white needles, mp 88.0–88.5 °C: ^{1}H NMR ($CDCl_3$) δ 2.01 (m, 2 H), 2.04 (s, 3 H), 2.34 (s, 3 H), 2.76 (t, J = 7.3, 7.3 Hz, 2 H), 3.94 (s, 3 H), 4.04 (s, 3 H), 4.13 (t, J = 6.5, 6.5 Hz, 3 H), 6.64 (s, 1 H), 6.92 (s, 1 H), 6.99 (s, 1 H), 7.10 (d, J = 8.8 Hz, 1 H), 7.45 (dd, J = 8.8, 1.7 Hz, 1 H), 7.46 (d, J = 1.7 Hz, 1 H); MS m/e 412 (M^+).

Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.93; H, 5.84.

5-(3-Acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (16). To a solution of the diester 15 (2.1 g, 5 mmol) in Me_2CO (20 mL) was added 10 N NH_4OH (10 mL) dropwise, and the mixture was stirred at rt for 40 min. TLC (EtOAc/C_6H_{14}, 1:1) indicated that the substrate disappeared, and then the pH value of the solution was adjusted to about 2 with 5 N HCl (20 mL). The organic solvent was evaporated in vaccum, the aqueous solution was extracted with EtOAc (3 × 50 mL), and the organic layer was washed with brine (2 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 200 g, EtOAc/C_6H_{14}, 1:1) to give product 16 (1.6 g, 85%) as a white solid, mp 80–80.5 °C: ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 2 H), 2.06 (s, 3 H), 2.73 (t, J = 7.2, 7.2 Hz, 2 H), 3.90 (s, 3 H), 4.01 (s, 3 H), 4.11 (t, J = 6.6, 6.6 Hz, 2 H), 6.06 (s, 1 H), 6.59 (d, J = 1.4 Hz, 1 H), 6.78 (s, 1 H), 6.93 (d, J = 1.4 Hz, 1 H), 6.95–7.37 (ABX, J = 8.2, 1.8, 0.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.9, 156.5, 146.8, 146.4, 144.8, 142.6, 136.8, 131.3, 123.0, 118.8, 114.8, 112.3, 107.8, 107.5, 99.9, 63.8, 56.1, 56.0, 32.4, 30.6, 20.7; MS m/e 370 (M^+).

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.98. Found: C, 67.89; H, 6.05.

General Procedure for Gattermann–Adams Formylation. (a) 5-(3-Acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (17).[28] A 50-mL three-necked round-bottomed flask was connected with a reflux condenser and an inlet tube extending nearly to the bottom of the flask. A safety bottle was placed in series with this tube and a dry HCl generator. The top of the condenser was connected to a tube leading into a wash bottle containing H_2SO_4, then to a safety bottle, and finally to the surface of aqueous NaOH. To a solution of the ester 16 (1.85 g, 5 mmol) in absolute Et_2O (25 mL) were added $Zn(CN)_2$ (0.79 g, 7.5 mmol) and KCl (20 mg). The mixture was cooled to 0 °C in an ice–salt bath, and anhydrous HCl gas (prepared by addition of concd H_2SO_4 to anhydrous NH_4Cl) was passed through the solution for 30 min with stirring. The Et_2O solution was decanted, and the residue was washed with Et_2O (2 × 10 mL), mixed with a solution of H_2O (30 mL) and EtOH (20 mL), and then heated at 50 °C for 30 min. The organic solvent was removed in vacuum, the yellowish solid was extracted with $CHCl_3$ (3 × 50 mL), and then the organic layer was washed with brine (2 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 100 g, $CHCl_3/C_6H_{14}$, 3:1) to give product 17 (1.02 g, 51%) as a yellowish solid, mp 109–110 °C: ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 2 H), 2.09 (s, 3 H), 2.81 (t, J = 7.2, 7.2 Hz, 2 H), 3.99 (s, 3 H), 4.03 (s, 3 H), 4.12 (t, J = 7.5, 7.5 Hz, 2 H), 6.21 (s, 1 H), 6.73 (s, 1 H), 7.07 (d, J = 7.7 Hz, 1 H), 7.38 (s, 1 H), 7.39 (d, J = 7.7 Hz, 1 H), 7.66 (s, 1 H), 10.28 (s, 1 H); MS m/e 398 (M^+).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.56. Found: C, 66.36; H, 5.75.

(b) 5-(2-(Methoxycarbonyl)ethyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (19). From 13 (1.78 g, 0.5 mmol), absolute Et_2O (20 mL), $Zn(CN)_2$ (0.87 g, 0.75 mmol), and KCl (30 mg); chromatography, silica gel (70–230 mesh, 200 g, $CHCl_3$/EtOH, 95:5); yield of 19, 1.02 g, 62% (yellowish solid), mp 137–138 °C: ^{1}H NMR ($CDCl_3$) δ 2.71 (t, J = 7.7, 7.7 Hz, 2 H), 3.06 (t, J = 7.8, 7.8 Hz, 2 H), 3.70 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 6.14 (s, 1 H), 6.76 (d, J = 1.3 Hz, 1 H), 7.06 (d, J = 8.1 Hz, 1 H), 7.37 (d, J = 2.1 Hz, 1 H), 7.39 (dd, J = 8.1, 2.1 Hz, 1 H), 7.67 (d, J = 1.3 Hz, 1 H), 10.28 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 186.5 (CHO), 173.2 (COOR), 165.8 (C-4′), 148.8 (C-1a), 147.1 (C-2), 144.8 (C-7), 142.1 (C-3′), 138.7 (C-3), 127.7 (C-5), 123.7 (C-6), 120.8 (C-3a), 116.8 (C-1′), 115.2 (C-4), 113.6 (C-2′), 111.4 (C-6′), 109.2 (C-5′), 56.4 (OMe), 56.3 (OMe), 51.6 (CO_2Me), 36.3 (C-9), 31.5 (C-8); MS m/e 384 (M^+).

Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.37; H, 5.10.

(c) 5-(3-Acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (17). From 26 (1.15 g, 2.5 mmol), Et_2O (25 mL), $Zn(CN)_2$ (0.4 g, 4 mmol), and KCl (10 mg); chromatography, silica gel (70–230 mesh, 100 g, $CHCl_3/C_6H_{14}$, 3:1); yield of 17, 0.42 g, 42% (yellowish solid). The physlical and ^{1}H NMR spectroscopic data are identical to an authentic sample prepared previously (vide supra).

(d) 5-(2-(Methoxycarbonyl)-*trans*-ethenyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (27). From **12** (0.5 g, 1 mmol), absolute Et_2O (25 mL), $Zn(CN)_2$ (0.24 g, 2 mmol), and KCl (10 mg); chromatography, silica gel (70–230 mesh, 50 g, $CHCl_3/C_6H_{14}$, 3:1); yield of **27**, 125 mg, 46% (yellowish solid), mp 128–130 °C: ^1H NMR ($CDCl_3$) δ 3.83 (s, 3 H), 4.02 (s, 3 H), 4.06 (s, 3 H), 6.12 (s, 1 H), 6.49 (d, J = 15.9 Hz, 1 H), 7.04 (d, J = 1.2 Hz, 1 H), 7.08–7.44 (ABX, J = 8.2, 1.7, 0.8 Hz, 3 H), 7.79 (d, J = 15.9 Hz, 1 H), 8.02 (d, J = 1.2 Hz, 1 H), 10.30 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 186.2 (CHO), 176.3 (CO_2Me), 167.4 (C-7a), 166.2 (C-4′), 149.1 (C-2′), 147.2 (C-7), 145.3 (C-3′), 145.0 (C-3), 144.3 (C-5), 132.7 (C-3a), 128.0 (C-1′), 123.8 (C-4), 120.4 (C-8), 117.9 (C-6), 116.7 (C-9), 115.3 (C-5′), 111.3 (C-2′), 107.5 (C-6′), 56.4 (OMe), 56.3 (OMe), 51.7 (OMe); MS m/e 382 (M^+).

Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.75. Found: C, 65.34; H, 4.52.

General Procedure for Saponification. (a) 5-(3-Hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (1). To a solution of aldehyde **17** (1 g, 2.5 mmol) in MeOH (35 mL) was added 2 N NaOH in MeOH (3 mL), the mixture was stirred at rt for 4 h, 2 N HCl (3 mL) was added, and the solution was evaporated to dryness. The residue was dissolved in $CHCl_3$, washed with H_2O (2 × 10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (230–400 mesh, 100 g, $CHCl_3/C_6H_{14}$, 95:5) to give product **1** (0.83 g, 93%) as a yellowish solid, mp 77–77.5 °C; ^1H NMR ($CDCl_3$) δ 1.94 (m, 2 H), 2.81 (t, J = 8.1, 8.1 Hz, 2 H), 3.70 (t, J = 6.3, 6.3 Hz, 2 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 5.99 (s, 1 H), 6.73 (d, J = 1.5 Hz, 1 H), 7.05 (d, J = 7.8 Hz, 1 H), 7.36 (d, J = 1.8 Hz, 1 H), 7.37 (dd, J = 8.3, 1.8 Hz, 1 H), 7.64 (d, J = 1.5 Hz, 1 H), 10.26 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 186.7 (CHO), 165.8 (C-4′), 148.7 (C-7a), 146.9 (C-2), 144.7 (C-7), 141.8 (C-3′), 140.0 (C-3), 127.4 (C-5), 123.7 (C-6), 120.8 (C-3a), 116.8 (C-1′), 115.1, 113.7, 111.1 (C-6′), 108.9 (C-5′), 56.3 (OMe), 56.1 (OMe), 62.3 (C-10), 34.8 (C-9), 32.6 (C-8); MS m/e 356 (M^+).

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.05; H, 5.52.

(b) 5-(2-Carboxyethyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (20). From **19** (384 mg, 1 mmol), MeOH (5 mL), 1 N NaOH (2.2 mL, 2.2 mmol), and 1 N HCl (2.2 mL, 2.2 mmol); chromatography, silica gel (70–230 mesh, 50 g, $CHCl_3$/EtOH/HOAc, 95:4.5:0.5); yield of **20**, 0.28 g, 75% (yellowish solid), mp 180.0–180.5 °C: ^1H NMR ($CDCl_3$) δ 2.60 (t, J = 7.5, 7.5 Hz, 2 H), 2.96 (t, J = 7.5, 7.5 Hz, 2 H), 3.92 (s, 3 H), 3.99 (s, 3 H), 6.91 (d, J = 1.2 Hz, 1 H), 7.00 (d, J = 8.3 Hz, 1 H), 7.39 (dd, J = 8.3, 1.9 Hz, 1 H), 7.40 (d, J = 1.9 Hz, 1 H), 7.56 (d, J = 1.2 Hz, 1 H), 9.89 (s, 1 H), 10.23 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 186.3, 173.6, 165.4, 150.3, 148.2, 144.4, 141.2, 138.9, 127.1, 123.1, 119.2, 118.7, 116.2, 115.8, 112.8, 109.2, 56.1, 56.1, 35.9, 31.0; MS m/e 370 (M^+).

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.98; H, 4.90. Found: C, 64.80; H, 4.43.

(c) 5-(2-Carboxy-*trans*-ethenyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (28). From **27** (100 mg, 0.4 mmol), MeOH (2 mL), 1 N NaOH (1 mL, 1 mmol), and 1 N HCl (1 mL, 1 mmol); chromatography, silica gel (70–230 mesh, 15 g, $CHCl_3$/EtOH/HOAc, 95:4.5:0.5); yield of **28**, 75 mg, 78% (yellowish solid), mp 147–149 °C: ^1H NMR (d_6-DMSO) δ 3.91 (s, 3 H), 4.03 (s, 3 H), 6.59 (d, J = 15.3 Hz, 1 H), 7.01 (d, J = 8.2 Hz, 1 H), 7.35 (s, 1 H), 7.41–7.47 (m, 2 H), 7.61 (d, J = 15.3 Hz, 1 H), 7.84 (s, 1 H), 8.29 (s, 1 H), 10.23 (s, 1 H); MS m/e 368 (M^+).

Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38. Found: C, 64.74; H, 4.43.

(d) 4-Acetyl-5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (33) and 3-Acetyl-5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (34). From **32** (500 mg, 1.1 mmol), MeOH (2 mL), 1 N NaOH in MeOH (2.5 mL), and 1 N HCl (2.6 mL); chromatography, silica gel (70–230 mesh, 30 g, Et_2O/$CHCl_3$/EtOH, 5:4:1); yield of **33**, 270 mg, 66% (yellowish solid), mp 126–128 °C: ^1H NMR ($CDCl_3$) δ 1.95 (m, 2 H), 2.69 (s, 3 H), 2.93 (t, J = 7.2, 7.2 Hz, 2 H), 3.62 (t, J = 5.8, 5.8 Hz, 2 H), 3.99 (s, 3 H), 4.06 (s, 3 H), 6.65 (s, 1 H), 6.94 (s, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 7.36 (d, J = 1.7 Hz, 1 H), 7.42 (dd, J = 8.3, 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 202.4, 157.5, 147.0, 146.7, 142.2, 138.1, 130.2, 125.2, 122.4, 119.3, 118.9, 115.0, 109.0, 108.0, 100.1, 61.4, 56.2, 56.2, 35.1, 31.9, 29.8; MS m/e 370 (M^+).

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.98. Found: C, 67.65; H, 5.75.

During the separation, compound **34** was obtained in a trace amount (25 mg) as a yellowish solid, mp 132–134 °C: ^1H NMR ($CDCl_3$) δ 1.96 (m, 2 H), 2.36 (s, 3 H), 3.42 (t, J = 7.0, 7.0 Hz, 2 H), 3.58 (t, J = 5.7, 5.7 Hz, 2 H), 3.99 (s, 3 H), 4.17 (s, 3 H), 6.44 (d, J = 1.2 Hz, 1 H), 6.84 (s, 1 H), 7.06 (d, J = 8.2 Hz, 1 H), 7.26 (d, J = 2.0 Hz, 1 H), 7.32 (dd, J = 8.2, 2.0 Hz, 1 H); MS m/e 370 (M^+).

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.98. Found: C, 68.17; H, 6.01.

(e) 3-Nitro-5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (37). From **36** (125 mg, 0.3 mmol), MeOH (5 mL), 1 N NaOH (1 mL, 1 mmol), and 1 N HCl (1.2 mL 1.2 mmol); chromatography, silica gel (70–230 mesh, 5 g, $CHCl_3$); yield of **37**, 92 mg, 82% (yellowish needles), mp 152–154 °C ($CHCl_3$): ^1H NMR ($CDCl_3$) δ 2.01 (m, 2 H), 3.17 (t, J = 7.6, 7.6 Hz, 2 H), 3.79 (t, J = 6.1, 6.1 Hz, 2 H), 4.03 (s, 3 H), 4.13 (s, 3 H), 6.69 (d, J = 1.5 Hz, 1 H), 7.02 (d, J = 8.3 Hz, 1 H), 7.58 (d, J = 1.5 Hz, 1 H), 7.65 (d, J = 1.5 Hz, 1 H), 7.67 (dd, J = 8.3, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 159.5, 147.7, 143.8, 137.2, 135.2, 134.5, 127.1, 122.1, 119.8, 115.1, 112.7, 109.5, 108.2, 100.8, 62.3, 56.7, 56.3, 34.1, 30.8; MS m/e 373 (M^+).

Anal. Calcd for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13; N, 3.75. Found: C, 60.61; H, 4.83; N, 3.55.

(f) 3-Cyano-5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (40). From **39** (150 mg, 0.35 mmol), MeOH (10 mL), NaOH (0.5 g), and 2 N HCl; extracted with EtOAc (3 × 20 mL); chromatography, silica gel (9 g, $CHCl_3$/EtOAc, 9:1); yield of **40**, 120 mg, 99% (yellowish solid), mp 167–167.5 °C: ^1H NMR ($CDCl_3$) δ 1.86 (m, 2 H), 2.75 (t, J = 7.7, 7.7 Hz, 2 H), 3.56 (t, J = 6.4, 6.4 Hz, 2 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 6.84 (s, 1 H), 6.94–6.97 (d, J = 8.8 Hz, 2 H), 7.48–7.58 (m, 2 H); MS m/e 353 (M^+).

Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.47; H, 5.26; N, 3.92.

5-(3-Hydroxypropyl)-3-(hydroxymethyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (21). Procedure I. To a solution of compoound **1** (150 mg, 0.42 mmol) in THF (5 mL) was added 5% Pd–C (10 mg), and the mixture was hydrogenated for 8 h at rt. The catalyst was filtered off through a short silica gel column (0.5 × 3 cm^2, THF), and the organic solvent was removed in vacuum. The residue was chromatographed on a silica gel column (70–230 mesh, 40 g, $CHCl_3$/EtOH, 95:5) to give product **21** (134 mg, 89%) as a semisolid: ^1H NMR ($CDCl_3$) δ 1.94 (m, 2 H), 2.80 (t, J = 7.2, 7.2 Hz, 2 H), 3.70 (t, J = 6.5, 6.5 Hz, 2 H), 3.97 (s, 3 H), 4.02 (s, 3 H), 4.89 (s, 2 H), 5.89 (s, 1 H), 6.66 (s, 1 H), 7.01 (d, J = 8.1 Hz, 1 H), 7.10 (s, 1 H), 7.32 (dd, J = 8.1, 1.8 Hz, 1 H), 7.41 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 146.9, 145.2, 137.9, 131.4, 122.8, 121.5, 116.4, 114.9, 113.9, 110.9, 110.5, 108.4, 62.4, 56.4, 56.3, 55.8, 31.8, 32.6; MS m/e 358 (M^+).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 66.56; H, 5.65.

Procedure II. To a solution of compound **1** (150 mg, 0.42 mmol) in THF (5 mL) was added $LiAlH_4$ (20 mg, 0.42 mmol) at 0 °C. The mixture was stirred at rt for 3 h and then decomposed with 5% H_2SO_4 (5 mL). The mixture was combined with ethyl acetate (20 mL), and the organic solution was washed with brine (2 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed as above to give compound **21** (87 mg, 58%) as a semisolid, which was identical in all aspects to an authentic sample.

General Procedure for Catalytic Hydrogenation under Acidic Conditions. (a) 5-(3-Hydroxypropyl)-7-methoxy-3-methyl-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (22). To a solution of compound **1** (356 mg, 0.1 mmol) in THF (10 mL) were added 5% Pd–C (20 mg) and two drops of concd HCl. The mixture was stirred under H_2 at rt for 12 h. TLC indicated that the substrate disappeared ($CHCl_3/C_6H_{14}$, 95:5). The catalyst was removed through a short column (0.5 × 3 cm^2, THF). The solvent was evaporated to dryness, and the residue was chromatographed

on a silica gel column (70–230 mesh, 30 g, $CHCl_3/C_6H_{14}$, 95:5) to give product **22** (280 mg, 82%) as a white solid, mp 157–159 °C: ^1H NMR ($CDCl_3$) δ 1.96 (m, 2 H), 2.40 (s, 3 H), 2.80 (t, J = 7.6, 7.6 Hz, 2 H), 3.72 (t, J = 6.4, 6.4 Hz, 2 H), 3.98 (s, 3 H), 4.03 (s, 3 H), 5.86 (s, 1 H), 6.65 (d, J = 1.4 Hz, 1 H), 6.94 (d, J = 1.4 Hz, 1 H), 7.00 (d, J = 8.2 Hz, 1 H), 7.27 (d, J = 1.9 Hz, 1 H), 7.35 (dd, J = 8.2, 1.9 Hz, 1 H); MS m/e 342 (M^+).

Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.85; H, 6.30.

(b) 5-(2-(Methoxycarbonyl)ethyl)-7-methoxy-3-methyl-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (24). From **19** (192 mg, 0.5 mmol), THF (10 mL), 5% Pd–C (20 mg), and two drops of concd HCl; TLC, $Et_2O/CHCl_3/C_6H_{14}$, 2:1:1; chromatography, silica gel (70–230 mesh, 20 g, $Et_2O/CHCl_3/C_6H_{14}$ 2:1:1); yield of **24**, 297 mg, 87% (white solid), mp 102–194 °C: ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.71 (t, J = 7.8, 7.8 Hz, 2 H), 3.05 (t, J = 7.8, 7.8 Hz, 2 H), 3.69 (s, 3 H), 3.97 (s, 3 H), 4.02 (s, 3 H), 5.80 (s, 1 H), 6.65 (d, J = 1.3 Hz, 1 H), 6.94 (d, J = 1.3 Hz, 1 H), 7.00 (d, J = 8.1 Hz, 1 H), 7.28 (dd, J = 8.1, 1.8 Hz, 1 H), 7.32 (d, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.4 (COO), 151.5 (C-4′), 146.7 (C-7a), 145.9 (C-2), 144.8 (C-3′), 141.7 (C-7), 135.8 (C-5), 133.2 (C-3a) 123.8 (C-1′), 123.6 (C-5′), 114.6 (C-2′), 110.8 (C-6′), 110.0 (C-3), 109.7 (C-6), 107.6 (C-4), 56.3 (OMe), 56.2 (OMe), 36.4 (C-9), 31.5 (C-8), 9.5 (Me); MS m/e 370 (M^+).

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 6.00. Found: C, 67.63; H, 5.78.

3-(Hydroxymethyl)-5-(2-(methoxycarbonyl)ethyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (23). To a solution of compound **19** (192 mg, 0.5 mmol) in THF (10 mL) was added 5% Pd–C (10 mg). The mixture was stirred under H_2 for 8 h at rt, and then the catalyst was filtered off through a short silica gel column (0.5 × 3 cm^2, THF). The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 40 g, $CHCl_3/C_6H_{14}$/EtOH, 75:20:5) to give **23** (158 mg, 82%) as a semisolid: ^1H NMR ($CDCl_3$) δ 2.67 (t, J = 7.8, 7.8 Hz, 2 H), 3.01 (t, J = 7.7, 7.7 Hz, 2 H), 3.67 (s, 3 H), 3.94 (s, 3 H), 4.00 (s, 3 H), 4.87 (s, 2 H), 6.05 (s, 1 H), 6.64 (d, J = 1.1 Hz, 1 H), 6.98 (d, J = 8.2 Hz, 1 H), 7.07 (d, J = 1.1 Hz, 1 H), 7.36 (dd, J = 8.2, 1.8 Hz, 1 H), 7.40 (d, J = 1.8 Hz, 1 H); MS m/e 386 (M^+).

Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 64.89; H, 5.48.

5-(3-Hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-(benzyloxy)phenyl)benzo[*b*]furan (25). To a suspension of $LiAlH_4$ (0.64 g, 17 mmol) in THF (50 mL) was added a solution of compound **12** (4.46 g, 10 mmol) in THF (50 mL) at −20 °C during 30 min. The mixture was stirred at rt for 4 h and then was decomposed with an ice–water solution of 5% H_2SO_4, and the solution was extracted with EtOAc (3 × 50 mL). The organic layer was evaporated to dryness, the residue was dissolved in EtOAc (150 mL), and then the solution was washed with brine (2 × 20 mL) and finally was dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 100 g, $CHCl_3/C_6H_{14}$/EtOH, 70:28:2) to give **25** (2.99 g, 72%) as a white solid, mp 118–119 °C: ^1H NMR ($CDCl_3$) δ 1.94 (m, 2 H), 2.78 (t, J = 7.8, 7.8 Hz, 2 H), 3.71 (t, J = 6.4, 6.4 Hz, 2 H), 3.98 (s, 3 H), 4.03 (s, 3 H), 5.20 (s, 2 H), 6.63 (d, J = 1.2 Hz, 1 H), 6.82 (s, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 6.97 (d, J = 1.2 Hz, 1 H), 7.31–7.47 (m, 7 H); MS m/e 418 (M^+).

Anal. Calcd for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26. Found: C, 74.18; H, 6.02.

5-(3-Acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-(benzyloxy)phenyl)benzo[*b*]furan (26). To a solution of compound **25** (2.1 g, 5 mmol) in pyridine (10 mL) was added Ac_2O (2 mL), and the mixture was stirred at rt for 18 h. The solvent was removed in vacuum (60 °C), and the residue was chromatographed on a silica gel column (230–400 mesh, 100 g, $CHCl_3/C_6H_{14}$, 2:1) to give compound **26** (1.84 g, 80%) as a white solid, mp 107–108 °C: ^1H NMR ($CDCl_3$) δ 2.00 (m, 2 H), 2.05 (s, 3 H), 2.73 (t, J = 8.1, 8.1 Hz, 2 H), 3.96 (s, 3 H), 4.01 (s, 3 H), 4.11 (t, J = 6.5, 6.5 Hz, 2 H), 5.15 (s, 2 H), 6.60 (d, J = 1.4 Hz, 1 H), 6.80 (s, 1 H), 6.90 (d, J = 8.2 Hz, 1 H), 6.94 (d, J = 1.4 Hz, 1 H), 7.31–7.54 (m, 7 H); MS m/e 460 (M^+).

Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 72.96; H, 5.98.

5-(Acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-acetoxyphenyl)benzo[*b*]furan-3-carbaldehyde (29). To a solution of compound **17** (2 g, 5 mmol) in pyridine (5 mL) was added Ac_2O (2 mL). The mixture was stirred at rt for 10 h, and then the solvent was removed in vacuum (60 °C). The residue was chromatographed on a silica gel column (230–400 mesh, 100 g, $CHCl_3/C_6H_{14}$; 3:1) to give compound **29** (1.92 g, 87%) as a white solid, mp 109–111 °C: ^1H NMR ($CDCl_3$) δ 2.03 (m, 2 H), 2.09 (s, 3 H), 2.81 (t, J = 7.2, 7.2 Hz, 2 H), 3.94 (s, 3 H), 4.03 (s, 3 H), 4.12 (t, J = 6.5, 6.5 Hz, 2 H), 6.75 (d, J = 1.2 Hz, 1 H), 7.22 (d, J = 8.0 Hz, 1 H), 7.42–7.47 (m, 2 H), 7.67 (d, J = 1.2 Hz, 1 H), 10.32 (s, 1 H); MS m/e 440 (M^+).

Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.31; H, 5.34.

4-Bromo-5-(3-hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldehyde (30).[33] To a solution of compound **29** (0.8 g, 1.8 mmol) in dry CCl_4 (20 mL) were added consecutively AIBN (50 mg, 0.3 mmol) and NBS (0.42 g, 2.32 mmol). The flask was placed in an oil bath preheated at 95 °C, and the heterogeneous mixture was stirred for 10 min. The mixture was cooled to 0 °C (ice–water bath), and n-butylamine (0.3 g, 4.1 mmol) was added dropwise with stirring. The ice bath was removed, and the mixture was stirred at rt for 10 min. The mixture was added to $CHCl_3$ (50 mL), and the organic layer was washed with brine (2 × 10 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, the residue was dissolved in MeOH (10 mL), and then 1 N NaOH (5 mL) was added. The mixture was stirred at rt for 1 h, and then the MeOH was removed in vacuum (30 °C). The residue was combined with H_2O (30 mL), and the mixture was extracted with $CHCl_3$ (2 × 10 mL). The water solution was acidified with 1 N HCl (5.5 mL) and then extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with brine (2 × 5 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 50 g, $CHCl_3$/EtOH, 95:5) to give **30** (45 mg, 5%) as a yellowish solid, mp 203–204 °C: ^1H NMR (d_6-DMSO) δ 1.79 (m, 2 H), 2.86 (t, J = 7.6, 7.6 Hz, 2 H), 3.52 (t, J = 6.6, 6.6 Hz, 2 H), 3.92 (s, 3 H), 3.98 (s, 3 H), 6.96 (d, J = 8.3 Hz, 1 H), 7.02 (s, 1 H), 7.55 (dd, J = 8.2, 2.0 Hz, 1 H), 7.76 (d, J = 2.0 Hz, 1 H), 10.85 (s, 1 H); ^{13}C NMR (d_6-DMSO) δ 186.0, 161.1, 150.3, 147.5, 144.4, 141.5, 139.1, 128.3, 123.4, 119.6, 115.8, 115.7, 113.6, 110.6, 103.9, 60.4, 56.1, 33.4, 32.9; MS m/e 435 (M^+).

Anal. Calcd for $C_{20}H_{19}O_6Br$: C, 55.19; H, 4.40. Found: C, 55.50; H, 4.06.

5-(3-Hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)-3-(1-hydroxyethyl)benzo[*b*]furan (31). To a solution of compound **29** (440 mg, 1 mmol) in THF (5 mL) was added MeLi (1.4 mol in Et_2O solution, 4 mL). The mixture was stirred at rt for 5 h and then was decomposed with H_2SO_4 (5% ice–H_2O solution, 10 mL). The solution was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 20 g, $CHCl_3/Et_2O/C_6H_{14}$/EtOH, 5:10:5:1) to give the product **31** (316 mg, 85%) as a semisolid: ^1H NMR ($CDCl_3$) δ 1.66 (d, J = 6.5 Hz, 3 H), 1.84 (m, 2 H), 2.67 (t, J = 7.6, 7.6 Hz, 2 H), 3.59 (t, J = 6.3, 6.3 Hz, 2 H), 3.81 (s, 3 H), 3.91 (s, 3 H), 5.29 (q, J = 6.6, 6.6, 6.6 Hz, 1 H), 6.57 (s, 1 H), 6.80 (s, 1 H), 6.89 (d, J = 8.2 Hz, 1 H), 7.06 (dd, J = 8.2, 1.1 Hz, 1 H), 7.17 (s, 1 H), 7.26 (d, J = 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 150.8, 145.9, 145.6, 143.9, 141.1, 136.3, 128.6, 121.8, 120.7, 117.5, 113.8, 111.9, 110.0, 106.7, 62.8, 61.1, 55.1, 33.6, 31.5, 21.9; MS m/e 372 (M^+).

Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.75; H, 6.11.

4-Acetyl-5-(3-acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-acetoxyphenyl)benzo[*b*]furan (32). To a solution of compound **14** (1.7 g, 5 mmol) in glacial HOAc (20 mL) was added a mixture of Ac_2O (4 mL) and 85% H_3PO_4 (0.3 mL). The mixture was stirred at 100 °C for 2 h and then passed through a silica gel column (70–230 mesh, 50 g, $CHCl_3/C_6H_{14}$, 3:1) to give a raw product, which was further chromatographed on a silica gel column (70–230 mesh, 100 g, $CHCl_3/Et_2O/C_6H_{14}$, 1:1:1) to give product **32** (1.5 g, 64%) as a yellowish solid, mp 86–87 °C: ^1H NMR ($CDCl_3$) δ 1.99 (m, 2 H), 2.08 (s, 3 H), 2.33 (s, 3 H), 2.66 (s, 3 H), 2.90 (t, J = 7.9, 7.9 Hz, 2 H), 3.91 (s, 3 H), 4.04 (s, 3 H), 4.14 (t, J = 6.1, 6.1 Hz, 2 H), 6.63 (s, 1 H), 7.06 (s, 1 H), 7.08 (d, J = 10.7 Hz, 1 H), 7.43–7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 201.1, 170.8,

168.5, 156.3, 156.3, 151.4, 146.5, 142.5, 140.5, 137.4, 129.8, 128.5, 125.0, 123.1, 117.8, 117.6, 109.3, 101.7, 63.7, 55.9, 31.7, 31.0, 30.5, 20.6, 20.3; MS m/e 454 (M^+).

Anal. Calcd for $C_{25}H_{26}O_8$: C, 66.07; H, 5.77. Found: C, 66.06; H, 5.22.

3-Nitro-5-(3-acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-(benzyloxy)phenyl)benzo[*b*]furan (35).[34] To a solution of compound **26** (1 g, 2.16 mmol) in glacial HOAc (10 mL) was added dropwise HNO_3 (0.4 mL, d = 1.4, 6.2 mmol) in glacial HOAc (0.4 mL) at 0 °C. The mixture was stirred at the same temperature for 20 min and at rt for 2 h. H_2O (40 mL) was added to the solution, and the separated gummy substance was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine (2 × 5 mL) and dried over anhydrous Na_2SO_4. The organic solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 50 g, $CHCl_3/C_6H_{14}$, 3:1) to give the raw material which was recrystallized ($CHCl_3/C_6H_{14}$, 3:1) to give product **35** (0.73 g, 67%) as a yellowish solid, mp 171–173 °C: ^1H NMR ($CDCl_3$) δ 2.03 (m, 2 H), 2.05 (s, 3 H), 2.81 (t, J = 8.0, 8.0 Hz, 2 H), 3.96 (s, 3 H), 3.99 (s, 3 H), 4.12 (t, J = 6.3, 6.3 Hz, 2 H), 5.23 (s, 2 H), 6.73 (s, 1 H), 6.99 (d, J = 9.2 Hz, 1 H), 7.29–7.46 (m, 5 H), 7.55 (s, 1 H), 7.64 (d, J = 1.8 Hz, 1 H), 7.66 (dd, J = 9.2, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 230.0, 170.7, 156.7, 151.5, 149.4, 145.1, 144.8, 144.1, 140.0, 136.5, 135.2, 133.7, 128.6, 128.0, 124.1, 123.8, 120.3, 113.6, 113.4, 112.6, 112.0, 109.8, 106.9, 71.1, 65.5, 56.3, 32.6, 30.5; MS m/e 505 (M^+).

Anal. Calcd for $C_{28}H_{27}NO_8$: C, 66.53; H, 5.34. Found: C, 66.52; H, 5.38.

3-Nitro-5-(3-acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan (36). To a solution of compound **35** (400 mg, 0.6 mmol) in THF (10 mL) was added 5% Pd–C (20 mg), and the mixture was stirred under H_2 at rt for 6 h. TLC indicated that the substrate disappeared ($Et_2O/CHCl_3/C_6H_{14}$, 2:1:1). The organic solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (70–230 mesh, 15 g, $Et_2O/CHCl_3/C_6H_{14}$, 2:1:1) to give product **36** (250 mg, 94%) as a yellowish solid, mp 135–137 °C: ^1H NMR ($CDCl_3$) δ 2.05 (m, 2 H), 2.09 (s, 3 H), 2.83 (t, J = 8.3, 8.3 Hz, 2 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 4.13 (t, J = 6.5, 6.5 Hz, 2 H), 6.75 (d, J = 1.4 Hz, 1 H), 7.05 (d, J = 8.9 Hz, 1 H), 7.58 (d, J = 1.4 Hz, 1 H), 7.64 (d, J = 1.9 Hz, 1 H), 7.66 (dd, J = 8.9, 1.4 Hz); MS m/e 415 (M^+).

Anal. Calcd for $C_{21}H_{21}NO_8$: C, 60.72; H, 5.10; N, 3.37. Found: C, 60.59; H, 4.78; N, 3.52.

5-(3-Acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-3-carbaldoxime (38).[41] To a solution of compound **17** (0.43 g, 1.08 mmol) in EtOH (20 mL) were added NH_2OH–HCl (0.8 g, 11.7 mmol) and NaOAc (1 g). The mixture was stirred at 60 °C for 2 h, the EtOH was removed, and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with distilled H_2O and dried over Na_2SO_4. The solvent was removed in vacuum, and the residue was chromatographed on a silica gel column (8 g, $CHCl_3$/EtOAc, 1:9) to give compound **38** (0.41 g, 91%) as a white solid, mp 174.5–175.5 °C: ^1H NMR ($CDCl_3$) δ 2.00 (m, 2 H), 2.04 (s, 3 H), 2.78 (t, J = 7.6 Hz, 2 H), 3.95 (s, 3 H), 4.00 (s, 3 H), 4.08 (t, J = 6.6 Hz, 2 H), 6.82 (d, J = 1.3 Hz, 1 H), 6.96 (d, J = 8.3 Hz, 1 H), 7.20 (dd, J = 8.2, 2.0 Hz), 7.31 (d, J = 1.9 Hz, 1 H), 7.52 (d, J = 0.8 Hz, 1 H), 8.41 (s, 1 H); MS m/e 413 (M^+).

Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39. Found: C, 63.62; H, 5.39; N, 3.29.

3-Cyano-5-(3-acetoxypropyl)-7-methoxy-2-(3′-methoxy-4′-acetoxyphenyl)benzo[*b*]furan (39).[41] Compound **38** (0.25 g, 0.6 mmol) was dissolved in Ac_2O (10 mL), and the mixture was refluxed at 135–140 °C for 15 h. The solvent was removed in vacuum, and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated to dryness in vacuum, and the residue was chromatographed on a silica gel column (7 g, $CHCl_3/C_6H_{14}$/EtOAc, 1:1:0.1) to give the compound **39** (210 mg, 81%) as a white solid, mp 129.5–130.5 °C: ^1H NMR ($CDCl_3$) δ 2.04 (m, 2 H), 2.09 (s, 3 H), 2.36 (s, 3 H), 2.80 (t, J = 7.7, 7.7 Hz, 2 H), 3.97 (s, 3 H), 4.04 (s, 3 H), 4.13 (t, J = 6.5, 6.5 Hz, 2 H), 6.74 (s, 1 H), 7.11 (s, 1 H), 7.20 (d, J = 8.8 Hz, 1 H), 7.79–7.82 (m, 2 H); MS m/e 437 (M^+).

Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20. Found: C, 65.77; H, 5.06; N, 3.10.

5-(3-Hydroxypropyl)-7-methoxy-2-(3′-methoxy-4′-hydroxyphenyl)benzo[*b*]furan-4-carbaldehyde (41).[36] To a solution of compound **14** (0.25 g, 0.8 mmol) in DMF (0.12 mL) was added $POCl_3$ (0.2 g, 1.2 mmol) at 0 °C. The mixture was stirred at rt for 30 min and then heated with a boiling H_2O bath for 1.5 h. The mixture was allowed to stand at rt overnight and decomposed with a solution of 5% NaOAc (5 mL). The isolated solid was filtered off and chromatographed on a silica gel column (230–400 mesh, 50 g, EtOAc/C_6H_{14}, 4:1) to give product **41** (165 mg), which was recrystallized ($CHCl_3/C_6H_{14}$, 2:1) to give the purified product **41** (150 mg, 55%) as a yellowish solid, mp 161.5–162 °C: ^1H NMR ($CDCl_3$) δ 2.16 (m, 2 H), 3.24 (t, J = 7.2, 7.2 Hz, 2 H), 3.59 (t, J = 6.2, 6.2 Hz, 2 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 5.95 (s, 1 H), 6.63 (s, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 7.36 (d, J = 1.8 Hz, 1 H), 7.48 (dd, J = 8.3, 1.9 Hz, 1 H), 7.68 (s, 1 H), 10.47 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 189.0 (CHO), 159.4 (C-4′), 149.1 (C-7a), 147.2 (C-2), 147.0 (C-7), 143.2 (C-3), 142.7 (C-4), 132.6 (C-5), 122.4 (C-3a), 119.5 (C-6), 115.0 (C-3′), 109.1 (C-2′), 108.1 (C-6′), 100.9 (C-5′), 56.5 (OMe), 56.3 (OMe), 44.0 (C-10), 35.6 (C-8), 29.5 (C-9); MS m/e 356 (M^+).

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 66.84; H, 5.55.

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Supplementary Material Available: ^1H NMR of compounds **1**, **6**, **8–10**, and **12–41**, ^{13}C NMR of compounds **1**, **13**, **16**, **19–21**, **27**, **28**, **30–33**, and **39–41**, 2D ^1H–^{13}C COSY of compound **16**, and 2D ^1H–^1H NOESY of compounds **19**, **27**, **34**, and **41** (59 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.